A Highly Diastereoselective Aldol Reaction
Using a Chiral Oxazolidinone Auxiliary

A. $\text{C}_6\text{H}_{5}\text{H}_2\text{C} \xrightarrow{1) \text{n-BuLi}} \text{C}_6\text{H}_{5}\text{H}_2\text{C}$
$\xrightarrow{2) \text{EtCOCl}} \text{C}_6\text{H}_{5}\text{H}_2\text{C}$

B. $\text{C}_6\text{H}_{5}\text{H}_2\text{C} \xrightarrow{1) \text{Bu}_2\text{BOTf, Et}_3\text{N}} \text{C}_6\text{H}_{5}\text{H}_2\text{C}$
$\xrightarrow{2) \text{PhCHO}} \text{C}_6\text{H}_{5}\text{H}_2\text{C}$

C. $\text{C}_6\text{H}_{5}\text{H}_2\text{C} \xrightarrow{\text{H}_2\text{O}_2, \text{LiOH}} \text{C}_6\text{H}_{5}\text{H}_2\text{C}$

Submitted by James R. Gage and David A. Evans.

Checked by:

1. Procedure

A. 3-(1-Oxopropyl)-4-(S)-phenylmethyl-2-oxazolidinone. A dry, 500-mL flask equipped with a magnetic stir bar is charged with 17.7 g (0.100 mol) of the starting oxazolidinone, capped with a rubber septum, and flushed with nitrogen. Anhydrous tetrahydrofuran, 300 mL (Note 1), is then added to the flask via
cannula, and the resulting solution is cooled to -78°C in an acetone-dry ice bath. A solution of 68.4 mL (0.101 mol) of 1.47 M n-butyllithium in hexane (Note 2) is transferred via cannula first to a dry, septum-stoppered 100-mL graduated cylinder with a ground glass joint, then to the reaction flask over a 10-min period. The solution may turn yellow and slightly cloudy. Freshly distilled propionyl chloride (9.6 mL, 0.11 mol, Note 3) is added in one portion by syringe after completion of the addition of n-butyllithium. The resulting clear, nearly colorless solution is stirred 30 min at -78°C, then allowed to warm to ambient temperature over a 30-min period. Excess propionyl chloride is quenched by the addition of 60 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotary evaporator (bath temp. ca. 25-30°C), and the resulting slurry is extracted with two 80-mL portions of dichloromethane. The combined organic extracts are washed with 75 mL of a 1 M aqueous sodium hydroxide solution and 75 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation, and the residue, a light yellow oil, is placed in a refrigerator overnight to crystallize. The resulting crystalline solid is pulverized and triturated with a minimum quantity of cold hexane. After filtration and drying 23.0 g (98.6%) of the desired product is obtained as a colorless crystalline solid, mp 40-43°C. (Notes 4 and 5).

B. The Boron Aldol Reaction. To a dry, 2-L flask equipped with a large magnetic stir bar is introduced 23.3 g (0.100 mol) of the acylated oxazolidinone. The flask is sealed with a rubber septum and swept with nitrogen. The solid is dissolved in 200 mL of anhydrous dichloromethane (Note 6), which is introduced via syringe. A thermometer is inserted through the rubber septum, and the contents of the flask are cooled to 0°C with an ice bath. To this cooled solution is added via syringe 27 mL (0.107 mol) di-(n-butyl)boryl triflate followed
by 16.7 mL (0.120 mol) of triethylamine (Note 7) dropwise at such a rate to keep the internal temperature below +3°C. The solution may turn slightly yellow or green during the di-(n-butyl)boryl triflate addition, and then to light yellow when triethylamine is added. The ice bath is then replaced with a dry ice-acetone bath (Note 8). When the internal temperature drops below -65°C, 10.3 mL (0.101 mol) of freshly distilled benzaldehyde is added over a 5-min period via syringe. The solution is stirred for 20 min in the dry ice-acetone bath, then 1 hr at ice bath temperatures. The reaction mixture is then quenched by the addition of 100 mL of a pH 7 aqueous phosphate buffer and 300 mL of methanol. To this cloudy solution is added by syringe 300 mL of 2:1 methanol-30% aqueous hydrogen peroxide at such a rate to keep the internal temperature below +10°C. After stirring 1 additional hr, the volatiles are removed on a rotary evaporator at a bath temperature of 25-30°C. The resulting slurry is extracted with three 500-mL portions of diethyl ether. The combined organic extracts are washed with 500 mL of 5% aqueous sodium bicarbonate and 500 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, affording 35-36 g of a white solid. The unpurified aldol adduct has a diastereomeric purity of at least 99% as determined by gas chromatography (Note 9). The solid is recrystallized from ca. 500 mL of 1:2 ethyl acetate-hexane, yielding 25.5 g (75%) of the desired aldol adduct, mp 89-92°C (Note 11). The mother liquor is purified by flash chromatography (column dimensions: 8 cm x 30 cm) with flash-grade silica gel (Note 12). Upon elution with 25% ethyl acetate-hexane, an additional 2.8 g (8%) of diastereomERICally pure material is obtained for a total yield of 83%.

C. Chiral auxiliary removal. A 500-mL flask fitted with a magnetic stir bar is charged with 8.48 g (0.025 mol) of the aldol adduct and 125 mL of 4:1 tetrahydrofuran-distilled water. The flask is sealed with a rubber septum,
purged with nitrogen, and cooled to 0°C in an ice bath. To this solution is added via syringe 10.2 mL (0.100 mol) of 30% aqueous hydrogen peroxide (Note 13) over a 5-min period, followed by 0.96 g (0.040 mol) of lithium hydroxide in 50 mL of distilled water. Some gas evolves from the clear solution. After stirring the solution for 1 hr, the septum is removed, and 12.6 g (0.100 mol) of sodium sulfite in 75 mL of distilled water is added. The bulk of the tetrahydrofuran is removed on a rotary evaporator at a bath temperature of 25-30°C, and the resulting mixture (pH 12-13) is extracted with three 100-mL portions of dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer is cooled in an ice bath and acidified to pH 1 by the addition of a 6 M aqueous hydrochloric acid solution. The resulting cloudy solution containing the β-hydroxy acid is then extracted with five 100-mL portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated, affording 5.1 g of a white crystalline solid, which is dissolved in approximately 200 mL of a 5% aqueous sodium bicarbonate solution. This solution is extracted with two 100-mL portions of dichloromethane and then acidified and extracted with ethyl acetate as before. The combined dichloromethane extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 4.35 g (99%) of the oxazolidinone auxiliary as a white crystalline solid. This solid is recrystallized from 50 mL of 2:1 ethyl acetate-hexane to give 3.95 g (89%) of the recovered oxazolidinone as white crystals, mp 85-87°C. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated affording 4.50 g (100%) of the desired hydroxy acid as a white crystalline solid, which is recrystallized from ca. 20 mL of carbon tetrachloride to give 4.35 g (97%) of the pure hydroxyacid, mp 87.5-88.5°C (Note 14).
2. Notes

1. Reagent grade tetrahydrofuran was purchased from Fisher Scientific Company and either freshly distilled from sodium metal and benzophenone or dried at least 3 days over activated Linde 4 Å molecular sieves before use in reaction A. It was used as received for reaction C.

2. N-Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. and titrated prior to use.³

3. Propionyl chloride (d 1.065) was obtained from Aldrich Chemical Company, Inc. and distilled prior to use.

4. Alternatively, the acylated oxazolidinone can be isolated by distillation (Kugelrohr, 125°C, 12 mtorr). Isolated yields are 97-99%.

5. The product has the following spectroscopic properties: infrared (solution in dichloromethane) cm⁻¹: 3030, 2980, 1780, 1705, 1455, 1385, 1245, 1210, 1080; ¹H NMR (CDCl₃) δ: 1.2 (t, 3H, CH₃), 2.8 (dd, 1H, CH₂C₆H₅), 2.9 (m, 2H, CH₂CH₃), 3.3 (dd, 1H, CH₂C₆H₅), 4.1 (m, 2H, CHCH₂O), 4.7 (m, 1H, NCH), 7.1-7.5 (m, 5H, ArH); [α]D +92.9° (ethanol, c. 1.01).

6. Dichloromethane was distilled from calcium hydride.

7. Di-((n-butyl)boryl triflate was prepared according to the method of Mukaiyama.⁴ It is also available from Aldrich Chemical Company, Inc. as a solution in dichloromethane or diethyl ether, but results with this material are inconsistent. It should be used within 2 weeks of preparation or redistillation, as yields of the aldol adduct begin to drop after this time. Triethylamine (Fisher Scientific Company) was distilled from calcium hydride immediately prior to use.

8. The entire reaction can be carried at 0°C if desired. The ratio of diastereomers in the unpurified product mixture falls slightly to 97.6:0.2:2.2 (Note 9).
9. Diastereomer ratios were determined by gas chromatography. Since
the aldol adduct undergoes retroaldol reaction on the column, it must be
silylated prior to injection. Approximately 5 mg of the crude adduct is filtered
through a short plug of silica gel to remove any trace metals. The material is
taken up into 1-2 mL of dichloromethane in a 2-mL flask or small test tube. To
this solution is added 4-5 drops of N,N-diethyl-1,1,1-trimethylsilylamine and a
small crystal of 4-(N,N-dimethylamino)-pyridine (Note 10). The solution is
stirred 2 hr and injected directly onto the column. (Column conditions: 30 m x
32 mm fused silica column coated with DB 5, 14 psi hydrogen carrier gas, oven
temperature 235°C).

10. N,N-Diethyl-1,1,1-trimethylsilylamine and 4-(N,N-dimethylamino)-
pyridine were purchased from Aldrich Chemical Company, Inc.

11. The product has the following spectroscopic characteristics: infrared
(solution in dichloromethane) cm⁻¹: 3520, 3040, 2980, 1780, 1695, 1455, 1385,
1210, 1110; ¹H NMR (CDCl₃) δ: 1.2 (d, 3H, CH₃), 2.8 (dd, 1H, CH₂C₆H₅), 3.1
(d, 1H, OH), 3.3 (dd, 1H, CH₂C₆H₅), 4.1 (m, 3H, CHCH₂O, CHCH₃), 4.6 (m, 1H,
NCH), 5.1 (m, 1H, HOCH), 7.1-7.5 (m, 10H, ArH); [α]D +75.7° (dichloromethane,
c. 1.00).

12. Kieselgel 60 was purchased from EM Science, Cherry Hill, NJ, an
affiliate of E. Merck, Darmstadt.

13. Hydrogen peroxide was obtained from Mallinckrodt, Inc.

14. The following spectroscopic characteristics were observed: infrared
(solution in dichloromethane) cm⁻¹: 3600, 3400-2300 broad hump, 3040, 3000,
1710, 1455, 1230; ¹H NMR (CDCl₃) δ: 1.2 (d, 3H, CH₃), 2.9 (m, 1H, CHCH₃),
5.2 (d, 1H C₆H₅CH), 7.2-7.4 (m, 5H, ArH). No epimerization was detected by
NMR.
3. Discussion

This procedure demonstrates a particularly effective method for controlling the relative and absolute stereochemistry of the aldol reaction. This reaction is quite general in scope. Alkyl-, aryl-, and $\alpha,\beta$-unsaturated aldehydes all give good results. In addition to chiral propionates, a range of related aldol reactions may be carried out. For example, the analogous aldol reactions of thioalkyl, benzylxoy, or haloacetate, as well as succinate and crotonate-derived carboximides, have been reported.

In addition to the high levels of asymmetric induction, two other attractive features of this sequence of reactions warrant comment. First, both acylation and hydrolysis of the chiral auxiliary are facile, high yielding reactions. Second, we have recently found that the lithium hydroperoxide hydrolysis protocol described in the preceding section is the method of choice for the "deacylation" process. This reagent exhibits remarkable regioselectivity for attack at the desired exocyclic acyl carbonyl moiety.

1. Department of Chemistry, Harvard University, Cambridge, MA 02138.
5. For a general review see: Evans, D. A. Aldrichimica Acta 1982, 15, 23.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)
Propionyl chloride: Propanoyl chloride (8,9); (79-03-8)
Di-(n-butyl)boryl triflate: Methanesulfonic acid, trifluoro-, anhydride with dibutylborinic acid (9); (60669-69-4)
Triethylamine: Ethanamine, N, N-diethyl (8,9); (121-44-8)
Benzaldehyde (8,9); (100-52-7)
Hydrogen peroxide (8,9); (7722-84-1)
4-N,N-Dimethylaminopyridine: 4-Pyridinamine, N,N-dimethyl (8,9); (1122-58-3)
N,N-Diethyl-1,1,1-Trimethylsilylamine (9); (66130-90-3)
Sodium sulfite: Sulfurous acid, disodium salt (8,9); (7757-83-7)