

# 4

## Reductions

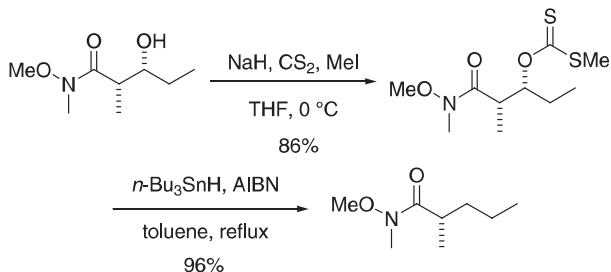
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### 4.1 Alcohols to Alkanes

#### 4.1.1 Tributyltin Hydride/2,2'-Azobisisobutyronitrile (Barton Deoxygenation)

The Barton deoxygenation (or Barton–McCombie deoxygenation) is a two-step reaction sequence for the reduction of an alcohol to an alkane. The alcohol is first converted to a methyl xanthate or thioimidazolyl carbamate. Then, the xanthate or thioimidazolyl carbamate is reduced with a tin hydride reagent under radical conditions to afford the alkane. Trialkylsilanes have also been used as the hydride source. Reviews: (a) McCombie, S. W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 4.2: Reduction of Saturated Alcohols and Amines to Alkanes, pp. 818–824. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413–1432.

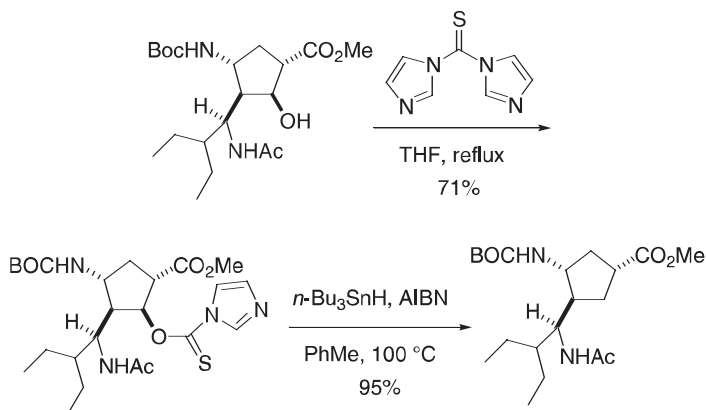
##### 4.1.1.1 Via a Methylxanthate



To a solution of the  $\beta$ -hydroxy-*N*-methyl-*O*-methylamide (0.272 g, 1.55 mmol) in tetrahydrofuran (THF) (30 mL) were added carbon disulfide (6.75 mL, 112 mmol) and iodomethane (6.70 mL, 108 mmol) at 0 °C. The mixture was stirred at this temperature for 0.25 h, and then sodium hydride (60% suspension in mineral, 136.3 mg, 3.4 mmol) was added. After 20 min at 0 °C, the reaction was quenched by slow addition to 60 g of crushed ice. (Caution: hydrogen gas evolution!). The mixture was raised to room temperature and separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (4  $\times$  15 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo, and purified ( $\text{SiO}_2$ , 5% EtOAc in hexanes) to afford 0.354 g (86%) of the xanthate. To a solution of the xanthate (2.95 g, 11.1 mmol) in toluene (100 mL) was added tributyltin hydride (15.2 mL, 56.6 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 0.109 g, 0.664 mmol). The reaction mixture was then heated to reflux for 1 h. The mixture was cooled, concentrated in vacuo, and purified ( $\text{SiO}_2$ , 100% hexanes to remove tin byproducts, followed by 10% EtOAc in hexanes to elute product) to afford 1.69 g (96%) of the *N*-methyl-*O*-methylamide.

Reference: Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500–7504.

#### 4.1.1.2 Via a Thioimidazolyl Carbamate



A mixture of the  $\beta$ -hydroxymethyl ester (10.0 g, 25 mmol) and 1,1'-thiocarbonyl-imidazole (9.0 g, 50 mmol) in anhydrous THF (130 mL) was heated at reflux for 16 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL), and the resulting solution was washed with 0.5 N HCl (3  $\times$  100 mL). The organic layer was dried, filtered, and concentrated. The residue was recrystallized from EtOAc/hexane to give 7.6 g (60%) of imidazolide thioester. The filtrate was concentrated, and the residue was purified by flash column chromatography using EtOAc/hexane as the eluent to give an additional 1.4 g (11%) of product.

A solution of the imidazolide thioester (5.0 g, 9.8 mmol) in dry toluene (130 mL) was treated at 100 °C with tributyltin hydride (3.4 mL, 12.6 mmol) followed by AIBN (0.1 g, 0.06 mmol), and the mixture was stirred at 100 °C for 10 min. The solvent was removed in vacuo, and the residue was dissolved in acetonitrile (100 mL)

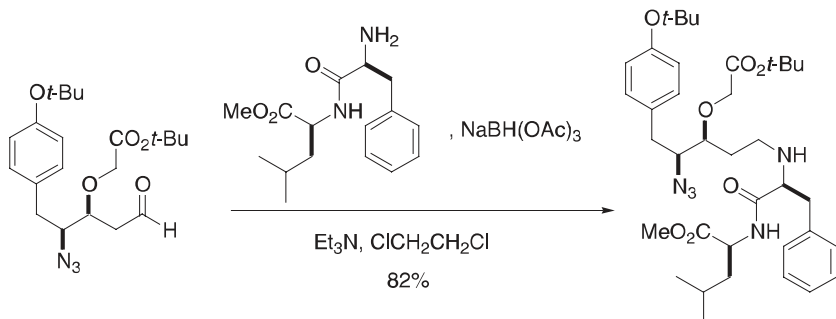
and washed with hexanes ( $3 \times 100$  mL). The acetonitrile layer was concentrated, and the residue was purified by flash chromatography using EtOAc/hexanes (0–50% mixture) as the eluent to deliver 3.6 g (95%) of the cyclopentane.

Reference: Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Babu, Y. S.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379–4392.

## 4.2 Aldehydes, Amides, and Nitriles to Amines

### 4.2.1 Reductive Amination with Sodium Triacetoxyborohydride

A popular and effective method for converting aldehydes to amines is through a reductive amination protocol. Typically, the aldehyde and amine react to form an intermediate imine or iminium ion and then a reducing agent (i.e., sodium triacetoxyborohydride) is added to carry out the reduction of the intermediate species to afford the amine. The reaction is accelerated in the presence of acetic acid (0.1–3 equivalents). Reviews: (a) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1–714. (b) Hutchins, R. O. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 1.2: Reduction of C=N to CHNH by Metal Hydrides, pp. 25–54.

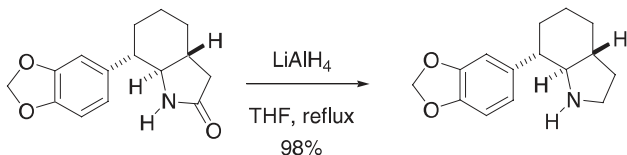


Triethylamine (0.32 mL, 2.22 mmol) and H-Phe-Leu-OMe (0.72 g, 2.16 mmol) were added to a solution of the aldehyde (0.67 g, 1.66 mol) in 1,2-dichloroethane (25 mL). The solution was stirred for 5 min, after which time sodium triacetoxyborohydride (0.57 g, 2.67 mmol) was added in 1 portion. Stirring was continued for 45 min followed by addition of saturated aqueous  $\text{NaHCO}_3$  and separation of the two phases. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc (3:1 to 1:1)) to give 0.93 g (82%) of the secondary amine as a slightly yellow oil.

Reference: Blomberg, D.; Hedenström, M.; Kreye, P.; Sethson, I.; Brickmann, K.; Kihlberg, J. *J. Org. Chem.* **2004**, *69*, 3500–3508.

## 4.2.2 Lithium Aluminum Hydride Reduction of an Amide

See section 4.3.1 for a description of lithium aluminum hydride (LAH).

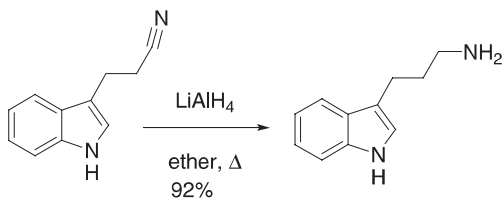


A mixture of the octahydroindolone (259 mg, 1.0 mmol) and  $\text{LiAlH}_4$  (76 mg, 2.0 mmol) in THF (5 mL) was stirred at reflux for 3 h and then successively treated with water (1 mL), 8% sodium hydroxide (3 mL), and water (3 mL). *Note: extreme care should be practiced during the quenching process. As this process is exothermic and produces flammable hydrogen gas, it is highly advisable to cool the reaction mixture to 0 °C prior to quenching and to add the water and aqueous solution of sodium hydroxide cautiously.* The mixture was extracted with  $\text{CHCl}_3$  (3 × 20 mL). The organic layers were concentrated and the crude product purified via chromatography eluting  $\text{CHCl}_3$ /methanol 10:1) to afford 241 mg (98%) of the octahydroindole as a pale yellow oil.

Reference: Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, 5, 1123–1126.

## 4.2.3 Lithium Aluminum Hydride Reduction of a Nitrile

See section 4.3.1 for a description of LAH.



A solution of LAH (1.0 M in ether, 36.5 mL, 36.5 mmol) was cooled to 0 °C, and a solution of the cyanoethyl indole (2.78 g, 16.3 mmol) was added slowly. Then, the solution was heated at reflux for 3 h. It was cooled to 0 °C and quenched by dropwise addition of water (20 mL) followed by 1 N sodium hydroxide (40 mL). The phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine and then dried (potassium hydroxide). Evaporation of the solvent gave 2.6 g (92%) of homotryptamine as a yellow oil, which solidified on standing. The hydrochloride was prepared by dissolving the amine in a minimum of ethanol and then a saturated solution of hydrogen chloride in ether was added until no additional salt formation was observed. The hydrochloride was recrystallized from ethanol.

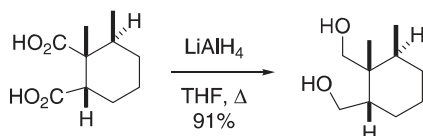
Reference: Kuehne, M. E.; Cowen, S. D.; Xu, F.; Borman, L. S. *J. Org. Chem.* **2001**, 66, 5303–5316.

### 4.3 Carboxylic Acids and Derivatives to Alcohols

#### 4.3.1 Lithium Aluminum Hydride

$\text{LiAlH}_4$  (LAH) is a non-selective hydride reducing agent that reduces a host of functional groups, including carboxylic acids, amides, esters, lactones, ketones, aldehydes, epoxides, and nitriles, to the corresponding alcohols and amines. Great care should be exercised in quenching excess LAH. Although several quenching methods exist, an excellent way to destroy LAH and remove the aluminium salts is to carefully add water ( $\times$  mL), 15% aqueous NaOH ( $\times$  mL), and water ( $4 \times$  mL), again in sequential order, at  $0^\circ\text{C}$  to the reaction mixture. Reviews: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, 35, 567–607. (c) Brown, W. G. *Org. React.* **1952**, 6, 469–509.

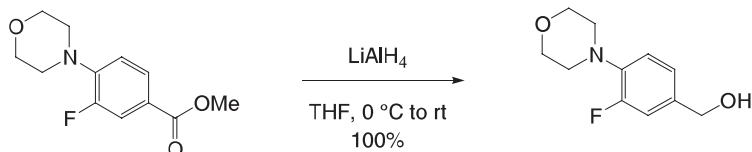
##### 4.3.1.1 Reduction of a Carboxylic Acid



To a suspension of LAH (6.50 g, 171 mmol) in THF (90 mL) at  $0^\circ\text{C}$  was added dropwise a solution of the diacid (3.40 g, 17.0 mmol) in THF (30 mL). The mixture was heated at reflux for 1 h and then cooled to  $0^\circ\text{C}$ . The mixture was then treated dropwise with water (13 mL) and 10% aqueous sodium hydroxide (10 mL). *Note: extreme care should be practiced during the quenching process. As this process is exothermic and produces flammable hydrogen gas, it is highly advisable to cool the reaction mixture to  $0^\circ\text{C}$  prior to quenching and to add the water and aqueous solution of sodium hydroxide cautiously.* The mixture was filtered over  $\text{Na}_2\text{SO}_4$ , and the filtrate was evaporated under reduced pressure to give 2.65 (91%) of the diol.

Reference: Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; Freire de Lima, M. E. Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, 124, 15313–15325.

##### 4.3.1.1 Reduction of an Ester



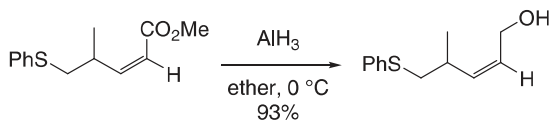
A solution of the methyl ester (3.35 g, 14.0 mmol) in dry THF (50 mL) was added dropwise to a slurry of LAH (0.797 g, 21.0 mmol) in dry THF at  $0^\circ\text{C}$  under a nitrogen atmosphere. When the addition was complete, the cooling bath was removed and the mixture was stirred at ambient temperature. After 16 h, thin layer chromatography (TLC 2:1 hexanes/EtOAc) revealed that the reaction was complete. The mixture was

cooled to 0 °C, and the reaction was carefully quenched with water (0.80 mL), 15% aqueous sodium hydroxide (0.80 mL), and water (2.4 mL). *Note: extreme care should be practiced during the quenching process. As this process is exothermic and produces flammable hydrogen gas, it is highly advisable to cool the reaction mixture to 0 °C prior to quenching and to add the water and aqueous solution of sodium hydroxide cautiously.* After being stirred for 30 min, the mixture was diluted with EtOAc (100 mL), filtered through Celite (EtOAc wash), and concentrated under reduced pressure to give 3.0 g (100%) of the benzyl alcohol as a white solid.

Reference: Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. H.; Slatter, J. G.; Sams, J. P.; Olien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. *J. Med. Chem.* **2003**, *46*, 284–302.

#### 4.3.2 Alane

Alane must be prepared in situ. It is an excellent reagent for the 1,2-reduction of  $\alpha,\beta$ -unsaturated esters. It selectively reduces esters in the presence of halogens and nitro groups. Reviews: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607.



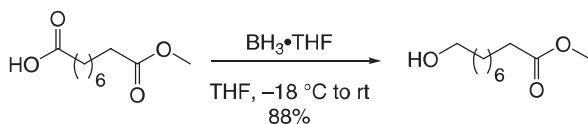
To a suspension of LAH (0.60 g, 16 mmol) in dry ether (50 mL) at 0 °C was added a solution of aluminum trichloride (3.2 g, 24 mmol) in dry ether (40 mL) over a period of 10 min. The above mixture was stirred for 30 min, and the solution of the  $\alpha,\beta$ -unsaturated ester (3.7 g, 16 mmol) in dry ether (25 mL) was added over a period of 10 min at 0 °C and stirred at the same temperature for 1 h. The reaction mixture was diluted with ether (100 mL), and small ice pieces *were added carefully*. The solid formed was filtered, and the filtrate was evaporated to afford 3.12 g (93%) of the allylic alcohol as a viscous liquid.

Reference: Raghavan, S.; Reddy, S. R.; Tony, K. A.; Kumar, Ch. N.; Varma, A. K., Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838–5841.

#### 4.3.3 Borane

Borane is typically used as a THF ( $\text{BH}_3\cdot\text{THF}$ ) or dimethylsulfide complex ( $\text{BH}_3\cdot\text{SMe}_2$ ). Although the reactivity of the two complexes is similar, the boron dimethylsulfide species is more stable over longer periods of time. Borane will chemoselectively reduce a carboxylic acid in the presence of an ester or nitrile. Reviews: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition. (b) Brown, H. C.;

Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607. (c) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773–799.



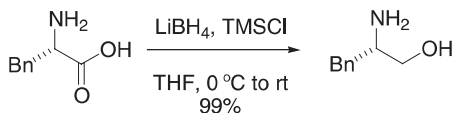
A 250-mL round-bottomed flask equipped with a stirring bar was charged with azelaic acid monomethyl ester (5.0 g, 24.7 mmol, 85% tech) and THF (12 mL). The solution was cooled to  $-18\text{ }^{\circ}\text{C}$  (ice–salt bath) before the addition of  $\text{BH}_3\cdot\text{THF}$  complex (24.7 mL of a 1.0 M solution in THF, 24.7 mmol) over 20 min. The reaction was stirred well, and the ice-bath was allowed to equilibrate slowly to room temperature. Progress of the reaction was monitored by  $^{13}\text{C}$  NMR. After 4 h, the reaction mixture was quenched with water (50 mL) at  $0\text{ }^{\circ}\text{C}$  and potassium carbonate (5.9 g) was added. The mixture was diluted with ethyl ether (100 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl ether ( $3 \times 100\text{ mL}$ ), and the organic layers combined, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography, with 30% EtOAc/hexanes, producing a yellow oil (88% yield based on 85% pure azelaic acid monomethyl ester).

Reference: Gung, B. W.; Dickson, H. *Org. Lett.* **2002**, *4*, 2517–2519.

#### 4.3.4 Lithium Borohydride

Lithium borohydride is more reactive than sodium borohydride, but less reactive than  $\text{LiAlH}_4$ . Reviews: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH; New York, 1997, 2<sup>nd</sup> edition. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607.

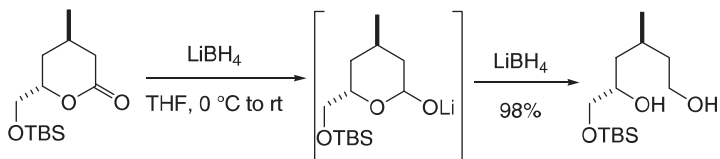
##### 4.3.4.1 Reduction of a Carboxylic Acid



To a  $0\text{ }^{\circ}\text{C}$  solution of lithium borohydride (1.32 g, 60.54 mmol) in THF (30 mL) was added trimethylsilyl chloride (15.40 mL, 121.1 mmol). The ice–water bath was removed, and the mixture was stirred at room temperature for 15 min. The mixture was cooled to  $0\text{ }^{\circ}\text{C}$  and (*S*)-phenylalanine (5.00 g, 30.27 mmol) was added. The ice–water bath was removed, and the reaction mixture was stirred for 16 h. The mixture was cooled again to  $0\text{ }^{\circ}\text{C}$  and methanol (45 mL) was added dropwise followed by a sodium hydroxide solution (2.5 M, 25 mL). The organic solvents were evaporated in vacuo and the residue was extracted with  $\text{CHCl}_3$  ( $5 \times 50\text{ mL}$ ). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo to leave 4.55 g (99%) of (*S*)-phenylalaninol as a white crystalline solid.

Reference: Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176–5183.

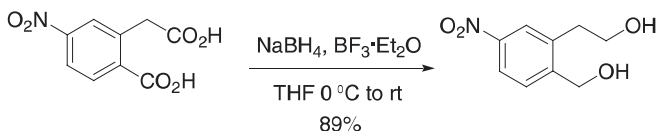
#### 4.3.4.2 Reduction of a Lactone



A solution of the lactone (3.40 g, 13.18 mmol) in dry THF (10 mL) was added dropwise to a solution of lithium borohydride (2 M in THF, 16 mL, 32 mmol) in THF (80 mL) at 0 °C. The mixture was stirred overnight allowing room temperature to be reached. The reaction was poured into a cold mixture of saturated ammonium chloride (300 mL) and diethyl ether (300 mL), the phases were separated, and the aqueous layer extracted with ether. The combined organic extracts were washed with water and brine, dried (magnesium sulfate), and concentrated. The residue was purified by chromatography [150 g silica gel, hexanes/EtOAc (3:1 to 3:2)] to afford 3.391 g (98%) of the diol as a colorless oil.

Reference: Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026–3042.

#### 4.3.5 Sodium Borohydride/Boron Trifluoride Etherate



Sodium borohydride (5.06 g, 133 mmol) was added in portions to a solution of 2-(carboxymethyl)-4-nitrobenzoic acid (10.0 g, 44.4 mmol) in THF (220 mL). The contents were cooled to 0 °C, and boron trifluoride diethyl etherate (21.3 mL, 133 mmol) was added dropwise over 1 h. The mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was then cooled to 0 °C and cautiously quenched with aqueous sodium hydroxide (1 N, 178 mL). The contents were stirred for 3 h, and the THF was removed under vacuum. The resulting aqueous suspension was cooled to 0 °C and the product was filtered off. After drying, 7.78 g (89%) of the diol was afforded as a white solid.

Reference: Quallich, G. J.; Makowski, T. W.; Sanders, A. F.; Urban, F. J.; Vazquez, E. *J. Org. Chem.* **1998**, *63*, 4116–4119.

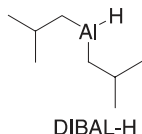
### 4.4. Esters and Other Carboxylic Acid Derivatives to Aldehydes

#### 4.4.1 Diisobutylaluminium Hydride

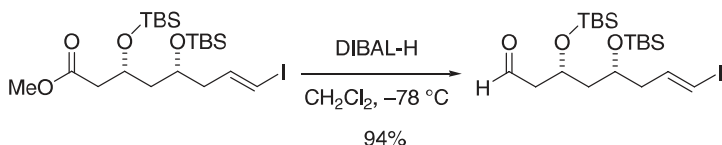
Diisobutylaluminium hydride (DIBAL–H) is a bulky hydride reducing agent that is very useful for the stereoselective reduction of prochiral ketones and reductions at



low temperatures of the carbonyl functionality. Saturated esters are reduced to aldehydes at temperatures below  $-70\text{ }^{\circ}\text{C}$ ; however,  $\alpha$ ,  $\beta$  unsaturated esters are reduced to the allylic alcohols even with careful monitoring of the internal reaction temperature. *N*-Methyl-*O*-methyl amides (Weinreb amides) are reduced to aldehydes. In addition, a lactone can be reduced to a lactol or further reduced to the diol. Reviews (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2nd edition. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607. (c) Winterfeldt, E. *Synthesis* **1975**, 617–630.



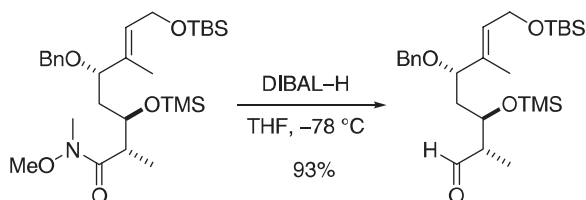
#### 4.4.1.1 Reduction of an Ester



To a solution of the methyl ester (3.72 g, 6.87 mmol) in  $\text{CH}_2\text{Cl}_2$  (70 mL) at  $-78\text{ }^{\circ}\text{C}$  was added DIBAL-H (8.2 mL of a 1.0 M solution in toluene, 8.2 mmol) slowly, *maintaining an internal temperature below  $-76\text{ }^{\circ}\text{C}$* . The reaction was stirred for 30 min and then quenched with methanol (3 mL). A saturated aqueous solution of Rochelle's salt (sodium potassium tartrate, 130 mL) was added, and the biphasic mixture stirred overnight. The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 40\text{ mL}$ ). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. Purification of the crude product by chromatography on  $\text{SiO}_2$  (5% EtOAc/hexane) gave 3.28 g (94%) of the aldehyde as a clear oil.

Reference: Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043–2046.

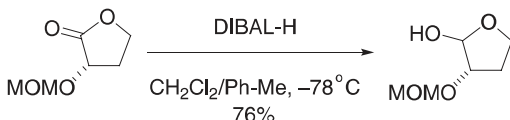
#### 4.4.1.2 Reduction of a Weinreb Amide



To a solution of the *N*-methyl-*O*-methyl amide (1.65 g, 3.06 mmol) in THF (30 mL) at  $-78\text{ }^{\circ}\text{C}$  was added DIBAL-H (2.90 mL of a 1.5 M solution in toluene, 4.35 mmol). After the reaction was stirred for 45 min, a saturated solution of potassium sodium tartrate (100 mL) was added and the mixture extracted with ether. The combined organic layers were dried, filtered, and concentrated. Purification by flash chromatography afforded 1.37 g (93%) of the aldehyde as a colorless oil.

Reference: Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215–4234.

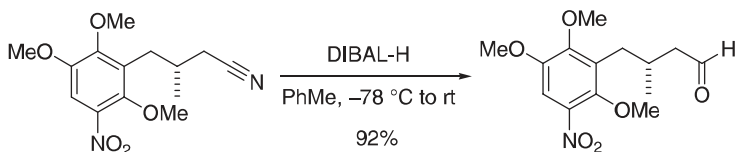
#### 4.4.1.3 Reduction of a Lactone



To a solution of the  $\gamma$ -lactone (0.880 g, 5.47 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) maintained at  $-78^\circ\text{C}$  was added DIBAL-H (1.5 M in toluene, 4.0 mL, 6 mmol), and the mixture was stirred for 30 min at  $-78^\circ\text{C}$ . Solid ammonium chloride (0.4 g) and methanol (1 drop) were added, and the mixture was filtered through a short column of silica gel which was subsequently rinsed with 5% methanol in EtOAc. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (20 g of silica gel, EtOAc:hexane, 1:1) to afford 0.621 g (76%) of the lactol as a colorless oil.

Reference: White, J. D.; Hrcnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142.

#### 4.4.1.4 Reduction of a Nitrile

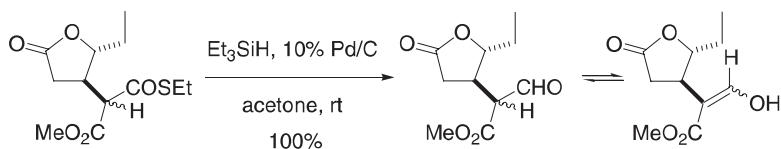


A flame-dried, 25-mL, round-bottomed flask was charged with the nitrile (0.150 g, 0.510 mmol) and dry toluene (6.5 mL). The solution was cooled to  $-78^\circ\text{C}$  under a nitrogen atmosphere and DIBAL-H (1.5 M in toluene, 0.68 mL, 1.02 mmol) was added slowly. The resulting reddish-orange solution was allowed to warm to ambient temperature over 1 h at which time 0.2 mL of acetone, 0.2 mL of EtOAc, and 0.2 mL pH 7 phosphate buffer were added in sequence. The mixture was then stirred vigorously for 20 min and anhydrous  $\text{Na}_2\text{SO}_4$  was added, maintaining the vigorous stirring for an additional 20 min. The resulting yellow solution was filtered over a pad of silica gel and  $\text{Na}_2\text{SO}_4$ . The filtrate was concentrated, and the residue thus afforded was purified via radial chromatography (20% EtOAc/hexanes) to afford 0.140 g (92%) of the aldehyde as a light yellow viscous oil.

Reference: Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162–8169.

#### 4.4.2 Triethylsilane and Pd/C (Fukuyama Reduction)

Fukuyama reduction is a mild method for the conversion of thioesters to aldehydes in the presence of other susceptible functional groups, including amides, esters, lactones, and acetonides. Review: Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87–96.

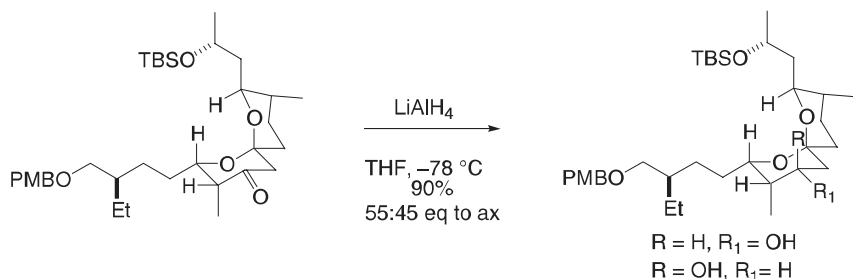


To a stirred mixture of the thioester (800 mg, 2.92 mmol) and 10% Pd on carbon (320 mg, 0.029 mmol) in acetone (7.5 mL) was added triethylsilane (1.4 mL, 8.77 mmol) at room temperature under an argon atmosphere. Stirring was continued for 3 h at room temperature. The catalyst was filtered off using Celite, and the filtrate was evaporated to give a crude residue that was chromatographed on silica gel (EtOAc/*n*-hexane, 1:2 to 1:1) to give 630 mg (100%) of an equilibrium mixture of the aldehyde and enol as a colorless oil.

Reference: Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967–2970.

## 4.5 Ketones or Aldehydes to Alcohols

### 4.5.1 Lithium Aluminum Hydride



To a solution of LAH (1.0 M in THF, 1.01 mL, and 1.01 mmol) was added a solution of the ketone (596 mg, 1.01 mmol) in THF (6 mL) at -78 °C under nitrogen. After 1 h, saturated aqueous sodium potassium tartrate (6 mL) was added carefully, and the mixture was stirred rapidly at ambient temperature for 1 h. The resulting mixture was diluted with water (6 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and purified by flash chromatography (20% EtOAc in hexane, then 50% EtOAc in hexane) to give 330.5 mg (55%) of the equatorial alcohol and 266.1 mg (45%) of the axial alcohol as colorless oils.

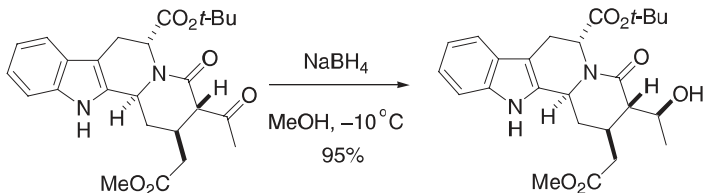
Reference: Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260–6268.

*Note: compare diastereoselectivity of the above reaction with example 4.5.8.*

### 4.5.2 Sodium Borohydride

Sodium borohydride is a widely used mild and selective reducing agent. It selectively reduces an aldehyde or ketone in the presence of esters, lactones, carboxylic acids, and amides in methanol or THF at room temperature. Reviews: (a) Seyden-Penne, J.

*Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607.

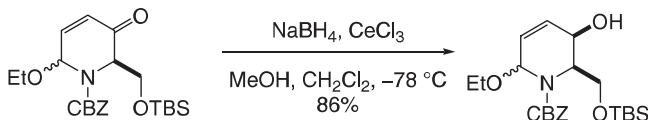


A mixture of the amido ketone (1.70 g, 3.86 mmol) and sodium borohydride (293 mg, 7.72 mmol) in anhydrous methanol (60 mL) was stirred at  $-10\text{ }^{\circ}\text{C}$  for 25 min. Saturated  $\text{NaHCO}_3$  (40 mL) and  $\text{CH}_2\text{Cl}_2$  (80 mL) were added, and the mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 5 min. The organic layer was removed, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 40\text{ mL}$ ). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give 1.68 g (95%) of the secondary alcohol as a white solid.

Reference: Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.

#### 4.5.3 Sodium Borohydride/Cerium Trichloride (Luche Reduction)

The Luche reduction is an excellent method for the 1,2-reduction of  $\alpha,\beta$ -unsaturated ketones. In addition, ketones are reduced selectively in the presence of aldehydes.



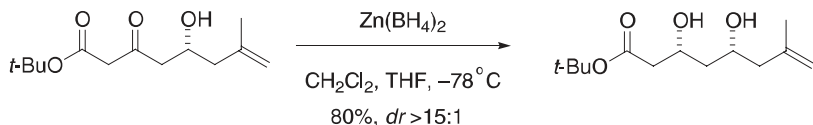
A 100-mL flask was charged with the enone (555 mg, 1.32 mmol), a magnetic stir bar, and  $\text{CH}_2\text{Cl}_2$  (6 mL). The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  in a dry ice–acetone bath under a nitrogen atmosphere. To this solution was added a 0.4 M solution of cerium trichloride in methanol (10 mL). After additional stirring and continued cooling, sodium borohydride (75 mg, 1.98 mmol) was added. The reaction was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$  until only alcohol was visible by TLC. The reaction was diluted with ether (15 mL) and quenched at  $-78\text{ }^{\circ}\text{C}$  by the addition of a 1 M aqueous solution of sodium bisulfate (4 mL). The mixture was stirred for 20 min and the phases were separated. The aqueous layer was extracted with ether ( $4 \times 10\text{ mL}$ ) and the combined organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Flash chromatography provided 477 mg (86%) of an anomeric mixture of the alcohol as a colorless oil.

Reference: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401–404.

#### 4.5.4 Zinc Borohydride

Because  $\text{Zn}^{2+}$  is a good chelating cation, highly diastereoselectivity reductions of  $\alpha$  or  $\beta$ -hydroxy ketones and esters can be achieved with zinc borohydride. Reviews: (a) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19–26.

(b) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition.

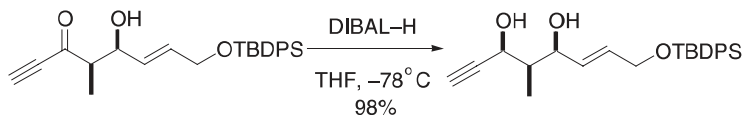


To a 500-mL round-bottomed flask charged with a magnetic stir bar was added keto ester (1.91 g, 7.88 mmol) and  $\text{CH}_2\text{Cl}_2$  (158 mL). The mixture was cooled to  $-78^\circ\text{C}$  and a freshly prepared solution of  $\text{Zn(BH}_4)_2$  (60 mL of 0.2 M in THF, 12 mmol) was added dropwise with stirring. The reaction was stirred for 2 h at this temperature before being quenched by the addition of a saturated aqueous solution of ammonium chloride (approximately 100 mL). The resulting solution was allowed to warm to room temperature with stirring for 12 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (three times). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated. The crude oil was purified by flash chromatography ( $\text{SiO}_2$ , 30% to 50% EtOAc/hexanes) to give 1.54 g (80%, *dr* >15:1) of the diol as a colorless oil.

Reference: Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, 5, 3995–3998.

#### 4.5.5 Diisobutylaluminum Hydride

See section 4.4.1 for a description of DIBAL-H.

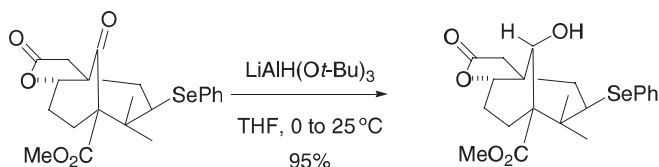


To solution of the ynone (0.893 g, 2.20 mmol) in THF (15 mL) at  $-78^\circ\text{C}$  under argon was added DIBAL-H (4.40 mmol of 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 4.40 mmol) dropwise. After 30 min, the reaction was quenched by the addition of EtOAc (0.1 mL) and saturated aqueous sodium potassium tartrate (15 mL), and the slurry was warmed to room temperature with vigorous stirring for 12 h. The resulting clear biphase was extracted with ether ( $3 \times 30$  mL), and the combined organic layers were washed with brine (30 mL) and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation in vacuo gave a pale yellow oil that was purified by silica gel chromatography (2:1 hexanes/EtOAc) to give 0.880 g (98%) of the diol.

Reference: Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, 125, 13531–13540.

#### 4.5.6 Lithium tri-*tert*-Butoxyaluminumhydride

Lithium tri-*tert*-Butoxyaluminumhydride is a bulky chemo- and stereoselective hydride reducing agent. Aldehydes are reduced chemoselectively in the presence of ketones and esters at low temperature. Ethers acetals, epoxides, chlorides, bromides, and nitro compounds are unaffected by this reagent. Reviews: (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition. (b) Málek, J. *Org. React.* **1985**, 34, 1–317.

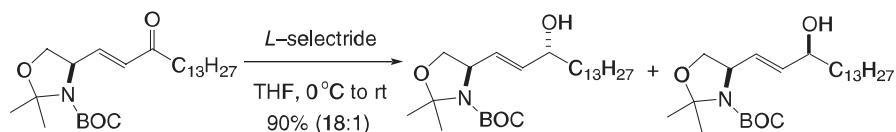
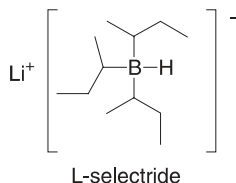


To a solution of the ketone (20.4 g, 46.9 mmol) in THF (500 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminumhydride [ $\text{LiAlH}(\text{O}t\text{-Bu})_3$ ] (61.0 mL of a 1.0 M solution in THF, 61.0 mmol). The resulting reaction mixture was stirred for 30 min at 0 °C and then for 30 min at 25 °C. After the reaction was complete, as established by TLC analysis, it was quenched by the addition of saturated ammonium chloride (200 mL) followed by addition of EtOAc (300 mL). The mixture was stirred at 25 °C for 2 h, followed by extraction with EtOAc (3 × 300 mL). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated to give the crude product, which was purified by flash chromatography (silica gel, 25% EtOAc in hexanes) to afford 19.4 g (95%) of the alcohol as a white solid.

Reference: Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724–4725.

#### 4.5.7 *L*-Selectride

*L*-Selectride is a bulky stereoselective hydride reducing agent for prochiral ketones. Review: Seyden-Penne, J. *Reductions by the Aluminio- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997, 2<sup>nd</sup> edition.



Other reducing agents

$\text{NaBH}_4$ ,  $\text{CeCl}_3$   
 DIBAL-H  
 $\text{BH}_3 \cdot \text{SMe}$ , oxazaborolidine  
 $\text{LiAlH}_4$ , chiral

yield and diastereomeric ratio

90% (1:1.8)  
 89% (1:1.1)  
 84% (2.3:1)  
 87% (5.2:1)

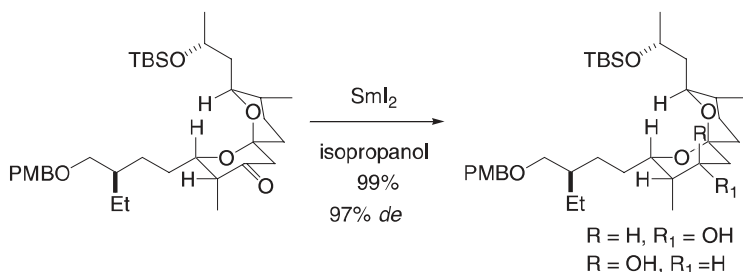
To a solution of the enone (101 mg, 0.23 mmol) in dry THF (10 mL) was added *L*-selectride (0.46 mL of 1.0 M solution in THF, 0.46 mmol) dropwise at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and then allowed to warm to room temperature for another 0.5 h. The mixture was then diluted with EtOAc (100 mL) and filtered through a pad of silica gel, which was rinsed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography

(hexane/EtOAc, 3:1) to give 86 mg (85%) of the *anti*-alcohol and 4.8 mg (4.7%) of the *syn*-alcohol as colorless oils in a diastereomeric ratio of 18:1.

Reference: Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355–359.

#### 4.5.8 Samarium Iodide/Isopropanol (Meerwein–Pondorf–Verlag)

This is a modification of the venerable Meerwein–Pondorf–Verlag reaction. Compare the example below with the reaction in section 4.5.1. Reviews: (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, *10*, 1007–1017. (b) Kellogg, R. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 1.3: Reduction of C=X to CHXN by Hydride Delivery from Carbon, pp. 88–91. (c) Wilds, A. L. *Org. React.* **1944**, *2*, 178–223.

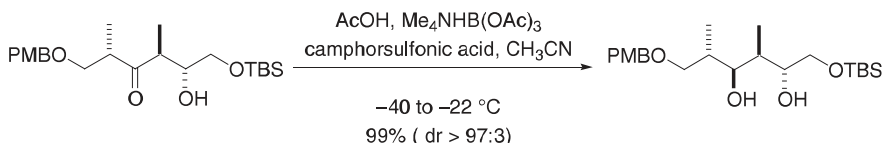


To a solution of the ketone (10.73 g, 18.2 mmol) in THF (62 mL) at ambient temperature under nitrogen were added degassed isopropanol (13.9 mL, 182 mmol) and samarium iodide (0.1 M in THF, 2.73 mL, 0.273 mmol). The resulting deep-green solution was stirred at ambient temperature for 18 h. Saturated  $\text{NaHCO}_3$  (60 mL) was added to quench the reaction. The mixture was diluted with diethyl ether (120 mL) and the layers were separated. The organic layer was washed with saturated  $\text{NaHCO}_3$  (60 mL). The combined aqueous layers were extracted with diethyl ether (2  $\times$  60 mL). The combined organic extracts were washed with aqueous sodium sulfite (1.5 N, 60 mL) and brine (60 mL). After drying over magnesium sulfate, the organic layer was purified by flash chromatography (18% EtOAc in hexane, then 50% EtOAc in hexane) to give 10.56 g (98%) of the equatorial alcohol and 0.14 g (1%) of the axial alcohol as colorless oils.

Reference: Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260–6268.

#### 4.5.9 Tetramethylammonium Triacetoxyborane

Tetramethylammonium triacetoxyborane is often used for the stereoselective reduction of  $\beta$ -hydroxyketones to form *anti*-1,3-diols.

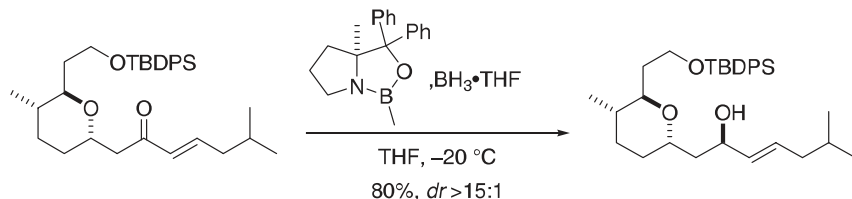


Acetic acid (2 mL) was added to a stirred suspension of tetramethylammonium triacetoxyborohydride (1.54 g, 5.85 mmol) in acetonitrile (2 mL) at room temperature. The mixture was stirred at room temperature for 30 min and then cooled to  $-40\text{ }^{\circ}\text{C}$ . The  $\beta$ -hydroxyketone (300 mg, 0.731 mmol) in acetonitrile (2 mL) was added dropwise at this temperature. A solution of camphorsulfonic acid (85 mg, 0.366 mmol) in a mixture of acetic acid:acetonitrile (1:1, 4 mL) was added, and the mixture was allowed to warm to  $-22\text{ }^{\circ}\text{C}$  over 18 h. The mixture was poured into saturated aqueous  $\text{NaHCO}_3$  (50 mL). A saturated aqueous solution of sodium potassium tartrate (50 mL) was added, followed by ether (100 mL), and the mixture was stirred vigorously at room temperature for 8 h. The layers were separated, and the aqueous layer was extracted with EtOAc ( $3 \times 50\text{ mL}$ ). The combined organic extracts were washed with water (50 mL), brine (50 mL), and dried ( $\text{MgSO}_4$ ). The solvent was removed under vacuum to afford 300 mg (99.5%, dr >97:3) of the *anti*-1,3-diol as a colorless oil.

Reference: Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150–160.

#### 4.5.10 Corey–Bakshi–Shibata Reduction

The Corey–Bakshi–Shibata reduction (CBS reduction) is a highly enantioselective method for arylketones, diaryl ketones, and dialkylketones. In addition, cyclic  $\alpha,\beta$ -unsaturated ketones, acyclic  $\alpha,\beta$ -unsaturated ketones, and  $\alpha,\beta$ -ynones are reduced enantioselectively in a 1,2-fashion. The high enantioselective nature of this reduction relies on the chiral oxazaborolidine catalyst, shown in the reaction scheme, in the presence of borane or a dialkylborane. Reviews: (a) Singh, V. K. *Synthesis* **1992**, 605–617. (b) Deloux, L.; Srebnik M. *Chem. Rev.* **1993**, *93*, 763–784. (c) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.



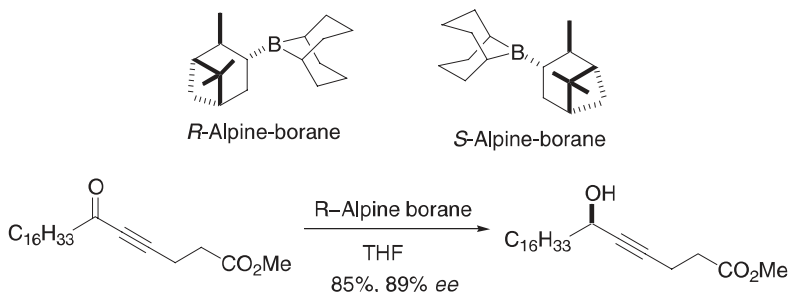
To a 100-mL round-bottomed flask charged with a magnetic stir bar was added a solution of (*S*)-CBS (1.0 M in toluene, 0.297 mL, 0.297 mmol). The toluene was then removed by placing the flask on a high vacuum pump for approximately 2 h. The flask was removed and THF (15 mL) was added. The mixture was cooled to  $-20\text{ }^{\circ}\text{C}$  and a solution of boron dimethylsulfide complex (10 M, 0.594 mL, 5.94 mmol) was added. To this reaction mixture, a solution of the ketone (1.51 g, 2.9 mmol) in THF (15 mL) was added dropwise. The reaction was stirred for 8 h at  $-20\text{ }^{\circ}\text{C}$  before methanol (15 mL) was carefully added to destroy excess borane. The reaction was diluted with saturated aqueous sodium chloride (approximately 25 mL) and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated. The crude oil was purified by flash chromatography ( $\text{SiO}_2$ , 0 to 10% EtOAc in hexanes) giving 1.21 g (80%, dr > 15:1) of the allylic alcohol as a colorless oil.

Reference: Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995–3998.



4.5.11 *R*-Alpine Borane (Midland Reduction)

Review: Midland, M. M. *Chem. Rev.* **1989**, 89, 1553–1561.

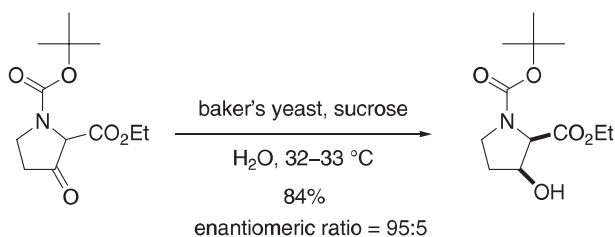


A solution of *R*-Alpine borane (0.5 M in THF, 57.2 mL, 28.6 mmol) was slowly added to the ynone (5.21 g, 14.3 mmol). The resulting solution was stirred for 36 h. After removal of solvent in vacuo, the residue was diluted with ether (200 mL). Ethanolamine (1.72 mL, 28.6 mmol) was slowly added, producing a yellow precipitate which was removed by filtration through Celite. The filtrate was concentrated and directly subjected to flash chromatography to yield 4.44 g (85%) of the alcohol as a white solid.

Reference: Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem.* **1999**, 64, 1789–1797.

## 4.5.12 Baker's Yeast

Baker's yeast offers the synthetic chemist an enzymatic method for the asymmetric reduction of  $\beta$ -keto esters,  $\alpha$ -hydroxyaldehydes and ketones, and  $\beta$ -diketones. Reviews: (a) Rene Csuk, R.; Glaenger, B. I. *Chem. Rev.* **1991**, 91, 49–97. (b) Servi, S. *Synthesis*, **1990**, 1–25.

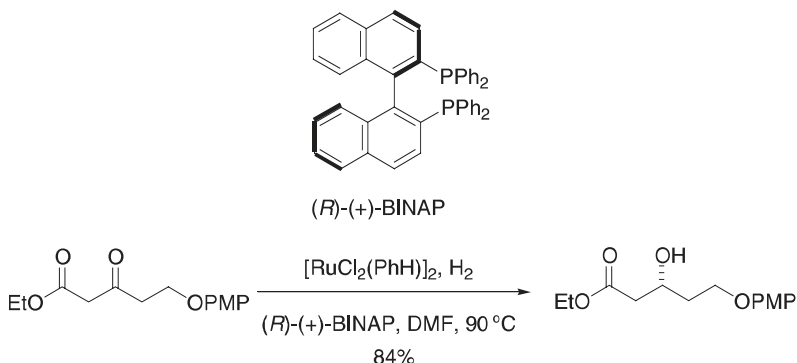


To a 6-L Erlenmeyer flask immersed in a water bath were added, in succession, the keto- ester (34.15 g, 0.133 mol), sucrose (513 g), and distilled water (2731 mL). The reaction mixture was stirred until the sucrose dissolved, after which dry baker's yeast (341 g, Red Star™) was added. The reaction mixture was stirred at 32–33 °C for 24 h and then centrifuged. The aqueous layer was extracted with ether (four times) and the combined organic extracts dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The crude product was purified by flash chromatography (silica; 4:1 then 2:1 hexanes/EtOAc) to afford 28.7 g (84%) of the  $\beta$ -hydroxy ester as a colorless oil.

Reference: Williams, R. M; Cao, J. Tsujishima, H; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172–12178.

#### 4.5.13 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl /Hydrogen (Noyori Asymmetric Reduction)

2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) is an excellent catalyst for the reduction of ketones under homogeneous hydrogenation conditions. Reviews: (a) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73. (b) Singh, V. K. *Synthesis* **1992**, 605–617. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.



Dry degassed DMF (3 mL) was added to a flask containing benzeneruthenium(II) chloride dimer (45 mg, 0.09 mmol) and (R)-(+)-BINAP (112 mg, 0.18 mmol). The slurry was heated to 90 °C with stirring for 20 min. The reddish-brown solution was allowed to cool to room temperature and was then added via cannula to a Parr flask containing a degassed solution of the  $\beta$ -keto ester (8.4 g, 30.0 mmol) in dry ethanol (15 mL). The hydrogenation flask was flushed several times with hydrogen and then pressurized with 4.0 bar hydrogen at 90 °C with vigorous shaking for 20 h. After the solution cooled to room temperature, the dark-red solution was concentrated in vacuo and purified by flash chromatography to provide 7.1 g (84%, >90% ee) of the  $\beta$ -hydroxy ester as a pale yellow liquid.

Reference: Herb, C.; Maier, M.E. *J. Org. Chem.* **2003**, *68*, 8129–8135.

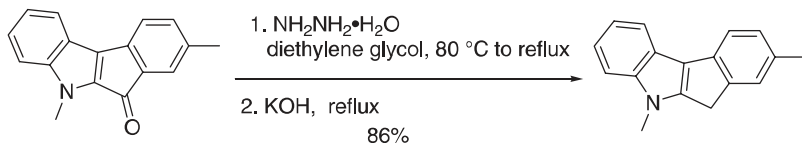
## 4.6 Ketones to Alkanes or Alkenes

### 4.6.1 Wolff–Kishner Reduction

The Wolff–Kishner reaction is a classical reduction method of ketones to alkanes. This method involves converting the ketone to its corresponding hydrazine; treatment of the resulting hydrazine with base affords the alkane and nitrogen gas. Because elevated temperatures (> 200 °C) and strong base are required, this method is harsh when sensitive functionality is present. However, milder methods have been developed including the Myers' modification where the reaction temperatures are much lower ( $\leq 100$  °C).

Reviews: (a) Hutchins, R.O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 1.14: Reduction of C=X to CH<sub>2</sub> by Wolff-Kishner and Other Hydrazone Methods, pp. 327–362. (b) Reusch, W. In *Reduction*; Austine, R. L., Ed.; Dekker: New York, 1968; pp. 171–221. (c) Szmant, H. H. *Angew. Chem. Int. Ed.* **1968**, 7, 120–128. (d) Todd, D. *Org. React.* **1948**, 4, 378–422.

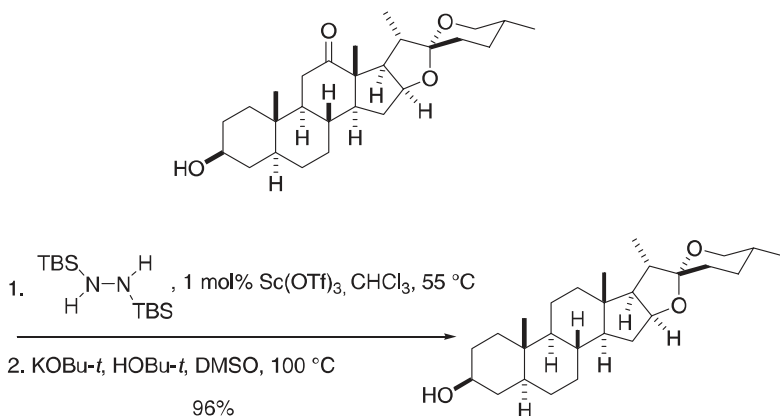
#### 4.6.1.1 Traditional



A mixture of the indolone (1.04 g, 4.2 mmol) and hydrazine monohydrate (1.12 mL, 22.4 mmol) in diethylene glycol (20 mL) was stirred at 80 °C for 1 h and then refluxed for 1 h. The resulting mixture was cooled to room temperature, treated with a solution of KOH (1.2 g, 21.4 mmol) in water (5 mL), and refluxed for 2 h. The resulting mixture was poured into water (100 mL), and the precipitate was filtered off, washed with water (5 × 50 mL), and dried to deliver 0.84 g (86%) of the indole as a greenish solid.

Reference: Kashulin, I. A.; Nifant'ev, I. E. *J. Org. Chem.* **2004**, 69, 5476–5479.

#### 4.6.1.2 Myers' Modification



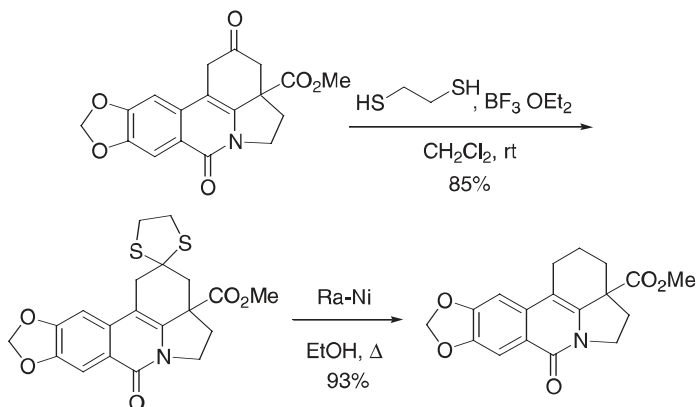
A 25-mL, pear-shaped flask equipped with a Teflon-coated stir bar was charged with scandium trifluoromethanesulfonate (0.002 g, 0.0058 mmol) and hecogenin (0.250 g, 0.581 mmol), a septum cap was affixed, and a needle connected to an argon balloon was inserted through the septum cap. 1,2-Bis-(*tert*-butyldimethylsilyl)hydrazine (0.461 g, 1.28 mmol) and dry  $\text{CHCl}_3$  (1.5 mL) were then introduced sequentially by syringe. The reaction flask was immersed in an oil bath, and the bath was heated to 55 °C. After stirring at 55 °C for 20 h, the heating bath was removed and the reaction

solution, a colorless liquid, was allowed to cool to ambient temperature. Dry *n*-hexane (3 mL) was added, providing a white suspension. The septum cap was removed, and the reaction mixture was filtered through a plug of glass wool into a 25-mL pear-shaped receiving flask. The filtration was quantitated with *n*-hexane (2 × 1 mL). The solvents were removed in vacuo on a rotary evaporator, and then the flask was flushed with dry argon, charged with a Teflon-coated stir bar, and capped with a rubber septum. A needle affixed to an argon balloon was inserted through the septum cap. A separate 25-mL pear-shaped flask equipped with a Teflon-coated stir bar was charged with potassium *tert*-butoxide (1.01 g, 9.00 mmol), and a needle affixed to an argon balloon was inserted through the septum cap. Dry dimethylsulfoxide (7.5 mL) was added via the syringe, and the mixture was stirred at 23 °C until all particulates had dissolved (about 15 min). *tert*-Butanol (0.861 mL, 9.00 mmol) was then added via the syringe, and the resulting solution was transferred by syringe to the flask containing the white solid TBSH derivative. The reaction flask was immersed in an oil bath, and the bath was heated to 100 °C. After stirring at 100 °C for 24 h, the bath was removed and the resulting brown slurry was allowed to cool to 23 °C. The reaction mixture was then poured into a solution of half-saturated brine (30 mL, precooled to 0 °C), and the transfer was quantitated with washes of water (2 × 1 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 × 1 mL). The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (7 × 4 mL). The organic extracts were combined and then dried over Na<sub>2</sub>SO<sub>4</sub>. Solids were removed by filtration and solvents were removed in vacuo. The concentrate was purified by flash chromatography (5:40:55, methanol/CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane) to provide 0.232 g (96%) of tigogenin as a white solid.

Reference: Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436–5445.

#### 4.6.2 Desulfurization with Raney Nickel

Raney Nickel (nickel–aluminium alloy) is an effective catalyst for the conversion of thioketals to alkanes. Ultimately, a ketone is converted to the alkane with this mild method through a thioketal. Review: Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356–529.



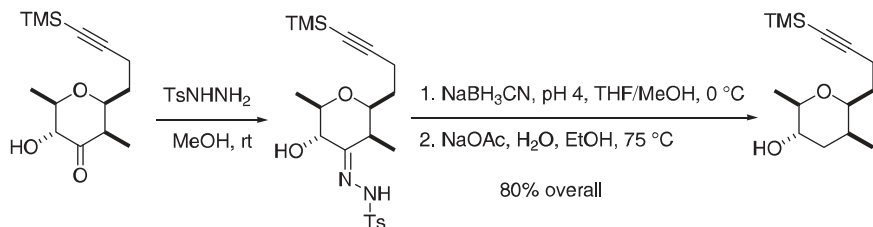
To a solution containing the ketone (0.2 g, 0.6 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 mL) were added 1,2-ethanedithiol (0.3 g, 3.0 mmol) and boron trifluoride etherate (0.3 g, 2.3 mmol). The mixture was stirred at room temperature for 24 h and quenched with aqueous  $\text{NaHCO}_3$  (10 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.2 g (85%) of the dithiane as a white solid.

To a solution containing the dithiane (0.6 g, 1.5 mmol) in absolute ethanol (100 mL) was added Raney nickel (2 g). The suspension was heated at reflux for 4 h, cooled to room temperature, and filtered through Celite with ethanol (200 mL). The solid was recrystallized from EtOAc to give 0.46 g (93%) of the reduced product as a white solid.

Reference: Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724.

#### 4.6.3 Reduction of Tosylhydrazones with Sodium Cyanoborohydride

A mild method for converting ketones to alkanes is via a two-step process involving a tosylhydrazone. First, the ketone is converted to the corresponding tosylhydrazone, and then treatment of the tosylhydrazone with the mild reducing agent sodium cyanoborohydride, under slightly acidic conditions, affords the alkane. Reviews: (a) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 1.14: Reduction of  $\text{C}=\text{X}$  to  $\text{CH}_2$  by Wolff-Kishner and Other Hydrazone Methods, pp. 343–362. (b) Lane, C. F. *Synthesis* **1975**, 135–146.



The hydroxyketone (748.3 mg, 2.79 mmol) was dissolved in methanol (36 mL), and  $\text{TsNHNH}_2$  (1.17 g, 6.98 mmol) was added. The reaction was stirred for 3 h at room temperature and then concentrated and filtered through a plug of silica gel with 10% ethanol/hexanes to remove excess  $\text{TsNHNH}_2$ . The filtrate was concentrated, and the residue (tosylhydrazone) was dissolved in THF (25 mL) and methanol (25 mL). A trace of methyl orange indicator was added, and the solution was cooled to 0 °C. Sodium cyanoborohydride (119.2 mg, 1.90 mmol) in methanol (2 mL) was added by syringe. Aqueous hydrochloric acid (1 N,  $5 \times 300 \mu\text{L}$  portions at 20 min intervals) was added dropwise by syringe. The progress of the reaction was monitored by TLC (40% EtOAc/hexanes). The color of the reaction was maintained yellow–orange ( $\text{pH} > 3.8$ ). After the fifth addition of 1 N HCl, all of the remaining starting material was consumed, as judged by TLC. The reaction was diluted with EtOAc (250 mL) and washed with water (50 mL), saturated  $\text{NaHCO}_3$  (50 mL), and brine (50 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and filtered through a plug of silica gel with 100% EtOAc. The filtrate

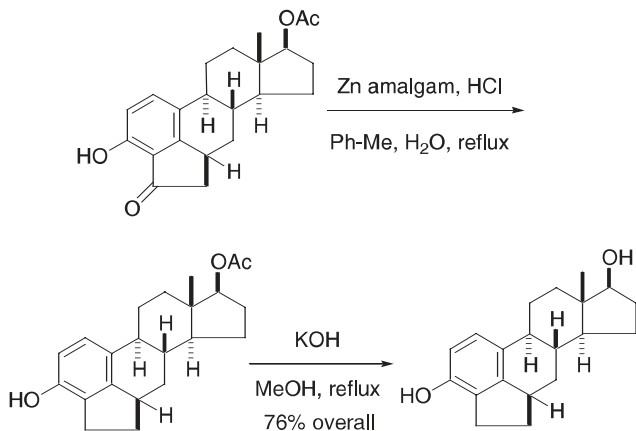
was concentrated to give a white foam (tosylhydrazine). The foam was dissolved in ethanol (52 mL), and the solution was degassed with nitrogen for 5 min. NaOAc·H<sub>2</sub>O (10.4 g) was added, and the mixture was degassed for a further 5 min. The reaction was then heated at 75 °C for 20 min, and the evolution of gas was observed. The reaction was cooled to room temperature, diluted with EtOAc (250 mL), and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. Purification by flash chromatography gave 570.5 mg (80%) of the alcohol.

Reference: Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983.

#### 4.6.4 Zinc Amalgam (Clemmensen Reduction)

The Clemmensen reduction is a classical method for the reduction of ketones to alkanes.

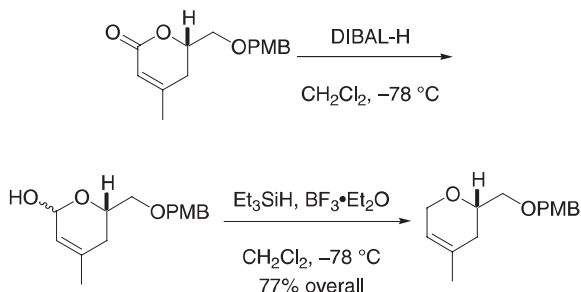
Reviews: (a) Motherwell, W. B.; Nutley, C. J. *Cont. Org. Synth.* **1992**, 219–241. (b) Yamamura, S.; Nishiyama, S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 1.13: Reduction of C=X to CH<sub>2</sub> by Dissolving Metals and Related Methods, pp. 309–313. (c) Vedejs, E. *Org. React.* **1975**, *22*, 401–422. (d) Martin, E. L. *Org. React.* **1942**, *1*, 155–209.



A mixture of mossy zinc (6 g) and 5% HgCl<sub>2</sub> solution (12 mL) was kept at room temperature for 1 h with occasional shaking, and the aqueous layer was then decanted. The amalgamated zinc was covered with concentrated hydrochloric acid (30 mL) and water (20 mL), and the ketone (0.8 g, 2.2 mmol) and toluene (7 mL) were added. The mixture was heated under reflux for 2.5 h, cooled, and worked up to give 0.69 g of a crude mixture. The mixture was completely hydrolyzed by refluxing for 2 h with a solution of 0.5 g of potassium hydroxide in methanol (10 mL). The methanol was removed, and the residue was diluted with water. The clear alkaline solution was acidified and worked up to furnish 0.575 g of the crude phenol. The phenol was recrystallized from ether/petroleum ether to afford 0.51 g (76%) of the phenol.

Reference: Ghosh, A. C.; Hazra, B. G.; Duax, W. L. *J. Org. Chem.* **1977**, *42*, 3091–3094.

## 4.6.5 Ionic Hydrogenation with Triethyl Silane and Boron Trifluoride

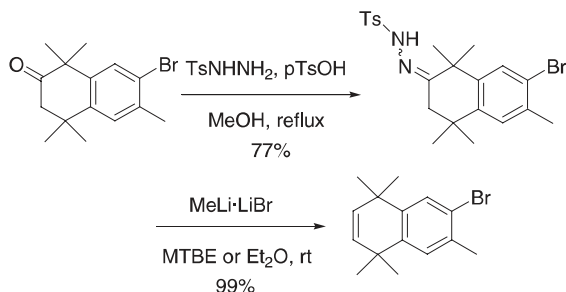


Diisobutylaluminium hydride (DIBAL-H) (1.0 M in heptane, 2.70 mL, 2.70 mmol) was added to a solution of the lactone (598 mg, 2.28 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $-78\text{ }^\circ\text{C}$ , and the resulting solution was stirred for 1 h. After this time, the reaction was quenched by pouring into a vigorously stirred mixture of EtOAc and potassium sodium tartrate solution. Once the two clear layers had formed, they were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried (magnesium sulfate), and concentrated under reduced pressure. The crude lactol was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and cooled to  $-78\text{ }^\circ\text{C}$ . Triethylsilane (0.55 mL, 3.42 mmol), followed by boron trifluoride etherate (0.29 mL, 2.28 mmol), were added, and the resulting solution was allowed to stir for 20 min. The reaction was quenched with saturated aqueous ammonium chloride. The layers were separated, and the aqueous phase was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with saturated aqueous  $\text{NaHCO}_3$  and brine, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with hexanes:EtOAc (10:1) to yield 435 mg (77%) of the cyclic ether as a clear colorless oil.

Reference: Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026–3042.

## 4.6.6 Shapiro Reaction

The Shapiro reaction is the conversion of ketone to an alkene via a tosylhydrazone. The tosylhydrazone is treated with two equivalents of strong base, typically *n*-BuLi or MeLi, to afford an alkenyllithium species which is quenched with an electrophile to form an alkene (see also chapter 5, 5.1.25 Shapiro reaction). Reviews: (a) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1–83. (b) Shapiro, R.H. *Org. React.* **1976**, *23*, 405.



A suspension of the ketone (30.5 g, 0.10 mol), *p*-toluenesulfonylhydrazide (22.1 g, 0.119 mol), and *p*-toluenesulfonic acid monohydrate (4.92 g, 25.9 mmol) in MeOH (611 mL) was heated at reflux under N<sub>2</sub> for 24 h. The resultant reaction slurry was cooled for 1 h in an ice-bath, filtered, and rinsed with cold MeOH (150 mL) to give 36.8 g (77%) of the hydrazone.

(Caution: this transformation produces nitrogen gas. The reaction system should be vented. Do not run in a closed system! This reaction may also be run with diethyl ether.) A suspension of the hydrazone (20.0 g, 43.2 mmol) in methyl *tert*-butylether (MTBE 400 mL) was treated with a solution of MeLi as a complex with LiBr (1.5 M in Et<sub>2</sub>O, 86.3 mL, 0.13 mol) at room temperature for 1 h, cooled to 0 °C, and quenched with water (500 mL). The reaction was extracted with MTBE (1 L), the organic layer was dried (MgSO<sub>4</sub>), and the solvent was removed in vacuo to give 12.0 g (99%) of the alkene as a white solid.

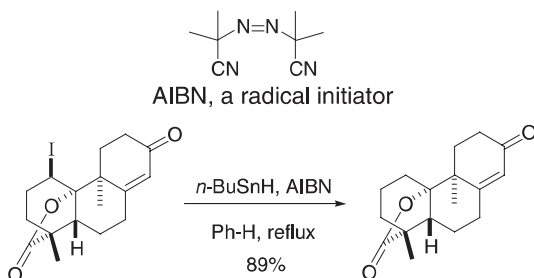
Reference: Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772–5782.

## 4.7 Reductive Dehalogenations

### 4.7.1 Tributyltin Hydride

Review: Neumann, W. P. *Synthesis* **1987**, 665–682.

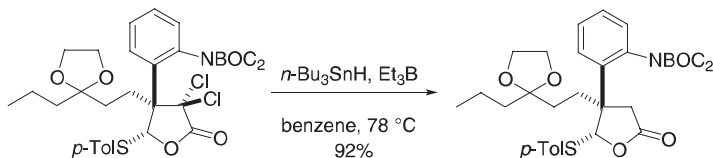
#### 4.7.1.1 With 2,2'-Azobisisobutyronitrile



To a stirred solution of the iodolactone (296 mg, 0.74 mmol) in dry benzene (6 mL) was added *n*-tributyltin hydride (0.40 mL, 1.5 mmol) and a catalytic amount of AIBN. The mixture was heated at reflux for 30 min. It was then cooled to room temperature and concentrated to approximately 2 mL under reduced pressure. Flash chromatography (50 g of silica gel, 2:1 ether:petroleum ether then 4:1 CH<sub>2</sub>Cl<sub>2</sub>:ether of the crude product) provided 180 mg (89%) of the lactone as a colorless solid.

Reference: Britton, R. A.; Piers, E.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 3068–3075.

#### 4.7.1.2 With Triethylborane



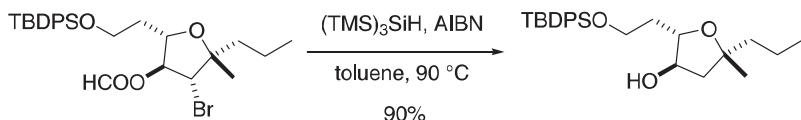


A solution of the dichlorolactone (1.5 g, 2.15 mmol) and freshly prepared tributyltin hydride (1.3 mL, 4.9 mmol) in benzene (20 mL) was heated at 78 °C for 15 min. in the presence of a catalytic amount of  $\text{Et}_3\text{B}$  (0.7 mL of a 1 M solution in THF, 0.7 mmol). After evaporation of the solvent in vacuo, the residue was dissolved in ether (25 mL). The ether solution was treated with a saturated aqueous solution of potassium fluoride (25 mL). The precipitated tri-*n*-butyltin fluoride was filtered and washed thoroughly with ether. The combined ether layers were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel using a gradient of eluents (hexanes:EtOAc, 20:1 to 4:1) giving 1.27 g (92%) of the lactone as a clear oil.

Reference: Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399.

#### 4.7.2 Trialkylsilanes

Reviews: (a) Chatgililoglu, C. *Organosilanes in Radical Chemistry Principles, Methods, and Applications*; Wiley&Sons, Ltd: West Sussex, U.K., 2004. (b) Chatgililoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.

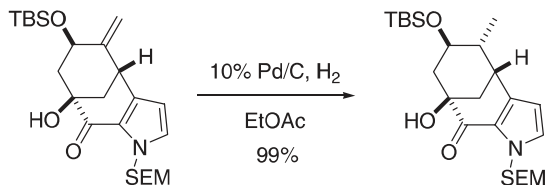


$(\text{TMS})_3\text{SiH}$  (850  $\mu\text{L}$ , 2.76 mmol) and AIBN (30 mg, 0.18 mmol) were added to a solution of the bromoformate (980 mg, 1.84 mmol) in toluene (90 mL), and the resulting mixture was stirred at 80 °C for 4 h. The solution was allowed to reach ambient temperature before the solvent was evaporated. The residue was dissolved in methanol (100 mL). Aqueous saturated  $\text{NaHCO}_3$  (about 12 mL) was added dropwise, and the reaction mixture was stirred for 2 h before it was diluted with water (25 mL). A standard extractive workup with MTBE followed by flash chromatography (hexanes:EtOAc, 8:1) of the crude product provided 705 mg (90%) of the alcohol as a colorless oil.

Reference: Lepage, O.; Kattinig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971.

## 4.8 Carbon–Carbon Double and Triple Bond Reductions

### 4.8.1 Pd/C, $\text{H}_2$



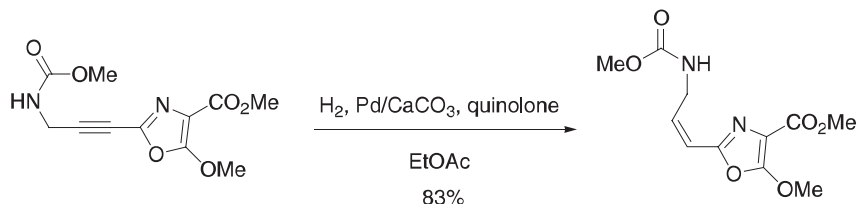
The unsaturated [3.3.1] bicycle (360 mg, 0.78 mmol), 10% Pd/C (130 mg, 0.12 mmol), and EtOAc (8 mL) were combined, and the reaction vessel was evacuated and back-filled with hydrogen (1 atm). The reaction mixture was stirred under hydrogen for 30 min and

then filtered over a plug of silica gel topped with Celite (EtOAc eluent) to afford 358 mg (99%) of the saturated bicycle as a colorless oil.

Reference: Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553.

#### 4.8.2 Lindlar's Catalyst

Converts alkynes to *cis*-olefins

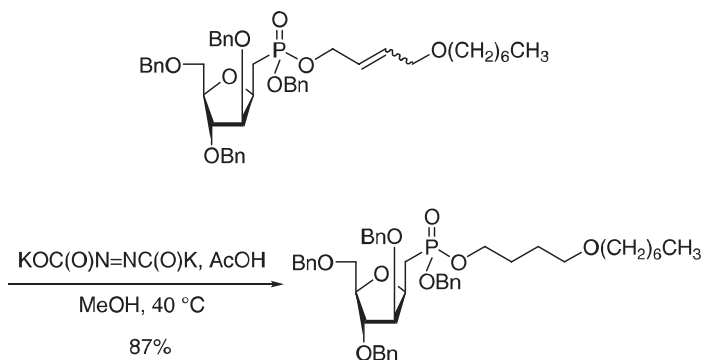


A suspension of Lindlar's catalyst [Pd (5% on  $\text{CaCO}_3$ ), 213 mg, 0.10 mmol], quinolone (0.81 mL, 6.8 mmol), and the alkyne (587 mg, 2.19 mmol) in EtOAc (22 mL) was stirred for 30 min. The flask was charged with hydrogen (1 atm), and the reaction mixture was stirred until  $^1\text{H}$  NMR analysis indicated complete conversion (14 h). The reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc/ $\text{CH}_2\text{Cl}_2$ , 1:5 then EtOAc) to give 487 mg (83%) of the *cis*-olefin as a white solid.

Reference: Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670–13671.

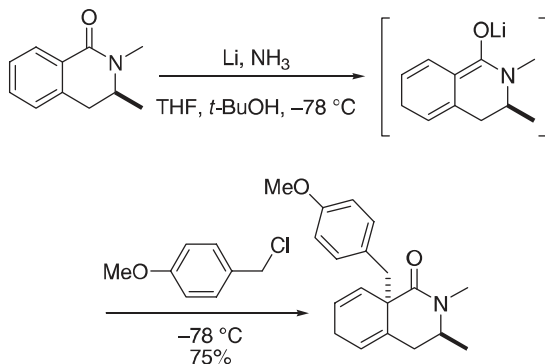
#### 4.8.3 Diimide

Diimide must be generated in situ. It is an effective reagent for the *syn*-reduction of alkenes and favors reduction of the more substituted olefin. Reviews: (a) Pasto, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 3.3: Reductions of  $\text{C}=\text{C}$  and  $\text{C}=\text{C}$  by Noncatalytic Chemical Methods, pp. 472–478. (b) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91–155.





a proton source or an electrophile. Reviews: (a) Rabideau, P.W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1–334. (b) Mander, L. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 3.4: Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods, pp. 490–514. (c) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1579–1603.



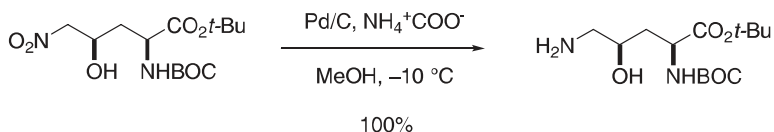
To a solution of the isoquinolinone (1.156 g, 9.90 mmol) and *tert*-butyl alcohol (0.88 mL, 11.9 mmol) in THF (30 mL) at  $-78\text{ }^{\circ}\text{C}$  was added liquid ammonia (about 280 mL). Lithium was added in small pieces until the blue coloration persisted, after which the solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min. The blue coloration was dissipated with piperlyne, 4-methoxybenzyl chloride (4.83 g, 31.00 mmol) in THF (5 mL) was introduced by syringe, and the mixture was stirred for an additional 150 min at  $-78\text{ }^{\circ}\text{C}$ . Solid ammonium chloride was added and then the ammonia was allowed to evaporate. The pale yellow residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (30 mL) and water (40 mL). The layers were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30\text{ mL}$ ). The combined organic layers were washed with 10% sodium thiosulfate solution (20 mL), dried over magnesium sulfate, and concentrated. Flash chromatography (EtOAc:hexane, 2:1) on silica gave 2.21 g (75%) of the tetrahydroisoquinolinone.

Reference: Schultz, A. G.; Guzi, T. J.; Larsson, E.; Rahm, R.; Thakker, K. Bidlack, J. M. *J. Org. Chem.* **1998**, *63*, 7795–7804.

## 4.9 Heteroatom–Heteroatom Reductions

### 4.9.1 Reduction of a Nitro Group to an Amine Using Ammonium Formate

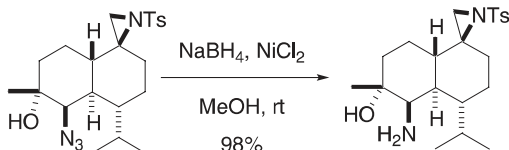
A mild method for converting a nitro group to an amino functionality is by using the hydrogen transfer reagent ammonium formate in the presence of Pd/C. Reviews: (a) Kabalka, G. W.; Varma, R. S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 8, Chapter 2.1: Reduction of Nitro and Nitroso Compounds, pp. 363–379. (b) Ram, S.; Ehrenkauffer, R.E. *Synthesis* **1988**, 91–94.



The nitroalcohol (5 g, 14.9 mmol) is dissolved in methanol (50 mL). The reaction mixture is cooled to  $-10\text{ }^{\circ}\text{C}$ , and palladium on carbon (10%, purissimum, Fluka, 2.5 g) and dry ammonium formate (9.43 g, 150 mmol) are added while maintaining the reaction temperature at  $-10\text{ }^{\circ}\text{C}$ . After stirring the reaction for 2 h, the catalyst is filtered off. The solvent is removed and EtOAc and saturated aqueous  $\text{NaHCO}_3$  solution are added ( $\text{pH} \geq 7$ ). The phases are separated and after two additional washings with EtOAc, the combined organic phases are washed with brine, dried over magnesium sulfate, and the solvent is removed in vacuo. The amino alcohol is obtained as a colorless yellow oil in a crude yield of 4.55 g (100%).

Reference: Rudolph, J.; Hanning, F.; Theis, H.; Wischnat, R. *Org. Lett.* **2001**, *3*, 3153–3155.

#### 4.9.2 Sodium Borohydride/Nickel Dichloride

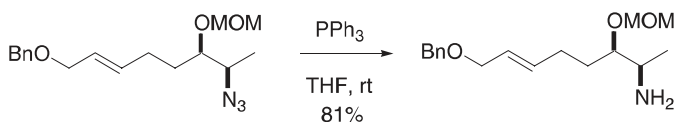


To a solution of the azide (617 mg, 1.43 mmol) in methanol/THF (30 mL, 3:1) at  $0\text{ }^{\circ}\text{C}$  was added nickel dichloride hexahydrate (542 mg, 2.28 mmol) followed by sodium borohydride (248 mg, 6.57 mmol) over 10 min. After 30 min, the black mixture was allowed to warm to  $25\text{ }^{\circ}\text{C}$ , diluted with EtOAc (40 mL), and filtered through Celite. The solution was further diluted with EtOAc (50 mL) and washed with brine ( $2 \times 25\text{ mL}$ ) and 0.01 M EDTA solution ( $1 \times 25\text{ mL}$ ,  $\text{pH} 7.5$ , K-phosphate buffer). After solvent removal in vacuo, the resulting oil was purified by silica gel chromatography (100% EtOAc then EtOAc:methanol, 12:1) to give 569 mg (98%) of the amine.

Reference: White, R. D.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1825–1827.

#### 4.9.3 Staudinger Reaction

The Staudinger reaction is a mild method for the conversion of azides to amines by treating the azide with triphenylphosphine in the presence of water. The water is necessary, because the intermediate iminophosphane is hydrolyzed to form the amine and triphenylphosphine oxide. Reviews: (a) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406. (b) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437–472.



To a solution of the azide (0.45 g, 1.4 mmol) in THF/water (10:1.5 mL) was added triphenylphosphine (0.41 g, 1.6 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The mixture was concentrated, and the residue was purified by preparative TLC eluted with CHCl<sub>3</sub>:MeOH (18:1) to afford 0.33 g (81%) of the amine as a colorless oil.

Reference: Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27–29.