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NMR studies of a ternary complex reagent of lithium ester enolate, chiral diether, and lithium diisopropylamide in an asymmetric Michael reaction

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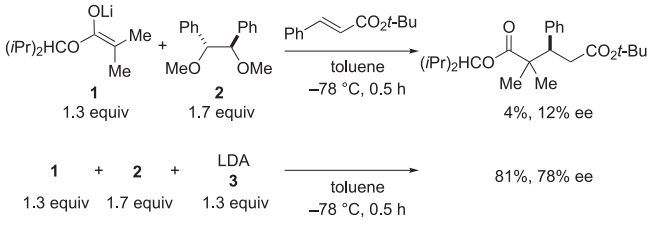
ABSTRACT

A ternary complex reagent of lithium ester enolate–chiral diether–lithium diisopropylamide was formed in an equimolar mixture of these reagents in toluene based on low-temperature NMR spectroscopy. The use of [^{6}Li,^{15}N]-lithium diisopropylamide as a lithiodeprotonation and complexing reagent produced two sets of doublet peaks in ^{6}Li NMR of a 1:1:1 mixture of lithium enolate–chiral diether–lithium diisopropylamide, indicating the formation of a ternary complex reagent.

1. Introduction

Organolithiums are one of the most frequently-used reagents in synthetic chemistry. To better understand their reactivity and reaction mechanisms, it is necessary to elucidate the structure of reactive organolithium reagents.[1] X-ray studies of the crystal structure revealed that organolithium reagents tend to aggregate with themselves in non-polar solvents and to form mixed aggregates with coordinating compounds such as THF, Et_2O, DME, and TMEDA.[1,2] Because it is not guaranteed that the solid state structure directly transfers to a solution structure, NMR spectroscopic analysis is a more powerful tool for analysis, because it can be used to detect the solution state structure, i.e., possible reactive species in the reaction medium.[3]

We previously reported asymmetric Mannich[4] and Michael[5] reactions of a lithium ester enolate mediated by chiral diether **2** and lithium amides. In these reactions, Lewis basic chiral diether **2** is not sufficient to enhance the reactivity of the lithium enolate **1**, and both diether **2** and lithium amide, such as LDA **3**, are required to achieve higher reactivity and stereoselectivity (Scheme 1).[5a] We postulated that the transition of the aggregate from a binary complex reagent **1**–**2** to a ternary complex reagent **1**–**2**–**3** changes the nature of the lithium enolate **1** (Fig. 1).[6] Herein, we report the detection of mixed aggregates of **1**–**2** and **1**–**2**–**3** by NMR spectroscopic analysis.



Scheme 1. Reactivity enhancement of **1** by **2** and **3**.

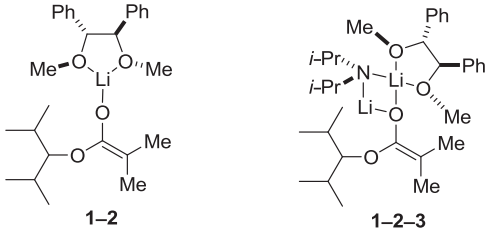


Figure 1. Putative binary complex reagent **1**–**2** and ternary complex reagent **1**–**2**–**3**.

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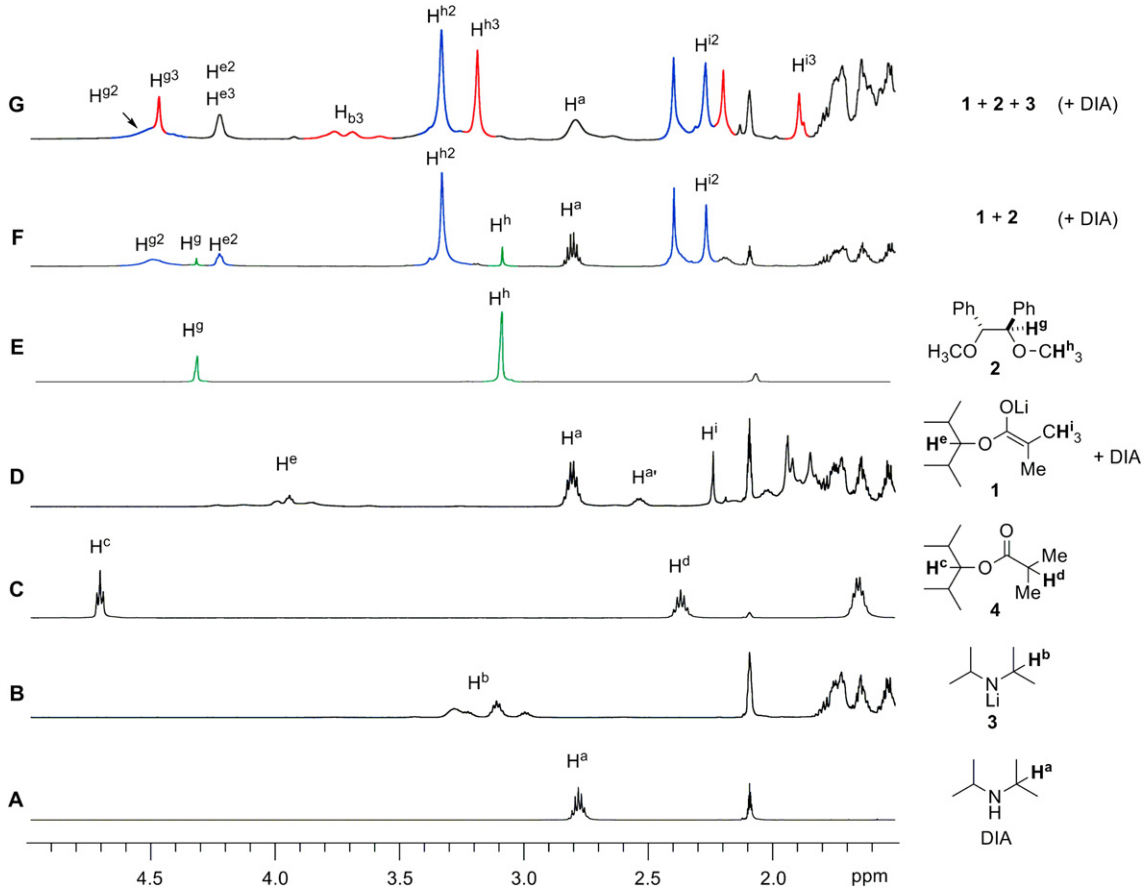


Chart 1. ^{1}H NMR spectra (toluene-d_8, −80 °C) of binary **1**–**2** and ternary **1**–**2**–**3** complex.

2. Results and discussion

First, we performed ^{1}H NMR analysis of lithium enolate **1** in toluene-d_8 at −80 °C. Treatment of 2,4-dimethyl-3-pentyl isobutylate **4** with 1.0 equiv of LDA induced the α-proton H^{d} of **4** (Chart 1, C) to disappear (D), ensuring the formation of enolate **1** (A–D). At the same time, diisopropylamine (DIA, Chart 1, A) was generated from LDA (B), and most of this amine seemed to be free from coordination to lithium atoms because the chemical shift of H^{a} (D) was identical to that of DIA alone (A). The newly appearing small peak $H^{a\prime}$ (D) was likely derived from the DIA–**1** complex.

We then performed ^{1}H NMR analysis of the binary complex **1**–**2**. By mixing equimolar lithium enolate **1** (D) and chiral diether **2** (E, green peaks), new peaks H^{h2} and H^{g2}, derived from methyl and benzyl protons of **2**, and ester methine proton H^{e2} and methyl protons H^{i2} of **1** appeared (F, blue peaks). DIA was generated again in this experiment and was also free from coordination to lithium atoms based on the chemical shift and integration of H^{a}. The integration ratio of $H^{e2}/H^{g2}/H^{h2}$ was 1/2/6, indicating that **1** and **2** formed a 1:1 complex. The H^{h2}/H^{h} ratio (F) was more than 95/5 and therefore most of **2** seemed to coordinate to the lithium atoms of enolate **1**. Moreover, NOE correlations were observed in H^{h2}/H^{i2} and H^{h2}/H^{e2}, which strongly suggested the formation of binary complex **1**–**2**.

After establishing the formation of binary complex **1**–**2**, we focused on the ternary complex **1**–**2**–**3**. The NMR sample was prepared by adding **2** (1 equiv) and **4** (1 equiv) to the solution of LDA (2 equiv, prepared from *i*-Pr_2NH and *n*-BuLi) in toluene-d_8 at −80 °C. A new methyl peak H^{i3}, derived from **1**, methyl H^{h3} and methine H^{g3} of **2**, and methine H^{b3} of **3** appeared (G, shown in red). H^{h2} remained, and therefore binary **1**–**2** and ternary **1**–**2**–**3** complexes coexisted. The integration ratio of H^{h2}/H^{h3} was approximately 3:2.

Analysis of ^{13}C NMR data supported the notion that both the binary and ternary complex reagents formed (Chart 2). In the 1:1 mixture of **1**–**2**, new peaks C^{g2} and C^{h2} of **2** appeared (L, blue peaks) and their chemical shifts were different from C^{g} and C^{h} of uncomplexed **2** (K, green peaks), which also suggested the formation of a binary complex. At the same time, a few small non-coordinated diether **2** signals of C^{g} and C^{h} were detected, as shown in ^{1}H NMR (Chart 1, F).

In the 1:1:1 mixture of **1**–**2**–**3**, generation of ternary complex reagent was confirmed based on the newly appearing C^{e3}, C^{f3} of **1**; C^{g3}, C^{h3} of **2**; and C^{b3} of **3,** as highlighted in red (Chart 2, M). The remaining C^{e2}, C^{f2}, C^{g2}, and C^{h2} provided support for the coexistence of a binary **1**–**2** complex.

The ^{6}Li NMR study with [^{6}Li,^{15}N]-LDA[7] strongly supported the notion that a binary complex and ternary complex had formed (Chart 3, ^{6}LiCl was used as an external standard). In the binary **1**–**2** complex, only one singlet Li^{1} appeared (O). This singlet peak provided evidence that *i*-$Pr_2{}^{15}$NH, generated by lithiodeprotonation of ester **4** with [^{6}Li,^{15}N]-LDA, did not coordinate to the lithium atom of ^{6}Li-**1**. In the ternary **1**–**2**–**3** complex, two doublet peaks Li^{2} and Li^{3} (red) as well as the singlet Li^{1} were observed (P). These two sets of doublets indicated that two different lithium atoms bonded to one nitrogen atom. These findings clearly indicated the existence of both the binary and ternary complexes.

Results of the ^{1}H–NOESY experiments provided insight into the higher reactivity of the ternary complex reagent (Scheme 2). The ternary **1**–**2**–**3** complex showed H^{h3}/H^{i3}, H^{h3}/H^{g3}, and H^{h3}/H^{b3} cross-peaks (see **6**), indicating that the bulky ester moiety of **1** was located far away from diether **2**, and the less-bulky isopropylidene group of **1** was situated close to **2**. In the Michael addition reaction of the ternary reagent with cinnamate **5**, the carbonyl oxygen of **5**

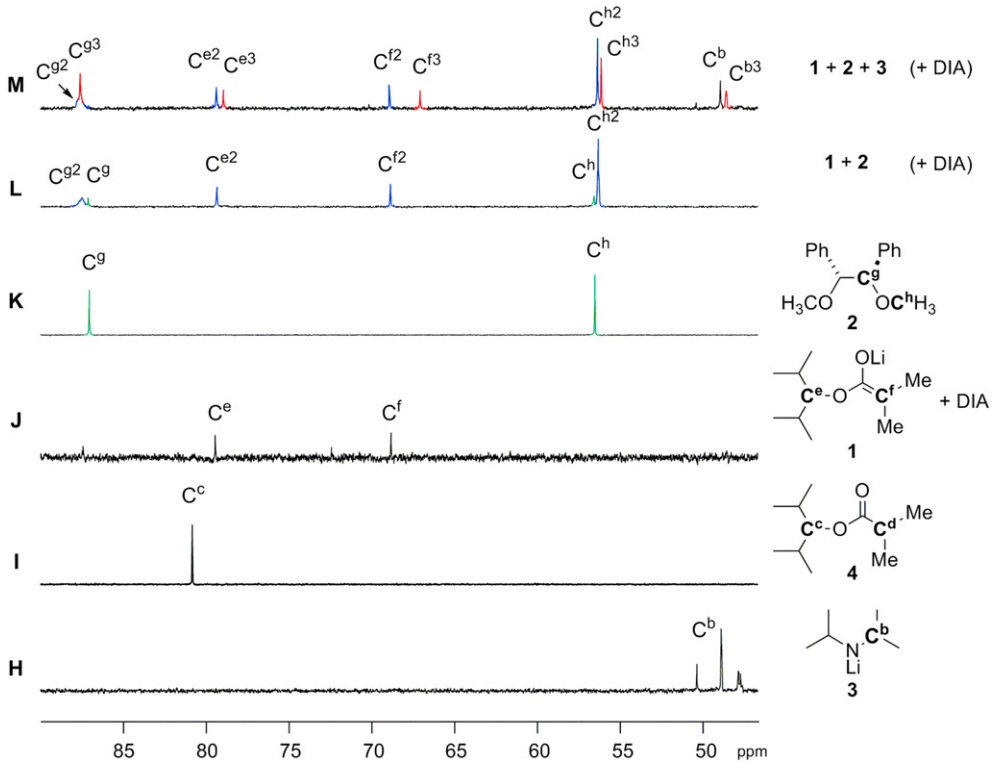


Chart 2. ^{13}C NMR spectra (toluene-d_8, −80 °C) of binary **1**–**2** and ternary **1**–**2**–**3** complex.

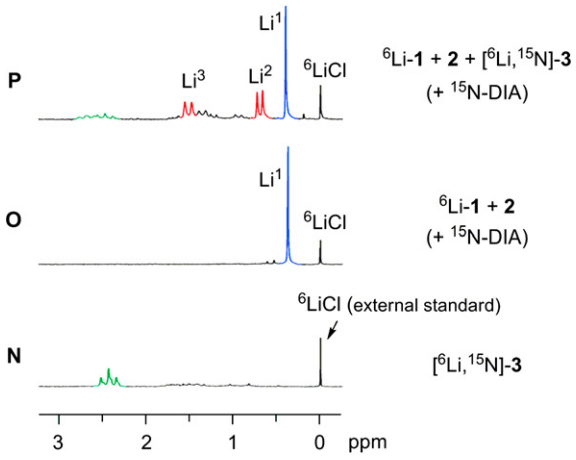
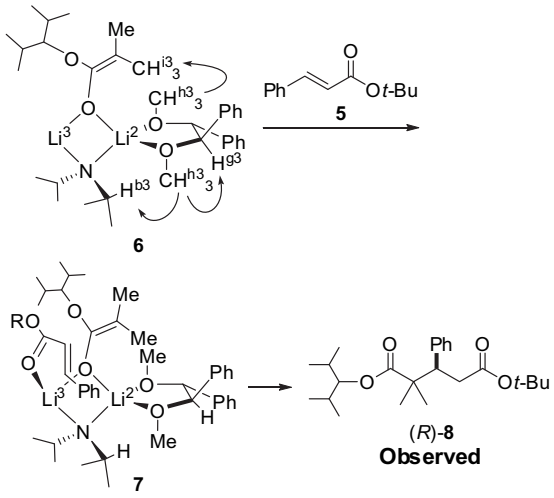


Chart 3. ^6Li NMR spectra (toluene-d_8, −80 °C) of binary **1**–**2** and ternary **1**–**2**–**3** complex.



Scheme 2. Plausible stereochemistry based on ^1H–NOESY correlation.

would coordinate to the Lewis acidic Li^3 from the opposite side of the methyl group of diether **2**, as shown in **7**, and therefore the reaction proceeded from the *Re*-face of **5** to give (*R*)-**8** with the observed absolute configuration.

3. Conclusion

The ternary complex reagent of lithium enolate **1**, chiral diether **2**, and LDA **3** was successfully confirmed by ^1H, ^{13}C, and ^6Li NMR. Although the aggregation state of these species were not determined at this stage and the structures suggested by NMR were not confirmed to represent the real active species, the existence of the less-coordinated and Lewis acidic lithium atom in the ternary reagents would account for the enhanced reactivity.

4. Experimental

4.1. General

All NMR samples were prepared in the flask and transferred to an NMR tube before measurement. All NMR tubes were dried under vacuum at 100 °C for 1 h, sealed with septa, and filled with argon gas before use. Toluene-d_8 was distilled from sodium/benzophenone. Ester **4** and *i*-Pr_2NH were distilled before use. All NMR experiments were recorded on a 500-MHz spectrometer with a variable-temperature unit. Measuring frequencies were 500 MHz (^1H), 125 MHz (^{13}C), and 73 MHz (^6Li). ^1H and ^{13}C chemical shifts were referenced to the solvent toluene-d_8 signals at δ 2.09 and δ 20.4, respectively. Lithium spectra were referenced to external

0.3 M ^{6}LiCl in MeOH-d_4 (δ 0.0). *i*-Pr$_2$^{15}NH and *n*-Bu^{6}Li was prepared according to the previously described procedure.[7]

4.2. Preparation of NMR samples

4.2.1. Ternary complex of 1–2–3. A dry round bottom flask was equipped with a stir bar and filled with argon by evacuation and refilled three times. *i*-Pr$_2$NH (0.364 mL, 2.6 mmol) and toluene-d_8 (4.0 mL) were added at room temperature and the mixture cooled to −78 °C. *n*-BuLi (1.53 M in hexane, 1.70 mL, 2.6 mmol) was added at −78 °C and the mixture was stirred for 0.5 h at −78 °C. A solution of chiral diether **2** (315 mg, 1.3 mmol) and ester **4** (242 mg, 1.3 mmol) in toluene-d_8 (4.5 mL) were added to this LDA solution over 5 min. The mixture was stirred for 1 h at −20 °C and then transferred to a dry NMR tube via a cannula.

*4.2.2. Binary complex of **1**–**2**.* LDA was prepared from *i*-Pr$_2$NH (0.182 mL, 1.3 mmol) and *n*-BuLi (1.53 M in hexane, 0.85 mL, 1.3 mmol) in toluene-d_8 (4.0 mL) at −78 °C. A solution of **2** (315 mg, 1.3 mmol) and **4** (242 mg, 1.3 mmol) in toluene-d_8 (4.5 mL) were added to this LDA solution. After stirring for 1 h at −20 °C, the solution was transferred to a dry NMR tube via a cannula.

4.2.3. LDA. The LDA solution was prepared from *i*-Pr$_2$NH (60.7 mg, 0.6 mmol) and *n*-BuLi (1.53 M in hexane, 0.39 mL, 0.6 mmol) in toluene-d_8 (4.0 mL) at −78 °C, and transferred to a dry NMR tube via a cannula.

*4.2.4. Lithium enolate **1**.* LDA was prepared from *i*-Pr$_2$NH (0.182 mL, 1.3 mmol) and *n*-BuLi (1.53 M in hexane, 0.85 mL, 1.3 mmol) in toluene-d_8 (4.0 mL) at −78 °C. A solution of **4** (242 mg, 1.3 mmol) in toluene-d_8 (4.5 mL) was added to this LDA solution. After stirring for 1 h at −20 °C, the solution was transferred to a dry NMR tube via a cannula.

*4.2.5. i-Pr$_2$NH, diether **2**, and ester **4**.* A 0.15 M solution in toluene-d_8 was prepared in a round bottom flask and transferred to the NMR tube with a syringe.

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