The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry†

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† Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

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Rafael Chinchilla (right) was born in Alicante and studied chemistry at the University of Alicante, from which he received B.S. (1985) and Ph.D. (1990) degrees. After a postdoctoral stay at the University of Uppsala, Sweden (1991–1992), he moved back to the University of Alicante, where he was appointed Associate Professor in 1997. He is coauthor of 70 papers and four patents. He is cofounder of the new chemical company MEDALCHEMY, S. L. as a spin-off of the University of Alicante. His current research interests include asymmetric synthesis, amino acid and peptide synthesis, and solid-supported reagents.

Carmen Nájera (left) was born in Nájera (La Rioja). She graduated from the University of Zaragoza in 1973 and obtained her doctorate in chemistry from the University of Oviedo in 1979, followed by postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She is coauthor of more than 200 papers and 30 reviews, and has been visiting professor at different universities, such as University of Arizona (Tucson, AZ, USA), Universidad Nacional del Sur (Bahia Blanca, Argentina), Université Louis Pasteur (Strassbourg, France), and Ecole Nationale Superiéure de Chimie de Paris (France). Prof. Nájera has received the 2006 Janssen Cilag Organic Chemistry Prize from the Spanish Royal Chemical Society of Chemistry and the 2006 Rosalind Franklin International Lectureship from the English Royal Society. She is cofounder of the new chemical company MEDALCHEMY, S. L. as a spin-off of the University of Alicante. Her current research interest is focused on sulfones, amino acids, polymer-supported reagents, asymmetric catalysis, and palladium catalysis.

1. Introduction

The array of transition-metal-catalyzed cross-coupling reactions can easily be considered nowadays cornerstones in the field of organic synthesis.[1,2] Among them, the palladium-catalyzed sp^2-sp coupling reaction between aryl or alkenyl halides or triflates and terminal alkynes, with or without the presence of a copper(I) cocatalyst, has become the most important method to prepare arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials (Scheme 1).[3]

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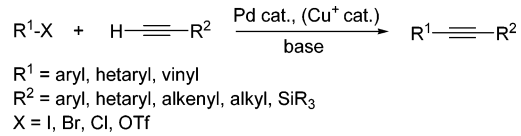
Scheme 1



The two earlier studies on this topic were reported independently by Heck[4] and Cassar[5] in 1975. Heck's procedure was based on the known Mizoroki−Heck reaction for the palladium-catalyzed arylation or alkenylation of alkenes, and consisted of performing the coupling employing a phosphane−palladium complex as a catalyst and triethylamine or piperidine as a base and solvent. Cassar's procedure involved the use of a phosphane−palladium catalyst in combination with sodium methoxide as a base and DMF as solvent. Both methods generally required high temperature (up to 100 °C). In the same year, Sonogashira and Hagihara reported that addition of a catalytic amount of copper(I) iodide greatly accelerates the reaction, thus enabling performance of the alkynylation at room temperature,[6] an observation related to the already known coupling between copper acetylides and phenyl or vinyl halides (the so-called Stephens−Castro reaction).[7] Therefore, the Sonogashira−Hagihara protocol (more often simply known as Sonogashira coupling) became the most popular procedure for the alkynylation of aryl or alkenyl halides. It is necessary to note that even primary alkyl bromides or iodides[8a] and secondary alkyl bromides[8b] have been alkynylated using a Sonogashira protocol, although this type of sp^3−sp coupling is very recent and remains almost unexplored.

The addition of copper salts as cocatalysts in the typical Sonogashira cross-coupling reactions also has drawbacks, apart from including in the reacting mixture another environmentally unfriendly and difficult to recover reagent. Thus, the in situ generation of copper acetylides under the reaction conditions often generates homocoupling products of the terminal alkyne (the so-called Glaser coupling),[9] along with the main reaction product, upon exposure to oxidative agents or air. This side reaction is especially problematic when the terminal acetylene is difficult to obtain or expensive, and although it has been shown that the presence of a reductive atmosphere formed by difficult-to-handle hydrogen can diminish homocoupling,[10] as well as the slow addition of the acetylene,[11] significant efforts have being dedicated to develop coupling procedures working in the absence of copper salts. These procedures generally aim to increase the reactivity of the catalytic system, thus making the presence of copper unnecessary. All these copper-free methodologies are usually called copper-free Sonogashira couplings, but (perhaps unfairly) not Heck and/or Cassar couplings. Frequently, these copper-free processes involve the use of excess amine (often even acting as solvent), something that diminishes to some extent the environmental and economical advantages of the methodology. Thus, the development of methods which allow the elimination of both copper and amine in the Sonogashira cross-coupling has been pursued in the past few years.

Other important problem to address when dealing with this type of alkynylation procedure is the applicability of the reaction to different substrates. Thus, the general reactivity order of the sp^2 species is vinyl iodide ≥ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate ≥ aryl bromide ≫ aryl chloride; therefore, the Sonogashira process usually runs smoothly when the more expensive and unstable aryl or vinyl iodides are used. Moreover, if the organic halide system is "activated", that is, electron-poor, the situation is even more favorable. Thus, deactivated aryl bromides are difficult starting materials for coupling reactions, whereas the cheapest aryl chlorides, if not strongly activated, represent a real challenge for any cross-coupling methodology.[12]

Although the most recent reviews about the Sonogashira reaction are fairly recent, covering up to 2002,[3] a simple computer search of the keyword "Sonogashira" in chemical databases reveals a similar amount of citations from 2003 to the present compared to the amount during the period of time from the discovery of this reaction (1975) to 2002. This indicates that in the last few years this has been a really fast-moving topic, with a fierce search for better catalysts, more convenient reaction conditions, and an understanding of the reaction mechanism, and also with a remarkable increase in the use of this cross-coupling reaction for the synthesis of interesting or promising compounds.

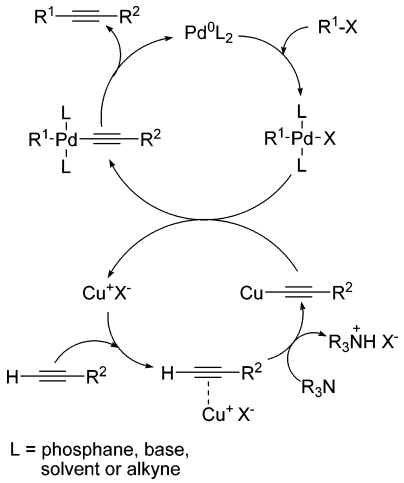
This review covers the developments in the Sonogashira cross-coupling reaction, as well as applications of this methodology since 2003, although older works can be commented on if necessary. In the cases for which some reviews on particular related topics have been published more recently, only the literature after them will be considered. When dealing with applications of this methodology, this review will not be fully comprehensive, although very extensive, as a complete coverage of all the literature containing an application of a Sonogashira reaction is almost impossible and would make this review never-ending.

2. Mechanistic Considerations

The exact mechanism of the homogeneous copper-cocatalyzed Sonogashira reaction is unknown, with some obscure points and not unequivocally proven assertions still remaining. Although physical measures suggest plausible mechanistic paths based on the identification of some of the transient species formed in the homogeneous catalytic reactions, it is a very difficult task to isolate and characterize the organometallic intermediates from a homogeneous mixture to validate a mechanism beyond any doubt. Therefore, some techniques have been developed to study this coupling process using heterogeneous catalysts in order to detect surface transient organometallic intermediates.[13] However, unexpected findings can add further complications to the always difficult study of mechanisms. Thus, the always useful kinetic measures could be in some cases dampened by details such as the recent finding that, in a Sonogashira cross-coupling reaction, turnover continues to occur in sample vials prepared for gas chromatography analysis after quenching by commonly employed silica adsorption methods, because trace quantities of palladium are carried through the silica.[14] More complications can arise from the finding that some commercially available common palladium salts such as palladium(II) dichloride or palladium(II) diacetate (the starting material for the preparation of many palladium complexes) contain, in fact, small amounts of copper, something that would raise reasonable doubts about some "copper-free" Sonogashira processes.[15]

The copper-cocatalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles as shown in Scheme 2, where a tertiary amine is represented as base, with other amines or inorganic bases performing similarly.[1−3] The generally accepted catalytic cycle for the

Scheme 2



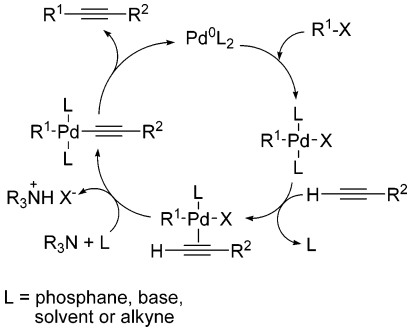
palladium catalysis (the Pd-cycle) is based on a usually fast oxidative addition of R^1-X (R^1 = aryl, hetaryl, vinyl; X = I, Br, Cl, OTf) to the real catalyst generated from the initial palladium complex. This is classically thought to be 14-electron Pd^0L_2, formed by reduction of different palladium(II) complexes under the employed reaction conditions, as it is known that n-electron donors, such as phosphanes, amines, and ethers, used as ligands and solvents, can reduce palladium(II) species typically via σ-complexation−dehydropalladation−reductive elimination.[1b] In the oxidative addition step, the characteristics of the R^1-X substrate are crucial, with this step being facilitated if X = I or OTf and if the electronic density is reduced on the C−X bond by the presence of electron-withdrawing groups. The next step in the Pd-cycle would connect with the cycle of the copper cocatalyst (the Cu-cycle). Thus, a usually rate-determining transmetalation from the copper acetylide formed in the Cu-cycle would generate a $R^1Pd(-C{\equiv}CR^2)L_2$ species, which gives the final coupled alkyne after *trans*/*cis* isomerization and reductive elimination with regeneration of the catalyst.

The second Cu-cycle is still poorly understood. In the "textbook" Cu-cycle, the base (generally an amine) is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming a copper acetylide in the presence of the copper(I) salt. It should be pointed out that the generally employed amines are usually not basic enough to deprotonate the alkyne in order to generate the anionic nucleophile that should form the copper acetylide. Therefore, a π-alkyne−Cu complex as shown in Scheme 2 could be involved in the cycle,[16] thus making the alkyne proton more acidic for easier abstraction. Recently, NMR studies have shown that π-alkyne−Ag complexes are formed after generation of silver acetylides in silver-cocatalyzed Sonogashira couplings,[17] something that could be extended to the typical copper-cocatalyzed reaction. In fact, the always assumed in situ formation of a copper acetylide as intermediate has never been proven, although recent indirect evidence has been found.[16] These copper acetylides could also be involved in the formation of the initial Pd^0L_2 catalytic species by reaction with the starting palladium(II) complexes, thus forming $Pd(-C{\equiv}CR^2)_2L_2$, which after reductive elimination would afford active Pd^0L_2 and some amounts of a diacetylene byproduct.

Some questions still arise about the nature of the real catalyst.[18] Thus, it has been shown that monoligated $Pd(PR_3)$ complexes can be formed when dealing with bulky phosphanes and have been suggested as possible catalytic species in coupling reactions.[18] In addition, in the presence of anions and halides, some results point to the formation of anionic palladium species, which would be the real catalysts instead of the coordinatively unsaturated Pd^0L_2. For instance, it is known that $Pd^0(PPh_3)_2$ does not exist in solution when generated in the presence of halide anions because they coordinate the palladium(0) center to form anionic species of the type $[L_2Pd^0Cl]^-$,[19] which can participate in cross-coupling reactions.[20]

The mechanism of the copper-free Sonogashira reaction is also not well-known. The first step would be the oxidative addition of R^1-X to the palladium(0) complex (Scheme 3).

Scheme 3



However, the second step is under debate. As previously mentioned, the amines generally employed are usually not able to deprotonate the alkyne for the reaction with the *trans*-R^1PdXL_2; therefore, complexation of the alkyne to the complex is supposed to proceed first with displacement of one ligand to give intermediate complex (η^2-RC≡CH)-$PdXL_2$.[21] The ligated alkyne would be more easily deprotonated by the amine, forming the new complex $R^1Pd(-C{\equiv}CR^2)L_2$, which gives the coupling product $R^1-C{\equiv}C-R^2$ by reductive elimination. In the absence of any amine, a carbopalladation step takes place,[22] which leads to $R^2-C(PdXL_2){=}CH-R^1$ complexes, presumably by formation of (η^2-RC≡CH)PdXL species.

The terminal alkynes involved in the coupling reactions can also play an important role in the Pd-cycle. Thus, the carbon−carbon triple bond is able to coordinate the palladium(0) active complex prior to the oxidative addition step, therefore producing a decelerating effect by formation of unreactive or low-reacting (η^2-RC≡CH)Pd^0L_2 complexes.[23] The stationary regime of a catalytic cycle is more easily reached if the reaction rates of all the elemental steps are as close as possible to each other. This can be achieved by accelerating the rate-determining step (i.e., destabilizing stable intermediate complexes) or decelerating the fast reactions by stabilizing high-energy species.[24] Whenever the oxidative addition is faster than the ensuing transmetalation, the decelerating effect of the nucleophilic alkyne in the oxidative addition is in favor of a better efficiency for the catalytic cycle, bringing the rate of the fast oxidative addition closer to that of the slow transmetalation step. However, if the oxidative addition (i.e., of aryl chlorides or activated aryl bromides) is slower than the transmetalation and is therefore the rate-determining step of the catalytic cycle, it will be even slower in the presence of the nucleophilic alkyne and the catalytic reaction would be less efficient, with any technique which allows maintaining a low concentration of the alkyne (i.e., slow addition) being beneficial for the

efficiency of the catalytic reaction.[23] The strong complexation of the active palladium(0) complex by some of the final acetylenic reaction products may explain why some catalytic reactions stop before total conversion of the reagents.

A further mechanistic complication has been found in copper-free Sonogashira reactions. In these processes, the role of the base is crucial, and specific amines (usually added in excess or as solvent) are required, with secondary amines such as piperidine, morpholine, or diisopropylamine proving to be efficient. It has been discovered that these amines can react with *trans*-$R^1PdX(PPh_3)_2$ complexes by substitution of one triphenylphosphane ligand to generate $R^1PdX(PPh_3)$-(amine) complexes in a reversible reaction whose equilibrium constant depends on R^1, X, the basicity, and the steric hindrance of the amine.[25] Therefore, competition between the amine and the alkyne for the substitution of one phosphane group in $R^1PdX(PPh_3)_2$ complexes may also occur. The fact that the amine is often used in large excess or as solvent encourages this substitution of the phosphane by the amine group; therefore, these complexes could have strong influence in the mechanism, at least in the copper-free Sonogashira reaction.

An additional debate has been established on the mechanism operating in Sonogashira coupling reactions when the catalytic species are semiheterogeneous palladium nanoparticles, generated by decomposition of some palladium reagents. In this case, the question remains if the catalytic cycle takes place at the rim of the nanoparticles or if these are just reservoirs of soluble palladium catalytic species (see section 3.7).

3. Catalysts and Reaction Conditions

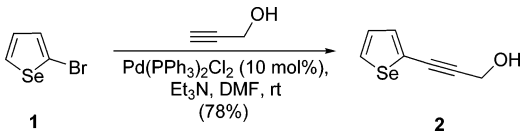
3.1. Palladium–Phosphorus Complexes

3.1.1. Unsupported Palladium–Phosphorus Complexes

The Sonogashira reaction is usually performed using a palladium−phosphane ligand complex as catalyst in the presence of a catalytic amount of a copper(I) salt and an amine (as a solvent or in large excess) under homogeneous conditions. The traditionally used catalysts are triphenylphosphane-related complexes, $Pd(PPh_3)_4$, with the more stable and soluble $Pd(PPh_3)_2Cl_2$ being the most common, although catalysts with bidentate ligands such as $Pd(dppe)Cl_2$, $Pd(dppp)Cl_2$, or $Pd(dppf)Cl_2$ have also been employed. Most frequently, rather high loadings of palladium (usually up to 5 mol %) and larger amounts of the copper(I) salt are required when these palladium species are employed, thus boosting the search for a more active catalyst for simpler, milder, and more effective reaction conditions.

However, examples of copper-free procedures using these "normal" catalysts can be found. For example, in 1986, the coupling of enol triflates with terminal alkynes under copper-free conditions using 5 mol % $Pd(OAc)_2(PPh_3)_2$ at 60 °C was reported,[26] and in 1993, it was found that cyclic amines such as pyrrolidine and piperidine as base and as solvent enhanced the reaction rate to promote the coupling of aryl or vinyl halides or triflates with terminal alkynes at room temperature using also 5 mol % of the palladium complex.[27] More recently, copper-free Sonogashira methodologies for coupling aryl iodides and activated aryl bromides with the traditional palladium complex $Pd(PPh_3)_2Cl_2$ (4 mol %) at 70 °C in neat piperidine,[28] for the preparation of 4-substituted aryl-1-butanones from aryl bromides,[29a] or for the copper-free Sonogashira coupling of iodonitrobenzoates,[29b] have been reported. In addition, this catalyst has been used recently in the copper-free cross-coupling of 2-haloselenophenes with terminal alkynes, as shown in Scheme 4 with the coupling

Scheme 4

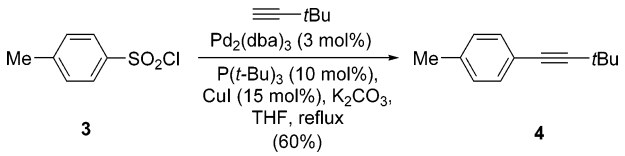


1 2

of 2-bromoselenophene (**1**) and propargyl alcohol to give alkynylated product **2**, with large amounts of the catalyst being required.[30] This copper-free system has been used in the synthesis of enynyl-substituted thioflavones and flavones,[31] or the preparation of supported PyOX ligands.[32] Moreover, in situ generated $Pd(PPh_3)_4$ in the presence of triethylamine has been used in the copper-free cross-coupling reaction of vinyl tosylates[33] or 10-bromoanthracene[34a] with terminal acetylenes, and, more recently, using potassium phosphate as base, for the coupling of aryl halides.[34b]

The change of the triphenylphosphane to more electron-rich phosphane ligands has been shown to produce an easier oxidative insertion to aryl halides, which is especially important when deactivated bromoarenes or usually low-reacting chloroarenes are employed. In addition, a ligand with a steric demand promotes an easier dissociation from the Pd^0L_2 resting state, which is necessary prior to oxidative addition.[35] Thus, bulky phosphanes such as $P(t\text{Bu})_3$ have been employed, with the catalyst generally being generated in situ by combination with a weakly ligated palladium source such as $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, or $Pd_2(dba)_3$. For example, the combination of $Pd(PhCN)_2Cl_2$/CuI/P(*t*-Bu)$_3$ has been found to be a catalytic system for the Sonogashira reaction of aryl bromides at room temperature with only an equimolecular amount of amine, although using a 3 mol % palladium loading.[36] Interestingly, when using this phosphane ligand and $Pd_2(dba)_3$ in a copper-free Sonogashira reaction of aryl bromides performed at room temperature, the coupling proceeded with only 0.5 mol % palladium and ligand,[37a] something that has also been achieved using the combination $[Pd(\eta^3\text{-}C_3H_5)Cl_2]/P(t\text{Bu})_3$, although the catalyst loading was higher (2.5 mol %).[37b] This air-sensitive and pyrophoric phosphane can be replaced with the air-stable phosphonium salt $[(t\text{-Bu})_3PH]BF_4$, although a loading of 3 mol % palladium and the presence of 2 mol % copper(I) iodide were also necessary.[38] The combination $Pd_2(dba)_3$/P(*t*-Bu)$_3$ (3:10 mol %) has been found to be the most appropriate for a recent palladium-catalyzed desulfitative cross-coupling of arenesulfonyl chlorides such as *p*-toluenesulfonyl chloride (**3**) and terminal alkynes to give the corresponding alkyne **4**, using K_2CO_3 as the most convenient base in refluxing THF, with the presence of copper cocatalysis being necessary (Scheme 5).[39]

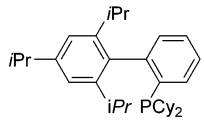
Scheme 5



3 4

Copper-free methodologies using also bulky phosphanes can be shown with the recent example of the use of $PdCl_2$-

$(PCy_3)_2$, which has allowed the coupling of aryl chlorides using cesium carbonate as base in DMSO as solvent at 100−120 °C.[40a] In addition, the in situ generated catalyst formed by mixing $Pd(OAc)_2$ and *rac*-BINAP has been shown to be reactive enough for the copper-free coupling of a 4-chloropyridine related to camtothecins with terminal alkynes using potassium carbonate as base.[40b] Related to these more reactive catalysts is the unexpected observation that the presence of the copper(I) cocatalysts can sometimes inhibit product formation.[41] Thus, aryl chlorides and even aryl tosylates can be coupled with alkynes using the combination of $Pd(PhCN)_2Cl_2$ (0.1 mol % for aryl chlorides, 5 mol % for aryl tosylates) and bulky electron-rich *o*-biphenylphosphane **5** using cesium carbonate as base at 70−95 °C, with the efficiency of the process being lowered when adding copper(I) iodide.[41]



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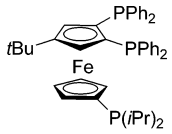

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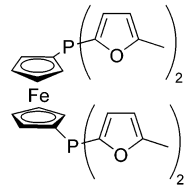

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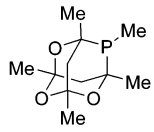

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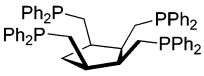

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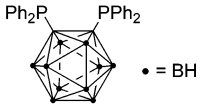

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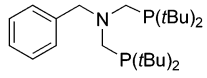

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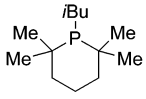


12

Thermally stable and insensitive to air or moisture, multidentate ferrocenyl phosphane **6** has been used to generate the active Sonogashira catalyst when mixed with $[Pd(\eta^3\text{-}C_3H_5)Cl_2]$ in the cross-coupling reaction of aryl iodides, bromides, and chlorides, with and without copper(I) iodide at 130 °C and 0.1−0.0001 mol % catalyst loading.[42a] The same catalyst loading has been employed when bis(2-furyl)phosphaneferrocene **7** has been mixed with the same palladium complex for the arylation of phenylacetylene 4-bromoacetophenone and 4-bromoanisole in the presence of copper(I) and potassium carbonate as base at 130 °C.[42b] In addition, the phosphadamantane **8** has been used mixed with $Pd_2(dba)_3{\cdot}CHCl_3$ for the in situ generation of the corresponding catalyst, which has been used for the copper cocatalyzed coupling of aryl iodides at room temperature or the copper-free coupling of aryl chlorides and bromides at 50 °C.[43] Moreover, the combination $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/tetraphosphane **9** (Tedicyp) has been employed for the copper cocatalyzed coupling of aryl bromides,[44a,b] heteroaryl halides,[44c] vinyl bromides,[44d] or aryl chlorides,[44e] with only 0.01 mol % catalyst loading and without the addition of copper, with the reaction usually taking place at 100 °C. Alkynols[44f] and propargyl amines[44g] have also been coupled using this catalytic system. Propargyl amines have also been employed as allenyl anion equivalents when coupling with aryl iodides using a one-pot Sonogashira reaction combined with a hydride transfer, with the catalytic system being a combination of $Pd_2(dba)_2{\cdot}CHCl_3$ and the 1,2-bis(diphenylphosphino)carborane **10** in the presence of copper and triethylamine as solvent at 80−100 °C.[45] Furthermore, bis(*tert*-butyl)aminomethylphosphane **11** reacted with $Pd(OAc)_2$ to give a palladium(II)−phosphane catalyst which has been used for a copper-free Sonogashira coupling of aryl iodides, bromides, and chlorides in neat triethylamine.[46] The phosphane **12** has been employed recently in the cross-coupling reaction of *p*-bromo- or *p*-iodoacetophenone or *p*-bromoanisol with phenylacetylene or 2-methylbut-3-yn-2-ol using $Pd(PhCN)_2Cl_2$ as palladium source, diisopropylamine as base, and dioxane as solvent at 100 °C, although copper cocatalysis was required.[47]

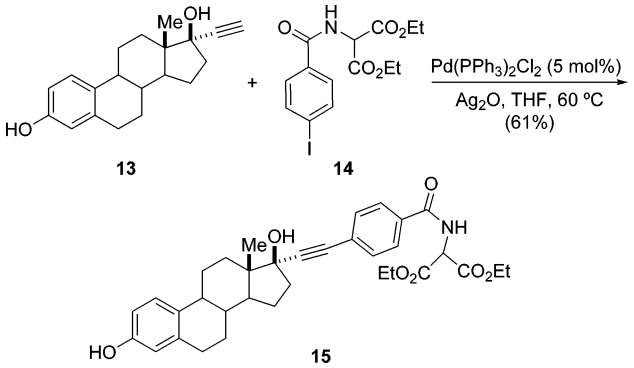
A problem with palladium(0) complexes is that the ligands needed to stabilize palladium(0) invariably have coordinating properties, which would hinder the formation of the active palladium(0) catalyst. The palladium(II) salts $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, or $PdCl_2(PhCN)_2$ are alternatives even though they require a preactivation to generate the active palladium(0), with amines or phosphanes acting as reducing agents. These salts still have coordinating ligands that might interfere with the formation of the active species. Therefore, a more active catalyst should be formed when the palladium(II) source contains ligands unable to stabilize palladium(0), with the only examples being chloride-containing palladium salts such as Na_2PdCl_4 or $PdCl_2$. Thus, a catalytic system for the Sonogashira coupling of activated and nonactivated aryl chlorides with terminal acetylenes at 100 °C using sodium carbonate as base, based on the combination Na_2PdCl_4 (2 mol %)/$(1\text{-Ad})_2$PBn/CuI (1-Ad = 1-adamantyl; Bn = benzyl), has been presented.[48] The benzyl group in the ligand $(1\text{-Ad})_2$PBn has been exchanged by triethylammonium- or triphenylphosphonium-containing benzylic groups, which are used as cationic phase tags for the coupling of aryl bromides and chlorides in DMSO/heptane, thus allowing recycling the DMSO-soluble catalysts.[49] In addition, the former procedure, applied to the coupling of aryl bromides, has been modified using the mixture Na_2PdCl_4/CuI/$[(t\text{-Bu})_3PH]BF_4$ in diisopropylamine as solvent, thus allowing excellent yields with very low palladium loading (0.005 mol %).[50]

An air-stable and easy-to-handle dative ligand is triphenylarsine, which, in spite of its toxicity, has allowed the copper-free Sonogashira coupling of free-base porphyrins,[51] with recent examples of its use combined with $Pd_2(dba)_3$ being frequent.[52] The absence of copper in this kind of chemistry is important, as copper readily inserts into free-base porphyrins, with the classical Sonogashira coupling only then being possible for metalloporphyrins. Other examples of strong dative ligands are aminophosphanes, which, together with $Pd(OAc)_2$ as the palladium source, have been used in copper- and amine-free Sonogashira reactions using inorganic bases.[53]

The presence of copper as cocatalyst in Sonogashira couplings has also been avoided by using silver(I) oxide as cocatalyst in the case of the coupling of aryl or vinyl iodides,[54a] with the procedure being rather sluggish and copper(I) iodide having to be added in a further improved procedure.[54b] In spite of this, this copper-free (but stoichio-

metric in silver) protocol has been used recently in the coupling of a iodobenzamide **14** to a ethynylestradiol **13** to give compound **15**, which can be used for the synthesis of an estrogenic malonate−platinum(II) complex with cytotoxic activity (Scheme 6).[55] It is interesting to remark that the use

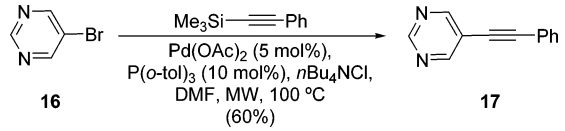
Scheme 6



of an excess of silver(I) oxide has allowed the coupling reaction between arylboronic acids and terminal alkynes using $Pd(dppf)Cl_2$ as catalyst in dichloromethane and at room temperature.[56] In addition, good results have been obtained in coupling 1-(trimethylsilyl)alkynes with vinyl triflates and aryl iodides when using the combination $Pd(PPh_3)_4$/AgI or AgCl as catalytic system, in the presence of potassium carbonate and methanol at room temperature. This reaction takes place by displacement of the in situ generated silicate by the more electropositive silver ion, creating a silver acetylide that takes the role of the copper acetylide in the classical Sonogashira reaction,[57] as it has been demonstrated that trimethylsilyl acetylenes can be deprotected by silver salts.[58] A similar process is the coupling of vinyl triflates with 1-(trimethylsilyl)alkynes using catalytic amounts of the combination $Pd(PPh_3)_4$/AgI, but in the presence of tetra-*n*-butylammonium fluoride (TBAF). The fluoride anion acts in this case as an activator to form a pentacoordinated organosilicate, which is again displaced by the silver ion.[59]

It has been observed that aryl or alkenyl triflates can be coupled directly with alkynylsilanes just by using the combination $Pd(PPh_3)_4$/CuCl as catalyst, in DMF as solvent at 80 °C. This process has been called a "sila"-Sonogashira cross-coupling and avoids totally the formation of the alkyne homocoupling Glaser-type product.[60] In this type of coupling, a transmetalation from silicon to copper has been proposed when using copper(I) cocatalysis.[60] However, the copper-free version of this "sila"-Sonogashira cross-coupling reaction has been achieved using a palladium/imidazolium salt system (see section 3.4.2).[61] This process has been applied more recently to the coupling of electron-poor aryl and hetaryl bromides or iodides, such as 5-bromopyrimidine (**16**), and 1-aryl-2-(trimethylsilyl)acetylenes, giving compound **17** by using the combination $Pd(OAc)_2/P(o\text{-tol})_3$ as catalyst in the presence of tetra-*n*-butylammonium chloride in DMF at 100 °C, with use of microwave heating to improve the coupling yields in reaction times up to 15 min (Scheme 7).[62] Somehow

Scheme 7



related to silylated acetylenes involved in Sonogashira reactions is the coupling of aryl or vinyl nonaflates and terminal alkynes under palladium(0) catalysis at room temperature facilitated by the presence of an additive such as polymethylhydrosiloxane (PMHS) in combination with cesium fluoride, although the presence of a copper cocatalysts is necessary.[63] The reaction probably takes place by in situ formation of an alkynylsiloxane with subsequent transmetalation between silicon and copper.

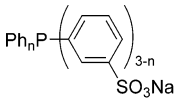
The same work that reported that copper(I) could be substituted by silver(I) oxide in the copper-free Sonogashira reaction[54a] also studied the effect of avoiding the copper salt by adding substoichiometric amounts of TBAF or tetra-*n*-butylammonium hydroxide (TBAOH) together with the catalyst-forming mixture $Pd_2(dba)_3/PPh_3$.[54] The effect of these ammonium salts could be twofold, with the salt acting as a base and also having an effect in the stabilization of possible active palladium nanoparticles generated in the decomposition of the catalyst, something observed when working with palladium-derived catalytic species.[64] It is known that ammonium salts can stabilize transition-metal nanoparticles by electrostatic and steric factors,[65,66] thus repelling the neighboring nanoparticles and preventing their aggregation with nonactive species such as palladium black. A recent example of the use of one of these ammonium salts as an additive is the copper-, amine-, and solvent-free Sonogashira alkynylation reaction of aryl iodides, bromides, and even deactivated chlorides in the presence 3 mol % $Pd(PPh_3)_2Cl_2$ and 3 equiv of TBAF at 80 °C.[67] The tetraalkylammonium cation could also act to stabilize possible anionic catalytic palladium species (see section 3.7);[68] therefore, its role as an additive could be multiple and difficult to elucidate.

Increasing environmental awareness has led to a tremendous interest in the use of alternative solvents to traditional organics for metal catalysis. Among them, water is an especially attractive option because it is inexpensive, nonflammable, nontoxic, and environmentally sustainable.[69] In addition, the use of water as part of a biphasic solvent system can simplify the separation if homogeneous hydrophilic metallic catalysts are used, something quite valuable in pharmaceutical synthesis.

The conventional copper-cocatalyzed Sonogashira coupling of iodoarenes has been achieved using $PdCl_2(PPh_3)_2$ and tri-*n*-butylamine in aqueous potassium carbonate at room temperature,[70] and more recently $Pd(PPh_3)_4$ has been used for the coupling of aryl iodides and bromides in water at 70 °C.[71] In addition, aqueous organic solvents have been used for the Sonogashira reaction using isolated or in situ generated $Pd(PPh_3)_4$ in the presence of quaternary ammonium salts (Jeffery's conditions).[72]

Homogeneous aqueous-phase Sonogashira couplings, similar to other transition-metal-catalyzed C−C bond-forming reactions, can be achieved employing hydrophilic palladium complexes.[73] As phosphanes are the typical ligands in palladium catalysts, an obvious way of getting water-soluble palladium complexes is the development of hydrophilic phosphanes. The sulfonated phosphane **18** ($n = 1$, TPPMS) was employed for the preparation of the water-soluble palladium(0) complex $Pd(TPPMS)_3$, which was pioneeringly used for different coupling reactions such as the Sonogashira cross-coupling of aryl iodides and bromides with terminal alkynes in a mixture of 50% aqueous acetonitrile at room temperature and in the presence of CuI as cocatalyst and triethylamine as base.[74] Since its first application in different

cross-coupling reactions in aqueous media,[75] the higher sulfonated phosphane **18** ($n = 0$, TPPTS) has been used in the in situ generation of the catalytic palladium species for Sonogashira reactions,[76] as recently, where mixing $Pd(OAc)_2$ (2.5 mol %) and **18** in 50% aqueous acetonitrile, with or without copper cocatalysis at 50 °C and using diisopropylamine as base, allowed the coupling of 4-bromotoluene and phenylacetylene although in rather low yields.[77] This ligand has also been used recently under similar reaction conditions in the copper-free coupling of differently metalated porphyrins and phenylacetylene.[78]



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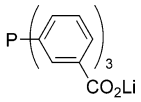

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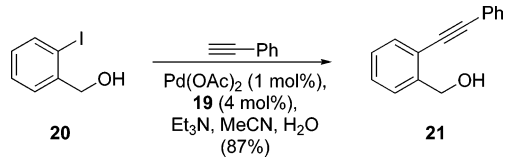
Related to the TPPTS ligand (**18**, $n = 0$), although with higher basicity, is the lithium carboxylate-containing phosphane **19** (*m*-TPPTC), which combined with $Pd(OAc)_2$ (1 mol %) has allowed the Sonogashira copper-free cross-coupling of aryl iodides, even sterically hindered, in a mixture of aqueous acetonitrile as solvent and using triethylamine or diisopropylamine as base at 60 °C.[79] An example is shown in the coupling reaction of *o*-iodinated benzyl alcohol **20** and phenylacetylene to give alkynylated product **21** (Scheme 8). It is interesting that this catalytic system can

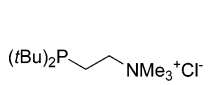
Scheme 8



20 **21**

be recycled, transporting the acetonitrile/water medium to a biphasic system, which allows the separation of the final coupling products and the reuse of the catalyst-containing aqueous system.[79]

Another active and recyclable in situ generated water-soluble palladium catalyst for the Sonogashira reaction is that obtained by the combination of $Pd(OAc)_2$ (2.5 mol %) and di-*tert*-butylphosphane **22**, which can couple aryl bromides in aqueous acetonitrile in the presence of copper iodide and diisopropylamine as base at 50 °C, with an activated aryl chloride even being used, although with low yield and increasing the palladium loading (5 mol %).[77] In addition, biphenyl sulfonated phosphane **23** creates a quite active catalyst when mixed with $PdCl_2(MeCN)_2$ (2.5 mol %) in aqueous acetonitrile, thus allowing a high yielding copper-free Sonogashira reaction of activated and unactivated aryl bromides and chlorides with terminal acetylenes, using cesium carbonate as base at 60−100 °C.[80] Moreover, phosphinous acids have been shown to be suitable ligands for the aqueous Sonogashira cross-coupling reaction. Thus, the palladium-phosphinous acid complex $PdCl_2[(t\text{Bu})_2\text{P-(OH)}]_2$ (10 mol %) has been employed in the copper cocatalyzed coupling of aryl halides, including chlorides, using pyrrolidine as base and tetra-*n*-butylammonium bromide (TBAB) as additive in water at 140 °C, with the positive effect of TBAB being also attributable to an enhancement of the solvation of the organic compounds.[81] However, the absence of the copper cocatalyst drove to lower yields.



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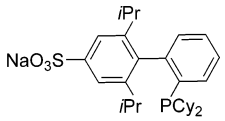

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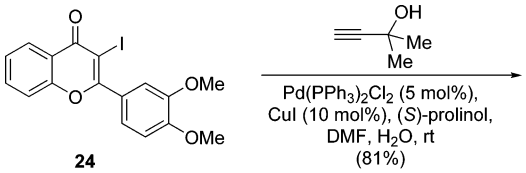
The conventional palladium catalysts can also be used in homogeneous catalysis under aqueous conditions if a proper additive is added. Thus, as the effect of TBAOH in promoting the Sonogashira coupling reaction is known,[54] it was supposed that the simpler ammonium hydroxide could perform similarly. Therefore, it was found that diluted aqueous ammonia (0.5−2 M) promoted the reaction of terminal alkynes with aryl iodides and bromides at room temperature using $PdCl_2(PPh_3)_2$ as catalyst and copper(I) iodide as cocatalyst.[82,83] The reaction was found to decrease the yield as the concentration of the employed ammonia solution increased, and its role could not be exclusively to act as a base, as other inorganic bases resulted in lower yields of the coupled products.[83] Moreover, the addition of (*S*)-prolinol to the typical Sonogashira catalytic mixture $PdCl_2(PPh_3)_2$/CuI has allowed the coupling of terminal alkynes to 3-iodoflavones in 20% aqueous DMF at room temperature, as shown in Scheme 9 with the cross-coupling of iodoflavone

Scheme 9



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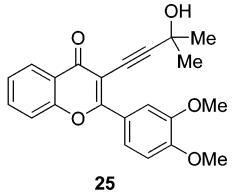


25

24 and 2-methylbut-3-yn-2-ol to give compound **25**. It has been suggested that (*S*)-prolinol stabilized the possibly generated catalytic anionic species and facilitated the reaction in aqueous media due to its interaction with water molecules via the hydroxyl group.[84]

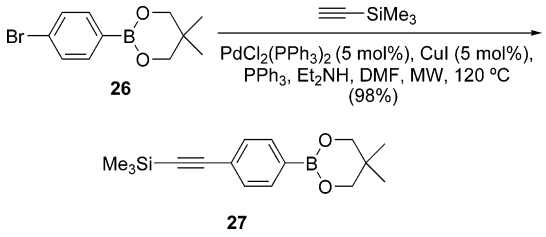
There is also a reported example of the use of palladium submicron powder for generation of the catalytic species in Sonogashira couplings in aqueous media. Thus, aryl iodides and bromides and also a vinyl iodide have been cross-coupled with aryl and alkyl terminal acetylenes in the presence of palladium powder, copper(I) iodide, and triphenylphosphine in aqueous THF at 60 °C.[85]

Room temperature ionic liquids have also been considered in recent years as an alternative to volatile organic solvents for numerous catalytic transformations,[86] with advantages also derived from the frequent ionic liquid ability to contain the catalytic system, thus allowing its reuse after separation of the final products. However, few examples can be found where a usual phosphane-containing palladium catalyst had been employed for Sonogashira reactions in ionic liquids. Thus, the system formed by the combination of $Pd(OAc)_2$/PPh_3 as catalyst and also copper(I) iodide and triethylamine in an ionic liquid such as 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm][PF_6]) at 80 °C was able to perform

the Sonogashira coupling of aryl iodides with different alkynes in good to moderate yields.[87] A copper-free version using this ionic liquid as solvent at 60 °C, but employing $PdCl_2(PPh_3)_2$ as reusable catalyst and diisopropylamine as base, has been employed for the coupling or aryl iodides or a vinyl bromide and terminal alkynes in high yields.[88] This reaction has been applied successfully to a microflow system.

The use of microwaves for achieving local overheating often results in considerable lowering of reaction times, which also drive to higher purity of the final products and, consequently, higher yields. Therefore, their use in organic synthesis is now frequent.[89] The procedure can usually be applied to Sonogashira coupling reactions, as, many times, the solvents employed for this reaction are polar molecules, being, therefore, microwave active. Thus, microwave heating has been used in homogeneous-phase Sonogashira reactions under typical reaction conditions [$Pd(PPh_3)Cl_2$/CuI, diisopropylamine, DMF as solvent, 120 °C] for the coupling of different aryl iodides, bromides, triflates, and also 2-chloropyridine with trimethylsilylacetylene, affording excellent yields in only 5−25 min.[90] Essentially the same experimental protocol has been used for other homogeneous Sonogashira reactions,[91] such as the case shown in Scheme 10, where

Scheme 10

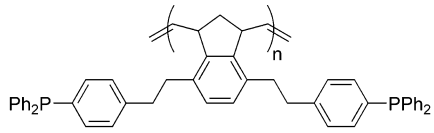


the bromoaryl boronate **26** is coupled to trimethylsilylacetylene under microwave-facilitated Sonogashira reaction conditions to give acetylene **27** in almost quantitative yield in only 25 min.[92] The same reaction carried out in refluxing DMF for 6 h failed, whereas heating at 130 °C during 30 min afforded only a 60% yield.

The microwave-assisted procedure can be especially interesting when working under heterogeneous conditions, as usually these reactions take place in longer reaction times than their homogeneous counterparts. Examples of applications of this microwave technique to Sonogashira coupling reactions can be seen in the rapid coupling reaction of solid-phase supported aryl iodides and bromides to acetylene derivatives,[93] or the coupling of PEG-supported iodobenzoic acid with terminal alkynes.[94] In addition, microwave heating allowed the high yielding, solventless Sonogashira coupling reaction between aryl or alkenyl iodides and terminal alkynes on palladium-doped alumina in the presence of triphenylphosphane and copper(I) iodide.[95]

3.1.2. Supported Palladium–Phosphorus Complexes

The problem associated with the recovery of the often expensive catalyst after product formation poses a serious drawback for large-scale application of homogeneous catalysis. Metalodendrimers combine the advantages of homogeneous and heterogeneous catalysts, as they are soluble and well defined on the molecular level, and yet they can be recovered by precipitation, ultrafiltration, or ultracentrifugation.[96] Some recent examples can be found about the use of dendritic palladium complex catalysts for the copper-free Sonogashira reaction. Thus, several generations of bidentate phosphanated palladium(II) polyamino dendritic catalysts have been used solubilized in triethylamine (1 mol % catalyst) for the coupling of aryl iodides and bromides at 25−120 °C, and of aryl chlorides, but in very low yields.[97] The dendrimeric catalysts could usually be recovered by simple precipitation and filtration and reused up to five times, with diminished activity produced by dendrimer decomposition and not by palladium leaching being observed. These dendrimeric catalysts showed a negative dendritic effect; that is, the catalyst efficiency decreases as the dendrimer generation increases. In addition, recyclable polymeric phosphane ligand **28**, obtained from ring-opening metathesis polymerization of a norbornene derivative, has been used in the copper cocatalyzed Sonogashira reaction of methyl *p*-iodobenzoate and phenylacetylene using $Pd(dba)_2{\cdot}CHCl_3$ (2.5 mol %) as palladium source in refluxing triethylamine.[98] The polymeric catalyst was recovered by filtration, although its catalytic activity decreased by approximately 4−8% in each recycle experiment.



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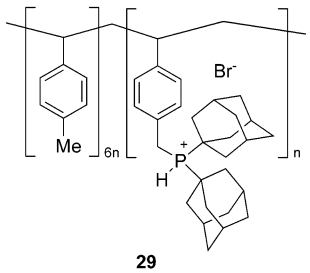

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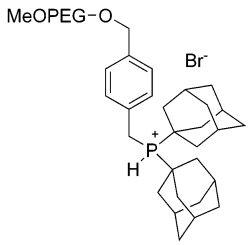

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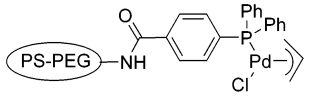

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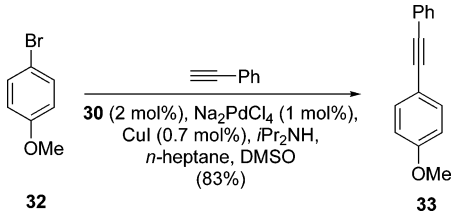
Soluble polymers can be used for the attachment of phosphanes, which can drive to phase-tagged biphasic catalytic species suitable for separation and recycling. Thus, linear poly(4-methylstyrene) has been used for this anchoring, as can be seen in the case of polymeric bis-adamantyl phosphonium salt **29**, which generated the free phosphane in the presence of diisopropylamine and combines in situ to $Pd(PhCN)_2Cl_2$ (1 mol %) to give a catalyst employed for the copper-cocatalyzed Sonogashira reaction of aryl bromides and terminal alkynes in the biphasic mixture cyclohexane/DMSO at 60 °C.[99] The catalyst remained dissolved in the nonpolar phase with very small loss (2%) to the polar phase and could be separated and reused. The reaction using this catalyst has also been performed in toluene as solvent, and in this case nanofiltration techniques have been used for the polymer recovery.[100] This bis-adamantyl phosphonium salt has also been attached to monomethyl PEG (MeOPEG) to give polymer **30**, which after in situ deprotonation with an amine and combination with Na_2PdCl_4 (1 mol %) as palladium source allowed the copper cocatalyzed coupling of aryl bromides to acetylenes in the biphasic mixture *n*-heptane/DMSO at 60 °C.[101a] An example of its use is the

cross-coupling of 4-bromoanisole (**32**) and phenylacetylene to give the corresponding product **33** (Scheme 11). The

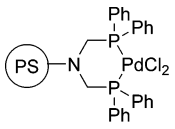
Scheme 11



32 **33**

palladium and copper catalysts remained in the polar phase after extraction of the low-polarity layer with total retention, but their activity showed a small but noticeable decrease after five runs. The initial activity was, however, recovered after addition of new copper(I) iodide. This catalyst has been applied to a continuous biphasic flow process.[101b] In addition, amphiphilic polystyrene−poly(ethylene glycol) (PS−PEG) resin-supported palladium−phosphane complexes such as **31** have been used in water for copper-free Sonogashira reactions.[102]

Immobilization of the palladium catalyst on a solid and insoluble support can drive to advantages related to its easier isolation and recycling compared to the cases of soluble counterparts.[103] An example of an insoluble phosphane palladium complex applied to the Sonogashira reaction is catalyst **34**, anchored to a cross-linked aminomethyl polystyrene. This supported complex, generated after reaction of the corresponding anchored diphosphane with $Pd(COD)Cl_2$, has been employed in the overnight copper cocatalyzed cross-coupling reaction of aryl iodides with terminal alkynes (4 mol % catalyst loading) in the mixture dioxane/piperidine as solvent at 60 °C, with the catalyst being recovered by filtration and reused up to four times without any loss of activity.[104] It is interesting to note that a quite similar supported palladium complex, now anchored to aminopropyltrimethoxysilane, has been employed (1 mol % catalyst loading) in the coupling reaction of aryl iodides and alkynes in piperidine at 70 °C, but now in the absence of copper cocatalyst and in only 10 min, although a reduction in the yield of the coupled product and longer reaction times (up to 50 min) were observed using the recycled catalyst.[105]



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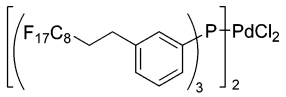

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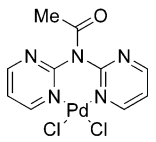
A curious example of supporting a phosphane ligand on a silica gel-derived solid support without covalent bonding can be seen in the case of perfluoro-tagged palladium complex **35**, which has been immobilized on a fluorous-modified silica gel and employed in the Sonogashira coupling of *p*-bromonitrobenzene and phenylacetylene in the presence of copper(I) iodide and di-*n*-butylamine in dimethoxyethane as solvent at 100 °C.[106] The leaching was 1.6−1.9%, and high yields were obtained with 2 mol % catalyst loading for three successive experiments using the recycled catalyst, whereas with 0.2 mol % loading the yield dropped when the catalyst was reused. Finally, a Nafion membrane, reinforced with Teflon, has been used for supporting a diphenylphosphane ligand, which after treatment with $Pd(OAc)_2$, allowed the preparation of a recyclable supported palladium catalyst able to perform the copper-free coupling of 2-iodothiophene with phenylacetylene (0.5 mol % catalyst loading), using triethylamine as base in acetonitrile at 100 °C.[107] The catalyst provided sufficient activity until the fifth run, with less than 0.1% of palladium leaching being observed.

3.2. Palladium–Nitrogen Complexes

3.2.1. Unsupported Palladium–Nitrogen Complexes

Pyridines and pyrimidines have shown good complexation properties for palladium and have been employed in the formation of catalysts suitable for Sonogashira couplings. Thus, the dipyrimidyl−palladium complex **36** (prepared by mixing the corresponding ligand with H_2PdCl_4) has been employed in the copper-free coupling of iodo-, bromo-, and chlorobenzene with phenylacetylene using tri-*n*-butylamine as base in THF at 65 °C.[108] More recently, the dipyridyl−palladium complex **37** has been obtained and has been used



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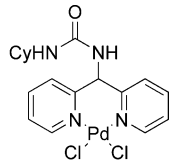
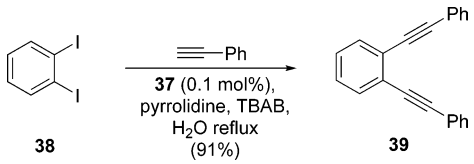


37

in the copper-free Sonogashira coupling reaction of aryl iodides and bromides in *N*-methylpyrrolidinone (NMP) using tetra-*n*-butylammonium acetate (TBAA) as base at 110 °C or at room temperature.[109] It is interesting to note that this complex **37** has also been used for the coupling of aryl iodides and bromides in refluxing water as solvent and in the presence of air, using pyrrolidine as base and TBAB as additive,[109] although its efficiency was higher in *N*-methylpyrrolidinone (NMP) as solvent. An example of use of complex **37** is shown in the double coupling of *o*-diiodobenzene (**38**) and phenylacetylene to give dialkynylated benzene **39** (Scheme 12).[109b] Complex **37** (0.1−1 mol % Pd

Scheme 12

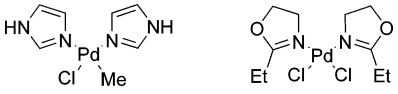


38 **39**

loading) has also been recently employed in the preparation of symmetrical diarylakynes by direct diarylation of alkynylsilanes, such as mono- and bis(trimethylsilyl)acetylene (TMSA and BTMSA), in water using pyrrolidine as base and TBAB as additive. This reaction probably takes place by succesive protiodesilylation−Sonogashira coupling.[15] Alternatively, the process can be performed in NMP as solvent in the presence of tetra-*n*-butylammonium acetate (TBAA) as base, with even lower palladium loading (0.001−1 mol %). Finally, an example of a pyridine-derived complex is also the in situ species formed by combination of $Pd(OAc)_2$ and 2-aminopyridine-4,6-diol, which has been employed in a copper-free coupling of aryl iodides and bromides using cesium carbonate as base.[110]

An example of a bis-imidazolyl-derived palladium catalysts is complex **40**, which performs a rapid copper-free Sonogashira coupling of aryl iodides and terminal alkynes

(0.02 mol % catalyst) in ionic liquids in the presence of piperidine at 120 °C.[111] The products could be extracted from the ionic liquid, which after washing with water to remove the formed piperidine salt, could be reused. There is also an example showing the use of a bis-oxazoline palladium complex in a Sonogashira coupling reaction. Thus, complex



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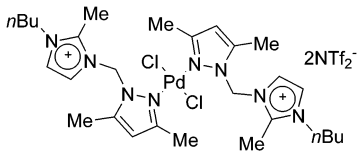
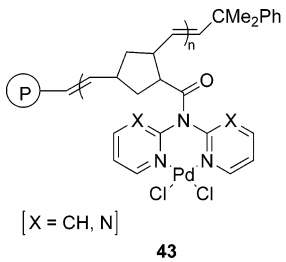


42

41 has been employed (0.055 mol %) in a rather low-yielding cross-coupling of iodobenzene and phenylacetylene in pyrrolidine at 90 °C, with a large amount of copper(I) iodide (50 mol %) also being necessary.[112] Similarly, ionic liquid-soluble bis-pyrazolyl-derived palladium complex **42** has also been used for coupling of aryl iodides and phenylacetylene (1 mol % catalyst loading), with the ionic liquid with the catalyst being reused up to six reaction cycles while maintaining its activity.[113] Furthermore, hetero-bimetallic palladium−copper catalysts with 2-hydroxypyridine ligands have been used for the coupling of 2-iodoaniline and phenylacetylene, although the catalysts are deactivated by air during the extraction procedure.[114] Finally, bi- and trinuclear oxalamidinate complexes of palladium have been used in the copper-free Sonogashira reaction between 4-bromoacetophenone and phenylacetylene.[115]

3.2.2. Supported Palladium–Nitrogen Complexes

Dipyridyl-based, ROMP-polymer-anchored palladium complex **43** (X = CH) has been used in an example of copper-free Sonogashira coupling between iodobenzene and TMSA,[116] whereas related dipyrimidyl-derived polymeric catalysts **43** (X = N) exceeded its nonpolymeric counterpart **36** in terms of reactivity when coupling iodo-, bromo-, or chlorobenzene to terminal alkynes using tri-*n*-butylamine as base in THF as solvent at 65 °C.[108] Dipyridyl-based poly-



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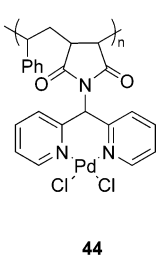
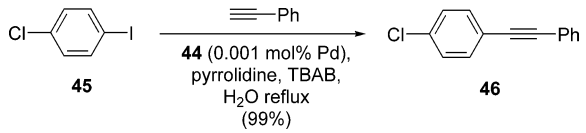


44

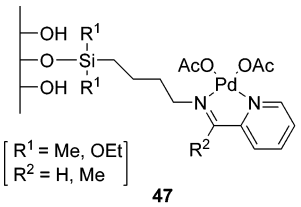
(styrene-*alt*-maleimide)-anchored palladium complex **44** (1.2 mmol/g of Pd) has been shown to be more efficient and has been used as a recyclable catalyst in copper-free Sonogashira couplings of electron-rich or -poor aryl iodides and electron-poor aryl bromides (0.1−0.2 mol % Pd loading) in refluxing water or under microwave heating using pyrrolidine as base and TBAB as additive, achieving TONs up to 10^5.[117] Under these conditions, the formation in the polymer surface of stabilized active palladium(0) nanoparticles was observed by transmission electron microscopy (TEM) determinations. The palladium loading could be decreased to 0.001 mol % in the coupling of phenylacetylene and 4-chloroiodobenzene (**45**) to give alkyne **46** (Scheme 13), although longer reaction

Scheme 13



times were needed. This polymeric catalyst showed a higher efficiency than its monomeric counterpart **37**, and also higher recyclability than that when using a polyurea-encapsulated palladium(II) catalyst such as Pd EnCat 40, being reused up to five times without appreciable lost of catalytic activity. In addition, this polymeric complex **44** has performed similarly to complex **37** in the direct diarylation of TMSA and BTMSA using the same reaction conditions.[15]

Supported dinitrogenated ligands useful in Sonogashira coupling reactions have been recently obtained by reaction of amino-containing silanes with silica gel. Thus, recyclable pyridine-oxime-containing palladium catalysts **47** (R^1 = Me; R^2 = H, Me) supported on silica gel have allowed the coupling of electron-poor aryl iodides and terminal alkynes (0.1−1 mol % Pd loading) in the absence of copper, using triethylamine as base in undecane as solvent at 70 °C.[118] These catalysts could be filtered and reused, showing a partial loss of performance after the third cycle. No catalytic activity was observed in the solution after filtration of supported catalysts, proving its heterogeneous behavior. A related palladium complex **47** (R^1 = OEt; R^2 = Me) has been anchored to the surface of expanded corn starch and used in the solventless, copper-free coupling reaction of electron-poor iodoarenes and phenylacetylene, using DABCO as base at 100 °C or microwave heating, achieving TONs up to 384 (thermal heating) or 326 (microwave heating) and giving no palladium leaching.[119] In contrast to silica-gel-based materi-



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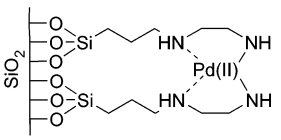


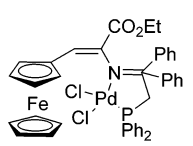
48

als, which have been proven by XPS to have all palladium(II) (therefore bound to the ligand), this starch-derived catalyst has been shown to contain palladium(0) nanoclusters produced after conditioning of the surface, which are stabilized by the support material and able to act catalytically. Also immobilized on silica gel is the 3-(2-aminoethylamino)-propyl-functionalized palladium catalyst with the uncertain structure **48**, prepared by reaction of the corresponding supported diamine with $Pd(OAc)_2$. This supported catalyst has been employed in the copper-free Sonogashira reaction of aryl iodides and bromides with acetylenes (1 mol % Pd loading) using potassium carbonate as base in ethanol as solvent at 80 °C, being recovered by filtration and reused up to 30 times without any decreases in the activity.[120] Related mesoporous molecular sieves of the type MCM-41 have been recently used for supporting palladium(0) complexes in the copper-cocatalyzed Sonogashira reaction of aryl iodides with terminal alkynes in piperidine at room temperature.[121]

Zeolites have been used for the immobilization of nitrogen-containing palladium complexes applicable to Sonogashira couplings. Thus, when NaY zeolite was ion-exchanged using a solution of $[Pd(NH_3)]^{2+}Cl^-$, the palladium zeolite [Pd-(NH_3)]−NaY was obtained.[122] This heterogeneous catalyst was employed for the copper-free cross-coupling reaction of aryl iodides (quantitative yields) and activated aryl bromides (moderate yields) with terminal alkynes (1 mol % Pd loading), using triethylamine as base in DMF/water at 80 °C. This catalytic system showed recyclability after five runs and no palladium leaching, with only a slight deactivation during the first run, which could suggest a change in the state of the catalyst during the first process.

3.3. Palladium–P,N- and Palladium–P,O Complexes

P,N-Donor bidentate ligands exhibit hemilabile behavior when coordinated to palladium, with the soft phosphorus atom coordinating strongly whereas the hard nitrogen donor is weakly bound. To this category belongs the palladium(II) complex **49**, containing a ferrocene-based phosphinimine−phosphane ligand, which has been used in the amine- and copper-free Sonogashira coupling of aryl iodides and aryl bromides in NMP as solvent at 110 °C (1−0.1 mol % catalyst loading) and in the presence of TBAA.[123] In addition, complexes **50** containing P,O-bidentate 3-oxo-1,3-diphosphapropene ligands have been assayed in the copper-cocatalyzed coupling of iodobenzene and phenylacetylene, using triethylamine as base and solvent at room temperature, with yields up to 68% (R = *p*-$MeOC_6H_4$).[124]



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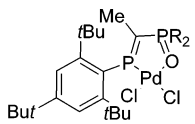


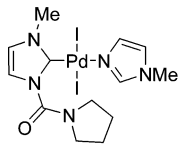
[R = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *n*Bu]

50

3.4. *N*-Heterocyclic Carbene (NHC) Palladium Complexes

3.4.1. Unsupported NHC Palladium Complexes

Nucleophilic *N*-heterocyclic carbenes (NHCs) behave like typical σ-donor ligands that can substitute classical 2-electron ligands such as amines and phosphanes in metal coordination chemistry, sometimes even more efficiently; therefore, they have found application to numerous areas of organometallic homogeneous catalysis.[125] The most easily available are stable carbenes derived from imidazole, not the least because numerous imidazolium precursor compounds can be made along various reliable routes, with the combination of the imidazolium salt with a palladium source under basic conditions generating the NHC−palladium complex. NHC-derived palladium(II) complex **51** (1 mol %) has been shown



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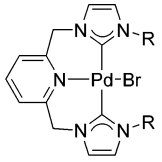
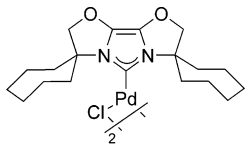


[R = Me, *n*Bu, Bn]

52

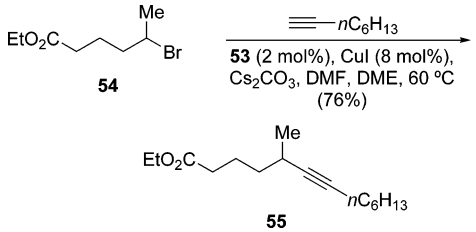
to promote the coupling of aryl bromides at 80 °C in DMF using triethylamine as base, although the presence of catalytic amounts of copper(I) iodide and triphenylphosphine was necessary.[126] Tridentate bis-carbene-pincer complex **52** has been also used in the copper-cocatalyzed Sonogashira reaction of iodobenzene with phenylacetylene in boiling pyrrolidine, affording a high yield, although a small amount of addition of the alkyne was necessary when aryl bromides were employed in order to avoid alkyne homocoupling.[127] The formation of palladium black was observed when using this catalyst if the temperature was maintained when all the substrates had been consumed.



53

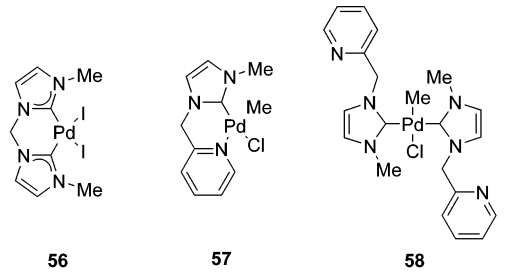
Also, copper cocatalysis was necessary in the promising Sonogashira-type reaction of unactivated alkyl halides, which has been achieved by means of NHC-derived palladium complexes.[8] Thus, primary alkyl bromides and iodides have been coupled to terminal alkynes using a catalytic system based on the combination of $[Pd(\eta^3\text{-}C_3H_5)Cl_2]$, *N*-bulky-substituted dihydroimidazole-derived ligands, a high amount of copper(I) iodide (22.5 mol %), and cesium carbonate as base at 45 °C.[8a] More recently, the coupling of secondary alkyl bromides, such as bromoester **54**, has been achieved using the same base and a combination of NHC−palladium complex **53** (2 mol %) and copper(I) iodide (8 mol %) in a mixture of DMF and DME as solvent at 60 °C, giving the corresponding alkynylated compound **55** when 1-octyne was used as terminal alkyne (Scheme 14).[8b]

Scheme 14

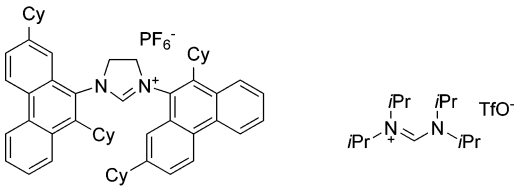


54 **55**

Copper-free Sonogashira protocols have also been developed using these types of carbene complexes. This is the case of the procedure described for the direct coupling of aryl bromides and alkynylsilanes using an in situ generated palladium carbene from $Pd(OAc)_2$ (3 mol %) and an imidazolium salt, in DMA as solvent at 80 °C.[61] Also a copper-free procedure is involved in the case of the NHC-derived catalyst **56**, which has been used (1 mol %) for the coupling of 2-bromoacetophenone with phenylacetylene in triethylamine as solvent at 90 °C.[128] The carbene-derived palladacycles **57** and **58** (0.1 and 0.2 mol % catalyst loadings, respectively) were used for the same coupling under identical reaction conditions, although achieving lower yields.[129] Bulky phenanthracenyl imidazolium-derived salts such as **59** have been investigated as ligands (3 mol %) in copper-free Sonogashira coupling of aryl iodides and bromides in combination with $PdCl_2(PPh_3)_2$ (3 mol %) with potassium *tert*-butoxide as base and 18-crown-6 in THF at 65 °C.[130] In addition, a recent example of application of an acyclic aminocarbene-derived complex, generated by deprotonation of amidinium salt **60** with LDA and combination with [Pd-



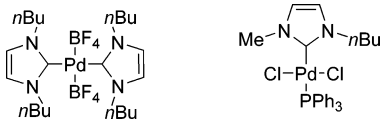
56 57 58



59 60

(η^3-C_3H_5)Cl_2] (1.5 mol %), for the room-temperature copper-free coupling of aryl bromides can be found.[131]

The palladium−biscarbene complex **61** has been characterized after being generated in situ by mixing $PdCl_2$ (2 mol %) and triethylamine as base in the ionic liquid 1,3-di-*n*-butylimidazolium tetrafluoroborate during the copper-free Sonogashira coupling of aryl iodides under ultrasound irradiation at 30 °C. Once generated in the reaction media, and not only under the sonochemical conditions, this complex **61** gives rise to stable, crystalline, and polydispersed pal-



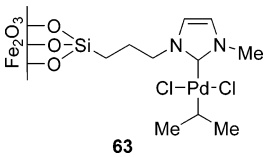
61 62

ladium(0) nanoparticles as the real catalyst for the reaction between aryl iodides or electron-poor aryl bromides and terminal alkynes.[132] This recent work raises again the open question of whether *N*-heterocyclic carbene palladium complexes are the real catalytic materials.[64,66b] In addition, the palladium−carbene complex **62** has been employed in a parallel Sonogashira coupling reaction of aryl iodides under copper-free conditions in ionic liquids using piperidine as base at 80 °C (5 mol % catalyst loading).[133]

3.4.2. Supported NHC Palladium Complexes

An example of a Sonogashira cross-coupling reaction achieved by supporting a palladium carbene ligand on an insoluble phase can be found in the immobilization of the mentioned palladium tridentate pincer bis-carbene catalyst **52** in smectite clays, which makes it recyclable and now highly stable, with no palladium black being formed upon heating.[127] The reaction is performed with iodobenzene and activated aryl bromides and phenylacetylene (6 mol % complex loading), with pyrrolidine as base and solvent or with piperidine and *N*,*N*-dimethylacetamide (DMAC) and solvent at 87−106 °C, with the presence of copper(I) as cocatalyst being necessary.

A palladium−carbene complex has been used anchored to nanoparticles of magnetic maghemite (γ-Fe_2O_3) coated with oleate, to form the iron oxide−palladium supported complex **63**. These superparamagnetic nanoparticles are partially soluble in organic solvents such as DMF and have been used as catalysts in homogeneous cross-coupling reactions such as the Sonogashira coupling of electron-rich



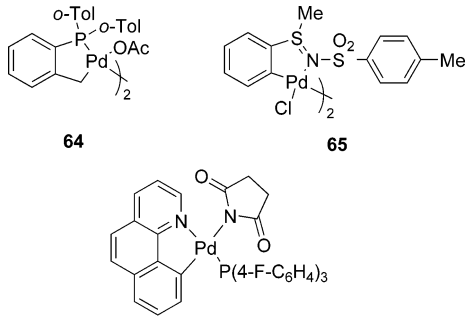
63

and poor aryl iodides and electron-rich aryl bromides with phenylacetylene (7.3 mol % complex loading) using sodium carbonate as base at 50 °C, although using copper as cocatalyst.[134] Interestingly, this catalyst was separated from the reaction mixture just by using an external permanent magnet, being reused up to three times without any loss of catalytic activity.

3.5. Palladacycle Catalysts

3.5.1. Unsupported Palladacycles

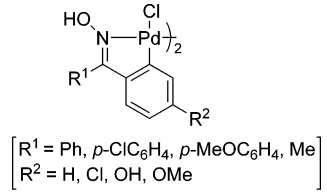
Palladacycles have emerged as a very promising family of organometallic catalyst precursors in C−C bond-forming processes, often showing interesting mixed characteristics such as high catalytic activity and, at the same time, high stability.[135] It has been proven that palladacycles are not the "true" active catalyst, but rather the precatalyst that undergoes an activation process acting as a source of low-coordinate palladium(0) such as palladium nanoparticles.[64,135] Some of these palladacycles have been employed in copper-free Sonogashira reactions, with the precursor being phosphapalladacycle **64**, which performed the coupling of aryl bromides



64 65 66

and phenylacetylene in triethylamine at 90 °C, achieving an up to 8×10^3 TON.[136] Sulfinimine palladacycle **65** performed less efficiently, being employed for the coupling of aryl iodides in triethylamine at 80 °C with TONs just up to 352, with the couplings of bromobenzene and especially chlorobenzene affording low yields.[137] In addition, the cyclopalladated compound **66** has been found to be the most effective from a series of related complexes in the Sonogashira reaction of *p*-bromoacetophenone and phenylacetylene, using triethylamine as cosolvent at 100 °C, although the presence of copper(I) enhanced the reaction rate.[138]

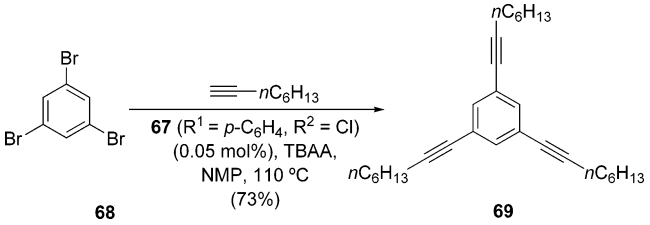
However, oxime-derived palladacycles[135d,139] have been shown to be the most efficient for this type of cross-coupling reaction. Thus, several benzophenone- and acetophenone-derived palladacycles **67** (R^1 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, Me; R^2 = H, Cl, OMe) have been employed first in a conventional copper-cocatalyzed Sonogashira coupling of iodobenzene and phenylacetylene in pyrrolidine at 90 °C.[140] However, a subsequent modification of the coupling protocol (TBAA as base and NMP as solvent at 110 °C) allowed the use of palladacycle **67** (R^1 = *p*-ClC_6H_4; R^2 = Cl) for the



67

copper- and amine-free coupling of aryl iodides and bromides and also vinyl bromides with terminal alkynes in high yields, with only 0.001 mol % Pd loading (for the coupling of 4-chloroiodobenzene and phenylacetylene).[141] An example of its use is the coupling of 1,3,5-tribromobenzene (**68**) with 1-octyne, to give trialkynylated benzene **69** (Scheme 15).[141b]

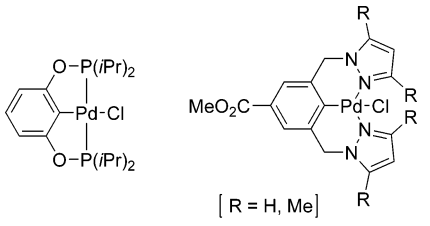
Scheme 15



68 **69**

Palladacycle **67** has also been used as an effective promoter of the direct coupling between alkynylsilanes, such as TMSA and BTMSA, and aryl iodides and bromides in the presence of copper or TBAB.[141b] Thus, diarylation was observed under copper(I) cocatalysis when the reaction was carried out with BTMSA in pyrrolidine as solvent at 90 °C, whereas the silylated alkyne was the main product in NMP as solvent in the presence of pyrrolidine and TBAB at 110 °C.[141b] Palladacycle **67** (R^1 = Me; R^2 = OH) has also been employed in the Sonogashira reaction using ionic liquids or PEG as recyclable solvents, which has been studied under copper-free conditions using cesium acetate as base and heating in ionic liquids at 120 °C, generally giving extensive palladacycle decomposition. This does not occur upon prolonged heating in PEG. Decomposition instead occurs under the real reaction conditions, giving rise to PEG-stabilized active nanoparticles in a homogeneous recyclable system.[142]

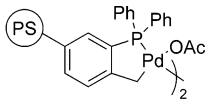
There are also examples of the use of palladium pincer complexes in Sonogashira couplings, such as the PCP pincer complex **70**, which was shown to be reactive enough to cross-couple a wide range of activated and nonactivated aryl chlorides with phenylacetylene using cesium carbonate as base, although $ZnCl_2$ should be added as additive and the reaction was performed in DMSO at 160 °C.[143] Moreover, the *N*-heterocyclic NCN pincer palladium complexes **71** have been recently employed in the coupling of aryl and naphthyl iodides and terminal alkynes (0.1 mol % catalyst loading) in pyrrolidine as solvent at 100 °C.[144]



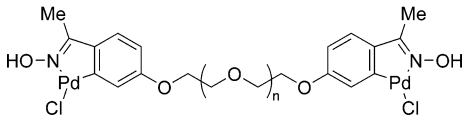
70 **71**

3.5.2. Supported Palladacycles

Few examples of the use of supported palladacycles in Sonogashira reactions can be found. Thus, soluble linear polystyrene-supported phosphapalladacycle **72** has been used in the almost quantitative, copper-free Sonogashira coupling of 4-bromoacetophenone and phenylacetylene in triethylamine at 90 °C (0.2 mol %), although with a reaction time of 3 days.[145] The polymeric catalyst was precipitated by



72



73

addition of ether and reused up to four times, keeping conversions of more than 90%, although the amount of recycled catalyst had to be increased to 5 mol %. No palladium leaching studies were performed. In addition, an oxime palladacycle was anchored to soluble PEG and the resulting polymer **73** was used as a catalyst solubilized in PEG for a copper-free Sonogashira reaction using cesium acetate as base at 150 °C.[146] The catalyst was effective in the coupling of a substrate such as 4-bromoacetophenone and phenylacetylene and can be reused after precipitation of the PEG in ether. The PEG-anchored carbopalladacycle was stable on heating in PEG, but it mostly decomposes during the first catalytic cycle, forming palladium nanoparticles stabilized by PEG, thus keeping its catalytic properties and avoiding palladium leaching from the PEG phase.

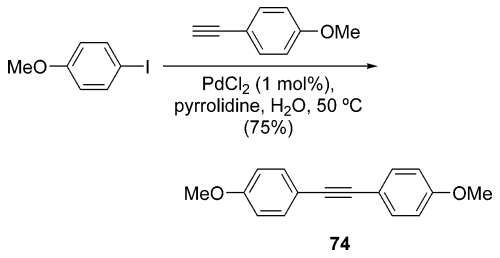
3.6. Ligand-Free Palladium Catalysts

3.6.1. Unsupported Ligand-Free Palladium Catalysts

The use of simple palladium salts as catalysts has advantages related to cost and to avoiding possibly sensitive ligands, although it also has some disadvantages related to the rather usually high amounts of palladium required. Some successful examples of the use of ligand-free palladium salts as catalysts are the copper-free Sonogashira coupling reactions of aryl iodides and bromides using $Pd(OAc)_2$ as catalyst at room temperature in DMF as solvent in the presence of TBAA as basic additive.[147] This catalytic system probably generates highly reactive palladium(0) nanoparticles, as carboxylated tetrabutylammonium salts are known to facilitate the reduction of $Pd(OAc)_2$ to catalytically active palladium(0) species.[148] Recently, it has been found that 1,4-diazabicyclo[2.2.2]octane (DABCO) can act as a superior ligand for the palladium compared to the cases of other tertiary amines in the copper-free Sonogashira cross-coupling reaction. Thus, the combination $Pd(OAc)_2$ (3 mol %)/DABCO (6 mol %) has been employed in the coupling of aryl iodides and activated bromides in the presence of cesium carbonate as base and at room temperature.[149] The palladium loading could be reduced to 0.0001 mol % (in the case of aryl iodides), keeping good yields, although with longer reaction times. The same catalytic combination also gave good yields in the absence of a base and even in the presence of air.[150] However, when the copper-free Sonogashira reaction using this catalytic system was attempted in aqueous media in the presence of polyethylene glycol-400 (PEG-400) as phase-transfer catalyst, rather low yields were obtained.[151] More successful results using water as solvent have been

reported. Thus, neat water has been used as solvent in the copper-free coupling of aryl and heteroaryl iodides and terminal acetylenes using $PdCl_2$ (1 mol %) as catalyst and pyrrolidine as base at room temperature (for activated aryl iodides) or at 50 °C, with an illustrative example being the coupling of *p*-iodoanisol and 1-ethynyl-4-methoxybenzene to give diarylacetylene **74** (Scheme 16).[152] It is interesting

Scheme 16

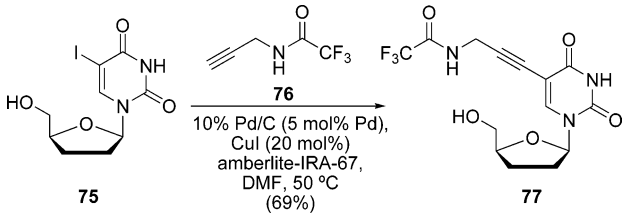


to note that other typical Sonogashira catalytic combinations gave only trace amounts of the desired products under these aqueous conditions. Similar reaction conditions, although in the presence of TBAB as additive and at 100 °C, have allowed lowering the amount of $PdCl_2$ down to 0.01 mol % in the case of the coupling of 4-chlorophenyl iodide and phenylacetylene.[109b] Finally, $PdCl_2$ has also been used recently as an efficient precatalyst for the direct di- and monoarylation of silylated alkynes either in water or in NMP as solvent, using pyrrolidine or TBAA as base, respectively.[15] In the case of TMSA and BTMSA, the double arylation took place affording symmetrical diarylated alkynes, whereas silylated terminal alkynes gave unsymmetrical systems.

3.6.2. Solid-Supported Ligand-Free Palladium Catalysts

Palladium on charcoal has been employed several times as a heterogeneous catalyst in Sonogashira cross-coupling reactions under different reaction conditions. Although certainly this is a "ligand-free" species, in some cases, triphenylphosphane is added to the reaction medium and a palladium−phosphane complex is formed. Thus, the first work which demonstrated the catalytic possibilities of this palladium source for Sonogashira reactions showed that the treatment of aryl bromides with monosubstituted acetylenes in the presence of palladium on charcoal, copper(I) iodide, and triphenylphosphane in triethylamine/DMF gave cross-coupled products.[153] In this work it was claimed that the palladium on charcoal was only a source of soluble palladium, as the reaction in the absence of the aryl halide and the acetylene gave $Pd(PPh_3)_4$. The use of this palladium source has proven effective in the case of the coupling of iodobenzene and phenylacetylene (0.125 mol % Pd) in the absence of copper cocatalysis, using pyrrolidine as base at room temperature at 100 °C, with the addition of copper(I) iodide not affording higher conversions.[154a] This process has been investigated more extensively in aryl and hetaryl bromides and chlorides (5 mol % Pd) in aqueous DMA as solvent,[154b] proving that certainly the palladium that leached into the solution was catalytically active. The filtrated palladium on charcoal after the coupling reaction has comparable activity to that shown by a "new" catalyst, which suggests that only a minor portion of the bound palladium is released into the solution (less than 2%), although this is enough for contaminating the reaction mixture.[154b] Palladium on charcoal can be employed, combined with a resin-bound tertiary amine (Amberlite IRA-67), for the copper-cocatalyzed coupling of *N*-protected propargyl amines to nucleoside-containing 5-iodouracil, 5-iodocytosine, and 2-bromoguanine,[155] as exemplified in the cross-coupling reaction of iodinated dideoxyuridine derivative **75** and propargylated trifluoroacetamide **76** to give compound **77** (Scheme 17).

Scheme 17



Palladium on charcoal has also been used for ligand- and copper-free processes. Thus, very recently, aryl bromides and even aryl chlorides have been coupled with phenylacetylene employing a combined halogen-exchange−copper-free Sonogashira procedure, consisting of the one-pot treatment of the aryl halide and the acetylene with potassium iodide, potassium fluoride, or TBAF as base and palladium on charcoal (3 mol % Pd), in the absence of solvent at 130 °C.[156] Aqueous organic solvents have been used with this palladium source, as in the case of the coupling of aryl bromides with an *N*-propargyl amino acid, under copper cocatalysis and in the presence of triphenylphosphane, in 50% aqueous dimethoxyethane as solvent at 80 °C.[157] In addition, a copper- and ligand-free coupling of aryl iodides and alkynes using sodium phosphate as base in 50% aqueous isopropanol as solvent at 80 °C with low catalyst loading (0.2 mol % Pd) has been reported, with the presence of air not affecting the final yield.[158] Moreover, neat water can be used as solvent when the combination formed by palladium on charcoal (3.8 mol % Pd), copper(I) iodide, and triphenylphosphane was employed in Sonogashira processes,[159] although the presence of amino alcohols such as (*S*)-prolinol[159a] or 2-aminoethanol[159b] was necessary.

The use of the Pearlman's catalyst $[Pd(OH)_2/C]$ in heterogeneous cross-coupling reactions can be a safer alternative to palladium on charcoal due to its nonpyrophoric character, although the presence of copper(I) iodide was necessary. There is an example of the use of this recoverable catalyst (0.5 mol %) in the Sonogashira reaction of 3-bromopyridine with phenylacetylene or 2-methylbut-3-yn-2-ol in the presence of triphenylphosphane and potassium carbonate, using aqueous dimethoxyethane as solvent at 80 °C.[160]

The so-called perovskites are a large number of natural and synthetic materials with the same structure as that of calcium titanate, which can be modified by exchanging metals.[161] Copper- and palladium-containing perovskites have found application in cross-coupling reactions, such as the Sonogashira reaction of electron-rich or -poor aryl iodides or *p*-bromonitrobenzene with aryl acetylenes (0.125 mol % Pd), using triethylamine as base in 5% aqueous DMAc or DMF as solvent at 120 °C.[162] In addition, magnesium oxide and mixed aluminum−magnesium oxides derived from hydrotalcites containing variable amounts of palladium and copper have been used as reusable solid catalysts for the Sonogashira coupling of iodobenzene and phenylacetylene in DMF/water as solvent using triethylamine as base at 100 °C (TONs up to 247).[163] Metal-leaching experiments showed that these systems were purely heterogeneous, with no palladium being detected in the reaction mixture.

An air- and moisture-stable Pd/MgLa mixed oxide, prepared by ion exchange of the MgLa mixed oxide with Na_2PdCl_4 and further reduction with hydrazine hydrate, has been used as a filtration-recoverable and no-leaching supported palladium(0) catalyst in the copper-free Sonogashira reaction of aryl iodides, bromides, and even unactivated aryl chlorides (1.5 mol % Pd), with the coupling taking place by heating in DMF at 80 °C in the presence of triethylamine as base.[164] There are also recent examples of a copper-free triethylamine-promoted Sonogashira reaction of aryl iodides and phenylacetylene in DMF as solvent at 120 °C using as recyclable catalyst palladium(0) supported on cellulose (1.9 mol % Pd), which was obtained by suspending a methanolic solution of palladium(II) chloride with microcrystalline cellulose and reducing the formed solid with hydrazine.[165] TEM analysis showed small palladium nanoparticles along with larger aggregates, with more aggregation being observed in the recycled catalyst. A 2.22% palladium leaching was detected in the reaction mixture after the fourth catalytic cycle.

3.7. Palladium Nanoparticles as Catalysts

Transition-metal nanoparticles are especially active catalytic systems due to their large surface area.[66] These catalysts can be considered rather at the border homogeneous−heterogeneous, depending on the particle size, and could be named as semiheterogeneous systems. As mentioned above, nanoparticles can be stabilized by some additives such as trialkylammonium salts or PEGs which can act as ligands surrounding the dispersed nanoparticles and therefore minimizing their tendency to undergo agglomeration.[66] The nanoparticle size is associated with its reactivity; thus, small nanoparticles would allow, for instance, more favorable oxidative addition of the metal to the carbon−halogen bond at the rim of the nanoparticle.[166] As has been mentioned, nowadays there are real proofs or indications that palladium(0) nanoparticles can in fact be the real catalyst in many of the processes already described, as a consequence of decomposition of the original palladium salt or complex. However, it has recently been demonstrated by TEM and kinetic studies that soluble palladium species can also be present when these palladium nanoclusters act as catalysts.[167,168] Thus, the copper-free Sonogashira reaction of 4-bromobenzonitrile and phenylacetylene using palladium nanoparticles, generated by reduction of $Pd(NO_3)_2$ with tetraoctylammmonium glycolate, as catalyst and TBAA as stabilizer showed similar kinetic profiles to that using a homogeneous $Pd(dba)_2$ complex. The palladium clusters were also prepared using other palladium salts, showing that the coordinating ability of anions to the cluster surface affects its stability (activity decreasing in the order $NO_3^- > Cl^- > OAc^-$), thus rendering the clusters more or less susceptible to leaching. The similar reactivity of the nanoparticles from $Pd(NO_3)_2$ to that of the soluble catalyst reflects the weaker coordination of NO_3^- and therefore the increasing palladium leaching rate. The solubilized palladium can be reclusterized after the catalytic process.[167] Although all these conclusions are based on circumstantial evidence, experiments based on two-compartment membrane separation of the palladium nanoparticles from the reaction mixture in Heck couplings have proved that leached catalyst-acting palladium species diffuse from the nanoparticles, with the results most probably being extendable to the Sonogashira reaction.[169] The discovery that reactive soluble catalytic palladium species are also present in nanoparticle-catalyzed reactions creates further questions related to the nature of the catalytic species in many transition-metal-catalyzed cross-coupling reactions.

As the surface of the particles is the crucial area for the catalytic activity, recent work has shown that it is also possible to economize expensive palladium metal in the preparation of active palladium nanoparticles by preparing nickel/palladium core/shell bimetallic species, obtained from the consecutive thermal decomposition of metal−surfactant complexes. These bimetallic nanoparticles show even higher catalytic activity in Sonogashira coupling reactions than nanoparticles containing an equal amount of palladium, although copper cocatalysis is necessary.[170] In addition, bimetallic hollow palladium−cobalt nanoparticles have been used as catalyst in aqueous media for the coupling of aryl iodides or bromides and phenylacetylene, with the presence of copper iodide still being required.[171]

Palladium(0) nanoparticles generated by heating a mixture of $Pd(PPh_3)_4$, tetra(ethylene glycol), and tetramethoxysilane [or titanium(IV) isopropoxide] were encapsulated in a silica matrix (or a titania matrix) by the subsequent treatment with water. These filtration-recyclable encapsulated nanoparticles were active as catalysts in the coupling of methyl *p*-iodobenzoate and phenylacetylene in triethylamine/DMF, although copper cocatalysis and a reaction temperature of 110 °C were necessary.[172] In addition, colloidal palladium has been stabilized and supported on poly(vinylpyrrolidone) (PVP) by heating $Pd(OAc)_2$ in the presence of PVP. The supported nanoparticle palladium(0) catalyzes the copper- and ligand-free Sonogashira reaction of aryl iodides and bromides with terminal alkynes using potassium carbonate as base in ethanol at 80 °C, with the palladium metal being recovered by decantation of the reaction solution and reused.[173]

3.8. Other Transition-Metal Complexes

Nickel is a well-established partner of palladium in other cross-coupling reactions, but there are very few examples of its use in the context of the Sonogashira alkynylation reaction. The reason is most likely the nickel inactivation due to coordination to the triple bond, as was observed by Cassar.[5] However, the nickel-catalyzed Sonogashira coupling has been carried out for activated aryl iodides and aromatic terminal alkynes using $NiCl_2(PPh_3)_2$ (5 mol %) in the presence of copper(I) iodide (10 mol %), with triethylamine as base and aqueous dioxane as solvent at 60−100 °C.[174] More general results for the coupling of terminal alkynes with aryl iodides, a vinyl iodide, and aryl bromides have been obtained in heterogeneous conditions using recyclable ultrafine nickel(0) powder in the presence of copper(I) iodide and triphenylphosphane, using potassium hydroxide as base in refluxing isopropanol.[175] A solvent-less version of this procedure has been developed using nanosized nickel(0) on potassium fluoride−alumina under microwave heating.[176]

The palladium-free alkynylation of aryl halides has also been performed under copper catalysis. Thus, the catalytic system copper(I) iodide/triphenylphosphane in the presence of potassium carbonate in DMF or DMSO at 120 °C has allowed the cross-coupling reaction of aryl and vinyl iodides and terminal alkynes,[177] with the reaction being performed faster under microwave heating.[178] Copper(I) iodide in the presence of sodium carbonate catalyzes the coupling of terminal alkynes and hypervalent iodonium salts to afford arylalkynes or enynes in aqueous dimethoxyethane at room

temperature,[179] whereas a copper(I) bromide complex of triphenylphosphane and 1,3-phenanthroline has been used as catalyst in the reaction of aryl iodides and phenylacetylene, using potassium carbonate as base in refluxing toluene.[180]

Copper(I) iodide has also been shown to catalyze the coupling of aryl iodides or bromides and terminal alkynes when *N*,*N*-dimethylglycine was used as additive, using potassium carbonate as base in DMF at 100 °C.[181] In addition, copper nanoclusters have been used in the presence of TBAA in the reaction of aryl iodides or activated aryl bromides,[182] whereas copper(I) has been immobilized on a functionalized silica gel and performed efficiently as a recoverable catalyst in the presence of triphenylphosphane for the coupling of aryl iodides or activated aryl bromides and terminal alkynes in DMF at 100 °C.[183] Moreover, a copper(I)−1,10-phenanthroline complex equipped with an affinity tag has been used in the synthesis of 2-phenylbenzofuran via a tandem Sonogashira/5-*endo*-dig cyclization (see section 4.6), being recovered from the crude reaction mixture on the basis of hydrogen-bonding interactions using a resin functionalized with complementary affinity tags.[184]

Ruthenium-supported on alumina (5 wt %, 5 mol %) has also been able to carry out the copper-free Sonogashira coupling of aryl iodides and different acetylenes using triethylamine as base in acetonitrile as solvent at 90 °C.[185] The heterogeneous catalyst has been filtered off after the coupling and used in a second cycle, keeping almost the same catalytic activity.

3.9. Transition-Metal-Free Reactions

There have been two independent reports that have shown a transition-metal-free Sonogashira coupling, both dealing with microwave irradiation using water as solvent and a phase-transfer catalyst.[186] Thus, one group reported that when different aryl or heteroaryl iodides and bromides were heated and irradiated in water at 170 °C in the presence of phenylacetylene, 1-hexyne, or trimethylsilylacetylene, as well as PEG and sodium hydroxide,[186a] the coupling products were obtained in good yields except in the case of nonarylated acetylenes. In addition, the other group reported that when the microwave heating was performed at 175 °C for aryl iodides or bromides and phenylacetylene, using TBAB and sodium carbonate as base, the corresponding coupling products were obtained.[186b] The mechanism of this rather surprising Sonogashira coupling reaction is unknown. However, serious doubts have been raised about the "transition-metal-free" nature of the coupling because recent studies from the second research group have shown that palladium contaminants down to 50 ppb found in commercially available sodium carbonate are responsible for the generation of biaryls in a related "transition-metal-free" Suzuki cross-coupling reaction.[187]

A transition-metal-free Sonogashira reaction can also be considered that was achieved by addition of 1 mol % indium(III) trichloride as catalyst, which has been shown to promote the cross-coupling of activated and unactivated aryl iodides, bromides, chlorides, and even fluorobenzene to phenylacetylene in dry benzene as solvent at 80 °C,[188] with no suggestion of the possible mechanism being given.

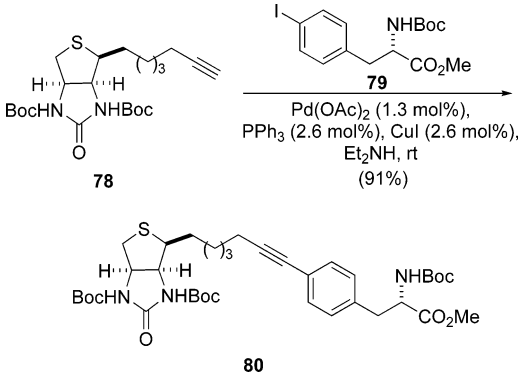
4. Applications

4.1. Alkynylation of Arenes

The coupling of a terminal alkyne and an aromatic ring is the pivotal reaction when talking about applications of the copper-promoted or copper-free Sonogashira reaction. The performance of practically all the catalysts and reaction conditions presented in section 3 has been determined for the coupling reaction of acetylenes with differently substituted halogenated arenes; therefore, many examples have already been presented. In addition, other parts in this review will show many Sonogashira reaction-obtained alkynylated arenes that have been transformed into different systems. This section will shown some examples of this key transformation, also pointing out some aspects about reagents employed profusely in the rest of the review or, on the other hand, less commonly employed substrates.

The list of cases where the typical Sonogashira reaction using aryl halides has been employed is large, and choosing illustrative examples is rather difficult. A recent use of this methodology is shown in Scheme 18 for the coupling of

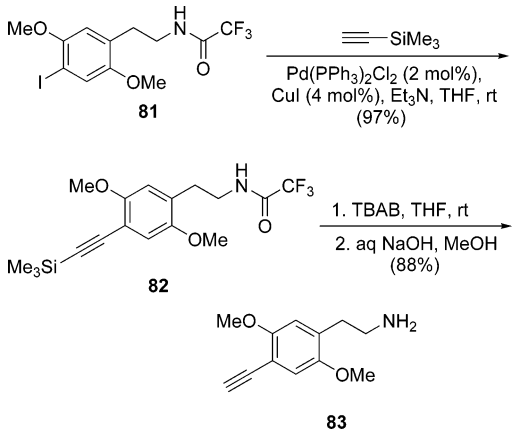
Scheme 18



iodinated phenylalanine **79** with a terminal alkyne derived from *d*-biotin **78** using an in situ generated palladium(0) species as catalyst, which allowed the preparation of alkyne-linked phenylalanine derivative **80** for bioanalytical applications.[189] Other recent examples involving aryl iodides or bromides and arylated,[190] alkylated,[191] or conjugate alkenylated[192] acetylenes, even with the aryl halide supported on a solid[193] or PEG-soluble[194] phase, can be found. There are also examples of the coupling partners both being attached to allyl resins, with the palladium(0) catalyst effecting cleavage of the substrates and subsequent Sonogashira coupling in solution.[195]

The generation of terminal arylalkynes is an important application of the palladium-catalyzed alkynylation reaction, as the final products can be of interest by themselves or can be used in subsequent couplings driving to diarylalkynes with frequent applications such as building blocks in electrooptical devices and material sciences (see sections 4.8 and 4.9, respectively).[196] Although aryl and hetaryl iodides have been coupled with the toxic and difficult to handle acetylene,[197] a frequently applied strategy is the coupling of the arene with TMSA or 2-methyl-3-butyn-2-ol, followed by desilylation or base-promoted elimination of acetone, respectively. A typical example showing the use of TMSA as acetylenic counterpart for the introduction of a terminal alkyne moiety is the preparation of amine **83** for structure−activity relationship investigations (Scheme 19). Thus, trifluoroacetylated iodophenethylamine **81** was alkynylated with TMSA under the typical Sonogashira conditions to give silylated acetylene **82**. Further desilylation and trifluoroacetamide hydrolysis droved to the final phenethylamine **83**.[198] Many examples of the synthesis of terminal alkynes of interest,[199] or for use as starting materials for diarylacetylene syntheses, using a

Scheme 19

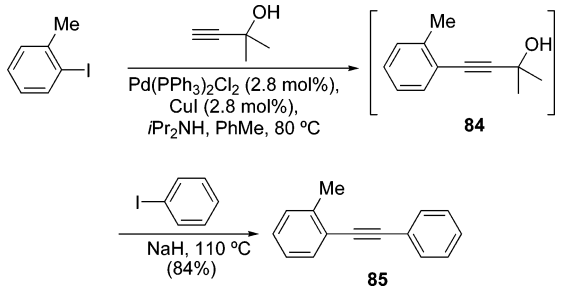


silylacetylene such as TMSA can also be found.[200]

The desilylation can be achieved in situ, which allows subsequent coupling, as in the case of performing the Sonogashira reaction of aryl halides and TMSA in the presence of an amidine as base and a substoichiometric amount of water, which gives rise to protodesilylation and subsequent coupling to afford diarylacetylenes.[201] This desilylation in the reaction medium has allowed the use of TMSA and BTMSA as acetylene equivalents when using nitrogenated complex **37**[15] (see section 3.2.1), palladacycle **67** ($R^1 = p\text{-}C_6H_4$; $R^2 = Cl$)[141b] (see section 3.5.1), or even $PdCl_2$[15] (see section 3.6.1) as catalysts in the preparation of symmetrical as well as unsymmetrical diarylacetylenes.

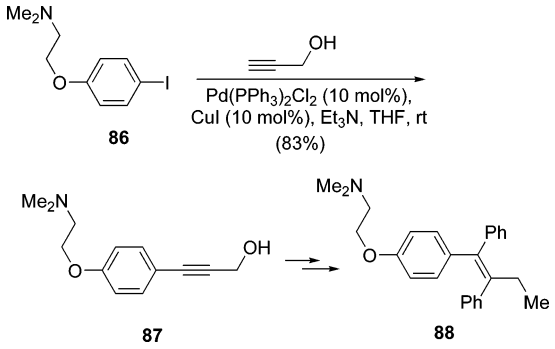
The use of 2-methyl-3-butyn-2-ol as acetylene source has also been frequent in Sonogashira couplings (see below). An interesting modification in the use of this reagent for the preparation of diarylalkynes has been the tandem Sonogashira coupling of an aryl halide such as 3-iodotoluene with 2-methyl-3-butyn-2-ol to give the alkynylated intermediate **84**, which is deprotected using a strong base and coupled again in the same pot to a second aryl halide such as iodobenzene to give diarylalkyne **85** (Scheme 20).[202]

Scheme 20



The use of propargyl alcohol as acetylenic counterpart in the Sonogashira coupling allows the synthesis of arylated acetylenic alcohols that can be interesting for the preparation of useful compounds containing an allylic alcohol moiety after the corresponding triple bond reduction.[203] An example is the synthesis of the estrogen receptor (*Z*)-tamoxifen (**88**) via Sonogashira cross-coupling reaction of aryl iodide **86** and propargyl alcohol, giving the acetylenic system **87**, which after several steps is converted into the final product (Scheme 21).[203a] In addition, homopropargylic alcohol has also been used in Sonogashira coupling reactions with aryl halides in order to incorporate an enyne moiety onto the aromatic ring after dehydration,[204] and longer chain acetylenic alcohols

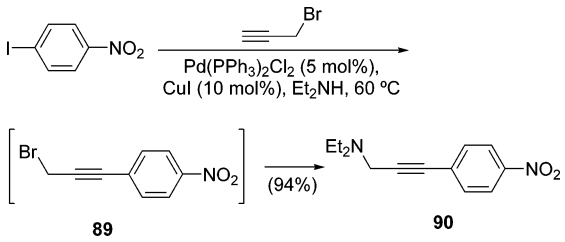
Scheme 21



have been coupled with methyl *o*-iodobenzoates for the synthesis of acetylene-containing macrolides.[205]

Propargyl halides have been used in combination with an aryl iodide and a secondary amine in a tandem amine propargylation−Sonogashira reaction.[206] For example, when propargyl bromide and *p*-iodonitrobenzene reacted under Sonogashira conditions in the presence of diethylamine as solvent, the propargyl amine **90** was obtained through intermediate **89** (Scheme 22). In addition, *N*,*N*-dialkylated

Scheme 22

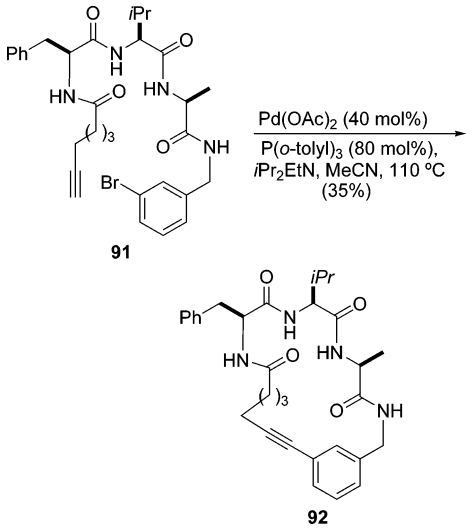


propargyl amines have been used for double Sonogashira coupling to diiodinated fluorenes in the synthesis of metal ligands[207] and also have been used as allenyl anion equivalents after coupling with aryl iodides and palladium-catalyzed hydrogen-transfer reactions.[208] Moreover, 1,3-oxazolidin-2-one-containing homopropargylamine has been used in cross-coupling reactions with aryl iodides in the preparation of non-nucleoside reverse transcriptase inhibitors.[209] Furthermore, ynamides bearing electron-withdrawing groups such as urethane and sulfonamide groups have been recently coupled to aryl iodides.[210]

Macrocyclizations have been achieved using the Sonogashira procedure, having found application in naturally occurring compounds (see section 4.7) or in the synthesis of pharmacologically interesting cyclic peptides.[211] An example of this second case is the conformationally constrained tripeptide **92**, prepared by intramolecular coupling of aryl bromide **91** employing in situ generated palladium catalysts with an electron-rich phosphane ligand which eliminates the use of copper cocatalysis, although employed in large amounts (Scheme 23).[212]

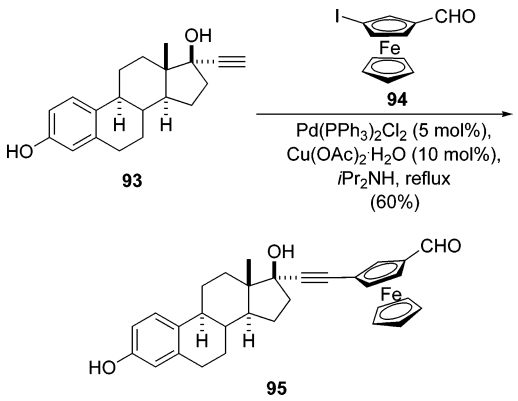
Enantiopure ferrocenes such as **94** have been coupled to 7α-ethynylestradiol (**93**) under the typical Sonogashira conditions [although using copper(II) acetate monohydrate instead of the usual copper(I) iodide], giving [(ferrocenyl)-ethynyl]estradiol **95** (Scheme 24), with the incorporation of the ferrocenyl system being useful for organometallic labeling of biomolecules.[213] In addition, alkynylated ferrocenyls have also been attached to an iodophenylalanine-containing dipeptide[214] or to iodinated bis(dimethylamino)benzenes, in

Scheme 23



91 **92**

Scheme 24



93 **94** **95**

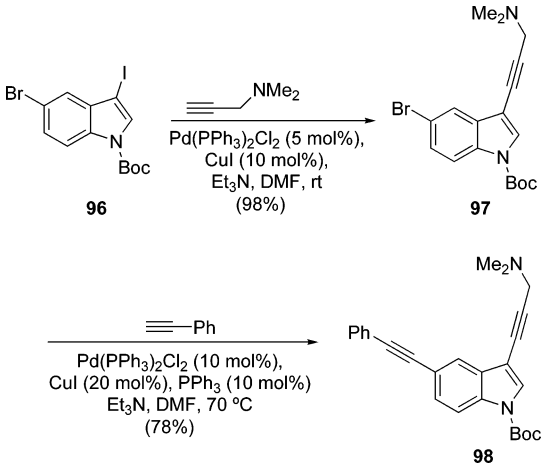
the last case for the creation of ligands for biferrocene NCN pincer palladium and platinum complexes.[215]

4.2. Alkynylation of Heterocycles

The alkynylation of aromatic heterocyclic systems by means of a transition-metal-catalyzed reaction where the oxidative addition is the rate-determining step is governed (as in carbocyclic systems) by the higher or lower electrophilicity of the carbon atom at the heterocycle. This means that electron-rich halogenated heterocycles would experience a more facile Sonogashira coupling than electron-deficient ones, whereas the more electrophilic position would be more easily alkynylated when dealing with polyhalogenated systems. However, it is necessary to remark that even cross-coupling reactions which proceed by a fast oxidative addition can exhibit unexpected selectivities if the subsequent steps counteract the selectivity in the first step. The oxidative addition can also be facilitated by coordination of the palladium(0) to a heteroatom, such as in nitrogen-containing heterocycles, thus making easier reaction at the C-2 position. The transition-metal-catalyzed cross-coupling reaction of multiple halogenated heterocycles has been recently reviewed,[216,217] and examples of alkynylation reactions of some heterocycles (i.e., halogenated thiophenes) using the Sonogashira methodology will also be shown below when dealing with some applications (see sections 4.8 and 4.9). This section presents some recent examples of the use of this heteroaryl−acetylene formation. Since the benzo derivatives often present similar reactivity to that of the the monocyclic compounds, they will be discussed together.

Although examples of alkynylation of pyrroles at the 2- and 3-positions can be found,[218] more frequent is the alkynylation of indoles. Thus, 2-iodoindoles and their *N*-protected derivatives have been exploited for the synthesis of 2-alkynyl indoles following the Sonogashira protocol,[219a] with good results also being achieved when using 2-triflates.[219b] Indoles have been successively alkynylated at the 3- and 5-positions starting from *N*-Boc-protected 5-bromo-3-iodoindoles. For example, dihalogenated indole **96** was employed for the coupling with *N*,*N*-dimethylprop-2-yn-1-amine under Sonogashira conditions affording bromoindole **97**, which was coupled again with phenylacetylene under more strict reaction conditions giving dialkynylated indole **98** (Scheme 25).[220] In addition, furans, as well as thiophenes and also

Scheme 25

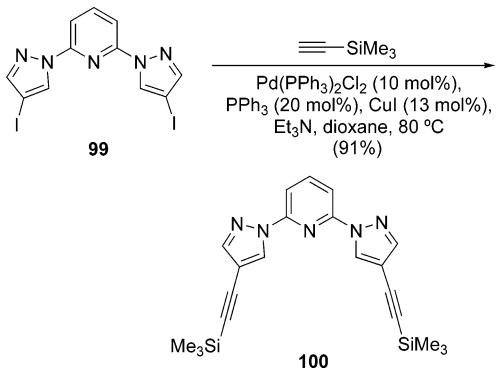


96 **97** **98**

their benzo derivatives, show C-2 as the most reactive position, with an example being the selective C-2 alkynylation of 2,3- and 2,6-dibromobenzofurans,[221] whereas 4-chloro-5-alkylidenebutenolides have been alkynylated in aqueous media under liquid−liquid phase-transfer conditions.[222] Moreover, a recent example of the Sonogashira reaction between a 4-iodoindazole and phenylacetylene has been reported.[223]

An example of the application of the Sonogashira methodology to the alkynylation of an iodinated pyrazole ring is the double alkynylation of the 2,6-bis(pyrazol-1-yl)pyridine system **99** with TMSA, which afforded the bis-alkynylated system **100**, useful in coordination chemistry (Scheme 26).[224]

Scheme 26

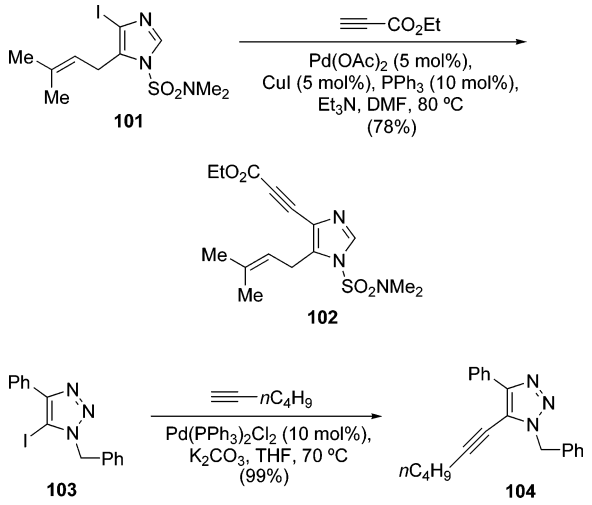


99 **100**

The most electrophilic position for cross-coupling reactions in imidazoles is C-2.[216] Not many Sonogashira cross-coupling reactions involving this position have been found. However, this palladium-promoted alkynylation reaction has been

employed recently on 4-iodo-substituted imidazoles such as **101** for the preparation of potentially useful drugs for the treatment of rheumatoid arthritis such as imidazole **102** by reaction with ethyl propiolate (Scheme 27).[225] In the case of

Scheme 27

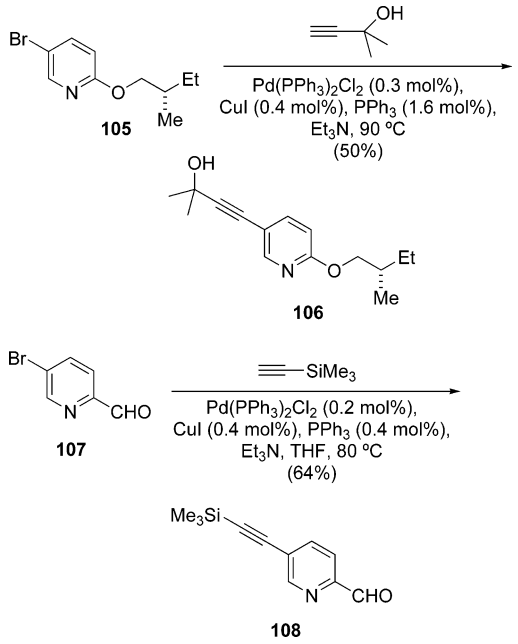


1-methyl-4,5-diodoimidazole, the corresponding dialkynylated systems have been employed as substrates in Bergman's cyclizations.[226] In addition, polyhalogenated thiazoles have been alkynylated preferentially at the 2-position.[227] Recently, a copper-free Sonogashira reaction has been applied to the alkynylation of 1,4-disubstituted 5-iodo-1,2,3-triazoles, as shown in Scheme 27 for the reaction of iodotriazole **103** with 1-hexyne to give alkynylated triazole **104** in almost quantitative yield.[228]

As electron-deficient heterocycles, pyridines usually react smoothly in Sonogashira reactions. Of course, if electron-releasing groups are present on the ring, the alkynylation is somewhat more difficult or lower-yielding. Examples of alkynylation on halopyridines when dealing with the preparation of conductive materials or metal ligands can be found (see section 4.8), Some illustrative cases are the coupling of 2-bromopyridine for the synthesis of pincer ligands,[229] a chiral 4-bromopyridine-bis(oxazoline),[230] or a 2,6-dibromopyridine in the preparation of polypyridyl bridging ligands.[231] Two recent applications of the Sonogashira coupling using 3-bromopyridines can be shown in Scheme 28. Thus, when 3-bromopyridine **105** was alkynylated using 2-methyl-3-butyn-2-ol as the acetylene equivalent under the typical Sonogashira conditions to give pyridine **106**, a 50% yield in the alkynylation step was achieved.[232] However, 3-bromopyridine **107**, bearing an electron-withdrawing group, gave a 64% yield in the alkynylation reaction with TMSA, giving compound **108** at lower temperature and catalyst loading.[233] Other recent examples of the use of this alkynylation in pharmacological studies[234] or in the preparation of heterocyclic allenes[235] can be found, as well as solid-supported versions.[236] Moreover, halogenated pyridines have also been prepared using heterogeneous palladium on charcoal as catalyst.[237]

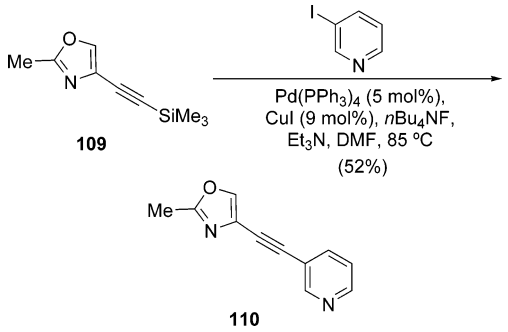
A recent example of an alkynylation reaction of 3-iodopyridine can be seen in the preparation of compound **110**, which is an antagonist for use in the treatment of drug abuse. Thus, in situ TBAF-promoted desilylation of oxazole derivative **109** and a subsequent palladium-copper-catalyzed cross-coupling reaction with 3-iodopyridine gave alkyne **110**

Scheme 28



(Scheme 29).[238a] Bromopyridines have been used in a similar coupling reaction with trimethylsilylated acetylenic thiazoles.[238b,c]

Scheme 29

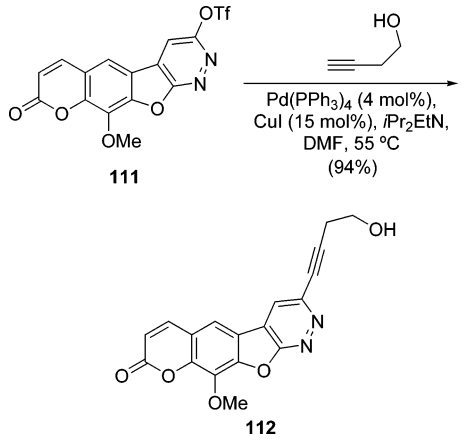


The regioselective Sonogashira cross-coupling reaction performed on 2,4-dihaloquinolines was achieved mainly by using different halides such as iodide and bromide, which drove to different reactivity.[239] When the reaction was performed on quinolines bearing the same halogen atom, such as 2,4-dibromoquinoline, the C-2 alkynylated product was the only one obtained.[240] In addition, brominated quinozilium cations have been alkynylated at the 2- and 3-positions under typical Sonogashira conditions to give the corresponding aryl- and heteroarylethynyl quinozilium cations.[241]

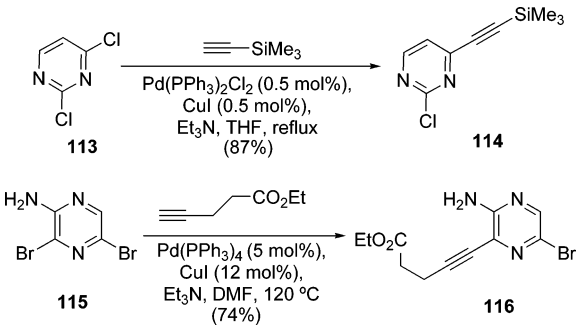
The functionalization of the pyridazine nucleus via palladium-catalyzed reactions has been reviewed recently.[242] An illustrative example of application of the Sonogashira coupling reaction on a pharmacologically interesting pyridazine ring system is shown in Scheme 30, where the reaction of triflate-containing pyridazino[4,3-*h*]psoralen derivative **111** with but-3-yn-1-ol under Sonogashira conditions gave the alkynylated derivative **112** in high yield.[243]

The preference for the more electrophilic pyrimidine position is illustrated by the reaction of 2,4-dichloropyrimidine (**113**) with TMSA under Sonogashira conditions, affording only the 4-alkynylated product **114** in good yield (Scheme 31).[244] Other examples of this selectivity using

Scheme 30



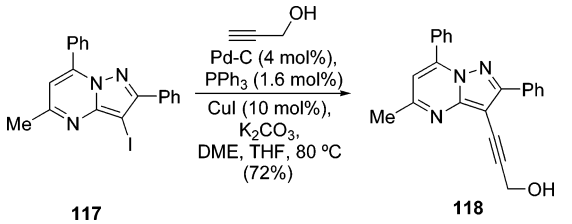
Scheme 31



dibrominated systems have also been reported.[245] The preference for this position has also been demonstrated by the alkynylation of 5-bromo-4-chloropyrimidines using palladium on charcoal as catalyst, which gave rise to reaction at the chlorinated 4-position, with the 5-position being preferred only if iodinated.[246] Cytostatic mono- and bisalkynylpyrimidines have also been obtained from 2,4-diamino-6-iodopyrimidine and 2-amino-4,6-dichloropyrimidine, respectively, and appropriated terminal alkynes under these reaction conditions.[247] In addition, the 3-position in 3,5-dibromopyrazin-2-amine (**115**) has been regioselectively alkynylated using ethyl pent-4-ynoate, affording derivative **116**, which has been used in the synthesis of compounds with chemiluminiscent properties (Scheme 31).[248] Moreover, substituted chlorotetrazines have been alkynylated in moderate yields, with the electron-donating properties of the substituent on the tetrazine core having a significant influence.[249]

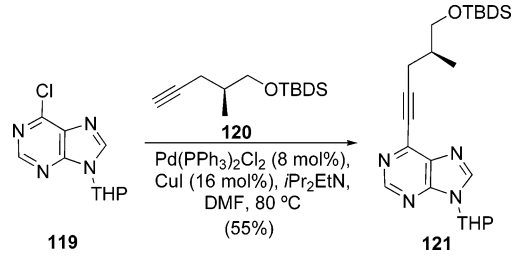
3-Alkynylpyrazolo[1,5-*a*]pyrimidines have been obtained from the corresponding 3-iodopyrazolopyrimidines using the Sonogashira methodology, with an example being the synthesis of pyrazolopyrimidine **118** by reaction of the corresponding iodinated derivative **117** with propargyl alcohol using palladium on charcoal as palladium source (Scheme 32).[250] In addition, two recent examples of Sonogashira reaction on 7-bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine[251] and on 4-iododihydrodipyridopyrazines can be found.[252]

Scheme 32



The purine heterocycle occurs in nucleosides and, therefore, has particular relevance for chemical modifications. Thus, 2,6-dichloro-9-isopropylpurine has been cross-coupled with (4-methoxyphenyl)acetylene under Sonogashira conditions to give the corresponding dialkynylated product in the search for analogues of the cytostatic myoseverin.[253] The order of the alkynylation was not determined, although the 6-position is probably alkynylated first, in line with the observed preference for a cross-coupling at C-4 in pyrimidines. In addition, 6-chloro-9-tetrahydropyranylpurine (**119**) has been alkynylated using the terminal acetylene **120** to give purine **121** in the search for cytokinin analogues and inhibitors of 15-lipoxygenase (Scheme 33).[254] 6-Halopurines

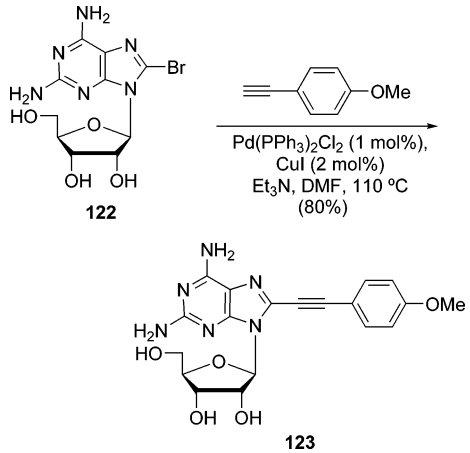
Scheme 33



have also been alkynylated recently with *o*−alkynylphenols or *o*-ethynyl(hydroxymethyl)benzene.[255]

Interest can also be found in the C-8 alkynylation under Sonogashira conditions of the bromide-containing purine nucleus in adenosine-based nucleosides.[256] An example is the Sonogashira alkynylation of unprotected 8-bromoadenosine (**122**) with (4-methoxyphenyl)acetylene to give alkynylated nucleoside **123** (Scheme 34), with the procedure

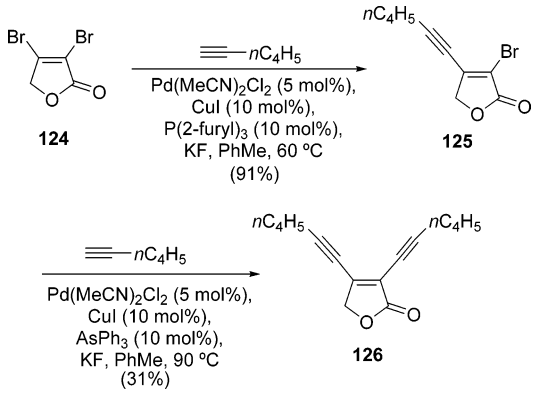
Scheme 34



also being applied to 8-bromoguanosine.[257]

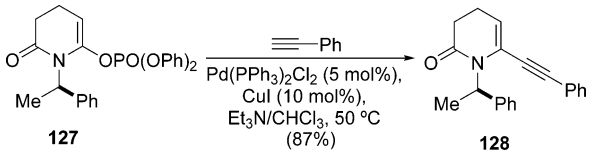
Halogenated 2-(5*H*)-furanones show the most electrophilic 4-position as the preferred one for Sonogashira alkynylations, and they are considered as α- and *β*-acylvinyl cation equivalents,[258] as was demonstrated by the cross-coupling reaction of 3,4-dibromo-2-(5*H*)-furanone (**124**) and 1-hexyne. The addition of an electron-rich phosphane such as P(2-furyl)$_3$ to the catalytic system allowed the high yielding preparation of the 4-alkynylated product **125** (Scheme 35).[259] Subsequent 3-alkynylation of **125** proved more difficult, and a low yield of the dialkynylated product **126** was obtained, even when $AsPh_3$ was added as a ligand.

Scheme 35



An example of a Sonogashira cross-coupling reaction using a vinyl phosphate is shown in the alkynylation reaction of chiral 3,4-dihydropyridin-2(1*H*)-one **127** with phenylacetylene, which gives the 6-alkynylated heterocyclic derivative **128** (Scheme 36), a compound being used as a diene in

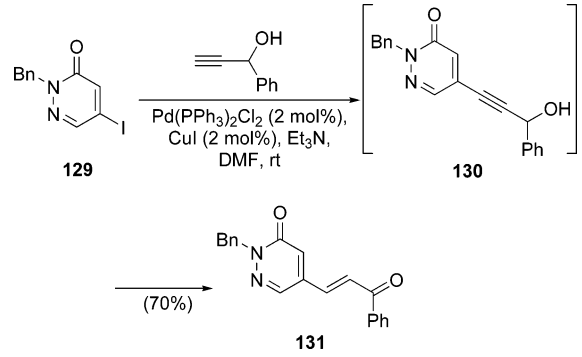
Scheme 36



Diels−Alder cycloaddition reactions, after partial hydrogenation of the triple bond.[260]

5-Bromopyridazinones[261a] and 4,5-dihalopyridazinones[261b] have been transformed into chalcones employing a Sonogashira alkynylation reaction using propargyl alcohols. For example, when the highly reactive 5-iodopyridazin-3(2*H*)-one **129** (a *β*-acylvinyl cation equivalent[258]) is alkynylated with 1-phenylprop-2-yn-1-ol employing the Sonogashira procedure at room temperature, the final (*E*)-chalcone **131** was obtained, with its formation being explained by a postcoupling base-promoted isomerization from intermediate **130** (Scheme 37).[262] In addition, 2-amino-6-chloropyrimidin-

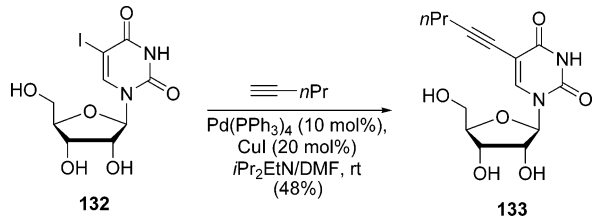
Scheme 37



4-one derivatives have been alkynylated with TMSA, with the resulting products being used in molecular recognition.[263]

The 5-iodouracil ring (a α-acylvinyl cation equivalent[258]) is quite reactive and can be alkynylated easily under Sonogashira conditions at room temperature, something that has been applied to the derivatization of nucleosides. Recent examples are the incorporation of fluorescent polycyclic aromatic systems[264] and porphyrins,[265] the formation of oligonucleosides,[266] the introduction of lipophilic moieties,[267] and the increment of pharmacological activity, for instance, against herpes simplex virus (HSV)[268] or mycobacteria.[269] An example of this last case is illustrated in Scheme 38,

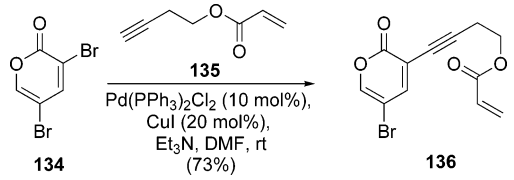
Scheme 38



with the cross-coupling reaction of 5-iodinated uridine **132** (an α-acylvinyl cation equivalent[258]) with 1-pentyne to give 5-pentynyluridine **133**. This methodology has also been applied to 2′-deoxycitidine.[269] Similarly, 3-iodoguanosine has also been alkynylated under Sonogashira conditions.[270]

The 2-pyrone motif is quite biodiverse and has many synthetic applications; therefore, its derivatization using different methodologies, such as the Sonogashira cross-coupling reaction, has been widely studied. For this reaction, the most reactive point in the 2-pyrone system is the 3-position, as has been shown in the competitive alkynylation of 3,5-dibromo-2-pyrone (**134**) (an α- and *γ*-acylvinyl cation equivalent[258]) with different alkynylated tethers such as acrylate **135** at room temperature, driving exclusively to monobrominated pyrone **136**, which is suitable for intramolecular Diels−Alder reactions (Scheme 39).[271] Obviously,

Scheme 39



the reaction turns more difficult when electron-releasing groups are present, as was the case for the alkynylation of 3-bromo-4-methoxy-6-methyl-2-pyrone, which gave very low yields.[272] In addition, other alkynylations at the 5-position starting from 5-bromo-6-methyl-2-pyrone using the Sonogashira cross-coupling reaction have been recently reported,[273] as has exchanging the bromo group by chloro, iodo, triflate, or even tosylate.[274] In addition, 4-*p*-tolsyloxycoumarins[275] and 6-iodoisocoumarins[276] have been alkynylated using the Sonogashira reaction, as well as 7-iodocoumarins,[277] 3-iodoflavones, and 3-iodothioflavones.[278]

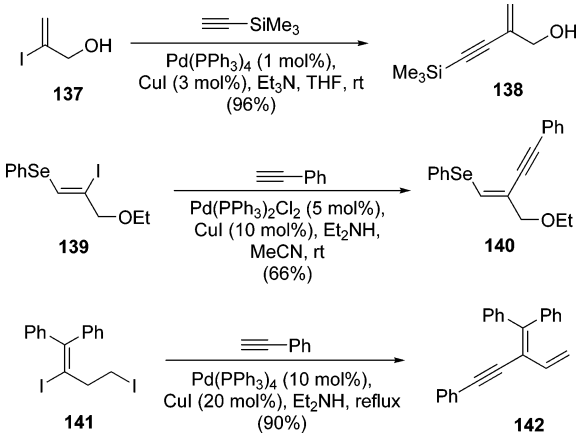
4.3. Synthesis of Enynes and Enediynes

The 1,3-enyne moiety is an important structural unit for biologically active and natural compounds (see section 4.7), and also new functional materials (see sections 4.8 and 4.9). Its generation from vinylic systems and terminal acetylenes is quite obvious by using a configuration-retention stereospecific procedure such as the Sonogashira methodology. Examples of recent applications of this cross-coupling reaction in the preparation of this unit for compounds of particular interest are quite numerous when dealing with new methodologies and specific applications, and some more general recent illustrative cases are shown in this section.

As already mentioned, vinyl iodides are the most reactive vinyl halides to palladium(0) oxidative addition, and their

use is therefore most frequent for Sonogashira cross-coupling reactions due to the usually milder conditions employed. Some examples are the coupling of 2-iodo-prop-2-enol (**137**) with a wide range of acetylenes such as TMSA to give enynyl alcohol **138**,[279] which can be oxidized to the corresponding α-alkynylated acroleins, and the preparation of selenated allylic ether **140** from the cross-coupling of vinyl iodide **139** and phenylacetylene (Scheme 40).[280] Other

Scheme 40



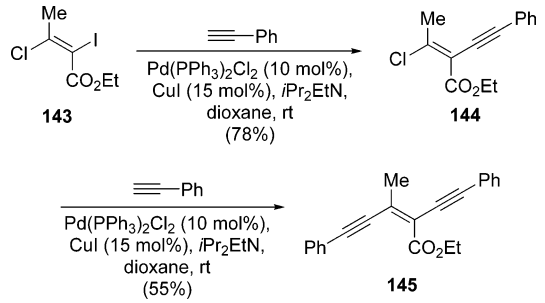
examples can be found,[281] including the formation of an enyne moiety for the introduction of a fluorescent probe in a phorboxazole analogue.[282] Alk-2-ynylbuta-1,3-dienes such as **142** can be obtained from the corresponding diiodide **141** by using the Sonogashira methodology combined with an in situ hydrogen iodide elimination reaction (Scheme 40),[283] and a similar procedure is applied to the enynylation of 2-iodo-4-(phenylchalcogenyl)-1-butenes.[284] In addition, α-iodovinyl sulfoxides have been alkynylated under the typical Sonogashira reaction conditions,[285] as well as perfluoroalkylated vinyl iodides.[286]

The effect of vicinyl olefinic halogens on the Sonogashira cross-coupling reaction has been determined using a series of *trans*-dihalogenated olefins such as 1-chloro- and 1-bromo-2-iodoethylene as well as 1,2-diiodoethylene when coupled with 1-hexyne, showing that the best substrate for the monoalkynylation reaction was 1-chloro-2-iodoethylene, with 1,2-diiodoethylene being surprisingly unreactive.[287] These types of vicinyl olefinic halogens have been used for the preparation of tetrasubstituted alkenes when starting from *β*-chloro-α-iodo-α,*β*-unsaturated esters, which can be considered as α- and *β*-acylvinyl cation equivalents.[258] Thus, unsaturated ester **143** reacted smoothly with phenylacetylene under Sonogashira conditions at the more reactive carbon−iodine bond to give *β*-chloroacrylate **144**, which can be used in different palladium-catalyzed cross-coupling reactions such as an additional Sonogashira coupling with phenylacetylene to give tetrasubstituted alkene **145** (Scheme 41).[288]

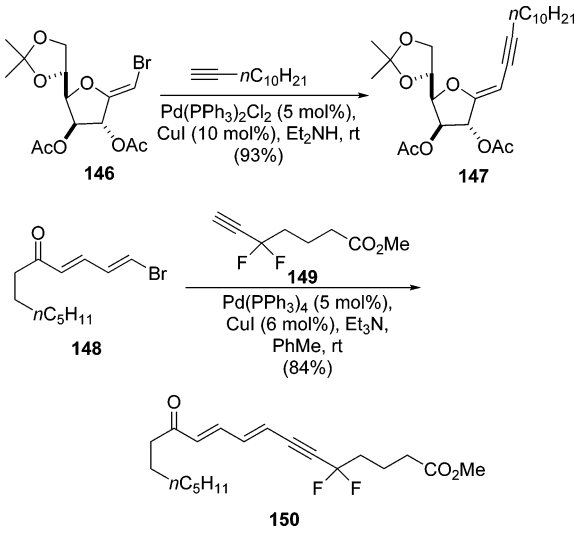
Examples of the preparation of enynes from vinyl bromides can be seen in Scheme 42, which shows the alkynylation reaction of bromo-*exo*-glycals, such as **146**, with terminal alkynes, such as 1-dodecyne, to give enyne **147**[289] (although slightly higher yields were obtained using the corresponding iodides). Scheme 42 also shows the reaction of dienyl bromide **148** (a *δ*-acyldienyl cation equivalent[258]) with difluorinated alkyne **149**, affording compound **150**, a precursor of 5,5-difluoro-(12*R*)-leukotriene B_3.[290]

1,1-Dibromo- and 1,1-dichloro-1-alkenes have been *trans*-monoalkynylated using different palladium catalysts, al-

Scheme 41



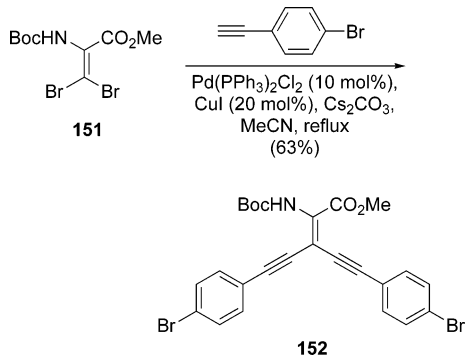
Scheme 42



though, in the case of the alkynylation of (2,2-dichlorovinyl)-benzene with TMSA, the *cis*-alkynylated enyne was the main compound when $Pd(PPh_3)_4$ was used as catalyst.[291] Examples of vinyl triflates and other perfluoroalkanesulfonates[292] or even activated tosylates[293] as alkene counterparts in Sonogashira coupling reactions can recently be found.

The diethynylethene (DEE) moiety is quite common in compounds with electrooptical properties or interesting structural features (see sections 4.8 and 4.9). Thus, *gem*-DEEs (the so-called Y-enynes) have been prepared by the Sonogashira procedure when starting from gem-dihaloalkenes. An example of this type of synthesis is the preparation of dehydroamino acid derivatives such as **152** by double cross-coupling reaction of dibrominated dehydroalanine derivative **151** with 1-bromo-4-ethynylbenzene (Scheme 43).[294] Obviously, the double coupling of these types of *gem*-

Scheme 43

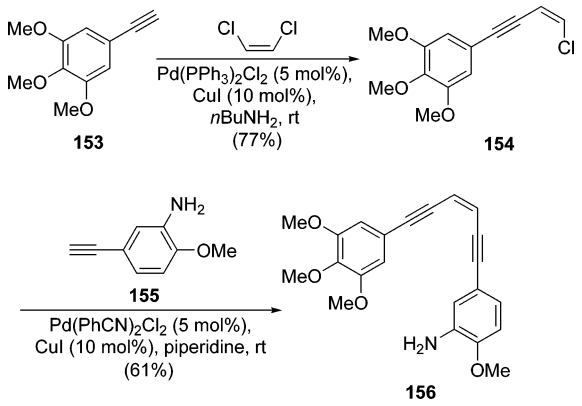


dihalides with the same alkyne does not present any problem

related to stereochemistry, nor was a problem presented when the double coupling was performed sequentially with two different terminal alkynes. However, an unusual solvent-dependent stereochemical inversion has recently been observed in the Sonogashira reaction of some (*Z*)-2-bromoenynes.[295]

(*E*)-DEE is a structural motif with an extended conjugation that has been synthesized profusely using the Sonogashira procedure when dealing with species that may find applications in molecular electronics (see section 4.8). However, the (*Z*)-DEE moiety[296] has frequently been the starting material for the Bergman cyclization[297] leading to 1,4-dehydrobenzyne diradicals[298] capable of abstracting two hydrogen atoms from DNA, as in natural enediyne antibiotics, as well as employed in the preparation of polymeric materials or polycyclic compounds (see section 4.6). An example of the preparation of a (*Z*)-DEE moiety by means of the Sonogashira methodology is the double alkynylation reaction of (*Z*)-1,2-dichloroethylene in the synthesis of an enediyne-containing ω-amino acid for studies on the thermal reactivity toward Bergman cyclization.[299] Another illustrative example is the synthesis of enediyne analogues of the cytotoxic natural stilbene combretastatin, such as **156** (Scheme 44). Thus, trimethoxyaryl alkyne **153** was cross-

Scheme 44

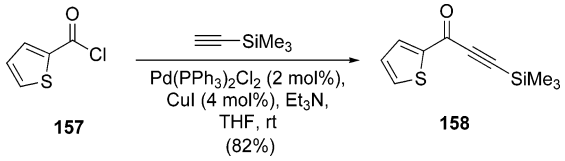


coupled with (*Z*)-1,2-dichloroethylene under Sonogashira conditions to give (*Z*)-chloroenyne **154**, which was cross-coupled again with alkynylated aniline **155** (also prepared by Sonogashira alkynylation) to give enediyne **156**.[300]

4.4. Synthesis of Ynones

Conjugated alkynyl ketones are useful intermediates, particularly for the synthesis of heterocycles (see section 4.6), which have been prepared by palladium-catalyzed coupling of a thiol ester and a terminal alkyne.[301] However, the most usual method is the coupling of an aroyl chloride with a terminal acetylene as was shown originally by Sonogashira et al. using the combination $Pd(PPh_3)_2Cl_2$/CuI as catalyst in triethylamine at room temperature, a procedure employed also for the synthesis of 2-alkynamides when starting from dimethylcarbamic chloride.[302] An example of the preparation of ynones using the Sonogashira procedure is the coupling of different aryloyl or heteroaryloyl chlorides, such as thiophene-2-carbonyl chloride (**157**), with TMSA using the original catalytic combination but with only 1 equiv of triethylamine in THF at room temperature (Scheme 45).[303] The obtained trimethylsilyl alkynones, such as **158**, are in fact synthetic equivalents of β-keto aldehydes and can react

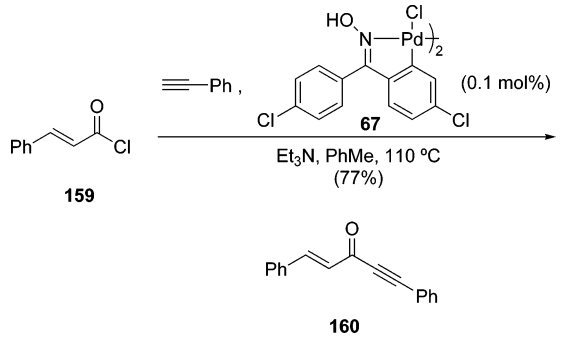
Scheme 45



in a Michael addition fashion with nucleophiles such as amines or alcohols, furnishing enaminones or β-ketoenol ethers, respectively, after protodesilylation. This catalytic combination has also been used for the generation of ynone intermediates in a one-pot synthesis of carbolines[304] or in the preparation of the microtubule depolymerization agent allocolchicinoid.[305] Moreover, the same catalytic mixture has been employed for the room-temperature Sonogashira cross-coupling of ferrocenylethyne and arenecarbonyl chlorides in triethylamine as solvent,[306] or in the coupling of (hetero)-arenecarbonyl chlorides with terminal alkynes using an excess of triethylamine as base in an approach to indolizines.[307] Furthermore, if DIPEA is used as base, not only aryl chlorides can be used as starting materials, but also isobutyryl chloroformate or methyloxalyl chloride.[308] If sodium lauryl sulfate is used as surfactant, the ynone formation using this catalytic combination can be carried out in water as solvent employing potassium carbonate as base.[309]

The coupling or acid chlorides and terminal alkynes can also be performed under copper-free Sonogashira conditions. Thus, the oxime-derived palladacycle **67** (R^1 = *p*-ClC_6H_4; R^2 = Cl) has been shown to be quite efficient for the acylation of terminal alkynes, using a very low catalyst loading (0.2−0.5 mol % Pd) in refluxing toluene as solvent and using triethylamine as base,[310] with an example being the coupling of cinnamoyl chloride (**159**) and phenylacetylene to give ynone **160** (Scheme 46). Acid chlorides can also

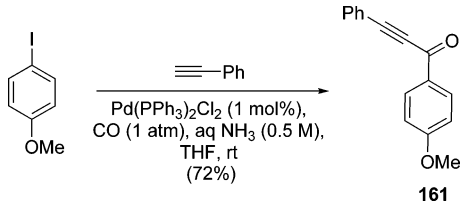
Scheme 46



be cross-coupled with terminal alkynes using $Pd(OAc)_2$ as catalysts, affording similar results to **67** (R^1 = *p*-ClC_6H_4; R^2 = Cl) when working at room temperature.[310] More recently, $Pd(OAc)_2$ has also been used as catalyst (0.2 mol %) at room temperature under solvent-free conditions, using triethylamine as base.[311]

Ynones can also be prepared by a convenient procedure developed for the coupling of aryl iodides and terminal acetylenes, using $Pd(PPh_3)_2Cl_2$ as catalyst in a mixture of aqueous ammonia and THF as solvent and in the presence of carbon monoxide (1 atm) at room temperature. When this procedure was applied to the coupling of 4-iodoanisol and phenylacetylene, the corresponding α,β-alkynyl ketone **161** was obtained (Scheme 47).[312] In this reaction it is interesting that the addition of copper(I) iodide as cocatalyst inhibits the formation of the desired ynone, with the usual Sono-

Scheme 47



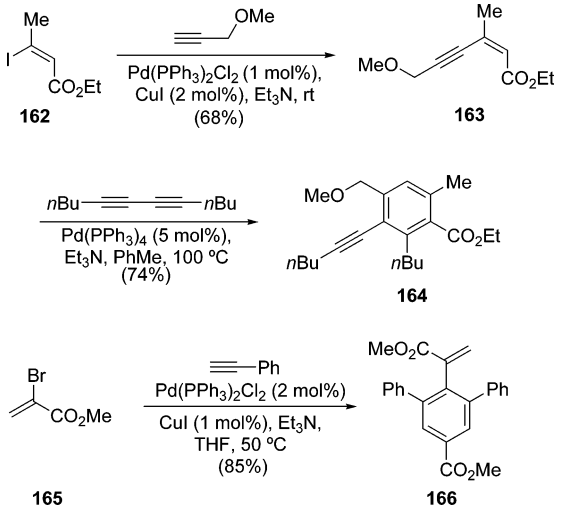
161

gashira coupling alkynylated product being the major product. The carbonylative Sonogashira reaction leading to ynones can also be performed using carbon monoxide at high pressure,[313] although the conventional copper cocatalyzed coupling using $Pd(PPh_3)_2Cl_2$ has also been employed with 3-iodoindoles under an atmospheric pressure of carbon monoxide.[314] This carbonylative reaction starting from aryl iodides has also been developed in water as solvent at room temperature when using the combination $PdCl_2/PPh_3$ as catalyst and triethylamine as base.[315] In addition, copper cocatalyzed Sonogashira couplings with aryl iodides have recently been performed in an ionic liquid using a multiphase microflow system and the NHC palladium catalyst **62**.[316]

4.5. Synthesis of Carbocyclic Systems

Enynes prepared by the Sonogashira coupling reaction (see section 4.3) can be used in the palladium-catalyzed [4 + 2] benzannulation reaction to enynophiles, leading to the construction of polysubstituted benzenes.[317] A recent example of this cycloaddition is shown in Scheme 48, where the

Scheme 48

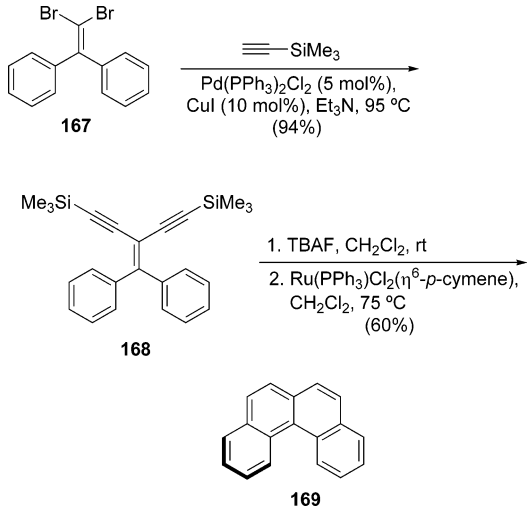


162 163 164 165 166

β-acylvinyl cation equivalent[258] β-iodobutenoate **162** reacts with methyl propargyl ether under Sonogashira conditions to give enyne **163**, which cyclized with dodeca-5,7-diyne under palladium(0) catalysis to give alkynylated benzoic ester **164**.[318] Another recent preparation of polysubstituted benzenes such as **166** has been performed using a one-pot multicomponent regioselective synthesis starting from 2-bromoacrylates such as **165** and a terminal alkyne such as phenylacetylene under palladium-catalyzed Sonogashira conditions (Scheme 48).[319]

Polycyclic aromatic hydrocarbons (PAHs) pervade many branches of chemistry and the allied sciences.[320] The Sonogashira reaction can be employed for the preparation of precursors suitable for the synthesis of some of these compounds, after cyclization promoted by different methods. An illustrative example is the synthesis of [4]helicene (**169**), which has been achieved starting from dibrominated diphenylethene **167**. Thus, double Sonogashira cross-coupling reaction of this compound and TMSA gives *gem*-enediyne **168**, which was desilylated and cyclized under transition-metal catalysis[317] using a ruthenium complex to give PAH **169** (Scheme 49).[321] Other PAHs and also heteroatom-

Scheme 49

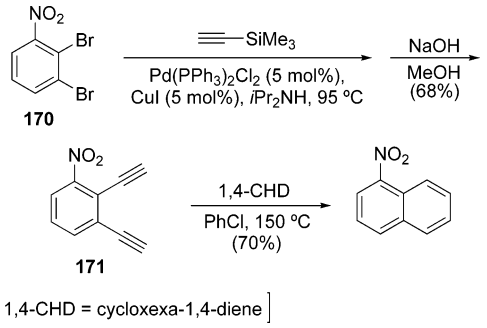


167 168 169

containing polycycles have been prepared using this methodology.[321]

The Bergman cycloaromatization[297] has been one of the principal uses for 1,2-enediynes[296] in order to generate an aromatic nucleus. For example, aromatic enediynyl systems, which can be prepared easily by Sonogashira coupling of *o*-dihalobenzenes or *o*-ditriflyloxybenzenes and terminal alkynes, can be cyclized to PAHs. In Scheme 50 is shown

Scheme 50



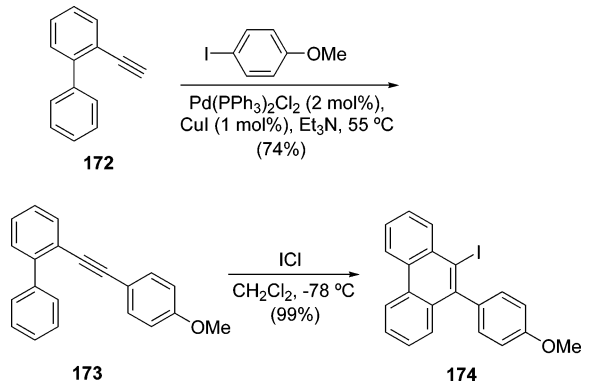
170 171

the Sonogashira coupling of dibromide **170** with TMSA to give dialkynylated compound **171** after silyl deprotection. Subsequent heating of **171** in the presence of 1,4-cyclohexadiene (1,4-CHD) gives 1-nitronaphthalene.[322] In addition, naphthalenes and indenes have been prepared via thermal radical cyclization of sulfonylated enediynes,[323] with the synthesis of other polycyclic systems such as benzofulvenes,[324] fluoranthrenes, and acephenanthrylenes[325] being recently reported. 1-Fluoro-1-substituted naphthalenes have been prepared by base-catalyzed cyclization of Sonogashira reaction-obtained (*E*)-monofluoroenynes.[326]

1-Iodo- and 1-acyl-2,3-disubstituted naphthalenes have been obtained from *o*-alkynylbenzaldehyde derivatives, readily accessible by the Sonogashira alkynylation reaction of the corresponding 2-iodobenzaldehydes. These carbonyl compounds can be cyclized using an iodonium source such

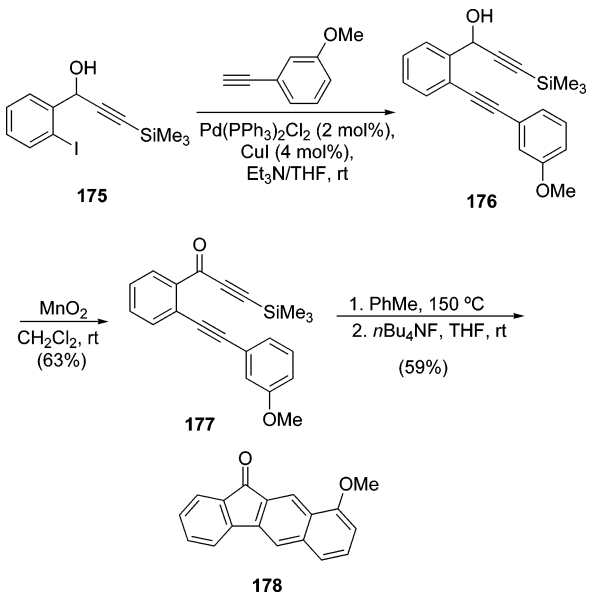
as IPy_2BF_4 in a 6-*endo*-dig fashion to pyrilium cations which, after Diels−Alder reaction with disubstituted acetylenes and carbon monoxide extrusion, gave the corresponding 1-iodonaphthalenes, whereas 1-acylnaphthalenes are generated when ring opening and HI elimination occurred.[327] In addition, polycyclic aromatic iodides have been prepared via electrophilic intramolecular cyclization of Sonogashira reaction-prepared 2-(arylethynyl)biphenyls bearing electron-donating or electron-withdrawing groups.[328] For example, 2-ethynylbiphenyl (**172**) reacted with *p*-iodoanisol under typical Sonogashira conditions to give (arylethynyl)biphenyl **173**, which cyclized in the presence of ICl, affording the polycyclic aromatic iodide **174** (Scheme 51).[328a]

Scheme 51



Benzofluorenones have been obtained by intramolecular thermal dehydro Diels−Alder reactions from (arylethynyl)-phenyl propynones, which are compounds accessible by means of the Sonogashira methodology, followed by oxidation reactions. Thus, benzo[*b*]fluorenone **178** has been obtained after cross-coupling of iodinated propargyl alcohol **175** to give propynone **177** after oxidation of alcohol **176**. Thermal cycloaddition, followed by desilylation gave benzo-[*b*]furanone **178** (Scheme 52).[329] The reaction can be

Scheme 52



switched to benzo[*c*]furanones by introducing different substituents. A similar cycloaddition has been used recently for the synthesis of the benzo[*b*]fluorene core of the kinamycin antibiotics.[330] In addition, enyne-allenes, generated from alcohols related to **175**, have been used in thermal cycloaromatizations (the so-called Myers−Saito cyclization).[331]

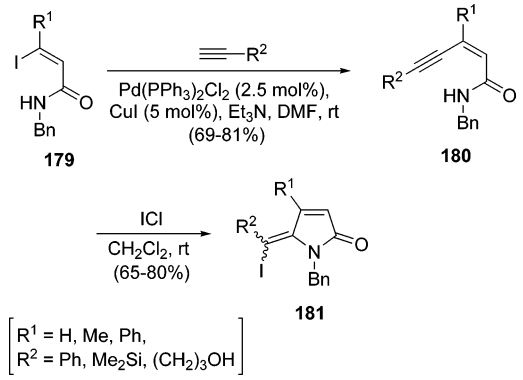
Tricyclic compounds have been obtained following a sequence involving Sonogashira coupling of 1-bromo-2-iodoarenes and acetylenic tosylates, followed by cobalt-catalyzed Diels−Alder reaction and a final cyclization.[332] Moreover, a platinum-catalyzed annulation reaction of Sonogashira reaction-prepared *o*-alkynyl benzaldehyde acetals has allowed the synthesis of indenes,[333] whereas platinum-promoted domino cyclization reactions from *o*-alkynyl benzaldehydes have also been used for the synthesis of naphthalenes with annulated carbocycles or heterocycles.[334]

4.6. Synthesis of Heterocyclic Systems

A number of synthetic approaches to heterocycles involved an intramolecular cyclization of an appropriately positioned nucleophilic heteroatom on the double bond of an enyne or on the aromatic ring of *ortho*-substituted arylacetylene moieties to a carbon−carbon triple bond. This cyclization is usually achieved by increasing the electrophilicity of the acetylenic system using different electrophilic reagents or transition metals. As an example of the latter methodology, complexes able to form palladium π-alkyne complexes can be powerful species for the construction of heterocycles in a process involving the fast and irreversible complexation of the alkyne by a palladium(II) salt. This complex can react in the presence of an internal nucleophile to give a σ-alkyl-metal complex, which can undergo different processes driving to a final heterocycle.[335] As the Sonogashira reaction is a process particularly suitable for the synthesis of enynes and arylacetylenes, this cross-coupling process combined with an internal electrophilic cyclization has been profusely applied to the preparation of many heterocyclic systems.

An example of the use of this methodology is the recent preparation of pyrrol-2(5*H*)-ones, which have been obtained from 3-iododienamides **179** (which can be considered as β-acylvinyl cation equivalents[258]) by means of a Sonogashira coupling with a terminal alkyne (Scheme 53).[336] The resulting

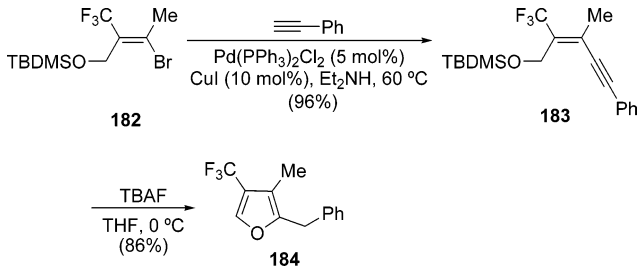
Scheme 53



alkenylamide **180** was cyclized using iodine monochloride to give (iodoalkylidene)-pyrrol-2(5*H*)-ones **181** as *Z*/*E* mixtures depending on the nature of the substituents.

Furans can also be prepared using suitable enynes following a two-step procedure. A recent example is the Sonogashira coupling of a vinyl bromide such as **182** and phenylacetylene to give *O*-silylated enyne **183**, which generates furan **184** after desilylation with TBAF and internal cyclization (Scheme 54).[337] Moreover, highly substituted

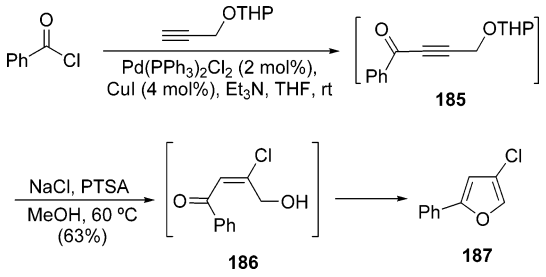
Scheme 54



furans have also been prepared via cyclization from Sonogashira-obtained 2-alkynyl-2-alken-1-ones.[338,339] Furthermore, *cis*-2-alken-4-yn-1-ones, prepared by Sonogashira coupling of the corresponding 3-chlorinated α,β-unsaturated ketone with TMSA and further deprotection, dimerize on treatment with weak acid to give 1,2-difurylethylenes.[340]

2-Halofurans have been prepared by a sequence of Sonogashira coupling and electrophilic addition to an ynone generated by alkynylation of an acyl chloride (see section 4.4). Thus, reaction of benzoyl chloride with tetrahydropyranyl-protected propargyl alcohol under Sonogashira conditions gave 2-phenyl-4-chlorofuran (**187**) (Scheme 55).[341] The

Scheme 55

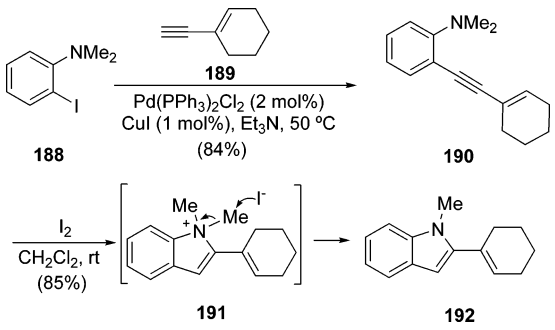


synthesis can be rationalized as a cross-coupling furnishing ynone **185**, which was solvolized under acid catalysis to give rise to a γ-hydroxy alkynone which affords chloroalcohol intermediate **186** after acid-assisted Michael addition of chloride. Further cyclization gives the final furan **187**. When Sonogashira reaction-obtained ynones are converted into the corresponding *O*-methylated oximes, isoxazoles are obtained after electrophilic cyclization.[342]

The synthesis of indoles with the participation of a Sonogashira reaction can be performed following one-pot methodologies, since it was pioneeringly observed that treatment of 1-alkynes with *o*-iodo-*N*-mesylanilides under Sonogashira conditions afforded indole products in a single operative step through a domino process.[343] The preparation of indoles has also been carried out in two steps consisting of palladium−copper-catalyzed cross-coupling of an *o*-haloaniline derivative followed by 5-*endo*-dig cyclization of the resulting 2-alkynylanilines using a variety of methods which include palladium, copper, metal alkoxides, fluorides, electrophilic reagents, etc.[344] even performed in water.[345]

N-Protected 2-alkynylated anilines, prepared by typical Sonogashira reactions, have been transformed recently into 3-iodoindoles by electrophilic cyclizations employing iodonium sources.[346] *N*,*N*-Dimethyl anilines can also be employed in this iodine-mediated cyclization,[347] as exemplified in Scheme 56, where 2-iodoaniline **188** is coupled to alkyne **189** under Sonogashira conditions to give aryl alkyne **190**, which, in the presence of iodine, cyclized to give indole **192**.[348] The cyclization proceeds by an attack of the nitrogen

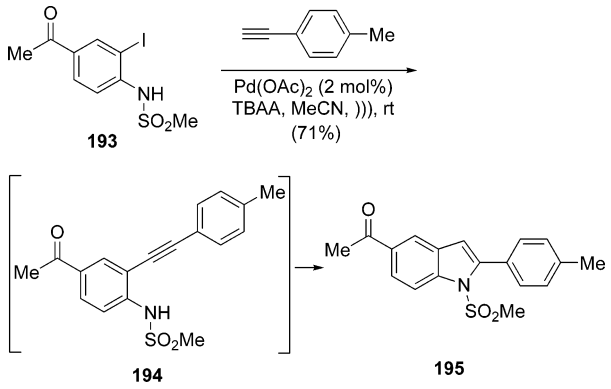
Scheme 56



on the iodonium-activated alkyne to give initially the indolium salt **191**, which loses a methyl group via either an S_N1 or S_N2 reaction. This reaction has also been performed using different alkyl groups on the nitrogen, although keeping a methyl group, but mixtures of 1-alkyl indoles were obtained.

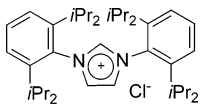
Indoles can be prepared from *N*-protected *o*-haloanilines by a one-pot palladium-catalyzed Sonogashira reaction followed by intramolecular cyclization. This indole synthesis has been recently performed using copper-cocatalysis and a palladium-supported source, such as palladium on charcoal in the presence of triphenylphosphane and 2-aminoethanol in water at 80 °C,[349] as well as using palladium(II)−NaY zeolites as catalysts, in DMF at 140 °C.[350] A convenient ligand-, copper-, and amine-free palladium-catalyzed one-pot cyclization to indoles starting form *N*-tosylated or *N*-mesylated *o*-iodoanilines has been developed, as shown in the reaction of iodinated sulfonamide **193** and *p*-tolyl acetylene affording indole **195** through Sonogashira intermediate **194** (Scheme 57).[351] The reaction takes place using

Scheme 57



palladium acetate as catalyst at room temperature in the presence of TBAA, with ultrasonic irradiation significantly improving the reaction rates. In addition, 2,3-disubstituted indoles have also been regioselectively prepared via a one-pot, three-component domino reaction including a copper-free Sonogashira coupling of trifluoroacetylated *o*-iodoanilines and aryl acetylenes, followed by a palladium-promoted cyclization and final coupling with aryl bromides.[352] The one-pot, palladium-catalyzed coupling−heteroannulation has also been applied to the synthesis of structures related to indoles, such as 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines.[353]

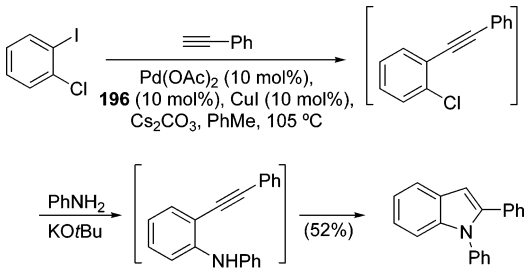
Recently, a one-pot procedure for the synthesis of indoles starting from *o*-dihaloarenes and using a palladium complex generated from the sterically hindered *N*-heterocyclic carbene



196

precursor **196** has been developed.[354] The methodology is shown in Scheme 58, where *o*-chloroiodobenzene was

Scheme 58

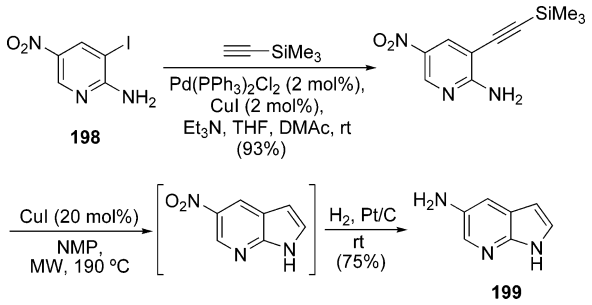


197

coupled to phenylacetylene under Sonogashira conditions to give the corresponding chlorinated alkyne intermediate. This species subsequently reacted with an amine such as aniline in the presence of potassium *tert*-butoxide to afford an intermediate acetylene which cyclized under the reaction conditions to give the corresponding indole **197**. Isoindolin-1-ones have been obtained by electrophilic cyclization of Sonogashira coupling-prepared *o*-alkynyl)benzamides, although is some cases isoquinolin-1-ones were the main products.[355]

An example of copper(I)-promoted heterocyclization from a Sonogashira-obtained product can be seen in the recent preparation of 5-amino-7-azaindole, an intermediate in the synthesis of anticancer agents. Thus, the iodopyridine **198** was coupled with TMSA under the typical Sonogashira reaction conditions to give a silylated acetylene (Scheme 59).[356] This compound cyclized under copper(I) catalysis and

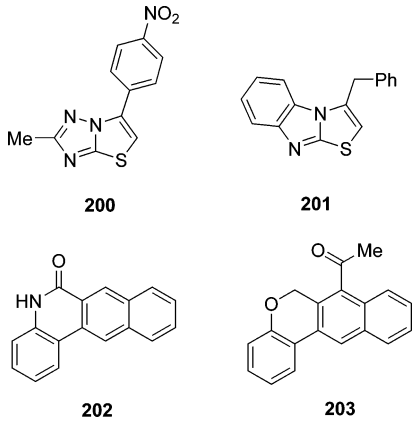
Scheme 59



198 199

microwave irradiation to give a nitroazaindole intermediate, which was transformed upon reduction into 5-amino-7-azaindole (**199**). 4-Azaindoles have been prepared from *N*-alkylated *o*-chloroarylamines via a one-pot process comprising a copper-free Sonogashira alkynylation using the combination $Pd(OAc)_2$/dppb as catalyst and a base-mediated indolization reaction.[357] Other indoles have also been prepared following this procedure.[357] Azaindoles have also been prepared by palladium-promoted cyclization of *o*-alkynylated trifluoroacetamidopyridines.[358]

Other nitrogenated heterocycles, such as isoindoles fused with triazoles, have also been prepared in a one-pot Sonogashira coupling and copper-promoted cyclization.[359] In addition, palladium catalysis has been used for the Sonogashira coupling−cyclization toward 6-benzylthiazolo[3,2-*b*]1,2,4-triazoles[360] and 3-benzylthiozolo[3,2-*a*]benzimidazoles,[361] such as **200** and **201**, respectively. Moreover,

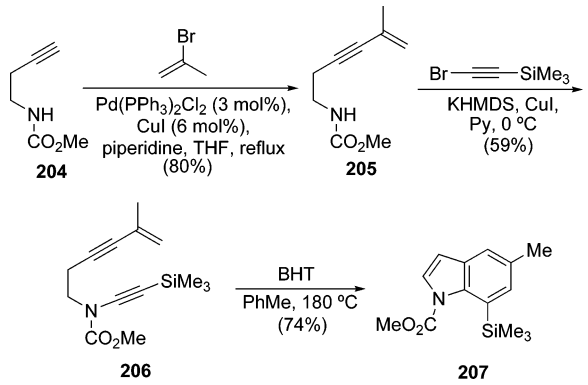


200 201 202 203

acridines have been obtained via alkynylation of 2-chloroquinolines bearing a ketone moiety at the 3-position followed by 6-*endo*-dig cyclization,[362] and benzophenanthridines such as **202** and naphthochromenes such as **203** have been prepared by thermal cyclization of Sonogashira reaction-obtained diarylacetylenic anilides or propiolates, respectively.[363]

Indoles have also been prepared in moderate yields via intramolecular [4 + 2] cycloaddition of suitable conjugated enynes prepared by a Sonogashira reaction.[364] For example, cross-coupling of acetylenic carbamate **204** with 2-bromopropylene under Sonogashira conditions afforded enyne **205**, which after *N*-acetynylation gave rise to ynamide **206** (Scheme 60). This compound is appropriate for a thermal

Scheme 60

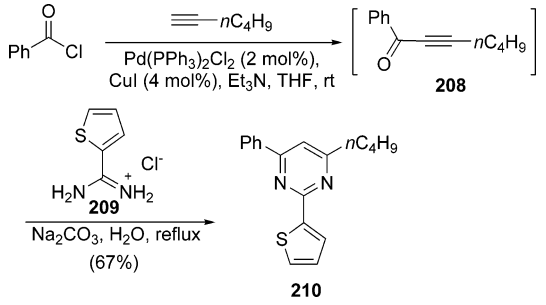


204 205 206 207

cycloaddition reaction, conducted in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as polymerization inhibitor (although perhaps also as a proton and/or hydrogen atom donor), to give indole **207**. Carbazoles have been obtained via intramolecular cyclization of anilines alkynylated at the 2-position with an enediyne system.[365]

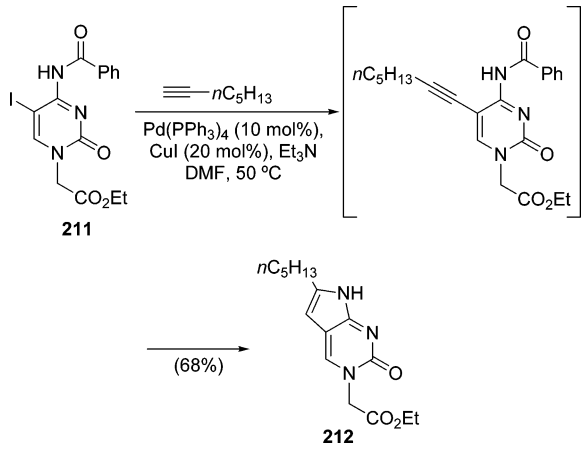
Pyrimidines have been prepared following a one-pot strategy consisting of a Sonogashira coupling of an acyl chloride and an alkyne and a subsequent reaction with an amidinium or guanidinium salt.[366] An example is shown in Scheme 61, where benzoyl chloride reacts with 1-hexyne under Sonogashira conditions to give the ynone intermediate **208**, which reacted with the amidinium salt **209** in a Michael addition−cyclocondensation fashion affording pyrimidine **210**.

Scheme 61



5-Iodocytosine derivatives can be transformed into fluorescent 7-deazapurines via a tandem Sonogashira cross-coupling followed by an annulation reaction with terminal alkynes. An example is the reaction of benzoylated 5-iodocytosine **211** with 1-octyne under Sonogashira conditions affording an alkynylated intermediate, which suffers in situ palladium-promoted heterocyclization to give deazapurine **212** (Scheme 62).[367] 5*H*-Cyclopentapyrazines have been

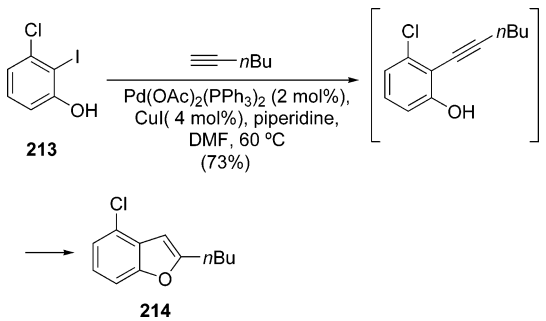
Scheme 62



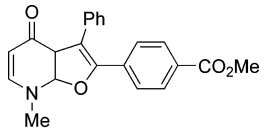
prepared by Bergman's cyclization of *C*,*N*-dialkynylimidazoles, with the C-acetylenic moiety being introduced by Sonogashira reaction on *N*-alkynylated 2-iodoimidazole.[368] On the other hand, dihydropyrid-2-ones have been prepared in moderate to good yields by a consecutive four-component synthesis, which includes the generation of an ynone by coupling of an acyl chloride and a terminal alkyne, a methodology also applied to the preparation of tetrahydro-β-carbolines.[369]

Benzo[*b*]furans are another type of heterocycles which have also been prepared by a tandem palladium-catalyzed Sonogashira coupling/5-*endo*-dig cyclization, now starting from *o*-halophenols.[109b,370] For example, reaction of 3-chloro-

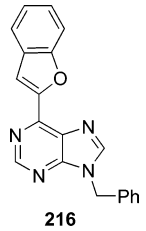
Scheme 63



2-iodophenol (**213**) with 1-hexyne under typical Sonogashira conditions afforded the 4-chlorobenzo[*b*]furan **214** through the corresponding alkynylated intermediate (Scheme 63).[371] A two-step synthesis of these heterocyclic systems has also been achieved from Sonogashira reaction-obtained *o*-alkynylphenyl acetals followed by platinum-promoted cyclization,[372] whereas furo[2,3-*b*]pyridones such as **215** have been obtained by palladium-promoted cyclization, starting from 3-iodopyridones.[373]

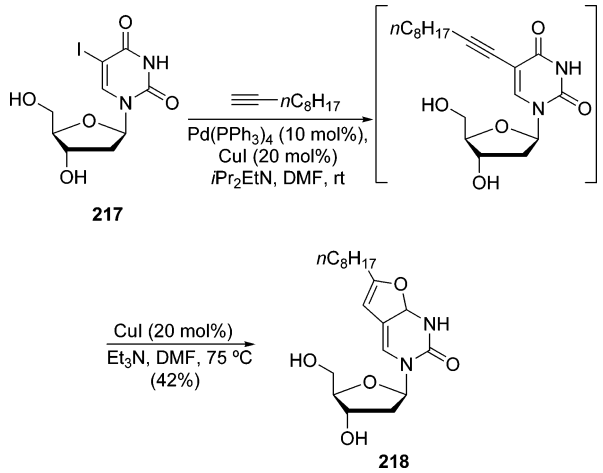


Benzo[*b*]furans have also been prepared from *o*-alkynylanisole derivatives using non-transition-metal cyclization promoters, such as iodine.[374a] This procedure has been applied to the preparation of furopyridines,[374a] which also can be obtained from Sonogashira-prepared 3-acetoxy-2-alkynylated pyridines by basic ester hydrolysis followed by in situ 5-*endo*-dig cyclization.[374b] Dibenzofurans have been prepared by Sonogashira coupling of *o*-iodoanisol and propargyl alcohol followed by several transformations and a benzannulation.[375] Moreover, a phthalide has been recently obtained by coupling of 2-iodobenzoic acid and dodeca-1,3-diyne and subsequent 5-*exo*-dig cyclization,[376] and 6-(2-benzofuryl)purines such as **216** are available by a one-pot coupling−cyclization reaction between a 6-iodopurine and 2-ethynylphenol.[377]



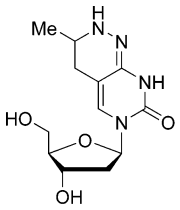
Nucleosides incorporating the furo[2,3-*d*]pyrimidin-2(3*H*)-one ring have been prepared from the corresponding ones containing a C-5 iodinated uracil by a procedure involving the Sonogashira reaction followed by 5-*exo*-dig cyclization. An application of this methodology is shown in Scheme 64.

Scheme 64

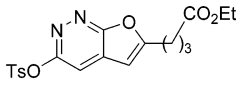


Thus, iodinated bis-deoxy nucleoside **217** reacted with

1-decyne under the typical Sonogashira conditions to give an alkynylated pyrimidinedione intermediate, which is cyclized in situ in the presence of copper(I) iodide, to give the corresponding furopyridinone-containing dideoxy nucleoside **218**, which is as a potent and selective inhibitor of varicella-zoster virus (VZV) and human cytomegalovirus (HCMV).[378] Other related nucleosides has also been recently prepared following this methodology.[379] Previously, it has been observed that when the obtained furopyridinone **218** (with the alkyl chain being a methyl group) reacted with hydrazine, a nucleophilic ring opening and a rearrangement took place providing pyrimidopyrazin-7-one **219**, which can be considered as a thymidine mimic.[380] The former furane-fused ring-forming 5-*exo*-dig cyclization has also been employed in 4-alkynylated pyridazinones, driving to furo[2,3-*c*]pyridazines such as **220**.[381]



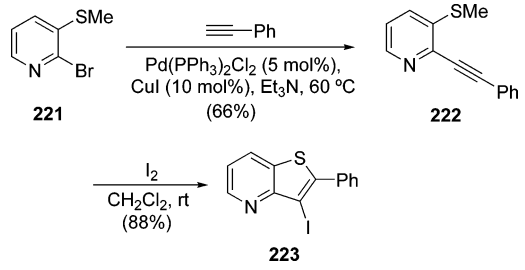
219



220

2-Substituted benzo[*b*]thiophenes have been prepared via Sonogashira coupling of terminal acetylenes with *o*-iodothioanisole and subsequent electrophilic cyclization of the resulting *o*-(1-alkynyl)thioanisole with reagents such as iodine, bromine, *N*-bromosuccinimide, or phenylselenium chloride.[382a] Following this strategy, thieno[3,2-*b*]pyridine derivatives such as **223** have been obtained through cross-coupling of 2-bromo-3-methylthiopyridine (**221**) with phenylacetylene followed by treatment of the resulting alkyne **222** with iodine (Scheme 65).[382b] An almost identical

Scheme 65

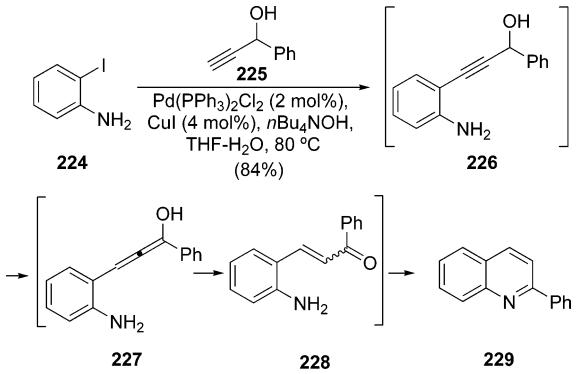


221 **222** **223**

procedure has been employed for the preparation of benzo[*b*]selenophenes starting from *o*-iodo(methylseleno)benzene.[383]

2-Iodoaniline (**224**) reacted with propargyl alcohols such as **225** under Sonogashira conditions in the presence of aqueous tetra-*n*-butylammonium hydroxide to afford the corresponding 2-arylquinoline **229**, probably following a sequence consisting of initial coupling to form acetylenic carbinol **226** followed by isomerization to α,β-unsaturated ketone **228**, through allene **227** and cyclization (Scheme 66).[384] 2-Aryl-4-aminoquinolines have been prepared by a palladium-catalyzed multicomponent reaction of Sonogashira coupling-obtained 2-ethynylarylamines, an aryl iodide, a primary amine, and carbon monoxide, in a process involving formation of an ynone.[385a] This procedure has been applied also to the synthesis of some naphthyridines.[385a] 2,4-Dichloroquinoline and 2,4-dichloroquinazoline have been

Scheme 66

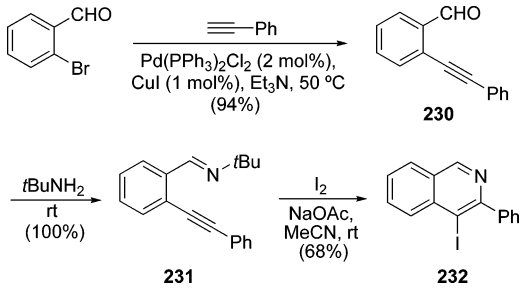


224 **226** **227** **228** **229**

prepared by diphosgene treatment of 2-ethynylaniline and anthranylonitrile, respectively, which were prepared by a Sonogashira cross-coupling reaction.[385b]

Several *N*-*tert*-butylimines from *o*-(1-alkynyl)benzaldehydes and analogous pyridine-carbaldehydes have been cyclized in the presence of electrophilic reagents,[386a] or under palladium(II)[386b] or copper(I)[386c] catalysis, to give substituted isoquinolines and naphthyridines, respectively. An example is represented in Scheme 67, where *o*-bromobenzaldehyde

Scheme 67



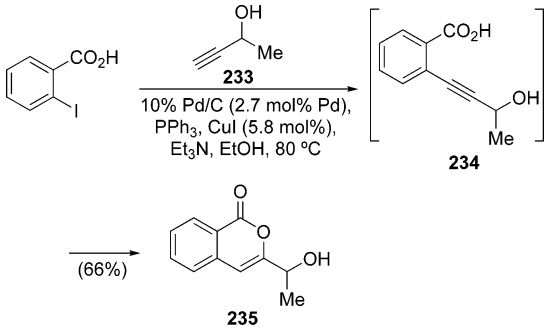
230 **231** **232**

was cross-coupled with phenylacetylene under Sonogashira conditions, affording diaryl alkyne **230**. This product was condensed with *tert*-butylamine to give imine **231**, which suffered an iodine-promoted 6-*endo*-dig cyclization with subsequent elimination of isobutene, driving to iodoisoquinoline **232**.[386a] These *o*-(1-alkynyl)benzaldehydes can also react with nucleophiles such as alcohols in the presence of alkyne-activating agents to give isochromenes after hydroxy attack to the triple bond in a 6-*endo*-dig cyclization.[387] In addition, 3,1-benzothiazines have been prepared by cyclization of Sonogashira reaction-obtained (2-thioformylamino)-diphenylacetylenes.[388] Moreover, indeno-fused derivatives of quinolizinium salts have been obtained recently from 1-bromo-2-iodobenzene via two consecutive Sonogashira couplings, generation of a pyridinium cation in a benzannulated enediyne and final cyclization.[389]

2-Substituted 4-iodoisochromenes have been obtained by iodonium-promoted cyclization from Sonogashira reaction-obtained *o*-alkynylated arylaldehydes, followed by nucleophile trapping.[390] Isocoumarins have also been prepared via cyclization from suitable *o*-(1-alkynyl)benzoic acids[391] or their esters,[392] obtained by Sonogashira coupling. The cyclization has been performed following two-step procedures with preliminary isolation of the Sonogashira product and cyclization with electrophilic reagents,[391a,392] or following one-pot procedures employing palladium on charcoal in the presence of triphenylphosphane and copper(I) iodide for a

coupling−cyclization process.[391b] An example of application of this last methodology is shown in Scheme 68, where

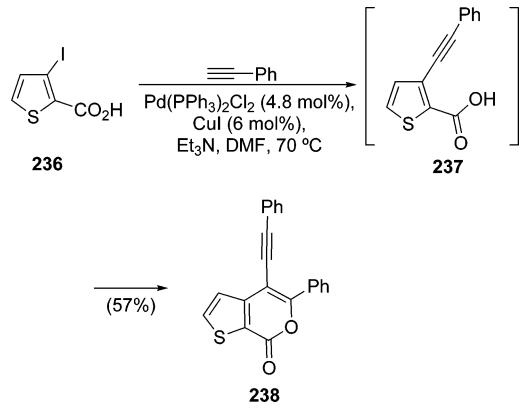
Scheme 68



o-iodobenzoic acid reacts with propargyl alcohol **233** under palladium on charcoal-catalyzed Sonogashira conditions to give 3-substituted isocoumarin **235** after in situ cyclization of intermediate **234**.[391b] Phosphaisocoumarins have been prepared by iodocyclization reactions from Sonogashira coupling-obtained *o*-(alkynyl)phenylphosphonates.[393]

4-Alkynylthieno[2,3-*c*]pyran-7-ones such as **238** have been recently prepared from 3-iodothiophene-2-carboxylic acid (**236**) and phenylacetylene by a tandem procedure involving formation of the alkynylated thiophene intermediate **237** by the typical Sonogashira protocol, followed by a 6-*endo*-dig cyclization promoted by a palladium(II) complex formed by insertion of the palladium(0) species into the acetylenic C−H bond (Scheme 69).[394]

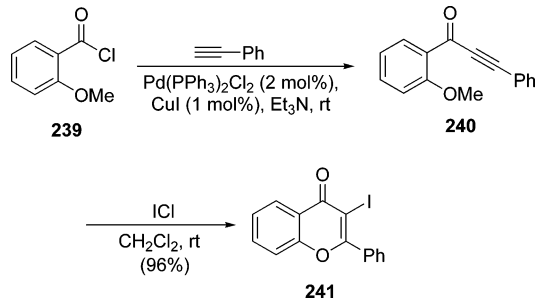
Scheme 69



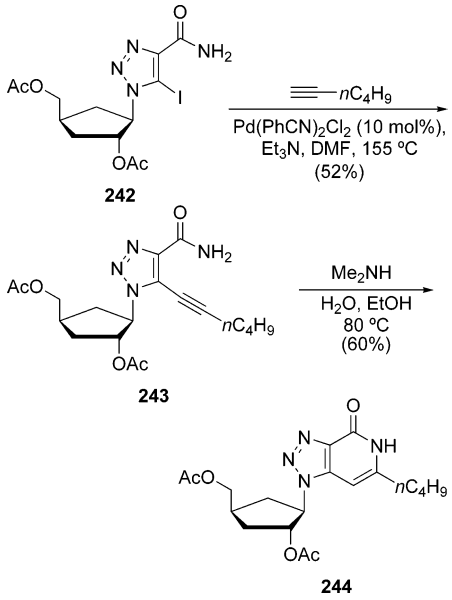
3-Iodochromones and heteroatom analogues have been prepared by ICl-induced cyclization of heteroatom-substituted alkynones, which can be obtained by Sonogashira coupling of the corresponding *o*-substituted acid chloride and a terminal acetylene (see section 4.4). An example of this methodology is the coupling of 2-methoxybenzoyl chloride (**239**) with phenylacetylene to give ynone **240**, which gave 3-iodochromone **241** after electrophilic cyclization (Scheme 70).[395]

When starting from 3-alkynylated allylic amides, 6-*endo*-dig cyclizations can drive to the generation of a pyridin-2(1*H*)-one system. A recent example of application of this methodology is the synthesis of several 8-aza-3-deazapurine analogues of 1,2,3-triazolo-3′-deoxycarbanucleosides. Thus, palladium-catalyzed coupling of iodinated deoxycarbanucleoside **242** with 1-hexyne gave C-5 alkynylated 1,2,3-triazole **243** (Scheme 71). It is interesting to remark that, in this rather exceptional case, the reaction conditions of the

Scheme 70

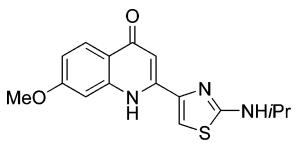


Scheme 71



cross-coupling reaction have been optimized and no addition of copper cocatalyst was needed, with no reaction being observed under typical Sonogashira conditions. Subsequent deacylation and ring closure in the presence of aqueous dimethylamine in refluxing ethanol led to the 8-aza-3-deazapurine **244**.[396]

The pyridin-2(1*H*)-one system has been prepared by thermolysis of appropriate carboxylated enyne-isocyanates. For example, Sonogashira cross-coupling of vinyl triflate **245** with but-3-ynylbenzene gave the corresponding enyne, which, after ester conversion to an isocyanate group by ester hydrolysis and reaction with diphenyl phosphorazidate, gave enyne-isocyanate derivative **246**. This compound cyclized upon thermolysis, giving annulated pyridinone **247** (Scheme 72).[397] In addition, quinolone **248**, which is a substructure of a hepatitis C virus protease inhibitor, has been prepared by a carbonylative copper-free Sonogashira reaction of an *o*-iodoaniline and a terminal thiazolyl acetylene in the presence of carbon monoxide, followed by a 6-*endo*-dig cyclization.[398]

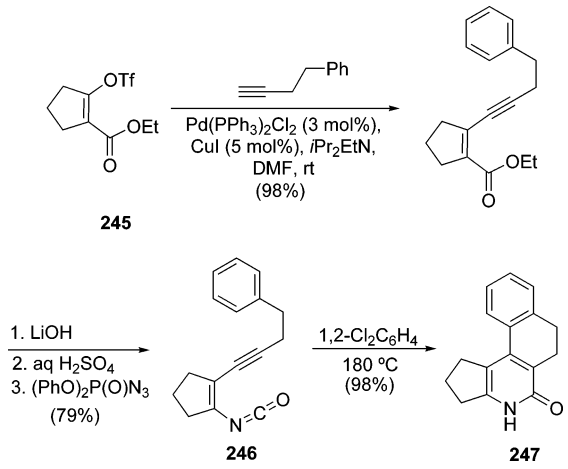


248

4.7. Synthesis of Natural Products

Many metabolites found in Nature contain alkyne or enyne moieties, and therefore, the Sonogashira reaction has found

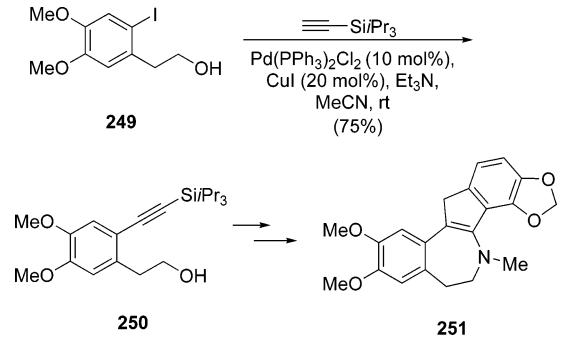
Scheme 72



frequent uses in their syntheses, with some selected examples being mentioned in more general reviews on cross-coupling reactions.[399] This section will cover very recent applications of this coupling methodology toward the total synthesis of natural products, with the typical copper-cocatalyzed reaction being employed almost exclusively.

An example of the coupling of an aryl iodide to an aryl acetylene can be seen in the reaction of the iodinated alcohol **249** and the tris(isopropyl)silylacetylene, which gave alkyne **250**, an intermediate in the total synthesis of the benzindenoazepine alkaloid bulgaramine (**251**) (Scheme 73).[400] There

Scheme 73

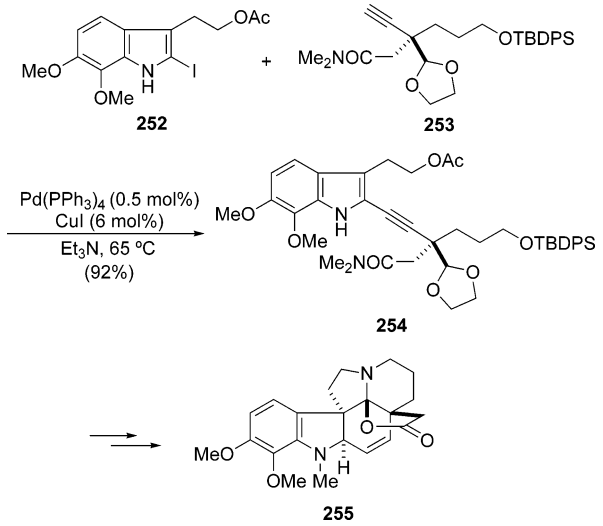


are other recent examples of the use of aryl iodides for the preparation of intermediates under typical Sonogashira conditions, which, after cyclization, afforded natural products such as benzylisoquinoline[401] or indole alkaloids,[402] as well as benzofuropyranones such as wedelolactone.[403] Other recent examples of the coupling of aryl iodides with alkynes can be seen in the synthesis of an immunosuppressive agent related to sphingosine ISP-I,[404] the phytoestrogenic metabolite coumestrol,[405] the antimitotic agents combrestastatins A-1 and B-1,[406] and the spiroketal skeleton of γ-rubromycin, where 2-methyl-3-butyn-2-ol as acetylene equivalent has been employed.[407]

Iodinated indoles have been used as the halide counterpart in Sonogashira couplings leading to natural alkaloids, with an example being shown in Scheme 74, where the reaction of 2-iodoindole **252** with alkyne **253** affords acetylene **254**, which has been employed in the total synthesis of (-)-aspidophytine (**255**).[408]

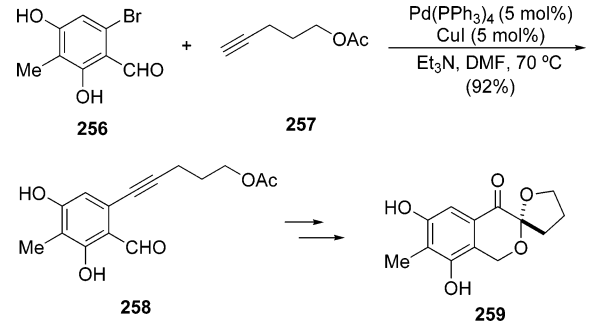
Bromoarenes can also be found as starting materials in the synthesis of natural products employing the Sonogashira methodology, as in the recent synthesis of the fungi

Scheme 74



metabolites frustulosin and frustulosinol,[409] (−)-frondosin B,[410] as well as the plant metabolite with benzo[*b*]furan structure cicerfuran,[411] and heliophenanthrone, a dehydrophenanthrone from *Heliotropium ovalifolium*.[412] In Scheme 75 is shown the cross-coupling of aryl bromide **256** and

Scheme 75

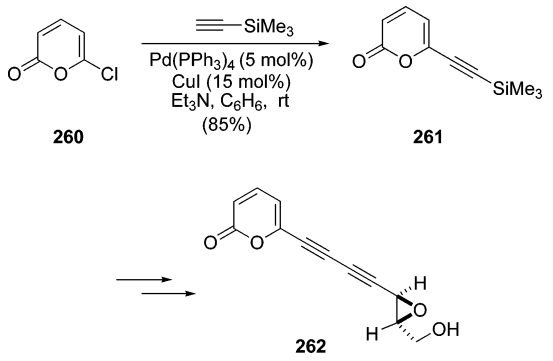


4-pentynyl acetate (**257**) to give benzylic aldehyde **258**, which has been employed in the total synthesis of (±)-terreinol (**259**),[413] a metabolite isolated from *Aspergillus terreus*. In addition, a 2,4-bromopyridine has been regioselectively coupled to TMSA at the 4-position in a convergent synthesis of the visual pigment A2E.[414]

Aryl chlorides have obviously not been employed very often in total syntheses involving the Sonogashira reaction due to their usual lack of reactivity. However, more reactive chlorinated heteroaromatics have been found to be suitable, with an example being the coupling of a dichloropyrimidine with 1-hexyne under Sonogashira reaction conditions at room temperature to give an intermediate in the total synthesis of the alkaloid from a venom ant (±)-tetraponerine T6.[415] Another example uses the highly reactive semiaromatic δ-acyldienyl cation equivalent[258] 6-chloro-2*H*-pyran-2-one (**260**) and TMSA, also under Sonogashira conditions at room temperature, for the synthesis of silylated acetylene **261**, which has been the starting material for subsequent couplings, leading to the synthesis of the antibacterial, antifungal, and cytotoxic basidiomycete metabolite (-)-nitidon (**262**) and also its enantiomer (Scheme 76).[416]

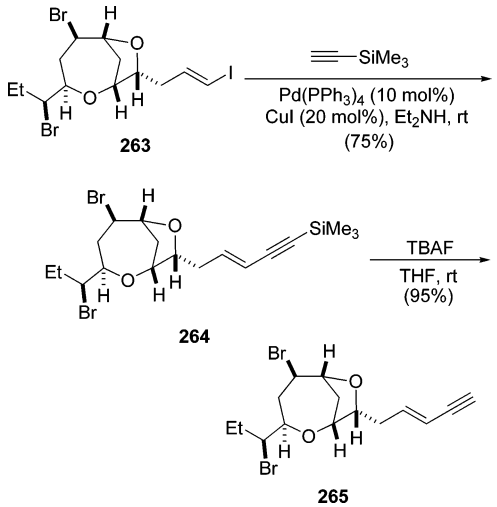
Aryl triflates have also been employed in total synthesis, with an example being a coupling reaction with TMSA in an indole preparation for a recent formal total synthesis of the *Streptomyces* metabolite 0231B.[417]

Scheme 76



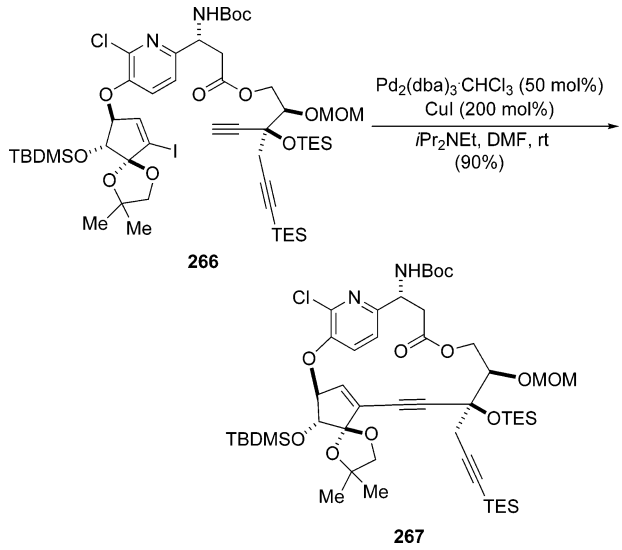
However, beyond any doubt, the most frequently employed partners of the alkynes for the typical Sonogashira reaction driving to natural product synthesis have been the vinylic halides, as the stereospecifically created enyne moiety (see section 4.3) is quite frequent in naturally occurring compounds, as well as the dienic moiety, which is easily generated by partial reduction of the triple bond. Among the vinyl halides, vinyl iodides have been the most commonly employed, due to their higher reactivity. The uses of vinyl iodides in this reaction in natural product syntheses in the last few years have been numerous, as in the case of the synthesis of (−)-disorazole C1,[418] (−)-callipeltoside A,[419a] leptofuranin D,[419b] borrelidin,[419c] annonaceous acetogenins,[419d] alkaloids hachijodines F and G,[419e] and a derivative of phorboxazole A.[419f] Other examples incude the preparation of tetrodotoxin,[419g] the polyacetylene bupleurynol,[419h] murisolin,[419i] the maduropeptin chromophore,[419j] precursors of (−)-cochleamycin A,[419k] the autacoid 12(*S*),20-dihydroxyeicosa-5(*Z*),8(*Z*),10(*E*),14(*Z*)-tetraenoic acid,[419l] cilindramide,[419m] murisolins,[419n] analogues of solamin,[419o] the DE ring system of the marine alkaloid upenamide,[419p] the acetylenic diols (+)-dipline C and E,[419q] the marine eicosanoid agardhilactone,[419r] and tetrahydro-disorazole C1.[419s] An illustrative example is the coupling reaction of TMSA with vinyl iodide **263** to give trimethylsilylated enyne **264**, which after silyl deprotection with tetra-*n*-butylammonium fluoride (TBAF) gave rise to (−)-isoprelaurefucin (**265**), a metabolite isolated from the red alga *Laurencia nipponica* (Scheme 77).[420]

Scheme 77



Another use can be seen in the macrocyclization of iodinated dialkyne **266**, which gave, in excellent yield, the conformationally defined ansamacrocyclic compound **267**, which is the key precursor in the total synthesis of the kedarcidin chromophore (Scheme 78).[421] In both cases, it can be

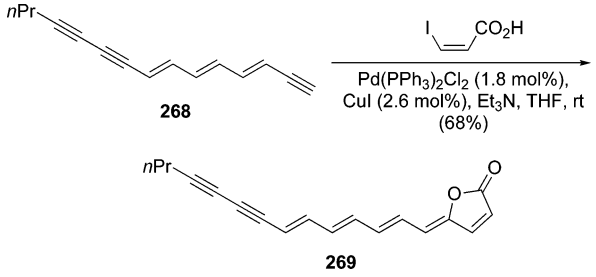
Scheme 78



observed that the Sonogashira coupling is performed efficiently at room temperature, although rather large amounts of palladium catalysts and copper salt are used, something very frequent when dealing with sensitive starting materials where mild reaction conditions are needed.

Another example of the use of a vinyl iodide is the preparation of the γ-alkylidene butenolide dihydroxerulin **269**, a potent inhibitor of the biosynthesis of cholesterol. Thus, pentadecatrientriyne **268** reacted with the β-acylvinyl cation equivalent[258] (*Z*)-3-iodoacrylic acid under Sonogashira conditions to furnish dihydroxerulin after a tandem cross-coupling/palladium-promoted 5-*exo*-dig cyclization (Scheme 79).[422] A similar procedure has been employed in the

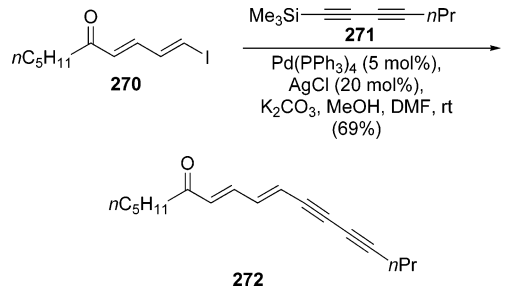
Scheme 79



synthesis of related xerulin. In addition, (*S*)-1-dehydroxyvirol A has been prepared by a silver cocatalyzed Sonogashira cross-coupling reaction of the δ-acyldienyl cation equivalent **270** with silylated diyne **271**, which previously suffered desilylation under the basic reaction conditions (Scheme 80).[423] The carbonyl group of the resulting compound **272** was then enantioselectively reduced using a chiral (*R*)-methyloxazaborolidine (the Corey−Bakshi−Shibata, CBS, reduction) to give the natural compound.

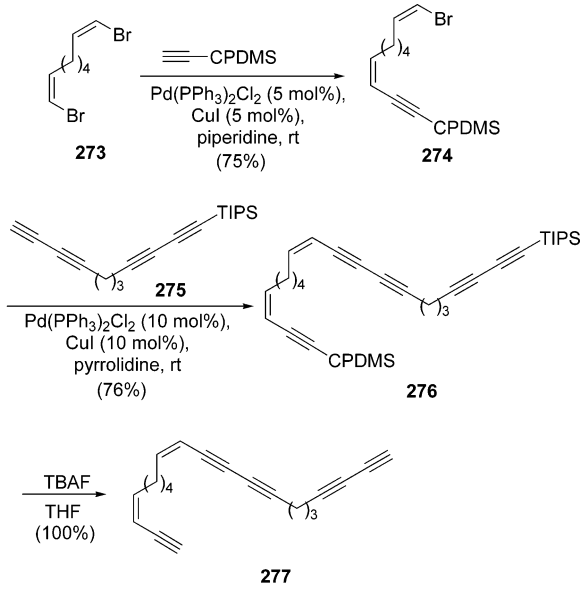
Examples of the use of vinyl bromides for this alkynylation reaction for the preparation of naturally occurring compounds are not as frequent as the use of vinyl iodides, although some recent examples can be found in the synthesis of diene-containing sapinofuranone B,[424] the pigment of a tangerine

Scheme 80



tomato,[425] and different straight-chain polyacetylenes.[426] Scheme 81 shows a strategy based strongly in the Sonogashira coupling reaction for the synthesis of the marine polyacetylene callyberine A (**277**), with other members of this family also being prepared.[427] Thus, dibromide **273** was coupled under Sonogashira conditions to [(3-cyanopropyl)-dimethylsilyl]acetylene, affording the mono-enyne **274** (although 9% of the corresponding di-enyne was also obtained), which was coupled again to monoprotected bis(diyne) **275** to give pentayne **276**. Final desilylation gave callyberine A.

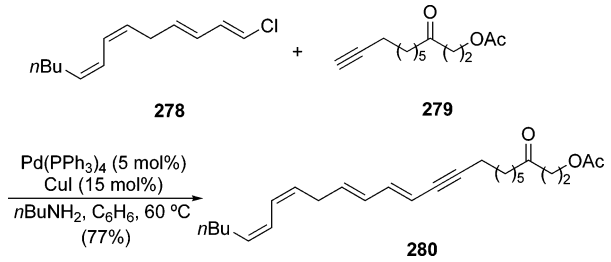
Scheme 81



[CPDMS = (3-cyanopropyl)dimethylsilyl]

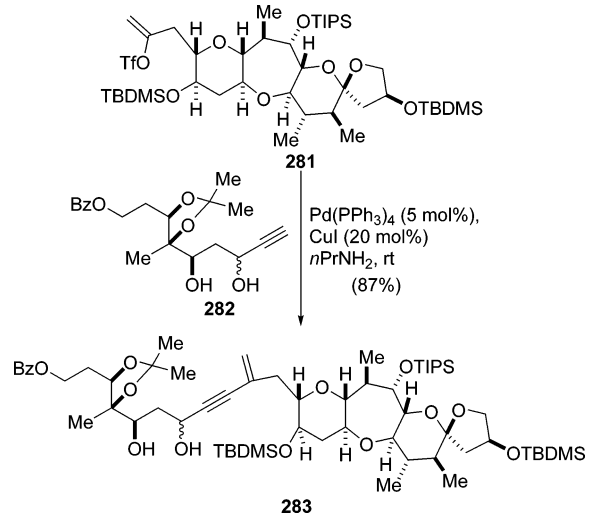
Less frequent is the use of vinyl chlorides in natural product synthesis employing the Sonogashira methodology, although some recent examples can be found, as in the total synthesis of (+)-virol C, a toxic component of the water hemlock *Cicuta viscosa*,[428] and also in the preparation of polyunsaturated acetate **280**, a potent ant venom, by coupling chlorinated tetraene **278** and alkyne **279** (Scheme 82).[429]

Scheme 82



Even recent examples of the use of vinyl triflates can be found, as is the case of the cross-coupling between triflate **281** and acetylenic diol **282**, which gave the corresponding coupling product **283** in high yield, in a synthesis of the right-hand segment of ciguatoxin (Scheme 83).[430]

Scheme 83



4.8. Synthesis of Electronic and Electrooptical Molecules

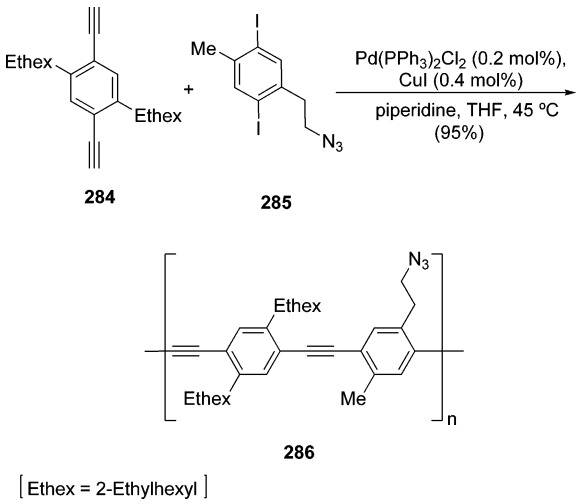
Extended organic molecules intercalating an aromatic ring and an alkyne moiety have been the focus of an enormous amount of attention in the last few years, because, as do all highly conjugated systems, they have properties of organic semiconductors and can act as molecularly wired sensors, polarizers for liquid crystalline displays, and light-emitting devices.[431] The Sonogashira cross-coupling methodology represents by far the most usual access to the conjugated chains of these poly(aryleneethynylene)s (PAEs) and oligo-(aryleneethynylenes) (OAEs).[432] The starting materials can be dihalogenated and dialkynylated arenes, or terminal halogenated arylalkynes, with the position of the halogen and alkynyl substituents on the arene rings determining the polymer or oligomer shape.

When considering the reaction conditions in the Sonogashira coupling applied to the synthesis of PAEs or OAEs, and particularly to poly(phenyleneethynylene)s (PPEs) and oligo(phenyleneethynylenes) (OPEs), there have not been very many changes or improvements in the last few years. Thus, the commercially available $Pd(PPh_3)_2Cl_2$ is very often the source of palladium, and copper(I) iodide is almost always added, as it does not seem to harm the progress of the reaction. Of course, iodoaromatics are preferred in the coupling, as they react under milder reaction conditions and lower catalyst loadings are necessary when compared to the cases of aryl bromides, with the presence of electron-withdrawing groups facilitating the process, although longer reaction times are always needed than when dealing with low-weight molecules. The formation of undesirable amounts of alkyne homocoupling products in this case can drive to more serious problems, as it decreases the degree of polymerization and can induce the presence of several percent of butadiyne defects. Diisopropylamine has been traditionally found to be particularly efficient as base in the synthesis of PPEs in combination with a palladium(0) source such as $Pd(PPh_3)_4$, although cheaper triethylamine can be

employed.[432e] In addition, piperidine usually outperforms triethylamine in the case of aryl diiodides, although is not so good when dealing with bromides, where triethylamine is also usually the base of choice and di(isopropyl)ethylamine performs even better. Frequently, the organic base is not the prime solvent, and the addition of a cosolvent such as THF, ether, or toluene, as well as chloroform or dichloromethane, is necessary to solubilize the formed polymer.[432e]

An example of preparation of a PPE is shown in Scheme 84, where a typical Sonogashira reaction has been used for

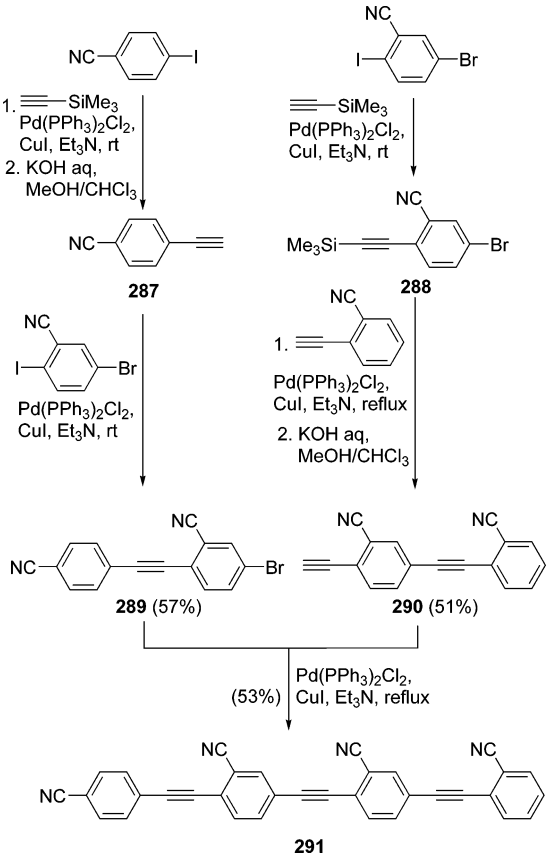
Scheme 84



a one-pot polymerization reaction, with the diacetylenic arene **284** and the diiodinated compound **285** acting as monomers.[433] The obtained polymer **286** not only has electrooptical properties but also has been employed for generation of permanent bubble arrays creating picoliter holes with a density of 40,000 holes/mm^2, which have high potential as microanalytical tools and as matrices for the fabrication of microlenses. Other examples of use of the Sonogashira reaction for polymerization to PPEs can be found.[434]

Frequently, OPEs are prepared by an iterative process or a convergent methodology, with profuse employment of the Sonogashira reaction, as can be seen in the synthesis of rod-shaped polycyano OPE **291** (Scheme 85), with the amounts of catalysts not being reported.[435] Thus, *p*-iodobenzonitrile is coupled with TMSA under Sonogashira conditions, giving, after silyl deprotection, the alkyne **287**. This compound is coupled with 5-bromo-2-iodobenzonitrile at room temperature, taking advantage of the higher reactivity of the carbon-iodide bond, affording diarylacetylene **289**. This was cross-coupled with the diacetylene **290** (also obtained from 5-bromo-2-iodobenzonitrile through a route involving Sonogashira reaction to compound **288** and subsequent coupling with 2-ethynylbenzonitrile followed by silyl deprotection), driving to final OPE **291**, which has been shown to be a strongly fluorescent material. Many other representative examples of the recent preparation of OPEs with multiple optical properties through Sonogashira reactions can be found,[436] as well as other PPE model systems,[437] even prepared by coupling vinyl triflates to the terminus of polyarylacetylenes by using the silver cocatalyzed Sonogashira procedure.[438] Moreover, oligoazulenes with ethynyl bridges have been recently prepared using consecutive Sonogashira reactions,[439] as well as ethynylhelicene oligomers[440] and anthrylene-ethynylene oligomers.[441] In addition, the copolymerization of diethynylsilane and dibromoarenes

Scheme 85

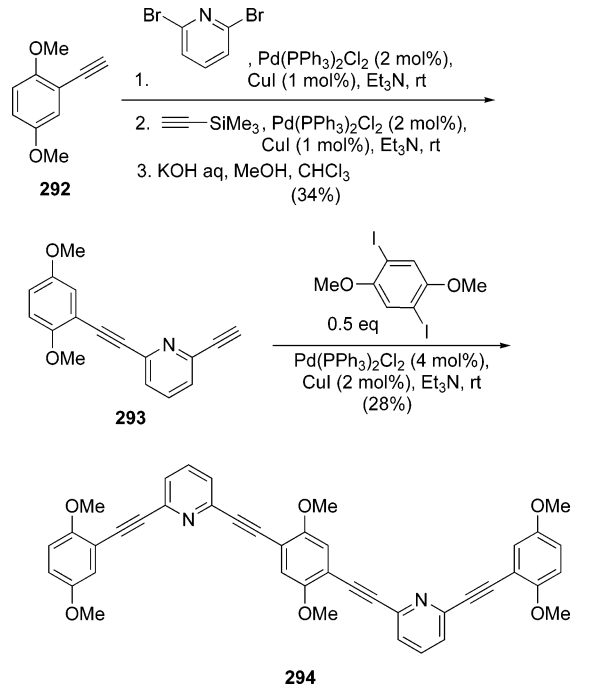


has been studied for the synthesis of PPE-*co*-diethynylenesilylenearylenes.[442] The palladium−copper promoted alkynylation has been used for the incorporation of linear aryleneethynyl units on [2.2]paracyclophanes[443] and in the preparation of poly(arylpropargyl)ether branches[444] or poly(ethynyl) linked aromatic amines.[445] Furthermore, alkynylated fluorescent systems from anthracene or pyrene,[446] as well as from 9-(cyclopentatrienylidene)fluorene,[447] have been prepared and used for the synthesis of fluorescent probes, as well as binuclear cyclometalated complexes attached to a OPE chain for molecular wires.[448]

The incorporation into the oligomers of electron-deficient rings such as azaheterocycles develops changes in their electronic properties. Thus, chains incorporating pyridine rings have been prepared, such as the donor−acceptor banana-shaped OAE **294**, which has been prepared by a process based on elongation of the oligomeric chain via Sonogashira cross-coupling of an arylacetylene **292** (also prepared using a Sonogashira reaction) with 2,6-dibromopyridine, followed by another coupling with TMSA (Scheme 86). Silyl deprotection to give diacetylenic pyridine **293** and final cross-coupling of two units of this compound with 1,4-diiodo-2,5-dimethoxybenzene afforded the pentameric banana-shaped system **294**.[449] Other examples of incorporating azaheterocycles include bipyrimidines,[450] as well as pyrimidine[451] or pyrazine[452] rings. In addition, other heterocycles have been incorporated, as in the recent preparation of a phenyleneethynylene-*alt*-thienyleneethynylene polymer.[453]

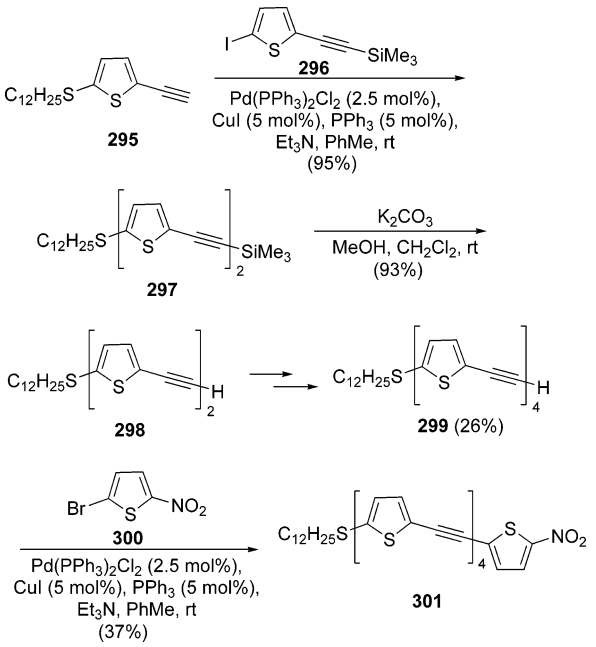
Oligo(thienyleneethynylene)s (OTEs) incorporating donor−acceptor end groups have, as do other donor−acceptor conjugated oligomers,[454] interesting linear and nonlinear optical (NLO) properties. An illustrative recent example of

Scheme 86



the preparation of one of these donor−acceptor OTEs is shown in Scheme 87, where iodothiophene **296** was coupled

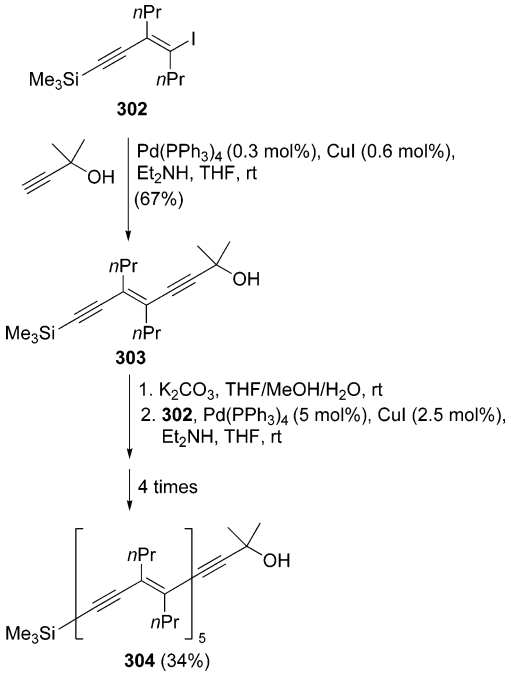
Scheme 87

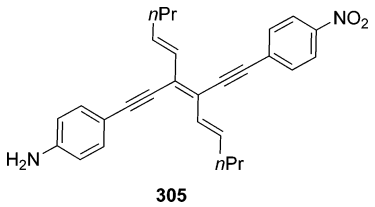


to alkyne **295** under Sonogashira conditions, giving compound **297** and, after desilylation, alkyne **298**.[455] Several subsequent elongations following the same methodology ended to furnish oligomer **299**, which was finally coupled with bromothiophene **300** to give OTE **301**. In addition, different NLO properties have been achieved by preparing oligomers containing the thiophenylethynyl moieties combined to aryl systems. Thus, oligomers incorporating the thienyleneethynylene unit and phenyl rings,[456] biphenyls,[457] bipyridines,[458] and oxadiazoles[459] have been recently prepared.

Oligoenynes based on the DEE unit are another type of linearly π-conjugated oligomers showing potentially interesting electronic and optical properties,[431,460] and the Sonogashira reaction has been found to be particularly suitable for their preparation, which has been recently reviewed.[461] An illustrative example of the application of the Sonogashira reaction to the preparation of a (*E*)-DEE-based oligomer is the linear synthesis of oligoenyne **304** starting from iodoenyne **302**, which was cross-coupled to 2-methylbut-3-yn-2-ol to give intermediate enediyne **303**. From this compound and following a series of protodesilylation reactions and Sonogashira couplings, the final oligoenyne was obtained (Scheme 88).[462] In addition, donor−acceptor 1,2-divinylethynylenes have been prepared by arylalkynylation of divinylated 1,4-dioodobenzenes,[463] as well as by Sonogashira reaction of the corresponding iodobenzenes and a 3,4-dialkynylated triene, as is the case of compound **305**.[464]

Scheme 88

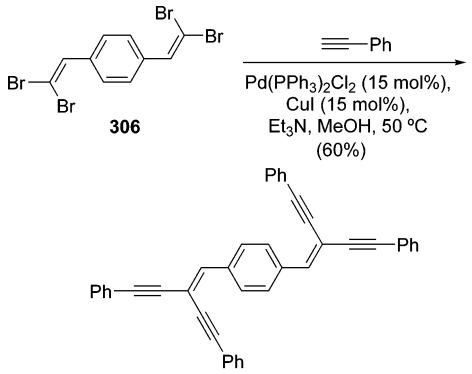




Highly conjugated systems containing the *gem*-DEE unit have shown interesting fluorescent properties, with their synthesis being frequently based on the Sonogashira cross-coupling methodology.[461] Scheme 89 shows an illustrative example of preparation of one of these systems. Thus, bis(*gem*-dibromoalkene) **306** has been coupled under Sonogashira conditions to phenylacetylene, affording bis-enediyne **307**,[465] whose properties as fluorophore are tunable by changing the dialkene aryl bridge. The syntheses of other related fluorophores have been performed by initial palladium-catalyzed coupling to TMSA followed by silyl deprotection and further cross-coupling to aryl halides.[465] Other Y-enynes with dendrimeric structure and high fluorescency have been prepared similarly.[466]

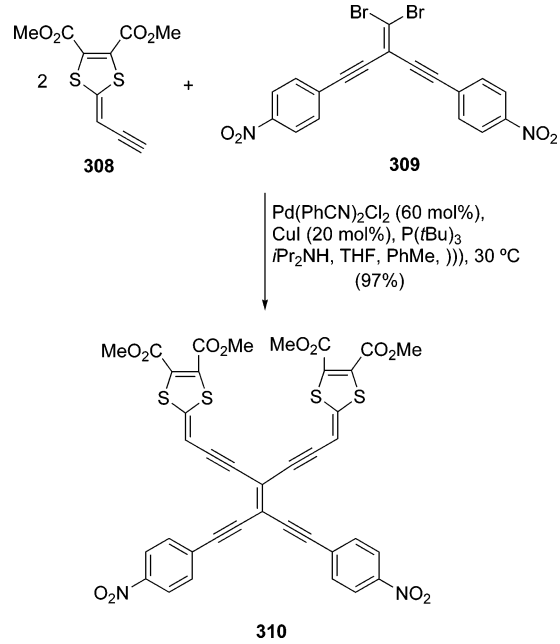
The triethynylethene (TriEE) and tetraethynylethene (TEE) moieties are also structural modules, which have been used

Scheme 89



for the construction of a large variety of conjugated molecules with interesting electrochemical and photophysical properties.[461] A recent example of employment of a Sonogashira reaction for creating a donor−acceptor system with a TEE core is shown in Scheme 90, where dialkynylated

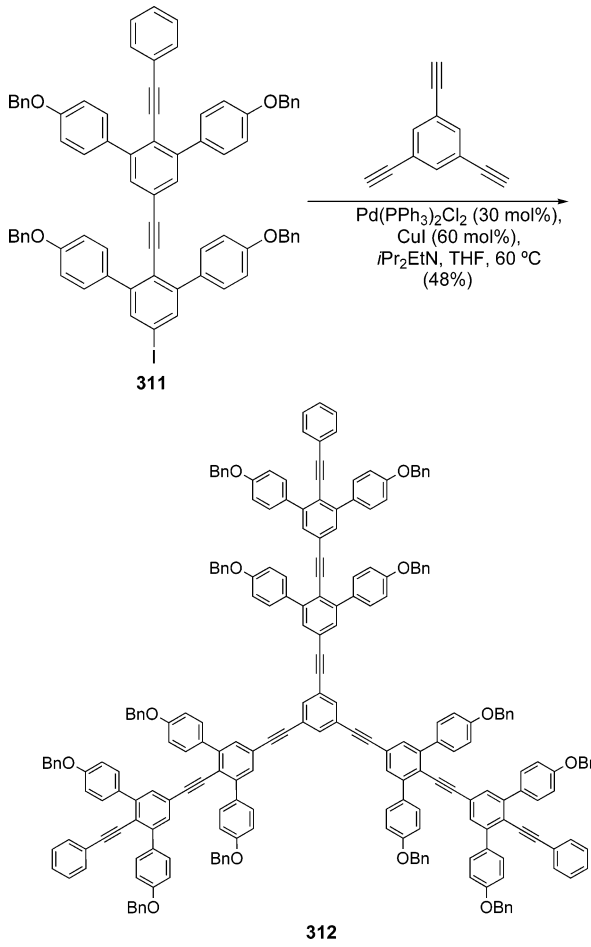
Scheme 90



gem-dibromide **309** was coupled under Sonogashira conditions to tetrathiafulvalene-derived terminal acetylene **308**, furnishing the conjugation-extended TEE derivative **310** in very high yield.[467] It is interesting to point out that, in this case, the copper cocatalyzed Sonogashira cross-coupling has been performed employing the more effective catalytic system formed by the bulky electron-rich phosphane P(*t*Bu)$_3$ and Pd(PhCN)$_2$Cl$_2$ under sonication, although with large catalyst loading, as very low yields were obtained using the "conventional" Pd(PPh$_3$)$_2$Cl$_2$ palladium source. When starting from a monoalkynylated dibromide, a related TriEE derivative was obtained.[467] In addition, the tetraphenylethylene (TPE) core has been alkynylated using the Sonogashira methodology for further attachment of donor or acceptor groups in the four phenyl corners.[468]

The structural rigidity and electronic conjugation of aryleneethynylenes have made them very useful building blocks, not only for the already mentioned preparation of polymers and oligomers, but also for the synthesis of dendrimers with interesting properties as new molecular electronic and photonic materials.[469] Some recent preparations of these type of dendrons using the Sonogashira cross-coupling reaction as the key step can be cited,[470] with one of them being the synthesis of snowflake-like dendrimer **312**, which has been prepared by Sonogashira coupling between aryl iodide **311** (also obtained by Sonogashira reactions) and 1,3,5-triethynylbenzene (Scheme 91).[471] In addition, ex-

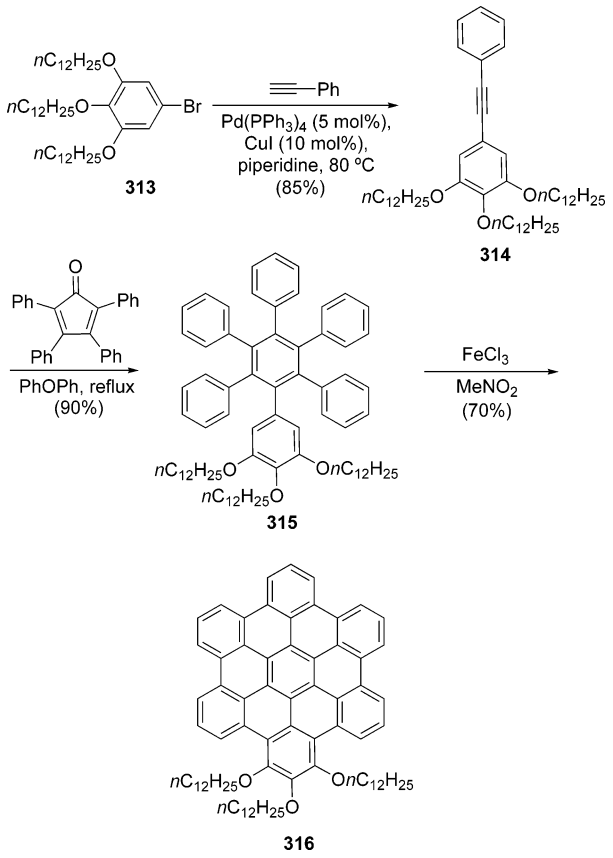
Scheme 91



amples of the preparation of nondendrimeric but radially structured tris-[472] and hexakis(ethylaryl)benzene derivatives,[473] polyalkynylated pyrenes,[474] and polyethynyl[2.2]-paracyclophenes[475] using this coupling procedure can be found. Octaethynylphenazine,[476] hexaethynylquinoxaline,[476] and benzo[2.1.3]thiadiazole[477] with NLO and fluorescence properties, and also bearing crown ethers,[478] have been obtained using this methodology.

Discotic polycyclic aromatic hydrocarbons such as hexa-*peri*-hexabenzocoronene (HBC) and its substituted or extended derivatives have attracted considerable interest in the last few years, because of their π-stacking self-assembling properties.[479] These disk-shaped molecules π-stack to form columnar thermotropic liquid crystalline phases which show very high charge carrier mobilities along the axis of the column, and they have found applications as organic field-effect transistors (OFETs) and as hole conducting layers in photovoltaic devices such as solar cells or light-emitting diodes (LEDs). An illustrative example of the use of the Sonogashira cross-coupling reaction for the synthesis of these types of polycyclic aromatic hydrocarbons is shown in Scheme 92. Thus, the HBC derivative **316** has been obtained

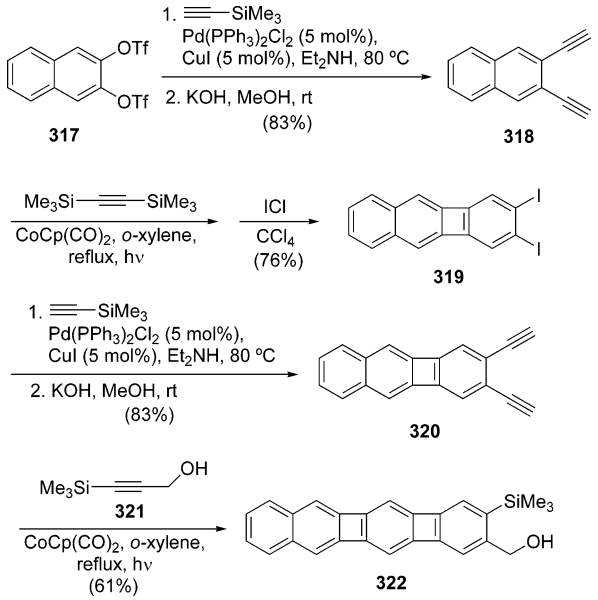
Scheme 92



by a method consisting of a Sonogashira coupling reaction between aryl bromide **313** and phenylacetylene to give diaryl alkyne **314**. Subsequent Diels−Alder reaction with 2,3,4,5-tetraphenylcyclopentadienone and carbon monoxide extrusion gave hexaarylated benzene **315**, which was dehydrogenated to give HBC derivative **316**.[480] This cycloaddition-including methodology has been used for the creation of other substituted HBCs,[481] as well as branched hydrocarbon propellers.[482]

The [N]phenylenes are linear polycyclic aromatic hydrocarbons formed by alternation of N benzene units fused to N-1 cyclobutadiene rings, and they are candidates for molecular electronics because of their extended π-conjugation. Their synthesis is frequently based on an iterative sequence including palladium-catalyzed alkynylations followed by cobalt-catalyzed cyclotrimerizations,[483] with an illustrative recent example being shown in Scheme 93. Thus, Sonogashira coupling of TMSA with bis-triflate **317**, followed by desilylation of both triple bonds, afforded diyne **318**. The cobalt-catalyzed [2 + 2 + 2] cyclotrimerization reaction of this compound and BTMSA under irradiation gave a benzophenylene, which was sequentially submitted to iododesilylation to give compound **319**. Further Sonogashira coupling with TMSA and desilylation furnished diyne **320**. A new cyclotrimerization with silylated propargyl alcohol **321** gave benzo[3]phenylene **322**, a compound that has been used anchored to a C_{60} fullerene.[484] Double-bent [5]phenylenes have been previously prepared following a similar procedure.[485] Moreover, other polycyclic systems have been prepared from Sonogashira reaction-prepared starting materials, such as 4*H*-cyclopenta[*def*]phenanthrenones via benzannulation of enediynyl propargyl alcohols,[486] atropoisomeric 1,2-bis[5-(11*H*-benzo[*b*]fluorenyl)]-benzenes via benzannulation of enyne-allene precursors,[487]

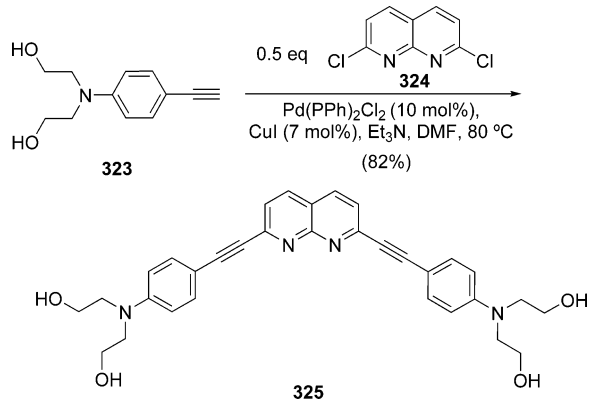
Scheme 93



and seven-ring fused benzodithiophenes from 3,7-diiodinated benzodithiophenes.[488]

The acetylene moiety has been incorporated to polynuclear nitrogen-containing heterocycles by means of the Sonogashira reaction in order to obtain organic and organometallic compounds for electroluminescent applications.[489] Another interesting application is the recent synthesis of the conjugated donor−acceptor−donor molecule **325**, incorporating a central moiety of naphthyridine (Scheme 94). This compound has been prepared from alkynylated aniline **323** (obtained by Sonogashira coupling of the corresponding iodide with TMSA and further deprotection) and dichloronaphthyridine **324** following a Sonogashira protocol.[490] The resulting product **325** showed a high selectivity toward mercury(II) ion, showing two-stage color changes, and therefore, has application as a visual detector. Related systems have also found applications as fluorescent sensors for monosaccharides.[491] In addition, alkynylated bisquinolines[492] and interesting electron-accepting polyoxometalated complexes covalently bonded to terpyridine ligands by means of a Sonogashira-created π-alkynylated bridge have been obtained.[493] Moreover, aryl alkyne substituents have been connected to the 4-position of concave pyridines using the Sonogashira methodology, with the resulting products showing solvatochromism in hydrogen bond creating solvents.[494]

Scheme 94

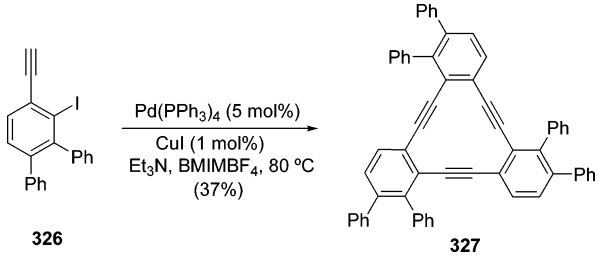


4.9. Synthesis of Molecules for Nanostructures

Macrocycles having rigid and noncollapsible unsaturated hydrocarbon backbones have attracted great interest in the past few years. Among them, the group formed by acetylene and benzene moieties such as phenylacetylene and phenyloligoacetylene macrocycles,[495] and also those formed by acetylene and other arene moieties,[496] has demonstrated tremendous synthetic versatility and the ability not only to create interesting electronic effects due to their highly conjugated structure, but also to spontaneously organize into ordered assemblies. Thus, three-dimensional nanostructures, discotic liquid crystals, extended tubular channels, guest−host complexes, porous organic solids, and so on have been obtained from these arylene−ethynylene macrocycles (AEMs).

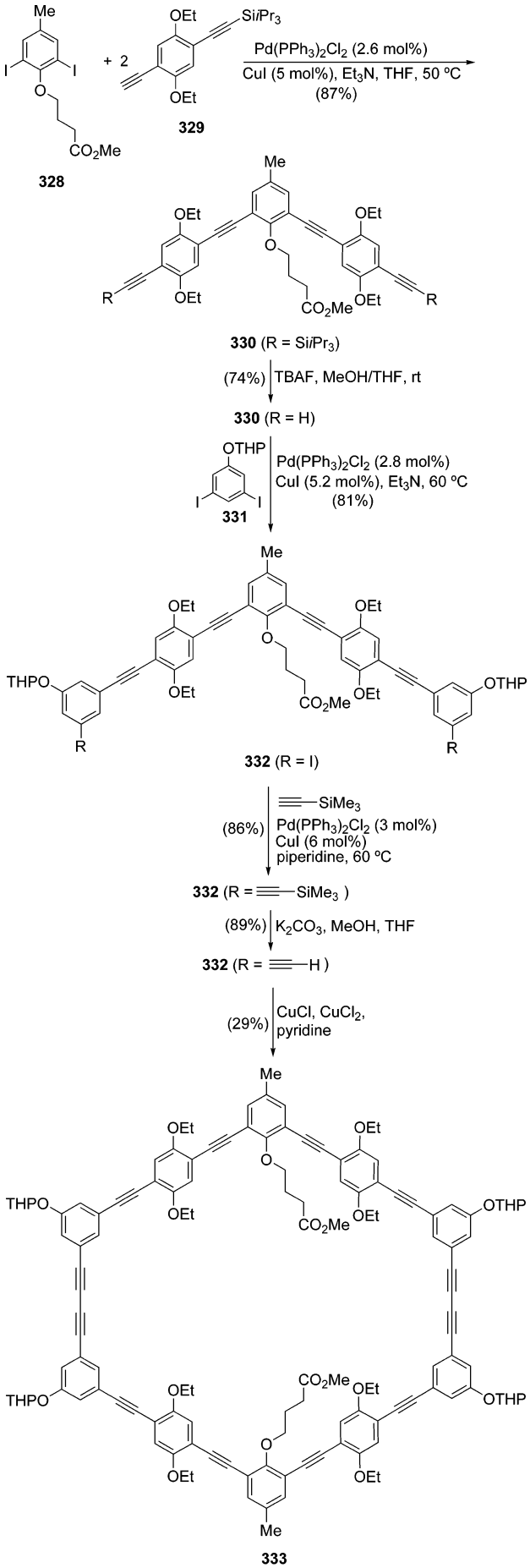
The Sonogashira cross-coupling reaction has obviously found a clear field of application in the preparation of these types of systems, with some recent examples being mentioned in this section. Thus, the most simple of these benzodehydroannulenes, tribenzohexadehydro[12]annulene, and some derivatives such as **327** have been prepared by cyclotrimerization of iodoalkyne **326** under Sonogashira conditions in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$) (Scheme 95).[497a] It is interesting to note that, under these reaction conditions, the amount of copper(I) iodide could be reduced to 1 mol %, therefore minimizing homocoupling. The reaction under the same conditions but in THF as solvent afforded just traces of the final product **327**. Related phenylene ethynylene cyclic trimers have also been recently prepared in high yields by alkyne metathesis from Sonogashira reaction-prepared acyclic precursors.[497b]

Scheme 95



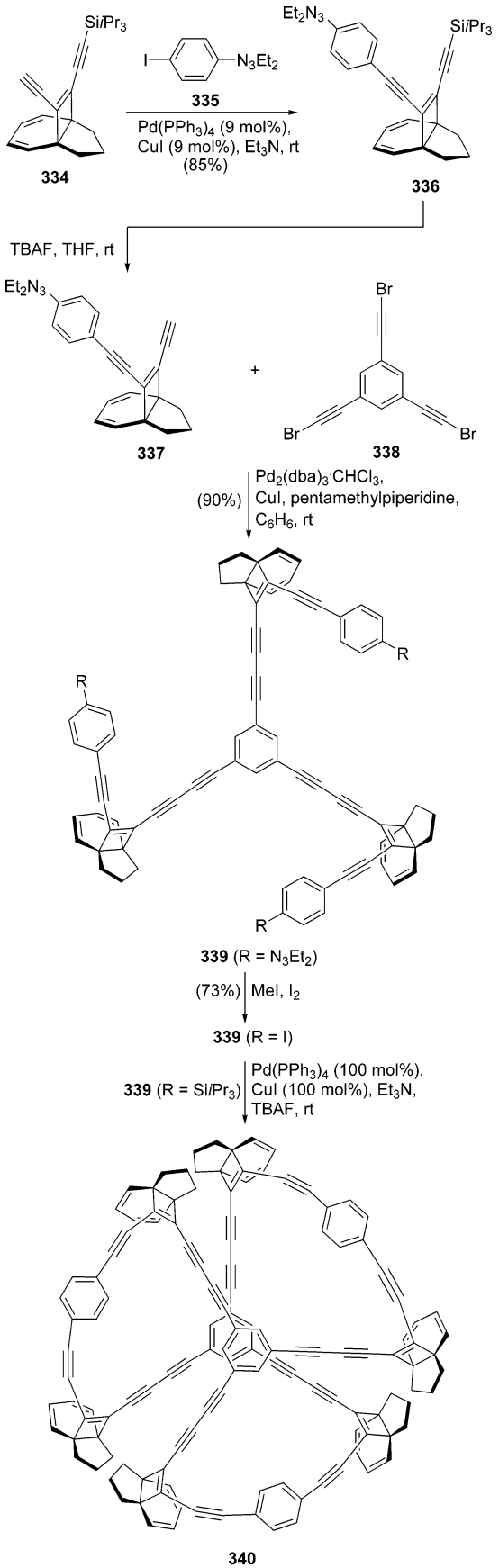
Macrocycles such as **333** have been prepared by several consecutive Sonogashira couplings and a final copper-mediated Glaser reaction. Thus, when diiodide **328** reacted with an excess of monosilylated dialkyne **329**, the tetraacetylene **330** was obtained. This compound was desilylated and coupled to iodide **331**, affording pentaarylated compound **332** (Scheme 96).[498] This derivative reacted with TMSA under Sonogashira conditions to give a hexaalkynylated derivative which was deprotected and suffered double homocoupling in the presence of copper(I) to give macrocycle **333**. External oligo-alkyl groups can be incorporated to this structure **333**, thus exhibiting stable liquid crystalline phases with a columnar order of the molecules. Other recent illustrative examples of the application of the palladium−copper promoted cross-coupling alkynylation reaction to the synthesis of related phenylene−acetylene macrocycles,[499] the asymmetric synthesis of macrocyclic binaphthol dimers,[500a] and the synthesis of phenylenebis(ethynyl)-tethered bis-BINOL ligands[500b] can be found. In addition, the Sonogashira coupling has been employed recently for the connection of an iodinated pyrimidinone to 34- or 36-crown-10 for the

Scheme 96



selective self-assembly of some hydrogen-bonded heterotrimers,[501] and for the alkynylation of dibenzo-24-crown-8 ethers for complexation studies.[502]

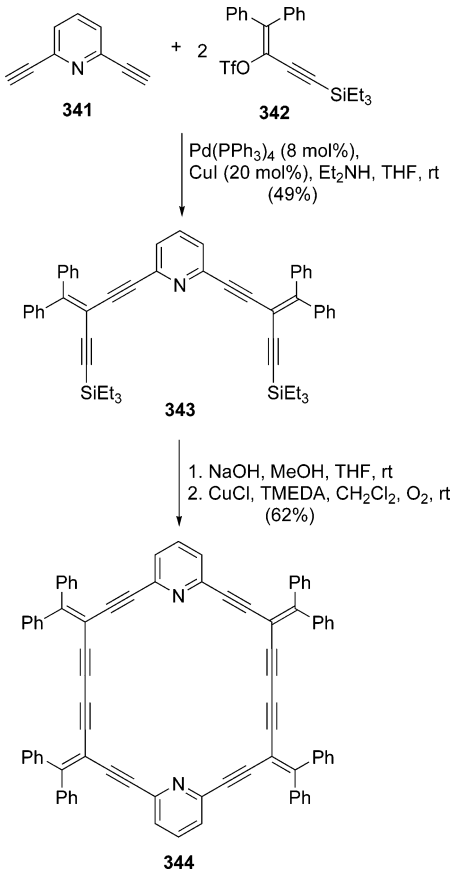
Scheme 97



Other recent examples of the Sonogashira reaction applied to the preparation of arylene−acetylene macrocycles containing substructures such as copper−cyclobutadiene complexes,[503] cyclopentadienes,[504] allenes,[505] and enediynes[506] can also be found. An example of the latter type is the synthesis of multicyclic cagelike cyclobutene-containing structure **340**, which has been prepared after Sonogashira cross-coupling reaction of diethynylpropellane derivative **334** with diethyl(4-iodophenyl)triazene (**335**) (Scheme 97). Subsequent silyl deprotection and coupling reaction of the obtained compound **337** with tris(bromoethynyl)benzene (**338**) gave the triad **339**. Subsequent transformation of the triazene to an iodo group gave **339** (R = I). The final Sonogashira cross-coupling reaction of this compound with an in situ generated terminal alkyne derived from **339** (R = Si*i*Pr$_3$) by removal of the triisopropylsilyl group yielded the multicyclic system **340**, which, after indane expulsion produced by laser irradiation, gave anions of C_{78} fullerene.[507] In this last reaction, stoichiometric amounts of the palladium catalysts and copper cocatalyst were used due to the small scale employed.

Heterocycles have also been incorporated to arylene−acetylene macrocycles. For instance, dehydropyridoannulene-type cyclophanes with metal ion binding sites have been obtained, with the Sonogashira reaction being a key step in their preparation.[508] In addition, 2,6-diethynylpyridine-containing macrocycles incorporating *gem*-enediyne moieties have been prepared, as shown in Scheme 98, where dialkynylated pyridine **341** reacted with 2 equiv of diphenylvinylidene-substituted triflate **342** under Sonogashira conditions, leading to oligomer **343**. Subsequent silyl deprotection and copper-catalyzed homocoupling afforded macrocycle **344**.[509] Other examples of the use of the Sonogashira reaction

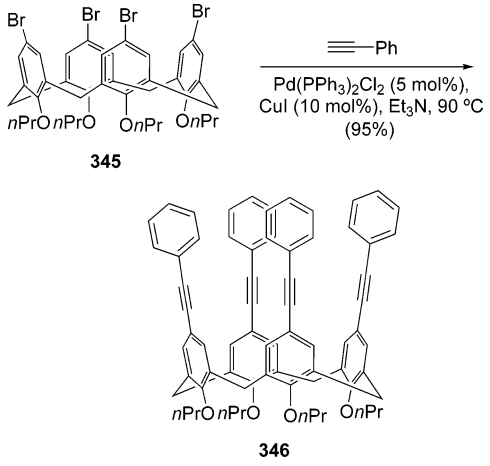
Scheme 98



in the preparation of arylene−ethynylene macrocycles containing amide[510] or thioether[511] moieties can recently be found, as well as in the synthesis of indole-based macrocycles,[512] polyenine macrocycles,[513] and indolophanetetrayne and indolophanehexayne cobalt complexes.[514] In addition, planar metallocyclophanes,[515] star-shaped ruthenium complexes,[516] or arylalkyne-linked metalloporphyrins for supramolecular assemblies[517] have also being obtained.

Calix[4]arenes fixed in the *cone* conformation are structures able to bind cations in their bowl shaped cavity. The creation of a relatively deep π-electron-rich cavity in the upper rim of calix[4]arenes has recently been performed by a fourfold Sonogashira cross-coupling reaction of tetrabrominated calixarene **345** and phenylacetylene to give tetraalkynylated calixarene **346** (Scheme 99).[518] Similarly, they

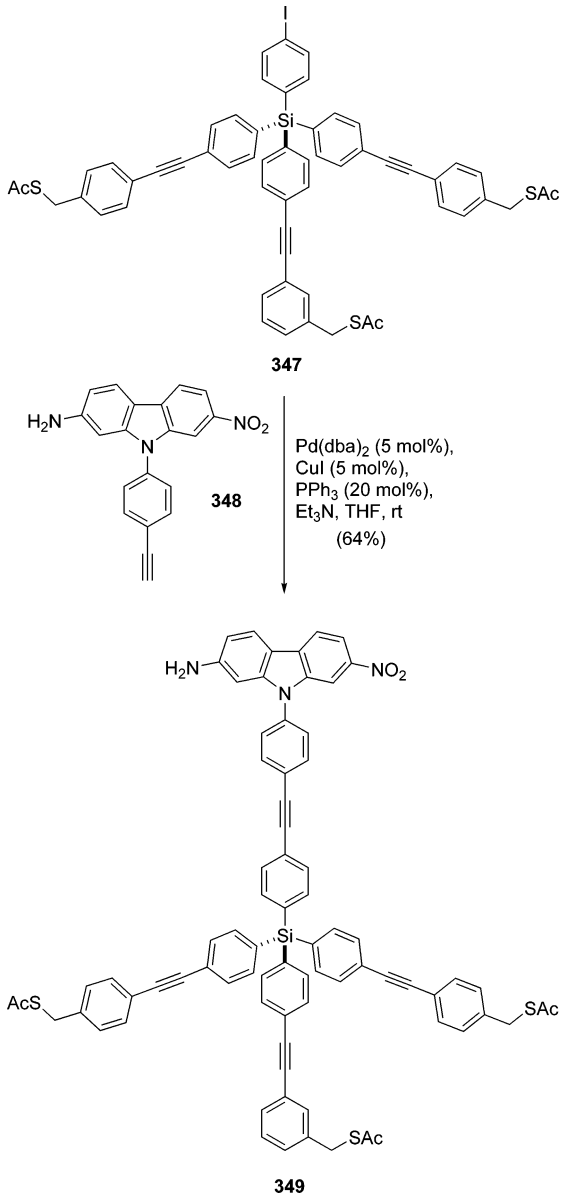
Scheme 99



have incorporated different pyridinylacetylenes,[518] studying the ability of the formed calix[4]arenes for binding pyridinium salts. In addition, other tetraalkynylated calix[4]arenes with advanced NLO properties have been prepared in the same way,[519] as well as OPE-derived calix[4]arenes[520] and lower rim alkynylated calix[4]arenes.[521] Moreover, the Sonogashira reaction has been employed in the derivatization of calix[8]arenes[522] or the alkynylation of calix[5]arenes for fullerene encapsulation.[523] Furthermore, dipyrrolidineboron difluoride dye pairs have been incorporated to resorcin[4]-arene cavitand based molecules by means of Sonogashira reaction-created OPE arms, obtaining molecular switches with multinanometer expansion/contraction motion,[524] and also OPE arms have been used for the attachment of carbon nanotubes to silicon surfaces.[525] This alkynylation procedure has also been used for the synthesis of β-cyclodextrin-based cluster mannosides.[526]

Caltrop-shaped molecules that could be used as surface-bound electric field-driven molecular motors have been obtained using the Sonogashira coupling as key reaction. Thus, the cross-coupling reaction of iodinated tetrathioloacetate **347** and carbazole derivative **348** (both incorporating acetylene moieties generated also by Sonogashira alkynylation) gave compound **349** (Scheme 100).[527] This molecular caltrop can assemble upright on a gold surface in the form of self-assembled monolayers, using the deprotected thiols as adhesion units, whereas the carbazole upper part bearing donor−acceptor groups can be controllable when electric fields are applied, thereby constituting a field-driven motor. Other related nanoscale molecular caltrops,[528] tripodal OPEs,[529] and tripodal tri-[530] and tetrasubstituted[531] adamantanes have

Scheme 100



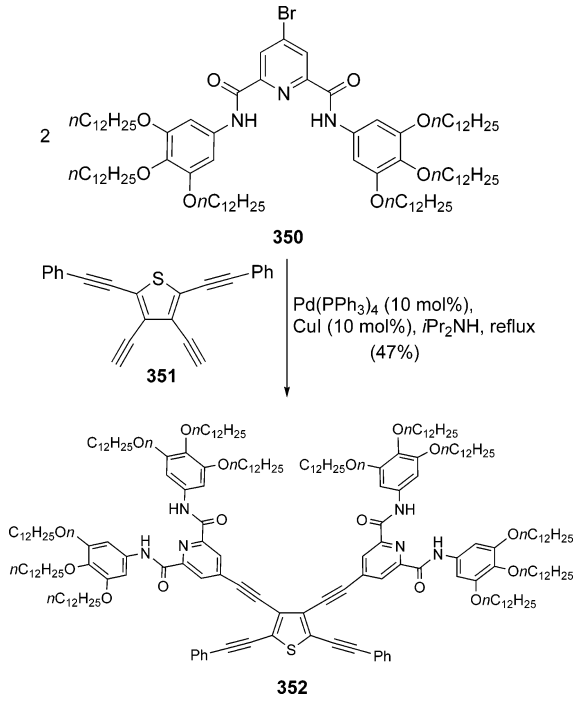
been recently prepared and used as single-molecule atomic force microscopy tips for imaging surfaces using Sonogashira reactions, as well as for photoinduced electron transfer[532] or ultrafast electron injection.[533] The synthesis of tripodal Sonogashira-obtained phenylacetylene compounds containing boroxine cores has also been accomplished.[534]

Amide-functionalized phenylethynylthiophene **352** has been prepared by Sonogashira cross-coupling reaction between 2 equiv of brominated pyridine dicarboxamide **350** and tetraalkynylated thiophene **351**, previously obtained from tetrabromothiophene by two consecutive Sonogashira couplings using phenylacetylene and TMSA (Scheme 101).[535] The resulting thiophene **352** has been used as a gelator to immobilize organic solvents via the cooperative effect of noncovalent interactions (hydrogen bonding, $\pi-\pi$ stacking, donor−acceptor) and Van der Waals interactions, with structural studies revealing the formation of fiberlike nanostructures.

5. Conclusions

This review has intended to illustrate how the Sonogashira alkynylation reaction is nowadays a key cross-coupling

Scheme 101



methodology with growing applications to many different areas of chemistry and material sciences. As the discovery of new products of interest available through this procedure increased, the search for more convenient reaction conditions increased dramatically in the last few years. Thus, the typical reaction conditions involving the use of commercial palladium complexes as catalysts in rather high amounts, accompanied by the addition of even larger amounts of a copper cocatalyst plus the use of an excess of an amine as base and high temperatures, made this reaction rather unfriendly from an economical and environmental point of view. After reading the first part of this review, where plenty of palladium ligands and palladium-containing species employed as catalysts are shown, it is easy to notice the considerable achievements made by creating more active catalysts which can perform the Sonogashira coupling under really low catalyst loadings, as is the case, for instance, for the new developed palladacycles. The increase in the reactivity of the catalysts has allowed coupling procedures which work in the absence of copper cocatalysis and has even made the presence of an amine and a phosphane unnecessary. These copper- and amine-free procedures can be driven closer to environmental perfection when aqueous solvents or even neat water are employed, with some quite simple palladium species such as palladium(II) chloride being found to work especially well in aqueous media. Moreover, the possibility of recycling the catalysts is particularly interesting for industrial purposes, and this review has shown the profuse search in the last few years for supported palladium catalysts able to add recyclability and no metal leaching to the former advantages.

Paralleling all these recent developments and improvements have been discussions about the real nature of the catalyst performing the cross-coupling reaction. It seems that many of these new catalysts are in fact just precatalysts, with nanoparticles formed after their decomposition being the real catalytic species, which open new possibilities for reactivity based on their higher or lower stabilization. Taking into account that the reaction probably not only takes place on the rim of the nanoparticle but also involves solubilized palladium species, the full understanding of the reaction mechanism still remains an open question.

In spite of these considerable improvements made to the Sonogashira procedure by using new catalysts and reaction conditions, it is rather surprising that the practical applications of these procedures have been so limited. Thus, from this review it is easy to notice that the old, typical copper cocatalyzed Sonogashira procedure is still being employed almost exclusively for all kinds of synthetic purposes. The new methodologies are probably so recent that there has still not been enough time to show their real synthetic possibilities. There is no doubt that, in a few years, an increasing number of synthetic applications using the more effective of these methods will be reported.

Although many advances dealing with the Sonogashira reaction have been made in the last few years, there is still a long way to go before achieving the ideal procedure. Many improvements are still necessary in order to fully develop general coupling procedures which allow good results regardless of the halide system used and maintaining very low catalyst loadings, low temperature, and clean reaction conditions as well as allowing catalyst recyclability. With all these challenges still present in the battlefield and with the growing interest in the products that could be obtained, it is certain that the Sonogashira reaction will still continue to be a fast-moving topic for the next several years.

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7. References

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