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Chiral organolithium species: determination of the rate of cyclization and extent of racemization

Iain Coldham* and Graham P. Vennall

School of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD. E-mail: I.Coldham@exeter.ac.uk

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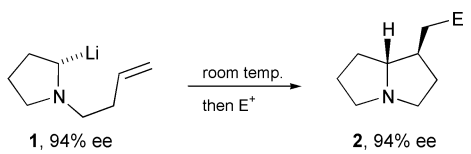
The rate of intramolecular carbolithiation onto an unactivated alkene to give a six-membered ring has been determined and follows first order kinetics with a half life of ~ 90 min at 23 °C; this allows significant racemization using a chiral organolithium species, although good levels of optical purity are obtained with a phenylthio-substituted alkene.

The ability to use enantiomerically enriched organometallic species in asymmetric synthesis hinges on the configurational stability at the chiral centre. Since Still and Sreekumar showed that chiral organolithium species could be generated from α-alkoxyorganostannanes and reacted stereospecifically,[1] the reactions of chiral α-hetero-substituted organolithium species have been the subject of extensive studies.[2] The majority of these studies focus on the intermolecular quench, which occurs with retention, inversion or racemization of configuration. We and others have demonstrated that intramolecular (anionic) cyclization occurs with complete retention of configuration at the carbanion centre and provides enantiomerically enriched heterocyclic and carbocyclic compounds.[3–5] For example, we have found that cyclization using the α-aminoorganolithium species **1** (formed from the corresponding organostannane, 94% ee) gives (Scheme 1) the hexahydro-1*H*-pyrrolizine alkaloid (+)-pseudoheliotridane† **2**, E = H with complete diastereoselectivity and enantiospecificity.[3] Unusually, the organolithium species **1** is formed at rt, yet no racemization takes place.[6] Such cyclizations from chiral organolithium species have, so far, been restricted to the formation of five-membered rings, and must occur at rates that are significantly greater than the rate of racemization. Bailey and co-workers have determined the rate of anionic cyclization to generate a cyclopentane ring and found that $t_{1/2} \approx 5.5$ min at 23 °C.[7] We were intrigued to determine the effect of ring size on the stereochemical integrity of the chiral organolithium species. In this paper, we report the first determination of the rate of anionic cyclization to give a six-membered ring and its comparison with the rate of racemization of the chiral organolithium species.

Stannane **3** was prepared by treatment of *N*-Boc-2-tributylstannylpyrrolidine[8] with *B*-bromocatecholborane, followed by acylation with pent-4-enoyl chloride and reduction with $LiAlH_4$.[3] Transmetallation of amine **3** in hexane–Et_2O (4:1) with ^{n}BuLi (3 molar equiv. in hexanes) at rt gave the enantiomerically enriched organolithium species **4** (Scheme 2) which cyclized to give, after quenching with MeOH, the diastereomeric octahydroindolizines **5** and **6** in high yield (80–87%) and diastereoselectivity (95:5, **5**:**6**).[9] Remarkably, the use of the solvent system hexane–Et_2O–TMEDA (4:1:1, equating to 15 molar equiv. of TMEDA) completely reversed the diastereoselectivity, giving predominantly **6** (10:90, **5**:**6**).

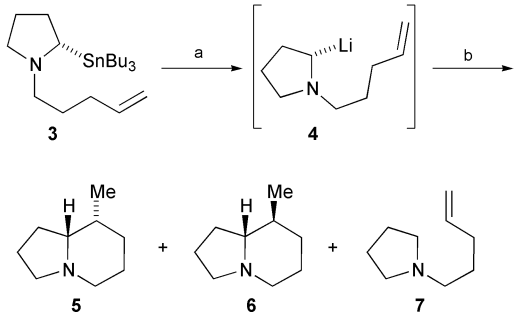


Scheme 1

In each case a small amount of proto-destannylated material **7** was formed. Intramolecular carbolithiation in hexane–Et_2O gave, after 6 h or more, **5** with 13% ee.[10] The presence of TMEDA caused complete racemization. By quenching the reaction mixture (in the absence of TMEDA) at shorter time intervals (*e.g.* 30 min), **5** and **6** (95:5) were obtained in low yield (22%) but enhanced enantiomeric excess (**5**, 62% ee). By taking aliquots of a reaction at different reaction times, it was possible to measure the rate of the cyclization. This followed first order kinetics with a rate constant, $k \approx 1.2 \times 10^{-4}$ s^{-1}, corresponding to a half-life for cyclization of approximately 90 min at 23 °C (complete transmetallation requires 20–30 min). This is significantly slower than the corresponding five-membered ring. Racemization can compete with cyclization, thereby accounting for the loss in enantiopurity. This is in stark contrast to the completely enantiospecific and diastereoselective cyclization of organolithium species **1**. The data reveal that the organolithium species **4** is racemic within approximately 30 min at rt in hexane–Et_2O and therefore the half-life for racemization of the organolithium species **4** must be less than 30 min.

In order to improve the optical purity of the indolizidine products, a method to slow the rate of racemization or to increase the rate of cyclization must be found. Alkenes substituted with an anion stabilising group have been shown to increase the rate of anionic cyclization reactions.[11] Thus the *E*- and *Z*-stannanes **8**, in which a phenylthio substituent is located at the terminus of the alkene, were prepared. The synthesis of the stannanes **8** was achieved by reductive amination.[12,13]

Stannanes **8** were treated with ^{n}BuLi in either hexane–Et_2O (4:1) or hexane–Et_2O–TMEDA (4:1:1), to give the diastereomeric cyclized products **9** and **10** (Scheme 3).‡ In the former solvent system, the organolithium species derived from stannane (*E*)-**8** gave predominantly **9** (77%, 70:30, **9**:**10**) in good ee (**9**, 75% ee; **10**, 72% ee). The organolithium species derived from the stannane *Z*-**8** cyclized to give a mixture of octahydroindolizines **9** and **10** (79%, 50:50, **9**:**10**) in slightly lower ee (**9**, 55% ee; **10**, 53% ee). In the presence of TMEDA, the organolithium species derived from stannane (*E*)- or (*Z*)-**8** cyclized to give racemic **10** exclusively in good yield (71–73%). The addition of TMEDA therefore appears to increase the rate



Scheme 2 *Reagents and conditions*: (a) 2.5 equiv. ^{n}BuLi, hexane–Et_2O (4:1) or hexane–Et_2O–TMEDA (4:1:1), 22 °C; (b) 6 h then MeOH, **5** and **6** (95:5, 80%), **5** (13% ee) and **7** 13%; or **5** and **6** (10:90, 76%), **6** (0% ee) and **7**, 21%.

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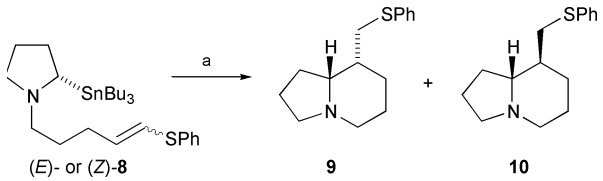

Scheme 3 *Reagents and conditions*: (a) 2.5 equiv. ^{n}BuLi, hexane–Et_2O (4:1) or hexane–Et_2O–TMEDA (4:1:1), 22 °C, 2 h then MeOH; see text for yields and selectivities.

of racemization, presumably *via* co-ordination of TMEDA to the lithium atom.[14] In the presence or absence of TMEDA, the cyclization is complete within approximately the same time as the substrate takes for complete tin–lithium exchange (≈30 min). The half-life for cyclization is therefore reduced considerably in comparison with the substrate **3**, in which no anion-stabilising phenylthio substituent is present at the terminus of the alkene.

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Notes and references

† The IUPAC name for heliotridane is 1-methylhexahydro-1*H*-pyrrolizine.

‡ *Cyclization of the stannane E*-**8**: The stannane *E*-**8** (1.16 g, 2.16 mmol) in hexane–Et_2O (25 cm^3, 4:1) was treated with *n*-butyllithium (2.6 cm^3, 6.50 mmol, 2.5 M in hexanes) at rt. After 2 h, MeOH (2 cm^3) was added, the solvent was removed under reduced pressure and the residue was purified by column chromatography on basic alumina, eluting with light petroleum (bp 40–60 °C)–EtOAc (1:0 to 4:1) to give the amines **9** and **10** (409 mg, 77%) as a 7:3 ratio of diastereomers as an oil; ν_{max}(neat)/cm^{-1} 3020 and 2935 (C-H); δ_H(400 MHz, $CDCl_3$) 1.25–2.21 (12H, m), 2.46–2.50 (0.3H, m), 2.62 (0.3H, dd, *J* 12.2 and 8.6), 2.93–3.03 (1.7H, m), 3.05 (0.3H, dd, *J* 12.2 and 3.7), 3.19 (0.7H, dd, *J* 12.3 and 9.0), 3.32 (0.7H, dd, *J* 12.3 and 4.5), 6.98–7.04 (1H, m), 7.09–7.14 (2H, m), 7.38–7.43 (2H, m); δ_C(100 MHz, $CDCl_3$) 20.8, 21.1, 25.7, 26.3, 28.5, 29.3, 31.4, 35.4, 37.7, 41.9, 52.5, 53.8, 54.4, 54.7, 66.6, 68.3, 125.3, 125.5, 127.7, 127.8, 128.8, 138.2, 138.3 (Found: M+H 248.1468. $C_{15}H_{22}NS$ requires M + H, 248.1473); *m/z* (CI) 248 (100%, M + H), 140 (62, $C_9H_{18}N$), 138 (60, M − C_6H_5S). The enantioselectivity of the cyclization was determined by treating the mixture of amines **9** and **10** with Raney® nickel in EtOH (60 °C, 30 min, 90%) to give the amines **5** and **6**.[10]

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