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COMPREHENSIVE REVIEW

Synthetic approaches toward stilbenes and their related structures

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Abstract Compounds belonging to the stilbene family have gained remarkable significance in pharmaceutical as well as material chemistry. The current review covers the various synthetic approaches for the syntheses of stilbene scaffold and related structures over last 30 years. In addition, this review also highlights the role of stilbene intermediates used in the synthesis of important molecules with diverse applications in the field of pharmaceutics and material science.

Keywords Stilbenes and related analogues · Olefination reactions · Palladium catalysis · Cyclization · Benzofluorenes

Introduction

Nature has been a source of medicinal compounds for thousands of years and large number of drugs have been isolated from natural products [1,2]. Stilbene (1,2-diphenylethene) does not exist in nature itself, but its derivatives as plant secondary metabolites are present in various plant species and some of them are considered phytoalexins [2–5]. Stilbene and its analogues hold enormous potential importance due to their diverse spectrum of biological applications such as anticancer [6–10], antiproliferative [11,12], antiangiogenesis [11,12], antimicrobial [13–17], antileukemic [17,18], antioxidant [17,19,20], anti-inflammatory [17], anti-HIV [21,22], anti herpes simplex virus [23] and tyrosine kinase inhibitors [24,25]. Stilbenes exist in *E* and *Z* conformations each eliciting different pharmacological activities. Research revealed that the *E* form or *trans* exhibits more potent anticancer activity compared to the *Z* form or *cis* form. The *trans* or *E* form is thermodynamically more stable. Many *trans*-stilbenes such as resveratrol **1**, oxyresveratrol **2**, pterostilbene **3**, piceatannol **4**, isorhapotigenin **5** and *cis* stilbene, combretastatin **6** (Fig. 1) exhibited varieties of biological activities [1,4,25]. Hydroxy stilbene, i.e., resveratrol (3,4,5-trihydroxystilbene), a non-flavonoid polyphenolic present in grapes, peanuts, berries and red wine was investigated due to its role in plants' defense against pathogens and pharmacological properties [26–32]. It shows significant effect against cancer, AIDS, antagonistic activity against aryl hydrocarbon receptor (AhR) and estrogenic potency [33,34]. Pterostilbene is used in the treatment of resistant hematology malignancies, diabetes and as antitumor agent [34].

Combretastatin A-4 (CA-4), a vascular disrupting agent (VDAs) and a vascular targeting agent (VTAs) present in the bark of *Combretum caffrum*, acts as antimitotic and exhibited antineoplastic, antioxidant and antiestrogenic properties [1, 35–37].

The non-availability of naturally occurring stilbenes in sufficient quantities dictated the development of synthetic methodologies for their preparation at large scale [3] such as Wittig or Horner–Wadsworth–Emmons (HWE) olefination, Perkin aldol condensation, transition metal coupling, i.e., Mizoroki–Heck, Negishi, Stille, Sonogashira, Suzuki–Miyaura, Grubbs & McMurry, Knoevenagel–Doebner, Ramberg–Bucklund reactions [7,34,38,39]. Stilbene derivatives also show industrial applications in electrochemical, dyes, dye laser, coloring textiles, organic LED, fluorescent and optical brightners [40–43]. Likhitwitayawuid identified dimeric stilbenes as tyrosinase inhibitor [44], whereas

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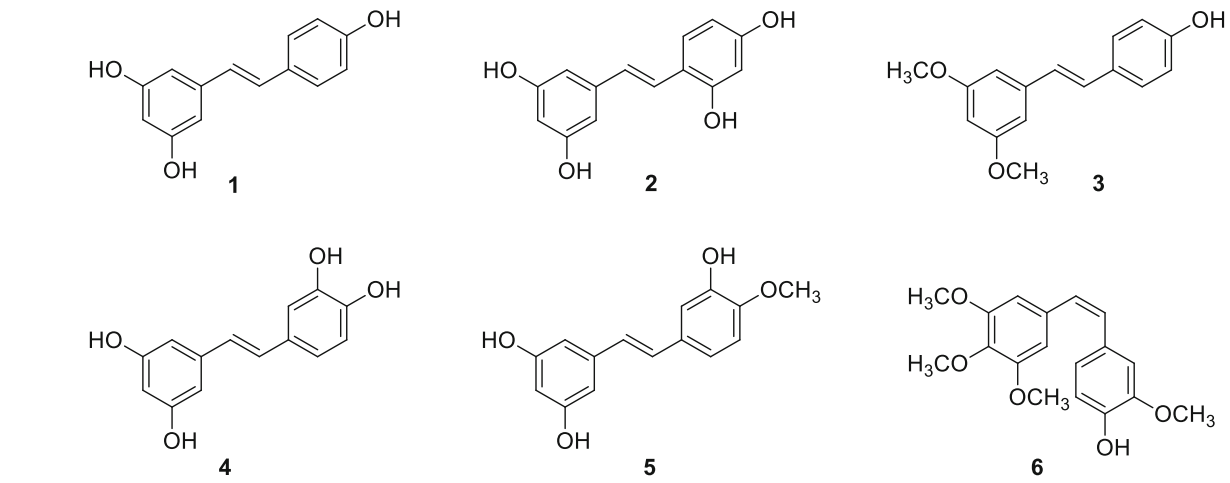
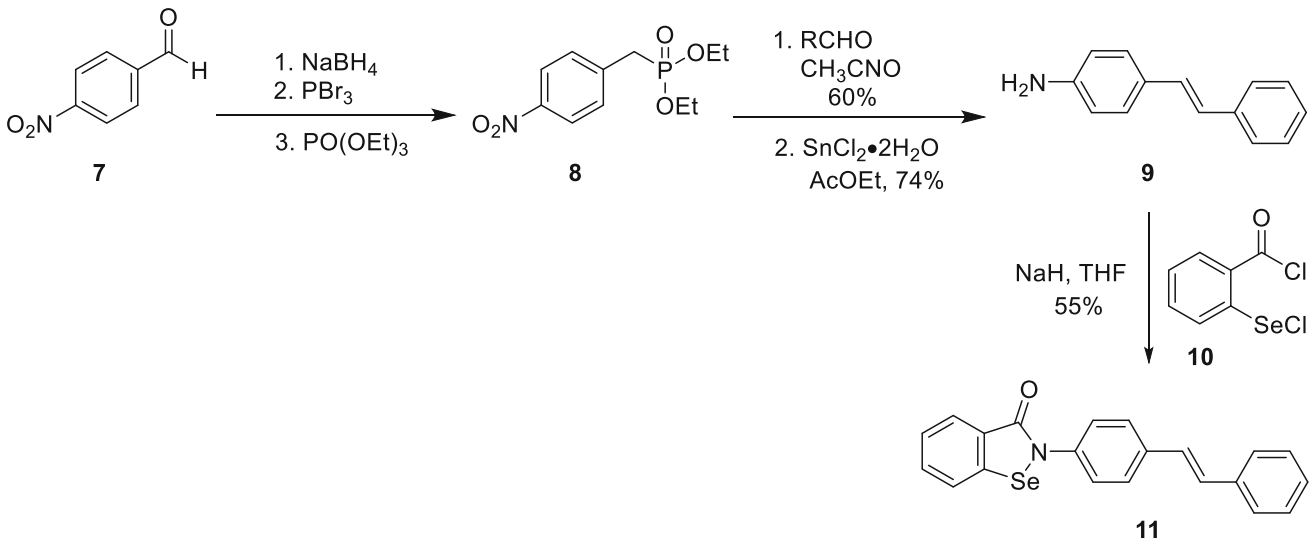


Fig. 1 Naturally occurring biologically active stilbene derivatives



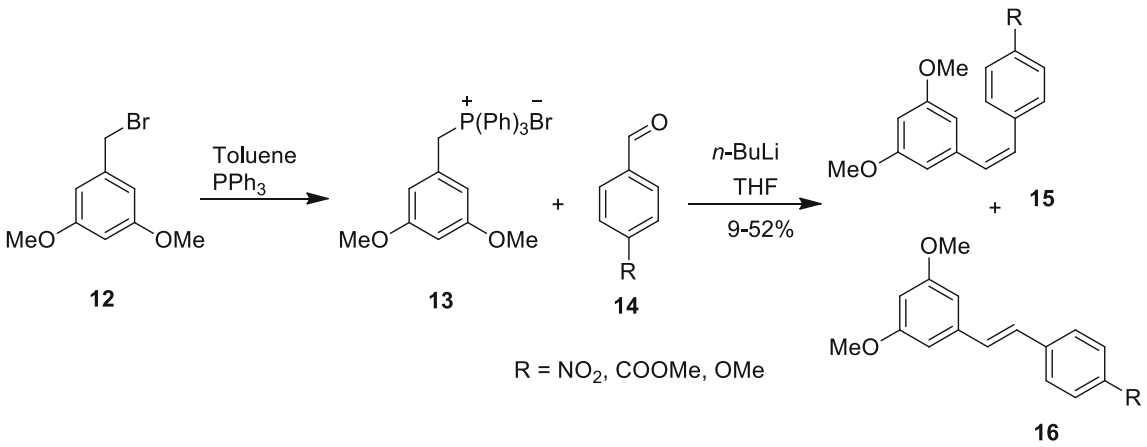
Scheme 1 Synthesis of benzoselenazole-stilbene **11**

Momotake and Arai wrote a review on photochemistry and photophysics of stilbene dendrimers and related compounds [45]. Shen et al. [46] presented an overview on natural stilbenes. Chaudhary et al. and Nam published reviews on Combretastatin A-4 analogues as anticancer and antimitotic antitumor agents, respectively [35,36]. Recently, Reinisalo et al. [47] presented a review on polyphenol stilbenes, Jørgensen reviewed the photochemical oxidative cyclization of stilbenes and stilbenoids (the Mallory-reaction) [48], Savage et al. [49] presented a review of semi-rigid, stilbene-containing alternating copolymers, Chong et al. [50] contributed a review on metabolism and roles of stilbenes in plants, and Waldeck reviewed the photoisomerization dynamics of stilbenes [51]. The current review covers the synthetic strategies to develop convenient methods for the construction stilbene architecture and related analogues over the past few decades.

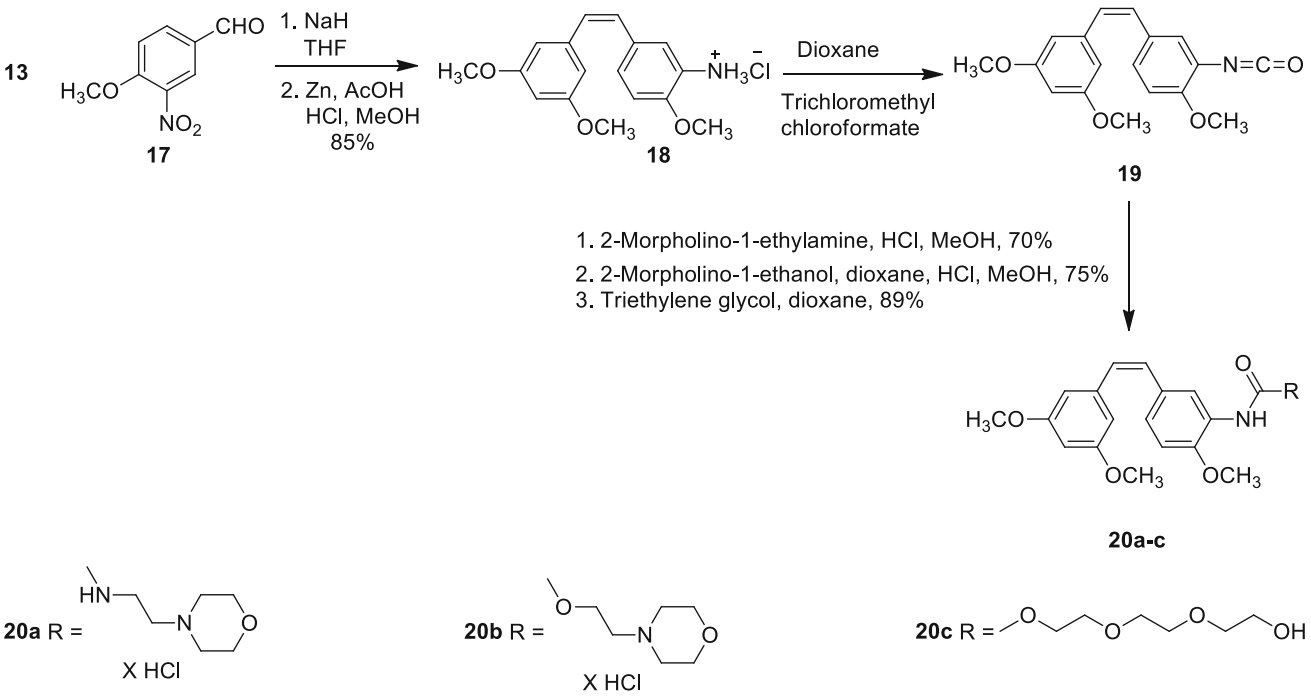
Synthetic strategies for stilbene analogues

Synthesis of stilbene analogues by the Wittig/Horner–Wadsworth–Emmons (HWE) reaction

Due to effective control of cancer by selenium-containing compounds, Yan et al. [30] prepared benzoselenazole-stilbene by the coupling of stilbene **10** with ebselen **11** as outlined in Scheme 1. For this purpose, phosphonate **8** was prepared in three steps by reacting nitrobenzaldehyde **7** with sodium borohydride in methanol, the resulting product was then treated with phosphorus tribromide in the presence of pyridine and finally refluxed with triethyl phosphite. Further, compound **8** was converted to amino stilbene **9** in 74% yield by reacting with benzaldehydes followed by reduction of nitro group with stannous chloride. Amino stilbene **9** was subsequently coupled with 2-(chloroseleno)benzoyl



Scheme 2 Synthesis of stilbene analogues **15** and **16**



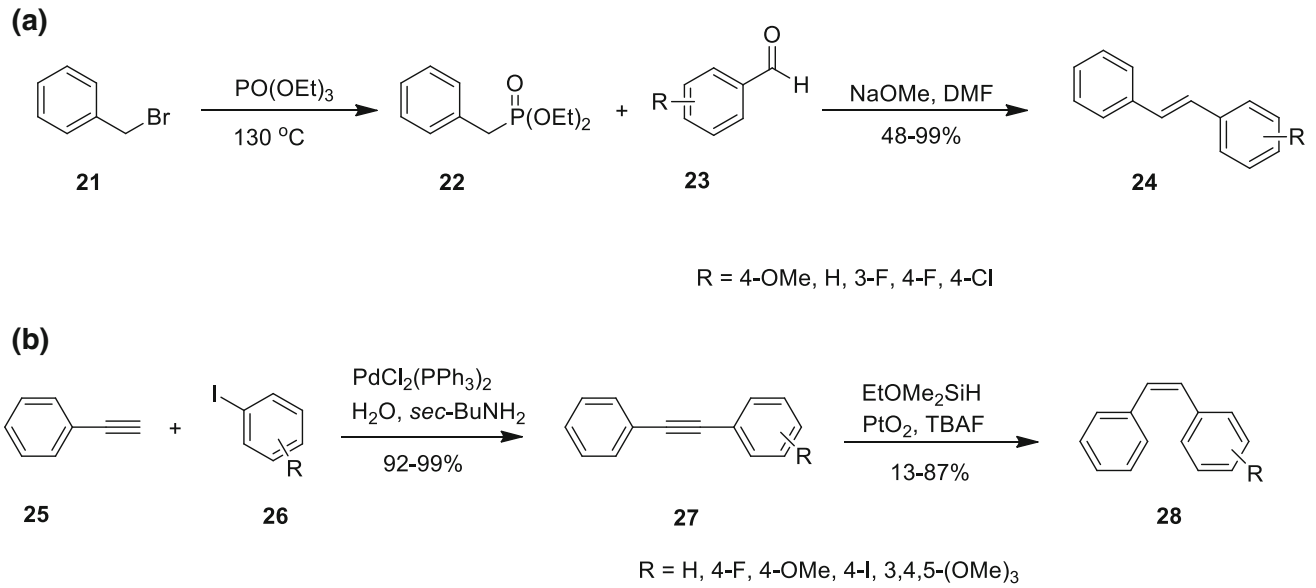
Scheme 3 Synthesis of *cis*-stilbene related to **CA-4** (**20a–c**)

chloride **10** in presence of sodium hydride to accomplish desired benzoselenazole-stilbene **11** in 55% yield.

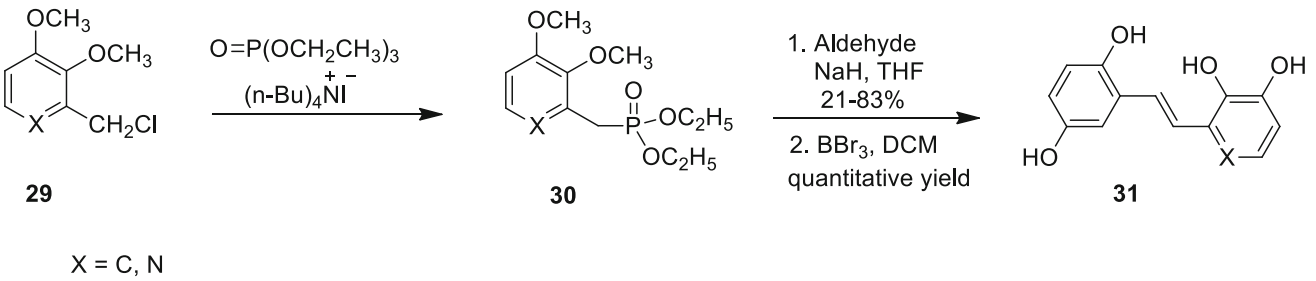
Bhat and Pezzuto [52] described chemotherapeutic property of stilbene-based resveratrol. Thus, keeping in mind the perspective applications of resveratrol, Paul et al. [53] synthesized both *cis* **15** and *trans*-stilbenes **16** via a Wittig reaction between phosphonium salt **13**, which is derived from compound **12** with appropriate aromatic aldehydes **14** but these stilbenes **15** and **16** were formed in 9–52% yields. Mizuno et al. [54] synthesized derivatives of pterostilbene by using a Wittig reaction similar to the route shown in Scheme 2.

Simoni et al. [26] prepared carbamates and uracil derivatives **20a–c** from *cis*-stilbene to test their potential antitumor activity. The Wittig reaction of aldehyde **17** with Wittig salt **13**, followed by reduction in the presence of Zn, generated hydrochloride salt **18** in 85% yield. Compound **18** was converted into intermediate isocyanate **19** by treating it with base and trichloromethyl chloroformate. The intermediate isocyanate **19** was finally converted into water soluble urea **20a** and carbamates **20b–c** in 70–89% yield as outlined in Scheme 3.

Roman et al. [8] prepared *E* and *Z* stilbenes as anti-invasive agents by different methods. *E*-stilbenes **24** were prepared in 48–99% yield using a Wittig reaction, in which benzyl bromide **21** was converted to phosphonate **22** and subsequently transformed to stilbenes **24** in an



Scheme 4 **a** Synthesis of *trans*-stilbenes **24**. **b** Synthesis of *cis*-stilbenes **28**



Scheme 5 Synthesis of hydroxylated stilbenes **31**

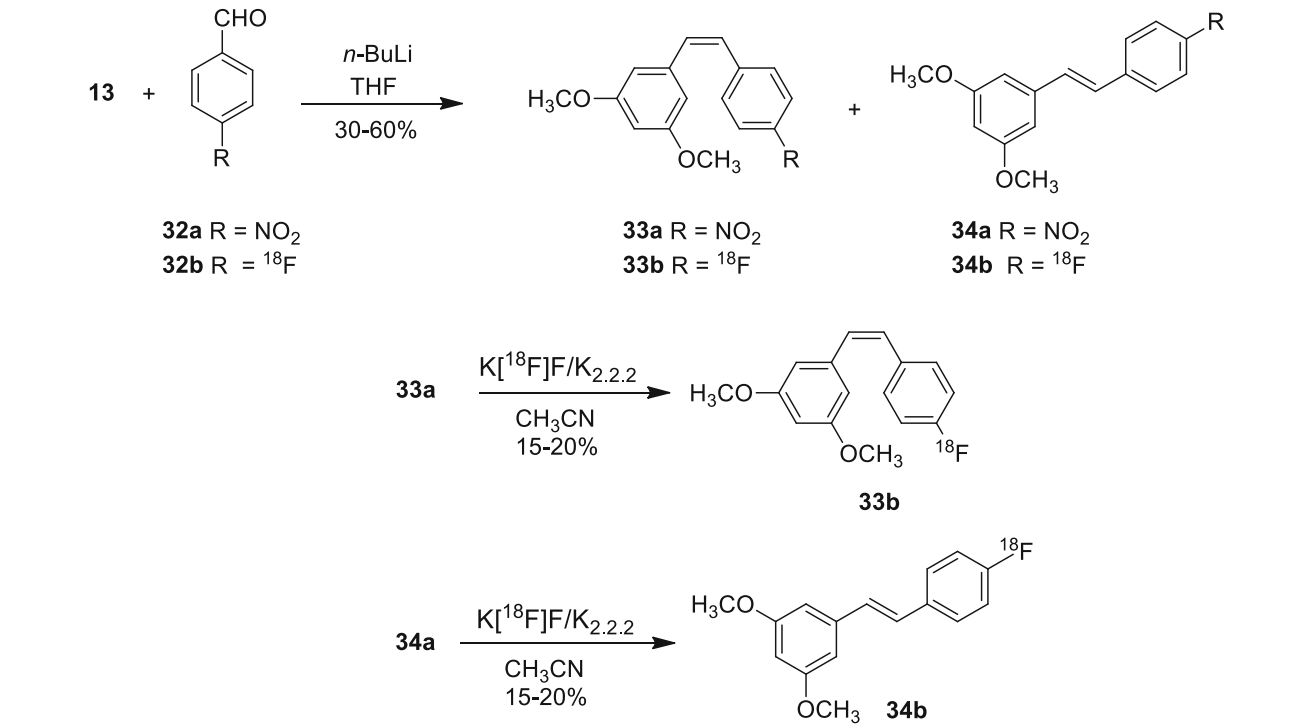
E/*Z* ratio 99:1 by reacting with benzaldehydes **23** under nitrogen atmosphere. A solvent-free Arbusov reaction generated triethylphosphite from benzyl bromide followed by a Horner–Wadsworth–Emmons reaction in (THF/KO^{t}Bu) and afforded *E*-selectivity with higher yields as shown in Scheme 4a. *Z*-stilbenes **28** were formed in 13–87% yield through the Sonogashira coupling of phenylacetylene **25** with aryl iodides **26**, which produced alkynes **27** in 92–99% yield. A wide range of alkynes **27** were converted into *Z*-stilbenes **28** via hydrosilylation (Chalk–Harrod mechanism) and TBAF mediated conversion of vinylsilanes. Lindlar's catalyst also afforded the *Z*-stilbenes as shown in Scheme 4b.

Li et al. [5] followed the same Wittig–Horner reaction to generate hydroxy stilbenes **31** as severe acute respiratory syndrome (SARS) inhibitors. Phosphonates of 3,5-dimethoxybenzyl chloride **30** were obtained by an Arbuzov reaction in (n-Bu)$_4$NI. The reaction of phosphonate anion from compound **30** with aryl aldehydes gave *E*-stilbenes, which subsequently were demethylated to hydroxylated stilbenes **31** in quantitative yield as outlined in Scheme 5.

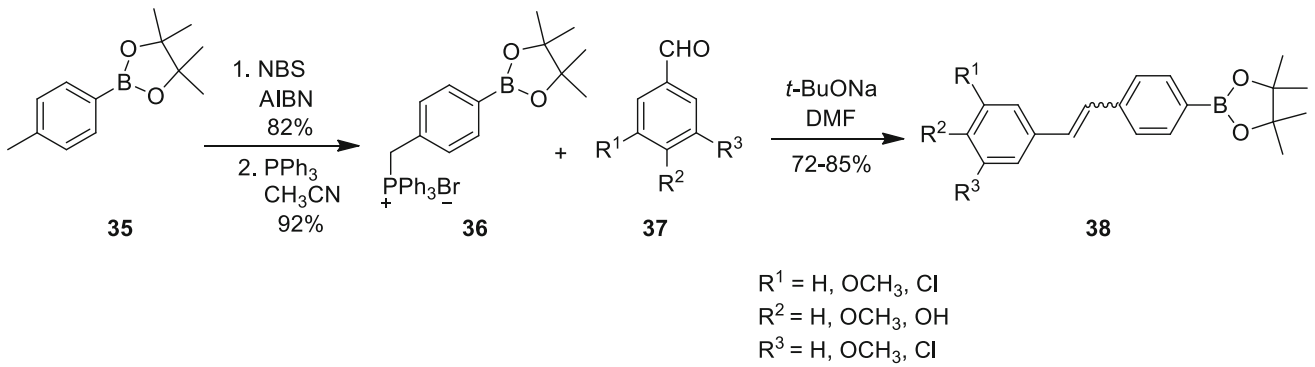
Gao et al. [17] synthesized radiolabeled stilbenes **33b** and **34b** as probes for cancer by treating Wittig salt **13** with 4-fluorobenzaldehyde **32b** and 4-nitrobenzaldehyde **32a**, respectively. Radiolabel precursors **33a** and **34a** were formed in 30–60% yield. Treatment of nitro precursors **33a** and **34a** with $K^{18}F$/Kryptofix$^{2.2.2}$ afforded fluorine-18 stilbenes **33b** and **34b** in 15–20% radiochemical yield as shown in Scheme 6.

Das et al. [55] synthesized pinacolyl boronate stilbenes **38** as lipogenic inhibitors using a Wittig strategy. Wittig salt **36** was formed as white solid in 92% yield from 4,4,5,5-tetramethyl-2-*p*-tolyl-1,3,2-dioxaborolane **35** in two steps, bromination was followed by a Wittig reaction. Wittig salt **36** on treatment with aldehydes **37** afforded the final products **38** in 72–85% yield as outlined in Scheme 7.

Srivastava and Lee [56] reported the use of a Wittig reaction for the synthesis of hybrid stilbenes **43** and **44** bearing a quinoline moiety to test their anticancer activity. Wittig salt **42** was prepared from benzyl bromide **41** in 60–80% yield while quinoline-3-carbaldehydes **40** were synthesized in 15–89% yield from aniline **39** through a Vilsmeier–Haack reaction. The reaction of Wittig salt **42** with quinoline-3-carbaldehyde **40** resulted in *cis*-product **43** in 21–75% yield and *trans*-product **44** in 2–10% yield as described in Scheme 8.



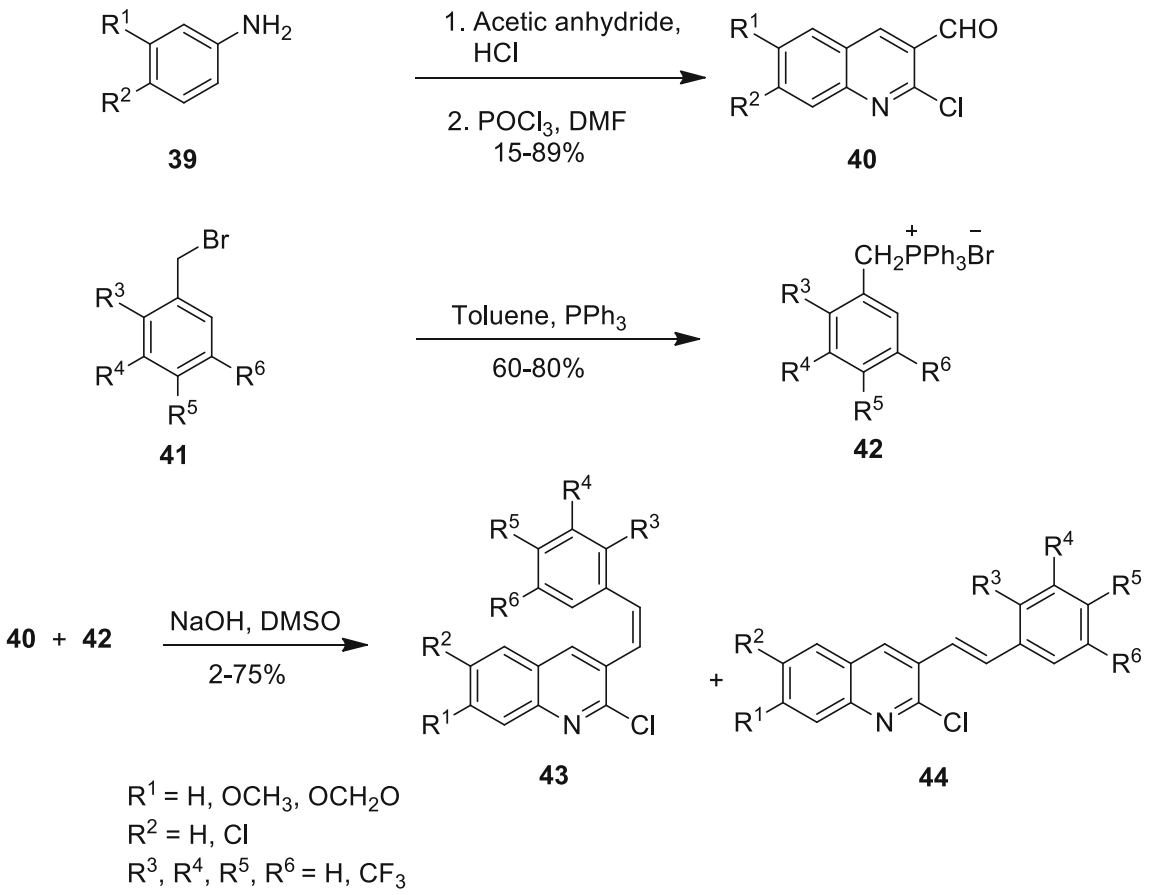
Scheme 6 Synthesis of radiolabeled stilbene **33b** and **34b**



Scheme 7 Synthesis of pinacolyl boronate stilbenes **38**

Jung et al. [57] prepared stilbenes (*E*/*Z* ratio 1/1) derivatives **50–56** in 77–90% yield as tyrosine phosphatase 1B inhibitors from the reaction of protected aromatic aldehyde **49** and aromatic ylide **47**. Deprotection of desired stilbene **50** was accomplished in 86% yield in the presence of tetrabutylammonium fluoride. The ester functionality of stilbene derivative **50** was reduced to stilbenes **52** and **53** and their subsequent deprotection afforded **54–56** in 77–90% yields as shown in Scheme 9a. Methyl-4-(chloromethyl) benzoate **57** was transformed into methyl-3[4-(iodomethyl)phenyl]-2-propenoate **60** in 90% yield via compounds **58** and **59**. Phosphonium salt **61** was obtained in 91% yield from compound **60**. Reaction of compound **61** with aldehyde **62** provided stilbene **63** in 62% yield. Final phenolic stilbene **64** was obtained in 28% yield by demethylation of stilbene **63** as shown in Scheme 9b. In continuation of their work, Jung et al. [58] obtained amides **65**–**66** by treating compound **51** with amines. Subsequent deprotection afforded *E*-stilbenes **67-68** in 60–74% yield as shown in Scheme 9c, and their antioxidant and neuroprotective potential was also evaluated.

Achalkumar and Yelamaggad [59] first reported the coupling of cyclohexane-1,3,5-trione with *E*-stilbenes **72** and **75** to form light emitting tris(N-salicylideneaniline) [TSANs] **77-78** as shown in Scheme 10. Diethyl(4-nitrobenzyl) phosphate **70** was prepared in 70% yield in two steps from 4-nitrotoluene **69** by benzylic bromination and a Michalis–Arbuzov reaction. The intermediate **70** furnished 1,2-bis(alkoxy)-4-(4-nitrostyryl)-benzenes **72** in 60–62% yield by a HWE reaction with 3,4-dialkoxybenzaldehydes **71** and subsequent reduction using indium as a source of



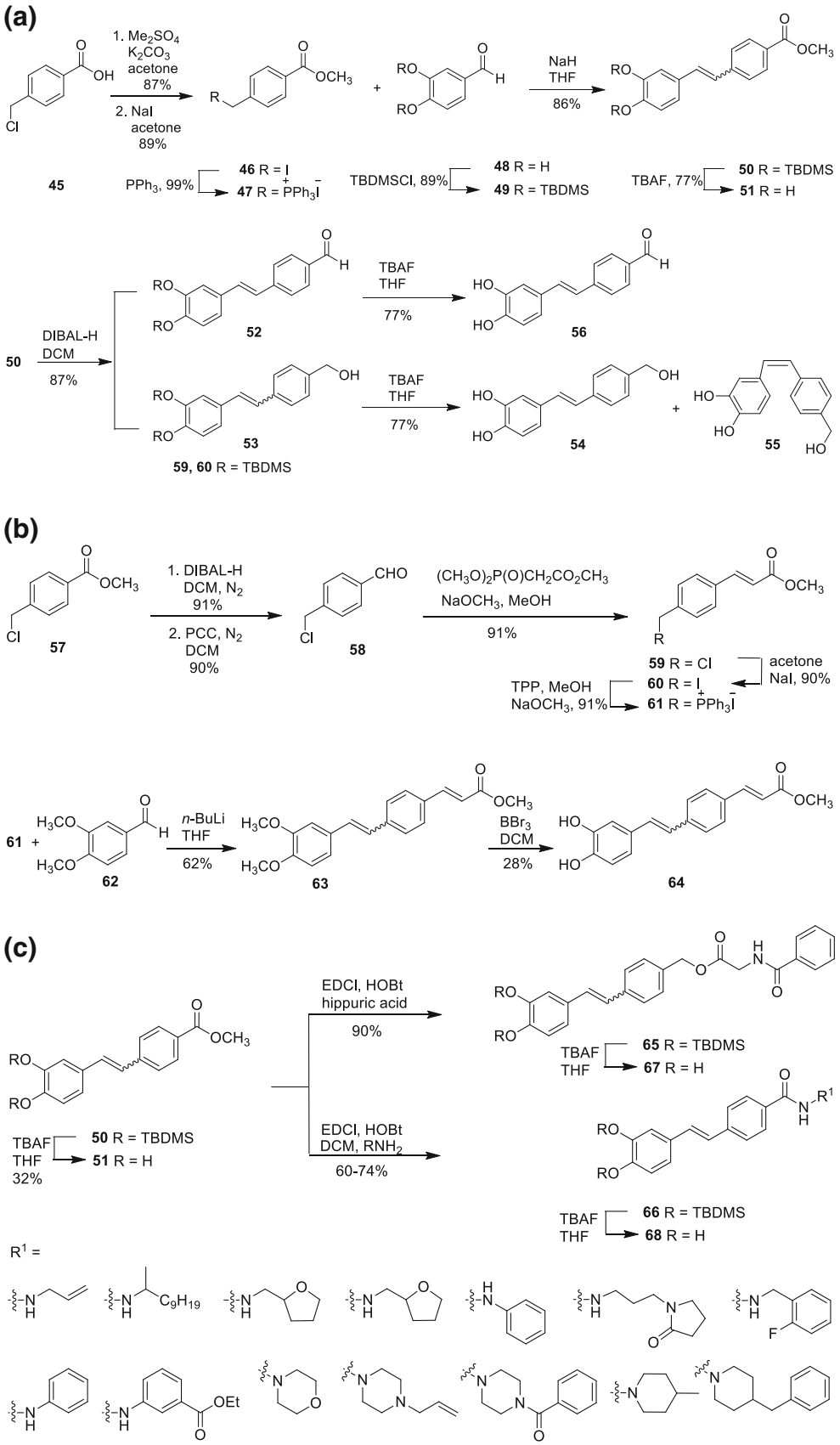
Scheme 8 Synthesis of quinoline-based stilbene **43–44**

reducing agent. 3,4,5-Trialkoxy aldehyde **74** was obtained in 68–80% yield by lithium aluminum hydride mediated reduction of the ester functional group of **73** into alcohols followed by oxidation of alcohols into aldehydes using PCC as oxidizing agent. The reaction of aldehyde **74** with intermediate **70** resulted in a nitrostilbene followed by reduction of nitro group to amine **75** in 60–64% yields. Finally, treatment of triformylphloroglucinol **76** with stilbenes **72** and **75** gave desired TSANs **77** and **78**, respectively, in 60–71% yields as yellow crystals.

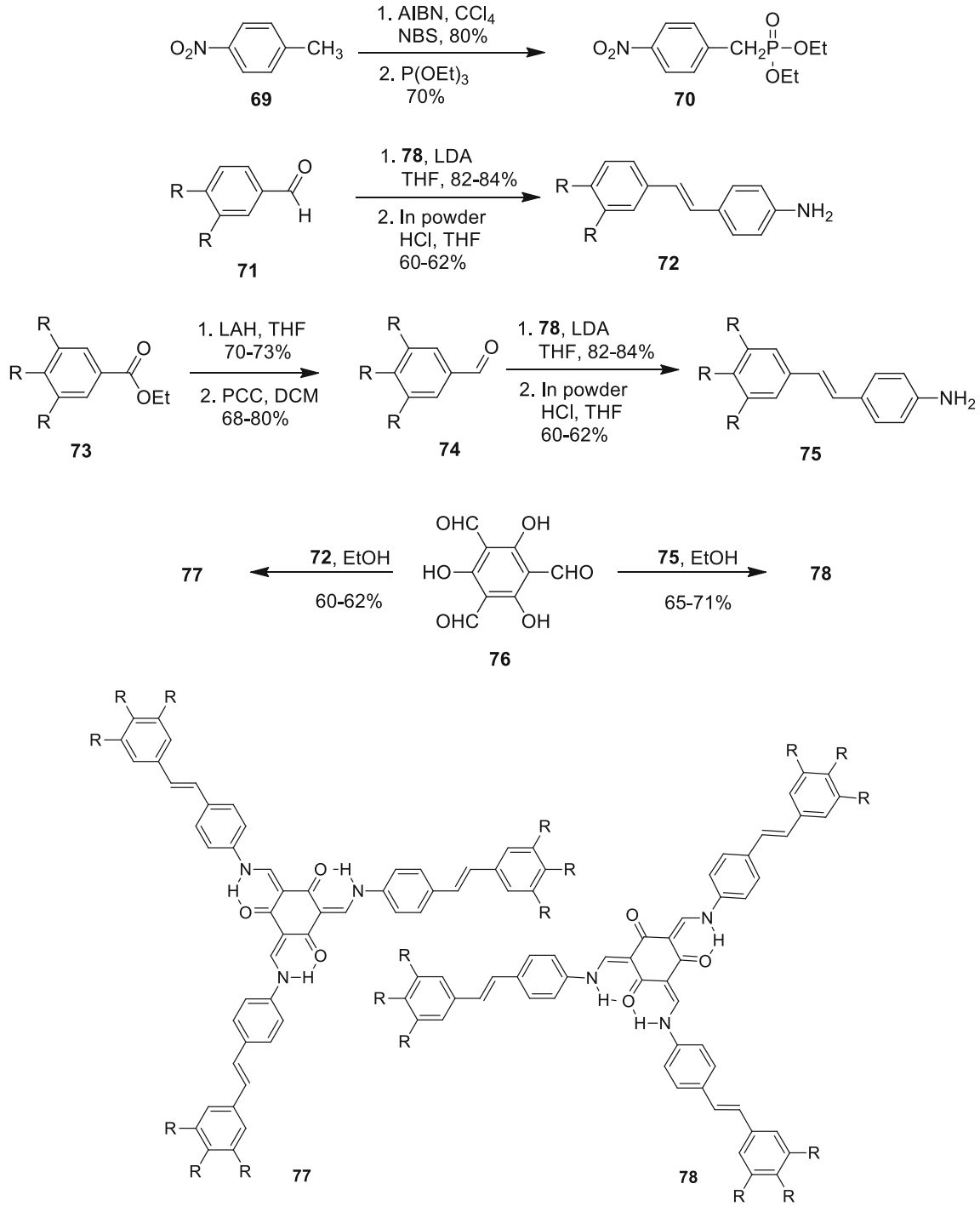
Belluti et al. [60] understood the biological importance of stilbene analogues and coumarins; therefore, they embedded coumarin units in various stilbene analogues. Methylcoumarines **79** generated intermediate phosphonic acid diethyl esters **80** in 60–81% yield. The intermediate **80** underwent HWE reaction with aldehydes, which afforded stilbene derivatives **81** in an *E*/*Z* ratio of 9/1 in 51–72% yield as outlined in Scheme 11.

McNulty and McLeod [61] investigated two Wittig routes for the synthesis of stilbene analogue *E*-pterostilbene **88**. Classical Wittig olefination usually yields poor *E*/*Z* stereocontrol, and it is highly desirable to improve stereoselectivity. In route A, phosphonium salt **86** was prepared from 3,5-dihydroxybenzoic acid **82** by converting acid **82** into ester **83** in 95% yield. Reduction of ester **83** into corresponding alcohol **84** was accomplished in 92% yield, which on direct reaction with triphenylphosphine HCl or through formation of benzyl chloride **85** (93% yield) gave compound **86** in 99% yield. However, compound **86** failed to react with 4-hydroxybenzaldehyde **87a**, but after protection of hydroxyl group **87b–d** gave pterostilbenes **3**, **88a-c** in 91% yield as shown in Scheme 12a. In route B, *p*-hydroxyphosphonium salt **90** was obtained in 91% yield using the above procedure. However, protection of the hydroxy group was required for the reaction of phosphonium salt **90** with an aldehyde. Here a deprotected phosphonium salt does not react with an aldehyde. Final product **3** was obtained in an *E*/*Z* ratio of 95/5 in 91% yield as shown in Scheme 12b.

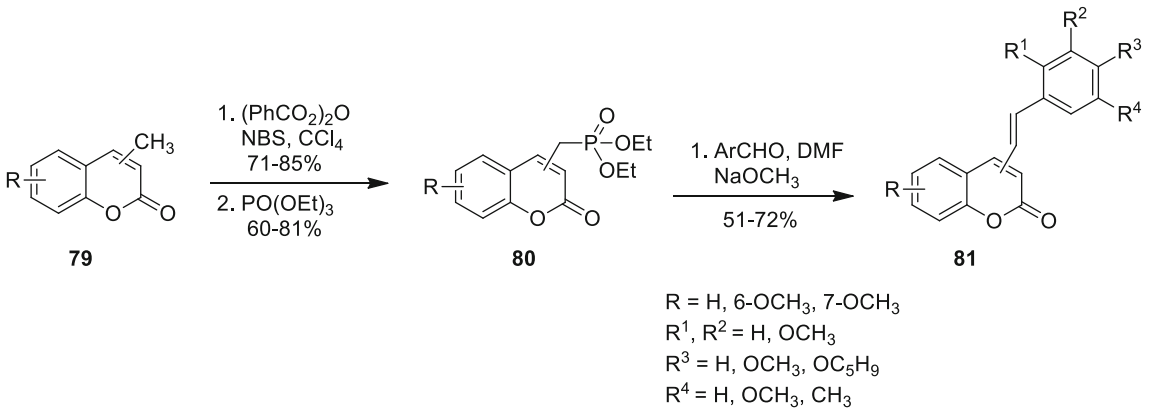
Anthracene-based stilbene derivatives **96** containing a 1,3,4-oxadiazole moiety were synthesized by Li and He [62] as shown in Scheme 13, and they also evaluated their optical properties. Anthracene-substituted 1,3,4-oxadiazole intermediate **94** was obtained in 78% yield by refluxing 4-methylbenzohydrazide **91** with anthracene-9-carbaldehyde **92** giving a yellow solution **93** to which chloramines-T were added and brominated with NBS to furnish compound **94**.



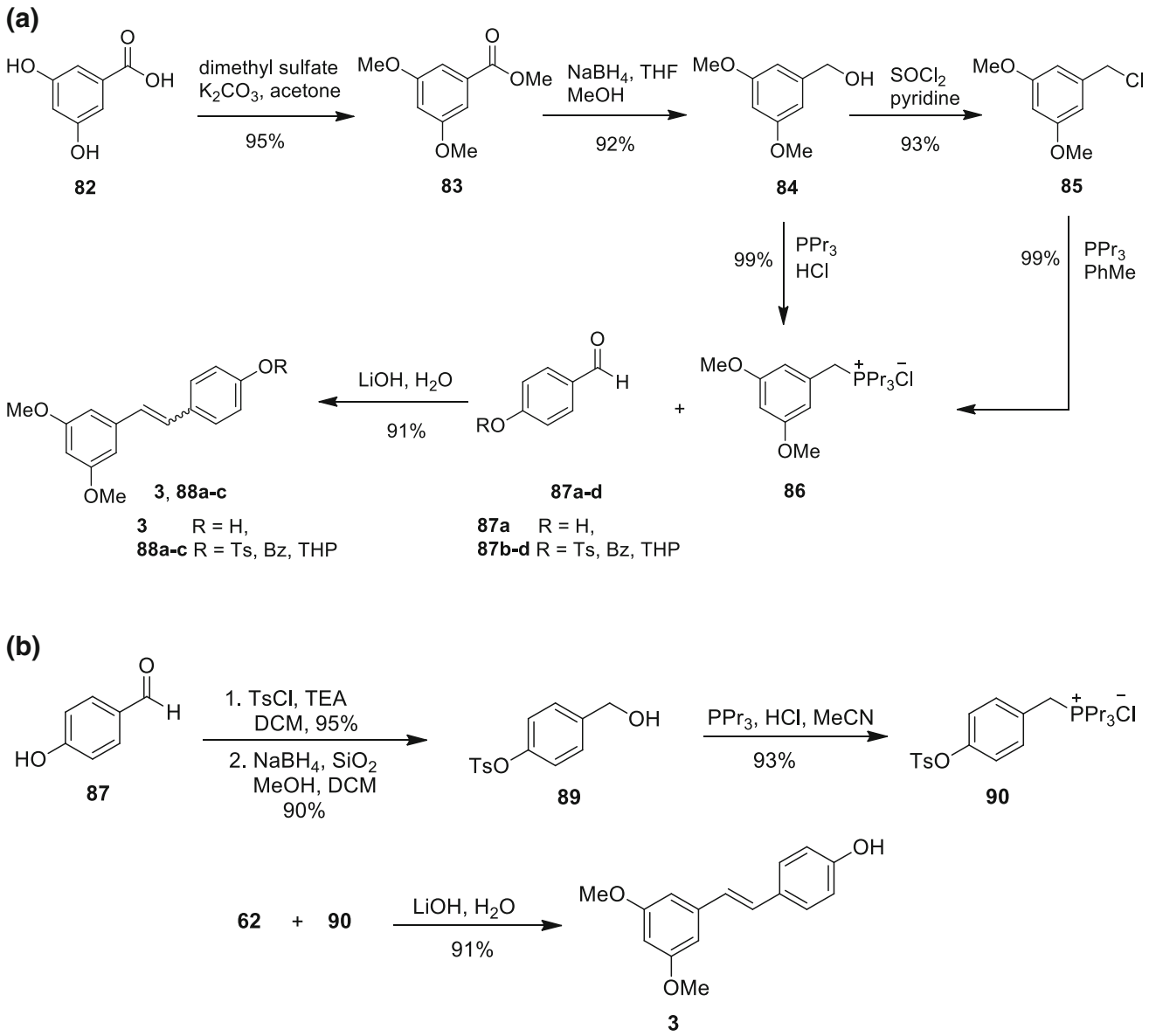
Scheme 9 **a** Synthesis of stilbene analogues **50–56**, **b** synthesis of stilbene analogues **63–64**, **c** synthesis of stilbene analogues **65–68**



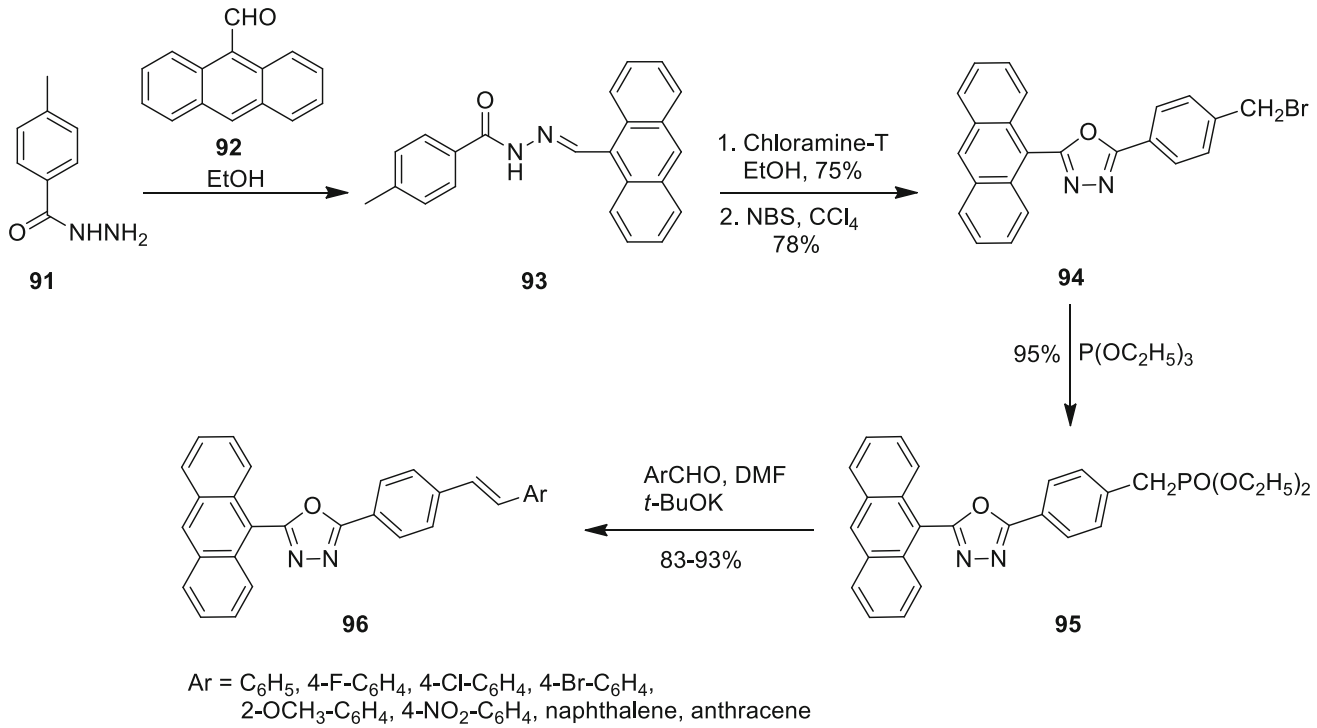
Scheme 10 Synthesis of star-shaped tris(*N*-salicylideneaniline) bearing *trans*-stilbene **77–78**



Scheme 11 Synthesis of stilbene–coumarin hybrid compounds **81**



Scheme 12 **a** Synthesis of pterostilbene **3**, **88a–c**. **b** Synthesis of pterostilbene **3**



Scheme 13 Synthesis of anthracene-based stilbene derivatives containing a 1,3,4-oxadiazole moiety **96**

Compound **94** furnished phosphonate ester **95** in 95% yield which, followed by a HWE reaction with aromatic aldehydes, afforded desired products **96** in 83–93% yield.

Lu and He [63,64] synthesized 1,3,4-oxadiazole derivatives containing stilbene and naphthalene units **101** from azomethine. Azomethine **98** was prepared from hydrazide **91** and aldehyde **97** [62]. Reaction of azomethine **98** with chloramine-T gave an intermediate having an oxadiazole ring. Bromonation afforded an oxadiazole bearing benzyl bromide **99**. Esterification of compound **99** followed by a Wittig–Horner reaction furnished product **101** in 81–91% yield as showed in Scheme 14.

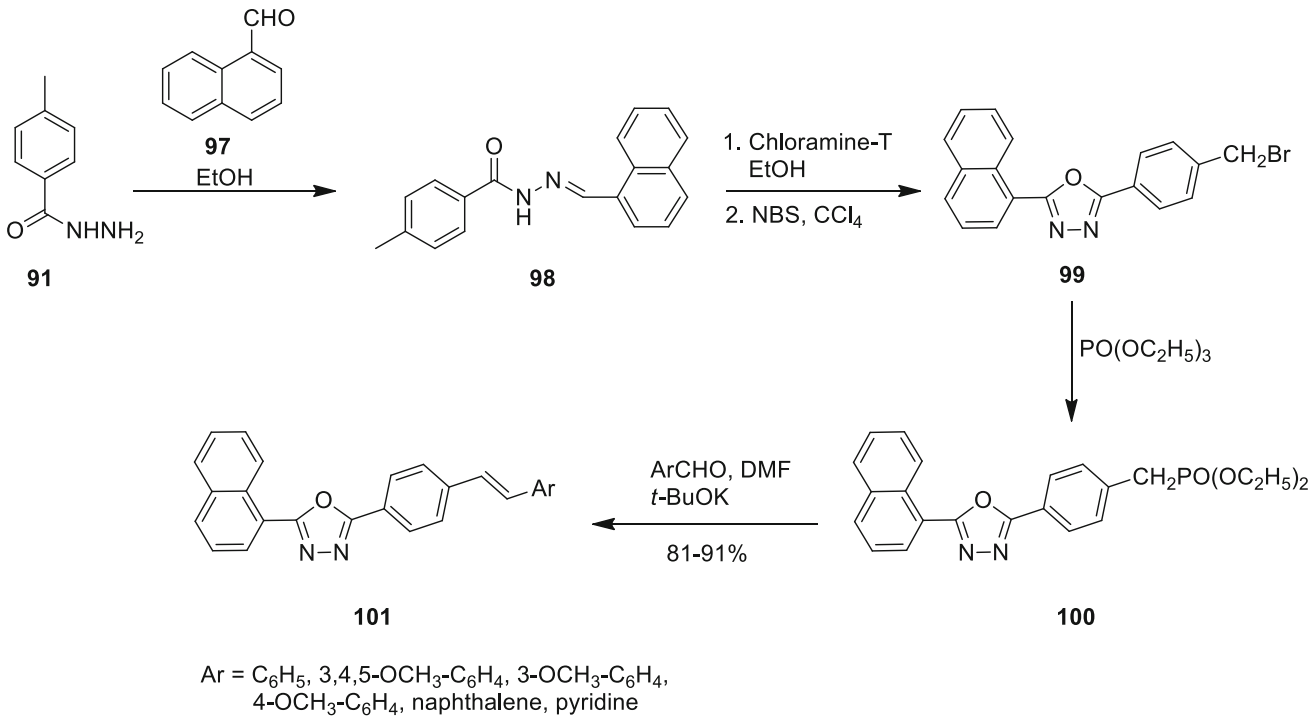
Zhu et al. [43] synthesized conjugated stilbenes carrying an oxadiazole moiety **107** to study their optical properties. Oxadiazole **104** was formed in 60% yield by direct reaction of *p*-toluic acid **102** with hydrazine hydrate **103** in the presence of polyphosphoric acid. Bromination of oxadiazole **104** followed by esterification with triethylphosphate afforded **106** in 80% yield. A Horner–Wadsworth–Emmons reaction of phosphonate ester **106** with appropriate aldehydes gave target stilbenes carrying an oxadiazole moiety **107** in 92% and 93% yield as outlined in Scheme 15a. In continuation of his work, Zhu et al. [65] synthesized two novel UV protectant compounds **109** in 35% yield and 68% yield by treating phosphonate ester **106** with respective aldehydes **108** under HWE reaction conditions as shown in Scheme 15b.

Hahm et al. [66] reported the synthesis of photosensitive polyimide (PSPI), ODPA-stilbene PSPI **115** that could be used as a liquid crystal display. (4-Nitrobenzyl)triphenylphosphonium bromide **111** was prepared from 4-nitrobenzyl bromide **110** in 83% yield. The subsequent reaction of compound **111** with 4-nitrobenzaldehyde gave 4,4′-dinitrostil bene **112** in 54% yield, which followed by nitro reduction with $SnCl_2$ produced 4, 4′-diaminostilbene **113** in 52% yield. Hybrid ODPA-stilbene **115** was formed when ODPA reacted with compound **113** under a nitrogen atmosphere in dry NMP as shown in Scheme 16.

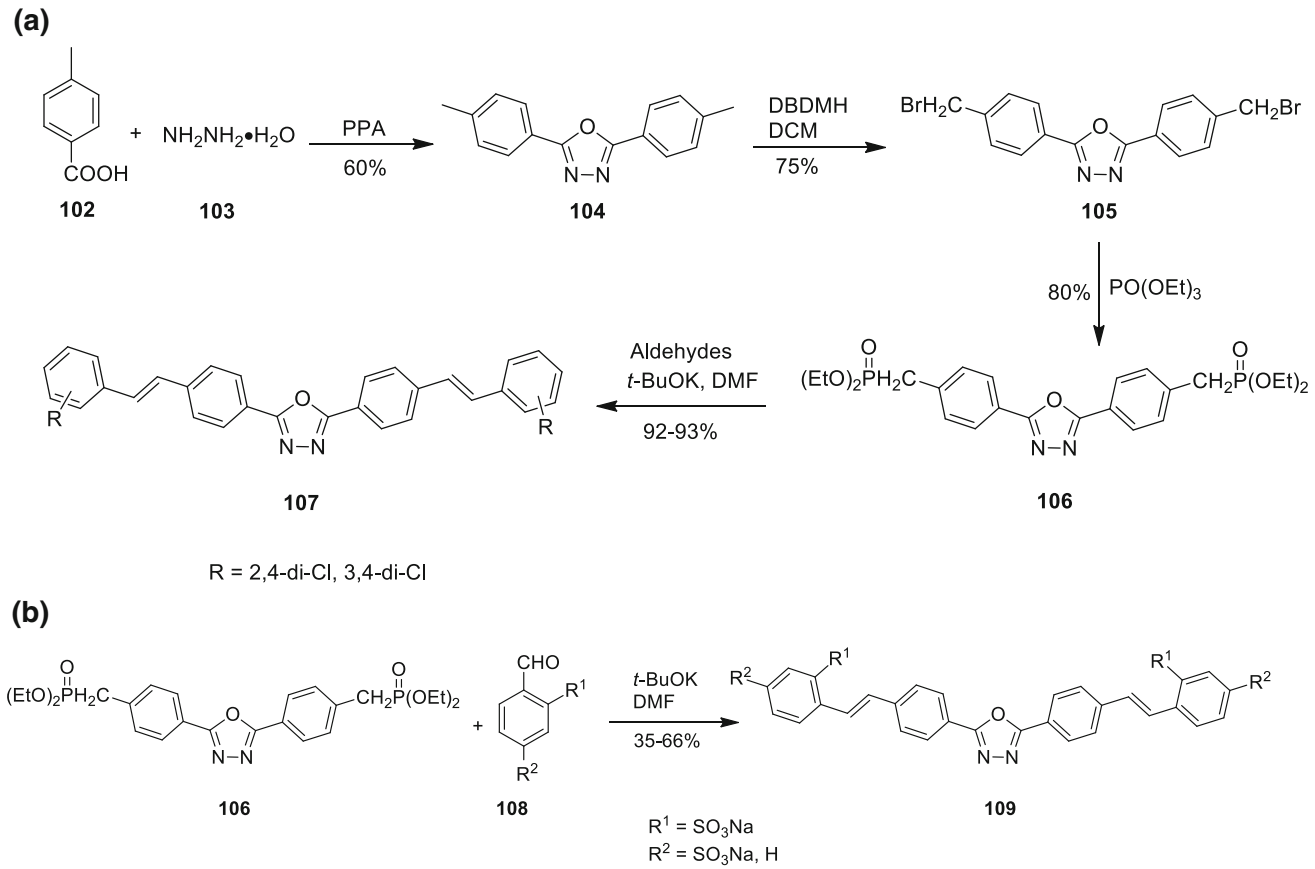
Metal-mediated syntheses of stilbene analogues

Considering the importance of quinazoline and stilbene as bioactive compounds, Mahdavi et al. [67] hybridized *trans*-stilbene with quinazolines to develop potent anticancer agents. The reaction of styrene **117** with bromobenzaldehyde **116** using palladium-catalyzed Mizoroki–Heck reaction conditions provided stilbene **118** in 90% yield. Treatment of isatoic anhydride **119** with relevant primary amines generated anthranilamide **120** in 85–95% yield, which on reflux with stilbene **118** furnished **121** in 90–95% yields. As described in Scheme 17, compound **121** was oxidized to quinazoline **122** in 75–90% yield using tetrabutyl ammonium bromide in the presence of base.

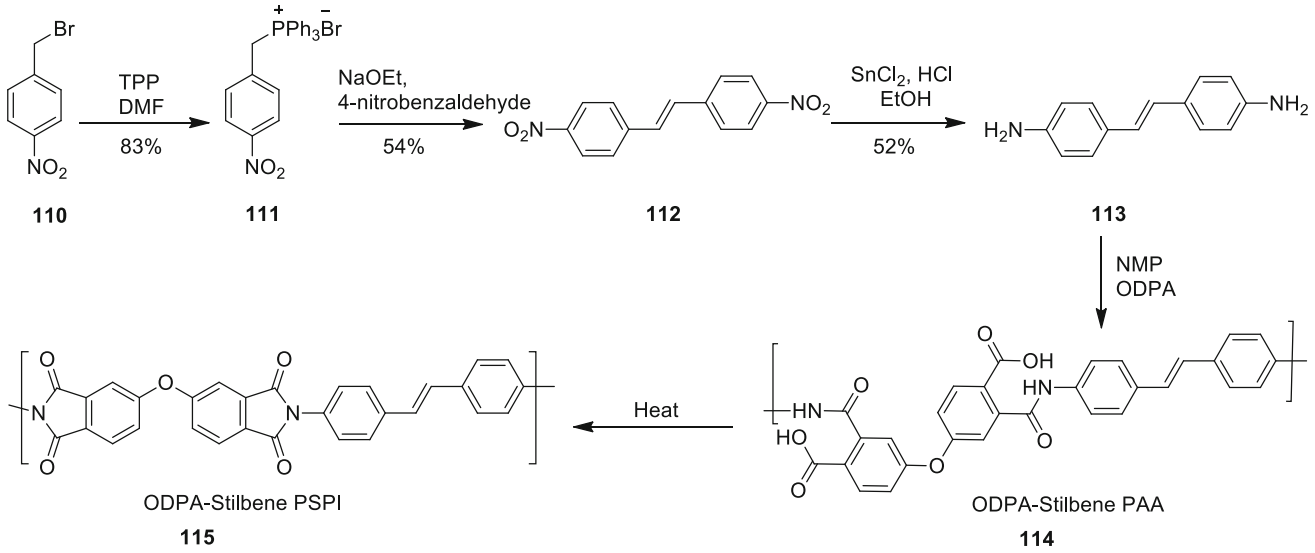
As indicated in Scheme 18, Marti-Centelles et al. [68] described palladium-catalyzed preparations of stilbenes **124** by the reaction of styrene **117** with halogenated derivatives **123** under two different reaction conditions (Methods **A** and



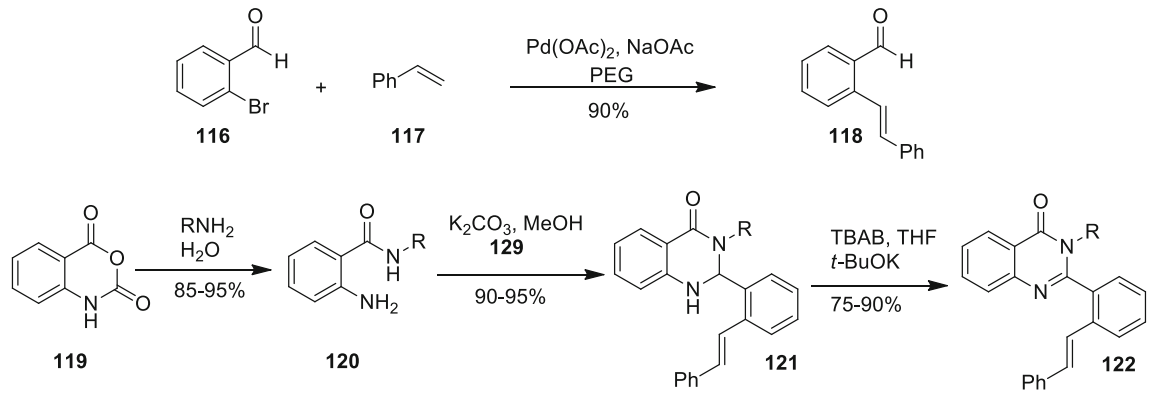
Scheme 14 Synthesis of naphthalene-based stilbene derivatives containing 1,3,4-oxadiazole moiety **101**



Scheme 15 **a** Synthesis of highly conjugated stilbenes carrying an oxadiazole moiety **107**. **b** Synthesis of conjugated stilbenes carrying an oxadiazole moiety **109**

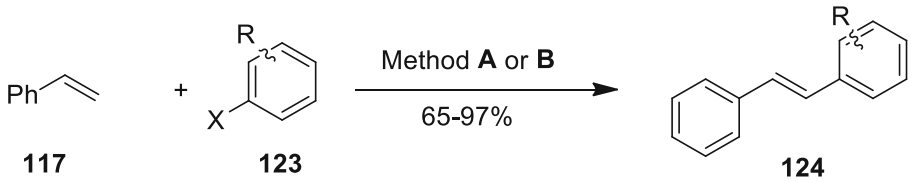


Scheme 16 Synthesis of photosensitive ODPA-stilbene PSPI **115**



Scheme 17 Synthesis of quinazoline-bearing stilbene moiety **122**

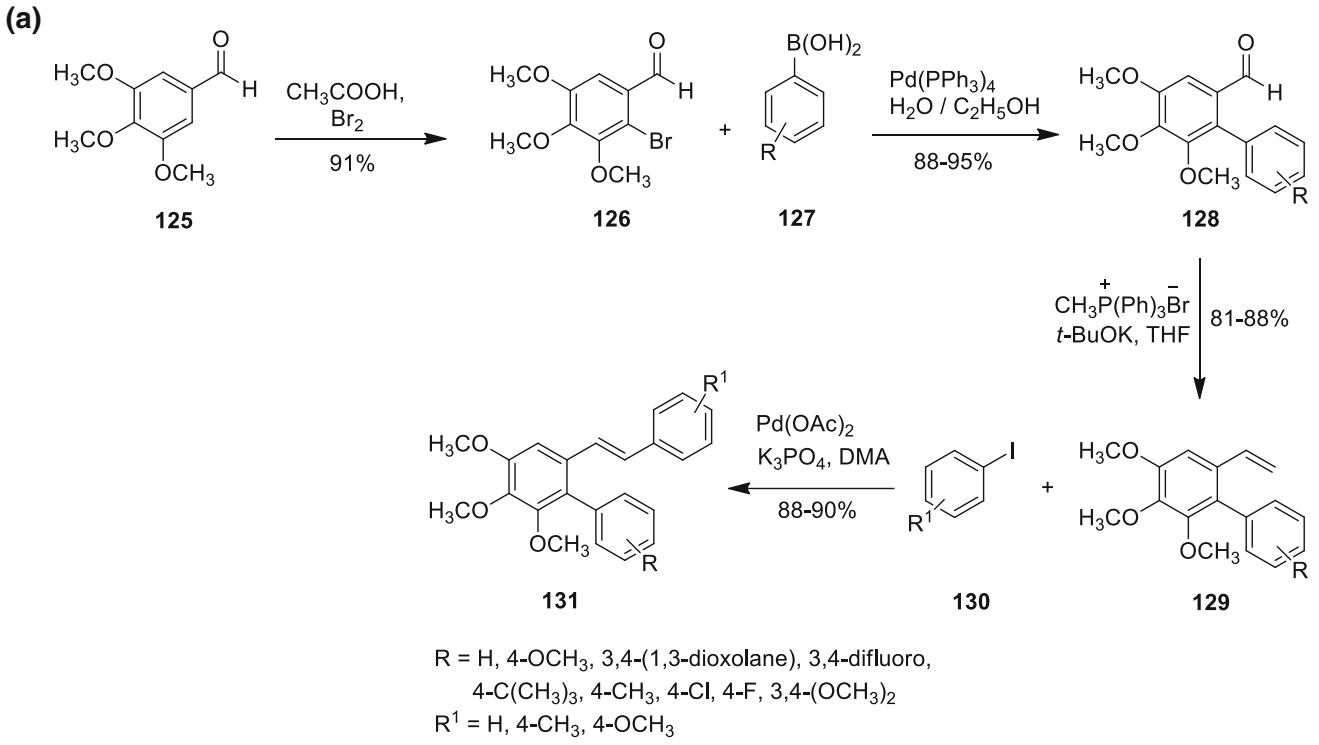
Scheme 18 Synthesis of stilbenes **124** by palladium-catalyzed Mizoroki–Heck reaction

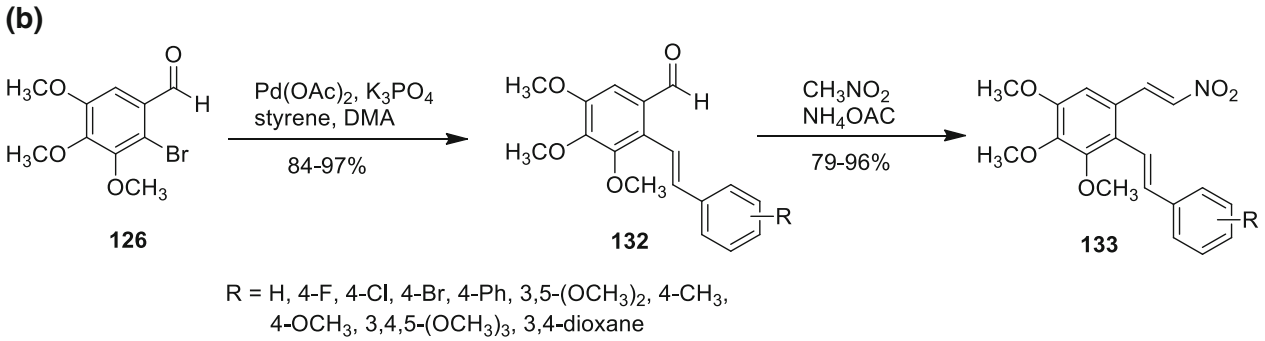


Method **A**: Pd(0), K_2CO_3, 170 °C, MW (70 W, 10 min)
Method **B**: $Pd(NH_3)_2Cl_2$, Bu_3N, TBAB, H_2O, Reflux, 24h

B). Both methodologies afforded desired stilbenes in good yields (65–97%).

A relatively new route to synthesize antitubulin agent, biaryl aryl stilbene **131** by utilizing Suzuki and Mizoroki–Heck cross coupling reactions, was disclosed by Kumar et al. [10]. Bromination of 3,4,5-trimethoxybenzaldehyde **125** followed by Suzuki cross coupling with aryl boronic acids **127** produced intermediate 4,5,6-trimethoxybiphenyl-2-carbaldehyde **128** in 88–95% yield. Wittig reaction of aldehyde **128** furnished 2,3,4-trimethoxy-6-vinylbiphenyls **129** followed by palladium-catalyzed Mizoroki–Heck coupling with aryl halides **130** afforded biaryl stilbene **131** in 88–90% yield as shown in Scheme 19a. Reddy et al. [69] synthesized nitrovinyl stilbenes **133** by using a similar methodology. Intermediate **126** produced stilbene **132** in 84–97% yield by way of a palladium-catalyzed Mizoroki–





Scheme 19 **a** Synthesis of biaryl aryl stilbenes **131**. **b** Synthesis of nitrovinyl stilbenes **133**

Heck reaction with styrene. The reaction of compound **132** with nitromethane gave nitrovinyl stilbenes **133** in 79–96% yield as shown in Scheme 19b.

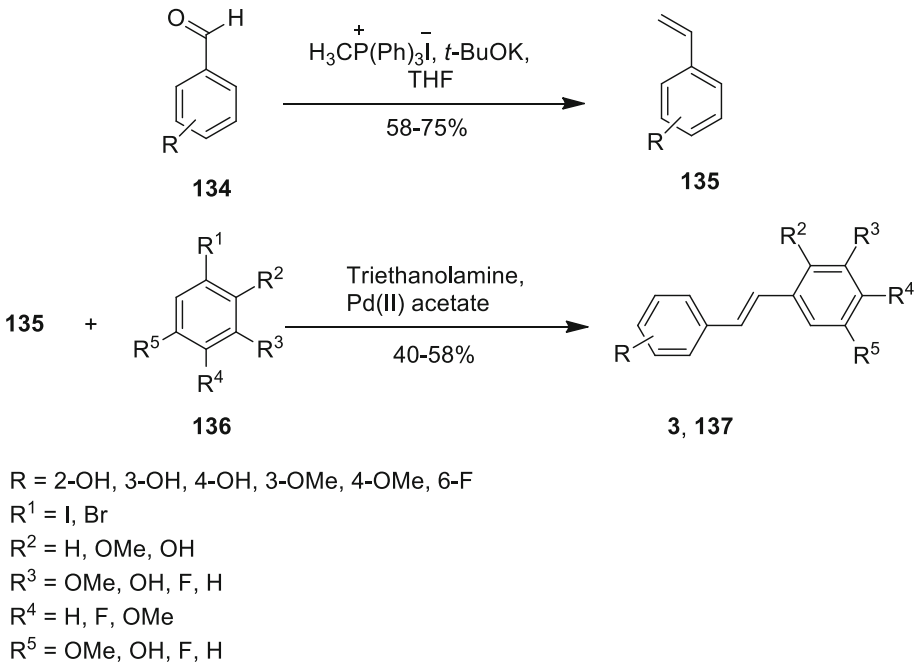
Albert et al. [70] followed a Mizoroki–Heck reaction protocol using triethanolamine, which acts as ligand, solvent as well as base [71] allowing the economic synthesis of *E*-stilbenes **3**, **137** to evaluate their antimicrobial activity. Substituted styrenes **135** were synthesized in 58–75% yield from benzaldehyde **134** by a Wittig reaction. Then, a Mizoroki–Heck reaction between styrene **135** and halogenated benzene **136** gave *E*-stilbenes **3**, **137** in good yields as outlined in Scheme 20.

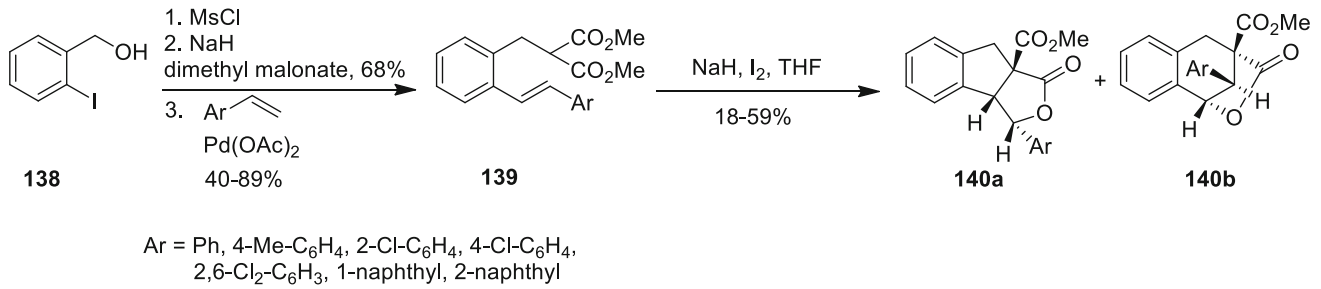
Khan et al. [72] synthesized stilbene derivatives **139** in 40–89% yields by mesylation of 2-iodobenzyl alcohol **138** with dimethylmalonate, which gave intermediate in 68% yield followed by a Mizoroki–Heck reaction with styrenes then gave stilbenes **139** as shown in Scheme 21. Further stilbene derivatives **139** were used in iodonium-promoted carbocyclizations to furnish a mixture of structurally complex indanes **140a** in 18–55% yields and tetrhydronaphthalenes **140b** in 18–59% yields with three new stereogenic centers.

Kabir et al. [13] reported the Pd-catalyzed regioselective synthesis of *E*-stilbene **144** in 74% yield by a Negishi cross coupling between arylvinyl iodide **143** and arylzinc reagent **142**. Arylvinyl iodide **143** was prepared in 84% yield [73], whereas arylzinc **142** was obtained by transmetallation of hydrogen-lithium exchange product of arylbromide **141** with zinc(II)chloride as outlined in Scheme 22.

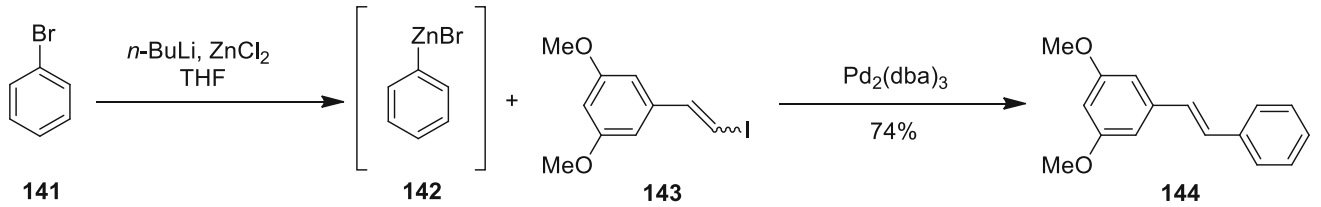
McDonald et al. [74] synthesized aza-stilbenes **147** to check their potency against the c-RAF enzyme. A range of styrenes **146** were created by the palladium-catalyzed Stille coupling of 5-bromo-nicotinonitrile **145** with tributylvinyl

Scheme 20 Synthesis of *E*-stilbene **3**, **137**





Scheme 21 Synthesis of stilbene derivatives **139**

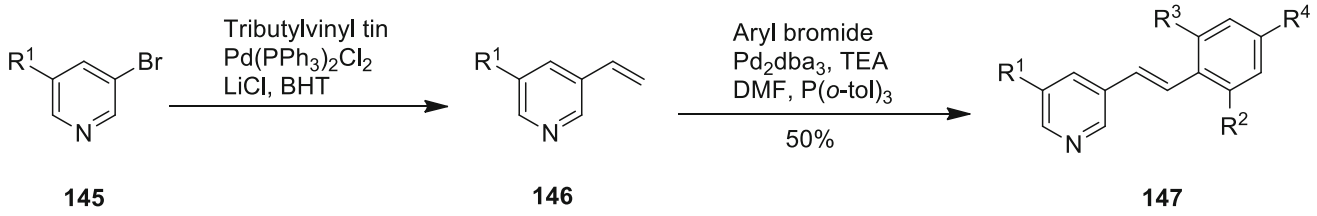


Scheme 22 Regioselective synthesis of *E*-stilbene **144**

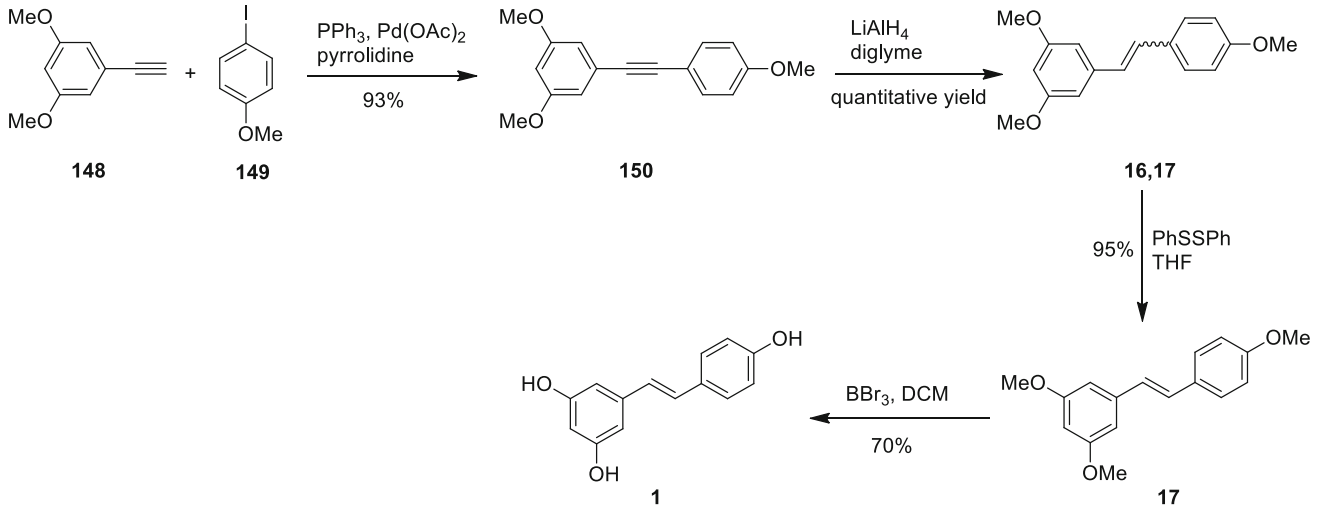
tin. Mizoroki–Heck cross coupling of substituted styrenes **146** with bromo benzene furnished aza-stilbenes **147** mostly in moderate yields as shown in Scheme 23.

Lara-Ochoa et al. [75] reported a new route to stilbene analogue resveratrol **1** using a Sonogashira coupling strategy. Acetylene precursor **150** was obtained in 93% yield under Sonogashira coupling conditions. Subsequent hydrogenation of acetylene **150** with $LiAlH_4$ gave an *E*/*Z* mixture of **16**, **17** (96/4 ratio) in quantitative yields. Diphenyldisulfide-assisted isomerization of an *E*/*Z* mixture of **16** and **17** gave *trans*-isomer **17** in 95% yield. Deprotection of the methoxy functional group in **17** in the presence of boron tribromide gave resveratrol **1** in 70% yield as described in Scheme 24.

Utilization of cyclic 1,1-bis(silyl)alkenes **151** to graft double bond on the aromatic ring for the selective preparation of *E*-stilbenes **154** was reported by Pawluc et al. [76]. Treatment of **151** with various aryl iodides **152** under Mizoroki–Heck coupling conditions furnished compounds **153** in good yields. Various *E*-stilbenes **154** were formed in good yields (62–92%) when compounds **153** were further coupled with various aryl iodides **152** using $[Pd(C_3H_5)Cl]_2$ as a catalyst in the presence of TBAF shown in Scheme 25.



Scheme 23 Synthesis of aza-stilbene **147**



Scheme 24 Synthesis of resveratrol **1**

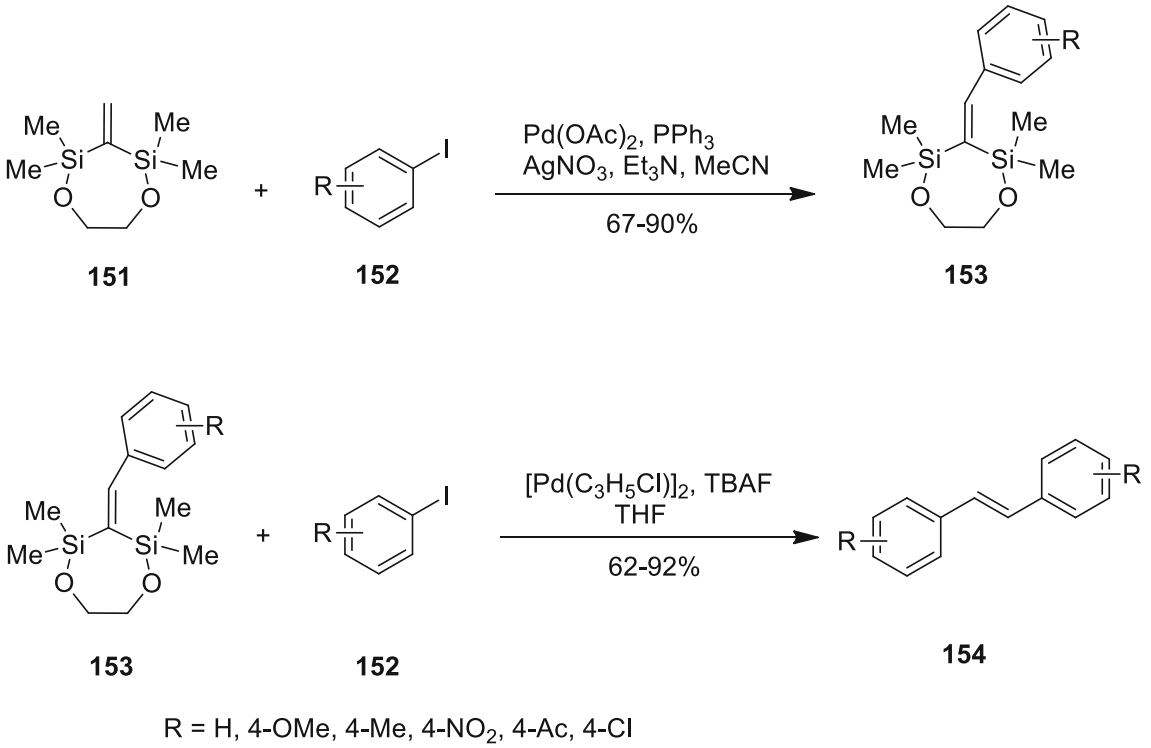
An efficient one-pot preparation of stilbene **154** under Mizoroki–Heck reaction conditions was presented by Saiyed and Bedekar [77]. This method reduces work-up, generates less waste and saves time and energy. Initially, styrene **117** was generated by dehydrohalogenation of (2-bromoethyl)benzene **156**, whereas the same styrene **117** can also be accessed from aldehyde **157** and phosphonium salt **42** using a Wittig reaction protocol as described in Scheme 26. Product **154** was obtained in 54-88% yield using a standard Mizoroki–Heck reaction as shown in Scheme 26.

Understanding the importance of sonochemistry in accelerating synthetic reactions, Cella et al. [78] utilized ultrasound to generate stilbenes from organotellurium compounds and potassium organotrifluoroborate salts under Suzuki cross coupling reaction conditions. *Z*-stilbenes **160** were obtained in 60–82% yield by ultrasound irradiation of *Z*-styryl *n*-butyltelluride **158** and potassium organotrifluoroborate **159** using $Pd(PPh_3)_4$ and Ag_2O. Whereas *E*-stilbenes **163** have been prepared by using *E*-styryltrifluoroborate **161** and *n*-butyl(aryl)tellurides **162** with potassium carbonate in 59–91% yield as shown in Scheme 27.

Copolymerization of benzotriazole (BTz) **166**, thiophene **168** and stilbene **167** was carried out by Karakus et al. [79] to study their electrochemical properties via Stille cross coupling reaction. Copolymers **169** (P_1, P_2 and P_3) were synthesized in different ratios of BTz and stilbene. Coupling of 4,7-dibromo-2-dodecylbenzotriazole **166**, *E*-1,2-bis(4-bromophenyl)ethane **167** and 2,5-bis(tributylstannyl) thiophene **168** using dichlorobis(triphenylphosphine)-palladium(II) gave the desired copolymers **169** (P_1, P_2 and P_3) as shown in Scheme 28.

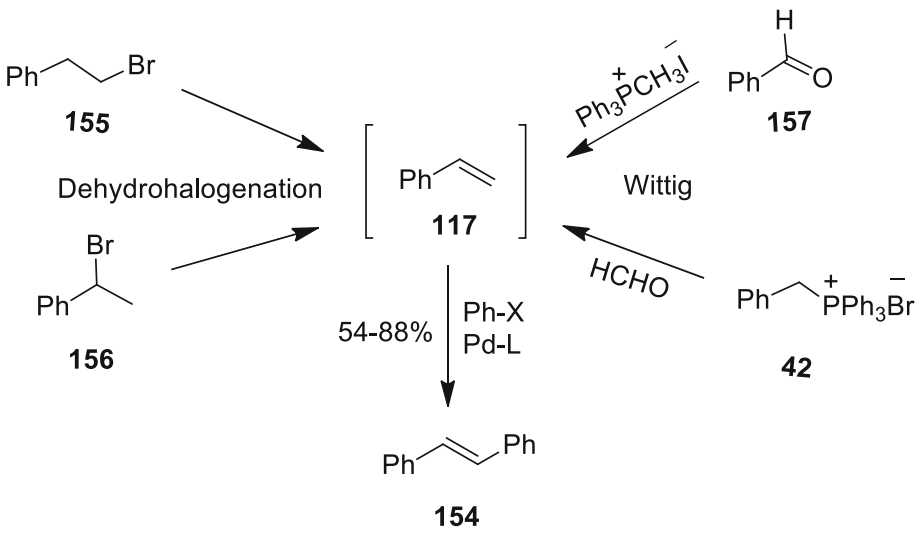
Zhang et al. [80] reported an efficient and simple method to synthesize 2-hydroxylated (*E*)-stilbenes **172** in good yield by oxidative coupling of 2-hydroxystyrene **170** with arylboronic acid **171** using $[CpRhCl_2]_2$ and $Cu(OAc)_2$ at room temperature as shown in Scheme 29, and they further investigated their antiproliferative activity.

Novel double carbocyclizations mediated by selenium were reported by Shahzad and Wirth [81]. Stilbenes **174** were generated from methyl-2-iodobenzoate **173** under palladium-catalyzed Mizoroki–Heck reaction conditions. Reduction of **174** and mesylation of compound **175** followed by subsequent nucleophilic substitution reaction furnished stilbenes **176**. On the other hand, 2-iodobenzyl chloride **177** also gave stilbenes **176** using the same route through compound **178**. These substituted stilbenes **176** were used as



Scheme 25 Synthesis of *E*-stilbenes **154**

Scheme 26 Two one-pot methods for synthesis of stilbene **154**

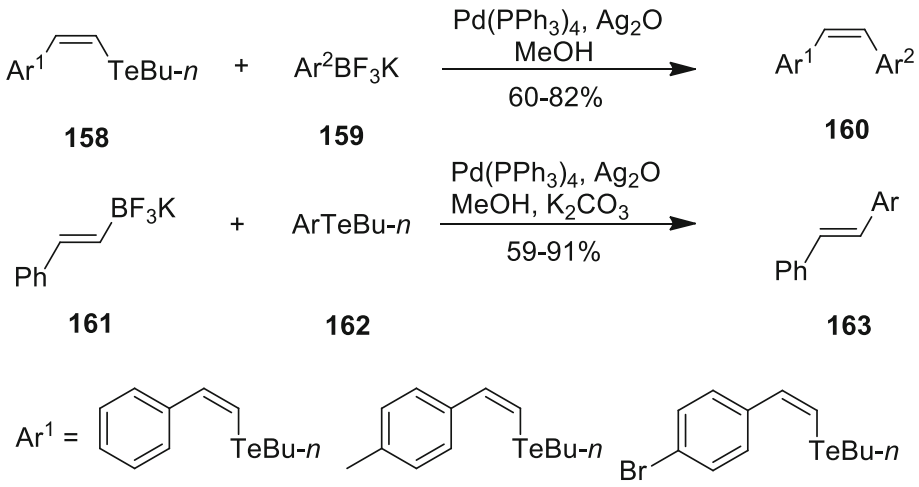


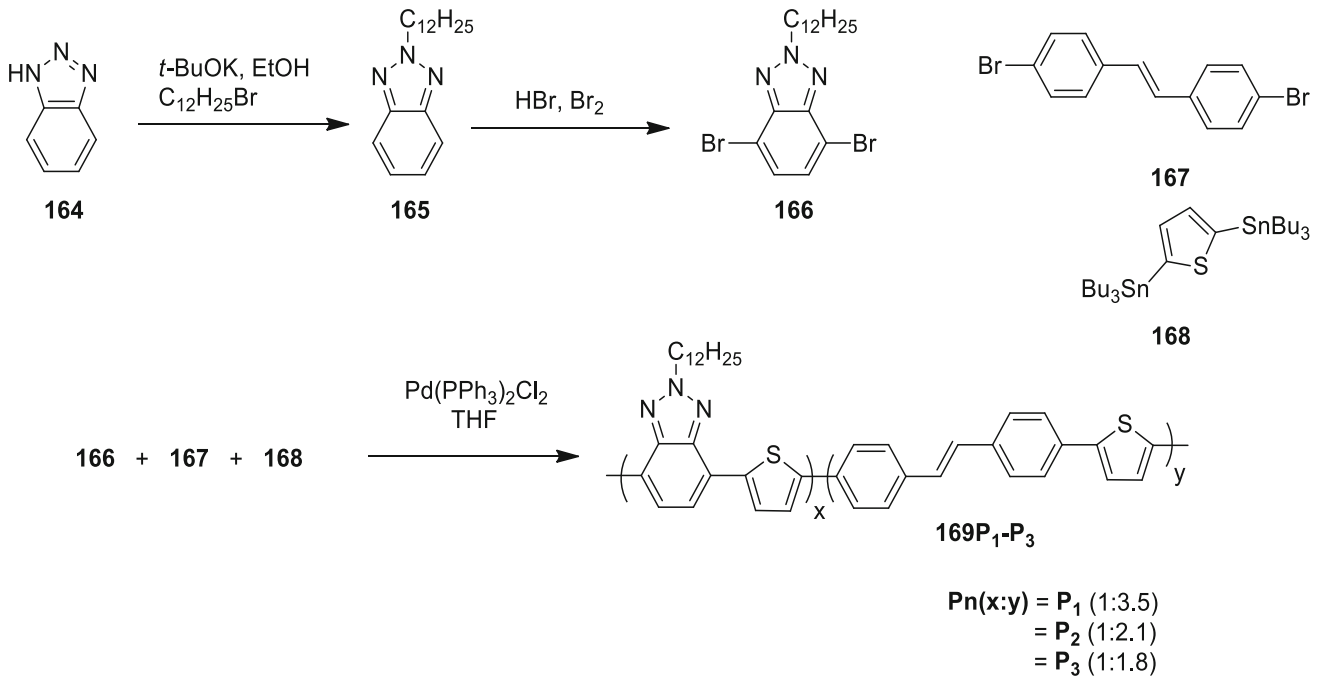
precursors to produce dihydronaphthalene **179** in 50–90% yields, which was then transformed to benzofluorenes **180** in 30–90% yields through a one-pot procedure using phenylselenium chloride as selenylating reagent with a Lewis acid as shown in Scheme 30a.

Shahzad et al. [82] used a malonate moiety on an alkene to synthesize dihydronaphthalene and benzofluorenes. Stilbenes **174** were obtained in 80–93% yields from methyl 2-iodobenzoate **173** under Mizoroki–Heck reaction conditions. Hydrolysis of **174** afforded carboxylic acids **175** in 87–100% yields. β-keto ester derivatives of stilbene **181** were obtained in 58–98% yields from corresponding acids **175** using potassium ethyl malonate. Stilbene precursor **181** was transformed to dihydronaphthalene **182** in 50–96% yields using a combination of a selenium electrophile as selenylating reagent with a Lewis acid as shown in Scheme 30b.

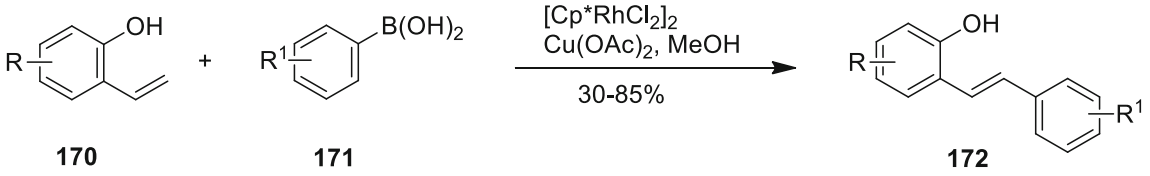
Shahzad et al. [83] also used diselenide and disulfide in the synthesis of isocoumarins **184**. Stilbene-based carboxylic acids **175** were obtained in 87–100% yields from corresponding esters by using lithium hydroxide. Compound **175** and its analogues were cyclized to dihydroisocoumarins **183** in

Scheme 27 Synthesis of *E* & *Z* stilbenes **160** and **163** by using ultrasound irradiation



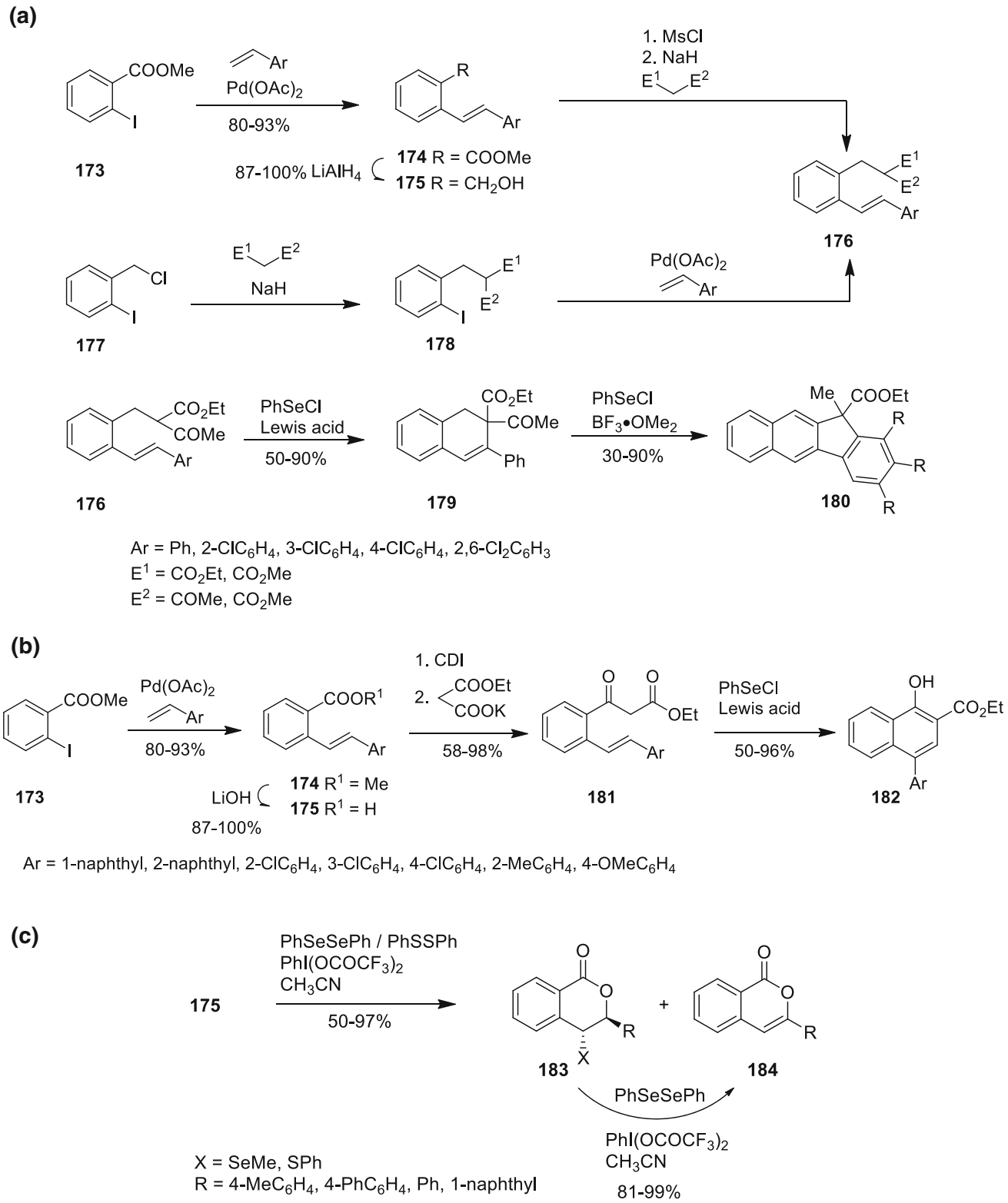


Scheme 28 Synthesis of stilbene-based copolymers **169**

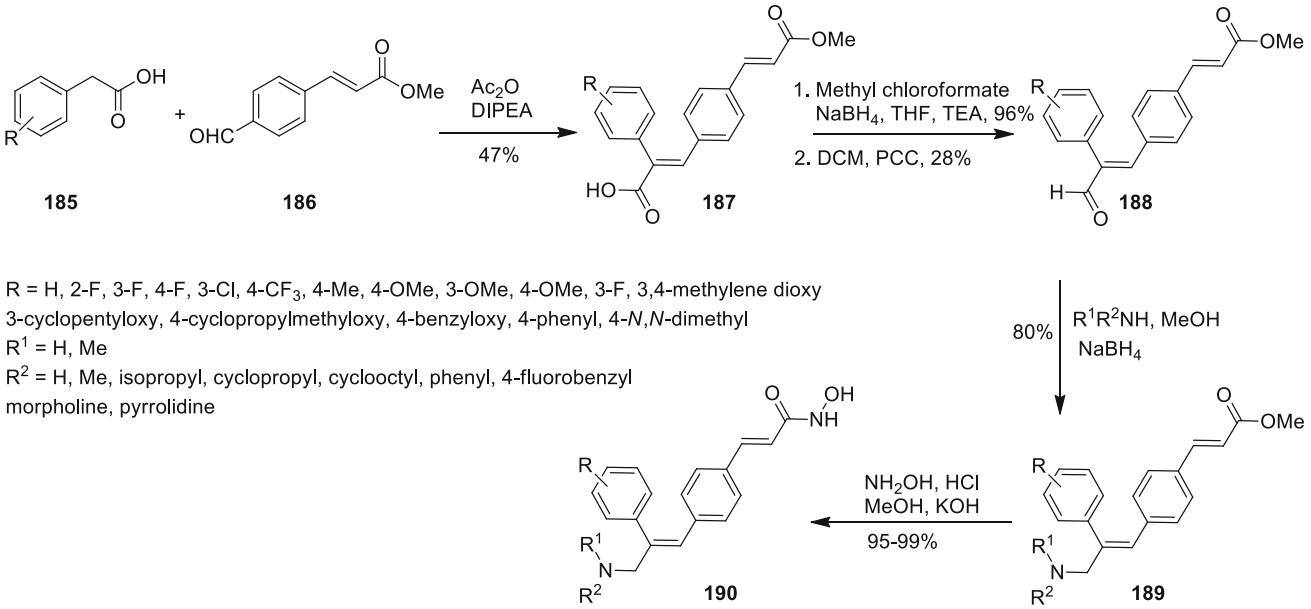


R = H, 3-OMe, 2-OMe, 4- Br, 4-NO_2
R^1 = H, 4-Me, 4-Br, 4-OH, 4-CN, 2,4-$(OMe)_2$, 3,5-$(OH)_2$, 3,5-$(OMe)_2$, 3,4,5-$(OMe)_3$, 3,5-Me_2

Scheme 29 Synthesis of 2-hydroxylated (*E*)-stilbenes **172**



Scheme 30 **a** Synthesis of stilbene precursor **176** and benzofluorene **180**. **b** Synthesis of stilbenes **175**, **181** and biaryls **182** through a convenient synthetic route. **c** Synthesis of stilbene precursor **175** and one-pot preparation of isocoumarin **184**



Scheme 31 Synthesis of stilbene-based hydroxamates **190**

50–97% and isocoumarins **184** in 81–99% yields using *N*-phenylselenosuccinimide (*N*-PSS). Because of the high cost of *N*-phenylselenosuccinimide (*N*-PSS), another methodology was developed by Shahzad and coworkers using diphenyl diselenide and [bis-(trifluoroacetoxy)iodo]benzene to synthesize isocoumarins **184**. Optimization concluded that 10 mol% use of catalyst diphenyl diselenide gave desired isocoumarins in excellent yield as shown in Scheme 30c.

Synthesis of stilbene analogues by Perkin condensation

Kachhadia et al. [84] designed stilbene-based hydroxamates **190** to inhibit histone deacetylases (HDACs), which are the cause of epigenetic states related to cancer. For this purpose, 4-formylcinnamic acid was converted to ester **186**, which undergoes Perkin condensation with substituted phenylacetic acids **185** to generate acrylic acids **187** in 47% yield. Compounds **187** were then reduced to alcohols and oxidized into aldehydes **188** in 28% yield using PCC. Compound **188** underwent reductive amination to amine **189**. The amines were finally converted into hydroxamic acid **190** in 95–96% yield by treating with hydroxylamine as shown in Scheme 31.

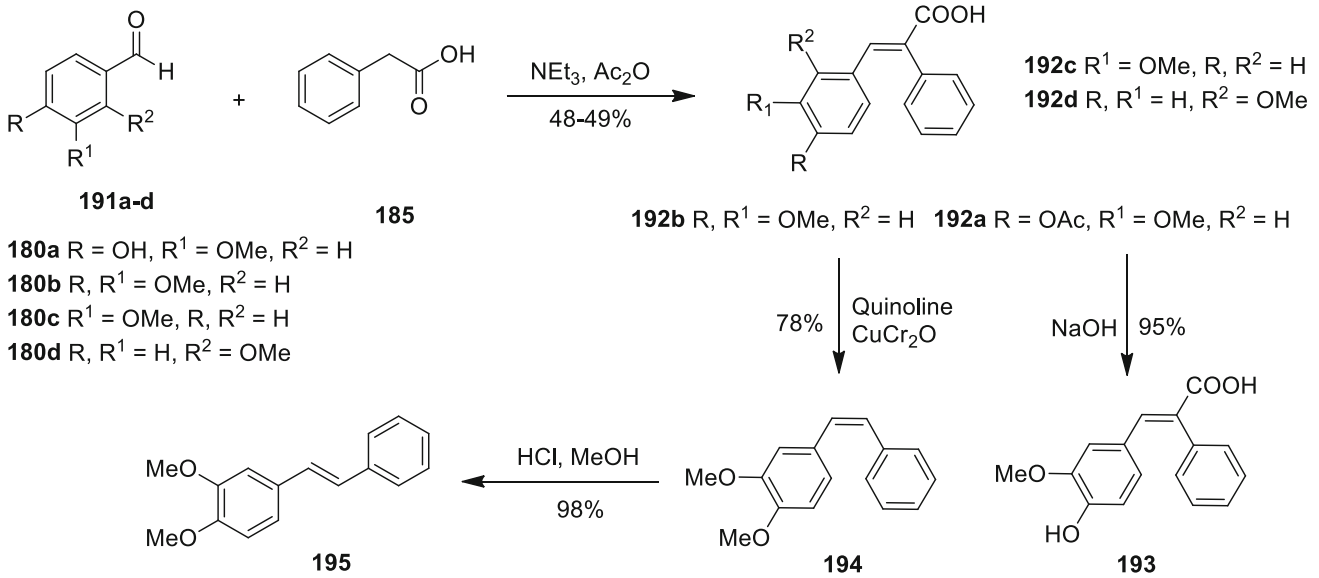
To assess the cytotoxicity of stilbene derivatives, efficient preparation of resveratrol analogue **195** was described by de Lima et al. [1] using Perkin reaction conditions. Condensation of aldehydes **191a–d** with phenyl acetic acid **185** provided carboxylic acid-substituted stilbenes **192a–d** in 48–49% yields. Compound **194** was formed in 78% yield when copper chromite in quinoline was used for the decarboxylation of compound **192b**. Compound **194** was isomerized to *trans*-analogue **195** in 98% yield in the presence of concentrated HCl. Hydrolysis of compound **192a** under basic conditions generated compound **193** in 95% yield as outlined in Scheme 32.

Other synthetic methodologies

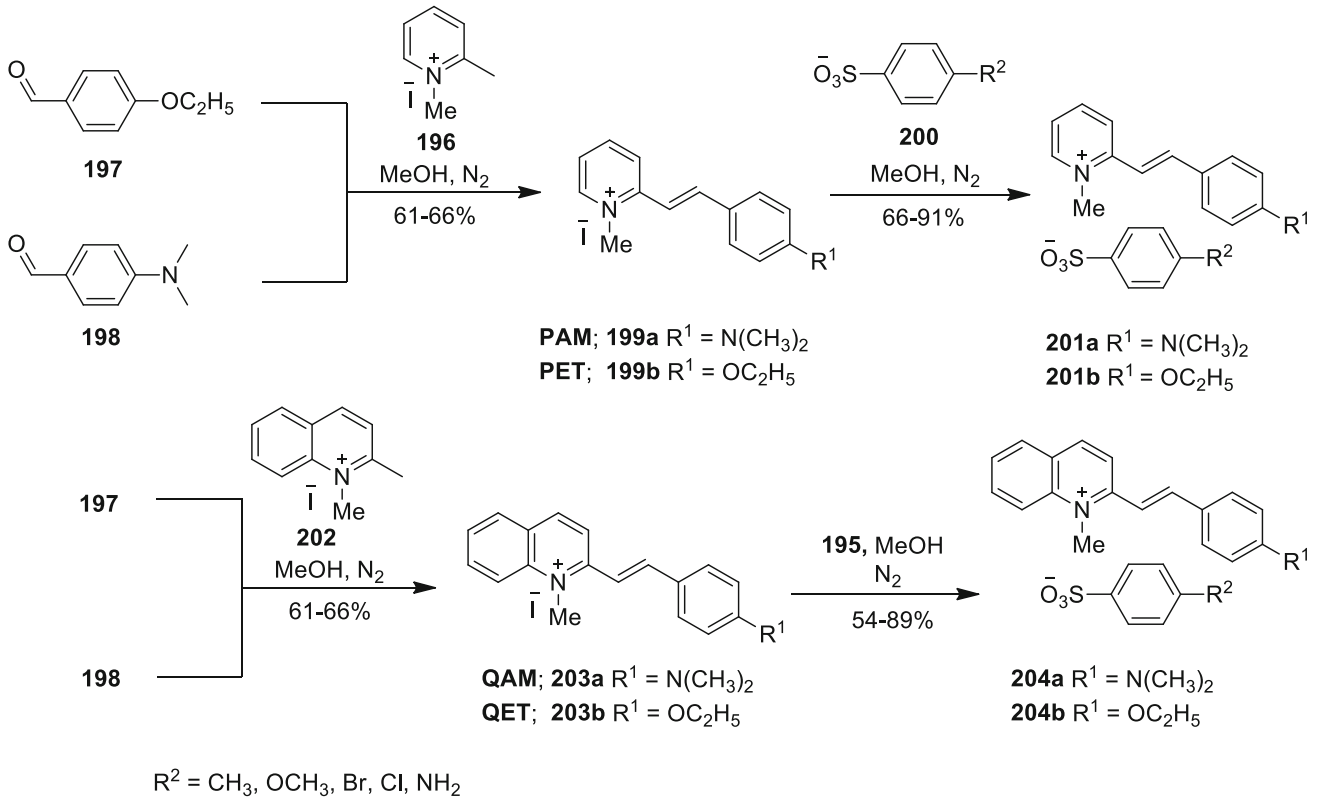
Chanawanno et al. [85] prepared and studied the antibacterial activity of pyridinium stilbene **199a**, **199b** and quinolinium stilbene **203a**, **203b**. 1,2-Dimethylpyridinium iodide **196** reacted with 4-dimethylaminobenzaldehyde **198** and 4-ethoxybenzaldehyde **197** separately to produce PAM **199a** in 61% yield and PET **199b** in 66% yield. Replacement of pyridinium iodide **196** with quinolinium iodide **202** generated QAM **203a** in 89% yield and QET **203b** in 54% yield. When stilbenes **199** and **203** were stirred with a silver salt of 4-substituted benzene sulfonates **200**, benzenesulfonates **201**, hybrid stilbenes with counter anions were formed in 66–91% yields and **204** in 54–89% yields as shown in Scheme 33.

Xiao et al. [4] reported the creation of hybrid structure coumarin-stilbenes **208** by locking the stilbene double bond in the benzopyrone ring and also studied their antitumor properties. 3-Arylcoumarins **207** were formed in 74–93% yield from substituted phenylacetic acids **205** and *o*-hydroxybenzaldehyde **206**. Hydrolysis of compounds **207** with HCl afforded compounds **208** in 90–95% yield as shown in Scheme 34.

Pratap et al. [3] reported the synthesis of stilbenes **211** in 26–81% yield and 212 in 60–65% yield (see Scheme 35)



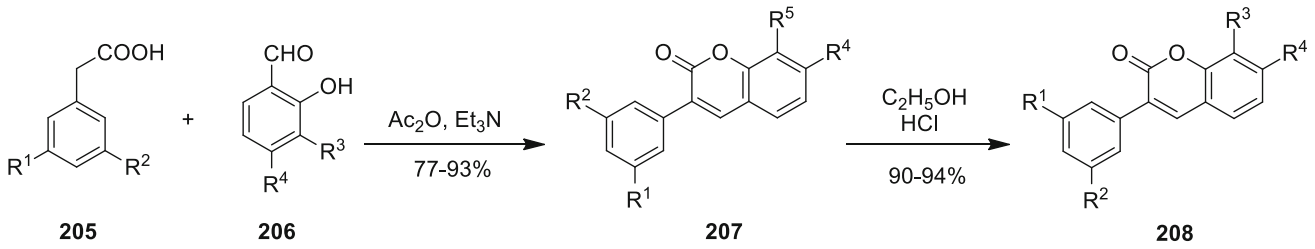
Scheme 32 Synthesis of *E* & *Z* stilbenes **192–195**



Scheme 33 Synthesis of stilbene hybrid benzenesulfonates **201** and **204**

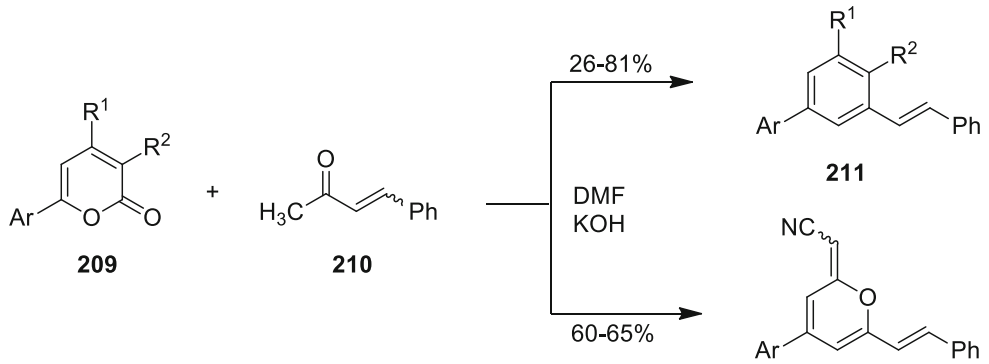
through a ring transformation between 4-phenyl-3-buten-2-one **210** and *2H*-pyran-2-one **209** using KOH.

Giraud et al. [25] developed a new and efficient method to synthesize *cis*-stilbenes analogue **6** and **215** by hydrosilylation–protodesilylation of diarylalkynes by following the protocol shown in Scheme 36 instead of using Lindlar's catalyst due to its drawbacks of isomerization and production of alkanes during the reaction. PtO_2 proved to be an efficient catalyst for hydrosilylation. Hydrosilylation of diarylalkynes **213** was done using PtO_2 and $HSiOEtMe_2$. Removal of $HSiOEtMe_2$ and protodesilylation of vinylsilane



$R^1 = R^2 = R^4 = OCH_3$
$R^3 = OH$, $R^5 = OAc$

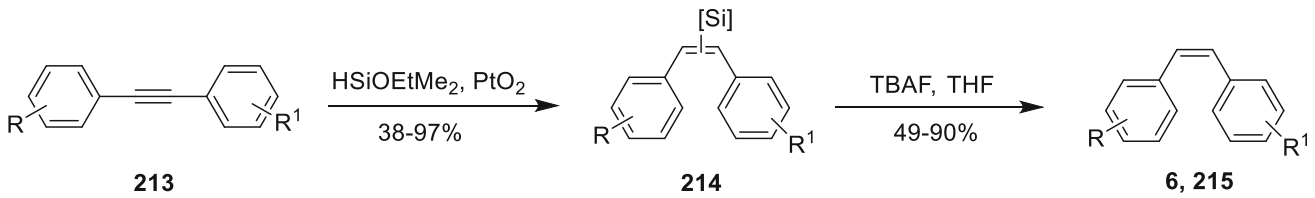
Scheme 34 Synthesis of coumarin-stilbene hybrid **208**



Ar = C_6H_5, 4-CH_3-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-CH_3O-C_6H_4, 3,4-CH_2O_2-C_6H_3, 1-naphthyl

R^1 = SCH_3, piperidin-1-yl-CN
R^2 = CN, $COOCH_3$

Scheme 35 Synthesis of *E*-stilbenes **211–212**



R = 4-OMe, 2,3,4-OMe
R^1= H, 3-OH, 4-OMe

Scheme 36 Synthesis of *Z*-stilbenes **6** and **215** by hydrosilylation-protodesilylation

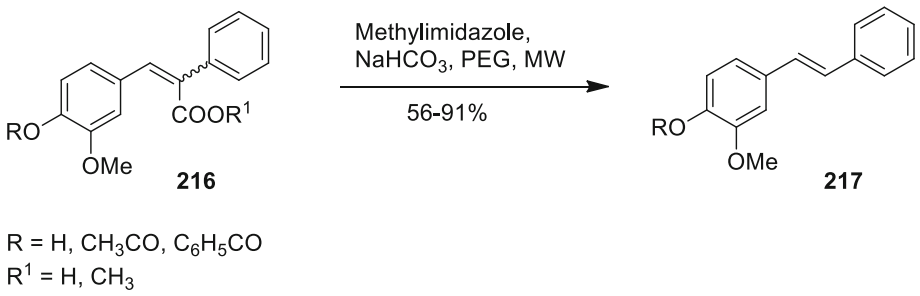
214 with TBAF afforded *Z*-stilbenes **6** and **215** in 49–90% yield.

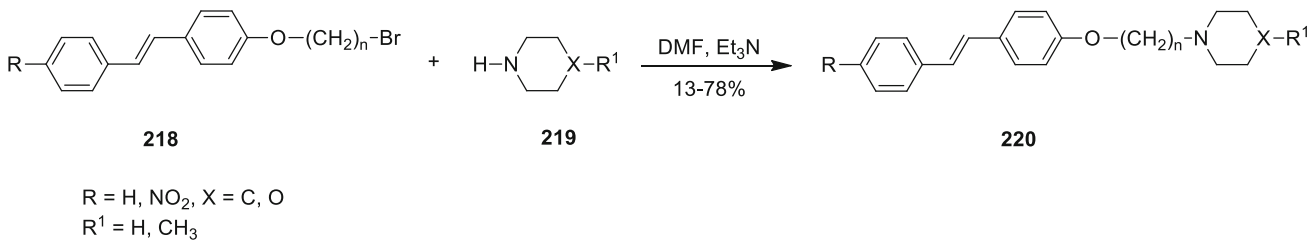
As shown in Scheme 37, Kumar et al. [86] performed microwave-assisted synthesis of hydroxylated stilbenes **217** in 56–91% yields from cinnamic acid derivatives **216** in a methyl-imidazole promoted decarboxylation.

Wyrzykiewicz et al. [27] introduced piperidine, morpholine and 4-methylpiperidine bearing stilbene moieties and also investigated their antimicrobial activity. Compounds **220** were formed in 13–78% yield by the reaction of *E*-4-(bromoalkoxy)stilbenes **218** and were treated with piperidine, morpholine and 4-methylpiperidine **219** separately. *E*-4-(bromoalkoxy)stilbenes **218** were prepared by a reported procedure [87] as shown in Scheme 38.

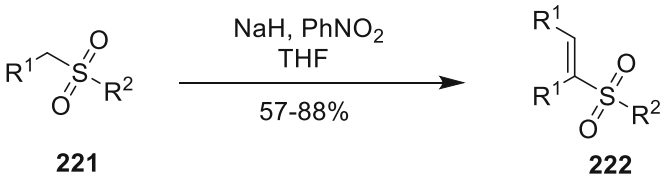
Chang et al. [88] synthesized sulfonyl (*E*)-stilbenes **222** in 57–88% yield from benzylic sulfones **221** by dimerizative desulfonation shown in Scheme 39. Different bases and additives were used for optimization, and results showed that NaH and $PhNO_2$ gave good yields.

Scheme 37 Synthesis of stilbenes **217** by microwave irradiation





Scheme 38 Synthesis of (*E*)-4-[piperidino(4′-methylpiperidino-,morpholino-)-*N*-alkoxy]stilbenes **220**



R^1 = Ph, 2-FPh, 4-FPh, 3-MeOPh, 4-MeOPh, 4-ClPh, 3,4-CH_2O_2Ph, 3,5-$(MeO)_2$Ph, 4-PhPh, *t*-$BuCH_2$, *n*-C_8H_{17}, *n*-$C_{12}H_{25}$, 2,6-F_2Ph, 4-NO_2Ph, 1-naphthalene, 2-naphthalene, 1-thiophene, 3-pyridine, 9-anthracene

R^2 = Tol, Ph, 4-MeOPh, 4-FPh, 3-MePh, 4-EtPh, 4-*i*-PrPh, 4-*n*-BuPh, 4-*t*-BuPh

Scheme 39 Synthesis of sulfonyl *E*-stilbenes **222** by dimerizative desulfonation

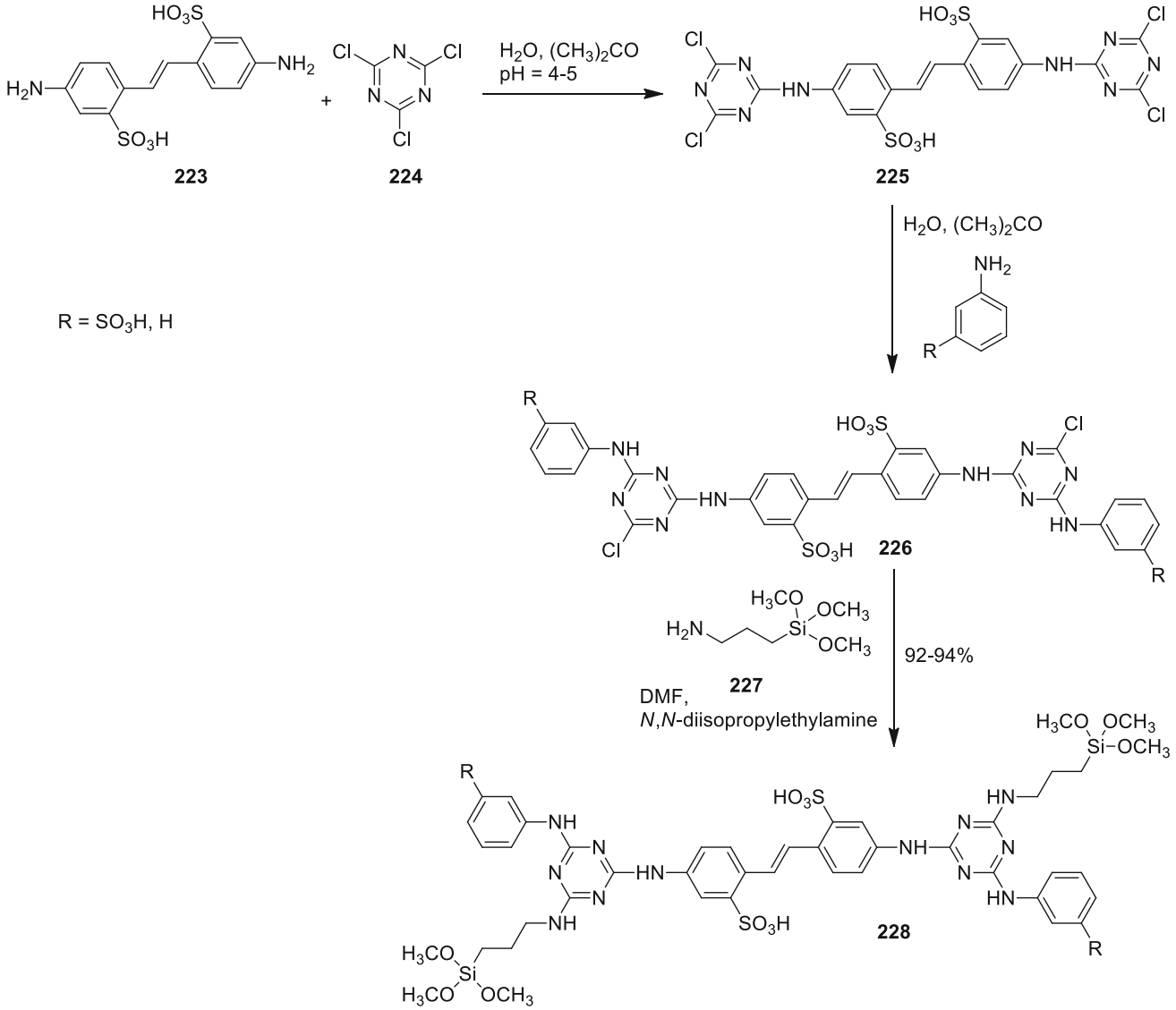
Because of the diverse applications of organosilanes in the chemical industry, Hussain et al. [89] synthesized silicone-based triazine–stilbene compounds **228** in three steps as shown in Scheme 40. In first step, the reaction of 4,4-diaminostilbene-2,2-disulfonic acid **223** with an ice-cold slurry of cyanuric chloride **224** generated intermediate **225**. In the second step, intermediate **225** was condensed with aromatic amines at pH 6. In the final step, compound **226** reacted with 3-aminopropyltrimethoxy silane **227** to yield **228** in 92–94%. Um et al. [90,91] used a similar methodology to synthesize triazine–stilbene as fluorescent brighteners.

Um et al. [41] prepared substituted triazine–stilbene **232** to test their brightness. Intermediate **230** was produced by reacting stilbene **229** with 2,4,6-trichloro-1,3,5-triazine **224** followed by treatment with different amines. Addition of phenolic derivatives to **231** gave products **232** in 70–98% yield as shown in Scheme 41.

Understanding the photophysical properties of stilbene, Buruiana et al. [92] prepared stilbene-containing polyacrylates **234**. The monomers (SUM) **233** were produced in 96% yield by adding 2-isocyanatoethylmethacrylate to *trans*-4-stilbene methanol. SUM (monomers) **233** were copolymerized with methyl methacrylate (MMA) by free radical mechanism. Stirring the mixture of SUM and MMA in the presence of an initiator (AIBN) gave polyacrylate (SUMMA) **234** in 48% yield as shown in Scheme 42.

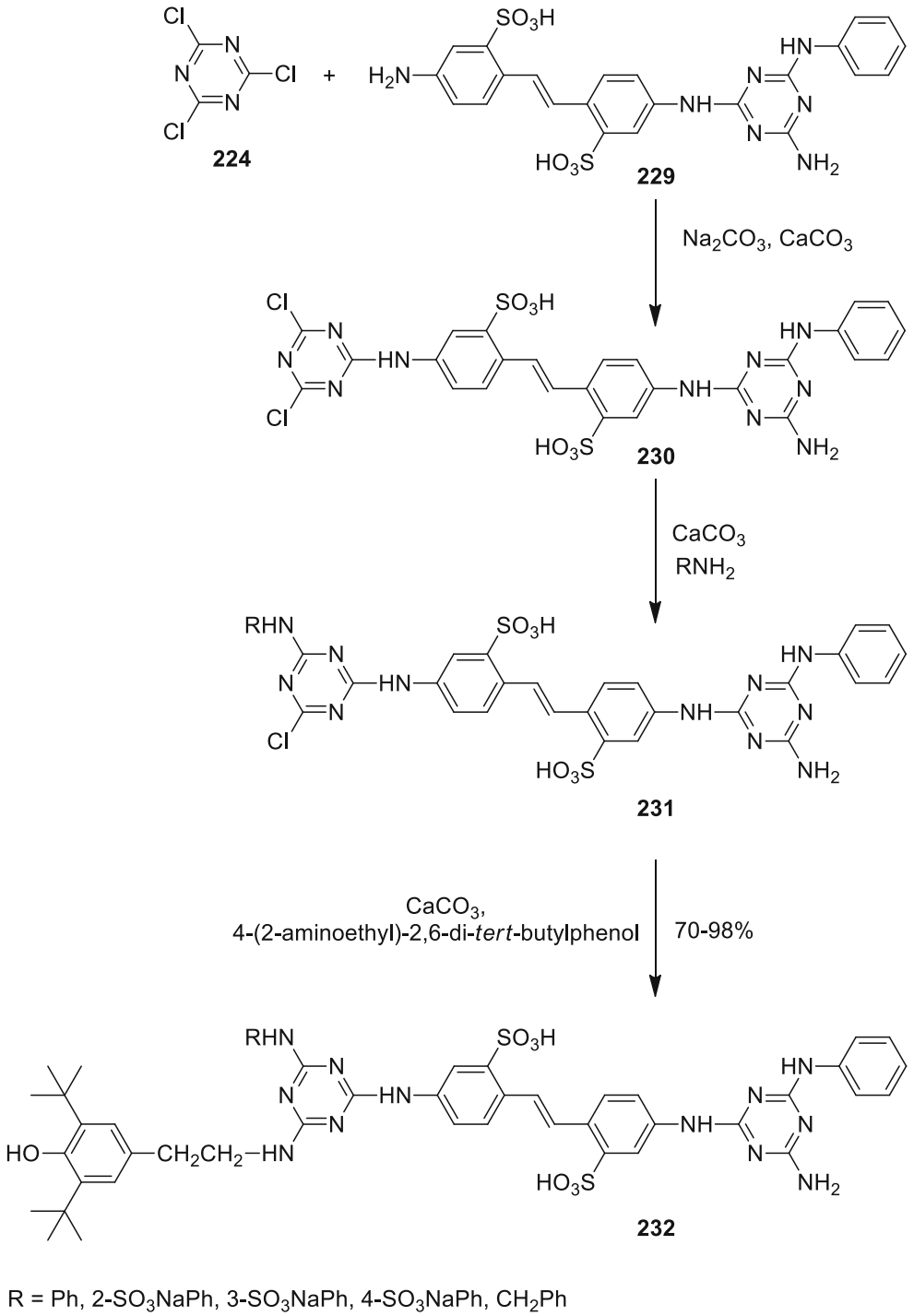
Conclusion

The significance of stilbenes and their related structures is prominent in the current literature such as publications, reviews, patents and books. In the last decade, different synthetic approaches have been devised to design novel

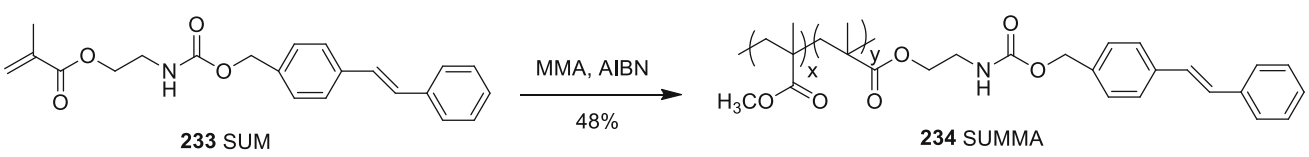


Scheme 40 Synthesis of stilbene-alkoxysilanes **228**

stilbene-based compounds. The classical approaches involve famous named reactions such as the Wittig reaction/Horner–Wadsworth–Emmons reaction, Mizroki–Heck reaction, Suzuki cross coupling reaction, Stille cross coupling reaction, Sonogashira cross coupling reaction, and Perkin condensation to synthesize stilbenes and related structures. It must be highlighted that these reactions have changed the science of synthesis. The most essential synthetic methodologies to synthesize *E* and *Z*-stilbene analogues have been summarized in this article. However, in our view, there will be further developments for the production of novel stilbene-based structures in the coming years. We hope will be useful for the scientific community, especially for those interested in the synthesis of stilbene analogues, which have a wide spectrum of applications in medicinal and material chemistry.



Scheme 41 Synthesis of substituted triazine–stilbene **232**



Scheme 42 Synthesis of polyacrylate SUMMA **234**

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