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Extending motifs in lithiocuprate chemistry: unexpected structural diversity in thiocyanate complexes†

Andrew J. Peel,^a Madani Hedidi,^{b,c} Ghenia Bentabed-Ababsa,^c Thierry Roisnel,^d Florence Mongin^b and Andrew E. H. Wheatley^{*a}

The new area of lithio(thiocyanato)cuprates has been developed. Using inexpensive, stable and safe CuSCN for their preparation, these complexes revealed Lipshutz-type dimeric motifs with solvent-dependent point group identities; planar, boat-shaped and chair shaped conformers are seen in the solid state. In solution, both Lipshutz-type and Gilman structures are clearly seen. Since the advent in 2007 of directed *ortho* cupration, effort has gone into understanding the structure-reactivity effects of amide ligand variation in and alkali metal salt abstraction from Lipshutz-type cuprates such as (TMP)₂Cu(CN)Li₂(THF) **1** (TMP = 2,2,6,6-tetramethylpiperidide). The replacement of CN[−] with SCN[−] is investigated presently as a means of improving the safety of lithium cuprates. The synthesis and solid state structural characterization of reference cuprate (TMP)₂Cu(CN)Li₂(THP) **8** (THP = tetrahydropyran) precedes that of the thiocyanate series (TMP)₂Cu(SCN)Li₂(L) (L = OEt₂ **9**, THF **10**, THP **11**). For each of **9–11**, preformed TMPLi was combined with CuSCN (2 : 1) in the presence of sub-stoichiometric Lewis base (0.5 eq. wrt Li). The avoidance of Lewis basic solvents incurs formation of the unsolvated Gilman cuprate (TMP)₂CuLi **12**, whilst multidimensional NMR spectroscopy has evidenced the abstraction of LiSCN from **9–11** in hydrocarbon solution and the *in situ* formation of Gilman reagents. The synthetic utility of **10** is established in the selective deprotometalation of chloropyridine substrates, including effecting transition metal-free homocoupling in 51–69% yield.

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Introduction

Enhanced methods for the regioselective functionalization of aromatics that avoid the complications associated with the use of traditional main group organometallic bases¹ are of ongoing interest. This search led, in 1999,² to the development of the first of what have become known as ‘synergic bases’³ of the type R_mM(NR′₂)_nAM (R = alkyl; *m* = 0, 2, 3; M = less polarizing metal; NR′₂ = amide; *n* = 1, 2, 3; AM = (more polarizing alkali metal)). These have, for example, previously incorporated

M = Al,⁴ Cd,⁵ Mg,⁶ Mn⁷ and Zn,⁸ and have shown hitherto unachievable potential in anionic activation⁹ and templated polymetalation.¹⁰ In a similar vein, new lithium cyanocuprates¹¹ have been central to the development of directed *ortho* cupration (DoC)¹² (Fig. 1).

Following the inception of lithium cuprate chemistry¹³ through the development of R₂CuLi,¹⁴ attempts have focused on enhancing reactivity. Modifications have taken two major forms. Firstly, lithium amidocuprates have been developed, offering often unique reactivities as well as the potential of the amido group as a non-transferable ligand and as a chiral auxiliary.¹⁵ Secondly, there has been a focus on the incorporation of LiCN within lithium cuprates,¹⁶ the presumption being that the cyano group would be transferred to Cu to give a higher order (tricoordinate) copper centre.¹⁷ The issue of the Cu-sequestering of cyanide has been discussed at length in the literature, though calculations,¹⁸ spectroscopy¹⁹ and X-ray diffraction²⁰ have increasingly pointed to the retention of lower order (dicoordinate) copper. This was noted too in the recently developed field of DoC transformations, with the 2 : 1 reaction of TMPLi (TMP = 2,2,6,6-tetramethylpiperidide) and CuCN giving complexes that could be characterized by X-ray diffraction. Results revealed that in the solid state such Lip-

^aDepartment of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK. E-mail: aehw2@cam.ac.uk; Fax: (+44 (0)1223 336362

^bChimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226, Université de Rennes 1-CNRS, Bâtiment 10A, Campus de Beaulieu, 35042 Rennes, France

^cLaboratoire de Synthèse Organique Appliquée, Faculté des Sciences, Université d'Oran 1 Ahmed Ben Bella, BP 1524 El M'Naouer, 31000 Oran, Algeria

^dCentre de Diffractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226, Université de Rennes 1-CNRS, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes, France

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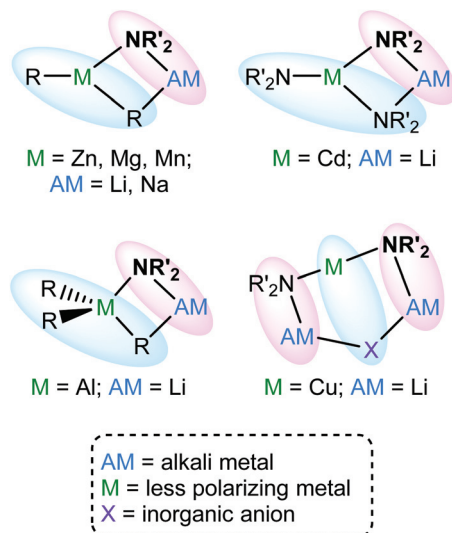


Fig. 1 Known structural motifs in synergic base chemistry.

shutz formulation cuprates were dimers based on $(\text{TMP})_2\text{Cu}(\text{CN})\text{Li}_2(\text{L})$ ($\text{L} = \text{OEt}_2$ **1**, THF **2**)^{12,21} monomers that clearly lacked Cu–CN interactions (Scheme 1).

Finally, the reaction of CuCN, RLi and TMPLi established that the inclusion of cyanide in the cuprate structure was by no means guaranteed, by furnishing the externally solvated amido(organyl) monomers $\text{RCu}(\text{TMP})\text{Li}(\text{L})_n$ ($\text{R} = \text{Ph}$, $\text{L} = \text{THF}$, $n = 3$; $\text{R} = \text{Me}$, $\text{L} = \text{TMEDA} = N,N,N',N'$ -tetramethylethylenediamine, $n = 1$ **4**).²² This observation took on added importance when recent DFT analysis suggested the *in situ* conversion of cyanide-incorporating cuprates to reactive Gilman reagents as the precursor to DoC reaction.²³

Recent studies have sought to extend the principles established by the isolation of **1** and **2** to the use of general inorganic anions. This has led to the isolation and full

characterization of $(\text{TMP})_2\text{Cu}(\text{X})\text{Li}_2(\text{L})$ ($\text{X} = \text{Cl}$ **5**, Br **6**, I **7**, $\text{L} = \text{OEt}_2$, THF).^{23,24} These species have been viewed as being Lipshutz-type by virtue of their demonstrating essentially the same structural principles as **1** and **2**. They have been successfully tested in the deprotonative metalation of halopyridines,²⁵ notably in the course of azafluorenone synthesis.²⁴ Herein we extend this principle further, introducing the use of the thiocyanate anion as a non-toxic but potentially synthetically useful analogue of the cyanide components in **1** and **2**. Preliminary results reveal novel variations in thiocyanatocuprate structure as a function of solvent both in the solid state and in solution.

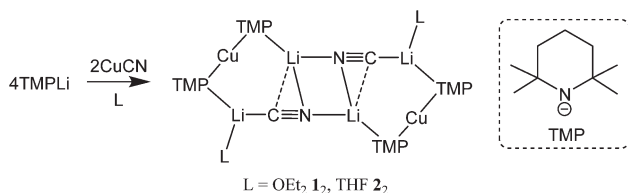
Results and discussion

Solid state analysis

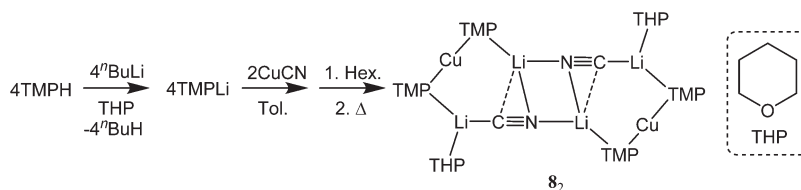
With this study aiming to probe new thiocyanatocuprate bases solvated by THF, OEt_2 and THP (= tetrahydropyran) it was first necessary to complete the series of cyanocuprates **1**,¹² **2**²¹ and $(\text{TMP})_2\text{Cu}(\text{CN})\text{Li}_2(\text{THP})$ **8**. To do this a hexane solution of TMPLi containing also THP (0.5 eq. wrt Li) was added to a suspension of CuCN (0.5 eq. wrt Li) in toluene. Following the addition of hexane the mixture was heated to reflux and then filtered to give a pale-straw coloured solution from which block-like crystals could be obtained (Scheme 2).

The product was shown by ^1H NMR spectroscopy to incorporate TMP and THP in a 2 : 1 ratio, suggesting a formulation analogous to that previously reported for **1** and **2**. Corroboration of this view came from X-ray diffraction, which established the product to be **8** and to be the analogue of **1** and **2** (Fig. 2). All three structures proved to be relatively flat. IR spectroscopy on **8** revealed a dominant $\text{C}\equiv\text{N}$ stretching mode at $\bar{\nu} = 2104.3 \text{ cm}^{-1}$, with a signal developing at 2138.3 cm^{-1} upon air exposure (see ESI, Fig. S1†), which compared closely with prior work.²²

Moving to the employment of CuSCN in an attempt to render a safer analogue of OEt_2 -solvate **1**, a low temperature solution of TMPH in Et_2O /toluene was treated with $n\text{BuLi}$. The resulting solution was transferred to a suspension of CuSCN in toluene. The mixture was heated to reflux, turning from pale cream to grey-black, whereupon filtration gave a yellow solution. Storage at room temperature gave a low yield of needle-like crystals after 1 day, which dissolved with further standing, and after several days were replaced with crystals of *pseudo*-rhombic habit in low yield. ^1H NMR spectroscopy revealed these to comprise TMP and OEt_2 in a 2 : 1 ratio. Though



Scheme 1 Formation of the dimers of cuprates **1** and **2**.



Scheme 2 Synthesis of **8**.



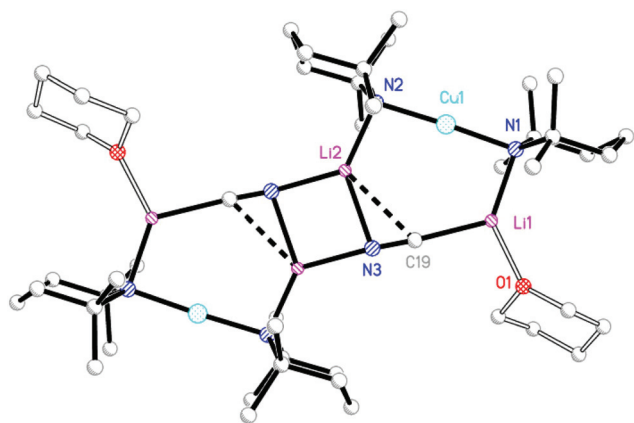


Fig. 2 Molecular structure of **8₂**. H-atoms and ligand disorder omitted. Selected bond lengths (Å) and angles (°): N1–Cu1 1.950(3), N2–Cu1 1.926(3), N1–Li1 1.981(7), N2–Li2 1.951(7), C19–Li1 2.111(13), N3–Li2 2.171(13), N3–Li2A 2.047(14), Cu1–N1–Li1 90.9(2), Cu1–N2–Li2 97.2(2), N1–Li1–C19 122.3(5), N2–Li2–N3 135.2(5), N2–Li2–N3A 130.5(5).

¹³C NMR spectroscopy failed to suggest the presence of SCN, this ligand was obviously incorporated, with IR spectroscopy revealing peaks at 2064.6 (s) and 1996.6 (m) cm^{−1} (Fig. S2†). Air exposure of the sample for 30 s. incurred the growth of a signal at 2107.1 cm^{−1}, which compared with 2066 and 2070 cm^{−1} for calculated free [SCN][−] and LiSCN, respectively.^{26,27} Overall, these data suggest the presence of [S–C≡N][−] moieties. This spectroscopic suggestion of a (TMP)₂Cu(SCN)–Li₂(OEt₂) formulation was verified by X-ray diffraction, which established an essentially flat dimer **9₂** (Scheme 3 and Fig. 3). The thiocyanatocuprate was found to be based on an essentially planar 8-membered (LiNCS)₂ metallocyclic core (the maximal deviation of any atom from a mean plane defined by the four Li⁺ ions and the two thiocyanate ligands being just 0.12 Å). The suggestion from vibrational spectroscopy that formally Li–S-bonded [S–C≡N][−] moieties are present²⁷ is perhaps most clearly reinforced crystallographically by the shortness of the N3–C19 distance (1.149(3) Å), though at 1.631(3) Å S1–C19 hints at some level of delocalization in the anionic ligand. Formal, S-anion behaviour is also suggested by the significantly inequivalent N3–Li1 and N3–Li2 distances (2.250(5) and 1.998(5) Å, respectively); these relative lengths are consistent with a single N-based lone pair bisecting the Li1–N3–Li2 angle

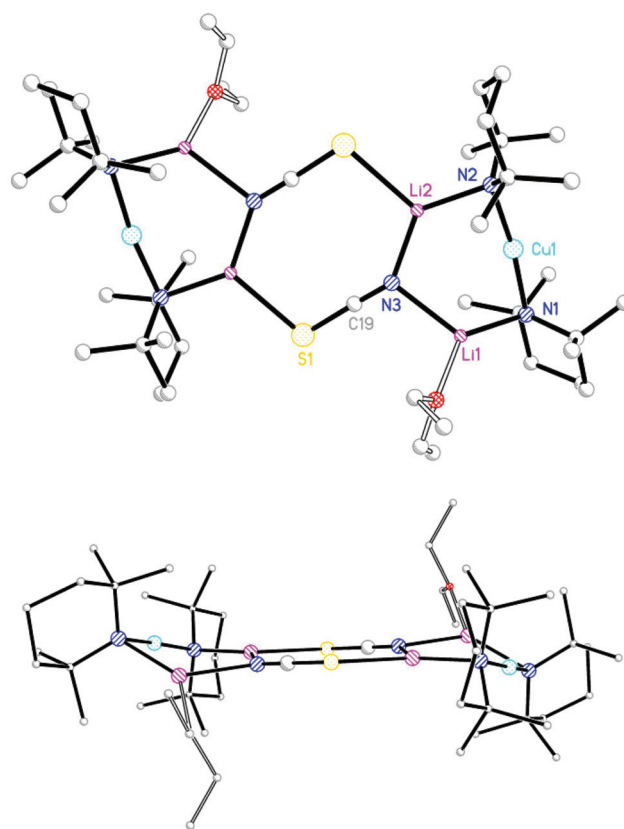
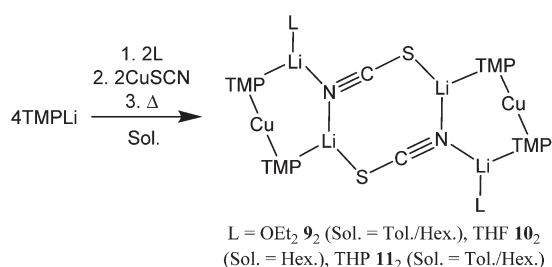


Fig. 3 (a) Molecular structure of **9₂**. H-atoms omitted. Selected bond lengths (Å) and angles (°): N1–Cu1 1.9175(18), N2–Cu1 1.9074(18), N1–Li1 2.015(4), N2–Li2 1.970(4), S1A–Li2 2.518(4), N3–Li1 2.250(5), N3–Li2 1.998(5), N3–C19 1.149(3), S1–C19 1.631(3), Cu1–N1–Li1 83.82(15), Cu1–N2–Li2 89.46(15), N1–Li1–N3 123.7(2), N2–Li2–N3 128.7(2), Li1–N3–C19 110.7(2), Li2–N3–C19 140.0(2), S1A–Li2–N3 113.17(19), Li2–S1A–C19A 103.92(13); (b) side-on view emphasising the essentially flat dimer core.

but favouring interaction with Li2 on grounds of electrostatic directionality (Fig. 3a).²⁸

Having obtained the OEt₂-solvate of (TMP)₂Cu(SCN)Li₂ and established its essential planarity, THF was introduced to probe whether the structure remained fundamentally unchanged (*cf.* **1** vs. **2**). TMPLi in hexane and THF (0.5 eq. wrt Li) was added to CuSCN, allowing the isolation of colourless prismatic crystals (Scheme 3). NMR spectroscopy revealed that, as for **9**, these crystals incorporated TMP and Lewis base in a 2 : 1 ratio and a SCN group (δ 141.5 ppm by ¹³C NMR spectroscopy). Corroboration of the last point came from IR spectroscopy, with two peaks seen at 2050.4 (s) and 1998.0 (m) cm^{−1} (Fig. S3,† *cf.* 2064.6 and 1996.6 cm^{−1} in **9₂**), the signals being replaced by a peak at 2105.7 cm^{−1} after air exposure for 30 s. X-ray diffraction was undertaken, with data revealing a dimer based on (TMP)₂Cu(SCN)Li₂(THF) **10**. However, in contrast to the structure of **9₂**, **10₂** exhibited a novel boat conformation (Fig. 4) based on the aggregation of two crystallographically independent monomers (of which one will be representatively discussed) and in which the geometry at



Scheme 3 Synthesis of **9–11**.



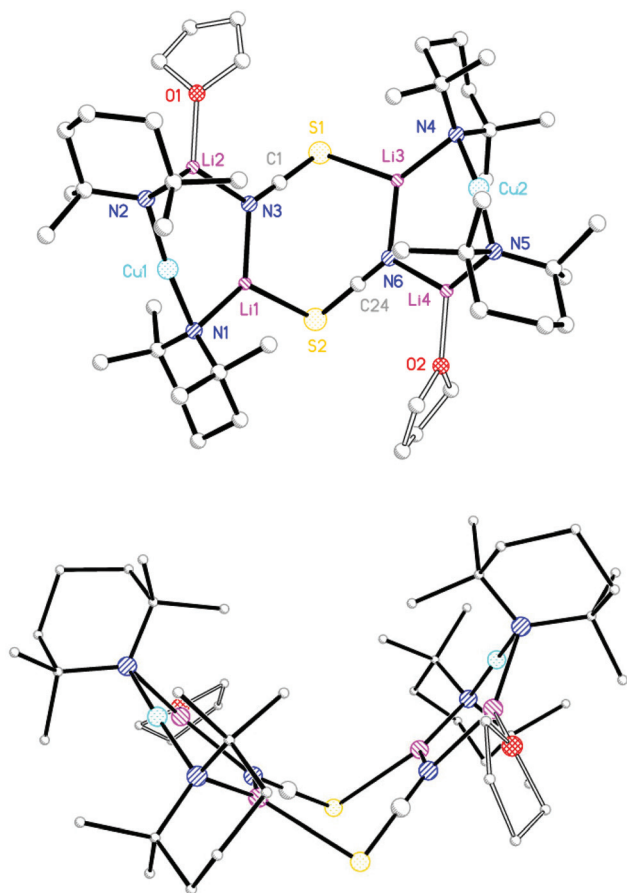


Fig. 4 (a) Molecular structure of **10₂**. H-atoms omitted. Selected bond lengths (Å) and angles (°): N1–Cu1 1.908(2), N2–Cu1 1.906(2), N1–Li1 1.977(5), N2–Li2 1.995(6), S2–Li1 2.500(6), N3–Li1 2.071(6), N3–Li2 2.105(6), N3–C1 1.159(4), S1–C1 1.627(3), Cu1–N1–Li1 87.45(18), Cu1–N2–Li2 87.66(18), N1–Li1–N3 130.7(3), N2–Li2–N3 128.9(3), Li1–N3–C1 125.0(3), Li2–N3–C1 124.8(3), S2–Li1–N3 108.8(2), Li1–S2–C24 91.72(17); (b) view emphasising the boat-shaped dimer core.

sulfur is fundamentally altered relative to that seen in **9₂**. The result is that the two sulfur centres in **10₂** constitute the hinge about which deviation from planarity of the dimer operates. In spite of this, diffraction fails to reveal any significant difference in the bond lengths associated with sulfur (*cf.* S1–C19 1.631(3), S1–Li2A 2.518(4) Å in **9₂** and S2–C24 1.625(3), S2–Li1 2.500(6) Å in **10₂**). This suggested equivalent thiocyanate anion structure to that seen in **9₂** even if the angle at sulfur now dramatically constricted on account of the dimer folding along the S...S vector (Li2–S1A–C19A 103.92(13)° in **9₂** compares with Li1–S2–C24 91.72(17)° in **10₂**). The two 6-membered Cu-containing CuLi₂N₃ rings in **10₂** are essentially planar (angles at Li1 and N3 sum to 359.9° and 359.6°, respectively).

Having established significantly different geometries for **9₂** and **10₂** attention switched to use of the Lewis base THP. TMPLi in hexane/toluene and THP (0.5 eq. wrt Li) was reacted with CuSCN, leading to the isolation of a modest yield of colourless blocks (Scheme 3). NMR spectroscopy revealed the presence therein of TMP and THP in a 2 : 1 ratio. Meanwhile,

IR spectroscopy demonstrated signals attributable to SCN at 2063.2 (s) and 2006.5 (w) cm^{−1}, these being replaced by peaks at 2173.7 and 2108.5 cm^{−1} upon air exposure for 30 s. (Fig. S4†). X-ray diffraction confirmed the expected formulation of the product as the dimer of (TMP)₂Cu(SCN)Li₂(THP) **11** but revealed a structure (Fig. 5) that, in contrast to the structures of **9₂** and **10₂**, exhibited a clear chair conformation ostensibly by virtue of the significant displacement (by ±0.43 Å) of Li2 and its symmetry equivalent from the mean plane described by the Li1–N3–C19–S1 fragment and its symmetry analogue. In order to allow this to occur not only S1 but also N3 necessarily deviate from planarity (in contrast to the geometry of N3 in **10₂**), with angles at nitrogen now summing to 351.6°. This small deviation from planarity (presumably limited to maximize the electrostatic directionality of nitrogen) is reflected also in the geometry at S1 for which, at 96.09(12)°, the Li–S–C angle is intermediate between those seen in the two previous structures (103.92(13)° in **9₂**, 91.72(17)° in **10₂**).

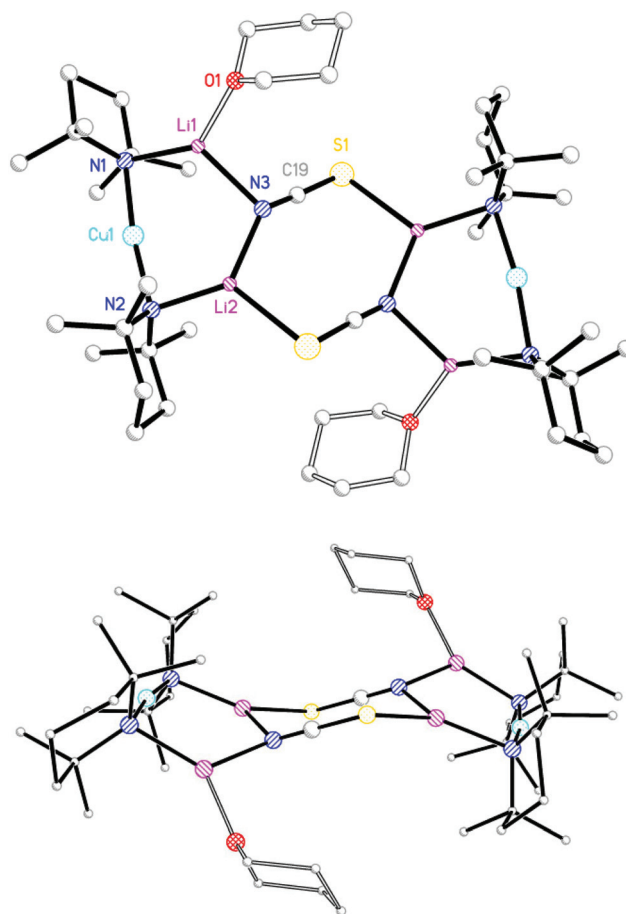


Fig. 5 (a) Molecular structure of **11₂**. H-atoms omitted. Selected bond lengths (Å) and angles (°): N1–Cu1 1.9204(17), N2–Cu1 1.9148(17), N1–Li1 1.990(4), N2–Li2 1.968(4), S1A–Li2 2.464(4), N3–Li1 2.164(5), N3–Li2 2.005(4), N3–C19 1.162(3), S1–C19 1.632(3), Cu1–N1–Li1 110.75(19), Cu1–N2–Li2 88.84(13), N1–Li1–N3 123.4(2), N2–Li2–N3 128.5(2), Li1–N3–C19 106.7(2), Li2–N3–C19 134.5(2), S1A–Li2–N3 107.90(18), Li2A–S1–C19 96.09(12); (b) the chair-shaped dimer core.



Diffraction reveals bond lengths of S1–C19 1.632(3), S1–Li2A 2.464(4) Å associated with sulfur, which are essentially the same as those seen in **9**₂ and **10**₂ and point to a common thiocyanate ligand electronic structure.

The solvent sensitivity of thiocyanatocuprate formation was also investigated by eliminating external Lewis bases. As described above, reaction of TMPLi (4 mmol) with CuSCN (2 mmol) in bulk hydrocarbon doped with L (= OEt₂, THF, TMP; 0.5 eq. wrt Li) gave (TMP)₂Cu(SCN)Li₂(L) **9–11**. However, crystallographic analysis of the product revealed that the avoidance of donor solvent afforded a convenient and clean route to material which demonstrated a single signal at δ 0.90 ppm by ⁷Li NMR spectroscopy. Crystallography subsequently revealed previously reported (TMP)₂CuLi **12**,²³ which was a dimer in the solid state, with IR spectroscopy corroborating the absence of SCN ligands (see ESI Fig. S5†). However, the suggestion from ⁷Li NMR spectroscopy that omitting Lewis base avoided contamination of the product with minor impurities²³ led us to undertake further re-characterization, obtaining a simple ¹³C NMR spectrum of the Gilman cuprate (see below) which served to aid our interpretation of the more complex behaviour of **9–11** in solution.

NMR spectroscopy

The improved synthesis of **12** made available clean NMR spectra of the Gilman cuprate (TMP)₂CuLi, with ¹³C and ⁷Li NMR spectra obtained in *d*₆-benzene that could then be deployed in order to deconvolute the solution behaviour of thiocyanates **9–11**. The ¹³C NMR spectrum revealed a simple set of signals attributable to [TMP][−] with singlets due to the 2,6-, 3,5- and 4-positions of the rings seen at δ 54.2, 42.1 and 19.2 ppm, respectively, and two Me signals located at δ 40.1 and 34.5 ppm (Fig. 6d). Comparison with the analogous spectrum obtained for diethyl ether complex **9** (at a concentration of ~20 mg/0.7 mL *d*₆-benzene, Fig. 6a) revealed it to be dominated by essentially identical signals, with a small amount of decomposition to give TMPH peaks, with minor traces of Lipshutz-type cuprate (see below) also manifest. These data strongly suggest ostensible conversion from the Lipshutz-type structure seen crystallographically for this system (Fig. 3a) to a Gilman formulation in solution.

Moving to the ¹³C NMR spectroscopic data for THF-solvate **10** at the same concentration, a more complicated system is revealed. (The SCN component itself can be located at δ

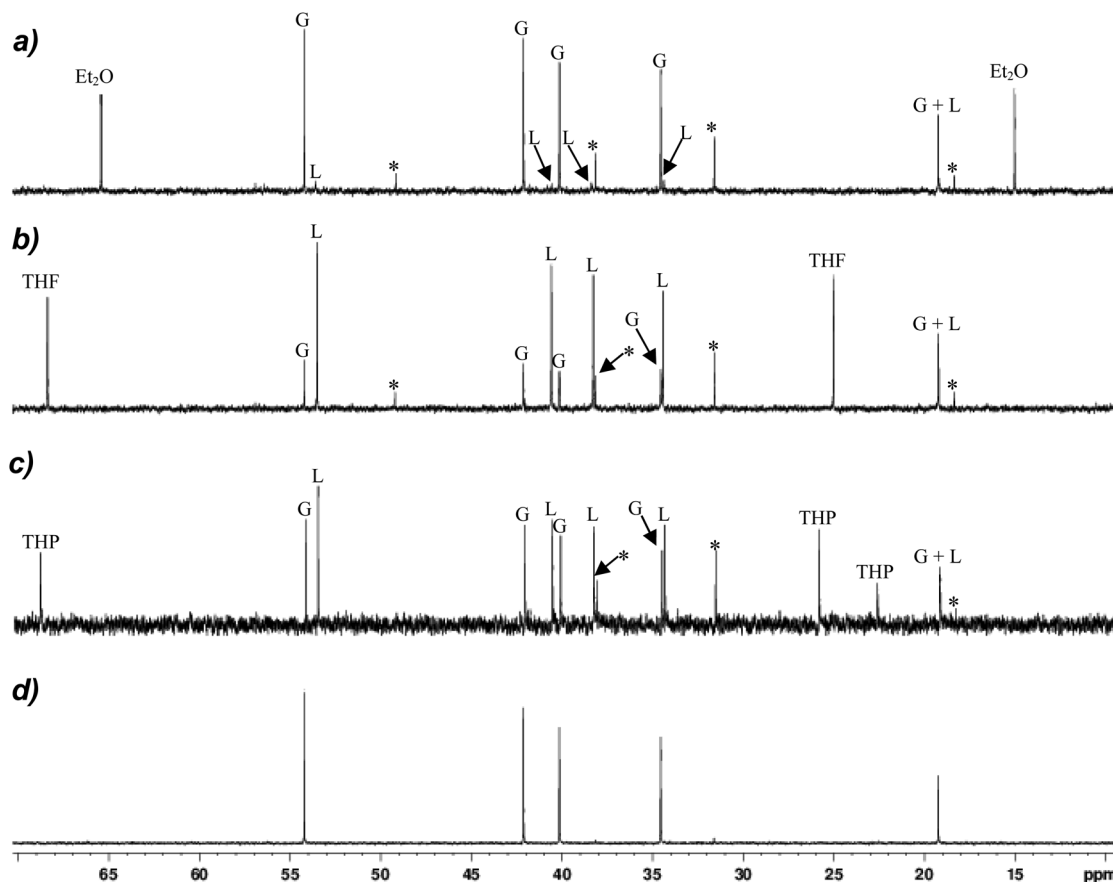


Fig. 6 ¹³C NMR spectroscopic data obtained in *d*₆-benzene for (a) **9**, (b) **10**, (c) **11**, (d) **12** (*TMPH, G = Gilman, L = Lipshutz-type). Sample concentrations for **9–11** were 20 mg/0.7 mL.



141.5 ppm for this system in a 50 mg/0.7 mL sample, Fig. S11†) It is immediately obvious that whilst signals attributable to the amide ligands in the Gilman cuprate remain, they no longer represent the dominant species in solution (Fig. 6b). Instead, major signals are now observed at the high-field side of each Gilman resonance (at δ 53.5, 40.6, 38.3, 34.4 ppm) and, in one case (δ 19.2 ppm), coincident with it. These are attributed to the corresponding carbon atoms in the Lipshutz-type structure, which appears to be substantially retained in solution, with an approximate Gilman : Lipshutz-type ratio of 1 : 3 suggested. Equivalently concentrated THP complex **11** (20 mg/0.7 mL in d_6 -benzene) revealed a similar picture to that demonstrated by **10**, albeit the distribution of Gilman and Lipshutz-type species is approaching equivalence (Fig. 6c). Moreover, similar to **10**, the analysis of a more concentrated sample (50 mg/0.7 mL in d_6 -benzene) located the thiocyanate resonance at δ 141.7 ppm (Fig. S11†).

Coincident with the near-quantitative *in situ* conversion of Lipshutz-type crystalline **9** to a Gilman cuprate in d_6 -benzene (Fig. 6a) the deposition of a white powder was observed in the NMR tube to which **9** (20 mg/0.7 mL) had been added. Based on a control experiment in which pre-isolated Lipshutz-type cuprate was dissolved in benzene and the resulting white deposit analyzed by IR spectroscopy, we attribute this observation to LiSCN precipitation (Fig. S6†). ^7Li NMR spectroscopy on this sample therefore accorded no signal attributable to LiSCN. Rather, it revealed a dominant peak precisely matching the δ 0.90 ppm Gilman cuprate peak in **12** (Fig. 7d) accompanied by the development of a minor high-field signal at δ 0.65 ppm (Fig. 7a). Consistent with the ^{13}C NMR spectroscopic data, the high-field signal can be attributed to the retention of a small amount of Lipshutz-type cuprate in hydrocarbon solution, with the relative integrations (of 1 and 0.4) suggesting an approximate Gilman : Lipshutz-type ratio of 5 : 1.

Moving to **10** in solution it is immediately apparent that the ^7Li NMR spectrum revealed a significant change in behaviour, with the high-field signal at δ 0.71 ppm now dominant (Fig. 7b). Taken together with ^{13}C NMR spectroscopic data, this confirms the attribution of the high-field signal as retained Lipshutz-type cuprate and emphasizes the solvent dependence of LiSCN abstraction, with a Gilman : Lipshutz-type ratio of 0.2 : 1 calculated based on the ^7Li NMR data – which substantiates the ^{13}C NMR spectrum in Fig. 6b. Fig. 7c reinforces this view, with the Gilman : Lipshutz-type ratio of 0.6 : 1 calculated from ^7Li NMR data for **11** correlating with the appearance of Fig. 6c.

Chloropyridine derivatization

Based upon recent work on the use of halide-containing Lipshutz-type cuprates to facilitate the synthesis of azafluorenone frameworks²⁴ it was decided to test the reactivity of new thiocyanocuprates in the selective elaboration of halopyridines. The *in situ* preparation of **10** was therefore undertaken using THF solvent and the resulting mixture was tested in the selective deprotometalation of both 2-chloropyridine **13** and 2,3-dichloropyridine **14**. Under the conditions employed it was expected

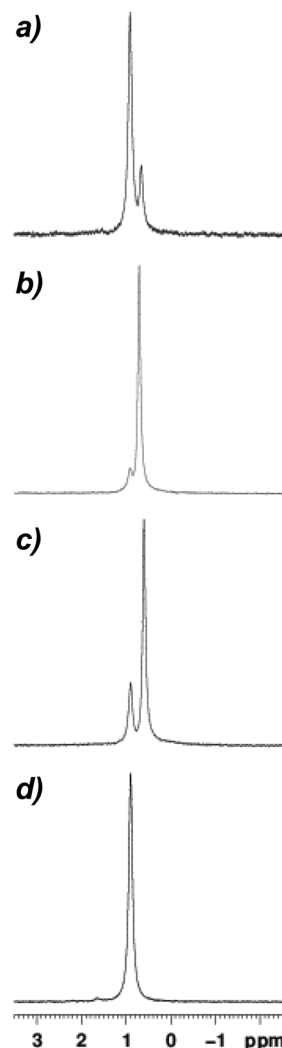


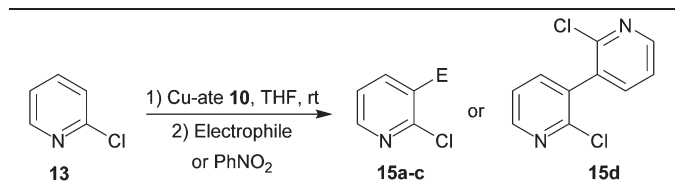
Fig. 7 ^7Li NMR spectroscopic data obtained in d_6 -benzene for (a) **9**, (b) **10**, (c) **11**, (d) **12**. Sample concentrations for **9**–**11** were 20 mg/0.7 mL.

that reaction of **13** would occur at the aromatic 3-position, while the employment of two adjacent acidifying halogens would promote attack of the 4-position in the dichlorinated substrate.

Results of the use of *in situ*-generated **10** in the selective metalation of **13** are reported in Table 1. Under the conditions employed, reaction afforded the 3-substituted derivatives **15a–c** in 46–71% yields after subsequent trapping with 4-methoxybenzoyl chloride, methyl iodide or phenyl disulfide, respectively (Table 1, entries 1–3 and Fig. S13†). In the light of cyanocuprate **2** having been shown to promote the quantitative homocoupling of *N,N*-diisopropylbenzamide in the presence of the oxidant PhNO_2 ,¹² so obviating the need for the inclusion of an additional transition metal-based catalyst, it was decided to test the efficacy of **10** in this respect as a safer alternative to the cyanocuprate. Accordingly, the formation of **15d** was observed in 69% yield (entry 4).

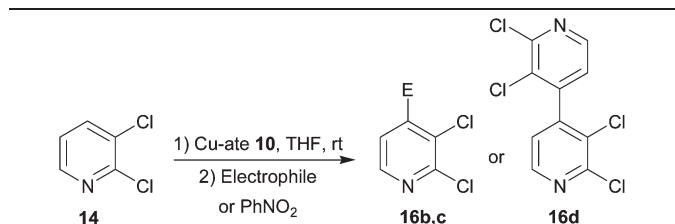
The response of 2,3-dichloropyridine **14** was tested next (Table 2). This is known to undergo lithiation at the 4-position



Table 1 Results of the reaction of **10** with 2-chloropyridine **13** in THF and subsequent reaction with electrophiles or in the presence of PhNO₂

Entry	Electrophile or PhNO ₂	E	Product, yield (%)
1	4-MeOC ₆ H ₄ COCl	COC ₆ H ₄ -4-OMe	15a , 46 ^{a,b}
2	MeI	Me	15b , 65 ^c
3	PhSPh	SPh	15c , 71 ^a
4	PhNO ₂	—	15d , 69 ^a

^a Isolated yield. ^b 55% yield by using CuCl instead of CuSCN. ^c Yield estimated by ¹H NMR spectroscopy due to volatile nature of the product.

Table 2 Results of the reaction of **10** with 2,3-dichloropyridine **14** in THF and subsequent reaction with electrophiles or in the presence of PhNO₂

Entry	Electrophile or PhNO ₂	E	Product, yield (%)
1	MeI	Me	16b , 58 ^a
2	PhSPh	SPh	16c , 62 ^b
3	PhNO ₂	—	16d , 51 ^b

^a Yield estimated by ¹H NMR spectroscopy due to volatile nature of the product. ^b Isolated yield.

in THF using either diisopropylamidolithium or butyllithium at −75 °C.²⁹ More recently, the putative bases (TMP)₃ZnLi and (TMP)₂CuLi were used to generate 4-iodo and 4-keto products from 2,3-dichloropyridine.²⁵ Results suggested essentially similar performance of **10** in the selective iodination and acylation of C4 in 2,3-dichloropyridine to that seen for C3 in 2-chloropyridine (Table 2, entries 1, 2 and Fig. S13†). Meanwhile, homocoupling now proceeded to give **16c** in 51% yield (entry 3).

Conclusions

The preparation of (TMP)₂Cu(CN)Li₂(THP) **8** served to extend the family of TMP-incorporating lithiocuprates based on the formulation (TMP)₂Cu(CN)Li₂(L) (L = OEt₂ **1**, THF **2**) and to establish the prevalence of approximately flat dimers for these

complexes in the solid state.^{12,21} The use of thiocyanate instead of cyanide was then probed to investigate the former as a convenient, cheap and safe alternative that avoids redirecting reactivity in ways recently described when cyanide has been replaced by halide.¹³ The resulting complexes showed interesting structural variability; the use of Et₂O incurring an essentially planar dimer akin to those of **1**, **2** and **8** but based on a (LiNCS)₂ core, while THF and TMP gave boat and chair conformers, respectively. These aggregates were best viewed as incorporating Li[S–C≡N] moieties. Consistent with recently developed theoretical views on cuprate reactivity,²³ solid state structures were not necessarily retained in solution, with at least some Gilman cuprate formation noted for each thiocyanate system in benzene. Lastly, preliminary synthetic investigations successfully applied **10** to the selective deprotometalation and homocoupling of halopyridines, with ongoing work seeking to establish the extent of the synthetic portfolio of these new reagents.

Experimental section

General synthetic and analytical details

Reactions and manipulations were carried out under an inert atmosphere of dry nitrogen, using standard double manifold and glove-box techniques. Solvents were distilled off sodium (toluene) or sodium–potassium amalgam (Et₂O, THF, hexane) immediately prior to use. Copper(i) thiocyanate and tetrahydropyran (THP, Sureseal) were purchased from Aldrich and 2,2,6,6-tetramethylpiperidine (TMPH) was purchased from Alfa Aesar. The amine was stored over molecular sieve (4 Å) while the other chemicals were used as received. ⁿBuLi (2.5 mL, 1.6 M in hexanes) was purchased from Acros and used as received. IR spectra were collected on a Bruker Alpha FT IR spectrometer. NMR data were collected on a Bruker Avance III HD 500 MHz Smart Probe FT NMR spectrometer (500.200 MHz for ¹H, 125.775 MHz for ¹³C, 194.397 for ⁷Li). Spectra were obtained at 25 °C and chemical shifts are internally referenced to *d*₆-benzene and calculated relative to TMS except for ⁷Li, for which an external reference was used (1 M LiCl in D₂O). Chemical shifts are expressed in δ ppm. The following abbreviations are used: br = broad, m = multiplet, s = singlet, G = Gilman cuprate, L = Lipshutz-type cuprate.

Crystallographic details

Compounds 8–12. For details of data collections see Table 3. Crystals were transferred directly from the mother liquor to a drop of perfluoropolyether oil mounted upon a microscope slide under a stream of cool nitrogen gas.³⁰ Suitable crystals were selected and attached to the goniometer head *via* a MicroLoop™, which was then centred on the diffractometer. Data were collected on a Bruker D8 Quest equipped with an Oxford Cryosystems low-temperature device (Cu-Kα, λ = 1.54184 Å, T = 180(2) K). Structures were solved using SHELXT,³¹ with refinement, based on F², by full-matrix least squares.³² Except when disordered, non-hydrogen atoms were



Table 3 X-ray crystal data for **8**, **9**, **10** and **11**

	8 ₂	9 ₂	10 ₂	11 ₂
Formula	C ₄₈ H ₉₂ Cu ₂ Li ₄ N ₆ O ₂	C ₄₆ H ₉₂ Cu ₂ Li ₄ N ₆ O ₂ S ₂	C ₄₆ H ₈₈ Cu ₂ Li ₄ N ₆ O ₂ S ₂	C ₄₈ H ₉₂ Cu ₂ Li ₄ N ₆ O ₂ S ₂
<i>M</i>	940.11	980.21	976.18	1004.23
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i>	9.0869(4)	16.1549(5)	15.1170(7)	15.8974(7)
<i>b</i>	11.3341(5)	11.4981(3)	14.7117(7)	8.1755(3)
<i>c</i>	13.6040(6)	15.2650(5)	25.3458(11)	22.0201(9)
α	86.210(2)	90	90	90
β	76.776(2)	98.687(2)	104.763(2)	100.199(2)
γ	82.219(2)	90	90	90
<i>V</i>	1350.49(10)	2802.96(15)	5450.7(4)	2816.7(2)
<i>Z</i>	1	2	4	2
ρ_{calcd}	1.156	1.161	1.190	1.184
μ	1.258	1.908	1.962	1.912
Data	13 834	29 571	73 948	41 304
Unique data	4736	4914	9650	4945
<i>R</i> _{int}	0.0324	0.0513	0.0610	0.0495
θ (°)	3.339–66.540	2.767–66.719	3.023–66.831	2.824–66.556
<i>wR</i> ₂	0.1896	0.1043	0.1294	0.0929
<i>R</i>	0.0624	0.0409	0.0474	0.0360
GoF	1.072	1.016	1.030	1.037
Parameters	393	326	575	297
Peak/hole (e Å ^{−3})	0.925/−0.446	0.538/−0.251	0.717/−0.556	0.545/−0.394

refined anisotropically and a riding model with idealized geometry was employed for the refinement of H-atoms. Compound **12** was subjected to a crystallographic cell check that corresponded to previously reported data.²³ Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 1429486 (**8**₂), 1429485 (**9**₂), 1429483 (**10**₂) and 1429484 (**11**₂).

Compounds 15c and 16c. Samples were studied using graphite monochromated Mo-K α radiation (λ = 0.71073 Å). X-ray diffraction data were collected using an APEXII, Bruker-AXS diffractometer at *T* = 150(2) K (**15c**) or a D8 VENTURE Bruker AXS diffractometer at 294(2) K (**16c**). The structures were solved by direct methods using the SIR97 program,³³ and then refined with full-matrix least-square methods based on *F*² (SHELX-97)³⁴ with the aid of the WINGX program.³⁵ Non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H-atoms were finally included in their calculated positions. Molecular diagrams (Fig. S13†) were generated by ORTEP-3 (version 2.02).³⁵

Synthesis and characterization of (TMP)₂Cu(CN)Li₂(THP) **8.** To a stirred solution of TMPH (0.68 mL, 4 mmol) and THP (0.17 mL, 2 mmol) in hexane (4 mL) was added ⁿBuLi (2.5 mL, 1.6 M in hexanes, 4 mmol) at −78 °C. The resulting solution was returned to room temperature to give a yellow solution that was transferred to a suspension of CuCN (0.179 g, 2 mmol) in toluene (6 mL) at −78 °C. The mixture was warmed to room temperature to give a pale cream-coloured suspension. Hexane (4 mL) was added and the mixture heated to reflux until most solid had dissolved. Immediate filtration gave a pale-straw coloured solution. Storage at room temperature for 24 h gave colourless block-like crystals. Yield 20 mg (27%), melting point 185–187 °C. Elemental Analysis,

C₄₈H₉₂Cu₂Li₄N₆O₂ requires (%) C 61.32, H 9.86, N 8.94; found (%) C 60.69, H 9.65, N 8.84. ¹H NMR spectroscopy (500 MHz, C₆D₆) δ 3.50 (m, 8H, THP), 2.13–1.80 (br, m, 4H, TMP-4), 1.74 (s, 24H, TMP-Me), 1.71–1.39 (br, m, 34H, TMP-3,5,-Me), 1.39–1.23 (m, 14H, THP, TMP-3,5), 1.23–1.15 (br, m, 4H, THP), 1.14 (m, 2H, TMP-3,5), 1.07 (s, 1.6H, TMPH-Me), 0.32 (br, s, 0.13H, TMPH-NH). ¹³C NMR (126 MHz, C₆D₆) δ 69.0 (THP), 54.2 (TMP-2,6, G), 53.7 (TMP-2,6, L), 49.2 (TMPH-2,6), 42.1 (TMP-3,5, G), 40.5 (br, TMP-3,5, L), 40.1 (TMP-Me, G), 38.4 (TMP-Me, L), 38.2 (TMPH-3,5), 34.5 (TMP-Me, G), 34.0 (TMP-Me, L), 31.6 (TMPH-Me), 25.7 (THP), 22.6 (THP), 19.4 (TMP-4, L), 19.2 (TMP-4, G), 18.4 (TMPH-4). ⁷Li NMR (194 MHz, C₆D₆) δ 0.90 (br, s, 0.2Li, G), 0.21 (s, 1Li, L). Selected IR spectroscopy (nujol) $\bar{\nu}$ 2104.3 cm^{−1} (m).

Synthesis and characterization of (TMP)₂Cu(SCN)Li₂(OEt)₂ **9.** To a stirred solution of TMPH (0.68 mL, 4 mmol) and Et₂O (0.21 mL, 2 mmol) in toluene (2 mL) at −78 °C was added ⁿBuLi (2.5 mL, 1.6 M in hexanes, 4 mmol). The solution was returned to room temperature whereupon it was transferred to a suspension of CuSCN (0.243 g, 2 mmol), in toluene (2 mL), at −78 °C. The mixture was warmed to room temperature to give a pale cream-coloured suspension which was then heated to reflux until it turned grey-black. The mixture was filtered immediately, giving a yellow solution. Storage at room temperature gave needle-like crystals after 1 day, which dissolved with further standing, to be replaced after several days with crystals of *pseudo*-rhombic habit. Yield 97 mg (10%), melting point 173–175 °C. Elemental Analysis, C₄₆H₉₂Cu₂Li₄N₆O₂S₂ requires (%) C 56.63, H 9.46, N 8.57; found (%) C 55.58, H 9.34, N 8.46. ¹H NMR spectroscopy (500 MHz, C₆D₆) δ 3.28 (q, *J* = 7 Hz, 8H, Et₂O), 1.89–1.76 (m, 4H, TMP-4), 1.66–1.61 (m, 8H, TMP-3,5), 1.60 (s, 24H, TMP-Me), 1.59–1.57 (m, 4H,



TMP-4), 1.56 (s, 24H, TMP-Me) 1.14–1.06 (m, 20H, Et₂O + TMP-3,5), 1.06 (s, 7H, TMPH-Me), 0.32 (br, s, 0.44H, TMPH-NH). ¹³C NMR (126 MHz, C₆D₆) δ 65.4 (Et₂O), 54.2 (TMP-2,6, G), 53.6 (TMP-2,6, L), 49.2 (TMPH-2,6), 42.2 (TMP-3,5, G), 40.6 (TMP-3,5, L), 40.1 (TMP-Me, G), 38.4 (TMP-Me, L), 38.2 (TMPH-3,5), 34.5 (TMP-Me, G), 34.4 (TMP-Me, L), 31.6 (TMPH-Me), 19.2 (TMP-4, G + L), 18.4 (TMPH-4), 15.0 (Et₂O). ⁷Li NMR (194 MHz, C₆D₆) δ 0.90 (s, 1Li, G), 0.65 (s, 0.4 Li, L). Selected IR spectroscopy (nujol) $\bar{\nu}$ 2064.6 cm⁻¹ (s), 1996.6 cm⁻¹ (m).

Synthesis and characterization of (TMP)₂Cu(SCN)Li₂(THF) 10.

ⁿBuLi (2.5 mL, 1.6 M in hexanes, 4 mmol) was added to a stirred solution of TMPH (0.68 mL, 4 mmol) and THF (0.16 mL, 2 mmol) in hexane (4 mL) at -78 °C. The resulting solution was returned to room temperature and transferred to a suspension of CuSCN (0.243 g, 2 mmol), in hexane (2 mL), at -78 °C. The mixture was warmed to room temperature to a give a pale cream-coloured suspension which was heated to reflux until it turned grey-black. Immediate filtration gave a pale yellow solution. Storage at -27 °C for 24 h gave colourless prismatic crystals. Yield 516 mg (53%), melting point 143–145 °C. Elemental Analysis, C₄₆H₈₈Cu₂Li₄N₆O₂S₂ requires (%) C 56.60, H 9.09, N 8.61; found (%) C 57.63, H 9.35, N 8.61. ¹H NMR spectroscopy (500 MHz, C₆D₆) δ 3.66 (m, 8H, THF), 1.99–1.75 (m, 4H, TMP-4), 1.66 (m, 24H, TMP-3,5, Me), 1.63–1.52 (br, m, 18H, TMP-4, Me), 1.50 (s, 18H, TMP-Me), 1.42 (m, 8H, THF), 1.21–1.06 (m, 8H, TMP-3,5), 1.07 (s, 5.4H, TMPH-Me), 0.33 (br, s, 0.3H, TMPH-NH). ¹³C NMR (126 MHz, C₆D₆) δ 141.5 (SCN), 68.4 (THF), 54.2 (TMP-2,6, G), 53.5 (TMP-2,6, L), 49.2 (TMPH-2,6), 42.1 (TMP-3,5, G), 40.6 (TMP-3,5, L), 40.1 (TMP-Me, G), 38.3 (TMP-Me, L), 38.2 (TMPH-3,5), 34.5 (TMP-Me, G), 34.4 (TMP-Me, L), 31.6 (TMPH-Me), 25.0 (THF), 19.2 (TMP-4, G + L), 18.4 (TMPH-4). ⁷Li NMR (194 MHz, C₆D₆) δ 0.89 (s, 0.2Li, G), 0.71 (s, 1Li, L). Selected IR spectroscopy (nujol) $\bar{\nu}$ 2050.4 cm⁻¹ (s), 1998.0 cm⁻¹ (m).

Synthesis and characterization of (TMP)₂Cu(SCN)Li₂(THP) 11.

A stirred solution of TMPH (0.68 mL, 4 mmol) and THP (0.17 mL, 2 mmol) in hexane/toluene (4 mL/2 mL) at -78 °C was treated with ⁿBuLi (2.5 mL, 1.6 M in hexanes, 4 mmol). The resulting solution was returned to room temperature whereupon it was transferred to a suspension of CuSCN (0.243 g, 2 mmol) in hexane/toluene (2 mL/1 mL) at -78 °C. The mixture was warmed to room temperature to a give a pale cream-coloured suspension which was then heated to reflux until it became grey-black. The mixture was filtered immediately. This gave a yellow solution, the storage of which at room temperature for 24 h gave colourless blocks. Yield 250 mg (27%), melting point 176–178 °C. Elemental Analysis, C₄₈H₉₂Cu₂Li₄N₆O₂S₂ requires (%) C 57.41, H 9.23, N 8.37; found (%) C 57.17, H 9.23, N 8.45. ¹H NMR spectroscopy (500 MHz, C₆D₆) δ 3.62 (t, ³J_{HH} = 5 Hz, 8H, THP), 1.98–1.75 (m, 4H, TMP-4), 1.73–1.52 (m, 46H, TMP-Me/3,5/4), 1.49 (s, 12H, TMP-Me), 1.32 (m, 8H, THP), 1.27–1.15 (m, 10H, THP + TMP-3,5), 1.15–1.04 (m, 4H, TMP-3,5), 1.07 (s, 5H, TMPH-Me), 0.32 (br, s, 0.4H, TMPH-NH). ¹³C NMR (125.8 MHz, C₆D₆)

δ 68.8 (THP), 54.2 (TMP-2,6, G), 53.5 (TMP-2,6, L), 49.2 (TMPH-2,6), 42.1 (TMP-3,5, G), 40.6 (TMP-3,5, L), 40.1 (TMP-Me, G), 38.3 (TMP-Me, L), 34.5 (TMP-Me, G), 34.4 (TMP-Me, L), 31.6 (TMPH-Me), 25.9 (THP), 22.7 (THP), 19.2 (TMP-4, G + L), 18.4 (TMPH-4). ⁷Li NMR (194.4 MHz, 27 °C, C₆D₆) δ 0.90 (s, 0.3Li, G), 0.60 (s, 1Li, L). Selected IR spectroscopy (nujol) $\bar{\nu}$ 2063.2 cm⁻¹ (s), 2006.5 cm⁻¹ (w).

Synthesis and characterization of (TMP)₂CuLi 12. ⁿBuLi (2.5 mL, 1.6 M in hexanes, 4 mmol) was added to a stirred solution of TMPH (0.68 mL, 4 mmol) in hexane/toluene (2 mL/2 mL) at -78 °C. The resulting solution was returned to room temperature and transferred to a suspension of CuSCN (0.243 g, 2 mmol), in hexane/toluene (2 mL/2 mL), at -78 °C. The mixture was warmed to room temperature to a give a pale cream-coloured suspension which was heated to reflux until it turned grey-black. Immediate filtration gave a pale yellow solution that was concentrated until precipitation occurred, after which the solid was redissolved by gentle warming. Storage of the resulting bright yellow solution at room temperature for 24 h gave very large blade-shaped crystals. Yield 201 mg (40%), melting point 198–200 °C. Elemental Analysis, C₃₆H₇₂Cu₂Li₂N₄ requires (%) C 61.60, H 10.34, N 7.98; found (%) C 60.83, H 10.30, N 7.89. ¹H NMR spectroscopy (500 MHz, C₆D₆) δ 1.89–1.77 (m, 4H, TMP-4), 1.67–1.61 (m, 8H, TMP-3,5), 1.60 (s, 24H, TMP-Me), 1.59–1.57 (m, 4H, TMP-4), 1.56 (s, 24H, TMP-Me), 1.14–1.06 (m, 8H, TMP-3,5). ¹³C NMR (126 MHz, C₆D₆) δ 54.2 (TMP-2,6), 42.1 (TMP-3,5), 40.1 (TMP-Me), 34.5 (TMP-Me), 19.2 (TMP-4). ⁷Li NMR (194 MHz, C₆D₆) δ 0.90 (s).

Synthesis and characterization of chloropyridine derivatives

A stirred solution of LiTMP was prepared at 0 °C by sequentially treating THF (5 mL) with 2,2,6,6-tetramethylpiperidine (0.68 mL, 4 mmol) and ⁿBuLi (2.5 mL, 1.6 M hexanes solution, 4 mmol). This reagent was then treated with copper(i) thiocyanate (0.24 g, 2 mmol). The mixture was stirred for 15 min at 0 °C before the introduction of 2-chloropyridine (**13**, 0.19 mL, 2 mmol) or 2,3-dichloropyridine (**14**, 0.30 g, 2 mmol). After 2 h. at RT, the electrophile (4 mmol) was added either as a neat liquid or as a solution in THF (5 mL). The mixture was stirred overnight at RT before addition of a 1 M aqueous solution of NaOH (20 mL) and extraction with Et₂O (2 × 20 mL). After washing the organic phase with an aqueous saturated solution of NH₄Cl (10 mL) and drying over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure and the product isolated after purification by flash chromatography on silica gel (the eluent is given in the product description).

2-Chloro-3-pyridyl 4-methoxyphenyl ketone **15a** was prepared from **13** by using 4-methoxybenzoyl chloride as the electrophile and was isolated (eluent: 8 : 2 heptane/AcOEt) in 46% yield as a yellow powder: mp 79 °C. The product was identified from a previous report.²⁴

2-Chloro-3-methylpyridine **15b** was prepared from **13** by using methyl iodide as the electrophile and was isolated (eluent: 9 : 1 heptane/AcOEt) as a yellow oil (estimated yield: 65%). The product was identified from a previous report.³⁶

2-Chloro-3-(phenylsulfanyl)pyridine **15c** (see Fig. S14†) was



prepared from **13** by using phenyl disulfide as the electrophile and was isolated (eluent: 9 : 1 heptane/AcOEt) in 71% yield as a greenish powder: mp 70–72 °C; IR(ATR): 689, 725, 745, 795, 909, 1021, 1029, 1060, 1146, 1382, 1434, 1474, 1547, 1736, 2927, 3062 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.02 (dd, *J* = 7.8 and 4.5 Hz, 1H), 7.08 (dd, *J* = 7.8 and 1.8 Hz, 1H), 7.41–7.56 (m, 3H), 7.48–7.54 (m, 2H), 8.13 (dd, *J* = 4.5 and 1.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 122.8 (CH), 129.6 (CH), 130.1 (2CH), 130.4 (C), 134.8 (2CH), 136.1 (C), 136.3 (CH), 145.9 (CH), 147.9 (C); X-ray diffraction data (CCDC-1427011): C₁₁H₈ClNS, *M* = 221.69, monoclinic *P*₂₁/*a* (I.T.#14), *a* = 9.0933(3), *b* = 11.0308(4), *c* = 10.0368(4) Å, β = 94.6760(10)°, *V* = 1003.40(6) Å³, *Z* = 4, ρ_{calcd} = 1.468 g cm⁻³, μ = 0.543 mm⁻¹ (a final refinement on *F*² with 2298 unique intensities and 127 parameters converged at *wR*(*F*²) = 0.0716 (*R*(*F*) = 0.0287) for 2067 observed reflections with *I* > 2σ(*I*). 2,2'-Dichloro-3,3'-bipyridine **15d** was prepared from **13** by using nitrobenzene (oxidative agent) and was isolated (eluent: 7 : 3 heptane/AcOEt) in 69% yield as a yellow powder: mp 118–120 °C. The product was identified by comparison with a commercial product.

2,3-Dichloro-4-methylpyridine **16b** was prepared from **14** by using methyl iodide as the electrophile and was isolated (eluent: 9 : 1 heptane/AcOEt) as a yellow oil (estimated yield: 58%). The product was identified from a previous report.³⁷ 2,3-Dichloro-4-(phenylsulfanyl)pyridine **16c** (see Fig. S15†) was prepared from **14** by using phenyl disulfide as the electrophile and was isolated (eluent: 9 : 1 heptane/AcOEt) in 62% yield as a yellow powder: mp 98 °C; IR(ATR): 690, 742, 750, 793, 1038, 1204, 1355, 1422, 1441, 1551, 1736, 3059 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.34 (d, *J* = 5.4 Hz, 1H), 7.40–7.51 (m, 5H), 7.82 (d, *J* = 5.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 119.2 (CH), 125.1 (C), 128.1 (C), 130.3 (2CH), 130.6 (CH), 135.8 (2CH), 145.7 (CH), 149.1 (C), 153.3 (C); X-ray diffraction data (CCDC-1427012): C₁₁H₇Cl₂NS, *M* = 256.14, monoclinic *P*₂₁ (I.T. # 4), *a* = 7.4916(7), *b* = 8.4263(9), *c* = 8.7496(9) Å, β = 93.708(4)°, *V* = 551.18(10) Å³, *Z* = 2, ρ_{calcd} = 1.543 g cm⁻³, μ = 0.740 mm⁻¹ (a final refinement on *F*² with 2275 unique intensities and 136 parameters converged at *wR*(*F*²) = 0.0788 (*R*(*F*) = 0.0299) for 2187 observed reflections with *I* > 2σ(*I*). Flack parameter = -0.02(7). 2,3,2',3'-Tetrachloro-4,4'-bipyridine **16d** was prepared from **14** by using nitrobenzene (oxidative agent) and was isolated (eluent: 8 : 2 heptane/AcOEt) in 51% yield as a white powder: mp 200–202 °C. The product was identified from a previous report.³⁸

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data repository (see <https://www.repository.cam.ac.uk/handle/1810/252480>). These include some data in the file formats fid (NMR spectroscopic data) and cif (crystallographic data), which can be opened using the programs TopSpin 3.2 (or similar) and Mercury CSD 3.5 (or similar), respectively.

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