Dihydropyridyl Complexes

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 60th birthday

Abstract: Generally considered kinetic intermediates in addition reactions of alkyllithiums to pyridine, 1-lithio-2-alkyl-1,2dihydropyridines 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 *tert*-butyl. Theoretical calculations probing the donor-free parent *tert*-butyl species reveal 12 energetically similar stereoisomers in two distinct cyclotrimeric (LiN)₃ conformations. NMR spectroscopy studies (including DOSY spectra) and thermal volatility analysis compare new *sec*-butyl and *iso*-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/Me₆TREN with two equivalents of pyridine results in non-alkylated 1-lithio-1,4-dihydropyridine·Me₆TREN and 2-*n*-butylpyridine, implying mechanistically the kinetic 1,2-*n*-butyl intermediate hydrolithiates the second pyridine.

Introduction

The dihydropyridyl unit^[1] is prevalent in both biological^[2] and medicinal chemistry^[3] 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



Figure 1. Structures of biochemically relevant dihydropyridyl containing compounds.

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^[4] as well as for pyridine functionalization.^[5]

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,^[6] generated from lithium aluminum hydride LiAlH₄ and excess pyridine and formulated as the pyridine-solvent-separated ion pair $[Li(NC_5H_5)_4]^+[Al(1,4-NC_5H_6)_4]^-$ (Figure 2, top),^[7] which acts as a selective reducing agent for aldehyde or ketone functionalities in the presence of carboxylic acid or ester groups. This 1-aluminato-1,4-dihydropyridyl complex (along with other related metallo-1,4-dihydropyridyl complexes including those of lithium,^[8] magnesium,^[9] zinc^[9a,10] and other aluminum complexes^[11]) is generally accepted as being the thermodynamically controlled isomer with the kinet-

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ic intermediate being a 1,2-dihydropyridyl isomer, leaving only limited synthetic access to the 1,2-isomer.^[12] 1-Metallo-1,2-dihydropyridines have been implicated as the active intermediates in the metal catalyzed 1,2-hydroboration of pyridine,^[13] 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.^[14]



Figure 2. 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, $M = K_r^{(15)} K/Zn_r^{(15)} Ca_r^{(16)} Al^{(17)}$). Steric blocking at the 2 and 6 positions of the pyridine ring for example with imino substituents, does not necessarily promote 1,4 addition.^[18] 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.^[16, 19]

Recently, we revisited the well known 1,2-nucleophilic addition reaction of alkyllithium reagents to pyridine,^[20] albeit by employing a stoichiometric volume of pyridine rather than the typical excess (Figure 2, bottom).^[21] This new approach allowed us to isolate and characterize some pure 1-lithio-2-alkyl-1,2-dihydropyridine (2-*n*BuC₅H₅NLi, 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 tert-butyl example 2-tBuC₅H₅NLi (1t) was hexane soluble. This solubility, which was attributed to the steric effect of the tertbutyl arm alpha to the N-Li bond and its consequent molecular constitution since in contrast the n-butyl isomer 2*n*BuC₅H₅NLi (**1 n**) is a hexane-insoluble polymer, makes it an excellent LiH surrogate complex, as exemplified by its hydrolithiation of benzophenone.^[22] Practical soluble sources of alkali-metal hydrides are coveted with only a select few examples reported.^[23] 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-tBuC₅H₅NLi·Me₆TREN, 1t·Me₆TREN. We have now extended this work here to look at both cheaper, commercially available polydentate donors for similar monomer stabilization and also synthetically safer alkyllithium 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-*tert*-butyl-1,2-dihydropyridine

Noting the incomplete $\eta^{\scriptscriptstyle 3}$ coordination of tetradentate Me₆TREN to lithium in 1t·Me₆TREN, we began by studying more readily available tridentate ligands in its place for oligomer to monomer deaggregation and stabilization. Although Me₆TREN has a proven record for stabilizing sensitive monomers,^[24] it is time-consuming to prepare and expensive to purchase commercially (£111 mL),^[25] 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, 24 pence per mL)^[25] and Me₄AEE (bis-[2-(N,N-dimethylamino)ethyl]ether, 23 pence per mL)^[25] 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 2tBuC₅H₅NLi·PMDETA (1t·PMDETA) and 2-tBuC₅H₅NLi·Me₄AEE (1 t·Me₄AEE), 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 tBu 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 (Figure 3, right-hand side).

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 Me₆TREN, 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 sp³ 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 ¹H and ¹³C NMR spectra of **1t**·PMDETA in C_6D_{12} solution closely resemble those of **1t**·Me₆TREN with all corresponding resonances appearing within 0.1 ppm (¹H) or 1 ppm (¹³C, Table 2), which may be expected given the close similarities between their molecular structures. The ⁷Li resonances and



Figure 3. Molecular structure of 2-*t*BuC₅H₅NLi·PMDETA (**1**t·PMDETA, top) and 2-*t*BuC₅H₅NLi·Me₄AEE (**1**t·Me₄AEE, 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.

their half height line widths are virtually identical at 0.81 (5.94 Hz) and 0.82 ppm (6.09 Hz). On moving to $1 t \cdot Me_4 AEE$, there is a more pronounced shielding of the H2/C2 resonances (3.46/66.9 ppm; c.f. 3.54/69.5 and 3.62/69.0 ppm for PMDETA and Me₆TREN solvates, respectively) and also a deshielding of the H3/C3 (4.18/97.2, c.f. 3.95/95.2; 4.03/95.7) and H5/C5 resonances (4.36/91.6, c.f. 4.07/87.4; 4.09/88.2) with respect to the N×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 ⁷Li resonance is noticeably shifted to 0.34 ppm (c.f. $1 t \cdot Me_6 TREN$, 0.81 ppm).

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Next we turned to the common and inexpensive bifunctional donor N,N,N',N'-tetramethylethylenediamine (TMEDA, 11 pence per mL),^[25] which when added to **1t** in hexane and cooled, afforded a non-X-ray quality crystalline product [2tBuC_sH_sNLi-TMEDA]₂.

¹H and ¹³C NMR analysis of 1 t-TMEDA in C₆D₁₂ solution unequivocally confirmed the regioselective 1,2 alkyllithium addition to pyridine and that the resulting dihydropyridyl/TMEDA ratio was 1:1. The ¹H NMR spectroscopic resonances of the ring hydrogen atoms appeared at values intermediate between those of monomeric, N-solvated complexes 1 t·Me₆TREN and 1 t-PMDETA and of unsolvated trimeric complex 1t (for example H5 resonates at 4.58 ppm in 1t.TMEDA, c.f. 4.07 in 1t.PMDE-TA and 4.92 in 1t; see Table 2 for full details), perhaps suggesting an intermediate aggregation scenario (that is, dimeric postulated in Figure 4: as

a common bonding scenario seen previously in TMEDA solvated lithium amides,^[26] including those formed through the alpha metalation of functionalized pyridines^[27]) although this could also be due to the fewer number of Lewis basic nitrogen atoms solvating the lithium atom. Cooling of a [D₁₄]hexane solution of **1 t**·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 $C_{2\nu}$ or C_{2h} symmetry) in the manner described previously by Harder.^[28]

In the absence of a solid-state structure for **1t**·TMEDA, we turned to a ¹H DOSY NMR spectroscopy study,^[29] which has

Table 1. Selected bond lengths [Å] and angles [°] for complexes 1 t·PMDETA and 1 t·Me ₆ TREN. ^[21]						
	1 t-PMDETA	1 t·Me ₆ TREN		1 t-PMDETA	1 t·Me ₆ TREN	
Li1-N1	1.976(2)	1.971(2)	N1-Li1-N2	122.4(1)	120.6(1)	
Li1–N2	2.153(2)	2.137(2)	N1-Li1-N3	123.4(1)	125.4(1)	
Li1–N3	2.180(2)	2.197(3)	N1-Li1-N4	115.1(1)	114.9(1)	
Li1–N4	2.194(3)	2.178(3)	N2-Li1-N3	84.6(1)	84.9(1)	
N1-C1	1.332(2)	1.336(2)	N2-Li1-N4	116.7(1)	117.8(1)	
C1–C2	1.379(2)	1.378(2)	N3-Li1-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)				



Figure 4. Proposed molecular structure of complex $[2-tBuC_5H_5NLi-TMEDA]_{2\nu}$ 1 t-TMEDA.

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Table 2. Comparison of ¹H, ¹³C and ⁷Li NMR spectroscopic data for solvated complexes of 1t in C_6D_{12} solution, of unsolvated complexes 1t and 1s in C_6D_{12} solution, and of complexes 1n and 1i in $[D_8]$ THF solution.

5 ⁻⁴ ≫3 ∥ 62 ⊖ Bu	1 t·Me ₆ TREN ^[21]	1 t-PMDETA	1 t∙Me₄AEE	1 t-TMEDA	1 t ^[21]	1 s	1 n ^[21]	1i
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	-	-	-
tBu (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

Theoretical calculations on oligomeric 2-tBuC₅H₅NLi

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,^[34] including the synthetically important utility amides^[35] LiHMDS^[36] and

been used effectively in organometallic chemistry for solution state molecular weight determination,^[30] again in C₆D₁₂, to estimate its aggregation state (n) in solution of [2tBuC₅H₅NLi·TMEDA]_n, the results of which suggested an estimated molecular weight of 420 at 0.2 mol L⁻¹ (refer to the Supporting Information 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^[31] that coordinated Lewis donors can undergo a rapid coordination/de-coordination event [Eq. (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):

[2- <i>t</i> BuC ₅ H ₅ NLi•TMEDA] ₂	► [2 <i>-t</i> BuC ₅ H ₅ NLi] ₂	2 + 2 TMEDA
(518)	(286)	(116)

We considered a second hypothesis for this DOSY result, namely that a complex of formula $[2-tBuC_5H_5NLI]_2$ -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 $MW_{DOSV} < 5\%$ error). Asymmetrically monosolvated dinuclear alkali-metal amides have been crystallographically characterized previously, for example the THF-solvated sodium 1,1,1,3,3,3-hexamethyldisilazide^[32] or the TMEDA-solvated heterometallic lithium/sodium 2,2,6,6-tetramethylpiperidide.^[33] However, we consider this reduced solvation to be unlikely in this instance since the $tBuC_5H_5N/TMEDA$ ratio is unity as determined by integration of the ¹H NMR spectrum.

LiTMP.^[37] 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 5 a) or those with two on one side and one on the other (type B, Figure 5 a). The calculations revealed that the dihydropyridyl rings did not lie perfectly perpendicular to the Li₃N₃ plane but rather tilted towards one of the neighboring lithium atoms due to a slight interaction of the π electron density with the Lewis acidic lithium neighbor. This resulted in a shorter (σ bonded) neighbor and a longer (π -bonded) neighbor (illustrated through single and dashed lines, respectively, in Figure 5 b) 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 1lithio-2-*tert*-butyl-1,2-dihydropyridine complexes (C2 atoms also bear a hydrogen atom which has been omitted for clarity); b) tilting movement of the NC₅ dihydropyridyl ring towards one of the adjacent lithium atoms resulting in a stereogenic nitrogen and a shorter (σ) and longer (π) Li-dihydropyridyl interaction (*t*Bu groups and H atoms have been omitted for clarity); c) cyclic structure with butyl groups included to emphasize 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 1 t.							
Entry	Model	C2	C2′	C2″	Absolute energy [kcal mol ⁻¹]	Relative energy [kcal mol ⁻¹]	
1	А	S	S	S	-1240.806479	0.000	
2	А	R	S	S	-1240.804562	+ 1.203	
3	А	R	R	S	-1240.801927	+2.856	
4	А	R	R	R	-1240.798594	+4.948	
5	В	S	S	S	-1240.804711	+ 1.109	
6	В	S	S	R	-1240.806342	+0.086	
7	В	R	S	S	-1240.801909	+2.868	
8	В	R	S	R	-1240.804633	+1.158	
9	В	S	R	S	-1240.802243	+2.658	
10	В	S	R	R	-1240.804634	+1.158	
11	В	R	R	S	-1240.798526	+4.991	
12	В	R	R	R	-1240.802058	+2.774	

The study showed that the approximately C_3 symmetric structure (entry 1 in Table 3, for full structural parameters see the Supporting Information) was the lowest energy conformation. Crucially, however, it showed that all twelve modeled structures came within 5 kcal mol⁻¹ of each other and indeed nine of the remaining eleven were less than 3 kcal mol⁻¹ 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*BuC₅H₅NLi, **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 tert-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 alkyllithium reagent.[38] 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 methylor ethyllithium. The good solubility of complex 1t was attributed to the steric effects of the tert-butyl group inhibiting polymerization and so we logically considered the branched i- and sec-butyl isomers. Like the n-butyl derivative, the iso-butyl complex 2-iBuC₅H₅NLi (1i) precipitated from solution almost immediately, even under dilute conditions, implying that a polymeric complex akin to **1 n** was being produced. ¹H and ¹³C NMR spectroscopy in [D₈]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 alkyllithium reagent. Moving to sec-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%, ¹H 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 C₆D₁₂ after a few seconds of gentle heating of the mixture, complex 1s displayed ¹H and ¹³C NMR spectra consistent with 1,2 addition of the alkyllithium 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_6D_{12} solution. This conversion from the 1,2-dihydropyridyl complex to a substituted pyridine was monitored with ¹H 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.

To study the conversion of 1s to LiH and 2-s-butylpyridine further we repeated the ¹H NMR spectroscopy study over time at a constant temperature (21 °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 (Figure 6b) 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 sec-butylpyridine as part of the conversion process which will be available to solvate the lithium center 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 ¹H 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).

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Figure 6. Top: section of ¹H NMR spectra over time of a **1s** sample in C_6D_{12} solution showing loss of five dihydropyridyl (non-aromatic) resonances and concomitant growth of four 2-substituted pyridyl (aromatic) resonances. Bottom: plot of concentration of **1s** and 2-s-butylpyridine as a function of time, carried out at 21 °C.



Figure 7. ¹H DOSY NMR spectrum of **1 s** in C_6D_{12} solution at 300 K 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).^[39] This showed (Figure 8) that evolution of a volatile material from **1s** commences close to 60° C and occurs over a narrower temperature range (approxi-

mately 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 ¹H and ¹³C NMR spectroscopy and their IR spectra were obtained (see the Supporting Information).

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Figure 8. Thermal volatility analysis thermograms for 1s (top) and 1i (bottom). The solid line represents total volatile products, and the dashed 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-*tert*-butyl-1,2-dihydropyridine **1t** for consistency and comparison, we prepared a sample of **1s** in hexane and introduced benzophenone. After approximately 10 min, a white precipitate formed which was isolated and confirmed by ¹H NMR spectroscopy as the anticipated lithium alkoxide LiOCH(Ph)₂. 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 *sec*-butylpyridine prior to the addition of benzophenone.

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Assessing the importance of pyridine stoichiometry

Finally, we carried out the reaction of pyridine with *n*BuLi in the presence of Me₆TREN 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 by X-ray crystallography to be the non-alkylated 1-lithio-1,4-dihydropyridine complex H₆C₅NLi·Me₆TREN, **2** (Figure 9), that is the expected "added" *n*-butyl ligand has been replaced by a hydride anion.



Presumably, **1** n·Me₆TREN 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 [Eq. (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.^[Bc] As in **1** t·Me₆TREN, the donor binds to lithium in a hypodentate η^3 fashion with one arm free, giving lithium an overall coordination number of four within a distorted tetrahedral geometry. This hypodentate binding



Figure 9. Molecular structure of monomeric 1,4-dihydropyridylLi-Me₆TREN (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).

mode is unlikely to be purely steric in origin since Me6TREN has previously been shown to bind in a η^4 fashion in the related complex 4-picolyllithium which has a virtually identical local environment around the anionic nitrogen atom (Figure 10).^[19] The six membered dihydropyridyl ring of 2 is clearly planar [C4 lies only 0.055(3) Å outside the plane of the remaining C₄N unit] with the shorter C_{\alpha}\!\!-\!\!C_{\beta} bonds [1.340(4)/1.343(4) Å] and longer C_{β} – C_{γ} bonds [1.503(4)/1.501(4) Å] indicative of double and single bonds, respectively. The hydrogen atoms at the 4position were located and refined, confirming this carbon is sp³ hybridized 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 α -(methylbenzyl)benzylamide [1.959(7) Å],^[40] lithium bis(α -methylbenzyl)amide [1.949(6) Å]^[41] and lithium 3,6-diethoxy-2,5-dihydro-2-isopropylpyrazide [1.965(3) Å]^[42] reported by Andrews et al., while the Li-N(Me₆TREN) 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-picolyllithium·Me₆TREN.

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_6D_6 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. ¹³C and ⁷Li NMR spectra corroborated this regiochemistry. Although the isolated yield of **2** was low, a ¹H 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 Me₆TREN.

Conclusion

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 $2-tBuC_5H_5NLiPMDETA$ (1t-PMDETA) and $2-tBuC_5H_5NLiMe_4AEE$ (1t·Me₄AEE) both of which show these kinetic intermediates can be stabilized in monomeric form using polydentate donor supports, as well as

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the non-alkyl complex 1,4-H₆C₅NLi·Me₆TREN (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 tert-butyl and sec-butyl isomers showing excellent solubility in aliphatic hydrocarbon solvents; whereas the *n*-butyl and *iso*-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 Section

General

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 argonfilled glove box. Hexane and THF were dried by heating to reflux over sodium-benzophenone and distilled under nitrogen prior to use. Me₆TREN was prepared according to a literature method.^[43] TMEDA, Me₄AEE and PMDETA were distilled over CaH₂ and stored over 4 Å molecular sieves prior to use. Pyridine (anhydrous, 99.8%), benzophenone, nBuLi (1.6 м in hexanes), iBuLi (1.7 м in heptane), sBuLi (1.4 м in cyclohexane), and tBuLi (1.7 м 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 ¹H, 155.50 MHz for ⁷Li and 100.62 MHz for ¹³C. All ¹³C spectra were proton decoupled. ¹H and ¹³C spectra were referenced to the appropriate solvent signal and ⁷Li spectra were referenced against LiCl in D₂O at 0.00 ppm. Elemental analyses were carried out on a PerkinElmer 2400 elemental analyzer. Satisfactory elemental analyses could not be obtained for 1s (due to its high reactivity and conversion into sec-butylpyridine and LiH, vide supra), 1i (presumably as a result of its sensitive nature) and 2 (which is predominantly an oil). ¹H NMR spectra of all new complexes are therefore provided in the Supporting Information 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, Karslruhe) and equipped with a BBFO-z-atm probe with actively shielded z-gradient coil capable of delivering a maximum gradient strength of 54 G cm⁻¹. Diffusion-ordered NMR data were acquired using the Bruker pulse program dstegp3 s employing a double stimulated echo with three spoiling gradients. Sineshaped 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 timedomain 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 μ L) and tetramethylsilane (TMS, 19.1 μ L) as inert internal reference standards in 0.5 mL of the desired solvent for a concentration of 0.2 mol L⁻¹. The ¹H 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_{Ka} radiation. Structures were solved using SHELXS-97,^[44] while refinement was carried out on F^2 against all independent reflections by the full-matrix least-squares method using the SHELXL-97 program.^[44] All non-hydrogen atoms were refined using anisotropic thermal parameters. Selected crystallographic details and refinement details are provided in Table 4. **1**t-Me₄AEE was treated as a twin. A *hklf* 5 formatted reflection file was created with the two twin components related by matrix -10 - 0.03 0 - 1 0 0 0 1. The twin ratio refined to 0.618(4):0.382(4). CCDC 1061251–1061253 contain the supplementary crystallographic data for this structure. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Theoretical calculations

DFT calculations were performed using the Gaussian 03^[45] package using the B3LYP^[46] density functional and the 6–311(d, $p)^{[47]}$ basis set. After each geometry optimization a frequency analysis was

Table 4. Crystallographic data and refinement details for complexes1t·PMDETA, 1t·Me_4AEE and 2.						
Compound	1 t-PMDETA	1 t ∙Me₄AEE	2			
formula formula weight crystal system space group wavelength [Å] a [Å] b [Å] c [Å] β [°] V [Å ³] Z refins. collected unique refins. R_{int} obs. refins. [$l > 2\sigma(l)$] goodness of fit $R[F^2 > 2\sigma]$, F R_w (all data), F^2 largest diff. peak/hole e [Å ³]	$\begin{array}{c} C_{18}H_{37}N_4Li\\ 316.46\\ monoclinic\\ P2_1/c\\ 0.71073\\ 9.1578(2)\\ 13.9331(3)\\ 16.2095(4)\\ 105.925(2)\\ 1988.90(8)\\ 4\\ 39810\\ 4732\\ 0.0469\\ 3410\\ 1.017\\ 0.0492\\ 0.1152\\ 0.277/-0.178\end{array}$	$\begin{array}{c} C_{17}H_{34}N_3LiO\\ 303.41\\ monoclinic\\ P2_1/c\\ 0.71073\\ 12.6639(19)\\ 9.5511(16)\\ 16.073(3)\\ 90.848(15)\\ 1943.8(6)\\ 4\\ 4860^{[a]}\\ 4860^{[a]}\\ 0.0573\\ 2278\\ 1.018\\ 0.0937\\ 0.2486\\ 0.366/-0.92 \end{array}$	$\begin{array}{c} C_{17}H_{36}N_5Li\\ 314.45\\ orthorhombic\\ Pca2_1\\ 1.54180\\ 13.4284(4)\\ 10.5694(3)\\ 14.1379(4)\\ 90\\ 2006.6(1)\\ 4\\ 7712\\ 3270\\ 0.0218\\ 3047\\ 1.046\\ 0.0570\\ 0.1600\\ 0.371/-0.187\\ \end{array}$			
[a] Twinned sample refined against a <i>hklf</i> 5 formatted reflection file.						

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performed. The energy values quoted include the zero point energy contribution.

Synthesis of 2-tBu(C₅H₅N)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 %). ¹H NMR (400.1 MHz, C_6D_{12} , 300 K): δ = 6.56 (1 H, d, ${}^{3}J_{\text{H-H}} \!=\! 4.70$ Hz, H6), 5.85 (1 H, t, ${}^{3}J_{\text{H-H}} \!=\! 5.82$ Hz, H4), 4.07 (1 H, t, ${}^{3}J_{\text{H-H}}$ _H=5.29 Hz, H5), 3.95 (1 H, brs, H3), 3.54 (1 H, brd, ³J_{H-H}=4.56 Hz, H2), 2.46 (4H, brs, 2×CH₂ PMDETA), 2.38 (7H, brs, CH₃+2×CH₂ PMDETA), 2.32 (12 H, s, 4×Me PMDETA), 0.87 ppm (9 H, s, CH₃); $^{13}\mathrm{C}\;\mathrm{NMR}$ (100.6 MHz, $\mathrm{C_6D_{12^{\prime}}}$ 300 K): $\delta\!=\!150.8$ (C6), 128.8 (C4), 95.2 (C3), 87.4 (C5), 69.5 (C2), 58.1 (CH₃ PMDETA), 55.0 (CH₂ PMDETA), 46.0 (4×Me PMDETA), 45.2 (CH₂ PMDETA), 41.1 (tBu quaternary), 25.7 ppm (CH₃); ⁷Li NMR (155.5 MHz, C₆D₁₂, 300 K): $\delta = 0.82$ ppm; elemental analysis (%) for $C_{18}H_{37}N_4Li$: calcd: C 68.31, H 11.78, N 17.70; found: C 67.64, H 11.85, N 17.33.

Synthesis of 2-tBu(C₅H₅N)Li·Me₄AEE (1 t·Me₄AEE)

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. Me₄AEE (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 °C for one week (yield 0.097 g, 32%). ¹H NMR (400.1 MHz, C₆D₁₂, 300 K): δ = 6.62 (1 H, d, ${}^{3}J_{H-H} = 5.60$ Hz, H6), 5.92 (1 H, dq, ${}^{3}J_{H-H} = 5.60$, 1.23 Hz, H4), 4.36 (1 H, dt, ${}^{3}J_{H-H} = 5.60$, 1.34 Hz, H5), 4.18 (1 H, dd, ${}^{3}J_{H-H} = 4.89$ Hz, H3), 3.55 (4 H, t, ³J_{H-H} = 5.52 Hz, O-CH₂ Me₄AEE), 3.46 (1 H, d, ³J_{H-H} = 5.00 Hz, H2), 2.50 (4H, t, ³J_{H-H} = 5.55 Hz, CH₂-N Me₄AEE), 2.24 (s, 12H, N-CH₃ Me₄AEE), 0.84 ppm (s, 9H, CH₃); ¹³C NMR (100.6 MHz, C₆D₁₂, 300 K): $\delta\,{=}\,151.0$ (C6), 128.2 (C4), 97.2 (C3), 91.6 (C5), 69.4 (O-CH_{2}~{\rm Me_{4}AEE}), 66.9 (C2), 59.4 (CH₂-N Me₄AEE), 45.8 (N-CH₃ Me₄AEE), 40.9 (tBu quaternary), 25.7 ppm (CH₃); ⁷Li NMR (155.5 MHz, C₆D₁₂, 300 K): $\delta =$ 0.34 ppm; elemental analysis (%) for C₁₇H₃₄N₃LiO: calcd: C 67.29, H 11.29, N 13.85; found: C 66.67, H 11.22, N 14.10.

Synthesis of 2-tBu(C₅H₅N)Li·TMEDA (1 t·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%). ¹H NMR (400.1 MHz, C₆D₁₂, 300 K): δ = 6.70 (1H, d, ³J_{H-H} = 5.19 Hz, H6), 6.04 (1H, t, ³J_{H-H} = 5.54 Hz, H4), 4.58 (1H, t, ³J_{H-H} = 5.19 Hz, H5), 4.07 (1H, m, ³J_{H-H} = 5.19 Hz, H3), 3.30 (1H, d, ³J_{H-H} = 4.67 Hz, H2), 2.34 (4H, s, CH₂ TMEDA), 2.26 (12H, s, Me TMEDA), 0.82 ppm (9H, s, CH₃); ¹³C NMR (100.6 MHz, C₆D₁₂, 300 K): δ = 151.3 (C6), 127.0 (C4), 94.4 (C3), 93.8 (C5), 66.2 (C2), 58.9 (CH₂ TMEDA), 46.8 (Me TMEDA), 41.6 (tBu quaternary), 26.0 ppm (CH₃); ⁷Li NMR (155.5 MHz, C₆D₁₂, 300 K): δ = -1.67 ppm.

Synthesis of 2-iBu(C₅H₅N)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 precipi-

tate formed almost immediately after the addition of *i*BuLi which was filtered and collected (yield 0.66 g, 4.62 mmol, 92%). ¹H NMR (400.1 MHz, [D₈]THF, 300 K): $\delta = 6.54$ (1H, d, ³J_{H-H} = 5.39 Hz, H6), 5.71 (1H, t, ³J_{H-H} = 5.59 Hz, H4), 4.25 (1H, t, ³J_{H-H} = 5.49 Hz, H5), 3.97 (1H, t, ³J_{H-H} = 5.59 Hz, H3), 3.63 (1H, quin, ³J_{H-H} = 4.51 Hz, H2), 1.84 (2H, m, ³J_{H-H} = 5.30 Hz, α -CH₂), 1.29 (1H, brs, CH), 0.83 ppm (6H, d, ³J_{H-H} = 6.57 Hz, CH₃); ¹³C NMR (100.6 MHz, [D₈]THF, 300 K): $\delta = 150.0$ (C6), 126.5 (C4), 95.1 (C3), 89.2 (C5), 53.3 (C2), 43.9 (α -CH₂), 23.8 (CH₃), 22.8 ppm (CH); ⁷Li NMR (155.5 MHz, [D₈]THF, 300 K): $\delta = 0.29$ ppm.

Synthesis of 2-sBu(C₅H₅N)Li (1 s)

Pyridine (1.12 mL, 14 mmol) was added to a Schlenk flask containing hexane (10 mL). sBuLi (10 mL, 1.4 μ 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 %). ¹H NMR (400.1 MHz, C₆D₁₂, 300 K): δ = 6.73 (1 H, d, ³J_{H-H} = 5.25 Hz, H6), 6.04 (1 H, m, H4), 5.08 (1 H, brt, ³J_{H-H} = 5.25 Hz, H5), 4.40 (1 H, brm, H3), 3.10 (1 H, brm, H2), 1.55 (2 H, m, α-CH + 1 from CH₂), 0.97 (1 H, m, 1 from CH₂), 0.85 (3 H, m, CH₃), 0.77 ppm (3 H, m, CH₃); ¹³C NMR (100.6 MHz, C₆D₁₂, 300 K): δ = 147.7 (C6), 125.7 (C4), 96.6 (C5), 95.1 (C3), 60.6 (C2), 37.2 (CH), 24.8 (CH₂), 15.0 (CH₃), 11.4 ppm (CH₃); ⁷Li NMR (155.5 MHz, C₆D₁₂, 300 K): δ = -1.97 ppm.

Synthesis of 1,4-dihydropyridylLi·Me₆TREN (2)

Pyridine (0.32 mL, 4 mmol) and Me₆TREN (0.52 mL, 2 mmol) were added to a Schlenk flask containing hexane (5 mL). *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 0.121 g, 19%). ¹H NMR (400.1 MHz, C₆D₆, 300 K): δ = 6.50 (2 H, d, ³J_{H-H} = 7.27 Hz, H2), 4.56 (2 H, m, H3), 4.38 (2 H, brt, H4), 2.01–1.91 ppm (brs with shoulder, 30 H, Me₆TREN); ¹³C NMR (100.6 MHz, C₆D₆, 300 K): δ = 143.5 (C2), 89.4 (C3), 57.5 (CH₂ Me₆TREN), 51.9 (CH₂ Me₆TREN), 45.6 (Me Me₆TREN), 27.9 ppm (C4); ⁷Li NMR (155.5 MHz, C₆D₆, 300 K): δ = 0.68 ppm.

2-i-Butylpyridine

¹H NMR (400.1 MHz, CDCl₃, 300 K): δ = 8.53 (1 H, brs, H6), 7.59 (1 H, t, ³J_{H-H} = 7.64 Hz, H4), 7.11 (2 H, brt, H3 + H5), 2.66 (2 H, d, ³J_{H-H} = 7.30 Hz, α-CH₂), 2.11 (1 H, m, ³J_{H-H} = 6.87 Hz, β-CH), 0.93 ppm (6 H, d, ³J_{H-H} = 6.61 Hz, CH₃); ¹³C NMR (400.1 MHz, CDCl₃, 300 K): δ = 161.6 (C2), 149.1 (C6), 136.3 (C4), 123.7 (C3), 121.0 (C5), 47.6 (CH₂), 29.3 (CH), 22.5 ppm (CH₃).

2-s-Butylpyridine

¹H NMR (400.1 MHz, CDCl₃, 300 K): δ =8.56 (1 H, d, ³*J*_{H-H} =5.05 Hz, H6), 7.65 (1 H, t, ³*J*_{H-H} =7.46 Hz, H4), 7.15 (2 H, m, H3 +H5), 2.87 (1 H, m, ³*J*_{H-H} =6.80 Hz, α -CH), 1.78 (1 H, m, ³*J*_{H-H} =7.46 Hz, CH₂), 1.65 (1 H, m, ³*J*_{H-H} =7.02 Hz, CH₂), 1.29 (3 H, d, ³*J*_{H-H} =7.02 Hz, CHCH₃), 0.87 ppm (3 H, t, ³*J*_{H-H} =7.46 Hz, CH₂CH₃); ¹³C NMR (400.1 MHz, CDCl₃, 300 K): δ =165.7 (C2), 147.9 (C6), 136.4 (C4), 121.3 (C3), 121.7 (C5), 42.8 (CH), 29.4 (CH₂), 19.8 (CHCH₃), 11.5 ppm (CH₂CH₃).

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- [1] a) U. Eisner, J. Kuthan, Chem. Rev. 1972, 72, 1-42; b) D. M. Stout, A. I. Meyers, Chem. Rev. 1982, 82, 223-243; c) R. Lavilla, J. Chem. Soc. Perkin Trans. 1 2002, 1141-1156.
- [2] N. Pollak, C. Dölle, M. Ziegler, Biochem. J. 2007, 402, 205-218.
- a) P. Ioan, E. Carosati, M. Micucci, F. Broccatelli, B. S. Zhorov, A. Chiarini, R. Budriesi, *Curr. Med. Chem.* 2011, *18*, 4901–4922; b) E. Carosati, P. Ioan, M. Micucci, F. Broccatelli, G. Cruciani, B. S. Zhorov, A. Chiarini, R. Budriesi, *Curr. Med. Chem.* 2012, *19*, 4306–4323.
- [4] a) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, Acc. Chem. Res. 2007, 40, 1327–1339; b) T. Marcelli, in *Enantioselective Organocatalyzed Reactions I* (Ed.: R. Mahrwald), Springer, London, 2011, pp. 43–65.
- [5] a) D. L. Comins, K. Higuchi, D. W. Young, Adv. Heterocycl. Chem. 2013, 110, 175–235; b) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, Chem. Rev. 2012, 112, 2642–2713.
- [6] P. T. Lansbury, J. O. Peterson, J. Am. Chem. Soc. 1963, 85, 2236-2242.
- [7] a) D. D. Tanner, C.-M. Yang, J. Org. Chem. 1993, 58, 1840–1846; b) K.
 Hensen, A. Lemke, T. Stumpf, M. Bolte, H. Fleisher, C. R. Pulham, R. O.
 Gould, S. Harris, Inorg. Chem. 1999, 38, 4700–4704.
- [8] a) D. Barr, R. Snaith, R. E. Mulvey, D. Reed, *Polyhedron* **1988**, *7*, 665–668;
 b) D. R. Armstrong, R. E. Mulvey, D. Barr, R. Snaith, D. Reed, *J. Organomet. Chem.* **1988**, *350*, 191–205; c) W. Clegg, L. Dunbar, L. Horsburgh, R. E. Mulvey, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 753–755; *Angew. Chem.* **1996**, *108*, 815–816.
- [9] a) A. J. de Koning, J. Boersma, G. J. M. van der Kerk, J. Organomet. Chem. 1980, 186, 159–172; b) E. C. Ashby, A. B. Goel, J. Organomet. Chem. 1981, 204, 139–145; c) M. S. Hill, D. J. MacDougall, M. F. Mahon, Dalton Trans. 2010, 39, 11129–11131; d) M. S. Hill, D. J. MacDougall, G. Kociok-Köhn, M. F. Mahon, C. Weetman, Organometallics 2015, 34, 2590–2599; for a rare example of a 1-metallo-1,2-dihydropyridyl complex which does not convert to the thermodynamically more stable 1,4 isomer, see: e) J. Intemann, M. Lutz, S. Harder, Organometallics 2014, 33, 5722– 5729; blocking the 4-position of pyridine with a methyl group can prevent the kinetic 1,2-isomer from converting to the thermodynamically more stable 1,4 isomer, see: f) M. S. Hill, G. Kociok-Köhn, D. J. MacDougall, M. F. Mahon, C. Weetman, Dalton Trans. 2011, 40, 12500–12509.
- [10] a) A. J. de Koning, J. Boersma, G. J. M. van der Kerk, J. Organomet. Chem. 1980, 195, 1–12; b) A. L. Spek, Cryst. Struct. Commun. 1982, 11, 1621– 1624.
- [11] R. J. Less, H. R. Simmonds, D. S. Wright, Dalton Trans. 2014, 43, 5785– 5792.
- [12] E. M. P. Silva, P. A. M. M. Varandas, A. M. S. Silva, Synthesis 2013, 45, A AK.
- [13] a) M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn, C. Weetman, Organometallics 2011, 30, 5556–5559; b) K. Oshima, T. Ohmura, M. Suginome, J. Am. Chem. Soc. 2012, 134, 3699–3702; c) A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro, T. J. Marks, Nat. Chem. 2014, 6, 1100– 1107.
- [14] A. J. de Koning, H. J. Alberts-Jansen, J. Boersma, G. J. M. van der Kerk, *Recl. Trav. Chim. Pays-Bas* **2010**, *99*, 316–321.
- [15] C. Lichtenberg, T. P. Spaniol, L. Perrin, L. Maron, J. Okuda, Chem. Eur. J. 2012, 18, 6448–6452.
- [16] P. Jochmann, T. S. Dols, T. P. Spaniol, L. Perrin, L. Maron, J. Okuda, Angew. Chem. Int. Ed. 2010, 49, 7795–7798; Angew. Chem. 2010, 122, 7962–7965.
- [17] C. Lichtenberg, T. P. Spaniol, J. Okuda, Organometallics 2011, 30, 4409– 4417.

- [18] a) Q. Knijnenburg, J. M. M. Smits, P. H. M. Budzelaar, Organometallics 2006, 25, 1036–1046; b) J. J. Sandoval, P. Palma, E. Álvarez, A. Rodríguez-Delgado, J. Cámpora, Chem. Commun. 2013, 49, 6791–6793.
- [19] See the following recent paper and references cited therein: A. R. Kennedy, R. E. Mulvey, R. I. Urquhart, S. D. Robertson, *Dalton Trans.* 2014, 43, 14265–14274.
- [20] a) R. A. Abramovitch, B. Vig, *Can. J. Chem.* 1963, *41*, 1961–1965; b) R. A. Abramovitch, G. A. Poulton, *Chem. Commun.* 1967, 274–275; a ¹H NMR spectrum of the in situ product of *n*BuLi and pyridine in diethyl ether was recorded: c) G. Fraenkel, J. C. Cooper, *Tetrahedron Lett.* 1968, *9*, 1825–1830; the products of the reaction of *n*BuLi or PhLi with pyridine in diethyl ether had their ¹H NMR spectra recorded in TMEDA but pure samples were never obtained: d) C. S. Giam, J. L. Stout, *Chem. Commun.* 1969, 142–143; e) C. S. Giam, J. L. Stout, *Chem. Commun.* 1970, 478; f) R. Levine, W. M. Kadunce, *Chem. Commun.* 1970, 921–922; g) R. F. Francis, W. Davis, J. T. Wisener, *J. Org. Chem.* 1974, *39*, 59–62; h) R. F. Francis, C. D. Crews, B. S. Scott, *J. Org. Chem.* 1978, *43*, 3227–3230.
- [21] S. D. Robertson, A. R. Kennedy, J. J. Liggat, R. E. Mulvey, Chem. Commun. 2015, 51, 5452-5455.
- [22] a) D. R. Armstrong, J. A. Garden, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 7190–7193; *Angew. Chem.* **2013**, *125*, 7331–7334; b) D. R. Armstrong, E. V. Brouillet, A. R. Kennedy, J. A. Garden, M. Granitzka, R. E. Mulvey, J. J. Trivett, *Dalton Trans.* **2014**, *43*, 14409–14423.
- [23] For an activated form of LiH by hydrogenating *n*BuLi in hexane in the presence of TMEDA see the following two references: a) P. A. A. Klusener, L. Brandsma, H. D. Verkruijsse, P. v. R. Schleyer, T. Friedl, R. Pi, Angew. Chem. Int. Ed. Engl. 1986, 25, 465–466; Angew. Chem. 1986, 98, 458–459; b) R. Pi, T. Friedl, P. v. R. Schleyer, P. Klusener, L. Brandsma, J. Org. Chem. 1987, 52, 4299–4303; for a variety of alkali-metal hydride containing cluster compounds see: c) D. Hoffmann, T. Kottke, R. J. Lagow, R. D. Thomas, Angew. Chem. Int. Ed. 1998, 37, 1537–1539; Angew. Chem. 1988, 110, 1630–1633; d) A. Stasch, Angew. Chem. Int. Ed. 2012, 51, 1930–1933; Angew. Chem. 2012, 124, 1966–1969; e) A. Stasch, Angew. Chem. Int. Ed. 2014, 53, 1338–1341; Angew. Chem. 2014, 126, 1362–1365; f) A. Stasch, Chem. Commun. 2015, 51, 5056–5058.
- [24] a) M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* 2011, *17*, 3364–3369; b) T. Cadenbach, E. Hevia, A. R. Kennedy, R. E. Mulvey, J.-A. Pickrell, S. D. Robertson, *Dalton Trans.* 2012, *41*, 10141–10144; c) D. R. Armstrong, M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Inorg. Chem.* 2013, *52*, 12023–12032.
- [25] Prices were taken from the online Sigma-Aldrich UK catalogue on March 26, 2015. Prices represent the cheapest available by purchasing in bulk. Me₆TREN is £110.50 mL, PMDETA is £237.50/1000 mL, Me₄AEE is £113.50/500 mL and TMEDA is £110.50/1000 mL.
- [26] a) D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, D. S. Wright, J. Chem. Soc. Chem. Commun. **1987**, 716–718; b) A. R. Kennedy, J. Klett, C. T. O'Hara, R. E. Mulvey, G. M. Robertson, Eur. J. Inorg. Chem. **2009**, 5029–5035.
- [27] a) R. I. Papasergio, B. W. Skelton, P. Twiss, A. H. White, C. L. Raston, J. Chem. Soc. Dalton Trans. 1990, 1161–1172; b) E. Anders, A. Opitz, R. Boese, Chem. Ber. 1992, 125, 1267–1271; c) W.-P. Leung, L.-H. Weng, R.-J. Wang, T. C. W. Mak, Organometallics 1995, 14, 4832–4836.
- [28] S. Harder, J. Boersma, L. Brandsma, J. A. Kanters, W. Bauer, R. Pi, P. v. R. Schleyer, H. Schöllhorn, U. Thewalt, *Organometallics* 1989, *8*, 1688– 1696.
- [29] a) A. Macchioni, G. Ciancaleoni, C. Zuccaccia, D. Zuccaccia, *Chem. Soc. Rev.* 2008, *37*, 479–489; b) D. Li, I. Keresztes, R. Hopson, P. G. Williard, *Acc. Chem. Res.* 2009, *42*, 270–280.
- [30] a) A.-C. Pöppler, M. M. Meinholz, H. Faßhuber, A. Lange, M. John, D. Stalke, Organometallics 2011, 30, 42-45; b) D. R. Armstrong, W. Clegg, P. García-Álvarez, M. D. McCall, L. Nuttall, A. R. Kennedy, L. Russo, E. Hevia, Chem. Eur. J. 2011, 17, 4470-4479; c) M. Granitzka, A.-C. Pöppler, E. K. Schwarze, D. Stern, T. Schulz, M. John, R. Herbst-Irmer, S. K. Pandey, D. Stalke, J. Am. Chem. Soc. 2012, 134, 1344-1351; d) S. E. Baillie, W. Clegg, P. García-Álvarez, E. Hevia, A. R. Kennedy, J. Klett, L. Russo, Organometallics 2012, 31, 5131-5142; e) D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, Dalton Trans. 2013, 42, 3704-3711; f) C. Su, R. Hopson, P. G. Williard, J. Am. Chem. Soc. 2013, 135, 14367-14379; g) C. Su, J. Guang, W. Li, K. Wu, R. Hopson, P. G. Williard, J. Am. Chem. Soc. 2014, 136, 11735-11747.

Chem. Eur. J. 2015, 21, 14410-14420

www.chemeurj.org

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- [31] D. R. Armstrong, P. García-Álvarez, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* 2011, *17*, 6725–6730.
- [32] Y. Sarazin, S. J. Coles, D. L. Hughes, M. B. Hursthouse, M. Bochmann, Eur. J. Inorg. Chem. 2006, 3211–3220.
- [33] D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* 2011, *17*, 8820–8831.
- [34] a) D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, J. Chem. Soc. Chem. Commun. 1984, 285–287; b) D. R. Armstrong, D. R. Baker, F. J. Craig, R. E. Mulvey, W. Clegg, L. Horsburgh, *Polyhedron* 1996, *15*, 3533–3542; c) D. R. Armstrong, K. W. Henderson, A. R. Kennedy, W. J. Kerr, F. S. Mair, J. H. Moir, P. H. Moran, R. Snaith, *J. Chem. Soc. Dalton Trans.* 1999, 4063– 4068.
- [35] R. E. Mulvey, S. D. Robertson, Angew. Chem. Int. Ed. 2013, 52, 11470– 11487; Angew. Chem. 2013, 125, 11682–11700.
- [36] D. Mootz, A. Zinnius, B. Böttcher, Angew. Chem. Int. Ed. Engl. 1969, 8, 378–379; Angew. Chem. 1969, 81, 398–399.
- [37] E. Hevia, A. R. Kennedy, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Eur. J.* 2013, 19, 14069–14075.
- [38] a) L. Degennaro, A. Giovine, L. Carroccia, R. Luisi, in *Lithium Compounds in Organic Synthesis From Fundamentals to Applications* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**, pp. 513–538; b) T. L. Rathman, J. A. Schwindeman, *Org. Process Res. Dev.* **2014**, *18*, 1192–1210.
- [39] a) I. C. McNeill, J. Polym. Sci. A-1 Polym. Chem. 1966, 4, 2479–2485;
 b) I. C. McNeill, Eur. Polym. J. 1967, 3, 409–421; c) I. C. McNeill, Eur. Polym. J. 1970, 6, 373–395; d) I. C. McNeill, L. Ackerman, S. N. Gupta, M. Zulfiqar, S. Zulfiqar, J. Polym. Sci. Polym. Chem. Ed. 1977, 15, 2381–2392; e) L. Turnbull, J. J. Liggat, W. A. MacDonald, Polym. Degrad. Stab. 2013, 98, 2244–2258.
- [40] P. C. Andrews, P. J. Duggan, G. D. Fallon, T. D. McCarthy, A. C. Peatt, J. Chem. Soc. Dalton Trans. 2000, 1937–1940.

- [41] P. C. Andrews, P. J. Duggan, M. Maguire, P. J. Nichols, *Chem. Commun.* 2001, 53–54.
- [42] P. C. Andrews, M. Maguire, E. Pombo-Villar, Helv. Chim. Acta 2002, 85.
- [43] G. J. P. Britovsek, J. England, A. J. P. White, *Inorg. Chem.* 2005, 44, 8125– 8134.
- [44] G. M. Sheldrick, Acta Crystallogr. Sect. A 2008, 64, 112-122.
- [45] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, V. Tomasi, B. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. B. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford, CT, 2004.
- [46] a) W. Kohn, A. D. Becke, R. G. Parr, J. Phys. Chem. 1996, 100, 12974– 12980; b) A. D. Becke, Phys. Rev. A 1988, 38, 3098–3100.
- [47] a) A. D. McLean, G. S. Chandler, J. Chem. Phys. 1980, 72, 5639–5648;
 b) R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, J. Chem. Phys. 1980, 72, 650–654.

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