Structural effects in lithium cuprate chemistry: the elucidation of reactive pentametal complexes

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Introduction
Since 1999, so-called synergic bases have gained traction for their utility in selective organic synthesis. [1] Alkali metal aluminates and zinicates have enabled advances in the elaboration of aromatics and attention has now switched to lithium cuprate bases and Directed ortho cupration (DoC) as a precursor to commercially attractive noble catalyst-free C–C bond formation (e.g., below). [2]  

Extending principles: Lipshutz-type cuprates

The bridging activity of cyanide has been replicated using copper(I) halides to yield what can be regarded as ‘Lipshutz-type’ cuprates. These establish the generality of the $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ ($X = \text{CN}$, halide) motif. [3,4]

The advent of cuprate adducts

To probe the role of steric effects in controlling amidocuprate reactivity we have replaced TMP with less bulky DMP. DMPH also retains a fraction of the cost of TPMH. In the case of DMPH, reaction with copper(I) halides has yielded an unprecedented series of complexes. [5]

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Reaction pathway and cuprate interconversion

Our own prior art has shown that Gilman cuprates show inferior DoC activity when compared to Lipshutz-type. [1] However, by DFT analysis a Gilman monomer accessed from a Lipshutz precursor emerges as the reactive base; [5] elimination of solvated LiCN from Lipshutz complex ($\text{Me}_2\text{N}_2\text{Cu}(\text{CN})\text{Li}_2\text{S}$) yields a Gilman-containing complex ($\text{IM}_1\text{L}_2$) that reveals a reduced +14.9 kcal/mol barrier to DoC.

Like other cuprates, bis(amido)cuprate types are differentiated by the inclusion or not of LiX ($X = \text{inorganic anion};$ above). Recently we have elucidated the true nature of Lipshutz ($X = \text{CN};$ left) and Gilman bis(amido)cuprates. [1,4] Studies are now extending to the use of various amido ligands in order to reduce system costs and we report here advances in DoC using 2,2,6,6-tetramethylpiperidine (TMPH) and cis-2,6-dimethylpiperidine (DMPH) as amido ligand sources.

Interpreting adducts e.g. 6 as resulting from LiX ($X = \text{Br}$) elimination from the corresponding Lipshutz-type dimer we monitored the synthesis of 8 using a ‘Lipshutz-type’ 4:2:1 ratio (i.e. 2 eq. Cu per arené). Meanwhile the use of 6 gave an essentially identical yield, suggesting adducts are an efficient source of Gilman monomers.

The ability of an adduct to effect DoC has been modelled. Conversion of reactants $\text{RT}_{\text{eq}}$ to complex $\text{IM}_1\text{L}_2$ between ($\text{Me}_2\text{N}_2\text{Cu}$(OMe)) and $\text{N,N}$-dimethylbenzamide is accompanied by a change in $\Delta G$ of only +6.1 kcal/mol. This reinforces our conclusion that adducts such as 6 represent viable new DoC reagents. [6]