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New amine-stabilized deuterated borane–tetrahydrofuran complex (BD_3–THF): convenient reagent for deuterium incorporations

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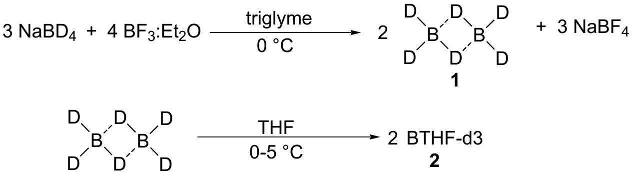
Abstract—Convenient methods for the preparation of BD_3–THF complex were developed. Certain amines stabilize the BD_3–THF for long-term storage. Regioselectivity studies were carried out with the new amine-stabilized BD_3–THF with representative olefins. Hydroboration of olefins provides a convenient tool for making corresponding deuterated alcohols after oxidation.

BH_3–THF (BTHF) is a reagent of choice for several synthetic transformations, such as reduction and hydroboration.[1] We recently sought a convenient synthesis of a borane-labeling reagent for introducing a deuterium label in a highly efficient and selective fashion. Though a few deuterium labeled reagents, such as $NaBD_4$, $LiAlD_4$ and Li(*sec*-butyl)$_3$BD are known, BD_3–THF is known to provide selective deuterium insertions, otherwise not possible.[2] The ideal reagent was to be highly stable and relatively easy to use, preferably as a solution. As borane–Lewis base complexes are finding an ever-increasing role in organic transformations, in particular borane tetrahydrofuran, we began looking into the synthesis, stability and synthetic utility of BD_3–THF. Herein we wish to report an improved synthesis of BD_3–THF, stability studies and applications in the hydroboration of representative olefins.

The method chosen for generating B_2D_6 (**1**) was modeled off the procedure reported by Brown and co-workers for generating diborane gas using boron trifluoride as the Lewis acid in glyme solvents.[3] Owing to its high purity and low volatility to other glyme type solvents, triglyme was chosen as the solvent of choice. Substituting $NaBD_4$ for $NaBH_4$, direct application of Brown's literature conditions for generating diborane succeeded in yielding a 1 M solution of borane-d_3 complex in THF quantitatively. THF complex **2** was generated by introducing the labeled diborane (B_2D_6) gas stream **1** from the reactor into a separate reactor containing THF, which was re-distilled over lithium aluminum deuteride prior to use (Scheme 1). The reaction proved amenable to scale up, with the same yield obtained whether on a 0.5 mol or 1.0 mol scale.[4]

Similar to BH_3–THF, BD_3–THF is also not stable at room temperature for extended periods of time.[5] Commercial BH_3–THF is stabilized with $NaBH_4$, $NaBD_4$ was used to stabilize BD_3–THF.[6] The presence of



Scheme 1.

Keywords: BD_3–THF complex; Stability; Hydroboration; Olefins; Regioselectivity.

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sodium borohydride as a stabilizer is known to create safety issues as well as some adverse affects in applications.[7,8] Recently, we have undertaken a detailed study to find more effective stabilizers for BH_3–THF and found that certain hindered amines are superior stabilizers of BH_3–THF compared to $NaBH_4$. Solutions of 1 M BTHF containing 0.005 M% *N*-isopropyl-*N*-methyl-*t*-butylamine (NIMBA) showed superior thermal properties, directly resulting in improved stability.[9] Similar stability effect was observed for BD_3–THF, when stabilized with 0.005 M% *N*-isopropyl-*N*-methyl-*t*-butylamine (NIMBA). These solutions did not show any noticeable degradation in hydride content by ^{11}B NMR, when stored at 4–8 °C for at least six months.

As a result, we also extended the stability studies at elevated temperatures for BD_3–THF. The adduct thus obtained (1 M solution in THF), maintained under nitrogen, was subjected to elevated temperature studies (50 °C) in sealed NMR tubes over a period of 96 h. When stabilized with 0.005 M *N*-isopropylmethyl-*t*-butylamine (NIMBA), the ^{11}B NMR showed approximately 90% BD_3–THF remained after 80 h of heating at 50 °C (Fig. 1).[10] Collecting concentration of BTHF versus time data for at least 3 half lives shows curvature indicating decomposition to be first order in BTHF. Decomposition furthermore appears to be an intermolecular event over intramolecular based on the rate of decomposition being directly proportional to the concentration of BTHF.

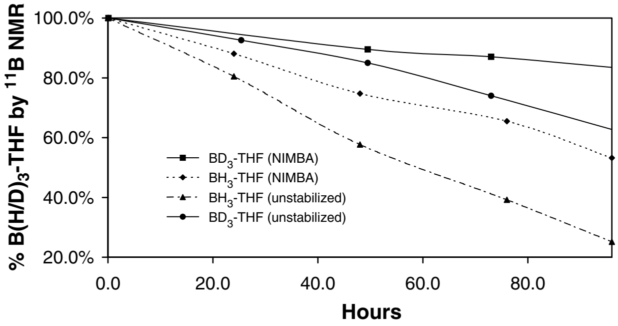


Figure 1.

Table 1. Regioselectivity of hydroboration–oxidation of representative olefins using BD_3–THF and BH_3–THF in THF at room temperature

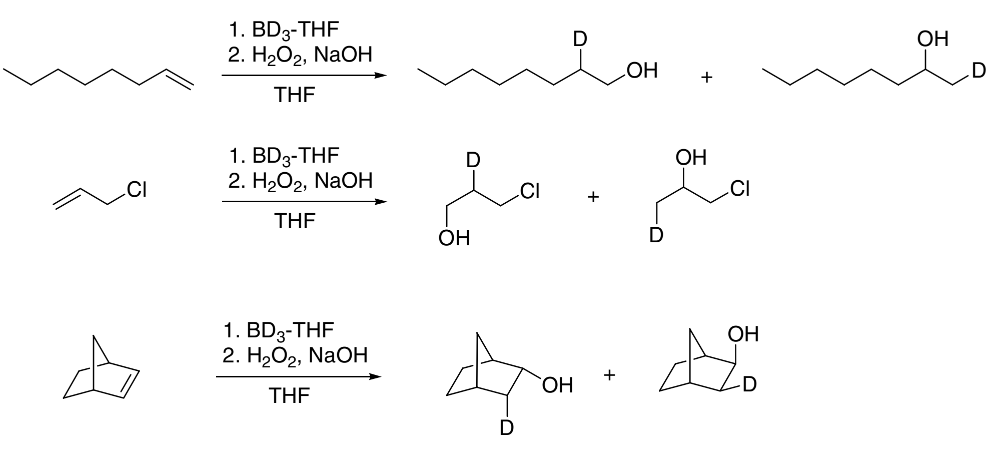
Olefin	BD_3–THF[a] (Terminal:internal)	BH_3–THF (Terminal:internal)
1-Octene	96:4	96:4
Styrene	87:13	85:15
Allyl chloride	78:22	72:28
2-Methyl-2-butene	94:6	98:2
Norbornene	94:6 (*exo*:*endo*)	97:3 (*exo*:*endo*)

[a] Reactions were carried out using borane **2** (5 mmol) and an olefin (15 mmol) in a total volume of 10 mL solution in THF.

Regioselectivity of hydroboration. 1-Octene, styrene, 4-bromostyrene, norbornene, 2-methyl-2-butene, 2,3-dimethyl-2-butene and allyl chloride were hydroborated using **2** at room temperature in THF, then subsequently oxidized to the corresponding alcohol.[11] 1-Ocetene and styrene were hydroborated in a 3:1 ratio (Scheme 2), whereas allyl chloride was hydroborated in a 1:1 molar ratio as reported for BH_3–THF.[1d,12] Intermediate organoboranes were oxidized with H_2O_2–NaOH, and the product alcohols analyzed by GC–MS, ^{1}H NMR and deuterium NMR. The results are tabulated in Table 1.

Although, the regioselectivity trends observed during hydroboration/oxidation of olefins with BD_3–THF is similar to that reported for BH_3–THF,[1a,d] minor differences obtained may possibly be due to a combination of steric and isotopic effects.

In conclusion, we report a new, convenient procedure for the preparation of deuterated borane–THF. The BD_3–THF thus prepared can be stabilized with 0.005 M *N*-isopropyl-*N*-methyl-*t*-butylamine (NIMBA) to provide thermally stable BD_3–THF. Regioselecivity studies with BD_3–THF showed similar results to that reported for BH_3–THF. Further works on the synthetic utility of this amine-stabilized BD_3–THF solutions are in progress and will be the subject of future publications.



Scheme 2.

Acknowledgement

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4. *Generation of diborane using borohydride in tetraglyme and BF_3–Et_2O.* The procedure followed for generating a 1 M BD_3–THF solution in THF is the same as that for BH_3–THF. In an oven-dried round-bottomed flask, $NaBD_4$ (26 g, 621 mmol) was charged along with anhydrous tetraglyme (175 mL, 968 mmol). The resulting turbid solution was then cooled to 0 °C. BF_3–Et_2O (105 mL, 0.826 mmol) was then charged to the reaction mixture over a period of 50 min at 0 °C. After ca. 50% of the etherate was added, diborane gas was then generated and allowed to pass through a −78 °C cold trap before being allowed to sparge into agitated anhydrous THF (600 g, 9 mol) at 0 °C. Diborane generation ceased 40 min upon completing the BF_3–Et_2O addition. ^{11}B NMR: −0.8 (quartet). Hydride analysis using a (1:1) glycerol:water solution: 1.05 M.
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6. See product details of BD_3–THF from Cambridge Isotope laboratories, Inc, cat # DLM-1315-0.25, this can be accessed via web at: http://www.isotope.com/cil/products/displayproduct.cfm?prod_id=5439.
7. (a) SADT testing of 1.0 M BTHF stabilized with 0.005 M $NaBH_4$, using the procedure described in Ref. 9, resulted in self-accelerating temperature of 42 °C; (b) For an industrial incident involving 2 M THF in a 400 L cylinder, please see: *Chem. Eng. News*, July 1, 2002 and safety highlights in *Org. Process. Res. Dev.*, **2003**, *7*, 1029.
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9. (a) Potyen, M.; Josyula, K. V. B.; Schuck, M.; Lu, S.; Gao, P.; Hewitt, C. *Org. Process. Res. Dev.*, in press; (b) For further details about the safe handling of new amine-stabilized BTHF solutions, please see Aldrich Technical Bulletin 218, which can be requested by e-mail: (aldrich@sial.com) or can be accessed on the web: http://www.sigmaaldrich.com/aldrich/bulletin/al_techbull_al218.pdf.
10. *Typical procedure for sealed NMR tube studies at 50 °C using 1.0 M BD_3–THF.* Freshly prepared unstabilized BD_3–THF solution was transferred to a nitrogen flushed oven-dried vessel and a calculated amount of the stabilizer was added. This solution was diluted to the required concentration by additional anhydrous THF. Solution (0.8 mL) was removed by nitrogen flushed syringe to a nitrogen flushed oven-dried NMR tube. The NMR tube was sealed and was placed in a temperature-controlled bath and heated for a fixed time then removed for evaluation by ^{11}B NMR.
11. Hydroboration of representative olefins, such as 1-octene, styrene, allyl chloride, 2-methyl-2-butene and norbornene, with NIMBA stabilized BTHF solution was carried out in THF. The procedure followed for all the olefins is the same. The procedure followed for 1-decene in THF using BD_3–THF is representative. In an oven-dried round-bottomed flask, the NIMBA stabilized BD_3–THF (1 M in THF, 7.5 mmol, commercially available from Aldrich, cat # 66,771-4) was diluted with 1.5 volumes of anhydrous THF. The diluted solution was cooled to 0 °C. 1-Decene (15 mmol) was added over 5 min. The reaction mixture was stirred with a magnetic stirrer at room temperature for 2 h. The reaction was cooled to 10 °C. A NaOH solution (3 M, 9 mL) was then added. Hydrogen peroxide (30 wt % in water, 3 mL) was then charged at 10 °C. The reaction mixture was stirred at 50 °C for 2 h and then cooled to room temperature. Ether (20 mL) was added. The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried over magnesium sulfate and filtered. Solvent was removed to record the crude yield and for GC quantification of regio-isomers 1- and 2-decanol. The clear liquid was passed through a silica gel plug (3 cm × 5 cm i.d.) with ether (150 mL) to give a quantitative yield. GC was used to quantify the ratios of the regio-isomers in the isolated product. Yield (97%) by GC; isolated 2.21 g (93%), GC was ran on HP5890 and an RTx-50 column with retention times 5.28 min (1-decanol) 4.21 (2-decanol); isomeric ratio 1-:2-decanol; 96:4 (100 °C (1 min), then 100–250 °C @ 10 °C/min; Inj. 200 °C, Det. 250 °C). (98% deuterium content by mass spectroscopy).
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