Catalysts for Fine Chemical Synthesis: Hydrolysis, Oxidation and Reduction. Volume 1
Edited by Stan M Roberts and Geraldine Poignant

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Part II: Procedures

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2 General Information

Before conducting an asymmetric synthesis, one needs to ensure that one is able to separate both enantiomers of the desired compound. The racemate (*RS*, 50% of each enantiomer) needs to be synthesized in order to study the different possibilities of differentiating each enantiomer.

Two enantiomers can be differentiated by their retention time (R_f) during chromatography on a chiral support, for example, using High Pressure Liquid Chromatography (HPLC) or Gas Chromatography (GC) over a chiral column. They can also be separated by derivatization with an homochiral auxiliary, affording the corresponding diastereomers. As the two diastereomers can have different chemical shifts in NMR spectra, their analysis by ^{1}H-, ^{13}C- or ^{19}F-NMR spectroscopy represents a useful method for the determination of the enantiomeric excess. (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid or its (*S*)-(−)-enantiomer (MTPA, Mosher acid) is used in the following chapters to determine the enantiomeric excess (e.g. of allylic alcohols). Chemical shift reagents such as [europium(III)-tris[3-(heptafluoropropylhydromethylene)-d-camphorate]] ($Eu(hfc)_3$) can also be used to assess the ratio in a mixture of enantiomers. Each method needs to be performed on the racemic compound in order to find the conditions to separate the two enantiomers.

For experiments conducted in Liverpool GC was performed on a Shimadzu GC-14A gas chromatograph using a SE30 capillary column with the injector and detector set to 250 °C; chiral GC was performed with chiral capillary columns (Lipodex® E and C as indicated) with the injector and detector set to 250 °C. HPLC was performed on a Gilson chromatograph equipped with chiral columns Daicel Chiralpack® AD and OD (wavelength 254 nm).

NMR spectra were recorded on Bruker AC200 spectrometers; unless indicated otherwise deuteriated chloroform was used as solvent and tetramethylsilane as internal reference. Chemical shifts (δ) are given in ppm. The following abbreviations were used to define the multiplicities; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; coupling constants (*J*) are measured in Hertz (Hz). IR spectra were recorded on a Nicolet Magna-550 FTIR

spectrometer. High Resolution Mass Spectra were recorded on a Kratos profile HV3, CIPOS, Fisons VG7070E spectrometer.

Some of the procedures described in the following chapters had to be carried out under an inert atmosphere, nitrogen or argon, to minimize contact with oxygen and moisture. It is then necessary to use Schlenk techniques including the utilization of a vacuum line connected to a high vacuum pump and an inert gas inlet. The use of such equipment requires experience in working under anhydrous conditions.

All the procedures described were performed using dry solvents which were freshly distilled under nitrogen. Tetrahydrofuran and ether were distilled from sodium benzophenone ketal under nitrogen, and dichloromethane from calcium hydride under nitrogen. Petroleum ether (b.p. 40–60 °C) was distilled. Starting materials and solvents were used as obtained from commercial suppliers without further purification unless specified otherwise.

Molecular sieves or magnesium sulfate were activated by heating at 500 °C for 2–14 hours and cooled in a desiccator under vacuum.

Flash column chromatography was performed using Merck 60-silica gel (40–63 μm) and solvents were obtained commercially and used as received.

Most of the reactions described in the following chapters were monitored by Thin Layer Chromatography (TLC) using plastic TLC plates coated with a thin layer of Merck 60 F_{254} silica gel. The products were detected by using an ultraviolet lamp or the TLC plates were treated with *p*-anisaldehyde reagent, prepared as explained below, and then heated to 120 °C to stain the spots. After visualization and measurement, the R_f values were recorded.

PREPARATION OF p-ANISALDEHYDE REAGENT

Materials and equipment

- Ethanol (370 mL)
- Concentrated sulfuric acid (14 mL)
- Glacial acetic acid (4 mL)
- *p*-Anisaldehyde

- Beaker, 500 mL with a magnetic stirrer bar
- Magnetic stirrer
- Glass bottle for storage, 500 mL

Procedure

The breaker was filled with ethanol (370 mL); concentrated sulfuric acid (14 mL) was added slowly followed by glacial acetic acid (4 mL) and then *p*-anisaldehyde (1 mL). The solution was stirred for 15 minutes and then transferred to a suitable labelled bottle for storage.