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Technical Notes

Diethylanilineborane: A Practical, Safe, and Consistent-Quality Borane Source for the Large-Scale Enantioselective Reduction of a Ketone Intermediate in the Synthesis of (*R*,*R*)-Formoterol

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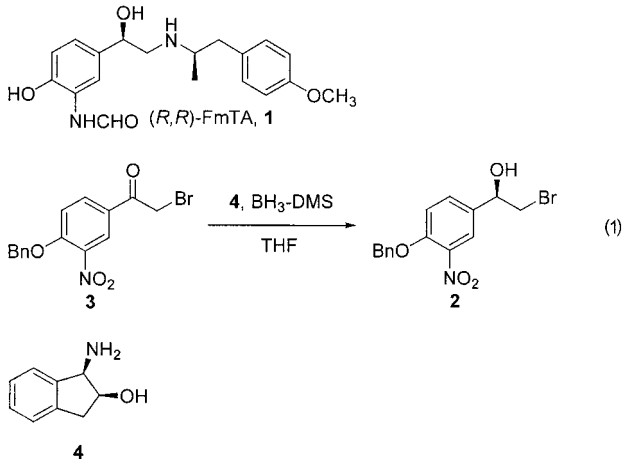
Abstract:

The development of a process for the use of *N*,*N*-diethylaniline−borane (DEANB) as a borane source for the enantioselective preparation of a key intermediate in the synthesis of (*R*,*R*)-formoterol L-tartrate, bromohydrin 2, from ketone 3 on kilogram scale is described. DEANB was found to be a more practical, safer, and higher-quality reagent when compared to other more conventional borane sources: borane−THF and borane−DMS.

Formoterol (Foradil) **1** is a long-acting β_2-agonist used as a bronchodilator in the therapy of asthma and chronic bronchitis.[1] The (*R*,*R*)-enantiomer has been shown to be more active than the racemic mixture and the other stereoisomers (*R*,*S*; *S*,*R*; *S*,*S*) of formoterol.[2−5] Continued interest in the development of the (*R*,*R*)-enantiomer[6] required the ability to efficiently prepare the key intermediate **2** in high enantiomeric purity on pilot-plant scale. The process mandated generation of the stereogenic benzylic carbinol center via an oxazaborolidine-catalyzed reduction of the corresponding ketone **3** (eq 1).[7]



(1)

Lab-Scale Synthesis. In the lab, the enantioselective reduction shown in eq 1 was efficiently conducted using BH_3−DMS and **4**. The reduction was studied in depth by varying the amounts of aminoindanol **4** and BH_3−DMS. As shown in Table 1, the enantiomeric excess of **2** decreased as the level of **4** decreased. Employing a stoichiometric amount of **4** provided **2** in 95:5 er (entry 1). The enantioselectivity was determined on the crude reaction mixture after quenching with acetone, but prior to workup and purification. The enantiomeric purity remained essentially unchanged as the loading of **4** was decreased to 1 mol % (entries 2−5). Similarly, varying the amount of BH_3−DMS did not have an effect on the enantiomeric purity of **2** (Table 2), until substoichiometric amounts of hydride were added. Using 0.7

Table 1. **Effect of the Loading of 4 on the Enantioselectivity of the Reduction of 3**[a]

entry	**4** (equiv)	er of **2** (*R*:*S*)[b]
1	1.0	95:5
2	0.2	95:5
3	0.1	95:5
4	0.05	95:5
5	0.01	94:6

[a] Conditions: 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

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Table 2. **Effect of the Amount of BH_3−DMS on the Enantioselectivity of the Reduction of 3[a]**

entry	BH_3−DMS (equiv)	er of **2** (*R*:*S*)[b]
1	2.0	95:5
2	1.2	95:5
3	1.0	94:6
4	0.7	95:5
5	0.3	87:13

[a] Conditions: 5 mol % **4**, 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

Table 3. **Effect of Temperature on the Reduction of 3 with Various Sources of Borane[a]**

entry	borane reagent	temperature (°C)	er of **2** (*R*:*S*)[b]
1	BH_3−DMS	40	89:11
2		**25**	**95:5**
3		0	91:9
4		−10	66:34
5	BH_3−THF	25	95:5
6		**0**	**97:3**
7		−10	94:6

[a] Conditions: 5 mol % **4**, 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

equiv of BH_3−DMS or greater resulted in consistently high enantiomeric purities (entries 1−4). However, with 0.3 equiv of BH_3−DMS (0.9 equiv of hydride), the enantiomeric purity plummeted to 87:13 er (entry 5).

Kilogram-Scale Development. During development of the process, consideration of the stench associated with DMS, the requirement for efficient scrubbing of vented gases during the process, and the additional time and costs needed for proper disposal of distillates, mother liquors, and washes laced with DMS dictated that the use of BH_3−DMS for large-scale synthesis be prohibited. A logical alternative reagent, BH_3−THF, was chosen. In the lab, BH_3−THF reproduced results the same as those for BH_3−DMS. An additional temperature study comparing the two reagents showed that BH_3−THF provided **2** in higher enantiomeric purity than BH_3−DMS (Table 3). The optimum enantioselectivity for BH_3−THF was 97:3 er at 0 °C, while BH_3−DMS gave an optimum selectivity of 95:5 er at 25 °C. Comparison of all data demonstrated that BH_3−THF would be the preferred reagent for large-scale synthesis.

The use of BH_3−THF on large scale required an evaluation of the reagent quality of various suppliers. Two vendors were identified: Aldrich Chemical Co. and Callery Chemical Co. Table 4 shows the molarity of various lots of BH_3−THF[8] and the enantioselectivity of the reduction in eq 1 based on various lots from the two vendors. Under our reaction conditions, the BH_3−THF purchased from Aldrich provided superior enantioselecitivities, but could not be supplied in a consistent and reliable concentration (entries 1 and 2). Callery, however, supplied the reagent at a consistent and reliable concentration (entries 3 and 4). However, the enantioselectivity of the reduction was inferior when compared to the results obtained from the Aldrich-supplied reagent. The cause for the lower enantioselectivies is not well understood.[9] The reagents that titrated to lower molarity were of additional concern due to formation of *n*-butoxyborane upon decomposition of THF by BH_3.[10] The presence of 1-butanol after quenching could jeopardize the isolation of **2**.

(8) Titrations were performed by volumetric measurement of the gas evolved upon addition of a standardized solution of phosphoric acid in methanol.

Table 4. **Activity and Enantioselectivity of the Reduction of 3 by BH_3−THF as Supplied from Various Vendors**

			molarity		
entry	vendor	lot size (L)	nom.	titr.	er **2** (*R*:*S*)
1	Aldrich	18	1.0	0.5	96:4
2	Aldrich	18	1.0	0.71	96:4
3	Callery	18	1.0	1.0	91:9
4	Callery	18	1.0	1.0	91:9

[a] Conditions: 5 mol % **4**, 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

Table 5. **Effect of Temperature on the Reduction of 3 by DEANB**

borane reagent	temperature (°C)	er of **2** (*R*:*S*)
DEANB	25	94:6
	0	**95:5**
	−10	92:8

[a] Conditions: 5 mol % **4**, 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

Due to the inconsistencies in the quality of BH_3−THF when purchased on large scale, an alternative borane reagent was investigated: BH_3−diethylaniline (DEANB). In lab-scale experiments, DEANB provided **2** in equal yield and comparable enantioselectivity when compared to BH_3−DMS and BH_3−THF. A reaction temperature study using DEANB showed that the optimal selectivity was achieved at 0 °C (Table 5). At optimal reaction temperature, DEANB provided **2** in 95:5 er, while BH_3−DMS and BH_3−THF generated **3** in 95:5 er at 25 °C and 97:3 er at 0 °C (vide supra), respectively. Although DEANB gave the product in slightly diminished selectivity, isolation of **2** by crystallization consistently provided the product in >99:1 er.

DEANB was purchased as a neat liquid at a concentration of 5.6 M, and had several advantages over BH_3−THF and BH_3−DMS: (1) no necessity for refrigeration of the reagent (vs BH_3−THF), (2) no odor and therefore no need to scrub the gas stream (vs BH_3−DMS), (3) consistent enantioselectivities (Table 5), (4) consistent reagent molarities, (5) better volume-productivity (vs BH_3−THF) due to the higher concentration, and (6) less pyrophoricity. BH_3−THF requires refrigeration during storage due to reductive ring-opening

(9) One explanation could be the effect of stabilizers added to the reagent. BH_3−THF supplied by Callery contains 0.5−1.0% $NaBH_4$ as a stabilizer; the Aldrich-brand reagent contains <0.5% $NaBH_4$. When 1.5% $NaBH_4$ was added to the Aldrich-brand reagent, the enantioselectivity diminished from 96:4 er to 95:5 er. This decrease, although significant, did not fully account for the lower er obtained with the Callery-brand reagent.

(10) A mode of deacitivation of BH_3−THF is by conversion to *n*-butoxyborane. Upon quenching, *n*-butanol is formed.

Table 6. **Scalability of DEANB on the Reduction of 3**[a]

entry	scale	vendor	er of **2** (*R*:*S*)[b]
1	50 g	Aldrich	95:5
2	100 g	Callery	94:6
3	135 g	Callery	95:5
4	2.3 kg	Callery	94:6

[a] Conditions: 5 mol % **4**, 25 °C, addition of **3** over 1 h. [b] Enantiomeric ratios were determined by chiral HPLC (Chiracel OJ, 70:30 hexane:IPA, 1.0 mL/min) on the crude reaction mixture, prior to purification.

Table 7. **Removal of Diethylaniline (DEA)**

entry	sample	DEA (mg/mL)
1	H_2SO_4 wash (1 equiv)	239
2	H_2SO_4 wash (1 equiv)	2.9
3	20% (w/w) NaCl	0.06
4	mother liquor	0.08
5	final product	0.00

of THF by borane and is available at a maximum concentration of 2 M on large scale; DEANB is a neat liquid and does not readily undergo decomposition during storage at ambient temperatures. DEANB is readily manufactured with consistent quality; lots purchased from Aldrich and Callery with nominal concentrations of 5.6 M titrated to a concentration of 5.6 and 5.5 M, respectively. Additionally, each lot of reagent provided **2** in identical enantiomeric purities: 95:5 er. A study on the scalability of the reagent was done, as shown in Table 6. On a scale from 50 g to 2.3 kg, the enantioselectivity remained consistent, and the chemical yields were >98% in solution. The desired product could be isolated from the reaction mixture by crystallization. Typically, a reaction mixture containing **2** in 95:5 er and 98% solution yield reproducibly provided the isolated material in >99:1 er, >98% chemical purity, and 80−85% yield. Having demonstrated the advantages of DEANB as a reagent for the reduction in eq 1, a final issue to address in the process was removal of diethylaniline from the reaction mixture.

The procedure for removal of diethylaniline from the reaction mixture after quenching the borane was performed with 1 M aqueous sulfuric acid. As shown in Table 7, the amount of diethylaniline in the aqueous washes, mother liquor, and product was monitored during the workup. After washing the quenched reaction mixture with 1 equiv of the aqueous H_2SO_4 solution, diethylaniline was present in the aqueous phase at a concentration of 239 mg/mL (entry 1). A second wash contained 2.9 mg/mL of the amine base, and a subsequent wash with 20% (w/w) aqueous NaCl contained only 0.06 mg/mL (entries 2 and 3). After isolation of **3**, the mother liquor contained 0.08 mg/mL of diethylaniline, and none of the amine could be detected in the product (entries 4 and 5).

A detailed description of the process demonstrated on 2.3 kg of **3** is as follows: A 50-L Ace reactor was charged with 2.3 kg of **3**, 18.4 kg of THF was added, and the mixture was agitated until a homogeneous solution was obtained. A separate 50-L Buchi reactor was charged with 50 g of aminoindanol **4**, followed by 5.75 kg of THF. To the stirred solution at 5−20 °C, 0.81 kg of DEANB was added. The contents of the reactor were mixed for 30 min at 5−15 °C. The temperature was adjusted to 0−5 °C, and the solution of **3** was added over 2 h. After the addition was complete, 1.8 kg of acetone was added while maintaining the temperature at 0−15 °C. The solution was warmed to 20−25 °C and mixed for 30 min. The solution was concentrated to approximately 7 L by vacuum distillation. After the addition of 13.8 kg of toluene, the solution was washed with 10 wt % aqueous sulfuric acid (2 × 6.9 kg) and 2.8 kg of DI water. The organic phase was concentrated to approximately 7 L via vacuum distillation, and cooled to 25 °C over 30 min. After the addition of 5.3 g of seeds of **2**, the mixture was stirred for 30 min and then cooled to 19 °C over 1 h. The slurry was agitated for 1 h, followed by the addition of 3.2 kg of heptane and stirring at 19 °C for 1 h. The slurry was filtered, and the wet-cake was washed with heptane and dried in vacuo to give 1.84 kg of **2** (80% yield, 99:1 er).

Conclusions

We have demonstrated the use of BH_3−diethylaniline (DEANB) as a reagent of reliable quality for the enantioselective reduction of **3** on large scale. While BH_3−DMS and BH_3−THF were good reagents for lab-scale synthesis, the chemical hazards and inconsistent reagent quality associated with these reagents, respectively, disqualified their use on large scale. DEANB, purchased as a neat liquid, provided **2** in consistently high yield (80−85%) and enantiomeric purity (94:6 to 95:5 er, crude reaction mixture) on scales ranging from 50 g to 2.3 kg. The results from numerous kilogram batches have continued to prove that DEANB is a superior source of borane for large-scale applications. This enantioselective reduction has been demonstrated several times in the pilot plant to consistently provide **2** in good yield and high enantiomeric purity during the production of (*R*,*R*)-formoterol L-tartrate. DEANB should find application in the chemical process community as a logical, practical and safe alternative to other borane sources.

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