



Synthetic approaches and biological Activity of chalcones

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ABSTRACT

Chalcones are the main building blocks for flavonoids and isoflavonoids biosynthesis. Chalcones are made up of a three-carbon, α,β -unsaturated carbonyl system. Chalcones are the products of aromatic aldehyde condensation with acetophenones in the presence of a catalyst. They are useful in the synthesis of pyrazoline, isoxazole, and a variety of heterocyclic compounds because they go through a variety of chemical reactions. For the synthesis of these compounds, a variety of methods and schemes have been reported. Aldol condensation and Claisen-Schmidt condensation are still at the top of the list. Other notable techniques, Chalcones are active lead compounds that can be used to find new medications in medicinal chemistry. This section will explain characteristics and biosynthesis

Keywords:

biological Activity, chalcones, Synthetic approaches

1 Introduction

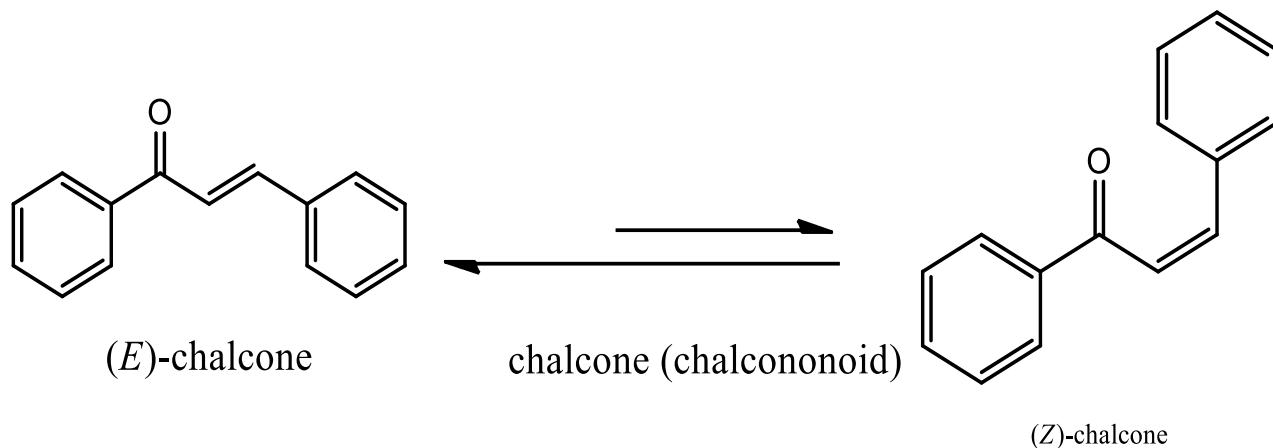
Chalcone is an aromatic ketone that is used to make a variety of key biological molecules. Chalcones are the biogenetic antecedents of flavonoids and isoflavonoids prevalent in plants. The chalcone's core consists of two aromatic rings joined by a three-carbon, -unsaturated carbonyl system with the molecular formula $C_{15}H_{12}O$, which can easily cyclize and generate flavonoid structures. Chalcone derivatives have anti-cancer, antioxidant, anti-inflammatory, antihypertensive, antimalarial, antiulcer, antiviral, antiprotozoal, cardiovascular, antiviral, antiprotozoal, and cardiovascular properties.

1.1 Nomenclature:

"Chalcone" is derived from the French word "chalcone." Although the Z conformer is more unstable due to the steric interaction of ring A with the carbonyl group, the Trans (E) and cis (Z) isomers of

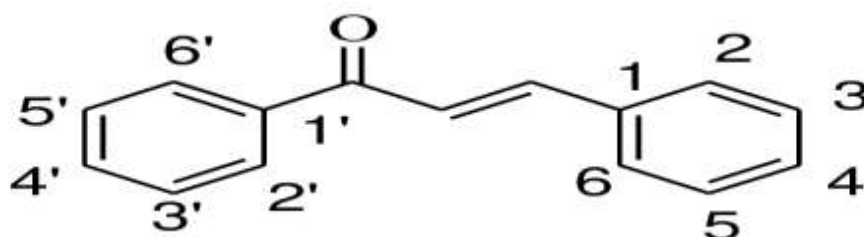
chalcone exist stereochemically. Two aromatic rings are in continuous conjugation with the electrophilic, -unsaturated carbonyl system in chalcones (scheme1)

Scheme1:

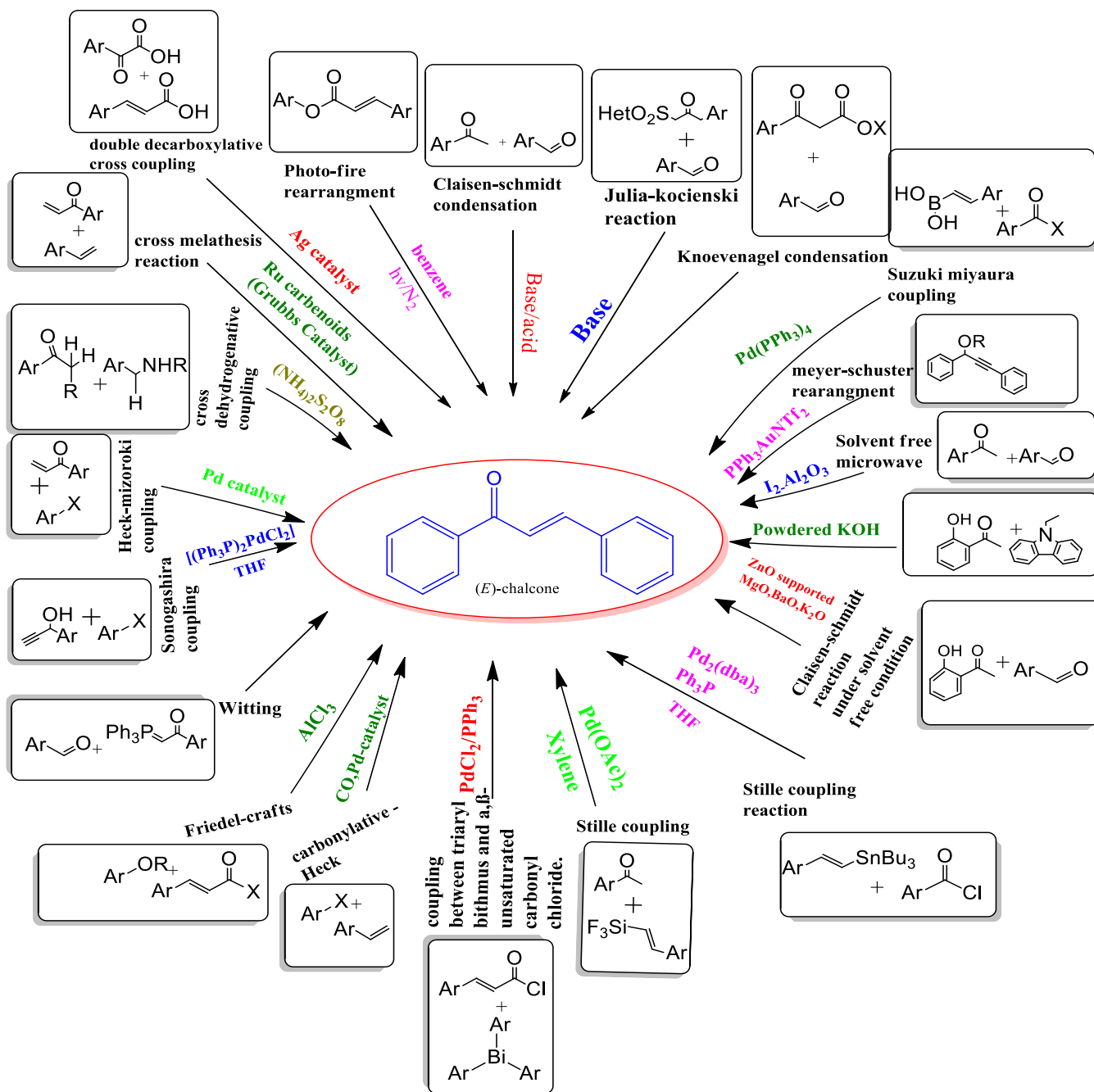


1.2. The following is the IUPAC-accepted chalcone naming convention:

According to IUPAC, chalcone is known as 1,3-diphenyl-2propen-1-one, which is a phenyl styli ketone. Due to a crucial difference in the numbering of locations of the chalcone nucleus, the flavonoid structure was reversed.



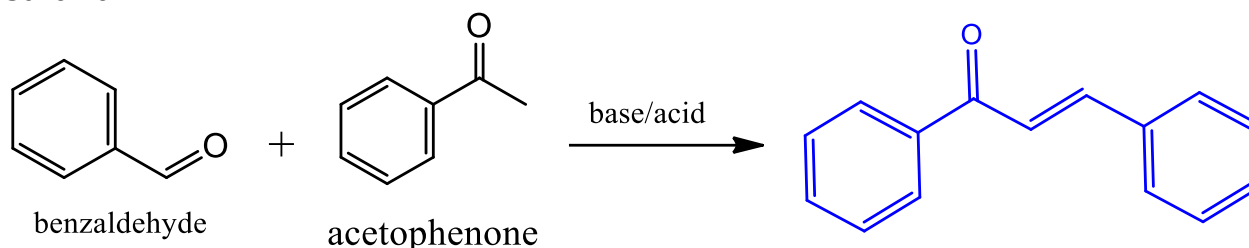
1.2 Synthetic review:



1.2.1 Claisen-Schmidt Condensation

The Claisen-Schmidt reaction is the most well-known in organic chemistry. This technique comprises condensation of acetophenone and aldehyde derivatives in the presence of acid or base catalysts in a polar solvent at 50–100 °C for many hours to produce chalcones derivatives. The Claisen-Schmidt reaction, named after two pioneering researchers R. L. Claisen⁹² and J. G. Scheme 2, explains the reaction between benzaldehyde and a methyl group. Ketone is condensed in the presence of catalysts.

Scheme2:



{Strong bases or acids are used as catalysts. The chalcone is generated from the aldol product via dehydration in an enolate mechanism in base catalysis, while it is generated via an enol mechanism in acid catalysis.}

In base condition: In methanol or ethanol at room temperature, the classical Claisen-Schmidt condensation is base-catalyzed with potassium tert-butoxide, sodium hydroxide, or potassium hydroxide. This reaction has been widely used to make hydroxyl-substituted chalcones, with typically good to excellent yields (60–90%).

Acid Condition): Although base catalysts are commonly used in the synthesis of chalcones, acid catalysts such as Brnsted acids, Lewis acids, and solid acids have also been used. The most common application, which uses ethanol saturated with Brnsted acid HCl, is only marginally successful, yielding only 10% to 40%. Because it acts as both a catalyst and a water-absorbent, dry HCl gas is more favorable to the reaction.

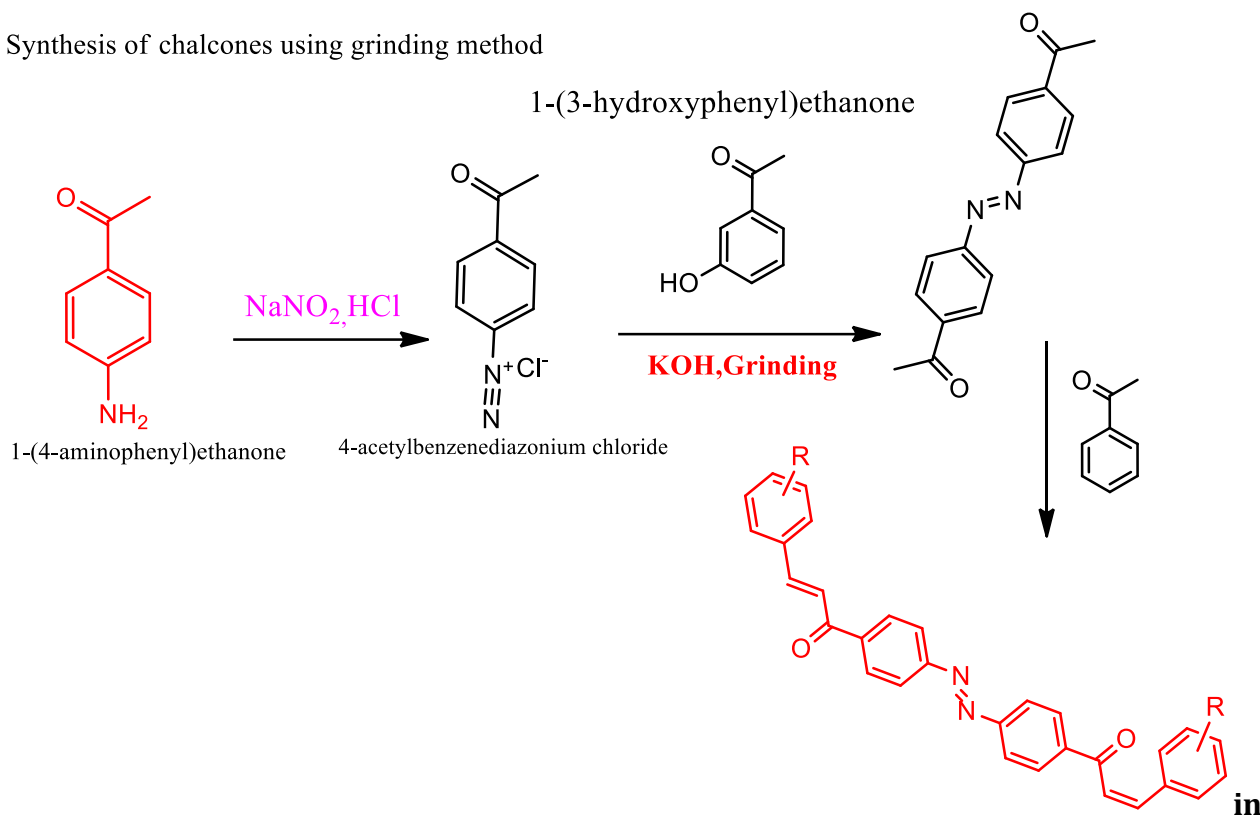
Condition: non-solvent

Chalcone synthesis has also been carried out under solvent-free conditions, such as grinding or microwave irradiation. Rateb and colleagues described a method for obtaining chalcone in an 80 percent yield by grinding sodium hydroxide with an aldehyde and ketone.

The chalcone core was also built using **microwave irradiation in no solvent systems**. The synthesis of chalcones under microwave conditions has been reported using a simple, solvent-free, eco-friendly method using calcium oxide as a solid base catalyst. In 57–88% percent of the time, zinc oxide-supported metal oxide catalysis produced fifteen chalcones with electron-donating and electron-withdrawing groups on both the ketone and aldehyde moieties. This method has also been used to report Claisen-Schmidt condensation of 2'-hydroxy acetophenone with aldehydes in solvent-free conditions.

Scheme3:

Synthesis of chalcones using grinding method



scheme3, Grinding is a simple, environmentally friendly, solvent-free method that produces quantitative yields in a short reaction time. Various chalcones were made by grinding a mixture of appropriate methyl ketones, aldehydes, and sodium hydroxide in an open mortar with a pestle.

1.2.2 Chalcone Synthesis Using Other Well-Known Methods

Because the Claisen-Schmidt condensation process can produce a complex mixture that is difficult to purify for the desired chalcone compound, other well-known reactions such as cross-coupling (e.g., Suzuki reaction, Heck reaction, Julia-Kocienski reaction, and Wittig reaction), Friedel-Crafts acylation, photo-Fries rearrangement, and one-pot synthesis from alcohols have been explored for the synthesis of chalcones.

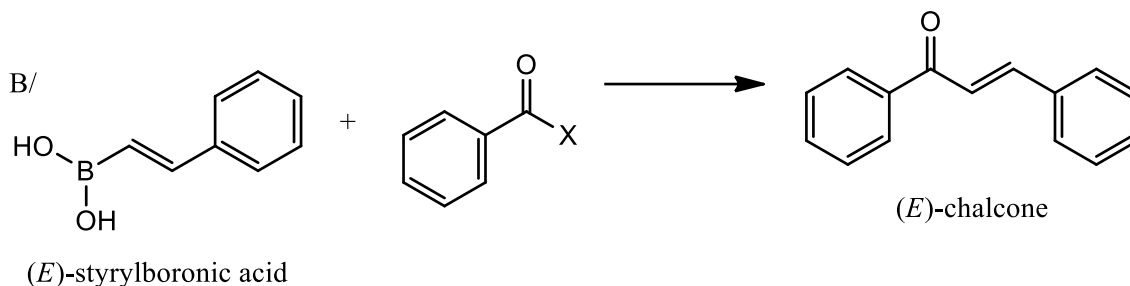
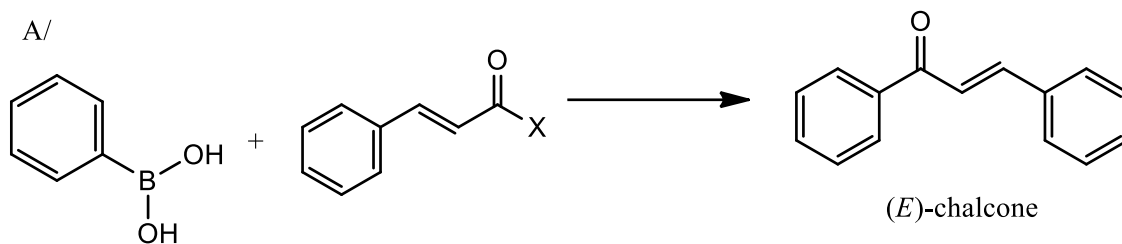
1.2.3 Cross-Coupling:

Suzuki coupling:

is a powerful carbon-carbon bond-forming reaction catalyzed by palladium. It was first used in the synthesis of chalcones. Two approaches to the synthesis of chalcones are possible based on the retrosynthetic analysis: coupling cinnamoyl chloride with phenylboronic acid (Scheme 4 A) and coupling benzoyl chloride with phenyl vinyl boronic acid (Scheme 4 B).

was first reported in 1979 by Akira Suzuki, who shared the 2010 Nobel Prize in Chemistry with Richard F. Heck and Ei-ichi Negishi for palladium-catalyzed.

scheme4:



1.2.4 The Suzuki coupling reaction]

has been used to make chalcones with electron-withdrawing or electron-donating substituents, indicating that the electronic properties of the substituents on the benzene rings have a minor impact. Buszek et al. published the first example of SuzukiMiyaura coupling for the synthesis of chalcones from N-vinyl pyridinium tetrafluoroborate salt, with yields of 60 to 81 percent (Scheme 5). These salts are a new type of palladium-catalyzed electrophilic coupling partner that reacts with a variety of boronic acids. The salts are also air-stable and do not form hygroscopic crystals, and they can be made quantitatively in one step using activated acetylenes and either pyridinium or trialkyl ammonium tetra fluoroborates.

Scheme5:

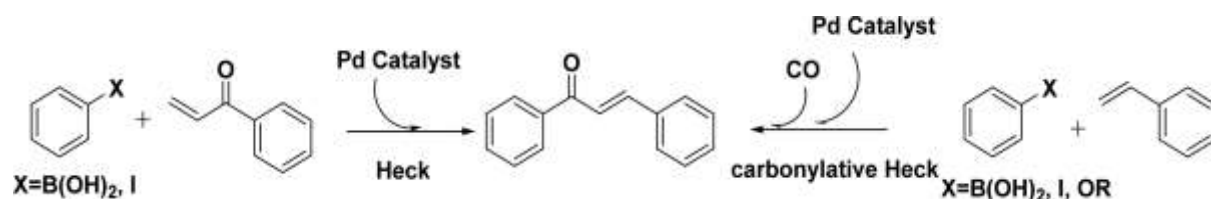
Suzuki–Miyaura coupling for the synthesis of chalcones;



1.2.5 Heck Reaction

which can be obtained by the classical Heck reaction of an aryl boronic acid or aryl iodide and an unsaturated ketone in the presence of a base and a palladium catalyst.

Scheme6:

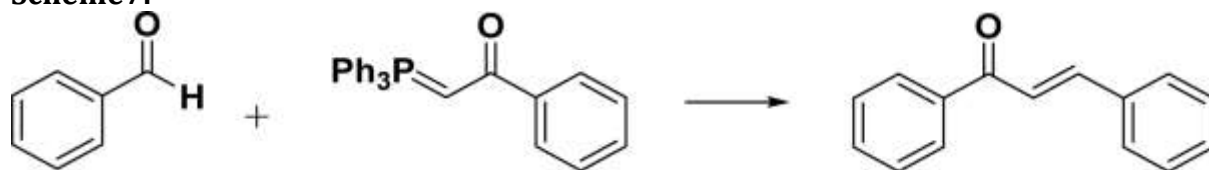


In scheme6, under catalytic conditions, they first reported the synthesis of aryl vinyl ketones and direct coupling with aryl iodides to rapidly-produce chalcone derivatives in excellent yields (75–96%) [Pd(OAc)₂, Ph₃P, CH₃CN, TEA].

1.2.6 Wittig reaction

Another simple way to make alkene compounds is through the **Wittig reaction**, also known as Wittig olefination. For the Wittig reaction strategy, chalcone is a reasonable alkene template).in scheme7, The first attempt, used triphenylbenzoyl methylene phosphorene and benzaldehyde and required 3 days of reflux in benzene or 30 hours in THF, yielded a good 70% yield.

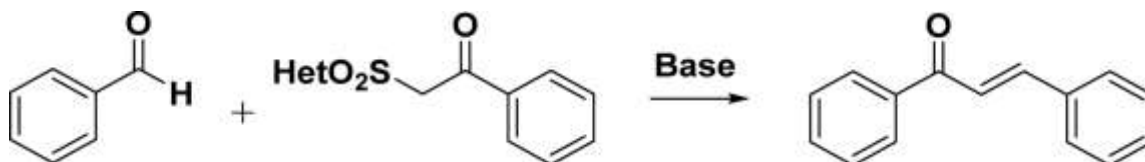
Scheme7:



1.2.7 the JuliaKocienski olefination

Kumar and co-workers in 2010 developed **the JuliaKocienski olefination**, a modification of the Julia olefination to synthesize chalcones. Jorgensen's method was used to make heteroaryl-sulfonyl phenylethanone. The Julia reagents and benzaldehyde were olefinoriginatedsic media to yield thirty-one chalcones. Several factors influenced this reaction, including the base, temperature, Julia reagent, and solvent. The most efficient base was 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), while the Julia reagent with benzothiazole as the heteroaryl was the best. Nonpolar solvents performed better than polar solvents, with yields decreasing in the order THF > DCM > CHCl₃ > CH₃CN > MeOH. When the temperature was 78 °C, the yield dropped dramatically. However, the trans-isomer remained the main product even at such low temperatures. where the stereoselectivity could be explained by the Newman projection.1)

Scheme8:



1.2.8 Cross-coupling

Scheme 9A :

In the presence of PdCl₂ (it bpf) as the catalyst and K₂CO₃, a direct cross-coupling reaction of benzoyl chlorides and potassium styryl tri fluoroborates to obtain the corresponding chalcones is carried out using microwave irradiation. This condition was used to synthesize eight chalcones, yielding good to excellent yields (56-96%).

Scheme9 B:

Another recently developed strategy for chalcone synthesis is palladium-catalyzed decarboxylative coupling using 3-benzoylacrylic acids (Scheme 8B). In the presence of a palladium catalyst and a copper salt oxidant [Cu(OAc)₂·2H₂O], 3- benzoyl acrylic acids react with aryl boronic acids or aryl halides to produce chalcone derivatives.

Scheme9 C:

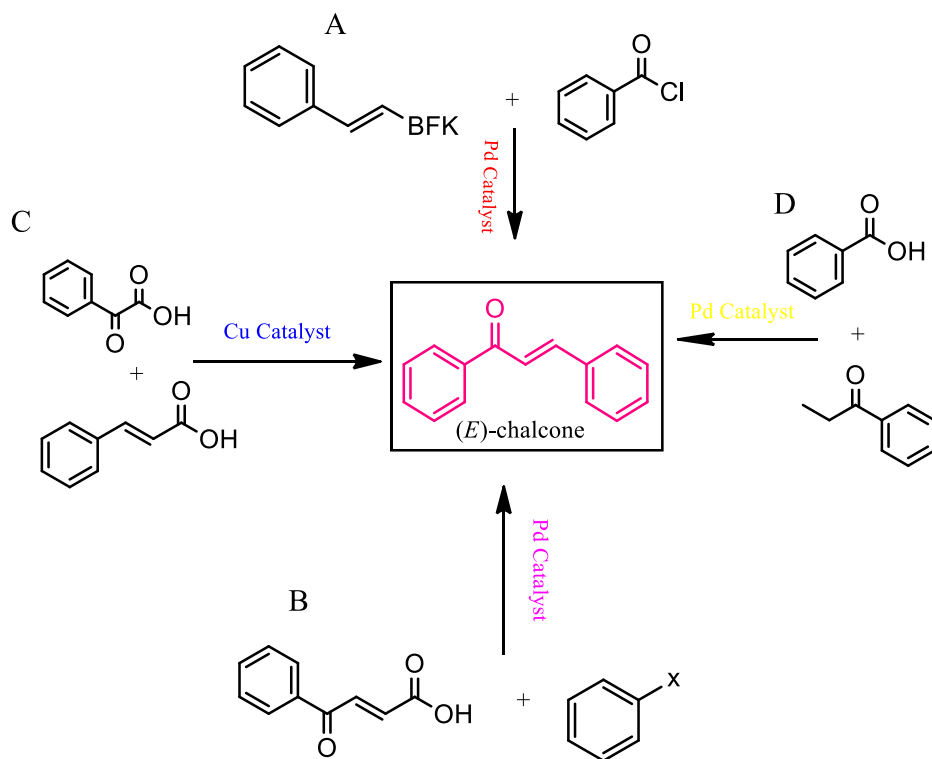
Another way to make chalcone scaffolds is to use a silver-catalyzed double-decarboxylative protocol. Chalcones have been synthesized with good yields from readily available -keto acids and cinnamic acids in the presence of silver nitrate (AgNO₃), sodium thiosulfate (Na₂S₂O₈), and potassium carbonate (K₂CO₃) in mild aqueous conditions.

. Scheme9 D:

The strategy of using saturated propiophenones to produce unsaturated chalcones has also been demonstrated using a combination of decarboxylation and dehydrogenation. The researcher's crosscoupled aryl carboxylic acids using a PCy₃-supported palladium catalyst to obtain chalcones in fair yields, which is an extension of the Heck reaction that overcomes the limits of its starting materials.

Other Cross-Couplings. In addition to the above cross-couplings, metal-catalyzed direct cross-coupling (using, for example, silver or palladium

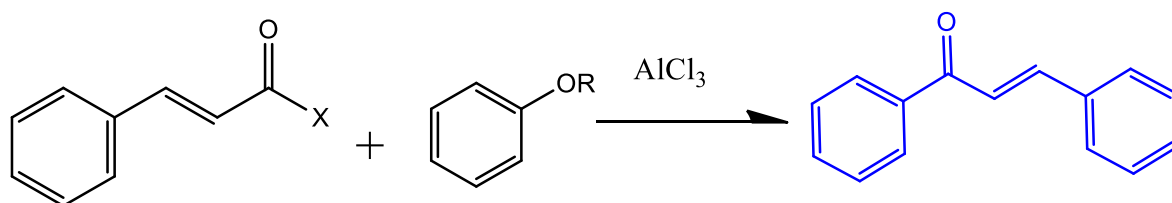
Scheme9:



1.2.9 Friedel-Crafts acylation

Chalcones can be made by Friedel-Crafts acylation of an aromatic ether and cinnamoyl chloride using a strong Lewis acid catalyst like aluminum trichloride. Reactions of unsaturated acid halides: Competitive Friedel-Crafts acylations and alkylations of monohalogenobenzenes by the bifunctional cinnamoyl chloride.

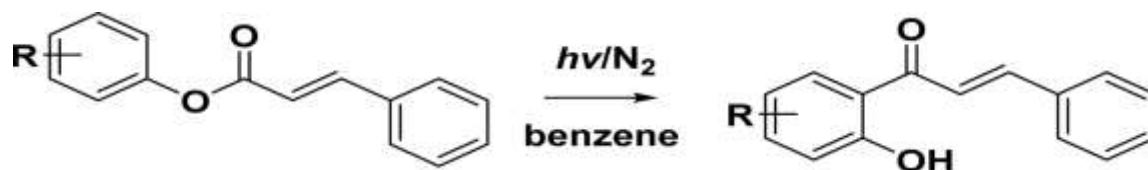
Scheme10:



1.2.10 Photo-Fries Rearrangement:

Photo-Fries Rearrangement of Phenyl Cinnamates. The photochemistry of chalcones has attracted researchers because, in the presence of Lewis acids, a convenient rearrangement reaction of phenyl cinnamate to hydroxy aryl ketone occurs. The reaction conditions, such as temperature and solvents, affect whether this is an ortho- or para-selective reaction.

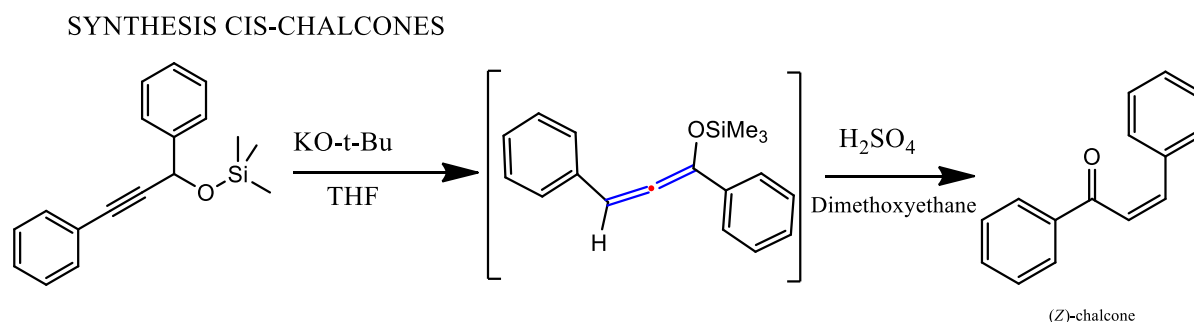
Scheme11:



1.2.11 Synthesis of cis-chalcones

When compared to the more stable trans-chalcones, the synthesis of cis-chalcones is a thermodynamically less stable isomer. Siloxypropynes and potassium tert-butoxide (t-BuOK) were combined at 78°C to produce important intermediates, siloxyallenes, which were then treated with a strong acid (H₂SO₄) and 1,2-dimethoxymethane (DME) to yield cis-chalcones.[20]

Scheme12:



1.2.12 One-Pot Synthesis of Chalcones:

Scheme13 A:

1st condition:

One-pot synthesis is a technique for increasing the efficiency of a reaction while avoiding the need to purify intermediates, saving time, and increasing overall yield. The chalcone scaffold was recently synthesized from alcohol and ketone in a one-pot reaction. In Scheme A, chromium (VI) oxide is slowly added to a mixture of primary alcohol and a ketone, resulting in moderate to high yields (65–98% percent) of chalcone.

2nd condition:

the one-pot reaction of an alcohol and various ketones with a catalyst consisting of copper iodide, 2,2'-bipyridine, and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) by changing the reaction temperature from 10 to 100 °C for 1096 hours (, condition II)

3rd condition:

prepared from PdCl₂ catalyzed the reaction effectively, yielding chalcones from -ketones and alcohols in 92 percent of cases (Scheme 11A, condition III)

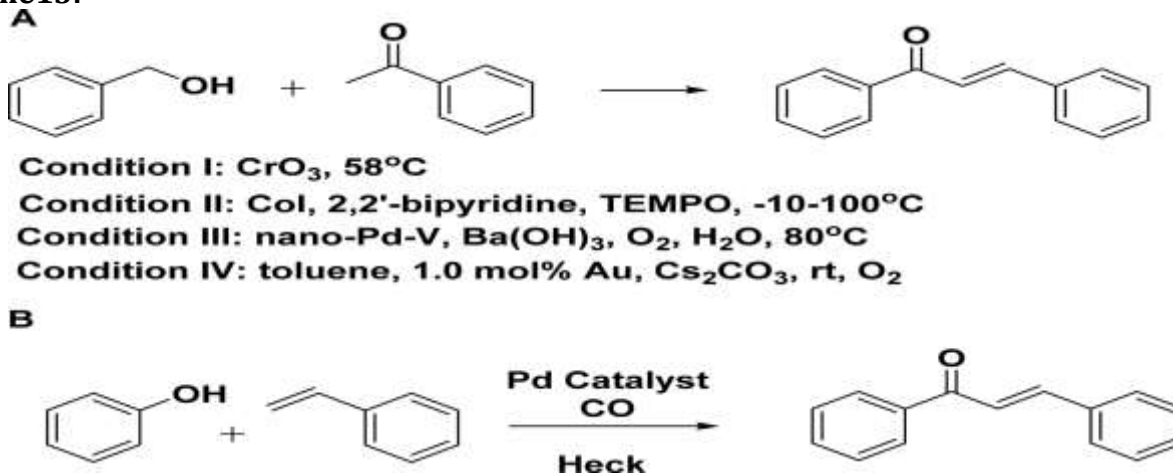
In the 4th condition:

the alkylation of ketones with primary alcohols was reported to be catalyzed by a heterogeneous and recyclable palladium catalyst [Pd/AlO(OH)] (, condition IV).

Scheme 13 B: Phenols have also been used in one-pot synthesis in addition to benzyl alcohols. The synthesis of chalcones from phenols, which was an extension of the above carbonylative Heck

coupling with the activation of phenol in a one-pot manner, was published as an example (Scheme B).[25]

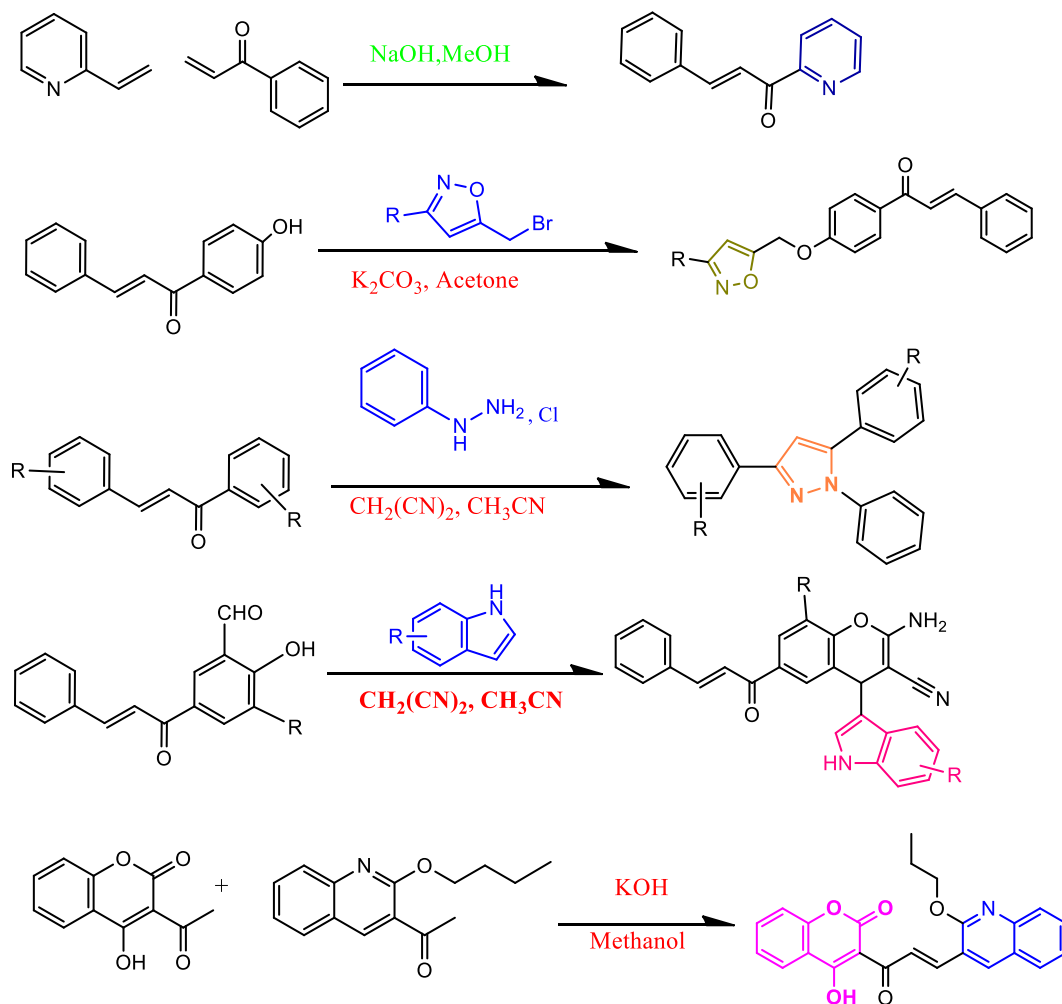
Scheme13:



1.2.13 Hybrid chalcones

Chalcones are versatile molecules that easily cyclize to form a flavonoid structure, which is an isomeric step in the biosynthetic pathway for skeletal modification. Due to their broad-spectrum pharmacological potentials, several synthetic attempts have been made to produce a new class of organic compounds based on the feature of structure modification, such as azachalcones, isoxazoles, pyrazoles, indole grounded chalcones, and coumarinyl-quinolinyl chalcones (Scheme 14).

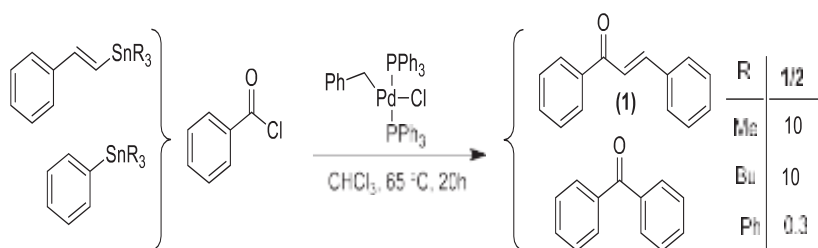
Scheme14:



1.2.14 Stille coupling reactions

The Stille coupling reaction, discovered by J.K. Stille in 1983, is a C–C bond coupling reaction between Organotin compounds (Organostannanes) and alkyl/aryl halides or triflates in the presence of Pd as a catalyst. In 1983, Stille reported the first example of chalcone synthesis by Stille coupling. Using HPLC, he was able to compare the relative reactivity rate of phenyl tributyltin and triphenylstlytin or trialkyltin derivatives. Trimethyltin and triphenylstly tin were found to be 10 times more reactive than tributylphenyl tin.

scheme15:

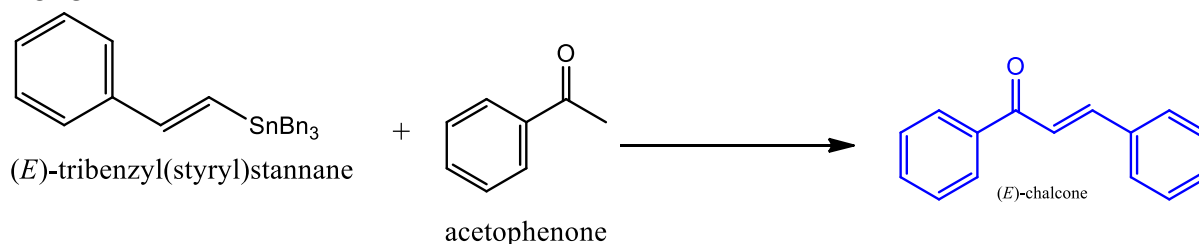


. Relative reactivity of styryltins and phenyltrialkyltin in Stille coupling reaction for chalcone synthesis.

1.2.15 Stille coupling

Stille coupling of the tribenzylstyryltin derivative and benzoyl chloride with $\text{Pd}_2(\text{dba})_3$ and Ph_3P in THF as vented to give the corresponding chalcones in 91 percent yield. The tribenzylstyryltin derivatives were made by hydrostannylation of a terminal alkyne with tributyltin hydride and triethylamine as a base.

Scheme 16:

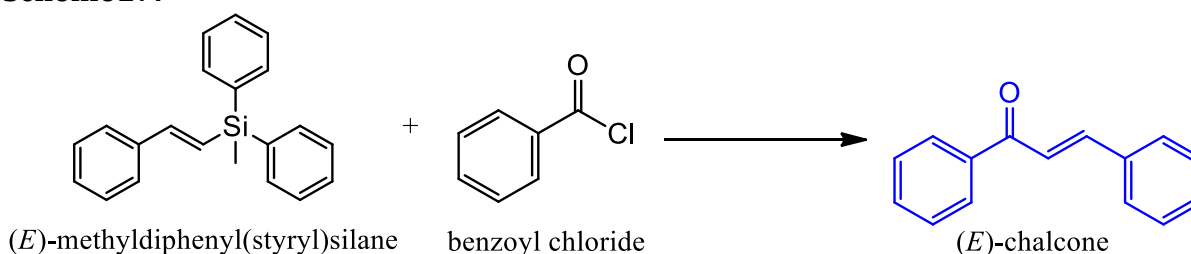


1.2.16 Hiyama coupling:

The Pd-catalyzed cross-coupling reaction between organosilanes and organic halides is known as Hiyama coupling. The $\text{Pd}(\text{OAc})_2/\text{Pt Bu}_3$ catalyzed aryl-acyl Hiyama coupling for the synthesis of chalcone derivatives was reported by Ogiwara et al (Scheme 17)

The use of a sterically hindered and electron-rich trialkylphosphine ligand, as well as a fluoride-substituted organosilicon reagent, were the two main factors in the reaction's success:

Scheme 17:

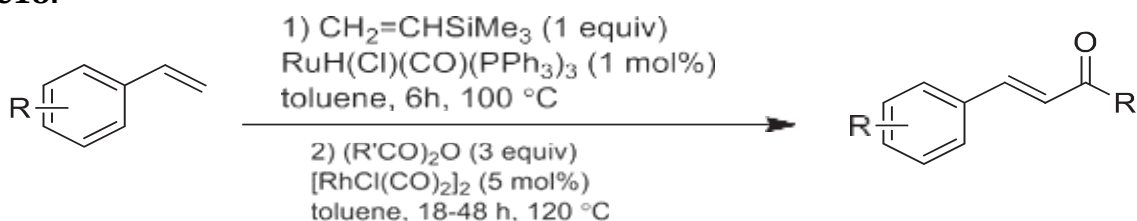


used $[\{\text{Ir}(\mu\text{-Cl})(\text{cod})\}_2]$ catalyst for the coupling between styryl silanes and acid anhydrides..

1.2.17 One-pot method

They've also developed a highly efficient stereo-selective one-pot method for the synthesis of (E)-, -unsaturated ketones from styrenes based on Ru-catalyzed silylating coupling followed by Rh-catalyzed desilylative acylation reactions.

scheme18:



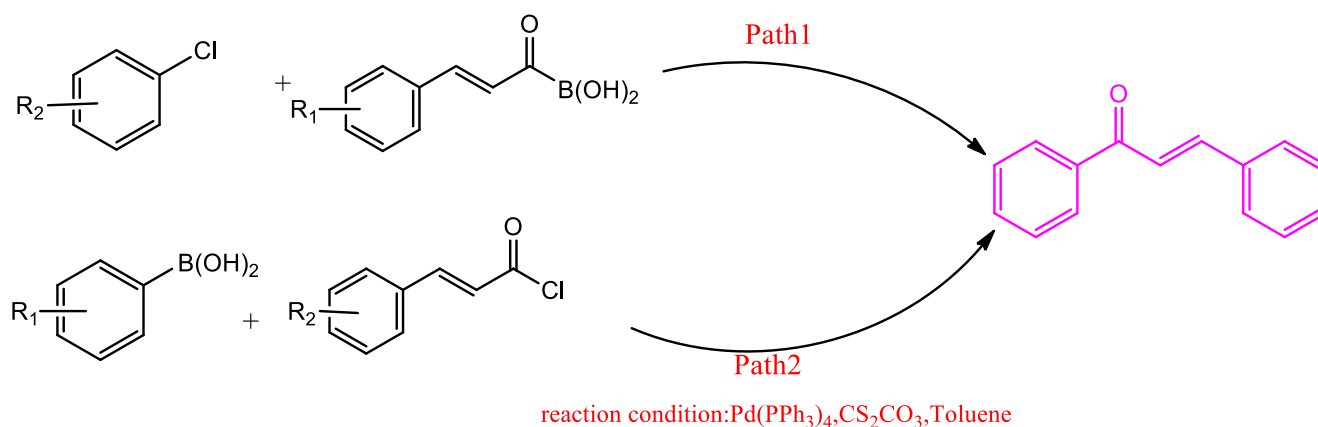
Scheme 18. One-Pot Synthesis of (E)- α,β -unsaturated ketones from Styrenes

1.2.18 Suzuki-Miyaura coupling reactions

. The cross-coupling of boronic acids and organic halides catalyzed by Pd(0) complexes is known as the Suzuki-Miyaura (SM) or Suzuki coupling reaction. The SM coupling reaction has been used to synthesize chalcones in two different ways, according to Eddarir and colleagues. The coupling of arylboronic acids and cinnamoyl chloride was the first pathway, while the coupling of styrylboronic acid and benzoyl chlorides was the second.[9]

Scheme19:

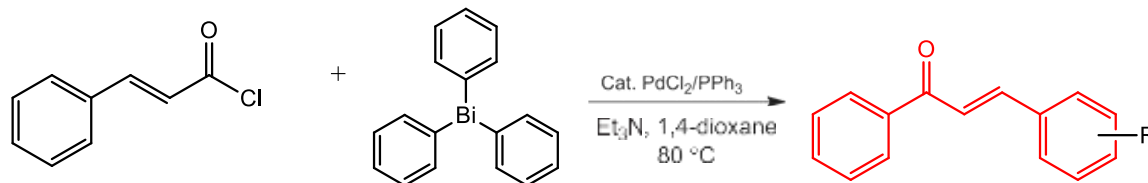
. Synthesis of Chalcones using SM coupling reaction



1.2.19 Cross-coupling reaction between triarylbiomuth and,-unsaturated carbonyl chloride

For the synthesis of chalcones, a cross-coupling reaction between triarylbiomuth and,-unsaturated carbonyl chloride is carried out using a Pd catalyst (Scheme 20). Because the stoichiometry ratio of,-unsaturated carbonyl chloride and triarylbiomuth is 3:1, this method could be used on a large scale with less organometallic reagent loading.

Scheme20:

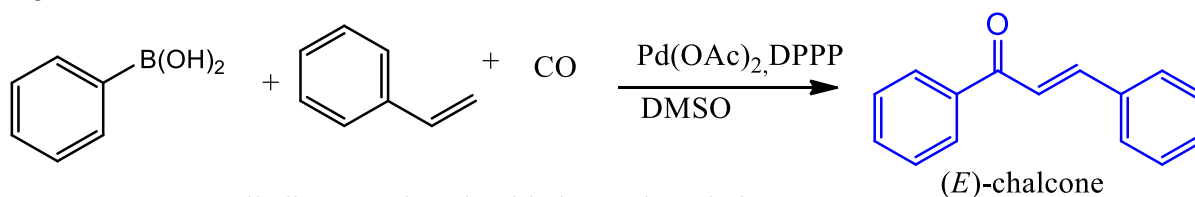


Coupling reaction between triarylboranes and α,β -unsaturated carbonyl chloride

1.2.20 Carbonylative coupling between arylboronic acids and various styrenes.

As a catalyst and ligand, Pd(OAc)₂ and DPPP (1,3-bis(diphenyl-phosphine)propane) were used. This reaction is carried out more mildly without the use of any additives and with the use of air for terminal oxidation.

Scheme21:



Palladium-catalyzed oxidative carbonylation.

1.2.21 Wittig reaction

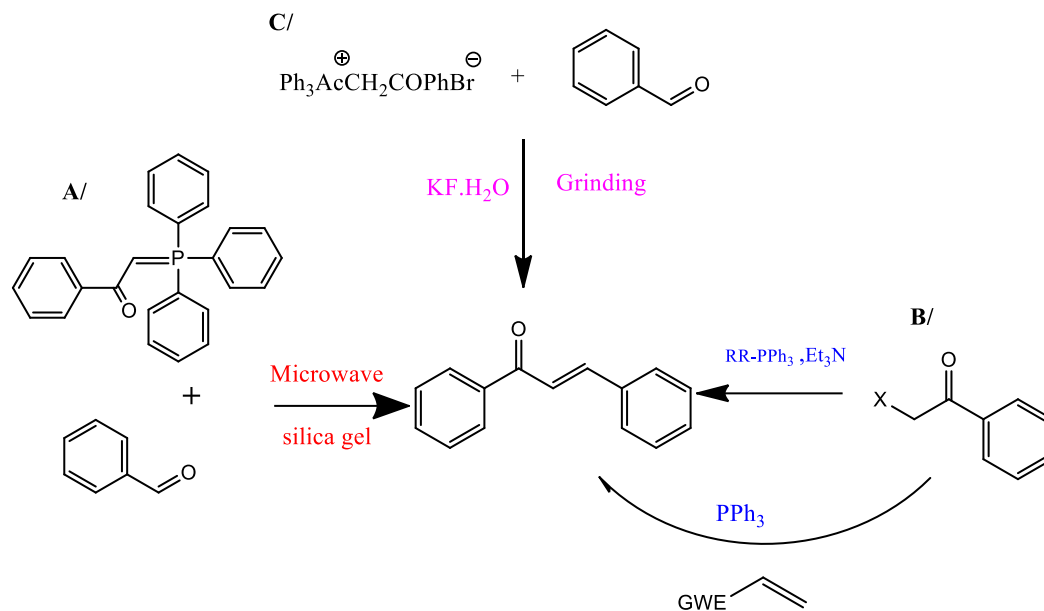
Scheme22A/

Remirez et al. reported the use of benzaldehyde and triphenylphosphenebenzoylmethylene as reactants in the synthesis of chalcones by Wittig olefination (Scheme 19). Initially, it took 3 days of reflux in benzene to complete the reaction; however, it has since been determined that 30 hours of reflux in THF is sufficient to complete the reaction (Yield: 70 percent) [13][14]. Xu et al. improved this reaction by switching from conventional heating to microwave irradiation, which reduced the reaction time from 30 hours to 5 minutes and resulted in a significant increase in yield of up to 96 percent. [35]

Scheme22B/. Rasta resin-PPh₃ (RR-PPh₃), a heterogeneous polystyrene-support reagent developed by Toy and colleagues, was used in a wide range of Wittig olefination reactions. In the presence of RR-PPh₃ and Et₃N, they synthesized chalcones by reacting aromatic aldehydes with alkyl/aryl halides, RR-PPh₃ and Et₃N were used in excess (2.0 equiv.) because RR-PPh₃ was involved in the in-situ preparation of the phosphorane reagent, whereas Et₃N was involved in the deprotonation of the phosphonium salt (Scheme 19). Other Rasta resins, such as Rasta Resin-PPh₃-NBnPr₂ and Rasta Resin-PPh₃-NBnBn₂, have also been explored for Wittig olefination reactions. For this type of olefination, Rommel et al. used a dual [Fe phosphine] catalyst. Using -halo carbonyl compounds, aldehyde, and terminal alkenes in the presence of triphenylphosphine, Liu et al. developed a novel one-pot method for the synthesis of chalcones in 60–94% yield (Scheme 19) The formation of a zwitterion by the reaction of terminal alkyne with phosphine, which acts as a base for this type of olefination reaction, is a plausible mechanism. Arsonium Ylide has been described by Changqing et al. as a solvent-free new process for chalcone synthesis.

Scheme22C/

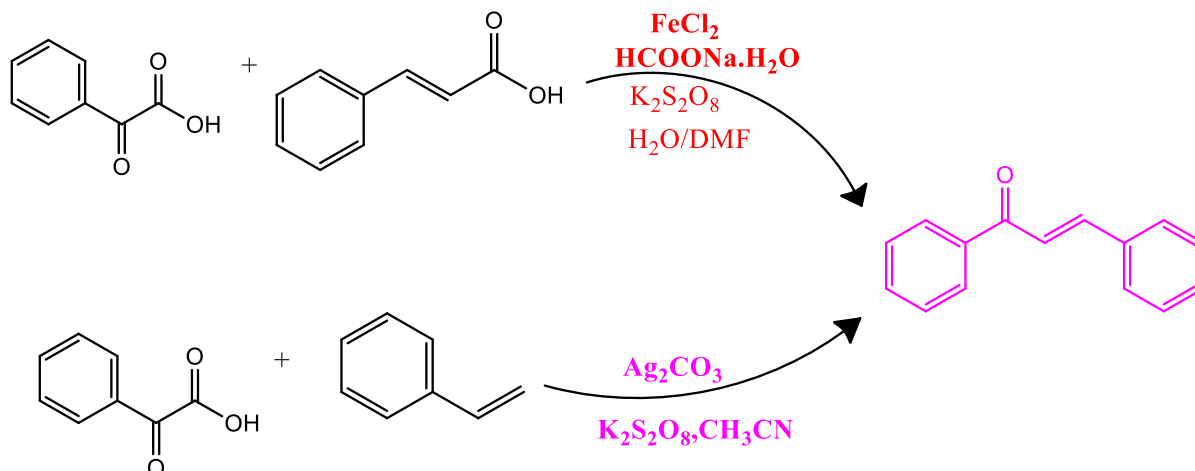
Grinding aromatic aldehyde and arsonium salt in the presence of $\text{KF}\cdot\text{H}_2\text{O}$ yielded the corresponding chalcones in 84–94 percent of the cases. Trofimov and colleagues described a stereoselective method for converting 1-acetyl-2-phenylacetylene to the respective chalcones by reducing it with Ph_3P in water

Scheme22:**1.2.22 Decarboxylative cross-coupling**

. Transition-metal-catalyzed decarboxylative coupling reactions can also be used to make chalcones or, -unsaturated ketones. Due to the high selectivity, efficacy, feasibility, and nontoxic behavior of by-products, the development of such reactions has gotten a lot of attention. In an aqueous solution, Jiang et al. reported a Fe catalyzed decarboxylative cross-coupling reaction between Cinnamic acid derivatives and α -Oxo carboxylic acid.

Scheme23:

Synthesis of Chalcones using decarboxylative cross coupling.

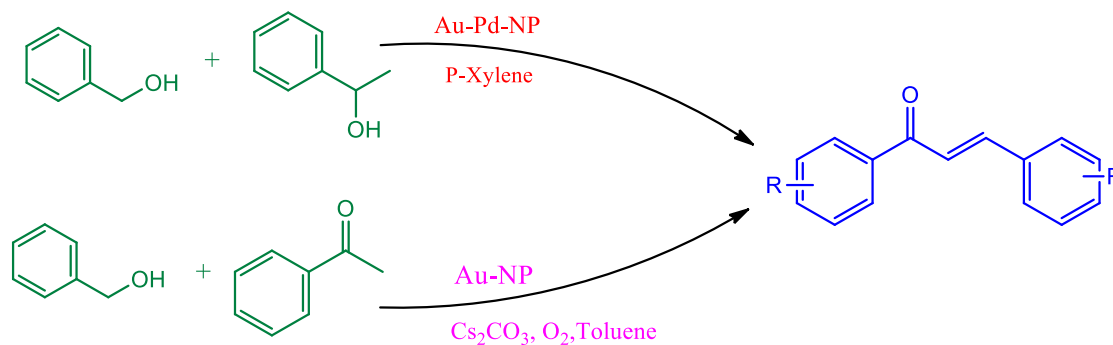


1.2.23 The aerobic oxidative cross-coupling reaction :

A/ between primary and secondary alcohol are used in a novel method for the preparation of chalcone. For this coupling reaction, they used a novel bimetallic catalyst, Au–Pd nanoparticles supported on the lay of hydrotalcite (HT), which yielded the corresponding chalcones in around 90% of the cases. This reaction has several advantages, including high catalytic activity with better selectivity,

B/ the absence of a base and ligand or co-catalyst, and the absence of a base and ligand or co-catalyst. Park and colleagues developed a novel nanoparticle catalyst for the synthesis of chalcones by coupling aryl methyl ketones and primary alcohols (Scheme 24)

. Synthesis of Chalcones using aerobic oxidative cross coupling

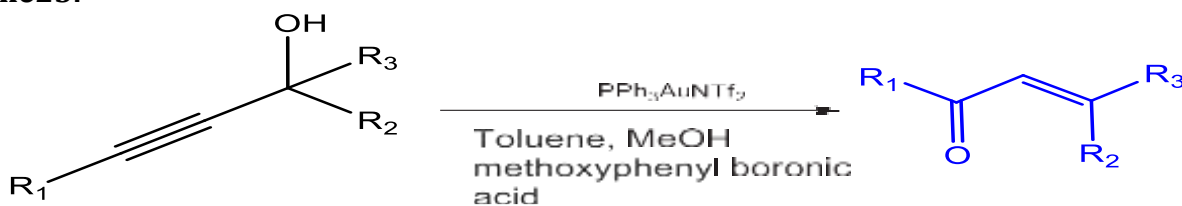


1.2.24 Meyer Schuster Rearrangement

is the conversion of propargyl alcohol to α,β -unsaturated ketones via a 1,3-hydroxyl shift followed by tautomerization. In the presence of catalytic amounts of methanol or 4-methoxyphenyl boronic acid [43] (Scheme 25), Pannel et al. reported Au catalyzed Meyer-Schuster rearrangement of propargylic alcohols to α,β -unsaturated ketones [44]. Using $[\text{PPh}_3\text{AuNTf}_2]_2\text{PhMe}$ ([Bis(trifluoromethanesulfonyl) imidate] (triphenylphosphine) gold (I) (2:1) toluene adduct) as catalyst and methanol or 4-methoxyphenyl boronic acid as an additive, this reaction proceeds at

room temperature, resulting in the formation of α,β -unsaturated ketones in good to excellent yield. In the absence of additives, this reaction proceeds very well with secondary and tertiary propargylic alcohols, but yields are lower.

Scheme 25:



1.2.25 Metal-catalyzed Heck coupling reactions,

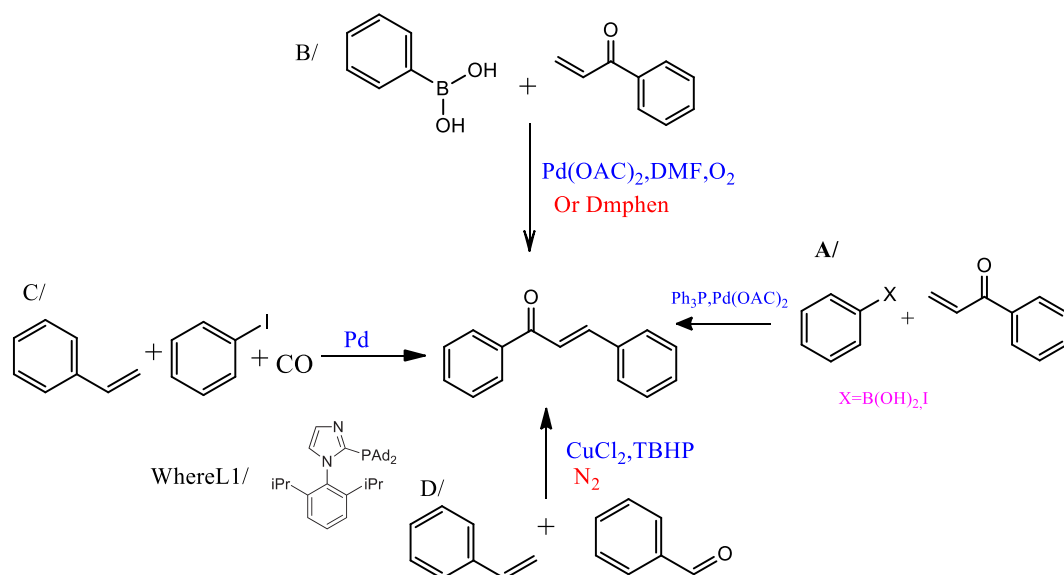
A/ in which C–C bonds are formed between the aryl vinyl ketone and the aryl boronic acid, can also be used to make chalcones. Hird et al. reported the synthesis of chalcones using Ph_3P , $Pd(OAc)_2$, K_2CO_3 , or triethylamine as the base and DMF as the solvent (Scheme 26).

B/ The cross-coupling reaction between α -chloroalkyl aryl ketones, amides, or esters has been reported by Guo et al. The reaction is initiated by domino dehydrochlorination, which is followed by a Heck coupling reaction catalyzed by $Pd(OAc)_2$. For these types of coupling reactions, $Ru(PPh_3)_3Cl$ has also been used as a catalyst, but the yield is only 20–25 percent (Scheme 26).

C/ For the synthesis of chalcones, Beller and colleagues described a palladium-catalyzed carbonylative Heck reaction between aryl halides and olefins in the presence of CO. They used a catalyst made up of $[(cinnamyl)PdCl]_2$ and the bulky ligand imidazolylphosphine L1, which allows them to synthesize chalcones competently and selectively under milder reaction conditions (Scheme 26).

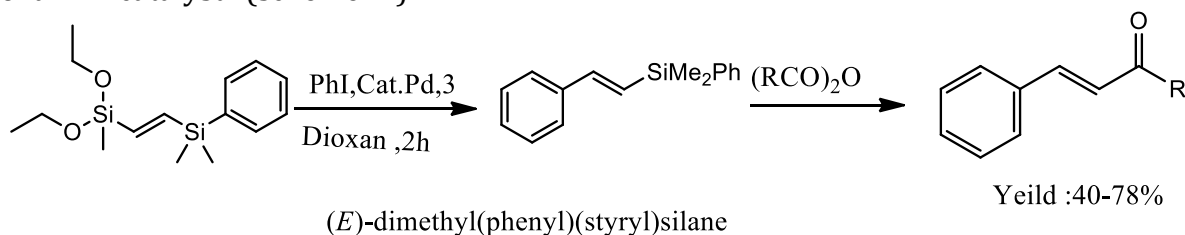
D/ In addition, for the carbonyl Heck reaction, 1,3-bis(diphenylphosphino)propane was used as a ligand for coupling between the aryl triflate and various styrene derivatives. Using a Cu catalyzed oxidative coupling reaction between the alkenes and the aldehydes (Scheme 26), Wang et al. reported a novel method for the synthesis of chalcones. This reaction uses a single electron transfer mechanism and can be carried out with a wide range of aldehydes and alkenes with various functional groups.

(Nagaiah and colleagues synthesized chalcones in two steps: (i) $Pd(OAc)_2$ oxidation of allyl alcohol, and (ii) $Dmphen$ oxidative arylation of boronic acid, boronic esters, or trifluoroborate salts (Scheme 26). This is a one-pot greener method that eliminates the need for intermediate isolation and the use of Cu salt.

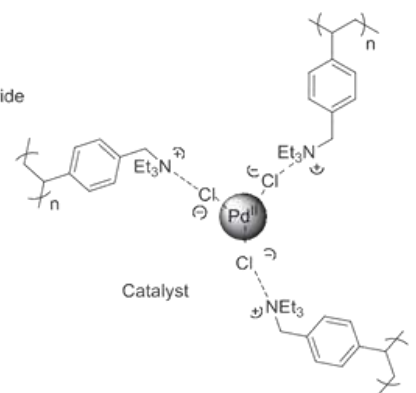


1.2.26 Sequential Hiyama/Narasaka coupling

That and co-workers used a **sequential Hiyama/Narasaka** coupling reaction (Scheme 12) to make chalcones. In the presence of a catalytic amount of ionic gel stabilized Pd catalyst and polymer-supported ammonium fluoride, (*E*)-1, 2-bis-diarylethene derivatives were reacted with aryl halides. The resulting mixture was then subjected to the Narasaka reaction, which was carried out with the help of an Rh catalyst. (scheme27)



3= Polymer supported ammonium fluoride



1.2.27 Deamination of aziridines:

Another method for making chalcones is by **deamination of aziridines**. Lee et al. reported the first method for the synthesis of chalcones by deamination of aziridines, which was accomplished in 10 minutes using N_2O_4 in the presence of triethylamine as a base and THF as a solvent at 23 C or 43 C

under an inert atmosphere. Other reagents used in the synthesis of chalcones by deamination of aziridines include nitrosyl chloride and methyl nitrite, N-nitroso-3-nitrocarbazole, n-butyl nitrite and organosilyllithium (**Scheme 28**).



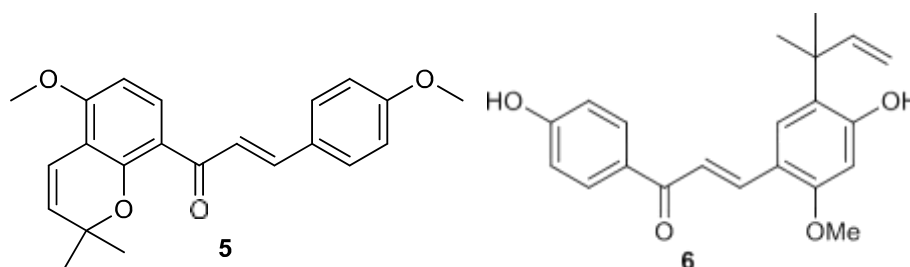
Scheme 28 Synthesis of Chalcones by deamination of aziridines.

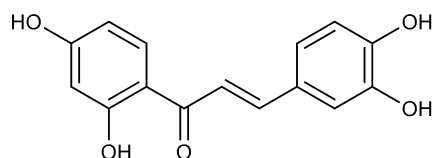
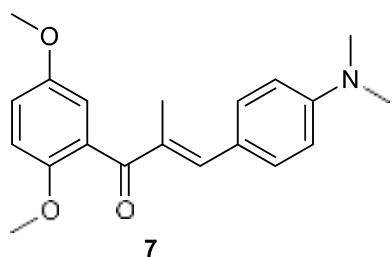
2 Biological activity of chalcones:

The chalcones and their derivatives have enormous importance in medicinal chemistry even in the twenty-first century because of their broad spectrum of the therapeutic potential and pharmacological properties. The chalcones derivatives show a variety of biological activities including anticancer, antibacterial, anticonvulsant, anti-HIV, antihyperglycemic, anti-inflammatory, antileishmanial, antimicrobial, antioxidant, antiprotozoal, antitubercular and antiviral, anti-ulcerative. A concise study about the biological importance of chalcones with examples is summarized below.

2.1 Anticancer activity:

Some chalcones from synthetic as well as natural origin were acknowledged as active against tumor cells along with antioxidant principles, by inhibiting superoxide production and lipid peroxidation. reported an anticancer chalcone, Millepachine is isolated from *Millettia pachycarpa*. Licochalcone A, isolated from *Glycyrrhiza infate*, is another anticancer chalcone which exhibited toxicity toward L1210 leukemia and B16 melanoma cells. A new class of chalcone proposed as an antimetastatic agent by increasing the survival of mice inoculated with L1210 leukemia with doses range of 2.65-5.0 mg/kg Butein (8) is another natural chalcone which can suppress the several human cancers including breast cancer, colon carcinoma, osteosarcoma and hepatic stellate cells in vitro.

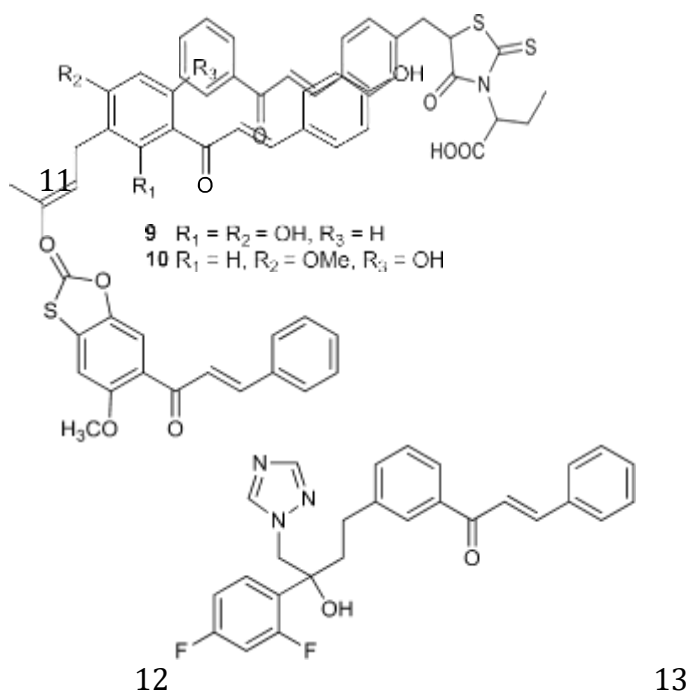




2.2 Antimicrobial activity

Antimicrobial activity of chalcones is believed owing to α , β -unsaturated carbonyl function. Isobavachalcone (9) and bavachalcone (10) are two important chalcones isolated from *Psoralea corylifolia* reported as antibacterial agents from the natural source.

A synthetic scaffold, 3-(carboxyalkyl) rhodanine (11) is an antimicrobial chalcone which displays potent inhibition at low concentration (1 $\mu\text{g}/\text{mL}$) against human pathogens and is documented as antibacterial as well as antifungal agent. Another, ring fused chalcone (12) is proposed as an antimicrobial scaffold for the treatment of oral infections[86]. A hybrid chalcone that comprises pharmacophore fluconazole (13) showed potent inhibition with 0.12 $\mu\text{g}/\text{mL}$ IC₅₀ concentration against *Candida albicans* and was patented as antifungal agent.



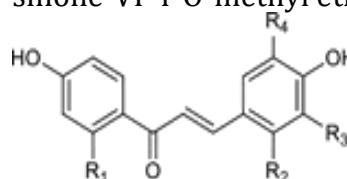
2.3 Anti-HIV

Few prominent chalcones were reported from natural and synthetic origin as active against human immune virus (HIV). The natural chalcone (14), xanthohumol isolated from Hops

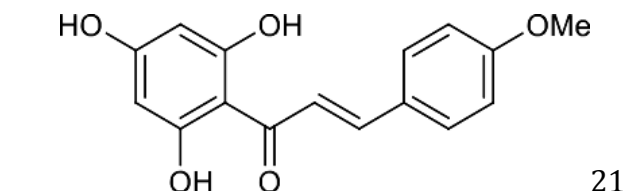
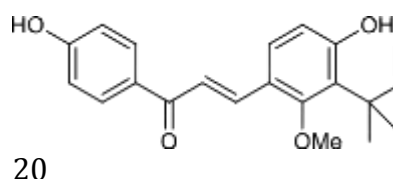
Humulus exhibits anti-HIV properties[88][89]. Nakagawa and Lee isolated a unique β -hydroxy chalcone from the genus *Desmos* that shows good anti-HIV activity.

2.4 Antidiabetic activity:

Chalcones were reported as potent inhibitors of α -glucosidase, dipeptidyl peptidase-4 (DPP4), peroxisome proliferator-activated receptors- γ (PPAR), protein tyrosine phosphatase 1B (PTP1B) and aldose reductase and are significant agents for the treating diabetes mellitus[86]. Isoliquiritigenin (17), echinatin (18), licochalcone A (6), licochalcone C (19) and licochalcone E (20) were isolated from *Glycyrrhiza inflata*, and its synthetic derivatives are reported as PTP1B which play vital role in treating type II diabetes and obesity, as a negative regulator of the insulin and leptin signaling pathway [5]. A novel chalcone, abysosinone-VI-4-O-methyl ether (21).



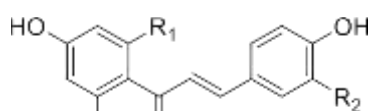
17, 18, 19
 $R_1 = \text{OH}, R_2 = R_3 = R_4 = \text{H}$
 $R_1 = R_2 = R_3 = R_4 = \text{OMe}$
 $R_1 = R_2 = \text{H}, R_3 = \text{OMe}, R_4 = \text{PhOCH}_3$



2.5 Anti-inflammatory activity

Naringenin-chalcone (30) is a well-known natural compound which exhibits anti-inflammatory activity by inhibiting the production of cytokines, a pro-inflammatory agent [90]. Isoliquiritigenin (31), isolated from Nepalese propolis, and butein (32) isolated from *Rhus vernicifua*, are another significant natural chalcones which exhibit potent anti-inflammatory activity by inhibiting LPS-induced iNOS and COX-2 expression. . reported a reduced chalcone (33) identified as anti-inflammatory agent by inhibiting the production of NO induced by LPS and INF- γ in murine microphage-like cell lines. Another synthetic heterochalcone (34)

Had been reported as a potent cytokine inhibitor used for the management of anti-inflammatory ailments



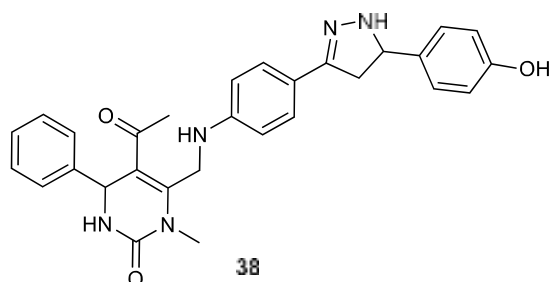
30 R₁ = OH, R₂ = H
 31 R₁ = R₂ = H
 32 R₁ = H, R₂ = OH

2.6 Antileishmanial activity

Licochalcone A (6) is a renowned natural antiparasitic agent used to treat various abdominal spasmodic symptoms by Japanese [93]. Kanzonol C (35), isolated from the licorice roots (*Glycyrrhiza eurycarpa*, Leguminosae), showed strong antileishmanial activity [94]. Crotaamosmin (36) is another important chalcone isolated from *Crotalaria rososissima*, which showed potent antileishmanial activity. A dihydro-chalcone (37) synthesized by [95] showed trivial antileishmanial activity. [96] synthesized a new class of dihydropyrimidine derivatives, and the compound (38) displayed antileishmanial activity against promastigotes of *Leishmania major* and *L. donovani* with the inhibitory

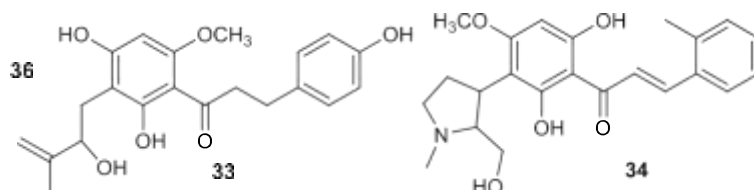
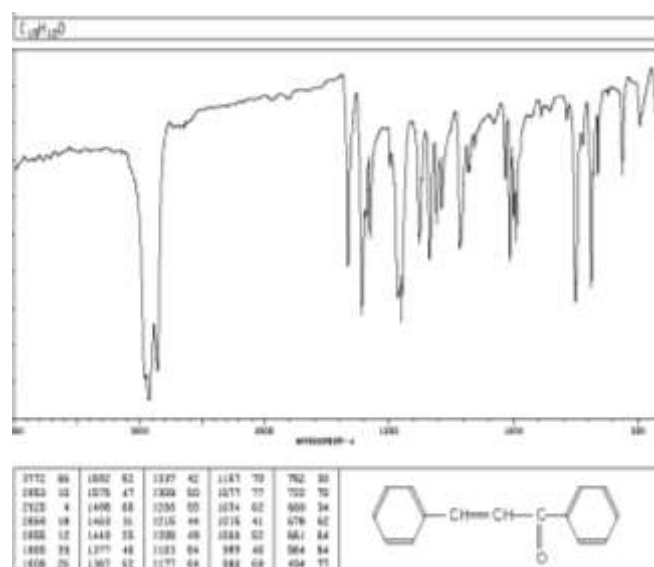
concentration of 0.47 $\mu\text{g/mL}$ and 1.5 $\mu\text{g/mL}$, respectively.

(30) i3.7 Antiviral activity



3 Scheme and figure (spectrum)

3.1 IR spectra of (E)-1,3-diphenylprop-2-ene-1-one (3a)



3.2 ¹H NMR spectrum for chalcone:

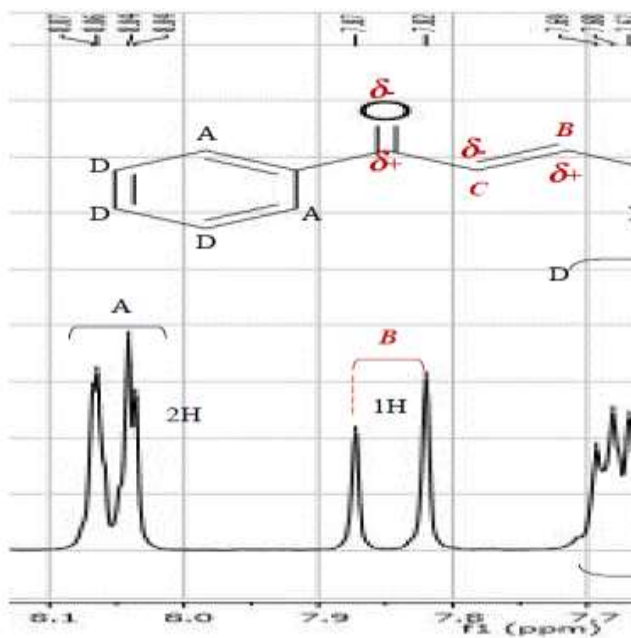


Figure 2. ¹H NMR spectrum of 1, 300 MHz, CDCl₃, δ from TMS. Assign

Conclusion:

Chalcone is a common structure found in a wide range of naturally occurring compounds, particularly those derived from plants. In addition, because of their ease of synthesis, many chalcone derivatives have been prepared. Because these natural and synthetic chalcone derivatives have shown numerous biological activities with clinical potential against various diseases, chalcone is regarded as a privileged structure of great practical interest. For the synthesis of these compounds, a variety of methods and schemes have been reported (1,3-diphenyl-2-propen-1-one). Aldol condensation and Claisen-Schmidt condensation are still at the top of the list. Suzuki reaction, Wittig reaction, Friedel-Crafts acylation with cinnamoyl chloride, Photo-Fries rearrangement of phenyl cinnamates, and others are notable techniques.

Reference:

- [1] A. Rammohan, J. S. Reddy, G. Sravya, C. N. Rao, and G. V. Zyryanov, "Chalcone synthesis, properties and medicinal applications: a review," *Environ. Chem. Lett.*, vol. 18, no. 2, pp. 433–458, 2020, doi: 10.1007/s10311-019-00959-w.
- [2] S. L. Gaonkar and U. N. Vignesh, "Synthesis and pharmacological properties of chalcones: a review," *Res. Chem. Intermed.*, vol. 43, no. 11, pp. 6043–6077, 2017, doi: 10.1007/s11164-017-2977-5.
- [3] Q. B. Song *et al.*, "Synthesis of Novel Chalcone Analogues of Ferrocene Biarenes," *Synth. Commun.*, vol. 33, no. 22, pp. 3935–3941, 2003, doi: 10.1081/SCC-120026317.
- [4] D. S. Dawson, M. T. Beachem, W. J. Feast, and R. Stephem, "New nitsochalcones," vol. 47, 1969.
- [5] N. M. Rateb and H. F. Zohdi, "Atom-efficient, solvent-free, green synthesis of chalcones by grinding," *Synth. Commun.*, vol. 39, no. 15, pp. 2789–2794, 2009, doi: 10.1080/00397910802664244.
- [6] P. Kulkarni, "Calcium Oxide Catalyzed Synthesis of Chalcone Under Microwave Condition," *Curr. Microw. Chem.*, vol. 2, no. 2, pp. 144–149, 2014, doi: 10.2174/221333560166614112622041
- [7] N. Miyaura and A. Suzuki, "Stereoselective Synthesis of Arylated (E)-Alkenes...," *J. Chem. Soc. Chem. Commun.*, no. 866, pp. 866–867, 1979.
- [8] N. Miyaura, K. Yamada, and A. Suzuki, "Our Continuous Discovered," *Tetrahedron Lett.*, vol. 20, no. 36, pp. 3437–3440, 1979, [Online]. Available: <http://linkinghub.elsevier.com/retrieve/pii/S0040403901954292>.
- [9] S. Eddarir, N. Cotelle, Y. Bakkour, and C. Rolando, "An efficient synthesis of

- chalcones based on the Suzuki reaction," *Tetrahedron Lett.*, vol. 44, no. 28, pp. 5359–5363, 2003, doi: 10.1016/S0040-4039(03)01140-7.
- [10] M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixão, and K. A. Jørgensen, "Asymmetric organocatalysis with sulfones," *Angew. Chemie - Int. Ed.*, vol. 49, no. 15, pp. 2668–2679, 2010, doi: 10.1002/anie.200906340.
- [11] P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, and T. Skrydstrup, "Ex situ generation of stoichiometric and substoichiometric 12CO and 13CO and its efficient incorporation in palladium catalyzed aminocarbonylations," *J. Am. Chem. Soc.*, vol. 133, no. 15, pp. 6061–6071, 2011, doi: 10.1021/ja200818w.
- [12] F. Ramirez and D. Samuel, "Phosphinemethylenes. 11. Triphenylphosphineacylrnethylenes," *J. Org. Chem.*, vol. 22, no. 1, pp. 41–45, 1957.
- [13] H. J. Bestmann and B. Arnason, "Reaktionen mit Phosphin-alkylenen, II. C-Acylierung von Phosphin-alkylenen. Ein neuer Weg zur Synthese von Ketonen," *Chem. Ber.*, vol. 95, no. 6, pp. 1513–1527, 1962, doi: 10.1002/cber.19620950631.
- [14] A. Kumar, S. Sharma, V. D. Tripathi, and S. Srivastava, "Synthesis of chalcones and flavanones using Julia-Kocienski olefination," *Tetrahedron*, vol. 66, no. 48, pp. 9445–9449, 2010, doi: 10.1016/j.tet.2010.09.089.
- [15] M. Al-Masum, E. Ng, and M. C. Wai, "Palladium-catalyzed direct cross-coupling of potassium styryltrifluoroborates and benzoyl chlorides - A one step method for chalcone synthesis," *Tetrahedron Lett.*, vol. 52, no. 9, pp. 1008–1010, 2011, doi: 10.1016/j.tetlet.2010.12.085.
- [16] N. Zhang *et al.*, "Silver-catalyzed double-decarboxylative cross-coupling of α -keto acids with cinnamic acids in water: A strategy for the preparation of chalcones," *J. Org. Chem.*, vol. 80, no. 6, pp. 3258–3263, 2015, doi: 10.1021/jo502642n.
- [17] J. Zhou, G. Wu, M. Zhang, X. Jie, and W. Su, "Pd-catalyzed cross-coupling of aryl carboxylic acids with propiophenones through a combination of decarboxylation and dehydrogenation," *Chem. - A Eur. J.*, vol. 18, no. 26, pp. 8032–8036, 2012, doi: 10.1002/chem.201200829.
- [18] R. G. Shotton, K. M. Johnston, and J. F. Jones, "Reactions of unsaturated acid halides-IV1 1 Part III. K.M. Johnston and J.F. Jones, *J. Chem. Soc. (C)*, 814 (1969). Competitive Friedel-Crafts acylations and alkylations of monohalogenobenzenes by the bifunctional cinnamoyl chloride," *Tetrahedron*, vol. 34, no. 6, pp. 741–746, 1978, doi: 10.1016/0040-4020(78)88113-7.
- [19] M. Sisa, S. L. Bonnet, D. Ferreira, and J. H. Van Der Westhuizen, "Photochemistry of flavonoids," *Molecules*, vol. 15, no. 8, pp. 5196–5245, 2010, doi: 10.3390/molecules15085196.
- [20] K. Yoshizawa and T. Shioiri, "Convenient stereoselective synthesis of (Z)-chalcone derivatives from 1,3-diaryl-2-propynyl silyl ethers," *Tetrahedron Lett.*, vol. 47, no. 28, pp. 4943–4945, 2006, doi: 10.1016/j.tetlet.2006.05.021.
- [21] Y. Li and D. Chen, "Novel and efficient one pot condensation reactions between ketones and aromatic alcohols in the presence of CrO₃ producing α,β -unsaturated carbonyl compounds," *Chinese J. Chem.*, vol. 29, no. 10, pp. 2086–2090, 2011, doi: 10.1002/cjoc.201180361.
- [22] C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing, and Z. Miao, "Chalcone: A Privileged Structure in Medicinal Chemistry," *Chem. Rev.*, vol. 117, no. 12, pp. 7762–7810, 2017, doi: 10.1021/acs.chemrev.7b00020.
- [23] Y. M. A. Yamada and Y. Uozumi, "Development of a convoluted polymeric

- nanopalladium catalyst: α -alkylation of ketones and ring-opening alkylation of cyclic 1,3-diketones with primary alcohols," *Tetrahedron*, vol. 63, no. 35, pp. 8492–8498, 2007, doi: 10.1016/j.tet.2007.05.071.
- [24] M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedra, and J. Park, "Recyclable palladium catalyst for highly selective α alkylation of ketones with alcohols," *Angew. Chemie - Int. Ed.*, vol. 44, no. 42, pp. 6913–6915, 2005, doi: 10.1002/anie.200502422.
- [25] X. F. Wu, H. Neumann, and M. Beller, "Palladium-catalyzed coupling reactions: Carbonylative heck reactions to give chalcones," *Angew. Chemie - Int. Ed.*, vol. 49, no. 31, pp. 5284–5288, 2010, doi: 10.1002/anie.201002155.
- [26] S. K. Radhakrishnan, R. G. Shimmon, C. Conn, and A. T. Baker, "Azachalcones: A new class of potent polyphenol oxidase inhibitors," *Bioorganic Med. Chem. Lett.*, vol. 25, no. 8, pp. 1753–1756, 2015, doi: 10.1016/j.bmcl.2015.02.060.
- [27] S. K. Radhakrishnan, R. G. Shimmon, C. Conn, and A. T. Baker, "Inhibitory Kinetics of Azachalcones and their Oximes on Mushroom Tyrosinase: A Facile Solid-state Synthesis," *Chem. Biodivers.*, vol. 13, no. 5, pp. 531–538, 2016, doi: 10.1002/cbdv.201500168.
- [28] J. W. Labadie and J. K. Stille, "Mechanisms of the Palladium-Catalyzed Couplings of Acid Chlorides with Organotin Reagents," *J. Am. Chem. Soc.*, vol. 105, no. 19, pp. 6129–6137, 1983, doi: 10.1021/ja00357a026.
- [29] T. Yamakawa, H. Kinoshita, and K. Miura, "Synthetic utility of tribenzyltin hydride and its derivatives as easily accessible, removable, and decomposable organotin reagents," *J. Organomet. Chem.*, vol. 724, pp. 129–134, 2013, doi: 10.1016/j.jorganchem.2012.11.007.
- [30] Y. Ogiwara, Y. Maegawa, D. Sakino, and N. Sakai, "Palladium-catalyzed coupling of benzoyl halides with aryltrifluorosilanes leading to diaryl ketones," *Chem. Lett.*, vol. 45, no. 7, pp. 790–792, 2016, doi: 10.1246/cl.160223.
- [31] M. Zaranek *et al.*, "Iridium-catalysed desilylative acylation of 1-alkenylsilanes," *J. Mol. Catal. A Chem.*, vol. 426, pp. 75–78, 2017, doi: 10.1016/j.molcata.2016.10.035.
- [32] P. Pawluć, J. Szudkowska, G. Hreczycho, and B. Marciniak, "One-pot synthesis of (E)-styryl ketones from styrenes," *J. Org. Chem.*, vol. 76, no. 15, pp. 6438–6441, 2011, doi: 10.1021/jo201036x.
- [33] M. L. N. Rao, V. Venkatesh, and D. N. Jadhav, "A palladium catalyzed atom-efficient cross-coupling reactivity of triaryl bismuths with α,β -unsaturated acyl chlorides," *J. Organomet. Chem.*, vol. 693, no. 15, pp. 2494–2498, 2008, doi: 10.1016/j.jorganchem.2008.05.012.
- [34] X. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, and M. Beller, "Acc Chem Res 2014 Wu XF.pdf," *Acc. Chem. Res.*, vol. 47, no. 4, pp. 1041–1053, 2014.
- [35] C. Xu, G. Chen, and X. Huang, "Chalcones by the Wittig reaction of a stable ylide with aldehydes under microwave irradiation," *Org. Prep. Proced. Int.*, vol. 27, no. 5, pp. 559–561, 1995, doi: 10.1080/00304949509458500.
- [36] P. S. W. Leung, Y. Teng, and P. H. Toy, "Chromatography-free Wittig reactions using a bifunctional polymeric reagent," *Org. Lett.*, vol. 12, no. 21, pp. 4996–4999, 2010, doi: 10.1021/ol1021614.