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Mixed Aggregates of an Alkyl Lithium Reagent and a Chiral Lithium Amide Derived from *N*-Ethyl-*O*-triisopropylsilyl Valinol

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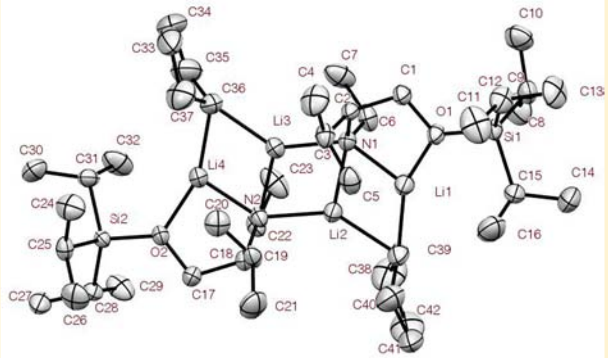
S *Supporting Information*

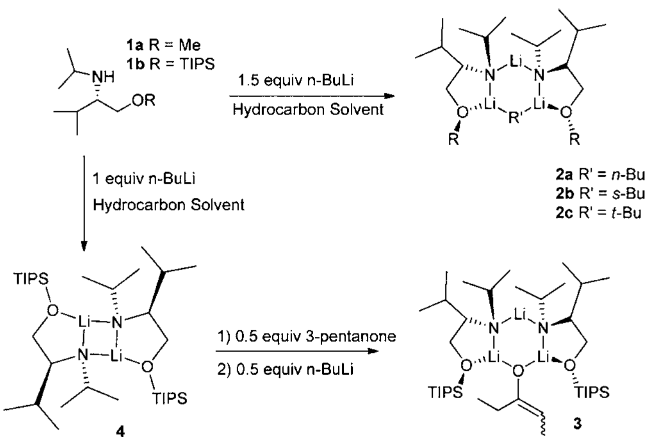


ABSTRACT: The crystal structure of a mixed aggregate containing lithiated (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)-butan-2-amine derived from (*S*)-valinol and cyclopentyllithium is determined by X-ray diffraction. The mixed aggregate adopts a ladder structure in the solid state. The ladder-type mixed aggregate is also the major species in a toluene-d_8 solution containing an approximately 1:1 molar ratio of the lithiated chiral amide to cyclopentyllithium. A variety of NMR experiments including diffusion-ordered NMR spectroscopy (DOSY) with diffusion coefficient-formula (D-FW) weight correlation analyses and other one- and two-dimensional NMR techniques allowed us to characterize the complex in solution. Solution state structures of the mixed aggregates of *n*-butyl, *sec*-butyllithium, isopropyllithium with lithiated (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine are also reported. Identical dimeric, ladder-type, mixed aggregates are the major species at a stoichiometric ratio of 1:1 lithium chiral amide to alkyllithium in toluene-d_8 solution for all of the different alkyllithium reagents.

■ INTRODUCTION

Organolithium reagents are among the most widely used reagents in organic synthesis.[1] Chiral lithium amide bases were developed for asymmetric addition and deprotonation.[2] Additionally, Koga et al. reported an intriguing asymmetric aldol reaction in the presence of chiral lithium amide bases implicating the influence of mixed aggregates.[3] Recent research indicates that chiral lithium amide bases are also useful for catalytic dynamic resolution in enantioselective synthesis.[4] Other organolithium reagents that form mixed aggregates have been reported by several groups including Collum et al.,[5] Davidsson et al.,[6] Duhamel et al.,[7] Hilmersson et al.,[8] McGarrity and Ogle,[9] Maddaluno et al.,[10] Reich et al.,[11] Thomas and Huang,[12] and Strohmann et al.[13] Many of these studies reveal that the reactivity and stereoselectivity of chiral lithium mixed aggregates depend on the aggregation state of the reagents.[6a,10b,14] Therefore, aggregation state determination of chiral, lithium mixed-aggregates is crucial to the interpretation of the reaction mechanism and the optimization of enantioselectivity in reactions involving chiral lithiated amide reagents.

Scheme 1. Trimeric 2:1 Complexes 2 and 3 and Homodimer 4



Previously we reported solid state structures of mixed trimers consisting of two equivalents of the chiral lithium amide derived from *N*-isopropyl valinol **1** and one equivalent of commercially available *n*-butyllithium (*n*-BuLi), *tert*-butyllithium (*t*-BuLi), or *sec*-butyllithium (*s*-BuLi) depicted as structure **2** in Scheme 1.[15] We also reported both the crystal structure and the solution state characterization of a similar trimeric complex consisting of two equiv of the chiral lithium amide and 3-pentanone lithium enolate complex depicted as complex **3**.[16] We also reported the asymmetric addition of n-BuLi from the mixed aggregate **2a** to aldehydes.[14c] Most recently, we characterized the solution state structure of the pure chiral lithium amide in the absence any additional reagents as the homodimer **4** in hydrocarbon solvent.[17] Moreover, Hilmersson and co-workers reported solution state characterization of a similar chiral lithium amide as a mixed dimer

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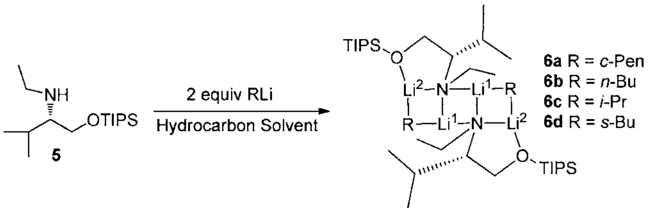
between *n*-BuLi and the chiral lithium amide in diethyl ether.[18] Herein we report the characterization of yet another structural motif described as the four-rung ladder structures **6a**−**d** depicted in Scheme 2 containing a 2:2 stoichiometric ratio the chiral lithium amide derived from *N*-ethyl-*O*-triisopropylsilyl valinol **5** and either *n*-BuLi, *s*-BuLi, *i*-PrLi, or cyclopentyllithium.

Scheme 2. The 2:2 Ladder Structure Mixed Aggregates 6



RESULTS AND DISCUSSION

Solid State Structure of 2:2 Mixed Aggregate of Lithiated (*S*)-*N*-Ethyl-3-methyl-1-(triisopropylsilyloxy)-butan-2-amine (5) and Cyclopentyllithium (c-PenLi) (6a). Chiral amine **5** was easily synthesized from (*S*)-valine in three steps following the procedure we have used previously to prepare the *N*-isopropyl derivative. Crystals suitable for X-ray diffraction were grown by adding 2 equiv of *c*-PenLi to the toluene solution of chiral amine **5** by keeping the resulting solution at −50 °C for a few days. The X-ray structure determination of the solid material that formed reveals a 2:2 chiral lithium amide to *c*-PenLi mixed aggregate that adopts a ladder-type structure shown in Figure 1. The structure contains two chiral lithium amide and two alkyllithium subunits with a Li_2N_2 core. Hilmersson and Davidsson have shown the existence of several 1:1 mixed aggregates of chiral lithium amides and *n*-butyllithium in solution state,[6,8h,18] and Maddaluno has also conducted solution state studies to characterize several 1:1 mixed aggregates of alkyllithium and chiral lithium amides derived from 4-hydroxy-proline.[10] To the best of our knowledge, there is no evidence for the existence of a 2:2 mixed aggregate of a chiral lithium amide and a simple alkyllithium reagent.

Solution State Characterization of a Mixed Aggregate 6a. The sample for NMR studies was prepared in situ by titrating (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine into a toluene-d_8 solution of ^{6}Li labeled cyclopentyllithium at −50 °C. The titration was monitored by ^{1}H and ^{6}Li NMR as depicted in Figures 2 and 3, respectively.

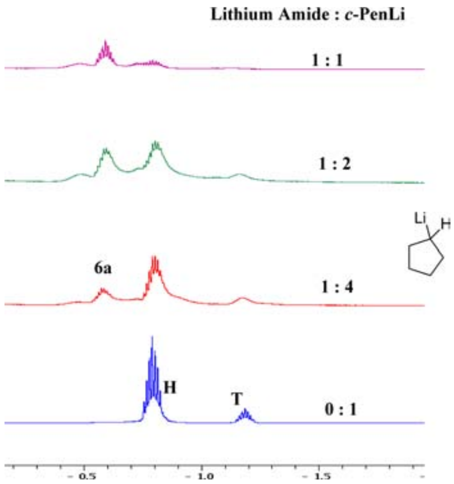


Figure 2. ^{1}H NMR spectra of chiral amine **5** titration of 0.47 M *c*-Pen^{6}Li toluene-d_8 solution at −50 °C. H represents the resonance of *c*-Pen^{6}Li in hexamer; T represents the resonance *c*-Pen^{6}Li in tetramer; 6a represents the resonance of the 2:2 mixed aggregate **6a**.

The methine region of *c*-PenLi was carefully monitored in ^{1}H NMR. With no amine added, *c*-PenLi exists as a mixture of hexamer (−0.77 ppm) and tetramer (−1.16 ppm).[19] Upon

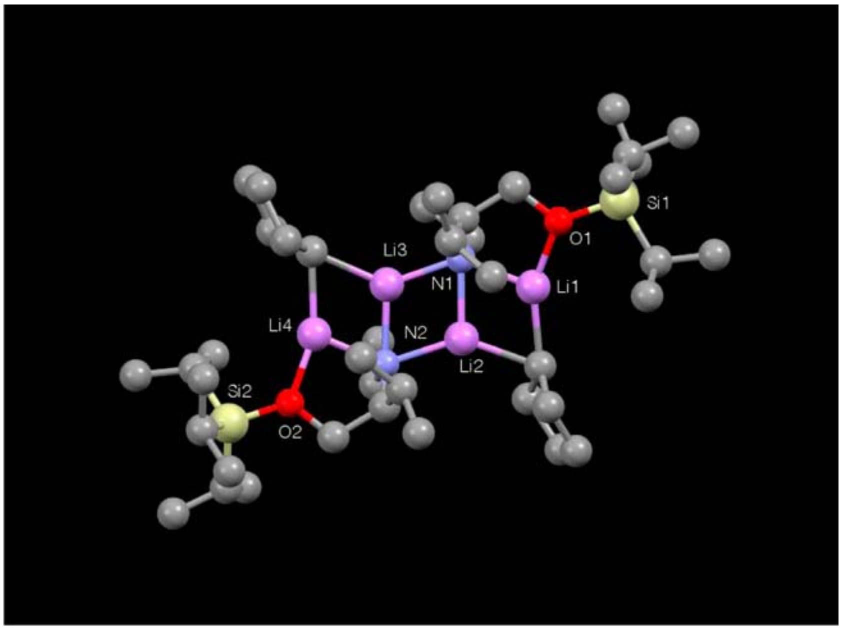


Figure 1. Crystal structure of the mixed aggregate of lithiated (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine and *c*-PenLi **6a**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

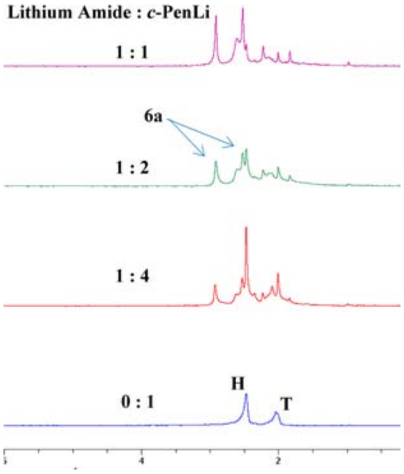


Figure 3. ^{6}Li NMR spectra of chiral amine **5** titration of 0.47 M *c*-Pen^{6}Li toluene-d_8 solution at −50 °C. H represents the resonance of *c*-Pen^{6}Li in hexamer; T represents the resonance *c*-Pen^{6}Li in tetramer; 6a represents the resonances of the 2:2 mixed aggregate **6a**. Smaller peaks are unassigned.

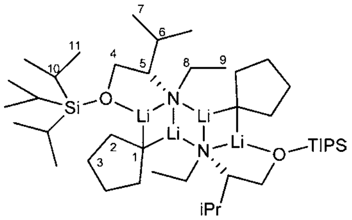
addition of chiral amine **5**, a new peak emerges at −0.59 ppm. As more chiral amine **5** is added to the solution, the intensity of the peak at −0.59 ppm increases significantly simultaneously with a decrease of the peaks due to the tetramer and hexamer of *c*-PenLi. As shown in Figure 2, when the mole ratio of lithiated chiral amine **5** to *c*-PenLi equals 1:1, the peak at −0.59 ppm is the major peak in the methine region of *c*-PenLi.

In ^{6}Li NMR in toluene-d_8, *c*-PenLi exhibits two peaks corresponding to a hexamer and a tetramer. After the addition of chiral amine **5**, several peaks emerge. When the ratio of lithiated chiral amine **5** to *c*-PenLi equals 1:1, there are two peaks with approximately same intensity that are significantly higher than the other peaks, Figure 3. These spectra are consistent with the 2:2 mixed aggregate. In conjunction with the ^{1}H NMR spectrum in Figure 2, this spectrum establishes the relative stoichiometry of the major species formed as 1:1.

To confirm that the two major peaks in ^{6}Li spectra belong to the same mixed aggregate, a ^{1}H{^{6}Li} heteronuclear multiple-bond correlation (HMBC) spectrum was performed. This spectrum is shown in Figure 4. The HMBC showed strong correlation from Li(1) to the protons of the methylene (2.95, 3.02 ppm) and methine (2.91 ppm) groups adjacent to nitrogen, as well as the methine peak (−0.59 ppm) of *c*-PenLi. Additionally, Li(2) also showed strong correlation to the methine proton of *c*-PenLi, as well as one of the protons of the methylene (3.51 ppm) group adjacent to oxygen. This spectrum confirmed the formation of a mixed complex between *c*-PenLi and the lithiated chiral amine **5**.

A series of ^{1}H and ^{13}C NMR experiments including ^{1}H NMR, ^{13}C NMR, correlated spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and HMBC were performed to confirm ^{1}H and ^{13}C chemical shift assignments. These results are summarized in Table 1. By comparing the

Table 1. ^{1}H and ^{13}C Signal Assignments of Mixed Aggregate 6a



carbon atom	^{13}C (ppm)	^{1}H (ppm)
1	24.7	−0.59
2	36.4	2.46, 1.61
3	29.4	2.03, 1.73
4	62.9	3.88, 3.51
5	65.8	2.91
6	36.2	1.80
7	20.0, 23.0	1.17, 1.08
8	44.0	3.02, 2.95
9	17.1	1.32
10	12.6	0.98
11	18.6, 18.5	1.02, 0.97

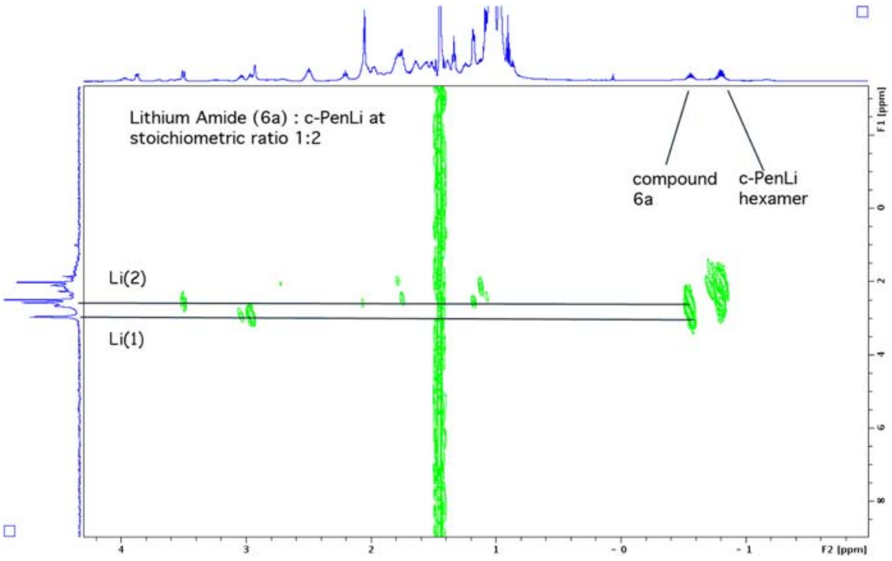


Figure 4. ^{1}H {^{6}Li} HMBC of **6a** in toluene-d_8 at −50 °C.

integration of the resonance of *c*-PenLi methine proton to the distinctive protons (2.5−4.0 ppm) of the chiral lithium amide, the mole ratio of chiral lithium amide to *c*-PenLi is approximately 1:1. The methine carbon (carbon atom 1) of *c*-PenLi within the mixed aggregate **6a** is a quintet (J = 10.3 Hz) at 24.7 ppm (Figure 5). This is consistent with with C(1) of *c*-PenLi interacting with two ^{6}Li atoms. Both the multiplicity and coupling constant comply with the Bauer−Winchester−Schleyer rule.[7,10e,20]

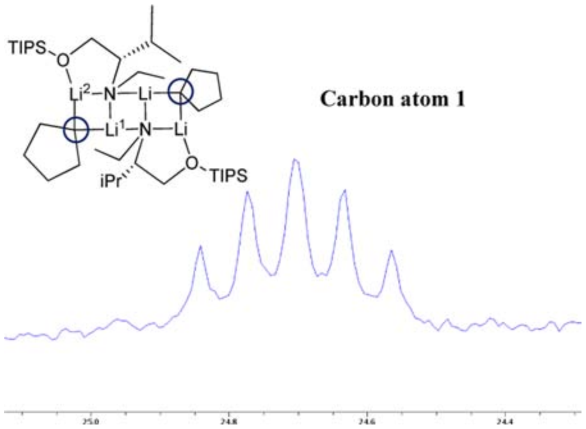


Figure 5. ^{13}C NMR of carbon atom 1 of mixed aggregate **6a** in toluene-d_8 at −50 °C.

To distinguish a 2:2 mixed aggregate from a 1:1 mixed aggregate, the formula weight of the complex must be established. Diffusion-ordered NMR spectroscopy and diffusion coefficient-formula weight (D-FW) correlation analysis have been established as an efficient method for the evaluation of formula weight of reactive organolithium complexes in solution.[15−17,21] Our lab has been instrumental in developing DOSY NMR with internal references for the determination of formula weights by D-FW correlation analysis. According to the empirical equation log D = A log FW + C where D equals the experimental relative diffusion coefficient and FW equals aggregate formula weight, a linear regression plot of logarithms of NMR determined diffusion coefficients against the formula weights of known reference compounds is used to deduce the formula weight of an unknown complex from its observed diffusion coefficient. Consequently, we add benzene (BEN, 78.11 g/mol), cyclooctene (COE, 110.2 g/mol), 1-tetradecene (TDE, 196.4 g/mol), and squalene (SQU, 410.7 g/mol) as internal references to the sample solution containing the putative complex **6a** to carry out D-FW correlation analysis.

After the addition of internal references, the resonances of the complex from 1.0 to 2.5 ppm overlapped with the resonances of the internal references; thus, distinct resonances of the chiral lithium amide from 2.5 to 4.0 ppm, as well as the resonance of the methine proton of *c*-PenLi at −0.59 ppm were utilized for our D-FW analysis. As seen in the ^{1}H DOSY spectrum (Figure 6), distinct peaks from lithiated chiral amine **5** and the peak of *c*-PenLi methine proton have very similar diffusion coefficients. The result is consistent with complexation between the lithiated chiral amine **5** and *c*-PenLi.

The correlation between log FW and log D of the linear regression is high (r^2 = 0.987), and the average predicted formula weight for the mixed aggregate **6a** is 694.6 g/mol, a 5.5% difference from the formula weight of mixed aggregate **6a** (735.4 g/mol) (Figure 7, Table 2). Assuming a 10% intrinsic error of the D-FW analysis,[20] our DOSY data are also consistent with a 2:1 mixed trimer (660.3 g/mol, 5.2% error) that adopts a structure similar to **2**. However, the 2:1 mixed trimer structure previously reported with the homologous *N*-isopropyl analogue of the chiral amide base utilized in this study does not match the ^{1}H NMR and ^{6}Li NMR data; therefore, it

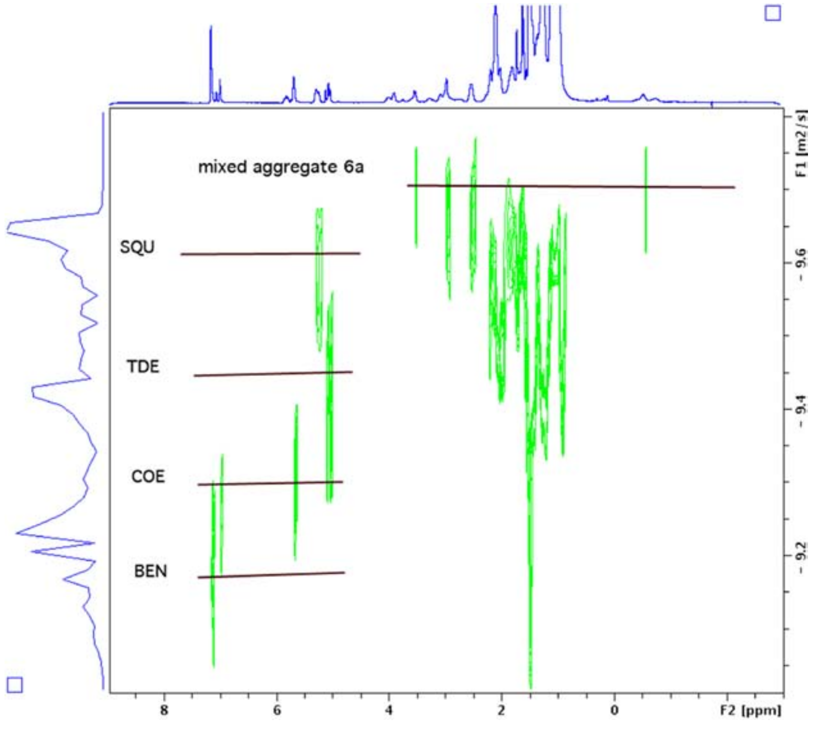


Figure 6. ^{1}H DOSY of mixed aggregate **6a** in toluene-d_8 at −50 °C.

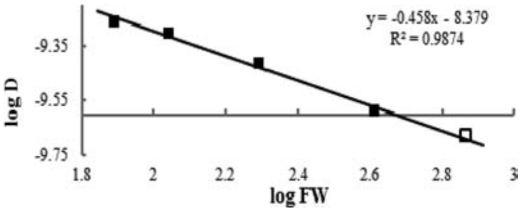


Figure 7. D-FW analysis of ^{1}H DOSY data. Internal references are shown as solid squares, and mixed aggregate **6a** is shown as an open square.

cannot be the major species in the sample solution. Thus we are forced to conclude that the solution structure is a 2:2 mixed dimer analogous to that determined in the solid state by XRD.

Solution State Characterization of a Mixed Aggregate of Lithiated Chiral Amine 5 and *n*-BuLi (6b). The sample for NMR studies was also prepared by titrating (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine into a toluene-d_8 solution of ^{6}Li labeled *n*-butyllithium at −50 °C. The titration was also monitored by ^{1}H and ^{6}Li NMR (Figures 8 and 9).

The *α*-methylene protons of *n*-BuLi were carefully monitored by ^{1}H NMR. As seen in Figure 8, a peak at −0.40 ppm increases in intensity as the amount of lithiated chiral amine **5** increases. It becomes the major peak when the ratio of lithiated chiral amine **5** to *n*-BuLi equals 1:1.3. Moreover, the ^{6}Li NMR data show very clearly the decrease of the resonance of the unsolvated hexameric *n*-BuLi aggregate and the rise of two sharp peaks with 1:1 ratio upon addition of chiral amine **5**. The two sharp peaks become the dominant peaks when the ratio of lithiated chiral amine **5** to *n*-BuLi equals 1:1.3. These results are also consistent with a 2:2 mixed aggregate shown as structure **6b**.

The ^{1}H {^{6}Li} HMBC (Figure 10) shows strong correlation from Li(1) to the *α*-methylene protons of n-BuLi (−0.40 ppm) and the protons of methylene (3.03 ppm) and methine (2.98 ppm) groups adjacent to nitrogen. Li(2) also strongly correlates to one of the protons of the methylene group (3.46 ppm) adjacent to oxygen and the *α*-methylene protons of *n*-BuLi. These spectra support the assignment of a 2:2 mixed complex between *n*-BuLi and the lithiated chiral amine **5**.

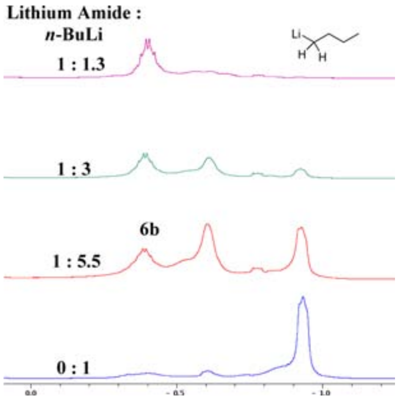


Figure 8. ^{1}H NMR spectra of chiral amine **5** titration of 0.45 M *n*-Bu^{6}Li toluene-d_8 solution at −50 °C. 6b represents the resonance of the 2:2 mixed aggregate **6b**.

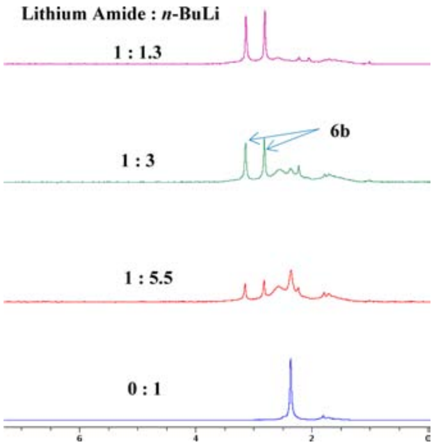


Figure 9. ^{6}Li NMR spectra of chiral amine **5** titration of 0.45 M *n*-Bu^{6}Li toluene-d_8 solution at −50 °C. 6b represents the resonance of the 2:2 mixed aggregate **6b**.

Chemical shift assignments are summarized in Table 3 as determined by ^{1}H and ^{13}C NMR experiments. The mole ratio of lithiated chiral amine **5** to *n*-BuLi is approximately 1:1 by comparing the integration of the resonances of distinctive protons. Because the *α*-methylene carbon (carbon atom 1) of *n*-BuLi of the mixed aggregate **6b** is a quintet (*J* = 10.8 Hz) at 10.1 ppm (Figure 11), the carbon atom 1 of *n*-BuLi is surrounded by two lithium-6 atoms.

Diffusion-ordered NMR spectroscopy and D-FW analysis were performed. Distinct resonances of the chiral lithium amide from 2.5 to 4.0 ppm and the resonance of the *α*-methylene protons of *n*-BuLi at −0.40 ppm were utilized for our D-FW analysis. The ^{1}H DOSY spectrum (Figure 12) reveals that the *α*-methylene protons of *n*-BuLi and distinct peaks from lithiated chiral amine **5** diffuse at a very similar rate.

Table 2. D-FW Analysis of ^{1}H DOSY Data of 6a

entry	compd	FW (g·mol^{-1})	10^{-10} D (m^{2}/s)	predicted FW (g·mol^{-1})	% error
1	BEN	78.11	5.458	85.07	−8.9
2	COE	110.2	4.997	103.1	6.4
3	TDE	196.4	3.849	182.4	7.1
4	SQU	410.7	2.588	433.9	−5.6
5	**6a**[a]	735.4[b]	2.085[a]	695.5	5.4
6	**6a**[a]	735.4[b]	2.092[a]	690.4	6.1
7	**6a**[a]	735.4[b]	2.075[a]	702.8	4.4
8	**6a**[c]	735.4[b]	2.093[c]	689.7	6.2
9	**6a**[d]	735.4[b]	2.086[d]	694.6	5.5

[a] The measured diffusion coefficients are from the resonances of chiral lithium amide. [b] 735.4 g mol^{-1} is the formula weight of 2:2 lithiated chiral amine **5**/*c*-PenLi (^{6}Li labeled) complex **6a**. [c] The measured diffusion coefficient is from the methine proton peak (−0.59 ppm) of *c*-PenLi. [d] The diffusion coefficient is the average of the above four values.

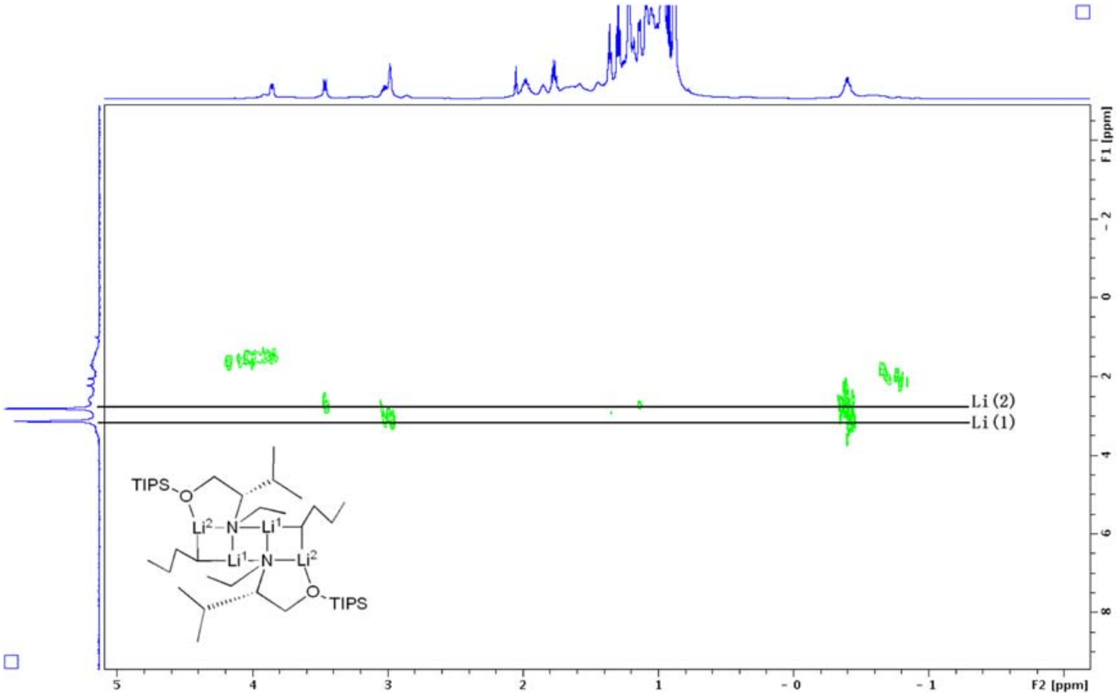
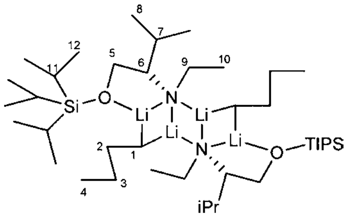


Figure 10. ^{1}H {^{6}Li} HMBC of **6b** in toluene-d_8 at −50 °C.

Table 3. ^{1}H and ^{13}C Signal Assignments of Mixed Aggregate 6b



carbon atom	^{13}C (ppm)	^{1}H (ppm)
1	10.1	−0.40
2	35.4	1.98
3	34.4	1.77
4	15.3	1.29
5	62.7	3.85, 3.46
6	65.3	2.98
7	35.9	1.85
8	22.9, 20.2	1.14, 1.09
9	45.3	3.03
10	16.8	1.36
11	12.5	0.96
12	18.5, 18.4	1.05, 0.97

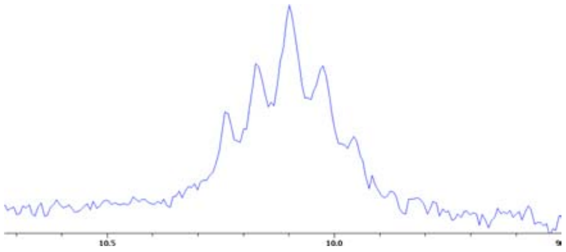


Figure 11. ^{13}C NMR of carbon atom 1 of mixed aggregate **6b** in toluene-d_8 at −50 °C.

From correlation between log FW and log *D*, the average predicted formula weight for the mixed aggregate **6b** is 706.9 g/mol. This represents a 0.6% difference from the formula weight of the 2:2 mixed aggregate **6b** (711.4 g/mol) (Figure 13, Table 4). Hence our NMR data support the formation of the 2:2 mixed aggregate **6b** between lithiated chiral amine **5** and *n*-BuLi in toluene when the mole ratio of chiral lithium amide to *n*-BuLi is approximately 1:1.

Solution State Characterization of a Mixed Aggregate of Lithiated Chiral Amine 5 and *i*-PrLi (6c). A sample was prepared by titrating (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine into a toluene-d_8 solution of ^{6}Li labeled isopropyllithium at −50 °C. The methine proton of *i*-PrLi was carefully monitored in ^{1}H NMR. Upon addition of chiral amine **5**, a peak at −0.39 ppm increases in intensity as the amount of lithiated chiral amine **5** increases as shown in Figure 14. It becomes the major peak when the mole ratio of lithiated chiral amine **5** to *i*-PrLi equals approximately 1:1. The ^{6}Li NMR spectrum, Figure 15, shows very clearly the emergence and rise of two sharp peaks with 1:1 intensity upon addition of chiral amine **5**. These two sharp peaks become dominant when the mole ratio of lithiated chiral amine **5** to *i*-PrLi equals 1:1.1. These results are consistent with a 2:2 mixed aggregate structure **6c**.

The ^{1}H {^{6}Li} HMBC (Figure 16) shows a strong correlation from Li(1) to the methine proton of *i*-PrLi (−0.39 ppm), to the protons of methylene (3.04, 2.96 ppm) and to the methine (2.98 ppm) groups adjacent to nitrogen. Additionally, Li(2) also shows strong correlation to the methine proton of *i*-PrLi, as well as one of the protons of the methylene (3.46 ppm) group adjacent to oxygen. The result confirms mixed complex formation between *i*-PrLi and the lithiated chiral amine **5**.

Assignments of ^{1}H and ^{13}C resonances are summarized in Table 5. The mole ratio of lithiated chiral amine **5** to *i*-PrLi is approximately 1:1 by comparing the integration of distinctive proton peaks. Moreover, the methine carbon (carbon atom 1)

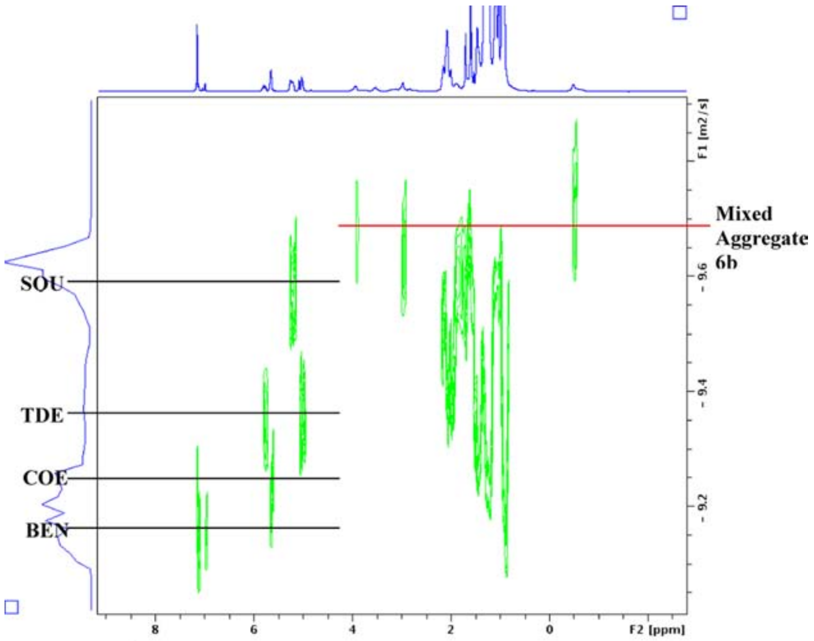


Figure 12. ^{1}H DOSY of mixed aggregate **6b** in toluene-d_8 at −50 °C.

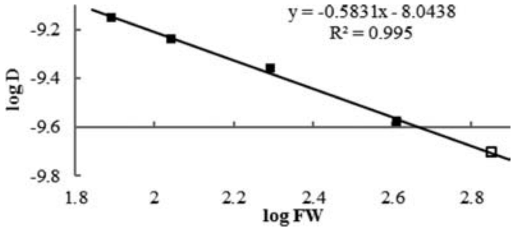


Figure 13. D-FW analysis of ^{1}H DOSY data. Internal references are shown as solid squares, and mixed aggregate **6b** is shown as an open square.

of *i*-PrLi of the mixed aggregate **6c** is a quintet (J = 10.6 Hz) at 11.5 ppm (Figure 17). This result indicates that carbon atom 2 in *i*-PrLi is surrounded by two lithium-6 atoms.

From the diffusion-ordered NMR spectroscopy (Figure 18) and D-FW analysis, we conclude that lithiated chiral amine **5** and isopropyllithium (−0.39 ppm) diffuse at a very similar rate. The average predicted formula weight for the mixed aggregate **6c** is 656.9 g/mol, a 3.9% difference from the formula weight of the 2:2 mixed aggregate **6c** (683.3 g/mol) (Figure 19, Table 6).

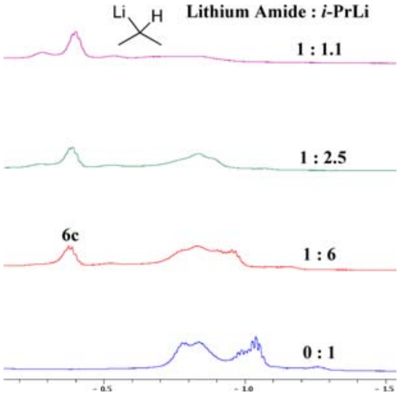


Figure 14. ^{1}H NMR spectra of chiral amine **5** titration of 0.35 M *i*-Pr^{6}Li toluene-d_8 solution at −50 °C. 6c represents the resonance of the 2:2 mixed aggregate **6c**.

Therefore, the 2:2 mixed aggregate **6c** is the major species in the toluene solution.

Solution State Characterization of a Mixed Aggregate of Lithiated Chiral Amine 5 and s-BuLi (6d). Upon

Table 4. D-FW Analysis of ^{1}H DOSY Data of 6b

entry	compd	FW (g·mol^{-1})	10^{-10} D (m^2/s)	predicted FW (g·mol^{-1})	% error
1	BEN	78.11	7.064	79.16	−1.3
2	COE	110.2	5.738	113.1	−2.6
3	TDE	196.4	4.347	182.0	7.3
4	SQU	410.7	2.647	426.1	−3.8
5	**6b**[a]	711.4[b]	2.018[a]	678.6	4.6
6	**6b**[a]	711.4[b]	1.862[a]	779.0	−9.5
7	**6b**[a]	711.4[b]	2.015[a]	680.3	4.4
8	**6b**[c]	711.4[b]	1.999[c]	689.7	3.1
9	**6b**[d]	711.4[b]	1.974[d]	706.9	0.6

[a] The measured diffusion coefficients are from the resonances of chiral lithium amide. [b] 711.4 g·mol^{-1} is the formula weight of 2:2 lithiated chiral amine **5**/*n*-BuLi (^{6}Li labeled) complex **6b**. [c] The measured diffusion coefficient is from the resonance of α-methylene protons (−0.40 ppm) of *n*-BuLi. [d] The diffusion coefficient is the average of the above four values.

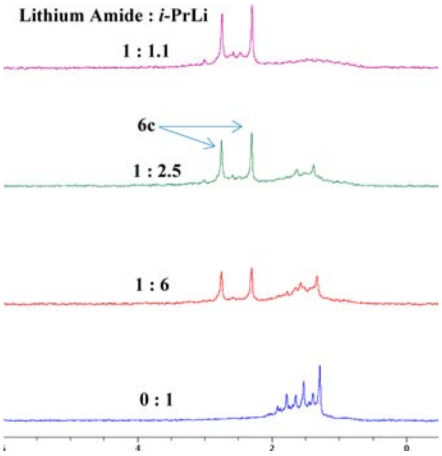
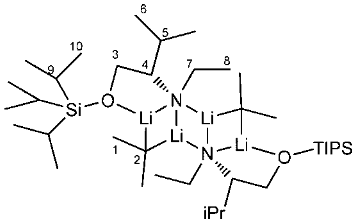


Figure 15. ^{6}Li NMR spectra of chiral amine **5** titration of 0.35 M *i*-Pr^{6}Li toluene-d_8 solution at −50 °C. 6c represents the resonance of the 2:2 mixed aggregate **6c**.

addition of chiral amine **5** to a solution of s-BuLi, a peak at −0.51 ppm from the methine proton of *s*-BuLi increases in intensity as the amount of lithiated chiral amine **5** increases in the ^{1}H NMR (Figure 20). In the ^{6}Li NMR spectra (Figure 21), the original hexamer, tetramer, and *s*-BuLi/*s*-BuOLi mixed aggregate[22] peaks disappear when 0.5 equiv of chiral amine **5** was added. A triplet and a singlet with 1:1 intensity emerge and increase in intensity with addition of chiral amine **5**. The two peaks become dominant when the mole ratio of lithiated chiral amine **5** to *s*-BuLi equals 1:1. The spectra of this complex are more complicated than that of **6a−c** because of the additional stereoisomers are possible by incorporation of an additional stereogenic center from *s*-BuLi. It is noteworthy that the N atoms in all of the complexes **6a−d** are also chiral, stereogenic centers. However, both the NMR spectra and the crystal structure of **6a** indicate that only a single disatereomer is formed. Assuming that the relative stereochemistry between N atoms and the chiral carbon in the valine derived residue in all of the complexes **6a−d** are similar, then we suggest that three peaks seen for Li(1) in Figure 9 are due to diastereomeric

Table 5. ^{1}H and ^{13}C Signal Assignments of Mixed Aggregate 6c



carbon atom	^{13}C (ppm)	^{1}H (ppm)
1	27.7	1.93
2	11.5	−0.39
3	62.6	3.84, 3.46
4	65.4	2.98
5	36.2	1.79
6	23.0, 19.9	1.17, 1.12
7	43.9	3.04, 2.96
8	16.9	1.38
9	12.5	0.95
10	18.5, 18.4	1.02, 0.96

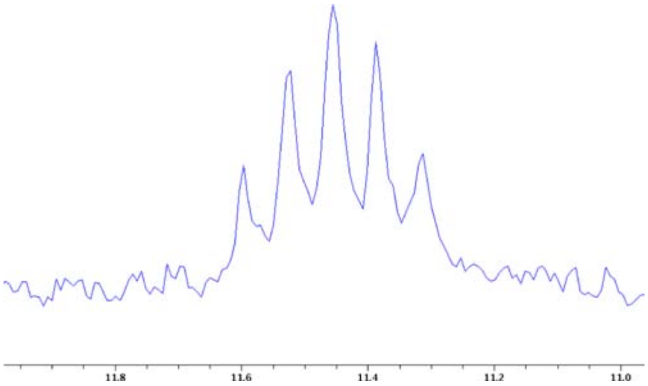


Figure 17. ^{13}C NMR of carbon atom 2 of mixed aggregate **6c** in toluene-d_8 at −50 °C.

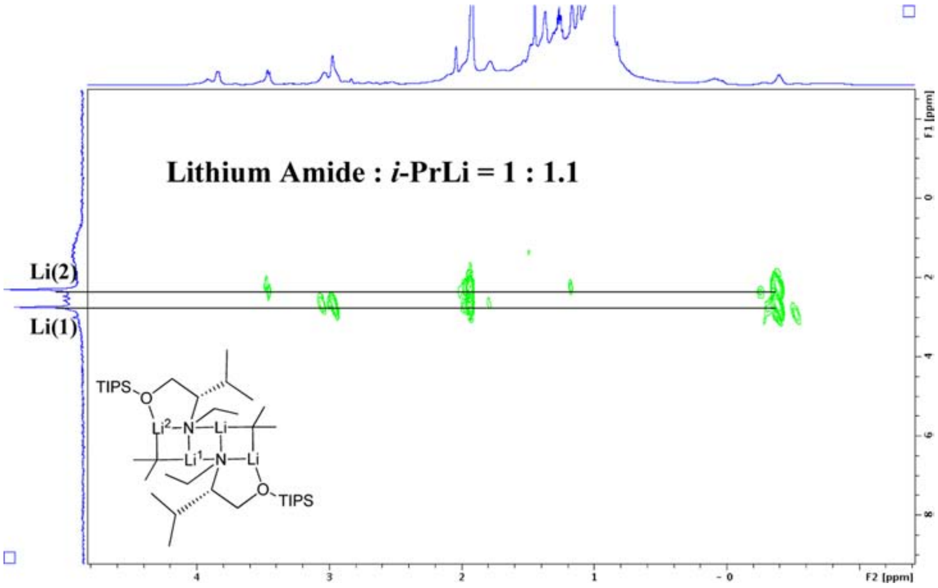


Figure 16. ^{1}H {^{6}Li} HMBC of **6c** in toluene-d_8 at −50 °C.

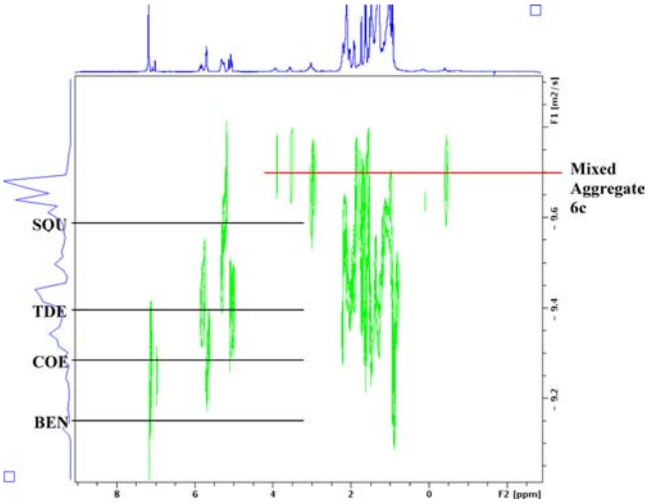


Figure 18. ^{1}H DOSY of mixed aggregate **6c** in toluene-d_8 at −50 °C.

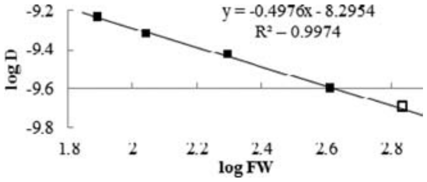


Figure 19. D-FW analysis of ^{1}H DOSY data. Internal references are shown as solid squares, and mixed aggregate **6c** is shown as an open square.

complexes that differ in relative stereochemistry of the C-2 of the *s*-BuLi residue.[23] It is noteworthy that only Li(1) is resolved into three peaks and Li(2) remains as a single peak as seen in the Figure 21 in the two middle spectra. However, it is also clear that at a 1:1 ratio of Li amide to *s*-BuLi, a distinctly new resonance close to that of Li(1) is apparent. We suggest that this is a disatereomeric complex.

The ^{1}H {^{6}Li} HMBC (Figure 22) spectrum reveals strong correlation from both the Li(1) and the Li(2) resonances to the methine proton of *s*-BuLi (−0.51 ppm). The protons on the methylene (3.11, 2.93 ppm) and methine (2.26 ppm) groups adjacent to nitrogen in the valine residue correlate to Li(1). Finally we note that Li(2) also correlates strongly to one of the protons of the methylene group (3.47 ppm) adjacent to oxygen. These results are consistent with a mixed 2:2 complex **5**.

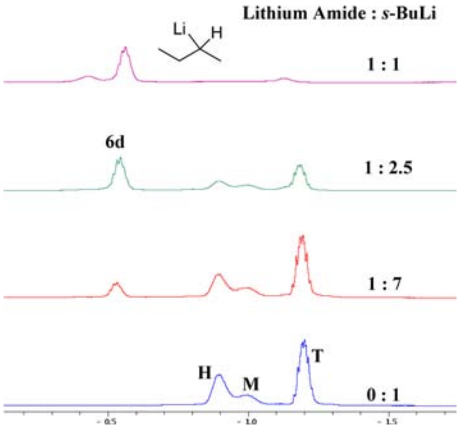


Figure 20. ^{1}H NMR spectra of chiral amine **5** titration of 0.38 M *s*-Bu^{6}Li toluene-d_8 solution at −50 °C. H represents the resonance of *s*-Bu^{6}Li in hexamer; T represents the resonance *s*-Bu^{6}Li in tetramer; M represents mixed aggregate of *s*-Bu^{6}Li/*s*-BuO^{6}Li, and 6d represents the resonance of the 2:2 mixed aggregate **6d**.

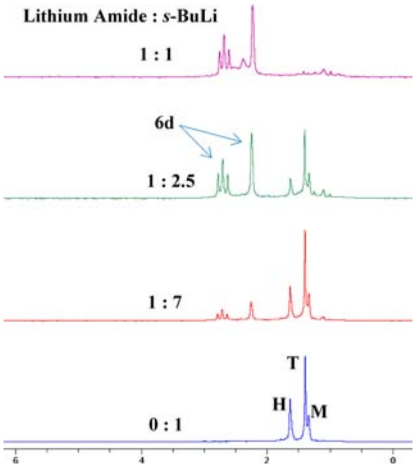


Figure 21. ^{6}Li NMR spectra of chiral amine **5** titration of 0.38 M *s*-Bu^{6}Li toluene-d_8 solution at −50 °C. H represents the resonance of *s*-Bu^{6}Li in hexamer; T represents the resonance *s*-Bu^{6}Li in tetramer; M represents mixed aggregate of *s*-Bu^{6}Li/*s*-BuO^{6}Li, and **6d** represents the resonance of the 2:2 mixed aggregate **6d**.

^{1}H and ^{13}C assignments are summarized in Table 7. The ratio of lithiated chiral amine **5** to *s*-BuLi in **6d** is approximately 1:1 by comparing the integration of distinctive proton peaks in the spectrum of the complex containing a 1:1 stoichiometric

Table 6. D-FW Analysis of ^{1}H DOSY Data of 6c

entry	compd	FW (g·mol^{-1})	10^{-10} D (m^2/s)	predicted FW (g·mol^{-1})	% error
1	BEN	78.11	5.817	77.40	0.9
2	COE	110.2	4.787	114.5	−3.9
3	TDE	196.4	3.748	187.2	4.7
4	SQU	410.7	2.512	418.4	−1.9
5	**6c**[a]	683.3[b]	1.946[a]	698.9	−2.3
6	**6c**[a]	683.3[b]	1.986[a]	670.9	1.8
7	**6c**[a]	683.3[b]	2.059[a]	624.0	8.7
8	**6c**[c]	683.3[b]	2.037[c]	637.6	6.7
9	**6c**[d]	683.3[b]	2.036[d]	656.9	3.9

[a] The measured diffusion coefficients are from the resonances of chiral lithium amide. [b] 683.3 g·mol^{-1} is the formula weight of 2:2 lithiated chiral amine **5**/*i*-PrLi (^{6}Li labeled) complex **6c**. [c] The measured diffusion coefficient is from the resonance of the methine proton (−0.39 ppm) of *i*-PrLi. [d] The diffusion coefficient is the average of the above four values.

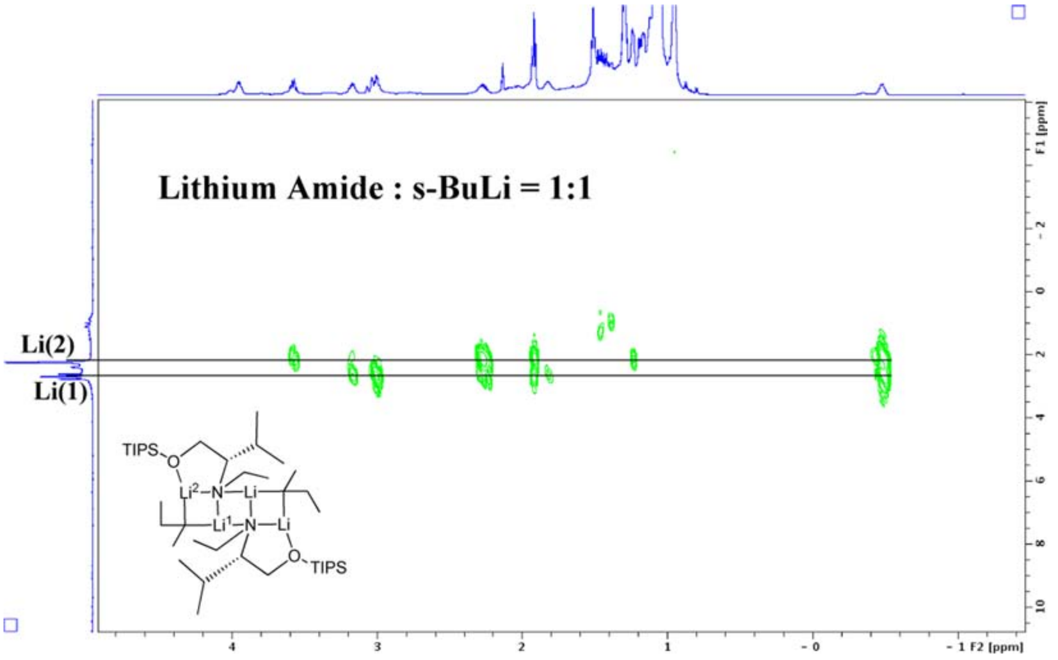
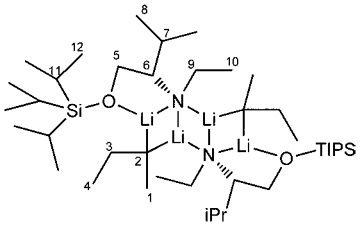


Figure 22. ^1H {^6Li} HMBC of **6d** in toluene-d_8 at −50 °C.

Table 7. ^1H and ^{13}C Signal Assignments of Mixed Aggregate 6d



carbon atom	^{13}C (ppm)	^1H (ppm)
1	25.0, 25.1, 24.7, 24.5	1.89
2	23.0, 22.9	−0.51
3	36.2, 36.1, 36.0, 35.9	2.26
4	19.4, 19.3, 19.2, 19.1	1.47
5	62.8, 62.7, 62.5	3.85, 3.47
6	66.5, 65.5, 64.5, 64.4	2.96
7	36.3	1.73
8	23.0, 22.9	1.10
9	44.6, 44.0, 43.3	3.11, 2.93
10	17.3, 17.1, 16.9, 16.7	1.37
11	12.6, 12.7	0.96
12	18.5, 18. 6, 18.4, 18.5	0.97

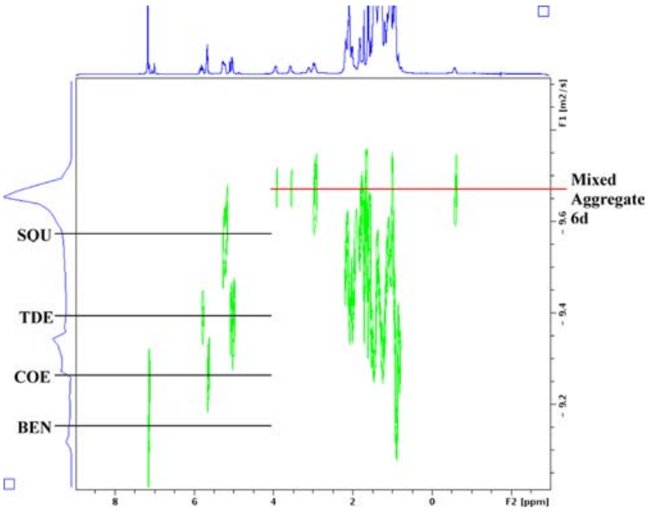


Figure 23. ^1H DOSY of mixed aggregate **6d** in toluene-d_8 at −50 °C.

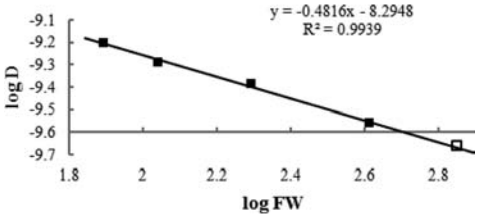


Figure 24. D-FW analysis of ^1H DOSY data. Internal references are shown as solid squares, and mixed aggregate **6d** is shown as an open square.

ration of *s*-BuLi to lithium amide. Unfortunately, we were not able to obtain an interpretable ^{13}C methine peak of *s*-BuLi, probably due to the presence of diastereomers.

The diffusion-ordered NMR spectroscopy (Figure 23) and D-FW analysis show that lithiated chiral amine **5** and *s*-BuLi (−0.51 ppm) have very similar diffusion coefficients. The average predicted formula weight for the resonances of mixed aggregate **6d** is 685.2 g/mol which is only 3.7% different from the formula weight of the 2:2 mixed aggregate **6d** (711.4 g/mol) (Figure 24, Table 8).

Overall, the ^1H NMR titration results suggest the formation of a complex with a 1:1 molar ratio of chiral lithium amide and *s*-BuLi, while ^1H {^6Li} HMBC confirms the complexation between chiral lithium amide and *s*-BuLi. The ^6Li NMR result is consistent with the 2:2 mixed aggregate **6d** but is not consistent with the 2:1 mixed aggregate. Therefore, our results point to the existence of 2:2 mixed aggregate **6d** as the major species in a toluene solution with a 1:1 molar ratio of lithiated chiral amine **5** and *s*-BuLi.

Table 8. D-FW Analysis of ^{1}H DOSY Data of 6d

entry	compd	FW (g·mol^{-1})	10^{-10} D (m^2/s)	predicted FW (g·mol^{-1})	% error
1	BEN	78.11	6.279	76.56	2.0
2	COE	110.2	5.110	117.4	−6.6
3	TDE	196.4	4.122	183.5	6.6
4	SQU	410.7	2.763	421.0	−2.5
5	**6d**[a]	711.4[b]	2.163[a]	699.9	1.6
6	**6d**[a]	711.4[b]	2.174[a]	692.6	2.6
7	**6d**[a]	711.4[b]	2.200[a]	675.7	5.0
8	**6d**[c]	711.4[b]	2.204[c]	673.1	5.4
9	**6d**[d]	711.4[b]	2.185[d]	685.2	3.7

[a]The measured diffusion coefficients are from the resonances of chiral lithium amide. [b]711.4 g·mol^{-1} is the formula weight of 2:2 lithiated chiral amine **5**/*s*-BuLi (^{6}Li labeled) complex **6d**. [c]The measured diffusion coefficient is from the resonance of the methine proton (−0.51 ppm) of *s*-BuLi. [d]The diffusion coefficient is the average of the above four values.

■ CONCLUSION

The formation of a 2:2 mixed aggregate between lithiated (*S*)-*N*-ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine and cyclopentyllithium, *n*-butyllithium, *sec*-butyllithium, or isopropyllithium has been established by X-ray diffraction and various NMR techniques including diffusion-ordered NMR spectroscopy (DOSY) with D-FW correlation analyses and other one- and two-dimensional NMR techniques. The 2:2 ladder-type mixed aggregate is found to be the major species in toluene-d_8 solutions containing approximately 1:1 molar ratio of the lithium chiral amide to any of the simple alkyllithium reagents.

The complete characterization of the 2:2 mixed aggregates enriches our knowledge of the structural motifs of chiral lithium amide mixed aggregates. It is well-established that lithiated *N*-isopropyl-*O*-triisopropylsilyl valinol **1b** forms a 2:1 mixed aggregate with *n*-butyllithium and that this mixed aggregate is responsible for the enantioselectivity of asymmetric addition of *n*-BuLi in the mixed aggregate to aldehydes. These results demonstrate the influence and importance of the N-substitute group of the chiral amine ligands since the simple replacement of an N-isopropyl group with an N-ethyl group leads to completely different mixed aggregates both in the solid state and in solution. These results are relevant to developing a mechanistic picture of the enantioselective reaction mediated by chiral lithium amide. We are currently conducting extensive work on both enantioselectivity and mechanism of the asymmetric addition of the alkyl lithium moiety in these 2:2 mixed aggregates to various electrophiles.

■ EXPERIMENTAL SECTION

Procedures for NMR Experiments. NMR samples were prepared in tubes sealed with rubber septa cap and parafilm. NMR tubes were evacuated in vacuo, flame-dried, and filled with argon before use. ^{1}H chemical shifts were referenced to toluene-d_8 at 7.09 ppm, and ^{13}C chemical shifts were referenced to toluene-d_8 at 137.86 ppm. All NMR experiments except DOSY experiments were acquired on a 600 MHz spectrometer. All DOSY experiments were acquired on a 400 MHz spectrometer equipped with a *z*-axis gradient amplifier with a *z*-axis gradient coil. The maximum gradient strength was 0.214 T/m. ^{1}H DOSY was performed using the standard programs, employing a double stimulated echo sequence, bipolar gradient pulses for diffusion, and three spoil gradients. The diffusion time was 200 ms, and the rectangular gradient pulse duration was 900 μs (**6b**) and 1000 μs (**6a,c,d**). Gradient recovery delays were 200 μs. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D-FW analysis were obtained using the T1/T2 analysis module in commercially available software.

The alkyllithium samples were prepared by laboratory synthesized alkyllithium hydrocarbon (pentane, heptane, or cyclohexane) solution. About 150−400 μL of the alkyllithium hydrocarbon solution was added via syringe to a NMR tube. After the addition, the NMR tube was evacuated in vacuo for 10−30 min at 0 °C to remove the hydrocarbon solvent. After filling with argon, toluene-d_8 was added via syringe to bring the total volume up to 600 μL.

The internal references (in a ratio of 1:3:3:1 for BEN, COE, TDE, and SQU, respectively) were titrated into the NMR tube and monitored by ^{1}H NMR. The titration was stopped when the peak intensity of benzene was about the two times as the methine proton peak of *i*-PrLi or *s*-BuLi and about the same as the α-methylene protons of *n*-BuLi or methine proton peak of *c*-PenLi.

Synthesis of (*S*)-*N*-Ethyl-3-methyl-1-((triisopropylsilyl)oxy)-butan-2-amine. The synthetic route of chiral amine **5** started from enantiomerically pure (*S*)-valine. The *N*-ethyl valine was prepared according to Ohfune's method.[24] The *N*-ethyl valine was then reduced by lithium aluminum hydride in anhydrous tetrahydrofuran to *N*-ethyl valinol. Chiral amine **5** was prepared as follows: To a solution of *N*-ethyl valinol (2.00 g, 15.2 mmol) and triethylamine (4.25 mL, 30.5 mmol) in 40 mL of CH_2Cl_2 was added slowly triisopropylsilyl triflate (5.82 g, 19.0 mmol) at 0 °C. The resulting solution was allowed to stir at room temperature for 4 h before quenching with 15 mL of 2 M $NaHCO_3$. The mixture was extracted with 20 mL of EtOAc three times, and the combined organic phase was washed by 10 mL of brine and dried over anhydrous Na_2SO_4. The solvent was then removed by rotary evaporation, and purification was performed by vacuum distillation. Purification (bp = 129 °C, 3 mmHg) gave a colorless oil (2.03 g, 7.06 mmol, 46.3%). ^{1}H NMR (Tol-d_8, 400 MHz) δ 3.73−3.55 (m, 2H), 2.70−2.53 (m, 2H), 2.34 (q, 1H, J = 5.0 Hz), 1.89−1.81 (m, 1H), 1.11−1.01 (m, 25H), 0.98 (dd, 6H, J = 9.1, 7.5 Hz); ^{13}C NMR (Tol-d_8, 100 MHz) δ 65.6, 63.5, 43.3, 29.9, 19.6, 19.5, 18.7, 16.6, 12.8; HRMS-ESI m/z: $[M + H]^+$. Calcd for $C_{16}H_{38}NOSi$: 288.2717, found: 288.2715.

Synthesis of *c*-Pen^{6}Li.[19] About 0.865 g (144 mmol) of finely cut ^{6}Li metal was placed into a flame-dried flask with a condenser attached that was flushed with argon. The condenser was fitted with a serum septum and sealed with parafilm. The metal was washed with dry pentane by adding 10 mL of pentane to the flask via syringe. The flask was then placed in an ultrasound bath for 15 minutes. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (3 times). Dry heptane (10 mL) was added to the flask, and the flask was then placed in an oil bath at 50 °C with stirring. A drop of methyl *tert*-butyl ether was added to 6.33 g (60.5 mmol) of chlorocyclopentane, and the resulting solution was added via syringe to the hot lithium metal heptane mixture in 2.5 h using a syringe pump. After the addition of chlorocyclopentane, the mixture was stirred overnight at room temperature, after which a purple slurry was obtained. The suspension was transferred via syringe to a clean, flame-dried vial flushed with argon, and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This cyclopentyllithium solution in heptane was titrated using 2,2-diphenylacetic acid in tetrahydrofuran and found to be 1.4 M.

Synthesis of *n*-Bu^{6}Li. The *n*-Bu^{6}Li solution was prepared in heptane according to the method that our group has published previously.[16]

Synthesis of *s*-Bu^{6}Li.[25] About 0.60 g (100 mmol) of finely cut ^{6}Li metal was placed into a flame-dried flask with a condenser attached that was flushed with argon. The condenser was fitted with a serum septum and sealed with parafilm. The metal was washed with dry pentane by adding 5 mL of pentane to the flask via syringe. The flask was then placed in an ultrasound bath for 15 minuntes. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (3 times). Dry cyclohexane (6 mL) was added to the flask, and the flask was placed in an oil bath at 50 °C with stirring. A drop of methyl *tert*-butyl ether was added to 3.50 g (37.8 mmol) of 2-chlorobutane, and the resulting solution was added via syringe to the hot lithium metal cyclohexane mixture in 2.5 h using a syringe pump. After the addition of 2-chlorobutane, the mixture was stirred overnight at room temperature, after which a purple slurry was obtained. The suspension was transferred via syringe to a clean, flame-dried vial flushed with argon, and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This *s*-Bu^{6}Li solution in cyclohexane was titrated using 2,2-diphenylacetic acid in tetrahydrofuran and found to be 0.57 M.

Synthesis of *i*-Pr^{6}Li.[26] About 0.60 g (100 mmol) of finely cut ^{6}Li metal was placed into a flame-dried flask with a condenser attached that was flushed with argon. The condenser was fitted with a serum septum and sealed with parafilm. The metal was washed with dry pentane by adding 5 mL of pentane to the flask via syringe. The flask was then placed in an ultrasound bath for 15 minuntes. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (3 times). Dry pentane (8 mL) was added to the flask, and the flask was placed in an oil bath at 40 °C with stirring. A drop of methyl *tert*-butyl ether was added to 3.00 g (38.2 mmol) of 2-chloropropane, and the resulting solution was added via syringe to the warm lithium metal pentane mixture in 2.5 h using a syringe pump. After the addition of 2-chloropropane, the mixture was stirred overnight at room temperature, after which a purple slurry was obtained. The suspension was transferred via syringe to a clean, flame-dried vial flushed with argon and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This *i*-Pr^{6}Li solution in pentane was titrated using 2,2-diphenylacetic acid in tetrahydrofuran and found to be 0.52 M.

Preparation of XRD Quality Crystals of the 2:2 Mixed Aggregate of Lithiated (*S*)-*N*-Ethyl-3-methyl-1-(triisopropylsilyloxy)butan-2-amine and Cyclopentyllithium 6a. To a solution of chiral amine **5** (0.050 g, 0.17 mmol) in 0.4 mL of toluene at 0 °C under Ar atmosphere was slowly added 2 equiv of *c*-PenLi. The reaction mixture was shaken vigorously at 0 °C. XRD quality crystals of **6a** were grown when the solution was stored at −50 °C for a few days.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supplemental NMR and crystallographic info (47 pages). This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 948999 contains 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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Notes

The authors declare no competing financial interest.

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