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Aggregation Studies of Complexes Containing a Chiral Lithium Amide and *n*-Butyllithium

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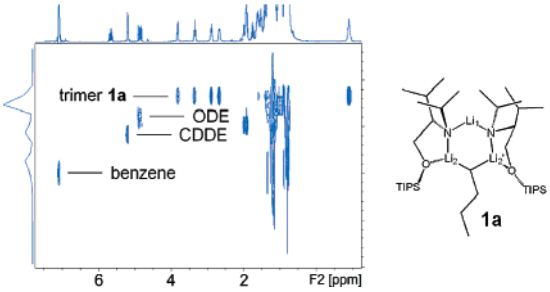

A system consisting of a chiral lithium amide and *n*-BuLi in tol-d_8 solution was investigated with ^{1}H and ^{13}C INEPT DOSY, ^{6}Li and ^{15}N NMR, and other 2D NMR techniques. A mixed 2:1 trimeric complex was identified as the major species as the stoichiometry approached 1.5 equiv of *n*-BuLi to 1 equiv of amine compound. ^{1}H and ^{13}C INEPT DOSY spectra confirmed this lithium aggregate in the solution. The formula weight of the aggregate, correlated with diffusion coefficients of internal references, indicated the aggregation number of this complex. Plots of log D_{rel} vs log FW are linear ($r > 0.9900$). ^{6}Li and ^{15}N NMR titration experiments also corroborated these results. These NMR experiments indicate that this mixed aggregate is the species that is responsible for asymmetric addition of *n*-BuLi to aldehydes.

Introduction

Organolithium reagents are the most frequently used organometallics in C−C bond formation reactions today.[1] Chiral lithium amides are widely used for asymmetric deprotonation and addition reactions.[2] Evidence of mixed lithium aggregates is increasing as numerous studies of chiral lithium aggregate structures in solution and in the solid state are reported.[2a,3−5] Extensive studies of mixed aggregate have been independently carried out by the groups of Collum,[6] Reich,[7] Hilmersson,[3a,8] Thomas,[9] Davidsson,[3b,10] van Koten,[11] Duhamel,[12] and Maddaluno.[13] However, the solution state structures of mixed aggregates are less well-known and their aggregation number and solvation state often require detailed studies.

In 1997[4] and 2000[5] we reported crystal structures of a mixed trimeric complex containing *n*-, *sec*-, *tert*-butyllithium (BuLi) or 3-pentanone enolate and 2 equiv of a chiral lithium amide derived from valine. The complex containing *n*-BuLi **1** (Scheme 1) was investigated for the asymmetric addition of *n*-BuLi to aldehydes to evaluate enantioselectivity.[14] Enantiomeric excesses

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(1) For leading references, see: (a) Rappoport, Z.; Marek, I., Eds. *The chemistry of organolithium compounds*; John Wiley & Sons, Ltd: New York, 2004. (b) Hodgson, D. *Organolithiums in enantionselective synthesis*; Springer: New York, 2003. (c) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596−2616. (d) Trost, B. M., Fleming I., Eds. *Comprehensive organic synthesis*; Pergamon: Oxford, UK, 1991.

(2) (a) Goldfuss, B. *Synthesis* **2005**, 2271−2280. (b) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264−271. (c) Parsons, R. L.; Fortunak, J. M.; Dorow, R. L.; Harris, G. D.; Kauffman, G. S.; Nugent, W. A.; Winemiller, M. D.; Briggs, T. F.; Xiang, B. S.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 9135−9143. (d) Huffman, M. A.; Yasuda, N.; Decamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590−1594. (e) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187−5190.

(3) (a) Granander, J.; Sott, R.; Hilmersson, G. *Chem.−Eur. J.* **2006**, *12*, 4191−4197. (b) Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175−179.

(4) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693−11694.

(5) Sun, C. Z.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829−7830.

(6) (a) Ramirez, A.; Sun, X. F.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326−10336. (b) Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L.; Davulcu, A. H.; Harris, G. D.; Fortunak, J. M.; Confalone, P. N. *J. Am. Chem. Soc.* **2004**, *126*, 5427−5435. (c) Zhao, P. J.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008−4009. (d) Sun, X. F.; Winemiller, M. D.; Xiang, B. S.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039−8046. (e) Briggs, T. F.; Winemiller, M. D.; Xiang, B. S.; Collum, D. B. *J. Org. Chem.* **2001**, *66*, 6291−6298. (f) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212−11218.

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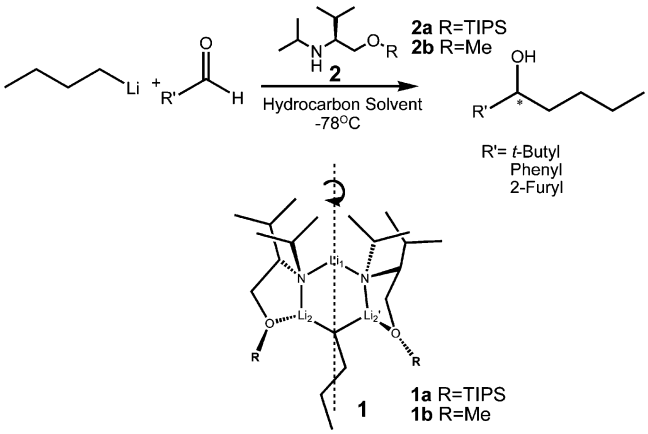
SCHEME 1. The Trimeric 2:1 Complex 1, Ligand 2, and Asymmetric Addition



up to 82.7% were obtained in the case of the addition of *n*-BuLi to pivaldehyde.

We now present results correlating the aggregate **1** in solution with the previously reported crystal structure.[4] A significant question is whether aggregate **1** is the only or the major aggregate in solution or whether it is one of several species that could be responsible for the asymmetric induction. We studied the solution structure of this aggregate by Diffusion-Ordered NMR Spectroscopy (DOSY) as a means of obtaining the formula weight and aggregation number of the mixed aggregate that exists in solution. DOSY has emerged as a promising technique in combinatorial chemistry and enzymatic dynamic studies.[15] DOSY can separate different species[16,17] by their hydrodynamic radii[18,19] and even their MW.[20,21] This makes DOSY a powerful technique for elucidation of the components of a mixture and identification of the aggregation state of a complex. As proof of principle of the applicability of DOSY to study organolithium compounds, we have previously reported the use of ^{1}H DOSY to differentiate dimeric and tetrameric *n*-BuLi,[22] lithium allylic amide aggregates,[23] and bis(diisopropylamino)boron enolate of *tert*-butyl methyl ketone[24] in the solution state based on their mobilities. DOSY has also been utilized in the identification of a magnesium enolate[25] and other transition metal complexes.[26,27] In this article we have utilized ^{1}H and ^{13}C INEPT DOSY to identify and characterize different aggregates in solution at 25 and −78 °C as the stoichiometry of *n*-BuLi increases relative to the valinol derived amine **2**. The mixed trimeric 2:1 complex of lithium amide and *n*-BuLi **1** was identified as the major species in solution under different conditions. This chiral 2:1 complex **1** will be shown to be the asymmetric intermediate for the chiral addition reaction. We also report that it is possible to estimate the formula weight of these aggregates in solution by using an internal reference correlation DOSY method. Additional ^{6}Li and ^{15}N NMR experiments also corroborated these results.

Results and Discussion

1. Identification of Chiral Amine Ligand (2a) by ^{1}H and ^{13}C DOSY Experiments: ^{1}H DOSY Characterization of Ligand (2a) and Internal References. The chiral amino ether ligand **2a** is easily synthesized from valinol in two steps.[28] On the basis of ^{1}H, ^{13}C, and other 2D NMR techniques and ms, the ligand structure is confirmed as *N*-isopropyl-*O*-triisopropyl silyl valinol **2a**. The complete assignments of the proton and ^{13}C signals are given in Table S1 (Supporting Information).

To establish the internal reference-correlated DOSY methodology, we first applied ^{1}H and ^{13}C INEPT DOSY to identify the ligand **2a** in the toluene-d_8 solution. To avoid artifacts generated by temperature fluctuation, viscosity change, and convection, we choose 1-octadecene (ODE), cyclododecene[29] (CDDE), and benzene[30] as the internal references in the DOSY experiments. The ^{1}H DOSY spectrum of ligand **2a** with the three internal references in toluene-d_8 solution separates into four components in the diffusion dimension. These are clearly identifiable in the DOSY spectrum reproduced in Figure 1. In

(7) Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492−3493.
(8) (a) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron*: *Asymmetry* **2006**, *17*, 2021−2027. (b) Sott, R.; Granander, J.; Williamson, C.; Hilmersson, G. *Chem.−Eur. J.* **2005**, *11*, 4785−4792. (c) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798−6805. (d) Sott, R.; Granander, J.; Diner, P.; Hilmersson, G. *Tetrahedron*: *Asymmetry* **2004**, *15*, 267−274. (e) Sott, R.; Granander, J.; Hilmersson, G. *Chem.−Eur. J.* **2002**, *8*, 2081−2087. (f) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717−4725. (g) Arvidsson, P. I.; Ahlberg, P.; Hilmersson, G. *Chem.−Eur. J.* **1999**, *5*, 1348−1354.
(9) (a) Delong, G. T.; Pannell, D. K.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1993**, *115*, 7013−7014. (b) Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109−5112. (c) Thomas, R. D.; Clarke, M. T.; Jensen, R. M.; Young, T. C. *Organometallics* **1986**, *5*, 1851−1857.
(10) (a) Arvidsson, P. I.; Hilmersson, G.; Davidsson, O. *Chem.−Eur. J.* **1999**, *5*, 2348−2355. (b) Hilmersson, G.; Arvidsson, P. I.; Davidsson, O.; Hakansson, M. *Organometallics* **1997**, *16*, 3352−3362. (c) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660−7669.
(11) Wijkens, P.; van Koten, E. M.; Janssen, M. D.; Jastrzebski, J. T. B. H.; Spek, A. L.; van Koten, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 219−222.
(12) (a) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042−10048. (b) Prigent, Y.; Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Duhamel, P.; Davoust, D. *J. Chim. Phys. Phys.-Chim. Biol.* **1998**, *95*, 401−405.
(13) (a) Harrison-Marchand, A.; Valnot, J.-Y.; Corruble, A.; Duguet, N.; Oulyadi, H.; Desjardins, S.; Fressigne, C.; Maddaluno, J. *Pure Appl. Chem.* **2006**, *78*, 321−331. (b) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigne, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *61*, 3325−3334. (c) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigne, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267−15279.
(14) Liu, J. Ph.D. Thesis, Brown University, 2007.
(15) For leading references, see: (a) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520−554. (b) Dehner, A.; Kessler, H. *ChemBioChem* **2005**, *6*, 1550−1565. (c) Valentini, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **2001**, *84*, 2833−2853. (d) Johnson, C. S. *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34*, 203−256.
(16) Groves, P.; Rasmussen, M. O.; Molero, M. D.; Samain, E.; Canada, F. J.; Driguez, H.; Jimenez-Barbero, J. *Glycobiology* **2004**, *14*, 451−456.
(17) Viel, S.; Capitani, D.; Mannina, L.; Segre, A. *Biomacromolecules* **2003**, *4*, 1843−1847.
(18) Sato, S.; Iida, J.; Suzuki, K.; Kawano, M.; Ozeki, T.; Fujita, M. *Science* **2006**, *313*, 1273−1276.
(19) Schlorer, N. E.; Cabrita, E. J.; Berger, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 107−109.
(20) Nishinari, K.; Kohyama, K.; Williams, P. A.; Phillips, G. O.; Burchard, W.; Ogino, K. *Macromolecules* **1991**, *24*, 5590−5593.
(21) Keresztes, I. Ph.D. Thesis, Brown University, 2002.
(22) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228−10229.
(23) Jacobson, M. A.; Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 4965−4975.
(24) Ma, L.; Hopson, R.; Li, D.; Zhang, Y.; Williard, P. G. *Organometallics* **2007**, *26*, 5834−5839.
(25) He, X. Y.; Morris, J.; Noll, B. C.; Brown, S. N.; Henderson, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 13599−13610.
(26) Pichota, A.; Pregosin, P. S.; Valentini, M.; Worle, M.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 153−156.
(27) Megyes, T.; Jude, H.; Grosz, T.; Bako, I.; Radnai, T.; Tarkanyi, G.; Palinkas, G.; Stang, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 10731−10738.

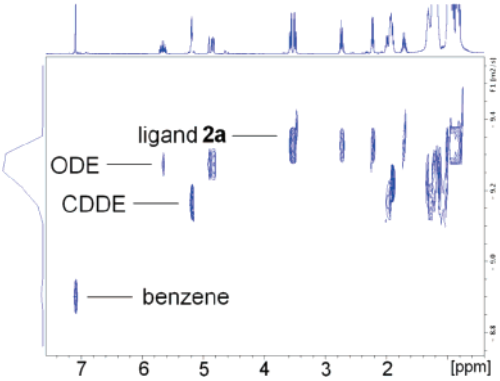


FIGURE 1. ^{1}H DOSY spectrum of ligand **2a** and three internal references in toluene-d_8 at 25 °C.

increasing order of diffusion coefficient (decreasing formula weight) these are the ligand **2** ($C_{17}H_{39}NOSi$, MW 301.6), ODE ($C_{18}H_{36}$, MW 252.3), CDDE ($C_{12}H_{22}$, MW 166.3), and benzene (C_6H_6, MW 78.1). The ^{1}H signals of the protons 1, 1′, 2, 3, and 5 in ligand **2a** (Figure 2, top) have identical diffusion coefficients. Previously we have suggested a correlation between diffusion coefficient and formula weight utilizing ^{1}H DOSY experiments to study vinylic lithiation of allylamine derivatives.[21] The current ^{1}H DOSY results strongly suggest that the diffusion coefficients and formula weights (Table 1) of ligand **2a** and the three internal references, ODE, CDDE, and benzene, can also be utilized to define a linear correlation between the relative log *D* (diffusion coefficient) and log FW (formula weight). The correlation between log FW and log *D* of the linear least-squares fit to reference points of all components in this mixture is extremely high, $r = 0.9904$ (Figure 3 and Table 1). This remarkable result highlights the ability to use suitable internal references in DOSY experiments to interpolate relative diffusion coefficients and formula weights. Ligand **2b** was investigated by the similar DOSY method (Figure S30, Supporting Information).

An added bonus of 2D-^{1}H DOSY spectra is to extract a one-dimensional ^{1}H spectrum slice at the diffusion coefficient of a particular species. To emphasize this point, we have depicted peaks of ligand **2a** (δ = 3.66, 3.60, 2.84, 2.35, and 1.85 ppm) in the slice of ligand **2a** (Figure 4b) to be compared with the spectrum of the pure, authentic sample (Figure 4b′). ^{1}H NMR slices taken at diffusion coefficients of ligand **2a** and internal references agree very well with their respective ^{1}H NMR spectra. Hence, the extracted ^{1}H spectra determined from the single 2D-^{1}H DOSY experiment resolved chemical shift information of every component in the mixture.

^{13}C INEPT DOSY Correlation of Ligand (2a) and Internal References. ^{13}C INEPT DOSY spectra provide better resolution, a wider chemical shift range than proton spectra, and the absence of homonuclear coupling. The ^{13}C DOSY spectrum of ligand **2a** with the three internal references in toluene-d_8 solution separates into four components in the diffusion dimension. These are clearly identifiable in the DOSY spectrum reproduced in Figure 5. In increasing order of diffusion coefficient (decreasing formula weight) these are the ligand **2a**, ODE, CDDE, and benzene. The ^{13}C signals of oxygen or nitrogen-attached carbon 1, 2, and 5 (δ 63.2, 61.9 and 46.5 ppm) in ligand **2a** have identical diffusion coefficients. The two olefinic carbons in ODE and the signals of CDDE also exhibit the same relative diffusion. The correlation between log FW and log *D* of the linear least-squares fit to reference points of ligand **2a** and the three internal references is even higher than ^{1}H DOSY experiment, $r = 0.9989$ (Figure 3 and Table 1). The DOSY slices of ligand **2a** illustrate the complete chemical shift resolution of carbons 1, 2, and 5 (Figure 6b). Separation of the three internal references (Figure 6c,d,e) is also satisfactory and comparable to the authentic samples (Figure 6c′,d′,e′).

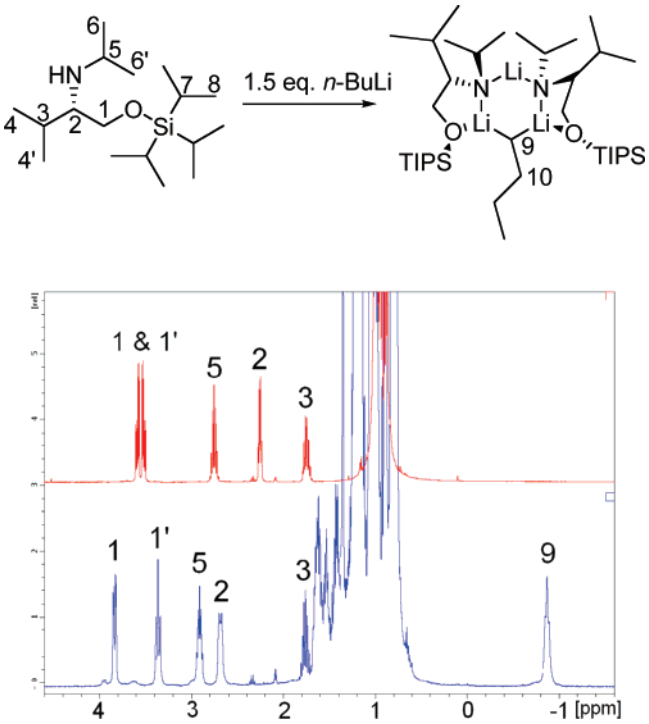


FIGURE 2. ^{1}H NMR comparison between ligand **2a** (top) and trimer **1a** (bottom).

2. Solution Structure of the 2:1 Complex (1): ^{1}H NMR Chemical Shift Changes. As 1.5 equiv of *n*-BuLi was added into the amine **2a** solution, ligand **2a** was converted into a novel lithium aggregate (see Figure 2, bottom). On the basis of 1D and 2D NMR techniques, the assignments of proton and ^{13}C signals are shown in Table S1 (Supporting Information). All the proton signals of the amide ligand in the new complex have different chemical shifts from the corresponding protons on the amine **2a**, especially protons on carbons 1, 1′, 2, and 5. (Table S1, Supporting Information) Also a new peak appears at δ −0.66 ppm, which is assigned to the C1-methylene protons of the *n*-BuLi. We use these five peaks as the fingerprints of the newly formed lithium amide trimeric complex. The α-methylene signals from *n*-BuLi in the complex occur as a singlet, which has a chemical shift and a peak pattern different from that of free *n*-BuLi in toluene-d_8 solution. The α-methylene signals

(28) Ohfune, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Chem. Lett.* **1984**, 441−444.

(29) Cyclododecene (CDDE) was purchased from Aldrich Chemical Company as a trans:cis (60:40) mixture. Olefin stereochemistry was confirmed by HSQC and ^{1}H NMR homodecoupling experiments utilizing ^{1}H-CW off-resonance spectra. See: (a) Radeglia, R. *J. Prakt. Chem./Chem.-Ztg.* **1993**, *335*, 291−293. (b) Radeglia, R.; Poleschner, H.; Haufe, G. *Magn. Reson. Chem.* **1993**, *31*, 1054−1056. (c) Radeglia, R.; Poleschner, H.; Haufe, G. *Magn. Reson. Chem.* **1993**, *31*, 639−641. (d) Radeglia, R.; Poleschner, H.; Theil, F. *J. Prakt. Chem./Chem.-Ztg.* **1993**, *335*, 673−679.

(30) There are three requirements for internal standards: (a) they should be inert to the components in solution, (b) the chemical shifts of these internal standards should not overlap with the components in solution, and (c) the internal standards should have no or little coordinating ability to the complexes in solution.

TABLE 1. Log *D* and Log FW Correlation of DOSY Experiments

	log *D*					
	benzene FW 78.1	CDDE FW 166.3	ODE FW 252.3	ligand **2a** FW 301.6	trimer **1a** FW 678.1	*r* (log *D* − log FW)
^{1}H, ligand **2a**, 25 °C	−8.879	−9.148	−9.235	−9.311		0.9904
INEPT, ligand **2a**, 25 °C	−8.876	−9.132	−9.255	−9.310		0.9989
^{1}H, trimer **1a**, 25 °C	−8.674	−8.921	−9.022		−9.306	0.9979
INEPT, trimer **1a**, 25 °C	−9.001	−9.254	−9.412		−9.745	0.9996
^{1}H, trimer **1a**, −78 °C	−9.758	−10.045			−10.441	0.9937
INEPT, trimer **1a**, −78 °C	−9.685	−9.848			−10.130	0.9997

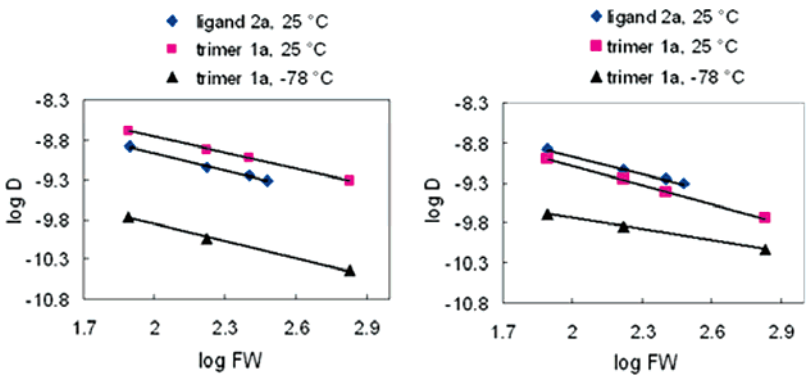


FIGURE 3. log *D*−log FW Correlation of ^{1}H (left) and ^{13}C INEPT (right) DOSY experiments of all the species in toluene-d_8 solution.

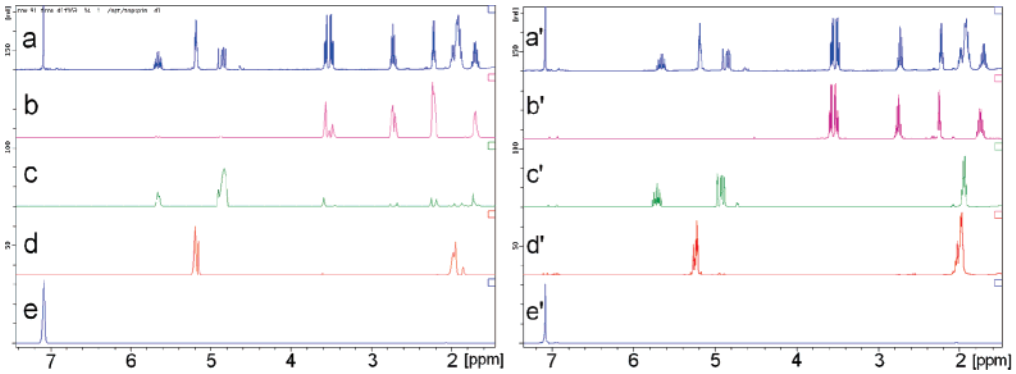


FIGURE 4. Comparison between slices of ^{1}H DOSY spectra (left) with ^{1}H NMR spectra (right) of authentic samples. From top to bottom: slice or spectrum of ligand **2a** with internal references, ligand **2a** without internal references, ODE, CDDE, and benzene.

from free *n*-BuLi in toluene-d_8 appear as three peaks with chemical shifts at δ −0.45, −0.68, and −0.88 ppm and the ratios among them are 1.0:1.3:11.8.[31] By comparing the chemical shifts and integrations, we propose that the *n*-BuLi in the complex has a different chemical environment than the free *n*-BuLi. As the stoichiometry of added *n*-BuLi varies from 1.10 to 1.75 equiv, integration of the proton peaks on the new aggregate increase proportionally with these variations (Figure S26, Supporting Information). However, the integration ratio between the α-CH_2 of *n*-BuLi and the peak of proton 2 on amide ligand remains constant at 1:1. This unchanged 1:1 area ratio suggests the formation of a new aggregate between the amide ligand and the *n*-BuLi. This 1:1 ratio also indicates 2 equiv of amide and 1 equiv of *n*-BuLi are included in the new aggregate, which is consistent with the solid-state structure.[4] Evidence presented below from DOSY and other NMR experiments supports the existence of the 2:1 trimeric complex **1** as the major lithium aggregate in toluene-d_8 solution.

(31) See the spectrum in Figure S31 in the Supporting Information.

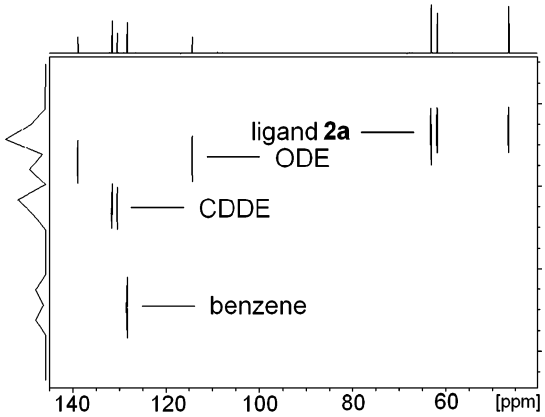


FIGURE 5. ^{13}C INEPT DOSY spectrum of ligand **2a** and three internal references in toluene-d_8 at 25 °C.

DOSY Identification of TIPS Trimer (1a) and Internal References at Room Temperature. As 1.5 equiv of *n*-BuLi

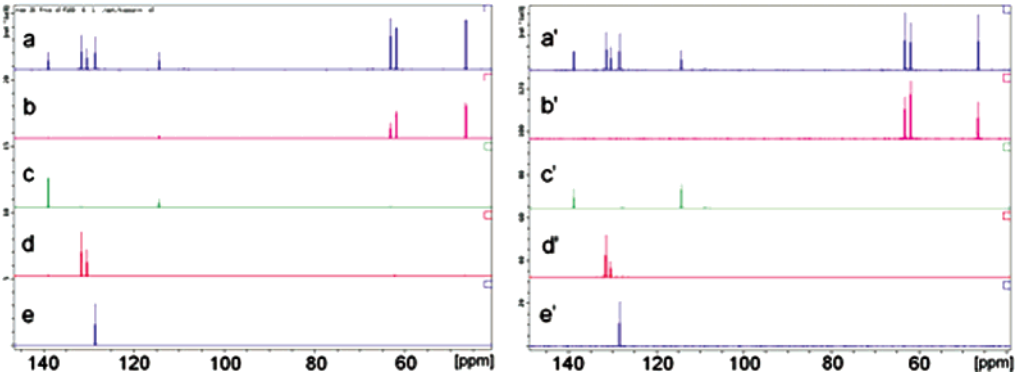


FIGURE 6. Comparison between slices of ^{13}C INEPT DOSY spectra (left) with ^{13}C INEPT NMR spectra (right) of authentic samples. From top to bottom: slice or spectrum of ligand **2a** with internal references, ligand **2a** without internal references, ODE, CDDE, and benzene.

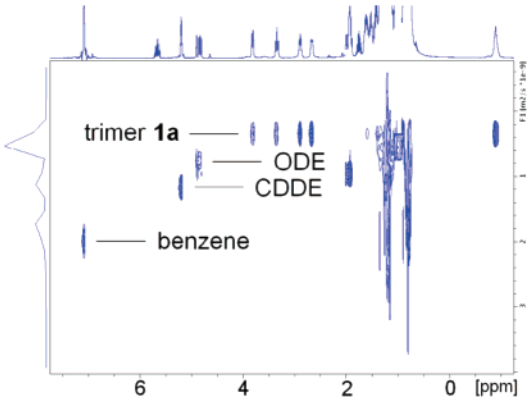


FIGURE 7. ^{1}H DOSY spectrum of trimer **1a** and internal references.

was added into 1 equiv of amine ligand **2a**, the DOSY spectrum was recorded as shown in Figure 7. Four components were separated on the diffusion dimension as the mixed aggregates **1a** and the three internal references. It is noteworthy that the α-CH_2 signal of *n*-BuLi (δ −0.66 ppm) has a similar diffusion coefficient to that from the signals on the amide part (protons on carbon 1, 1′, 2, 3, and 5). If this *n*-BuLi were free in the solution, it should have a much smaller diffusion coefficient than the lithium amide.[22] The similarity between the diffusion characteristics of the NMR signals from the lithium amide ligand and from the α-CH_2 of *n*-BuLi indicates that a complex is formed between the lithium amide and *n*-BuLi. By applying the previous formula weight−diffusion coefficient correlation method, we calculated the linear least-squares fit to reference points of trimer **1a** and the three internal references $r = 0.9979$ (Figure 3 and Table 1). The extracted ^{1}H NMR spectra from DOSY of all components agree very well with the authentic samples (Figure S14, Supporting Information). ^{13}C INEPT DOSY of trimer **1a** and internal references also demonstrate a similar separation (Figure S15, Supporting Information), linear least-squares fit ($r = 0.9996$, Figure 3 and Table 1), and similarity between DOSY slices and ^{13}C INEPT spectra of the authentic samples (Figure S16, Supporting Information). Hence this diffusion coefficient measurement supports the aggregation state of the aggregate **1a** at room temperature as a mixed trimer.

DOSY Correlation of TIPS Trimer (1a) and Internal References at −78 °C. By utilizing the same samples in the above section, DOSY and other NMR experiments were carried out at −78 °C, which was the temperature of asymmetric butylation to aldehydes. Because of ODE's high melting point (14−16 °C), the liquid ODE at room temperature crystallized from the solution at −78 °C and all the signals of ODE disappeared in all spectra. In both ^{1}H and ^{13}C INEPT DOSY spectra (Figures S21 and S23, Supporting Information), only three components were separated on the diffusion dimension as the mixed aggregate **1a**, CDDE and benzene. Their DOSY-extracted spectra agree well with the spectra from authentic samples (Figures S22 and S24, Supporting Information). The linear least-squares fit of all components in solution are fairly good for ^{1}H ($r = 0.9937$) and ^{13}C INEPT ($r = 0.9997$) DOSY experiments. Hence, this DOSY evidence suggests the trimeric complex **1a** exists at both room and low temperature (−78 °C).

In total, six DOSY experiments were carried out for ligand **2a** and trimer **1a**. They all showed good separation between different components according to their diffusion coefficients or formula weights. The least-squares fits between log *D* and log FW are remarkably high (>0.9900) and the average is 0.9967.

Low-Temperature ^{1}H NMR and COSY Studies. In the chiral trimeric complex **1b**, the two protons of the α-methylene in *n*-BuLi should be diastereotopic. It is possible these two proton signals may split into two peaks at subambient temperature even though they appear as a singlet at room temperature. Hence, a series of low-temperature ^{1}H NMR spectra were recorded. As the temperature decreases to −92 °C, the α-CH_2 peak of *n*-BuLi splits into 2 peaks with chemical shifts at δ −0.38 and −0.92 ppm (Figure 8d). The ratio between these two peaks is about 1:1. In a separate COSY experiment of sample **1a** at −92 °C (Figure 9), the cross-peaks between these two signals (highlight in the box) confirm they are on the same carbon. The difference in chemical shift of these diastereotopic protons is very similar to that observed by Davidsson.[32] No additional peaks are observed in the negative chemical shift region, i.e., δ <0.0 ppm. Hence neither free amine nor free hexameric *n*-$Bu^{6}Li$ was observed.[33] Therefore we conclude that disproportionation of the complex assigned as **1b** is not observed. These results confirm the diastereotopic relationship between the two α-methylene protons in *n*-BuLi. This result also suggests that the mixed trimeric aggregate **1** may exhibit enhanced enatioselectivity in its reactivity at low temperature.

(32) Hilmersson, G.; Davidsson, O. *Organometallics* **1995**, *14*, 912−918.

(33) Thomas, R. D.; Clarke, M. T.; Young, T. C. *J. Organomet. Chem.* **1987**, *328*, 239−248.

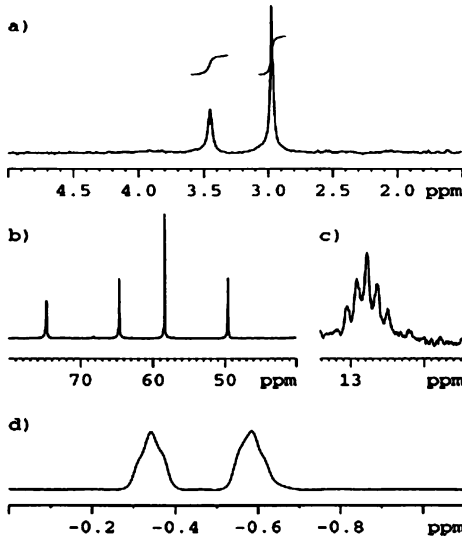


FIGURE 8. NMR spectra of crystalline trimer **1b** dissolved in toluene-d_8 at −92 °C: (a) ^{6}Li NMR spectrum with two peaks integrated 1:2; (b) part of the ^{13}C NMR spectrum showing there is only one set of peaks from the chiral Li-amide ligand in **1b**; (c) upmost field of the ^{13}C NMR spectrum showing the dicoordinated α-carbon of the butyl group in **1b** ($^1J_{^6Li-^{13}C} \approx 10$ Hz); and (d) upmost field part of ^{1}H NMR spectrum showing the two diastereotopic α-protons on the butyl group in **1b**. Not a trace of free hexameric *n*-Bu^{6}Li can be observed in parts a, c, or d.

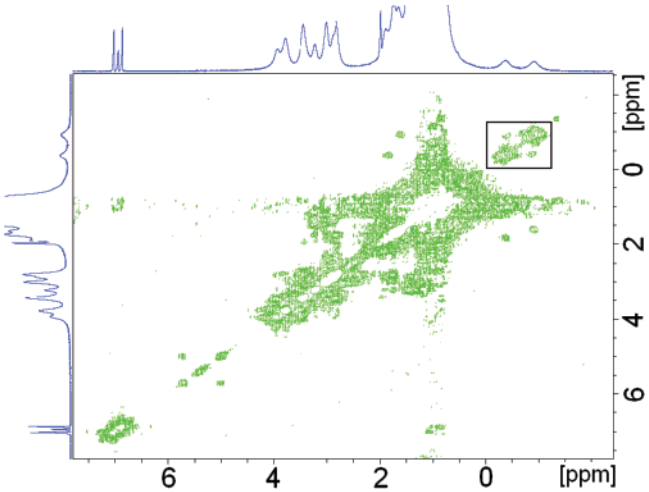


FIGURE 9. COSY of the 2:1 complex **1a** at −92 °C.

^{6}Li and ^{15}N NMR Studies of Mixed Aggregate (1b). We have developed the technique to grow relatively large and clear crystals of **1b**. Consequently, we initiated our investigation of the solution structure of the chiral *n*-butyllithium aggregate by analyzing NMR spectra derived from dissolving crystals of **1b** in deuterated hydrocarbon solvents. Thus average 2 × 2 × 1 mm^3 size crystals were generated from ^{6}Li-enriched *n*-BuLi[12a,34] and **2b**, washed twice with heptane and once with toluene-d_8 in a −78 °C bath. These clear crystals were dissolved in 0.7 mL of toluene-d_8 and the resulting solution was transferred via syringe into a NMR tube, which had been flame dried under vacuum, flushed with argon, and sealed with a rubber septum. The NMR tube was then flame sealed at −78 °C under reduced pressure and stored in −78 °C bath before it was put into the precooled NMR probe.[35] The ^{6}Li NMR spectrum at −78 °C exhibits two singlets at δ 2.97 and 3.46 ppm that integrated in a ratio 2:1 (Figure 8a) regardless of the concentration (ranging from 0.l to 0.3 M in toluene-d_8) or temperature (ranging from −90 to −20 °C). This ^{6}Li NMR spectrum does match that of the 2:1 complex **1b**. It was tempting but premature to conclude that the smaller peak at δ 3.45 ppm is $Li_{(1)}$ while the larger peak at δ 2.96 is from $Li_{(2)}$ and $Li_{(2')}$ in **1b**, so additional experiments were conducted. This NMR result provided incentive to examine the ^{6}Li−^{6}Li exchange spectroscopy (EXSY)[36] at −20 °C. The EXSY experiments revealed cross-peaks for the two ^{6}Li signals suggesting that these two lithium atoms exchange and are very likely in the same complex.[37]

The ^{13}C NMR of the dissolved crystal of **1b** is a simple spectrum with one set of peaks and part of the spectrum between δ 40 and 80 ppm is shown here, see Figure 8b. The peaks are assigned as follows: the two methine carbons next to the N atom appear at δ 64.62 and 49.54 ppm, the sole methylene carbon in the valinol residue is at δ 74.76 ppm, and the methoxy carbon is assigned to the peak at δ 58.35 ppm. The simplicity of this spectrum further confirms that there is only one Li-amide aggregate in solution. Only one quintet appears at δ 12.73 ppm in Figure 8c. This peak is assigned to the α-carbon of a butyl anion coordinated to two lithium cations.[38] This ^{13}C spectrum along with the EXSY results proves that there is only one complex in solution and that this species incorporates both the *n*-butyl residue and the chiral lithium amide. This evidence strongly supports the conclusion that the aggregate in solution has the structure indicated as **1b**.

All the NMR spectra presented support the conclusion that the solution aggregation state and structure matches exactly that found in the solid state by X-ray diffraction. Since we have prepared these NMR samples by growing crystals first and then dissolving them in hydrocarbon solvents, we are certain that we have started the NMR experiments using exclusively the 2:1 Li-amide/*n*-BuLi complex **1b**. These NMR experiments lead only to the conclusion that the chiral complex **1b** retains its integrity and persists as the only species upon dissolution in toluene-d_8 solution. Hence we conclude that the complex **1b** is present and likely to play a key role in the asymmetric induction in the *n*-BuLi addition when benzaldehyde is added to this solution.

NMR Titration Experiments: Titration of an *n*-Bu^{6}Li Solution with Amine (2b). The method given above for preparing the chiral Li-amide/*n*-BuLi complex **1b** is one of the cleanest methods to verify the exact aggregate species that we are utilizing. However, this process is experimentally time-

(34) (a) Waldmueller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119* (23), 5479−5480. (b) Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1993**, *115* (4), 1568−1572.

(35) We have observed that this sample is stable at −50 °C for at least a month and 0 °C for at least a day without any noticeable changes either by visual inspection or in the NMR spectrum.

(36) (a) Meier, B. H.; Ernst, R. R. *J. Am. Chem. Soc.*, **1979**, *101*, 6441−6442. (b) Jeener, J.; Meier, B. H.; Bachman, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546−4553.

(37) Sun, C. Ph.D. Thesis, Brown University, 2001. ^{6}Li−^{6}Li EXSY results suggest an intramolecular-only Li−Li exchange pattern in very similar complexes. Thus, in the NMR sample containing three different complexes, i.e., a chiral Li-amide/*n*-BuLi complex, a chiral Li-amide/Li-enolate complex, and a chiral Li-amide complex in toluene-d_8, the ^{6}Li−^{6}Li EXSY cross peaks are only observed between ^{6}Li signals from within the same complex.

(38) Heinze, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848−1862.

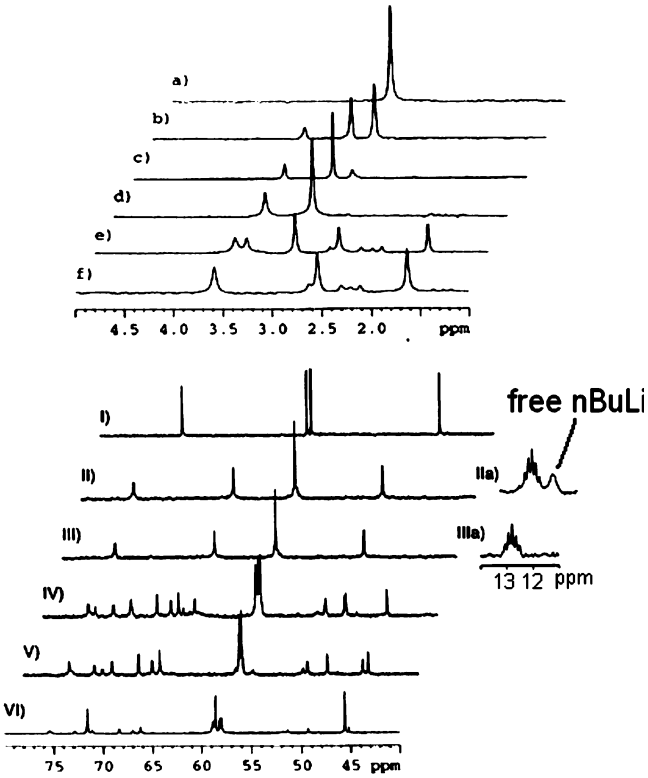


FIGURE 10. ^{6}Li (a−f) and ^{13}C (I−VI) NMR spectra (part) of addition of (a) 0, (b) 1.0 equiv, (c) and (II) 1.65 equiv, (d) and (III) 2.0 equiv, (e) and (IV) 2.35 equiv, (f) and (V) 3.05 equiv and (VI) 5.0 equiv of **2b** into 3 equiv of *n*-Bu^{6}Li in tol-d_8 at −92 °C. (I) ^{13}C NMR spectrum of free **2b** in tol-d_8 at −92 °C. (IIa) Upmost field part of spectrum II showing the coexistence of *n*-Bu^{6}Li in complex **1b** (quintet at 12.73 ppm) and free hexameric *n*-Bu^{6}Li. (IIIa) Upmost field part of spectrum III showing that free *n*-BuLi totally disappeared.

consuming and relatively inefficient since it involves crystallization and isolation of the complex **1b**. This procedure is unlikely to be utilized on a preparative scale. An experimentally much simpler procedure is to mix the amine and *n*-BuLi to obtain the complex **1b** directly in hydrocarbon solvents. Hence we sought to determine if it is possible to prepare the aggregate **1b** exclusively in solution by mixing 2 equiv of **2b** and 3 equiv of *n*-BuLi directly without having to crystallize and isolate the solid complex. The sequence of NMR experiments described below was performed to determine whether other mixed aggregates containing both Li-amide and *n*-BuLi are formed initially despite what crystallizes out of the solution.

A series of NMR samples were made by varying the amount of the amine **2b** while using the same amount of *n*-Bu^{6}Li. In the ^{6}Li NMR spectra, addition of less than 2 equiv of **2b** into 3 equiv of *n*-Bu^{6}Li in toluene-d_8 resulted in a constant decrease of the original free *n*-BuLi signal at δ 2.78 ppm. Two new ^{6}Li peaks began to appear which were identical with the peaks in Figure 8a indicating that **1b** was forming, see Figure 10a−c. Only one set of four new peaks appeared in the ^{13}C NMR spectra as shown in Figure 10(II−III). A quintet together with the multiplet from free *n*-BuLi appeared at highest field in Figure 10(II-a). The set of four new peaks and the quintet are at the same chemical shift as those recorded for the complex **1b** in Figure 8c. After exactly 2 equiv of amine **2b** was added, the NMR signals for free *n*-BuLi completely disappeared. At this stoichiometry, no extra peaks appeared in the NMR spectrum, see Figure 10d, as this spectrum (and stoichiometry) was identical with that in Figure 8a. The ^{13}C NMR spectra, depicted in Figure 10(III) and Figure 10(III-a), and ^{1}H NMR were also identical with those depicted in Figure 8b, 8c and 8d from dissolved crystals of the complex **1b**. The unambiguous conclusion is that the only complex in the solution is the 2:1 Li-amide/*n*-BuLi complex **1b**. Hence we have successfully verified that the chiral Li-amide-containing *n*-BuLi complex **1b** forms in situ in solution exclusively and that it is identical with that which crystallizes out of solution. This observation also lends credence to our assumption that the nucleophile responsible for asymmetric induction in the addition reaction is **1b** because this complex is formed exclusively in solution by mixing **2b** and *n*-BuLi without the necessity of growing and isolating crystals.

Further addition of amine **2b**, up to 3 equiv relative to *n*-BuLi, resulted in the loss of **1b** and the appearance of three extra major peaks and several minor ones in ^{6}Li NMR as shown in Figure 10e,f. ^{13}C NMR, Figure 10(IV−VI), provided the same information since the set of four peaks shown in Figure 10(III) disappeared and three new sets of peaks grew in and remained until **2b** was in excess. All these new peaks are assigned to different Li-amide-only aggregates and not from *n*-BuLi-containing complexes. All of these peaks in Figure 10f remained while the two peaks from **1b** totally disappeared when free amine **2b** was in excess, i.e., when considerably more than 3 equiv of amine was added. Therefore, throughout the titration, **1b** was the only complex containing both Li-amide and *n*-BuLi moieties. This information is valuable because it proves that it is safe to add a small excess of amine in preparative scale reactions to ensure that no free *n*-BuLi remains in solution. It is extremely important to ensure that no excess *n*-BuLi remains in solution because we have observed that the *n*-BuLi is more reactive.[39] Its existence in solution, presumably as a hexamer, is presumed to be detrimental to the enantioselectivity in addition reactions because it is achiral. Hence, we conclude unambiguously that complex **1b** exists as the only chiral species in solution in the asymmetric addition reactions when we add more than 2 equiv and less than 3 equiv of **2b** into 3 equiv of *n*-BuLi and until the amine is added in significant excess.

^{15}N NMR of ^{15}N Labeled Mixed Trimer (1b). ^{15}N and ^{6}Li double labeling is utilized as a powerful tool for Li-amide aggregation state and lithium coordination state determination.[40] The splitting patterns in ^{6}Li NMR and ^{15}N NMR spectra reveal core connectivity of lithium and nitrogen atoms in the amide base aggregates. Alternatively the coupling constant $J^{15}_{N-^{6}Li}$ provides information about the coordination states of lithium atoms.[41] Having established that mixing **2b** with *n*-Bu^{6}Li in toluene leads only to complex **1b**, the ^{15}N-enriched sample of **1b** was prepared by simply mixing 2 equiv of {^{15}N}-**2b** and 3 equiv of *n*-Bu^{6}Li.

(39) (a) A procedure to determine the relative reactivity from the following was used: Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175−179; Rucker, C. *Chem. Rev.* **1995**, 95, 1009−1064. Thus, benzaldehyde was added to a NMR sample containing **2b** and excess free *n*-BuLi in toluene-d_8 at −78 °C. The ^{6}Li signal at δ 2.69 ppm, which belongs to free hexameric *n*-BuLi, is the first one to disappear. (b) We have observed the coexistence of a 2 equiv Li-amide/1 equiv *n*-BuLi complex containing a similar chiral amide and the free amine indicating that the basicity of *n*-BuLi in the complex is reduced.

(40) (a) Gunther, H. *J. Braz. Chem. Soc.* **1999**, *10*, 241−262. (b) Collum, D. B. *Acc. Chem. Res.* **1993**, *26* (5), 227−234.

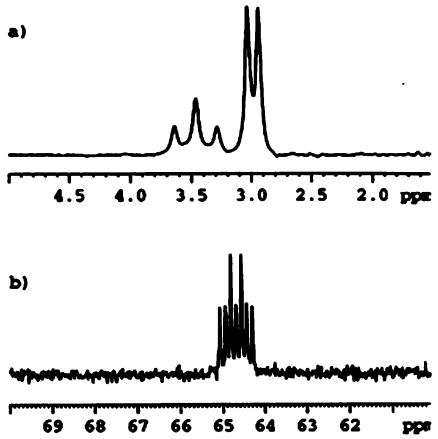


FIGURE 11. ^{6}Li and ^{15}N NMR spectra of 2 equiv of {^{15}N}-amine **2b** mixed with 3 equiv of *n*-Bu^{6}Li in Tol-d_8 at −78 °C. (a) ^{6}Li NMR spectrum displaying a triplet at 3.46 ppm ($^{1}J_{N-Li}$ = 7.7 Hz) and a doublet at 2.97 ppm ($^{1}J_{N-Li}$ = 4.2 Hz) with integrated ratio of 1:2. (b) ^{15}N NMR spectrum displaying a triplet of triplets ($^{1}J_{Li-N}$ = 7.7, 4.2 Hz).

The ^{6}Li NMR, Figure 11a, of the sample prepared from 2 equiv of {^{15}N}-**2b** and 3 equiv of *n*-Bu^{6}Li appears as one triplet and one doublet as expected. These peaks have the same chemical shifts and integration ratio as the sample that is not ^{15}N-enriched in Figure 8a. The $Li_{(1)}$ (Scheme 1) signal at δ 3.46 ppm is split by two equivalent ^{15}N (spin 1/2) atoms (($^{1}J_{N-Li}$ = 7.7 Hz) and the $Li_{(2)}$ and $Li_{(2')}$ signal at δ 2.97 ppm is split by one ^{15}N atom ($^{1}J_{N-Li}$ = 4.2 Hz). The ^{15}N NMR, Figure 11b, appears cleanly as a triplet of triplets at δ 64.69 ppm ($^{1}J_{Li-N}$ = 7.7, 4.2 Hz) indicating the two equivalent ^{15}N atoms are each coupled with two distinguishably different Li atoms. These coupling constants agree closely with those reported by Hilmersson.[3a] If the Li atoms are not quite different, that is if both were coupled to two nitrogen atoms, the ^{15}N NMR would be only a quintet. This is also expected because $Li_{(1)}$ is dicoordinated while $Li_{(2)}$ and $Li_{(2')}$ are tricoordinated. Further addition of the {^{15}N}-**2b** provides the same pattern as in Figure 10e,f, only showing multiplets instead of singlets. The coupling pattern in both the ^{6}Li and ^{15}N NMR spectra provide useful information for confirmation of the aggregation states of the complexes containing only Li-amides. However, due to the complicated nature of the aggregation states of the Li-amides, we are still unable to address this issue with certainty. The only definitive conclusion is that these signals arise from Li-amide-only aggregates. In fact, we have subsequently learned that Li-amides derived from similar amines give different patterns of aggregation states in toluene (vide infra). Thus more detailed work will be required to pursue the structures of the Li-amide-only complexes in hydrocarbon solvents. Furthermore, the ambiguity associated with the Li-amide-only aggregates might make the stereoselective deprotonation by this kind of Li-amide incomparable to each other because of the different aggregation states in solution. In conclusion, the ^{6}Li and ^{15}N NMR spectra further confirm the six-membered-ring core structure of Li−N_2−Li_2−C as in the solid-state structure of complex **1b** when there is an excess of *n*-BuLi in solution or when the stoichiometry is at or close to 2:1 amide base/*n*-BuLi.

Conclusions

All the NMR spectra presented support the conclusion that the solution aggregation state and structure matches exactly that found in the solid state by X-ray diffraction. Since we have prepared these NMR samples by growing crystals first and then dissolving them in hydrocarbon solvents, we are certain that we have started the NMR experiments using exclusively the 2:1 Li-amide/*n*-BuLi complex **1**. These NMR experiments lead only to the conclusion that the chiral complex **1** retains its integrity and persists as the only species upon dissolution in toluene-d_8 solution. This observation also lends credence to our assumption that the nucleophile responsible for asymmetric induction in the addition reaction is **1** because this complex is formed exclusively in solution by mixing **2** and *n*-BuLi without the necessity of growing and isolating crystals. Hence we conclude that the complex **1** is present and likely to play a key role in the asymmetric induction in the *n*-BuLi addition when aldehydes are added to this solution.

By using ^{1}H and ^{13}C INEPT DOSY, ^{6}Li, ^{15}N, and other 1D and 2D NMR techniques (^{1}H, ^{13}C, COSY, HSQC, HMBC, EXSY, and low-temperature NMR), we investigated the valinol-derived amino ether system as a chiral amide ligand for asymmetric alkylation reaction. We identified the structures of the trimeric 2:1 complex as the major species in toluene-d_8 solution. To the best of our knowledge, this is the first application of both the ^{1}H and ^{13}C INEPT internal-standard DOSY method to calculate the formula weights of lithium amide aggregates in solution. These NMR methods can be applied to other organolithium and organometallic systems.

Experimental Section

General. All NMR samples were directly prepared in the NMR tubes. All NMR tubes were sealed with a septum and then flame-dried under vacuum and filled with argon before use. Toluene-d_8 was kept with 4 Å molecular sieves under argon. *n*-BuLi was obtained from Aldrich Chemical Co. (2.5 M in hexanes), and the exact concentration of the solution was titrated with diphenyl acetic acid in THF. NMR experiments in Figures 8, 10, and 11 were recorded on a Bruker Avance DPX 300 spectrometer with a variable-temperature unit unless otherwise noted. A 5 mm BBO probehead was used. Measuring frequencies were 300.13 (^{1}H), 75.47 (^{13}C), 44.17 (^{6}Li), and 30.41 MHz (^{15}N). ^{6}Li spectra were referenced to external 0.3 M ^{6}LiCl in MeOH-d_4 set at δ 0.0 ppm. ^{15}N spectra were referenced to external 0.15 M {^{15}N}-aniline in THF-d_8 set at δ 50.0 ppm. XWINNMR software was used to process the spectra. All other NMR experiments were recorded on a Bruker DRX 400 spectrometer with a variable-temperature unit. The data were processed with the Topspin 1.3 pl6 software. Standard ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively. All ^{13}C spectra are proton decoupled. ^{1}H and ^{13}C chemical shifts were referenced to the toluene-d_8 signals at δ 2.08 and 20.4 ppm, respectively, in toluene-d_8.

DOSY Experiments. DOSY experiments were performed on a Bruker DRX400 spectrometer equipped with an Accustar *z*-axis

(41) (a) Arvidsson, P. I.; Davidsson, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 1467−1470. (b) Sun, X. F.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459−2463. (c) Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 10198−10202. (d) Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981−2987. (e) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081−4086. (f) Huls, D.; Gunther, H.; van Koten, G.; Wijkens, P.; Jastrzebski, J. T. B. H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2629−2631. (g) Sato, D.; Kawasaki, H.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 1399−1402. (h) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Romesberg, F. E.; Gilchirst, J. H.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748−5754. (i) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567−5572. (j) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *Tetrahedron*, **1997**, *53*, 7191−7200.

gradient amplifier and an ATMA BBO probe with a *z*-axis gradient coil. Maximum gradient strength was 0.214 T/m. Bipolar rectangular gradients were used with total durations of 0.5 to 3ms. Gradient recovery delays were 0.5 to 1 ms. Diffusion times were between 500 and 2000 ms. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected.

Synthesis of Chiral Amino Ether Ligand (2). The synthetic route adopted to prepare chiral amino ether ligands **2** started from enantiomerically pure L-valine. The amino group was condensed with acetone to afford the corresponding imine, and reduced with sodium cyanoborohydride.[28] The *N*-isopropyl valine was subsequently reduced into the desired amino alcohol with lithium aluminum hydride. Ligand **2a** was prepared from amino alcohol by using triisopropylsilyl triflate as a silylation reagent and triethyl amine as a base. Ligand **2b** was synthesized from amino alcohol by using MeI as the methylating reagent and NaH as a base.

Preparation of NMR Samples. The NMR samples were prepared by mixing 0.2 M ligand **2** as 1 equiv and the corresponding amounts of *n*-BuLi in 0.8 mL of toluene-d_8 solution under argon. Then 0.2 M ODE, 0.2 M CDDE, and 0.033 M benzene were added to the above sample as internal references for DOSY experiments. ^{1}H, ^{13}C, COSY, HSQC, HMBC, and DOSY spectra were recorded.

Acknowledgment. This work is supported through the NSF Grant 0718275 and in part by the National Institutes of Health Grant GM-35982.

Supporting Information Available: The ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectra of free ligand **2** and 2:1 complex **1** and the ^{1}H NMR spectrum of *n*-BuLi. This material is available free of charge via the Internet at http://pubs.acs.org.

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