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Organolithium-Induced Alkylative Ring Opening of Aziridines: Synthesis of Unsaturated Amino Alcohols and Ethers

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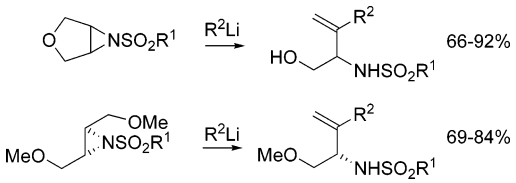
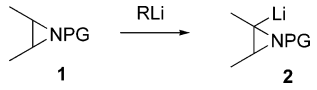


Organolithium-induced alkylative ring opening of *N*-sulfonyl-protected aziridinyl ethers is described. The reactions were efficiently carried out with a variety of organolithiums, providing a promising new strategy to unsaturated amino alcohols and ethers. *Cis*- and *trans*-1,4-dimethoxybut-2-ene-derived aziridines were prepared, and their propensity to undergo organolithium- induced alkylative desymmetrization is detailed. Use of a single enantiomer of the latter aziridine provides a route to enantiopure unsaturated amino ethers.

Introduction

On exposure to strong bases, suitably *N*-protected aziridines **1** (Scheme 1, PG = protecting group) can, like their more thoroughly investigated epoxide cousins, undergo α-metalation (typically lithiation) of the three-membered ring.[1] In the absence of an additional anion-stabilizing substituent, the resulting ring-metalated (carbenoid) species **2**[2] are rather unstable, although under certain conditions they can be trapped with electrophiles.[3] The instability of these species mainly arises from the fact that they possess a nitrogen (or oxygen) leaving group at the site of metalation, whose α-elimination would also relieve ring strain. Some cycloalkene-derived 2,3-disubstituted aziridines have previously been shown on lithiation to preferentially react by

SCHEME 1. Aziridine α-Lithiation



intramolecular C−H insertion,[4] and we have recently utilized the carbenoid character of lithiated terminal aziridines in synthetically useful dimerizations[5] and (with unsaturated substrates) intramolecular cyclopropanations.[6]

The electrophilicity[2] of α-lithiated aziridines (and epoxides) also makes them potentially susceptible to insertion by an organolithium (typically, but not always, by an excess of the base used in the initial deprotonation). With epoxides **3** this is now a reasonably well-studied pathway to alkenes **4** (Scheme 2),[7] and as originally demonstrated by Mioskowski and co-workers, loss of the oxygen atom (as Li_2O) derived from the

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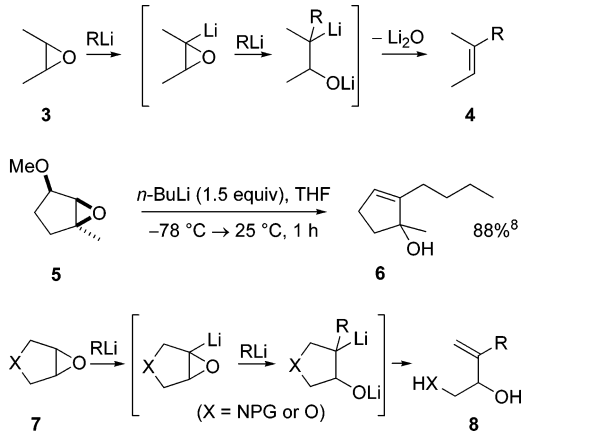
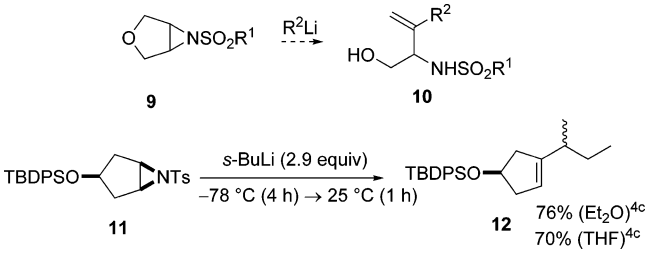
SCHEME 2. Alkenes from Epoxides Using Organolithiums



three-membered heterocycle can be avoided if a suitably positioned (and better) leaving group is present in the substrate (e.g., **5** → **6**).[8] We have previously developed this process further with epoxides of 2,5-dihydro-pyrrole (and -furan) **7** (PG = protecting group), in which the leaving group involved in alkene formation is not lost from the product, resulting in routes to 3-substituted 1-aminobut-3-en-2-ols (and but-3-ene-1,2-diols) **8**.[9]

Arising from these latter studies, we considered whether the corresponding dihydrofuranyl aziridines **9** might react similarly to provide synthetically valuable[10] unsaturated 1,2-amino alcohols **10** (Scheme 3); the latter are regioisomeric to the amino alcohols **8** (X = NPG) previously obtainable, with the additional potential of accessing α-amino acids following oxidation.[11] In the present paper, we detail our studies on the scope of this process, which provides a versatile route to unsaturated 1,2-amino alcohols. At the outset of our investigations there was a single example of insertion of an organolithium into an α-lithiated (tosyl-protected) aziridine (Scheme 3).[4c] However, in that case alkene generation occurred from aziridine **11** with concomitant loss of the valuable amino functionality (as $TsNH_2$) to give cyclopentene **12**. Following our initial communication in this area,[12] O'Brien and co-workers subsequently reported related chemistry to give substituted cyclic unsaturated amines, following adaptation of the Mioskowski-type process to aziridines.[13]

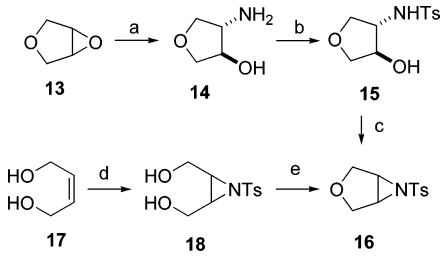
SCHEME 3. Alkenes from Aziridines Using Organolithiums



Results and Discusion

To begin to examine our above strategy to unsaturated amino alcohols **10**, we required access to suitably protected aziridines **9**. Both tosyl and acid-labile *tert*-butylsulfonyl (Bus)[14] nitrogen protection have proven useful in many of our other base-induced transformations of epoxides and aziridines,[3b,5,6,9] and the corresponding protected aziridines were examined in the current chemistry. Although the tosyl-protected aziridine **16** (Scheme 4) could not be directly prepared by Sharpless aziridination[15] of commercially available 2,5-dihydrofuran, it could be obtained in three steps by ring opening of the corresponding epoxide **13**[16] using aqueous ammonium hydroxide to give the amino alcohol **14**[17] (95%), which was subsequently N-tosylated (89%) and the resulting hydroxy sulfonamide **15** cyclized (92%) under Mitsunobu conditions[18] with diisopropyl azodicarboxylate (DIAD). A more concise (two-step) approach, which also used a cheaper starting material, proceeded from *cis*-but-2-ene-1,4-diol (**17**) by aziridination[15] (54%),[19] followed by Mitsunobu ring closure of the resulting aziridine diol **18**[20] (68%).

SCHEME 4. Synthesis of NTs Aziridine 16[a]



[a] Reagents and conditions: (a) NH_4OH (35% in H_2O, 13 equiv), *i*-PrOH, 80 °C, 12 h (95%); (b) TsCl (1.1 equiv), Et_3N (2 equiv), MeCN, 0 °C, 2 h (89%); (c) DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, −78 °C, 1 h, then −30 °C, 5 h (92%); (d) TsNClNa (1.1 equiv), $PhMe_3NBr_3$ (0.1 equiv), MeCN, 25 °C, 24 h (54%); (e) DIAD (1.5 equiv), Ph_3P (1.5 equiv), THF, −78 °C 1 h, then 25 °C, 7 d (68%).

As direct aziridination of diol **17** could not be achieved using BusNClNa,[21] the Bus-protected aziridine **20** was synthesized as shown in Scheme 5. Sulfinylation of amino alcohol **14** using

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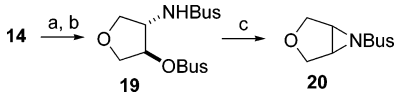
SCHEME 5. Synthesis of NBus Aziridine 20[a]



[a] Reagents and conditions: (a) *t*-BuSOCl (2.2 equiv), Et_3N (2.5 equiv), MeCN-DMF (5:1), 0 °C, 5 h; (b) MCPBA (2.2 equiv), CH_2Cl_2, 0 to 25 °C, 1 h (63% over two steps); (c) K_2CO_3 (12 equiv), MeCN, 25 °C, 24 h (86%).

t-BuSOCl[21] gave, following oxidation (MCPBA) of the crude *N*,*O*-bis-*tert*-butylsulfinyl intermediate, the *N*,*O*-Bus-protected amino alcohol **19** (63% from **14**). Cyclization of the latter using K_2CO_3 gave the *N*-Bus-protected aziridine **20** (86%). An alternative three-step procedure to Bus-protected aziridine **20** that proceeds by ring opening of epoxide **13** with $BusNH_2$ has recently been reported.[22]

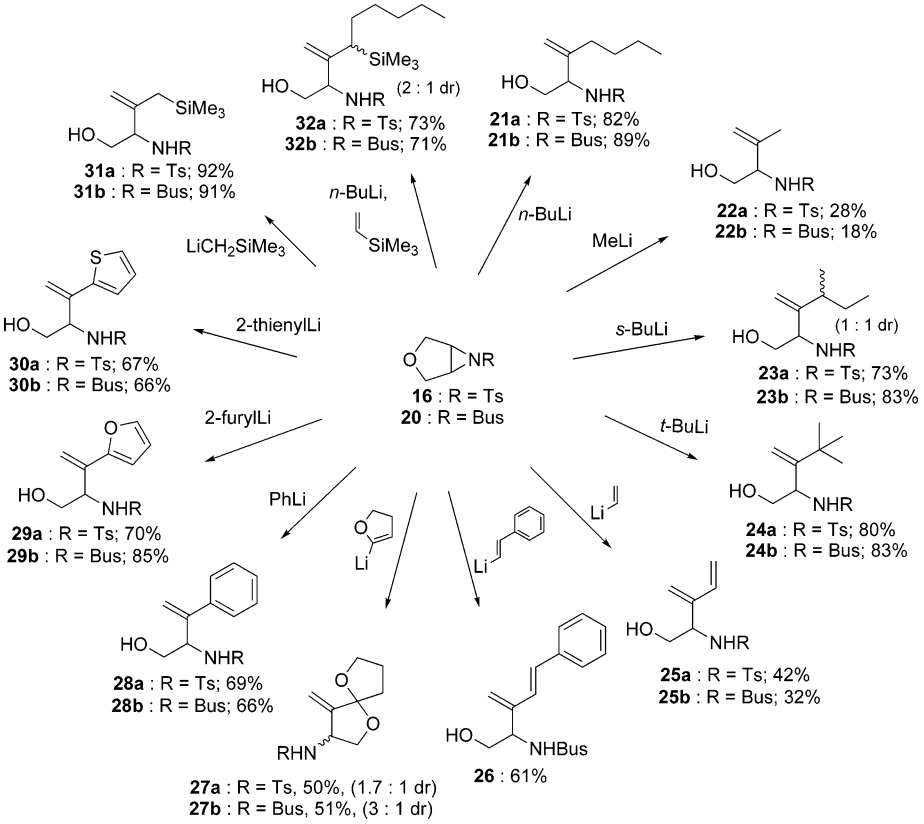
Initially, addition of tosyl-protected aziridine **16** to *n*-BuLi (3 equiv) was examined in three different solvents (Et_2O, THF, and toluene) at −78 °C (1 h, followed by warming to 0 °C over 3 h). In all three cases the desired amino alcohol **21a** was observed, in 66%, 82%, and 38% yields, respectively (Scheme 6); $TsNH_2$ was also detected as a minor (<20%) side product.[4c] The amount of $TsNH_2$ observed was not reduced if either the order of addition was reversed, i.e., by dropwise addition of *n*-BuLi to a solution of the aziridine **16**, or if only 2 equiv of *n*-BuLi was used. The scope of the reaction was then investigated using a variety of organolithiums under the initial conditions in THF (Scheme 6). Although reaction of aziridine **16** with MeLi gave mainly rearranged *N*-tosyl 2,3-dihydro-furan-3-amine (45%), along with some of the desired amino alcohol **22a** (28%, Scheme 6), no rearranged allylic amine was isolated from reactions with other organolithiums. Secondary, tertiary, vinyl, aryl, and heteroaryl organolithiums all underwent successful reaction with aziridine **16**. With 4,5-dihydrofuran-2-yllithium, a subsequent spirocyclization occurred presumably during workup to give spiroketal **27a** as a 1.7:1 mixture of diastereomers. Given the utility of allylsilanes in synthesis,[23] the direct formation of allylsilane **31a** using commercially available Me_3SiCH_2Li is noteworthy. Formation of allylsilane **32a** makes use of the addition of organolithiums to vinylsilane to give substituted α-silyl anions,[24] and in the present case allows a straightforward approach for the preparation of more substituted allylsilanes.

Reaction of organolithiums with Bus-protected aziridine **20** showed a reaction profile similar to that observed with the tosyl-protected aziridine **16** (Scheme 6), although the yields were more sensitive to the reaction conditions. With less basic and more nucleophilic organolithiums (e.g., $TMSCH_2Li$), complete consumption of aziridine **20** required longer reaction times as well as warming to higher reaction temperatures (−78 to −30 °C).

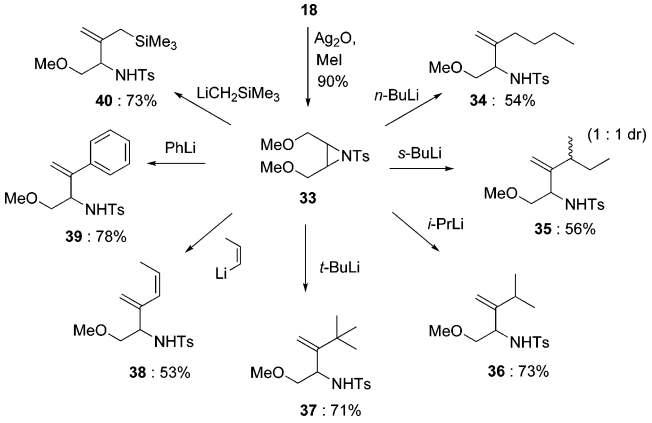
To investigate the effect of the structure of the achiral aziridine on the alkylative ring-opening process, we also examined a non-ring-fused aziridine **33** (prepared by methylation of aziridine diol **18**, Scheme 7).

cis-Aziridine **33** displayed a useful reactivity profile, providing access to a range of unsaturated amino ethers **34**−**40**. Et_2O is the preferred solvent, as reactions in THF did not always proceed to completion. Interestingly, no loss of alkene geometry was observed in the formation of diene **38** from *Z*-1-propenyllithium. This suggests that the putative tertiary organolithium intermediate **42** (R = *Z*-C═CHMe) generated from the lithiated aziridine **41** (possibly by a 1,2-metalate shift,[2,25] as shown in Scheme 8) undergoes elimination with loss of MeOLi to the alkene **43** more rapidly than isomerization by allylic Li transposition.

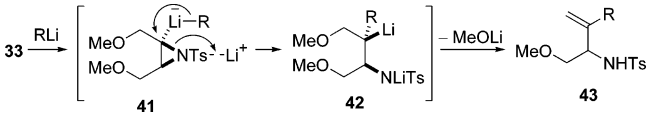
SCHEME 6. Organolithium-Induced Alkylative Ring Opening of Aziridines 16 and 20



SCHEME 7. Preparation and Alkylative Ring Opening of *cis*-Aziridine 33



SCHEME 8. Possible Reaction Pathway for Alkylative Ring Opening Process



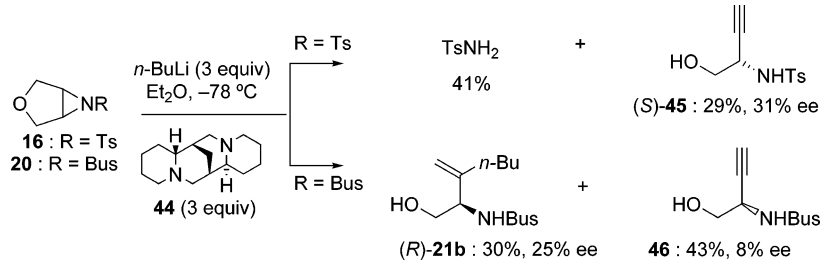
The results with *cis*-aziridine **33** are noteworthy given that the corresponding epoxides of acyclic allylic ethers have been reported not to undergo organolithium-induced alkylative ring opening.[9a,c] It is evident that the aziridine does not need to be fused to a (five-membered) ring to allow the chemistry to proceed satisfactorily.

In seeking to extend the above alkylative ring-opening reaction of aziridines to provide enantioenriched unsaturated amino alcohols and ethers, we initially investigated enantioselective desymmetrization of aziridines **16** and **20** in the presence of (−)-sparteine **44** as an external chiral ligand (Scheme 9).[26] However, application of typical conditions [dropwise addition of a solution of aziridine **16** to a preformed complex of *n*-BuLi and sparteine **44** (3 equiv each) at −78 °C in Et_2O for 1 h, followed by slow warming over 3 h to 0 °C] gave no amino alcohol **21a**; instead, starting aziridine **16** was recovered (60−70% yield), along with a small amount of $TsNH_2$ (∼10%). Using the (achiral) diamine TMEDA (3 equiv) as an additive under these conditions also resulted in recovery of **16**. With sparteine **44**, prolonged reaction time (48 h at −78 °C) did result in consumption of aziridine **16**, to give $TsNH_2$ (41%) and isomerization[27] to (*S*)-*N*-Ts 2-amino-3-butyn-1-ol (**45**)[28] (29%, 31% ee, Scheme 9). Under the same conditions, Bus-protected aziridine **20** did give some of the desired unsaturated amino alcohol (*R*)-**21b**[29] (30% yield, 25% ee), along with alkyne **46** (43%, 8% ee); compared to sparteine, the use of other ligands gave amino alcohol **21b** in significantly improved yields but lower ee's.[29] With *n*-BuLi and sparteine **44**, *cis*-aziridine **33** gave only 6% of unsaturated amino ether (*S*)-**34** (30% ee).[29] Interestingly, with sparteine the sense of asymmetric induction in the α-deprotonation of tosyl-protected aziridines **16** and **33** is the same as that observed by Müller with other tosyl-protected achiral aziridines,[4] whereas the opposite sense of induction seen for Bus-protected aziridine **20** is the same as that found using **16** (when Ts = 2,4,6-triisopropylbenzenesulfonyl).[27]

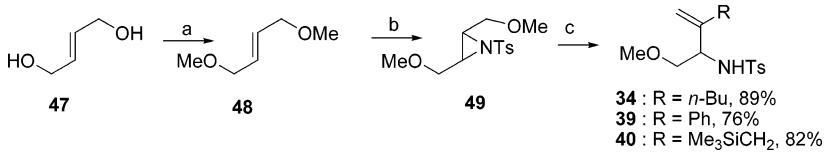
Due to the limitations found above for enantioselective synthesis with an external chiral ligand induction strategy, we considered an alternative asymmetric entry using desymmetrization of C_2-symmetric aziridines. First, we established the viability of alkylative ring opening of such a *trans* aziridine, **49**, in the racemic sense, obtaining unsaturated amino ethers **34**, **39**, and **40** in good yields (Scheme 10).

Encouraged by the results with racemic *trans* aziridine **49**, we undertook syntheses of enantiopure aziridines (*S*,*S*)-**49** and (*S*,*S*)-**53** (Scheme 11). L-Tartaric acid was converted to cyclic sulfate **50** in 54% overall yield, following literature precedent.[30] Shi et al.[30d] described the formation of aziridine **51** from cyclic sulfate **50** by a two-step procedure involving ring opening with LiN_3, followed by $LiAlH_4$ reduction−cyclization in a moderate 40% overall yield. The low yield for this transformation, together with the use of LiN_3, prompted us to develop an alternative method. Thus, treatment of cyclic sulfate **50** with *i*-PrOH−NH_4-OH solution (sealed tube, 80 °C, 8 h) resulted in the formation of an aminosulfate, which was subsequently cyclized using $LiAlH_4$[31] to aziridine **51** in excellent yield. Protection of aziridine **51** resulted in the formation of aziridines (*S*,*S*)-**49** and (*S*,*S*)-**53**, and the latter underwent alkylative ring opening in good yields (Scheme 11). Chiral HPLC analyses of unsaturated

SCHEME 9. Influence of (−)-Sparteine (44) with Aziridines 16 and 20

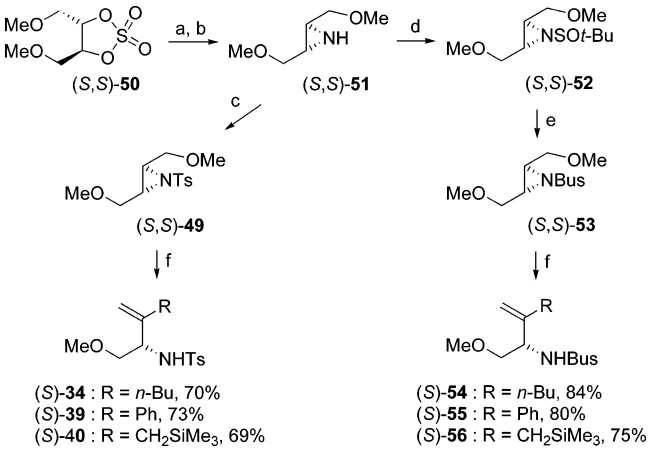


SCHEME 10. Preparation and Alkylative Ring Opening of *trans*-Aziridine 49[a]



[a] Reagents and conditions: (a) MeI (5 equiv), NaH (2.4 equiv), THF, 0 °C 1 h, then 25 °C 24 h, 86%; (b) TsNClNa (1.1 equiv), $PhMe_3NBr_3$ (0.1 equiv), MeCN, 25 °C, 3 d, 42%; (c) RLi (3 equiv), Et_2O, −78 °C, 1 h, then −78 to 0 °C, 3 h.

SCHEME 11. Synthesis of Enantiopure Unsaturated Amino Ethers[a]



[a] Reagents and conditions: (a) NH_4OH, (25%, H_2O, 13.5 equiv), THF, 80 °C, 8 h, 94%; (b) $LiAlH_4$ (1.1 equiv), THF, 25 °C, 12 h, 85%; (c) TsCl 1.1 equiv), Et_3N (1.5 equiv), MeCN, 25 °C, 18 h, 82%; (d) *t*-BuSOCl (1.1 equiv), Et_3N (1.5 equiv), THF, 0 °C 1 h, then 25 °C, 12 h, 61%; (e) MCPBA (1.1 equiv), CH_2Cl_2, 0 to 25 °C, 3 h, 89%; (f) RLi (3 equiv), Et_2O, −78 °C, 1 h, then −78 to 0 °C, 3 h, HCl (1 M) (5 equiv).

amino ethers (*S*)-**34** and (*S*)-**39** established that no loss of enantiopurity occurred during the alkylative ring-opening process.

Conclusions

Alkylative and arylative double ring opening of 2,5-dihydrofuran-derived aziridines is shown to proceed by intermolecular C−C bond-forming reaction with co-generation of unsaturation and the reorganization of two functional groups, leading to nucleophile incorporation at a vinylic position as well as the synthetically valuable 1,2-amino alcohol functionality. Extension of this methodology to acyclic examples broadens the synthetic applicability and with enantiomerically pure C_2-symmetric aziridines provides access to substituted allylic amino ethers in enantiopure form.

Experimental Section

General experimental details are described in Supporting Information.

***trans*-4-Aminotetrahydro-3-furanol (14).**[17] A solution of 3,6-dioxabicyclo[3.1.0]hexane (**13**)[16] (1.50 g, 17.5 mmol) in *i*-PrOH (5 mL) was added to NH_4OH (25 mL, 35% in water, 0.23 mol). The mixture was then heated with stirring in a sealed tube at 80 °C. After 12 h, the mixture was cooled and evaporated under reduced pressure, to give amino alcohol **14** (1.72 g, 95%), which was used without further purification: ν_{max}/cm^{-1} (film) 3345br, 2952w, 28882w, 1601m, 1472m, 1069m, 1045m, 973m, 893m; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86−3.79 (m, 3H), 3.44 (dd, 1H, J = 8.5, 1.5 Hz), 3.31 (dd, 1H, J = 8.5, 2.5 Hz), 3.14−3.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.7, 73.5, 73.1, 59.1.

***trans*-*N*-(4-Hydroxytetrahydrofuran-3-yl)-4-methylbenzenesulfonamide (15).** To a solution of amino alcohol **14** (1.88 g, 18.3 mmol) in dry MeCN (50 mL) was added TsCl (3.83 g, 20.1 mmol). The resulting solution was cooled to 0 °C, and then Et_3N (5.0 mL, 35.6 mmol) was added. After 2 h, the mixture was evaporated under reduced pressure, and the residue diluted with water (40 mL) and extracted with EtOAc (6 × 30 mL). The combined organic extracts were dried ($MgSO_4$), evaporated under reduced pressure, and recrystallized (EtOAc−petroleum ether) to give the hydroxy sulfonamide **15**[22] as a white solid (3.87 g, 89%): R_f 0.20 (EtOAc−petroleum ether, 3:2); mp 98−99 °C (lit.[22] 80−82 °C); ν_{max}/cm^{-1} (KBr) 3303br, 3164br, 2887m, 1596w, 1469m, 1338s, 1277m, 1217m, 1160s, 1088s, 1063s, 995s, 972m, 884s, 812s, 736br, 657m, 565s; ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (bd, 1H, J = 6.0 Hz), 7.71−7.69 (m, 2H), 7.41−7.39 (m, 2H), 5.21 (bd, 1H, J = 4.0 Hz), 3.99−3.97 (m, 1H), 3.76 (dd, 1H, J = 4.5, 9.5 Hz), 3.69 (dd, 1H, J = 5.0, 9.0 Hz), 3.43 (dd, 1H, J = 1.5, 9.5 Hz), 3.40−3.33 (m, 2H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.7, 137.9, 129.6, 126.5, 74.8, 73.0, 70.5, 60.6, 20.9; *m*/*z* [CI + (NH_3)] 275 (M + NH_4^+, 100%), 240 (M + H^+ − H_2O, 90), 86 (30). Found: M + H^+ − H_2O, 240.0694; $C_{11}H_{14}NO_3S$ requires 240.0694.

(*Z*)-2,3-Bis(hydroxymethyl)-1-[(4-methylbenzene)sulfonyl]-aziridine (18). To a solution of commercial (*Z*)-2-butene-1,4-diol (**17**) (0.530 g, 6.02 mmol) and anhydrous chloramine-T (1.50 g, 6.60 mmol) in dry MeCN (30 mL) was added PTAB (0.23 g, 0.60 mmol) at room temperature. After stirring for 24 h, the reaction mixture was filtered, concentrated to ∼1/3 volume, then cooled in a refrigerator (at 0 °C for 24 h), and filtered to give a white solid, aziridine diol **18**[20] (0.70 g, 45%). The filtrate was evaporated under reduced pressure and purified by column chromatography (EtOAc) yielding additional aziridine diol **18 (**0.16 g, 9%): R_f 0.27 (EtOAc); mp 119−121 °C; ν_{max}/cm^{-1} (KBr) 3335br, 3232br, 3051w, 2931w, 1596m, 1452m, 1395w, 1325s, 1237m, 1162s, 1091m, 1046s, 947s, 863w, 815m, 730s, 675s, 572s, 544s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.62 (m, 2H), 7.25−7.21 (m, 2H), 4.05 (bs, 2H), 3.87−3.66 (m, 4H), 3.17−3.06 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 134.4, 129.6, 127.8, 58.3, 43.8, 21.5; *m*/*z* [CI + (NH_3)] 275 (M + NH_4^+, 15%), 258 (M + H^+, 35), 108 (100), 104 (40), 91 (50), 86 (45), 72 (60). Found: MH^+, 258.0800; $C_{11}H_{16}NO_4S$ requires 258.0799. Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.31; H, 5.93; N, 5.48.

6-[(4-Methylbenzenel)sulfonyl]-3-oxa-6-azabicyclo[3.1.0]-hexane (16). Procedure A: To a stirred solution of PPh_3 (3.06 g, 11.7 mmol, 1.5 equiv) in THF (50 mL) at −78 °C under argon was added DIAD (2.30 mL, 11.7 mmol, 1.5 equiv) dropwise over 30 min. The reaction mixture was stirred for 30 min until a pale yellow suspension formed. A solution of hydroxy sulfonamide **15** (2.00 g, 7.8 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 1 h and then at −30 °C for 6 h. The reaction mixture was then filtered and evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether−EtOAc, 3:2) to give the *N*-Ts aziridinyltetrahydrofuran **16**[22] (1.71 g, 92%): R_f 0.37 (petroleum ether−EtOAc, 1:1); mp 117−117.5 °C (lit.[22] 96−98 °C); ν_{max}/cm^{-1} (KBr) 2956w, 2868w, 1323m, 1159s, 1093m, 1077m, 10007w, 962m, 897m, 876m, 848w, 816w, 716m; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−7.84 (m, 2H), 7.36−7.34 (m, 2H), 4.00 (s, 1H),

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3.98 (s, 1H), 3.72−3.69 (m, 2H), 3.66 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 135.1, 129.7, 127.8, 67.8, 44.8, 21.6; *m*/*z* [CI + (NH_3)] 257 (M + NH_4^+, 100%), 240 (M + H^+, 90), 204 (15), 86 (30). Found: MH^+, 240.0694; $C_{11}H_{14}NO_3S$ requires 240.0694. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.10; H, 4.98; N, 6.10. Procedure B: To a stirred solution of PPh_3 (1.53 g, 5.84 mmol, 1.5 equiv) in THF (15 mL) at −78 °C under argon was added DIAD (1.18 g, 5.84 mmol, 1.5 equiv) dropwise over 15 min. The reaction mixture was stirred for a further 30 min until a pale yellow suspension formed. A solution of aziridine diol **18** (1.00 g, 3.89 mmol) in THF (5 mL) was then added dropwise, and the reaction mixture was stirred at −78 °C for 1 h and then allowed to attain room temperature. After 7 d, the reaction mixture was then filtered and evaporated under reduced pressure, and the residue purified by column chromatography (petroleum ether−EtOAc, 3:2) to give the *N*-Ts aziridinyltetrahydrofuran **16** (0.63 g, 68%). Data as for procedure A above.

***trans*-4-[(*tert*-Butylsulfonyl)amino]tetrahydrofuran-3-yl 2-methylpropane-2-sulfonate (19).** To an ice-cold solution of amino alcohol **14** (1.00 g, 9.71 mmol) and Et_3N (2.35 g, 23.3 mmol) in MeCN (50 mL) and DMF (10 mL) was added dropwise *tert*-butylsulfinyl chloride[21] (3.00 g, 21.4 mmol). After 5 h at 0 °C, the mixture was diluted with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried (Mg_2SO_4) and concentrated under reduced pressure. To a solution of the residue (1.93 g) in CH_2Cl_2 (100 mL) at 0 °C was added MCPBA (6.14 g, 60% w/w, 21.4 mmol) in five portions, and the reaction mixture was then allowed to reach room temperature over 1 h. The reaction mixture was then diluted with a mixture of saturated aqueous $NaHSO_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried (Mg_2SO_4) and concentrated under reduced pressure. The residue was slurried in Et_2O (20 mL) and filtered, giving the *N*,*O*-Bus-protected amino alcohol **19** (2.10 g, 63%): mp 153−154 °C; ν_{max}/cm^{-1} (KBr) 3266br, 2992m, 2942m, 1482m, 1458m, 1338s, 1309s, 1212w, 1146s, 1112s, 1081s, 1045m, 1011m, 958s 895s, 818m, 767m, 672s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13−5.11 (m, 1H), 4.69 (bd, 1H, J = 9.0 Hz), 4.20−4.16 (m, 2H), 4.09 (dd, 1H, J = 9.5, 5.0 Hz), 3.94 (dd, 1H, J = 11.0, 2.5 Hz), 3.79 (dd, 1H, J = 9.5, 2.5 Hz), 1.48 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.8, 72.5, 71.7, 60.4, 60.2, 59.7, 24.3, 24.2; *m*/*z* [CI + (NH_3)] 361 (M + NH_4^+, 80%), 223 (100), 206 (70). Found: M + NH_4^+, 361.1463; $C_{12}H_{29}N_2O_6S_2$ requires 361.1462.

6-(*tert*-Butylsulfonyl)-6-aza-3-oxabicyclo[3.1.0]hexane (20). To a solution of *N*,*O*-Bus-protected amino alcohol **19** (0.10 g, 0.30 mmol) in MeCN (10 mL) was added K_2CO_3 (0.5 g, 3.6 mmol) at room temperature. After 24 h, the reaction mixture was filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with water (2 × 20 mL). The organic layer was dried (Mg_2SO_4) and evaporated under reduced pressure, giving *N*-Bus aziridinyltetrahydrofuran **20**[22] (52 mg, 86%): R_f 0.35 (petroleum ether−EtOAc, 1:1); mp 59−61 °C (lit.[22] 64−66 °C); ν_{max}/cm^{-1} (KBr) 2982w, 2869w, 1478w, 1383w, 1305s, 1191w, 1128s, 1076m, 1009w, 956m 895m, 715m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07−4.05 (m, 2H), 3.77−3.74 (m, 2H), 3.62 (bs, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.8, 59.5, 44.2, 24.0; *m*/*z* [CI + (NH_3)] 223 (M + NH_4^+, 100%), 86 (30). Found: M + NH_4^+, 223.1111; $C_8H_{19}N_2O_3S$ requires 223.1115.

General Procedure for Organolithium-Induced Alkylative Double Ring Opening of *N*-Ts Aziridinyltetrahydrofuran 16 in THF. A solution of aziridine **16** (0.096 g, 0.40 mmol) in THF (4 mL) was added dropwise to a stirred solution of an organolithium (3 equiv) at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to 0 °C over a period of 3 h and then quenched by addition of aqueous HCl (5 mL, 1 mol dm^{-3}) or, in the cases of [(trimethylsilyl)methyl]lithium and [1-(trimethylsilyl)hexyl]lithium, by addition of saturated aqueous NH_4Cl (3 mL). The reaction mixture was extracted with Et_2O (5 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was then purified by column chromatography (SiO_2).

***N*-[2-Butyl-1-(hydroxymethyl)prop-2-enyl]-4-methylbenzenesulfonamide (21).** Following the general procedure above using *n*-BuLi (0.75 mL, 1.6 mol dm^{-3} in pentane, 1.2 mmol) gave after purification by column chromatography (EtOAc−petroleum ether, 2:3) a colorless oil, the amino alcohol **21** (98 mg, 82%): R_f 0.22 (EtOAc−petroleum ether, 2:3); ν_{max}/cm^{-1} (film) 3502br, 3277br, 2953m, 2929m, 1647w, 1598w, 1326m, 1159s, 1093m, 956w, 901w, 814m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (m, 2H), 7.30−7.28 (m, 2H), 5.33 (d, 1H, J = 7.5 Hz), 4.91 (s, 1H), 4.85 (s, 1H), 3.80−3.75 (m, 1H), 3.59−3.58 (m, 2H), 2.42 (s, 3H), 2,-26 (bs, 1H), 1.83−1.79 (m, 2H), 1.26−1.13 (m, 4H), 0.82 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 143.5, 137.2, 129.6, 127.3, 112.4, 64.1, 59.3, 33.1, 29.6, 22.3, 21.5, 13.8; *m*/*z* [CI + (NH_3)] 315 (M + NH_4^+, 45%), 189 (100), 144 (52), 112 (30). Found: M + NH_4^+, 315.1747; $C_{15}H_{27}N_2O_3S$ requires 315.1742.

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Supporting Information Available: Full experimental details of syntheses and characterization of azridine substrates and amino alcohols/ethers not described in the Experimental Section, data for ligand screening reactions, X-ray data for aziridine **16** and spiroketal **27b** in CIF format, and copies of ^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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