JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

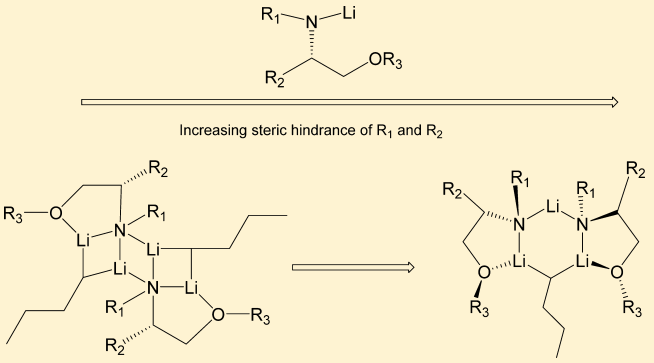
Influence of Steric Factors on Chiral Lithium Amide Aggregates

Chicheung Su, Russell Hopson, and Paul G. Williard*

Department of Chemistry, Brown University, 324 Brook Street, Providence, Rhode Island 02912 United States

Supporting Information

ABSTRACT: The solution structures of three mixed aggregates dissolved in toluene-d_8 consisting of the lithiated amides derived from (*S*)-*N*-isopropyl-1-((triisopropylsilyl)-oxy)propan-2-amine, (*R*)-*N*-(1-phenyl-2-((triisopropylsilyl)-oxy)ethyl)propan-2-amine, or (*S*)-*N*-isobutyl-3-methyl-1-((triisopropylsilyl)oxy)butan-2-amine and *n*-butyllithium are characterized by various NMR experiments including diffusion-ordered NMR spectroscopy with diffusion coefficient-formula weight correlation analyses (D-FW) and other one- and two-dimensional NMR techniques. We report that steric hindrance of R_1 and R_2 groups of the chiral lithium amide controls the aggregation state of the mixed aggregates. With a less hindered R_2 group, lithium (*S*)-*N*-isopropyl-1-((triisopropylsilyl)oxy)propan-2-amide forms mostly a 2:2 ladder-type mixed aggregate with *n*-butyllithium. Increase of steric hindrance of the R_1 and R_2 groups suppresses the formation of the 2:2 mixed aggregate and promotes formation of a 2:1 mixed aggregate. We observe that lithium (*S*)-*N*-isobutyl-3-methyl-1-((triisopropylsilyl)oxy)butan-2-amide forms both a 2:2 mixed aggregate and a 2:1 mixed trimer with *n*-butyllithium. Further increase in the steric hindrance of R_1 and R_2 groups results in the formation of only 2:1 mixed aggregate as observed with lithium (*R*)-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)propan-2-amide.

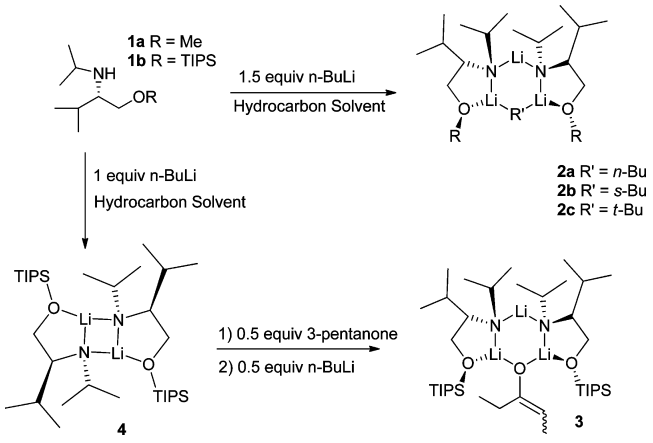


INTRODUCTION

Organolithium amide bases such as lithium diisopropylamide and lithium hexamethyldisilazide are generally used to deprotonate weakly acidic organic compounds such as ketones, esters, etc.[1] Chiral lithium amide bases have also been developed for use in asymmetric deprotonation and addition reactions.[2] As a representative example, Koga and co-workers reported a highly enantioselective aldol reaction in the presence of chiral lithium amide bases strongly implicating the influence of mixed aggregates.[3] Several groups including Collum,[4] Davidsson,[5] Duhamel,[6] Hilmersson,[7] McGarrity,[8] Maddaluno,[9] Reich,[10] Strohmann,[11] and Thomas[12] also reported the formation of mixed aggregates that incorporate lithium amide bases.

We previously reported the crystal structures of mixed trimers containing two equivalents of the chiral lithium amide derived from *N*-isopropyl valinol **1** and one equivalent of the alkyl lithium reagents depicted as structure **2** in Scheme 1.[13] Later, we also reported both the solid state structure and the solution state characterization of a similar trimeric complex consisting of two equivalents of the chiral lithium amide and 3-pentanone lithium enolate depicted as complex **3**.[14] More recently we reported the homodimeric solution structure **4** of the pure lithiated chiral amine **1** in the absence of any additional reagents in hydrocarbon solvent.[15] Most recently, we reported the four-rung ladder structures **6a**–**d** (Scheme 2) of mixed aggregates consisting of a 2:2 stoichiometric ratio of the chiral lithium amide derived from *N*-ethyl-*O*-triisopropylsilyl valinol **5** and either *n*-butyllithium (*n*-BuLi), *sec*-butyllithium (*s*-BuLi), or isopropyllithium (*i*-PrLi) or cyclopentyllithium.[16] Since the amino acid derived chiral amides are shown to be useful in asymmetric addition and deprotonation reactions,[17] and also since the reactivity and stereoselectivity of chiral lithium mixed aggregates depend on the aggregation state of the reagents,[6,7,10,18] the aggregation state determination of these chiral lithium mixed aggregates is crucial in controlling

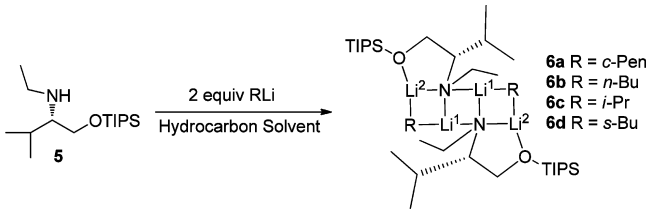
Scheme 1. Trimeric 2:1 Complexes 2 and 3 and the Homodimer 4



Received: December 5, 2013
Published: January 22, 2014

   dx.doi.org/10.1021/ja4123957 | *J. Am. Chem. Soc.* 2014, 136, 3246–3255

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



the mechanism of reactions in which they are employed and in designing new chiral lithium reagents. A comprehensive review of the extant breadth and scope of the influence of mixed aggregates on reactivity containing single and multiple anions and single and multiple cations has recently been published.[19]

In an attempt to rationalize the formation of completely different mixed aggregates, we synthesized chiral amines **7**, **8**, and **9** (Scheme 3) and characterized the mixed aggregates of

Scheme 3. Chiral Amines 7, 8, and 9

7 R_1 = *i*-Pr, R_2 = Me
8 R_1 = *i*-Pr, R_2 = *i*-Bu

9 R_1 = *i*-Pr, R_2 = Ph

lithium amides derived from **7**, **8**, and **9** with *n*-BuLi. We report that the steric factors of R_1 and R_2 groups dictate the formation of 2:2 mixed aggregates or 2:1 mixed trimers. With a sterically less hindered methyl group at the R_2 position, lithiated chiral amine **7** forms exclusively 2:2 mixed aggregate with the same motif as aggregates **6**. When the methyl group is replaced by a sterically more hindered isobutyl group at the R_2 position, lithiated chiral amine **8** forms both 2:2 mixed aggregate and 2:1 mixed trimer similar to the structure of complex **2a**. Further increase in the steric hindrance of the R_2 group prevents the formation of 2:2 mixed aggregate, as lithiated chiral amine **9** with a phenyl group at its R_2 position forms 2:1 mixed trimer and only a small amount of homodimer resembling the structure of complex **4**. No 2:2 mixed aggregate is observed with chiral amide derived from **9**.

RESULTS AND DISCUSSION

Solution State Characterization of the 2:2 Mixed Aggregate of Lithiated Chiral Amine 7 and *n*-BuLi. Chiral amine **7** was easily synthesized from (*S*)-alanine in three steps following the procedure we have used previously to prepare the *N*-isopropyl-*O*-triisopropylsilyl valinol.[13] The sample for NMR studies was prepared *in situ* by titrating (*S*)-*N*-isopropyl-1-((triisopropylsilyl)oxy)propan-2-amine **7** into a toluene-d_8 solution of ^{6}Li labeled *n*-BuLi at −40 °C. The titration was monitored by ^{1}H and ^{6}Li NMR as depicted in Figures 1 and 2, respectively.

Before the addition of chiral amine **7**, *n*-BuLi exists mostly as hexamer (−0.92 ppm)[20] and a small amount of *n*-BuLi/ *n*-butoxide (*n*-BuOLi) mixed aggregate (at approximately −0.55 ppm). Alkyllithium reagents are known to form mixed aggregates with lithium alkoxide.[8,12,21] Upon addition of chiral amine **7**, a new peak at −0.50 ppm increases significantly simultaneously with a decrease of the peaks due to the hexamer of *n*-BuLi. When the mole ratio of lithiated chiral amine **7** to *n*-BuLi equals 1:1.5, the peak at −0.59 ppm dominates the α-methylene region of *n*-BuLi.

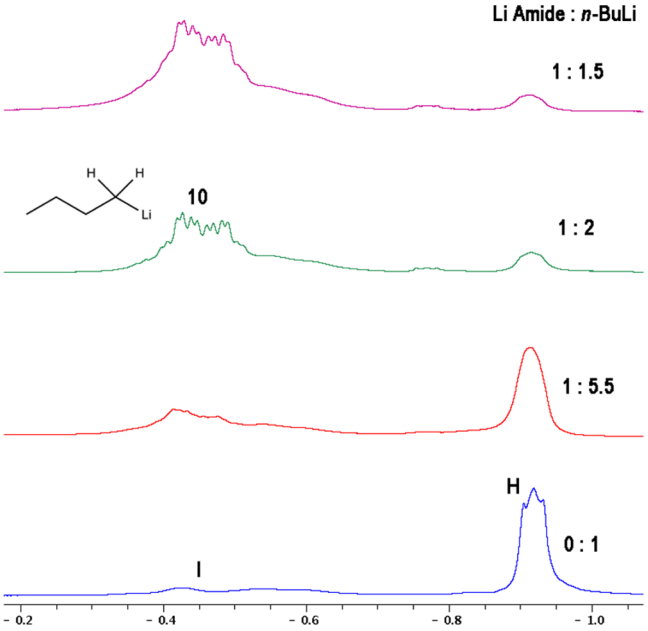


Figure 1. ^{1}H NMR spectra of chiral amine **7** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 10 represents the resonances of the 2:2 mixed aggregate **10**.

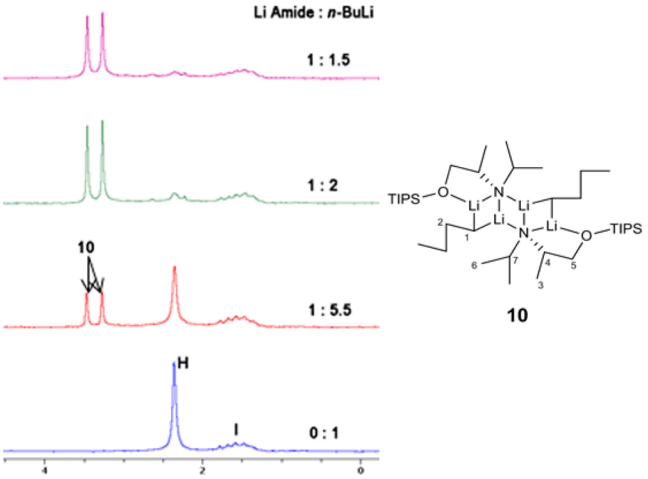


Figure 2. ^{6}Li NMR spectra of chiral amine **7** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 10 represents the resonances of the 2:2 mixed aggregate **10**.

In the ^{6}Li NMR spectra, *n*-BuLi exhibits one major peak corresponding to a hexamer and a minor broad peak corresponding to some unknown aggregate(s) of *n*-BuLi and *n*-BuOLi. The spectra show 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 **7**. These two sharp peaks dominate when the ratio of lithiated chiral amine **7** to *n*-BuLi equals 1:1.5. These spectra are consistent with a 2:2 mixed aggregate structure **10** depicted in Figure 2.

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

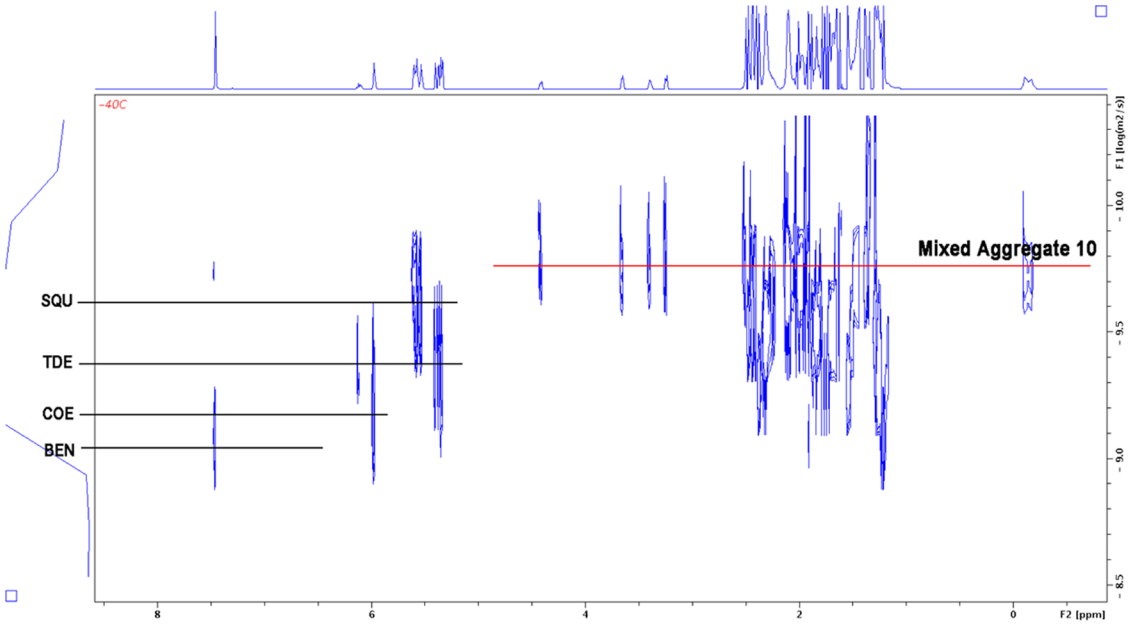


Figure 3. ^{1}H DOSY of mixed aggregate **10** in toluene-d_8 at −40 °C.

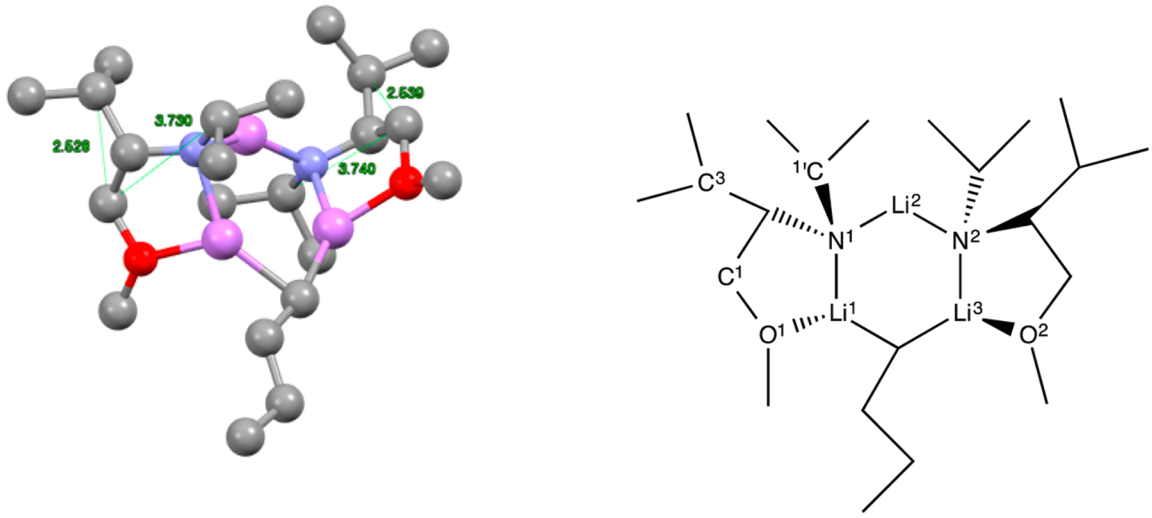


Figure 4. Crystal structure of mixed aggregate **2a**.

The ^{1}H{^{6}Li} HMBC spectrum confirms the formation of a mixed aggregate because both sharp peaks in the ^{6}Li correlate to the protons of lithiated chiral amine **7** and the α-methylene protons of *n*-BuLi. ^{1}H and ^{13}C NMR experiments including ^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC confirm the ^{1}H and ^{13}C chemical shift assignments given in the Supporting Information.[22]

To distinguish a 2:2 mixed aggregate from a 1:1 mixed aggregate, diffusion-ordered NMR spectroscopy and diffusion coefficient-formula weight (D-FW) correlation analysis were performed.[15,16,17a,23] In this experiment, 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) were added to the sample solution as internal molecular weight references. As seen in the ^{1}H DOSY spectrum (Figure 3), the α-methylene protons of *n*-BuLi and distinct peaks from lithiated chiral amine **7** have very similar diffusion coefficients. This result establishes complexation between the lithiated chiral amine **7** and *n*-BuLi. From the D-FW experiment, the average predicted formula weight of mixed aggregate **10** is 667 g/mol, a 2.4% difference from the expected formula weight of the 2:2 mixed aggregate **10** (683.3 g/mol). Details of the D-FW experiment are outlined in the Supporting Information..

Overall, our NMR experiments confirm that when the mole ratio of chiral lithium amide to *n*-BuLi is approximately 1:1, the solution structure of the mixed aggregate between lithiated, chiral amine **7** and *n*-BuLi in toluene is the 2:2 mixed aggregate **10**. This resembles the structure of mixed aggregate **6b**.

Previously we reported that lithiated chiral amine **1b** forms the 2:1 mixed trimer **2a** with *n*-BuLi, whereas lithiated chiral amine **5**, with simple substitution of the R_1 isopropyl group of **1b** to an ethyl group, forms 2:2 mixed aggregate **6b**. Interestingly, the results of this study illustrate that lithiated chiral amine **7**, with simple replacement of the R_2 isopropyl group of **1b** to a methyl group, also forms a 2:2 mixed aggregate. This latter substitution represents a change from valine to alanine as the starting substrate. This observation

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

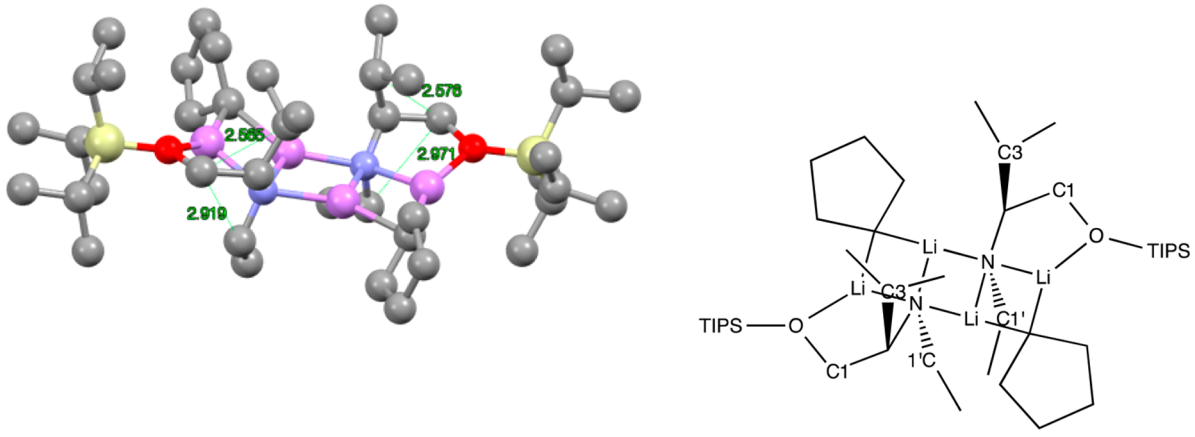
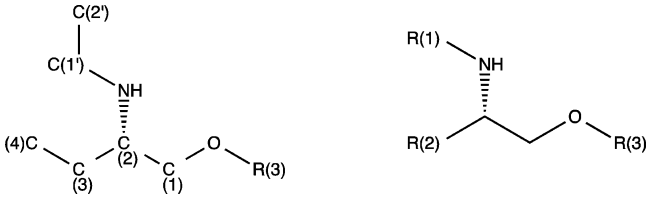


Figure 5. Crystal structure of mixed aggregate **6a**.

prompted us to compare the crystal structures of **2a**[13b] and **6a**[16] more carefully.

As depicted in Figures 4 and 5, the distances from C(3) and C(1′) carbon to C(1) (Scheme 4) in structure **6a** are 2.92 and 2.57 Å, respectively, while the corresponding distances in structure **2a** are 3.74 and 2.54 Å, respectively. Therefore, the steric effect between R_1, R_2 groups and C(1) methylene group is significantly reduced when a 2:1 mixed trimer is formed instead of a 2:2 mixed aggregate. Thus, we propose that the steric bulk of the R_1 and R_2 groups, especially the hindrance on the C(3) and C(1′) carbons, predetermines the formation of 2:2 mixed aggregate or 2:1 mixed trimer. With relatively less hindered R_1 and R_2 groups, lithiated chiral amines **5** and **7** form 2:2 mixed aggregates with *n*-BuLi, while lithiated chiral amines **1a** and **1b** containing relatively hindered R_1 and R_2 groups form 2:1 mixed trimers with *n*-BuLi. To verify our hypothesis, we synthesized and characterized lithiated chiral amine **8**, which has an isobutyl R_2 group and is sterically less hindered than chiral amine **1b** in its C(3) position.

Scheme 4. Numbering and Labeling Scheme of Chiral Amines



Solution State Characterization of the Mixed Aggregates of Lithiated Chiral Amine 8 and *n*-BuLi (12 and 13). Chiral amine **8** was easily synthesized from (*S*)-leucine in three steps. The sample for NMR studies was prepared by titrating (*S*)-*N*-isobutyl-3-methyl-1-((triisopropylsilyl)oxy)-

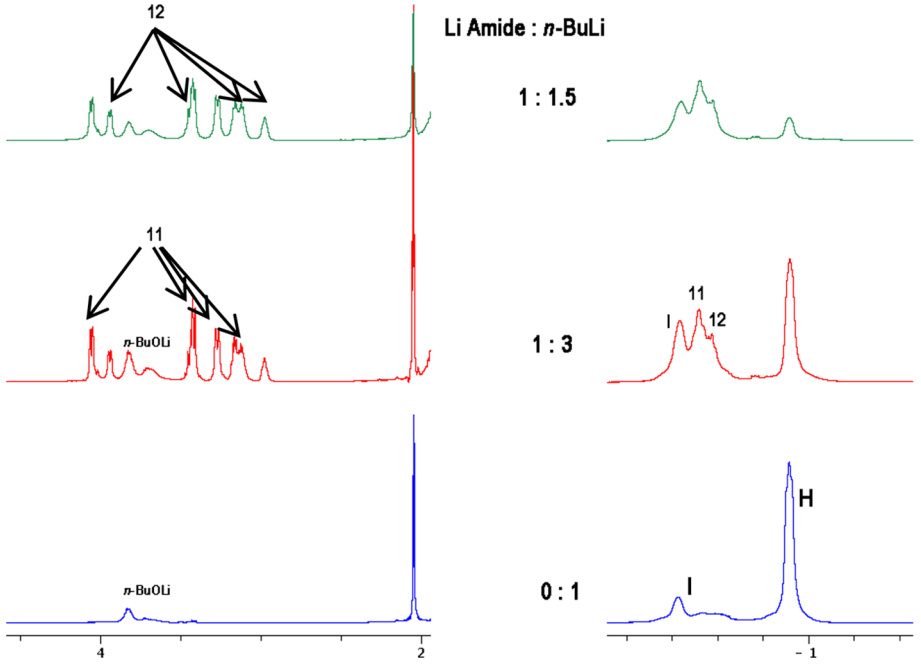


Figure 6. ^{1}H NMR spectra of chiral amine **8** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li in hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 11 represents the resonances of the 2:2 mixed aggregate **11**; 12 represents the resonances of the 2:1 mixed trimer **12**.

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

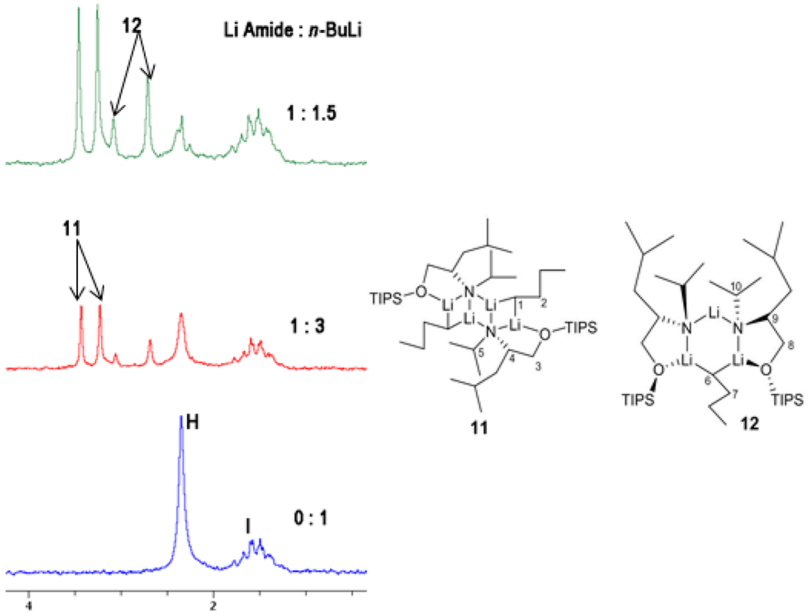


Figure 7. ^{6}Li NMR spectra of chiral amine **8** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li in hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 11 represents the resonances of the 2:2 mixed aggregate **11**; 12 represents the resonances of the 2:1 mixed trimer **12**.

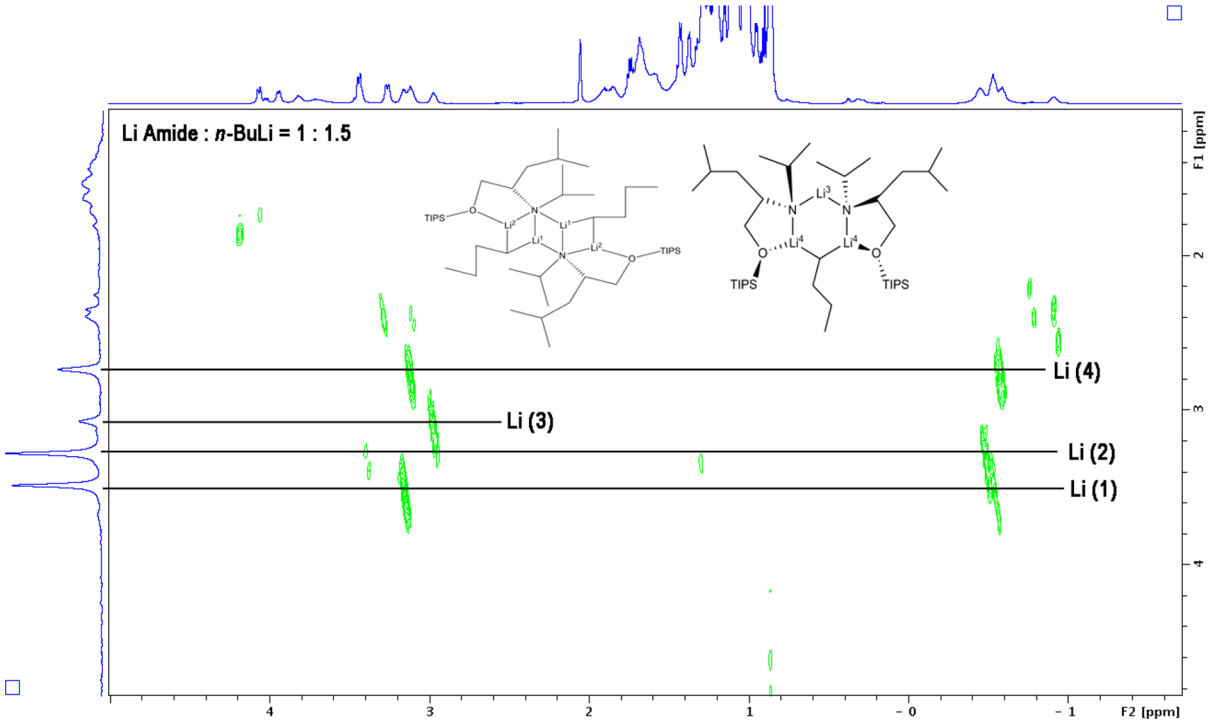


Figure 8. ^{1}H{^{6}Li} HMBC of **11** and **12** in toluene-d_8 at −40 °C.

butan-2-amine **8** into a toluene-d_8 solution of ^{6}Li labeled *n*-butyllithium at −40 °C. The number of peaks is double the number of peaks of nonlithiated chiral amine **8**, implicating the formation of more than one type of lithiated, chiral-amine aggregate, see Figure 6. The ^{6}Li NMR shows very clearly the emergence and rise of two downfield sharp peaks with 1:1 intensity upon addition of chiral amine **8**, as well as two sharp peaks with 1:2 intensity slightly upfield of the 1:1 sharp peaks, see Figure 7. From our previous work,[13,16] we postulate that the 1:1 peaks correspond to 2:2 mixed aggregate **11** and the 1:2 peaks correspond to 2:1 mixed trimer **12** as depicted in Figure 7.

To verify the existence of the putative mixed aggregates **11** and **12**, we obtained the ^{1}H {^{6}Li} HMBC spectrum. As depicted in Figure 8, Li(1) shows a strong correlation to the α-methylene protons of *n*-BuLi (−0.52 ppm) and the proton of the methine (3.16 ppm) group adjacent to nitrogen. Additionally, Li(2) also shows a strong correlation to the α-methylene protons of *n*-BuLi and one of the protons of the methylene (3.42 ppm) group adjacent to oxygen. Moreover, Li(3) shows a

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

strong correlation to the proton of the methine (2.98 ppm) group adjacent to nitrogen while Li(4) shows a strong correlation to the α-methylene protons of *n*-BuLi (−0.58 ppm) and the proton of the methine (3.12 ppm) group adjacent to nitrogen. These results are consistent with Li(1) and Li(2) representing the 2:2 mixed complex **11** between *n*-BuLi and the lithiated chiral amine **8** and Li(3) and Li(4) representing the 2:1 mixed trimer **12**.

A series of ^{1}H and ^{13}C NMR experiments including ^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC confirm the ^{1}H and ^{13}C chemical shift assignments of complexes **11** and **12**.[22] Notably the α-methylene carbon (carbon atom 1) of *n*-BuLi within the mixed aggregate **11** is a quintet (J = 10.2 Hz) at 11.7 ppm (Figure 9). This suggests that C(1) of *n*-BuLi interacts with two ^{6}Li atoms. Moreover, as depicted in Figure 9, the α-methylene carbon (carbon atom 7) of *n*-BuLi within the mixed aggregate **12** at 13.7 ppm is also a quintet (J = 10.4 Hz) as a consequence of the interaction of C(6) with two equivalent ^{6}Li atoms.

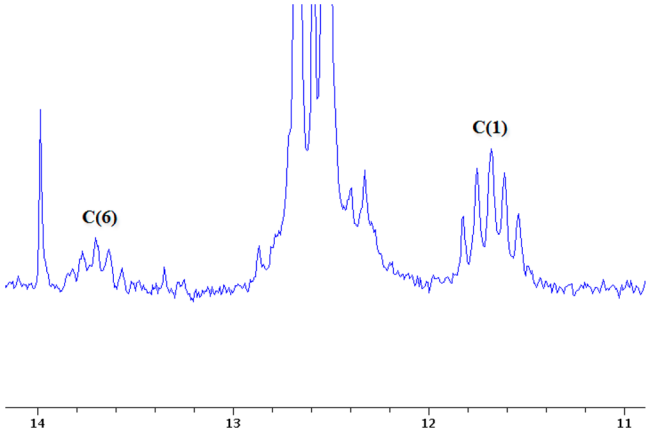


Figure 9. ^{13}C NMR of carbon atoms 1 and 7 of mixed aggregates **11** and **12** in toluene-d_8 at −40 °C.

Four distinct peaks of the two different putative complexes from δ 2.9 to δ 4.1 ppm were utilized for our D-FW analysis because other resonances overlapped. The ^{1}H DOSY spectrum (Figure 10) shows that the putative complexes diffuse considerably slower than squalene, indicating that the formula weights of these complexes are significantly higher than the formula weight of squalene.

This D-FW experiment yields a predicted formula weight of 712 g/mol for the 2:2 mixed aggregate **11** and an average predicted formula weight of 758 g/mol for the mixed aggregate **12**. These results differ by 7.2% from the expected formula weight of the 2:2 mixed aggregate **11** (765.5 g/mol) and 7.7% from the expected formula weight of the 2:1 mixed aggregate **11** (704.4 g/mol). Thus, these D-FW experiments unambiguously define the aggregation state of the species in solution with molecular weights in the range 700−750. However, these D-FW results alone cannot distinguish between the aggregates **11** and **12**.

Taken together, our NMR data support the existence of both 2:2 mixed aggregate **11** and 2:1 mixed trimer **12** between lithiated chiral amine **8** and *n*-BuLi in toluene when the mole ratio of *n*-BuLi to chiral lithium amide **8** is more than 1:1.5.

Solution State Characterization of the Mixed Aggregate of Lithiated Chiral Amine 9 and *n*-BuLi 13 and Homodimer 14. Chiral amine **9** was synthesized from (*R*)-phenylglycine in three steps. Compound **9** is more sterically hindered than chiral amine **8** at the C(3) position. An NMR sample was prepared by titrating (*R*)-*N*-(1-phenyl-2-((triisopropylsilyl)oxy)ethyl)propan-2-amine into a toluene-d_8 solution of ^{6}Li labeled *n*-butyllithium at −40 °C. The number of peaks in the 2.9−4.5 ppm region is double the number of peaks of nonlithiated chiral amine **9**, suggesting that lithiated chiral amine **9** forms more than one type of aggregate, see Figure 11. As depicted in Figure 12, the ^{6}Li NMR also shows

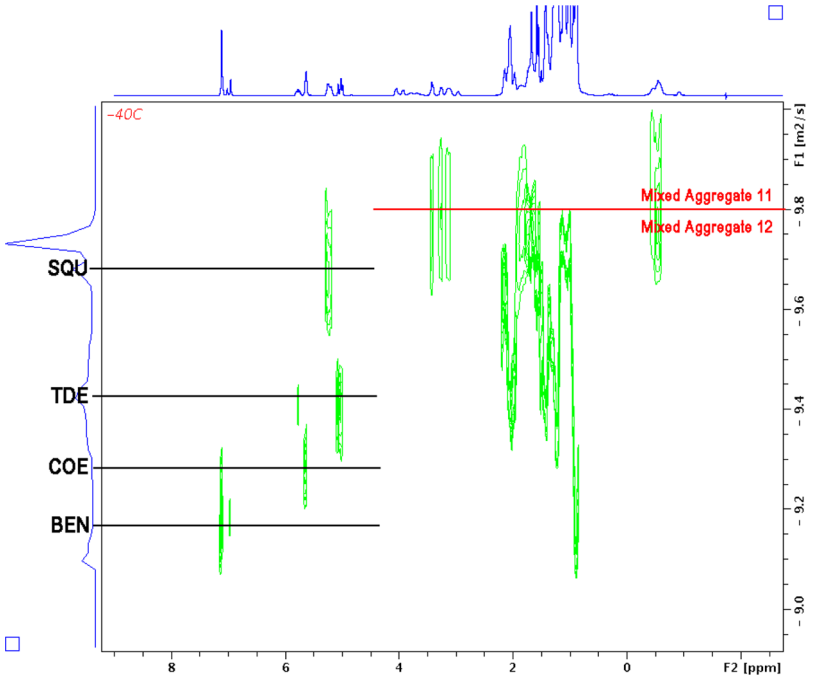


Figure 10. ^{1}H DOSY of mixed aggregates **11** and **12** in toluene-d_8 at −40 °C.

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

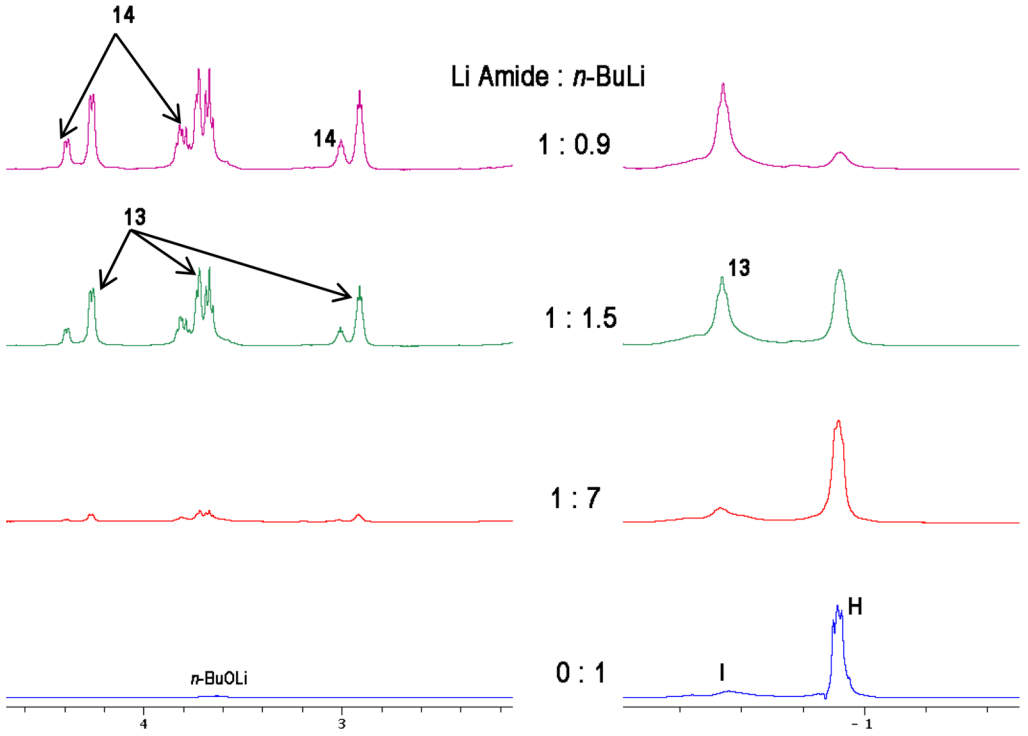


Figure 11. ^{1}H NMR spectra of chiral amine **9** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li in hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 13 represents the resonances of the 2:1 mixed trimer **13**; 14 represents the resonances of homodimer **14**.

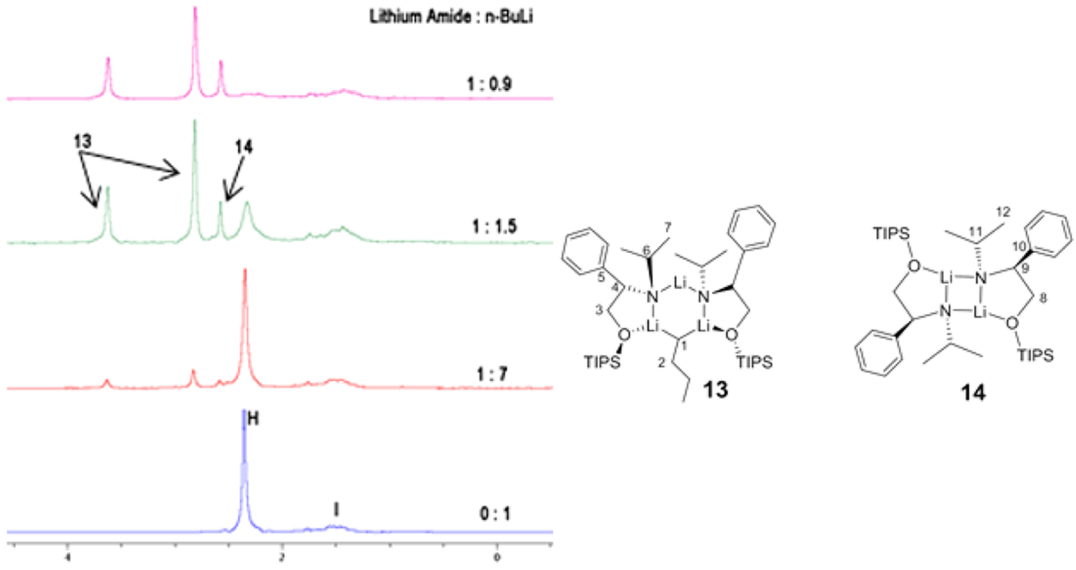


Figure 12. ^{6}Li NMR spectra of chiral amine **9** titration of 0.2 M *n*-Bu^{6}Li toluene-d_8 solution at −40 °C. H represents the resonance of *n*-Bu^{6}Li in hexamer; I represents the resonances of impurities and mixed aggregates of *n*-Bu^{6}Li and *n*-BuO^{6}Li; 13 represents the resonances of the 2:1 mixed trimer **13**; 14 represents the resonances of homodimer **14**.

very clearly the emergence and rise of two sharp peaks with 1:2 intensity upon addition of chiral amine **9**, as well as a minor sharp peak slightly upfield of the 1:2 peaks. These three sharp peaks dominate when the mole ratio of lithiated chiral amine **9** to *n*-BuLi equals 1:0.9. These results are similar to the titration results of chiral amine **1b** with *n*-BuLi.[13,15] Thus, we suggest that the 1:2 peaks correspond to the 2:1 mixed trimer **13** and the minor upfield peak corresponds to the homodimer **14**..

The ^{1}H{^{6}Li} HMBC spectrum (see Figure S32 in Supporting Information) shows a strong correlation from Li(1) to the proton of the methine (4.26 ppm) group adjacent to nitrogen while Li(2) shows a strong correlation to the α-methylene protons of *n*-BuLi and the proton of another methine (2.91 ppm) group adjacent to nitrogen. Meanwhile, Li(3) shows a strong correlation to the proton of methine groups (4.45, 3.07 ppm) adjacent to nitrogen. These results are consistent with the assignment of Li(1) and Li(2) to the 2:1 mixed trimer **13** between *n*-BuLi and the lithiated chiral amine **9** and Li(3) to the homodimer **14**.

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

All assignments of ^{1}H and ^{13}C resonances for aggregates **13** and **14** are summarized in the Supporting Information. As illustrated in Figure 13, the α-methylene carbon (carbon atom 1) of *n*-BuLi of the putative mixed trimer **13** is a quintet (J = 10.1 Hz) at 13.5 ppm. This pattern indicates that carbon atom 1 in *n*-BuLi is *J*-coupled to two ^{6}Li atoms.

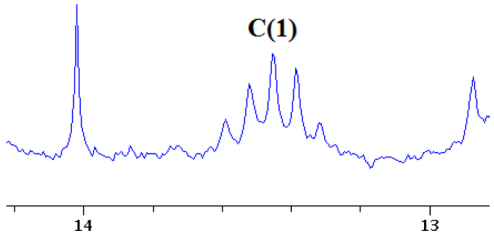


Figure 13. ^{13}C NMR of carbon atoms 1 of mixed trimer **13** in toluene-d_8 at −40 °C.

Diffusion-ordered NMR spectroscopy (Figure 14) and D-FW analysis reveal that the major peaks of the lithiated chiral amine **9** from 2.9 to 4.3 ppm and *n*-butyllithium (−0.54 ppm) diffuse at a very similar rate. The average experimentally determined formula weight for the mixed aggregate **13** is 678 g/mol, an 8.8% difference from the expected formula weight for the 2:1 mixed aggregate **13** (743.4 g/mol). Moreover, the average experimentally determined formula weight for the homodimer **14** is 649 g/mol, a 4.7% difference from the expected formula weight of homodimer **14** (681.2 g/mol). Overall, the combination of all these NMR experiments supports the formation of the 2:1 mixed trimer **13** between lithiated chiral amine **9** and *n*-BuLi, as well as the formation of homodimer **14** in toluene when the mole ratio of *n*-BuLi to chiral lithium amide is more than 1:0.9.

The aggregation states of the mixed complexes between *n*-butyllithium and different lithium chiral amides with various R_1 and R_2 groups are summarized in Table 1. When R_1 and R_2 groups are relatively unhindered, a 2:2 mixed aggregate is the dominant species as with chiral amine **5** and **7**. A 2:1 mixed trimer is observed when the steric hindrance of R_1 and R_2 groups increases. Lithiated chiral amine **8** forms a significant amount of both 2:2 mixed aggregate and 2:1 mixed trimer with *n*-butyllithium. Further increase in the steric hindrance at C(3) position inhibits the formation of 2:2 mixed aggregate; therefore, lithiated chiral amines **1b** and **9** preferably form 2:1 mixed trimers with *n*-butyllithium.

Table 1. Aggregation States of Different Lithium Chiral Amide/*n*-BuLi Complexes

R_1 group	R_2 group	aggregation state
isopropyl	methyl	dominantly 2:2 mixed aggregate
ethyl	isopropyl	dominantly 2:2 mixed aggregate
isopropyl	isobutyl	2:2 mixed aggregate and 2:1 mixed trimer
isopropyl	phenyl	majorly 2:1 mixed trimer
isopropyl	isopropyl	majorly 2:1 mixed trimer

CONCLUSION

The size of R_1 and R_2 groups significantly influences the aggregation state of the mixed complexes between lithiated chiral amines and *n*-BuLi. When the R_1 and R_2 groups are relatively unhindered, a 2:2 mixed aggregate dominants. Increase in the steric hindrance of R_1 and R_2 groups inhibits the formation of this 2:2 mixed aggregate and promotes the formation of the 2:1 mixed trimer.

It is well-established that lithiated *N*-isopropyl-*O*-triisopropylsilyl valinol **1b** forms a 2:1 mixed trimer with *n*-BuLi and that this mixed aggregate is responsible for the enantioselectivity of asymmetric addition of *n*-BuLi in the mixed aggregate to aldehydes.[17] Hence, knowledge of the aggregation state of

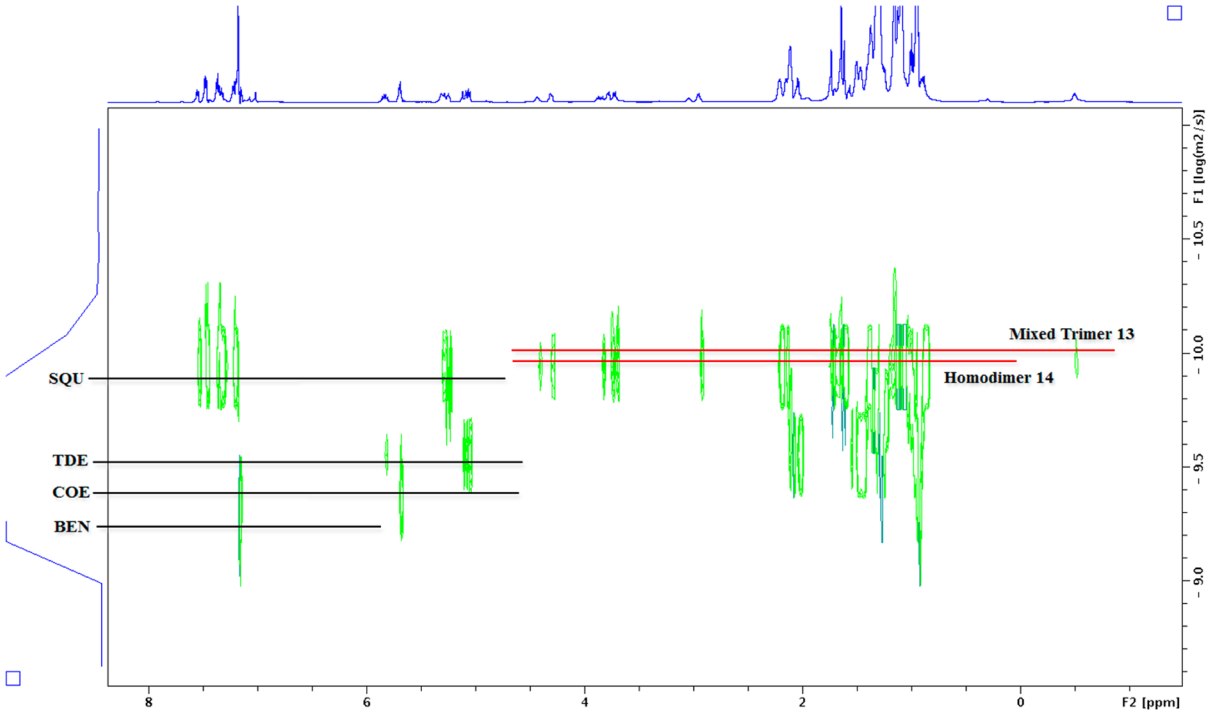


Figure 14. ^{1}H DOSY of mixed trimer **13** and homodimer **14** in toluene-d_8 at −40 °C.

dx.doi.org/10.1021/ja4123957 | J. Am. Chem. Soc. 2014, 136, 3246−3255

mixed aggregates is crucial in unveiling the origin of the enantioselectivity of chiral lithium amides. Moreover, the ability to predict the formation of different mixed aggregates enables us to design chiral amines with desired enantioselectivity most efficiently. Extensive work on both enantioselectivity and mechanism of the asymmetric addition of the alkyllithium moiety to electrophiles using these chiral lithium amide/alkyllithium mixed aggregates to various electrophiles is in progress.

EXPERIMENTAL SECTION

Procedures for NMR Experiments. NMR samples were prepared in tubes sealed with rubber septa caps 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. DOSY experiments were acquired on a 600 or 400 MHz spectrometer equipped with a *z*-axis gradient amplifier with a *z*-axis gradient coil. Maximum gradient strength was 0.5 T/m and 0.214 T/m, respectively. ^{1}H DOSY was performed using the standard programs, employing a double stimulated echo sequence, bipolar gradient pulses for diffusion, and 3 spoil gradients. Diffusion time was 200 ms, and the rectangular gradient pulse duration was 700 μs (lithiated chiral amine **8**) and 1000 μs (lithiated chiral amine **7** and **9**). 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 ^{6}Li labeled *n*-butyllithium samples were prepared by laboratory synthesized ^{6}Li labeled *n*-butyllithium heptane solution. About 40 μL of the 2.4 M *n*-butyllithium heptane 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 in order to remove the heptane. After filling with argon, toluene-d_8 was added via syringe to bring the total volume up to 500 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 same as the α-methylene protons of *n*-BuLi for lithiated chiral amine **7**, about 0.67 times the intensity as the α-methylene protons of *n*-BuLi for lithiated chiral amine **8** and about 1.5 times the intensity as the α-methylene protons of *n*-BuLi for lithiated chiral amine **9**.

Synthesis of (*S*)-*N*-Isopropyl-1-((triisopropylsilyl)oxy)-propan-2-amine 7. The synthetic route of chiral amine **7** started from enantiomerically pure (*S*)-alanine. The *N*-isopropyl alanine was prepared according to Ohfune's method.[24] The *N*-isopropyl alanine was then reduced by lithium aluminum hydride in anhydrous tetrahydrofuran to *N*-isopropyl alaninol. Chiral amine **7** was prepared as follows: To a solution of *N*-isopropyl alaninol (2.20 g, 18.8 mmol) and triethylamine (10.5 mL, 37.5 mmol) in 60 mL of CH_2Cl_2 was added slowly triisopropylsilyl triflate (6.34 g, 23.5 mmol) at 0 °C. The resulting solution was allowed to stir at room temperature for 4 h before quenching with 25 mL of 2 M $NaHCO_3$. The mixture was extracted with 30 mL of EtOAc three times, and the combined organic phase was washed by 20 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 = 115 °C, 5 mm Hg) gave a colorless oil (4.12 g, 15.1 mmol, 80.2%). ^{1}H NMR (Tol-d_8, 400 MHz) δ 3.57−3.45 (m, 2H), 2.91−2.78 (m, 2H), 1.14−1.04 (m, 21H), 1.04−0.97 (m, 10H). ^{13}C NMR (Tol-d_8, 100 MHz) δ 68.8, 52.5, 46.2, 24.8, 23.7, 18.7, 18.6, 12.8. HRMS-ESI *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{36}NOSi$, 274.2561; found, 274.2564.

Synthesis of (*S*)-*N*-Isopropyl-1-((triisopropylsilyl)oxy)-propan-2-amine 8. (*S*)-*N*-Isobutyl-3-methyl-1-((triisopropylsilyl)-oxy)butan-2-amine **8** was synthesized using the same method described above from *N*-isopropyl (*S*)-leucinol (1.70 g, 10.7 mmol). Purification (bp = 132 °C, 5 mm Hg) gave a colorless oil (2.77 g, 8.77 mmol, 82.0%). ^{1}H NMR (Tol-d_8, 400 MHz) δ 3.65 (dd, 1H, J = 4.7, 9.5 Hz), 3.51 (dd, 1H, J = 4.4, 9.5 Hz), 2.92 (septet, 1H, J = 6.2 Hz), 2.70 (m, 1H), 1.83 (m, 1H), 1.41−1.29 (m, 2H), 1.13−1.00 (m, 28H), 0.99−0.92 (m, 6H). ^{13}C NMR (Tol-d_8, 100 MHz) δ 66.4, 54.8, 46.1, 43.3, 25.5, 24.7, 24.1, 24.0, 23.4, 18.7, 12.8. HRMS-ESI *m*/*z*: $[M + H]^+$ calcd for C18H42NOSi, 316.3036; found, 316.3035.

Synthesis of (*R*)-*N*-(1-Phenyl-2-((triisopropylsilyl)oxy)ethyl)-propan-2-amine 9. (*R*)-*N*-(1-Phenyl-2-((triisopropylsilyl)oxy)-ethyl)propan-2-amine **8** was synthesized using the same method described above from *N*-isopropyl (*R*)-phenylglycinol (2.40 g, 13.4 mmol). Purification (bp = 163 °C, 5 mm Hg) gave a colorless oil (3.58 g, 10.7 mmol, 79.6%). ^{1}H NMR (Tol-d_8, 400 MHz) δ 7.44 (d, 2H, J = 7.28 Hz), 7.24−7.10 (m, 3H), 3.99 (dd, 1H, J = 4.1, 8.9 Hz), 3.74 (dd, 1H, J = 4.1, 9.6 Hz), 3.71−3.59 (m, 1H), 2.71 (septet, 1H, J = 6.28 Hz), 1.75 (br, 1H), 1.12−0.97 (m, 27H). ^{13}C NMR (Tol-d_8, 100 MHz) δ 143.1, 128.9, 128.5, 127.9, 70.0, 63.8, 47.0, 25.2, 22.9, 18.6, 12.7. HRMS-ESI *m*/*z*: $[M + H]^+$ calcd for $C_{20}HNOSi$, 336.2723; found, 336.2715.

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.[15]

ASSOCIATED CONTENT

Supporting Information

Supplemental NMR spectra and data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

pgw@brown.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported through NSF Grant 1058051. We thank Mr. Chang Liu for synthesizing the chiral amines used in this study.

REFERENCES

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991. (c) Lucht, B.; Collum, D. *Acc. Chem. Res.* **1999**, *32*, 1035−1042. (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002. (e) Hodgson, D. *Organolithiums in Enantionselective Synthesis*; Springer: New York, 2003. (f) *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons, Ltd.: West Sussex, U.K., 2004. (g) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596−2616. (h) Collum, D.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002−3017.

(2) (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755−756. (b) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *45*, 5187−5190. (c) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543−545. (d) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523−544. (e) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108−6113. (f) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519−1523. (g) Simpkins, N. S.; Hume, S. C. *J. Org. Chem.* **1998**, *63*, 912−913. (h) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266−8275. (i) Matsuo, J.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345−348. (j) Arvidsson, P. I.; Davidsson, O.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527−534. (k) De Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron* **2002**, *58*, 4643−4654. (l) Flinois, K.; Yuan, Y.; Bastide, C.; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707−4716. (m) Rodeschini, V.; Simpkins, N. S.; Wilson, C. *J. Org. Chem.* **2007**, *72*, 4265−4267.

(n) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936−11939.
(3) (a) Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 337−338. (b) Uragami, M.; Tomioka, K.; Koga, K. *Tetrahedron: Asymmetry* **1995**, *6*, 701−704.
(4) (a) Ma, Y.; Stivala, C. E.; Wright, A. W.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 16853−16864. (b) Gruver, J. M.; West, S. P.; Collum, D. B.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 13212−13213. (c) Ramirez, A.; Sun, X. F.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326−10336. (d) 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. (e) Zhao, P. J.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008−4009. (f) Sun, X. F.; Winemiller, M. D.; Xiang, B. S.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039−8046. (g) Briggs, T. F.; Winemiller, M. D.; Xiang, B. S.; Collum, D. B. *J. Org. Chem.* **2001**, *66*, 6291−6298. (h) 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.
(5) (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. (d) Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175−179.
(6) (a) Prigent, Y.; Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Duhamel, P.; Davoust, D. *J. Chim. Phys. Phys.-Chim. Biol.* **1998**, *95*, 401−405. (b) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266−8275. (c) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042−10048.
(7) (a) Granander, J.; Sott, R.; Hilmersson, G. *Chem.—Eur. J.* **2006**, *12*, 4191−4197. (b) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021−2027. (c) Sott, R.; Granander, J.; Williamson, C.; Hilmersson, G. *Chem.—Eur. J.* **2005**, *11*, 4785−4792. (d) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798−6805. (e) Sott, R.; Granander, J.; Diner, P.; Hilmersson, G. *Tetrahedron: Asymmetry* **2004**, *15*, 267−274. (f) Sott, R.; Granander, J.; Hilmersson, G. *Chem.—Eur. J.* **2002**, *8*, 2081−2087. (g) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717−4725. (h) Arvidsson, P. I.; Ahlberg, P.; Hilmersson, G. *Chem.—Eur. J.* **1999**, *5*, 1348−1354.
(8) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805−1810.
(9) (a) Oulyadi, H.; Fressigne, C.; Yuan, Y.; Maddaluno, J.; Harrison-Marchand, A. *Organometallics* **2012**, *31*, 4801−4809. (b) Pate, F.; Duguet, N.; Oulyadi, H.; Harrison-Marchand, A.; Fressigne, C.; Valnot, J.-Y.; Lasne, M.-C.; Maddaluno, J. *J. Org. Chem.* **2007**, *72*, 6982−6991. (c) 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. (d) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigne, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *61*, 3325−3334. (e) 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.
(10) Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492−3493.
(11) (a) Strohmann, C.; Dilsky, S.; Strohfeldt, K. *Organometallics* **2006**, *25*, 41−44. (b) Strohmann, C.; Abele, B. C. *Organometallics* **2000**, *19*, 4173−4175.
(12) (a) Thomas, R. D.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 11239−11240. (b) DeLong, G. T.; Hoffmann, D.; Nguyen, H. D.; Thomas, R. D. *J. Am. Chem. Soc.* **1997**, *119*, 11998−11999. (c) DeLong, G. T.; Pannell, D. K.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1993**, *115*, 7013−7014.
(13) (a) Li, D.; Sun, C.; Liu, J.; Hopson, R.; Li, W.; Williard, P. G. *J. Org. Chem.* **2008**, *73*, 2373−2381. (b) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693−11694.
(14) (a) Li, D.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 11726−11736. (b) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829−7830.
(15) Kagan, G.; Li, W.; Li, D.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2011**, *133*, 6596−6602.
(16) Su, C.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2013**, *135*, 14367−14379.
(17) (a) Liu, J.; Li, D.; Sun, C.; Williard, P. G. *J. Org. Chem.* **2008**, *73*, 4045−4052. (b) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717−4725. (c) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021−2027. (d) Arvidsson, P. I.; Hilmersson, G.; Davidsson, O. *Chem.−Eur. J.* **1999**, *5*, 2348−2355. (e) Ronnholm, P.; Sodergren, M.; Hilmersson, G. *Org. Lett.* **2007**, *9*, 3781−3783. (f) Sott, R.; Granander, J.; Williamson, C.; Hilmersson, G. *Chem−Eur. J.* **2005**, *11*, 4785−4792. (g) Sott, R.; Granander, J.; Hilmersson, G. *Chem.−Eur. J.* **2002**, *8*, 2081−2087.
(18) (a) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. . *J. Am. Chem. Soc.* **1992**, *114*, 761−763. (b) Arvidsson, P. I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* **1999**, *121*, 1883−1887. (c) Lecachey, B.; Duguet, N.; Oulyadi, H.; Fressigne, C.; Harrison-Marchand, A.; Yamamoto, Y.; Tomioka, K.; Maddaluno, J. *Org. Lett.* **2009**, *11*, 1907−1910.
(19) Mongin, F.; Harrison-Marchand, A. *Chem. Rev.* **2013**, *113*, 7563.
(20) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664−4670.
(21) Su, C.; Hopson, R.; Williard, P. G. *Eur. J. Inorg. Chem.* **2013**, *24*, 4136−4141.
(22) For miscellaneous NMR spectra including ^{1}H NMR, ^{6}Li NMR, ^{13}C NMR, COSY, HSQC, ^{1}H{^{6}Li} HMBC and ^{1}H{^{13}C} HMBC, please see Supporting Information.
(23) (a) Li, D.; Hopson, R.; Li, W.; Liu, J.; Williard, P. G. *Org. Lett.* **2008**, *10*, 909−911. (b) Li, D.; Kagan, G.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 5627−5634. (c) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270−280. (d) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2009**, *11*, 4818−4821. (e) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2010**, *12*, 520−523. (f) Li, W.; Kagan, G.; Yang, H.; Cai, C.; Hopson, R.; Sweigart, D. A.; Williard, P. G. *Org. Lett.* **2010**, *12*, 2698−2701. (g) Li, W.; Kagan, G.; Yang, H.; Cai, C.; Hopson, R.; Dai, W.; Sweigart, D. A.; Williard, P. G. *Organometallics* **2010**, *29*, 1309−1311. (h) Socha, A. M.; Kagan, G.; Li, W.; Hopson, R.; Sello, J. K.; Williard, P. G. *Energy Fuels* **2010**, *24*, 4518−4521. (i) Kagan, G.; Li, W.; Sun, C.; Hopson, R.; Williard, P. G. *J. Org. Chem.* **2011**, *76*, 65−70. (j) Lecachey, B.; Oulyadi, H.; Lameiras, P.; Harrison-Marchand, A.; Gerard, H.; Maddaluno, J. *J. Org. Chem.* **2010**, *75*, 5976−5983. (k) Consiglio, G. B.; Queval, P.; Harrison-Marchand, A.; Mordini, A.; Lohier, J.; Delacroix, O.; Gaumont, A.; Gerard, H.; Maddaluno, J.; Oulyadi, H. *J. Am. Chem. Soc.* **2011**, *133*, 6472−6480. (l) Armstrong, D. R.; Garcia-Alvarez, P.; Kennedy, A. R.; Mulvey, R. E.; Robertson, S. D. *Chem.—Eur. J.* **2011**, *17*, 6725−6730.
(24) Ohfune, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Chem. Lett.* **1984**, *13*, 441−444.