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A fruitful century for the scalable synthesis and reactions of biphenyl derivatives: applications and biological aspects

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This review provides recent developments in the current status and latest synthetic methodologies of biphenyl derivatives. Furthermore, this review investigates detailed discussions of several metalated chemical reactions related to biphenyl scaffolds such as Wurtz–Fittig, Ullmann, Bennett–Turner, Negishi, Kumada, Stille, Suzuki–Miyaura, Friedel–Crafts, cyanation, amination, and various electrophilic substitution reactions supported by their mechanistic pathways. Furthermore, the preconditions required for the existence of axial chirality in biaryl compounds are discussed. Furthermore, atropisomerism as a type of axial chirality in biphenyl molecules is discussed. Additionally, this review covers a wide range of biological and medicinal applications of the synthesized compounds involving patented approaches in the last decade corresponding to investigating the crucial role of the biphenyl structures in APIs.

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1. Introduction and scope

For many decades, biphenyl compounds and their isosteres have been considered a fundamental backbone in synthetic organic chemistry and natural products due to their omnipresence in medicinally active compounds, marketed drugs and natural products. For example, there are various biologically active natural products that contain biaryl scaffolds (vancomycin,[1,2] WS 43708A[3] and Arylomycin A[4]) (Fig. 1).

Since biphenyls are neutral molecules without a functional group, functionalization is required for them to react. Biphenyls consist of two benzene rings linked at the [1,1′] position. The reactions of biphenyls are similar to benzene as they both undergo electrophilic substitution reaction. Biphenyl derivatives which are used to produce an extensive range of drugs, products for agriculture, fluorescent layers in organic light-emitting diodes (OLEDs)[5,6] and building blocks for basic liquid crystals are significant intermediates in organic chemistry besides being the structural moiety of an extensive range of compounds with pharmacological activities.[7–10] Whereas several biphenyl derivatives serve as versatile and multifaceted platforms in medicinal chemistry, as large number of biphenyl derivatives are patented and broadly used in medicine as the antiandrogenic,[11] immunosuppressant, antifungal, antibacterial, antimicrobial, anti-inflammatory, anti-proliferative, osteoporosis, antihypertensive, antitumor, β-glucuronidase inhibition activity, anti-leukemia agent hypotensive, anticholinesterase, anti-diabetic and antimalaria drugs.[12] In addition, 6-(3-(adamantan-1-yl)-4-methoxyphenyl)-2-naphthoic acid which trademark drug (adapalene) as a third-generation topical retinoid primarily used for treating acne vulgaris, anti-inflammatory, antibacterial.[13] Another example is sonidegib which acts as a drug for basal cell carcinoma.[14] Additionally, other manufactured naturally occurring chemicals, including the biphenyl nucleus, have shown noteworthy biological activities, such as the antipyretic properties of fenbufen[15] and flurbiprofen and their role as non-steroidal anti-inflammatory drugs (NSAIDs) (Fig. 2).[16]

2. Synthesis of biphenyl systems

Wurtz reported the first trial for carbon–carbon bond formation reactions between two alkyl halides in the presence of sodium metal. Then, Fitting expanded this work to include the C(sp^2)–C(sp^2) homodimerization of aryl halides. Whereby, Ullmann described the Cu-catalyzed homocoupling reaction involving halo-arenes in 1901. In 1914, Bennett and Turner demonstrated the homodimerization of Grignard reagent and phenyl magnesium bromide which promoted by chromium(III) chloride ($CrCl_3$) or anhydrous cupric chloride ($CuCl_2$).[17] Kumada depicted the reaction of aryl halides with arylmagnesium halide or organozinc in the presence of transition metal catalysts.[18–20] Whereas, Hiyama produced biaryls *via* coupling the readily available organosilanes with organohalides.[21,22] In the same context, Negishi *et al.*[23] reported a regio- and chemoselective method for biaryl synthesis.[24,25] In 1986, a new methodology for cross coupling reaction of organic electrophiles with organostannanes was discovered by Stille.[26,27] After that, Suzuki–Miyaura cross coupling became one of the most effective and widely used ways for forming carbon–carbon bonds.[15,28,29] As biphenyl scaffolds are a key step to produce bioactive molecules

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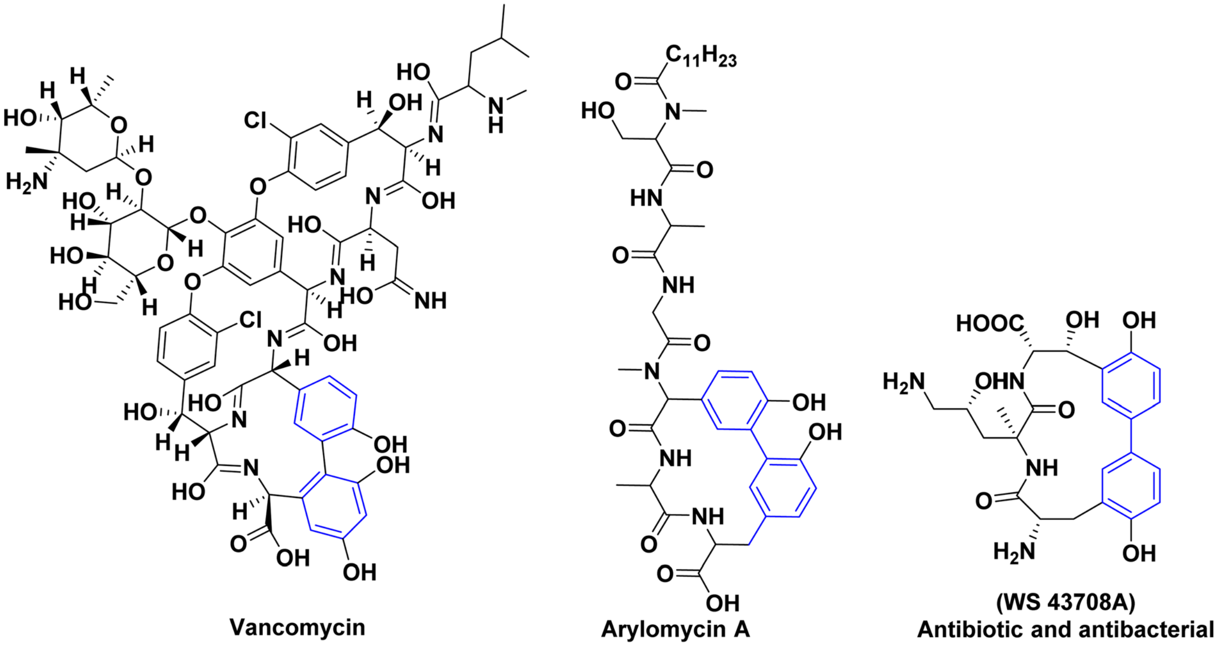


Fig. 1 Exemplary skeletons for natural products containing biphenyl moieties.

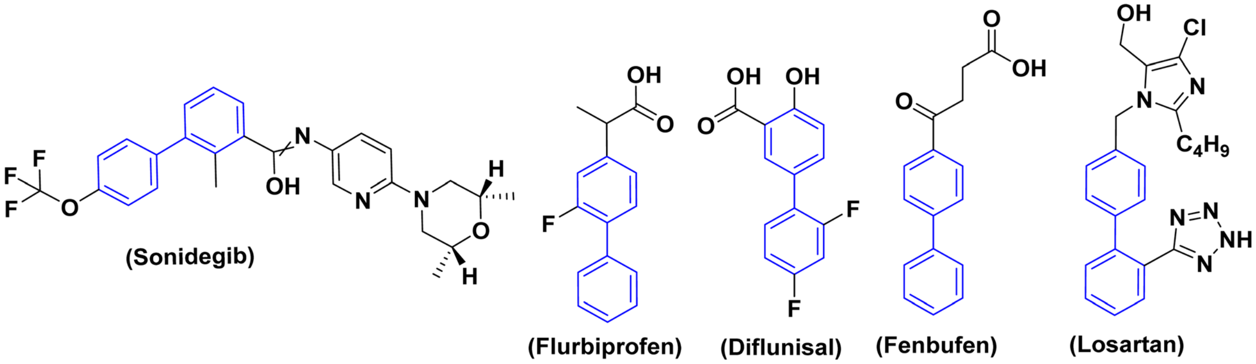


Fig. 2 Representative examples for biphenyl containing marketed drugs.

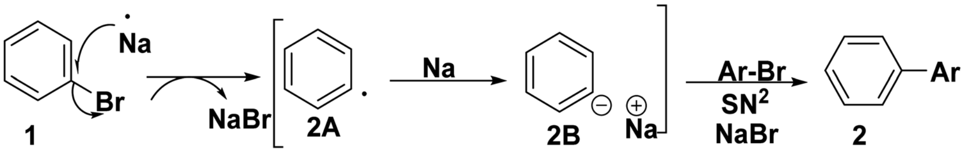
used for medicine. In addition, biphenyl compounds were isolated by distillation from natural sources such as crude oil, natural gas, and coal tar.[6] Several methods are available in the literature for the synthesis of substituted biphenyl scaffolds *through* using various chemical building blocks according to the following reaction routes:

2.1 Wurtz–Fittig reaction

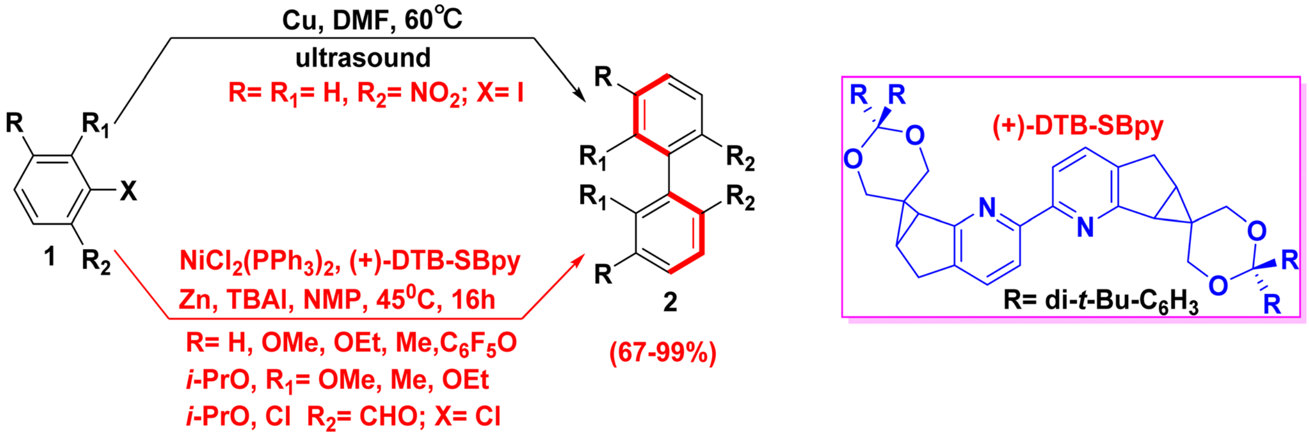
The history of the chemistry of biphenyl derivatives can be traced back almost 160 years ago. As the synthesis trials of biphenyl scaffolds started from 1855 till the end of the 19th century by many researchers as in 1855. Wurtz reported the first trial for C(sp^3)–C(sp^3) bond formation *through* using the sodium-mediate coupling reaction of two alkyl halides.[17] In 1862, the reaction was extended by Fittig to include coupling between aryl anion and an electrophile such as aryl halide in the presence of various metal surface such as Na, Li, Au, Cu and Ag.[30] Wurtz–Fittig reaction could be achieved *via* the free radical mechanism[31] in three steps; dehalogenation, followed by diffusion of the dehalogenated molecules, and finally, coupling process between two aryl halides **1** to afford biphenyl derivative **2**.[32] It is worthy to mention that, bulky substitution group leads to kinetically prevent Wurtz–Fittig coupling as one of its drawbacks.[33] Also, Wurtz–Fittig reaction plays an important role in the synthesis of thermoplastics polymer synthesis (polyphenylenes and oligophenylenes) (Scheme 1).[34]

2.2 Ullmann reaction

The Ullmann reaction was known since 1901,[35] as it has attracted the attention of many chemists trying to synthesize chiral substituted biphenyl. Moreover, the Ullmann reaction usually is achieved at lower temperatures and shorter time frame *through* coupling the aryl halide **1** in the presence of powdered copper or nickel catalysts, but it has changed in



Scheme 1 Free radical mechanism for Wurtz–Fittig reaction.

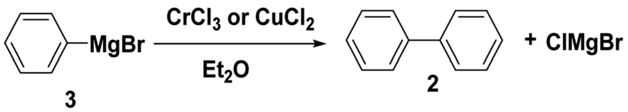


Scheme 2 General Ullman cross-coupling reaction for the synthesis of biphenyl derivatives.

recent years.[36,37] It is worth mentioning that, the degree of stability of substituted chiral biphenyl depends on the nature of the *ortho* substituents when this asymmetric Ullman coupling.[38] Whereas, enantioselective biphenyls **2** were obtained *via* the reaction of *ortho*-chlorinated benzaldehyde derivatives **1** in the presence of Ni catalyst (Scheme 2).[39]

2.3 Bennett–Turner

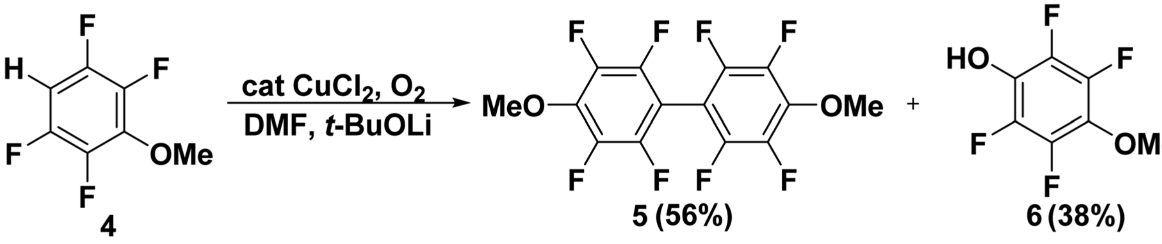
In 1914, the coupling reaction was investigated by Bennett–Turner[40] who reported the synthesis of biphenyl compound **2** *via* homocoupling reaction of phenylmagnesium bromide (**3**) and $CrCl_3$ in diethyl ether (Et_2O), incidental to an attempt to prepare organochromium compound.[41] Bennett–Turner reaction can be achieved by using $CuCl_2$.[42] In this context, noteworthy is the contribution of Krizewsky with Turner using a $CuCl_2$ promoted homocoupling reaction instead of $CrCl_3$ (Scheme 3).[17,42,43]



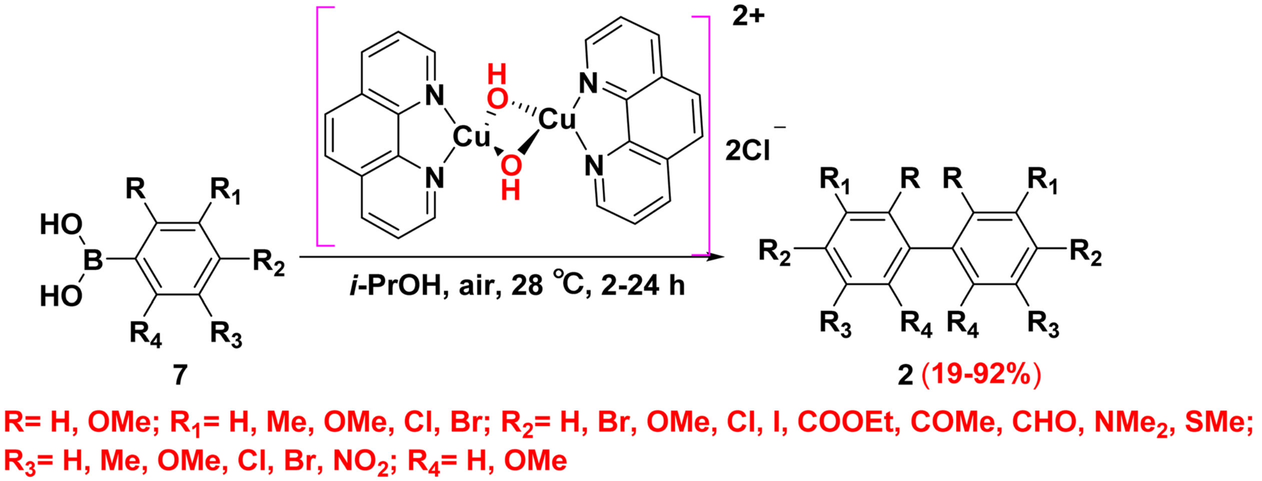
Scheme 3 Preparation of biphenyls *via* Bennett–Turner.

Ultimately, treatment of the tetrafluoro-3-methoxybenzene (**4**) with $CuCl_2$ and lithium *tert*-butoxide (*t*-BuOLi) in the presence of O_2 gas produced a mixture of biphenyl coupling product **5** (56%) and the corresponding phenol **6** (38%). The proposed mechanism involves *in situ* deprotonation with oxidative dimerization has been studied by Do *et al.*[44] The production of corresponding phenol was reasonable *through* trapping of the formed aryl lithium with oxygen gave rise to an aryl anion species which was less prone to oxygenation and more likely to form a copper adduct that would undergo oxidative coupling reaction (Scheme 4).

In 2003, Demir and coworkers reported using of low-cost copper salts (Cu(I) and Cu(II)) as they are able to mediate the dimerization of arylboronic acids **7** to afford the corresponding symmetrical substituted biaryl **2** in good yields. The reaction can be possibly catalyzed under an oxygen atmosphere without a significant loss of yields.[45] In 2009, Kirai *et al.*[46] improved the



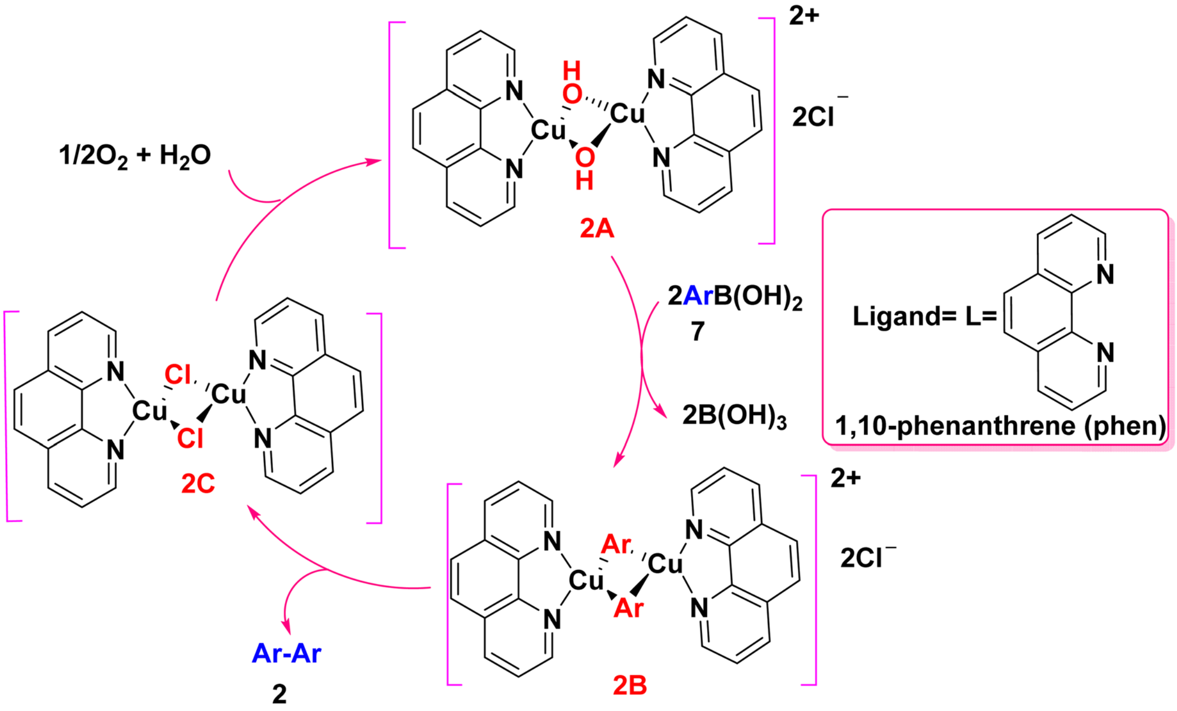
Scheme 4 Copper catalyzed reaction of aryl lithium with oxygen.



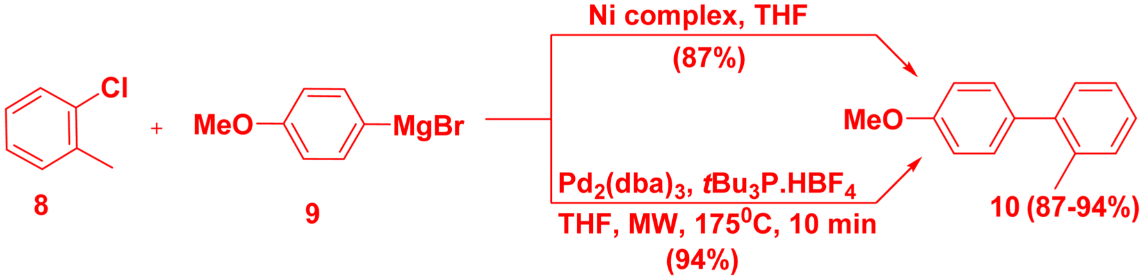
Scheme 5 A reasonable mechanism for the Cu-catalyzed homocoupling of aryl boronic acids.

previous protocol for oxidative dimerization which relying on catalysts that would facilitate transmetalation. As they reported a new effective methodology for homocoupling of aryl boronic acid derivatives **7** under stirring conditions *through* using the catalytic amount of $[\{(\text{phen})\text{Cu}(\mu\text{-OH})\}_2\text{Cl}_2]\cdot3\text{H}_2\text{O}$. It is worthy to mention that the homocoupling reaction proceeds without any additives such as oxidant or base. Besides, this method tolerates different substituents on the arylboronic acids such as nitro group, halogens and carbonyls (Scheme 5).

The formation of symmetrical substituted biaryl **2** is explained according to the following postulated mechanism: the reaction proceeds by the hydroxido ligand attacks the oxophilic boron center, followed by transmetalation of arylboronic acids **7** with (μ-hydroxido)copper(II) complex **2A** to yield bimetallic arylcopper(II) intermediate **2B** without using any base. Biaryl products **2** afford *through* the concomitant one-electron reduction of each copper center $[2\text{LCu}^{\text{II}}\text{–Ar} \rightarrow 2\text{LCu}^{\text{I}} + \text{Ar–Ar}]$. As the binuclear copper models efficiently activate molecular oxygen, in the same time the molecular oxygen smoothly bind to the resulting bimetallic intermediate $[\{(\text{phen})\text{Cu}^{\text{I}}(\mu\text{-Cl})\}_2]$ **2C**, which is reoxidized to afford (μ-hydroxido)copper(II) complex **2A** (Scheme 6). The present binuclear O_2 activation and binuclear reductive elimination mechanism is quite different from that proposed for palladium-catalyzed aerobic homocoupling.[46]



Scheme 6 Possible mechanism for copper catalyzed homocoupling reaction.



Scheme 7 Kumada cross-coupling reaction for biaryl synthesis.

2.4 Kumada cross coupling

Since 1972, Kumada catalyzed cross coupling reaction of organozinc or organomagnesium with arylhalide in the presence of Pd, Ni, Cu, Fe or Co catalyst.[18–20] However, this reaction was limited with Pd catalyst compared to Ni catalyst due to the high reactivity of organomagnesium,[47] as well as less toxicity and non-expensive Ni catalyst.[48] Besides, arylchlorides were preferable than aryliodides and arylbromides because of low price. Treatment of chloromethylbenzene **8** with (methoxyphenyl) magnesium bromide **9** in the presence of Ni complex and THF afforded 4′-methoxy-2-methyl-biphenyl **10** in (87%) yield.[49] Whereas, in the presence of Pd catalyst, product **10** produced in (94%) yield (Scheme 7).[50]

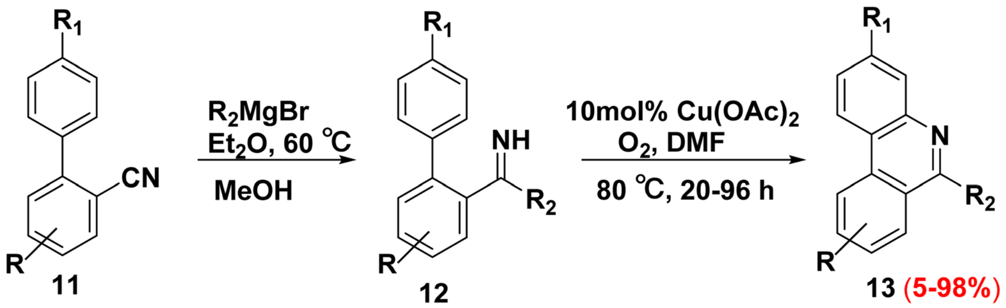
Recent research has largely been focused on directed C–H activation. Primary imines **12** produced by a Grignard reagent's nucleophilic addition to nitrile group **11** which is susceptible to attack make it easier to introduce copper(II) into a close C–H bond. Primary imine derivatives **12** underwent a closure under oxygen-mediated elimination affording the respective phenanthridine derivatives **13** (Scheme 8).[51,52]

The proposed mechanism for the synthesis of the phenanthridine derivatives **13** is illustrated in Scheme 9. This involves the nucleophilic addition of biaryl-2-carbonitriles **11** and Grignard reagents to produce N–H imines **12**, followed by their Cu-catalyzed C–N bond led to formation of the aromatic C–H bond, in which molecular oxygen is a necessary component to complete the catalytic process (Scheme 9).[51,52]

2.5 Hiyama cross-coupling

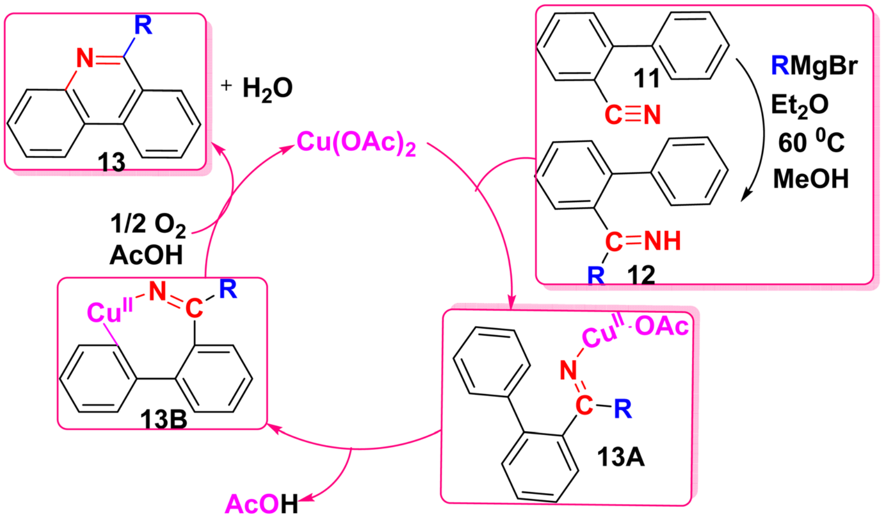
One of the most important corn stone for synthesizing biaryl is Hiyama cross-coupling due to the distinctive features of organosilane reagent such as less reactivity, availability, non-toxicity, high sustainability and cheap, in addition to its ability to functionalize stereo and regioselective compounds.[53–55] Rhodium-catalyzed *o*-C–H arylation reaction of arylsilane **14** with ethyl benzimidate **15** with in the presence of pentamethylcyclopentadienyl rhodium dichloride dimer [Cp*RhCl$_2$]$_2$, silver hexafluoroantimonate(V) (AgSbF$_6$), silver oxide (Ag$_2$O) and TBAF produced biphenyl-2-carbonitrile derivative **16**.[56] Whereby, refluxing a mixture of arylsilane **14** with arylhalide **1** in a mixture of AcOH and toluene, Pd catalyst, and tetrabutylammonium fluoride (TBAF) as a base afforded biphenyl **2**. Furthermore, this method was applied under mild condition and tolerated high functional groups (Scheme 10).[57–59]

Noor and coworkers[57] suggested the proposed mechanism for Hiyama cross coupling. Analogous to other metal catalyzed cross coupling mechanism, Hiyama cross coupling passed through three steps. The oxidative addition of aryl halide to palladium metal leaded to the conversion of Pd(0) to Pd(ii). Then, transmetallation step occurred in the presence of base such as (KF, *n*-Bu$_4$NF) which encouraged the C–Si bond to split and establish a new C–Pd bond.[53,60] Finally, in the reductive elimination step a new C–C bond was formed and Pd returned back to the oxidation state (0) (Scheme 11).[24]

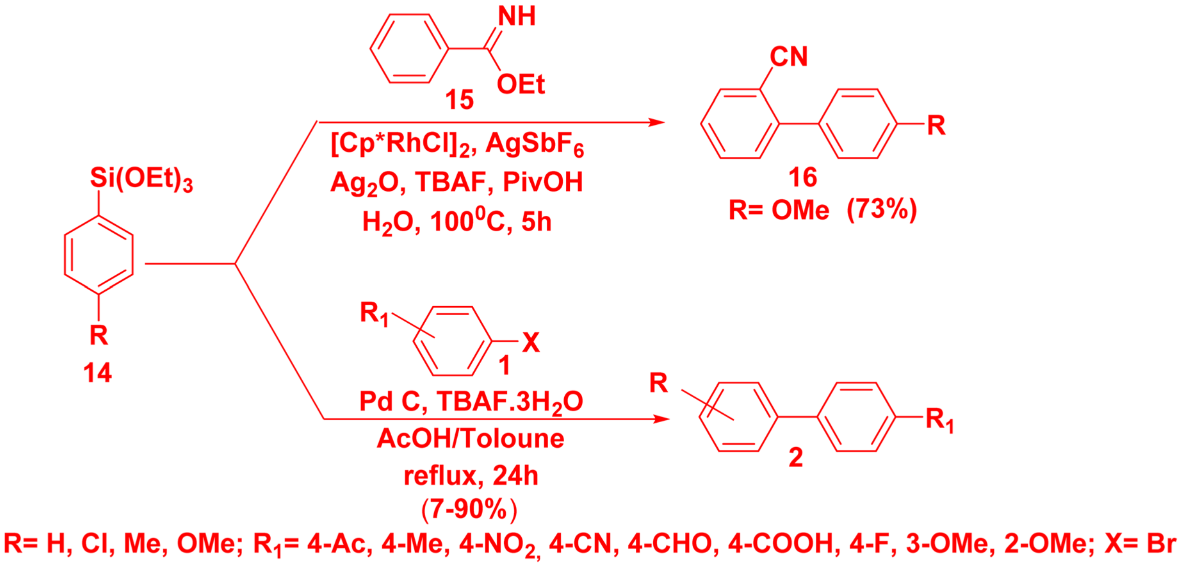


R= H, F, Me; R$_1$= H, Me, Ph, CF$_3$, Cl, OMe; R$_2$= *p*-tol, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$;2-thienyl, CH$_2$CH$_2$Ph, *i*-Pr

Scheme 8 Copper catalyzed oxidation phenanthridine.



Scheme 9 Mechanism for the oxidative formation of phenanthridine.

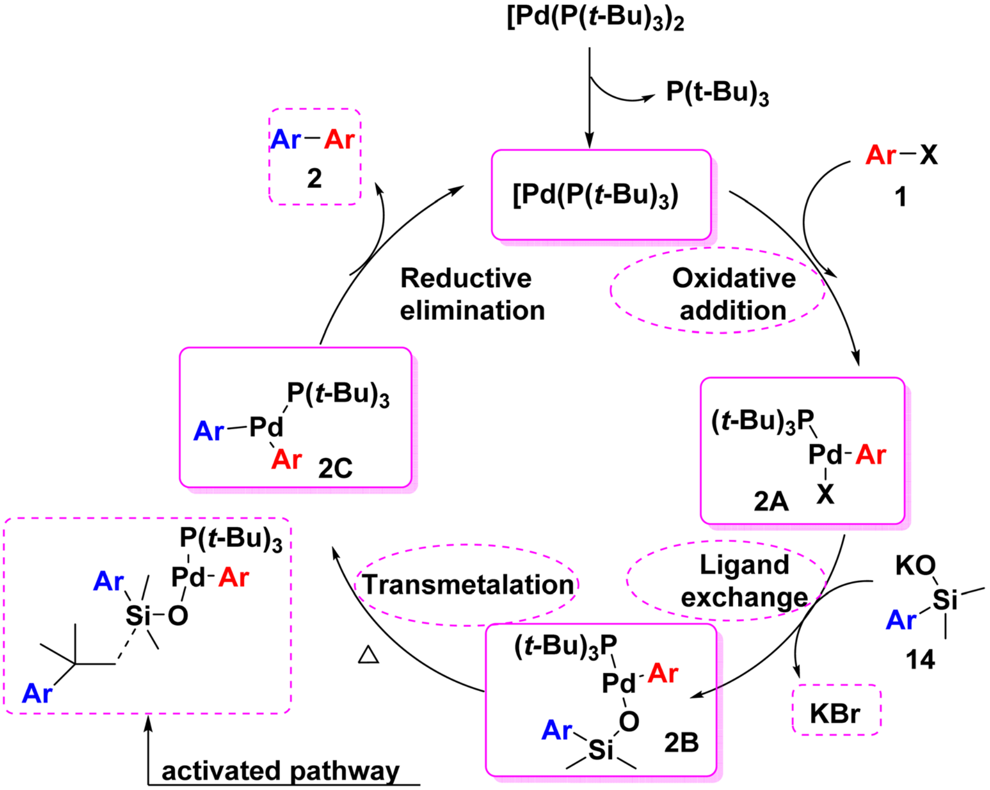


Scheme 10 Synthesis of biphenyls **2** *via* Hiyama cross-coupling.

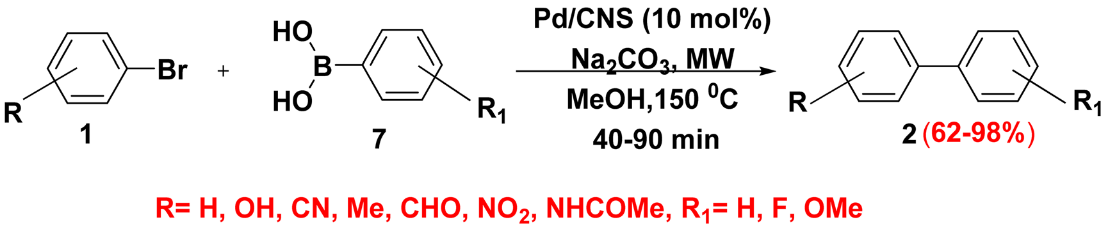
2.6 Suzuki–Miyaura cross-coupling

In the last decade, Suzuki–Miyaura coupling reaction (SMC) has witnessed an increase interest due to its widespread academic and industrial application in the production of fine chemicals, polymers, materials, and pharmaceuticals.[61] SMC reaction is also used to tag DNA with luminous intercalator substituents for DNA sequencing and diagnostics.[62] In 1979, Akira Suzuki, Norio Miyaura and Kinji Yamada reported SMC which is the most common method in the formation of carbon–carbon bond in drug discovery.[28,29] In the context, the reaction of various aryl bromide derivatives **1** with commercially available aryl boronic acids **7** under action of palladium-catalyzed Suzuki coupling reaction on porous carbon nanospheres (Pd/CNS) afforded biphenyl derivatives **2**. It is worthy to mention that, using (Pd/CNS) as catalyst is preferable than other Pd salts due to its highly effective, and lower cost (Scheme 12).[63]

The simple mechanism for (SMC) reaction passed *through* three steps.[23,64] The first step is the oxidative addition in which organo palladium(II) complex **2A** is formed *via* coupling of aryl halide **1** with palladium catalyst and this is happening *via* breaking carbon–halogen bond and by squeezing palladium between the aryl and halogen group. The second step is the transmetalation whereas organoboron compound is converted to nucleophilic borate in the presence of base such as sodium *tert*-butoxide and carbonate salts then attacking on a Pd(II) complex **2B** to form **2C** complex. Finally, reductive elimination step in which the two aryl groups are reductively eliminated from Pd(II) complex **2C** and combine together to form C–C bond and the palladium is reformed (Scheme 13).[65,66]



Scheme 11 The postulated mechanism for Hiyama cross-coupling reaction.

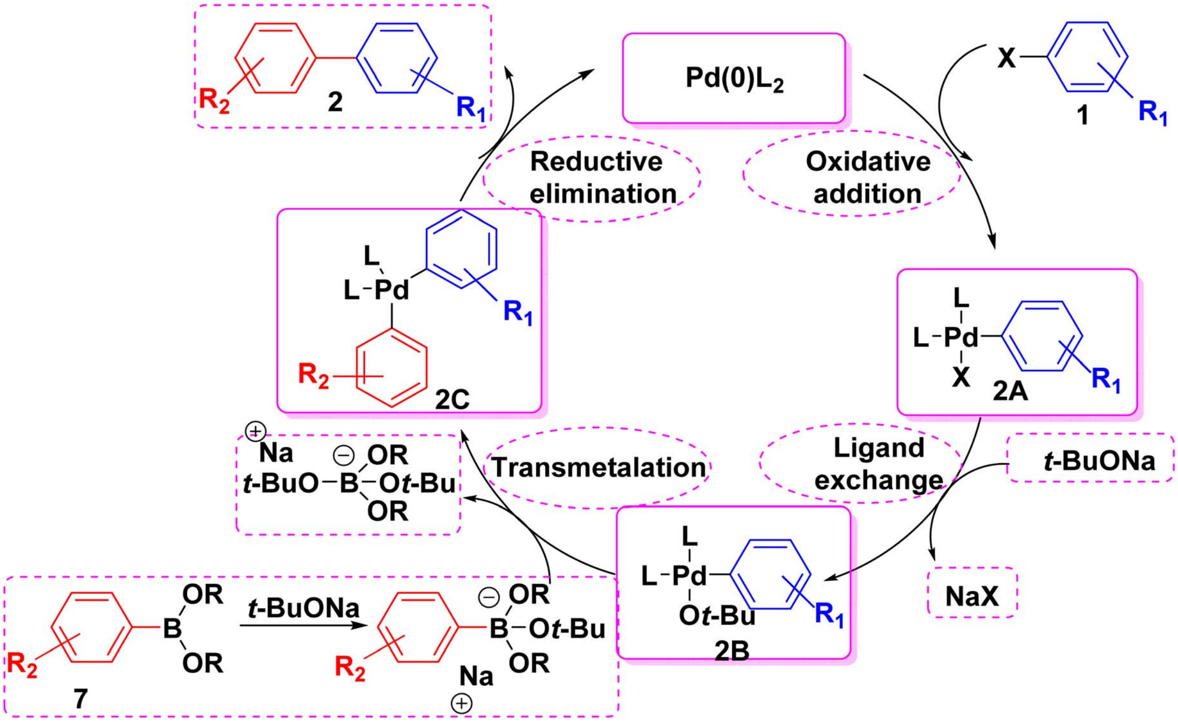


Scheme 12 Suzuki coupling reaction toward synthesis of biphenyl derivatives.

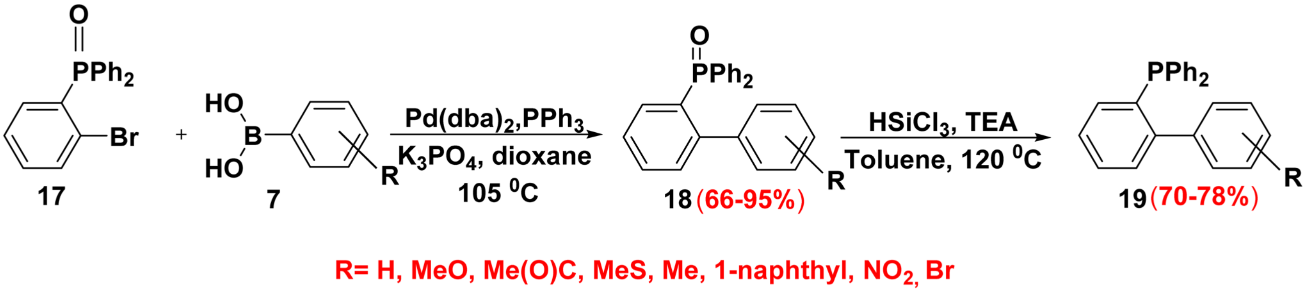
Biphenyl phosphine was effective ligand in metal catalyzed reaction as hydroformylation, asymmetric hydrogenation and allylic alkylation. Reaction of equimolar amount of (2-bromophenyl)diphenylphosphine oxide (($(2\text{-BrC}_6H_4)OPPh_2$) **17** with aryl boronic acids **7** in the presence of bis(dibenzylideneacetone)palladium catalyst ($Pd(dba)_2$), triphenylphosphine (PPh_3) (4 equiv.) and potassium phosphate (K_3PO_4) (2 equiv.) as a base in refluxing dioxane at 105 °C yielded biphenyl phosphine oxide derivatives **18** followed by reduction with a mixture of trichlorosilane and catalytic drops of triethylamine (TEA) produced biphenyl phosphine derivatives **19** (Scheme 14).[67]

Substituted biphenyl anilines play a vital role in the synthesis of pharmaceutical, dyes, organometallic complexes and ferromagnetic materials due to the ability of amino group to react with aldehyde and ketone to produce Schiff products with strong electronic donor and versatile frameworks.[68] Furthermore, treatment of 4-chloroaniline (**20**) with fluorinated phenyl boronic acid **7** in refluxing a mixture of toluene and water with a catalytic amount of palladium acetate ($Pd(OAc)_2$) and bulky phosphine ligand (SPhos) yielded fluorinated aminobiphenyl derivatives **21**.[69] Analogously, refluxing of 4-chloroaniline (**20**) with fluorinated phenyl boronic acid **7** with DMF in the presence of catalytic $Pd(OAc)_2$ and K_3PO_4 as a base at 80 °C afforded fluorinated aminobiphenyl derivatives **21** (Scheme 15).[68]

Fluorinated biphenyls are scaffolds for various applications due to their rigidity, chemical stability and electron poor nature. Furthermore, fluorinated biphenyls are used to develop OLEDs, liquid crystal displays (LCDs), organic semiconductors, metal–organic frameworks (MOF), and organic polymer of intrinsic microporosity (OMIMs). In addition, organoflourine as substituents of biphenyl have become widespread drug motifs, as they affect nearly adsorption, metabolism, distribution and excretion properties of lead compounds.[70] Bulfield *et al.*[71] prepared a mixture of fluorinated biphenyl compounds **22**, **23** *via* Suzuki–Miyaura cross coupling reaction of tetrafluoroiodobenzene **1**



Scheme 13 The postulated mechanism for biphenyl synthesis *via* Suzuki–Miyaura coupling reaction.

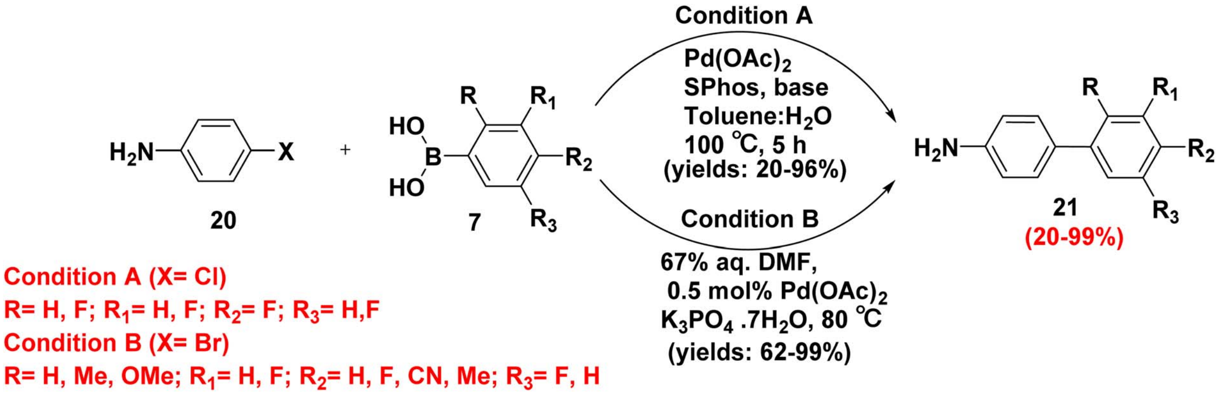


Scheme 14 Synthetic pathway to generate biphenyl-based phosphine.

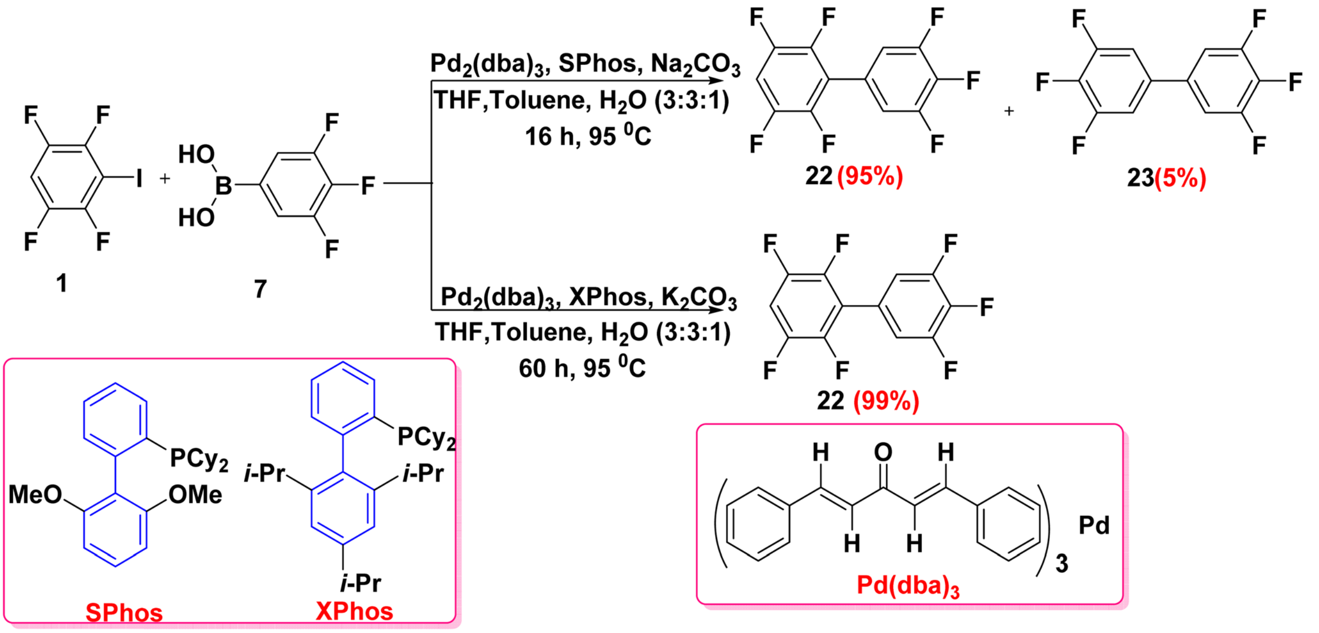
with trifluoroboronic acid **7** in the presence of sodium carbonate (Na_2CO_3) as a base and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) as a catalyst with SPhos as a ligand in refluxing with a mixture of THF, toluene, and H_2O. Whereas, using XPhos as a ligand and potassium carbonate (K_2CO_3) as base afforded fluorinated biphenyl **22** only with an excellent yield (99%) (Scheme 16). The reactivity of aryl halides is dependent on the dissociation energy of the C–X bond according to (I > Br > Cl > F). As a larger halogen atom will be a better leaving group due to having a lower bond dissociation, thus increasing the reactivity. As a result of aforementioned information, boronic derivative **7** couples with iodide atom faster than fluorine atom (Scheme 16).[72]

Whereby, reaction of aryl halide **1** with various fluorinated boronic acids **7** in the presence of palladium catalyst complex and K_3PO_4 as a base in a refluxing solvent mixture of tetrahydrofuran (THF) and water furnished fluorinated biphenyl **24**.[6] Additionally, fluorinated biphenyl **26** was synthesized by refluxing iodobenzene **1** and arylboronate **25** in Cu catalyst, phenanthroline ligand (phen) and DMF (Scheme 17).[73]

Palladium catalyst was predominantly used in Suzuki coupling reaction, but due to its scarcity and high price, it was replaced by Ni and Co catalyst. Cobalt salts have stronger catalytic activity and a reduced tendency to yield homocoupling by-products. However, iron was considered the best substitute for a Pd catalyst because it was the least toxic and the most abundant transition metal.[74] Biphenylpyrrole derivative **29** was obtained *via* the reaction of arylhalide **28** with lithium arylboronates **27** in the presence of Fe catalyst and 1,3-bis(-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IMes) as a ligand.[75] Whereas, the reaction of chloromethylbenzene **30** with **27** in the presence of cobalt(II) chloride ($CoCl_2$) and a ligand/precursor named bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium afforded methylbiphenyl **31** (Scheme 18).[76]



Scheme 15 Preparation of amino biphenyl derivatives.



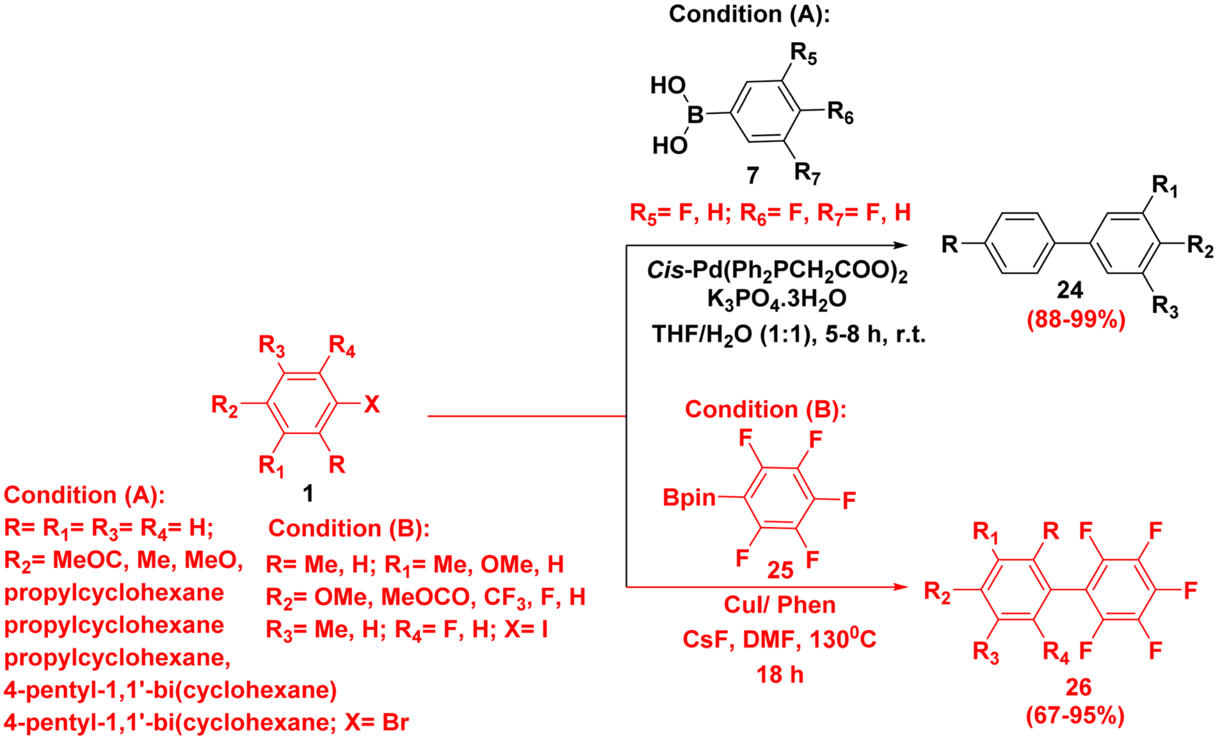
Scheme 16 Preparation of fluorinated biphenyl *via* Suzuki–Miyaura cross coupling reaction.

The suggested mechanism involved the formation of a low-valent molecular iron complex that engages in the reversible coordination of both bromide and the pyrrole-containing substrate **28**. The C–Cl bond in **28** is reductively activated by the resulting ferrate complex. The biphenylpyrrole product **29** was delivered by reductive elimination, and the active catalyst was renewed by bromide abstraction (Scheme 19).[75]

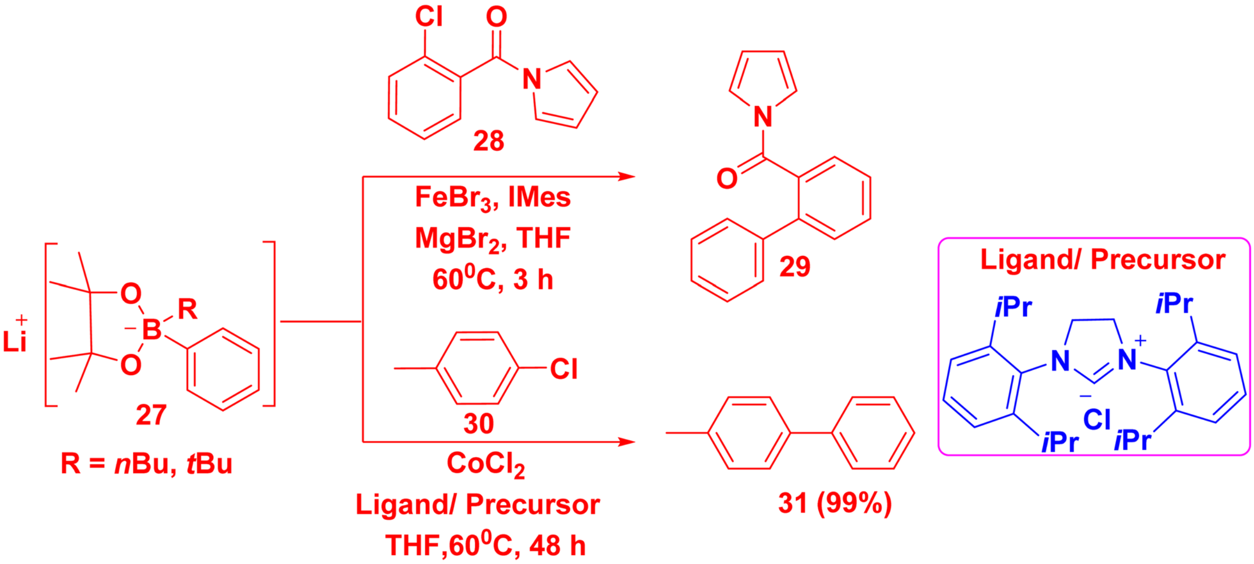
Additionally, nickel catalyzed Suzuki coupling reaction of chlorobenzene derivative **1** with substituted phenylboronic acid **7** in the presence of Ni catalyst, ferrocenylmethylphosphines derivative as a ligand, K_3PO_4 and THF afforded biphenyl derivative **2** (Scheme 20).[77]

Biphenyl tyrosine derivatives are biologically active molecules including arylomycin A_2 act as an antibacterial drug. Tyrosine derivatives were keys for the synthesis of biaryl derivatives *via* SMC reaction. Nevertheless, tyrosine compounds must be protected in order to react. 3-Iodo tyrosine (**32**) was esterified using methanol (MeOH) with thionyl chloride ($SOCl_2$) to afford 2-amino-3-iodophenyl-propanoate **33**. Then, the amino group was protected using *tert*-butyloxycarbonyl (*t*-Boc) and sodium bicarbonate ($NaHCO_3$) in MeOH to furnish *N-tert*-butyloxycarbonyl-3-iodotyrosine methyl ester (**34**). Refluxing *N-tert*-butyloxycarbonyl-3-iodotyrosine ester **34** in the presence of $Pd(OAc)_2$, K_2CO_3 and hetero aryl trifluoroborate salt **35** in MeOH to afford *t*-butoxycarbonyl-(6-hydroxy-[biphenyl]-yl) propanoate derivatives **36**. Finally, deprotection of compounds **36** was achieved *via* heating them with dil. HCl at 70 °C for 3 h to give the free amino acid **37** (Scheme 21).[4]

Burmaoglu *et al.*[78] synthesized new biphenyl chalcone derivatives **42** according to the reaction sequences. First, preparation of 3-bromo-2,4,6-trimethoxyacetophenone (**39**) *through* bromination reaction of 2,4,6-trimethoxy acetophenone (**38**)



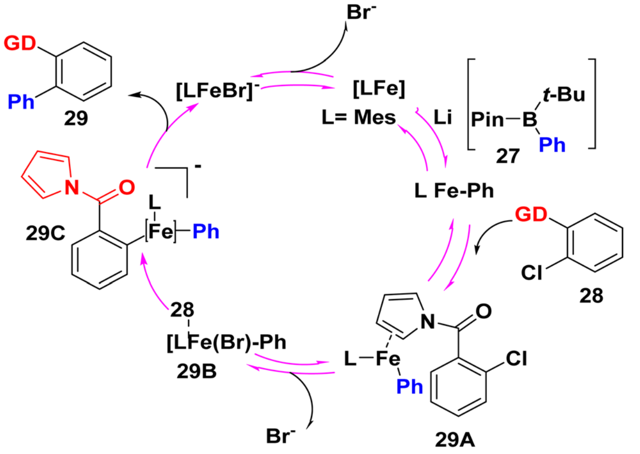
Scheme 17 Formation of fluorinated biphenyls.



Scheme 18 Iron catalyzed Suzuki–Miyaura cross coupling reaction for biphenyl synthesis.

with ceric ammonium nitrate (CAN) and lithium bromide (LiBr) in acetonitrile (CH_3CN), followed by applying SMC of compound **39** with phenylboronic acid (**7**) in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in a mixture of ethanol (EtOH) and toluene afforded 2,4,6-trimethoxy-[1,1′-biphenyl]ethan-1-one **40** (Scheme 22). Claisen–Schmidt condensation reaction of substituted biphenyl **40** and benzaldehydes **41** yielded biphenyl chalcone derivatives **42** (Scheme 22). Consequently, biphenyl-substituted chalcone scaffolds which are classified as privileged metabolic enzyme inhibitor motifs which essential support in the treatment of Alzheimer's disease (AD) and glaucoma due to hydrophobic effect and their ability to bind with multiple receptors.

Treatment of methyl 2-bromo-6-iodobenzoate (**43**) with (4-methoxyphenyl)boronic acid (**7**) in the presence of Na_2CO_3, bis-triphenylphosphine palladium dichloride ($PdCl_2(PPh_3)_2$), and

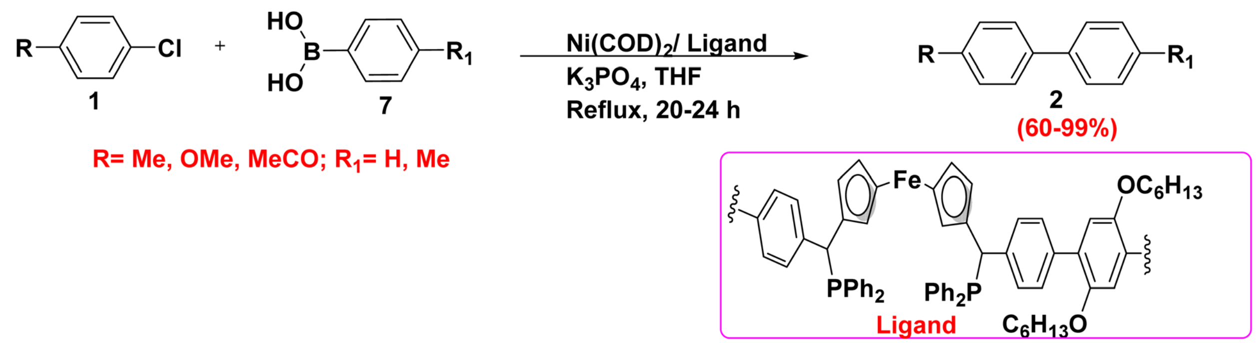


Scheme 19 The suggested mechanism for biphenylpyrrole synthesis.

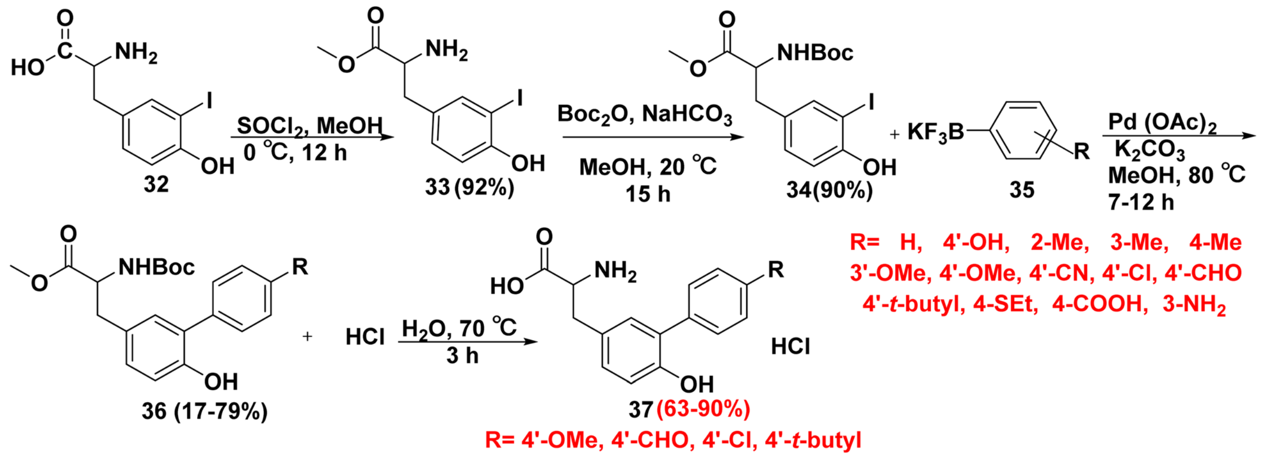
a mixture of H_2O and THF afforded methyl-3-bromo-4′-methoxy-[1,1′-biphenyl]-2-carboxylate (**44**). In order to produce biphenyl acetylene derivatives **46**, compound **44** was reacted with phenylacetylene derivatives **45**[79] (Scheme 23). Diphenylacetylene-based all-*trans* retinoic acid (ATRA) analogues with enhanced stability may hold tremendous promise as therapies for large number of cancers and neurological conditions.[80] In addition, diphenylacetylene derivatives acted as antimicrobial peptide mimetics.[81]

Over the past decade, olefinic polymerization which catalyzed by transition metals has great prominence in both academic and industrial research.[82,83] Due to the recent adoption of high-throughput screening (HTS) methods, the field of olefin polymerization facilitated by Ziegler–Natta catalysts is particularly active.[84] A significant number of novel non-metallocene ligands have been discovered using these techniques for polymerization catalysis. Application of SMC of 2,2′-biphenyldiboronic acid **47** with 2-bromoindene **48** in the presence of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] furnished polycyclic 2,2′-di(1*H*-inden-2-yl)-1,1′-biphenyl (**49**) which showed promising activities in olefin metathesis polymerization (Scheme 24).[85]

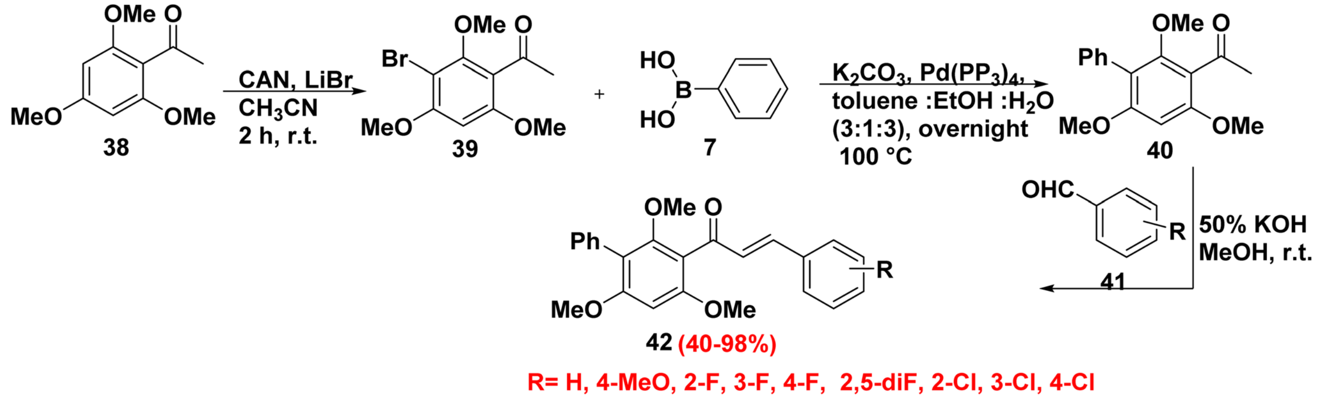
Polyaromatic hydrocarbons are distinguishable class of aromatic compounds. As aromatic polyphenyl scaffolds give a crowded molecule that usually relieves the congestion by distortion from planarity displaying highly reversible electrochemical properties as this merit shared by a few organic compounds.[86] Whereas, a mixture of four different polycyclic products **52–55** were furnished by reaction of 2,2′-diiodobiphenyl **50** with (1*H*-inden-2-yl)boronic acid (**51**) in the presence of palladium catalyst [$Pd(PPh_3)_4$] and K_3PO_4 in refluxing DME/H_2O (Scheme 25).[85]



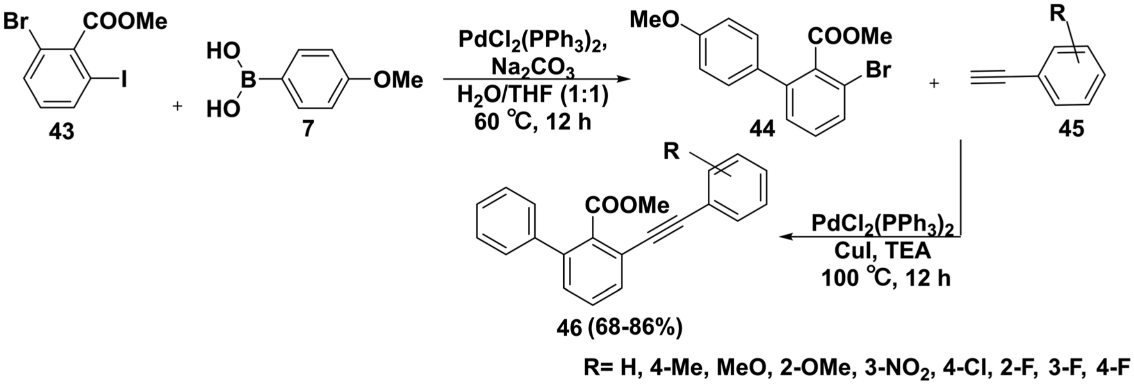
Scheme 20 Synthesis of biphenyl derivatives **2** *via* nickel catalyzed SMC.



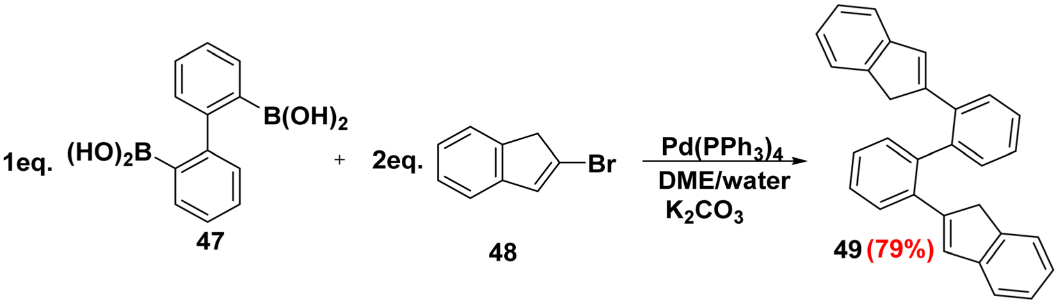
Scheme 21 Synthetic strategy for preparation of biphenyl tyrosine using aryl trifluoroborate salts.



Scheme 22 Formation of biphenyl chalcone derivatives by SMC.



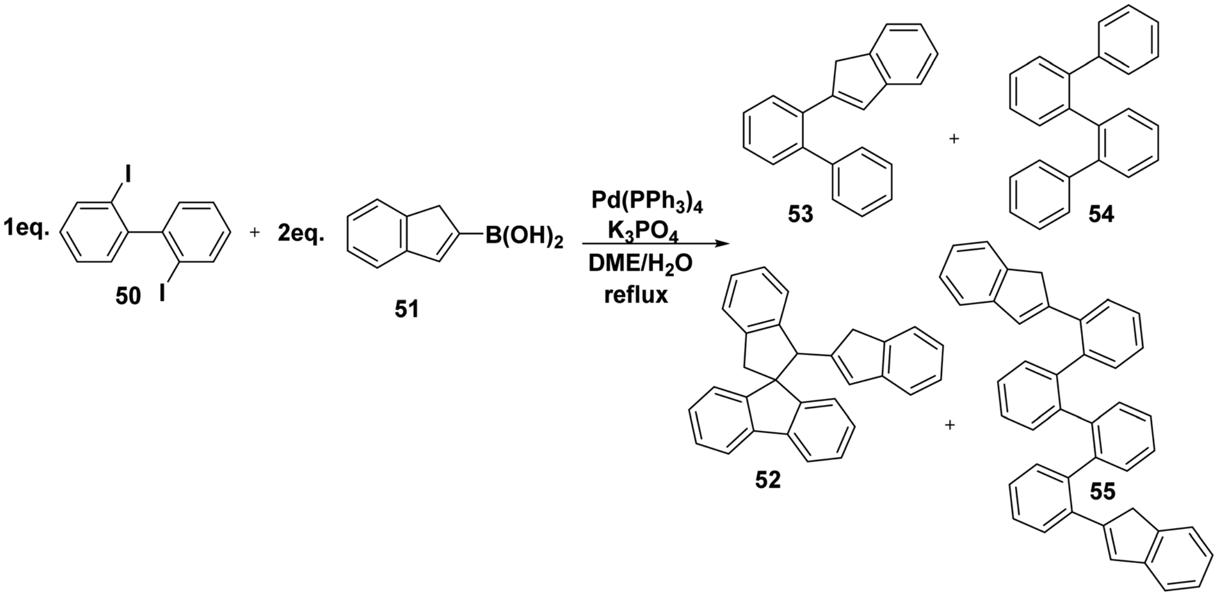
Scheme 23 Synthesis of phenylacetylene derivatives.



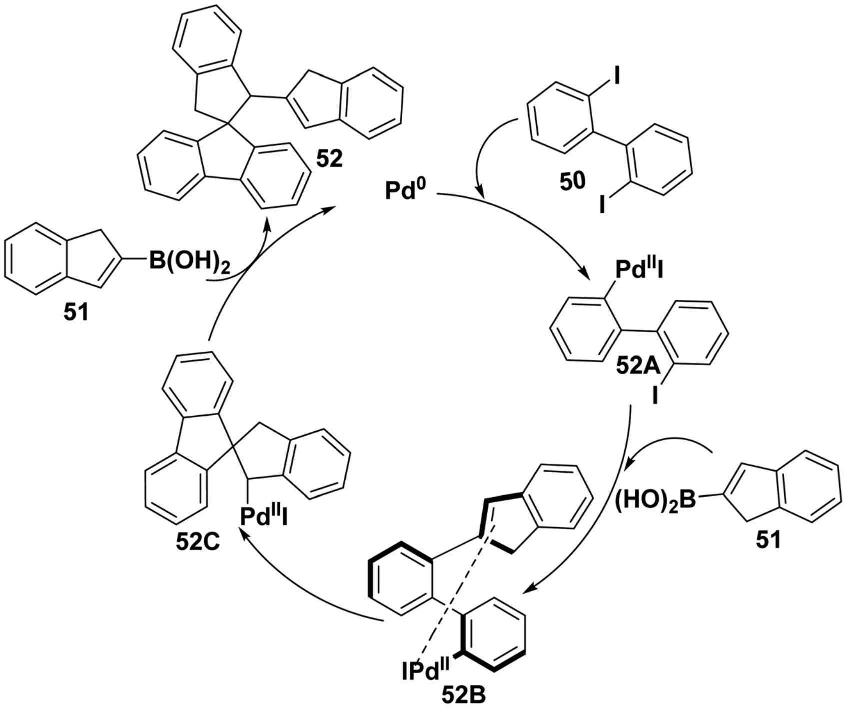
Scheme 24 Synthesis of (1*H*-inden-2-yl) biphenyl *via* palladium-catalyzed Suzuki–Miyaura coupling reaction.

Therefore, a proposed mechanism for the formation of 1*H*-inden-1′,3′-dihydrospiro[fluorene-9,2′-indene] **52** is depicted in Scheme 26. Initially, a palladium catalyst is inserted between C–I bond, then (1*H*-inden-2-yl) boronic acid (**51**) is coupled with (2′-iodo-[1,1′-biphenyl]-2-yl) palladium(II)iodide (**52A**), followed by intramolecular Heck reaction from **52B** to **52C**. Finally, Suzuki coupling reaction of (1′,3′-dihydrospiro[fluorene-9,2′-inden]-1′-yl) palladium(II) iodide (**52C**) with (1*H*-inden-2-yl) boronic acid (**51**) to afford 1*H*-inden-2-yl-dihydrospiro[indene] **52** with 58% yield (Scheme 26).[85]

Biphenyl benzamide derivatives inhibit the filamenting temperature-sensitive mutant Z (FtsZ) protein, in addition to having antibacterial activities.[87] Firstly, 2,6-difluoro-3-hydroxybenzoic acid (**56**) was alkylated with 3-bromobenzyl bromide (**57**) in the presence of sodium iodide (KI) and K_2CO_3 to furnish fluorinated acid derivative **58**. Then, fluorinated acid derivative **58** was reacted with oxalyl chloride $(COCl)_2$ in the presence of a mixture of dimethylformamide and dichloromethane (DMF/DCM) to afford difluorobenzoyl chloride derivative **59**. The acid was transformed to benzamide **60** by using



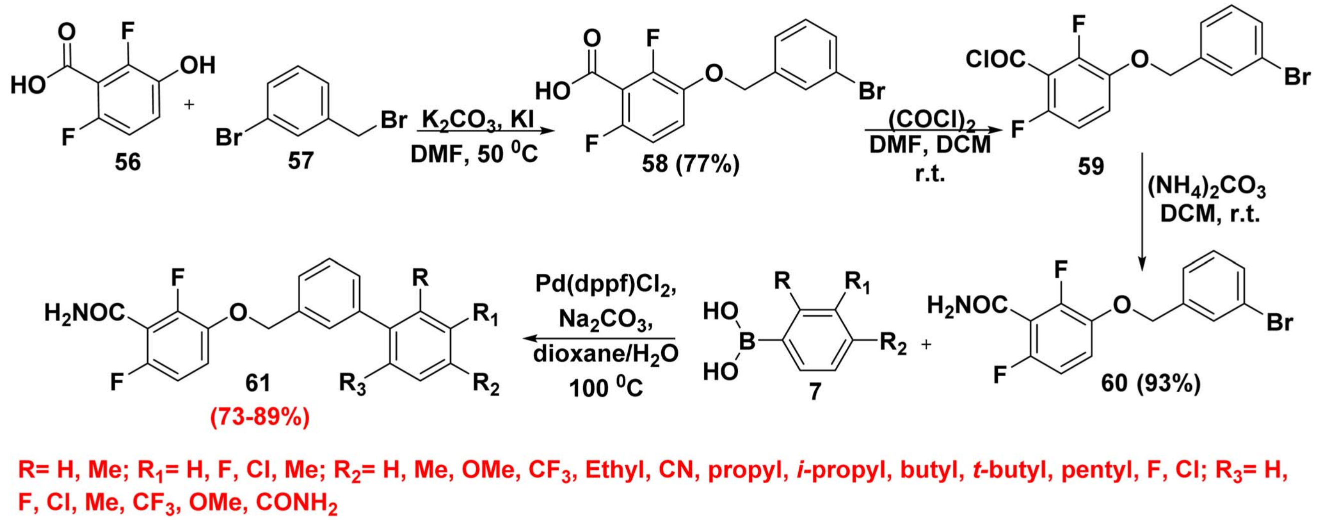
Scheme 25 Synthesis of polycyclic biphenyl compounds.



Scheme 26 The proposed mechanism for the formation of polycyclic product **52**.

oxalyl chloride, then treatment with ammonium carbonate ($(NH_4)_2CO_3$). Finally, biphenyl benzamide derivatives **61** were produced in a wide range of yields (73–89%) *via* coupling commercially available boronic acids **7** with compound **60** (Scheme 27).[87]

N-Biphenyl pyrrolidine derivatives are employed as ligand in arylaminations that are catalyzed by palladium. Furthermore, 2′-bromo-2-fluoro-5-nitro-1,1′-biphenyl (**63**) were produced in (81% yield) *via* Suzuki–Miyaura cross coupling between 2-iodo 4-nitro fluorobenzene (**62**) and boronic acid **7** in the presence of palladium catalyst and PPh_3 in refluxing dioxane. Then, the fluorine atom was nucleophilically substituted by (*R*)-(3-*N*,*N*-dimethylamino)pyrrolidine (**64**) in the presence of K_2CO_3 in DMF to yield 1-(2′-bromo-5-nitro-[1,1′-biphenyl]-2-yl)-*N*,*N*-dimethylpyrrolidin-3-amine (**65**). (*R*)-[1-(2′-Bromo-5-amino-biphenyl]-2-yl)-pyrrolidin-3-yldimethylamine (**66**) was

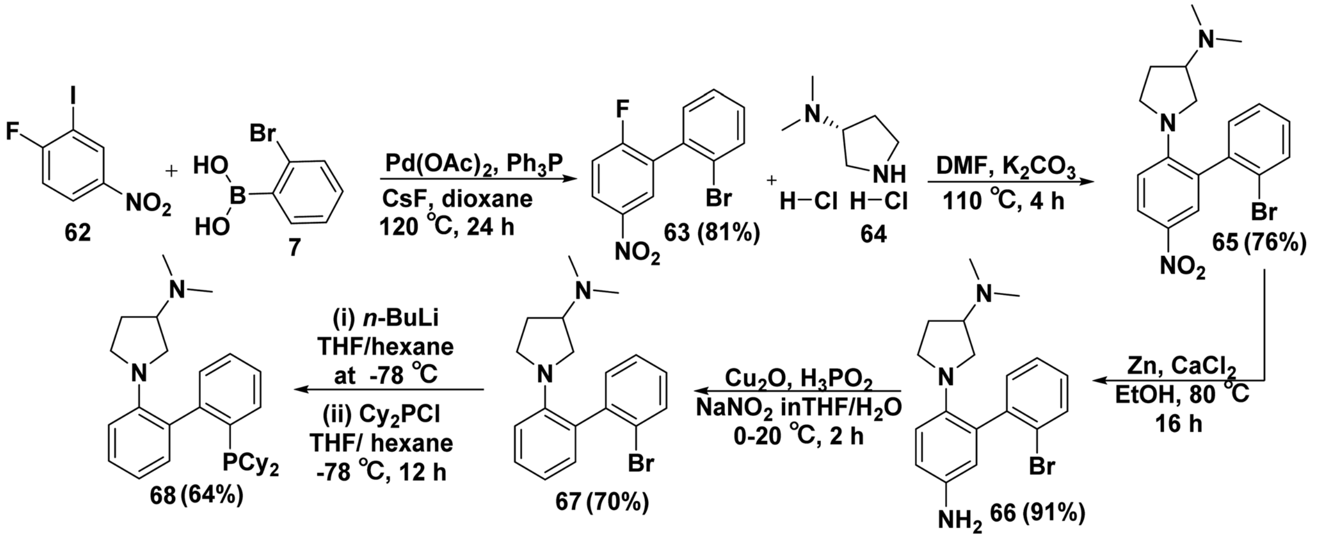


Scheme 27 Formation of biphenyl benzamide derivatives.

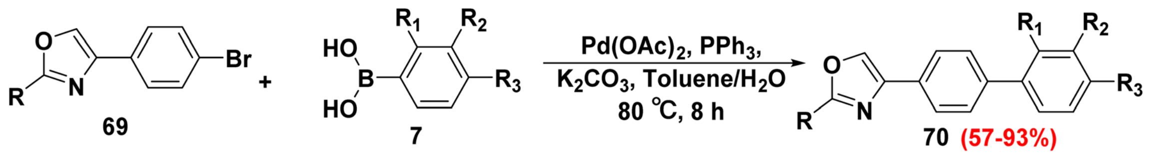
produced by refluxing zinc powder and calcium chloride ($CaCl_2$) with compound (*R*)-**65** in EtOH. After that, hypophosphorous acid (H_3PO_2) was added to compound (*R*)-**66** in a mixture of THF and H_2O, followed by treatment with cupper(I)oxide, and sodium nitrite ($NaNO_2$) furnished bromo(biphenyl-2-yl)-dimethylpyrrolidin-3-amine **67**. Finally, 2′-(dicyclohexylphosphaneyl)-[1,1′-biphenyl]-2-yl-*N*,*N*-dimethylpyrrolidin-3-amine **68** was obtained in two steps involving adding *n*-butyl lithium dropwise to compound (*R*)-**67** in a mixture of THF and hexane as first step. In the second step, chlorodicyclohexylphosphane (Cy_2PCl) was added with stirring to replace bromide by dicyclohexylphosphane group (Scheme 28).[88]

The synthesis of biphenyl oxazole derivatives **70** was reported by Ahmad *et al.*[89] under mild conditions which were enzyme inhibitors and estimated as therapeutic seeds for ailments associated with NPP1 and NPP3 isozymes *via* Suzuki–Miyaura cross coupling of bromo-phenyloxazole **69** with various boronic acids **7** in a mixture solvent system (toluene/water) (Scheme 29).

Moreover, an efficient synthesis of biphenyl oxazole derivatives **77** was achieved *through* alkylation reaction of 1-bromo-3-(chloromethyl)-2-methylbenzene (**71**) with 3-chloro-4-hydroxybenzaldehyde (**72**) produced 4-((3-bromo-2-methylbenzyl)oxy)-3-chlorobenzaldehyde (**73**). Next, refluxing 4-((3-bromo-2-methylbenzyl)oxy)-3-chlorobenzaldehyde (**73**) with bis(pinacolato)diboron (B_2pin_2) (**74**) in 1,4-dioxane and potassium acetate (CH_3COOK) in the presence of 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride diCrCl-chloromethane complex [pd(dppf)$Cl_2CH_2Cl_2$] afforded 3-chloro-4-((2-methyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy) benzaldehyde (**75**). Finally, compound **75** was reacted with (3-bromophenyl)isoxazole derivatives **76** *via* Suzuki coupling reaction yielded biphenyl oxazole derivatives **77** (Scheme 30).[90]

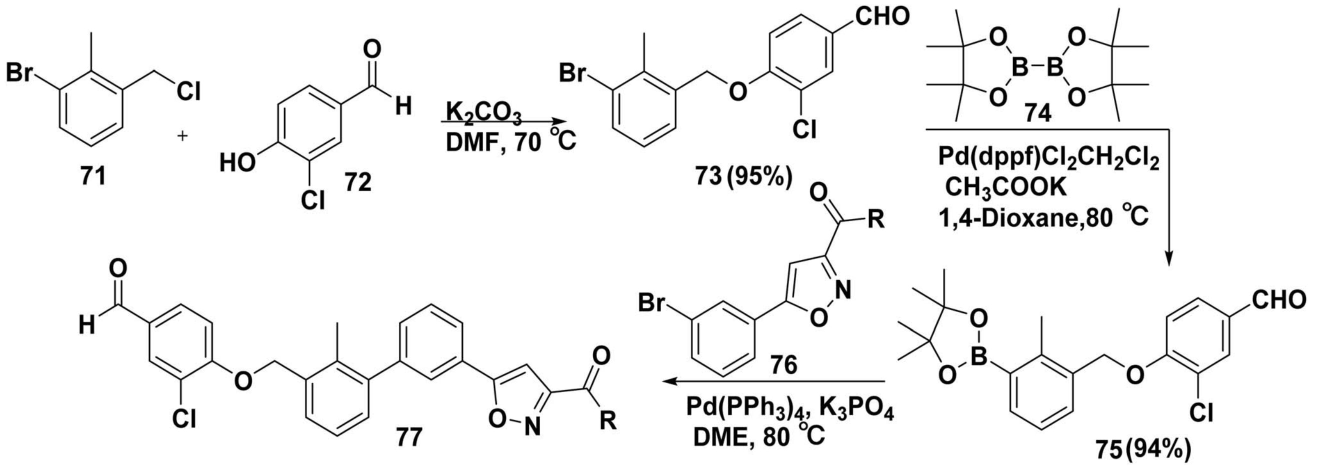


Scheme 28 Synthesis of *N*-biphenyl pyrrolidine derivatives.



R= Me, Ph, 2EtOPh; R_1= H, Me; R_2= H, Me; R_3= H, Me, OMe, OBn

Scheme 29 Suzuki coupling reaction for synthesis of biphenyl oxazole derivatives.



R= piperidin-4-ylmethanol (84%), (R)-pyrollidin-3-ol, piperidin-4-ol

Scheme 30 Synthesis of biphenyl oxazole derivatives.

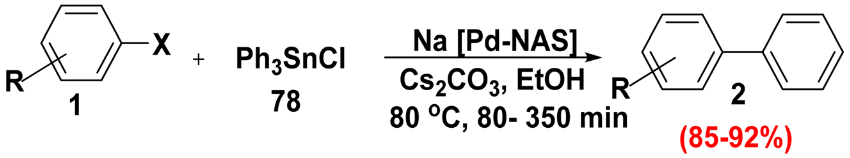
2.7 Stille cross coupling

Stille cross coupling reaction is one-step coupling reaction for nucleosides synthesis was first reported in 1986.[26,91] Stille cross coupling is still a significant reaction to form C–C bond, and one of the most selective and general methods for palladium catalyzed cross coupling reaction. Therefore, it was constituted to produce a various ring system bearing functional groups and to synthesize several alkenes, alkenyls, oligoarylenes and biaryls.[92–94] The interesting advantage of Stille reaction is the using of organotin compounds which are mild reagents and tolerate numerous of functional groups. On the other hand, the only drawback is the water insoluble tin reagents and toxicity of the hydrophobic.[92] Stille cross coupling reaction of aryl halide **1** with triphenyl tin chloride (Ph_3SnCl) (**78**) in the presence of catalytic amount of palladium grafted on natural asphalt sulfonate Na[Pd-NAS], cesium carbonate (Cs_2CO_3) as a base in refluxing ethanol furnished biphenyl derivatives **2** (Scheme 31).[88,95]

In 1986, Chemie John K. Stille described the possible mechanism for Stille cross coupling reaction. Stille cross coupling mechanism passed *through* three steps: oxidative addition, transmetalation and reductive elimination. In oxidative addition step, the catalytic species Pd(0)Ln is reacted with aryl halide **1** to form Pd(II) complex **2A**. In transmetalation step, Pd(II) complex **2A** cleavage the C–Sn bond of organotin reagent **78** to produce complex **2B**. Finally, reductive elimination step for forming C–C bond and the catalyst is regenerated at the same time (Scheme 32).[96]

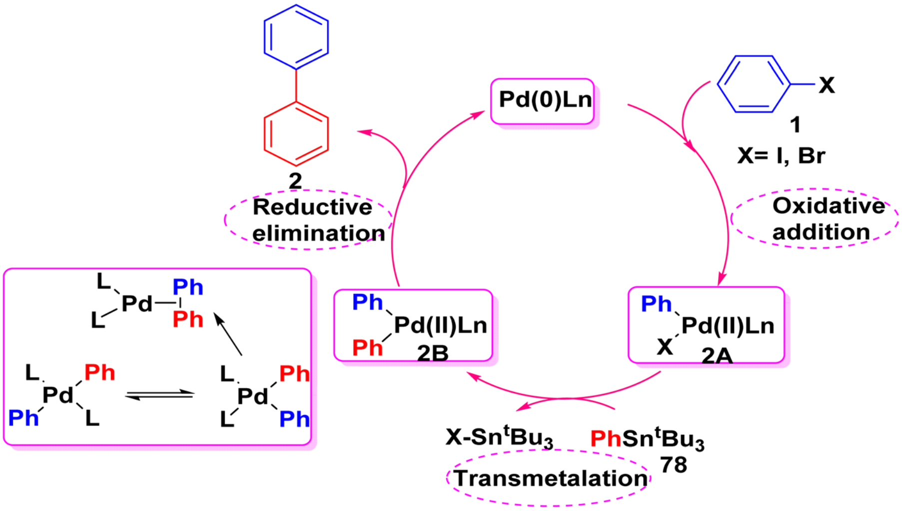
2.8 Negishi cross coupling

Negishi cross coupling reaction among the most important in organic chemistry for forming C–C bond between electrophiles



R= H, 2-Me, 4-Me, 4-OMe, 4-CN, 4-NO_2; X= Br, I

Scheme 31 Synthesis of parent biphenyl *via* Stille cross coupling.



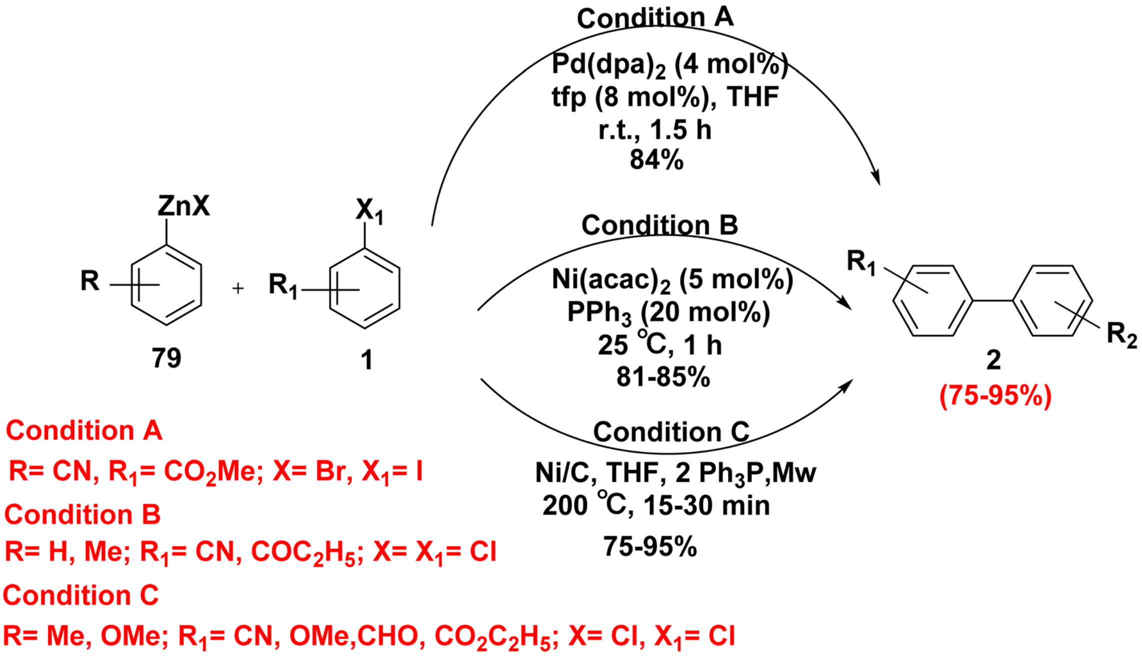
Scheme 32 The proposed mechanistic pathway for Stille cross coupling reaction.

with organozinc reagents and organic halides. Negishi reported an easy regio- and chemoselective method for the synthesis of unsymmetrical biaryl using an aryl–aryl coupling process that is catalyzed by nickel salts.[25,97] Treatment of cyanophenyl zinc bromide **79** with *o*-iodobenzoate **1** in the presence of palladium bis(dibenzylideneacetone) (Pd(dba)$_2$) and tris-*o*-furylphosphine (tfp) furnished biphenyl derivatives **2**.[98] In 2009, Phapale and Cárdenas[99] discovered that Ni-based catalysts (Ni(acac)$_2$/PPh$_3$) facilitate coupling between aryl zinc chlorides **79** and haloarenes **1** affording biphenyl derivatives **2**. The reaction of aryl zinc halide **79** and aryl halide **1** in the presence heterogeneous Ni catalyst on charcoal and microwave irradiation afforded biphenyls **2** in acceptable yields (75–95%) (Scheme 33).

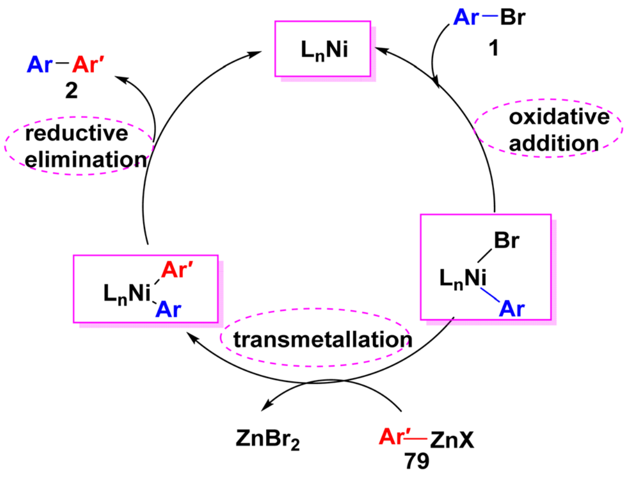
Mechanism of Negishi cross coupling reaction passed *through* three steps. Initially, an organohalide or pseudohalide (such as triflate) is oxidatively added to a low valent metal complex to produce an organometallic derivative with a higher formal oxidation state on the metal center. Then, producing diorganometal species is processed, whereby, the nucleophilic carbon is transmetalate from the nucleophile to the transition metal complex. Finally, a new C–C bond is formed by further reductive elimination, which reproduces the catalytically active species (Scheme 34).[99]

2.9 Ball-milling method

Recently, direct mechanocatalysis in ball-milling as a highly efficient synthetic tool applied for the cocondensation of alkali



Scheme 33 Synthesis of biphenyl derivatives *via* Negishi cross coupling reaction.



Scheme 34 Plausible mechanism of the formation of biphenyl derivatives *via* Negishi cross coupling reaction.

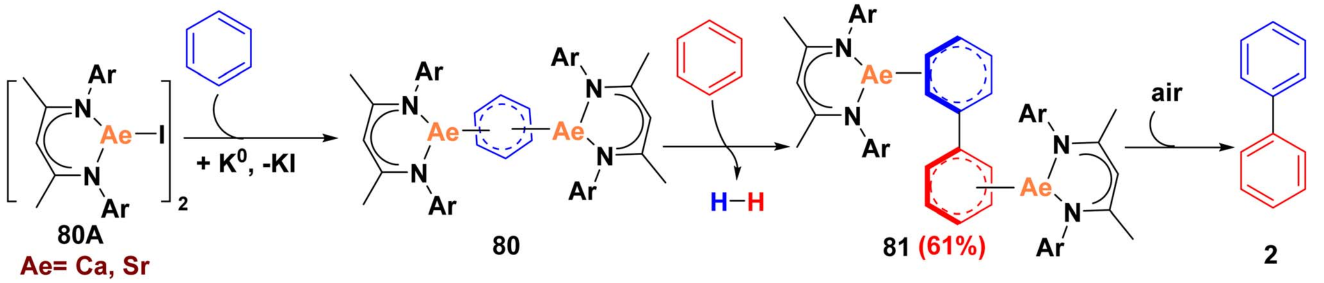
metals earth (Ae) such as K, Cs or Rb with benzene afforded $C_6H_5^{\bullet -}$ salts and radical coupling to (biphenyl)$^{2-}$ companied with emission of H_2 gas. Similarly, the direct dehydrogenative coupling of benzene through low-valent alkaline-earth metals (Ae) intermediates was achieved *via* formation of metal (Ae) complex with a $C_6H_5^{2-}$ dianion which acts as reducing agent to bulky β-diketiminate ligand BDI **80A** to yield $[(^{DIPeP}BDI)Ca]_2$(-biphenyl) **81** as dianionic *N*,*C*-chelating ligand, which rapidly decomposed to afford biphenyl scaffold **2** (Scheme 35).[100]

3. Chemical reactions

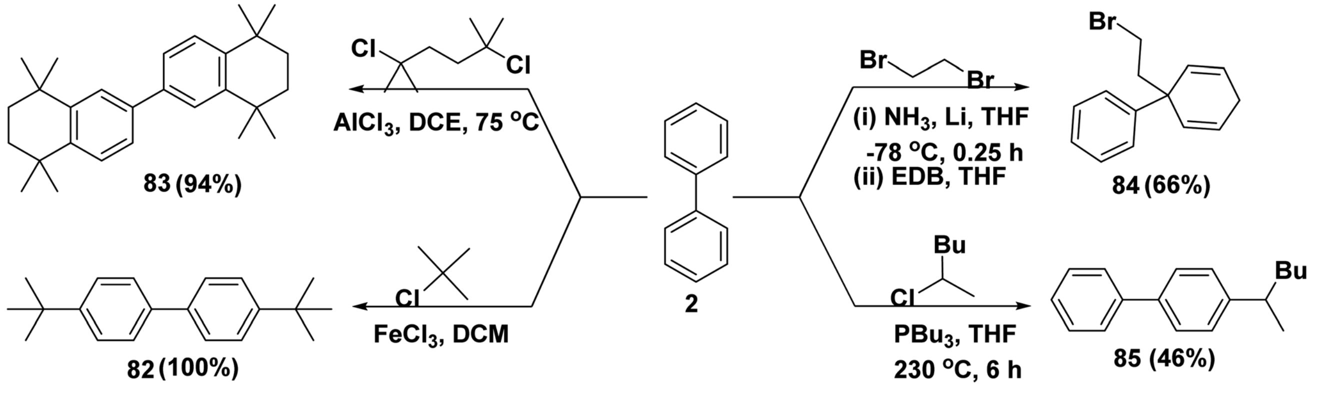
3.1 The Friedel–Crafts

Friedel–Crafts reactions are subdivided into two fundamental types: alkylation and acylation reactions.[101] Whereby, ionic liquids have already been used in a number of Friedel–Crafts processes, which could significantly reduce the associated environmental concerns.[102]

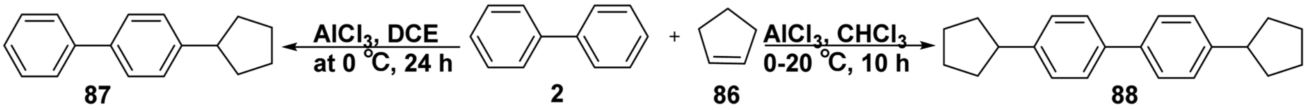
3.1.1 Friedel–Crafts alkylation of biphenyl with haloalkane. For more than a century, Friedel–Crafts alkylation reaction is a vital reaction for the synthesis of alkyl substituted aromatic compounds.[103] 4,4′-Di-*tert*-butylbiphenyl (**82**) was synthesized from biphenyl (**2**), which then, in the presence of catalytic amounts of anhydrous ferric chloride ($FeCl_3$), interacted with *tert*-butyl chloride in halogenated solvents.[104] In the same manner, Friedel–Crafts cycloannulation process produced octamethyl-octahydro-2,2′-binaphthalene **83** *through* adding catalytic amounts of anhydrous $AlCl_3$ to a solution of biphenyl (**2**) in 1,2-dichloroethane (DCE) followed by dropwise addition of readily available 2,5-dichloro-2,5-dimethylhexane.[105] In the same context, a mixture of ammonia and lithium was added dropwisely to a solution of biphenyl (**2**) in THF till brick red suspension was formed. Then, a quick addition of 1,2-dibromoethane (EDB) was added to afford 2-bromoethyl-1,1′-biphenyl **84**.[106] A mixture of biphenyl (**2**), 2-chlorohexane and tributyl phosphine (PBu_3) was heated for 6 h to afford 4-(hexan-2-yl)-1,1′-biphenyl (**85**) (Scheme 36).[103]



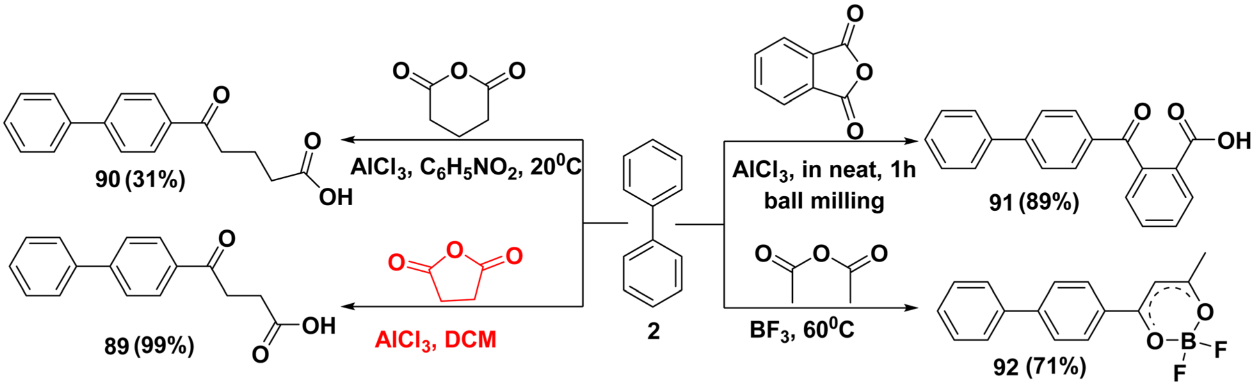
Scheme 35 Dehydrogenative benzene–benzene coupling for biphenyl synthesis.



Scheme 36 Friedel–Crafts alkylation of biphenyl with haloalkane.



Scheme 37 Reaction of biphenyl with cyclopentene.

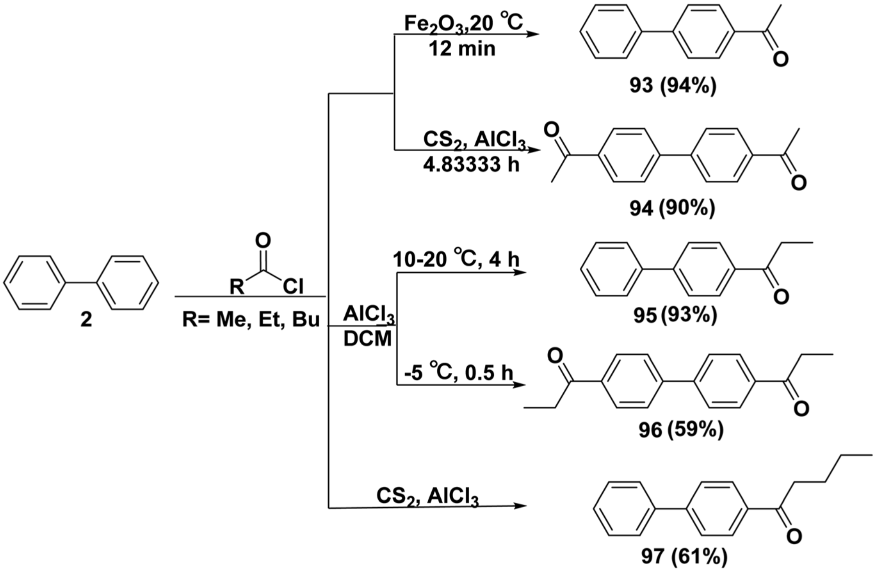


Scheme 38 Friedel–Crafts acylation of biphenyl with anhydrides.

Moreover, treatment of biphenyl (**2**) with cyclopentene (**86**) in the presence of $AlCl_3$ and DCE at 0 °C for 24 h afforded 4-cyclopentyl-1,1′-biphenyl (**87**).[107] Additionally, using trichloromethane ($CHCl_3$) instead of DCE at 20 °C for 10 h led to formation of 4,4′-dicyclopentyl-1,1′-biphenyl (**88**) (Scheme 37).[108]

3.1.2 Friedel–Crafts acylation. The Friedel–Crafts acylation is the reaction of acid anhydrides or acyl chlorides with aromatic compounds in the presence of Lewis acid catalyst for the synthesis of methyl aryl ketone, which are used in pharmaceuticals and fine chemical such as ibuprofen, naproxen, dyes, agrochemicals, and fragrances.[109,110]

3.1.2.1 Reaction of biphenyl with acid anhydride. 4-Phenylbenzoyl-propionic acid (**89**) can be easily prepared *via* Friedel–Crafts acylation of biphenyl (**2**) and succinic anhydride in the presence of $AlCl_3$ and dichloromethane (DCM).[111] While, treatment of biphenyl (**2**) with dihydro-2*H*-pyran-2,6(3*H*)-dione in the presence of $AlCl_3$ and nitrobenzene ($C_6H_5NO_2$) afforded biphenyl-4-yl-5-oxopentanoic acid (**90**).[112] Further, biphenyl-4-carbonyl-benzoic acid (**91**) was synthesized *through* free-solvent mechanochemical ball milling method *via* reaction of biphenyl (**2**) with phthalic anhydride in the presence of $AlCl_3$.[113] Whereas, gaseous boron trifluoride (BF_3) was passed *through*

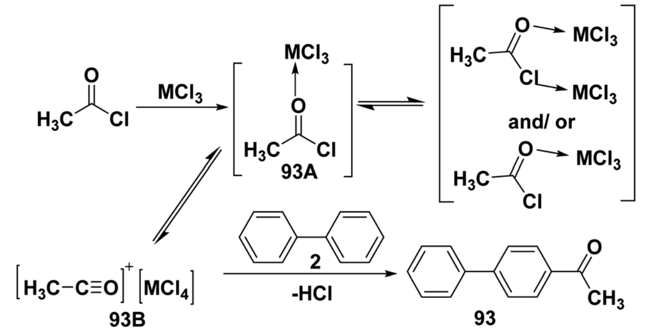


Scheme 39 Reaction of biphenyl with acyl chloride derivatives.

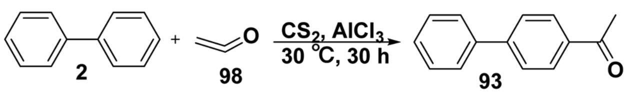
a homogenous mixture of biphenyl (**2**) and acetic anhydride to synthesize biphenyl-4-yl-2,2-difluoro-6-methyl-dioxaborinine (**92**) (Scheme 38).[114]

3.1.2.2 Reaction of biphenyl with acid chloride. Reaction of biphenyl (**2**) with a mixture of activated iron(III)oxide (Fe_2O_3) and acetyl chloride, 1-([1,1′-biphenyl]-4-yl)ethan-1-one (**93**) was produced.[110] In contrast, acetyl chloride in dried carbon disulfide (CS_2) was added drop by drop with stirring into a suspension solution containing biphenyl (**2**), anhydrous $AlCl_3$, and dried (CS_2) to obtain 1,1′-([1,1′-biphenyl]-4,4′-diyl)bis(ethan-1-one) (**94**).[115] Additionally, biphenyl (**2**) was refluxed with propionyl chloride for 4 h in DCM containing a catalytic amount of $AlCl_3$ to furnish 1-([1,1′-biphenyl]-4-yl) propan-1-one (**95**),[116] whereas 1,1′-([1,1′-biphenyl]-4,4′-diyl)bis(propan-1-one) (**96**) was produced by refluxing biphenyl (**2**) with propionyl chloride for 2 h at −5 °C.[117] Under anhydrous conditions, a stirred mixture of CS_2, biphenyl (**2**), and anhydrous $AlCl_3$ was treated with pentanoyl chloride to afford 1,1′-biphenyl-4-pentan-1-one (**97**) (Scheme 39).[118]

The proposed mechanism for Friedel–Crafts acylation shows that the reaction began with the Lewis acids MCl_3 (M = Fe or Al) activating the acetyl chloride to produce an adduct of acyl chloride with MCl_3 (**93A**). This complex is quickly equilibrated with the acylium ion $[CH_3CO]^+[MCl_4]$ (**93B**), which then attacks biphenyl (**2**) to produce biphenyl alkyl ketone **93** (Scheme 40).[102]



Scheme 40 Friedel–Crafts acylation mechanism.



Scheme 41 Reaction of biphenyl (**2**) with ethenone.

3.1.2.3 Reaction of biphenyl with ketene. 1-([1,1′-Biphenyl]-4-yl)ethan-1-one (**93**) was synthesized *via* Friedel–Crafts reaction by stirring ethenone (**98**) with a solution of biphenyl (**2**) in CS_2, then adding $AlCl_3$ (Scheme 41).[119]

3.1.2.4 Reaction of biphenyl with oxalyl chloride. A facile synthesis of 4,4′-biphenyl ketone **99** was accomplished *via* the reaction of biphenyl (**2**) with oxalyl chloride $(ClCO)_2$ in the presence of $AlCl_3$ and DCM.[120] While, the reaction of biphenyl (**2**) with oxalyl chloride under the influence of $AlCl_3$ in DCE produced 1-([1,1′-biphenyl]-4-yl)ethan-1-one (**93**) and 1,2-di([1,1′-biphenyl]-4-yl)ethane-1,2-dione (**100**) (Scheme 42).[121]

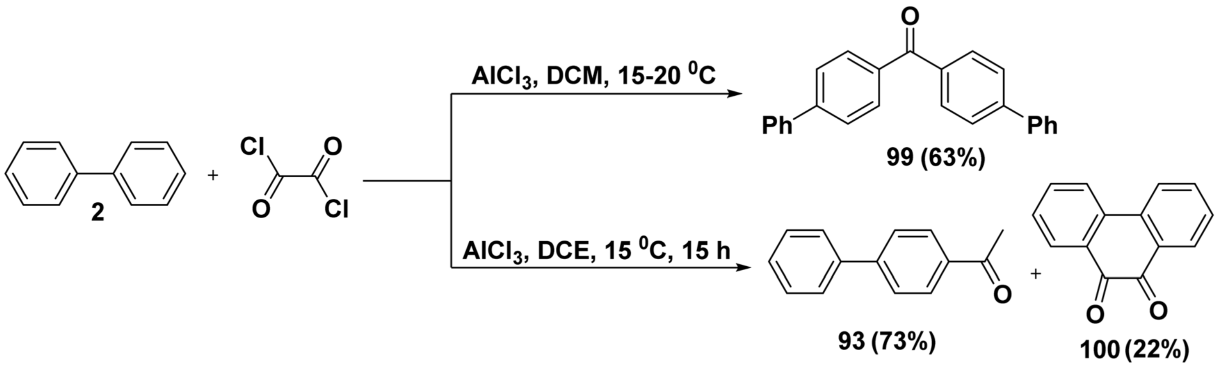
3.2 Isopropylation reaction of biphenyl

Reaction of biphenyl with propene (**101**) in the presence of lithium metal (Li), and THF, followed by hydrolysis afforded a mixture of 4-isopropyl-1,4-dihydro-1,1′-biphenyl (**102**) and 4-isopropyl-3,4-dihydro-1,1′-biphenyl (**103**).[122] Furthermore, a mixture of 4-isopropyl-1,1′-biphenyl (**104**), 4,4′-diisopropyl-biphenyl (**105**), and 3,4′-diisopropyl-1,1′-biphenyl (**106**) were produced *through* the reaction of biphenyl (**2**) with propene (**101**) in the presence of [Fe]-SSZ-24 catalyst (Scheme 43).[123]

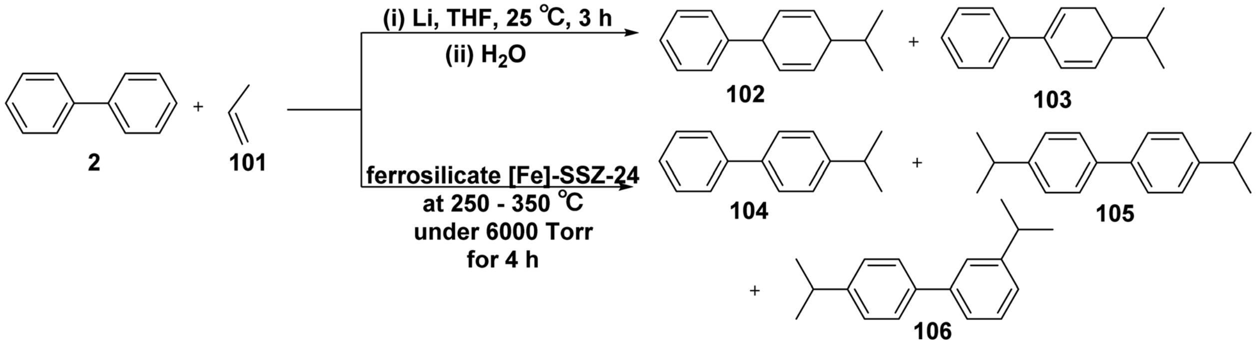
The proposed mechanism for the synthesis of isopropyl biphenyl derivatives starts with *in situ* formation of carbolithiation step in which the biphenyl (**2**) is doubly reduced in a mixture of lithium metal (Li) and THF affording biphenyl dianion intermediate **102A**. Then, biphenyl dianion **102A** reacted with propene (**101**) in THF, followed by addition step to yield intermediate **102B**, finally the hydrolysis step is achieved to furnish 4-isopropyl-1,4-dihydro-1,1′-biphenyl (**102**) and 4-isopropyl-3,4-dihydro-1,1′-biphenyl (**103**) (Scheme 44).[122]

3.3 Halogenation reactions

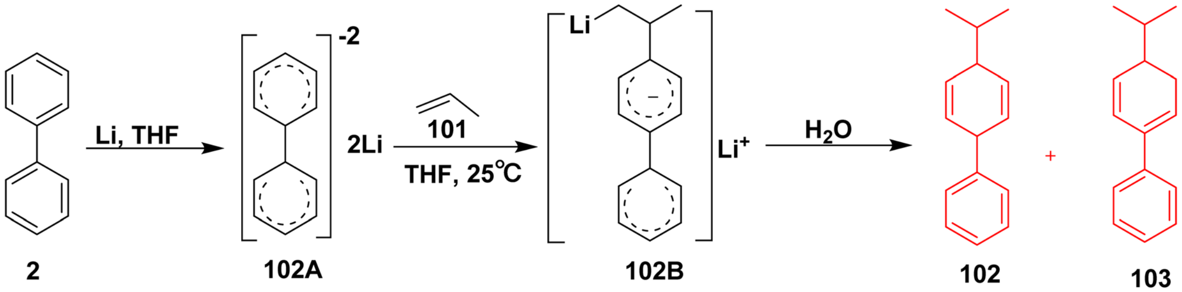
3.3.1 Chlorination reactions. Polychlorinated biphenyls (PCBs) are a class of chlorinated organic compounds which were widely used in commercial and industrial applications. PCBs have many industrial applications including heat transfer, electrical, lubricants, and hydraulic equipment; as plastics,



Scheme 42 Acylation of biphenyl with $(ClCO)_2$.



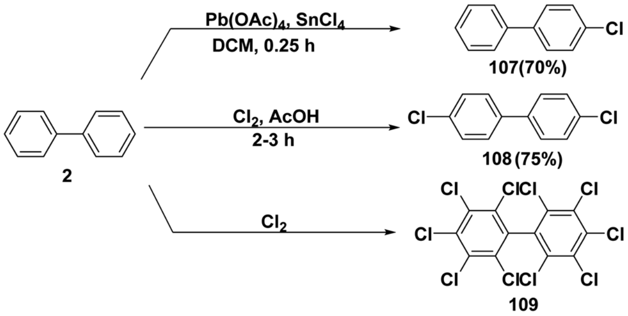
Scheme 43 Reaction of biphenyl with propene.



Scheme 44 A postulated mechanism for biphenyl isopropyl synthesis.

rubber products, coating, adhesive, capacitors, and plasticizers in paints; carbonless copy paper, and dyes.[124] A solution of biphenyl (**2**) and anhydrous tin(IV)chloride ($SnCl_4$) in DCM was stirred, then lead tetraacetate $Pd(OAc)_4$ was added in portion to produce 4-chloro-1,1′-biphenyl (**107**).[125] Whereby, dichlorobiphenyl **108** was synthesized *through* passing chlorine gas (Cl_2) to a solution of biphenyl (**2**) in glacial acetic acid (AcOH).[126] On the other hands, biphenyl (**2**) was exposed to chlorine gas to obtain poly chlorinated biphenyl derivative **109** (Scheme 45).[127]

3.3.2 **Bromination reactions.** On the area of research, the study of bromine containing molecules has been found to have an extensive range of biological activities, including those that are antiparasitic, antibacterial, antiviral, antioxidant, anti-inflammatory, and anticancer. Furthermore, mixtures of poly-brominated biphenyls (PBBs) have been employed as additives in polymers as well as flame retardants in the textile and electronic sectors.[128,129] Stirring of biphenyl (**2**) with *N*-bromosuccinimide (NBS) in 2-methyltetrahydrofuran (2-MTHF) as solvent furnished mono bromobiphenyl **110**.[130] Whereas, the bromination of compound **2** by NBS in the presence of $AgSbF_6$ and Trip-SMe in DCE furnished dibromo-biphenyl **111**.[131] Further, bromine gas (Br_2) was mixed with biphenyl (**2**), cooled in an ice bath, and $AlBr_3$ was added dropwise under the synthesis of HBr to afford PBBs **112**, **113** (Scheme 46).[129]

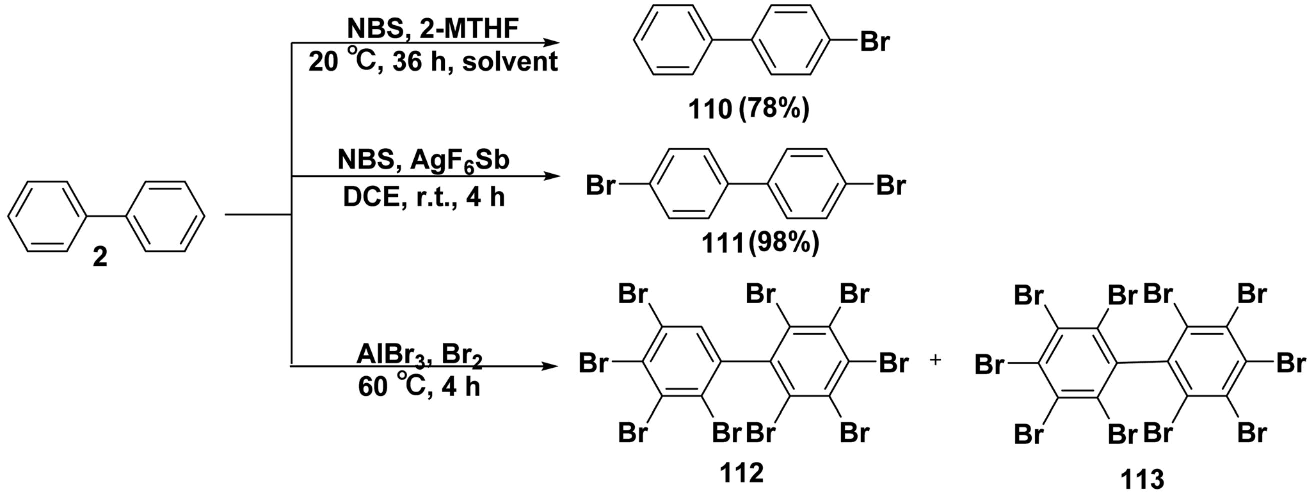


Scheme 45 Chlorination of biphenyl.

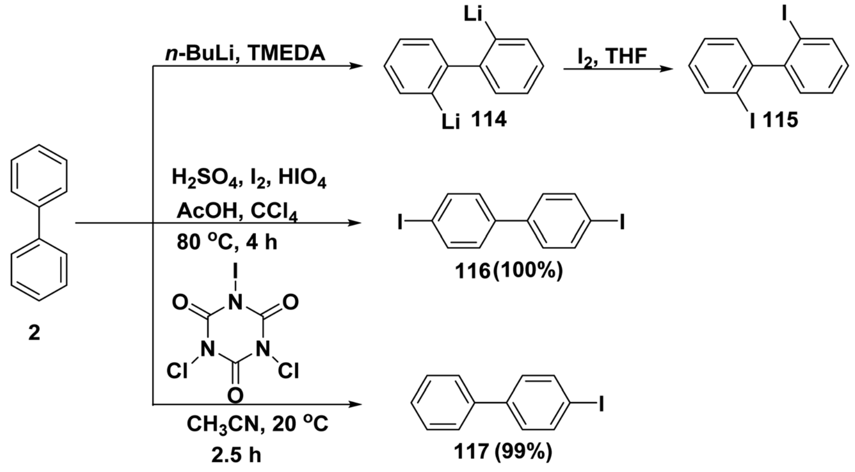
3.3.3 **Iodination reactions.** Iodo-organic molecules are extensible and useful synthetic intermediates which have numerous applications in pharmacology, medicine, and polymer science.[132] Lithiation of biphenyl (**2**) with *n*-butyllithium (*n*-BuLi) in the presence of tetra methyl ethylenediamine (TMEDA) led to formation of 2,2′-dilithiobiphenyl (**114**). Then, dilithiobiphenyl **114** reacted with iodine gas (I_2) in THF to give 2,2′-diiodobiphenyl (**115**).[133,134] On the other hand, a mixture of biphenyl (**2**), water, AcOH, concentrated sulfuric acid (H_2SO_4), I_2, periodic acid (HIO_4), and carbon tetrachloride (CCl_4) was heated for 4 h to produce diiodobiphenyl **116**.[135] Furthermore, stirring of biphenyl (**2**) with dichloroiodoisocyanuric acid (DCICA) in CH_3CN afforded 4-iodo-1,1′-biphenyl (**117**) (Scheme 47).[132]

3.4 Chloromethylation reaction of biphenyl

Chloromethyl-substituted aromatic compounds are significant intermediates due to their easy transformation into a wide range of fine or special chemicals, pharmaceuticals, and polymers.[136] The chloromethylation reaction of biphenyl (**2**) with formalin (HCHO) in the presence of HCl and $FeCl_3$ produced 4-

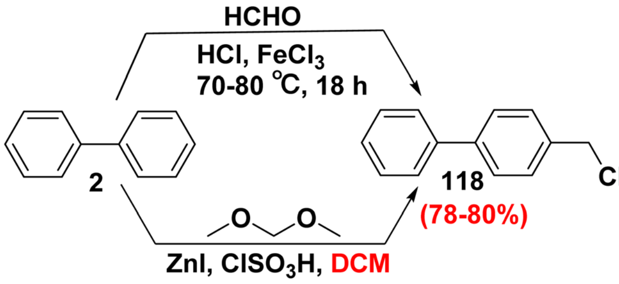


Scheme 46 Bromination of biphenyl.



Scheme 47 Different iodinated derivatives of biphenyl.

(chloromethyl)-1,1′-biphenyl (**118**) in 80% yield.[137] Whereas, 4-(chloromethyl)-1,1′-biphenyl (**118**) was afforded in 78% yield *through* the treatment of biphenyl (**2**) with dimethoxymethane ($CH_2(OCH_3)_2$) and chlorosulfonic acid ($ClSO_3H$) in the presence of a catalytic amount of zinc iodide (ZnI_2) in DCM (Scheme 48).[136]

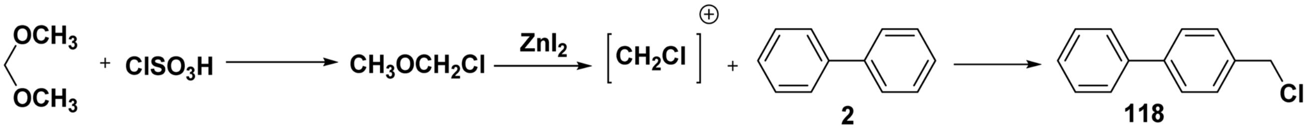


Scheme 48 Chloromethylation of biphenyl.

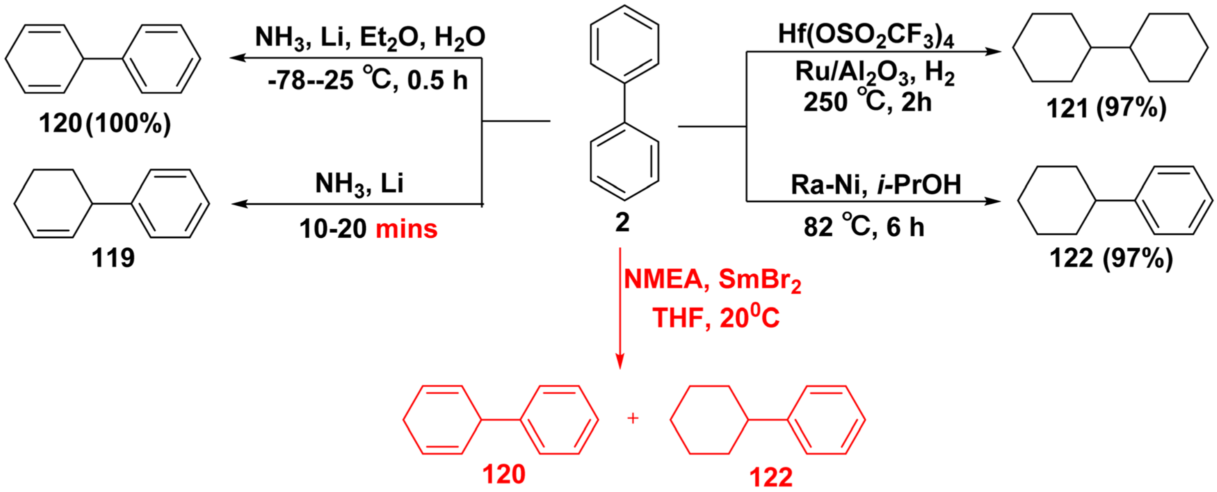
Scheme 49 depicts a probable mechanism for the formation of chloromethyl-1,1′-biphenyl **118**. The first step involves treatment of $CH_2(OCH_3)_2$ with $ClSO_3H$ affords methyl chloromethyl ether. Then, ZnI_2 promotes the production of the chloromethyl cation ($[ClCH_2]^+$). Finally, a chloromethylated derivative **118** is obtained by the electrophilic substitution reaction of biphenyl **2** with $[ClCH_2]^+$ (Scheme 49).[136]

3.5 Reduction of biphenyl

Reduction of biphenyl (**2**) with reducing lithium metal and ammonia afforded tetrahydro-1,1′-biphenyl **119**.[138] Analogously, 3-phenyl-1,4-cyclohexadiene (**120**) was synthesized when liquid ammonia was added to Et_2O containing biphenyl (**2**), followed by the addition of lithium metal.[139] While, the treatment of biphenyl (**2**) with a noble metal catalyst (*e.g.*, Ru/C) in the presence of Lewis acid ($Hf(OTF)_4$) and octane (OCT) furnished 1,1′-bi(cyclohexane) (**121**).[140] Whereas, nickel catalyzed hydrogenation of biphenyl (**2**) in the presence of isopropyl alcohol (i-PrOH) as a hydrogen donor afforded cyclohexylbenzene (**122**).[141]



Scheme 49 Possible mechanism of chloromethylation of biphenyl.



Scheme 50 Reduction of biphenyl.

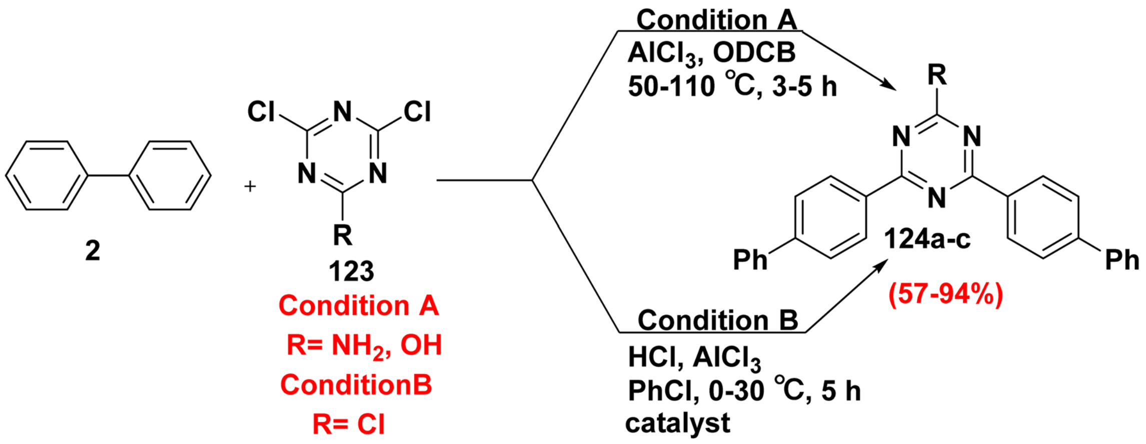
Whereby, reduction of biphenyl **2** with a combination of samarium dibromide ($SmBr_2$) and *N*-methylethanolamine (NMEA) as a chelating ligand furnished a mixture of **120** and **122** (Scheme 50).[142]

3.6 Reaction of biphenyl with triazine derivatives

4,6-Di([1,1′-biphenyl]-4-yl)-1,3,5-triazin-2-amine (**124a**) and 4,6-di([1,1′-biphenyl]-4-yl)-1,3,5-triazin-2-ol (**124b**) were synthesized by heating 4,6-dichloro-1,3,5-triazin derivatives **123** with a solution of *o*-dichlorobenzene (ODCB) with $AlCl_3$, followed by adding a biphenyl solution of ODCB.[143,144] In addition, biphenyl (**2**) was allowed to react with 2,4,6-trichloro-1,3,5-triazine (**123**) in the presence of hydrogen chloride (HCl) and $AlCl_3$ in chlorobenzene yielded trisubstituted-6-chloro-1,3,5-triazine **124a–c** (Scheme 51).[145]

3.7 Rection of biphenyl with acid

Acetylation of arenes is a significant reaction and still essential need in chemistry. Oxygenated arenes, for example aryl acetates, are valuable synthetic precursors for pharmaceuticals, natural products, and functional materials.[146] Luke *et al.*[147] investigated the use of β-aryl-β-ketophosphonates as bone anabolic agent, thyroid receptor ligands, and tumor cell profiler inhibitors. Dimethyl(2-([biphenyl]-4-yl)-2-oxoethyl)phosphonate **126** was synthesized by stirring biphenyl (**2**) with trifluoroacetic anhydride (TFAA), which was then treated with

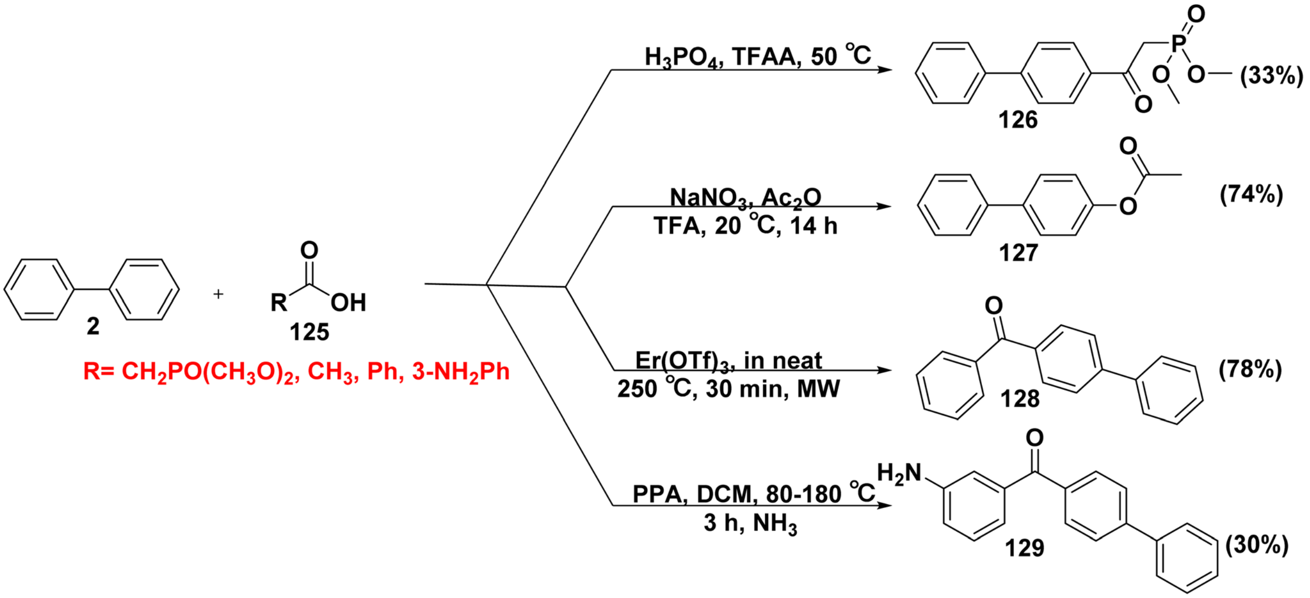


Scheme 51 Formation of biphenyl triazine scaffolds.

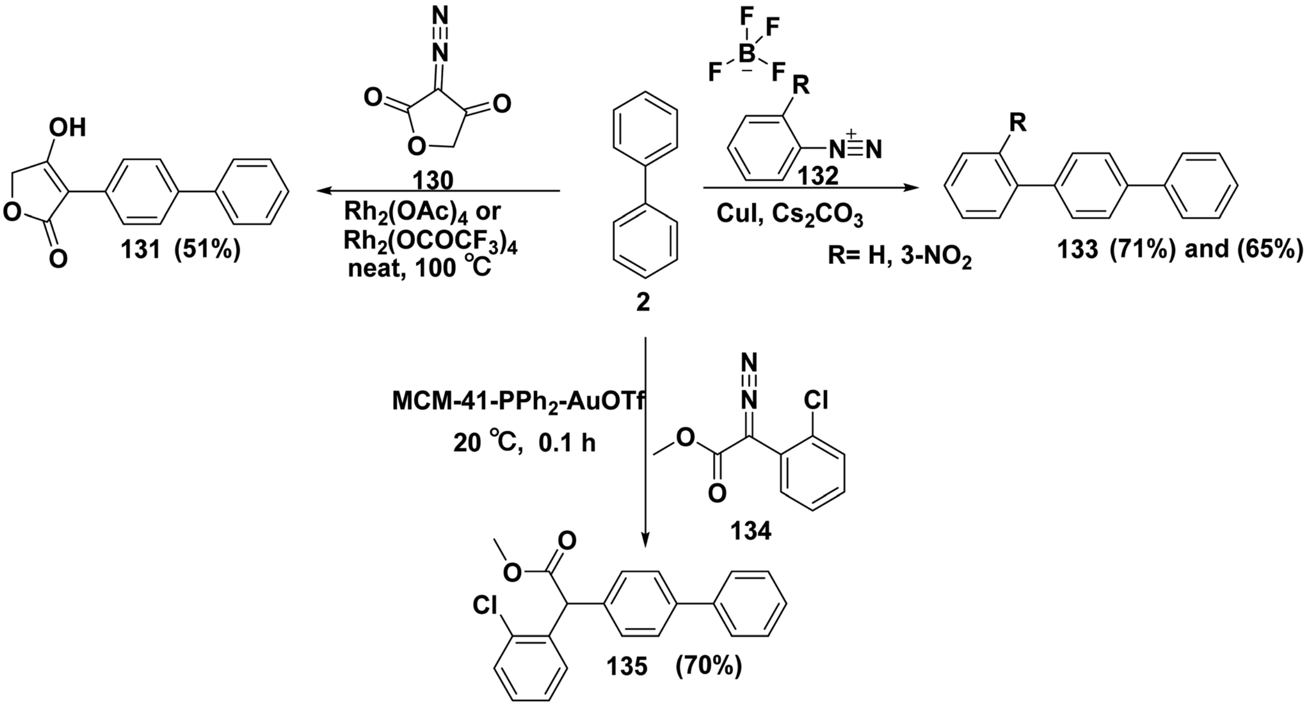
dimethylphosphonoacetic acid (**125**) and phosphoric acid (H_3PO_4). Under purified nitrogen condition, a mixture of sodium nitrate ($NaNO_3$) in trifluoroacetic acid (TFA), ACOH, and Ac_2O was mixed with a solution of biphenyl (**2**) afforded [1,1′-biphenyl]acetate (**127**).[146] Erbium(III) triflate ($Er(OTf)_3$) catalyzed Friedel–Crafts acylation of biphenyl (**2**) using acylating agent, such as benzoic acid (**125**) under microwave irradiation furnished [1,1′-biphenyl]-4-yl(phenyl)methanone (**128**).[148] Furthermore, (3-amino-phenyl)-biphenyl-4-yl-methanone (**129**) was obtained by adding 3-aminobenzoic acid (**125**) and polyphosphoric acid (PPA) to biphenyl (**2**) (Scheme 52).[149]

3.8 Rection of biphenyl with diazonium salt

Manchoju *et al.*[150] emphasized that several tetronic acid derivatives displayed a wide range of pharmacological activities, including acaricidal, insecticidal, HIV-I protease inhibitory,



Scheme 52 Acetoxylation of biphenyl with various acids.



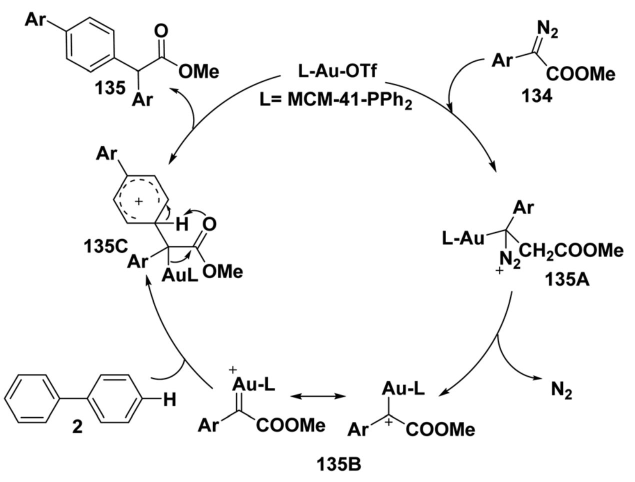
Scheme 53 Reaction of biphenyl with diazonium salts.

anti-inflammatory, antineoplastic, and cyclooxygenase inhibitory activity. Under conventional heating, synthesis of 1,1′-bipheny-4-hydroxyfuran-2(5*H*)-one **131** was achieved in excellent yield (51%) by reaction of biphenyl (**2**) and 3-diazofuran-2,4-dione **130**. Gomberg–Bachmann–Hey reactions of benzendiazonium tetrafluoroborate derivatives **132** with biphenyl (**2**) in the presence of copper catalyst and cesium carbonate (Cs_2CO_3) in CH_3CN afforded terphenyl derivatives **133**.[151] In the same context, heterogeneous gold(I)-catalyzed reaction of biphenyl (**2**) with 2-chlorophenyl-2-diazoacetate **134** afforded methyl 2-([biphenyl]-4-yl-2-chlorophenyl)acetate **135** (Scheme 53).[152]

Heterogeneous gold(I)-catalyzed mechanism of inactivated arenes is passed *via* sequence steps. Initially, for the synthesis of diazonium ion intermediate **135A**, the cationic gold MCM-41–PPh_2–AuOTf exchanges ligands with the diazo ester **134**. Then, intermediate **135A** collapses to produce the MCM-41-bound gold(I)carbene intermediate **135B**, followed by combination between the nucleophilic arene **2** and the electrophilic gold(I) carbene intermediate **135B**, the gold ionic intermediate **135C** is produced. Last, intermediate **135C** goes *through* 1,4-*H* shift and deauration to afford product **135** and MCM-41–PPh_2–AuOTf complex is regenerated (Scheme 54).[152]

3.9 Reaction of biphenyl with isothiazol-3(2*H*)-one-1,1-dioxide derivatives

Copper-catalyzed reaction of biphenyl (**2**) with saccharin derivatives **136** in the presence of 1,10-phenanthroline (phen), K_2CO_3, and selectfluor as oxidant in refluxing CH_3CN furnished biphenyl saccharin derivatives **137** (Scheme 55).[153]



Scheme 54 Heterogeneous gold(I)-catalytic cycle mechanism.

3.10 Nitration of biphenyl

Several reagents could be used to perform the nitration of aromatic compounds. The nitro aromatic compounds are extensively used in the manufacture of perfumes, pharmaceuticals, explosives, plastics, and dyes. Nitration of biphenyl (**2**) gave various oriented nitrated products **138** and **139** depending upon the nature of conditions and reagents applied on the reaction, as the nitration of biphenyl (**2**) was employed by refluxing $NaNO_3$with SO_3H-functionalized magnetic core/shell nano catalyst in DCM furnished 4-nitro-1,1′-biphenyl (**138**).[154] While, treatment of a biphenyl with nitric acid (HNO_3) in CCl_4 solvent afforded 2-nitro-biphenyl **139** (Scheme 56).[155]

3.11 Reaction of biphenyl with fused compounds

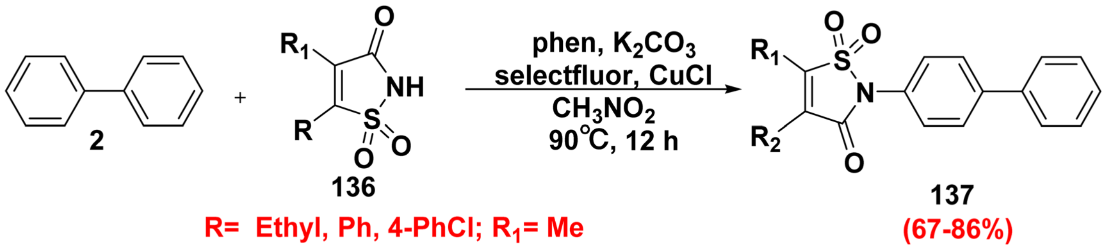
A class of fused ring, such as thioxanthone, dibenzothiophene, and thianthrene are applied as cationic photo-initiator, specifically for usage in surface coating applications, for example, varnishes and inks. 5-([1,1′-biphenyl]-4-yl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium-hexafluorophosphate(V) (**141**) was obtained in two steps (Scheme 57) starting of mixing biphenyl (**2**) and dibenzo[*b*,*d*]thiophene 5-oxide (**140**) with AcOH and Ac_2O in DCM, followed by adding sulfuric acid (H_2SO_4) dropwise. In the second stage, the intermediate product was neutralized by potassium hexafluorophosphate (KPF_6) in water. Under the same conditions, compounds **143** and **145** were produced by reacting biphenyl (**2**) with thianthrene 5-oxide (**142**) and 2-chloro-9*H*-thioxanthen-9-one 10-oxide (**144**), respectively (Scheme 57).[156]

3.12 Reaction of biphenyl with phenol

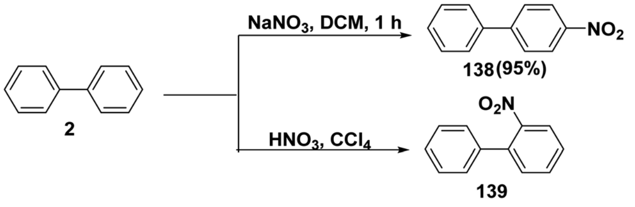
Terphenyl-3,5-diol **147** was synthesized *through* stirring phloroglucinol (**146**) with $AlCl_3$ in chlorobenzene (PhCl), followed by adding biphenyl (Scheme 58).[157]

3.13 Rection of biphenyl with sulfonanilide derivatives

The development of new methods for C–N bond synthesis is of great importance due to the prevalence nitrogenous compounds in numerous synthetic intermediates, natural products, pharmaceutical agents, and biologically active molecules. Sulfonanilides are a crucial class of synthetic scaffolds used in organic synthesis due to their potent electron-



Scheme 55 Formation of biphenyl saccharin derivatives.



Scheme 56 Nitration of biphenyl.

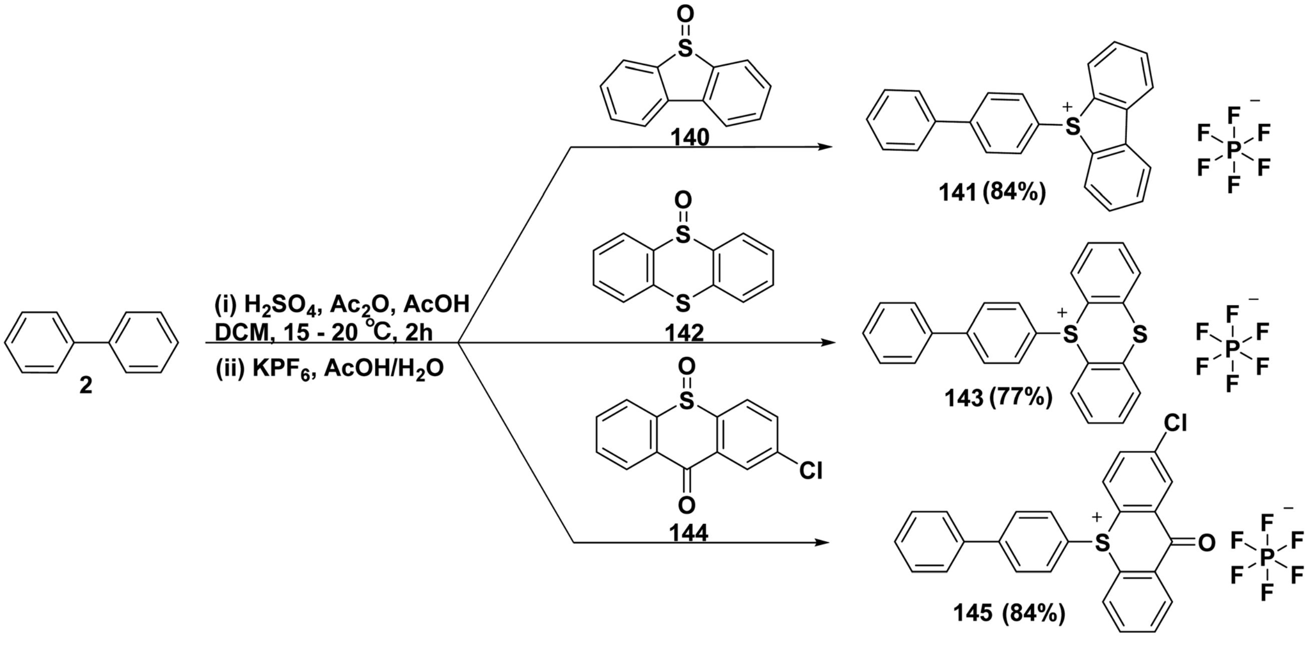
withdrawing effect of the connected sulfonyl group, in addition to, sulfonanilides have a special reactivity toward hypervalent iodine(III). Biphenyl sulfonanilide derivatives **149** were produced in wide range yields (33–87%) by adding *meta*-chloroperbenzoic acid (*m*CPBA) to a stirred solution of sulfonamide derivatives **148**, biphenyl **2**, and iodobenzene (PhI) in a mixture of hexafluoroisopropanol (HFIP) and DCM (Scheme 59).[158]

3.14 Amination reaction

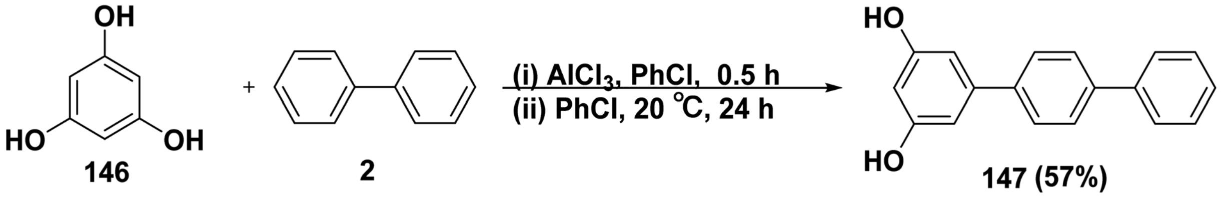
Primary aromatic amines are important building blocks for the formation of biologically active pharmaceutical and agrochemical chemicals, as well as organic functional materials like dyes and pigments. Electrochemical oxidation of biphenyl (**2**) in a solution of tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) and a mixture of CH_3CN and pyridine followed by adding piperidine afforded aminobiphenyl **150** (Scheme 60).[159] Analogously, under an oxygen atmosphere conditions, the reaction of ammonium carbamate ($H_2NCO_2^-H_4N^+$) as a nucleophile with biphenyl (**2**) as the arene coupling partner in the presence of a catalytic amount of mesityl acridinium salt, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and a mixture of DCE and H_2O afforded *para* and *ortho* aminobiphenyl products **150** and **151** respectively (Scheme 60).[160]

A proposed mechanism for 4-aminobiphenyl (**150**) synthesis involves the nucleophilic attack of pyridine on biphenyl (**2**), followed by one-electron oxidation to produce the intermediate ion **150A** which is underwent aromatization process to yield *N*-arylpyridinium ion intermediate **150B**. Then, piperidine is added to the 2-position of the *N*-arylpyridinium ion **150B**, accompanied by ring opening and imine hydrolysis (Scheme 61).[159]

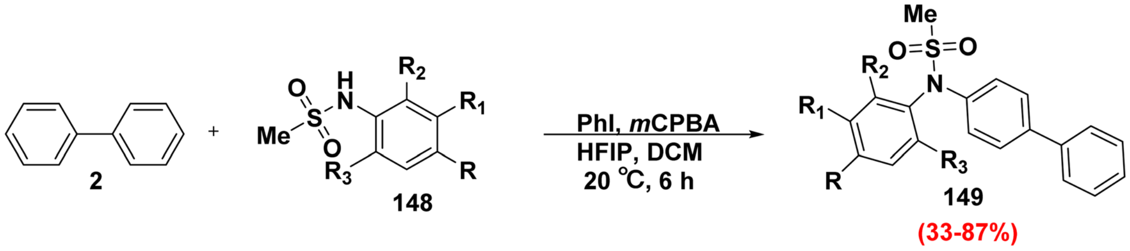
On the other hand, the proposed mechanism for the formation of aminobiphenyl **150** involves photoinduced electron transfer (PET) of biphenyl **2** in the presence of acridinium salt as a catalyst to an excited state photoredox radical (cat*) and biphenyl cation radical **150A**, which reacted with amine derivatives to yield distonic cation radical **150B**. Then, the



Scheme 57 Reaction of biphenyl with fused compounds.

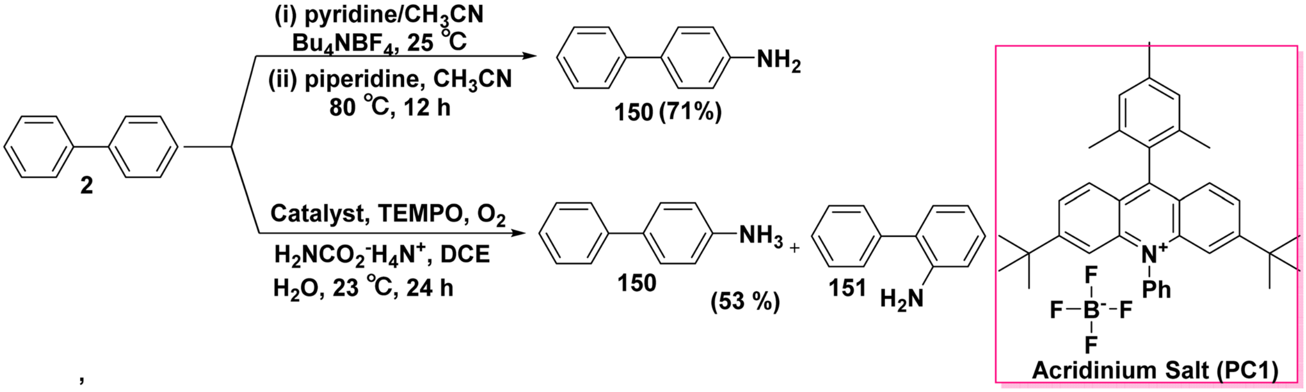


Scheme 58 Reaction of biphenyl with phenol.

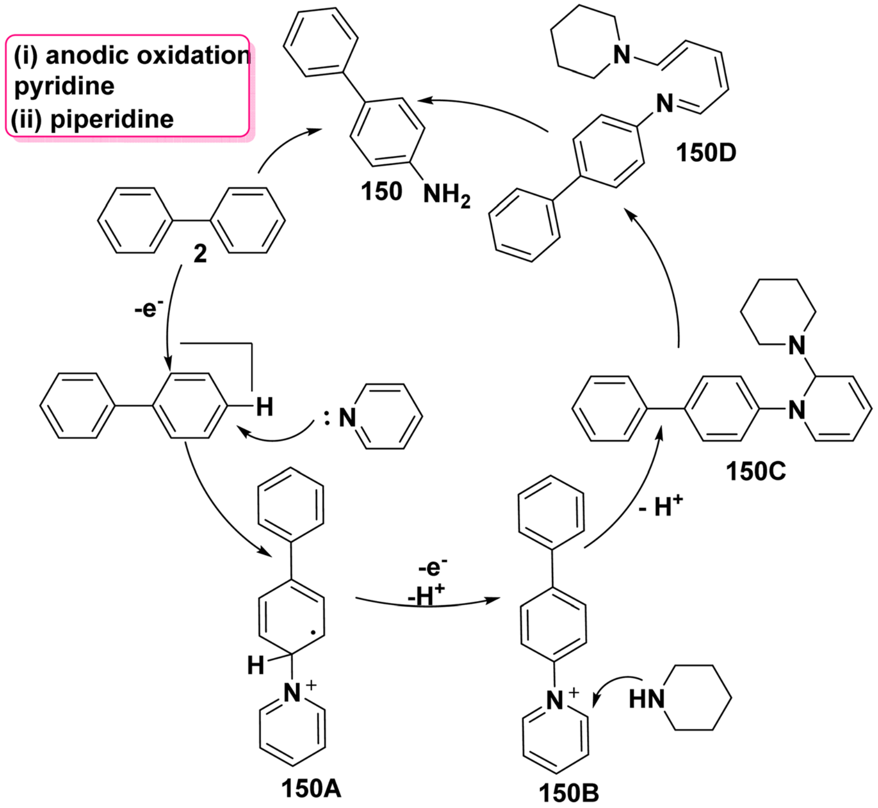


R= H, Me, F, Cl, Br, Et, i-Pr, CN, NO$_2$, Ph, *t*-Butyl; R$_1$= H, Me, Cl; R$_2$= H, Me, PhCO; R$_3$= H, Me

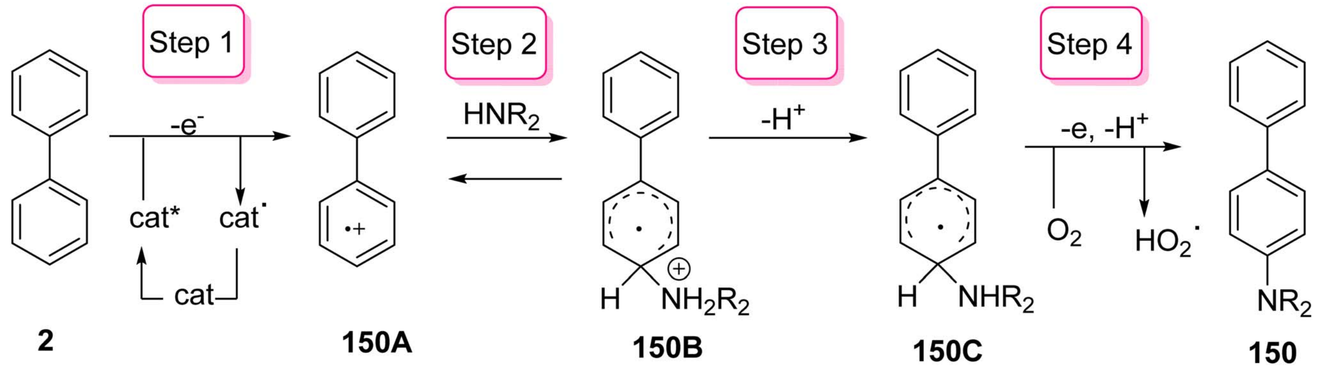
Scheme 59 Synthesis of biphenyl sulfonanilide derivatives.



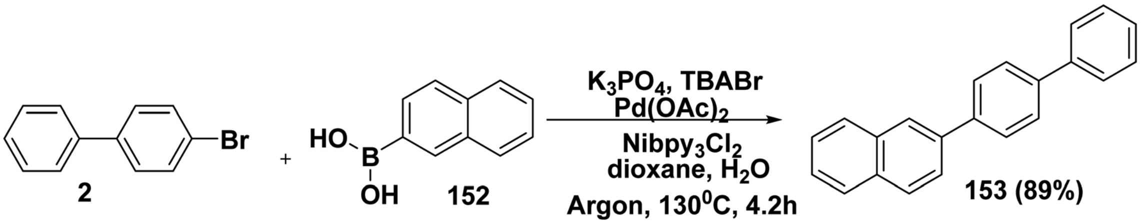
Scheme 60 Reaction of biphenyl with different amines.



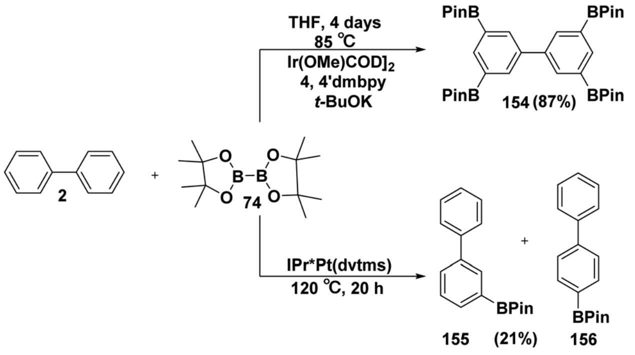
Scheme 61 The possible mechanism for aminobiphenyl synthesis.



Scheme 62 A postulated mechanism for the formation of aminobiphenyl.



Scheme 63 Synthesis of biphenyl naphthalene derivative.



Scheme 64 Borylation of biphenyl.

deprotonation reaction of **150B** furnished the radical intermediate **150C**, which led to production of aminobiphenyl **150** by oxidative aromatization (Scheme 62).[160]

3.15 Reaction of bromo-biphenyl with boronic acid

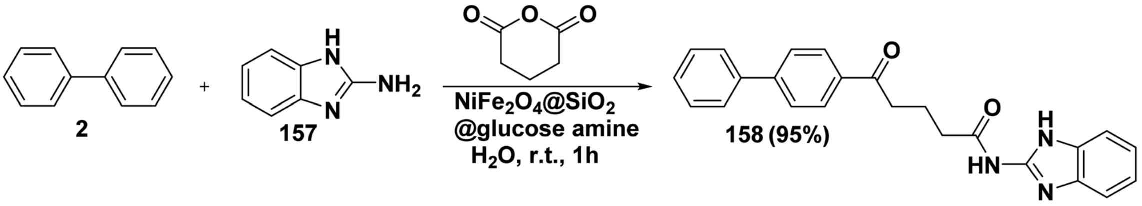
Kashid and coworkers[161] reported the synthesis of biphenyl-4-yl-naphthalene **153** *via* the treatment of bromo-biphenyl **2** with naphthalen-2-yl-boronic acid (**152**) in the presence of tetrabutylammonium bromide (TBABr), K_3PO_4, $Pd(OAc)_2$ and Ni complex in a mixture of dioxane and water (Scheme 63).

3.16 Reaction of biphenyl with bis(pinacol)diborane

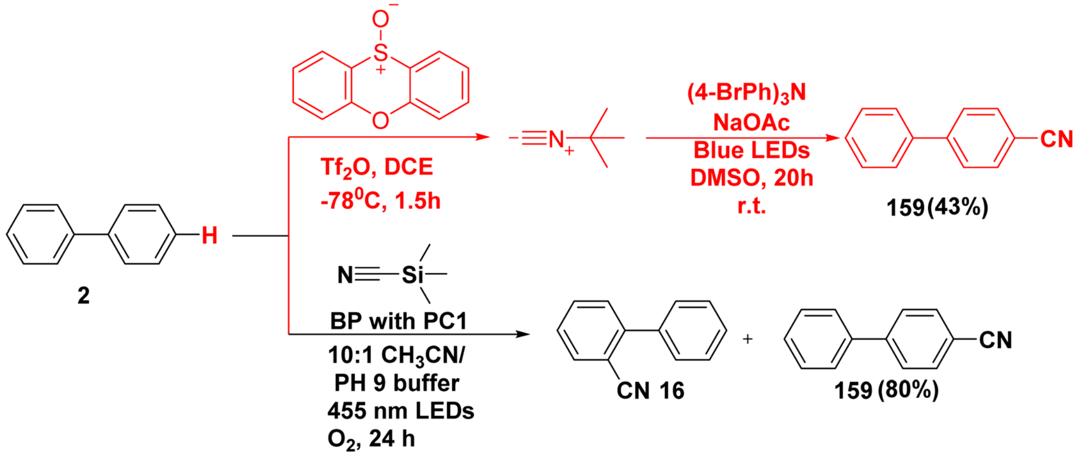
The borylation reaction of biphenyl (**2**) with B_2pin_2 **74** in the presence of potassium *t*-butoxide (*t*-BuOK) and (1,5-cyclooctadiene) (methoxy)iridium(I) dimer ([Ir(OMe)COD]$_2$) catalyst in THF with dimethylbipyridyl (dmbpy) afforded tetrakis(Bpin) biphenyl **154**.[162] On the other hand, refluxing of biphenyl 2 with B_2pin_2 **74** and a catalytic amount of *N*-heterocyclic carbene platinum(0) complex (IPr*Pt(dvtms)) gave two different oriented products namely, *meta*-(Bpin)biphenyl (**155**) and *para*-(Bpin) biphenyl (**156**) (Scheme 64).[163]

3.17 MCRs for the synthesis of biphenyl amide derivative

Multicomponent reaction (MCRs) of biphenyl **2**, 2-aminobenzoimidazole (**157**), and dihydro-2*H*-pyran-2,6-dione in the presence of 4-amino glucose functionalized silica propyl coated nickel ferrite nanoparticle ($NiFe_2O_4@SiO_2$-



Scheme 65 MCRs for the synthesis of biphenyl amide derivative.



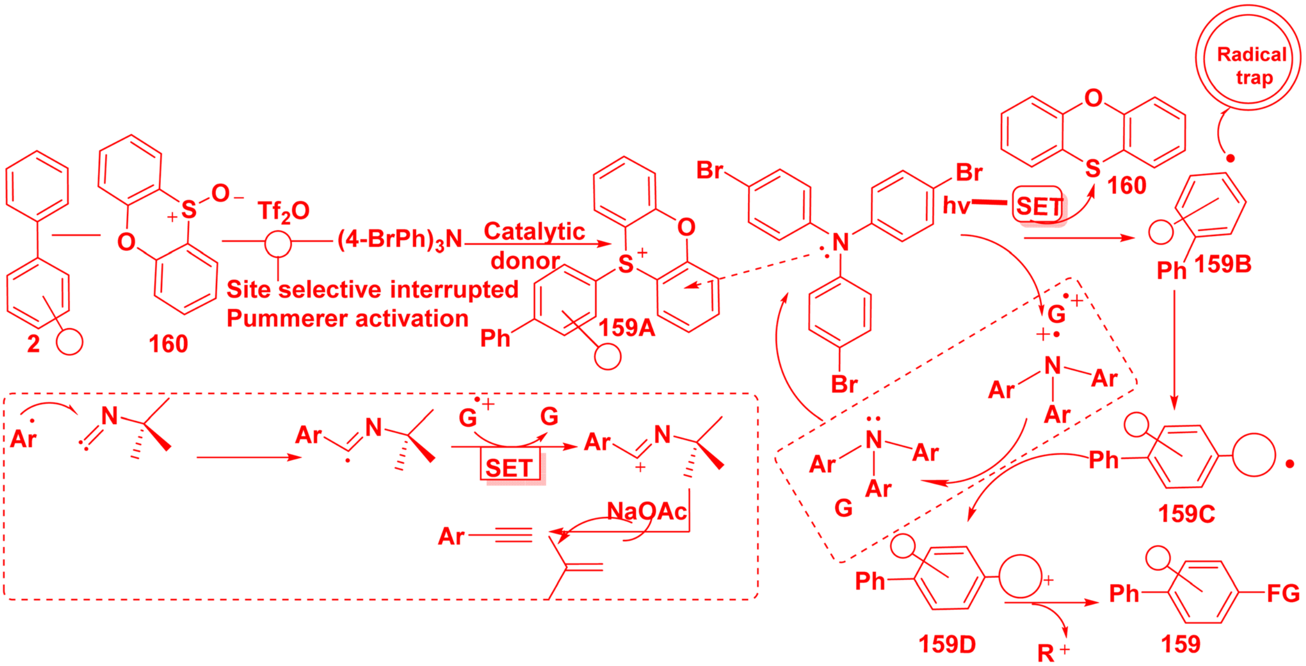
Scheme 66 Construction of biphenyl nitrile derivative.

propyl@glucosamine) catalyst and H_2O were stirred at room temperature for 1 h afforded biphenyl amide derivative **158** (Scheme 65).[164]

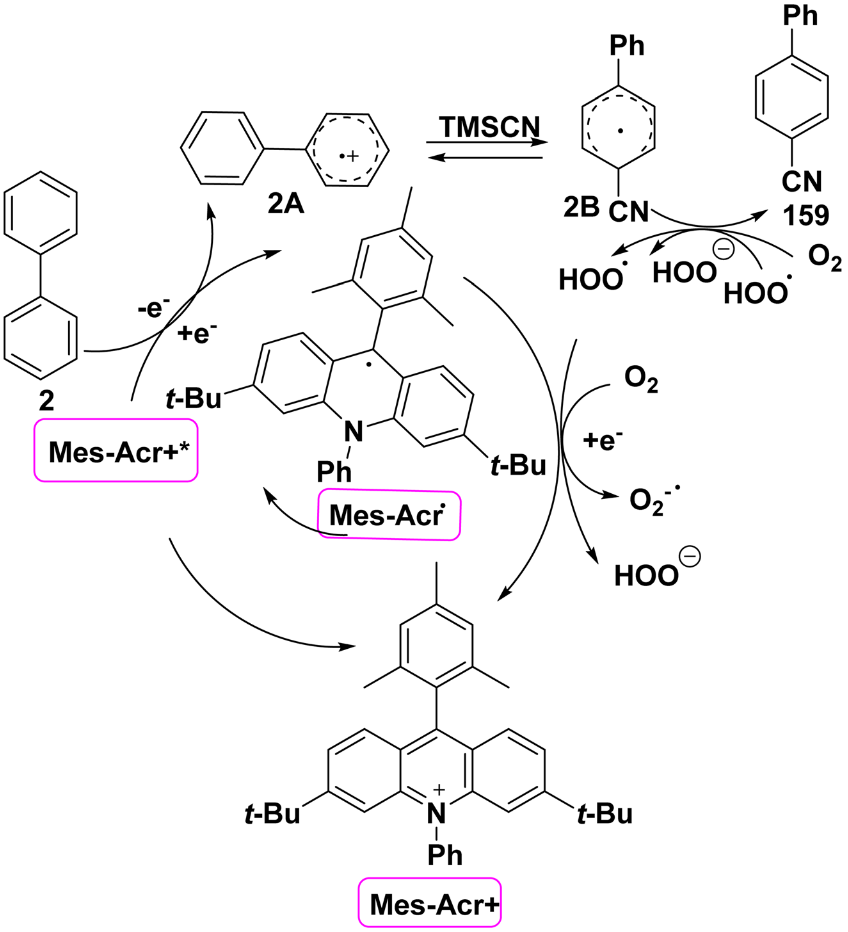
3.18 Cyanation reaction of biphenyl

One-pot arene C–H cyanation reaction of biphenyl **2**, phenoxathiine-10-oxide and *tert*-butyl isocyanide mediated by photoactive electron acceptor donor complex (EDA) such as tris(4-bromophenyl)amine in the presence of Tf_2O, DCE and basic additive (NaOAc) under blue-light irradiation produced biphenyl carbonitrile **159** (Scheme 66).[165] Whereby, phenylbenzonitrile derivatives **159** and **16** were obtained *through* the reaction of biphenyl (**2**) with trimethylsilyl cyanide (TMSCN) in the presence of acridinium photocatalyst and phosphate buffer in O_2-sparged CH_3CN.[166]

According to the proposed mechanism supporting the photochemical arene C–H functionalization method. Sulfonium salt **159A** is produced by site-selective addition of heteroaromatic sulfoxides **160** to unfunctionalized biphenyl **2** *via* interrupted Pummerer reactivity. The sulfonium salt **159A** label's electron-deficient heteroaromatic system can form photoactive electron donor–acceptor (EDA) complexes with triaryl amine donors. Blue-light irradiation of the EDA complex causes single-electron transfer (SET) from the amine donor to salt **159A**, which forms the radical cation of the electron donor and stimulates the synthesis of the aryl radical **159B.** The radical trap **159B** intercepting the aryl radical intermediate produces open shell species **159C**, which are prone to oxidation to yield cations **159D**, then the active electron-donor catalyst is regenerated. Finally, fragmentation of either *tert*-butyl isocyanide



Scheme 67 The postulated mechanism for biphenyl carbonitrile synthesis.



Scheme 68 The suggested mechanism for the synthesis of cyano biphenyl.

cation from **159D** yields the required C–H functionalization products **159** (Scheme 67).[165]

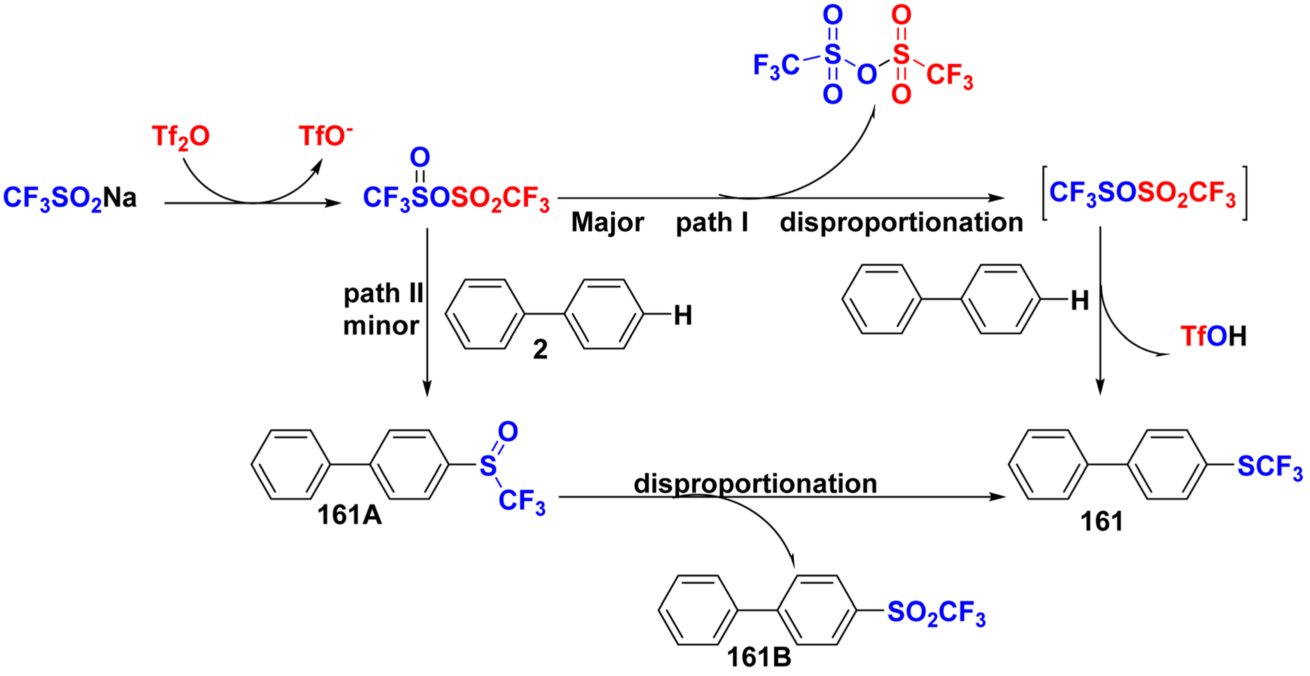
The proposed mechanism for phenylbenzonitrile synthesis **159** starts with photo irradiation of acridinium catalyst to its oxidizing excited state Mes-Ac^{+}*, followed by oxidation of biphenyl **2** to its radical cation **2A** to produce the reduced acridinium Mes-Ac radical. Then, cyanide engages with **2A** at *ortho* or *para* position. According to Fukuzumi cyclohexadienyl radical (**2B**) undergoes oxidation using molecular oxygen to give phenylbenzonitrile **159**. Finally, molecular oxygen or hydroperoxy radical oxidizes Mes-Ac radical to reproduce the catalyst (Scheme 68).[166]

3.19 Reaction of biphenyl with sulfonium salt

Several methods reported for the introduction of SCF_3 group into biphenyl derivative, for example stirring of sodium trifluoromethanesulfinate (CF_3SO_2Na) with biphenyl derivative **2** in trifluoromethanesulfonic anhydride (Tf_2O) and DCM at ambient conditions furnished [1,1′-biphenyl]-4-yl(trifluoromethyl)sulfane derivatives **161** in range yields (65–82%) (Scheme 69).[167]

The proposed mechanism for the synthesis of [1,1′-biphenyl]-4-yl(trifluoromethyl)sulfane **161** starts with the promotion of trifluoromethylthiolation using Tf_2O and CF_3SO_2Na to afford an intermediate sulfonate sulfinate anhydride

Scheme 69 Trifluoromethylthiolation of biphenyl derivatives **161**.

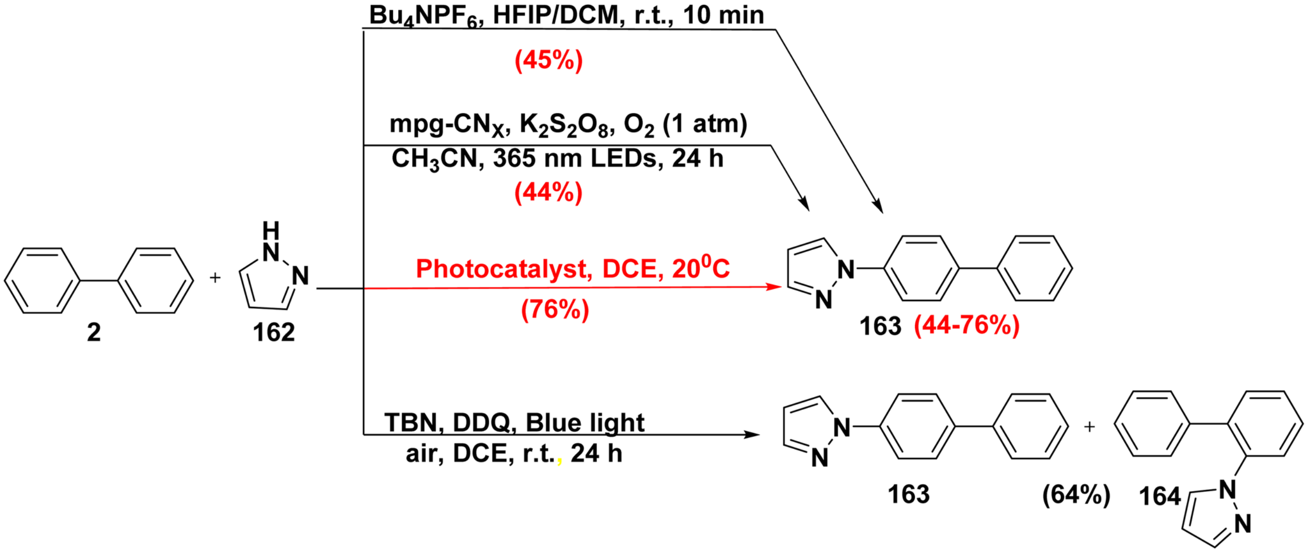


Scheme 70 Mechanism pathway for biphenyl SCF_3 synthesis.

through self-disproportionation. Two possible routes lead to the final product. In path I, half of sulfonate sulfinate anhydride intermediate was oxidized to form TfO-SO_2CF_3 and another part is reduced to form $CF_3SOSO_2CF_3$. Finally, the transfer of trifluoromethylthiolation from $CF_3SOSO_2CF_3$ to biphenyl (**2**) to afford SCF_3 product **161** (Scheme 70).[167]

3.20 Reaction of biphenyl with azole

N-Aryl azoles are a key motif in a number of biologically active compounds used in medicinal chemistry and crop protection science. The reaction of biphenyl (**2**) with parent pyrazole **162** in a mixture of HFIP and DCM,[168] or in the presence of dipotassium peroxodisulfate ($K_2S_2O_8$) and CH_3CN under O_2 atmosphere produced 4′-(1*H*-pyrazol-1-yl)-[1,1′-biphenyl]-4-ylium (**163**).[169] Whereby, Sen *et al.*[170] reported oxidative azolation of unactivated biphenyl derivatives *via* using phenalenyl-based organic Lewis acid as powerful photooxidant in DCE to afford compound **163**. While, under blue light irradiation, the photocatalytic oxidation of biphenyl **2** with azole **162** using DDQ catalyst and *tert*-butyl nitrite (TBN) yielded 1*H*-pyrazol-biphenyl-4-ylium **163** and 1-([1,1′-biphenyl]-2-yl)-1*H*-pyrazole (**164**) (Scheme 71).[171]



Scheme 71 Synthesis of biphenyl pyrazole derivative.

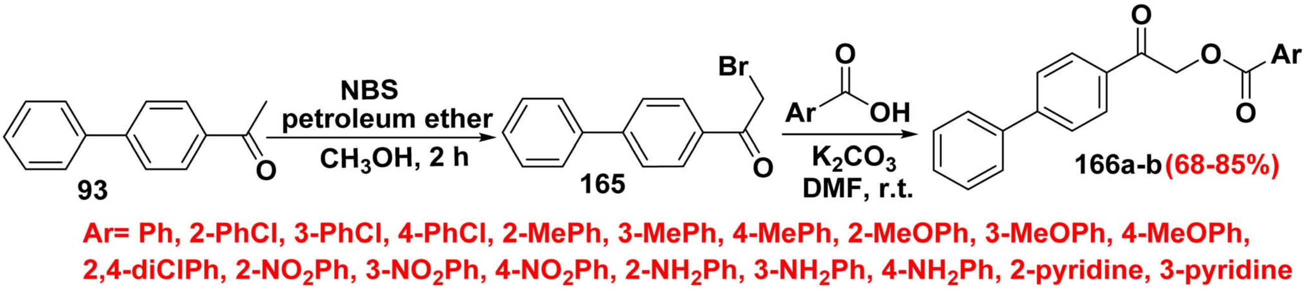
3.21 Reaction of related biphenyl

The anti-tyrosinase properties of biphenyl ester makes it effective for treating dermatological conditions and for cosmetic lightening. A series of [1,1′-biphenyl]-4-yl-oxoethylbenzoate derivatives **166** were produced *through* two stages. First step involving a mixture of NBS, and 1-([1,1′-biphenyl]-4-yl)ethan-1-one (**93**) was refluxed in a mixture of petroleum ether (PET) and methanol for 2 h afforded 1-([1,1′-biphenyl]-4-yl)-2-bromoethan-1-one (**165**). In the second stage, compound **165** was reacted with different phenyl carboxylic acid derivatives in the presence of K_2CO_3 in DMF at room temperature led to formation of 2-([1,1′-biphenyl]-4-yl)-2-oxoethyl benzoate derivatives **166a**. Biphenyl-4-yl-oxoethyl-pyridine carboxylate derivatives **166b** were obtained by stirring of 1-([1,1′-biphenyl]-4-yl)-2-bromoethan-1-one (**165**) with pyridine carboxylic acid derivatives in DMF containing anhydrous K_2CO_3 (Scheme 72).[10]

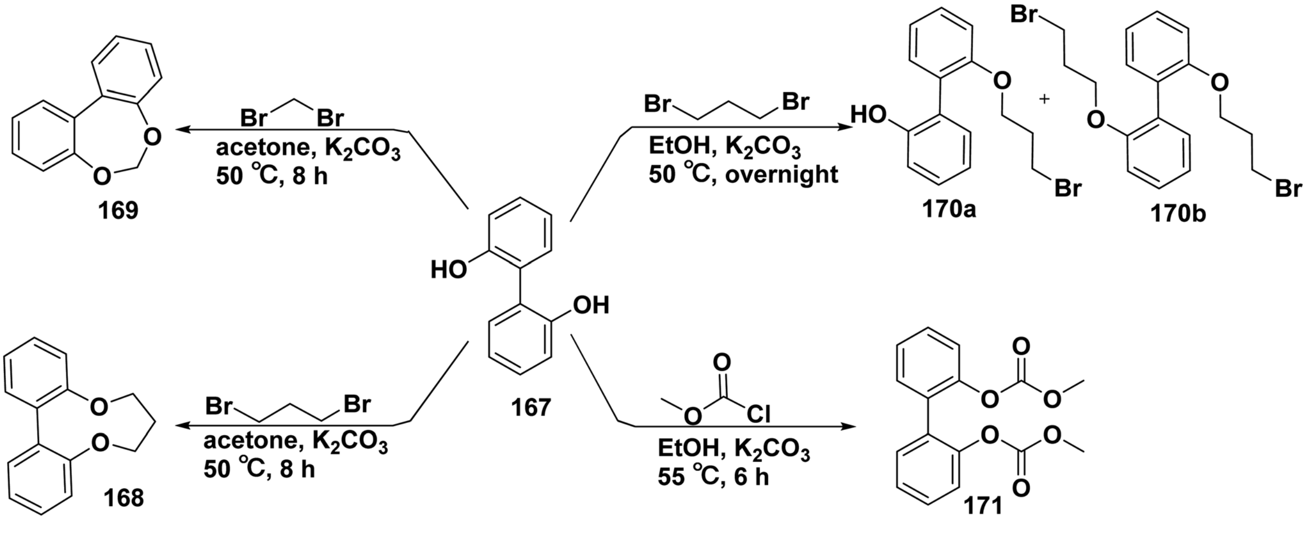
Compounds containing biphenyl underwent electrophilic substitution to aromatic substrates. Dihydro-6*H*-dibenzo[1,5] dioxonine **168** was produced by refluxing biphenyl-diol **167** with dibromopropane in acetone containing catalytic amount of anhydrous K_2CO_3. Whereas, under the same condition, refluxing of biphenyl-2,2′-diol (**167**) with dibromomethane afforded dibenzo[1,3]dioxepine **169**. Furthermore, treatment of biphenyl-2,2′-diol (**167**) with 1,3-dibromopropane and K_2CO_3 in EtOH gave a mixture of 2′-(3-bromopropoxy)-[biphenyl]-2-ol **170a** and bis(3-bromopropoxy)biphenyl **170b.** In the same manner, a mixture of biphenyl-diol derivative **167** and methyl carbonochloridate in EtOH afforded biphenyl derivative **171.** It is worthy to mention that *o*-alkylated biphenyl derivatives exhibit excellent scavenging of superoxide anion radical and β-glucuronidase inhibition activity (Scheme 73).[12]

According to Suzuki–Miyaura and Hantazch reactions, treatment of 4′-formylbiphenyl (**172**) with active methylene namely acetone derivatives or substituted pyrazole derivatives and ammonium hydroxide (NH_4OH) gave tricyclic ring of 4-biphenyl-1,4-dihydropyridine derivatives **173** and pentacyclic ring of [4-biphenyl]-1,7-dihydrodipyrazolo[3,4-*b*]pyridine derivatives **175**, respectively. Then, oxidation of **173** and **175** with nitric acid (HNO_3) afforded 4-(biphenyl-4-yl)-pyridine derivatives **174** and 4-biphenyl-dipyrazolo[3,4-*b*]pyridine derivatives **176**, respectively which are used as anti-microbial resistance, antibacterial, antifungal and anticancer (Scheme 74).[172]

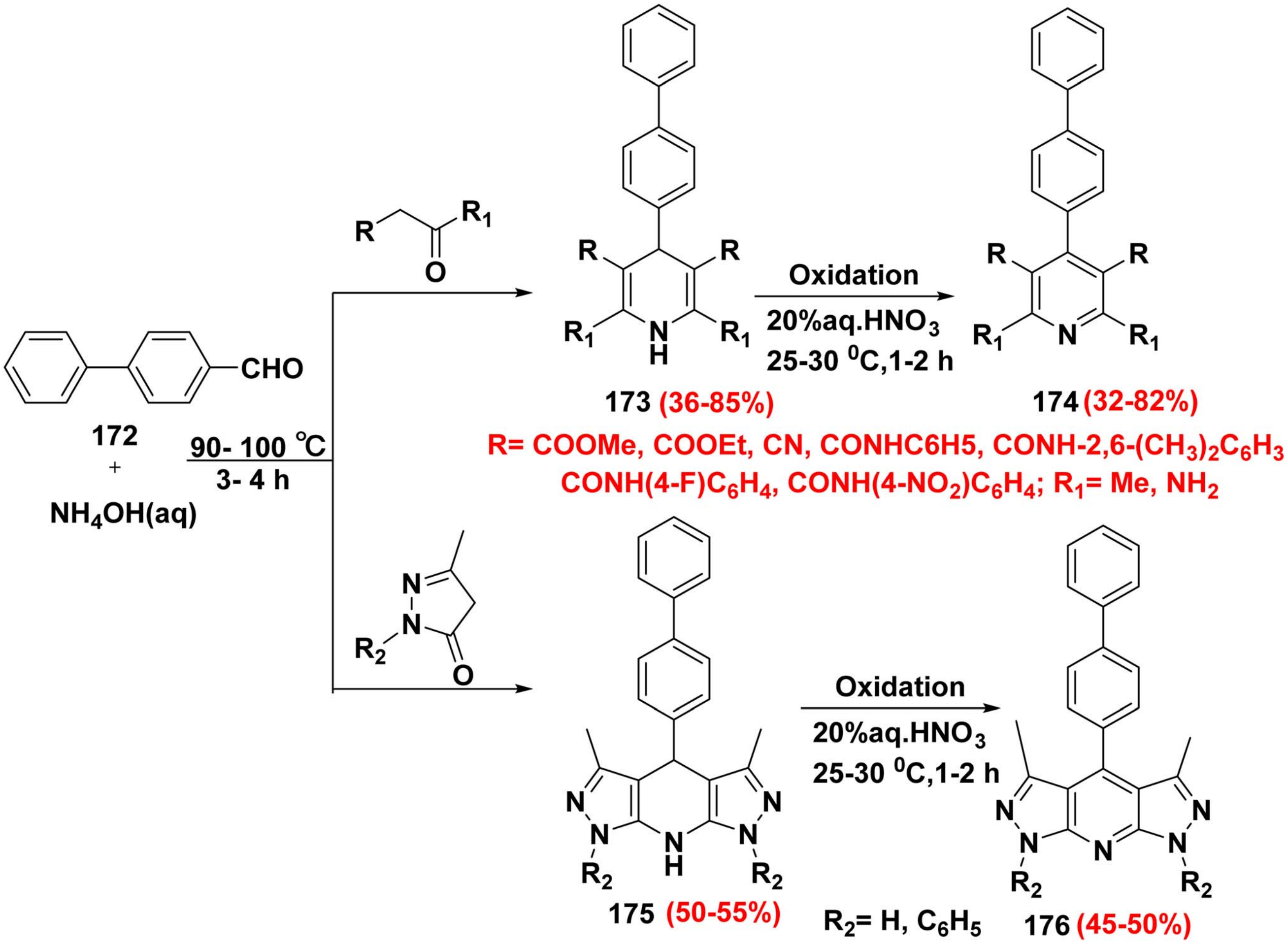
Reduction of biphenyl dicarboxylic acid **177** with lithium aluminum hydride ($LiAlH_4$) afforded biphenyl diol **178**, followed by bromination reaction with phosphorus tribromide (PBr_3) produced biphenyl dibromide **179.** Then, compound **179** underwent cyclization reaction to produce azepine derivative **180.** Finally, dealkylation of compound **180** furnished biphenyl diazepine derivative **181** (Scheme 75).[173]



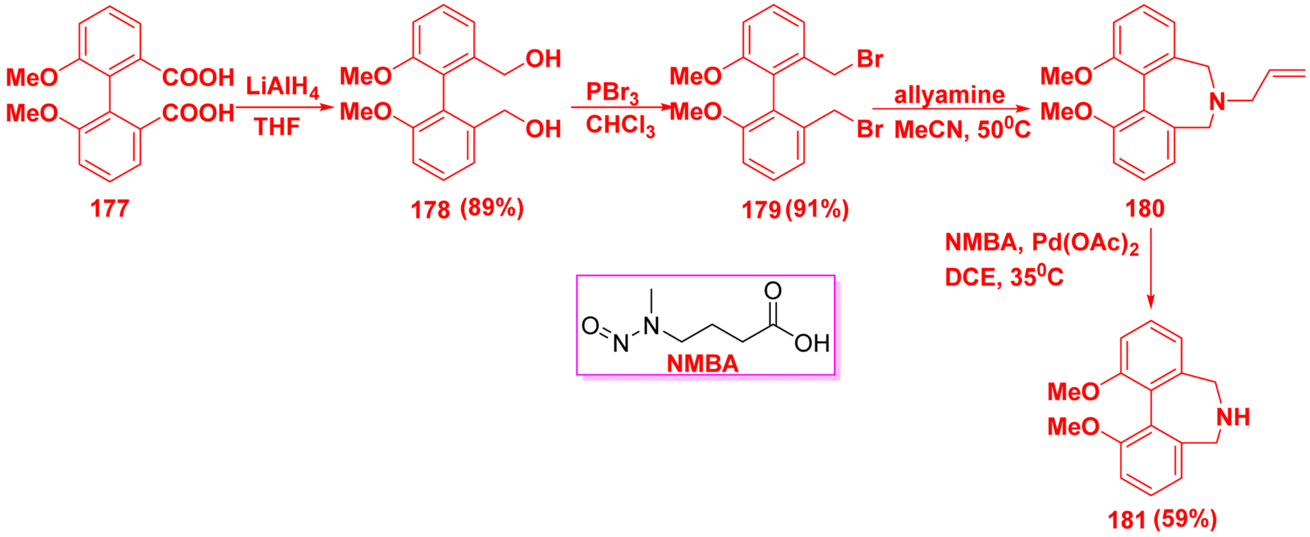
Scheme 72 Formation of biphenyl ester.



Scheme 73 Reaction of biphenyl diol with various halo-derivatives.



Scheme 74 Suzuki–Miyaura and Hantazch reaction for preparation of annulated pyridine systems.



Scheme 75 Synthesis of biphenyl diazepine derivative **181**.

4. Biphenyl atropisomerism

As reflected in the last few years, the crest of a sizable wave in the development of new ligands in drug discovery and medicinal chemistry, the recent literature addressing atropisomerism has been hard to miss, as biphenyl atropisomers have received considerable attention as chiral building blocks for chiral catalysts in asymmetric syntheses field. The first experimentally

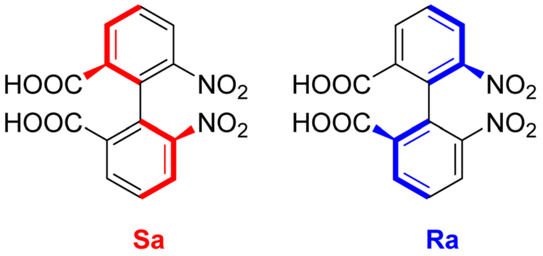


Fig. 3 Atropisomerism of biphenyl compound **2**.

described molecule with atropisomerism phenomenon was 6,6′-dinitro-2,2′-diphenic acid by Christie and Kenner in 1922.[174,175] As the inclusion of the biphenyl isosteres represent 4.3% of all known drugs.[176] Atropisomerism is defined as stereochemistry arising from highly hindered bond rotation that creates a chiral axis. The rotational barrier of an atropisomeric molecule is sufficiently high to allow for isolation of the individual conformers. Whereby, atropisomeric pharmaceutical ingredients can differ in their pharmacokinetic and selectivity properties towards a hitting target (Fig. 3).[177–183]

Table 1 Examples of a vast array of biologically active molecules towards some diseases

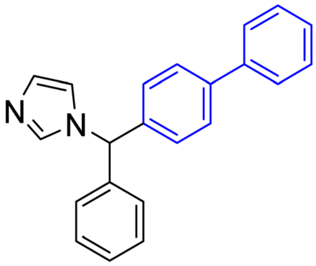
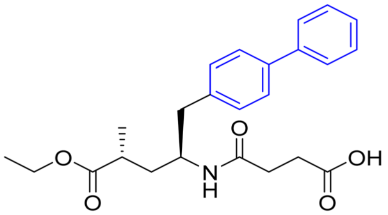
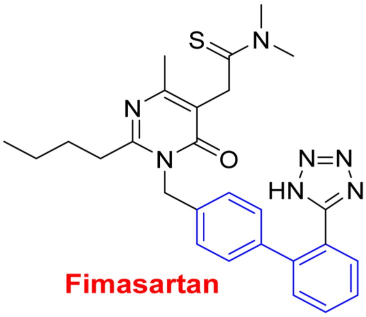
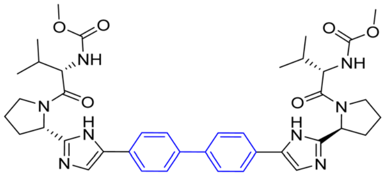
Structure	Activities	Action mechanism & references
 **Bifonazole**	Antibacterial: (*Staphylococcus aureus* and *Salmonella* spp.) Therapy for dermatomycoses Antifungal: (*Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*)[184,185]	The inducing of chlorine atoms on the biphenyl ring connected to the imidazole ring led to alterations in the physico-chemical properties, therefore these factors can affect the affinity of molecules for the iron of the heme binding site.[184] Addition of biphenyl moiety improves its antifungal selectivity, potency and bioisosteric effects[185]
 **Sacubitril**	Anti-tubercular: (dormant tuberculosis) Treatment of heart failure with a combination of valsartan Neprilysin inhibitor[186,187]	Due to the presence of substituted biphenyl increases the polarity of the heterocyclic skeleton which might be the reason for high anti-tubercular (anti-TB) activities *via* interacting with the MurB inhibitors[186]
 **Fimasartan**	Antihypertensive Anti-inflammatory[188]	Since inhibition of angiotensin II type 1 (AT1) receptor reduces chronic inflammation associated with hypertension, we evaluated the anti-inflammatory potential and the underlying mechanism of fimasartan[188]
 **Daclatasvir**	Antiviral Treatment selections for hepatitis C virus[189,190]	As a result of sp^2 hybridization of CNTs between the drug and target protein sequence, leads to improving the fluorescence reactivity. Because the conjugated system of biphenyl and the presence of Cs/CNT can increase the electroactive surface area of the electrode, leading to an increase in the number of structural flaws[189]

Table 1 (*Contd.*)

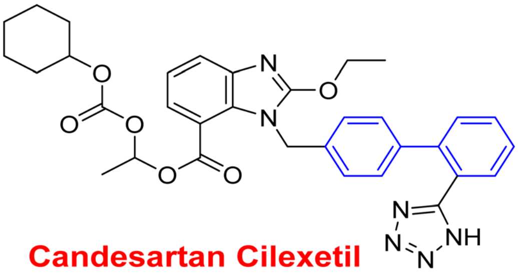
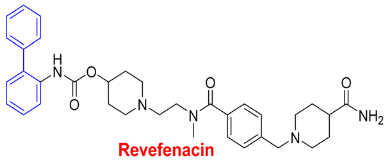
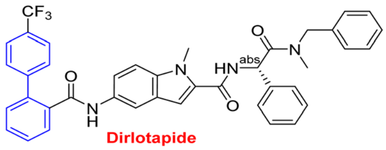
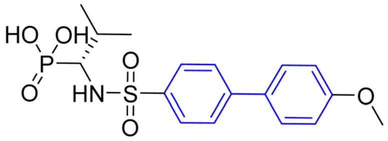
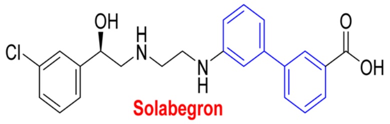
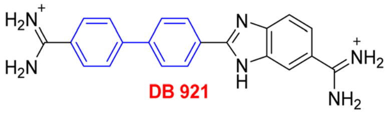
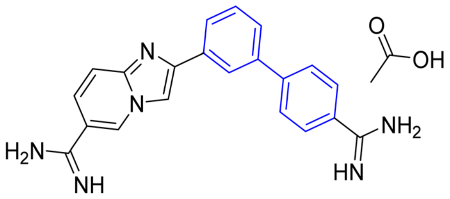
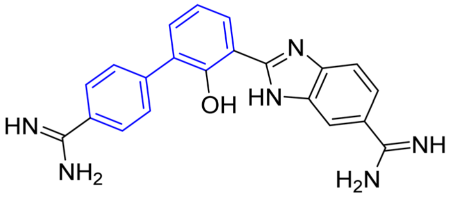
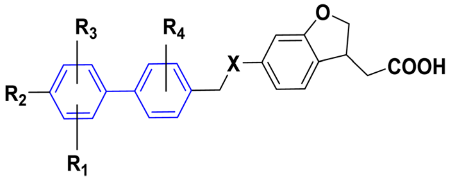
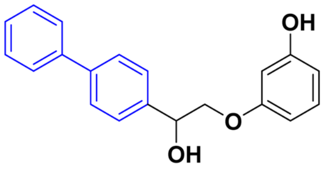
Structure	Activities	Action mechanism & references
	Antihypertensive Active for the AT1 receptor[191–193]	Biphenyl acts as lipophilic moiety in candesartan drug; whereas the candesartan is a selective nonpeptide angiotensin II type 1 (AT1) receptor antagonist which reduces blood pressure effectively.[191] Sartans incorporates with membrane receptor in lipid bilayers causing highly transportation possibility of sartans *via* the receptor[192]
	Lung-selective muscarinic cholinergic receptor (mAChR) antagonist Nebulized inhalation solution to produce long-acting bronchodilation[194]	Biphenyl moiety enhances long-lasting and potency of mediated antagonism of mAChR-causing contraction of human bronchial tissues[194]
	Microsomal triglyceride transfer protein inhibitor Treatment for human dyslipidemias[195]	Biphenyl scaffold for nesting
	Anti-human neutrophil collagenase (MMP-8)[196]	Biphenyl residues hit the active site close the catalytic zinc ion that would consequently inhibit the collagenase activity[196]
	β_3-Adrenergic receptor agonist Evokes bladder relaxation Overactive urinary bladder Increases micturition reflex threshold in the dogs[197–199]	RHS of biphenyl ring affords potent human β3-AR agonists with a chlorophenyl ring on the LHS side[197]
	Analysis of water mediated binding in the context of a DNA complex Promising agent against parasites Change in AT sequences with destruction of the kinetoplast and cell death[200]	The interactions of the molecules containing of biphenyl with DNA AT sites increasing DNase I footprinting depending on increasing conjugation process which enhancing biosensor-surface plasmon resonance, circular dichroism microcalorimetry, and isothermal titration[200]
	Antiprotozoal Anti-trypanosomal[201]	Biphenyl scaffold for nesting

Table 1 (*Contd.*)

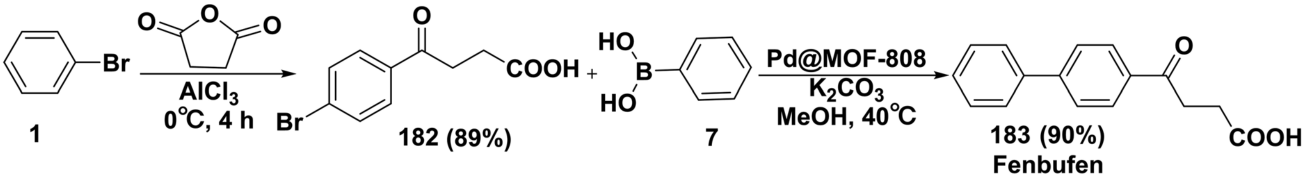
Structure	Activities	Action mechanism & references
	Anti-protozoan[202]	Biphenyl scaffold for nesting
 X= O, CH_2, S, NH, N R_1, R_2, R_3, R_4= H, F, Cl, Br, CN	Treating diabetes mellitus[203]	Biphenyl scaffold for nesting
	Treatment CNs impairments involving major depressive disorder[204]	Biphenyl-based NMDA negative allosteric modulator (NAM) has low affinity for the human ether-a-go-go-related gene ion channel (hERG) and the dynamics calculations suggest a various binding mode (ifenprodil-like) compared to another biaryl-based NMDA NAM EVT-101 [204]

5. Applications

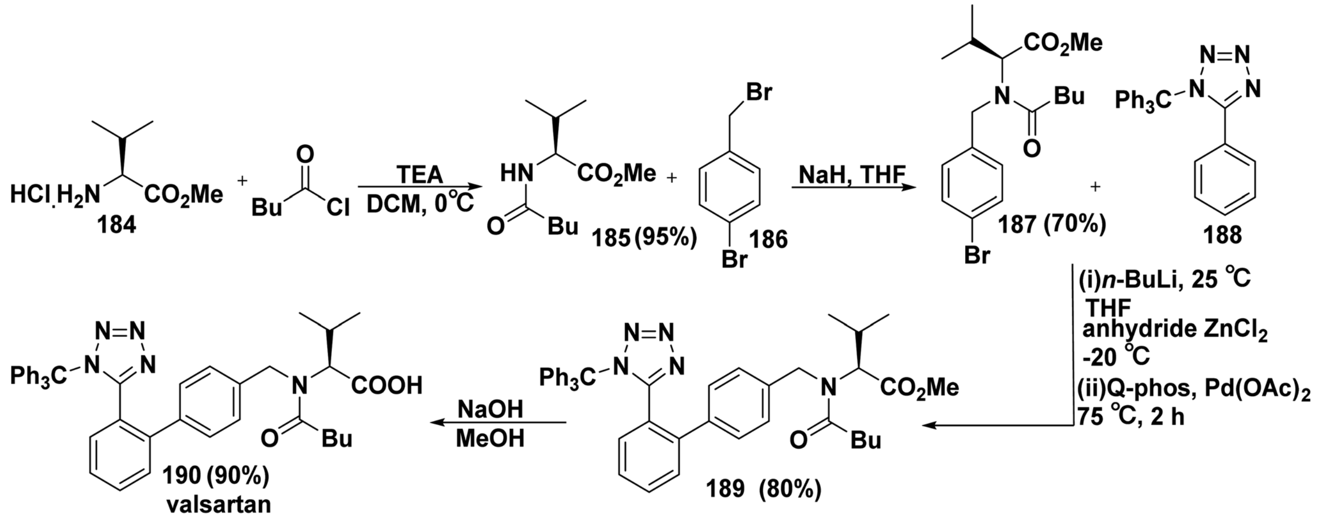
Fenbufen is a non-steroidal anti-inflammatory, antipyretic effects (NSAIDs) and analgesic drug with less irritative effect on gastrointestinal tract (Table 1). The synthesis of fenbufen (**183**) was performed in two steps. First, Friedel–Crafts acylation reaction of bromobenzene (**1**) and succinic anhydride catalyzed by $AlCl_3$ afforded 1-(4-bromophenyl)-4-hydroperoxybutan-1-one (**182**), then coupling the product **182** with phenyl boronic acid (**7**) (Scheme 76).[15]

The trade name for valsartan is Diovan, valsartan belongs to the non-peptide angiotensin (II) receptor class and is used to treat cardiovascular disorders that are connected to hypertension. Synthesis of valsartan (**190**) began with coupling reaction of L-valine methyl ester hydrochloride (**184**) with valeryl chloride in the presence of triethylamine (Et_3N) in DCM to produce methyl *N*-pentanoyl-L-valinate (**185**). N-Protection of compound (**185**) with 1-bromo-4-(bromomethyl) benzene (**186**) in the presence of sodium hydride (NaH) in THF furnished methyl *N*-(4-bromobenzyl)-*N*-pentanoyl-D-valinate (**187**). Then, organozinc compound was synthesized *via o*-metalation of 5-phenyl-1-trityl-1*H*-tetrazole (**188**) with *n*-butyllithium (*n*-BuLi), followed by adding zinc chloride ($ZnCl_2$). Negishi coupling reaction of organozinc chloride compound with aryl bromide **187** in the presence of palladium acetate ($Pd(OAc)_2$) with 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene (Q-phos) ligand in THF afforded *N*-pentanoyl-*N*-(2′-(1-trityl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)-valinate (**189**). Finally, valsartan **190** was produced *via* hydrolysis of ester **189** with sodium hydroxide (Scheme 77).[205]

The synthesis of 2-fluoro-[1,1′-biphenyl]-4-yl-propanoic acid which trade name mark (flurbiprofen) **197** has been achieved in subsequent steps. First step involving the reaction of 2,4-difluoronitrobenzene (**191**) with diethyl 2-methylmalonate (**192**) in the presence of NaH to afford diethyl 2-(3-fluoro-4-nitrophenyl)-2-methylmalonate (**193**), followed by catalytic hydrogenation of compound **193** to 4-amino-3-fluorophenyl-2-methylmalonate **194**. After that, diazotization of the amino

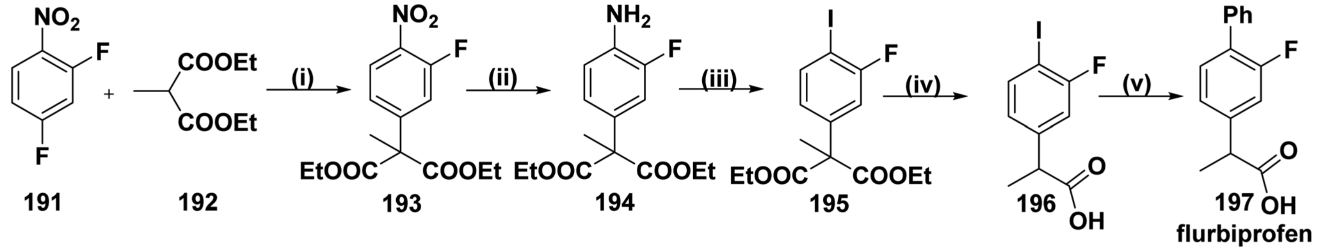


Scheme 76 Synthetic strategy for the preparation of fenbufen.

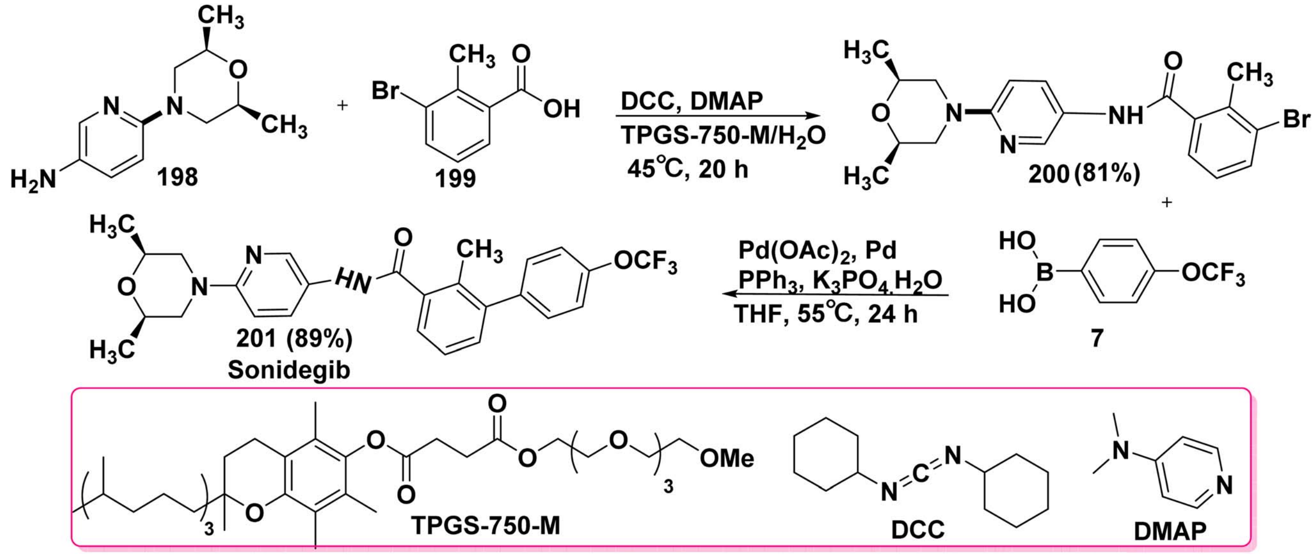


Scheme 77 Negishi coupling reaction for valsartan synthesis.

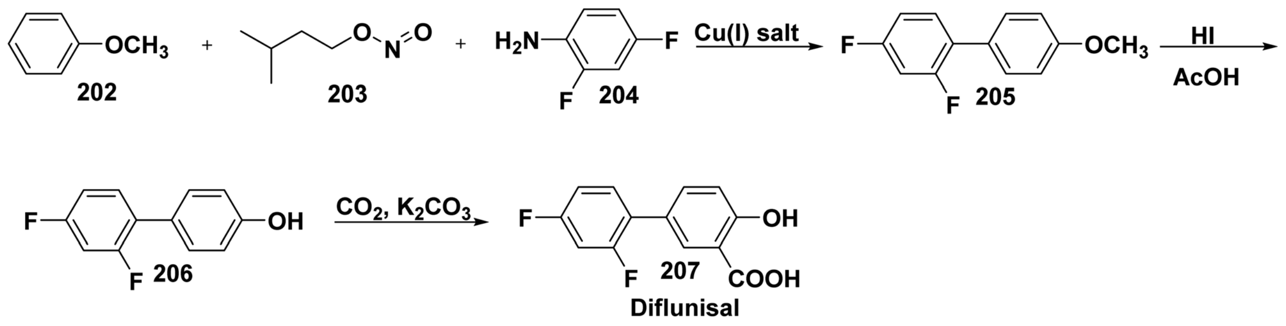
compound **194** into corresponding diazonium salt which then reacted with potassium iodide (KI) to produce diethyl 2-(3-fluoro-4-iodophenyl)-2-methylmalonate (**195**). Compound **195** underwent hydrolysis and decarboxylation reaction to yield 2-(3-fluoro-4-iodophenyl)propanoic acid (**196**). Finally, SMC reaction of 3-fluoro-4-iodophenylpropanoic acid **196** with phenylboronic



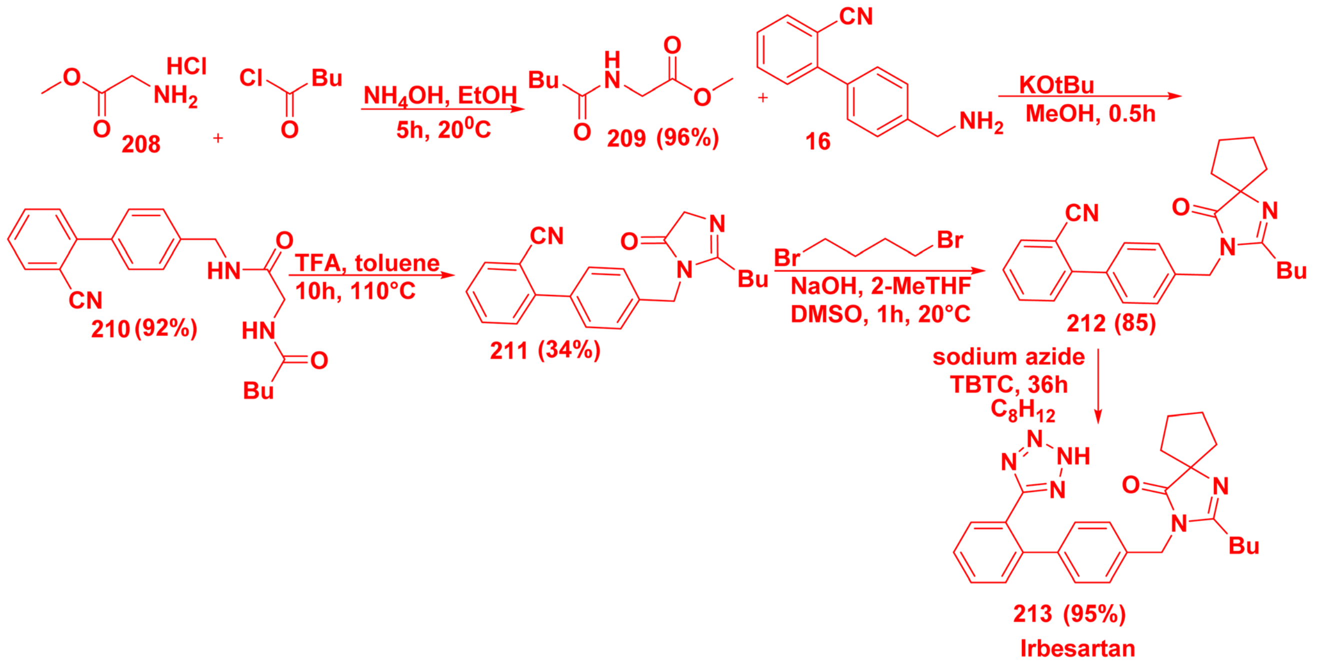
Scheme 78 Synthesis of flurbiprofen. Reagents and conditions: (i) NaH, DMSO; (ii) H_2, Pd/C; (iii) 1. $NaNO_2$, HCl, 0 °C; 2. KI; (iv) NaOH, EtOH–H_2O, 100 °C, 57% (four steps); (v) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME-H_2O, 80 °C.



Scheme 79 SMC reaction for biphenyl synthesis.



Scheme 80 MCRs for the synthesis of diflunisal.



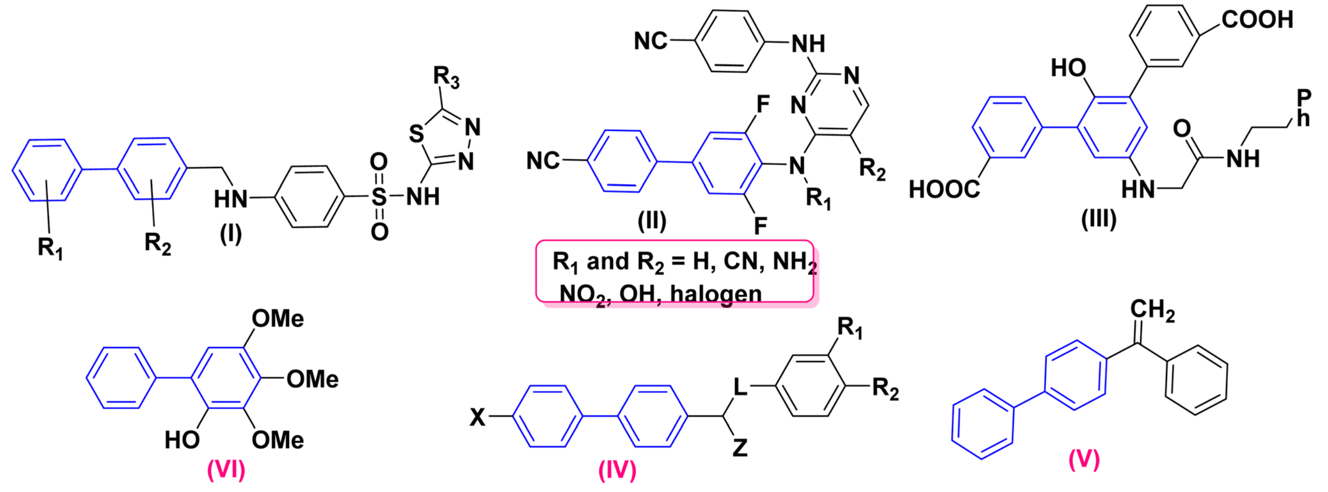
Scheme 81 Synthetic strategies for irbesartan synthesis.

acid in the presence of a catalytic amount of $Pd(PPh_3)_4$, 1,2-dimethoxyethane and Na_2CO_3 produced flurbiprofen (**197**). Flurbiprofen, a prostaglandin biosynthesis inhibitor, is extensively used as potent anti-inflammatory, antifungal, antipyretic, analgesic, in addition to, treatment Alzheimer's disease (AD) (Scheme 78).[206,207]

Sonidegib which is marketed under Odomzo trade name is a Hedgehog pathway inhibitor. Sonidegib is effective against skin cancer, tumor, and medulloblastoma. Synthesis of sonidegib **201** started with the coupling of dimethylmorpholinopyridin-3-amine **198** with 3-bromo-2-methylbenzoic acid (**199**) in the presence of coupling agent such as dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino) pyridine (DMAP) and TPGS-750-M-H_2O as a surfactant to afford 3-bromo-(2,6-dimethylmorpholino)pyridin-3-yl)-2-methylbenzamide **200**. Then, SMC reaction of compound **200** with (4-(trifluoromethoxy)phenyl)boronic acid (**7**) in the presence of $Pd(OAc)_2$, PPh_3, Pd, K_3PO_4 and THF (Scheme 79).[208]

One-pot three component synthesis of 4-(2,4-difluorophenyl) anisole (**205**) *through* stirring a mixture of anisole (**202**), isoamyl nitrite (**203**), and 2,4-difluoroaniline (**204**) in the presence of cupper(i)salt. Demethylation reaction of difluorophenylanisole (**205**) with hydrogen iodide (HI) afforded 4-(2,4-difluorophenyl)-phenol (**206**). Kolbe–Schmitt phenol carboxylation of **206** with carbon dioxide (CO_2) in the presence of K_2CO_3 afforded diflunisal (**207**). Whereby, diflunisal (**207**) has anti-inflammatory, anti-fever, and analgesic properties. In cases of osteoarthritis and rheumatoid arthritis, it is utilized to relief pain (Scheme 80).[209,210]

Reaction of glycine methylester **208** with pentanoyl chloride in TEA produced methyl pentanoylglycinate (**209**). Compound **209** reacted with biphenylcarbonitrile derivative **16** in the presence of KO*t*-Bu afforded biphenylamide derivative **210**. Then, cyclization reaction of compound **210** in the presence of TFA afforded imidazobiphenyl carbonitrile derivative **211**. Alkylation reaction of compound **211** with dihaloalkane



R_1 and R_2 = H, CN, NH_2 NO_2, OH, halogen

Fig. 4 Some biologically active biphenyl derivatives.

furnished spirocyclic compound **212**.[211] Finally, irbesartan (**213**) was synthesized *via* reaction of key intermediate **212** with sodium azide, tributyltin chloride (TBTC) and dimethoxycyclohexadiene **213**. In pancreatic cancer, irbesartan overcomes gemcitabine resistance by decreasing iron metabolism and stemness *via* inhibition of the Hippo/YAP1/c-Jun axis.[212] In addition, irbesartan lowers cholesterol *via* inhibiting the expression of the low-density lipoprotein receptor. Furthermore, irbesartan is used for the treatment of hypertension and type 2 diabetes (Scheme 81).[213]

6. Patents

Biphenyl sulfothiadiazole derivatives (**I**) are used in clinical immunotherapy of tumour patients and act as a PD1/PDL1 inhibitor.[214] Whereas, biphenyl biaryl pyrimidine derivatives (**II**) are utilized to treat AIDS and are expected to be anti-HIV drugs.[215] 5′-((2-((3,4-Dimethoxyphenethyl)amino)-2-oxoethyl)amino)-2′-hydroxy-[1,1′:3′,1′′-biphenyl]-3,3′′-dicarboxylic acid (**III**) is developed to treat malignant tumours and as a transcription factor.[216] 3-(2-([1,1′-Biphenyl]-4-yl)-2-hydroxyethoxy)phenol (**IV**) is a therapy for a disorder or disease accompanied by high activation of the NMDA receptor.[217] 4-(1-Substituted phenylvinyl)biphenyl derivatives (**V**) can be used for the manufacture of protein kinase, tubulin inhibitors and drugs for colon and breast cancer.[218] 2-[(3,5-Difluoro-3′-methoxy-1,1′-biphenyl-4-yl)amino]nicotinic acid is used to treat psoriasis disease.[219] (2*E*)-[2-(Biphenyl)imidazo[1,2-*a*]pyrimidine-3-yl](4-nitrophenyl)-prop-2-en-1-one, 2-(biphenyl)imidazo[1,2-*a*]pyrimidine-3-carbaldehyde and 6-[2-(biphenyl)imidazo[1,2-*a*]pyrimidine-3-yl]-4-nitro pyrimidine-2(1*H*)-one exhibit promising antitumor activity by reducing the level of liver function enzyme near the normal level after damaged by CCl_4.[220] Whereby, trimethoxy-[1,1′-biphenyl]-2-ol (VI) displays anti-inflammatory activity[221] (Fig. 4).

7. Conclusion

With the continuously increasing importance of biphenyl scaffolds as the structurally decisive scaffolds in bioactive natural products and pharmaceuticals drugs, formidable efforts have been carried out to summarize gradual developments of biphenyl compounds and their isosteres *via* metallic catalyzed reaction which covered the literature reported in the last decades based on this thrilling area of research. In this review several chemical reactions of biphenyl with different reagents have been discussed. The profound discussion of different captivating mechanisms associated with the role of numerous key catalysts and reagents *through* this review is believed to be beneficial for the synthetic community to apply these methods for practical purposes. Additionally, the efficacy of biphenyl compounds in medicinal chemistry and academic industry has been covered, and thereby will be helpful for future research. Although, obtaining these frameworks with particular substitution patterns is still an intimidating exercise. Atropisomerization phenomena of biphenyl derivatives also has taken into account Therefore, we believe that this review can be a guiding principle for synthetic and medicinal chemists working in this field.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Abbreviations

$H_2NCO_2^-H_4N^+$	Ammonium carbamate
AD	Alzheimer's disease
ATRA	All-*trans* retinoic acid
$NiFe_2O_4$@SiO_2-propyl@glucosamine	4-Amino glucose functionalized silica propyl coated nickel ferrite nanoparticle

Ae	Alkali metals earth
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium
$PdCl_2(PPh_3)_2$	Bis-triphenylphosphine palladium dichloride
B_2pin_2	Bis(pinacolato)diboron
IMes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2-*H*-imidazol-2-ylidene
$(2\text{-}BrC_6H_4)OPPh_2$	(2-Bromophenyl)diphenylphosphine oxide
$[pd(dppf)Cl_2CH_2Cl_2]$	1,1′-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
$CrCl_3$	Chromium(III) chloride
Cy_2PCl	Chlorodicyclohexylphosphane
CAN	Ceric ammonium nitrate
$[Ir(OMe)COD]_2$	(1,5-Cyclooctadiene)(methoxy) iridium(I) dimer
$CoCl_2$	Cobalt(II) chloride
DCM	Dichloromethane
EDB	1,2-Dibromoethane
DCICA	Dichloroiodoisocyanuric acid
$K_2S_2O_8$	Dipotassium peroxodisulfate
dmbpy	Dimethylbipyridyl
DCC	Dicyclohexylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
FtsZ	Filamenting temperature-sensitive mutant Z protein
HTS	High-throughput screening
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
LCDs	Liquid crystal displays
$LiAlH_4$	Lithium aluminium hydride
MOF	Metal–organic frameworks
2-MTHF	2-Methyltetrahydrofuran
*m*CPBA	*meta*-Chloroperbenzoic acid
MCRs	Multicomponent reaction
NBS	*N*-Bromosuccinimide
NSAIDs	Non-steroidal anti-inflammatory drug
NMEA	*N*-Methylethanolamine
OLEDs	Organic light-emitting diodes
$(COCl)_2$	Oxalyl chloride
OMIMs	Organic polymer of intrinsic microporosity
ODCB	*O*-Dichlorobenzene
Pd/CNS	Palladium-catalyst on porous carbon nanospheres
Na[Pd-NAS]	Palladium grafted on natural asphalt sulfonate
PCBs	Polychlorinated biphenyls
PBBs	Polybrominated biphenyls
PPA	Polyphosphoric acid
phen	1,10-Phenanthroline
KPF_6	Potassium hexafluorophosphate
$[Cp^*RhCl_2]_2$	Pentamethylcyclopentadienyl rhodium dichloride dimer
PBr_3	Phosphorus tribromide
SMC	Suzuki–Miyaura coupling reaction
CF_3SO_2Na	Sodium trifluoromethanesulfinate
$AgSbF_6$	Silver hexafluoroantimonate (V)
Ag_2O	Silver oxide
$SmBr_2$	Samarium dibromide
SET	Single-electron transfer
PPh_3	Triphenylphosphine
TEA	Triethylamine
$(Pd_2(dba)_3)$	Tris(dibenzylideneacetone) dipalladium(0)
$SOCl_2$	Thionyl chloride
Ph_3SnCl	Triphenyltin chloride
tfp	Tris-*o*-furylphosphine
$SnCl_4$	Tin(IV)chloride
PBu_3	Tributyl phosphine
$CHCl_3$	Trichloromethane
t-Boc	*tert*-Butyloxycarbonyl
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine) palladium
TMEDA	Tetra methyl ethylenediamine
TFAA	Trifluoroacetic anhydride
Bu_4NBF_4	Tetrabutylammonium tetrafluoroborate
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TBABr	Tetrabutylammonium bromide
TMSCN	Trimethylsilyl cyanide
Tf_2O	Trifluoromethanesulfonic anhydride
TBN	*tert*-Butyl nitrite
TBTC	Tributyltin chloride

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