Lithium Heterocuprates: The Influence of the Amido Group on Organoamidocuprate Structure

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<td>Complete List of Authors:</td>
<td>Bomparola, Roberta; Imperial College London, Dept of Chemistry Davies, Robert; Imperial College London, Dept of Chemistry Hornauer, Stefan; Imperial College London, Dept of Chemistry White, Andrew; Imperial College London, Department of Chemistry</td>
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Lithium Heterocuprates: The Influence of the Amido Group on Organoamidocuprate Structure

Roberta Bomparola, Robert P. Davies*, Stefan Hornaeur and Andrew J. P. White

*Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, UK.

E-mail: r.davies@imperial.ac.uk; Tel: +44 (0)207 5945754

Abstract

Lithium organoamidocuprates of general stoichiometry LiCuR(NR’2) are an important class of organocupper reagent and have found widespread application in conjugate addition and other bond forming reactions. The dependency of the structures and equilibrium of these species upon the steric and electronic properties of the amido group is reported in both the solid state and solution.

Three different cuprate complexes have been crystallographically characterized: the organoamidocuprate [Cu₂Li₂Mes₂TMP₂] (2) (TMP = 2,2,6,6-tetramethylpiperidide) which is shown to adopt a head-to-tail confirmation; [Cu₂Li₂N(CH₂Ph)CH₂CH₂NMe₂]₄ (3) which is an homoamidocuprate and contains additional coordination of the lithium centres from intra-molecular tertiary amine groups; and the diastereomeric organoamidocuprate [Cu₂Li₂Mes₂(N(R-CH(Ph)Me)(CH₂CF₃))₂] 4 which adopts a head-to-head confirmation. Complex 4 is unique in being the first crystallographically characterised example of a head-to-head isomer of a heterocuprate and its structure also has implications for the use of scalemic amidocuprates in asymmetrically induced conjugate addition. The solution equilibriums of all new complexes have also been studied using ⁷Li NMR spectroscopy and in each case the species observed in the crystal structure was shown to also be the predominate isomer in solution.
Introduction

Lithium organoamidocuprates constitute an important sub-class of stoichiometric organocopper reagents, with well-documented applications in a number of organic bond-forming transformations, most notably conjugate addition.\(^1\)\(^2\) They conform to the general stoichiometry LiCuR(NR')\(^2\) and therefore differ from traditional Gilman homocuprates (LiCuR\(^2\)) by replacement of one of the reactive organo groups (R) with a non-transferable amido group (NR'). These species were originally introduced as a means of combating one of main drawbacks associated with lithium homocuprate reagents, namely that in most applications one of the potentially valuable organo R groups remains attached to the copper center and is therefore not transferred to the substrate and is effectively wasted. In addition, they often exhibit significant advantages in terms of thermal stability and ease of use. Scalemic amidocuprates have also been studied in depth and with some limited success for applications in asymmetric synthesis.\(^3\)\(^-\)\(^5\)

In recent years there has been much progress towards building a more thorough understanding of Gilman homocuprates, including their solid-state\(^6\) and solution\(^7\) structures and mechanisms of operation\(^8\). However, in comparison there are far fewer reported structural and mechanistic studies of organo-amidocuprates. Our group has recently reported on the lithium organo-amidocuprate [Cu\(_2\)Li\(_2\)Mes\(_2\){N(CH\(_2\)Ph)\(_2\)}] (Mes = 2,4,6-trimethylphenyl) which was shown to adopt a dimeric head-to-tail confirmation in the solid-state (I, Scheme 1) and exist in non-polar solvents in equilibrium with a range of dimeric aggregates including the head-to-tail isomer (I) a head-to-head isomer (II), a mixed homocuprate isomer (III) and the parent homo-diorganocuprate and homo-\textit{bis}(amido)cuprate species (IV and V respectively).\(^9\) These species were identified with the aid of inverse-detected \(^1\)H-\(^7\)Li 2H HOESY NMR spectroscopy. The presence of more than one isomer in solution is significant for the synthetic applications of these reagents, especially since the most thermodynamically stable isomer is not necessarily the kinetically reactive one. This is of particular relevance to asymmetric addition
reactions involving scalemic lithium amidocuprate reagents, and may in part explain the difficulties often encountered when trying to achieve high enantiomeric excesses with these reagents.

\[
\begin{align*}
\text{Scheme 1} & \quad \text{Solution equilibrium for Lithium organo-amidocuprates}^{9} \\

\end{align*}
\]

The structures and reactivity of lithium diorganocuprates (LiCuR\(_2\)) have previously been shown to be highly dependent upon the solvent system, and thus solvent effects have also been studied for organoamidocuprates LiCuR(NR’)\(_2\) for R = Mes, R’ = CH\(_2\)Ph\(^{10}\) and R = nBu, R’ = N-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine\(^{11}\). Unlike diorganocuprates whose contact ion pair (CIP) form undergoes dissociation in the presence of strongly lithium-coordinating solvents such as THF to give solvent separate ion pairs (SSIPs), addition of THF to organo-amidocuprates has been shown to lead to disaggregation of the dimer and the formation of solvated CIP monomers (VI, Scheme 2). In addition, some decomposition to give the homo-metallic lithium amide and organocopper parent species has been observed.\(^{10,11}\)
Despite these recent advances, structural and mechanistic knowledge of organo-amidocuprates still significantly lags that of diorganocuprates, and is currently limited to a few specific amido groups. This is particularly evident with respect to solid-state characterizations of these species: only one example of a head-to-tail dimer (I) has been reported (vide supra), and there are no reported examples of the proposed head-to-head (II) and mixed homocuprate (III) dimeric configurations. In this work the structures (both solid state and solution) of some novel organo-amidocuprates are presented. A number of new amido groups have been employed in this study including a sterically bulky amido group, an amido group functionalized with an additional tertiary amine donor site and a chiral (entantiomerically pure) amido group.

**Results and Discussion**

Lithium organocuprates and heterocuprates tend to be highly air, moisture and temperature sensitive, often decomposing rapidly at temperatures below 0 °C. This has made the study of their structures and mechanism of operation highly challenging. Nevertheless, previous work in our group has shown organocuprates containing the aromatic mesityl group can act as ideal models for these species, being easier to handle and thermally stable up to much higher temperatures. This can be attributed, at least in part, to their lack of β-hydrogens, thus avoiding decomposition by β-hydride
elimination pathways. For example \([\text{Cu}_2\text{Li}_2\text{Mes}_2]\) (Mes = \(\text{C}_6\text{H}_2\text{Me}_3\cdot2,4,6\)) was shown to be thermally stable up to 189 °C.\(^{12}\) Lithium organoamidocuprates presented in this work have been prepared in high purity from the treatment of copper(I) mesityl (CuMes) with the appropriate lithium amide. Identification of the aggregates present in solution is based primarily upon the interpretation of \(^7\text{Li}\) NMR data and, where applicable, also using modified Pulsed Field Gradient (PFG) inverse-detected \(^1\text{H}-^7\text{Li}\) HOESY NMR spectroscopy. The organoamidocuprate \([\text{Cu}_2\text{Li}_2\text{Mes}_2\text{(N(CH}_2\text{Ph})_2}]\) 1 was the first heterocuprate to be studied in depth using these techniques\(^9\) and the results presented here build upon this previous work, drawing comparisons with these earlier findings in order to highlight the influence of the differing steric properties and functionalization of the amido group.

\[\text{[Cu}_2\text{Li}_2\text{Mes}_2\text{TMP}_2]\] (2)

The 2,2,6,6-tetramethylpiperidide (TMP) group has been widely employed and studied in main group coordination chemistry, particularly in combination with s-block metals,\(^{13,14}\) and is a key component in a large number of organic synthetic protocols.\(^{14-17}\) The four methyl groups in TMP provide increased steric bulk around the nitrogen centre and also lead to a larger concentration of negative charge on the nitrogen anion when compared to other common amido ligands such as the dibenzylamido group present in 1. This makes the TMP ligand an interesting target for incorporation into organoamidocuprates.

Treatment of CuMes with LiTMP in toluene gave a clear solution from which crystals of \([\text{Cu}_2\text{Li}_2\text{Mes}_2\text{TMP}_2]\) 2 were obtained. Single crystal X-ray diffraction studies reveal 2 to adopt a head-to-tail motif (type I in Scheme 1) in which two \([\text{RCu(TMP)})]\ cuprate units lie antiparallel to one another to impart a dimeric centrosymmetric conformation (Figure 1). Within the structure of 2 both copper atoms adopt near-to-linear arrangements (N1-Cu-C11 = 177.85(5)°), with Cu-N1 and Cu-C11 bond lengths of 1.9277(11) and 1.9124(14) Å respectively. The lithium cation is coordinated to an
amido nitrogen (Li-N = 1.964(3) Å) and is also η⁶ coordinate to a mesityl aryl ring (Li-C range 2.355(3) to 2.506(3) Å, mean 2.416 Å). The head-to-tail isomeric form and also the bonding parameters exhibited by TMP cuprate 2 are very similar to those previously reported for the dibenzylamido complex [Cu₂Li₂(Mes)₂(N(CH₂Ph)₂)₂] 1.⁹ Hence, despite an increase in amido steric bulk for the TMP group there is little overall effect on the observed structure (at least in the solid state). Complex 2 represents only the second structurally characterised example of a dimeric organoamidocuprate – although a small number of THF solvated monomeric organoamidocuprates have also been reported in the literature.¹⁰,¹⁸

![Figure 1](image.png)

**Figure 1.** The molecular structure of [Cu₂Li₂Mes₂TMP₂] (2); thermal ellipsoids are set at 50% and hydrogen atoms have been omitted for clarity.

Nevertheless, the solution behaviour of 2 in toluene, as studied using ⁷Li NMR spectroscopy (Figure 2), does show some distinct differences to that previously reported for 1 (also reproduced in Figure 2
for comparison). The largest resonance in the $^7$Li NMR spectrum of 2 at -4.96 ppm is distinctive of a lithium cation coordinated to a nitrogen anion and $\eta^6$-coordinate to one aryl ring, thus leading to an upfield shift. This resonance can therefore be assigned to the head-to-tail dimer (I, Scheme 1) which is the structure also observed for 2 in the solid state (Figure 1). The weaker resonance at -10.95 ppm is attributable to a lithium cation sandwiched between two aryl groups, and thus experiencing an increased upfield shift from both ring systems. This peak can be explained by the presence in solution of the head-to-head isomer II. The corresponding bis-amido coordinated lithium atom in isomer II can be assigned to the broad resonance at 1.79 ppm, although this resonance could also potentially be explained by the presence of a homoamidocuprate of type V. However the absence of a resonance attributable to the homo-organocuprate [Cu$_2$Li$_2$Mes$_4$] IV ($\delta = -9.99$) suggests the former of these assignments (the head-to-head isomer II) to be the more likely as V would be expected to form concurrently with IV (see Scheme 1). The resonance at -3.35 ppm can tentatively be explained by a lithium cation coordinated both by a nitrogen anion and $\eta^1$ to an aryl ring, such as in the mixed homo-cuprate species III.

![Figure 2. $^7$Li NMR spectrum of 1 (top) and 2 (bottom) in [D$_8$]-toluene (298 K)](image)
Direct comparison of the $^7$Li NMR spectra of 1 and 2 (Figure 2) reveals small changes in chemical shifts associated with the different amido groups, and more revealing an increased predominance of the head-to-tail isomer I in the TMP adduct 2 and the absence of any homocuprate isomers (IV, V).

One possible explanation for these observations is that the head-to-head and homoamidocuprate isomers are destabilised in the TMP complexes due to increased steric interaction between the adjacent TMP ligands. To further explore this density functional calculations (B3LYP) were performed on the model system $[\text{Cu}_2\text{Li}_2\text{Me}_2(N\text{R}_2)_2]$ where $R = \text{H, Me, tBu}$ in order to investigate the effect of increasing steric bulk of the amido group on the relative thermodynamic stabilities of the different isomers (Table 1). In all cases the head-to-tail isomer I was shown to be the lowest energy conformation and this is in agreement with previous research on 1. However, the energy gap between this and the other isomers such as the head-to-head dimer (II) and the homodimers (IV and V) increases with increasing steric bulk of the amido group, particularly for the tBu substituted amide. The 3:1 and 1:3 isomers $[\text{Cu}_2\text{Li}_2\text{Me}_3(N\text{R}_2)]$ (VII) and $[\text{Cu}_2\text{Li}_2\text{Me}(N\text{R}_2)_3]$ (VIII) were also included for completeness, although at present there is no experimental evidence for either of these isomers in organoamidocuprate solutions.

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<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0.744</td>
<td>1.052</td>
<td>6.250</td>
</tr>
<tr>
<td>III</td>
<td>1.763</td>
<td>1.235</td>
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These calculations are therefore congruent with the NMR spectra, indicating an increased preference for the head-to-tail isomer with the more bulky amido ligand. It should be noted that although the head-to-head and homocuprate species are considered thermodynamically disfavoured in the solution equilibrium of \( \text{2} \), the relative energy of these species is not so prohibitively high to prevent their formation. Indeed the homoamidocuprate species \( \text{V} \) for complex \( \text{2} \), \([\text{Cu}_2\text{Li}_2\text{TMP}_4]\), has recently been prepared by Komagawa and co-workers from the direct reaction of \( \text{CuI} \) with two equivalents of \( \text{LiTMP} \).\(^{19}\)

\[ [\text{Cu}_2\text{Li}_2(\text{N(CH}_2\text{Ph})\text{CH}_2\text{CH}_2\text{NMe}_2)_4] (3) \]

The introduction of donor ligands such as \( \text{THF} \) and \( \text{TMEDA} \) (\( N,N,N',N' \)-tetramethylethane-1,2-diamine) has been shown to break up organoamidocuprate aggregates to give monomeric species (see Scheme II and discussion above). This led us to now investigate amido ligands that also contain additional donor-functionality. Thus, the role of an additional tertiary amine group on cuprate equilibrium and possible disaggregation processes was studied using the amine \( N'\)-benzyl-\( N,N \)-dimethylethane-1,2-diamine.

Treatment of \( N'\)-benzyl-\( N,N \)-dimethylethane-1,2-diamine with \( n \)-butyllithium gave the corresponding lithium amide which was further treated with copper(I) mesityl in toluene to give a red solution. Colourless crystals were obtained from such a solution on standing for 48 hours. X-ray structural

| \( \frac{1}{2} (\text{IV} + \text{V}) \) | 1.152 | 2.014 | 6.095 |
| \( \frac{1}{2} (\text{VII} + \text{VIII}) \) | 2.010 | 1.090 | 13.923 |

Table 1 Relative energies (kcal mol\(^{-1}\)) of potential equilibrium species (shown above) at the B3LYP/631AS level.
studies on these crystals (Figure 3) reveal surprisingly not a heterocuprate, but the homoamidocuprate \([\text{Cu}_2\text{Li}_2\{\text{N}((\text{CH}_3)\text{Ph})\text{CH}_2\text{CH}_2\text{NMe}_2\}_4]\) (3).

![Figure 3. Orthogonal views of the molecular structure of \([\text{Cu}_2\text{Li}_2\{\text{N}((\text{CH}_3)\text{Ph})\text{CH}_2\text{CH}_2\text{NMe}_2\}_4]\), 3; thermal ellipsoids are set at 40% and hydrogen atoms have been omitted for clarity.](image)

In the dimeric complex 3 both amidocuprate units are close to linear at (N6-Cu1-N66 = 177.85(10)°; N26-Cu2-N46 = 178.43(10)°). Cu-N(amide) distances range from 1.884(2) to 1.896(2) Å (mean, 1.889 Å) and are therefore comparable to Cu-N distances in 1 and 2. However, in contrast to 1 and 2
where the cuprate units lie approximately parallel to one another, in 3 the cuprate units are significantly twisted with respect to each other (see Figure 3), adopting a closer to orthogonal arrangement (N6-Cu1-Cu2-N26 torsion angle = 66.08(11)°, N66-Cu1-Cu2-N46 torsion angle = 67.15(11)°). Each lithium cation in 3 is tetracoordinated by two amido nitrogen anions and two amine nitrogens in a distorted tetrahedral fashion. Mean Li-N(amido) distances (2.047 Å) are significantly shorter than the mean Li-N(amine) distances (2.229 Å). The amido nitrogen atoms in 3, by virtue of being attached to four different groups (Cu, Li, CH$_2$Ph and CH$_2$CH$_2$NMe$_2$), become chiral with only the R, R, R, R (shown in Figure 3) and S, S, S, S diastereoisomers found in the crystal lattice.

Although previous solution studies have suggested homoamidocuprate aggregates (V) to be present in heteroamidocuprate reaction mixtures (Scheme 1), as far as we are aware this is first time that crystals of a homoamidocuprate have been obtained from such as solution. Indeed, examples of structurally characterised homoamidocuprates are very rare in the literature although a small number of TMP based lithium homocuprate aggregates have been prepared by direct synthesis.

Solution spectroscopic studies on crystals of 3 in D$_8$-toluene revealed a single broad resonance in the \textsuperscript{7}Li NMR spectrum at 0.30 ppm. This is in the region expected for a fourfold nitrogen coordinated lithium and is consistent with retention of the solid-state structure in solution. In the corresponding \textsuperscript{1}H NMR spectrum the benzylic protons are split giving two doublets at 4.75 and 5.21 ppm, again indicating retention of the dimeric structure on the NMR timescale.

The reaction mixture between the lithium amide and copper(I) mesityl was also analysed by \textsuperscript{7}Li NMR spectroscopy. In addition to the broad peak at 0.30 ppm due to 3, there was an addition peak at -9.93 ppm that can be attributed to [Cu$_2$Li$_2$Mes$_4$] (δ = -9.99). This is expected to form concurrently with 3 (see Scheme 1). However, no other isomeric species were observable in the spectrum suggesting the equilibrium lies almost exclusively on the side of the homocuprates IV and V. It is not clear at present whether this is due to steric or electronic effects caused by the incorporation of the additional amine-donor group, and further studies to fully explore this are ongoing.
[Cu$_2$Li$_2$Mes$_2$(N(R-CH(Ph)Me)(CH$_2$CF$_3$)$_2$)] (4)

Lithium organoamidocuprates with scalemic amido groups have previously attracted much attention for applications in enantioselective synthesis.$^{3-5,22}$ However, success in this area has been somewhat limited to date with many reactions suffering from either poor enantiomeric excess or poor yield. It has been suggested that the symmetric head-to-tail dimeric isomer (I, Scheme 1) is key to promoting asymmetric induction in conjugate addition reactions with these reagents.$^{23,24}$ Although NMR studies with chiral amidocuprates have shed light on the potential role of a dimeric diastereomeric aggregate in solution,$^{11,25}$ there are currently no structurally characterised examples of chiral organoamidocuprates in the literature.

The enantiopure amine (R)-1-phenylethyl-2,2,2-trifluoroethylamine was first prepared by Koga,$^{26}$ and the corresponding chiral lithium amide has also been studied in some depth by Simpkins.$^{27}$ In this work reaction of LiN(R-CH(Ph)Me)(CH$_2$CF$_3$) with CuMes in toluene gave a solution from which crystals of the organoamidocuprate [Cu$_2$Li$_2$Mes$_2$(N(R-CH(Ph)Me)(CH$_2$CF$_3$)$_2$)] (4) were obtained. X-ray diffraction studies (Figure 4) show 4 to be a heterocuprate with head-to-head (II) conformation. The N-Cu-C based cuprate anions run parallel to one another so that two amido nitrogens bond to one lithium (Li1), with the other lithium (Li2) sandwiched between two aryl groups. Although head-to-head heterocuprates have previously been proposed by us based upon the interpretation of NMR spectroscopy solution studies,$^{9}$ this result is significant in that it represents the first crystallographically characterised example of such an isomer.
The two C-Cu-N heterocuprate units within 4 are both close-to-linear in geometry (C1-Cu1-N1, 177.0(3)°; C2-Cu2-N2 = 177.4(2)°). Within these cuprate units Cu-C distances are, at 1.903(6) Å (Cu1-C1) and 1.903(5) Å (Cu2-C20), the shortest so far observed for a copper-mesityl bond, whilst Cu-N distances (both 1.910(5) Å) are similar in magnitude to Cu-N distances in 1 and 2 and slightly shorter
than Cu-N(amide) distances in 3. Uniquely, as well as being coordinated by two amido-nitrogens Li1 also forms short Li-F interactions (Li1•F2, Li1•F4) with the two neighbouring trifluoromethyl groups (mean Li-F, 2.202 Å). These additional interactions give rise to elongated Li-N(amide) distances in 4 (Li1-N1, 2.045(10) Å; Li-N2 2.008(10) Å) when compared to 1 or 2, although they are comparable in length to those reported above for 3 where an additional lithium coordinating group is also present. The other lithium cation, Li2, is sandwiched directly between the two mesityl aromatic rings via η6,η6 coordination with a mean Li-C distance of 2.282 Å (range, 2.2297(13)-2.437(12) Å) and is closely comparable to the η6,η6-coordinated lithium cation previously reported in [Cu3LiMes4]. However, in contrast to [Cu3LiMes4] the mesityl rings in 4 are staggered with respect to each other by approximately 27° (see Figure 4) which more readily allows accommodation of the elongated Li-N(amide) distances and F·Li interactions as discussed above.

The solid-state structure of 4 possess a total of four stereocentres; two carbon centred R stereocentres (C10 and C20), from the original enantiopure amine, and two stereocentres at the amido nitrogens (N1 and N2) generated by assembly of the dimer (in analogous fashion to the chiral amido nitrogen centres in 3). Both amido-nitrogens in 4 adopt an S configuration, resulting in the CH2CF3 groups being sited on opposite sides of the eight-membered (CCuNLi)2 ring, thus allowing both to coordinate to the lithium centre whilst minimising steric congestion. An R, S or S, R conformation at these positions would site the CH2CF3 groups on the same side of the ring, and an R, R configuration would result in the methyl groups pointing directly towards the CH2CF3 groups (assuming the benzyl group orientations remain unchanged), all of which would seem unfavourable on steric grounds.

The 7Li NMR spectrum of 4 in D8-toluene displays a number of resonances in the range δ = 2.11 to -11.63 (Figure 5) with many similarities to the 7Li NMR spectra of 1 and 2 shown in Figure 1. The resonances with the largest intensities are a sharp peak at -11.63 ppm and a broader peak at 2.11 ppm. These two resonances can be assigned to the two different lithium cation environments in
the head-to-head isomer \( \text{II} \), which is the isomeric form observed in the solid state (Figure 4). The resonance with chemical shift -11.63 is shifted significantly upfield and is indicative of a lithium cation directly \( \eta^6,\eta^6 \)-sandwiched between two aryl rings and therefore experiencing the upfield shift from both rings. A similarly \( \eta^6,\eta^6 \)-coordinated lithium cation has previous been reported in homocuprate \([\text{Cu}_3\text{LiMes}_4]\) (\( \delta = -11.02^{12} \)). The resonance at 2.11 ppm can be assigned to the \textit{bis}(amido) coordinated lithium cation in \( \text{II} \). Further evidence for these assignments is provided by the PFG inverse-detected \(^1\text{H}-^7\text{Li} \) HOESY NMR spectrum of 4 (see Supplementary Information) with the \(^7\text{Li} \) NMR resonance at -11.63 ppm showing cross-correlations solely to protons on the mesityl groups and the resonance at 2.11 ppm displaying cross-correlations solely to methyl protons on the amido ligand. Less intense resonances at -11.33 and 1.25 ppm have similar chemical shifts to those discussed above and can tentatively also be ascribed to a head-to-head dimer \( \text{II}' \), with the differing chemical shifts possibly due to different stereochemistry at the amido nitrogen centres, \( (R, R \text{ or } S) \).

\[\text{Figure 5.} \; ^7\text{Li} \; \text{NMR spectrum of 4 in [D}_8\text{-toluene} \,(298 \text{ K})}\]
The existence of head-to-tail isomers in solution can be inferred from the characteristic $^7$Li NMR resonances at -5.25 and -5.90 ppm (vide supra), with the presence of two peaks in this region suggesting two different head-to-head isomers (I and I') - possibly diastereoisomers of the same head-to-tail complex. The small signal at -9.97 ppm can be assigned to the homo-organocuprate species [Cu$_2$Li$_2$Mes$_4$] (IV) (lit. -9.99 ppm$^{12}$) with the corresponding homo-amidocuprate [Cu$_2$Li$_2$(N($R$-CH(Ph)Me)(CH$_2$CF$_3$)$_4$] (V) cautiously assigned to the broad resonance centered at 0.90 ppm.

In contrast to organoamidocuprates 1 and 2 in which the head-to-tail isomers (I) were shown to dominate, the NMR spectra for 4 indicates the head-to-head isomer (II) to be the most abundant species. This head-to-head isomer doesn’t fit the model previously prescribed by Rossiter and others$^3, 11, 23, 24$ for enantioselectivity in asymmetric addition reactions, since both faces of the complex are equally sterically hindered and therefore are not able to chaperone the enone into the preferred conformation for controlled asymmetric addition. If appreciable quantities of head-to-head isomers are also present in the solutions of other chiral organoamidocuprates this could perhaps go some way towards explaining why high enantioselectivity has often proven so elusive with these reagents.

Conclusions

A wide variety of amido groups, including scalemic amido groups, have been reported in the literature for the preparation of heterocuprates. These organoamidocuprates have well-documented applications in organic synthesis, and in particular in conjugate addition reactions. However, studies to date on the mechanisms and solid-state and solution structures of organoamidocuprates have focussed on a very narrow range of amido groups. This work reported
herein has demonstrated how the steric and electronic properties of the amido group can significantly influence where their solution equilibrium lies, and has also led to the isolation and crystallographic characterisation of the first example of a head-to-head isomer of a heterocuprate (4).

For the system $[\text{Cu}_2\text{Li}_2\text{(Mes)}_2(\text{NR}_2)_2]$ in non-polar solvents, increasing the steric bulk of the amido ($\text{NR}_2$) group from $\text{N(CH}_2\text{Ph)}_2$ (1) to TMP (2) has been shown to move the solution equilibrium increasingly towards the head-to-tail isomer (see Scheme 1). DFT calculations have also shown how increasing steric bulk is likely to favour this isomer as the amido groups are sited on opposite corners of the dimer with each coordinating to a different lithium cation, thus minimising steric interactions.

The influence of incorporating additional Lewis base donor group functionality on the amido group was also explored. Treatment of the lithium amide $\text{LiN(CH}_2\text{Ph)}\text{CH}_2\text{CH}_2\text{NMe}_2$ with $\text{CuMes}$ yielded just the lithium homoamidocuprate 3 with the newly introduced tertiary amine functionality coordinating to the lithium cation in the solid-state structure of this complex. Solutions studies show just the homoamidocuprate 3 and homoorganocuprate $[\text{Cu}_2\text{Li}_2\text{Mes}_4]$ to be present in solution, with no evidence of any heterocuprate species.

Lastly the organoamidocuprate $[\text{Cu}_2\text{Li}_2\text{Mes}_2(\text{N(R-CH(Ph)Me)})\text{(CH}_2\text{CF}_3)_2]$ (4) has been prepared containing an enantiopure amido group. In contrast to complexes 1 and 2, cuprate 4 adopts a head-to-head motif in the solid state, and the solution equilibrium is also shown to be shifted towards this isomer. As well as being of interest as the first crystallographically characterised head-to-head heterocuprate, the structure of 4 is of particular significance as it represents a potential model for scalemic amidocuprates which have applications in asymmetric conjugate addition reactions. Previous models for asymmetric induction with organoamidocuprates have assumed the reagent to adopt a head-to-tail isomeric form, however from this work it is clear that other solution isomers (which are likely to have different selectivity) need also to be considered. Work to extend this
research to more amido groups and also to fully access the role the differing isomeric structures have on reactivity and the mechanism of reaction is ongoing.

**Experimental**

**General**

All experimental work was carried out under an inert atmosphere of nitrogen using standard Schlenk double manifold and glovebox techniques. Purification and drying of the solvents was carried out following standard methods or using an Innovative Technologies PureSolv Solvent Purification System with purification grade solvents. Copper(I) mesityl$^{28}$ and (R)-1-phenylethyl-2,2,2-trifluoroethylamine$^{26}$ were prepared according to the literature procedures and their purities were monitored by NMR and elemental analyses. NMR spectra were recorded on a Bruker DPX400 spectrometer with internal standards. Melting points were measured in capillaries sealed under nitrogen. The high air and moisture sensitivity of products 2-4 precluded the collection of satisfactory microanalysis data on these complexes.

**Synthesis of [Cu$_2$Li$_2$Mes$_2$TMP$_2$] (2)**

A solution of n-BuLi in hexanes (1.6 M, 1.25 ml, 2 mmol) was added drop-wise to a solution of tetramethylpiperidine (0.22 ml, 2 mmol) in 5 ml toluene at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 hour. A solution of copper(I) mesityl (366 mg, 2 mmol) in 5 ml toluene was then added drop-wise and the reaction mixture was stirred for a further 1 hour. Storage of the resultant solution at room temperature for 12 h yielded a batch of colourless crystals of [Cu$_2$Li$_2$Mes$_2$TMP$_2$] (2) suitable for X-ray analysis (0.402 g, 61%). M.p. 190 °C (decomp.). $^1$H-NMR (400 MHz, 25 °C, [D$_8$]-toluene): $\delta = 6.83$ (s, 2H, Ar-H); 6.78 (s, 2H, Ar-H); 3.04 (s, 12H, ortho-CH$_3$); 2.27 (s,
3H, para-CH₃); 2.13 (s, 3H, para-CH₃); 1.65 (m, 4H, CH₂ in TMP); 1.35 (t, 8H, J = 6.0 Hz, CH₂ in TMP);
1.17 (s, 24H, CH₃ in TMP). ⁷Li NMR (155.6 MHz, 25°C, [D₈]-toluene): δ = -10.95; -4.96; -3.35; 1.79 (see Figure 1).

**Synthesis of [Cu₂Li₂(N(CH₂Ph)CH₂CH₂NMe₂)₄] (3)**

A solution of tert-BuLi in pentane (1.5 M, 1.33 ml, 2 mmol) was added drop-wise to a solution of N’-
benzyl-N,N-dimethylethane-1,2-diamine (0.41 ml, 2 mmol) in 3 ml toluene at 0 °C to give a dark pink
solution. The mixture was stirred for 1 hour, and a solution of copper(I) mesityl (366 mg, 2 mmol) in
3 ml toluene was then added drop-wise. The reaction mixture was stirred for a further 15 minutes,
filtered over Celite and the volume reduced in vacuo to 2 ml. After storage for 2 days at 4 °C large, a
batch of colourless prismatic needless of [Cu₂Li₂(N(CH₂Ph)CH₂CH₂NMe₂)₄] (3) were obtained (yield
0.543 g, 74 %). M.p. 108-110 °C. ¹H NMR (400 MHz, 25 °C, [D₈]-toluene): δ = 7.44–7.23 (Ar-H, m, 5H);
5.21 (benzyl-CH₂, d, J = 14.6 Hz, 1H); 4.75 (benzyl-CH₂, d, J = 14.6 Hz, 1H); 4.18–4.27
(N(CH₂Ph)CH₂CH₂NMe₂); m, 2H), 2.81-3.06 (N(CH₂Ph)CH₂CH₂NMe₂, m, 2H); 2.31 (methyl, s, 6H). ⁷Li
NMR (155.6 MHz, 25°C, [D₈]-toluene): δ = 0.30.

**Synthesis of [Cu₂Li₂Mes₂(N(R-CH(Ph)Me)(CH₂CF₃))₄] (4)**

A solution of n-BuLi in hexanes (1.6 M, 1.25 ml, 2 mmol) was added drop-wise to a solution of (R)-1-
phenylethyl-2,2,2-trifluoroethylamine (0.406 g, 2 mmol) in 5 ml toluene at 0 °C and stirred for 1
hour. A solution of copper(I) mesityl (365 mg, 2 mmol) in 5 ml toluene was then added drop-wise
and the reaction mixture was stirred for a further 30 minutes at 0 °C. The resulting solution filtered
over Celite and the volume reduced in vacuo to 2 ml. After storage for 7 days at -20 °C a batch of
light brown crystals of [Cu₂Li₂Mes₂(N(R-CH(Ph)Me)(CH₂CF₃))₄] (4) were obtained (yield 177 mg, 23 %).
¹H NMR (400 MHz, 25 °C, [D₈]-toluene): δ = 7.77–6.20 (m, 7H, Ar-H); 4.33–2.61 (m, 3H,
N(CH(CH₃)CH₃)(CH₂CF₃); 2.46 (s, 3H, ortho-CH₃); 2.45 (s, 3H, ortho-CH₃); 1.76, 1.75 (2s, 3H, para-CH₃); 2.09–0.78 (m, 3H, N(CH(CH₃)CH₃)(CH₂CF₃). ^{7}Li NMR (155.6 MHz, 25°C, [D₈]-toluene): δ = 2.11; 1.25; 0.90 (br); -5.25; -5.90; -9.97; -11.33; -11.63 (see Figure 5).

X-ray structure determinations of 2, 3 and 4

The crystals were all taken directly from the mother liquor, covered with a perfluorinated ether, and mounted on the top of a glass capillary under a flow of cold gaseous nitrogen. The data were collected using an Oxford Diffraction Xcalibur PX Ultra diffractometer (2), Oxford Diffraction Xcalibur 3 diffractometer (3) or Nonius Kappa-CCD diffractometer (4), all fitted with Oxford Cryostream low-temperature devices. The structures were refined based on F² using the SHELXTL and SHELX-97 program systems. Table 2 provides a summary of the crystallographic data for all compounds. The crystal structure data have been deposited with the Cambridge Crystallographic Data Center under deposition numbers CCDC 994559 (2), 994560 (3), and 994561 (4).

Table 2. Summary of Crystal Structure Data for 2, 3 and 4

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**Calculations**

All calculations were carried out with a Gaussian 09 package. The density functional theory method was employed using the B3LYP hybrid functional. Structures were optimised with a basis set consisting of the all electron SVP basis set by Horn and Ahlrichs for copper and 6-31G(d) for all other atoms. The method and basis set used here (denoted as B3LYP/631AS) have been applied to the optimisation of other lithium cuprates and are known to give reliable results. Frequency analysis was carried out after geometry optimization to confirm the models were true energy minima with no imaginary frequencies.

**Acknowledgements**

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**References**


Lithium Heterocuprates: The Influence of the Amido Group on Organoamidocuprate Structure

Roberta Bomparola, Robert P. Davies, Stefan Hornaeur and Andrew J. P. White

The structural isomers of a number of lithium heteroamidocuprates LiCuR(NR')₂ have been studied in the solid state and solution, with the steric and electronic properties of the amido group (NR')₂ shown to significantly influence the solid-state structures and the position of the solution equilibrium.