

# Developing Lithium Chemistry of 1,2-Dihydropyridines: From Kinetic Intermediates to Isolable Characterized Compounds

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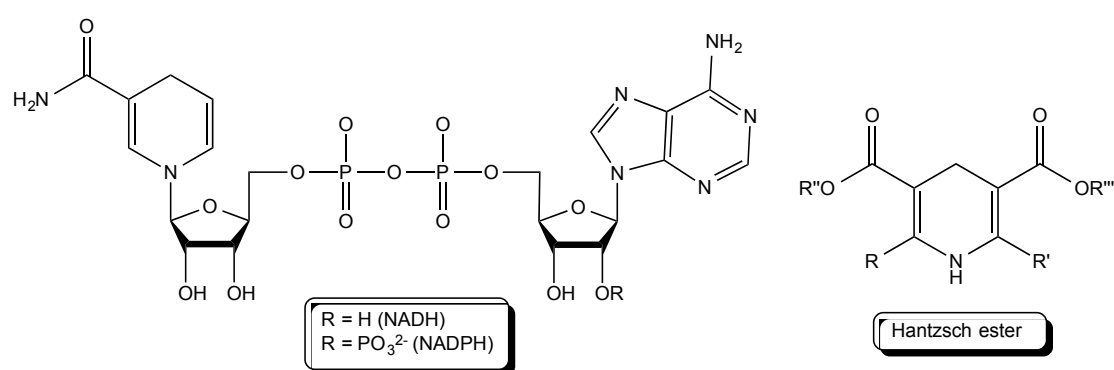
Dedicated to Professor Manfred Scheer on the happy occasion of his 60<sup>th</sup> birthday

## Abstract

Generally considered kinetic intermediates in addition reactions of alkyllithiums to pyridine, 1-lithio-2-alkyl-1,2-dihydropyridines have been rarely isolated or characterized. This study develops their “isolated” chemistry. By a unique stoichiometric (that is 1:1, alkyllithium:pyridine ratios) synthetic approach using tridentate donors we show it is possible to stabilize and hence crystallize monomeric complexes where alkyl is *t*-butyl. Theoretical calculations probing the donor-free parent *t*-butyl species reveal 12 energetically similar stereoisomers in two distinct cyclotrimeric (LiN)<sub>3</sub> conformations. NMR studies (including DOSY spectra) and thermal volatility analysis compare new *s*-butyl and *i*-butyl isomers showing the former is a hexane soluble efficient hydrolithiation agent converting benzophenone to lithium diphenylmethoxide. Emphasizing the criticalness of stoichiometry, reaction of *n*BuLi/Me<sub>6</sub>TREN with two equivalents of pyridine results in non-alkylated 1-lithio-1,4-dihydropyridine·Me<sub>6</sub>TREN and 2-*n*-butylpyridine, implying mechanistically the kinetic 1,2-*n*-butyl intermediate hydrolithiates the second pyridine.

## Introduction

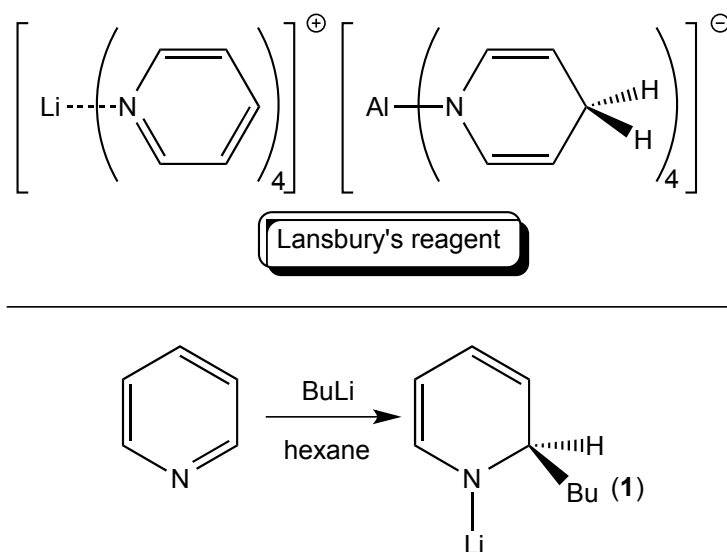
The dihydropyridyl unit <sup>1</sup> is prevalent in both biological <sup>2</sup> and medicinal chemistry <sup>3</sup> as a transfer hydrogenation (reduction) agent. In the former case this takes the form of naturally occurring nicotinamide adenine dinucleotide (NADH) or its phosphorylated derivative NADPH (figure 1), which act as cofactors for mediating redox processes such as photosynthesis. In the latter case, Hantzsch esters (figure 1) can be utilized as calcium antagonists to treat hypertension (high blood pressure). Dihydropyridyl units have also been comprehensively studied in organic chemistry for asymmetric transfer hydrogenation purposes <sup>4</sup> as well as for pyridine functionalization.<sup>5</sup>



**Figure 1** ChemDRAW representations of structures of biochemically relevant dihydropyridyl containing compounds

The driving force behind the utility of dihydropyridyl systems is the rearomatization of the ring to give an aromatic pyridine derivative. In both of the cases depicted in figure 1 the reactive species has been identified as the 1,4-dihydropyridyl isomer. Closely related to this work, the N-metallo dihydropyridyls, with greater negative charge, would appear to be ideal hydrometallation reagents operating under the same principles with a rearomatization engine driving their reductive capability. This logic has indeed been proved correct with for example Lansbury's reagent,<sup>6</sup> generated from lithium aluminum hydride LiAlH<sub>4</sub> and excess pyridine and formulated as the pyridine-solvent-separated ion pair [Li(NC<sub>5</sub>H<sub>5</sub>)<sub>4</sub>]<sup>+</sup> [Al(1,4-NC<sub>5</sub>H<sub>6</sub>)<sub>4</sub>]<sup>-</sup> (figure 2, top),<sup>7</sup> which acts as a selective reducing agent for aldehyde or ketone functionalities in the presence of carboxylic acid or ester groups. This 1-aluminate-1,4-dihydropyridyl complex (along with other related metallo-1,4-dihydropyridyl complexes including

those of lithium,<sup>8</sup> magnesium,<sup>9</sup> zinc<sup>9a, 10</sup> and other aluminium complexes<sup>11</sup>) is generally accepted as being the thermodynamically controlled isomer with the kinetic intermediate being a 1,2-dihydropyridyl isomer, leaving only limited synthetic access to the 1,2-isomer.<sup>12</sup> 1-Metallo-1,2-dihydropyridines have been implicated as the active intermediates in the metal catalyzed 1,2-hydroboration of pyridine,<sup>13</sup> while the presence of a metal salt such as a zinc or magnesium dihalide is known to activate the reduction of unactivated ketones and aldehydes by 1-methyl-1,4-dihydropyridines.<sup>14</sup>



**Figure 2** ChemDRAW representation of molecular structure of Lansbury's reagent and general synthetic protocol for preparation of 1-lithio-2-butyl-1,2-dihydropyridines

The addition of metal-carbon bonds to pyridines gives either the 1,2- or 1,4-addition product (e.g., organoanion = allyl, M = K;<sup>15</sup> K/Zn,<sup>15</sup> Ca;<sup>16</sup> Al<sup>17</sup>). Steric blocking at the 2 and 6 positions of the pyridine ring for example with imino substituents, does not necessarily promote 1,4 addition.<sup>18</sup> A ring substituent may be susceptible to deprotonative attack if it contains hydrogen atoms which are sufficiently inductively acidified by the pyridyl ring, for example a methyl group, as in picoline.<sup>16, 19</sup>

Recently, we revisited the well known 1,2-nucleophilic addition reaction of alkyl lithium reagents to pyridine,<sup>20</sup> albeit by employing a stoichiometric volume of pyridine rather than the typical excess (figure 2, bottom).<sup>21</sup> This new approach allowed us to isolate and characterize some pure 1-lithio-2-alkyl-1,2-dihydropyridine (2-*n*BuC<sub>5</sub>H<sub>5</sub>NLi, **1**, figure 2 bottom) complexes (that is suspected kinetic

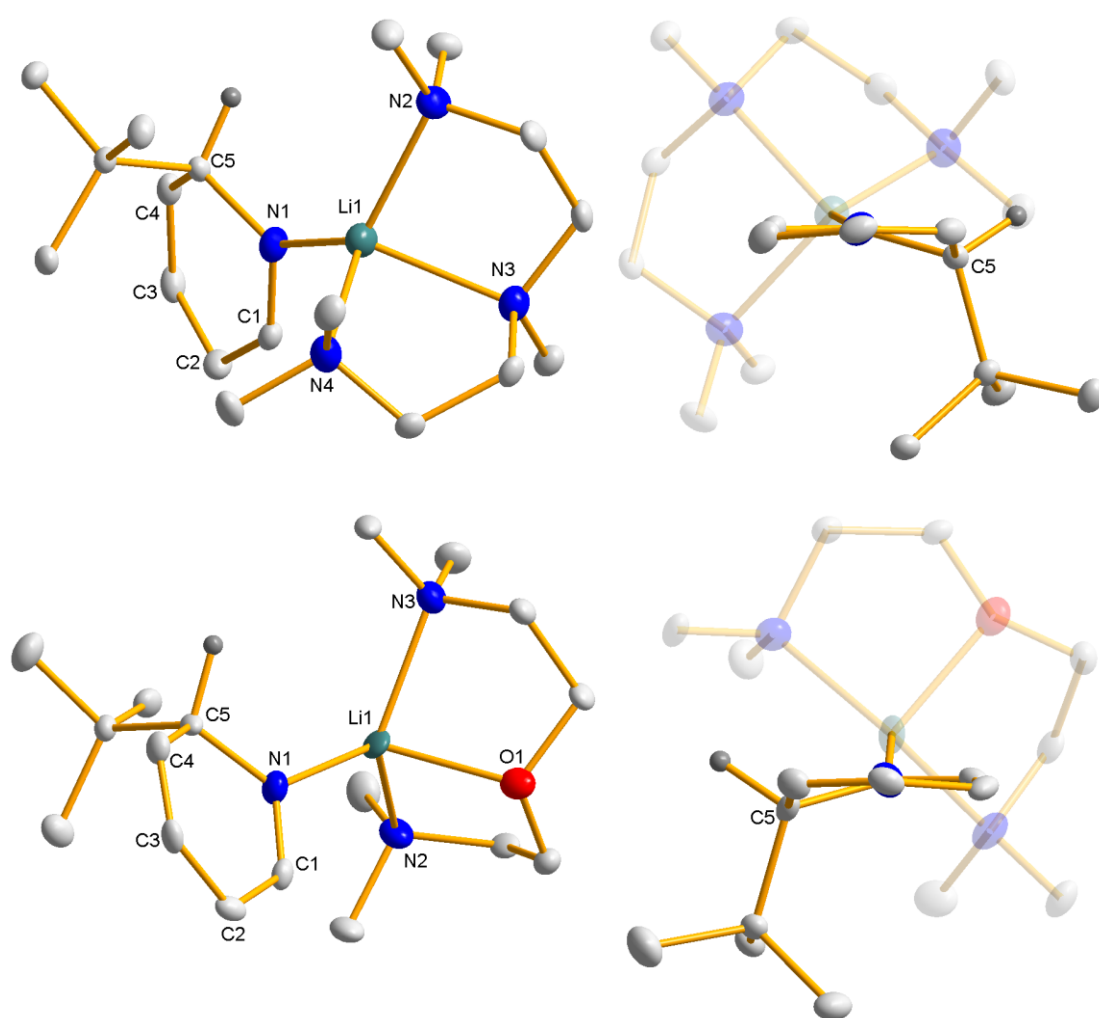
intermediates), normally utilized *in situ* for the purpose of pyridine functionalization, which somewhat surprisingly were thermally robust and in the case of the *t*-butyl example 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi (**1t**) was hexane soluble. This solubility, which was attributed to the steric effect of the *t*-butyl arm alpha to the N-Li bond and its consequent molecular constitution since in contrast the *n*-butyl isomer 2-*n*BuC<sub>5</sub>H<sub>5</sub>NLi (**1n**) is a hexane-insoluble polymer, makes it an excellent LiH surrogate complex, as exemplified by its hydrolithiation of benzophenone.<sup>22</sup> Practical soluble sources of alkali-metal hydrides are coveted with only a select few examples reported.<sup>23</sup> Furthermore it was possible to characterize this 1,2-dihydropyridyl complex crystallographically as a monomer, presumably a more reactive form than an aggregated type, by coordinatively saturating the lithium with a polydentate neutral donor in 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·Me<sub>6</sub>TREN, **1t**·Me<sub>6</sub>TREN. We have now extended this work here to look at both cheaper, commercially available polydentate donors for similar monomer stabilization and also synthetically safer alkyl lithium reagents in the pursuit of alternative soluble sources of lithium hydride. Their solubility, thermal robustness and utility as hydrolithiation reagents have been appraised. The importance of utilizing stoichiometric pyridine in the pursuit of a 1,2-dihydropyridyl complex is also emphasized by our findings. All complexes have been compared in solution by multinuclear NMR spectroscopy and in the solid state by X-ray crystallography where possible, while a theoretical study of the trimeric complex **1t** has also been carried out.

## Results and Discussion

### Donor stabilized monomers of 1-lithio-2-*t*-butyl-1,2-dihydropyridine

Noting the incomplete  $\eta^3$  coordination of tetradentate Me<sub>6</sub>TREN to lithium in **1t**·Me<sub>6</sub>TREN, we began by studying more readily available tridentate ligands in its place for oligomer to monomer deaggregation and stabilization. Although Me<sub>6</sub>TREN has a proven record for stabilizing sensitive monomers,<sup>24</sup> it is time-consuming to prepare and expensive to purchase commercially (£111/mL),<sup>25</sup> meaning that a commercially available, cheaper alternative would be more practical and economical. To explore this possibility experimentally, equimolar amounts of commercially available PMDETA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine, 24p/mL)<sup>25</sup> and Me<sub>4</sub>AEE (bis-[2-(*N,N*-dimethylamino)ethyl]ether, 23p/mL)<sup>25</sup> were introduced to a yellow hexane solution of **1t** and cooled in a freezer to afford crystalline complexes

identified by X-ray crystallographic analyses as monomeric 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·PMDETA (**1t**·PMDETA) and 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·Me<sub>4</sub>AEE (**1t**·Me<sub>4</sub>AEE) respectively (figure 3). Only the former crystal structure determination was of sufficient quality to discuss bond parameters although the latter unambiguously confirms the molecular connectivity and oligomerization state. In each case the structure is mononuclear, with the *t*Bu group and one donor atom lying below the plane of the pyridyl ring and the other two donor atoms lying above to minimize steric repulsion (see figure 2, right hand side).



**Figure 3** Molecular structure of 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·PMDETA (**1t**·PMDETA, top) and 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·Me<sub>4</sub>AEE (**1t**·Me<sub>4</sub>AEE, bottom). Ellipsoids are displayed at 50% probability and all hydrogen atoms except that on the saturated C5 of the dihydropyridyl ring are omitted for clarity.

**Table 1** Selected bond lengths (Å) and angles (°) for complexes **1t**·PMDETA and **1t**·Me<sub>6</sub>TREN<sup>21</sup>

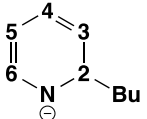
|        | <b>1t</b> ·PMDETA | <b>1t</b> ·Me <sub>6</sub> TREN |               | <b>1t</b> ·PMDETA | <b>1t</b> ·Me <sub>6</sub> TREN |
|--------|-------------------|---------------------------------|---------------|-------------------|---------------------------------|
| Li1-N1 | 1.976(2)          | 1.971(2)                        | N1-Li1-<br>N2 | 122.4(1)          | 120.6(1)                        |
| Li1-N2 | 2.153(2)          | 2.137(2)                        | N1-Li1-<br>N3 | 123.4(1)          | 125.4(1)                        |
| Li1-N3 | 2.180(2)          | 2.197(3)                        | N1-Li1-<br>N4 | 115.1(1)          | 114.9(1)                        |
| Li1-N4 | 2.194(3)          | 2.178(3)                        | N2-Li1-<br>N3 | 84.6(1)           | 84.9(1)                         |
| N1-C1  | 1.332(2)          | 1.336(2)                        | N2-Li1-<br>N4 | 116.7(1)          | 117.8(1)                        |
| C1-C2  | 1.379(2)          | 1.378(2)                        | N3-Li1-<br>N4 | 85.2(1)           | 85.0(1)                         |
| C2-C3  | 1.421(2)          | 1.424(2)                        |               |                   |                                 |
| C3-C4  | 1.345(2)          | 1.341(2)                        |               |                   |                                 |
| C4-C5  | 1.516(2)          | 1.510(2)                        |               |                   |                                 |
| C5-N1  | 1.483(2)          | 1.479(2)                        |               |                   |                                 |

Comparison of the pertinent bond parameters presented in table 1 confirms that the bonding between the polydentate donor and lithium-dihydropyridyl moiety is very similar in each case and that as with Me<sub>6</sub>TREN, the three N donor atoms of PMDETA are sufficient for stabilization of the reactive monomer. In particular, the conjugated double bond system is evident by the alternating short and long bonds in the C1-C2-C3-C4-C5 unit [1.378(2)/1.424(2)/1.341(2)/1.510(2) Å] while C5 is again clearly sp<sup>3</sup> hybridized with a distorted tetrahedral coordination sphere, lying 0.387(1) Å outside of the mean plane of the C1=C2-C3=C4 unit.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1t**·PMDETA in C<sub>6</sub>D<sub>12</sub> solution closely resemble those of **1t**·Me<sub>6</sub>TREN with all corresponding resonances appearing within 0.1 ppm (<sup>1</sup>H) or 1 ppm (<sup>13</sup>C, table 2), which may be expected given the close

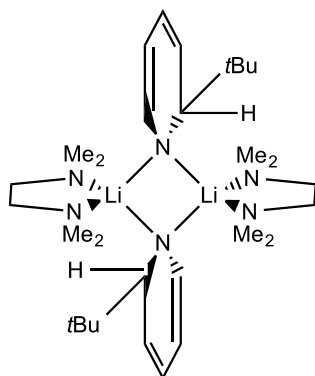
similarities between their molecular structures. The  $^7\text{Li}$  resonances and their half height line widths are virtually identical at 0.81 (5.94 Hz) and 0.82 (6.09 Hz) ppm. On moving to **1t**·Me<sub>4</sub>AEE, there is a more pronounced shielding of the H<sub>2</sub>/C<sub>2</sub> resonances (3.46/66.9 ppm; *cf* 3.54/69.5 and 3.62/69.0 ppm for PMDETA and Me<sub>6</sub>TREN solvates respectively) and also a deshielding of the H<sub>3</sub>/C<sub>3</sub> (4.18/97.2, *cf* 3.95/95.2; 4.03/95.7) and H<sub>5</sub>/C<sub>5</sub> resonances (4.36/91.6, *cf* 4.07/87.4; 4.09/88.2) with respect to the N x 3 donor solvated derivatives, most likely as a consequence of changing one of the Lewis donating atoms to more electronegative oxygen which will in turn subtly alter the electronics of the dihydropyridyl ring. Likewise, the  $^7\text{Li}$  resonance is noticeably shifted to 0.34 ppm (*cf* **1t**·Me<sub>6</sub>TREN, 0.81 ppm).

**Table 2** Comparison of  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^7\text{Li}$  NMR spectroscopic data for solvated complexes of **1t** in  $\text{C}_6\text{D}_{12}$  solution, of unsolvated complexes **1t** and **1s** in  $\text{C}_6\text{D}_{12}$  solution, and of complexes **1n** and **1i** in  $d_8$ -THF solution.

|  | <b>1t</b> ·Me <sub>6</sub> TREN <sup>21</sup> | <b>1t</b> ·PMDETA | <b>1t</b> ·Me <sub>4</sub> AEE | <b>1t</b> ·TMEDA | <b>1t</b> <sup>21</sup> | <b>1s</b>  | <b>1n</b> <sup>21</sup> | <b>1i</b>  |
|---|---|-------------------|--------------------------------|------------------|-------------------------|------------|-------------------------|------------|
| H2/C2   | 3.62/69.0                                     | 3.54/69.5         | 3.46/66.9                      | 3.30/66.2        | 3.12/66.1               | 3.10/60.6  | 3.54/57.6               | 3.63/53.3  |
| H3/C3   | 4.03/95.7                                     | 3.95/95.2         | 4.18/97.2                      | 4.07/94.4        | 4.37/95.1               | 4.40/95.1  | 4.08/96.7               | 3.97/95.1  |
| H4/C4   | 5.88/128.7                                    | 5.85/128.8        | 5.92/128.2                     | 6.04/127.0       | 6.12/127.9              | 6.04/125.7 | 5.72/126.4              | 5.71/126.5 |
| H5/C5   | 4.09/88.2                                     | 4.07/87.4         | 4.36/91.6                      | 4.58/93.8        | 4.92/95.1               | 5.08/96.6  | 4.29/90.0               | 4.25/89.2  |
| H6/C6   | 6.53/151.1                                    | 6.56/150.8        | 6.62/151.0                     | 6.71/151.3       | 6.85/150.0              | 6.73/147.7 | 6.55/150.0              | 6.54/150.0 |
| Quaternary C  | 42.1  | 41.1              | 40.9                           | 41.6             | 39.3                    | -          | -                       | -          |
| <i>t</i> Bu (H/C)   | 0.86/25.4                                     | 0.87/25.7         | 0.84/25.7                      | 0.82/26.0        | 0.83/25.6               | -          | -                       | -          |
| Li  | 0.81  | 0.82              | 0.34                           | -1.67            | -1.79                   | -1.97      | 2.17                    | 0.29       |



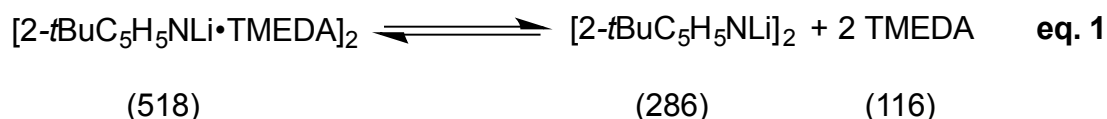
Next we turned to the common and inexpensive bifunctional donor *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 11p/mL),<sup>25</sup> which when added to **1t** in hexane and cooled, afforded a non X-ray quality crystalline product [*2-t*BuC<sub>5</sub>H<sub>5</sub>NLi·TMEDA]<sub>2</sub>.



**Figure 4** Proposed molecular structure of complex [*2-t*BuC<sub>5</sub>H<sub>5</sub>NLi·TMEDA]<sub>2</sub>, **1t**·TMEDA.

<sup>1</sup>H and <sup>13</sup>C NMR analysis of **1t**·TMEDA in C<sub>6</sub>D<sub>12</sub> solution unequivocally confirmed the regioselective 1,2-alkyllithium addition to pyridine and that the resulting dihydropyridyl:TMEDA ratio was 1:1. The <sup>1</sup>H NMR spectroscopic resonances of the ring hydrogen atoms appeared at values intermediate between those of monomeric, N-solvated complexes **1t**·Me<sub>6</sub>TREN and **1t**·PMDETA and of unsolvated trimeric complex **1t** (for example H5 resonates at 4.58 ppm in **1t**·TMEDA, *cf* 4.07 in **1t**·PMDETA and 4.92 in **1t**; see table 2 for full details), perhaps suggesting an intermediate aggregation scenario (that is, dimeric as postulated in figure 4: a common bonding scenario seen previously in TMEDA solvated lithium amides,<sup>26</sup> including those formed through the alpha metalation of functionalized pyridines<sup>27</sup>) although this could also be due to the fewer number of Lewis basic nitrogen atoms solvating the lithium atom. Cooling of a *d*<sub>14</sub>-hexane solution of **1t**·TMEDA to -70°C resulted in a broadening of the TMEDA resonances but no splitting of them, meaning we were unable to infer whether the dimer adopts a *cisoid* or *transoid* conformation with respect to the two *t*Bu groups (that is C<sub>2v</sub> or C<sub>2h</sub> symmetry) in the manner described previously by Harder.<sup>28</sup>

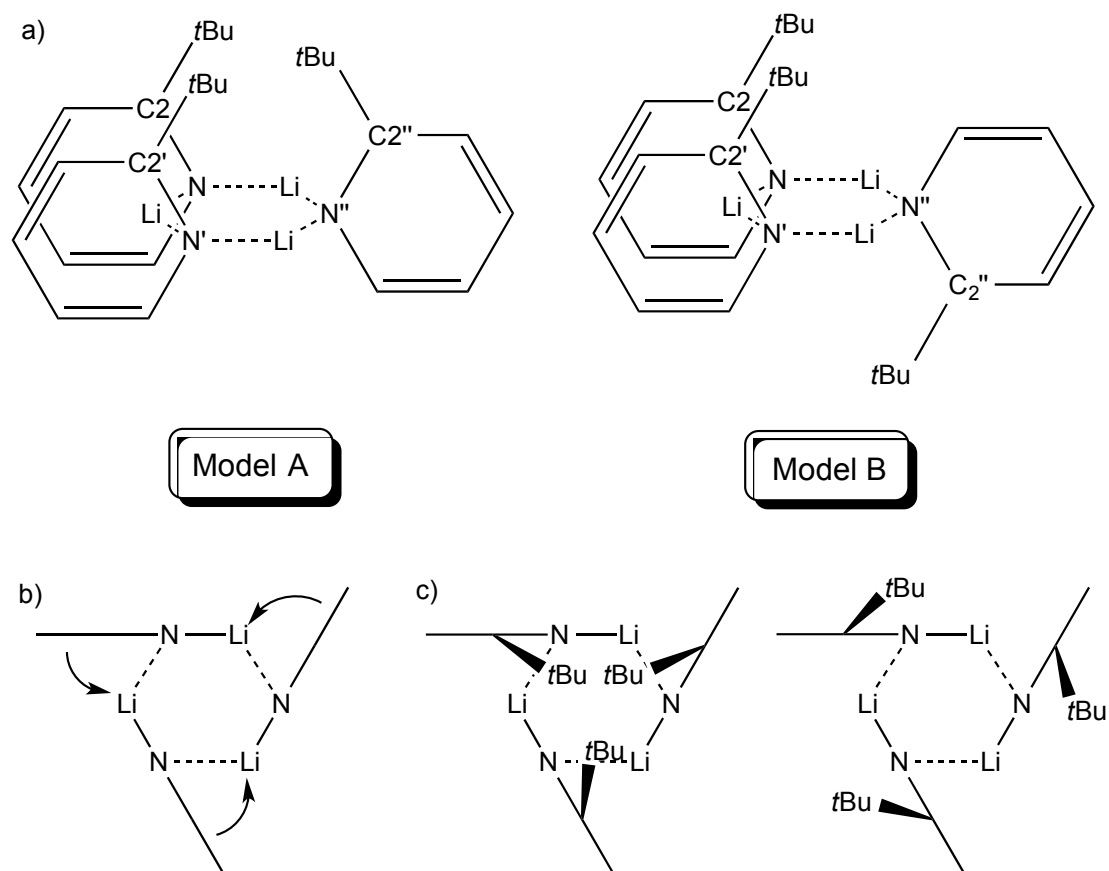
In the absence of a solid state structure for **1t**·TMEDA, we turned to a <sup>1</sup>H DOSY NMR spectroscopy study,<sup>29</sup> (which has been used effectively in organometallic chemistry for solution state molecular weight determination<sup>30</sup>), again in C<sub>6</sub>D<sub>12</sub>, to estimate its aggregation state (n) in solution of [2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi·TMEDA]<sub>n</sub>, the results of which suggested an estimated molecular weight of 420 at 0.2 mol L<sup>-1</sup> (refer to SI for details). This value lies intermediate between the calculated molecular weights of a monomer (n = 1; 259) and dimer (n = 2; 518). While considerably removed from either value, this result is possibly indicative of a dimer in solution as it has previously been noted<sup>31</sup> that coordinated Lewis donors can undergo a rapid coordination/decoordination event (equation 1) which can be seen on the DOSY NMR timescale, resulting in an estimated molecular weight value intermediate between the solvated (518) and unsolvated (286) aggregate. Typically, further evidence for this is an estimated molecular weight for the coordinating Lewis donor lower than that of the complex but higher than that of the free Lewis donor itself. In this example we note the estimated molecular weight for TMEDA as calculated using the resonances at 2.25 and 2.34 ppm is 169 (TMEDA itself has a significantly lower molecular weight of 116).



We considered a second hypothesis for this DOSY result, namely that a complex of formula [2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi]<sub>2</sub>·TMEDA is present in solution, that is an asymmetric structure in which only one of the lithium cations is solvated by TMEDA (such a complex would have a molecular weight of 402, much closer to the experimentally determined MW<sub>DOSY</sub>, < 5% error). Asymmetrically mono-solvated dinuclear alkali-metal amides have been crystallographically characterized previously, for example the THF-solvated sodium 1,1,1,3,3,3-hexamethyldisilazide<sup>32</sup> or the TMEDA-solvated heterometallic lithium/sodium 2,2,6,6-tetramethylpiperidide.<sup>33</sup> However, we consider this reduced solvation to be unlikely in this instance since the *t*BuC<sub>5</sub>H<sub>5</sub>N:TMEDA ratio is unity as determined by integration of the <sup>1</sup>H NMR spectrum.

### Theoretical calculations on oligomeric 2-*t*BuC<sub>5</sub>H<sub>5</sub>NLi

Having postulated that unsolvated complex **1t** is a cyclotrimer, we turned to DFT calculations using the B3LYP density functional and 6-311(d, p) basis set, to probe if such oligomerization is reasonable. Such a motif is well-documented in structural lithium amide chemistry,<sup>34</sup> including the synthetically important utility amides<sup>35</sup> LiHMDS<sup>36</sup> and LiTMP.<sup>37</sup> Because of the tetrahedral nature of the nitrogen atoms we modeled two distinct ring types, namely those with the *t*Bu groups on the same side of the ring (type A, figure 5a) or those with two on one side and one on the other (type B, figure 5a). The calculations revealed that the dihydropyridyl rings did not lie perfectly perpendicular to the Li<sub>3</sub>N<sub>3</sub> plane but rather tilted towards one of the neighboring lithium atoms due to a slight interaction of the  $\pi$  electron density with the Lewis acidic lithium neighbor. This resulted in a shorter ( $\sigma$ -bonded) neighbor and a longer ( $\pi$ -bonded) neighbor (illustrated through single and dashed lines respectively in figure 5b) giving axial chirality and meaning that the *S,S,S* system (entry 1) is not the same as the *R,R,R* system (entry 4) as might have been thought originally. Table 3 summarizes the findings of this study.



**Figure 5** a) Possible variable structural conformations for cyclotrimeric 1-lithio-2-*t*-butyl-1,2-dihydropyridine complexes (C2 atoms also bear a hydrogen atom which has been omitted for clarity); b) tilting movement of the NC<sub>5</sub> dihydropyridyl ring towards one of the adjacent lithium atoms resulting in a stereogenic nitrogen and a shorter ( $\sigma$ ) and longer ( $\pi$ ) Li-dihydropyridyl interaction (*t*Bu groups and H atoms have been omitted for clarity); c) cyclic structure with butyl groups included to emphasise difference between *R,R,R* and *S,S,S* enantiomers due to axial chirality.

**Table 3** Calculated energies of different possible configuration sets of complex **1t**

| Entry | Model | C2 | C2' | C2'' | Absolute energy<br>(kcal mol <sup>-1</sup> ) | Relative energy<br>(kcal mol <sup>-1</sup> ) |
|-------|-------|----|-----|------|--|--|
| 1     | A     | S  | S   | S    | -1240.806479                                 | 0.000  |
| 2     | A     | R  | S   | S    | -1240.804562                                 | +1.203                                       |
| 3     | A     | R  | R   | S    | -1240.801927                                 | +2.856                                       |
| 4     | A     | R  | R   | R    | -1240.798594                                 | +4.948                                       |
| 5     | B     | S  | S   | S    | -1240.804711                                 | +1.109                                       |
| 6     | B     | S  | S   | R    | -1240.806342                                 | +0.086                                       |
| 7     | B     | R  | S   | S    | -1240.801909                                 | +2.868                                       |
| 8     | B     | R  | S   | R    | -1240.804633                                 | +1.158                                       |
| 9     | B     | S  | R   | S    | -1240.802243                                 | +2.658                                       |
| 10    | B     | S  | R   | R    | -1240.804634                                 | +1.158                                       |
| 11    | B     | R  | R   | S    | -1240.798526                                 | +4.991                                       |
| 12    | B     | R  | R   | R    | -1240.802058                                 | +2.774                                       |

The study showed that the approximately C<sub>3</sub> symmetric structure (entry 1 in table 3, for full structural parameters see SI) was the lowest energy conformation. Crucially however, it showed that all twelve modeled structures came within 5 kcal mol<sup>-1</sup> of each other and indeed nine of the remaining eleven were less than 3 kcal mol<sup>-1</sup> higher in energy than the energy minimum, entry 1. This narrow range of energies for the different conformations suggests the possibility that multiple conformations might be

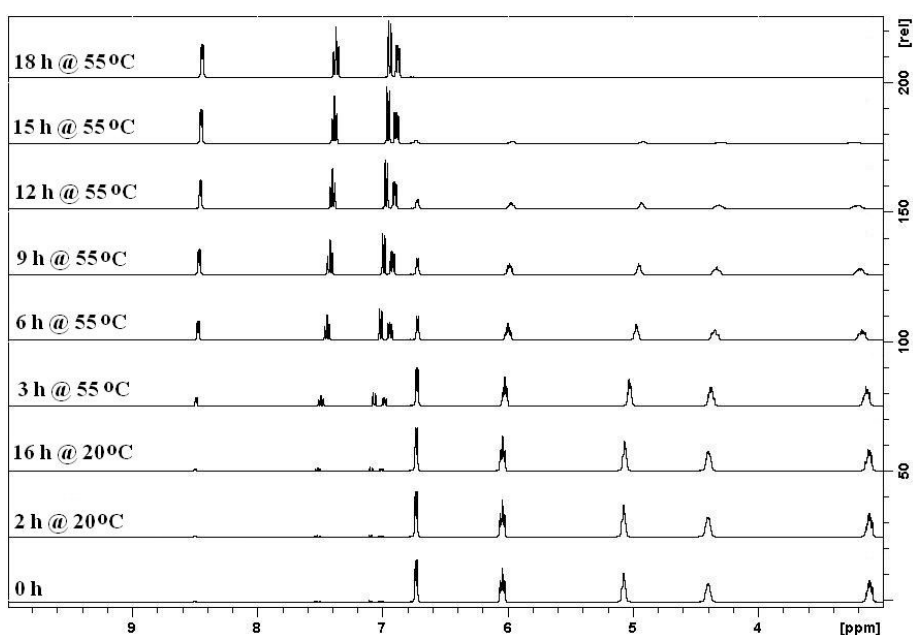
present in a sample and can potentially also explain why single crystals of the trimeric complex **1t** (or indeed 2-*s*BuC<sub>5</sub>H<sub>5</sub>NLi, **1s**, *vide infra*) cannot be obtained.

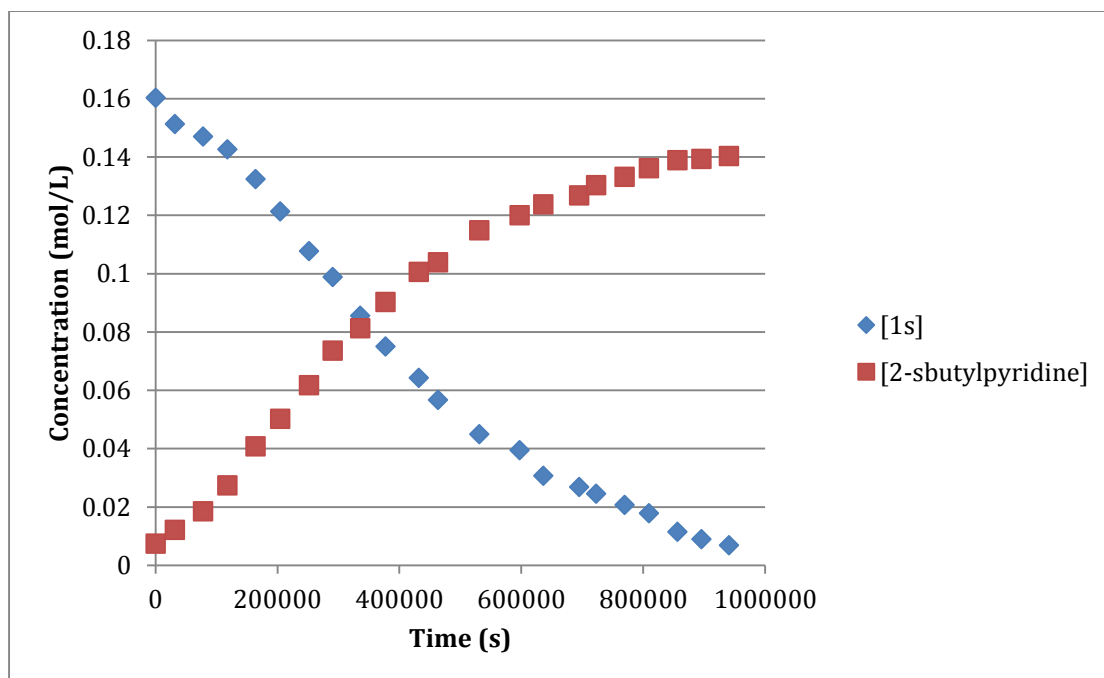
### Searching for an alternative hexane soluble 1-lithio-2-alkyl-1,2-dihydropyridine

In order to minimize the usage of highly pyrophoric *t*-butyllithium in the laboratory, our next aim was to ascertain whether an equally reactive congener of **1t** could be prepared using an alternative but less pyrophoric alkyl lithium reagent.<sup>38</sup> Given that the *n*-butyl adduct **1n** is hexane insoluble (and presumably polymeric) we immediately ruled out other straight chain alkyl groups such as those from commercially available methyl- or ethyllithium. The good solubility of complex **1t** was attributed to the steric effects of the *t*-butyl group inhibiting polymerization and so we logically considered the branched *i*- and *s*-butyl isomers. Like the *n*-butyl derivative, the *i*-butyl complex 2-*i*BuC<sub>5</sub>H<sub>5</sub>NLi **1i** precipitated from solution almost immediately, even under dilute conditions, implying that a polymeric complex akin to **1n** was being produced. <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy in *d*<sub>8</sub>-THF solution confirmed this product to be the desired one, with the chemical shifts indicating loss of aromaticity and the presence of five distinct ring resonances indicating loss of symmetry and thus 1,2 addition of the alkyl lithium reagent. Moving to *s*-butyllithium, the resulting yellow product **1s** remained in solution for a prolonged period of time, with a yellow microcrystalline product precipitating upon cooling to -30°C. Although the recrystallized material represented a fairly moderate yield of 44%, <sup>1</sup>H NMR interrogation of the filtrate suggested the reaction was virtually quantitative and that therefore any pre-prepared solutions could be used *in situ* with confidence in their molarity for subsequent stoichiometric reactions. The filtered product appeared to start degrading on the filter stick upon prolonged application of dynamic vacuum, although if collected in an inert atmosphere after only a short period of vacuum application then the product appeared to have a longer lifespan. Soluble in C<sub>6</sub>D<sub>12</sub> after a few seconds of gentle heating of the mixture, complex **1s** displayed <sup>1</sup>H and <sup>13</sup>C NMR spectra consistent with 1,2 addition of the alkyl lithium to pyridine, specifically via shielding of the five pyridyl resonances consistent with loss of both aromaticity and symmetry (table 2). However, the presence of other small resonances indicated that this was not the only species present in solution, specifically four extra

resonances were evident in the aromatic region of the spectrum indicative of aromaticity and more specifically a 2-substituted pyridine.

The deterioration issue under vacuum coupled with this NMR evidence hinted that LiH was being extruded from complex **1s** under only mild (ambient) conditions and that **1s** is therefore potentially more reactive than its *t*Bu isomer **1t**, which, in contrast, is thermally robust in C<sub>6</sub>D<sub>12</sub> solution. This conversion from the 1,2-dihydropyridyl complex to a substituted pyridine was monitored via <sup>1</sup>H NMR spectroscopy over time (see figure 6a for full details) which confirmed that complex **1s** converts cleanly to 2-*s*-butylpyridine in cyclohexane at 55°C in less than a day.



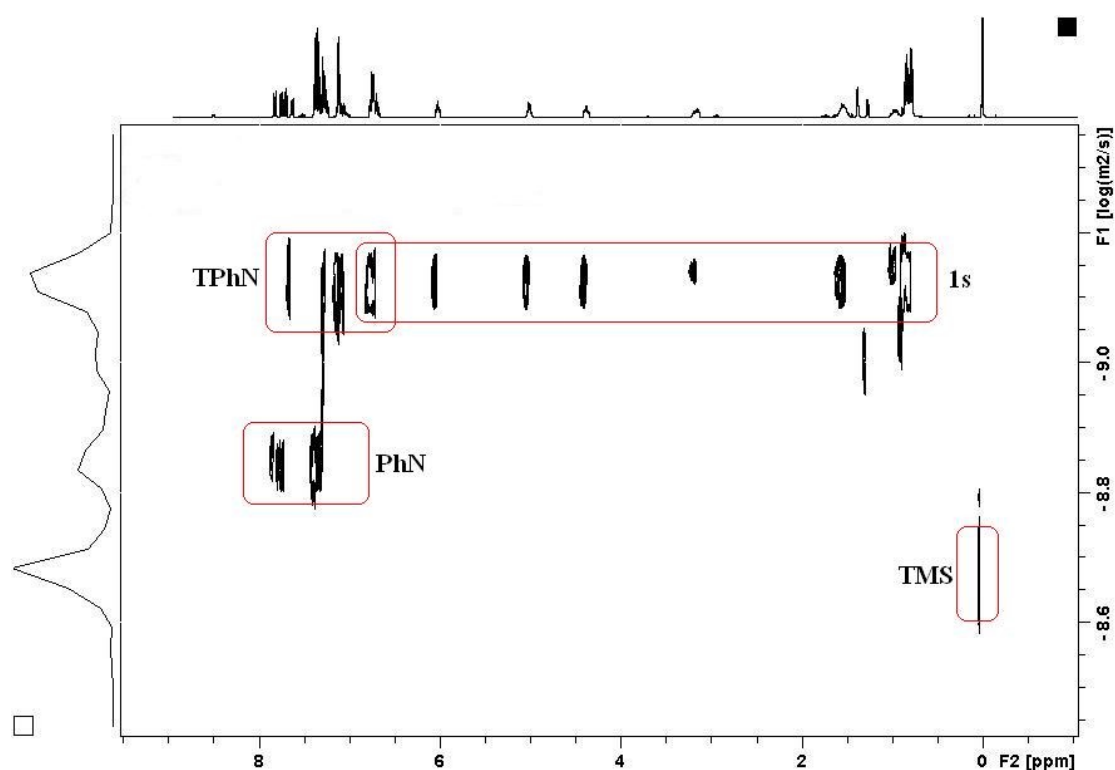


**Figure 6** a (top) Section of  $^1\text{H}$  NMR spectra over time of a **1s** sample in  $\text{C}_6\text{D}_{12}$  solution showing loss of five dihydropyridyl (non-aromatic) resonances and concomitant growth of four 2-substituted pyridyl (aromatic) resonances and b (bottom) Plot of concentration of **1s** (blue) and 2-*s*-butylpyridine (red) as a function of time

To study the conversion of **1s** to LiH and 2-*s*-butylpyridine further we repeated the  $^1\text{H}$  NMR study over time at a constant temperature ( $21^\circ\text{C}$ ) in the presence of the inert standard hexamethylbenzene to allow accurate concentration determination at each interval. After almost two weeks the conversion was virtually complete. A plot of **1s** and 2-*s*-butylpyridine concentration versus time showed that the conversion appears to follow two distinct phases. The first, which occurs over a time period of approximately two days, behaves according to zero order kinetics. The data following this are then consistent with a first order process. This can perhaps be attributed to the preparation of Lewis donor *s*-butylpyridine as part of the conversion process which will be available to solvate the lithium centre of **1s**, reducing its oligomerization to first dimeric (similar to complex **1t**·TMEDA) and then to monomeric (similar to complex **1t**·PMDETA) as its relative concentration increases.

To ascertain the aggregation state of **1s** in solution, we again turned to  $^1\text{H}$  DOSY NMR spectroscopy. Unfortunately, due to the conversion of **1s** to 2-*s*-butylpyridine it

was impossible to quantify the estimated molecular weight since the resonances of the developing aromatic species coincided with those of the aromatic standards 1-phenylnaphthalene (PhN) and 1,2,3,4-tetraphenylnaphthalene (TPhN) and thus interfered with their integration, which is necessary for the calculation of diffusion coefficients. However, qualitative perusal of the resulting spectrum (figure 7) certainly supports the suggestion that **1s** is trimeric in solution since its resonances appear in line with those of TPhN which has a molecular weight of 432.55 (the molecular weight of a trimer would be 429.47).

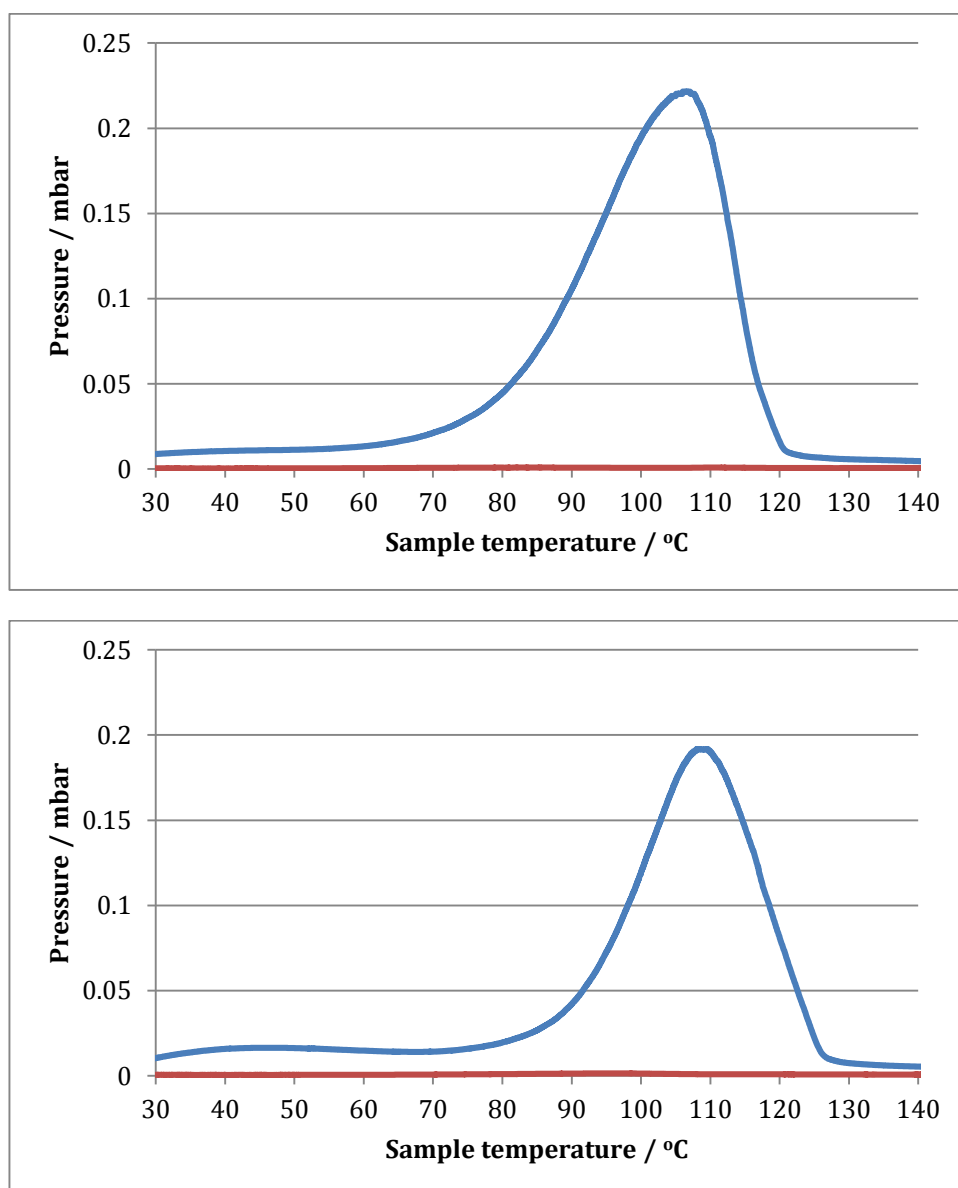


**Figure 7**  $^1\text{H}$  DOSY NMR spectrum of **1s** in  $\text{C}_6\text{D}_{12}$  solution at 300K containing the inert standards 1,2,3,4-tetraphenylnaphthalene (TPhN), 1-phenylnaphthalene (PhN) and tetramethylsilane (TMS).

To further study the ease with which LiH is liberated from a solid sample of **1s** (and **1i** for comparison) we turned to thermal volatility analysis (TVA).<sup>39</sup> This showed (figure 8) that evolution of a volatile material from **1s** commences close to 60°C and occurs over a narrower temperature range (approx. 60°C) than for **1n** or **1t** (both approximately 100°C) with a maximum pressure seen just below 110°C. In



comparison, **1i** did not start to liberate volatiles until 70°C and this liberation was not complete until almost 130°C. In each case there was no sign of non-condensable volatile products. The condensable products were identified as the appropriate 2-butylpyridine by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and their IR spectra were obtained (see SI).

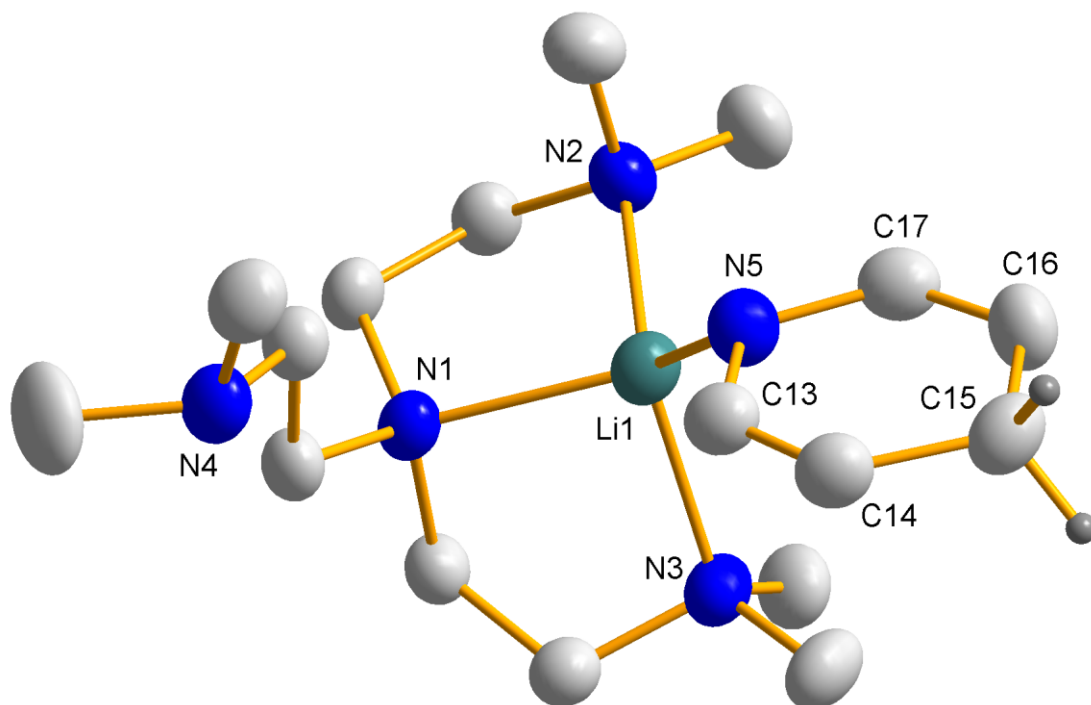


**Figure 8** Thermal Volatility Analysis thermograms for **1s** (top) and **1i** (bottom). The blue line represents total volatile products, and the red line non-condensable volatile products.

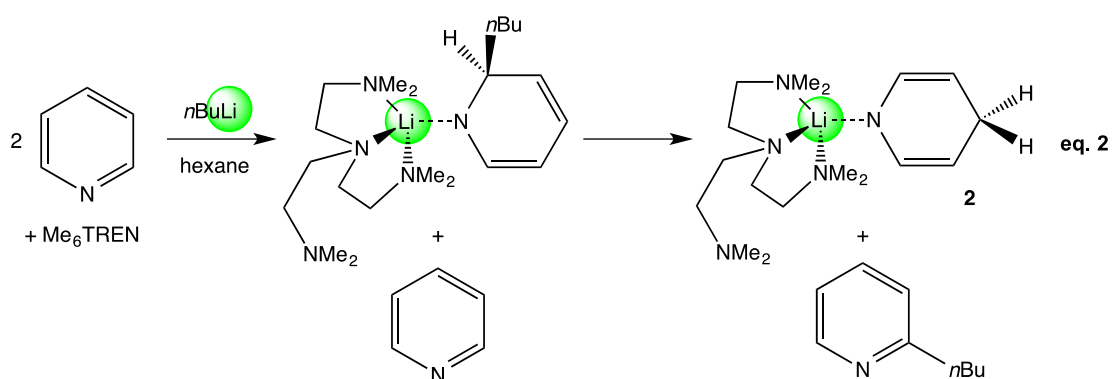
With a hexane soluble complex in hand, we next studied its ability to operate as a lithium hydride transfer reagent. Mirroring our recent studies of 1-lithio-2-*t*-butyl-1,2-dihydropyridine **1t** for consistency and comparison, we prepared a sample of **1s** in hexane and introduced benzophenone. After approximately 10 minutes, a white precipitate formed which was isolated and confirmed by <sup>1</sup>H NMR spectroscopy as the anticipated lithium alkoxide LiOCH(Ph)<sub>2</sub>. A total isolated yield of 71% was comparable with that obtained using **1t** (83%), suggesting that this synthetically safer *s*Bu isomer is essentially as efficient a hydrolithiation agent as its *t*Bu isomer. The marginally lower yield might be due to **1s** starting to degrade partially to *s*-butylpyridine prior to the addition of benzophenone.

### **Assessing the importance of pyridine stoichiometry**

Finally, we carried out the reaction of pyridine with *n*BuLi in the presence of Me<sub>6</sub>TREN in hexane solution but this time increasing the number of pyridine equivalents from one to two in order to judge the importance of keeping the ratio at unity for the synthesis of a 1,2-dihydropyridyl complex capable of acting as a LiH transfer reagent. This mixture was heated for 1 hour at 50°C then allowed to cool slowly, resulting in a red oily product from which a small crop of crystals developed. These crystals were identified via X-ray crystallography to be the non-alkylated 1-lithio-1,4-dihydropyridine complex H<sub>6</sub>C<sub>5</sub>NLi·Me<sub>6</sub>TREN, **2** (figure 9), that is the expected “added” *n*-butyl ligand has been replaced by a hydride anion.

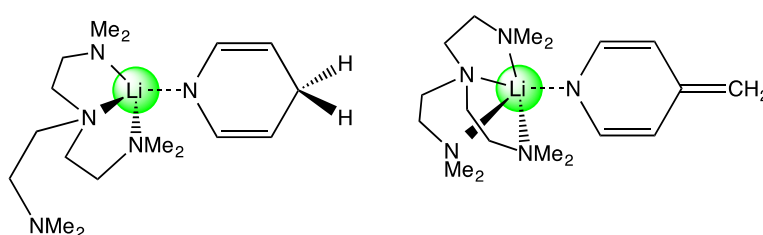


**Figure 9** Molecular structure of monomeric 1,4-dihydropyridylLi·Me<sub>6</sub>TREN (**2**). Ellipsoids are displayed at 50% probability and all hydrogen atoms except those on C15 are omitted for clarity. Selected bond lengths (Å) and angles (°): Li1-N1 2.139(5); Li1-N2 2.108(4); Li1-N3 2.105(5); Li1-N4 4.604(5); Li1-N5 1.969(5); N5-C13 1.385(3); C13-C14 1.340(4); C14-C15 1.503(4); C15-C16 1.501(4); C16-C17 1.343(4); C17-N5 1.375(3); N1-Li1-N2, 85.2(2); N1-Li1-N3, 88.7(2); N1-Li1-N5, 132.1(2); N2-Li1-N3, 119.2(2); N2-Li1-N5, 118.2(2); N3-Li1-N5, 110.1(2).



Presumably, **1n**·Me<sub>6</sub>TREN is formed first *in situ* and then an intermolecular 1,4-addition of LiH to the extra pyridine molecule occurs to give **2** with 2-*n*-butylpyridine being the other product (equation 2). Complex **2** can be considered a monomeric

variant of the previously reported pyridine solvate of 1-lithio-1,4-dihydropyridine which is dimeric in the solid state and is made in a similar fashion.<sup>8c</sup> As in **1t**·Me<sub>6</sub>TREN, the donor binds to lithium in a hypodentate  $\eta^3$  fashion with one arm free, giving lithium an overall coordination number of 4 within a distorted tetrahedral geometry. This hypodentate binding mode is unlikely to be purely steric in origin since Me<sub>6</sub>TREN has previously been shown to bind in a  $\eta^4$  fashion in the related complex 4-picolylithium which has a virtually identical local environment around the anionic nitrogen atom (figure 10).<sup>19</sup> The six membered dihydropyridyl ring of **2** is clearly planar [C4 lies only 0.055(3) Å outside the plane of the remaining C<sub>4</sub>N unit] with the shorter C $\alpha$ -C $\beta$  bonds [1.340(4)/1.343(4) Å] and longer C $\beta$ -C $\gamma$  bonds [1.503(4)/1.501(4) Å] indicative of double and single bonds respectively. The hydrogen atoms at the 4-position were located and refined, confirming this carbon is sp<sup>3</sup> hybridised and that the ligand is a dihydropyridyl anion. The Li-N5(pyr) distance [1.969(5) Å] is consistent with other crystallographically characterized monomeric, four-coordinate lithium secondary amides such as PMDETA-solvated lithium  $\alpha$ -(methylbenzyl)benzylamide [1.959(7) Å],<sup>40</sup> lithium bis( $\alpha$ -methylbenzyl)amide [1.949(6) Å]<sup>41</sup> and lithium 3,6-diethoxy-2,5-dihydro-2-isopropylpyrazide [1.965(3) Å]<sup>42</sup> reported by Andrews *et al.*, while the Li-N(Me<sub>6</sub>TREN) distances [2.105(5)-2.139(5) Å] are longer reflecting the weaker donor acceptor nature of these interactions.



**Figure 10** molecular structures of **2** (left) and 4-picolylithium·Me<sub>6</sub>TREN

Unlike the 2-alkyl-1,2-dihydropyridyl complexes mentioned thus far (**1t**-donor), **2** is insoluble in aliphatic cyclohexane and thus its NMR spectra were collected in C<sub>6</sub>D<sub>6</sub> solution. These spectra confirm that mirroring the molecular structure, the dihydropyridyl anion is in its 1,4 isomeric form and not the 1,2. Specifically, there

are only three dihydropyridyl resonances of equal intensity (located at 6.50, 4.58 and 4.36 ppm), consistent with a symmetric, non-aromatic 1,4 isomer.  $^{13}\text{C}$  and  $^7\text{Li}$  NMR spectra corroborated this regiochemistry. Although the isolated yield of **2** was low, a  $^1\text{H}$  NMR spectrum of the filtrate confirmed that this was the exclusive lithium-containing product, with no evidence of a 1,2 isomer. The by-product, 2-*n*-butylpyridine was also clearly present along with some free uncoordinated  $\text{Me}_6\text{TREN}$ .

## Conclusions

This study has advanced the chemistry of 1-lithio-2-alkyl-1,2-dihydropyridines. The key to this progress has been to use stoichiometric amounts of pyridine in reactions with alkyllithium compounds as opposed to the more common usage of excess pyridine. Three new crystalline complexes have emerged from this study in the 1,2-alkyl complexes 2-*t*-BuC<sub>5</sub>H<sub>5</sub>NLi·PMDETA (**1t**·PMDETA) and 2-*t*-BuC<sub>5</sub>H<sub>5</sub>NLi·Me<sub>4</sub>AEE (**1t**·Me<sub>4</sub>AEE) both of which show these kinetic intermediates can be stabilized in monomeric form using polydentate donor supports, as well as the non-alkyl complex 1,4-H<sub>6</sub>C<sub>5</sub>NLi·Me<sub>6</sub>TREN, **2**, which demonstrate that 1,2-alkyl isomers can react with any available excess pyridine to generate thermodynamic lithio 1,4-dihydropyridines and 2-alkylpyridine byproducts. The study also brings to the fore the subtle effect the alkyl substituent can have on the solubility of the complex, with the *t*-butyl and *s*-butyl isomers showing excellent solubility in aliphatic hydrocarbon solvents; whereas the *n*-butyl and *i*-butyl isomers are essentially insoluble. These differences appear to reflect the different aggregation states involved with the former pair molecular and the latter pair probably polymeric. Though the hydrolithiation properties of these new isolated lithio dihydropyridines have been touched upon here, the fact that these complexes are easily synthesized and (some) exhibit excellent solubility, suggest their application as transporters of molecular LiH will increase in the future.

## Experimental

### General experimental

All reactions and manipulations were carried out under a protective dry argon atmosphere using standard Schlenk techniques. Products were isolated and NMR

samples pre-prepared in an argon-filled glove box. Hexane and THF were dried by heating to reflux over sodium-benzophenone and distilled under nitrogen prior to use. Me<sub>6</sub>TREN was prepared according to a literature method.<sup>43</sup> TMEDA, Me<sub>4</sub>AEE and PMDETA were distilled over CaH<sub>2</sub> and stored over 4 Å molecular sieves prior to use. Pyridine (anhydrous, 99.8%), benzophenone, *n*BuLi (1.6 M in hexanes), *i*BuLi (1.7 M in heptane), *s*BuLi (1.4 M in cyclohexane), and *t*BuLi (1.7 M in pentane) were purchased from Aldrich and used as received. NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer, operating at 400.13 MHz for <sup>1</sup>H, 155.50 MHz for <sup>7</sup>Li and 100.62 MHz for <sup>13</sup>C. All <sup>13</sup>C spectra were proton decoupled. <sup>1</sup>H and <sup>13</sup>C spectra were referenced to the appropriate solvent signal and <sup>7</sup>Li spectra were referenced against LiCl in D<sub>2</sub>O at 0.00 ppm. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. Satisfactory elemental analyses could not be obtained for **1s** (due to its high reactivity and conversion into *s*-butylpyridine and LiH, *vide supra*), **1i** (presumably as a result of its sensitive nature) and **2** (which is predominantly an oil). <sup>1</sup>H NMR spectra of all new complexes are therefore provided in the SI as an alternative proof of purity.

### **DOSY NMR Spectroscopy**

Diffusion-Ordered Spectroscopy (DOSY) NMR experiments were performed on a Bruker AVANCE 400 NMR spectrometer operating at 400.13 MHz for proton resonance under TopSpin (version 2.0, Bruker Biospin, Karlsruhe) and equipped with a BBFO-z-atm probe with actively shielded z-gradient coil capable of delivering a maximum gradient strength of 54 Gcm<sup>-1</sup>. Diffusion-ordered NMR data were acquired using the Bruker pulse program dstegp3s employing a double stimulated echo with three spoiling gradients. Sine-shaped gradient pulses were used with a duration of 4 ms together with a diffusion period of 100 ms. Gradient recovery delays of 200 μs followed the application of each gradient pulse. Data were systematically accumulated by linearly varying the diffusion encoding gradients over a range of 2% to 95% of maximum for 64 gradient increment values. The signal decay dimension on the pseudo-2D data was generated by Fourier transformation of the time-domain data. DOSY plots were generated by use of the DOSY processing module of TopSpin. Parameters were optimized empirically to find the best quality of data for presentation

purposes. Diffusion coefficients were calculated by fitting intensity data to the Stejskal-Tanner expression.

Samples were prepared by introducing the desired complex (0.1 mmol) to a NMR tube containing 1,2,3,4-tetraphenylnaphthalene (TPhN, 15 mg), 1-phenylnaphthalene (PhN, 13.2  $\mu$ L) and tetramethylsilane (TMS, 19.1  $\mu$ L) as inert internal reference standards in 0.5 mL of the desired solvent for a concentration of 0.2 mol/l. The  $^1\text{H}$  DOSY NMR data were recorded at 300 K. From the diffusion coefficients of the internal standards, linear calibration graphs were obtained by plotting  $\log D$  versus  $\log FW$ . Using the diffusion coefficients for the signals corresponding to the species under study an estimate of FW in solution was obtained.

### X-ray crystallography

Crystallographic data were collected on Oxford Diffraction instruments with Mo or Cu  $K\alpha$  radiation. Structures were solved using *SHELXS-97*,<sup>44</sup> while refinement was carried out on  $F^2$  against all independent reflections by the full-matrix least-squares method using the *SHELXL-97* program.<sup>44</sup> All non-hydrogen atoms were refined using anisotropic thermal parameters. Selected crystallographic details and refinement details are provided in table 4. **1t**·Me<sub>4</sub>AEE was treated as a twin. A hklf 5 formatted reflection file was created with the two twin components related by matrix -1 0 -0.03 0 -1 0 0 0 1. The twin ratio refined to 0.618(4):0.382(4). CCDC-1061251 – CCDC-1061253 contain the supplementary crystallographic data for this structure. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

**Table 4** Crystallographic data and refinement details for complexes **1t**·PMDETA, **1t**·Me<sub>4</sub>AEE and **2**.

| Compound       | <b>1t</b> ·PMDETA                                 | <b>1t</b> ·Me <sub>4</sub> AEE                     | <b>2</b>  |
|----------------|---|--|---|
| Formula        | C <sub>18</sub> H <sub>37</sub> N <sub>4</sub> Li | C <sub>17</sub> H <sub>34</sub> N <sub>3</sub> LiO | C <sub>17</sub> H <sub>36</sub> N <sub>5</sub> Li |
| Formula weight | 316.46  | 303.41   | 314.45  |
| Crystal system | monoclinic  | monoclinic   | orthorhombic                                      |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Space group   | P 2 <sub>1</sub> /c | P 2 <sub>1</sub> /c | P c a 2 <sub>1</sub> |
| Wavelength/Å  | 0.71073             | 0.71073             | 1.54180              |
| <i>a</i> /Å   | 9.1578(2)           | 12.6639(19)         | 13.4284(4)           |
| <i>b</i> /Å   | 13.9331(3)          | 9.5511(16)          | 10.5694(3)           |
| <i>c</i> /Å   | 16.2095(4)          | 16.073(3)           | 14.1379(4)           |
| $\beta$ /°  | 105.925(2)          | 90.848(15)          | 90                   |
| Volume/Å <sup>3</sup>                                   | 1988.90(8)          | 1943.8(6)           | 2006.6(1)            |
| <i>Z</i>  | 4                   | 4                   | 4                    |
| Reflns. collected                                       | 39810               | 4860 <sup>a</sup>   | 7712                 |
| Unique reflns.  | 4732                | 4860 <sup>a</sup>   | 3270                 |
| <i>R</i> <sub>int</sub>                                 | 0.0469              | 0.0573              | 0.0218               |
| Obs. Reflns. [ <i>I</i> > 2σ( <i>I</i> )]               | 3410                | 2278                | 3047                 |
| Goodness of fit   | 1.017               | 1.018               | 1.046                |
| <i>R</i> [ <i>F</i> <sup>2</sup> > 2σ], <i>F</i>        | 0.0492              | 0.0937              | 0.0570               |
| <i>R</i> <sub>w</sub> (all data), <i>F</i> <sup>2</sup> | 0.1152              | 0.2486              | 0.1600               |
| Largest diff. peak/hole e/ Å <sup>-3</sup>              | 0.277/-0.178        | 0.366/-0.92         | 0.371/-0.187         |

<sup>a</sup> Twinned sample refined against a hklf 5 formatted reflection file.

### Theoretical calculations

DFT calculations were performed using the Gaussian<sup>45</sup> 03 package using the B3LYP<sup>46</sup> density functional and the 6-311(d, p)<sup>47</sup> basis set. After each geometry optimization a frequency analysis was performed. The energy values quoted include the zero point energy contribution.

### Synthesis of 2-*t*Bu(C<sub>5</sub>H<sub>5</sub>N)Li·PMDETA (**1t**·PMDETA)

A sample of **1t** (143 mg, 1 mmol) was added to a Schlenk flask and dissolved in hexane (5 mL) by gently warming with a heat gun for a few seconds. PMDETA (0.21 mL, 1 mmol) was added via syringe producing a thick oil. THF was slowly added dropwise with stirring until a homogeneous yellow solution was obtained. Yellow crystals formed after standing the solution at -30°C for one week (yield 0.211 g, 67 %).



$^1\text{H}$  NMR (400.1 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  6.56 (1H, d,  $^3J_{\text{H-H}} = 4.70$  Hz, H6), 5.85 (1H, t,  $^3J_{\text{H-H}} = 5.82$  Hz, H4), 4.07 (1H, t,  $^3J_{\text{H-H}} = 5.29$  Hz, H5), 3.95 (1H, br s, H3), 3.54 (1H, br d,  $^3J_{\text{H-H}} = 4.56$  Hz, H2), 2.46 (4H, br s, 2 x  $\text{CH}_2$  PMDETA), 2.38 (7H, br s,  $\text{CH}_3$  + 2 x  $\text{CH}_2$  PMDETA), 2.32 (12H, s, 4 x Me PMDETA), 0.87 ppm (9H, s,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  150.8 (C6), 128.8 (C4), 95.2 (C3), 87.4 (C5), 69.5 (C2), 58.1 ( $\text{CH}_3$  PMDETA), 55.0 ( $\text{CH}_2$  PMDETA), 46.0 (4 x Me PMDETA), 45.2 ( $\text{CH}_2$  PMDETA), 41.1 ( $\square\square\square\square\square\square\square\square\square\square\square\square$ ), 25.7 ppm ( $\text{CH}_3$ ).

$^7\text{Li}$  NMR (155.5 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  0.82 ppm.

Elemental analysis (%) for  $\text{C}_{18}\text{H}_{37}\text{N}_4\text{Li}$ : calcd: C 68.31, H 11.78, N 17.70; found: C 67.64, H 11.85, N 17.33.

#### Synthesis of 2-*t*Bu( $\text{C}_5\text{H}_5\text{N}$ )Li $\cdot$ Me<sub>4</sub>AEE (**1t** $\cdot$ Me<sub>4</sub>AEE)

A sample of **1t** (143 mg, 1 mmol) was added to a Schlenk flask and dissolved in hexane (5 mL) by gently warming with a heat gun for a few seconds. Me<sub>4</sub>AEE (0.19 mL, 1 mmol) was added via syringe producing a thick oil. THF was slowly added dropwise with stirring until a homogeneous yellow solution was obtained. Yellow crystals formed after standing the solution at  $-30^\circ\text{C}$  for one week (yield 0.097 g, 32 %).

$^1\text{H}$  NMR (400.1 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  6.62 (1H, d,  $^3J_{\text{H-H}} = 5.60$  Hz, H6), 5.92 (1H, dq,  $^3J_{\text{H-H}} = 5.60$ , 1.23 Hz, H4), 4.36 (1H, dt,  $^3J_{\text{H-H}} = 5.60$ , 1.34 Hz, H5), 4.18 (1H, dd,  $^3J_{\text{H-H}} = 4.89$  Hz, H3), 3.55 (4H, t,  $^3J_{\text{H-H}} = 5.52$  Hz, O- $\text{CH}_2$  Me<sub>4</sub>AEE), 3.46 (1H, d,  $^3J_{\text{H-H}} = 5.00$  Hz, H2), 2.50 (4H, t,  $^3J_{\text{H-H}} = 5.55$  Hz,  $\text{CH}_2$ -N Me<sub>4</sub>AEE), 2.24 (s, 12H, N- $\text{CH}_3$  Me<sub>4</sub>AEE), 0.84 ppm (s, 9H,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  151.0 (C6), 128.2 (C4), 97.2 (C3), 91.6 (C5), 69.4 (O- $\text{CH}_2$  Me<sub>4</sub>AEE), 66.9 (C2), 59.4 ( $\text{CH}_2$ -N Me<sub>4</sub>AEE), 45.8 (N- $\text{CH}_3$  Me<sub>4</sub>AEE), 40.9 ( $\square\square\square\square\square\square\square\square\square\square\square\square$ ), 25.7 ppm ( $\text{CH}_3$ ).

$^7\text{Li}$  NMR (155.5 MHz,  $\text{C}_6\text{D}_{12}$ , 300 K):  $\delta$  0.34 ppm.

Elemental analysis (%) for C<sub>17</sub>H<sub>34</sub>N<sub>3</sub>LiO: calcd: C 67.29, H 11.29, N 13.85; found: C 66.67, H 11.22, N 14.10.

#### Synthesis of 2-*t*Bu(C<sub>5</sub>H<sub>5</sub>N)Li·TMEDA (**1t**·TMEDA)

A sample of **1t** (143 mg, 1 mmol) was added to a Schlenk flask and dissolved in hexane (5 mL) by gently warming with a heat gun for a few seconds. TMEDA (0.15 mL, 1 mmol) was added via syringe giving a homogeneous yellow solution. Orange crystals formed after standing the solution at -30°C for one week (yield 0.212 g, 82 %).

<sup>1</sup>H NMR (400.1 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K): δ 6.70 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.19 Hz, H6), 6.04 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.54 Hz, H4), 4.58 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.19 Hz, H5), 4.07 (1H, m, <sup>3</sup>J<sub>H-H</sub> = 5.19 Hz, H3), 3.30 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 4.67 Hz, H2), 2.34 (4H, s, CH<sub>2</sub> TMEDA), 2.26 (12H, s, Me TMEDA), 0.82 ppm (9H, s, CH<sub>3</sub>).

<sup>13</sup>C NMR (100.6 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K): δ 151.3 (C6), 127.0 (C4), 94.4 (C3), 93.8 (C5), 66.2 (C2), 58.9 (CH<sub>2</sub> TMEDA), 46.8 (Me TMEDA), 41.6 (□□□□□□□□□□□□□□□□), 26.0 ppm (CH<sub>3</sub>).

<sup>7</sup>Li NMR (155.5 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K): δ -1.67 ppm.

#### Synthesis of 2-*i*Bu(C<sub>5</sub>H<sub>5</sub>N)Li (**1i**)

Pyridine (0.40 mL, 5 mmol) was added to a Schlenk flask containing hexane (10 mL). *i*BuLi (3.12 mL, 1.6 M in hexane, 5 mmol) was added via syringe, giving a yellow solution. A pale yellow precipitate formed almost immediately after the addition of *i*BuLi which was filtered and collected (yield 0.66 g, 4.62 mmol, 92 %).

<sup>1</sup>H NMR (400.1 MHz, d<sub>8</sub>-THF, 300 K): δ 6.54 (1H, d, <sup>3</sup>J<sub>H-H</sub> = 5.39 Hz, H6), 5.71 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.59 Hz, H4), 4.25 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.49 Hz, H5), 3.97 (1H, t, <sup>3</sup>J<sub>H-H</sub> = 5.59 Hz, H3), 3.63 (1H, quin, <sup>3</sup>J<sub>H-H</sub> = 4.51 Hz, H2), 1.84 (2H, m, <sup>3</sup>J<sub>H-H</sub> = 5.30 Hz, α-CH<sub>2</sub>), 1.29 (1H, br s, CH), 0.83 ppm (6H, d, <sup>3</sup>J<sub>H-H</sub> = 6.57 Hz, CH<sub>3</sub>).

$^{13}\text{C}$  NMR (100.6 MHz,  $d_8$ -THF, 300 K):  $\delta$  150.0 (C6), 126.5 (C4), 95.1 (C3), 89.2 (C5), 53.3 (C2), 43.9 ( $\alpha$ -CH<sub>2</sub>), 23.8 (CH<sub>3</sub>), 22.8 ppm (CH).

$^7\text{Li}$  NMR (155.5 MHz,  $d_8$ -THF, 300 K):  $\delta$  0.29 ppm.

#### Synthesis of 2-*s*Bu(C<sub>5</sub>H<sub>5</sub>N)Li (**1s**)

Pyridine (1.12 mL, 14 mmol) was added to a Schlenk flask containing hexane (10 mL). *s*BuLi (10 mL, 1.4 M in hexane, 14 mmol) was added via syringe, giving a yellow solution. A pale yellow precipitate formed upon cooling the solution to -30°C which was filtered and collected (yield 0.88 g, 6.16 mmol, 44 %).

$^1\text{H}$  NMR (400.1 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K):  $\delta$  6.73 (1H, d,  $^3J_{\text{H-H}} = 5.25$  Hz, H6), 6.04 (1H, m, H4), 5.08 (1H, br t,  $^3J_{\text{H-H}} = 5.25$  Hz, H5), 4.40 (1H, br m, H3), 3.10 (1H, br m, H2), 1.55 (2H, m,  $\alpha$ -CH + 1 from CH<sub>2</sub>), 0.97 (1H, m, 1 from CH<sub>2</sub>), 0.85 (3H, m, CH<sub>3</sub>), 0.77 ppm (3H, m, CH<sub>3</sub>).

$^{13}\text{C}$  NMR (100.6 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K):  $\delta$  147.7 (C6), 125.7 (C4), 96.6 (C5), 95.1 (C3), 60.6 (C2), 37.2 (CH), 24.8 (CH<sub>2</sub>), 15.0 (CH<sub>3</sub>), 11.4 ppm (CH<sub>3</sub>).

$^7\text{Li}$  NMR (155.5 MHz, C<sub>6</sub>D<sub>12</sub>, 300 K):  $\delta$  -1.97 ppm.

#### Synthesis of 1,4-dihydropyridylLi•Me<sub>6</sub>TREN (**2**)

Pyridine (0.32 mL, 4 mmol) and Me<sub>6</sub>TREN (0.52 mL, 2 mmol) were added to a Schlenk flask containing hexane (5mL). *n*BuLi (1.25 mL, 1.6 M in hexane, 2 mmol) was added via syringe, giving an orange solution. This solution was heated at 50°C for one hour then allowed to slowly cool, depositing an orange-red oil which contained a small crop of crystalline material. The oil and solvent mixture was decanted off and the sticky crystals dried and collected (yield 0.121g, 19 %).

$^1\text{H}$  NMR (400.1 MHz, C<sub>6</sub>D<sub>6</sub>, 300 K):  $\delta$  6.50 (2H, d,  $^3J_{\text{H-H}} = 7.27$  Hz, H2), 4.56 (2H, m, H3), 4.38 (2H, br t, H4), 2.01-1.91 ppm (br s with shoulder, 30H, Me<sub>6</sub>TREN).

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{C}_6\text{D}_6$ , 300 K):  $\delta$  143.5 (C2), 89.4 (C3), 57.5 ( $\text{CH}_2$  Me<sub>6</sub>TREN), 51.9 ( $\text{CH}_2$  Me<sub>6</sub>TREN), 45.6 (Me Me<sub>6</sub>TREN), 27.9 ppm (C4).

$^7\text{Li}$  NMR (155.5 MHz,  $\text{C}_6\text{D}_6$ , 300 K):  $\delta$  0.68 ppm.

### 2-*i*-butylpyridine

$^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ , 300 K):  $\delta$  8.53 (1H, br s, H6), 7.59 (1H, t,  $^3J_{\text{H-H}} = 7.64$  Hz, H4), 7.11 (2H, br t, H3 + H5), 2.66 (2H, d,  $^3J_{\text{H-H}} = 7.30$  Hz,  $\alpha$ - $\text{CH}_2$ ), 2.11 (1H, m,  $^3J_{\text{H-H}} = 6.87$  Hz,  $\beta$ -CH), 0.93 ppm (6H, d,  $^3J_{\text{H-H}} = 6.61$  Hz,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR (400.1 MHz,  $\text{CDCl}_3$ , 300 K):  $\delta$  143.5 (C2), 89.4 (C3), 57.5 (C4), 51.9 (C5), 45.6 (CH), 27.9 (CH<sub>3</sub>).

### 2-*s*-butylpyridine

$^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ , 300 K):  $\delta$  8.56 (1H, d,  $^3J_{\text{H-H}} = 5.05$  Hz, H6), 7.65 (1H, t,  $^3J_{\text{H-H}} = 7.46$  Hz, H4), 7.15 (2H, m, H3 + H5), 2.87 (1H, m,  $^3J_{\text{H-H}} = 6.80$  Hz,  $\alpha$ -CH), 1.78 (1H, m,  $^3J_{\text{H-H}} = 7.46$  Hz,  $\text{CH}_2$ ), 1.65 (1H, m,  $^3J_{\text{H-H}} = 7.02$  Hz,  $\text{CH}_2$ ), 1.29 (3H, d,  $^3J_{\text{H-H}} = 7.02$  Hz,  $\text{CH}_3$ ), 0.87 ppm (3H, t,  $^3J_{\text{H-H}} = 7.46$  Hz,  $\text{CH}_2\text{CH}_3$ ).

$^{13}\text{C}$  NMR (400.1 MHz,  $\text{CDCl}_3$ , 300 K):  $\delta$  143.5 (C2), 89.4 (C3), 57.5 (C4), 51.9 (C5), 45.6 (CH), 27.9 (CH<sub>3</sub>), 11.8 (CH<sub>2</sub>CH<sub>3</sub>).

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