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Generation, Stability, and Utility of Lithium 4,4′-Di-*tert*-butylbiphenylide (LiDBB)

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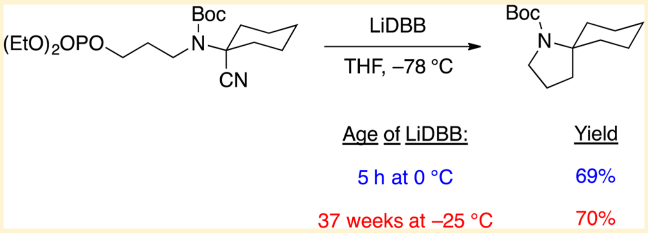
Supporting Information

ABSTRACT: Several procedures were evaluated for the preparation of lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB, Freeman's reagent) from lithium metal and 4,4′-di-*tert*-butylbiphenyl (DBB) in THF. Solutions with nominal concentration of 0.4 and 1.0 M were formed. The stability of LiDBB solutions was evaluated over time, and the gradual uptake of lithium metal was observed. At 0 °C the LiDBB solutions were stable for over a week in THF. At 20 °C the LiDBB solution underwent various decomposition pathways, which led to uptake of more lithium metal and the accumulation of side products. These decomposition pathways were studied, and the importance of ethene in the destruction of THF by LiDBB was observed. On a practical note, LiDBB solutions in THF were stable and effective for over a week at 0 °C or for more than 37 weeks when stored under argon at −25 °C. These observations will extend the utility of LiDBB as a reagent in organic synthesis.

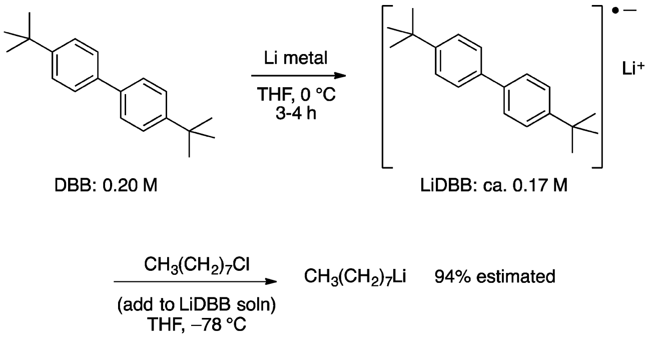


INTRODUCTION

In 1976, Freeman and Hutchinson introduced a new radical anion generated by reduction of Di-*tert*-ButylBiphenyl (DBB) with lithium metal to produce Lithium Di-*tert*-ButylBiphenylide (LiDBB). They demonstrated the superiority of this reagent for the generation of alkyllithium reagents from alkyl chlorides when compared with lithium naphthalide (LiN).[1,2] The LiDBB system exhibited fewer side reactions with the alkyllithium reagent than LiN,[3] and the higher reduction potential of the DBB anion extended the substrate scope.[4] Several other radical anions have been used to generate alkyllithium reagents,[5] and methods with lithium metal and a catalytic arene have been successfully developed.[5,6] Stoichiometric LiDBB is still the reagent of choice for the reductive generation of sensitive alkyllithium regents from alkyl chlorides[1] and alkyl phenyl sulfides.[7,8] It is also employed for many other single electron reduction processes.[9] We have used LiDBB extensively in our research program, first to reductively remove nitriles,[9a] and later to generate alkyllithium reagents.[10] Subsequently we developed reductive lithiations followed by intramolecular alkylations to form new rings.[11] Since LiDBB requires time and labor to produce, we sought to systematically explore its generation and stability, with the goal of improving its utility in the lab. The results of these studies are presented herein.

Freeman's standard preparation of LiDBB is shown in Scheme 1, along with the preparation of a typical alkyllithium reagent.[1] The reduction is carried out using Li metal in a dry solution of THF under argon.[12] The original preparation produced a ca. 0.17 M solution of LiDBB after 3−4 h, and the use of freshly prepared solutions was recommended. The LiDBB solution is deep green or blue-green, and the loss of color can be used as an indication of reagent consumption. In the preferred preparation of an alkyllithium reagent, the alkyl halide was added to a modest excess of the LiDBB solution. Alkyllithium reagents are now often prepared from alkyl phenyl sulfides rather than halides,[7] although the reduction of other functional groups such as oxiranes[13] and oxetanes have proven effective.[14] Several interesting LiDBB reductions are presented in Figure 1 to illustrate the broad utility of this reagent in organic synthesis.

Scheme 1. Preparation and Utility of LiDBB by Freeman's Protocol



The common preparation of LiDBB is very similar to Freeman's protocol.[16] The preferred concentration is nominally 0.4 M, and the reagent is prepared at 0 °C and used that day. From the standpoint of a practicing chemist, this protocol is tedious as 4 or 5 h are required to prepare fresh reagent prior to its use. The 0.4 M concentration produces an upper limit on

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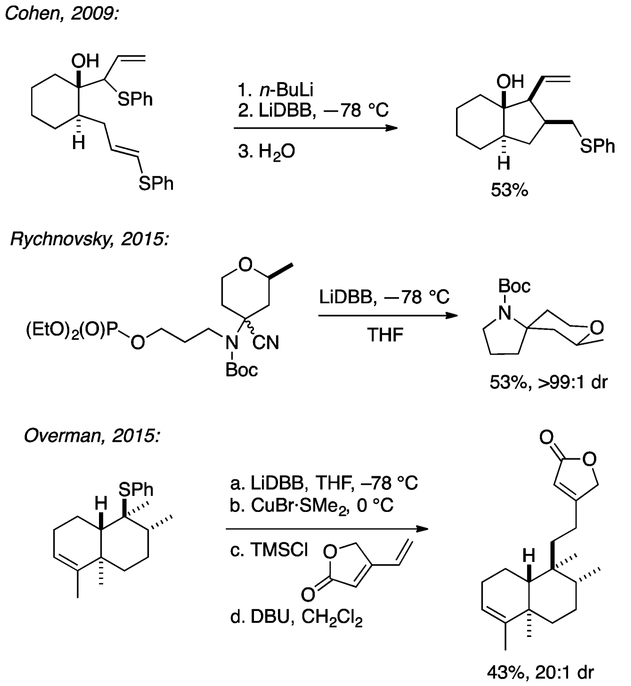

Figure 1. Examples of carbon−carbon bond-forming reactions using LiDBB that proceed through intermediate alkyllithium reagents.[15]

the alkyllithium concentration of less than 0.2 M, as 2 equiv of LiDBB are needed for each mole of RLi generated. This concentration limit is clearly undesirable from the standpoint of large-scale work, as is the separation of excess DBB from the reaction products. A number of alternatives have been proposed, including the use of 1-*N*,*N*-dimethylaminonaphthalene (DMAN), which is used stoichiometrically or catalytically. DMAN can be separated from the desired products by an acid extraction step, but LDMAN (Lithium 1-*N*,*N*−dimethylaminonaphthalenide) is unstable above −45 °C and has not gained wide acceptance.[5] Reactive Li powder may be used with catalytic DBB or naphthalene to generate alkyllithium reagents.[6] Cohen has recently shown that the catalytic procedures lead to different reduction preferences than stoichiometric radical anion reductions and conclude that these are surface reactions.[17] He demonstrated that other aromatic catalysts such as dimethylaniline are effective in a catalytic protocol.[17c] An advantage of LiDBB and the reason for its continued popularity is LiDBB can generate sensitive alkyllithium reagents at low temperature with higher yields than any other reagent (Figure 1).[2] We have investigated the generation of LiDBB solutions and their stabilities to improve upon the utility of this reagent.

RESULTS AND DISCUSSION

Generation of LiDBB Solutions in THF. Different concentrations of DBB were reduced with excess Li metal in THF under modified Freeman's conditions, and the results are shown in Table 1. The resulting LiDBB concentration was determined by titration with thioanisole in THF at 0 °C.[18] Most of the DBB is converted to the radical anion when starting concentrations of DBB were 0.4 and 1.0 M. The 2.0 M DBB solution led to lower conversion, and the 3.1 M (saturated) DBB solution led to a very viscous solution with only a modest concentration of LiDBB. We concluded that 1.0 and 0.4 M DBB solutions were the most promising to explore in further experiments.

Table 1. Maximum Concentration of LiDBB with Different Starting Concentrations of DBB and Excess Li Metal after 2−3 h at 20 °C

[DBB]	[LiDBB]
0.4	0.37
1.0	0.82
2.0	1.26
3.1	1.0

The generation of LiDBB solutions was explored at different temperatures. Using 0.4 M DBB solutions (Figure 2) and an excess of Li metal[19] in THF, the concentration of LiDBB in solution increased at essentially the same rate either at 0 °C or at 20 °C. The terminal concentration was 0.36−0.37 M after 4 h. The 1.0 M solution of DBB (Figure 2) showed a difference in rate at the two temperatures, with the 20 °C solution arriving at a final concentration after about 1 h. In contrast, the 0 °C solution reached a similar final concentration (0.82 M) only after 7 h. The final conversion of the 0.4 M DBB solution to LiDBB was about 90%, while the conversion of the 1.0 M solution of DBB was 82%. At higher concentrations (Table 1) the conversion was greatly reduced. Producing LiDBB solutions at 20 °C presents a minor advantage at the 1.0 M concentration, but does not provide any advantage at the lower concentration.

Both the nominal 1.0 and 0.4 M solutions of LiDBB maintained their concentration at 0 °C. The 0.36 M solution led to a slight increase in concentration when cooled to −25 °C, but the concentration of the 0.82 M solution decreased by 14% when cooled to −25 °C for several hours, perhaps due to precipitation of the reagent (Figure 3). Adding a nominal 1.0 M LiDBB solution slowly to a low temperature reaction mixture would not be expected to present a problem because it would be diluted into the flask, and electron transfer reactions are normally rapid enough to prevent a buildup of the reagent. Both solutions could be stored at 0 °C without an observed drop in molarity.

Stability of LiDBB Solutions in THF. The normal preparation of LiDBB requires 5 h, and it is recommended that the reagent be freshly prepared.[20] We were interested in ascertaining whether or not LiDBB solutions could be prepared and stored for prolonged periods of time prior to use, which would represent a considerable savings of time and effort in the lab. In order to follow the decomposition of LiDBB solutions to its unidentified products, we decided to track the uptake of Li metal by the solution as it aged. All reactions of LiDBB should produce an anion and 1 equiv of Li^+ ion. The LiDBB was prepared with a 10-fold excess of lithium metal, which was available to regenerate the LiDBB from the obvious reduction product, DBB. The solutions were generated and left to stir under argon at the appropriate temperature. Aliquots were taken periodically, worked up by extraction into water, and diluted into volumetric glassware, and the resulting concentration of Li^+ ion was determined by atomic absorption spectroscopy. The results of three decomposition experiments are shown in Figure 4. All of the solutions maintained a blue-green color of active LiDBB for the duration of the experiment.

The 0 °C solutions at 0.36 and 0.82 M LiDBB very slowly took up Li metal. Oxidation rates of lithium in these reactions were found to be 0.030 and 0.041 equiv of lithium per day,

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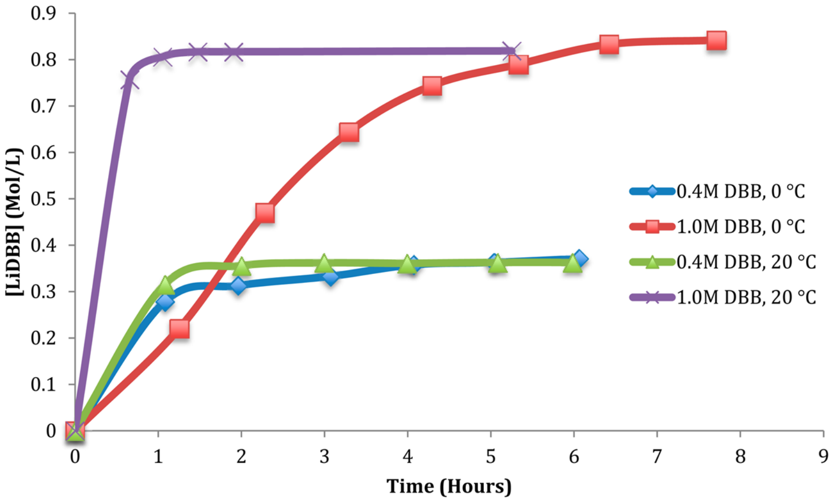


Figure 2. Generation of LiDBB solutions in THF as a function of concentration, temperature and time with an excess of Li metal. The concentrations of the solutions were determined by titration with thioanisole.[18]

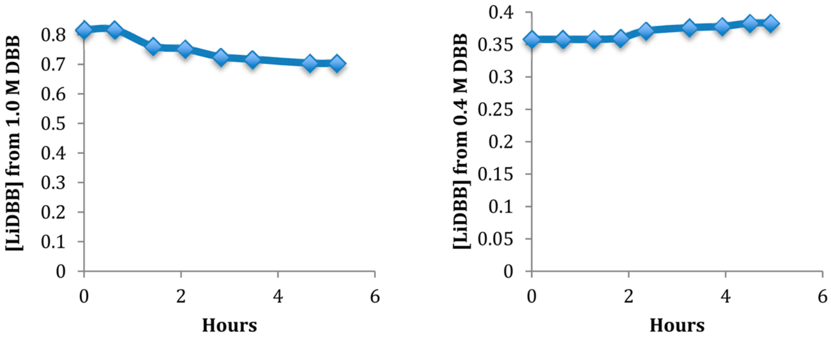


Figure 3. Preparation of LiDBB solutions and cooling them to −25 °C leads to apparent precipitation of LiDBB in the 0.82 M solution but not the 0.36 M solution.

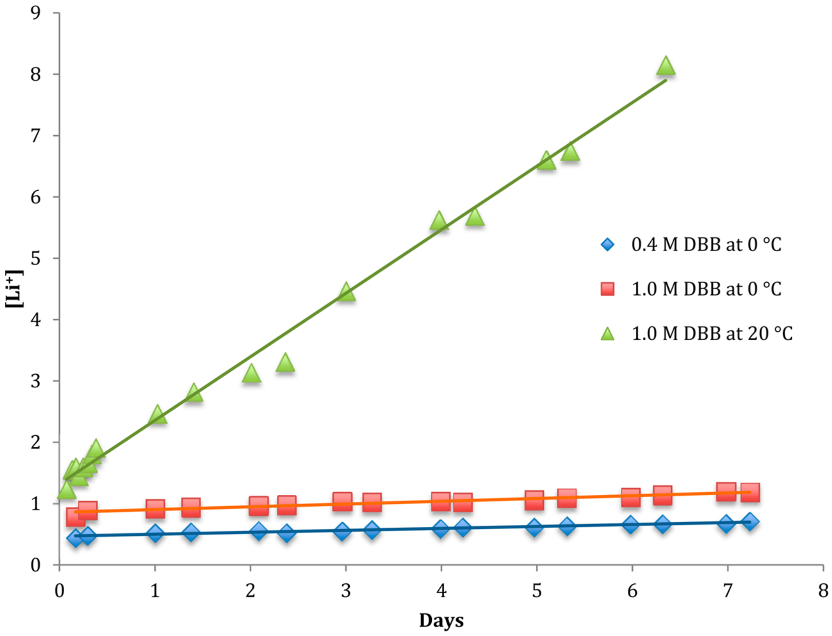


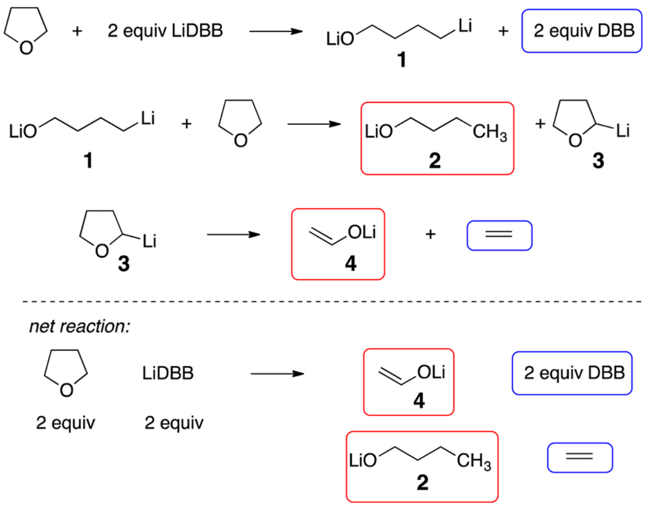
Figure 4. Lithium consumption by LiDBB solutions in THF stored with excess lithium metal at 0 or 20 °C (see text for method). The starting DBB concentration of solution A was 0.40 M, and the starting DBB concentration of solution B was 1.0 M.

respectively. As can be seen from the graph, these solutions are stable at 0 °C for many days and can be used without any problem. Similar tests with a nominal 1.0 M LiDBB solution at 20 °C found 1.02 equiv of lithium per day were consumed.

LiDBB solutions stored in THF at 20 °C become unusable in less than a day due to the buildup of many other lithium species. It is interesting that the solution still had the deep green-blue color of LiDBB after 7 days and only lost this color after approximately 10 days. The loss of LiDBB color presumably corresponds to the consumption of all Li metal, and its complete conversion to various lithium byproducts. Storing solutions of LiDBB over excess Li metal in THF at 0 °C resulted in minimal decomposition over the course of a week.

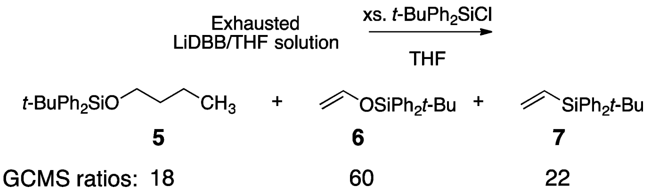
Decomposition of LiDBB Solutions. The dark green LiDBB color fades from THF solutions on storing at room temperature for several days. What happens to the LiDBB solution? The room temperature solutions are not a practical source of LiDBB reagent, but aging solutions this way provides a straightforward method of observing the byproducts formed on decomposition. The solutions are stirred under argon, and the only components of the mixture are DBB, lithium metal, and THF. A plausible hypothesis for the decomposition is the reduction of THF by LiDBB, which has precedent from the direct reduction of THF by lithium metal at reflux[21] and by the $BF_3{\cdot}OEt_2$ induced reductive opening of THF by LiDBB at low temperature.[22] Sonication of LiDBB solutions at room temperature has also been reported to reduce THF.[23] The initial product, lithium (4-oxidobutyl)lithium (**1**), is an alkyllithium reagent and will react with another equivalent of THF to deprotonate it.[24] The 2-lithiotetrahydrofuran (**3**) spontaneously eliminates ethene to generate lithium ethenolate (**4**).[25] The net reaction, shown at the bottom of Scheme 2, would consume 2 equiv of THF and 2 equiv of LiDBB to generate 1 equiv of ethene, 2 equiv of DBB, and 1 equiv each of lithium species **2** and **4**. The DBB would react with excess Li metal to regenerate LiDBB, at least until all of the lithium was consumed. This hypothesis would account for the gradual consumption of Li metal in the LiDBB solution.

Scheme 2. Hypothesis for the Decomposition of LiDBB Solutions in THF



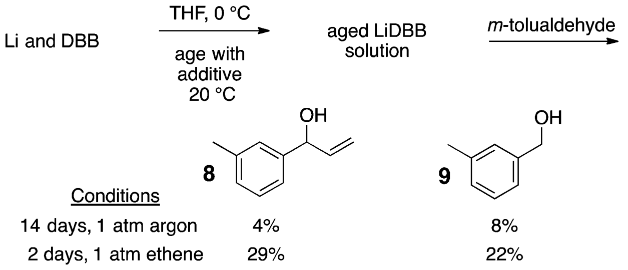
Scheme 3 presents an experiment designed to test this hypothesis. A 0.4 M LiDBB solution was prepared in THF with 10 equiv of Li metal and allowed to age for 10 days at 20 °C until a dark green color had faded to a reddish-brown color. The mixture was quenched with ca. 5 equiv of t-$BuPh_2SiCl$ and diluted with wet CH_2Cl_2. The crude products were identified by GCMS against authentic standards prepared separately. We did observe the expected silylated butanol **5** and silylated acetaldehyde **6**, but vinyl t-$BuPh_2Si$ (**7**) was also identified. In addition, the amount of silylated acetaldehyde **6** was much larger than the silylated butanol **5**, but according to the hypothesis outlined in Scheme 2, they should have been formed in a 1:1 ratio. The significant deviation from the expected ratio and the unexpected side product suggested that the original hypothesis was too simplistic and that more was going on in the decomposition of the LiDBB solution.

Scheme 3. Products from the Decomposition of an LiDBB Solution after Treatment with t-$BuPh_2SiCl$



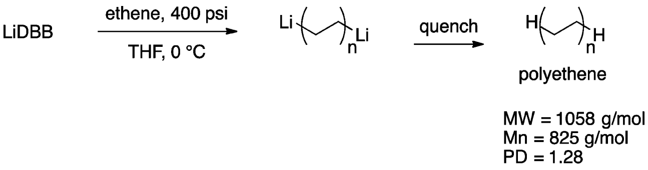
The complexity originates with ethene. Ethene is known to react with lithium biphenylide to give a number of products that include lithium hydride, vinyllithium, 1,4-dilithiobutane, and higher homologues.[26] The vinyllithium component would react with t-$BuPh_2SiCl$ in the quenching reaction to deliver the corresponding vinyl silane **7** that was observed in the quenching study. In addition, aged LiDBB solution often violently gave off gas on quenching with water, which would be consistent with the accumulation of lithium hydride in the mixture. These processes were probed by control experiments shown in Schemes 4 and 5. A nominal 0.4 M solution of LiDBB was prepared and stored under argon for 14 days at 20 °C, followed by addition of 3-methylbenzaldehyde. The vinyllithium addition product (**8**) was observed by NMR spectroscopy, along with the reduced product **9**. Storing the LiDBB solution under an atmosphere of ethene leads to much more vinyllithium addition product. These experiments confirm that

Scheme 4. Reaction of 3-Methylbenzaldehyde with an Aged Solution of LiDBB[a]



[a]Because of uncertainty regarding the limiting reagent, listed %'s are conversion based on the addition of a standard quantity of 3-methylbenzaldehyde.

Scheme 5. Formation of Polyethene in the Presence of a Large Excess of Ethene Using LiDBB

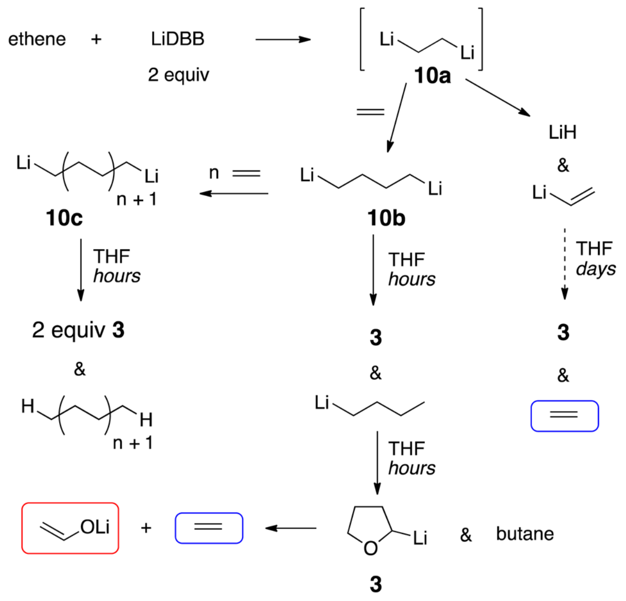


solutions of LiDBB stored at room temperature under argon produce vinyllithium. The reaction of ethene with LiDBB to produce vinyllithium (and LiH) explains some of the complexity of the decomposed LiDBB mixtures.

Another reported reaction of lithium with ethene is the formation of polyethene.[26] The aged solutions of LiDBB often contained varying amounts of an insoluble white solid. To aid in the isolation and analysis, a solution of LiDBB was treated with ethene under 400 psi for 15 h at 20 °C. The solution absorbed many equivalents of ethene. Ethene oligomers were isolated from the reaction, with a MW of about 1000 g/mol and a PD of 1.28. Part of the ethene produced from LiDBB solutions by the decomposition of 2-lithiotetrahydrofuran is incorporated into ethene oligomers.

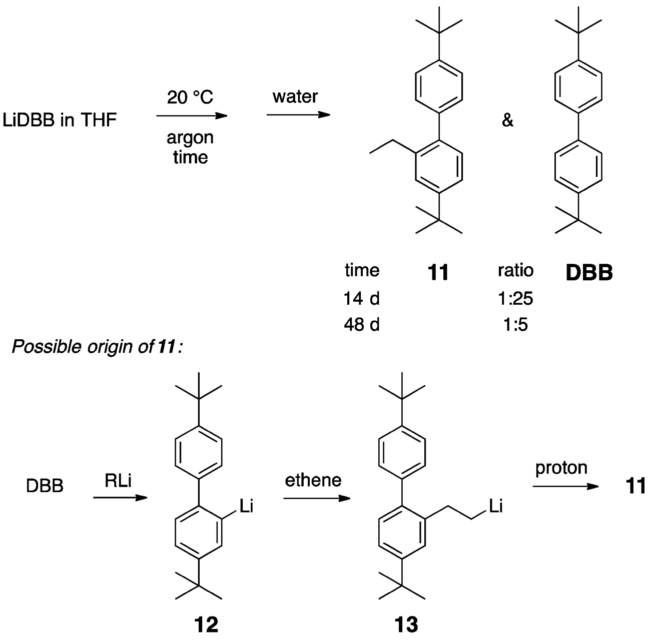
A more complete picture of the decomposition of THF by LiDBB is presented in Schemes 6 and 2. As described in Scheme 2, the process begins with the reduction of THF to lithium 4-oxidobutyllithium (**1**) with 2 equiv of LiDBB. This alkyllithium reagent deprotonates THF, and the subsequent retro-[2 + 3] reaction generates 1 equiv of lithium ethenolate (**4**) and 1 equiv of ethene. The presence of ethene leads to several more pathways as shown in Scheme 6. Reduction of ethene generates 1,2-dilithioethane (**10a**), which can add one or more times to ethene to produce 1,4-dilithiobutane (**10b**) or dilithiopolyethene (**10c**).[27] As described in Scheme 5, ethene under pressure will lead to polyethene. Dilithioethane can also decompose to vinyllithium and lithium hydride.[26] The vinyllithium is expected to react only very slowly with THF to form 2-lithiotetrahydrofuran (**3**),[28] based on the rate of reaction of aryllithium reagents with THF.[29] All of the sp^3-lithium species (**10a**−**c**) are expected to react with THF within hours to generate 2-lithiotetrahydrofuran (**3**),[30] which will decompose to produce 1 equiv of ethene. If the dominant pathway goes to **10b** rather than vinyllithium, as much ethene is generated as is consumed and the process would be effectively catalytic in ethene. Although lithium metal can participate in the direct reduction of THF or ethene, the rates appear to be much slower than the LiDBB reductions and should not be a major factor in the decomposition.[21,31] Schemes 2 and 6 explain most of the products formed in the decomposition of aged LiDBB solutions.

Scheme 6. Decomposition Pathways for Ethene and LiDBB in THF



Another unexpected product was identified when the spent DBB was analyzed as shown in Scheme 7. GCMS identified a compounds with a MW of 294, 28 greater than DBB. An ethene addition product was suspected, and an independent synthesis of 4,4′-di-*tert*-butyl-2-ethyl-1,1′-biphenyl (EtDBB, **11**) led to a compound that was identical by GCMS retention time, fragmentation pattern, and NMR characterization. Significant amounts of the EtDBB (**11**) were only formed on prolonged storing (≥14 days at 20 °C) of the LiDBB solution at room temperature. A possible mechanism for its formation is presented in Scheme 7. Deprotonation of DBB by one of the many alkyllithium reagents in solution would produce alkyllithium **12**.[3] Addition of ethene,[27] followed by protonation by the solvent would produce EtDBB (**11**). In our view, this type of process is the one most likely to lead to EtDBB.

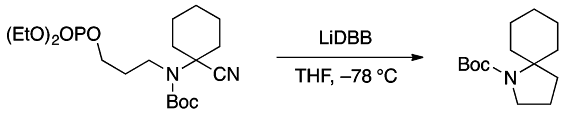
Scheme 7. Identification of 4,4′-Di-*tert*-butyl-2-ethyl-1,1′-biphenyl (11) from LiDBB Solutions



The decomposition of LiDBB solutions at 20 °C lead to a variety of side products. The generation of ethene and its subsequent reaction with LiDBB or alkyllithium reagents are responsible for many of the decomposition products.

Utility of LiDBB Solutions. The original goal of the project was to determine the utility of stored LiDBB solutions. They do decompose at 20 °C, and the buildup of some of the decomposition products, such as vinyllithium, would clearly interfere with the desired LiDBB reactions. Figure 4 shows the rate of consumption of lithium in the solutions. Storing LiDBB solutions for many hours at 20 °C leads to the consumption of large amounts of Li metal, accompanied by the buildup of various decomposition products. At 0 °C, however, the consumption of lithium metal is very slow. After 1 week, only 0.21 equiv of Li has been consumed by a 0.36 M solution. Based on these experiments, stored 0.35 and 0.8 M LiDBB solutions at 0 °C were found to reliably provide good activity. Storing a 0.4 M LiDBB solution at −25 °C for several months also led to good results.[32] Table 2 demonstrates the utility of

Table 2. Reductive Cyclization of Cyano Phosphate 14 Using LiDBB Solution That Has Been Stored in a −25 °C Freezer



14 15

entry[a]	LiDBB age	yield (%)
1	5 h	69
2	1 week	69
3	3 weeks	70[b]
4	8 weeks	66[b]
5	16 weeks	69
6	29 weeks	70
7	37 weeks	70

[a] Use of an old LiDBB solution (ca. 0.35 M) prepared with 10-fold excess of lithium metal. It was stored in a −25 °C freezer in a Schlenk flask. The solution was warmed to 0 °C and stirred for 1 h prior to use. [b] The starting phosphate used in these experiments had partially decomposed. The yield shown is based on the isolated product mass and the mass of starting material corrected for the loss of the Boc group by ^{1}H NMR integration.

stored 0.35 M LiDBB solutions in reductive cyclization reactions. The reductive lithiation of nitrile **14** and subsequent cyclization of the alkyllithium reagent are a reliable reaction to produce the spiropyrrolidine **15**.[33] The old LiDBB solutions stored at −25 °C in a Schlenk flask continued to be effective in this reaction for 37 weeks.

CONCLUSION

The stability and utility of LiDBB solutions were evaluated. Solutions of nominal 0.4 M LiDBB were ready for use in 4 h at 0 °C or 2 h at 20 °C, while nominal 1.0 M LiDBB solutions were ready in 8 h at 0 °C or 2 h at 20 °C. Trapping studies confirmed two types of THF ring-opening pathways during decomposition, and ethene generated in the process led to further decomposition reactions. The rate of lithium uptake was found to be modest at 0 °C but unacceptably high at 20 °C. Solutions of LiDBB could be used for over a week when stored at 0 °C under argon. Nominal 0.4 M solutions of LiDBB could be stored at −25 °C in a Schlenk flask under argon and were still effective after 37 weeks. This project demonstrates that LiDBB solutions can be prepared in advance and stored for months with appropriate precautions. These observations will extend the utility of LiDBB as a reagent in synthesis.

EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were carried out in a flame- or oven-dried flasks equipped with a magnetic stir bar under an argon atmosphere. All commercially available reagents were used as received unless stated otherwise. All reactions with LiDBB used glass stir bars. Thin layer chromatography (TLC) was performed on 250 μm layer silica gel plates, and developed plates were visualized by UV light, *p*-anisaldehyde, potassium permanganate, or vanillin. *tert*-Butyldiphenyl(vinyloxy)silane (**6**) was prepared from THF as described by Cohen and Stokes.[34] The analytical data matched those previously reported.[35] *tert*-Butyldiphenyl(vinyl)silane (**7**) was prepared from tetravinyltin as described by Gerstenberger and Konopelski, and the analytical data matched those previously reported.[36]

^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in Hertz (Hz), and integration. Infrared spectra were recorded on NaCl plates. High resolution mass spectrometry was performed using ESI-TOF.

LiDBB Formation in THF. LiDBB was prepared by adding 4,4′-di-*tert*-butylbiphenyl (DBB, 1.50 g, 5.64 mmol, 1 equiv), to a 50 mL flask, followed by evacuating and flame-drying. Once the DBB was melted, the flask was backfilled with argon and allowed to cool. An ice bath was applied, and lithium wire (0.39 g, 56.4 mmol, 10 equiv) was clipped into the flask under a stream of argon. THF (14 mL) was added, and the solution turned green, darkening over for 5 h at 0 °C. This resulted in a nominal 0.4 M LiDBB solution.

Nominal 1.0 M LiDBB was prepared by the above method by increasing the amount of DBB (3.85 g, 14.5 mmol, 1 equiv) and lithium (1.00 g, 144.5 mmol, 10 equiv) added.

Nominal 2.0 M LiDBB was prepared by the above method by increasing the amount of DBB (7.40 g, 27.8 mmol, 1 equiv) and lithium (1.93 g, 277.8 mmol, 10 equiv) added.

Nominal 3.1 M LiDBB was prepared by the above method by increasing the amount of DBB (11.6 g, 43.5 mmol, 1 equiv) and lithium (3.02 g, 435.4 mmol, 10 equiv) added.

Titrations of Nominal 0.4 M LiDBB. To a 50 mL volumetric flask, thioanisole (1.20 mL, 10.2 mmol) and THF (degassed by freeze−pump−thaw) were added to form a 0.20 M solution. A dry 10 mL flask was evacuated and backfilled with argon 3 times and cooled to 0 °C, and 1.00 mL of the 0.20 M thioanisole solution was added. LiDBB was then added dropwise until a persistent dark-green color was observed. The titrated solution was removed, and the procedure was repeated three times. The first trial was excluded, and the average volume added from titrations 2−4 was used to calculate the molarity of the LiDBB.

Titrations of Nominal 1.0, 2.0, 3.1 M LiDBB. Titrations of nominal 1.0, 2.0, and 3.1 M LiDBB followed the same procedure for nominal 0.4 M LiDBB except the molarity of the thioanisole solution was increased to 0.40 M.

Trapping of LiDBB Decomposition Products (Scheme 3). A nominal 0.4 M LiDBB solution was prepared at 20 °C and allowed to stir for 14 days. To a dram vial, *t*-BuPh$_2$SiCl (0.2 mL, 0.77 mmol) and LiDBB (0.2 mL) were added and stirred for 2 days. Addition of 1.00 mL of wet CH$_2$Cl$_2$ and removal of 4 μL of this solution for GC-HRMS analysis led to the identification of **5**, **6**, and **7**.

Trapping Study with 3-Methylbenzaldehyde (Scheme 4). A nominal 0.4 M LiDBB solution was prepared at 20 °C and allowed to stir for 14 days. 3-Methylbenzaldehyde (0.10 mL, 0.85 mmol) and 0.5 mL (nominal 0.20 mmol) of the LiDBB solution were added to a 5 mL flask and allowed to stir for 18 h. After quenching with NH$_4$Cl$_{(aq)}$ (2 mL), the reaction was diluted with CH$_2$Cl$_2$ (2 mL) and the aqueous layer was extracted with 3 × 2 mL of CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated to give a yellow oil. Using the added DBB as an internal standard, 1-(*m*-tolyl)prop-2-en-1-ol (**8**) and *m*-tolylmethanol (**9**) were quantified from the reaction mixture by ^{1}H NMR. The analytical data matched those previously reported.[37,38]

Atomic Absorption Spectroscopy in the Determination of Lithium. Three solutions of LiDBB were prepared: Nominal 0.4 M LiDBB prepared at 0 °C (2.6 g DBB, 0.67 g Li metal, 24 mL THF), nominal 0.4 M LiDBB prepared at 20 °C (2.6 g of DBB, 0.67 g of Li metal, 24 mL of THF), and nominal 1.0 M LiDBB prepared at 0 °C (6.6 g of DBB, 1.72 g of Li metal, 24 mL of THF). Each of these solutions was maintained at their respective temperatures, and a 0.50 mL aliquot was removed twice daily. After quenching with 0.05 M H$_2$SO$_{4(aq)}$ (10 mL), the aliquot was diluted with CH$_2$Cl$_2$ (10 mL) and the aqueous layer was added to a 100 mL volumetric flask. The organic layer was extracted with 5 × 10 mL of 0.05 M H$_2$SO$_{4(aq)}$, and the aqueous layers were added to the volumetric flask. This was repeated for each aliquot in a separate 100 mL volumetric flask.

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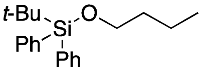
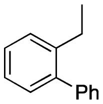
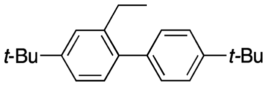
Using these volumetric solutions, between 2 and 5 mL were removed and diluted in a 50 mL volumetric flask such that the absorbance from the spectrometer was between 0.000 and 0.120. A calibration curve was used to assign the concentration of Li^+. Details of the calibration procedure are described in the Supporting Information.



Synthesis of Authentic Standards. *Butoxy(tert-butyl)diphenylsilane (5).* To a solution of *n*-butanol (0.20 mL, 2.2 mmol, 1 equiv) in THF (2.2 mL), Et_3N (0.45 mL, 3.3 mmol, 1.5 equiv) and *t*-$BuPh_2SiCl$ (0.63 mL, 2.4 mmol, 1.1 equiv) were added. After stirring for 18 h, the reaction was quenched with a 10% $NaHCO_3$ solution (4 mL), and the solution was diluted with ethyl acetate (4 mL). The organic layer was extracted, the aqueous layer was washed with ethyl acetate (3 × 2 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*, giving a yellow oil. Flash column chromatography (8:1 Hexanes/CH_2Cl_2) gave butoxy(*tert*-butyl)diphenylsilane in 25% yield (259 mg) as a clear oil. The analytical data matched those previously reported.[39]



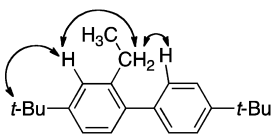
2-Ethyl-1,1′-biphenyl (16). A mixture of DMF (2.8 mL) and H_2O (0.56 mL) was degassed by freeze−pump−thaw, followed by addition of phenyl boronic acid (85 mg, 0.70 mmol, 1 equiv), K_2CO_3 (193 mg, 1.39 mmol, 2 equiv), 1-ethyl-2-iodobenzene (0.1 mL, 0.70 mmol, 1 equiv), and $PdCl_2(Ph_3)_2$ (9.8 mg, 0.014 mmol, 0.02 equiv). The reaction was heated to 60 °C for 18 h. The solution was diluted with H_2O (5 mL) and pentane (5 mL), and the organic layer was extracted. The aqueous layer was washed with pentane (3 × 3 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*, giving a yellow oil. Flash column chromatography (100% hexanes) gave 2-ethyl-1,1′-biphenyl (**16**) in 87% yield (110 mg) as a clear oil. The analytical data matched those previously reported.[40]



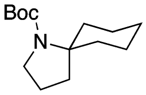
4,4′-Di-tert-butyl-2-ethyl-1,1′-biphenyl (EtDBB, 11). To a solution of 2-ethyl-1,1′-biphenyl (**16**) (0.10 g, 2.2 mmol, 1 equiv) in $MeNO_2$ (0.6 mL), *tert*-butyl chloride (0.133 mL, 1.21 mmol, 2.2 equiv), followed by $AlCl_3$ (22 mg, 0.16 mmol, 0.3 equiv), was added. After gas evolution stopped (ca. 5 min), the reaction was poured over crushed ice and diluted with hexanes (3 mL). The hexane layer was extracted, the aqueous/NO_2Me layers were washed with hexanes (3 × 2 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*, giving a yellow oil. Preparatory plate chromatography (100% Hexanes) gave 4,4′-di-*tert*-butyl-2-ethyl-1,1′-biphenyl (**11**) in 2% yield (3 mg) as a white solid. The relevant NOSEY correlations are shown below. Melting point = 109−111 °C; ^1H NMR (CD_2Cl_2, 500 MHz) δ 7.49−7.40 (m, 2H), 7.34−7.31 (m, 1H), 7.27−7.22 (m, 3H), 7.13−7.09 (m, 1H), 2.61 (q, J = 7.5 Hz, 2H), 1.36 (s, 9H), 1.35 (s, 9H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.1, 149.4, 141.3, 139.0, 138.8, 129.9, 129.1, 125.6, 125.0, 122.7, 34.7, 31.6, 26.5, 16.1; IR (thin film) 3025, 2961, 2887, 1608, 1491 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{30}NH_4$ [M + NH_4^+] 312.2691, found 312.2686.

Compound **11** was separately isolated from crude material recovered from aged LiDBB solutions. The crude DBB material was recrystallized from $MeNO_2$ to remove DBB and to concentrate the minor components in the mother liquor. The mother liquor was chromatographed on a reversed-phase column to deliver EtDBB. Characterization data matched those from the synthetic procedure described above.

NOESY Correlations



Cyclization of Nitrile 14 To Form Spirocycle 15 with Stored LiDBB Solutions. *tert-Butyl 1-Azaspiro[4.5]decane-1-carboxylate (15).* An oven-dried round−bottom flask equipped with a glass stir bar was cooled under vacuum and backfilled with argon. The flask was charged with 1,10-phenanthroline (1 crystal) and a 0.05 M solution of phosphate **14** (1 equiv) in THF. The solution was cooled to −78 °C, and *n*-BuLi (ca. 2 M solution in hexane) was added until a dark brown color persisted (2 drops). To that solution at −78 °C was added LiDBB (~0.5 M, >2.1 equiv) via syringe to produce a solution that remained dark green for ca. 20 s. The mixture was stirred for 1 h and then quenched with MeOH (0.1 mL) and saturated aq. NH_4Cl. The reaction mixture was diluted with Et_2O, and the aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a light yellow viscous solid. Purification by column chromatography (gradient 97:3 hexane/CH_2Cl_2 then 98:2 hexane/EtOAc to 95:5 hexane/EtOAc) gave the title compound. The analytical data matched those previously reported.[33]



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01748.

^1H and ^{13}C NMR spectra EtDBB (**11**), and calibration data for atomic absorption determination of lithium ion (PDF)

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Notes

The authors declare no competing financial interest.

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