JOC The Journal of Organic Chemistry

Article

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Possible Reason for the Unusual Regioselectivity in Nucleophilic Ring Opening of Trisubstituted Aziridines under Mildly Basic Conditions

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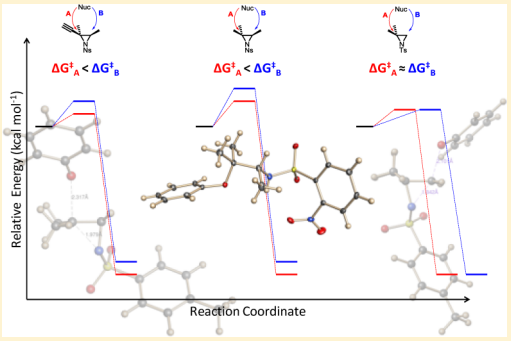
Supporting Information

ABSTRACT: 2,2,3-Trisubstituted aziridines are known to undergo ring opening at the more substituted carbon under mildly basic conditions. However, the reason for the formation of the more sterically encumbered product has never been examined. Several trisubstituted aziridines, with different substitution patterns at the C-2 and C-3 carbons, were synthesized to change the electronics of the aziridine ring system. These changes had no effect on the regioselectivity of the ring-opening reaction. Using the B3LYP/6-31G* DFT basis set it was determined that the transition state for opening at the more substituted carbon proceeds at a lower energy than the transition state at the less substituted carbon.



INTRODUCTION

β-Substituted quaternary compounds (**1**; Figure 1) are present in many products such as quaternary β-substituted amino acids, which are important enzyme inhibitors and are incorporated in peptides to modulate secondary and tertiary conformations.[1] We have previously reported a stereospecific ring opening of a trisubstituted aziridine (**2**) that displayed regioselectivity for the more substituted carbon and applied it to the synthesis of a variety of products (Figure 1). We have achieved the ring opening of trisubstituted aziridines with a variety of nucleophiles. Using trisubstituted aziridines and heteroatom nucleophiles, tertiary moieties[2] as well as 1,2-diamines[3] were synthesized in good yield. Trisubstituted aziridines were also valuable in the total syntheses of ustiloxin D[4−6] and phomopsin B.[7] The use of an ethynyl trisubstituted aziridine facilitated the synthesis of ustiloxin D, resulting in its shortest synthesis to date[4,6] and making it amenable to the preparation of ustiloxin analogues.[8] Carbon nucleophiles were also used to make quaternary centers and allenes.[9] These ring openings occur under non Lewis acidic conditions and occur regioselectively at the more substituted carbon. The only instance where addition at this carbon was not observed was with organocuprates, a reaction that produced allenes (Figure 1).

The Bæyer strain and the electronegative atom enclosed in a three-membered ring cause aziridines to undergo nucleophilic ring opening even under mild conditions.[10] The synthetic utility of aziridines has been the topic of many reviews.[11−18] However, nucleophilic attack on unsymmetrically substituted aziridines can lead to two regioisomeric products. Under non Lewis acidic conditions most nucleophiles attack preferentially at the less substituted carbon, and this behavior is typically attributed to sterics. Attack at the more substituted carbon can be achieved by electronic bias either with Lewis acid catalysis or with an aryl or other π bond containing substituent on the aziridine ring. Nonetheless, some trisubstituted aziridines display unique regioselectivity with ring opening at the more substituted carbon. A unique characteristic of the reaction profile is its stereospecificity, proceeding with inversion of configuration.

Within the past decade, several other research laboratories have used trisubstituted aziridines to advance their research goals. Chandrasekaran and co-workers synthesized unsymmetrical β-sulfonamido disulfides (**4**; Figure 2a) by ring opening of aziridines with the use of benzyltriethylammonium tetrathiomolybdate as a sulfur transfer reagent in the presence of symmetrical disulfides.[19] In the investigation of trisubstituted aziridine **3** with benzyl disulfide in the presence of the tetrathiomolybdate species, regioselective ring opening was observed at the more substituted carbon (Figure 2a). Another interesting reaction that has been applied to trisubstituted aziridines is the C−C bond breakage of the ring.[20−22] Trisubstituted aziridines bearing an electron-withdrawing group on one or both carbons (**5**, Figure 2b) can undergo C−C ring opening under Lewis acid catalysis to form azomethine ylides (**6**). The zwitterion can undergo [3 + 2] cycloaddition to form a new ring system (**7**; Figure 2b).[23]

The synthesis of chiral trisubstituted aziridines can include many steps; thus, an asymmetric approach to these compounds has been of much interest.[24−40] The use of strong, chiral Brønsted acids has been effective in transforming *N*-Boc imines and α-diazocarbonyl compounds into trisubstituted aziridines. Wulff[41] (Figure 3a) and Maruoka[42] (Figure 3b) both published their respective asymmetric reactions where Wulff used the axially chiral (*R*)-VANOL to achieve asymmetric induction, and Maruoka employed the highly acidic *N*-triflyl phosphoramide

Received: March 22, 2014
Published: May 6, 2014

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

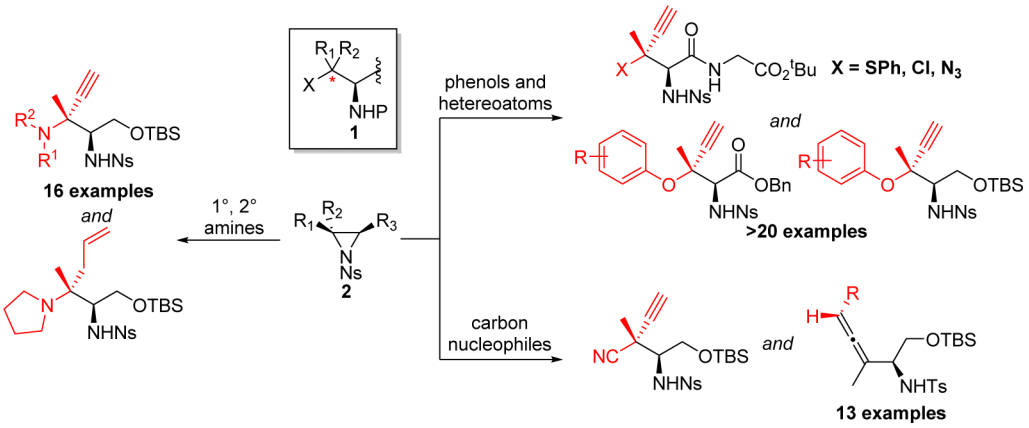


Figure 1. Recent applications of the nucleophilic ring opening of a trisubstituted aziridine with an array of nucleophiles to synthesize an assortment of synthetic moieties in natural products and other structures.

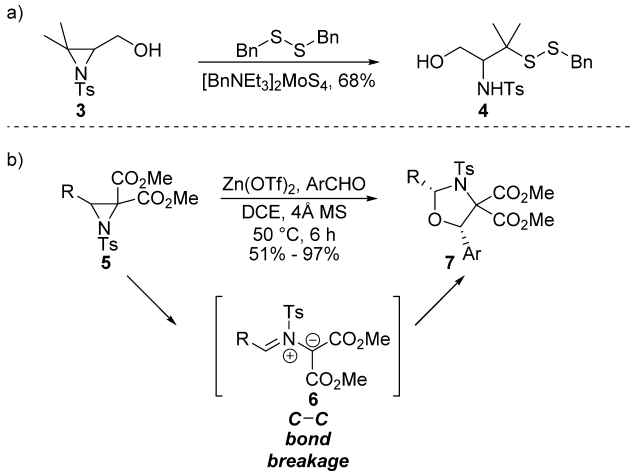


Figure 2. (a) Applications of a trisubstituted aziridine in the synthesis of β-substituted disulfides. (b) Lewis acid catalyzed C−C ring opening of a trisubstituted aziridine to give an azomethine ylide that undergoes a [3 + 2] cycloaddition.

developed by Yamamoto.[43] Both approaches were effective transformations of relatively simple substrates to chiral trisubstituted aziridines. Recently a mild, versatile method for the direct stereospecific conversion of structurally diverse mono-, di-, tri-, and tetrasubstituted olefins to the corresponding *N*-H or *N*-Me aziridines has been reported. The reaction proceeds via a rhodium-catalyzed pathway free from external oxidants. The transformation takes place by reacting the olefin with *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) and Du Bois' catalyst, $Rh_2(esp)_2$, in 2,2,2-trifluoroethanol.[44] This method will allow trisubstituted aziridines to be rapidly accessed from olefins, as opposed to the multistep approach that we used.

RESULTS AND DISCUSSION

Carbon Nucleophiles. Expanding the ring-opening reactions of trisubstituted aziridines with carbon nucleophiles was of interest because, upon successful ring opening, a quaternary center can be synthesized in a regioselective and stereospecific manner. Joullié and co-workers have reported that cyanides are effective nucleophiles in opening an ethynyl trisubstituted aziridine at the more substituted carbon.[9] While cyanides can serve as surrogates for other useful functional groups, e.g. malonates, their use as a carbon nucleophile is severely limited.

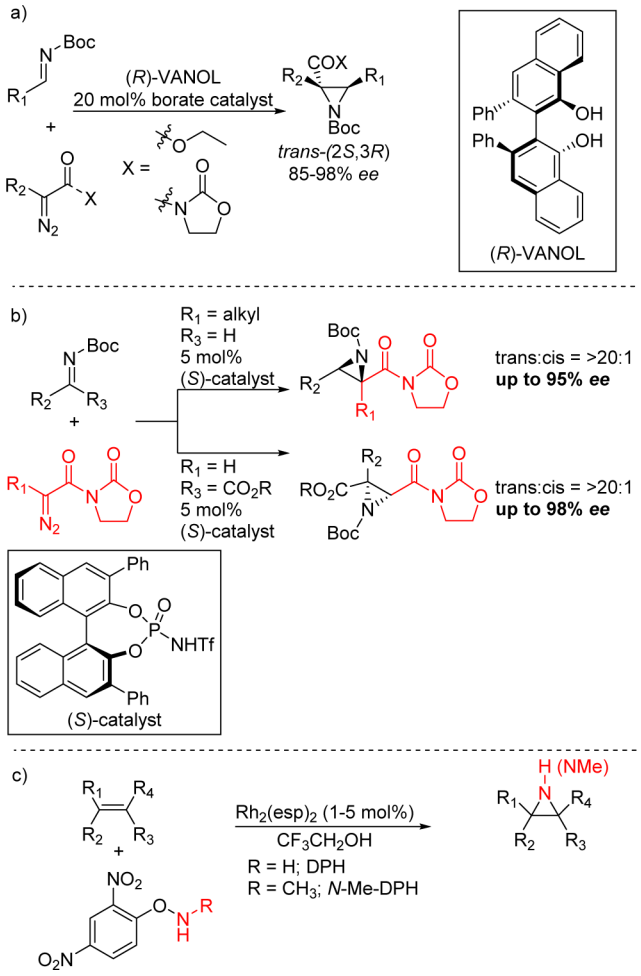


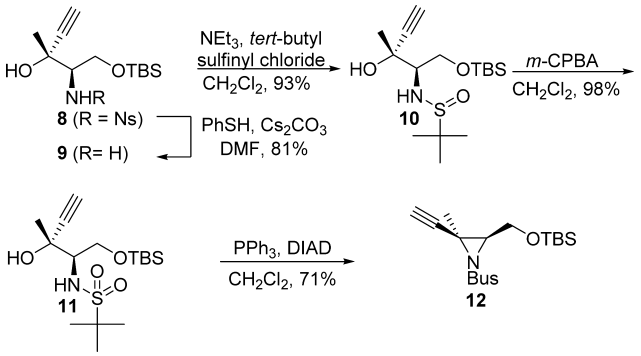
Figure 3. (a) Wulff's approach to the asymmetric synthesis of trisubstituted aziridines. (b) Maruoka's approach to the asymmetric synthesis of trisubstituted aziridines. (c) Ess's, Kürti's, and Falck's stereospecific synthesis of unprotected mono-, di-, and trisubstituted aziridines.

In order to investigate further the use of carbon nucleophiles, the 2-nitrobenzenesulfonyl (Ns) group was replaced with the *tert*-butylsulfonyl (Bus) group,[45] as the nitro groups would not be compatible with hard carbon nucleophiles. This protecting group was chosen over the 4-toluenesulfonyl group (Ts) because it can easily be removed under mildly acidic

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

conditions.[46] However, *tert*-butylsulfonyl chloride is unstable; therefore, the protecting group had to be synthesized. Using intermediate **8**,[2] removal of the Ns group gave the free amine **9**, followed by reaction with *tert*-butylsulfinyl chloride, to produce **10** as a mixture of diastereomers. Oxidation of the sulfinyl group to the sulfone (**11**) using *m*-CPBA was followed by ring closure under Mitsunobu conditions to afford aziridine **12** (Scheme 1).

Scheme 1. Synthesis of *tert*-Butylsulfonyl Aziridine 12

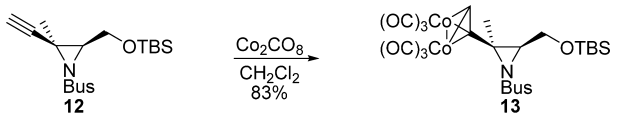


Upon treatment with numerous organometallic reagents (Grignard, organolithium, aluminum, and cerium reagents) only starting material and a trace amount of the enyne product, which was a result of elimination from the C2 methyl, were isolated. This finding was disappointing ,because on the basis of a previous result of Grignard reagents with trisubstituted epoxides[47] the combination of Lewis basicity and nucleophilicity should have been sufficient to achieve ring opening.

In an effort to improve the reaction with organometallic carbon nucleophiles, the Nicholas reaction[48,49] was proposed. Dicobalt octacarbonyl is a reagent that was originally used as an alkyne protecting group,[49] but in the Nicholas reaction dicobalt octacarbonyl is used to activate propargylic leaving groups to generate stabilized carbocations. If this reaction is applied to a progargylic aziridine, the aziridine could react with dicobalt octacarbonyl, losing 2 equiv of carbon monoxide, to produce a $Co_2(CO)_6$–alkyne complex. If the complex were to be treated with a protic or Lewis acid, a stabilized carbocation could be generated. This carbocation could be trapped by a nucleophile to generate an addition product. Upon reaction with an oxidant the alkyne would be restored.

The *tert*-butylsulfonyl aziridine **12** was complexed in good yield (Scheme 2). The structure of the compound could not be

Scheme 2. Synthesis of Dicobalt Aziridine Complex 13



determined by NMR; therefore, it was confirmed by X-ray (Supporting Information). It is important to note that aziridines protected with Ts and Ns groups decomposed upon reaction with dicobalt octacarbonyl.

Unfortunately, the Nicholas complex was unable to yield the desired ring-opened product. It is not known whether the rate of elimination is faster than nucleophilic addition, but protic (HBF_4) and Lewis ($BF_3{\cdot}OEt_2$ and $TiCl_4$) acids with phenol and anisole as nucleophiles were unsuccessful in giving the addition product. Only the previously reported enyne product[2] was isolated in trace quantities.

Investigation of Regioselectivity: Synthesis of Aziridines. To investigate the regioselectivity of the ring-opening reaction, several unique trisubstituted aziridines were synthesized, different from those that were used previously in natural product syntheses (**14**[50] and **16**[6]) and in the formation of fully substituted carbon centers[2] (**14**, **15**, and **17**) (Figure 4a).

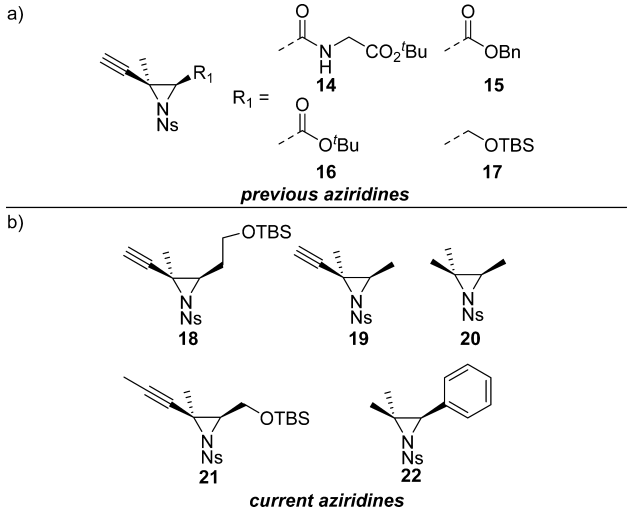


Figure 4. (a) Previous ethynyl aziridines used in ring-opening reactions for the syntheses of natural products and quaternary centers. (b) Aziridines of interest to investigate the regiochemistry of the ring opening.

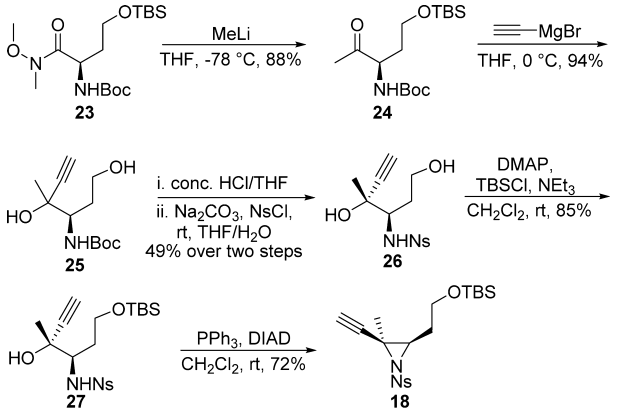
Aziridine **18** has an additional methylene carbon in the C-3 functional group. Aziridine **19** only has a methyl group on C-3, and aziridine **20** has only methyl substituents. The reason for synthesizing these compounds was to change the electronics of the substituents to see whether they determined the regioselectivity. In addition, aziridine **21** has a methyl-substituted alkyne, and aziridine **22** has a ring activating group on the less substituted carbon. This distinct aziridine is still trisubstituted but with the phenyl on the less substituted carbon. This structural modification should determine which factor is the more important, the trisubstituted nature of the aziridine or the activating group (Figure 4b). The aziridines synthesized are shown in Figure 4.

The synthesis of homologated aziridine **18** started from the known Weinreb amide (**23**, Scheme 3).[51−54] Attack of the Weinreb amide with methyllithium afforded ketone **24**, which when treated with an ethynyl Grignard gave an inseparable mixture of diastereomeric tertiary alcohols (**25**). The acid-labile protecting groups were removed and the amine was reprotected with the Ns group to yield compound **26.** The diastereomeric diols were separable by recrystallization, and diol **26** was reprotected as the silyl ether **27**. Under Mitsunobu conditions the desired aziridine (**18**) was formed in acceptable yield (Scheme 3). Although this aziridine was used in the regioselective ring opening with pyrrolidine,[3] the different reaction conditions with the weaker phenol nucleophile could lead to a mixture of regioisomeric products.

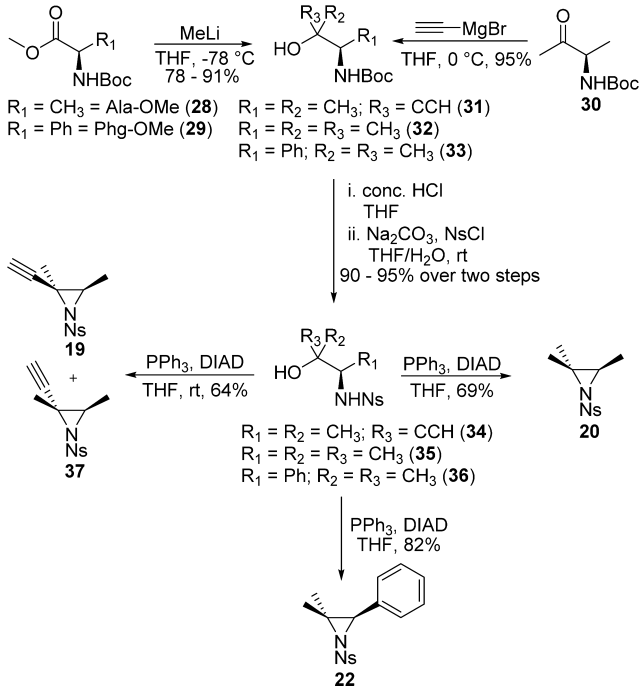
The syntheses of azirdines **19**, **20**, and **22** proceeded through a similar synthetic sequence (Scheme 4). The synthesis of **19** started from the known ketone **30**,[55] which after Grignard

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

Scheme 3. Synthesis of Homologated Aziridine 18



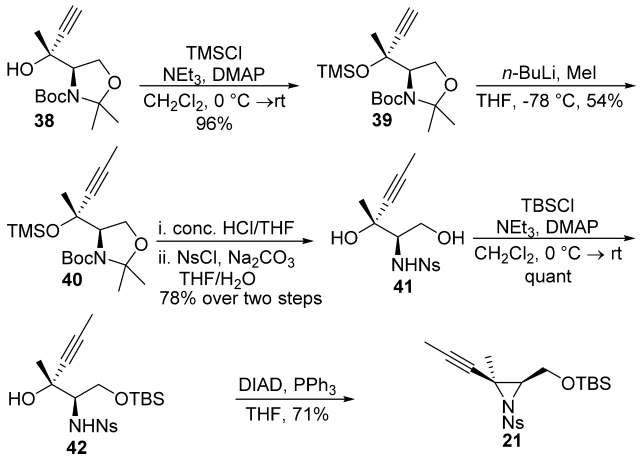
Scheme 4. Synthesis of Diastereomeric Aziridines 19, 20, and 22



addition gave the tertiary alcohol **31** as a mixture of diastereomers. The synthesis of aziridines **20** and **22** begin from their respective methyl esters (**28** and **29**). Methyllithium addition to the methyl esters gave the known tertiary alcohols **32** and **33**.[56] Removal of the carbamates followed by reprotection with the Ns group gave sulfonamides **34**–**36**. Each sulfonamide was subjected to Mitsunobu conditions, which gave a separable mixture of diastereomeric aziridines **19** and **37** and also aziridines **20** and **22** in good yield (Scheme 4).

The methyl alkynyl aziridine **21** was synthesized in six steps from the known tertiary alcohol **38** (Scheme 5). The alcohol was protected as the silyl ether with trimethylsilyl chloride to give **39**. Silyl ether protection was necessary for deprotonation with *n*-butyllithium. The acetylide anion was quenched with methyl iodide to give the methyl-substituted alkyne **40**. The alcohol was protected to avoid *O*-alkylation. Compound **40** was treated with concentrated HCl to remove the protecting groups, and the amine was reprotected with the Ns group to give **41**. The primary alcohol of **41** was protected with the TBS

Scheme 5. Synthesis of Methyl Alkynyl Aziridine 21



group to give **42**, and aziridine **21** was formed under Mitsunobu conditions (Scheme 5).

Crystallographic Analysis of Unsymmetrical Aziridines. Several X-ray structures of the aziridines were determined to obtain the bond lengths and geometry around the ring system (Table 1). In each of the aziridines, the C2–N bond (the more substituted) is longer than the C3–N bond (the less substituted), suggesting that the C2–N is the weaker bond. The bond lengths may be explained by the donor–acceptor interactions generated by the substitution pattern across the ring system. A stereoelectronic effect between the filled σ_{C-H} orbitals of the methyl groups and the empty σ^*_{C-N} orbital of the C2–N bond of the aziridine would explain why the more substituted bond is longer than the less substituted bond. The C2 carbon has more substituents, either alkyl or ethynyl, that can donate into the σ^*_{C2-N} bond. In comparison to the less substituted C3–N bond, this increased donation into the C2–N antibonding orbital would lengthen/weaken this bond.

Using aziridine **20** as a representative, looking at the steric environment, the methyl–C2–methyl bond angle is much greater than that of a normal tetrahedral carbon at 116° (Supporting Information, Table 41). This angle suggests that even though the carbon is fully substituted the substituents are not oriented in a manner that would block the carbon for backside attack in contrast with S_N2 attack on a linear substrate.

Ring-Opening Reactions. After the desired aziridines were synthesized, the next step was to determine if the changes would provide different regioisomeric products under the reaction conditions. The crystallographic information suggests that the weaker C2–N bond would be broken under the nucleophilic conditions. All of the trisubstituted aziridines underwent ring opening in good yield to afford a single regioisomer with attack at the more substituted carbon (Chart 1). The regioisomer of the products could be determined from the ^{1}H NMR, where the sulfonamide N–H has a doublet splitting pattern. In addition, the X-ray structure of **45** showed the phenol bonded to the more substituted carbon of the aziridine (Supporting Information).

In an effort to alter the substitution pattern around the aziridine ring system, the known 2,2-*gem*-dimethyl-*N*-tosyl aziridine **48**[57] was synthesized and subjected to the ring-opening conditions. Upon treatment with 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) and phenol a mixture of regioisomeric products (**49** and **50**) was isolated in a 1:1 ratio. This result is

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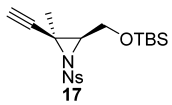
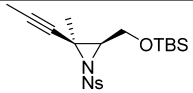
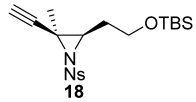
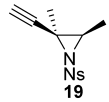
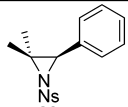
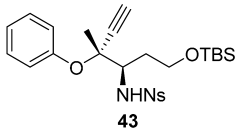
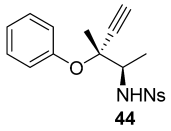
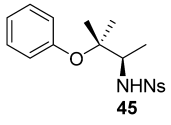
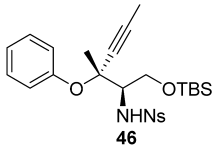
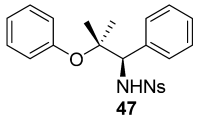
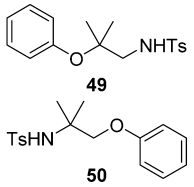
Table 1. Crystallographic Analysis of Aziridines and Their Carbon−Nitrogen Bond Lengths[a]

 17 m.p. = 100 - 102 °C		 21 m.p. = 65 - 67 °C		 18 m.p. = 63 - 65 °C		 19 m.p. = 94 - 96 °C	
Bond Length (Å)		Bond Length (Å)		Bond Length (Å)		Bond Length (Å)	
C2-N	C3-N	C2-N	C3-N	C2-N	C3-N	C2-N	C3-N
1.508	1.476	1.519	1.476	1.505	1.469	1.515	1.487

 20 m.p. = 77 - 79 °C		 22 m.p. = 94 - 96 °C		 48 m.p. = 177 - 179 °C	
Bond Length (Å)		Bond Length (Å)		Bond Length (Å)	
C2-N	C3-N	C2-N	C3-N	C2-N	C3-N
1.521	1.495	1.512	1.492	1.506	1.488

[a]C2 is the more substituted carbon, C3 is the less substituted carbon, and N is the aziridine nitrogen. The bond distances are in angstroms. Aziridine **20** has four structures in the unit cell, but only one is reported. Aziridine **19** has two structures in the unit cell, but only one is reported.

Chart 1. Results of Aziridine Ring-Opening Reactions with a Phenol Nucleophile[a]

Aziridine	Product(s)	Yield
18	 **43**	84%
19	 **44**	68%
20	 **45**	84%
21	 **46**	78%
22	 **47**	77%
48	 **49** **50**	64%[b]

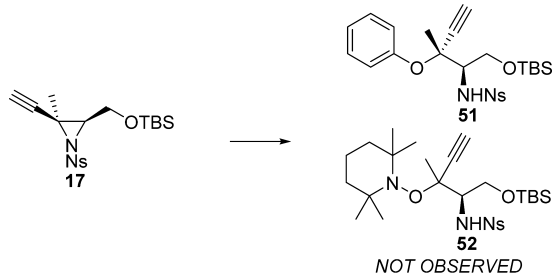
[a]Conditions: phenol (2 equiv), TBD (2 equiv), $PhCH_3$. [b]A 1:1 mixture of product was isolated.

not the first instance in which aziridine **48** gave a mixture of regioisomers upon nucleophilic ring opening,[58] but this was our first observed example of a mixture of regioisomers from an unsymmetrical aziridine. Although a mixture of regioisomers was isolated, the reaction displayed no preference for either carbon of the ring system. This outcome contradicts the notion that the longer, weaker bond is broken in the ring-opening reaction.

Additional Investigation of the Reaction Regioselectivity. Although a better understanding of the aziridine ring system was obtained through the X-ray structures, the unusual regioselectivity of the ring-opening reaction was not explained. The reaction provides a single stereoisomer with inverted configuration. However, unsymmetrical aziridines are known to undergo ring opening via a SET pathway.[57,59−63] Upon ring opening the more stable radical is formed and this radical would be generated on the more substituted carbon of the aziridine. While the possibility of this reaction type was low, an experiment was done to rule out a radical ring opening (Scheme 6).

No radical byproducts were observed when the radical trap TEMPO was added to the reaction mixture, and the ring-opened product isolated was a single stereoisomer whose spectroscopic data matched those of the known compound.[2]

Scheme 6. Aziridine Ring-Opening Reaction in the Presence of TEMPO[a]

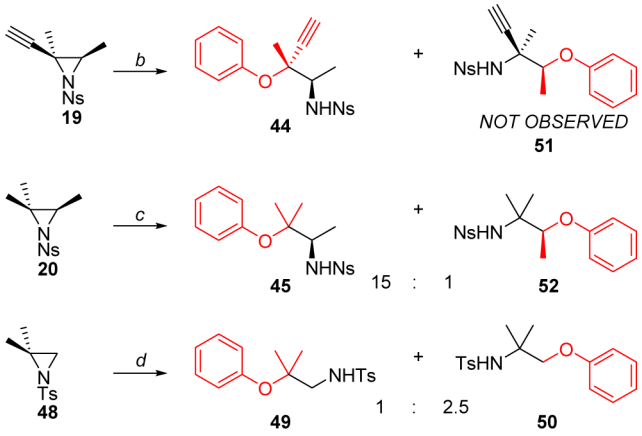


[a]Conditions: phenol (2 equiv), TDB (2 equiv), TEMPO (2 equiv), $PhCH_3$, 69% yield.

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

To get a better analysis of the reaction, TBD and phenol were replaced with potassium phenoxide. The TBD omission is important as the guanidine base, TBD, can act as a hydrogen bond donor and activate the aziridine for attack at the more substituted carbon.[64,65] When TBD was replaced with potassium hydride (KH), the ring-opening reactions proceeded in a similar manner (Scheme 7). For the trisubstituted aziridine

Scheme 7. Ring-Opening Reactions using KH as a Base[a]



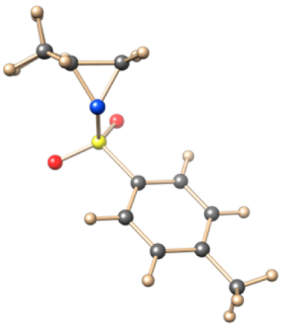
[a]Conditions: phenol (4 equiv), KH (4 equiv), 18-crown-6 (4 equiv), THF. [b]80% isolated yield. [c]79% isolated yield. [d]75% isolated yield.

19 the only reaction observed was attack at the more substituted carbon. This result could be explained by the stabilization of the transition state of the alkynyl substituent.[66] When aziridine **20** was used, a slight mixture of regioisomers was observed. This observation was the first instance where a trisubstituted aziridine gave a mixture of regioisomers. However, attack at the more substituted carbon was the major isomer. Aziridine **48** gave a mixture of regioisomers in a 1:2.5 ratio favoring attack at the less substituted carbon.

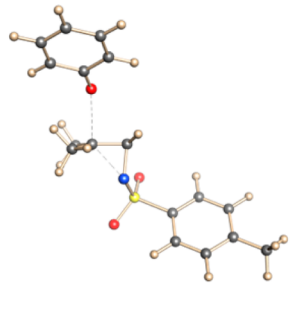
To examine the electronics of the ring-opening reaction, density functional theory (DFT) molecular modeling calculations were performed. Using the Gaussian 09 program package at the B3LYP/6-31G* basis set, ground state and transition state calculations were performed to get the optimized geometries along with the free energies and the natural bond orbital (NBO) charges of the atoms involved in the reactions. The charges of the atoms will allow for the examination of the electronics of the aziridines and transition states.[66] The reactions were implicitly solvated in a self-consistent reaction field (SCRF) of THF.

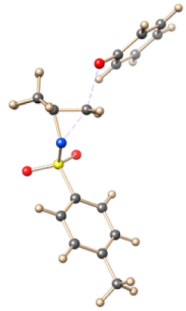
The computational model was designed to mimic the experimental conditions of the potassium phenoxide ring-opening conditions (Scheme 7). The ground state geometries were determined for each aziridine, and in each geometry optimization the more substituted carbon has a higher δ^+ charge (Tables 2 and 3). This finding is consistent with our previous work[2] but cannot explain the regioselectivity. The geometry optimization of aziridine **48** (Table 2) also has a large δ^+ charge at the more substituted carbon, but the ring-opening reaction proceeds to give a mixture of regioisomers (Chart 1; Scheme 7). A transition state model was optimized for aziridines **19**, **20**, and **48**, where the phenoxide attacks both the more substituted and less substituted carbons. The approach of the nucleophile was consistent with Walsh orbitals.[67,68] In a typical S_N2 reaction, the approach of the

Table 2. Optimized Ground State and Transition State Geometries, with the Transition State Energies and NBO Charges of the Carbons, of Aziridine 48



Aziridine **48**	
δ-charges	
C2: +.132	C3: −.259





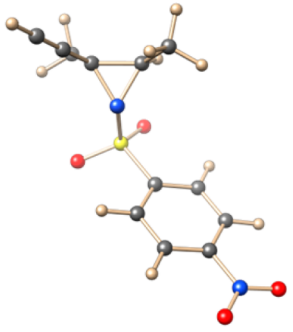
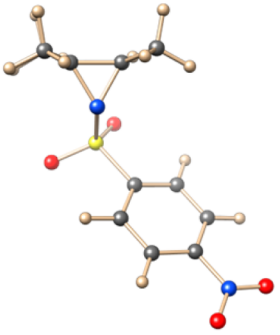
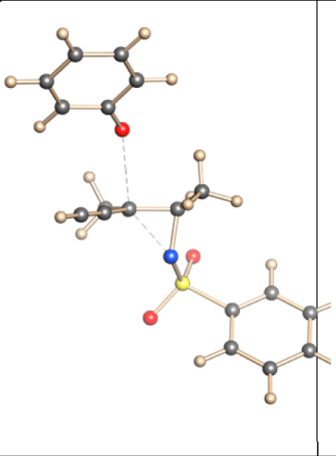
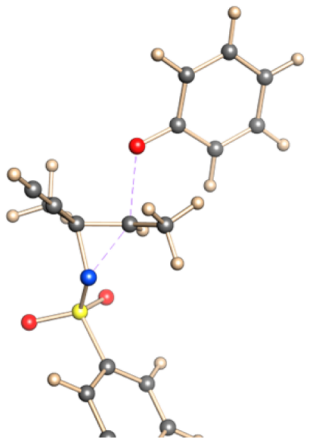
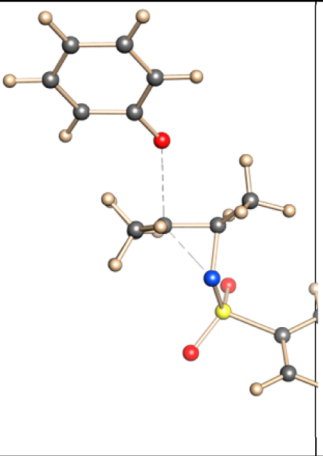
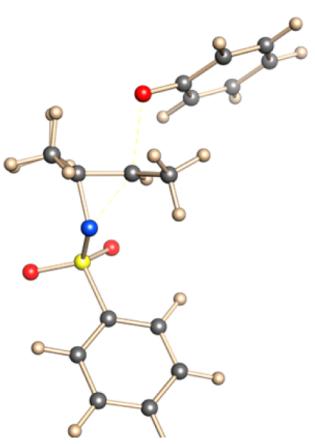
δ-charges		δ-charges	
C2: +.290	C3: −.290	C2: +.094	C3: −.158
$\Delta G^{\ddagger}$ = 21.50 kcal•mol^{-1}		$\Delta G^{\ddagger}$ = 20.66 kcal•mol^{-1}	
$\Delta\Delta G^{\ddagger}$ = 0.84 kcal•mol^{-1}			

nucleophile is in line with the bond that is being broken, which is not the case for the aziridine ring opening due to the bent nature of the aziridine bonding system. This fact in conjunction with our experimental results suggests a more favored attack trajectory in contrast to the course of a typical S_N2 reaction (Tables 2 and 3).

Each of the geometries resembles an early transition state, where the C−N bond of the aziridine is breaking before the new C−O bond is formed. Within the transition state geometry optimization, the δ^- charges of the aziridine carbon change. When the nucleophile approaches the carbon involved in the reaction, the carbon increases in δ^+ charge. This observation is consistent for the six geometries, but the free energies for the ring openings vary. The transition state energy for aziridine **19**, where the ring opening occurred at the more substituted carbon, is $\Delta G^{\ddagger}$ = 16.23 kcal mol^{-1}. The energy for ring opening at the less substituted carbon is 20.22 kcal mol^{-1}. This value generates $\Delta\Delta G^{\ddagger}$ = 3.99 kcal mol^{-1}. The large difference in the transition state energies would lead to only one regioisomeric product formed favoring the attack at the more substituted carbon, since that has the lower transition state energy. This difference was observed experimentally, where in Scheme 7, only one regioisomeric product was observed. The ring-opening transition state of aziridine **20** exhibited a similar trend. The attack at the more substituted carbon has an energy of

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

Table 3. (a) Optimized Ground State and Transition State Geometries,[a] with the Transition State Energies and NBO Charges of the Carbons, of Aziridines 19 and 20

			
Aziridine **19**		Aziridine **20**	
δ-charges		δ-charges	
C2: +.070	C3: −.031	C2: +.200	C3: −.019
			
δ-charges	δ-charges	δ-charges	δ-charges
C2: +.177 / C3: −.069	C2: +.040 / C3: +070	C2: +.295 / C3: −.088	C2: +.106 / C3: +.062
$\Delta G^{\ddagger}$ = 16.23 kcal•mol^{-1}	$\Delta G^{\ddagger}$ = 20.22 kcal•mol^{-1}	$\Delta G^{\ddagger}$ = 18.24 kcal•mol^{-1}	$\Delta G^{\ddagger}$ = 20.25 kcal•mol^{-1}
$\Delta\Delta G^{\ddagger}$ = 3.99 kcal•mol^{-1}		$\Delta\Delta G^{\ddagger}$ = 2.01 kcal•mol^{-1}	

[a]The geometries were optimized with the B3LYP/6-31G* basis set in a SCRF of THF.

$\Delta G^{\ddagger}$ = 18.24 kcal mol^{-1}. The attack at the less substituted carbon has an energy of $\Delta G^{\ddagger}$ = 20.25 kcal mol^{-1}. This energy difference generates $\Delta\Delta G^{\ddagger}$ = 2.01 kcal mol^{-1} and a predicted product distribution of 30:1 favoring attack at the more substituted carbon. These data correlate well to the experimental outcome of 15:1 in Scheme 7. A possible explanation for the higher transition state energy for the attack at the less substituted carbon is unfavorable electronics. In the transition state optimizations for attack at the less substituted carbon for aziridines **19** and **20** (Table 3) both carbons of the aziridine have a δ^{+} charge. The positive charges in close proximity could explain why attack at the less substituted carbon is higher in energy. This higher energy is supported by the transition state geometries of aziridine **48**. The NBO charges of the aziridine carbons in the transition state geometries in Table 3 do not have the neighboring positive charges. Consequently, the transition state energies for attack at the more and less substituted carbon are $\Delta G^{\ddagger}$ = 21.50 and 20.66 kcal mol^{-1}, respectively. This explanation generates $\Delta\Delta G^{\ddagger}$ = 0.84 kcal mol^{-1} and a 4:1 product distribution favoring attack at the less substituted carbon. The calculated product ratio agrees with the experimentally observed 2.5:1 product ratio.

CONCLUSIONS

2,2,3-Trisubstituted aziridines undergo a regio- and stereoselective ring opening that occurs exclusively at the most encumbered carbon with inversion of configuration. A computational model designed to mimic the experimental conditions allowed calculation of the ring-opening transition state energies of three differently substituted aziridines. The differences in transition state energies agreed with the experimental product distribution. Unfavorable electronics at the less substituted carbon and an alternate attack trajectory could explain the unique preference for attack at the more substituted carbon.

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, unless otherwise mentioned. ^{1}H NMR chemical shifts are reported in parts per million (ppm) from the solvent resonance ($CDCl_3$ 7.27 ppm). The data are reported as follows: chemical shift, number of protons, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad, m = multiplet), and coupling constants. Proton-decoupled ^{13}C NMR chemical shifts are reported in ppm from the solvent resonance ($CDCl_3$ 77.0 ppm). High-resolution mass spectra (HRMS) were obtained on a Micromass AutoSpec electrospray/chemical ionization spectrometer (GC-TOF). Melting points (°C) were uncorrected. The reaction solvents $PhCH_3$ and CH_2Cl_2 were all distilled over calcium hydride. THF was distilled over sodium/benzophenone. Triethylamine was distilled over calcium hydride, but all other reagents were used without further purification. All Grignard and alkyllithium reagents were titrated with salicylaldehyde phenylhydrazone prior to use. All calculations were performed using Gaussian 09. All geometries were optimized in a SCRF of THF.

(3*R*,4*R*)-4-Amino-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpent-1-yn-3-ol (9). The known sulfonamide **8** (2.16 g, 5.04 mmol) was dissolved in anhydrous DMF (50 mL) and cooled to 0 °C under argon. Cesium carbonate (2.46 g, 7.56 mmol) and thiophenol (1.54 mL, 15.1 mmol) were added sequentially to the solution, and the reaction was monitored by TLC. The reaction was complete after 3 h. The solution was diluted with EtOAc (100 mL) and partitioned with saturated $NaHCO_3$ (50 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with H_2O (6 × 100 mL), after which the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (10% EtOAc−90% hexanes →100% EtOAc) to give the desired product as an amorphous white solid (988 mg, 81%); R_f 0.10 (70% EtOAc−30% hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.73 (1H, dd, J = 5.7, 10.0 Hz), 3.53 (1H, dd, J = 6.5, 10.0 Hz), 2.76 (1H, m), 2.57 (2H, bs), 2.32 (1H, s), 1.33 (1H, s), 0.77 (9H, s), −0.04 (3H, s), −0.05 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 86.2, 71.8, 69.9, 64.5, 59.0, 25.9, 25.5, 17.8, −5.9; IR (film): 3371 (s), 2359 (s), 3309 (s), 2954 (s), 2930 (s), 2858 (s), 1586 (w), 1472 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{26}NO_2Si$ (M + H)$^+$ 244.1733, found 244.1761; $[\alpha]_D^{25}$ = 9.2° (c 0.95, $CHCl_3$).

***N*-((2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-3-methylpent-4-yn-2-yl)-2-methylpropane-2-sulfinamide (10).** The amine **9** (1.22 g, 5.01 mmol) was dissolved in dry CH_2Cl_2 (50 mL) under argon and cooled to 0 °C. Dry triethylamine (3.5 mL, 25.1 mmol) and *tert*-butylsulfinyl chloride (931 μL, 7.52 mmol) were added sequentially to the reaction mixture. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated $NaHCO_3$ (70 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The reaction was purified by silica gel chromatography (50% EtOAc−50% hexanes) to give **10** as a yellow oil (1.62 g, 93%); R_f 0.60 (50% EtOAc−50% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (1H, s), 4.19 (1H, dd, J = 4.1, 10.4 Hz), 4.01 (1H, dd, J = 8.5, 10.4 Hz), 3.45 (1H, d, J = 10.2 Hz), 3.32 (1H, m), 2.50 (1H, s), 1.63 (3H, s), 1.25 (9H, s), 0.92 (9H, s), 0.15 (3H, s), 0.14 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.1, 72.9, 71.4, 64.9, 63.2, 56.3, 27.7, 25.6, 22.5, 17.8, −5.8, −5.9; IR (film): 3311 (s), 2955 (s), 2930 (s), 2858 (s), 1472 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{34}NO_3SSi$ (M + H)$^+$ 348.2029, found 348.2045.

***N*-((2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-3-methylpent-4-yn-2-yl)-2-methylpropane-2-sulfonamide (11).** Sulfinyl compound **10** (1.62 g, 4.66 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C under argon. *m*-CPBA (77%; 1.36 g, 6.06 mmol) was added in one portion, and the reaction was monitored by TLC. After completion in 1 h, the reaction mixture was filtered through a pad of Celite and concentrated. The reaction was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product **11** (1.67 g, 98%) as a colorless oil: R_f 0.50 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (1H, s), 4.21 (1H, d, J = 10.5 Hz), 4.12 (1H, dd, J = 3.5, 10.5 Hz), 4.06 (1H, dd, J = 6.5, 10.5 Hz), 3.50 (1H, m), 2.52 (1H, s), 1.63 (3H, s), 1.45 (9H, s), 0.91 (9H, s), 0.15 (3H, s), 0.14 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.2, 73.4, 71.5, 65.5, 60.6, 60.3, 28.2, 25.7, 24.3, 18.1, −5.7, −5.7; IR (film): 3280 (s), 2935 (s), 1716 (w), 1457 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{33}NO_4SSiNa$ (M + Na)$^+$ 386.1797, found 386.1788; $[\alpha]_D^{25}$ = −16.9° (c 0.96, $CHCl_3$).

(2*S*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-(*tert*-butylsulfonyl)-2-ethynyl-2-methylaziridine (12). Sulfoxide **11** (740 mg, 2.09 mmol) was dissolved in CH_2Cl_2 (21 mL) under argon and was cooled to 0 °C. Triphenylphosphine (1.10 g, 4.18 mmol) and diisopropyl azodicarboxylate (829 μL, 4.18 mmol) were added sequentially to the solution. The reaction mixture was stirred overnight at room temperature by allowing the ice bath to melt. The following day, the reaction mixture was diluted with 20 mL of EtOAc and quenched with 10 mL of 1 N NaOH. The heterogeneous solution was stirred for 20 min to completely hydrolyze the diisopropyl azodicarboxylate. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2), with triethylamine-neutralized silica to afford aziridine **12** as a colorless oil (511 mg, 71%): R_f 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (1H, dd, J = 5.4, 5.4 Hz), 3.81 (1H, dd, J = 5.9, 5.9 Hz), 3.00 (1H, t, J = 5.7), 2.30 (1H, s), 1.90 (3H, s), 1.49 (9H, s), 0.91 (9H, s), 0.09 (3H, s), 0.09 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.9, 71.2, 62.6, 60.7, 51.5, 41.9, 25.8, 24.1, 20.6, 18.2, −5.3, −5.4; IR (film): 3263 (s), 2955 (s), 2932 (s), 2858 (s), 1723 (s), 1472 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{31}NO_3SSiNa$ (M + Na)$^+$ 368.1692, found 368.1684; $[\alpha]_D^{20}$ = +72.1° (c 2.57, $CHCl_3$).

Cobalt Complex 13. Aziridine **12** (874 mg, 2.53 mmol) was dissolved in dry CH_2Cl_2 under argon. Dicobalt octacarbonyl (1.00 g, 2.78 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and purified by silica gel chromatography (20% EtOAc−80% hexanes) to yield complex **13** (1.36 g, 83%) as a red solid: R_f 0.50 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, bs), 3.89 (1H, bs), 3.78 (1H, bs), 3.31 (1H, bs), 2.12 (3H, bs), 1.46 (9H, bs), 0.90 (9H, bs), 0.07 (6H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 198.8, 94.0, 71.6, 61.8, 61.1, 56.8, 50.2, 25.8, 24.2, 22.5, 18.3, −5.5; IR (film): 2956 (s), 2931 (s), 2858 (s), 2095 (s), 2029 (s), 2056 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{31}Co_2NO_9SSiNa$ (M + Na)$^+$ 654.0050, found 654.0073; mp 277−279 °C.

(*R*)-*tert*-Butyl 1-(*tert*-Butyldimethylsilyloxy)-4-oxopentan-3-ylcarbamate (24). In a 1 L round-bottomed flask, (*R*)-*tert*-butyl 3,9,9,10,10-pentamethyl-4-oxo-2,8-diaoxa-3-aza-9-silaundecan-5-ylcarbamate (**23**; 17.5 g, 46.5 mmol) was dissolved in THF (120 mL) under argon. The solution was cooled to −78 °C, and methyllithium (22.0 mL; 1.6 M in diethyl ether) was added via cannula. The solution was stirred at −78 °C under argon for 4 h. After completion, the reaction mixture was quenched at −78 °C with 150 mL of saturated NH_4Cl. The solution was warmed to room temperature, and 20 mL of water was added to dissolve the white solid. The aqueous layer was extracted with diethyl ether (5 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified using silica gel chromatography (20% EtOAc−80% hexanes) to afford (*R*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)-4-oxopentan-3-ylcarbamate (**24**) as a yellow oil (13.51 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (1H, d, J = 5.1 Hz), 4.22 (1H, dd, J = 5.5 Hz, 5.0 Hz), 3.64 (2H, t, J = 5.5 Hz), 2.16 (3H, s), 2.02−1.98 (1H, m), 1.91−1.84 (1H, m), 1.37 (9H, s), 0.82 (9H, s), −0.01 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 155.5, 79.3, 59.6, 58.6, 33.1, 28.2, 26.7, 25.7, 18.0, −5.8.[3]

***tert*-Butyl (3*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-4-methylhex-5-yn-3-ylcarbamate (25).** In a 1 L round-bottomed flask, the ketone **24** (7.26 g, 21.9 mmol) was dissolved in THF (62 mL) under argon. The solution was cooled to 0 °C, and ethynylmagnesium bromide (136 mL; 0.5 M in tetrahydrofuran) was added to the flask. The ice bath was removed, and the reaction was stirred overnight. After completion, the reaction mixture was cooled to

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0 °C and quenched with 125 mL of saturated NH_4Cl. The reaction mixture was warmed to room temperature to allow the white solid to dissolve in enough water (10 mL). The aqueous layer was extracted with diethyl ether (5 × 125 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (7% acetone−93% hexanes) to afford *tert*-butyl (3*R*)-1-(*tert*-butyldimethylsilyloxy)-4-hydroxy-4-methylhex-5-yn-3-ylcarbamate (**25**) as a yellow oil that was a 1:1 mixture of diastereomers (7.35 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (1H, d, J = 8.7 Hz), 4.97 (1H, d, J = 8.6 Hz), 4.63 (1H, m), 4.60 (1H, m), 3.73 (6H, m), 2.45 (1H, s), 2.41 (1H, s), 2.08 (2H, m), 1.95 (2H, m), 1.46 (3H, s), 1.45 (3H, s), 1.41 (18H, bs), 0.88 (9H, s), 0.87 (9H, s), 0.05 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 156.3, 86.1, 86.1, 79.6, 79.5, 73.0, 72.3, 70.6, 69.8, 60.6, 59.3, 57.5, 56.6, 33.8, 33.2, 28.3, 27.2, 26.4, 25.8, 18.1, 18.1, −5.5, −5.6.[3]

***N*-((3*R*,4*R*)-1,4-Dihydroxy-4-methylhex-5-yn-3-yl)-2-nitrobenzenesulfonamide (26).** A diastereomeric mixture of tertiary alcohols **25** (304 mg, 0.851 mmol) was dissolved in THF (4 mL), and 1.5 mL of concentrated HCl was added dropwise to the solution. The reaction mixture was stirred at room temperature for 2 h. The THF was removed, and the water was azeotropically removed with MeCN (5 × 10 mL). The crude mixture was redissolved in 4 mL of THF−H_2O (2:1), and sodium carbonate (451 mg, 4.225 mmol) was slowly added to the solution. The pH was checked to ensure that the solution was basic (pH 10), and 2-nitrobenzenesulfonyl chloride (189 mg, 0.851 mmol) was added. The reaction mixture was stirred at room temperature overnight. The next day the reaction mixture was partitioned between 10 mL of brine and 10 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The mixture of diastereomers was purified by silica gel chromatography (70% EtOAc−30% hexanes) to give the product (136 mg, 49%) as a cloudy, yellow oil. The mixture of diastereomers was separated by crystallization in chloroform, and the crystalline diastereomer *N*-(3*R*,4*R*)-1,4-dihydroxy-4-methylhex-5-yn-3-yl)-2-nitrobenzenesulfonamide (**26**) was isolated as a white solid: ^{1}H NMR (360 MHz, MeOH-d_4) δ 8.13 (1H, dd, J = 8.7 Hz, 6.1 Hz), 7.88 (1H, m), 7.78 (2H, dd, J = 3.2 Hz, 5.9 Hz), 3.61 (2H, m), 3.52 (1H, m), 2.81 (1H, s), 2.11 (1H, qd, J = 3.0 Hz, 7.4 Hz), 1.80 (1H, m); ^{13}C NMR (90 MHz, MeOH-d_4) δ 149.3, 136.7, 134.8, 133.9, 131.8, 126.1, 86.9, 74.7, 70.8, 61.6, 59.8, 35.4, 28.3.[3]

***N*-(3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-4-methylhex-5-yn-3-yl)-2-nitrobenzenesulfonamide (27).** The tertiary alcohol **26** (119 mg, 0.362 mmol) was suspended in CH_2Cl_2 (4 mL), under argon, and was cooled to 0 °C. Triethylamine (252 μL, 1.810 mmol), *tert*-butyldimethylsilyl chloride (82 mg, 0.543 mmol), and 4-dimethylaminopyridne (4 mg, 0.0362 mmol) were added to the reaction mixture sequentially. The reaction mixture was stirred overnight at room temperature by allowing the ice bath to melt. The following day, the reaction was partitioned between 5 mL of H_2O and 5 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 10 mL of brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by silica gel chromatography (60% EtOAc−40% hexanes) to afford the product **27** as a thick oil (136 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, m), 7.86 (1H, m), 7.73 (2H, m), 5.82 (1H, d, J = 8.6 Hz), 4.52 (1H, s), 3.82 (1H, m), 3.74 (1H, m), 3.62 (1H, m), 2.51 (1H, s), 2.23 (1H, qd, J = 4.3 Hz, 8.7 Hz), 1.93 (1H, m), 1.32 (3H, s), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 134.7, 133.4, 132.8, 130.2, 125.1, 85.2, 74.0, 68.9, 60.4, 58.3, 34.5, 27.1, 25.7, 18.1, −5.5.[3]

(2*R*,3*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-ethynyl-2-methyl-1-(2-nitrophenylsulfonyl)aziridine (18). The viscous oil **27** (879 mg, 2.03 mmol) was dissolved in CH_2Cl_2 (21 mL) under argon and was cooled to 0 °C. Triphenylphosphine (798 mg, 3.04 mmol) and diisopropyl azodicarboxylate (603 μL, 3.04 mmol) were added sequentially to the solution. The reaction mixture was stirred overnight at room temperature by allowing the ice bath to melt. The following day, the reaction mixture was diluted with 30 mL of EtOAc and quenched with 15 mL of 1 N NaOH. The heterogeneous solution was stirred for 20 min to completely hydrolyze the diisopropyl azodicarboxylate. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (15% EtOAc−85% hexanes), with triethylamine-neutralized silica to afford the aziridine as a white solid (620 mg, 72%). The structure was determined by X-ray analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (1H, m), 7.74 (3H, m), 3.67 (2H, m), 3.45 (1H, dd, J = 5.2 Hz, 7.9 Hz), 2.55 (1H, s), 1.98−1.90 (1H, m), 1.70−1.64 (1H, m), 1.58 (3H, s), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 134.1, 133.5, 132.1, 131.0, 124.3, 80.7, 74.2, 60.3, 53.1, 42.9, 30.4, 25.9, 20.2, 18.3, −5.4.[3]

***tert*-Butyl ((2*R*)-3-Hydroxy-3-methylpent-4-yn-2-yl)-carbamate (31).** Ketone **30** (2.89 g, 15.4 mmol) was dissolved in dry THF (74 mL) under argon and cooled to 0 °C. Ethynylmagnesium bromide (80 mL, 0.5 M in THF) was added to the solution and was slowly warmed to room temperature and stirred overnight. Once the reaction was complete, the mixture was cooled to 0 °C and quenched with saturated NH_4Cl (50 mL). The mixture was warmed to room temperature, and 15 mL of H_2O was added to dissolve the white solid. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (25% acetone−75% hexanes) to give the product **31** as a colorless oil in a 1:1 mix of diastereomers (3.10 g, 95%): R_f 0.43 (25% acetone−75% hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.81 (2H, m), 3.71 (2H, m), 3.55 (2H, s), 2.44 (1H, s), 2.42 (1H, s), 1.44 (3H, s), 1.46 (3H, s), 1.40 (9H, s), 1.39 (9H, s), 1.27 (3H, d, J = 4.0 Hz), 1.25 (3H, d, J = 4.9 Hz), 1.21 (3H, d, J = 5.1 Hz), 1.20 (3H, d, J = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 156.2, 85.9, 85.1, 79.4, 79.8, 72.8, 72.5, 71.2, 54.9, 54.1, 28.3, 28.3, 27.1, 25.8, 17.6, 17.1, 16.1; IR (film): 3407 (s), 3310 (s), 2981 (s), 2936 (s), 1692 (s), 1509 (s) cm^{-1}; HRMS (CI) m/z calcd for $C_{11}H_{20}NO_3$ $(M + H)^+$ 214.1443, found 214.1446.

***tert*-Butyl (*R*)-(3-Hydroxy-3-methylbutan-2-yl)carbamate (32).** Methyl (*tert*-butoxycarbonyl)-D-alaninate (**28**; 3.16 g, 15.6 mmol) was dissolved in dry THF (52 mL) under argon and cooled to −78 °C. Methyllithium (34 mL, 1.6 M in Et_2O) was added to the solution, and the reaction mixture was stirred and monitored by TLC. After 2 h, the reaction was complete and the mixture quenched with saturated NH_4Cl (100 mL). The partition was warmed to room temperature, and enough H_2O (10 mL) was added to dissolve the white solids. The two layers were separated, and the aqueous layer was extracted with Et_2O (150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography to give the tertiary alcohol **32** (2.48 g, 78%): R_f 0.42 (40% EtOAc−60% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (1H, d, J = 8.5 Hz), 3.55 (1H, m), 2.76 (1H, m), 1.40 (9H, s), 1.18 (3H, s), (3H, s), 1.09 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 79.2, 72.8, 54.4, 28.3, 27.9, 25.5, 16.0; IR (film): 3440 (s), 2979 (s), 2934 (s), 1690 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{21}NO_3Na$ $(M + Na)^+$ 226.1419, found 226.1421; $[\alpha]_D^{25}$ = +1.8° (c 4.21, $CHCl_3$).

***tert*-Butyl (*R*)-(2-Hydroxy-2-methyl-1-phenylpropyl)-carbamate (33).** The ester **29** (12.9 g, 48.5 mmol) was dissolved in dry THF (145 mL) under argon and cooled to −78 °C. Methyllithium (97 mL; 2.0 M in Et_2O) was added via cannulation. The reaction mixture was slowly warmed to 0 °C and monitored by TLC. After completion, the reaction mixture was cooled to −78 °C and quenched with saturated NH_4Cl (200 mL). The mixture was slowly warmed to room temperature, and enough H_2O was added to dissolve the white solid. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (10% → 20% → 30% EtOAc−hexanes) to give product **33** as a white solid (11.4 g, 89%): R_f 0.32 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (5H, m), 5.55 (1H, d, J = 8.5 Hz), 4.52 (1H, bs),

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

1.73 (1H, bs), 1.41 (9H, bs), 1.34 (3H, bs), 1.06 (3H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 139.7, 128.2, 127.9, 127.5, 79.5, 72.8, 62.8, 28.3, 27.6, 27.5; IR (film): 3440 (s), 2978 (s), 1695 (s), 1496 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{23}NO_3Na$ $(M + Na)^+$ 288.1576, found 288.1588; $[\alpha]_D^{20}$ = −21.2° (c 0.59, $CHCl_3$); mp 113−115 °C.

***N*-((2*R*)-3-Hydroxy-3-methylpent-4-yn-2-yl)-2-nitrobenzenesulfonamide (34).** Carbamate **31** (3.43 g, 16.1 mmol) was dissolved in THF (64 mL), and concentrated HCl (17 mL) was added to the solution. The reaction was monitored by TLC. After 1 h, the reaction mixture was concentrated and azeotroped with MeCN to remove the water. The crude amine was dissolved in THF/H_2O (44 mL/22 mL), and Na_2CO_3 (8.52 g, 80.4 mmol) and 2-nitrobenzenesulfonyl chloride (3.56 g, 16.1 mmol) were added sequentially to the reaction mixture. The reaction was monitored by TLC and stirred overnight. After completion the reaction mixture was diluted with EtOAc (100 mL) and partitioned with brine (30 mL). The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (40% EtOAc−60% hexanes) to give the product as a pale yellow oil as a 1:1 mix of diastereomers (4.41 g, 95%): R_f 0.68 (60% EtOAc−40% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18−8.16 (2H, m), 7.90−7.88 (2H, m), 7.78−7.73 (4H, m), 5.60 (1H, d, J = 9.5 Hz), 5.55 (1H, d, J = 9.0 Hz), 3.64−3.58 (1H, m), 3.57−3.52 (1H, m), 2.73 (1H, s), 2.54 (1H, s), 2.40 (1H, s), 2.35 (1H, s), 1.52 (3H, s), 1.48 (3H, s), 1.21−1.18 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 134.8, 134.6, 133.7, 133.5, 133.0, 132.9, 130.7, 130.6, 125.4, 125.3, 84.4, 83.7, 74.1, 73.6, 70.4, 70.3, 59.3, 58.3, 26.6, 17.4, 16.6; IR (film): 3514 (s), 3363 (s), 3293 (s), 3097 (s), 2987 (s), 1535 (s), 1415 (s) cm^{-1}; HRMS (CI) m/z calcd for $C_{12}H_{13}N_2O_4S$ $(M - OH)^+$ 281.0596, found 281.0591.

***(R)*-*N*-(3-Hydroxy-3-methylbutan-2-yl)-2-nitrobenzenesulfonamide (35).** Carbamate **32** (1.49 g, 7.33 mmol) was dissolved in THF (29 mL), and concentrated HCl (8 mL) was added to the solution. The reaction was monitored by TLC. After 1 h, the reaction mixture was concentrated and azeotroped with MeCN to remove the water. The crude amine was dissolved in THF/H_2O (20 mL/10 mL), and Na_2CO_3 (3.88 g, 36.7 mmol) and 2-nitrobenzenesulfonyl chloride (1.62 g, 7.33 mmol) were added sequentially to the reaction mixture. The reaction mixture was monitored by TLC and stirred overnight. After completion the reaction was diluted with EtOAc (50 mL) and partitioned with brine (250 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (60% EtOAc−40% hexanes) to the product as a pale yellow oil (1.75 g, 83%): R_f 0.20 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, m), 7.86 (1H, m), 7.75 (2H, m), 5.49 (1H, d, J = 8.5 Hz), 3.39 (1H, m), (1H, bs), 1.12 (3H, s), (3H, s), 1.05 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 134.6, 133.5, 132.9, 130.7, 125.3, 72.3, 59.1, 27.1, 25.4, 16.4; IR (film): 3537 (s), 3368 (s), 2982 (s), 2937 (s), 1542 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O_5SNa$ $(M + Na)^+$ 311.0678, found 311.0677; $[\alpha]_D^{21}$ = −140.9° (c 1.24, $CHCl_3$).

***(R)*-*N*-(2-Hydroxy-2-methyl-1-phenylpropyl)-2-nitrobenzenesulfonamide (36).** Carbamate **33** (11.4 g, 43.0 mmol) was dissolved in THF (215 mL), and concentrated HCl (54 mL) was added to the solution. The reaction was monitored by TLC. After 1 h, the reaction mixture was concentrated and azeotroped with MeCN to remove the water. The crude amine was dissolved in THF/H_2O (144 mL/72 mL), and Na_2CO_3 (22.8 g, 215 mmol) and 2-nitrobenzenesulfonyl chloride (9.52 g, 43.0 mmol) were added sequentially to the reaction mixture. The reaction mixture was monitored by TLC and stirred overnight. After completion the reaction mixture was diluted with EtOAc (300 mL) and partitioned with brine (100 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as a pale purple solid (13.6 g, 90%): R_f 0.42 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.63 (1H, m), 7.48−7.43 (2H, m), 7.27−7.24 (1H, m), 7.10−7.09 (2H, m), 7.01−6.98 (3H, m), 6.48 (1H, d, J = 9.5 Hz), 4.34 (1H, d, J = 9.5 Hz), 1.82 (1H, bs), 1.46 (3H, s), 1.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 136.7, 134.3, 132.6, 132.2, 130.4, 128.1, 127.9, 127.7, 124.5, 72.7, 66.8, 27.7, 27.4; IR (film): 3533 (s), 3358 (s), 3097 (s), 3030 (s), 2979 (s), 1540 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{18}N_2O_5SNa$ $(M + Na)^+$ 373.0834, found 373.0837; $[\alpha]_D^{22}$ = −267.8° (c 1.56, $CHCl_3$); mp 114−116 °C.

***(2S,3R)*-2-Ethynyl-2,3-dimethyl-1-((2-nitrophenyl)sulfonyl)-aziridine (19).** The tertiary alcohol **34** was dissolved in dry THF (27 mL) and cooled to 0 °C. Triphenylphosphine (1.54 g, 6.07 mmol) and diisopropyl azodicarboxylate (1.19 mL, 6.07 mmol) were added sequentially to the solution, and the reaction mixture was warmed to room temperature. The reaction mixture was monitored by TLC and stirred overnight. Upon completion, the reaction mixture was diluted with EtOAc (30 mL), cooled to 0 °C, and quenched with 1 N NaOH (20 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine and separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (100% CH_2Cl_2) to give the diastereomeric aziridines **19** and **37** (726 mg, 64%): R_f 0.88 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (1H, m), 7.75 (3H, m), 3.46 (1H, q, J = 6.0 Hz), 2.56 (1H, s), 1.57 (3H, s), 1.34 (3H, d, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 134.3, 134.1, 132.6, 130.8, 124.3, 80.4, 72.4, 50.6, 47.1, 21.3, 14.4; IR (film): 3285 (s), 3098 (s), 2984 (w), 2934 (w), 1545 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{13}N_2O_4S$ $(M + H)^+$ 281.0605, found 281.0596; $[\alpha]_D^{21}$ = +287.2° (c 0.80, $CHCl_3$); mp 94−96 °C.

***(2R,3R)*-2-Ethynyl-2,3-dimethyl-1-((2-nitrophenyl)sulfonyl)-aziridine (37):** R_f 0.82 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (1H, bs), 7.76 (3H, bs), 3.46 (1H, q, J = 5.5 Hz), 2.56 (1H, s), 1.57 (3H, s), 1.34 (3H, d, J = 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 134.1, 133.8, 132.3, 131.1, 124.3, 80.7, 74.1, 51.1, 42.5, 19.6, 12.4; IR (film): 3266 (s), 3101 (w), 2939 (w), 1699 (w), 1542 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}N_2O_4SNa$ $(M + Na)^+$ 303.0413, found 303.0415; $[\alpha]_D^{23}$ +214.9° (c 1.04, $CHCl_3$); mp 158−159 °C.

***(R)*-2,2,3-Trimethyl-1-((2-nitrophenyl)sulfonyl)aziridine (20).** Sulfonamide **35** (1.70 g, 5.88 mmol) was dissolved in THF (59 mL) under argon and was cooled to 0 °C. Triphenylphosphine (2.31 mg, 8.82 mmol) and diisopropyl azodicarboxylate (1.73 mL, 8.82 mmol) were added sequentially to the solution. The reaction mixture was stirred overnight, at 50 °C. The following day, the reaction mixture was diluted with 100 mL of EtOAc and quenched with 50 mL of 1 N NaOH. The heterogeneous solution was stirred for 20 min to completely hydrolyze the diisopropyl azodicarboxylate. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2), to afford the aziridine as a white solid (1.09 g, 69%): R_f 0.59 (40% EtOAc−60% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (1H, m), 7.71 (3H, m), 3.12 (1H, q, J = 6.0 Hz), 1.74 (3H, s), 1.34 (3H, m), 1.28 (3H, d, J = 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 135.0, 133.5, 132.2, 130.3, 124.1, 54.4, 50.7, 22.6, 20.4, 12.9; IR (film): 3283 (s), 2922 (s), 1542 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{14}N_2O_4SNa$ $(M + Na)^+$ 293.0574, found 293.0572; $[\alpha]_D^{22}$ = +295.5° (c 1.18, $CHCl_3$); mp 77−79 °C.

***(R)*-2,2-Dimethyl-1-((2-nitrophenyl)sulfonyl)-3-phenylaziridine (22).** Sulfonamide **36** (12.9 g, 36.9 mmol) was dissolved in THF (246 mL) under argon and was cooled to 0 °C. Triphenylphosphine (14.5 g, 55.4 mmol) and diisopropyl azodicarboxylate (10.9 mL, 55.4 mmol) were added sequentially to the solution. The reaction mixture was stirred for 3 h, and the reaction was complete as monitored by TLC. The reaction mixture was diluted with 200 mL of EtOAc and quenched with 100 mL of 1 N NaOH. The heterogeneous solution was stirred for 20 min to completely hydrolyze the diisopropyl azodicarboxylate. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

were washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2), to afford the aziridine as a white solid (10.1 g, 82%): R_f 0.37 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25−8.24 (1H, m), 7.75−7.73 (3H, m), 7.28−7.24 (3H, m), 7.14−7.13 (2H, m), 4.23 (1H, s), 1.93 (3H, s), 1.15 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 134.4, 133.9, 133.8, 132.1, 130.4, 128.2, 127.7, 126.9, 124.3, 56.3, 55.7, 22.5, 20.3; IR (film): 3093 (w), 2997 (w), 2932 (w), 1592 (w), 1544 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{16}N_2O_4SNa$ $(M + Na)^+$ 355.0728, found 355.0737; $[\alpha]_D^{22}$ = +100.4° (c 1.57, $CHCl_3$); mp 94−96 °C.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-((*R*)-2-((trimethylsilyl)oxy)but-3-yn-2-yl)oxazolidine-3-carboxylate (39).** To a solution of compound **38** (1.04 g, 3.86 mmol) in CH_2Cl_2 (39 mL) at 0 °C were added triethylamine (1.42 mL, 19.3 mmol), trimethylsilyl chloride (588 μL, 4.63 mmol), and 4-dimethylaminopyridine (47.0 mg, 0.386 mmol) sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed to room temperature overnight. The reaction mixture was partitioned between 75 mL of EtOAc and 75 mL of H_2O. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine (50 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (30% EtOAc−70% hexanes) to afford **39** as a white amorphous solid (1.27 g, 95%): R_f 0.51 (10% EtOAc−90% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 54.21 (1H, bs), 4.03−3.93 (2H, m, rotamers), 2.44 (1H, s), 1.67 (3H, bs), 1.49 (15H, s), 0.20 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 80.3, 73.5, 72.3, 65.5, 65.1, 28.3, 1.9; IR (film): 2976 (s), 1702 (s), 1358 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{31}NO_4SiNa$ $(M + Na)^+$ 364.1920, found 364.1914; $[\alpha]_D^{21}$ = +63.2,° (c 1.87, $CHCl_3$).

***tert*-Butyl (*R*)-2,2-Dimethyl-4-((*R*)-2-((trimethylsilyl)oxy)pent-3-yn-2-yl)oxazolidine-3-carboxylate (40).** Compound **39** (1.27 g, 3.72 mmol) was dissolved in dry THF (37 mL), under argon, and was cooled to −78 °C. *n*-Butyllithium (1.60 mL, 4.09 mmol) was added dropwise, and the solution was stirred at −78 °C for 15 min. After this, methyl iodide (277 μL, 4.46 mmol) was added and the reaction mixture was stirred for 1 h and monitored by TLC. When the reaction was complete, saturated NH_4Cl (50 mL) was added to quench the reaction. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by silica gel chromatography (50% EtOAc−50% hexanes) to give the product **39** (708 mg, 54%) as a colorless oil: R_f 0.51 (10% EtOAc−90% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (1H, bs), 4.03−3.93 (2H, m, rotamers), 2.44 (1H, s), 1.67 (3H, bs), 1.49 (15H, s), 0.20 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 80.3, 73.5, 72.3, 65.5, 65.1, 28.3, 1.9; IR (film): 2976 (s), 1702 (s), 1358 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{31}NO_4SiNa$ $(M + Na)^+$ 364.1920, found 364.1914; $[\alpha]_D^{21}$ +63.2° (c 1.87, $CHCl_3$).

***N*-((2*R*,3*R*)-1,3-Dihydroxy-3-methylhex-4-yn-2-yl)-2-nitrobenzenesulfonamide (41).** Carbamate **40** (708 mg, 1.99 mmol) was dissolved in THF (8 mL), and concentrated HCl (2 mL) was added to the solution. The reaction was monitored by TLC. After 1 h, the reaction mixture was concentrated and azeotroped with MeCN to remove the water. The crude amine was dissolved in THF/H_2O (6 mL/3 mL), and Na_2CO_3 (1.06 g, 9.96 mmol) and 2-nitrobenzenesulfonyl chloride (441 mg, 1.99 mmol) were added sequentially to the reaction mixture. The reaction mixture was monitored by TLC and stirred overnight. After completion the reaction was diluted with EtOAc (20 mL) and partitioned with brine (10 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as a white foam (510 mg, 78%): R_f 0.08 (30% acetone−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16−8.15 (1H, dd, J = 2.0 Hz), 7.89−7.88 (1H, dd, 1.5 Hz), 7.78−7.71 (2H, m), 3.88−3.84 (1H, m), 3.82−3.79 (1H, dd, J = 4.5, 12.0 Hz), 3.54−3.52 (1H, m), 1.72 (3H, s), 1.43 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 134.6, 133.5, 130.5, 125.3, 82.5, 79.5, 70.6, 63.2, 62.0, 28.2, 3.5; IR (film): 3361 (s), 2924 (w), 1541 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{16}N_2O_6SNa$ $(M + Na)^+$ 351.0627, found 351.0634; $[\alpha]_D^{21}$ = +10.1° (c 1.17, $CHCl_3$).

***N*-((2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-3-methylhex-4-yn-2-yl)-2-nitrobenzenesulfonamide (42).** To a solution of compound **41** (510 mg, 1.55 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added triethylamine (1.10 mL, 7.76 mmol), *tert*-butyldimethylsilyl chloride (304 mg, 2.02 mmol), and 4-dimethylaminopyridine (19.0 mg, 0.155 mmol) sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed to room temperature overnight. The reaction mixture was partitioned between 50 mL of EtOAc and 30 mL of H_2O. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine (30 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (30% EtOAc−70% hexanes) to afford **42** as a pale yellow oil (691 mg, quantitative); R_f 0.40 (30% acetone−70% hexanes): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.11 (1H, m), 7.87−7.85 (1H, m), 7.76−7.70 (2H, m), 5.73 (1H, d, J = 9.0 Hz), 4.22 (1H, s), 3.91−3.85 (2H, m), 3.54−3.50 (1H, m), 1.72 (3H, s), 1.31 (3H, m), 0.84 (9H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 134.7, 133.5, 132.9, 130.3, 125.2, 81.8, 79.5, 77.2, 70.8, 64.8, 60.8, 27.8, 25.6, 17.9, 3.3, −5.9; IR (film): 3374 (s), 2928 (s), 2857 (s), 1541 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{29}N_2O_6SSi$ $(M - H)^-$ 441.1516, found 441.1517; $[\alpha]_D^{21}$ = +51.5° (c 0.91, $CHCl_3$).

(2*S*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyl-1-((2-nitrophenyl)sulfonyl)-2-(prop-1-yn-1-yl)aziridine (21). The tertiary alcohol **42** was dissolved in dry THF (16 mL) and cooled to 0 °C. Triphenylphosphine (615 mg, 2.34 mmol) and diisopropyl azodicarboxylate (464 μL, 2.34 mmol) were added sequentially to the solution, and the reaction mixture was warmed to room temperature. The reaction mixture was monitored by TLC and stirred overnight. Upon completion, the reaction was diluted with EtOAc (30 mL), cooled to 0 °C, and quenched with 1 N NaOH (20 mL). The two layers separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel chromatography (100% CH_2Cl_2) to give aziridine **21** (464 mg, 71%): R_f 0.50 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.25 (1H, m), 7.77−7.72 (3H, m), 4.03 (1H, dd, J = 4.5, 10.8 Hz), 3.66 (1H, dd, J = 7.5, 10.5 Hz), 3.30 (1H, dd, J = 4.0, 7.5 Hz), 1.98 (3H, s), 1.86 (3H, s), 0.87 (9H, s), 0.05−0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 134.5, 133.9, 132.4, 130.9, 124.4, 81.1, 75.9, 61.9, 54.1, 47.9, 25.8, 22.2, 18.2, 3.8, −5.3, −5.4; IR (film): 3374 (s), 2928 (s), 2857 (s), 1541 (s) cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{29}N_2O_5SSi$ $(M + H)^+$ 425.1566, found 425.1564; $[\alpha]_D^{21}$ = +145.8° (c 0.91, $CHCl_3$); mp 65−67 °C.

***N*-((3*R*,4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-4-phenoxyhex-5-yn-3-yl)-2-nitrobenzenesulfonamide (43).** Aziridine **18** (31.4 mg, 0.0740 mmol) and phenol (14.0 mg, 0.148 mmol) were placed in a flask and dissolved in dry $PhCH_3$ (736 μL). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD; 21.0 mg, 0.148 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as an amorphous solid (32.3 mg, 84%): R_f 0.45 (30% acetone−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14−8.12 (1H, m), 7.86−7.84 (1H, m), 7.64−7.59 (2H, m), 7.24−7.21 (2H, m), 7.08−7.05 (1H, m), 7.00−6.98 (2H, m), 5.71 (1H, d, J = 9.5 Hz), 4.12−4.08 (1H, m), 3.73−3.70 (1H, m), 3.60−3.55 (1H, m), 2.45 (1H, s), 2.35−2.29 (1H, m), 1.78−1.71 (1H, m), 1.53 (3H, s), 0.91 (9H, m), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 147.5, 135.7, 132.8, 132.7, 130.7, 128.9, 125.0, 123.7, 122.1, 82.5, 78.3, 59.9, 59.5, 34.5, 25.9, 23.4, 18.3, −5.2, −5.3; IR (film): 3356 (w), 3284 (w), 2954 (s), 2927 (s), 1592 (s), 1540 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{34}N_2O_6SSiNa$ $(M + Na)^+$ 541.1805, found 541.1793; $[\alpha]_D^{23}$ = +20.7° (c 1.48, $CHCl_3$).

***N*-((2*R*,3*R*)-3-Methyl-3-phenoxypent-4-yn-2-yl)-2-nitrobenzenesulfonamide (44).** Aziridine **19** (30.8 mg, 0.110 mmol) and

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

phenol (21.0 mg, 0.220 mmol) were placed in a flask and dissolved in dry $PhCH_3$ (1.10 mL). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD; 31.0 mg, 0.220 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as a colorless oil (27.9 mg, 68%): R_f 0.30 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−8.17 (1H, m), 7.89−7.87 (1H, m), 7.73−7.68 (2H, m), 7.25−7.24 (2H, m), 7.09−7.07 (3H, m), 5.77 (1H, d, J = 9.0 Hz), 3.92−3.86 (1H, m), 2.45 (1H, s), 1.56 (3H, s), 1.36 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 147.8, 135.2. 133.3, 132.9, 130.6, 128.9, 125.3, 123.7, 121.8, 82.2, 77.9, 58.7, 23.4, 16.9; IR (film): 3288 (s), 2921 (s), 1590 (s), 1541 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2O_5SNa$ $(M + Na)^+$ 397.0833, found 397.0834; $[\alpha]_D^{22}$ = −40.3° (c 1.31, $CHCl_3$).

With Potassium Hydride. Potassium hydride (suspension in mineral oil; 13.0 mg, 0.334 mmol) was placed in a vial and was washed several times with hexanes (5 × 1 mL). After several washes, the potassium hydride was placed under reduced pressure to remove the residual hexanes and then suspended in dry THF (200 μL). Phenol (31.0 mg, 0.334 mmol) dissolved in dry THF (250 μL) was added dropwise to the suspension, and the solution was stirred until effervescence stopped. Aziridine **19** (23.0 mg, 0.0835 mmol) and 18-crown-6 (88.0 mg, 0.334 mmol) were dissolved in THF (450 μL) and added to the solution. The reaction was monitored by TLC. After completion the reaction was quenched with 1 M HCl (2 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product (25.0 mg, 80%) as an amorphous solid. The product ratio was determined by ^{1}H NMR.

(*R*)-*N*-(3-Methyl-3-phenoxybutan-2-yl)-2-nitrobenzenesulfonamide (45). Aziridine **20** (41.2 mg, 0.152 mmol) and phenol (28.7 mg, 0.305 mmol) were placed in a flask and dissolved in dry $PhCH_3$ (1.5 mL). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD; 42.4 mg, 0.305 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as a white solid (46.7 mg, 84%): R_f 0.38 (30% EtOAc−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, dd, 1.7, 7.3 Hz), 7.83 (1H, dd, 1.7, 6.3 Hz), 7.66 (2H, m), 7.23 (1H, t, J = 7.5 Hz), 6.86 (2H, d, J = 8.0 Hz), 5.83 (1H, d, J = 5.5 Hz), 3.65 (1H, m), 1.28 (3H, d, J = 7.0 Hz), 1.25 (3H, s), 1.19 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 147.7, 135.3, 133.1, 132.7, 130.4, 129.0, 125.2, 123.9, 81.4, 59.3, 24.0, 23.1, 16.8; IR (film): 3383 (s), 3096 (s), 3071 (s), 3036 (w), 2964 (s), 1593 (s), 1541(s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{20}N_2O_5SNa$ $(M + Na)^+$ 387.0991, found 387.1006; $[\alpha]_D^{21}$ = −14.4° (c 1.31, $CHCl_3$); mp 96−98 °C.

With Potassium Hydride. Potassium hydride (suspension in mineral oil; 35.8 mg, 0.893 mmol) was placed in a vial and was washed several times with hexanes (5 × 1 mL). After several washes, the potassium hydride was placed under reduced pressure to remove the residual hexanes and then suspended in dry THF (500 μL). Phenol (84.0 mg, 0.893 mmol) dissolved in dry THF (500 μL) was added dropwise to the suspension, and the solution was stirred until effervescence stopped. Aziridine **20** (60.3 mg, 0.223 mmol) and 18-crown-6 (236 mg, 0.893 mmol) were dissolved in THF (1.2 mL) and added to the solution. The reaction was monitored by TLC. After completion the reaction mixture was quenched with 1 M HCl (2 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the products (64.2 mg, 79%) as a white solid. The product ratio was determined by ^{1}H NMR.

***N*-((2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-3-phenoxyhex-4-yn-2-yl)-2-nitrobenzenesulfonamide (46).** Aziridine **21** (46.7 mg, 0.110 mmol) and phenol (21.0 mg, 0.220 mmol) were placed in a flask and dissolved in dry $PhCH_3$ (1.1 mL). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD; 31.0 mg, 0.148 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated and purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the product as an amorphous solid (44.5 mg, 78%): R_f 0.38 (30% EtOAc−70% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14−8.12 (1H, m), 7.90−7.88 (1H, m), 7.66−7.60 (2H, m), 7.24−7.21 (2H, m), 7.06−7.03 (1H, m), 6.97−6.96 (2H, m), 6.07 (1H, d, J = 8.5 Hz), 4.06−4.02 (1H, m), 3.95−3.91 (2H, m), 1.77 (3H, s), 1.55 (3H, s), 0.84 (9H, s), −0.02 (3H, s), −0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 147.6, 136.9, 130.5, 128.7, 125.1, 123.3, 122.2, 85.8, 78.1, 77.4, 63.5, 62.5, 25.8, 24.3, 18.3, 3.6, −5.6; IR (film): 3385 (w), 2928 (s), 2856 (s), 1592 (s), 2964 (s), 1593 (s), 1542 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{35}N_2O_6SSiNa$ $(M + Na)^+$ 541.1805, found 541.1807; $[\alpha]_D^{21}$ = −38.7° (c 0.925, $CHCl_3$).

4-Methyl-*N*-(2-methyl-2-phenoxypropyl)benzenesulfonamide (49) and 4-Methyl-*N*-(2-methyl-1-phenoxypropan-2-yl)benzenesulfonamide (50). Aziridine **48** (67.0 mg, 0.297 mmol) and phenol (56.0 mg, 0.595 mmol) were placed in a flask and dissolved in dry $PhCH_3$ (3.0 mL). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD; 83.0 mg, 0.595 mmol) was added in one portion, and the reaction was monitored by TLC. After completion, the reaction was concentrated and purified by silica gel chromatography (20% EtOAc−80% hexanes) to give the product as an amorphous solid (58.3 mg, 64%): R_f 0.50 (30% EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−7.75 (4H, m), 7.35−7.33 (2H, m), 7.27−7.22 (4H, m), 7.19−7.17 (2H, m), 7.11−7.09 (1H, m), 6.98−6.95 (1H, m), 6.86−6.85 (2H, m), 6.78−6.77 (2H, m), 5.11 (1H, m), 5.05 (1H, t, J = 5.5 Hz), 3.65 (2H, s), 3.07 (2H, s), 2.45 (3H, s), 2.35 (3H, s), 1.34 (6H, m), 1.26 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 153.9, 143.4, 142.9, 139.9, 136.9, 129.7, 129.4, 129.1, 127.1, 126.9, 124.1, 123.8, 121.2, 114.4, 79.2, 74.3, 56.2, 52.8, 29.7, 24.8, 24.2, 21.5; IR (film): 3281 (s), 3062 (w), 3039 (w), 2979 (s), 2923 (s), 1597 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_3SNa$ $(M + Na)^+$ 342.1140, found 342.1140.

With Potassium Hydride. Potassium hydride (suspension in mineral oil; 26.6 mg, 0.663 mmol) was placed in a vial and was washed several times with hexanes (5 × 1 mL). After several washes, the potassium hydride was placed under reduced pressure to remove the residual hexanes and then suspended in dry THF (400 μL). Phenol (62.4 mg, 0.663 mmol) dissolved in dry THF (450 μL) was added dropwise to the suspension, and the solution was stirred until effervescence stopped. Aziridine **48** (37.3 mg, 0.166 mmol) and 18-crown-6 (175 mg, 0.663 mmol) were dissolved in THF (850 μL) and added to the solution. The reaction was monitored by TLC. After completion the reaction mixture was quenched with 1 M HCl (2 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by silica gel chromatography (30% EtOAc−70% hexanes) to give the products (39.8 mg, 75%) as an amorphous solid. The product ratio was determined by ^{1}H NMR.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving X-ray crystallographic data for **13**, **17**−**22**, **45**, and **48**, ^{1}H and ^{13}C NMR spectra, and computational details. 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.

dx.doi.org/10.1021/jo5006685 | J. Org. Chem. 2014, 79, 5121−5133

■ ACKNOWLEDGMENTS

We thank Drs. George Furst and Rakesh Kohli for assistance in obtaining high-resolution NMR and mass spectral data, respectively. We thank Drs. David Chenoweth and William Dailey for useful suggestions and discussions with regard to the aforementioned research. Financial support for this research was provided by the NSF (CHE-0951394).

■ REFERENCES

(1) Formaggio, F.; Baldini, C.; Moretto, V.; Crisma, M.; Kapstein, B.; Broxterman, Q. B.; Toniolo, C. *Chem. Eur. J.* **2005**, *11*, 2395.
(2) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullie, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463.
(3) Kelley, B.; Joullié, M. M. *Org. Lett.* **2010**, *12*, 4244.
(4) Li, P.; Evans, C. D.; Joullié, M. M. *Org. Lett.* **2005**, *7*, 5325.
(5) Li, P.; Evans, C. D.; Forbeck, E. M.; Park, H.; Bai, R.; Hamel, E.; Joullié, M. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4804.
(6) Li, P.; Evans, C. D.; Wu, Y.; Cao, B.; Hamel, E.; Joullié, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 2351.
(7) Grimley, J. S.; Sawayama, A. M.; Tanaka, H.; Stohlmeyer, M. M.; Woiwode, T. F.; Wandless, T. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8157.
(8) Joullié, M. M.; Berritt, S.; Hamel, E. *Tetrahedron Lett.* **2011**, *52*, 2136.
(9) Kelley, B. T.; Joullié, M. M. *Tetrahedron: Asymmetry* **2013**, *24*, 1233.
(10) Cox, J. D. *Tetrahedron* **1963**, *19*, 1175.
(11) Dahanukar, V. H.; Zavialov, L. A. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918.
(12) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999.
(13) Lowden, P. A. S. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.
(14) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *2000*, 1347.
(15) Padwa, A.; Murphree, S. S. *ARKIVOC* **2006**, *3*, 6.
(16) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
(17) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.
(18) Zwanenburg, B.; Holte, P. t. *Top. Curr. Chem.* **2001**, *216*, 94.
(19) Sureshkumar, D.; Ganesh, V.; Vidyarini, R. S.; Chandrasekaran, S. *J. Org. Chem.* **2009**, *74*, 7958.
(20) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, *6*, 3123.
(21) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397.
(22) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, *6*, 4363.
(23) Jiang, Z.; Wang, J.; Lu, P.; Wang, Y. *Tetrahedron* **2011**, *67*, 9609.
(24) Bottaro, J. C. *J. Chem. Soc., Chem. Commun.* **1980**, 560.
(25) Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, 2011.
(26) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley: Hoboken, NJ, 2009
(27) Chawla, R.; Singh, A. K.; Yadav, L. D. S. *RSC Adv.* **2013**, *3*, 11385.
(28) Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539.
(29) Chemla, F.; Hebbe, V.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 8093.
(30) Jenkins, D. M. *Synlett* **2012**, *23*, 1267.
(31) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.
(32) Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 1571.
(33) Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797.
(34) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15146.
(35) Ohno, H.; Toda, A.; Takemoto, Y.; Fuji, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. I* **1999**, 2949.
(36) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.
(37) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509.
(38) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911.
(39) Tanner, D. *Pure Appl. Chem.* **1993**, *65*, 1319.
(40) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599.
(41) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892.
(42) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730.
(43) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.
(44) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, *343*, 61.
(45) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604.
(46) Sakakibara, K.; Nozaki, K. *Org. Biomol. Chem.* **2009**, *7*, 502.
(47) Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900.
(48) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.
(49) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *12*, 3475.
(50) Li, P. Ph.D. Thesis, University of Pennsylvania, 2005.
(51) Koubeissi, A.; Raad, I.; Ettouati, L.; Guilet, D.; Dumontet, C.; Paris, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5700.
(52) Natelson, S.; Natelson, E. A. *Microchem. J.* **1989**, *40*, 226.
(53) Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J.; Chou, T.-C.; Guan, Y. *J. Org. Chem.* **2001**, *66*, 4369.
(54) Weitz, I. S.; Pellegrini, M.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **1997**, *62*, 2527.
(55) Mansour, T. S.; Evans, C. A. *Synth. Commun.* **1989**, *19*, 667.
(56) Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Shyam Prasad, R.; Sanganee, H. J. *Synlett* **1998**, , 519.
(57) Stamm, H.; Assithianakis, P.; Buchholz, B.; Weiss, R. *Tetrahedron Lett.* **1982**, *23*, 5021.
(58) Sureshkumar, D.; Ganesh, V.; Vidyarini, R. S.; Chandrasekaran, S. *J. Org. Chem.* **2009**, *74*, 7958.
(59) Bentz, G.; Werry, J.; Stamm, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, , 2793.
(60) Falkenstein, R.; Mall, T.; Speth, D.; Stamm, H. *J. Org. Chem.* **1993**, *58*, 7377.
(61) Lin, P.-y.; Bellos, K.; Stamm, H.; Onistschenko, A. *Tetrahedron* **1992**, *48*, 2359.
(62) Stamm, H.; Sommer, A.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946.
(63) Werry, J.; Lin, P.-Y.; Bellos, K.; Assithianakis, P.; Stamm, H. *J. Chem. Soc., Chem. Commun.* **1990**, , 1389.
(64) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
(65) Selig, P. *Synthesis* **2013**, *45*, 703.
(66) Galabov, B.; Nikolova, V.; Wilke, J. J.; Schaefer, H. F.; Allen, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 9887.
(67) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809.
(68) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179.

■ NOTE ADDED AFTER ASAP PUBLICATION

The version published ASAP May 21, 2014 contained some duplicate and inaccurate references; the correct version reposted May 28, 2014.