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for the Preparation
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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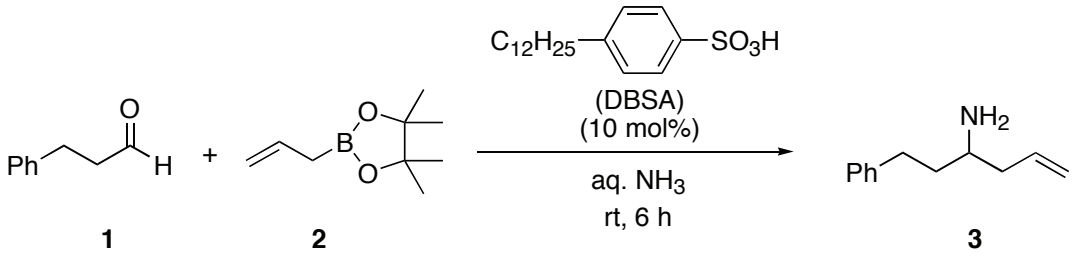
ALLYLBORONATION OF IMINES: 1-PHENYLHEX-5-EN-3-AMINE



Submitted by Masaharu Sugiura, Keiichi Hirano, and Shū Kobayashi.[1]
Checked by Nai-Wen Tseng and Mark Lautens.

1. Procedure

Caution! The reaction should be conducted in a well-ventilated hood. An oven-dried, 250-mL, two-necked, round-bottomed flask is charged with dodecylbenzenesulfonic acid (1.307 g, 4.0 mmol) (Note 1), flushed with argon, and equipped with a magnetic stirring bar, a rubber septum, and an argon inlet. The flask is charged with 80 mL of 28% aqueous ammonia (Note 2) by syringe. After the gas evolution ceases, the mixture is stirred at 23–25 °C to give a clear solution, then cooled to 0 °C in an ice-water bath. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**) (8.120 g, 9.0 mL, 48.3 mmol) (Note 3) is added dropwise over 5 min via a syringe (Note 4) and the mixture is stirred at 23–25 °C for 30 min. 3-Phenylpropionaldehyde (**1**) (5.328 g, 5.3 mL, 39.7 mmol) (Note 5) is added dropwise via a syringe over 5 min at 23–25 °C. The slurry mixture is vigorously stirred at 23–25 °C for 6 h (Note 6) and transferred to a 1-L separatory funnel with water (100 mL) and saturated aqueous NaCl solution (200 mL). The aqueous layer is extracted three times with diethyl ether (200, 150, and 150 mL), and the combined organic layers are washed with saturated aqueous NaCl solution (200 mL), dried over anhydrous sodium carbonate (Na_2CO_3), filtered, and concentrated under reduced pressure to afford crude amine **3** as a yellow oil (Note 8). The crude material is chromatographed on a 5.5 x 45 cm column containing 300 g of silica gel (Note 9). A mixture of hexane/isopropyl amine (20/1) is used as the eluent. Fractions (27 mL each) are collected in 30-mL test tubes (Note 10). Fractions containing the product are evaporated under reduced pressure (30 °C, 200 mmHg) to afford the amine as yellow oil. In

order to completely remove the pinacol, the amine is diluted with diethyl ether (200 mL) and extracted three times with 1 M hydrochloric acid (3 x 50 mL). The combined aqueous layers are washed twice with diethyl ether (2 x 100 mL), carefully basified with 6 M sodium hydroxide (60 mL) (Note 7), and extracted three times with dichloromethane (200, 150, and 150 mL). The combined organic layers are dried over anhydrous sodium carbonate (Na_2CO_3), filtered, concentrated under reduced pressure (30 °C, 200 mmHg) and dried under vacuum (approximately 0.2 mmHg, 15 min) to afford 6.680 g of **3** (96%) as yellow oil (Note 11).

2. Notes

1. Dodecylbenzenesulfonic acid (soft type) (>90.0%) was purchased from Tokyo Kasei Kogyo Co., Ltd. or TCI America, and used without purification. This viscous liquid material was measured directly in the reaction flask using a 5-mL pipette.

2. Aqueous ammonia solution (25.0-27.9%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received. The checkers used aqueous ammonia solution (28.0-30.0%) purchased from Aldrich Chemical Company, Inc.

3. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**) (95%) was purchased from Aldrich Chemical Company, Inc. This material included white precipitates. Therefore, it was filtered with diethyl ether, evaporated (30 °C, 200 mmHg), and distilled (72-73 °C, 27 mmHg, the boiling point is uncorrected) prior to use.

4. On addition of **2**, colorless precipitates were formed to give a slurry mixture.

5. 3-Phenylpropionaldehyde (**1**) (>90% GC) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used after distillation. The checkers purchased this reagent from Aldrich Chemical Company, Inc.

6. As the reaction progressed, the precipitates gradually dissolved to give a cloudy solution. The reaction could be monitored by TLC analysis on Merck silica gel 60 F_{254} plates and visualization with UV and phosphomolybdic acid [sodium phosphomolybdate hydrate (9.7 g) in 85% phosphoric acid (6.0 mL), concentrated sulfuric acid (20 mL), and water (400 mL)]. The checkers used 5% phosphomolybidic acid in ethanol as the TLC indicator. Disappearance of **1** was observed within 30 min. Compound **1** has R_f = 0.68 with hexane/ethyl acetate (3/1) as eluent (UV absorption,

gray spot). Compound **3** has R_f = 0.13 with hexane/ethyl acetate (1/1) as eluent and R_f = 0.63 with hexane/isopropyl amine (10/1) as eluent (UV absorption, white spot). Pinacol has R_f = 0.30 with hexane/ethyl acetate (1/1) as eluent and R_f = 0.33 with hexane/isopropyl amine (10/1) as eluent (UV inactive, blue spot).

7. After addition of sodium hydroxide, the pH was checked by a pH-test paper to be approximately 9.

8. The crude material was a mixture of **3** and pinacol (ca. 10/1 molar ratio). Distillation under reduced pressure (88 °C, 3 mmHg) gave almost pure **3**, but could not separate pinacol completely.

9. Silica gel 60 70-230 mesh ASTM (Merck Ltd.) was used. Checkers used Silica gel 60 40-63 mm (EMD Chemicals, Inc.).

10. The column fractions were checked by TLC analysis on Merck silica gel 60 F_{254} plates with hexane/isopropyl amine (20/1) as eluent and visualization with UV and phosphomolybdic acid. R_f values are given in Note 6.

11. The physical properties of **3** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (brs, 2 H), 1.61 (dddd, *J* = 13.6, 10.1, 7.9, 5.7 Hz, 1 H), 1.76 (dddd, *J* = 13.5, 10.3, 6.2, 5.4 Hz, 1 H), 2.03 (dddt, *J* = 13.8, 7.9, 7.9, 0.9 Hz, 1 H), 2.27 (dddt, *J* = 13.7, 6.3, 4.8, 1.4 Hz, 1 H), 2.64 (ddd, *J* = 13.6, 10.1, 6.2 Hz, 1 H), 2.75 (ddd, *J* = 13.7, 10.2, 5.7 Hz, 1 H), 2.82 (tt, *J* = 7.9, 4.6 Hz, 1 H), 5.09 (dm, *J* = 10.0 Hz, 1 H), 5.10 (dm, *J* = 17.2 Hz, 1H), 5.79 (dddd, *J* = 17.2, 10.0, 7.9, 6.4 Hz, 1 H), 7.15–7.21 (m, 3 H), 7.25–7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.6, 39.4, 42.7, 50.1, 117.4, 125.7, 128.31, 128.33, 135.6, 142.2; HR-ESIMS calcd for $C_{12}H_{18}N$ ($M+H^+$) 176.1439, found 176.1435; Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.92; H, 9.77; N, 7.89.

Safety and Waste Disposal Information

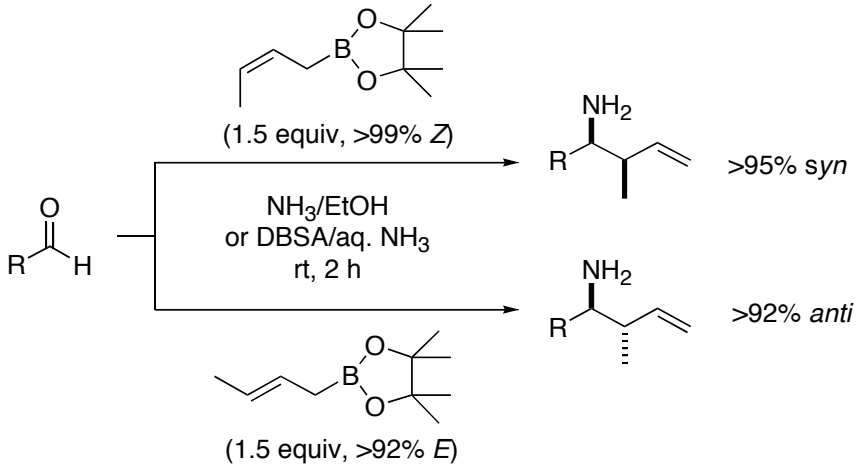
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Addition of allylmetals to C=N double bonds is a useful synthetic method for formation of homoallylic amine derivatives.[2] However, in order

to obtain synthetically versatile homoallylic primary amines, removal of substituents on the nitrogen is often necessary. To address this issue, hydrolytically labile *N*-silyl, *N*-boryl, or *N*-metalloimines have been utilized frequently as precursors to the primary amines; however, pre-formation of those imines are required. In contrast, the method in this procedure is based on in situ formation of ammonia-derived imines and subsequent chemoselective allylation.[4,5] Thus, homoallylic primary amines are directly obtained from the three components without incorporation and cleavage of *N*-substituents. Additionally, when (*E*)- and (*Z*)-crotylboronates are used, *anti*- and *syn*-crotylated products can be obtained with high diastereoselectivities, respectively (Scheme 1).

Scheme 1.



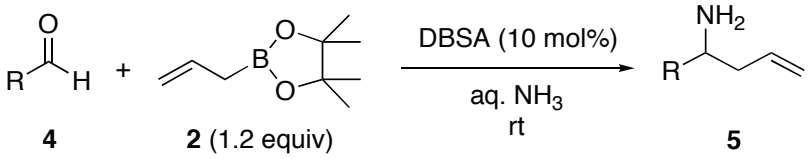
R = Ph, *p*-$NO_2C_6H_4$, CO_2H, 2-pyridyl etc.

Use of ammonia as the nitrogen source is key in this process. In contrast to ammonia, primary amines scarcely undergo the reaction, and hence highly selective formation of homoallylic primary amines (suppression of over-reaction of the products) has been attained. Although ammonia in ethanol was utilized previously,[4] use of aqueous ammonia in the presence of DBSA has made the reaction more practical.[5] A variety of additives were examined for the reaction of 3-phenylpropionaldehyde (**1**) with allylboronate (**2**) in aqueous ammonia. Among them, DBSA was found to be the best, whereas lauric acid, sodium dodecyl sulfate, and sodium dodecylbenzenesulfonate were effective as well. In the absence of any additive, the yield of **3** and the chemoselectivity of the reaction (formation of **3** vs the corresponding homoallylic alcohol) were low. The hydrophobic alkyl chain of DBSA plays an important role, since *p*-toluenesulfonic acid

showed much lower activity. In reactions performed with DBSA, a variety of aliphatic, aromatic, heteroaromatic, and a,b-unsaturated aldehydes afford the corresponding homoallylic primary amines in good to excellent yields (Table 1).[5]

However, addition of DBSA is not always necessary; hydrophilic carbonyl compounds such as a-oxo carboxylic acids and hydroxy aldehydes or ketones, including carbohydrates, were found to undergo the reactions smoothly with high selectivity as shown in Schemes 2 and 3.[6]

Table 1. Amine Formation

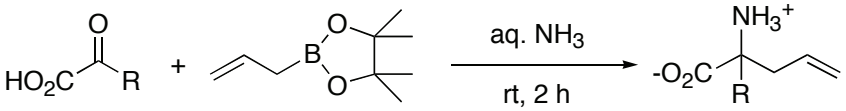


4 **2** (1.2 equiv) **5**

entry	R (**4**)	time/h	%yield of **5**[a]
1	Ph	6	61
2	*p*-$NO_2C_6H_4$	6	60
3	*p*-$MeOC_6H_4$	6	60
4	*o*-HOC_6H_4	6	75
5	2-Pyridyl	6	88
6	3-Pyridyl	2	85
7	4-Pyridyl	2	83
8	2-Thienyl	6	60
9	3-Thienyl	2	95
10	2-Furyl	2	53
11	3-Furyl	2	93
12	(*E*)-PhCH=CH	2	78
13	*c*-C_6H_{11}	6	68
14	*n*-C_5H_{11}	2	49

[a] Isolated yields.

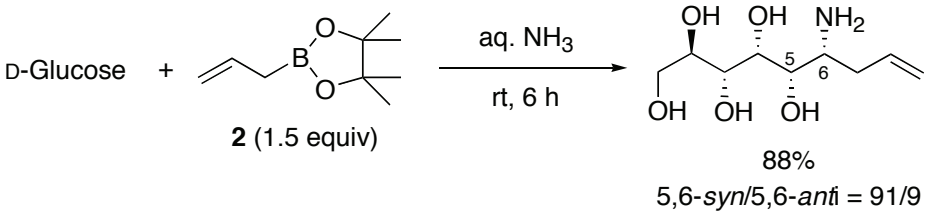
Scheme 2.



2 (1.5 equiv) 76-91%

R = H, Me, $(CH_2)_2CO_2H$, Bn, Ph

Scheme 3.



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6. Unpublished results.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dodecylbenzenesulfonic acid; (27176-87-0)
2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 1,3,2-Dioxaborolane, 4,4,5,5-tetramethyl-2-(2-propenyl)-; (72824-04-5)
3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0)

NT-06-26-1H_400

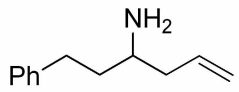
Data Collected on:
nmr2-mercury400
Archive directory:
/export/home/ntseng/vnmrsys/data
Sample directory:

File: NT-06-26-1H_400

Pulse Sequence: s2pul
Solvent: CDCl3

Temp. 25.0 C / 298.1 K
Operator: ntseng

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.664 sec
Width 7199.4 Hz
16 repetitions
OBSERVE H1, 399.7532506 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min



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