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Chirality transfer in the synthesis of homoallylic alcohols

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CHIRALITY TRANSFER IN THE SYNTHESIS OF HOMOALLYLIC
ALCOHOLS

Simon Paul Drew

Submitted in partial fulfillment
of the requirements for
Honors in the Department of Chemistry

UNION COLLEGE
June, 1987

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ABSTRACT

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1987.

Previous studies on the reaction of the optically active organotin, diallylisopropylmyrtanyltin, to produce homoallylic alcohols, using boron trifluoride as a Lewis acid, produced racemic mixtures regardless of the aldehyde used.¹ In this experiment bromine was attached to the tin atom in allylmyrtanylphenyltin bromide, letting tin become an internal Lewis acid.

Benzaldehyde was reacted with this compound to see if a single optically active product could be synthesized. After the alcohol had been separated out using vacuum distillation, the optical rotation of the product was taken and showed no appreciable rotation; thus a racemic mixture was produced.

I would like to acknowledge the guidance of Professor McGahey and Jeff Osofsky, who laid the ground work for this project and helped me throughout this year.

Simon P. Chew

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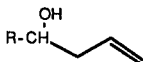
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Background and Theory

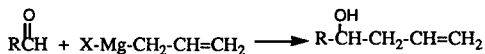
In order to obtain optically active products in organic synthesis a reaction must have a compound with at least one chiral center as a starting product. Another restriction on the reaction if one enantiomer is to be selected for is that the transition states must differ enough in their activation energies; thus the transition state must be a diastereometric transition state. The reasoning behind this statement is that diastereomers can differ in their activation energies, whereas enantiomers cannot. Therefore, if we want to select for one enantiomer in the products we must have at least two chiral centers in the transition state; that is, to have diastereomers we need at least two chiral centers.

One product that can be formed through this type of transition state is a homoallylic alcohol, a useful product in complex natural products, which has this general form:



R = any organic substituent

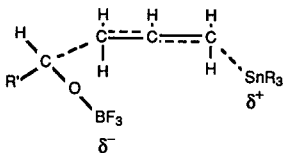
This product is formed by reacting an aldehyde with an allyl Grignard by this reaction:



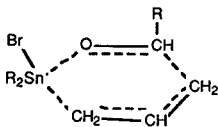
where X is any halide. Notice that this product has only one chiral center and that the reactants in the above equation have no chiral centers. This means that we must synthesize homoallylic alcohols in such a way as to have one chiral center in the product and have one near the reaction site contained in one of the reactants. Also by using one enantiomer, say the R form we have two possible formations for the products, either the R or S configurations, and activation energy differences should select one or the other of these two diastereomers since one should form faster than the other. In our work we use myrtanyl tin compounds, since in the myrtanyl constituent there are three chiral centers and the myrtanyl group provides sufficient steric hinderance that also helps in obtaining activation energy differences.

In previous work done by J. Osofsky, boron trifluoride

was used as a Lewis acid catalyst in the reaction of three aldehydes, benzaldehyde, *o*-chloro benzaldehyde, and 2-ethyl hexanal, with diallylisopropylmyrtanyl tin.¹ Each of these reactions yielded racemic mixtures and it was determined that the reason for this is the reaction passes through a non cyclic transition state:



This project was committed to the task of developing a reaction of this type in which a cyclic transition state would be achieved. The compound used here was allylmyrtanylphenyltin bromide (1). The beauty of this compound is the tin acts as an internal Lewis acid due to it being bonded to bromine; thus upon reaction with benzaldehyde a cyclic transition state can be achieved.



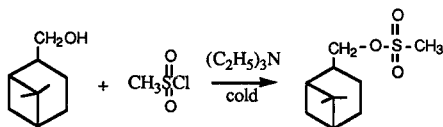
Since the chiral group is close to the reaction site this reaction should favor one transition state over the other and hopefully favor one enantiomer of the homoallylic alcohol in the products.

Results

In order to synthesize 1-phenyl-3-butene-1-ol, a homoallylic alcohol, from benzaldehyde, **1** must be synthesized first from optically active myrtanol. This process can be accomplished in five steps. These steps are the mesylation of myrtanol, the preparation of triphenylmyrtanyltin (**5**), the dibromination of **5**, the addition of two allyl groups to the tin, and finally a single bromination of the tin. After **1** is made, it can be reacted with benzaldehyde resulting in the homoallylic alcohol 1-phenyl-3-butene-1-ol.

Preparation of Myrtanyl Methanesulfonate:

In order to attach the myrtanyl group to a tin atom the hydroxy group on myrtanol must be replaced by a better leaving group. This is achieved by reacting myrtanol with methanesulfonyl chloride in CH_2Cl_2 :



The yield for this process was 91% assuming the product was pure, however, both the IR and nmr indicate some alcohol is still present (Tables 1 and 2).

Table 1: Important IR bands for Myrtanyl Methanesulfonate in Figure 1

BAND(cm^{-1}), DESCRIPTION:	ASSIGNMENT:
1300-1400 strong	S-O stretch
2800-3100 strong	C-H stretch
1130-1200 strong	S=O stretch
769-1000 strong	S-O-C stretches
3460-3660 medium	OH left over

Table 2: Important nmr peaks of Myrtanyl Methanesulfonate
in Figure 2

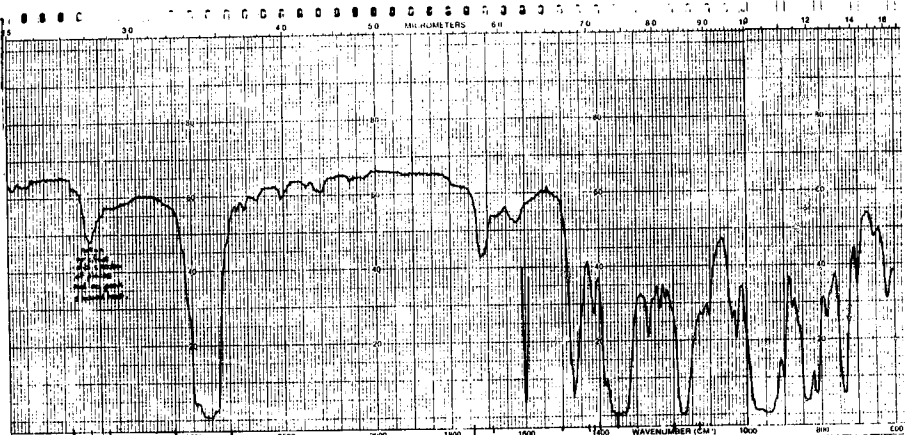
PEAK ppm:	TYPE:	DESCRIPTION:
5.4	singlet	$\text{CH}_2^* \text{Cl}_2$
4.2	doublet	$\text{H-C-CH}_2^* \text{-O}$
3.0	singlet	$\text{CH}_3^* \text{-S(=O)}_2$

* indicates which H is providing the signal

Preparation of Triphenylmyrtanyltin

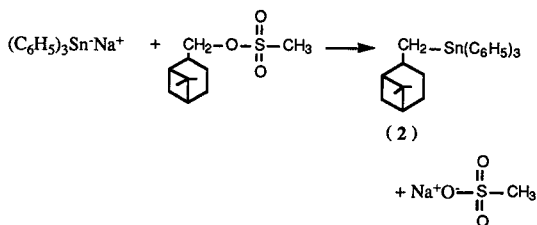
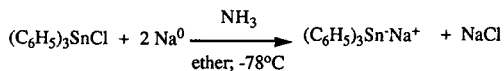
The next step in the preparation of the final tin compound is a tin anion reaction followed immediately by reaction with the previous mesylate. The two reactions are as follows:

Figure 1: IR Spectrum of Myrtanyl Methanesulfonate



SAMPLE NO. A8 ORIGIN	REMARKS <i>None</i>	SOLVENT CONCENTRATION CELL PATH REFERENCE <i>Polystyrene</i>	REP. SCAN HIGH LIMIT LOW LIMIT	ABSORBER EXPANSION SUPPRESSION TIME DRIVE	SCAN TIME 12 RESPONSE SALT PROGRAM 6	DATE TIME OPERATOR	CHECKED BY ANALYST APPROVED BY
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Figure 2: nmr Spectrum of Myrtanyl Methanesulfonate



Triphenylmyrtanyltin was produced with a yield of 26.5% and its melting point was determined to be 64 to 66°C. During recrystallization it was determined that one of the crops was triphenyltin chloride. However, this was only 2.97 g, an unappreciable amount, since it was a small amount of the excess triphenyltin chloride used. This crop melted at 100 to 102°C and its structure was determined by nmr spectroscopy (figure 4). Notice the change in the aryl peaks around 7ppm in figures 3 and 4. These differences were used to determine the nature of this 2.97g of material.

Figure 3: nmr Spectrum of Triphenylmyrtanyltn

Figure 4: nmr Spectrum of Triphenyltin Chloride

An optical rotation was then taken of **2**, these results are displayed in Table 3.

Table 3: Optical rotation data for **2**

grams **2**: 0.2019 ± 0.0001

volume solution: 5.00 mL

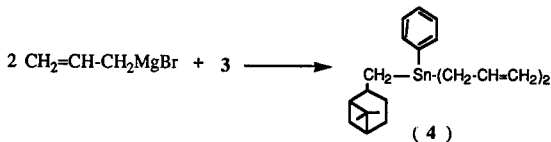
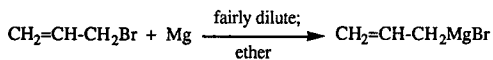
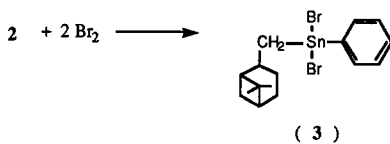
concentration **2**: 4.038×10^{-2} g/ml CHCl_3

α_{obs} : $-00.51^\circ \pm 0.03^\circ$

$[\alpha]_{\text{D}}^{22.7}$: $-12.63^\circ \pm 0.74^\circ$

Preparation of diallylmyrtanylphenyltin

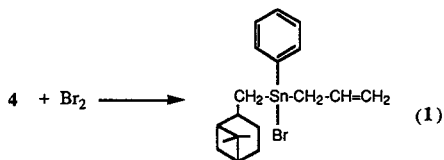
The next step in this synthesis involves the placement of two allyl groups on the tin atom. Three steps are involved in this process: first the dibromination of the tin, second the production of allyl magnesium bromide and finally the reaction of this Grignard with the tin atom. Two allyl groups are placed on the tin since allyl groups bonded to tin atoms react faster with bromine than phenyl groups in the same situation. This would then only produce one product, not a series of products. The synthesis proceeds like this:



The yield after these three processes is 34%.

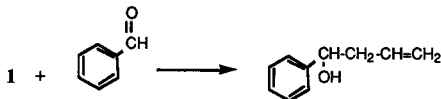
Preparation of allylmyrtanylphenyltin bromide

The final step in this synthesis involves attaching a single bromine to the tin atom. This process finally makes the tin the Lewis acid and will allow for a cyclic transition state on reaction with aldehydes. The reaction here proceeds as follows:



Reaction of allylmyrtanylphenyltin bromide

Finally benzaldehyde was reacted with **1** first at room temperature for 48 hours and then for 15 hours at 50°C and yet produced 1-phenyl-3-butene-1-ol with a yield of 8% after purification, see Experimental page 37. Benzaldehyde present at the end seems to suggest that the reaction still did not go to completion, the reaction follows this procedure:



Note in figure 6 also that there are three aryl peaks, two for benzaldehyde and one for the alcohol.

Table 4: Important IR bands for 1-phenyl-3-butene-1-ol in
Figure 5

BAND (cm ⁻¹), DESCRIPTION:	ASSIGNMENT:
3200-3660 broad	OH stretch
2660-3100 strong	aliphatic and aromatic C-H stretch
1640 weak	C=C stretch
1700 strong	C=O stretch

Table 5: Optical rotation data for 1-phenyl-3-butene-1-ol

grams alcohol: 0.294 ± 0.0001

ml solution: 5.00

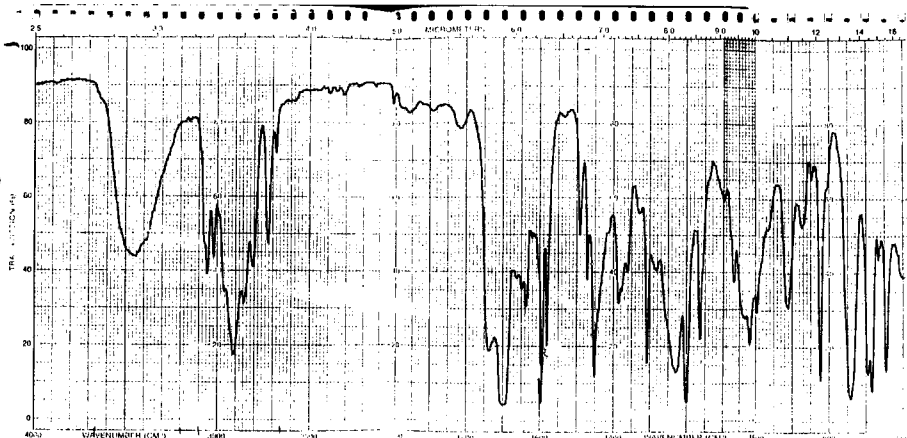
concentration alcohol: 5.88×10^{-2} g/ml CCl_4

α_{obs} : ave = $-0.09 \pm 0.03^\circ$

$[\alpha]_D$: ave = $-1.62^\circ \pm 0.04^\circ$

Note: not appreciable rotations within errors in
measurements.

Figure 5: IR Spectrum of 1-phenyl-3-butene-1-ol



CHANNEL <i>①</i> INPUT A-27	RESISTANCE	NAME NEAT DESCRIPTION SERIAL NUMBER <i>ph/1/1000</i>	REFERENCE FREQUENCY TIME PERIOD	AMPLITUDE VOLTAGE CURRENT POWER	RANGE RANGE RANGE RANGE RANGE	SCALE RANGE RANGE RANGE RANGE	RANGE RANGE RANGE RANGE RANGE	RANGE RANGE RANGE RANGE RANGE	RANGE RANGE RANGE RANGE RANGE
--------------------------------------	------------	--	---------------------------------------	--	---	---	---	---	---

Figure 6: nmr of 1-phenyl-3-butene-1-ol

Conclusion

Upon reaction of 1 with Benzaldehyde an unappreciable optical rotation was measured. This seems to indicate that the activation energies of the two diastereomeric transition states do not differ by appreciable amounts. Another factor could also have led to this same result. The temperature at which these compounds were reacted, after no appreciable amount of product was formed at room temperature, could have been high enough to close the gap in the activation energy difference.

The next step in this project could follow one of two paths. First, a study of the effects of reaction temperatures between 25°C and 50°C could be studied in order to obtain an ideal temperature to react these two species. This would take into account not only maximizing yields and obtaining the best enantiomeric separation, but also minimize the time needed for reaction. A second path would be to try attaching Chlorine and or butyl groups to the tin instead of a phenyl group as Tagliavini shows in his article on the studies of aldehydes to allyl tin compounds.²

The phenyl group may be too large providing much steric hindrance, thus inhibiting the aldehyde from reacting with the tin compound altogether. This possibly explains why a long reaction time and low yield is noticed.

Experimental

Preparation of Myrtanyl Methanesulfonate:

A three necked 2-L round-bottom flask was fitted with a thermometer and a 125-mL addition funnel. Added to this flask was a stir bar, myrtanol (44.67g, 0.290 moles, prepared by Osofsky¹), $(C_2H_5)_3N$: (50 mL, 0.359 moles), and 725 mL of CH_2Cl_2 (enough to produce an alcohol concentration of 0.4 M). Methane sulfonyl chloride (25 mL, 0.323 moles) and 45 mL of CH_2Cl_2 were then added to the addition funnel.

The apparatus was placed in an ice bath and the contents stirred until an internal temperature of $\leq 5^\circ C$ was established. Next the contents of the addition funnel were added slowly so as to keep the internal temperature below $10^\circ C$. The funnel was then washed with 25 mL of CH_2Cl_2 and stirred in the ice bath for 30 minutes. Finally, the flask was removed from the bath and allowed to stir at room temperature for 4 hours 15 minutes.

Next the reaction mixture was split in half and the first half was poured over a 500 mL 50:50 solution of

ice:water and stirred by hand until the ice melted. The CH_2Cl_2 layer was separated off using a 2-L separatory funnel. Next, this layer was washed two times with 150-mL portions of 10% HCl, once with 150 mL of aqueous sodium bicarbonate and once with a 150-mL portion of brine. The CH_2Cl_2 layer was then dried over 4A molecular sieves. This sequence was then repeated with the second half of the reaction mixture and both of the CH_2Cl_2 layers were combined and the solvent "rotovapped" off (bath temp = 30°C). This product was then placed under high vacuum for 4 hours 20 minutes and placed under N_2 and in the refrigerator for use later. IR and nmr spectra were then taken to determine structure and the yield was calculated to be 91% assuming the product is pure.

Preparation of 2:

A three necked 2-L round-bottom flask was fitted with a mechanical stirrer, a 500-mL self-equalizing addition funnel, and a two-necked adapter which was fitted with a vacuum adapter and a gas condenser. A N_2 line was placed on the top of the gas condenser and the funnel was

capped. The 2-L flask was placed in a plastic bucket. The vacuum adapter was fitted to a rubber hose which in turn was connected to a one necked 1-L round bottom flask that sat in a heating mantle.

To the 2-L flask was added triphenyltin chloride (109.13 g, 0.28 moles) and 500 mL of anhydrous ether. Dry ice was added to the plastic bucket and the gas condenser. Liquid ammonia (500 mL) was added to the 1-L flask and Na^0 was added slowly to dry the ammonia until it no longer changed to colorless. The heating mantle was then turned on and the ammonia was distilled into the reaction flask and then the vacuum adapter was replaced with a glass stopper and the mantle turned off.

Sodium metal (14.65g, 0.637 moles) was then added, in chunks after its oxide coat was removed, slowly to the reaction mixture for 40 minutes. The reaction was stirred at -78°C , dry ice temperature, for 2.5 hours and then the bucket was removed. Next the reaction was stirred under reflux at -33°C , liquid ammonia temperature, for 2.75 hours while the mesylate (61.38g, 0.26 moles) was added slowly to keep the ammonia from boiling off. Finally the N_2

was shut off and the 2-L flask was left open to the atmosphere and the ammonia allowed to evaporate out over night.

Water(500 mL) was then added to the reaction flask slowly to prevent emulsification. This mixture was then separated in a 2-L separatory funnel, saving the ether layer and extracting the water layer with 100 mL of ether; and this second ether layer was separated off and added to the first. The ether layer was then washed with one 250-mL portion of brine and dried over potassium carbonate. The solution was then filtered by gravity and the ether was "rotovapped" off (bath temperature = 70° C) and the flask was left open to the room overnight. An nmr spectra was taken and there was evidence of ether left over so the material was "rotovapped" another 15 minutes at 75° C and then placed in ice water to cool.

A recrystallization in ethanol was then performed to obtain pure product. This was done both to the solution and to some left over material in the original Erlenmeyer flask that was not picked up by the first addition of ethanol (the "sludge" crop). After Buchner filtration each time the

ethanol was concentrated and another crop grown until unappreciable amounts of crystals were obtained. The masses and melting points for all of these crops are found in the tables below.

 Table 6: Data for first recrystallization

<u>CROP</u>	<u>WEIGHT (g)</u>	<u>MELTING POINT</u>	<u>COMMENTS</u>
1	30.44	62-68° C	shrinks and
2	7.50	62-68° C	sweats at 54° C

 Table 7: Data for second recrystallization of combined crops 1 and 2 above.

<u>CROP</u>	<u>WEIGHT (g)</u>	<u>MELTING POINT</u>	<u>COMMENTS</u>
1	31.35	69-72° C	sweats at 59° C
2	3.69	68-70° C	sweats at 62° C
both	35.04	64-66° C	sweats at 58° C

 Table 8: Data for first "sludge" recrystallization

<u>CROP</u>	<u>WEIGHT (g)</u>	<u>MELTING POINT</u>	<u>COMMENTS</u>
1	11.61	66-70° C	sweats at 61° C
2	2.44	none taken	

A melting point of the recrystallization of the two crops in table 10 gave a range of 100-102°C and weighed 2.97 g. This was then determined to be triphenyltin chloride by nmr. The optical rotation data for **2**, all crops combined, can be found in table 5 in the results section. The nmr of **2** was also taken in carbon tetrachloride to determine the structure of this product (Figure 3).

Dibromination of 2:

A one necked 1-L flask was fitted with a 125 mL self-equalizing addition funnel. CCl₄ (150 mL) and **2** (33.5g, 0.069 moles) were added to the reaction flask along with a magnetic stirrer. Bromine(7.1 mL, 0.138 moles) and double its volume of CCl₄ were added to the addition funnel in small amounts. First 3.1 mL of bromine and 5 mL CCl₄ was added over 30 minutes, then 2 mL of bromine and 3 mL CCl₄ was added over 15 minutes, and finally 2mL of bromine and 2mL CCl₄ was added over 20 minutes. Finally, the funnel was rinsed with 10 mL of CCl₄ and this was added to the solution. This mixture was then rotovaped to remove the

CCl_4 (bath temperature = 45°C) and then filtered by gravity to remove solid particles contaminating the solution. Finally, this product was placed under high vacuum for 5.5 hours to remove trace volatiles.

Preparation of allyl magnesium bromide:

Magnesium (14.1g, 0.580 moles) and 195 mL anhydrous ether were added to a three-necked 500-mL round-bottom flask along with one crystal of iodine. The flask was fitted with a 125-mL addition funnel that was capped, a mechanical stirrer, and a condenser fitted with a CaCl_2 drying tube. The reaction flask was then immersed in an ice bath. Allyl bromide (21.0 mL, 0.243 moles) was placed in the addition funnel, added to the reaction flask slowly for 1 hour 20 minutes, and then the reaction mixture stirred in an ice bath for 20 minutes.

Preparation of 4:

Allyl magnesium bromide (34.87g, 0.240 moles) was decanted from the reaction flask in the previous step into a 1-L three necked round bottomed flask with a magnetic

stirrer; the magnesium left over was washed twice with 25 mL of ether and this ether was then added to the second reaction flask. This reaction flask was then fitted with a 125-mL addition funnel, a condenser and a CaCl_2 drying tube. **3** (33.53g, 0.068 moles) was placed in the addition funnel and added neat to the reaction flask to create a gentle boil (about 15 minutes). The funnel was then rinsed with 25 mL ether and added to the reaction mixture. This was stirred off and on for 30 minutes and was then sealed to the air and left to stand at room temperature over night.

Water (100 mL) was then added to the funnel, the drying tube removed, and the reaction flask placed in an ice bath. The water was added slowly (30 minutes) to keep the ether from boiling out of the condenser. This mixture was then transferred to a 2-L separatory funnel and the ether layer was set aside. The water layer was then extracted with 25 mL of ether and this ether was added to the ether collected before. The ether was then dried with potassium carbonate and gravity filtered into a one-necked 500-mL round-bottom flask. Ether was then removed by "rotovapping" (bath temperature = 20°C). The impure **4** was

then transferred to a 200-mL one-neck round-bottom flask and hooked up to the vacuum pump in a -60°C water bath for three hours to remove excess ether and bromobenzene. The yield was calculated to be 34%.

Monobromination of 4:

All of 4 from the last procedure was placed in a 500 mL one-neck round-bottom flask with 100 mL CCl_4 , a magnetic stirrer, and 40 mL CH_3OH . The flask was then fitted with a self-equalizing addition funnel. Bromine (1.2 mL, 0.023 moles) and 3 mL CCl_4 were added to the funnel and then added dropwise for 15 minutes. The funnel was then rinsed with 10 mL CCl_4 and this was also added to the flask. All of the above was done without the hood lights on. Next, the CCl_4 and CH_3OH were rotovaped off (bath temperature = 45°C) and the final product was placed under N_2 and in the refrigerator.

Reaction of 1 with Benzaldehyde:

Benzaldehyde was first purified by simple distillation under N_2 . Benzaldehyde (2.4 mL, 0.023 moles) was added to

the 250-mL one-necked round bottom from the last procedure which contains crude 1 and stirred for two days. After an IR spectrum was taken it was determined that much benzaldehyde remained unreacted so the flask was placed in a $<50^{\circ}\text{C}$ water bath for three hours; another IR showed much benzaldehyde remained still. The reaction was followed in the same way for 12 more hours when a noticeable change in the IR carbonyl peak was found indicating that the reaction had taken place.

The reaction was worked up first by mixing it with 20 mL ammonium chloride(aqueous) and 20 mL ether. This mixture was then transferred to a 125-mL separatory funnel and the ether layer was saved after separation. The water layer was extracted with 20 mL of ether and this was added to the first ether solution. This ether mixture was then dried with magnesium sulfate and gravity filtered. Next, the ether was extracted with 25 mL sodium bisulfite, 25 mL sodium bicarbonate, and 25 mL potassium fluoride. The ether was then dried with magnesium sulfate, gravity filtered, and "rotovapped"(bath temperature= 35°C) to remove the ether.

This product was then run through a chromatography column (0.5" sand, 30g silica gel, 1" sand) with an eluent of 150 mL hexanes and 50 mL ethyl acetate. Two 100 mL fractions were collected and "rotovapped" these separately (bath temperature = 40°C). IRs were taken of both fractions after solvent removal and both were transferred to a micro vacuum distillation apparatus. Both flasks were washed with two 2mL portions of CH₂Cl₂ and the CH₂Cl₂ was distilled off at atmospheric pressure. The vacuum was then applied and 1-phenyl-3-butene-1-ol was collected at 90-147°C and 27 mmHg pressure. An IR spectrum showed some benzaldehyde left, so it was left open to the atmosphere overnight to convert any left over benzaldehyde to benzoic acid, redistilled and collected at 96-105°C at the same pressure. A final IR and nmr showed we had obtained 1-phenyl-3-butene-1-ol, however, with some impurities. An optical rotation was also taken and this data can be found in table 7 in the results section. The calculated yield was determined to be 8%.

References

1. Osofsky, J. L. Senior Research Thesis, Union College 1986.
2. Tagliavini, G.; Gambaro, A.; Marton, D.; Peruzzo, V. *Journal of Organometallic Chemistry* 1982, 226, 149.