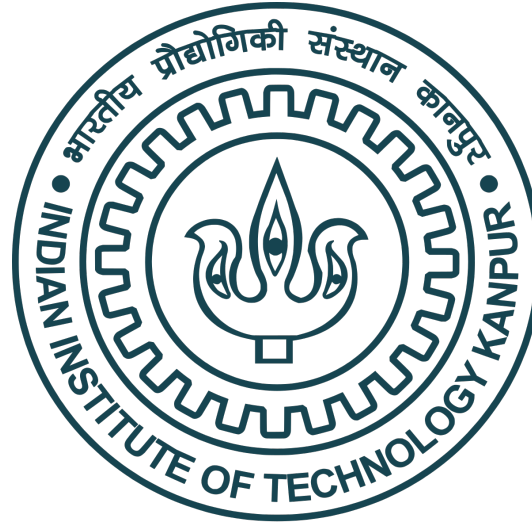


# **Lecture 19**

## **Fundamentals and Applications (CSO201A)**



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# Coupling Reaction

A coupling reaction in organic chemistry is a general term for a variety of reactions where two fragments are joined together with the aid of a metal catalyst. In one important reaction type, a main group organometallic compound of the type R-M (R = organic fragment, M = main group center) reacts with an organic halide of the type R'-X with formation of a new carbon-carbon bond in the product R-R'. The most common type of coupling reaction is the cross coupling reaction

- ✓ 1. Homo-coupling types
- ✓ 2. Cross-coupling types

**Homo-coupling types:** A) Wurtz reaction. B) Pinacol coupling reaction. C) Glaser coupling. D) Ullmann reaction

**Cross-coupling types:** A) Grignard reaction. B) Negishi coupling. C) Stille cross coupling. D) Suzuki reaction. E) Buchwald-Hartwig reaction. F) Sonogashira coupling. G) Heck reaction. H) Kumada coupling.

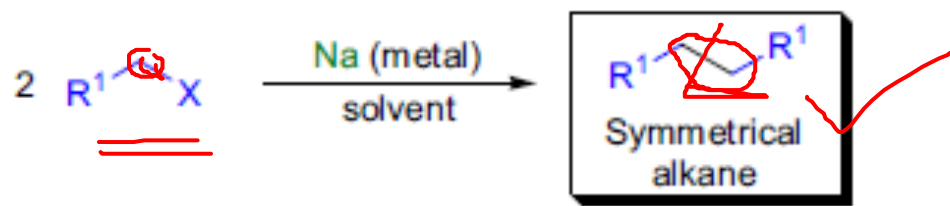


# 1. Homo-coupling types

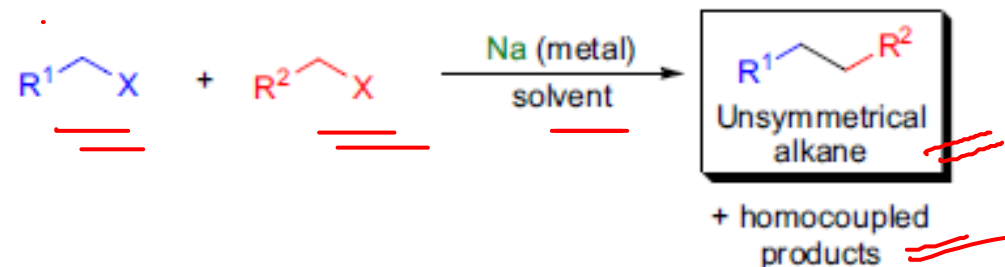
## A) Wurtz Reaction

The coupling of two sp<sup>3</sup>-carbon centers by the treatment of alkyl or benzyl halides with sodium metal is known as the *Wurtz coupling*. When metals other than sodium are used, this transformation is referred to as a *Wurtz type coupling*. The coupling of an alkyl and an aryl halide in the presence of sodium metal to get the corresponding alkylated aromatic compound is called the *Wurtz-Fittig reaction*.

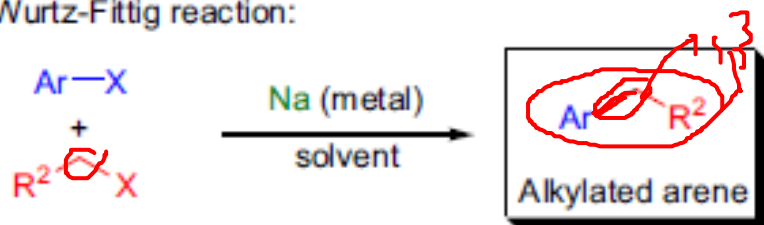
Wurtz homocoupling (dimerization):



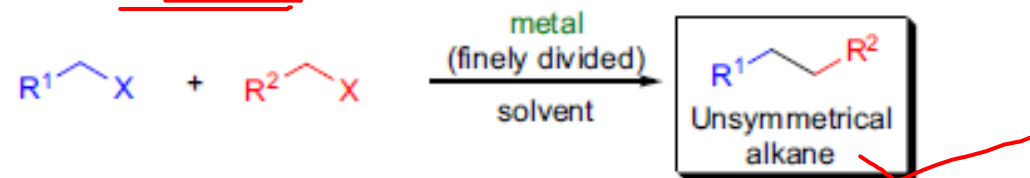
Wurtz heterocoupling (cross-coupling):



Wurtz-Fittig reaction:



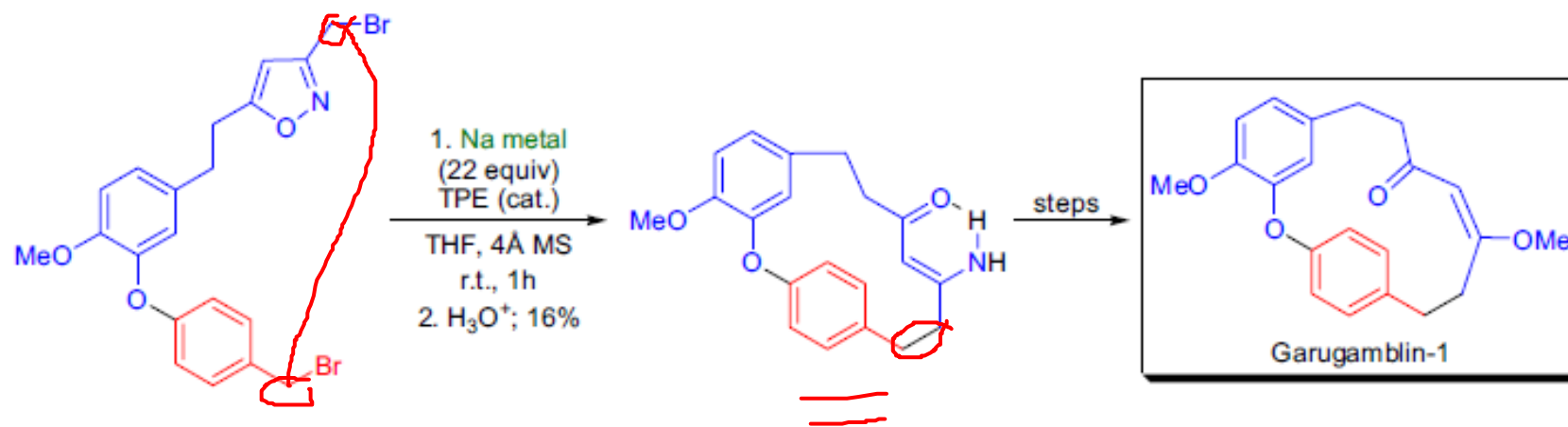
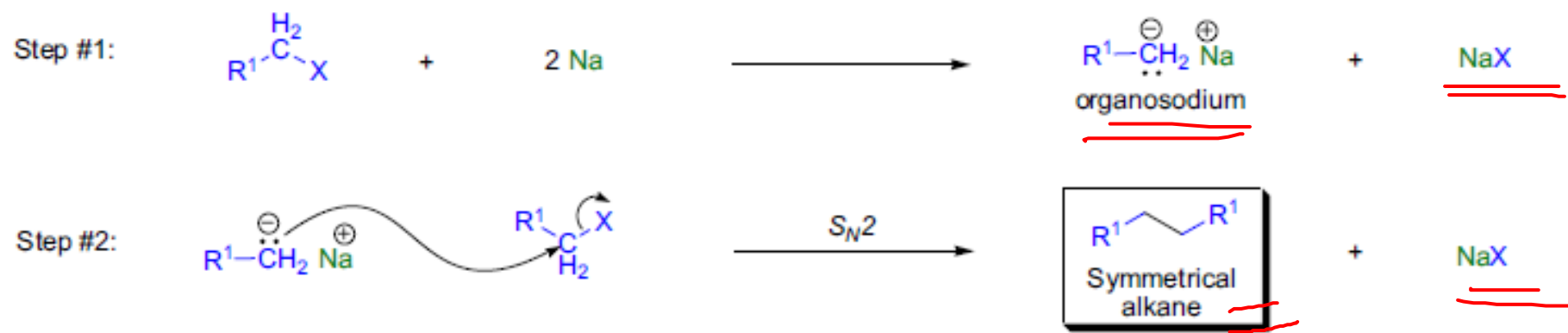
Wurtz-type coupling:

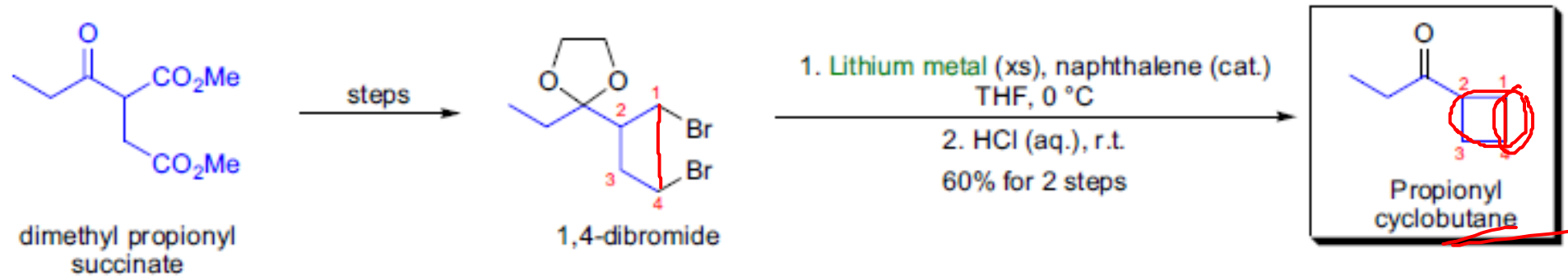
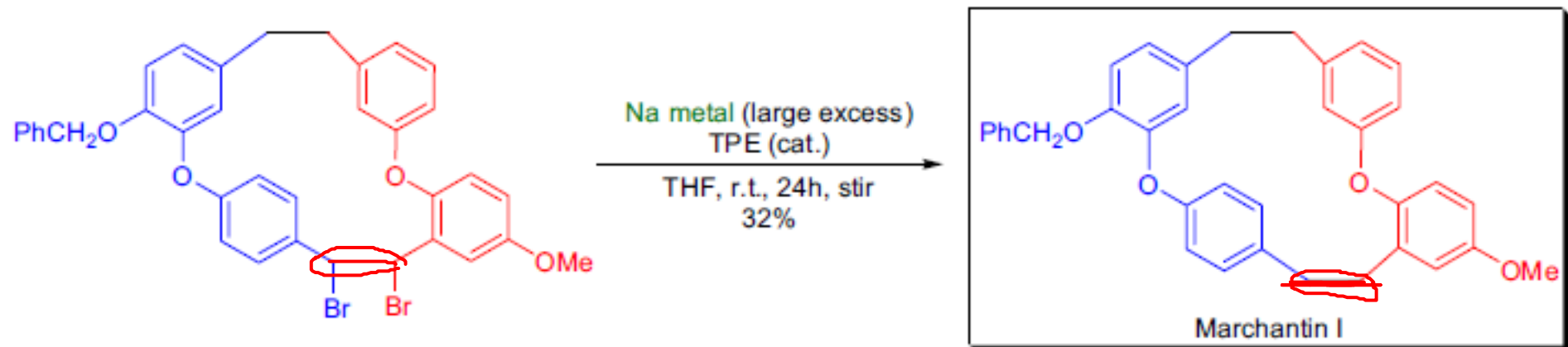


$R^1 = 1^\circ$  alkyl, aryl;  $R^2 = 1^\circ$  alkyl, aryl;  $Ar$  = electron-rich and electron-poor substituted aryl; metal = K, Mg, Zn, Cu etc.;  
solvent = THF, Et<sub>2</sub>O, dioxane, xylenes



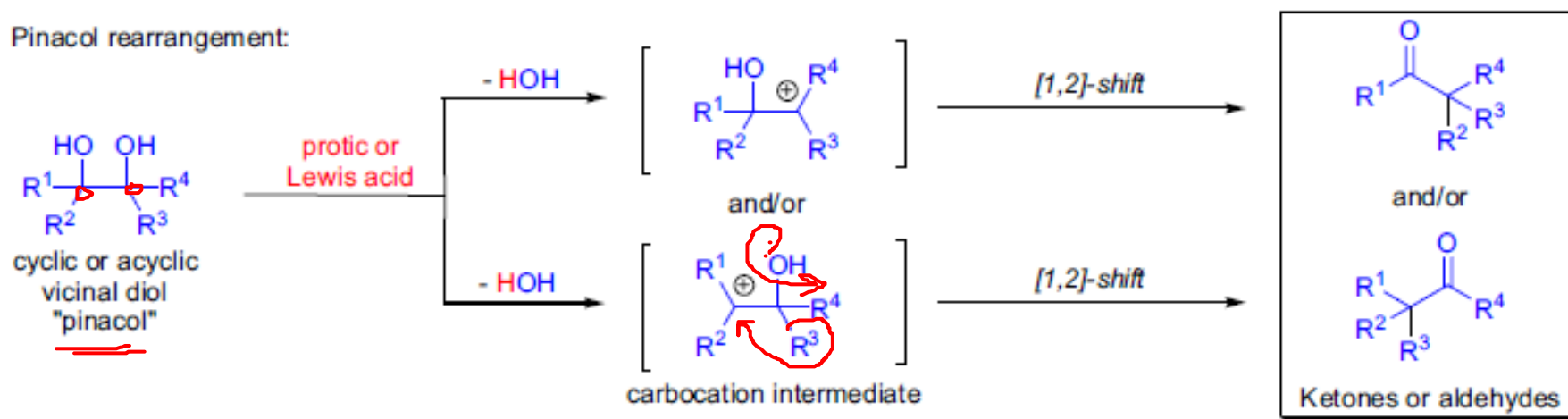
The ***mechanism*** of the Wurtz coupling is not well understood, and the currently accepted mechanism involves two steps: 1) formation of a carbanionic organosodium compound via metal-halogen exchange; and 2) the displacement of the halide ion by the organosodium species in an  $S_N2$  reaction. Alternatively, a radical process can also be envisioned, although to date there has been no experimental evidence to support this assumption.



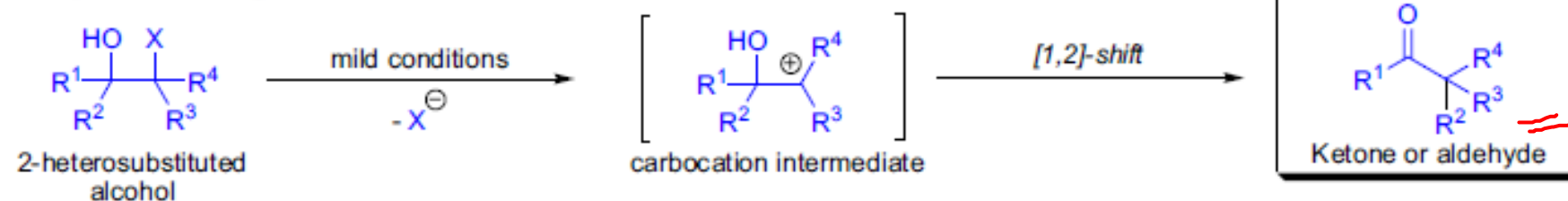


# B) Pinacol Rearrangement

This acid-catalyzed transformation of vicinal diols is known as the *pinacol rearrangement*. The general features of the reaction are: 1) virtually any cyclic or acyclic vicinal glycol can undergo the rearrangement, and, depending on the substitution pattern, aldehydes and/or ketones are formed; 2) when all four substituents are identical, the rearrangement yields a single product; 3) when the four substituents are not identical, product mixtures are formed; 4) the product is usually formed via the most stable carbocation intermediate when the glycol substrate is unsymmetrical.



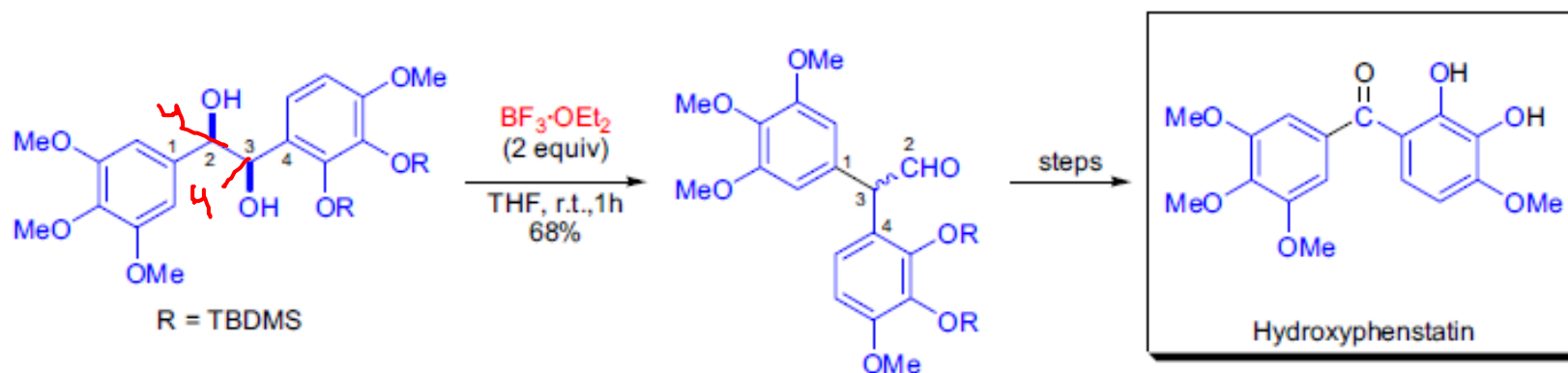
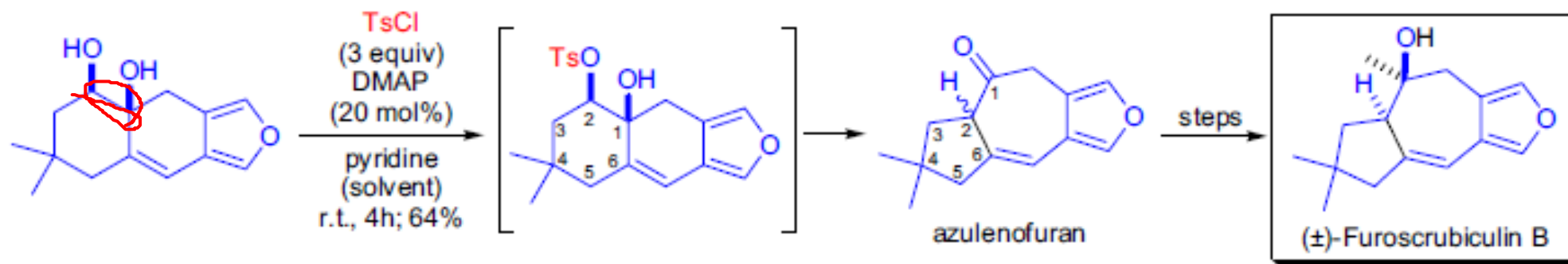
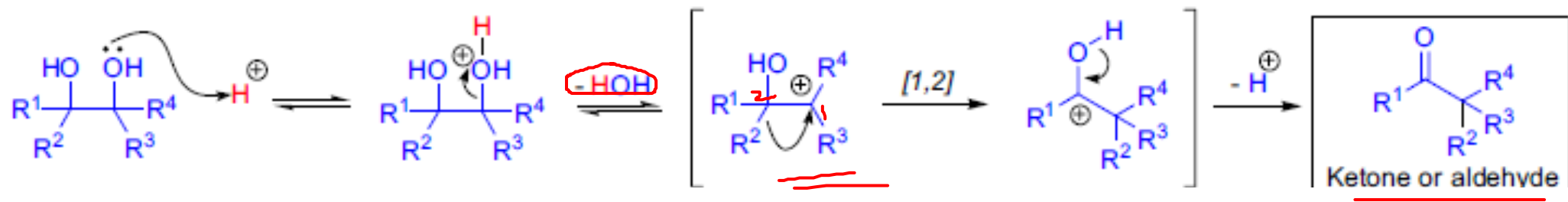
Semipinacol rearrangement:



$\text{R}^{1-4}$  = H, alkyl, aryl, acyl;  $\text{X}$  = Cl, Br, I, SR, OTs, OMs,  $\text{N}_2^+$  (Tiffeneau-Demjanov rearrangement); protic acid:  $\text{H}_2\text{SO}_4$ ,  $\text{HClO}_4$ ,  $\text{H}_3\text{PO}_4$ , TFA, TsOH; Lewis acid:  $\text{BF}_3 \cdot \text{OEt}_2$ , TMSOTf; mild conditions:  $\text{LiClO}_4/\text{THF}/\text{CaCO}_3$ ,  $\text{Et}_3\text{Al}/\text{DCM}$ ,  $\text{Et}_2\text{AlCl}/\text{DCM}$ , etc.

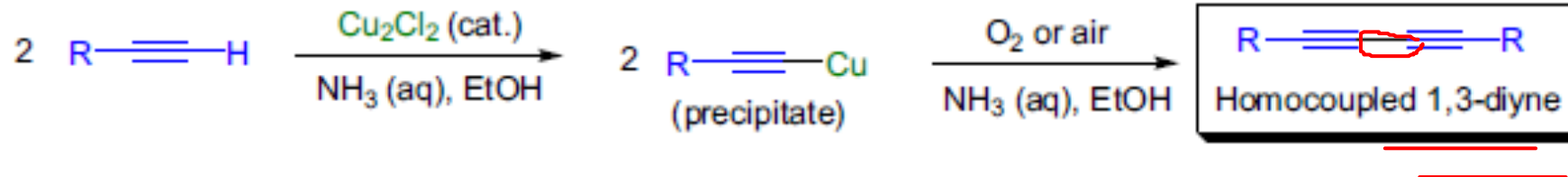


The first step of the process is the protonation of one of the hydroxyl groups, which results in the loss of a water molecule to give a carbocation intermediate. This intermediate undergoes a [1,2]-shift to give a more stable carbocation that upon the loss of proton gives the product. The pinacol rearrangement was shown to be exclusively intramolecular, and both inversion and retention were observed at the migrating center.

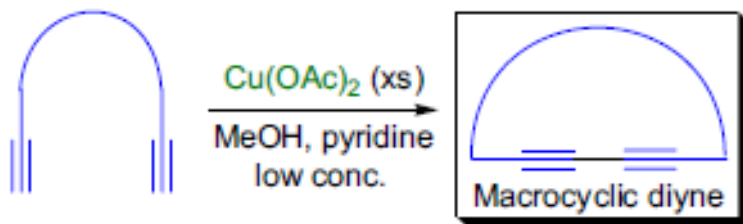


## C) Glaser Coupling

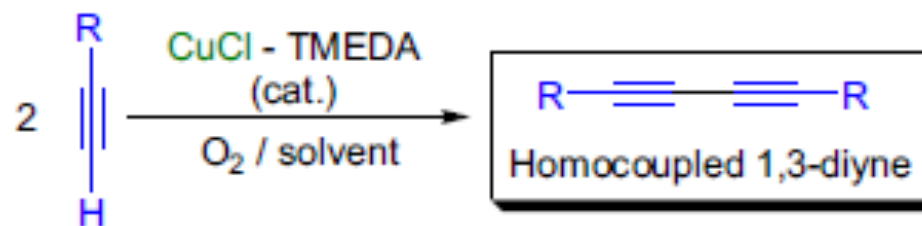
The preparation of symmetrical conjugated diynes and polyynes (linear or cyclic) by the oxidative homocoupling of terminal alkynes in the presence of copper salts is known as the Glaser coupling. There are numerous versions of the original procedure developed by Glaser, and these differ mainly in the type and amount of oxidants used: 1) besides oxygen and air,  $\text{CuCl}_2$  and  $\text{K}_3\text{Fe}(\text{CN})_6$  are used most often as oxidizing agents; 2) Glaser's procedure was heterogeneous and slow, but G. Eglinton and A.R. Galbraith showed that using  $\text{Cu}(\text{OAc})_2$  in methanolic pyridine made the process homogeneous and faster (Eglinton procedure). This method was successfully applied to the synthesis of macrocyclic diynes and 3) A.S. Hay used tertiary amines such as pyridine or the bidentate ligand TMEDA as complexing agents to solubilize the  $\text{Cu}(\text{I})$ -salt. Next, oxygen gas was passed through this solution to give the homocoupled product in a few minutes at room temperature in almost quantitative yield (Hay coupling conditions)



Eglinton procedure:

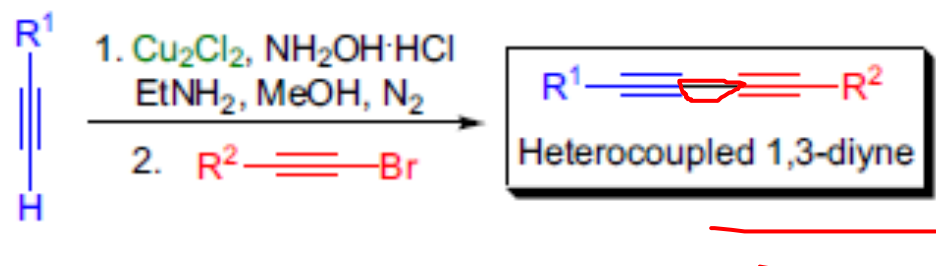


Hay's conditions:

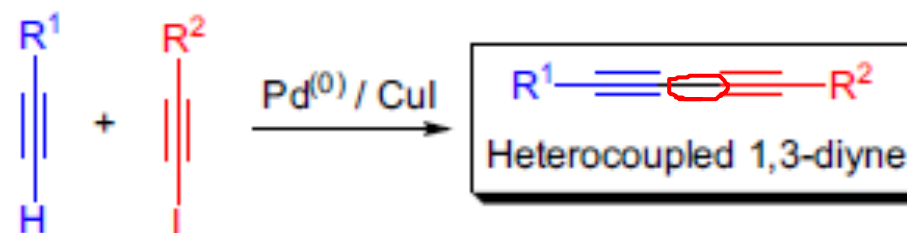




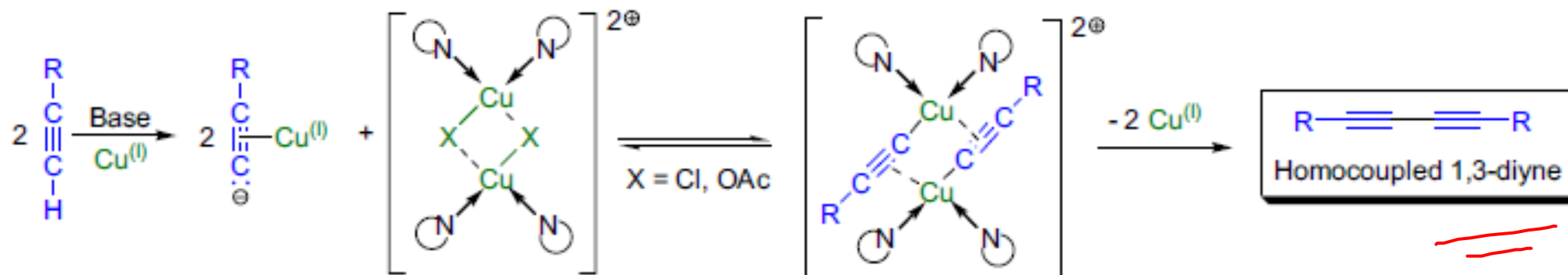
Chodkiewicz-Cadiot heterocoupling:

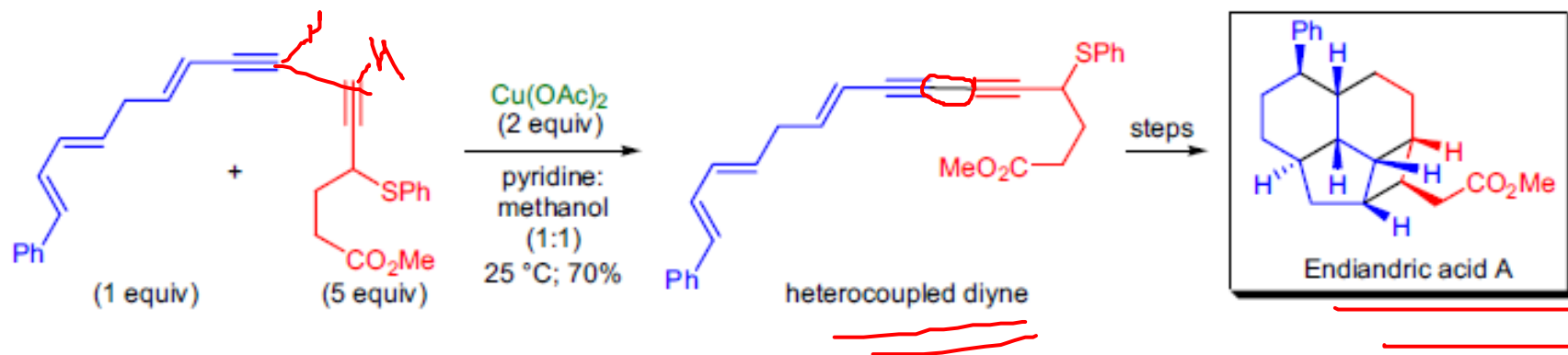
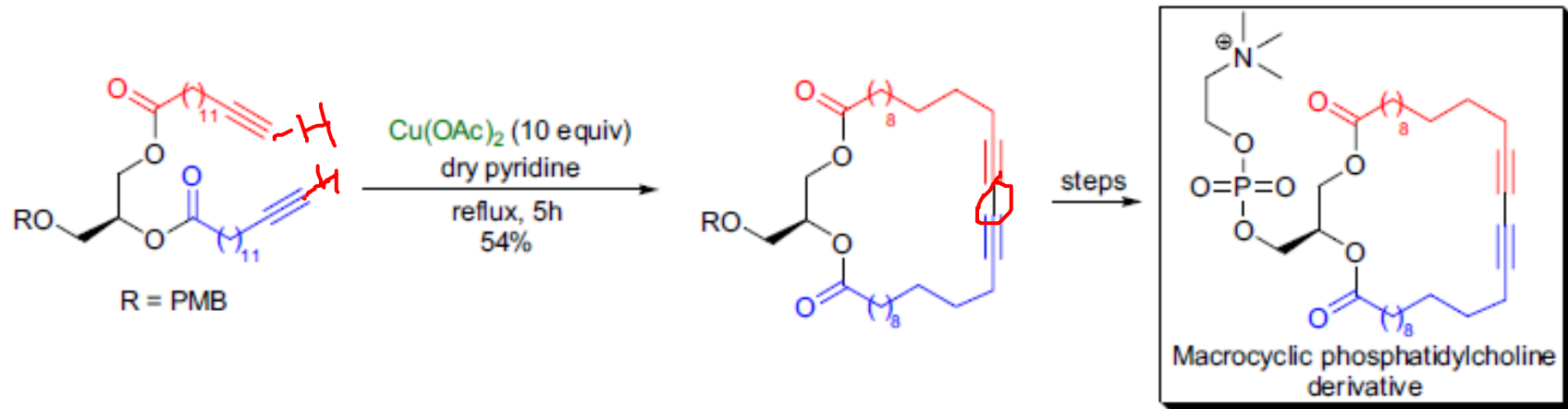


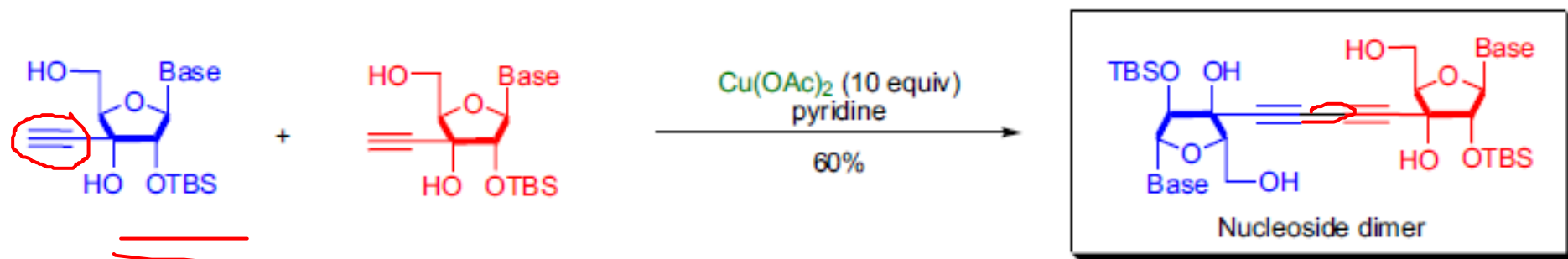
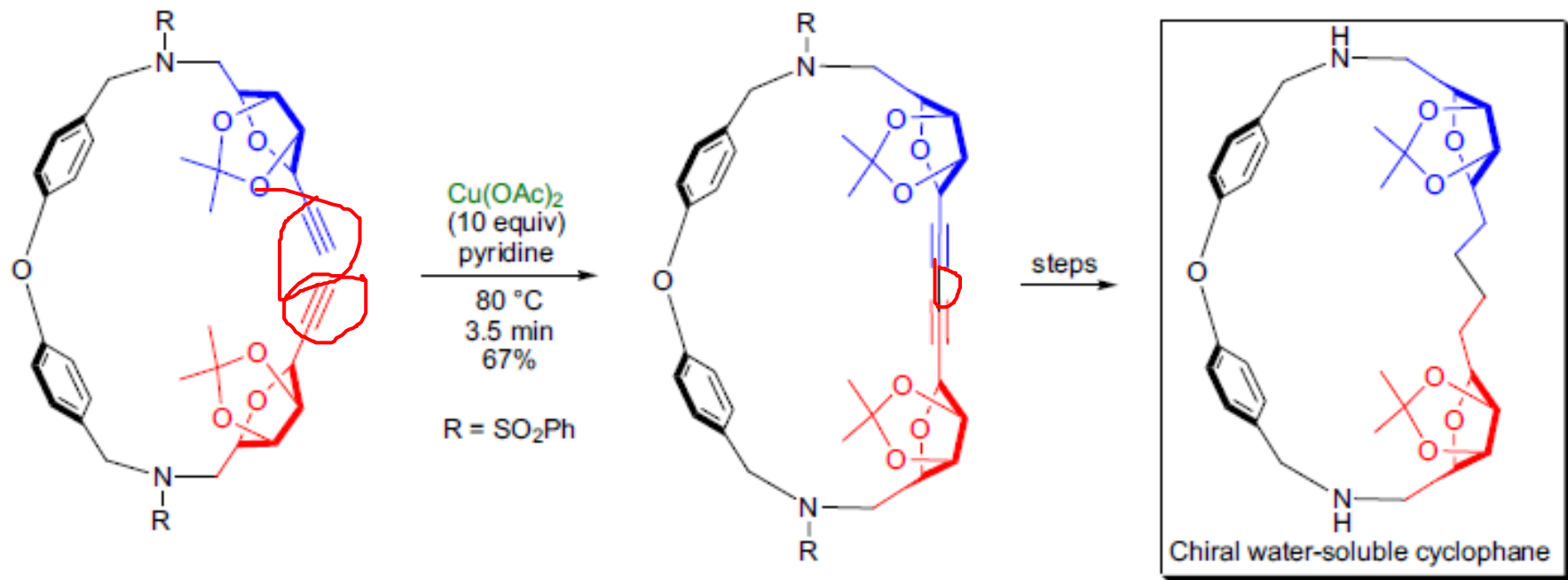
Pd-catalyzed heterocoupling:



The mechanism of the *Glaser coupling* and related methods is very complex and is not fully understood. Studies revealed that the mechanism is highly dependent on the experimental conditions. The early proposal involving a radical mechanism has been rejected. The currently accepted mechanism involves dimeric copper(II)acetylide complexes.



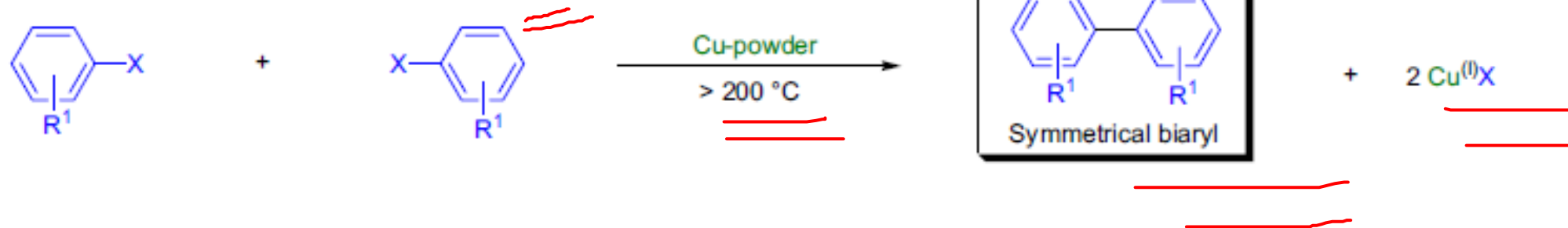




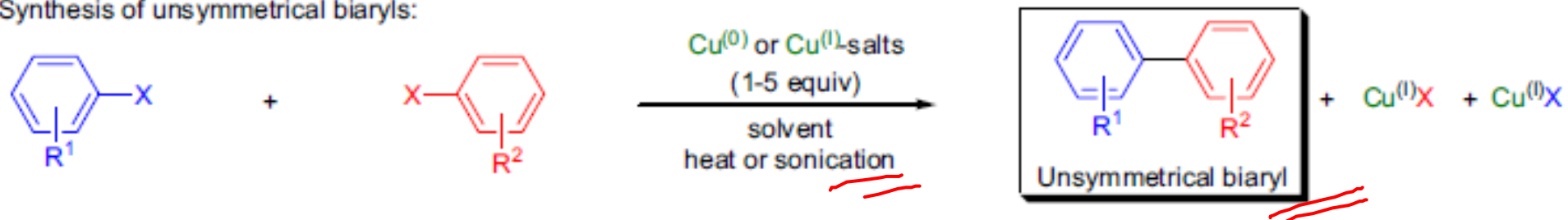
# D) Ullmann Reaction/Coupling / Biaryl Synthesis

This condensation of two aryl halides in the presence of copper to give symmetrical or unsymmetrical biaryls is now referred to as the Ullmann reaction (Ullmann biaryl synthesis or Ullmann coupling).

Synthesis of symmetrical biaryls (Ullmann, 1901):



Synthesis of unsymmetrical biaryls:

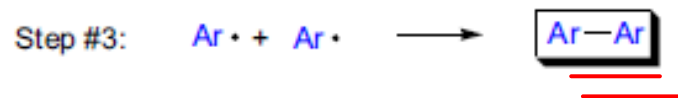
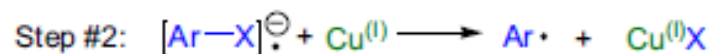
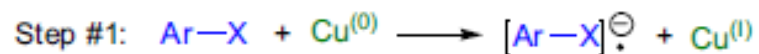


$R^1, R^2 = \text{H, CN, NO}_2, \text{CO}_2\text{R, I, Br, Cl}$ ;  $X = \text{I, Br, Cl, SCN}$ ; solvent: DMF, pyridine, quinoline, nitrobenzene, *p*-nitro toluene



The exact mechanistic pathway of the Ullmann coupling is not known. There are two main pathways possible: 1) formation of aryl radicals or 2) the formation of aryl copper [ArCu(I), ArCu(II) and ArCu(III)] intermediates. Currently the most widely accepted mechanism assumes the formation of aryl copper intermediates, since many of these species can be isolated and they can react with aryl halides to give biaryls.

Pathway involving aryl radicals:



Pathway involving arylcopper intermediates:

