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A diversity-oriented strategy using palladium-catalysed cross-coupling reactions for the synthesis of the enone system of chalcones†

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†This paper is dedicated to Professor Bohari M. Yamin (co-author) on the occasion of his retirement
Abstract: In this review, we will discuss some of the important palladium catalysed cross-coupling reactions utilized in the synthesis of the enone system of chalcones. Examples given here not only exemplify the efficiency and practicality of new C-C bond formation of the enone system via palladium catalysed reactions but also reflect some of the revolutionary methods used for the preparation of a more complex and valuable chalcone scaffold which is known to be a privileged structure in the field of medicinal chemistry.

1. Introduction

Chalcones or chemically known as 1, 3-diaryl-2-propen-1-ones are key precursors to many of flavonoids found in nature. These secondary metabolites can be formed via the shikimate and the acetate/mevalonate pathways.[1, 2] In flowers, they normally appear in yellow.[3] It is considered that the colour of flowers in most angiosperms plays a crucial role in pollination (fertility and pollen germination) by attracting pollinator (e.g. insects and bird) for plant growth and reproduction purposes. Their presence not only restricted to flowers but also widely distributed in fruits, vegetables, spices, teas, soy and many different parts of plant.[4] Collectively, flavonoids and chalcones have been implicated in the chemosystematics, biochemistry, physiology and ecology of plants including UV light protection,[5] enzyme inhibition,[6] pathogen protection,[7] insect antifeedants[8] and molecular signalling in symbiotic systems or allelopathic.[9] Many scientific reports also revealed that they have benefits to human health and can be potentially used as nutraceuticals with array of interesting biological activities.[10]

The substantial pharmacophore of chalcones render them as a privileged structure in medicinal chemistry.[10a, 10c, 11] Clinical records have shown that they can be found in several clinically used drugs.[10b, 12] For example, metochalcone (vesidryl®) 1 was marketed as a choleretic drug while sofalcone 2 as an anti-peptic ulcer, mucoprotective drug (Figure 1).[13] On the other hand, Ro-09-0410 3 and its prodrug, Ro-09-0415 4, have been tested for prophylaxis against rhinovirus infection in human volunteers.[14] In addition, hesperidin methylchalcone 5 have been tested for chronic venous lymphatic insufficiency[15] and hesperidin trimethylchalcone 6 was evaluated for trunk or branch varicosis.[16] Apart from that, they possess a wide range of pharmacological activities including anti-oxidant,[17] anti-microbial,[18] anti-cancer,[19] anti-tumor,[20] anti-malarial,[21] antileishmanial,[22] anti-HIV,[23] anti-ulcers,[24] anti-inflammatory[10a, 10b] and etc.

In the last two decades, we noted that there is a significant rising of interest in publications and patents related to chalcones.[114] A brief search on the keyword “chalcone” using the scientific research finding tool, CAS (SciFinder®) (Figure 2) revealed a total of 5,225 publications and 522 patents published from year 1999 to 2008. Since then the number has remarkably doubled to 12,897 publications and 932 patents from year 2009 to first semester of 2019. Therefore, the continuing advances of methods in chalcone synthesis remain relevant since it will continue to serve as a major source of new structural leads in medicinal chemistry in addition to effective drug development in the future.

Figure 1. Examples of clinically used drug that comprises the scaffold of chalcone.
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Mohd Fadhilzil Fasih Mohd Aluwi, born in 1984 in Malaysia, studied at Faculty of Pharmacy, Universiti Kebangsaan Malaysia (Malaysia), where he obtained his Ph.D in Medicinal Chemistry in 2017 with Dr. Lam Kok Wai. He obtained his BSc and MSc in Chemistry from Universiti Teknologi MARA (UiTM). After a postdoctoral research at Alta-ur-Rahman Institute of Natural Product Discovery (AuRINs), UiTM with Prof. Dr. Norhadani Ismail, he joined the Faculty of Industrial Science & Technology, Universiti Malaysia Pahang in 2018. His research interest is Medicinal Chemistry, mainly synthesis of bioactive natural product analogues, computational chemistry and pharmaceutical chemistry.

Bohari M. Yamin was born in a small village called Bagan Pinang, Port Dickson, Negeri Sembilan, Malaysia. He obtained his bachelor’s degree in chemistry from University of Malaya (UM) in 1973. He completed his PhD thesis entitled kinetic and mechanistic studies on the reaction of some organic compounds with Pd(II) complexes from King’s College, London University in 1977. He was then appointed as lecturer at Universiti Kebangsaan Malaysia (UKM). He spent one year at Essex University in 1984 as Commonwealth Research Fellow working with Dr R.M.G. Roberts. In 1990 under the same fellowship, he was a visiting fellow at Oxford University working with Prof. M.L.H. Green. His research interest is on chemical synthesis, inorganic chemistry and chemical crystallography. He initiated collaborative research with chemists from many countries including Australia, Japan, France, Pakistan, Indonesia, Vietnam, Kazakhstan and Thailand. He is well known to many students in the region who gained help in solving X-ray structures from him. He retired in Jan 2017 after 43 years of academic life at Universiti Kebangsaan Malaysia.

In general, the synthesis of chalcone can be easily accomplished via Claisen-Schmidt condensation reaction by mixing a benzaldehyde with an active acetophenone under either strong basic or acidic condition. It is noteworthy to mention that other uncommon reactions such as the Friedel-Crafts alkylation, Knoevenagel condensation, Julia-Kocienski have also been explored and studied. Other atypical reactions including the olefin cross-metathesis reaction, the silver-catalysed double-decarboxylative cross coupling, bioderived ZnO nanoflower and the green metal-free synthesis via a tandem cross-dehydrogenative coupling/elimination reaction have also been reported. Propargyl alcohol derivatives have also been used as precursors for isomerization reaction or through the Meyer-Schuster rearrangement to produce the corresponding enones. On the other hand, a particular propargyl amine derivatives could also be transformed to chalcones when irradiated under microwaves in the presence of montmorillonite doped with copper (I) chloride and water. Recently, there is a large in-flux of data available regarding the use of cross-coupling palladium-mediated, e.g. Heck-Mizoroki coupling, Suzuki-Miyaura coupling, Stille coupling, Hiyama coupling, Sonogashira coupling and Tsuji-Trost coupling reactions in the synthesis of chalcones. Scheme 1 summarizes the most recent cross coupling reactions used in chalcone synthesis. In this review, we aim to cover as many of the success stories of palladium-catalysed reactions employed in the synthesis of chalcones.
2. Synthesis of chalcones via Heck-Mizoroki coupling reaction

Palladium-catalysed reactions are commonly used for the formation new carbon-carbon bonds. Due to its rapid growth in the last several years, it has been recognized as an essential toolbox in the area of organic synthesis and medicinal chemistry, as evidenced by the growing number of publications/patents in this area. Among the methods applied in the synthesis of chalcones and related compounds facilitated by the Pd-mediated reaction, Heck reaction appears to be the most popular. This reaction can be generally defined as the Pd-catalysed carbon-carbon coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes to yield the products resulted from the substitution of a hydrogen atom in the alkene coupling (Scheme 2). This reaction was first reported by Tsutomu Mizoroki in 1971 and was further improved attributed to the work of Richard F. Heck (1972), Akira Suzuki and Ei-ichi Negishi (recipients of Nobel Prize Award in Chemistry in 2010). In 2003, Cavarischia et al. reported a new route of the intermediate chalcone synthesis via the Heck reaction. This reaction involved direct coupling of an aryl vinyl ketone with an aryl iodide in the presence of Pd(OAc)₂ and PPh₃ (Scheme 3). After 4 h of reflux (85°C) under inert argon gas condition, the target α,β-unsaturated ketone product was obtained in high yield. The versatility of the method in generating novel chalcone derivatives have also been reported in several other publications by the same group. Overall, this marked a huge improvement in term of reaction yield as compared to the classical Claisen-Schmidt condensation.
Joon Ching Juan received his BSc (2003) and PhD (2007) from Universiti Kebangsaan Malaysia (UKM). Currently he is an Associate Professor of Catalysis at Nanotechnology and Catalysis Research Centre (NANOCAT), University of Malaya (UM) and Senior Research Fellow (Adjunct) position at Monash University, Sunway Campus. He has been actively involved in various research activities especially in the area of catalysis. Up to date, he has managed to publish more than 100 publications, co-author 4 book chapters and his h-index is 29 (2019). He is the recipient of several awards including National Academic Awards (2018), Malaysia Research Star Award (2017), National Young Scientist Award (2016), and just few to mention National Young Scientist Award (2016), and just few to mention.

Lam Kok Wai received his PhD in Medicinal Chemistry from University Putra Malaysia in 2011. Currently, he is working as a Senior lecturer at the Faculty of Pharmacy, Universiti Kebangsaan Malaysia (UKM). His core research interest is on computational drug design and synthesis.

The insertion of carbon monoxide (CO) as a carbonyl fragment, using the established palladium-catalysed reactions have been reported recently for the synthesis of chalcones and related compounds. The earliest example can be traced back to the work of Beller et al., who have initiated the development of general intermolecular carbonylative coupling of a wide range of aryl halides or triflates with terminal olefins. Initially, they observed an unexpected formation of a low yield chalcone side product (8%) when phenyl triflate was reacted with styrene and carbon monoxide (CO, 10 bar) in the presence of 1 mol% of [(cinnamyl)PdCl₂] and 1, 2-bis(diadamantyl)-xylylphosphine. When the optimization was carried out with different bases and solvents particularly in toluene with the presence of the best ligand 1, 3-bis(diphenylphosphino)propane (dppp) resulted in a significant increase in the yield of the isolated chalcones.[48, 49] This remarkable reaction is also known as the carbonylative Heck reaction. Scheme 4 shows the general reaction equation of aryl/alkenyl triflates with styrenes. Some of the final products were efficiently obtained in excellent yields as high as 95%.

In addition, they group also successfully applied the Pd-catalysed carbonylative coupling technique on different aryl iodides with various classes of olefins such as styrenes, acrylates and enol ethers to afford clean conversion and good yields of the corresponding isolated chalcone product (41-90%) with >99% trans selectivity as shown in Scheme 5. Notably, the aryl iodides building blocks are easily available in the market and the final products could be obtained under very mild reaction conditions.[50] The synthesis of chalcones from various (hetero)aryl bromides and the presence of PPh₃ ligand is inexpensive considering that it utilizes a very convenient catalyst system as shown in Scheme 6 (A).[51] Scheme 6 (B) shows the proposed mechanism for the reaction based on the experimental results and DFT calculations. Moreover, the presence of TsOH·H₂O in Pd/dppp catalytic system is highly crucial for effective carbonylative dimerization coupling of alkenes.[52] In this fact, the symmetrical 1, 5-diarylpent-1-ene-3-ones have been successfully synthesized in excellent yields (up to 95%) from a commercially styrenes (Scheme 7, A). In the initial step, the active Pd⁺-ligand complexes precursor is formed followed by metatation and insertion of selected alkene molecule. Consequently, insertion of CO into the palladium alkyl bond leads to the formation of the palladium acyl complex. Subsequently, the insertion coordination by metatation with a second alkene and following β-hydride elimination is formed the desired product of

![Scheme 4](image_url)

**Scheme 4.** Synthesis of chalcones via the Pd-catalysed carbonylative Heck coupling reaction of aryl triflates with styrenes.
chalcones, while the active palladium precursor is regenerated for the next catalytic cycle reaction (Scheme 7, A).

Scheme 5. Synthesis of chalcones via the Pd-catalysed carbonylative Heck coupling reaction of aryl iodide with alkenes.

Although CO gas is a good source for the carbonyl group, many are still unconvinced of its use and applicability in both academia and industry. This is undoubtedly related to the properties of CO gas, being a highly toxic gas, which could exclude the oxygen from binding to haemoglobin leading to a condition known as asphyxiation.[53] Furthermore, CO is invisible, odourless, tasteless and its side effects will only appear in very late stage. To prevent this, CO must be handled with extreme caution, including storage and transport. Typically, its use is often accompanied with CO detectors and other specialized high-pressure equipment. To counter these limitations, Skrydstrup and co-researchers have discovered an exclusive technique for ex-situ generation of CO that can be efficiently incorporated to palladium catalysed carbonylation reaction using a simple sealed two-chamber system.[54] In this instance, the carbonylative Heck reaction of various aryl iodides and styrene derivatives can be performed using only a slight excess of CO in the presence of [(cinnamyl)PdCl₂] and cataCXium® A as ligand. Scheme 8 shows some of the chalcones obtained in good yields as high as 81%.[55]
catalysed cross-coupling reaction in the presence of Ag$_2$CO$_3$ as oxidant between aryl carboxylic acids and saturated propiophenones. When electron rich and heterocyclic carboxylic acids were used, Cu(OAc)$_2$ or CuF$_2$ was found to be more efficient than Ag$_2$CO$_3$. Overall, the Heck-type products were obtained after through combination of decarboxylation and dehydrogenation reactions (Scheme 10, A). [57]

Apart from that, the occurrence of in situ dehydrogenation of saturated substrates to the corresponding olefins could also serve as a useful strategy in the current modern streamline organic synthesis. In the following year, another versatile method was developed for the facile synthesis of chalcone through the Pd-catalysed dehydrogenative cross-coupling between (hetero)-arenes and (hetero)-aryl ethyl ketones. [58]

The reaction was presented by an oxidative coupling of 2-methyliophene with propiophenone in 1, 2-dimethoxyethane at 100°C. The model system reaction was further optimized using Pd(OAc)$_2$ as a catalyst and Ag$_2$CO$_3$ as an oxidant. The formation of the cross-coupling chalcone product increased from good to excellent yield (up to 90%) when TEMPO (2, 2, 6, 6-tetramethylpiperidine-N-oxyl) was used as a co-oxidant possibility due to its ability to accelerate re-oxidation of Pd$^0$ to Pd$^{II}$ (Scheme 10, B).

To the best of our knowledge, in 2008, Kunick et al. reported the first new Heck-type coupling reaction using the ketone Mannich bases as enone precursors with aryl iodides to prepare the target chalcone products (Scheme 11, A). [59] Similarly, Feng and colleagues employed the Pd-catalysed Heck-type coupling via C-N cleavage between the arenes and ketone Mannich bases to obtain the corresponding chalcones (Scheme 11, B). [60]

Some control experiments suggest that the reaction proceeds through a similar in situ olefin intermediate and a subsequent oxidative coupling mechanism. Notably, this method affords good yields of up to 85% and tolerates a broad range of functional groups. In 2015, Guo et al. introduced a Pd-catalysed oxidative annulation pathway of in-situ generated enones (chalcones) from pyrroles as depicted in Scheme 12. [61]

The oxidative coupling between the two hydrocarbons occurs via the Heck-type reaction, therefore provides a concise route to heterocyclic functionalized chalcone derivatives.

Scheme 8. Synthesis of chalcones via carbonylative Pd-catalysed Heck reaction using ex situ CO generation in a sealed two-chamber system.

Scheme 9. Synthesis of chalcones via domino dehydrochlorination/Pd(OAc)$_2$-catalysed Heck coupling reaction with in-situ generated enones.

Scheme 10. Synthesis of chalcones via decarboxylative Pd-catalysed cross-coupling Heck reaction between (A) aryl carboxylic acids and (hetero)aryl ethyl ketones and (B) (hetero) arenes with (hetero)aryl ethyl ketones.
Scheme 1

**Synthesis of chalcones via Pd-catalysed Heck-type coupling reaction by C-N cleavage.**

![Diagram of Heck-type coupling reaction](image)

<table>
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<tr>
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The earliest example of chalcone synthesis using the Suzuki coupling reaction can be traced back to the work of Rolando et al. in 2003. Although the reaction was based on the pioneering work of the McCarthy’s group, they have managed to synthesize a series of chalcones by coupling various phenylboronic acids with acyl chlorides. Scheme 15 (A) depicts the general coupling reaction equation of cinnamoyl chloride with various phenylboronic acids using Pd(PPh$_3$)$_4$ catalyst in anhydrous toluene in moderate yields. Remarkably, substitution of cinnamoyl chloride with different benzoyl chlorides resulted in excellent yields (Scheme 15 (B)). Overall, the pattern of substitution group in the benzoyl chlorides did not affect the reaction yield.

In 2007, Buszek et al. reported the synthesis of chalcones from N-vinylpyridinium tetrafluoroborate salts, which is a new class of electrophilic coupling partner for the Suzuki cross-coupling reaction. Herein, N-vinylpyridinium tetrafluoroborate salts represent an attractive alternative to vinyl halides and triflates in the Pd-catalysed Suzuki cross-coupling reaction with aryl boronic acids. In the presence of Pd$_2$(dba)$_3$ as a catalyst and tricyclohexylphosphine (PCy$_3$) as a ligand in anhydrous THF, chalcones have been prepared in good to excellent yield (60-92%) (Scheme 16). It is worth to mention that these salts have been used as dienophiles or better known as Jung’s dienophile in the Diels-Alder cycloaddition reaction. Interestingly, replacing the phosphine ligand PCy$_3$ with PPh$_3$ halted the reaction due to the formation of symmetrical 1, 6-dioxa-2, 4-diene, a dimer of α, β-unsaturated probably via reductive dimerization.
In 2007, Occhiato et al. conducted a thorough study on the carbonylative Suzuki-Miyaura cross-coupling reaction of enol triflates with alkenylboronic acids for the synthesis of unsymmetrical dienones. Several chalcone derivatives were formed from moderate to good yield using Pd(OAc)$_2$ as catalyst and PPh$_3$ as ligand in the presence of CsF as base to activate the boronic acid in anhydrous THF solvent at room temperature under 1 bar of CO (Scheme 18). This method allows a convergent and rapid preparation of substrates for instance unsymmetrical divinyl ketones, which are highly useful in further conjugate additions and Nazarov reactions. Recently, Beller et al. reported the Pd-catalysed oxidative carbonylative Suzuki-Miyaura coupling process of arylboronic acids with various styrenes (Scheme 19). The reactions proceeded cleanly in the presence of Pd(OAc)$_2$ and various ligands under mild conditions using air as the terminal oxidant reagent. During the optimization process, 1,3-bis(diphenylphosphino)propane (dpdp) was identified as the best phosphine ligand as it significantly increased the formation of chalcones up to 97% of yield when applied in DMSO at 60°C. The plausible mechanism for the oxidative vinylation of arylboronic acids is shown in Scheme 20. First, the arylboronic acid complex undergoes trans-metalation with the active palladium (II) complex. The corresponding acyl palladium species starts to form after the insertion of CO followed by coordination and insertion of styrene to the acyl palladium centre. After elimination with the concomitant generation of a palladium hydride complex the terminal product is finally formed. Next, the complex is recycled to the active species, which completes the whole catalytic cycle.

On the other hand, Rao et al. have synthesized and isolated a series of functionalized chalcones in high yields up to 90% using the cross-coupling reaction of triarylboronates with α, β-unsaturated acyl chlorides (Scheme 17, A). This marked an improvement to the work of Rolando et al., where they generally observed poor reactivity of α, β-unsaturated acyl chlorides with phenylboronic acids as nucleophilic coupling partners in chalcone synthesis (see Pathway A, Scheme 15). Thus, it is important to note that the Pd-catalysed cross-coupling between atom efficient nucleophilic of triphenylbismuth and cinnamoyl chlorides under these conditions is highly selective and efficient. In addition, Al-Masum et al. have performed a direct cross-coupling reaction of benzoyl chlorides with potassium styryltrifluoroborates in the presence of PdCl$_2$(dpdp) catalyst to afford the chalcones when irradiated under microwave (Scheme 17, B).
The first carbonylative Suzuki-Miyaura coupling reaction of allylic acetates with aryl boronic acids under carbon monoxide (CO, 5 bar) was presented by Ma et al. in 2015 (Scheme 21). The reaction involved the carbonylation of a range of allylic acetates and reacted with various aryl boronic acids using Pd/PCy3 catalyst to afford α, β-unsaturated aryl ketones in good to excellent yields (up to 90%). It was suggested that the reaction mechanism involves the insertion of the carbon monoxide to the least substituted terminal allylic carbon and the resulting β, γ-unsaturated aryl ketones usually isomerize to the α, β-unsaturated aryl ketones.

Decarboxylative cross-coupling is a modern strategy for the regioselectivity carbon-carbon bond formation without resorting to stoichiometric amounts of organometallic catalytic reagent. The reaction generally involves a catalytic transformation of carboxylic acids, giving access to various valuable classes of product. In 2013, Miura et al. reported the palladium-catalysed decarboxylative reaction of acylacrylic acids with aryl boronic acids in the presence of copper salt oxidant to afford chalcone derivatives. In their work, Pd(OAc)2 catalyst and Cu(OAc)2·H2O oxidant with K2CO3 as an additive were added and heated in DMF at 120°C for 4-5 h under N2 atmosphere for the effective coupling reaction as depicted in Scheme 22. It is worth to mention here that substitution with other additives such as NaOAc and LiOAc were less effective. To expand the applicable scope of this reaction, the decarboxylative arylation is tested using different aryl halides as an alternative aryl source.
4. Synthesis of chalcones via Stille coupling reaction

Despite the limitations of using tin reagents in the palladium-catalysed Stille cross-coupling, this reaction is still widely used for the C-C bond formation (Scheme 23). The first example of using organotin in the synthesis of chalcones can be traced back to the work of Stille et al., who discovered the reaction in 1983. In their work, several competitive coupling reactions were performed between phenyltributyltin and trimethyl-, tributyl- or triphenylstyrlytin (Scheme 24). The results showed that both trimethyl- and tributylstyrlytin were approximately 10 times more reactive than tributylphenyltin.\(^{[75]}\) It was suggested that the lower reactivity was due to the electron-withdrawing effect of the phenyl groups thus reducing their ability to support a positive charge on tin in the transition state. Additionally, they also described the first palladium-catalysed carbonylative coupling reaction of aryl triflates with organostannanes in the presence of carbon monoxide (CO, 1 atm) and lithium chloride under relatively mild conditions to afford a chalcone in good yield (68%) (Scheme 25).\(^{[76]}\) In his influential review, Stille proposed the mechanisms for the direct coupling and the carbonylative coupling reactions of organic halides with organotin compounds (Scheme 26).\(^{[77]}\)

![Scheme 23](https://example.com/scheme23)

Scheme 23. General representation of Stille cross-coupling reaction.

![Scheme 24](https://example.com/scheme24)

Scheme 24. Reactivity of styryltins relative to phenyltributyltin for the synthesis of chalcone via Stille coupling reaction.

![Scheme 25](https://example.com/scheme25)


West et al. reported that the inclusion of 35 mol % of CuI or CuBr as cocatalyst was necessary for the carbonylative Stille coupling of vinylstannanes with vinyl triflates. Under these conditions some of the rare chalcone derivatives have been produced in relatively good yields (Scheme 27).\(^{[78]}\) This finding will essentially accelerate the optimization process of complex chalcone derivatives in the future.

![Scheme 26](https://example.com/scheme26)

Scheme 26. General catalytic cycles for Stille reaction; (A) Mechanism of the Pd-catalysed direct coupling reaction (B) Mechanism of the Pd-catalysed carbonylative Stille reaction.

![Scheme 27](https://example.com/scheme27)

Scheme 27. Examples of CuX-promoted carbonylative Stille coupling reaction.
5. Synthesis of chalcones via Hiyama coupling reaction

The Hiyama cross-coupling is the palladium-catalysed cross-coupling reaction of organosilane compounds with various organic halides (Scheme 28). Indeed, comparable to the Suzuki coupling, this reaction necessitates the use of an activating agent such as a fluoride ion or a base. The first report of this reaction can be traced back to 1989.[78] In 2009, Wagner et al. described the application of (E)-1, 2-disilylethene as an essential functional building block in a sequential Hiyama/Narasaka coupling reaction.[80] This reaction is highly impactful and useful for the rapid and versatile building of α, β-unsaturated chalcones in good yields. Due to the differential intrinsic reactivity of the two carbon-silicon bonds, the (E)-1, 2-bis-silylated reagent is selectively and sequentially activated by polyionic-gel-stabilized palladium nanoparticle catalyst, a heterogeneous palladium catalyst, to furnish the (E)-α, β-unsaturated ketones in the presence of a variety of halides and anhydride acids. Moreover, the catalyst represents a viable alternative to the ionic liquids as solvent or reaction media for recyclable heterogeneous catalytic systems (Scheme 29).


6. Synthesis of chalcones via Sonogashira coupling reaction

Another effective carbon-carbon bond formation coupling reaction that is widely used in organic synthesis is the Sonogashira coupling reaction. The reaction can be defined as a coupling of terminal alkynes with aryl or vinyl halides as depicted in Scheme 30. It was first reported by Sonogashira et al. in 1975. The process is easily achievable with palladium catalyst e.g. PdCl₂(PPh₃)₂ combined with a co-catalytic amount of CuI in diethylamine solvent under inert gas condition at room temperature.[81] The exact mechanism of the palladium/copper-catalysed Sonogashira reaction is yet to be fully understood, mainly due to the difficulties of analyzing the combined action of two metal catalysts present. It has been proposed that the reaction takes place through two independent catalytic cycles as shown in Scheme 31.[82]

Scheme 30. General representation of Sonogashira cross-coupling reaction.

Scheme 31. General catalytic cycle for Sonogashira coupling reaction with copper as co-catalyst.
In 2000, Muller et al. reported an unexpected Sonogashira coupling product of chloroarene complexes with 1-aryl prop-2-ynoles. The reaction furnished the isomeric aryl complexed chalcones in good yields instead of the alkyne coupling products (Scheme 32 (A)). Several chalcone derivatives have been successfully synthesized using similar method. Generally, the reaction requires [PdCl₂(PPh₃)₂] and CuI as co-catalyst in a boiling mixture of triethylamine and THF, giving rise to the formation of the desired chalcones in moderate to excellent yield (41-98%). With respect to the outcome of this transformation, the reaction is known as the coupling-isomerization reaction (CIR) (Scheme 32 (B)). Moreover, mechanistic studies revealed that the CIR proceeds through a rapid palladium/copper-catalysed alkyne coupling followed by a rate-determining base-catalysed propargyl alcohol to enone isomerization. Kinetic studies of the isomerization step showed that the reaction proceeds fastest when more than five-fold excess of amine base were used in a dipolar aprotic medium. Even though the CIR is a mild and versatile method, it has some limitations and weaknesses under the conditions of conductive heating. Apart from the limited choice of reaction media, a relatively large excess of base, longer reaction time (16-24 h) and the demand for an activating electron-deficient (hetero)aryl halide as a coupling partner cause this reaction to be highly disadvantageous. To counter these limitations, they developed a generalization of the CIR method under microwave irradiation, also known as MACIR (Microwave-Assisted Coupling-Isomerization Reaction) for the synthesis of chalcones. Under these conditions, chalcones have been obtained from good to excellent yield within 8-30 mins.

The mechanistic rationale behind the leading technique CIR has been well studied by kinetic investigations. To gain more insights into the rate-determining isomerization step, Muller et al. explained that the timescale of the propargyl alcohol-enone isomerization is an important parameter for the formation of chalcone product. The reaction model shown in Scheme 33 displays the isomerization of propargyl alcohol to enone. Interestingly, the catalytic isomerization of propargylic alcohols promoted by transition-metals represents a straightforward and an appealing route to synthetically useful α, β-unsaturated carbonyl compounds. In 2011, Sheppard et al. reported an one-pot procedure for the conversion of the primary propargylic alcohols into β-arylketones via the Meyer-Schuster rearrangement promoted by [PdCl₂(DPPB)/P₂NEt₃] and CuI (Scheme 35). Zang et al. have developed the use of efficient gold-catalysed method for the preparation of chalcones from propargylic acetates. Besides, Dudley et al. have also reported the use of gold (III) chloride (AuCl₃) as the preferred choice of catalyst for the chalcone synthesis through the Meyer-Schuster rearrangement (see Scheme 34). Recently, Bao et al. have reported an efficient method of Sonogashira coupling reaction for the chemoselective synthesis of chalcones. Palladium-catalysed carboxylative addition of aryl bromides to terminal arylalkynes have been carried out to produce the target chalcones in satisfactory to excellent yield. The unprecedented carboxylation reaction proceeded smoothly under mild conditions in the presence of a simple palladium catalyst system ([PdCl₂(DPPB)/P₂NEt₃]) in N, N-dimethyl formamide (Scheme 35).

Scheme 32. Synthesis of chalcones via coupling-isomerization reaction (CIR) through palladium-catalysed Sonogashira coupling reaction.

Scheme 33. Synthesis of chalcones via propargyl alcohol-enone CIR through Sonogashira coupling reaction.


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Keywords: Palladium-catalysed • chalcone • enones • C-C bond formation •


7. Conclusions

Chalcones have always been regarded as privileged structures with great practical interests in medicinal chemistry due to its prolific biological activities with clinical potential against various diseases. With the advancement of the palladium catalysed cross-coupling reactions i.e. Heck-Mizoroki, Suzuki-Miyaura, Stille, Hiyama and Sonogashira in recent years, it is not difficult to imagine that more exciting and complex chalcone structures will be discovered. Nevertheless, the examples given in this review suggest that even the most complex chalcones can be synthesized with high chemical efficiency, in a small number of steps and with minimal cogeneration of any waste products. This in turn would allow the optimization and improvement of the pharmacokinetic and pharmacodynamic profiles of the current chalcones to be conducted with ease. We believe that the next few years will be a critical period for the discovery of new and novel chalone-based drugs witnessed by the large amount of published publications and patents available.

Scheme 34. Synthesis of chalcones via Meyer-Schuster rearrangement.

Scheme 35. Synthesis of chalcones via palladium-catalysed carboxylative Sonogashira coupling reaction.
The innovative palladium catalyses cross-coupling reaction utilized in the tremendous application synthesis of enone system of chalcones. The continue advances of methods in chalcone synthesis leads to serving complexity of the structure of chalcone in medicinal chemistry.

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A diversity-oriented strategy using palladium-catalysed cross-coupling reactions for the synthesis of the enone system of chalcones