

Review

Palladium and Copper Catalyzed Sonogashira cross Coupling an Excellent Methodology for C-C Bond Formation over 17 Years: A Review

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Abstract: Sonogashira coupling involves coupling of vinyl/aryl halides with terminal acetylenes catalyzed by transition metals, especially palladium and copper. This is a well known reaction in organic synthesis and plays a role in sp^2 - sp C-C bond formations. This cross coupling was used in synthesis of natural products, biologically active molecules, heterocycles, dendrimers, conjugated polymers and organic complexes. This review paper focuses on developments in the palladium and copper catalyzed Sonogashira cross coupling achieved in recent years concerning substrates, different catalyst systems and reaction conditions.

Keywords: cross coupling; copper; palladium; transition; Sonogashira

1. Introduction

The transition metal catalyzed cross-coupling reactions have played an important role in the field of organic synthesis [1,2]. Among them, the palladium catalyzed sp^2 - sp couplings between aryl or alkenyl halides or triflates and terminal alkynes in presence or absence of Copper (I) cocatalyst has become the most important method to prepare aryl-alkynes and conjugated enynes (Figure 1), which are precursors for pharmaceuticals, natural products and organic materials and this type of coupling commonly known as Sonogashira coupling [3–5]. This reaction was named after the scientists Sonogashira, Tohda, and Hagihara in 1975.

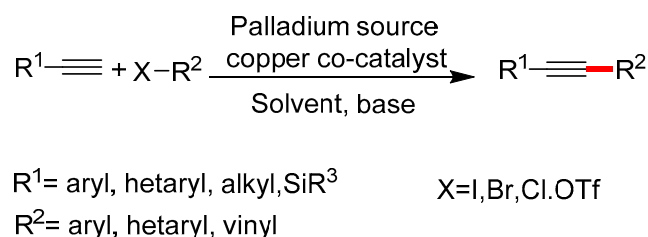


Figure 1. General schematic presentation of Sonogashira Cross Coupling reaction.

This research came after Cassar [6] and Dieck and Heck [7] disclosed that it was possible to perform this coupling only under palladium catalyst at high temperatures. Sonogashira and Hagihara reported that addition of catalytic amount of Copper (I) iodide accelerates the C-C bond formations at room temperature [8]. However, addition of copper has many benefits, but it has some drawbacks associated with it, the main one being the necessity of avoiding the presence of oxygen in order to block the undesirable formation of alkyne homocoupling through a copper-mediated Hay/Glaser reaction [9] along with the main product and difficulty in recovery of reagents. To overcome this issue, elimination of the copper was a solution, so perhaps in this case the process may be called copper-free Sonogashira reaction, or Heck-Cassar reaction, Heck alkynylation or perhaps Sonogashira-Heck-Cassar coupling. Significant efforts were made to develop the coupling reaction and enhancement of reactivity of catalytic system in absence of copper sources. The copper free coupling process involves the use of excess amine which often acts as a solvent, but the environmental and economic advantages of the methodology end here. Thus, efforts were made to develop Sonogashira cross-coupling reaction in absence of both copper and amines [10]. In the Sonogashira process, different substrates have different reactivities as sp² species reactivity order was found to be vinyl iodide > vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate > aryl bromide > aryl chloride. In organic halides, which are activated (electron-poor), the situation is even more promising [11]. The products obtained in Sonogashira reaction have various applications in the diverse areas of chemistry, such as electronics, dyes, polymers, sensors, natural products and in synthesis of heterocycles. Remarkable research on this topic has been going on for decades to search for more convenient reaction conditions and a better, efficient catalytic system and for synthesis of promising compounds. This review covers the developments in the Sonogashira cross-coupling reaction, as well as applications of this methodology from 2002 to 2018.

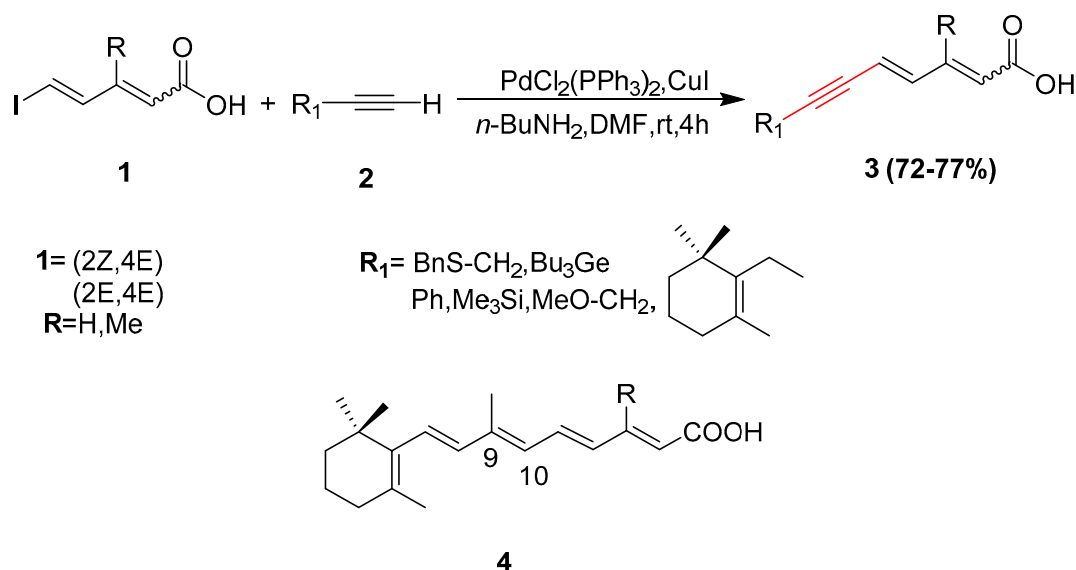
2. Literature Review

The palladium catalyzed cross coupling between carbon halides and terminal acetylenes have been reported by various research groups [12]. These cross couplings have used the formation of a carbon-carbon bond. The copper as co-catalyst with palladium complexes were used for Sonogashira cross coupling [13]. The Sonogashira cross coupling was also used for the preparation of compounds which are pharmacologically and biologically active. In this cross coupling, the various ligands with palladium and copper co-catalyst have been used by various research groups.

2.1. In 2002

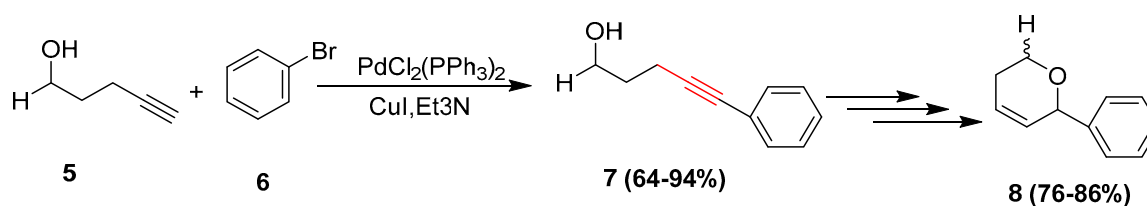
The Sonogashira cross coupling was used for synthesizes of different organic compounds which are used as precursors for biologically active molecules. Earlier, the triple bond in C-9 and C-10 of Stereo-selective 9,10-didehydro retinoic acids **4** were formed “by Wittig reaction” and by addition reaction of 4-methyl-pyrylium tetra-fluoro-borate on appropriate substrate, but protection and de-protection steps were used in these reactions. In 2002, the Sonogashira cross coupling was used by Abarbri and co-workers for the synthesis of **4** Stereo-selective 9,10-didehydro retinoic acids without protection and de-protection of carboxylic acid. The dienoic acid **3** was also synthesized via di-chloro-bis (tri-phenyl phosphine) palladium (II) and copper iodide catalyzed Sonogashira cross

coupling (Scheme 1). The yield was 77% when the reagent **1** is (2Z,4E), **R** is Me and when **R**² is Me₃Si, the yield is 77% [14].



Scheme 1. Stereoselective Synthesis of 9,10-didehydro retinoic acids.

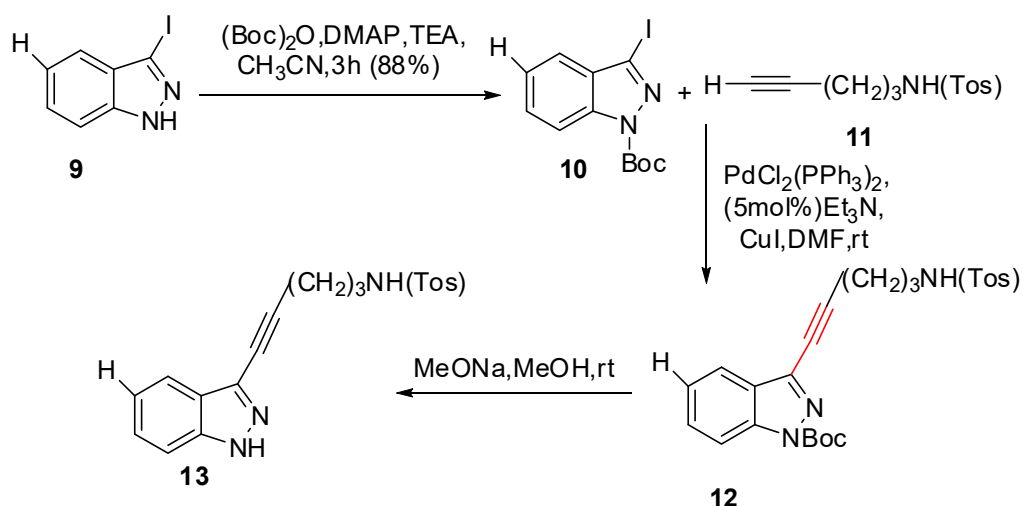
Similarly, the 5-phenylpent-4-yn-1-ol **7** was synthesized via Sonogashira cross coupling without the protection of hydroxy group. The **7** was used as precursor for the synthesis of 2-aryl-2,5-dihydro-2H-pyrans **8**. An aryl di-hydro-pyran precursor was synthesized via etherification of an aryl bishomoallylic alcohol. Sonogashira coupling of homo-propargylic alcohols with aryl bromides gave the (E)-arylhydroxyalkene cyclization precursors. The substituted acetylenes were reduced to the alkenols. The phenyl-selenenyl chloride in dichloromethane was used for synthesis of trans 2,3-disubstituted tetrahydropyrans. The oxidative-elimination proceeded by using 30% hydrogen peroxide and pyridine in THF giving **8** in good yield (Scheme 2) [15].



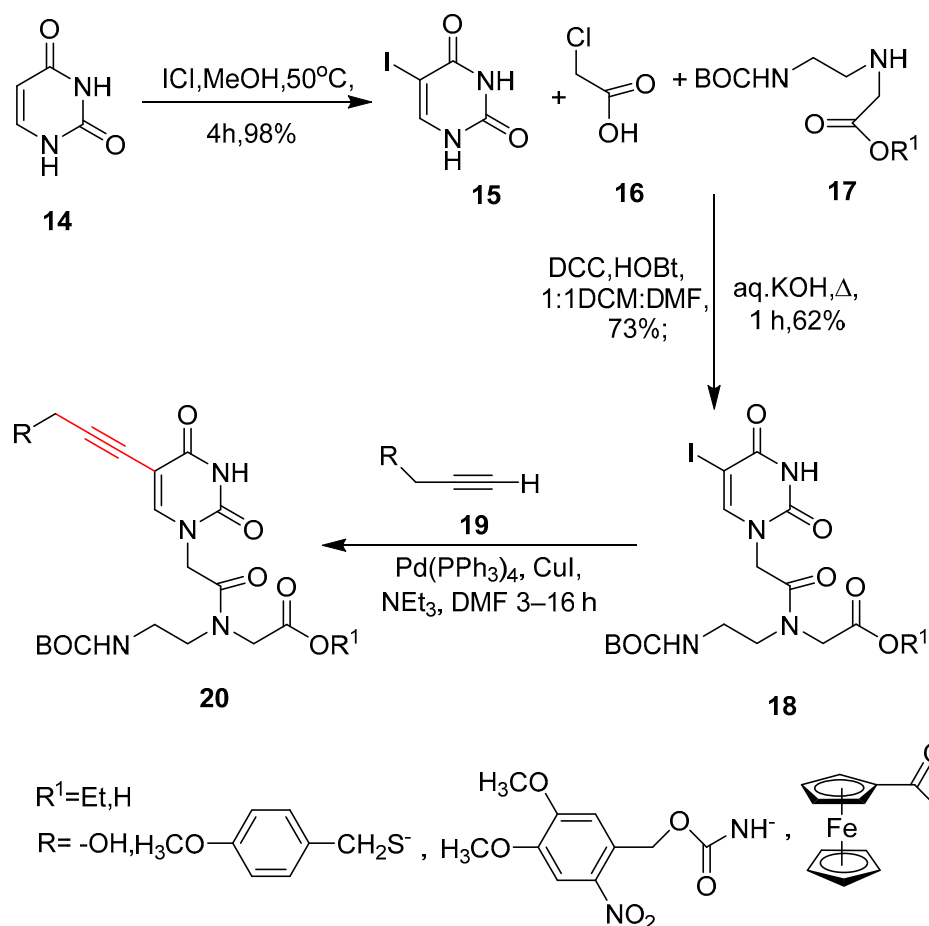
Scheme 2. Sonogashira Cross Coupling of homo-propargylic alcohols with bromobenzene.

It was observed that Sonogashira cross coupling is a good methodology for the coupling of nitrogen containing heterocycles with terminal acetylenes. The 3-iodoindazoles were coupled with various propiolic or propargylic derivatives via palladium and copper catalyzed Sonogashira coupling to prepare the building blocks of interest in medicinal chemistry as tryptamine derivatives. As mentioned, in Scheme 3 the N-1 of the 3-iodo-1H-indazole **9** was protected and compound **12** was synthesized and 99% yield produced via this methodology. There was no coupling in position 3 of **9** without protection of N-1 [16].

Similarly, the nitrogen containing heterocycles as in Scheme 4, 5-iodouracil PNA-residues was synthesized via Sonogashira cross coupling in solution and solid phase by reaction with different alkynes. In solution phase the yield was 38–53% and in solid phase, the yield was essentially quantitative. PNA is an oligonucleotide and it forms complexes with DNA and RNA [17].



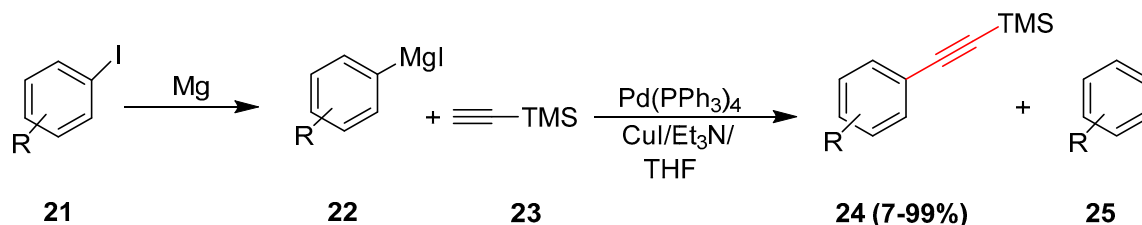
Scheme 3. Synthesis of aza tryptamines via Sonogashira Cross Coupling.



Scheme 4. Synthesis of 4, 5-iodouracil PNA-residues via Sonogashira Cross Coupling in solution and solid phase.

However, Grignard reaction is excellent methodology for the carbon-carbon formation [18,19]. The organic-halide with magnesium gives a Grignard reagent. The Grignard reagent is used for functional group transformation [20]. In addition, the Grignard Reagent was also used as an alternative source of aryl halide in Sonogashira Cross Coupling catalyzed by palladium and Copper iodide in Scheme 5. The different electron donating groups and electron withdrawing groups were used with

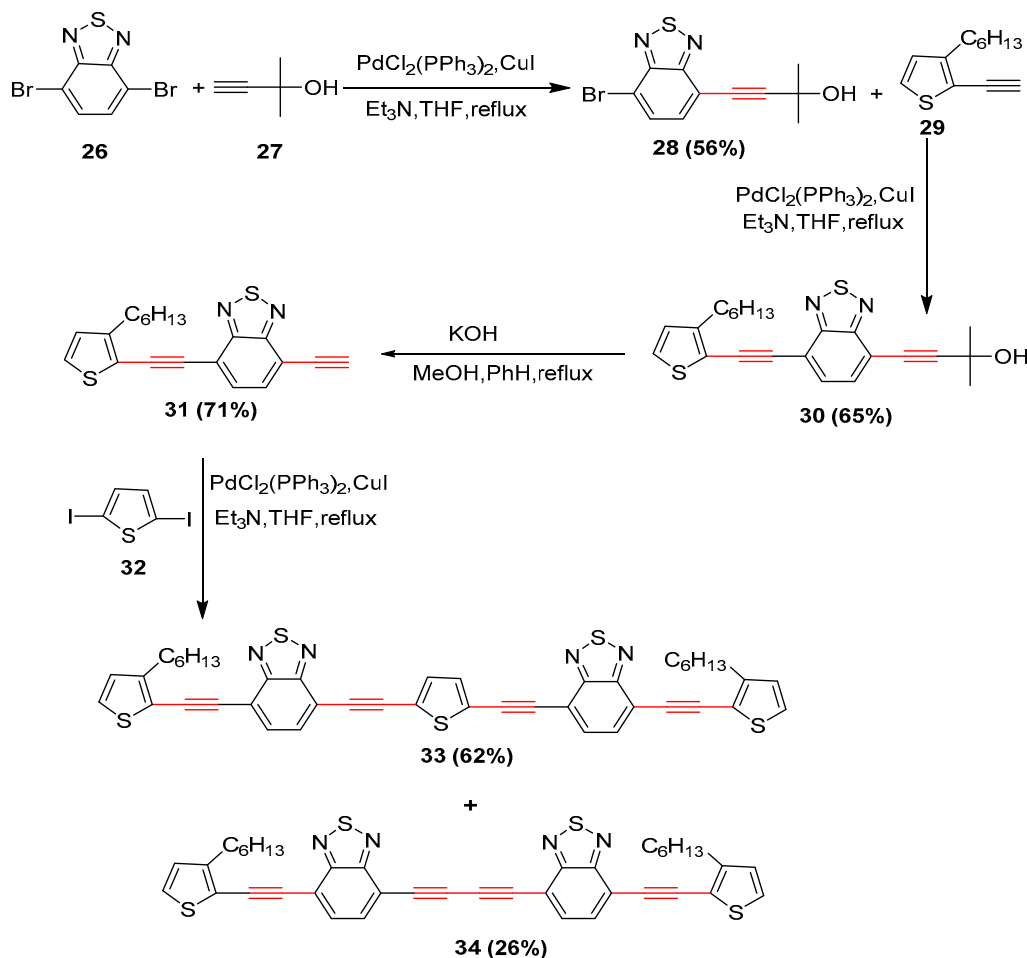
Grignard reagent. The $-\text{CF}_3$ and $-\text{CH}_2\text{CH}_3$ at ortho, meta and para position gave more than 99% yield. The Grignard-Sonogashira reaction was a facile and moderate method for the carbon-carbon bond formation [21].



$\text{R} = -\text{CF}_3, -\text{CO}_2\text{Me}, -\text{NO}_2, -\text{CH}_3, -\text{CH}_2\text{CH}_3, -\text{OH}, -\text{OCH}_3, \text{NH}_2$

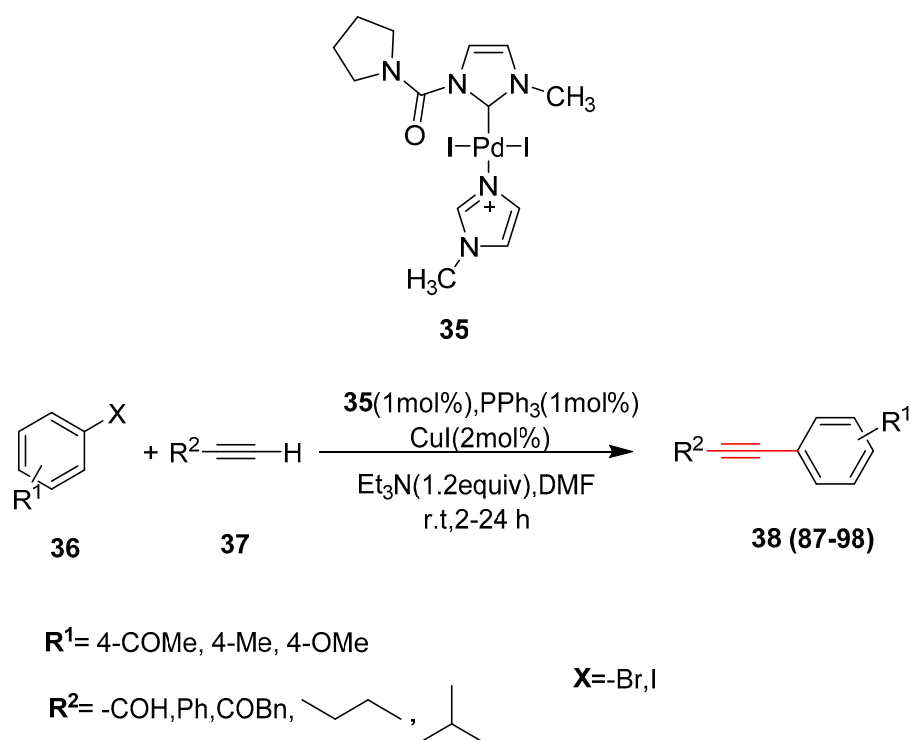
Scheme 5. Synthesis of trimethyl(phenylethynyl)silane by Palladium and Copper catalyzed reaction.

It was noted that the linear conjugated oligomers have attracted considerable attention of scientists due to their potential use in molecule-based electronics as molecular wires [22,23]. Kitamura and co-workers described the synthesis of a new class of linear conjugated oligomers by bi-directional method using Sonogashira cross coupling. The route for ethyne linked alternating π -donor and π -acceptor system was developed as in Scheme 6. The change of substrate effects the yield and homo-coupling yields 26%. The [2+1+2] method was used as a bi-directional method [24].



Scheme 6. Synthesis of Oligomers via Sonogashira cross coupling followed by [2+1+2]bi-directional method.

It was also noted that Nucleophilic N-heterocyclic carbenes Pd (II) complex **35**, especially imidazole-2-ylidene, was used as an alternative for phosphine ligands in homogeneous catalysis. In Sonogashira cross coupling, these Pd complexes were used as the palladium source and copper iodide was used as the co-catalyst for coupling of terminal acetylenes with aryl-halide Scheme 7. The palladium carbene complex alone produce 50% yield and with PPh₃ yield was 97%. The aryl bromide derivatives with electron donating groups on the ring show less reactivity [25].

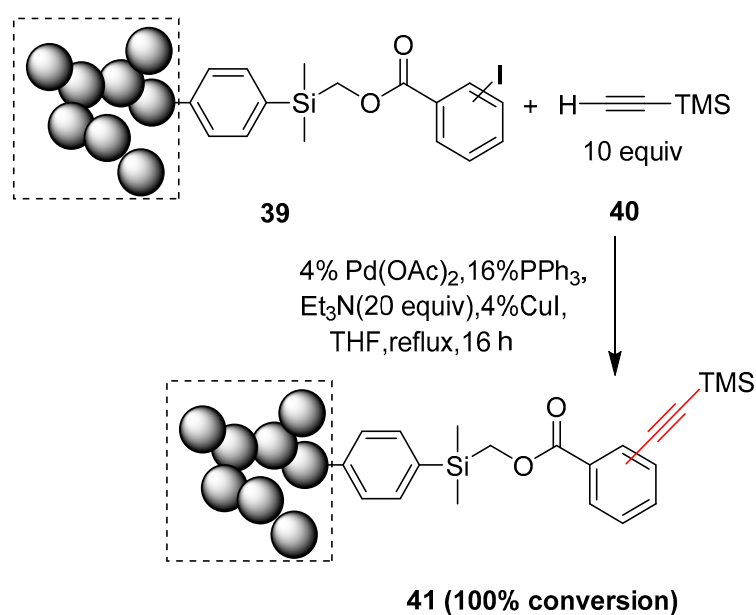


Scheme 7. Sonogashira cross coupling of substituted alkyl halide and terminal acetylene.

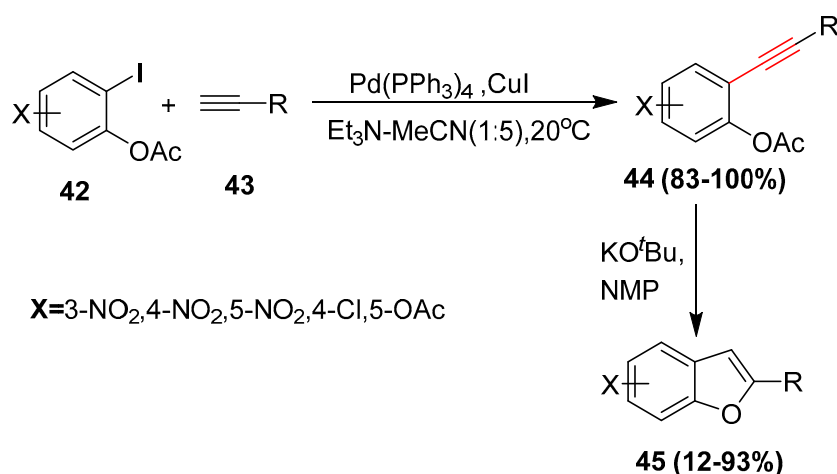
In addition, the synthesis of organic molecules on polymeric support was an excellent strategy for the identification of new organic compounds [26]. The palladium catalyzed cross coupling reaction on the solid support was developed for the synthesis of new drugs [27]. Duboc and co-worker reported the synthesis of new stable silylated polystyrene via palladium and copper mediated Sonogashira cross coupling. The mild conditions were used for cleaving of products from support and scavenger ionic resin was used for purification. The supported aryl iodides were coupled with tri-methyl-silyl-acetylene via Pd (OAc)₂(PPh₃) and copper iodide catalyzed Sonogashira cross coupling and the conversion was 100% (Scheme 8) [28].

Mostly, Benzo[b]furans exhibit diverse biological activities and used as the inhibitors of β -amyloid aggregation and cyclo-oxygenase-2 [29]. Thus, 4, 5 and 6-nitro-benzo[b]furans were synthesized by using 2-amino-nitro-phenols via coupling cyclization reaction. The 2-iodo-nitro-phenols were converted to corresponding acetates because the direct cross coupling gave low yield. The acetates were coupled with acetylene via Pd (PPh₃)₄ and CuI catalyzed Sonogashira cross coupling which were then reacted with KO^tBu, and the nitro-benzo[b]furan **45** was obtained (Scheme 9) [30].

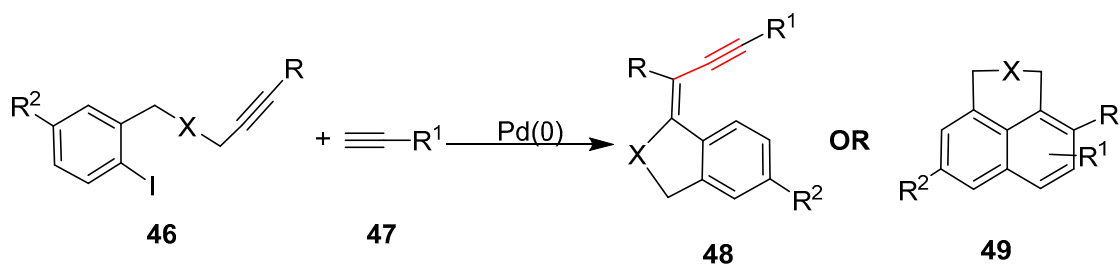
It was observed that the nature of catalyst controls the Sonogashira cross coupling. Teply and co-workers reported that the copper as co-catalyst played important role for the formation of coupled product. The phenyl iodides were coupled with terminal acetylenes; in the absence copper co-catalyst, the cyclized product was formed (Scheme 10) [31].



Scheme 8. Synthesis of Silylated Polystyrene.

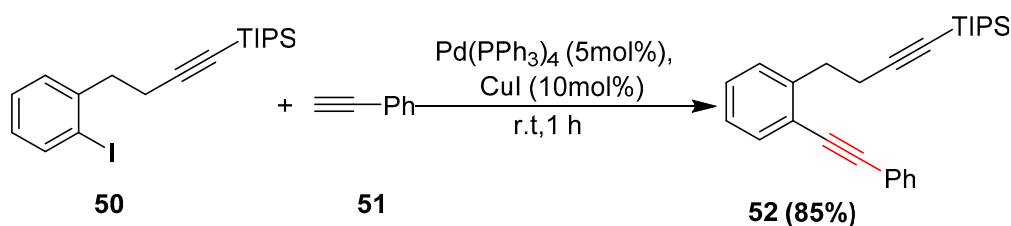


Scheme 9. Sonogashira cross coupling of substituted iodo-acetates with terminal alkynes.



Scheme 10. Sonogashira Cross Coupling of alkyne-substituted phenyl iodides with terminal alkynes.

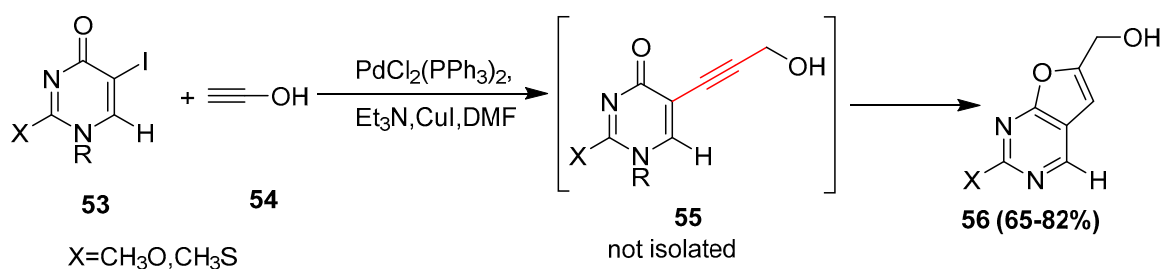
Furthermore, the phenyl iodides were coupled with terminal acetylenes via Palladium (0) and Copper (I) catalyzed Sonogashira cross coupling and 92% yield of coupled product was obtained (Scheme 11) [31].



Scheme 11. Sonogashira Cross Coupling of alkyne-substituted phenyl iodides with terminal alkynes via Palladium and Copper Catalyst.

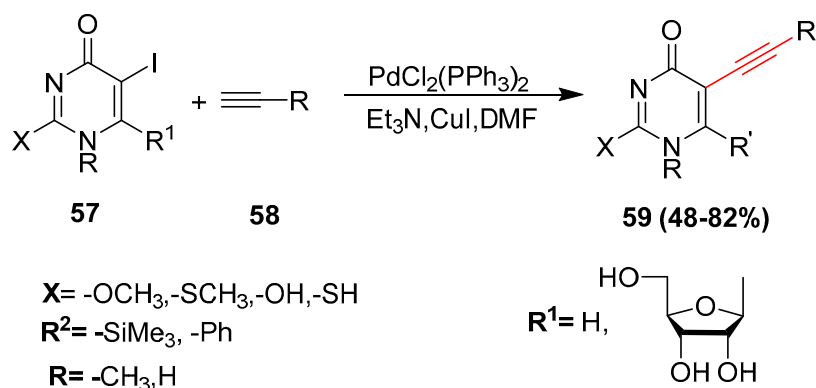
2.2. In 2003

In 2003, various scientists and researchers reported the Sonogashira reaction catalyzed via palladium and copper and different reaction conditions. As previously discussed, nitrogen containing heterocycles showed many biological activities such as anti-viral and anti-cancer [32,33]. The alkynyl derivatives starting from 5-iodinated pyrimidinone derivatives were obtained by protecting the N-1 or 2,4-positions of uracils. Petricci and co-workers reported that the 5-alkynyl derivatives were synthesized from pyrimidinones and uridine via Sonogashira cross coupling reaction catalyzed by palladium and copper. The pyrimidinones and uridine were coupled in the presence of DMF solution, Et_3N , $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI with propargyl alcohol at room temperature gave moderate yield and were not isolated. It underwent cyclization (Scheme 12) [34].



Scheme 12. Palladium and Copper catalyzed coupling of pyrimidinones and uridine with ethynol.

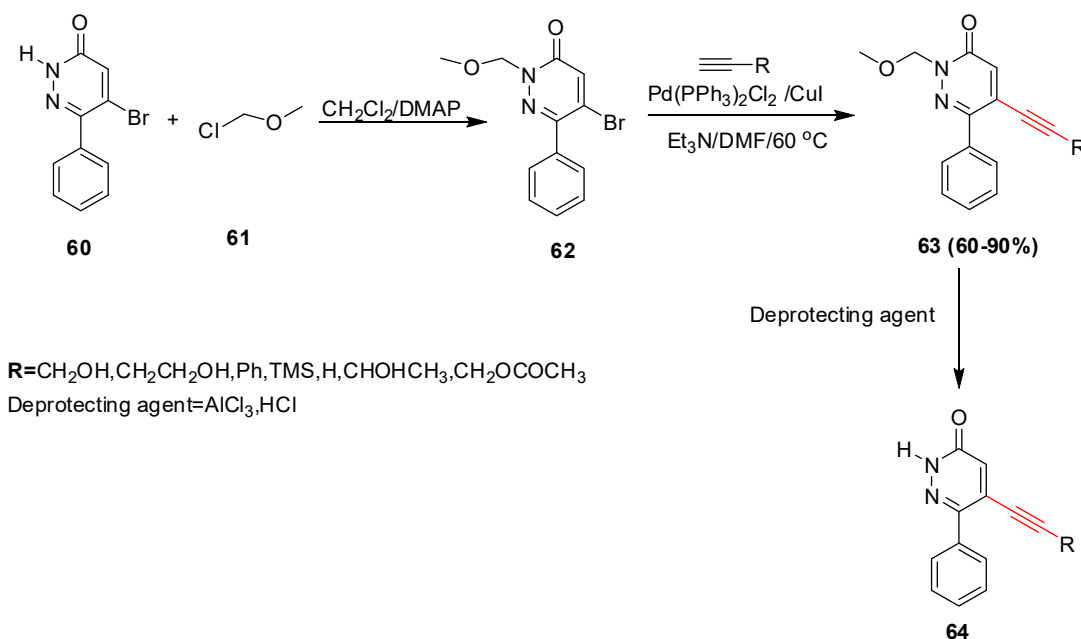
Furthermore, Petricci and co-workers reported that the terminal alkynes irradiated with microwave for 5 min at 45°C were coupled with pyrimidinones via Sonogashira cross coupling reaction catalyzed by palladium and copper gave good yield as in Scheme 13 [34].



Scheme 13. Microwave enhanced Sonogashira coupling.

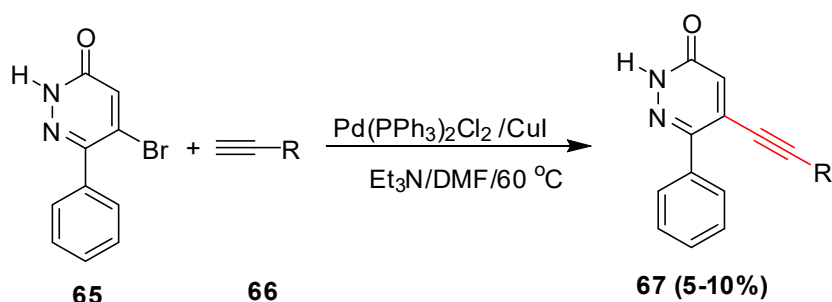
It can be additionally noted that the nitrogen containing heterocycles, especially pyridazinones, show various biological activities and used as drugs in cardiovascular system and as agrochemicals [35,36].

So, synthesis of these nitrogen-containing molecules with short and comprehensive route is of great concern for various researchers. Thus, Coelho and co-workers synthesized the 5-alkynyl pyridazinones derivatives. The NH group of pyridazinone **60** was protected with the methoxymethyl group to synthesized protected pyridazinone **62**. The protected pyridazinone **62** was coupled with terminal alkyne by using bis (tri-phenyl-phosphine)-palladium chloride, copper iodide as a co-catalyst, triethylamine as a base and DMF as a solvent. The 2-methoxymethyl-3-pyridazinone was de-protected either with hydrochloric acid or AlCl_3 as in Scheme 14. The unprotected product **64** was synthesized [37].



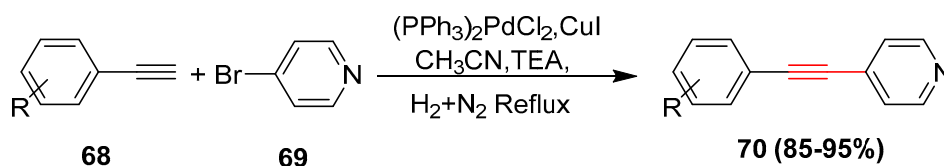
Scheme 14. Sonogashira cross coupling of 5-bromo-2-(methoxymethyl)-6-phenylpyridazin-3(2H)-one with chloro(methoxy)methane.

In contrast, terminal acetylenes and 5-bromo-6-phenyl-3(2H)-pyridazinone without protection of NH group were coupled and gave only around 5–10% of the 5-alkynyl pyridazinones **67** derivatives and more than 85% of reactant was recovered (Scheme 15). The low reactivity was due to the acidity of the NH group [37].



Scheme 15. Sonogashira cross coupling of 5-bromo-6-phenylpyridazin-3(2H)-one with terminal alkynes.

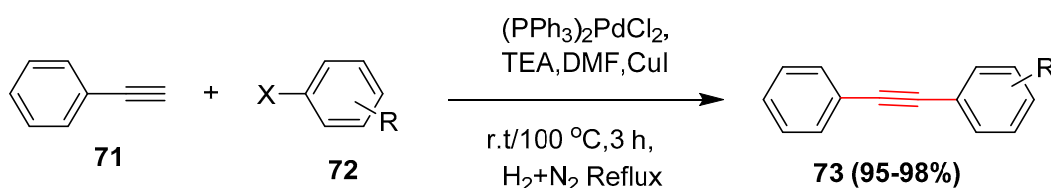
It was noted that π -conjugated compounds have versatile applications as in light emitting diodes, carbohydrates sensing and in molecular electronics [38]. The aryl donors were coupled with aryl and heteroaryl acceptors via Sonogashira cross coupling [39]. Elangovan and co-workers used an atmosphere of Hydrogen gas diluted with nitrogen or argon with palladium and copper catalyst to synthesized terminal aryl ethynes and aryl-pyridyl-ethynes with donor substituents in very good yields via a Sonogashira coupling reaction in Scheme 16 [40].



R=2,4-dimethyl,4;OMe,4-NMe₂,4-NEt₂,4H,4-Me

Scheme 16. Synthesis of internal Ethynes via Sonogashira cross coupling.

Similarly, di-aryl-ethynes were synthesized via previously mentioned reaction conditions (Scheme 17) [40].

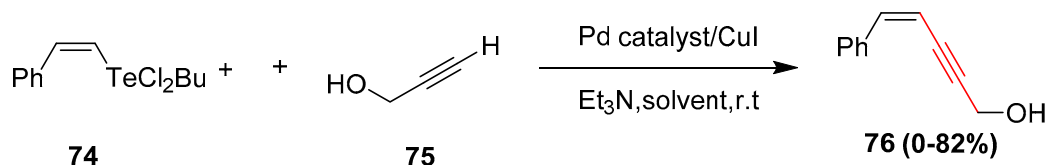


R=2,4-dimethyl,4;OMe,4-CN,4-NO₂,4-CHO,4-COCH₃

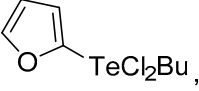
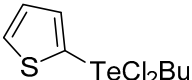
X=I,Br

Scheme 17. Synthesis of Diarylethynes via Sonogashira cross coupling.

In addition, organotellurium compounds are a very important class [41]. The 2-alkynyl substituted hetero-aromatic 76 and similar compounds were synthesized by coupling of vinylic and hetero-aromatic tellurium di-chlorides via palladium and copper catalyzed Sonogashira cross coupling (Scheme 18). The various palladium catalysts with CuI were used in this reaction. It was noted that the same compounds show 82% yield when the reaction is applied with PdCl₂ [42].



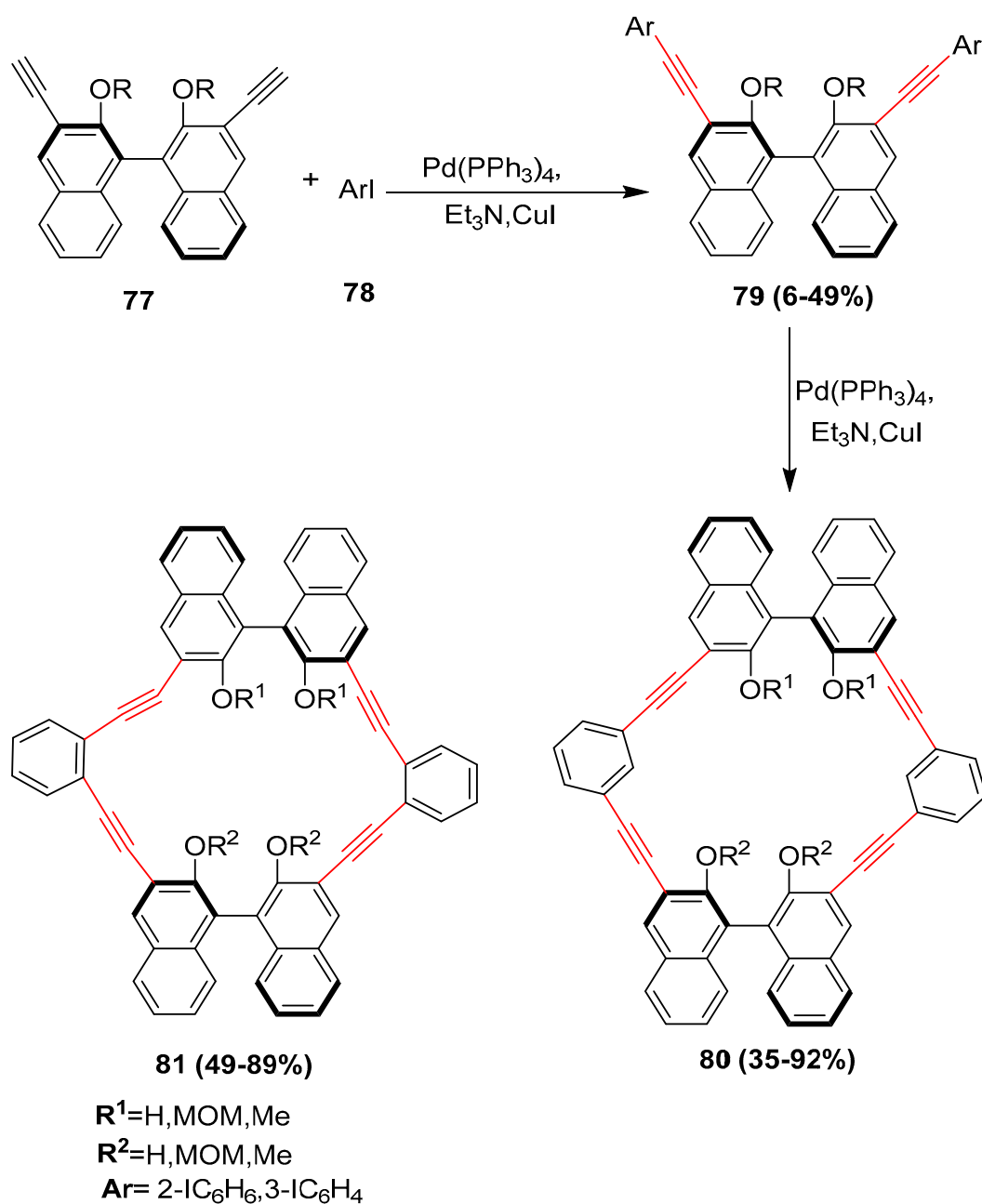
Pd Catalyst = PdCl₂, Pd(OAc)₂, Pd(PPh₃)Cl₂

Ph=C₆H₆, C₈H₁₇, (EtO)₂(O)P, , 

Solvent= MeOH, THF,

Scheme 18. Palladium and Copper catalyzed Coupling of substituted tellurium di-chlorides with prop-2-yn-1-ol.

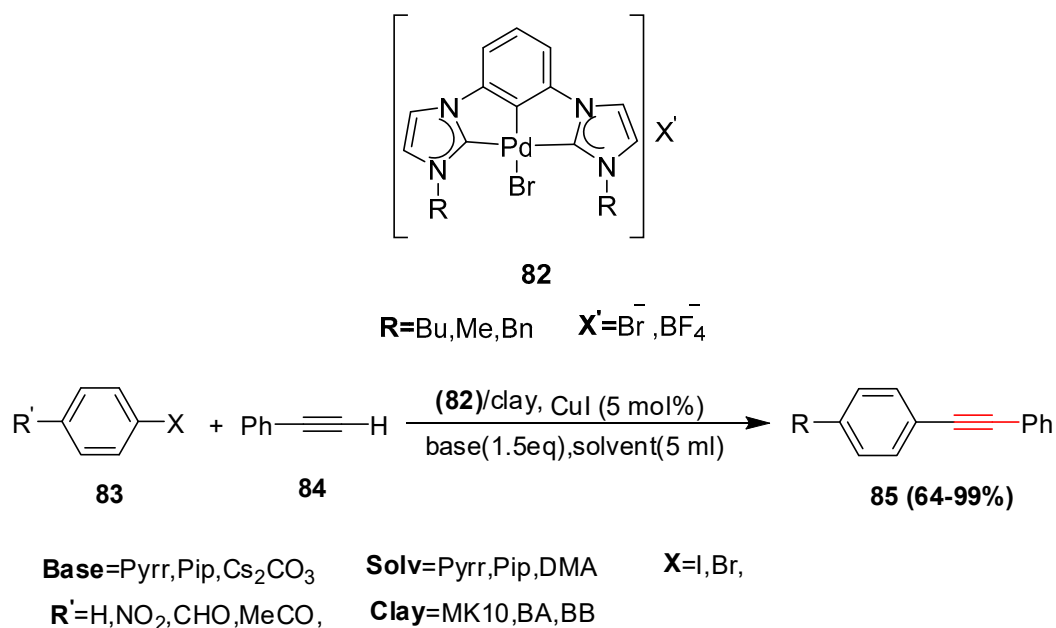
Moreover, the macrocyclic molecules are an important class of super molecular chemistry. So, Sonogashira cross coupling is an efficient methodology for synthesis of macrocyclic molecules. The 1,1'-Bi-2-naphthol (BINOL) and their derivatives were used in asymmetric synthesis [43]. Therefore, Harada and co-workers reported the synthesis of 24- and 26-membered macro-cyclic bi-naphthol dimers 80 and 81 were synthesized via Pd (PPh₃)₄ and CuI catalyzed Sonogashira Cross Coupling shown in Scheme 19 [44].



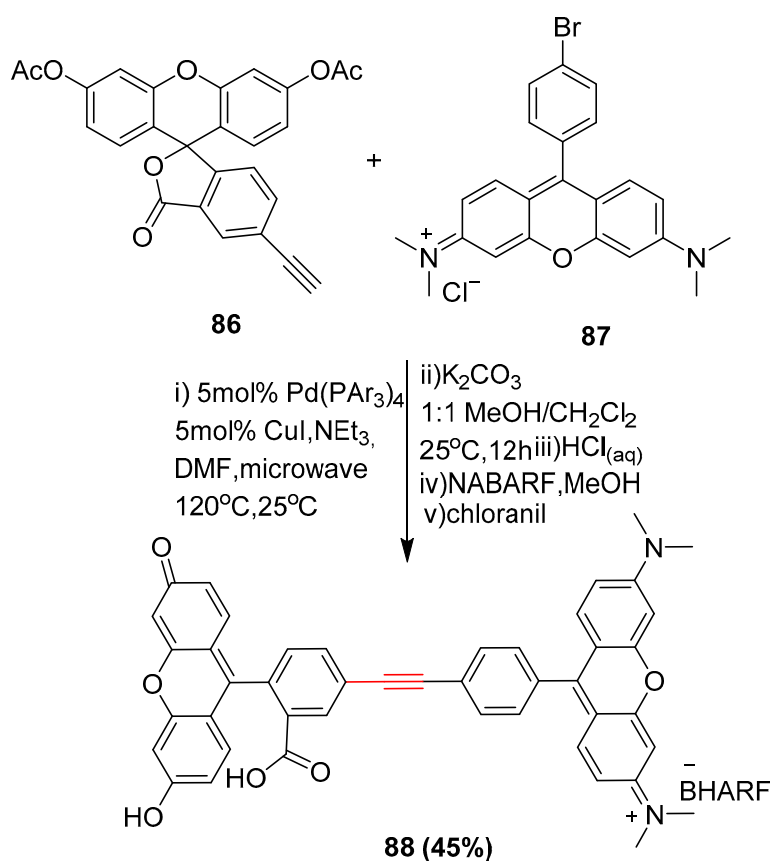
Scheme 19. Synthesis of 24- and 26-membered macro-cyclic bi-naphthol dimmers via Palladium and Copper Catalyzed Coupling.

As discussed earlier, the Nucleophilic N-heterocyclic carbenes was used as an alternative source for palladium phosphine ligands in organo-transition-metal catalysis. The CNC-pincer biscarbene ligand $[\text{PdBr}(\text{CNC-Bu}_2)]\text{X}$ (**82**) was used as a Pd catalytic source with copper iodide for the Sonogashira cross coupling of aryl-chlorides with alkynes as in Scheme 20. The piperidine used as base and DMF as solvent gave a good yield. It was noted that $[\text{PdBr}(\text{CNC-Bu}_2)]\text{X}$ (**82**) had great influence compared with commercially available palladium catalyst [45].

Similarly, the organometallic coupling was rarely used for fluorescein and rhodamine based system. Han and coworkers developed the Sonogashira cross coupling of fluorescein and rhodamine derivatives with **86** and **87** catalyzed by $\text{Pd}(\text{PAr}_3)_4$ and CuI (Scheme 21). Fluorescein and rhodamine derivatives were stable at high temperatures. The Sonogashira cross coupling worked well under microwave irradiation [46].

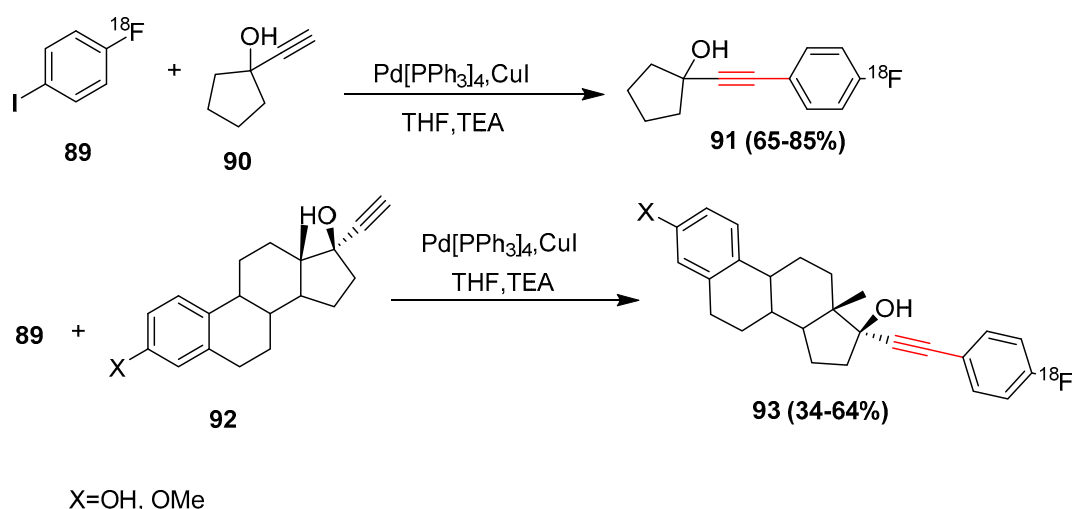


Scheme 20. Synthesis of 4-(phenylethynyl)benzene derivatives via Pd and Cu catalyzed Coupling.



Scheme 21. Sonogashira Cross Coupling of bromorosamine with substituted isobenzofuran acetate.

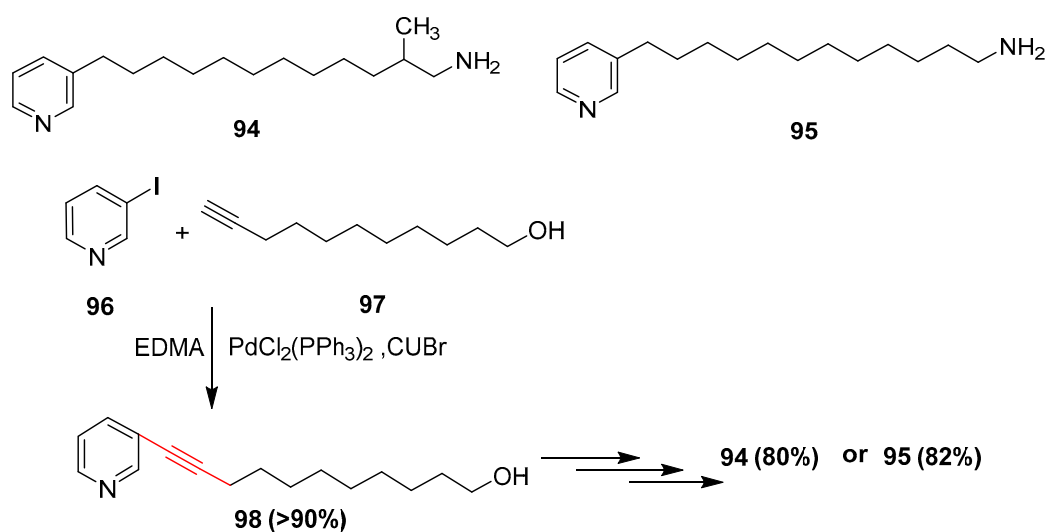
In addition, the ¹⁸F-labelled aryl halides were used as the coupling partners in the palladium and copper catalyzed Sonogashira cross-coupling. The 4-fluorophenyl group was also present in drugs [47]. Wust and Kniess reported, for the first time, Sonogashira cross-coupling in ¹⁸F chemistry. The coupled product was synthesized from Pd (PPh₃)₄ and CuI catalyzed Sonogashira cross coupling of 4-[¹⁸F] fluoro-iodo-benzene with terminal alkyne Scheme 22 [48].



Scheme 22. Palladium Cross Coupling of ^{18}F -labelled aryl halides with 1-ethynylcyclopentanol.

2.3. In 2004

It was noted that Nitrogen-containing heterocycles as pyridine alkaloids were used as precursors for the synthesis of bis-pyridine alkaloids like cyclostelletamine B [49]. These alkaloids showed antimicrobial and cytotoxic activities [50]. The di-chloro-bis (tri-phenyl-phosphine) palladium (II) and copper bromide catalyzed Sonogashira cross coupling was a key step for the synthesis of Niphatesine C 94 and Norniphatesine C 95 (Scheme 23) [51].



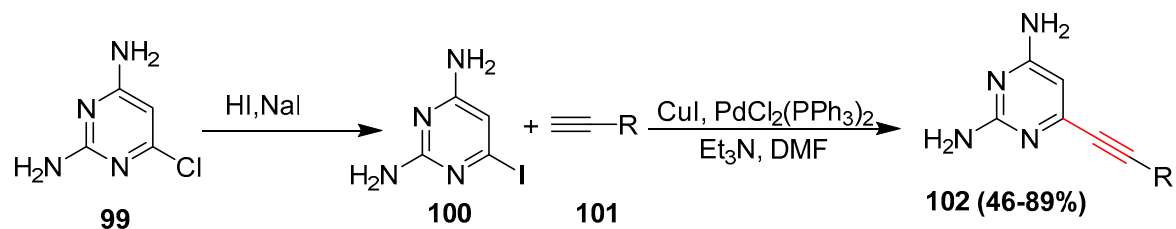
Scheme 23. Synthesis of Niphatesine and Norniphatesine via Sonogashira Coupling.

In addition, the nitrogen-containing heterocycles such as pyrimidines show many biological activities such as adenosine kinase inhibitors [52], anti-tumor and antibiotics [53]. The tri-substituted pyrimidine derivatives were synthesized via di-chloro-bis (tri-phenyl-phosphine) palladium (II) and copper iodide catalyzed Sonogashira cross coupling, as shown in Scheme 24 [54].

2.4. In 2005

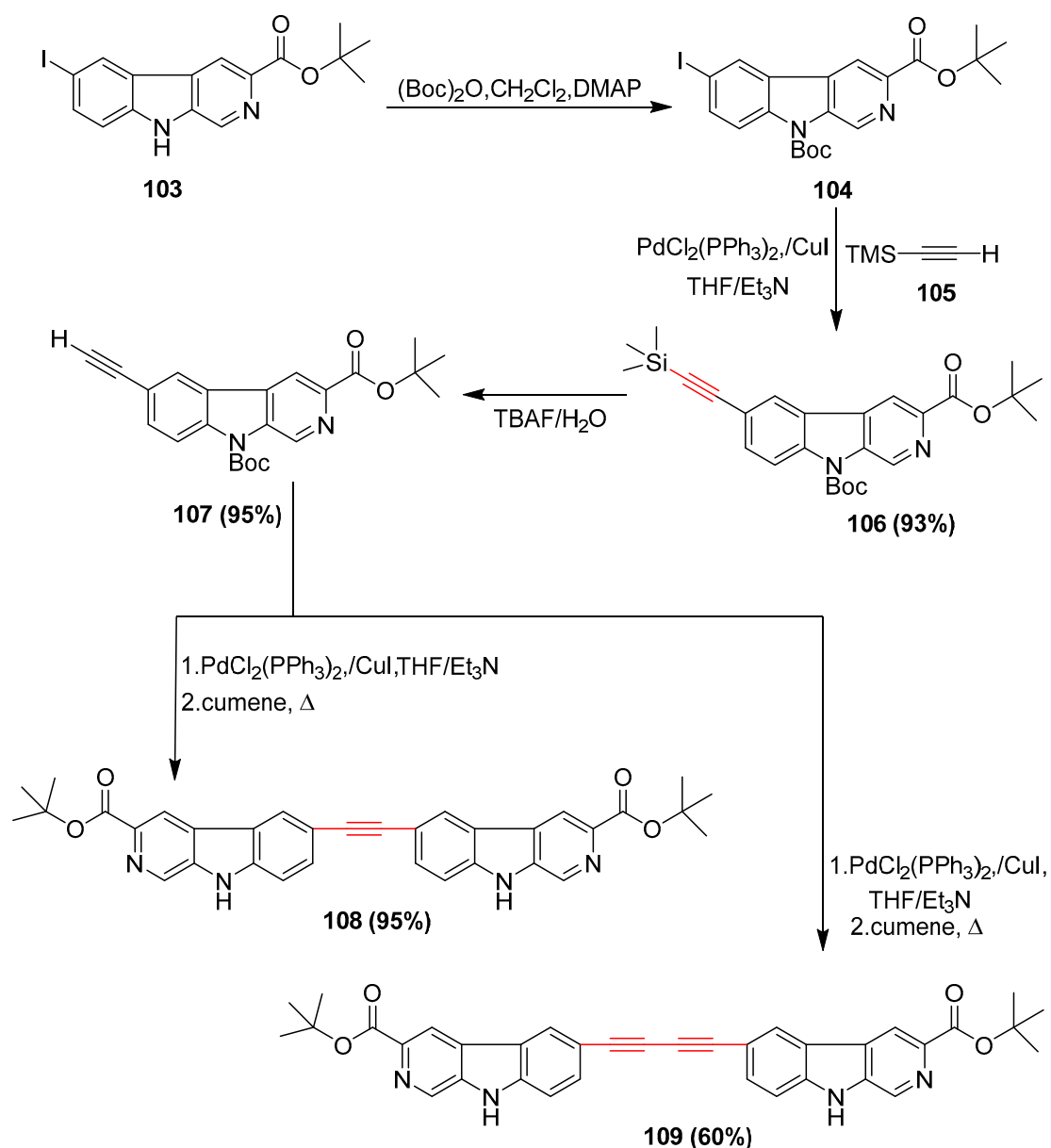
As previously discussed, the nitrogen containing heterocycles are biologically active. The bivalent ligands of β -carboline-3-carboxylate derivatives were used to treat human alcoholics [55]. The bivalent analogues of β -carboline-3-carboxylates were synthesized via di-chloro-bis (tri-phenyl-phosphine)

palladium (II) and copper iodide catalyzed Sonogashira cross coupling. The iodo- β CCt intermediate was formed. The protection and deactivation of N-H group of indole was necessary for the synthesis of bivalent ligands of β -carboline-3-carboxylates (Scheme 25) [56].



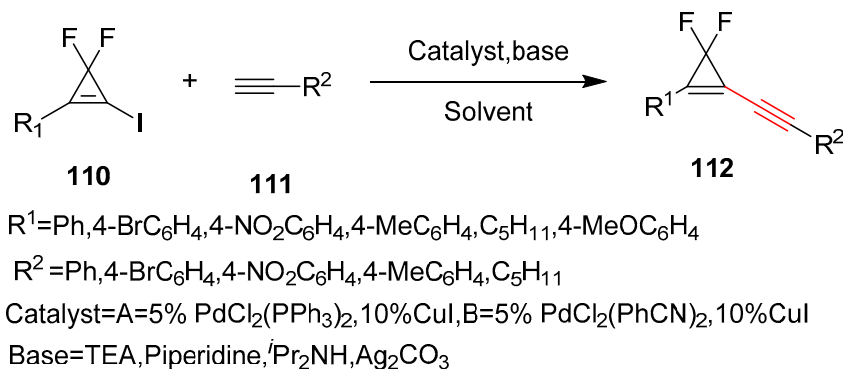
R=Ph, (CH₂)₃CH₃, Si(CH₃)₃, CH₂OH, CH(Ph)OH, CH(CH₃)OH, (CH₂)₂OH, H

Scheme 24. Synthesis of tri-substituted pyrimidine derivatives via Sonogashira cross coupling.



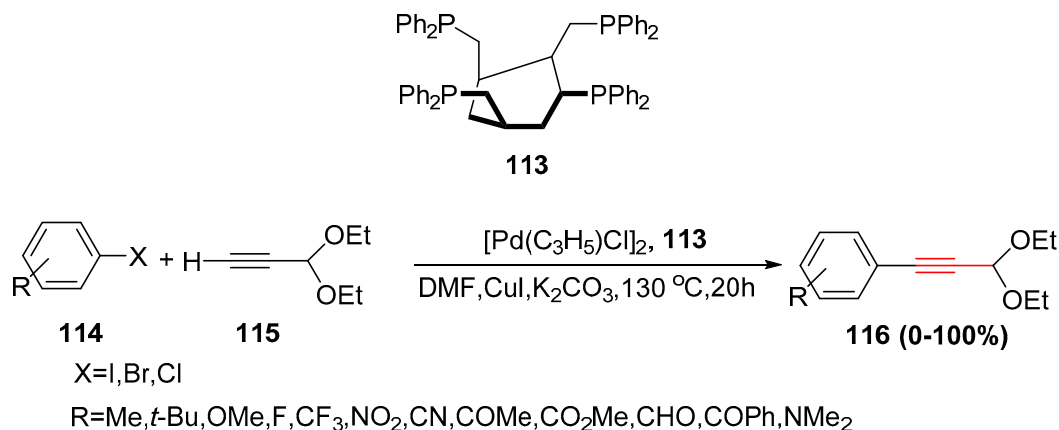
Scheme 25. Synthesis of bivalent analogues of β -carboline-3-carboxylates.

However, the insertion of di-fluorocarbene into carbon-carbon triple bonds is one of the most convenient methods for synthesizing of organic fluoride compounds [57]. The *gem*-di-fluoro-cyclopropenyl-alkynes were synthesized by using Sonogashira cross coupling catalyzed via copper iodide and different ligands with palladium Scheme 26. The amine as base gave poor yield and the use of Cs₂CO₃ gave 70% yield. The phenyl with electron donating groups gave lower yield and the yield of phenyl with electron withdrawing groups was higher [58].



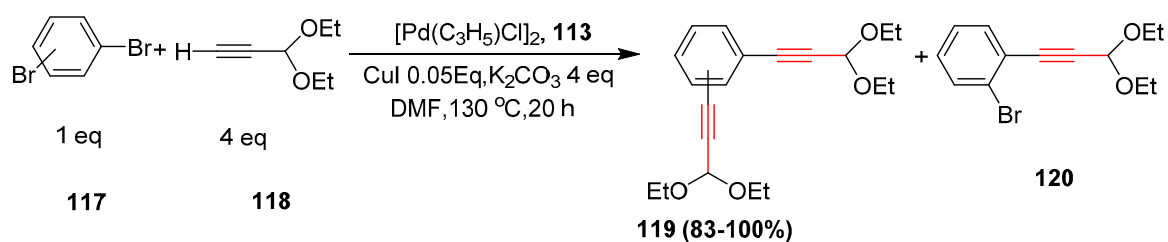
Scheme 26. Palladium and Copper catalyzed coupling of iodo-di-fluoro-cyclopropenyl-alkene with terminal alkynes.

It was noted that thermally stable palladium catalysts were also used for Sonogashira reaction [59]. In the literature survey, (PPh)₃ ligand was used for coupling of aryl halides with propiol-aldehyde diethyl acetal [60]. Lemhadri and coworkers used the tetrapodal phosphine ligand, Tedicyp **113** as a palladium source with copper for Sonogashira cross coupling of para-substituted aryl bromides with propiol-aldehyde diethyl acetal (Scheme 27). The 0.01% of catalyst with aryl bromides was used. All functional groups and hetero-atomic substrates were used in the presence of Tedicyp palladium system [61].



Scheme 27. Synthesis of internal Ethynes via Sonogashira Cross Coupling.

The same research group also reported that the product **119** was selectively obtained in 92% yield in the presence of 0.1% catalyst with 1,4-dibromobenzene substrate. The mixtures of products **119** and **120** were obtained with 1,2-di-bromo-benzene when ratios substrate/catalyst of 1000 and 10,000 were used, as in Scheme 28. The slower reaction rate observed with 1,2-di-bromo-benzene probably is due to steric reasons [61].

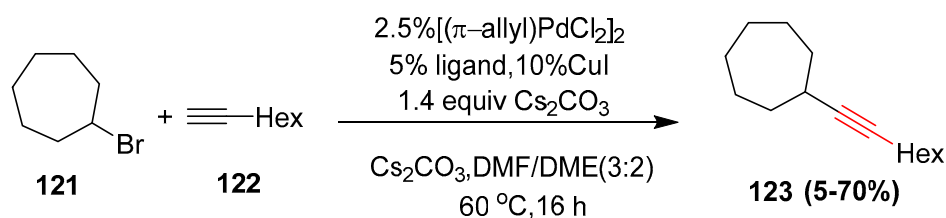


Substrate=1,2-dibromobenzene, 1,4-dibromobenzene,

Scheme 28. Sonogashira cross coupling of 1,4-dibromobenzene with 3,3-diethoxyprop-1-yne.

2.5. In 2006

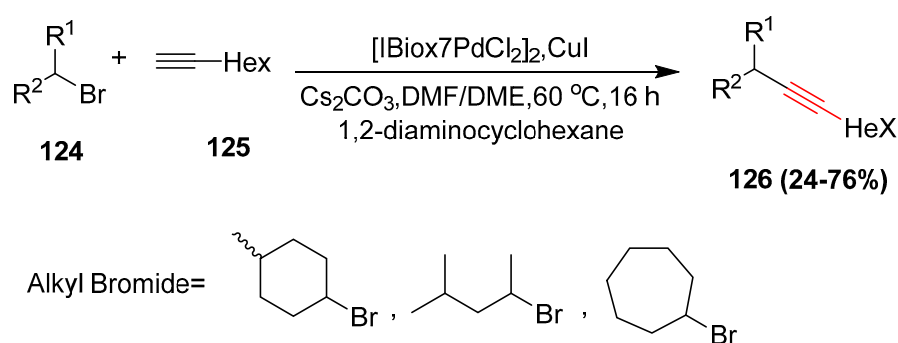
As previously described, palladium-*N*-heterocyclic carbene complexes were used for the Sonogashira cross coupling. Altenhoff and co-workers reported the first Sonogashira cross coupling of alkynes with secondary alkyl bromides in the presence of palladium-*N*-heterocyclic carbene complexes and copper iodide was used as co-catalyst in Scheme 29 [62].



Ligand=IMes.HCl, IAd.HCl, IBioxMe₄.HOTf, IBioxpent₄.HOTf, IBiox6.HOTf, IBiox7.HOTf, [IBiox7PdCl₂]₂, IBiox8.HOTf, IBiox12.HOTf, PPh₃, PCy₃

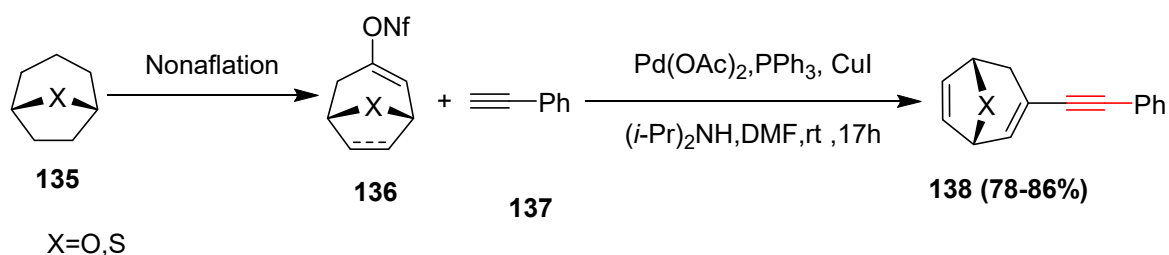
Scheme 29. Sonogashira cross coupling of Secondary alkyl bromides with oct-1-yn-3-one.

In addition, the 1,2-di-amino-cyclohexane was used with palladium-*N*-heterocyclic carbene complex as in Scheme 30 by the same research group. It improved the yield of the coupled product [62].



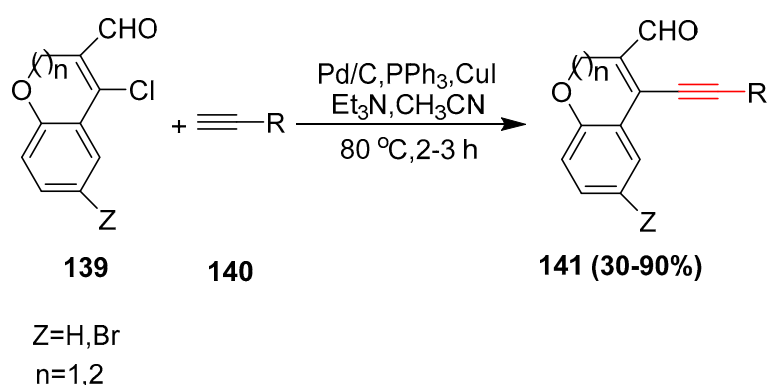
Scheme 30. Palladium-*N*-heterocyclic carbene complex and Copper Iodide Catalyzed Sonogashira Cross Coupling of disubstituted alkyl bromides with oct-1-yn-3-one..

Moreover, the polymer supported palladium catalysts were also used for the Sonogashira cross coupling. In the past, the poly-styrene and silica supported phosphine palladium catalysts were used with copper iodide for coupling [63]. The [MCM-41-SH-Pd(0)] complex was used as a palladium source with copper iodide in the Sonogashira cross coupling of aryl iodides with terminal alkynes Scheme 31 [64].



Scheme 33. Sonogashira cross coupling of bicyclic nonaflate with phenyl alkyne.

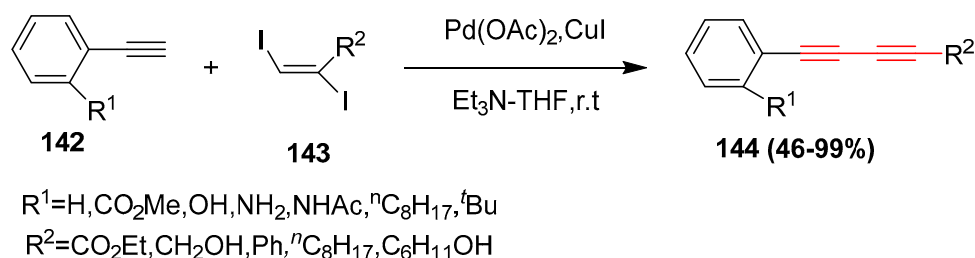
In addition, the vinyl chloride was least reactive while used in the synthesis of natural products and biologically active compounds [69]. Bera and coworkers used the Pd/C–CuI–PPh₃ catalyzed Sonogashira cross coupling for alkylation of β-chloroacroleins (–CCl=CCHO–). The 4-alkynyl-2H-chromene-3-carbaldehydes and 5-alkynyl-2,3-dihydro benzo[b]oxepine-4-carbaldehydes were synthesized via Cu and Pd/C-mediated Sonogashira cross coupling Scheme 34. The Pd/C–CuI–PPh₃ catalytic system was efficient for this coupling [70].



Scheme 34. Sonogashira cross coupling of β-chloroacroleins under Pd/C–CuI–PPh₃ catalytic system.

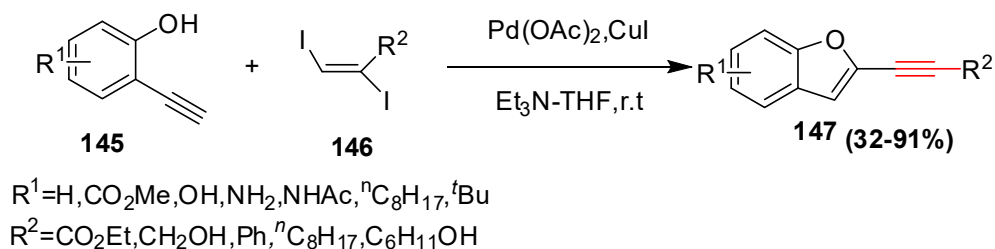
2.7. In 2008

Moreover, Buta-1,3-diyne were present in natural products and bioactive molecules, and found to be intermediate in synthesis [71]. The (E)-1,2-di-iodoalkenes were used as building blocks for the synthesis of unsymmetrical buta-1,3-diyne and 2-ethynyl-benzo-furans. The unsymmetrical buta-1,3-diyne were synthesized via palladium and copper catalyzed Sonogashira cross coupling in good yields (Scheme 35) [72].



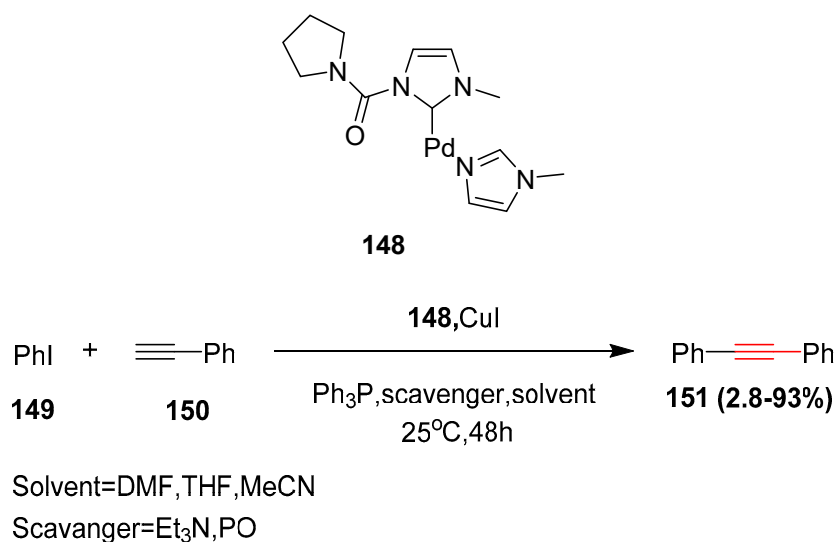
Scheme 35. Synthesis of unsymmetrical buta-1,3-diyne via Palladium and Copper Catalyzed Coupling.

Furthermore, 2-ethynylbenzo-furans were synthesized by Sonogashira cross coupling of 2-ethynyl-phenol with (E)-1,2-di-iodo-alkenes catalyzed via Pd (II) acetate, and CuI Scheme 36 [72].



Scheme 36. Coupling of (E)-1,2-di-iodo-alkenes with 2-ethynyl-phenol.

It was noted that N-Carbamoyl heterocyclic carbene complex of palladium was developed as palladium source in 2002 while in 2008 it was used in base free Sonogashira cross coupling. The base sensitive substrates were used and catalyzed by palladium complex **148** and copper. The iodobenzene was coupled with terminal acetylenes in absence of base and catalyzed via N-Carbamoyl heterocyclic carbene complex of palladium and copper iodide Scheme 37. A good yield of the coupled product was obtained [73].



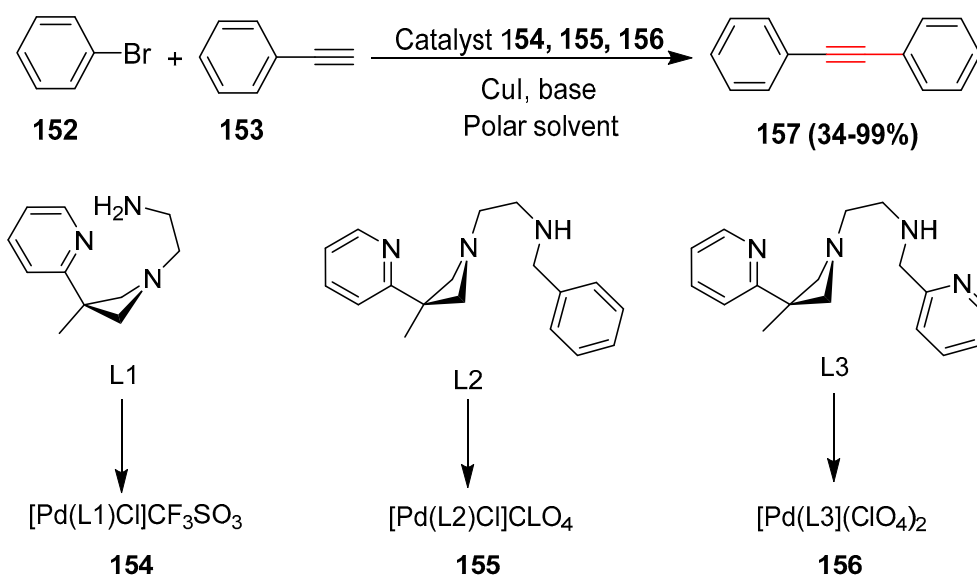
Scheme 37. Base free Sonogashira cross coupling of phenyl iodide and phenyl alkyne.

2.8. In 2009

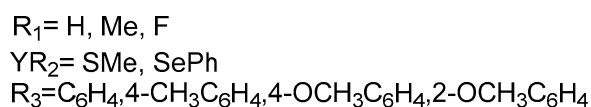
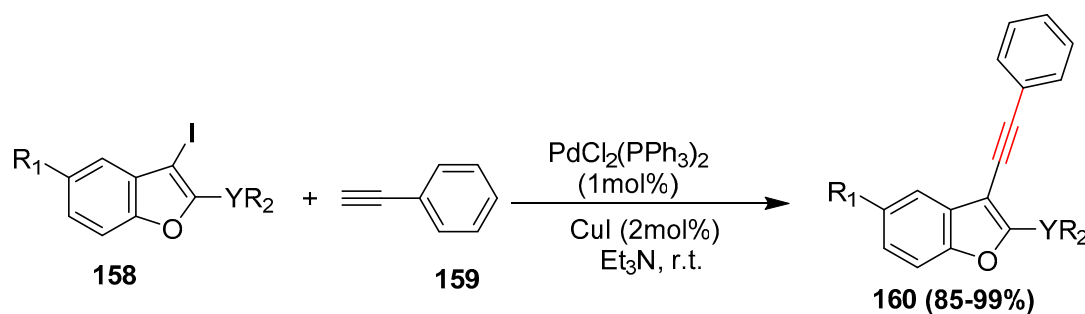
Usually, the Sonogashira reaction is performed by using Pd–phosphine complex and CuI in the presence of secondary or tertiary amine or various simple bases. Many of these complexes are sensitive to both moisture and air. Previously, non-phosphine Sonogashira cross coupling was used, as discussed earlier in this review. However, only activated aryl-chlorides can couple in the presence of these catalysts. Thus, the search for coupling catalysts that show excellent activity and broad applicability continues. In 2009, Lee and Coworkers synthesized efficient water stable phosphine free pyridyl-azetidine based Pd (II) complexes (**154**, **155**, **156**) for the Sonogashira reaction [74]. Various aryl bromides and aryl chlorides efficiently coupled with **153** under different catalyst loadings. The addition of Copper Iodide increased the rate of reaction (Scheme 38).

Oxygen containing heterocycles possess many biological activities, such as anti-inflammatory [75], anticancer [76], antioxidative [77], antiviral [78] and antifungal activity [79]. It was a major challenge for organic chemists to synthesize heterocyclic compounds with a high degree of selectivity, specially the benzo[b]furan from a simple synthon. The typical structure of these compounds has a substituent at the C-2 and C-3 of benzofuran skeleton. Thus, Manarin and coworkers reported the preparation of **160** through the Sonogashira reaction of compound **158** in the presence of Palladium and Copper [80]

as shown in (Scheme 39). Different alkyl and aryl terminal alkynes, as well as propargyl alcohols and protected propargyl alcohols were used.

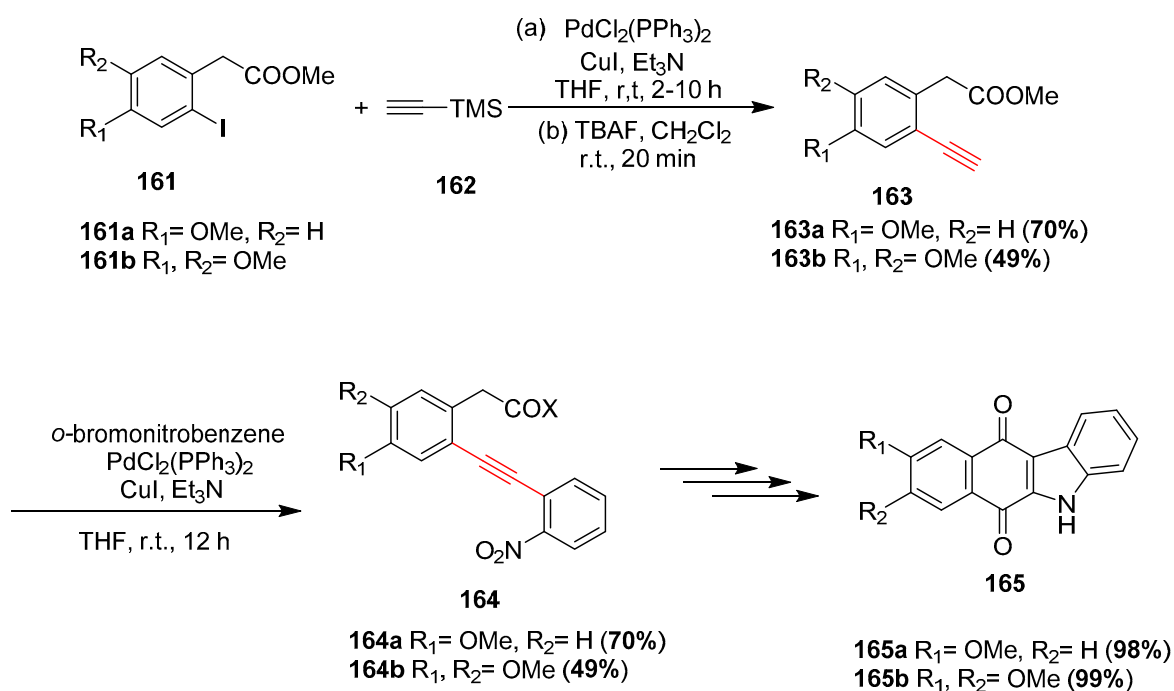


Scheme 38. Sonogashira cross coupling of bromobenzene with terminal phenyl alkyne.



Scheme 39. Sonogashira Cross Coupling of 3-Iodobenzo[*b*]furans with phenyl alkyne.

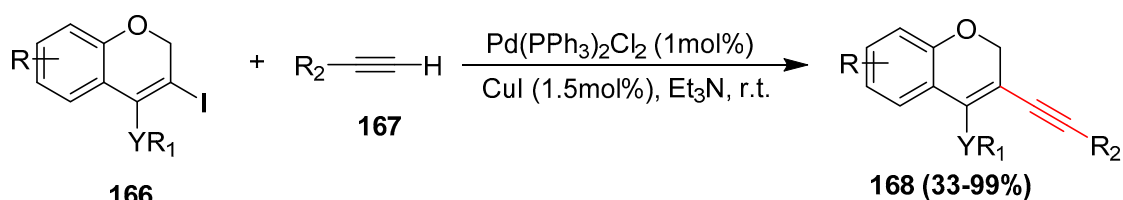
Similarly, in organic synthesis, alkynes are of great interest because of their use in the synthesis of heterocyclic compounds via intra-molecular hetero-annulation of amines, alcohols, carboxylic acids and amides to a C–C triple bond. Thus, Salas and Coworkers reported a nitro-group mediated regio-controlled hetero-annulation of 2-[2-(phenylethynyl)phenyl] acetic acids to (Z)-1-(2-nitrobenzylidene)iso-chroman-3-ones (Scheme 40) [81]. Cross coupling of ester of o-iodophenyl acetic acid with Trimethylsilyl-acetylene and then Trimethylsilyl group was deprotected by using TBAF, which provided the derivative of phenyl-acetylene **163**, which was then subjected to a second Sonogashira cross coupling with o-bromo nitrobenzene. This resulted in the formation of **164**. Phenyl acetate derivatives formed by basic hydrolysis of **164** underwent cyclo-isomerization, resulting in the formation of expected lactone, which on reaction with NaOMe in CH₃OH, furnished the required nitrophenyl-naphthoquinone, which was then easily converted into **165**.



Scheme 40. Synthesis of 5H-benzo[b]carbazole-6,11-dione via Palladium and Copper Catalyzed Coupling.

2.9. In 2010

Among heterocycles, pyrans are the most common structural moieties present in various natural products. In particular, 2H-benzopyrans are present in a various compounds that exhibit important biological and pharmaceutical activities such as coutareagenin and dauri-chromenic acid show anti-diabetic properties [82] and anti-HIV activity [83] respectively. The applicability of the selectivity of alkyne at 3-position and chalcogen at 4-position of benzopyran can constitute a synthetic approach to the synthesis of biological active compounds. Thus, Speranca and coworkers reported the synthesis of 3-alkynyl-4-chalcogen-2H-benzopyrans (as shown in Scheme 41) via Sonogashira reaction of **166** with various terminal-alkynes in the presence of Pd and Cu catalyst [84]. The obtained product was effective for successive hydro-telluration at the triple bond. They compare the influence of different catalysts such as $\text{Pd}(\text{PhCN})_2\text{Cl}_2$, PdCl_2 , $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and $\text{Pd}(\text{PPh}_3)_4$. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ was found to be the most efficient catalyst. It was also noted that in the absence of CuI, no coupling product was formed. In addition to using Et_3N as base and solvent, we tried other solvents and bases.



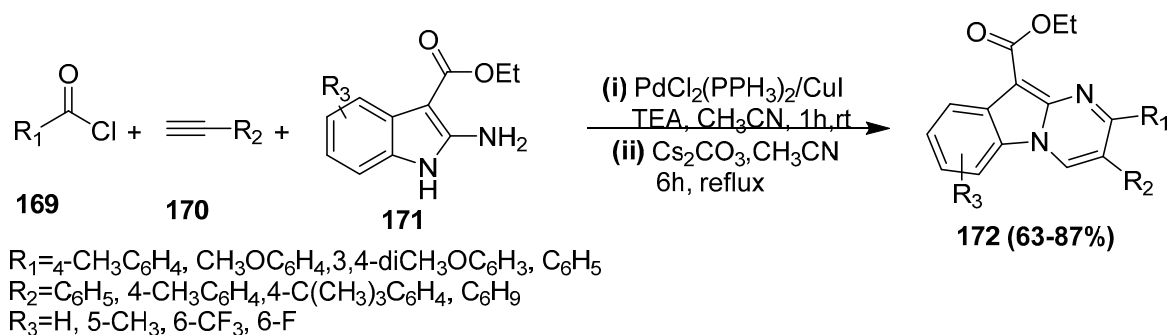
Y = S, Se; R = Me, naphthyl; R_1 = Me, butyl; R_2 = alkyl, aryl, alcohol, ether

Scheme 41. Synthesis of 3-alkynyl-4-chalcogen-2H-benzopyrans via sonogashira reaction.

2.10. In 2011

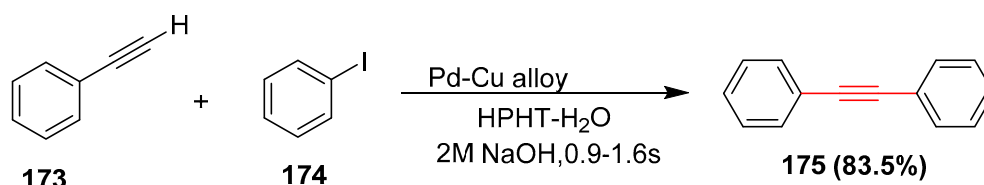
As an extension of our study of preparation of heterocycles, in 2011, Gupta et al. synthesized a highly diverse pyrimido[1,2-a]indoles through subsequent Sonogashira reaction and [3+3] cyclo-condensation reaction [85]. They synthesized 1-(4-methylphenyl)-3-phenylprop-2-yn-1-one

by cross coupling of **169** and terminal acetylene in the presence of Pd/Cu and triethyl amine, as shown in Scheme 42. The resulting product was then treated with **171** at 90 °C in the presence of Sodium carbonate and acetonitrile to furnish **172** as a single regio-isomer through [3+3] cyclo-condensation. This approach failed to yield the required product, when both these conditions were combined in multicomponent tandem format in one-pot. Therefore, they optimized the conditions of reaction by using various different bases, solvents and Pd catalysts. However, after investigating various solvents and bases, the use of Pd(PPh₃)₂Cl₂, CuI and triethyl amine, followed by addition of **171** and 1.5 equiv of Cs₂CO₃ under reflux for 6 h were found to be efficient reaction conditions.



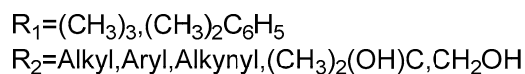
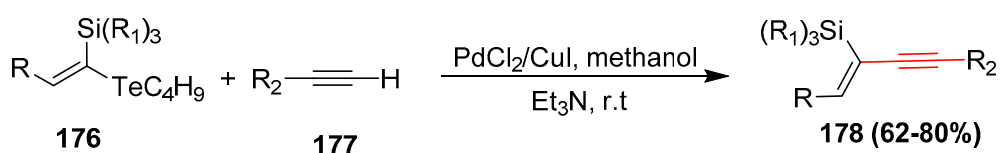
Scheme 42. Synthesis of pyrimido-indoles via Sonogashira Coupling and [3+3] Cyclocondensation.

In addition, in the last few years, in the field of synthetic chemistry, H₂O has gained significant attention due to its unique characteristic properties, especially at high pressure and high temperature conditions [86]. Various organic reactions including C–C coupling, de-hydrations and rearrangement reactions have been carried out in H₂O [87,88]. Thus, Javaid and coworkers studied Sonogashira cross coupling reaction in high-pressure and high-temperature (HPHT) water using tubular reactors coated with Palladium and Palladium-Copper alloy [89]. The reaction was dependent on pressure and temperature. Under optimized conditions of reaction, 16 MPa of pressure and 250 °C temperature and alkaline aqueous medium, cross coupling of iodo-benzene and **173** was investigated by using this system, and diphenyl ethyne was obtained with 100% selectivity. The freshly Palladium plated reactor gave very poor conversion. Therefore, for Sonogashira coupling, the catalytic activity of Palladium was increased by using Pd-Cu alloy, which enhanced the efficiency of the reaction because of the co-catalytic effect that facilitated the transfer of electron between two-metals. This catalytic system offers various advantages such as shortest reaction time, reusable and leaching free process, and high-selectivity of the required product (Scheme 43).



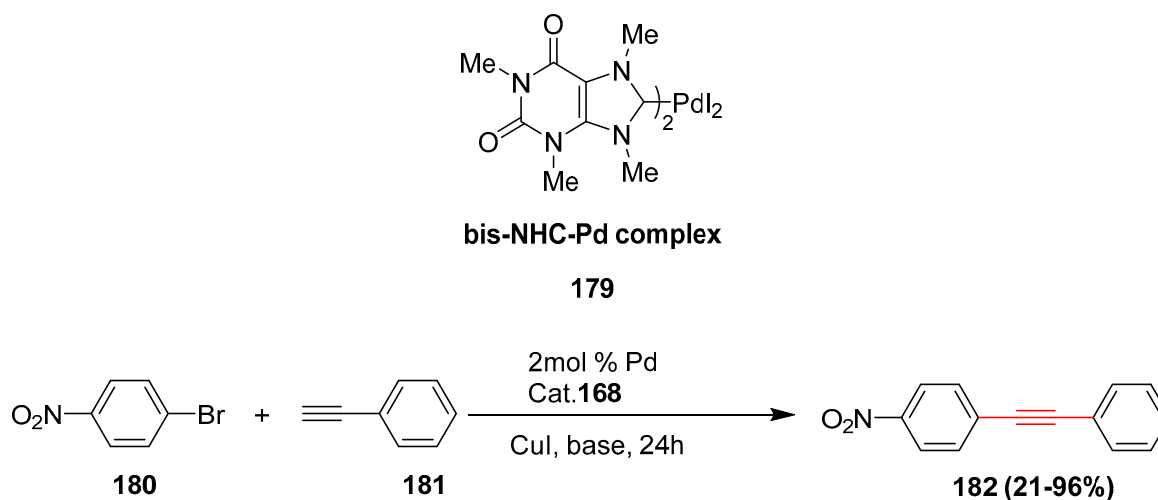
Scheme 43. Pd-Cu Catalyzed Sonogashira cross coupling of phenyl iodide and phenyl acetylene.

In 2011, Kawasoko synthesized (E)-telluro(silyl)ketene acetals and used them as a substrate in Pd and Cu catalyzed Sonogashira reactions (Scheme 44) [90]. (Z)-1,4-diorganyl-2-(triorganyl)-silyl-1-buten-3-yne was obtained via cross coupling 1.0 equiv of (E)-telluro(silyl) ketene acetal (**176**) with 2 equivalents of **177** by using 20 mol % of both PdCl₂ and CuI and CH₃OH/Et₃N as solvent under sonication.



Scheme 44. Synthesis of (Z)-1,4-diorganyl-2-tri(organyl)silyl-1-buten-3-yne via Cross Coupling.

Recently, a wide variety of cross coupling reactions catalyzed by Palladium complexes containing N-heterocyclic carbene (NHC) as a ligand have been reported. NHC derived from disubstituted imidazolium salt engaged the attention of researchers [91]. N-heterocyclic carbene formed a stronger bond with most of the metals than phosphine ligands due to their good σ -donating ability [92]. Indeed, in many catalytic reactions metal complexes containing NHC ligand have been proved to be more efficient catalysts as compared to phosphine-containing metal-complexes [93]. Thus, Luo and coworkers synthesized a new bis-N-heterocyclic carbene-PdI₂ catalyst **179** from caffeine, as shown in Scheme 45. Under various conditions Palladium Catalyst **179** was used in Sonogashira cross coupling of para-bromo nitrobenzene **180** and phenylacetylene **181**. The reaction did not proceed very well in H₂O, even at 90 °C [94]. The 1 equivalent of Brij 30 was added in the reaction mixture as the non-ionic surfactant and NaO-*t*-Bu and KOH as the base, and it improved yield as the temperature was raised from 25 °C to 90 °C.

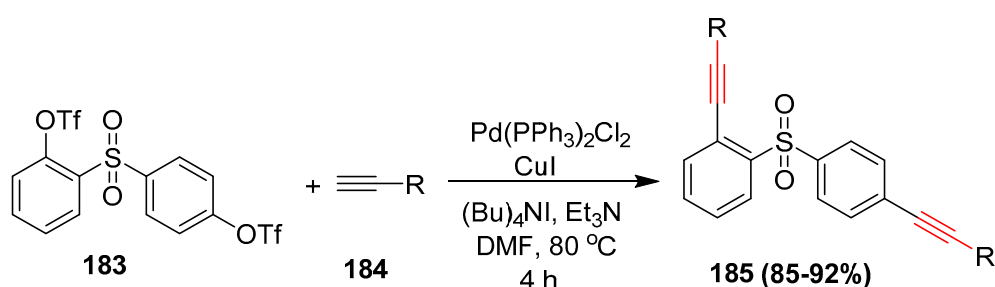


Base= NaO^tBu, KOH

Scheme 45. Copper and bis-NHC-PdI₂ catalyzed Sonogashira Cross Coupling of para-bromo nitrobenzene with phenylacetylene.

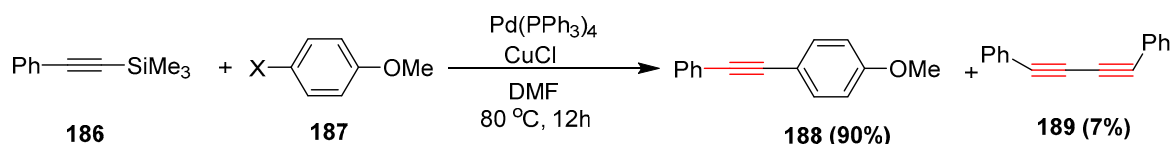
2.11. In 2012

Khera and coworkers reported Pd catalyzed reactions and synthesis of bis(triflates) of 2,4'-bis(hydroxy) diphenyl sulfone [95]. In medicinal chemistry, arylated sulfones are important structural moieties because of their various biological activities such as anti-bacterial activity [96], antiHIV [97] and anti-cholesteremic [98]. The Sonogashira cross coupling of **183** with alkynes **184** gave 2,4'-bis(alkynyl)diphenyl sulfones **185** containing two different aryl groups (Scheme 46). The reaction was carried out by using Copper Iodide and [Pd(PPh₃)₂Cl₂] as a catalyst, triethyl amine as a base and DMF as the solvent.



Scheme 46. Synthesis of 2,4'-bis(alkynyl)diphenyl sulfones via Sonogashira Reaction.

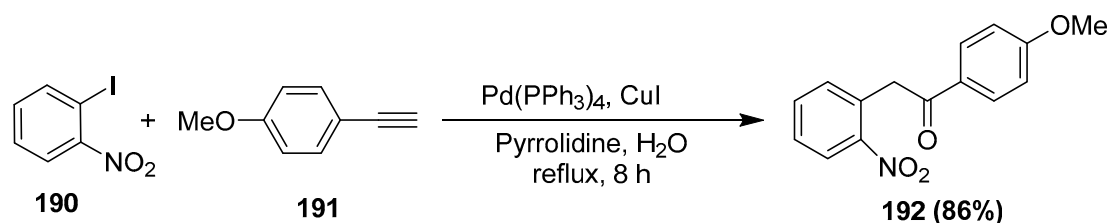
Similarly, Nishihara and coworkers synthesized unsymmetrically disubstituted ethynes by the Pd-Cu(I) co-catalyzed Sonogashira-Hagihara cross coupling reactions of 1-aryl-2-trimethylsilyl ethynes with aryl iodides, bromides, and chlorides [99]. Unsymmetrical diarylethyne moieties are common in the pharmaceutical industry, natural products and materials science. Compounds containing this moiety can easily be synthesized by using of the Sonogashira-Hagihara cross coupling reaction of terminal alkynes with aryl halides, or pseudo-halides (Scheme 47).



Scheme 47. Synthesis of unsymmetrically disubstituted ethynes by the Pd-Cu catalyzed coupling.

2.12. In 2013

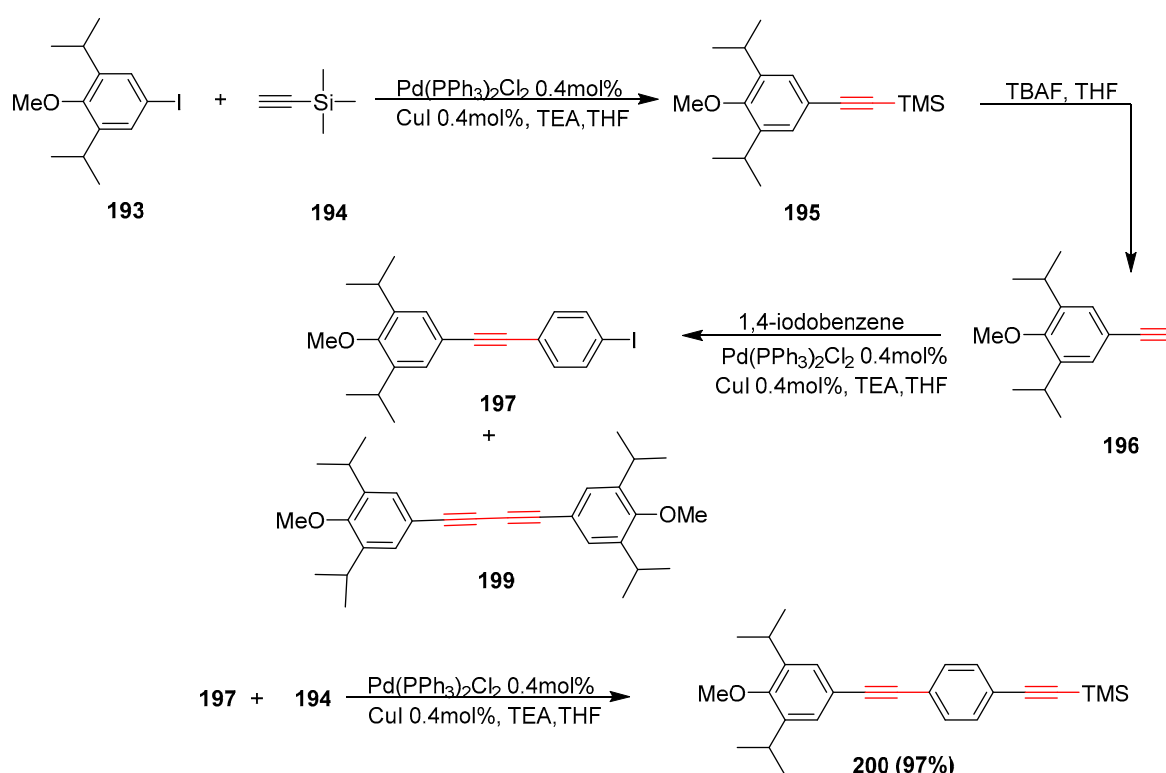
Ahmed used the Sonogashira reaction for the synthesis of 2-(2-nitrophenyl)-1-aryl ethanones, a valuable precursor for the synthesis of indoles [100]. In the presence of pyrrolidine, the alkyne formed via Palladium and Copper catalyzed coupling of 190 with 1-ethynyl-4-methoxybenzene continue with simultaneous regio-selective hydration, which resulted in the formation of corresponding aryl-ketone (Scheme 48). This method has various significant features such as high yields, reaction in H₂O, and magnificent regio-selectivity.



Scheme 48. Synthesis of 2-(2-nitrophenyl)-1-aryl ethanones via Sonogashira cross coupling followed by hydration reaction.

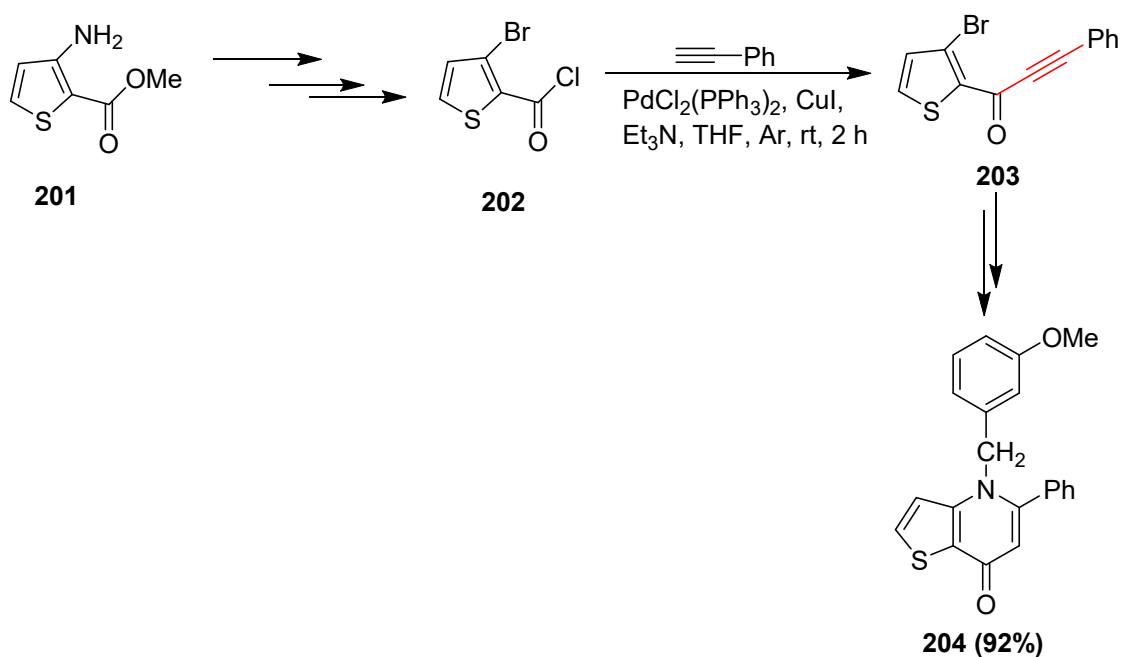
The Phenylene-ethynylene oligomers and polymers are of great interest, because of their use for fabrication of optoelectronic and electronic devices [101,102]. In recent years, great progress has been made in the synthesis of numerous triple bond containing oligomers and rod like rigid p-arylacetylene polymers; however, because of intrinsic limitations of many synthetic methods, synthesis of highly conjugated arylene-ethynylene polymers and large oligomers is impossible. Defects in the conjugated system restrict their use in photonics and molecular electronics. For the preparation of triple bond containing π -conjugated systems Sonogashira cross coupling is the only effective method [103]. Hetero-coupling of terminal alkynes and iodo substituted aromatic compounds is more difficult than the homo coupling of the two terminal alkynes [104]. The synthesis of arylene ethynylene oligomers

via Sonogashira reaction is also complicated because of competing homo coupling induced by the oxidizing agent (O_2) and Copper iodide. Thus, under oxygen-free conditions Bai and coworkers synthesized **193** monomer by methylation of 2,6-di-tert-butylphenol, followed by iodination. It was then coupled with Trimethylsilyl acetylene (TMSA) under the conditions of Sonogashira cross coupling reaction to furnish the monomer protected with Trimethylsilyl, followed by deprotection by using tetra-*n*-butyl ammonium fluoride resulted in the formation of **196**. This was then reacted with excess 1,4-diiodobenzene to yield dimersubstituted with iodo [**105**]. A small amount of side product formed by homo-coupling was also obtained. Repeating this cycle of mono-alkynylation of diiodo-phenylene, coupling with Trimethylsilyl acetylene (TMSA) and then deprotection of TMS, resulted in the formation of tri, tetra and pentamer along with homo coupling side products. Efficiency of the Sonogashira reaction decreases as the size of coupling partners increases, even if there is no steric hinderance at the reaction site (Scheme 49).



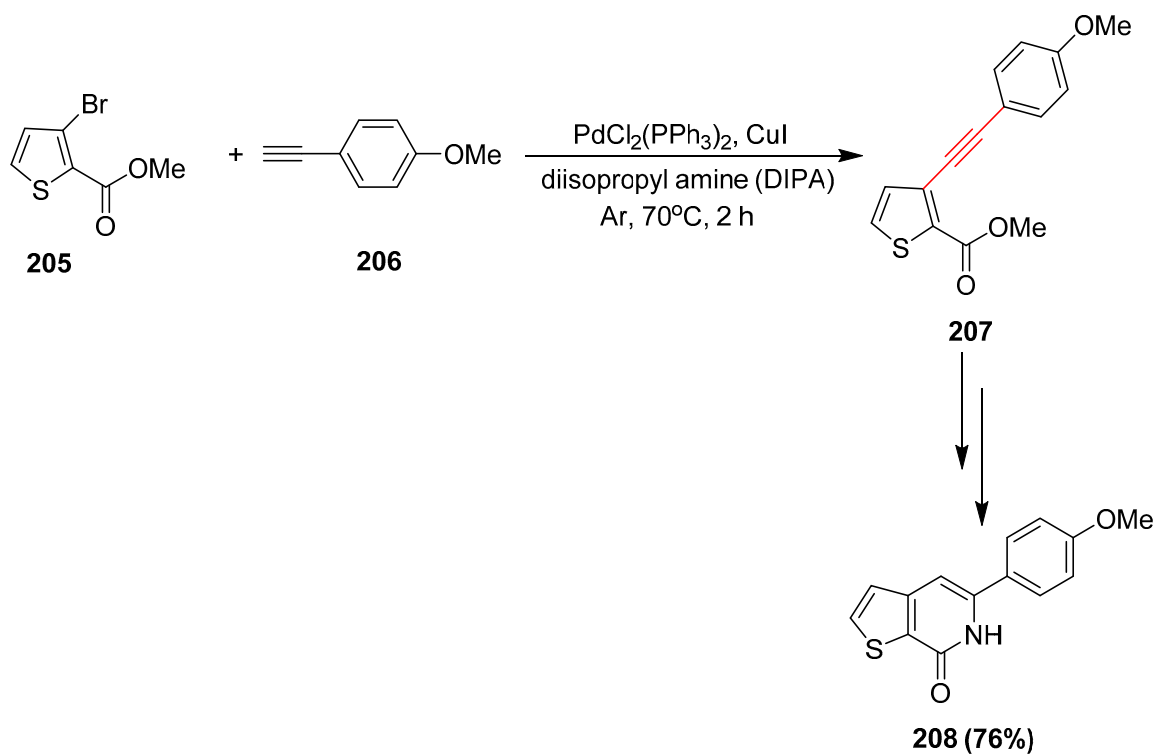
Scheme 49. Synthesis of dimer via oxygen-free Sonogashira Cross Coupling.

Iaroshenko described an effective method for the synthesis of thieno[3,2-*b*]-, [2,3-*c*]-, and [3,2-*c*] pyridones via Sonogashira cross coupling of thienyl acetylenes with bromo thiophenes using Et_3N or di-isopropyl amine, followed by subsequent addition of amines/ammonium to the thienyl acetylenes intermediate [**106**]. The suitable substrate for the synthesis of **204** is 1-(3-bromothiophen-2-yl)-3-arylprop-2-yn-1-ones (**203**). Compound **203** was achieved by Sonogashira reaction of **202** with terminal aryl acetylenes using Pd and Copper in the presence of Et_3N in Tetrahydrofuran as shown in Scheme 50. Then the reactions of ketone with amines in the presence of $Pd_2(dba)_3$, BINAP, 1.4 equivalent of Cs_2CO_3 and toluene as a base and solvent, respectively, resulted in the formation of thieno[3,2-*b*] pyridones **204**.



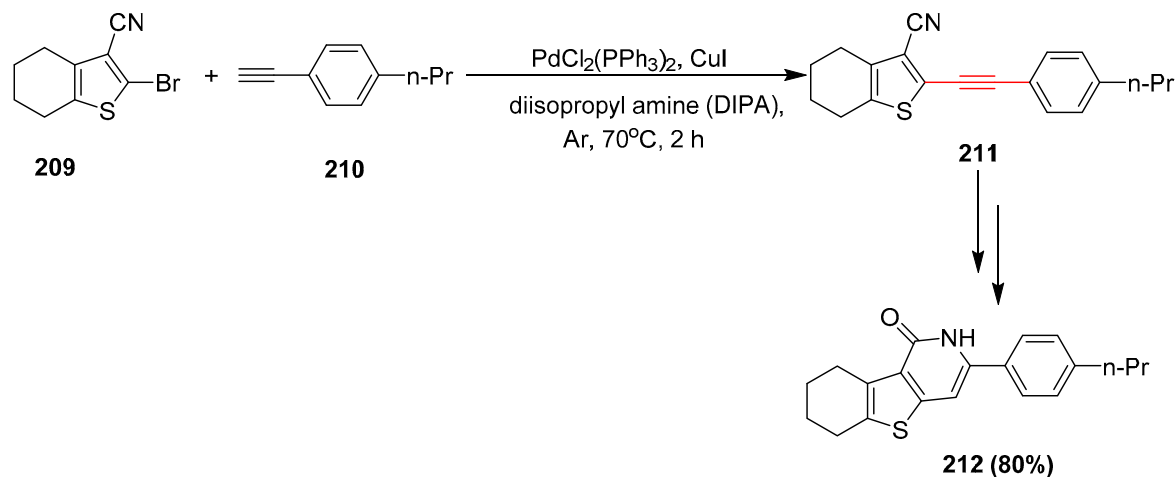
Scheme 50. Synthesis of 4-(3-methoxybenzyl)-5-phenylthieno[3,2-b]pyridin-7(4H)-one.

They synthesized thieno[2,3-c]pyridones by Sonogashira reaction of **205** with terminal alkyne followed by a base mediated intra-molecular C-N bond forming reaction (Scheme 51). It was found that in the presence of Pd/Cu, reaction of **205** with **206** resulted in the formation of thienyl alkyne **207**. Reaction of **207** with aq.NH₃ at heating produced amides which react with sodium methoxide in CH₃OH at reflux furnished thieno[2,3-c] pyridones **208** by intramolecular cyclization reaction [106].



Scheme 51. Synthesis of 5-(4-methoxyphenyl)thieno[2,3-c]pyridin-7(6H)-one.

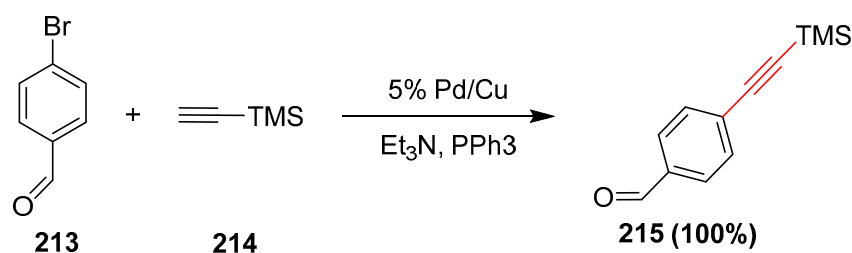
Thieno[3,2-c]pyridines was also synthesized by Pd/Cu catalyzed Sonogashira reaction of the corresponding alkyne with **209**, followed by hydrolysis of CN group of the **211** under the action of Trifluoroacetic acid-H₂SO₄ system to amides and their intramolecular cyclization with sodium methoxide [106] (Scheme 52).



Scheme 52. Synthesis of 3-(4-propylphenyl)-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one.

2.13. In 2014

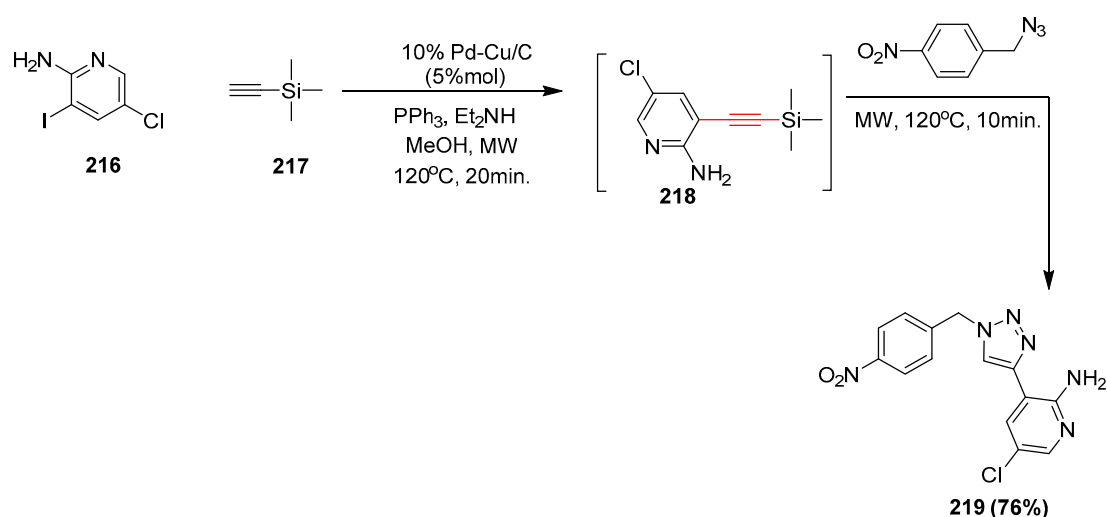
Korzec and coworkers developed a less costly and more efficient bimetallic nano Pd/PdO/Cu catalytic system for Sonogashira cross coupling as shown in Scheme 53. They checked the catalytic activity of different bimetallic catalysts during cross coupling reaction of **213** with tri-methyl silyl acetylene. Catalysts differ in their metal loadings, type of carrier metal and Concentration of Pd [107]. The carrier metals played a role both as cocatalyst to help the trans-metalation step in the Sonogashira reaction and the Pd support for the heterogenous catalysis. Among all the checked bimetallic composition, only Palladium/Copper composite were found to be active. The catalytic ability of the Palladium/Copper catalytic system was affected by the conditions of the reaction, especially the temperature and concentration of phosphine ligands.



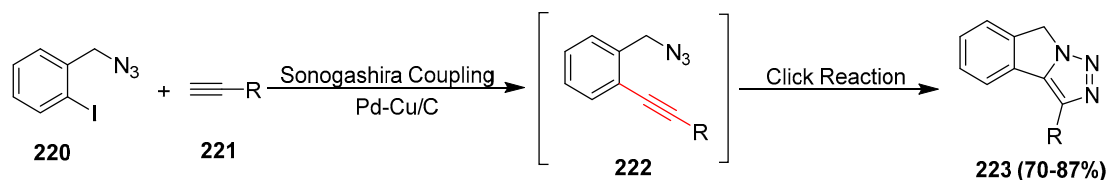
Scheme 53. Palladium and Copper catalyzed Sonogashira cross coupling of tri-methyl silyl acetylene.

A new heterogeneous Pd-Cu/C catalytic system for Sonogashira alkynylation-[3+2]-cyclo addition leading to triazoles was developed by Rossy and coworkers (Scheme 54) [108]. The Sonogashira step is suitable for both electron-donating and with-drawing substituents on the iodoaryl. This protocol allows the synthesis of various useful heterocycles with an inexpensive base and ligand in hydrophilic solvents.

The same authors also studied the chances of intra-molecular reaction in order to get structurally intriguing iso-indolines fused triazoles. According to the kinetic of reactions, the reaction can proceed by two pathways. In path I, the series involves firstly Click and then Heck reaction while Path II involves Sonogashira and then Click transformations (Scheme 55).

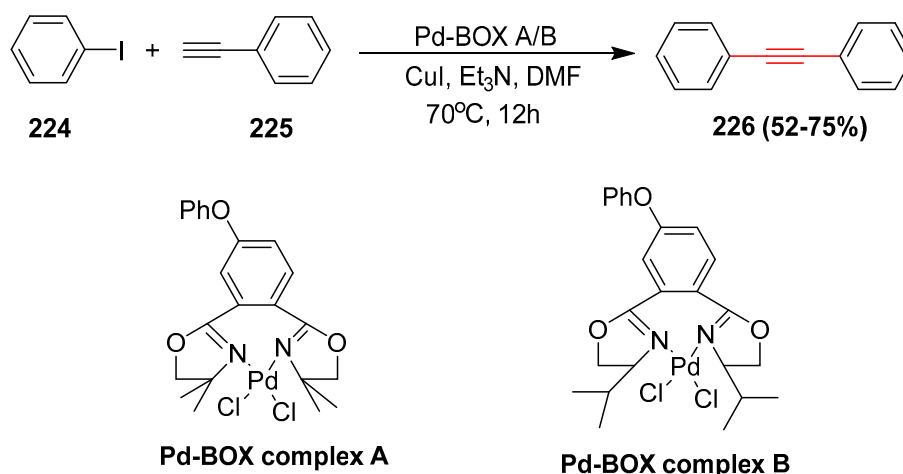


Scheme 54. Synthesis of triazoles Sonogashira alkyne-azide cross-coupling catalyzed via Pd and Cu supported on charcoal.



Scheme 55. Pd-Cu supported on Charcoal catalyzed sequential Sonogashira-Click reaction.

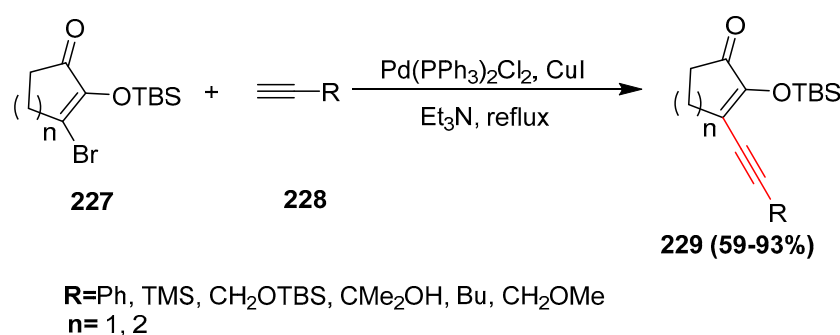
In another study, Pd-bis(oxazoline) (Pd-BOX) A and B complexes were synthesized and their catalytic activities were checked in Sonogashira cross coupling by Hussain and coworkers (Scheme 56) [109]. The reaction of phenyl acetylene and iodo-benzene in the presence of Pd-BOX (A) or (B) and CuI and Et₃N as a base at 70 °C. The results showed good conversion of iodo-benzene (77%) in the presence of Palladium-BOX (A) and slightly lower conversion (57%) with Palladium-BOX (B), affording the di-phenylacetylene as the only product.



Scheme 56. Sonogashira coupling reaction of iodobenzene with phenyl acetylene.

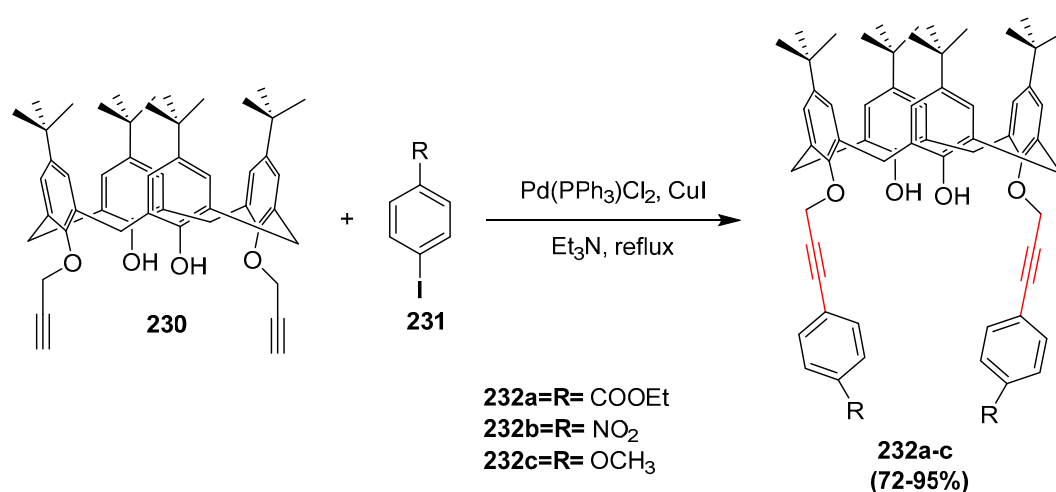
It was observed that enols of cyclic 3-alkynyl substituted 1,2-diones can be achieved via Sonogashira reaction. As shown in Scheme 57, an efficient Sonogashira reaction of substituted acetylenes with enolate of 3-bromocyclopentane and 3-bromocyclohexane-1,2-diketones was developed by Paju and

coworkers [110]. In a short reaction time, the protocol affords enols of 1,2-diketonescyclohexane and 3-alkynylsubstituted cyclopentane with good yield. In order to find favorable conditions for Sonogashira reaction of cyclic 3-bromo-1,2-diones they investigated the reaction of 3-bromo-1,2-diones with Phenyl acetylene and trimethylsilyl acetylene (TMSA). Phenyl acetylene reaction in the presence of Pd and Cu and TMSA with unprotected 3-bromo Cyclopentane-1,2-diketones gave a low yield 13% of Phenyl acetylenic and 15% for Trimethylsilyl acetylenic compound. In the same reaction conditions, the bromide of silyl enol ether reacted smoothly with phenylacetylene and TMSA at the same time, affording the corresponding products in 90% and 83% yield respectively. Therefore, only protected cyclic 3-bromo-1,2-diones **227** were used in Sonogashira. A medium presence of CuI supported the reaction.



Scheme 57. Cross Coupling of cyclic 3-bromo-1,2-diketones with terminal acetylene.

Double Sonogashira reaction is an excellent method for the synthesis of calix-arenes with electron rich cavities. Due to unique and tunable three-dimensional structure, Calix[4]arene is broadly used in the design of fluorescent receptors as a molecular scaffold [111,112]. Thus, Sun and coworkers reported synthesis of derivatives of calix[4]arene through Palladium catalyzed Sonogashira reaction from **230** and 25,27-dipropargyl-calix[4]arene [113]. Calix[4]arene derivatives show different fluorescent properties due to the different nature of substituents Calixarenes containing the electron-donating groups such as methoxy enhanced the intensity of fluorescence, while in a-protic solvents, the electron-withdrawing groups containing Calixarenes are not apparently fluorescent. This effect was estimated mainly due to the increase of delocalization of the p- π electron (Scheme 58).

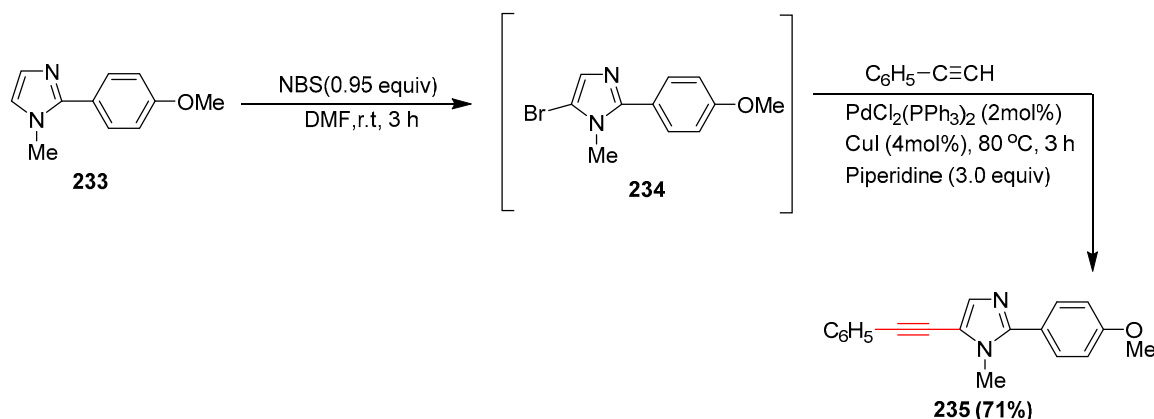


Scheme 58. Synthesis of calix[4]arene derivatives via Palladium and Copper catalyzed Coupling.

2.14. In 2015

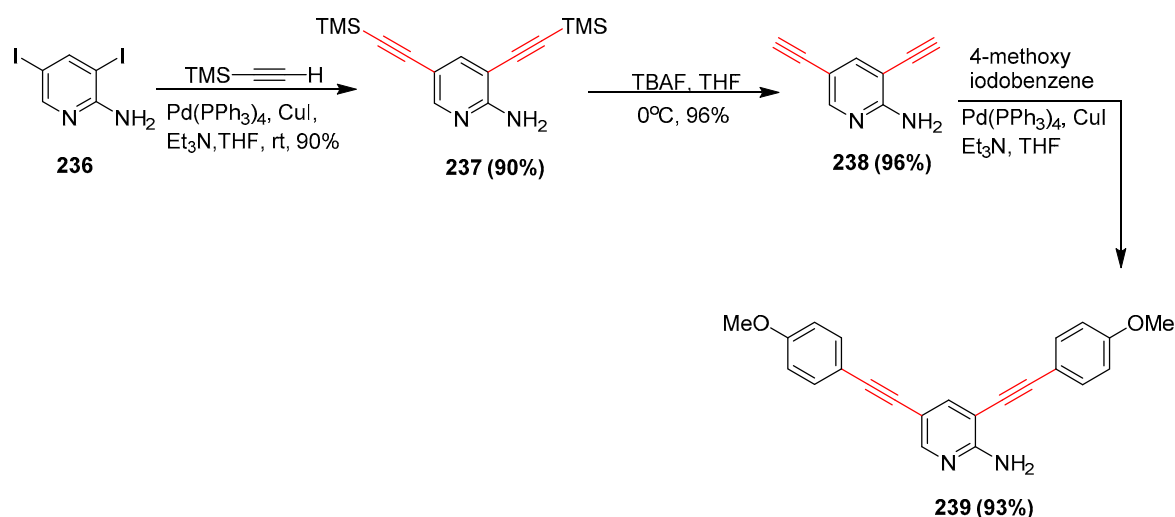
Bellina and coworkers in 2015 developed substituted alkynyl imidazoles via a one pot sequential reaction involving a highly regio-selective electrophilic C-5 bromination of substituted imidazoles,

followed by an efficient Sonogashira Coupling [114]. They observed that the use of piperidine as a base instead of Et_3N increased the yield (Scheme 59). The typical approach for the synthesis of hetero aryl alkynes relies on the Sonogashira reaction, in which terminal-alkynes and hetero-aryl halides are cross coupled in the presence of Palladium-Copper [115,116].



Scheme 59. One-pot sequential bromination of substituted imidazoles via Sonogashira Coupling.

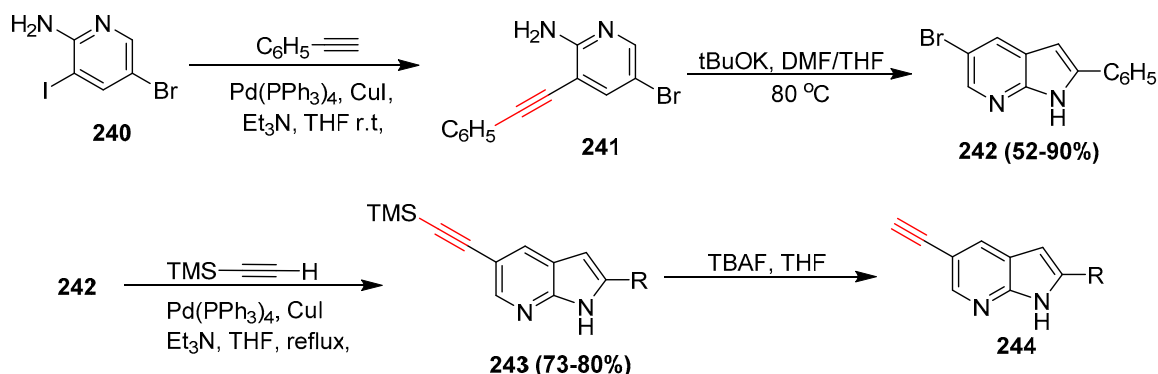
The Synthesis of 7-azaindoles having triazole and quinoxaline substituents at C-5, via double Sonogashira cross coupling of di-halogenated amino pyridines was reported by Leboho and coworkers in 2015 (Scheme 60) [117]. A double Sonogashira coupling of 3,5-diiodoaminopyridine with TMS-acetylene gave compound **237**. Removal of TMS with TBAF resulted in the formation of **238** which on further double Sonogashira with 4-methoxy iodobenzene gave compound **239**. After that, compound **239** on treatment with TFAA was converted into trifluoroacetamide and then it was subjected to the Cacchi-reaction and 2,3,5-trisubstituted 7-azaindoles was achieved.



Scheme 60. Synthesis of 3,5-bis((4-methoxyphenyl)ethynyl)pyridin-2-amine via Pd and Cu catalyzed Cross Coupling.

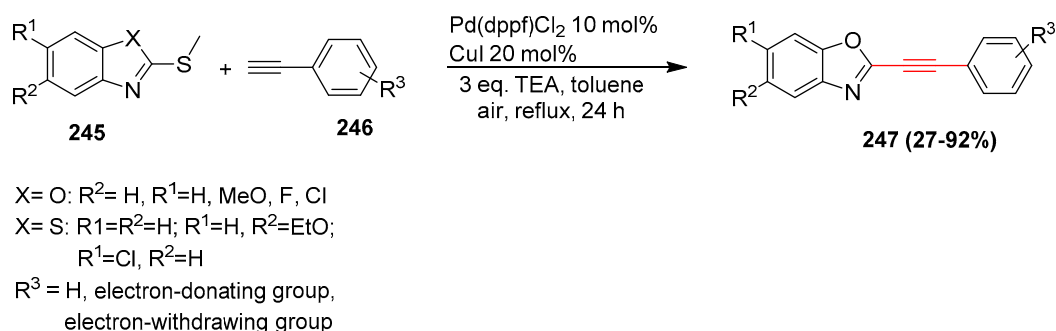
The same authors also reported that when **240** was exposed to acetylene under Sonogashira conditions, coupling occurred at the position of iodine. Then, the azaindole nucleus was formed by using KOtBu in a mixture of Di-methyl formamide and tetra-hydro furan, followed by another Sonogashira cross coupling reaction at the bromo substituted site of azaindoles, which resulted in the formation of **243**. This was then subjected to tetra-*n*-butylammonium fluoride (TBAF) for the removal

of the trimethylsilyl. Then 7-azaindoles having quinoxaline and triazole substituents at C-5 were easily accomplished through an alkyne-azide cycloaddition (Scheme 61).



Scheme 61. Synthesis of 5-ethynyl-2-phenyl-1H-pyrrolo[2,3-b]pyridine via Sonogashira reaction.

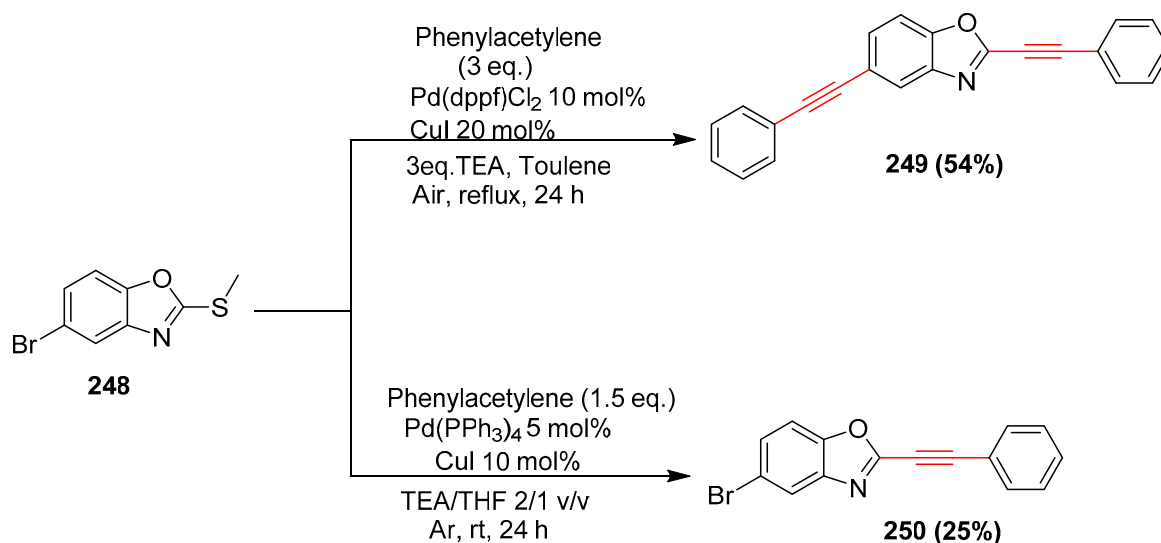
Similarly, derivatives of 2-alkynyl benzoxazole and 2-alkynyl benzothiazole was synthesized via Sonogashira of the terminal alkynes and thio-ethers under aerobic conditions, using Pd(dppf)Cl₂ and CuI by Paun and coworkers as shown in Scheme 62 [118]. The nature of benzoxazoles and benzo-thiazoles were also checked in the de-sulfitative Sonogashira. The reaction occurred better in aerobic conditions than inert atmosphere, although increased amounts of the diyne side product were formed.



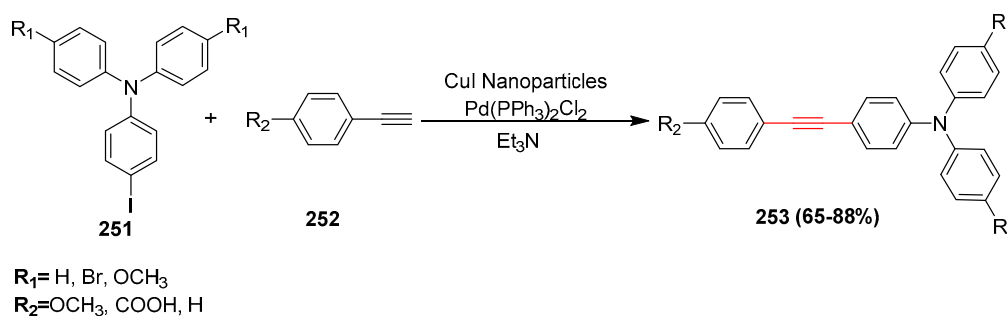
Scheme 62. Synthesis of 2-alkynyl benzoxazole and -thiazole via Sonogashira Cross Coupling.

In aerobic conditions, the authors also coupled **248** with phenyl acetylene, which showed C–S and C–Br coupling of the alkyne. Under aerobic conditions, methyl thio-benzoxazoles brominated analog gave product **249** (Scheme 63). Increasing the equivalents of alkyne did not improve the yield of coupling reaction. Under inert atmosphere, an attempt to selective Sonogashira cross coupling of 5-bromo-2-(methylthio) benzoxazole surprisingly gave compound **250**, with preservation of the bromine substituent which allowed the opportunity to further functionalize the benzoxazole nucleus through reactions of the C–Br bond.

Triaryl amines linked with aryl-ethynyl (Ar-ethynyl-TAA) are of great interest because of their wide use in the synthesis of various natural products [119,120] and polymers [121–123]. Numerous methods have been reported for the synthesis of Ar-ethynyl-TAA by Sonogashira coupling using Pd and Cu which were applied in low yields of products at long reaction times. Thus, Safaei-Ghomi and coworkers developed an efficient method for the preparation of various derivatives of Aryl ethynyl linked triaryl amines via Sonogashira cross coupling using Pd/Cu nanoparticles under ultrasonic irradiation [124]. This solvent-free method offers several advantages such as high yields, green procedure, short reaction times. Behaviors of different catalytic systems were checked, among which Pd (PPh₃)₂Cl₂/CuI nanoparticle showed excellent catalytic activity (Scheme 64).



Scheme 63. Sonogashira Cross Coupling of 5-bromo-2-(methylthio)benzoxazole with phenylacetylene.



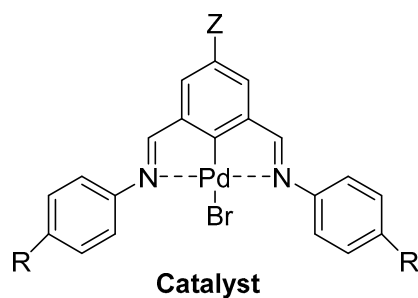
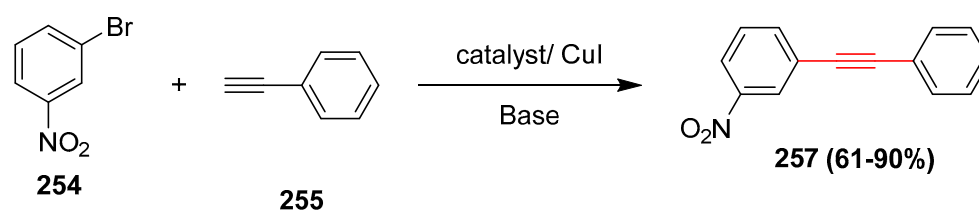
Scheme 64. Synthesis of arylethynyl linked triarylamine with substituted phenylacetylene.

Pd-pincer complexes have been widely used as a catalyst in a various C-C or carbon-hetero bond formation [125]. In past decades, due to low costs and wide scope applications, NCN-Pd pincer complexes have attracted much attention. Thus, in 2015, Zhang and coworkers synthesized PdII-**257**, **258** and **259** pincer complexes and checked their activity in Sonogashira reaction (Scheme 65) [126]. In the Sonogashira reaction, **258b** was used as a precatalyst to optimize the conditions of reaction, in order to check the catalytic activity of these complexes. Different solvent and bases were used, and it was found that the cross-coupling reaction gave excellent yield of products, when KOAc and DMAC were used as the base and solvent respectively. Similarly, the other items such as loading of catalyst 1mmol%, temperature of reaction 90°C as well as reaction time of 12h are also optimized. Using these optimized conditions of reactions, they checked the catalytic ability of the other Pd pincer complexes in the same cross coupling reaction. Their catalyzed results showed that **259a** was the most active catalyst and the general order of catalytic ability was as follows, **259** > **258** > **257**. Furthermore, varying Z from Bu^t to NO₂ suggest that presence of the electron-withdrawing groups at the 4th position of Pd enhanced its catalytic activity.

2.15. In 2016

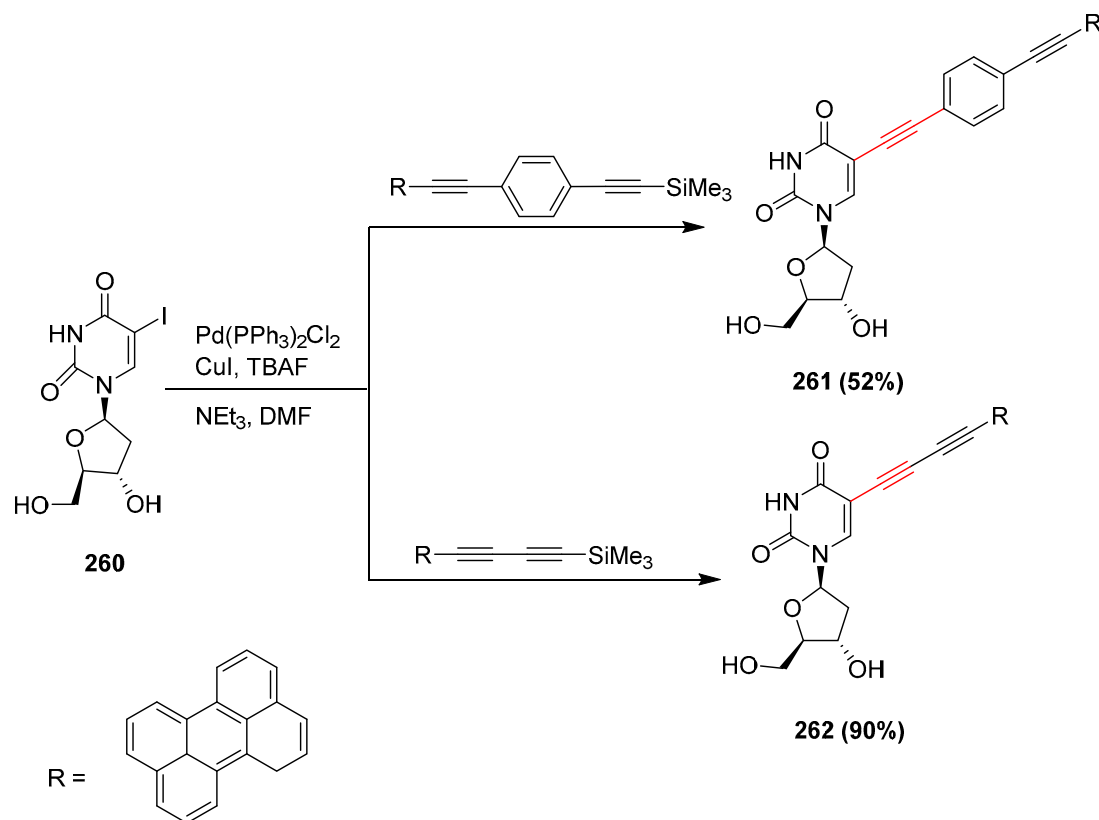
A synthetic strategy for the formation of perylene nucleoside containing elongated rigid link between hydrocarbon and nucleobase through Sonogashira cross coupling was developed by Chistov and coworkers in 2016 [127]. 5-iodo-2'-deoxyuridine **260** was protected by Propinaylation and then coupled with Trimethylsilyl. Alkynes were added in the presence of Pd and Cu and TBAF in the reaction which promote Silyl deprotection. Propinyl protection of both OH groups make both coupling products soluble enough to be purified by column chromatography. Both the OH groups are then

deprotected in the presence of K_2CO_3 , MeOH/H₂O to afford the desired product **261** and **262**, which are highly fluorescent (Scheme 66).



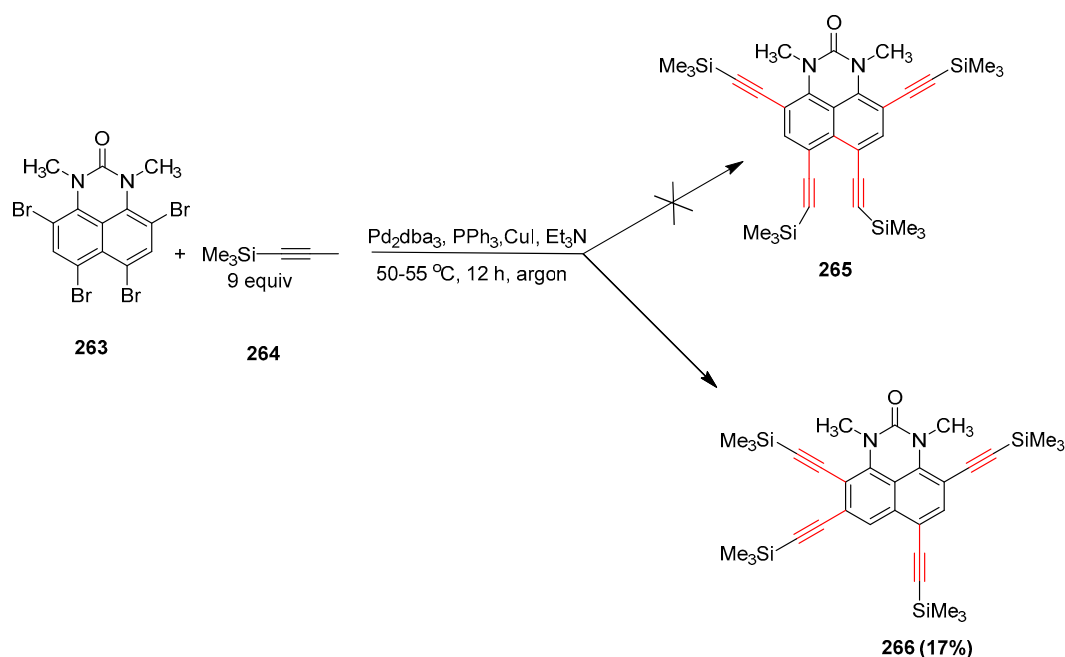
- 257** Z= Bu^t R=4-CH₃(a), H(b), 4-Cl(c)
258 Z= H R=4-CH₃(a), H(b), 4-Cl(c), 4-CH₃O(d)
259 Z=NO₂ R=4-CH₃(a), H(b), 4-Cl(c)

Scheme 65. Sonogashira Cross Coupling under Copper and NCN Palladium pincer complex catalytic system.



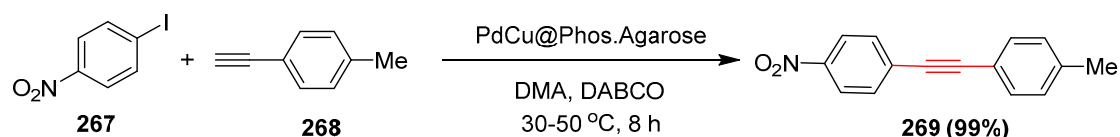
Scheme 66. Synthesis of rigid perylene nucleosides via Sonogashira cross coupling.

The synthesis of a series of mono, di, tri and tetra-alkynyl derivatives of 1,3-dimethyl- and 1,3-diethyl-1*H*-perimidine-2(3*H*)-ones from the corresponding bromides via the Sonogashira cross coupling was reported by Filatova, as shown in Scheme 67 [128]. It was found that placing two Trimethylsilyl-ethynyl groups at 6 and 7 positions of the perimidone made a sterically hindered system and, sometimes, is accompanied by a previously unknown 1,2-migration of the Pd(II)-X group in the intermediate complex. When tetrabromide **263** was coupled with Trimethylsilyl acetylene **264** an unexpected result was observed. The reaction was slow when carried out in ordinary conditions, and inseparable products were obtained. However, when Trimethylsilyl acetylene was used in the presence of Pd₂dba₃/PPh₃, CuI, triethylamine, and the system was heated for 12 h, a crystalline bright yellow compound **266** was obtained instead of the expected product **265** due to 1,2-Pd migration in an intermediate complex (Scheme 67).



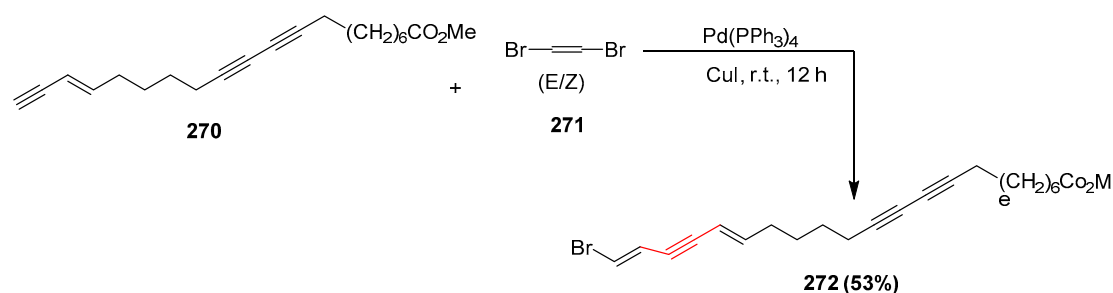
Scheme 67. Cross coupling of 4,6,7,9-tetrabromo-1,3-dimethyl-1*H*-perimidin-2(3*H*)-one with TMSA.

In 2016, Gholinejad and coworkers synthesized and characterized an efficient heterogeneous catalyst Pd and Cu nanoparticles supported on phosphinite functionalized Agarose biopolymer [129]. The activity of this catalytic system was checked in Sonogashira reaction of aryl-iodide and substituted phenylacetylene at room temperature by using DABCO as a base and Dimethylacetamide (DMA) as a solvent and 0.05% mol Pd (Scheme 68).



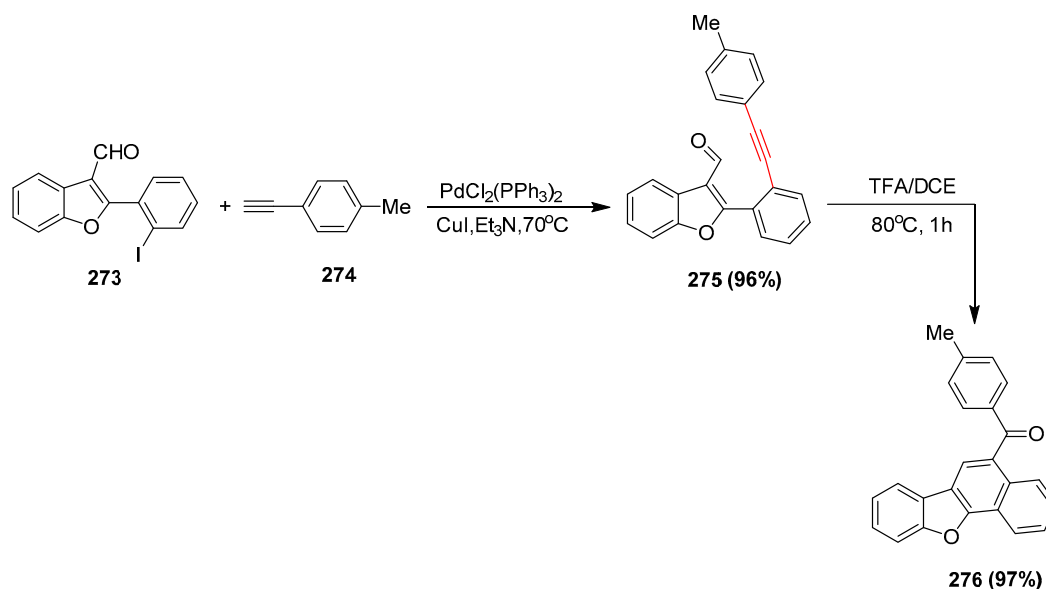
Scheme 68. Agarose Functionalized Phosphorus containing Palladium and Copper Nanoparticles catalyzed Sonogashira reaction of aryl-iodide and substituted phenylacetylene.

The synthesis of a marine brominated poly-unsaturated lipid xestosponginyne **272** having pancreatic lipase inhibitory activity through Sonogashira cross coupling of **270** with *E/Z* isomer of 1,2-dibromoethene in the presence of Pd and Copper Catalyst in triethylamine was reported by Gong (Scheme 69) [130]. The resulting moderate yield might be because of the lower reactivity of **271** in Pd catalyzed reactions. Generally, the (*E*) isomer of 1,2-dibromoethene is more reactive than the *Z* isomer.



Scheme 69. Synthesis of xestosponginyne pancreatic lipase inhibitor via Palladium and Copper catalyzed reaction.

In 2016, Nayak and coworkers reported the preparation of 5 and 6-acylated naphtho[1,2-b]benzofuran derivatives by the means of Sonogashira cross coupling and intra-molecular alkyne carbonyl metathesis (Scheme 70) [131]. Sonogashira coupling of **273** with 1-ethynyl-4-methylbenzene (**274**) in the presence of Pd and Cu resulted in the formation of **275** in 96% yield which, upon heating in Trifluoroacetic acid/DCE at 80 °C for 1h, produced desired product **276** in excellent yield.



Scheme 70. Synthesis of naphtho[1,2-b]benzofuran-5-yl(p-tolyl)methanone (**276**) by Sonogashira reaction.

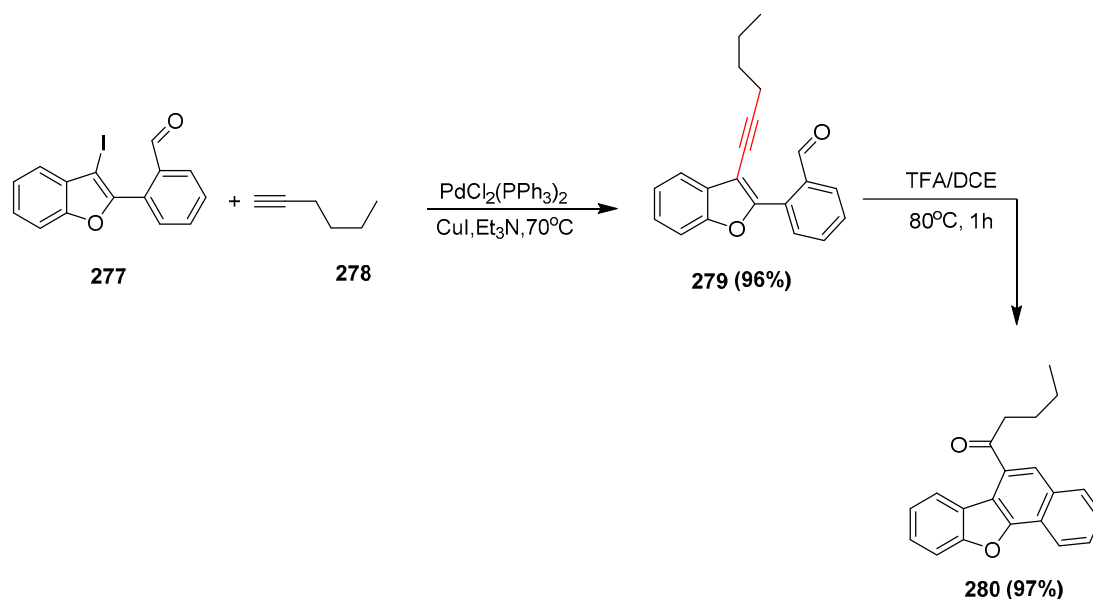
Similarly, they performed Palladium and Copper catalyzed Sonogashira of **277** with hex-1-yne (**278**) in the presence of Et₃N at 70 °C, and produced Compound **279** in 96% yield. Subjection of **279** in TFA/DCE for 1 h at 80 °C produced 6-acylaed product **280** in 97% yield (Scheme 71).

An efficient synthesis of 2,5-disubstituted Alkynyl bridged 1,3,4-Oxadiazole through Sonogashira cross coupling between arylacetylene and oxadiazole substituted phenyl bromides in the presence of Palladium and Copper was reported by Paun and coworkers [132]. This strategy is very suitable for the synthesis of Luminescent small molecules or precursor of other complex derivatives that are helpful as electron transporting components in the preparation of OLEDs (Scheme 72).

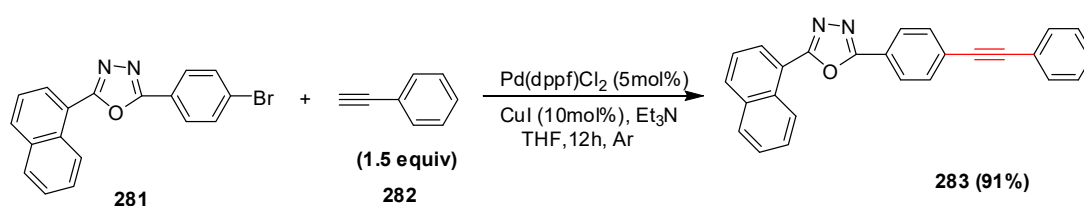
2.16. In 2017

Liu and coworkers reported FeCl₃ catalyzed synthesis of iodo-3*H*-pyrazoles derivatives [133]. 3*H*-pyrazoles derivatives are important heterocyclic compounds because of their extensive use in cyclopropanes, carbene intermediates, and diazoalkenes synthesis. To signify the effectiveness of the

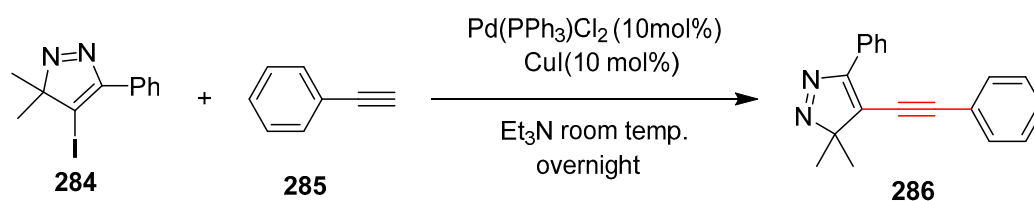
synthetic method they performed derivatization reaction of iodo-3*H*-pyrazole, as shown in Scheme 73. Pd and Cu catalyzed Sonogashira cross coupling of iodo-3*H*-pyrazole proceeded smoothly and the resulting product **286** was formed in 85% yield.



Scheme 71. Synthesis of 1-(naphtho[1,2-b]benzofuran-6-yl)pentan-1-one via Pd and Cu mediated Cross Coupling.



Scheme 72. Synthesis of 2-naphthalen substituted oxadiazole via Sonogashira Cross Coupling.

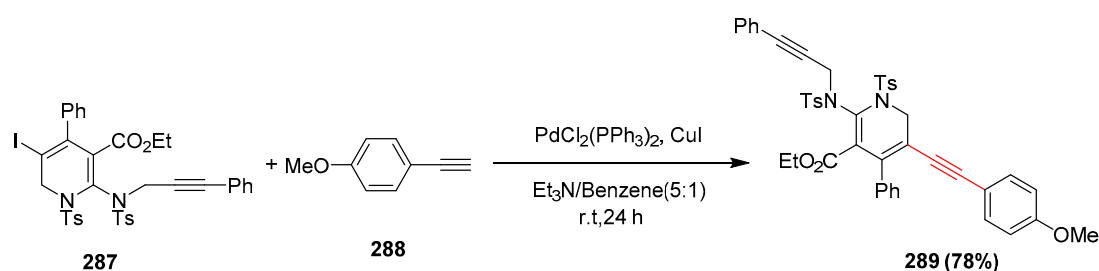


Scheme 73. Pd-Cu catalyzed Sonogashira cross coupling of 4-iodo-3,3-dimethyl-5-phenyl-3*H*-pyrazole with phenyl acetylene.

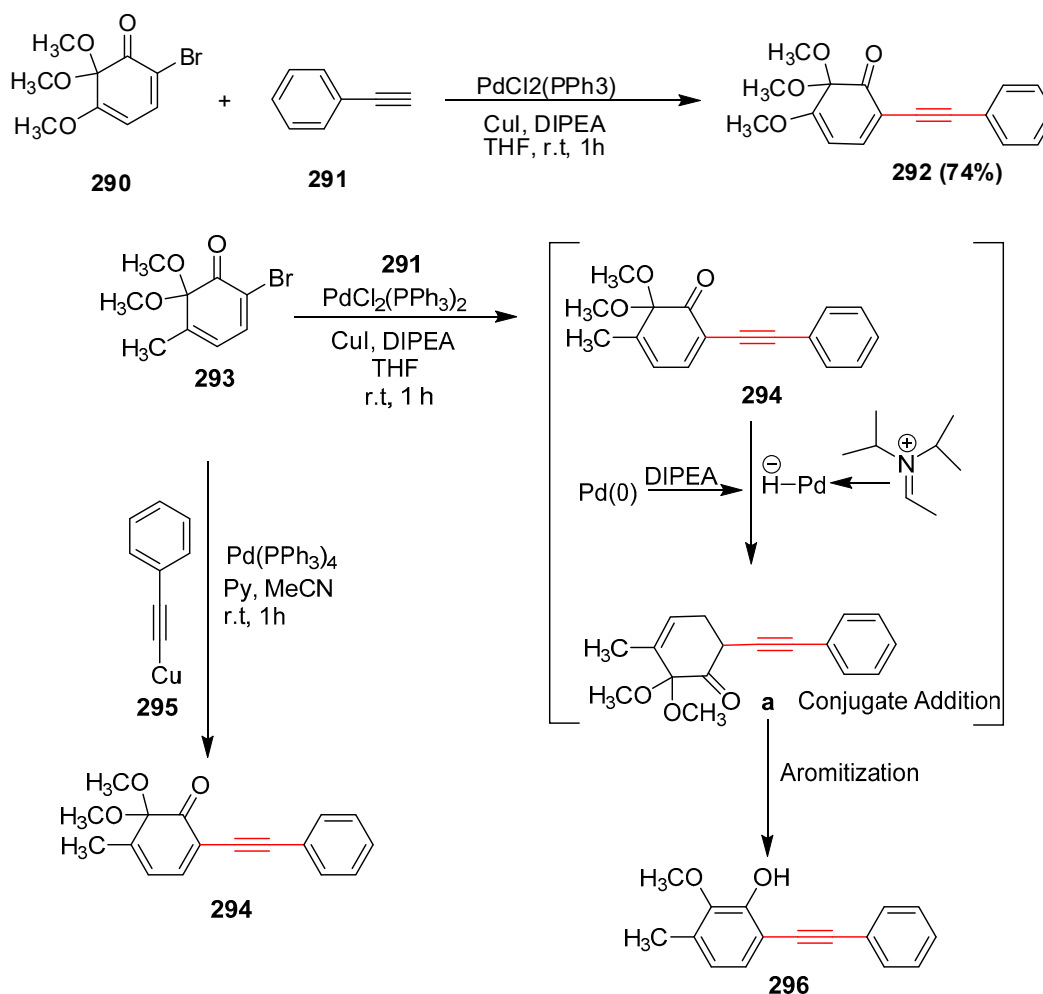
The silver catalyzed synthesis of derivatives of Azepine fused with Cyclobutene and 1,2-Dihydropyridine from ketene *N,N*-acetals was reported by S. Nayak and coworkers. They enlarged the Dihydropyridine ring by Sonogashira cross coupling of alkenyl iodo moiety [134]. Sonogashira Coupling of **287** yield extended π conjugated System **289** (Scheme 74).

A facile synthetic approach to functionalize cyclohexa-2,4-dienones was developed by Chittimalla and coworkers [135]. Cyclohexa-2,4-dienones are important synthetic precursors in the synthesis of various structurally diverse molecules [136,137]. A range of reactions, including organometallic coupling protocols, have been applied on these newly obtained halogenated cyclohexa-2,4-dienones. α -halo-dienones were subjected to Sonogashira cross coupling reaction. 2-bromo-5,6,6-trimethoxycyclohexa-2,4-dienone undergoes Pd-Cu catalyzed Sonogashira coupling with compound **290** and formed the adduct (**292**) in 74% yield (Scheme 75). Surprisingly, under same

conditions, compound **293** and phenylacetylene gave product **294** in 80% yield. They guess that hydrido-Pd intermediate formed from Pd (0) and DIPEA could reduce the conjugated-double bond to give an intermediate, which is then aromatized to give the 2-methoxy-3-methyl-6-(phenyl ethynyl) phenol (**294**). To check whether aromatization or Sonogashira Coupling occurred first, a reaction was performed at $-10\text{ }^{\circ}\text{C}$. After 30 min of reaction, thin layer chromatography and $^1\text{H-NMR}$ analysis showed 3 products; **293**, **294** and **296**, which indicates that in this reaction Sonogashira Coupling was followed by aromatization reaction. To avoid the generation of hydrido-Pd intermediate they used an alternative Sonogashira coupling procedure. In this procedure, Pre-synthesized $\text{Pd}(\text{PPh}_3)_4$ was used as a catalyst, Cu(I)-Phenylethyne was used as a reactant, and pyridine was used as a base. Under these reaction conditions, Sonogashira coupled product **294** was obtained in 93% yield.

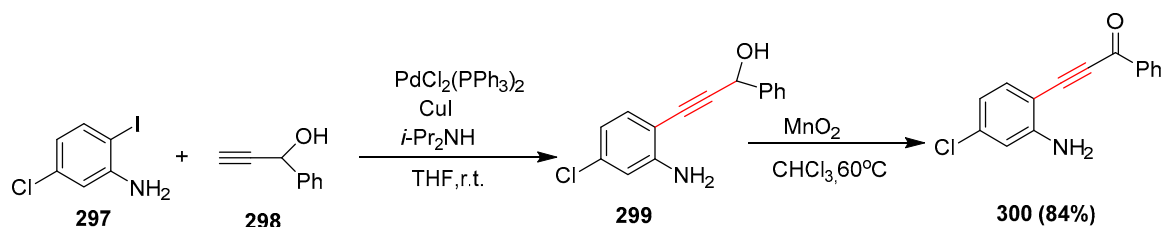


Scheme 74. Synthesis of derivatives of Azepine fused with Cyclobutene and 1,2-Dihydropyridine via Sonogashira cross Coupling.



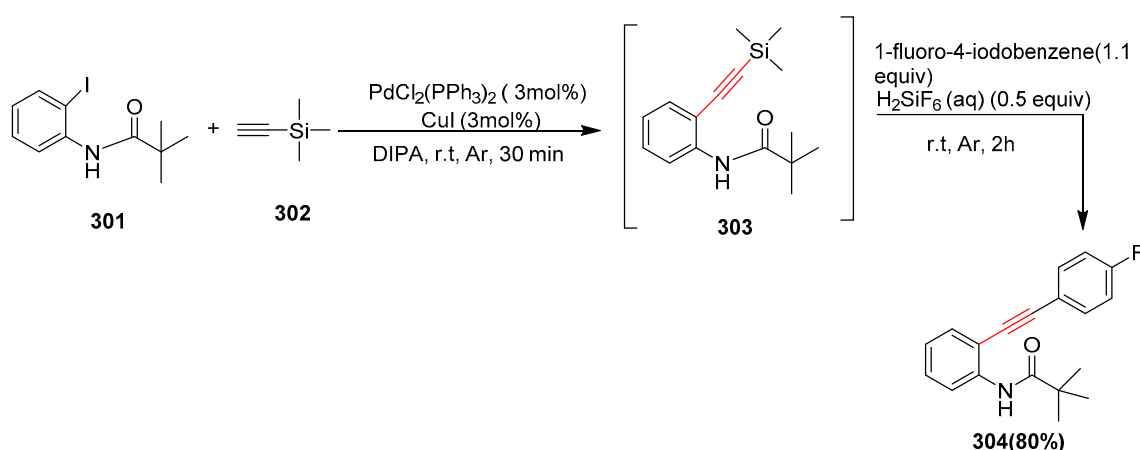
Scheme 75. Sonogashira coupling of substituted o-benzoquinones with phenyl acetylene.

Sonogashira cross coupling reaction can also be used for the synthesis of ynones that are important building blocks for the synthesis of quinoline. In 2017, Rode and coworkers synthesized 4-nitroquinolines and 4-sulfonylquinolines via reaction of ynones with nitrite and sulfinate anions in the presence of NH_4Cl as a proton source [138]. Starting ynones were prepared by using Sonogashira cross coupling of substituted iodoaniline with **298** and then oxides caused the resulting product **299** with MnO_2 (Scheme 76).



Scheme 76. Sonogashira reaction of 5-chloro-2-iodoaniline with hydroxyl-phenylacetylene.

In organic synthesis, silyl groups are widely used. Deprotection of silyl-ethynyl intermediate is typically done by using a Fluoride source. However, the use of a Fluoride source is not suitable due to the high price of fluoride salts and low fluoride content mass, and another issue is the origin of fluorinated reagent. Due to these issues, Sinai and coworkers developed a cheap, nontoxic and easily available deprotecting agent H_2SiF_6 for the deprotection of ethynyl-trimethyl silane to form terminal acetylenes (Scheme 77) [139]. This reagent was used in Sonogashira reaction for the synthesis of derivatives of arylethynylpivalanilides and amines, 2-arylbenzofurans, and N-benzyltriazole. Transformation of terminal acetylenes catalyzed by transition metal is one of the most frequently used methods for the synthesis of heterocycles and internal-acetylenes. H_2SiF_6 showed efficient reactivity and its presence had no deleterious effect on Sonogashira cross coupling.



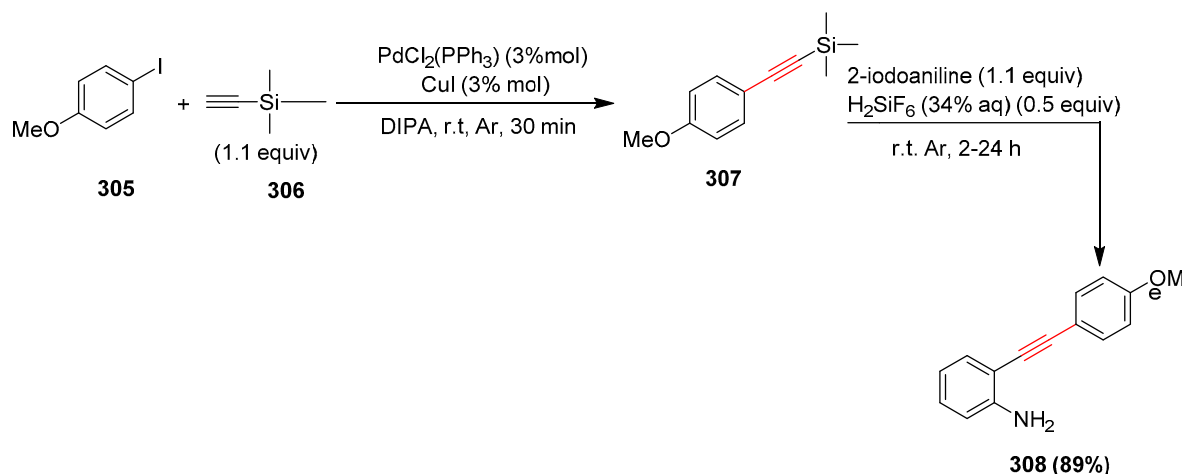
Scheme 77. Synthesis of arylethynyl pivalanilides via Pd and Cu Coupling.

Similarly, 1-iodo-4-methoxybenzene (**305**) coupled with protected terminal acetylene in the presence of DIPA solvent and Pd/Cu catalyst. The desired intermediate **307** is formed in 30 min and then the Silyl protecting group is removed by adding Hexafluoro silicic Acid. After deprotection, the intermediate coupled readily with 2-iodoaniline and resulted in the formation of **308** in 89% yield (Scheme 78).

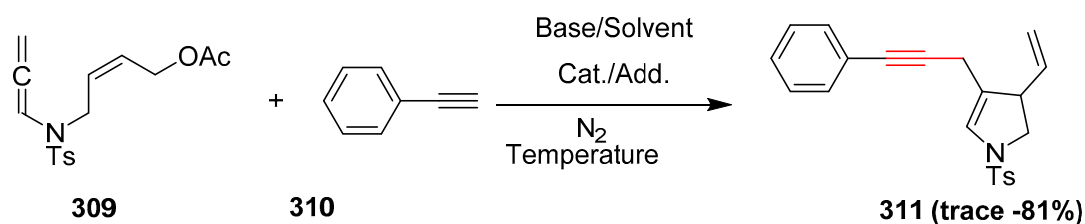
2.17. In 2018

As previously mentioned, the nitrogen containing heterocycles have attracted the attention of many research groups. The Poly-functional pyrroles are present in many naturally occurring compounds as vitamin B₁₂, Chlorins and Porphins [140]. The Poly-functional pyrroles are used as precursor for

synthesizing many biologically active drugs and *N*-methyl-pyrrole-carboxylic acid is used as building block in pharmaceutical chemistry [141]. Liang and coworkers synthesized the 2,3-di-hydro-pyrrole derivatives by using terminal alkyne and allenamide allyl acetate via palladium and copper catalyzed Sonogashira reaction (Scheme 79). The different ligands were used with palladium and copper catalysts. Both the electron donating and electron withdrawing substrates gave good yield [142].



Scheme 78. Synthesis of 2-((4-methoxyphenyl)ethynyl)aniline via sonogashira Cross Coupling.



Cata. = PdCl₂(PPh₃)₂, Pd(PPh₃)₄

Add. = CuI, CuBr, CuClCuCl/PPh₃

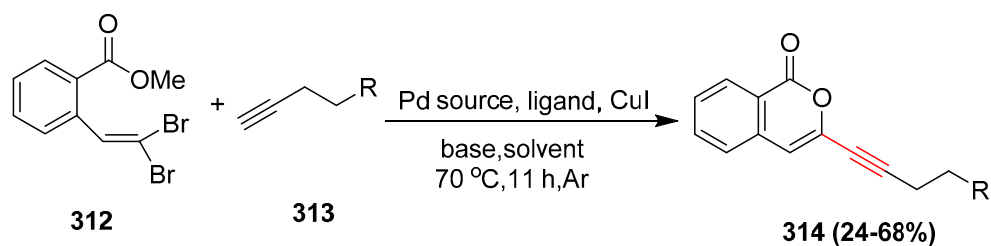
Solvent = THF, dioxane, toluene, ether

Base = TEA, K₃PO₄, tBuONa, CsF, DIEA, CsF, pyridine, K₃PO₄·3H₂O

Scheme 79. Synthesized the 2,3-di-hydro-pyrrole derivatives via Pd and Cu catalyzed Cross Coupling.

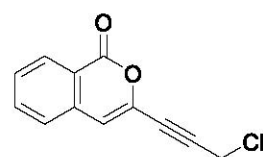
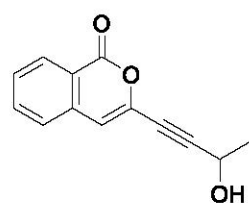
It was also noted that isocoumarins are naturally occurring lactones and are biologically active. They are used as a precursor for synthesis of bio active complex compounds [143]. The 3-alkynyl isocoumarins were synthesized via palladium and copper catalyzed Sonogashira cross coupling of methyl 2-(2',2'-dibromo vinyl) benzoate with terminal alkyne by Liu and co-workers. The naturally occurring compounds 3'-hydroxycorfin and gymnopalyne A were also synthesized via palladium and copper catalyzed Sonogashira cross coupling as a key step (Scheme 80) [144].

In addition, *N*-Heterocyclic carbenes are widely used as ligands with palladium catalyst and are important for Sonogashira cross coupling [145]. Shen and co-workers reported that the acenaphthoimidazolylidene palladium complex and copper co catalyst showed high catalytic activity for the Sonogashira Cross Coupling of bulky and heterocyclic halides with heteroaryl alkynes (Scheme 81) [146].

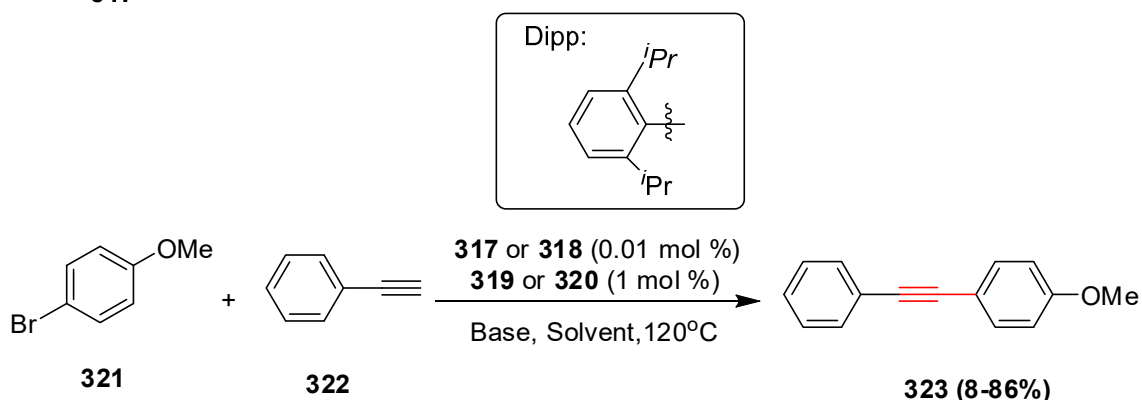
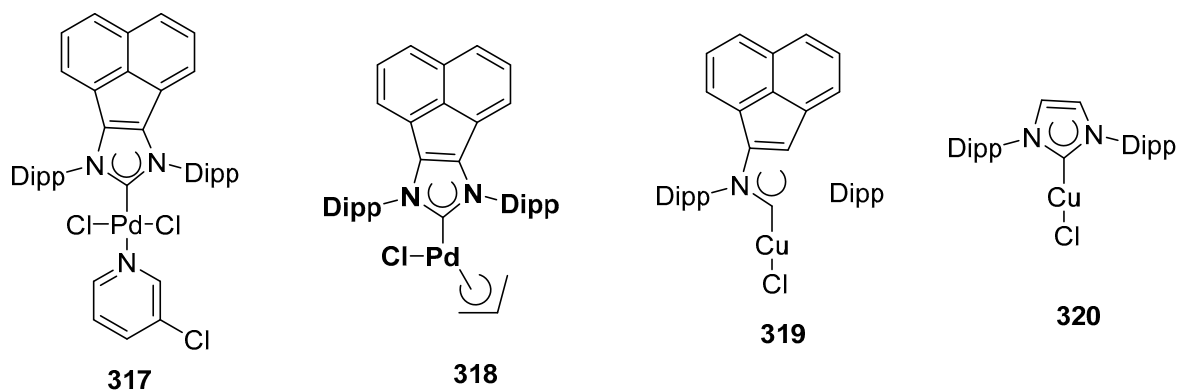


Pd source = PdCl₂, PdCl₂(PPh₃)₂, Pd₂(dba)₃,
 [PdCl(C₃H₅)₂], Pd(OAc)₂, PdCl(PPh₃)₄,
 Ligand = PPh₃, Ad₂PbuPCy₃, TFP

Base = Cs₂CO₃, TEA, DIPEA, K₂CO₃, Na₂CO₃
 Solvent = THF, Toluene, DMF, MeCN, THF/*i*-PrOH
 R = OTBDMS



Scheme 80. Sonogashira cross coupling of methyl 2-(2',2'-dibromo vinyl) benzoate with substituted terminal alkyne.



Base = K₃PO₄, CsF, Na₂CO₃, CsCO₃
 Solvent = DMSO, THF

Scheme 81. Sonogashira cross coupling of bulky and heterocyclic halides with heteroaryl alkynes.

3. Conclusions

In summary, Sonogashira cross-coupling is used for the synthesis of different organic bioactive and pharmacologically important compounds. This review article highlighted the palladium and copper-based catalysts for Sonogashira cross-coupling. The Pd-Cu-catalyzed cross-coupling of terminal acetylenes with sp^2 -C halides is a broadly useful method for conjugated acetylenes. In particular, the search for more reactive and long-living catalysts for the aryl chlorides remains a challenging object for future research.

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