The Structure of a Chiral Lithium Amidocuprate in Solution Determined by Multinuclear NMR Spectroscopy

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Organocuprates have been of extensive use in synthetic chemistry.[1−3] To add further versatility to the organocopper reagents recent developments have focused on utilizing chiral amines to gain enantioselectivity in the reactions.[4−10] A thorough understanding regarding the structure and mechanism of these reagents are therefore of special importance for ligand optimization. Rossiter and co-workers experimentally identified the crucial moieties in an amidocuprate reagent with respect to chemical yield and enantiomeric excess (ee).[6] A structure for the reactive chiral lithium amidocuprate complex was tentatively proposed, mainly based upon some previous work by Dieter and co-workers.[11] The lithium amidocuprate complex was proposed to adopt a dimeric structure in relatively nonpolar solvents such as diethyl ether (DEE).

The solution structure and dynamics of a lithium amidocuprate prepared from the lithium salt of (*S*)-^{15}*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine[12] (**1**) and *n*-butylcopper, have been studied by NMR spectroscopy. This constitutes the first structure of a chiral lithium amidocuprate complex in solution. The solvent dependent structural changes account for the effects on chemical yield and stereoselectivity observed.

The lithium amidocuprate complex was analyzed using 1D and 2D experiments based on ^{1}H-, ^{6}Li-, ^{13}C-, ^{15}N NMR correlation spectroscopies, ^{6}Li^{15}N NMR coupling patterns and magnitudes. The amidocuprates were generated in situ, employing conditions used in general synthetic applications. An NMR tube was charged sequentially with CuI (94.2 mg, 0.49 mmol), 600 μL of DEE-d_{10}, amine **1** (89 μL, 0.49 mmol), and *n*-Bu^{6}Li (0.98 mmol) at −70 °C. The reaction mixture was heated to −40 °C for 1 min to allow formation of the lithium amidocuprate complex. The ^{6}Li NMR spectrum of the resulting chiral lithium amidocuprate complex at −50 °C displayed a singlet at δ 0.84 ppm, two doublets in a 1:1 ratio centered at δ 1.91 ppm, with J ^{6}Li,^{15}N = 4.9 Hz, and a second doublet centered at δ 2.01 ppm, J ^{6}Li,^{15}N = 5.9 Hz Figure 1a.

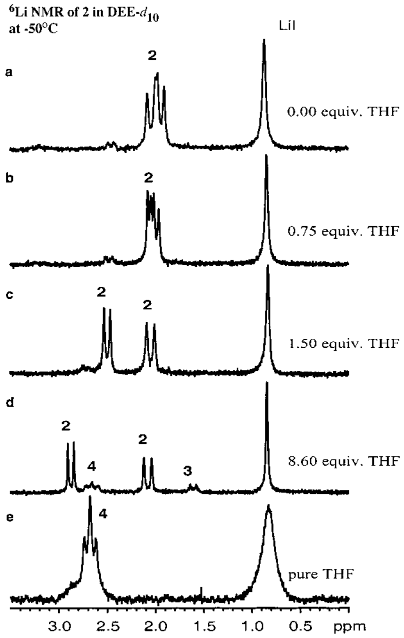

Figure 1. ^{6}Li NMR spectra of **2** at −50 °C in (a) DEE-d_{10}, (b) DEE-d_{10} with 0.75 equiv of THF-d_8, (c) DEE-d_{10} with 1.5 equiv of THF-d_8, (d) DEE-d_{10} with 8.6 equiv of THF-d_8, (e) THF-d_8. The ^{6}Li NMR signals were referenced using a 0.3M LiCl solution in methanol-d_4 (δ 0.0 ppm).

The singlet at δ 0.84 ppm originates from ^{6}LiI formed in the preparation of the lithium amidocuprate. A heterocorrelated 2D ^{6}Li,^{15}N NMR spectrum verified that the two ^{6}Li doublets correlate with only one ^{15}N atom indicating a Li−N connectivity consistent with a [(lithium amide)/(*n*-BuCu)]$_2$ complex **2**,[13] see Scheme 1.

The magnitude of the ^{6}Li ^{15}N NMR coupling constants are very dependent upon the coordination number at the lithium rather than the aggregation state. This has been verified both experimentally and by computational means.[14] The difference in ^{6}Li ^{15}N NMR coupling constants in **2** indicate that there is a difference in the coordination environment at the lithiums.[15] The observation of only one benzylic and quaternary ^{13}C NMR signal at δ 72.4 and 149.0 ppm, respectively, at −50 °C, showed that the reaction solution only contains one major complex.[13] In the ^{1}H NMR spectrum of **2** in DEE at −50 °C one signal appears at δ −0.30 ppm. This signal could be assigned to the α-methylene protons in the complexed *n*-BuCu.[13] Upon titration of the above solution with THF the ^{6}Li NMR signals showed significant changes in chemical shifts. After addition of 8.6 equiv of THF, the ^{6}Li NMR signal at δ 1.91 ppm had shifted downfield to δ 2.87 ppm with a slight decrease in the ^{6}Li,^{15}N coupling constant (J ^{6}Li,^{15}N = 4.9 to 4.5 Hz), whereas the ^{6}Li NMR signal at δ 2.01 ppm was found to shift slightly downfield to δ 2.07 ppm with unchanged ^{6}Li,^{15}N coupling constant (Figure 1a−e). This observation shows that one of the two lithiums in **2** is more accessible to solvent coordination. Furthermore, two new ^{6}Li NMR signals appeared, a triplet at δ 2.66 ppm (J ^{6}Li,^{15}N = 4.1 Hz) and a doublet at δ 1.61 ppm (J ^{6}Li,^{15}N = 4.4 Hz). The triplet at δ 2.66 ppm originates from a previously described lithium amide dimer **4**.[16]

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(13) See Supporting Information.

(14) Ab Initio MO calculations of ^{6}Li, ^{15}N coupling constants, performed by Kikuchi and co-workers, show that the coupling constants vary with the degree of coordination (~6 Hz for tri-coordinated and ~4 Hz for tetra-coordinated ^{6}Li). Koizumi, T.; Morihashi, K.; Kikuchi O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305−309. Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981−2987.

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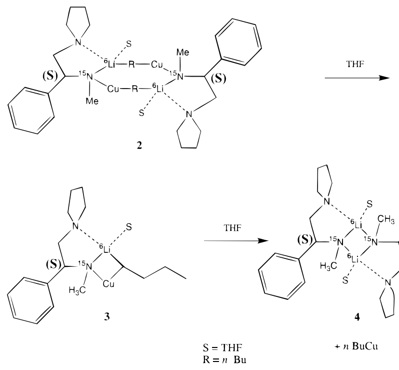
10.1021/ja9940773 CCC: $19.00

Scheme 1



The doublet at δ 1.61 ppm was tentatively assigned to lithium amide/*n*-BuCu complex **3** (Scheme 1).

The incremental additions of THF also resulted in two new sets of benzylic ^{13}C NMR signals at δ 72.0 and 73.1 ppm and two new sets of quaternary ^{13}C NMR signals at δ 148.5 and 151.0 ppm, respectively.[13] This is consistent with the formation of two new species, in concordance with the observations made in the ^{6}Li NMR spectra. Attempted preparation of **2** in pure THF resulted in a ^{6}Li NMR spectrum displaying a ^{6}Li NMR triplet at δ 2.68 ppm (J ^{6}Li,^{15}N = 4.6 Hz), originating from the complex **4**, and a singlet at δ 0.84 ppm from LiI.

A DEE solution of **2** was also titrated with tetrahydrothiophene (THT). At 2.8 equiv of THT, the ^{6}Li NMR spectrum at −55 °C showed insignificant changes both with respect to chemical shift and coupling constants of the signals originating from **2**. Clearly, THT show weak coordination to the lithiums in **2** and therefore does not have the ability to dissociate **2** into **3**. A search in the CSD crystallographic database revealed no examples of sulfur coordination to diagonal Cu(I), and therefore coordination of THT to copper in **2** seems less likely.[17]

A control experiment was performed to obtain complex **3** in high concentration. First we prepared *n*-BuCu in DEE at −70 °C by addition of *n*-BuLi to CuI. To the obtained *n*-BuCu/LiI mixture we added a DEE solution of the lithium salt of **1** at −70 °C, prepared in another NMR tube. The resulting ^{6}Li NMR spectra displayed three signals upon addition of <1 equiv of **1** with respect to *n*-BuCu. One signal at δ 0.84 ppm from LiI, a doublet at δ 1.54 ppm (J ^{6}Li,^{15}N = 4.6 Hz) resulting from **3**, and finally two doublets at δ 2.00 and 2.06 ppm (J ^{6}Li,^{15}N = 6.0 and 4.8 Hz, respectively) originating from **2**. The ^{6}Li NMR signal at δ 1.54 has to originate from **3** due to that two sets of ^{13}C NMR signals are observed and that the ^{6}Li-^{15}N coupling constant (J ^{6}Li,^{15}N = 4.6 Hz) is in the range found for a tetracoordinated lithium, Figure 2.

With this experiment we have shown that there is a concentration dependent equilibrium between **2** and **3**.

In another experiment we started from a mixture of CuI and **1** in DEE which was titrated by *n*-BuLi. In this case we observed that *n*-BuCu was first formed followed by formation of the lithium salt of **1**, which immediately forms **3** with *n*-BuCu. Further additions of up to 2 equiv *n*-BuLi with respect to CuI, gave a ^{6}Li NMR spectrum consistent with **2**.

The ^{1}H NMR spectrum at −70 °C showed three different α-methylene proton signals from *n*-BuCu, at δ 0.06, −0.03, and −0.25. The signals at δ 0.06 and −0.03 ppm were found to be in a 1:1 ratio, indicating that these α-methylene protons originate from one and the same complex and that they are diastereotopic.[13] The appearance of diastereotopic α-methylene protons due to complexation of *n*-BuLi to chiral lithium amides has previously been reported.[18] Raising the temperature well above −30 °C for 10 min, however, results in the disappearance of all the α-methylene proton signals from *n*-BuCu in **2**. Vinylic proton signals appeared at δ 4.96 (2H) and 5.86 (1H) due to 1,2-elimination of *n*-BuCu to butene.

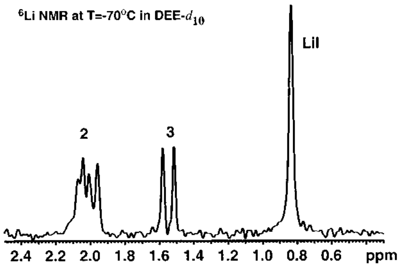


Figure 2. ^{6}Li NMR spectra of **2** in DEE-d_{10} with approximately 1.5 equiv of *n*-BuLi with respect to **1**, showing the complex **2**, **3**, and LiI.

To summarize, the findings from our NMR spectroscopic studies show that the complex initially formed is indeed the dimeric structure proposed by Rossiter and co-workers.[6] When excess or neat THF is used, the equilibrium disfavors the amidocuprate complexes **2** and **3** for the dimeric lithium amide complex **4** and *n*-BuCu. The released *n*-BuCu is not stable in THF or DEE at temperatures above −50 °C, affording butene. Thus, there is a difference in stability of *n*-BuCu when complexed in **2** and **3** as compared to noncomplexed *n*-BuCu.[19] The decomposition of the amidocuprate **2** to **3**, and finally to **4** and noncomplexed *n*-BuCu, will also result in loss of enantioselectivity.

The ee and yield obtained by Rossiter and co-workers using DEE, dimethyl sulfide (DMS), and THF can be explained as follows; in DEE the yield and ee are high as the reactive amidocuprate complex **2** is intact. In DMS, on the other hand, the ee was found to drop, but the yield was still high. This is in agreement with our findings when **2** was titrated with THT; the complex **2** was found to be intact, suggesting a very weak coordination of THT to lithium, and therefore the yield is high. The effect upon the enantiomeric excess has to be explained by important solvent molecule interactions in the transition state. Finally, in THF the complex **2** ultimately deaggregates into **4** and *n*-BuCu, resulting in low ee and yield due to loss of stereocontrol and 1,2-elimination of *n*-BuCu. The magnitude of the ^{6}Li,^{15}N coupling constants indicate that the pyrrolidinyl ring remains coordinated to the lithium cation in **2**, **3**, and **4** even if THF or THT are used.

The origin of the observed enantioselectivity in the 1,4 alkylation of enones is a consequence of the substrates preferred coordination to only one of the two Li cations in the catalytic amidocuprate complex **2**. The copper atoms are thus accessible for coordination to the enone double bond, forming an activated complex.

Supporting Information Available: ^{1}H, ^{13}C, NMR spectra and a heterocorrelated 2D ^{6}Li,^{15}N HMQC NMR spectrum of the [(lithium amide)/(*n*-BuCu)]$_2$ complex **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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