

Diastereoselective Synthesis of (+/-)-1,2-Diphenyl-1,2-propanediol

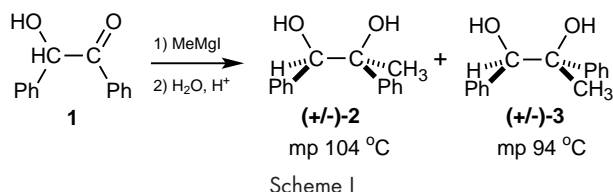
A Discovery-Based Grignard Reaction Suitable for a Large Organic Lab Course†

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An number of “puzzle-oriented” undergraduate introductory organic laboratory experiments combining synthesis and mechanistic discovery have appeared in this *Journal*. Those involving reactions with organometallic reagents fall into several categories: 1,4- vs 1,2-addition to conjugated ketones and nitriles (1); dehydration of alcohols produced by addition of Grignard reagents to ketone carbonyls, with chromatographic or mass spectrometric analysis of the resulting isomeric alkenes (2); identification of alcohols produced by reaction of unknown Grignard reagents with unknown ketones (3); and identification of unexpected reaction products (4). Diastereoselective 1,2-addition of Grignard reagents to α -chiral carbonyl compounds is a powerful method of stereocontrol in synthesis (5, 6). As far as we know, no undergraduate experiment has been reported that involves diastereoselective addition of Grignard reagents to carbonyl compounds. This paper describes an operationally straightforward experiment that asks students to probe the diastereoselectivity of the reaction between a Grignard reagent and a common, inexpensive α -chiral ketone.

Reaction of (+/-)-benzoin (**1**) with MeMgI can afford two diastereomers of (+/-)-1,2-diphenyl-1,2-propanediol ((+/-)-**2** and (+/-)-**3**) (7) (Scheme I).



The reaction is highly diastereoselective (the ratio of (+/-)-**2** to (+/-)-**3** is approx. 97:3),¹ affording purified (+/-)-**2** after only two or three recrystallizations from petroleum ether. Students use mp determination to identify the major diastereomer, thereby establishing the reaction's diastereoselectivity. After a discussion of diastereofacial selectivity, Cram's rule, and its variations (6), students are asked to rationalize the stereochemical outcome of their Grignard reaction.

Experimental Section

Students enrolled in the second-semester organic chemistry laboratory at Fordham University performed this experiment. A single 4-h lab period was used for the preparation of

MeMgI, its reaction with **1**, and recrystallization of the crude product; further recrystallizations and mp determinations were carried out as additional tasks during a second period. Benzoin was recrystallized from 95% ethanol. All other reagents were used as received from the supplier (Aldrich Chemical Co.) without additional purification. *No flame-drying or oven-drying of glassware was necessary.* Students used air-dried glassware washed during the previous week, and anhydrous diethyl ether was used directly from the reagent bottle. TLC analyses were performed using Hard Layer Silica Gel GHF UNIPATES with inorganic binder (Analtech, Inc.) and Riedel-deHaen TLC plates, silica gel (60 F 254), 0.2 mm thickness on aluminum (available from Aldrich) with 5:1 (v/v) petroleum ether–ethyl acetate as eluent. NMR spectra were recorded on a Bruker Avance DPX300 spectrometer; ¹H spectra were recorded at 300 MHz and ¹³C at 75 MHz, and chemical shifts were measured relative to internal TMS. An ethereal MeI stock solution should be prepared for students in advance of the lab. Having students transfer the required amount directly into their addition funnels using an adjustable dispenser (e.g., REPIPET brand) that directly connects to the stock bottle placed in a fume hood minimizes handling.

Preparation of Methylmagnesium Iodide

A 1.0 M solution of MeI in anhydrous diethyl ether (12.0 mL, 12.0 mmol) was added slowly over 30 min from an addition funnel to magnesium turnings (290 mg, 12.0 mmol) in a 250-mL three-neck round-bottom flask adapted with a reflux condenser and a stopper.² The suspension was periodically swirled and hand-warmed during addition, and reaction proceeded spontaneously. After addition was complete, the contents of the flask were refluxed using a suitable heat source (a heating mantle with voltage regulator or a hot-water bath) until most of the Mg metal had reacted and the solution was cloudy gray or white (usually 30 min). If a significant amount of unreacted Mg remained, the mixture was cooled to room temperature and treated with an additional 1–2 mL of 1.0 M ethereal MeI. The reaction was continued at room temperature and then heated to reflux as before until most of the Mg had reacted.

Grignard Reaction of MeMgI with Benzoin; Synthesis of (+/-)-**2**

The ethereal MeMgI solution in the 250-mL three-neck round-bottom flask was cooled in an ice-water bath. (+/-)-Benzoin (500 mg, 2.36 mmol) in anhyd CH₂Cl₂ (10 mL) (**8**) was added slowly from an addition funnel over 2–3 min

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while the mixture was periodically swirled (the solution frothed slightly owing to methane evolution). After addition was complete, the ice-water bath was removed and the mixture was refluxed for 25 min using a suitable heat source. After cooling to room temperature, the mixture was treated with 10% H_2SO_4 (50 mL), vigorously swirled for 1–2 min, and poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted once with 15 mL of ether. The combined organic layers were dried over anhyd MgSO_4 , filtered into a preweighed flask, and concentrated on a rotary evaporator to afford 495 mg (92%, the average yield) of an amber solid (average mp 83–88 °C) or an amber oil, which partially solidified upon cooling. Recrystallization using ca. 5 mL of high-boiling petroleum ether for every 100 mg of crude (+/–)-2 gave the following results (av weights and mp ranges): 1st crystallization, 188 mg (97–100 °C); 2nd crystallization, 118 mg (102–103 °C); 3rd crystallization, 108 mg (102–103 °C). For each recrystallization, the mother liquor was decanted away from any undissolved solid and was *not* cooled in an ice-water bath. The product (+/–)-2 (mp 103–104 °C [7]) was obtained as white needles:

^1H NMR (CDCl_3) δ 7.2–7.0 (m, 10 H, Ph), 4.65 (s, 1H, $\text{PhCH}(\text{OH})$); 2.70 (s, 2H, OH, D_2O exchangeable), 1.60 (s, 3H, CH_3);

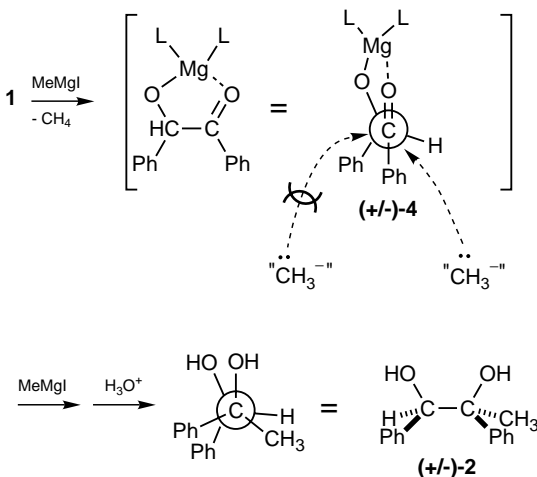
^{13}C NMR (CDCl_3) δ 143.48, 139.32, 127.61, 127.57, 127.42, 126.93, 126.00, 80.89 (C1), 76.75 (C2), 25.48 (C3).

Hazards

Students should be required to wear gloves when handling solutions of MeMgI , as it is toxic and possibly carcinogenic (9). Diethyl ether and petroleum ether are flammable liquids, and magnesium is a flammable solid.

Discussion

Diastereomer identification is straightforward, as the mp ranges of (+/–)-2 and (+/–)-3 are separated by 10 °C.³ The reaction's diastereoselectivity can be rationalized by the preferential addition of MeMgI to the least sterically hindered face of the carbonyl group in a rigid, five-membered cyclic intermediate ((+/–)-4) (the "Cram chelate model") (5, 6) (Scheme II).



Scheme II

Students encountered few difficulties in either the preparation of MeMgI or its reaction with benzoin. An excess of MeMgI is used to ensure that most of the benzoin is consumed. A typical crude sample from the Grignard reaction that contained as much as 10% unreacted benzoin (ratio based on ^1H NMR integration of the methines of unreacted benzoin and (+/–)-2) required only three recrystallizations to obtain a constant mp range. Some students obtained samples that melted sharply after only one recrystallization. The presence of benzoin in the crude product is easily established by TLC analysis (benzoin: R_f = 0.30; (+/–)-2: R_f = 0.20), and the Grignard reaction can be monitored by ether (1 mL) extraction of an aliquot quenched with 10% H_2SO_4 (1 mL).

Summary

This experiment introduces students to π -facial discrimination by having them establish the stereochemical course of kinetically controlled nucleophilic addition to the carbonyl of an inexpensive α -chiral ketone. It is well suited to courses with large enrollment because (i) it is run on a small scale, reducing material costs and increasing lab safety; (ii) common lab glassware and chemicals are used; (iii) no sophisticated instrumentation is needed (mp determination is sufficient for students to establish the reaction's diastereoselectivity); and (iv) the reaction is highly diastereoselective, affording reasonable yields of a single diastereomer after recrystallization. It has the benefit of being as operationally straightforward as more traditional Grignard experiments such as synthesis of triphenylmethanol from benzophenone (10) or methyl benzoate (11), while serving as a meaningful exercise in mechanistic problem solving.

Acknowledgments

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Supplemental Material

Background material, detailed instructions for the experiment, and sample spectra are available in this issue of *JCE Online*.

Notes

1. The ratio of (+/–)-2 to (+/–)-3 was established by integration of their ^1H NMR methyl singlets ((+/–)-2, δ = 1.60; (+/–)-3, δ = 1.35). Compound (+/–)-3 was prepared by treatment of (+/–)-1-hydroxy-1-phenyl-2-propanone with PhMgBr (7).
2. In place of a three-neck round-bottom flask, a Claisen adapter equipped with an addition funnel and reflux condenser could be connected to a one-neck round-bottom flask.
3. For further proof of identity, students can perform a mixed mp analysis on a fully characterized sample. To obviate the need to

obtain spectral data on all student samples, students can be provided with copies of NMR spectra.

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