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Copper-Catalyzed Tethered Aziridination of Unsaturated *N*-Tosyloxy Carbamates

Renmao Liu, Steven R. Herron, and Steven A. Fleming*

Department of Chemistry, Brigham Young University, Provo, Utah 84602

steve_fleming@byu.edu

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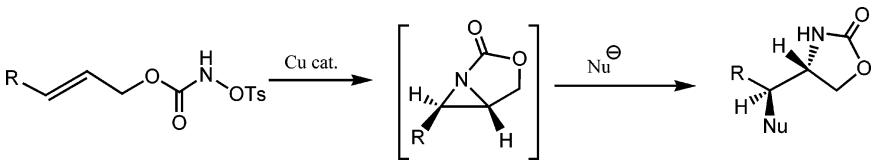

Aziridines were formed by copper-catalyzed intramolecular nitrene addition to alkenes. The carbamate group was used as the tether between the alkene and the nitrene. Subsequent nucleophilic attack of the aziridine was accomplished using RSH, R_2NH, N_3^-, or ROH as the nucleophile. This addition was found to be regio- and stereoselective. This methodology has been used to demonstrate its utility in the regio- and stereoselective synthesis of a 1,2-diamino-3-hydroxycyclohexane. This substitution pattern is found in natural products such as Tamiflu.

Introduction

Remarkable advances have been made in methods for aziridination using transition-metal-catalyzed nitrene addition to olefins during the past decade.[1−3] One efficient process makes use of *N*-arene sulfonyl iminoiodinanes as the nitrene source.[3a] Other alternative nitrogen sources include carbamate esters,[3b,c] sulfamate esters,[3d,e] and sulfonamides[2e,3g] in combination with hypervalent iodine reagents. However, one of the major drawbacks of these particular routes is the formation of a stoichiometric amount of iodobenzene. Recently, Lebel et al. have reported a highly efficient method using rhodium catalysis for nitrenes which undergo C−H insertion to give amines or alkene addition to give aziridines.[4] They used *N*-tosyloxy derivatives of carbamates as nitrene sources, thus avoiding addition of hypervalent iodine reagents which generate iodobenzene. More recently, Donohoe et al. successfully employed these carbamates as reoxidants for the aminohydroxylation reaction under conditions more convenient and mild than traditional methods.[5] Our interest is to investigate copper complexes as catalysts in this new aziridination reaction since copper complexes are readily available and have shown high efficiency in previous aziridination applications. We describe here the copper-catalyzed version of this process and, in particular, report the regio- and stereoselective nucleophilic opening of these bicyclic fused aziridines.

Results and Discussion

The starting *N*-sulfonyloxy carbamates were prepared from the corresponding alcohols in a good yield using a known two-pot procedure, as shown in Scheme 1 (CDI = 1,1′-carbonyl diimidazole).

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(3) (a) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (b) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863. (c) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137. (d) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (e) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481. (f) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.

(4) (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (b) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363.

(5) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514.

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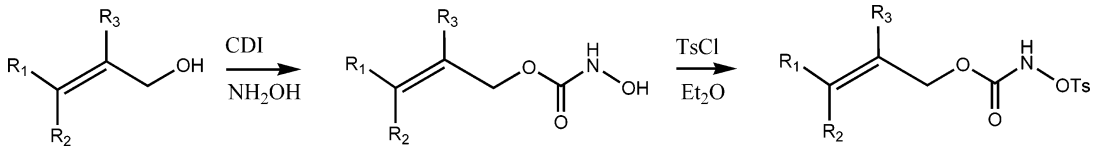
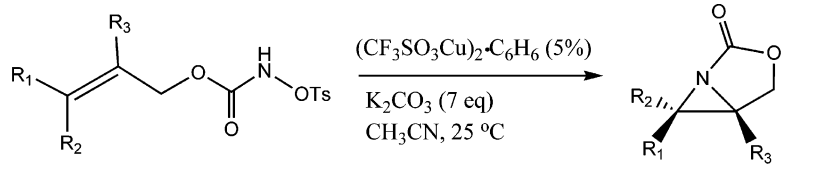
SCHEME 1. Synthesis of *N*-Tosyloxy Carbamates

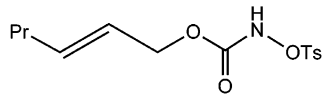
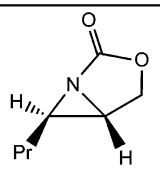
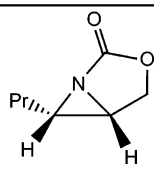
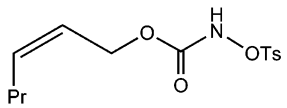
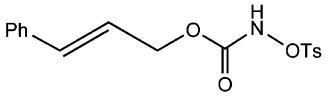
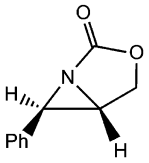
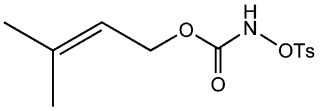
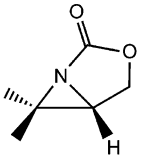
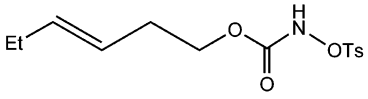
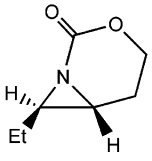


Typical experimental conditions for intramolecular aziridination employed 5−10 mol % of a copper salt and an excess of K_2CO_3 (usually 7 equiv) in acetonitrile (0.05 M) with stirring at room temperature for 16 h. Moderate to good yields were obtained (see Table 1). Different copper complexes, including $Cu(CH_3CN)_4PF_6$, $(CF_3SO_3Cu)_2 \bullet C_6H_6$, $(CF_3SO_3)_2Cu$, and CuBr, were studied using compound **1a**. Although each of these complexes led to aziridine formation, $(CF_3SO_3Cu)_2 \bullet C_6H_6$ provided the highest efficiency for the reaction. So $(CF_3SO_3Cu)_2 \bullet C_6H_6$ was chosen as our standard catalyst for this study. Use of potassium bases proved to be critical to the experiment. For example, K_2CO_3 was the most convenient base, although other potassium bases, such as KOH, were equally efficient. Bases such as Na_2CO_3, Cs_2CO_3, and Ag_2CO_3 gave only low conversion. Acetonitrile was used as the standard solvent, but similar yields were obtained in acetone. Under the standard conditions described above, the two monosubstituted allylic carbamates (**1a** and **1b**) gave modest isolated yields of the *trans* product. The reaction is not stereospecific.[6] The *trans*-alkene (**1a**) gives predominantly *trans*-aziridine (**2a**), but the *cis* isomer results in a 1.5:1 ratio of *trans:cis* aziridine diastereomers. Calculations on the aziridine products (**2a** and **2b**) at the ab initio level show that they differ in energy by only 1.5 kcal/mol.

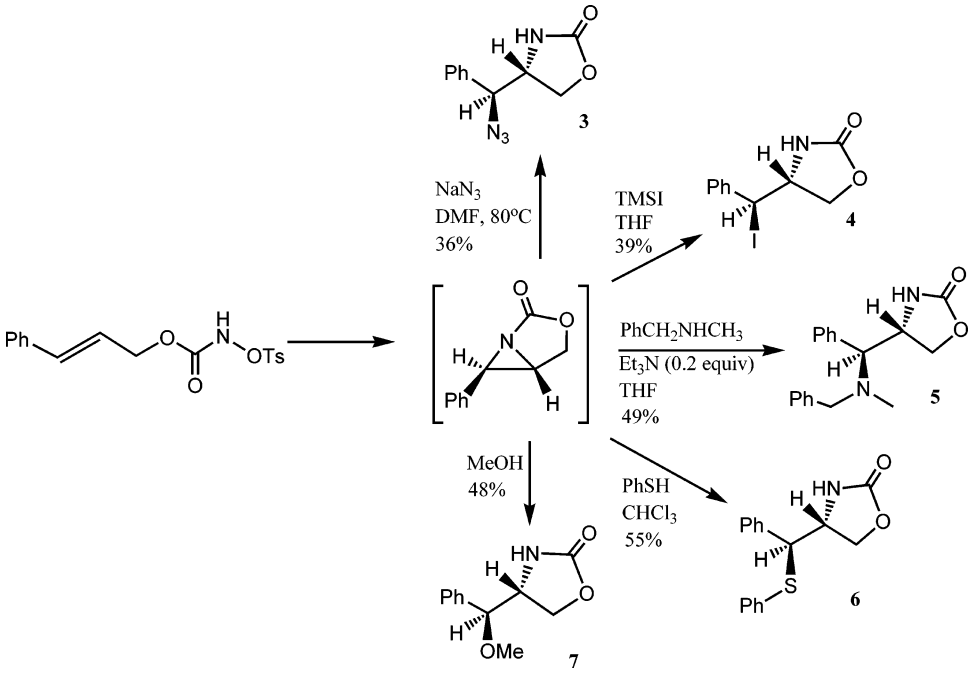
This reflects the preference for the *trans* isomer at room temperature from either starting material and supports the radical nature of the copper-catalyzed reaction.[2a,3a] The dimethyl- and phenyl-substituted carbamates (**1c** and **1d**) gave excellent yields (>90%). The yields of the latter two substrates were based on the NMR spectrum of the crude products. Attempts to further purify these products by chromatography on silica gel failed because of significant decomposition of the strained bicyclic compound. The high efficiency for the latter two substrates can be attributed to the electron-rich double bonds which make them

TABLE 1. Intramolecular Aziridination of Various Alkenes



Substrate		% Yield	Products (ratio)	
	1a	53	 2a (10)	 2b (1)
	1b	42	2a (1.5)	2b (1)
	1c	>90		2c
	1d	>90		2d
	1e	45		2e

SCHEME 2. Aziridination and Subsequent Ring Opening of Cinnamyl Moiety

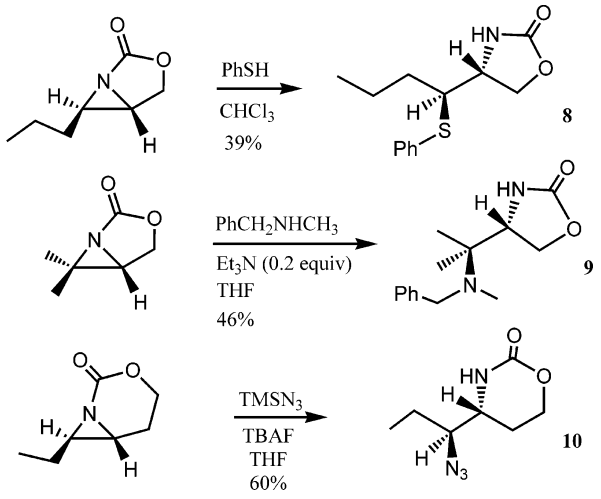


a better match for the electron-deficient nitrenes generated from the carbamates. The reaction also worked well for homoallylic carbamates (**1e**). A side reaction of detosylation produced a measurable amount of carbamates (15−30%), which decreased the efficiency of aziridination and resulted in the relative low yield for **1a**, **1b**, and **1e**. For **1e**, a small amount (<8%) of C−H insertion was also observed. For all of the *trans* substrates, the aziridination reaction is stereoselective, as the stereochemistry of the major product is also *trans*.

Studies were also carried out to probe the electrophilic reactivity of these heterocyclic aziridines, particularly with respect to the regio- and stereoselectivity of ring opening.[3b,7] In our first analysis, crude aziridine **2d** was reacted without purification with different types of nucleophiles (*N*-methyl benzylamine, thiophenol, methane, sodium azide, and TMSI). This approach afforded the oxazolidinones **3**−**7** in moderate overall yields for the two steps. Only one diastereomer generated by nucleophilic attack at the less substituted aziridine carbon was obtained for each substrate (Scheme 2). The structures were confirmed by the X-ray crystallography of **5** and analysis of the 2D ^{1}H NMR.[8]

The X-ray structure established that the ring opening occurs with high stereoselectivity to afford **3**−**7** with inversion of configuration at the reaction site. We then tested the other crude aziridines **2a**, **2c**, and **2e**, and similar results were obtained (Scheme 3), except for the thiophenol addition to aziridine **2a**, which also gave a minor amount (ca. 10%) of the presumed diastereomeric ring-opened product. The X-ray structure of **9** further confirmed that the ring-opening process was regioselective for this particular reaction. We were surprised that the nucleophilic attack occurred selectively at the nonbridgehead

SCHEME 3. Ring Opening of Bicyclic Aziridines



aziridine carbon in light of the report by Duran et al.[3e,9] that the sulfamate-fused aziridine undergoes ring opening at a bridgehead carbon. Their work, however, dealt with the [4.1.0] bicyclic sulfamate system rather than the bicyclo[3.1.0]carbamate structures that is the target of this report. In this work, even the [4.1.0]carbamate undergoes ring opening at the nonbridgehead carbon (see Scheme 3). Our ab initio calculations of the aziridines of the carbamate and the sulfamate show that the LUMO density correctly predicts the aziridine opening to give the larger ring for the sulfamate and the smaller ring in the carbamate system. The reason for this selectivity is not apparent.

We chose to apply this aziridination and ring-opening methodology to cyclic substrates such as **1f** (Scheme 4). In our first attempt, an unexpected non-aziridine product was obtained.

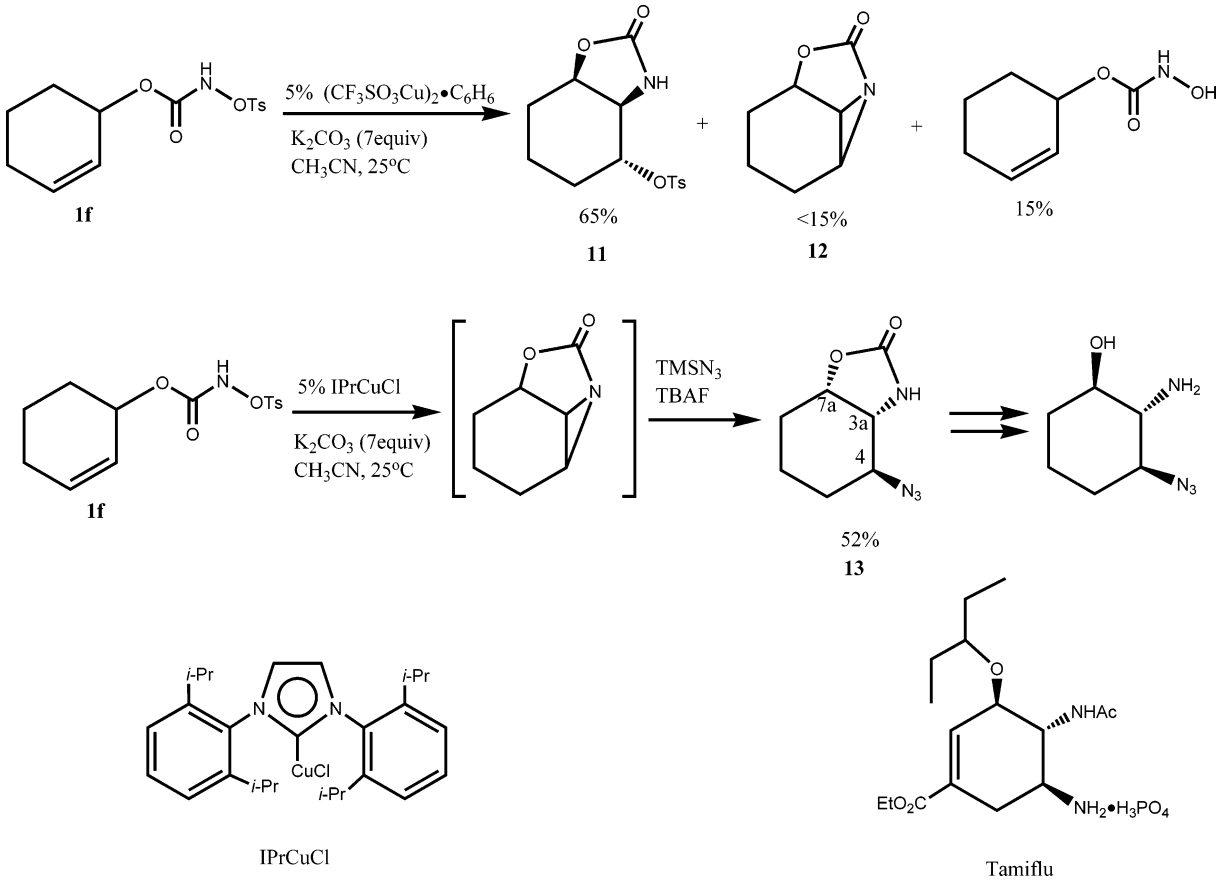
(6) We appreciate the comments from the reviewer concerning this nonstereospecific addition. For a similar observation, see: Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109.

(7) (a) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449. (c) Hayes, C. J.; Beavis, P. W.; Humphries, L. A. *Chem. Commun.* **2006**, 4501. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2071.

(8) See the Supporting Information.

(9) Guthikonda, K.; When, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2007**, *62*, 11331.

SCHEME 4. Intramolecular Aziridination of Cyclohexene



After further study, the product **11** was isolated and we surmised that it results from in situ ring opening of the strained aziridine by the weakly nucleophilic tosylate group, which is formed during the reaction. A second minor product which results from hydrolysis of the starting carbamate was also isolated, as shown in Scheme 4. When we shortened the reaction time, we did observe a minor amount of the desired aziridine. Its presence was confirmed by ^{1}H NMR analyses of the crude reaction mixture. In an attempt to improve the aziridination process in this system, we explored the use of other copper catalysts. Recently a N-heterocyclic carbene copper chloride complex has been successfully used for the aziridination reaction during the total synthesis of agelastatin A.[10,11] Considering its efficiency for the addition to the electron-deficient cyclopentene in the synthesis of agelastatin A, we chose to employ this catalyst with substrate **1f**. We were pleased to find that the desired aziridine was the major product in this run as determined by ^{1}H NMR analysis of the crude product. Unfortunately, further attempts to purify the strained tricyclic compound by silica gel chromatography led to significant decomposition. Thus, we opted to trap the crude aziridine by nucleophilic ring opening using $TMSN_3$ as an in situ nucleophile (Scheme 4). This strategy provides a potential way to assemble the stereochemistry of three adjacent functional groups, such as the 1,2-diamino-3-hydroxy unit. The stereochemical assignment for the three consecutive stereocenters of compound **13** is supported by the NMR data. The coupling constants for the H_{3a} doublet of doublets (see Scheme 4) are 8.06 Hz with H_4 and 6.05 Hz with H_{7a} as verified by 2D NMR. These values are consistent with an axial−equatorial relationship for $H_{3a}-H_{7a}$ and an axial−axial relationship for $H_{3a}-H_4$, which is expected for a *trans* relationship between the nitrogen groups on the cyclohexane ring and a *cis* relationship for the carbamate group. Inversion of the oxygen substituent would give the 1,2-diamino-3-hydroxy combination that occurs on Tamiflu (oseltamivir phosphate), which is receiving intense scrutiny as an oral drug for avian flu.[12]

In conclusion, copper-catalyzed intramolecular aziridination of unsaturated carbamates has been described as a complement to the previous rhodium-catalyzed version. Different nucleophiles can be introduced both regioselectively and stereoselectively on these heterocycles. The unique regioselectivity for this process has been established by X-ray of two ring-opened products. Improvement of the reaction efficiency and application of this strategy to the total synthesis of natural products is under further investigation.

Experimental Section

General Procedure A: Synthesis of Allylic *N*-Hydroxy Carbamates.[4a,5] 1,1′-Carbonyldiimidazole (1.5 equiv) was added to a solution of alcohol (1.0 equiv) in acetonitrile (5 mL/mmol of

(10) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054.

(11) For other recent examples using N-heterocyclic carbene copper complexes, see: (a) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417. (b) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Diaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846. (c) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadigih, J. P. *Organometallics* **2004**, *23*, 1191.

(12) (a) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310. (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

substrate) and stirred, under argon, at room temperature until TLC indicated complete consumption of the alcohol (typically after 2 h). Imidazole (4.0 equiv) and hydroxylamine hydrochloride (5.0 equiv) were added, and stirring continued until TLC showed complete consumption of the initial alcohol adduct. After removal of the reaction solvent, the residue was partitioned between ethyl acetate and 1 M HCl followed by extraction of the aqueous phase with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography using 40% ethyl acetate−hexane.

General Procedure B: Synthesis of *N*-Tosyloxy Carbamates.[4a,5] To a solution of *N*-hydroxy carbamate (6 mmol) in Et_2O at 0 °C was added *p*-toluenesulfonyl chloride (1.26 g, 6.60 mmol). Triethylamine (0.85 mL, 6.1 mmol) was then added slowly, and the resulting white suspension was stirred for 12 h at room temperature. The mixture was washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the tosyloxy carbamate was purified by flash chromatography using 25% ethyl acetate−hexane as the eluent.

General Procedure C: Aziridination of *N*-Tosyloxy Carbamates.[4a] The *N*-tosyloxy carbamate (1.00 mmol), K_2CO_3 (0.967 g, 7.00 mmol), and $(CF_3SO_3Cu)_2 \cdot C_6H_6$ (25.2 mg, 0.050 mmol) were dissolved in acetonitrile (20 mL) at 25 °C. The mixture was stirred vigorously for 16 h. Dichloromethane (30 mL) was added, and the solution was filtered. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel using 30% EtOAc−hexane as the eluent or the aziridine was directly used for the next ring-opening step.

General Procedure for the Nucleophilic Ring Opening of Aziridines: Using *N*-Methyl Benzylamine. To a solution of aziridine **2c** in THF were added *N*-methyl benzylamine (1.2 equiv) and triethylamine (0.2 equiv) at 25 °C under nitrogen. The reaction mixture was stirred for 5 h and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the desired compound. Then the compound was recrystallized from a mixture of hexane and EtOAc.

Using Thiophenol on Bicyclo[3.1.0]aziridines. To a solution of aziridine **2c** in $CHCl_3$ was added thiophenol (1.5 equiv) at 25 °C under nitrogen. The reaction mixture was stirred for 48 h and concentrated under reduced pressure. The residue was purified by flash chromatography with 25% ethyl acetate−hexane on silica gel to give the desired compound.

Using Sodium Azide. To a solution of aziridine **2c** in DMF was added NaN_3 (3 equiv) under nitrogen. The reaction mixture was stirred for 24 h at 80 °C, cooled to room temperature, and poured into water and brine. The mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 30% ethyl acetate−hexane as eluent to give the desired compound as a yellow oil.

Using in situ Azide on Bicyclo[4.1.0]aziridine. To a solution of 0.3 mmol aziridine **2e** in THF were added azidotrimethylsilane (1.1 equiv) and TBAF (1.0 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 36 h, and filtered through silica gel. The filter pad was washed with EtOAc, and the filtrate and washing were evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography using 30% ethyl acetate−hexane on silica gel to give the desired compound as a colorless oil (yield of 60%). Starting material was also recovered (ca. 30%).

Using in situ Azide on Tricyclic Aziridine. To a solution of 0.5 mmol crude product after aziridination of *N*-tosyloxy carbamate **1f** in THF were added azidotrimethylsilane (1.1 equiv) and TBAF (0.1 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 4 h, and filtered through silica gel. The filter pad was washed with EtOAc, and the filtrate and washing were evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography on silica gel using 30% ethyl acetate−hexane to give the desired compound as a white amorphous solid (40%).

Using Methanol. The phenyl-substituted bicyclo[3.1.0]aziridine **2c** (1.0 mmol) was dissolved in methanol (5 mL) and stirred for 48 h at 25 °C under nitrogen. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography 30% ethyl acetate−hexane as eluent on silica gel to give the desired compound.

Using Sodium Iodide. To a solution of phenyl-substituted bicyclo[3.1.0]aziridine **2c** in THF were added iodotrimethylsilane (1.1 equiv) and TBAF (0.1 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature, stirred for 4 h, and filtered through silica gel. The filter pad was washed with EtOAc, and the filtrate and washing were evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography using 30% ethyl acetate−hexane on silica gel to give the desired compound.

Supporting Information Available: The general experimental procedures for this work and the spectral data for **1a**−**f**, **2a**−**e**, and **3**−**13** are provided as supplemental information. Crystallographic data for compounds **5** and **9** and their ORTEP drawings are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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