

MASSACHUSETTS INSTITUTE OF TECHNOLOGY  
DEPARTMENT OF CHEMISTRY

**5.32 Intermediate Chemical Experimentation**

**EXPERIMENT #1: ASYMMETRIC CATALYSIS OF DIELS-ALDER REACTIONS<sup>1</sup>**

**I. PURPOSE**

The purpose of this experiment is to prepare and use an asymmetric boronic acid catalyst (**BLn\***) for a Diels-Alder reaction.<sup>2</sup> The catalyst, mono(2,6-dimethoxybenzoyl)tartaric acid, is synthesized from L-(+)- or D(-)-tartaric acid in the following manner. The carboxyl groups of the tartaric acid are protected by esterification (Scheme 1a). One of the hydroxyl groups of the resulting dibenzyl tartrate is acylated with 2,6-dimethoxybenzoyl chloride (Scheme 1b) and the protecting groups are removed (Scheme 1c). The mono(2,6-dimethoxybenzoyl)tartaric acid is purified and combined with borane or a boronic acid to form the active catalyst (**BLn\***, Scheme 1d). Finally, the Diels-Alder reaction of cyclopentadiene (**1**) with methacrolein (**2**), or another diene/dienophile combination, is performed (Scheme 1e). The product (**exo-CHO-3**) is purified, and its enantiomeric purity will be measured.

**II. REFERENCES**

**A. THE DIGITAL LAB TECHNIQUES MANUAL** (link from the 5.32 website)

3. TLC – the Basics
4. TLC – Advanced
5. Reaction Workup I
6. Reaction Workup II
7. Filtration
10. Column Chromatography

**B. TEXTS**

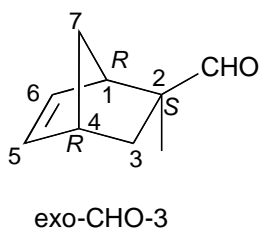
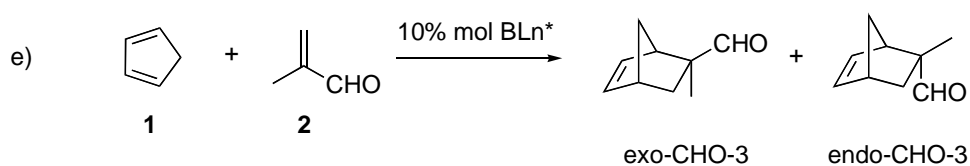
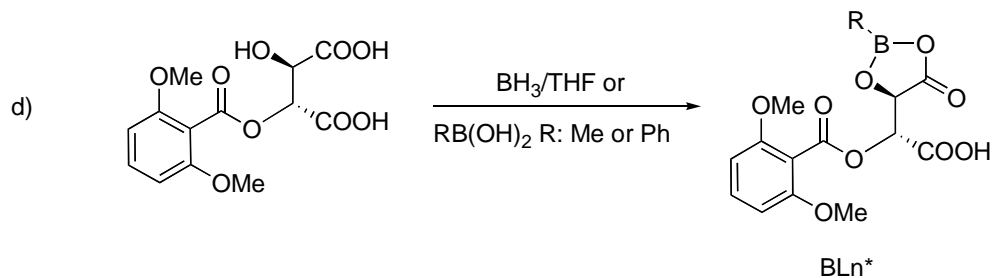
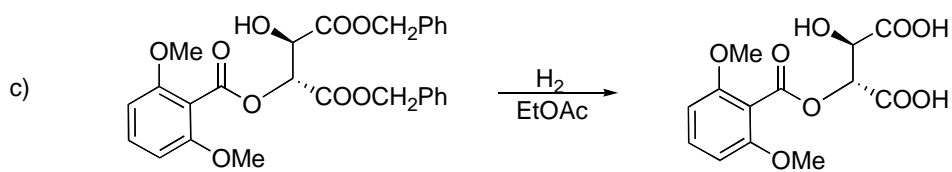
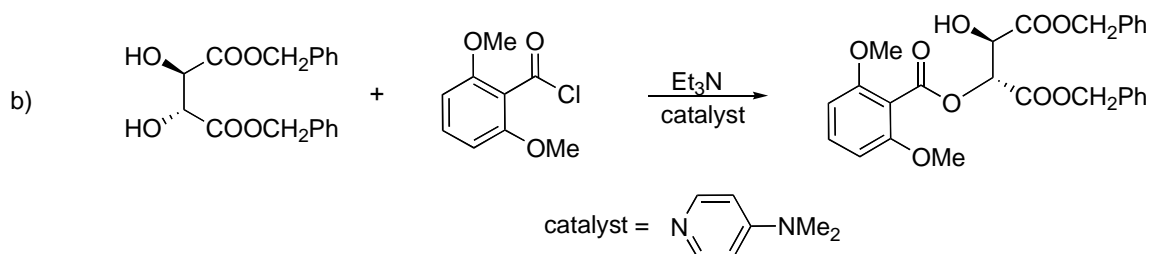
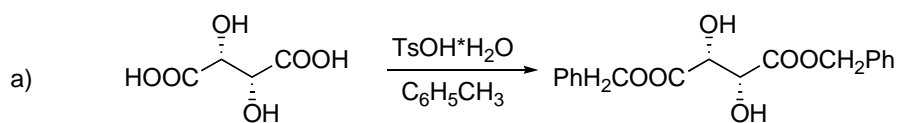
1. Zubrick, J. W.; *The Organic Chemist Lab Survival Manual: A Student Guide to Techniques*; Wiley: New York, 2001.
2. Leonard, J.; Lygo, B.; Procter, G.; *Advanced Practical Organic Chemistry*, 2nd ed.; Blackie Academic & Professional: London, 1995.

**Scheme 1.**

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<sup>1</sup> Redesigned and updated by Mircea D. Gheorghiu

<sup>2</sup> Furuta, K.; Shimizy, S.; Miwa, Y.; Yamamoto, H, *J. Org. Chem.* **1989**, *54*, 1481.



Chemical Abstracts 9<sup>th</sup> Collective Index (9CI) name:

**Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde, 2-methyl-, (1R,2S,4R)**

Diels-Alder-2

### III. ASYMMETRIC REACTIONS<sup>3</sup>

Biological systems are made of asymmetric molecules and are, thus, affected differently by opposite enantiomers. Because of the prevalence of enantiomers in nature, considerable interest exists in making single, pure enantiomers for the pharmaceutical industry, to use as flavors and fragrances, to react with compounds of biological relevance, etc. Although this goal can be accomplished by resolving racemic mixtures into separate enantiomers, it is potentially more efficient to synthesize the single enantiomer itself.

Asymmetric synthesis requires a means of distinguishing one enantiomer from the other at the time the asymmetry is introduced. This distinction can only be made by molecules that are, themselves, asymmetric. A number of natural, asymmetric compounds have been used as chirality sources, including alkaloids, sugars, amino acids, and terpenoids. One of the most inexpensive and easily available of these is tartaric acid. Natural L-(+)-tartaric acid will be used as the source of chirality in this experiment. "Unnatural" D-(-)-tartaric acid is more expensive than L-(+)-tartaric acid and can be synthesized from a carbohydrate. Because both enantiomers of tartaric acid are available as the source of asymmetry, either enantiomer of product can be synthesized via this asymmetric source molecule.

An asymmetric source molecule can be used in several ways. One method works by converting natural materials to other molecules that retain the stereocenters of the original natural product. In such instances, the asymmetry can only be used once and, if multistep synthesis is required, the yield of the desired asymmetric product may be only a small fraction of the amount of the starting material required. A more efficient method of synthesizing an asymmetric molecule involves the use of a chiral auxiliary. A chiral auxiliary is connected to a molecule at a critical stage in the synthesis to induce asymmetry. After the asymmetry of an intermediate has been established, the chiral auxiliary can be disconnected (for example, by ester hydrolysis, or whatever means is appropriate for the system) and recycled.

**The most efficient** use of the asymmetric source molecule is to incorporate it into a catalyst. Catalysts, by definition, are not consumed in the reaction and are recoverable after the desired reaction is over. As a practical matter, catalysts often degrade slowly as a result of side reactions, and recovery is not 100%, but one molecule of an efficient asymmetric catalyst may generate thousands of molecules of asymmetric product during its lifetime.

**Tartrate<sup>4</sup> chemistry:** The catalyst used in this experiment is derived either from L-tartaric acid or D-tartaric acid (*see Appendix 4 for more information regarding the stereochemistry of tartaric acids*). The carboxyl groups are first protected by esterification with benzyl alcohol, one hydroxyl group is acylated with 2,6-dimethoxybenzoyl chloride, and benzyl ester groups are cleaved by hydrogenolysis.

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<sup>3</sup> For further reading see: (a) Procter, G. *Asymmetric Synthesis*, Oxford University Press: Oxford, 1996: Chaps. 1,2 and 6 (QD262.P76); (b) Atkinson, R. S. *Stereoselective Synthesis*, Wiley: New York, 1995, Chaps.1 and 6 (QD481.A79); (c) Eliel, E. L. Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley, New York, 1994. (QD.481.E).

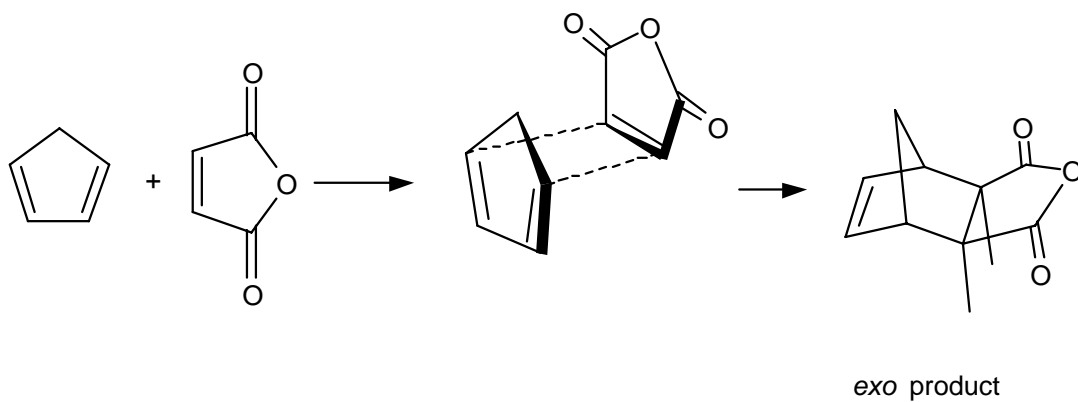
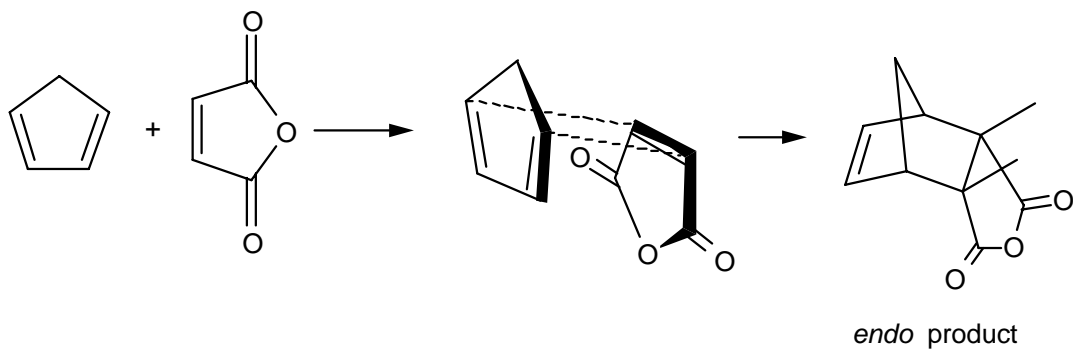
<sup>4</sup> Gawronski, N.; Gawronska, K. *Tartaric and Malic Acid in Synthesis*, Wiley: New York, 1999. (QD305.A2.G217).

Benzyl esters are often used in place of methyl or ethyl esters when a possibility of side reactions may result during ester hydrolysis. Hydrogen and palladium cleave benzyloxy groups to toluene and hydroxyl, often faster than double bonds are hydrogenated.

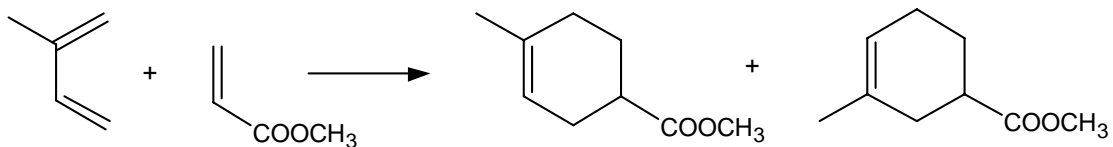
The acylated tartaric acid reacts with borane-THF to form a cyclic boronic acid derivative of the tartrate. Alternatively, phenyl boronic acid or methylboronic acid may be used to form tartrate derivatives. These cyclic boronic ester/anhydrides are active Lewis acid catalysts for promotion of Diels-Alder reactions (and other kinds of reactions subject to acid catalysis). The asymmetry of the tartrate induces a high degree of asymmetry in the products in favorable cases.

***Diels-Alder Reactions*** (a more advanced discussion can be found in Appendix): Diels-Alder reactions simultaneously make two carbon-carbon bonds and, if the product lacks a plane of symmetry, create four stereocenters in the process. Thus, a synthesis of a molecule containing several stereocenters via a Diels-Alder reaction may be particularly efficient, provided that the relative and absolute stereochemistry of the Diels-Alder reaction can be controlled. No general way exists of accomplishing this objective for all types of Diels-Alder reactions. However, the catalyst developed recently in Hisashi Yamamoto's group (Nagoya University) provides good stereocontrol with a number of useful combinations of substrates.

A classical example of a Diels-Alder reaction is that of maleic anhydride with cyclopentadiene. Because all the possible products contain a plane of symmetry, this reaction is not a candidate for asymmetric control. However, two kinds of relative stereoisomers result. The major product in this case is the *endo* isomer, and the minor product is the *exo* isomer. The *endo* transition state provides more extensive  $\pi$ -overlap than the *exo*, and accordingly, stronger bonding between the two fragments. However, many Diels-Alder reactions also exist in which the *exo* isomer is favored for steric reasons.

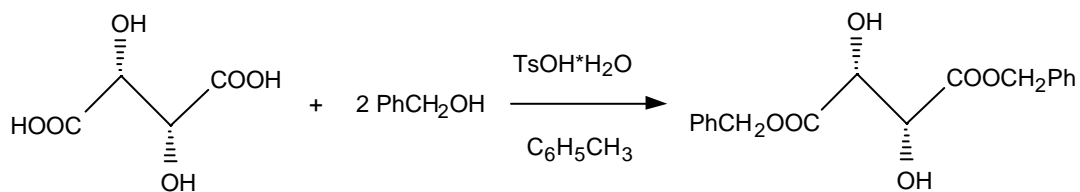


Diels-Alder reactions with asymmetrically placed substituents on each reactant provide possibility for regioisomerism.



## IV. PROCEDURE<sup>5</sup>

### A. PREPARATION OF DIBENZYL TARTRATE (DLTM: 5, 6, 7)



#### 1. Reagents

**L-Tartaric acid, D-Tartaric acid:** Irritant

**Benzyl Alcohol:** Severe irritant, harmful liquid, target organ: nerves

**p-Toluenesulfonic acid monohydrate:** Toxic, corrosive, oxidizer, hygroscopic; avoid contact and inhalation

**Caution:** Contains sulfuric acid-may cause cancer by inhalation.

**Toluene:** Flammable liquid, toxic

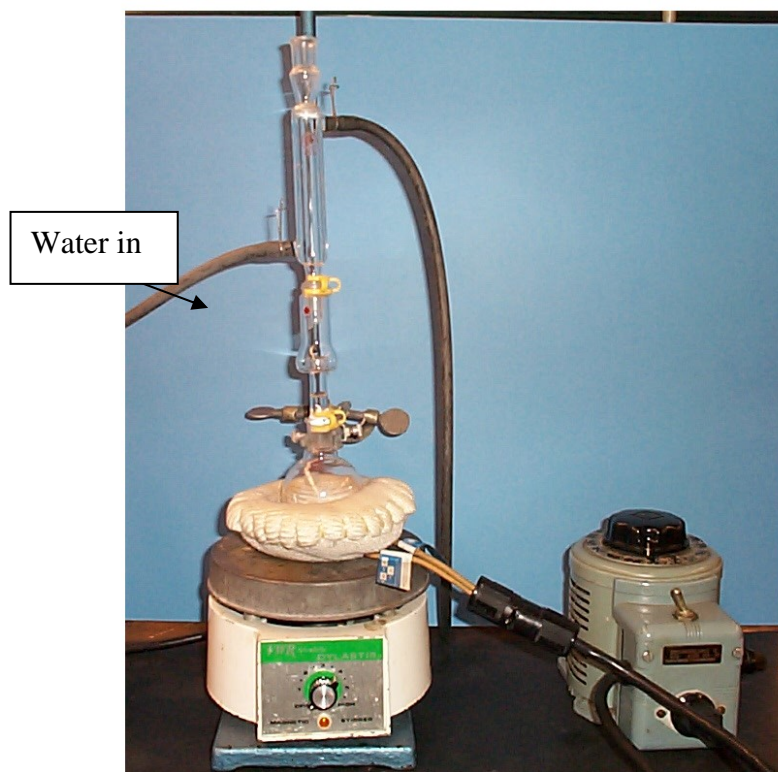
Reagent	Amount	F.W.	m.p. (b.p.) °C	d g/mL
L-(+)-Tartaric acid or D-(-)-Tartaric Acid	3.0 g (20 mmol)	150.09	171-174 (dec)	
Benzyl alcohol	6.5 g (60 mmol)	108.14	-15 (205)	1.045
TsOH·H <sub>2</sub> O	47.5 mg (0.25 mmol)	190.22	103-106	-----
Toluene	40 mL	92.14	-93 (110.6)	0.865

#### 2. Experimental

In a 100 mL, one necked, round-bottomed flask equipped with a magnetic stirrer, a Hickman still and a reflux condenser are placed 3.0 g either L-(+)-tartaric acid (“natural” tartaric acid) or D-(-)-tartaric acid (**record the isomer that you are using!**), benzyl alcohol (6.5 g), 40 mL toluene, and 47.5 mg *p*-toluenesulfonic acid monohydrate. The mixture is stirred and heated (heating mantel) under reflux overnight. Water (theory: 0.72 mL) is collected in the Hickman still (*should be tilted slightly to collect water*). The mixture is allowed to cool to room temperature, diluted with ether (50-100 mL), and poured into 50 mL of saturated aqueous sodium bicarbonate.

**CAUTION:** Gas evolution and possible foaming is expected

<sup>5</sup> Adapted after: Furuta, K.; Gao, O.-z.; Yamamoto, H. *Org. Synth.* **1995**, 72, 86-94.



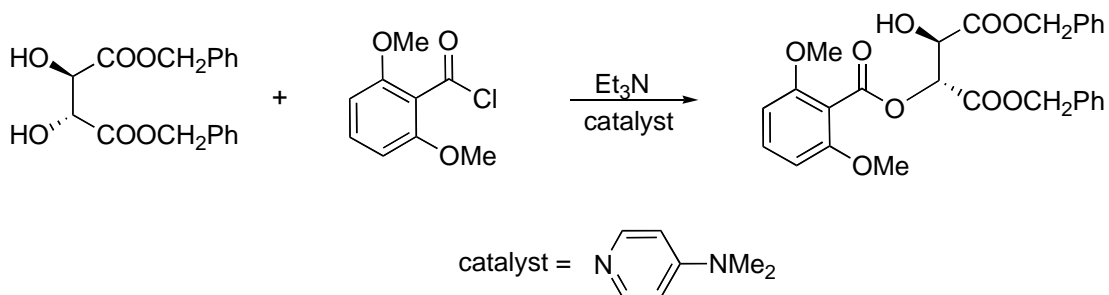
**Figure 1.** Apparatus for esterification of tartaric acid.

The phases are separated in a separatory funnel and the aqueous phase is extracted with two 20-mL portions of ether. The organic solutions are combined, dried over anhydrous sodium sulfate, filtered, and concentrated in a rotary evaporator. The residue is triturated<sup>6</sup> with a mixture of 200 mL of hexane and 10 mL of ether to yield white crystalline (-)-dibenzyl tartrate. The crystalline product is collected by filtration and washed with a mixture of 20 parts hexane to 1 part ether. Concentration of the filtrate yields a second crop of a crystalline dibenzyl tartrate. The total yield is 6.2 g (94 %), m.p. 49-50 °C; the <sup>1</sup>H-NMR spectrum should be recorded,<sup>7</sup>  $[\alpha]_D^{24} -10.2^\circ$  (CHCl<sub>3</sub>, c 1.03).

<sup>6</sup> To rub, crush, grind, or pound into fine particles or a powder; pulverize. A triturated substance, especially a powdered drug.

<sup>7</sup> From *Org. Synth.*: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz,  $\delta$ ): **3.15** (d, 2H, J=7.5), **4.6** (d, 2H, J=7.5), **5.27** (s, 4H), **7.35** (s, 10H).

**B. PREPARATION OF DIBENZYL MONO(2,6-DIBENZYL MONO(2,6-DIMETHOXYBENZOYL)TARTRATE (DLTM: 3, 4, 5, 6, 7, 10)**



**1. Reagents**

**Dibenzyl tartrate:**

**Dichloromethane:** Toxic irritant

**Triethylamine:** Flammable liquid, corrosive

**4-Dimethylaminopyridine<sup>8</sup>:** Highly toxic, corrosive, readily absorbed through skin; avoid contact and inhalation

**2,6-Dimethoxybenzoyl chloride:** Corrosive, moisture-sensitive

**Silica gel (70-230 mesh):** Harmful dust, avoid inhalation, hygroscopic

Reagent	Amount	F.W. g/mol	m.p. (b.p.) °C	d g/mL
Dibenzyl tartrate	6.1 g (18.5 mmol)	329.7	49-50	
Dichloromethane	100 mL	84.93	-97 (40)	1.325
Triethylamine	4 mL, (28.8 mmol)	101.19	-115 (88.8)	0.726
4-dimethylaminopyridine	50 mg, (0.4 mmol)	122.17	112-114	
2,6-Dimethoxybenzoyl chloride	3.65 g, (18.2 mmol)	200.62	64-66	

**2. Experimental**

A 250-mL three-necked round-bottom flask is equipped with a magnetic stirrer and a reflux condenser, with a nitrogen inlet capping the top of the condenser.<sup>9</sup> In the flask are placed 6.1 g dibenzyl tartrate, 100 mL dichloromethane, 4 mL triethylamine, and 50 mg 4-dimethylaminopyridine. The mixture is stirred and cooled to 0 °C.

<sup>8</sup> Widely used and versatile hypernucleophilic acylation catalyst.

<sup>9</sup> Use of a three-necked flask allows easier access when material is added or withdrawn for TLC, but except during these operations, two of the necks are merely stoppered (see Fig. 2). The nitrogen inlet should be connected to a T-stopcock, with a second branch of the tube connected to the system and the third branch be connected to a bubbler. The nitrogen flow rate is adjusted so that a bubble escapes through the bubbler every few seconds. Use at the beginning of the flushing a vent syringe needle inserted in the septum. Then, remove the needle and allow the nitrogen flushing to continue another 2-3 minutes.



Then, 3.65 g<sup>10</sup> of 2,6-dimethoxybenzoyl chloride is added<sup>11</sup> in five approximately equal portions at 10-minute intervals. The mixture is then warmed to reflux temperature and stirred under reflux overnight. The progress of the reaction may be monitored by TLC [mixture of hexane, ether, and dichloromethane (ratio 3:1:5) the R<sub>f</sub> value is about 0.35]. After cooling to room temperature, the mixture is poured in 100 mL water and the phases are separated in a separatory funnel. The aqueous phase is extracted with two 75-mL portions of dichloromethane. The combined organic solutions are dried over the minimum required amount of sodium sulfate, filtered, and concentrated on a rotary evaporator to yield a viscous oil.<sup>12</sup> This material is purified by flash column chromatography (see Appendix 3) on silica gel (~100 mL), eluting with a mixture of hexane, ether, and dichloromethane (ratio 3:1:5). Concentration yields 7.1-7.5 g, 78-82% oily liquid dibenzyl mono(2,6-dimethoxybenzoyl) tartrate; the NMR spectrum should be recorded;<sup>13</sup>  $[\alpha]_D^{24}$  -60.1° (CHCl<sub>3</sub>, c 1.15).



**Figure 2.** Apparatus for benzoylation of dibenzyl tartrate.

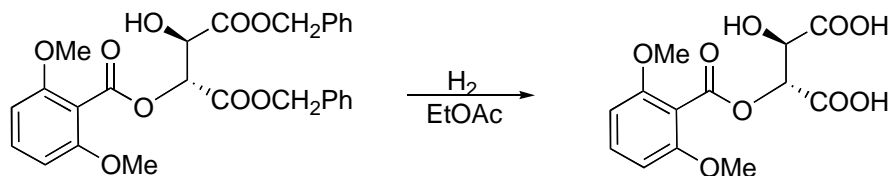
<sup>10</sup> Because the acid chloride supplied by Aldrich is only 90% pure, this calculation as published in *Org. Synth.* is incorrect. It is possible that the yield can be increased by 10% and the purification of the product made easier if the amount of acid chloride is increased to a true 18.2-18.5 mmol. The effect of small excess, up to 20 mmol total, would also be of interest. The student record the amount actually used.

<sup>11</sup> If a three-neck flask is used, one stopper may be removed briefly while material is added. If a one-necked flask is used, the nitrogen connection is separated momentarily and the acid chloride is added through the top of the reflux condenser.

<sup>12</sup> Although the *Org. Synth.* prep does not call for it, it is suggested that the oil be dissolved in diethyl ether and extracted with three portions of saturated sodium bicarbonate to remove carboxylic acid impurities before chromatography. It is of interest to check the purity of the material by <sup>1</sup>H-NMR at each stage.

<sup>13</sup> From *Org. Synth.*: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz,  $\delta$ ): **3.24** (d, 1H, J=9); **3.7** (s, 6H); **4.89** (dd, 1H, J=2.5 and 9); **5.08-5.34** (4H); **5.99** (d, 1H, J=2.5); **6.53** (d, 2H, J=8.5), **7.25-7.4** (m, 11H).

**C. PREPARATION OF MONO(2,6-DIMETHOXYBENZOYL)TARTRATE**  
(DLTM: 3, 4)



**1. Reagents**

**10% Palladium on charcoal:** Flammable solid, irritating dust, store under nitrogen! Often ignites solvents such as ethyl acetate if added to the solvent in air!<sup>14</sup>

**Ethyl acetate:** Flammable liquid (Fp -3 °C), irritant

Reagent	Amount	F.W.	m.p. (b.p.) °C	Density g/mL
10 wt % Pd on activated charcoal	580 mg		-	-
Ethyl acetate	100 mL	88.11	-84 (76.5-77.5)	0.902
Dibenzyl mono(2,6-dimethoxybenzoyl)tartrate	5.8 (11.7 mmol)	495.73		

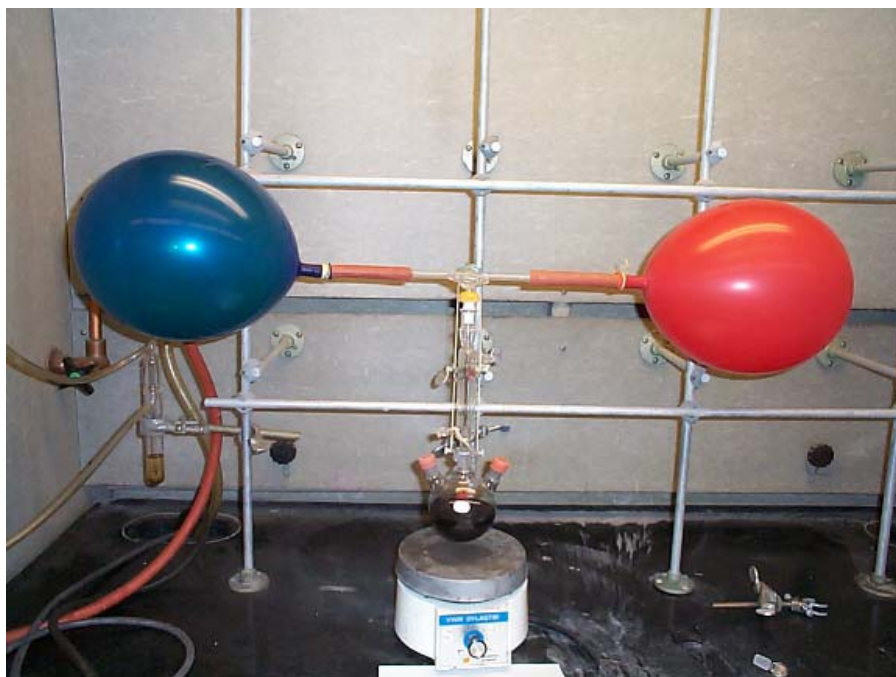
A three-neck 250-mL round-bottomed flask is equipped with septum caps, a condenser (used as a spacer), and a magnetic bar. Two hydrogen balloons connected to the branches of a T-stopcock (see Fig. 3, the T stopcock is open such as that only the two balloon communicate) are mounted on the top of the condenser. The apparatus is first flushed with nitrogen. Nitrogen flows into a bubbler then into the round bottom flask via a syringe needle inserted in the side arm septum. A second syringe needle, used for venting, is inserted into the septum covering the second neck. The nitrogen flow rate is adjusted so that a bubble escapes through the bubbler every few seconds. Allow the nitrogen flushing to continue for 4-5 minutes. Under slight positive nitrogen pressure, remove the septum (with the inserted vent needle) and charge the flask with 580 mg 10% palladium on charcoal, 100 mL ethyl acetate (see footnote #24) and 5.8 g dibenzyl mono(2,6-dimethoxybenzoyl)tartrate. After the reagents are in the flask, cap the flask with the rubber septum (and the vent needle) and continue to flush with nitrogen 3-4 minutes more. Remove the nitrogen-in and the exit-needle. Turn the T stopcock such as that hydrogen can enter into the round bottom flask. Leave the hydrogenation overnight (*come back the next day to refill balloons if necessary*) or over the weekend. The progress of the hydrogenolysis is monitored by TLC. The mixture is filtered through a

<sup>14</sup> A good procedure is to put the catalyst in the empty flask, flush the flask with a gentle stream of nitrogen, and cover the catalyst with a part of solvent. The remainder of the solvent may be used to aid transfer of the tartrate ester. **As a safety measure**, before introducing hydrogen into the flask, be sure that all of the catalyst is under the solution, and flush the apparatus with nitrogen before introducing hydrogen.

pad of Celite.<sup>15</sup> **SAVE** the collected palladium catalyst in a special jar for palladium wastes for recycling.

The filtrate is concentrated on a rotary evaporator. The residue is thoroughly dried<sup>16</sup> under vacuum at 80 °C, < 1 torr (vacuum pump) over night, yielding practically pure solid mono(2,6-dimethoxybenzoyl)tartric acid, m.p. 184-186 °C, suitable for use in the next step; <sup>1</sup>H-NMR should be recorded<sup>17</sup>;  $[\alpha]_D^{24}$  -73.0° (EtOH, c 1.03).

**CAUTION: Palladium catalyst sometimes ignite during filtration!**



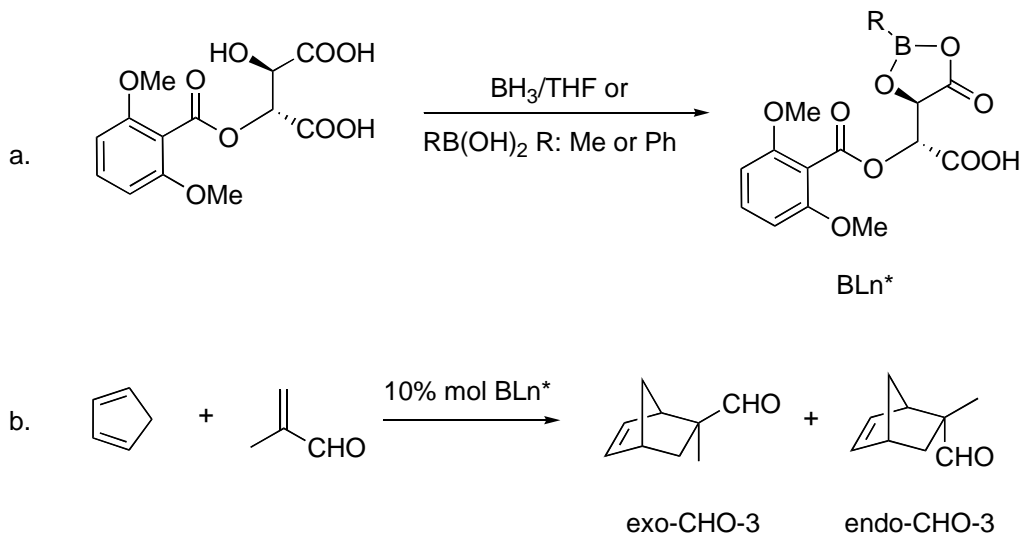
**Figure 3.** Apparatus for hydrogenation.

<sup>15</sup> Finely divided catalyst tends to plug filters.

<sup>16</sup> Thorough drying is essential to obtain the % ee as described.

<sup>17</sup> From *Org. Synth.*: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz,  $\delta$ ): **3.63** (s, 6H); **4.61** (d, 1H, J=2); **5.61** (d, 1H, J=2); **6.38** (d, 2H, J=9), **7.13** (t, 1H, J=9).

**D. PREPARATION OF (1*R*,2*R*,4*R*)- OF (1*R*,2*S*,4*R*)-*exo*-2-METHYLBICYCLO[2.2.1]HEPT-5-ENE-2-CARBOXALDEHYDE**



**1. Reagents**

**Dichloromethane:** Toxic irritant!

**BH<sub>3</sub>-THF:** Flammable liquid (Fp -17 °C), Moisture-sensitive

**Methacrolein:** Flammable liquid (Fp-15 °C), Corrosive

**Cyclopentadiene** (freshly distilled by the TAs): Flammable liquid

Reagent	Amount	F.W.	m.p. (b.p.) °C	d g/mL
Mono(2,6-dimethoxybenzoyl)-tartaric acid	1.57 g (5 mmol)	314.0		
Dichloromethane	50 mL	84.93	-97 (40)	1.325
BH <sub>3</sub> -THF	5 mL, 1M (5 mmol)	85.94		0.898
methacrolein	4.14 mL (50 mmol)	70.09	-81 (69)	0.847
cyclopentadiene	5 mL (60 mmol)	66.10	-85 (41.5-42)	0.8021 (@ 20 °C)

A 125-mL three-necked tapered flask is equipped with a stirring bar, a Vigreux column that is attached to a 3-way stopcock through a Teflon adaptor, a low temperature thermometer in the threaded side neck, and a rubber septum covering the second side neck (see Fig. 4). The stopcock side arms are connected to nitrogen and to a bubbler. The air is replaced by repeated flushing with nitrogen, first (3-5 minutes) using a vent syringe needle inserted in the septum followed by continuing the nitrogen flushing for an additional 4 minutes after the vent needle has been removed. Remove the septum charge the flask with 1.57 g mono(2,6-dimethoxybenzoyl)tartronic acid and 50 mL dichloromethane (previously stored on 4 Å molecular sieves) under a slight positive

nitrogen pressure. Put the septum back securely. The mixture is cooled with an ice bath. Turn the T stopcock to shut off the incoming nitrogen. Add the borane-THF solution (5 mL of 1M, 5 mmol) dropwise from a syringe (with the needle through the rubber septum) to a stirred, cooled solution over a period of 30 min.



**Figure 4.** Apparatus for cycloaddition.

**CAUTION:** Borane-THF is highly flammable and evolves hydrogen on contact with water and hydroxylic solvents.

Vigorous hydrogen evolution occurs during the addition and can be observed through the bubbler. Continue stirring at 0 °C for 15 min after the addition is complete. Reconnect the nitrogen-in flow by turning the T-stopcock into the appropriate position. The mixture is then cooled with a dry ice acetone bath (-78 °C). Freshly distilled methacrolein (4.14 mL) is added dropwise from a syringe, followed by 5 mL cyclopentadiene.

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**Caution:** Methacrolein is toxic and volatile and should be handled strictly in the hood.

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The mixture is stirred well and kept at -78 °C for 12 hours. (A large Dewar half-filled with dry ice will allow 24-hour storage.) The cold mixture is poured into 150 mL

of ice-cooled saturated sodium bicarbonate solution). The product is extracted with three 200-mL portions of hexane. The sodium bicarbonate solution is saved for catalyst recovery, and the combined hexane solutions are washed with brine (i.e., saturated sodium chloride), two 200-mL portions, dried over MgSO<sub>4</sub> and concentrated on a rotary evaporator. The crude adduct (yield 85%) consists of an endo/exo mixture ratio of 11/89 (verify this information by taking a <sup>1</sup>H NMR of the crude adduct in CDCl<sub>3</sub>).<sup>18</sup> The **endo-CHO-3** adduct was removed by column chromatography (24:1 hexane/ethyl acetate) to give exo adduct **3** as a colorless solid (bp 74-75 °C /15 Torr; mp 67-68 °C<sup>19</sup>). The Diels-Alder adduct has *R* configuration if the catalyst derived from natural tartaric acid; the *S* isomer results from a catalyst derived from unnatural tartaric acid. The NMR spectrum of pure **exo-CHO-3** should be recorded<sup>20</sup>; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -23.3° (ethanol).<sup>21</sup>

Catalyst recovery: The sodium carbonate solution containing the mono(2,6-dimethoxybenzoyl) tartaric acid is acidified with 4 M HCl (gas evolution) and extracted with three portions (~ 50 mL) ethyl acetate. Concentration of ethyl acetate solution and vacuum drying yields the recovered catalyst (~1.57 g, 97%), which needs no further purification.

## E. OTHER DIELS-ALDER REACTIONS

Time permitting, other Diels-Alder reactions can be tested with any of the above described catalyst systems. Methyl acrylate, methyl methacrylate, acrylic acid, methacrolein, or other similar compounds might be tested with 2,3-dimethylbutadiene, isoprene, cyclopentadiene, cyclohexadiene, or other available dienes.

## F. MEASUREMENT OF ENANTIOMERIC EXCESS

Optical rotation provides a rough measurement of enantiomeric excess if the rotation of the pure enantiomer is known. However, rotation measurements are subject to considerable experimental error and the rotations found in the literature are often inaccurate. Before NMR and chromatography were commonly available, literature rotations were generally the highest rotation anyone had obtained on the purest sample that had been made. Resolutions were considered complete when rotation no longer increased on recrystallization of the combination of the resolving agent and compound, but false plateaus have frequently occurred. Although impurities usually lower rotations, a diastereoisomer or optically active impurity with a high rotation can increase the

<sup>18</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> δ): 9.33 (s, 1H, CHO, **endo**); 9.56 (s1H, CHO, **exo**); see: Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930.

<sup>19</sup> Beckmann, S.; Bamberger, R. *Liebigs Ann. Chem.* **1953**, *580*, 198.

<sup>20</sup> From: Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930: *exo*-2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz, δ): **0.76** (d, J=12.0 Hz, 1H); **1.01** (s, 3H), **1.38-1.40** (m, 2H); **2.25** (dd, j=3.8, 5.7 Hz, 1H), **2.82** (bs, 1H); **2.90** (bs, 1H), **6.11** (dd, j=3.0, 5.7 Hz, 1H), **6.30** (dd, 1H, J=3.0, 5.7 Hz, 1H); **9.69** (s, 1H).

<sup>21</sup> Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.*, **1979**, 437.

observed rotation. The experimental sample also has to be highly purified, with the same errors possible.

More accurate measurements of enantiomeric purity can be made with the aid of a chiral auxiliary and NMR or gas chromatographic analysis. For example, the enantiomeric purity of (1*R*,2*R*,5*R*)-exo-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde can be measured by making a cyclic acetal with (2*R*,4*R*)-2,4-pentanediol as described by Furuta, Gao and Yamamoto (see ref. in footnote #1). Similar derivatives of most aldehyde can be made. Acids are converted to esters of chiral alcohols. Alternatively, an NMR spectrum can be taken in the presence of chiral shift reagent or/and GC on chiral column (see Appendix 2). It will be of interest to measure the enantiomeric excess of any synthesized sample of Diels-Alder adduct if time permits.

## FIRST REPORT.

### QUESTIONS:

#### 1. Tartaric acid and ester chemistry:

- (a) What is the absolute configuration of natural L-tartaric acid in the Cahn-Ingold-Prelog nomenclature (*R/S*) system?
- (b) Dimethyl (L)-tartrate can be purchased cheaply. Why would chemists choose to use the benzyl ester in this case? If methyl ester were used, in what part of the synthesis might side reactions be encountered, and what kinds of side reactions might be observed?
- (c) The rate constant for the alkaline hydrolysis of the first methoxy group from dimethyl tartrate in water at 35 °C has been estimated to be  $10 \text{ M}^{-1}\text{sec}^{-1}$  [Genevois, L. *Bull. Soc. Chim. Fr.* **1937**, 1506-1508.] Assuming this rate constant is accurate, if a 1M aqueous solution of dimethyl tartrate is kept a constant pH of 12 for 12 hours at 35 °C, what is the molarity of the remaining dimethyl tartrate?

#### 2. Diels-Alder chemistry:

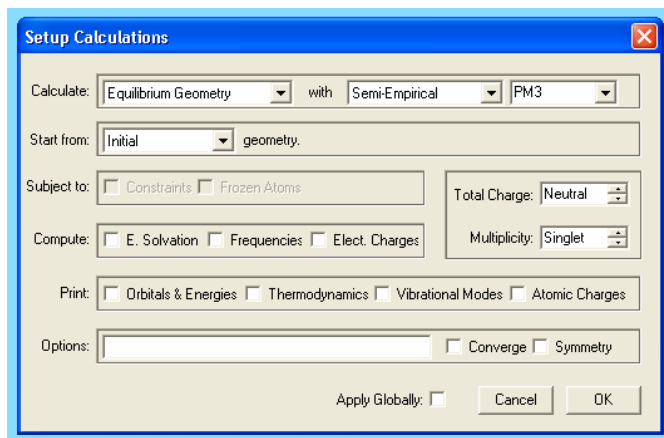
- (a) Outline a mechanism of the uncatalyzed Diels-Alder reaction between methacrolein and cyclopentadiene.
- (b) From the product you have obtained in this reaction, determine whether the relationship of the diene to the dienophile is *exo* or *endo*. Evaluate computationally at PM3, *ab-initio* 3-21G\* and Density Functional Theory (DFT) level of theory (see Appendix 1) the thermodynamic stability of *exo-CHO-3* and *endo-CHO-3* diastereoisomers. Attach the results to your First Report.



To work with PC Spartan Pro 1.0.5. installed on the Dell Optiplex GX1 PC read the Appendix 1 (Ferrocene experiment) from the 5.311 manual. Run only optimization.<sup>22</sup>

Suggestions:

- Start calculation at semi-empirical PM3 level.

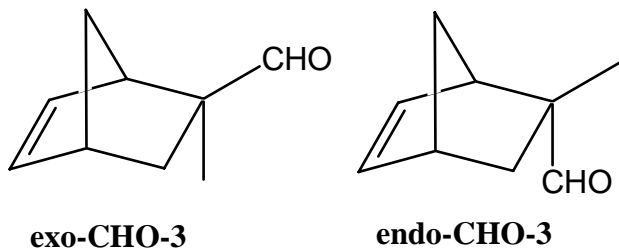


When the computation has finished **Save As...** the file, for example as “**BCH\_CH3\_exo\_CHO\_PM3**” (BCH is from bicyclo[2.2.1]heptane, which is the carbon skeleton of the adduct). PM3 is a very quick computation, taking *ca* 2 minutes. Fill in the Table below the heat of formation value (which are in kcal/mol).

- Then **Save As...**the same file, for example as “**BCH\_CH3\_exo\_CHO\_321G**”; start a new calculation at *ab-initio* level with 3-21G\* basis set. It takes about 45 minutes to complete this calculation.
- Repeat the above steps (semi-empirical PM3, *ab-initio* 3-21G\* and DFT/SVWN/DN\* for **BCH\_CH3\_endo\_CHO\_xxx**”
- Fill in the Table below. Which diastereoisomer is more stable?

Diels-Alder adduct	PM3 (kcal/mol)	Ab-initio 3-21G* (a.u., hartree)	DFT/SVWN/DN* (a.u., hartree)
<b>exo-CHO-3</b>			
<b>endo-CHO-3</b>			
<b>Energy difference:</b> <b>E<sub>exo</sub>-E<sub>endo</sub></b> (kcal/mol) 1 a.u.=627.5095 kcal/mol			

<sup>22</sup> For more information consult “PC Spartan *plus*. Tutorial and User’s Guide”



(c) Outline a probable mechanism for the Diels-Alder reaction in the presence of the asymmetric boronic ester/tartrate catalyst. What kinds of interactions may be significant? The dimethoxyphenyl group plays a role in the transition state interactions, and such groups as *tert*-butyl in its place yield little if any enantioselection. Account for this fact in your postulated transition state structure. Calculate at PM3 level of theory the conformation of the complex chiral boron catalyst\*methacrolein. Build the catalyst in two assumptions by starting from (i) L-tartaric acid and (ii) from D-tartaric acid. Establish in each case which face, *re* or *si*, of the CC double of methacrolein is available for cyclopentadiene addition. Attach the molecular pictures of the computed structure for case (i) and (ii) to your First Report.

(d) Does the favored absolute configuration of the product depend on whether the reaction proceeds an *exo* or an *endo* transition state? Explain. Does your mechanistic model suggest that an *exo* or an *endo* transition state prevails in the reaction of  $\alpha$ -methylacrolein?

### FINAL REPORT.

You will be expected to provide a final (written or oral) report describing your experiments and observations. If your experiments deviate from those outlined in any significant way, a brief written outline of the experimental conditions and the results should be provided, since we are attempting to develop a new experiment for future use.