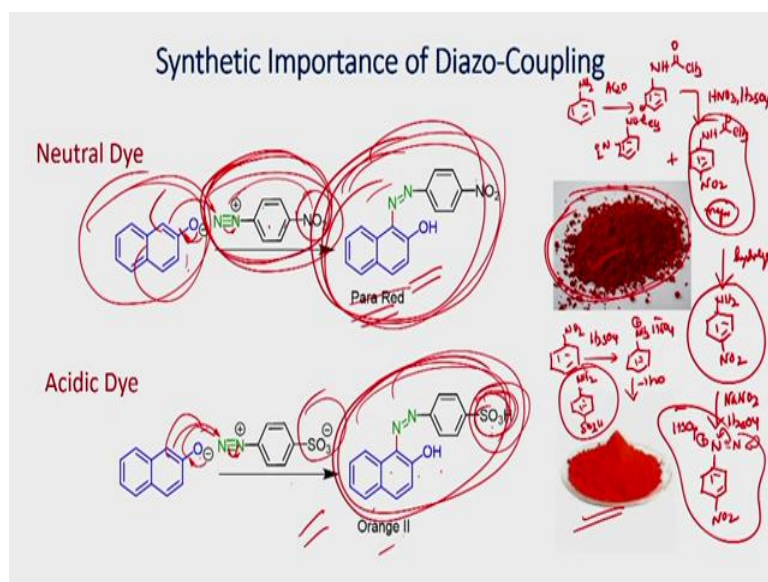


Principles of Organic Synthesis
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Lecture 21
Aromatic Diazonium Salts

Welcome you all to Principles of Organic Synthesis. At present, we study the aromatic diazonium salts. In this topic, we had two lectures focusing on the preparation and reaction of the diazonium salts. In this lecture, we will continue to learn the application of the diazonium salts in the synthetic and material sciences.

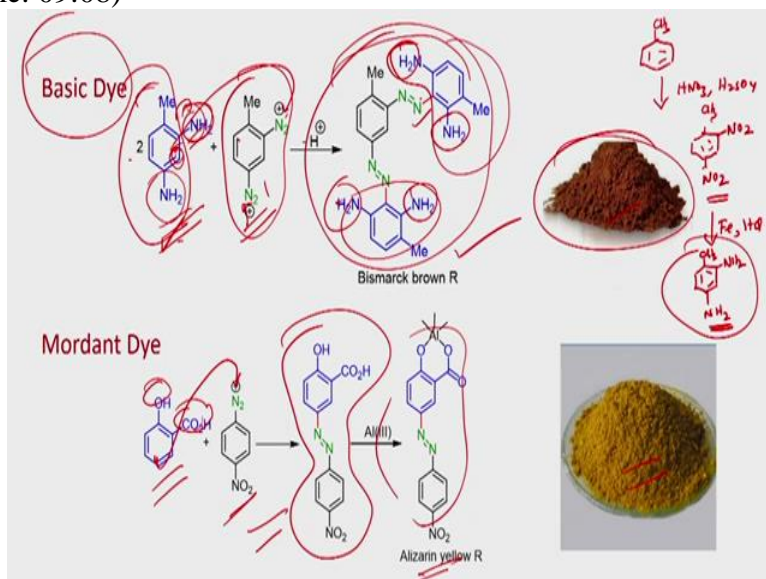
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Let us begin with the application of the diazonium salts in dye synthesis. The first example involves the reaction of naphthalene oxide with 4-nitrophenyldiazonium salt to produce the *para* red, which we use to make the colour of the wool, paper and many other materials. Aniline with acetic anhydride produces acetanilide, which leads to nitration at *p*-position as the major product using nitric acid in the presence of sulfuric acid. Hydrolysis followed by the diazotization of 4-nitroaniline using nitrous acid and HCl produces the diazonium salt.

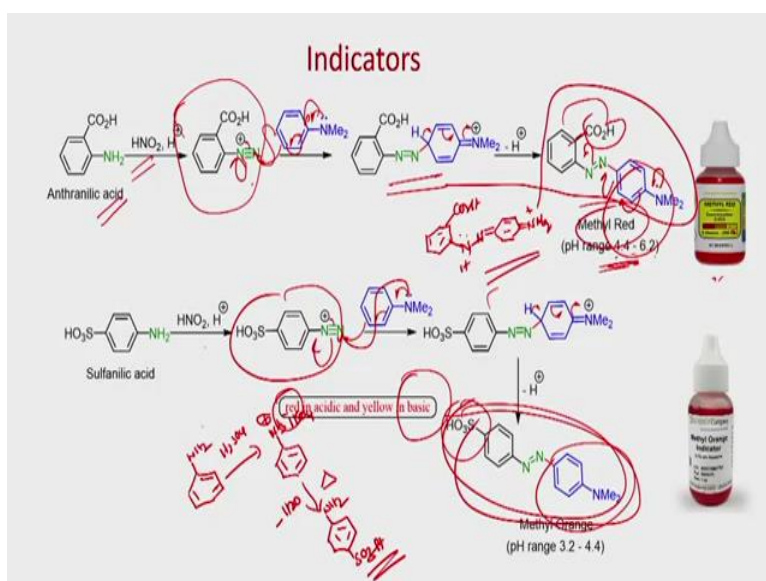
The next example involves the preparation of the orange II acidic dye using naphthalene oxide with diazoniobenzenesulfonate. Aniline with sulfuric acid gives the salt, which on heating rearranges to sulfanilic acid that can be diazotized using NaNO₂ and H₂SO₄. We utilize this dye for colouring of materials like paper and wool. The sulfonate can strongly bind with the material.

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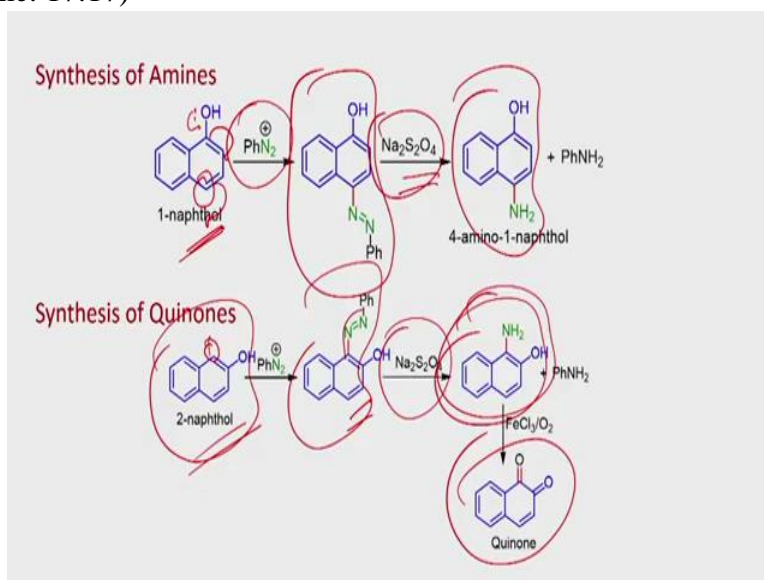
Here let us look at the use of 2,4-diaminotoluene as the substrate precursor for the preparation of the diazonium cation as well as the coupling partner for the diazo coupling to produce bismarck brown R. Nitration of toluene can produce 2,4-dinitrotoluene, which can be reduced to 2,4-diaminotoluene using Fe/HCl. Diazotization using nitrous acid and HCl can produce the diazonium salt, which can be coupled using two equiv of 2,4-diaminotoluene to furnish the dye. Since this dye has four free NH₂, we call as basic dye that finds applications to colour the material for example nylon. The next example involves the diazo coupling of salicylic acid with 4-nitrobenzenediazonium salt to give alizarin yellow R, which we use as the pH indicator. This dye can be complexed with aluminium(III) salt and linked to wool and other materials.

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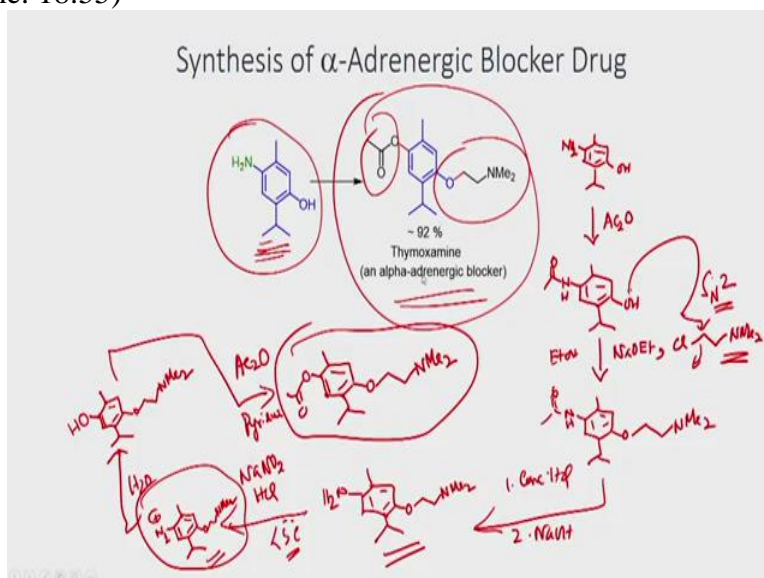
Here is the preparation of pH indicators. The first example involves the diazotization of anthranilic acid using nitrous acid followed by the diazo coupling with dimethylaniline to produce methyl red. Similarly, diazotization of sulfanilic acid using nitrous acid gives the diazonium salt, which can be reacted with dimethylaniline to furnish methyl orange.

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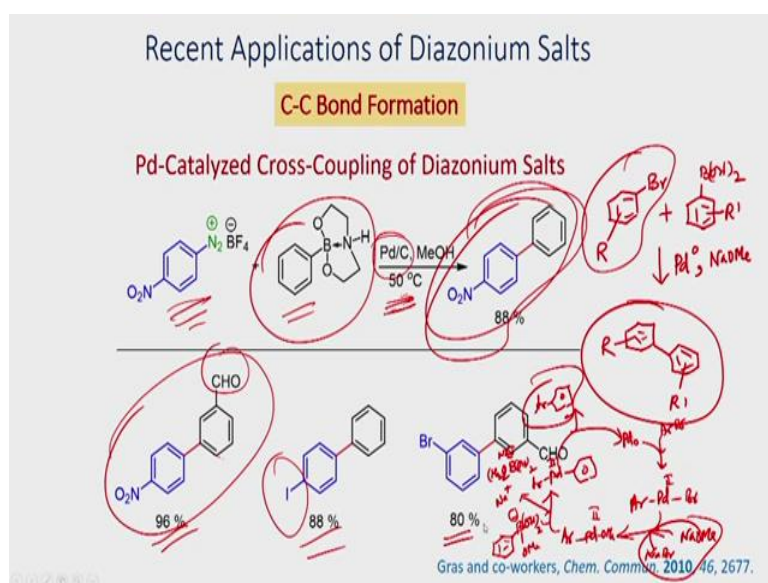
Now, let us look at the application for the synthesis of substituted aromatic compounds. For example, 1-naphthol with phenyldiazonium salt gives the azo compound, which is reduced to 4-amino-1-naphthol using $\text{Na}_2\text{S}_2\text{O}_4$. Similarly, 2-naphthol with phenyldiazonium salt yields the azo coupling, which can be reduced to produce 1-amino-2-naphthol that can be oxidized to quinone using FeCl_3 under oxygen atmosphere.

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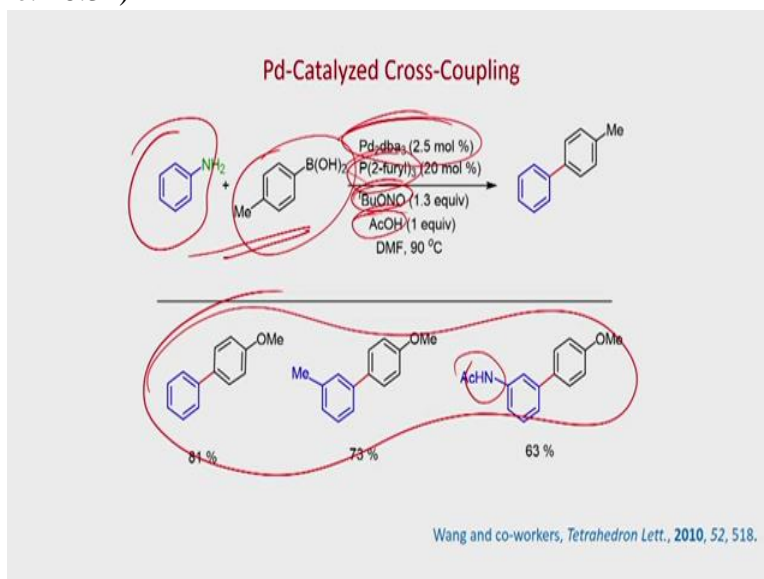
The next example involves the application of diazonium salt in medicinal chemistry. Let us look at this substituted phenol, which has been converted to thymoxamine that is widely used in urology. Protection of the amino group using acetic anhydride followed by S_N2 reaction of the OH group with 2-chloro-N,N-dimethylethanamine produces O-alkylamine. Hydrolysis of acetamide followed by diazotization using nitrous acid produces the diazonium salt, which reacts with water in acidic medium to give the phenol derivative. Acetylation using acetic anhydride in the presence of pyridine affords thymoxamine. So the diazonium salts find broad utilities not only in synthetic chemistry, we can also use in medicinal science.

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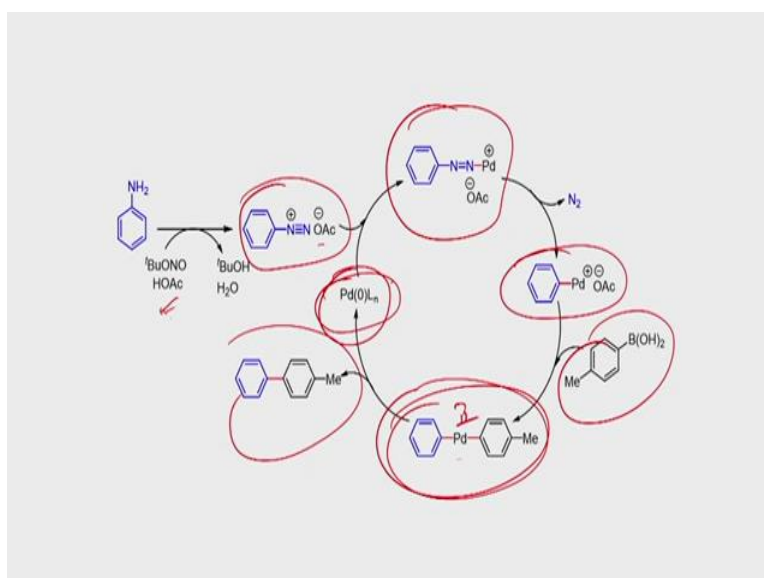
Now let us see the application of aryldiazonium salts for the Pd-catalyzed C-C cross-coupling reactions. For example, the C-C cross-coupling of 4-nitrobenzenediazonium fluoroborate with borane is successful using Pd/C to produce the biaryl compound with good functional group tolerance. If you remember the Suzuki C-C cross-coupling of aryl halide with boronic acid to give the biaryl compound, where aryl halide undergoes oxidative addition with Pd(0) to give the Pd(II) species, which reacts with external base. Similarly, the base activates the boronic acid, which reacts with Pd(II) species via the transmetalation. *Cis-trans* isomerization followed by the reductive elimination gives the biaryl compound with Pd(0) to complete the catalytic cycle.

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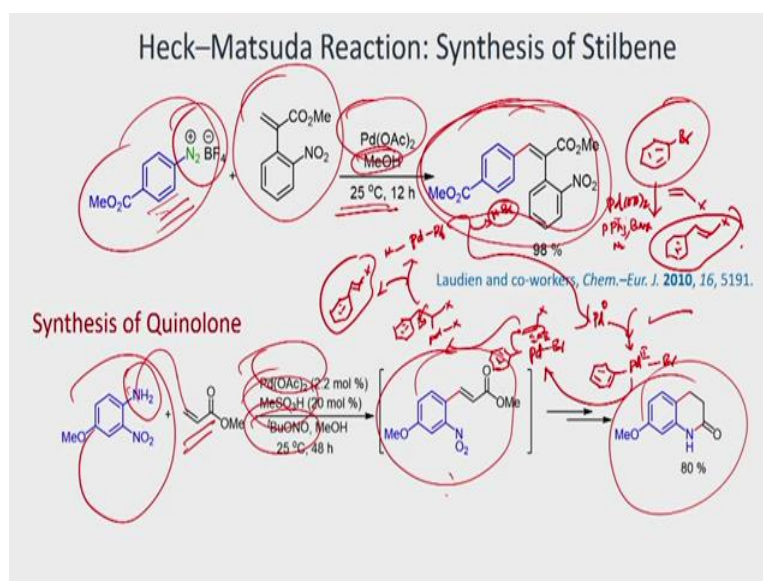
Similarly, the coupling of the aryldiazonium acetate can be coupled with boronic acid using Pd-catalysis to produce the biaryl compound. For example, aniline with organic nitrite in AcOH produces the phenyldiazonium acetate, which couples with boronic acid using the Pd-catalysis to give the biaryl compound with functional group diversity. If you remember we have seen that the diazonium salt using organic nitrite in AcOH can be precipitated using ether. Thus, the diazonium acetate can be isolated and used for the cross-coupling reactions.

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The diazonium acetate reacts with Pd(0) complex to give Pd(II) species, which loses nitrogen to give aryl Pd(II) species. Transmetalation with boronic acid gives the diaryl Pd(II) species, which gives the biaryl by the reductive elimination.

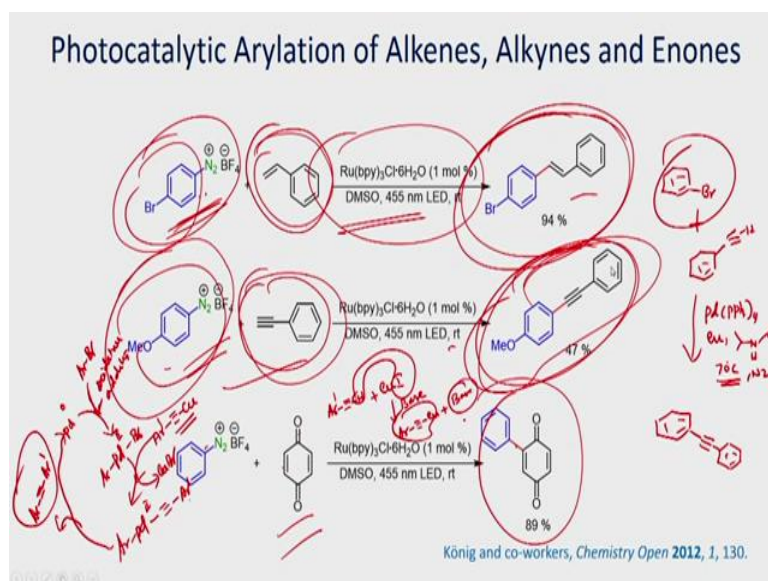
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Here the Pd-catalyzed C-C cross-coupling of the aryldiazonium fluoroborate with activated alkene is shown at room temperature. If you remember the Heck reaction, where aryl halide undergoes an oxidative addition with Pd(0) to give Pd(II) species, which makes chelation with alkene and insertion takes place to produce Pd(II) species. *Syn*- β -Hydride elimination produces styrene and H-Pd-X species, which converts to Pd(0) to complete the catalytic cycle and base is essential to remove HX.

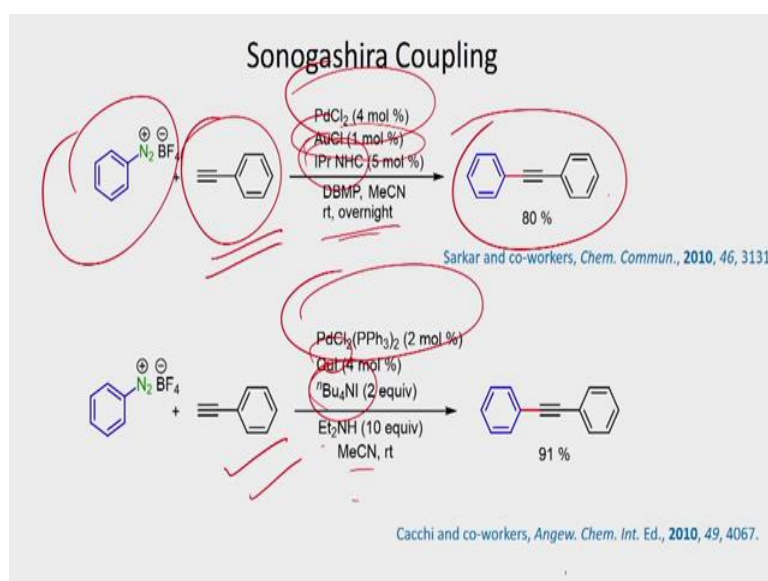
The next example shows the diazotization of aniline derivative with organic nitrite and methanesulfonic acid to give the diazonium acetate, which has been reacted with methyl acrylate to produce the cinnamic ester that has been converted to 3,4-dihydroquinolinone. Therefore, if you have the diazonium salt, which can be readily reacted with activated alkene in the presence of Pd-catalysis.

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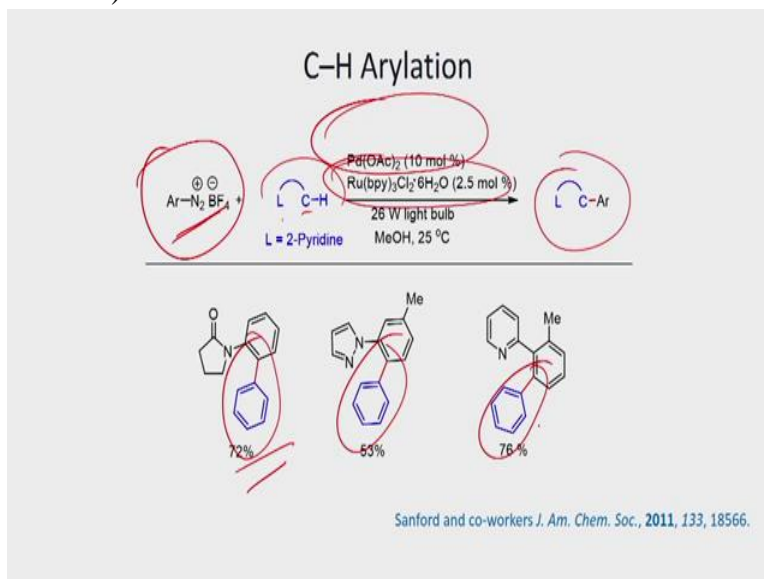
Efforts are also made on the coupling of the diazonium salt with alkene as well as alkyne using photocatalysis. The first example shows the C-C cross-coupling of the aryldiazonium fluoroborate with styrene using Ru-based photocatalysis. These reaction condition is also effective for the coupling of the diazonium salt with terminal alkyne as well as benzoquinone. These are the important advances in the development of sustainable technologies. If you remember Sonogashira coupling, where aryl halide undergoes oxidative addition with Pd(0) to give the Pd(II) species. While terminal alkyne reacts with copper(I) halide in the presence of base to give copper(I) alkyne species that reacts with Pd(II) species via the transmetalation to give aryl alkynyl Pd(II) that gives Pd(0) and alkynyl arene by the reductive elimination.

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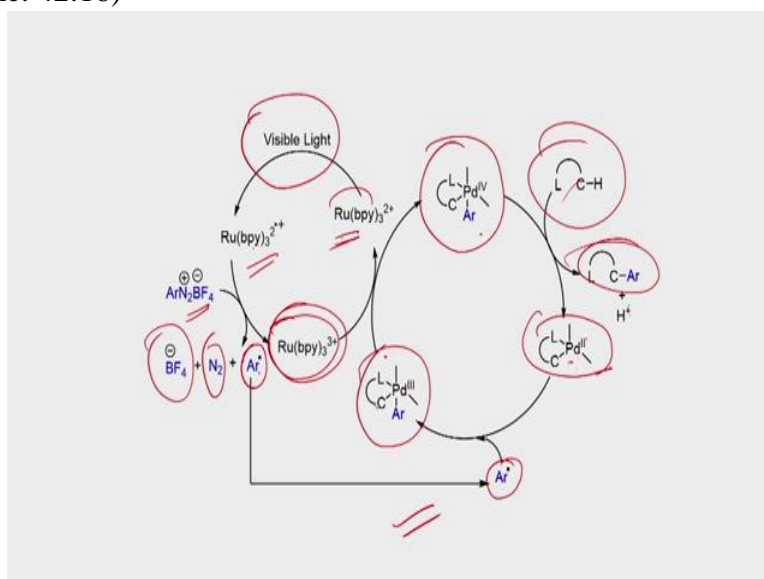
Here are examples for the Sonogashira coupling of aryldiazonium fluoroborate with terminal alkyne using Pd-catalysis. The first example shows the C-C coupling of phenyldiazonium fluoroborate with phenylacetylene using Pd(II)-NHC and AuCl to produce diphenylacetylene. The second example uses the combination of PdCl₂(PPh₃)₂ and CuI to accomplish the same transformation in higher yield. The advantage of the reactions is they are effective at room temperature.

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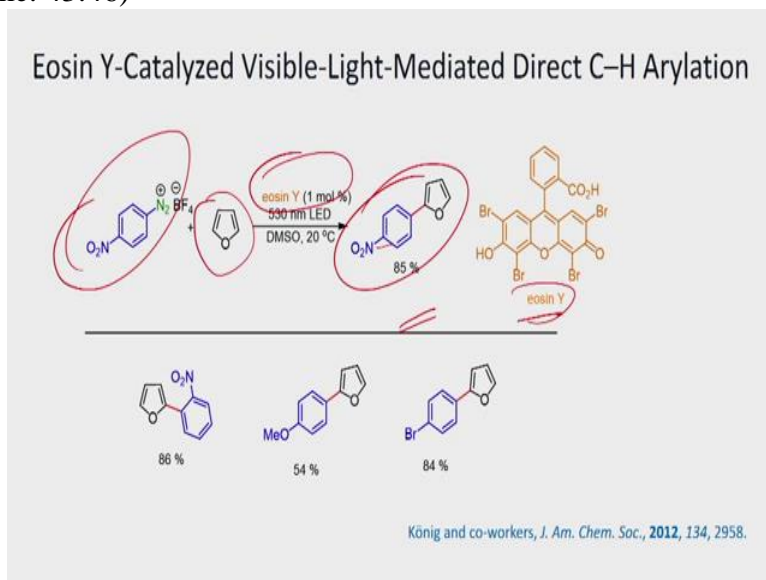
Now let us look at the chelation assisted Pd-catalyzed C-H arylation using aryldiazonium fluoroborates with Ru-photocatalysis. The reaction is effective at room temperature with good substrate scope.

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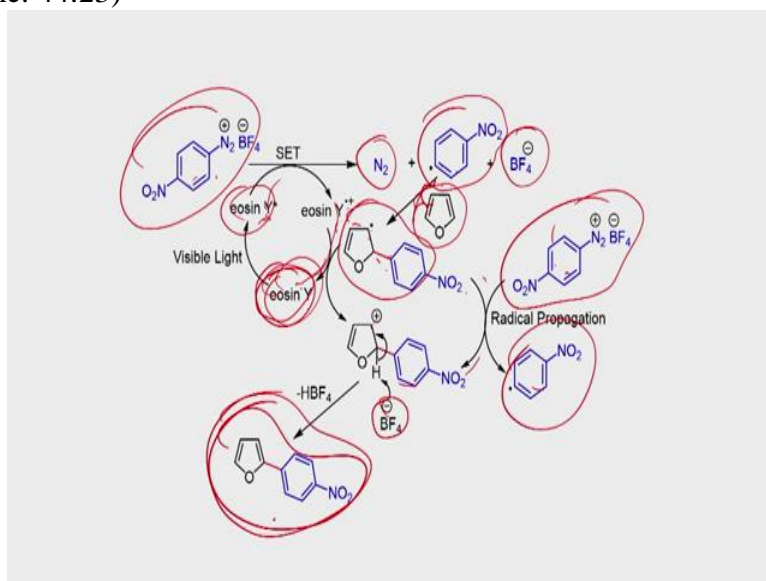
$\text{Pd}(\text{OAc})_2$ makes chelation with the substrate and activates the C-H bond to produce $\text{Ar}'\text{-Pd}(\text{II})$. While $\text{Ru}(\text{II})$ using light converts the aryldiazonium fluoroborate to Ar radical, which with $\text{Ar}'\text{-Pd}(\text{II})$ produces $\text{Ar}'\text{Pd}(\text{III})\text{-Ar}$ that converts to $\text{Ar}'\text{Pd}(\text{IV})\text{-Ar}$ to reduce $\text{Ru}(\text{III})$ to $\text{Ru}(\text{II})$. Reductive elimination of $\text{Pd}(\text{IV})$ to $\text{Pd}(\text{II})$ produces the arylated product.

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Here the organophotocatalysis of aryldiazonium fluoroborate with furan is shown to produce arylation product.

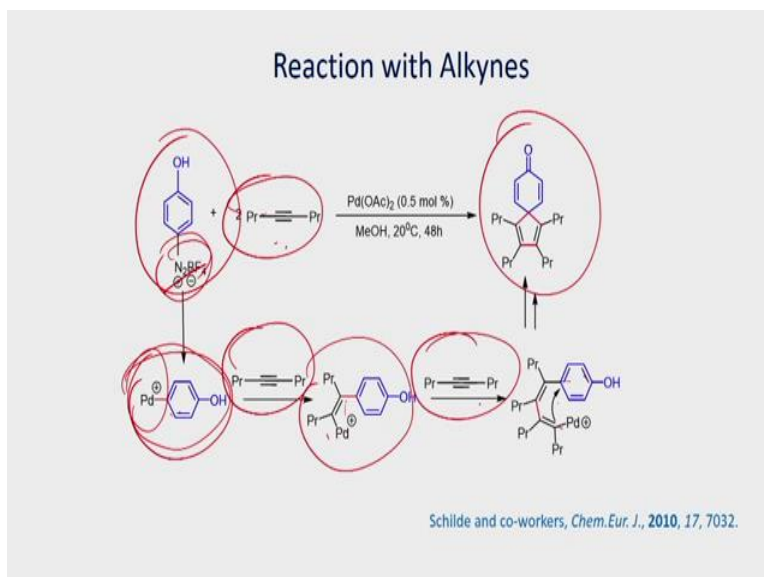
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Eosin Y in the presence of light reduces the aryldiazonium salt to aryl radical via single electron transfer (SET). The aryl radical then undergoes addition reaction with furan to

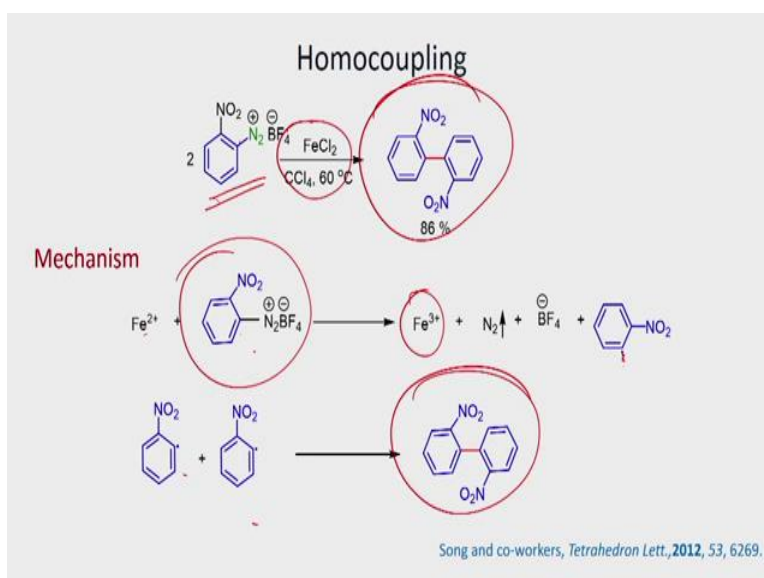
produce the furyl radical that converts to furyl carbocation. Deprotonation using fluorate anion gives the 2-arylfuran.

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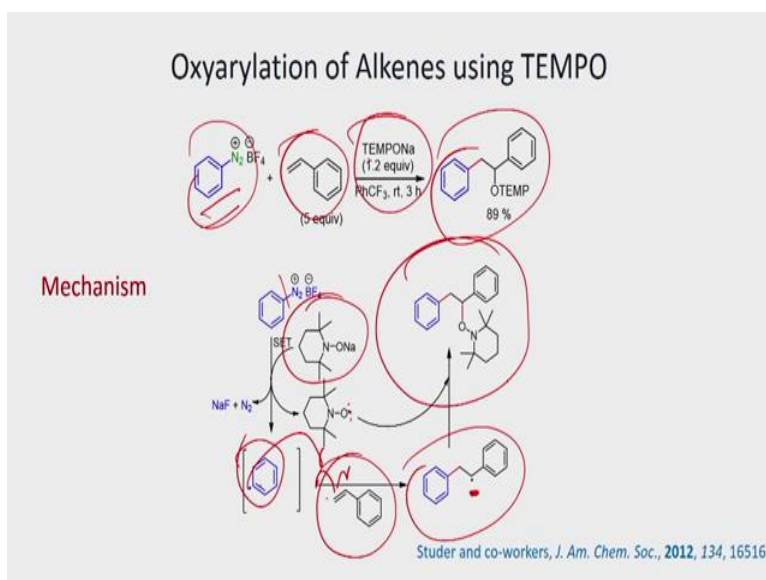
Here a Pd-catalyzed coupling of internal alkyne with phenoldiazonium fluoroborate produces 1,2,3,4-tetraphenylspiro[4.5]-deca-1,3,6,9-tetraene-8-one. Diazonium salt with Pd(II) gives phenol-Pd(II) species by the replacement of nitrogen. Tandem double insertion with two molecules of alkyne followed by cyclization with aryl ring gives the spirocyclic compound.

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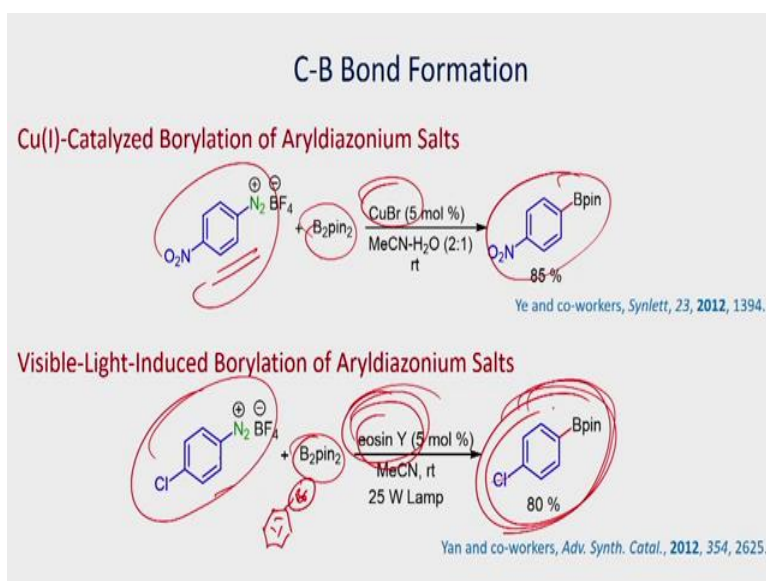
Here is the homocoupling of the aryldiazonium fluoroborate using FeCl_2 to produce biaryl compound. In this reaction, the diazonium salt is reduced using FeCl_2 to produce the aryl radical, which is dimerized to the biaryl compound.

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Phenyldiazonium fluoroborate reacts with TEMPO to produce the aryl radical via SET. Addition of the aryl radical with the double bond of styrene gives the benzyl radical that can be trapped by TEMPO in high yield.

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The aryldiazonium fluoroborate can be reacted with pinacol borane using CuBr to produce the aryl boronate. This transformation is also effective using eosin Y based photocatalysis at room temperature.

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In summary, the first part focused on the utilization aryldiazonium salts for the preparation of dyes, pH indicator, synthetic and medicinal compounds, while the second part covered the use of aryldiazonium fluoroborate for the Suzuki, Heck and Sonogashira C-C cross-coupling reactions. Efforts are also made for the direct C-H arylation using the combination of Pd-catalyzed C-H activation and Ru-based photocatalysis. Progress has also been made on the use of photocatalysis for the C-C coupling of the aryldiazonium fluoroborate with alkenes. The coupling of pinacol borane with the aryldiazonium fluoroborate has also been successful using CuBr as well as eosin Y photocatalysis. Aryldiazonium salts are thus important substrate precursors, which find broad utilities in synthetic, medicinal and material sciences. With this we conclude this lecture. Thank you very much.