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Dynamic Thermodynamic and Dynamic Kinetic Resolution of 2-Lithiopyrrolidines

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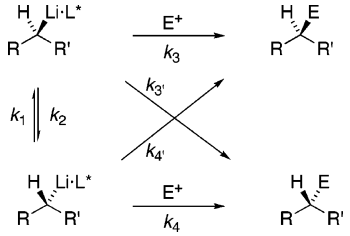
Abstract: Dynamic resolution has been studied as a method for the asymmetric synthesis of 2-substituted pyrrolidines. Highly enantioselective electrophilic substitutions of racemic 2-lithiopyrrolidines in the presence of a chiral ligand have been achieved. The organolithium compounds were prepared by tin−lithium exchange from the corresponding tributylstannanes and *n*-butyllithium or by deprotonation of *N*-(*tert*-butyloxycarbonyl)-pyrrolidine with *sec*-butyllithium. A range of *N*-substituents and chiral ligands were investigated for the dynamic resolution. Electrophilic quench of the resolved diastereomeric 2-lithiopyrrolidine−chiral ligand complexes provided the enantiomerically enriched 2-substituted pyrrolidines. With *N*-alkyl derivatives, the resolution occurs conveniently at (or just below) room temperature and either enantiomer of the product can be formed by appropriate choice of the chiral ligand. The asymmetric induction occurs as a result of a thermodynamic preference for one of the diastereomeric complexes. The minor complex was found to have a faster rate of reaction with the electrophile. The use of *N*-allylic derivatives provides a means to prepare the *N*-unsubstituted pyrrolidine products. Best results were obtained with the *N*-2,3-dimethylbut-2-enyl derivative, and this *N*-substituent could be cleaved using 1-chloroethyl chloroformate. With *N*-Boc-2-lithiopyrrolidine, the enantioselectivity arises by a kinetic resolution and high levels of asymmetric induction in the presence of excess *n*-butyllithium can be obtained. Dynamic kinetic resolution of the *N*-Boc derivative is limited in the scope of electrophile that can be used.

Introduction

Organolithiums are arguably the most widely used organometallic reagents in the whole of synthetic chemistry. With the steady increase in importance of stereoselective synthesis over the past few decades, it is not surprising that there is a significant and growing interest in chiral organolithium species (sp^3-hybridized carbanion center).[1] There are two methods by which asymmetric induction with such species can be promoted. One approach is to prepare the organolithium species in enantioenriched form, for example by an asymmetric deprotonation or a stereospecific transmetalation (particularly tin−lithium exchange) under conditions that maintain the configurational stability of the organolithium species. Stereoselective electrophilic quench of the chiral organolithium species then provides the enantioenriched product. Alternatively, an asymmetric substitution of the organolithium in the presence of some stereochemical bias, such as a chiral ligand (L*) or chiral auxiliary, can be effective. This latter method can make use of a chiral organolithium that is racemic (or enantioenriched) and which ideally is configurationally unstable, such that dynamic resolution occurs (Scheme 1; k_1, $k_2 \neq 0$). Such dynamic resolution and asymmetric induction on quench with an electrophile (E^+) can result either from a thermodynamic preference for one of the two diastereomeric organolithium−chiral ligand complexes (referred to as dynamic thermodynamic resolution),[2] which is followed by stereoselective quench with the electrophile (with retention or inversion of configuration at the carbanion center), or from a kinetic preference ($k_3 \neq k_4$ or $k_3' \neq k_4'$) for reaction of one of these complexes with the electrophile (referred to as dynamic kinetic resolution). In dynamic thermodynamic resolution, electrophilic quench is faster than interconversion of the diastereomeric complexes (k_3, $k_4 > k_1$, k_2), although there can still be a kinetic preference for reaction of either of the two complexes. In dynamic kinetic resolution, electrophilic quench is slower than interconversion of the diastereomeric complexes

Scheme 1



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10.1021/ja061963m CCC: $33.50

(k_3, $k_4 < k_1$, k_2). There can, of course, be a combination of both thermodynamic and kinetic factors that contribute to the enantiomer ratio (er) of the products, depending on the relative rates of these processes.

Significant advances in the use of chiral organolithium species were made with the discovery that certain dipole-stabilized α-alkoxy- and α-amino-organolithium species could be generated enantioselectively by asymmetric deprotonation with butyllithium and (−)-sparteine as the chiral ligand.[3] These organolithium species are configurationally stable at low temperature (−78 °C is normally used) and react stereoselectively with a range of electrophiles.[4,5] In contrast, α-thio- and α-seleno-organolithium species are configurationally labile at low temperature, and this has allowed asymmetric substitution by dynamic thermodynamic or dynamic kinetic resolution, with high selectivities being achieved particularly using chiral bis(oxazoline) ligands.[6] Benzylic and allylic organolithium species are also prone to racemize at low temperature, and these organolithiums can be suitable substrates for asymmetric substitution.[2,7]

To promote successful asymmetric induction with a chiral organolithium species, it is important to have some understanding of its rate of enantiomerization and, ideally, how this rate compares with the rate of reaction with the electrophile. The majority of reactions that make use of chiral organolithium species are carried out at low temperature, and this has perhaps fuelled the misconception that only allylic, benzylic, or α-thio-/α-seleno-organolithium species can readily undergo dynamic resolution. In reality, any chiral organolithium species can potentially undergo equilibration, particularly on warming, and successful dynamic resolution requires a rate of enantiomerization that is faster than its rate of decomposition or other side reactions.

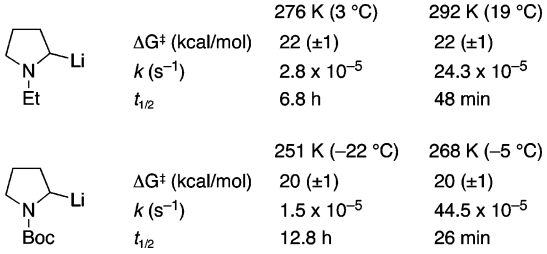

Figure 1. Barrier, rate constant, and half-life of enantiomerization of 2-lithiopyrrolidines in hexanes−Et_2O.[8]

Hence, although chiral α-amino-organolithium species are configurationally stable at low temperature,[5] at room temperature enantiomerization takes place readily (as found initially during a study of the enantioselectivity on anionic cyclization to give indolizidines).[5b] To gain further understanding of the factors affecting the enantiomerization, the barrier to inversion of several chiral 2-lithiopyrrolidines was determined in the solvent hexanes−Et_2O (4:1) (Figure 1).[8] It is clear from these data that *N*-alkyl-2-lithiopyrrolidines have a slightly higher barrier to inversion (22 kcal/mol) than the corresponding *N*-(*tert*-butyloxycarbonyl) (*N*-Boc) derivative (20 kcal/mol), and consequently, a higher temperature is required to allow dynamic equilibration of *N*-alkyl-2-lithiopyrrolidines. In the presence of a chiral ligand, it should be possible to effect dynamic resolution of such organolithiums, and we have verified that this is, indeed, the case.[9−11] Extremely high selectivities can be obtained in

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Scheme 2

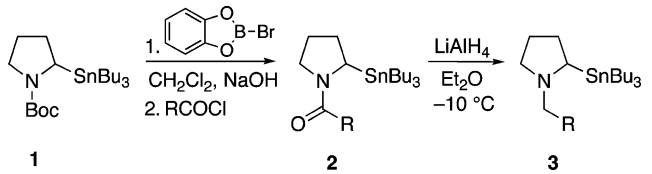
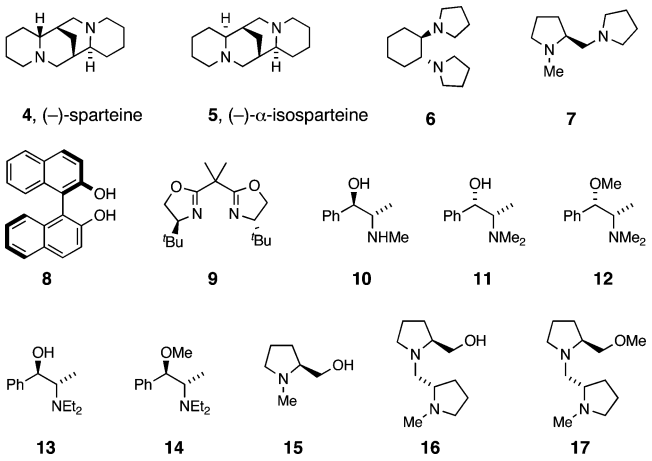


Chart 1



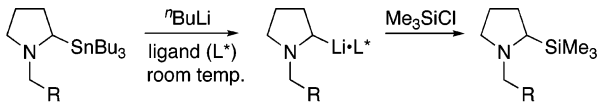
the asymmetric substitution of both *N*-alkyl- and *N*-Boc-2-lithiopyrrolidines. Remarkably, reactions occur by either a dynamic thermodynamic resolution (using the *N*-alkyl derivatives) or a dynamic kinetic resolution (using the *N*-Boc derivative). A full account of these dynamic resolutions is given here, including results not previously reported on the influence of a wide selection of different ligands and the extension from *N*-alkyl to *N*-allylic derivatives that can be cleaved and thus provide a method to access the *N*-unsubstituted pyrrolidine products.

Results

Dynamic Resolution of *N*-Alkyl-2-lithiopyrrolidines. A selection of *N*-alkyl-2-tributylstannylpyrrolidines **3** was prepared from *N*-Boc-2-tributylstannylpyrrolidine (**1**).[12] Removal of the *N*-Boc group using *B*-bromocatecholborane, followed directly by acylation, gave the amides **2**, which were reduced with $LiAlH_4$ to give the desired stannanes **3** (Scheme 2). Different chiral ligands (Chart 1) were probed for the subsequent asymmetric substitution reaction, and the results of this study are given in Table 1. Chiral ligands with an OH or NH group were treated with 1.2 equiv of *n*-BuLi prior to addition to the organolithium derived from the stannane **3** and *n*-BuLi.

Asymmetric substitution with the ligand (−)-sparteine (**4**, entries 1−3 in Table 1) gave low to moderate levels of selectivity.[10] On increasing the time or the temperature, similar or lower yields and selectivities were obtained. The major enantiomer of the product **19** had the *R*-absolute configuration, which contrasts with the major enantiomer obtained using (−)-sparteine as a chiral ligand for asymmetric deprotonation of *N*-Boc-pyrrolidine.[13] Other diamine ligands (**5**−**7**, entries 4−6) or β-amino-alcohol-derived ligands (**10**−**15**, entries 9−14) also gave low levels of selectivity. The ligand BINOL (**8**, entry 7) did not promote any asymmetric induction, and on addition of the bisoxazoline **9** (entry 8), a deep yellow color was obtained and none of the desired product **19** was formed. However, the diamino-alcohol **16** (entry 16) was found to give excellent levels of asymmetric induction. This reaction was best carried out in Et_2O as solvent, since the lithium alkoxide generated from addition of *n*-BuLi to the ligand **16** was not very soluble in the less polar solvent hexane. The ligand **17** (entry 17), which is the methyl ether of ligand **16**, gave no asymmetric induction.

Table 1. Resolution of *N*-Alkyl-2-lithiopyrrolidines and Quench with Trimethylsilyl Chloride



entry	R	chiral ligand	conditions	yield **19** (%)	er (*R*:*S*)
1	Me	**4**	hexane, 30 min	81	73:27
2	$CH_2CH_2CH_3$	**4**	hexane, 1 h	74	74:26
3	$CHMe_2$	**4**	hexane, 1 h	78	85:15
4	Me	**5**	hexanes−Et_2O (1:7), 30 min	48	70:30
5	Me	**6**	hexanes−Et_2O (4:1), 30 min	50	53:47
6	$CHMe_2$	**7**	hexanes−Et_2O (4:1), 1 h	45	46:54
7	Me	**8**	hexanes−Et_2O (4:1), 30 min	50	50:50
8	$CHMe_2$	**9**	hexanes−Et_2O (4:1), 1 h	0	
9	$CHMe_2$	**10**	hexanes−Et_2O (4:1), 1 h	60	50:50
10	$CHMe_2$	**11**	hexanes−Et_2O (4:1), 1 h	41	50:50
11	$CHMe_2$	**12**	hexanes−Et_2O (4:1), 1 h	41	43:57
12	$CHMe_2$	**13**	hexanes−Et_2O (4:1), 1 h	45	39:61
13	$CHMe_2$	**14**	hexanes−Et_2O (4:1), 1 h	38	44:56
14	$CHMe_2$	**15**	hexanes−Et_2O (4:1), 1 h	76	58:42
15	Me	**16**	hexane, 30 min	10	22:78
16	$CHMe_2$	**16**	Et_2O, 1 h	75	3:97
17	$CHMe_2$	**17**	Et_2O, 1 h	42	50:50

From these studies, it was clear that the best ligand was the diamino-alcohol **16**. This ligand is commercially available but can also be prepared readily in two steps from proline methyl ester.[14] In regard to the 2-lithiopyrrolidine substrate, on increasing the steric bulk in the substituent on the nitrogen atom, slight improvements to the level of asymmetric induction were obtained (entries 1−3). Thus, compound **18**, R = $CHMe_2$, together with ligand **16** were selected to study the scope of the reaction with a variety of electrophiles (Table 2). In each case, the stannane **3** was treated with *n*-BuLi in Et_2O at room temperature for 1 h prior to addition of the ligand **16**. The ligand **16** was pretreated with *n*-BuLi (1.2 equiv) in Et_2O at −30 °C for 10 min and then allowed to warm to room temperature. The electrophilic quench was best carried out after the mixture was cooled.

The products **19**−**24** were obtained with excellent levels of enantioselectivity. The absolute configuration of the major enantiomer was determined by comparison of the specific rotation with that of an authentic sample, prepared from the enantioenriched stannane **1** (see Supporting Information). These asymmetric substitution reactions were successful with a variety of electrophiles, including acetone (Table 2, entry 3) that bears enolizable protons. Only with benzaldehyde (entry 5) was the er reduced, possibly due to partial single-electron transfer.[5a] The

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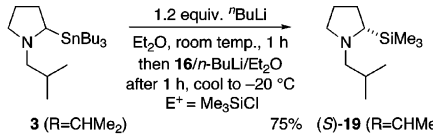
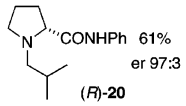
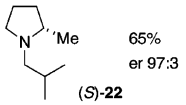
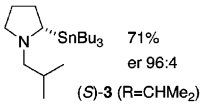
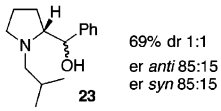
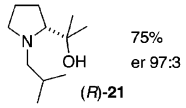
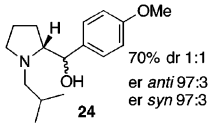
Table 2. Resolution of *N*-Isobutyl-2-lithiopyrrolidine with Ligand **16**

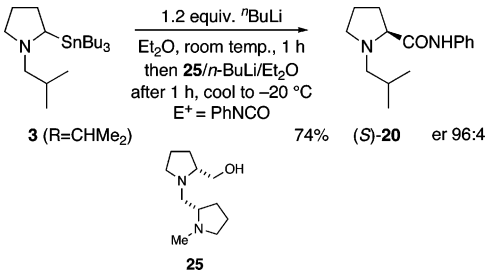


3 (R=CHMe$_2$) 75% (*S*)-**19** (R=CHMe$_2$) er 97:3

entry	E$^+$	product		entry	E$^+$	product	
1	PhNCO		61%, er 97:3, (*R*)-**20**	4[a]	Me_2SO_4		65%, er 97:3, (*S*)-**22**
2	Bu_3SnCl		71%, er 96:4, (*S*)-**3** (R=CHMe$_2$)	5[a]	PhCHO		69% dr 1:1, er *anti* 85:15, er *syn* 85:15, **23**
3	Me_2C=O		75%, er 97:3, (*R*)-**21**	6[a]	*p*-MeOC$_6$H$_4$CHO		70% dr 1:1, er *anti* 97:3, er *syn* 97:3, **24**

[a] Cool to −70 °C prior to electrophilic quench.

Scheme 3



3 (R=CHMe$_2$) 74% (*S*)-**20** er 96:4

25

chiral ligand could be recovered after column chromatography and distillation, without any loss of enantiopurity.

If the chiral ligand **16** was added to the organolithium species after cooling to −78 °C, then electrophilic quench gave the desired products with no enantioselectivity (er 50:50). However, if only a small amount of the electrophile Me_3SiCl was added to the organolithium·**16** complex at −78 °C, then the product **19** (R = CHMe$_2$) was formed with low selectivity in favor of the opposite major enantiomer (er 39:61, *S*:*R*). These results suggest that the asymmetric induction arises from a dynamic thermodynamic resolution. Hence, the ratio of enantiomers given in Tables 1 and 2 arises from the ratio of the diastereomeric complexes **18**.

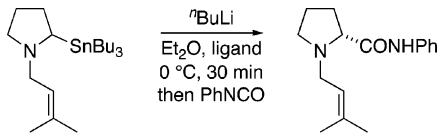
The ligand **16** contains two stereogenic centers, and it was important to probe the extent of asymmetric induction with its diastereoisomer. Ligand **25** was therefore prepared from D-proline methyl ester according to the published procedure.[15] Efficient dynamic resolution was achieved with this ligand, quenching with phenyl isocyanate to give the product **20** with high enantioselectivity (Scheme 3). The chiral ligands **16** and **25** promote the formation of different stereoisomeric products (compare Table 2, entry 1, with Scheme 3), and the asymmetry therefore arises from the absolute configuration of the (lithiated) hydroxymethyl group of the ligand.

Dynamic Resolution of 2-Lithiopyrrolidines Bearing *N*-Allylic Substituents. Although excellent levels of enantioselectivity arise from the dynamic resolution of *N*-isobutyl-2-lithiopyrrolidine, a drawback with these compounds is that the *N*-isobutyl group cannot be cleaved from the 2-substituted products. We therefore sought to find an alternative *N*-substituent that allowed efficient dynamic resolution and subsequent cleavage from the product. An initial investigation using *N*-benzyl-2-lithiopyrrolidine provided a mixture of products containing only a small amount of the desired product, together with the destannylated compound *N*-benzylpyrrolidine and some 1,2-rearrangement product 2-benzylpyrrolidine. We therefore turned to *N*-allylic derivatives. These were prepared from *N*-Boc-2-tributylstannylpyrrolidine (**1**) by removal of the *N*-Boc group (using *B*-bromocatecholborane) and acylation, followed by reduction in the same way as shown above (Scheme 2, except using reduction with AlH_3 formed from $LiAlH_4$ and $AlCl_3$), or by removal of the *N*-Boc group and allylation with the required bromide.[16] Initially we prepared the stannane **26**, which was treated with *n*-BuLi to effect tin−lithium exchange (Table 3). The transmetalation was carried out at 0 °C to avoid any potential sigmatropic rearrangement at elevated temperature.[16] Using the ligand **16** (deprotonated with *n*-BuLi prior to addition), good levels of asymmetric induction were obtained (Table 3, entry 1). This was a marked improvement over the use of the ligand (−)-sparteine (**4**), which gave (entry 2, in hexane rather than Et_2O and after quench with Me_3SiCl) the product *N*-prenyl-2-trimethylsilylpyrrolidine in 69% yield and with er 25:75 (opposite absolute configuration of the major product with this ligand). We decided to screen some other chiral ligands, as shown in Chart 2. High levels of selectivity were obtained using ligand **28** (Table 3, entry 3), which is related to **16** but lacks the additional stereogenic center. However, the ligand **29** was poorly selective (entry 4), thus demonstrating the requirement for both nitrogen atoms in the ligand. Enhancing the steric bulk of the ligand (using ligand **30**, entry 5) did not improve the results in comparison with those obtained with ligand **16** (the yields of these reactions are unoptimized). Finally, an attempt with the ligand **31** failed to give any product **27**.

(15) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148.

(16) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817.

Table 3. Resolution of *N*-Prenyl-2-lithiopyrrolidine

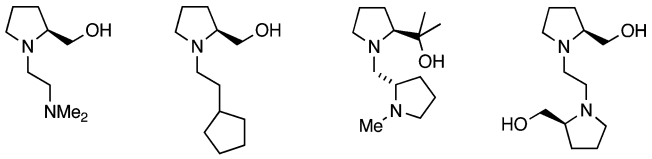


26 (*R*)-**27**

entry	chiral ligand[a]	yield **27** (%)	er (*R*:*S*)
1	**16**	72	87:13
2	**4**	69[b]	25:75
3	**28**	40	83:17
4	**29**	35	47:53
5	**30**	20	83:17
6	**31**	0	

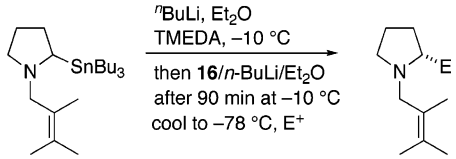
[a] The lithium alkoxides of ligands **16** and **28**−**31** were used. [b] Quench with Me_3SiCl.

Chart 2



28 **29** **30** **31**

Table 4. Resolution of *N*-Trimethylallyl-2-lithiopyrrolidine



32 **33**

entry	E^+	E	yield **33** (%)	er (*R*:*S*)
1	PhNCO	CONHPh	51	96:4
2[a]	PhNCO	CONHPh	70	96:4
3	Me_3SiCl	$SiMe_3$	62	5:95
4	Me_2SO_4	Me	59	6:94
5	$^cC_6H_{10}O$	$C(OH)C_5H_{10}$	48	95:5

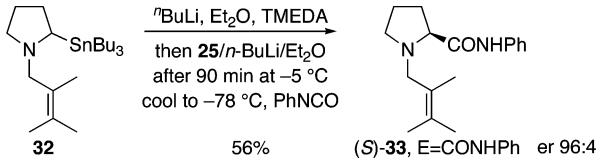
[a] No TMEDA, but 2.7 equiv of aged BuLi and 1.5 equiv of **16** were used.

The levels of asymmetric induction obtained using the *N*-prenyl compound **26**, although good, were not as high as that obtained using the *N*-isobutyl compound **3** (R = $CHMe_2$). We therefore prepared the branched compound **32**, which is more structurally related to compound **3** (R = $CHMe_2$). The stannane **32** was reluctant to undergo transmetalation, but this could be induced in the presence of the additive TMEDA (1.2 equiv, 1 h). This concerned us somewhat, as the ligand TMEDA could potentially compete with the chiral ligand for complexation to the organolithium (**18**). However, we were pleased to find that excellent levels of asymmetric induction were obtained using the chiral ligand **16** (Table 4; ligand **16** was deprotonated with *n*-BuLi in Et_2O prior to addition). The best results were obtained when the mixture was allowed sufficient time (>1 h) before quenching with the electrophile. This should allow the formation of the thermodynamic ratio of diastereomeric complexes. Transmetalation is slow in the absence of TMEDA but improves when using *n*-BuLi that has aged. This result suggests that the products of decomposition of BuLi enhance the rate of transmetalation. The dynamic resolution was effective for a selection of electrophiles, as shown in Table 4. Using PhNCO gave the product (*R*)-**33**, E = CONHPh, and the enantiomer ratio was determined by chiral HPLC (see Supporting Information). The enantiomer ratio of the product **33**, E = $SiMe_3$, from quench with Me_3SiCl was determined by removal of the *N*-allyl group (see below), protection with Boc_2O, and chiral GC. The electrophile Me_2SO_4 gave the product **33**, E = Me (together with some protodestannylated product), and the electrophile MeI gave none of the desired product. The enantiomer ratio of the product **33**, E = Me, was determined by chiral GC analysis. The electrophile cyclohexanone (Table 4, entry 5) gave the product **33**, E = $C(OH)C_5H_{10}$, and the enantiomer ratio was determined by chiral GC analysis. Use of the electrophile Bu_3SnCl was successful (yield of **33**, E = $SnBu_3$ = **32** was 60%), but a reduced enantiomer ratio (er *R*:*S* 23:77 as judged by specific rotation) was obtained due to the presence of residual starting material **32** that had resisted transmetalation; by allowing a longer time (3 h) for transmetalation at higher temperature (−5 °C), some improvement in the enantiomer ratio was obtained (er *R*:*S* 14:86, yield 56%).

The same transformation using the diastereomeric ligand **25**, quenching with phenyl isocyanate, gave the product **33**, E = CONHPh, with high enantioselectivity (Scheme 4).

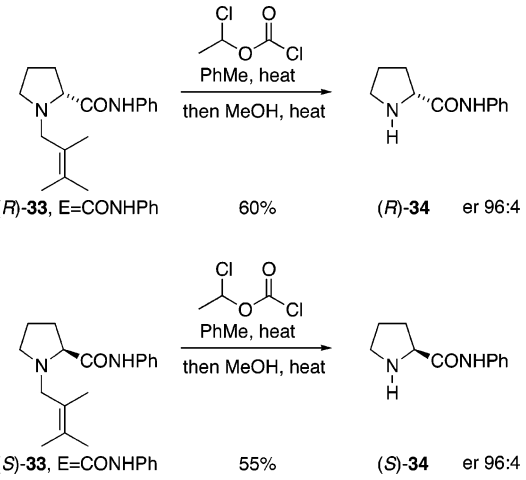
Deallylation of the products **33** was investigated under a selection of different conditions. Although the *N*-prenyl group could be cleaved using $Pd(dba)_2$, dppb, and thiosalicylic acid in THF, these conditions were unsuccessful for the more hindered compound **33**. However, the desired *N*-unsubstituted products **34** could be obtained by heating with α-chloroethyl chloroformate in PhMe, followed by heating in MeOH (Scheme 5). Both (*R*)- and (*S*)-**34** could be obtained in this way. The absolute configurations of these compounds were verified from their specific rotations, which matched those in the literature.[17]

Scheme 4



32 56% (*S*)-**33**, E=CONHPh er 96:4

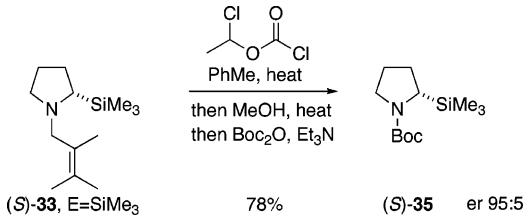
Scheme 5



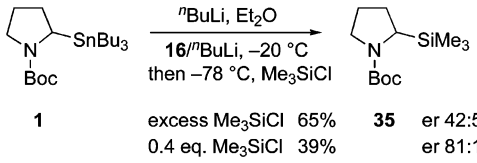
(*R*)-**33**, E=CONHPh 60% (*R*)-**34** er 96:4

(*S*)-**33**, E=CONHPh 55% (*S*)-**34** er 96:4

Scheme 6



Scheme 7



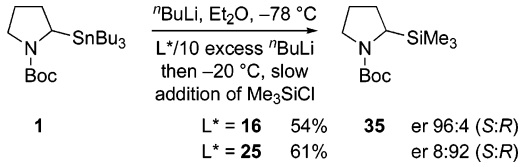
The same procedure was applied to the silane **33**, E = $SiMe_3$, to give, after protection with Boc_2O, the product **35** (Scheme 6).

Dynamic Resolution of *N*-Boc-2-lithiopyrrolidine. The kinetic data shown in Figure 1 indicate that it should be possible to effect dynamic resolution of the organolithium species derived from the *N*-Boc compound **1**. As the stannanes used in our dynamic resolutions described above are prepared from compound **1**, such chemistry may avoid the need to convert compound **1** to the *N*-alkyl or *N*-allyl derivatives. Formation of *N*-Boc-2-lithiopyrrolidine from compound **1** (or from deprotonation of *N*-Boc-pyrrolidine) is well known, and although this organolithium maintains its configurational stability at −78 °C for several hours, it is known to lose optical purity at −40 °C.[13] Beak and co-workers reported that no asymmetric substitution of this organolithium occurs in the presence of (−)-sparteine (**4**) as a chiral ligand.[13] This experiment is reported to have been conducted at low temperature with excess Me_3SiCl to quench the organolithium, and under such conditions no resolution would be observed. We therefore probed this reaction and found that the product *N*-Boc-2-trimethylsilylpyrrolidine (**35**) is formed as a racemic mixture by using higher temperatures (e.g. −20 or 0 °C that should allow the dynamic equilibration) or substoichiometric amounts of Me_3SiCl as the electrophile. The chiral ligand (−)-sparteine (**4**) is therefore not suitable to promote dynamic resolution of *N*-Boc-2-lithiopyrrolidine. Despite this, we thought that it would be appropriate to test whether the ligand **16** could be used in this chemistry.

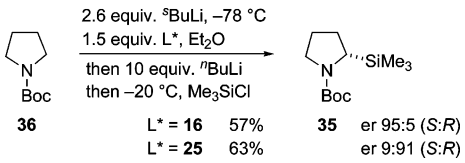
First, we tested the chiral ligand **16** (pretreated with *n*-BuLi) at −20 °C for 20 min, followed by cooling to −78 °C and quenching with Me_3SiCl. The product **35** was isolated as a mixture of enantiomers in a ratio 42:58, with the (*R*)-enantiomer as the major absolute configuration (determined by comparison with an authentic sample) (Scheme 7).[13] Longer reaction times or elevated temperature gave similar results. However, quenching with 0.4 equiv of Me_3SiCl gave the product **35** with er 81:19 in favor of the (*S*)-enantiomer. It appears, therefore, that the chiral ligand complex with the (2*S*)-*N*-Boc-2-lithiopyrrolidine reacts faster than that with the (2*R*)-enantiomer.

Attempts were made to optimize this er by altering the solvent, concentration, amount of *n*-BuLi, temperature, and rate of addition of Me_3SiCl. In all cases, the er was poor when the mixture was cooled to −78 °C and quenched with excess Me_3SiCl. However, very good er's could be obtained when a substoichiometric amount of Me_3SiCl was added or when Me_3SiCl was added slowly at −20 °C. This was particularly so when excess *n*-BuLi was present. For example, formation of the organolithium in the presence of 1.5 equiv of the chiral ligand **16** and an overall excess of 10 equiv of *n*-BuLi gave, after quenching with 5 equiv of Me_3SiCl, the product **35** in 42% yield and with er 98:2 (*S*:*R*). The use of 10 equiv of excess *n*-BuLi gave better selectivities than 3.25 or 6.25 equiv of excess *n*-BuLi. The high er must be a reflection of the improved relative rate of reaction between the diastereomeric complexes. To improve the yield in this kinetic resolution, we needed to carry out the electrophilic quench at a temperature that allows dynamic equilibration. Using the stannane **1** and the chiral ligand **16** as above, with 10 equiv of excess *n*-BuLi, followed by warming to −20 °C and slow addition of Me_3SiCl (16 equiv) over 90 min at this temperature, gave the product (*S*)-**35** with er 96:4 (Scheme 8). Likewise, the use of the diastereomeric ligand **25** gave the product (*R*)-**35** with er 92:8. In the absence of excess *n*-BuLi, poor er's were obtained.[11]

Scheme 8



Scheme 9

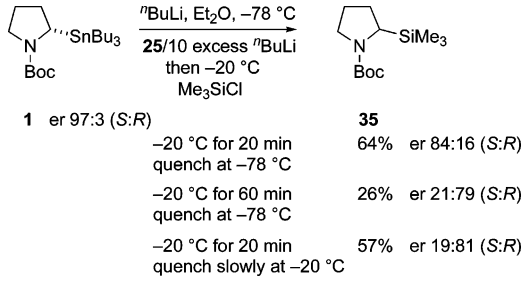


As an alternative method that avoids tin−lithium exchange, *N*-Boc-pyrrolidine **36** was treated with *sec*-BuLi (2.6 equiv) and the chiral ligand **16** (1.5 equiv) in Et_2O at −78 °C. After 6 h, 10 equiv of *n*-BuLi was added. Slow addition of Me_3SiCl (16 equiv) at −20 °C over 30 min gave the product (*S*)-**35** with er 95:5 (Scheme 9). Likewise, the use of the diastereomeric ligand **25** gave the product (*R*)-**35** (er 9:91). In this case, it was preferable to complete the electrophilic quench over about 30 rather than 90 min to minimize the formation of the byproduct Bu_2CO, presumably formed from attack of the excess *n*-BuLi with the Boc group.

The transformation given in Scheme 9 is actually an asymmetric deprotonation at −78 °C, followed by equilibration at −20 °C. Indeed, Beak and co-workers have described this asymmetric deprotonation with the ligand **16** and quench at low temperature to give product **35** (er 87:13 *S*:*R*).[15] To verify that our enhanced enantioselectivity arises from a kinetic resolution, we carried out the following three experiments, all using enantioenriched stannane **1** (er 97:3 *S*:*R*) and the chiral ligand **25**, representing the "mismatched" arrangement (Scheme 10). Allowing a short period of time at −20 °C before cooling and quenching with Me_3SiCl gave the product **35**, predominantly as the (*S*)-enantiomer (er 84:16), indicating that there was insufficient time for equilibration. However, after 60 min at −20 °C, the enantiomer ratio had changed to 21:79 in favor of the (*R*)-enantiomer. Crucially, allowing just 20 min at −20 °C

(17) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111.

Scheme 10



before quenching the organolithium slowly over 30 min at −20 °C, the product **35** was formed with er 19:81 in favor of the (*R*)-enantiomer. Hence, despite the fact that only a small amount of the (*R*)-enantiomer (of the organolithium) is present under these conditions, the (*R*)-enantiomer of the product is produced predominantly.

The optimized method to allow dynamic kinetic resolution is therefore to deprotonate *N*-Boc-pyrrolidine **36** with *sec*-BuLi and the chiral ligand (**16** or **25**) and then add excess *n*-BuLi, warm to −20 °C, and quench slowly. This is effective for electrophilic quench with Me_3SiCl but was unsuccessful with other electrophiles, such as acetone and PhNCO. The electrophile MeI did give the desired product, but the yield and enantioselectivity were moderate. The electrophile Bu_3SnCl gave racemic organostannane **1**.

Discussion

Dynamic Resolution of *N*-Alkyl- and *N*-Allyl-2-lithiopyrrolidines. Excellent levels of asymmetric induction are possible from 2-lithiopyrrolidines bearing *N*-isobutyl- and *N*-2,3-dimethylbut-2-enyl substituents (compounds **3**, R = $CHMe_2$, and **32**) using the chiral ligands **16** and **25** (Tables 2 and 4). The asymmetry arises from a dynamic thermodynamic resolution, as shown by the fact that similar er's are obtained if the mixture is cooled to −78 °C prior to quenching with the electrophile. Also, if only a small amount of electrophile is added, then a different er is obtained (showing that the asymmetry does not arise from a kinetic resolution). Thus, the organolithium prepared from the stannane **3**, R = $CHMe_2$, and *n*-BuLi, on cooling to −78 °C then addition of the chiral ligand **16** followed by addition of only 0.3 equiv of Me_3SiCl, gave the product **19** with er 39:61 (*S*:*R*). Electrophilic quench of the organolithium species is believed to occur with retention of configuration at the carbanion center;[10] hence, using the ligand **16**, the enantiomer (*R*)-2-lithiopyrrolidine reacts slightly faster than the (*S*)-enantiomer ($\Delta\Delta G^{\ddagger}$ must be about 0.7 kJ/mol). However, the (*S*)-enantiomer predominates at equilibrium to the extent of at least 97:3 (*S*:*R*), and this ratio is reflected in the er of the products given in Table 2. The reaction energy profile can be described as shown in Figure 2. As the ratio of enantiomers of the products reflects the ratio of diastereomeric complexes, the difference in the energy of these complexes, $\Delta G°$, must be about 8 kJ/mol. The barrier to inversion of the diastereomeric complexes will alter with the temperature; as there is a slight preference for reaction of the minor (*R*)-diastereomer in these dynamic thermodynamic resolutions, the electrophilic quenches are best carried out at low temperature, where no interconversion takes place. However, good er's can be obtained by quenching at the temperature required for equilibration.

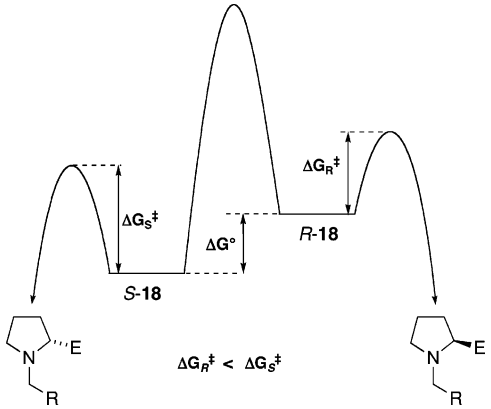


Figure 2. Assumed energy diagram for dynamic thermodynamic resolution of *N*-alkyl- and *N*-allyl-2-lithiopyrrolidines.

As the products from dynamic resolution and electrophilic quench of the *N*-allylic substrate **32** are formed in good yield and high enantiomeric excess, and the *N*-substituent can be cleaved from the product, this methodology is favored over the use of the *N*-alkyl substrates **3**. The chemistry provides access to either enantiomer of the 2-substituted pyrrolidine products, depending on the choice of the chiral ligand.

In an attempt to probe the structure and relative stability of these organolithium species, we carried out ab initio calculations on the diastereomeric complexes. All calculations were performed using the Gaussian03 program package.[18] Different basis sets were used within the framework of density functional theory using the B3LYP functional.[19,20] However, all calculations of the organolithium (with different *N*-alkyl or *N*-allyl substituents) complexed with ligand **16** resulted in similar energies between the diastereomeric complexes. Further calculations, including solvent interactions, indicated that there is a significant effect of binding Et_2O to the vacant Li coordination site. Recalculating the energies of our structures using second-order Møller−Plesset perturbation theory within the counterpoise framework[21] did give relative energies that were in good agreement with experiment in some cases (see Supporting Information for details). However, in these cases the diastereomer predicted to be more stable was the one that requires an inversion of configuration at the carbanion center on going from the organolithium to the product. This is less likely than a retentive electrophilic quench but cannot be ruled out with certainty, as the absolute configuration of the *N*-alkyl-2-lithiopyrrolidines complexed with the chiral ligand is unknown. It is widely accepted that tin−lithium exchange occurs with retention of configuration but that subsequent electrophilic quench can occur with retention, inversion, or racemization.[1] As we can prepare the enantioenriched stannane **32**, it is easy to confirm that tin−lithium exchange, followed by electrophilic quench, occurs with overall retention of configuration. For example, treatment of the enantioenriched stannane (*S*)-**32** [absolute configuration derived from (*S*)-**1**][13,22] (er 97:3) with BuLi/TMEDA at −10 °C for 90 min (to allow transmetalation without complete racemization), followed by cooling to −78 °C and quenching with PhNCO, gave the amide

(18) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
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(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
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(*R*)-**33** (80%, er 73:27 by chiral HPLC) (absolute configuration by comparison of the specific rotation of the *N*-deprotected compound proline-*N*-phenylamide with the literature[17]). This result confirmed the overall retention of configuration from the stannane to the amide (partial racemization of the organolithium occurs under these conditions). Alongside this experiment, we carried out the same reaction, but after cooling to −78 °C, the ligand **16** (deprotonated with BuLi) was added. After 90 min at −78 °C, the mixture was quenched with PhNCO. The amide (*R*)-**33** (65%, er 74:26) was formed. The fact that the same enantiomer ratio and the same major enantiomer were produced confirms that the electrophilic quench in the presence of the chiral ligand **16** proceeds with the same absolute sense. These results support a double retention on going from the stannane to the product via the organolithium. Therefore, the ab initio calculations appear to predict the wrong absolute configuration of the organolithium. The reason for this is unclear, but it could be that the monomeric organolithium (complexed with the chiral ligand) that we have modeled does not match the solution structure and there may be a dimeric or other oligomeric complex present.

Dynamic Resolution of *N*-Boc-2-lithiopyrrolidine. Excellent levels of asymmetric induction are possible from *N*-Boc-2-lithiopyrrolidines using the chiral ligands **16** and **25** (Schemes 8 and 9). The asymmetry arises from a dynamic kinetic resolution, as shown by the fact that a warm−cool protocol gives lower selectivities and that different er's are obtained under different reaction conditions and using different rates of addition of the electrophile. The organolithium *N*-Boc-2-lithiopyrrolidine is believed to react with Me_3SiCl with retention of stereochemistry at the carbanion center;[13] hence, using the chiral ligand **16** and excess *n*-BuLi, the (*S*)-2-lithiopyrrolidine enantiomer reacts faster than the (*R*)-enantiomer ($\Delta\Delta G^{\ddagger}$ must be about 8 kJ/mol). However, in the absence of excess *n*-BuLi, there is less difference in the rate of reaction. The ratio of the diastereomeric complexes is close to 50:50 in the absence of excess *n*-BuLi, although this ratio appears to be of the order of 80:20 in the presence of excess *n*-BuLi. This thermodynamic selectivity matches the kinetic preference for reaction. Thus, using ligand **16**, the (*S*)-enantiomer of *N*-Boc-2-lithiopyrrolidine is formed by an asymmetric deprotonation (er ~87:13), and this ratio is maintained for extended periods in the presence of excess *n*-BuLi at −20 °C, as judged by cooling the complexes to −78 °C after different time periods, quenching the reaction mixture using Me_3SiCl, and measuring the er (by chiral GC). Hence, using the optimized conditions (Scheme 9) with the ligand **16**, an er of approximately 87:13 (*S*:*R*) of *N*-Boc-2-lithiopyrrolidine (obtained initially by asymmetric deprotonation) converts on warming to −20 °C to a ratio of approximately 80:20 (*S*:*R*) (by dynamic equilibration to the thermodynamic ratio of complexes), and then reaction with Me_3SiCl at −20 °C occurs faster with the (*S*)-enantiomer of *N*-Boc-2-lithiopyrrolidine to give the product **35** (er 95:5 *S*:*R*). However, even when the mismatched arrangement is present, such that the enantiomer that reacts faster is present as the minor component, high er's of the product **35** can be obtained as a result of faster reaction of the minor diastereomeric complex in an equilibrating mixture (Scheme 10). These facets imply that the energy profile of the reaction can be described as shown in Figure 3 (using the ligand **16**).

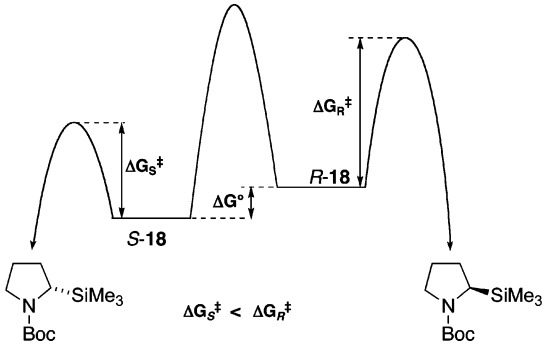

Figure 3. Assumed energy diagram for dynamic kinetic resolution of *N*-Boc-2-lithiopyrrolidine in the presence of excess BuLi.

The energy profile for a dynamic kinetic resolution typically has a relatively high barrier to reaction with the electrophile in comparison to interconversion of the complexes. In our case, reactions are best carried out at −20 °C, where interconversion takes place (albeit slowly), and high enantiomer ratios with yields greater than 50% are possible if the electrophile is added slowly. Hence, the barrier to inversion of the diastereomeric complexes may be higher than the barriers to reaction with the electrophile, but slow addition of the electrophile allows re-equilibration so that there is always present some of the faster-reacting enantiomer (in this case, the (*S*)-enantiomer using ligand **16**).

The addition of electrophiles other than Me_3SiCl gave poor results. This indicates that Me_3SiCl reacts with the 2-lithiopyrrolidine, whereas other electrophiles react competitively with BuLi, thereby giving mixtures of products and reduced enantioselectivity. For example, addition of Bu_3SnCl gave racemic organostannane **1**. This is likely due to repeated tin−lithium exchange and final quench of the organolithium in the absence of excess BuLi, although a contributory factor could come from a variation in the relative rate of reaction of the diastereomeric organolithium−chiral ligand complexes, depending on the nature of the electrophile.

The rate of enantiomerization for *N*-Boc-2-lithiopyrrolidine has been determined to be of the order of 1.5×10^{-5} s^{-1} at −22 °C in hexanes−Et_2O (4:1) (Figure 1). In Et_2O as the solvent, the rate of enantiomerization is about 3.6×10^{-4} s^{-1} at −17 °C and 2.8×10^{-5} s^{-1} at −26 °C.[8] These values would equate to a half-life for enantiomerization of about 30 min at −17 °C and about 7 h at −26 °C, and they appear to be somewhat slow for efficient dynamic resolution at the temperature that we use (−20 °C). It is likely, however, that the chiral ligand exerts an influence on the rate of enantiomerization. To probe this issue, the enantioenriched organolithium formed from asymmetric deprotonation of *N*-Boc-pyrrolidine **36** using the ligand **16** and no excess BuLi (compare with Scheme 10) was allowed to age over different time periods at −20 °C, followed by cooling to −78 °C and electrophilic quench with Me_3SiCl. The enantiomer ratios of the products **35** were determined by chiral GC, and this showed a gradual loss of er over time. Only a limited number of data points were collected, but these followed an exponential decay, suggesting first-order kinetics. Using these data, the rate of enantiomerization, *k*, was determined as approximately 1.5×10^{-3} s^{-1} at −20 °C, which equates to a barrier to inversion, $\Delta G^{\ddagger} = 18$ kcal/mol and a

half-life of about 8 min. This represents a faster rate of enantiomerization in the presence of the ligand.

Conclusions

Dynamic resolution of 2-lithiopyrrolidines under either thermodynamic or kinetic control can occur with excellent levels of asymmetric induction. The best chiral ligand is the diproline derivative **16**; its diastereomer **25** can be used to provide the opposite absolute configuration of the products. Resolution of *N*-Boc-2-lithiopyrrolidine is complicated by the need for excess *n*-BuLi for highly selective kinetic resolution. Resolution of *N*-(2,3-dimethylbut-2-enyl)-2-lithiopyrrolidine occurs by a dynamic thermodynamic resolution, and the products can be converted easily to their *N*-unsubstituted derivatives.

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Supporting Information Available: Experimental and computational details, including procedures and spectroscopic data for compounds **19**−**24**, **27**, **29**, **32**−**35**, plus the complete ref 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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