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Arynes in Natural Product Synthesis

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Abstract: ***Arynes are a unique class of intermediates used in synthetic organic chemistry, and research interest has been intensely focused on their peculiar reactivities. Arynes have been researched for almost a century. However, difficulties in monitoring these reactive species, as well as difficulties in creating synthetically viable techniques for their synthesis and trapping, have restricted their application. A key tactic for achieving the racemic and enantiopure total synthesis of a broad variety of natural compounds or their structural derivatives. The chemistry of arynes has advanced significantly over the past thirty years, particularly in the field of transition metal carbon- carbon and carbon-heteroatom bond-forming mechanisms. The field's fast growth is largely attributable to the development of mild aryne production processes. To create a natural product with complex organic molecules, the role of aryne intermediates was non-replaceable. These organic substances are often used in medicine, therapies, or as raw material for the synthesis of other substances. Moreover, they may perform important biological tasks. There are numerous methods for synthesizing natural compounds including total synthesis, semi-synthesis, and biosynthesis. Total synthesis is the process of creating natural products entirely chemically from basic precursors as well as it can be produced in large quantities and can reveal information about its biological activity. One of the developments in Arynes' chemistry is the chemical rearrangements brought about by this electrophilic intermediate. It is not feasible to use conventional methods in a single step. This review article discusses how arynes are used to create natural products. Arynes has a wide range of functionality in the field of scientific research. The evolution of this method has made a tremendous change in the total synthesis of natural products. Benzynes enabled creative synthesis in mild conditions. The transformation has expanded to investigate various reaction classes such as nucleophilic addition, (4+2), and (2+2) cycloaddition strategies and metal-catalyzed reactions are shown and explained in this article. This review will provide an idea about how the arynes act as an intermediate in those reaction mechanisms and enlighten the scope of these aryne intermediate.***

I. INTRODUCTION

Natural products are substances produced from plants or any other living organisms found in nature. It is frequently used in medical, healthy diets, aesthetic procedures, food preservatives, etc. This study deals with the production of natural products using arynes as the intermediates. The formal formation of arynes and heteroarynes respectively includes removing two neighboring hydrogen atoms formally from an aromatic ring[1]. J D Roberts took 14 years to reveal the first structure of benzyne[2]. Because of its exceptionally high reactivity, benzyne be a certain way produced in situ from its forerunner and quickly captured by adequate arynophiles. Otherwise, it will easily decompose on its own[3]. The most representative generation of arynes involves the dissolution of an orthogonal-departing group via an aryl anion species. These include β removal of aryl halide using a base[4], exclusion from an aryl halide with orthogonal-leaving groups did occur after halogen-metal exchange[5], or fluoride-induced desilylation of aryl trimethyl silanes, benzene-diazonium-2-carboxylate thermolysis, which was frequently applied throughout an era. As arynes as intermediated approximately 75 natural products has synthesized. Depending on the aryne transition, this synthesis can take many different forms and be divided into numerous groups, including (i) Pericyclic reactions[6] which include Diels's alder reactions,[4+2] and [2+2] cycloaddition, 1,3 dipolar cycloaddition, 1,4 dipolar cycloaddition, ene reactions (ii) Nucleophilic addition[7] to arynes (iii) transition metal catalyzed reactions[8].

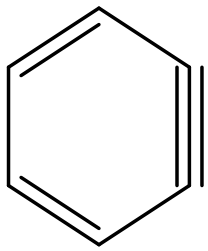
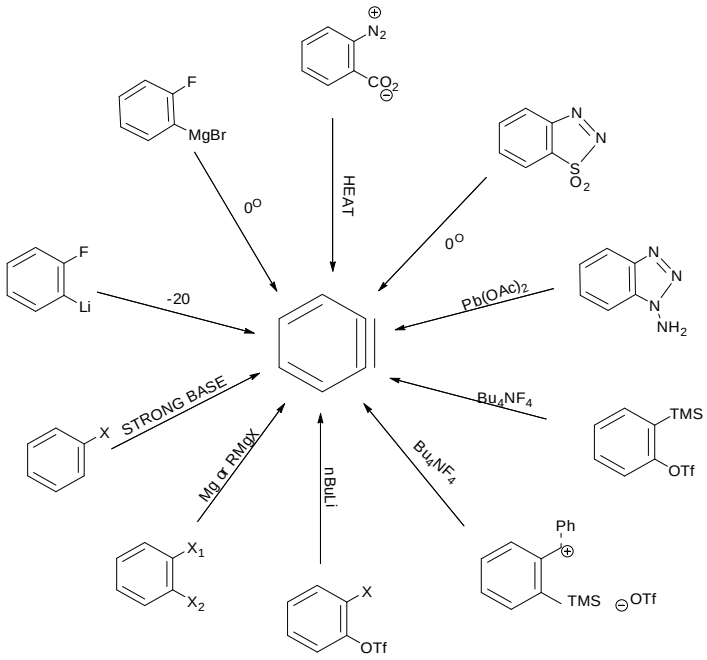


figure 1: structure of aryne

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A. Generation Of Arynes From Various Methods



Scheme 1: benzyne formation

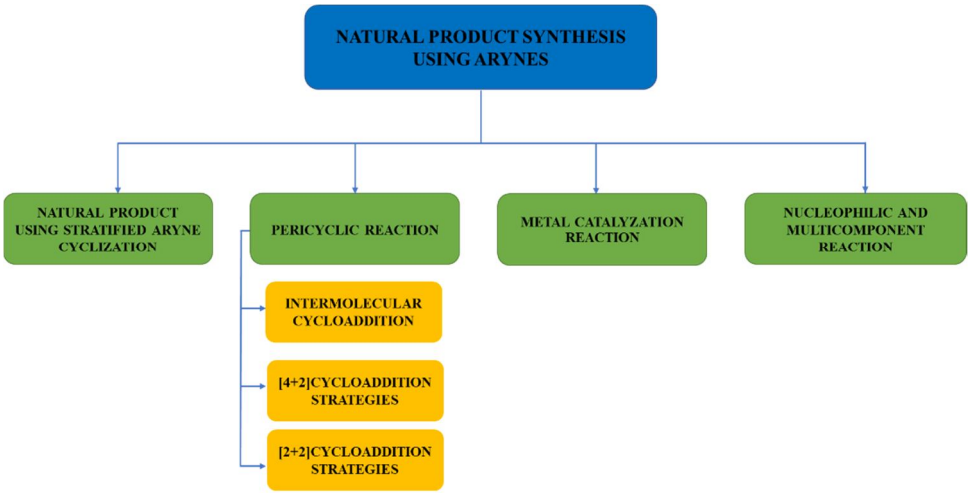
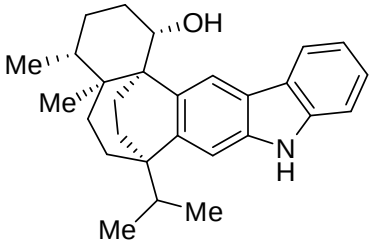


Figure 2 Classification of synthesis of natural products using aryne intermediates

II. TOTAL SYNTHESIS OF NATURAL PRODUCT USING STRATIFIED ARYNE CYCLIZATION

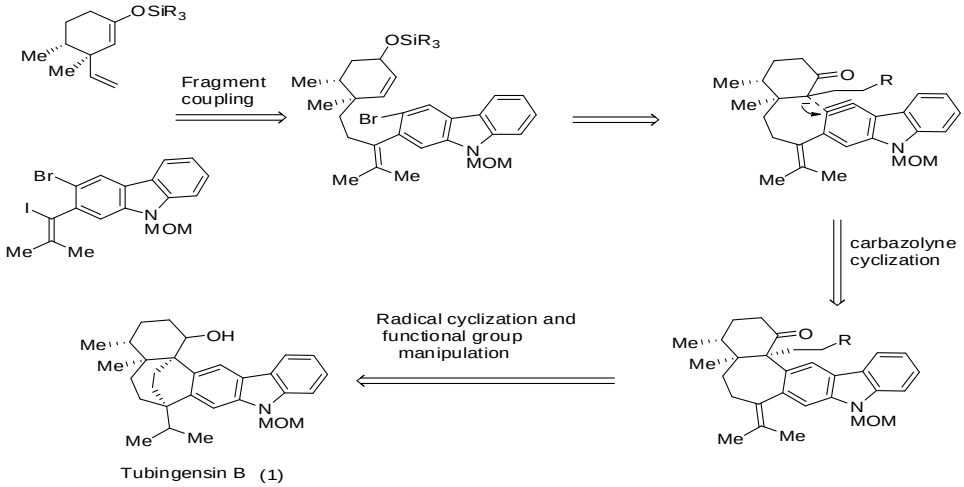
A series of carbazolyne cyclization[9] followed by determining the vicinal quaternary stereocenters and the seven-membered ring of the bioactive chemical by Rh-catalyzed fragmentation[10]. An intimidating chemical structure is included in the indole diterpenoid tubingensin B (1), which has five stereogenic centers, three of which are quaternary, a decorated [3.2.2] bridged cycle and a disubstituted carbazole unit. Using a transitory aryne intermediate strategically will lead to a brief and enantiospecific total synthesis of tubingensin B. The current study focuses on the indole diterpenoid tubingensin B, which was found in the fungus Aspergillus[11] tubingensin in 1989. In the same year, X-ray crystallography[12] was employed to determine its precise structure. Tubingensin B, a secondary metabolite is typically thought to assist in defending the producing fungus from overhunting in a feeding trial, it showed effectiveness against the common crop bug Heliothis zea, causing 10% fatality at 125 ppm. Moreover, tubingensin B has an IC_{50} of 4 g ml^{-1} against cells of cervical cancer.



(-)-Tubingensin B (1)

A. Synthesis OF (-) Tubingensin B

In the beginning, known aryl triflate was used to create vinyl iodide[13] to create carbazole fragments. As well (-) olefin undergoes hydroboration to create an alkyl boron derivative, which is then coupled with dihalocarbazole by Suzuki-Miyaura[14] coupling to create dimethyl(isopropyl)silyl enol ether. Functionalized C-20 dimethylsilyl enol ether, which was then processed through three steps of carbazolyn cyclization at 60°c to get the required pentacyclic product. Many functional group modifications were used to create the precursor for radicle cyclization. In addition, the radical cyclization[15] allowed the [3.2.2] nonane core's effective assembly as well as generated bicycle. All that was for completing the formulation using bicycle was the elimination of protective groups and reversal of the C19 stereocenter. Laborious efforts produce the penultimate ketone intermediate; conventional alcohol oxidation has performed after tips cleavage. Then, the protecting group underwent acid-mediated cleavage. For the final phase of the whole synthesis, several reducing agents, including hydride donors, single-electron donors, and heterogeneous hydrogenation catalysts were assessed. The controlled catalytic reaction of diacetate[(S)-2,2-bis(diphenylphophino)-1,1-binaphthyl ruthenium (II)(S)-Ru $(OAc)_2$(BINAP)] with ketone results in the quantification of tubingensin B and epi-tubingensin B in a ratio of 1:4.



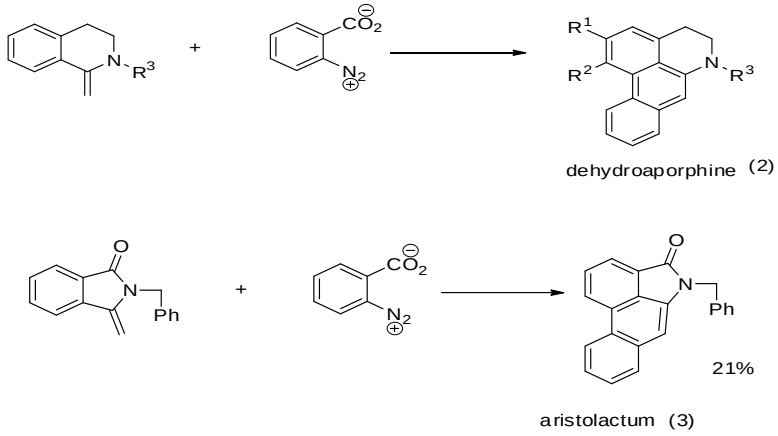
Scheme 2: schematic diagram of the formation of tubingensin B: was prepared and employed using fragment coupling, carbazolyne cyclization, and radical cyclization method. MOM-methoxymethyl

III. PERICYCLIC REACTIONS OF ARYNES

Arynes have a high degree of electrophilicity[16] in their carbon-carbon triple bonds, which makes them excellent dienophiles in pericyclic processes. Pericyclic reactions[17] of arynes are widely employed to monitor the synthesis of arynes in solutions. Moreover, by giving favorable circumstances, complex arenes can be synthesized in one step as a result of these reactions. Witting and Pohmer generated the epoxynaphthalane derivative in good yields by successfully[18] capturing produced aryne intermediate and treating it with furan in the [4+2] cycloaddition procedure. Arynes are widely recognized for taking part, because of their substantial dienophilicity and increased electron affinity, carbon- carbon doubles can undergo the [2+2] cycloaddition mechanism. For instance, it has been discovered that enamides and aryne [2+2] cycloaddition can be used to create benzocyclobutenes. Arynes are widely recognized for taking part in dipolar cycloaddition reactions[19] in addition to [4+2] and [2+2] reactions. Arynes can fuse five-membered benzo rings by adding to various 1,3 dipoles.

A. Intermolecular Cycloaddition

In Diels alder reaction, intermolecular cycloaddition reactions are done for the formation of biological products, an aporphinoid skeleton would be synthesized by this cycloaddition. The synthesis of two compounds dehydroaporphine (2) and aristolactams(3) [20] are given (Scheme 3).

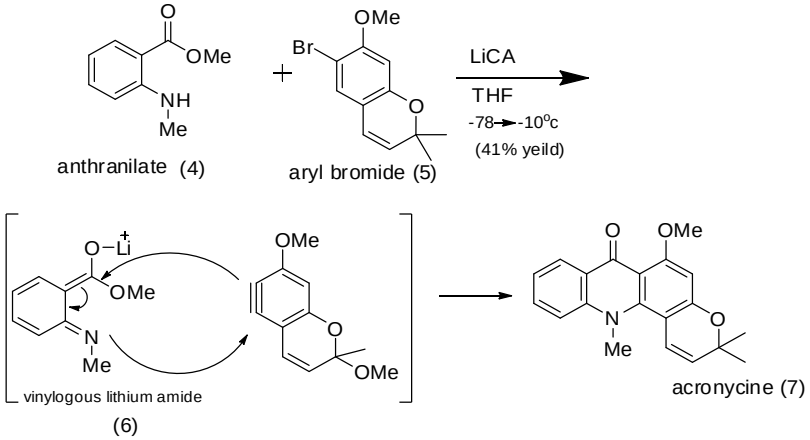


Scheme 3. Synthesis of dehydroaporphines and aristolactams

One of the special characteristics of aryne chemistry is the synthetic methodology that simultaneously stabilizes two vicinal positions of benzene with various combination of substituent[21]. [4+2] and [2+2] cycloaddition is the basic example of pericyclic reaction[22] which is predicted to occur in by single transition state, without the generation of any intermediates. Several diene compounds such as furan pyrrole and anthracenes are applicable in [4+2] cycloadditions. As well as frontier molecular orbital theory [2+2] cycloaddition is symmetry forbidden This is a combined state of an alkene with enone resulting cyclobutane, and it is a stepwise reaction with various intermediates

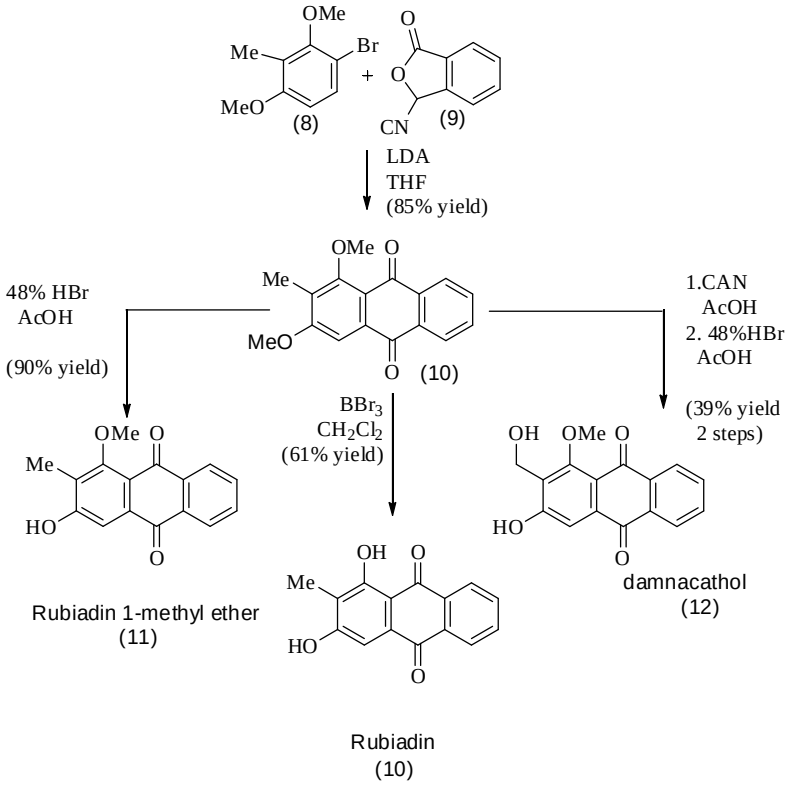
B. [4+2] Cycloaddition Strategies

After nucleophilic addition, the [4+2] cycloaddition is frequently used for the complete construction of natural products. The [4+2] cycloaddition aryne method is a viable way to synthesize natural products on large volume approaches. However, the major limitation on [4+2] aryne cycloaddition is that most reaction under this category requires cyclic dienes most commonly furans[23]. Acronycine (3,12-dihydro-6-methoxy-3,3,12-trimethyl-7H-pyrano[2,3-c]acridin-7-one) is a naturally occurring alkaloid[24]. Acronycine (4), an anticancer acridone alkaloid[25], was synthesized by Watanabe and co-workers using the intermolecular forms of benzyne. Anthranilate (4), an amino anion and an unsymmetrical aryne made from aryl bromide(5), performed a systematic [4+2] cycloaddition. Formation of successive bonds between vinylogous lithium amide(6) and aryl anion to the aryne and suspended ester are annulated respectively, yielding acronycine(7) with a yield of 41%.



Scheme 4 Watanabe's Synthesis of Acronycine

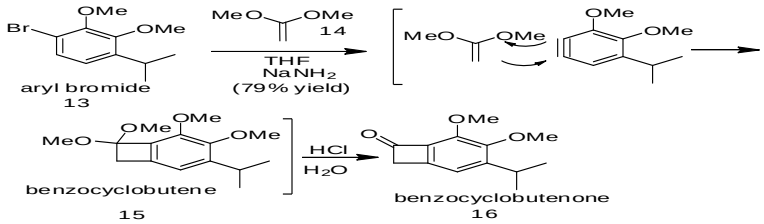
Biehl's and coworkers developed three different anthraquinone natural products[26]. The cycloaddition mechanisms are carried out using aryl bromide(8) and lithium diisopropyl amide (LDA)(9) as common reagents for the construction of Rubiadin[27] (11), Rubiadin 1- methyl ether (12), and damnacathol(13)[28] was developed by them. Initially, trisubstituted bromo aryne is replaced by dioxolane for the formation of anthraquinone (10). Further reaction on Antraquinone forms Rubiadin 1- methyl ether which is produced by mono demethylation with HBr in the presence of acetic acid, Rubiadin is produced via bis-demethylation with BBr, when anthraquinone undergoes benzylic oxidation, followed by demethylation, to create damnacathol.

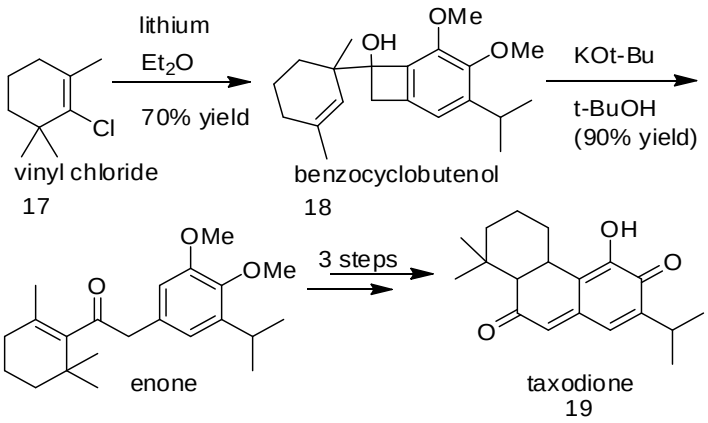


Scheme 4 Synthesis of rubiadin 1-methyl ether,rubiadin, damnacathol

C. [2+2] Cycloaddition

Remarkably, benzynes undergo [2+2] thermal cycloaddition with alkenes and alkynes[29]. In the sense [2+2] cycloaddition strategy is much poor way of synthesis due to large by-products. Bisacchi and Steven are the people who brought [2+2] cycloaddition in between arene and ketene acetal for the preparation of quinone methide diterpene, taxodione[30]. At first, they treated aryl bromide(13) in presence of 1,1 dimethoxyethylene(14) in THF with sodamide this resulted in the formation of benzocyclobutenes(15) which is a regioselective reaction. The subsequent step produces benzocyclobutenone(16) by hydrolyzing benzocyclobutenes. When the vinyl chloride(17)-derived organolithium reagent is added to benzocyclobutenone(18), the ensuing benzocyclobutenol undergoes regioselective, although contra-steric, ring fragmentation to produce enone, which is quickly converted to taxodione(19). This is a common medication used in pharmacies that have been said to have HIV-1 inhibitory properties[31].





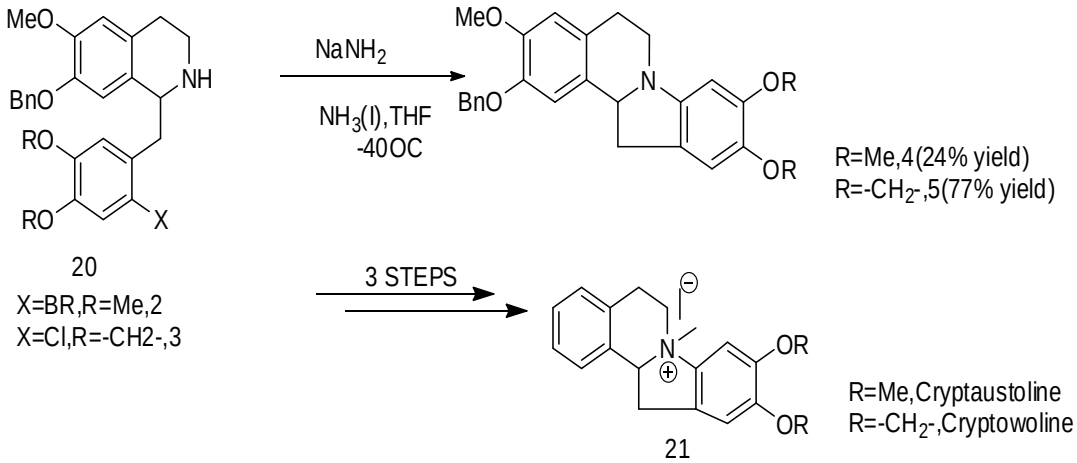
Scheme 5 Stevens' 1982 Synthesis of Taxodione

IV. NUCLEOPHILIC ADDITION AND MULTICOMPONENT REACTION STRATEGIES

Nucleophiles are nuclear-loving species which means the compound will attract toward the positive part of a molecule[32]. The multicomponent reaction is a kind of synthetic process that can produce one product from three or more reactants[33]. Nucleophilic addition to arynes is a method of synthesis of natural products[34]. This synthesis can be separated into simple nucleophilic addition, which can only form a bond between a carbon and heteroatom, and multicomponent reactions, which can form two additional bonds to the arynes by adding three or more components at once

A. Nucleophilic Addition To Benzynes

Kametani and co-workers used arynes for the total synthesis of natural products for the first instance at Tokyo University in 1967. In the given scheme 5, tetrahydroisoquinolines 2,3(20) are treated with sodamide in the presence of liquid ammonia to produce tetracycles 4 and 5 respectively, then the secondary amine goes through the secondary addition to form pendant aryne. However, from here tetracycle 4 will be converted to cryptaustoline[35] as well as tetracycle 5 will convert to crytowoline (21). The nucleophilic addition had done from the early period but the multicomponent method came to use only within a few decades past.

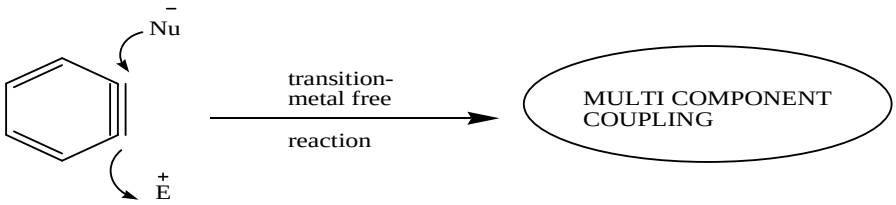


Scheme 6 . The synthesis of cryptowoline and crypttaustoline by Kametani

B. Aryne Multicomponent Reaction

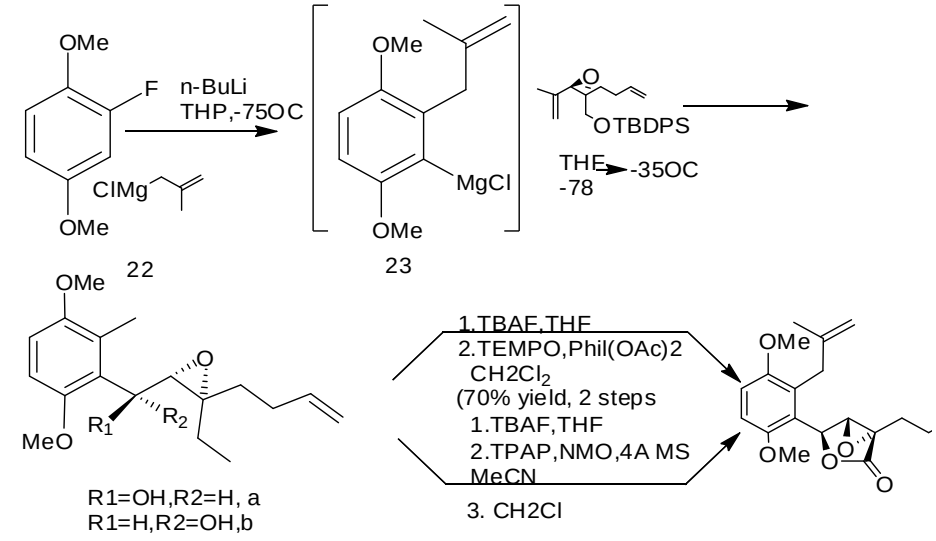
Arynes often perform best as multicomponent reaction species. This reaction involves generating three and four-component coupling to 1,2 disubstituted arynes[36]

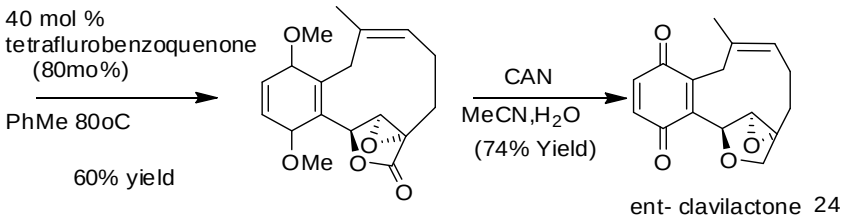
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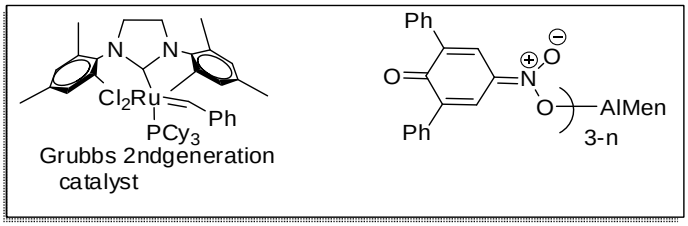


By involving three component coupling on aryne Barret and co-workers synthesized entclavilacetoneB[37]. Fluoroarene (22) was processed with nBuLi to produce aryne, which was then linked with methylmagnesium chloride (23). The presently formed aryne magnesium compound is then gone through the third addition aldehyde gives benzylic alcohol as diastereomers a(23) and b(24). These diastereomers a and b are then converted to a lactone(25). Using Grubbs catalyst[38] and oxidation the ring close is done which gives ent-clavilactone B (26).

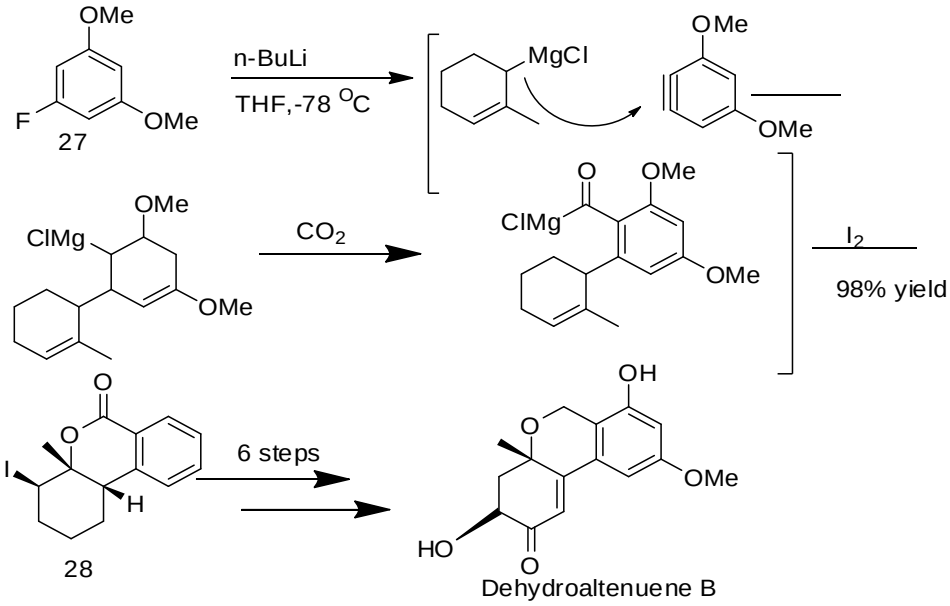
Four-component coupling was used by Barrette and colleagues to create dehydroaltenuene B scheme 6[39]. The reaction begins with the elimination of fluoroarene (27) which gives aryne and the sequential addition of three components like carbon dioxide, iodine, and cyclohexyl magnesium chloride this result in the generation of iodolactone(28). Organomagnesium is added to the arene then carboxylation will result in the aryl magnesium species and diastereoselective iodolactonization[40]. Following the conversion of multicomponent addition and further six processes, the dehydroaltenuene B (29) is produced.







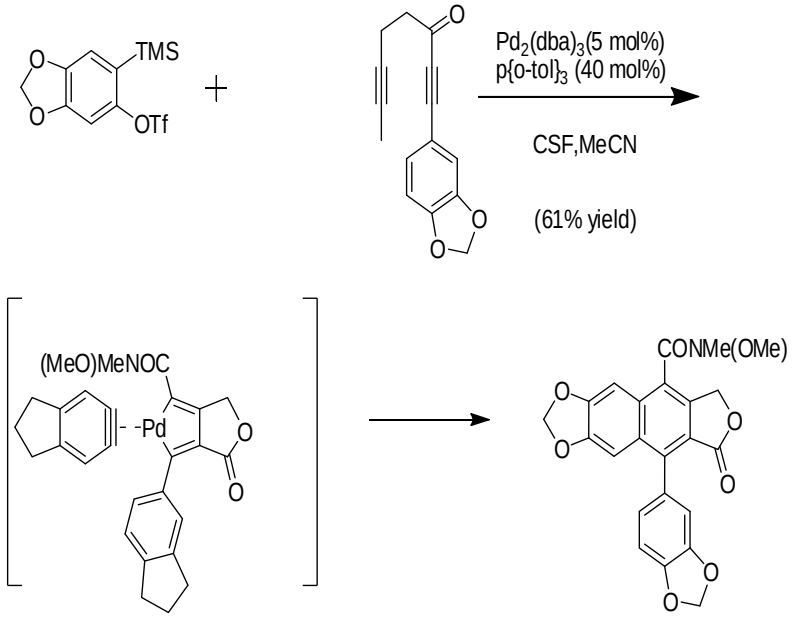
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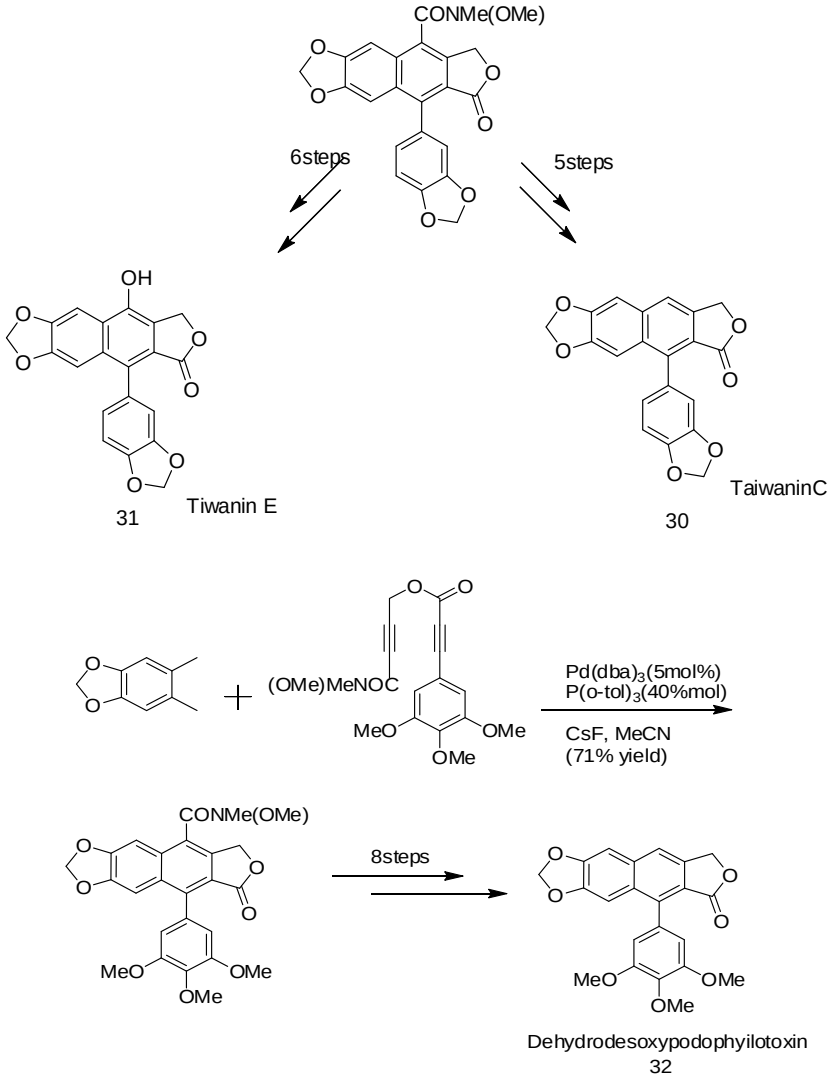


Scheme 7 barrett synthesis of dehydroaltenuene

V. METAL CATALYZATION- BASED REACTION:

This reaction was conducted by Mori and his colleagues, and it is believed that the reaction an underdeveloped. The regioselectivity of the natural product synthesis is influenced by metal catalyst reaction[41]. Aryl naphthalene lignans are the end product of this metal-catalyzed process the entire synthesis of natural products [42]. In this process, an aryne and diyne were co-cyclized with palladium to target the naphthyl segments of Taiwanins C (30) and E(31)[43] as well as dehydrodesoxypodophyllotoxin (32). On the other hand, using diyne a compound obtained from 3- (trimethoxyphenyl) propiolic acid in the palladium-catalyzed [2+2+2]- co-cyclization procedure. Trimethoxyarylnaphthalene, that gone through eight different transformations before becoming dehydrodesoxypodophyllotoxin. The primary medical use of podophyllotoxin is to prevent mollusccum contagiosum[44] and genital warts[45].

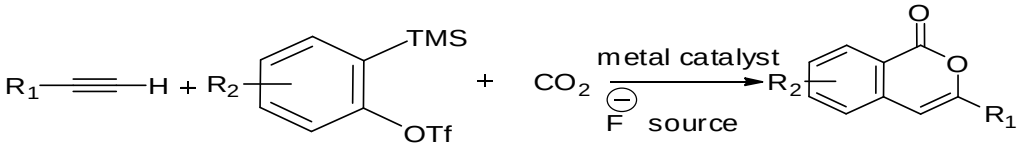




Scheme 8 Mori's synthesis of Tiwanin C and Tiwanin E

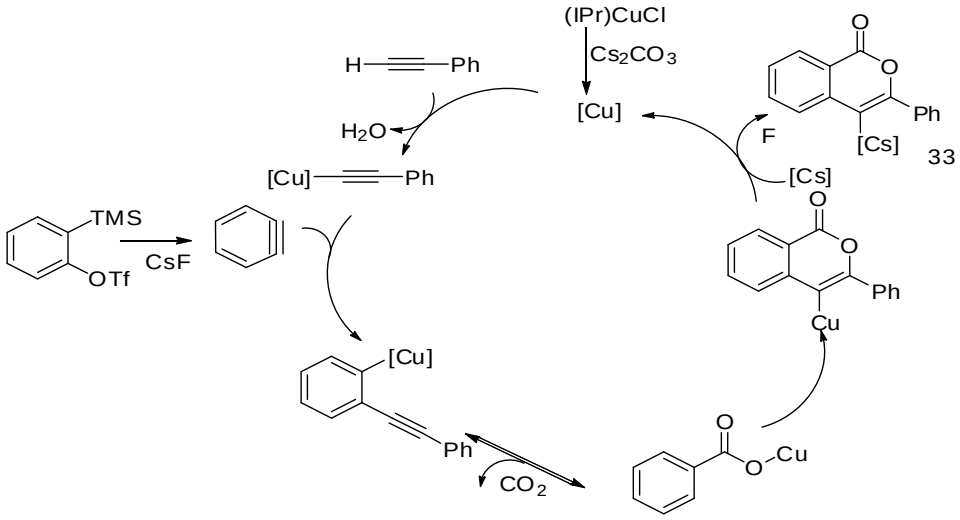
A. Isocoumarin Synthesis Using Multi-Component Coupling

Isocoumarin(33) is a highly essential component necessary for various natural products having a wide range of biological processes [46]. The intramolecular cyclization of ortho-alkynyl-benzoic acid derivatives is the most applicable method to produce an isocoumarin ring [47]. Even though it is easy there are some limitations, multistep is required to get 2-alkynyl-benzoic acid. The application of CO_2 in the feedstock and to access value-added material in the reaction medium[48]. Moreover, CO_2 is easy to handle, at a reasonable price as well as easily accessible. Even though CO_2 in its advantage due to intrinsic kinetic and thermodynamic stability it is hard to use in the organic reaction[49], to avoid this a multicomponent is used along with the catalyst. Here in the synthesis of isocoumarin, NHC (N-heterocyclic carbene) copper complex is used as the catalyst, for the three-component coupling reaction of 2-(trimethylsilyl)aryl triflates, terminal alkynes, and CO2 to produce isocoumarins (Scheme 8).



Scheme 9 General reaction of multi-component coupling using terminal alkynes, arynes, and CO_2. TMS= trimethylsilyl, OTF= trifluoromethane sulfonate

The tentative mechanism for the synthesis of isocoumarin



Scheme 10 Mechanism of three component coupling involving CO_2 2-(trimethylsilyl) aryl triflates, and [(IPr)CuCl].

In this reaction, ortho-arynes are used as the intermediates[50]. The beginning copper acetylide is generated by deprotonating NHC-copper hydroxide/carbonate to the terminal alkyne. The electrophilic intermediate is induced to this reaction to react with copper complex to give ortho alkynyl copper complex. In the absence of CO_2, the three-component coupling is carried out in specific conditions[51], and diphenylacetylene is created as a result of this. The nucleophilic addition of CO_2 with copper acetylide is ineffective due to the strong electrophilicity of ortho-benzyne[52]. On the other hand, ortho-alkynyl copper complexes are nucleophilically added to CO_2 to produce ortho carboxylate [53], this leads to the 6-endo-dig-cyclization, resulting in an endocyclic copper heterocycle. The complex that took place in between two phases led to a competition between 5-exo-dig-cyclization and 6-endo-dig-cyclization. Thereafter in the absence of [(IPr)CuCl] a major Regio isomer is formed. In the multicomponent reaction with deuterium-enriched alkyne later at the end of the reaction isocoumarin delivered a higher yield.

VI. CONCLUSION

After J D ROBERTS has given the benzyne structure it leads to countless development in the synthesis of arynes[54]. The major reason is that the benzynes are highly stable and easy to make complexes[55]. This made the organic chemistry community explore widely in natural product synthesis[56][57]. Since they have been around for a century, arynes are transient intermediates that are now mildly and easily accessible using straightforward precursors. This has significantly broadened the range of uses for this reactivity intermediate. There has been a substantial revolution in this field. Cycloaddition reaction, insertion reaction, multicomponent reaction, transformation catalyzed by transition metals, and aryne-induced molecular rearrangement can all be used to categorize the reactivity of arynes. A class of molecular rearrangement reactions that use arynes as aryl sources have quickly emerged, according to recent advancements in the field. Through the synthesis of various heterocycle-fused ring systems[58], various heterocyclic arynes' potential synthetic utility has recently been studied. The trifunctionalization of arynes[59], domino aryne[60] method and arynes technique are recent developments that have been employed to synthesize many natural compounds. The production of arynes using a mild and transition-metal-free technique is anticipated to inspire synthetic chemists to explore novel reactions and applicational domains based on the principle of arynes.

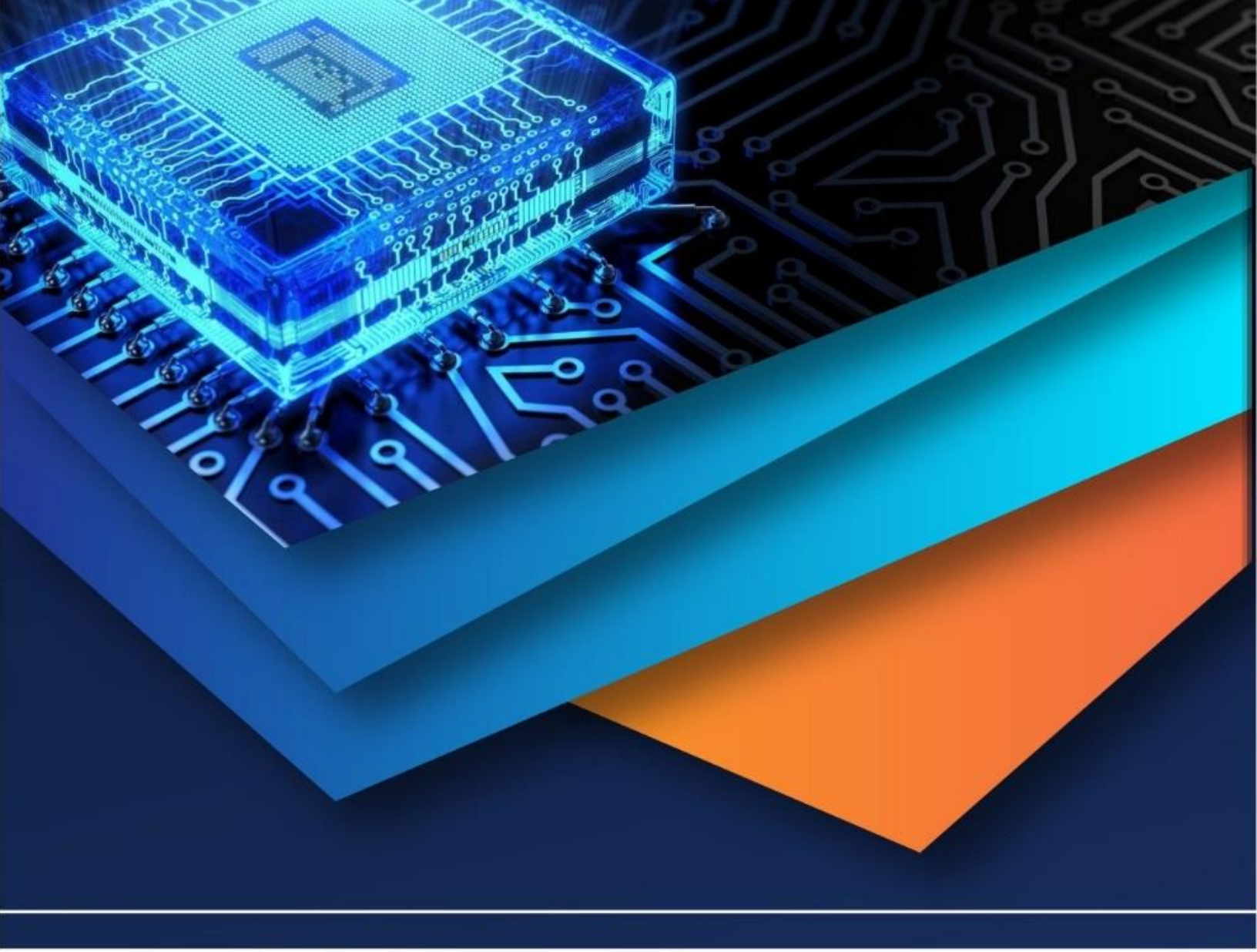
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