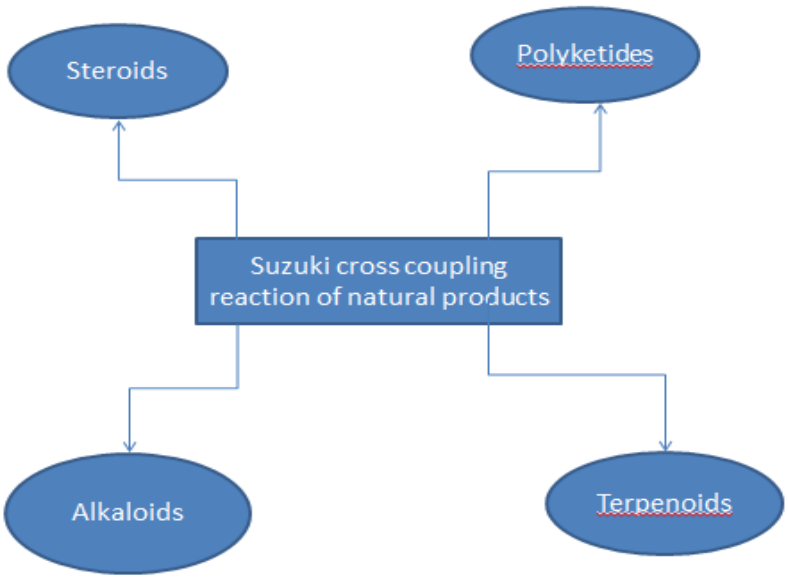
Suzuki Coupling: A powerful tool for the synthesis of natural products: A review

Asma Zafar[1], Syed Ali Hassan Naqvi[1], Freeha Hafeez[1*], Muhammad Suleman[1], Komal Sana[1], Ayesha Riaz[1]
[1]Department of Chemistry, Faculty of Engineering and Applied Sciences, Riphah International University Faisalabad, Faisalabad, Pakistan
*Correspondence

Abstract

In this review, the several sets have described important influences in Suzuki–Miyaura (SM) coupling process in carbon-based production Suzuki cross coupling reaction remains one of the greatest well-known process in the field of chemistry. It remains actual active process for manufacture C-C links. In this review, we have concentrated on the application of cross-coupling reactions like Suzuki in the whole production of certain natural-products of latest years. It takes been far used in the manufacturing of several C particles including the greatest compound ones. Fundamentally compound alkaloids, terpenoids, steroids, polyketide natural products, iso-lated from a diversity of aquatic as well as native bases, remain to give an appreciated source of worthwhile goals for the man-made chemist to challenge. The current review article highlighting on C-C link development like cross coupling reaction, mechanism as well as use in a natural-product production.



Introduction

The stimulus of the Suzuki Miyaura reaction (SMC) on theoretical as well as industrialized research, as well as on manufacture, has been vast.[1-3] Previous one decade, it has established uncertainly one of the highest effective method for the manufacture of bi-aryl or side products aromatic moieties; complexes that have these sub-structures found significant construction blocks of polymers, [4] salts, [5] an extensive range of natural products such as alkaloids, as well as abundant naturally active medications.[6]

The vital assistances of the Suzuki Miyaura reaction remain the minor circumstances under that have accompanied, the abundant acceptance to functional groups that was detected, the viable availability as well as constancy of boronic acids to temperature, oxygen as well as water as well as the comfort of usage as well as departure of boron having by-products since the reaction mixes.[7] These required structures made Suzuki Miyaura reaction an essential implement in pharmaceutical attraction and in the comprehensive production of medicines as well as complexes.[8] In addition to aryl and hetero-aryl boronic acids as well as esters, vinyl and alkyl end product was correspondingly generally used in the SMC**.**

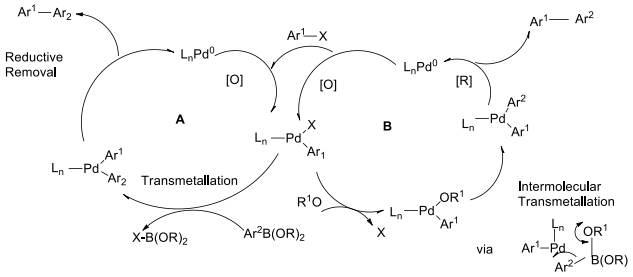


Figure1. General framework of Suzuki Miyaura coupling.

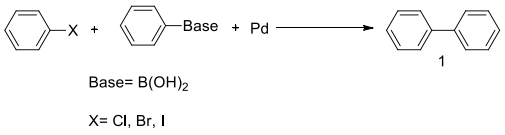
The infinitely growing importance in the Suzuki Miyaura cross-coupling process and their uses, using extra than last four decades, takes improved exponentially in latest ten years, which circumstances capacities approximately its use as well as efficiency. This extensively used potent process runs a useful artificial method for the straight development of C-C links, which has establish extensive theoretical as well as industrialized usage for the construction of polymers, fine compounds as well as constituents, in totaling to entire synthesis as well as medicines.

SMC reaction was a process for carbon-carbon attachment progress which was an extremely advantageous as well as useful technique desirable for the progress of recent drug detection as well as in the manufacturing of numerous ordinary products, polymers as well as further carbon-based complexes. While the scheme has established many uses in manufacturing many different particles, that was static abundant research to do on the progress towards a well-organized enzyme appropriate for structurally different substrates. That was a requirement to improvement more real element for the process so as to increase the effectiveness as well as proficiency of the process. Correspondingly that was an need to effort taking place the use of the process near the interaction of natural yields therefore that the ordinary yields that was pharmacologically significant as well as whose presence was partial could be made by used that process.

In latest eras Suzuki- miyaura process that was further generally recognized as Suzuki coupling process was individual of the greatest beneficial natural products process amongst Ar or vinyl boronic acid with Ar or vinyl-X as well as correspondingly with different components approximating olefins, alkynes, -NH_2, pseudo-halides complexes etc. speed up through Pd compounds [9-11]. It was generally used in the manufacture of alkenes styr-enes as well as side chain bi-phenyls was among certain mutual instances. Usually an alternate of boron-ic acid that was organ-otri-floro-borate ligands was in communal usage. Pd-catalyst Suzuki cross coupling process was among the utmost potent as well as greatest appropriate technique for Carbon—Carbon link development [12-14]. That process was usually accepted obtainable at heating range of 60–80°C with usually brilliant products consequences. Even with

the obtainability of other cross pairing process via: heck process, stille process to term a limited, but owing to numerous circumstances like: 1) Milder reaction conditions. 2) Commercial availability of the various boronic acids products that was naturally harmless than the other organo-metallic reagents. 3) The usage as well as elimination of boron-containing consequences was relaxed as related to further organo-metallic components, particularly in situation of significant production of a yield.

Cross coupling process take place by d-block elements have changed the field of carbon-based production. Such process take in the Suzuki cross pairing process, are called as the Suzuki–Miyaura reaction [3, 15]. That was a Pd-catalyst reaction by which an organo-boron complex was react with a X (halogens) containing hydro-carbon or an aryl tri-flate. The final product was greatest frequently a bi-aryl complex **(Scheme 1).**



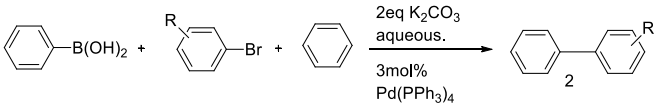
Scheme 1. General scheme of Suzuki-reaction

The carbon-carbon pairing process must develop actually vital ways in ordinary creation manufacturing, resources science, organic, pharmaceutical, as well as supra molecular chemistry, as well as consistently in catalysis, co-ordination chemistry as well as polymer production.[16-18] The SMC process has been greatly exploited in last one decades, particularly process that deliver fast access to bi-aryl frame-works like sp2 –sp2 bonds.[19, 20] That process was usually used because the positive characteristics like the slight reaction circumstances, the profitable obtainability of an arrangement of pioneers, the efficient group compatibility, the great strengths to appearance as well as humidity, as well as the organization of non-toxic as well as easily manufactured boronic acids. A latest review of the works exposes numerous examples of Pd, Ni as well as gold compounds as well-organized reagents for the cross coupling process; [21-23]. Abundant estimates on the SMR must provide awareness in the works, [24-26] with the early unique existence write by Suzuki as well as Miyaura (in 1995). Presently, abundant papers must occur on the Suzuki reaction in an actually volatile development arrangement including various fields was illustrated in **Fig. 1**.

Though abundant progresses in metallic investigated cross-coupling process, its efficiency was frequently cooperated by substituents chain process, reducing the product, or else demanding a great additional of 1 element. Suzuki Miyaura, cross-coupling was not exclusion, as that boron-ic acid functionality could be vulnerable to a series of un-desired developments. Amount of processes must establish to moderate these sideways chain process, as well as here-in application on the less proclamation scheme. Those circumstances take in organization of a disguising catalyst which shields the susceptible boronic acid functionality from de-gradation, mainly proto-desboronation, even as instantaneously enabling measured release of the dynamic catalysts into the enzymatic milieu. Below appropriately custom-made circumstances, that double act methodology confirms its awareness of the permitted boron-ic acid was reduced, therefore decreasing its de-gradation then static enabling trans-metallation of the organo-boron kinds with the crucial organo-palladium inter-mediate.

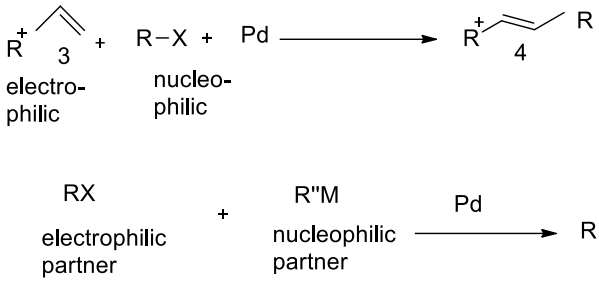
The environment of the dynamic kinds take part in PdNP-catalyzed cross-couplings was attained,[27] El-Sayed as well as co-workers [28] opened the door to a homogeneously activated catalyst in the SMC reaction. The feature that Ostwald evolving takes place through the reaction points to the presence of a significant degree of atomic conclusion. Therefore, nano-particles, specially their low co-ordination sites, would act as a reservoir of active solvable molecular Pd. It was correspondingly accurate that in particular circumstances, not great differences in the Pd-NP size spreading earlier as well as after the process have been reported. That consequence may be recognized to the well-organized re-deposition framework onto the maintenance with the accomplishment of the process.

Consequently that Suzuki cross pairing process takes an verge done the added cross pairing reactions as that process was no single limited to simple developments then was often used in the manufacture of compound complexes moreover [29, 30].



Scheme 2. Example of Suzuki coupling

The estimation framework of Pd catalyst cross pairings was those 2 compounds were adsorbed on the alkaline elements like the establishment of metal-carbon links like hetero-geneous catalyst. In that way the carbon elements certain to Pd was carried actual nearby to one another. In the following stage that pair to one another as well as that leads to the progress of a novel C-C single link. That have 2 kinds of cross pairing reactions giving to this opinion that have develop significant in carbon-based manufactured. These 2 kinds of process were as follows:

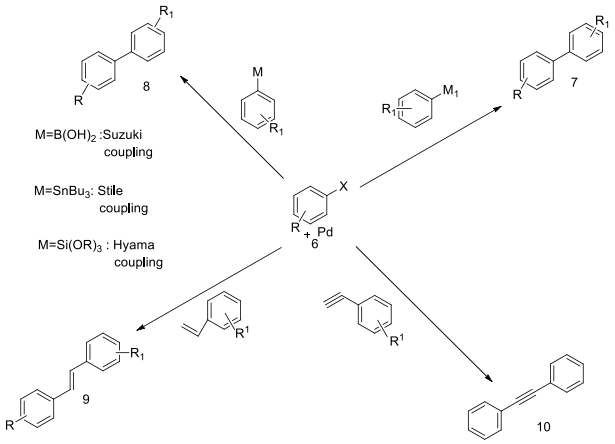


Scheme 3: electrophilic and nucleophilic reaction

Both processes were take place by zero-valent palladium as well as equally reactions work organo-halide alkyl halogens as the electron loving pairing partner. Though, the nucleus loving pairing significant other diverges in the 2 process. In the main kind of process it was alkenes while another kind of reaction it was an organo-metallic complex R''M. A communal properties of the 2 kinds of cross pairings was that the carbon-based set since the catalyst was accumulated on Pd. Also, equally process initiate by producing an organo-palladium compound alkyl palladium halogens since the process of the R-X with palladium. The organo-palladium kinds alkyl palladium halogens will consequently reaction with the nucleus loving coupling partner. The process was actual slight later that use R-X as well as alkenes or organo-metallic complexes R''M of less reactivity, wherever M was characteristically Zn, B, and Tn.

In universal, in these process **(Scheme 4)** a homo-geneous Pd reagent intercedes the process amongst a less-reactive organic electron loving, characteristically Ar-X, as well as altered C nucleus loving [31]. In the SMC C-C link development taking amongst Ph-boronic acid as well as vinyl or Ar-X; [32] while in the Sonogashira process, reaction made usage of the terminated alkynes [33]. In both cases, the process was speed up by using the palladium formed in situ. The [B], in the SMC, shows multiple

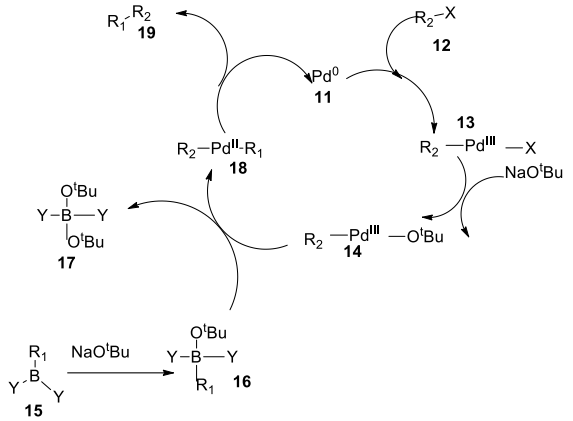
roles, supporting both the rate-determining trans-metalation as well as reductive removal, however restrictive the reaction by development of the un-reactive negative ions, consequently that the whole re-activity was organized by the attentiveness of hydroxyl as well as permits done extreme as the awareness of [B] was increased [34]. Homo-geneous cross-coupling process, still, must several short-comings, like inadequate re-usability of the exclusive reagents as well as Pd contagion in the yields [35]. Removing remaining pd in a medicinal matter to decrease its contented to the extreme suitable attentiveness boundary (Table 1) needs a low as well as expensive distillation procedure [36].



Scheme 4. Pd-catalyzed Carbon-Carbon coupling methods categorized according to the Carbon Nucleophile

Framework of the Suzuki-Coupling

The straightforward as well as greatest simple framework for Suzuki-reaction **(scheme 5)** was considered by Pd as a reagent. The initial phase of which was added by oxidation of Pd to the alkyl halogen to form an organo-palladium type **(13),** accumulation of a B to the Reaction provides inter-mediate **(14)** like trans-metalation [37] , through the boronate compound **(16)** forms an organo-palladium types **(18).** The chosen product **(19)** was then acquired by reductive removal as well as the catalyst Pd was reinstated. That kind of framework was a type of Heterogeneous catalysis.

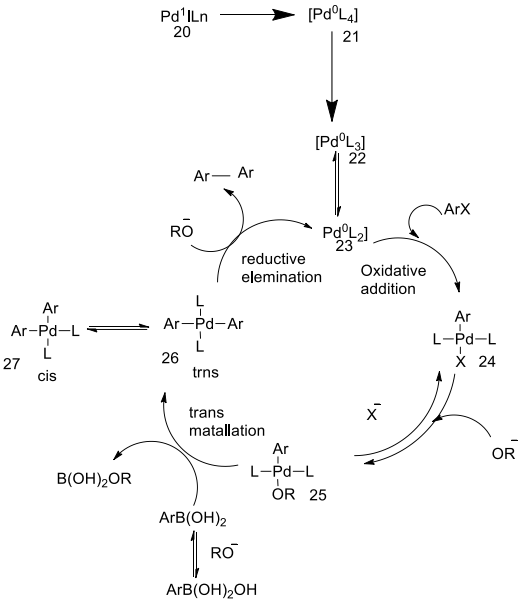


Scheme 5. Framework of Suzuki reaction

Established mechanism of Suzuki Natural-Products

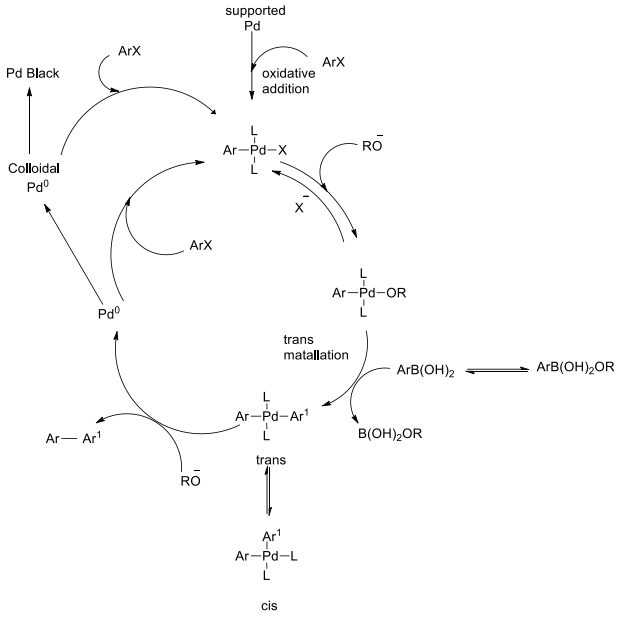
The Suzuki–Miyaura cross-coupling reaction [3, 12, 32, 38] was one of the greatest useful as well as often employed methods for Carbon–Carbon link development. It contains of the coupling of organo-boron complexes with aryl, alkenyl as well as alkynyl halogens. Presently, a great difference of boronic acids was commercially obtainable. The overall Suzuki–Miyaura enzymatic sequence follows done oxidative addition, trans-metallation as well as reductive removal [32, 34, 39, 40]. Later development of the enzymatic kinds palladium, produced in situ initial from Pd straight from Pd products, oxidative addition of the Ar-X provides the Pd-compound (ArPdXLn). The trans-metallation stage take place by change of the Pd-X (Ar-PdXLn) in the occurrence of the base alkyl oxidation to a nucleus loving Pd-alkoxy complex (Ar-PdORLn). That compound then reacted with a neutral organo-

boron complex Ar-B(OH)$_2$ to afford the di-aryl compound (Ar-PdAr-Ln) in a cis trans balance. Formerly, reductive removal of the cis technique provides the bi-aryl derived aryl-aryl as well as palladium **(Scheme 6)**.



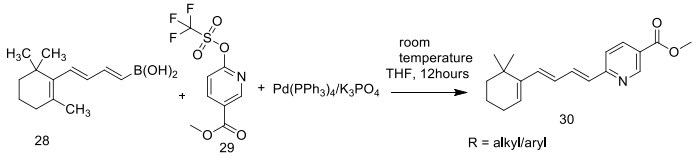
Scheme 6. Framework of the Homogeneous SMR

By supported Pd-reagent, Suzuki–Miyaura cross pairing process was a hetero-geneous catalysis [41]. Through the process, the palladium could be relief from the external of the compact sustenance as well as that leaching Pd could be liable for the catalysis as a homo-geneous framework **(Scheme 7)** [42, 43].



Scheme 7. Framework of Heterogeneous SMR

de Lera et al. [44] distributed the usage of the Suzuki natural products for the research of retinoid, arotinoids as well as its heterogeneous products. Process remained exposed to be of common use. Particularly, the method was suitable to the production of the thermally un-stable common retinoid under actual negligible conditions. That was exemplified in **Scheme 7.**

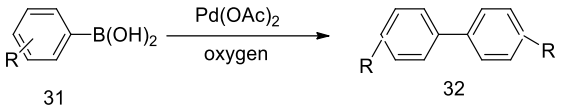


Scheme 7. Production of retinoid

Cross-coupling of aryl-borane derivatives

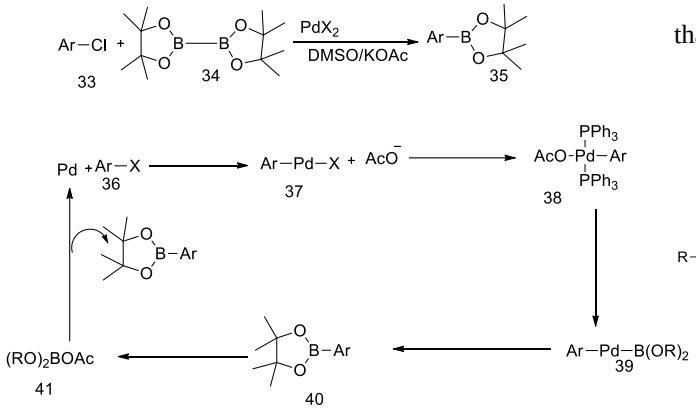
Although experimental earlier that the research of bi-phenyl from phenyl-boronic acid in an-hydrous conditions by palladium (OAc)$_2$ with triphenyl-phosphorous as reagent as well as Cu(OAc)$_2$ under N

[32]. Newly, Jackson et al. must described that linear bi-aryls could be gained below actual minor circumstances in good products by Pd reagents pairing of Ar-boron-ic acids in aq.C_2H_5OH 95% having Na_2CO_3 at ambient heat as well as in the existence of O **(Scheme 8)** [45]. Paper dealing pre-dominantly by schematic characteristics of those Pd reagent homo-coupling process takes seemed [46].



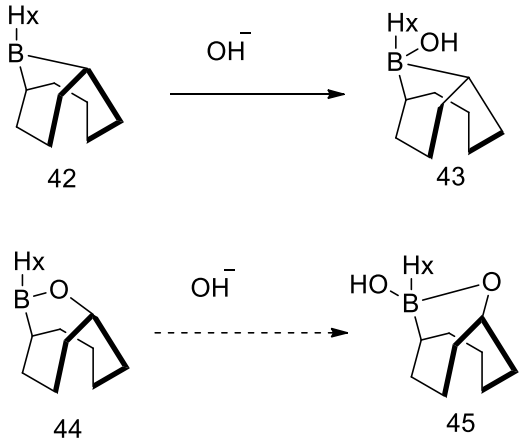
Scheme 8. General reaction

The Pd catalyst natural products procedure about pina-col ester of di-boronic acid with halo-arenes provides a direct process for aryl-boronic esters from Ar-X in a range of 60–98% [47]. Process remained take place by palladium dichloride at 80°C as well as accessible by many functional-groups. The trans-Ar-Pd(II)(OAc)$(PPh_3)_2$ intermediate remained iso-lated as well as categorized to recommend the catalytic cycle connecting the trans-metalation amongst the Ph-Pd acetate as well as **(Scheme 9).**



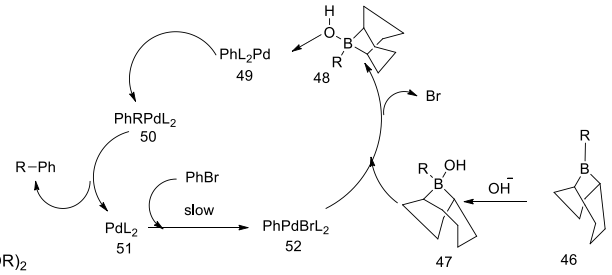
Scheme 9. Cyclic transmetallation

The part of [B] in the link reaction was detected by using nuclear magnetic resonance. Specifically, B-hexyl-9-BBN (42h) in THF displays their distinguishing absorbance at d 87.7 as well as at d 3.3 upon the adding of NaOH **(Scheme 10).** Those information obviously specify a 42h/43h symmetry where in the borane was largely current as its hydroxyl-borate compound (93h).



Scheme 10. Hydroxyl borate compound

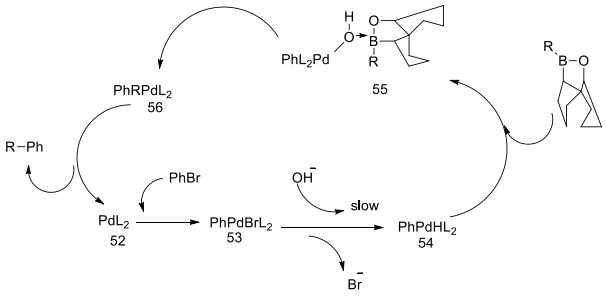
Through the adding of 2 equals of sodium hydro-oxide to the 46/PPh_3 combination in THF, that have experiential that 46 was incompletely hydrolysis, providing the mono-meric HOPdPh$(PPh_3)_2$. Heating that mix at temperature hastens the 46 to 47 change that influences.



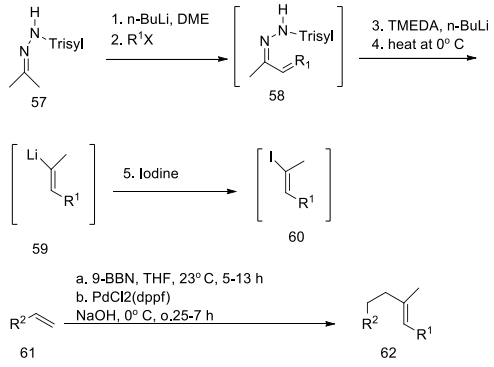
Scheme 11. Enzymatic natural products

Dynamic studies expose that the natural products was zero order in the borane then for 46 display a main order requirement on phenyl bromine although for 44

display a first order requirement on hydrolysis. That information was taken in terms of violence of 52 by 47 to form a hydroxo m2 linked intermediary 48. That runs the pioneer to trans-metalation done a 4-centered transition state 51, as shown in **Scheme 11** for the enzymatic of the natural products amongst the organo-borane 52 as well as phenyl bromide. absent, 53 was hydrolyzed by OH− forming 54 in a slower process, with this ultimately reacting with 53 to form a related intermediate 55 which also collapses to products through 91 **(Scheme 12).**Natural products of 60 and the R-borane derivative from 9-BBN hydroboration of terminal alkenes 61 yields tri-substituted alkenes **(Scheme 13).**



Scheme 12. Schemetic representation



Scheme 13. Synthetic route

Production of alkaloids

(±)-Aspergilline A 63 was a cyclo-piazonic acid derivative alkaloid with a firm as well as greatly oxygenated hexacyclic structure which was based on in-dole, tetra-hydrofuran as well as tetra-mic acid moieties **(Fig. 2).** That ordinary product displays inhibitory action beside tobacco-mosaic-virus as well as modest cytotoxicity in numerous human cell lines [48]. Nakhla as well as Wood [49] designated the whole production of (±)-aspergilline A 63 in 16 steps by employing Sonogashira coupling in addition to various protocols like oxidation, cyclization, [3+2] cyclo-addition as well as Aldol-reaction **(Scheme 14).**

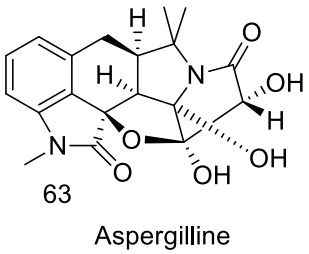
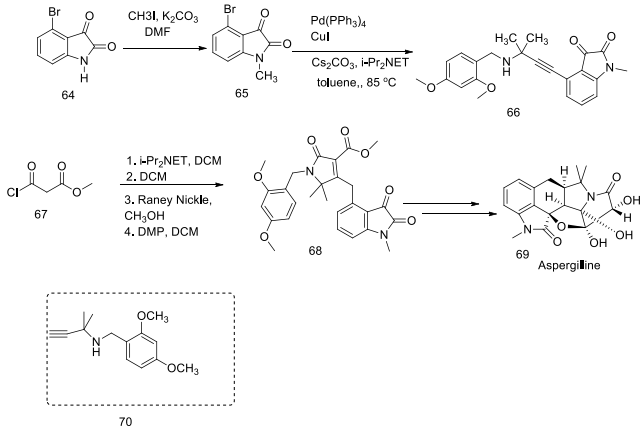


Figure 2 Structure of Aspergilline



Scheme 14. Synthesis of Aspergilline

The production remained commence from N-methylation of freely obtainable bromoisatin 64 to get N-methylated product 65 (by CH_3I as well as

K_2CO_3) in good products which on natural products with propargyl-amine 66 in the presence of 4 mol% Pd(PPh3)4, 8 mol% CuI, Cs_2CO_3 and i-Pr_2NEt in toluene at 85 °C gave isatin 66 in 72% products. Aldol-substrate 68 was organized in 69% product from acid chloride 67 by premixing it with i-Pr_2NEt followed by the addition of isatin 66, Raney nickel and DMP. The complex 68 remained additional transformed into (±)-aspergilline A 69 over numerous stages. Cyclopiamide A 71 as well as speradine E 72 was N-methyl-2-oxindoles [50] taking fundamental similarity to alkaloid 69. Still, speradine E 72 contains of an additional β-dicarbonyl idea than cyclopiamide A 71 **(Fig. 3)**

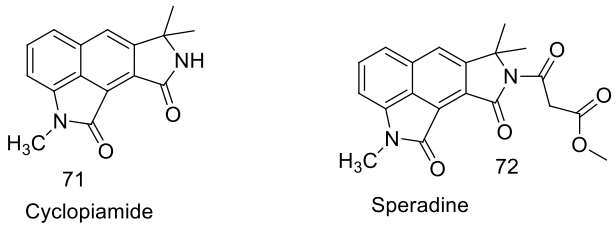
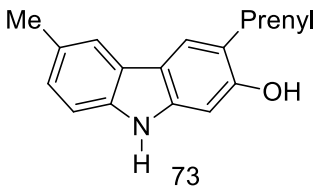


Figure 3. Structure of cyclopiamide and speradine

Carbazole alkaloids

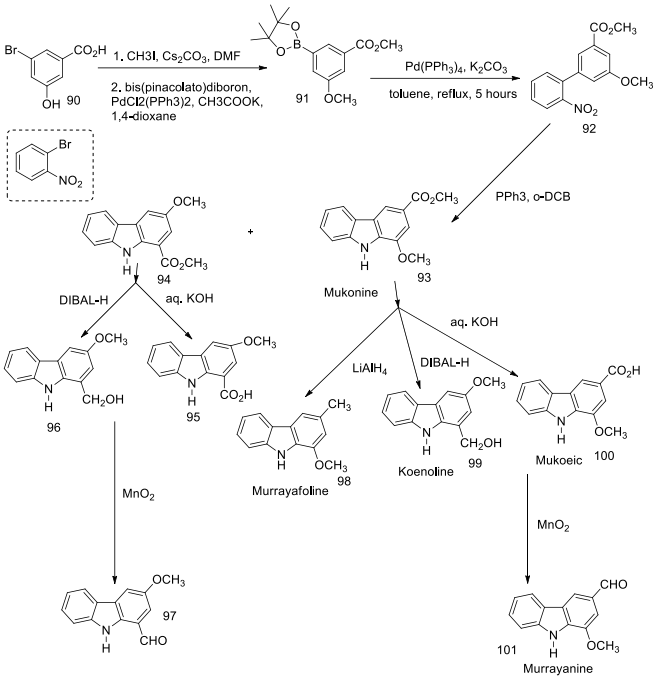
A difference of fundamentally different carbazole alkaloids have been iso-lated from dissimilar normal bases over the earlier times [51-56]. The genus Murraya, vegetation increasing in southern Asia, signifies the greater cause of carbazole alkaloids after global vegetation, mainly for 2-oxygenated tri-cyclic carbazole alkaloids **(Scheme 15).** Definite of these developments display appropriate carbon-based accomplishments. For instance, in 2000,[57] well-known a bio-assay directed fractionation about citation important to the iso-lation of a novel carbazole alkaloid, siamenol, that displays significant anti HIV action, reaching 50–60% maximum protection in Thailand.



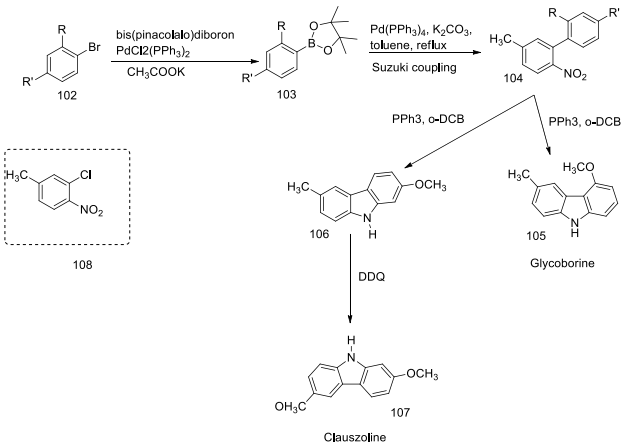
Scheme 15. Naturally occurring 2-oxygenated tricyclic carbazole alkaloids

Carbazole alkaloids behavior pyrole ring start a main class of coupling products as well as their cause of removal has many vegetation kinds with microorganisms as well as yeasts. From the previous few years, universal research has been recognized out on carbazole developments because to their valuable organic features as well as organic potentials [58]. Definite of the naturally significant carbazole alkaloids 74-89 was recorded in **Fig. 4**.[59]. A appropriate approach for the whole production of carbazole alkaloids 74-89 with modest to exceptional productss. Artificial way convoluted Suzuki cross-coupling as well as Cadogan reductive cyclic process. Production of mukonine 74 was started from benzo-ic acid 25 which undertook esterification with (CH_3I, Cs_2CO_3, 99%) tracked by adding of bis-pinacolato di-boron to give complex 26. Coupling of complex 26 with o-nitro-benzene 27 via $Pd(PPh_3)_4$ as well as K_2CO_3 in refluxing toluene in five hour provided the coupled creation 28 in 88% produce. Reduction of complex 74 with di-iso-butyl-aluminium hydride (DIBAL-H) as well as $LiAlH_4$ gave koenoline 78 as well as murrayafoline A 82, correspondingly, however [O] of complex 78 with MnO_2 provided murrayanine. Saponification of complex 74 used

aq.KOH produced mukoeic acid products. Carbazole 75 providing region-isomers 77, 79 and 81 below saponification, reduction as well as [O] circumstances, consistently **(Scheme 16).** Production of glycol-borine 83 as well as clauszoline K 84 was attained in 93% and 75% produce by complex 103 as well as 2-cholro-4-methyl-1-nitrobenzene 108 as Suzuki coupling followers **(Scheme 17).** Usage of complex 111 (obtained from 4-bromotoluene 110) with o-nitrobenzene 113 in the occurrence of $Pd(PPh_3)_4$ provided bi-phenyl 43 in 86% produce which was cyclized (using PPh_3, o-DCB) to acquire 2-methyl-9H-carbazole 89 (94%). Additionally, the usage of 3-bromophenol 109 as initial material as well as 2-cholro4-methyl-1-nitrobenzene 108 (for Suzuki coupling) framed the organizations of glycozolicine 85 (38%), glycozoline 86 (38%), mukolidine 87 (85%) and mokuline 88 (91%) **(Scheme 18).[**59**].**



Scheme 16. Synthesis of carbazole alkaloids



Scheme 17. Synthesis of carbazole alkaloids

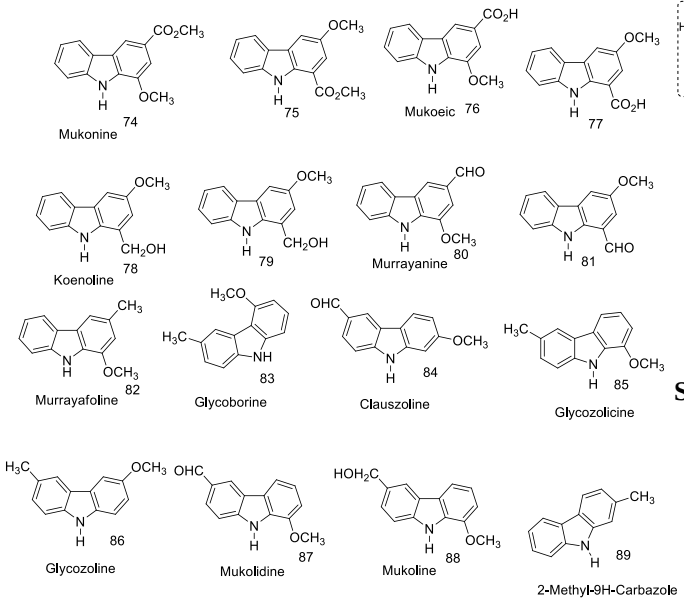
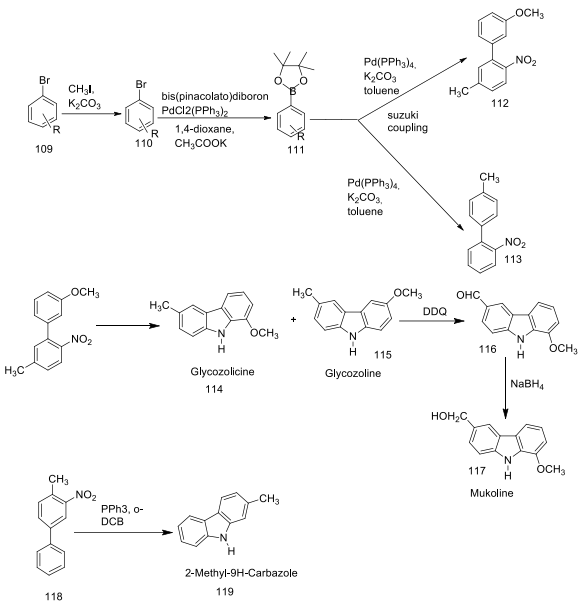
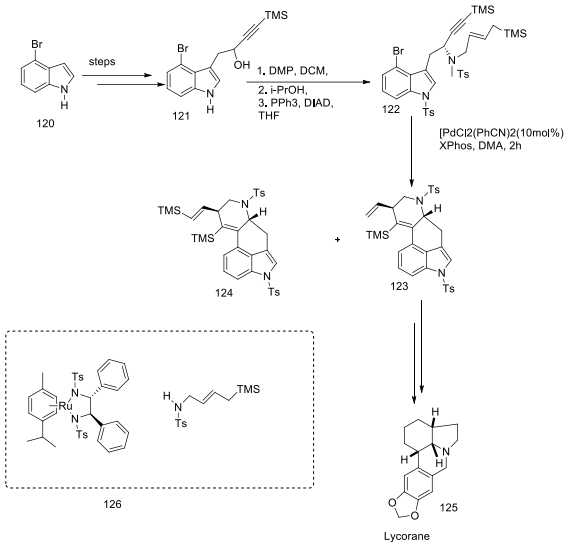


Figure 4. Structure of carbazole alkaloids



Scheme 18. Production of carbazole alkaloids

Ergot alkaloid was a cause of in-dole alkaloids showing a complete range of carbon-based accomplishments like anti-prolactin as well as anti-Parkinson's action. That was attained from fungus that produces on rye as well as extra smidgens. (+)-Lysergol 127 was indole alkaloids have its place of natural-products (Fig. 33) [60]. Ensuing from complex 123, the final structure of (+)-lysergol 127 was able over numerous steps. Lycorine-type alkaloids was consequent from plants as well as show anti-mitotic, anti-viral as well as anti-neoplastic accomplishments, etc. (±)-γ-Lycorane 127 was not accompanying with any important medicinal possessions; though, it has develop a general molecule in the characteristic of relating the potential of novel artificial methods for the arrangement of remains in lycorine-type alkaloids (Fig. 34) [61]. Monaco et al. [62] described the production of (±)-γ-lycorane 252 like Heck cyclization reaction **(Scheme 18).** Tuberculosis (TB) was an infectious disease as well as desires to be preserved with effective drugs. Introduction of novel treatments with low toxicity, high potency, good interaction and new mechanism of action remains a task for the preserve of tuberculosis. Though, normal properties help greatest in manufacturing particles by single organic as well as organic characteristics. 3, 4-Diarylpyrrole alkaloids are suitable example of captivating bioactive metabolites obtained from marine species **(Fig.5)** [63].



Scheme 19

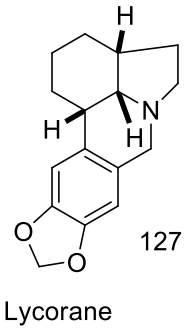


Figure 5 Structure of Lycorane

Production of terpenoids

Plant of East Asia of genus Isodon was used as old treatment for the usage of changed contaminations

containing respirational system, cancer as well as inflammation difficulties in China. Principally, their airborne fragment like stalks as well as shrubs was used for this persistence as well as certain kinds of Isodon allows puffy rhizomes which correspondingly display therapeutic importance. Hispidanin was irregular di-meric di-terpenoids which have been attained from rizhomes of Isodon **(Fig. 6)** [63].

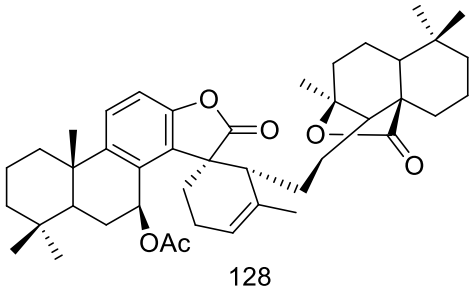
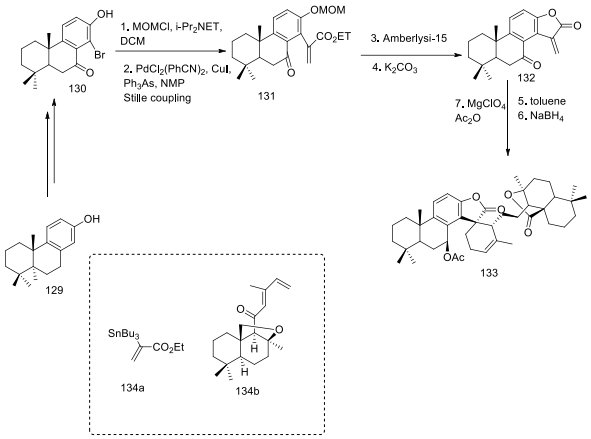


Figure 6. Structure of Hispidanin

Deng et al. described the a-symmetric total production of hispidanin 128 like Stille coupling method **(Scheme 20).** Complex 129 produced 130 over 3 steps, covering of C_6H_5OH of tri-cyclic complex 130 as well as coupling with products 134a in the occurrence of Pd catalyst $PdCl_2(PhCN)_2$, CuI, Ph3As in NMP at 120 °C furnished compound 131 in 75% yield (2 steps). The complex 131 upon de-protection tracked by base stimulated lactone-zation (with K_2CO_3) provided di-enophile 294. Diels–Alder cyclo-addition was accompanied amongst piece 132 and diene 134b in toluene monitored by adding of NaBH4 as well as MgClO4, acetic an-hydride to produce di-terpenoid 289 in 75% produces.



Scheme 20. Production of Hispidanin

Cleviolide 135 was a chief mono-terpene iso-lated from Senecio clevelandii by Bohlmann et al. [64] It was described as a predecessor of 2 mono-terpenes termed cis-di-hydro-cleviolide (obtained from S. clevelandii) as well as trans-di-hydro-cleviolide (obtained from Psathyrella scobinacea) **(Fig. 7)** [65]. The 3-step research of natural acetylenic mono-terpene cleviolide 145 was described by Cheval et al. [66] in 40% over-all produce like Sonogashira coupling **(Scheme 19).** Nosylate 136 bearing 2, 5-di-hydro-furan-2-one was a element of numerous natural-products as well as has been used for the production of cleviolide 135. Nosylate 136 as well as 4-methylpentyn-3-ol 139 was reacted in the occurrence of $PdCl_2$ $(PPh_3)_2$ as catalyst, CuI as cocatalyst as well as i-Pr_2NEt as base in aceto-nitrile to produce complex 137 in 67% produce. Usage of complex 137 with di-phosphorous penta-oxide in benzene provided the preferred natural-product cleviolide 135 in good produce. Vinyl nosylates could be well-organized coupling partners for Sonogashira coupling method either in the occurrence of Cu or Ag salts as well as p-nitro side chain nosylate acceptable this cross-coupling to be completed at room temperature. Over the years,

natural-products have been measured as appreciated complexes in man-made as well as beneficial industry due to the variety in their chemical constructions as well as organic competences. That was attained since numerous kinds. In this respect, daphnane 140 as well as tigliane 141 have been removed from thymelaeaceae as well as euphorbiaceae **(Fig. 8).** Daphnane as well as tigliane was basically compound obviously taking place di-terpenes containing of [5–7-6] tricyclic C structure as well as those natural complexes was of excessive significance because to their anti-malarial, anti-microbial, anti-HIV as well as neuro-trophic possessions [67, 68].

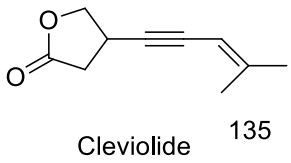
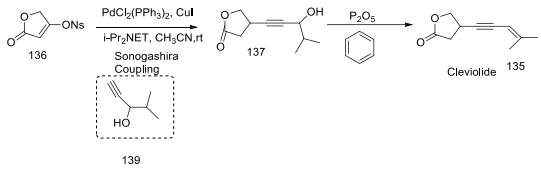
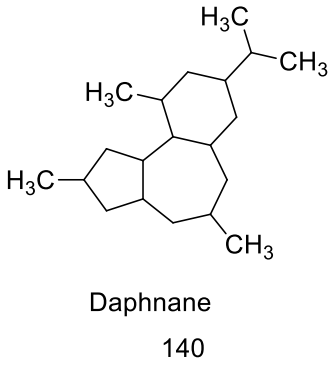


Figure 7 Structure of Cleviolide



Scheme 21 Sonogashira coupling reaction



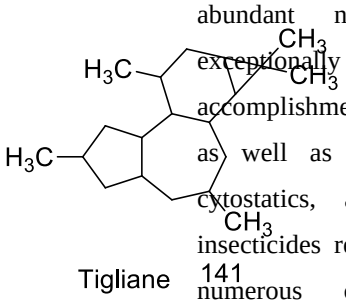


Figure 8. Structure of Daphnane and Tigliane

Production of steroids

Amongst totally classifications of coupling products, steroids must a dynamic part in inducing newest thoughts in whole production. An important quantity of information takes remained additional to carbon-based attraction in the perspective of following recommendations for the assemblage of residues to form steroids. Obviously, that inquisitiveness remains to current time. Aplykurodine attained from mollusks signifies a class of utmost de-graded steroids as well as aplykurodinone-1 142 have its place to this intimate of coupling products. Its Basic contains of a cis-fused ring with epi-meric C-8, un-saturated substituents [69] as well as 6 attached stereo-centers **(Fig. 9)** [70].

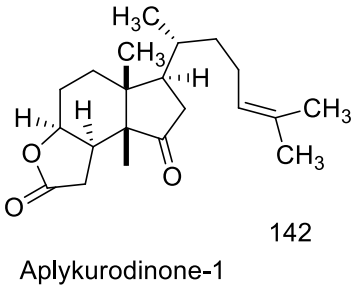


Figure 9. Structure of Aplykurodinone

Production of polyketides

Polyketides remain a fundamentally various family of abundant natural-products. They cover an exceptionally wide-ranging of natural accomplishments as well as medicinal characteristics as well as polyketide anti-biotics, anti-fungals, cytostatics, anti-parasitics as well as natural insecticides remain in viable application [71-74].In numerous circumstances, specific molecular objectives remain addressed at a molecular level, which enhances to their attraction for additional development [75].

Anthra-cyclines description for a physically main class of aromatic poly-ketides as well as establish anticancer prospective. Their organization covers aglycone chromo-phore bonded with 1 or other de-oxy-sugars. Nogalamycin 143 retains anti-bacterial as well as anti-cancer potential, however its semi-synthetic derived, menogaril 144 displayns anti-cancer possessions. This complex was obviously happening poly-ketides **(Fig 10)** [76].

Production of anthrax-cyclines 143 and 144 remained attained by Peng as well as VanNieuwenhze [77] like application of natural products procedure for the research of the density field theory-cyclic system 65 **(Scheme 21).** In this respect, enol tri-fate 145 as well as D-ring predecessor 146 in the existence of $PdCl_2$ (dppf) as well as potassium hydroxide in toluene at (room temperature) manufactured natural products 147 in 69% products. Formerly, complex 147 on later main –OH group shield take place by Staudinger reduction providing $–NH_2$ that remained additional secure with 2-naphthyl-sulfonyl group. In the subsequent step, adding of formic acid selectively cleaved the primary TBS group to yield complex 148 (88% over 3 steps) which on usage with $PySO_3$ followed by the addition of $HC(OCH_3)_3$ able di-methyl acetal 149 in an outstanding produce (95% over 2 steps). Epoxidation of olefins 149 remained conceded out with m-chloro-per-oxy-benzoic acid that was condensed as well as cyclic in acid circumstances to afford density field theory-ring system 150 in 77% produce.

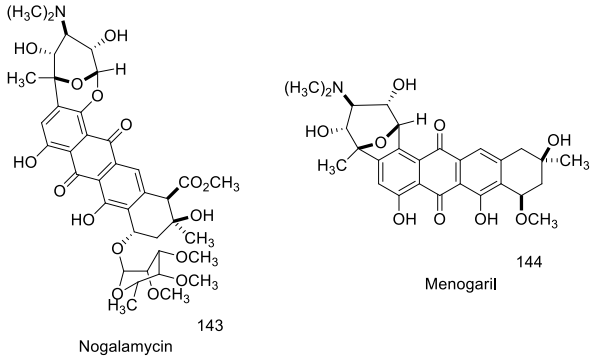
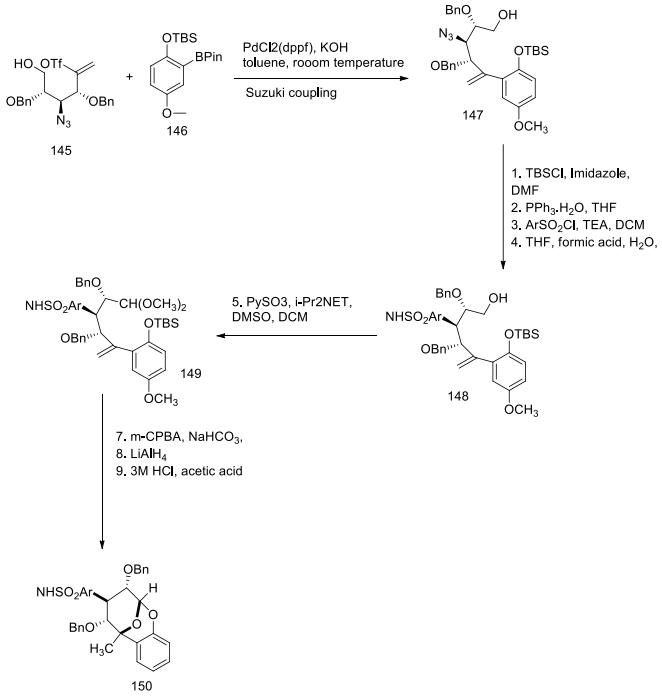


Figure 10 Structure of Nogalamycin and Menogaril

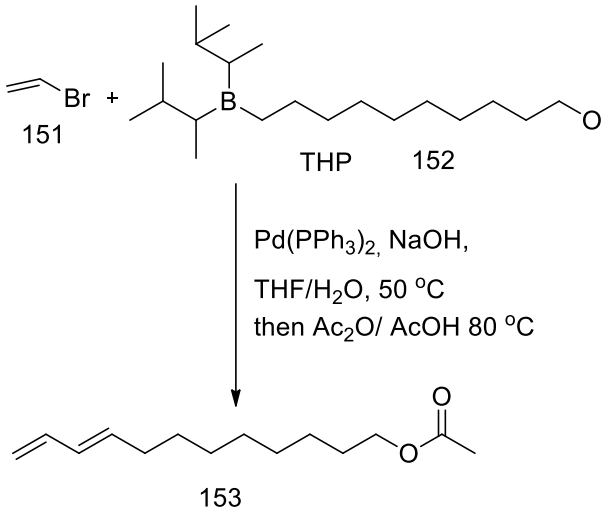


Scheme 22 Synthesis of DFT of Nogalamycin and Menogaril

Use of Suzuki cross coupling reaction in natural-product manufacturing

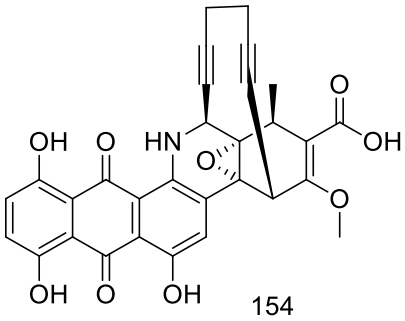
1) The main use of suzuki cross-coupling process in ordinary yields manufacture remained described in the year 1981 by Rossi as well as his co-workers in which an

insect pheromone iso-lated from Di-paropsis castanea has been manufactured [78].



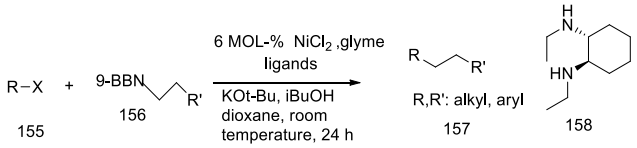
Scheme 23.

2) (+)-dynemicin A effective ordinary anti-tumor cause has been positively synthesized in laboratory. By a great products by Suzuki cross coupling reaction [79].



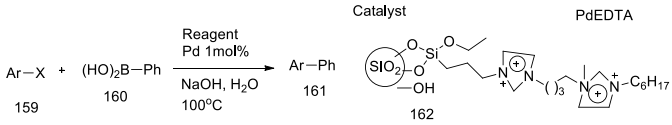
Structure of dynemicin

3) A effective effort has been complete to made R-R Suzuki cross pair of deactivated minor R-X at very slight conditions [80].



Scheme 24.

4) Greatly well-organized as well as recyclable catalyst Palladium-EDTA which was detained in an Ionic Liquid brush can be used in Suzuki-Miryaura process in H_2O[81].



Conclusion

Suzuki cross coupling method remains a process for C-C link development that remains a highly valuable as well as useful process desired for the progress of current drug finding as well as in the production of numerous natural products, polymers as well as extra carbon-based complexes. While the process has established numerous uses in manufacturing numerous changed particles that remains still abundant effort to prepare on the improvement to well-organized substance appropriate for fundamentally changed products. There remains a basic to progress extra active catalyst for the process so as to improve the effectiveness as well as efficacy of the process. Likewise there remains need to emphasis on the use of the process to the chemistry of natural-products so that the natural-products which remain pharma-cologically significant as well as whose existence remains partial can be manufactured by this process.

References

1. De Meijere, A., F. Diederich, and A. de Meijere, *Metal-catalyzed cross-coupling reactions*. Vol. 1. 2004: Wiley-VCH Weinheim.
2. Rossi, R., F. Bellina, and A. Carpita, *Palladium catalysts for the Suzuki cross-coupling reaction: an overview of recent advances.* Synthesis, 2004. **2004**(15): p. 2419-2440.
3. Miyaura, N. and A. Suzuki, *Palladium-catalyzed cross-coupling reactions of organoboron compounds.* Chemical reviews, 1995. **95**(7): p. 2457-2483.
4. Kertesz, M., C.H. Choi, and S. Yang, *Conjugated polymers and aromaticity.* Chemical reviews, 2005. **105**(10): p. 3448-3481.
5. Kaye, S., et al., *The Use of Catalytic Amounts of CuCl and Other Improvements in the Benzyne Route to Biphenyl-Based Phosphine Ligands.* Advanced Synthesis & Catalysis, 2001. **343**(8): p. 789-794.
6. Kotha, S., K. Lahiri, and K. Dhurke, *Recent applications of the Suzuki–Miyaura cross-coupling reaction in organic synthesis.* 2002.
7. Martin, R. and S.L. Buchwald, *Palladium-catalyzed Suzuki– Miyaura cross-coupling reactions employing dialkylbiaryl phosphine ligands.* Accounts of chemical research, 2008. **41**(11): p. 1461-1473.
8. Lipton, M.F., et al., *The synthesis of OSU 6162: efficient, large-scale implementation of a Suzuki coupling.* Organic process research & development, 2003. **7**(3): p. 385-392.
9. Gopichand, Y. and F. Schmitz, *Marine natural products: Fistularin-1,-2 and-3 from the sponge Aplysina fistularis forma fulva.* Tetrahedron Letters, 1979. **20**(41): p. 3921-3924.
10. Miyaura, N. and A. Suzuki, *Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst.* Journal of the Chemical Society, Chemical Communications, 1979(19): p. 866-867.
11. Zhang, D. and Q. Wang, *Palladium catalyzed asymmetric Suzuki–Miyaura coupling reactions to axially chiral biaryl compounds: Chiral ligands and recent advances.* Coordination Chemistry Reviews, 2015. **286**: p. 1-16.
12. Miyaura, N., T. Yanagi, and A. Suzuki, *The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases.* Synthetic Communications, 1981. **11**(7): p. 513-519.
13. Suzuki, A., *Pure & Appl. Chem., 57, 1749 (1985);(b) N. Miyaura, A. Suzuki.* Chem. Rev, 1995. **95**: p. 2457.
14. Zou, G., Y.K. Reddy, and J. Falck, *Ag (I)-promoted Suzuki–Miyaura cross-couplings of n-alkylboronic acids.* Tetrahedron Letters, 2001. **42**(41): p. 7213-7215.
15. Miyaura, N. and A. Suzuki, *The palladium-catalyzed "head-to-tail" cross-coupling reaction of 1-alkenylboranes with phenyl or 1-alkenyl iodides. A novel synthesis of 2-phenyl-1-alkenes or 2-alkyl-1, 3-alkadienes via organoboranes.* Journal of Organometallic Chemistry, 1981. **213**(2): p. C53-C56.
16. Heravi, M.M. and E. Hashemi, *Recent applications of the Suzuki reaction in total synthesis.* Tetrahedron, 2012. **68**(45): p. 9145-9178.
17. Cocuzza, A.J., et al., *Use of the Suzuki reaction for the synthesis of aryl-substituted heterocycles as corticotropin-releasing hormone (CRH) antagonists.* Bioorganic & medicinal chemistry letters, 1999. **9**(7): p. 1063-1066.
18. Yokoyama, A., et al., *Chain-growth polymerization for the synthesis of polyfluorene via Suzuki– Miyaura coupling reaction from an externally added initiator unit.* Journal of the American Chemical Society, 2007. **129**(23): p. 7236-7237.
19. Ocansey, E., J. Darkwa, and B.C. Makhubela, *Synthesis, characterization and evaluation of bulky bis (pyrazolyl) palladium complexes in Suzuki–Miyaura cross-coupling reactions.* RSC advances, 2018. **8**(25): p. 13826-13834.
20. Cornelio, B., et al., *Palladium nanoparticles in catalytic carbon nanoreactors: the effect of confinement on Suzuki–Miyaura reactions.* Journal of Materials Chemistry A, 2015. **3**(7): p. 3918-3927.
21. Wolf, C. and H. Xu, *Efficient synthesis of sterically crowded biaryls by palladium-phosphinous acid-catalyzed cross-coupling of aryl halides and aryl grignards.* The

Journal of Organic Chemistry, 2008. **73**(1): p. 162-167.
22. Tobisu, M., et al., *Nickel-catalyzed Suzuki–Miyaura reaction of aryl fluorides.* Journal of the American Chemical Society, 2011. **133**(48): p. 19505-19511.
23. Johansson Seechurn, C.C., et al., *Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize.* Angewandte Chemie International Edition, 2012. **51**(21): p. 5062-5085.
24. Polshettiwar, V., et al., *Suzuki–Miyaura Cross-Coupling Reactions in Aqueous Media: Green and Sustainable Syntheses of Biaryls.* ChemSusChem: Chemistry & Sustainability Energy & Materials, 2010. **3**(5): p. 502-522.
25. Fihri, A., et al., *Nanocatalysts for Suzuki cross-coupling reactions.* Chemical Society Reviews, 2011. **40**(10): p. 5181-5203.
26. Hu, F. and X. Lei, *A nickel precatalyst for efficient cross-coupling reactions of aryl tosylates with arylboronic acids: vital role of dppf.* Tetrahedron, 2014. **70**(25): p. 3854-3858.
27. Pérez-Lorenzo, M., *Palladium nanoparticles as efficient catalysts for Suzuki cross-coupling reactions.* The Journal of Physical Chemistry Letters, 2012. **3**(2): p. 167-174.
28. Narayanan, R., C. Tabor, and M.A. El-Sayed, *Can the observed changes in the size or shape of a colloidal nanocatalyst reveal the nanocatalysis mechanism type: homogeneous or heterogeneous?* Topics in Catalysis, 2008. **48**: p. 60-74.
29. Danishefsky, S.J. and M.T. Bilodeau, *Glycals in organic synthesis: the evolution of comprehensive strategies for the assembly of oligosaccharides and glycoconjugates of biological consequence.* Angewandte Chemie International Edition in English, 1996. **35**(13-14): p. 1380-1419.
30. Liu, J., S.D. Lotesta, and E.J. Sorensen, *A concise synthesis of the molecular framework of pleuromutilin.* Chemical communications, 2011. **47**(5): p. 1500-1502.
31. Schaarschmidt, D. and H. Lang, *P, O-Ferrocenes in Suzuki– Miyaura C, C Couplings.* ACS Catalysis, 2011. **1**(4): p. 411-416.
32. Suzuki, A., *Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles, 1995–1998.* Journal of Organometallic Chemistry, 1999. **576**(1-2): p. 147-168.
33. Chinchilla, R. and C. Nájera, *The Sonogashira reaction: a booming methodology in synthetic organic chemistry.* Chemical reviews, 2007. **107**(3): p. 874-922.
34. Amatore, C., A. Jutand, and G. Le Duc, *Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base.* Chemistry–A European Journal, 2011. **17**(8): p. 2492-2503.
35. Yang, Q., et al., *A water-compatible, highly active and reusable PEG-coated mesoporous silica-supported palladium complex and its application in Suzuki coupling reactions.* Chemical communications, 2006(23): p. 2495-2497.
36. Garrett, C.E. and K. Prasad, *The art of meeting palladium specifications in active pharmaceutical ingredients produced by Pd-catalyzed reactions.* Advanced Synthesis & Catalysis, 2004. **346**(8): p. 889-900.
37. Matos, K. and J.A. Soderquist, *Alkylboranes in the Suzuki– Miyaura coupling: Stereochemical and mechanistic studies.* The Journal of organic chemistry, 1998. **63**(3): p. 461-470.
38. Miyaura, N., K. Yamada, and A. Suzuki, *A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides.* Tetrahedron Letters, 1979. **20**(36): p. 3437-3440.
39. Amatore, C., A. Jutand, and G. Le Duc, *Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH−, CO32−) as Modulated by their Countercations (Na+, Cs+, K+) in Palladium-Catalyzed Suzuki–Miyaura Reactions.* Chemistry–A European Journal, 2012. **18**(21): p. 6616-6625.
40. Carrow, B.P. and J.F. Hartwig, *Distinguishing between pathways for transmetalation in Suzuki− Miyaura reactions.* Journal of the American Chemical Society, 2011. **133**(7): p. 2116-2119.
41. Cantillo, D. and C.O. Kappe, *Immobilized transition metals as catalysts for cross-couplings in continuous flow—a critical assessment of the reaction mechanism and*

metal leaching. ChemCatChem, 2014. **6**(12): p. 3286-3305.
42. Narayanan, R. and M.A. El-Sayed, *Effect of catalysis on the stability of metallic nanoparticles: Suzuki reaction catalyzed by PVP-palladium nanoparticles.* Journal of the American Chemical Society, 2003. **125**(27): p. 8340-8347.
43. Kashin, A.S. and V.P. Ananikov, *Catalytic C–C and C–heteroatom bond formation reactions: in situ generated or preformed catalysts? Complicated mechanistic picture behind well-known experimental procedures.* The Journal of Organic Chemistry, 2013. **78**(22): p. 11117-11125.
44. Torrado, A., et al., *General synthesis of retinoids and arotinoids via palladium-catalyzed cross-coupling of boronic acids with electrophiles.* Synthesis, 1995. **1995**(03): p. 285-293.
45. Smith, K.A., et al., *High yields of symmetrical biaryls from palladium catalysed homocoupling of arylboronic acids under mild conditions.* Synlett, 1997. **1**(01): p. 131-132.
46. Moreno-Mañas, M., M. Pérez, and R. Pleixats, *Palladium-catalyzed Suzuki-type self-coupling of arylboronic acids. A mechanistic study.* The Journal of organic chemistry, 1996. **61**(7): p. 2346-2351.
47. Ishiyama, T., M. Murata, and N. Miyaura, *Palladium (0)-catalyzed cross-coupling reaction of alkoxydiboron with haloarenes: a direct procedure for arylboronic esters.* The Journal of Organic Chemistry, 1995. **60**(23): p. 7508-7510.
48. Zhou, M., et al., *Aspergillines A–E, highly oxygenated hexacyclic indole–tetrahydrofuran–tetramic acid derivatives from Aspergillus versicolor.* Organic letters, 2014. **16**(19): p. 5016-5019.
49. Nakhla, M.C. and J.L. Wood, *Total Synthesis of (±)-Aspergilline A.* Journal of the American Chemical Society, 2017. **139**(51): p. 18504-18507.
50. Uka, V., et al., *Unravelling the diversity of the cyclopiazonic acid family of mycotoxins in Aspergillus flavus by UHPLC triple-TOF HRMS.* Toxins, 2017. **9**(1): p. 35.
51. Wiegrebe, W., W.J. Kramer, and M. Shamma, *The emetine alkaloids.* Journal of Natural Products, 1984. **47**(3): p. 397-408.
52. Chakraborty, D. and S. Roy, *Progress in the chemistry of organic natural products.* Springer Verlag, Wien, 1991. **57**: p. 71.
53. Ghosh, D., et al., *Sequential Aza-Claisen Rearrangement and Ring-Closing Metathesis as a Route to 1-Benzazepine Derivatives.* Synlett, 2008. **2008**(19): p. 3011-3015.
54. Verpoorte, R., R. van der Heijden, and P.R. Moreno, *Biosynthesis of terpenoid indole alkaloids in Catharanthus roseus cells*, in *The alkaloids: Chemistry and pharmacology*. 1997, Elsevier. p. 221-299.
55. Campbell, N. and B.M. Barclay, *Recent advances in the chemistry of carbazole.* Chemical Reviews, 1947. **40**(3): p. 359-380.
56. Chakraborty, D., B. Barman, and P. Bose, *On the constitution of murrayanine, a carbazole derivative isolated from Murraya koenigii Spreng.* Tetrahedron, 1965. **21**(2): p. 681-685.
57. Meragelman, K.M., T.C. McKee, and M.R. Boyd, *Siamenol, a new carbazole alkaloid from Murraya siamensis.* Journal of natural products, 2000. **63**(3): p. 427-428.
58. Tabassum, S., et al., *Cross-coupling reactions towards the synthesis of natural products.* Molecular Diversity, 2021: p. 1-43.
59. kumar goud Bhatthula, B., et al., *Total synthesis of carbazole alkaloids.* Tetrahedron, 2019. **75**(7): p. 874-887.
60. Inuki, S., et al., *Enantioselective total synthesis of (+)-lysergic acid,(+)-lysergol, and (+)-isolysergol by palladium-catalyzed domino cyclization of allenes bearing amino and bromoindolyl groups.* The Journal of Organic Chemistry, 2011. **76**(7): p. 2072-2083.
61. Angle, S.R. and J.P. Boyce, *A stereoselective formal synthesis of (±)-(γ)-lycorane.* Tetrahedron letters, 1995. **36**(35): p. 6185-6188.
62. Monaco, A., et al., *Short Total Synthesis of (±)-γ-Lycorane by a Sequential Intramolecular Acylal Cyclisation (IAC) and Intramolecular Heck Addition Reaction.* Chemistry–A European Journal, 2017. **23**(20): p. 4750-4755.
63. Murali Krishna Kumar, M., et al., *Denigrins A–C: new antitubercular 3, 4-diarylpyrrole alkaloids from Dendrilla nigra.* Natural Product Research, 2014. **28**(12): p. 888-894.

64. Bohlmann, F., et al., *The first acetylenic monoterpene and other constituents from Senecio clevelandii.* Phytochemistry, 1981. **20**(10): p. 2425-2427.
65. Rossi, R., F. Bellina, and M. Biagetti, *A concise and efficient novel synthesis of cleviolide.* Synthetic communications, 1999. **29**(19): p. 3415-3420.
66. Cheval, N.P., et al., *Vinyl nosylates as partner in copper and silver co-catalyzed Sonogashira cross-coupling reactions.* Tetrahedron, 2018. **74**(50): p. 7111-7119.
67. Sarotti, A.M., *Structural revision of two unusual rhamnofolane diterpenes, curcusones I and J, by means of DFT calculations of NMR shifts and coupling constants.* Organic & Biomolecular Chemistry, 2018. **16**(6): p. 944-950.
68. Wang, H.-B., et al., *Tigliane diterpenoids from the Euphorbiaceae and Thymelaeaceae families.* Chemical Reviews, 2015. **115**(9): p. 2975-3011.
69. Zhang, Y. and S.J. Danishefsky, *Total synthesis of (±)-aplykurodinone-1: traceless stereochemical guidance.* Journal of the American Chemical Society, 2010. **132**(28): p. 9567-9569.
70. Peixoto, P.A., et al., *Formal Enantioselective Synthesis of Aplykurodinone-1.* Angewandte Chemie International Edition, 2013. **27**(52): p. 6971-6973.
71. Hertweck, C., *The biosynthetic logic of polyketide diversity.* Angewandte Chemie International Edition, 2009. **48**(26): p. 4688-4716.
72. Menche, D., *New methods for stereochemical determination of complex polyketides: configurational assignment of novel metabolites from myxobacteria.* Natural Product Reports, 2008. **25**(5): p. 905-918.
73. Weissman, K.J. and R. Müller, *Myxobacterial secondary metabolites: bioactivities and modes-of-action.* Natural product reports, 2010. **27**(9): p. 1276-1295.
74. Kretschmer, M. and D. Menche, *Recent Advances in the Stereochemical Determination and Total Synthesis of Myxobacterial Polyketides.* Synlett, 2010. **2010**(20): p. 2989-3007.
75. Namba, K., H.-S. Jun, and Y. Kishi, *A Simple but Remarkably Effective Device for Forming the C8− C14 Polycyclic Ring System of Halichondrin B.* Journal of the American Chemical Society, 2004. **126**(25): p. 7770-7771.
76. Siitonen, V., et al., *Identification of late-stage glycosylation steps in the biosynthetic pathway of the anthracycline nogalamycin.* ChemBioChem, 2012. **13**(1): p. 120-128.
77. Peng, R. and M.S. VanNieuwenhze, *Construction of the DEF-ring system of nogalamycin and menogaril via an efficient Suzuki-Miyaura reaction.* Tetrahedron Letters, 2017. **58**(23): p. 2236-2239.
78. Rossi, R., A. Carpita, and M.G. Quirici, *Dienic sex pheromones: Stereoselective syntheses of (7E, 9Z)-7, 9-dodecadien-1-yl acetate,(E)-9, 11-dodecadien-1-yl acetate, and of (9Z), 11E)-9, 11-tetradecadien-1-yl acetate by palladium-catalyzed reactions.* Tetrahedron, 1981. **37**(15): p. 2617-2623.
79. Myers, A.G., et al., *A convergent synthetic route to (+)-dynemicin A and analogs of wide structural variability.* Journal of the American Chemical Society, 1997. **119**(26): p. 6072-6094.
80. Saito, B. and G.C. Fu, *Alkyl− alkyl Suzuki cross-couplings of unactivated secondary alkyl halides at room temperature.* Journal of the American Chemical Society, 2007. **129**(31): p. 9602-9603.
81. Wei, J., et al., *zhang XR, Shi XY, Chen ZG.* J Org Chem, 2009. **74**: p. 5967-5974.

AUTHORS

First Author – Ms. Asma Zafar, M.Phil Chemistry, Riphah International University, faisalabad

Second Author – Mr. Syed Ali Hassan Naqvi, Riphah International University, faisalabad

Third Author – Dr. Freeha Hafeez, PhD Chemistry, Riphah International University, faisalabad

Fourth Author – Dr. Muhammad Suleman, PhD Chemistry, Riphah International University, faisalabad .

Fifth Author – Ms. Komal Sana, PhD Scholar, Riphah International University, faisalabad

Sixth Author – Dr. Ayesha Riaz, PhD, Riphah International University, Faisalabad
Correspondence Author – Dr. Freeha Hafeez, PhD Chemistry, Riphah International University, faisalabad