Electrophile dependent mechanisms in the asymmetric trapping of \( \alpha \)-lithio-\( N \)-(tert-butoxythiocarbonyl)azetidine

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Electrophile dependent (Scheme 1B). This has prompted us to investigate the origins of asymmetric substitution of \( N \)-Boc azetidine through \( \alpha \)-lithiation, with emphasis on how the process proceeds with respect to different electrophiles (Scheme 1C).

Enantioselectivity can originate from three distinct pathways (Scheme 2).\(^1\) An organolithium base coordinated with a chiral ligand could preferentially remove the \( \text{pro-R} \) or \( \text{pro-S} \) hydrogen to give a configurationally stable anion; if an introduced electrophile reacts stereospecifically then asymmetric induction is controlled by the lithiation rate difference (e.g., \( k_{\text{Boc}} > k_{\text{H}} \)). Enantioselectivity can also arise post-deprotonation when a configurationally unstable anion is formed (Scheme 2). Dynamic thermodynamic resolution (DTR) occurs if the lithiated complexes (e.g., \((R)\)-11-6 and \((S)\)-11-6) equilibrate to a thermodynamically controlled ratio and substitute with an electrophile at a rate faster.
deprotonation that is then reduced on equilibration. Sn-Li exchange with enantoienriched stannane \([R]-10\) in the presence of racemic DIANANE \((\pm)-6\) at \(-98^\circ C\) for 1 min before acetone trapping, resulted in essentially racemic alcohol \(8\) \((51:49\ \text{er}, 39\%)\). Assuming stereoretensive Sn-Li exchange (although see below), this demonstrates configurational instability of the organolithium complexes even at \(-98^\circ C\) when the anion is formed by transmetallation. However, in contrast to anion generation through Sn-Li exchange, partial configurational stability was demonstrated in deprotonations with different incubation temperatures and times. Lithiation of azetidine \(5\) in the presence of DIANANE \((S)-6\) and incubation for 1 h at \(-98^\circ C\) before trapping gave alcohol \((R)-8\) with moderate enantioselectivity \((65:35\ \text{er}, 38\%)\), showing incomplete equilibration. But when deprotonation and incubation were performed at \(-78^\circ C\) for 1 h, then cooling to \(-98^\circ C\) before trapping, this gave alcohol \((R)-8\) with good enantioselectivity \((88:12\ \text{er}, 55\%)\), indicating that high enantioselectivity can be achieved with trapping at \(-98^\circ C\). Deprotonation and incubation at \(-98^\circ C\) for 3 h before trapping gave alcohol \((R)-8\) in \(86:14\ \text{er}\) \((51\%)\), with the high er suggesting equilibration is almost complete at \(-98^\circ C\) after 3 h. These time-dependent enantioselectivities imply DTR, with acetone (for a full table of acetone trapping studies and similar results obtained with aromatic aldehydes, see the ESIF), and indicate the organolithium complexes possess greater configurational stability at \(-98^\circ C\) when formed through deprotonation.

Remarkably, compared to 65:35 er obtained from deprotonation for 1 h at \(-98^\circ C\), increased enantioselectivity was observed through Sn-Li exchange of stannane \((\pm)-10\) when carried out under the same conditions in the presence of DIANANE \((S)-6\), giving alcohol \((R)-8\) in \(84:16\ \text{er}\) \((41\%)\). This difference at \(-98^\circ C\) can be rationalised by ‘unproductive’ kinetic deprotonation (preferential generation of the thermodynamically less stable lithiated complex) and a longer equilibration time, relative to transmetallation. Alternatively, Sn-Li exchange with stannane \((\pm)-10\) could be occurring non-stereospecifically in the presence of DIANANE \((S)-6\), although precedent for non-retentive Sn-Li exchange is very limited,\(^{16}\) no transmetallation occurred without the ligand present. Non-retentive Sn-Li exchange could explain the rapid racemisation observed at \(-98^\circ C\) after 1 min with enantoienriched stannane \((R)-10\). The possibility of non-stereospecific Sn-Li exchange was probed using stannane \((\pm)-10\) with DIANANE \((S)-6\) and in situ acetone. This gave trace amounts (1\%) of essentially racemic alcohol \(8\) \((52:48\ \text{er})\), indicating Sn-Li exchange is occurring stereospecifically with some degree of ‘microscopic’\(^{17}\) configurational stability, relative to the rate of acetone trapping.

In a ‘poor man’s Hoffmann test’,\(^{12}\) azetidine \(5\) was deprotonated \((1\ h, \ -78^\circ C)\) and reacted with sub-stoichiometric acetone \(0.5\) and 0.1 equiv.) to give alcohol \((R)-8\) in \(61:39\ \text{er}\) \((29\%)\) and \(60:40\ \text{er}\) \((2\%)\), respectively. Decreased enantioselectivity (compared with \(89:11\ \text{er using 3 equiv. earlier}\) suggest the minor lithiated complex reacts marginally faster than the major complex\(^{15}\) \((R)-11\) \(6\) faster than \((S)-11\), assuming retentive substitution, \(S_2\text{ret}, \text{with acetone}\)\(^{11}\). The difference in enantioselectivity shows epimerisation...
is not occurring on the timescale of acetone trapping at −78 °C, confirming a DTR process.

A sacrificial electrophile has been previously used to improve enantioselectivity in a reaction where DTR operates. Generation of α-lithio-NBotc azetidine in the presence of DIANANE (S)-6 at −78 °C, then reaction with MeI (0.2 equiv.) for 5 min before addition of acetone (3 equiv.) only led to alcohol (R)-8 (58%) with a slight reduction in er (80 : 20). However, the enantioenrichment of the traces (1%) of isolated methylated azetidine (5) is similar to that found at this temperature for (S)-7 (73 : 27 er) is similar to that found at this temperature for (S)-7 (77 : 23 er) using only MeI (3 equiv.), sampled as the reaction progressed (5–120 min, Scheme 4). While these results do not strictly discriminate between DTR and DKR (as potentially (5–120 min, Scheme 4). While these results do not strictly discriminate between DTR and DKR (as potentially cf. )), enantioselectivity independent of reaction conversion and (also in contrast to acetone) improved enantioenrichment at −98 °C after 1 h [91 : 9 er], support a DKR process with this slower reacting19 electrophile.

With Me₂SnCl as the electrophile, both variation in reaction time and temperature altered asymmetric induction (Table 1).

Lithiation of NBotc azetidine 5 in the presence of DIANANE (S)-6 at −78 °C for 1 h led to stannane (R)-10 in 67 : 33 er (90%, Table 1, entry 1). An otherwise identical reaction, but without warming to rt following Me₂SnCl addition, resulted in stannane (S)-10 in similar enantioselectivity (61 : 39 er, entry 2) in 80% yield. However, reducing the lithiation time to 5 min before stannylation inverted the sense of asymmetric induction, to give stannane (R)-10 in 54 : 46 er (62%). Decreasing the lithiation temperature to −98 °C for 3 h before trapping at the same temperature gave stannane (S)-10 in 64 : 36 er (77%, entry 4). However, reducing the lithiation time to 1 h at −98 °C again resulted in a change in the sense of asymmetric induction to 54 : 46 er (entry 5). The dependence of asymmetric induction on lithiation time at −78 °C and −98 °C indicates DTR in stannylation, similar to trapping with acetone. These results also suggest deprotonation-derived organolithium complex equilibration is incomplete after 5 min at −78 °C and reinforces the earlier observation with acetone of increased time required for complex equilibration at −98 °C, due to a less configurationally labile anion at this lower temperature. The reduced overall levels of enantioselectivity compared with optimised conditions for acetone trapping suggests either an interfering DKR mechanism in which the thermodynamically less stable complex reacts with a faster rate with Me₂SnCl, or possible competing non-stereospecific electrophile trapping (S₂2ret and S₂2inv).11

Use of an internal electrophile such as TMSCl has been previously used to ascertain the degree of an asymmetric deprotonation.15 Two parallel ‘in situ’ trapping experiments were performed at −78 °C using NBotc azetidine 5 and stannane (±)-10 substrates (Scheme 5). These reactions gave silane (R)-12 in identical enantioenrichment (70 : 30 er), showing the level of asymmetric induction with this electrophile is independent of the method of anion generation. TMSCl is a slower reacting electrophile19 and the matching enantioselectivity could therefore be due to DKR. A deprotonation reaction with a 1 h incubation period at −78 °C before external addition of TMSCl gave silane (R)-12 in 52% yield and essentially the same enantioselectivity (68 : 32 er). A ‘poor man’s Hoffmann test’ with 0.5 equiv. of TMSCl, gave silane (R)-12 in 69 : 31 er (34%), providing further evidence for DKR. With TMSOTf, a more reactive silylating agent, a change in the sense of asymmetric induction was observed, giving (S)-12 in 58 : 42 er (28%); this is most likely a result of diminished influence of a DKR mechanism.

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### Table 1: Asymmetric stannylation of N-Botc azetidine 5

| Entry | Lithiation temp (time) | Stannylation temp (time) | Yield 10 | er (R:S) | Recovered 5 |
|-------|------------------------|-------------------------|----------|----------|-------------|
| 1     | −78 °C (1 h)           | −78 °C (30 min) then rt (30 min) | 90%      | 33 : 67  | 0%          |
| 2     | −78 °C (1 h)           | −78 °C (30 min)         | 80%      | 39 : 61  | 0%          |
| 3     | −78 °C (5 min)         | −78 °C (30 min) then rt (30 min) | 62%      | 54 : 46  | 38%         |
| 4     | −98 °C (3 h)           | −98 °C (30 min)         | 77%      | 36 : 64  | 21%         |
| 5     | −98 °C (1 h)           | −98 °C (30 min)         | 70%      | 54 : 46  | 24%         |
For the two electrophiles which trap through DKR (MeI and TMSCl), the predominant sense of asymmetric induction is opposite to those electrophiles which proceed through DTR (acetone, benzaldehyde+, and Me2SnCl). This could be due either to preferential invertive S,S2inv trapping, not uncommon for mesomerically stabilised organolithiums reacting with alkyl halides, to retentive trapping in which the minor diastereomeric organolithium complex is the faster reacting species, as was observed earlier in the ‘poor man’s Hoffmann test’ with acetone.

O’Brien and co-workers previously established with N-thiopivaloyl azetidine that asymmetric induction occurs post deprotonation; however, no distinction between DTR or DKR was made. They also speculated the origin of configurational instability may due to the longer C=S bond leading to a weaker C-Li bond. To discriminate between the C=S group or azacyle size being responsible for the configurational instability of N-Boc azetidine lithiated complexes ([R]-11·6 and [S]-11·6), we sought to access the lithiated N-Boc azetidine equivalents. We previously found that direct α-lithiation of N-Boc azetidine is problematic, but access to α-lithiated N-Boc azetidine is achievable by Sn–Li exchange from N-Boc stannane 13 (Scheme 6). Stannane 13 was accessed by deprotection/reprotection of N-Boc stannane 10, using TMSI for deprotection (66%). Under identical transmetllation conditions used for stannane 10 in the presence of DIANANE (S)-6, stannane (±)-13 underwent Sn–Li exchange and trapping with acetone to give racemic N-Boc alcohol (±)-14 (47%). Transmetllation of enantioenriched N-Boc stannane (S)-13 (66 : 34 er) using s-BuLi with racemic DIANANE (±)-6 led to enantioenriched alcohol (R)-14 in 67 : 33 er (40%). These results demonstrate, for the first time, access to a configurationally stable α-lithiated azetidine and indicate the C=S group is responsible for the configurational instability of α-lithio N-Boc azetidine.

In summary, the present studies show configurational instability of α-lithiated N-Boc azetidine complexes ([R]-11·6 and [S]-11·6). These diastereomeric complexes reach thermodynamic equilibrium after 1 h at −78 °C (3 h at −98 °C). They react with a fast trapping electrophile such as acetone via DTR, producing α-substituted azetidines with enantioselectivities (≈90:10) that reflect the complexes dr. Slower trapping electrophiles (MeI and TMSCl) react by DKR; this provides an explanation as to why different enantioselectivities are observed when conditions for optimal DTR are used with these electrophiles and also rationalises the different sense of enantioinduction. This change in mechanism could also be occurring with N-thiopivaloyl azetidine. In the current work, an intriguing difference in configurational stability of the anion formed by lithiation versus transmetllation was also observed (further discussed in the ESI†). Finally, the origin of configurational instability was determined to be the presence of C=S group, as demonstrated by the configurational stability of α-lithiated N-Boc azetidine. The stereochemical lability may be due to the longer C=S bond and/or the greater polarisability of S, compared to O, allowing greater charge transfer from N to S.20

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### Conflicts of interest

There are no conflicts to declare.

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