Pergamon

Tetrahedron 58 (2002) 7153–7163

TETRAHEDRON

Base-promoted elaboration of aziridines

Alessandro Mordini,* Francesco Russo, Michela Valacchi, Lorenzo Zani, Alessandro Degl'Innocenti and Gianna Reginato

Dipartimento di Chimica Organica "U. Schiff", Istituto di Chimica dei Composti Organometallici, via della Lastruccia 13, 50019 Sesto Fiorentino, Firenze, Italy

Received 17 May 2002; accepted 23 May 2002

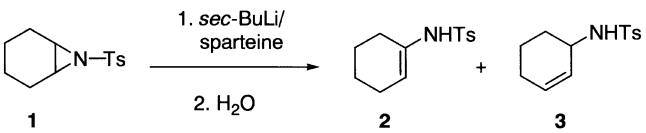
Abstract—The base-promoted isomerization of aziridines to allyl amines is still an almost unknown reaction. However, the use of superbasic reagents has shown to be able to promote a regio- and stereoselective conversion of monocyclic and bicyclic sulfonyl aziridines. Moreover, the use of alkoxy substituted aziridines opens new routes to non-natural α- and β-amino acids. © 2002 Elsevier Science Ltd. All rights reserved.

Aziridines are valuable intermediates in organic synthesis owing to their easy availability and versatility. Their high ring tension (26 kcal/mol) coupled with the polarization of the C–NR bond, originates their rich reactivity as demonstrated by the great number of synthetic elaborations reported so far.[1–5] In analogy with oxiranes, nucleophilic ring-openings are certainly the most widely studied reactions of aziridines. There is however a notable difference between the two heterocycles concerning their reactivity with bases. While α-lithiation is well-known[6] for both classes of compounds, β-deprotonation leading to ring-opening and isomerization is widely studied in the oxirane series[7] but almost unknown for aziridines.

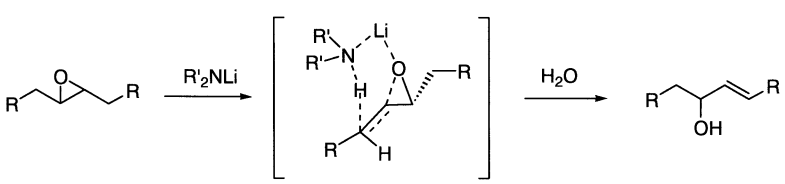
By treatment with organolithium reagents or lithium amides, epoxides are known to be converted into allylic alcohols through a *syn*-periplanar, β-elimination process[8,9] (Scheme 1). The reaction lacks some selectivity because of several alternative pathways which can be minimized[10] by using superbasic reagents[11,12] such as the lithium diisopropyl amide/potassium *tert*-butoxide mixture.[13]

Asymmetric variants of this reaction have also been the subject of many recent investigations.[14–17] Good levels of enantioselectivity have been achieved[18–24] in the desymmetrization of epoxycycloalkanes with chiral lithium amides, even in catalytic amounts.[23,25,26]

Despite this large array of information on oxiranes, the base-promoted β-elimination of aziridines has been almost ignored until very recently. Probably the first example of aziridine–allylamine conversion was reported by Scheffold in 1993[27] by using cob(I)alamin as a catalyst although the reaction was very slow and took place actually through an addition–elimination pathway. The first true base-promoted isomerization was published in 2001 by Müller[28] who described the desymmetrization of the *meso*-sulfonyl aziridine **1** with *sec*-butyllithium/sparteine. Unfortunately, under these conditions, the aziridine isomerization was not regioselective yielding both α- and β-deprotonation (to the enamine **2** and allylamine **3** respectively, Scheme 2) and the enantioselectivity in the formation of the allylamine **3** was quite low.



Scheme 2.



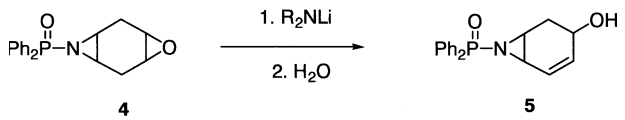
Scheme 1.

Keywords: aziridines; superbase; rearrangement; allyl amine; amino acid.

* Corresponding author. Tel.: +39-55-4573555; fax: +39-55-4573531; e-mail: alessandro.mordini@unifi.it

PII: S0040-4020(02)00729-9

In addition, O'Brien[29] showed that the *meso*-aziridino cyclohexene oxide **4** underwent rearrangement on the oxirane ring only (to the aziridino allylic alcohol **5**, Scheme 3) and that in the absence of the epoxide ring no reaction occurred when employing unactivated bases such as lithium diisopropylamide. The reactivity of aziridines with bases seems then much lower in comparison with the analogous oxygenated heterocycles.

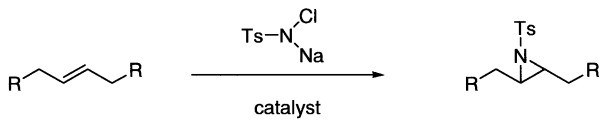


4 **5**

Scheme 3.

This lack of information prompted us to extend our experience on the base-promoted isomerization of oxiranes[30–37] to the aziridine series.

The aziridine ring can be obtained in a number of ways[1,3] both as racemic and enantioenriched compounds. The most straightforward method is the direct aziridination reaction with chloramine-T and analogues (Scheme 4), which can be performed according to several different procedures, to access racemic sulfonyl aziridines. Copper,[38,39] palladium[40] and iron[41,42] catalysts in addition to substoichiometric amounts of bromine[43] and iodine[44,45] have been used in the aziridination with chloramine-T or bromamine-T.



Scheme 4.

An alternative, longer but usually high yielding method, is the three-step procedure which leads to N–H aziridines from alkenes through epoxidation, opening with azide and reductive ring closure with triphenylphosphine[3,5,46] (Scheme 5).

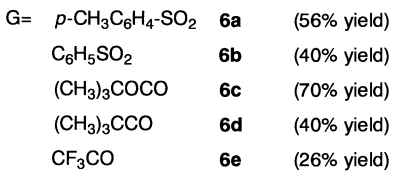


Figure 1.

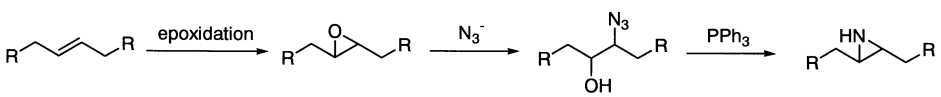
In a first series of experiments we have examined the superbase promoted isomerization of 7-azabicyclo[4.1.0]-heptanes **6a–e** to the corresponding allylic amines as a function of various reaction conditions and of activating groups on nitrogen (Fig. 1).

Benzenesulfonyl, *tert*-butoxycarbonyl (Boc) and pivaloyl aziridines (**6b**, **6c** and **6d**, respectively) have been obtained via the oxirane elaboration while the tosyl aziridine **6a** has been easily prepared by direct aziridination with the Komatsu method.[44] The trifluoroacetyl aziridine **6e** cannot be prepared by the use of these standard procedures owing to its high propensity to undergo ring-opening under these reaction conditions. It has been obtained however using a modified method starting from 2-aminocyclohexanol through selective trifluoroacetylation of the amino group, mesylation of the hydroxy substituent and ring closure by treatment with lithium hexamethyldisilazide (Scheme 6).

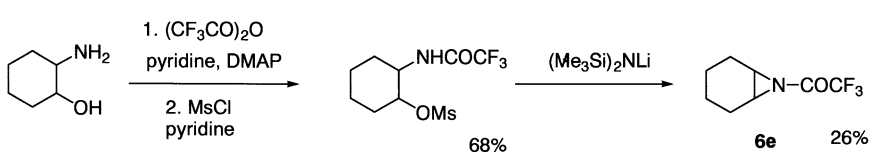
The N-substituted aziridines **6a–e** have been then submitted to treatment with the superbasic mixtures butyllithium/potassium *tert*-butoxide (LICKOR) or lithium diisopropylamide/potassium *tert*-butoxide (LIDAKOR).

While the two sulfonyl aziridines **6a** and **6b** undergo a regioselective rearrangement to the corresponding allylic sulfonyl amide **7a** and **7b** by treatment with LIDAKOR both in pentane at 25°C and in THF at −50°C, the Boc- and pivaloyl aziridines **6c** and **6d** are simply deprotected to 7-azabicyclo[4.1.0]heptane **8** (Scheme 7).

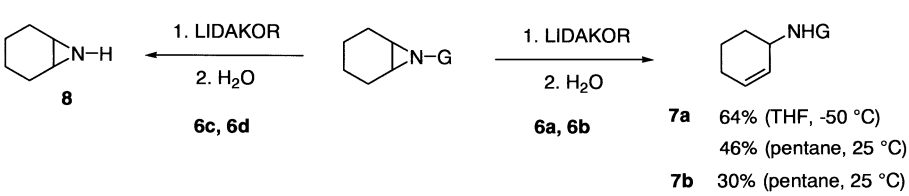
In this case, most likely, the base acts as a nucleophile on the carbonyl group, thus inducing the C–N bond breaking at a later stage.[47] It is worth noting that the rearrangement of the



Scheme 5.



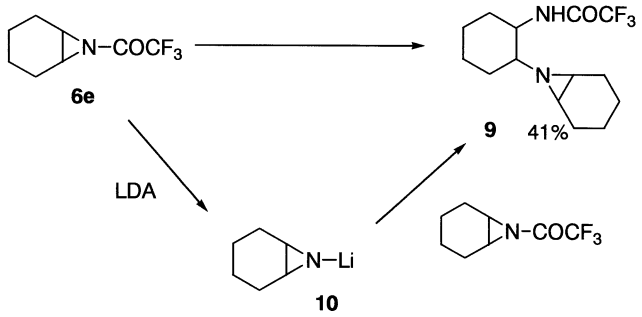
Scheme 6.



Scheme 7.

sulfonyl aziridine **6a** is highly regioselective, the allyl amide being the only detectable product, while the use of simple lithium amides gives a mixture of the two isomeric amines[28] as previously discussed.

The trifluoroacetyl substituted substrate **6e** reacts even with non-activated lithium amides to yield the diamine **9**, probably derived from initial deprotection to the lithio aziridine **10** followed by nucleophilic ring opening of a second activated aziridine molecule (Scheme 8).



Scheme 8.

According to these initial investigations, the tosyl group is certainly the best one for the purpose of promoting a base-induced rearrangement. Tosyl aziridines are easily accessed as shown above and react with high regioselectivity and good yields with mixed metal bases. We have then prepared a series of *N*-tosyl aziridines **11**–**15** (Fig. 2) making use of the Komatsu[44] protocol, and we have submitted all of them to treatment with superbasic reagents.

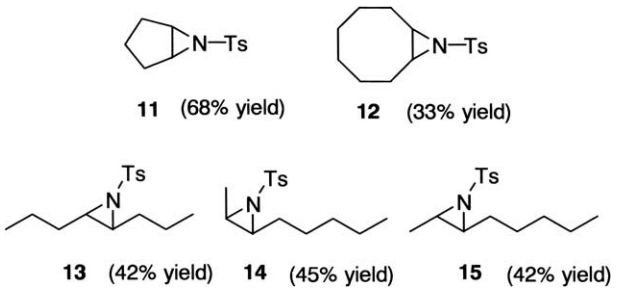
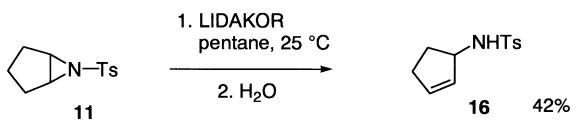


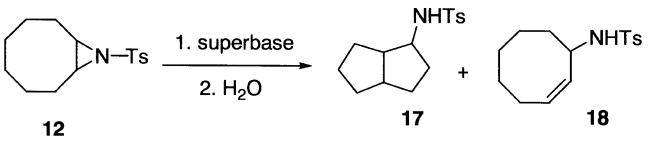
Figure 2.

6-Tosyl-6-azabicyclo[3.1.0]hexane **11** behaves similarly to the homologue **6a** giving the corresponding allyl tosylamide **16** even if in lower yields (Scheme 9). Both aziridines show a reactivity which is similar to the corresponding oxiranes but require more drastic reaction conditions; while oxiranes react with superbases even in THF at low temperature,[10] aziridines give usually the best results when treated in pentane at room temperature.



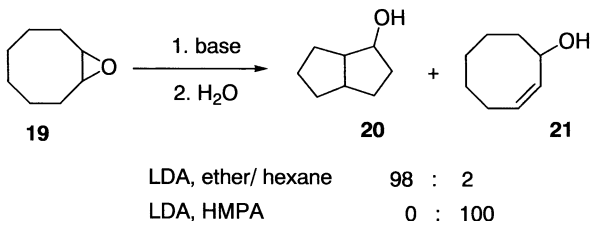
Scheme 9.

9-Tosyl-9-azabicyclo[6.1.0]nonane **12** shows an interesting reactivity with superbases. When treated with LIDAKOR in pentane at room temperature a completely regioselective conversion to the 1-*N*-tosylamino[3.3.0]octane **17** in a 64% yield is observed. If the reaction is conducted at lower temperature in THF with LICKOR, then a mixture of **17** and the *N*-tosyl allyl amine **18** is obtained (Scheme 10). At −20°C still the bicyclic amine is preferred over the allylic one with a 80:20 ratio while at −50°C, an almost equal amount (45:55) of the two amines is formed in a 60% overall yield.



Scheme 10.

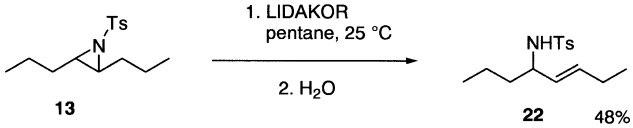
The behavior in pentane again reflects that recently reported by Müller[28] but is in sharp contrast with the reactivity of the corresponding oxirane which gives exclusively the allylic alcohol when treated with superbases even in non-polar solvents.[10] On the other hand, it is known that cyclooctenoxide **19** is selectively converted into cyclo-octen-2-enol **21** when lithium amides in the presence of HMPA are used[48] and into bicyclo[3.3.0]octan-1-ol **20** if the lithium amide is employed in ether/hexane (Scheme 11).



Scheme 11.

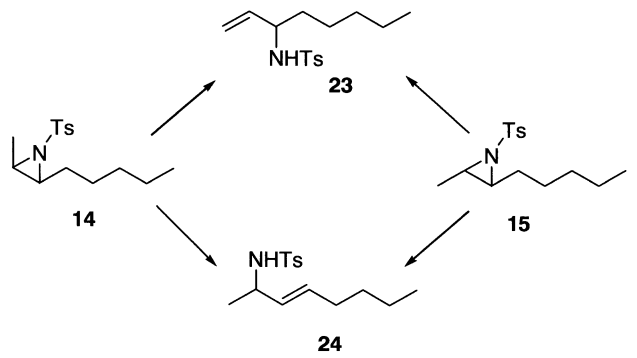
This has been attributed to a β-elimination process in polar medium where more reactive monomeric species are more likely to be present and to a α-metalation in the presence of more aggregated lithium species.[9,49] Our results with the tosyl-aziridine derived from cyclooctene seem to confirm this hypothesis and indicate that, in this particular case, an α-elimination process takes place even with superbases in pentane.

The monocyclic symmetrical aziridine **13** is also regio- and stereoselectively converted into the corresponding allylic amine **22** by treatment with LIDAKOR in pentane at room temperature (Scheme 12).



Scheme 12.

It is worth noting that **22** is obtained as a pure *E*-isomer while the LIDAKOR promoted isomerization of the corresponding oxirane affords a 1:2, *Z*/*E* mixture of allylic



Scheme 13.

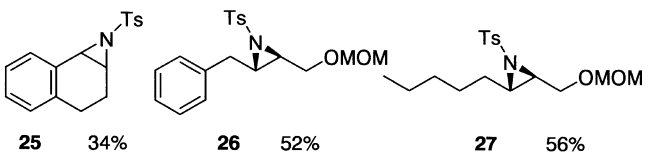


Figure 3.

alcohols.[10] The higher selectivity showed by tosyl aziridines may be due to an increased steric crowding caused by the presence of the large tosyl group on nitrogen in the *syn*-periplanar arrangement required for the elimination.[7]

Both *Z*- and *E*-aziridines **14** and **15** behave exactly in the same way affording a mixture of the two tosyl allyl amines **23** and **24** in the same ratio (33:67) with a 60% overall yield (Scheme 13).

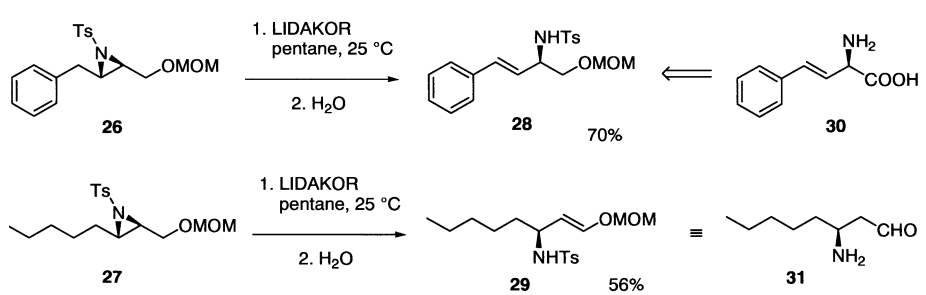
The observed preference for methylene deprotonation is quite surprising if one compares it again with what found in the isomerization of oxiranes. In the latter case indeed, only the allylic alcohol with the terminal double bond is formed, deriving from proton abstraction from the kinetically more acidic methyl group. However, it must be observed that oxirane isomerization with superbases is always carried out in THF at low temperature while aziridine rearrangement occurs only in hydrocarbon solvents at room temperature. The required conditions appear then to favor an equilibration towards the more stable internal double bond.

The presence of additional functional groups on the aziridine substrates has been also investigated. Aryl, alkylaryl and alkoxy substituted aziridines **25**–**27** (Fig. 3) have been prepared either by direct aziridination of the corresponding alkene (**25**) or via epoxide elaboration (**26** and **27**) in an enantioenriched form by using the Sharpless asymmetric epoxidation of the corresponding allylic alcohols (94% ee from *E*-4-phenyl-2-butenol and 84% ee from *E*-2-octenol, respectively).

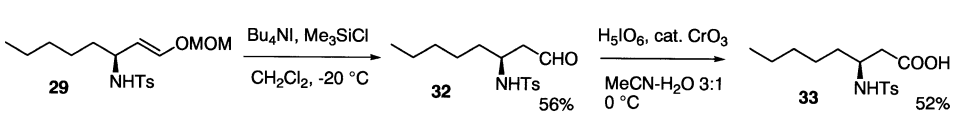
While the aziridine derived from dihydronapthalene **25** upon treatment with superbasic reagents shows only products deriving from a nucleophilic ring-opening, aziridines **26** and **27** give a more synthetically useful result. The benzyl substituted substrate **26** undergoes deprotonation on the benzylic methylene group thus affording the allyl amino ether **28** with perfect regio- and stereocontrol. Aziridine **27**, on the other hand, is regioselectively deprotonated only on the methylene adjacent to the alkoxy substituent thus giving, after quenching with water, the amino vinyl ether **29** as a pure *E*-isomer[50] (Scheme 14). Allyl amines **28** and **29** have the same optical purities than those of starting aziridines thus showing a perfect sterocontrol during the isomerization step.

Both products are very useful intermediates in non-natural amino acid synthesis; **28** can be considered as a precursor of the β,γ-unsaturated α-amino acid styrylglycine **30** while **29** can be viewed as β-amino aldehyde **31** equivalent and thus precursor of β-amino acids. Indeed, such a transformation is easily accomplished by simple removal of the methoxymethyl group to the aldehyde **32** and subsequent oxidation with periodic acid in the presence of a catalytic amount of chromium oxide to the *N*-tosyl β-amino acid **33** (Scheme 15).

Presently, superbases offer then a quite unique chance to perform the aziridine–allylamine isomerization. Such reaction opens new routes and new fields of investigations in comparison with what already well established for oxiranes. Moreover, functionalized aziridines may give



Scheme 14.



Scheme 15.

access to a wide variety of amino derivatives of synthetic interest such as amino acids.

1. Experimental

1.1. General procedures

Air- and moisture-sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. Purifications by flash column chromatography[51] were performed using glass columns (10–50 mm wide); silica gel 230–400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 200 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (J) are measured in Hz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of a doublet), m (multiplet), bs (broad singlet). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential.

1.2. Materials

Starting materials were commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropyl amine, which was distilled over calcium hydride. Tetrahydrofuran was obtained anhydrous by distillation over sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl[52] was found to persist. Pentane was stored over lithium aluminum hydride. Methylene chloride was dried over calcium chloride and stored over 4 Å molecular sieves. Petroleum ether, unless specified, was the 40–70°C boiling fraction.

1.3. General procedure for the synthesis of *N-p*-toluenesulfonylaziridines (6a, 11–15, 25)

In a round bottomed flask, a solution of chloramine-T (0.704 g, 2.5 mmol) and iodine (0.254 g, 1.0 mmol) in acetonitrile (10 mL) was prepared. After the complete dissolution of iodine, 5.0 mmol of the suitable alkenes (**11**: cyclopentene, 0.340 g; **6a**: cyclohexene, 0.410 g; **12**: cyclooctene, 0.551 g; **13**: *trans*-4-octene, 0.561 g; **14**: *cis*-2-octene, 0.561 g; **15**: *trans*-2-octene, 0.561 g; **25**: dihydronaphtalene, 0.651 g) were added. The mixture was stirred at room temperature for 24 h before quenching with H_2O (50 mL), and extracted with CH_2Cl_2 (3×50 mL); the organic layers were combined and washed with H_2O (2×50 mL) and brine (2×50 mL), and then dried. Evaporation of the solvent gave the aziridines **6a**, **11**–**15**, **25**, which were purified by flash chromatography.

1.3.1. *N-p*-Toluenesulfonyl-6-azabicyclo[3.1.0]hexane 11.[43] Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 68%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.78–7.82 (2H, m); 7.29–7.33 (2H, m); 3.32 (2H, m); 2.43 (3H, s); 1.87–1.99 (2H, m); 1.25–1.68 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 144.0; 136.0; 129.6; 127.5; 46.7; 26.9; 21.6; 19.5.

1.3.2. *N-p*-Toluenesulfonyl-7-azabicyclo[4.1.0]heptane 6a.[53] Purification: eluent petroleum ether/ethyl acetate 9:2; yield: 56%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.79–7.83 (2H, m); 7.30–7.34 (2H, m); 2.96 (2H, m); 2.43 (3H, s); 1.78 (4H, m); 1.30 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.9; 135.8; 129.5; 127.5; 39.8; 22.8; 21.6; 19.4. MS (*m/z*, %): 155 (1); 96 (100); 91 (23); 69 (50); 67 (10); 65 (19); 55 (12).

1.3.3. *N-p*-Toluenesulfonyl-9-azabicyclo[6.1.0]nonane 12.[53] Purification: eluent petroleum ether/diethyl ether 5:2; yield: 33%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.79–7.83 (2H, m); 7.30–7.34 (2H, m); 2.77 (2H, m); 2.44 (3H, s); 1.97–2.04 (2H, m); 1.25–1.75 (10H, m).

1.3.4. *trans-N-p*-Toluenesulfonyl-2,3-dipropylaziridine 13.[53] Purification: eluent petroleum ether/ethyl acetate 9:1; yield: 42%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.81–7.85 (2H, m); 7.29–7.33 (2H, m); 2.64 (2H, q, J=4.9 Hz); 2.43 (3H, s); 1.50–1.80 (4H, m); 1.25–1.45 (4H, m); 0.90 (6H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.7; 138.0; 129.4; 127.4; 49.6; 31.8; 21.6; 20.7; 13.7.

1.3.5. *cis-N-p*-Toluenesulfonyl-2-pentyl-3-methylaziridine 14.[44] Purification: eluent petroleum ether/ethyl acetate 10:1; yield: 45%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.79–7.83 (2H, m); 7.30–7.34 (2H, m); 2.91 (1H, dq, J=5.9, 7.2 Hz); 2.61 (1H, dt, J=5.4, 7.5 Hz); 2.43 (3H, s); 1.36–1.44 (2H, m); 1.17–1.22 (9H, m); 0.77–0.90 (3H, m).

1.3.6. *trans-N-p*-Toluenesulfonyl-2-pentyl-3-methylaziridine 15.[44] Purification: eluent petroleum ether/ethyl acetate 9:1; yield: 34%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.81–7.85 (2H, m); 7.29–7.33 (2H, m); 2.68 (2H, m); 2.43 (3H, s); 1.40–1.65 (5H, m); 1.05–1.35 (6H, m); 0.90 (3H, t, J=6.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.7; 138.1; 129.4; 127.3; 49.7; 45.8; 31.2; 30.4; 26.8; 22.4; 21.5; 14.7; 13.8.

1.3.7. *N-p*-Toluenesulfonyl-1,2,3,4-tetrahydronaphtalene-1,2-amine 25.[54] Purification: recrystallization from hexane; yield: 34%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.84–7.80 (2H, m); 7.03–7.33 (6H, m); 3.82 (1H, d, J=7.4 Hz); 3.56 (1H, bd, J=6.6 Hz); 2.73 (1H, dd, J=6.6, 13.0 Hz); 2.48–2.59 (1H, m); 2.42 (3H, s); 2.21–2.31 (1H, m); 1.61–1.76 (1H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 144.2; 136.6; 130.0; 129.7; 129.4; 128.7; 128.6; 128.4; 126.3; 127.6; 42.1; 41.7; 24.7; 21.6; 20.0. MS (*m/z*, %): 147 (12); 146 (11); 145 (27); 118 (21); 117 (31); 116 (21); 115 (28), 114 (14); 105 (34); 104 (27); 103 (100); 91 (27); 84 (61); 76 (47); 65 (16); 62 (29), 50 (38); 49 (30); 43 (38), 40 (46).

1.4. Preparation of other N-activated aziridines

1.4.1. 2-Azidocyclohexanol.[55] A solution of cyclohexene oxide (9.815 g, 100 mmol) and sodium azide (16.260 g, 250 mmol) in 110 mL of a 1:1 mixture of acetone/water was heated at reflux for 17 h. The reaction was then cooled to room temperature, and acetone was removed under reduced pressure; the residual aqueous layer was washed with

methyl *tert*-butyl ether (3×50 mL) and CH_2Cl_2 (3×50 mL); the organic layers were combined, washed with H_2O (3×50 mL) and dried. Evaporation of the solvent gave 14.10 g of 2-azidocyclohexanol (100 mmol, yield 100%) as a pale yellow oil. The product was used in the following reaction without any further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.30–3.41 (1H, m); 3.10–3.22 (1H, m); 2.58 (1H, bs); 1.94–2.08 (2H, m); 1.68–1.76 (2H, m); 1.22–1.35 (4H, m). ^{13}C NMR (50 MHz) δ: 73.5; 67.1; 32.9; 29.7; 24.2; 23.8.

1.4.2. 7-Azabicyclo[4.1.0]heptane 8.[27,55] To a solution of 2-azidocyclohexanol (14.100 g, 100 mmol) in 50 mL of anhydrous THF, triphenylphosphine (26.230 g, 100 mmol), dissolved in 30 mL of anhydrous THF, was added dropwise over 30 min; the resulting mixture was heated at reflux and the reaction was allowed to proceed for 17 h. The reaction was then cooled to room temperature and the solvent was removed by distillation at atmospheric pressure. Distillation at reduced pressure (bp 55–57°C/6.8 mm Hg) afforded 7.510 g of pure **8** (77 mmol, yield 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.14–2.17 (2H, m); 1.77–1.84 (4H, m); 1.21–1.40 (4H, m); 0.60 (1H, bs). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 29.3; 24.5; 20.0. MS (*m*/*z*, %): 97 (2, M^+); 96 (13, M^+-1); 82 (49); 69 (49); 68 (100); 54 (11).

1.4.3. *N*-Benzenesulfonyl-7-azabicyclo[4.1.0]heptane 6b.[56] To a solution of **8** (0.971 g, 10 mmol) in 50 mL of anhydrous pyridine, few crystals of DMAP were added; after cooling the solution to 0°C, benzenesulphonyl chloride (1.765 g, 10 mmol) was added under nitrogen. The reaction was allowed to proceed for 2 h, then, after warming to room temperature, 150 mL Et_2O were added, the organic layer was washed with a saturated solution of $CuSO_4$ (until complete disappearance of the blue color of the copper/pyridine complex), and subsequently with H_2O (2×50 mL), and then dried. Evaporation of the solvent gave the desired product **6b**, which was purified by flash column chromatography (petroleum ether/ethyl acetate 8:1; yield 40%; pale yellowish oil). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.92–7.97 (2H, m); 7.50–7.66 (3H, m); 3.00 (2H, m); 1.77–1.82 (4H, m); 1.21–1.41 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 138.8; 133.1; 128.9; 127.5; 40.0; 22.8; 19.4. MS (*m*/*z*, %): 141 (2); 96 (100); 77 (30); 69 (51); 55 (11); 51 (19).

1.4.4. *N-tert*-Butoxycarbonyl-7-azabicyclo[4.1.0]heptane 6c.[27] Under a nitrogen atmosphere, **8** (0.194 g, 2 mmol), triethylamine (0.525 g, 5.2 mmol) and DMAP (few crystals) were dissolved in 3 mL anhydrous CH_2Cl_2. The solution was cooled to 0°C and then di-*tert*-butyldicarbonate (0.905 g, 5.2 mmol) was added; after stirring for 10 min at 0°C, the mixture was warmed to room temperature and the reaction was allowed to proceed for 2 h. The reaction was then quenched with H_2O (20 mL), and the resulting mixture was diluted with a saturated solution of ammonium chloride (20 mL). The aqueous phase was extracted with Et_2O (2×25 mL) and the combined organic layers were washed with saturated solutions of $KHSO_4$ (20 mL), Na_2CO_3 (20 mL) and NaCl (20 mL), and dried. Evaporation of the solvent gave crude **6c**, which was purified by flash column chromatography (5% ethyl acetate in petroleum ether; yield 70%; yellow oil). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.54–2.56 (2H, m); 1.70–1.95 (4H, m); 1.16–1.54 (4H, m); 1.44 (9H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 163.3; 80.5; 36.9; 28.0; 23.8; 19.9. MS (*m*/*z*, %): 141 (31); 126 (13); 124 (8); 97 (74); 96 (100); 82 (60); 81 (55); 69 (21); 68 (11); 57 (46); 41 (10).

1.4.5. *N*-Pivaloyl-7-azabicyclo[4.1.0]heptane 6d.[57] Under a nitrogen atmosphere, **8** (0.194 g, 2 mmol), triethylamine (0.222 g, 2.2 mmol) and DMAP (few crystals) were dissolved in 4 mL of anhydrous THF. The solution was cooled to 0°C, and then a solution of pivaloyl chloride (0.241 g, 2 mmol) in 1 mL anhydrous THF was added. After stirring for 15 min at 0°C, the mixture was warmed to room temperature, and the reaction was allowed to proceed for 20 h. The solution was then quenched with H_2O (5 mL), the aqueous layer was extracted with Et_2O (4×10 mL), the combined organic layers were washed with brine (2×20 mL), and dried. Evaporation of the solvent gave crude **6d**, which was purified by flash column chromatography (6% ethyl acetate in petroleum ether; yield 40%; colorless oil). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.62–2.64 (2H, m); 1.76–2.02 (4H, m); 1.27–1.46 (4H, m); 1.23 (9H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 192.3; 41.2; 36.0; 28.1; 23.8; 20.0. MS (*m*/*z*, %): 181 (9, M^+); 180 (12, M^+-1); 166 (63); 138 (19); 131 (33); 100 (11); 97 (19); 96 (100); 85 (10); 67 (51); 55 (33); 54 (32); 53 (29); 41 (74).

1.4.6. 2-Trifluoroacetylaminocyclohexanol. Under a nitrogen atmosphere, 2-aminocyclohexanol hydrochloride (1.213 g, 8 mmol), pyridine (2.513 g, 32 mmol) and DMAP (few crystals) were dissolved in 50 mL of anhydrous CH_2Cl_2. The solution was cooled to −16°C and then trifluoroacetic anhydride was added (3.360 g, 16 mmol). The mixture was warmed to room temperature and the reaction was allowed to proceed for 1 h. The solvent was subsequently removed in vacuo, and replaced with 60 mL methanol; the resulting mixture was stirred for 2 h, then methanol was evaporated and replaced with 60 mL ethyl acetate. The organic phase was washed with a saturated solution of $NaHCO_3$ (2×60 mL) and the aqueous layer was extracted with ethyl acetate (4×40 mL). The combined organic layers were finally washed with brine (2×60 mL) and dried. Evaporation of the solvent afforded 1.345 g of pure 2-trifluoroacetylaminocyclohexanol (6.4 mmol, yield 80%) as a white solid, which was then used without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.53 (1H, m); 3.64 (1H, m); 3.41 (1H, m); 2.06–2.12 (2H, m); 1.72–1.81 (3H, m); 1.16–1.39 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 156.0; 116.0 (q, J=278 Hz); 73.4; 56.4; 34.6; 30.9; 24.3; 24.1. MS (*m*/*z*, %): 193 (22); 114 (20); 98 (67); 97 (20); 86 (17); 81 (17); 80 (29); 79 (17); 70 (27); 69 (54); 68 (18); 58 (16) 57 (55); 56 (18); 55 (25); 54 (16); 44 (45); 43 (56); 42 (45); 41 (100); 40 (29).

1.4.7. 1-Methansulfonyloxy-2-trifluoroacetylaminocyclohexane. 2-Trifluoroacetylamino-cyclohexanol (1.335 g, 6.3 mmol) was dissolved in 10 mL of anhydrous pyridine, under nitrogen. The resulting solution was cooled to 0°C and methanesulfonyl chloride (0.802 g, 7 mmol) was added dropwise. After stirring for 2 h, the reaction was warmed to room temperature and 80 mL ethyl acetate were added. The organic layer was washed with a saturated solution of $CuSO_4$ (until complete disappearance of the blue color of the copper/pyridine complex), H_2O (2×80 mL) and brine

(2×80 mL), and dried. Evaporation of the solvent afforded 1.552 g of pure 1-methansulfonyloxy-2-trifluoroacetylaminocyclohexane (5.4 mmol, yield 85%) as a white solid, which was then used without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.83 (1H, m); 4.56 (1H, dt, J=4.6, 10.6 Hz); 3.92 (1H, m); 3.03 (3H, s); 2.11–2.30 (2H, m); 1.57–1.86 (2H, m); 1.27–1.38 (4H, m). MS (*m*/*z*, %): 210 (22); 194 (20); 193 (22); 166 (38); 165 (100); 152 (84); 126 (42); 124 (32); 97 (81); 96 (26); 81 (46); 80 (72); 79 (88); 69 (46); 41 (29).

1.4.8. *N*-Trifluroacetyl-7-azabicyclo[4.1.0]heptane 6e. 1-Methansulfonyloxy-2-trifluoroacetylamino-cyclohexane (0.145 g, 0.5 mmol) was dissolved in 4.5 mL anhydrous THF, under nitrogen. The resulting solution was cooled to −78°C, and then a solution of 1 M LiHMDS in THF (0.5 mL, 0.5 mmol) was added dropwise. After 3 h, the solvent was removed in vacuo and replaced with an equal volume of anhydrous pentane; the solution was filtered over a fritted-glass septum and the solvent evaporated, affording 25 mg of **6e** (0.13 mmol, yield 26%) as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.96 (2H, bs); 1.62–2.10 (4H, m); 1.25–1.50 (4H, m). MS (*m*/*z*, %): 193 (3, M^+); 96 (100); 82 (4); 81 (20); 69 (51); 42 (13); 41 (17).

1.5. General procedure for the isomerization of *N*-sulfonylaziridines using LIDAKOR in pentane at room temperature

A solution of BuLi in hexane (0.66 mL of a 1.5 M solution, 1.0 mmol) was mixed with pentane (1.5 mL), diisopropylamine (101 mg, 1.0 mmol) and potassium *tert*-butoxide (112 mg, 1.0 mmol), at 0°C under nitrogen; the mixture was stirred at 0°C for 15 min, after which the aziridine (0.5 mmol) was added and allowed to react for 15–18 h at room temperature. The reaction was then quenched with H_2O (10 mL) and extracted with Et_2O (3×10 mL). The organic layers were combined and washed with H_2O (2×15 mL) and brine (2×15 mL), and then dried. Evaporation of the solvent gave the isomerization products, which were purified by flash chromatography.

1.5.1. 3-*N*-*p*-Toluenesulfonylamino-cyclopentene 16.[58] Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 42%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.75–7.79 (2H, m); 7.29–7.33 (2H, m); 5.87 (1H, m); 5.43 (1H, m); 4.40 (2H, m); 2.42 (3H, s); 2.00–2.40 (2H, m); 1.20–1.80 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.2; 138.1; 135.0; 130.4; 129.6; 127.0; 59.8; 31.6; 30.8; 21.5. MS (*m*/*z*, %): 149 (100); 104 (12); 76 (24); 65 (10); 57 (11); 55 (10).

1.5.2. 3-*N*-*p*-Toluenesulfonylaminocyclohexene 7a.[28] Purification: eluent petroleum ether/ethyl acetate 9:2; yield: 46%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.74–7.78 (2H, m); 7.26–7.30 (2H, m); 5.75 (1H, m); 5.30 (1H, m); 4.60 (1H, m); 3.78 (1H, bs); 2.41 (3H, s); 1.10–1.90 (6H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.1; 138.3; 131.4; 129.6; 127.0; 126.9; 49.0; 30.2; 24.5; 21.5; 19.3. MS (*m*/*z*, %): 159 (4); 155 (21); 96 (47); 91 (100); 82 (2); 81 (11); 80 (14); 79 (25); 77 (11); 69 (11); 68 (29); 67 (14); 65 (44).

1.5.3. 3-*N*-Benzenesulfonylaminocyclohexene 7b.[59] Purification: eluent petroleum ether/ethyl acetate 3:1; yield: 30%; pale yellowish oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.87–7.91 (2H, m); 7.51–7.58 (3H, m); 5.74–5.80 (1H, m); 5.30–5.35 (1H, m); 4.41–4.58 (1H, m); 3.82 (1H, bs); 1.25–1.94 (4H, m); 0.79–0.97 (2H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.8; 132.5; 131.7; 129.1; 126.9; 49.1; 30.3; 24.5; 19.3. MS (*m*/*z*, %): 96 (28); 91 (17); 79 (19); 77 (100); 76 (48); 68 (25); 67 (25); 66 (17); 55 (16); 54 (17); 53 (23); 51 (55); 50 (58); 49 (21); 43 (16); 42 (22), 41 (86); 40 (69).

1.5.4. 1-*N*-*p*-Toluenesulfonylaminobicyclo[3.3.0]octane 17.[28] Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 64%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.74–7.78 (2H, m); 7.27–7.31 (2H, m); 4.47 (1H, m); 3.54 (1H, m); 2.41 (3H, s); 2.20–2.40 (2H, m); 0.90–1.90 (10H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.1; 137.8; 129.5; 127.0; 57.0; 45.5; 41.2; 35.5; 30.6; 29.4; 28.1; 27.3; 21.5. MS (*m*/*z*, %): 155 (17); 124 (14); 109 (3); 92 (11); 91 (100); 89 (10); 77 (8); 65 (19); 55 (17); 41 (13).

1.5.5. 5-*N*-*p*-Toluenesulfonylamino-3-octene 22. Purification: eluent petroleum ether/ethyl acetate 8:1; yield: 48%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.69–7.73 (2H, m); 7.24–7.28 (2H, m); 5.36 (1H, dt, J=15.4, 6.2 Hz); 5.01 (1H, dd, J=15.4, 7.4 Hz); 4.28 (1H, m); 3.71 (1H, m); 2.41 (3H, s); 1.82 (2H, quint, J=6.6 Hz); 1.22–1.43 (4H, m); 0.84 (3H, t, J=7.2 Hz); 0.79 (3H, t, J=7.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 142.9; 138.3; 134.1; 129.3; 128.3; 127.2; 55.9; 38.2; 25.0; 21.4; 18.6; 13.6; 13.1. MS (*m*/*z*, %): 281 (6, M^+); 239 (16); 238 (91); 207 (20); 155 (55); 92 (13); 91 (100); 83 (12); 80 (11); 79 (12); 73 (16); 65 (25); 55 (13). Anal. calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98. Found: C, 63.91; H, 8.16; N, 4.90.

1.5.6. 3-*N*-*p*-Toluenesulfonylamino-1-octene 23.[60] Purification: eluent petroleum ether/ethyl acetate/triethylamine 87:11.5:1.5; yield: 20%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.74–7.78 (2H, m); 7.29–7.33 (2H, m); 5.54 (1H, ddd, J=6.4, 10.0, 16.8 Hz); 4.98 (1H, d, J=16.8 Hz); 4.95 (1H, d, J=10.0 Hz); 4.57 (1H, m); 3.85 (1H, q, J=6.4 Hz); 2.43 (3H, s); 0.82–1.36 (11H, m). MS (*m*/*z*, %): 210 (67); 155 (60); 126 (6); 91 (100); 79 (11); 77 (11); 73 (21); 68 (11); 67 (12); 65 (34); 55 (12); 54 (11).

1.5.7. 2-*N*-*p*-Toluenesulfonylamino-3-octene 24. Purification: eluent petroleum ether/ethyl acetate/triethylamine 87:11.5:1.5; yield: 40%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.71–7.75 (2H, m); 7.25–7.29 (2H, m); 5.39 (1H, dt, J=15.5, 6.4 Hz); 5.14 (1H, dd, J=15.5, 6.6 Hz); 4.55 (1H, m); 3.73 (1H, quint, J=6.6 Hz); 2.43 (3H, s); 1.83 (2H, m); 0.82–1.36 (10H, m). MS (*m*/*z*, %): 267 (11); 198 (5); 155 (32); 126 (22); 111 (11); 110 (25); 92 (12); 91 (100); 82 (15); 81 (12); 79 (11); 73 (24); 70 (11); 69 (10); 68 (29); 67 (11); 65 (24); 55 (25). Anal. calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.11; H, 8.29; N, 5.08.

1.6. General procedure for the isomerization of *N*-tosylaziridines using LICKOR in THF at −50°C (−20°C)

Hexane was stripped off from a solution of BuLi (0.66 mL of a 1.5 M solution, 1.0 mmol) and precooled THF (2.0 mL) was added at −78°C under nitrogen, followed by potassium

tert-butoxide (112 mg, 1.0 mmol). The mixture was stirred at −78°C for 30 min, after which the aziridine (0.5 mmol) was added and allowed to react for 15–18 h at −50°C (−20°C). The reaction was then quenched with H_2O (10 mL), and extracted with Et_2O (3×10 mL). The organic layers were combined and washed with H_2O (2×15 mL) and brine (2×15 mL), and then dried; evaporation of the solvent gave the isomerization products which were purified by flash chromatography.

1.6.1. 3-*N*-*p*-Toluenesulfonylaminocyclooctene 18.[61] Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 33% (at −50°C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.71–7.75 (2H, m); 7.26–7.30 (2H, m); 5.56 (1H, q_{app}, J=9.0 Hz); 5.11 (1H, t_{app}, J=9.2 Hz); 4.39 (1H, m); 4.20 (1H, m); 2.42 (1H, s); 2.05 (2H, m); 1.00–1.80 (8H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.1; 133.5; 131.0; 130.2; 129.4; 127.1; 51.5; 37.1; 29.7; 29.0; 26.4; 24.2; 21.5. MS (*m*/*z*, %): 155 (13); 124 (98); 109 (2); 92 (13); 91 (100); 89 (11); 77 (10); 68 (11); 67 (13); 65 (24); 55 (36); 53 (12); 41 (13).

1.6.2. 1-*N*-*p*-Toluenesulfonylaminobicyclo[3.3.0]octane 17.[28] Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 48% (at −20°C).

1.7. General procedure for the isomerization of *N*-tosylaziridines using LIDAKOR in THF at −50°C

Hexane was stripped off from a solution of BuLi (0.66 mL of a 1.5 M solution, 1.0 mmol) and precooled THF (2.0 mL) was added at −78°C under nitrogen, followed by diisopropylamine (101 mg, 1.0 mmol) and potassium *tert*-butoxide (112 mg, 1.0 mmol). The mixture was stirred at −78°C for 30 min, after which the aziridine (0.5 mmol) was added and allowed to react for 15–18 h at −50°C. The reaction was then quenched with H_2O (10 mL) and extracted with Et_2O (3×10 mL). The organic layers were combined and washed with H_2O (2×15 mL) and brine (2×15 mL), and then dried; evaporation of the solvent gave the isomerization products which were purified by flash chromatography.

1.7.1. 3-*N*-*p*-Toluenesulfonylaminocyclohexene 7a.[28] Purification: eluent petroleum ether/ethyl acetate 9:2; yield: 64%.

1.8. Preparation of heterosubstituted aziridinyl ethers

1.8.1. (2*R*,3*R*)-4-Phenyl-2,3-epoxy-1-butanol. Molecular sieves 4 Å (1.26 g), CH_2Cl_2 (50 mL), (D)-(−)-diethyl tartrate (0.42 mL, 2.43 mmol) and $Ti(O^iPr)_4$ (0.60 mL, 2.01 mmol) were mixed under nitrogen and cooled to −23°C. ^{t}BuOOH (5.9 mL of a 5.5 M solution in decane, dried over molecular sieves 4 Å, 32.28 mmol) was then slowly added and the mixture maintained at −23°C for 30 min before (*E*)-4-phenyl-but-2-en-1-ol (1.99 g, 13.45 mmol) in CH_2Cl_2 (7 mL) was slowly added. After 48 h a solution obtained by dissolving 33 g of $FeSO_4{\cdot}7H_2O$ and 11 g citric acid in 100 mL of H_2O and cooled at 0°C was added and the mixture warmed up to room temperature. The two phases, which were formed after stirring, were separated; the water phase was extracted with Et_2O (3×30 mL) and the organic phases were added to a solution obtained by dissolving 5 g of NaCl and 30 g of NaOH in 90 mL of H_2O. After 1 h of vigorous stirring, the two phases were separated, the water phase was extracted with Et_2O (3×50 mL) and the organic layers were combined and dried. Evaporation of the solvent gave 1.83 g of the desired product (83%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.45–7.10 (5H, m); 3.89 (1H, bd, J=12.6 Hz); 3.61 (1H, bd, J=12.6 Hz); 3.22 (1H, td, J=5.6, 2.2 Hz); 3.04–2.98 (1H, m); 2.96–2.90 (2H, m); 2.45 (1H, bs).

1.8.2. (2*R*,3*R*)-1-Methoxymethoxy-2,3-epoxy-4-phenylbutane. To a solution of (2*R*,3*R*)-4-phenyl-2,3-epoxy-1-butanol (1.82 g, 11 mmol) in CH_2Cl_2 (25 mL) at 0°C, *N*,*N*-diisopropylethylamine (3.80 mL, 22 mmol) and chloromethyl methyl ether (1.25 mL, 16.6 mmol) were added under nitrogen. The mixture was stirred at room temperature for 14 h and then washed with an aqueous solution of 10% HCl (25 mL), sat. $NaHCO_3$ (3×30 mL) and brine (3×30 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude oxiranyl ether obtained (2.04 g, 89%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.10 (5H, m); 4.62 (2H, s); 3.73 (1H, dd, J=11.8, 3.6 Hz); 3.54 (1H, dd, J=11.8, 5.6 Hz); 3.34 (3H, s); 3.10 (1H, td, J=5.6, 2.2 Hz); 3.04–2.96 (1H, m); 2.92–2.86 (2H, m).

1.8.3. (2*S*,3*S*)-1-Methoxymethoxy-2-hydroxy-3-azido-4-phenylbutane, (2*S*,3*R*)-1-methoxymethoxy-2-azido-3-hydroxy-4-phenylbutane. To (2*R*,3*R*)-1-methoxymethoxy-2,3-epoxy-4-phenylbutane (1.94 g, 9.3 mmol) in 2-methoxyethanol/water, 8:1 (63 mL), NaN_3 (3.63 g, 55.8 mmol) and NH_4Cl (1.00 g, 18.6 mmol) were added under N_2. The mixture was stirred at 80°C for 6 h before H_2O (20 mL) and Et_2O (40 mL) were added. The water phase was extracted with Et_2O (3×50 mL) and the organic layers were collected, washed with H_2O (3 60 mL) and dried. Evaporation of the solvent gave 1.88 g (80%) as a mixture of regioisomeric azido alcohols as a brown oil. MS (*m*/*z*, %): 177 (2, $M^+-OH-N_3-CH_3$); 161 (2, $M^+-OH-N_3-OCH_3$); 146 (3); 133 (5); 105 (17); 91 (100, $C_7H_7^+$); 73 (42); 65 (32).

1.8.4. (2*R*,3*S*)-3-Benzyl-2-methoxymethoxymethylaziridine. A mixture of (2*S*,3*S*)-1-methoxymethoxy-2-hydroxy-3-azido-4-phenylbutane and (2*S*,3*R*)-1-methoxymethoxy-2-azido-3-hydroxy-4-phenylbutane (1.74 g, 6.9 mmol), anhydrous toluene (30 mL) and triphenylphosphine (2.18 g, 8.3 mmol) was refluxed under N_2 for 24 h. After removing the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and filtered over Celite® to remove $OPPh_3$. The filtrated was evaporated giving 1.48 g (quantitative) of crude aziridine. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.50–7.10 (5H, m); 4.60 (2H, s); 3.68 (1H, dd, J=12.0, 5.3 Hz); 3.47 (1H, dd, J=12.0, 4.0 Hz); 3.40 (1H, m); 3.33 (3H, s); 2.80 (2H, m); 2.20–2.00 (2H, m).

1.8.5. (2*R*,3*S*)-3-Benzyl-2-methoxymethoxymethyl-1-*p*-toluenesulfonylaziridine 26.[50] To a solution of (2*R*,3*S*)-2-[(methoxymethoxy)methyl]-3-benzylaziridine (1.55 g, 7.48 mmol) in CH_2Cl_2 (40 mL) at 0°C, 4-(dimethylamino)-pyridine (170 mg, 0.7 mmol), triethylamine (2.1 mL,

15 mmol) and *p*-toluenesulfonyl chloride (2.16 g, 11.3 mmol) were added under nitrogen. The reaction mixture was stirred at 25°C for 12 h before H_2O (30 mL) was added. The water phase was then extracted with CH_2Cl_2 (3×40 mL) and the organic layers were collected and washed with H_2O (3×50 mL), brine (3×40 mL) and dried. The solvent was evaporated under reduced pressure and the crude was then purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) affording 1.24 g (46%, 94% ee determined via Mosher ester) of **26** as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.74 (2H, d, J=8.2 Hz); 7.15–7.00 (7H, m), 4.52 (2H, s); 3.79 (2H, m); 3.25 (3H, s); 3.10–3.00 (4H, m); 2.43 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.8; 137.3; 137.2; 129.3; 128.5; 128.4; 127.4; 126.5; 96.3; 65.6; 55.2; 47.6; 47.2; 35.6; 21.5. MS (*m*/*z*, %): 286 (8, M^+-CH_2OMOM); 270 (6, $M^+-C_7H_7^+$); 210 (11); 194 (3); 174 (6); 155 (8, Ts); 146 (24); 139 (44); 138 (17); 129 (13); 117 (9); 104 (14); 91 (100, $C_7H_7^+$); 77 (30); 65 (49); 54 (56). Anal. calcd for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88. Found: C, 63.21; H, 6.29; N, 3.68.

1.8.6. (2*S*,3*S*)-2,3-Epoxyoctanol. Molecular sieves 4 Å (0.6 g), CH_2Cl_2 (70 mL), (L)-(+)-diethyl tartrate (266 mg, 1.3 mmol) and $Ti(O^iPr)_4$ (412 mg, 1.44 mmol) were mixed under N_2 and cooled to −23°C. ^{t}BuOOH (7.4 mL of a 5.5 M solution in decane, dried over molecular sieves 4 Å, 40.6 mmol) was then slowly added and the mixture maintained at −20°C for 30 min before (*E*)-2-octenol (2.56 g, 20 mmol) was added. After 18 h, a solution obtained by dissolving 3.55 g of $FeSO_4$ and 1.35 g citric acid in 10 mL of H_2O and cooled at 0°C was added and the mixture warmed up to room temperature. The two phases, which were formed after stirring, were separated; the water phase was extracted with Et_2O (3×10 mL) and the organic phases were added to a solution obtained by dissolving 0.5 g of NaCl and 3.0 g of NaOH in 9.0 mL of H_2O. After 45 min of vigorous stirring the two phases were separated, the water phase was extracted with Et_2O (3×10 mL) and the organic layers were combined and dried. Evaporation of the solvent gave 2.33 g of the desired product (81%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.90 (1H, dd, J=12.8, 2.6 Hz); 3.60 (1H, dd, J=12.8, 4.4 Hz); 2.94 (2H, m); 2.20 (1H, bs); 1.54 (2H, m); 1.30 (6H, m); 0.90 (3H, t, J=6.6 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 61.7; 58.6; 56.0; 31.5; 31.5; 25.6; 25.6; 13.9. MS (*m*/*z*, %): 101 (4, $M^+-C_3H_7$); 83 (95); 71 (10); 69 (12); 61 (11); 57 (67); 56 (44); 55 (100).

1.8.7. (2*S*,3*S*)-1-Methoxymethoxy-2,3-epoxyoctane. To a solution of (2*S*,3*S*)-2,3-epoxyoctanol (927 mg, 6.4 mmol) in CH_2Cl_2 (40 mL) at 0°C, *N*,*N*-diisopropylethylamine (2.2 mL, 12.8 mmol) and chloromethyl methyl ether (0.73 mL, 9.6 mmol) were added under nitrogen. The mixture was stirred at room temperature for 12 h and then washed with 10% HCl (30 mL), sat. $NaHCO_3$ (3×25 mL) and brine (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave (2*S*,3*S*)-1-methoxymethoxy-2,3-epoxyoctane (1.04 g, 87%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.64 (2H, s); 3.73 (1H, dd, J=11.4, 5.4 Hz); 3.53 (1H, dd, J=11.4, 3.4 Hz); 3.37 (3H, s); 2.92 (1H, ddd, J=5.4, 3.4, 2.4 Hz); 2.83 (1H, ddd, J=6.1, 5.4, 2.4 Hz); 1.5 (2H, m); 1.3 (6H, m); 0.87 (3H, t, J=7.2 Hz).

1.8.8. (2*R*,3*R*)-1-Methoxymethoxy-2-hydroxy-3-azidooctane, (2*R*,3*S*)-1-methoxymethoxy-3-hydroxy-2-azidooctane. To the oxiranyl ether (1.65 g, 8.7 mmol) in 2-methoxyethanol/water, 8:1 (55 mL), NaN_3 (3.45 g, 53 mmol) and NH_4Cl (0.96 g, 18 mmol) were added under N_2. The mixture was stirred at 80°C for 12 h then H_2O (30 mL) and Et_2O (100 mL) were added. The two phases were separated; the water phase was extracted with Et_2O (3×30 mL), and the organic layers were washed with H_2O (3×50 mL), dried and evaporated. The resulting azido alcohol was purified by flash chromatography (petroleum ether/AcOEt, 2:1) affording 1.21 g (60%) of a mixture of regioisomers. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.65 (2H, s); 3.7 (4H,m); 3.37 (3H, s); 2.82 (1H, bs); 1.5 (2H, m); 1.29 (6H, m); 0.88 (3H, t, J=6.6 Hz). MS (*m*/*z*, %): 105 (33, $CH_3OCH_2OCH_2CH{=}OH^+$); 98 (11); 87 (8); 75 (13); 73 (100); 71 (15); 57 (22); 56 (17); 55 (25).

1.8.9. (2*R*,3*R*)-1-Methoxymethoxy-2-methansulfonyloxy-3-azidooctane, (2*R*,3*S*)-1-methoxymethoxy-3-methansulfonyloxy-2-azidooctane. The mixture of (2*R*,3*R*)-1-methoxymethoxy-2-hydroxy-3-azidooctane and (2*R*,3*S*)-1-methoxymethoxy-3-hydroxy-2-azidooctane (1.62 g, 7.0 mmol) and anhydrous pyridine (16 mL) were mixed under N_2 and cooled at 0°C. Methanesulfonyl chloride (985 mg, 8.6 mmol) was added and the mixture stirred at room temperature for 24 h before Et_2O was added (16 mL). The mixture was then washed with sat. $CuSO_4$ (until complete disappearance of the blue color of the copper/pyridine complex), H_2O (3×20 mL), dried and evaporate, giving 1.73 g (80%) as a mixture of mesylated azido alcohols. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.69 (1H, dt, J=5.6, 4.6 Hz); 4.65 (2H, s); 3.79 (1H, d, J=1.2 Hz); 3.76 (1H, m); 3.70 (1H, m); 3.37 (3H, s); 3.10 (3H, s); 1.6–1.1 (8H, m); 0.89 (3H, m).

1.8.10. (2*S*,3*R*)-2-Methoxymethoxymethyl-3-pentylaziridine. The mixture of (2*R*,3*R*)-1-methoxymethoxy-2-methansulfonyloxy-3-azidooctane and (2*R*,3*S*)-1-methoxymethoxy-3-methansulfonyloxy-2-azidooctane (0.36 g, 1.18 mmol) in THF (5 mL) was stirred under nitrogen at 0°C. $LiAlH_4$ (3.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h it was warmed up to 50°C for 12 h. The reaction was then quenched with H_2O and aqueous NH_4Cl, after cooling to 0°C. The mixture was filtered over Celite® and the organic layer was dried. The evaporation of the solvent gave 0.209 g (94%) of the desired aziridine. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.62 (2H, s); 3.63 (1H, dd, J=10.8, 4.6 Hz); 3.43 (1H, dd, J=10.8, 6 Hz); 3.35–3.34 (1H,m); 3.33 (3H, s); 1.85 (1H, m); 1.78 (1H, m); 1.40 (2H, m); 1.25 (6H,m); 0.89 (3H, m). MS (*m*/*z*, %): 188 (2, M^++1); 156 (2, M^+-CH_3O); 142 (4, $M^+-CH_3OCH_2$); 126 (52, $M^+-CH_3OCH_2O$); 112 (53, M^+-CH_2OMOM); 82 (34); 69 (100); 56 (86).

1.8.11. (2*S*,3*R*)-2-Methoxymethoxymethyl-3-pentyl-1-*p*-toluenesulfonylaziridine 27.[50] To a solution of (2*S*,3*R*)-2-methoxymethoxymethyl-3-pentylaziridine (0.807 g, 4.31 mmol) in anhydrous pyridine (40 mL) at 0°C, *p*-toluenesulfonyl chloride (0.820 g, 4.3 mmol) was added under N_2. The reaction mixture was stirred at 0°C for 20 min before Et_2O (20 mL) was added. The mixture was then washed with sat. $CuSO_4$ solution (until complete disappearance of

the blue color of the copper/pyridine complex), H_2O (3×30 mL), dried and the solvent removed under vacuum. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) giving 0.965 g (65%, 84% ee determined via Mosher ester) of pure **27**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.84 (2H, m); 7.30 (2H, m); 4.54 (2H, s); 3.76 (2H, m); 3.27 (3H, s); 2.92 (1H, dt, J=5.8, 4.4 Hz); 2.74 (1H, dt, J=6.6, 4.4 Hz); 2.42 (3H, s); 1.75 (2H, m); 1.25 (6H, m); 0.84 (3H, m,). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 146.0; 143.1; 129.9; 127.3; 108.0; 95.6; 56.5; 53.9; 36.2; 31.0; 25.1; 23.0; 21.8; 15.6; 14.0. MS (*m*/*z*, %); 210 (37); 186 (28, M^+-Ts); 155 (35, Ts); 140 (8); 91 (100); 69 (16); 65 (39); 55 (18); 54 (31). Anal. calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 59.76; H, 8.02; N, 4.18.

1.9. Isomerization of heterosubstituted aziridines

1.9.1. (3*E*)-(2*R*)-1-Methoxymethoxymethyl-4-phenyl-2-(*N*-*p*-toluenesulfonyl)ammino-3-butene 28.[50] The general procedure with LIDAKOR in pentane was used on aziridine **26**, obtaining a crude product which was then purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) giving 76 mg (70%, 91% ee determined via Mosher ester) of **28**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.73 (2H, d, J=8.6 Hz); 7.30–7.10 (7H, m); 6.39 (1H, d, J=15.8 Hz); 5.86 (1H, dd, J=15.8, 7.4 Hz); 5.21 (1H, d, J=7.0 Hz); 4.56 (2H, s); 4.12 (1H, m); 3.58 (2H, d, J=4.8 Hz); 3.32 (3H, s); 2.33 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 143.3; 138.0; 136.1; 132.7; 129.5; 128.4; 127.9; 127.3; 126.4; 125.8; 96.7; 70.5; 55.7; 55.5; 21.4. MS (*m*/*z*, %): 300 (1, M^+-OMOM); 286 (64, M^+-CH_2OMOM); 206 (2); 226 (1); 184 (3); 176 (4); 155 (33); 145 (6); 130 (33); 115 (25); 103 (7); 91 (100); 77 (1); 65 (23). Anal. calcd for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88. Found: C, 63.26; H, 6.49; N, 3.69.

1.9.2. (1*E*)-(3*R*)-1-Methoxymethoxy-3-*N*-*p*-toluenesulfonylamino-1-octene 29.[50] The general procedure was used on aziridine **27**, obtaining 1.21 g (78%) of a crude product which was then purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) giving 864 mg (56%, 81% ee determined via Mosher ester) of **29**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.73 (2H, m); 7.28 (2H, m); 6.09 (1H, dd, J=12.5, 0.8 Hz); 4.68 (1H, dd, J=12.5, 4.7 Hz); 4.62 (2H, s); 4.58–4.42 (1H, m); 3.80–3.46 (1H, m); 3.29 (3H, s); 2.41 (3H, s); 1.6–1.0 (8H, m); 0.88 (3H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 145.9; 143.0; 138.4; 129.1; 127.2; 107.8; 95.5; 55.7; 53.2; 36.5; 31.2; 25.1; 22.4; 21.4; 13.9. MS (*m*/*z*, %): 254 (10); 210 (91); 187 (71, M^+-91); 171 (5, NH_2Ts); 155 (83, Ts); 140 (19); 91 (100); 84 (53); 69 (15); 68 (24); 65 (15); 57 (13). Anal. calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 59.72; H, 7.92; N, 4.13.

1.10. Elaboration of amino vinyl ethers

1.10.1. (3*R*)-3-*N*-*p*-Toluenesulfonylammino-1-octanal 32.[50] To a solution of **29** (68 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) at −78°C, Bu_4NI (74 mg, 0.2 mmol) and Me_3SiCl (0.17 mL, 0.2 mmol) were added under nitrogen. The reaction mixture was stirred at −20°C for 24 h, before sat. $NaHCO_3$ (1 mL) and THF (3 mL) were added. The mixture was stirred for 10 min and then extracted with Et_2O (3×5 mL), washed with brine (3×5 mL), dried and evaporated. The crude was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) giving 34 mg (56%) of aldehyde **32**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 9.64 (1H, s); 7.74 (2H, m); 7.29 (2H, m); 4.82 (1H, d, J=8.4 Hz); 3.57 (1H, m); 2.62 (2H, m); 2.42 (3H, s); 1.42 (2H, m); 1.30–1.00 (6H, m); 0.79 (3H, t, J=6.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 205.0; 143.5; 138.0; 130.0; 127.0; 49.5; 38.0; 35.0; 31.0; 25.0; 23.0; 21.0; 14.0. MS (*m*/*z*, %): 254 (7, M^+-CH_2COH); 226 (20); 207 (3); 172 (24); 155 (82); 142 (10); 91 (100); 65 (6). Anal. calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.72; H, 7.90; N, 4.63.

1.10.2. (3*R*)-3-*N*-*p*-Toluenesulfonyl-octanoic acid 33.[50,62] To a solution of aldehyde **32** (49 mg, 0.16 mmol) in MeCN/H_2O, 3:1 (0.8 mL) at 0°C, 0.94 mL of a solution obtained dissolving H_5IO_6 (5.7 g) and CrO_3 (11.5 mg) in MeCN: H_2O, 3:1 (5.7 mL) was slowly added. The reaction mixture was stirred for 6 h before sat. Na_2HPO_4 (4 mL) and toluene (4 mL) were added. The organic phase was washed with a solution of brine: H_2O, 1:1 (5 mL), sat. $NaHSO_3$ (3×5 mL) and brine (3×5 mL). After evaporation of the solvent, the crude was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) affording 26 mg (52%) of pure acid **33**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.77 (2H, d, J=8.4 Hz); 7.29 (2H, d, J=8.4 Hz); 5.40–4.80 (1H, bs); 3.49 (1H, m); 2.48 (2H, d, J=5.2 Hz); 2.42 (3H, s); 1.45 (2H, m); 1.40–1.00 (6H, m); 0.81 (3H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 173.7; 141.1; 135.5; 127.8; 124.5; 46.5; 38.2; 32.1; 28.5; 22.3; 20.0; 19.7; 11.8.

References

1. Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519–1559.
2. McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.
3. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.
4. Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A, p 1.
5. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
6. Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.
7. Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345.
8. Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, 92.
9. Morgan, K. M.; Gronert, S. *J. Org. Chem.* **2000**, *65*, 1461.
10. Mordini, A.; BenRayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401.
11. Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.
12. Mordini, A. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds. (McKillop, A. volume Ed.) Pergamon: Oxford, 1995; Vol. 11, p 93.
13. Margot, C.; Schlosser, M. *Tetrahedron Lett.* **1985**, *26*, 1035.
14. Asami, M. *J. Synth. Org. Chem. Jpn* **1996**, *54*, 188.
15. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.
16. Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.
17. O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.
18. Milne, D.; Murphy, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 884.
19. Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373.

20. Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108.
21. Asami, M. *Chem. Lett.* **1984**, 829.
22. Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760.
23. Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425.
24. Asami, M.; Inoue, S. *Tetrahedron Lett.* **1995**, *51*, 11725.
25. Bertilsson, S. K.; Södergren, M. J.; Andersson, P. G. *J. Org. Chem.* **2002**, *67*, 1567.
26. Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610.
27. da Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602.
28. Müller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662.
29. O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett.* **1999**, *40*, 8427.
30. Mordini, A.; Pecchi, S.; Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Reginato, G.; Ricci, A. *J. Org. Chem.* **1994**, *59*, 4784.
31. Mordini, A.; Bindi, S.; Pecchi, S.; Degl'Innocenti, A.; Reginato, G.; Serci, A. *J. Org. Chem.* **1996**, *61*, 4374–4378.
32. Mordini, A.; Bindi, S.; Pecchi, S.; Capperucci, A.; Degl'Innocenti, A.; Reginato, G. *J. Org. Chem.* **1996**, *61*, 4466–4468.
33. Mordini, A.; Valacchi, M.; Pecchi, S.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron Lett.* **1996**, *37*, 5209.
34. Mordini, A.; Valacchi, M.; Nardi, C.; Bindi, S.; Poli, G.; Reginato, G. *J. Org. Chem.* **1997**, *62*, 8557–8559.
35. Mordini, A.; Bindi, S.; Capperucci, A.; Nistri, D.; Reginato, G.; Valacchi, M. *J. Org. Chem.* **2001**, *66*, 3201.
36. Thurner, A.; Faigl, F.; Mordini, A.; Bigi, A.; Reginato, G.; Toke, L. *Tetrahedron* **1998**, *54*, 11597.
37. Thurner, A.; Faigl, F.; Toke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* **2001**, *57*, 8173.
38. Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309.
39. Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569.
40. Antunes, A. M. M.; Marto, S. J. L.; Branco, P. S.; Prabhakar, S.; Lobo, A. M. *Chem. Commun.* **2001**, 405.
41. Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161.
42. Simkhovic, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089.
43. Jeoung, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.
44. Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485.
45. Kano, D.; Minakata, S.; Komatsu, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3186.
46. Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619.
47. Boc is not always inert towards nucleophile as recently underlined in the following review article: Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701.
48. Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541.
49. It has been reported that α-elimination occurs with dimeric LDA while β-elimination is favoured with monomeric reagent: Ramirez, A.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 11114.
50. These results have been already published in a preliminary communication: Mordini, A.; Sbaragli, L.; Valacchi, M.; Russo, F.; Reginato, G. *Chem. Commun.* **2002**, 778.
51. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
52. Schlenk, W.; Bergmann, E. *Liebigs Ann. Chem.* **1928**, *464*, 22.
53. Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30.
54. Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.
55. Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, *57*, 1765.
56. Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.
57. Tisue, G. T.; Linke, S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6303.
58. Kim, D. Y.; Kim, H. S.; Choi, Y. J.; Mang, J. Y.; Lee, K. *Synth. Commun.* **2001**, *31*, 2463.
59. Barashenkov, G. G.; Derkach, N. Y. *J. Org. Chem. USSR* **1986**, 1069.
60. Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Synlett* **2001**, 1608.
61. Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927.
62. Jefford, C. W.; McNulty, J.; Lu, Z. H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203.