

# ORGANIC CHEMISTRY

## Lab Course

### Selective Organic Synthesis KD 2390

Period 1, 2013

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## Reports

The deadline for handing in reports is November 1

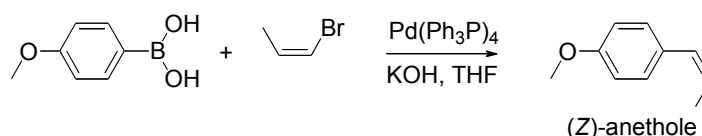
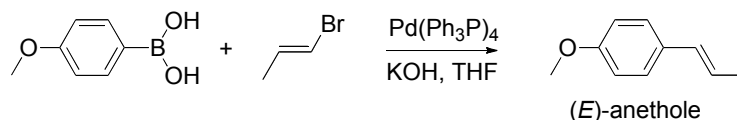
### Writing the report

#### The report should contain:

- i* Front page with title of synthesis, your name, and date
- ii* Reaction Scheme (no mechanism)
- iii* Introduction where the background of the synthesis is described; the importance/usefulness of the reaction, products of particular interest. Give answers to the specific questions
- iv* Results & Discussion. Describe the procedure in general terms, whether inert atmosphere is necessary, choice of reagents etc. Show the mechanism of the reaction(s). Discuss problems encountered during the synthesis. Discuss possible improvements.
- v* Experimental Section. Describe the details of the synthesis, including amounts of reagents and starting materials, and yields and, if relevant, ee:s of products. All spectral data should be included.
- vi* References
- vii* Copies of spectra and chromatograms

# 1. Stereospecific Synthesis of (Z)- and (E)-Anethole by Pd(0)-catalyzed Suzuki coupling<sup>1</sup>

(E)-Anethole is the major component of anise oil, which is used as flavoring of cookies and liquors and is also a substitute for licorice root extract in licorice sticks.



*Procedure:* 4-Methoxyphenylboronic acid (84 mg, 0.55 mmol), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) and KOH (1.1 mL 1 M) are dissolved in THF (2 mL). (Z)- or (E)-1-Bromo-1-propene (178  $\mu$ L, 2.1 mmol) is added and the reaction mixture stirred under nitrogen (inert atmosphere gives better result but is not necessary) at 60 °C for 1 h. Check by TLC (eluent EtOAc) that product has formed. Water (1 mL) is then added and the mixture extracted with pentane (5 x 1 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and the residue obtained after evaporation of the solvent is dissolved in five 1 mL portions of pentane and the solutions filtered through a 1 cm silica gel column (Pasteur pipette) to remove polar impurities. The solvent is evaporated and the product analyzed by GLC and <sup>1</sup>H NMR spectroscopy.

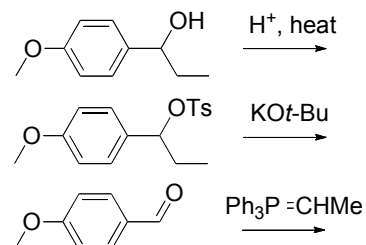
Compare the chromatograms, NMR spectra and smell (be careful) of the two stereoisomers.

*Hazards:* The boronic acids and the vinyl halides are irritants. Tetrahydrofuran, pentane, and ethyl acetate are flammable solvents and irritants. KOH is corrosive and can cause severe damage to eyes and skin.

*Lab report:* The following should be included in the report

1. Explain how the configuration of the olefinic bond can be determined.
2. Explain the difference between a stereoselective and a stereospecific reaction.
3. Why is a base needed for the Suzuki coupling?
4. Anethole can be prepared by several other methods, such as

- i) Acid-catalyzed dehydration of an alcohol,
- ii) Elimination of a tosylate
- iii) Wittig reaction



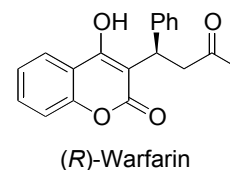
Discuss the stereochemistry of the products obtained via the three methods. What is the advantage of the Suzuki procedure?

<sup>1</sup> T. Grove, D. DiLella, E. Volker, *J. Chem. Ed.* **2006**, 83, 1055-1057.

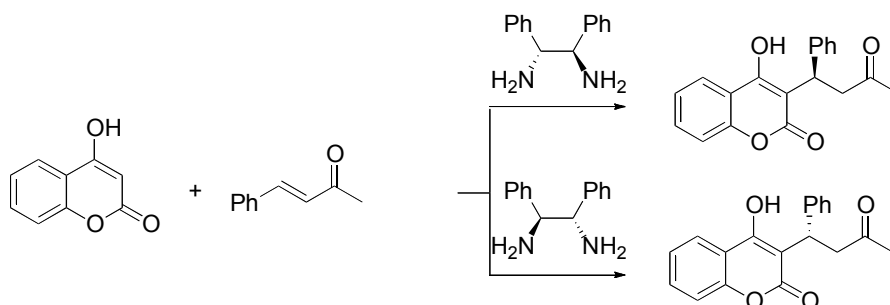
## 2. A Green, Enantioselective Synthesis of Warfarin<sup>2</sup>

*Key words:* imine-iminium formation; keto-enol tautomerism; Michael addition; enamine hydrolysis, organocatalysis; enantioselectivity; keto-ketal equilibrium

Warfarin, first reported in 1944, is a commercial anticoagulant and rat poison. It is a coumarin, which normally is sold in racemic form, though the (*R*) and (*S*) enantiomers differ in potency, metabolism, and interactions with other drugs. It is named after Wisconsin Alumni Research Foundation (the patent holders) and coumARIN. Fears about its toxicity to humans declined after an unsuccessful suicide attempt in 1951.<sup>3</sup> It is a vitamin K antagonist, and it attenuates the biosynthesis of vitamin K dependent blood clotting factors.



This synthesis of enantioenriched warfarin uses an organocatalyst, (*R,R*)- or (*S,S*)-1,2-diphenylethylenediamine (dpn), which can be obtained by resolution of the racemic diamine.



*Procedure:* *trans*-4-Phenyl-3-buten-2-one (87.8 mg, 0.60 mmol), (*R,R*)- or (*S,S*)-1,2-diphenylethylenediamine (dpn, 10.3 mg, 0.049 mmol), and 4-hydroxycoumarin (81.4 mg, 0.50 mmol), acetic acid (0.32 mL, 5.60 mmol), and THF (1 mL) are added to a vial. The reaction mixture is stirred overnight or longer. The progress of the reaction is checked with TLC using pure CH<sub>2</sub>Cl<sub>2</sub> as eluent. At completion, the previously peach or pink solution should be clear yellow.

The solvent and acetic acid are removed by rotary evaporation. The product is purified by column chromatography using 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent. Alternatively, the product can be purified by crystallization from acetone/water (this requires 4 times as large scale): dissolve the crude product in minimal amount of boiling acetone. Add boiling water dropwise until the solution becomes significantly cloudy. Heat the mixture to dissolve the crystals, adding a few drops of boiling acetone if necessary. Slowly cool the solution to room temperature and then in an ice bath. Collect the crystalline product by filtration and rinse carefully with a small amount of ice-cold 4:1 acetone/water.

Determine the melting point of the product. Analyze the product by <sup>1</sup>H NMR spectroscopy and measure the optical rotation or run chiral HPLC.

*Hazards:* *trans*-4-Phenyl-3-buten-2-one is an irritant and possible sensitizer. 4-Hydroxycoumarin and 1,2-diphenylethylenediamine are irritants. Acetic acid is

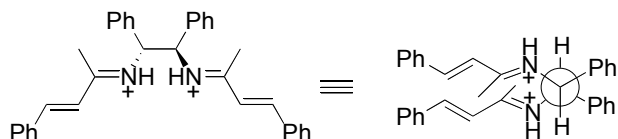
<sup>2</sup> H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, *8*, 5239-5242; T. C. Wing, C. M. Sultana, D. A. Vosburg, *J. Chem. Ed.* **2010**, *87*, 194-195.

<sup>3</sup> R. W. Holmes, J. Love, *J. Am. Med. Assoc.* **1952**, *148*, 935-937

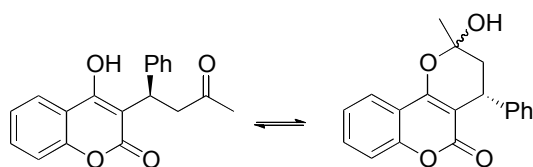
flammable and causes burns. Tetrahydrofuran is flammable and an irritant and can form explosive peroxides. Warfarin is a commercial anticoagulant and should be avoided by hemophiliacs. Methanol is flammable, toxic if ingested, harmful if inhaled, and may be absorbed through skin. Acetone and 2-propanol are flammable. Deuterated chloroform is a cancer suspect agent and mutagen.

*Lab report:* The following should be included in the report

1. Explain the formation of enantioenriched product (use molecular models); *hint:* a bisiminium compound is a crucial intermediate.



2. What is the role of acetic acid?
3. Determine the keto/ketal ratio from the  $^1\text{H}$  NMR spectrum.
4. Determine the enantiomeric excess from the optical rotation
4. Which of the criteria defining “green chemistry” are fulfilled?

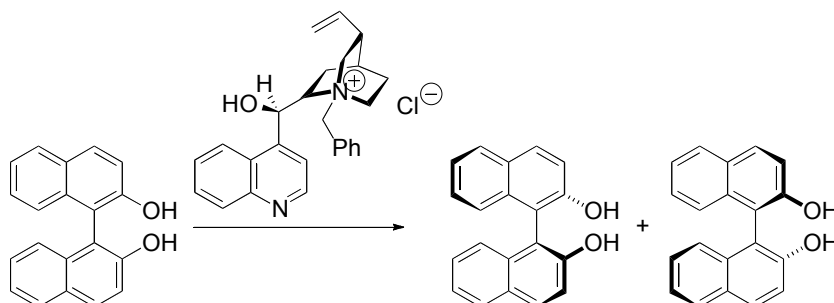


*The 12 principles of Green Chemistry are:*

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

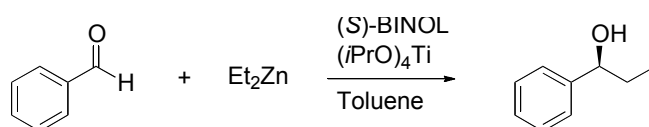
### 3. Enantioselective Addition of Diethylzinc to Benzaldehyde<sup>4</sup>

#### Resolution of BINOL



*Procedure:* To a solution of *rac*-BINOL (2.5 g) in acetonitrile (30 mL) is added *N*-benzylquinconidinium chloride (0.55 equiv). The resulting suspension is refluxed for 4 h, then cooled to room temperature and stirred overnight. The reaction mixture is then kept at 0 °C for 2 h and the precipitate removed by filtration. The filtrate is evaporated and the remaining solid dissolved in EtOAc (30 mL). The organic phase is washed with 1 M HCl (2 x 20 mL) and brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent is evaporated to yield a pale brown compound (the (*S*)-enantiomer). The filter cake is washed with acetonitrile (10 mL) and then suspended in MeOH (10 mL). The suspension is refluxed for 24 h, then cooled to room temperature and filtered. The filter cake is washed with MeOH and then dissolved in a mixture of EtOAc (30 mL) and 1 M HCl (20 mL). The phases are separated and the organic phase is washed with 1 M HCl (20 mL) and brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent is evaporated to yield an off-white solid (the (*R*)-enantiomer). The products are analyzed by <sup>1</sup>H NMR and optical rotation.

#### (*S*)-1-Phenylpropanol



*The reaction is performed using dry glassware and under inert atmosphere.*

*Procedure:* A solution of (*S*)-BINOL (0.2 mmol) and titaniumisopropoxide (1.2 mmol) in dry toluene (1 mL) is prepared and left to stir at room temperature for 30 min. The solution is cooled to 0 °C and diethylzinc (1 M in hexane, 3 mmol) is added. The resulting solution is stirred for 30 min, benzaldehyde (1 mmol) is added, and the reaction mixture is stirred for 1 h. A sample (50 μL) is taken, filtered through a short silica plug (EtOAc as eluent) and analyzed by GC. The reaction is quenched by the addition of HCl (1 M, 5 mL). The product is extracted with EtOAc, the organic phase is dried (MgSO<sub>4</sub>), and the solvent evaporated. The enantiomeric excess is determined

<sup>4</sup> D. Cai, D. L. Hughes, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.* **1995**, 36, 7991-7994.

by chiral GC. The product is purified by column chromatography and analyzed by  $^1\text{H}$  NMR and GC-MS.

*Hazards:* Diethylzinc is flammable.

*Lab report:*

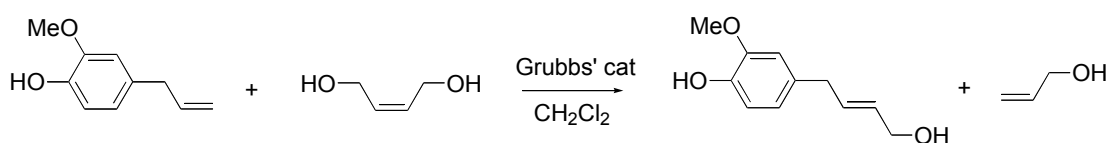
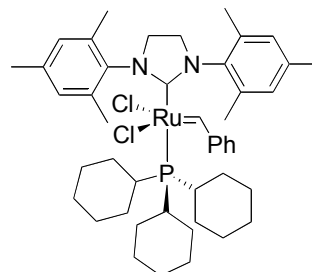
1. Discuss alternative methods for the preparation of enantiomerically enriched alcohols.
2. Describe how optical rotation can be used to determine the ee of the product.
3. Explain why  $\text{Et}_2\text{Zn}$  cannot be replaced by  $\text{EtLi}$ .

#### 4. Natural Product Synthesis: Grubb's Cross Metathesis of Eugenol with *cis*-2-Butene-1,4-Diol<sup>5</sup>

Tricyclohexylphosphine[1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]-ruthenium(IV) dichloride, the "Grubbs' second generation catalyst", has found wide application in industrial and academic research.

##### (*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-2-enol

(*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-2-enol was originally isolated from the roots of *Zingiber cassumunar*, a medical plant from southeast Asia possessing antioxidant and anti-inflammatory properties.<sup>6</sup>



**Procedure:** Eugenol<sup>7</sup> (125 mg, 0.75 mmol) and *cis*-2-butene-1,4-diol (350 mg, 4.0 mmol) are weighted directly into a 5 mL round bottomed flask (or vial). Petroleum ether (3 mL) is added followed by the catalyst (22 mg, 0.025 mmol). The flask is sealed and the mixture left to stir for two days or more, preferably under nitrogen.

The product is analyzed by TLC, using methyl *tert*-butyl ether (MTBE) as eluent. The spots can be visualized in an iodine chamber or under UV light (provided the plates have a fluorescent indicator).  $R_f$  of product: 0.44 (the product may be difficult to detect).

The reaction mixture is transferred to a 50 mL round bottomed flask (rinse with some acetone or dichloromethane). Silica gel (1-1.5 g) is added and the solvents evaporated. The residue is purified by column chromatography using a dry-packed column (ca 2 cm diameter, ca 25 g silica gel is added followed by the silica gel containing the product and sand). A gradient consisting of

- 40 mL petroleum ether,
- 40 mL 10% MTBE in petroleum ether,
- 40 mL 20% MTBE in petroleum ether
- 40 mL 33% MTBE in petroleum ether
- 75 mL 50% MTBE in petroleum ether
- 75 mL 66% MTBE in petroleum ether
- 40 mL MTBE

<sup>5</sup> D. F. Taber, K. J. Frankowski, *J. Chem. Ed.* **2006**, *83*, 283-284.

<sup>6</sup> T. Masuda, A. Jitoe, *Phytochemistry* **1995**, *39*, 459-461.

<sup>7</sup> Eugenol is a clear to pale yellow oily liquid extracted from certain essential oils; it is the main component in the essential oil extracted from cloves, comprising 72-90% of the total. It has a spicy, clove-like aroma. The name is derived from the scientific name for clove, *Eugenia aromaticum* or *Eugenia caryophyllata*. Eugenol is used in perfumeries, flavorings, essential oils and in medicine as a local antiseptic and anesthetic (Wikipedia).

is used. 40 mL portions are collected and analyzed by TLC (with MTBE as eluent). The fractions containing the product are collected. After evaporation of the solvents, the product should crystallize. If still an oil, add small amount of petroleum ether and scratch the bottom of the flask with a glass rod. Excess butenediol contaminates the product mixture and prevents crystallization of the desired product, and it must therefore be removed by column chromatography. This stage of isolation must be performed with patience; if this step is rushed, the product may be contaminated with butenediol and difficult to purify properly.

The product is recrystallized from dichloromethane (ca 4 mL; low boiling solvent – be careful).

Determine the melting point of the recrystallized product. Analyze by  $^1\text{H}$  NMR spectroscopy.

*Hazards:* Eugenol and *cis*-2-butene-1,4-diol are irritants. Petroleum ether and MTBE are flammable solvents. Silica gel is an inhalation hazard owing to its small particle size. The Grubbs' catalyst has not been fully tested for toxicity and therefore should be handled with care.

*Lab report:* The following should be included in the report

1. What other possible metathesis product(s) could form in this experiment? What causes the cross metathesis product to dominate over other product(s)?
2. Why is the trans alkene formed?
3. Why is a gradient used for the chromatographic separation?
4. Ruthenium complexes can move the location of the double bonds within a molecule to form more stable isomers. If the reaction mixture were allowed to stir over the entire semester, what might be the structure of the major side product?

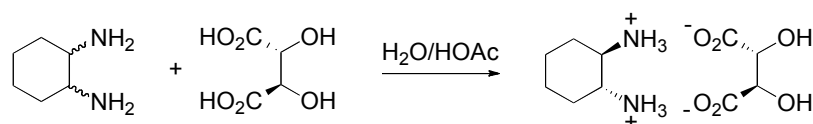
## 5. Synthesis and Use of Jacobsen's Catalyst: Enantioselective Epoxidation<sup>8</sup>

In 1994 *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, Jacobsen's catalyst, was awarded the Fluka prize "Reagent of the Year" for its ability to produce enantiomerically highly enriched epoxides from unfunctionalized olefins.

The reagent is stable to air and water and is typically used in catalytic amounts (0.25 – 10 mol %) with sodium hypochlorite (bleach) as ultimate oxidant.

### Resolution of *rac*-1,2-diaminocyclohexane

(*R,R*)-1,2-Diaminocyclohexane can be obtained from racemic *trans*-1,2-diaminocyclohexane<sup>9</sup> or from a mixture of all three stereoisomers<sup>10</sup> by crystallization of its (+) tartrate salt.



*Procedure:* In a beaker or Erlenmeyer flask containing a magnetic stir bar, L-(+)-tartaric acid (2.63 g, 17.5 mmol) is dissolved deionized in water (7 mL). The solution is heated to 90-95 °C. At the same time, deionized water is heated in a separate beaker (or Erlenmeyer flask). *Rac*-1,2-diaminocyclohexane (2.1 mL, 17.5 mmol) is slowly added to the tartaric acid solution under stirring. At the same time enough hot water is added to prevent precipitation of the salt. After complete addition of the diamine, the solution is allowed to cool to room temperature. Complete crystallization is achieved by keeping the beaker in the fridge overnight. The crystals are filtered off, washed with ice-cold water, and dried in a desiccator.

*Alternative procedure:* In a beaker or Erlenmeyer flask containing a magnetic stir bar, L-(+)-tartaric acid (2.63 g, 17.5 mmol) is dissolved in deionized in water (8 mL). The solution is heated to 90-95 °C. 1,2-Diaminocyclohexane (a mixture of *cis* and *trans* isomers, 3.8 g (4.1 mL), 33 mmol) is slowly added to the tartaric acid solution under stirring (exothermic reaction). A slurry is formed initially but complete dissolution is observed once the addition is complete. After a few minutes, glacial acetic acid (5 mL) is added in one portion. The product starts to precipitate shortly after the addition and is completed by cooling the mixture in an ice/water bath. After about 30 min the crystals are filtered off, washed with ice cold water (ca 2 mL) followed by methanol (4 x 2 mL). The product is purified by recrystallization from water (approximately 1:10 W/v), and dried in a desiccator.

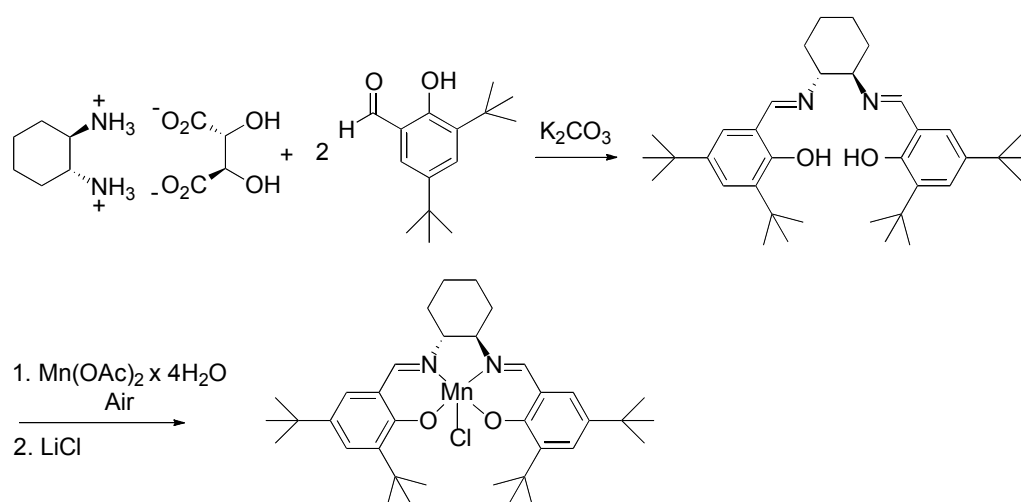
<sup>8</sup> J. Hanson, *J. Chem. Ed.* **2001**, 78, 1266-1268.

<sup>9</sup> P. J. Walsh, D. K. Smith, C. Castello, *J. Chem. Ed.* **1998**, 75, 1459-1462.

<sup>10</sup> J. F. Larrow, E. N. Jacobsen, *Org. Synth. Vol 75*; Wiley, New York, 1998, pp 1-11.

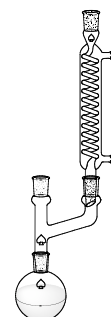
### **(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine**

A 100 mL round-bottomed flask equipped with a magnetic stir bar is charged with water (6.0 mL), (*R,R*)-1,2-diaminocyclohexane mono-(+)-tartrate salt (1.11 g, 4.22 mmol) and potassium carbonate (1.16 g, 8.41 mmol). The mixture is stirred until dissolution is achieved, then ethanol (22 mL) is added. The flask is equipped with a reflux condenser, and the cloudy mixture is heated to reflux. 3,5-Di-*tert*-butylsalicylaldehyde (2.00 g, 8.56 mmol) is dissolved in ethanol (10 mL) in a beaker; this requires careful heating on a hot plate. This solution is added through the condenser with a Pasteur pipette. The pipette and beaker are rinsed with hot ethanol (2 mL). After heating at reflux for one h, heating is discontinued. Water (6 mL) is added and the mixture is cooled to 5 °C and left to stand at that temperature for 30 min. The yellow solid formed is collected by vacuum filtration and washed with ethanol (4-5 mL). The solid is dissolved in dichloromethane (25 mL) and the solution is washed with water (2 x 5 mL), followed by saturated aqueous NaCl (5 mL). The organic layer is dried over Na<sub>2</sub>SO<sub>4</sub>, then filtered to remove the drying agent. The solvent is removed by evaporation to yield the product as a yellow solid that is characterized by mp (lit<sup>10</sup> 200-203 °C), and optical rotation ( $[\alpha]_{\text{D}}^{20} = -315^{\circ}$  (c = 1, CH<sub>2</sub>Cl<sub>2</sub>).



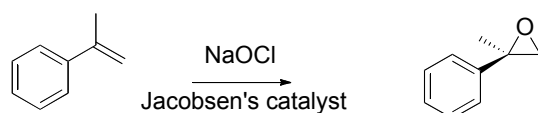
### **[(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2)] manganese(III) chloride (Jacobsen's catalyst)**

A 25 mL round-bottomed flask equipped with a magnetic stir bar, Claisen adapter, septum, and reflux condenser is charged with (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (500 mg, 0.92 mmol) and ethanol (13 mL 99.5%). After heating the mixture to reflux, Mn(OAc)<sub>2</sub> x 4 H<sub>2</sub>O (449 mg, 1.83 mmol) is added in one portion. The reaction mixture is heated to reflux for an additional 30 min, then air is bubbled through the solution (through a needle; adjust the stream of gas by bubbling into ethanol, then transfer the needle through the septum into the solution) while keeping the solution at reflux. The reaction is monitored by TLC (EtOAc:hexane 1:4). When the ligand has disappeared, LiCl (116 mg, 2.73 mmol) is added in one portion (exothermic reaction), and the reaction mixture is heated to reflux for another 30 min. The solvent is



evaporated and the residue dissolved in dichloromethane (12 mL). The organic phase is washed with water (2 x 10 mL) and brine (10 mL) and dried over MgSO<sub>4</sub>. After removal of MgSO<sub>4</sub>, heptane (15 mL) is added and part of the solvent evaporated (mostly dichloromethane). The flask containing the product is cooled with an ice bath during 30 min. The brown solid obtained is collected by filtration and allowed to dry in the air. The melting point is determined (lit<sup>10</sup> 324-326 °C).

### Enantioselective epoxidation of $\alpha$ -methylstyrene



*General epoxidation procedure:* A solution of 0.05 M Na<sub>2</sub>HPO<sub>4</sub> (5 mL) is added to commercial household bleach (Klorin, 12.5 mL). The pH of the resulting buffered solution (ca 0.55 M in NaOCl) is adjusted to 11.3 by addition of approximately 1 drop of 1 M NaOH solution. The buffered bleach solution is then added to a solution of the alkene (0.5 g) and Jacobsen's catalyst (10 mol %) dissolved in dichloromethane (5 mL) in a 50 mL Erlenmeyer flask equipped with a stir bar. The flask is capped and the two-phase mixture is stirred vigorously at room temperature. The progress of the reaction is monitored by TLC (40% CH<sub>2</sub>Cl<sub>2</sub> in hexane; turn off the stirrer while taking a sample); visualize using UV and *p*-anisaldehyde.

When the starting material has disappeared (usually within 2 h), the stir bar is removed and dichloromethane (approximately 50 mL) added. The brown organic phase is separated and washed with brine (2 x 10 mL), and then dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product obtained after evaporation of the solvent is purified by flash chromatography. The product is analyzed by <sup>1</sup>H NMR and chiral GLC.

Epoxidation of  $\alpha$ -methylstyrene: A column with ca 2 cm diameter and with ca 15 cm silica gel is used. Eluent: dichloromethane:hexane 1:1.

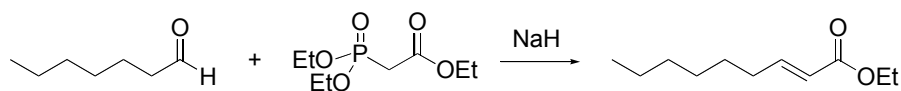
*Hazards:* Occasionally fumes coming from the top of the condenser are observed when air is bubbled through the refluxing reaction mixture during production of the catalyst. Deuterated chloroform and aromatic epoxides are cancer suspect agents.

*Lab report:* The following should be included in the report

1. Suggest some other method for the resolution of *rac*-1,2-diaminocyclohexane.
2. The product may be contaminated with an aldehyde (2-phenylpropanal in the reaction with  $\alpha$ -methylstyrene). Suggest how this aldehyde may form.
3. Describe how the opposite enantiomer of the product can be obtained.

## 6. Enantioselective Synthesis of an Epoxy Alcohol

### Horner-Emmons synthesis of non-2-enoic acid ethyl ester



*Dry glassware and dry THF should be used.*

*Procedure:* NaH (60% in oil, 1.3 equiv) is weighted directly into a pear-shaped flask and washed with pentane (3 x 10 mL). *Any remaining NaH in the pentane is destroyed with ethanol.* The flask is purged with nitrogen, THF (40 mL) is added and the mixture cooled to 0 °C. Triethylphosphono acetate (1.05 equiv) is added followed by dropwise addition of heptanal (2 g, 1 equiv). The reaction mixture is stirred at 0 °C. The reaction is followed by TLC. After complete reaction (1-3 h), the reaction mixture is poured into water (50 mL) and extracted with diethyl ether (3 x 50 mL). The organic phase is dried over MgSO<sub>4</sub> and the solvent evaporated. The E/Z ratio of the product is determined by <sup>1</sup>H NMR. If necessary, the product is purified by chromatography (pentane:EtOAc 20:1).

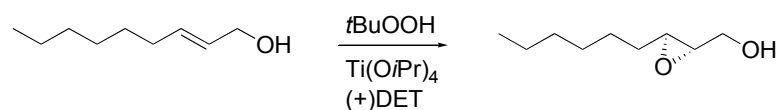
### Reduction of non-2-enoic acid ethyl ester with DIBALH



*Dry glassware and dry dichloromethane should be used.*

*Procedure:* Non-2-enoic acid ethyl ester (2 g, 1 equiv) is dissolved in dichloromethane (30 mL) under nitrogen and the solution is cooled to -78 °C. DIBALH (1.5 M in toluene, 2.5 equiv) is added dropwise over 30 min. The reaction mixture is stirred at -70 °C. The reaction is followed by TLC. After about 1-2 h, the reaction is quenched by the dropwise addition of methanol (ca 15 mL) at -70 °C. When excess DIBALH has been destroyed, the reaction mixture is allowed to reach room temperature and poured into a saturated solution of potassium tartrate (so called Rochelle salt, 70 mL). The mixture is extracted with dichloromethane (3 x 30 mL), the combined organic phases are washed with brine (20 mL) and dried over MgSO<sub>4</sub>, and the solvent is evaporated. The crude product is purified by chromatography (gradient). The pure product is analyzed by TLC and <sup>1</sup>H NMR.

### Sharpless epoxidation of non-2-en-1-ol



*Dry glassware and dry dichloromethane should be used.*

*Procedure:* Dichloromethane (30 mL) is added to a flask containing ground molecular sieves (4Å, 0.6 g). Ti(IV)(OiPr)<sub>4</sub> (0.1 equiv), (+)-diethyl tartrate (0.15 equiv) and *t*BuOOH (5 M in nonane, 2.2 equiv) are added at -20 °C and the mixture is stirred at -25 to -20 °C during 30 min. Non-2-enol 1.3 g, 1 equiv) dissolved in dichloromethane (20 mL) is then added. The reaction mixture is kept in the freezer overnight. Check that the reaction is complete with TLC and quench the reaction by the addition of water (ca 5 mL) at 0 °C. The mixture is allowed to reach room temperature and 30% NaOH saturated with NaCl (1 mL) is added, and the mixture stirred for 15 min. The phases are separated and the aqueous phase extracted with dichloromethane (2 x 15 mL). The combined extracts are dried over MgSO<sub>4</sub>. The mixture is analyzed by TLC, the solvent evaporated, and the residue purified by chromatography. The product is analyzed by NMR, and the ee determined by HPLC.

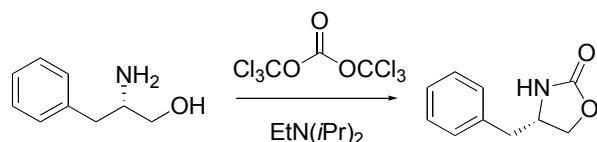
*Hazards:* Tetrahydrofuran is flammable and an irritant and can form explosive peroxides.

*Lab report:*

1. Describe the difference between the Wittig and Horner-Emmons reactions, in particular with respect of the configuration of the double bond.
2. Explain how an enantiomerically enriched compound is formed.
3. How can the enantiomeric excess of the product be analyzed?

## 7. Diastereoselective Aldol Condensation Using Chiral Auxiliary<sup>11</sup>

### Synthesis of chiral auxiliary, (*S*)-4-(phenylmethyl)-2-oxazolidone “Evans oxazolidone”

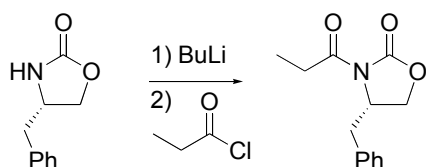


*Dry glassware and dry dichloromethane should be used.*

*Procedure:* Diisopropylethylamine, distilled from CaH<sub>2</sub>, (2.0 equiv) is added to a round-bottomed flask containing (*S*)-2-amino-3-phenyl-1-propanol ((*S*)-phenylalaninol, 2.5 g, 13.2 mmol) in dichloromethane (50 mL) under nitrogen, and the mixture is cooled to 0 °C. Triphosgene (2.0 equiv) is dissolved in dichloromethane (15 mL) under nitrogen in another round-bottomed flask, and this solution is transferred by a syringe to the cooled flask. The reaction mixture is allowed to reach room temperature. The reaction, which takes 3-6 h, is followed by TLC (EtOAc:MeOH 4:1 + 1% NH<sub>4</sub>OH). The reaction is quenched by the addition of water, and the mixture is stirred in the open vessel for 20 min. The mixture is washed with water (50 mL), the organic phase dried over MgSO<sub>4</sub>, and the solvent evaporated. The crude product is purified by crystallization (pentane:EtOAc 1:1) or chromatography (pentane:EtOAc 1:1; evaporate the product with silica since it has poor solubility in the eluent) and analyzed by TLC, <sup>1</sup>H NMR, and melting point.

*Hazards:* Triphosgene is converted to phosgene, which is very toxic.

### Coupling of substrate and chiral auxiliary



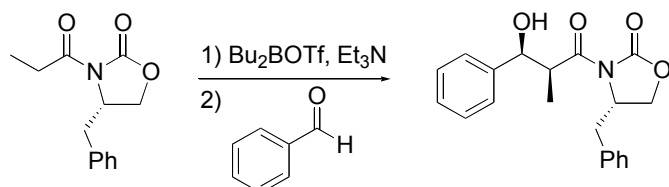
*Dry glassware and dry dichloromethane should be used.*

*Procedure:* (*S*)-4-(Phenylmethyl)-2-oxazolidone (1.5 g, 1 equiv) is dissolved in THF (25 mL) under nitrogen. The flask is cooled to -78 °C and butyl lithium (2.5 M in hexane, 1.1 equiv) is added dropwise during 10 min. The solution can become yellow and a little cloudy. Freshly distilled propionyl chloride (1.1 equiv) is then added and the reaction mixture is stirred at -78 °C for 30 min. The flask is allowed to reach room temperature during 30 min and the reaction mixture is analyzed by TLC. The reaction is quenched by the addition of saturated aqueous ammonium chloride (5 mL), and the reaction mixture concentrated. The remaining slurry is extracted with dichloromethane (2 x 10 mL) and the combined extracts washed with 1 M NaOH (10 mL) and brine (10 mL). The organic phase is dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent

<sup>11</sup> J. R. Gage, D. A. Evans, *Org. Synth.* **1989**, 68, 77-91.

evaporated. The remaining pale yellow oil is kept in the fridge overnight and allowed to crystallize. The solid product is pulverized, a small amount of cold hexane is added and decanted. The product is dried under vacuum and analyzed by TLC,  $^1\text{H}$  NMR, and melting point.

### Enantioselective aldol condensation

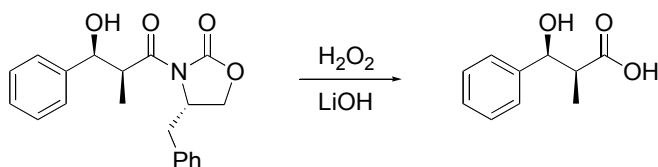


*Procedure:* Dibutylboron triflate (1 M in  $\text{CH}_2\text{Cl}_2$ , 1 equiv) is slowly added to the *N*-acylated oxazolidone (1.0 g) in dichloromethane (10 mL) under nitrogen at  $0^\circ\text{C}$ , followed by freshly distilled triethylamine (1.3 equiv). The solution can become pale yellow or green when the boron triflate is added, and yellow when the base is added. The reaction mixture is cooled to  $-78^\circ\text{C}$  and distilled benzaldehyde (1.1 equiv) is added dropwise over 5 min. The reaction mixture is stirred at  $-78^\circ\text{C}$  for 20 min followed by 1 h at  $0^\circ\text{C}$ . The reaction is followed by TLC and the reaction quenched by the addition of phosphate buffer pH 7 (5 mL) and methanol (14 mL). A mixture of methanol and hydrogen peroxide (2:1, 15 mL) is added, and the mixture stirred for another h. The reaction mixture is concentrated and the remaining slurry extracted with diethyl ether (3 x 25 mL). The organic phase is washed by 5% sodium bicarbonate in water (25 mL) and brine (25 mL), dried ( $\text{MgSO}_4$ ), and concentrated. The remaining solid is crystallized from EtOAc:hexane 1:2 (an oil may be obtained if too much hexane is used). Additional product may be obtained by chromatography (EtOAc:hexane 1:3) of the evaporated mother liquor. The product is analyzed by TLC,  $^1\text{H}$  NMR, COSY, and melting point.

*Additions must be slow in order to avoid an increase in temperature of the reaction mixture, as this would lead to decreased selectivity.*

#### *Hazards:*

The last step, which is not included in this sequence, is the formation of the final acid.



#### *Lab report:*

1. Why is it necessary to use a strong base for the acylation?
2. Why do oxazolidones serve as efficient chiral auxiliaries?
3. Explain the stereochemistry of the reaction.
4. How can the diastereomeric excess be determined?