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Scalable Synthesis of *N*-Acylaziridines from *N*-Tosylaziridines

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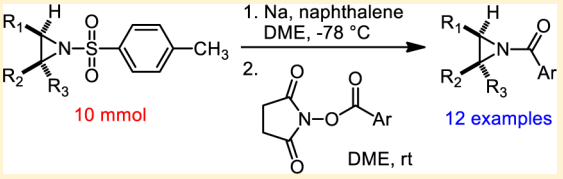
Supporting Information

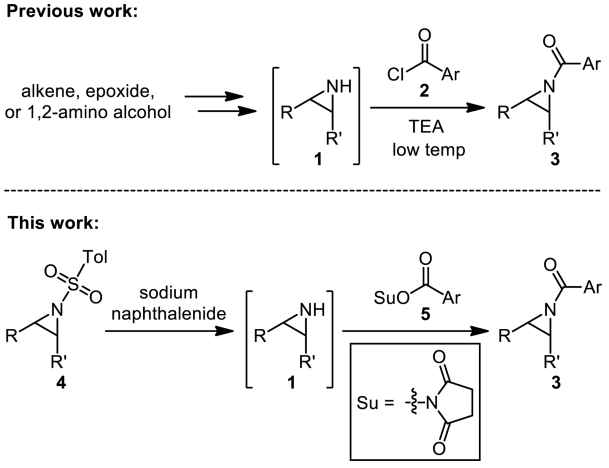
ABSTRACT: *N*-Acylaziridines are important starting materials for the synthesis of chiral amine derivatives. The traditional methods for producing these activated aziridines have significant drawbacks. The gram scale synthesis of *N*-acylaziridines by deprotection of *N*-tosylaziridines and reprotection with *N*-hydroxysuccinimide derivatives is described. Mono- and disubstituted aziridines perform well, with complete retention of stereochemical purity. The consistently moderate yields are linked to the *N*-tosylaziridine deprotection step, while acylation with *N*-hydroxysuccinimide derivatives is highly efficient.



N-Acylaziridines are strategic organic intermediates for the synthesis of nitrogen-containing small molecules.[1,2] Early synthetic efforts describing the formation of these activated aziridines were met with challenges associated with thermal aziridine rearrangement.[3] As appreciation grew for the sensitive nature of *N*-acylaziridines, rearrangement reactions were developed utilizing both Lewis acidic[4−8] and Lewis basic[9−11] reaction conditions. Current research has taken advantage of the chiral or prochiral nature of *N*-acylaziridines to generate enantioenriched building blocks by catalytic asymmetric desymmetrization[2,12−20] and kinetic resolution.[21,22] A direct catalytic, asymmetric synthesis of *N*-acylaziridines remains elusive.

Methods for the synthesis of *N*-acylaziridines (**3**) by cyclization of amide precursors are rare;[23−25] subsequently, **3** is most often prepared by acylation of 1*H*-aziridines (**1** → **3**, Scheme 1). Various methods for the production of **1** have been developed depending on the necessary aziridine substituents (e.g., R and R′).[26] Alkene[27,28] and epoxide[29,30] starting materials require installation of nitrogen, often from azide sources, followed by a reductive cyclization. 1,2-Amino alcohols undergo direct cyclization in the presence of hypervalent phosphorus reagents[31,32] or by Wenker conditions[33,34] to generate **1**. Alternatively, the desulfonation of *N*-tosylaziridines has been reported[35,36] for the synthesis of **1**, where the *N*-tosylaziridines are readily available from alkenes[37−41] or 1,2-amino alcohols.[42] Challenges related to the purification of **1** should not be overlooked as the stability of 1*H*-aziridines can be variable.

Scheme 1. Proposed Synthesis of *N*-Acylaziridines



Our recent efforts to synthesize and exploit the reactivity of electron-deficient *N*-acylaziridines required us to generate gram quantities of these intermediates.[11,22] Specifically, the 3,5-dinitrobenzoyl (DNB) nitrogen protecting group was necessary. Employing the reaction conditions described above, various issues were encountered leading to low yields of *N*-DNB-aziridines (**3** where Ar = 3,5-dinitrophenyl, Scheme 1). Challenges and concerns with the current methods include (1) byproducts related to aziridine ring-opening were produced when synthesizing *N*-acylaziridines thereby complicating purification, (2) cyclization reactions to generate **1** gave various yields depending on the nature of R and R′, and (3) potentially hazardous organic azides are produced as intermediates. Therefore, we have developed an alternative procedure for the large scale synthesis of **3** from *N*-tosylaziridines (**4**) utilizing *N*-hydroxysuccinimide benzoates (**5**) as the source of acyl group (Scheme 1).

A survey of common methods for amide formation was conducted to identify optimum aziridine acylation conditions. Commercially available *rac*-2-methylaziridine (**6**) was subjected to various reaction conditions in THF in an effort to synthesize *N*-DNB-aziridine **10** (Table 1). Reaction outcome was determined by ^{1}H NMR of the unpurified mixture following

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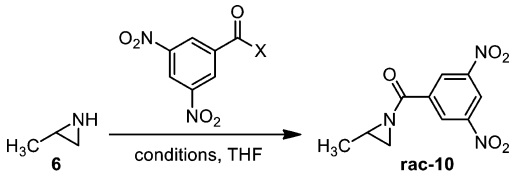
Table 1. Conditions for 1*H*-Aziridine Acylation



X = Cl, **7**; OH, **8**; OSu, **9**

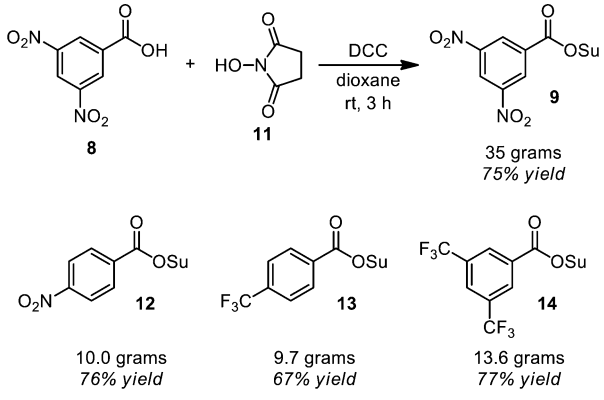
entry	acyl group	conditions[a]	yield[b] (%)
1	**7**	TEA, −78 to −30 °C to rt, 1 h	53
2	**7**	pyridine, −78 to −30 °C to rt, 1 h	22
3	**7**	1 M NaOH (aq), 0 °C to rt, 16 h	0
4	**7**	1 M Na_2OH_3 (aq), 0 °C to rt, 16 h	4
5	**8**	DCC, 0 °C to rt, 16 h	90
6	**8**	EDCI, 0 °C to rt, 16 h	0[c]
7	**9**	0 °C to rt, 16 h	99

[a]Reactions perform on a 1 mmol scale. For detailed procedures, see Experimental Section. [b]Yields determined by ^{1}H NMR following the addition of 1,3,5-trimethoxybenzene as an internal standard. [c]A product consistent with hydrochlorination of **10** was observed in 22% yield.

aqueous workup. Acid chloride **7**, which has often been employed for *N*-DNB-aziridine synthesis,[11,13,16] gave low to moderate yields in the presence of standard bases (entries 1−4). The high reactivity of **7** requires careful temperature control in the presence of amine bases (entries 1 and 2) and may also explain the lack of product formation in biphasic conditions (entries 3 and 4). DCC coupling of carboxylic acid **8** was highly efficient;[43] however, EDCI coupling produced only products related to chloride opening of **10** (entries 5 and 6). *N*-Hydroxysuccinimide (NHS) derivative **9** was the most efficient with nearly a quantitative yield. The excellent yield observed with **9** together with ability to remove the NHS byproduct by aqueous workup directed us to select NHS derivatives for the scale-up synthesis of *N*-acylaziridines.

NHS derivatives are readily synthesized from low-cost carboxylic acids by standard DCC coupling. Amide synthesis from NHS derivatives is common; however, to our knowledge 1*H*-aziridines have not been employed as substrates in this type of amide formation. The requisite DNB reagent (**9**) was synthesized by slight modification of a published procedure (Scheme 2).[44] DCC coupling of carboxylic acid **8** and *N*-hydroxysuccinimide (**11**) proceeded smoothly at room temperature over 3 hours in dioxane. The urea byproduct was

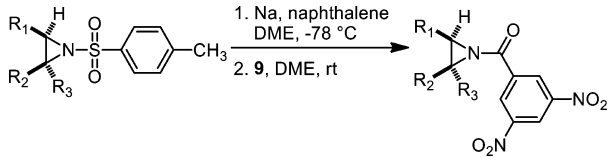
Scheme 2. Synthesis of *N*-Hydroxysuccinimide Benzoates

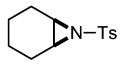
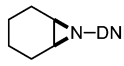
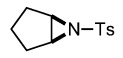
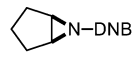
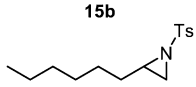
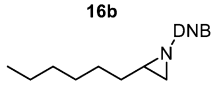
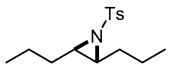
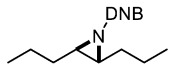
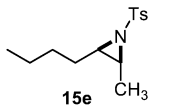
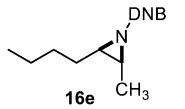
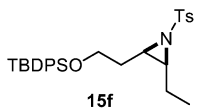
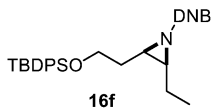
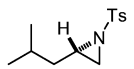
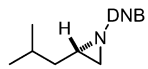
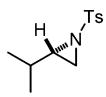
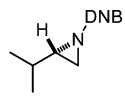
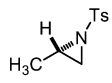
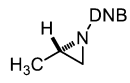


removed though filtration, and 35 g of **9** was isolated as a white solid in 75% yield following suspension in DCM and filtration. Other electron-deficient NHS benzoates were synthesized in a similar manner on a 50 mmol scale in good yield. Benzoates **12** and **13** could be purified by the standard procedure; however, compound **14** has higher solubility in DCM and was purified by column chromatography.

A series of structurally diverse *N*-DNB-aziridines were synthesized on gram scale from the necessary DNB-OSu (**9**) by performing a deprotection/reprotection sequence beginning with *N*-tosylaziridines (Table 2). Literature detosylation conditions with sodium naphthalenide were employed as

Table 2. Substrate Scope for *N*-Acylaziridine Synthesis by Deprotection/Reprotection on a 10 mmol Scale[a]



entry	substrate[c]	product[c]	yield (%)[b]
1	 **15a**	 **16a**	63
2	 **15b**	 **16b**	65
3	 **15c**	 **16c**	65
4	 **15d**	 **16d**	52
5	 **15e**	 **16e**	67
6	 **15f**	 **16f**	55
7	 **15g**	 **16g**	53
8	 **15h**	 **16h**	61
9	 **15i**	 **10**	15

[a]Conditions: (1) *N*-tosylaziridine (10 mmol), sodium naphthalenide (25 mmol), DME, −78 °C, 0.25 h; then H_2O quench, ether extraction; (2) **9** (12 mmol), 0 → 25 °C, 12 h. [b]Isolated yield from a single run. [c]Ts = *p*-toluenesulfonyl; DNB = 3,5-dinitrobenzoyl.

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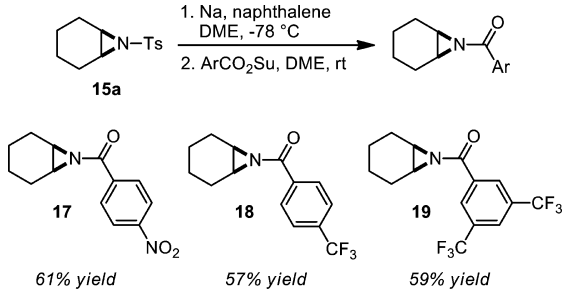
described, followed by aqueous workup.[36] Moderate functional group compatibility has been demonstrated for this method, though pendent esters and 2-aryl-*N*-tosylaziridines are problematic. In our hands, other *N*-tosylaziridine deprotection conditions proved no more efficient than sodium naphthalenide.[35] Reprotection with **9** could be performed at room temperature in consistently moderate yields over the deprotection/reprotection sequence. Disubstituted (entries 1, 2, 4–6) and terminal (entries 3, 7–9) aziridines gave comparable yields, with the noticeable outlier being the 2-methyl substrate (entry 9). The low boiling point of 2-methylaziridine is likely to blame, since removal of solvent is required prior to reprotection. Silyl ethers are unaffected during deprotection (entry 6). As expected, stereodefined (entries 4–6) and enantioenriched (entries 7–9) aziridines maintain stereochemical purity during the nitrogen protecting group exchange.

Other electron-deficient NHS benzoates performed equally well. Aziridine **15a** was prepared by direct aziridination of cyclohexene on large scale. Deprotection of **15a** under standard conditions followed by reprotection with electron-deficient acyl groups proceeded smoothly in moderate yields on a 10 mmol scale (Scheme 3). *N*-Acylaziridines **17**–**19**, which have previously been prepared in 3 steps from cyclohexene oxide, are common substrates for nucleophilic desymmetrization reactions.[2]

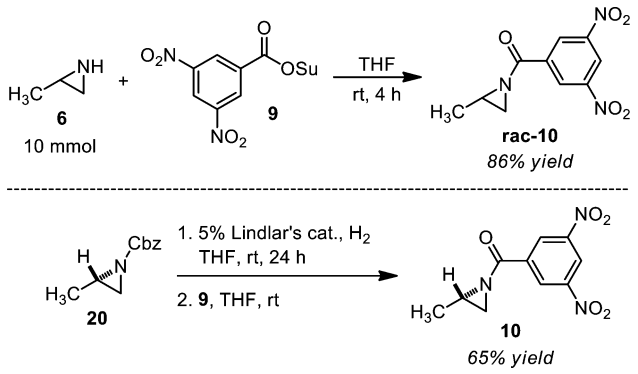
Scheme 3. Synthesis of Electron-Deficient *N*-Acylaziridines on a 10 mmol Scale



The described deprotection/reprotection of *N*-tosylaziridines is sufficient for the scale-up synthesis of *N*-acylaziridines; however, we were generally unsuccessful in efforts to push yields above 70%. To better understand material loss, commercially available *rac*-2-methylaziridine (**6**) was subjected to acylation at room temperature to produce **rac-10** (Scheme 4). A jump to 86% yield suggests significant material loss was occurring during *N*-tosylaziridine deprotection and workup. Utilizing milder deprotection conditions for 1*H*-aziridine formation can be further explored for improving the overall synthetic procedure. To this end, enantiopure *N*-Cbz-aziridine (**20**) can be deprotected under hydrogenation conditions utilizing Lindlar's catalyst, followed by reprotection with **9** in moderate yield. Since *N*-Cbz-aziridines are available from various starting materials,[45−47] they represent a viable alternative to *N*-tosylaziridines.

In conclusion, a scalable method for the synthesis of electron-deficient *N*-acylaziridines is disclosed. Terminal and disubstituted *N*-tosylaziridines perform equally well in the deprotection/reprotection method, consistently producing moderate yields of *N*-acylaziridines on gram scale. Improved access to *N*-acylaziridines will facilitate future studies of stereospecific and enantioselective aziridine ring-opening reactions.

Scheme 4. Alternative Synthesis of 10



EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and assignment. ^{13}C NMR spectra were recorded on the same spectrometer (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$, 77.0 ppm). High resolution mass spectrometry was acquired with a TOF-Q instrument via electron spray ionization (ESI, positive mode). Infrared (IR) spectra were obtained using an FT-IR spectrometer.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 32–63 μm). Thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 plates. Visualization was achieved UV light (254 nm) or basic potassium permanganate in water followed by heating. High pressure liquid chromatography (HPLC) was performed on an instrument equipped with an autosampler and a UV detector. A Daicel Chiralpak IA or IB (0.46 cm × 25 cm) column with a mixed solvent (hexane/isopropanol) at a flow rate of 1 mL/minute was used for data pertaining to enantiomeric excess calculations, unless otherwise noted.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of argon. All solvents were purchased as anhydrous solvents under an inert atmosphere, except 1,4-dioxane, which was purchased as ACS grade in 500 mL portions. 2-Methylaziridine (90%, technical grade) was purchased from Aldrich Chemical Co. All purchased chemicals were used as received.

Survey of 1*H*-Aziridine Acylation Conditions. 3,5-Dinitrobenzoyl chloride (**7**, 0.282 g, 1.2 mmol) was added to a flame-dried round-bottom flask with a Teflon coated stir bar. THF (4 mL, 0.25 M) was added, and the reaction flask was cooled to −78 °C. Triethylamine or pyridine was added (1.2 mmol), followed by *rac*-2-methylaziridine (**6**, 78.5 μL, 1 mmol) dropwise. The reaction mixture was warmed to −30 °C and stirred for 1 h under argon. After this time, the reaction was slowly brought to room temperature and quenched with 20 mL of water. The mixture was diluted with 20 mL of ethyl acetate, and the layers were separated. The organic layer was washed with 10 mL of water and 10 mL of brine, dried over magnesium sulfate, and filtered. The contents were dried by rotary evaporation and were left under high vacuum for 3 h. 1,3,5-Trimethoxybenzene (approximately 20 mg) was added, and the entire mixture was dissolved in chloroform-D for ^{1}H NMR analysis. NOTE: For aqueous bases, THF was reduced to 2 mL, and 2 mL of 1 M Na_2CO_3 or 1 M NaOH were added at 0 °C followed by warming to room temperature for 16 h. For carbodiimide couplings, 3,5-dinitrobenzoic acid (**8**, 0.26 g, 1.2 mmol) was dissolved in 4 mL of THF and cooled to 0 °C prior to the addition of aziridine

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(1 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) or *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) (1.2 mmol). The reactions were warmed to room temperature for 16 h. For the *N*-hydroxysuccinimide reagent, **9** was dissolved in 4 mL of THF and cooled to 0 °C prior to the addition of aziridine (1 mmol). The reaction was warmed to room temperature for 16 h.

Representative Procedure for the Synthesis of *N*-Hydroxysuccinimide Benzoates. The following procedure is a slight modification to a published procedure.[44] To a flame-dried 1-L round-bottom flask equipped with a Teflon-coated magnetic stir bar was added *N*-hydroxysuccinimide (1 equiv), followed by 3,5-dinitrobenzoic acid (1 equiv) and dry 1,4-dioxane (0.3 M). To this solution was added *N*,*N*′-dicyclohexylcarbodiimide (1.05 equiv). A precipitate began to form, and the mixture warmed slightly. The reaction was stirred for approximately 3 h at which time the thick suspension was filtered. The solid was resuspended in fresh 1,4-dioxane (same volume used during the reaction) and stirred for an additional 15 min. The suspension was filtered once more, and the combined supernatants were concentrated via rotary evaporation. The yellow solid was suspended in hot dichloromethane (∼1 M). After cooling to room temperature, the product was collected by suction filtration. The solid was rinsed with dichloromethane.

2,5-Dioxopyrrolidin-1-yl 3,5-Dinitrobenzoate (9). Synthesized from 3,5-dinitrobenzoic acid (31.82 g, 150 mmol) to afford an off-white solid (34.93 g, 75% yield). HRMS calcd for $C_{11}H_7N_3NaO_8^+$: 332.0131 (M + Na^+), found 332.0154 (M + Na^+); ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.17 (t, J = 2.0 Hz, 1H), 9.02 (d, J = 2.0 Hz, 2H), 2.93 (s, 4H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 170.3, 159.6, 149.19, 130.18, 127.55, 124.87, 26.07; IR (NaCl plate) 3076, 1776, 1740, 1542 cm^{-1}.

2,5-Dioxopyrrolidin-1-yl 4-Nitrobenzoate (12). Synthesized from 4-nitrobenzoic acid (8.36 g, 50 mmol) to afford a white solid (9.99 g, 76% yield). All spectroscopic data were consistent with literature values.[48]

2,5-Dioxopyrrolidin-1-yl 4-(Trifluoromethyl)benzoate (13). Synthesized from 4-trifluoromethylbenzoic acid (9.51 g, 50 mmol) to afford a white solid (9.69 g, 67% yield). HRMS calcd for $C_{12}H_8F_3NNaO_4^+$: 310.0303 (M + Na^+), found 310.0296 (M + Na^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 8.0, 2H), 7.80 (d, J = 8.4, 2H), 2.93 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.93, 160.89, 136.22 (q, J = 32.4 Hz), 131.0, 128.51, 125.99 (m, J = 3.2 Hz), 123.25 (q, J = 271.3 Hz); IR (NaCl plate) 3070, 1772, 1731 cm^{-1}.

2,5-Dioxopyrrolidin-1-yl 3,5-Bis(trifluoromethyl)benzoate (14). Low isolated yields by crystallization from dichloromethane required purification of the total crude solid via silica gel column chromatography (2:1 hexanes/ethyl acetate). Synthesized from 3,5-bis-trifluoromethylbenzoic acid (13.83 g, 50 mmol) to afford a white solid (13.66 g, 77% yield). HRMS calcd for $C_{13}H_7F_6NNaO_4^+$: 378.0177 (M + Na^+), found 378.0172 (M + Na^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 2H), 8.20 (s, 1H), 2.96 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.60, 159.69, 132.89 (q, J = 34.3 Hz), 130.57 (d, J = 3.2 Hz), 128.23 (t, J = 3.2 Hz), 127.536, 122.49 (q, J = 271.4 Hz) ; IR (NaCl plate) 3096, 2952, 1783, 1745 cm^{-1}.

General Procedures for Aziridine Synthesis. Iodine-Catalyzed Aziridination of Olefins. The following procedure is a slight modification to a published procedure.[39] A flame-dried round-bottom flask equipped with a Teflon-coated magnetic stir bar was charged with the respective olefin (1 equiv) dissolved in a 0.5 M solution of 3:1 deionized water/dichloromethane and then purged with argon. Chloramine-T trihydrate (1.2 equiv) was added, followed by tetrabutylammonium bromide (TBAB) (0.1 equiv) and iodine (0.1 equiv). The biphasic solution was allowed to stir at room temperature, under argon, for 24 h. After this time, the organic phase was collected, and the aqueous phase was extracted three times with dichloromethane (equal volume to reaction volume). The combined organics were washed with sodium thiosulfate and brine and then dried over $MgSO_4$. The solvent was removed by rotary evaporation. The crude material was purified by silica gel chromatography with hexanes/ethyl acetate mixtures to yield *N*-tosylaziridine.

***N*-(*p*-Toluenesulfonyl)-7-azabicyclo[4.1.0]heptane (15a).** Synthesized from cyclohexene (8.10 mL, 80 mmol). Purification by silica gel chromatography (5:1 hexanes/ethyl acetate) afforded a pale yellow solid (16.38 g, 82% yield). All spectroscopic data were consistent with literature values.[37,49]

***N*-(*p*-Toluenesulfonyl)-2-*n*-hexylaziridine (15c).** Synthesized from 1-octene (15.75 mL, 100 mmol). Purification by silica gel chromatography (5:1 hexanes/ethyl acetate) afforded a pale yellow oil (20.06 g, 71% yield). All spectroscopic data were consistent with literature values.[49]

Bromine-Catalyzed Aziridination of Olefins. *N*-Tosylaziridine was prepared from the corresponding alkene, Chloramine-T trihydrate (1.1 equiv), and phenyltrimethylammonium tribromide (PTAB) (0.1 equiv) according to the published procedure.[38]

***N*-(*p*-Toluenesulfonyl)-6-azabicyclo[3.1.0]hexane (15b).** Synthesized from cyclopentene (3.66 mL, 40 mmol). All spectroscopic data were consistent with literature values.[38]

***trans*-*N*-(*p*-Toluenesulfonyl)-2,3-di-*n*-propylaziridine (15d).** Synthesized from *trans*-4-octene (2.58 mL, 15 mmol). Purification by silica gel chromatography (9:1 hexanes/ethyl acetate) afforded a pale yellow oil (3.91 g, 93% yield). All spectroscopic data were consistent with literature values.[37]

***cis*-*N*-(*p*-Toluenesulfonyl)-2-*n*-butyl-3-methylaziridine (15e).** Synthesized from *cis*-2-heptene (2.08 mL, 15 mmol). Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a pale yellow oil (3.49 g, 87% yield). HRMS calcd for $C_{14}H_{21}NNaO_2S^+$: 290.1191 (M + Na^+), found 290.1185 (M + Na^+). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 2.62−2.56 (m, 1H), 2.44−2.39 (m, 1H), 2.12 (s, 3H), 1.22−1.20 (m, 1H), 1.19−1.15 (m, 1H), 1.00−0.85 (m, 7H), 0.52 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.9, 135.5, 129.4, 127.6, 44.6, 39.8, 29.0, 25.8, 22.0, 21.2, 13.6, 11.7; IR (NaCl plate) 2957, 2930, 2872, 1323, 1160 cm^{-1}.

***cis*-*N*-(*p*-Toluenesulfonyl)-2-(2-((*tert*-butyldiphenylsilyl)oxy)-ethyl)-3-ethylaziridine (15f).** *cis*-3-Hexen-1-ol (1.77 mL, 15.0 mmol) was converted to the corresponding *N*-tosylaziridine by the standard bromine-catalyzed aziridination procedure. Following a silica gel plug, the hydroxyl group was silylated in dichloromethane (50 mL) by the addition of *tert*-butyldiphenylsilyl chloride (4.29 mL, 16.5 mmol), imidazole (2.04 g, 30.0 mmol), and DMAP (0.18 g, 1.5 mmol). The mixture was stirred under argon atmosphere for 24 h at room temperature. After this time, 30 mL of water was added, and the mixture was extracted three times with 50 mL of dichloromethane. The organic layers were combined, washed with brine, and dried over magnesium sulfate. Purification by silica gel chromatography (4:1 hexanes/ethyl acetate) afforded a yellow oil (6.93 g, 91% yield). HRMS calcd for $C_{29}H_{38}NO_3SSi^+$: 508.2336 (M + H^+) found (M + H^+). 508.2336; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.4 Hz, 2H), 7.80−7.61 (m, 4H), 7.46−7.24 (m, 6H), 7.22 (d, J = 8.4 Hz, 2H), 3.57 (d, J = 7.0 Hz, 1H), 3.55 (d, J = 7.0 Hz, 1H), 1.79−1.72 (m, 1H), 1.65−1.57 (m, 1H), 2.39 (s, 3H), 1.79−1.72 (m, 1H), 1.65−1.57 (m, 1H) 1.55−1.45(m, 1H), 1.46−1.35 (m, 1H), 1.06 (s, 9H), 1.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 135.5, 135.5, 135.2, 133.6, 129.7, 129.5, 128.0, 127.7, 61.7, 46.0, 42.6, 30.0, 26.9, 21.6, 20.3, 19.2, 11.6; IR (NaCl plate) 3048, 2961, 2930, 1360, 1325, 1184 cm^{-1}.

Cyclization of 1,2-Amino Alcohols. *N*-Tosylaziridine was prepared from the corresponding enantiopure amino alcohol by ditosylation and base-promoted cyclization according to a literature procedure.[42]

***(S)*-*N*-(*p*-Toluenesulfonyl)-2-isobutylaziridine (15g).** Synthesized from L-leucinol (2.6 mL, 20 mmol). Purification by silica gel chromatography (5:1 hexanes/ethyl acetate) afforded a yellow oil (2.96 g, 58% yield). HRMS calcd for $C_{13}H_{19}NNaO_2S^+$: 276.1023 (M + Na^+) found 276.1029 (M + Na^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 2.78−2.70 (m, 1H), 2.58 (d, J = 6.8 Hz, 1H), 2.40 (s, 3H), 1.99 (d, J = 4.4 Hz, 1H), 1.64−1.52 (m, 1H), 1.33−1.26 (m, 2H), 0.85 (d, J = 2.6 Hz, 3H), 0.83 (d, J = 2.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.5, 135.1, 129.6, 127.9,

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40.4, 39.0, 34.0, 26.7, 22.8, 21.9, 21.6. IR (NaCl plate) 3102, 2959, 1544, 1386 cm^{-1}.

(*S*)-*N*-(*p*-Toluenesulfonyl)-2-isopropylaziridine (15h). Synthesized from L-valinol (3.3 mL, 30 mmol). Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a white solid (5.33 g, 75% yield). HRMS calcd for $C_{12}H_{18}NO_2S^+$: 240.1065 (M + H^+) found 240.1062 (M + H^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 2.63 (d, J = 7.2 Hz, 1H), 2.55−2.50 (m, 1H), 2.46 (s, 3H), 2.11 (d, J = 4.8 Hz, 1H), 1.45−1.38 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.4, 135.1, 129.6, 128.1, 46.27, 32.7, 30.1, 21.6, 19.6, 19.1; IR (NaCl plate) 3052, 2965, 1669, 1318 cm^{-1}.

(*S*)-*N*-(*p*-Toluenesulfonyl)-2-methylaziridine (15i). Synthesized from (*S*)-2-amino-1-propanol (2.3 mL, 30 mmol). Purification by silica gel chromatography (3:1 hexanes/ethyl acetate) afforded a white solid (4.39 g, 70% yield). All spectroscopic data were consistent with literature values.[50]

Synthesis of *N*-Acylaziridines by Deprotection and Reprotection of *N*-Tosylaziridines. In a flame-dried round-bottom flask equipped with a Teflon-coated magnetic stir bar, the sodium naphthalenide reagent was freshly prepared by vigorously stirring finely chopped sodium metal (1.0 equiv) and naphthalene (1.1 equiv) in dry 1,2-dimethoxyethane (1 M) under argon for 2−3 h at room temperature.[36]

A flame-dried round-bottom flask equipped with a Teflon-coated magnetic stir bar was charged with *N*-tosylaziridine (10 mmol) and 40 mL of 1,2-dimethoxyethane. The solution was cooled to −78 °C in a dry ice and acetone bath taking care that the solution did not freeze. The sodium naphthalenide reagent was added dropwise until the dark green end point was observed (~25 mL of stock 1 M solution). The reaction was quenched with 0.36 mL of water and slowly warmed to room temperature. An additional 100 mL of water was added, and the resulting mixture was extracted three times with 80 mL of ether. The organic layers were combined and dried over magnesium sulfate. The organics were filtered and concentrated by rotary evaporation to approximately 30 mL of solution. The flask was purged with argon and then cooled to 0 °C. The required *N*-hydroxysuccinimide benzoate (12 mmol) was added all at once to the stirred solution. The suspension was allowed to slowly warm to room temperature and stirred for a total of 15 h. After this time, the mixture was concentrated via rotary evaporation, affording the crude product, which was purified by silica gel chromatography to yield the desired *N*-acylaziridine.

***N*-(3,5-Dinitrobenzoyl)-7-azabicyclo[4.1.0]heptane (16a).** Purification by silica gel chromatography (4:1 hexanes/ethyl acetate) afforded a white solid (1.83 g, 63% yield). All spectroscopic data were consistent with literature values.[13]

***N*-(3,5-Dinitrobenzoyl)-6-azabicyclo[3.1.0]hexane (16b).** Purification by silica gel chromatography (4:1 hexanes/ethyl acetate) afforded a white solid (1.79 g, 65% yield). All spectroscopic data were consistent with literature values.[13]

***N*-(3,5-Dinitrobenzoyl)-2-*n*-hexylaziridine (16c).** Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a white solid (2.09 g, 65% yield). HRMS calcd for $C_{15}H_{19}N_3NaO_5^+$: 344.1217 (M + Na^+), found 344.1218 (M + Na^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.23 (t, J = 2.2 Hz, 1H), 9.17 (d, J = 2.0 Hz, 2H), 2.69−2.75 (m, 1H), 2.63 (d, J = 6.0 Hz, 1H), 2.38 (d, J = 4.0 Hz, 1H), 1.94−1.87 (m, 1H), 1.60−1.26 (m, 9H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 148.6, 136.9, 128.8, 121.9, 39.9, 32.3, 31.9, 31.6, 28.9, 26.4, 22.5, 14.0; IR (KBr plate) 3099, 1686, 1545, 1345 cm^{-1}.

***trans*-*N*-(3,5-Dinitrobenzoyl)-2,3-di-*n*-propylaziridine (16d).** Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a white solid (1.67 g, 52% yield). HRMS calcd for $C_{15}H_{19}N_3NaO_5^+$: 344.1217 (M + Na^+), found 344.1214 (M + Na^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (t, J = 2.2 Hz, 1H), 9.13 (d, J = 2.0 Hz, 2H), 2.70−2.67 (m, 2H), 1.72−1.64 (m, 2H), 1.53−1.46 (m, 4H), 1.25−1.17 (m, 2H), 0.96 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 148.6, 137.9, 128.5, 121.7, 45.3, 33.5, 20.4, 13.7; IR (KBr plate) 3103, 2875, 1675, 1345 cm^{-1}.

***cis*-*N*-(3,5-Dinitrobenzoyl)-2-*n*-butyl-3-methylaziridine (16e).** Purification by silica gel chromatography (7:1 hexanes/ethyl acetate) afforded a white solid (2.16 g, 67% yield). HRMS calcd for $C_{14}H_{17}N_3NaO_5^+$: 330.1060 (M + Na^+), found 330.1057 (M + Na^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (t, J = 2.1 Hz, 1H), 9.12 (d, J = 2.1 Hz, 2H), 2.77−2.70 (m, 2H), 1.85−1.75 (m, 1H), 1.71−1.62 (m, 1H), 1.55−1.39 (m, 7H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ175.1, 148.6, 137.0, 128.7, 121.8, 43.0, 39.2, 29.3, 27.1, 22.4, 13.9, 12.9; IR (KBr plate) 3088, 2937, 1677, 1336 cm^{-1}.

***cis*-*N*-(3,5-Dinitrobenzoyl)-2-(2-((*tert*-butyldiphenylsilyl)-oxy)ethyl)-3-ethylaziridine (16f).** Purification by silica gel chromatography (9:1 hexanes/ethyl acetate) afforded a white solid (2.62 g, 55% yield). HRMS calcd for $C_{29}H_{33}N_3NaO_6Si^+$: 570.2031 (M + Na^+), found 570.2027 (M + Na^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.19 (t, J = 2.2 Hz, 1H), 9.12 (d, J = 2.0 Hz, 2H), 7.67−7.63 (m, 4H), 7.47−7.35 (m, 6H), 3.91−3.82 (m, 2H), 2.92 (q, J = 6.4 Hz, 1H), 2.65 (q, J = 6.4 Hz, 1H), 2.11−2.03 (m, 1H), 2.00−1.91 (m, 1H), 1.85−1.74 (m, 1H), 1.69−1.58 (m, 1H), 1.07 (t, J = 7.5 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4, 148.5, 137.1, 135.5, 133.4, 129.7, 128.8, 127.7, 121.8, 61.5, 44.7, 41.2, 30.7, 26.8, 21.2, 19.1, 11.4; IR (KBr plate) 3102, 2931, 1684, 1344 cm^{-1}.

(*S*)-*N*-(3,5-Dinitrobenzoyl)-2-isobutylaziridine (16g). Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a white solid (1.55 g, 53% yield). HRMS calcd for $C_{13}H_{15}N_3NaO_5^+$: 316.0904 (M + Na^+), found 316.0903 (M + Na^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.23 (t, J = 2.2 Hz, 1H), 9.17 (d, J = 2.0 Hz, 2H), 2.78−2.75 (m, 1H), 2.64 (d, J = 6.0 Hz,1H), 2.39 (d, J = 4.0 Hz, 1H), 1.90−1.78 (m, 2H), 1.38−1.02 (m, 1H), 1.01 (d, J = 2.4 Hz, 3H), 1.00 (d, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 148.6, 136.9, 128.7, 121.9, 40.9, 38.5, 33.0, 26.9, 22.6, 22.4; IR (KBr plate) 3102, 1683, 1545, 1345 cm^{-1}.

(*S*)-*N*-(3,5-Dinitrobenzoyl)-2-isopropylaziridine (16h). Purification by silica gel chromatography (6:1 hexanes/ethyl acetate) afforded a white solid (1.70 g, 61% yield). HRMS calcd for $C_{12}H_{14}N_3O_5^+$: 280.0928 (M + H^+), found 280.0930 (M + H^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (t, J = 2.2 Hz, 1H), 9.15 (d, J = 2.0 Hz, 2H), 2.63−2.58 (m, 1H), 2.54 (d, J = 6.4 Hz, 1H), 2.46 (d, J = 4.0 Hz, 1H), 1.91−1.83 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 148.6, 136.9, 128.8, 121.9, 45.0, 31.1, 30.0, 19.9, 18.4; IR (KBr plate) 3094, 1671, 1545, 1342 cm^{-1}.

(*S*)-*N*-(3,5-Dinitrobenzoyl)-2-methylaziridine (16i). Purification by silica gel chromatography (5:1 hexanes/ethyl acetate) afforded a white solid (0.38 g, 15% yield). HRMS calcd for $C_{10}H_{10}N_3O_5^+$: 252.0615 (M + H^+), found 252.0615 (M + H^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.23 (t, J = 2.0 Hz, 1H), 9.17 (d, J = 2.4 Hz, 2H), 2.79−2.73 (m, 1H), 2.69 (d, J = 6.0 Hz, 1H), 2.35 (d, J = 3.6 Hz, 1H), 1.51 (d, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 148.7, 136.9, 128.7, 121.9, 35.8, 32.9, 17.6; IR (KBr plate) 3099, 1681, 1542, 1340 cm^{-1}.

***N*-(4-Nitrobenzoyl)-7-azabicyclo[4.1.0]heptane (17).** Purification by silica gel chromatography (8:1 hexanes/ethyl acetate) to afford a white solid (1.50 g, 61% yield). All spectroscopic data were consistent with literature values.[13]

***N*-(4-Trifluoromethylbenzoyl)-7-azabicyclo[4.1.0]heptane (18).** Purification by silica gel chromatography (3:1 hexanes/ethyl acetate) to afford a white solid (1.66 g, 57% yield). All spectroscopic data were consistent with literature values.[7]

***N*-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[4.1.0]-heptane (19).** Purification by silica gel chromatography (8:1 hexanes/ethyl acetate) to afford a white solid (1.99 g, 59% yield). All spectroscopic data were consistent with literature values.[14]

Synthesis of 16i from 2-Methylaziridine. To a flame-dried round-bottom flask equipped with a Teflon-coated magnetic stir bar were added THF (30 mL, 0.3 M) and 2-methylaziridine (0.8 mL, 10 mmol). The solution was cooled to 0 °C and 2,5-dioxopyrrolidin-1-yl 3,5-dinitrobenzoate (**9**) (3.71 g, 12 mmol) was added all at once. The ice bath was removed, and the mixture was stirred for 4 h. After this time, the suspension was diluted with 50 mL of ethyl acetate and washed two times with 30 mL of deionized water. The organics were

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then washed with brine and dried over magnesium sulfate. The mixture was filtered, and volatiles were removed by rotary evaporation. The product was purified by silica gel chromatography (loaded in toluene, 3:1 hexanes/ethyl acetate) affording a white solid (2.15 g, 86% yield).

Benzyl 2-Methylaziridine-1-carboxylate (20). Cbz-L-Alaninol (4.7 g, 22 mmol) and triphenylphosphine (6.9 g, 26.4 mmol) were added to a flame-dried round-bottom flask equipped with a Teflon-coated magnetic stir bar. The solids were dissolved in 74 mL of toluene (0.3 M). DIAD (5.2 mL, 26.4 mmol) was added dropwise with stirring. After 1 h, the mixture was concentrated via rotary evaporation. The product was purified by silica gel chromatography (loaded in toluene, 2:1 hexanes/ethyl acetate) affording a pale yellow oil (2.99 g, 71% yield). HRMS calcd for $C_{11}H_{13}NNaO_2^+$: 214.0844 (M + Na^+), found 214.0845 (M + Na^+). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.31 (m, 5H), 5.20−5.10 (m, 2H), 2.26−2.50 (m, 1H), 3.52 (d, J = 3.2 Hz, 1H), 1.97 (d, J = 4.0 Hz, 1H), 1.29 (d, J = 2.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 135.9, 128.6, 128.3, 128.2, 68.1, 33.9, 32.7, 17.5; IR (NaCl plate) 3033, 2969, 1718, 1298 cm^{-1}.

Synthesis of 16i; Deprotection and Reprotection of 20. Benzyl 2-methylaziridine-1-carboxylate (**20**) (2.8 g, 14.6 mmol) and 45 mL of tetrahydrofuran (0.33 M) were added to a flame-dried argon-purged round-bottom flask equipped with a Teflon-coated magnetic stir bar. Lindlar's catalyst (774 mg, 0.365 mmol) was added. The suspension was purged with hydrogen gas for 2 min and then stirred at room temperature for 18 h under a hydrogen atmosphere. The flask was purged with argon, and 2,5-dioxopyrrolidin-1-yl 3,5-dinitrobenzoate (**9**) (5.4 g, 17.5 mmol) was added all at once. After stirring for 3 h, the reaction mixture was filtered through Celite and rinsed with 80 mL of ethyl acetate. The solution was washed with 100 mL of deionized water, washed with brine, and dried over magnesium sulfate. The mixture was filtered, and volatiles were removed by rotary evaporation. The product was further purified by silica gel chromatography (4:1 hexanes/ethyl acetate) affording a white solid (2.37 g, 65% yield).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all purified compounds and HPLC data for compounds **16g−i**. 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.

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