

AL-218

Technical Bulletin

New, Safer, Amine-Stabilized Borane-Tetrahydrofuran Solutions for Hydroboration and Reduction

NOTE: 1.0M BH₃-THF, whether stabilized with amines PMP (1,2,2,6,6-pentamethyl-piperidine) or NIMBA (N-isopropyl-N-methyl-tert-butylamine) or with NaBH₄, should be stored at 2-8 °C.

Product No. 65,039-0

Borane-tetrahydrofuran complex, 1.0M solution in THF, stabilized with 0.005M 1,2,2,6,6-pentamethylpiperidine (PMP). (Packaged under nitrogen, 100 mL, 800 mL in Sure/Seal™ bottles, 8.0 L, 18.0 L and larger bulk in metal cylinders.)

Product No. 65,041-2

Borane-tetrahydrofuran complex, 1.0M solution in THF, stabilized with 0.005M *N*-isopropyl-*N*-methyl-*tert*-butylamine (NIMBA). (Packaged under nitrogen, 100 mL, 800 mL in Sure/Seal™ bottles, 8.0 L, 18.0 L and larger bulk in metal cylinders.)

Borane-THF has long been a reagent of tremendous importance to synthetic organic chemists, utilized in reduction and hydroboration-oxidation as well as other transformations¹⁻². As part of our ongoing commitment to safety, Sigma-Aldrich now introduces amine-stabilized BH₃-THF solutions³. While Sigma-Aldrich continues to provide 1.0M BH₃-THF stabilized with 0.005M NaBH₄ (product no. 17,619-2), the corresponding amine-stabilized solutions have a practical advantage in that all pack sizes offered (100 mL, 800 mL, 8L, 18L, and bulk) meet Self-Accelerated Decomposition Temperature (SADT) thresholds required for safe shipment at room temperature. In contrast, as a safety precaution for 1.0M BH₃-THF stabilized with 0.005M NaBH₄, Sigma-Aldrich currently ships pack sizes above 100 mL only under cooled conditions.

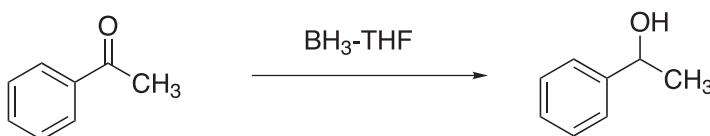
Applications

In a reduction and hydroboration comparative study, both amine-stabilized BH₃-THF solutions were demonstrated to perform at the same high level as NaBH₄-stabilized reagent (Tables 1 and 3). For asymmetric reduction of acetophenone with Me-CBS in combination with BH₃-THF, enantioselectivities were improved for amine-stabilized solutions as compared to NaBH₄-stabilized reagent (Table 2).

For applications where the amine stabilizer is to be removed by a method other than acidic work-up, users may find reagent stabilized with *N*-isopropyl-*N*-methyl-*tert*-butylamine (NIMBA) preferable due to its lower boiling point (127 °C, 760 mm Hg)⁴ and hence its simplified removal by evaporation versus PMP.

Table 1.

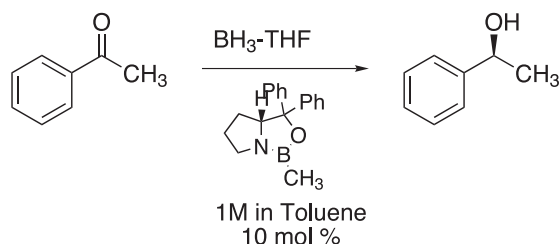
Reduction of acetophenone



Cat. No.	(1.0M BH ₃ -THF)	Stabilizer (0.005M)	GC yield (%)	Isolated yield (%)
17,619-2		NaBH ₄	98	94
65,039-0		PMP	99	95
65,041-2		NIMBA	98	94

General procedure for racemic reduction of acetophenone.

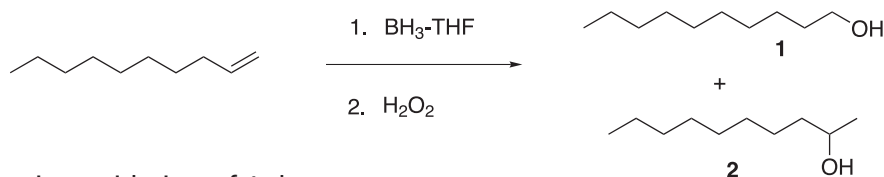
To an oven-dried round-bottom flask was added stabilized BH₃-THF (1.0M, 13.3 mmol). The solution was diluted with two volumes of anhydrous THF and cooled to 0°C. Acetophenone (10 mmol) was added over 5 min and the reaction mixture was stirred with magnetic stirrer at room temperature for 18 h. The reaction was quenched by addition of H₂O (10 mL). Ether (10 mL) was added and the mixture was washed with 3M HCl (10 mL). The organic phase was washed with H₂O (10 mL) and brine (10 mL), dried over magnesium sulfate and filtered. The solvent was removed to record the crude yield and for GC quantification. The clear liquid was passed through a silica gel plug (2 cm x 4 cm i.d.) with ether (100 mL) to yield isolated 1-phenylethanol.

Table 2. Asymmetric reduction of acetophenone using (*R*)-Me-CBS-oxazaborolidine

Cat. No. (1.0M BH ₃ -THF)	Stabilizer (0.005M)	GC yield (%)	ee (%)	Temp.(C°)
17,619-2	NaBH ₄	98	93.6	5
65,039-0	PMP	97	94.9	5
65,041-2	NIMBA	98	94.8	5
17,619-2	NaBH ₄	97	90.3	25
65,039-0	PMP	98	96.1	25
65,041-2	NIMBA	98	96.2	25

General procedure for asymmetric reduction of acetophenone with BH₃-THF and (*R*)-2-methyl-CBS-oxazaborolidine [(*R*)-MeCBS]

To an oven-dried, nitrogen-flushed flask was added BH₃-THF (1.0M, 25.0 mmol) followed by (*R*)-Me-CBS (2.5 mmol, 1.0M solution in toluene). After stirring the reaction mixture at intended temperature (either 5°C or 25°C), a solution of acetophenone (3.00 g, 25.0 mmol) in THF (50 mL) was added dropwise over a period of 75 min while maintaining the reaction at the intended temperature (either 5°C or 25°C, ± 1°C). The reaction mixture was stirred for 60 min at the intended temperature, and then quenched by addition of 2.0M HCl (24 mL). Diethyl ether (50 mL) was added and the organic phase was washed with 3 X 20 mL brine, 3 X 20 mL satd. NaHCO₃, and 3 X 20 mL brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated to give crude 1-phenylethanol, which was analyzed by chiral GC to determine optical purity (Beta Dex 120 column; injector 250°C; detector 250°C, oven 100°C isothermal, run time 60 min; sample preparation included dilution of sample in dichloromethane).

**Table 3.** Hydroboration-oxidation of 1-decene

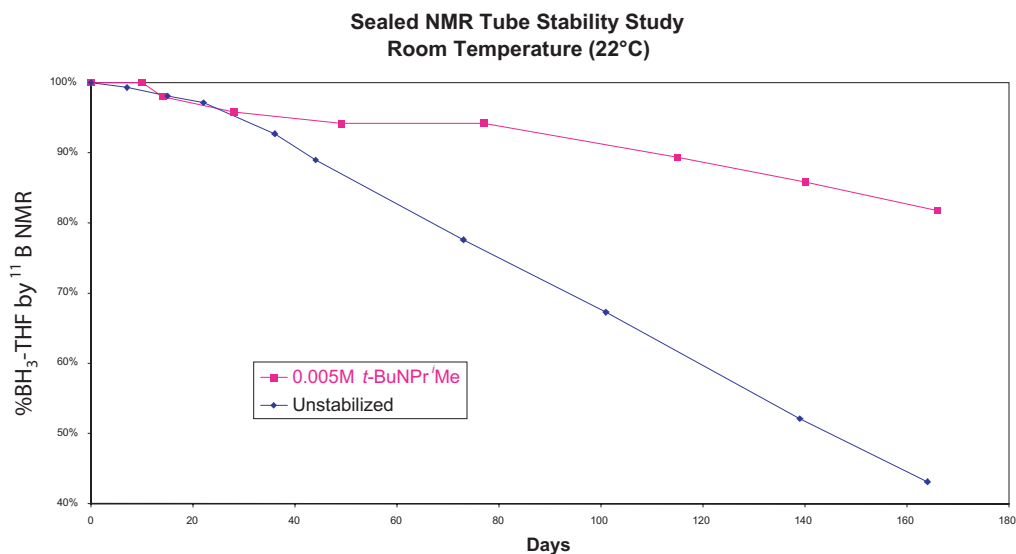
Cat. No. (1.0M BH ₃ -THF)	Stabilizer (0.005M)	GC yield (%)	Isolated Yield (%)	Regioselectivity (1:2)
17,619-2	NaBH ₄	96	92	94:6
65,039-0	PMP	94	90	93:7
65,041-2	NIMBA	97	93	94:6

General procedure for hydroboration-oxidation of 1-decene.

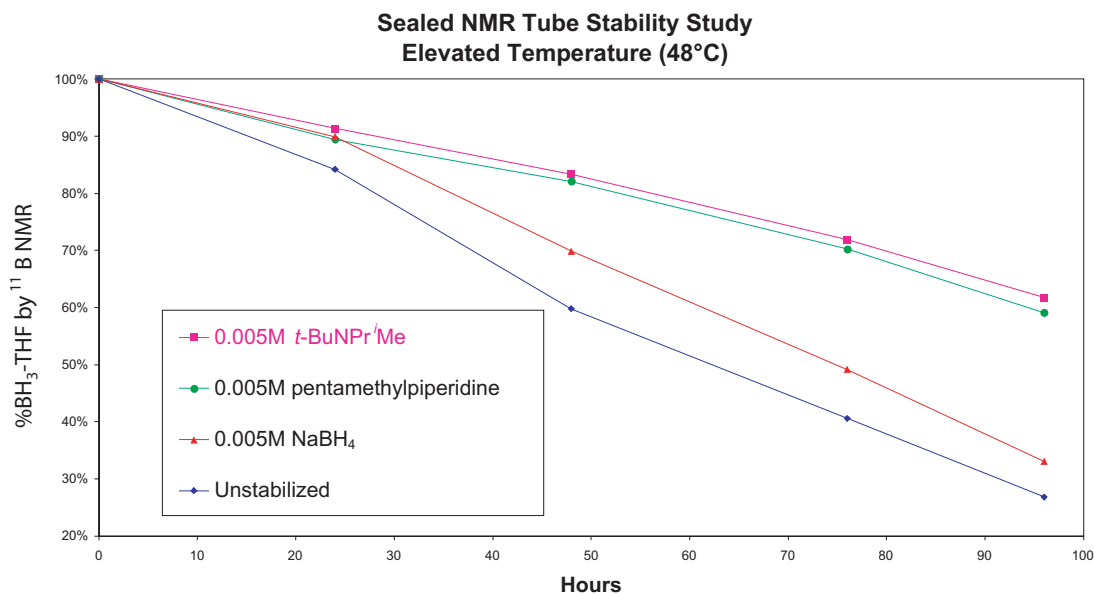
To an oven-dried round-bottom flask was added stabilized BH₃-THF (1.0M, 7.5 mmol). The solution was diluted with 1.5 volumes of anhydrous THF and cooled to 0°C. 1-Decene (15 mmol) was added over 5 min and the reaction mixture was stirred with magnetic stirrer at room temperature for 2 h. The reaction was cooled to 10°C followed by addition of NaOH solution (3M, 9 mL). Hydrogen peroxide (30 wt. % in water, 3 mL) was added 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 and the organic phase was washed with H₂O (20 mL), brine (20 mL), dried over magnesium sulfate and filtered. Solvent was removed to record the crude yield. The clear liquid was passed through a silica gel plug (3 cm x 5 cm i.d.) with ether (150 mL) to give isolated yield. Ratios of regioisomers 1- and 2-decanol were determined by GC analysis.

Stability and Storage

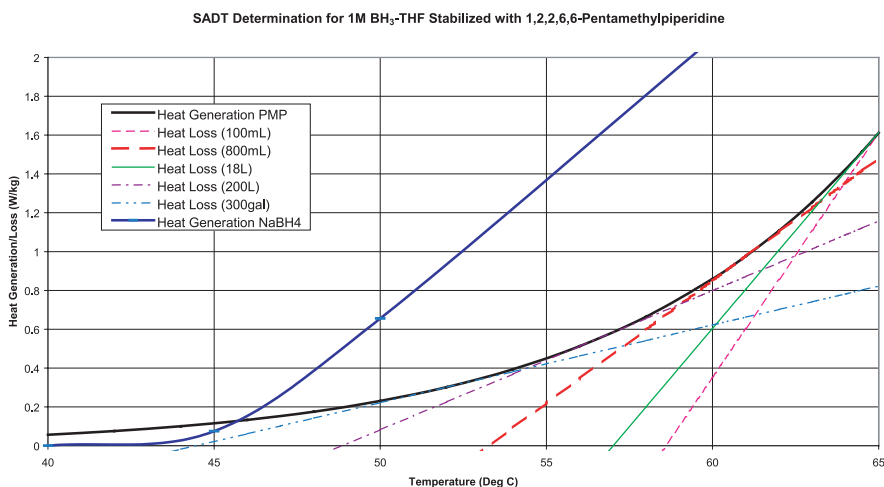
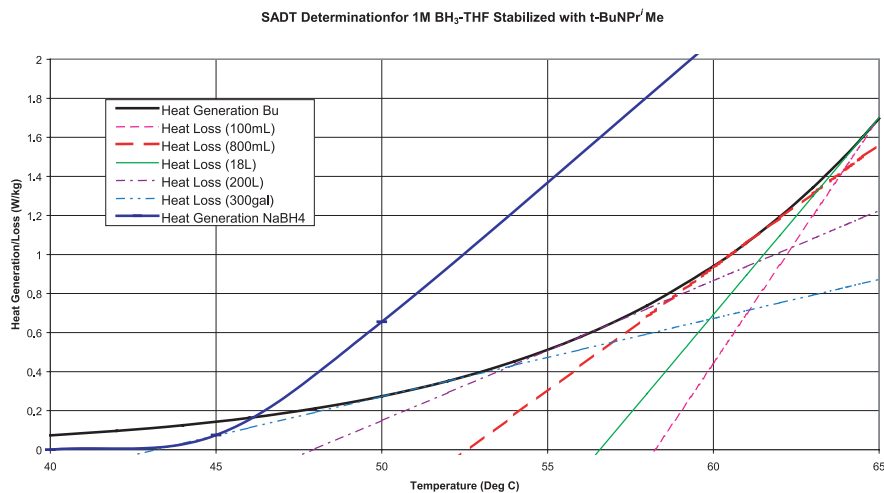
1.0M BH_3 -THF, whether stabilized with amines PMP (1,2,2,6,6-pentamethyl-piperidine) or NIMBA (*N*-isopropyl-*N*-methyl-*tert*-butylamine) or with NaBH_4 , should be stored at 2-8 °C. Stability studies do not indicate significant degradation/impurities when stored at 2-8 °C for 6 months. However, when stored at room temperature, degradation varies with stabilizer and 1.0M BH_3 -THF exhibits superior stability when either PMP or NIMBA are used as stabilizers versus 1.0M BH_3 -THF unstabilized or stabilized with 0.005M NaBH_4 .



These amine-stabilized 1.0M BH_3 -THF solutions also showed considerable stability over unstabilized or stabilized with 0.005M NaBH_4 1.0M BH_3 -THF at higher temperatures.



Most importantly the 1.0M BH_3 -THF, stabilized with either PMP or NIMBA, shows higher critical ambient temperatures resulting in higher SADT. The SADT is a measure of the lowest temperature at which a self-accelerating decomposition may occur. The SADT accounts for the combined effect of the ambient temperature, decomposition kinetics, package size and the heat transfer properties of the material and its packaging. For safe shipment of goods at room temperature, the United Nations (UN) and United States Department of Transportation (DOT) requirements are that SADT must be > 50 °C.⁵ Both amine-stabilized 1.0M BH_3 -THF solutions showed SADT temperatures above 50°C.



In contrast, a similar test for 1.0M BH₃-THF stabilized with 0.005M NaBH₄ gave critical ambient temperatures around 42 °C for various containers, except the 100 mL pack size. Accordingly, the SADT for pack sizes above 100 mL is 45 °C. In other words, this material is capable of self-accelerating decomposition from 40°C under low heat loss, low thermal inertia conditions, making pack sizes above 100 mL unacceptable for room temperature shipping, under United Nations (UN) and DOT regulations.

Toxicity and Handling

Contact with the product may cause irritation. Avoid prolonged or repeated exposure. Handle and store under inert gas. This product may develop pressure – open carefully. For safe handling procedures refer to Aldrich Technical Bulletin AL-134 "Handling air-sensitive reagents."

References

- (1) Brown, H. C.; Zaidlewicz, M. *Organic Synthesis via Boranes*; Aldrich Chemical: Milwaukee, 2001; Vol. 2. Product Number Z40,095-5. (2) Zaidlewicz, M.; Brown, H. C. *Encyclopedia or Reagents for Organic Synthesis*; Paquette, L. A., Ed.; J. Wiley: New York, 1995; vol. 1, p 638. (3) Josyula, K. V. B.; Potyen, M.; Gao, P.; Hewitt, C. (4) Josyula, K. V. B.; Potyen, M.; Schuck, M.; Thomas, R.; Lu, S.; Gao, P. Hewitt, C. Presented at ACS Great Lakes Regional Meeting, Peoria, IL, PR-176, 2004 (5) a) Code of Federal Regulations 49 CFR 173.21(f), 10-1-03 edition, US Government Printing Office, p417. A link to this reference can be found at http://www.access.gpo.gov/nara/cfr/waisidx_03/49cfr173_03.html. b) SADT plots were generated according to UN Test Method H2, *Recommendations on the Transport of Dangerous Goods, Manual and Test Criteria*, Fourth revised edition, United Nations, New York and Geneva, 2003, p 303.