

**JoVE: Science Education**  
**The Grignard Reaction**  
--Manuscript Draft--

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<b>Corresponding Author:</b>	Vy Dong UNITED STATES
<b>Corresponding Author Secondary Information:</b>	
<b>Corresponding Author's Institution:</b>	
<b>Corresponding Author's Secondary Institution:</b>	
<b>First Author:</b>	Vy Dong
<b>First Author Secondary Information:</b>	
<b>Order of Authors:</b>	Vy Dong
<b>Order of Authors Secondary Information:</b>	

**PI Name:** Vy M. Dong & Faben Cruz

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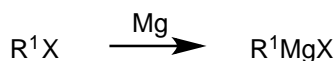
## Overview

This experiment will demonstrate how to properly carry out a Grignard reaction. The formation of an organometallic reagent will be demonstrated by synthesizing a Grignard reagent with magnesium and an alkyl halide. To demonstrate a common use of a Grignard reagent, a nucleophilic attack onto a carbonyl will be performed to generate a secondary alcohol by forming a new C–C bond.

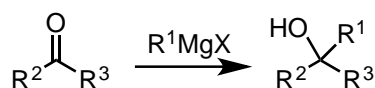
## Principles

The Grignard reaction is a method for forming carbon-carbon bonds between alkyl/aryl halides and carbonyls like aldehydes, ketones, or esters. This Nobel-Prize-winning chemistry consists of two steps: Grignard *reagent* formation and subsequent Grignard addition into a carbonyl to construct a new carbon-carbon bond. A Grignard reagent is an organometallic compound, specifically an organomagnesium compound. The synthesis of a Grignard reagent requires an alkyl or aryl halide (chlorides, bromides, or iodides) and magnesium. In this step the electrophilic (an electrophile is electron deficient and wants to accept electrons) alkyl halide is transformed into a nucleophilic (a nucleophile is electron rich and wants to donate electrons) carbanion-like compound. The second step of the Grignard reaction entails a nucleophilic addition of the Grignard reagent into a carbonyl. After this step a new carbon-carbon bond is formed and the carbonyl is transformed into an alcohol. It is important to perform both steps under moisture-free conditions otherwise the Grignard reagent used will react with water, resulting in no desired Grignard or C–C bond formation. The Grignard reaction is an important and widely used tool that allows synthetic chemists to take any alkyl or aryl halide and transform it into an organomagnesium compound, which can be used to construct carbon-carbon bonds.

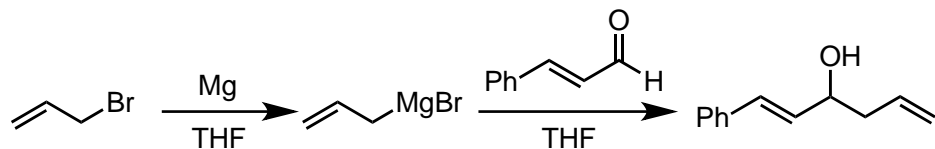
### Grignard Formation



### Grignard Addition



## Procedure



### 1. Grignard Reagent Formation

- 1.1. Flame-dry a round bottom flask equipped with a magnetic stir bar.
- 1.2. Add magnesium ( $\text{Mg}$ , 1.1 equiv.) to the round bottom flask.
- 1.3. Add a small amount of iodine ( $\text{I}_2$ , a few crystals). Addition of iodine is to help remove any  $\text{MgO}$  on the surface of the  $\text{Mg}$ . Removing  $\text{MgO}$  allows for  $\text{Mg}$  and the aryl/alkyl halide to come into contact and react. Sonication or addition of methyl iodide or 1,2-dibromoethane can also help with initiation.
- 1.4. Cool the reaction mixture to  $0^\circ\text{C}$  with an ice-water bath
- 1.5. Slowly add a THF (1 M) solution of allyl bromide (1 equiv.) to the round bottom flask with magnesium.
- 1.6. After adding the solution of allyl bromide, stir the reaction mixture for 3 hours at room temperature.

### 2. Nucleophilic Addition

- 2.1. In a separate flame-dried round bottom flask, add *trans*-cinnamaldehyde (0.85 equiv.) and THF (0.5 M with respect to *trans*-cinnamaldehyde) and cool to  $0^\circ\text{C}$ .
- 2.2. Slowly add the THF solution of the Grignard reagent (allyl-magnesium bromide) to the *trans*-cinnamaldehyde solution.
- 2.3. After addition, warm the reaction mixture to room temperature by removing the ice-water bath and stir for 4 hours.
  - 2.3.1. Monitor reaction progress *via* TLC by looking for the disappearance of *trans*-cinnamaldehyde.
- 2.4. After reaction completion, cool the mixture to  $0^\circ\text{C}$  with an ice-water bath.
- 2.5. Slowly quench the reaction with a saturated aqueous solution of ammonium chloride ( $\text{NH}_4\text{Cl}$ ).

- 2.6. Transfer the mixture into a separatory funnel and extract the aqueous layer with ethyl acetate 3x.
- 2.7. Combine the organic layers and wash with water and brine (a saturated aqueous solution of NaCl).
- 2.8. Dry the organic layer with anhydrous  $\text{MgSO}_4$ , filter, and evaporate the solvent *via* rotatory evaporation.
- 2.9. Purify the crude residue *via* flash column chromatography.

## Representative Results

The purified product should have the following  $^1\text{H}$  NMR spectrum:  $^1\text{H}$  NMR  $\delta$  7.23-7.39 (m, 5H), 6.60 (d,  $J=16.0$  Hz, 1H), 6.23 (dd,  $J=6.4$  Hz, 1H), 5.84 (m, 1H), 5.14-5.20 (m, 2H), 4.35 (q,  $J=6.4$  Hz, 1H), 2.37-2.43 (m, 2H), 1.9 (br s, 1H).

## Summary

This experiment has demonstrated how to synthesize a Grignard reagent from an aryl/alkyl halide and how to use the Grignard reagent to perform a nucleophilic addition into a carbonyl compound to construct a new carbon-carbon bond.

## Applications

The Grignard reaction is widely used in the synthetic chemistry world. You can find this reaction being used in university research labs, national laboratories, and pharmaceutical companies. Simple Grignard reagents are commercially available, but often times unique and specialized Grignard reagents are necessary. The Grignard reaction allows synthetic chemists to access the necessary compounds from aryl or alkyl halides. In addition to performing nucleophilic additions into carbonyls, Grignard reagents can be used as nucleophiles in combination with a large variety of other electrophilic compounds. An example of a specialized Grignard reagent can be found in the synthesis of phorboxazole A, a natural product found to exhibit potent anti-bacterial, anti-fungal, and anti-proliferative properties.

### Figure 1

Another way to generate Grignard reagents is *via* magnesium-halogen exchange. This method uses a premade Grignard reagent instead of using magnesium to generate the desired Grignard. The most commonly used Grignard for magnesium-halogen exchange is *i*-PrMgCl or *i*-PrMgBr, both of which are commercially available. Magnesium-halogen exchange has been shown to exhibit broad functional group tolerance.<sup>1</sup> As a result, this

method has proven to be a useful way to generate highly functionalized Grignard reagents. Alkyl/aryl halides with functional groups that typically react with Grignard reagents can be used to make Grignard reagents *via* magnesium-halogen exchange. Esters, nitriles, and alkyl chlorides remain intact during magnesium-halogen exchange. In addition, iodides can selectively undergo magnesium-halogen exchange in the presence of bromides.

## Figure 2

Grignard reagents typically act as nucleophiles and add into carbonyl compounds, but side reactions can occur depending on the nature of the Grignard and carbonyl used. A common side reaction is a Wurtz coupling, where the Grignard reagent couples to itself to form a dimer. Sterically bulky Grignards or carbonyls can make the nucleophilic addition challenging. No addition or reduction of the carbonyl *via*  $\beta$ -hydride transfer are potential outcomes with sterically bulky substrates. The presence of enolizable protons in the carbonyl can also make nucleophilic addition challenging due to competitive carbonyl enolization. A common way to suppress these side reactions and promote nucleophilic addition is to use lanthanide salts, especially  $\text{CeCl}_3$ , as additives. Lanthanide salts are oxophilic (attracted to oxygen), therefore they coordinate to the carbonyl oxygen and increase the electrophilicity of the carbonyl. The addition of cyclopentyl  $\text{MgCl}$  into cyclohexenone would be expected to give the tertiary alcohol, instead the carbonyl is reduced to give the secondary alcohol. This side reaction can be suppressed in favor of the desired Grignard addition by adding  $\text{LaCl}_3$ .

## Figure 3

### References

<sup>1</sup> *Angew. Chem. Int. Ed.*, **2003**, 42, 4302.

### Legend

**Figure 1. Phorboxazole A**

**Figure 2. Magnesium-Halogen Exchange**

**Figure 3. Lanthanide Salt Promoted Grignand Addition**

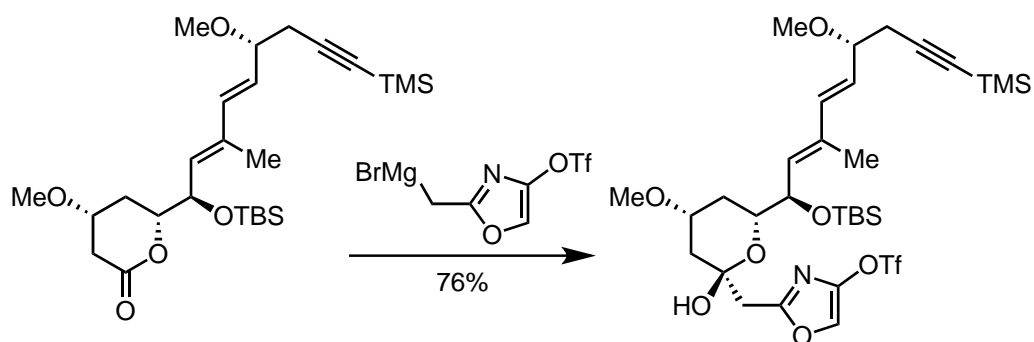


Figure 1

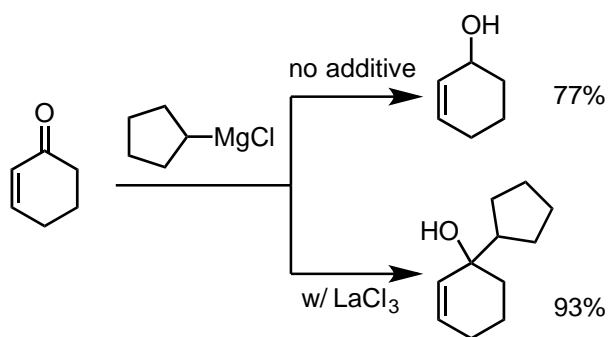
**Lanthanide Salt Promoted Grignard Addition**

Figure 2

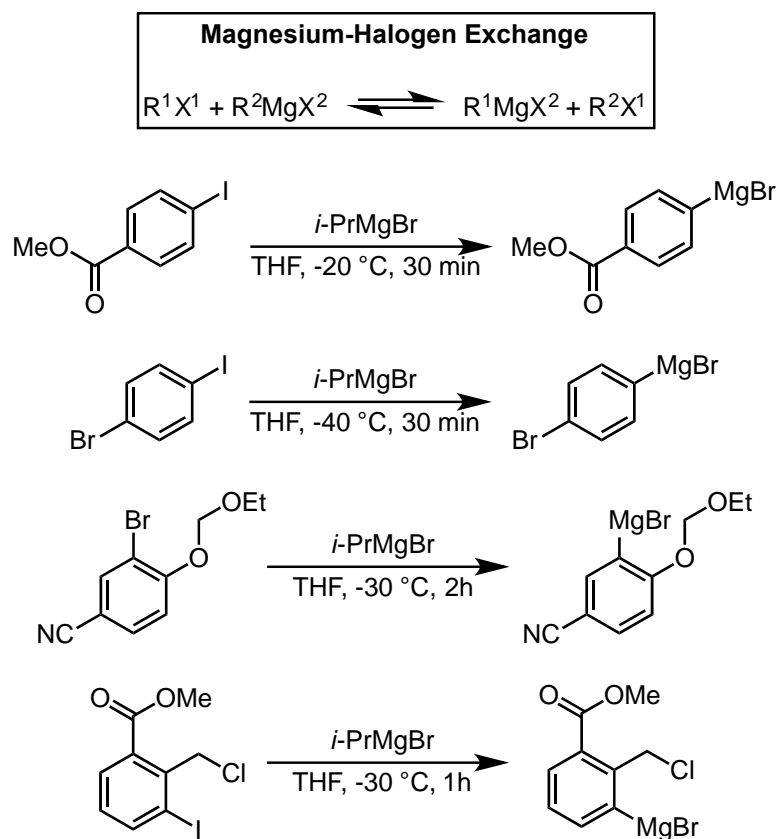


Figure 3