CHAPTER 3. ELECTROCHEMICAL OXIDATIONS ON SOME STILBENE ANALOGUES

Electrolysis can be one of the important techniques in generating efficient and selective C,C-bond and functional group interconversions by activation of substrates *via* electron transfer, generated by direct electric current (DC). To explore the synthetic application of this technique to our molecules, some of the stilbene derivatives we have prepared (Figure 2.2 and 2.3, Chapter 2) were subjected to anodic oxidations after measurement of their oxidation potentials as described below. This chapter is divided into three sections; introduction to stilbene oxidation and electrochemistry, results and mechanistic discussions on the application of electrochemistry technique on stilbene derivatives and finally, their experimental procedures.

3.1. Introduction to stilbene oxidation and electrochemistry

In this section, some generalizations on phenolic oxidation as well as general concepts on phenol electrochemical oxidation are discussed. In conjunction to this, anodic oxidations work on some stilbene derivatives that have been published by several authors have been reviewed herein as well.

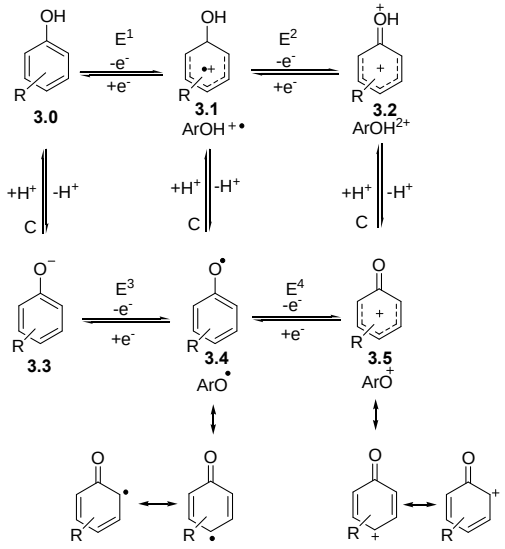
3.1.1. Generalities on phenolic oxidation

The biosynthesis of most complex plant-derived phenolic products results of radical coupling reactions that are initiated by one electron oxidations of free arenols.[1a,1b] Herein, the conversion of arenol derivatives to either $ArO^{•}$, ArO^{+}, or $ArOR^{+•}$ is highlighted. These reactive intermediates can be obtained not only by the standard chemical reaction but also through the electrochemical oxidative activation modes, which will be discussed in detail.

Different kinds of radical combination lead to various types of regioisomeric coupling products. According to Waterôs proposal, apart from the C-O coupling products, *ortho-ortho*, *para-para* and *ortho-para* C-C coupling are also possible.[2a,2b] The relative proportions of these products are dependent on the steric factor and electronic properties of the substituted aromatic ring that influence the generation of $ArO^{•}$ intermediate.

Studies have shown that phenols are easily oxidized to give quinolide systems, which might be rearomatised or transformed into many other useful classes of compounds. The primary oxidation process involves electron transfers (ó*E*ô processes) and proton transfers (ó*C*ô chemical processes) as shown in Scheme 3.1.[3] All three species, neutral phenol **3.0**, cation radical **3.1** and dication **3.2** undergo two successive one-electron transfers, which are in equilibrium with their deprotonated forms, anion **3.3** neutral phenoxyl radical **3.4** and phenoxenium cation **3.5** respectively. Electroanalytical studies revealed two interesting results that depend on the absence and presence of a base. In the absence of a base, phenol **3.0** is oxidized to cation-radical **3.1** at E^1 (1.0 ï 1.4 V) *via* a one-electron transfer followed by deprotonation to give the neutral phenoxyl **3.4**. Since $E^4 < E^1$ **3.4** is spontaneously oxidized to the cation **3.5** at the applied potential (ECE reaction). Alternatively, reaction condition in

the presence of a base produces phenolate **3.3** from **3.0** followed by anodic oxidation to generate phenoxyl radical **3.4** at E^3 = -0.6 to +0.3 V selectively (CE process). When the potential, E^4 is higher than E^3 (E^4 = 0.7 to 0.8 V) radical **3.4** is further oxidized to phenoxenium ion **3.5** in a one-electron transfer manner (CEE) despite of its instability in basic medium. In conclusion, phenoxyl **3.4** or phenoxenium ion **3.5** can be selectively generated by modifying the potentials and acidity/basicity of the medium. The reactivity of the phenoxyls **3.4** and phenoxenium ions **3.5** are the controlling factors in determining the formation of final reaction products. The resonance structures of both the species are shown in Scheme 3.1.



Scheme 3.1: Phenol oxidation producing $ArOH^{+Å}$, $ArO^{Å}$or ArO^{+}.[3]

The electrochemical processes that are shown in Scheme 3.1 are also applicable to reactions carried out in presence of chemical oxidants. In this case, oxidant and substrate now have to come into contact in a bimolecular step, which then will influence the kinetics. The potential of the oxidant is fixed (unless a limited influence is possible via pH adjustment) while the electrode is changeable.[3] The

reaction between oxidant and any of the electrochemically generated species (**3.0**-**3.5**) as a result of non-redox processes also should be considered.

Transition and heavy metals such as copper(I/II), silver(I/II), mercury(II), cobalt(III), iron(III), thalium(III), manganese(III/IV), cerium(IV), lead(IV), ruthenium(IV), titanium(IV), zirconium(IV), vanadium(IV/V), bismuth(V), chromium(VI), and molybdenum(VI) are some of the oxidizing reagents used in either one- or two-electron oxidation of phenolic compounds into $ArO^{Å}$ and ArO^{+} species respectively.[3-6] Below are some examples.

a) one-electron oxidants:

   alkaline potassium hexacyanoferrate(III), silver(I) oxide, silver(I) acetate, iron(III) chloride.

b) two- electron oxidants[7-10]:

   thalium(III) trinitrate, lead(IV) tetraacetate (LTA), copper(II)-amine/oxygen complexes, vanadium(V) oxytrifluoride and manganese(III) tris(acetylacetonate).

Non-metallic oxidizing agents such as iodobenzene diacetate (PIDA), iodobenzene bis(trifluoroacetate) (PIFA), *ortho*-quinone chloranil (tetrachloro-1,2-benzoquinone) and *para*-quinone DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) are organic species with a potential high enough to perform two-electron oxidation of phenolic compounds.[2,3]

Oxidase enzymes also share the single electron transfer properties of certain transition metals like iron, copper and manganese to undergo catalytic radical-mediated transformations in the presence of oxygen or hydrogen peroxide. Some of the examples of oxidase enzymes are laccases, peroxidases, tyrosinases, catecholases and polyphenoloxidases.[2b,3,11-14]

3.1.2. Concepts on phenol electrochemical oxidation

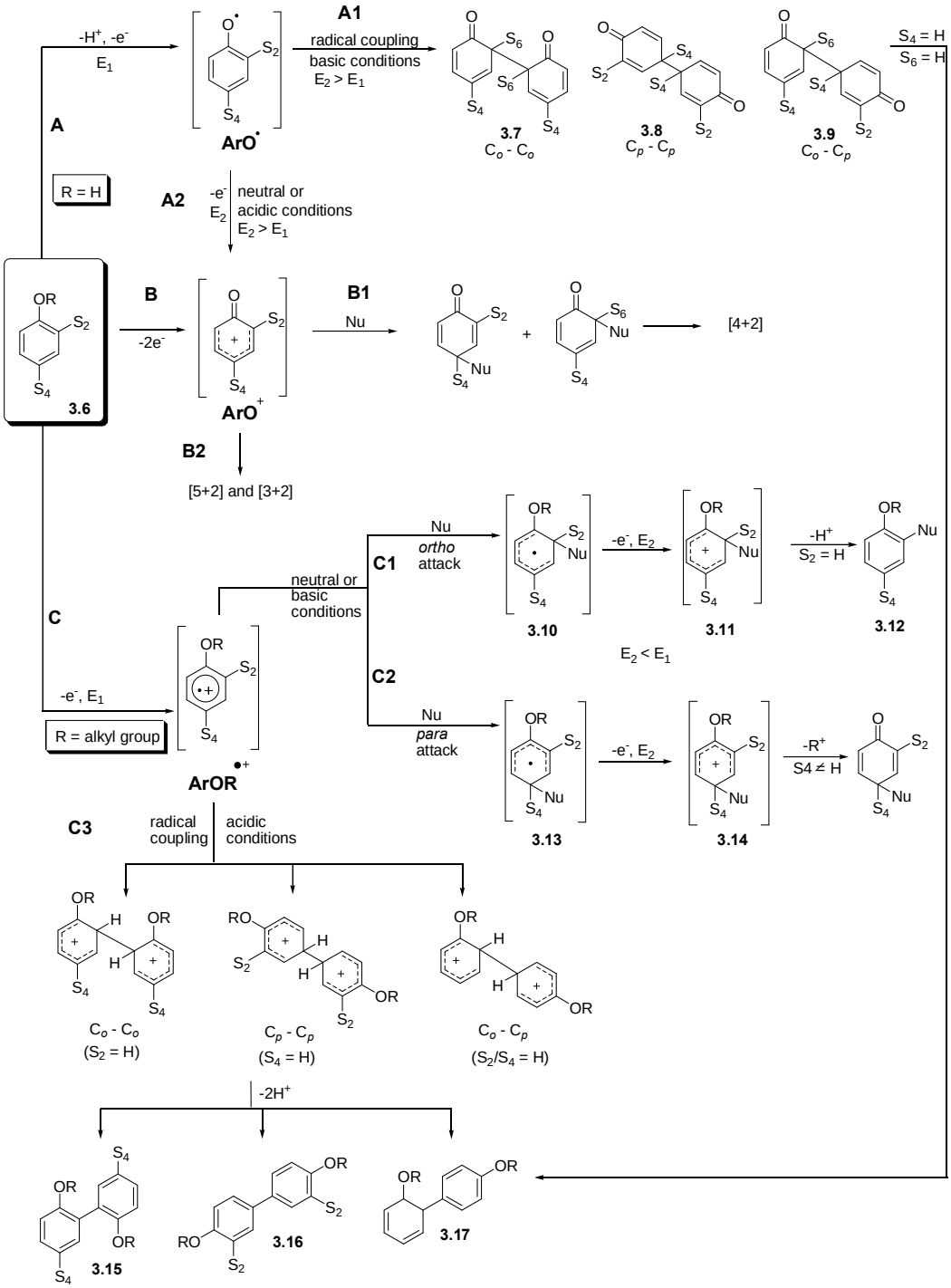
Electrochemical conversions can be carried out in two ways: constant-current or controlled-potential electrolysis. Both these methods have their advantages and disadvantages. Controlling the electric current and electric potential is equivalent to controlling the amount of reagent and reactivity in chemical reactions.

In constant current electrolysis (CCE), the flow of current through the electrochemical cell is kept at constant value while the anode potential rises up to a value enough for oxidizing the species with the lowest oxidation potential. Due to the increasing potential at the anode, loss of selectivity can appear at the end of the electrolysis, and anodic oxidation of the product or other species can take place before total conversion of the starting material.

In contrast, controlled-potential anodic oxidation has high selectivity, since the anode potential is kept constant in relative to a reference electrode. At a particular applied potential value, only substrates with oxidation potential equal to or lower than that the set potential for anode will be oxidized. In general, products formed at anode will not go through the reverse reaction at the cathode. Therefore, an undivided cell is sufficient to carry out electrochemical reaction. If the reaction is reversible or when the desired product formed at one electrode can react unfavorably with the product generated at the other electrode, then a divided cell is used.[15]

Below are some of the examples on different types of radical combinations. For instance, neutral phenoxyl radical generates three different types of coupling products such as **3.7-3.9**, which eventually transformed into biaryls **3.15-3.17** through prototropic tautomerism when S_6 and/or S_4 are hydrogen atoms (Scheme 3.2, path A1). Nonhebel and co-workers proposed that C-C coupling is the result of combination of two $ArO^{Å}$ intermediates in a sandwich-like geometry so as to maximize

SOMO-SOMO interactions and to minimize electrostatic repulsion between the two oxygen atoms.[16] In the case of steric hindrance due to bulky ring substituents, then C-O coupling becomes the favored route since the sandwich-like geometry is not feasible.



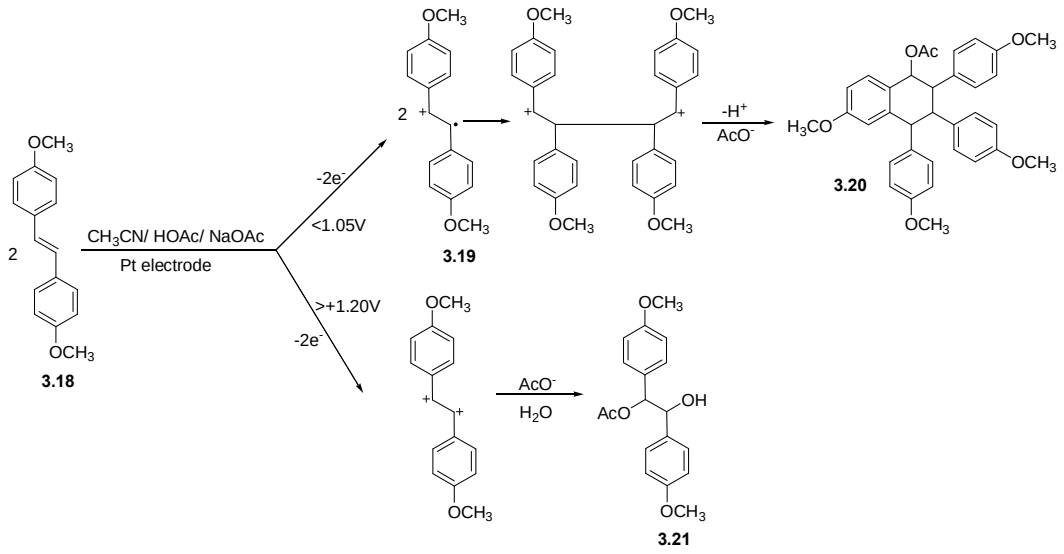
Scheme 3.2: Electrochemical mechanistic considerations for intermediates $ArO^{\cdot}$, ArO^{+}, or $ArOR^{+\cdot}$ in various conditions.[15]

The fact that ArO^{+} ions are unlikely to dimerise as neutral $ArO^{\cdot}$ radicals do, limits the number of coupling products. Scheme 3.2 path B1 shows phenoxenium

cation is susceptible to nucleophilic attacks either at *ortho*- or *para*-positions already bearing substituents, which should preferably be electron- releasing for better regiochemical control.[17-19] The third intermediate, $ArOR^{+Å}$ is obtained upon one-electron oxidation of aryl alkyl ether **3.6,** R = alkyl group (Scheme 3.2 path C). In neutral or basic conditions, cation radical, $ArOR^{+Å}$ is quenched by a nucleophile to give radical **3.10** or **3.13**. This radical is more easily oxidized than the starting arenol ether **3.6**, which then generate arenium ion intermediate **3.11/3.14** followed by rearomatization to afford **3.12** (Scheme 3.2 path C1).[20] Besides this, $ArOR^{+Å}$ also can undergo radical coupling to dicationic species en route leading towards biaryl products **3.15-3.17** (Scheme 3.2 path C3).

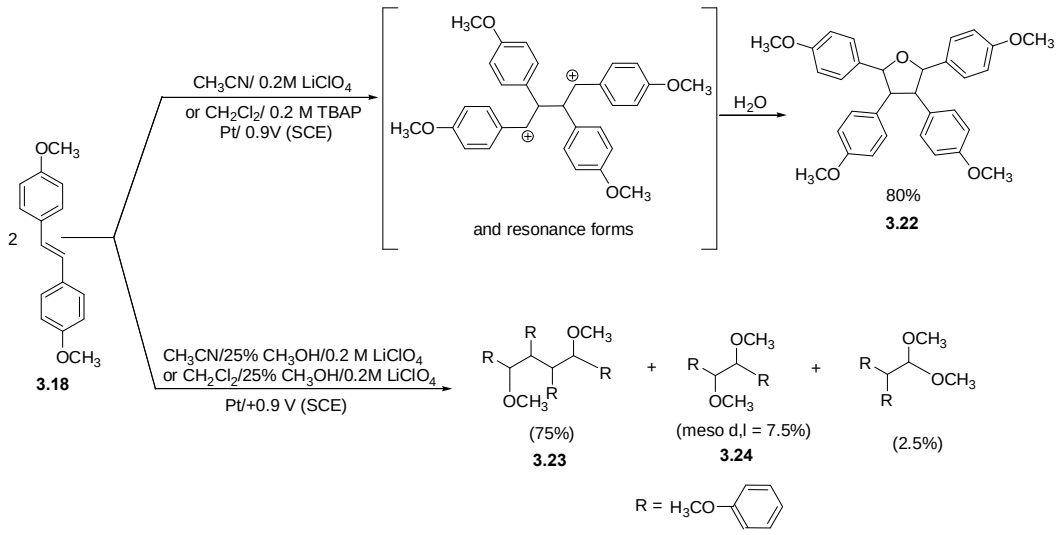
3.2. Previous work on stilbene electrochemistry

Eberson and Parker (1969)[21] described the formation of tetralin derivative **3.20** (stereochemistry not reported) by dimerization of 4,12-dimethoxystilbene **3.18** in the presence of acetate ion *via* cation radical cation intermediate **3.19** (Scheme 3.3). They proposed that at lower potentials a one-electron oxidation of 4,12-dimethoxystilbene takes place, which then leads to a rapid dimerisation, while at higher potentials a two-electron oxidation yields a monomeric adduct **3.21**.



Scheme 3.3: Anodic oxidative dimerization of 4,12-dimethoxystilbene in acetate buffer.[21]

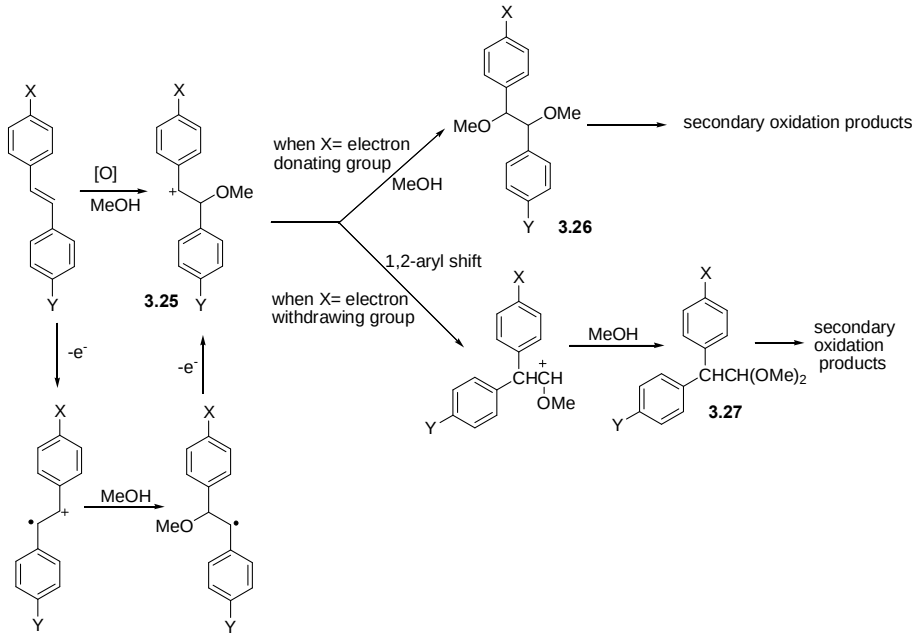
In 1978, Steckhan[22] published a detailed study of the anodic oxidation of 4,12-dimethoxystilbene **3.18** with Pt electrodes in different solvents. When carried out in CH_3CN or CH_2Cl_2 at controlled potential the formation of 2,3,4,5-tetraanisyltetrahydrofuran **3.22** is observed (Scheme 3.4). Under similar conditions using solvent mixtures of CH_3CN/CH_3OH or CH_2Cl_2/CH_3OH (2:1, v/v), the main product was the dimethoxylated open-chair dimer 1,2,3,4-tetraanisyl-1,4-dimethoxybutane **3.23** in 75% yield and 1,2-dianisyl-1,2-dimethoxyethane **3.24** as a minor product (7.5% yield).



Scheme 3.4: Anodic oxidative dimerization of 4,12-dimethoxystilbene in presence and absence of MeOH.[22]

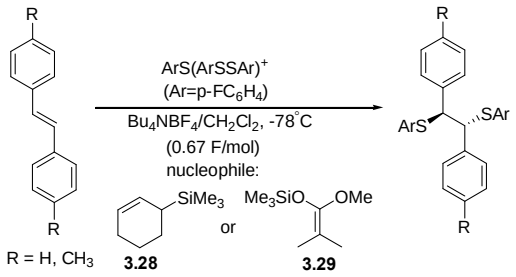
In Steckhanôs view, the anodic oxidative dimerization of olefins is governed by two mechanistic pathways, radical dimerization or electrophilic attack of the cation to the native substrate. He concluded that the radical dimerization of 4,12-dimethoxystilbene$^{+Å}$**3.19** dominates over its electrophilic attack to the native substrate in absence of a nucleophile. On the other hand, in presence of nucleophilic CH_3OH, the reaction of 4,12-dimethoxystilbene$^{+Å}$ **3.19** with the nucleophile predominates.

It is worth noting that Fry[23,24] has anodically oxidized substituted stilbenes bearing electron-withdrawing and/or donating groups in a divided cell in CH_3OH at a controlled potential. The products that were obtained resulted from cleavage, methoxy adducts **3.26**, occasionally accompanied with 1,2-aryl shift derivatives **3.27** (Scheme 3.5). No dimeric species was reported. According to them, the 1,2-aryl shift is dependent on the type of substituent present in the aromatic ring. For instance, if the substituent is an electron donor, the cation intermediate **3.25** can be stabilized against rearrangement by reducing the driving force for rearrangement.



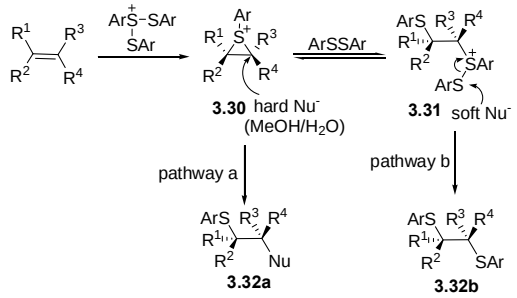
Scheme 3.5: Anodic oxidation of stilbene derivative at constant potential and itôs mechanistic consideration (adapted from reference 23).

Fujie *et al*. described the anodic oxidation of diaryl sulfides (ArSSAr) in CH_2Cl_2 (-78ºC) at constant current produced arylbis(arylthio)sulfonium ions [ArS(ArSSAr)$^+$], then reacted with stilbene derivatives and quenched with soft nucleophiles like allylsilanes **3.28**, ketene silyl acetals **3.29**, and triethylamine to furnish diarylthio-substituted compounds in a stereospecific manner (Scheme 3.6).[25]



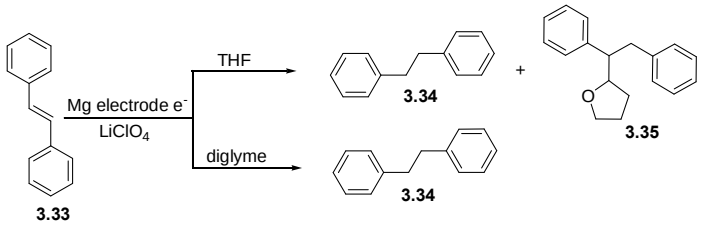
Scheme 3.6: Electrochemical oxidation of stilbene derivatives in presence of nucleophile.[25]

The mechanistic pathway is shown in Scheme 3.7 . Episulfonium ion intermediate **3.30** is the key intermediate in this mechanistic pathway, where it can also be in equilibrium with sulfonium intermediate **3.31** upon exposure of the three membered ring **3.30** to nucleophilic attack by ArSSAr. The type of nucleophile present, whether hard or soft will determine the choice of route either pathway a or b leading to **3.32a** and **3.32b** respectively.[25]



Scheme 3.7: Possible mechanistic pathways of episulfonium ion intermediate **3.30**.[25]

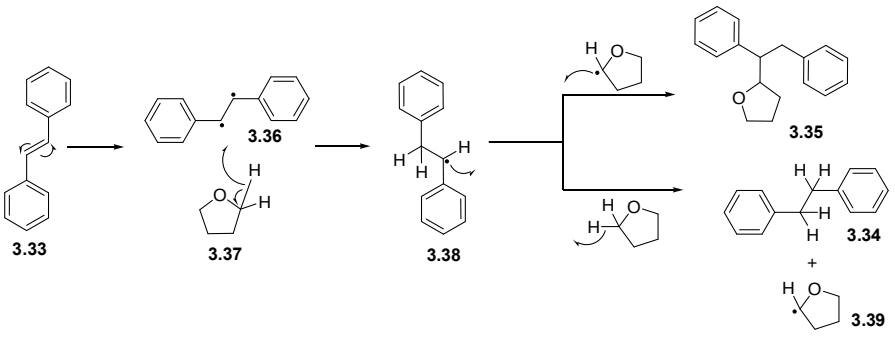
Jang *et al*. reported the electro reductive organic synthesis of bibenzyl **3.34** and 2-(1,2-diphenylethyl)tetrahydrofuran **3.35** by subjecting stilbene **3.33** to constant current in $LiClO_4$ as an electrolyte and Mg metal as an electrode (Scheme 3.8)[26]



Scheme 3.8: Electro reduction of stilbene.[26]

Bibenzyl **3.34** was obtained through abstraction of α-hydrogen atom from THF **3.37** by biradical **3.36** while compound **3.35** is obtainable through coupling of the resulting THF radical **3.39** with the monoradical **3.38** (Scheme 3.9). However,

replacing THF with diglyme as a solvent, produced bibenzyl **3.34** solely suggesting that diglyme radical equivalent to **3.39** has a short life time in the reaction medium.[26]



Scheme 3.9: Mechanistic consideration of stilbene electrochemical reduction in presence of solvent THF.[26]

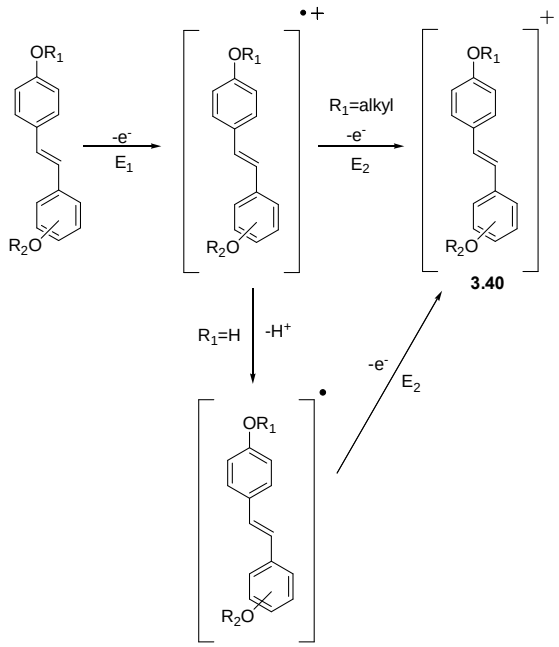
3.3. Results and discussion

In this study, constant current electrolysis (CCE) was carried out on some stilbenoids containing free hydroxyl and electron withdrawing substituents in pure CH_2Cl_2 and CH_2Cl_2/MeOH mixture to observe the resulting pattern of electrochemical oxidation. Prior to the application of this technique, oxidation potentials of a series of stilbene derivatives are measured in order to assess their redox properties. This will be followed by a spectroscopic as well as mechanistic discussions on the above anodic oxidations products.

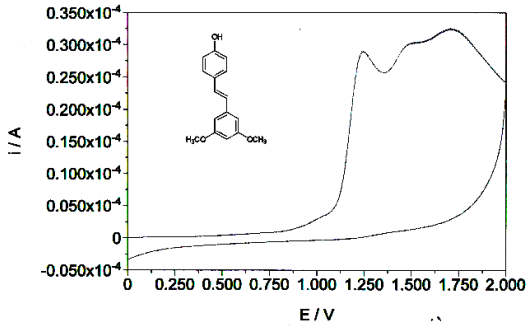
3.3.1. Measurement of oxidation potentials of stilbene derivatives

To study the electrochemical properties of some stilbene derivatives, we performed cyclic voltammetric studies on the oxidation potentials of various substituted stilbenes. The measurements of oxidation potentials were performed in MeCN containing n-Bu_4NBF_4 using Ag/AgCl as a reference electrode and platinum as anode and cathode. Voltammograms (Figure 3.1a-h) results are summarized in Table

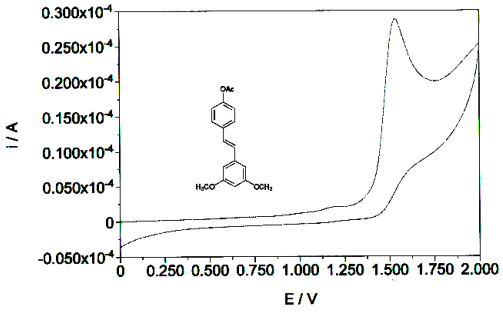
1, which show the measured oxidation potentials of the stilbene derivatives. In general cyclic voltammograms of substrates provide a set of anodic (positive current) and cathodic (negative current) peaks. The anodic peak on the forward scan of the cyclic voltammograms indicates oxidation process, while the cathodic peak on the reverse scan represent the reduction process of the oxidized species back to the original substrate. Typical cyclic voltammograms showing oxidation potentials at which the current peaks on the anodic scans of various stilbene derivatives can be seen in Figure 3.1a-h. Stilbenoid oxidation to its cation species **3.40** in neutral condition, gave rise to the anodic peak. Since $E_2<E_1$, the stilbenoid spontaneously undergoes a two-electron oxidation mechanism (Scheme 3.10).



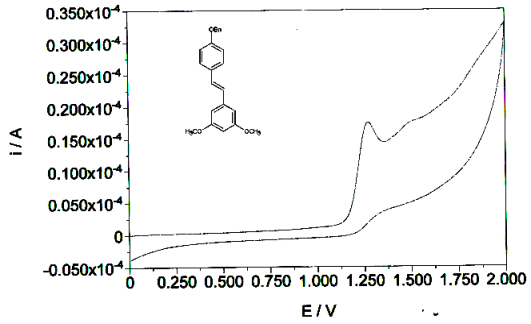
Scheme 3.10: Two electron anodic oxidation of stilbenoid under neutral condition



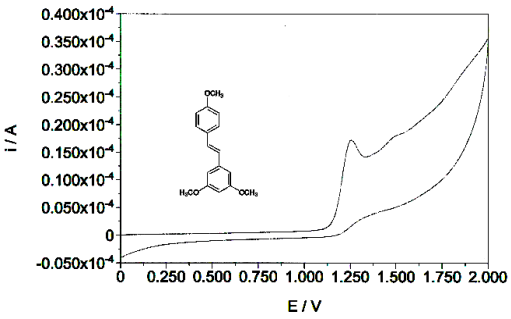
a: CV for **1.2**



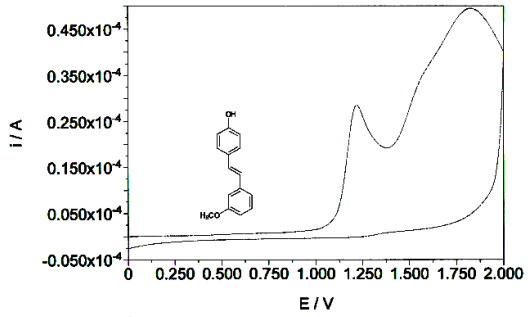
b: CV for **2.46**



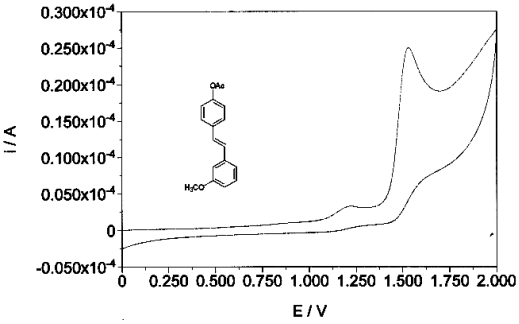
c: CV for **2.74**



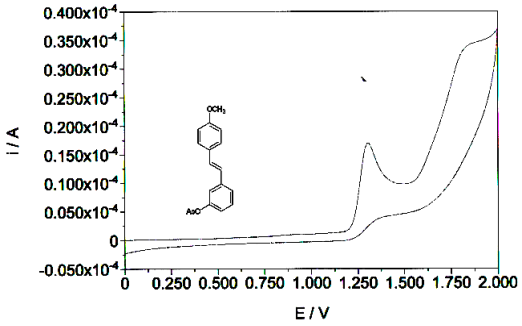
d: CV for **2.8**



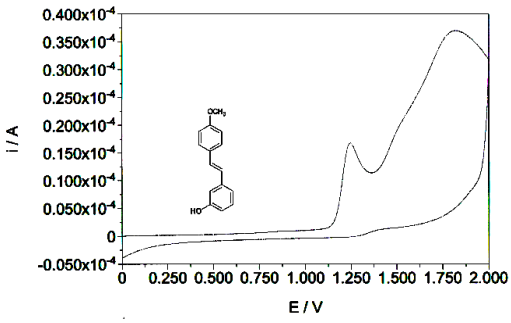
e: CV for **2.56**



f: CV for **2.53**



g: CV for **2.55**



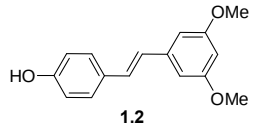
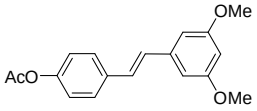
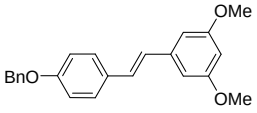
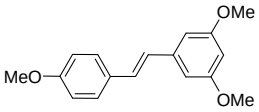
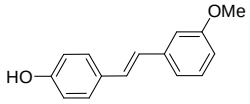
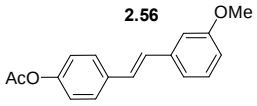
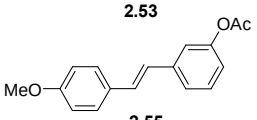
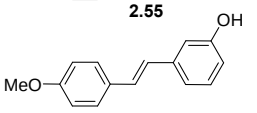
h: CV for **2.57**

Figure 3.1(a-h): Cyclic voltammograms (CV) of various substituted stilbene derivatives

The four stilbenes with resorcinolic dimethoxy substitution pattern **1.2**, **2.46**, **2.74** and **2.8** with variation of substituents ranging from free hydroxyl, acetate, benzyloxy and methoxy at *para* positions exhibit major peaks of oxidation potentials at 1.25 V, 1.53 V, 1.27 V and 1.26 V respectively (Table 3.1). Another type of substitution pattern that is *meta* mono substituted stilbenes such as **2.56**, **2.53**, **2.55** and **2.57** were also studied to obtain oxidation potentials. *Meta* methoxy substituted stilbenes bearing *para* hydroxyl **2.56** and *para* acetate substituents **2.53** possess main oxidation potential of 1.21 V and 1.53 respectively. *Para* methoxy stilbenes **2.55** and **2.57** bearing acetate group and hydroxyl at *meta* position respectively show key oxidation potential of 1.30 V and 1.29 V correspondingly (Table 3.1).

In general, stilbenes with acetate groups at *para* position have higher oxidation potential compared to other substituted stilbenes. This is in agreement with the electron withdrawing property of the acetate group resulting in reduction of electron density in the aromatic ring. From the above observed results, acetate group at *meta* position has not much impact on influencing the overall oxidation potential of stilbene as it does in *para* substituted position. This indicates that electron is abstracted from the *para* substituted position of stilbene, thus providing a better stabilized resonance structure for the stilbene radical.

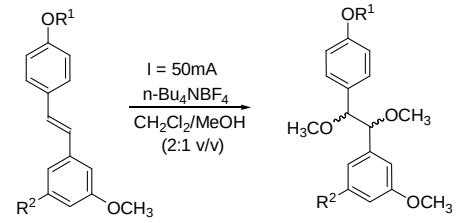
Table 3.1: Oxidation potentials of various substituted stilbene derivatives

Stilbene	Lowest Oxidation Potential Ep/ (Ag/AgCl) (V)
 **1.2**	1.25
 **2.46**	1.53
 **2.74**	1.27
 **2.8**	1.26
 **2.56**	1.21
 **2.53**	1.53
 **2.55**	1.30
 **2.57**	1.29

3.3.2. Anodic oxidation of *para*-hydroxy and- acetate stilbenes in CH_2Cl_2/MeOH

Substituted stilbene analogues with free hydroxyls (**2.56** and **1.2**) and acetates (**2.53** and **2.46**) at *para* positions were subjected to constant current electrolysis at 50 mA with consumption of almost 180 Coulomb (C) in CH_2Cl_2/MeOH (2:1 v/v) containing n-Bu_4NBF_4. Dimethoxy adducts **3.41**, **3.42**, **3.43a**, **3.43b**, **3.44**, **3.45**, **3.46a** and **3.46b** were formed at the platinum anode (Scheme 3.11). 12-Hydroxy- and 12-

acetoxy-3-methoxystilbenes (**2.56** and **2.53** respectively) undergo reactions leading to the formation of diastereoisomers **3.41** and **3.42**, which could be isolated in a pure state, as well as an inseparable diastereoisomers mixture of **3.43a** and **3.43b**. Similarly, anodic oxidation of 12-hydroxy-3,5-dimethoxystilbene **1.2** (pterostilbene) gave **3.44** and **3.45** (both obtained in 10% yield) as two different pure diastereisomers. In contrast, 12-acetoxy-3,5-dimethoxystilbene **2.46** yielded **3.46a** and **3.46b** which is a mixture of diastereoisomers that could not be separated. In general, 12-hydroxy substituted stilbenes gave separable diastereoisomers while 12-acetate substituted stilbenes produced inseparable mixture of diastereoisomers. The structural elucidation of compounds **3.41**, **3.42**, **3.43a**, **3.43b**, **3.44**, **3.45**, **3.46a** and **3.46b** will be discussed in section 3.3.4. The low yields observed for mixtures of **3.43a** and **3.43b** as well as **3.46a** and **3.46b** are consistent with the presence of withdrawing acetoxy groups in starting materials. The main result of this anodic oxidation at constant current is the addition of two methoxy groups onto the olefinic bond instead of dimerisation of stilbene as observed in the chemical oxidation (see Chapter 4).



2.56, **2.53**, **1.2**, **2.46**

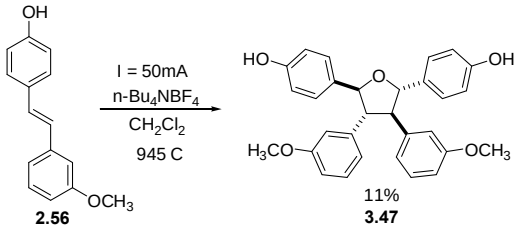
3.41, **3.42**, **3.43a** & **3.43b**, **3.44**, **3.45**, **3.46a** & **3.46b**

Starting Material	R^1	R^2	Q(C)	Product	Yield (%)
2.56	H	H	180	**3.41**	23
				3.42	28
2.53	Ac	H	180	**3.43a** & **3.43b**	23
1.2	H	OMe	180	**3.44**	10
				3.45	10
2.46	Ac	OMe	165	**3.46a** & **3.46b**	17

Scheme 3.11: Anodic oxidation of stilbene derivatives producing stilbene adducts.

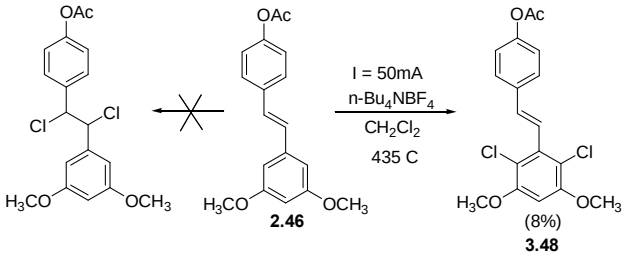
3.3.3. Constant current electrolysis of *para* hydroxy 2.56 and acetate 2.46 stilbenes in pure CH_2Cl_2

Constant current electrolyses were carried out for **2.56** and **2.46** at I = 50 mA in pure CH_2Cl_2 at a platinum anode containing Bu_4NBF_4 where 945 C and 435 C were consumed respectively. Compound **3.47** with a tricuspidatol-A like skeleton was obtained from **2.56** in 11% yield (Scheme 3.12).



Scheme 3.12: Anodic oxidation of **2.56** producing dimerised compound **3.47**

When the *para* hydroxyl of the stilbene is replaced with a *para* acetoxy group **2.46**, dichlorostilbene **3.48** was obtained in 8% yield (Scheme 3.13).[5] This substitution of chlorine atoms on the 3,5-dimethoxylated aromatic ring contrasts with the previous addition of methoxyls on the olefinic double bond. Yet, both adducts result from reaction with the solvent.



Scheme 3.13: Anodic oxidation of **2.46** produced halogenated monomer **3.48**

3.3.4. Spectroscopic evidence of stilbene adducts 3.41, 3.42, 3.44, 3.45, 3.48 together with mixtures of 3.43a & 3.43b and 3.46a & 3.46b.

The assignments of all the protons and carbons resonances in the NMR spectra were made by means of homonuclear (1 H-H COSY), heteronuclear (HMQC, HMBC) 2D chemical shift correlations and ES-TOF-MS in positive mode for **3.48** and **3.47** only. Appendix 27 and 28 show spectra of ^{1}H NMR and ^{13}C NMR of **3.48** respectively. X-ray crystallography (ORTEP) structure of compound **3.48** finalized the confirmation of (*E*)-4-(2,6-dichloro-3,5-dimethoxystyryl)phenyl acetate (Appendix 29). ES-TOF-MS (+) spectrum of compound **3.48** is shown in Appendix 30. The spectroscopic discussion of compound **3.47** will be discussed in Chapter 4. Remaining stilbene adducts diastereoisomers **3.41**, **3.42**, **3.44**, **3.45** together with inseparable mixture of **3.43a** and **3.43b** as well as **3.46a** and **3.46b** mixture were characterized based on ^{1}H NMR and HRMS spectra as well as comparison with their starting materials (stilbenoids) ^{1}H NMR spectra, since they share similar back bone skeleton. Four pairs of diastereoisomers (I & III / I & IV / II & III / II & IV) (Figure 3.2) are possible since the stilbene adduct possess two stereogenic centers. The stereochemistry of all the diastereoisomers is yet to be determined.

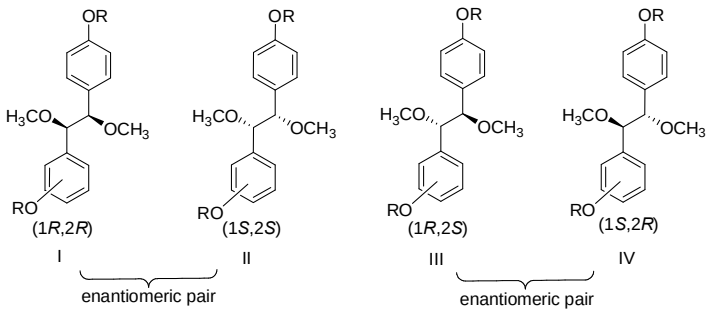


Figure 3.2: Possible enantiomeric and diastereomeric pairs.

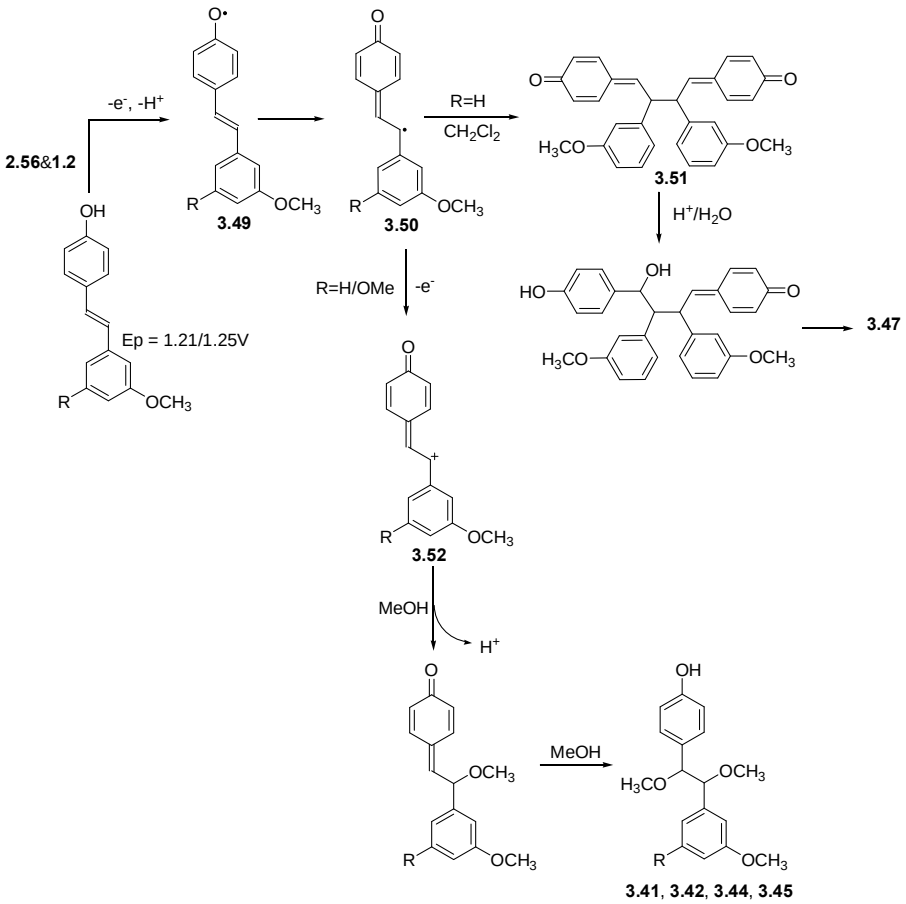
Appendix 31, 32, 33, 34, 35 and 36 show ^{1}H NMR spectra of **3.41**, **3.42**, **3.44**, **3.45**, mixture of diastereoisomers **3.43a** & **3.43b** and mixture of diastereoisomers **3.46a** & **3.46b** respectively. The major differences lie with signals associated with hydrogen atoms at position 7 and 8. The ^{1}H NMR shows 2-spin systems with coupling constants around 5-8 Hz resonating from 4.2 to 4.9 ppm. Inseparable **3.43a** and **3.43b** are in a ratio of 1.6:1 while **3.46a** and **3.46b** in a ratio of 1.1:1 as determined by the ratio of the surface areas of the two different methoxy peaks from two different compounds at carbon position 3 and/5. Appendix 37, 38, 39 and 40 show ES-TOF-MS (+) spectra of **3.44**, **3.41**, mixture of diastereoisomers **3.43a** and **3.43b** and mixture of diastereoisomers **3.46a** and **3.46b** respectively.

3.3.5. Mechanistic discussion

The above mentioned results can be explained in terms of stability of the radical cation species formed during the reaction.[3,15,27] The controlling factors are the electron-donating or -withdrawing properties of the substituents, nucleophilic properties of the solvents and electrophilic properties of the side products generated in the electrochemical cell.

Para-hydroxy stilbenes **2.56** and **1.2**, under electrochemical conditions, lose an electron from the free hydroxy group followed by the loss of a proton to produce phenoxy radical **3.49** (Scheme 3.14). The lone electron then delocalizes to give the quinone methide radical **3.50**. In presence of non-nucleophilic solvent like CH_2Cl_2, two quinone methide radicals **3.50** will undergo radical coupling leading to **3.51**. Water, which was formed as a result of side reaction of HCl and O_2 due to prolonged reaction, will act as the nucleophile attacking **3.51** to form tetraaryltetrahydrofuran **3.47** in 11% yield (Scheme 3.14).

However, if subjected to a nucleophilic solvent like MeOH, **3.50** will undergo a second oxidation to generate a carbocation at C-7. This carbocation species **3.52** is susceptible to nucleophilic attack by the solvent followed by a second addition of MeOH at C-8 and protonation will regenerate the aromatic ring leading to **3.41**, **3.42**, **3.44** and **3.45** (Scheme 3.14). This observation contrasts with Steckhanôs anodic oxidation of 4,4ô-dimethoxystilbene in CH_2Cl_2/MeOH where the dimethoxylated open-chain dimer was generated in 75% yield. Steckhan also obtained high yield of 2,3,4,5-tetraanisyltetrahydrofuran. We could rationalize our above observed low yields as being the result of the presence of free hydroxy groups in stilbenes where oligomerisation or polymerization is expected to a great extent, a well known phenomenon in phenolic oxidations. Constant current electrolysis also could be another factor accounting for the observed low yield products as the potential steadily increases resulting in a variety of follow-up oxidation processes of the initial products.

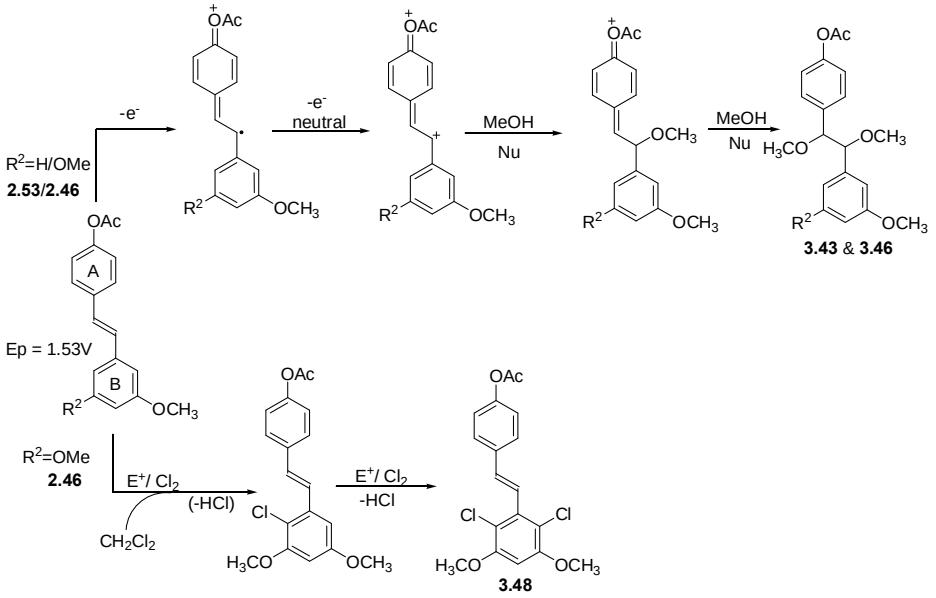


Scheme 3.14: Anodic oxidation of stilbene derivative in different solvents (pure CH_2Cl_2 and CH_2Cl_2/MeOH mixture)

When the substituted *para*-acetylated (electron withdrawing group) stilbenoids **2.53** and **2.46** was subjected to CCE in CH_2Cl_2/MeOH mixture, the above explanation can be applied as well to understand the formation of diastereoisomers **3.43** & **3.46** (Scheme 3.15). Compounds **3.43** & **3.46** were produced in low yields due to the lack of stability of stilbene radical cation as the acetate group reduces the electron density in the aromatic ring. This is in agreement with the electrode potential of 1.53V, which is higher than that of the *para* hydroxy stilbenoid (E = 1.21 V/1.25 V).

Anodic oxidation of the same *para*-acetoxy stilbene **2.46** at CCE but now in pure CH_2Cl_2 leads to the formation of **3.48** whereby two chlorine atoms are added to the aromatic B ring of the stilbene (Scheme 3.15 and 3.16). There are two possible

mechanistic pathways to explain the above observation, electrophilic aromatic substitution and E-C-E-C pathway (E = electrochemical process, C = chemical process).



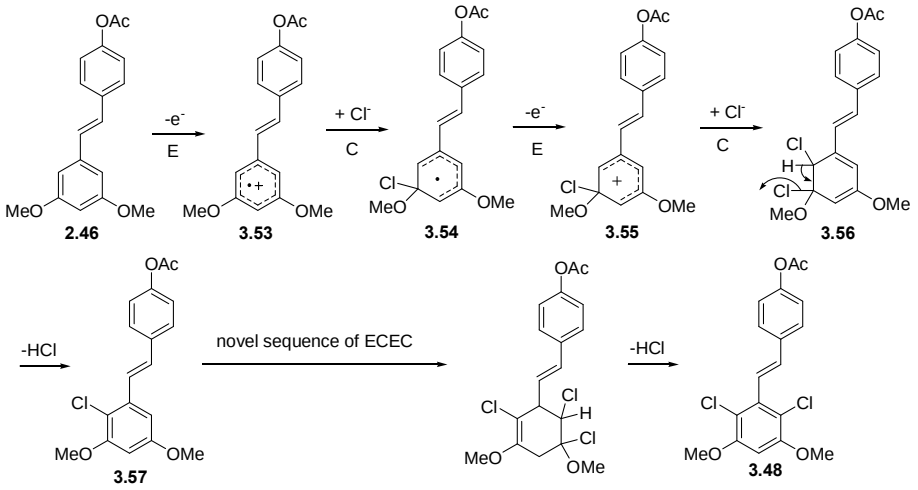
Scheme 3.15: Electrophilic aromatic substitution of *para*-acetylated stilbene **2.46** in CH_2Cl_2.

Relatively long electrochemical reaction time with consumption of 435 C [Q = I (A) x t (s); 0.05 A x 8700 s = 435 C] in CH_2Cl_2 in a monocompartment cell led to the reduction of CH_2Cl_2 at cathode generating chloride ions. These chloride ions can thereafter either oxidize at the anode to give chlorine molecules or to added to carbocationic species since the oxidation and reduction potentials are not controlled. As a result, the chlorine can possibly undergo an electrophilic aromatic substitution on the ring B with disubstituted methoxy groups as it has higher electron density than that of ring A (with electron withdrawing group). A double electrophilic aromatic substitution leads to the formation of **3.48** (Scheme 3.15).

A second possibility is that the produced chloride ion reacts with a radical cation intermediate **3.53** resulting from the anodic oxidation of the stilbene **2.46.**

Since, the radical cation is better stabilized at disubstituted methoxy ring of intermediate **3.53**, the attack of a chloride ion on this intermediate would lead to the formation of a radical **3.54** (Scheme 3.16). Radical species **3.54** is more easily oxidized than the starting material **2.46** as the electrode potential of **3.54** is lesser (E<1.53 V) than that of **2.46**. This results in the generation of cation intermediate **3.55**, which was successively trapped by the chloride ion to produce **3.56** and a consecutive elimination of HCl gave **3.57**. A combination of double E-C-E-C reaction followed by a double elimination of HCl would lead to the product formation of **3.48**. The final product is only obtained in a very minute quantity, indicating that it is likely resulted from a secondary reaction (Scheme 3.16).

The most probable pathway is the electrophilic aromatic substitution, since chlorines were not added to the olefinic bond of the stilbene as we observed previously in the case of nucleophilic solvent (methanol) addition.



Scheme 3.16: *Para*-acetylated stilbene **2.46** undergoes E-C-E-C pathway to produce halogenated product **3.48**

In summary, two types of oxidative products are obtained: solvent addition products (mainly) and dimerization products. When the current is kept constant and therefore, the potential increases, nucleophilic solvent (MeOH) addition to the

stilbenoid is possible. This solvent addition enhances the two electron oxidation processes. In the presence of non nucleophilic solvent like CH_2Cl_2, one electron oxidation step occurs followed by radical coupling (dimerization). If *para*-hydroxyl of the stilbene is replaced with an electron-withdrawing group (OAc) in CH_2Cl_2, then electrophilic aromatic substitution takes place due to the higher electron density in the substituted B ring with dimethoxy groups and the existence of an electrophilic source.

3.4. Experimental section

The experimental work on electrochemical oxidation of stilbene derivatives were carried out at Institut Européen de Chimie et Biologie, Université Bordeaux 1, France, under the supervision of Dr. Denis Deffieux and Prof. Stéphane Quideau. Electrochemical oxidations were carried out using a Autolab galvanometer. NMR spectra (^1H and ^{13}C, 2D homo and heteronuclear) were recorded on a Bruker Avance 300 and Jeol JNM-LA400. ORTEP and High-resolution MS experiments were performed in Université Bordeaux 1. At the time of printing we could not obtain full experimental details on experimental conditions.

3.4.1. Measurement of oxidation potentials of stilbene derivatives

Cyclic voltammograms were recorded using a standard potentiostat for a series of stilbenoids **1.2**, **2.46**, **2.53**, **2.55**, **2.56**, **2.57**, **2.74** and **2.8**. Two platinum electrodes were used as a working electrode and the other as a counter electrode while Ag/AgCl as a reference electrode. At least three cyclic voltammograms were recorded for each solution at a scan rate of 0.2 V/s and increased up to 2 V to enable the stilbenoids oxidation peaks to be examined in detail. The stilbenoids (3-5 mg) were dissolved in 10 ml of MeCN solution containing electrolyte, n-Bu_4NBF_4 (300 mg),

before the cyclic voltammograms were recorded. Background cyclic voltammograms were performed in MeCN solution containing n-Bu_4NBF_4 and were recorded on the same day as the other samples. Then, the background cyclic voltammograms were subtracted from the cyclic voltammograms obtained from the stilbenoids, in order for the oxidation and reduction processes to be more clearly revealed.

3.4.2. Constant current electrolysis of stilbene derivatives

Constant current electrolyses for all the substituted stilbenes **2.56**, **2.53**, **1.2** and **2.46** were carried out independently in a 100 ml undivided, cylindrical cell, equipped with a platinum-coated titanium grid (50 g Pt/m^2, 40x60 mm) as the anode and a copper wire (0.5 mm diameter) as the cathode. n-Bu_4NBF_4 is the electrolyte (1.5 g, 0.0046mol) and was dissolved in an anhydrous mixture of CH_2Cl_2/MeOH (35 ml / 17 ml) followed by addition of starting material, substituted stilbene (0.1 g, 0.0004 mol). The electrolysis was then performed at 50 mA using a regulated DC power supply until the desired total electric charge passed. The total electric charge passed through the substance was calculated by using the Faraday equation as stated below. All the electrochemical oxidations corresponding to substrates **2.56**, **2.53** and **1.2** consumed 180 Coulomb (C) while reaction with **2.46** as starting material consumed 165 C for completion. All reactions were vigorously stirred under nitrogen at 0ºC. The progress of the reaction was monitored by TLC. After the complete consumption of starting material, the reaction mixture was extracted with ethyl acetate. The organic layer was then washed with water, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was purified by column chromatography and preparative thin layer chromatography to give the desired products. Starting material **1.2** produced **3.44** (12 mg, 10%) & **3.45** (12 mg, 10%),

2.56 produced **3.41** (29 mg, 23%) & **3.42** (36 mg, 28%), as pure diastereoisomers, while stilbenoids **2.53** and **2.46** produced inseparable mixture of diastereoisomers **3.43** (27 mg, 23%) and **3.46** (20 mg, 17%) respectively. Their relative stereochemistry remains to be determined. Compounds **2.46** and **2.56** were also subjected to anodic oxidation using the above reaction conditions by replacing CH_2Cl_2/MeOH mixture with pure distilled CH_2Cl_2 only. These resulted in a halogenated compound **3.48** (10 mg, 8%) and a dimer **3.47** (34 mg, 11%) respectively after consumption of 435 C and 945 C correspondingly.

Faraday's equation $\Rightarrow$ n x F x z = I x t = Q

n = mass of the substance liberated at an electrode/molar mass of the substance = m/M

F = Faraday constant = 96500 C mol^{-1} (C = Coulomb)

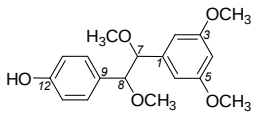
z = valency number of ions of the substance (electrons transferred per ion)

I = electric current (A)

t = total time (s) of the constant current was applied

Q = total electric charge passed through the substance

Diastereoisomers 4-(2-[3,5-dimethoxyphenyl]-1,2-dimethoxyethyl)phenol **3.44** & **3.45**



*Diastereoisomer **3.44***

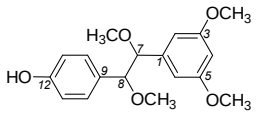
^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.06 (d, 2 H, J = 8.4 Hz, H10/14), 6.75 (d, 2 H, J = 8.0 Hz, H11/13), 6.37 (t, 1 H, J = 2.4 Hz, H4), 6.32 (d, 2 H, J = 2.4 Hz, H6/2), 4.27 (d, 1 H, J = 5.6 Hz, H7*), 4.22 (d, 1 H, J = 5.2 Hz, H8*), 3.72 (s, 6 H, 5/3-OCH_3), 3.19 (s, 3 H, 7-$OCH_3^{\#}$), 3.16 (s, 3 H, 8-$OCH_3^{\#}$)

ESI-TOF-MS(+): $[M+Na]^+$; m/z 341.1369 measured, 341.1365 calculated for $C_{18}H_{22}NaO_5$, qpm/m = 1.2 ppm

*Diastereoisomer **3.45***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 6.91 (d, 2 H, J = 8.3 Hz, H10/14), 6.66 (d, 2 H, J = 8.3 Hz, H11/13), 6.26 (s, 1 H, H4), 6.17 (s, 2 H, H6/2), 5.22 (bs, -OH), 4.22 (ñdò, 1 H, J = 7.56 Hz, H7*), 4.19 (ñdò, 1 H, J = 7.56 Hz, H-8*), 3.7 (s, 6 H, 5/3-OCH_3), 3.24 (s, 3 H, 7- $OCH_3^{\#}$), 3.22 (s, 3 H, 8-$OCH_3^{\#}$)

Diastereoisomers 4-(1,2-dimethoxy-2-[3-methoxyphenyl]ethyl)phenol **3.41** & **3.42**



*Diastereoisomer **3.41***

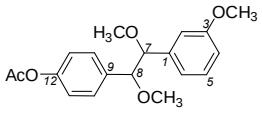
^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.04 (t, 1 H, J = 7.8 Hz, H5), 6.85 (d, 2 H, J =8.3 Hz, H10/14) 6.68 (dd, 1 H, J = 7.8 Hz; 2.4 Hz, H6), 6.65 (d, 2 H, J = 8.3 Hz, H11/13), 6.56 (d, 1 H, J = 7.8 Hz, H4), 6.53 (s, 1 H, H2), 6.08 (s, -OH), 4.24 (ñdò, 1 H, J = 8.8 Hz, H7*), 4.22 (ñdò, 1 H, J = 8.3 Hz, H8*), 3.65 (s, 3 H, 3- OCH_3), 3.22 (s, 3 H, 7-$OCH_3^{\#}$), 3.20 (s, 3 H, 8-$OCH_3^{\#}$)

ESI-TOF-MS(+): $[M+Na]^+$; m/z 311.1260 measured, 311.1259 calculated for $C_{17}H_{20}NaO_4$, qpm/m = 0.3 ppm

*Diastereoisomer **3.42***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.19 (t, 1 H, J = 7.8 Hz, H5), 7.04 (d, 2 H, J = 8.5 Hz, H10/14), 6.81 (dd, 1 H, J = 2.7 Hz; 8.3 Hz, H6), 6.77 (d, 1 H, J = 7.6 Hz, H4), 6.73 (d, 2 H, J = 8.6 Hz, H11/13), 6.72 (s, 1 H, H2), 5.97 (s, -OH), 4.32 (d, 1 H, J = 5.6 Hz, H7*), 4.25 (d, 1 H, J = 5.6 Hz, H8*), 3.73 (s, 3 H, 3- OCH_3), 3.17 (s, 3 H, 7- $OCH_3^{\#}$), 3.15 (s, 3 H, 8- $OCH_3^{\#}$)

Diastereoisomers 4-(1,2-dimethoxy-2-[3-methoxyphenyl]ethyl)phenyl acetate **3.43a** and **3.43b** (inseparable mixture)



ESI-TOF-MS(+): $[M+Na]^+$; m/z 353.1366 measured, 353.1365 calculated for $C_{19}H_{22}NaO_5^+$, qpm/m = 0.3 ppm

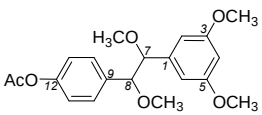
*Diastereoisomer **3.43a***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.30 (d, 2 H, J = 8.3 Hz, H10/14), 7.20 (t, 1 H, J = 8.0 Hz, H5), 6.99 (d, 2 H, J = 8.6 Hz, H11/13), 6.88 (d, 1 H, J = 7.8 Hz, H4), 6.84 (s, 1 H, H2), 6.75-6.71 (m, 1 H, H6), 4.92 (d, 1 H, J = 7.3 Hz, H7*), 4.19 (d, 1 H, J = 7.6 Hz, H8*), 3.77 (s, 3 H, 3- OCH_3), 3.31 (s, 3 H, 7- $OCH_3^{\#}$), 3.30 (s, 3 H, 8- $OCH_3^{\#}$), 2.26 (s, 3 H, $COCH_3$).

*Diastereoisomer **3.43b***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.09 (t, 1 H, J = 8.1 Hz, H5ô), 7.03 9 (d, 2 H, J = 8.6 Hz, H10ô/14ô), 6.91 (d, 2 H, J = 8.5 Hz, H11ô/13ô), 6.75-6.72 (m, 1 H, H6ô), 6.61 (d, 1 H, J = 7.6 Hz, H4ô), 6.53 (s, 1 H, H2ô), 4.30 (d, 1 H, J = 7.1 Hz, H7ô*), 4.25 (d, 1 H, J = 7.1 Hz, H8ô*), 3.67 (s, 3 H, 5- OCH_3ô), 3.28 (s, 3 H, 7-OCH_3ô$^{\#}$), 3.27 (s, 3 H, 8- OCH_3ô$^{\#}$), 2.26 (s, 3 H, $COCH_3$ô).

Diastereoisomers 4-[2-(3,5-dimethoxyphenyl)-1,2-dimethoxyethyl]phenyl acetate **3.46a** and **3.46b** (inseparable mixture)



ESI-TOF-MS(+): $[M+Na]^+$; m/z 383.1465 measured, 383.1471 calculated for $C_{20}H_{24}NaO_6$, qpm/m = 1.6 ppm

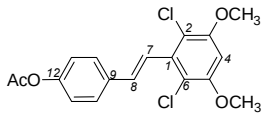
*Diastereoisomer **3.46a***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.30 (d, 2 H, J = 8.8 Hz, H10/14), 6.99 (d, 2 H, J = 8.8 Hz, H11/13), 6.45 (d, 2 H, J = 2.2 Hz, H6/2), 6.31 (t, 1 H, J = 2.2 Hz, H4), 4.90 (d, 1 H, J = 7.6 Hz, H7*), 4.14 (d, 1 H, J = 7.6 Hz, H8*), 3.76 (s, 6 H, 3/5- OCH_3), 3.33 (s, 3 H, 7- $OCH_3^{\#}$), 3.28 (s, 3 H, 8- $OCH_3^{\#}$), 2.27 (s, 3 H, $COCH_3$).

*Diastereoisomer **3.46b***

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.05 (d, 2 H, J = 8.5 Hz, H10ô/14ô), 6.92 (d, 2 H, J = 8.6 Hz, H11ô/13ô), 6.29 (t, 1 H, J =2.2 Hz, H4ô), 6.16 (d, 2 H, J = 2.4 Hz, H6ô/2ô), 4.28 (d, 1 H, J = 7.08 Hz, H7ô*), 4.20 (d, 1 H, J = 7.1 Hz, H8ô*), 3.66 (s, 6 H, 3ô/5ô- OCH_3), 3.29 (s, 6 H, 7ô/8ô- OCH_3), 2.27 (s, 3 H, $COCH_3$ô).

Compound (*E*)-4-(2,6-dichloro-3,5-dimethoxystyryl)phenyl acetate **3.48**



IR (film) ν_{max}: 1761 cm^{-1}

ESI-TOF-MS(+): $[M+Na]^+$; m/z 389.0331 measured, 389.0323 calculated for $C_{18}H_{16}Cl_2NaO_4$, qm/m = 2.1 ppm

^{1}H NMR ($CDCl_3$, 400MHz) ŭ 7.56 (d, 2 H, J = 8.8 Hz, H10/14), 7.10 (d, 2 H, J = 8.5 Hz, H11/13), 7.05 (s, 2 H, H7/8), 6.52 (s, 1 H, H4), 3.94 (s, 6 H, 3/5-OCH_3), 2.30 (s, 3 H, 12-$OCOCH_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) ŭ 169.4 (12-O<u>C</u>OCH_3), 154.5 (3/5), 150.6 (12), 136.2 (8*), 136.1 (1*), 134.6 (9), 127.8 (10/14), 123.2 (7), 121.8 (11/13), 114.4 (2/6), 96.3 (4), 56.6 (3/5-OCH_3), 21.1 (12-OCO<u>C</u>H_3)

Compound **3.47**

Refer Chapter 4 for a discussion on the structural analysis.

3.5. References

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