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NMR studies on the structure of a lithium amide–chiral diether complex for an asymmetric reaction

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ABSTRACT

The combination of a chiral diether ligand and a lithium benzyl(trimethylsilyl)amide is a powerful lithium amide reagent for asymmetric conjugate amination of enoate in a toluene solvent. The structure of the chiral diether–lithium amide complex in solution was analyzed by low-temperature NMR. ^{6}Li NMR suggested the formation of a cyclic heterodimer. The stereochemical pathway is predictable based on the structure of the lithium amide–chiral diether complex.

1. Introduction

The dimethyl ether of (*R*,*R*)- and (*S*,*S*)-1,2-dihydroxy-1,2-diphenylethane **1** is a powerful and widely applicable chiral external ligand[1] for asymmetric reactions of lithiated reagents, such as organolithium,[2] lithium enolate, and lithium amide.[3] Since the first report on the utility of chiral diether **1** in the catalytic and stoichiometric asymmetric conjugate addition of organolithiums to unsaturated imines,[4] further applications to an asymmetric S_NAr reaction giving biaryls,[5] a conjugate addition to enoates,[6] an asymmetric addition to imines,[7] an enantioselective opening of oxiranes and oxetanes,[8] an asymmetric Horner–Wadsworth–Emmons reaction,[9] and natural *Amaryllidaceae* alkaloid total synthesis[10] have been developed. The utility was further extended to the reaction of lithium enolate, and an asymmetric Mannich-type reaction with imines,[11] asymmetric Peterson reaction,[12] asymmetric Michael reaction with enones[13] and enoates,[14] and its application to the total synthesis of marine natural products bearing quaternary carbons[15] have been reported. It was an unexpected discovery that a ternary complex of lithium enolate with lithium amide as well as diether ligand **1** is a more reactive enolate reagent than enolate–diether and enolate–lithium amide binary complexes.[16] Lithium amide[17] has also become a powerful chiral nitrogen nucleophile in the conjugate addition reaction with enoates, giving β-amino acid derivatives.[18,19] Application to the asymmetric total synthesis of natural indole-alkaloids was the subject of our recent study.[20] The utility of diether in other types of asymmetric reactions has also been reported by other research groups.[21]

Formation of lithiated reagent–chiral diether **1** complex **2** was conceptually designed, as shown in Fig. 1, and experimentally supported by the variety of highly efficient asymmetric reactions described above. The two methyl groups on the oxygen atom situate up and down face of the five-membered chelation because of trans-arrangement toward the phenyl group. If a reaction occurs upon coordination to lithium, the two methyl groups support the closest stereocontrolling groups. Proof of concept, however, should be demonstrated by a structure study of the lithiated reagent–chiral diether **1** complex **2**. Also, studies on the structure are important to understand the stereochemical control in these asymmetric reactions. Therefore, we investigated the structure of the lithiated ester enolate–chiral diether **1** complex using NMR technology. It is important to note that a ternary complex of lithium ester enolate with chiral diether and lithium amide is the most reactive enolate reagent in a toluene solvent.[22] Because lithium amide is widely used as a base or a nitrogen nucleophile in organic synthesis,[23,24] structural studies of the lithium amide–chiral diether complex are also important.

We previously developed a chiral diether **1**-mediated asymmetric conjugate addition reaction of lithium benzyl(trimethylsilyl)

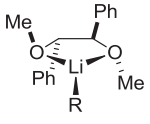

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Fig. 1. Lithium reagent–chiral diether **1** complex **2**.

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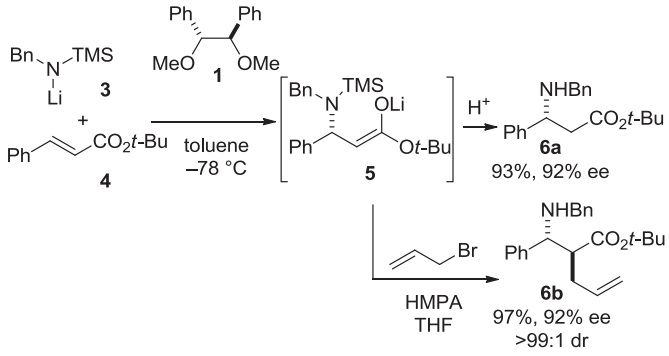
amide **3** with *tert*-butyl cinnamate **4** in a toluene solvent to give β-aminoester **6a** in 93% yield with 92% ee.[18,25] A tandem alkylation reaction of the nucleophilic lithium enolate intermediate **5** with alkyl halide was possible to efficiently construct two adjacent chiral centers **6b** (Scheme 1).[18d,20] The conceptual basis of these asymmetric transformations is the putative five-membered chelate **7a** of lithium amide and ligand **1**, around which a chiral environment was effectively created, as shown in **7b** (Fig. 2). In this paper, we focused on the NMR behavior of the lithium amide **3**-diether **1** complex in toluene solvent and the relation to stereochemical control in asymmetric conjugate amination.



Scheme 1. Asymmetric conjugate amination reaction of **3** mediated by **1**.

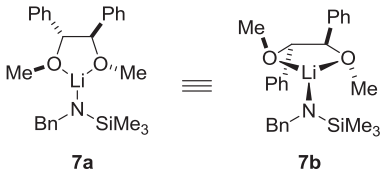


Fig. 2. Putative binary complex **7** of **1** and **3**.

2. Results and discussion

We performed ^{1}H NMR analysis of lithium amide **3** in toluene-d_8 at −100 °C. Treatment of benzyl(trimethylsilyl)amine **8** (Chart 1A) with 1 equiv of a hexane solution of *n*-BuLi indicated that methyl protons H^a and benzyl protons H^b of **8** were shifted to H^c and H^d, as shown in blue, respectively (B). Upon addition of 1 equiv of diether **1** (C) to the solution of **3** in toluene-d_8, new peaks H^{e2} (two peaks) and H^{f2}, derived from methyl and methine protons of **1**, and downfield shifted H^{c2} and H^{d2} of **3** appeared (D), strongly supporting the coordination of **1 to 3**.[26] H^e and H^f of coordination-free **1** were also observed, and most of **1** seemed to coordinate to **3** based on a H^{e2}/H^e integration ratio of 4/1. The split of H^{e2} of **1** and H^{d2} of **3** suggests that the two methyl groups of **1** and the benzyl protons of **3** were not equivalent at this temperature. At an elevated temperature, −40 °C, similar ^{1}H NMR shifts of H^c and H^d of **3** and H^e and H^f of **1** were observed (Chart 2E–G). Protons of non-coordinated diether **1** were not observed at all in the 1:1 mixture of **1** and **3**, indicating that the coordination and dissociation equilibrium of **1** with **3** was a faster process than the NMR time scale at −40 °C.[27]

Analysis by ^{13}C NMR at −100 °C (Chart 3) indicated the formation of lithium amide **3** (I) from amine **8** (H) with *n*-BuLi by a downfield shift of C^a and C^b to C^c and C^d, respectively. In the 1:1 mixture of **1**–**3**, new peaks C^{c2} and C^{d2} of **3** and C^{e2} and C^{f2} of **1** appeared, as shown in red, and their chemical shifts were different from that of C^e, C^f, C^c, and C^d of uncomplexed **1** (J) and **3** **(I)**,

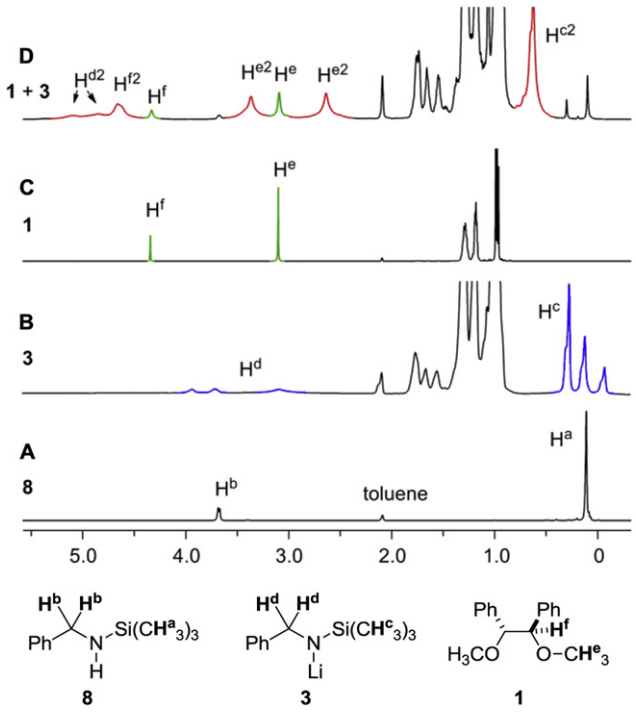


Chart 1. ^{1}H NMR spectra (toluene-d_8, −100 °C) of the **1**–**3** complex.

respectively, which also suggested the formation of binary complex **1**–**3** (K). At the same time, C^e and C^f of uncomplexed **3** were observed. These results strongly supported the existence of both of **1**–**3** and uncomplexed **1**, as shown in ^{1}H NMR (Chart 1D).

The number of connected ^{6}Li and ^{15}N atoms can be analyzed by ^{6}Li and ^{15}N NMR.[28] We then prepared ^{6}Li and ^{15}N-labeled lithium amide **3**, and measured ^{6}Li NMR.[29]

^{6}Li NMR of [^{6}Li,^{15}N]-**3**, prepared from *n*-Bu^{6}Li and [^{15}N]-**8**, showed a triplet signal at −40 °C (Chart 4L), which is indicative of N–Li–N connectivity and the existence of a cyclic dimer.[30] Lowering the temperature to below −80 °C changed a complex signal to a signal comprising mainly two triplets with overlapping components (M, N). *Cis*- and *trans*-cyclic dimers **9** and **10** are possible structures (Fig. 3),[31] and these stereoisomeric cyclic dimers give two triplet signals, consistent with the ^{6}Li NMR of [^{6}Li,^{15}N]-**3** at −80 and −100 °C (M, N). In the 1:1 mixture of **1** and [^{6}Li,^{15}N]-**3** at −80 °C, a triplet signal appeared (O), indicative of N–Li–N connectivity. At −100 °C, three triplets appeared from a complex signal

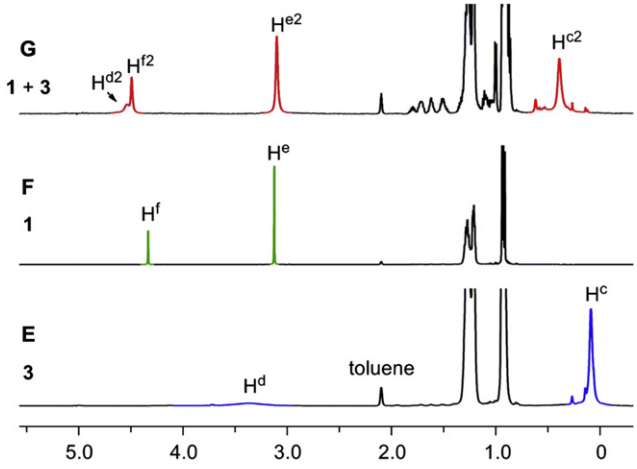


Chart 2. ^{1}H NMR spectra (toluene-d_8, −40 °C) of the **1**–**3** complex.