

Principles of Organic Synthesis
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Lecture 17
Nucleophilic Aromatic Substitution

Welcome you all to Principles of Organic Synthesis. Presently, we study the nucleophilic aromatic substitution. So far, in this module, we had one lecture where we studied the addition-elimination and elimination-addition (benzyne) reactions.

If you remember the addition-elimination, the substrates with good leaving group at the *ortho* or *para* position with respect to the strong electron withdrawing group proceed the reaction. In that case, the nucleophile undergoes substitution via the addition followed by elimination reaction.

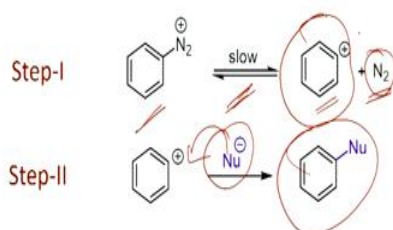
In case of elimination-addition, which involves the benzyne intermediate, if the aromatic system has halogen that is not activated, those substrates can be reacted with the strong base like sodamide to produce benzyne via elimination. Which can readily undergo addition reaction to give the carbanion that is protonated. Thus, this reaction involves elimination of HX followed by addition of the NuH.

In this lecture, we will study the reaction of diazonium salts, reactions of aryl halides with nucleophiles using solvated electrons, heat or light which involve radical intermediate. We will cover Ullmann coupling for the C-C and carbon-heteroatom bond formation with aryl halides as well as the recent developments for the C-C and carbon-heteroatom bond formation of aryl C-H bonds.

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S_N1 Mechanism

- This mechanism operates in the reaction of diazonium salts with nucleophiles
- The driving force resides in the strength of the bonding in the nitrogen molecule that makes it a particularly good leaving group



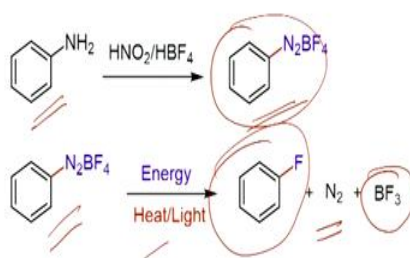
For example, if you have the diazonium salt, when you apply energy, it loses nitrogen molecule to form the carbocation, which reacts with the nucleophile. In this way you can introduce nucleophile.

The driving force resides in the strength of the bonding in the nitrogen molecule. So once if you apply the light or heat energy, it loses the nitrogen molecule, you will be able to generate the carbocation, which can undergo reaction with nucleophile. The first step is slow, and the addition of nucleophile is faster.

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Schiemann Reaction

- Diazotization of aniline in the presence of tetrafluoroborate



- Cleavage of aryldiazonium fluoroborate gives aryl cation that reacts with fluoroborate anion to yield fluorobenzene.

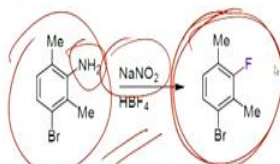
Aniline with HNO₂ and tetrafluoroborate produces aryldiazonium fluoroborate that converts to fluorobenzene on heating or expose to light. This reaction generates nitrogen and BF₃ as the products.

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Mechanism



Examples

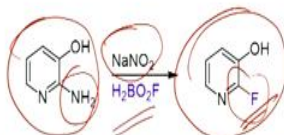


H Hant, J F Jansen, *J. Org. Chem.* **1970**, 35, 3637.

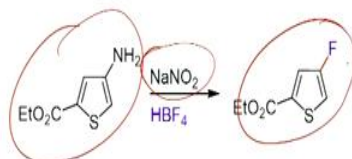
In the presence of light or heat, aryl diazonium fluoroborate loses N_2 molecule to produce aryl carbocation, which converts to fluorobenzene.

For example, the aniline derivative can be reacted with $NaNO_2$ and tetrafluoroborate to furnish the fluorobenzene derivative.

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F Dolle, I Dolei, H Valette, F Hinnen, F Vaufrey, H Guenther, C Fuscay, C Coulon, M Buttalender, C Crouzel, *J Med. Chem.* **1999**, 42, 2251.



Kiryanov, A.; Seed, A.; Sampson, P.; *Tetrahedron Lett.* **2001**, 42, 8797.

Likewise, 2-amino-3-hydroxypyridine can be reacted with $NaNO_2$ and H_2BO_2F to provide 2-fluoro-3-hydroxypyridine. Further, ethyl 4-amino-2-thiophenecarboxylate can be reacted with $NaNO_2$ and HBF_4 to give 4-fluoro-2-thiophenecarboxylate. As you can see the hydroxyl and ester groups are compatible under these conditions.

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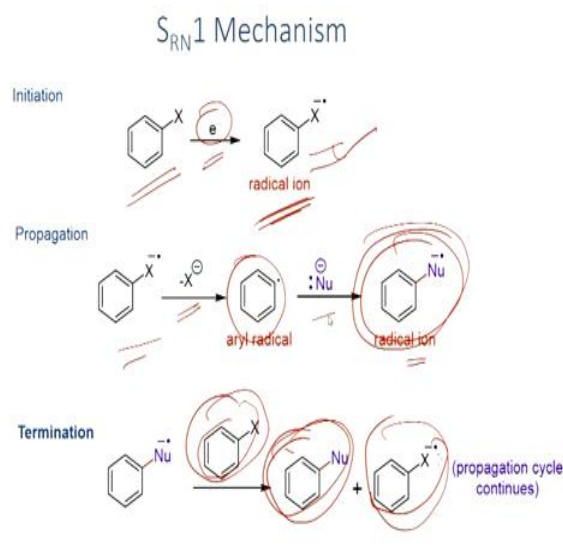
S_{RN}1 Mechanism

□ S_{RN}1 (Unimolecular Radical Nucleophilic Substitution) reaction takes place via free-radical intermediate and has wide substrate scope

- Initiation by solvated electrons
- Photochemically
- Electrochemically
- Thermally

So far we have seen the reaction of aryldiazonium fluoroborate to aryl fluoride. Now let us focus on the reaction of aryl halides that involve radical intermediate. These reactions are initiated by solvated electrons, light, heat and electrochemically.

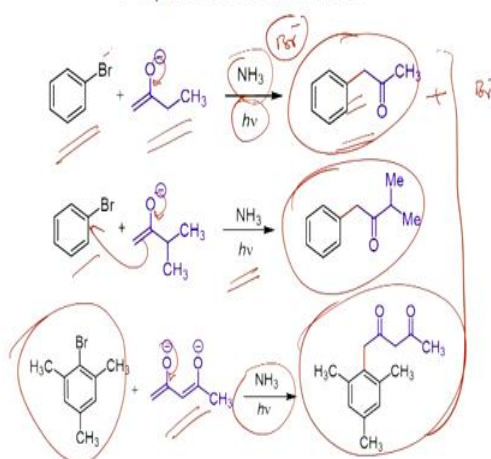
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The general mechanism of the transformation is here shown. As you can see, when you have the aryl halides, you can add electron and convert to radical ion. This is known as an initiation step. The radical ion can lose the halide ion to produce the aryl radical, which can react with nucleophile to give the radical ion. This is known the propagation step. The radical ion can transfer an electron to aryl halide to produce the nucleophile substituted compound and the aryl halide radical ion. This is the termination step.

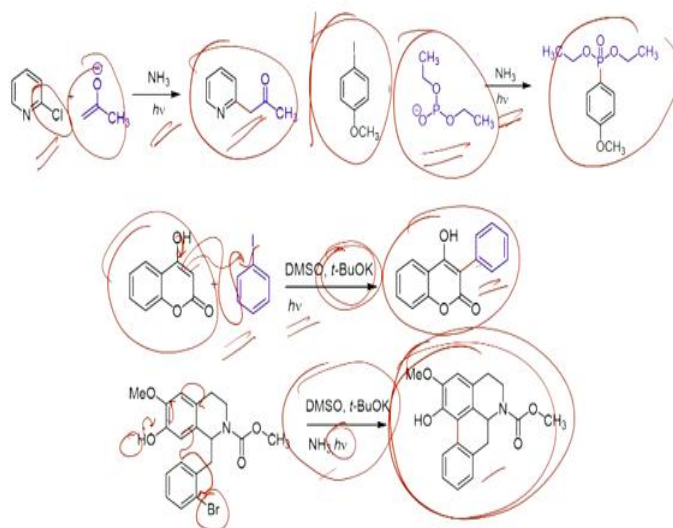
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Arylation of Ketones



Let us see the application of this synthetic strategy for the arylation of ketones. The coupling of the enolate of ethyl methyl ketone with bromobenzene can be accomplished in the presence of ammonia and light. Similarly, the enolate of isopropyl methyl ketone with bromobenzene produces the benzyl isopropyl ketone using ammonia and light. Further, 2,4,6-trimethylbromobenzene with enolate of acetylacetone produces arylated acetylacetone in the presence of ammonia and light.

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Let us see some more examples. The reaction of enolate of acetone with 2-chloropyridine can be accomplished in the presence of ammonia and light. Under these conditions, phosphite ion can be coupled with 4-iodoanisole. Further, 4-hydroxycoumarin couples with iodobenzene using potassium t-butoxide and light, whereas the intramolecular coupling of aryl bromide

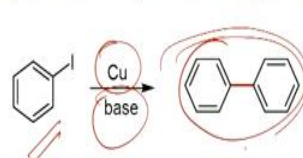
with aryl system can be accomplished using potassium t-butoxide, ammonia and light. Under these conditions, hydroxyl and ether functional groups are intact.

So far we have discussed two types of reactions. The first type involves the transformation aryl diazonium fluoroborate to aryl fluoride via the aryl carbocation intermediate under heating or light. Then, we have seen the reaction of aryl halide with nucleophile for the C-C as well as C-P bond formation via aryl radical intermediate using the solvated electron, light, heat or electrochemical.

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Ullmann reaction

□ Coupling of aryl halides in the presence of copper to yield biaryls



▪ This method of limits to electron withdrawing substituents with high yield

▪ Applicable to synthesis of unsymmetrical biaryls



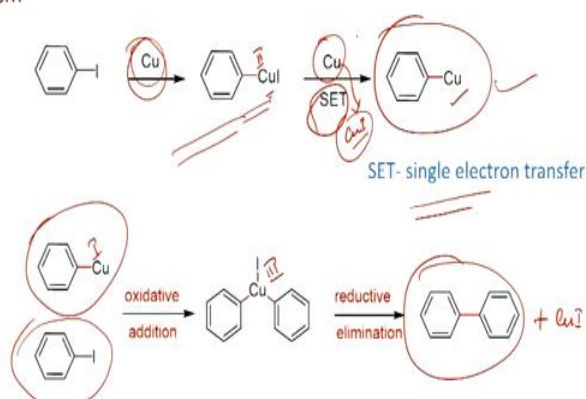
Fritz Ullmann
1875-1939

Now let us focus on the copper-based cross-coupling reactions, which are powerful synthetic tool for the carbon-carbon and carbon-heteroatom bond formation with aryl halides. In 1900, Ullmann first reported the coupling aryl iodides using copper under heating in the presence of based. This reaction has been carried out using stoichiometric amount of copper at around 150 °C.

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Ullmann Reaction

Mechanism



The mechanism of the Ullmann coupling is shown. Copper undergoes oxidative addition with iodobenzene to produce the Cu(II) species, which is converted to arylcopper(I) via the single electron transfer (SET). Oxidative addition of iodobenzene with arylcopper(I) produces diarylcopper(III) iodide, which is converted to biaryl by reductive elimination.

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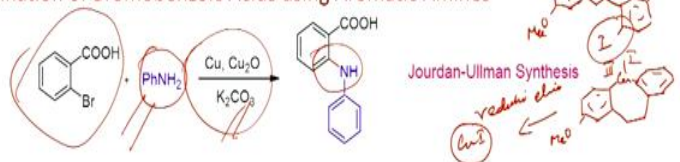
Synthesis of Phenanthrene



Coupling of Hetero-Aryl Halide



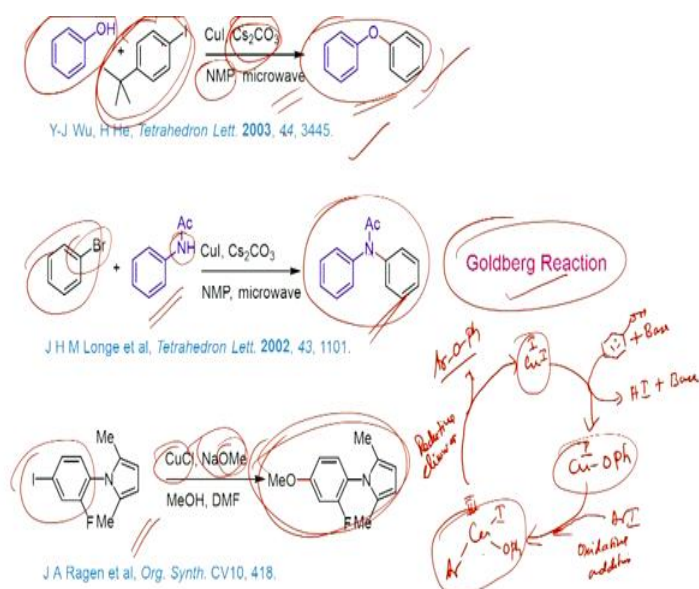
Amination of Bromobenzoic Acids using Aromatic Amines



Let us see some examples. The first one involves the intramolecular diaryl C-C coupling to give the tricyclic compound. As we have seen earlier, oxidative addition of aryl iodide with copper produces copper(II) species, which is converted to arylcopper(I) by SET. Oxidative addition with aryl iodide gives copper(III) that can give the tricyclic compound via the reductive elimination.

Similarly, the homocoupling of 2-bromopyridine can be accomplished using $\text{Cu}(\text{OTf})_2$ in the presence of ammonia. All these reactions involve homocoupling via C-C bond formation. The strategy can be applied for the carbon-heteroatom coupling. For example, 2-bromobenzoic acid couples with aniline via C-N bond formation employing a mixture of copper and copper(I) oxide in the presence of K_2CO_3 . This is known as Jourdan-Ullmann synthesis.

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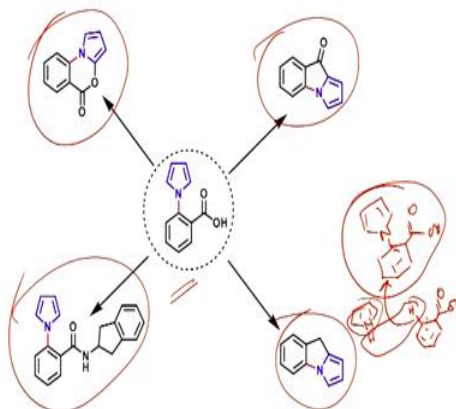
Let us see some examples for the carbon-heteroatom bond formation. The first example involves the coupling of phenol with 4-*tert*-butylaryl iodide using CuI under microwave irradiation. Reaction of phenoxide with CuI will produce copper(I) phenoxide, which can undergo oxidative addition to give copper(III) species that can give the product by reductive elimination.

The next example involves the coupling of aryl bromide with N-acetylaniline using CuI to give N-acetylbiarylamine, which is known as Goldberg reaction.

The other example involves the coupling of NaOMe with aryl iodide to give aryl methyl ether derivative. These reactions are carried out in the presence of base to remove the hydrogen halide is generated.

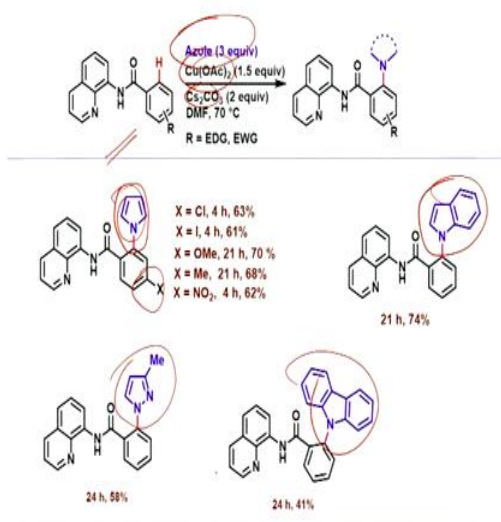
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C-H Functionalization Synthetic Utilities of 2-Pyrrole Benzoic Acid



Recently, efforts are made on the carbon-nitrogen bond formation via C-H functionalization. This is attractive because atom economical and can have broad substrate scope. For example, 2-pyrrolbenzoic acid acts as the precursor for the preparation a variety of medicinally important compounds. Thus, development C-H functionalization strategy for the construction of 2-pyrrolebenzoic would be valuable.

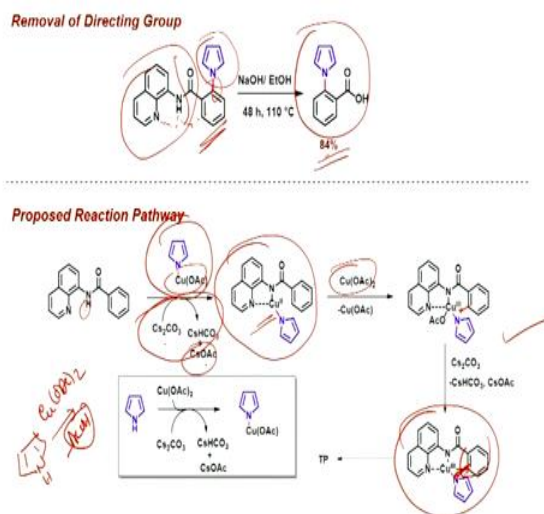
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P. Sadhu, T. Punniyamurthy, Chem. Commun. 2016, 52, 2803.

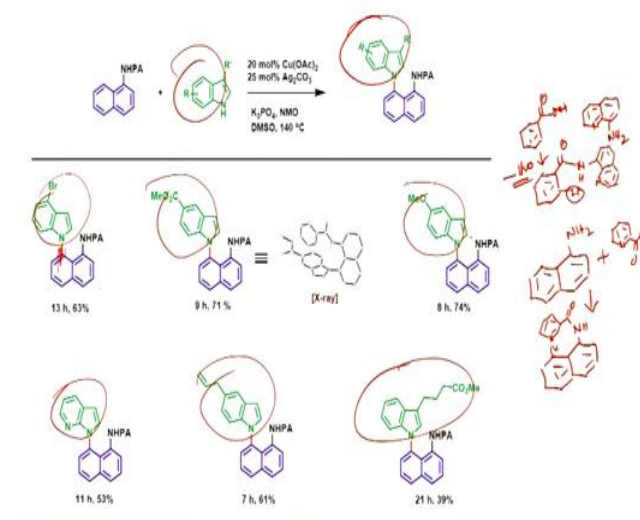
Here the coupling of a series of azoles with 8-aminoquinoline benzamides is shown using $\text{Cu}(\text{OAc})_2$ in the presence of base. The excess of azoles and $\text{Cu}(\text{OAc})_2$ are needed because of their complex formation. The *ortho* C-H bond of benzamide can be selectively coupled with azole to give the C-N coupled product.

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The chelating group, 8-aminoquinoline, can be removed by base hydrolysis to produce 2-pyrrolebenzoic acid, which we have seen as the substrate precursor for the construction of a variety of heterocycles. The mechanism involves the reaction of azole with $\text{Cu}(\text{OAc})_2$ to produce $\text{Cu}(\text{II})$ species, which reacts with the substrate to give the copper(II) intermediate. Oxidation of $\text{Cu}(\text{II})$ to $\text{Cu}(\text{III})$ by redox process, followed by C-H activation, can give the copper(III) species, which gives the product via the reductive elimination. In this reaction, 8-aminoquinoline acts as the directing group, which assists the chelation with $\text{Cu}(\text{OAc})_2$ to produce the active $\text{Cu}(\text{III})$ that activates benzamide *ortho* C-H bond through cyclometalation.

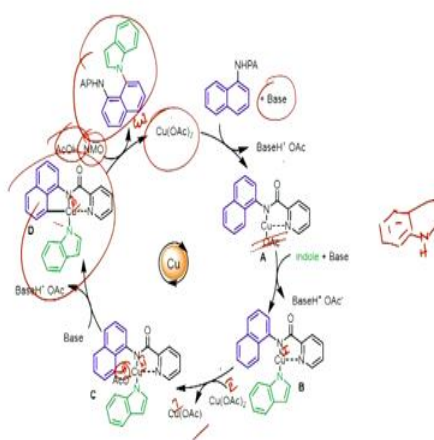
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Just we have seen the *ortho* C-H functionalization 8-aminoquinoline benzamides that are prepared from benzoic acid and 8-aminoquinoline. Similarly, the functionalization of the γ -C-H bond of N-(naphthyl)picolinamide, that can be prepared from 1-naphthylamine and picolinic acid, can be achieved. The coupling of indole is effective using $\text{Cu}(\text{OAc})_2$, where Ag_2CO_3 acts as an additive and NMO is used as the oxidant. The catalytic system is effective for the coupling of a series of substrates.

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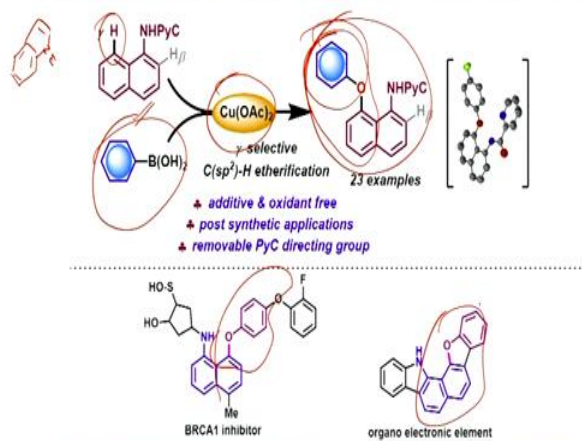
Proposed Catalytic Cycle



Substrate with $\text{Cu}(\text{OAc})_2$ produces Cu(II) species **A**, which reacts with indole to give Cu(II) species **B**. The transformation of Cu(II) to Cu(III) by redox process gives **C**, which activates the C-H bond through cyclometalation to give **D**. Reductive elimination gives the product.

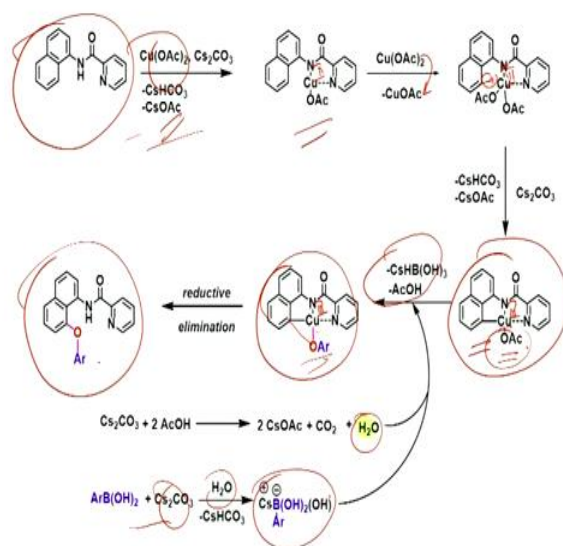
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Etherification of Naphthylamides with Boronic Acid



The reaction is extended to the coupling aryl boronic acid. Interestingly, the corresponding ethers are formed. Mechanistic studies suggest that the ether oxygen comes from water. Aryl ethers are important compounds, which are usually prepared from phenols with aryl halides via C-O cross-coupling.

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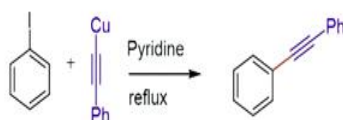


The mechanism of the transformation is here shown. The substrates with Cu(OAc)_2 forms the copper(II) species. Which is oxidized to copper(III) by redox process, which can activate the C-H bond through cyclometalation. Aryl boronic acid with base and water generates the salt, which reacts with copper(III) to produce substituted copper(III) species that can give the product by the reductive elimination.

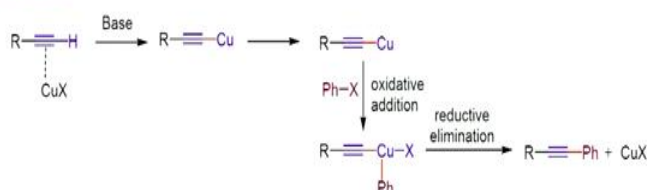
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Stephens-Castro coupling

□ Unactivated aryl halides react with copper acetylides to give disubstituted acetylene derivative



Mechanism



So far we have seen the C-N and C-O bond formation with aryl C-H bonds. Now let us see the arylation of terminal alkyne with aryl halide. For example, aryl iodide couples with copper(I) acetylide to give diaryl acetylene in the presence of pyridine. Phenylacetylene with Cu(I) halide in the presence of base produces copper(I) acetylide, which undergoes oxidative addition with aryl iodide to give the copper(III) species that gives the diaryl acetylene via the reductive elimination. The reaction is known as Stephens-Castro C-C coupling.

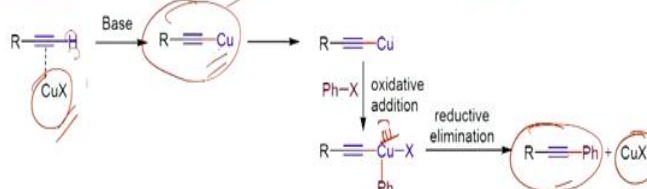
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Stephens-Castro coupling

□ Unactivated aryl halides react with copper acetylides to give disubstituted acetylene derivative

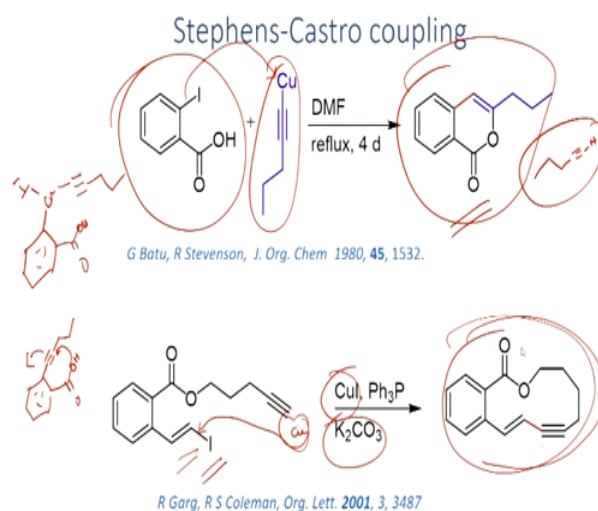


Mechanism



In the Stephens-Castro coupling, terminal alkyne reacts with copper(I) halide to produce copper(I) acetylide that undergoes oxidative addition with aryl halide to produce copper(III) species, which gives C-C coupled product via reductive elimination.

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Let us see some examples. The first one involves the coupling of copper(I) acetylide with 2-iodobenzoic acid to give the bicyclic lactone. In this reaction, copper(I) acetylide couples to give 2-alkynyl benzoic acid, which undergoes intramolecular cyclization to give the lactone, which can be assisted by the copper via chelation to the double bond.

The reaction conditions can be extended to the coupling of vinyl iodide. For example, the intramolecular C-C coupling of vinyl iodide with copper(I) acetylide can be accomplished to produce the macrocyclic lactone. Stephens-Castro coupling finds broad utilities in synthetic chemistry.

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Summary

- ❖ S_N1 Mechanism
- ❖ $S_{RN}1$ Mechanism (radical ion)
- ❖ Ullmann Coupling
- ❖ C-H Functionalization
- ❖ Stephens-Castro coupling

In summary, we have seen the reaction of aryldiazonium fluoroborate to aryl fluoride. This reaction is carried out under heat or light via aryl cation intermediate.

We have the reaction of aryl halides with nucleophiles using solvated electrons, heat, light or electrochemically. These reactions involve aryl radical intermediate.

We have seen the coupling of aryl halides with aryl halides, phenol and amines using copper based systems. The reaction was discovered in the beginning 1900 and known as Ullmann coupling. This reaction affords powerful synthetic for the C-C, C-N and C-O coupling reactions. Since the original reaction involves stoichiometric amount of copper and elevated temperature, efforts have been made for the past two decades to develop catalytic systems at milder reaction conditions.

Efforts are also made for the C-C, C-O and C-N bond formation with aryl C-H bond using transition-metal-catalyzed reactions. We have seen coupling of azoles with aryl and naphthyl systems using directing groups. We have also seen the introduction of aryl ether moiety in the naphthyl system via C-H functionalization where the oxygen comes from water.

Finally, we have seen the coupling of terminal alkynes with aryl and vinyl halides that can lead to macrocyclic systems, with this we conclude this lecture. Thank you very much.