Dynamic resolution of *N*-Boc-2-lithiopiperidine†

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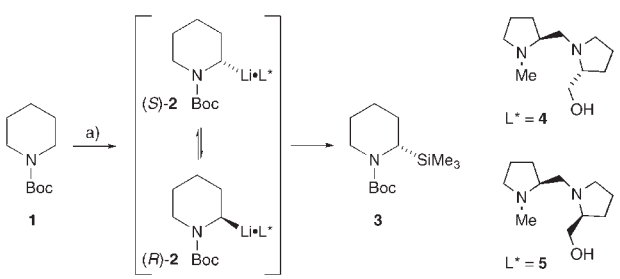
Dynamic thermodynamic resolution of *N*-Boc-2-lithiopiperidine is possible using a chiral ligand; the two enantiomers of this organolithium can be resolved with selectivities of up to 85 : 15 from a selection of 26 chiral diamino-alkoxide ligands screened.

A popular and valuable method for asymmetric synthesis involves the formation and reaction of chiral organolithiums.[1] Of particular importance is the asymmetric deprotonation of substrates such as *O*-alkyl-carbamates and *N*-(*tert*-butoxycarbonyl)pyrrolidine (*N*-Boc-pyrrolidine) using *sec*-butyllithium and (−)-sparteine as the chiral base.[1,2] However, a problem with this chemistry is that it is limited to certain substrates. For example, extension of asymmetric deprotonation to the important piperidine ring system (using *N*-Boc-piperidine) occurs with low yields and/or low selectivities.[3] Recently, building on work on the analogous pyrrolidines,[4] we have found that highly enantioselective *substitution* of *N*-Boc-2-lithiopiperidine is possible.[5] In this case, the asymmetry arises from the faster reaction of one of the diastereomeric complexes between the chiral organolithium and the chiral ligand. Hence, using the ligand L* = **4**, the two organolithiums *S*-**2** and *R*-**2** can interconvert at −20 °C, and organolithium *S*-**2** reacts much faster than *R*-**2** to give the product **3** with high enantioselectivity (er 93 : 7 *S* : *R* in Et_2O and er 95 : 5 in THF) (Scheme 1).[5] However, high selectivities were obtained only with trimethylsilyl chloride (TMSCl) as the electrophile. To provide a general approach to 2-substituted piperidines we needed either to optimize this process for different electrophiles or find a ligand that is suitable for dynamic resolution under thermodynamic control.[6] Under thermodynamic conditions (by cooling to −78 °C to prevent further interconversion) the ligand **4** gives the product **3** with poor selectivity (er 42 : 58 *S* : *R* in Et_2O, representing a small preference for the organolithium (*R*)-**2**). The diastereomeric ligand **5**, although poor in the dynamic kinetic resolution, was better in this regard, providing the product **3** with reasonable selectivity (er 77 : 23 *S* : *R* in Et_2O) [the ligand (−)-sparteine gave poor selectivity (55 : 45 *S* : *R* in Et_2O)].[5] Due to the importance of the piperidine ring system in natural products and medicinal drugs, we have screened a number of ligands to effect dynamic resolution of organolithium **2** under these conditions and report here some of the results of this study.

It appeared that diamino-alkoxide ligands such as **5** were most promising to promote, on complexation, a preference for one of the chiral organolithiums **2**. We therefore concentrated our efforts on such chiral ligands. A selection of 24 ligands is shown in Fig. 1. These were prepared either by coupling of an *N*-protected amino-acid with an amino-ester, followed by $LiAlH_4$ reduction,[7] or by addition of proline methyl ester to an intermediate aziridinium ion[8] followed by reduction (see Supplementary Information†). As a general procedure for the dynamic resolution, *N*-Boc-piperidine **1** and 1.1–1.2 equiv. of TMEDA in Et_2O were treated with 1.1–1.2 equiv. of *sec*-BuLi at −78 °C for 3 h,[9] followed by the addition of the chiral ligand (1.2–1.5 equiv.). The ligand was pre-treated with an equivalent of *n*- or *sec*-BuLi in Et_2O to form the lithium alkoxide. The temperature was then raised to allow equilibration (between −40 and −10 °C).[10] After 1 or 1.5 h at this temperature the mixture was cooled to −78 °C and 3 equiv. of the electrophile TMSCl were added. Sufficient time was allowed for electrophilic quench before methanol was added. Purification of the silane was followed by enantiomer ratio determination by chiral GC (β-cyclodextrin column).[5]

The results of this study are summarised in Table 1. The simplest chiral ligand **6**, with one stereocentre, is clearly poor at resolving the *S*- and *R*-organolithiums **2**. With two stereocentres some good selectivities can be achieved. Comparison of the ligands **4** and **5** with ligands **7** and **8** (derived from valine) shows that having a branched (^{i}Pr) substituent alpha to the nitrogen atom enhances the selectivity. This is confirmed with the ligands **9** and **10** (derived from isoleucine) and the poorer results using ligands **11** and **12** (derived from alanine). Interestingly, the ligand **13** was good, giving the product **3** with er 85 : 15 (*S* : *R*), whereas its diastereomer **14** was



Scheme 1 Dynamic kinetic resolution.[5] (a) *sec*-BuLi (1.2 equiv.), THF, TMEDA (1.2 equiv.), −78 °C, 3 h, then **4** (1.5 equiv.) (pre-treated with *n*-BuLi in Et_2O), then −20 °C, 2 min then 4 equiv. TMSCl added over 50 min at −20 °C, 60%, er 95 : 5, *S* : *R*.

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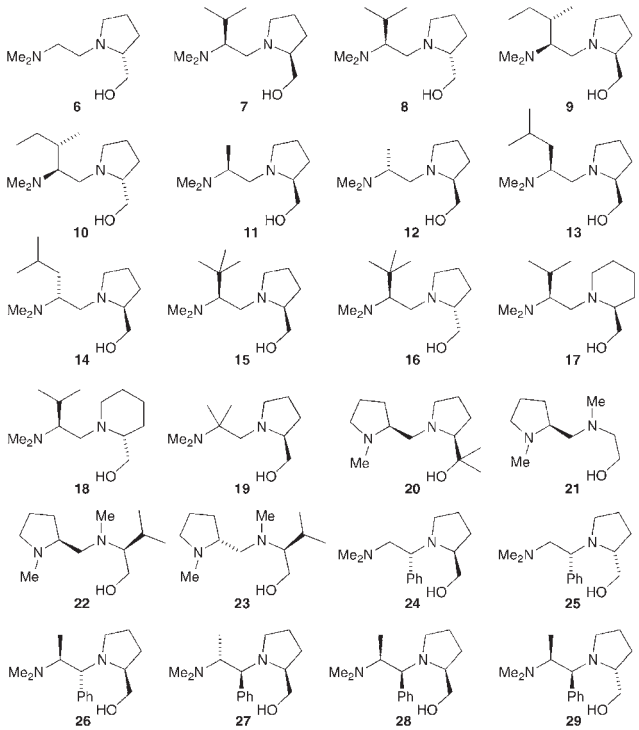


Fig. 1 Structures of ligands **6–29**.

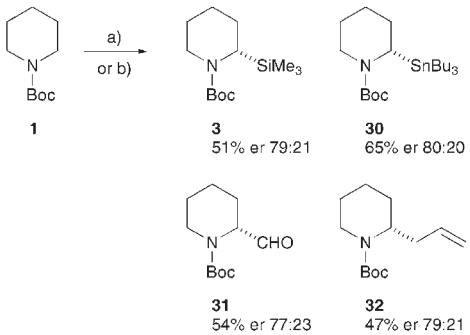
Table 1 Enantiomer ratio of **3** by dynamic thermodynamic resolution using ligands **4–29**

Ligand	**3**, er (S : R)[a]	Ligand	**3**, er (S : R)[a]
4	42 : 58	**17**	56 : 44
5	77 : 23	**18**	20 : 80
6	41 : 59	**19**	55 : 45
7	80 : 20	**20**	72 : 28
8	15 : 85	**21**	46 : 54
9	82 : 18	**22**	55 : 45
10	22 : 78	**23**	50 : 50
11	51 : 49	**24**	52 : 48
12	51 : 49	**25**	51 : 49
13	85 : 15	**26**	57 : 43
14	49 : 51	**27**	51 : 49
15	65 : 35	**28**	81 : 19
16	23 : 77	**29**	30 : 70

[a] The absolute configuration of the major enantiomer was determined by comparison with an authentic sample prepared according to ref. 3.

poor. Further branching with the *tert*-butyl derivatives **15** and **16** did not enhance the selectivity and neither did the use of the piperidine analogues **17** and **18**. Incorporation of *gem*-dimethyl groups in ligands **19** and **20** reduced the effectiveness of the ligands. The prolinol motif seems to be important as more flexible amino-alcohol portions (ligands **21–23**) gave essentially racemic product **3**. We then turned to ligands prepared from styrene epoxide (**24–25**) or *N*-methylephedrine (**26–27**) or pseudoephedrine (**28–29**). Of these, only ligand **28** gave good selectivity in the dynamic resolution reaction.

The enantioselectivity was not improved by using longer reaction times or higher temperatures prior to cooling and quenching. Likewise, no improvement in the enantiomer ratio was obtained by using other solvents or by forming the



Scheme 2 Quenching with different electrophiles. (a) *sec*-BuLi (1.1 equiv.), Et_2O, TMEDA (1.1 equiv.), −78 °C, 3 h, then **7** (1.2 equiv.) (pre-treated with *sec*-BuLi in Et_2O), then −40 °C, 90 min then −78 °C, 3 equiv. electrophile Me_3SiCl, Bu_3SnCl or DMF; (b) as (a) but, prior to addition of the electrophile allyl bromide, was added $ZnCl_2$ (1.3 equiv.) in THF then CuCN·2LiCl (1.2 equiv.) in THF.

organolithium from *N*-Boc-2-tributylstannylpiperidine and minimising the amount of TMEDA present (the use of *n*-BuLi and 10 mol% TMEDA allows efficient tin–lithium exchange). This is consistent with the diamino-alkoxides being better ligands than TMEDA.[4] The chiral ligands can be recovered after the reaction by column chromatography and distillation.

The yields in these dynamic resolutions were typically in the 30–60% region, with about 30% recovered starting material **1**. Interestingly, the yields were best using aged bottles of *sec*-BuLi. Aged *sec*-BuLi contains a significant amount of *sec*-BuOLi (verified by ^{1}H NMR spectroscopy)[11] and it was possible to obtain satisfactory yields (>50%, together with some recovered starting material) using either aged *sec*-BuLi or freshly acquired *sec*-BuLi in the presence of a small amount (5 mol%) of ^{i}PrOLi.

Using one of the best ligands in Table 1, namely ligand **7**, we prepared a selection of 2-substituted *N*-Boc-piperidines (Scheme 2).‡ Deprotonation of *N*-Boc-piperidine (1.2 g) with *sec*-BuLi and TMEDA in Et_2O followed by addition of the deprotonated ligand **7**, and warming to –40 °C for 1.5 h (to set up the dynamic resolution), then cooling to –78 °C, followed by addition of Bu_3SnCl gave the 2-substituted product **30** in 65% yield. Similarly, quenching with DMF gave the aldehyde **31**. As expected, the enantiomer ratios of the products **30–31** were similar (in comparison with the silane **3**) on altering the electrophile, which is consistent with a resolution in which (in this case) the organolithium (*S*)-**2** is preferred. The product **32** was prepared using allyl bromide as the electrophile after transmetallation to the zinc-cuprate species.[12] Reduction of the alkene and hydrolysis of the carbamate provides an overall three-step synthesis of the alkaloid coniine.[13]

The enantioselectivity could arise from a dynamic thermodynamic resolution,[6] or from a preference for the chiral ligand to complex to one enantiomer of the interconverting organolithiums. There was no crystallization and we have drawn the organolithium as a monomer, although the structure has not been determined. In contrast to previous studies,[5] the selectivity does not arise from a dynamic kinetic resolution. For example, ligand **8** provides the silane product **3** with er 15 : 85 (S : R) (Table 1), whereas under conditions for dynamic kinetic resolution (slow quench with TMSCl at –40 °C),[5] the same ligand **8** was found to give the product **3** with er 84 : 16

(*S* : *R*). This indicates that there is interconversion between the diastereomeric complexes (either directly or *via* their uncomplexed forms) and that these complexes react at different rates, with the minor complex reacting faster.

Hence, this chemistry provides a general method to access enantiomerically enriched 2-substituted piperidines.[14] Either enantiomer can be prepared by choice of the diastereomer (or enantiomer) of the chiral ligand. This chemistry therefore provides a solution to the poor yields and/or low levels of asymmetric induction obtained using either asymmetric deprotonation of *N*-Boc-piperidine or asymmetric substitution with different electrophiles of *N*-Boc-2-lithiopiperidine by dynamic kinetic resolution.

Notes and references

‡ General procedure: *N*-Boc-piperidine **1** (0.3 g, 1.6 mmol) and TMEDA (0.27 mL, 1.8 mmol) in Et_2O (3 mL) were treated with *sec*-BuLi (1.4 mL, 1.8 mmol, 1.3 M in hexanes) at −78 °C. After 3 h, the deprotonated ligand **7** [prepared by adding *sec*-BuLi (1.6 mL, 2.0 mmol, 1.3 M in hexanes) to **7** (0.42 g, 1.9 mmol) in Et_2O (3 mL) at 0 °C] was added. The mixture was warmed to −40 °C. After 90 min the mixture was cooled to −78 °C and the electrophile TMSCl (0.6 mL, 4.8 mmol) was added. The mixture was allowed to warm slowly (over 18 h) to room temperature and MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with light petroleum (bp 40–60 °C)–EtOAc (98 : 2) to give the piperidine (*S*)-**3** (213 mg, 51%), $[\alpha]_D^{22}$ + 18.5 (0.5, $CHCl_3$), lit.[5] for (*S*)-**3**, er 95 : 5, $[\alpha]_D^{24}$ + 36.4 (1.95, $CHCl_3$); other data as reported;[3] er 79 : 21 determined by GC [β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl) siloxane, nitrogen carrier at 14 psi, retention times 31.5 min (major) and 32.4 min (minor) (at 85 °C)]. The chiral ligand **7** can be recovered by column chromatography, eluting with CH_2Cl_2–MeOH (7 : 3), followed by evaporation of the solvent, acid/base wash (acidify with 2 M HCl, wash with CH_2Cl_2, basify with NaOH pellets and extract with CH_2Cl_2) and distillation under reduced pressure.

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