CHAPTER-1

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BUCHWALD-HARTWIG REACTION

Introduction

Coupling of aryl electrophiles and nucleophiles to form new carbon-carbon bonds is of great utility. However, although carbon-carbon bond formation processes dominated the beginnings of cross-coupling chemistry in recent years. The scope of metal-mediated cross-coupling has expanded immensely, with carbon-nitrogen cross-coupling emerging to the forefront as a versatile and useful method of preparing arylamines. Such nitrogen-containing fragments are ubiquitous in biologically-relevant molecules, pharmaceuticals, herbicides, as well as their smaller, organic precursors, making their efficient preparation of great interest. Traditionally, these compounds were prepared via classical methods, such as nitration, reduction/reductive alkylation, copper-mediated chemistry at high temperatures, or direct nucleophilic substitution on electron-poor aromatic or hetero aromatic halides. Several drawbacks are associated with these methods, including safety, cost, waste products, toxicity and synthetic efficiency. As such, a number of these methodologies have been abandoned in favor of catalytic methods, particularly as the scope and efficiency of catalytic C-N bond-forming methods has been expanded.

A breakthrough in palladium-mediated carbon-nitrogen bond formation occurred in 1995, when Hartwig and Buchwald concomitantly reported practical protocols for the catalytic generation of arylamines using the same catalyst system initially reported by Migita. This new cross-coupling reaction utilized aryl bromides and simple secondary amines, eliminating the need for aminostannane reagents, as well as ameliorating or eliminating many of the other drawbacks of those previous reactions, including the need to generate the reactive amine in situ, thereby eliminating the formation of byproducts altogether (Figure 1).

(Figure 1)
The palladium-catalyzed coupling of amines with aryl halides or aryl alcohol derivatives, commonly dubbed Buchwald–Hartwig amination, has matured from a synthetic laboratory procedure to a technique that is widely used in natural product synthesis as well as in other fields of academic interest. Furthermore, due to the versatility and reliability of this reaction, researchers in industrial environments have included this methodology in their toolbox as a standard procedure for the synthesis of amine derivatives. Palladium-catalyzed amination of aryl, vinyl and heteroaryl halides and pseudohalides has rapidly emerged as a valuable tool in the synthesis of pharmaceuticals, natural products and novel materials. The development of Pd-catalyzed C–N coupling has significantly contributed to the streamlining of the synthesis of small molecule pharmaceutical agents, allowing more efficient syntheses and facilitating a modular approach to analogue synthesis. The significance of this methodology in this regard stems from the prevalence of aromatic amines in biologically active molecules; important classes include kinase inhibitors, antibiotics, and CNS active agents. Buchwald –Hartwig reaction has been known for a full century and served well for C-N, C-S, C-O and some other bond formation reactions.

Components of the Catalytic System

Buchwald–Hartwig aminations usually require a catalytic system containing four components to efficiently generate the desired C-N bond (Figure 2). A palladium precursor is typically stabilized in solution by an adequate ligand that also raises the electron density at the metal to facilitate oxidative addition and provides sufficient bulkiness to accelerate reductive elimination. A base is required to deprotonate the amine substrate prior to or after coordination to the palladium centre. Owing to the often heterogeneous nature of the reaction due to solubilities of the base or the substrates, the solvent plays a more prominent role than in other transition metal-mediated processes. These four parameters greatly influence the performance of any given C-N coupling reaction and are all of similar importance in designing a screening or reaction set-up.
Ligands

Although catalyst systems containing no ligand have been reported over the last years for some organometallic transformations,\textsuperscript{18,19} C-N coupling reactions are usually carried out with an added ligand. The ratio of ligand to palladium depends mostly on the ligand employed and can have a distinct influence on the catalytic performance.
Figure 3
Bidentate ligands
The quest for suitable ligands showing higher reactivity and selectivity has been a field of enormous activity over the last years.\textsuperscript{20-24} The development of adequate systems has passed through various stages. The first ligands to be used were P(o-Tol)\textsubscript{3}\textsuperscript{25, 26} and P(t-Bu)\textsubscript{3}\textsuperscript{27} (Figure 4)\textsuperscript{28} The chelating bisphosphines BINAP, DPPF and DtBPF used by Buchwald and Hartwig then defined the state of the art until Buchwald reported the synthesis of monodentate phosphine ligands with a biphenyl backbone in 1998.\textsuperscript{28} These ligands greatly enhanced the scope of aminations to aryl chlorides and unactivated aryl halides even under very mild conditions.\textsuperscript{29} The design of the new bulky 2,4,6-triisopropyl-substituted ligand X-Phos led to the most active and stable biphenyl based ligand to date. The binaphthyl version of Buchwald’s biphenyl ligands, MAP, originally designed and prepared as a ligand for allylic substitution by Kocovsky in 1997, could also later be successfully applied in aromatic amination,\textsuperscript{30} therefore underlining the privileged nature of the biphenyl type phosphines. With the advent of carbenes showing outstanding performance in other organometallic transformations as sterically bulky and good electron-donating ligands, these non-phosphorus-based ligand systems increased the variety of ligand architectures.\textsuperscript{31-35}
In parallel, van Leeuwen developed XantPhos and DPEPhos (Figure 3) that show especially high activity for coupling of aryl halides with amides, hydrazines, oxazolidinones and ureas. These bisphosphines interestingly can act in a trans-chelating mode. Whereas the above-mentioned ligands constitute the most versatile choice with respect to performance and reliability, new lines of ligand design have led to other classes as well.

Verkade reported the use of triaminophosphines as electron-rich ligands with a rigid framework that can be handled in air. The scope is very broad including aryl iodides and aryl chlorides. Heterocyclic subtypes of Buchwald’s biphenyl-based ligand systems (Figure 4) were reported by Singer in 2003. These pyrrole- and pyrazole-based systems are characterized by the synthetic ease of their formation while their use still requires the combination with the strong base t-BuONa. Beller developed these systems further and recently presented new ligands based on N-arylindole substructures. For a potential recycling of the ligand, Buchwald developed a solid-phase bound version of his biphenyl-based ligands. The systems thus obtained allowed aminations down to a loading of 1 mol % palladium and could be recycled at least three times. Beller reported about adamantyl-substituted alkylphosphines, n-BuPAd2, which showed good activity in the activation of aryl chlorides. Finally, Guram reported the synthesis of phenyl backbone-derived compounds that are efficient for general aminations of aryl chlorides, bromides and iodides. Especially attractive is the synthetic simplicity of these ligands compared to binaphthyl- and ferrocenyl-derived systems. Recently developed ligands are summarized in Figure 5.
The choice of a suitable palladium precursor for conducting an amination reaction is far more limited than the choice of the ligand. Typically, Pd(0) or Pd(II) precursors which are reduced if necessary in situ to the corresponding zero oxidation state, most often by the amine in the presence of phosphine and base, are used. The most prominent Pd(0) precursors are Pd$_2$(dba)$_3$ and Pd(dba)$_2$. Nevertheless, the release of dba during the catalysis can have an effect on the performance of the reaction and has to be taken into account. The most versatile Pd(II) precursor is Pd(OAc)$_2$. Nevertheless, [allyl PdCl]$_2$ or Pd(acac)$_2$ also show remarkable activity in special cases. If amine substrates lacking b-hydrogens are used as coupling partners, it can be advisable to add a reducing agent to the catalyst mixture. Most versatile additives are phenylboronic acid, alkylamines or sodium formate. One of the most abundant Pd(II) salts is PdCl$_2$. Nevertheless it is rarely used and only Buchwald reported the use of this precursor in 2001 in the amination of aryl bromides. The effectiveness is comparable to the other precursors when bisphosphine ligands are used but it was incompatible with the use of biphenyl-based monophosphines. Concerning the catalyst loading, the range is much broader than in other types of cross-coupling reactions. While special substrates can be coupled with palladium loadings down to 0.01 mol %, it is much more typical to start a screening set-up with 1 – 2 mol % of palladium. An important point concerning the reliability of the reaction in general is the purity of the components of the catalyst system. Organic or inorganic impurities in the ligand or palladium precursor can have a large impact on the performance of the reaction. Therefore, it is advisable to use material from different suppliers to test for differences in reactivity. Especially when moving to a
larger scale, commercial palladium precursors should be use-tested and a minimum of different palladium batches (ideally one) should be used during a production campaign.

**Bases**

The third crucial component of the reactive system is the base which deprotonates the amine before or after coordination to palladium. Owing to this, at least stoichiometric quantities of this component are needed. Two types can be distinguished: bases that are only sparingly soluble in the typically used apolar solvent (e.g., toluene) and bases that give nearly homogeneous reaction mixtures. The most common bases for C-N couplings are: t-BuONa, t-BuOK, LHMDS, Cs₂CO₃, K₂CO₃, K₃PO₄, NaOMe, NaOH, KOH and t-AmONa. The vast majority of side-reactions to be found in Buchwald–Hartwig aminations are caused by the added base. The functional group tolerance of the strong tert-butoxide bases first used in this type of chemistry is inherently low. The relative base strength determines the functional group tolerance. Unfortunately, direct comparisons of base strengths are difficult owing to heterogeneous mixtures in which solubilities play a significant role, as well as to the broad variety of solvents employed. Nevertheless, a general trend can be outlined. This is effected by the counterion of the base (Cs₂CO₃ > K₂CO₃ > Na₂CO₃) as well as more subtle parameters such as the particle size of the base. Due to the larger surface area, it is usually advantageous to use finely powdered bases for heterogeneous reaction set-ups.

Apart from the base-sensitivity of the substrate, the combination of base and ligand as well as base/temperature are also important parameters. Regrettfully, only very general trends are reported in the literature. Strong bases such as t-BuONa have been used very frequently and these are very suitable for low temperature processes and/or low catalyst loadings. Cs₂CO₃ is most effective when chelating bisphosphine ligands are used and many transformations using this base have been reported recently. ²⁹, ³⁷-³⁹, ⁴², ⁴⁴ K₃PO₄ tends to show good results with biphenyl-based systems ²¹, ²⁹, ⁵³, ⁵⁴ and P(t-Bu)₃ but is less useful with chelating ligands, which seems to be a general trend.²³ Hartwig and Buchwald even reported the use of the most inexpensive bases (KOH, NaOH) in aqueous solution which are active in combination with biphenyl-based systems as well as Hartwig’s palladium-dimer complex. When carbenes are used as ligands, the base also serves as the deprotonating agent for the imidazolium salt precursor, which often requires the use of a strong base. ³³, ⁵⁵ LHMDS proved to be especially useful for the coupling of amines with aryl halides containing
hydroxy, amide or enolizable keto groups in conjunction with bulky biphenyl-based ligands at least in catalytic amounts.

**Solvents/Temperature**

Buchwald–Hartwig aminations are usually run within an organic solvent system. The role of the solvent is twofold. Apart from dissolving the coupling partners as well as parts of the base and allowing for a respective temperature window for the reaction, the solvent also plays a crucial role in stabilizing intermediates in the catalytic cycle. The majority of the reactions reported is run in toluene. Frequently, ethers such as DME, THF or dioxane are used. For solubility reasons the polar solvents DMF, NMP or DMSO can also be used for C-N coupling. The solvents usually have to be dry and deoxygenated but this is strongly dependent on the air-sensitivity of the catalyst system used. In special cases using only slightly air-sensitive phosphines, reactions can be run entirely in air without significant changes in yield. Also, the addition of water can even be beneficial as can be seen from the use of aqueous bases in the amination reaction. Nevertheless, this only holds true for substrates that are not hydrolyzed under basic conditions. Some aminations can even be run in water as the only solvent. Other additives reported by Buchwald are alcohols, especially the low nucleophilic tert-butyl alcohol to increase conversion. Mixed solvent systems can have a great impact mostly on the degree of conversion in certain amination reactions, often owing to the solubilities of the components. Sometimes it is beneficial to premix the catalyst and the ligand in a suitable solvent such as THF to allow time for the formation of the catalytically active complex before adding this to the actual reaction mixture. Amination reactions can be run even under rather concentrated conditions up to 30% w/w which is important for the space-time yield on a production scale. In most cases the concentration is limited by the undissolved components such as base, starting material or product forming suspensions with stirring becoming a limiting factor. Regarding the temperature, usually a range between room temperature for the most active ligand systems such as P(t-Bu)_3, some biphenyl-based systems and carbenes up to 140 °C for palladacyclic complexes is reasonable. The vast majority of reactions is run inside a range of 70 –110 °C which can be considered as typical for biphenyl-based ligands.
**Mechanism of Buchwald-Hartwig reaction**

The generally accepted catalytic cycle for C-N cross-coupling featuring a palladium-based catalyst is outlined in (Figure-6). The cycle begins by activation of the precatalyst by base, and is followed by oxidative addition of the aryl halide to the activated LnPd(0) species, which is then followed by coordination of the amine to the resulting Pd(II) intermediate. The amine can then undergo deprotonation by the base, and reductive elimination of the resulting amido species yields the arylamine product, and regenerates the active catalyst.

![Figure-6](image_url)

**Figure-6**

Although rates of oxidative addition are certainly catalyst dependent (in that more electron-rich, sterically unhindered complexes promote oxidative addition more favourably), the steric and electronic characteristics of the substrates also influence reaction rates.63, 64 For example, electron-rich aryl halide species can be more challenging to undergo oxidative addition with the palladium catalyst, and are often referred to as ‘deactivated’ substrates. Electron-poor aryl halides, on the other hand, typically undergo oxidative addition more easily, and are hence referred to as ‘activated’ substrates. In addition to the electronic properties of the aryl halide, steric properties can also play an important role, as more hindered substrates may also undergo oxidative addition more slowly than unhindered ones. The nature of the halide itself is also of great importance, both in terms of halide-carbon bond
strength, and due to the fact that the mechanism of oxidative addition can vary depending on the halide in question.  

The amine-binding step is also dependent on both the catalyst and the substrate. More electron-rich (basic) amines typically bind more favorably with metal species, as do those that are not sterically hindered. Consequently, less basic or more sterically hindered amines often exhibit weaker coordination with the catalytic species, which can result in poorer reaction rates or yields. Deprotonation of the bound amine, on the other hand, depends primarily on the propensity of the amine to undergo deprotonation (e.g. ‘acidity’). Binding to a transition metal centre greatly increases the relative acidity of the amine protons, but the fundamental acidity of the amine itself can still play an important role in determining conversion, and in the case of systems containing multiple amines, product formation.

The rate of reductive elimination of the arylamine product is primarily a function of the metal/ligand characteristics. In general, electron-poor complexes have a tendency to undergo reductive elimination more quickly, as do complexes that have bulky ancillary ligands, as reductive elimination reduces steric strain and renders a transition metal centre more electron-rich. Within these general guidelines lie a number of factors that can also influence rates of reductive elimination in these systems, particularly the nature of the reacting ligands in question. For example, bulky groups on the metal-bound reactive ligands can also help to promote reductive elimination. Additionally, in complexes containing bidentate phosphine ligands, it has been demonstrated that reductive elimination to form a new carbon-nitrogen bond proceeds more quickly when a more electron-rich amido reacting ligand is involved. Similar studies with the same type of complexes have also shown that reductive elimination is also faster when a more electron-poor aryl group is bound to the palladium centre.
References


SUZUKI REACTION

Introduction

Transition metals have a unique ability to activate various organic compounds and through this activation they can catalyze the formation of new bonds. One metal that was used early on for catalytic organic transformations was palladium. In general, transition metals, and in particular palladium, have been of importance for the development of reactions for the formation of carbon-carbon and carbon-nitrogen bonds. The principle of palladium-catalyzed cross couplings is that two molecules are assembled on the metal via the formation of metal-carbon bonds. In this way the carbon atoms bound to palladium are brought very close to one another. In the next step they couple to one another and this leads to the formation of a new carbon-carbon or carbon-nitrogen single bond.¹

In 1979 Suzuki and co-workers reported in two papers that organoboron compounds in the presence of a base can be used as coupling partners in palladium-catalyzed cross coupling with vinyl and aryl halides.²,³ (Figure 1) Thus, base activation of organoboron reagents as boronate intermediates facilitated the transfer of the organic group from boron to palladium (transmetallation). The reaction has later been extended to include couplings with alkyl groups.

\[ \text{R-BY}_2 + \text{R'}-\text{X} \xrightarrow{\text{Pd}} \text{R-R'} + \text{BY}_2\text{X} \]

\( \text{R, R'} = \text{aryl, vinyl, alkyl} \\
\text{X} = \text{halide, triflate, etc} \)

Figure 1

A further significant development came from the observation that arylboronic acids are able to participate as coupling partners in the palladium-catalyzed cross-coupling reaction. In the latter case the reaction was even more efficient and weaker bases could be employed. The stability and weak nucleophilic nature of organoboron compounds has made this reaction very practical. It tolerates a wide range of functional groups and it is highly chemoselective. Furthermore, boron compounds are generally non-toxic and the reaction can be run under very mild conditions. This has made the reaction popular in the pharmaceutical industry. The reaction is called the Suzuki-Miyaura cross-coupling reaction.³
The Suzuki-Miyaura cross-coupling has several advantages since mild reaction conditions can be used. The reagents for the reaction are easily available and the reaction proceeds in the presence of wide variety of functional groups. Several organometallic reagents are used for analogous cross-coupling reactions but organoboron compounds are interesting reagents because they are thermally stable, inert to water and oxygen and thus easy to handle. In addition, inorganic by-products are non-toxic which makes the coupling reaction suitable also for industrial processes. Suzuki-Miyaura reaction is one of the most popular reactions in modern organic chemistry. Generally, it is a palladium-catalyzed process of cross-coupling of an organoboron compound with an organic halide which produces a bis-aryl via direct C-C bond formation. The reaction has plenty of applications in organic synthesis, material and medicinal chemistry and it is still an area of intense research. The reaction mechanism has been largely studied and reviewed but the organic partners involved in the reaction have had much less attention. One common group of substrates of Suzuki-Miyaura cross-coupling reactions are boronic acids and esters.

**Components of the Catalytic System**

It is obvious that the selection of a proper catalytic system is fundamental for achieving the best efficiency in a given Suzuki reaction. However the catalyst efficiency is not only uniquely related to its catalytic activity or selectivity, but also to the possibility of recovery and re-utilisation of its components. At the same time, it is also desirable in every case to minimize the generation of waste and the environmental impact, especially for possible applications on an industrial scale. According to these very basic principles, significant efforts have been made in recent years to develop more simple, but efficient, catalytic systems.

Suzuki reaction generally requires a catalytic system containing four components to efficiently formation of C-C bond. A palladium precursor is typically stabilized in solution by an adequate ligand that also raises the electron density at the metal to facilitate oxidative addition and provides sufficient bulkiness to accelerate reductive elimination. It is known that the base is involved in the coordination sphere of the palladium and accelerate the transmetallation step. Owing to the often heterogeneous nature of the reaction due to solubility of the base or the substrates, the solvent plays a more prominent role than in other transition metal-mediated processes. These four parameters greatly influence the
performance of any given C-N coupling reaction and are all of similar importance in designing a screening or reaction set-up.

**Palladium Precursors**

The combination of catalysts, bases and solvents has a great effect on the yields and selectivity of the cross-coupling reaction products.\(^6\)

Organoboron compounds can be synthesized by cross-coupling reactions of tetra-(alkoxo)diborons catalyzed by transition-metals.\(^7\) Palladium catalysts with bulky, electron-donating alkylphosphines are recognized to be excellent catalysts in cross-coupling reactions of haloarenes. \(\text{PdCl}_2(\text{dppf})\) is the most suitable catalyst for borylation of haloarenes having both an electron-withdrawing and -donating group, even for chloroarenes.

Palladium-catalyzed cross-coupling reactions of aryl halides with arylboronic acids are one of the most important ways of making symmetric and nonsymmetric biaryls.\(^8\) A variety of homogenous catalysts have been used but they are difficult to recover and reuse and they could not be used in large-scale synthesis because of environmental and economic reasons and therefore a reusable and recoverable heterogeneous catalyst is needed. In large-scale industrial processes it is advantageous to use aqueous media because of the simplicity of the catalyst separation, economy and safety.\(^9\) However, complete conversion of the catalyst is not always possible especially in slow reactions of electron-rich and sterically hindered substrates even though rapid coupling reaction in aqueous media do occur. Supported palladium-phosphines have been suitable catalysts in coupling reactions of arylboronic acids.\(^8,10\)

**Ligand**

There is a wide variety of ligands available which give high catalyst efficiency and selectivity.\(^11\) Phosphine ligands are effective in stabilizing the palladium(0) species but the bulkiness, stoichiometry of phosphine to palladium or donating ability of phosphine ligands makes the catalyst more susceptible towards oxidative addition, reductive elimination and transmetallation. Depending upon the bulkiness of the ligands phosphine complexes are in equilibrium with coordinatively unsaturated compounds. Either monophosphine \(\text{Pd}(0)\text{L}\) or biphosphine \(\text{Pd}(0)\text{L}_2\) complex is responsible for the oxidative addition of organic halides. Palladium complexes with less than four phosphine ligands or weakly coordinating ligands, such as AsPh\(_3\), are highly reactive catalysts because of the easy formation of coordinatively
unsaturated species. The ligand donates an electron to the palladium(0) metal center. 12, 13 Triarylphosphines are effective ligands for coupling reaction of organic iodides, bromides, triflates and activated chlorides because of their air-stability. However, they do not catalyze reactions of electronrich chlorides. Bulky and easily donating ligands, such as P(t-Bu)$_3$, function as highly active catalysts even at room temperature. These ligands have an ability to donate electrons to the metal center which assures their accelerating effect on the reaction. Common ligands used in palladium catalysts are shown in previous reaction.

Less bulky phosphines are suitable for slow reactions of functionalized substrates because they yield thermally stable complexes. For example, (t-Bu)$_2$POH and N-heterocyclic carbenes are suitable for the reactions at high temperatures. Bisphosphines, such as 1,3-bis(diphenylphosphinyl)propane, dppp, 1,4-bis(diphenylphosphinyl)butane, dppb, and 1,1’-bis(diphenylphosphino)ferrocene, dppf, have a large P-M-P angle and accelerate the reductive elimination in the coupling reaction of alkylmetals. In addition, the ligand dppf works well for coupling reactions of l-alkenyl- and arylboronic acids. Palladocycles derived from tris(o-tolyl)phosphine, triarylphosphite, benzoxime and bis(phosphinite) are air stable catalysts with high catalytical efficiency in coupling reactions of arylboronic acids and bromoarenes or activated chloroarenes. 

Because the best catalyst for coupling reactions of arylboronic acids with haloarenes is dependent on reaction conditions, reactants and solvents, it is often chosen by screening. 14a Alkylphosphines, such as t-Bu$_3$P and BuP(Ad)$_2$, are suitable ligands for chloroarenes and for slow reactions of electron-rich bromoarenes. Specific methods are needed for synthesis of di-ortho-substituted biaryls. 14b A phenanthrene ligand-based catalyst allows the synthesis of sterically hindered biaryls where the reactants have two ortho-substituents. As an example of cross-coupling reaction of hindered substrates, 2,4,6-trimethylphenyl bromide reacts with 2,4,6-trimethylphenyl boronic acid and gives 1,3,5-trimethyl-2-(2,4,6-trimethylphenyl)benzene (Figure 2). 1,2,3-Trimethylbenzene is formed as by-product.
Only the phenanthrene ligand-based catalyst allows the synthesis of sterically hindered biaryls with two ortho-substituents (Figure 3). The corresponding naphthyl- and biphenyl-based ligands give significantly lower yields and low conversions. The mechanism of the phenanthrene ligand action is based on a highly stabilized monophosphine palladium (0) in phenanthrene/Pd(dba)$_2$ complex with an unusual π-coordination of a phenanthrene moiety to a palladium metal center.

The traditional catalysts in palladium-catalyzed C-C and C-heteroatom bond forming reactions are simple Pd(0) species and Pd(II) salts, such as Pd(PPh$_3$)$_3$, Pd$_2$(dpa)$_3$ and PdCl$_2$(PPh$_3$)$_2$. However, they have some drawbacks, such as sensitivity to air and moisture and the need of large loading, 5 mol % or more. In contrast, cyclopalladated ferrocenyli$^{15b}$ limines are air-stable and efficient palladium catalyst precursors which are easy to handle. They can be applied to wide variety of reactions, such as Suzuki, Heck and Buchwald-Hartwig couplings and reactions of arylboronic acids. A variety of palladacycles are suitable catalyst precursors for the Suzuki-Miyaura reaction of organoboron compounds with aryl halides in organic solvent or water. For example, palladacycle (Figure 4) is effective in reactions of aryl iodides, aryl bromides and electron-poor aryl chlorides.
Tricyclohexylphosphine adducts of cyclopalladated ferrocenylimines (Figure 5) can act as the catalyst precursor for Suzuki-Miyaura reaction of the deactivated aryl chlorides due to their bulky, sterically hindered alkylphosphine ligands.\textsuperscript{15a} Good yields can be gained even with low catalyst loading (0.1 mol %).

Palladacycles with phosphine or carbene ligand enhance the catalyst activity which leads to activation of C-Cl bond.\textsuperscript{15a} Palladacycles with 2,2'-bipyridine ligand can act as catalyst for various reactions of arylboronic acids and can be used in water. The greatest advantage of palladacycles is its low catalyst loading of 0.1-1 % or lower, the possibility to perform the reactions under mild conditions and suitability for a wide variety of functional groups. The mechanism of the catalytic cycle consists of oxidative addition, transmetallation and reductive elimination.\textsuperscript{16} The modification of the ligand affects the catalytic cycle but the effect is not always straightforward. For example, for monodentate phosphines the presence of labile ligands, such as dibenzylideneacetone, halide ligands and acetate, can change the kinetics of the reaction by coordination to the low-valent palladium intermediates. Because reductive elimination is the reverse reaction of oxidative addition, ligand effects are often
As the bite angle of the multiple-dentate ligand increases, both oxidative addition and reductive elimination reactions become faster. The optimum angle of P-Pd-P varies between 85-111° depending on ligand.

**Base**

In the cross-coupling reactions of diboronic acids, a suitable base is essential in order to achieve a successful reaction. The right base ensures high selectivity and high yield of the target product. Milder base, such as KOAc is preferable, since the stronger bases, such as K₃PO₄, K₂CO₃, promote further reactions of aryloboronic esters with haloarenes and formation of high amounts of dimers. In the catalytic cycle of the cross-coupling reaction, the transmetallation process is highly dependent on the organometallics and the conditions used in the reaction. Even though the transmetallation is not well understood as oxidative addition and reductive elimination, it is thought that the base accelerates the transmetallation rate. The negatively charged base coordinates to the boron atom thus increasing its nucleophilicity for transmetallation to the palladium halide. On the other hand, the base displaces the palladium halide to give an alkoxy-, hydroxyl- or acetoxopalladium(II) species in solution which transmetallate with organoboron compounds under neutral conditions. According to ¹B NMR analysis, it is clear that the latter mechanism is predominant for acetopalladium(II) species. The high reactivity of oxopalladium complexes towards transmetallation with organoboron compounds is caused by the high reactivity of the Pd-O bond which consists of a mild acid and a strong base combination and the high oxophilicity of the boron center. In the transmetallation process first the coordination of the alkoxy ligand to the boron atom takes place and is followed by the transfer of the organic group from boron to the palladium atom. A negatively charged base, such as a solution of sodium or potassium carbonate, phosphate or hydroxide is needed in cross-coupling reactions of organoboronic acids with organic halides or triflates. Na₂CO₃ is a mild base and is suitable for different kinds of coupling reactions of aryloboronic acids. However, it is inefficient for sterically hindered reactants with several ortho-substituents. In the reactions of mesityl boronic acid with iodosobenzene the base has an effect on the order of reactivity: TIOH > Ba(OH)₂, Tl₂CO₃ > NaOH > Cs₂CO₃, K₃PO₄ > Na₂CO₃ > NaHCO₃. Cesium bases, such as Cs₂CO₃ and CsOH, have a greater accelerating effect than sodium or potassium salts.
The effects of the bases can be roughly estimated by the basic strength and affinity of counter ions for halide ions.\(^{20}\) Because the transmetallation involves nucleophilic displacement, the reaction can be fast for counter ions with a high stability constant for halide ions (Ag\(^+\)>Tl\(^+\)>>Ba\(^{2+}\)>Cs\(^+\)>K\(^+\)). Hydroxyborate anion \([R_2B(OH)_3]M\) in alkaline solution is in equilibrium with a free organoboronic acid and its concentration increases as the basic strength increases (OH\(^-\)>MPO\(_4^-\)>MCO\(_3^-\)>HCO\(_3^-\)). The counter cation may have an effect on the solubility of \([R_2B(OH)_3]M\) in organic solvents.

**Solvents**

The rate of the cross-coupling depends on solvent, since polar solvents increase the reaction rate.\(^ {17,21}\) Reaction is accelerated in the order of toluene<dioxane<DMF<DMSO. However, DMF causes low yield and low selectivity because it induces decomposition of dialkoxyboranes to diborane, B\(_2\)H\(_6\).

For sometimes, the cross-coupling reactions of organoboronic acids with organic halides or triflates are often carried out in a two-phase system of organic and basic aqueous solutions. In case of that, phase transfer catalysts must be used.\(^ {22}\) In basic solutions esters may saponify, optically active compounds racemize and aldol condensations of carbonyl compounds may occur. These difficulties can be overcome by using bases in heterogeneous phase systems. For example, in a two-phase system of aqueous K\(_2\)CO\(_3\) and toluene, esters remain intact and anhydrous K\(_2\)CO\(_3\) suspended in toluene does not cause racemization of optically pure compounds. Even though anhydrous inorganic bases are used with organic solvents, the presence of water may be preferred.\(^ {23}\)

Water as solvent accelerates the cross-coupling reactions of arylboronic acid with bromoarenes since the anion ArB(OH)_3\(^-\) is 106 times more reactive than the neutral boronic acid in electrophilic reactions. In the cross-coupling reactions 1 mol of water and 1 mol of carbonate are required to activate the boronic acid. Another mol of each is used to neutralize boric acid, the coupling reaction by-product, as shown in Figure 6.

\[
ArB(OH)_2 + K_2CO_3 + H_2O \rightarrow ArB(OH)_3^-K^+ + KHCO_3
\]
\[
B(OH)_3 + K_2CO_3 + H_2O \rightarrow B(OH)_4^-K^+ + KHCO_3
\]

Figure 6
**Boronic acid derivatives for cross-coupling reactions**

Boronic acids are classified in subtypes as alkyl-, alkenyl-, alkynyl- and arylboronic acids. The reactivity of boronic acids depends on the nature of the substituent directly bonded to boron. The crystals of alkyl or aryl boronic acids are orthorhombic and the asymmetric units of two distinct molecules are bound through a pair of O-H···O hydrogen bonds. Structurally, boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent and two hydroxyl groups to fill the valences of the boron atom. Oxygenated organoboron compounds are presented in Figure 7 below.

![Figure 7](image)

The dimeric ensemble is linked with hydrogen bonds to four similar units. The geometry of boronic acid group is trigonal and fairly coplanar with an aryl group but it can be almost 10 perpendicular to the aryl ring if there is steric strain caused by an ortho-substituent. The C-B bond of boronic acids and esters is slightly longer (1,55-1,59 Å) than typical C-C single bonds. The average bond energy (323 kJ/mol) is also slightly lower than that of C-C bonds (358 kJ/mol). The B-O distances of tricoordinate boronic acids are fairly short, about 1,35-1,38 Å and slightly larger than those of boronic esters.

Boronic acids and their esters may also coordinate basic molecules to complete borons octet and form stable tetracoordinated adducts. Examples of boronic acid derivatives are shown in Figure 8. When tetracoordinated, the B-O bond of boronic esters increases to about 1,43-1,47 Å and the bond becomes comparable to normal C-O ether linkages (~1,43 Å).
The bond strength is caused by conjugation between the lone electron pairs on the oxygen’s and boron’s vacant orbital and this explains a partial double bond character to the B-O linkage. In rare cases boronic acid derivatives may be hypervalent. For example, in case of catechol ester 39, the boron atom is pentacoordinated (Figure 9). Each ether group donates lone pair of electrons to both lobes of the vacant p-orbital of boron.
Mechanism of the Suzuki Coupling

The mechanism of the Suzuki reaction is best viewed from the perspective of the palladium catalyst. (Figure 10) The first step is the oxidative addition of palladium to the halide to form the organopalladium species. Reaction with base gives intermediate, which via transmetalation with the boron-ate complex forms the new organopalladium species. Reductive elimination of the desired product restores the original palladium catalyst which completes the catalytic cycle. The Suzuki coupling takes place in the presence of a base and for a long time the role of the base was never fully understood. The base was first believed to form a trialkyl borate, in the case of a reaction of an trialkylborane (BR₃) and alkoxide (-OR); this species could be considered as being more nucleophilic and then more reactive towards the palladium complex present in the transmetalation step. Duc and coworkers investigated the role of the base in the reaction mechanism for the Suzuki coupling and they found that the base has three roles: Formation of the palladium complex [ArPd(OR)L₂], formation of the trialkyl borate and the acceleration of the reductive elimination step by reaction of the alkoxide with the palladium complex. 

![Figure 10](image-url)
**Oxidative Addition**

Attaching of the palladium catalyst to the alkyl halide gives rise to the organopalladium complex (Figure 11). In most cases the oxidative addition is the rate determining step of the catalytic cycle. During this step, the palladium catalyst is oxidized from palladium(0) to palladium(II). The palladium catalyst is coupled with the halide to yield an organopalladium complex. As presented in the diagram the oxidative addition step breaks the carbon-halogen bond where the palladium is now bound to both the halogen and the R group.

![Oxidative Addition Diagram](image)

**Figure 11**

**Transmetalation**

Transmetalation is an organometallic reaction where ligands are transferred from one species to another. In the case of the Suzuki coupling the ligands are transferred from the organoboron species to the palladium (II) complex where the base that was added in the prior step is exchanged with the R1 substituent on the organoboron species to give the new palladium(II) complex. The exact mechanism of transmetalation for the Suzuki coupling remains to be discovered. The organoboron compounds do not undergo transmetalation in the absence of base and it is therefore widely believed that the role of the base is to activate the organoboron compound as well as facilitate the formation of R2-Pd-OtBu from R2-Pd-X. Reaction does not occur in the absence of base.
Reductive Elimination

This final step of catalytic cycle gives the desired product and it also regenerates the palladium catalyst so that it can participate again in the catalytic cycle (Figure 13). Using deuterium labelling, Ridgway et al. have shown the reductive elimination proceeds with retention of stereochemistry.\(^{30}\)

Figure 12

Figure 13
References


MEDICINAL CHEMISTRY

The great expansion in medicinal research in past has contributed much to the unparalleled progress of medicine during that period. Improved and basically more meaningful biological test procedures and methods of diagnosis have provided better guidance in drug discovery by pointing out suggestive observations which could be used in the design of new prophylactic and therapeutic agents. The growth of molecular biology with its chemical insight into experimental biology has contributed to more significant pharmacological theories. The elucidation of the structure of many metabolites, and of polypeptides, enzymes, polynucleotides and other biopolymers has also made possible a more rational study of the chemical mode of action of such compounds, and their interaction with drugs. Medicinal chemistry has taken advantage of these investigations, and of the refinement of pertinent chemical theories, to establish itself firmly as an interdisciplinary science. It has become the acknowledged meeting ground of modern organic and physical chemistry, and of biochemistry in the application of these fields to drugs, with its own literature and procedures.

Today a large number of diseases are cured or at least controlled by drug therapy. The fight against bacterial and fungal infections has been largely won and significant progress has been made in treating disturbed mental, cardiovascular, gastrointestinal condition. To boast, it can be claimed that certain form of cancers can be cured by chemotherapy.

Medicinal Chemistry:

Medicinal chemistry is defined as a field that applies the principles of chemistry and biology to the creation of knowledge leading to the introduction of new therapeutic agents. Hence, the medicinal chemist must not only be a competent organic chemist but he must have a basic background in the biological sciences, especially biochemistry and pharmacology.

The basis of understanding in the medicinal chemistry lies in an awareness of the relationships between the chemistry of particular compound or group of compounds and their inter-action with body, which are known as structure-activity relationships (SAR), and the mechanism by which the compound influences the biological system, which is known as its mode of action. The objective of these studies is to improve the beneficial or therapeutic effect of a drug, whilst at the same time minimizing undesirable side effect.
Drugs:

The word ‘drug’ is derived from the French word drogue, which means a dry herb. In general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals. According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological system or pathological states for the benefit of the recipient.

In order to be a useful drug, it must not show toxicity, must show good pharmacokinetic properties, must not be rapidly metabolized and most optimally, must be absorbed after oral administration. Thus, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of compounds must be investigated early in the drug discovery path to clarify clinical utility of new genes as targets. Very few drugs satisfy all the above conditions. However, the search for ideal drug continues.

There have been three approaches to the problem of finding a drug to combat a particular disease:

1. The method of trial and error. This involves the trial of all kinds of compounds, natural and synthetic.
2. The method of requiring knowledge of cell system, and then synthesizing compounds, which interfere with it.
3. The method in which one starts with a compound known to have some of the required activity (this information has been gained from the previous method), and then to vary the structure of the molecule systematically. This, method has, so far been proved to be the most fruitful.

The drugs are converted into pharmacologically active metabolite by biotransformation. These metabolites are highly active. This activity contributes to pharmacological effect ascribed to parent drugs. In some cases inactive parent drug gets converted to biologically active metabolite. Since all the metabolites are non-toxic, many toxic side effects like tissue necrosis, carcinogenecity are observed. The formation of water-soluble metabolite enhances elimination and pharmacologically inactive, non-toxic and polar compound formation. Most of the drugs undergo metabolic transformation in the body. The main site of metabolism is liver.
**Phamacophore:**

The physiological activity of drugs has been found to depend upon the presence of particular functional groups or structural units. Such a part of the drug, which causes the actual physiological effect, is known as pharmacophore.

When a pharmacophore is introduced into biological inactive compound, this makes the compound biologically active many times. Thus, it is possible to make the compounds biologically active but less toxic by introducing various pharmacophores. Some examples of pharmacophores are alkyl, hydroxy, alkoxy, aldehyde or ketone, acidic, nitro, nitrile, effect of unsaturation, effect of isomerism, halogens and unsaturated lipids.

**Chemotherapy:**

The treatment of infectious disease by using a chemical agent is called chemotherapy. The substance so employed is referred to as chemotherapeutic agent. These agents are designed in such a way that they kill or destroy the disease-producing organisms without any harmful effect on the cells in which organisms are present.

Paul Ehrlich (1854-1915) did outstanding work in medicinal chemistry and therefore called ‘Father of Chemotherapy’. He gave original ideas about the models of action of drugs. According to him, there are some cellular constituents in mammalian cells, which were earlier called receptors by Langley (1878). Ehrlich defined chemotherapy as *the use of drugs to injure an invading organism without causing injury to the host.*

**Antibacterial Chemotherapy:**

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. Bacteria are commonly responsible for many diseases, which were considered until recently to be resistant to chemotherapy.

**Bacteria:**

These are a group of microorganisms, which are unicellular and surrounded by rigid, complex, protein cell wall. These may be free living, saprophytic or parasitic; some are pathogenic to man, animals and plants.
Bacteria are classified into two types, i.e. gram-positive and gram-negative according to method developed by Christian Gram, which is as follows:

In this method, the fixed bacterial smear is first treated with a solution of crystal violet and then with iodine solution, which reacts with the dye and the cell constituents. The smear is then washed with alcohol (decolourizing agent) and safranine or some other counter stain is added.

The bacteria that retain the colour of crystal violet and appear deep violet (in colour) are called Gram-positive bacteria, whereas those, which lose the violet colour and get counterstained by safranine and appear red in colour, are called Gram-negative bacteria. The following are some of the disease causing bacteria classified in this manner:

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria bacillus</td>
<td>Coli and Typhoid bacillus</td>
</tr>
<tr>
<td>Leprosy bacillus</td>
<td>Gonococcus</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Meningococcus</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>Plague bacillus</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Spiirochaetes</td>
</tr>
<tr>
<td>Tubercle bacillus</td>
<td>Vibrios (V. Cholerae)</td>
</tr>
</tbody>
</table>

**Antibacterial agents:**

The history of antibacterial has been dynamic, characterized by the constant emergence of new challenges followed by investigation, discovery and the production of new drugs. A complete review of the various agents employed as antibacterial would be beyond the scope of this work and hence is not attempted. A brief summary of the important classes of antibacterial compounds are given below.

**Synthetic antibacterial agents:**

The synthetic antibacterial agents are comprised of two major classes of compounds; those effective systematically and those used topically.
[A] **Topical antibacterial agents:**

Antibacterial agents that are employed topically are commonly termed antiseptics, disinfectants or preservatives depending on how they are employed. Since there is a considerable degree of overlap in usage among these three groups, the more convenient method of classifying them, i.e., according to structural types.

The antiseptics and disinfectants are a large, diverse group of chemical compounds that play an important role in the maintenance of human and animal health. Although they are often improperly utilized and overrated in their effectiveness by both lay and medical personnel, they are invaluable when properly employed. The hexachlorophene tragedy has shown that extensive toxicological studies are just as important for topical agents as for systematic, and older agents should be employed with due care.

Topical synthetic antibacterials are classified as follows:

1. Halogens and Halophors
2. Phenols
3. Alcohols
4. Aldehydes
5. Quaternary Ammonium compounds
6. Dyes
7. Ureas, Amidines and Biguanides
8. Heavy Metal Compounds
9. Miscellaneous

[B] **Systematically antibacterial agents:**

The systematically active antibacterial has been divided into three groups, two of which, are sulfonamides and the antimycobacterial agents. The remaining compounds principally agents for the treatment of urinary tract infections.

Except for the sulfonamides and antimycobacterial drugs, only a few systematically active synthetic antibacterials are commercially important today. The multitudes of highly effective relatively nontoxic antibiotics available for the treatment of bacterial infections have
provided stiff competition for the medicinal chemist attempting to synthesize new antibacterial agents.

Systematic synthetic antibacterials are classified as follows:

1. Antimycobacterial agents\textsuperscript{19,20}
2. β-Lactam antibiotics\textsuperscript{21-26}
3. Trimethoprim, Cotrimoxazole\textsuperscript{27}
4. Methanamine
5. Nitrofurans\textsuperscript{28}
6. Quinolones\textsuperscript{29}
7. Sulfonamides\textsuperscript{30}

According to the effect produced, antibacterial drugs can be bacteriostatic (inhibit growth of bacteria) or bactericidal (kill the bacteria). Commonly used bacteriostatic and bactericidal drugs are given below.

<table>
<thead>
<tr>
<th>Bactericidal Drugs</th>
<th>Bacteriostatic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Nitrofurans</td>
</tr>
<tr>
<td>Polymyxin, Colistin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Lincomycin</td>
</tr>
</tbody>
</table>

Mechanism of action of antimicrobial agents:

The mechanisms of action of specific chemotherapeutic agents are taken up in more detail when individual drugs and groups of drugs are discussed later in this chapter. A few general observations are offered at this point. It is important to know something about the mechanisms of drug action because such knowledge helps in explaining the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.
Antimicrobial drugs can damage pathogens in several ways. As can be seen in table-2, which summarizes the mechanisms of the antibacterial drugs listed in table-1. The most selective antibiotics are those that interfere with the synthesis of bacterial cell walls (e.g., penicillins, cephalosporins, vancomycin, and bacitracin). These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in eucaryotic cells.

Streptomycin, gentamicin, chloramphenicol. Tetracycline, erythromycin and many other antibiotics inhibit protein synthesis by binding with the procaryotic ribosome. Because these drugs discriminate between procaryotic and eukaryotic ribosomes, their therapeutic index is fairly high, but not as favorable as that of cell wall synthesis inhibitors. Some drugs bind to the 30S (small) subunit, while others attach to the 50S (large) ribosomal subunit. Several different steps in the protein synthesis mechanism can be affected: aminoacyl-tRNA binding, peptide bond formation, mRNA reading, and translocation. For example, fusidic acid binds to EF-G and blocks translocation, whereas mucopirocin inhibits isoleucyl-tRNA synthetase.

The antibacterial drugs that inhibit nucleic acid synthesis or damage cell membranes often are not as selectively toxic as other antibiotics. This is because procaryotes and eucaryotes do not differ as greatly with respect to nucleic acid synthetic mechanisms or cell membrane structure. Good examples of drugs that affect nucleic acid synthesis or membrane structure are quinolones and polymyxins. Quinolones inhibit the DNA gyrase and thus interfere with DNA replication, repair and transcription. Polymyxins act as detergents or surfactants and disrupt the bacterial plasma membrane.

Based on the above literature survey and studied the mentioned name reaction, various bioactive molecules have been synthesized through sequential steps and maintain reaction conditions. Biological profiles of all the synthesized compounds are carried out against a panel of organism and their SAR have been discussed in individual series.
## Table-1: Mechanism of Antibacterial Drug Action

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Wall Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.</td>
</tr>
<tr>
<td>Methicillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation.</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.</td>
</tr>
<tr>
<td><strong>Protein Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Binds to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Binds to the 50S ribosomal subunit and interferes with aminoacyl-tRNA binding.</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Binds to the 30S ribosomal subunit and interferes with aminoacyl-tRNA binding.</td>
</tr>
<tr>
<td>Erythromycin and clindamycin</td>
<td>Binds to the 30S ribosomal subunit and inhibit peptide chain elongation.</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Binds to the 30S ribosomal subunit and interferes with aminoacyl-tRNA binding.</td>
</tr>
<tr>
<td><strong>Nucleic Acid Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin and other quinolones</td>
<td>Inhibit bacterial DNA gyrase and thus interfere with DNA replication, transcription and other activities involving DNA.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.</td>
</tr>
<tr>
<td><strong>Cell Membrane Disruption</strong></td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Binds to the plasma membrane and disrupts its structure and permeability properties.</td>
</tr>
<tr>
<td><strong>Metabolic Antagonism</strong></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Inhibit folic acid synthesis by competition with p-aminobenzoic acid.</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Interferes with folic acid synthesis.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid “cord factor”.</td>
</tr>
</tbody>
</table>
References:

17. C. L. Fox, *Arch. Surg.*, 1968, 96, 184