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Review

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1,3-Diarylpropenes (cinnamylphenols): a comprehensive overview of natural occurrence, synthesis, applications, and biological significance

Lingaiah Maram, [a, b] and Bahaa Elgendy [a, b] *

[a] Department of Anesthesiology, Washington University School of Medicine in St. Louis, St. Louis, MO 63110, USA. [b] Center for Clinical Pharmacology, Washington University School of Medicine and University of Health Sciences and Pharmacy, St. Louis, MO 63110, USA

Email: belgendy@wustl.edu

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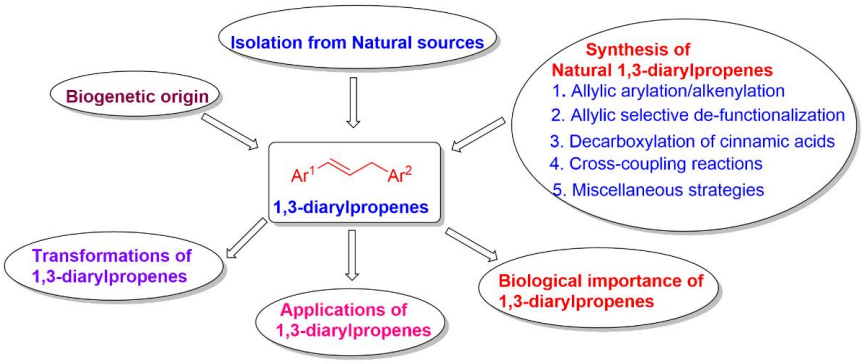
Abstract

1,3-Diarylpropenes represent a versatile class of compounds with diverse biological activities, including antibacterial, antifungal, cytotoxic, anti-malarial, insect growth inhibition, anti-inflammatory, and nitric oxide inhibition. These properties make them highly valuable in medicinal chemistry and therapeutic development. This review provides a comprehensive overview of the isolation sources and biological activity of the natural 1,3-diarylpropenes, along with their biosynthesis. It categorizes synthetic strategies for 1,3-diarylpropenes, including methods like allylation of arenes, allylic selective de-functionalization, decarboxylative functionalization, cross-coupling, and miscellaneous approaches. Additionally, transformations of 1,3-diarylpropenes, such as electrophilic addition, oxidative C-C bond formation, and metal-catalyzed C-C bond formation, are discussed. The review also explores the potential applications of 1,3-diarylpropenes in the synthesis of natural products and their analogs, along with their biological activities. Recent advancements in the design and synthesis of 1,3-diarylpropenes are highlighted, offering insights into their therapeutic potential and guiding future research in drug discovery and medicinal chemistry.



Keywords: 1,3-Diarylpropenes, isolation, biosynthesis, biological activities, synthetic strategies, applications in the natural product synthesis, medicinal chemistry, drug discovery

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1. Introduction

Flavonoids are a diverse group of low molecular weight polyphenolic compounds with a basic structure of 15 carbon atoms arranged in a C6–C3–C6 configuration, consisting of two aromatic rings linked by a three-carbon chain. Synthesized in plants via the phenylpropanoid pathway, flavonoids are derived from aromatic amino acids like phenylalanine and tyrosine, as well as malonate. Over 8,000 distinct flavonoids have been identified in various plant-based foods and beverages, including fruits, vegetables, nuts, seeds, tea, cocoa, and red wine. They are predominantly found in the epidermal cells of leaves and the skins of fruits, where they play critical roles in pigmentation, UV protection, and defense against pathogens. In human nutrition, flavonoids offer significant health benefits due to their antioxidant and anti-inflammatory properties, potentially reducing the risk of cardiovascular diseases, cancer, and neurodegenerative conditions, while also alleviating allergy symptoms. Thus, flavonoids are integral to both plant health and human well-being.[1]

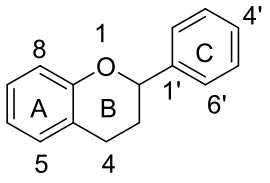
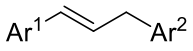


Figure 1. General chemical structure of flavonoids.

1,3-Diarylpropenes, also known as cinnamyl phenols, are a distinct class of compounds characterized by the C6–C3–C6 chemical framework (Figure 2), which places them within the flavonoid family. Their structural motif features two aromatic rings connected by a three-carbon chain, a core element that contributes to their biological activities and synthetic versatility. These compounds are of considerable interest due to their broad spectrum of pharmacological properties. Their anticancer activity has been demonstrated through various studies, where they have shown the ability to inhibit cancer cell growth and induce apoptosis. This makes

them promising candidates for the development of new cancer therapies. Their antioxidant properties are significant as they help neutralize free radicals, reducing oxidative stress and potentially lowering the risk of chronic diseases linked to oxidative damage. Additionally, 1,3-diarylpropenes exhibit anti-inflammatory effects, which can be beneficial in treating inflammatory conditions such as arthritis. Their anti-platelet activity is noteworthy in cardiovascular health, where they can help prevent blood clot formation, reducing the risk of heart attacks and strokes. Furthermore, these compounds have demonstrated anti-malarial properties,[2] providing a potential avenue for developing new treatments against malaria, a major global health issue.

Beyond their direct pharmacological effects, 1,3-diarylpropenes also serve as key intermediates in the synthesis of various natural products and biologically active compounds. Their role in medicinal chemistry is enhanced by their ability to be modified and incorporated into complex molecular structures, facilitating the creation of new drugs and therapeutic agents. In recent years, there has been a growing interest in the synthesis and application of these privileged scaffolds. Researchers are exploring new methods to efficiently produce 1,3-diarylpropenes and their derivatives, aiming to harness their potential for drug development and other industrial applications. This increased focus reflects their importance in the ongoing search for novel compounds with therapeutic value.



1,3-diarylpropene

Figure 2. General chemical structure of 1,3-Diaryl propene's.

This review offers a comprehensive overview of 1,3-diarylpropenes, or cinnamyl phenols, covering their natural occurrence, biogenetic origins, and synthetic strategies. It begins by detailing the sources from which these compounds are isolated, including various fruits, vegetables, and herbs. The review explores their biogenetic origin through the phenylpropanoid pathway, highlighting the conversion of aromatic amino acids and malonate into these compounds. It further discusses the diverse synthesis strategies employed to create 1,3-diarylpropenes, from traditional methods to advanced techniques, and examines their role as intermediates in the synthesis of complex natural products and bioactive compounds. Additionally, the review emphasizes the physiological significance of 1,3-diarylpropenes, noting their pharmacological activities such as antioxidant, anti-inflammatory, anticancer, anti-platelet, and anti-malarial effects. Through this detailed overview, the review underscores the importance of 1,3-diarylpropenes in both chemical research and in the therapeutic development.

2. Isolation of 1,3-Diarylpropenes

The isolation of new 1,3-diarylpropenes and the investigation of biological functions is still a growing area of natural product chemistry. In the past two decades more than a hundred new 1,3-diarylpropenes with unusual skeletons have been isolated from various sources such as plants and microbes. In this section, we provide an overview of the names of the isolated 1,3-diarylpropenes, the source of isolation, and their bioactivities. These 1,3-diaryl propene's with different substituents on aromatic ring systems and some of the 1,3-diaryl propene's with spiro structural units are described. The 1,3-diarylpropenes are tabulated (Table 1), below, and the table

includes their names, source of isolation, bioactivities, and related references. They are then described according to their chemical structures. Finally, the biosynthesis of 1,3-diarylpropenes is also discussed.

Table 1. Isolation of 1,3-diarylpropenes from natural sources

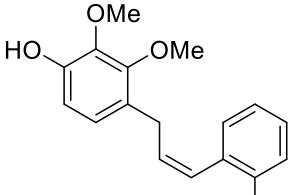
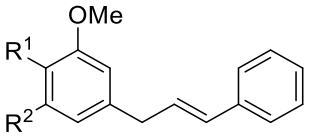
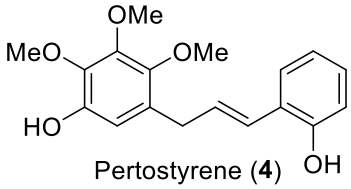
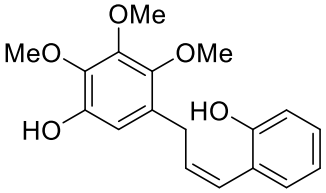
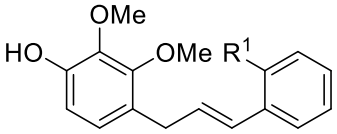
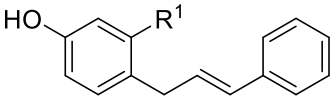
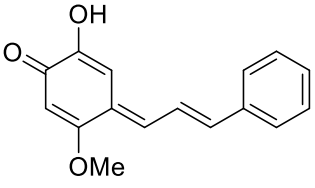
Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
1	 Villostyrene (**1**)	Benzene extract of the heartwood of *Machaerium villosam* Vog.	-	-[3]
2	 R^1 = OH, R^2 = OMe; Violastyrene (**2**) R^1 = OMe, R^2 = OH; Isoviolastyrene (**3**)	Heartwood of *Daibergia miscolobium*	-	-[4]
3	 Pertostyrene (**4**)	Trunkwood of *Machaerium acutifolium Vog.*	-	-[5]
4	 Kuhlmannistyrene (**5**)	Trunkwood of *Machaerium kuhlmanii.*	-	-[6]
5	 R^1 = H; Mucronustyrene (**6**) R^1 = OH; Mucronulastyrene (**7**)	Trunkwood of *Manchaerium mucronulatum* Mart. Ex Benth.	-	-[7]
6	 R^1 = H; Obtusastyrene (**8**) R^1 = OMe; Obtustyrene (**9**)  Obtusaquinone (**10**)	Heartwood of *Dalbergia retusa.*	-	-[8]

Table 1. Continued

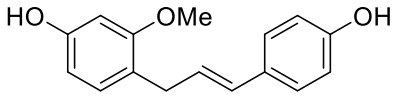
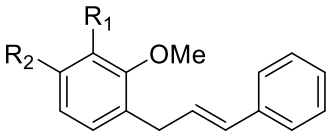
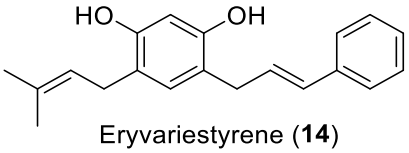
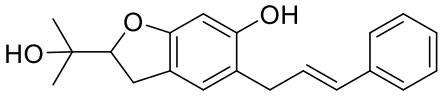
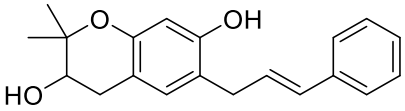
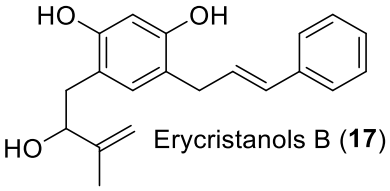
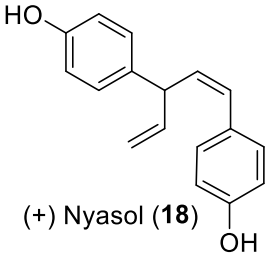
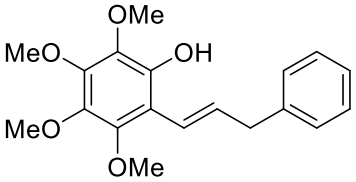
Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
7	 Xenognosin A (**11**)	Exudate of *Astragalus spp.*	Host recognition for Parasitic angiosperms and cytotoxic activity	-[9]
8	 R^1 = OH, R^2 = OMe; Isomucronustyrene (**12**) R^1 = R^2 = OH; Hydroxyobtustyrene (**13**)	Root heartwood of *Dalbergia odorifera* T. CHEN (Leguminosae)	Chinese medical drug used for stagnant blood syndrome and compound **12** showed cytotoxic activity.	-[10]
9	 Eryvariestyrene (**14**)	Roots of *Erythrina uariegata.*	-	-[11]
10	 Erycristanols A(**15**)  Erycristanols C (**16**)  Erycristanols B (**17**)	Heartwood of *Erythrina crista-galli*	-	-[12]
11	 (+) Nyasol (**18**)	*Asparagus africanus Lam.* (Liliaceae)	Potentially inhibits the growth of *Leishmania major* promastigotes and moderately inhibits *plasmodiumfalciparum* schizonts.	-[13]
12	 (*E*)-2,3,4,5-tetramethoxy-6-(3-phenylprop-1-en-1-yl)phenol (**19**)	Twigs of *Lindera lucida*	-	-[14]

Table 1. Continued

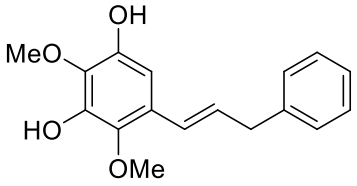
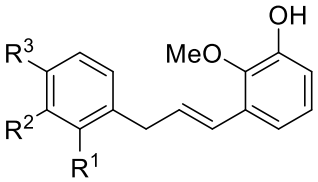
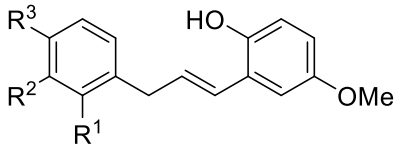
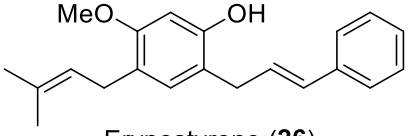
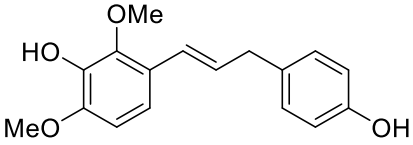
Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
13	 Macharistol (**20**)	Stems of *Manchaerium aristulatum*	cytotoxic activity	-[15]
14	 R^1 = R^2 = OMe, R^3 = OH; Dalberatin A (**21**) R^1 = R^3 = OMe, R^2 = OH; Dalberatin C (**22**) R^1 = OMe, R^2 = R^3 = OH; Dalberatin E (**23**)  R^1 = R^2 = OMe, R^3 = OH; Dalberatin B (**24**) R^1 = R^3 = OMe, R^2 = OH; Dalberatin D (**25**)	Plants of the *Dalbergia* species	Inhibitory activity against Epstein-Barr virus early antigen (EBV-EA)	-[16]
15	 Erypostyrene (**26**)	Roots of Erythrina poeppigiana (Leguminosae)	Antimicrobial activity	-[17]
16	 Dalparvinene (**27**)	Stems of *Dalbergia parviflora* Roxb. (Leguminosae)	Cytotoxic activity	-[18]

Table 1. Continued

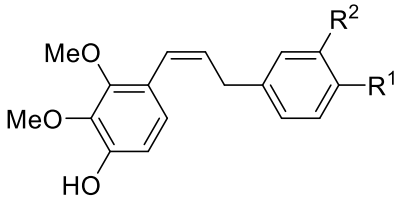
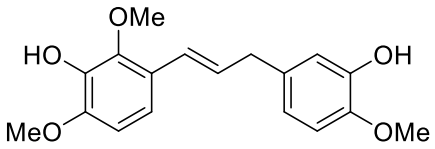
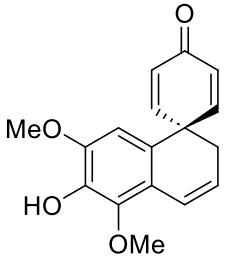
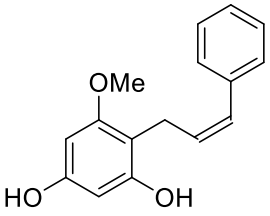
Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
17	 R^1 = OH, R^2 = H; Pulchelstyrene A (**28**) R^1 = OH, R^2 = OMe; Pulchelstyrene B (**29**)  Pulchelstyrene C (**30**)  Pulchelstyrene D (**31**)	Aerial part of *Phyllodium pulchellum*	Cytotoxic activity	-[19]
18	 Dalparvinene B (**32**)	Isolated from *Dalbergia parviflora*	Cytotoxic activity	-[20]

Table 1. Continued

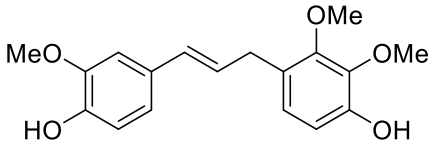
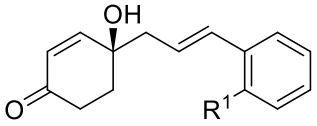
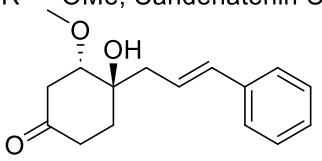
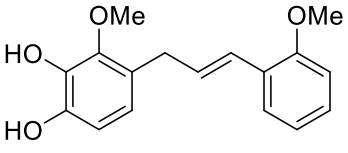
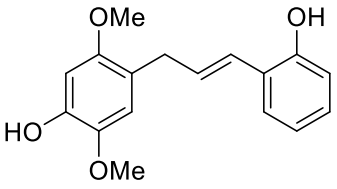
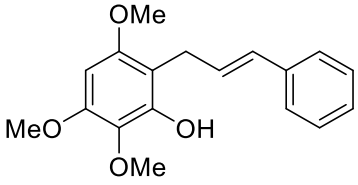
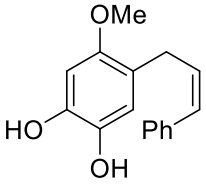
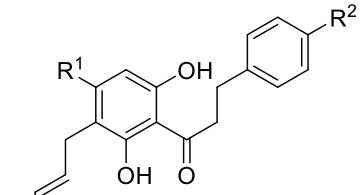
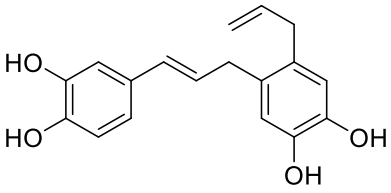
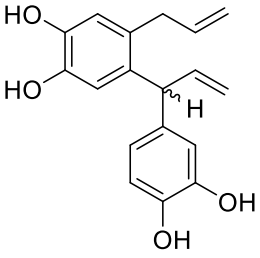
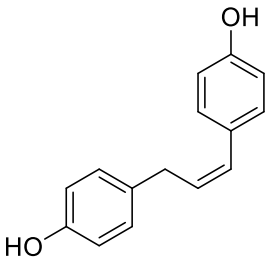
Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
19	 Candenatenin A (**33**)  R^1 = H; Candenatenin B (**34**) R^1 = OMe; Candenatenin C (**35**)  Candenatenin D (**36**)  Candenatenins G (**37**)  Candenatenins H (**38**)	Isolated from CH_2Cl_2 extract of the heartwood of *Dalbergia candenatensis and* (**33**) was isolated form another source *Arundina gramnifolia*	Compounds **33** and **38** showed cytotoxic activity, **33** showed anti-tobacco mosaic virus (anti-TMV) activity and **38** exhibited potent activity against **DPPH** radical.	-[21]
20	 Welwitschin A (**39**)	Isolated from *Uvaria welwitschia*	-	-[22]
21	 (*Z*)-1-(2-methoxy-4,5-dihydroxyphenyl)-2-(3-phenyl)propene (**40**)	Isolated from a red-type Mexican Propolis sample. First compound found in propolis.	-	-[23]

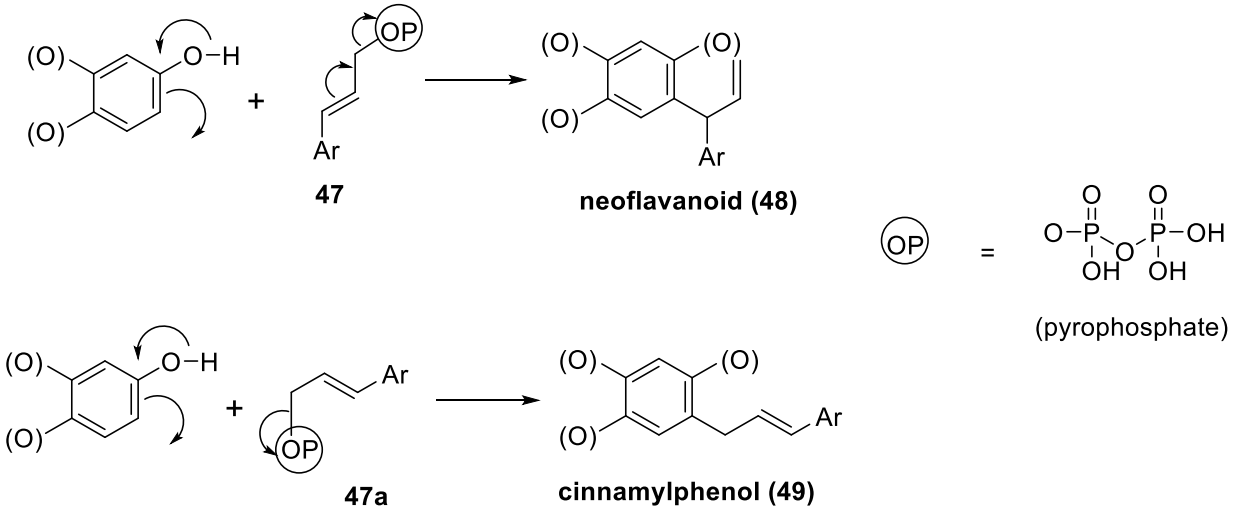
Table 1. Continued

Entry	Compound Name/Numbers	Source of isolation	Bioactivity	Reference
22	 R^1 = OMe, R^2 = OH; Balsacone A (**41**) R^1 = OH, R^2 = OMe; Balsacone B (**42**) R^1 =OH, R^2 = H; Balsacone C (**43**)	Isolated from buds of *Populus balsamifera*	The compounds showed significant antibacterial activity against staphylococcus aureus.	-[24]
23	 Neotaiwanensol A (**44**)  Neotaiwanensol B (**45**)	Isolated from bioassay-guided fractionation of roots from *Piper Taiwanese and* Isolated from another source *Piper hymenophyllum*	Showed potent inhibitory activity towards acetylcholinesterase (AChE) and butylcholinesterase (BChE)	-[25]
24	 (*Z*)-4,4'- (prop-1-ene-1,3-diaryl)diphenol (**46**)	Isolated from *Lawsonia inermis* Linn (Lythraceae, also known as henna)	Compound **46** exhibited potent nitric oxide (NO) inhibition in RAW 264.7 cells	-[26]

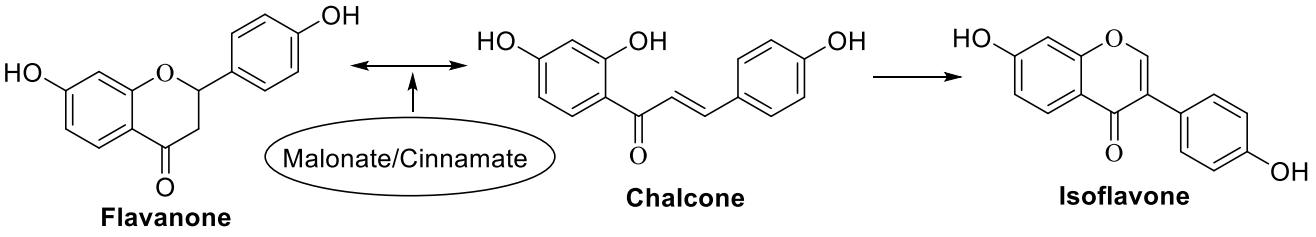
3. Biogenetic Origin

Eyton et al. proposed a unified biosynthetic model explaining the interrelationships among dalbergiones, dalbergins, and benzophenones, with cinnamyl pyrophosphate (or a similar precursor) serving as the key starting point. According to their model, cinnamyl pyrophosphate is the foundational substrate from which neoflavanoids are synthesized (Scheme 1a).

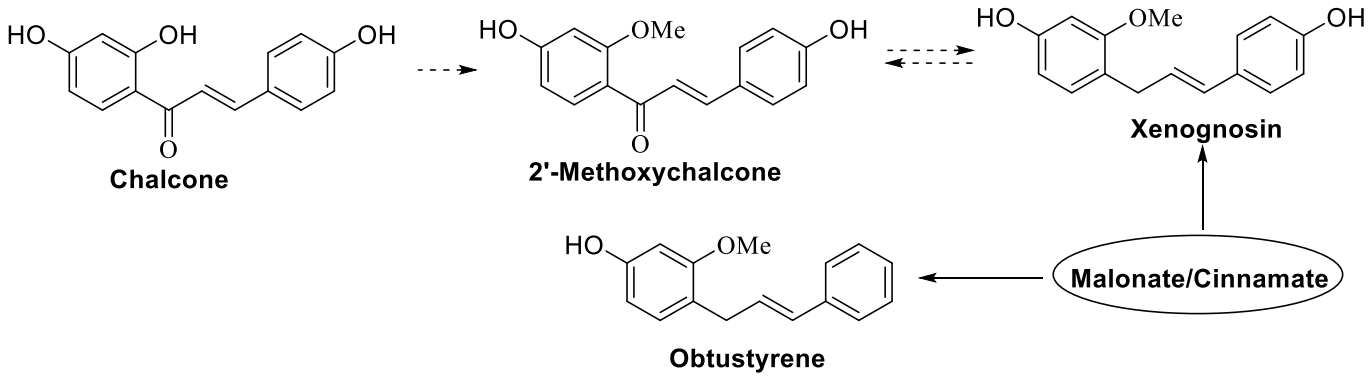
(a) Eyton et al. proposed plausible biogenetic pathway for formation of 1,3-diarylpropenes.



(b) Eyton et al. proposed plausible biosynthesis of Flavanone, Isoflavone and chalcones.



(c) Dolphin et al. proposed plausible biogenetic pathway for the formation of 1,3-diarylpropenes.



Scheme 1. The plausible biogenetic pathways for the synthesis of 1,3-diarylpropenes, Flavones, Isoflavones and Chalcones and their interconversion.

These neoflavanoids then undergo a series of transformations to produce dalbergiones and dalbergins, indicating that these compounds share a common biosynthetic origin. Further, the model suggests that dalbergiones, dalbergins, and benzophenones are interrelated as transformation products of these neoflavanoids (Scheme 1b). This pathway highlights how these compounds are chemically and structurally connected, with transformations such as oxidation and rearrangement leading from neoflavanoids to their diverse forms. The proposed biosynthetic route provides a coherent framework for understanding the synthesis and relationships of these flavonoid derivatives.[27]

Dolphin et al. isolated several 1,3-diarylpropene analogues, including Obtustyrene and Xenognosin, as well as other related compounds such as 2-(4-hydroxyphenyl)ethylene and the chalcone 4,4'-dihydroxy-2'-methoxychalcone (Scheme 1c) from Pisum sativum. Their research demonstrated that these compounds accumulate as de novo metabolites in response to plant stress. Based on these findings, Dolphin et al. proposed a model elucidating the biosynthetic pathways and stress response mechanisms associated with these metabolites. This model suggests that the accumulation of these flavonoid derivatives is part of the plant's adaptive response to environmental stress, highlighting their potential role in plant defense and adaptation.[28]

4. Synthesis of Natural 1,3-Diarylpropenes

The total synthesis of natural cinnamyl phenols has emerged as an area of research in synthetic chemistry, primarily due to the unique structures and significant biological activities these compounds exhibit. Despite their potential, cinnamyl phenols are typically found in nature only in minute or trace amounts, posing challenges for their direct extraction and study. As a result, chemists have increasingly turned to total synthesis to access and study these valuable compounds. This review categorizes cinnamyl phenols into five distinct sub-classes, each defined by specific structural features and biological properties.

The focus of the review is on the key synthetic strategies employed to construct the core cinnamyl scaffolds. These strategies include a range of methodologies such as cross-coupling reactions, which are often used to form carbon-carbon bonds; rearrangement reactions, which can create or modify complex ring systems; and various functional group manipulations, which are crucial for introducing the necessary functional groups at specific positions in the molecule. In addition to these strategies, the review also delves into specific chemical transformations that are frequently encountered in the synthesis of cinnamyl phenols. These transformations include the use of protecting group strategies to safeguard sensitive functional groups during multi-step synthesis, as well as oxidation and reduction reactions that adjust the oxidation state of the molecules. Functional group interconversions are also highlighted, demonstrating the versatility required to achieve the desired molecular architecture.

4.1. Strategies used for the synthesis of 1,3-diarylpropenes (Cinnamyl phenols)

The synthesis of 1,3-diarylpropenes, which includes cinnamyl phenols, can be categorized into five broad strategic methods. These methods are chosen based on the specific requirements of the target compounds, such as substitution patterns and functional group tolerance. The five categories are

4.1.1) Allylic arylation/alkenylation
4.1.2) Allylic selective de-functionalization
4.1.3) Decarboxylation of cinnamic acids

4.1.4) Cross-coupling reactions of potassium alkenyl trifluoroborates with benzyl halides
4.1.5) Miscellaneous strategies

4.1.1. Synthesis based on allylic arylation/alkenylation of arenes. From 1969 to 2014, researchers made significant advancements in the synthesis of 1,3-diarylpropenes, utilizing allylic arylation or alkenylation strategies through innovative catalytic systems with novel reagents and reaction conditions. In 1969, Jurd and co-workers[29] (Scheme 2a) initiated this field with a biogenetic-type synthesis of obtusastyrene (**8**) and cinnamyl quinol (**8a**) by treating cinnamyl alcohol with phenol and methoxy quinol, using ascorbic acid and citric acid to minimize quinone formation. In the same year, Maheswaran et al.[30] synthesized various 1,3-diarylpropenes by reacting cinnamyl alcohol with resorcinol or pyrogallol in the presence of 50% aqueous formic acid, selectively yielding cinnamyl phenols while suppressing the formation of neoflavonoids, such as violastyrene, isoviolastyrene, and obtusastyrene enabling the synthesis of five natural cinnamyl phenols (Scheme 2b): violastyrene (**2**), isoviolastyrene (**3**), mucronustyrene (**6**), obtusastyrene (**8**), and obtustyrene (**9**), with ortho-cinnamyl phenol formation observed in some cases.

In 1981, Kikukawa and co-workers[31] used a Pd (0)-catalyzed coupling of arene diazonium salts with allylbenzene for synthesizing 1,3-diarylpropenes (Scheme 2c) (**48**), though a notable side product was the formation of a styrene isomer. Two years later, in 1983, Wenkert and his team[32] introduced a low-valent nickel-mediated Grignard reaction that facilitated the efficient formation of C–C bonds, aiding the synthesis of naturally occurring 1,3-diarylpropenes (**8**) (Scheme 2d). Batt et al., in 1993, employed an $AlCl_3$-catalyzed Friedel–Crafts alkylation method to react 1,3,5-trimethoxybenzene with cinnamyl chloride to yield the corresponding 1,3-diarylpropenes (**49**) [33] (Scheme 2e), though it achieved only a modest yield of 25%.

In 1995, Moreno-Manas et al.[34] made a significant advancement with the development of a palladium-catalyzed Suzuki coupling reaction. This reaction enables the synthesis of 1,3-diarylpropenes (**50**) by coupling cinnamyl bromides with aryl boronic acids (Scheme 2f), facilitating the introduction of a variety of aryl substitutions. Around the same period, Shimizu and co-workers (1997)[35] introduced a molybdenum- or tungsten-catalyzed method for the cinnamylation of arenes. This approach employs cinnamyl esters or ethers under neutral conditions, resulting in the formation of 1,3-diarylpropenes (**51**) (Scheme 2g) with moderate yields.

In 1997, Hidai and co-workers[36] pioneered a novel method utilizing a thiolate-bridged diruthenium complex for the high-yield allylation of cinnamyl alcohols with arenes. This approach involves dehydrative carbon-carbon bond formation, leading to efficient synthesis of the 1,3-diarylpropenes (**52**) (Scheme 2h). Meanwhile, Malkov et al. (1997, 1999)[37,38] reported a molybdenum (II)-catalyzed para-directed alkylation of electron-rich aromatics using allylic acetates. This method successfully produced 1,3-diarylpropenes (**53**) (Scheme 2i) in high yields. However, it proved to be ineffective for electron-deficient aromatics. Nishibayashi et al. (1997, 2004),[39,40] also employed thiolate-bridged diruthenium catalysis for synthesizing 1,3-diarylpropenes (**54**) (Scheme 2j) in high yields.

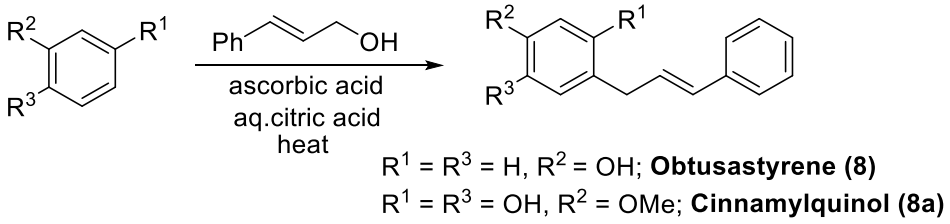
By 2000, Moreno-Manas and co-workers[40] developed a novel Suzuki-type cross-coupling method for synthesizing 1,3-diarylpropenes (**55**) (Scheme 2k) with high yields. This method was refined using a 15-membered macrocyclic triolein-coordinated Pd (0) complex, which significantly enhanced the reaction's efficiency. Additionally, the catalyst could be reused for multiple consecutive runs without losing activity, offering a more sustainable and efficient approach. In 2001, Champagne and co-workers[41] developed a cross-metathesis strategy using Grubbs' first-generation catalyst to synthesize 1,3-diarylpropenes (**56**) (Scheme 2l) by reacting protected 2-allylphenols with styrene derivatives.

In 2004, Martin and Furstner[42] introduced a method that utilized low-valent iron complexes to cross-couple 1,3-dichloroprop-1-ene with phenyl magnesium bromide, producing 1,3-diphenylpropene (**57**) (Scheme 2m) with high efficiency. In 2007, Nieves et al. developed a Friedel-Crafts-type allylation reaction[43] for the synthesis of 1,3-diarylpropenes (**58**) (Scheme 2n), catalyzed by a Ru (IV) complex, for reacting allylic alcohols with phenols. Rao and co-workers in 2010[44] devised a palladium-catalyzed cross-coupling method for synthesizing 1,3-diarylpropanes (**59**) (Scheme 2o) using allyl carbonates and triaryl bismuths as multi-coupling atom-efficient nucleophiles. Around the same time, Sarkar et al.[45] (2010) introduced a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction for the synthesis of 1,3-diarylpropenes (**60**) (Scheme 2p) involving aryl, heteroaryl, and allyl chlorides with phenyl boronic acid, achieving high yields.

Mino and co-workers[46, 47] (2012, 2013) developed a Mizoroki-Heck-type reaction, followed by an allyl cross-coupling with aryl boronic acids, using a hydrazone ligand that facilitated efficient synthesis of unsymmetrical 1,3-diarylpropenes (**62** and **64**) (Schemes 2q and 2s). Additionally, Li et al. (2012)[48] reported a regioselective and stereospecific Suzuki-Miyaura coupling for synthesizing 1,3-diarylpropenes (**63**) (Scheme 2r) using allylic carbonates and aryl boronic acids.

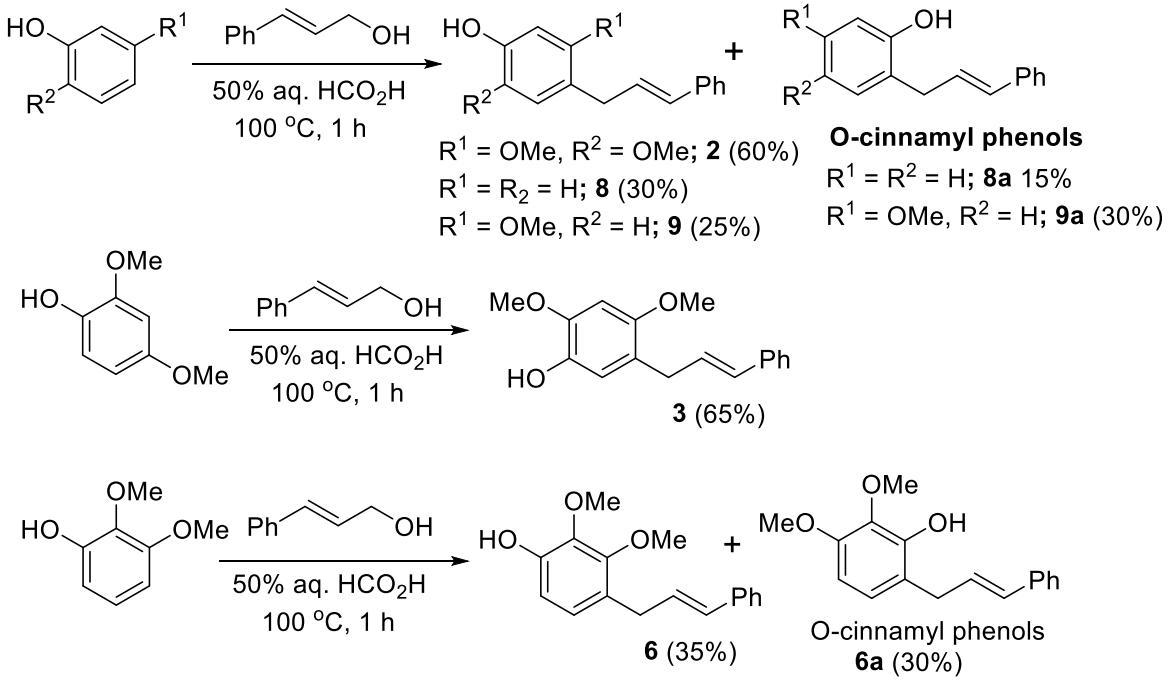
Finally, in 2014, Watanabe et al.[49] described the use of hydrazone-Pd $(OAc)_2$ as a catalytic system for the allylic arylation of cinnamyloxyphenyl boronic acid pinacol esters, producing 1,3-diarylpropene derivatives (**65**) (Scheme 2t) efficiently. This method leveraged a selective coupling mechanism, demonstrating another effective approach for synthesizing these valuable compounds. This body of work highlights decades of innovation in synthetic organic chemistry, with researchers continuously refining reaction conditions, developing novel catalytic systems, and achieving higher yields and selectivity in the synthesis of 1,3-diarylpropenes. These contributions significantly advanced the field and provided a variety of reliable synthetic routes for these biologically and industrially important compounds.

a. Synthesis of 1,3-diarylpropene natural products **8** and **8a**.

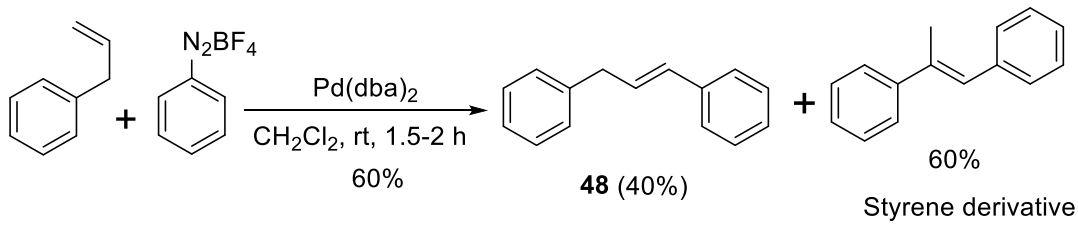


$R^1 = R^3 = H$, $R^2 = OH$; **Obtusastyrene (8)**
$R^1 = R^3 = OH$, $R^2 = OMe$; **Cinnamylquinol (8a)**

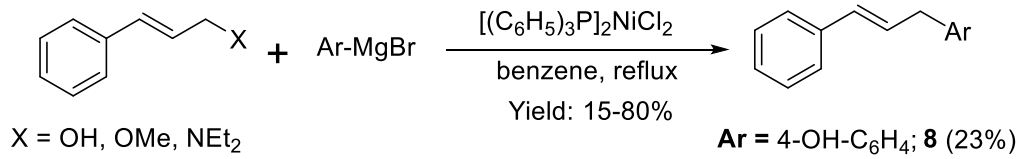
b. Synthesis of 1,3-diarylpropene natural products **2**,**3**, **6**,**8** and **9**.

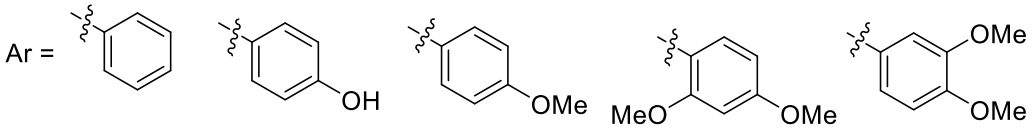


c. Synthesis of 1,3-diarylpropenes by Pd-Catalyzed arylation of allylbenzene.

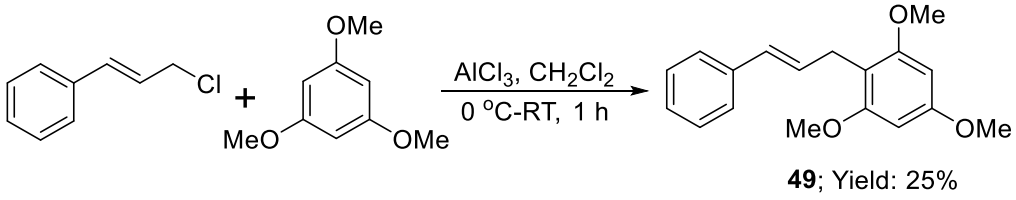


d. Synthesis of natural 1,3-diarylpropene **8** and its derivatives by arylation of allyl alcohols or ethers or 3°-amines with Grignard reagent in presence of Ni-Catalyst.

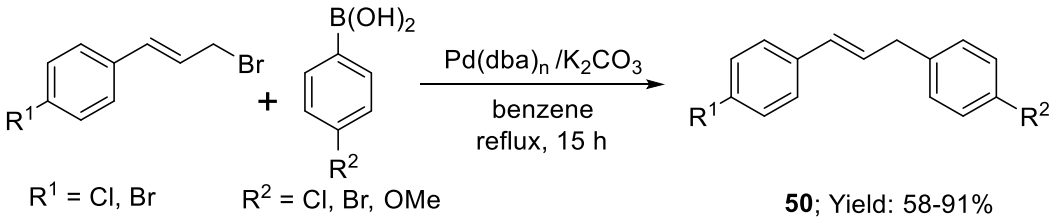




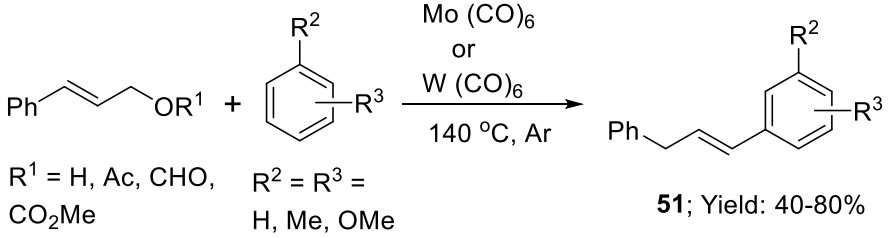
e. Synthesis of 1,3-diaryl propene derivative by Lewis's acid catalyzed Friedel craft allylation.



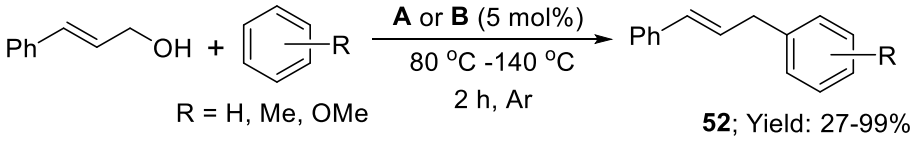
f. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation with aryl boronic acids.



g. Synthesis of 1,3-diarylpropenes by Mo or W-catalyzed allylation of activated arenes.



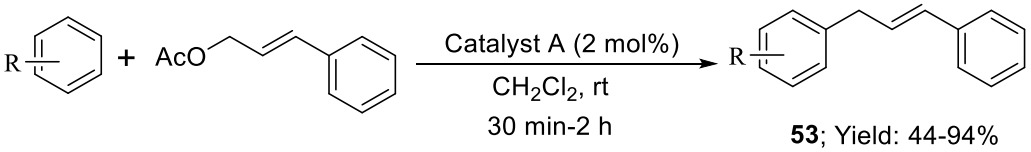
h. Synthesis of 1,3-diarylpropenes by dehydrative allylation on activated arenes.



Catalyst A = $[(C_5Me_5)RuCl(^iPrS)_2Ru(OH_2)(C_5Me_5)]OTf$

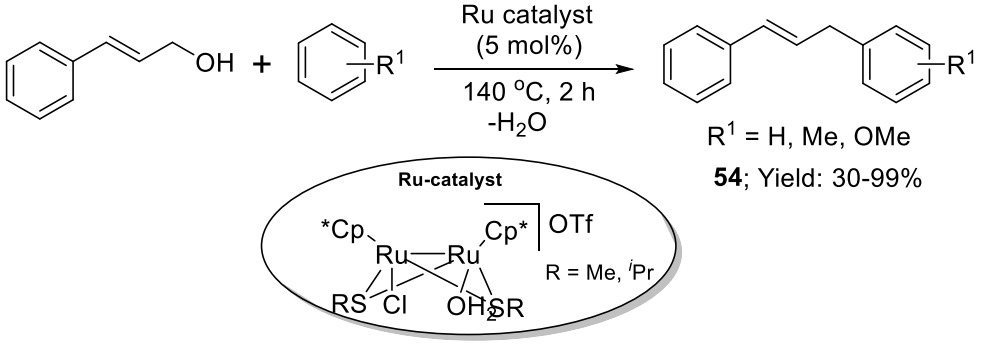
Catalyst B = $[(C_5Me_5)Ru(S^iPr)Cl]_2[OTf]$

i. Synthesis of 1,3-diarylpropenes by Mo-catalyzed allylation of arenes.

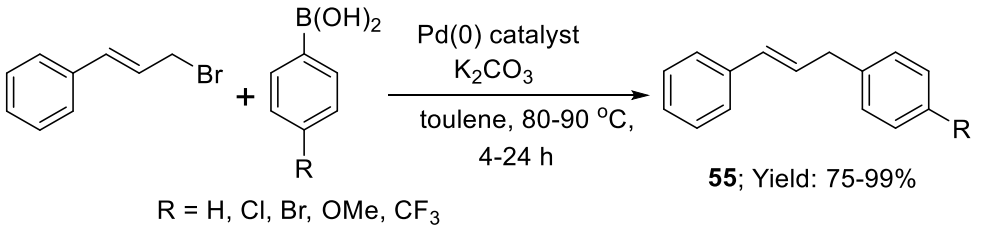


Catalyst A = $[Mo(CO)_4Br]$

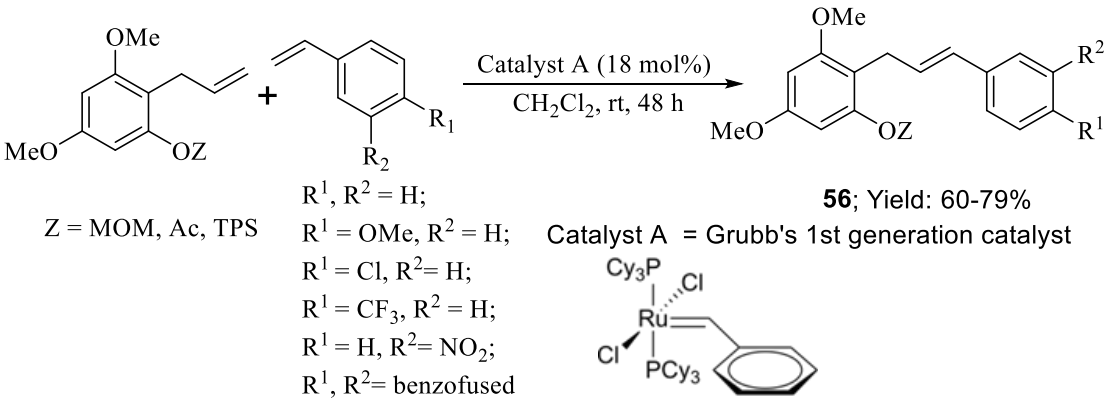
j. Synthesis of 1,3-diarylpropenes by dehydrative allylation on electron rich arenes.



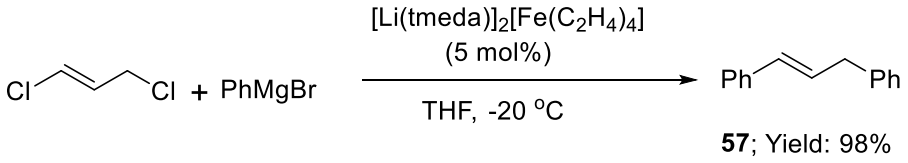
k. Synthesis of 1,3-diarylpropenes by Pd-catalyzed allylation of aryl boronic acids.



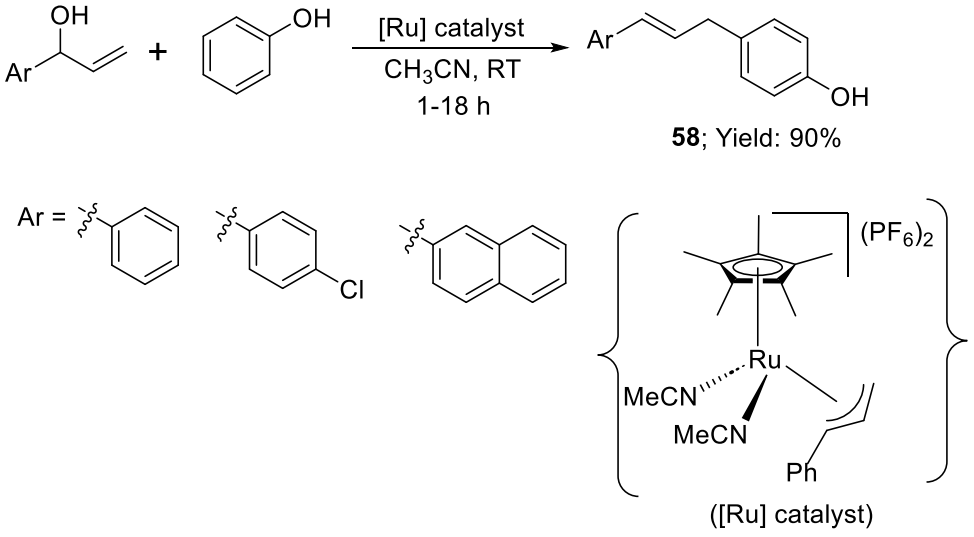
l. Synthesis of 1,3-diarylpropenes by ruthenium catalysed cross metathesis with olefins



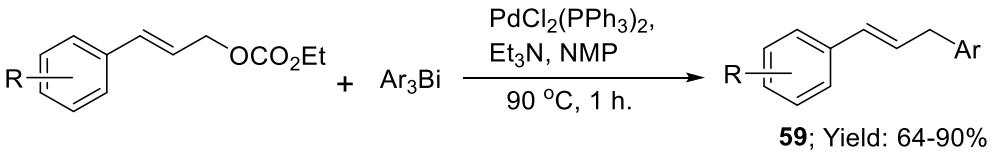
m. Synthesis of 1,3-diarylpropenes by low-valent iron complexes catalyzed cross-coupling with Grignard reagent



n. Synthesis of 1,3-diarylpropenes by ruthenium catalyzed dehydrative arylation of allyl alcohols

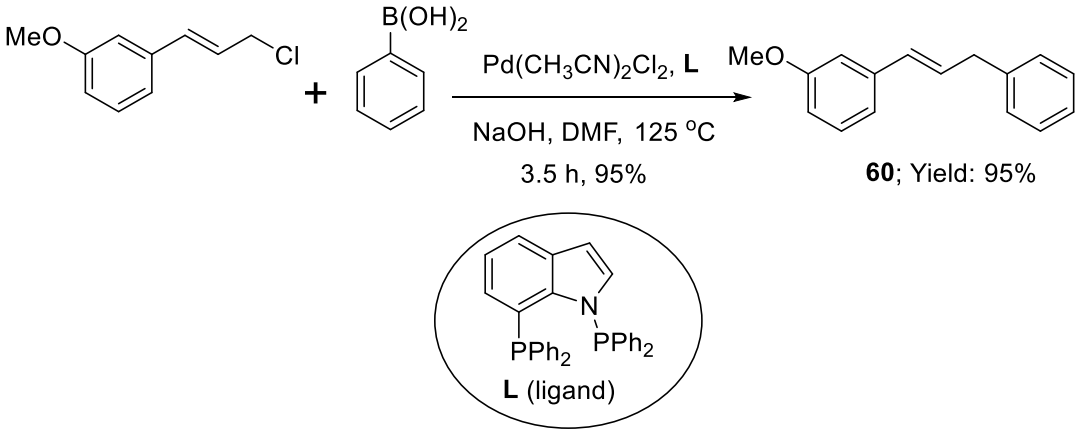


o. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl esters



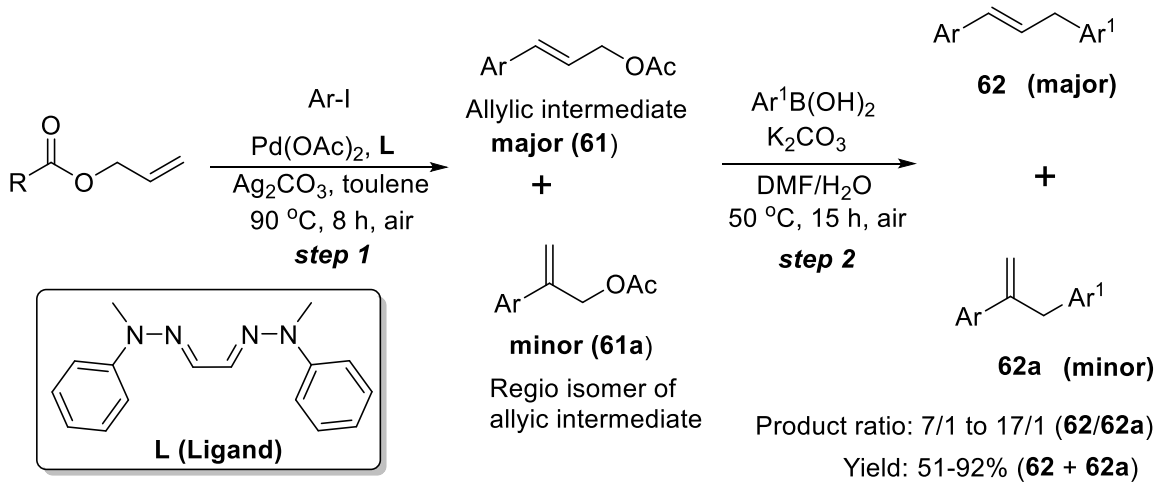
59; Yield: 64-90%

p. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl chlorides

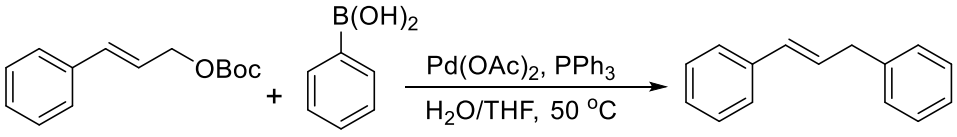


60; Yield: 95%

q. Synthesis of 1,3-diarylpropenes by Pd-catalyzed Heck-coupling with allyl esters and aryl iodides.

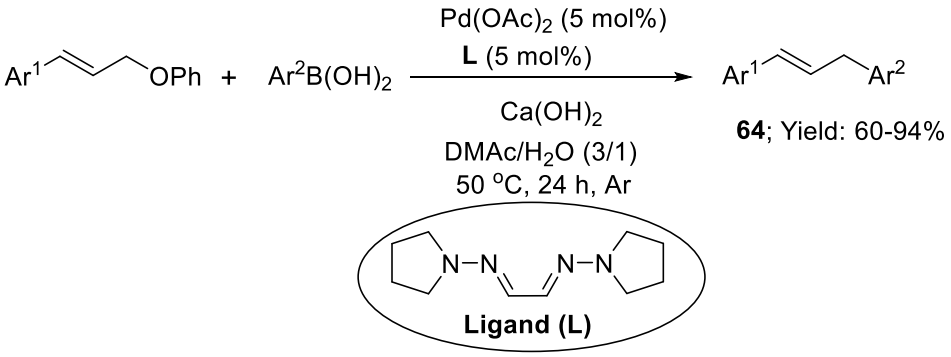


r. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl Boc-ether

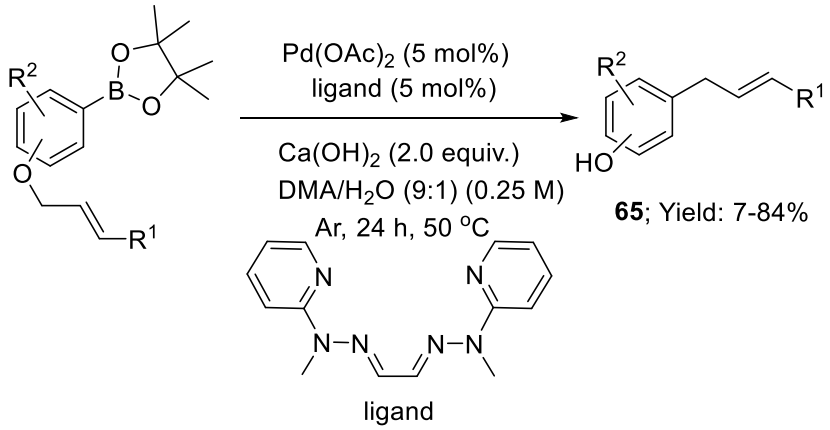


63; Yield: 86%
E/*Z* (>20:1)

s. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl ethers



t. Synthesis of 1,3-diarylpropenes by Pd-catalyzed Claisen rearrangement



Scheme 2. Synthesis of 1,3-diarylpropenes (a-t) based on Allylic arylation/alkenylation of arenes.

4.1.2. Synthesis based on Allylic selective de-functionalization. Synthesis based on allylic selective de-functionalization involves the removal or replacement of functional groups especially carbonyl group or alcohol or ether or amine groups at the allylic position in the molecules, allowing for the introduction of new functional groups or the creation of simpler structures. This strategy is particularly useful in 1,3-diarylpropenes synthesis for modifying molecules in a regioselective and stereoselective manner. Here are some key approaches and methodologies for allylic selective de-functionalization.

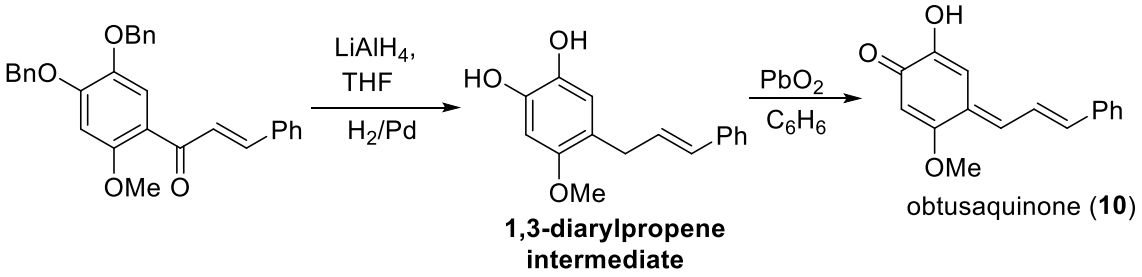
In 1968, Ollis et al.[50] used lithium aluminum hydride (LAH) for selective deoxygenation, generating a 1,3-diarylpropene (Scheme 3a) intermediate to confirm the structure of obtusaquinone (**10**). In 1983, Suzuki et al.[51] combined LAH with P_2I_4 to selectively reduce chalcones into 1,3-diarylpropenes (**66**) (Scheme 3b) in boiling benzene, enhancing the mildness and selectivity of the process. In 1999, Uozumi et al.[52] introduced a palladium-catalyzed cross-coupling of allyl acetates with aryl boronic acids in water using a resin-supported palladium catalyst, promoting greener reactions with recyclable catalysts for the synthesis of 1,3-diarylpropenes (**67**) (Scheme 3c).

Zhou et al. in 2009[53] developed a highly selective allylic reduction using benzyl alcohol as a reducing agent under neutral conditions to efficiently produce 1,3-diarylpropenes (**68**) (Scheme 3d). That same year, Yamada et al.[54] pioneered a rapid palladium-catalyzed cross-coupling of allylic esters with aryl boron reagents in microchannel reactors, achieving 1,3-diarylpropenes (**69**) (Scheme 3e) in high yields in just one second of residence time. In 2010, Yang and Tian[55] demonstrated a Brønsted acid-catalyzed reduction of N-benzylic

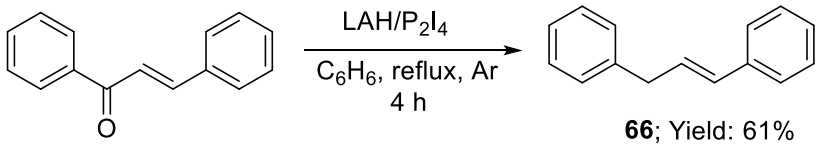
sulfonamides using triethyl silane, offering a practical approach to reducing sulfonamides for the synthesis of 1,3-diarylpropenes (**70**) (Scheme 3f).

In 2012, Yamada et al.[56] developed a highly efficient metalloenzyme-inspired palladium catalyst (MEPI-Pd) for allylic arylation with arylboronic acids for synthesis of 1,3-diarylpropenes (**71**) (Scheme 3g), achieving remarkable turnover numbers in alcohol or water with minimal loading of palladium catalyst. Finally, Kumar and Laali[57] synthesized 1,3-diarylpropenes (**72**) (Scheme 3h) via deoxygenation of alcohols using triethyl silane and bismuth triflate in an ionic liquid medium, offering mild and efficient reaction conditions. These breakthroughs showcase the continuous evolution of synthetic methods, driving the development of selective, green, and efficient processes to produce 1,3-diarylpropenes.

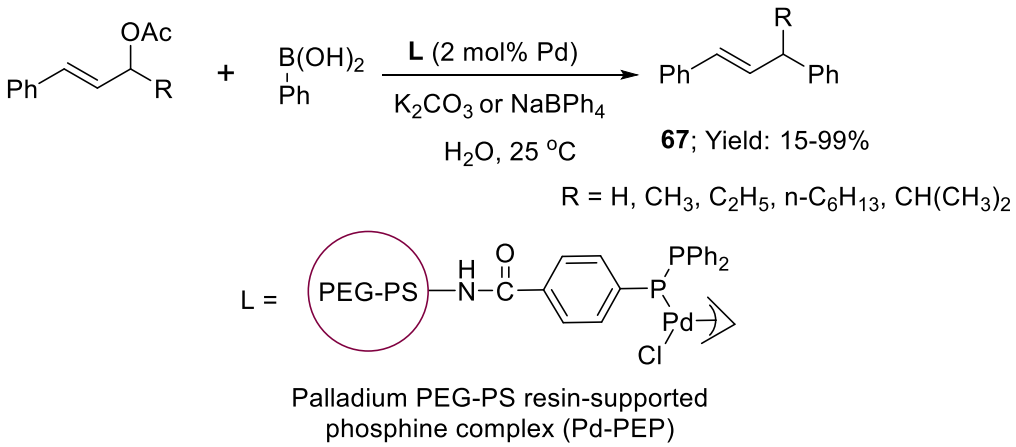
a. Synthesis of 1,3-diarylpropenes by allylic deoxygenation with LAH and Pd/H_2



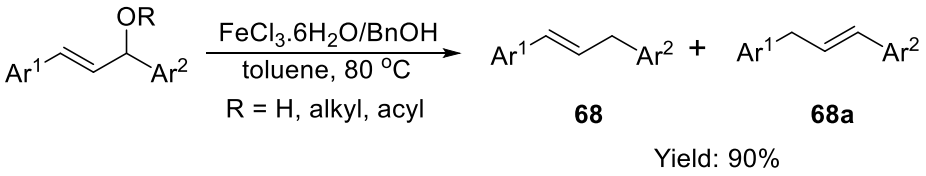
b. Synthesis of 1,3-diarylpropenes by allylic deoxygenation with LAH and P_2I_4



c. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl acetates



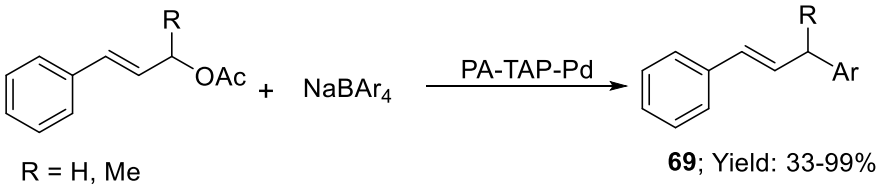
d. Synthesis of 1,3-diarylpropenes by Fe-catalyzed reductive elimination



68 **68a**

Yield: 90%

e. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl acetates

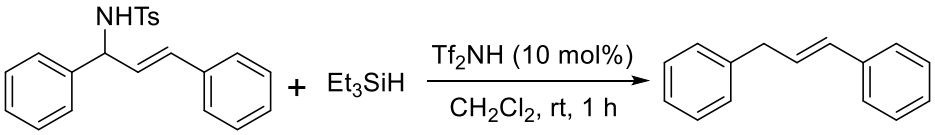


R = H, Me

69; Yield: 33-99%

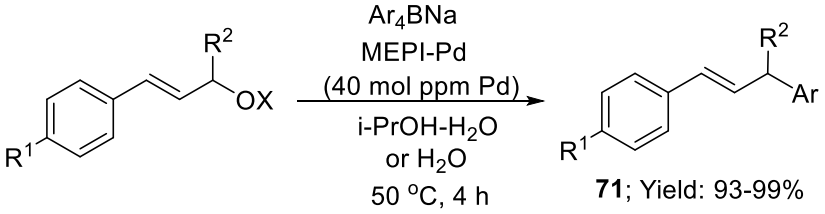
PA-TAP-Pd = poly(acrylamide)-triarylphosphine-palladium

f. Synthesis of 1,3-diarylpropenes by reductive elimination with hydro silane



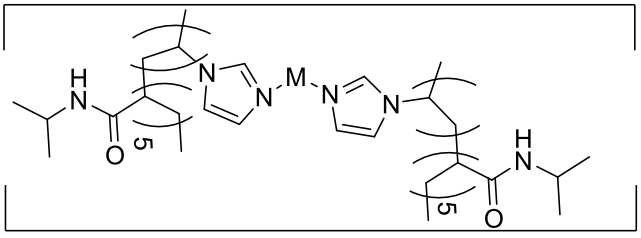
70; Yield: 98%

g. Synthesis of 1,3-diarylpropenes by Pd-catalyzed arylation of allyl esters



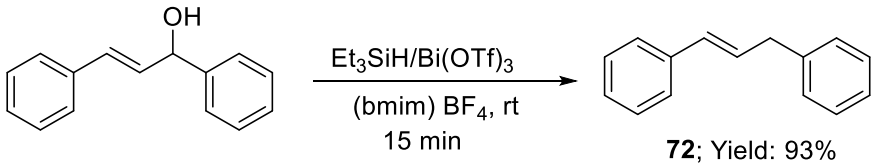
71; Yield: 93-99%

R^1 = H, Cl, F, NO_2, Me, OMe; R^2 = H, Me, Et, n-C_6H_{13}; X = Ac, CO_2Me
Ar = C_6H_5, 4-CH_3-C_6H_4, 4-F-C_6H_4, 4-CH_3O-C_6H_4



L: MEPI-Pd; M = Pd(II)Cl_2 and Pd(0)

h. Synthesis of 1,3-diarylpropenes by Lewis's acid catalyzed hydrogenation of allyl alcohols



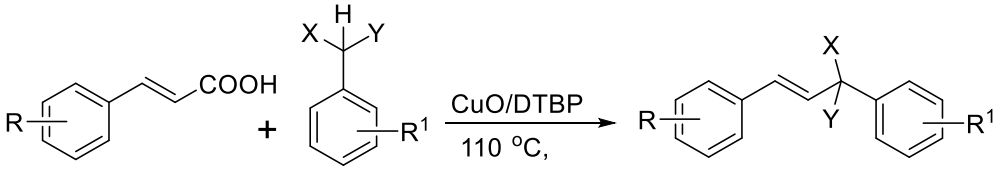
Scheme 3. Synthesis of 1,3-diarylpropenes (a-h) based on based on Allylic selective de-functionalization.

4.1.3. Synthesis based on decarboxylation of cinnamic acids. Decarboxylation of cinnamic acids is a well-established method for synthesizing various substituted 1,3-diarylpropenes. Here are the very few approaches reported to this process:

Yang et al. (2012)[58] introduced an innovative method for decarboxylative C(sp^2)–C(sp^3) coupling using copper as a catalyst without the need for palladium or ligands, facilitating the coupling of cinnamic acids with arenes through C–H functionalization to form 1,3-diarylpropenes (**73**) (Scheme 4a). Building on this, Mao et al. (2013)[59] developed an efficient ferrocene-catalyzed decarboxylative C(sp^2)–C(sp^3) coupling of cinnamic acids with substituted toluene's, notable for its ligand-free conditions and yielding moderate to good results for synthesis of 1,3-diarylpropenes (**74**) (Scheme 4b).

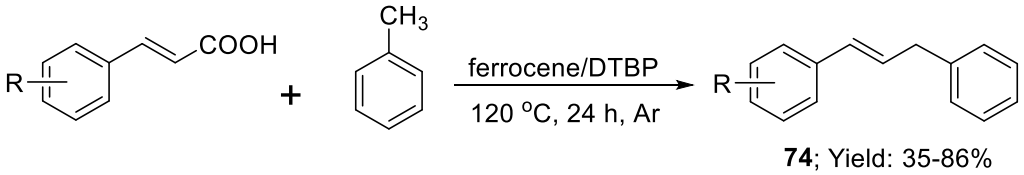
Additionally, Zhao et al. (2014)[60] combined a Knoevenagel reaction with decarboxylation and Csp3-H activation under copper catalysis, providing a versatile method for synthesizing 1,3-diarylpropenes (**75**) (Scheme 4c) and the yields of this approach, ranging from 34% to 78%, suggest varying effectiveness depending on the electronic properties of the substituents on the benzaldehyde and toluene, underscoring the importance of substrate selection and optimization in achieving desired outcomes.

a. Synthesis of 1,3-diarylpropenes by CuO/DTBP decarboxylation of cinnamic acids followed by oxidative radical coupling with toluene and its analogues



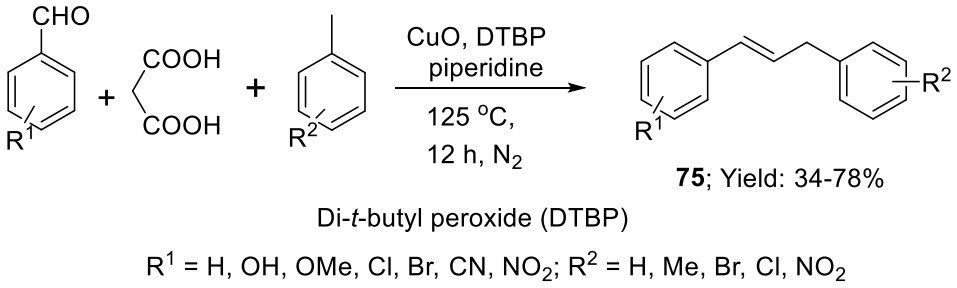
R = H, Cl, F, Me, OMe; R^1 = Me, Cl, Br, I; X, Y = H, Me

b. Synthesis of 1,3-diarylpropene's by iron catalyzed decarboxylation of cinnamic acids followed by oxidative coupling with toluene and its analogues



R = H, OMe, Cl, F, Me, CN, NO_2, OAc, ^{i}Pr, CO_2Me

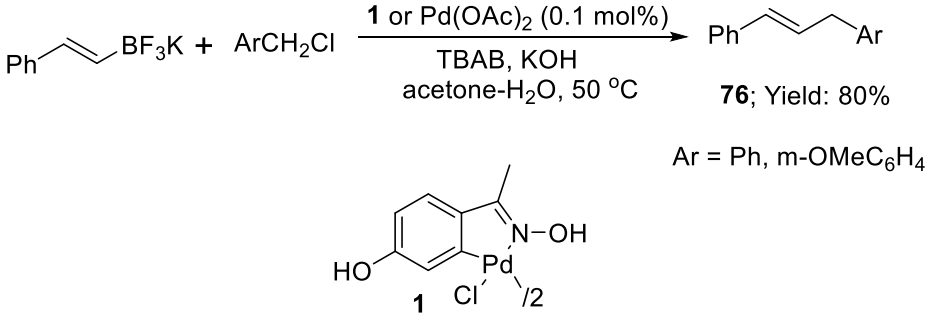
c. Synthesis of 1,3-diarylpropene's CuO/DTBP/piperidine one-pot strategy for synthesis and decarboxylation of cinnamic acids followed by oxidative radical coupling with toluene and its analogues



Scheme 4. Synthesis of 1,3-diarylpropenes (a-c) based on Decarboxylation of cinnamic acids.

4.1.4. Synthesis of 1,3-diarylpropenes based on cross-coupling reactions of potassium alkenyl trifluoroborates with benzyl halides. The cross-coupling reaction between potassium alkenyl trifluoroborates and benzyl halides is a valuable strategy for synthesizing 1,3-diarylpropenes. This approach leverages the reactivity of alkenyl trifluoroborates and the versatility of benzyl halides in a palladium-catalyzed cross-coupling process.

Al-acid and co-workers in 2008 and 2009[61, 62] made a significant advancement in the synthesis of 1,3-diarylpropenes (**76**) (Scheme 5) through palladium-catalyzed cross-coupling reactions of potassium alkenyl-trifluoroborates with benzyl chloride in aqueous media. This innovative approach not only showcases the versatility of palladium catalysis but also highlights the use of potassium alkenyl-trifluoroborates as effective nucleophiles in water, enhancing the sustainability and practicality of the reaction conditions. By conducting these reactions in aqueous environments, this methodology offers a valuable addition to the toolkit for synthesizing 1,3-diarylpropenes.



Scheme 5. Synthesis of 1,3-diarylpropenes based on cross-coupling reactions of potassium alkenyl trifluoroborates with benzyl halides.

4.1.5. Miscellaneous strategies for synthesis of 1,3-diarylpeopenes. Presented below are various strategies for synthesizing 1,3-diarylpropenes, each offering distinct benefits and presenting unique challenges.

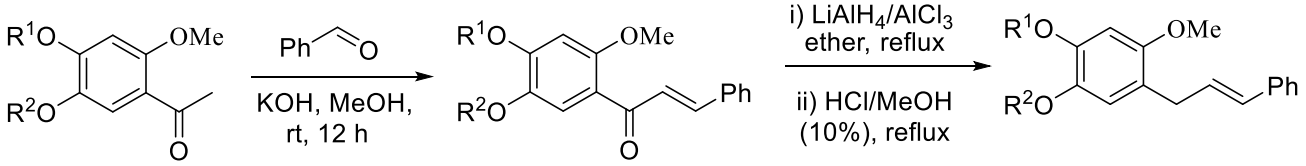
In 1978, Gregson et al.[63] isolated the natural 1,3-diarylpropenes **2** and **3** from *Dalbergia miscolobium* and synthesized through a condensation reaction of ketones (**77**, **77a**) with benzaldehyde, followed by reductive dehydration of the corresponding chalcones (**78**, **78a**) by using $LiAlH_4$ and HCl, with structures confirmed by spectral data (Scheme 6a).

In 1982, El-Feraly and Hufford[64] achieved the first synthesis of Xenognosin A (**11**) from umbelliferone, converting it to a key aldehyde (**79**) and reacting it with ArLi, ultimately yielding Xenognosin A (**11**) at 55% via treatment with dimethyl sulfate (Me_2SO_4) (Scheme 6b). Also in 1982, Kamat et al.[65] reported an efficient synthesis of Xenognosin A (**11**) and its analogues from umbelliferone to the key aldehyde intermediate (**80**) for expanding the scope of 1,3-diarylpropenes (Scheme 6c).

In 1988, Achenbach et al.[66] isolated and synthesized obtustyrene (**9**) from *Bauhinia munca* and evaluated its antifungal activity (Scheme 6d). Kagabu et al.[67] reported a method in 1991 for synthesizing 1,3-diarylpropenes (**81**) through the condensation of arylmethanesulfonyl fluorides with phenylacetaldehyde, utilizing potassium carbonate and crown ether (Scheme 6e). In 1998, Leong et al.[68] isolated a 1,3-diarylpropene (**19**) from *Lindera lucida*, synthesized from the corresponding ketone via reduction with $NaBH_4$ and dehydration with $SOCl_2$ and pyridine (Scheme 6f).

Hilt et al.[69] introduced a cobalt(I)-catalyzed Diels-Alder reaction in 2007, using butynyl phosphonium salts and 1,3-dienes, followed by a one-pot Wittig-type olefination to efficiently create 1,3-diarylpropene (**82**) products (Scheme 6g). Finally, in 2016, Lin et al.[70] described an iodine-promoted, metal-free head-to-tail dimerization of styrene's, leading to substituted 1,3-diarylpropenes (**83**) in moderate yields (Scheme 6h).

a. Synthesis of 1,3-diarylpropenes starting from ketones through chalcones by allylic deoxygenation with $LAH/AlCl_3$

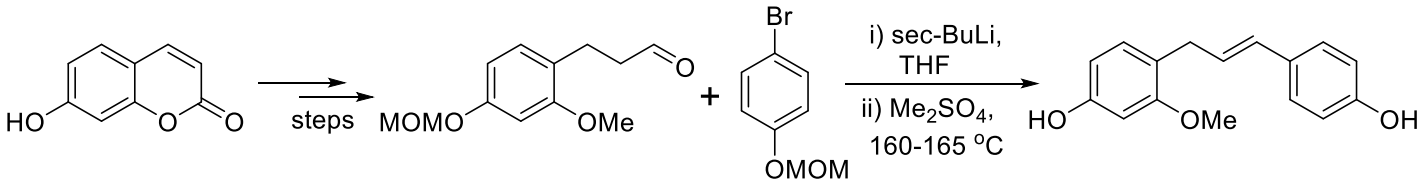


77; R^1 = Bn, R^2 = Me
77a ; R^1 = Me, R^2 = Bn

78; R^1 = Bn, R^2 = Me
78a; R^1 = Me, R^2 = Bn

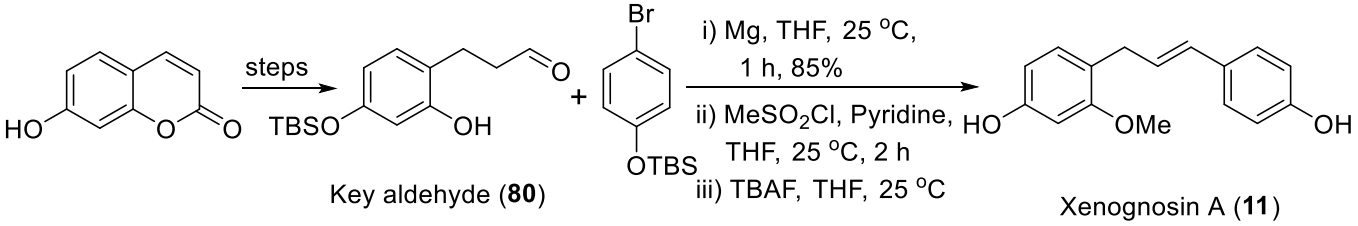
2; R^1 = H, R^2 = Me
3; R^1 = Me, R^2 = H

b. Synthesis of natural 1,3-diarylpropene Xenognosin A (**11**) from Umbelliferone



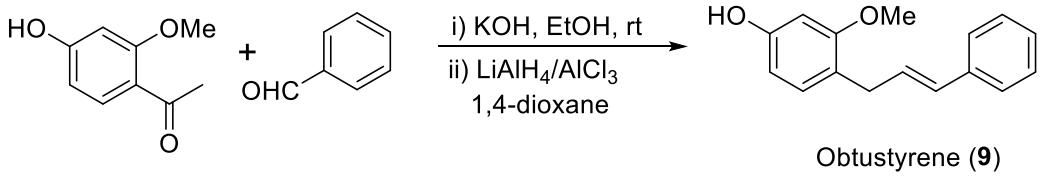
Umbelliferone | Key aldehyde (**79**) | Xenognosin A (**11**)

c. Synthesis of natural 1,3-diarylpropene Xenognosin A (**11**) from Umbelliferone by Grignard strategy

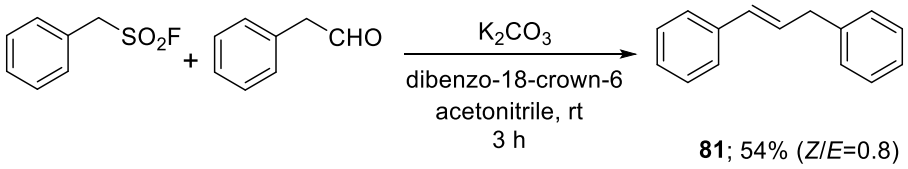


Key aldehyde (**80**) | Xenognosin A (**11**)

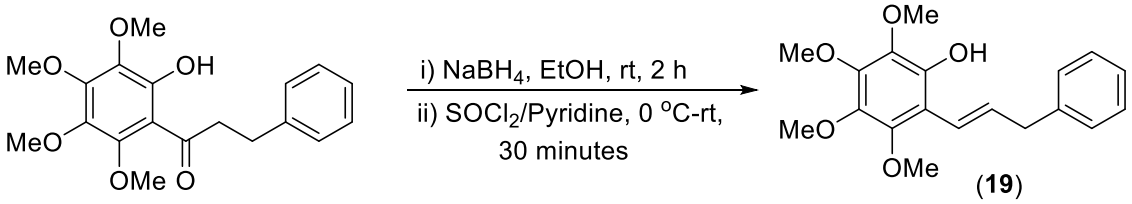
d. Synthesis of natural 1,3-diarylpropene Obtustyrene (**9**) a ketone through chalcones by allylic deoxygenation with LAH/$AlCl_3$



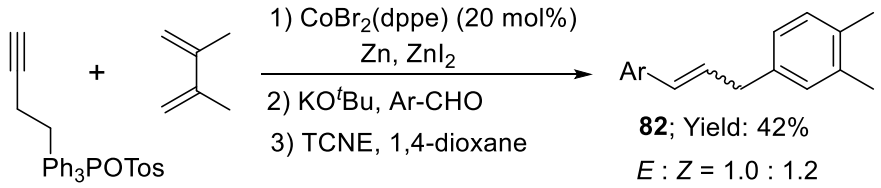
e. Synthesis of 1,3-diarylpropenes by base catalyzed olefin formation



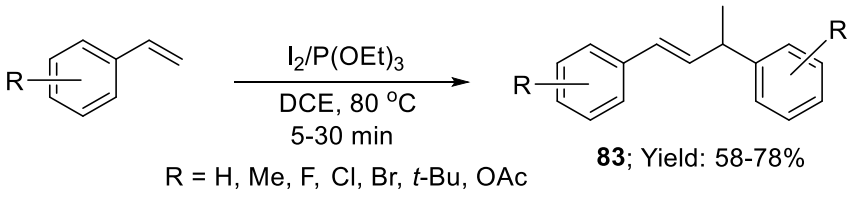
f. Synthesis of natural 1,3-diarylpropene (**19**) through reduction followed by elimination strategy



g. Synthesis of 1,3-diarylpropenes by cobalt(I)-catalyzed Diels-Alder strategy



h. Synthesis of 1,3-diarylpropenes by iodine catalyzed self-coupling of olefins



Scheme 6. Miscellaneous strategies for synthesis of 1,3-diarylpeopenes (a-h).

5. Transformations of 1,3-Diarylpropenes

1,3-Diarylpropenes are highly versatile compounds in organic synthesis due to their reactive double bonds and aryl groups. They can be subjected to hydrogenation to yield 1,3-diarylpropane derivatives, modifying the degree of unsaturation. Electrophilic addition reactions, such as halogenation or nitration, can introduce various functional groups into the molecule. Ozonolysis of 1,3-diarylpropenes cleaves the double bond, producing carbonyl compounds like aldehydes or ketones. Oxidation reactions can convert these compounds into dihydroxy derivatives or other oxidized forms.

Additionally, 1,3-diarylpropenes can be used in cross-coupling reactions, such as Suzuki or Heck reactions, to form substituted aryl compounds. The reactive double bond also enables polymerization to produce poly(1,3-diarylpropene) materials. Furthermore, they can participate in Diels-Alder reactions with dienes to form cyclohexene derivatives, and the aryl groups can be functionalized through Friedel-Crafts alkylation or acylation to introduce diverse substituents. These transformations highlight the value of 1,3-diarylpropenes as versatile intermediates and essential building blocks in organic synthesis and materials science. Some key transformations are described below.

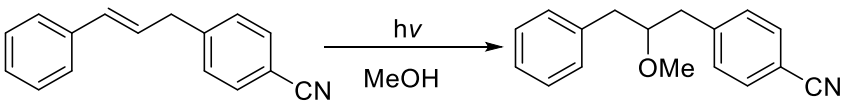
In 1972, Hixson discovered[71] an unusual anti-Markovnikov methanol addition to 1,3-diarylpropenes under photochemical conditions. This reaction, driven by radical intermediates, favored the less substituted carbon of the double bond, providing a rare example of anti-Markovnikov regioselectivity (**84**) (Scheme 7a). In 2009, Mo and co-workers developed[72] an oxidative cross-coupling reaction between 1,3-diarylpropenes and indoles, using palladium chloride and DDQ as the catalyst and oxidant, respectively, yielding 1,3-diphenylallylindoles (**85**) (Scheme 7b) in high efficiency under mild conditions. The following year, Mo and Bao reported[73] an iron-catalyzed sp^3 C-H activation and C-C bond formation between 1,3-diarylpropenes and ethynylbenzenes, facilitated by benzoquinone (BQ), producing complex 1-halo-1,4-pentadiene derivatives (**86**) (Scheme 7c).

In a metal-free alternative, Jin et al. in 2010[74] used DDQ to promote cross-dehydrogenative coupling of allylic sp^3 C-H bonds of 1,3-diarylpropenes and oximes, efficiently forming oxime ethers (**87**) (Scheme 7d). In 2012, Wang and co-workers[75] utilized DDQ to drive a dehydrogenative cross-coupling between 1,3-diarylpropenes and anilines, selectively producing allylic amines, with options for both mono- and di-allylation (**88**) (Scheme 7e). That same year, Gandeepan and Cheng[76] introduced a Pd-catalyzed ortho-C-H olefination of 1,3-diarylpropenes, using O_2 as an oxidant, offering a mild and green approach to functionalization on arene part of the moiety (**89**) (Scheme 7f).

In 2014, Cheng's group[77] advanced oxidative ether (**90**) formation between 1,3-diarylpropenes and alcohols, promoted by NHPI under an oxygen atmosphere and catalyzed by $CuBr/NiCl_2$, achieving moderate to good yields (Scheme 7g). Cheng[78] further expanded the scope by using DDQ and AIBN in oxidative coupling with propane-1,3-diones, under molecular oxygen, resulting in efficient C-C bond product formation (**91**) (Scheme 7h).

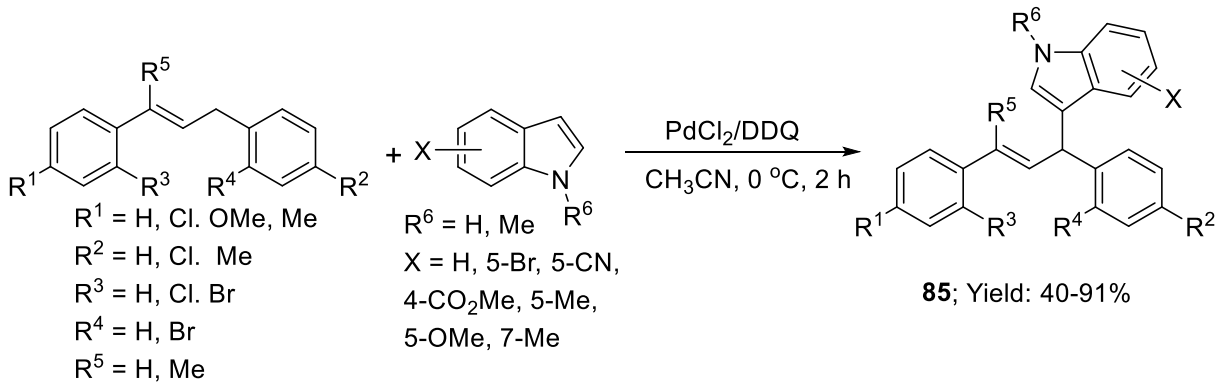
Finally, in 2015, Yuan and co-workers reported[79] an Ir-catalyzed allyl-allyl cross-coupling of allylic carbonates with 1,3-diarylpropenes, leading to the regioselective formation of linear 1,5-dienes (**92**) (Scheme 7i) in high yields. Together, these methods underscore the versatility of 1,3-diarylpropenes in organic synthesis, highlighting diverse catalytic systems-from metal-free to palladium, iron, and iridium catalysts-that enable efficient and selective functionalization of this valuable scaffold.

a. Addition to 1,3-diarylpropene's in an anti-Markovnikov fashion under photochemical conditions



84; Yield: 21%

b. DDQ promoted oxidative cross-coupling reaction between 1,3-diarylpropene's and indoles

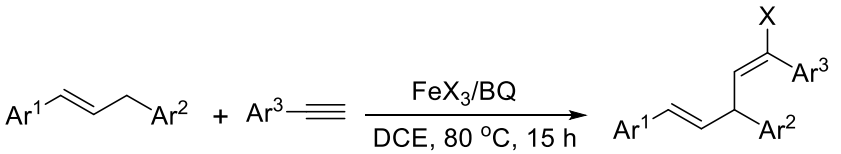


R^1 = H, Cl. OMe, Me
R^2 = H, Cl. Me
R^3 = H, Cl. Br
R^4 = H, Br
R^5 = H, Me

R^6 = H, Me
X = H, 5-Br, 5-CN, 4-CO_2Me, 5-Me, 5-OMe, 7-Me

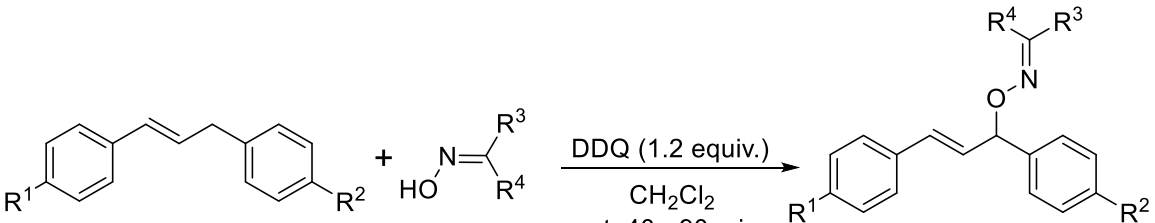
85; Yield: 40-91%

c. Iron-Promoted sp^3 C-H Bond activation between 1,3-Diarylpropenes and Ethynylbenzenes Using (BQ) Benzoquinone as an Oxidant



86; Yield: 47-79%

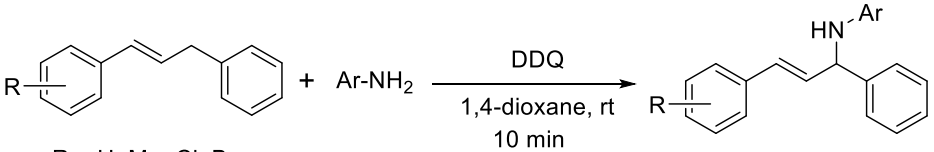
d. Metal-free approach to synthesizing oxime ethers promoted by DDQ



R^1 = R^2 = H, Cl, Me R^3 = Ar, R^4 = H

87; Yield: 52-85%

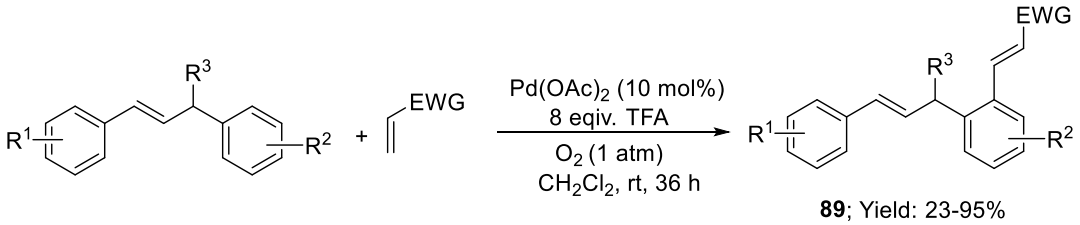
e. Dehydrogenative cross-coupling reaction of aromatic anilines, secondary anilines, carboxamides, and sulfonamides with 1,3-diarylpropenes



R = H, Me, Cl, Br

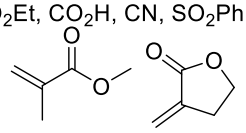
88; Yield: 65-97%

f. Pd-catalyzed C-C double bond-assisted selective ortho-C−H olefination of 1,3-diarylpropenes

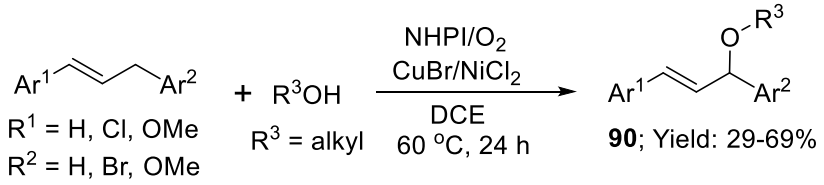


R^1, R^2 = H, Cl, OMe, Me, F, Ph, *t*-Bu; R^3= H, Me

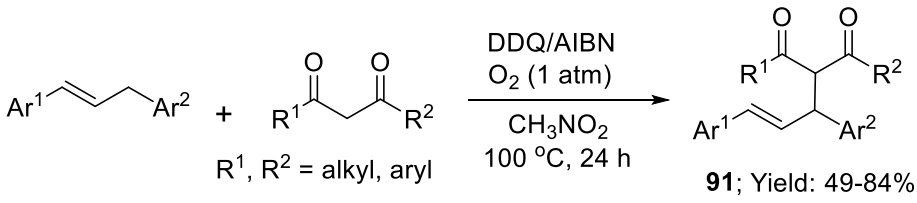
EWG = CO_2-*n*-Bu, CO_2-*t*-Bu, CO_2Me, CO_2Et, CO_2H, CN, SO_2Ph, C(O)NH_2, C(O)$N(Me)_2$, C(O)NH_2CH_2Ph, $CO_2C_6H_{11}$, CO_2CH_2Ph,



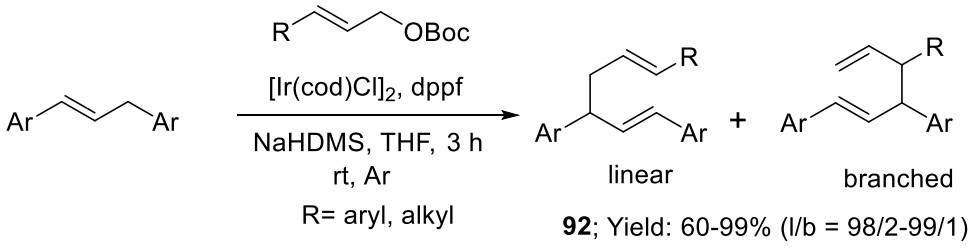
g. Oxidative ether formation between 1,3-diarylpropene and alcohols



h. DDQ promoted oxidative coupling of 1,3-diarylpropenes with propane-1,3-diones



i. Ir-catalyzed allyl-allyl cross-coupling reaction of allylic carbonates with (*E*)-1,3-diarylpropenes



Scheme 7. Transformations of 1,3-diarylpropenes (a-i).

6. Applications of 1,3-Diarylpropenes

1,3-Diarylpropenes are highly versatile organic compounds with a wide array of applications across various fields. In pharmaceuticals and drug development, they are notable for their potential as anticancer agents,

anti-inflammatory and antioxidant agents, and neuroprotective agents, due to their ability to influence cellular pathways and enzyme activity.

In organic synthesis, these compounds serve as valuable intermediates, enabling the construction of complex molecules and facilitating ligand design for catalytic processes. Their applications extend to materials science, where they are used in the development of liquid crystalline materials for display technologies and as components in polymers to modify physical properties. In agriculture, some 1,3-diarylpropenes have been explored for use in pesticides and herbicides, offering innovative solutions for pest management. Additionally, they are utilized in the production of flavors and fragrances.

In research and development, 1,3-diarylpropenes are employed as biological probes to study biochemical processes and are included in compound libraries for high-throughput screening in drug discovery and chemical biology. Some of the important applications of the 1,3-diarylpropenes are discussed here.

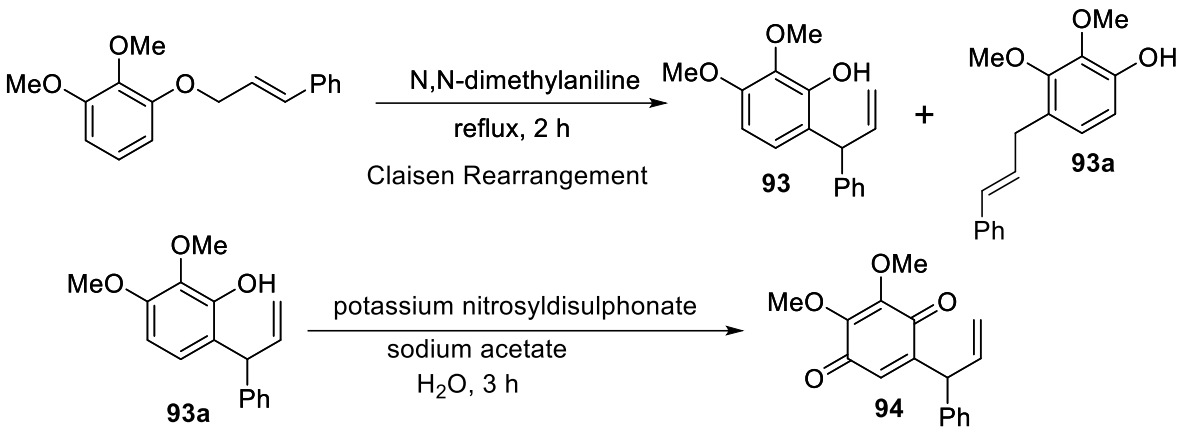
Since 1965, synthetic methodologies involving 1,3-diarylpropenes have played a crucial role in organic synthesis and natural product chemistry. In 1965, Barnes et al.[80] pioneered this field by employing Claisen rearrangement in the synthesis of (±)-3,4-dimethoxydalbergione (**94**) (Scheme 8a), using NMR spectroscopy to elucidate structural details. The synthesis involved a key Claisen rearrangement step, during which the 2,3-dimethoxy-4-cinnamylphenol (**93**) was utilized and the by-product of this reaction is 1,3-diarylpropene (**93a**).

Cardillo et al.[81] developed a DDQ-promoted cyclization of cinnamyl phenols in boiling benzene for 12 to 20 hours, leading to the efficient synthesis of flav-3-enes (**95a-f**) (Scheme 8b) and DDQ involved in facilitating the cyclization for flavonoid synthesis. In 1982, Zanarotti et al.[82] employed 1,3-diarylpropenes in the oxidation of cinnamyl phenols to synthesize malvidin (**96**) (Scheme 8c), and In 1997, Van Rensburg et al.[83] explored enantioselective dihydroxylation of 1,3-diarylpropenes for the synthesis of catechin derivatives (**98a-d**) (Scheme 8d), while Nel et al.[84, 85] applied these intermediates in the 1999 synthesis of the rare flavan-3-ol class compound guibourtinidol (**99a, 99b**) and asymmetric dihydroxylation was also pivotal in Nel's 1999 work on stereoselective synthesis of flavan-3-ols (**100a-d**) (Schemes 8e and 8f).

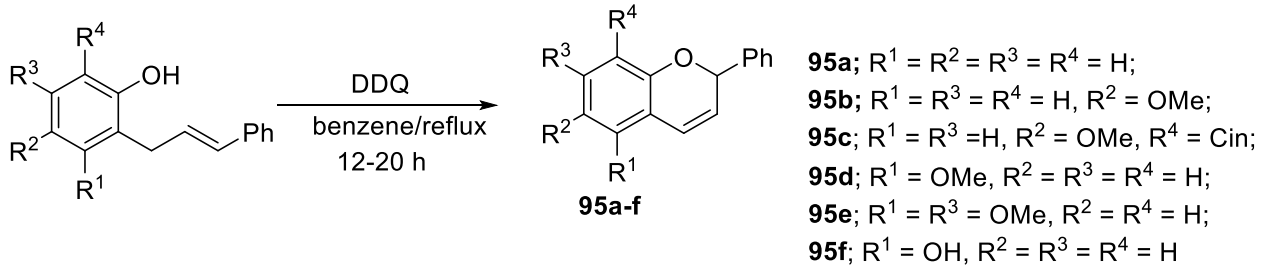
In 2002, Rawat et al.[86] used 1,3-diarylpropenes to achieve the total synthesis of the marine alkaloid Ningalin C (**101**) (Scheme 8g), while Grubbs et al. in 2002[87] employed ruthenium-catalyzed olefin metatheses to synthesize flavanols (**104a, 104b**) (Scheme 8h). In 2004, Yang et al.[88] advanced this chemistry with the selective alkylation of phenols using mesoporous silicas, forming flavans (**105**) (Scheme 8i) through 1,3-diarylpropene intermediates. In 2005, Anderson et al.[89] synthesized epicatechin gallate analogues (**110a, 110b**) (Scheme 8j) to combat β-lactam resistance in methicillin-resistant Staphylococcus aureus.

In 2006, Su et al.[90] used the Wittig reaction with 1,3-diarylpropenes to synthesize the anti-inflammatory compound viscolin (**111**) (Scheme 8k), and in 2008, Hirooka et al.[91] applied a 6-endo-cyclization approach for the synthesis of gallocatechin-3-gallate derivatives (**112a, 112b**) (Scheme 8l). Finally, in 2011, Heckeloer et al.[92] developed an oxidative cyclization of α-benzyl cinnamates using hypervalent iodine, a key step in synthesizing Metasequirin-B (**113**) (Scheme 8m). These studies collectively underscore the importance of 1,3-diarylpropenes in constructing complex molecular architectures with broad applications in synthetic and medicinal chemistry.

a. 1,3-diarylpropenes in the synthesis of (±)-3,4-dimethoxydalbergione through Claisen Rearrangement

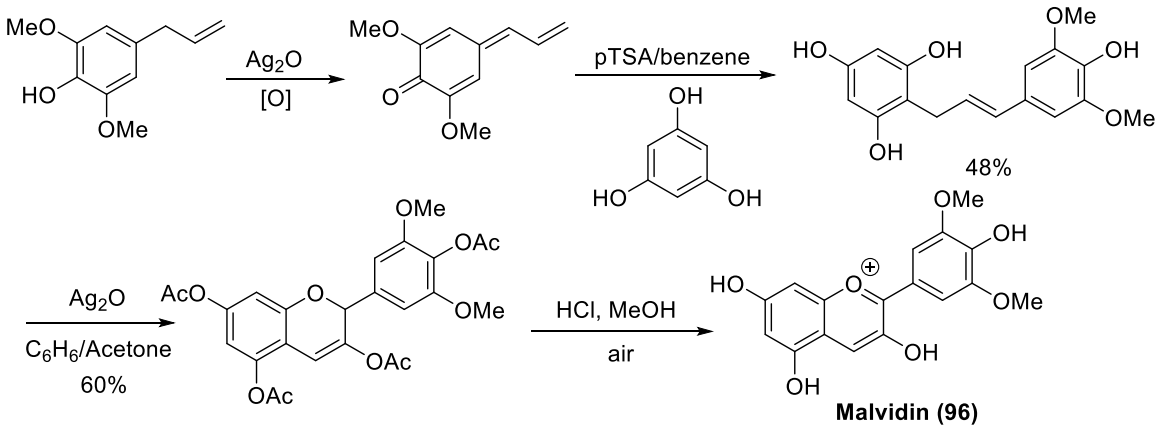


b. 1,3-diarylpropenes in the synthesis of flav-3-enes by DDQ promoted cyclisation

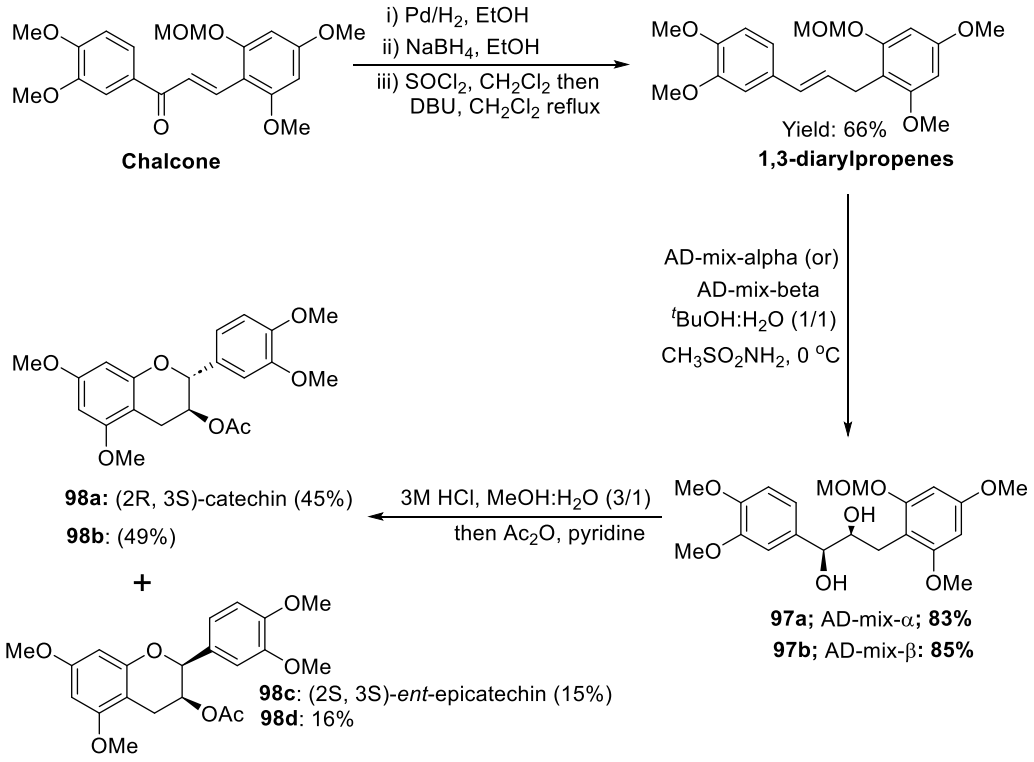


95a; $R^1 = R^2 = R^3 = R^4 = H$;
95b; $R^1 = R^3 = R^4 = H$, $R^2 = OMe$;
95c; $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = Cin$;
95d; $R^1 = OMe$, $R^2 = R^3 = R^4 = H$;
95e; $R^1 = R^3 = OMe$, $R^2 = R^4 = H$;
95f; $R^1 = OH$, $R^2 = R^3 = R^4 = H$

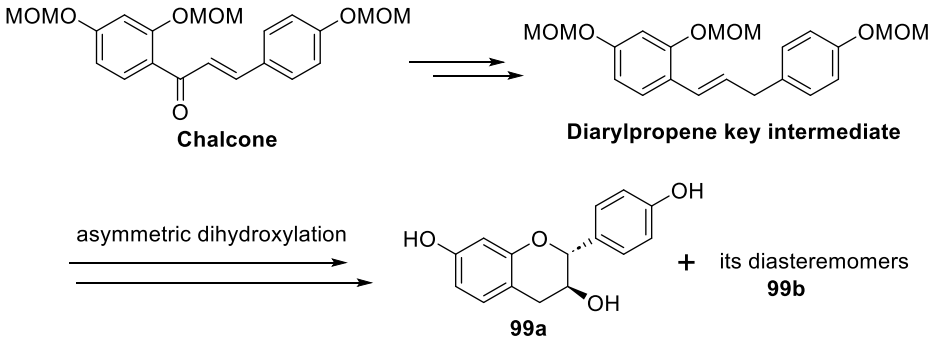
c. 1,3-diarylpropenes in the synthesis of naturally occurring anthocyanidin, a type of plant pigment malvidin



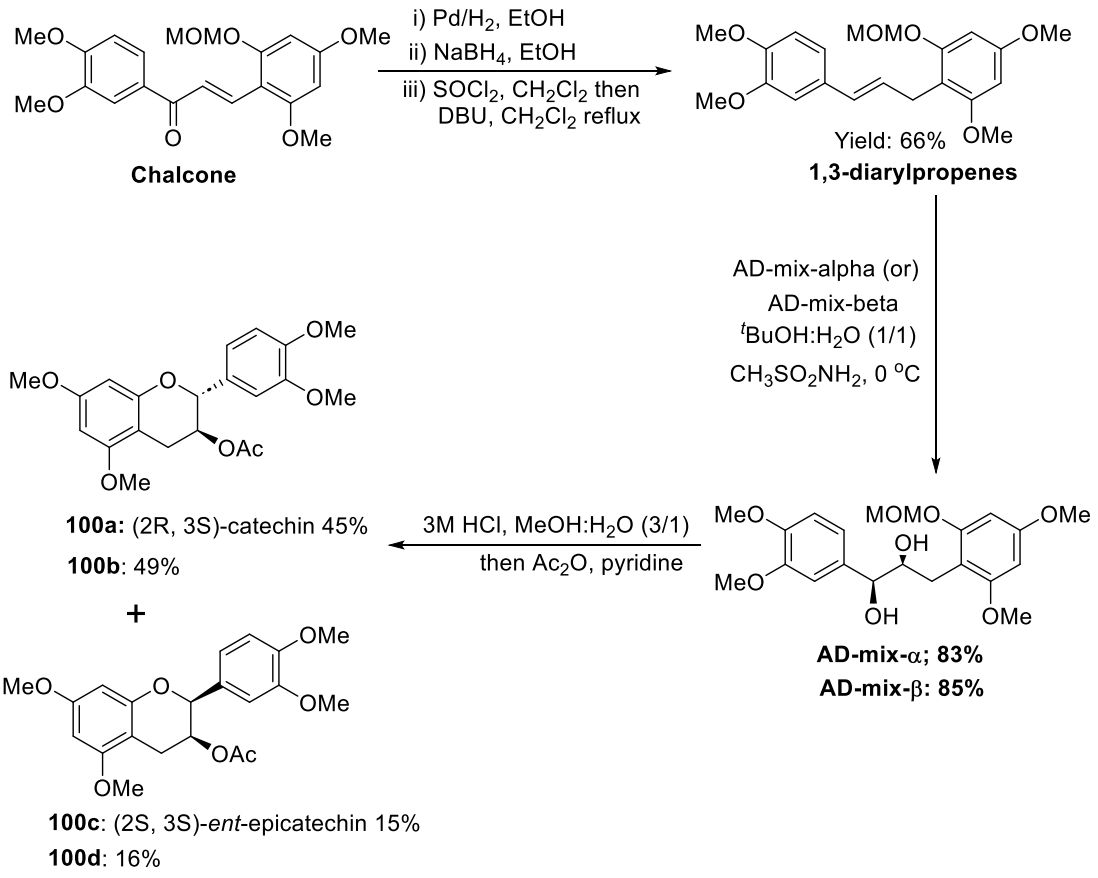
d. 1,3-diarylpropenes in the enantioselective synthesis of four catechin diastereomer derivatives



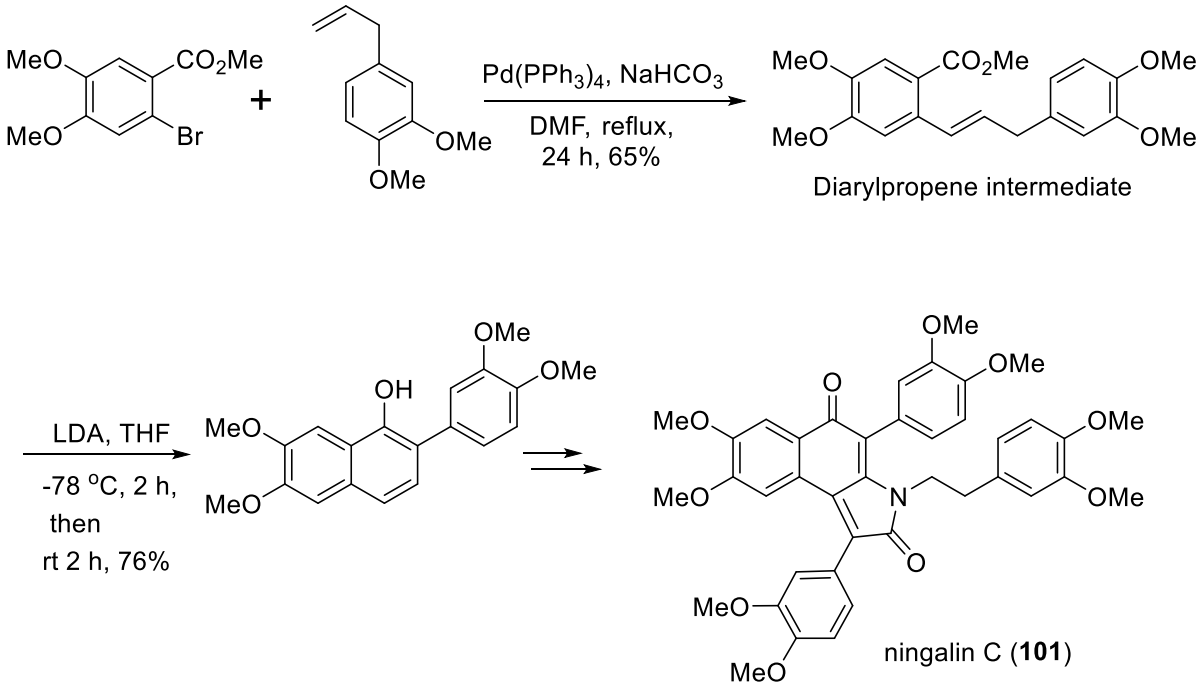
e. 1,3-diarylpropenes in the stereoselective synthesis of guibourtinidol



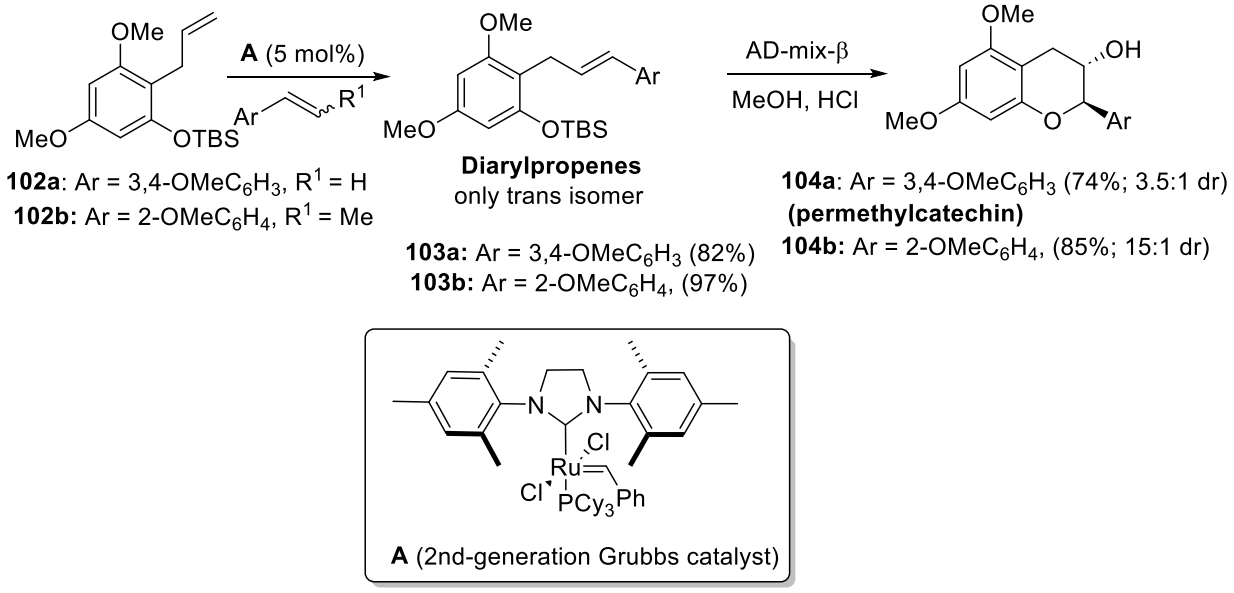
f. 1,3-diarylpropenes in the enantioselective synthesis of four catechin diastereomer derivatives



g. 1,3-diarylpropenes in the synthesis of anti-cancer pyrrole alkaloid Ningalin C



h. 1,3-diarylpropenes cross metathesis route to synthesis of 3-flavanols

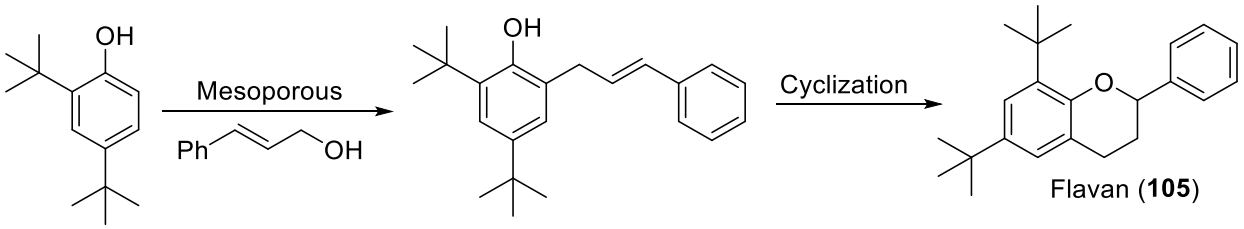


102a: Ar = 3,4-$OMeC_6H_3$, R^1 = H
102b: Ar = 2-$OMeC_6H_4$, R^1 = Me

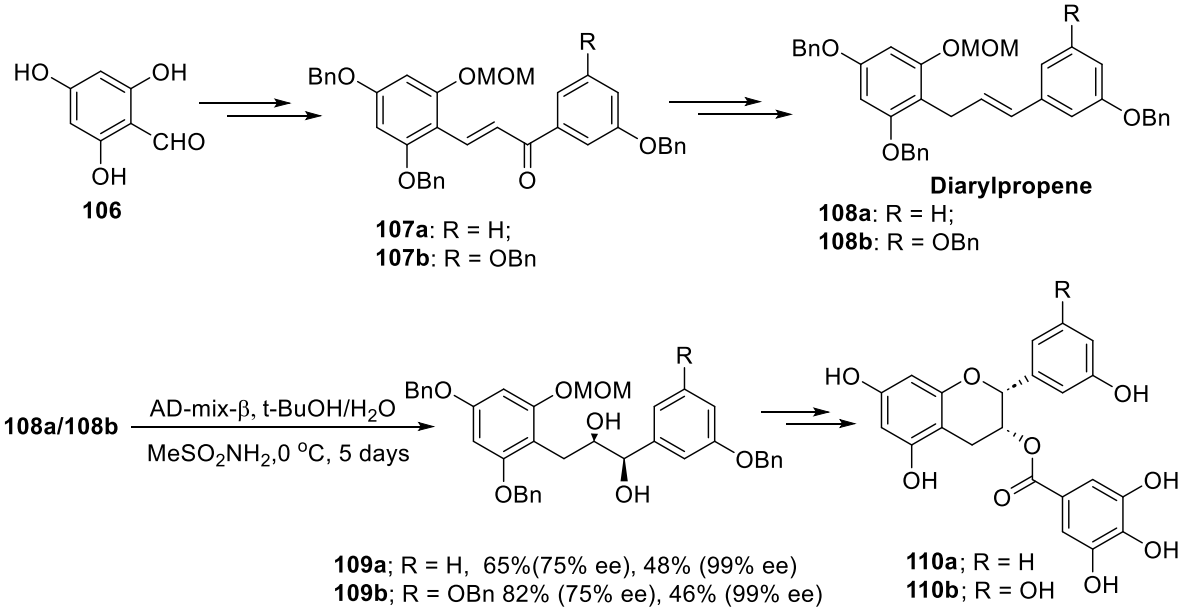
103a: Ar = 3,4-$OMeC_6H_3$ (82%)
103b: Ar = 2-$OMeC_6H_4$, (97%)

104a: Ar = 3,4-$OMeC_6H_3$ (74%; 3.5:1 dr)
(permethylcatechin)
104b: Ar = 2-$OMeC_6H_4$, (85%; 15:1 dr)

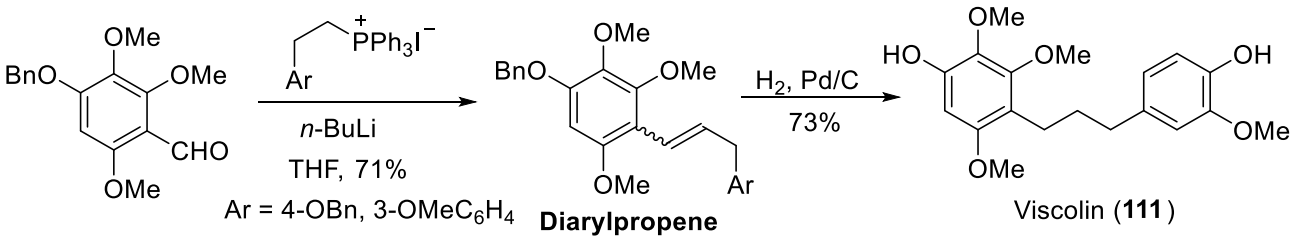
i. 1,3-diarylpropenes in the synthesis of Flavan's



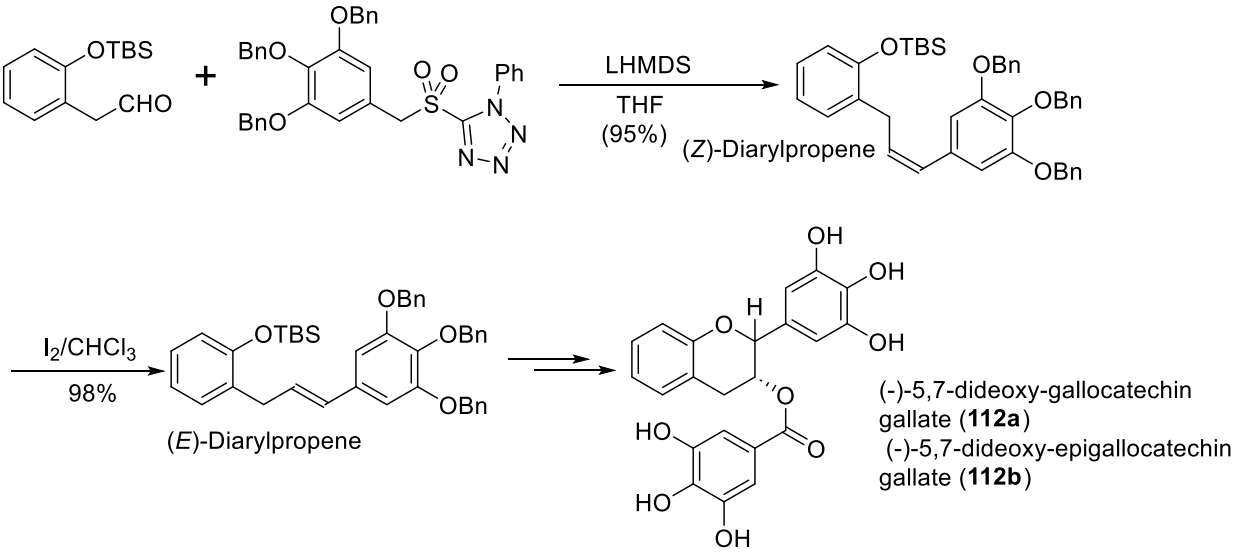
j. 1,3-diarylpropenes synthesis of two enantiomerically pure B-ring modified analogues of (–)-epicatechin gallate



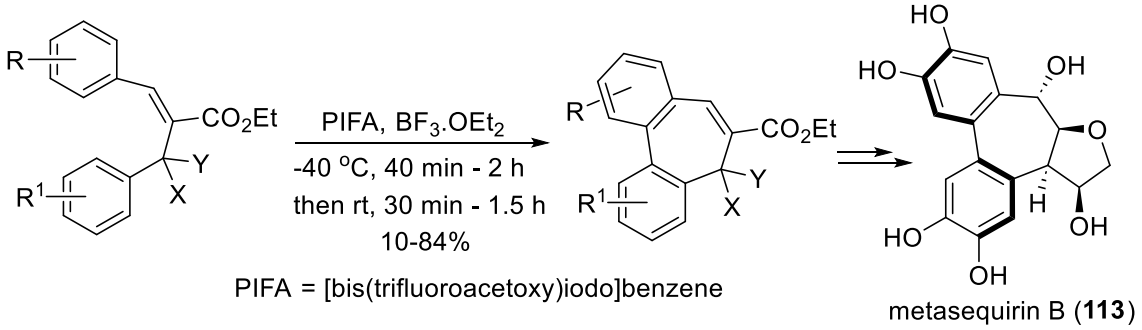
k. 1,3-diarylpropenes synthesis of anti-inflammatory 1,3-diphenylpropane Viscolin



l. 1,3-diarylpropenes in the synthesis of gallocatechin-3-gallate derivatives



m. 1,3-diarylpropenes the synthesis of a central intermediate for natural product Metasequirin-B



Scheme 8. Applications of 1,3-diarylpropenes in the synthesis of bioactive natural products (a-m)

7. Biological Importance of 1,3-Diarylpropenes

1,3-Diarylpropenes are a class of compounds with notable pharmacological and therapeutic significance due to their diverse biological activities which includes antimicrobial activity, anti-cancer activity, anti-inflammatory activity, anti-malarial activity etc. The 1,3-diarylpropene obtusastyrene exhibits microbiocidal and algicidal properties at low concentrations (10-25 ppm), aiding Dalbergia retusa in resisting marine boring organisms.[93-102] Additionally, compounds like cinnamyl methoxy catechol and obtusaquinone, along with their synthetic analogs, show effectiveness as marine borer larvicides.[93-102] 4,6-Di-tert-butyl-2-cinnamylphenol is

effective in controlling mosquito populations by inhibiting larval growth[103], while alkyl ethers of methylenedioxy analogs of obtusastyrene disrupt insect reproduction.[103]

Obtusastyrene also demonstrates potent antimicrobial activity against gram-positive bacteria, yeasts, and molds, with minimum inhibitory concentrations (MICs) ranging from 12-25 µg/mL for bacteria and 12-100 µg/mL for fungi.[104] Cinnamyl pyrogallol exhibits the strongest antifungal activity among related compounds, although its efficacy diminishes over time, while cinnamylphloroglucinol shows moderate antifungal activity [105]. Obtusastyrene and obtusaquinone are effective against brown-rot fungi, controlling decay at concentrations of 3% and 3.5%, respectively.[106]

In anti-inflammatory research, synthesized 1,3-diarylpropene analogs have displayed significant anti-inflammatory properties, as measured by the rat paw edema assay.[107] However, their analgesic activity varies independently of their potency on the EP3 receptor, nor is it related to their plasma concentration.[107]

Prenylated cinnamyl phenols exhibit promising chemo-preventive effects in mouse skin tumor models.[108-109] Eugenol template-based 1,3-diarylpropenes show significant anticancer activity by inducing apoptosis and causing cell cycle arrest at the G2/M phase.[112] Bi-aryl methyl eugenol analogs have demonstrated anti-invasive effects on breast cancer cells, and their activity is linked to changes in cell morphology rather than direct cytotoxicity.[110] Natural 1,3-diarylpropenes such as dalparvinene and dalberatins A-D significantly inhibit inflammatory-mediated nitric oxide production in macrophages, with IC_{50} values ranging from 4.05 to 16.76 µM.[111] Finally, human EP3 receptor ligands developed from this class of compounds have demonstrated affinities in the nanomolar range, further highlighting their potential for therapeutic applications.[112]

Conclusions

1,3-Diarylpropenes are a highly versatile class of compounds with significant potential in medicinal chemistry, characterized by their diverse biological activities, including antimicrobial, antifungal, anti-inflammatory, anticancer, and insecticidal properties. Their occurrence in both natural products and synthetic analogues underscores their adaptability and relevance in therapeutic development.

This review has focused on the collection of natural 1,3-diarylpropenes from different sources, detailing their sources of isolation and biological activities over the years, alongside the notable progress in their synthesis. Innovative methods such as allylation, selective de-functionalization, cross-coupling, and oxidative C-C bond formation have enhanced our ability to control their chemical structures, leading to the development of compounds with improved pharmacological profiles.

The exploration of their biological properties—from marine microbicides to EP3 receptor antagonists and cancer chemo preventive agents—highlights the broad spectrum of applications that 1,3-diarylpropenes offer. As research advances, the therapeutic promise of these compounds in areas such as anti-inflammatory, anticancer, and antimicrobial treatments remain robust. Future efforts should focus on translating these findings into clinical applications, emphasizing the optimization of pharmacokinetic and pharmacodynamic properties. Additionally, exploring novel derivatives and hybrid molecules could open new avenues for drug discovery. Overall, 1,3-diarylpropenes present a unique and promising platform for the development of next-generation therapeutics, with the potential to address unmet medical needs across a variety of diseases.

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Authors' Biographies

Dr. Lingaiah Maram, from Hyderabad, India, earned his Ph.D. in 2016 under the supervision of Dr. Biswanath Das at the Indian Institute of Science and Technology (IICT), Osmania University, Hyderabad, India. After completing his Ph.D., he worked as a postdoctoral fellow at the Okinawa Institute of Science and technology (OIST), Okinawa, Japan from 2016 to 2019. He currently holds the position of Staff Scientist in Elgendy lab in the Department of Anesthesiology at the Washington University School of Medicine in St. Louis. His research focuses on drug-discovery and medicinal chemistry to develop small molecules targeting nuclear hormone receptors, metabolic disorders, cancer, and neurodegenerative diseases.

Bahaa Elgendy, Ph.D., is a Professor of Medicinal Chemistry at the Department of Anesthesiology at Washington University School of Medicine, St. Louis. He earned his B.Sc. and M.Sc. degrees in Chemistry from Benha University, Egypt, followed by a Ph.D. from the University of Florida working with Prof. Alan R. Katritzky. He completed postdoctoral training at the Scripps Research Institute before joining academia. Prior to his current role, he held positions at Benha University, Egypt, and Saint Louis University School of Medicine, USA. Dr. Elgendy's research endeavors revolve around pioneering advancements in the development of small molecule modulators targeting various nuclear hormone receptors. His work holds significant promise for

therapeutic interventions spanning across cancer, fatty liver diseases, Alzheimer's disease, and pain management. He was awarded The Egyptian State Prize in Chemical Science and the Presidential Medal of Excellence (First Class) from the President of Egypt for outstanding contributions.