Dynamic kinetic resolution of *N*-Boc-2-lithiopyrrolidine

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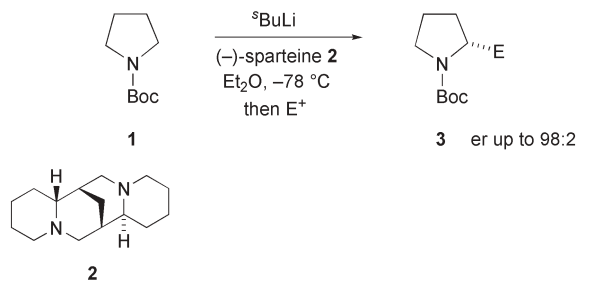
Asymmetric substitution of the organolithium derived either from *N*-Boc-2-tributylstannylpyrrolidine by tin–lithium exchange or from *N*-Boc-pyrrolidine by deprotonation occurs in the presence of a commercially available chiral diamine ligand with high levels of enantioselectivity by a dynamic kinetic resolution pathway.

One of the most important developments in chiral organolithium chemistry was the discovery by Beak and co-workers that (–)-sparteine **2** and *sec*-BuLi allowed the efficient asymmetric deprotonation of *N*-Boc-pyrrolidine **1** (Scheme 1),[1] following earlier work by Hoppe and co-workers with alkoxy substrates.[2] The procedure allows the synthesis of a selection of 2-substituted pyrrolidines **3** with high enantioselectivity (although in only one enantiomeric form) and has been further expanded by Dieter and co-workers by conversion of the chiral organolithium species to the corresponding organocuprate prior to quenching.[3] Of a selection of ligands, the only one to give very high selectivity was (–)-sparteine.[4] However, O'Brien and co-workers have recently reported a new ligand that selectively provides predominantly the opposite absolute configuration of the chiral organolithium species.[5] Rationales for the asymmetric deprotonation have been proposed,[6] and there are a number of reviews describing this chemistry.[7]

At low temperature, the two diastereomeric organolithium·(–)-sparteine complexes do not interconvert and there was very little selectivity (er up to 55 : 45) on preparing the racemic organolithium species, adding (–)-sparteine and quenching the mixture of complexes.[1] In the asymmetric deprotonation, enantiomer ratios are reduced if the chiral organolithium species is allowed to warm to −40 °C prior to quenching. This suggests that the organolithium species can racemize at elevated temperatures. Recent kinetic studies have shown that the barrier to enantiomerization of *N*-Boc-2-lithiopyrrolidine at −33 °C in Et_2O is of the order of 20 kcal/mol.[8]



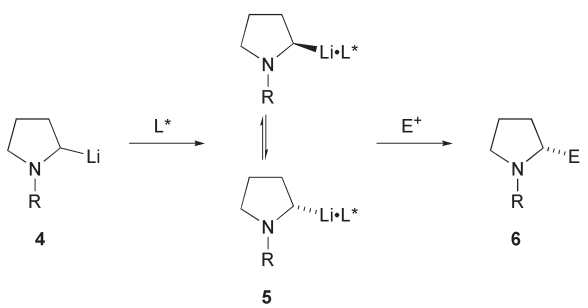
Scheme 1

The ability of the organolithium species **4** (R = Boc) to undergo racemization prompted us to study its dynamic resolution in the presence of a chiral ligand, L* (Scheme 2). This stems from our work on the related *N*-alkyl derivatives (*e.g.* R = ^{i}Bu), in which dynamic thermodynamic resolution operates, with the high enantiomer ratios of the products being a reflection of the high ratio of the two diastereomeric organolithium·chiral ligand complexes.[9,10] This type of asymmetric substitution is known for a selection of chiral organolithium complexes, although it has not been reported for *N*-Boc-2-lithiopyrrolidine.[11]

The racemic organolithium species **4**, R = Boc was prepared by tin–lithium exchange from *N*-Boc-2-tributylstannylpyrrolidine **7** and *n*-butyllithium in Et_2O.[1] Addition of the chiral ligand (–)-sparteine and electrophilic quench with TMSCl gave only racemic product **10** under a variety of conditions, including the use of elevated temperatures that should allow dynamic resolution. It appears therefore that there is no energetic preference for one of the two diastereomeric organolithium complexes **5** (R = Boc, L* = sparteine). Equally, there was no selectivity on quenching with less than one molar equivalent of TMSCl, in which any kinetic selectivity for reaction could be determined.

We therefore turned to other chiral ligands, in particular to the ligands **8** and **9** that are successful for dynamic thermodynamic resolution of the organolithium **4**, R = alkyl.[9,12] Formation of the organolithium **4**, R = Boc from the corresponding racemic tributylstannane **7**, followed by addition of the ligand **8** (that had been deprotonated with *n*-butyllithium in Et_2O), followed by electrophilic quench with TMSCl was investigated (Scheme 3). Initially variable enantiomer ratios of the product **10** were obtained in this reaction.

We therefore probed this transformation in more detail. Transmetallation of the stannane **7** (1.5 equiv. BuLi) occurs rapidly at −78 °C in Et_2O. Addition of 1.5 molar equivalents of the chiral ligand **8** (pre-treated with BuLi using 1.1 equivalents in comparison to the ligand) and warming to −20 ° C for 20 min allows equilibration of the diastereomeric complexes (**5**, R = Boc,



Scheme 2

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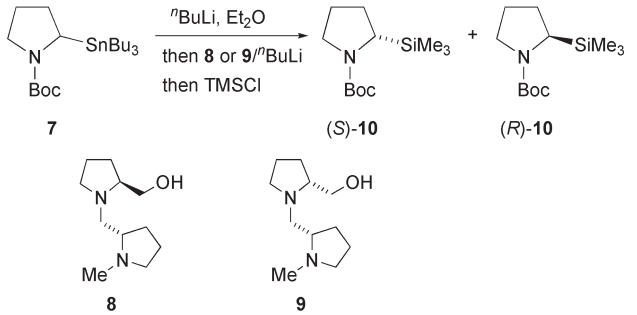


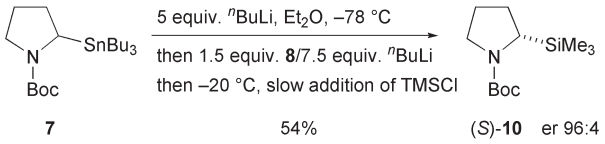
Scheme 3

L* = **8**). The mixture was then cooled to −78 °C and quenched with TMSCl (3 equivalents). The product **10** was isolated in 65% yield as a mixture of enantiomers in a ratio 42 : 58 (in favour of the (*R*) enantiomer as determined by comparison with an authentic sample).[1] This result suggests that there is only a slight thermodynamic preference for one of the two diastereomeric complexes, probably the enantiomer (*R*)-*N*-Boc-2-lithiopyrrolidine based on the assumption that electrophilic quench occurs with retention of configuration at the carbanion centre.[1] Increasing the time allowed or the temperature of equilibration gave similar results, so it seems that it is not possible to effect useful dynamic thermodynamic resolution of this organolithium species with the chiral ligands **2** or **8**.

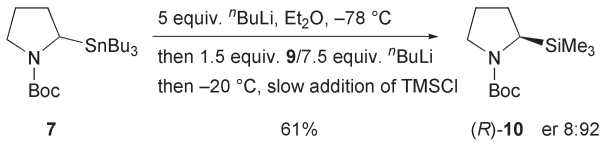
The same experiment (in the absence of excess BuLi) in which the organolithium complexed to **8** was quenched (at −20 °C) with 0.4 equivalents of TMSCl gave the product **10** in 39% yield and with er 81 : 19 in favour of the (*S*) enantiomer. This result suggests that there is a kinetic component to this reaction and that one diastereomeric complex reacts faster than the other.

After considerable experimentation, in which variable enantiomer ratios were obtained under similar reaction conditions, we started to wonder if the excess BuLi was affecting the aggregate structure and whether this had a bearing on the relative rate of reaction of the diastereomeric complexes.[13] Transmetallation of **7** with 5 equivalents of BuLi and addition of 1.5 equivalents of the chiral ligand **8**, which had been deprotonated with 7.5 equivalents BuLi relative to **7** (such that the overall excess of ^{n}BuLi amounted to 10 equivalents), gave some interesting results. Equilibration at −20 °C for 20 min then cooling to −78 °C and quenching with excess TMSCl (16 equiv.) gave the product **10** in good yield (88%) but with poor selectivity (er 56 : 44 in favour of the *S* enantiomer). However, quenching with 5 equivalents of TMSCl gave (*S*)-**10** in 42% yield and with er 98 : 2. It appears that the organolithium is more reactive than BuLi to TMSCl and so reasonable yields of the product can be obtained.

These results support the explanation that one of the diastereomeric complexes is more reactive than the other, particularly in the presence of excess BuLi. The use of 10 equivalents of excess BuLi appears to be optimum, as experiments with 3.25 or 6.25 excess BuLi gave lower selectivities. We then turned to improving the yield of the reaction while maintaining high enantioselectivity. One way that this may be achieved would be to add the electrophile slowly at a temperature that allows dynamic resolution. Thus, transmetallation of **7** and addition of the chiral ligand **8** as above (with overall 10 equivalents of excess BuLi), followed by slow addition of TMSCl (16 equivalents) over



Scheme 4



Scheme 5

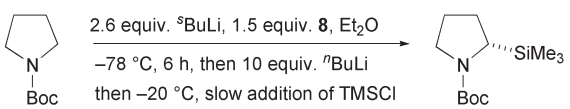
90 min gave the product (*S*)-**10** in 54% yield and with er 96 : 4 (Scheme 4).† This represents a useful method for the formation and reaction of *N*-Boc-2-lithiopyrrolidine.

The same experiment with no excess butyllithium was investigated and the mixture was quenched slowly at −20 °C with excess TMSCl to give the product (*S*)-**10** in 45% yield and with er 67 : 33.

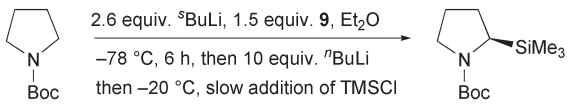
Use of the ligand **9** (a diastereomer of the ligand **8**)[12] with excess BuLi and slow addition of excess TMSCl at −20 °C gave the product (*R*)-**10** in 61% yield and with er 8 : 92 (*S* : *R*) (Scheme 5). Hence either enantiomer of the product can be prepared by choosing the appropriate chiral ligand.

An alternative and more convenient method to prepare the racemic organolithium species required for this asymmetric substitution reaction is by simple proton abstraction of *N*-Boc-pyrrolidine. Following the reported method,[4] *N*-Boc-pyrrolidine **1** was treated with a mixture containing *sec*-BuLi (2.6 equivalents) and the chiral ligand **8** (1.5 equivalents) in Et_2O at −78 °C. After 6 h, 10 equivalents of ^{n}BuLi was added and the mixture was warmed to −20 °C for 5 min. Slow addition of TMSCl (16 equiv.) over 30 min gave the product (*S*)-**10** in 57% yield and with er 95 : 5 (Scheme 6). The same experiment without addition of excess ^{n}BuLi gave the product (*S*)-**10** with er 63 : 37. Using the ligand **9** rather than **8** (together with 10 excess equivalents of ^{n}BuLi), the major product was the enantiomer (*R*)-**10** (63%, er 9 : 91) (Scheme 7).

The results reported here show that *N*-Boc-2-lithiopyrrolidine can undergo dynamic resolution in the presence of a chiral ligand. Very high levels of enantioselectivity can be achieved by this



Scheme 6



Scheme 7

asymmetric substitution, which occurs by a dynamic kinetic resolution and either enantiomer of the 2-substituted *N*-Boc-pyrrolidine can be prepared.

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Notes and references

† Butyllithium (0.87 mL, 2.2 mmol, 2.5 M in hexanes) was added to the stannane **7**[1] (200 mg, 0.44 mmol) in Et_2O (1 mL) at −78 °C. After 5 min, the deprotonated ligand **8** [prepared by adding BuLi (1.3 mL, 3.3 mmol) to **8** (129 mg, 0.65 mmol) in Et_2O (1 mL) at 0 °C for 30 min then cooling to −78 °C] was added. The mixture was warmed to −20 °C and after 20 min, TMSCl (0.77 mL, 6.9 mmol) was added slowly (over 90 min) using a syringe pump. The mixture was quenched with MeOH (1 mL), evaporated and purified by column chromatography on silica, eluting with light petroleum–EtOAc (98 : 2) to give the silane **10** (57 mg, 54%), $[\alpha]_D^{24}$ + 67.7 (1.0, $CHCl_3$), er 96 : 4 determined by chiral GC (β-cyclodextrin 120 fused silica column, 30 × 0.25 mm i.d., 2.7 mL/min and nitrogen carrier at 10 psi, retention times: 39.9 min for *S*-**10** and 40.9 min for *R*-**10**), spectroscopic data identical to that reported.[1,14]

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12 Ligand **8** is commercially available but can be prepared in 2 steps (by coupling L-proline methyl ester with L-*N*-Cbz-proline followed by reduction) according to T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111; see also ref. 4. Ligand **9** can be prepared in the same way, but using D-proline methyl ester and L-*N*-Cbz-proline.
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