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Asymmetric Substitutions of 2-Lithiated *N*-Boc-piperidine and *N*-Boc-azepine by Dynamic Resolution

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Abstract: Proton abstraction of *N*-*tert*-butoxycarbonyl-piperidine (*N*-Boc-piperidine) with *s*BuLi and TMEDA provides a racemic organolithium that can be resolved using a chiral ligand. The enantiomeric organolithiums can interconvert so that a dynamic resolution occurs. Two mechanisms for promoting enantioselectivity in the products are possible. Slow addition of an electrophile such as trimethylsilyl chloride allows dynamic resolution under kinetic control (DKR). This process occurs with high enantioselectivity and is successful by catalysis with substoichiometric chiral ligand (catalytic dynamic kinetic resolution). Alternatively, the two enantiomers of this organolithium can be resolved under thermodynamic control with good enantioselectivity (dynamic thermodynamic resolution, DTR). The best ligands found are based on chiral diamino-alkoxides. Using DTR, a variety of electrophiles can be used to provide an asymmetric synthesis of enantiomerically enriched 2-substituted piperidines, including (after Boc deprotection) the alkaloid (+)-β-conhydrine. The chemistry was extended, albeit with lower yields, to the corresponding 2-substituted seven-membered azepine ring derivatives.

Keywords: amines · asymmetric synthesis · carbanions · lithium · organometallic compounds

Introduction

Enantiomerically enriched products can be generated from chiral organolithiums by stereoselective electrophilic quench.[1] Typically the chiral organolithium is generated by asymmetric deprotonation or stereospecific tin–lithium exchange. Asymmetric deprotonation requires that the substrate is amenable to deprotonation at the required position and that a suitable chiral base can be found to effect this process. Tin–lithium exchange requires a method to prepare the organostannane in enantioenriched form and relies on the successful transmetallation to the organolithium species. The organolithium formed by either of these methods must maintain its configurational stability under the reaction conditions. Low temperatures are normally required so as to avoid enantiomerization.

An alternative to these methods is the use of an asymmetric substitution of the organolithium in the presence of a chiral ligand (L*). A considerable advantage of this approach is that a racemic organolithium can be used which ideally is configurationally unstable, so that dynamic equilibration of the enantiomeric organolithiums occurs (Scheme 1; k_1, $k_2 \neq 0$). Therefore low-temperature conditions are not a necessity and indeed are not preferable (except to impart greater chemical stability). Asymmetric induction after quench with an electrophile (E^+) arises from a thermodynamic preference for one of the diastereomeric organolithium·chiral ligand complexes (known as dynamic thermodynamic resolution, DTR),[2] and/or from a kinetic preference ($k_3 \neq k_4$ or $k_{3'} \neq k_{4'}$) for reaction of one of the diastereomeric organolithium·chiral ligand complexes with the electrophile (known as dynamic kinetic resolution, DKR). In all cases, the electrophilic quench needs to be stereoselective (occurring with retention or inversion of configuration at the carbanion center).

In dynamic resolution under thermodynamic control, electrophilic quench is faster than interconversion of the diastereomeric complexes (k_3, $k_4 > k_1$, k_2). This does not preclude a kinetic preference for reaction of either of the complexes.

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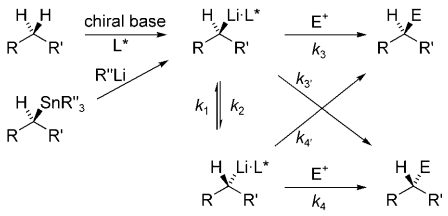


Scheme 1. Pathways for asymmetric induction with a chiral organolithium.

In dynamic kinetic resolution, electrophilic quench is slower than interconversion of the diastereomeric complexes (k_3, $k_4 < k_1$, k_2). In reactions of chiral organolithiums it is important to be aware that there can be a combination of both thermodynamic and kinetic factors that affect the enantiomer ratio (er) of the product.

The area of asymmetric organic synthesis with chiral organolithiums made significant steps forward with the discovery of highly selective asymmetric deprotonations by using *s*BuLi and the chiral ligand (−)-sparteine to give dipole-stabilized α-alkoxy- and α-amino-organolithium species.[3] These organolithium species are typically configurationally stable at low temperatures such as −78 °C and react stereoselectively with various electrophiles.[4,5] The first examples of highly selective asymmetric substitutions by dynamic resolution of chiral organolithiums were reported with benzylic organolithiums.[2,6] Benzylic organolithium species are often prone to racemize even at low temperature, thereby favouring resolution through a dynamic process. Good results in the dynamic resolution of allylic, α-thio- and α-seleno-organolithium species at low temperature also rely on the configurational lability of these species.[7] To effect dynamic resolution of α-amino-organolithium species temperatures higher than −78 °C are typically required. Recent kinetic studies have determined the barriers to enantiomerization of several chiral α-amino-organolithium species.[8] These show that dipole-stabilized species such as *N*-*tert*-butoxycarbonyl-2-lithiopyrrolidine (*N*-Boc-2-lithiopyrrolidine) have slightly lower barriers to inversion than so-called "non-stabilized" species such as *N*-alkyl-2-lithiopyrrolidines. Pertinent to this paper, the organolithium *N*-Boc-2-lithiopiperidine (in Et_2O with one equivalent of TMEDA) has been found to have a barrier to enantiomerization, $\Delta G^{\neq} \approx 17$ kcal mol^{-1} at −30 °C.[8d]

Previously, we have reported that various *N*-substituted 2-lithiopyrrolidines can be resolved in the presence of a chiral ligand.[9] High levels of enantioselectivity are possible by a dynamic kinetic or a dynamic thermodynamic resolution, depending on the *N*-substituent and the conditions. This paper describes in full our results on the dynamic resolution of the corresponding six- and seven-membered ring analogues, namely *N*-Boc-2-lithiopiperidine and *N*-Boc-2-lithioazepine. This builds on some preliminary studies communicated with *N*-Boc-2-lithiopiperidine.[10]

Results and Discussion

The starting material, *N*-Boc-piperidine (**16**) is available commercially or can be prepared by simple protection of piperidine with Boc_2O. Following the method described by Beak and co-workers,[11] *N*-Boc-2-lithiopiperidine was prepared by proton abstraction of *N*-Boc-piperidine with *s*BuLi, TMEDA in Et_2O at −78 °C. This organolithium could be trapped with electrophiles to give a variety of racemic 2-substituted *N*-Boc-piperidines.

In contrast to the five-membered ring analogue,[12] asymmetric deprotonation of *N*-Boc-piperidine is typically low yielding or occurs with low enantioselectivity.[13] Therefore, asymmetric substitution could provide a useful strategy for the formation of enantiomerically enriched 2-substituted piperidines.

A selection of chiral ligands (Figure 1) was prepared (see Supporting Information) to test the asymmetric substitution reaction. Scheme 2 shows the general Scheme for the experiments conducted under conditions for DTR and Table 1 outlines the results. When the chiral ligand has an OH group then it was first treated with an equivalent of BuLi prior to addition to *N*-Boc-2-lithiopiperidine. The mixture was warmed to −40 °C for 1.5 h or −30 °C for 1 h to promote formation of the thermodynamic ratio of the organolithium·L* complexes **17** prior to cooling and electrophilic quench with TMSCl. The organolithium complexes do not crystallize but remain in solution. The chiral ligand could be recovered by column chromatography and distillation. Experiments at higher temperatures or for longer time periods did not improve the results, suggesting that the thermodynamic ratio had been reached. This was in agreement with the kinetic parameters for dynamic resolution of this organolithium in the presence of TMEDA and the ligand **3**, in which the rate constant $k = 5.5 \times 10^{-4}$ s^{-1} was determined, equating to a half-life, $t_{1/2} \approx 21$ min at −30 °C.[8d]

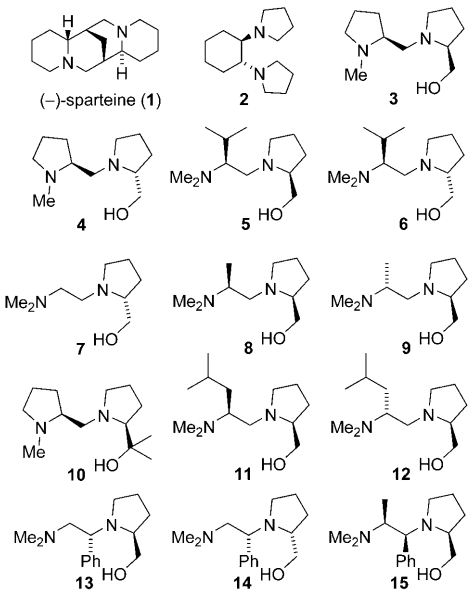
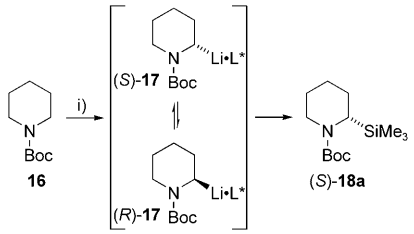


Figure 1. Chiral ligands L*.



Scheme 2. Procedure for DTR of **17**. i) *s*BuLi (1.2 equiv), Et_2O, TMEDA (1.2 equiv), −78 °C, 3 h, then L* (**1**–**15**) (1.2 equiv) (L* for **3**–**15** pre-treated with *s*BuLi in Et_2O), then −40 °C, 90 min (or −30 °C, 1 h), then −78 °C, 3 equiv Me_3SiCl.

From Table 1 it can be seen that the best ligands were diamino-alcohols **6** and **11**, leading to opposite major enantiomers of the product **18a**. The absolute configurations were verified by preparation of an authentic sample using the low-yielding asymmetric deprotonation of *N*-Boc-piperidine with *s*BuLi and the chiral ligand (−)-sparteine.[13]

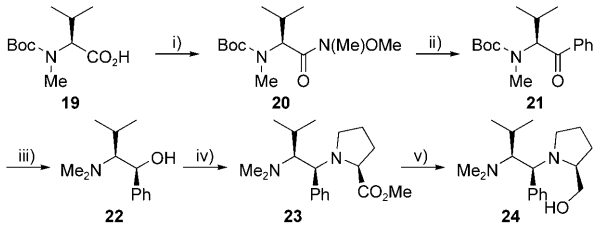
Table 1. Enantiomer ratio (er) for **18a** from DTR of **17** with ligands **1**–**15**.

Ligand L*	er (*S*/*R*)[a]	Ligand L*	er (*S*/*R*)[a]
1	45:55	**9**	51:49
2	50:50	**10**	72:28
3	77:23	**11**	85:15
4	42:58	**12**	28:72[b]
5	80:20	**13**	52:48
6	15:85	**14**	51:49
7	41:59	**15**	81:19
8	51:49		

[a] Determined by chiral GC. [b] Corrected from ref. [10].

A comparison of ligands **14** and **15** reveals that the extra methyl group in **15** provides an enhancement to the enantioselectivity. In contrast to ligand **15**, ligand **8** (which lacks the phenyl group) was poor. Replacing the methyl group (ligand **8**) with an isopropyl or isobutyl group (ligands **5** and **11**) gave significantly improved selectivities. Therefore, we wondered whether replacing the methyl group of ligand **15** with an isopropyl or isobutyl group would enhance the selectivity further.

To test this hypothesis, we selected ligand **24** as shown in Scheme 3. The known amino-acid derivative **19** was prepared in two steps from valine according to the literature.[14] This was converted to the Weinreb amide **20** which was treated with phenyl magnesium chloride to give the ketone **21**. Reduction of the ketone with simultaneous reduction of the *N*-Boc group gave the amino-alcohol **22**. This was formed with high diastereoselectivity (dr 11:1) in favour of the desired isomer **22** (as determined by comparison with related amino alcohols).[15] After separation of the minor isomer, the amino-alcohol **22** was converted to the ester **23** via the intermediate aziridinium ion.[16] Finally, reduction of the crude ester gave the ligand **24**. The structure of the ligand **24** was confirmed by single crystal X-ray analysis (see Supporting Information).

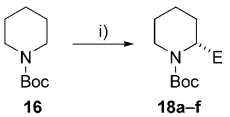


Scheme 3. Preparation of ligand **24**. i) MeNHOMe·HCl (1.5 equiv), EDCI, DMAP, CH_2Cl_2, RT, 4 h, 78 %; ii) PhMgCl (6 equiv), THF, 0 °C to RT, 2 d, 93 %; iii) $LiAlH_4$, THF, −10 °C, 1 h then heat, 19 h, 84 %, dr 11:1; iv) MsCl, Et_3N, THF, 0 °C, 2 h, then evaporate and add CH_2Cl_2, Et_3N and proline methyl ester hydrochloride, heat, 25 h; v) $LiAlH_4$, THF, 0 °C then heat, 15 h, 86 % over two steps.

Ligand **24** was tested in the DTR reaction of the organolithium **17**. On the first attempt, the product **18a** was formed with high selectivity (er 92:8, *S*/*R*), which seemed to verify our hypothesis. However we have been unable to reproduce this enantioselectivity and this ligand has more consistently provided the product **18a** with an er 85:15.

Due to the lengthy synthesis of ligand **24**, we selected ligand **11** as the optimum ligand from those that we had screened. Further optimization studies were conducted to improve the conversion to the product **18a** as, using conditions in Scheme 2, this product was typically formed in 40–50 % yield (together with about 30 % yield of recovered *N*-Boc-piperidine **16**). Addition of LiCl (10 mol %) or water (5 mol %) gave slightly reduced yields but unchanged er. Addition of 5–10 mol % Li*O*i*Pr did give a slight improvement in the yield. Carrying out the resolution in the solvent hexane (instead of Et_2O) gave racemic product and using 2-methyltetrahydrofuran (2-Me-THF) or *tert*-butyl methyl ether (TBME) gave similar yields to the use of Et_2O but with slightly lower er (~70:30). However, we found improved yields with good enantiomer ratio (er 85:15) by adding, after addition of the chiral diaminoalkoxide ligand (dissolved in Et_2O), hexane [to provide a final solution of Et_2O/hexane 1:1 with concentration of 0.09 M]. This gave the silane **18a** in 65 % yield (the piperidine **16** was the only other identifiable product recovered). We then screened a selection of electrophiles using these optimized conditions (Scheme 4) and the structures of the products with yields and enantiomer ratios are given in Figure 2.

The organolithium **17** resolves to a ratio of about 85:15 (*S*/*R*) in the presence of the chiral ligand **11**. By cooling this



Scheme 4. Optimized procedure for DTR of organolithium **17** (formed by deprotonation of **16**). i) *s*BuLi (1.2 equiv), Et_2O, TMEDA (1.2 equiv), −78 °C, 3 h then **11** (1.2 equiv) (pre-treated with *s*BuLi in Et_2O), then hexane, then −30 °C, 1 h then −78 °C, 3 equiv electrophile E^+; E^+ = Me_3SiCl, Bu_3SnCl, CO_2, PhSSPh, acetone (for **18e** add MeOH prior to warming slowly to RT).

complex to −78 °C equilibration is prevented and the enantiomer ratio of the products reflects the thermodynamic ratio of the organolithium·**11** complexes. Good selectivities were obtained using the electrophiles TMSCl, Bu_3SnCl and CO_2 to give **18a–c** (Figure 2). There was sometimes some erosion in the er, as observed for the electrophile PhSSPh (or with *p*-TolSSTol) to give **18d**, or with acetone, which gave the alcohol product **18e** if methanol was added at −78 °C. However, if the mixture was allowed to warm to room temperature before addition of methanol, then the product was the oxazolidinone **18f**. With MeI (or Me_2SO_4) as the electrophile, the yield was very poor (<10%) but the selectivity was high (er 84:16 *S*/*R*).

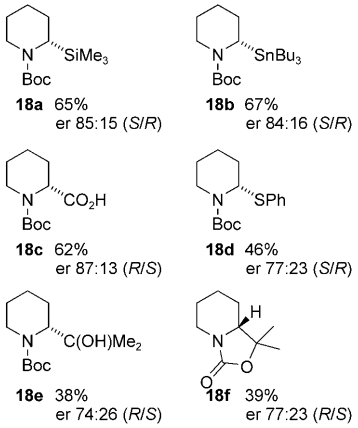
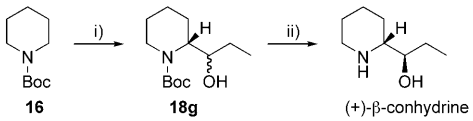


Figure 2. Products from DTR of **17** with ligand **11** and different electrophiles.

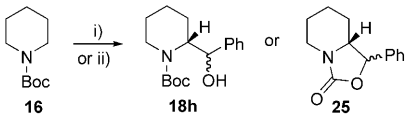
Carrying out the DTR of the organolithium **17** with the chiral ligand **11** followed by electrophilic quench with propionaldehyde gave the product **18g** as a mixture of diastereomers (dr 62:38) (Scheme 5). Chiral GC analysis gave four separate peaks (one for each enantiomer of the diastereomers) and revealed good enantioselectivity (major diastereomer er 84:16, minor diastereomer er 82:18). The diastereomers were separated by column chromoatography and hydrolysis of the major diastereomer gave the alkaloid (+)-β-conhydrine (er 84:16; NMR spectroscopic data matched the literature for this diastereomer).[17] The specific rotation, $[\alpha]_D^{22} = +6.0$ (1.0, EtOH) was in line with that expected based on the literature value for enantiopure β-conhydrine, $[\alpha]_D^{20} = +8.3$ (0.9, EtOH).[17c] This two-step procedure (overall yield from **16**, 48%) represents a remarkably rapid access to this alkaloid. As far as we are aware, there are only four previous syntheses of enantioenriched (+)-β-conhydrine and these have required 4–11 steps.[17]

Addition of benzaldehyde as the electrophile to the resolved organolithium **17**·**11** gave the desired alcohols **18h** (er not determined) (Scheme 6). By allowing the product mixture to warm to room temperature before addition of methanol, the oxazolidinones **25** were obtained directly from *N*-Boc-piperidine **16**. The oxazolidinones **25** were formed with reasonable diastereoselectivity (dr 80:20) and



Scheme 5. Synthesis of (+)-β-conhydrine. i) *s*BuLi, Et_2O, TMEDA, −78 °C, 3 h then **11** (pre-treated with *s*BuLi in Et_2O), then hexane, then −30 °C, 1 h then −78 °C, propionaldehyde, then after 1 h MeOH and warm to RT gave **18g**, 77%, dr 62:38, er major 84:16, er minor 82:18, yield of major diastereomer 48%; ii) using major diastereomer of **18g**, TFA, CH_2Cl_2, RT gave β-conhydrine, 100%, er ~84:16.

good enantioselectivity (er 87:13 for major isomer, as determined by ^1H NMR spectroscopy with the Pirkle solvating agent). A similar (but racemic) procedure has been conducted on a 4-substituted *N*-Boc-piperidine as part of a synthesis of an NK_1 antagonist.[18]



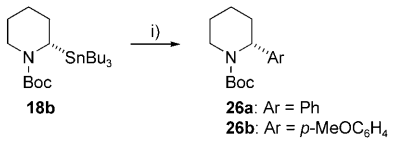
Scheme 6. Synthesis of products **18h** and **25**. i) *s*BuLi, Et_2O, TMEDA, −78 °C, 3 h then **11** (pre-treated with *s*BuLi in Et_2O), then hexane, then −30 °C, 1 h then −78 °C, benzaldehyde, then after 3.5 h MeOH and warm to RT to give **18h**, 43%, dr 58:42; or ii) as above but with warming to RT prior to addition of MeOH to give **25**, 48%, dr 80:20, er major 87:13, er minor 75:25.

In 2008, we reported that the organolithium derived from deprotonation of *N*-Boc-piperidine with *s*BuLi and TMEDA could be converted to its organozinc derivative and used in Negishi-type coupling reactions with aryl bromides to give 2-arylpiperidines.[19] To our disappointment, this procedure was unsuccessful using the DTR method. It appears that transmetallation of the resolved organolithium **17**·**L*** to the organozinc species was taking place (since subsequent addition of CuCN·2 LiCl then allylation was successful).[10b] However, in the presence of the chiral diamino-alkoxide ligand, no transmetallation with the aryl palladium bromide takes place, possibly due to the presence of the bulky ligand that can coordinate to the zinc metal. Attempts to swamp this species with excess TMEDA to allow ligand exchange followed by Negishi reaction were unsuccessful.

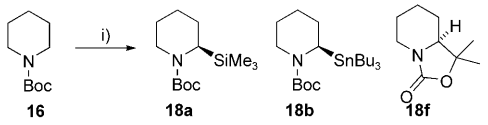
Therefore, to prepare enantiomerically enriched 2-arylpiperidines, we took the organostannane **18b** (er 84:16) and prepared the organolithium in the absence of the chiral ligand by transmetallation with *n*BuLi and TMEDA (Scheme 7). Subsequent addition of $ZnCl_2$ then a mixture of the bromobenzene, $Pd(OAc)_2$ and $(tBu)_3P{\cdot}HBF_4$ gave the desired 2-phenylpiperidine (**26a**).[19] The same procedure with 4-bromoanisole gave the piperidine **26b**. In each case the 2-arylpiperidines were formed with er 82:18 (determined by chiral HPLC), showing that there was little or no racemization during the whole transmetallation and arylation process. The absolute configuration of the products **26** was assumed to be *R* on the basis of expected retention of configu-

ration[20] and by analogy with other electrophiles (Figure 2). This was verified from the specific rotation of compound **26a** which was measured as $[\alpha]_D^{22} = +63.0$ (0.88, $CHCl_3$), and which compares with the reported value for (*R*)-**26a**, $[\alpha]_D^{25} = +83.7$ (0.98, $CHCl_3$).[21a]

Using the optimized DTR procedure with the ligand **6** resulted in the formation of the opposite major enantiomer of the products **18a**, **18b** and **18f** (Scheme 8).



Scheme 7. Synthesis of 2-arylpiperidines. i) *n*BuLi, Et_2O, TMEDA, −78 °C, 1 h then $ZnCl_2$, warm to RT, then ArBr, $Pd(OAc)_2$ and $(tBu)_3P{\cdot}HBF_4$, RT, 16 h, Ar = Ph 71 %, er 82:18, Ar = *p*-$MeOC_6H_4$ 56 %, er 82:18.



Scheme 8. Formation of the enantiomeric products using DTR with ligand **6**. i) *s*BuLi (1.2 equiv), Et_2O, TMEDA (1.2 equiv), −78 °C, 3 h then **6** (1.2 equiv) (pre-treated with *s*BuLi in Et_2O), then hexane, then −30 °C, 1 h then −78 °C, 3 equiv electrophile E^+; $E^+ = Me_3SiCl$, Bu_3SnCl or acetone to give, respectively, **18a** 59 %, er 80:20, **18b** 60 %, er 80:20 or **18f** 33 %, er 75:25.

Hence, by using DTR, the organolithium **17** can be resolved with good enantioselectivity and can be converted to a selection of enantioenriched 2-substituted piperidines. Attempts were made to conduct the DTR of **17** with substoichiometric amounts of chiral ligand[8c] (**3**, **5** or **11**) using various temperatures and equilibration times. However, after electrophilic quench at low temperature with TMSCl, the silane **18a** was isolated with very little or no enantioselectivity.

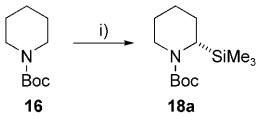
For comparison with the DTR chemistry, we wanted to determine whether the organolithium **17**, when complexed to a chiral ligand, could undergo dynamic kinetic resolution (DKR). It is quite possible that one of the diastereomeric complexes **17·L**** is more reactive than the other. To test for DKR, we need the rate of electrophilic quench to be slower than the rate of interconversion of the diastereomeric organolithium complexes. This can be achieved by adding the electrophile slowly at a temperature in which equilibration occurs. We screened several of the chiral ligands shown in Figure 1 for DKR with the electrophile TMSCl, which was added slowly (over ~1 h) at −10 or −40 °C (Table 2). The ligand (−)-sparteine (**1**) and the diamine **2** gave poor results. However the ligands **3**, **4**, **6** and **7** gave significant asymmetric induction. The ligand **3** has previously been found to give good selectivity for the DKR of *N*-Boc-2-lithiopyrrolidine.[9c] The best er value was obtained with the ligand **4**. Notably, the major enantiomer was opposite to that obtained in the DTR chemistry [for example, DTR with ligand **4** gave silane **18a**, er 42:58 (*S*/*R*)]. This shows that the minor diastereomeric complex is more reactive.

Table 2. Results for DKR of **17**.[a]

Ligand L*	Yield [%] **18a**, er (*S*/*R*)	Ligand L*	Yield [%] **18a**, er (*S*/*R*)
1	55, 47:53	**4**	62, 93:7
2	86, 49:51	**6**	71, 82:18
3	45, 28:72	**7**	60, 89:11

[a] Starting with racemic stannane **18b** and using *n*BuLi, Et_2O, TMEDA then L*, −78 °C then warm to −40 °C or above then slow addition of TMSCl.

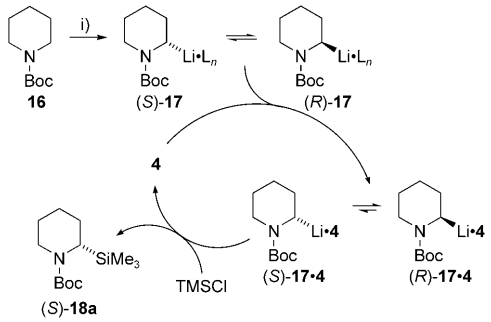
The DKR protocol was then carried out using proton abstraction of *N*-Boc-piperidine (**16**) with *s*BuLi, Et_2O and TMEDA followed by addition of the ligand **4** (pre-treated with an equivalent of BuLi). Slow addition of TMSCl at −20 °C gave the desired product **18a** (66 %, er 92:8, *S*/*R*). We found some improvement in the er by conducting the DKR in the solvent THF (Scheme 9). Under these conditions using chiral ligand **4**, the product (*S*)-**18a** was formed with er 95:5. Normally THF is a poor solvent for asymmetric organolithium chemistry as it competes with the chiral ligand for complexation to the lithium atom. Clearly in this case it is slightly preferable for kinetic resolution.



Scheme 9. Optimized procedure for DKR of organolithium **17** (formed by deprotonation of **16**). i) *s*BuLi (1.2 equiv), THF, TMEDA (1.2 equiv), −78 °C, 3 h then **4** (1.5 equiv) (pre-treated with *n*BuLi in THF), then −20 °C, then slow addition of TMSCl (4 equiv) over 1 h, **18a** 60 %, er 95:5 (*S*/*R*).

The good results for the DKR indicate that the organolithium **17** complexed with the ligand **4** is considerably more reactive to TMSCl than any organolithium complexed with THF, Et_2O or TMEDA. To test this, we wondered if the DKR reaction could be conducted with substoichiometric amounts of the chiral ligand **4**. This would rely on ligand exchange, a process that is known with related organolithiums and used for catalytic asymmetric deprotonation.[22] We were pleased to find that catalytic DKR was possible using as little as 10 mol % **4** in Et_2O or THF using a slightly slower rate of addition of TMSCl (2 equiv over 1.5 h) (Scheme 10). This gave the silane **18a** in reasonable yield (54 %) and very good enantioselectivity (er 96:4 *S*/*R*). Higher yields (77 %, er 90:10) could be obtained by using the racemic stannane **18b** as the starting material (with tin–lithium exchange using *n*BuLi to form the organolithium **17**). This result is an interesting example of a catalytic dynamic kinetic resolution. A reason for its success could be due to the higher reactivity of the chiral ligand complex over other complexes in solution and that ligand exchange is faster than electrophilic quench. A possible catalytic cycle is represented in Scheme 10 (the organolithiums are drawn as

monomers although the aggregation state is unknown). The chiral ligand must be able to displace the solvent or TMEDA (represented by L_n in Scheme 10) from the organolithium **17**·L_n (since good er values are obtained by DTR). With 10 mol% of the chiral ligand **4**, a small amount of the complexes **17·4** will be formed and interconversion between the diastereomeric complexes at −20°C leads to a (slight) preference for (*R*)-**17·4** (see Table 1, er 42:58 *S*/*R*). Addition of TMSCl then leads to reaction preferentially with (*S*)-**17·4**. This releases the lithium alkoxide of the ligand **4** to allow re-complexation with **17**·L_n and continuation of the catalytic cycle.



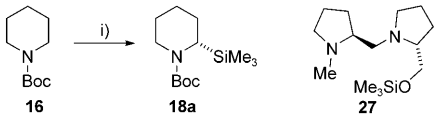
Scheme 10. Catalytic DKR of **17**. i, *s*BuLi (1.2 equiv), Et_2O, TMEDA (1.2 equiv), −78°C, 3 h then **4** (0.1 equiv) (pre-treated with *n*BuLi in Et_2O), then −20°C, then slow addition of TMSCl (2 equiv) over 1.5 h, **18a** 54%, er 96:4 (*S*/*R*).

For a successful catalytic cycle, the electrophilic quench must occur only with **17·4** and must be much slower with **17**·L_n. This was possible with TMSCl, but low er values were obtained with other electrophiles (Bu_3SnCl, DMF, allyl bromide, Me_2SO_4), even using stoichiometric amounts of the chiral ligand **4**. Good selectivity was obtained using slow addition of $PhMe_2SiCl$ to give *N*-Boc-2-(dimethylphenylsilyl)-piperidine (58% yield, er 88:12). The poor selectivity with electrophiles other than silyl chlorides shows that the enantioselectivity is dependent on the electrophile, and this would be expected for a kinetic resolution. Our understanding is that more reactive electrophiles are less able to discriminate between the diastereomeric complexes (which are present in almost equal amounts for ligand **4**). By using electrophiles that react faster than TMSCl, or are less selective for one of the complexes, there will be less effective kinetic resolution.

There are, however, several other possible explanations for the high selectivities obtained only with silyl halides. Firstly, we wondered whether the presence of LiCl could be a factor (which would be formed after reaction with TMSCl as the electrophile) and could potentially provide a different organolithium aggregate structure. Therefore, we added LiCl (1.1 equiv in THF) to **17·4** followed by warming to −20°C and slow addition of Me_2SO_4. However this resulted in racemic *N*-Boc-2-methylpiperidine.

An alternative explanation for the high selectivities with silyl halides could be that the electrophile reacts first with the chiral ligand and is then transferred to the organolithium. This might be expected to be favoured for the silyl halides that could have a fast reaction with a lithium alkoxide. We therefore wanted to test the ability of the trimethylsilyl ether of the chiral ligand **4** to promote DKR. Previous work using chiral ligands that lack the OH group (e.g. the methyl ether of diamino-alcohol **3**) has led to poor enantioselectivities in related dynamic resolutions.[9d]

The silyl ether **27** was prepared according to a related method,[23] and was purified by two successive distillations under reduced pressure. The organolithium **17** was prepared by deprotonation of *N*-Boc-piperidine (**16**) using *s*BuLi, THF and TMEDA at −78°C, then a solution of the silyl ether **27** (1 equiv) in THF was added (Scheme 11). In one experiment the temperature was maintained at −78°C for 2 h then was quenched by addition of MeOH. This gave the silane product **18a** in low yield (14%, with 75% recovered **16**) but as essentially a single enantiomer (*R* enantiomer could not be detected by chiral GC analysis). In another experiment, the mixture was warmed to −20°C. After 2 h, MeOH was added and purification by column chromatography gave the silane **18a** in reasonable yield (48%, with 40% recovered **16**) and excellent enantiopurity (er 99:1 *S*/*R*).

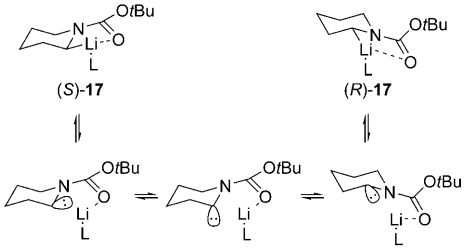


Scheme 11. Kinetic resolution of organolithium **17** (formed by deprotonation of **16**) with silyl ether **27**. i) *s*BuLi (1.2 equiv), THF, TMEDA (1.2 equiv), −78°C, 2 h then **27** (1 equiv), and either 2 h then MeOH to give **18a** 14% er >99.5:<0.5 (*S*/*R*), or warm to −20°C, then 2 h then MeOH to give **18a** 48%, er 99:1 (*S*/*R*).

These results show that silyl ether **27** provides excellent control of the enantioselectivity in the kinetic resolution of the organolithium **17**. At low temperature there must be a 50:50 mixture of the enantiomeric organolithiums to which the silyl ether **27** was added. This silyl ether is not a good electrophile and either selects to react (on the basis of relative kinetics) with one of the enantiomeric organolithiums (coordinated to TMEDA), or this diamino-silyl ether can coordinate to (*S*)-**17**, or more likely to both (*S*)- and (*R*)-**17**, and then delivers the silyl group with a strong preference to (*S*)-**17**. These results tend to favour an explanation for the high enantioselectivity in the DKR experiments with silyl electrophiles as involving an unusual intermolecular retro-Brook type rearrangement. However, it is possible that, after partial reaction, the released lithium alkoxide of ligand **4** could then be coordinating to the organolithium **17** and (*S*)-**17·4** could then react with the silyl ether **27** by an intermolecular process (possibly with double asymmetric induction). Unfortunately, low yields and no enantioselectivity

were obtained in the corresponding reaction of the tributylstannyl ether of ligand **4**.

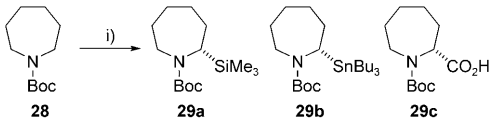
Deprotonation α- to the nitrogen atom in *N*-acylpiperidines is known to provide the 2-lithiated intermediate in which the carbon–lithium bond is equatorial.[13a,24] This allows coordination of the lithium atom to the carbonyl oxygen atom. Subsequent reaction with an electrophile occurs with retention of configuration to give equatorially substituted products. Therefore, proton abstraction of *N*-Boc-piperidine with *s*BuLi in Et_2O/TMEDA provides a mixture of the epimeric organolithiums (*S*)- and (*R*)-**17** (Scheme 12, where L = TMEDA or an added chiral ligand). These are drawn as monomers (the aggregation state is unknown), as calculations on the related *N*-Boc-2-lithiopyrrolidine suggest that inversion occurs through the monomer.[8a] A possible mechanism for interconversion between these species involves breakage of the carbon–lithium bond to give the carbanion and lithium cation which may be associated with the carbonyl oxygen atom (conducted tour type mechanism[25]). Inversion of the carbanion is required (drawn as sp^3 hybridised but it could be sp^2) together with a ring-flip from one chair conformation to the other, so that re-association of the lithium cation provides the equatorial carbon–lithium bond.



Scheme 12. Possible interconversion mechanism for **17**.

Finally, we studied the dynamic resolution of the corresponding seven-membered ring. Racemic deprotonation of *N*-Boc-azepine with *s*BuLi in Et_2O/TMEDA is known and electrophilic quench has been reported with TMSCl or Bu_3SnCl.[26] Hence, treatment of the organolithium derived from deprotonation of *N*-Boc-azepine (**28**) with the chiral ligand **11** (pre-treated with *s*BuLi) then (after addition of hexane) warming to −30 °C for 1 h (to allow equilibration to the thermodynamic ratio of complexes), followed by cooling to −78 °C and electrophilic quench with TMSCl, Bu_3SnCl or CO_2 gave the products **29a-c** (Scheme 13).

We screened several of the chiral ligands for the formation of the silane **29a** and found the best result using ligand **11**, which gave **29a**, er 92:8 (ligands **3**, **5** and **24** gave **29a** with er 77:23, 83:17 and 89:11, respectively). This is an improved enantioselectivity in comparison with the corresponding DTR of the six-membered ring **16**. The yield of the silane **29a** was low, although the DTR was not optimized for temperature or time and some azepine **28** was recovered from the reactions. The stannane **29b** was formed



Scheme 13. Procedure for DTR of **28**. i) *s*BuLi (1.2 equiv), Et_2O, TMEDA (1.2 equiv), −78 °C, 3 h then **11** (1.2 equiv) (pre-treated with *s*BuLi in Et_2O), then hexane, then −30 °C, 1 h then −78 °C, 3 equiv Me_3SiCl, **29a** 33% er 92:8 (35% recovered **28**); Bu_3SnCl, **29b** 29% er 90:10; CO_2, **29c** 18% er ~87:13.

with similar yield and er. The acid **29c** was formed in low yield but again with similar er. In this case the er was estimated from a comparison of the specific rotation with the literature: found $[\alpha]_D^{22} = +46.3$ (1.0, MeOH), lit. for *S* enantiomer, er 95:5, $[\alpha]_D^{20} = -59.1$ (1.0, MeOH).[27] This verified that the major enantiomer was (*R*)-**29c**, as shown in Scheme 13, and as expected based on electrophilic quench with retention of configuration from (*S*)-*N*-Boc-2-lithioazepine (the *S*- organolithium was expected for ligand **11**, as found for the 2-lithiopiperidine **17**).

The azepine substrate **28** appears to be a poorer substrate for proton abstraction than the corresponding five- and six-membered analogues, so yields tend to be low. However, enantioselectivities are good in the DTR with diamino-alkoxide ligands, so there is scope for this chemistry in asymmetric synthesis after finding an alternative method for the formation of the organolithium.

Conclusion

The organolithiums *N*-Boc-2-lithiopiperidine and *N*-Boc-2-lithioazepine can be resolved in the presence of a chiral ligand. The dynamic equilibration of the diastereomeric complexes occurs within one hour at −30 °C. After electrophilic quench, good enantiomer ratios of several 2-substituted *N*-Boc-piperidines and *N*-Boc-azepines can be obtained. Using *N*-Boc-2-lithiopiperidine and TMSCl as the electrophile, a highly enantioselective catalytic dynamic kinetic resolution can be promoted.

Experimental Section

General procedure for the dynamic thermodynamic resolution of *N*-Boc-2-lithiopiperidine: *s*BuLi (1.2 equiv, 1.3 M in hexanes) was added to *N*-Boc-piperidine **16** (1.0 equiv) and TMEDA (1.2 equiv) in Et_2O (0.5 M) at −78 °C. After 3 h, the deprotonated ligand **11** [prepared by adding *s*BuLi (1.25 equiv, 1.3 M in hexanes) to a 0.5 M solution of **11** (1.2 equiv) in Et_2O at 0 °C for 30 min] was added. The mixture was diluted by a factor of two by the addition of hexane and was warmed to −30 °C. After 1 h, the mixture was cooled to −78 °C and the electrophile (3.0 equiv) was added. The mixture was allowed to warm slowly (over 18 h) to room temperature and MeOH was added. The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with hexane-EtOAc, to give the product. The chiral ligand **11** was 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.

Procedure for the catalytic dynamic kinetic resolution of *N*-Boc-2-lithiopiperidine: *s*BuLi (1.2 equiv, 1.3 M in hexanes) was added to *N*-Boc-piperidine **16** (1.0 equiv) and TMEDA (1.2 equiv) in Et_2O (0.5 M) at −78 °C. After 3 h, the deprotonated ligand **4** [prepared by adding *s*BuLi (0.1 equiv, 1.3 M in hexanes) to a 0.5 M solution of **4** (0.1 equiv) in Et_2O at 0 °C for 30 min] was added. The mixture was warmed to −20 °C and TMSCl (2.0 equiv) was added slowly (over 1.5 h). Methanol was added, the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with hexane/EtOAc 98:2, to give the product **18a**.

General procedure for the dynamic thermodynamic resolution of *N*-Boc-2-lithioazepine: *s*BuLi (1.2 equiv, 1.3 M in hexanes) was added to *N*-Boc-azepine **28** (1.0 equiv) and TMEDA (1.2 equiv) in Et_2O (0.5 M) at −78 °C. After 3 h, the deprotonated ligand **11** [prepared by adding *s*BuLi (1.2 equiv, 1.3 M in hexanes) to a 0.5 M solution of **11** (1.2 equiv) in Et_2O at 0 °C for 30 min] was added. The mixture was diluted by a factor of two by the addition of hexane and was warmed to −30 °C. After 1 h, the mixture was cooled to −78 °C and the electrophile (3.0 equiv) was added. The mixture was allowed to warm slowly (over 18 h) to room temperature and MeOH was added. The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with hexane-EtOAc, to give the product.

Procedures and data for the ligand syntheses **2**–**15**, **24** and **27** are given in the Supporting Information.

Data for the piperidines **18a**–**h**, (+)-β-conhydrine, **25**, **26a**–**b** and azepines **29a**–**c** are given in the Supporting Information.

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[28] CCDC 747987 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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