## Regiospecific Deuterium Incorporation via the Reduction of Tosylhydrazones to the Corresponding Methylene Derivatives

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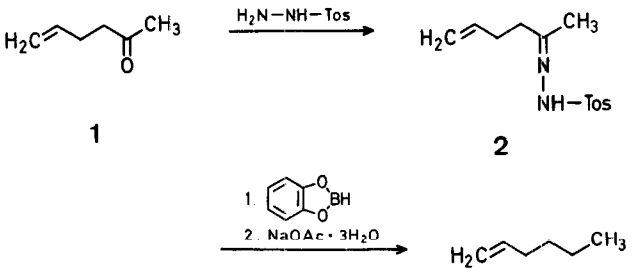
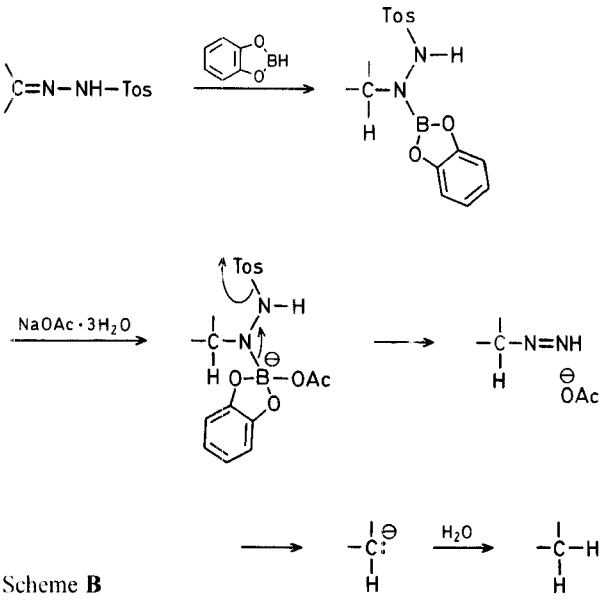
The reduction of tosylhydrazones by boron hydride reagents provides a convenient and mild alternative to the Wolff-Kishner and Clemmensen reductions[2,3]. We recently reported that the use of catecholborane (1,3,2-benzodioxaborole) in tosylhydrazone reductions offers significant advantages over the traditional methods[2]. Using catecholborane, the reductions can be carried out in any of the common, aprotic, organic solvents; furthermore, tosylhydrazones are selectively reduced in the presence of nearly all organic functional groups[4]. As an example, 5-oxo-1-hexene (**1**) can be converted to 1-hexene (**3**) in nearly quantitative yields in chloroform via the reduction of the corresponding tosylhydrazone (**2**) (Scheme **A**).




Scheme **A**

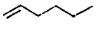
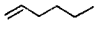
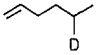
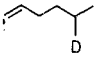
The available data support a mechanism for the reduction which proceeds via decomposition of the corresponding diazene in Scheme **B**[2,3]. The formation of a diazene is consistent with the known propensity of boron reagents to eliminate a boron atom when the boron is adjacent to a good leaving group (tosyl in this instance)[5]. In the proposed mechanism, the second hydrogen is delivered as a proton (either from the diazene or from the hydrate) rather than a hydride and thus the reaction held promise as a convenient method for regiospecific isotopic labelling[6].




Scheme **B**

A series of experiments were carried out in which 5-oxo-1-hexene (**1**) was reduced to the corresponding 1-hexene (**3**) [via the corresponding tosylhydrazone (**2**)] utilizing various combinations of deuterated reagents. The results are summarized in Table 1 and they clearly demonstrate that the last proton (deuteron) is delivered from the most acidic source, $H_2O$ or $D_2O$[7]. This fact makes possible a simple isotopic labelling technique in which the deuterium is delivered via the most readily available sources, namely, the corresponding oxide.

**Table 1.** The Reduction of the Tosylhydrazone of 5-Oxo-1-hexene with the Undeuterated and Various Deuterated Reagents[a]

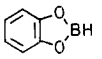
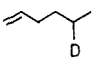
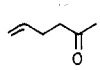
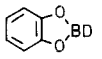
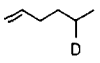
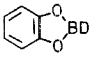
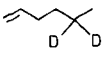
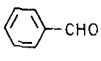
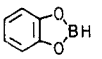
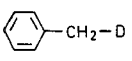
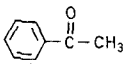
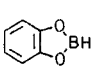
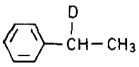
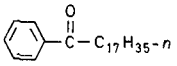
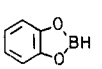
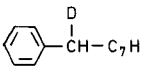
| Solvent | Base | Product[b] | Yield [%][c] |
|---|---|---|---|
| $CHCl_3$ | NaOAc · 3 $H_2O$ |  | 97 |
| $CDCl_3$ | NaOAc · 3 $H_2O$ |  | 97 |
| $CHCl_3$ | NaOAc · 3 $D_2O$ |  | 97 |
| $CDCl_3$ | NaOAc · 3 $D_2O$ |  | 97 |

[a] The reactions were performed by dissolving the tosylhydrazone of 5-oxo-1-hexene (2.5 mmol) in $CHCl_3$ [$CDCl_3$] (6 ml) at 0° and then adding catecholborane (3.75 mmol). The solution was allowed to react for one hour and then NaOAc·3$H_2O$ [NaOAc·3$D_2O$] (15 mmol) was added and the mixture was stirred at room temperature overnight.

[b] Isolated by preparative G.L.P.C. (conditions: see procedure for 1-hexene) and characterized by N.M.R.

[c] Determined by G.L.P.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 25°).

**Table 2.** The Reduction of the Various Tosylhydrazones with Labelled Reagents

| Carbonyl Compound[a] | Borane | Base | Product[b] | Yield [%][c] |
|---|---|---|---|---|
|  |  | $NaOAc \cdot 3D_2O$ |  | 97 |
|  |  | $NaOAc \cdot 3H_2O$ |  | 97 |
|  |  | $NaOAc \cdot 3D_2O$ |  | 95 |
|  |  | $NaOAc(CH_3OD)$ |  | 87 |
|  |  | $NaOAc(CH_3OD)$ |  | 70 |
|  |  | $NaOAc(CH_3OD)$ |  | 82 (73)[d] |

[a] The corresponding tosylhydrazones were reduced.
[b] Isolated by preparative G.L.P.C. and characterized by N.M.R.
[c] Determined by G.P.L.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 60°).
[d] Value in brackets is for isolated product.

Double labelling of substrates is also possible using the readily obtainable deuterated catecholborane [1,3,2-benzodioxaborole-2-*d*]. The results of our experiments are summarized in Table 2 and demonstrate the utility of the technique.

**Materials:**

The *tosylhydrazones* of 5-oxo-1-hexene (m.p. 96–97°), benzaldehyde (m.p. 129–130°), acetophenone (m.p. 141–143°), and stearophenone (m.p. 78–80°) were prepared according to a published procedure[2, 3].

*Catecholborane* was purchased from Aldrich Chemical Company and was also prepared via Brown's procedure[8].

*Sodium acetate-deuterium oxide* complex (assumed to be the tri "hydrate" form) was prepared by dissolving anhydrous sodium acetate in a slight excess of deuterium oxide and the crystalline product collected by filtration and dried.

*1,3,2-Benzodioxaborole-2-d* (deuterated catecholborane) was prepared by substituting $BD_3$ for $BH_3$ in Brown's procedure[8]. The $BD_3$ was prepared according to our published procedure[9].

*Methanol-OD* was purchased from Aldrich Chemical Co. Inc.

**Preparation of 1-Hexene (3):**

The tosylhydrazone of 5-oxo-1-hexene (2.5 mmol, 0.665 g) was dissolved in chloroform (6 ml) contained in a 25 ml round-bottomed flask fitted with a septum inlet. The system was flushed with nitrogen and then catecholborane (0.41 ml, 3.75 mmol) was added. The reduction was allowed to proceed for two hours. Sodium acetate trihydrate (2 g, 15 mmol) was then added and the reaction mixture was stirred at room temperature overnight. G.L.C. analysis indicated a 97% yield of 1-hexene. Preparative G.L.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 25°) afforded the analytical sample; b.p. 64°.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 5$ Hz), 1.32 (m, 4H), 2.00 (m, 2H), 4.86 (m, 1H), 4.90 (m, 1H), 5.66 ppm (m, 1H).

**Preparation of 1-Hexene-5-*d*:**

The reduction was carried out as described above except that sodium acetate · 3 deuterium oxide (2 g, 15 mmol) was utilized instead of sodium acetate trihydrate. Identical products were obtained whether chloroform or deuterochloroform was employed as solvent. Preparative G.L.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 25°) afforded an analytically pure sample; b.p. 64°.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 5$ Hz), 1.32 (m, 3H), 2.00 (m, 2H), 4.86 (m, 1H), 4.90 (m, 1H), 5.66 ppm (m, 1H).

**Preparation of 1-Hexene-5,5-$d_2$:**

The tosylhydrazone of 5-oxo-1-hexene was reduced as described above utilizing catecholborane-*d* in place of catecholborane. The decomposition was induced utilizing $NaOAc \cdot 3D_2O$. The product was isolated by preparative G.L.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 25°); b.p. 64°.

$^1$H-N.M.R. ($CCl_4$): $\delta = 0.88$ (m, 3H), 1.35 (m, 3H), 2.01 (m, 2H), 4.86 (m, 1H), 4.90 (m, 1H), 5.66 ppm (m, 1H).

**Preparation of Toluene-α-*d*:**

The tosylhydrazone of benzaldehyde (1.37 g, 5 mmol) was dissolved in deuterochloroform (10 ml) contained in a flame-dried, nitrogen-flushed flask. The solution was stirred at room temperature and catecholborane (1.09 ml, 10 mmol) was added. The reduction was allowed to proceed for one hour, methanol-OD (1.22 ml, 30 mmol) was then added followed by anhydrous sodium acetate (0.41 g, 5 mmol). Perdeuterodimethyl sulfoxide (2 ml) was added to solubilize the sodium acetate and the mixture refluxed for one hour. The yield of toluene-α-*d* was 87% (G.L.P.C.; conditions: 15% SE 30 on Chromosorb W, 6 ft, 60°). An analytical sample was obtained by preparative G.L.C. (conditions: 15% SE 30 on Chromosorb W, 6 ft, 100°); b.p. 110°.

Mass spectrum: $m/e = 93$ ($C_7H_7D$, $M^{\oplus}$).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 2.35$ (s, 2H), 7.20 ppm (s, 5$H_{arom}$).

**Preparation of 1-Phenylethane-1-*d*:**

The tosylhydrazone of acetophenone (1.442 g, 5 mmol) was dissolved in deuterochloroform (10 ml) as described above. Catecholborane (1.09 ml, 10 mmol) was added to the solution and the mixture stirred for one hour, then methanol-OD (1.22 ml, 30 mmol), sodium acetate (0.41 g, 5 mmol), and perdeuterodimethyl sulfoxide (2 ml) were added and the mixture refluxed for one hour. The yield was 70% (N.M.R.); an analytical sample was obtained by column chromatography (silica gel, hexane as eluent) after removing the perdeuterodimethyl sulfoxide by extraction with water (6 × 10 ml); b.p. 136°.

Mass spectrum: $m/e = 107$ ($C_8H_9D$, $M^{\oplus}$).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 1.18$ (d, 3H), 2.23 (m, 1H), 7.10 ppm (s, 5$H_{arom}$).

**Preparation of 1-Phenyloctadecane-1-*d*:**

The tosylhydrazone of stearophenone (5.13 g, 10 mmol) was dissolved in deuterochloroform (15 ml). Catecholborane (2.18 ml, 20 mmol), was added to the mixture and stirred for one hour at room temperature. Then methanol-OD (2.44 ml, 60 mmol), sodium acetate (0.82 g, 10 mmol), and perdeuterodimethyl sulfoxide (4 ml) were added and the mixture brought to reflux. After one hour the yield of product was 82% (N.M.R.). The product was isolated by column chromatography (silica gel, hexane as eluent); yield: 2.42 g (73%); m.p. 36°.

Mass spectrum: $m/e = 331$ ($C_{24}H_{41}D$, $M^{\oplus}$).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.9$ (m, 3H), 1.15 (s, 32H), 2.46 (m, 1H), 7.10 ppm (m, $5H_{arom}$).

Received: July 7, 1976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[4] G. W. Kabalka, J. D. Baker, Jr., G. Neal, *J. Org. Chem.* in press.

[5] (a) D. J. Pasto, R. Snyder, *J. Org. Chem.* **31**, 2444 (1966).
(b) H. C. Brown, R. M. Gallivan, *J. Am. Chem. Soc.* **90**, 2906 (1968).

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[7] The results do not differentiate between an intermolecular and intramolecular decomposition of the diazene intermediate. Control experiments indicate that the proton on the nitrogen in the tosylhydrazone (and, presumably, the reduced species) is readily exchanged for deuterium under the reaction conditions.

[8] H. C. Brown, *Organic Synthesis via Boranes*, Wiley Interscience, New York, N. Y., pp. 63–65.

[9] G. W. Kabalka, N. S. Bowman, *J. Org. Chem.* **38**, 1607 (1973).