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Asymmetric Deprotonation using *s*-BuLi or *i*-PrLi and Chiral Diamines in THF: The Diamine Matters

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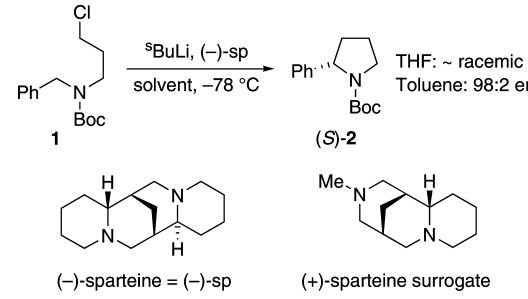
Abstract: The solution structures of [^{6}Li]-*i*-PrLi complexed to (−)-sparteine and the (+)-sparteine surrogate in Et_2O-d_{10} and THF-d_8 at −80 °C have been determined using ^{6}Li and ^{13}C NMR spectroscopy. In Et_2O, *i*-PrLi/(−)-sparteine is a solvent-complexed heterodimer, whereas *i*-PrLi/(+)-sparteine surrogate is a head-to-tail homodimer. In THF, there was no complexation of (−)-sparteine to *i*-PrLi until ≥3.0 equiv (−)-sparteine and with 6.0 equiv (−)-sparteine, a monomer was characterized. In contrast, the (+)-sparteine surrogate readily complexed to *i*-PrLi in THF, and with 1.0 equiv (+)-sparteine surrogate, complete formation of a monomer was observed. The NMR spectroscopic study suggested that it should be possible to carry out highly enantioselective asymmetric deprotonation reactions using *i*-PrLi or *s*-BuLi/(+)-sparteine surrogate in THF. Hence, three different asymmetric deprotonation reactions (lithiation-trapping of *N*-Boc pyrrolidine, an *O*-alkyl carbamate, and a phosphine borane) were investigated; it was shown that reactions with (−)-sparteine in THF proceeded with low enantioselectivity, whereas the corresponding reactions with the (+)-sparteine surrogate occurred with high enantioselectivity. These are the first examples of highly enantioselective asymmetric deprotonation reactions using organolithium/diamine complexes in THF.

Introduction

It is well-known that asymmetric deprotonation reactions using a chiral base derived from an organolithium reagent (e.g., *s*-BuLi or *n*-BuLi) and (−)-sparteine proceed with negligible enantioselectivity if carried out in THF.[1−8] This was first noted by Hoppe et al. in 1995[1] and is usually rationalized by the THF complexing preferentially to the organolithium.[1,9] An example from Beak's work is illustrative: the *s*-BuLi/(−)-sparteine-mediated asymmetric deprotonation−cyclization of *N*-Boc amino chloride **1** to arylated pyrrolidine (*S*)-**2** proceeds in a racemic fashion in THF but in 98:2 er in toluene (Scheme 1).[2] Hence, noncoordinating solvents such as Et_2O, toluene, pentane, or hexane must be employed for highly enantioselective deprotonation processes using *s*-BuLi or *n*-BuLi and (−)-sparteine.[10] It is tempting to assume that similar behavior would be observed with other chiral diamines such as the structurally similar (+)-sparteine surrogate [(+)-(1*R*,2*S*,9*S*)-11-methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane] (Scheme 1) developed in our laboratory.[11,12] However, in this contribution, we demonstrate that such an assumption is not at all valid, and three different examples of highly enantioselective asymmetric deprotonation processes using *s*-BuLi or *i*-PrLi/(+)-sparteine surrogate in THF are presented. Our synthetic results were guided by determination of the solution structures of [^{6}Li]*i*-PrLi/chiral diamine complexes using ^{6}Li and ^{13}C NMR spectroscopy.

Scheme 1



Results and Discussion

Investigation of the Solution Structure of *i*-PrLi Complexed with (−)-Sparteine and the (+)-Sparteine Surrogate using NMR Spectroscopy. The most commonly used reagents for asymmetric deprotonations are complexes of (−)-sparteine and *n*-BuLi or *s*-BuLi;[10] however, despite their widespread use, very little is known about their solution structure and aggregation states. In

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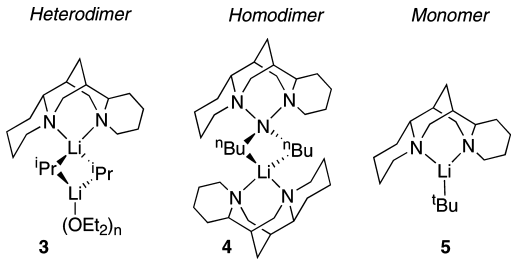

Figure 1. Structures for complexes of organolithium reagents and (−)-sparteine.

1992, Beak and co-workers used ^{6}Li, ^{13}C, and ^{1}H NMR spectroscopy to characterize a complex of *i*-PrLi (a model for *s*-BuLi) and (−)-sparteine in Et_2O as heterodimer **3** (Figure 1).[13] In contrast, using a similar spectroscopic approach, Collum et al. identified homodimer **4** as the solution structure for the less sterically demanding *n*-BuLi/(−)-sparteine complex in toluene.[14] More recently, Strohmann and colleagues have characterized heterodimer **3** ($n = 1$) and homodimer **4** in the solid-state by X-ray crystallography.[15] Furthermore, Strohmann et al. have also reported the X-ray crystal structure of monomer **5** for the *t*-BuLi/(−)-sparteine complex.[16] A comprehensive overview of the solid-state and solution structures of organolithium reagents has been published by Strohmann and co-workers.[17]

Due to the limited information on solution structures of organolithium/(−)-sparteine complexes, we embarked on a NMR spectroscopic study of the solution structure of [^{6}Li]-*i*-PrLi[18] complexed to (−)-sparteine and the (+)-sparteine surrogate in Et_2O-d_{10} and THF-d_8 at −80 °C (the usual temperature employed for asymmetric deprotonation reactions). To start with, we reproduced Beak's characterization of heterodimer **3** for *i*-PrLi/(−)-sparteine in Et_2O. [^{6}Li]-*i*-PrLi was prepared according to a literature method.[19] The ^{6}Li NMR spectrum of [^{6}Li]-*i*-PrLi in Et_2O-d_{10} has one signal at δ 2.60 ppm and was assigned to an Et_2O-solvated dimer (concentration of *i*-PrLi in Et_2O-d_{10} = 0.07 M). Addition of 2 equiv (−)-sparteine gave a complex that was characterized as heterodimer **3** on the basis of the following NMR spectroscopic data: the ^{6}Li NMR spectrum showed two signals at δ 2.83 and δ 2.63 ppm in a 1:1 ratio; the ^{13}C NMR spectrum showed two approximate quintets at δ 13.89 ppm ($^{1}J(^{6}\mathrm{Li},^{13}\mathrm{C}) = 8.0$ Hz) and δ 11.86 ppm ($^{1}J(^{6}\mathrm{Li},^{13}\mathrm{C}) = 8.5$ Hz) for the CH carbons of the *i*-Pr groups (the quintets indicate that each CH couples to two lithium atoms) as well as signals due to uncomplexed and complexed (−)-sparteine; the $^{1}J(^{6}\mathrm{Li},^{13}\mathrm{C})$ values of 8.0 and 8.5 Hz suggest a dimeric aggregate based on the empirical Bauer−Winchester−Schleyer rule for coupling constants ($J(^{6}\mathrm{Li},^{13}\mathrm{C}) = (17 \pm 2)/n_C$ where n_C is the number of ^{6}Li cations directly connected to the observed ^{13}C),[20] and the ^{6}Li,^{1}H-HOESY spectrum[21] showed NOEs from signals due to the (−)-sparteine ligand to only one of the ^{6}Li signals (2.63 ppm). Full details are provided in the Supporting Information.

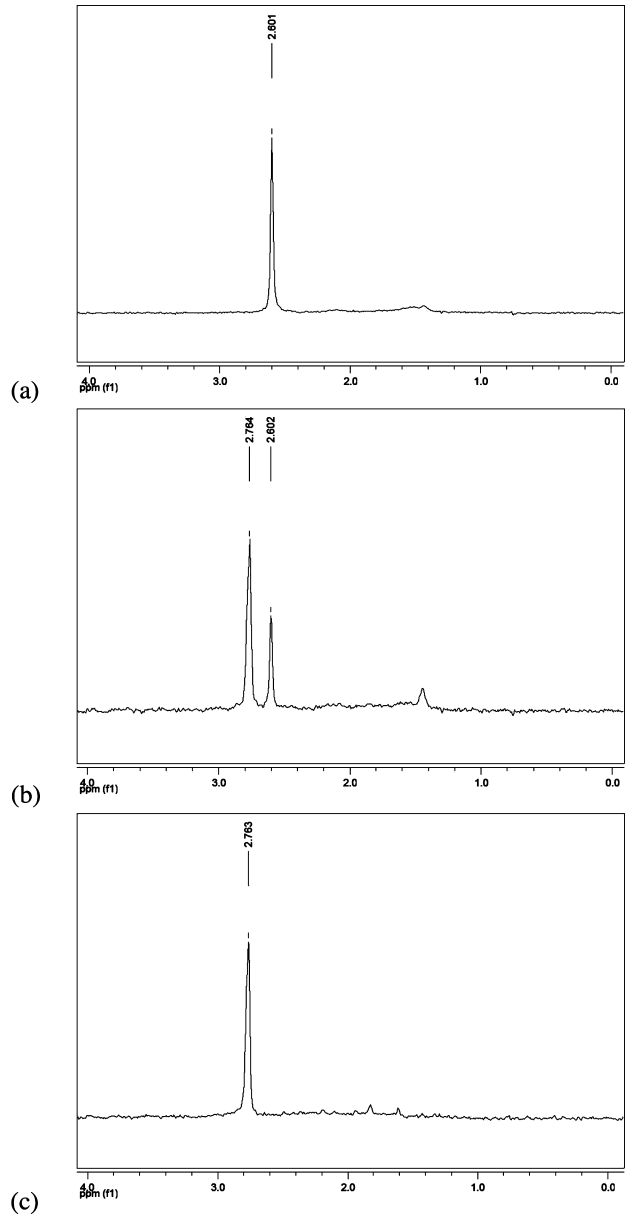

Figure 2. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(+)-sparteine surrogate in Et_2O-d_{10} at −80 °C: (a) No (+)-sparteine surrogate; (b) 1.0 equiv (+)-sparteine surrogate; (c) 2.0 equiv (+)-sparteine surrogate.

Next, we established the solution structure of the *i*-PrLi/(+)-sparteine surrogate complex in Et_2O in a similar fashion. Starting from the dimeric [^{6}Li]-*i*-PrLi in Et_2O-d_{10} at −80 °C, we added 0.5-equiv aliquots of the (+)-sparteine surrogate and recorded the ^{6}Li NMR spectrum. The results are shown in Figure 2. As more (+)-sparteine surrogate was added, a new signal was observed in the ^{6}Li NMR spectrum, and this was the only signal present after addition of ≥1.5 equiv (+)-sparteine surrogate. Thus, the heterodimer similar to **3** observed for *i*-PrLi/(−)-

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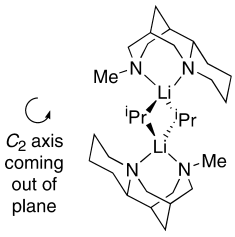

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Figure 3. Head-to-tail homodimer **6** for *i*-PrLi/(+)-sparteine surrogate complex in Et_2O.

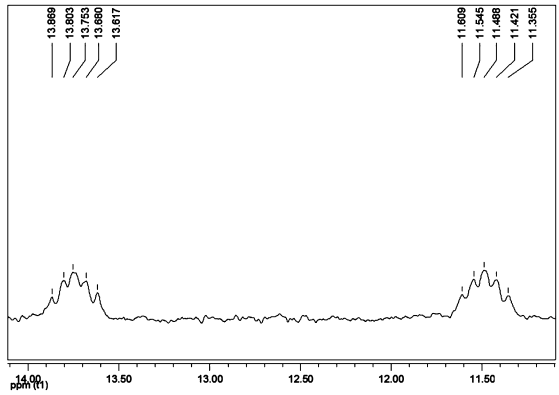

Figure 4. Part of the ^{13}C NMR spectrum of [^{6}Li]-*i*-PrLi/(+)-sparteine surrogate (1.5 equiv) in Et_2O-d_{10} at −80 °C.

sparteine in Et_2O can be ruled out. Instead, the *i*-PrLi/(+)-sparteine surrogate complex (1.5 equiv) in Et_2O was characterized as the head-to-tail homodimer **6** (Figure 3). Key spectroscopic features are as follows. The ^{6}Li NMR spectrum contained one signal at δ 2.76 ppm, indicating only one lithium environment. In contrast, the ^{13}C NMR spectrum (Figure 4) showed two approximate quintets at δ 13.75 ppm ($^1J(^6Li,^{13}C)$ = 8.0 Hz) and δ 11.49 ppm ($^1J(^6Li,^{13}C)$ = 8.0 Hz) for the CH carbons of the *i*-Pr groups (as well as signals due to uncomplexed and complexed (+)-sparteine surrogate). The magnitudes of the $^1J(^6Li,^{13}C)$ coupling constants (8.0 Hz) suggest a dimeric aggregate based on the empirical Bauer−Winchester−Schleyer rule for coupling constants.[20] The quintet multiplicity indicates that each CH is bonded to two lithium atoms, and so the solution structure must be dimeric. Only the head-to-tail homodimer **6** has equivalent lithium atoms and inequivalent carbon atoms (the alternative head-to-head homodimer has equivalent lithium and carbon atoms - see Supporting Information).[22] Thus, under identical conditions in Et_2O-d_{10} at −80 °C, *i*-PrLi/(−)-sparteine exists as heterodimer **3**, whereas *i*-PrLi/(+)-sparteine surrogate complex exists as homodimer **6**. Presumably, the less sterically hindered (+)-sparteine surrogate allows homodimer formation.

The corresponding NMR titration experiments were then carried out using *i*-PrLi and (−)-sparteine or the (+)-sparteine surrogate in THF-d_8 at −80 °C. As shown by the ^{6}Li NMR spectra (Figure 5), there was a significant difference in behavior with the two ligands. The ^{6}Li NMR spectrum of [^{6}Li]-*i*-PrLi in THF-d_8 shows one signal at δ 0.92 ppm and was assigned to a THF-solvated dimer. In the presence of 0.5 equiv or 1.0 equiv (−)-sparteine, there was no change in the ^{6}Li NMR spectrum (Figure 5b and c). A new, minor signal (δ 1.27 ppm) was observed only when an excess of (−)-sparteine was added (3.0 equiv) (see Supporting Information). In contrast, with the (+)-sparteine surrogate, a new signal was observed in the ^{6}Li NMR spectrum at δ 1.43 ppm after 0.5 equiv (+)-sparteine surrogate was added (Figure 5b), and this was the only signal present after addition of 1.0 equiv (+)-sparteine surrogate (Figure 5c). The ^{13}C NMR spectrum of *i*-PrLi in the presence of 1.0 equiv (+)-sparteine surrogate contained a 1:1:1 triplet ($^1J(^6Li,^{13}C)$ = 14.0 Hz) at δ 16.36 ppm (Figure 6), suggesting a monomeric structure. The magnitude of the $^1J(^6Li,^{13}C)$ coupling constant (14.0 Hz) is slightly lower than expected for a monomeric aggregate based on the Bauer−Winchester−Schleyer rule.[20] Thus, we characterized monomer **7** (Figure 7) for *i*-PrLi/(+)-sparteine surrogate in THF. This is the first example of characterization of a simple organolithium/diamine monomer in solution. A similar monomeric structure was observed for *i*-PrLi and a large excess of (−)-sparteine (6.0 equiv) in THF (see Supporting Information).

The most striking feature of the ^{6}Li NMR spectra presented in Figure 5 is that the (+)-sparteine surrogate complexes readily to *i*-PrLi in THF (fully complexed with 1.0 equiv ligand present), whereas complexation of *i*-PrLi with (−)-sparteine in THF is much weaker: the *i*-PrLi/(−)-sparteine complex is only detected with excess (≥3.0 equiv) of (−)-sparteine (Figure 5c and Supporting Information). Thus, through characterization of the solution structure of *i*-PrLi in THF, the low enantioselectivity of *i*-PrLi/(−)-sparteine reactions in THF can be rationalized. However, of far more interest, the NMR spectroscopic studies reveal that the (+)-sparteine surrogate does complex to the *i*-PrLi even in THF, and this suggested to us that it might be possible to carry out highly enantioselective asymmetric deprotonation reactions using *i*-PrLi/(+)-sparteine surrogate in THF.

Investigation of Asymmetric Deprotonation Reactions Using *i*-PrLi and *s*-BuLi with Chiral Diamines in Different Solvents. From a mechanistic and synthetic point of view, arguably the most widely studied asymmetric deprotonation reaction using organolithium/diamine complexes is Beak's lithiation-trapping of *N*-Boc pyrrolidine **8**.[23] As a result, we selected the lithiation and benzaldehyde trapping of *N*-Boc pyrrolidine **8** (→ *syn*-**9** and *anti*-**9**[24]) as a suitable reaction to investigate the enantioselectivity with different organolithium reagents (*i*-PrLi and *s*-BuLi) and solvents (Et_2O, TBME, THF, and 2-methyl-THF[25]). The general procedure involved lithiation of *N*-Boc pyrrolidine **8** using 1.3 equiv organolithium/diamine complex in solvent at −78 °C for 3 h (concentration of *i*-PrLi or *s*-BuLi in solvent = 0.4 M). Subsequent trapping with benzaldehyde gave two diastereomeric hydroxy pyrrolidines *syn*-**9** and *anti*-**10** (formed in ∼75:25 dr) which were separated by chromatography and the enantioselectivity was determined using CSP-HPLC. To start with, we investigated the use of (−)-sparteine as a ligand (Table 1).

As expected, using *i*-PrLi or *s*-BuLi in Et_2O or TBME, high enantioselectivity (95:5−98:2 er) in the formation of hydroxy pyrrolidines *syn*-**9** and *anti*-**10** ensued (entries 1−3). In contrast,

(22) Interestingly, the less sterically hindered complexes of MeLi/(+)-sparteine surrogate and MeLi/(−)-sparteine have both been characterised in the solid-state as head-to-head homodimers. Strohmann, C.; Strohfeldt, K.; Schildbach, D.; McGrath, M. J.; O'Brien, P. *Organometallics* **2004**, *23*, 5389.

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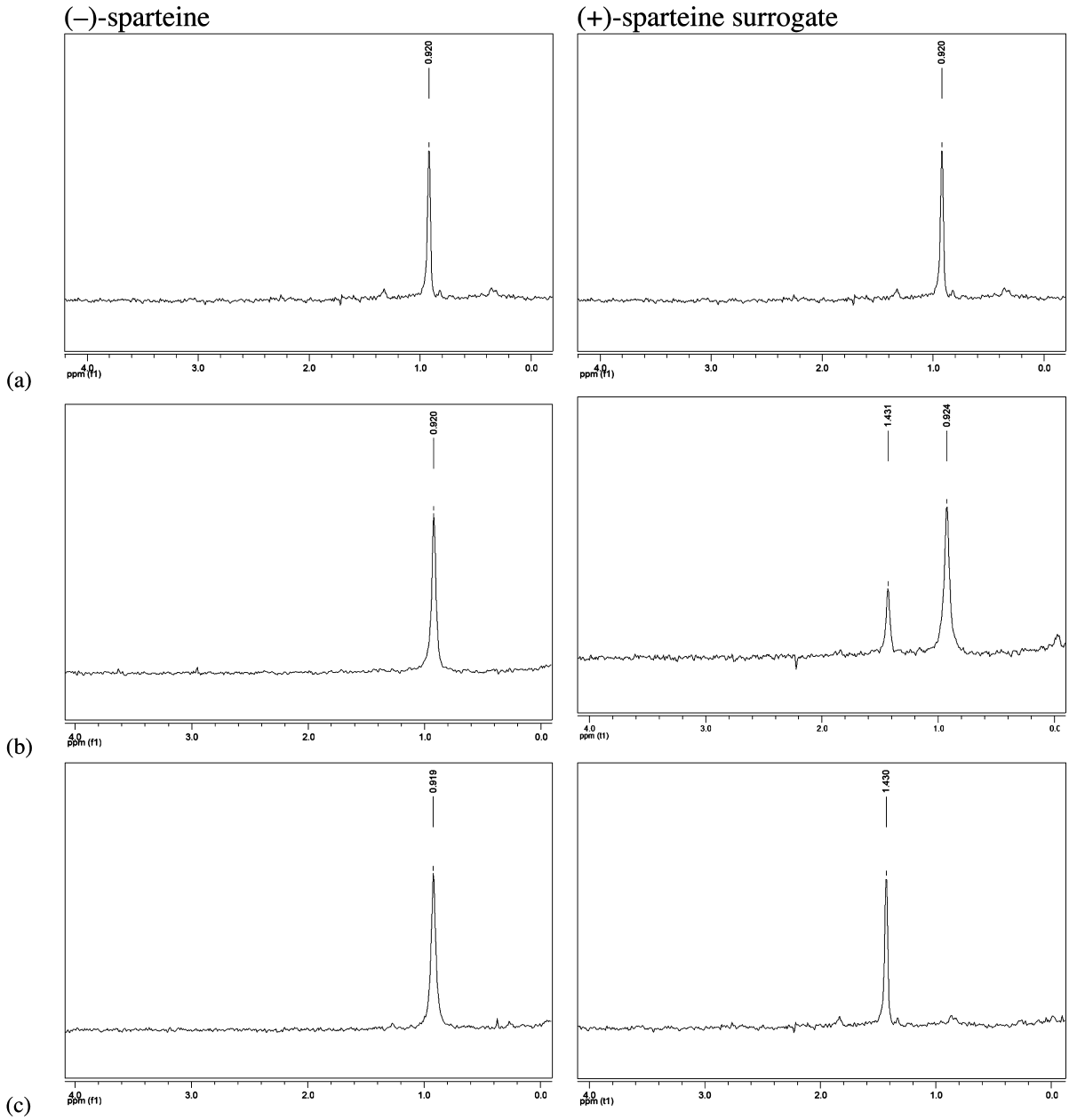

Figure 5. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(−)-sparteine and (+)-sparteine surrogate in THF-d_8 at −80 °C: (a) No diamine; (b) 0.5 equiv diamine; (c) 1.0 equiv diamine.

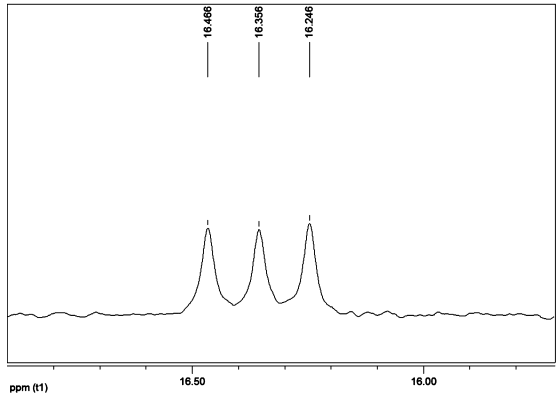

Figure 6. Part of the ^{13}C NMR spectrum of [^{6}Li]-*i*-PrLi/(+)-sparteine surrogate (1.0 equiv) in THF-d_8 at −80 °C.

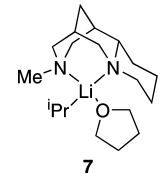

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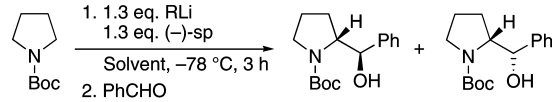
Figure 7. Monomer **7** for *i*-PrLi/(+)-sparteine surrogate complex in THF.

use of *i*-PrLi in THF gave *syn*-**9** in 63:37 er (65% yield) and *anti*-**10** in 60:40 er (22% yield) (entry 4). This result is consistent with the NMR spectroscopic study. Even lower enantioselectivity (51:49 er) was observed using *s*-BuLi/(−)-sparteine in THF (entry 5). Finally, we demonstrated that 2-methyl-THF was "THF-like" since poor enantioselectivity resulted in using *s*-BuLi/(−)-sparteine in 2-methyl-THF (entry 6).

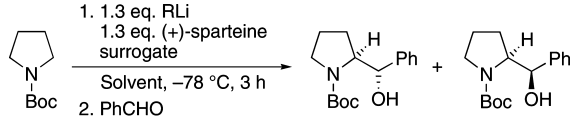
Table 1. Asymmetric Lithiation−Trapping of *N*-Boc Pyrrolidine **8** Using (−)-Sparteine



entry	RLi	solvent	yield of *syn*-**9** (%)[a]	er of *syn*-**9**[b]	yield of *anti*-**10** (%)[a]	er of *anti*-**10**[b]
1	*i*-PrLi	Et_2O	64	97:3	22	95:5
2	*s*-BuLi	Et_2O	63	97:3	23	97:3
3	*s*-BuLi	TBME	51	97:3	24	98:2
4	*i*-PrLi	THF	65	63:37	22	60:40
5	*s*-BuLi	THF	50	51:49	14	51:49
6	*s*-BuLi	2-methyl-THF	50	59:41	29	55:45

[a] Yield after purification by column chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC.

Table 2. Asymmetric Lithiation−Trapping of *N*-Boc Pyrrolidine **8** Using the (+)-Sparteine Surrogate



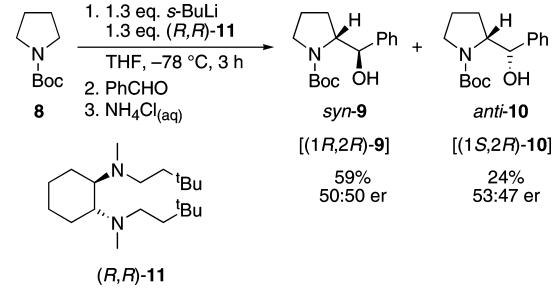
entry	RLi	solvent	yield of *syn*-**9** (%)[a]	er of *syn*-**9**[b]	yield of *anti*-**10** (%)[a]	er of *anti*-**10**[b]
1	*i*-PrLi	Et_2O	68	98:2	23	95:5
2	*s*-BuLi	Et_2O	58	95:5	23	94:6
3	*s*-BuLi	TBME	56	94:6	31	93:7
4	*i*-PrLi	THF	66	97:3	21	97:3
5	*s*-BuLi	THF	45	95:5	20	95:5
6	*s*-BuLi	2-methyl-THF	53	93:7	22	93:7

[a] Yield after purification by column chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC.

The same set of experiments was then carried out with the (+)-sparteine surrogate (Table 2). In this case, high enantioselectivity (93:7−98:2 er) in the opposite sense was obtained in all cases (entries 1−6). Thus, using *i*-PrLi/(+)-sparteine surrogate in THF gave *syn*-**9** in 97:3 er (66% yield) and *anti*-**10** in 97:3 er (21% yield) (entry 4). A similar result was obtained using *s*-BuLi (entry 5), a more commonly used reagent. As predicted by the NMR spectroscopic study, it is indeed possible to carry out highly enantioselective asymmetric deprotonation reactions using *s*-BuLi or *i*-PrLi/(+)-sparteine surrogate in THF or 2-methyl-THF. Our results also show that *i*-PrLi (used in the NMR spectroscopy study) and *s*-BuLi behave in a similar fashion.

Recently, we have shown that diamine (*R*,*R*)-**11**, originally developed by Alexakis et al.,[26] can be used as an effective sparteine surrogate in the asymmetric lithiation-trapping of *N*-Boc pyrrolidine **8**.[27,28] Hence, we attempted the asymmetric deprotonation−benzaldehyde trapping with *s*-BuLi/diamine (*R*,*R*)-**11** in THF at −78 °C (Scheme 2). From this reaction, we isolated *syn*-**9** in 59% yield and 50:50 er together with *anti*-**10** in 24% yield and 53:47 er. Clearly, diamine (*R*,*R*)-**11** does not complex to *s*-BuLi in THF, resulting in low enantioselectivity, and behaves in an analogous fashion to (−)-sparteine.

Scheme 2



The results obtained with *N*-Boc pyrrolidine **8** and (−)-sparteine and the (+)-sparteine surrogate were verified using two other *s*-BuLi-mediated asymmetric deprotonation reactions. First, we carried out Hoppe's[29] lithiation−MeO_2CCl trapping of *O*-alkyl carbamate **12** (→ **13**) using 1.2 equiv *s*-BuLi/chiral diamine complex in Et_2O and THF (concentration of *s*-BuLi in solvent = 0.3 M) (Table 3). Reactions using *s*-BuLi/(−)-sparteine in THF proceeded with low enantioselectivity (61:39 er) (entries 2 and 3). Low enantioselectivity (61:39 er) was even obtained using an excess of (−)-sparteine (3.3 equiv relative to *s*-BuLi) in THF (entry 3). Significantly, use of *s*-BuLi/(+)-sparteine surrogate in THF gave adduct (*S*)-**13** in 72% yield and 93:7 er (entry 5).

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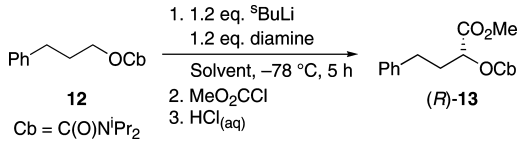
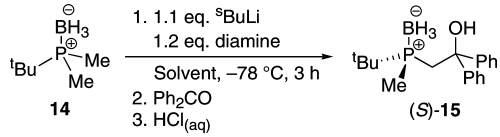
Table 3. Asymmetric Lithiation−Trapping of *O*-Alkyl Carbamate **12** Using (−)-Sparteine and the (+)-Sparteine Surrogate



entry	diamine	solvent	yield (%)[a]	er (*R*:*S*)[b]
1	(−)-sparteine	Et_2O	84	97:3
2	(−)-sparteine	THF	68	61:39
3	(−)-sparteine[c]	THF	24	61:39
4	(+)-sparteine surrogate	Et_2O	67	7:93
5	(+)-sparteine surrogate	THF	72	7:93

[a] Yield after purification by column chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC. [c] 3.3 equiv (−)-sparteine relative to *s*-BuLi was used.

Table 4. Asymmetric Lithiation−Trapping of Phosphine Borane **14** Using (−)-Sparteine and the (+)-Sparteine Surrogate



entry	diamine	solvent	yield (%)[a]	er (*S*:*R*)[b]
1	(−)-sparteine	Et_2O	88	95:5
2	(−)-sparteine	THF	30	50:50
3	(+)-sparteine surrogate	Et_2O	89	5:95
4	(+)-sparteine surrogate	THF	44	12:88
5	(+)-sparteine surrogate	THF[c]	78	9:91

[a] Yield after purification by column chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC. [c] Concentration of *s*-BuLi in solvent = 0.3 M whereas concentration for entries 1−4 = 0.1 M.

A similar set of results was obtained in Evans-style[30] lithiation−trapping of phosphine borane **14** (→ **15**) (Table 4). Use of *s*-BuLi/(−)-sparteine in THF (concentration of *s*-BuLi in THF = 0.1 M) gave a 30% yield of racemic adduct **14** (entry 2) whereas high enantioselectivity (88:12 er, 44% yield) was maintained using *s*-BuLi/(+)-sparteine surrogate in THF at the same concentration (entry 4). Due to the low solubility of phosphine borane **14** in Et_2O at −78 °C, these reactions are typically carried out under dilute conditions (concentration of *s*-BuLi in THF = 0.1 M). However, due to the higher solubility of **14** in THF at −78 °C, we were able to carry out the same reaction at higher concentration (0.3 M) and obtained a better result: adduct (*R*)-**15** of 91:9 er was generated in 78% yield (entry 5).

Conclusion

In conclusion, we demonstrate that it is possible to carry out highly enantioselective asymmetric deprotonation reactions using *s*-BuLi/chiral diamines in THF, provided that a suitable diamine is selected. Thus, as previously noted by others[1−8] and confirmed by our studies, (−)-sparteine in THF is not suitable and the reactions proceed with low enantioselectivity. The Alexakis diamine (*R*,*R*)-**11** in THF is also not suitable. However, use of *s*-BuLi and the (+)-sparteine surrogate does facilitate high enantioselectivity even in THF. These results are fully supported by the NMR spectroscopic results which show that, in contrast to (−)-sparteine, the (+)-sparteine surrogate readily complexes to *i*-PrLi in THF. Fundamentally, our results demonstrate that the diamine matters. This is particularly surprising for (−)-sparteine and the (+)-sparteine surrogate as they are structurally so closely matched. There are also potential synthetic benefits of our results: THF is preferred to Et_2O for large-scale industrial applications due to the low flash point of Et_2O; there are substrates for deprotonation that will be insoluble in Et_2O at −78 °C but soluble in THF, and 2-methyl-THF is becoming a more popular solvent in industry as it is derived from a renewable resource.[25] Our results can also explain Fukuyama et al.'s successful use of *s*-BuLi and the (+)-sparteine surrogate for the regioselective deprotonation of an unsymmetrical substituted *N*-Boc pyrrolidine during their total syntheiss of (−)-kainic acid even though the reaction was carried out in THF.[31] Finally, it should also be highlighted that significant differences were observed for the solution structures of *i*-PrLi/(−)-sparteine and *i*-PrLi/(+)-sparteine surrogate in Et_2O and THF. In Et_2O, *i*-PrLi/(−)-sparteine is an Et_2O-complexed heterodimer whereas *i*-PrLi/(+)-sparteine surrogate is a head-to-tail homodimer. In THF, a 1:1 mixture of *i*-PrLi and (−)-sparteine did not form a complex, whereas a 1:1 mixture of *i*-PrLi and the (+)-sparteine surrogate gave a monomer. This is the first time that a monomeric organolithium/diamine complex has been characterized in solution by ^{6}Li and ^{13}C NMR spectroscopy. Overall, the results presented in this study suggest that, for diamines other than (−)-sparteine and (*R*,*R*)-**11**, THF should be considered as a viable solvent since high enantioselectivity can be obtained using *s*-BuLi/(+)-sparteine surrogate-mediated asymmetric deprotonation reactions in THF.

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Supporting Information Available: Full experimental procedures and data, ^{1}H/^{13}C NMR spectra of new compounds and full details of the ^{6}Li and ^{13}C NMR spectroscopic study. This material is available free of charge via the Internet at http://pubs.acs.org.

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