



Structural effects in lithiocuprate chemistry: the elucidation of reactive pentametal complexes^[1]

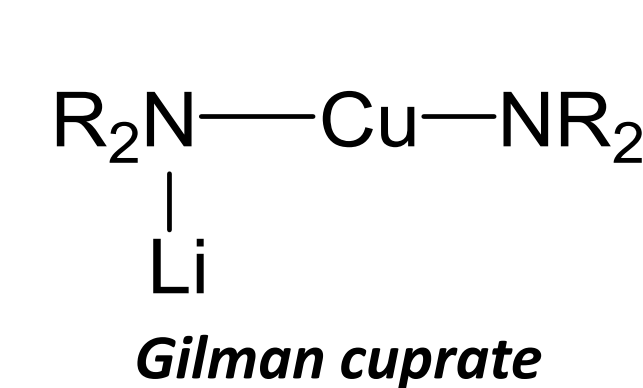
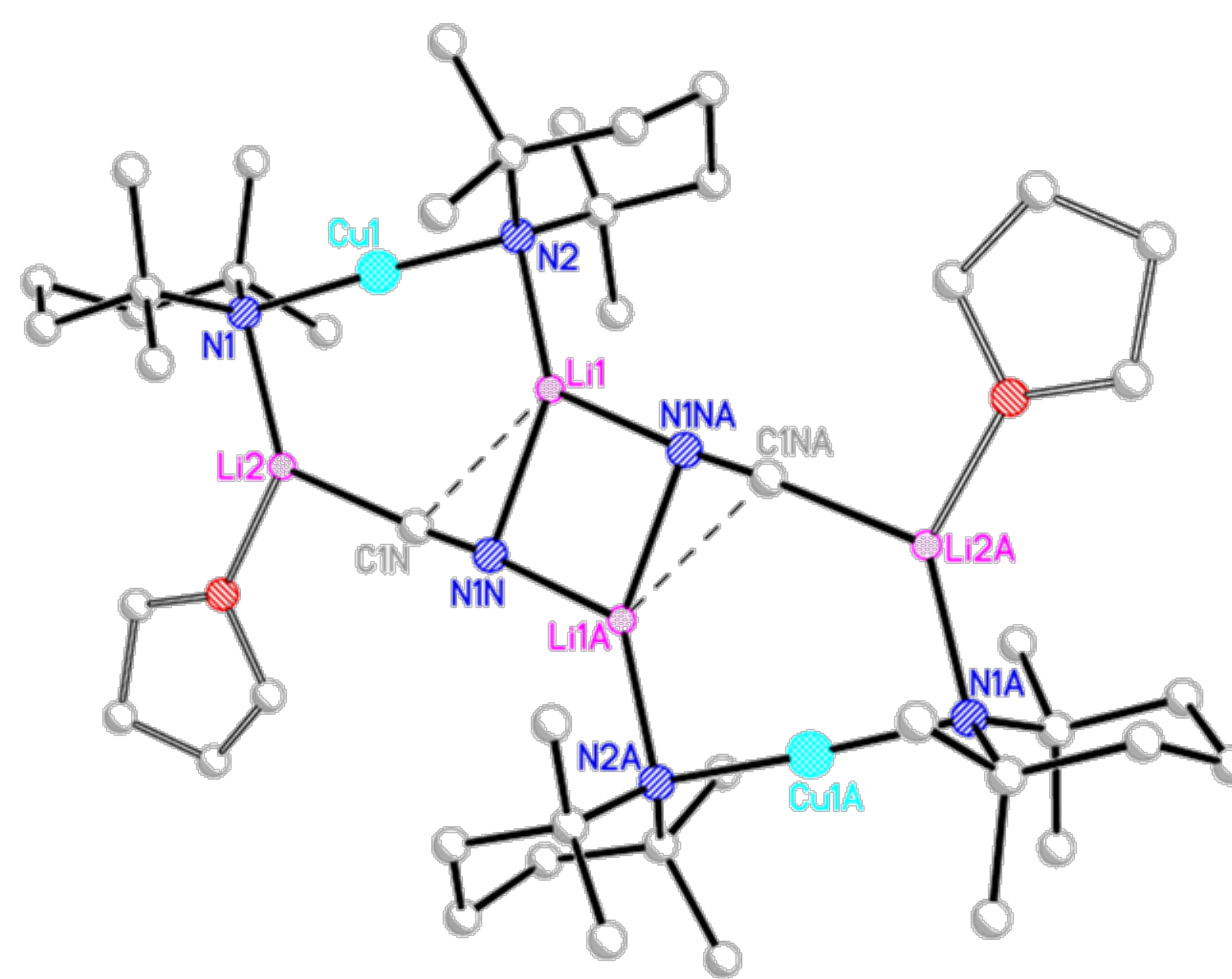
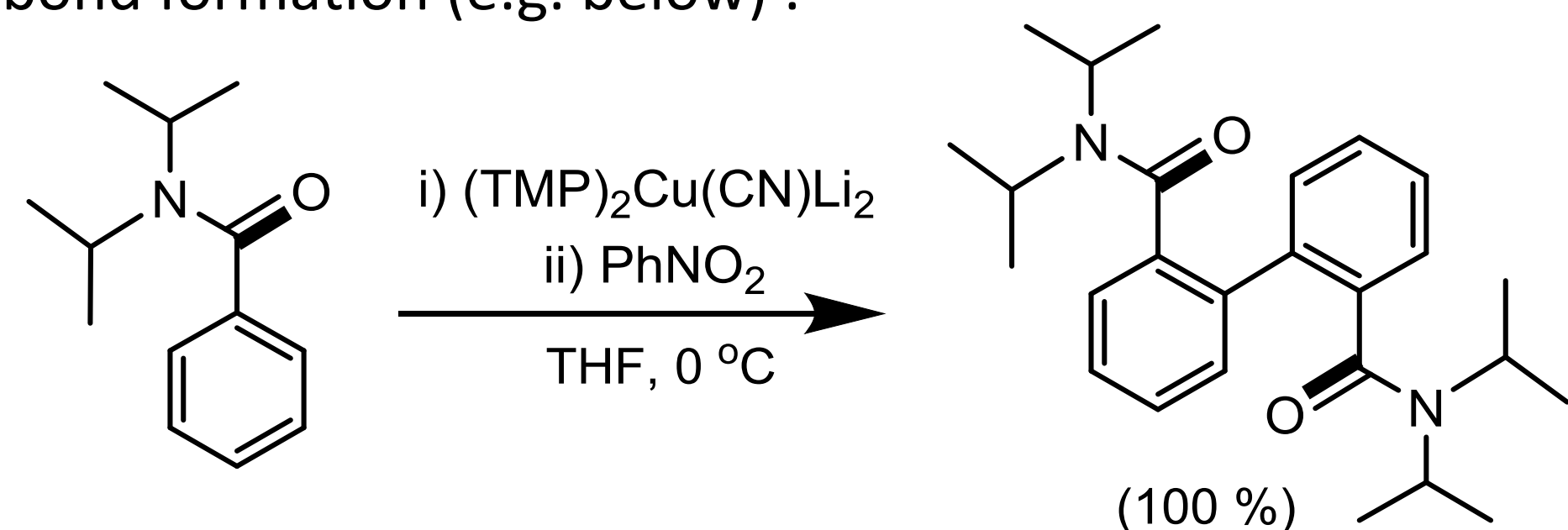
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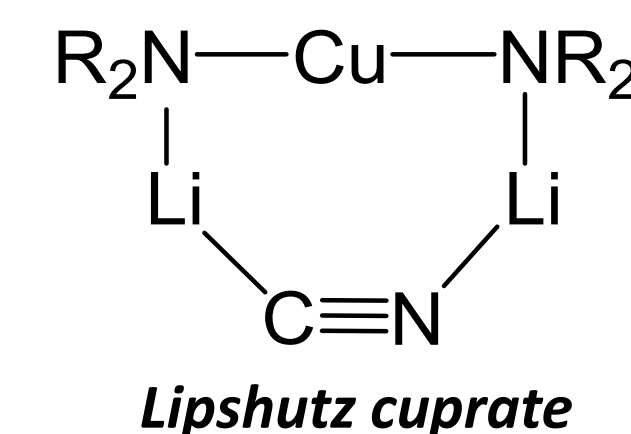
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Introduction

Since 1999, so-called synergic bases have gained traction for their utility in selective organic synthesis.^[2] Alkali metal aluminates and zincates 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).^[3]



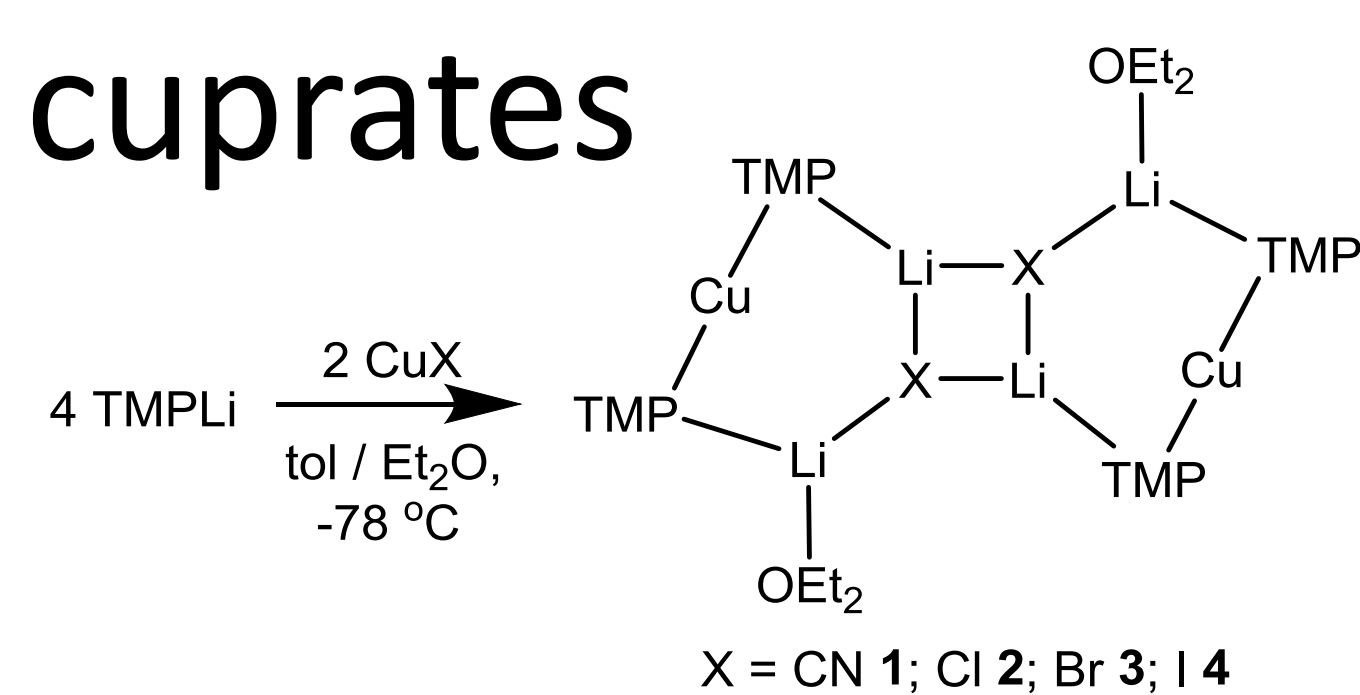
Gilman cuprate



Lipshutz cuprate

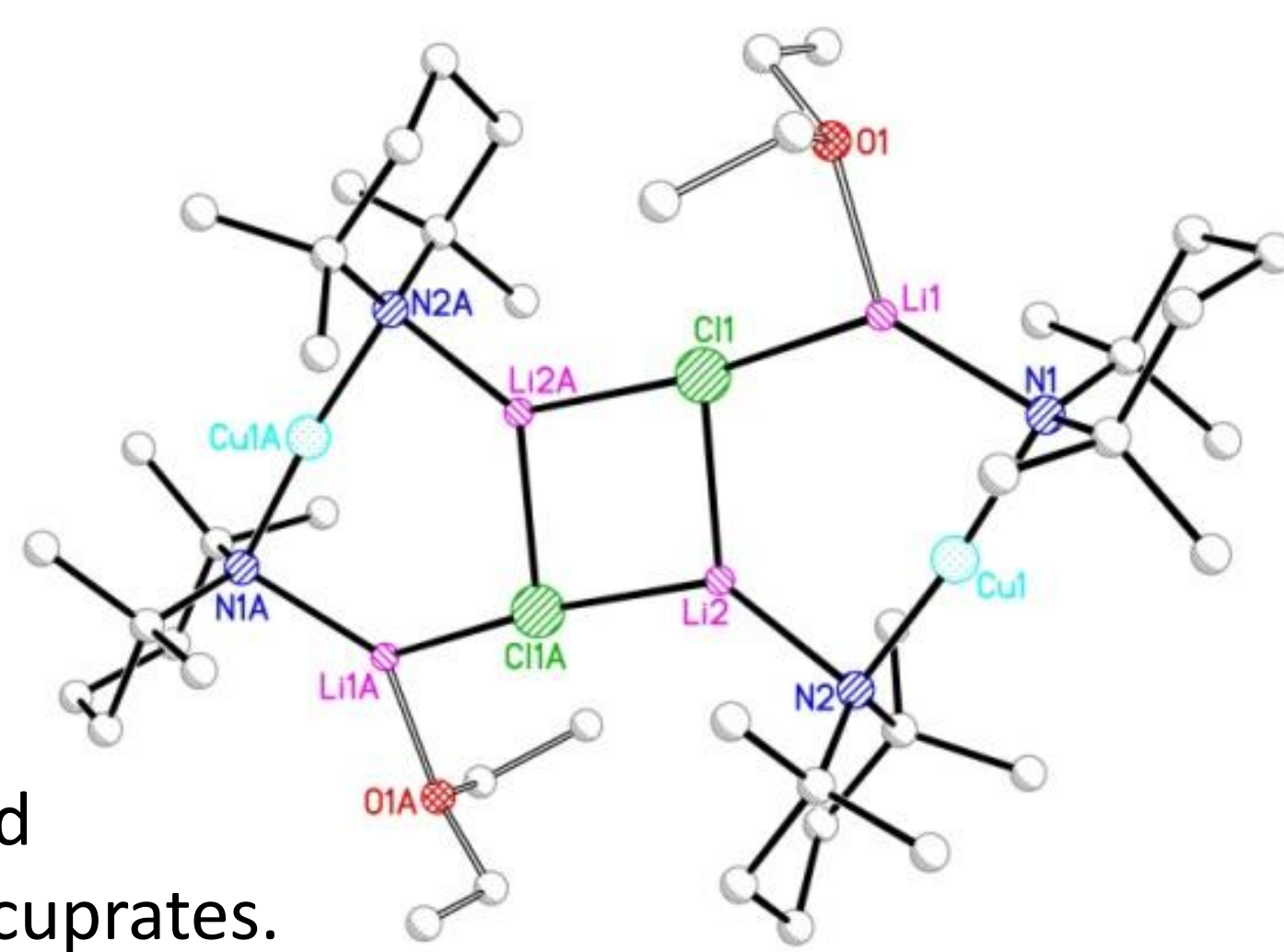
Like other cuprates, bis(amido)cuprate types are differentiated by the inclusion or not of LiX (X = inorganic anion; above). Recently we have elucidated the true nature of Lipshutz (X = CN; left) and Gilman bis(amido)cuprates.^[3,4] Studies are now extending to the use of various amido ligands in order 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.

Extending principles: Lipshutz-type cuprates

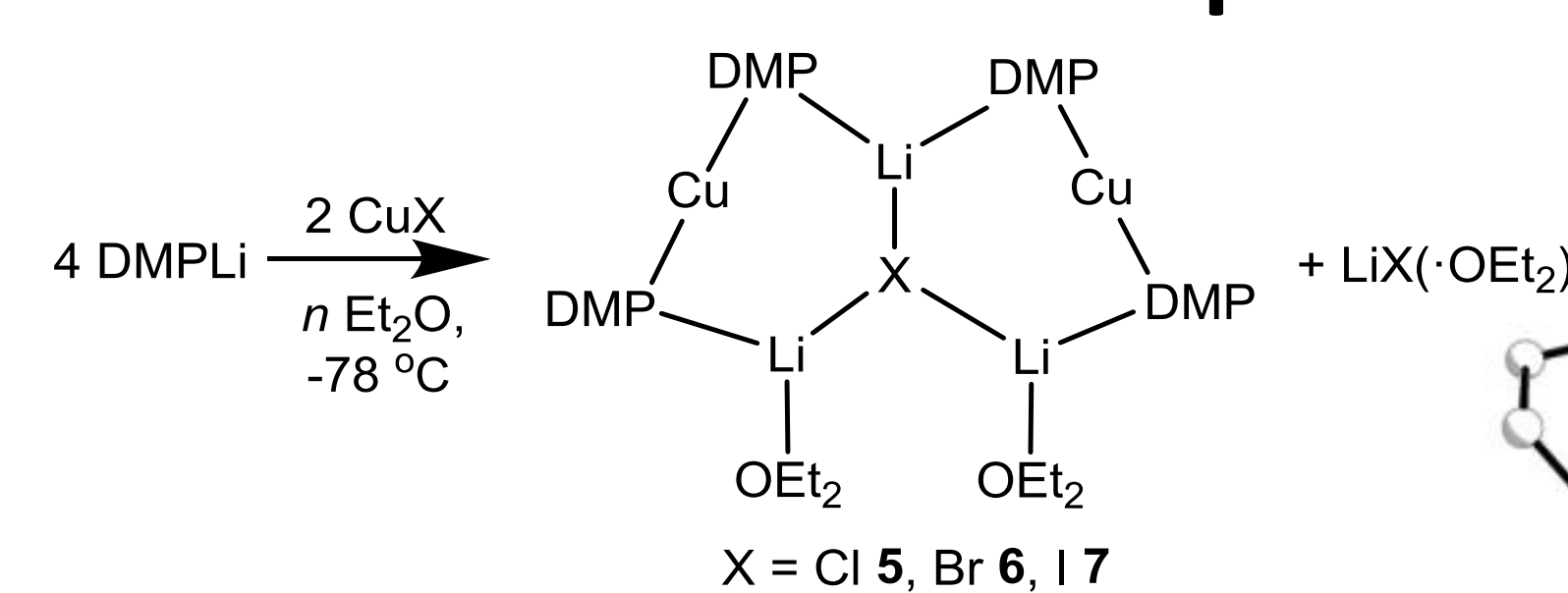


The bridging activity of cyanide has been replicated using copper(I) halides to yield what can be regarded as 'Lipshutz-type' cuprates.

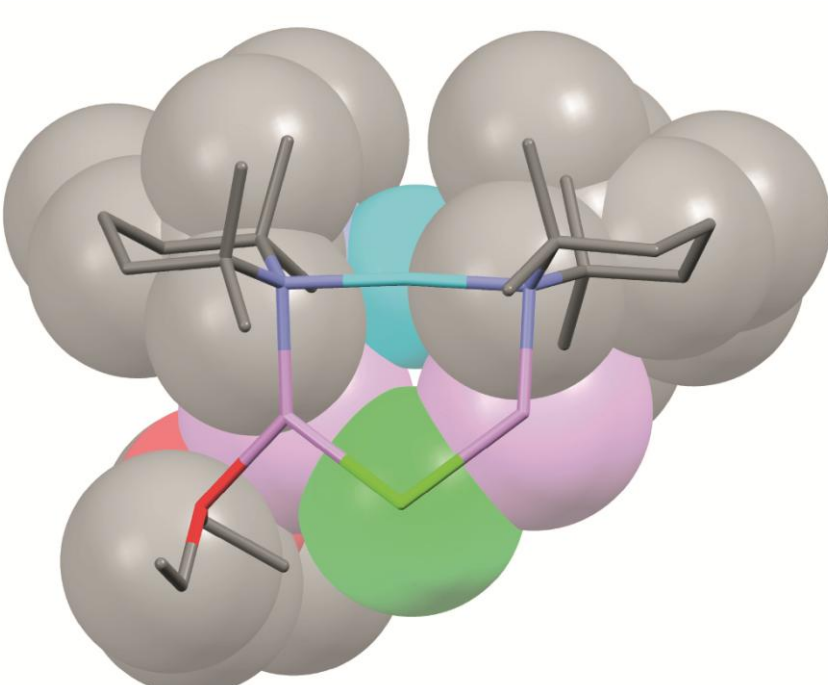
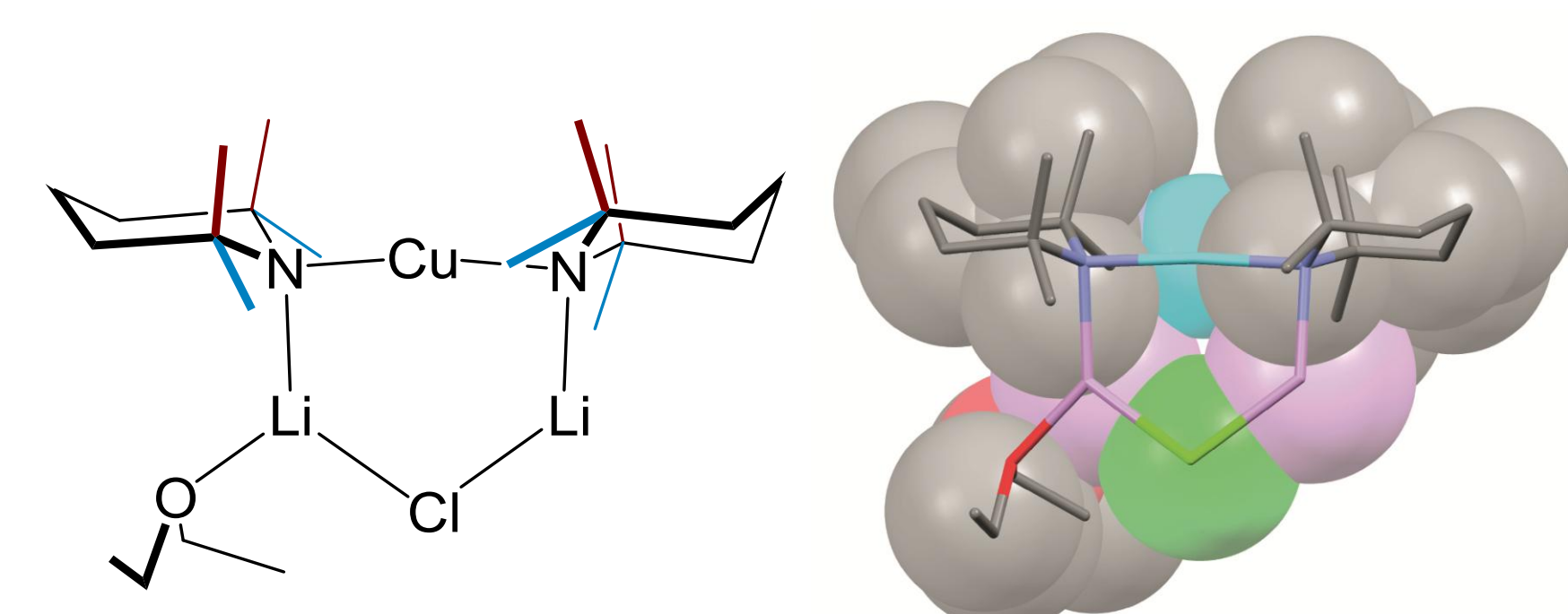
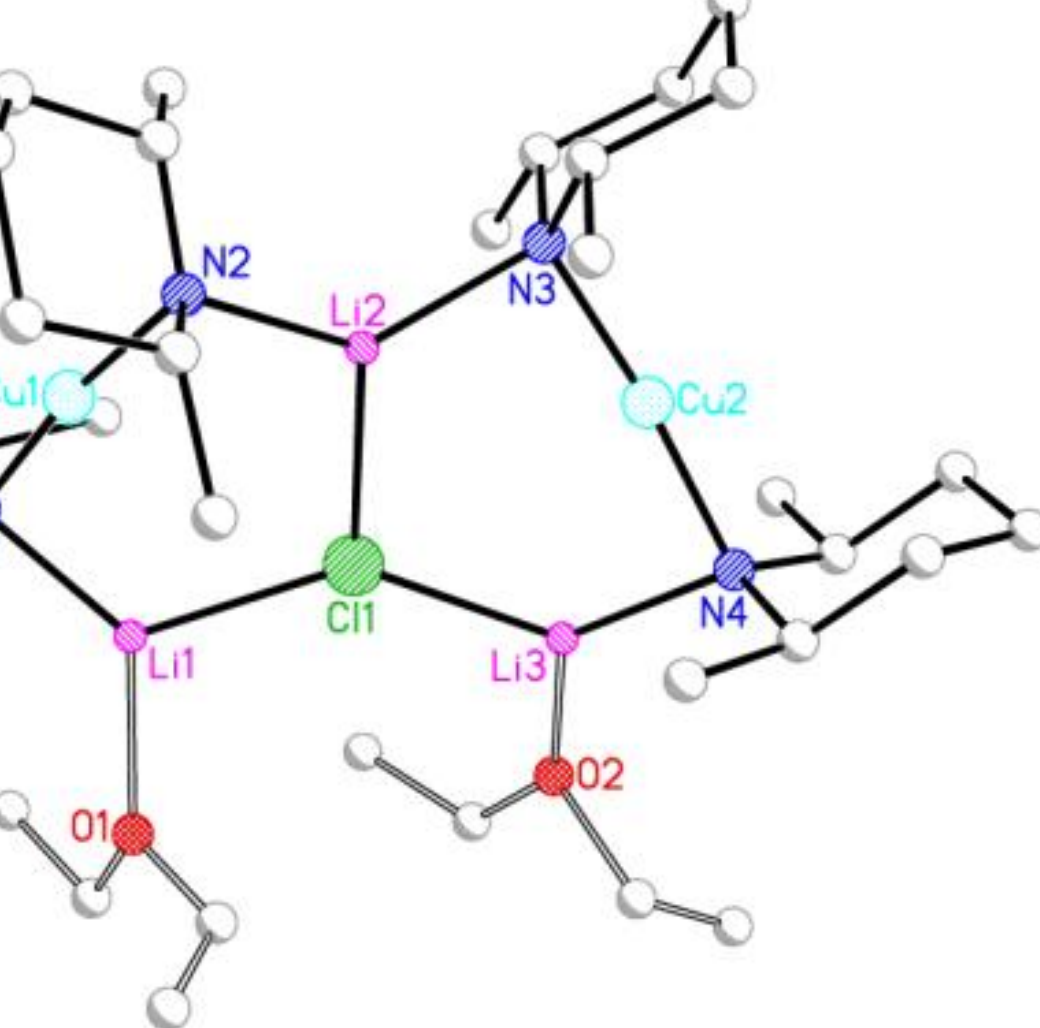
These establish the generality of the R₂Cu(X)Li₂ (X = CN, halide) motif.^[5,6]



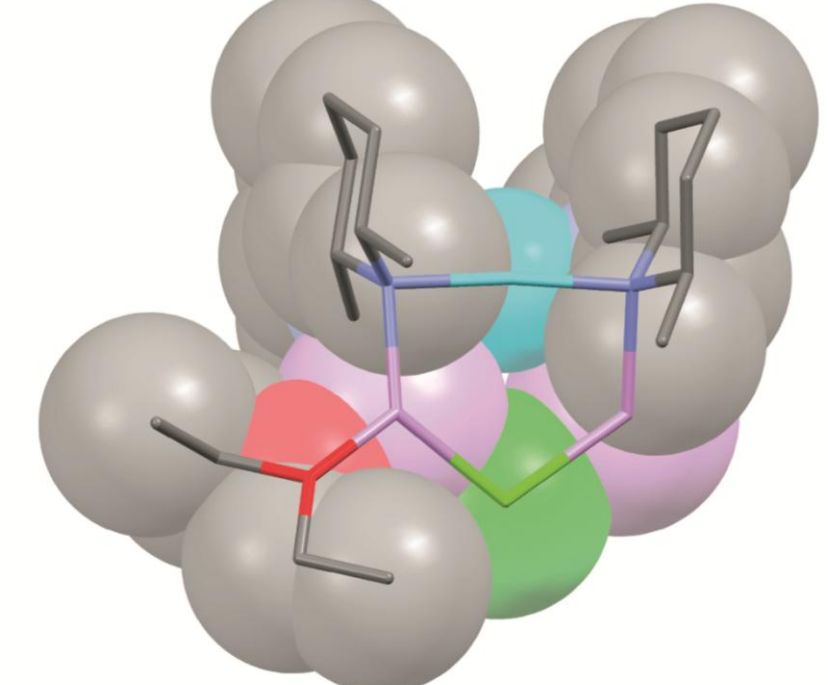
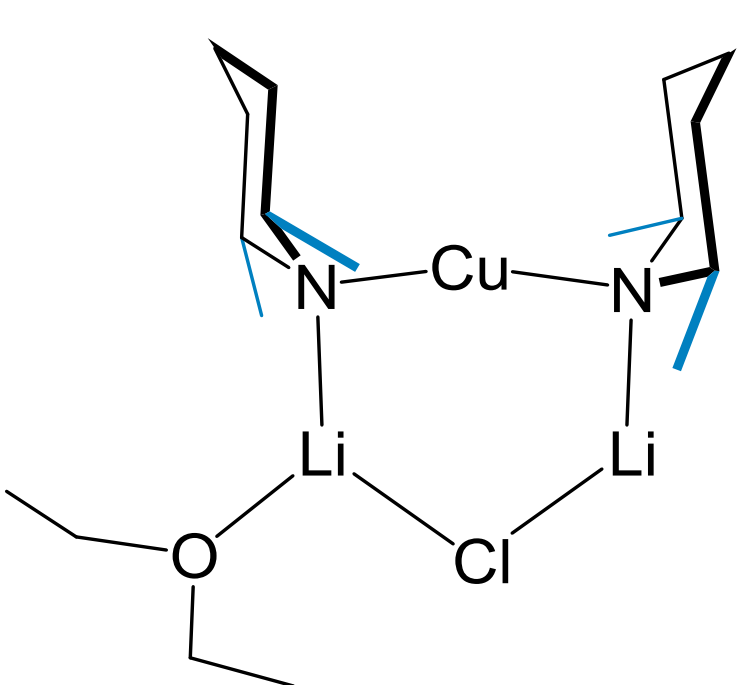
The advent of cuprate adducts



To probe the role of steric effects in controlling amidocuprate reactivity we have replaced TMP with less bulky DMP. DMPH also retains at a fraction of the cost of TMPH. In the case of DMPLi, reaction with copper(I) halides has yielded an unprecedented series of complexes.^[1]



Lipshutz-type components that form part of the dimer of TMP-based chloride **2** (left top) and DMP-based adduct **5** (left bottom). In **2** the piperidine rings lie flat in order that the axial Me-groups (red) do not sterically interact. In **5** only equatorial Me-groups are present (blue) and the piperidine rings can reside side face-on.



Acknowledgements

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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.^[3] 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 (Me₂N)₂Cu(CN)Li₂(S) yields a Gilman-containing complex (**IM1_G**) that reveals a reduced +14.9 kcal/mol barrier to DoC.

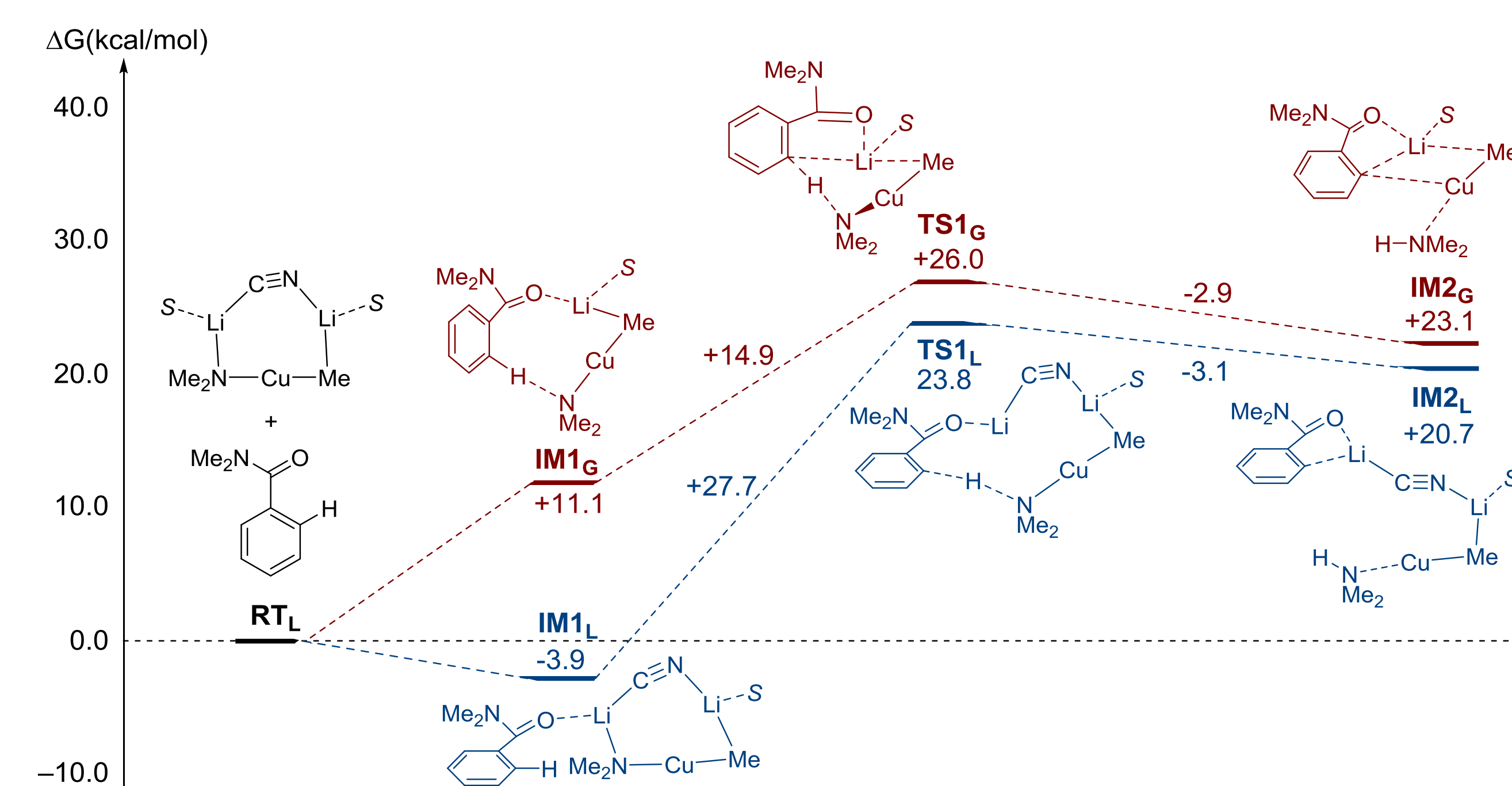


Figure 1. DFT modelling (B3LYP using SVP all-electron basis set for Cu and 6-31+G* for other atoms) of pre-reaction complex formation (**IM1**) and subsequent access to the transition state (**TS1**) for DoC.^[5] Red data: Gilman pathway via elimination of LiCN(S) from Lipshutz species (Me₂N)₂Cu(CN)Li₂(S). Blue data: Lipshutz pathway. S = Me₂O.

Interpreting adducts e.g. **6** as resulting from LiX (X = 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 arene). Meanwhile the use of **6** gave an essentially identical yield, suggesting adducts are an efficient source of Gilman monomers.

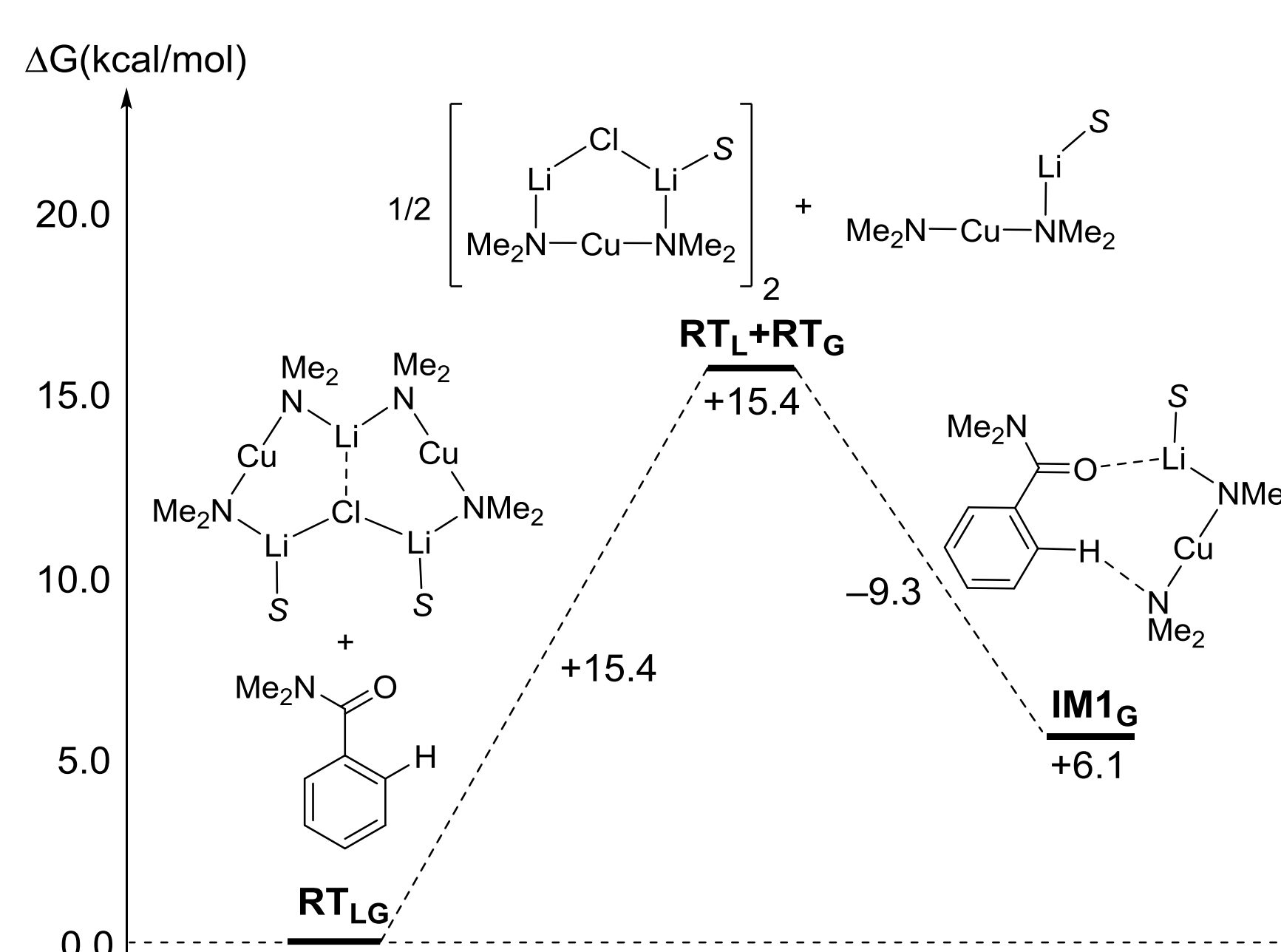
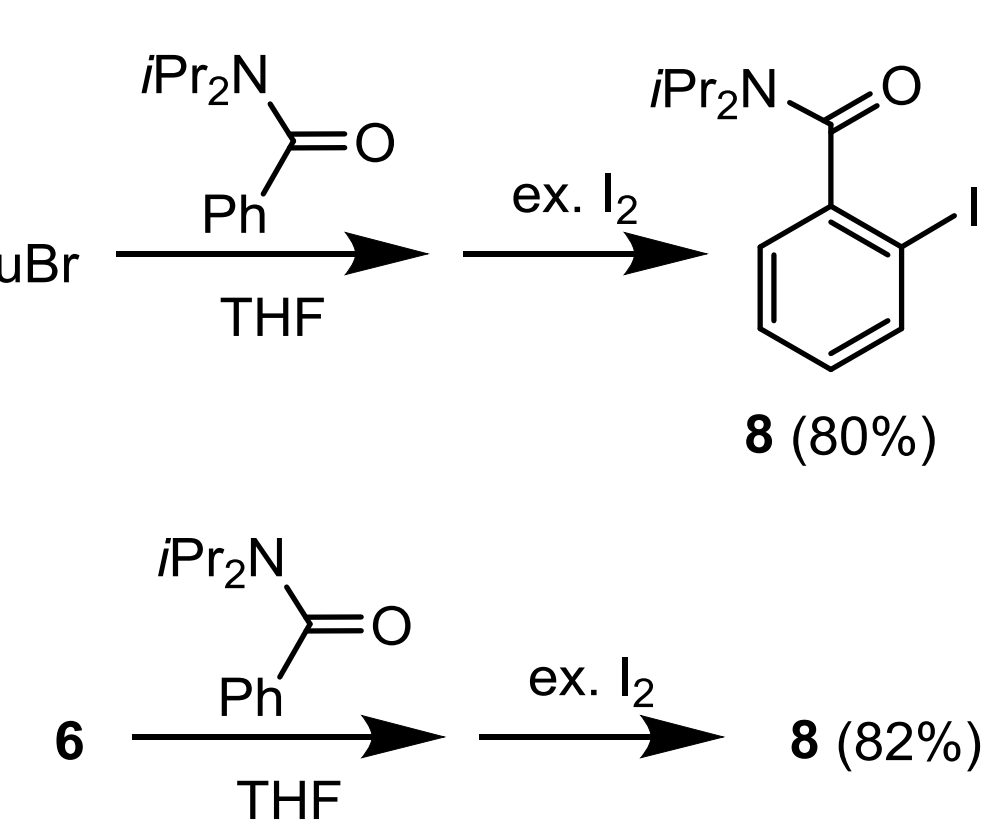


Figure 2. DFT modelling of pre-reaction complex formation (**IM1_G**) from a cuprate adduct.^[1] S = Me₂O.

The ability of an adduct to effect DoC has been modelled. Conversion of reactants RT_{LG} to complex **IM1_G** between (Me₂N)₂CuLi(OMe₂) and *N,N*-dimethylbenzamide is accompanied by a change in ΔG of only +6.1 kcal/mol. This reinforces our conclusion that adducts such as **6** represent viable new DoC reagents.^[6]

1) P. J. Harford, A. J. Peel, J. P. Taylor, S. Komagawa, P. R. Raithby, T. P. Robinson, M. Uchiyama and A. E. H. Wheatley, *Chem. Eur. J.*, 20, 3908 (2014); 2) Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, *J. Am. Chem. Soc.*, 121, 3539 (1999); 3) S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley and M. Uchiyama, *J. Am. Chem. Soc.* 129, 15102 (2007); 4) J. Haywood, J. V. Morey, A. E. H. Wheatley, C. Liu, S. Yasuie, J. Kurita, M. Uchiyama and P. R. Raithby, *Organometallics*, 28, 38 (2009); 5) S. Komagawa, S. Usui, J. Haywood, P. J. Harford, A. E. H. Wheatley, Y. Matsumoto, K. Hirano, R. Takita and M. Uchiyama, *Angew. Chem., Int. Ed.*, 51, 12081 (2012); 6) P. J. Harford, A. J. Peel, F. Chevallier, R. Takita, F. Mongin, M. Uchiyama and A. E. H. Wheatley, *Dalton Trans.*, 43, 14181 (2014).