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## New options in directed cupration: Studies in heteroleptic bis(amido) cuprate formation

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Dedicated to the memory of Jack Lewis.

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## ABSTRACT

The 2:1 combination of MPLi (MP = 2-methylpiperidide) with CuBr gives the novel complex [(MP)<sub>2</sub>CuLi(THF)<sub>2</sub>]<sub>2</sub>LiBr **12** and introduces the chiral ligand MP to the evolving field of Directed *ortho* Cupration reagents. Subsequent syntheses have focused on developing heteroleptic bis(amido) arrangements at Cu, with 1:1 mixtures of two out of MPLi, DMPLi and TMPLi (DMP = 2,6-*cis*-dimethylpiperidide; TMP = 2,2,6,6-tetramethylpiperidide) being reacted with Cu<sup>I</sup> salts in the presence of THF. Resulting lithiocuprates reveal solid state dimers based on the heteroleptic bis(amido) formulations R<sub>2</sub>N(TMP)Cu(Br)Li<sub>2</sub>(THF)<sub>2</sub> (R<sub>2</sub>N = MP **13**; R<sub>2</sub>N = DMP **14**). The heteroleptic Gilman lithiocuprate PIP(TMP)CuLi (PIP = piperidide) **15** has also been prepared. In each of **12**–**15**, significant variations in the orientations of the amide ligands can be rationalized in terms of steric effects and, in the case of **15**, stabilization of the alkali metal by Me...Li interaction is evidenced.

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## 1. Introduction

Improved methods for regioselectively functionalizing aromatics, which avoid the complications of selectivity [1] and product stability [2] that arise from the use of highly polar organometallic bases are of major importance to synthetic chemists. In this context, the advent of so-called ‘synergic bases’ of the type R<sub>m</sub>M<sup>IP</sup>(NR'<sub>2</sub>)<sub>n</sub>AM (R = alkyl; m = 2, 3; M<sup>IP</sup> = less polarizing metal; NR'<sub>2</sub> = amide; n = 1, 2; AM = alkali metal) has furnished reagents capable of unprecedented behaviour [3]. The first such base to be reported was the putative lithium zincate (*t*-Bu)<sub>2</sub>Zn(TMP)Li (TMP = 2,2,6,6-tetramethylpiperidide) and was effective in the *ortho* metalation of alkyl benzoates and the α-deprotonation of π-deficient azaromatics [4].

More recently, alkali metal complexes featuring Zn [5], Al [6], Mn [7] and Mg [8] as the less polarizing metal (Fig. 1) have demonstrated anionic activation [9], reduced aggregation [10], and scope in templated polymetalation [8c], and as a part of the growth of this field, organocuprates have also been explored [11]. First reported to result from the treatment of CuI with MeLi to give ‘lower-order’ or ‘Gilman’ cuprate Me<sub>2</sub>CuLi **1** [12], recent focus has been on lithium

amidocuprates in general (including heteroleptic structures) [13] and lithium (TMP)cuprates specifically. In relation to the former, dimers of MesNHCu(PhNH)Li·DME **2** (Mes = mesityl, DME = 1,2-dimethoxyethane) [14] and MesCu(NBz)<sub>2</sub>Li **3** (Bz = benzyl) [15] have been reported. In relation to the latter, the cyclic dimer of (TMP)<sub>2</sub>CuLi **4** [16], and the amido(organyl) monomers PhCu(TMP)Li·3THF **5** and MeCu(TMP)Li·TMEDA **6** (TMEDA = *N,N,N',N'*-tetramethylethylenediamine; Scheme 1) [17] have been isolated.

Attempts to enhance cuprate reactivity [11] have focused on treating lower-order cuprates with LiX (X = halide, cyanide) [18,19]. This led to discussion over whether the resulting cuprates were lower-order [20] or whether sequestering of the inorganic anion by Cu would render a ‘higher-order’ structure based on 3-coordinate Cu [21], with calculations [22,23], solution [24] and solid state [25–27] analysis suggesting the former. The issue of the Cu-sequestering of cyanide in lithiocuprates was most recently visited on account of the emergence of the field of Directed *ortho* Cupration (DoC) [28], with reaction of TMPLi and CuCN giving reactive complexes, which were found by X-ray diffraction to be dimers based on (TMP)<sub>2</sub>Cu(CN)Li<sub>2</sub>(L) (L = THF **7a**, Et<sub>2</sub>O **8a**) monomers that lacked CuCN components (Scheme 2). The ability to subsequently generate analogous cuprates using halide salts of Cu<sup>I</sup> in either THF [16,29] or Et<sub>2</sub>O [30], combined with the similarity between these structures and that of (Ph<sub>2</sub>N)<sub>2</sub>Cu(NPh<sub>2</sub>)Li<sub>2</sub>·2(OEt<sub>2</sub>)<sub>2</sub> **9** [14], has allowed LiX-incorporating species to generally be

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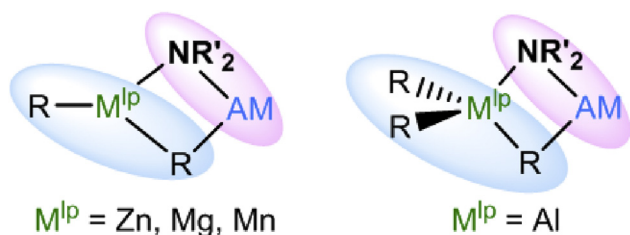
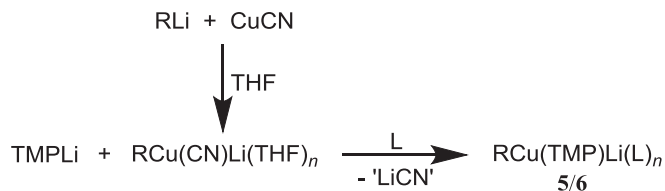
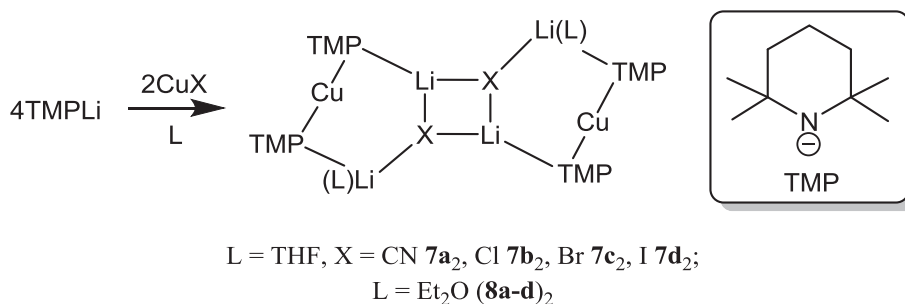


Fig. 1. AM = alkali metal,  $M^{lp}$  = less polarizing metal.



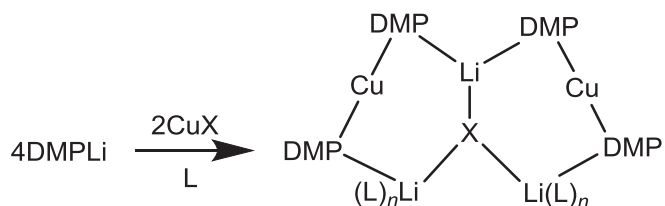
Scheme 1. Formation of **5** ( $R = \text{Ph}$ ,  $n = 3$ ,  $L = \text{THF}$ ) and **6** ( $R = \text{Me}$ ,  $n = 1$ ,  $L = \text{TMEDA}$ ).



Scheme 2. Formation of the dimers of cuprates **7** and **8**.

classified as ‘Lipshutz-type’ [31]. Understanding of the structural principles at work in these systems has proved important in fully appreciating differences in the outcomes of their reactions; explaining these in terms either of variations in reagent structure and type or factors such as organocopper abstraction by cuprates [32].

Very recently, amidocuprate preparation has utilized DMPH (= 2,6-*cis*-dimethylpiperidine) as the amido ligand source, with the aim of significant cost reduction [33,34]. However, the differing sterics significantly effected ligand orientation and led to the isolation of a new class of lithocuprate adduct. While the combination of DMPLi with CuCl in the presence of etherate solvents produced disorder at the metal sites [35], exactly controlling the amount of ether wrt metal obviated this and yielded both  $[(\text{DMP})_2\text{CuLi}(\text{OEt}_2)]_2\text{LiX}$  **10** and  $[(\text{DMP})_2\text{CuLi}(\text{THF})_2]_2\text{LiBr}$  **11** (Scheme 3) [30], which were interpreted as adducts between



Scheme 3. Synthesis of lithocuprate adducts ( $L = \text{Et}_2\text{O}$ ,  $n = 1$ ,  $X = \text{Cl}$  **10a**,  $\text{Br}$  **10b**, **110c**;  $L = \text{THF}$ ,  $n = 2$ ,  $X = \text{Br}$  **11**).

Gilman  $(\text{DMP})_2\text{CuLi(L)}_n$  and Lipshutz-type  $(\text{DMP})_2\text{Cu(X)Li}_2(\text{L})_n$  ( $L = \text{Et}_2\text{O}$ ,  $n = 1$ ,  $X = \text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ ;  $L = \text{THF}$ ,  $n = 2$ ,  $X = \text{Br}$ ) species.

The transition in structure-type from Lipshutz-type dimers to adducts has been argued to be of mechanistic importance, with **10b** successfully used in DoC chemistry [30]. That said, ambiguity over the structural options available to different amido ligands, combined with a general paucity of data on heteroleptic bis(amido) cuprates, led to the present work; the Lipshutz(-type) and adduct structures outlined above being homoleptic with respect to the choice of amido ligand. Herein we utilize the amines MPH (= 2-methylpiperidine), DMPH and TMPH to fabricate heteroleptic bis(amido)cuprates of the type  $\text{NR}_2(\text{NR}'_2)\text{Cu(X)Li}_2(\text{L})_n$  and  $\text{NR}_2(\text{NR}'_2)\text{CuLi}$  ( $\text{NR}_2$ ,  $\text{NR}'_2$  = different amido ligands). The choice of ligands is designed to explore the scope for reducing the costs of DoC [34] (100 mL MPH = £19, 100 g DMPH = £23 and 100 g TMPH = £274 at time of writing), whilst also probing the steric effects of Me-group inclusion. These are already suggested to be structure-defining [30], and investigating the effects of sterically-based ligand reorientation in heteroamido cuprates promises not only new modes of reactivity but also insights into the transition from a preference for Lipshutz-type structures to one for Gilman-

(Lipshutz-type) adducts [30,31]. Moreover, ligand variation will allow the ability of Me-groups to stabilize the alkali metal in Gilman cuprates to be investigated; the relevance of this lies in the recent establishment that Gilman reagents promote effective DoC [16].

## 2. Results and discussion

In seeking to utilize chiral amides in lithium cuprate chemistry, the racemic substrate MPH was used in the attempted synthesis of an analogue of the recently reported pentametal adducts of the type  $[(\text{NR}_2)_2\text{CuLi(L)}_n]_2\text{LiX}$ . To do this, a preformed hexane solution of MPLi containing also THF (1 eq. wrt Li) was added to CuBr (0.5 eq. wrt Li) in hexane. Upon prolonged chilling, the resultant orange solution yielded crystalline material that was shown to incorporate MP and THF in a 1:1 ratio by  $^1\text{H}$  NMR spectroscopy and so to be consistent with a formulation analogous to that of previously reported adduct **11**. Corroboration of this view came from  $^7\text{Li}$  NMR spectroscopy, which revealed two Li environments in a 1:2 ratio (Fig. 2) – this behaviour having been previously interpreted in terms of the retention of solid-state structural characteristics by adducts (e.g. **10** and **11**) in hydrocarbon solution [30].

The  $^{13}\text{C}$  NMR spectrum is noteworthy; sharp resonances were located for THF but all other carbon resonances appeared as clusters of peaks. APT NMR spectroscopy identified the cluster at  $\delta$  59.3–57.4 ppm as being due to the chiral tertiary carbon atom at the 2-position of the ligand. The 3-, 5- and 6-position carbon atoms

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