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α-Lithiation-rearrangement of *N*-toluenesulfonyl aziridines with *sec*-butyllithium and (−)-sparteine: opposite sense of asymmetric induction to epoxides

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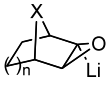
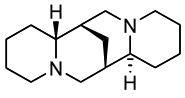
Abstract—The α-lithiation rearrangement of three cyclic *N*-toluenesulfonyl (tosyl) aziridines has been carried out using *sec*-butyllithium/(−)-sparteine. In each case, it was established that preferential lithiation of the *S*-aziridine stereocentre occurred. This is the opposite sense of asymmetric induction to that observed with epoxides.

Since Cope's seminal contribution in 1951,[1] a wealth of synthetic and mechanistic chemistry associated with lithiated epoxides (oxiranyl anions) has been investigated.[2,3] Most recently, Hodgson and co-workers have made significant progress in harnessing the synthetic potential of enantioenriched lithiated epoxides generated by direct lithiation of epoxides using alkyllithiums in the presence of (−)-sparteine.[3–5] In *all* of the epoxides studied by Hodgson, the use of (−)-sparteine as a chiral ligand leads to preferential lithiation of the *R*-epoxide stereocentre (to varying degrees, depending on the substrate), thus generating lithiated epoxides **1** and **2**.

1; n = 1-5
range of substitution patterns



2; X = CH_2, NR or O
n = 1, 2; *range of substitution patterns*



(−)-sparteine

In contrast, the chemistry of lithiated aziridines (aziridinyl anions) has received much less attention and has generally involved the use of an anion stabilising group attached directly to the aziridine.[2] Examples of the direct interaction of strong bases with aziridines lacking an anion stabilising group are limited to Beak's α-lithiation-in situ trapping of *N*-Boc aziridines,[6] Vedejs' use of *N*-alkyl aziridines complexed by borane,[7] Mordini's reactions of superbases (e.g. LDA/KO^{t}Bu or *n*-butyllithium/KO^{t}Bu) with *N*-tosyl aziridines[8] and Müller's use of *sec*-butyllithium and (−)-sparteine to desymmetrise *N*-tosyl aziridines.[9] Due to our ongoing interest in sparteine-like diamines[10] and aziridines,[11] we became interested in further extending the pioneering contribution of Müller and Nury.[9] In particular, we wished to establish the sense of asymmetric induction in the proposed α-lithiation of cyclic *N*-tosyl aziridines, as this had not been commented on in the original disclosure. Herein, we present the results of this stereochemical study.

N-Tosyl aziridines **3**, **5** and **7** were prepared by Sharpless aziridination of the corresponding cycloalkenes.[11,12] An Et_2O solution of each of these aziridines was added to *sec*-butyllithium/(−)-sparteine (2.9 equiv.) in Et_2O at −78°C. After 4 h at −78°C, the solution was allowed to warm to room temperature over 1 h. Standard aqueous work-up and chromatography furnished the rearranged products (*R*)-**4**, (*R*)-**6** and **8** in the yields and ee's (determined by chiral HPLC) indicated in Scheme 1. Presumably, aziridine α-lithiation is followed by insertion into an adjacent C–H bond to give (*R*)-**4** and (*R*)-**6** or into a transannular C–H bond to give **8**. The ee's were dependent on the aziridine ring size and the highest yields were obtained with the 6- and 8-ring aziridines (**5** and **7**).

Keywords: aziridines; rearrangement; lithiation; sulfonamides; stereochemistry.
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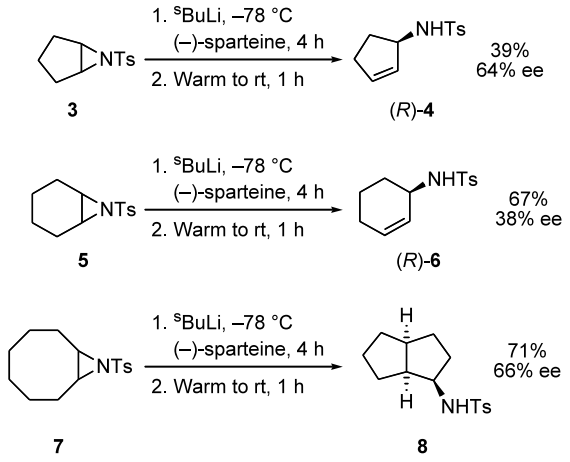
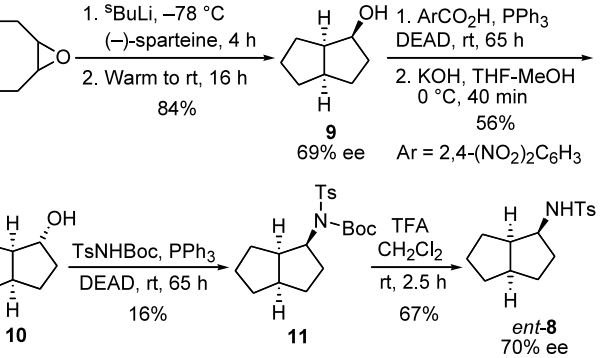


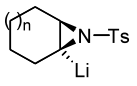
Scheme 1.

The stereochemistry of the major enantiomer of **4** and **6** was assigned as (*R*) by conversion of each of them into the corresponding known[13] NHBoc compounds (Boc protection followed by Na/NH_3 tosyl deprotection) and comparison of optical rotation data. The stereochemistry of bicyclic sulfonamide **8** was established by independent synthesis of *ent*-**8** as described in Scheme 2. Alcohol **9** (69% ee, prepared by *sec*-butyllithium/(–)-sparteine rearrangement of cyclooctene oxide[4]) was converted into alcohol **10** via Mitsunobu inversion and reaction with KOH. Then, alcohol **10** was reacted with Weinreb's TsNHBoc reagent[14] to give Boc protected sulfonamide **11** in a disappointing yield of only 16% (despite an extended reaction time). No other diastereomeric product was generated from this reaction and the low yield reflects the difficulty of carrying out a S_N2 reaction on the sterically hindered *endo*-face of the bicyclic system. Finally, Boc deprotection of **11** using TFA gave sulfonamide *ent*-**8**, as judged by the sign of the optical rotation and the chiral HPLC retention times.

Thus, the sense of asymmetric induction in the lithiation-rearrangement of *N*-tosyl aziridines **3**, **5** and **7** has been unequivocally established. Our results indicate that the use of (–)-sparteine with *N*-tosyl aziridines leads to preferential α-lithiation of the *S*-aziridine stereocentre to give lithiated aziridines **12**. This is the opposite sense of asymmetric induction to all of the epoxide examples reported by the Hodgson group, which proceed through lithiated epoxides **1** and **2**.[3–5] The presence of a *N*-tosyl group in aziridines permits a changeover of the enantiodiscriminating interactions between the alkyllithium–(–)-sparteine complex and the substrate. With *N*-tosyl aziridines, it is possible that stereoselective complexation of the alkyllithium to one of the enantiotopic S=O groups could be the source of the reversal in stereoselectivity compared to epoxides. Recent work from the Müller group has confirmed that the *S*-aziridine stereocentre is lithiated preferentially in three other related *N*-tosyl aziridine examples.[15]



Scheme 2.



12
n = 0, 1 or 3

In conclusion, the predominant sense of asymmetric induction in the lithiation-rearrangement of *N*-tosyl aziridines **3**, **5** and **7** using *sec*-butyllithium/(–)-sparteine is *opposite to the corresponding epoxides*. Further work in our group will focus on rationalising the difference in enantioselectivity between epoxides and aziridines.

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