

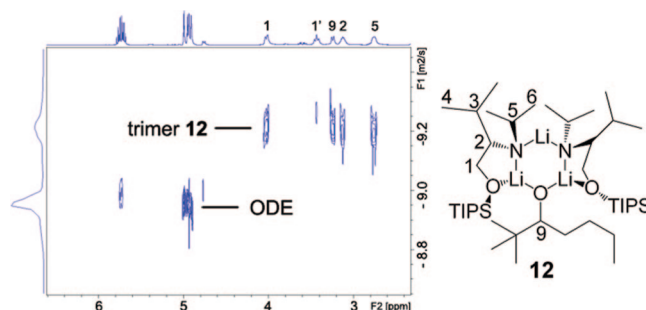
Analysis of an Asymmetric Addition with a 2:1 Mixed Lithium Amide/*n*-Butyllithium Aggregate

Jia Liu, Deyu Li, Chengzao Sun, and Paul G. Williard*

Department of Chemistry, Brown University, Providence, Rhode Island 02912

pgw@brown.edu

Received March 18, 2008



A 2:1 lithium amide/*n*-butyllithium aggregate **1** is investigated as an asymmetric addition template in hydrocarbon solvents. Several different chiral lithium amides were synthesized from L-valine and tested in the asymmetric addition of *n*-BuLi to various aldehydes. Enantiomeric excesses up to 83% were obtained in the case of the addition of *n*-BuLi to pivaldehyde at $-116\text{ }^{\circ}\text{C}$ in pentane. ^1H and ^{13}C INEPT DOSY were utilized to characterize a new trimeric complex **12** between 2 equiv of lithium amide and 1 equiv of lithium alkoxide. This mixed aggregate strongly indicates the possibility of product-induced chirality inhibition that is detrimental to the enantioselectivity of asymmetric addition reaction.

Introduction

Asymmetric addition of organometallic reagents to aldehydes allows for construction of chiral alcohols.¹ Reactions involving Grignard reagents, organozinc, and other organotransition metal reagents have been extensively investigated by others.^{1,2} However, the use of alkyllithium reagent complexes in chiral C–C bond formation is limited because of their high reactivity, their propensity to form aggregates, and the relatively modest enantioselectivity reported to date. Previous work in this area has been focused on the efficiency of various polydentate chiral

amine ligands, which form mixed aggregates with organolithium reagents.^{2g,3} The aggregates are assumed responsible for chiral induction when organolithium reagents add to aldehydes.

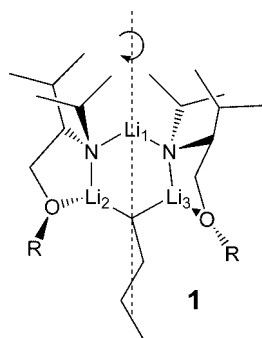
We and others have observed that lithium aggregates are strictly solvent dependent and undergo dynamic processes in solution.^{3–5} For example, in ethereal solvents a variety of ligands yield high enantioselectivities over 90% enantiomeric excess (ee) for asymmetric butylation of benzaldehyde.^{3f,g,i} However,

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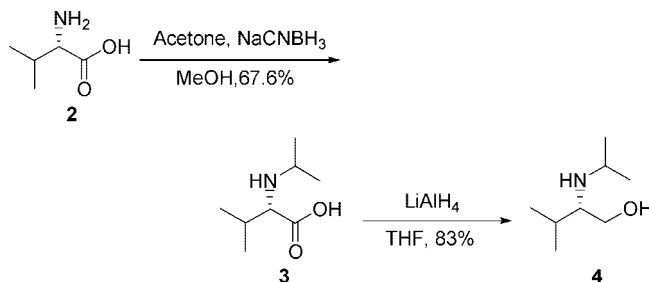
SCHEME 1. Mixed Trimeric Complex 1 between 2 equiv of Lithium Amide and 1 equiv of *n*-BuLi


much less is known about their chiral induction potential in hydrocarbon solvent. Hence, we analyzed the asymmetric induction potential of lithium aggregate in the absence of coordinating solvent.

In 1997 we reported a mixed trimeric complex **1** (Scheme 1) containing 1 equiv of *n*-butyllithium (*n*-BuLi) and 2 equiv of lithium amide.^{4a} Crystallization^{4a} combined with diffusion-ordered NMR spectroscopy (DOSY) studies⁶ indicated that it is the major species in hydrocarbon solvent. This prompted us to explore the chiral induction potential of the mixed trimers with various lithium amides derived from *L*-valine. These natural amino acid derivatives have been shown to form a 1:1 mixed dimer with *n*-BuLi in ethereal solvent and the enantioselective addition reactions have been intensively studied.^{3f,g,i} In contrast, little attention has been devoted to the 2:1 trimer in hydrocarbon solvent and its capability for asymmetric induction. In this paper we wish to report results of enantioselective addition using the trimeric aggregate **1** as the asymmetric template. We also demonstrate a product-induced chirality inhibition phenomenon^{3i,7,8} by DOSY experiments.

Results and Discussion

Synthesis of Chiral Amino Ether Ligands. The synthetic route we adopted to prepare chiral amino ether ligands started from enantiomerically pure *L*-valine **2** (Scheme 2). The amino group condensed with acetone to afford the corresponding imine, and subsequently reduced with sodium cyanoborohydride to

SCHEME 2. Synthesis of Amino Alcohol 4


yield product **3**.⁹ The *N*-isopropyl valine **3** was then reduced to the desired amino alcohol **4** with lithium aluminum hydride as depicted in Scheme 2.¹⁰

From amino alcohol **4**, two paths were developed to synthesize the chiral ligands (Scheme 3). In the first route, the amino alcohol **4** was deprotonated by being refluxed with sodium hydride in THF for 18 h, before it reacted with methyl iodide or *n*-butyl bromide. The reflux was necessary to avoid *N*-alkylation byproducts. The resulting **5** and **6** were easily purified by flash chromatography followed by distillation.

In the second synthetic route (Scheme 3), ligand **7** was prepared from amino alcohol **4** by using *tert*-butyldimethylsilyl chloride and imidazole. Ligand **8** was synthesized in a similar route with triisopropylsilyl triflate as a silylating reagent and triethylamine as a base.

Asymmetric Addition of *n*-BuLi to Aldehydes. The amino ethers **5–8** were then utilized as chiral ligands in the addition reaction of *n*-BuLi to benzaldehyde and pivaldehyde to evaluate their ability for chiral induction. We surveyed all ligands individually in either toluene or pentane. To a solution of 1 equiv of each pure ligand at $-78\text{ }^{\circ}\text{C}$, 1.45 equiv of *n*-BuLi was added dropwise to form the complex **1**. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ for 20 min before it was cooled again to $-78\text{ }^{\circ}\text{C}$. After the solution equilibrated for 30 min, a solution of aldehyde was added either all at once or slowly via a syringe pump. The reaction was quenched 1 h after addition of aldehyde with methanol and saturated aqueous ammonium chloride. Purified product alcohol was analyzed by chiral stationary-phase GC. The results are summarized in Table 1.

The chiral lithium amide ligands effected moderate to good enantioselectivities. Comparison of entry 1 to 2 and entry 3 to 4 showed that the enantioselectivity is generally lower in toluene. Therefore, the remaining experiments were carried out in pentane. Entries 4, 5, 6, and 7 illustrated that relative size of

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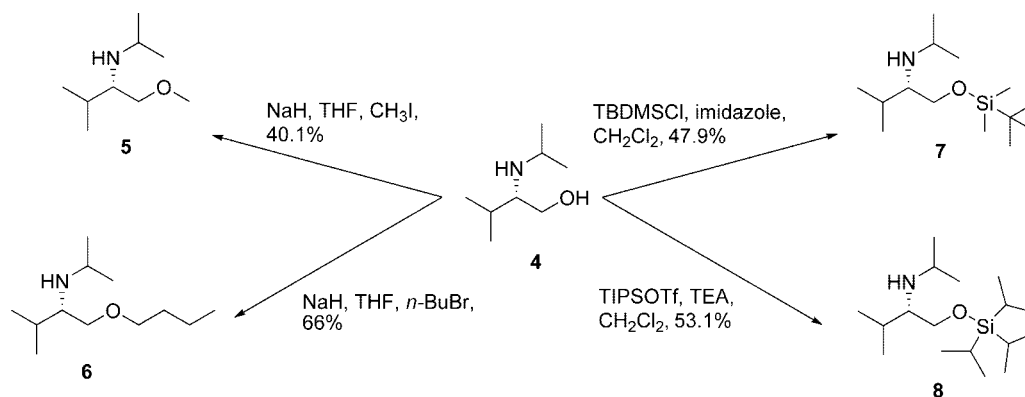
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SCHEME 3. Synthesis of Chiral Amino Ether Ligand 5–8

TABLE 1. Asymmetric Alkylation of Aldehydes with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ in the Presence of Chiral Lithium Amides

entry	ligand/ R_1	R	solvent	ee (%)
1	8/TIPS	Ph	toluene	45 ^a (S)
2	8/TIPS	Ph	pentane	60 ^a (S)
3	8/TIPS	<i>tert</i> -butyl	toluene	48 ^b (S)
4	8/TIPS	<i>tert</i> -butyl	pentane	75 ^b (S)
5	7/TBDMS	<i>tert</i> -butyl	pentane	54 ^b (S)
6	5/methyl	<i>tert</i> -butyl	pentane	6 ^b (R)
7	6/ <i>n</i> -butyl	<i>tert</i> -butyl	pentane	25 ^b (R)

^a Product ee was determined by Mosher's ester method. ^b Product ee was determined by chiral GC, using a CP-Chirasil-DEX CB column.

the substituent on oxygen in ligands **5**–**8** affects not only enantioselectivity, but also surprisingly the configuration of the addition product. Ligands **7** and **8** yielded a carbinol product with S configuration, while ligands **5** and **6** gave the carbinol with the enantiomeric R configuration. Amino silyl ether **8** provided the best ee value (entry 4, 75% ee) among the four ligands compared in this reaction. These results highlight that these amino ether ligands are highly adaptable for configuration differentiation. Although they are all derived from the same precursor L-valinol **4**, different protecting groups on the alcohol yield totally reverse enantiomeric configuration in the products.

Because the reactions involving ligand **8** yielded the highest ee value in hydrocarbon solvent among all the ligands **5**–**8**, we then turned our attention to the asymmetric additions of *n*-BuLi to various aldehydes in the presence of ligand **8**. These results are summarized in Table 2.

In these addition reactions, enantiomeric excesses up to 83% were observed and yields were moderate to good. The influence of temperature is apparent that better ee is achieved by lowering the temperature. Hence, the highest ee was obtained in the asymmetric addition on pivaldehyde at $-116\text{ }^{\circ}\text{C}$ (Table 2, entry 5). We found ee is also sensitive to the rate of addition of aldehyde to the preformed lithium complex **1** solution. When 0.22 mmol of pivaldehyde solution in 3 mL of pentane was added slowly into the reaction mixture via a syringe pump at $-116\text{ }^{\circ}\text{C}$, the reaction yielded a low ee of 76% (Table 2, entry 4). However, when 0.22 mmol of pivaldehyde in 0.4 mL of pentane was added all at once at the same temperature, the ee went up to 83% (Table 2, entry 5). In contrast, when 2-fural-

TABLE 2. Asymmetric Alkylation of Aldehydes with *n*-BuLi in the Presence of the Chiral Ligand **8**

entry	R	temp ($^{\circ}\text{C}$)	ee ^a (%)	yield (%)
1	Ph	-78	61 ^b	96
2	Ph	-116	76 ^b	88
3	<i>t</i> -butyl	-78	79 ^b	60
4	<i>t</i> -butyl	-116	76 ^b	— ^d
5	<i>t</i> -butyl	-116	83 ^c	62
6	2-furyl	-78	59 ^b	65
7	2-furyl	-78	50 ^c	— ^d
8	2-furyl	-116	74 ^b	79
9	2-furyl	-116	70 ^c	— ^d

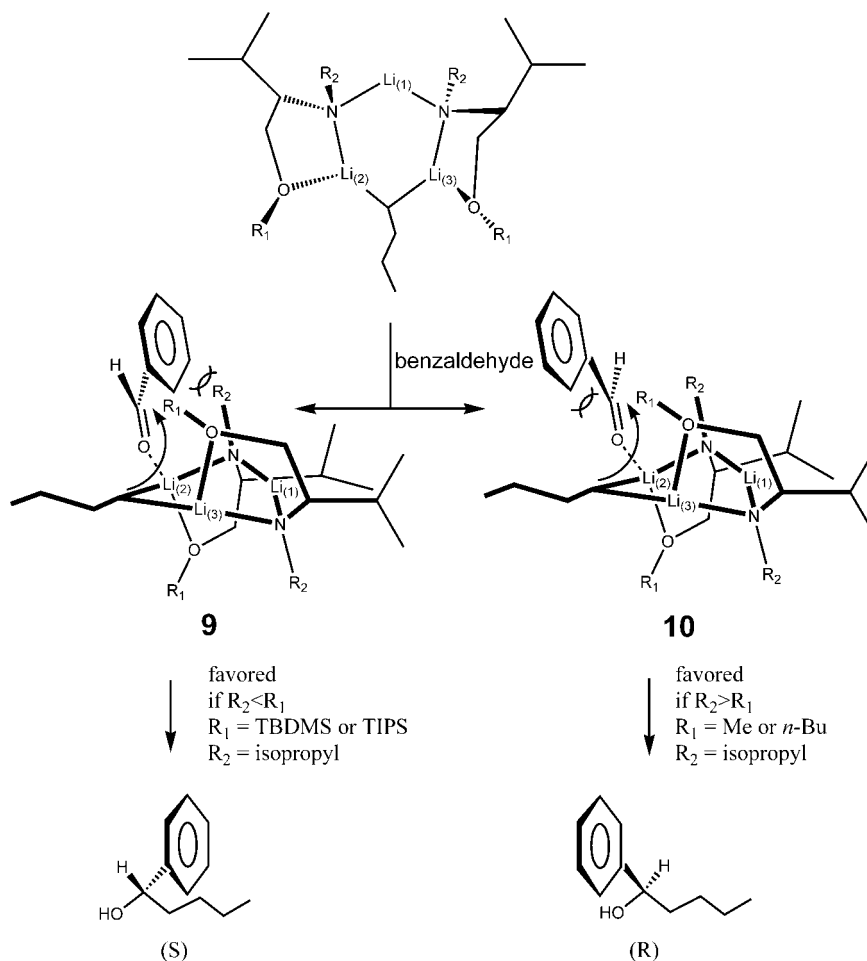
^a Product ee was determined by chiral GC, using a CP-Chirasil-DEX CB column. ^b Aldehyde solution was injected slowly into the cold reaction mixture via syringe pump over 1 h. ^c Aldehyde solution was injected into the cold reaction mixture all at once. ^d Yield was not determined.

dehyde was added to complex **1** at -78 and $-116\text{ }^{\circ}\text{C}$, addition all at once yielded lower ee (50% and 70% ee, respectively, Table 2, entries 7 and 9) than slow addition of the aldehyde to the lithium complex (59% and 74% ee respectively, Table 2, entries 6 and 8).

We noticed solvent variation (toluene versus pentane) and temperature change (-78 versus $-116\text{ }^{\circ}\text{C}$) yield consistent ee changes. However, the inconsistent observations in ee for the addition rate led us to suspect that product-induced chirality inhibition by an aggregate including the lithium alkoxide product might be responsible for the unpredictable chiral inductions.^{7,8}

We further reasoned that the asymmetric butylation is probably not a catalytic reaction due to the following observations. Under stoichiometric conditions, i.e., preformation of the 2:1 complex **1** (6.8 equiv of *n*-BuLi, 5 equiv of amine **8** and 1 equiv of pivaldehyde, Table 2, entry 3) at $-78\text{ }^{\circ}\text{C}$, all *n*-BuLi is incorporated into the trimeric complex **1** with lithium amide and 79% ee was obtained. Under nonstoichiometric conditions (10 equiv of *n*-BuLi, 5 equiv of amine **8** and 1 equiv of pivaldehyde), 2.5 equiv of trimeric complex **1** and 2.5 equiv of uncomplexed *n*-butyllithium coexist in the solution and the ee decreased to 38%. This result indicates that the racemic addition by uncomplexed *n*-BuLi competes favorably with the addition

SCHEME 4. Proposed Models of Asymmetric Induction



of mixed chiral complex **1** to aldehydes. Hence, a stoichiometric quantity of the chiral complex **1** is required to achieve the highest ee.

On the basis of the published crystal structure^{4a} and results from the chiral butylation reactions reported in this paper, we propose a model to explain the origin of chiral induction as depicted in Scheme 4. After formation of the mixed aggregate **1** in hydrocarbon solvent, the carbonyl oxygen of the added electrophilic aldehyde can coordinate to either Li_2 or Li_3 , but not to the more Lewis-acidic Li_1 because of the extreme steric hindrance generated by the four isopropyl groups. The crystal structure of **1** clearly shows the pocket of Li_1 is not big enough for binding the aldehyde. Upon coordination, steric hindrance occurs between the R group in aldehyde and either the R_1 group on oxygen or isopropyl moiety on nitrogen. If R_1 is bulkier (such as TBDMS and TIPS) than the R_2 -isopropyl group, model **9** is favored; if R_1 is smaller (such as Me and *n*-Bu group) than the isopropyl group, model **10** is favored. In cases of ligands Li-5 and Li-6, model **10** is favored and leads to secondary alcohol with enrichment in R configuration. In cases of Li-7 and Li-8, aldehydes will orient the R groups toward the smaller isopropyl moiety and the product will be mostly S enantiomer.

Comparing model **9** and model **10**, we notice the following differences. If R_1 equals Me or *n*-Bu group, the size difference between isopropyl and Me or *n*-Bu group is fairly small thus yielding lower ee of the R enantiomer. On the contrary, if R_1 equals TBDMS or TIPS, the size difference between the isopropyl group and these two silyl protecting groups is much

more significant than the previous case. Under these circumstances, the S enantiomer products yield a much higher ee than the R enantiomers. Since the TIPS group is the bulkiest group among the four and also displays the largest size difference, it produces the highest ee among all entries (Table 2, entry 5).

NMR Investigation of Product-Induced Chirality Inhibition. ¹H NMR Chemical Shift Changes. In 1997^{4a} and 2000^{4b} we reported a series of mixed trimeric crystal structures containing 2 equiv of lithium amide and 1 equiv of *n*-BuLi, *s*-BuLi, *t*-BuLi, or lithium enolate. On the basis of these structures, we suspect the initial addition product, i.e., the lithium alkoxide, should also become incorporated into a similar trimeric aggregate such as complex **12** in Figure 1.

We performed the following NMR experiments to investigate this possibility. In ¹H NMR spectra, protons 1, 1', 2, and 5 of the ligand **8** and proton 9 of the addition product **11** are clearly separable from other proton signals (see Figure 1). We utilized these five peaks as the fingerprints to monitor the ¹H NMR variation between different species. When 1.5 equiv of *n*-BuLi is added to a mixture of 1 equiv of ligand **8** and 0.5 equiv of alcohol **11** in toluene-*d*₈, the proton of the secondary amine in ligand **8** and the proton of the hydroxyl group in alcohol **11** are completely deprotonated. To verify this, we monitor the following chemical shift: δ 4.04, 3.45, 3.15, and 2.78 ppm for protons 1, 1', 2, and 5 on lithium amide respectively, and δ 3.27 ppm for the proton on carbon 9 in lithium alkoxide (see Figure 1a, Table 3). Also the ¹H NMR integration of complex **12** shows a 2:1 ratio between the lithium amide and the lithiated

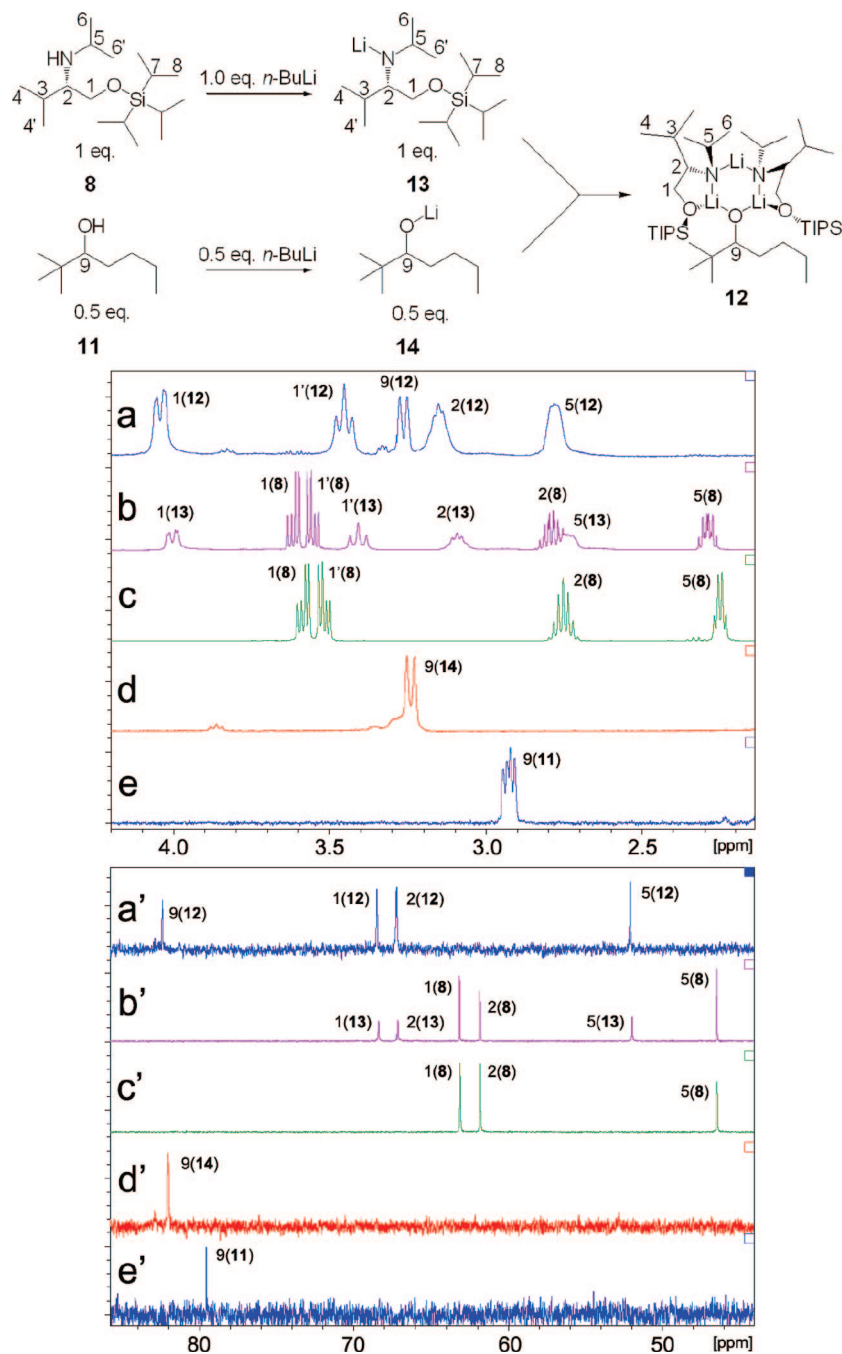


FIGURE 1. ^1H and ^{13}C chemical shift changes: (a–e) ^1H NMR spectra; (a'–e') ^{13}C NMR spectra; (a/a') trimer **12**; (b/b') ligand **8** plus lithium amide **13**; (c/c') ligand **8**; (d/d') lithium alkoxide **14**; (e/e') alcohol **11**.

TABLE 3. ^1H and ^{13}C NMR Chemical Shifts of Components Related to Complex **12**

spectra/compds	^1H NMR chemical shifts	^{13}C NMR chemical shifts
a/a': complex 12	4.04 (d), ^a 3.45 (t), ^a 3.27 (d), ^b 3.15 (br), ^a 2.78 (br) ^a	82.4, ^b 68.5, ^a 67.2, ^a 52.1 ^a
b/b': amide 13 + ligand 8	amide: 4.00 (q), 3.41 (t), 3.09 (t), 2.73 (m) ligand: 3.60 (q), 3.55 (q), 2.79 (m), 2.29 (m)	amide: 68.4, 67.2, 52.0 ligand: 63.2, 61.8, 46.5
c/c': ligand 8	3.58 (q), 3.52 (q), 2.75 (heptat), 2.25 (q)	63.1, 61.8, 46.5
d/d': lithium alkoxide 14	3.24 (d)	82.0
e/e': alcohol 11	2.93 (q)	79.6

^a Lithium amide, ^b Lithium alkoxide.

carbinol (see Figure S19 in the Supporting Information). This newly formed complex has totally different chemical shifts from the amino ether ligand **8** for protons 1, 1', 2, and 5 (Figure 1c, δ 3.58, 3.52, 2.75, and 2.25 ppm, respectively) and alcohol **11**

for proton 9 (Figure 1e, δ 2.93 ppm). However, the ^1H NMR spectrum of this new complex shares very similar chemical shifts and peak patterns to the lithium amide **13** (Figure 1b) and to the initial addition product lithium alkoxide **14** (Figure 1d).

We noted that after 0.42 equiv of *n*-BuLi was added to 1 equiv of amine **8** in toluene-*d*₈ solution, ligand **8** coexists with the newly formed lithium amide **13** seen in the ¹H NMR (Figure 1b). All the proton signals of the lithium amide **13** have different chemical shifts than the corresponding protons on the amine **8**, especially protons on carbons 1, 1', 2, and 5 (δ 4.00, 3.41, 3.09, and 2.73 ppm). Upon addition of 1.0 equiv of *n*-BuLi to the carbinol **11** in toluene-*d*₈ solution, the carbinol was converted into the corresponding lithium alkoxide **14**. The NMR spectrum of the lithium alkoxide **14** is depicted in Figure 1d. The chemical shift of the 2° carbinol proton on carbon 9 appears at δ 3.24 ppm and provides a signature of lithium alkoxide **14**. With the five peaks in complex **12** unambiguously identified, we carried out ¹H DOSY experiments to confirm the solution structure and aggregation state of this new trimeric complex.

¹H DOSY Characterization of Complex 12. DOSY is a powerful tool to identify solution state structure of organometallic complexes.^{11,12} DOSY can separate different species^{13,14} by their hydrodynamic radii^{15,16} and even their MW.^{17,18} To avoid artifacts generated by temperature fluctuation, viscosity change, and convection,¹⁹ we chose 1-octadecene (ODE) as the internal reference²⁰ for our DOSY experiments. The ¹H DOSY spectrum of mixed trimeric complex **12** with ODE in toluene-*d*₈ solution separates into two components in the diffusion dimension. These are clearly identifiable in the DOSY spectrum reproduced in Figure 2. In increasing order of diffusion coefficient (decreasing formula weight) these are the complex **12** (C₄₃H₉₅Li₃N₂O₃Si₂, FW 765.2) and ODE (C₁₈H₃₆, FW 252.3). The ¹H signals of the protons 1, 1', 2, 3, and 5 on ligand and proton 9 on alkoxide in complex **12** (Figure 2) have identical diffusion coefficients. The similar diffusion behavior confirms that the lithium alkoxide and the lithium amide are in the same complex. Previously we have suggested a correlation between diffusion coefficient and formula weight utilizing ¹H DOSY experiments to study dimeric and tetrameric *n*-BuLi,²¹ lithium allylic amide aggregates²² and bis(diisopropylamino)boron

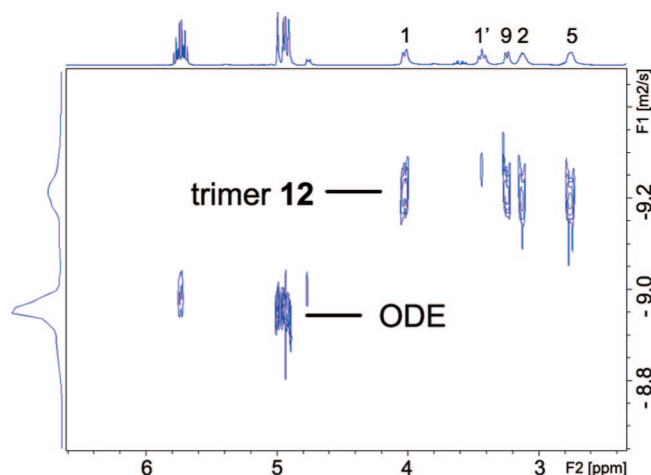


FIGURE 2. ¹H DOSY of trimeric complex **12** and ODE in toluene-*d*₈.

enolate of *tert*-butyl methyl ketone,²³ and solution structure of trimeric complex **1**.⁶ As we have previously noted, ¹H DOSY results allow us to correlate the diffusion coefficients and formula weights of complex **12**, ODE, and toluene-*d*₈. (Table S1 in the Supporting Information) The correlation between log FW (formula weight) and log *D* (diffusion coefficient) of the linear least-squares fit to reference points of all components in this mixture is extremely high, *r* = 0.9961 (Figure S22 in the Supporting Information). This result establishes the complex **12** as a mixed trimeric aggregate consisting of 2 equiv of lithium amide and 1 equiv of lithium alkoxide.

Having established the identity of compound **12**, we propose the following processes for chirality inhibition. Formation of alkoxide containing complex **12** during the reaction competes for the chiral lithium amide ligand with the *n*-BuLi containing aggregate **1**. As a consequence this competition destroys the chiral environment of *n*-BuLi and is ultimately detrimental to the enantioselective addition of *n*-BuLi to an electrophile. The rate of formation of the trimeric complex between lithium amide and lithium alkoxide is likely to be not identical for ligands **5**–**8** and this rate difference accounts for the inconstancy in chiral induction for different aldehyde addition methods.

¹³C NMR Chemical Shift Changes. The ¹³C NMR experiments confirm the conclusions drawn from the ¹H NMR investigations since they display similar variations to the ¹H NMR spectra for the components involved in product-induced chirality inhibition. Hence, we monitor the following ¹³C chemical shift for complex **12**: δ 68.5, 67.2, and 52.1 ppm for carbons 1, 2, and 5 on lithium amide and δ 82.4 ppm for the carbon 9 in lithium alkoxide (see Figure 1a' and Table 3). ¹³C NMR spectrum of complex **12** has totally different chemical shifts from the amino ether ligand **8** for carbons 1, 2, and 5 (Figure 1c', δ 63.1, 61.8, and 46.5 ppm, respectively) and alcohol **11** for proton 9 (Figure 1e', δ 79.6 ppm). However, the ¹³C NMR spectrum of this new complex shares very similar chemical shifts to the lithium amide **13** (Figure 1b') and to the addition product lithium alkoxide **14** (Figure 1d').

We noticed that after 0.42 equiv of *n*-BuLi was added to 1 equiv of amine **8** in toluene-*d*₈ solution, ligand **8** coexists with the lithium amide **13** seen in the ¹³C NMR (Figure 1b'). All the carbon signals of the lithium amide **13** have different chemical shifts than the corresponding carbons on the amine **8**, especially

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(20) 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.

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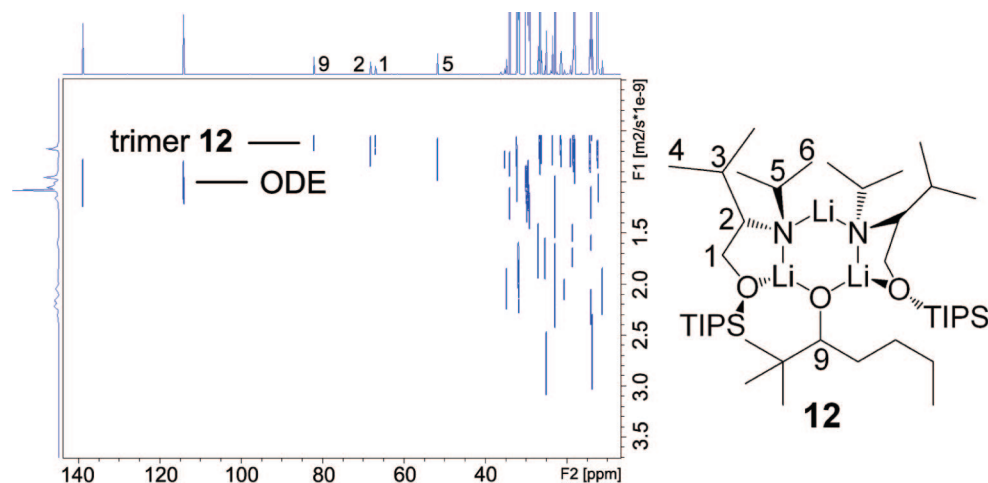


FIGURE 3. ^{13}C INEPT DOSY of trimeric complex **12** and ODE in toluene- d_8 .

carbons on carbons 1, 2, and 5 (δ 68.4, 67.2 and 52.0 ppm). Upon addition of 1.0 equiv of *n*-BuLi to the carbinol **11** in toluene- d_8 solution, the carbinol was converted into the corresponding lithium alkoxide **14**. The NMR spectrum of **14** is depicted in Figure 1d'. The chemical shift of the 2° carbinol carbon 9 appears at δ 82.0 ppm and provides a signature of the lithium alkoxide **14**. Hence, with the four peaks in complex **12** unambiguously identified and assigned, we felt confident in carrying out ^{13}C INEPT DOSY experiments to confirm the solution structure of this trimeric complex.

^{13}C INEPT DOSY Characterization of Complex 12. We obtained ^{13}C INEPT DOSY spectra because ^{13}C NMR spectra provide better resolution and a wider chemical shift range than proton spectra and the absence of homonuclear coupling simplifies their interpretation.²⁴ The ^{13}C DOSY spectrum of complex **12** with ODE in toluene- d_8 solution also separates into two components in the diffusion dimension.²⁵ These are clearly identifiable in the DOSY spectrum reproduced in Figure 3. In increasing order of diffusion coefficient (decreasing formula weight) these are the complex **12** and ODE. The ^{13}C signals of oxygen or nitrogen-attached carbon 1, 2, and 5 (δ 68.5, 67.2, and 52.1 ppm) in lithium amide and carbon 9 in lithium alkoxide (δ 82.4 ppm) have identical diffusion coefficients. These results corroborate the conclusions drawn from the ^1H -DOSY experiment that the alkoxide does indeed form a complex with the lithium amides.

Conclusions

In this paper we have demonstrated that asymmetric *n*-butylation of prochiral aldehydes is possible in hydrocarbon solvent. The 2:1 chiral lithium amide/*n*-BuLi aggregate **1** serves as the chiral addition template. Up to 83% ee has been achieved when *n*-BuLi adds to pivaldehyde in pentane at -116°C . Our results suggest that the protecting group on oxygen in a ligand is very important to control not only enantiomeric excess but also configuration of products since both R and S carbinol have been obtained by using L-valine derived ligands with different

groups on oxygen. Hence, asymmetric addition, which maximizes either R or S configuration in the product, can be carried out without using the more expensive D-valine derivatives. We utilized both ^1H and ^{13}C INEPT DOSY to characterize an additional mixed trimeric complex **12** between lithium amide and lithium alkoxide. We suggest that this complex **12** exhibits a product-induced chirality inhibition phenomenon that is detrimental to the asymmetric addition reaction. The chirality inhibition we have observed is analogous but opposite in effect to the chirality enhancement phenomena in product autoinduction. Finally, we conclude that optimization of chiral induction correlates strongly with formation of the product containing complex **12**. These DOSY investigations of chirality inhibition provide a new tool to analyze the versatility and complexity of lithium aggregate chemistry.

Experimental Section

Reactions of asymmetric additions were preformed in flame-dried glassware under an inert atmosphere of ultra pure Argon. All reaction temperatures corresponded to external bath temperatures. Solvents for these reactions were distilled from calcium hydride. Flash column chromatography was performed by using 150 mesh activated basic aluminum oxide. *n*-BuLi was titrated according to the method of Kofron.²⁶ ^1H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR spectra were recorded at 75 or 100 MHz by using CDCl_3 or toluene- d_8 as solvents. Optical rotations were recorded on a FTIR spectrometer. GC analyses were carried out by using a gas chromatograph equipped with a chiral stationary-phase column. Analyses were carried out by using helium (0.9 mL min $^{-1}$) as the carrier gas (injector 250°C , detector 275°C). All separation methods for chiral material were calibrated with racemic samples. Compound **3**, **4**, and **5** were synthesized according to literature procedures.^{9,10}

DOSY Experiments. DOSY experiments were performed on a 400 MHz spectrometer equipped with a z-axis gradient amplifier and 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 3 ms. 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.

Compound 5. (*S*)-*N*-Isopropyl-*O*-methylvalinol: ^1H NMR (toluene- d_8 , 300 MHz) δ 3.23–3.13 (2H, m), 3.10 (3H, m), 2.79 (1H, sept, J = 6.2 Hz), 2.46 (1H, dd, J = 10.2, 5.1 Hz), 1.79 (1H, m), 0.98

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(6H, dd, $J = 6.2, 2.7$ Hz), 0.94 (6H, d, $J = 6.9$ Hz); ^{13}C NMR (toluene- d_8 , 75 MHz) δ 73.4, 59.8, 58.6, 46.6, 30.1, 24.0, 23.8, 19.2, 18.8.

Synthesis of Compound 6. To a suspension of sodium hydride (0.3 g, 60% dispersion in mineral oil, 7.5 mmol) in THF (40 mL) was added compound **4** in THF (11 mL) dropwise (0.72 g, 5 mmol) at room temperature and the mixture was heated to reflux overnight. The mixture was cooled to 0 °C and *n*-butyl bromide (0.83 g, 6 mmol in THF 10 mL) was added dropwise. The reaction mixture was heated to reflux for 2 h. Saturated aqueous sodium chloride was slowly added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane twice. The combined organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography (aluminum oxide, 150 mesh, basic, activated) followed by distillation to yield colorless oil (0.66 g, 66%, bp 104–105 °C/20 mmHg). ^1H NMR (300 MHz, CDCl_3) δ 3.43–3.38 (m, 3H), 3.31 (dd, 1H, $J = 9.4, 5.9$ Hz), 2.86 (hept, 1H, $J = 6.2$ Hz), 2.54 (q, 1H, $J = 5.2$ Hz), 1.84 (m, 1H), 1.56 (tt, 2H, $J = 6.5$ Hz), 1.37 (m, 2H), 1.05 (d, 6H, $J = 6.1$ Hz), 1.04 (d, 6H, $J = 6.1$ Hz), 0.95–0.90 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 71.4, 71.0, 59.6, 46.6, 31.8, 29.4, 23.7, 23.6, 19.4, 18.6, 18.6, 13.9; IR (KBr) 3330, 3178, 2962, 2729, 2609, 2365, 2336, 2103, 1464, 1408, 1380, 1334, 1304, 1249, 1174, 1105, 1050, 999, 975, 919, 899, 852, 736, 646 cm^{-1} ; optical rotation $[\alpha]^{25}_D -5.4$ (c 1.0, EtOH); HRMS (FAB) MH^+ , found 202.2180, $\text{C}_{12}\text{H}_{27}\text{NO}$ calcd 202.2171.

Synthesis of Compound 7. *tert*-Butyldimethylsilyl chloride (1.24 g, 8.2 mmol) was added to an ice-cooled solution of **4** (0.72 g, 5 mmol) and imidazole (0.89 g, 13 mmol) in dichloromethane (40 mL). The reaction mixture was stirred and allowed to warm to room temperature. The reaction was quenched with NaHCO_3 (10 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography (aluminum oxide, 150 mesh, basic, activated) followed by distillation to give colorless oil (0.62 g, 47.9%, bp 79–80 °C/2.2 mmHg). ^1H NMR (300 MHz, CDCl_3) δ 3.60 (dd, 1H, $J = 10.0, 5.3$ Hz), 3.51 (dd, 1H, $J = 10.0, 5.3$ Hz), 2.83 (m, 1H), 2.38 (m, 1H), 1.81 (m, 1H), 1.05 (d, 3H, $J = 6.1$ Hz), 1.03 (d, 3H, $J = 6.1$ Hz), 0.88–0.93 (m, 15H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 62.7, 61.4, 46.6, 29.3, 25.9, 23.7, 23.5, 18.9, 18.6, 18.2, -5.5 ; IR (KBr) 3330, 3175, 2955, 2858, 2738, 2710, 2635, 2363, 2337, 1922, 1749, 1651, 1468, 1382, 1364, 1334, 1254, 1218, 1174, 1094, 1007, 979, 956, 939, 908, 835, 777, 730, 671, 611 cm^{-1} ; optical rotation $[\alpha]^{24}_D -11.4$ (c 1.0, EtOH); HRMS (FAB) MH^+ , found 260.2418, $\text{C}_{14}\text{H}_{33}\text{NOSi}$ calcd 260.2410.

Synthesis of Compound 8. To a solution of **4** (2.9 g, 20 mmol) and triethylamine (5.58 mL, 40 mmol) in 60 mL of CH_2Cl_2 was added at 0 °C triisopropylsilyl triflate (6.93 mL, 25 mmol). The mixture was stirred and allowed to warm to room temperature in 4 h. The reaction was quenched with 20 mL of 2 M NaHCO_3 . After 3×20 mL ether washes of the aqueous layer, the organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude yellow liquid was purified by flash column chromatography (aluminum oxide, 150 mesh, basic, activated) followed by distillation to give colorless oil (3.2 g, 53.1%, bp 87 °C/2.5 mmHg). ^1H NMR (300 MHz, CDCl_3) δ 3.70 (dd, 1H, $J = 9.9, 5.2$ Hz), 3.60 (dd, 1H, $J = 9.9, 5.5$ Hz), 2.85 (heptat, 1H, $J = 6.2$ Hz), 2.39 (q, 1H, $J = 5.2$ Hz), 1.83 (m, 1H), 1.44–1.02 (m, 27H), 0.93 (d, 3H, $J = 6.9$ Hz), 0.92 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 63.1, 61.7, 46.7, 29.3, 23.7, 23.6, 22.1, 18.9, 18.7, 17.5, 13.9, 12.2, 11.9, 11.6; IR (KBr) 2954, 2867, 2722, 2631, 2362, 1464, 1382, 1333, 1249, 1174, 1099, 1067, 1011, 883, 772, 730, 683 cm^{-1} ; optical rotation $[\alpha]^{24}_D -8.9$ (c 1.0, EtOH); HRMS (FAB) MH^+ , found 302.2875, $\text{C}_{17}\text{H}_{39}\text{NOSi}$ calcd 302.2879.

Determination of the Absolute Configuration of Secondary Alcohols. (*S*)-1-phenyl-1-pentanol: GC retention time on chiral stationary-phase at 130 °C, 29.8 (*S*) and 31.2 (*R*) min, 76% ee. Absolute stereochemistry was assigned in accord with the published value of GC retention time.³¹

(*S*)-2,2-Dimethyl-3-heptanol: $[\alpha]^{24}_D -16.8$ (c 0.25, cyclopentane), 83% ee. Absolute stereochemistry was assigned in accord with the published value of optical rotation.²⁷

(*S*)- α -Butyl-2-furanmethanol: $[\alpha]^{24}_D -10.4$ (c 1.00, CHCl_3), 74% ee. Absolute stereochemistry was assigned in accord with the published value of optical rotation.²⁸

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

Supporting Information Available: ^1H NMR, ^{13}C NMR, and IR spectra of ligands **5–8**, ^1H NMR and ^{13}C NMR spectra and GC analysis of the three addition products, and ^1H NMR, ^{13}C NMR, ^1H DOSY, and ^{13}C INEPT DOSY spectra of complex **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO800592D

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