

Review

Catalytic methods for the synthesis of stilbenes with an emphasis on their phytoalexins

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Abstract

This review aims at summarizing the recent significant advances in catalytic methods available for the synthesis of stilbene and functionalized stilbenes with an emphasis on their phytoalexins. Most strategies developed so far involve palladium-mediated coupling reactions. Among them, the Heck and Suzuki reactions stand out for their synthetic versatility and efficiency, but the Stille and Negishi reactions have also found useful applications. Palladium also served as a catalyst to convert *Z*-stilbenes into the corresponding *E*-isomers. Other transition metal promoted stilbene syntheses include the McMurry coupling of aldehydes and ketones and alkene cross metathesis. Because non transition metal catalyzed syntheses of hydroxystilbenes continue to attract a lot of attention, significant recent developments in this area are also reported.

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1. Introduction

Although stilbene itself (1,2-diphenylethene) is not a natural product, a large number of its derivatives have been

isolated from various plant species. Among these naturally occurring stilbenoid compounds, polyhydroxystilbenes and their glucosides are currently attracting considerable attention, because of their wide range of biological activities and potential therapeutic value. These molecules are found mainly among members of the vegetable kingdom classified as spermatophytes, but also in bryophytes and pteridophytes [1]. Numerous structural variations have been identified,

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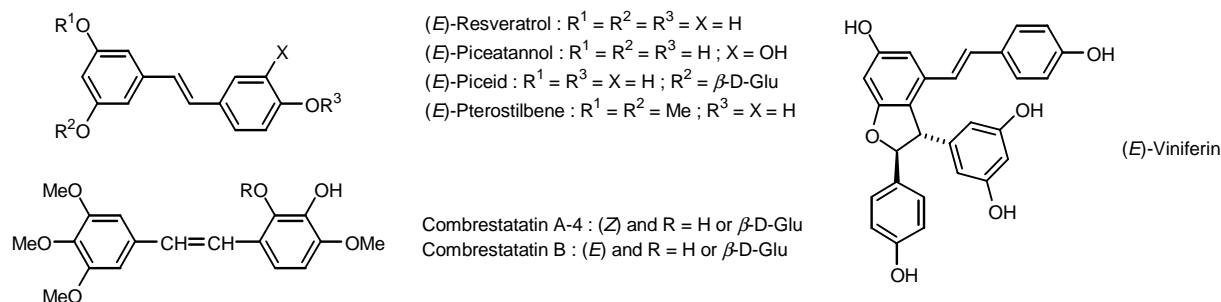


Fig. 1. Structures of some important phytoalexins.

depending on the configuration of the carbon–carbon double bond, the number of hydroxyl functionalities, and the extent to which the phenol groups are substituted with sugars, methoxy, or other alkoxy groups.

Frequently encountered natural hydroxylated stilbenes include inter alia resveratrol (*E*-3,5,4'-trihydroxystilbene), which has been identified in more than 70 different plant species, pterostilbene (a dimethylated derivative of resveratrol), piceid (the 3- β -D-glucoside of resveratrol), and viniferins, which are resveratrol oligomers (see Fig. 1). The utmost importance of viniferins and of stilbene derivatives in phytochemistry lies in their property of acting as “plant antibiotics” by inhibiting the growth of pathogenic fungi. As such, they are classified as phytoalexins (from the Greek $\alpha\lambda\epsilon\xi\omega$, $\alpha\lambda\epsilon\xi\epsilon\upsilon\nu$, to repel, to ward off). Phytoalexins are defense compounds that plants, notably grapevines, synthesize in response to pathogen agents and abiotic stress. Among them, resveratrol and its glucoside have been identified as two of the major active compounds of stilbene phytoalexins. Their structures, together with some other important phytoalexins, are shown in Fig. 1.

The biological activity of natural phenolic compounds has been well established over the past decades through a number of physiological and pathological studies. Most of them concerned molecules possessing a flavonoid structure, but the stilbenoid derivatives were also investigated. Resveratrol is presumed to be beneficial for the human health and is a constituent of traditional oriental medicines. In the western world, the interest in stilbene derivatives present in grapevines was stimulated when epidemiological studies showed an inverse correlation between red wine consumption and the incidence of cardiovascular diseases, the so-called “French paradox” [2]. Resveratrol is thought to be responsible for this Mediterranean diet effect, where high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart diseases and cancers. More recently, resveratrol has also drawn a lot of publicity, because of its various therapeutic properties, which include anti-oxidative and antimutagenic activities [3]. Resveratrol is an inhibitor of the dioxygenase activity of lipooxygenase and protects against platelet aggregation [4,5]. Its field of application also extends to antifungal, cytotoxic, anti-inflammatory, antiviral, and antibacterial uses [6,7].

Although there are fewer studies about related molecules, it seems that the glucoside derivatives are more efficiently absorbed than the aglycon *trans*-resveratrol itself. Indeed, *trans*-piceid also displays highly interesting physiological properties [8].

Given the minute amounts of resveratrol and its analogues present in plants, it comes as no surprise that other sources of supply than nature are needed in order to satisfy the increasing demand for stilbene derivatives. Reliable and efficient synthetic methods are therefore highly desirable. The first laboratory preparation of resveratrol dates back to 1941 [9]. Since then, organic synthesis has attained an unprecedented sophistication due in large measure to the influx of recent, rapidly evolving organometallic methodologies. With the advent and continuing refinement of transition metal assisted organic synthesis, a number of new reactions have not only expanded the scope of fundamental transformations available to chemists, but also imparted greater latitude to their practical application.

The search for selective carbon–carbon coupling reactions has commanded the attention of organic chemists from the very origin of the science. In particular, the problem of C=C double bond formation remained an extremely sensitive issue until the discovery of the Wittig reaction in 1953. Yet, however useful this reaction and its variations are, they remain stoichiometric in essence and limited to molecules containing a carbonyl functionality. The first significant catalytic breakthrough in the field was the discovery in the 1970s of the reductive dimerization of C=O double bonds of aldehydes and ketones into olefins upon treatment with low-valent titanium species (the McMurry reaction, see Section 3.2) [10]. Since these early days, several catalytic approaches have been proposed and investigated for the synthesis of stilbenoid compounds. Among them, methods based on the Heck and Suzuki reactions stand out for their synthetic versatility and efficiency. Recent progress in olefin metathesis, and more specifically the emergence of new catalysts for efficient and selective cross metathesis, also paves the way to future exciting developments.

This review aims at summarizing the recent significant advances in catalytic methods available for the synthesis of stilbene and functionalized stilbenes with an emphasis on their phytoalexins. To the best of our knowledge, the last surveys

related to this topic date back to 1983 [11] and 1985 [12], respectively, although the latter article was exclusively devoted to “classical” synthetic approaches (Wittig-type chemistry) and did not include metal-catalyzed reactions. In this rapidly expanding field, palladium-mediated coupling reactions have been the most widely used so far. Accordingly, they are reviewed first in this article. Other transition metal promoted stilbene syntheses are reported next, before addressing the point of stilbene isomerization. Because non transition metal catalyzed syntheses of hydroxystilbenes continue to attract a lot of attention, significant recent developments in this area are also included at the end of this contribution.

2. Palladium-catalyzed syntheses of stilbenes

2.1. The Heck reaction

The palladium-catalyzed olefination of aryl halides, generally known as the Heck reaction (or Mizoroki-Heck reaction), is a well-established method for effecting C–C coupling reactions. Because it is remarkably chemoselective and amenable to a large variety of starting materials, it has become one of the true power tools of contemporary organic synthesis [13–16]. The reaction is catalyzed by either Pd(0) or Pd(II) complexes in solution, usually in the presence of a stoichiometric amount of a base. A coordinating ligand, most often a phosphine, is added. According to this approach, stilbenes may be obtained by coupling a styrene with an aryl derivative Ar–X. Three Heck products may be formed: the *cis*- and *trans*-stilbenes, and 1,1-diphenylethylene (Scheme 1). The regioselectivity of the addition can be controlled by a careful choice of the reaction conditions [17].

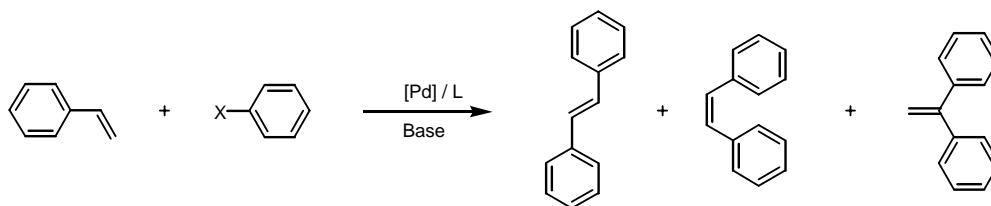
The Heck reaction is now so widely used that writing a comprehensive survey covering its different applications looks like a hopeless task. An excellent review discussing

the mechanistic aspects, the intriguing flexibility and adaptability, as well as the unpredictability of palladium-catalyzed arylations and vinylations of olefins was published in 2000 [13]. To cite but a few recent results in the field of styrene synthesis, the Heck reaction provided a ready access to oligomeric styrylpyrroles [18], oligo(phenylenevinylene) derivatives [19], stilbenoid dendrimers [20], and new non linear optical electron donor–acceptor substituted stilbene derivatives [21]. It also served as the key step in the synthesis of various polyhydroxylated stilbenes, including resveratrol (Scheme 2) [22] and related highly oxygenated stilbenoid dimers [23].

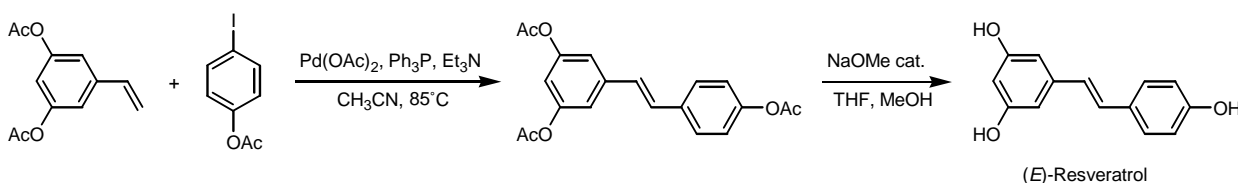
2.1.1. Aryl halides as electrophiles

Industrial applications of the Heck reaction are rare because the reactivity of aryl halides decreases dramatically in the order $\text{ArI} > \text{ArBr} \gg \text{ArCl}$, which means that the cheap chlorides and even some bromides do not afford sufficiently high yields, turnover numbers (TONs), and selectivities. A lot of efforts has been put recently into improving the catalyst activity in order to overcome these limitations. For instance, Beller and Zapf have demonstrated that the coupling of styrene with chloro- and bromoarenes proceeded smoothly in the presence of palladium acetate $\text{Pd}(\text{OAc})_2$ and phosphites $\text{P}(\text{OR})_3$ as ligands (Scheme 3) [24].

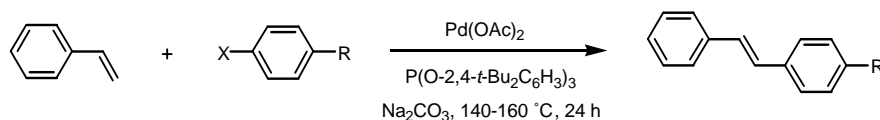
Another study by Reetz et al. revealed that the use of simple palladium salts in the presence of tetraphenylphosphonium chloride, Ph_4PCl , instead of phosphine or phosphite ligands led to highly active catalytic systems, even with chloroarenes. Optimization of the reaction between chlorobenzene and styrene showed that a $\text{Ph}_4\text{PCl}/\text{Pd}$ molar ratio of 6 led to the best results. Sodium acetate was suitable as a base and *N*-methylpyrrolidinone (NMP) served as solvent. Interestingly, the regioselectivity for the *E*-1,2-stilbene was enhanced upon addition of a small amount of *N,N*-dimethylglycine (DMG), as the yield of the 1,1-isomer decreased (Scheme 4) [25].



Scheme 1.

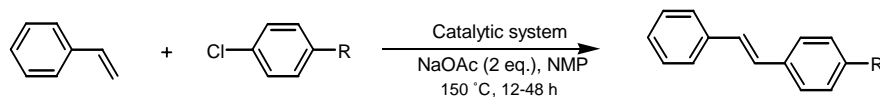


Scheme 2.



| X | R | Conditions | Yield (%) | TON |
|----|-------------------|-------------------------------------|-----------|------|
| Cl | 4-CF ₃ | Pd/P/Bu ₄ NBr = 1:10:200 | 84 | 840 |
| Br | 4-OMe | Pd/P = 1:10 | 100 | 1000 |

Scheme 3.



| R | Catalytic system (2 mol%) | DMG (mol%) | Conversion (%) | Selectivity (<i>trans</i> : <i>cis</i> : 1,1-regioisomer) |
|-----|---|------------|----------------|--|
| H | [Pd(CH ₃ CN) ₂ Cl ₂] · 6 Ph ₄ PCl | 12 | 96 | 96:1:3 |
| CHO | [Pd(CH ₃ CN) ₂ Cl ₂] · 6 Ph ₄ PCl ^a | 0.6 | 98 | 98:<1:2 |
| H | Pd(OAc) ₂ · 6 Ph ₄ PCl | 12 | 79 | 97:1:2 |
| H | [[Pd(-Cl)(PPh ₃)(Ph)] ₂] · 6 Ph ₄ PCl | – | 86 | 85:1:14 |
| H | [[Pd(-Cl)(PPh ₃)(Ph)] ₂] · 6 Ph ₄ PCl | 12 | 80 | 97:1:2 |

^a 0.1 mol %

Scheme 4.

Complexes of Pd(II) with chelating phosphines are also efficient catalysts for Heck reactions of standard aryl bromides and iodides with styrene. Yields are excellent and turnover numbers very high. It is, however, preferable to use preformed complexes rather than attempting to generate active species in situ from a Pd(0) or Pd(II) source and a diphosphine [26]. Further improvement of catalyst efficiency resulted from the development of new palladium pincer complexes (Fig. 2). Andersson et al. have synthesized a bis-chelated, air-stable aliphatic PC(sp³)P pincer Pd(II) complex (**1**), which displayed a high catalytic activity for the Heck coupling reaction between styrene and iodobenzene (yield = 95%, TON = 190–200) [27]. The stabilizing effects imposed by chelation and/or steric shielding of the metal center were held responsible for the prolonged catalyst stability after long reaction times at high temperature. Good results were also obtained with the phosphinito PC(sp²)P pincer palladium complex [PdCl{C₆H₃(OPPr^{*i*})₂-2,6}] (**2**), which catalyzed the olefination of a broad scope of aryl

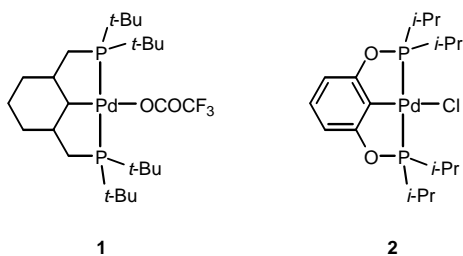
**1****2**

Fig. 2. Palladium PCP pincer catalysts for stilbene synthesis via Heck reactions.

chlorides in high yield (81–99%) and *trans*-selectivity [28].

The most severe drawbacks associated with the Heck reaction result from the oxidative degradation and other side reactions observed with phosphines, hence the importance of investigating non phosphine-based complexes as catalyst precursors. Indeed, nitrogen-, oxygen-, and sulfur-containing palladacycles can provide excellent alternatives to their phosphorus-based counterparts for the catalytic coupling of aryl halides with styrene. For instance, good results were obtained with *ortho*-metallated oxime and amine palladacycles **3** and **4** bearing a saturated *N*-heterocyclic carbene ligand (Fig. 3). These metal complexes displayed a very high thermal stability and were insensitive toward air and moisture. A small amount of catalyst precursor (0.002–0.02 mol%) was sufficient to obtain an excellent activity and high TONs for the reaction of aryl bromides Ar–Br (Ar = C₆H₅, C₁₀H₇, 4-MeCOC₆H₄, 4-CNC₆H₄) with styrene in the presence of sodium acetate

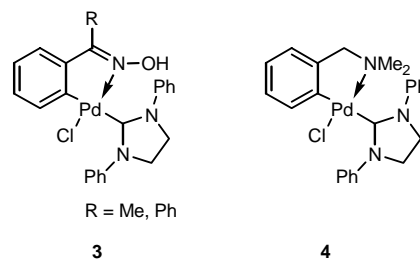
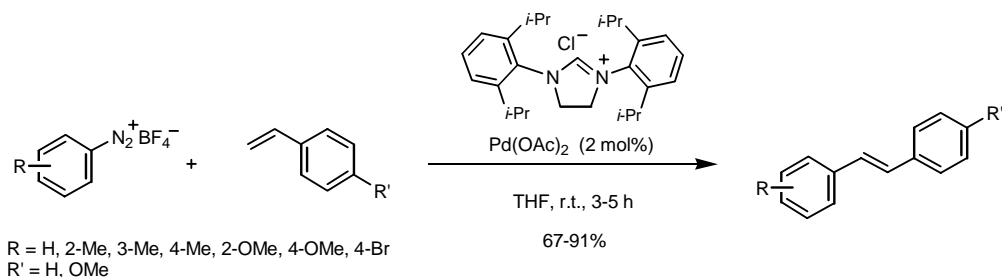
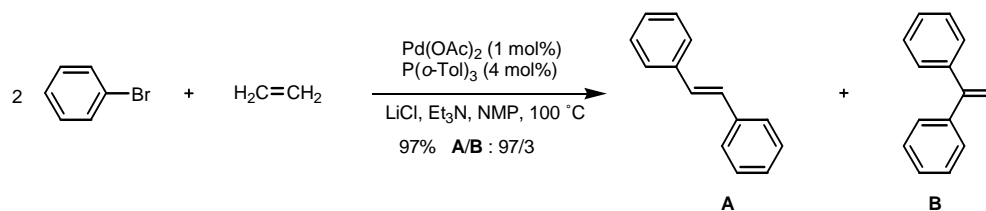
**3****4**

Fig. 3. Non phosphine-based palladium catalysts for stilbene synthesis via Heck reactions.



Scheme 5.



Scheme 6.

as a base and NMP as solvent. Yields were lower with chloroarenes (34–76%, TON = 1705–4111), although the substrates investigated possessed an activating *para*-acetyl or *para*-cyano group on their aromatic ring [29] (see also ref. [30,31]).

Palladium(II) supported on hydrotalcite was an efficient and reusable catalyst for heterogeneous Heck reactions between substituted aryl halides and styrene. Stilbene derivatives were isolated in moderate to good yields (48–87%) and the catalyst could be recycled without any treatment [32]. The Heck arylation of styrene was also carried out in the absence of any ligand under normal atmosphere using colloidal palladium(0) generated *in situ* from PdCl₂ and sodium formate as reducing agent [33].

2.1.2. Aryldiazonium salts as electrophiles

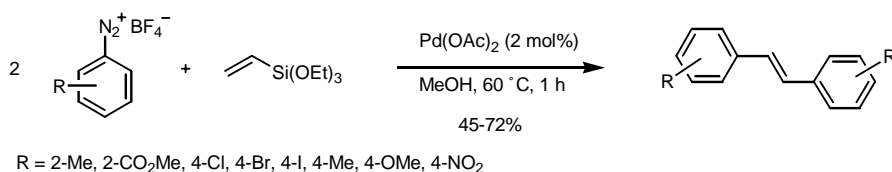
Besides halides and triflates, other electrophiles have been tested in Heck-type reactions. Among them, aryl diazonium salts are even more reactive than aryl iodides and do not require the presence of a base nor phosphine ligands. Indeed, coupling reactions with diazonium salts are fast and proceed smoothly, but usually require a relatively high load of palladium (1–2 mol%). For instance, a 1:1 mixture of palladium acetate and an imidazolium salt (2 mol% each) readily arylated olefinic substrates in high yield at room temperature (Scheme 5). The acetate anion presumably served as a base to produce the active palladium catalyst in this system. It is

noteworthy that the diazonium salts could be generated *in situ* from the corresponding aniline precursors. However, the coupling products were obtained in lower yield (17–62%) under these conditions than with the preformed diazonium electrophiles [31].

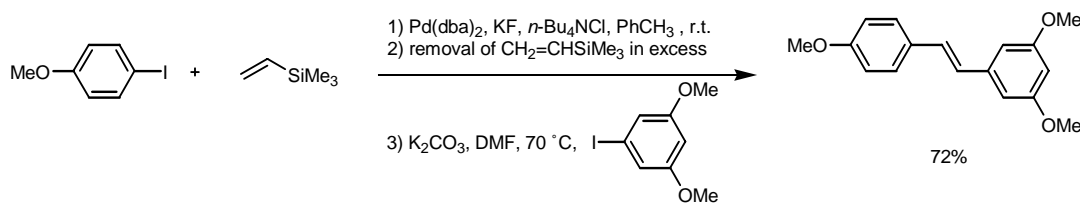
2.1.3. Heck reactions with ethene

Symmetrical *trans*-stilbenes may be formed by a two-fold coupling of ethene with two equivalents of bromoarene [34,35]. The ratio of stilbene to by-products (styrene and 1,1-substituted adducts) depends on the solvent, the ethylene pressure, and the bromoarene concentration. Addition of lithium chloride increases the regioselectivity. This approach also leads to the formation of a small amount of oligomers and polymers of poly(*p*-phenylenevinylene). The best conditions for the palladium-catalyzed coupling of bromobenzene with ethylene are summarized in Scheme 6 [34].

Since the above procedure involves the introduction of ethylene in a 1:2 stoichiometric ratio compared to the halogenoarene, it is necessary to control precisely the amount of gas used. This usually implies a complex experimental set-up. To circumvent this constraint, liquid vinyltrialkylsilanes and vinyltrialkoxysilanes were used as more convenient to handle ethylene substitutes. For example, a double Heck reaction of aryl diazonium salts with vinyltriethoxysilane led to symmetric *trans*-stilbene derivatives in moderate to good yields (Scheme 7) [36].



Scheme 7.



Scheme 8.

In 2002, Jeffery and Ferber reported a highly selective one-flask synthetic procedure for the construction of symmetrical and unsymmetrical *trans*-stilbene derivatives based on two sequential Heck-type reactions using vinyltrimethylsilane as ethene equivalent. This strategy is illustrated in Scheme 8 for the synthesis of methylated resveratrol. Treatment of 4-methoxyiodobenzene with vinyltrimethylsilane under arylation-desilylation conditions produced 4-methoxystyrene, which was arylated by 3,5-dimethoxyiodobenzene in the same flask. Demethylation of the trimethoxystilbene by boron trichloride/tetra-*n*-butylammonium iodide in a subsequent step cleanly afforded resveratrol in 61% overall yield [37].

2.1.4. Decarbonylative Heck reactions

The decarbonylative Heck reaction is known since the beginning of the eighties. Spencer has described the palladium-catalyzed arylation of alkenes with aroyl chlorides in the presence of a tertiary amine [38,39]. He has also applied this method to the arylation of ethylene into styrene and stilbene derivatives, the ratio of styrene to stilbene being dependent on the ethylene pressure [40]. More recently, this coupling method was employed for the synthesis of the phytoalexin resveratrol. 3,5-Diacetoxybenzoic acid chloride was coupled with 4-acetoxystyrene in the presence of palladium acetate and *N,N'*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride to give resveratrol triacetate in 73% yield (Scheme 9). The nature of the added base was critical for the success of the transformation. Non-coordinating amines such as *N*-ethylmorpholine (NEM) and *N,N*-dimethylbenzylamine proved optimal. Resveratrol itself was obtained in pure form from the triester by basic hydrolysis in THF followed by acidification. An overall 53% yield was achieved

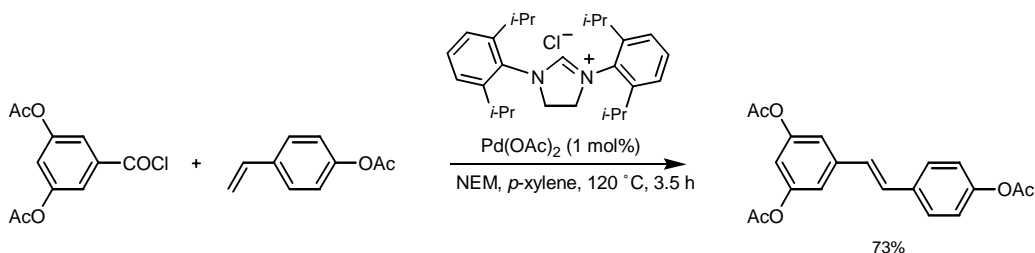
starting from commercially available α -resorcylic acid (3,5-dihydroxybenzoic acid) [41,42].

2.2. The Suzuki reaction

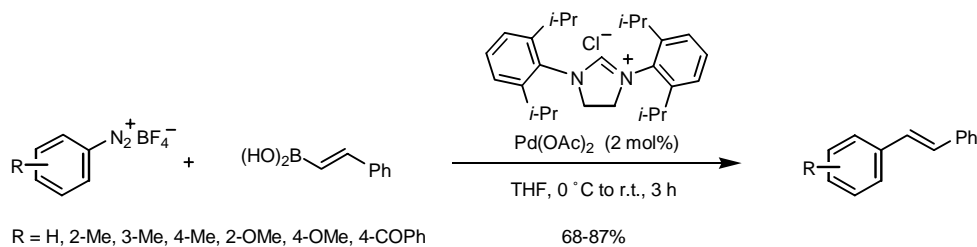
In addition to conventional Heck reactions of unsaturated compounds with aryl diazonium salts or organic halides as electrophiles, the use of nucleophilic organoboron species has attracted substantial attention for the synthesis of stilbene derivatives. The palladium cross coupling of boranes or boronic acids and esters with organic halides or diazonium salts (known as the Suzuki reaction) is usually highly selective and tolerant of functional groups on either coupling partners. Reagents are easy to prepare and largely insensitive toward water.

The Suzuki coupling between a 1,1-bromofluorostyrene and a phenylboronic acid served as a general method for the synthesis of polyhydroxylated stilbenes monofluorinated on the central double bond [43]. Cross-couplings between styrylboronic acid and aryl diazonium salts using a catalytic system based on palladium(II) acetate together with an imidazolium ligand precursor also led to the formation of various stilbene derivatives. The reactions proceeded in the absence of any added base under mild conditions and with high yields (68–87%) (Scheme 10). Diazonium ions could be generated in situ without significant detrimental consequences, provided that reaction times were extended [30].

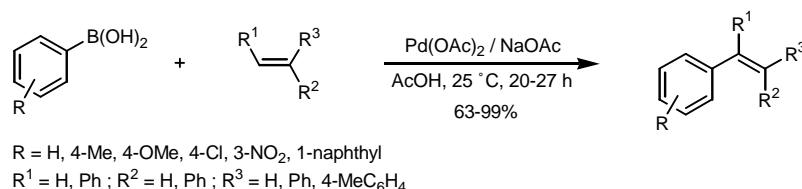
Palladium-catalyzed cross coupling of arylboronic acids with alkenes in acetic acid at 25 °C afforded stilbene derivatives in satisfactory to good yields (63–99%) (Scheme 11). Experimental evidences indicated that the reaction most likely occurred via oxidative addition of Pd(0) to a carbon–boron bond [44]. Conversely, Pd(II)-promoted catalytic pathways took over when an appropriate oxidant such



Scheme 9.



Scheme 10.



Scheme 11.

as copper(II) acetate [45] or molecular oxygen [46] was introduced in the reaction medium (Scheme 12).

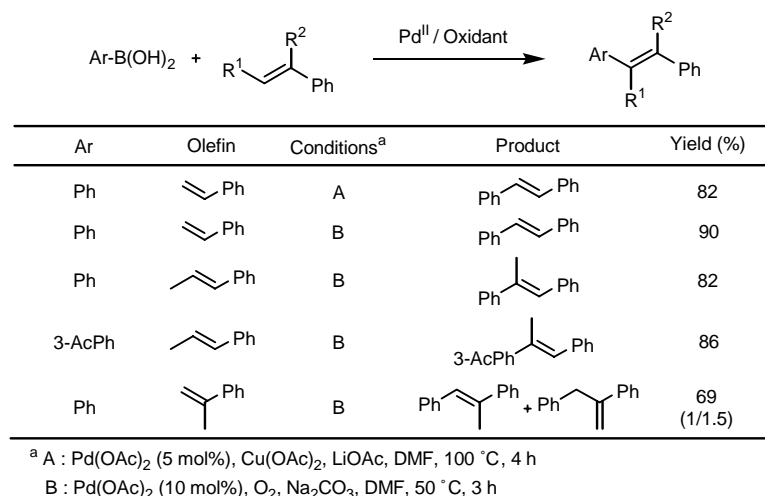
2.3. The Stille reaction

The palladium-catalyzed coupling of organotin reagents with organic electrophiles such as aryl and vinyl halides or triflates is known as the Stille reaction. In comparison to the Suzuki coupling, the Stille reaction does not require the addition of a base and is applicable to a wider spectrum of electrophiles, including saturated aliphatic halides and some alcohol derivatives. However, although organostannanes are extremely valuable synthetic intermediates because of their compatibility with most functional groups and the mildness of their reaction conditions, hardly any syntheses of stilbene derivatives via Stille vinylation were reported in the literature.

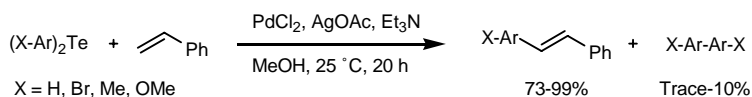
α -Styryltrimethyltin was reacted with a number of aryl-diazonium salts to give the 1,2-disubstituted (*cine*) products in moderate to poor yields [47]. The same reaction carried out with halopyridines yielded mixtures of *cine* and *ipso* (1,1-disubstituted) isomers, with electron-withdrawing substituents shifting the ratio toward formation of the *ipso* isomers [48]. Organic tellurides reacted more efficiently with various alkenes in the presence of Pd(II) salts to give the corresponding substituted stilbenes. The reaction was first carried out using a stoichiometric amount of palladium acetate or chloride together with triethylamine, but it became catalytic when an oxidant (silver acetate) was added to the system (Scheme 13) [49].

2.4. The Negishi reaction

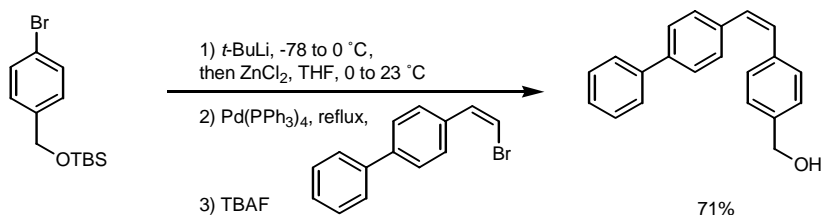
It is noteworthy that the majority of methods described so far allowed the formation of either mixtures of *E*-



Scheme 12.



Scheme 13.



Scheme 14.

and *Z*-stilbenoids or of pure *E*-isomers. In order to obtain a *Z*-configuration of the double bond in diarylalkenes, Bosanac and Wilcox have applied a variant of Negishi's process. In this palladium-catalyzed reaction, an organozinc reagent was coupled with an organohalide to yield the *Z*-adduct, as illustrated in Scheme 14. Deprotection of the *t*-butyldimethylsilyl-capped benzyl alcohol was carried out with tetra-*n*-butylammonium fluoride (TBAF) to afford (*Z*)-4-hydroxymethyl-4'-phenylstilbene in 71% overall yield. Incidentally, this alcohol was designed to act as an ancillary group for the automated synthesis of β -ketoesters through an ingenious isomerization/precipitation strategy, the *Z*-isomer being soluble in the reaction medium, whereas the *E*-isomer is insoluble, allowing reaction products to be isolated by simple filtration [50].

3. Coupling reactions with non palladium-based metal catalysts

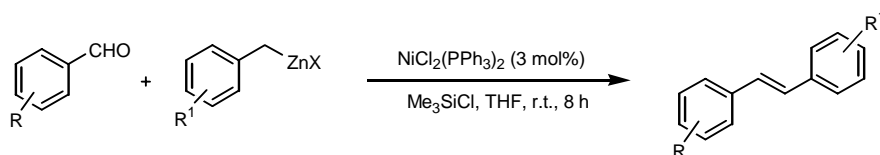
3.1. Heck-type reactions

Other metals than palladium were investigated as catalysts for the vinylation of aryl halides in Heck-type reactions. The platinum complex Pt(COD)Cl₂ (COD is

1,5-cyclooctadiene) allowed the formation of stilbene via the coupling of iodobenzene with styrene, although the conversion and the selectivity were not impressive (27% yield of *trans*-stilbene) [51]. The efficiency of two copper(I) catalysts, viz. CuBr and CuI, was somewhat better (46–80% yield) [52], but superior results were obtained with triphenylphosphino complexes of cobalt, rhodium, and iridium. Indeed, all three CoCl(PPh₃)₃, RhCl(PPh₃)₃, and IrCl(CO)(PPh₃)₂ species afforded stilbene in the 80% yield range after 24 h of reaction at 110 °C [53]. Heterogeneous catalysts based on cobalt, nickel, or copper were also investigated. They were prepared by reducing the corresponding metal halides onto alumina or HY zeolite and gave moderate to good yields (50–85%) of 4-substituted stilbenes [54].

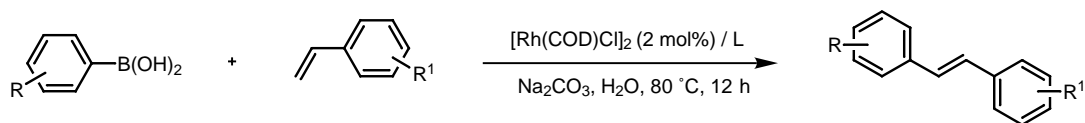
In 2002, a convenient method for the efficient and highly stereoselective synthesis of *E*-alkenes from the corresponding aldehydes and functionalized organozinc reagents in the presence of a silylating agent and a catalytic amount of NiCl₂(PPh₃)₂ was devised. For the benzylic zinc halides, reactions could be carried out at room temperature and afforded the corresponding *E*-stilbenes in good yields after 8 h at room temperature (63–92%, Scheme 15) [55].

The rhodium-catalyzed addition of various boronic acids to styrene took place in organoaqueous media with high



| R | R ¹ | X | Yield (%) |
|-------|----------------|----|-----------|
| H | H | Cl | 88 |
| 2-OMe | H | Cl | 79 |
| 4-OH | H | Cl | 78 |
| 4-Cl | H | Br | 87 |
| H | 3-Cl | Br | 81 |
| H | 3-Br | Br | 63 |
| H | 4-Br | Br | 85 |
| 4-OMe | H | Cl | 92 |

Scheme 15.



| R | R' | L | Phase transfert | Yield (%) |
|-------|----|-----------------|-----------------|-----------|
| H | H | / | / | 99 |
| H | H | <i>m</i> -TPPTC | / | 79 |
| H | H | TPPTS | / | 31 |
| H | H | TPPDS | / | 77 |
| H | H | TPPDS | SDS | 80 |
| 4-OMe | H | / | / | 84 |
| 4-OMe | H | <i>m</i> -TPPTC | / | 71 |
| 4-OMe | H | TPPTS | / | 32 |
| 4-OMe | H | TPPDS | / | 20 |
| 4-OMe | H | TPPDS | SDS | 85 |

| R | R' | L | Phase transfert | Yield (%) |
|------------|-------|-----------------|-----------------|-----------|
| 4-Br | H | / | / | 99 |
| 4-Br | H | <i>m</i> -TPPTC | / | 96 |
| 4-Br | H | TPPTS | / | 24 |
| 4-OAc | H | TPPDS | / | 20 |
| 4-OAc | H | TPPDS | SDS | 73 |
| 3-I | H | TPPDS | SDS | 72 |
| 2-Me | H | TPPDS | SDS | 86 |
| 2-naphthyl | H | TPPDS | SDS | 67 |
| H | 4-OMe | TPPDS | SDS | 76 |
| H | 4-F | TPPDS | SDS | 81 |

Scheme 16.

selectivities and yields. Stilbene derivatives were obtained in 84–99% isolated yields in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ as catalyst (Scheme 16). The addition of water-soluble ligands like the tris(*m*-sulfonatophenyl)phosphane trisodium salt (TPPTS) or tris(*m*-carboxyphenyl)phosphane trilitium salt (*m*-TPPTC) allowed to recycle the rhodium catalyst, although yields were then lower (24–96%) [32]. A phase transfer agent (sodium dodecyl sulfate, SDS), was required with the bis(*p*-sulfonatophenyl)phosphane dipotassium salt ligand (TPPDS) [56].

3.2. The McMurry coupling of aldehydes and ketones

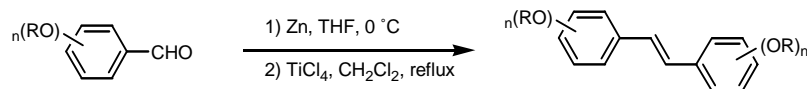
Aldehydes and ketones undergo reductive dimerization to yield alkenes upon treatment with low-valent titanium reagents. Such a carbonyl coupling reaction is usually referred to as the McMurry coupling. It plays a significant role in the synthesis of phytoalexins, because it provides a ready access to symmetrical stilbenes from the corresponding aldehydes or ketones [10]. Thus, symmetrical polyalkoxy- and polysilyloxystilbenes were obtained by reductive coupling of alkoxy- and silyloxybenzaldehydes, respectively, with zinc and titanium tetrachloride (Scheme 17) [57,58]. All the products isolated under these conditions possessed a *trans* double bond. Some of these compounds showed rather potent ne-

matocidal activity, but only after the phenol functionalities were totally or partially deprotected [57].

Although the McMurry coupling reaction usually gives almost exclusively *E*-stilbenes, the *Z*-isomers may be predominantly obtained if geometric constraints control the orientation of the two carbonyl moieties [59]. Mixed coupling reactions usually lead to a statistical mixture of all possible alkenes. Reasonable yields of a single cross-coupled product can nevertheless be achieved if one of the substrates is introduced in excess or if the two substrates exhibit sufficiently different redox potentials. Furthermore, mixed coupling reactions are also favored when one of the components is a diaryl ketone. Indeed, coupling of a diaryl ketone with an equimolar amount of any ketone or aldehyde predominantly yields the mixed coupled product. This strategy has been used as the key step in the synthesis of the antitumor agent tamoxifen and a series of its derivatives (Scheme 18) [60–62].

3.3. Alkene cross metathesis

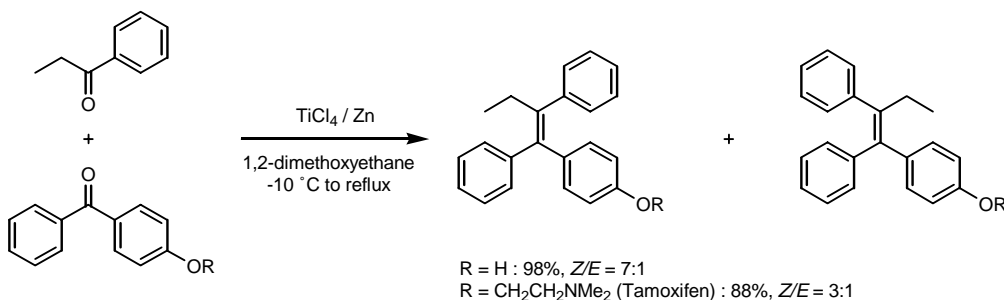
Olefin metathesis reactions have been known for a number of years, but their application to organic synthesis was rather limited until the discovery of highly efficient, well-defined initiators tolerant of many functionalities by Grubbs and



R = Me, *i*-Pr, *t*-butyldimethylsilyl

| Benzaldehyde | Stilbene | Yield (%) |
|---|--|-----------|
| 2-methoxy | 2,2'-dimethoxy | 71 |
| 3-methoxy | 3,3'-dimethoxy | 57 |
| 3,5-dimethoxy | 3,3',5,5'-tetramethoxy | 42 |
| 4- <i>t</i> -butyldimethylsilyloxy | 4,4'-di- <i>t</i> -butyldimethylsilyloxy | 52 |
| 3,5-di- <i>t</i> -butyldimethylsilyloxy | 3,3',5,5'-tetra- <i>t</i> -butyldimethylsilyloxy | 79 |
| 3,5-diisopropoxy | 3,3',5,5'-tetraisopropoxy | 66 |

Scheme 17.

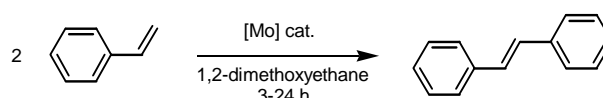


Scheme 18.

Schrock in the early 1990s (see Fig. 4). Since then, spectacular advances were made in designing even more active catalysts and understanding their mode of operation. Despite intense research in the field, cross metathesis (CM) has not yet reached the same level of recognition than ring closing metathesis (RCM) or ring opening metathesis polymerization (ROMP) within the chemical community. This is largely due to inherent difficulties in controlling selectivities. Minimization of unproductive self-coupled alkenes and concomitant maximization of the desired cross product is a crucial issue to address when performing CM, together with controlling the stereochemistry of the newly formed double bond. Catalytic engineering is currently making fast progress to relieve these concerns, and a general empirical model has recently been proposed for the prediction of chemo-, regio-, and stereoselectivity in olefin cross metathesis [63].

To the best of our knowledge, only two examples of stilbene formation by cross metathesis have been reported so far. The coupling of terminal alkenes to give symmetrical internal olefins was investigated by Schrock and coworkers in 1994 using a range of molybdenum(VI) imido alkylidene complexes. Only *trans*-stilbene was obtained when styrene served as substrate, but the yields remained low except when complex **6** was employed as catalyst under carefully adjusted conditions (Scheme 19) [64].

More recently, solid-phase cross metathesis of styrenyl ether with substituted styrenes afforded stilbenoid derivatives in high yields and with complete *E*-selectivity using the ruthenium-carbene complex (SIMes)(PCy₃)Cl₂Ru=CHPh (**8**) as catalyst. Preliminary experiments showed that when



| [Mo] cat. (mol%) | Time | Yield (%) |
|------------------|--------|-----------|
| 5 (0.5) | 3-24 h | 35 |
| 5 (0.02) | 4 h | 4 |
| 6 (0.027) | 2.5 h | 36 |
| 6 (0.1) | 10 h | 95 |

Scheme 19.

two different styrenes were allowed to react freely in solution without any polymer anchorage, homo- and cross coupling products were obtained in a rather statistical 1:1:1 distribution (77–98% yield) and formed an inextricable mixture. Conversely, when 4-vinylphenol was attached to a Merrifield resin and the resulting supported styrenyl ether was coupled with various styrene derivatives, cross coupling products could be isolated in high yields (>95%) after filtration and cleavage of the resin with 20% trifluoroacetic acid (TFA) in dichloromethane (Scheme 20) [65]. Thus, the advantages of the solid-phase metathesis approach lie in the expected inhibition of the supported substrate self-coupling, as well as the ease of product separation from the reaction mixture.

4. Palladium-catalyzed isomerization of stilbenes

Stilbene remains one of the most popular models for studying the *E*–*Z* photoisomerization of polyenes, a topic that has recently been reviewed [66]. The photochemical isomerization of arylenes usually takes place in the excited state through rotation around the C=C double bond. For instance, highly branched stilbene dendrimers with molecular weights of over 6000 underwent *E*–*Z* isomerization in less than 10 ns, the lifetime of the excited singlet state [67].

In many stilbene syntheses (e.g., through Wittig reactions or olefin cross metathesis) mixtures of *E*- and *Z*-isomers are formed. Efficient and mild methods for isomerizing the *Z*-isomers into the (usually) biologically active *E*-isomers in the series of hydroxy- or alkoxy-substituted stilbenes are

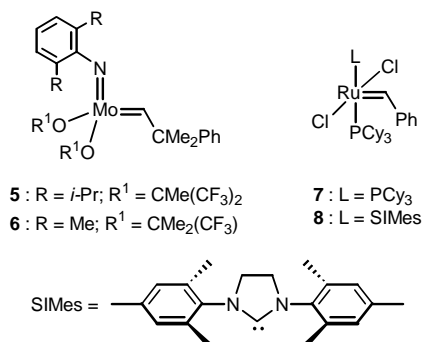
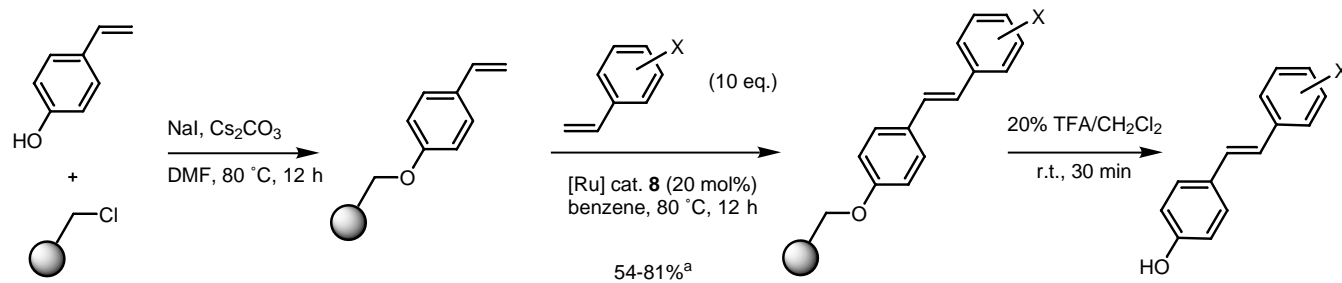


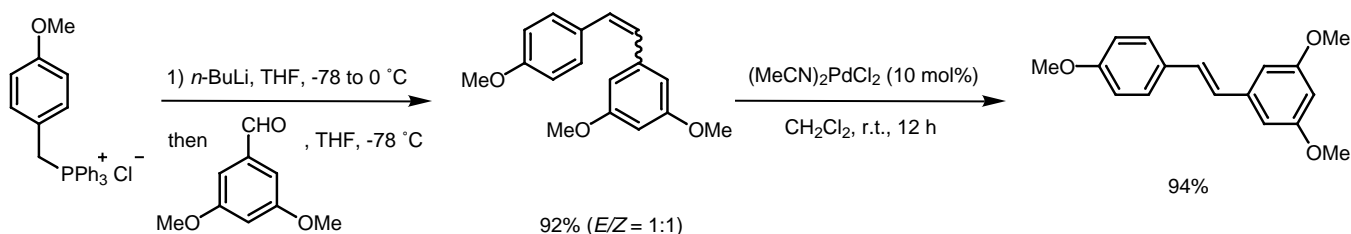
Fig. 4. Well-defined metal-alkylidene catalysts for alkene metathesis.



X = H, 4-Cl, 4-CF₃, 4-OAc, 4-Me, 4-OMe, 3,4-(OCH₂OCH₃)₂, 3,4-(OAc)₂

^a Isolated yield (over three steps) after cleavage of the resin

Scheme 20.



Scheme 21.

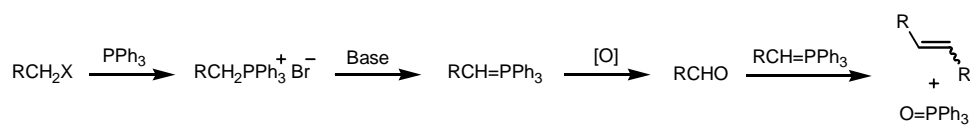
rare. Radical or photochemical methods are useful but often involve rather harsh reaction conditions. A convenient new method for the conversion of alkene mixtures or pure *Z*-aryllkenes into the corresponding *E*-isomers using a palladium(II) complex was reported in 2002 [68]. Although the catalyst loading was rather high (10 mol%), the synthetic potential of the methodology was demonstrated in the case of trimethoxyresveratrol. Thus, a 1:1 *Z/E* mixture of this stilbene afforded the pure *E*-isomer in 94% yield using bis(acetonitrile)palladium(II) chloride in dichloromethane at room temperature (Scheme 21).

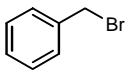
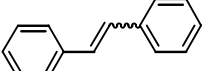
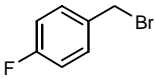
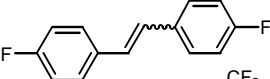
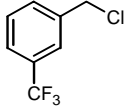
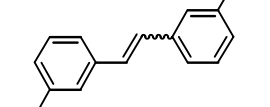
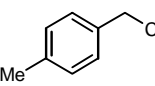
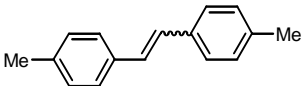
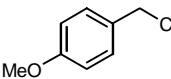
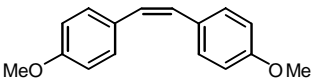
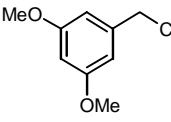
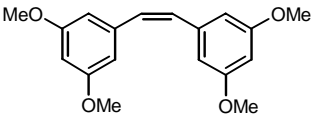
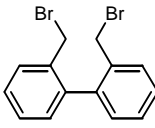
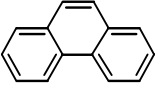
5. Variae: non transition metal catalyzed syntheses of hydroxystilbenes

Wittig-, Wittig–Horner-, or Horner–Emmons reactions and their variations are still popular synthetic tools for the preparation of potentially biologically active polyphenolic stilbenes or their alkoxy and glycoside derivatives, which include inter alia the combretastatin and resveratrol families of phytoalexins [42,57,69–73]. As an alternative to the classical Wittig conditions, potassium hydroxide and a catalytic amount of 18-crown-6 were used for the synthesis of *meta*- and *para*-substituted stilbene derivatives in a solid–liquid biphasic system. Interestingly, benzyltriphenylphosphonium iodides always led to an almost complete *Z*-stereospecificity (*Z/E* > 98:2) regardless of the nature of the substituents on the benzyl group, whereas benzyldiphenylchlorophosphonium bromides exhibited the opposite behavior (*Z/E* < 2 : 98) [74].

The preparation of symmetric stilbenes from phosphonium salts under an oxygen atmosphere in the presence of vanadyl acetylacetonate, VO(acac)₂, was reported in 2002 by Shi and Xu. This reaction is believed to proceed via an oxidative coupling of ylides generated in situ from the corresponding phosphonium salts, as shown in Scheme 22 [75]. A solid–liquid biphasic system (K₂CO₃/PhCH₃) with 18-crown-6 as phase transfer agent was suitable for phosphonium salts having an electron-withdrawing or a weak electron-donating substituent on the benzyl group (method A). Ylide precursors bearing strong electron-donating substituents on their benzyl group required the use of a strong base under strictly anhydrous conditions (potassium *t*-butoxide in dichloromethane, method B). *Z/E* mixtures of olefins were isolated in moderate to good yields, depending on the reaction conditions adopted. The stereoselectivities observed were generally the same as those obtained under typical Wittig conditions. Yet, it is noteworthy that applying method B to methoxystyrene derivatives afforded stilbenoid compounds with a preferential *Z*-configuration.

The reaction of the trimethylsilyl ether of 3,5-dimethoxybenzyl alcohol with benzaldehyde and benzaldehyde derivatives in the presence of lithium powder and a catalytic amount of naphthalene (4 mol%) gave access to the hydroxylated stilbenes pinosilvine, resveratrol, and piceatanol after subsequent dehydration and demethylation steps. Overall yields were negatively affected by the difficulty to quantitatively condense the silyl ether with the benzaldehyde. Attempts to improve the outcome of this critical first step remained unsuccessful [76]. In another variation on aldol-type reactions, the synthesis of resveratrol and of



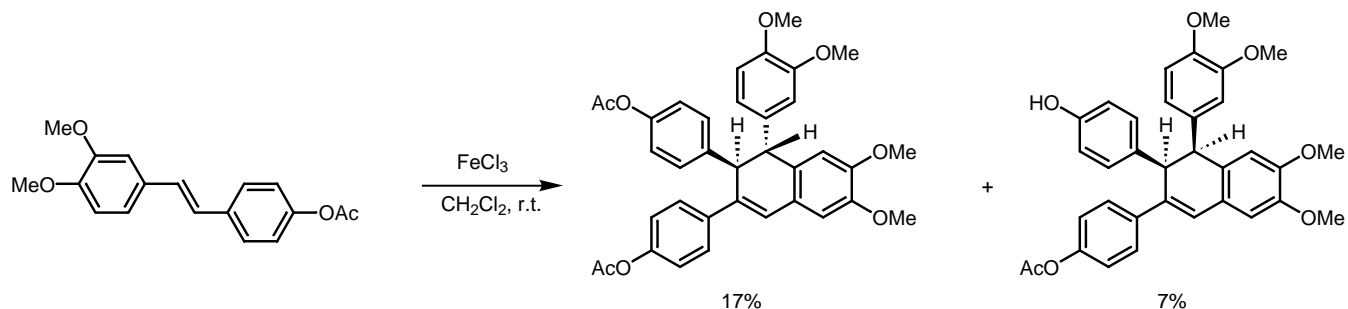
| Halide | Product | Reaction conditions | Isolated yield (%) | Z/E |
|---|---|---------------------|--------------------|--------|
|  |  | A | 93 | 1.7:1 |
|  |  | A | 83 | 1.6:1 |
|  |  | A | 84 | 1.3:1 |
|  |  | A | 75 | 1.3:1 |
|  |  | B | 55 | 98:2 |
|  |  | B | 51 | >98:<2 |
|  |  | A | 70 | |

Method A: PhMe, K₂CO₃ (2.5 eq.), 18-crown-6 (0.01 eq.), O₂ atm., VO(acac)₂ (0.01 eq.), 60–70 °C
 Method B: CH₂Cl₂, t-BuOK (1.5 eq.), 18-crown-6 (0.01 eq.), O₂ atm., VO(acac)₂ (0.01 eq.), r.t.

Scheme 22.

pinostilbene was achieved through benzylic deprotonation of a η^6 -arene-Cr(CO)₃ complex and subsequent coupling of the resulting anion with *para*-anisaldehyde. In this case, the condensation was facilitated by the presence of the tricarbonylchromium moiety and the key adduct was obtained in 85% yield [77]. The Perkin reaction was also recently revisited for the synthesis of resveratrol and related compounds. Thus, methyl or isopropyl ethers of *p*-hydroxyphenylacetic

carboxylic acid were used as starting materials. The Perkin reaction was also recently revisited for the synthesis of resveratrol and related compounds. Thus, methyl or isopropyl ethers of *p*-hydroxyphenylacetic



Scheme 23.

acid and 3,5-dihydroxybenzaldehyde were condensed into methoxy or isopropoxy arylcinnamic acids in 66 and 72% yield, respectively, in the presence of triethylamine and acetic anhydride at 90 °C. These acids were then decarboxylated upon treatment with copper chromite in quinoline to yield the corresponding stilbene derivatives. In a final step, the protecting alkoxy groups were cleaved with boron trichloride. The isopropyl ethers could be removed quantitatively at lower temperature than their methyl counterparts, thereby avoiding any unwanted isomerization [78].

The biochemistry of the stilbenoids is very rich and still largely unexplored in its synthetic aspects. It is noteworthy that resveratrol is also the biosynthetic progenitor of a family of oligostilbenoid polyphenols [6]. In living organisms, these oligomers are generated by oxidative phenolic coupling and some of them display interesting biological activities. To date, only a few stilbenoid dimers were prepared in the laboratory by oxidative coupling with one-electron oxidants (Scheme 23) [23], but this research area remains largely uncharted.

Acknowledgements

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