The effects of stoichiometry and starting material on the product identity and yield in Grignard addition reactions

Supplementary Material

This experiment has been performed both in the 150 person standard introductory organic chemistry laboratory (taught primarily by undergraduate teaching assistants in five sections of 30-40 students) and in a special introductory organic chemistry laboratory for freshman, taught to 23 students in sections of 7 and 16. This course is the first organic laboratory for these students but has been taught in the spring semester along with the second semester of organic lecture. The lab periods for this course are five hours long, and this experiment is typically performed in the latter half of the semester. This experiment is used to illustrate to students the importance of planning their time in lab; they must be out of the lab in the 5 hours allotted. While many students finish the experiment in this time, others plan to finish the following week along with a shorter experiment. Those who were running behind were encouraged to finish through the drying of their organic layer with $MgSO_4$ and set up the distillation the following week. When doing this they should make sure that their organic layer is in a closed container to prevent evaporation of their product.

Moisture Sensitive Conditions

There are many diverse protocols for maintaining the anhydrous conditions required to successfully prepare and utilize Grignard reagents. We typically open a fresh can of anhydrous ether and dispense it directly, without additional drying in a still or air sensitive techniques for solvent transfers.

Students should clean their glassware with acetone in the previous laboratory period. We have not needed to oven dry the glassware. However, typically when a student decides to wash glassware with acetone during the same laboratory period we have been unable to initiate the Grignard reaction. We have utilized drierite filled drying tubes to emphasize to students the side reaction with water. Everett et al. reports the reaction of alkyl Grignards with ketones without the use of drying tubes, however, he recommends that students flame or oven dry their glassware.[1] In general the spontaneous initiation of the reaction between ethyl bromide and magnesium is much more facile than the initiation of the reaction between bromobenzene and magnesium. Furthermore, if the ethylmagnesium bromide does react with water the produced ethane is a gas and does not need to be purified away from the reaction product.

Experimental Concerns

Initiation of Grignard reagents by undergraduates is an area of concern, and for this reason it has been suggested that the commercially available Grignard reagent is purchased.[2] While ethylmagnesium bromide is commercially available, the cost proved prohibitive, given the number of students and scale of the reaction required for purification *via* distillation. Students are asked to initiate the reaction themselves, though if this does not occur spontaneously, a crystal of iodine is added. Students are then instructed to add a small amount of additional alkyl halide and continue to wait until initiation has begun. Frequently, the students have mistaken the bubbles produced from rapid stirring as a sign that initiation has occurred; video demonstrations have been helpful in minimizing this confusion. Heating the reaction to induce initiation is discouraged; the difference between room temperature and boiling ether is less than 10 ºC. Also, the heat generated by the formation of the Grignard reagent is sufficient to auto-reflux the reaction by itself; heating the reaction independently makes it much more difficult to determine when initiation has commenced. Approximately 30% of student's reactions initiate spontaneously, though almost all reactions initiate after the addition of iodine. Typically, 1-5% of students need to reset up the reaction. In these rare cases, oven dried glassware is provided, and this second reaction has always initiated.

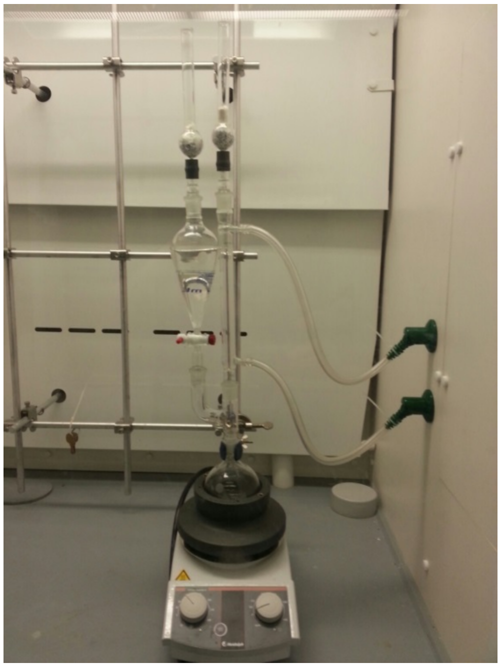

Figure SM 4.2.1.1.1: Grignard reaction dropwise addition apparatus

One of the most common and potentially dangerous errors occurs when students add the alkyl bromide to the separatory funnel without first closing the stopcock, thereby adding all of the alkyl bromide before initiation has occurred. In this case, the setup is placed into an ice bath immediately.

Though the reaction usually initiates under these conditions, it is important to warn students about this particular mishap.

The addition of the electrophile to the Grignard is extremely exothermic, and must be performed very slowly after cooling the reaction mixture. If this addition is too rapid, excess pressure will build up, occasionally causing the drying tube to pop off their apparatus. If students allow the ether to boil off (which occurs when heating mantles are too hot during reflux, the addition of the electrophile is too rapid or the water in the reflux condenser is too warm) additional ether must be added. Even with this additional ether some salts will precipitate out of solution during the addition of the electrophile; if too much precipitation is observed, additional anhydrous ether can be added.

Once complete, the reaction is quenched by pouring onto an ice cold solution of dilute sulfuric acid. It is important to rinse the reaction flask with both ether and sulfuric acid so that as much of the product is transferred as possible. After converting the magnesium alkoxide salt to the resulting alcohol, sulfuric acid will begin to scavenge any remaining unreacted magnesium, generating magnesium sulfate and hydrogen gas and converting insoluble magnesium hydroxide salts into soluble magnesium sulfate. Both of these steps can be quite slow, and often additional sulfuric acid is required. In order to accelerate this process, the instructor will typically add concentrated sulfuric acid dropwise. It is important to prevent excessive heating of the reaction or complete evaporation of the ether. It can occasionally take up to an hour to complete the quenching process; in these circumstances students have been encouraged to stop after this step and store their reactions until the following week.

After separating the layers, we have found that it is very important to wash the organic layer with water before washing it with bicarbonate. If students forget to first wash with water the amount of sodium bicarbonate needed and the therefore the amount of carbon dioxide produced in the separatory funnel is substantially increased. This can lead to a buildup of pressure in the separatory funnel, and if it is not properly vented the loss of product. The steps to remove residual acid are necessary to avoid formation of the olefin, *via* acid catalyzed elimination during the distillation.

The distillation presents a challenge because if students have properly maintained the volume of their organic layer, a large distillation flask would be required to avoid overfilling the flask, which in turn will increase the amount of the high boiling alcohol that is not distilled. Students are encouraged to distill of most of the ether and then transfer the remaining solution to a smaller flask, before proceeding with their distillation. If a student has performed the reaction correctly there will be more than sufficient material for distillation. In the case of the smaller class, this was the first distillation students had been asked to perform. The students are encouraged to tare several vials so that they can collect multiple fractions.

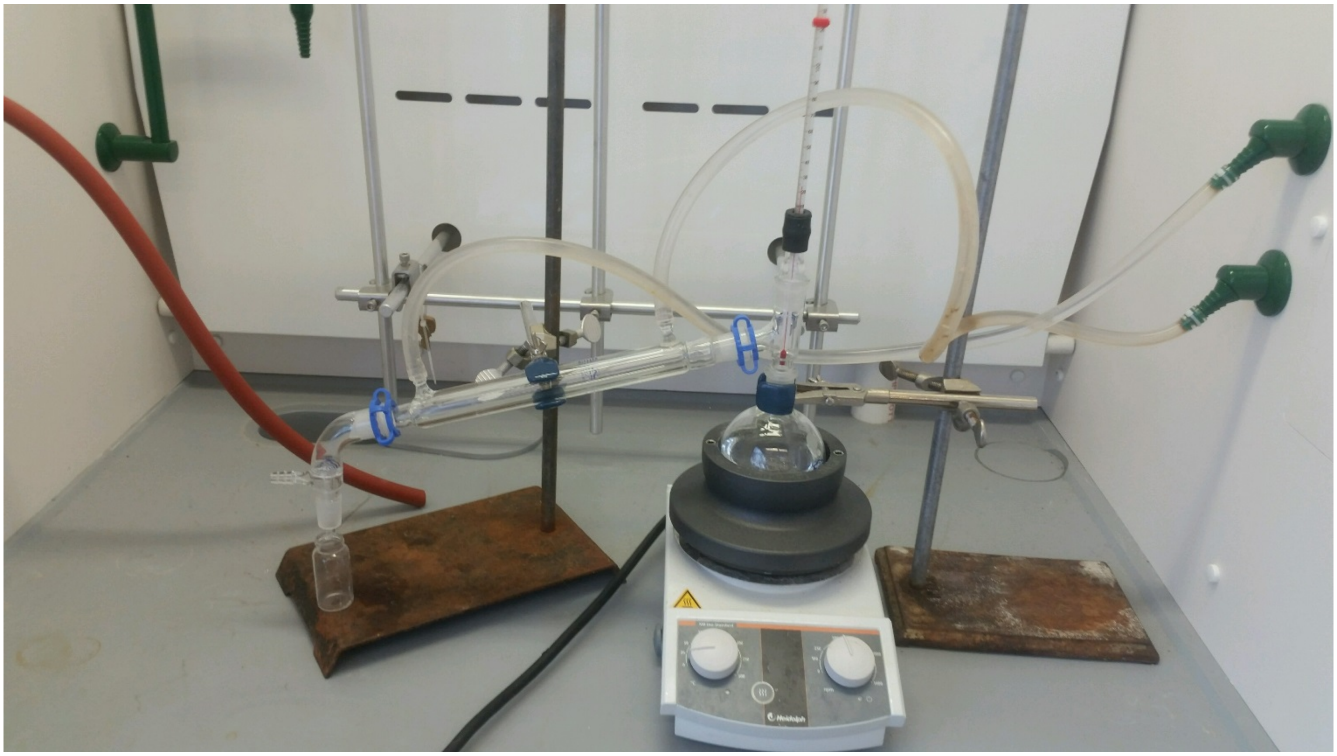

Figure SM 4.2.1.1.2: Distillation apparatus

Evaluation of Products

In the first implementation of this experiment we evaluated the products by GC and boiling point. Chromatograms were obtained on both the crude reaction mixture and distilled products. Students could determine that there was no 2-butanone present by the absence of signal compared to the retention time of the standard. The crude GC also revealed the compounds, such as unreacted starting material that were present. We used the Vernier mini GC, which can detect carbonyl compounds and alcohols but not alkanes. This low cost GC[3] operates on room air. The conditions for the GC run included a start temperature of 35°C, a hold time of 2 minutes, followed by a ramp rate of a 1°C/min to 37°C to give a total length run of 4 minutes at a pressure of 10.0 kPa. Students were both given chromatograms of the pure compounds that were possibly present as well as encouraged to spike their samples with known compound to verify their peak assignments. The GC ratios were not corrected for response factors.

In the second implementation students obtained ^{1}H NMR spectra of their products. All ^{1}H spectra were acquired on a 400 MHz Bruker spectrometer and reported in parts per million (δ) referenced against a residual solvent peak. $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA). As shown in representative spectra from all conditions pure product was obtained by the students.

3-methylpentan-3-ol: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.46 (q, *J* = 7.53 Hz, 4H), 1.34 (b s,1H), 1.11 (s, 3H), 0.89 (t, *J* = 7.53 Hz, 6H).

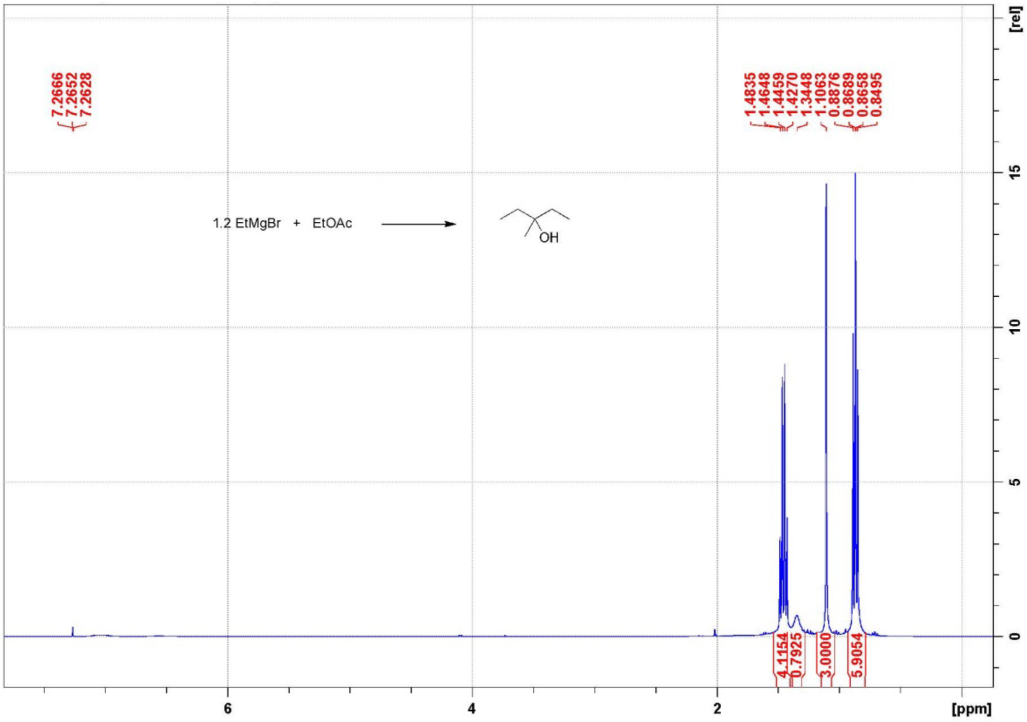

Figure SM 4.2.1.1.3: ^{1}H NMR crude spectrum of EtOAc + 1.2 equiv. EtMgBr

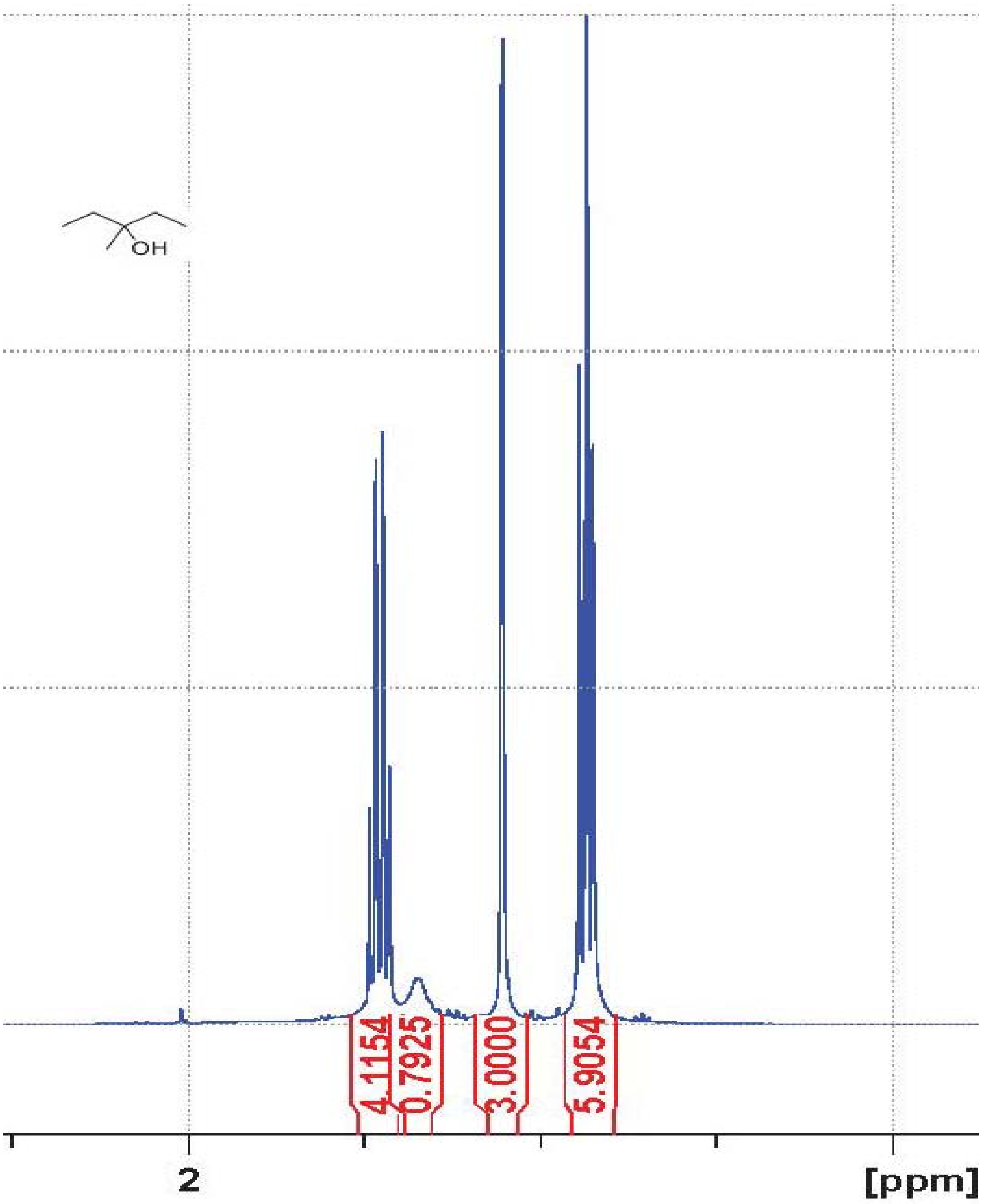

Figure SM 4.2.1.1.4: ^{1}H NMR crude spectrum of EtOAc + 1.2 equiv. EtMgBr (alkyl region)

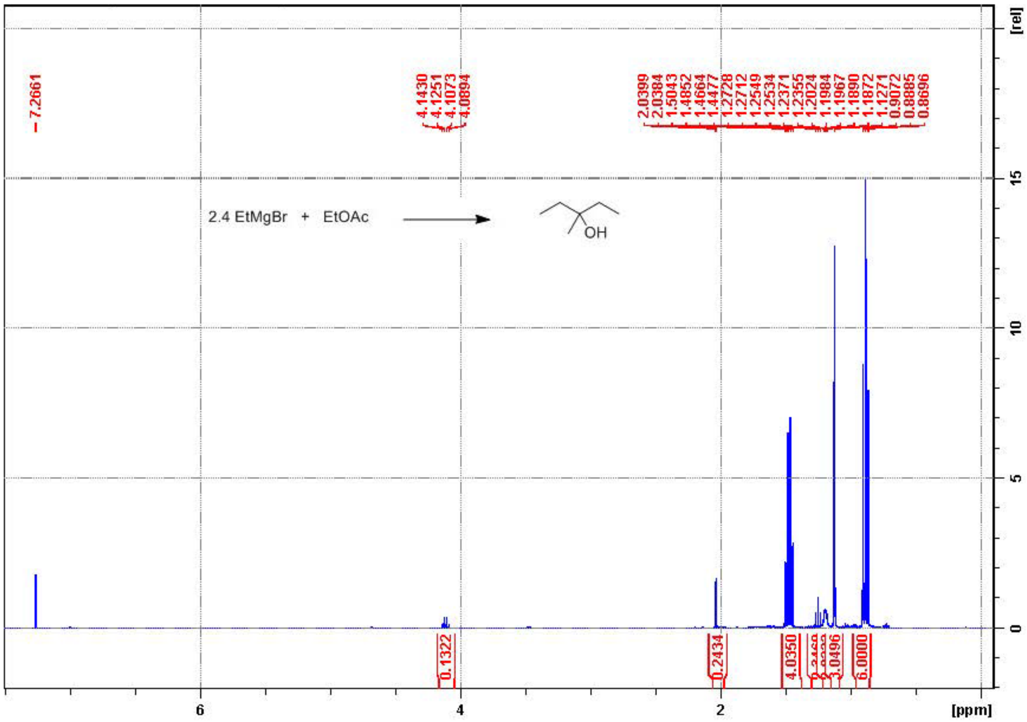

Figure SM 4.2.1.1.5: ^{1}H NMR crude spectrum of EtOAc + 2.4 equiv. EtMgBr

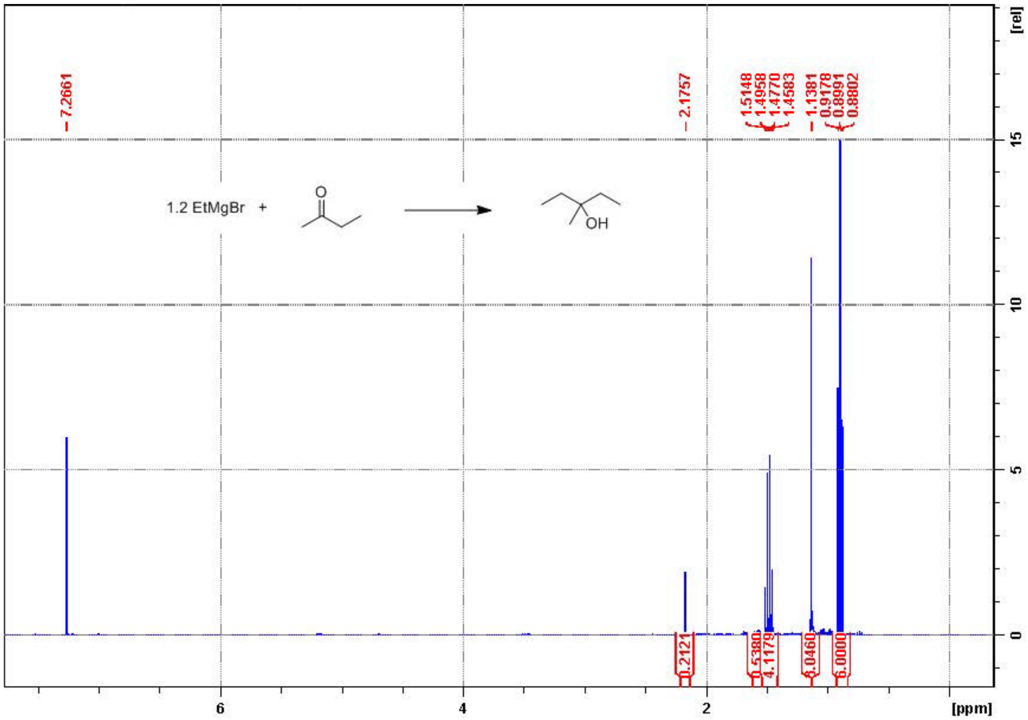

Figure SM 4.2.1.1.6: ^{1}H NMR crude spectrum of 2-Butanone + 1.2 equiv. EtMgBr

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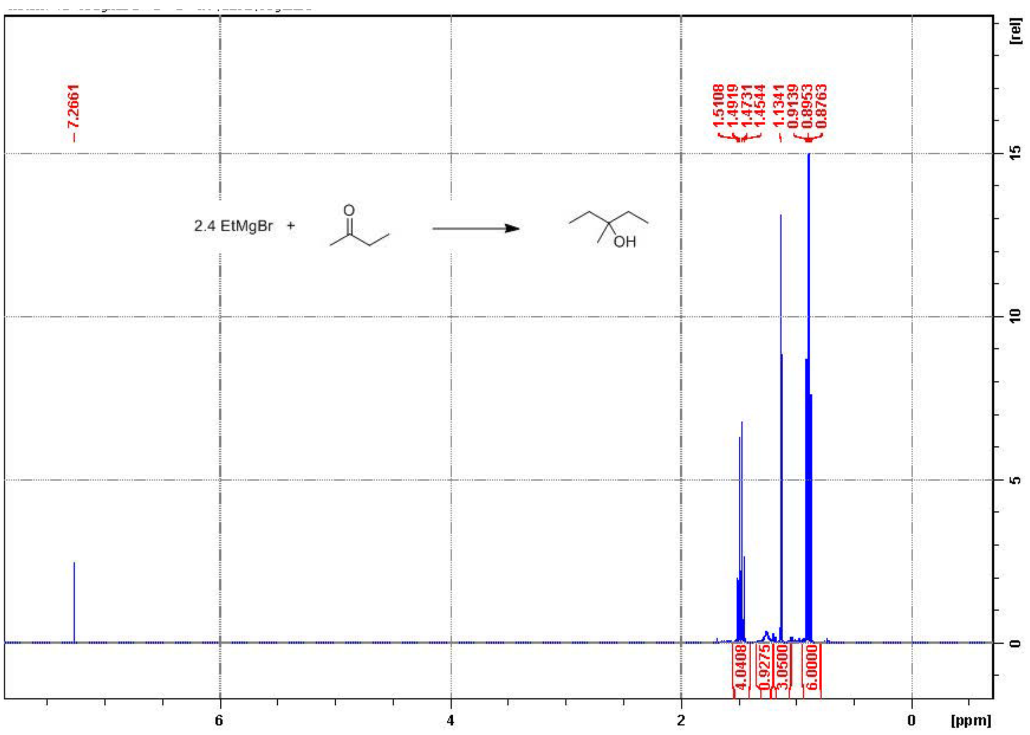

Figure SM 4.2.1.1.7: ^{1}H NMR crude spectrum of 2-Butanone + 2.4 equiv. EtMgBr

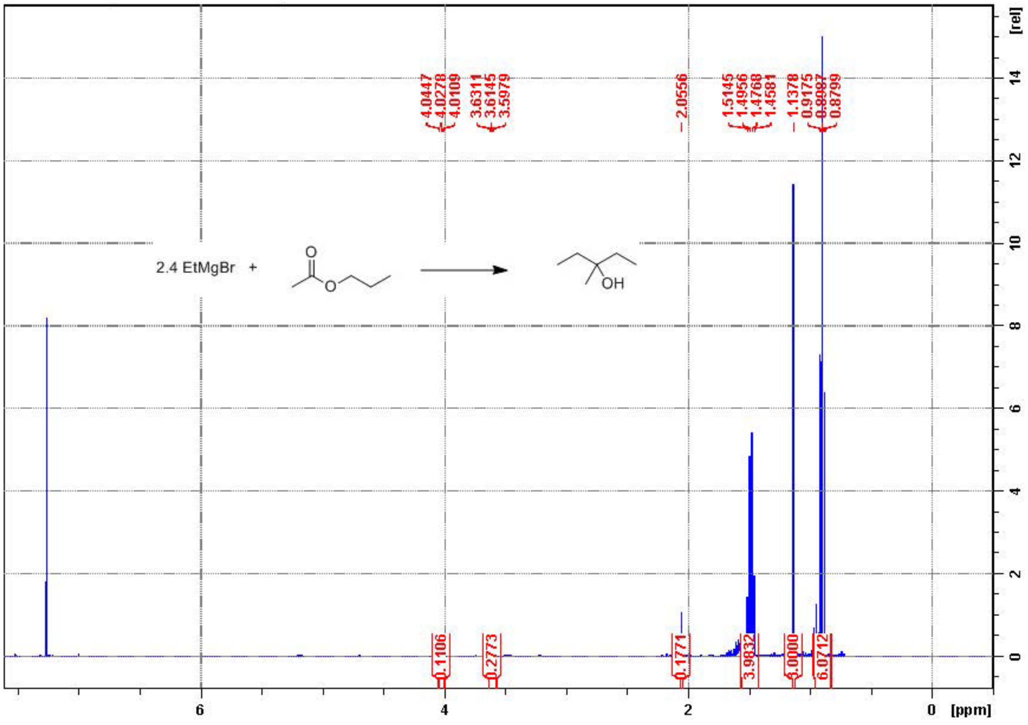

Figure SM 4.2.1.1.8: ^{1}H NMR crude spectrum of Propyl Acetate + 2.4 equiv. EtMgBr

Class Discussion of Results

In this implementation of the course, the lecture period following the lab was used for a discussion of the class data to help clarify the concepts and have the students think about the results of the experiment. Data obtained from the class is given in Table SM 4.2.1.1.1. The reaction conditions were initially chosen to illustrate that 2-butanone could not be isolated out of the reaction of ethyl acetate and ethyl magnesium bromide. In order to set up the reactions in parallel and demonstrate that higher yield of the desired alcohol, in the cases where 2 equivalents EtMgBr was used, was not simply due to the presence of excess Grignard reagent, 2-butanone was also reacted with 2 equivalents of EtMgBr. We were surprised to find that that the reaction of 2-butanone with 2 equivalents of EtMgBr resulted in a lower percent yield of 3-methyl-3-pentanol than the reaction of 2-butanone with 1 equivalent of Grignard reagent. This can possibly be attributed to the large amount of acid required to quench the unreacted Grignard reagent and protonate the resulting magnesium hydroxide salts. This acid, and the time that the reaction is exposed to acidic conditions, presumably leads to greater dehydration. Furthermore, the more magnesium salts that need to be quenched the more acid is used and the more heat that is generated in the quenching. As the 3-methyl-3-pentanol product is volatile, with the additional heat diethyl ether and some 3-methyl-3-pentanol will most likely evaporate during the quenching process. The lower yield for this set of conditions was consistent throughout the two classes. While this provides an opportunity to discuss the idea of optimizing reaction conditions and that more is not always better, it would also be possible to drop this condition for a smaller class. The conditions with propyl acetate were designed to illustrate the importance of the structure of the ester rather than simply the molecular weight. It is slightly more difficult to isolate the 3-methyl-3-pentanol from propanol than from ethanol, one student isolated 1-propanol rather than 3-methy-3-pentanol.

While a few students obtained little to no product, overall most students obtained over 1.0 grams of product with all of the scenarios evaluated. As individual student’s results may skew averages, in addition to the average results from each scenario in **Table SM 4.2.1.1.1**, we have included a complete data set for a student at the median yield in **Table SM 4.2.1.1.2**.

Table SM 4.2.1.1.1: Average class results obtained in the large class implementation

Scenario	# of students	Average mass obtained of pure product (g)	GC Purity of purified product	Ratio of 3-methyl-3-pentanol to unreacted ester in GC of the crude reaction mixture	% Yield range	% of students assigned scenario obtaining 1.00 gram or more product
butanone + 1.2 equiv ethyl bromide	28	4.11	98%	--	11-67%	94%
butanone + 2.4 equiv ethyl bromide	20	1.96	99%	--	3-95%	77%
ethyl acetate + 1.2 equiv ethyl bromide	24	2.24	93%	2.86:1	6-57%	81%
ethyl acetate + 2.4 equiv ethyl bromide	26	2.67	95%	102:1	5-72%	85%
propyl acetate + 2.4 equiv ethyl bromide	27	1.94	84%	1.6:1	1-96%	68%

Table SM 4.2.1.1.2: Complete data for the student with the median yield of each scenario

Scenario	Median yield (g)	GC Purity of purified product	Ratio of 3-methyl-3-pentanol to unreacted ester in GC of the crude reaction mixture
butanone + 1.2 equiv ethyl bromide	4.668	100%	--
butanone + 2.4 equiv ethyl bromide	1.705	98%	--
ethyl acetate + 1.2 equiv ethyl bromide	2.047	95%	1.07:1
ethyl acetate + 2.4 equiv ethyl bromide	2.849	99.6%	36:1
propyl acetate + 2.4 equiv ethyl bromide	1.677	99.9%	31:1

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[1] T. S. Everett, *J. Chem. Educ.*, 1998, **75**, 86.

[2] R. D. Pointer, M. A. G. Berg *J. Chem. Educ.*, 2007, ***84***, 483.

[3] http://www.vernier.com/products/sensors/gc-mini/

Synthesis of methyl triphenylmethyl ether

Supplementary Material

The synthesis of triphenylmethanol (first step) has been performed since the 1980s to illustrate a Grignard reaction. Since 2001 the second step of this synthesis was introduced as a classroom experiment. The experimental procedure for the preparation of the ether is simple and a good example of a S_N1 reaction, thus appropriate for first-year undergraduate students since the mechanisms of the reactions involved are taught during the first semester of Organic Chemistry. An important feature of this synthesis is the extraordinary stabilization of the carbocation, which can be observed by students during the experiment. Also, the product cannot undergo E1 elimination due to the absence of β-protons and no side products are formed. On the other hand, the synthesis of the alcohol involves a Grignard reaction performed under anhydrous conditions and is suitable for second-year undergraduate students.

Additional notes on the preparation of triphenylmethanol:

Great care is required to ensure water-free conditions once Grignard reagent reacts as a strong base with water or alcohols. All glassware must be dried thoroughly in the oven and removed only to assemble the reaction apparatus (**Figure SM 4.2.1.2.1**). The mechanical stirrer can be replaced by a vigorous magnetic one.

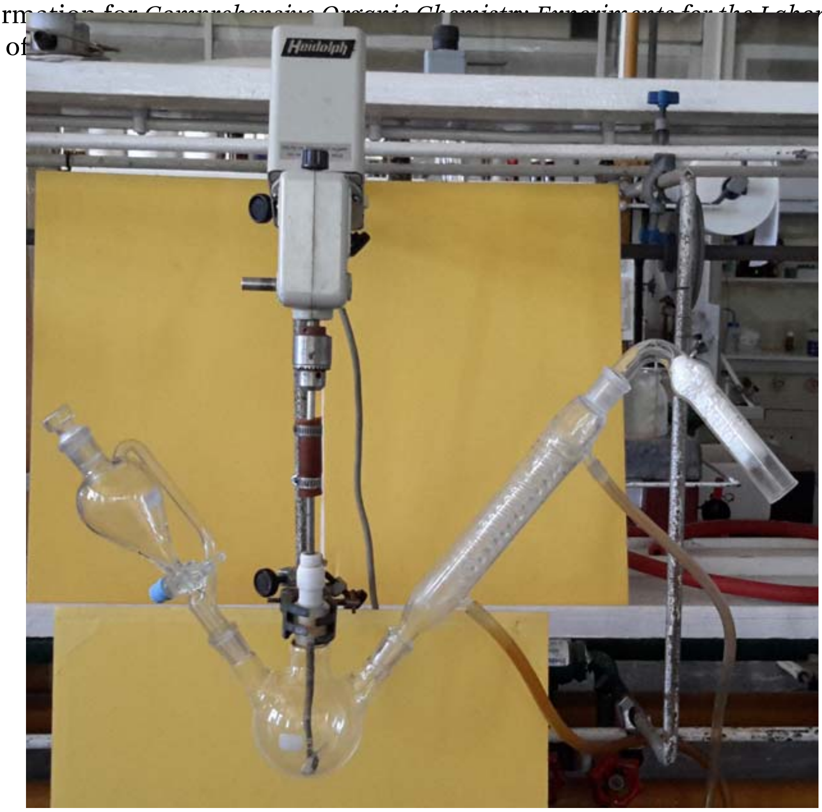


Figure SM 4.2.1.2.1 – Reaction set apparatus for triphenylmethanol

All adjustments needed to guarantee an effective stirring must be performed upon complete assembly, without any reactant or solvent inside the flask. Only then students can measure the chemicals and introduce them immediately into the reaction flask. The reaction initiates once bromobenzene is added, but sometimes some gentle warming is required. In general there is no need to add a crystal of iodine. If ethyl benzoate is used instead of benzophenone, two molar equivalents of Grignard reagent are required to produce the alcohol. The reaction mixture using the ester has a different color and consistence. There are two side products formed in this reaction: Biphenyl (Ph-Ph) and benzene that can be separated using a steam distillation apparatus as is shown in **Figure SM 4.2.1.2.2** (Photo of steam distillation apparatus taken for another experiment; the residue contained in the flask does not correspond to reaction mixture).

Figure SM 4.2.1.2.2 – Steam distillation apparatus

The average yield is 30-35% and it is highly affected by any residual humidity present in the apparatus and the chemicals used. The TLC plate should contain samples of both crude and recrystallized product, benzophenone and the mother liquor from recrystallization. The products and benzophenone should be dissolved in dichloromethane. Since the compounds are colorless, a UV light is required to reveal the spots on the plate. The impurity corresponding to benzophenone can be easily identified by comparing the R_f (**Figure SM 4.2.1.2.3**).

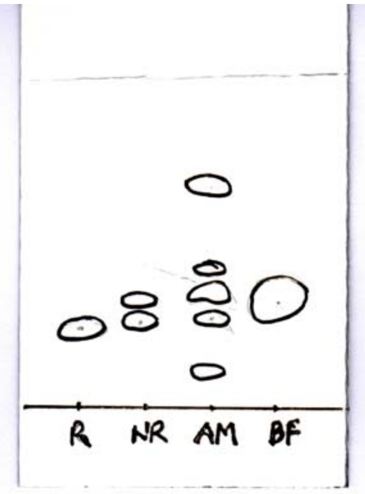
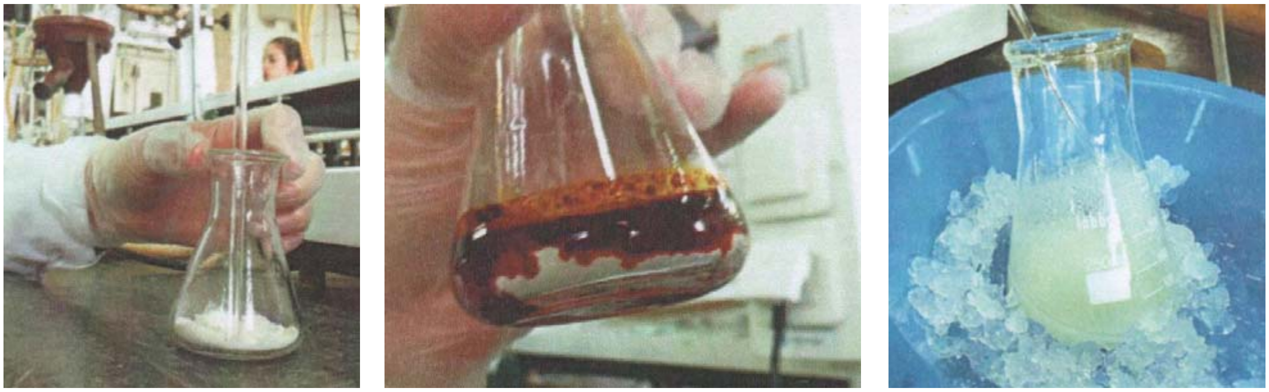


Figure SM 4.2.1.2.3 - TLC eluted with dichloromethane/petroleum ether (40-60) (1:1) where R= recrystallized triphenylmethanol, NR=crude triphenylmethanol (not recrystallized), AM=mother liquor from recrystallization and BF=benzophenone.

Melting points are between 135 and 145ºC for the crude product and between 156 and 163ºC for the recrystallized product (164.2ºC[1]).

Additional notes on the preparation of methyl triphenylmethyl ether:



a) b) c)

Figure SM 4.2.1.2.4 – Preparation of methyl triphenylmethyl ether: a) triphenylmethanol before addition of sulfuric acid; b) red-brown solution after addition of sulfuric acid; c) Methyl triphenylmethyl ether precipitation after methanol addition.

The product is obtained with an average yield of 45-50%. Melting points are usually between 80 and 83ºC, with a melting point range never higher than 2ºC (81-83ºC[2]).

IR and ^{1}H NMR spectra:

Students easily identify in **Figure SM 4.2.1.2.5** a broad absorption near 3472 cm^{-1} in the IR spectrum due to the OH group. The same absorption can be detected for methyl triphenylmethyl ether **(Figure SM 4.2.1.2.6)** due to insufficient drying of the product. Spectral data for triphenylmethanol can be found on SDBS[3] database, under number 5971. The ^{1}H NMR spectra for methyl triphenylmethyl ether can be found elsewhere on literature[4].

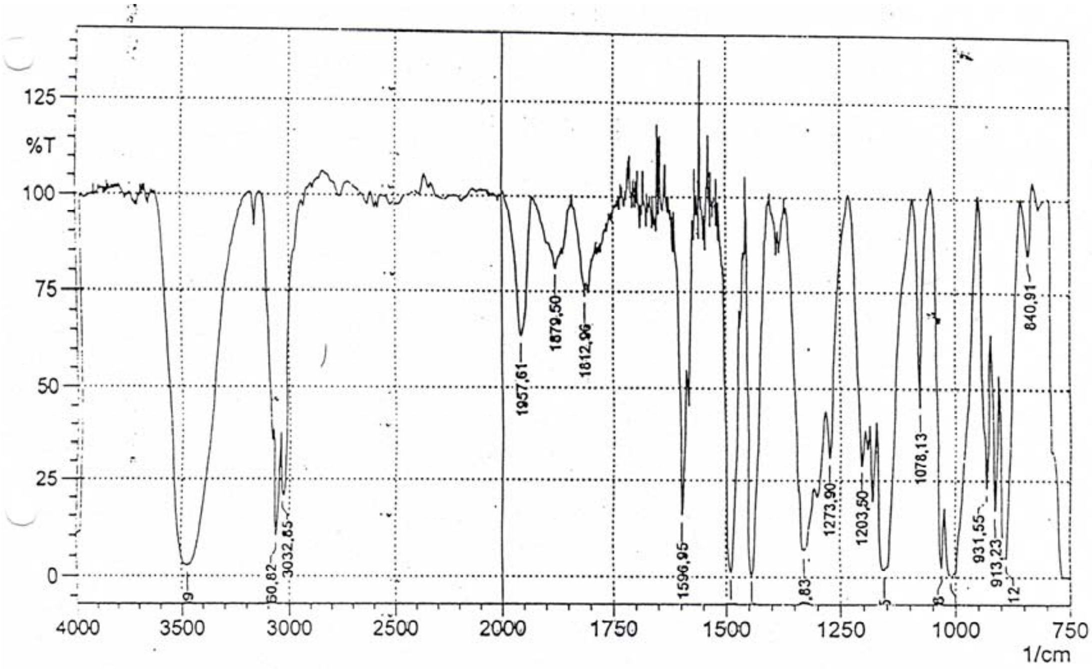


Figure SM 4.2.1.2.5: IR (KBr) of triphenylmethanol

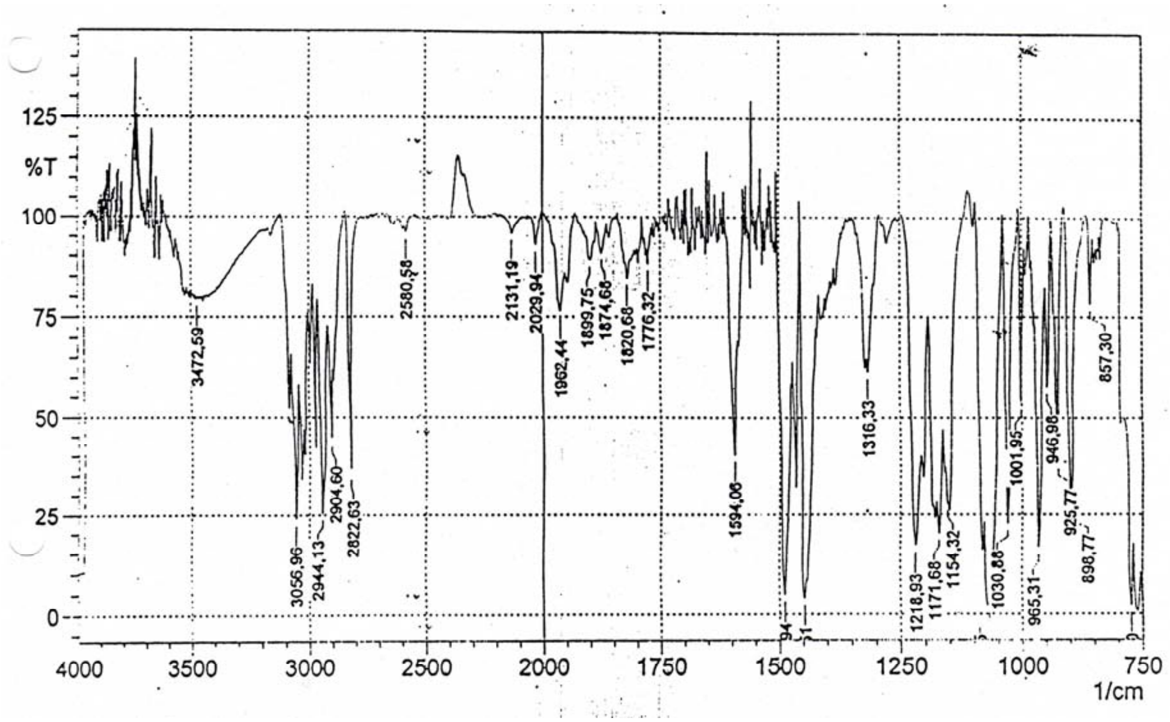


Figure SM 4.2.1.2.6: IR (KBr) of methyl triphenylmethyl ether

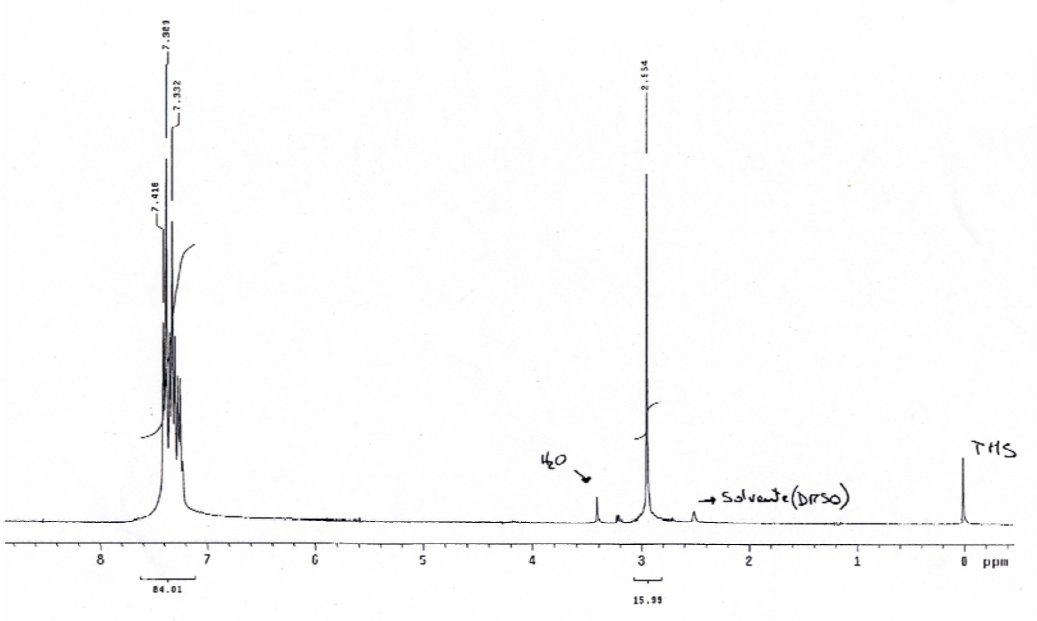


Figure SM 4.2.1.2.7: ^{1}H NMR (DMSO-d_6) of methyl triphenylmethyl ether[5]

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[1] *Handbook of Chemistry and Physics*, CRC Press,1st Student Ed., C-534
[2] http://www.sigmaaldrich.com/catalog/product/aldrich/69493?lang=pt&region=PT, accessed in May 2015
[3] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_search.cgi, accessed in May 2015.
[4] L. F. Fieser, K. L. Williamson, *Organic Experiments*, Houghton Mifflin Company, 8th Ed., 1998, 324.

Grignard-like reaction in water

Supplementary Material

Experiment notes:

This chemical transformation has been proven to be quite reproducible. The reaction is usually complete after 10 to 45 minutes (TLC, eluent CH_2Cl_2). For the students, it is interesting to see the reaction progression after allyl bromide addition as it changes appearance (Figure SM 4.2.1.3.4). The yields obtained by the students (15 groups of 2 students) for three consecutive semesters were always close to 85%. For the cases with inefficient stirring the transformation may not be complete. The reaction must be followed by TLC to assure complete consumption of benzaldehyde. Note to the Instructor: In some cases, the product may not be detected under UV light, but is revealed nicely in phosphomolybdic acid stain. Consider using both methods of detection (Figure SM 4.2.1.3.5). In Figures SM 4.2.1.3.1, SM 4.2.1.3.2 and SM 4.2.1.3.3 is provided the ^{1}H MMR spectrum of used benzaldehyde, allyl bromide and obtained product, respectively.

Environmental-factor (E-factor):

The E-factor is a green chemistry concept that measures the amount of waste produced in a chemical process, considering everything but the desired product and any water used in the process as waste (reagents, solvents, inorganic salts, etc.). The E-factor is calculated according to the formula:

$$E\text{-}factor = \frac{Waste(Kg)}{Product(Kg)} \quad \text{(Equation SM 4.2.1.3.1)}$$

Naturally, a higher E-factor means a greater negative environmental impact associated with the process, and should be kept as low as possible.[1]

The E-factor associated with this chemical process is approximately 20.8.

Atomic efficiency:

The atomic efficiency is another green chemistry concept useful to rapidly evaluate the waste that will be produced by a chemical process. It is calculated by dividing the molecular weight of the product by the sum of the molecular weights of all substances formed in the reaction.[1]

The chemical equation of this reaction is as follows:

$$\mathrm{CH_2CHCH_2Br + C_6H_5CHO + Zn + H^+ \rightarrow C_6H_5CHOHCH_2CHCH_2 + ZnBr^+}$$

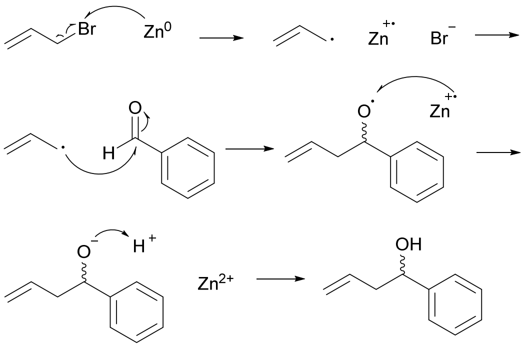
(Equation SM 4.2.1.3.2)

Following this chemical equation, the reaction has an atomic efficiency of 50.5%.

Mechanism:

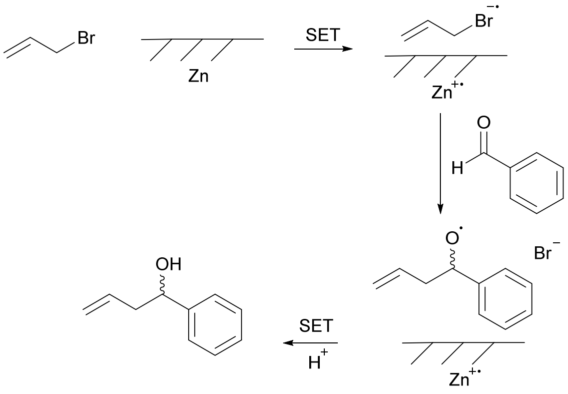
Unlike typical Grignard reactions, the mechanism for the Barbier reaction is not well known. There is disagreement in the literature regarding this topic and three major mechanisms have been proposed.[2]

Luche *et al.*[3] suggest that a radical pair process is involved in the reaction and that a radical derived from the halide attacks the carbonyl group (Scheme SM 4.2.1.3.1).



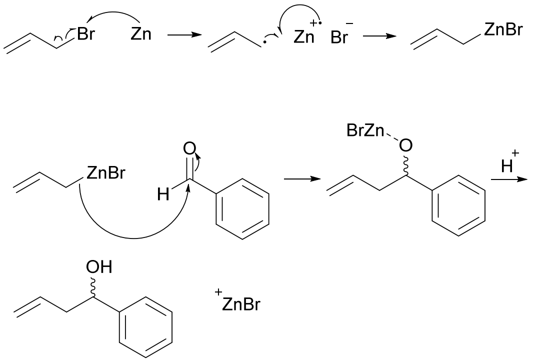
Scheme SM 4.2.1.3.1: Barbier reaction mechanism proposed by Luche *et al.*[3]

A second mechanism, proposed by Chan and Li,[4] involves a radical anion that is coordinated on the metal surface, followed by a single electron transfer (SET) process (Scheme SM 4.2.1.3.2).



Scheme SM 4.2.1.3.2: Barbier reaction mechanism proposed by Chan and Li.[4]

A mechanism similar to the Grignard reaction is also possible, where an organometallic intermediate is initially formed (Scheme SM 4.2.1.3.3).[2]



Scheme SM 4.2.1.3.3: Barbier reaction mechanism involving an organometallic intermediate.[2]

[1] R. A. Sheldon, *Chem. Ind. (London)*, 1992, **23**, 903.

[2] C. J. Li, *Tetrahedron*, 1996. **52**, 5643.

[3] C. Pettier and J. L. Luche, *J. Org. Chem*. 1985, **50**, 910.

[4] C. J. Li and T. H. Chan, *Organometallics*, 1991, **10**, 2548.

^{1}H NMR spectra:

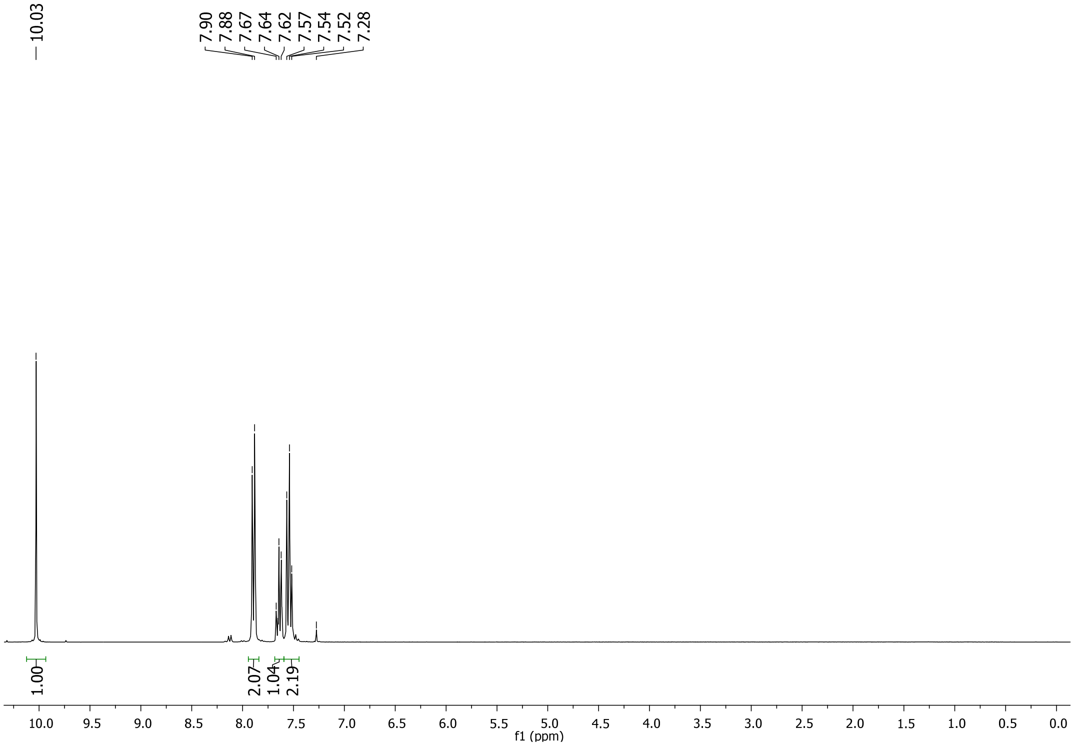


Figure SM 4.2.1.3.1: ^{1}H NMR spectrum ($CDCl_3$) of benzaldehyde.

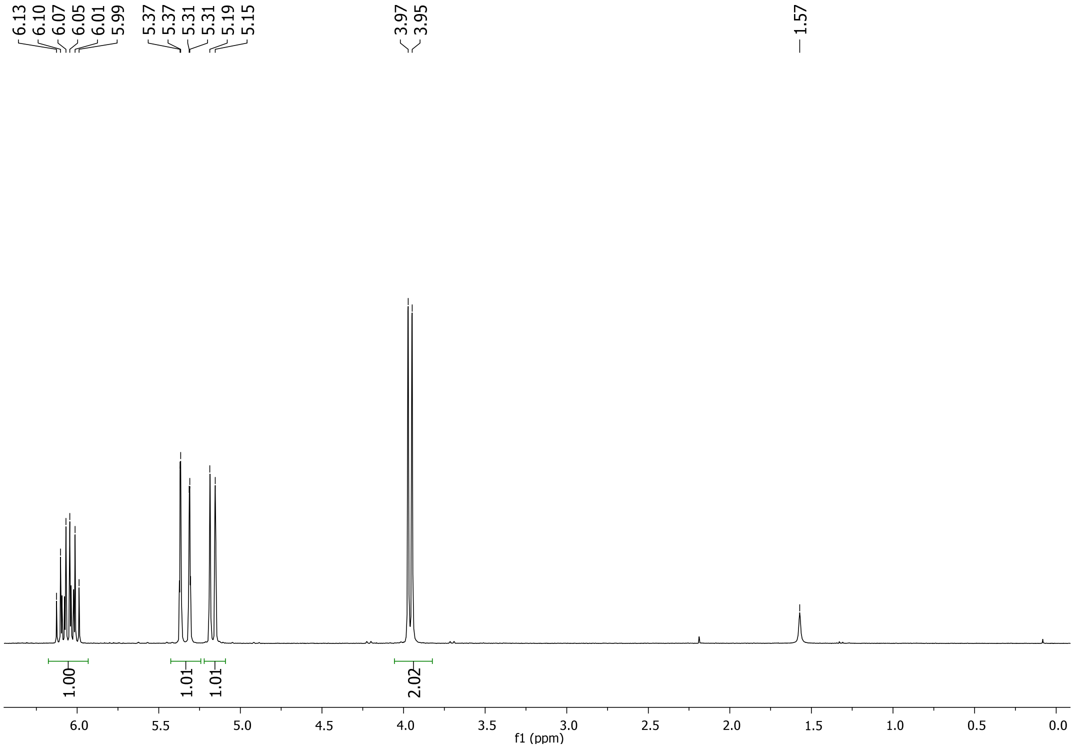


Figure SM 4.2.1.3.2: ^{1}H NMR spectrum ($CDCl_3$) of allyl bromide.

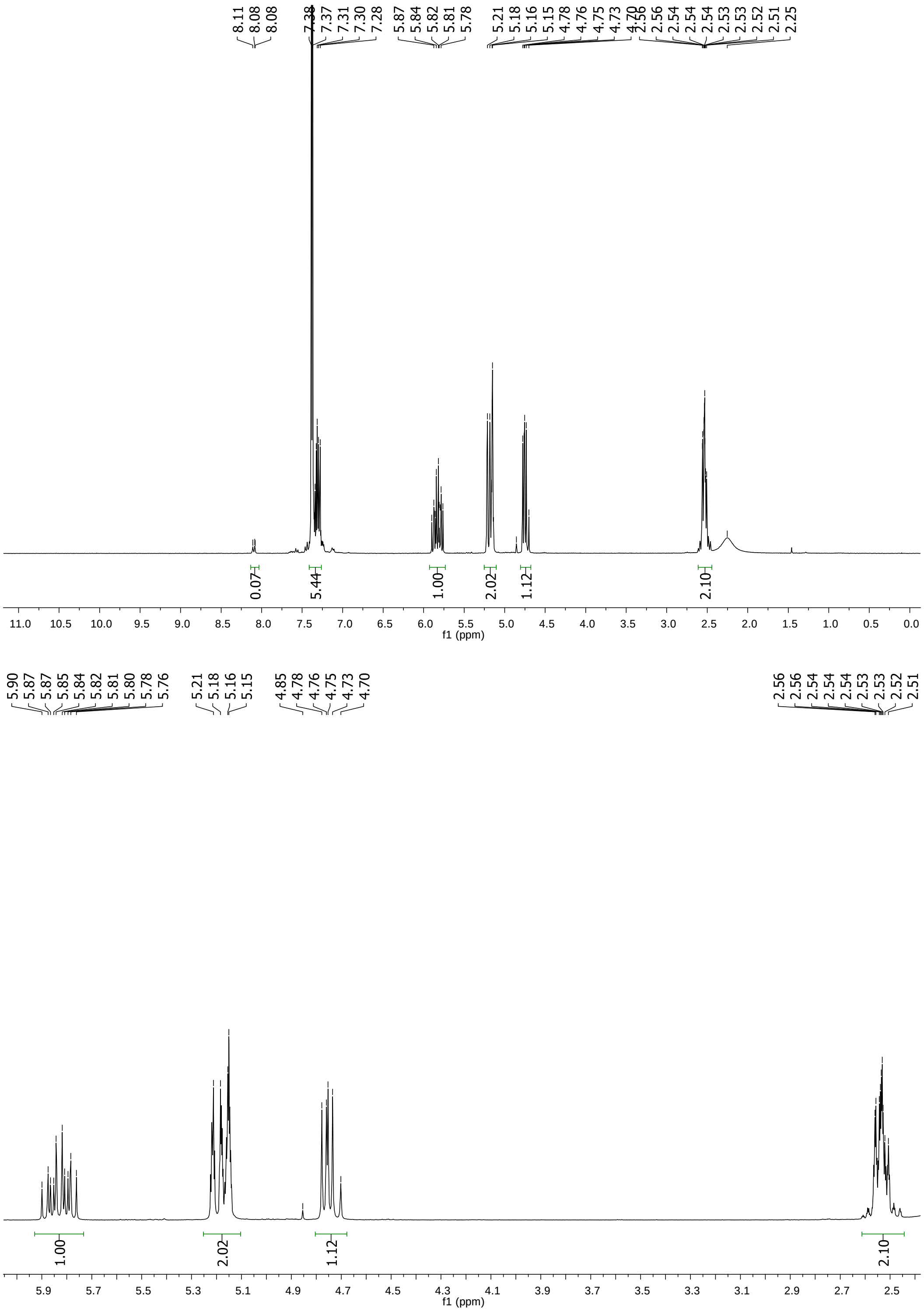


Figure SM 4.2.1.3.3: ^{1}H NMR spectrum ($CDCl_3$) of the obtained product.

Experiment figures:

Figure SM 4.2.1.3.4: Reaction apparatus before addition of allyl bromide (left, grey appearance) and 10 minutes after addition of allyl bromide (right, white appearance).

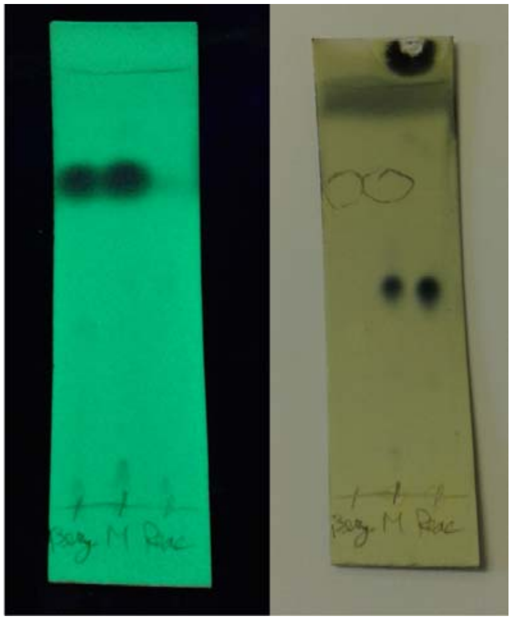


Figure SM 4.2.1.3.5: TLC of the reaction (CH_2Cl_2 as eluent), with complete conversion of benzaldehyde, revealed in the UV chamber (left) and stained with phosphomolybdic acid (right). Legend: Benz: benzaldehyde; M: mixture, Reac: reaction.

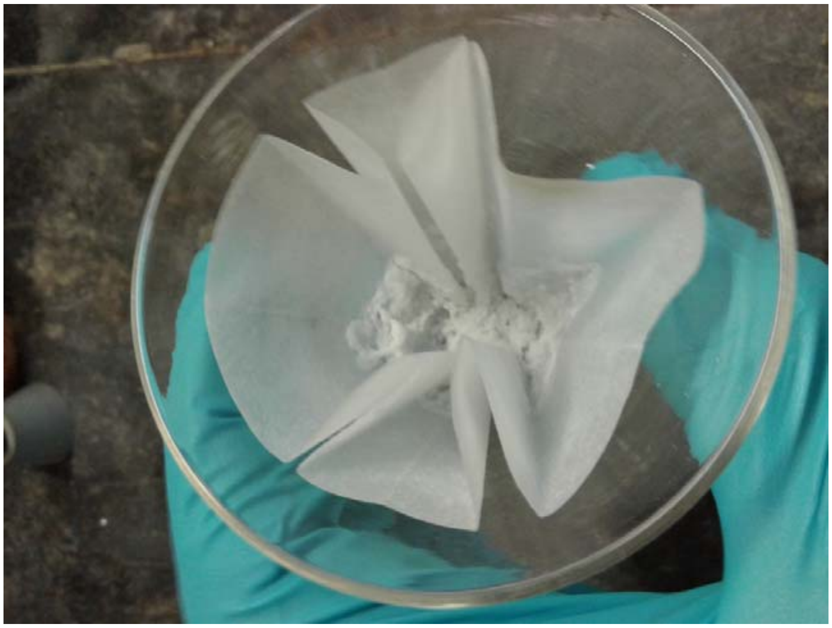


Figure SM 4.2.1.3.6: White solid discarded after filtration.

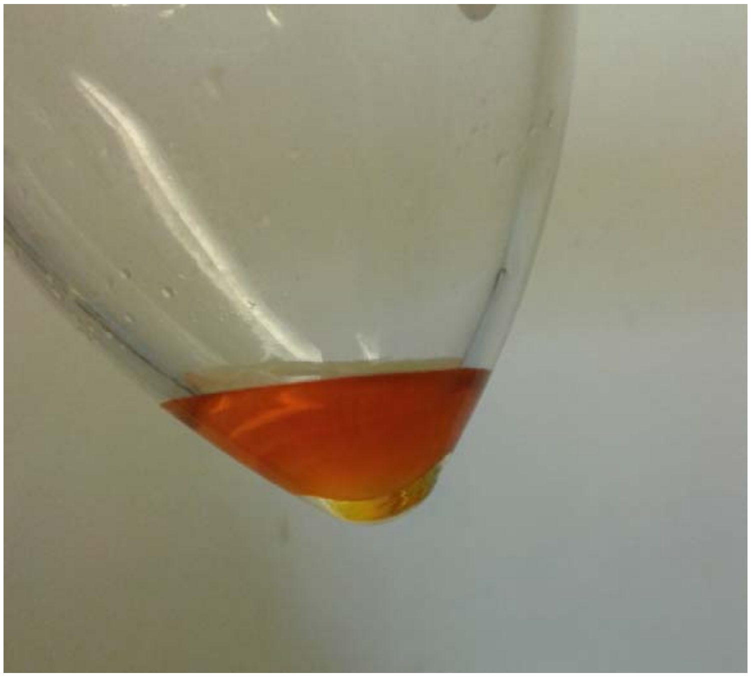


Figure SM 4.2.1.3.7: Final product obtained as an orange liquid.

Cram's Rule – Diastereoselective Grignard addition to 2-phenylpropanal

Supplementary Material

Background

This experiment has run in the second year undergraduate laboratories at Keele University for 20 years and has never failed. Students work individually and it is their first introduction into using air sensitive reagents and undertaking reactions under an inert atmosphere. It is also the students first experience of using ^{1}H NMR to distinguish between diastereoisomers and measure stereoselectivity.

As a repeat of a seminal experiment undertaken in the 1950's it gives students a historical context in which to place the science and an appreciation of how chemistry evolves. The scaling of the reaction also gives an insight into how much synthetic organic chemistry has changed in the laboratory during the intervening 60+ years.

At Keele this experiment coincides with students learning about stereocontrol including stereoselective nucleophilic additions and aldol reactions and this topic is further developed later in the course when asymmetric synthesis is considered. The Felkin-Anh model of predicting diastereoselectvity is commonly covered in undergraduate textbooks and therefore it is not necessary for students to go back to primary literature to gain an understanding of these concepts.

Experimental Procedure

For students who have not previously undertaken experiments under an inert atmosphere and using syringes then instruction must be given on how to do this. If anhydrous diethyl ether is available then this should be used, however as a cheaper alternative we have found that fresh diethyl ether from a bottle opened on the day of the laboratory is perfectly adequate. Students should note in their observations that upon addition of the phenylmagnesium bromide a white precipitate appears, which is the alkoxide salt which then dissolves upon quenching with the ammonium chloride. Extraction, drying and evaporation is straight forward. At Keele we operate an open access to the 300 MHz NMR instrument and students use ACD NMR to process the data and generate the spectra and expansions.

Prelab

At Keele students are required to complete the following prelab before the laboratory session in addition to completing appropriate COSHH forms.

Scaling a reaction: It is not uncommon if you are repeating a published reaction that you need to scale the quantities of the reagents. In Crams' original paper, an extract of which is shown below, they made the Grignard reagent instead of using a prepared reagent out of the bottle. Study the extract of the paper which is below in italics. Work out the number of equivalents for the two reagents and then calculate the volume of 3 M phenylmagnesium bromide solution required for your reaction in which only 0.54 g of 2-phenylpropanal will be used.

The Preparation of 1,2-diphenyl-1-propanol from 2-phenylpropionaldehyde and the separation of diastereomers in this system: To a Grignard reagent prepared from 60.8 g of magnesium, 391 g of bromobenzene and 1500 mL of dry ether was added 268 g of 2-phenylpropionaldehyde. The reaction mixture was worked up in the usual way to give 394 g (94% yield) of a colorless oil, b.p. 139–143 °C. This mixture could not be induced to crystallise.

Analysis of Data

Prediction of the ^{1}H NMR

The approach we recommend to the students to analyse the ^{1}H NMR spectrum of the mixture is to first get them to predict what they expect to see. We suggest the students do this while the reaction is stirring so that they can discuss their predictions with a demonstrator.

Initially we suggest that the students predict the ^{1}H NMR of one of the diastereoisomers. Students are always keen on predicting the aromatic signals around 7 ppm and a broad OH peak even though these are unlikely to be very distinctive for either diastereoisomer. More importantly they need to predict the two doublets, one for the methyl group expected around 1 ppm and the other for the C$\underline{H}$OH which they will estimate to be around 4 ppm. The C$\underline{H}$ adjacent to the methyl and phenyl is more difficult to pin down with regards to its coupling it could appear as a quintet or a doublet of quartets and the shift is not as clear cut probably 2-3 ppm. Students then need to understand that each diastereoisomer will produce its own set of signals and therefore these predicted signals will double up with one set of signals being larger than the other.

Analysis of the ^{1}H NMR spectrum

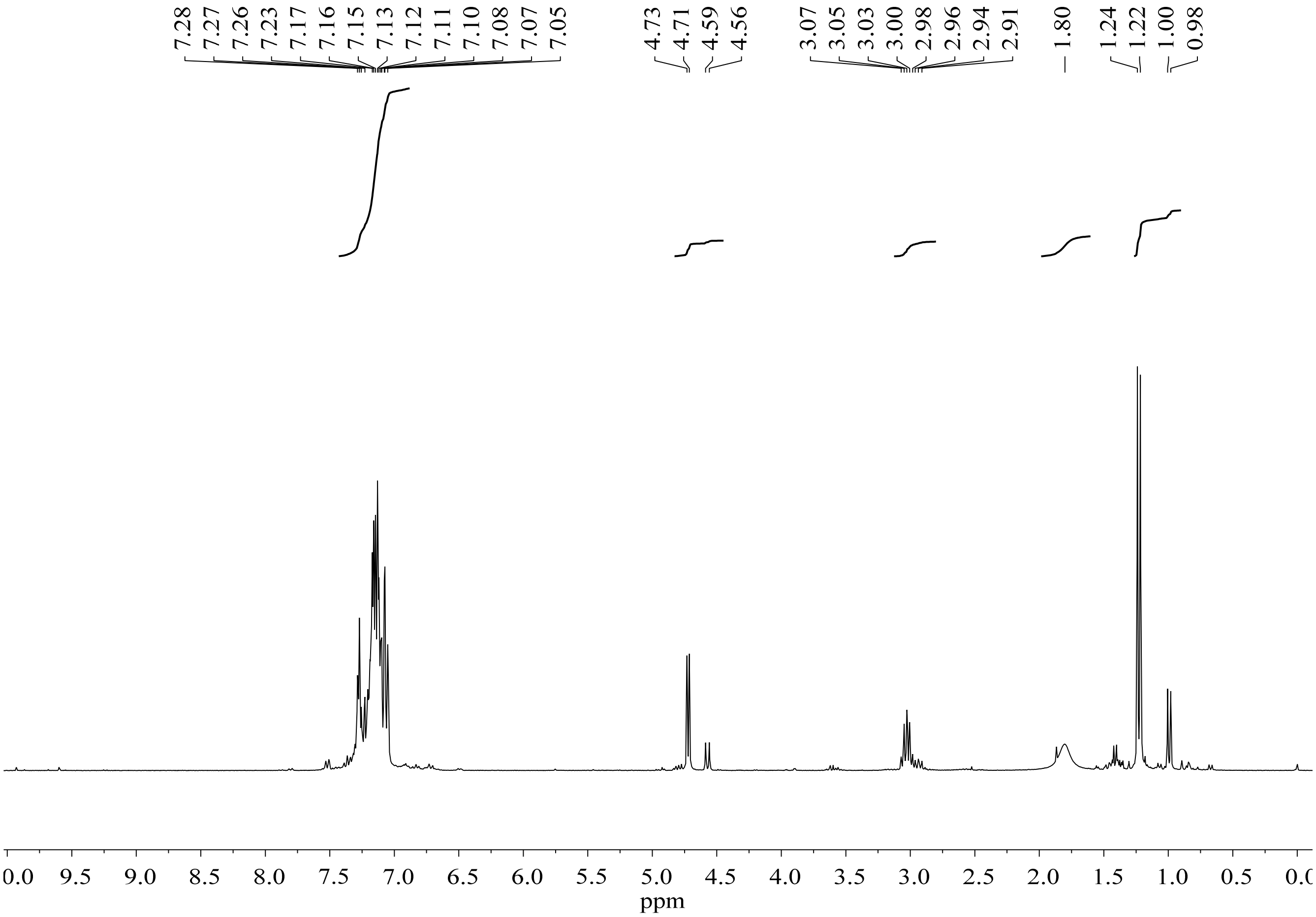


Figure SM 4.2.1.4.1 0-10 ppm ^{1}H NMR with integrations and peak pickings in ppm

Interrogation of the ^{1}H NMR spectrum shows a predictably complex aromatic region (Figure SM 4.2.1.4.1). At 4.72 ppm and 4.57 ppm two clear doublets can be seen, the former larger in intensity than the latter. These are the signals for the two C<u>H</u>OH hydrogens (Figure SM 4.2.1.4.2). At 1.23 and 0.99 ppm the two doublets can be seen for the methyl groups, the larger one of which integrates for three hydrogens in comparison to the major C<u>H</u>OH signal at 4.72 ppm. More complex are the signals for the C<u>H</u>(CH_3)Ph- hydrogens that appear around 3 ppm. The major diastereoisomer is a reasonable quintet however the minor diastereoisomer is less distinct and slightly obscured by the major diastereoisomer.

We expect our students to process the ^{1}H NMR using ACD NMR software and to produce a 0-10 spectrum with integrations and ppm peak pickings (Figure SM 4.2.1.4.1) and expansions (Figure SM 4.2.1.4.2) with Hz peak pickings so that coupling constants can be calculated and a separate set of expansions with integrations so that the ratio of the diastereoisomers can be calculated. We also expect our students to tabulate and analyse this data and to write it out in journal format.

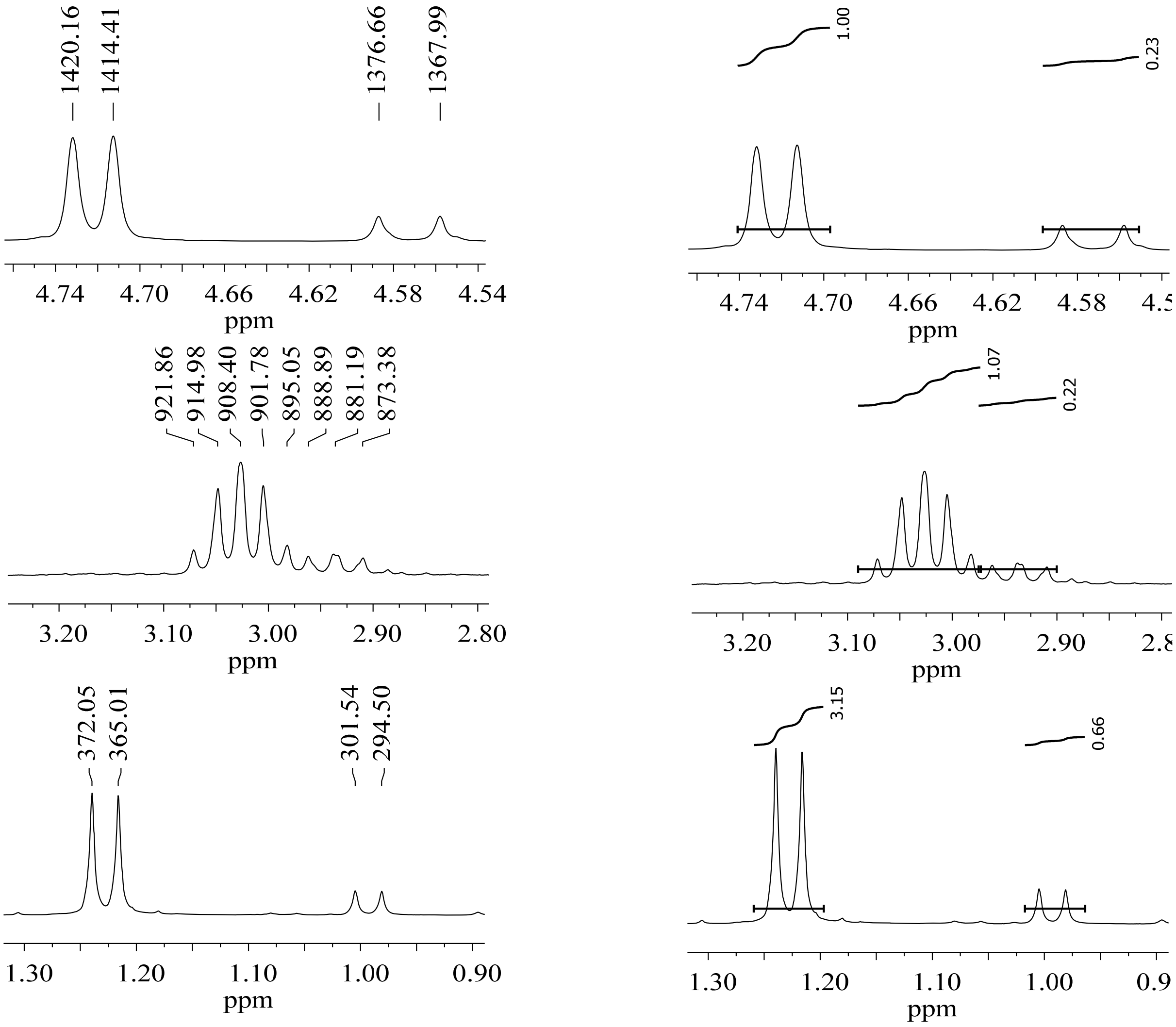


Figure SM 4.2.1.4.2 Expansions of the three important signals with peak pickings in Hz and integrations

Calculation of the diastereoselecivity of the reaction

The ratio of the diastereoisomers is best calculated from the integration of the C<u>H</u>OH doublets at 4.72 ppm (1.00) and 4.57 ppm (0.23) and calculates to a diastereomeric excess of 62% or a diastereoselectivity of 81%. By comparison of the coupling constants for the same doublets the structure of the diastereoisomers can be assigned which is in agreement with the predicted major and minor diastereoisomers from the Felkin-Anh Model, Figure SM 4.2.1.4.3.

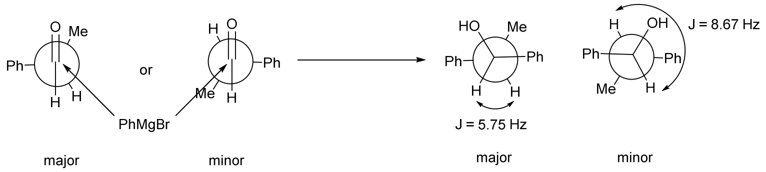


Figure SM 4.2.1.4.3 Major and Minor diastereoisomers as predicted by Felkin-Anh Model and by assignment using ^{1}H NMR coupling constants.

Preparation of (4R,5R)-4,5-Bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane ((-)-TADDOL)

Supplementary Material

The purpose of this experiment is to introduce an undergraduate student to a classical procedure for the preparation of simple Grignard reagents. Furthermore, the organomagnesium generated will be employed to build an enantiopure chiral molecule of remarkable importance in asymmetric synthesis, (-)-TADDOL.[1]

The experiment is devised to take 5h, organized in the following manner: 2h30 for the preparation of phenylmagnesium bromide and 2h30 for its addition to diethyl 2,3-O-isopropylidene-L-tartrate prepared in the previous experimental class (*cf.* expt 149). The preparation of the Grignard reagent usually takes about 1h30. An additional period of 1h is given in order to prepare the reaction set-up. The phenylmagnesium bromide addition to diethyl 2,3-O-isopropylidene-L-tartrate is sometimes reported in the literature to proceed under the reflux of THF for 1h30.[2] This heating is not necessary and the reaction proceeds well at room temperature (~23^{o}C) for the same reaction period, 1h30. An additional period of 1h is considered in the overall time of the experiment in order to allow the student to prepare the reaction set-up, perform the work-up procedure and to concentrate the solution under vacuum. If necessary, the prepared solution of PhMgBr in THF can be stored in a fridge (-4°C) under an inert gas atmosphere (Ar or N_2) for 1-2 weeks, without any significant loss of activity. For this purpose, the use of a schlenk flask is advised.

Stored Mg turnings typically become dark grey over time due to its oxidation under air, thus giving origin to MgO on its surface (Figure SM 4.2.1.5.1). In order to clean the surface of the Mg, the following procedure is employed: 1g of Mg is washed three times with portions of 3 mL HCl 3M, three times with portions of 3 mL of water, three times with portions of 3 mL of acetone. The resulting shining silver-colored Mg turnings (~550mg) are then dried under high vacuum for three hours (Figure

SM 4.2.1.5.2). This procedure can be carried out by an assistant, before the envisioned experimental class. In this case, a greater amount of starting Mg should be employed, thus aiming at having enough clean Mg to the whole group of students; or this acidic treatment can be carried out by the students individually during the previous class, when they are preparing diethyl 2,3-O-isopropylidene-L-tartrate (*cf.* expt 149).

When preparing the organomagnesium compound, it is customary to slowly add the solution of alkyl halide into the refluxing THF that contains the magnesium turnings (Figure SM 4.2.1.5.3). This avoids any chances of a violent reaction (and also minimizes Wurtz-*type* couplings[3]). In our case, by following the experimental procedure described in the main text, we never observed anything similar to this scenario. Furthermore, no product of a Wurtz-*type* reaction is observed during the preparation of phenylmagnesium bromide (Figure SM 4.2.1.5.4 - 4.2.1.5.7).

Although Grignard reagents do react with oxygen,[4] the reaction can be quickly opened to air, if necessary (for instance, when collecting a sample for TLC), with no serious prejudices to the final outcome. However, this should be performed at room temperature. At low temperatures, water can condense inside the flask. Water is a much more serious problem. All glassware should be cleaned and allowed to dry in an oven (~120 ^{o}C) overnight one day before the experiment. This normally secures that the glassware will be appropriately dry. Yet, if desired, one can still further dry the flasks with a heat gun under vacuum. Only dry THF must be employed (typically obtained either from a distillation over sodium/ benzophenone, or from a solvent purification system, SPS).

The phenylmagnesium bromide can be transferred to a solution of diethyl 2,3-O-isopropylidene-L-tartrate either *via cannula* or using a syringe, as indicated in our reaction protocol (Figure SM 4.2.1.5.8). A TLC analysis of this reaction does not easily distinguish between starting material and the final product (Figure SM 4.2.1.5.9).

The compound obtained, (-)-TADDOL (Figure SM 4.2.1.5.10), can be purified either by washing with hexanes/DCM (Figure SM 4.2.1.5.11) or *via* flash column chromatography (Figure SM 4.2.1.5.12-13). The isolated yields obtained were in the range 37-50% for one washing (Figure SM

4.2.1.5.14) and 61-80% for the flash column chromatography (Figure SM 4.2.1.5.15), as typically obtained by 3rd year undergraduate students. An experienced PhD student obtained 55% for the washing and 90% for the flash column chromatography.

Photo Gallery

Synthesis of PhMgBr:

Figure SM 4.2.1.5.1 Mg turnings before acidic treatment

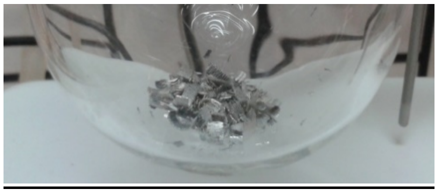


Figure SM 4.2.1.5.2 Mg turnings after acidic treatment

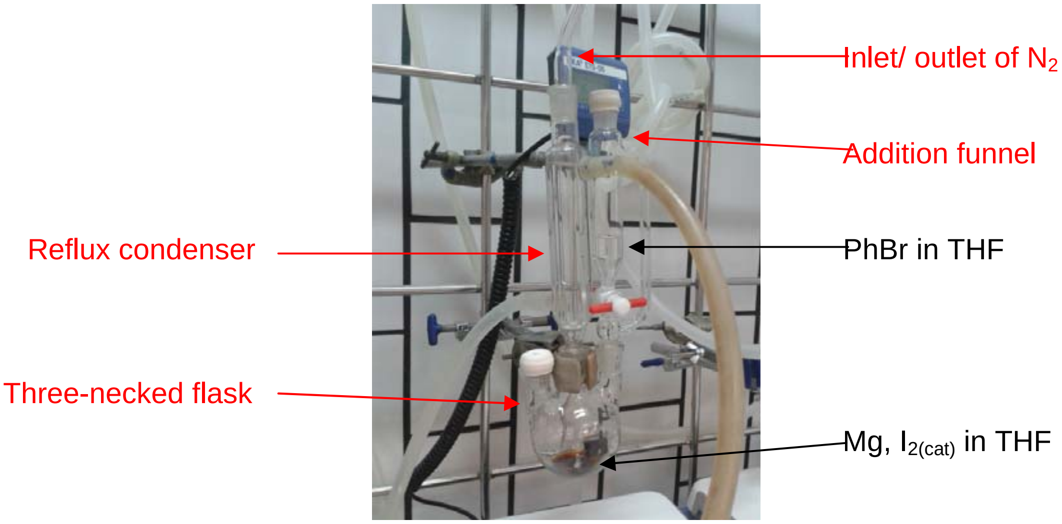


Figure SM 4.2.1.5.3: Reaction set-up for the preparation of PhMgBr, initial scenario before starting the addition of bromobenzene and the reflux of THF.

Zoom on the flask during different moments of the preparation of PhMgBr:

Figure SM 4.2.1.5.4: Mg turnings in the flask

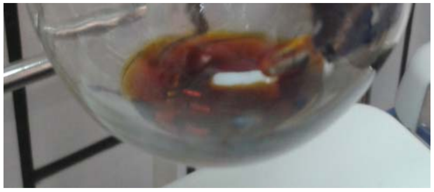


Figure SM 4.2.1.5.5: Solution with Mg, $I_{2(cat)}$ and 1/3 of solution PhBr added, in THF.

Figure SM 4.2.1.5.6: Consumption of I_2, solution becomes transparent (@ 70^{o}C)

Figure SM 4.2.1.5.7: Almost entire consumption of Mg. The PhMgBr produced is ready to be used.

Synthesis of (-)-TADDOL:

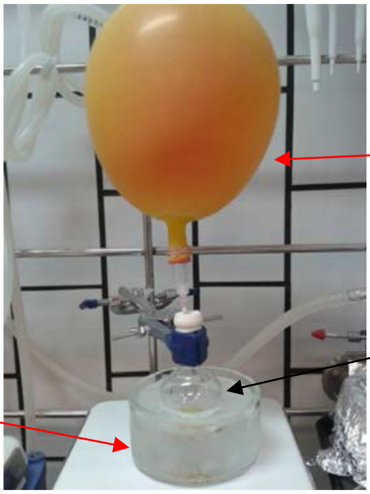
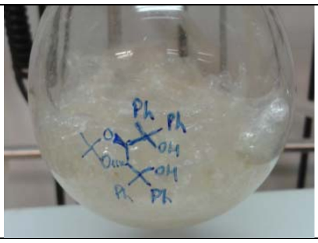


Figure SM 4.2.1.5.8: Reaction set-up for the addition of PhMgBr to diethyl 2,3-isopropylidene-L-tartrate at 0 ^{o}C.

		
Figure SM 4.2.1.5.9 TLC of Grignard addition *Eluent 9/1 hexanes:AcOEt Stain solution 4-anisaldehyde. Left: SM, starting Material; Middle: M, mixture (SM + R); Right: R, reaction* ***SM and product are not easily distinguishable***	Figure SM 4.2.1.5.10: Crude reaction mixture after concentration under vacuum, a white/ pale brown foam is obtained.	Figure SM 4.2.1.5.11 *Purification strategy 1: dissolve (-)-TADDOL* in hexanes(5 mL) /DCM (500 µL), then filtrate, washing with hexanes (duration ~ 30 min)

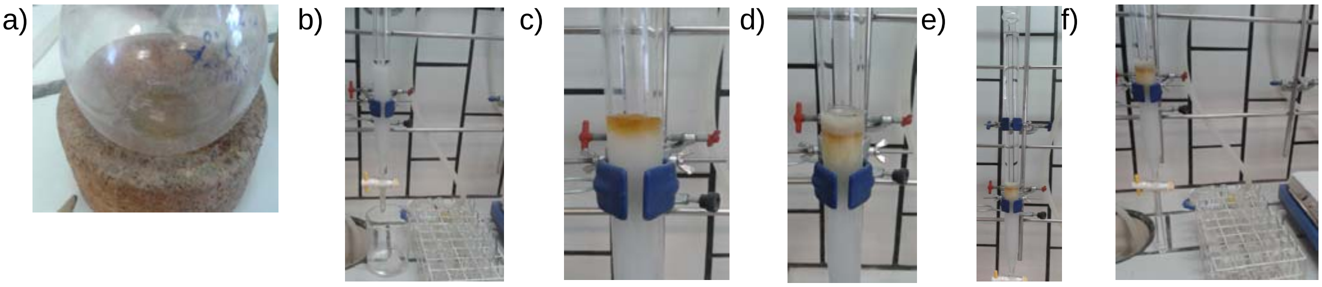


Figure SM 4.2.1.5.12 *Purification strategy 2:* Detailed steps for running this flash column chromatography. a) Dissolve the crude reaction mixture (solid) in a minimum amount of DCM in order to deposit on top of the column chromatography. b) Pack the silica (20 g) dissolved in hexanes in an appropriate glass column. Use compressed air to push it down and remove any air inside the silica. c) Deposit the crude product dissolved in DCM on top of the silica and push it inside with the compressed air. d) Add enough sand to make a small cylinder of height ~0.5 cm. Use hexanes to properly accommodate the sand. e) Fill the column with hexanes (50 mL) and push it down to remove the DCM introduced when depositing the sample. f) Fill again the column with a 95/5 mixture hexanes:AcOEt (50 mL) and push it down using compressed air, while collecting the fractions in test tubes. Then, repeat the process using a 9/1 mixture hexanes:AcOEt (50 mL), followed by 8/2 hexanes:AcOEt (100 mL). Add the selected fractions in a tared round bottomed flask and concentrate under vacuum (duration ~ 2h30min.)

Figure SM 4.2.1.5.13 TLC of the fractions separated during the flash column chromatography. Purified (-)-TADDOL appears in fractions 25-34. Eluent employed for TLC: 9/1 hexanes:AcOEt. Stain solution employed for TLC: 4-anisaldehyde.

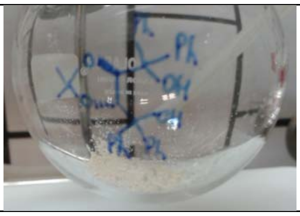
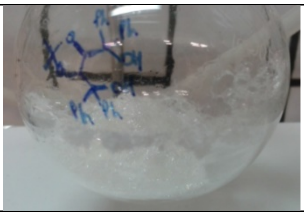
	

Figure SM 4.2.1.5.14: (-)-TADDOL purified by washing with Hexanes/DCM (average ~40% yield).	Figure SM 4.2.1.5.15 (-)-TADDOL purified by flash column chromatography (average ~75% yield)

Elements for answering the proposed questions:

1) What is the mechanism for the formation of an organomagnesium halide starting from R-X and Mg? Describe the main features.

The whole picture is quite complex and there is a debate of possible reaction pathways for the formation of Grignard reagents (RMgX) starting from RX and Mg. Experimental studies demonstrated that the mechanisms implicated by the use of such chemicals, under numerous reaction conditions are actually very similar. Importantly, it is believed that Mg atoms can combine into clusters which may play an important role in the activation of the C-X bond. For all these cases, a radical pathway is believed to be dominant (either *via* paths a or b, Figure SM 4.2.1.5.16), which shall lead to the formation of racemic Grignard reagents. Nevertheless, non-radical pathways are sometimes possible, which presumably lead to retention of configuration (either *via* paths c or d, Figure SM 4.2.1.5.16).[5]

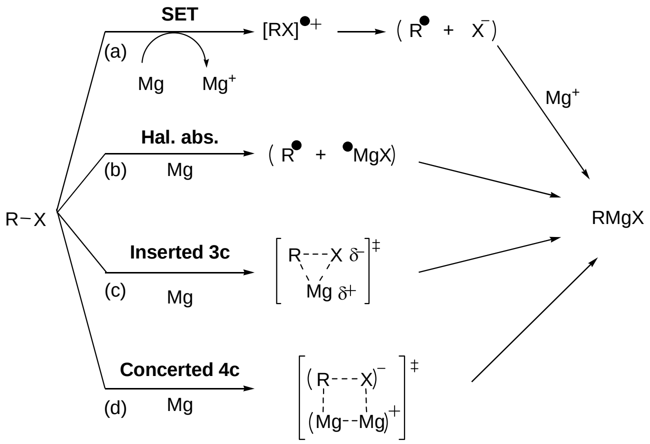


Figure SM 4.2.1.5.16: Most often mechanisms employed to describe the synthesis of Grignard reagents starting from RX and Mg.

2) What is the role of I_2 in the preparation of PhMgBr? Which other chemical(s) can be employed instead?

The use of a catalytic amount of I_2 (sometimes called the Gilman catalyst) can be used to activate the magnesium metal towards the preparation of a number of Grignard reagents. It is believed that I_2 reacts with Mg to form MgI. MgI is more reactive and more soluble than Mg, and is regenerated during the process. Therefore, the MgI generated might act as a catalyst for the formation of the Grignard reagent. A proposal for the mechanism is shown in Figure SM 4.2.1.5.17:

$$\mathrm{I_2} + \mathrm{Mg} \longrightarrow \mathrm{MgI_2}$$

$$\mathrm{Mg} + \mathrm{MgI_2} \longrightarrow 2\ \mathrm{MgI}$$

$$\mathrm{R{-}X} + \mathrm{MgI} \longrightarrow \mathrm{R^{\bullet}} + \mathrm{XMgI}$$

$$\mathrm{XMgI} + \mathrm{Mg} \longrightarrow \mathrm{MgX} + \mathrm{MgI}$$

$$\mathrm{R^{\bullet}} + \mathrm{MgX} \longrightarrow \mathrm{RMgX}$$

Figure SM 4.2.1.5.17: Proposed reaction mechanism involved in the activation of Mg by catalytic I_2.

Other common chemicals which can also be employed as activators are methyl iodide and 1,2-dibromoethane (both acting by entrainment). Other methods of activation include washing the magnesium surface with a mineral acid, metal atom vaporization, the use of ultrasound, among others.[6]

3) What would be the major compound of this reaction if only 2 equiv. of PhMgBr were employed? Explain.

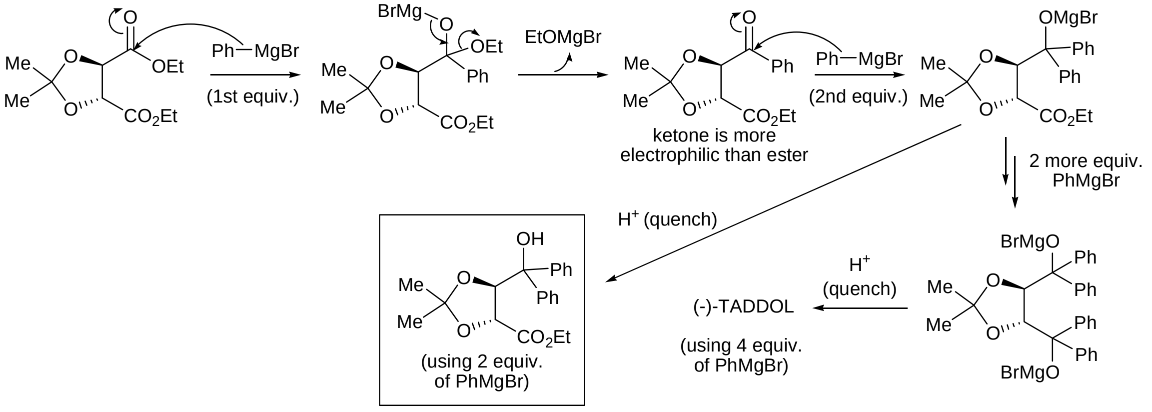


Figure SM 4.2.1.5.18: Reaction mechanism for the addition of either 2 or 4 equiv. of PhMgBr to Diethyl 2,3-O-isopropylidene-L-tartrate .

4) Interpret the ^{1}H and ^{13}C NMR spectra obtained for (-)-TADDOL.

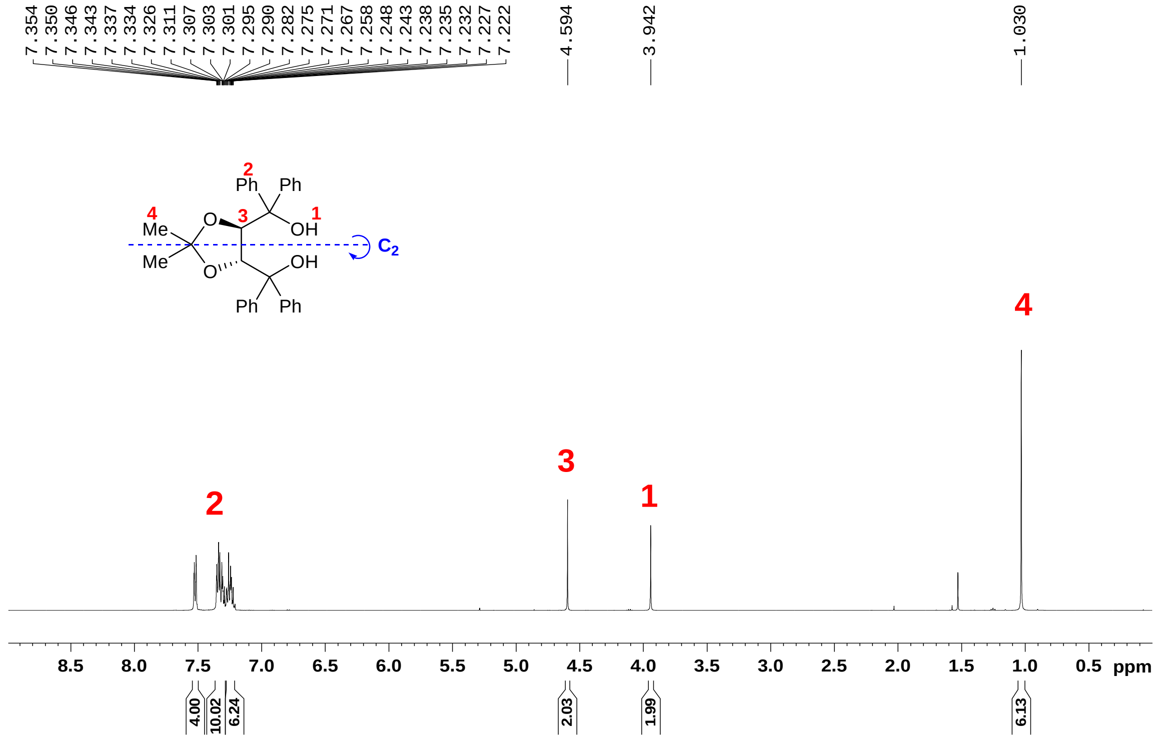


Figure SM 4.2.1.5.19: ^{1}H NMR of the isolated (-)-TADDOL.

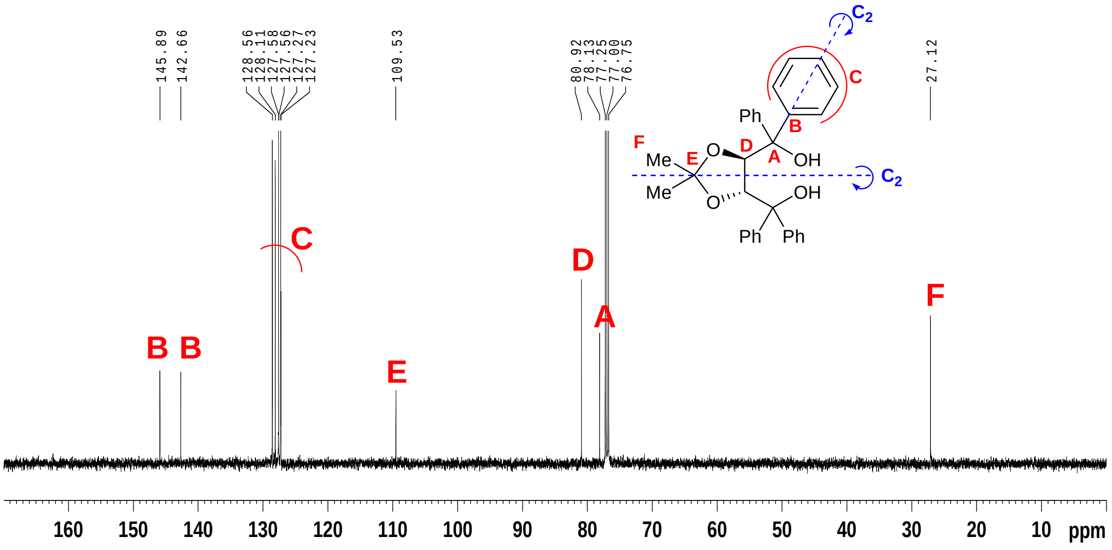


Figure SM 4.2.1.5.20: ^{13}C NMR of the isolated (-)-TADDOL.

5) Compare the melting point and the optical rotation of obtained (-)-TADDOL with the reported values from the literature.

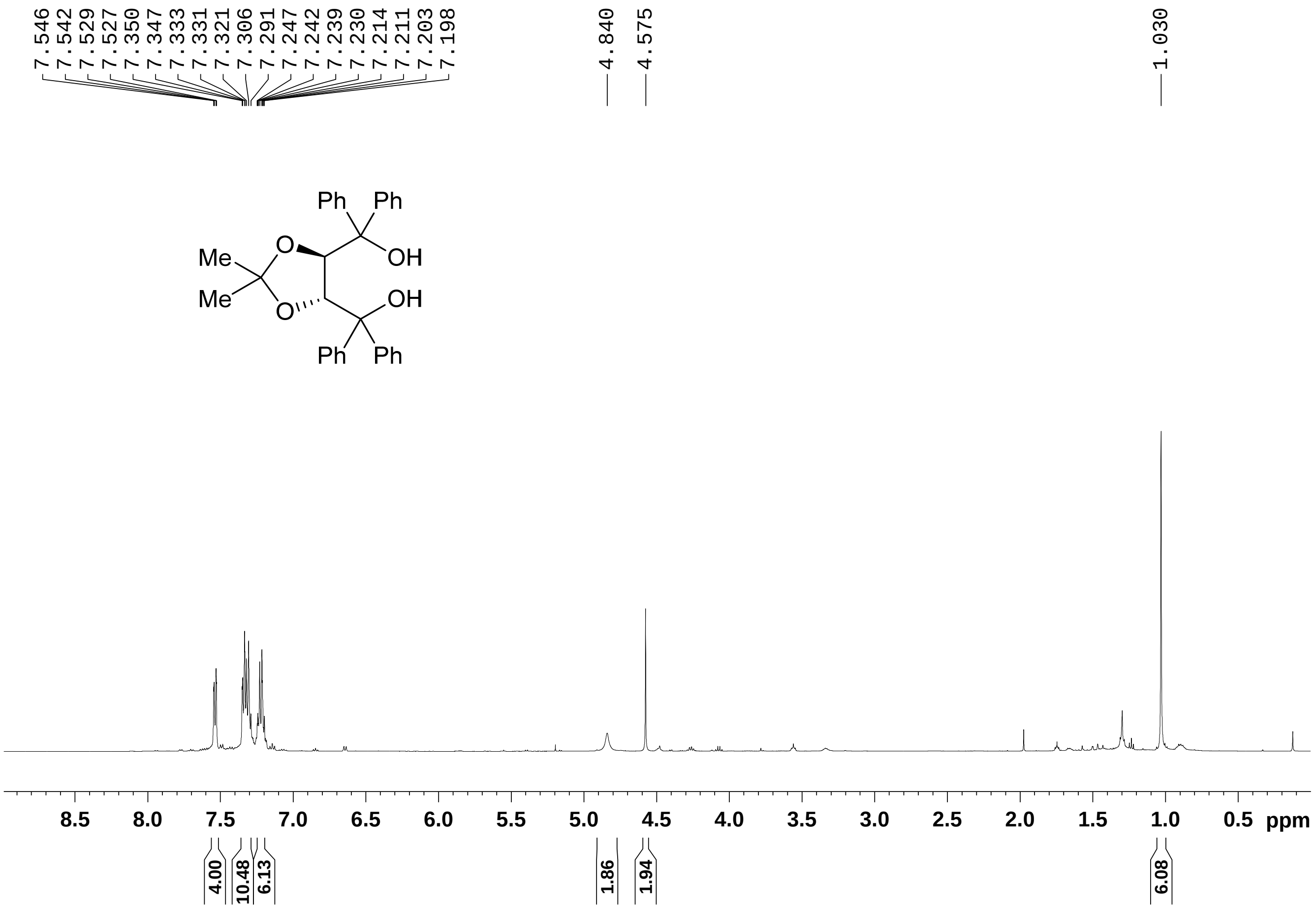
From two different sources, we have:

i) $[\alpha]_D$ = - 65 (c = 1.0, $CHCl_3$), mp = 185 ^{o}C.[7]

ii) $[\alpha]_D$ = - 62.6 (c = 1.0, $CHCl_3$), mp = 193-195 ^{o}C.[8]

NMR spectra:

Crude reaction mixture, ^{1}H NMR (500MHz, $CDCl_3$)



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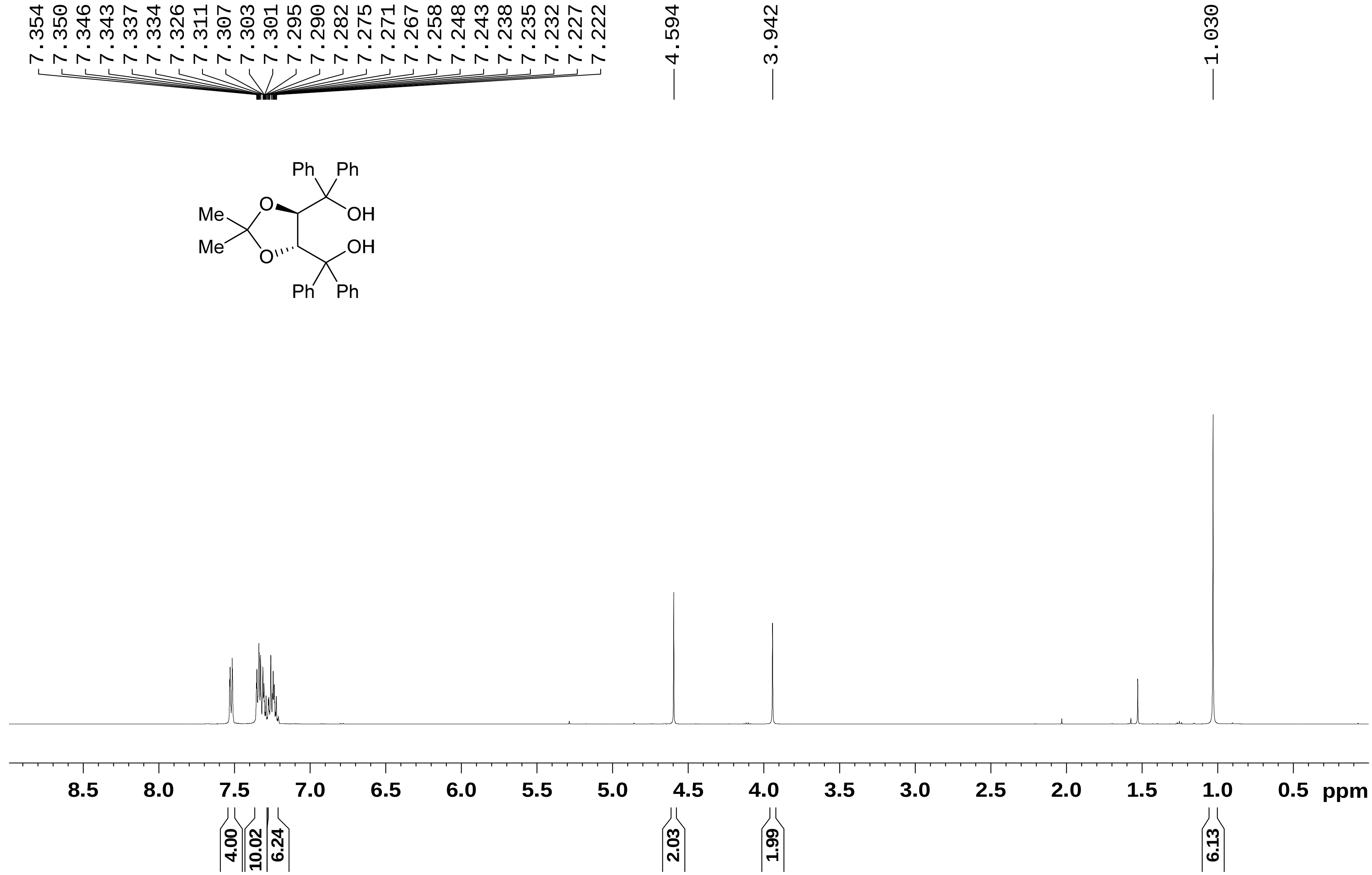
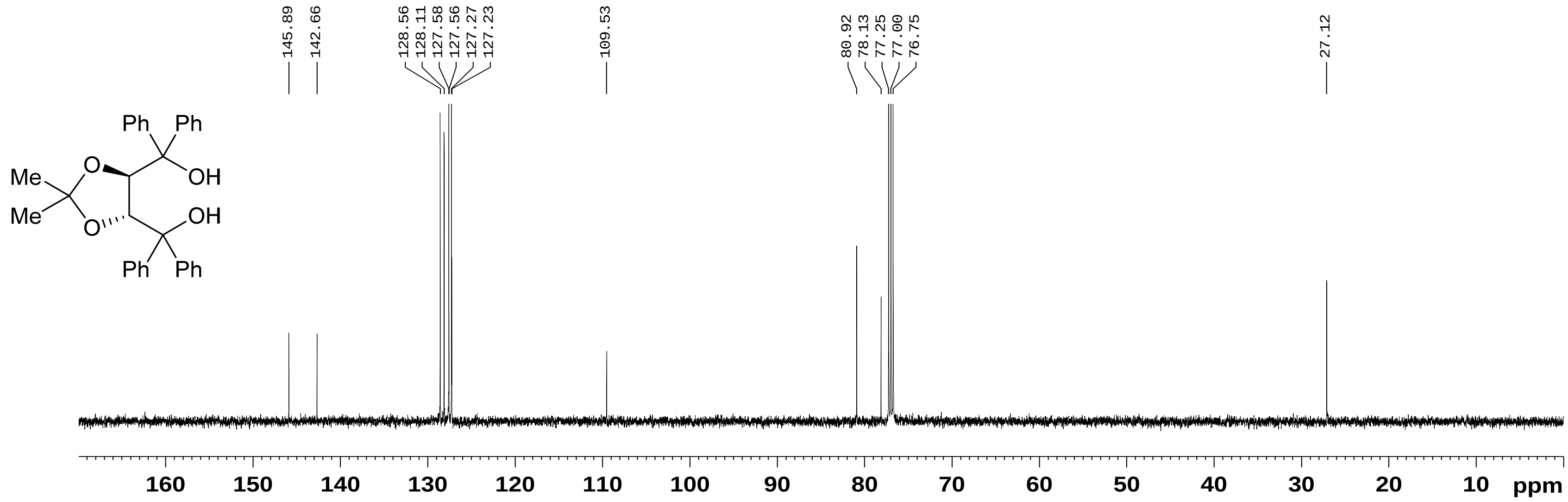
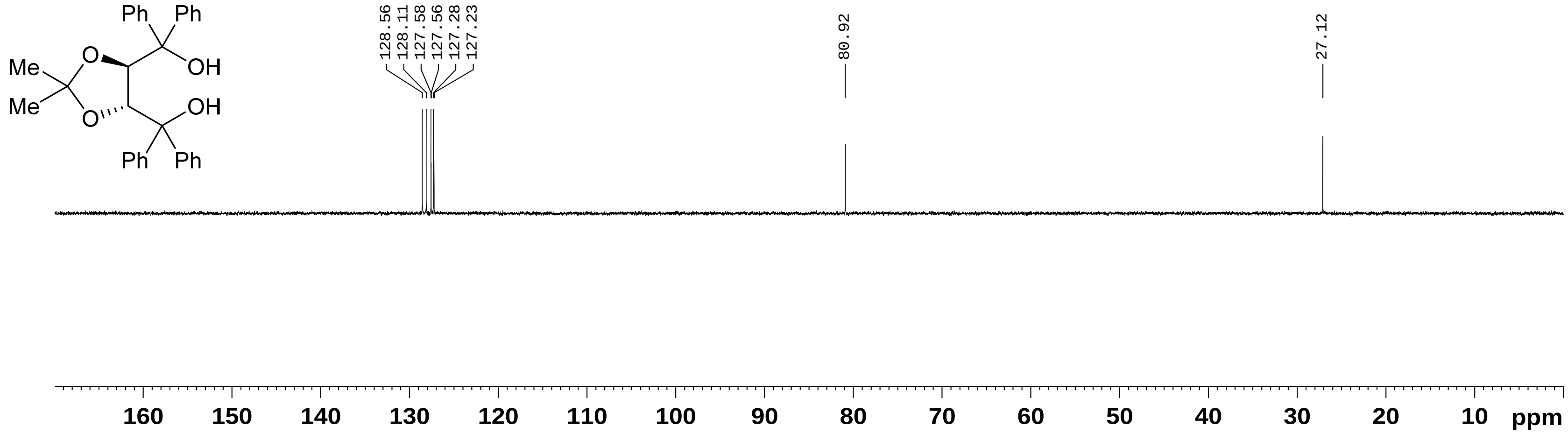
Isolated (-)-TADDOL, ^{1}H NMR (500MHz, $CDCl_3$)



Isolated (-)-TADDOL, ^{13}C NMR NMR (125MHz, CDCl$_3$)



Isolated (-)-TADDOL, DEPT-135 NMR (125MHz, CDCl$_3$)



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[1] D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem. Int. Ed.* 2001, **40**, 92.

[2] See, for instance: a) L. Zhou, B. Wang, H. Mu, H. Zhang, Y. Song, J. Qu, *Org. Lett.* 2013, **15**, 3106. b) H. Du, D. Zhao, K. Ding, *Chem. Eur. J.* 2004, **10**, 5964

[3] a) A. Wurtz, *Ann. Chim. Phys.* 1855, **44**, 275. b) A. Wurtz, *Ann.* 1855, **96**, 364. See also: c) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier, California, 1st ed., 2005, 498-499.

[4] C. Walling, S. A. Buckler, *J. Am. Chem. Soc.* 1955, **77**, 6032.

[5] For a discussion in more details, see: Z.-N. Chen, G. Fu, X. Xu, *Org. Biomol. Chem.* 2012, **10**, 9491 and references therein.

[6] R. D. Rieke, M. S. Sell, *Handbook of Grignard Reagents*. ed. G. S. Silverman, P. E. Rakita, Marcel Dekker, Inc., New York, 1996, Chapter 4, 53-76.

[7] S. Müller, M. C. Afraz, R. de Gelder, G. J. A. Ariaans, B. Kaptein, Q. B. Broxterman, A. Bruggink, *Eur. J. Org. Chem. 2005, **6**, 1082.*

[8] US Sigma-Aldrich catalog: http://www.sigmaaldrich.com/catalog/product/aldrich/265004?lang=en&region=US

Synthesis of (*S*)-diphenyl(pyrrolidin-2-yl)methanol

Supplementary Material

1. Experiment Notes

Students are strongly recommended to follow Laboratory techniques described in specialized literature.[1]

Dry tetrahydrofurane (THF) and super-dry MeOH are prepared following protocols described in literature.[2] All reagents were used as received from Sigma-Aldrich.

This experiment describes the preparation of (*S*)-diphenyl(pyrrolidin-2-yl)methanol **3** following a general protecting group strategy. The synthesis was optimized by laboratory technicians and PhD students and performed by under-graduate students with good and reproducible results. The project was executed employing seven-eight laboratory sessions of 3-5 hours in a project-based laboratory course (10 students).

Laboratory session 1:

Super-dry MeOH is essential to avoid use a large excess of $SOCl_2$, affording higher yields.

MeOH (HPLC grade) might be used instead, although in this case, the ester is obtained with moderate yields.

Laboratory session 2:

Benzyl chloride might be used instead of benzyl bromide to get slightly lower yields. In this step, dry MeOH is essential to get clean, high yielding protection. If MeOH HPLC grade is used instead, a mixture of methyl and benzyl esters are obtained (via basic hydrolysis of methyl ester, see below):

---

[1] L. M. Harwood, C. J. Moody, J. M. Percy, *Experimental Organic Chemistry* Standard and Microscale, Blackwell Science Ltd, Oxford, UK, 2nd Ed., 2006.

[2] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, Ed. Butterworth-Heinemann, Elsevier Inc., Oxford, UK, 7th Ed, 2013.

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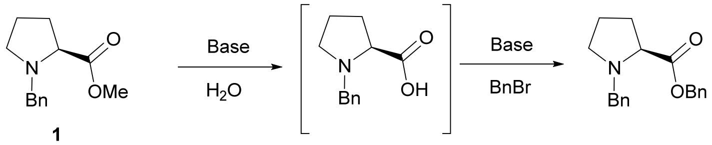


ALTERNATIVE PROCEDURE FOR THE BENZYLATION STEP:

Benzyl bromide (11 mL, 93 mmol) was added to a cooled (0 ˚C) solution of L-proline methyl ester hydrochloride (15 g, 91 mmol) and triethylamine (13 mL, 91 mmol) in dry diethyl ether (500 mL). A second portion of triethylamine (13 mL, 91 mmol) in dry diethyl ether (500 mL) was added. The reaction mixture was slowly warm to room temperature and refluxing under stirring for 2 days. The salts were removed by filtration and washed with diethyl ether (3 x 100 mL). The combined organic layers were washed with a saturated $NaHCO_3$ aqueous solution (150 mL) and subsequently with a saturated ammonium chloride aqueous solution (150 mL). The combined organic layers were dried with magnesium sulfate and concentrated in vacuo.

Laboratory session 4-5: Synthesis of (*S*)-(1-benzylpyrrolidin-2-yl)diphenylmethanol (**2**).

As a heterogeneous reaction mixture is formed, it is very important that vigorous stirring is used along the process. Refluxing the reaction mixture overnight ensures reaction completion.

Alternatively, reaction mixture might be stirred at room temperature (at least for 3 days) before purification.

Laboratory session 6: Synthesis of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**3**).

The hydrogenolysis reaction might be also performed employing a hydrogen bomb reactor (400 psi) in shorter reaction times.

Usually the product **3** does not require additional purification.

^{1}H-NMR is used as analytical technique to determine purity of compounds.

About planning the laboratory sessions:

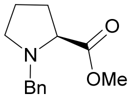
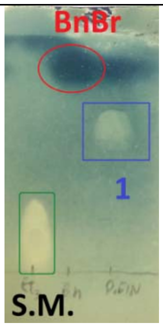
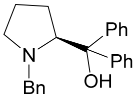
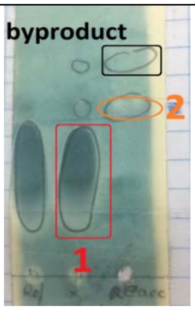
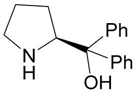
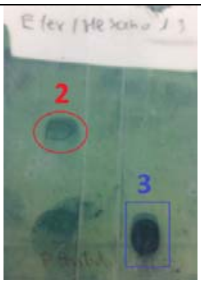
In case there is no possibility of consecutive sessions in the lab, we have proposed a Schedule indicating in which step of the synthesis the sessions can be postponed several days:

- Notes 1-5 should be performed in two consecutive days. The (*S*)-proline methyl ester hydrochloride (light yellow residue) can be stored in freezer until next laboratory session (several days).
- Notes 6-12 should be performed in two consecutive days. Crude compound **1** can be stored in freezer until next laboratory session (several days).

- Notes 13-20 should be performed in two consecutive days. Crude compound **2** can be stored in freezer until next laboratory session (several days). If note 16 is performed at room temperature instead of under reflux, the reaction can be stirred at this temperature for three or four days before note 18.
- Recrystallization of compound **2** (notes 21-22) can be performed in a separate session.
- Notes 23-30 should be performed in two consecutive days. Crude compound **3** can be stored in freezer until next laboratory session (several days).
- Recrystallization of compound **3** (note 31) can be performed in a separate session.

A typical recrystallization would need 50-100 mL of solvent. Product is dissolved on warming and the mixture is allowed to cool to room temperature overnight (or if necessary, two or three days).

Typical yields and R_f values (tlc):

	Yields (%)	R_f	TLC
 **1**	60-87	0.5 (hexane/Et_2O, 2:1)	
 **2**	50-79	0.6 (hexane/Et_2O, 4:1)	
 **3**	70-90	0.1 (hexane/Et_2O, 3:1)	

TLC plates have been visualized employing UV lamp and a phosphomolibdic stain (5g phosphomolibdic acid in 100 mL EtOH 96%).

2.1. Selected pictures of required equipments

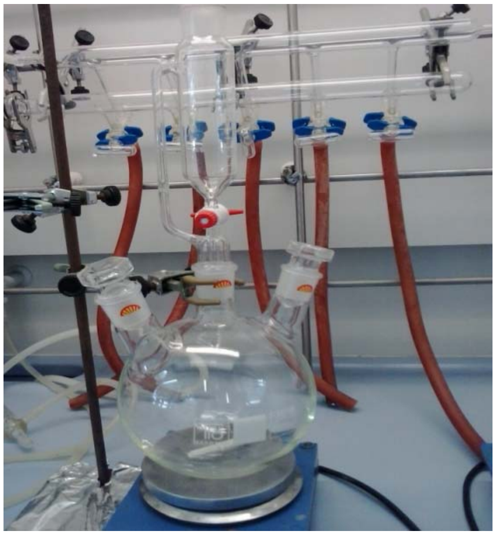


Figure SM 4.2.1.6.1. Three-necked round-bottom flask, equipped with addition funnel with pressure-equalization arm and with a magnetic stir bar.

Figure SM 4.2.1.6.2. Filtration (benzylation step)

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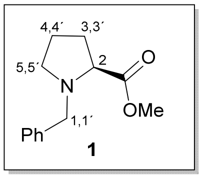
Figure SM 4.2.1.6.3. Round-bottom flask, equipped with a magnetic stir bar and a balloon with H_2 (Hydrogenation step)

2.2. ^{1}H-NMR spectra



1

^{1}H NMR (300 MHz, $CDCl_3$): 7.28-7.12 (m, 5H, Ph), 3.81 (d, J = 12.8 Hz, 1H, H_1), 3.57 (s, 3H, OMe), 3.50 (d, J = 12.8 Hz, 1H, $H_{1'}$), 3.18 (dd, J = 8.8, 6.2 Hz, 1H, H_2), 3.02-2.93 (m, 1H, H_5), 2.32 (dd, J = 17.0, 8.1 Hz, 1H, $H_{5'}$), 2.13-1.97 (m, 1H, H_3), 1.96-1.60 (m, 3H, $H_{3'}$, $H_{4,4'}$).

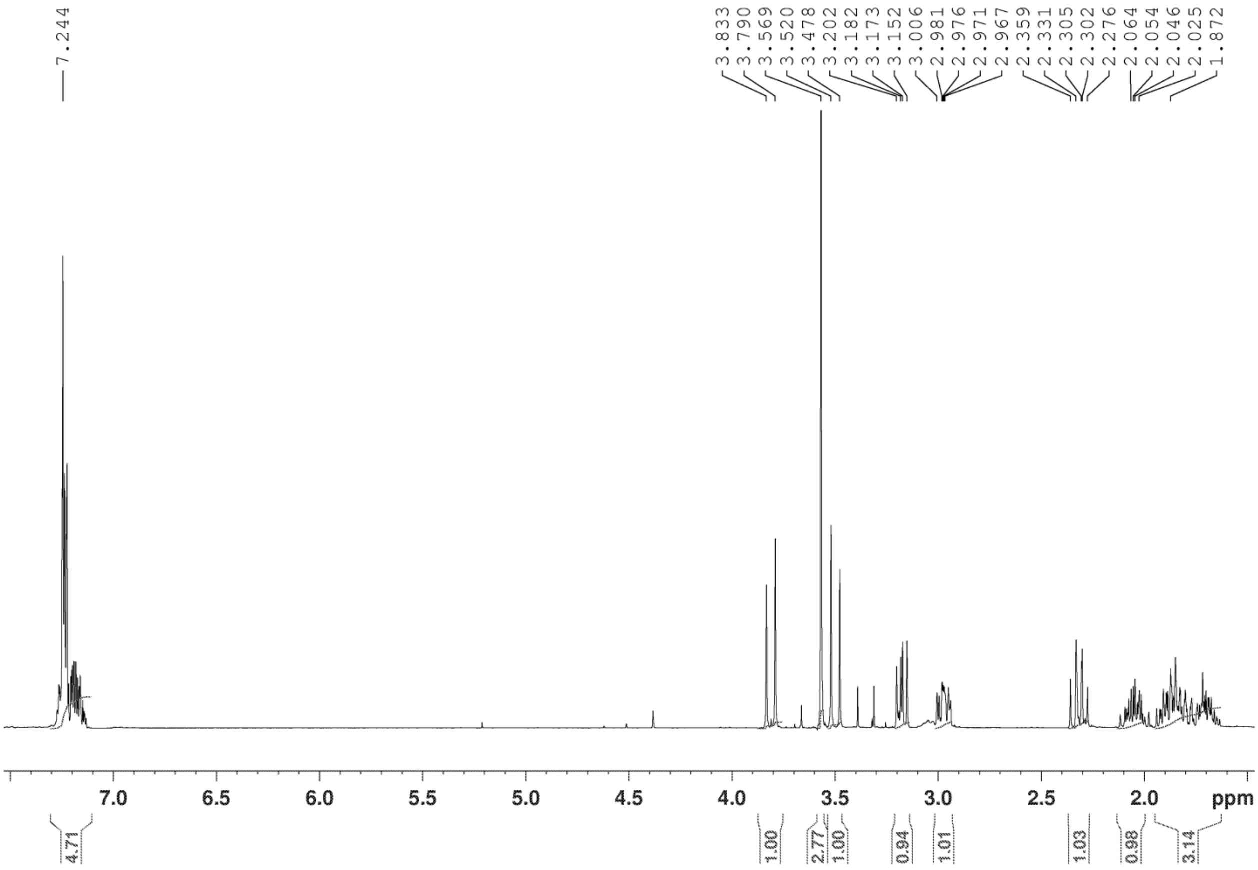
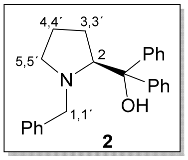


Figure SM 4.2.1.6.4. ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **1**.



2

^{1}H NMR (300 MHz, CDCl$_3$): 7.73 (dd, *J* = 8.5, 1.2 Hz, 2H, Ph), 7.58 (dd, *J* = 8.4, 1.3 Hz, 2H, Ph), 7.39-6.96 (m, 11H, Ph), 4.93 (s, 1H, OH), 3.98 (dd, *J* = 9.4, 4.6 Hz, 1H, H_2), 3.23 (d, *J* = 12.6 Hz, 1H, H_1), 3.03 (d, *J* = 12.6 Hz, 1H, $H_{1'}$), 2.97-2.86 (m, 1H, H_5), 2.36 (dt, *J* = 9.2, 7.8 Hz, 1H, $H_{5'}$), 2.06-1.87 (m, 1H, H_3), 1.83-1.70 (m, 1H, H_4), 1.69-1.57 (m, 2H, $H_{3'}$, $H_{4'}$).

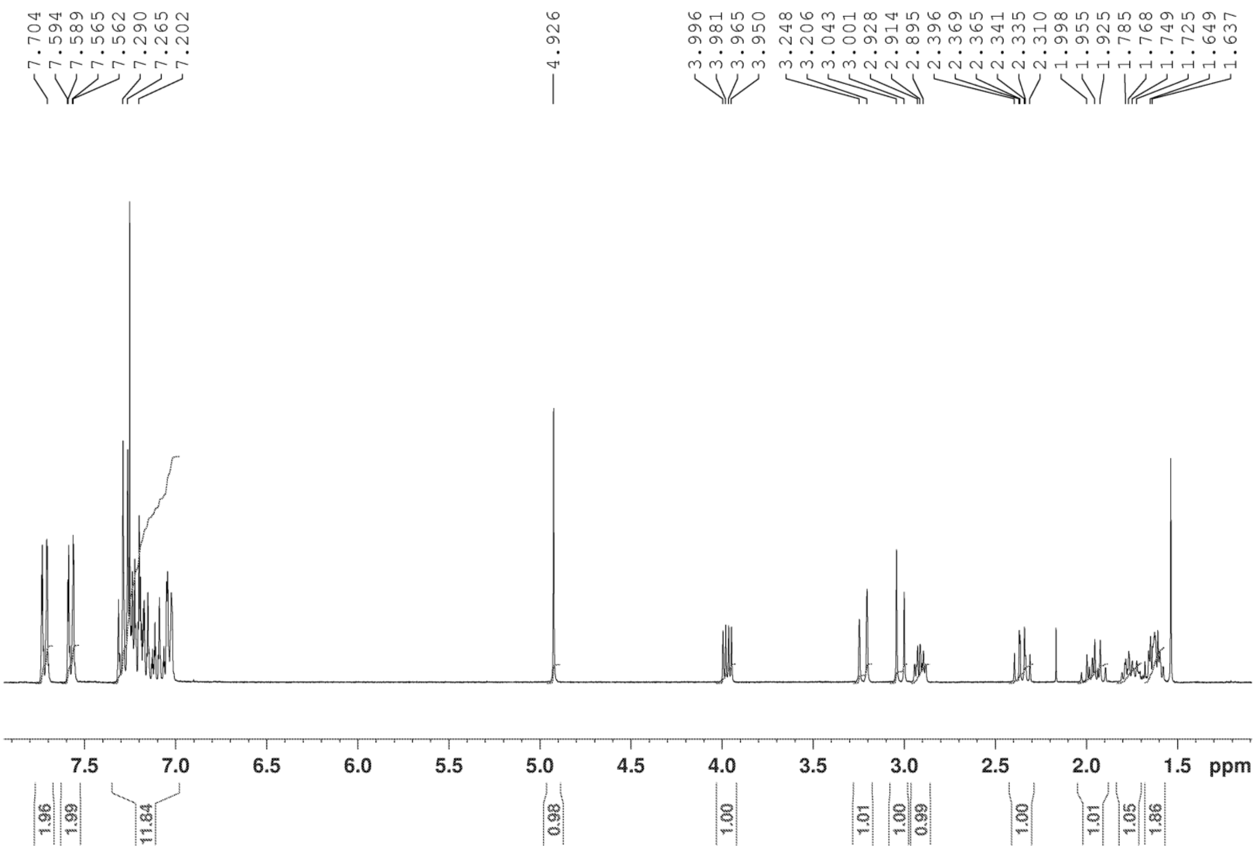
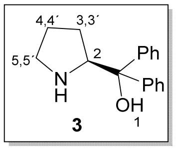


Figure SM 4.2.1.6.5. ^{1}H-NMR spectrum (300 MHz, CDCl$_3$) of compound **2**.



^{1}H NMR (300 MHz, CDCl$_3$): 7.60-7.54 (m, 2H, Ph), 7.53-7.45 (m, 2H, Ph), 7.34-7.22 (m, 4H, Ph), 7.20-7.12 (m, 2H, Ph), 4.25 (t, *J* = 7.6 Hz, 1H, H_2), 3.08-2.87 (m, 2H, $H_{5,5'}$), 1.83-1.49 (m, 4H, $H_{3,3'}$, $H_{4,4'}$).

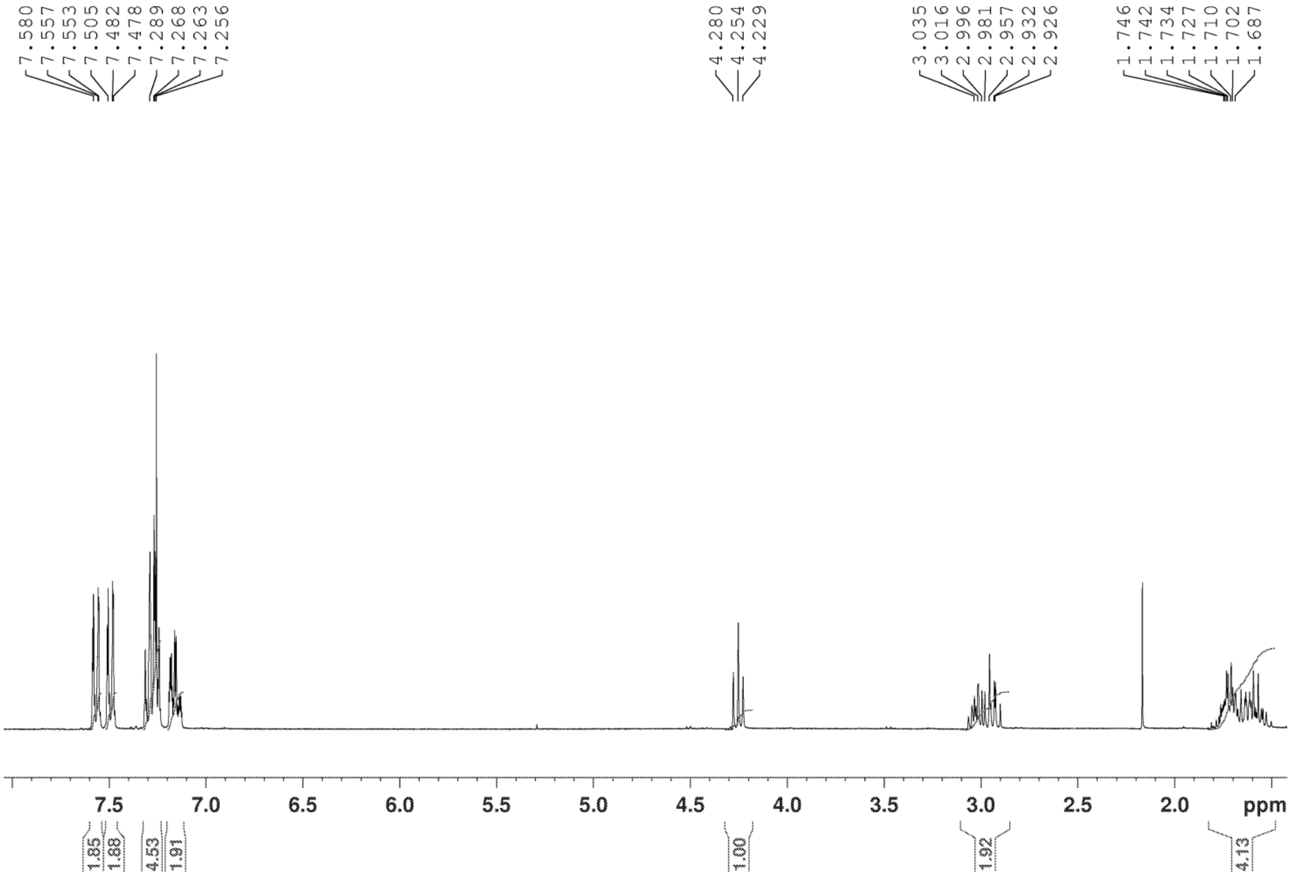


Figure SM 4.2.1.6.6. ^{1}H-NMR spectrum (300 MHz, CDCl$_3$) of compound **3**.