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Organocatalyzed Aziridination of α-Branched Enals: Enantioselective Synthesis of Aziridines with a Quaternary Stereocenter

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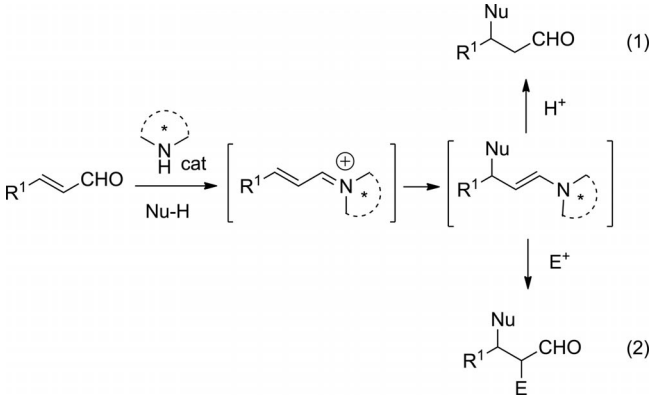
Organocatalytic access to *N*-tosylaziridines catalyzed by diarylprolinol trimethylsilyl ether [Ar = 3,5-$(CF_3)_2C_6H_3$] starting from different α-substituted-α,β-unsaturated aldehydes is described. The products were obtained in good yields (up to 86 %) and enantioselectivities (up to 90 % *ee*) and could rapidly be transformed under various conditions, including ring opening, to afford useful small molecules possessing not only the aziridine and aldehyde moieties but also other functionalities such as alcohol, acid, ester, or amino alcohol.

Introduction

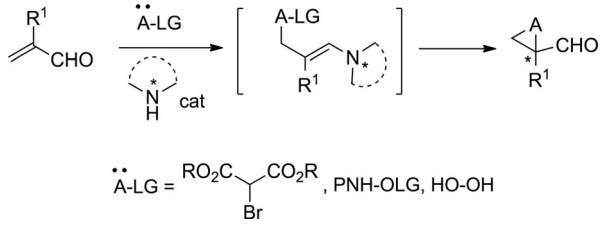
The use of chiral secondary amines as organocatalysts to activate α,β-unsaturated aldehydes has, over the last few years, witnessed considerable development[1,2] and numerous nucleophiles (electron-rich aromatics; malonates; hydrides; nitrogen, oxygen, and sulfur nucleophiles) have been successfully used in these asymmetric Michael-type additions [Scheme 1, Equation (1)]. Moreover, in the presence of a suitable electrophile, the intermediate enamine can also be trapped, intra- or intermolecularly, in a tandem iminium–enamine domino process [Scheme 1, Equation (2)].[3,4] This concept has initially been illustrated by developing highly efficient cyclopropanation,[5] epoxidation,[6] and aziridination[7] reactions.

Paradoxically, until very recently,[8] the use of α-branched α,β-unsaturated aldehydes (Scheme 2) in these reactions has been scarcely described, and sluggish enamine activation rates or even inert capacities are generally observed for secondary amino catalysts, which usually results in moderate stereoselectivity at the α-position.[9] Stimulated by a seminal paper by Melchiorre[8b] on the intermolecular aryl amination and thioamination of α-branched α,β-unsaturated aldehydes, we thus embarked on a program dealing with the



Scheme 1. Tandem iminium–enamine domino process.

functionalization of these α-branched enals in the presence of ambiphilic (bearing both nucleophilic and electrophilic parts) substrates such as bromomalonates, activated hydroxylamines, or hydrogen peroxide (Scheme 2).



Scheme 2. Functionalization of α-branched enals with ambiphilic A-LG substrates. P = protecting group.

We first examined the use of bromomalonates in these reactions with the aim to construct cyclopropanes bearing a chiral quaternary center.[8c] Previously described catalytic

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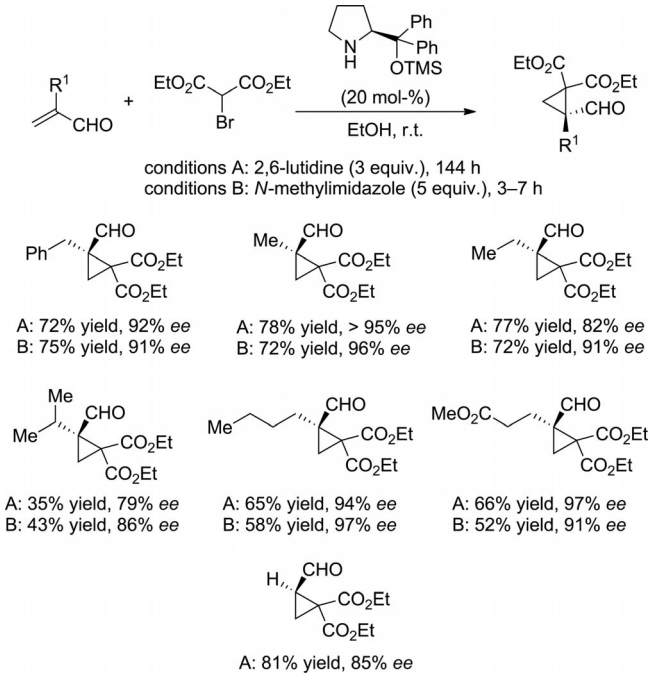
systems[5a,5b] proved in this case inefficient, leading to either low enantioselectivity (Córdova's conditions in the presence of triethylamine) or no conversion (Wang's conditions using 2,6-lutidine in dichloromethane). However, moving to ethanol at room temperature, in the presence of 2,6-lutidine, the corresponding cyclopropanes could be obtained in good yields and enantioselectivities. It should also be emphasized that replacing 2,6-lutidine with *N*-methylimidazole resulted in a considerably shorter reactions time (144 and 3 h, respectively; Scheme 3).

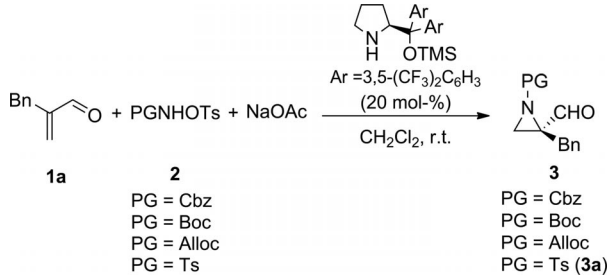


Scheme 3. Cyclopropanation of α-branched enals.[8c]

Starting from these initial results, we next planned to explore other ambiphilic substrates such as activated hydroxylamines. A recent publication by Córdova[8g] describing related experiments prompts us to disclose our findings in this area. Thus, in this paper, we report our efforts towards the enantioselective aziridination of α-substituted α,β-unsaturated aldehydes **1** with *N*-protected-*O*-(*p*-toluenesulfonyl)-hydroxylamines **2**.

Results and Discussion

Our investigations started by exploring the capacity of 2-benzylpropenal (**1a**) to undergo aziridination in the presence of different *N*-protected-*O*-(*p*-toluenesulfonyl)hydroxylamines **2** by using the conditions described by Jørgensen (Scheme 4).[10] When the nitrogen was protected as a carbamate such as Cbz, Boc, or Alloc,[11] the reaction proved to be very efficient as judged by a clean and complete conversion (the crude product was checked by ^{1}H NMR spectroscopy) to aziridines. However, we were unable to purify these compounds on silica gel (even if the silica gel was pretreated with Et_3N) or alumina, as any attempt led to extensive decomposition. Further transformations of crude carbamate-protected aziridines either by $NaBH_4$ reduction or Horner–Wadsworth–Emmons reactions also proved to give, in our hands, extensive decomposition. Indeed, it has been previously shown that carbamate *N*-protected carboxylate aziridines are sensitive towards ring-opening reactions in the presence of different nucleophiles,[12] which could be explained through anchimeric assistance of the carbamate.[13] To avoid this problem of stability, other nitrogen protecting groups were explored.

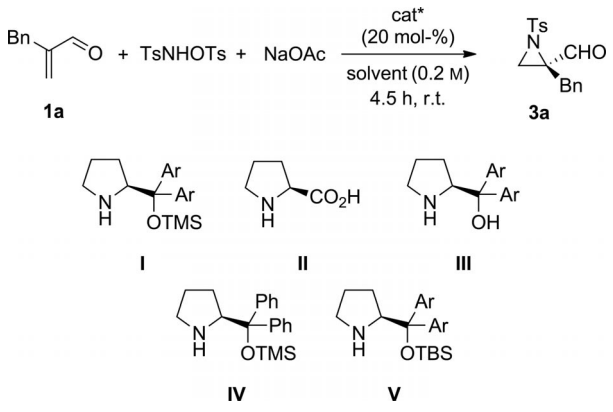


Scheme 4. Aziridination using different *N*-protected-*O*-(*p*-toluenesulfonyl)hydroxylamines **2**.

Fortunately, moving from carbamates to sulfonamide (TsNHOTs) afforded stable carbaldehyde **3a** in excellent yield (95%) and moderate enantioselectivity (67%). On the basis of this preliminary result, we then decided to screen different catalysts and solvents to optimize the reaction conditions and to improve the selectivities (Table 1). As anticipated, the enantioselectivity was very poor when proline (**II**) or trifluoromethyl-substituted diaryl prolinol **III** was used as the catalyst (Table 1, Entries 2 & 3). Hayashi–Jørgensen catalyst **IV** did not improve the result in terms of selectivity (Table 1, Entry 4). Diaryl prolinol silyl ether **I** was found to be the most efficient catalyst (Table 1, Entry 1). The reaction was not efficient in either polar solvents such as MeCN, THF, or DMF (Table 1, Entries 6–8) or in protic polar solvent such as *i*PrOH (Table 1 as observed when the reaction was conducted in toluene (60% yield, 70%*ee*; Table 1, Entry 11). We then tried to catalyze the reaction with sterically hindered catalyst **V**,[14] but we did not observe any enhancement in terms of reactivity or selectivity (Table 1, Entry 12). Finally, the best result was obtained when the reaction was run at 0 °C in toluene. In this case, carbaldehyde **3a** was isolated in 72% yield and 80%*ee* (Table 1, Entry 13).

With these conditions in hand, we then turned our attention to the scope of the aziridination reaction using various aldehydes[15] (Table 2). All reactions were very clean and *N*-tosylaziridines were obtained in good yields (69–86%) and acceptable enantioselectivities (up to 90%*ee*). Different alkyl groups at the α-position of the aldehyde (R = Bn, Me, Pent, and *i*Pr) were well tolerated (Table 2, Entries 1–4). Functionalized aldehydes can also efficiently participate in these reactions (Table 2, Entries 5 & 6). A terminal olefin side chain at the α-position can take part in the transformation with a good 84%*ee* and 82% yield (Table 2, Entry 5). A bromide-substituted chain was also a suitable substrate to afford the corresponding *N*-tosylaziridine **3f** in 78% yield and 79%*ee* (Table 2, Entry 6).

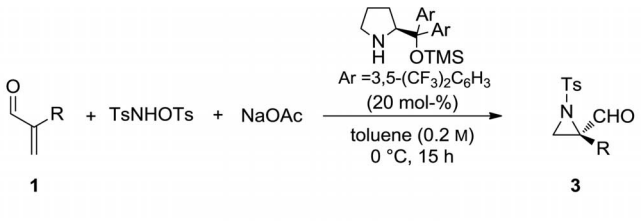
Table 1. Catalyst and solvent screening.[a]

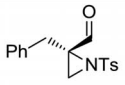
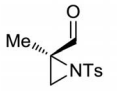
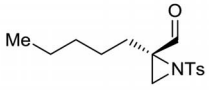
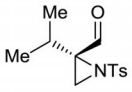
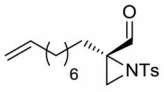
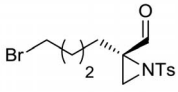


Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**I**	CH_2Cl_2	95	67
2	**II**	CH_2Cl_2	56	7
3	**III**	CH_2Cl_2	56	9
4	**IV**	CH_2Cl_2	82	37
5	**I**	$CHCl_3$	95	67
6	**I**	CH_3CN	82	28
7	**I**	THF	66	26
8	**I**	DMF	63	17
9	**I**	*i*PrOH	69	38
10	**I**	hexane	63	63
11	**I**	toluene	60	70
12	**V**	toluene	55	70
13[d]	**I**	toluene	72	80

[a] Reaction conditions: 2-benzylpropenal (0.50 mmol), TsNHOTs (0.25 mmol), NaOAc (0.75 mmol), catalyst (0.05 mmol), and solvent (1.25 mL) at r.t. for 4.5 h. See the Experimental Section for details. Ar = 3,5-$(CF_3)_2C_6H_3$. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC analysis after conversion of the aldehyde into its corresponding unsaturated ester. [d] Reaction run at 0 °C over 15 h.

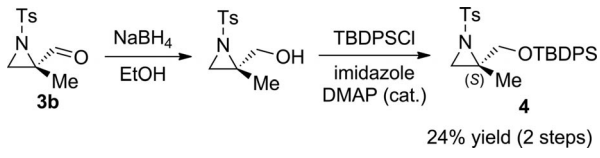
Table 2. Aldehyde scope of organocatalytic aziridination.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **3a**	72	80[d]
2	 **3b**	70	90[d]
3	 **3c**	86	87
4	 **3d**	69	76
5	 **3e**	82	84
6	 **3f**	78	79

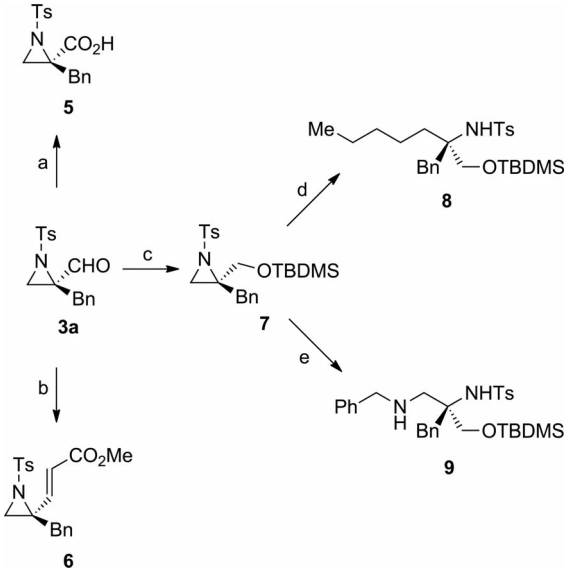
[a] Reaction conditions: aldehyde (0.50 mmol), TsNHOTs (0.25 mmol), NaOAc (0.75 mmol), catalyst (0.05 mmol), and solvent (1.25 mL) at 0 °C for 15 h. See the Experimental Section for details. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC analysis. [d] The *ee* was determined by chiral-phase HPLC analysis after conversion of the aldehyde into its corresponding unsaturated ester (see the Experimental Section for details).

Our next goal was to determine the absolute configuration of aziridines **3**. Aziridine **3b** was thus converted into known aziridine **4** by first converting the aldehyde into the primary alcohol and then protecting it as a TBDPS silyl ether (Scheme 5). The optical rotation of compound **4** {$[\alpha]_D^{20}$ = –28 (*c* = 1, CH_2Cl_2)} was found to be in good agreement with that reported value {$[\alpha]_D^{26}$ = –25.8 (*c* = 1.1, CH_2Cl_2)}.[16] The absolute configuration of the quaternary stereocenter formed during this sequence was determined to be (*S*), in agreement with the absolute configuration observed with cyclopropanes (Scheme 3).



Scheme 5. Determination of the absolute configuration.

To illustrate the synthetic scope of this methodology, we modified resulting *N*-tosylaziridine aldehyde **3a**, as shown in Scheme 6. The aldehyde moiety was oxidized under smooth conditions to afford *N*-protected cyclic amino acid **5** (91% yield), or it was transformed into compound **6** through Wittig olefination (78% yield), or it was reduced and protected as a silyl enol ether to give rise to fully protected cyclic amino alcohol **7** (77% yield from **3a**). To synthesize quaternary α-amino acids,[17] aziridine **5** was treated with the higher order cuprate $Bu_2CuCNLi_2$. Unfortunately, the corresponding amino acid was not observed. In a second attempt, aziridine **7** was treated with the higher order cuprate $Bu_2CuCNLi_2$, and opening product **8** (29% yield from **3a**) was obtained. The ring opening of aziridine **7** was also effective with a nitrogen nucleophile to give protected diamino alcohol **9** (66% yield from **3a**).[16]



Scheme 6. Reagents and conditions: (a) KH_2PO_4, $NaClO_2$, H_2O_2, MeOH/MeCN/H_2O (1:1:1), 0 °C to r.t., 2 h, 91%; (b) Ph_3PCHCO_2Me, THF, 0 °C to r.t., 2 h, 78%; (c) 1. $NaBH_4$, EtOH, 0 °C, 15 min, 89%; 2. TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., overnight, 87%; (d) $Bu_2CuCNLi_2$, THF, –78 °C to r.t., overnight, 38%; (e) $BnNH_2$, reflux, 42 h, 85%. See the Experimental Section for details.

Conclusions

We have described straightforward organocatalytic access to *N*-tosylaziridines derived from α-branched enals. The transformation takes place through iminium/enamine catalysis in the presence of diarylprolinol trimethylsilyl ether **I** [Ar = 3,5-$(CF_3)_2C_6H_3$] and gives rise to aziridines bearing a quaternary stereocenter in good yields (up to 86%) and enantioselectivities (up to 90%*ee*). Preliminary and promising studies on the ring opening of the obtained aziridines were realized, which allowed us to prepare useful small molecules possessing not only the aziridine and aldehyde moieties but also other functionalities (Scheme 6). Undoubtedly, all these possibilities provide versatile synthetic tools for the asymmetric synthesis of more complex molecules, and further work is aimed to this purpose within our research groups.

Experimental Section

General Information: Unless otherwise stated all commercial materials were used without further purification. TLC analysis of all reactions was performed on silica gel 60 F254 TLC plates and revealed at 254 nm UV light and/or with phosphomolybdic acid stain. Flash chromatography was carried out on silica gel 60 A (35–70 μm). ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz or 300 and 75 MHz, respectively. Chemical shifts (δ) for ^1H and ^{13}C are given in ppm relative to residual signal of the solvent ($CHCl_3$). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br. s, broad signal. High-resolution mass spectra were obtained with a Waters XevoQTOF. HPLC analysis was performed by using chiral AS-H columns with *i*PrOH/heptane as the eluent. HPLC traces were compared with racemic samples obtained by using a mixture of (*R*)- and (*S*)-diphenylprolinol trimethylsilyl ether as catalyst. The α-methylene aldehydes were prepared according to the procedure described by Pihko.[15] 4-Methyl-*N*-(tosyloxy)benzenesulfonamide (TsNHOTs) was synthesized following Jørgensen's procedure.[10a]

General Procedure for the Organocatalyzed Asymmetric Aziridination: To a solution of α-substituted α,β-unsaturated aldehyde **1** (0.50 mmol, 2.00 equiv.) in toluene (1.25 mL) was successively added TsNHOTs (85.4 mg, 0.25 mmol, 1.00 equiv.), NaOAc (262 mg, 0.75 mmol, 3.00 equiv.), and organocatalyst **I** (30.0 mg, 0.05 mmol, 20 mol-%). The reaction mixture was rapidly cooled to 0 °C and stirred for 15 h. The reaction mixture was then filtered through a pad of Celite (EtOAc), and the solvent was evaporated. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 6:1) to afford aziridines **3a**–**f**.

(*S*)-2-Benzyl-1-tosylaziridine-2-carbaldehyde (3a): Yield: 61.0 mg (72%); HPLC analysis was not performed on the aldehyde but on its corresponding unsaturated ester (see below, compound **6**). $[\alpha]_D^{20}$ = +56 (*c* = 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.25–7.18 (m, 5 H), 3.28 (s, 2 H), 3.19 (s, 1 H), 2.64 (s, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.2, 145.0, 136.0, 135.5, 130.0, 129.9, 128.4, 127.7, 127.0, 56.0, 38.1, 33.8, 21.8 ppm. FTIR: $\tilde{\nu}$ = 2927, 2856, 1724, 1593, 1313, 1274, 1156, 1093, 986, 876, 812, 690 cm^{-1}. HRMS: calcd. for $C_{17}H_{17}NO_3SNa$ $[M + Na]^+$ 338.0827; found 338.0818.

(*S*)-2-Methyl-1-tosylaziridine-2-carbaldehyde (3b): Yield: 42.0 mg (70%); HPLC analysis was not performed on the aldehyde but on its corresponding unsaturated ester (see below). $[\alpha]_D^{20}$ = +36 (*c* = 1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.07 (s, 1 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 2.88 (s, 1 H), 2.83 (s, 1 H), 2.45 (s, 3 H), 1.68 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.6, 145.1, 136.4, 129.9, 127.8, 52.1, 37.9, 21.8, 12.8 ppm. FTIR: $\tilde{\nu}$ = 2919, 2848, 1720, 1590, 1321, 1160, 1120, 880, 832, 686 cm^{-1}. HRMS: calcd. for $C_{11}H_{14}NO_3S$ $[M + H]^+$ 240.0694; found 240.0685.

(*R*,*E*)-Methyl 3-(2-Benzyl-1-tosylaziridin-2-yl)acrylate: To a stirred solution of **3b** (30.0 mg, 0.12 mmol) in THF (1.20 mL) at 0 °C was added methyl (triphenylphosphoranylidene)acetate (50.0 mg, 0.15 mmol). The mixture was warmed to room temperature and stirred for 2 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3×). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 6:1) to afford the desired compound. Yield: 76%; 90%*ee*; HPLC (AD-H column, heptane/*i*PrOH = 80:20, flow rate = 0.8 mL/min, 30 °C, λ = 260 nm): t_R = 9.1 (minor), 10.1 (major) min. $[\alpha]_D^{20}$ = –26 (*c* = 1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.90 (d, *J* = 15.7 Hz, 1 H), 6.07 (d, *J* = 15.7 Hz, 1 H), 3.74 (s, 3 H), 2.74 (s, 1 H), 2.61 (s, 1 H), 2.43 (s, 3 H), 1.72 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.1, 146.5, 144.5, 137.1, 129.7, 127.6, 123.5, 51.9, 47.9, 42.4, 21.7, 18.1 ppm. FTIR: $\tilde{\nu}$ = 2923, 1724, 1653, 1592, 1323, 1277, 1161, 822, 706, 674 cm^{-1}. HRMS: calcd. for $C_{14}H_{18}NO_4S$ $[M + H]^+$ 296.0957; found 296.0970.

(*S*)-2-Pentyl-1-tosylaziridine-2-carbaldehyde (3c): Yield: 68.4 mg (86%); 87%*ee*; HPLC (AS-H column, heptane/*i*PrOH = 95:5, flow rate = 0.9 mL/min, 30 °C, λ = 260 nm): t_R = 13.8 (minor), 16.8 (major) min. $[\alpha]_D^{20}$ = +32 (*c* = 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 7.84 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* =

8.3 Hz, 2 H), 3.12 (s, 1 H), 2.69 (s, 1 H), 2.45 (s, 3 H), 2.10–2.00 (m, 1 H), 1.74–1.64 (m, 1 H), 1.46–1.37 (m, 2 H), 1.30–1.25 (m, 4 H), 0.89–0.84 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 144.9, 136.3, 129.9, 127.7, 56.6, 38.7, 31.8, 28.7, 25.5, 22.5, 21.8, 14.0 ppm. FTIR: $\tilde{\nu}$ = 2954, 2927, 2860, 1716, 1321, 1278, 1156, 1136, 1081, 841, 809, 706, 679 cm^{-1}. HRMS: calcd. for $C_{15}H_{21}NO_3SNa$ [M + Na]$^+$ 318.1140; found 318.1137.

(*S*)-2-Isopropyl-1-tosylaziridine-2-carbaldehyde (3d): Yield: 50.0 mg (69%); 76%*ee*; HPLC (AS-H column, heptane/*i*PrOH = 95:5, flow rate = 0.9 mL/min, 30 °C, λ = 260 nm): t_R = 18.3 (minor), 20.9 (major) min. $[\alpha]_D^{20}$ = +64 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.50 (s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 3.20 (s, 1 H), 2.66 (s, 1 H), 2.45 (s, 3 H), 2.40 (quint., J = 6.9 Hz, 1 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 144.9, 136.4, 129.9, 127.7, 60.6, 38.0, 26.9, 21.8, 18.8, 17.4 ppm. FTIR: $\tilde{\nu}$ = 2967, 2923, 2872, 1716, 1317, 1160, 1085, 836, 702, 651 cm^{-1}. HRMS: calcd. for $C_{13}H_{17}NO_3SNa$ [M + Na]$^+$ 290.0827; found 290.0821.

(*S*)-2-(Non-8-enyl)-1-tosylaziridine-2-carbaldehyde (3e): Yield: 82.8 mg (82%); 79%*ee*; HPLC (AS-H column, heptane/*i*PrOH = 80:20, flow rate = 0.8 mL/min, 30 °C, λ = 260 nm): t_R = 7.8 (minor), 8.7 (major) min. $[\alpha]_D^{20}$ = +21 (c = 1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 5.90–5.70 (m, 1 H), 5.03–4.90 (m, 2 H), 3.13 (s, 1 H), 2.68 (s, 1 H), 2.45 (s, 3 H), 2.13–1.98 (m, 3 H), 1.76–1.62 (m, 1 H), 1.28 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.8, 144.9, 139.2, 136.4, 129.9, 127.7, 114.3, 56.6, 38.7, 33.9, 29.6, 29.3, 29.1, 29.0, 28.7, 25.8, 21.8 ppm. FTIR: $\tilde{\nu}$ = 2927, 2855, 1724, 1331, 1305, 1161, 1088, 845, 814, 707, 687 cm^{-1}. HRMS: calcd. for $C_{20}H_{31}NO_4SNa$ [M + MeOH + Na]$^+$ 404.1871; found 404.1864.

(*S*)-2-(4-Bromobutyl)-1-tosylaziridine-2-carbaldehyde (3f): Yield: 81.1 mg (78%); 79%*ee*; HPLC (AS-H column, heptane/*i*PrOH = 80:20, flow rate = 0.8 mL/min, 30 °C, λ = 260 nm): t_R = 16.4 (minor), 19.6 (major) min. $[\alpha]_D^{20}$ = +9 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 7.86 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 8.3 Hz, 2 H), 3.39 (t, J = 6.7 Hz, 2 H) 3.17 (s, 1 H), 2.70 (s, 1 H), 2.46 (s, 3 H), 2.19–2.11 (m, 1 H), 1.94–1.85 (m, 2 H), 1.71–1.56 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 145.1, 136.1, 130.0, 127.7, 56.2, 38.9, 33.3, 32.5, 27.9, 24.5, 21.8 ppm. FTIR: $\tilde{\nu}$ = 2923, 2860, 1720, 1321, 1282, 1156, 1128, 844, 809, 682 cm^{-1}. HRMS: calcd. for $C_{15}H_{22}BrNO_4SNa$ [M + MeOH + Na]$^+$ 414.0351; found 414.0346.

(*S*)-2-*tert*-Butyldiphenylsilanylmethyl-2-methyl-1-(toluene-4-sulfonyl)aziridine (4): To a stirred solution of **3b** (70.0 mg, 0.29 mmol) in EtOH (2.90 mL) at 0 °C was added $NaBH_4$ (10.0 mg, 0.26 mmol). The reaction mixture was stirred for 15 min, quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alcohol was used in the next step without further purification. To a stirred solution of crude (*S*)-(2-methyl-1-tosylaziridin-2-yl)methanol (70.0 mg, 0.29 mmol) in CH_2Cl_2 (1.50 mL) at 0 °C was added, successively, imidazole (30.0 mg, 0.44 mmol), DMAP (7.00 mg, 0.06 mmol), and TBDPSCl (150 μL, 0.58 mmol). The mixture was stirred for 3 h at 0 °C. Then, the reaction mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/EtOAc, 95:5) to afford desired compound **4** (33.0 mg, 24% over two steps). $[\alpha]_D^{20}$ = –28 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.2 Hz, 2 H), 7.66–7.62 (m, 4 H), 7.44–7.26 (m, 8 H), 3.72 (d, J = 10.9 Hz, 1 H), 3.59 (d, J = 10.9 Hz, 1 H), 2.61 (s, 1 H), 2.42 (s, 3 H), 2.27 (s, 1 H), 1.76 (s, 3 H), 1.02 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.9, 137.9, 135.7, 135.7, 133.2, 129.9, 129.9, 129.6, 127.9, 127.5, 68.0, 50.5, 38.6, 26.8, 21.7, 19.4, 15.5 ppm. Data are in accordance with those previously reported.[16]

(*S*)-2-Benzyl-1-tosylaziridine-2-carboxylic Acid (5): To a stirred solution of **3a** (219 mg, 0.69 mmol) in MeOH/MeCN/H_2O (1:1:1, 10.5 mL) at 0 °C was added successively KH_2PO_4 (376 mg, 2.76 mmol), $NaClO_2 \cdot 1H_2O$ (240 mg, 2.21 mmol), and H_2O_2 (30% w/w in H_2O, 3.50 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was then acidified to pH 3 with HCl (1 N), cooled to 0 °C, and treated with a saturated aqueous solution of Na_2SO_3. The mixture was then re-acidified to pH 3 with HCl (1 N) and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford desired compound **5** (208 mg, 91%). $[\alpha]_D^{20}$ = +17.7 (c = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.29–7.23 (m, 5 H), 3.70 (d, J = 14.6 Hz, 1 H), 3.35 (d, J = 14.6 Hz, 1 H), 3.03 (s, 1 H), 2.83 (s, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9, 144.9, 136.6, 135.8, 129.9, 129.5, 128.7, 127.9, 127.3, 50.8, 37.6, 35.2, 21.8 ppm. FTIR: $\tilde{\nu}$ = 3283, 3029, 2957, 2926, 1747, 1719, 1595, 1449, 1321, 1286, 1154, 1082, 905 cm^{-1}. HRMS: calcd. for $C_{17}H_{17}NO_4SNa$ [M + Na]$^+$ 354.0776; found 354.0771.

(*R*,*E*)-Methyl 3-(2-Benzyl-1-tosylaziridin-2-yl)acrylate (6): To a stirred solution of **3a** (70.0 mg, 0.22 mmol) in THF (2.20 mL) at 0 °C was added methyl (triphenylphosphoranylidene)acetate (90.0 mg, 0.26 mmol). The mixture was warmed to room temperature and stirred for 2 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3×). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 6:1) to afford desired compound **6**. Yield: 78%; 80%*ee*; HPLC (AS-H column, heptane/*i*PrOH = 80:20, flow rate = 0.8 mL/min, 30 °C, λ = 260 nm): t_R = 16.4 (minor), 19.6 (major) min. $[\alpha]_D^{20}$ = +4.3 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 7.9 Hz, 2 H), 7.28–7.19 (m, 5 H), 7.08 (d, J = 15.8 Hz, 1 H), 6.07 (d, J = 15.6 Hz, 1 H), 3.71 (s, 3 H), 3.36–3.24 (m, 2 H), 2.76 (s, 1 H), 2.72 (s, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 144.6, 143.5, 136.9, 135.7, 129.8, 129.5, 128.7, 127.8, 127.2, 124.7, 51.9, 50.9, 41.0, 38.8, 21.8 ppm. FTIR: $\tilde{\nu}$ = 3061, 2943, 2907, 2848, 1704, 1657, 1591, 1491, 1436, 1317, 1271, 1148, 978, 848, 809, 674, 643 cm^{-1}. HRMS: calcd. for $C_{20}H_{21}NO_4SNa$ [M + Na]$^+$ 394.1089; found 394.1081.

(*S*)-2-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-1-tosylaziridine (7): To a stirred solution of **3a** (218 mg, 0.69 mmol) in EtOH (6.90 mL) at 0 °C was added $NaBH_4$ (26.0 mg, 0.69 mmol). The reaction mixture was stirred for 15 min, quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/EtOAc, 3:1) to afford the desired alcohol (195 mg, 89%). $[\alpha]_D^{20}$ = +86 (c = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 7.30–7.21 (m, 5 H), 3.98 (dd, J = 13.3, 9.4 Hz, 1 H), 3.80 (d, J = 13.1, 5.2 Hz, 1 H), 3.48 (d, J = 14.1 Hz, 1 H), 2.94 (d, J = 14.1 Hz, 1 H), 2.77–2.72 (m, 1

H), 2.72 (s, 1 H), 2.52 (s, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.4, 137.3, 136.3, 129.8, 129.8, 128.7, 127.4, 127.1, 62.5, 55.7, 38.4, 38.0, 21.8 ppm. FTIR: $\tilde{\nu}$ = 3514, 3026, 2918, 1598, 1495, 1453, 1317, 1304, 1148, 1082, 978, 843 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}NO_3SNa$ [M + Na]$^+$ 340.0983; found 340.1000. To a stirred solution of (*S*)-(2-benzyl-1-tosylaziridin-2-yl)methanol (181 mg, 0.57 mmol) in CH_2Cl_2 (5.70 mL) at 0 °C was added, successively, imidazole (155 mg, 2.28 mmol) and TBDMSCl (103 mg, 0.68 mmol). The mixture was allowed to warm to room temperature and stirred for 15 h. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 10:1) to afford desired compound **7** (214 mg, 87%). $[\alpha]_D^{20}$ = +6.0 (*c* = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.28–7.22 (m, 5 H), 3.80 (d, *J* = 11.0 Hz, 1 H), 3.61 (d, *J* = 11.0 Hz, 1 H), 3.28 (d, *J* = 14.1 Hz, 1 H), 3.20 (d, *J* = 14.0 Hz, 1 H), 2.59 (s, 1 H), 2.49 (s, 1 H), 2.43 (s, 3 H), 0.87 (s, 9 H), 0.02 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.0, 137.8, 137.1, 129.8, 129.6, 128.5, 127.6, 126.9, 63.3, 54.7, 37.4, 36.5, 25.9, 21.7, 18.4, –5.3, –5.3 ppm. FTIR: $\tilde{\nu}$ = 3029, 2952, 2925, 2883, 1598, 1495, 1232, 1250, 1157, 1093, 983, 832, 773, 702, 683, 561 cm^{-1}. HRMS: calcd. for $C_{23}H_{33}NO_3SSiNa$ [M + Na]$^+$ 454.1848; found 454.1826.

(*R*)-*N*-[2-Benzyl-1-(*tert*-butyldimethylsilyloxy)heptan-2-yl]-4-methylbenzenesulfonamide (8): All glassware and equipment were oven-dried and flushed with argon prior to use. In a 15-mL Schlenk tube, Cu^{I}CN (32.0 mg, 0.36 mmol) was introduced and heated under vacuum to thoroughly and then purged with argon. Freshly distilled THF (0.40 mL) was added, and the solution was cooled to –78 °C. *n*BuLi (1.60 M in hexanes, 490 μL, 0.78 mmol) was added dropwise to the solution. The resulting mixture was stirred at –78 °C for 30 min and warmed to room temperature over 30 min. The reaction mixture was cooled to –78 °C, and a solution of **7** (65.0 mg, 0.15 mmol) in THF (0.40 mL) was added dropwise. The solution was stirred for 4 h at –78 °C and slowly warmed to room temperature overnight. The reaction was quenched with H_2O (2.00 mL), filtered through a pad of Celite (EtOAc), acidified to pH 3 with an aqueous solution of citric acid (5%), and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 8:1) to afford desired compound **8** (28.0 mg, 38%). $[\alpha]_D^{20}$ = +3.4 (*c* = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2 H), 7.30–7.21 (m, 7 H), 4.61 (s, 1 H), 3.36 (d, *J* = 9.8 Hz, 1 H), 3.32 (d, *J* = 9.6 Hz, 1 H), 2.95 (d, *J* = 13.5 Hz, 1 H), 2.90 (d, *J* = 13.5 Hz, 1 H), 2.41 (s, 3 H), 1.65–1.57 (m, 1 H), 1.50–1.41 (m, 1 H), 1.21–0.98 (m, 6 H), 0.92 (s, 9 H), 0.80 (t, *J* = 6.7 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.0, 140.8, 136.7, 130.9, 129.5, 128.3, 127.0, 126.8, 65.3, 63.7, 41.3, 33.6, 32.3, 26.0, 23.3, 22.7, 21.6, 18.3, 14.2, –5.3, –5.4 ppm. FTIR: $\tilde{\nu}$ = 3276, 2953, 2925, 2854, 1597, 1462, 1321, 1250, 1155, 1092, 832, 774, 754, 699, 660 cm^{-1}. HRMS: calcd. for $C_{27}H_{44}NO_3SSi$ [M + H]$^+$ 490.2811; found 490.2814.

(*S*)-*N*-[2-Benzyl-1-(benzylamino)-3-(*tert*-butyldimethylsilyloxy)-propan-2-yl]-4-methylbenzenesulfonamide (9): To a stirred solution of **7** (30.0 mg, 0.07 mmol) in THF (2.30 mL) at 0 °C was added benzylamine (40.0 μL, 0.35 mmol). The resulting mixture was heated at reflux for 42 h, and the solvent was evaporated in vacuo. Purification was performed by column chromatography on silica gel (pentane/Et_2O, 4:1) to afford desired compound **9** (32.0 mg, 85%). $[\alpha]_D^{20}$ = +12.4 (*c* = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.1 Hz, 2 H), 7.32–7.18 (m, 12 H), 5.30 (br. s, 1 H), 3.58 (s, 2 H), 3.53 (d, *J* = 9.8 Hz, 1 H), 3.45 (d, *J* = 9.8 Hz, 1 H), 3.05 (d, *J* = 13.3 Hz, 1 H), 2.92 (d, *J* = 13.3 Hz, 1 H), 2.65 (s, 2 H), 2.38 (s, 3 H), 1.58 (br. s, 1 H), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.2, 140.7, 140.1, 136.4, 130.8, 129.7, 128.4, 128.3, 128.1, 127.0, 126.8, 126.8, 65.5, 63.3, 54.2, 52.1, 39.8, 26.0, 21.6, 18.2, –5.4, –5.4 ppm. FTIR: $\tilde{\nu}$ = 3270, 2954, 2926, 2853, 1599, 1492, 1320, 1252, 1154, 1091, 983, 835, 775, 701, 663 cm^{-1}. HRMS: calcd. for $C_{30}H_{43}N_2O_3SSi$ [M + H]$^+$ 539.2764; found 539.2786.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra of new compounds and chiral HPLC traces for determination of the enantiomeric excess values for aziridines **3a**–**f**.

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