Application of Palladium Chemistry in Organic Synthesis Techniques

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Article Synopsis

The Larock Indole Synthesis is a method, discovered by Richard Larock in 1991, to produce indole, an important biological molecule. In this literature review, Ghosal talks about the historical overview, the advantages of the Larock Indole synthesis over earlier techniques, and the mechanism of the reaction. Ghosal also elaborates the various applications of this technique in organic chemistry.

Application of Palladium Chemistry in Organic Synthesis Techniques: the Larock Indole Synthesis, a Literature Review

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Abstract

As one of the most important biologically active and naturally occurring molecules, indole is an organic compound of great importance. For more than a century, the standard method of lab preparation of the indole family of compounds has been the Fischer indole synthesis. In 1994, Richard C. Larock and Eul Kgun Yum prepared indole and indole derivatives using a new technique involving organometallic chemistry, what has since then come to be known as the Larock indole synthesis [1]. In this literature review, we give a background to the techniques involved in the Larock indole synthesis, including similar precursor methods in palladium chemistry. We mention the motivations for this reaction method, based on earlier work done. We then give a detailed overview of Larock's work, including the reaction mechanism, kinetic effects, and effects of substituents. We also consider limitations of the Larock indole synthesis. We then study the various applications of this synthesis technique, especially synthesis of those compounds with pharmaceutical applications. We also then consider improvement to Larock's original work, including newer, more improved techniques that built on Larock's work, and how these newer discoveries are more beneficial to us. We end this review paper with some future questions to pursue.

Keywords: larock indole synthesis, organic synthesis, indole, palladium chemistry, organometallic chemistry

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Relevance and Justification

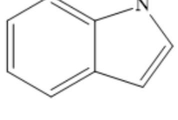

Fig 1a: Indole

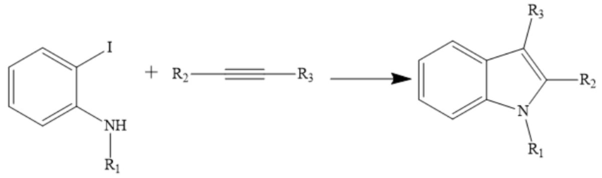

Fig 1b: Overall Reaction in Larock Indole Synthesis

Indole (Fig 1a) is one of the most important biologically active molecules and is a key example of an aromatic heterocyclic compound, composed of two rings. For example, it is a biological precursor to the synthesis of the essential amino acid tryptophan, which is also crucial to the synthesis of the neurotransmitter serotonin. After tryptophan is converted into 5-HTP, it is converted into serotonin, a neurotransmitter that relays signals between brain cells. 5-HTP dietary supplements help raise serotonin levels in the brain. Thus, effective laboratory and industrial preparation of indole has been a significant achievement in organic chemistry.

History and Introduction:

Fischer Indole Synthesis: Overview and Limitations

One of the earliest syntheses of indole is the landmark Fischer indole synthesis (Fig 2), which used phenylhydrazines [2] as the starting product.

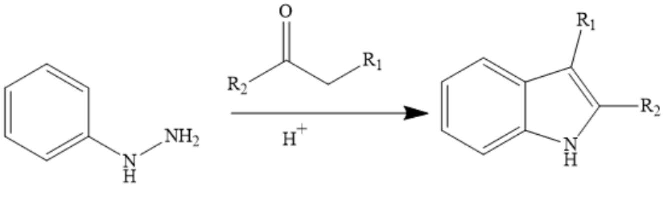

Fig 2: Fischer Indole Synthesis

This reaction involves condensation to form a phenylhydrazone, then isomerization to an enamine, a cyclic [3,3] sigmatropic rearrangement to form an imine. The imine then cyclizes to a cyclic aminoacetal, which then eliminates ammonia under acidic workup. As the final elimination involves an acidic workup, this reaction can be catalyzed by acids such as p-toluenesulphonic acid or even Lewis acids such as zinc chloride or aluminium chloride.

This reaction mechanism is classical, with the condensation-rearrangement-cyclization steps. As is described later, such classical techniques have some limitations which could only be overcome with the development of organometallic chemistry, including techniques such as the Larock indole synthesis. The Fischer synthesis came out in 1884 [2], while the Larock synthesis came out in 1991 [1], more than a hundred years later.

The methodologies used in the Fischer indole synthesis were soon used to synthesize other heterocyclic aromatic compounds, including the Borsche-Drechsel synthesis of carbazole [3]. Carbazole has been used to manufacture pigments, as well as carprofen, a non-steroidal anti-inflammatory drug of the propionic acid class. The broad techniques used in this class of reactions involved ring formation by dehydrogenation, and this is used to manufacture a series of compounds in the first half of the 19th century, which involved an indole nucleus and multiple rings.[4] (Fig 3)

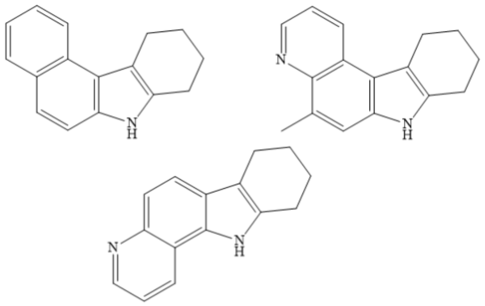

Fig 3: Compounds Prepared using Fischer Indole Synthesis

However, there are multiple issues with this method of synthesis [4].

1. For heavier organic compounds, the yield is extremely low, with the dehydrogenated final product found as intractable tars.
2. Over-dehydrogenation cannot be controlled, as the use of an acidic catalyst often meant a fully aromatized compound is prepared, instead of just the required indolized aromatic nucleus.
3. Furthermore, attempts were made to make the Fischer indole synthesis more dynamic and flexible by considering substituted phenylhydrazones, but these fail in many cases. For example, both 2-ketoester phenylhydrazones and 3-ketoacid phenylhydrazones fail to cyclize and form the aromatic indole nucleus. 2-ketoester phenylhydrazines tend to produce pyrazolones, while 3-ketoacid phenylhydrazines form pyridazinones (Fig 4). Similar results are obtained for other substituted phenylhydrazines. As this article later explores, these issues can be solved by using the Larock indole synthesis.

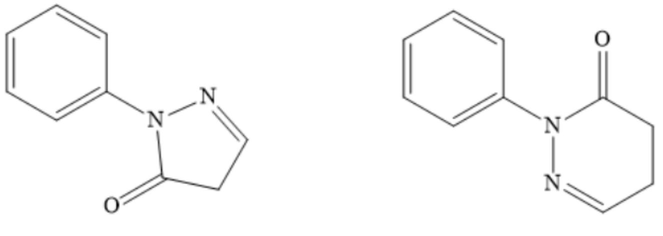

Fig 4: pyrazolone (left), pyridazinones (right)

4. Similarly, indolization of pyridylhydrazones and pyrimidylhydrazones have failed [5], with other

heterocyclic aromatic compounds being produced as by-products (Fig 5).

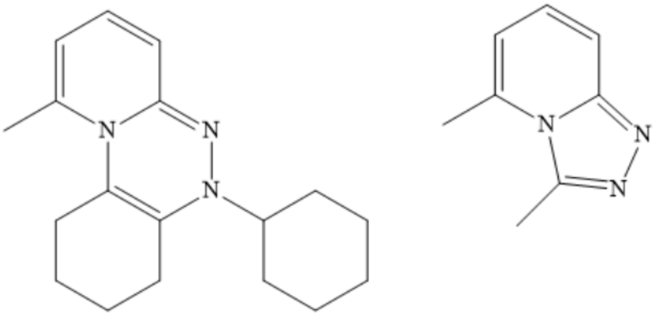

Fig 5: By-products from Fischer indole synthesis

5. Fischer synthesis is most useful for generating 2,3-substituted indoles, where the indole formation can be done in a single pot because it is not required to separate the intermediate aryl hydrazones. However, in the Fischer synthesis, unsymmetric ketones give two region-isomeric 2,3-displaced indoles with a region-selectivity depending on medium acidity, hydrazine substitution and steric effects. 1,2-diketones can give both mono-indoles and bis-indoles, which are usually formed by strong acid catalysts in refluxing alcohols.

The next big breakthrough in indole synthesis came from the development in organometallic chemistry in the second half of the 20th century, as advances in theoretical chemistry allowed us to understand the reactions of transition metals better.

The Fischer indole synthesis is ultimately a purely classical organic synthesis, as it involves techniques such as electrophilic substitution for a π-electron-rich system. Similar approaches were used to develop alternate ways of synthesizing indole, for example, the Leimgruber-Batcho indole synthesis (Fig 6) [6], which uses orthonitro toluenes as the starting product instead. A likewise formation of enamine using a base, is followed up by cyclisation, in this case, using Raney nickel as a reducing agent. This technique became more used than the Fischer indole synthesis in certain pharmaceutical applications [6], because of higher yield in some cases, and better availability of starting products. Yet, the reaction did not prove to be as versatile as latter developments.

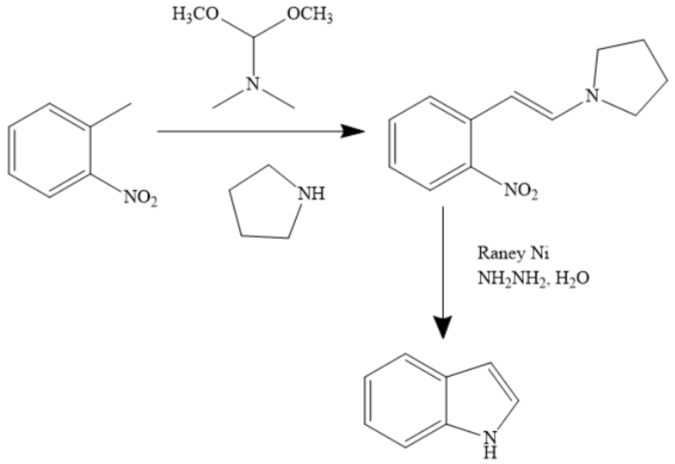

Fig 6: Leimgruber-Batcho indole synthesis

In the middle 20th century, with the refinement of transition metal chemistry, it was learnt that for most organic functional groups, there exist some transition metal, which will produce a reactive organometallic intermediate. This complex formation is specific and eliminates the need for protecting groups (which form a temporary protection of a different reactive functional group, and is removed later), as the selective activation of one functional group is possible.[7]

<u>Prior Work Done in Palladium Chemistry</u>

Palladium exists in two major oxidation states – Pd0 and PdII , apart from the normal Pd0 metal .Palladium is also a good catalyst because it has a relatively low activation barrier between the oxidation states of 0 and +2 corresponding to the stable d10 and d8 configurations. These oxidation states are important for oxidative insertion and reductive elimination. The lower the activation barrier of the transition from 0 to +2 and back again, the more rapidly the catalytic reactions can take place. The faster and more favourable these reactions are, the higher the turnover rate for the catalyst.

Palladium and some other transition metals are suitable at holding on to reactants. Transition metals to the left end, such as titanium, are very reactive, and have a tendency of oxidizing and then not reacting further. At the other extreme, metals like gold are too less reactive for the organic catalytic syntheses palladium is used for. Palladium will hold on to reactants, let them rearrange into products, and then allow them to leave/desorb after the reaction is done.

Palladium can be oxidized to form palladium salts. In particular, [PdCl2]n is a bridged polymer, which is itself insoluble in organic solvents, but readily forms soluble solvates when reacted with a metallic chloride or an alkyl nitrile.[7]

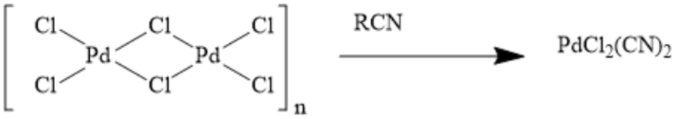

Fig 7: Formation of Palladium Salts

Palladium salts were observed to be highly electrophilic, e.g., towards alkene double bonds. The organometallic intermediate was flexible in synthesis of many different organic functional groups (Fig 8).

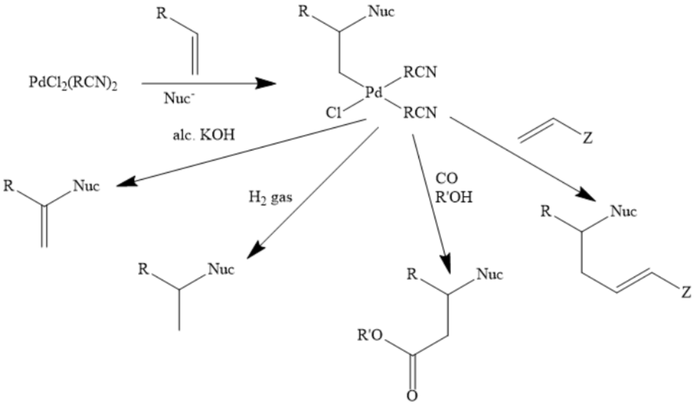

Fig 8: Initial Usage of Palladium Salts in Organic Synthesis

This was the start of the usage of palladium and techniques in organometallic chemistry in heterocyclic synthesis[8]. Soon, researchers in Japan, with Itihara being a prominent name, was able to synthesize more complex multicyclic aromatic compounds from less complex multicyclic compounds [9] (Fig 9). Here, the role of palladium diacetate as a catalyst was to add onto two benzene rings as an electrophilic aromatic substituent, forming a bridge in its +2 oxidation state, and then coupling together the rings.

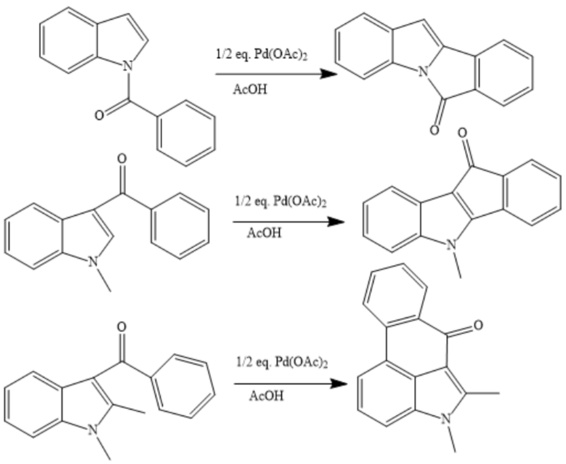

Fig 9: Using $Pd(OAc)_2$ to form complex multicyclic aromatic compounds

The versatility of palladium salt-catalyzed heterocyclic synthesis was further found when it was used to insert substituents in an indole nucleus [9] (Fig 10) and perform a single-electron-transfer to form dihydroindole compounds[10](Fig 11).

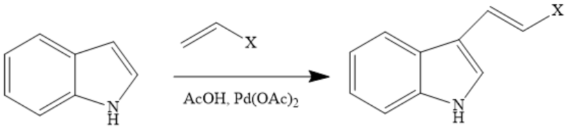

Fig 10: Insertion of Substituent in Indole nucleus

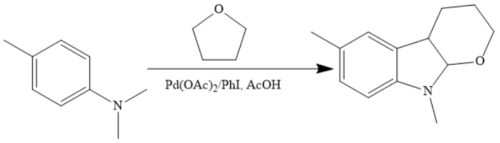

Fig 11: Formation of Dihydroindole compounds using $Pd(OAc)_2$ catalyst

This salt of palladium was applied later in the Larock indole synthesis.

Use of Alkynes in Organometallic Synthesis

The growth in organometallic chemistry also led to the development of synthesis techniques using alkynes. For example, several functional groups were successfully synthesized from alkynes, using transition metals as catalysts, including the synthesis of pyridines (Fig 12) and quinones (Fig 13)[11], among others.

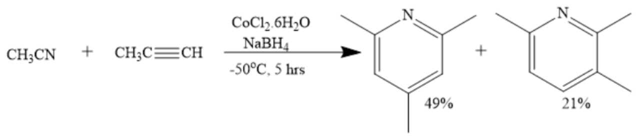

Fig 12: Transition Metal Catalyzed Alkyne Synthesis of Pyridines

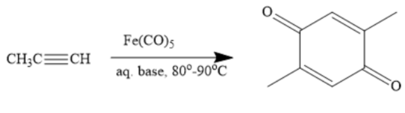

Fig 13: Transition Metal Catalyzed Alkyne Synthesis of Quinones

Using palladium catalysts in particular, alkynes were shown to undergo an intermolecular cocyclotrimerization[11] to form aromatic molecules. In these reactions, two molecules of alkynes reacted with one other molecule to form the benzene nucleus (Fig 14). Excess of alkynes are used with the Palladium-ring complex being the limiting reagent.

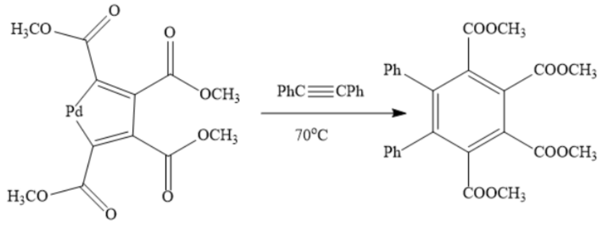

Fig 14: Palladium Catalyzed Organic Synthesis Using Alkynes

This success inspired chemists to try annulating onto an existing aromatic benzene ring to form multicyclic compounds, using alkynes and a palladium catalyst. However, intermolecular attempts to annulate onto alkynes using a palladium catalyst on an existing aromatic nucleus resulted in either multiple alkyne insertion or subsequent cyclization back onto the initial aromatic nucleus[18] (Fig 15).

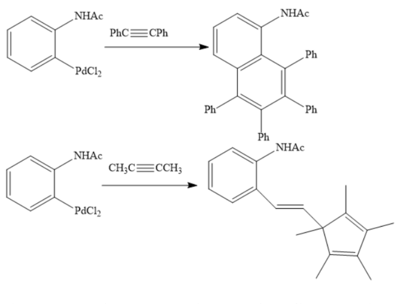

Fig 15: Multiple Alkyne Insertion Products in Palladium Catalyzed Annulation Attempts

Now, the main Larock indole synthesis is discussed.

Reaction Discussion:

Initial Discovery

Richard Larock, a professor of chemistry at Iowa State University, had palladium-catalyzed organic synthesis, as one of his primary interests. Prior to the discovery of the Larock indole synthesis, his research group had done extensive work on annulation (ring formation) using dienes. His research group was able to carboannulate 1,2-dienes using ortho-substituted aryl halides using palladium catalysts[12] (Fig 16).

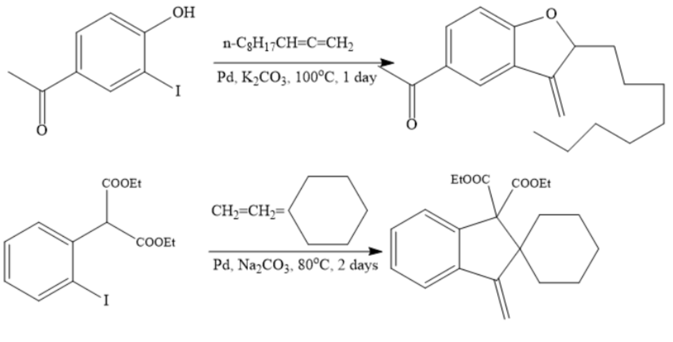

Fig 16: Carboannulation of 1,2 dienes

This prior success inspired the group into using alkynes in annulation reactions.
In 1991, Larock reported a flexible high-yield method of synthesizing indole and indole-family compounds using palladium acetate salt as the catalyst. Ortho-iodoaniline and its derivatives were used as the starting material.[1] This was the initial discovery of the Larock indole synthesis. (Fig 17a) An example is shown below. (Fig 17b)

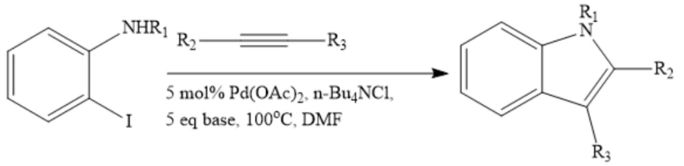

Fig 17a: Initial Larock Indole Synthesis

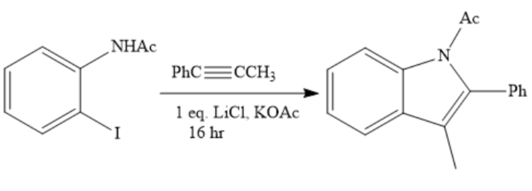

Fig 17b: Example of a Larock indole synthesis

This reaction was a significant improvement upon previous techniques for multiple reasons.

1. Firstly, compared to earlier techniques such as the Fischer indole synthesis and the Leimgruber-Batcho indole synthesis, the Larock indole synthesis was more flexible. The three variable chains (marked R1, R2, R3) could be a diverse set of organic groups, and this enabled a greater variety of compounds to be synthesized.
2. The yield obtained was much better than the low yield attempts to synthesize indoles from N-methyl-p-toluidines and acetylenedicarboxylate esters, as done by Sakakibara and Tanaka.[13] (Fig 18) Although the earlier techniques used were similar, earlier methods produced many difficult-to-separate by-products too.
3. In many cases, the Larock indole synthesis is regioselective, enabling us to selectively synthesize in drug design applications.

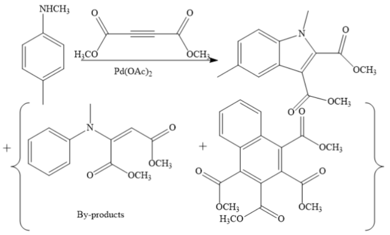

Fig 18: Sakakibara's Low-Yield Indole Synthesis using Alkynes with Palladium Catalysts

Potassium carbonate and acetate bases proved to suitable bases for the Larock indole synthesis. A catalytic amount of PPh3 was used initially, but later it was found out that Ph3P was superfluous and did not affect the reaction activity that much. Moreover, using PPh3 at temperatures higher than 100o C often caused multiple alkyne insertion.

Initially, n-Bu4NCl was used as the base by Larock's research team, using only 1 equivalent of it per equivalent of iodoaniline. However, later the researchers discovered that using lithium chloride (LiCl) was more effective and reproducible.[1] It was further observed that LiCl has a critical concentration, as using more than 1 equivalent of lithium chloride lowered yield due to multiple insertion products as by-products, the same problem Sakakibara faced.

Larock later published a much-more detailed stoichiometric analysis[14] of the Larock indole synthesis in 1998. There, Larock investigated the stereochemical and stoichiometric aspects of the reaction, as well as key aspects – the effect of concentration of alkyne used, a comparison of various bases used at different temperatures, and the stereochemical effect of various substituents on the alkyne. These experiments enabled Larock to determine the reaction mechanism.

Reaction Mechanism and Method of Determination

Prior reactions using palladium catalysts, where palladium formed a bridge between the aryl nucleus and the functionality that is being added[9], allowed Larock to deduce the possible reaction mechanism of the Larock indole synthesis. (Fig 19)

The steps in this reaction are:

1. Reduction of the Pd(OAc)2 to Pd0. Both Pd2+ and Pd0 states have space for two more ligands, and in the solution, palladium is usually bound to solvent molecules or other ions.
2. Coordination of the chloride ion from the base to form a chloride-ligated Pd0 species[14]. The chloride ion comes from the base (LiCl or n-Bu4NCl).
3. Oxidative addition of the aryl iodide onto the chloride-ligated Pd0 species.
4. Coordination of the alkyne onto the palladium atom of the resulting arylpalladium intermediate.
5. Subsequent Regioselective syn-insertion into the arylpalladium bond of the alkyne. If the alkyne is substituted, due to this step, the substituents in the final indole molecule are always cis with respect to the double bond. The regioselectivity will be elaborated on later.
6. Nitrogen displacement of the halide in the resulting vinylic palladium intermediate. This forms a six-member heteroatom-containing palladacycle.[14]
7. Reductive elimination of the indole molecule to regenerate the Pd0 species that was formed.

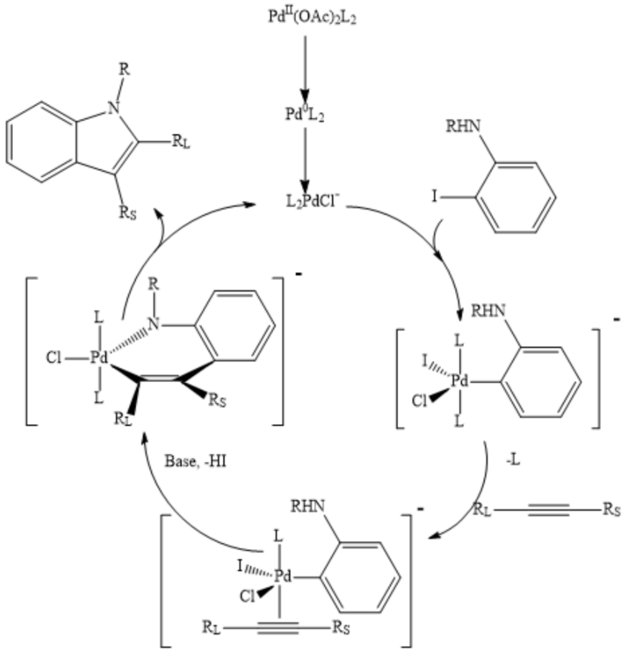

Fig 19: Reaction Mechanism of the Larock Indole Synthesis

Here, RL denotes a sterically larger substituent, while RS denotes a sterically smaller substituent.

Among the various steps, the redox reaction thus described had been encountered in earlier palladium-catalyzed synthesis reactions.[10] The chloride ligation step was theorized by Amatore[17] earlier to explain various kinetic results associated with the oxidative addition of aryl iodides to Pd0 species. The syn-addition of alkynes had been theorized earlier as well in particular the low-yield method of obtaining indole described earlier.[13] The fact that the palladium catalyst is regenerated means that we can recycle this reagent, leading to better efficiency in the synthesis procedure.

The palladacycle formed is too short-lived to isolate it in the Larock indole synthesis, however in a study by Driver and Hartwig[22], an arylpalladium amide analogously formed a carbon-nitrogen bond, providing more support to the reaction mechanism described.

It was observed that in place of ortho-iodoanilines, ortho-bromoanilines cannot be used as the starting material. This is because the insertion of palladium in the aryl-bromide bond, and subsequent elimination of HBr is not thermodynamically favourable (HI is a stronger acid, more ionic, and exits faster).

The work by Pfeffer et al[18] regarding chemical kinetics for various halides in palladium-catalyzed reactions hypothesized that the formation of the carbon-nitrogen bond for only a single alkyne insertion, as in the Larock indole synthesis, is due to the poor σ-donor properties of the iodine atom in the reactant. That is why, usage of ortho-chloroanilines causes the formation of multiple insertion products instead.

Concentration of Alkynes Used

It was observed that higher yields were obtained with higher concentration of alkynes, especially for volatile alkynes.[1] (Fig 20). With 5 equivalents of alkynes, Larock obtained an 80% yield. However, even with lower concentrations of alkynes, yield was significant. The higher yield for more concentration of alkynes meant that in practical uses, an excess of alkynes is used (especially if product purity is important).

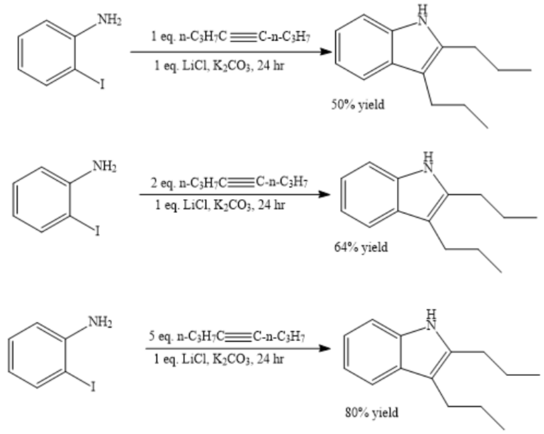

Fig 20: Effect of Concentration of Alkyne on Yield (Palladium catalyst used)

Kinetic Comparison of Various Bases Used

1. **KOAc**: Potassium acetate has a low yield if neither LiCl nor PPh3 is used. If 1 equivalent of LiCl is used, the yield is good if performed at a temperature of 120o C. LiBr and LiI cannot be used in place of LiCl if KOAc is used due to kinetic effects. There was no reaction if the temperature was lowered to 100o C or lower. At the temperature of 120o C, addition of PPh3 was unnecessary as it gave a lower yield.
2. **K2CO3**: Potassium carbonate has slightly lower yield than even potassium acetate if LiCl is not added. However, potassium carbonate is compatible with both LiBr and LiI, and gives an

ever higher yield if slightly more concentration of LiCl is used. There is similar behavior with respect to temperature at 120o C, but K2CO3 can even produce indoles at 100o C.

3. **NaOAc**: Produces an inferior yield than the equivalent potassium base.
4. **Na2CO3**: Produces an inferior yield than the equivalent potassium base.

Thus, potassium acetate and potassium carbonate are the ideal bases for the Larock indole synthesis.

Effects of Substituents on the Nitrogen of the Iodoaniline

The Larock indole synthesis was flexible enough that the nitrogen atom in the final indole nucleus could have a variety of substituents. Larock was successful in using N-methyl-2-iodoaniline, 2-iodoacetanilide and N-tosyl-2-iodoaniline (Fig 21) as starting products. This was especially significant because previous work by Pfeffer[18] with different reaction conditions was not able to undergo high-yield annulation if 2-iodoacetanilide was the starting product. The reactivity increases if electron withdrawing substituents are present in the benzene nucleus, because of the stabilized intermediate. The intermediate has a negative charge, so electron withdrawing substituents lower the transition state energy.

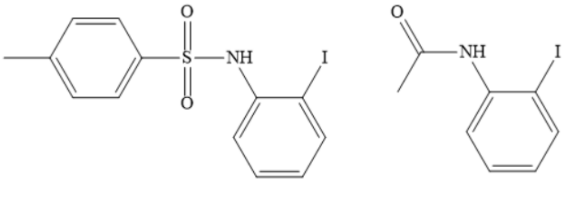

Fig 21: N-tosyl-2-iodoaniline (left), 2-iodoacetanilide (right)

Effect of Substituents in the Alkyne

The alkyne used in the Larock indole synthesis can have a wide variety of substituents, without affecting the yield. Simple unhindered alkyl-substituted alkynes, such as 4-octyne, also provide a high yield, unlike previous attempts[18]. However, the reactivity for such unhindered alkynes tends to be high, and if the temperature is too high, there is possibility of multiple insertion. Thus, moderately sterically hindered alkynes, for example, tertiary butyl substituted alkynes or trimethylsilyl alkynes, tend to give a higher yield in such cases, due to lack of multiple insertion by-products.

There is thus an interacting trade-off between maximizing yield with unhindered alkynes at moderate temperatures versus hindered alkenes at higher temperatures.

The alkyne can also have other functional groups such as alcohols. Indeed, analogous work in hydroarylation of alkynols by Cacchi[19][20] showed that alkynols can be utilized in the conditions used in the Larock indole synthesis. (Fig 22)

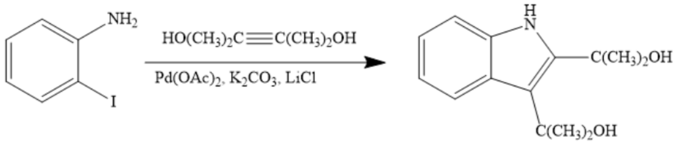

Fig 22: Indole synthesis using Hydroxyalkyl-substituted Alkynes

Regioselectivity

It was confirmed by works by both Larock[14] and Cacchi[20] that the reaction for an asymmetric alkyne is highly regioselective. The sterically bulky group ends up in the 2-position in the indole nucleus formed, nearer the nitrogen. Only the preferred isomer is formed if the alkyne is bulky, e.g., 1-phenyl-1-propyne. If the alkyne is less bulky, e.g., 2-pentyne, both isomers are formed, with the preferred isomer highly dominating. [1](Fig 23)

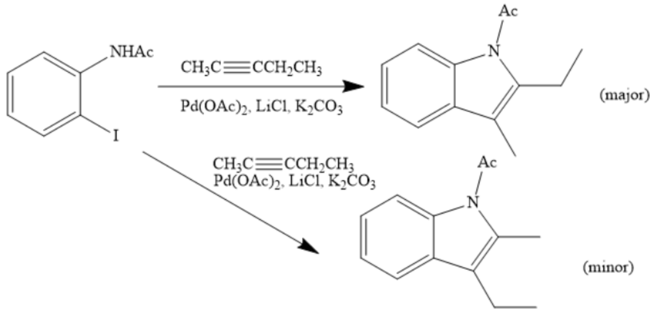

Fig 23: Major and Minor products for Asymmetric Alkynes

The transition state (Fig 24) places the more sterically hindered group next to palladium. (Fig 24) The controlling factor behind this regioselective behavior is likely the steric hindrance present in the developing carbon-carbon bond between the benzene ring and the alkyne. Thus, the orientation of the alkyne prior to the syn-insertion into the aryl-palladium bond is in a way such that the steric strain in the developing carbon-carbon bond.[14] Here, it is important that the alkyne is parallel and cis-coordinated to the arylpalladium bond for the syn addition to take place.

A similar regioselectivity is observed for annulation using alkynes onto an aromatic ketone using manganese catalysts, as in the works of Liebeskind et al.[21]

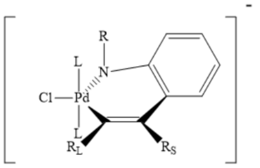

Fig 24: Transition State having the Larger Substituent nearer the Palladium Atom

In addition to the steric effects, if one of the substituents in an alkyne contains a hydroxy (-OH) group, it occupies the position nearer the palladium atom (RL in Fig 24), and thus is the substituent on the 3-position in the finally formed indole, because of coordination between the lone pair of oxygen and the palladium atom. This is analogous to the similar effect in hydroarylation of alkynes.[19][20]

Limitations due to Unexpected Products

Some reactants do not form the standard product formed in the Larock indole synthesis. These exceptional behaviors are mentioned now:

1. Migration of Acetyl Group from N-acetyl-iodoaniline

   If the alkyne has one substituent containing an alcohol group, the final product has the alcohol acylated instead with the previously acylated amine forming a free amine instead. This is due to a base-catalyzed acetyl group shift.[14] (Fig 25)

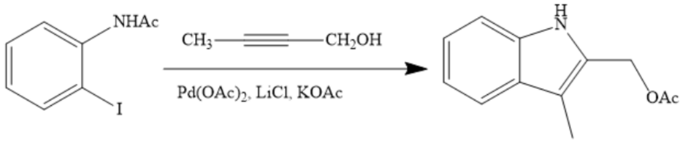

Fig 25: Shift in Acetyl Group in Larock Indole Synthesis

2. Reaction of Hindered Disilyl alkynes to form Monosilyl substituted indoles

   If a hindered disilyl alkyne is used as the starting reactant, for example, bis(trimethylsilyl)acetylene, the product formed by the conditions for Larock indole synthesis has only one trimethylsilyl group. The elimination of one silyl group is likely due to steric factors. (Fig 26)

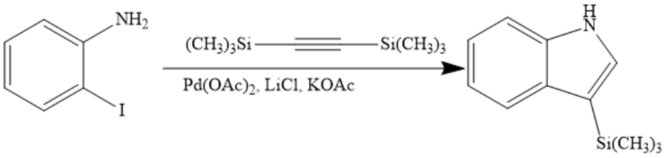

Fig 26: Bis(Trimethylsilyl)acetylene forming trimethylsilylindole

Other Limitations

1. Cost-Effectiveness due to Availability of Reagents

   Ortho-iodoaniline is far better reactive than ortho-bromoaniline and ortho-chloroaniline. However, ortho-iodoaniline is less easily available in the laboratory and is costlier. Thus, the Fischer indole synthesis remains a good alternative technique for those indole molecules which can be synthesized without the problems of the Fischer indole synthesis. However, if complex salts of palladium are used, ortho-bromoaniline is also reactive.

2. Limitation if 7-Position has Bulky Substituent

   If the 7-position in the indole nucleus has a bulky substituent, it is difficult to use the Larock indole synthesis due to steric hindrance when the palladacycle is formed.

Immediate Impact in Other Synthesis Techniques

It was recognized by Larock that this reaction mechanism enabled a broad variety of synthesis. For example, if one of the substituents on the alkyne was a silyl group (such as Si(CH3)3), the silylindole produced could further form a variety of substituted indoles through disilylation and halogenation (Fig 27), followed by the Heck reaction to form more complex substituted indoles.[15](Fig 28)

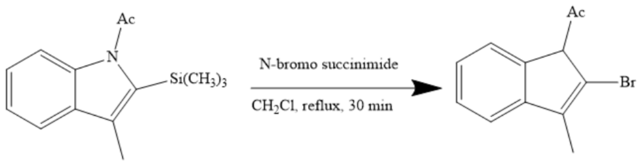

Fig 27: Halogenation of Silylindole formed to form acylated 2-bromindole

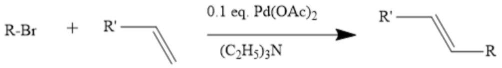

Fig 28: Heck reaction

Further Annulation Reactions

The success in synthesizing indole led to Larock successfully reporting the synthesis of a wide variety of heterocyclic compounds based on palladium-catalyzed addition of alkynes. These included 1,2-dihydroisoquinolines (Fig 29), benzofurans, benzopyrans and isocoumarins.[16] The reaction conditions used were similar – this included 5% molar Pd(OAc)2, sodium or potassium acetate or carbonate as the base, and LiCl or n-Bu4NCl as the base, with DMF as the solvent.

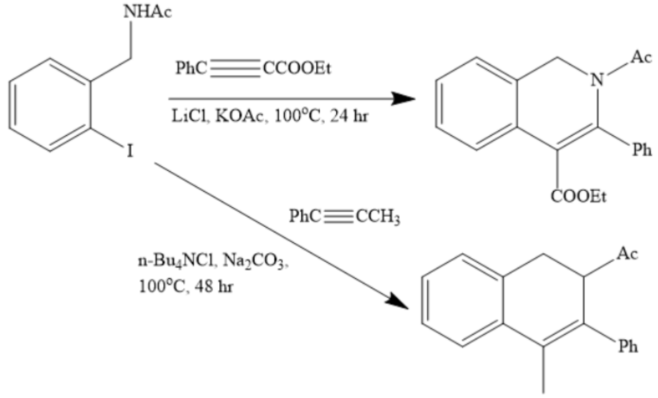

Fig 29: Synthesis of 1,2-dihydroisoquinolines

The synthesis of dihydroisoquinolines was slow with ortho-iodobenzylamine as the starting product, with a low yield. However, using the corresponding acetamide produced a much better yield[16], as shown in Fig 29.

Analogous annulation reactions can also be done using oxygen as the nucleophilic atom. However, the analogous reaction with ortho-iodophenol instead of ortho-iodoaniline was extremely slow and only possible for selective alkynes at a higher temperature. Unlike what Larock had observed for the indole synthesis, where less hindered alkynes also reacted very fast, only heavily hindered alkynes (such as trimethylsilyl alkynes) reacted with ortho-iodophenol. These reactions were also regioselective, like the Larock indole synthesis. Fig 30 shows the synthesis of a benzofuran, while Fig 31 shows the synthesis of an isocoumarin in this manner.

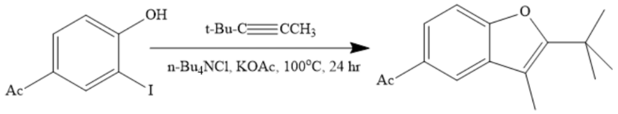

Fig 30: Synthesis of Benzofuran using analogous reaction conditions (palladium catalyst)

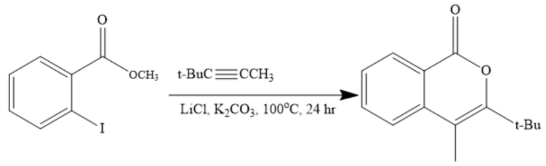

Fig 31: Synthesis of Isocoumarin using analogous reaction conditions (palladium catalyst)

If the alkyne used is asymmetric, these analogous reactions are generally regioselective, with the bulkier substituent appearing near the heteroatom (nitrogen or oxygen). The reason is the same as that mentioned for the regioselective nature of the Larock indole synthesis.[16]

Just as the Larock indole synthesis can be used to further prepare more substituted indole compounds, the analogous reactions for oxygen as the heteroatom can be used to prepare more substituted benzofurans. For example, reacting a triisopropylsilyl alkyne produces a triisopropylsilyl substituted benzofuran, which is readily desilylated to form 3-substituted benzofurans, which would be difficult to produce directly (as the alkyne would not have been hindered enough for the direct reaction). CH3CN is often used as a solvent for that reaction.(Fig 32)

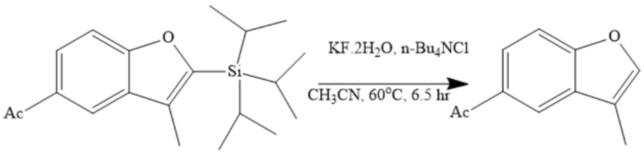

Fig 32: Using Triisopropylsilyl Benzofuran to form 3-substituted Benzofurans

Applications in Synthesis:

Here, some synthetic applications of the Larock indole synthesis are elaborated upon. Indole being such a biologically active molecule, has been used to develop many families of alkaloids.

Alkaloid Synthesis using Intermolecular Larock Synthesis of 3,4 Fused Tricyclic Indoles

The indole nucleus can be found in a variety of natural biomolecules. Some of the most important biologically active indole family molecules are 3,4-fused indoles, including lysergic acid and Penitrem A. Some of the amides of lysergic acid, called lysergamides, have agonist or antagonist activity at various serotonin and dopamine receptors. Penitrem A (tremortin), on the other hand, is an indole-diterpenoid mycotoxin, that can affect the central nervous system by bypassing the blood-brain barrier.

These molecules are synthetically challenging due to its tricyclic nature. Some of them are shown below. (Fig 33) Previous attempts to synthesize similar 3,4-fused tricyclic indoles usually involved introduction of functional groups in the 3- and 4- positions of an already existing indole and then cyclization.[23] However, electrophilic aromatic substitution prefers the 5- and 7-positions.Thus, using the Larock indole synthesis, one can determine an alternate pathway, where the alkyne is inserted as a functional substitutent onto the 4- position of an ortho-iodoaniline. A sample reaction is given below (Fig 34).

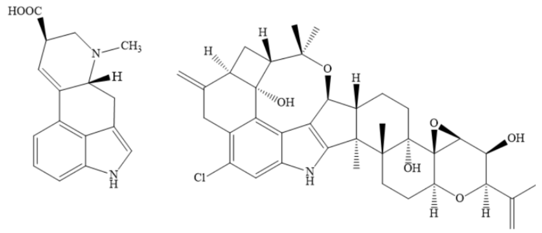

Fig 33: 3,4-Fused Tricyclic Indoles: Lysergic Acid (left), Penitrem A (Right)

Such techniques can even be used to generate macrocyclic indole compounds with 18 compounds in a ring.[26](Fig 34b)

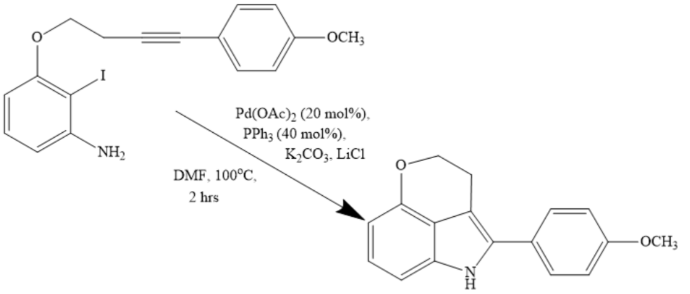

Fig 34a: Intramolecular Larock Synthesis of 3,4-Fused Tricyclic Indoles

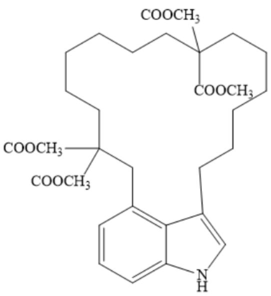

Fig 34b: 18-cyclic macrocyclic indole prepared

A small amount of palladium catalyst is then sufficient for Larock indole synthesis. This technique was used by Shan et al[23] to generate the alkaloid Fargesine, extracted from the root and stem of Evodia fargesii. The insertion of the alkyne chain was done by imine formation from an aldehyde and subsequent reduction. (Fig 35a) Likewise techniques can be done to synthesize complex 3,4-fused alkaloids by choosing appropriate starting materials. Using a tosylated 3,4-fused indole compound can be further used to synthesize tetrahydropyrroloquinoline (Fig 35b)[26].

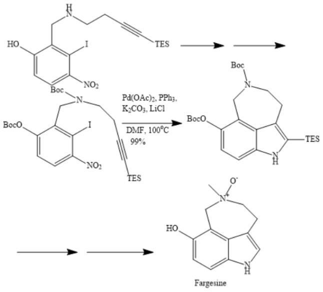

Fig 35a: Synthesis of Fargesine

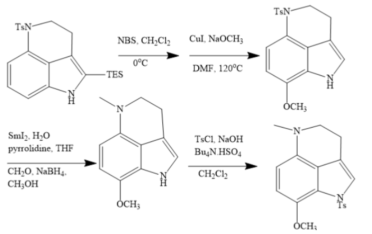

Fig 35b: Synthesis of Tetrahydropyrroloquinoline

Tetrahydropyrroloquinoline can be used as an antifungal and cytotoxic agent.

Use in Synthesis of HIV Protease Inhibitors

Palladium catalyzed annulation of alkynes, e.g., acetylenes, has also been used in medicine. For example, an important class of antiviral drugs used against HIV/AIDS are HIV protease inhibitors, which prevent viral replication by selective binding to HIV-1 protease, a retroviral aspartyl protease virus essential in the HIV life-cycle. One of those candidates is L-754394 (Fig 36)[24]. Such drugs need furopyridine structural units to be synthesized, which can be manufactured using the Larock indole synthesis-inspired heterocyclic annulation using alkynes with palladium catalysts.

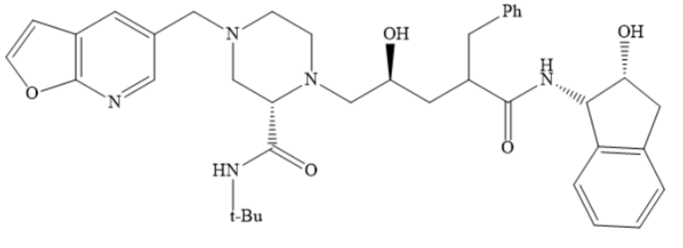

Fig 36: L-754394

The furopyridine nucleus can be manufactured using palladium-catalyzed coupling ethyl 2-hydroxy nicotinate, and the following synthesis is possible. (Fig 37) Here, kinetic studies showed that n-BuNH2 worked as a better base than KOAc or K2CO3. The concentration of alkynes is typically around 5 equivalents at least. CuI is used alongside palladium as a catalyst for higher yield. In large-scale production, CuI is more cost-effective.[24] The starting benzene nucleus has an electron-withdrawing ester group, because electron-rich indole formation is unstable.

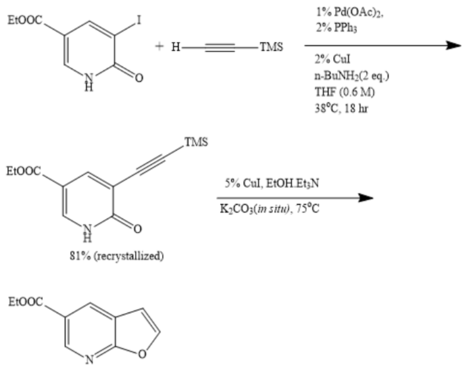

Fig 37: Synthesis of Furopyridine using Palladium-Catalyzed Alkyne Insertion

Manufacture of Serotonin Family Anti-Migraine Drugs with Heterocycle Moiety

The monoamine serotonin is a neurotransmitter with multifaceted functions, including regulation of mood, cognition, reward, learning and memory. Its role as a vasoconstrictor in the brain makes it beneficial in migraine therapy. However, its potential as a pharmaceutical agent is limited due to in vivo rapid metabolism.[25] N, N-dialkyltryptamines have been developed as 5-HT1D receptor agonists for the treatment of migraines. This include sumatriptan. Synthesis of analogous MK-0462 compound cannot be done using the Fischer indole synthesis, due to presence of benzyl triazole moiety – the Fischer synthesis is sensitive to additional functional groups such as the triazole, which would lead to a very poor yield. Such compounds need to be synthesized using techniques such as the Larock indole synthesis, which are not sensitive to triazole and other nitrogen-containing heterocycle substituents. Fig 38a shows the compounds serotonin, sumatriptan and MK-0462. Fig 38b shows the Larock synthesis of this drugs. Sumatriptan can also be synthesized in this manner.[25]

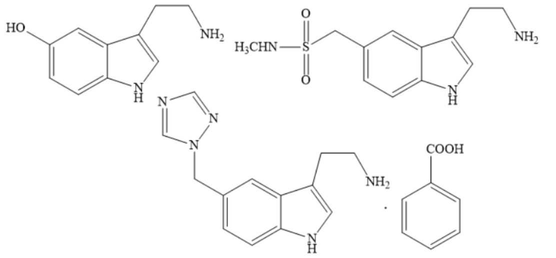

Fig 38a: Serotonin (Top-left), Sumatriptan (Top-right), MK-0462 (Bottom)

The alcohol used in this Larock reaction must have a protecting group initially, and then be deprotected for the reaction to have high yield of the product desired.

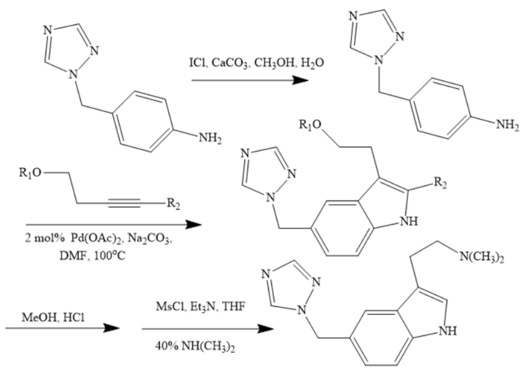

Fig 38b: Synthesis of Serotonin-Family Migraine Drugs using Larock indole synthesis

Use in Total Synthesis of Complex Macromolecules: Chloropeptin II (Complestatin)

Chloropeptin II (Complestatin) is a complex macromolecule isolated from Streptomyces lavendulae, noted for its HIV infectivity and cytopathic effects. It is structurally similar to glycopeptide antibiotics like vancomycin, but notably, one of the characteristic biaryl ether linkages is replaced with a biaryl linkage. The compound is atropisomerically chiral.

Chloropeptin II was discovered to have HIV inhibitory and cytopathic effects. Biogenetically, both chloropeptin I and chloropeptin II are linear non-ribosomal peptides that have undergone oxidative phenolic coupling to produce a rigid cross-linked architecture.[41]

Boger et al[27] used an intramolecular Larock indole synthesis to create the initial macrocyclization. The overall retrosynthetic broken bonds are indicated along with the structure in Fig 39, while the Larock indole synthesis used is provided in Fig 40. Later, a different synthesis by Wang et al[41] used intramolecular Suzuki–Miyaura and SNAr reactions for the construction of two macrocycles in Chloropeptin II by the formation of aryl–aryl and aryl–aryl ether bonds, respectively.

Complex salt catalysts which allow ortho-bromoaniline to be used are used in the process described by Boger et al[27]. The intramolecular Larock indole synthesis guarantees that the indole cyclization is regioselective.[27]

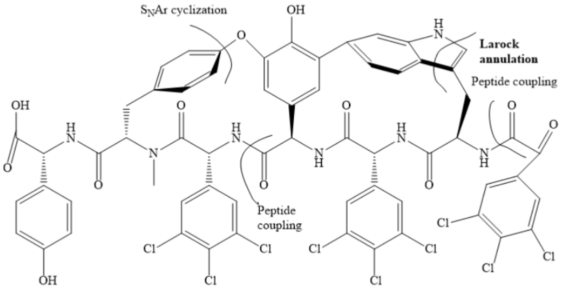

Fig 39: Retrosynthetic breakdown of bonds in total synthesis of Chloropeptin II

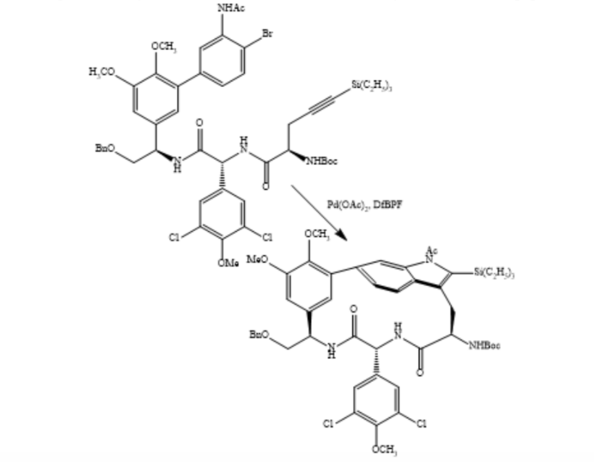

Fig 40: Larock annulation step in total synthesis of Chloropeptin II

Use in Total Synthesis of Chemotherapy Targets

Dictyodendrins are a family of alkaloids having a pyrrolo[2,3-c] carbazole moiety and having at least one sulphate group. They are isolated from the sponge of Dictyodendrilla verongiformis. These compounds are telomerase enzyme inhibitors. Telomerase enzymes are overexpressed in tumor cells compared to normal cells, thus, dictyodendrins are possible targets for cancer chemotherapy.[28]

The total synthesis of dictyodendrins involve a palladium-catalyzed Larock indole synthesis which then undergoes N-alkylation, bromination, followed by Buchwald-Hartwig amination, to form an intermediary which undergoes a carbazole formation to give dictyodendrins. [28]The Larock indole synthesis step is given in Fig 41a, while the final product is shown in Fig 41b. In this case, t-BuONa was experimentally determined as the best base, with DMSO at 160o C being the best solvent.

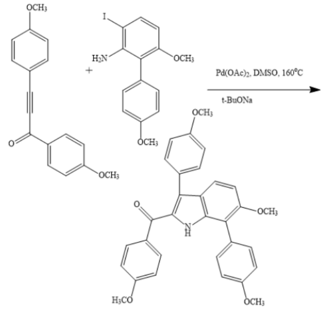

Fig 41a: Larock indole synthesis in dictyodendrin synthesis

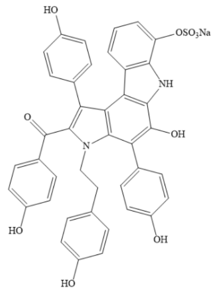

Fig 41b: Dictyodendrin B

Use in Antibacterial, Antiviral and Antifungal Alkaloid Synthesis: Total synthesis of Dragmacidin

Dragmacidin D is a member of the Dragmacidin family of heterocyclic bis(indole) compounds. It has one stereogenic centre and was found to be a potent inhibitor of serine/threonine phosphatases. It is known to have antiviral, antibacterial, and antifungal activity, as well as invitro cytotoxicity against murine leukemia, and some varieties of human lung, colon and mammary cancers.[29]

The structure of Dragmacidin D consists a central pyrazinone core with two indole substituents, one of which is further linked to an aminoimidazole unit. The first indole nucleus is created through the Larock indole synthesis, while the second indole nucleus (separately prepared) then attaches in a Friedel-Crafts type arylation. The catalyst used here is a more complex chelated sandwich-compound of palladium. n-Bu4NBr was used as the base here. Fig 42a shows the Larock indole synthesis step in this synthesis[29] while Fig 42b shows the final product.

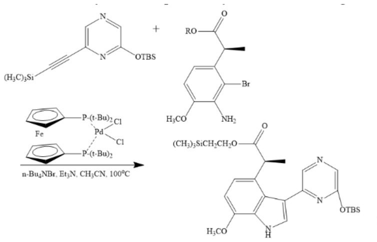

Fig 42a: Larock indole synthesis in Dragmacin D synthesis

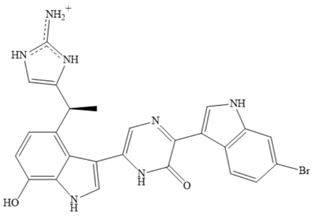

Fig 42b: Dragmacin D

Subsequent Development and Conclusion:

Here, the subsequent developments in the Larock indole synthesis and subsequent development in palladium-catalyzed annulation reactions are covered, especially those involving alkynes. Many of these developments were crucial in the synthetic methodologies developed, that were covered in the past section.

Effect on Regioselectivity in Larock indole synthesis with 2-alkynylpyridines

If the alkyne is asymmetric, Larock[1][14] had earlier provided a steric hindrance based explanation to explain the regioselectivity in the indole formed regarding position of substituents. The sterically bulky group ends up in the 2-position, near the nitrogen atom. In 2008, Senanayake et al[30] published their findings where the regioselectivity seemed to be affected if a 2-alkynylpyridine is used, i.e., one of the substituents in the alkyne is a pyridine ring, attached at the 2-position (ortho to the nitrogen atom). In particular, he compared the molar ratio of isomers formed when the alkyne used is 2-cyclopentylethynylpyridine versus cyclopentylethynylbenzene (compounds shown in Fig 43).

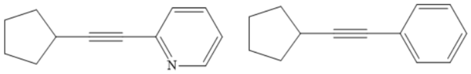

Fig 43: Compound A (2-cyclopentylethynylpyridine) (left), Compound B (cyclopentylethynylbenzene) (right)

For Compound A, the ratio of isomers was unusually high (94:6). For Compound B, the ratio of isomers was 67:33, despite the two compounds having similar sizes sterically. If 3-cyclopentylethynylpyridine was used, the ratio was 68:32, similar to that for Compound B. This is because if one of the substituents are such that there is possible σ-donation from an electron-rich centre (e.g., nitrogen atom in the 2-cyclopentylethynylpyridine) to the palladium atom, regioselectivity is increased.[30] Thus, 2-pyridin-2-ylindoles are preferred over 3-pyridin-2-ylindoles. The modified reaction mechanism is given in Fig 44.

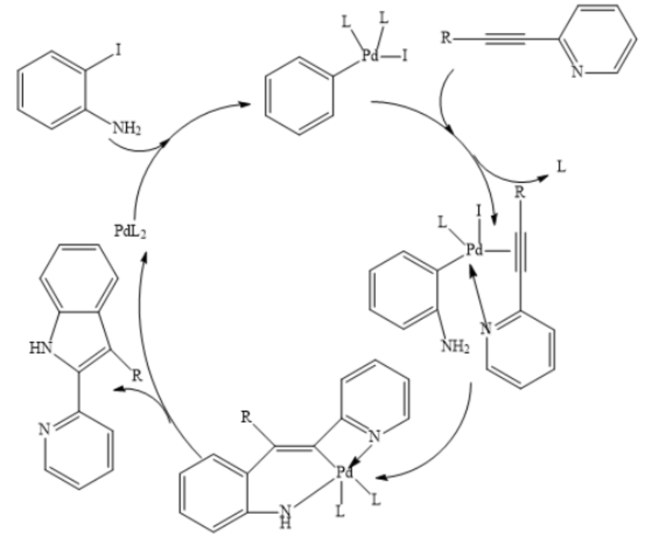

Fig 44: Modified Reaction Mechanism for 2-alkynylpyridines

The difference in this reaction mechanism is that the nitrogen atom forms an additional coordinate bond with the palladium atom to form one additional palladacycle. Thus, the regioselectivity is enhanced because of this additional ring formation.[30]

Development of Alternate Catalysts and Reacting Conditions

The Larock indole synthesis and the analogous heterocyclic annulation reactions both involve an expensive palladium catalyst, which is not cost-efficient for large-scale industrial use. Moreover, the original reaction conditions given by Larock involved specialized ancillary ligands, high temperatures, and an excess of the alkyne.

Ni(dppp)Cl2, or 1,3-bis(diphenylphosphino) propanonickel chloride is a nickel-based catalyst that was used by Weng, Xie et al earlier [31] to form isoquinolines starting from 2-haloaldimines and alkynes under very mild conditions. This catalyst proved to be useful for the Larock-type indole synthesis, as well as the synthesis of ketones of isoquinolines from ortho-iodobenzamides. 2 equivalents of Et3N needs to be used as the base, and CH3CN is the ideal solvent for this reaction. The reaction is shown in Fig 45.

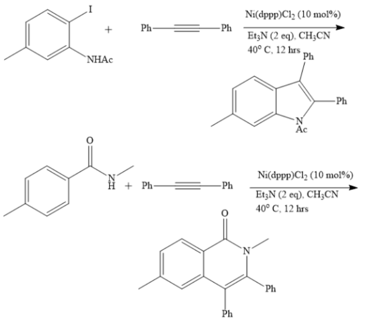

Fig 45: Nickel-synthesized heteroannulation of ortho-iodoacetanilides (top), ortho-iodobenzamides (bottom)

Weng et al further determined that this reaction does not involve any aryl radical intermediate, and instead consists of Ni(0) formed from in situ reduction of the complex salt, as the catalyst, which then undergoes oxidative addition into the C-I bond. The deprotonation of the amide hydrogen by the Et3N base forms a five-membered nickelacycle intermediate. Then there is a coordinative insertion of alkynes, followed by reductive elimination to obtain the product.[31]

This reaction mechanism is strikingly like the original Larock indole synthesis.

Monguchi et al also developed a more effective synthetic method for indole derivatives that did not need the LiCl salt. The catalysts used were palladium on carbon (Pd/C) and NaOAc in heated NMP (N-methyl-2-pyrrolidone).[33]

He, Du, Liu et al developed an N-heterocyclic carbene based palladium complex for the Larock indole synthesis. This catalyst proved to be not only suitable for ortho-iodoanilines, but also suitable for ortho-bromoanilines. Use of complex salts of palladium became a better catalyst for cost-effectiveness, as ortho-bromoaniline is cheaper and easier available in labs than ortho-iodoaniline [32]. A common catalyst used is Ferrocenyl NHC-Pd-Pyridine complex, shown in Fig 46.

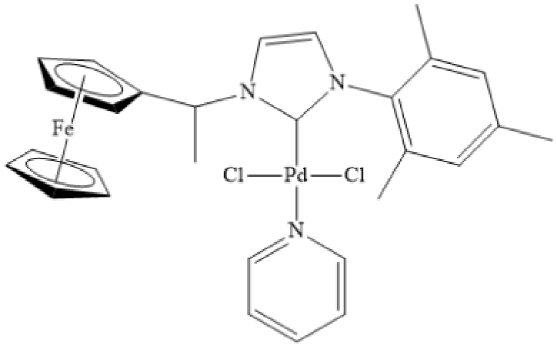

Fig 46: Ferrocenyl NHC-Pd-Pyridine Complex

This catalyst takes part in a similar mechanism as the Larock indole synthesis. The PdII atom reduces to Pd0 in situ from the complex and gets oxidatively added to the C-X bond to produce a PdII-aryl complex. Then the alkyne coordinates and inserts into the Pd(II)-aryl bond. Deprotonation, followed by reductive elimination forms the final product.[32]

So far, most procedures have used soluble catalysts, including soluble palladium catalysts with costly phosphine ligands. Separation of the catalytic material from the reaction mixture, and ligand contamination of the reaction mixture cannot be allowed for biological applications. Thus, heterogenous catalysts are preferred for such applications.[34]. Earlier, Batail, Bendjeriou, et al, had used the heterogenous palladium catalyst Pd/C or Pd/NaY for indole and benzofuran syntheses under both ligand-free and salt-free conditions.[35]

However, that technique lacked recyclability of the catalyst due to relative lack of catalyst activity. Later, Batail, Bendjeriou, et al derived a hybrid catalyst based on SBA-15 mesoporous silica modified by grafted palladium complexes bearing other phosphine or cyano ligands.[34] The covalent immobilization of Pd+2 complexes allowed for a highly ordered mesostructured. This heterogenous catalyst was particularly useful for multiple recycling, as the material could be used to convert ortho-iodoaniline into indole over multiple cycles without significant dip in reactivity.[34] Recycling of the expensive palladium-based reagent made the synthesis procedures much cheaper.

Catalyst Loading using Nanochemistry Techniques

From an industrial point of view, reducing catalyst loading is highly desirable and thus transition-metal nanoclusters (NCs) are attractive for chemical and medical research. Onishi, Oikawa et al[36] prepared N, N-dimethylformamide (DMF) stabilized transition-metal nanoparticles, which showed high catalytic capacity in other organometallic reactions such as the Ullmann reaction and the Suzuki coupling reaction. Those DMF-stabilized palladium nanoparticles were also suitable as catalysts for the Larock indole reaction. The NCs were recycled at least 3 times, and the typical particle size of the nanoparticles is between 1-3 nm.[35]

Further Development in Synthetic Techniques

1. Buchwald Modification

The Larock indole synthesis inspired newer methodologies for the Fischer indole synthesis. In particular, Buchwald et al [37] discovered a palladium-catalyzed method for the preparation of indoles via the Fischer indole synthesis, using the same catalyst used in the Larock indole synthesis. This proved to be extremely useful especially if the starting material was a hydrazone. Such starting materials are not stable enough to undergo the traditional Fischer indole synthesis. The base used in this reaction (shown in Fig 47) is usually bulky, such as t-BuONa.[37]

The use of a Pd/BINAP-based catalyst produced N-aryl benzophenone hydrazones in good yields. After this, the N-aryl benzophenone hydrazones can be converted to indole products via the in-situ Fischer cyclization. This method can also be used to generate N-alkylindoles via N-aryl-N-alkylbenzophenone hydrazones. [37]

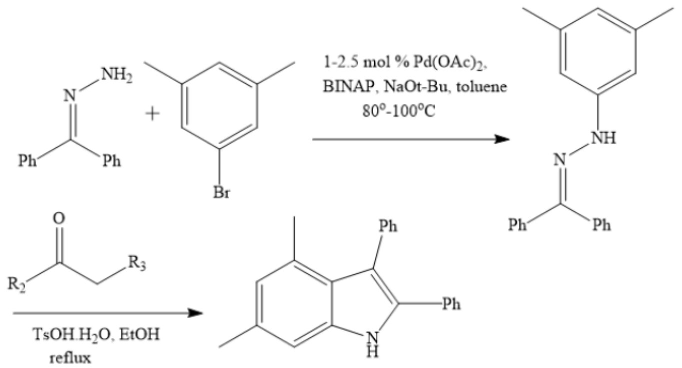

Fig 47: Palladium Catalyzed Fischer Indole Synthesis

2. Palladium-catalyzed Oxidative Indole Synthesis

The palladium catalyst was found to be useful in oxidative cyclization of N-aryl imines into indole as well. (Fig 48) Wei, Deb et al[38] observed that this oxidation can happen even in presence of aerobic oxygen and is highly tolerant of other functional groups. Two-fold oxidative cyclizations also happen. An imine-enamine transformation, followed by a Larock-like reaction, where a six-membered palladacycle is formed, ended by reductive elimination, is the mechanism here as well.

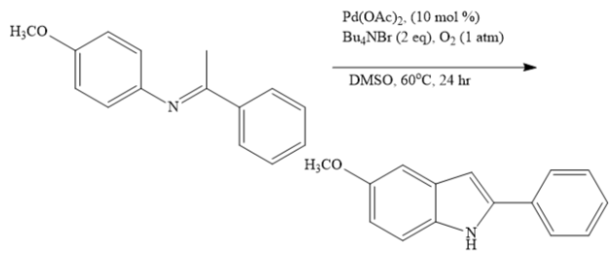

Fig 48: Palladium-catalyzed Aerobic oxidation of Imines to Indoles

Versatility when paired with Sonogashira Coupling

The Larock indole synthesis becomes very versatile when paired with Sonogashira coupling, yet another innovative technique in organometallic chemistry.[8][39] Using a palladium catalyst as well as a copper cocatalyst, it forms a carbon-carbon bond between a terminal alkyne and an aryl or vinyl halide. (Fig 49)

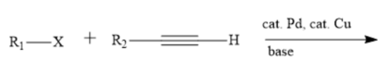

Fig 49: Sonogashira coupling

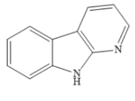

Fig 50: beta-Carboline

The reason why the Larock indole synthesis becomes even more powerful when used alongside Sonogashira coupling is because they can be together used to synthesize large polycyclic alkaloid macromolecules. The typical procedure goes this way:

a. Formation of aryl halide and Sonogashira coupling with alkyne to form alkyne substituent
b. Larock indole synthesis of the substrate with ortho-iodoaniline

Such steps have been used by Pan and Bannister[40] to successfully synthesize beta-carboline (norharmane) (Fig 50) containing alkaloids.

Fig 51 shows the likewise synthesis of indolopyridocoline triflate, a beta-carboline containing alkaloid, whose synthesis involves preparing the substrate for the Larock indole synthesis using Sonogashira coupling. Fig 52 likewise shows you the synthesis step of the alkaloid mitragynine that involves the Larock indole synthesis (the substrate comes from Sonogashira coupling).[40]

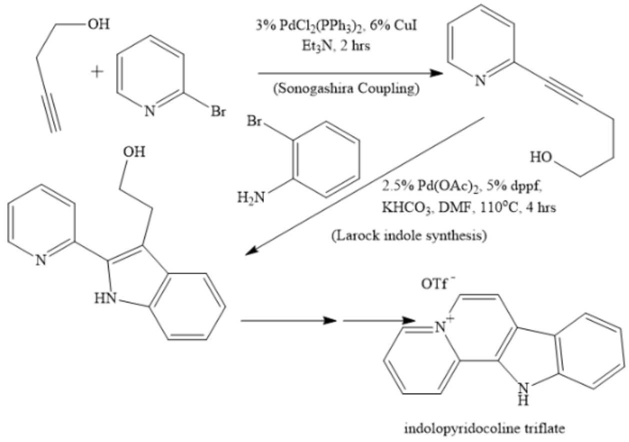

Fig 51: Synthesis of Indolopyridocoline Triflate

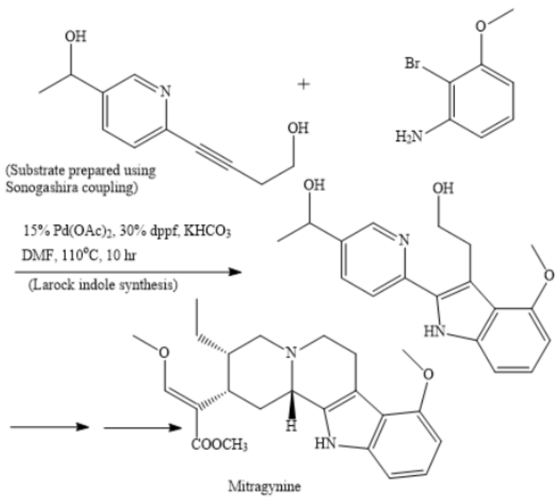

Fig 52: Synthesis of Mitragynine (Larock indole synthesis step)

Limitations

1. The effects of solvents and bases regarding the Larock indole synthesis have not been fully formulated. Depending on the compounds used as reactants, chemists are still dependent on experimentally using various combinations of bases and solvents and choosing the one with the highest yield. Thus, the choice of reaction conditions is only empirically determined and is a theoretical black-box.
2. Although multiple synthesis techniques to make indole have been discovered, there is no one synthesis technique is the one-size-fits-all best method for all indole family molecules. Depending on the target molecule, purity level, and cost-effectiveness, and functional groups, different reaction techniques are best-suited. An organic synthesist should be aware of the various methodologies possible in this regard.
3. Palladium is not the only metal that is suitable as the catalyst. Nickel catalysts have been tried for the Larock-like indole synthesis. It is yet to be determined if other transition metals, possibly cheaper, could be used as catalysts in any way or not.

Future Suggestions

1. The indole molecule is the nucleus of a variety of important drugs, such as indometacin and triptan (Fig 53a-53b). These drugs have been manufactured using techniques not involving the Larock indole synthesis or other palladium/transition-metal catalyzed heteroannulation. These drugs are manufactured purely using classical techniques mostly. With the innovation in cheap heterogenous catalysts [34], is it possible to synthesize these drugs using the latest organometallic techniques?

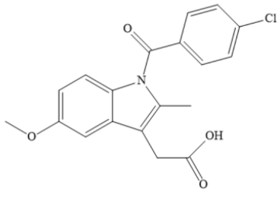

Fig 53a: Indometacin

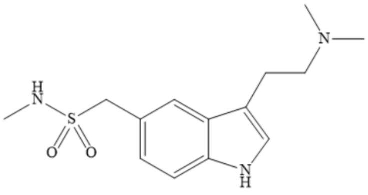

Fig 53b: Triptan (Sumatriptan)

2. Further studies should be undertaken, using tools from inorganic chemistry, to determine why certain transition metals act as good catalysts for these reactions, while others do not. It should also be studied why certain ligands bound to transition metals enable the synthesis to occur, while others do not. The kinetic effects of various neighboring ligands are not fully understood yet and need to be pursued.

Conclusion:

Overall, the Larock indole synthesis is a cornerstone in modern organometallic synthetic techniques. The technique shows remarkable flexibility compared to past techniques and has seen applications in numerous fields. It has been used in synthesis of alkaloids, HIV protease inhibitors, anti-migraine drugs, chemotherapy targets, antibacterial chemicals and antifungals, and total synthesis of macromolecules, as well as development of better catalysts. It is a method that is likely to come to use to an organic synthesist in some way or the other. Recent innovations in other areas of chemistry, such as solid-state chemistry and nanochemistry, are pushing the frontiers of organometallic chemistry forward, and allowing us to develop newer novel methodologies.

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