

## Organometallics in Synthesis

### Primary Reading:

1. P.R. Jenkins, "Organometallics in Synthesis", OUP Primer No 3 (Chapters 1-2)
2. Clayden, Greeves, Warren & Wothers, Chapter 9.
3. Lecture Notes

This is all about the generation and reactivity of the equivalent of carbanions of alkyl groups,  $R^-$ . These species can react either as nucleophiles or as strong bases, or under certain circumstances as hydride donors. The metal ion (the counter ion) makes an important difference to the reactivity of the organometallic reagent, so you should ensure that you know the differences in reactivity between lithium, magnesium, cadmium, copper and zinc compounds. It may be easier to treat Grignard reagents as the standard, and compare the other organometallics to these. [N.B. Organometallics have C-metal bonding, so  $NaBH_4$ ,  $LiAlH_4$  etc. are not classified as organometallics.]

### Preparation of organometallics

Look up methods for making these reagents: the classic example is reaction of alkyl halide with magnesium in dry ether. This changes the carbon of an alkyl halide from being subject to nucleophilic attack to being itself a strong nucleophile. Be aware that the preparation of acetylenic Grignards depends on the relative acidity of alkynes versus alkanes. Why are these reagents made in dry ether and under an inert atmosphere? What would happen if you tried to generate them in water?

### Reactivity

As a nucleophile, base, or as a hydride ion donor.

- i) For nucleophilic substitutions at  $sp^3$  carbon the reaction is usually poor, since elimination and other reactions (such as metal/halogen exchange) can compete. Note that the addition of copper(I) can make this a much better reaction.
- ii) The major and most useful reaction in synthesis is the addition of  $R^-$  as a nucleophile across a polar  $C=X$ , most particularly across the  $C=O$  group:  
The addition step exchanges an alkyl anion ( $pK_a$  of around 50) for an alkoxide ion if  $X = O$  ( $pK_a$  of around 16) and therefore is a completely irreversible reaction. The alkoxide product is essentially ionic. If  $Y$  is a reasonable leaving group, the tetrahedral intermediate will collapse in situ to generate a ketone and there will be further reaction (via nucleophilic addition) of the organometallic to this ketone before the aqueous work-up. Overall, this is a nucleophilic substitution reaction at  $sp^2$  C by a stepwise addition-elimination process. Compare this mechanism with that of  $B_{AC}2$  or  $A_{AC}2$  ester hydrolysis, or addition of an amine to an acid chloride.
- iii) Organometallics are very strong bases, so beware of acidic or even remotely acidic protons; particularly those next to electron-withdrawing groups.
- iv) In special circumstances (namely, when nucleophilic addition and deprotonation are blocked) organometallics may act as hydride donors by delivery of a  $\beta$ -hydrogen via a 6-membered cyclic transition state.

### Aqueous work-up

The aqueous work-up at the end of the reactions provides the protons. You should therefore know when a tetrahedral intermediate is likely to break down spontaneously during the course

of the reaction. This will usually happen if the pKa of the conjugate acid of the leaving group is roughly the same as that of an alcohol: under those circumstances the tetrahedral intermediate will collapse. This explains why treatment of an ester is not a good way of making a ketone, whereas treatment of a nitrile (cyanide) with a Grignard followed by work up with aqueous acid, is a good method of making ketones from organometallics.

**Grignards:** Preparation; reactivity as bases, nucleophiles and hydride donors; main use in C-C bond formation in preparation of alcohols, aldehydes, ketones and carboxylic acids; also 1,2 vs 1,4 addition to  $\alpha,\beta$ -unsaturated carbonyls (note use of Cu(I) catalysis).

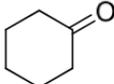
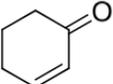
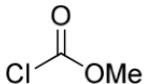
**Organolithium:** Preparation; reactivity as bases and nucleophiles (compare strength to Grignards); main use as a strong base (e.g. BuLi, LDA); preparation of ketones from carboxylic acids; reaction with CO<sub>2</sub>; 1,2 addition to  $\alpha,\beta$ -unsaturated carbonyls.

**Organocopper:** Preparation; reactivity differences from Li and Mg; 1,4 addition to  $\alpha,\beta$ -unsaturated carbonyls; SN<sub>2</sub> reactions with epoxides, etc.

**Organozinc:** Preparation; the Reformatsky reaction. Make your own notes but do not give them in.

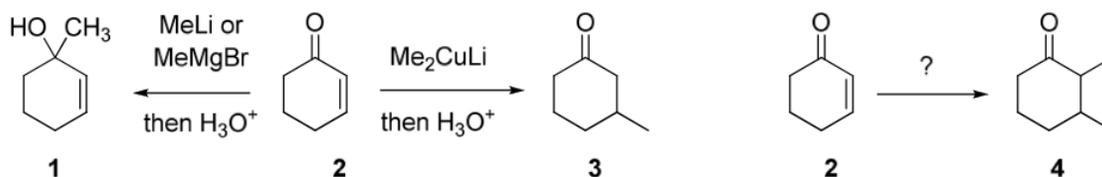
#### Problems

1. How would you expect ethylmagnesium bromide in ether to react with the following

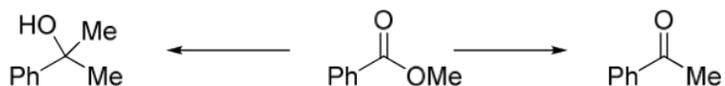
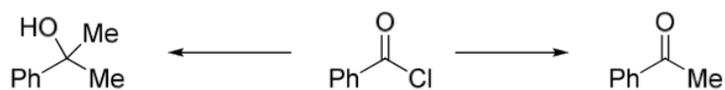
- |   |  |  |  |
|---|--|--|--|
| i) CH <sub>3</sub> CO <sub>2</sub> H  | ii) CH <sub>3</sub> CN   | iii) CO <sub>2</sub>   | iv) CS <sub>2</sub>  |
| v) D <sub>2</sub> O   | vi) CH <sub>3</sub> COOC <sub>2</sub> H <sub>5</sub>                                       | vii) CH <sub>3</sub> CON(C <sub>2</sub> H <sub>5</sub> )                                 | viii) PhNH <sub>2</sub>  |
| ix) CH <sub>3</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>                      | x)      | xi) H <sub>3</sub> C-C≡CH  | xii) (CH <sub>3</sub> ) <sub>3</sub> CBr   |
| xiii) CH <sub>3</sub> CH=CHCH <sub>2</sub> Br   | xiv) PhCOCl  | xv)  | xvi)  |
| xvii)  | xviii)  |  |  |

2a) PhCOOH reacts with an excess of MeLi to give, after aqueous workup, PhCOCH<sub>3</sub>. In contrast, when PhCOOH is treated with an excess of MeMgBr under similar conditions, only starting material is obtained. Explain these observations

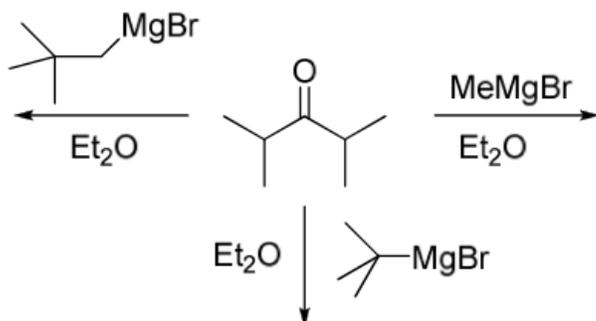
b) MeMgBr and MeLi add in a 1,2 fashion to 2, while the corresponding cuprate adds 1,4 to 2. Explain these observations. How can this reactivity difference be used to prepare 4 from 2.



c) Dialkylcopper reagents are far less reactive than their lithium or magnesium counterparts and can therefore be useful in synthesis. Illustrate this point by giving organometallic reagents for the following transformations

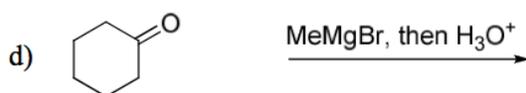
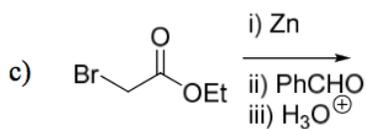
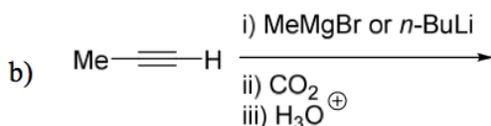
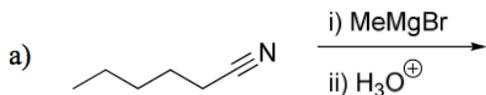


3a) Outline the possible modes of reactivity of Grignard reagents with respect to the following compounds.



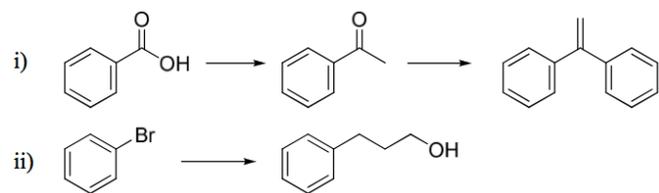
b) How would you make the following from PhMgBr? i) PhD ii) PhCOMe iii) PhCH<sub>2</sub>CH<sub>2</sub>OH iv) Ph<sub>2</sub>(OH)Me

4. Give mechanisms for the following transformations.



5a) Organometallic reagents are often used as synthetic intermediates. Illustrate this statement describing both the preparations and chemical properties of such reagents including organolithiums, organomagnesiums and organozincs. [20]

b) Suggest reagents for the following transformations.



7. Indicate the reactions involved and show the products formed in the following sequences.

