GRIGNARD REACTION

What is Grignard regents and Grignard reaction?

In 1900, V. Grignard reported that an alkyl halide (RX) reacts with magnesium metal (Mg) in diethyl ether to give a cloudy solution of an organomagnesium compound (RMgX), which upon reaction with aldehydes and ketones afforded secondary and tertiary alcohols, respectively.1 These organomagnesium compounds are called *Grignard reagents, and their addition across carbon-heteroatom multiple bonds is referred to as the Grignard reaction.*

The general features of Grignard reagents and their reactions:

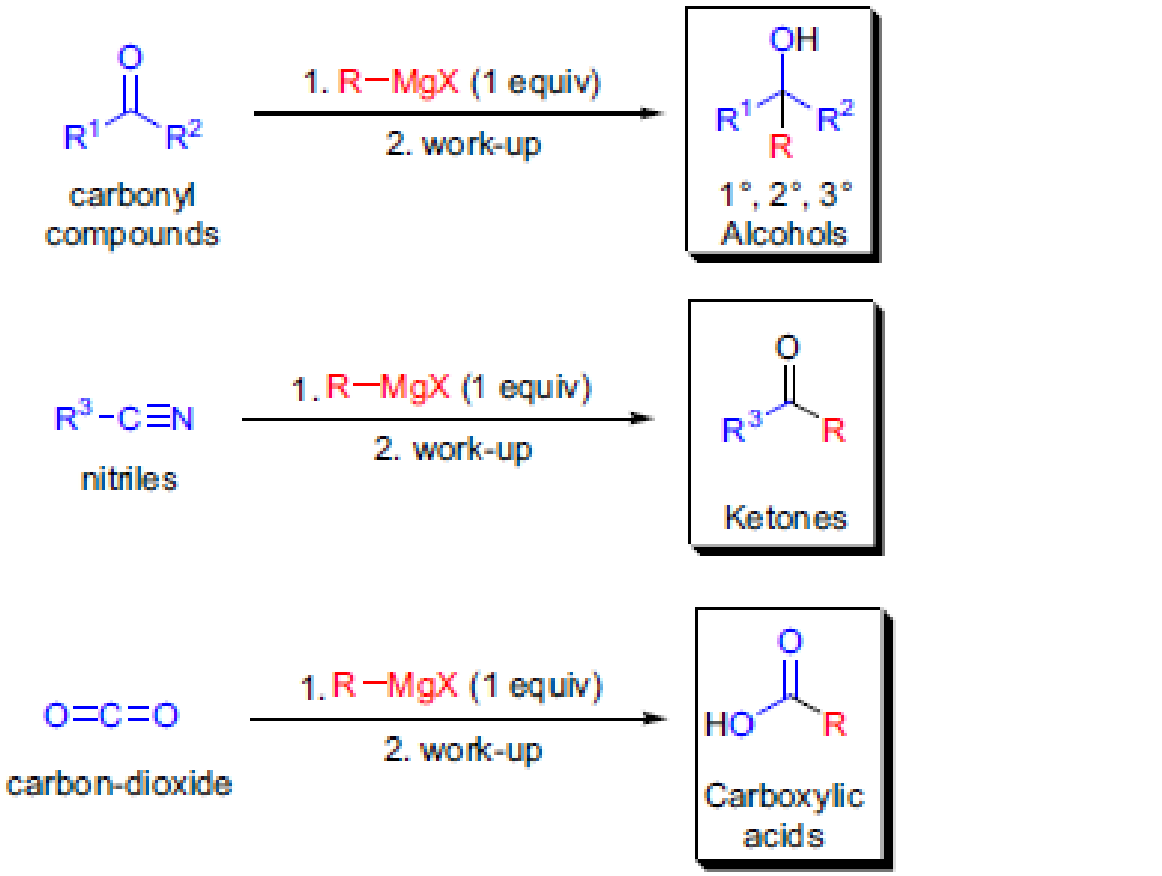
1) the reagents are predominantly prepared by reacting alkyl, aryl, or vinyl halides with magnesium metal in aprotic nucleophilic solvents (e.g., ethers, tertiary amines);

2) the reagents are usually thermodynamically stable but air and moisture sensitive and incompatible with acidic functional groups (e.g., alcohols, thiols, phenols, carboxylic acids, 1°, 2° amines, terminal alkynes);

3) the C-Mg bond is very polar and the partial negative charge resides on the carbon atom, so Grignard reagents are excellent carbon nucleophiles (in the precursor halides the carbon has a partial positive charge so overall a reversal of polarity known as *umpolung takes place upon formation of the reagent);*

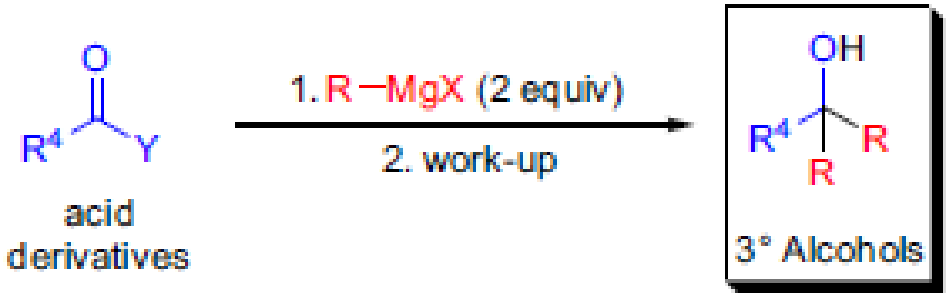
4) in most carbon-heteroatom multiple bonds the carbon atom is partially positively charged so the formation of C-C bonds with the nucleophilic Grignard reagents is straightforward;

5) addition of one equivalent of Grignard reagent followed by a work-up converts aldehydes to secondary alcohols (formaldehyde to primary alcohols), ketones to tertiary alcohols, nitriles to ketones and carbondioxide to acids;

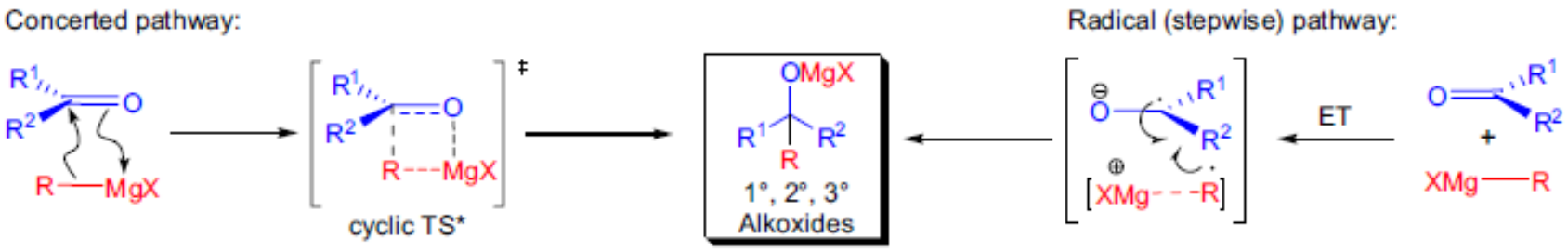


R^1, R^2 = alkyl, aryl, H; R^3 = alkyl, aryl; R^4 = alkyl, aryl; Y = OR, Cl, Br, I; R = alkyl, aryl; X = Cl, Br, I

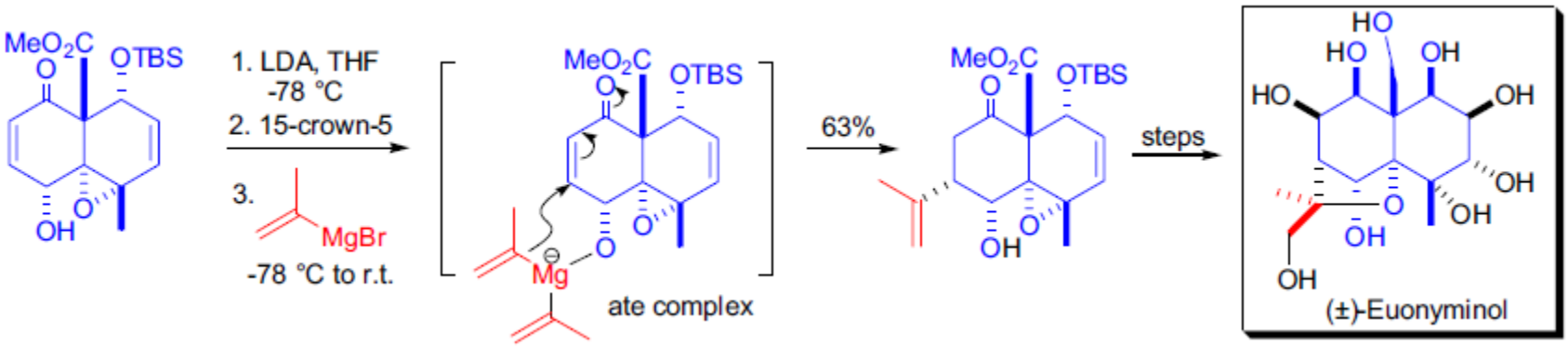
6) acid derivatives react with two equivalents of Grignard reagent: esters and acyl halides (RCOX) are converted to tertiary alcohols;

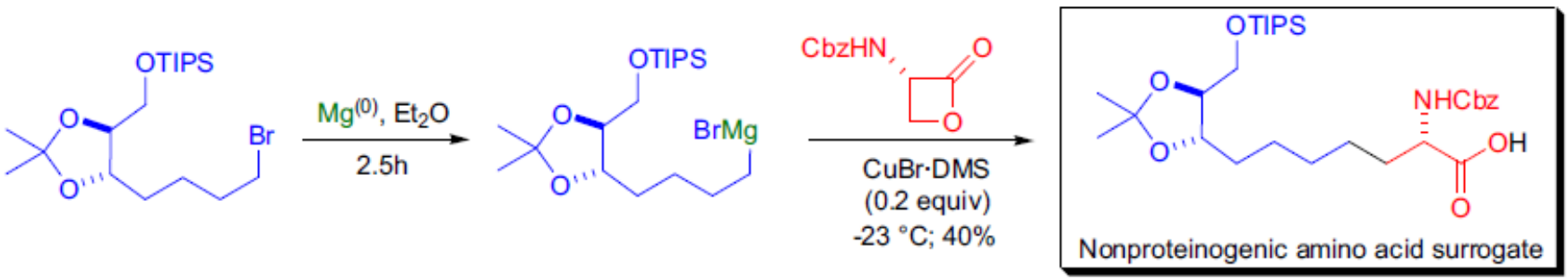


Machanism:


Concerted pathway:
cyclic TS*
1°, 2°, 3°
Alkoxides
Radical (stepwise) pathway:
ET

Synthetic Applications:




OTIPS
O
O
Br
Mg(0), Et2O
2.5h
OTIPS
O
O
BrMg
CbzHN
O
O
CuBr·DMS
(0.2 equiv)
-23 °C; 40%
OTIPS
O
O
NHCbz
OH
O
Nonproteinogenic amino acid surrogate