

CHAPTER 2. STILBENE SYNTHESIS

2.1. Brief overview of stilbene monomer syntheses

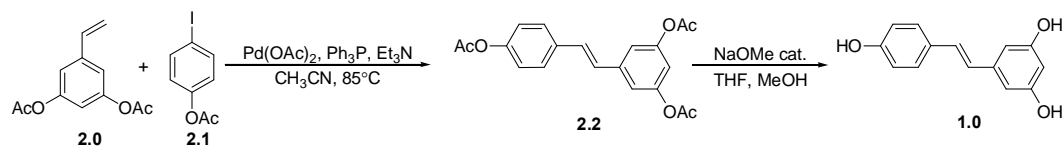
Syntheses of functionalized stilbenes have attracted immense attention over the past decades and have been reported in several research papers and reviews.¹⁻⁴ Stilbene derivatives have been studied for biological activities that include anti-microbial, antifungal, antioxidant, hepatoprotective, anti-HIV, cytotoxic, anti-inflammatory and antiplatelet. Stilbenes are also widely used in the manufacture of industrial dyes, dye lasers, optical brighteners and other materials as they possess fluorescence properties (due to the presence of conjugated system in stilbenes) and, in extended structures, liquid crystal properties. Herein, we have categorized the reported synthetic methods of stilbene derivatives into two major categories; palladium and non palladium-catalysed syntheses of stilbenes.

2.1.1. Palladium-catalysed syntheses of stilbenes

Palladium-mediated cross-coupling resulting in the formation of C-C bonds can be exploited for preparation of functionalized stilbenes. The following section presents various palladium-catalysed reactions inclusive of Heck reaction, decarbonylative Heck reaction, Heck-type decarboxylative coupling, Suzuki-Miyaura reaction, Stille reaction, Negishi cross-coupling and silylative and Hiyama couplings.

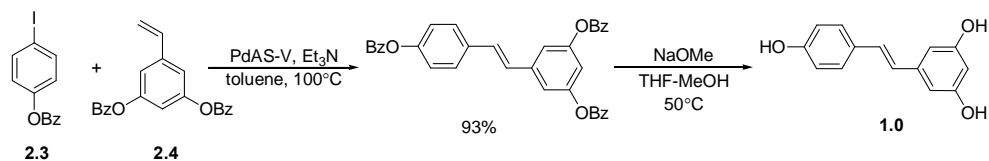
2.1.1.1. Heck reaction

Palladium mediated Heck coupling is a well established method for the construction of C-C bonds in organic chemistry. Heck coupling can be performed by reacting an alkene with aryl or alkenyl halogenide forming vinylarenes or dienes in the presence of a stoichiometric amount of a base. The active species in this reaction is Pd(0) catalyst. This can be achieved by either direct addition of Pd(0) complex with tertiary phosphine-ligands or *in situ* generation by reduction of Pd salts [Pd(II) reduced to Pd(0)] with an appropriate phosphine-ligand. The rate determining step is governed by the reactivity of aryl halide as it decreases in the order $\text{ArI} > \text{ArBr} \gg \text{ArCl}$. Heck cross coupling is commonly employed for stilbene synthesis.



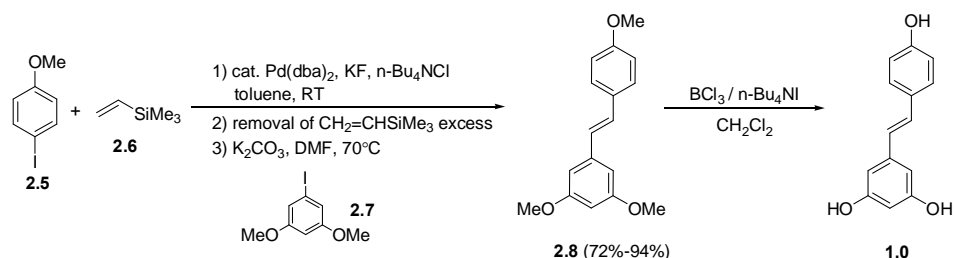
Scheme 2.1: Palladium acetate catalysed Heck coupling.⁵

Guiso *et al.* (2002)⁵ reported the synthesis of fully protected resveratrol 2.2 (70%) by coupling reaction of 3,5-diacetoxystyrene 2.0 with *p*-iodophenyl acetate 2.1 in acetonitrile containing $\text{Pd}(\text{OAc})_2$ as catalyst, PPh_3 as ligand and Et_3N as base (Scheme 2.1). A standard deacetylation provides the targeted resveratrol 1.0. The acetyl derivatives are used as coupling precursors since Heck reaction gives better yields if the phenolic groups are protected.



Scheme 2.2: Heck coupling catalysed by palladium cross linked polymer⁶.

Yamada *et al.* (2004)⁶ have developed a networked supramolecular Pd complex (PdAS-V), where the polymers are cross-linked by palladium to produce a reusable catalyst. The application of PdAS-V in Heck coupling of 2.3 and 2.4 produced resveratrol 1 efficiently (Scheme 2.2).

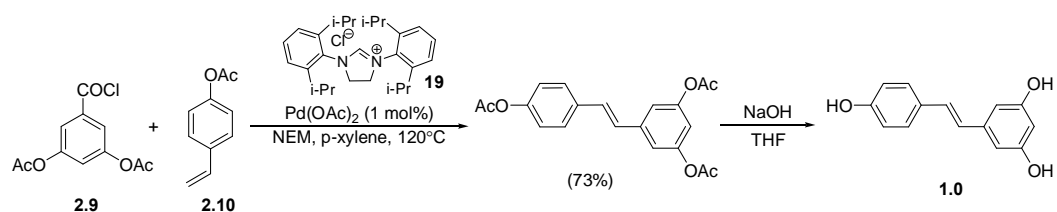


Scheme 2.3: Stilbene synthesis through two sequential Heck-type reactions.⁷

Jeffery and Ferber (2003)⁷ described a one-pot synthesis of unsymmetrical or symmetrical *E*-stilbenes *via* two sequential Heck-type reactions. Haloarenes and vinyltrimethylsilane are reacted together in presence of a tetraalkylammonium salt-based catalyst system. In this reaction, the arylation of vinyltrimethylsilane leads to the corresponding styrene derivative, which is then coupled with another heteroaromatic halides leading to a stilbene derivative. As an example, 2.8 was synthesized by first treating *p*-iodoanisole 2.5 and vinyltrimethylsilane 2.6 (in excess) in catalyst system Pd/KF/n-Bu₄NCl (Scheme 2.3). The excess of 2.6 is then removed under reduced pressure. A second Heck reaction with iodoaryl 2.7 is carried out in DMF in presence of K₂CO₃ and the above-mentioned catalyst system already present in the reaction mixture. Deprotection of 2.8 leads to resveratrol 1.0. This one-pot two-step reaction is claimed to be highly chemo-, regio-, and stereoselective.

2.1.1.2. Decarbonylative Heck reaction

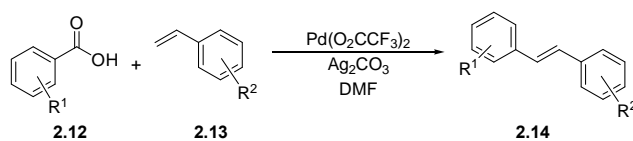
Andrus *et al.* (2003)⁸ have obtained resveratrol (73%) through a decarbonylative Heck approach by coupling of 4-acetoxy styrene **2.10** with acyl chloride **2.9** instead of the standard aryl halide (Scheme 2.4): This coupling was carried out in *p*-xylene containing Pd(OAc)₂ catalyst, *N,N*-bis-(2,6-diisopropyl)dihydroimidazolium chloride **2.11** as a ligand and non-coordinating amine base *N*-ethylmorpholine (NEM). Since the common phosphine ligand inhibits the reaction in the presence of acyl chloride, carbene-type ligand **2.11** and palladium(II) acetate were used instead. This strategy was further applied to the synthesis of acetate and fluororesveratrol derivatives.⁹



Scheme 2.4: Synthesis of resveratrol *via* decarbonylative Heck reactions.⁸

2.1.1.3. Heck-type decarboxylative coupling

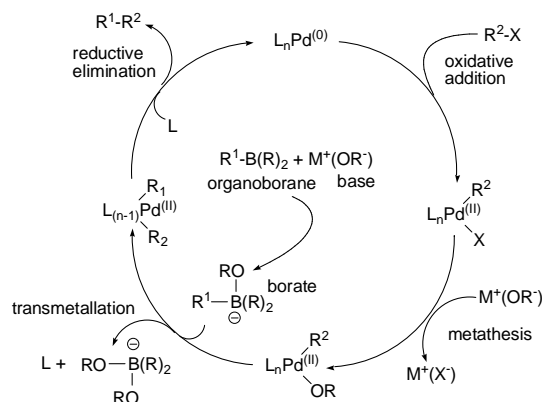
Myers *et al.* (2002)¹⁰ have obtained a series of stilbenes **2.14** (70%-90%) possessing electron rich as well as electron withdrawing substituents *via* palladium-catalysed Heck-type decarboxylative coupling. In general, this reaction involves the coupling of arene carboxylates with olefinic substrates with loss of carbon dioxide followed by steps common to the Heck coupling process. Myers *et al.* have coupled aryl alkene **2.13** with arene carboxylic acid **2.12** (in replacement of the standard aryl halide) in DMSO-DMF mixture of Pd(O₂CCF₃)₂ and Ag₂CO₃ (Scheme 2.5) to produce the target cross-coupled products. The same group provided some further insights on the mechanism of this coupling.¹¹



Scheme 2.5: Stilbene synthesis through Heck-type decarboxylative coupling.¹⁰

2.1.1.4. Suzuki-Miyaura reaction

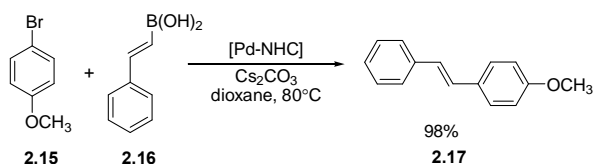
The Suzuki-Miyaura cross coupling involves the reaction between organoboron compounds and organic halides or triflates by means of palladium catalyst to form a C-C sigma bond. Like any other palladium catalysed reaction, a few key steps are involved in the catalytic cycle: oxidative addition [converting Pd(0) to Pd(II)], exchange of the anion attached to the palladium complex with the anion from the base (metathesis), transmetallation between alkylborate complex and Pd(II) species and reductive elimination to form the desired cross coupling product by regenerating the Pd(0) complex (Scheme 2.6).



Scheme 2.6: Catalytic cycle involved in Suzuki-Miyaura reaction¹²

Tudose *et al.* (2006)¹³ performed the Suzuki-Miyaura reaction of aryl halides **2.15** with *trans*-2-phenylvinylboronic acid **2.16** to generate stilbene **2.17** (Scheme 2.7). They carried out this coupling in 1,4-dioxane using Cs₂CO₃ as a base together

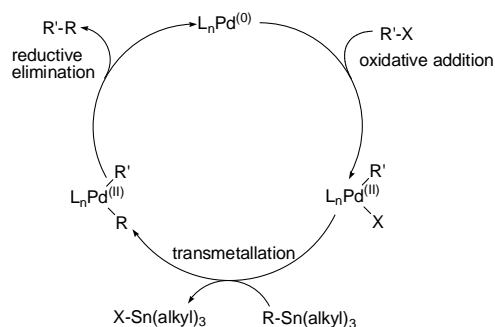
with *in situ* generated *N*-heterocyclic carbene palladium(II) complexes (Pd-NHC). However, the nature of the catalyst system significantly affects the reaction efficiency.



Scheme 2.7: Stilbene synthesis promoted by Suzuki-Miyaura coupling (adapted from reference 13).

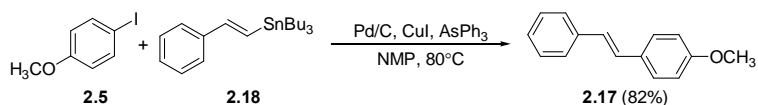
2.1.1.5. Stille reaction

The Stille reaction is a palladium-catalysed coupling of aryl or vinyl halides and triflates with organostannenes. The catalytic cycle is similar to other palladium catalysed cross-coupling reactions with three steps containing oxidative addition, transmetallation and reductive elimination (Scheme 2.8). Pd(0) complex is the active species involved, which can be generated *in situ*.¹²



Scheme 2.8: Catalytic cycle involved in Suzuki-Miyaura reaction.¹²

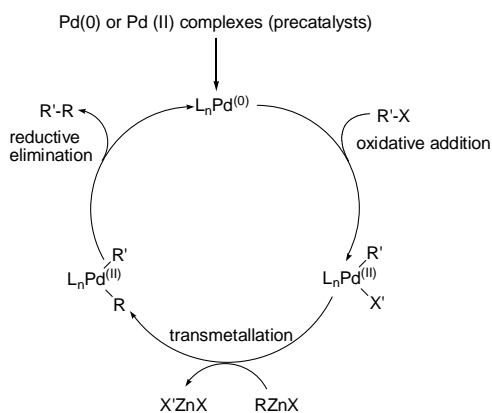
Roth and Farina (1995)¹⁴ have optimized the Stille reaction of **2.5** with **2.18** by addition of co-catalytic copper iodide and ligand triphenylarsine to produce stilbene **2.17** in 82% yield (Scheme 2.9).



Scheme 2.9: Stilbene synthesis by Stille coupling (adapted from reference 14).

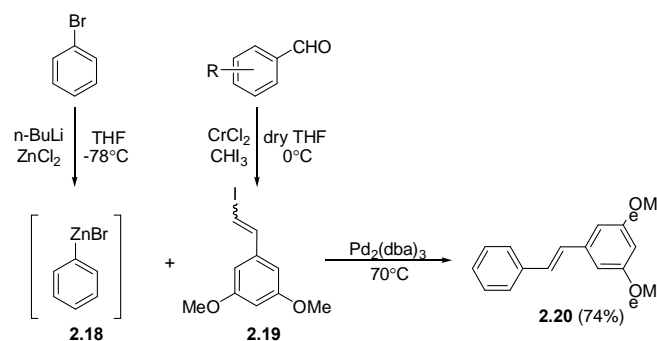
2.1.1.6. Negishi cross-coupling

The Pd-catalysed stereoselective cross-coupling between organozinc and aryl-, alkenyl- or alkynyl halides is known as the Negishi cross-coupling. Pd(0) is the active species in this reaction and undergoes three key steps, *i.e.* oxidative addition, transmetallation and reductive elimination as shown in Scheme 2.10.¹²



Scheme 2.10: Catalytic cycle involved in Negishi cross-coupling.¹¹

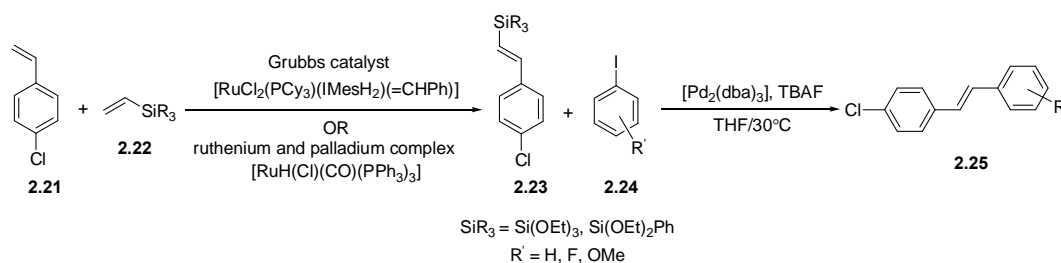
Kabir *et al.* (2007)¹⁵ prepared a series of substituted stilbenes with electron donor and withdrawing groups *via* Negishi cross-coupling without any additional ligand. The active species, arylzinc reagent **2.18** is reacted with arylvinyl iodide **2.19** in the presence of $Pd(PPh_3)_4$ to give stilbene **2.20**. The aryl zinc reagent is prepared by treating aryl bromide with $ZnCl_2$ in basic medium (Scheme 2.11).



Scheme 2.11: Stilbene synthesis by Negishi cross-coupling (adapted from reference 15).

2.1.1.7. Tandem cross-metathesis (or silylative coupling) and Hiyama coupling

Hiyama's coupling is the coupling reaction between aryl and alkenyl-halogenides or triflates with organo-silanes catalysed by a palladium reagent. It has an added advantage over the Stille coupling as the toxic tin-compounds are not used.¹² Prukala *et al.* (2006)¹⁶ reported the Hiyama coupling of 1-(4-chlorophenyl)-2-(triethoxysilyl or diethoxyphenylsilyl)ethene **2.23** with iodobenzene derivatives **2.24** to obtain 4-chlorostilbene and its derivatives **2.25** in good yields (Scheme 2.12). The reaction is catalysed by $[\text{Pd}_2(\text{dba})_3]/\text{TBAF}$ system in THF. 1-(Phenyl)-2-(silyl)ethenes **2.23** can be prepared by cross-metathesis of 4-chlorostyrene **2.21** with vinylsilane **2.22** either in the presence of second generation of Grubbs catalyst $\text{Cl}_2(\text{PCy}_3)(\text{IMesH}_2)\text{Ru}(\text{=CHPh})$ or $\text{RuH}(\text{Cl})(\text{CO})(\text{PPh}_3)_3$ complex (silylative coupling).



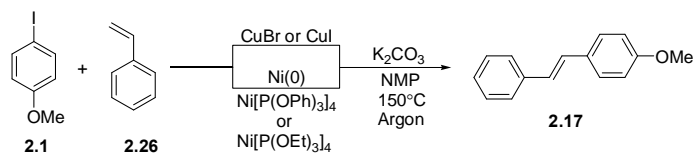
Scheme 2.12: Stilbene synthesis by Hiyama coupling (adapted from reference 16).

2.1.2. Non-palladium-catalysed syntheses of stilbenes

This section reviews the utilization of transition metals other than palladium, such as nickel-, copper-, titanium-, ruthenium- and cobalt mediated cross-coupling in stilbene derivatives syntheses. In addition, Wittig-Horner, Knoevenagel type and Perkin type reactions as well as lithium mediated cross-coupling employed in stilbenoids preparation are described below.

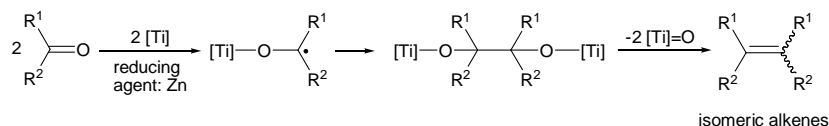
2.1.2.1. Ni(0) or Cu(I) salts-catalysed vinylation

Iyer *et al.* (1997)¹⁷ reported the Heck application of Cu(I) salts and/or Ni(0) complexes in the synthesis of stilbene derivatives instead of palladium catalyst (Scheme 2.13). Aryl halide **2.1** was coupled with styrene **2.26** in *N*-methylpyrrolidone containing CuI and K₂CO₃ to give stilbene **2.17** in 80% yield. The yield was increased to 95% by catalyzing the cross coupling with Ni(0), Ni[P(OPh)₃]₄.¹⁸



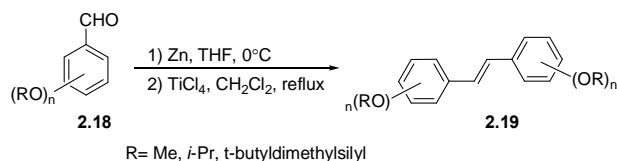
Scheme 2.13: Cu(I) and Ni(0) catalysed couplings in stilbene synthesis (adapted from references 17 & 18).

2.1.2.2. McMurry coupling



Scheme 2.14: Mechanism of the McMurry coupling (adapted from references 12, 19).

The McMurry coupling is known as the reductive dimerisation of carbonyl compounds like aldehyde and ketone by low-valent titanium complexes [mixture of Ti(II) and Ti(0)] to produce alkenes. Most commonly, low-valent titanium is prepared by reducing TiCl_3 with a zinc-copper couple (Zn-Cu) in DME.^{12, 19} The mechanism of the McMurry coupling consists of metalpinacol formation and deoxygenation to the alkene (Scheme 2.14). This reaction is typically a homocoupling leading to symmetrical alkenes. Heterocoupling is only possible when one of the substrates is introduced in excess. Ali *et al* (1992)²⁰ synthesized symmetrical stilbene derivatives **2.19** by aryl aldehydes **2.18** reductive coupling in THF containing TiCl_4 and Zn as reducing agent (Scheme 2.15).



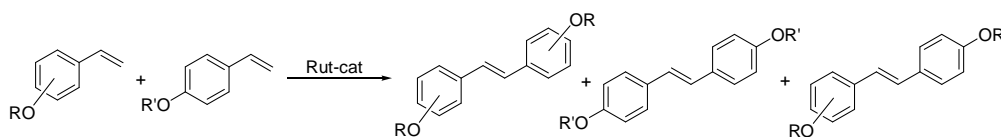
Scheme 2.15: McMurry coupled aldehydes to stilbene derivatives (adapted from reference 20).

In 2005, Stühr-Hansen²¹ reported the syntheses of symmetrical stilbene derivatives including sulfur end-capped analogues *via* low valent titanium McMurry coupling. High yields (around 90%) were obtained under microwave irradiation at 110°C for 10 minutes only.

2.1.2.3. Ruthenium-catalysed cross-metathesis

Alkene cross-metathesis is known as the coupling of two different terminal alkenes into combinations of homocoupling and heterocoupling resulting in symmetrical and unsymmetrical internal olefins. Indeed, this cross-metathesis can also provide an easy access to stilbenoid derivatives. Ferré-Filmon *et al.* in 2005 reported

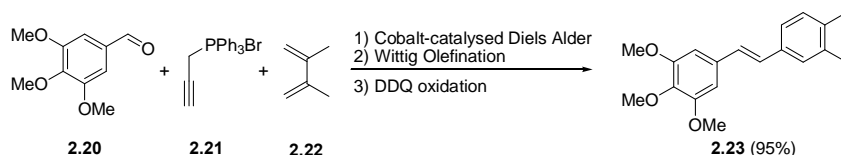
the construction of symmetrical and unsymmetrical (*E*)-polymethoxystilbene and (*E*)-polyhydroxystilbene derivatives by ruthenium-catalyzed cross-metathesis with help of second generation Grubbs catalysts (Scheme 2.16).²² They were of the opinion that the selectivity of the unsymmetrical cross-product can be enhanced almost up to 95% yield by introducing one of the reacting substrates in excess.



Scheme 2.16: Synthesis of (*E*)-hydroxystilbenoids by metathesis.²²

2.1.2.4. Cobalt-catalysed Diels-Alder/Wittig olefination

Hilt and Hengst (2007)²³ reported a series of stilbene derivatives *via* a one-pot reaction sequence that involves cobalt-catalysed Diels-Alder reaction followed by Wittig olefination and DDQ oxidation generating three new C-C bonds. Treating propargylic phosphonium salts **2.21** with 1,3-diene **2.22** undergoes a Diels-Alder reaction leading to a dihydroaromatic phosphonium salt intermediate ready for Wittig olefination with aldehyde **2.20**. Subsequent oxidation by DDQ produced stilbene type products **2.23** (Scheme 2.17).

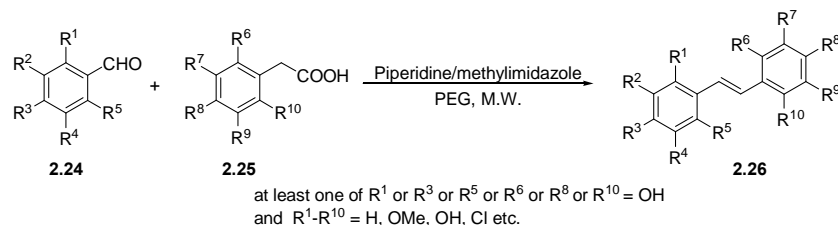


Scheme 2.17: Stilbene synthesis by Co-catalysed Diels-Alder/Wittig olefination.²³

2.1.2.5. Modified Perkin reaction

Sinha *et al.* (2007)²⁴ synthesized a series of hydroxylated stilbenes in moderate yields through a one-pot modified Perkin reaction. The standard Perkin

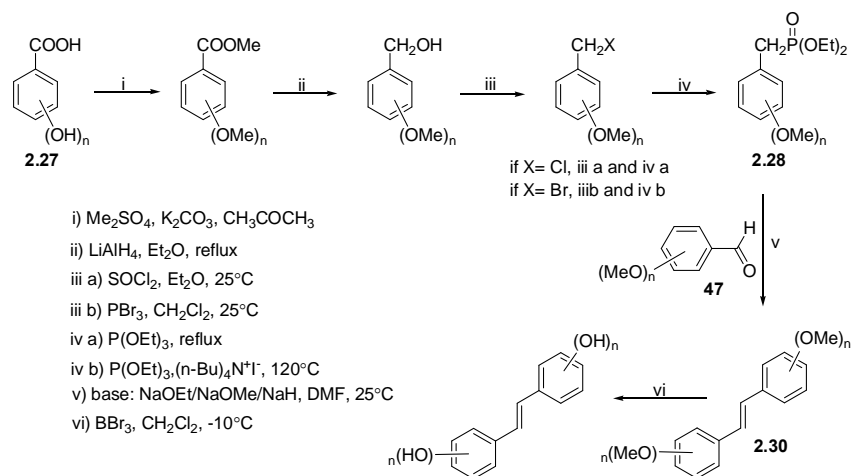
reaction involves the condensation of aromatic aldehydes with the anhydrides of aliphatic carboxylic acids in the presence of a weak base to yield α,β -unsaturated carboxylic acids. The authors treated aryl aldehydes **2.24** with phenylacetic acids **2.25** in polyethylene glycol (PEG) containing piperidine and methylimidazole under microwave irradiation to produce hydroxylated stilbenes **2.26** via simultaneous condensation-decarboxylation pathway (Scheme 2.18).



Scheme 2.18: Hydroxylated stilbene synthesis *via* a modified Perkin reaction.²⁴

2.1.2.6. Horner-Wadsworth-Emmons olefination

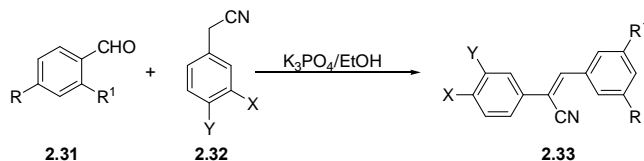
Wang *et al.* (1999),²⁵ Kim *et al.* (2002),²⁶ Murias *et al.* (2004),²⁷ Chen *et al.* (2005),²⁸ Lion *et al.* (2005),²⁹ Heynekamp *et al.* (2006)³⁰ and Fukuhara *et al.* (2008)³¹ independently performed Horner-Wadsworth-Emmons olefinations to generate a series of stilbene derivatives. Treating substituted benzylphosphonic acid diethyl esters **2.28** under Horner-Wadsworth-Emmons condition with substituted benzaldehydes **2.29** produced the corresponding stilbene derivatives **2.30** through the formation of phosphonate carbanions (Scheme 2.19). The phosphonate **2.28** can be prepared in four steps starting from substituted benzoic acids **2.27** undergoing esterification, reduction, and halogenation leading to an aryl halide, which then finally converted to a phosphonate (**2.28**) by heating with P(OEt)₃.



Scheme 2.19: Stilbene synthesis through Horner-Wadsworth-Emmons olefinations between aldehydes and phosphonates (adapted from references 25-31).

2.1.2.7. Knoevenagel condensation

Al-Shihry (2004)³² reported the synthesis of stilbene derivatives **2.33** (80%-95%) with electron withdrawing groups *via* Knoevenagel condensation (Scheme 2.20). This reaction is carried out between aldehyde **2.31** and active methylene compounds **2.32** in polar solvent, ethanol added with K_3PO_4 .

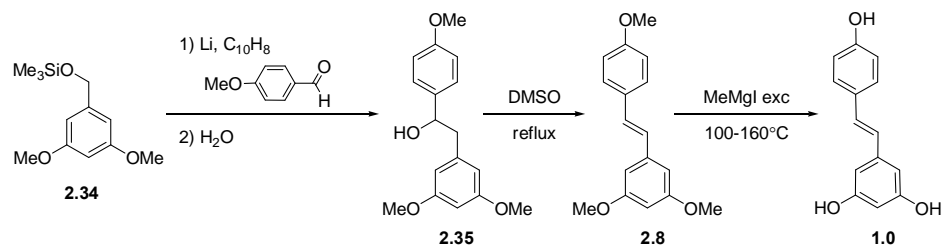


Scheme 2.20: Knoevenagel condensation for preparing stilbenes with electron withdrawing groups (adapted from reference 32).

2.1.2.8. Lithium-mediated cross coupling

Alonso *et al.* (1997)³³ reported the preparation of stilbene derivatives with 3,5-*O*-substituted resorcinols. 3,5-Dimethoxybenzyl trimethylsilyl ether **2.34** is treated with anisaldehyde in the presence of lithium powder and a catalytic amount of naphthalene to afford alcohol **2.35** after hydrolysis (Scheme 2.21). Upon refluxing in

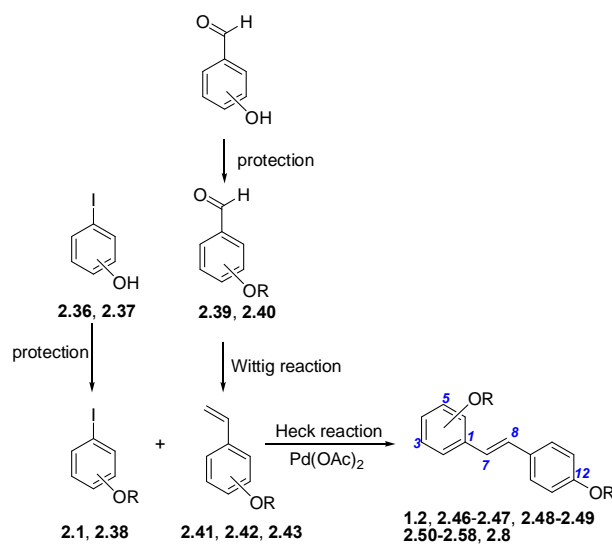
DMSO, alcohol **2.35** was dehydroxylated into permethylether resveratrol **2.8** subsequently demethylated by methyl magnesium iodide to yield resveratrol **1.0**. Trimethylsilyl ether **2.34** can be prepared upon treatment of 3,5-dimethoxybenzylic alcohol with chlorotrimethylsilane and triethylamine in THF.



Scheme 2.21: Preparation of resveratrol through Li-mediated coupling (adapted from reference 33).

2.2. Results and discussion

Since Heck cross coupling is commonly employed for stilbene synthesis, this method is applied to prepare 16 different stilbene analogues possessing resorcinol (3,5-substituted) substitution and 3-substituted pattern (resveratrol analogues). Scheme 2.22 shows the outlined synthetic plan of stilbene derivatives.



Scheme 2.22: Proposed synthetic plan of stilbene derivatives.

2.2.1. Synthesis of stilbene building blocks **2.1**, **2.38**, **2.39**, **2.40**, **2.41**, **2.42**, and **2.43**

The first series of building blocks, protected iodophenols (**2.1** and **2.38**) for stilbenes syntheses were prepared. 4-Iodophenol **2.36** was first protected with acetic anhydride. Sodium hydride was used as the base to remove the proton from the 4-iodophenol leading to formation of phenolate anion. Nucleophilic attack took place at the carbonyl of the acetic anhydride to form the required product **2.1** (Figure 2.1). This reaction was repeated on 3-iodophenol **2.37** (section 2.3) using potassium *tert*-butoxide (base) as a substitute to sodium hydride to generate compound **2.38** (Figure 2.1). The protected iodophenols **2.1** and **2.38** were obtained in high yields, 99% and 96% respectively. The spectroscopic evidence of **2.1** and **2.38** are based on their ¹H-NMR spectra (Appendix 1 and 2 respectively).

For the second series of building blocks, protected benzaldehydes **2.39** and **2.40** were prepared in a similar manner as above in 80% and 52% respectively (Figure 2.1). These protection steps were carried out using two different protecting reagents such as benzyl bromide BnBr and *tert*-butyldimethylsilyl chloride TBDMS-Cl. The spectroscopic evidence for **2.39** and **2.40** are based on their ¹H-NMR spectra (Appendix 3 and 4 respectively).

The final building blocks (**2.41**, **2.43** and **2.42**) (Figure 2.1) were prepared by converting the protected benzaldehydes **2.40**, **2.39** and commercially available 3,5-dimethoxybenzaldehyde **2.44** (section 2.3) to the corresponding styrene through Wittig methodology. Potassium *tert*-butoxide was used as the base to generate the ylide of the methyl triphenyl phosphonium iodide. The reaction mixture acquired a milky appearance after adding the benzaldehyde. The protected styrenes **2.41**, **2.42** and **2.43** were isolated from the worked up reaction mixture after purification by column

chromatography in 37%, 55% and 63% yields respectively. The spectroscopic evidence of **2.41**, **2.42** and **2.43** are based on their $^1\text{H-NMR}$ spectra (Appendix 5, 6 and 7 respectively). The presence of the vinyl system in the compound was proven by $^1\text{H-NMR}$ spectroscopic experiment with coupling constant of 16 Hz and 10 Hz of the *trans* and *cis* coupling.

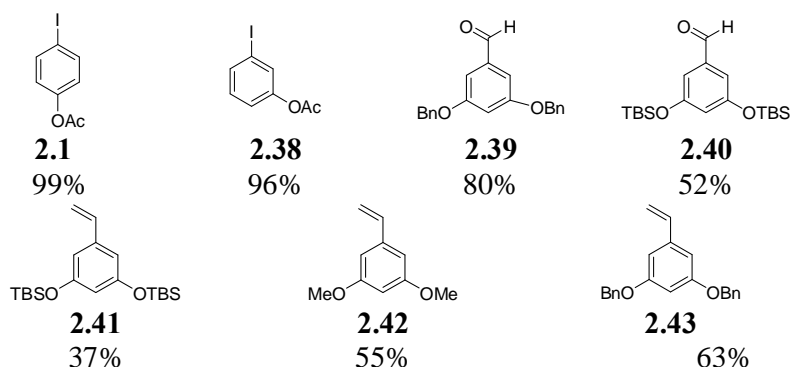


Figure 2.1: Synthesized building blocks of stilbenoids.

2.2.2. Synthesis of stilbenes possessing resorcinol (3,5-disubstitution) and the 3-substitution pattern (resveratrol analogues)

A series of protected iodophenols were reacted with various styrene derivatives in a mixture of $\text{H}_2\text{O}/\text{MeCN}$ containing $\text{Pd}(\text{OAc})_2$, PPh_3 , K_2CO_3 and $n\text{-Bu}_4\text{N}^+\text{Cl}^-$ at 50°C to form fully and partially protected stilbenes. Treating protected iodophenol **2.1** with styrene derivative **2.42** produced stilbene **2.46** and **1.2** (Figure 2.2), while treatment of **2.43** (styrene derivative) with the same compound **2.1** produced stilbene **2.47** and **2.49** (Figure 2.2). When commercially available *meta* substituted iodophenol **2.37** (section 2.3) and *para*-acetoxy styrene **2.45** (Experimental section 2.3.4.8) were reacted together, stilbenes **2.56** and **2.53** were produced (Figure 2.3), while treating the same **2.45** with 3-iodophenyl acetate **2.38** gave stilbenes **2.58** and **2.54** (Figure 2.3). Treatment of 1-iodo-4-methoxybenzene **2.5** with styrene

derivatives **2.42** and **2.41** respectively produced stilbene analogues **2.8** and **2.51** (Figure 2.2).

Employing the above Heck coupling in a slightly different condition, that is in the absence of phase transfer agent, to the compounds **2.38** and **2.5** (Experimental section 2.3.4.9) generated stilbenes **2.55** and **2.57** (Figure 2.3).

Under different Heck conditions without phosphine ligand and phase transfer agent **2.5** and **2.41** were coupled resulting in stilbenes **2.48** and **2.50** (Figure 2.2).

In contrast, stilbene **2.52** (Figure 2.2) was obtained by cleaving benzyl groups of **2.47** in dichloromethane solution containing AlCl_3 and *N,N*-dimethylaniline at 0°C .

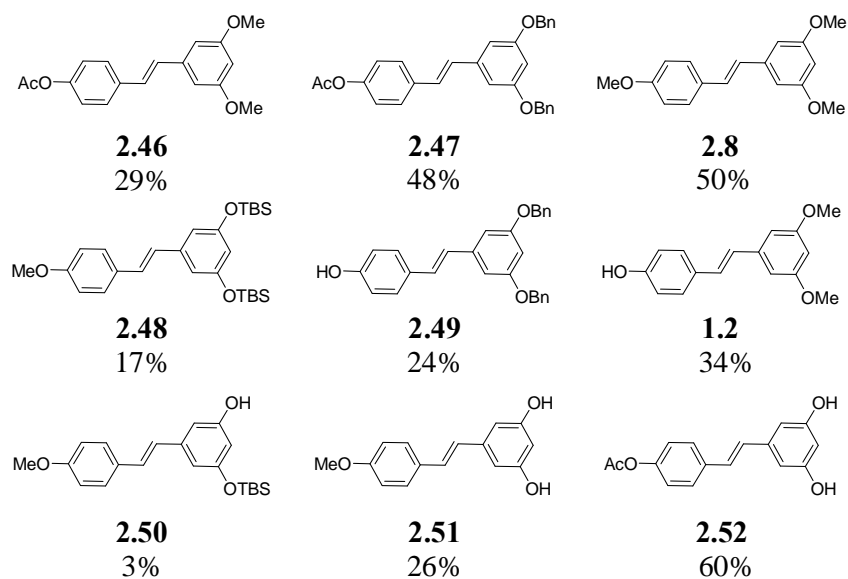


Figure 2.2: Synthesized fully and partially protected resveratrol analogues with 3,5-substitution pattern.

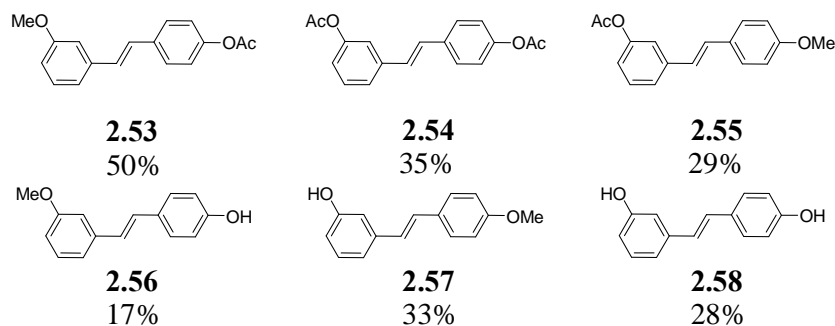
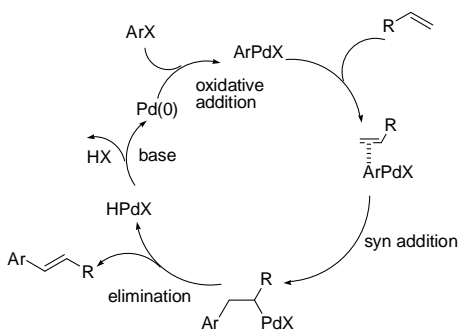


Figure 2.3: Synthesized fully and partially protected resveratrol analogues with 3-substitution pattern.

The Heck reaction, a palladium (0)-catalysed coupling reaction of an aryl or a vinyl halide with an alkene, has established itself as a powerful and efficient method for the construction of heterocycles as well as carbocycles. A generally accepted mechanism of the Heck reaction can be summarized in the following five steps; (i) oxidative addition of an aryl halide to a Pd(0) species to form an ArPdX intermediate, (ii) formation of a π -complex from the arylpalladium intermediate with an alkene, (iii) decomposition of the π -complex with the carbon-carbon bond and carbon-Pd bond formation in a *syn*-addition manner to produce a σ complex, (iv) β elimination of hydridopalladium halide (HPdX) if a β -H having cis-stereochemical relationship to the PdX species is present, and (v) reductive elimination of HX from HPdX into Pd(0) by a base to start another catalytic cycle (Scheme 2.23).^{34,35,36}



Scheme 2.23: Heck catalytic cycle.

Based on the literature,³⁷⁻⁴⁰ the Heck coupling mechanism, which accounts for the stilbenes synthesis is described below. The mechanistic interpretation of the Heck coupling is shown in Scheme 2.24. Pd(OAc)₂ undergoes transformation in a number of steps. The palladium species (**2.59** and **2.60**) involve palladium atom with oxidation state of 2+. The Pd (II) substrates spontaneously converted into palladium (0) substrates, (**2.61**, **2.62** and **2.63**). Complex **2.63** is formally co-coordinately unsaturated and highly nucleophilic undergoes a rapid oxidative reaction with **2.1** to give complex **2.64** with Pd (0) returning to its initial oxidation state 2+. The anionic property of complex **2.63** plays an important role in the oxidative addition of **2.63** to **2.1**. Acetate ion is displaced by solvent, MeCN, resulting in complex **2.65**. The dissociation of solvent transform the complex **2.65** with reactive 5 coordination sites into 4 coordination sites complex **2.66**. In the presence of phase transfer agent, n-Bu₄N⁺Cl⁻, iodide ion in complex **2.66** is displaced by chloride ion from the n-Bu₄N⁺Cl⁻ to form **2.67**. To activate the alkene **2.42**, a vacant site has to be created in palladium complex of **2.67** by displacing the phosphine ligand with alkene **2.42** to form complex **2.68**. The coordinated alkene then goes through *syn* addition, producing an unstable σ-bonded complex **2.69**. This unstable complex, then rotate around the carbon-carbon bond in order for the palladium and β-hydrogen to be *syn* coplanar **2.70**. Subsequent β-hydride elimination produced *trans* substituted stilbene and the catalytically inactive HPdCl(PPh₃)₂. One of the possible mechanisms to explain the regeneration of zerovalent palladium catalyst is discussed as follows. This involves an exchange process between the phase transfer agent n-Bu₄N⁺Cl⁻ and the inorganic salt K₂CO₃, prior to proton abstraction of hydridopalladium halide by n-Bu₄N⁺Cl⁻ in the organic phase, resulting in regeneration of the active Pd(0) species.

2.52, 2.53, 2.54, 2.55, 2.56, 2.57 and **2.58**. The major differences lie with signals associated with hydrogen atoms at position 7 and 8 whereby the ^1H NMR shows 2 spin system with *trans* coupling of 16 Hz overlapping at the aromatic region. Appendix 23 and 24 show spectra of ^{13}C NMR of compounds **1.2** and **2.56** respectively. ESI-TOF-MS(-) spectra of compounds **1.2** and **2.56** are shown in Appendix 25 and 26 respectively.

In summary, both transition and non transition metals mediated cross coupling produced good yields of stilbene derivatives as reviewed earlier in section 2.1.1 and 2.1.2. In common, both the reactions have same approach, that the key precursor components are synthesized in parallel and linked them together at the last stage of the reaction instead of the standard linear strategy. In particular, palladium mediated vinylation of aryl halides provides a very convenient method in constructing C-C bonds at unsubstituted vinylic positions. The active species involved in these transition metal mediated reactions are always Pd(0) species, generated *in situ*, resulted from reduction of the added Pd (II) salt with other species present in the reaction mixture. Using the Heck approach, 15 stilbene derivatives, which are partially and fully protected, have been prepared in reasonable yield.

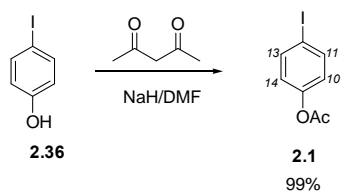
2.3. Experimental section

All reagents used were commercial products and were used without further purification. Preparative thin layer chromatography (PTLC) was performed on silica gel plates with a fluorescent indicator that was visualized with light at 254 nm (Merck). Flash chromatography was performed using a Master Personal⁺ from Argonaut Inc. connected to a fraction collector Teledyne ISCO[®]-Retriever 500. Column chromatographic purifications were carried out on silica gel Merk Kieselgel

60. Infra red (IR) spectra were recorded on a Perkin Elmer 1600 series FTIR, while ultra violet (UV) spectra were recorded on a Varian Cary 50 Conc. NMR spectra (^1H and ^{13}C , 2D homo and heteronuclear) were recorded on a Bruker Avance 300, Jeol JNM-LA400, or Jeol ECA 500. High-resolution MS experiments were performed using a JEOL JMS-700TZ time-of-flight mass spectrometer.

2.3.1. Synthesis of protected iodophenol

2.3.1.1. Preparation of 4-iodophenylacetate **2.1**

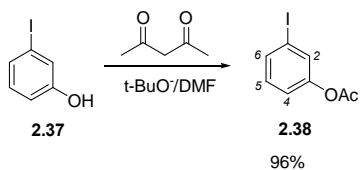


Para-iodophenol **2.36** was added (2g, 0.009 mol) to dry DMF (40 mL) stirred under nitrogen. Sodium hydride, (0.37g, 0.009 mol) was added to the solution mixture followed by the addition of acetic anhydride (1.71 mL, 0.018 mol). The mixture was left stirring overnight at room temperature. After the complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to produce **2.1** in 99% yield.

4-iodophenylacetate **2.1** (CAS No: 936753-64-9)

^1H NMR (300 MHz, CDCl_3) δ ppm: H13/11 7.70 (d; J = 8.7 Hz; 2 H), H14/10 6.87(d; J = 9 Hz; 2 H), -COCH₃ 2.31 (s; 3 H).

2.3.1.2. Preparation of 3-iodophenylacetate **2.38**



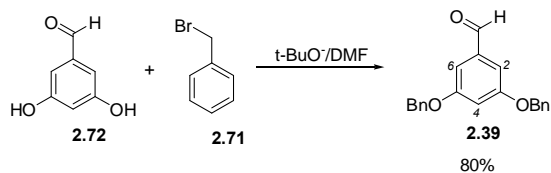
Replacement of **2.36** with 3-iodophenol **2.37** (5 g, 0.0227 mol) in the presence of (4.3 mL, 0.0454 mol) with potassium tertiary butoxide (3.82g, 0.03405 mol) in DMF (100 mL) reaction formed **2.38** in 96% yield as a solid.

3-iodophenylacetate **2.38** (CAS No: 42861-71-2)

^1H NMR (300 MHz, CDCl_3) δ ppm: H5 7.55 (m; 1 H), H2 7.46 (t; $J = 3.9$ Hz, 1.8 Hz; 1 H), H6 7.08 (m; 1 H), H4 7.08 (m, 1 H), $-\text{COCH}_3$ 2.30 (s; 3 H).

2.3.2. Synthesis of protected 3,5-dihydroxybenzaldehyde

2.3.2.1. Preparation of 3,5-dibenzyloxybenzaldehyde **2.39**



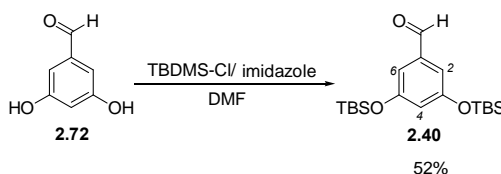
Potassium tertiary butoxide (8 g, 0.072 mol) was added to a stirring solution of 3,5-dihydroxybenzaldehyde **2.72** (5 g, 0.036 mol) in dry DMF (150 mL) under nitrogen. After ten minutes, benzyl bromide **2.71** (8.5 mL, 0.072 mol) was added to the reaction mixture and was left to stir overnight. As there was complete consumption of the starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced

pressure. The crude mixture was separated by column chromatography to produce **2.39** in 80% isolated yield

3,5-dibenzyloxybenzaldehyde **2.39** (CAS No: 14615-72-6)

^1H NMR (300 MHz, CDCl_3) δ ppm: CHO 9.10 (s; 1 H), 7.20- 7.50 (m; 10H), $\text{H}_{6/2}$ 7.15 (s; 2 H), H_4 6.90 (s, 1 H), CH_2 5.12 (s; 4 H).

2.3.2.2. Preparation of 3,5-bis(*tert*-butyldimethylsilyloxy)benzaldehyde **2.40**



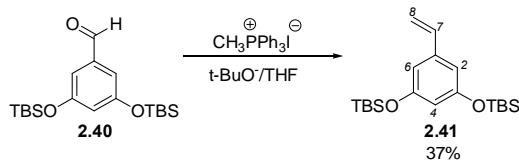
Imidazole (2.45 g, 0.036 mol) was added to a stirring solution of **2.72** (1 g, 0.0072 mol) in dry DMF (20 mL) under nitrogen. After 10 minutes, TBDMS-Cl (2.6 g, 0.0144 mol) was added to the reaction mixture at room temperature and left to stir overnight. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to produce **2.40** in 52% isolated yield.

3,5-bis(*tert*-butyldimethylsilyloxy)benzaldehyde **2.40** (CAS No: 187803-40-3)

^1H NMR (300 MHz, CDCl_3) δ ppm: CHO 9.88 (s, 1 H), $\text{H}_{6/2}$ 6.97 (d; $J = 2.1$ Hz; 2 H), H_4 6.61 (t; $J = 2.4$ Hz; 1 H), *t*-Bu 1.01 (s; 18 H), Si- CH_3 0.24 (s; 12 H).

2.3.3. Synthesis of protected styrenes

2.3.3.1. Preparation of 3,5-bis(*tert*-butyldimethylsilyloxy)styrene **2.41**

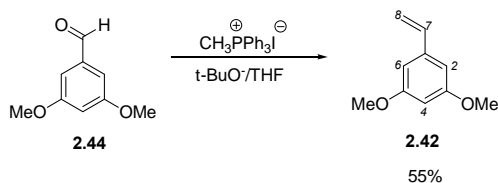


Potassium tertiary butoxide (3.5 mL, 0.0035 mol) was added to a stirring solution of methytriphenylphosphonium iodide (1.41 g, 0.0035 mol) in THF (65 mL) under nitrogen in an ice bath (0°C). Then, 3,5-bis(*tert*-butyldimethylsilyloxy)benzaldehyde **2.40** (1.2 g, 0.0035 mol) was added to the reaction mixture and continuously stirred overnight. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was purified by column chromatography to produce **2.41** in 37% yield.

3,5-bis(*tert*-butyldimethylsilyloxy)styrene **2.41** (CAS No: 193695-64-6)

^1H NMR (400 MHz, CDCl_3) δ ppm: H7 6.38 (dd; $J = 17.6$ Hz, 10.8 Hz, 1 H), H6/2 6.32 (d, $J = 2$ Hz; 2 H), H4 6.06 (t; $J = 2.4$ Hz; 1 H), H $^{\alpha}$ 8 5.46 (d; $J=17.6$ Hz; 1 H), H $^{\beta}$ 8 4.99 (d; $J = 10.8$ Hz; 1 H), t-Bu 0.79 (s; 18 H), Si-CH₃ 0.0 (s; 12 H).

2.3.3.2. Preparation of 3,5-dimethoxy styrene **2.42**

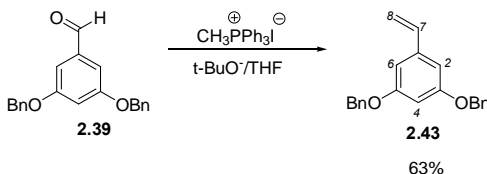


Potassium tertiary butoxide (15 mL, 0.015 mol) was added to a stirring solution of methytriphenylphosphonium iodide (6.1 g, 0.015 mol) in THF (125 mL) under nitrogen in an ice bath (0°C). Then, 3,5-dimethoxybenzaldehyde, **2.44** (1.2 g, 0.0035 mol) was added to the reaction mixture and was left to stir overnight. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to produce **2.42** in 55% isolated yield.

3,5-dimethoxy styrene **2.42** (CAS No: 40243-87-6)

¹H NMR (300 MHz, CDCl₃) δ ppm: H⁷ 6.65 (dd; J = 17.7 Hz; 11.1 Hz; 1 H), H^{6/2} 6.57 (d; J = 2.1 Hz, 2 H), H⁴ 6.39 (t; J = 3.0 Hz, 1.5 Hz; 1 H), H^α 5.73 (d, J = 17.7, 1 H), H^β 5.25 (d, J = 10.8 Hz; 1 H), OCH₃ 3.81 (s; 3 H).

2.3.3.3. Preparation of 3,5-dibenzyloxy styrene **2.43**



Potassium tertiary butoxide (0.5 g, 0.0044 mol) was added to a stirring solution of methytriphenylphosphonium iodide (1.8 g, 0.0044 mol) in THF (70 mL) under nitrogen in an ice bath (0°C). Then, **2.39** was (1.4 g, 0.0044 mol) added to the

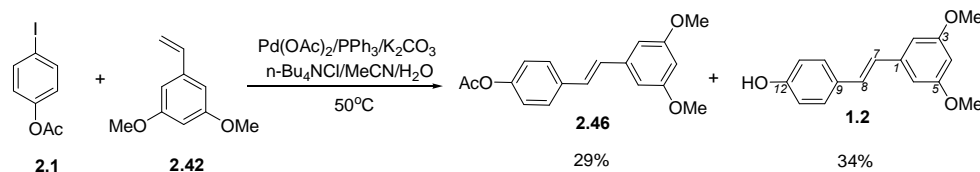
reaction mixture and was left to stir overnight. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to produce **2.43** in 63% isolated yield.

3,5-dibenzyloxy styrene **2.43** (CAS No: 185254-54-0)

^1H NMR (300 MHz, CDCl_3) δ ppm: 7.25-7.5 (m; 10H), H6/2 6.71 (s; 2 H), H7 6.20 (dd; $J = 16.5$ Hz, 10 Hz; 1 H), H α 8 5.75 (d; $J = 16.5$ Hz; 1 H), H4 5.68 (s; 1 H), H β 8 5.28 (d; $J = 10$ Hz; 1 H), CH₂ 5.09 (s; 4 H).

2.3.4. Synthesis of substituted stilbenes

2.3.4.1. Preparation of **2.46** & **1.2**



To a solution of $\text{Pd}(\text{OAc})_2$ (0.035 g, 0.075 mmol), PPh_3 (0.039 g, 0.15 mmol), K_2CO_3 (0.52 g, 3.75 mmol) and $n\text{-Bu}_4\text{NCl}$ (0.42 g, 0.0015 mol) in a 4 mL mixture of $\text{MeCN}/\text{H}_2\text{O}$ (1:1, v/v) were added **2.1** (0.4 g, 0.0015 mol) and **2.42** (0.3 g, 0.0018 mol) and the mixture was stirred for 24 hours at 50°C . As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced

pressure. The crude mixture was separated by column chromatography to produce **2.46** (29%) and **1.2** (34%).

Compound 1.2 (CAS No: 1158183-45-9)

UV: (λ_{max} , MeOH): 305 nm.

IR (film) ν_{max} : 3392 cm^{-1}

ESI-TOF-MS(-): $[\text{M-H}]^-$; m/z 255.1031 measured, 255.1021 calculated for $\text{C}_{16}\text{H}_{15}\text{O}_3$,
 $m/m = 3.9$ ppm

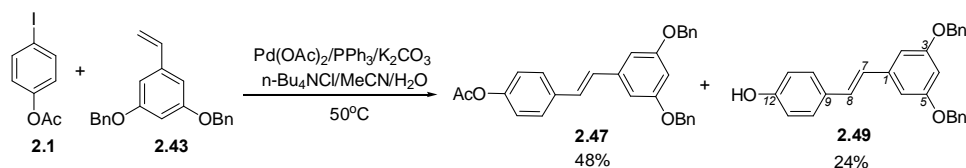
^1H NMR (500 MHz, CDCl_3) δ ppm: H14/10 7.4 (d; $J = 8.6$ Hz; 2 H), H7 7.02 (d; $J = 16.1$ Hz; 1 H), H8 6.89 (d; $J = 16.1$ Hz; 1 H), H13/11 6.82 (d; $J = 8.8$ Hz; 2 H), H6/2 6.65 (d; $J = 2.2$ Hz; 2 H), H4 6.38 (t; $J = 2.2$ Hz; 1 H), $-\text{OCH}_3$ 3.83 (s; 3 H).

^{13}C NMR (125 MHz, CDCl_3): C5/3 160.96, C12 155.34, C1 139.68, C9 130.16, C14/10 128.03, C7 128.71, C8 126.66, C13/11 115.65, C6/2 104.43, C4 99.68, OCH_3 55.39

Compound 2.46 (CAS No: 63366-83-6)

^1H NMR (400 MHz, CDCl_3) δ ppm: H13/10 7.48 (d, $J = 8.5$ Hz; 2 H), H14/11 7.08 (d; $J = 8.3$ Hz; 2 H), H7 7.05 (d, $J = 15.88$ Hz; 1 H), H8 6.97 (d; $J = 16.4$ Hz; 1 H), H6/2 6.66 (d, $J = 1.92$ Hz; 2 H), H4 6.40 (t, $J = 1.92$ Hz; 1 H), $-\text{OCH}_3$ 3.81 (s; 6 H), $-\text{COCH}_3$ 2.29 (s; 3 H)

2.3.4.2. Preparation of 2.47 & 2.49



Compound **2.43** was added (0.88 g, 0.0028 mol) followed by addition of **2.1** (0.72 g, 0.0028 mol), $\text{Pd}(\text{OAc})_2$ (0.064 g, 0.14 mmol), PPh_3 (0.072 g, 0.28 mmol),

K₂CO₃ (0.95 g, 0.007 mol) and n-Bu₄NCl (0.87 g, 0.0028 mol) in 6 mL mixture of MeCN/H₂O (5:1, v/v) to produce stilbenes **2.47** and **2.49** in 48% and 24% isolated yields respectively.

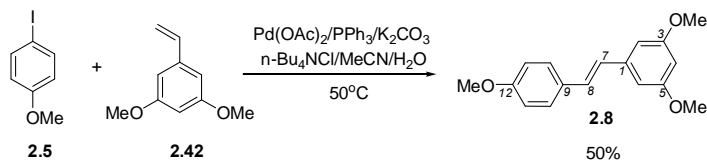
Compound **2.47**

¹H NMR (500 MHz, CDCl₃) δ ppm: H14/10 7.53 (d; J = 8.1 Hz; 2 H), 7.52-7.35 (m; 10H), H13/11 7.13 (d, J = 8.1 Hz, 1 H), H7 7.09 (d; J = 16.3 Hz; 1 H), H8 7.01 (d; J = 16.3 Hz; 1 H), H6/2 6.83 (d, J = 2.2 Hz, 2 H), H4 6.61 (t, J = 2.2 Hz; 1 H), -CH₂ 5.11 (s; 4 H) -COCH₃ 2.31 (s; 3 H).

Compound **2.49** (CAS No: 678149-05-8)

¹H NMR (500 MHz, CDCl₃) δ ppm: 7.55-7.35 (m; 10H), H14/10 7.37 (d; J = 8.5 Hz; 2 H), H7 7.04 (d; J = 16.2 Hz; 1 H), H8 6.91 (d; J = 16.3 Hz; 1 H), H13/11 6.84 (d; J = 8.45 Hz; 2 H), H6/2 6.79 (d, J = 1.9 Hz; 2 H), H4 6.58 (s; 1 H), -CH₂ 5.11 (s, 4 H).

2.3.4.3. Preparation of **2.8**

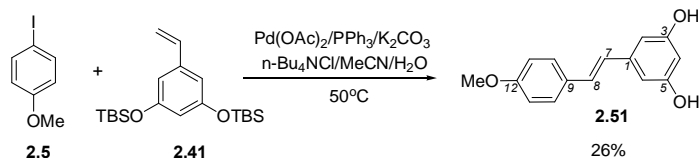


Compound **2.43** was replaced by **2.42** (0.17 g, 0.0009 mol) and **2.1** with **2.5** (0.2 g, 0.0009 mol). The solution was stirred in 2 mL of H₂O with Pd(OAc)₂ (0.02 g, 0.045 mmol), PPh₃ (0.02 g, 0.09 mmol), K₂CO₃ (0.29 g, 0.002mol) and n-Bu₄NCl (0.24 g, 0.0009 mol) to produce stilbene **2.8** in 50% isolated yield.

Compound **2.8** (CAS No: 916484-65-6)

¹H NMR (300 MHz, CDCl₃) δ ppm: H13/10 7.48 (d; J = 8.7 Hz; 2 H), H7 7.08 (d; J = 16.2 Hz, 1 H), H8 6.95 (d; J = 16.2 Hz, 1 H), H14/11 6.93 (d, J = 8.7 Hz; 2 H), H6/2 6.69 (d, J = 2.1 Hz; 2 H), H4 6.42 (t, J = 2.1 Hz; 1 H), OCH₃ 3.89 (s; 9 H).

2.3.4.4. Preparation of 2.51

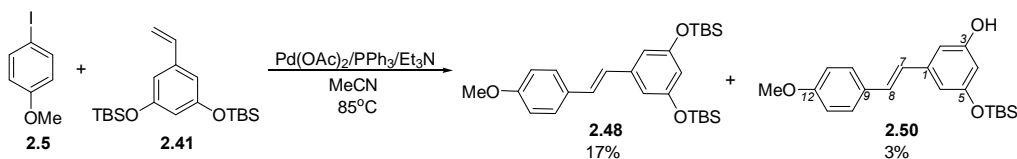


To a solution of $\text{Pd}(\text{OAc})_2$ (0.02 g, 0.075 mmol), PPh_3 (0.04 g, 0.15 mmol), K_2CO_3 (0.52 g, 3.75 mmol) and $n\text{-Bu}_4\text{NCl}$ (0.12 g, 0.18 mmol) in a 4 mL mixture of $\text{MeCN}/\text{H}_2\text{O}$ (1:1, v/v) were added **2.5** (0.4g, 0.0015 mol) and **2.41** (0.3g, 0.0018mol) and the mixture was stirred for 24 hours at 50°C . As there was complete consumption of starting material, the mixture was quenched with saturated NaCl and extracted with ethyl acetate. The combined ethyl extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by flash column chromatography on a Flashmaster Personal⁺ on a Isolute[®] SPE silica cartridge to yield **2.51** (26%).

Compound **2.51** (CAS No:905434-23-3)

^1H NMR (400 MHz, deuterated acetone) δ ppm: $-\text{OH}$ 8.15(br s), H14/10 7.36 (d; $J = 8.8$ Hz; 2 H), H7 6.92 (d, $J = 16.4$ Hz, 1 H), H8 6.80 (d, $J = 16.4$ Hz, 1 H), H13/11 6.78 (d; $J = 8.8$ Hz; 2 H), H6/2 6.42 (d; $J = 2$ Hz; 2 H), H4 6.15 (t; $J = 2$ Hz; 1 H), $-\text{OCH}_3$ 3.67 (s; 3 H).

2.3.4.5. Preparation of 2.48 & 2.50



To a solution of $\text{Pd}(\text{OAc})_2$ (0.026 g, 0.055 mmol), PPh_3 (0.09 g, 0.35 mmol), Et_3N (17 mL, 0.12 mol) in 33 mL of MeCN were added **2.5** (1.54 g, 0.0066 mol) and

2.41 (2.0g, 0.0055 mol) and the mixture was stirred for 48 hours at 85°C. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to yield **2.48** (17%) and **2.50** (3%).

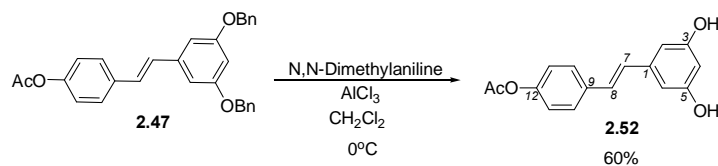
Compound **2.48** (CAS No:192710-87-5)

¹H NMR (400 MHz, CDCl₃) δ ppm: H14/10, 7.22 (d; J = 8.5 Hz; 2 H), H7 6.75 (d, J = 16.1 Hz; 1 H), H13/11 6.67 (d, J = 8.8 Hz; 2 H), H8 6.62 (d, J = 16.4 Hz, 1 H), H6/2 6.38 (d; J = 2.2 Hz, 2 H), H4 6.02 (t, J = 2.2 Hz, 1 H), -OCH₃ 3.62 (s; 3 H), t-Bu 0.80 (s; 18 H), Si-CH₃ 0.0 (s; 12 H).

Compound **2.50**

¹H NMR (400 MHz, CDCl₃) δ ppm: H14/10 7.21 (d; J = 8.8 Hz; 2 H), H7 6.75 (d; J = 16.0 Hz; 1 H), H13/11 6.67 (d; J = 8.8 Hz; 2 H), H8 6.61 (d; J = 16.4 Hz; 1 H), H6 6.37 (s; 1 H), H2 6.33 (s; 1 H), H4 6.03 (t, 1 H, J = 2 Hz), -OCH₃ 3.60 (s; 3 H), t-Bu 0.77 (s; 9 H), Si-CH₃ 0.0 (s; 6 H).

2.3.4.6. Preparation of 2.52



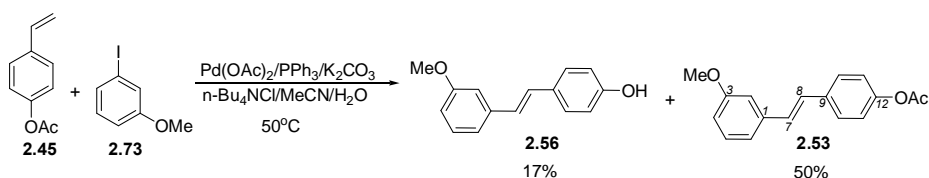
To a solution of **2.47** (0.05 g, 0.11 mmol) and *N,N*-dimethylaniline (0.5 ml, 3.3 mol) in 5 mL of CH₂Cl₂ was added AlCl₃ (0.09 g, 0.66 mol). The mixture was stirred for 24 hours at 0°C. As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl

acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by preparative silica-gel TLC to yield **2.52** (60%).

Compound **2.52** (CAS No:411233-11-9)

^1H NMR (500 MHz, deuterated acetone) δ ppm: -OH 8.26 (br s), H14/10 7.60 (d; J = 8.6 Hz; 2 H), H13/11 7.11 (d; J = 8.8 Hz, 2 H), H7 7.10 (d; J = 16.35 Hz, 1 H), H8 7.06 (d; J = 16.35 Hz, 1 H), H6/2 6.59 (d; J = 2.1 Hz, 2 H), H4 6.32 (t, J = 2.52 Hz, 1 H), -COCH₃ 2.07 (s; 3 H).

2.3.4.7. Preparation of 2.56 & 2.53



Compound **2.42** was replaced by **2.45** (3.3 g, 0.0204 mol) and **2.1** by commercially available **2.73** (4 g, 0.017 mol). The solution was stirred in 22 mL mixture of MeCN/H₂O (10:1, v/v) with Pd(OAc)₂ (0.4 g, 0.001 mol), PPh₃ (0.45 g, 0.002 mol), K₂CO₃ (5.87 g, 0.051 mol) and n-Bu₄NCl (4.72 g, 0.0204 mol) to produce stilbenes **2.56** (17%) and **2.53** (50%).

Compound **2.56** (CAS No:128294-46-2)

UV: (λ_{max} , MeOH): 315, 305 nm.

IR (film) ν_{max} : 3308 cm^{-1}

ESI-TOF-MS(-): [M-H]⁻; m/z 225.0917 measured, 225.0916 calculated for C₁₅H₁₃O₂,

m/m = 0.44 ppm

^1H NMR (500 MHz, CDCl₃) δ ppm: H14/10 7.40 (d; J = 8.5 Hz; 2 H), H5 7.25 (t; J = 7.81 Hz; 1 H), H6 7.08 (d; J = 7.6 Hz; 1 H), H7 7.04 (d; J = 16.4 Hz; 1 H), H2 7.02 (s;

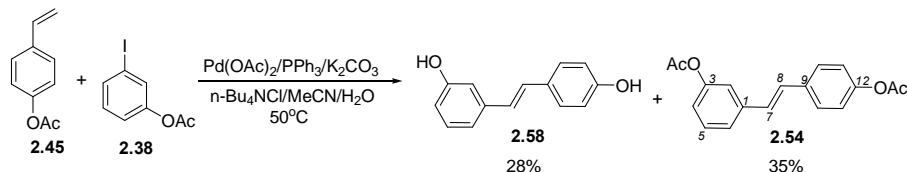
1 H), H8 6.93 (d; J = 16.4 Hz; 1 H), H13/11 6.82 (d; J = 8.5 Hz; 2 H), H4 6.80 (dd; J = 8.3 Hz, J = 2.0 Hz; 1 H), -OCH₃ 3.84 (s; 3 H).

¹³C NMR (125 MHz, CDCl₃): C3 159.86, C12 155.30, C1 139.11, C9 130.29, C5 129.62, C7 128.5, C14/10 127.99, C8 126.59, C6 119.07, C13/11 115.64, C4 112.95, C2 111.58, OCH₃ 55.28

Compound 2.53

¹H NMR (400 MHz, CDCl₃) δ ppm: H14/10 7.51 (d; J = 8.6 Hz; 2 H), H5 7.28 (t; J = 7.8 Hz; 1 H), H6 7.11-7.07 (m, 1 H), H13/11 7.08 (d; J = 8.6 Hz; 2 H), H7 7.07 (d; J = 16.1 Hz; 1 H), H2 7.04 (s; 1 H), H8 7.02 (d; J = 16.1 Hz; 1 H), H4 6.82 (dd; J = 7.56 Hz, 2.0 Hz; 1 H), -OCH₃ 3.88 (s; 3 H), -COCH₃ 2.30 (s; 3 H).

2.3.4.8. Preparation of 2.58 & 2.54



Compound **2.42** was replaced by **2.45** (3.2 g, 0.02 mol) and **2.5** with **2.38** (5.0 g, 0.02 mol). The solution was stirred in 28 mL mixture of MeCN/H₂O (25:3, v/v) with Pd(OAc)₂ (0.47 g, 0.001mmol), PPh₃ (0.52 g, 0.002 mol), K₂CO₃ (6.9 g, 0.05mol) and n-Bu₄NCl (6.4 g, 0.02 mol) to produce stilbenes **2.58** and **2.54** in 58% and 5% isolated yields respectively.

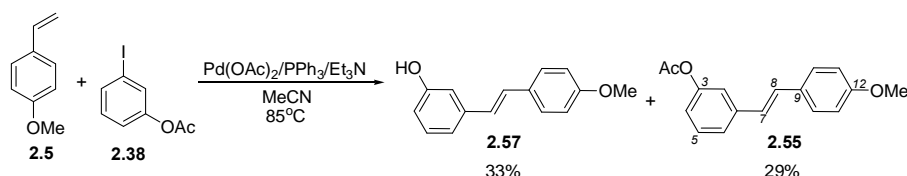
Compound 2.58 (CAS No:63877-76-9)

¹H NMR (500 MHz, deuterated acetone) δ ppm: -OH 8.37 (s), H14/10 7.44 (d; J = 8.4 Hz; 2 H), H5 7.17 (t; J = 8.1 Hz; 1 H), H7 7.09 (d; 16.4 Hz; 1 H), H6&2 7.05-7.00 (m; 2 H), H8 6.98 (d; 16.4 Hz; 1 H), H13/11 6.85 (d; J = 8.5 Hz; 2 H); H4 6.73 (d; J = 8.2 Hz; 1 H).

Compound 2.54 (CAS No:65819-32-1)

^1H NMR (500 MHz, CDCl_3) δ ppm: H14/10 7.51 (d; $J = 8.6$ Hz; 2 H), H6&H5 7.40-7.32 (m; 2 H), H2 7.25 (br s; 1 H), H13/11 7.10 (d; $J = 8.5$ Hz; 2 H), H7 7.08 (d; $J = 16.3$ Hz; 1 H), H8 7.03 (d; $J = 16.3$ Hz; 1 H), H4 7.02-6.08 (m; 1 H), $-\text{COCH}_3$ 2.33 (s; 3 H), $-\text{COCH}_3$ 2.32 (s; 3 H).

2.3.4.9. Preparation of 2.57 & 2.55



To a solution of $\text{Pd}(\text{OAc})_2$ (0.16 g, 0.34 mmol), PPh_3 (0.06 g, 0.23 mmol), Et_3N (11 mL, 0.079 mol) in 24 mL of MeCN were added **2.45** (0.6 mL, 0.0045 mol) and **2.38** (1.0 g, 0.0045 mol) and the mixture was stirred for 48 hours at 85°C . As there was complete consumption of starting material, the mixture was quenched with a saturated NaCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was separated by column chromatography to yield **2.57** (33%) and **2.55** (29%).

Compound 2.57 (CAS No:110993-22-1)

^1H NMR (400 MHz, CDCl_3) δ ppm: H14/10 7.45 (d; $J = 8.6$ Hz; 2 H), H5 7.21 (t; $J = 8.1$ Hz; 1 H), H6 7.06 (d; $J = 7.6$ Hz; 1 H), H7 7.03 (d; $J = 16.3$ Hz; 1 H), H2 6.97 (br t; $J = 2.0$ Hz; 1 H), H8 6.91 (d; $J = 16.3$; 1 H), H13/11 6.89 (d; $J = 8.5$ Hz; 2 H), H4 6.71 (dd; $J = 8.1$ Hz, 2.4 Hz; 1 H), $-\text{OCH}_3$ 3.87 (s; 3 H)

Compound 2.55

^1H NMR (400 MHz, CDCl_3) δ ppm: H14/10 7.45 (d; $J = 8.8$ Hz; 2 H), H5/6 7.38-7.32 (m; 2 H), H-2 7.23 (br s; 1 H), H7 7.06 (d; $J = 16.1$ Hz; 1 H), H4 6.99-6.95 (m; 1 H), H8 6.94 (d; $J = 16.1$ Hz; 1 H), H13/11 6.91 (d; $J = 8.8$ Hz; 2 H), $-\text{OCH}_3$ 3.83 (s; 3 H), $-\text{COCH}_3$ 2.32 (s; 3 H).

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