

Chemicals from Alkynes with Palladium Catalysts

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
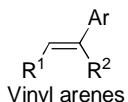
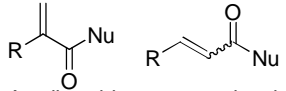
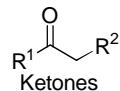
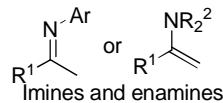
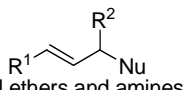
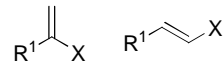
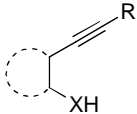
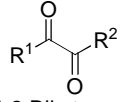
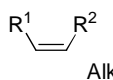
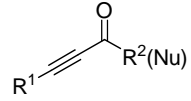
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1. Introduction

The carbon-carbon triple bond of alkynes is one of the basic functional groups, its reactions belonging to the foundations of organic chemistry. In the past decades, acetylene chemistry has experienced a renaissance due to, not only its occurrence in molecules in the frontiers of organic chemistry such as biochemistry or material sciences, but also as building blocks or versatile intermediates for the synthesis of a vast array of chemicals.¹ This boost to the alkyne chemistry has been fueled mainly by the development of new synthetic methodologies based on transition metal catalysis, a field where palladium always occupies a leading position.

This review presents an overview of the use of alkynes as starting materials for the preparation of compounds, using procedures carried out under palladium catalysis. Many different reactions leading to many different chemicals could be included in such a review, and trying to cover all possibilities and particularities in a fully comprehensive way would be an overwhelming task. Thus, this review will present coverage of the main palladium-catalyzed reactions of alkynes leading to different chemical compounds, ordered by reaction type and chemical class. The 'alkynes' involved as starting materials in this review will only be those containing H or C-substituted carbon-carbon triple bonds. Therefore, palladium-catalyzed couplings involving alkynyl metals or other non-strictly considered alkyne-hydrocarbons, such as 1-haloalkynes, will be excluded. A summary of the transformations considered in this review is shown in Table 1. Only 'direct' reactions of alkynes will be shown, the preliminary transformation of the acetylene into an intermediate followed by a palladium-promoted conversion being not considered, as well as multi-step processes such as hydro/carbo-metalation-coupling sequences. When previous reviews of a particular palladium-catalyzed topic exist, significant or relevant methodologies, as well as the most recent examples will be presented.

Table 1. Summary of the palladium-catalyzed transformations of alkynes presented in this review.

Alkyne + Other component	Reaction type	Product	Section
$R^1\text{---}R^2$ (or + $o\text{-TfOC}_6\text{H}_4\text{SiMe}_3$ or + ArH) $R^1, R^2 = \text{H, Alkyl, Ar}$	Intermolecular addition	Aromatics and polyaromatics	2.1
$R^1\text{---}R^2$ +  $X = \text{Cl, Br, I; Z = OH, NH}_2, \text{NHR, CO}_2\text{R, CONHR}$ $R^1, R^2 = \text{Alkyl, Ar, Het}$		Heterocycles	2.2
$R^1\text{---}R^2$ + ArX ($X = \text{H, Hal, B(OH)}_2, \text{N}_2^+\text{X}$) $R^1, R^2 = \text{H, Alkyl, Ar, CO}_2\text{R, COR}$		 Vinyl arenes	2.3
$R\text{---}$ + CO, NuH ($\text{Nu} = \text{OH, RO, NR}_2$) $R = \text{Alkyl, Ar, Het}$		 Acrylic acids, esters and amides	2.4
$R^1\text{---}R^2$ + H_2O $R^1, R^2 = \text{H, Alkyl}$		 Ketones	2.5
$R^1\text{---}$ + ArNH_2 or HNR_2^2 $R^1 = \text{Alkyl, Ar}$		 Imines and enamines	2.7
$R^1\text{---}R^2$ + NuH ($\text{Nu} = \text{OR, NR}_2$) $R^1 = \text{Alkyl, Aryl; R}^2 = \text{H, Alkyl, Aryl}$		 Allyl ethers and amines	2.6, 2.7
$R^1\text{---}$ + XH ($X = \text{R}^2\text{S, R}^2\text{Se, R}_2\text{P(O), ROP(O)R}^1, \text{ROP(O)H, R}_2\text{P(O)}$) $R = \text{Alkyl, Ar, Het}$		 Vinyl sulfides, selenides, phosphines, phosphine oxides and phosphonates	2.8, 2.9
 $R = \text{H, Alkyl, Ar, Het}$ $X = \text{CZ}_2, \text{NH, NR, OH, CO, CO}_2$	Intramolecular addition	Carbocycles and heterocycles	3.1, 3.2
$R^1\text{---}R^2$ + oxidant $R^1, R^2 = \text{Alkyl, Ar, Het}$	Oxidation	 $R\text{---CO}_2\text{Me}$ 1,2-Diketones Methyl esters	4.1, 4.2
$R^1\text{---}R^2$ + H_2 (or hydrogen donor) $R^1, R^2 = \text{H, Alkyl, Ar, Het}$	Reduction	 Alkenes	5
$R^1\text{---}$ + X-R^2 or H-Het $R^1 = \text{Alkyl, Ar, Het}$ $R^2 = \text{Alkenyl, Ar, Het}$ $X = \text{Cl, Br, I, OTs}$	C-C Coupling	$R^1\text{---}R^2(\text{Het})$ Alkynes and 1,3-enynes	6.1, 6.2, 6.3
$R^1\text{---}$ + $\text{---}R^1$ or $\text{X---}R^2$ $R^1, R^2 = \text{Alkyl, Ar, Het}$ $X = \text{Br, I}$		$R^1\text{---}R^1(R^2)$ 1,3-Diynes	6.4
$R^1\text{---}$ + R^2COCl (or $\text{CO} + \text{R}^2\text{Hal}$) + $\text{CO} + \text{NuH}$ ($\text{Nu} = \text{OR, NR}_2^2$) $R^1, R^2 = \text{Alkyl, Ar, Het}$		 Yrones, ynoates and ynamides	6.5, 6.6

2. Chemicals by Palladium-Catalyzed Intermolecular Additions to Alkynes

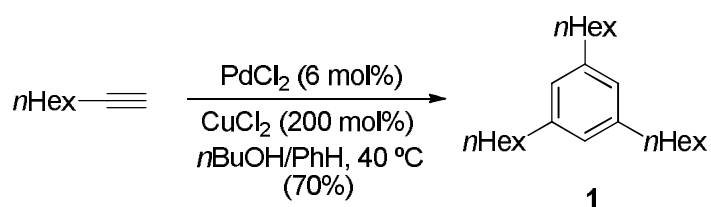
The formal intermolecular addition reaction involving only the carbon atoms of an alkyne system is an approach which can lead directly to the synthesis of carbocyclic systems, a process which can be achieved under palladium-catalysis. In addition, the palladium-catalyzed intermolecular annulation of alkynes with halogenated heteroatom-bearing systems is also a formal addition to alkynes which leads to heterocycles. Other intermolecular additions to alkynes can be achieved under palladium-catalysis, as hydroarylation, hydrocarbonylation or the addition of heteroatomic nucleophiles to alkynes, a practical way of preparing a large variety of alkene-bearing chemicals, once the adequate regio- and stereocontrol are achieved. This section will present examples of carbocycles and heterocycles obtained by all these approaches, as well as a survey of chemicals obtained by palladium-catalyzed intermolecular addition of C, N, O, S, Se and P nucleophiles to alkynes.

2.1. Carbocycles

The transition metal-catalyzed conversion of internal and terminal alkynes to substituted benzene derivatives by a cyclotrimerization process is an old procedure which has also been achieved using palladium species as catalysts.² The process has been traditionally considered to occur via coordination of two alkyne moieties to the metal, coupling reaction giving a metallacyclopentadiene, and further insertion or addition of an alkyne to the metallacycle giving a six-carbon metalacycle which forms the benzene ring after reductive elimination.² Thus PdCl_2 ³ and $\text{PdCl}_2(\text{PhCN})_2$ ⁴ catalyze the cyclotrimerization of alkynes to benzene derivatives, the yields generally depending on the alkyne substituents, as regioisomers are normally obtained in the case of unsymmetrical acetylenes. However, it has been shown that the addition of CuCl_2 (200 mol%) to the reaction mixture, not only increases the yield of the process, as discovered in the case of the PdCl_2 -catalyzed cyclotrimerization of oct-4-yne to give 1,2,3,4,5,6-hexapropylbenzene,⁵ but also induces regiospecificity in the process. Thus, unsymmetrical alkynes, such as oct-1-yne, were cyclotrimerized regiospecifically to benzene derivatives such as **1** under PdCl_2 catalysis (6 mol%) in the presence of CuCl_2

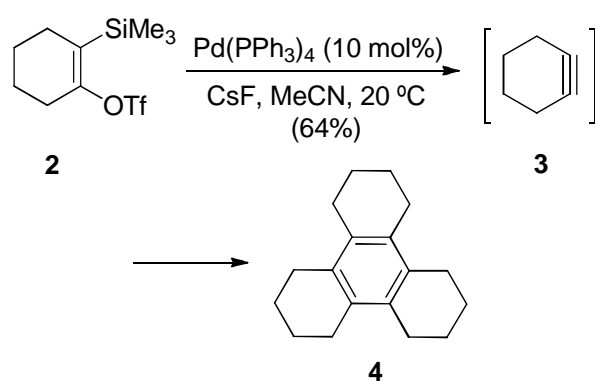
and a mixture of *n*-butanol/benzene as solvent at 40 °C (Scheme 1),⁶ diphenylacetylene affording no reaction. In addition, the presence of carbon dioxide was found to favor this PdCl₂-catalyzed/CuCl₂-assisted process when performed in water.⁷ Moreover, the reaction has also been carried out in supercritical carbon dioxide.⁸

Scheme 1



The palladium-catalyzed cyclotrimerization was also applied to strained cycloalkynes.⁹ For instance, Pd(PPh₃)₄ (10 mol%) catalyzed the cyclotrimerization of cyclohexyne (**3**), generated in situ by a fluoride-induced β-elimination in trimethylsilylated triflate **2**, to dodecahydrotriphenylene **4** in 64% yield (Scheme 2), but subjecting cyclopentyne to the same conditions failed to afford isolable amounts of the cyclotrimer.¹⁰

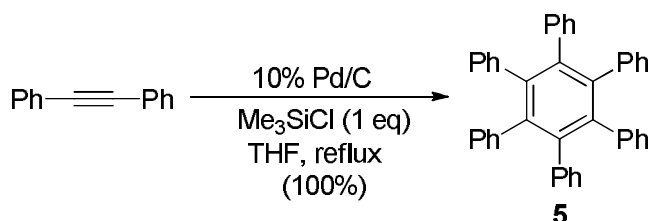
Scheme 2



This cyclotrimerization reaction can also be performed using non-soluble palladium reagents as catalysts. Thus, the transformation of acetylene into benzene¹¹ has been catalyzed by alumina-supported palladium¹² and Pd(111) single crystals.¹³ In addition, the trimerization of alkynes has also been achieved using 10% Pd/C as catalyst in the presence of trimethylsilyl chloride, which is suggested to form highly dispersed

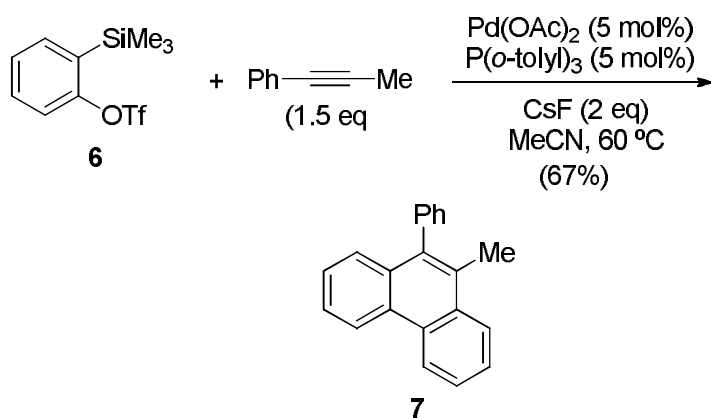
palladium nanoparticles (PdNPs), in refluxing THF.¹⁴ Under these conditions, symmetrical alkynes such as diphenylacetylene gave quantitatively the corresponding hexasubstituted benzene **5** (Scheme 3), whereas unsymmetrical alkynes gave mixtures of regioisomers.

Scheme 3



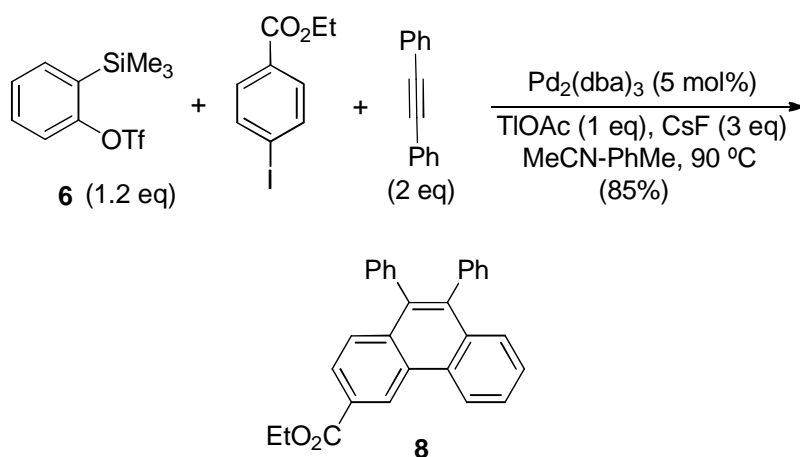
Alkynes have been co-trimerized with arynes under palladium catalysis to give different arenes.¹⁵ For example, co-cyclization of electron-deficient alkynes and arynes afforded phenanthrene derivatives when catalyzed by $\text{Pd}(\text{PPh}_3)_4$, whereas naphthalene derivatives were obtained under $\text{Pd}_2(\text{dba})_3$ catalysis (dba = dibenzylideneacetone).¹⁶ In addition, the co-trimerization of internal alkynes with benzyne, obtained in situ similarly than in the former case by fluoride-mediated triflic acid elimination in the corresponding arene **6**, has been carried out using the combination $\text{Pd}(\text{OAc})_2$ (5 mol%) and $\text{P}(o\text{-tolyl})_3$ (5 mol%) as catalyst, in acetonitrile as solvent at 60 °C, as exemplified in the formation phenanthrene **7** from phenylmethylacetylene (Scheme 4).¹⁷

Scheme 4



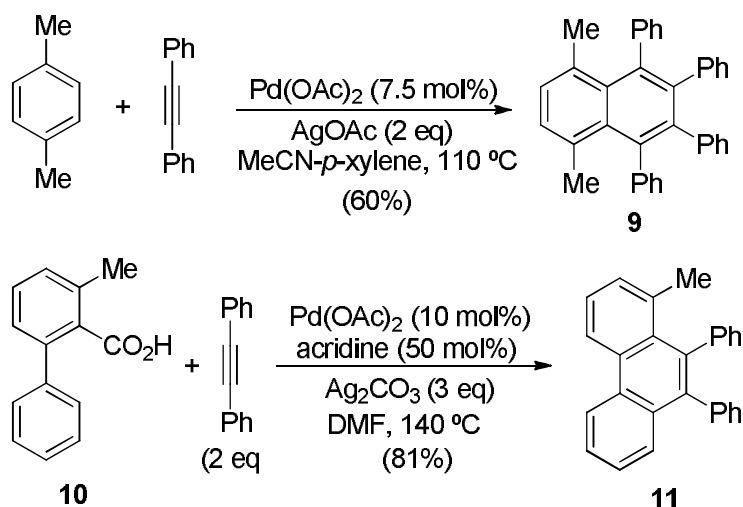
Benzynes have been generated as above and react with internal alkynes in the presence of an aryl iodide to give substituted phenanthrenes under $\text{Pd}_2(\text{dba})_3$ catalysis (5 mol%). An example of this methodology is the 3-components reaction of the generated benzyne from **6** with diphenylacetylene and ethyl 4-iodobenzoate to give phenanthrene **8**, the process being carried out in the presence of equimolecular amounts of TIOAc in a mixture of acetonitrile/toluene as solvent at 90 °C (Scheme 5).¹⁸ In addition, a recent example of the use of arynes in these co-trimerization processes generates benzyne from benzoic acid in the presence of $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2$, which co-cyclizes with diphenylacetylene to give the corresponding phenanthrene if an excess of benzoic acid is added, or 1,2,3,4-tetraphenylnaphthalene if diphenylacetylene is present in excess.¹⁹

Scheme 5



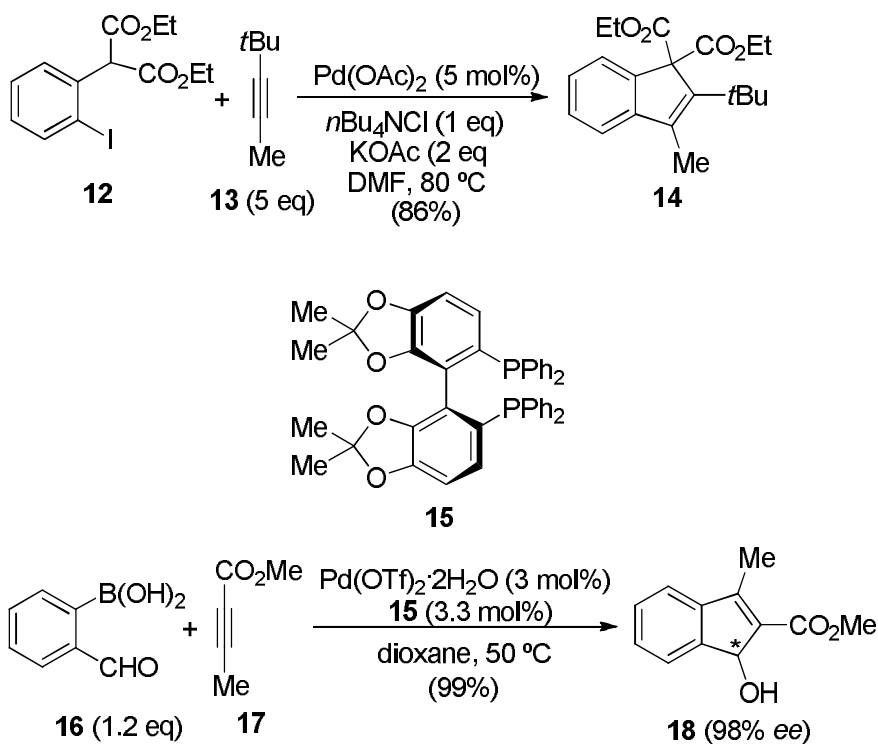
Palladium-catalyzed oxidative carbocyclization processes are interesting routes for the preparation of highly substituted arenes.²⁰ For example, highly substituted naphthalenes have been obtained by treatment of arenes, such as *p*-xylene, with diarylated alkynes, such as diphenylacetylene, using $\text{Pd}(\text{OAc})_2$ as catalyst and AgOAc as oxidant in acetonitrile/*p*-xylene as solvent at 110 °C, to afford naphthalene **9** (Scheme 6).²¹ *N*-Arylated acetamides have also been used as arene counterparts in this reaction leading to naphthalenes, using $\text{K}_2\text{S}_2\text{O}_8$ as oxidant in the presence of *p*-toluenesulfonic acid in toluene as solvent at 80 °C.²² In addition, 2-phenylbenzoic acids have been annulated with disubstituted alkynes in a decarboxylative approach catalyzed by $\text{Pd}(\text{OAc})_2$ (10 mol%),²³ using acridine as ligand (50 mol%) and silver carbonate as oxidant, in DMF at 140 °C, as exemplified in Scheme 6 with the annulation of acid **10** and diphenylacetylene leading to phenanthrene **11**.

Scheme 6



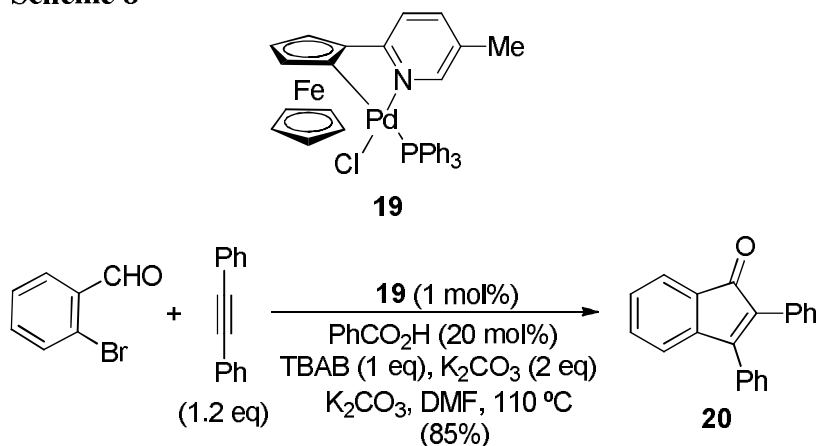
Highly substituted indenes have been obtained by palladium-catalyzed carboannulation of internal alkynes using appropriately functionalized aryl halides,²⁴ the operating mechanism being considered similar to the one suggested for the formation of heterocycles (see Section 2.2). Thus, iodinated arenes bearing highly acidic hydrogens such as **12** reacted with internal alkynes such as **13** under Pd(OAc)₂ catalysis (5 mol%), in the presence of *n*Bu₄NCl and KOAc, to give indenes such as **14** with high regioselectivity (Scheme 7), which is probably due to the steric hindrance present in the developing C-C bond. In addition, enantiomerically enriched indenols have been obtained by a Pd(OTf)₂·2H₂O (3 mol%)-promoted tandem [3+2] annulation of 2-acylarylboronic acids with internal electron-deficient alkynes employing the chiral biarylphosphine **15** as ligand (3.3 mol%).²⁵ An example of this asymmetric transformation is shown in the preparation of optically active indenol **18** from formylated boronic acid **16** and propynoate **17** (Scheme 7).

Scheme 7



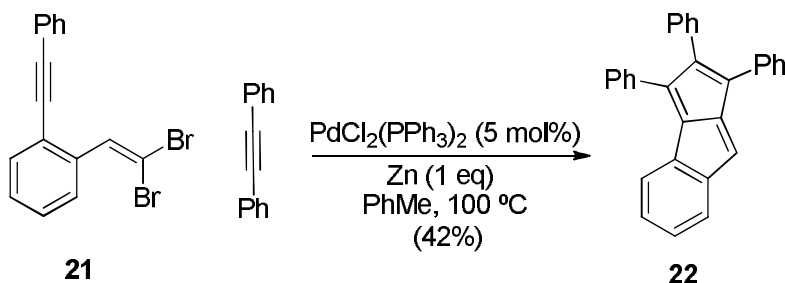
2,3-Disubstituted indenones can be obtained directly by palladium-catalyzed reaction of internal alkynes and *o*-halobenzaldehydes, a synthetic procedure that can be carried out using Pd(OAc)₂ as catalyst (5 mol%).²⁶ More recently, palladacycles have also been used successfully as catalysts for this transformation,²⁷ as exemplified in the reaction of 2-bromobenzaldehyde and diphenylacetylene to give indenone **20** (Scheme 8), a process catalyzed by cyclopalladated ferrocenylimine **19** (1 mol%) in the presence of potassium carbonate as base and a mixture of tetra-*n*-butylammonium bromide (TBAB)/benzoic acid as additive, in DMF at 110 °C.²⁸

Scheme 8



Monoannulated pentalenes have been prepared by a cascade carbopalladation reaction between alkynes and *gem*-dibromoolefins.²⁹ The reaction is catalyzed by PdCl₂(PPh₃)₂ (5 mol%) in the presence of zinc dust in toluene as solvent at 100 °C and allow the direct preparation of pentalenes in moderate yield, as exemplified in Scheme 9 with the synthesis of pentalene **22** from dibrominated olefin **21** and diphenylacetylene.

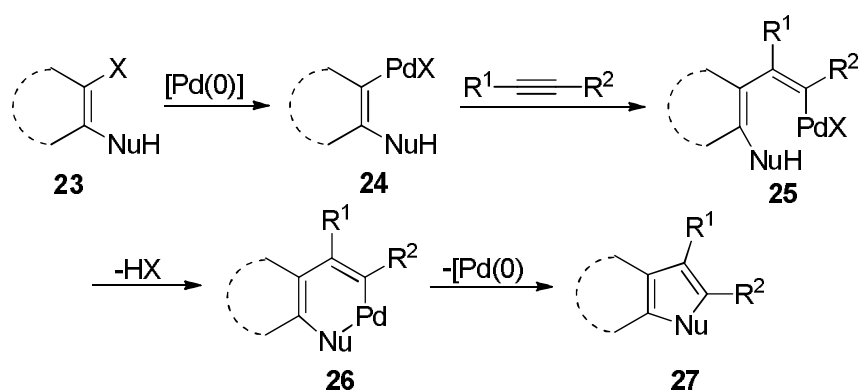
Scheme 9



2.2. Heterocycles

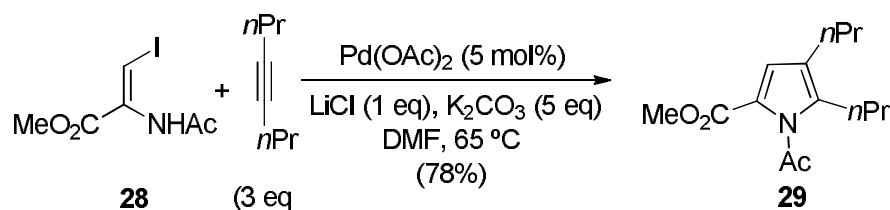
The palladium-catalyzed intermolecular annulation of alkynes is particularly effective for the synthesis of a variety of heterocycles.³⁰ The reaction usually takes place starting from an aryl or vinyl halide bearing a neighboring nucleophile **23** which is oxidatively palladated to **24**. After subsequent *cis* carbopalladation of the alkyne leading to **25**, the internal nucleophile may affect intramolecular displacement of the palladium towards heterocycle **27**, probably by prior formation of a palladacycle **26** and reductive elimination (Scheme 10).^{30b}

Scheme 10



An example of application of this heterocyclic synthesis is the preparation of highly substituted pyrroles, such as **29**, by reaction between stabilized iodoenamines, such as **28**, with internal alkynes, the reaction being catalyzed by $Pd(OAc)_2$ (5 mol%) in the presence of $LiCl$ as additive and potassium carbonate as base in DMF at 65 °C (Scheme 11).³¹

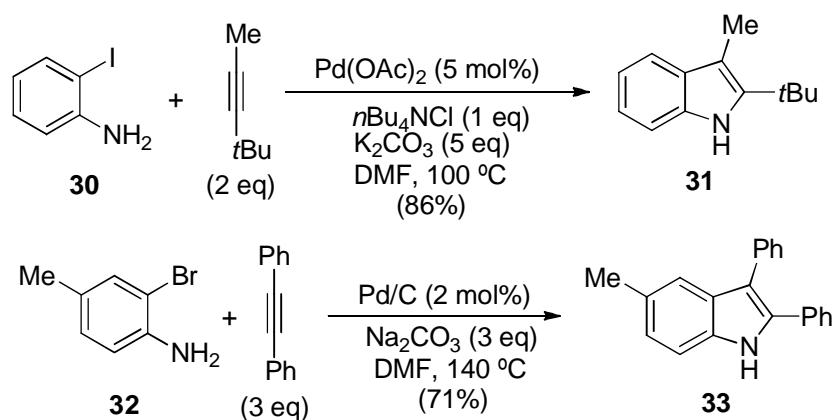
Scheme 11



The indole skeleton is one of the most important in the world of heterocycles due to their presence in a huge number of interesting biologically active systems, and their synthesis via palladium-catalyzed reactions has been particularly intense.^{30b,30d,32} Among the developed methodologies, the intermolecular palladium-catalyzed reaction of *o*-iodoaniline derivatives with internal alkynes (Larock's intermolecular indole synthesis) was shown as a powerful procedure for the preparation of 2,3-disubstituted indoles from alkynes.³³ Thus, in the presence of a catalytic amount of $Pd(OAc)_2$ (5 mol%), a source of chloride anions (nBu_4NCl or $LiCl$) and a base such as potassium carbonate or acetate in DMF at 100 °C, *o*-iodoaniline derivatives add formally to internal alkynes to give 2,3-disubstituted indoles, as exemplified in Scheme 12, with the preparation of indole **31** from iodoaniline **30** and 4,4-dimethylpent-2-yne.^{33b} As observed, the more sterically hindered group on the alkyne results normally attached at

position C-2 of the indole. This process has also been carried out using oxime-derived palladacycles using only 1 mol% of the catalyst, potassium carbonate as base in the presence of TBAB in DMF at 130 °C.^{27a} In spite of these strongly ionic conditions, which suggest the presence of charged palladium species, most mechanistic approaches for this reaction are based on neutral conditions. In addition, heterogeneous versions of this Larock annulation have been reported.³⁴ Thus, palladium (2 mol%) has been supported on NaY zeolite, which has allowed suppressing the presence of a chloride source and recycle the catalyst up to four times,^{34a} and on mesoporous silica SBA-15.^{34b} In addition, the use of Pd/C as catalyst (2 mol%) has allowed the preparation of indoles starting from less reactive *o*-bromoanilines, the reaction taking place in the presence of sodium carbonate as base, in DMF as solvent at 140 °C, as shown in Scheme 12 with the preparation of indole **33** from *o*-bromoaniline **32** and diphenylacetylene.^{34c} Moreover, other related systems such as 2,3-disubstituted 5-azaindoles have been recently obtained using this heteroannulation reaction between 4-acetamido-3-iodopyridines and internal alkynes under PdCl₂(PPh₃)₂ catalysis (5 mol%).³⁵

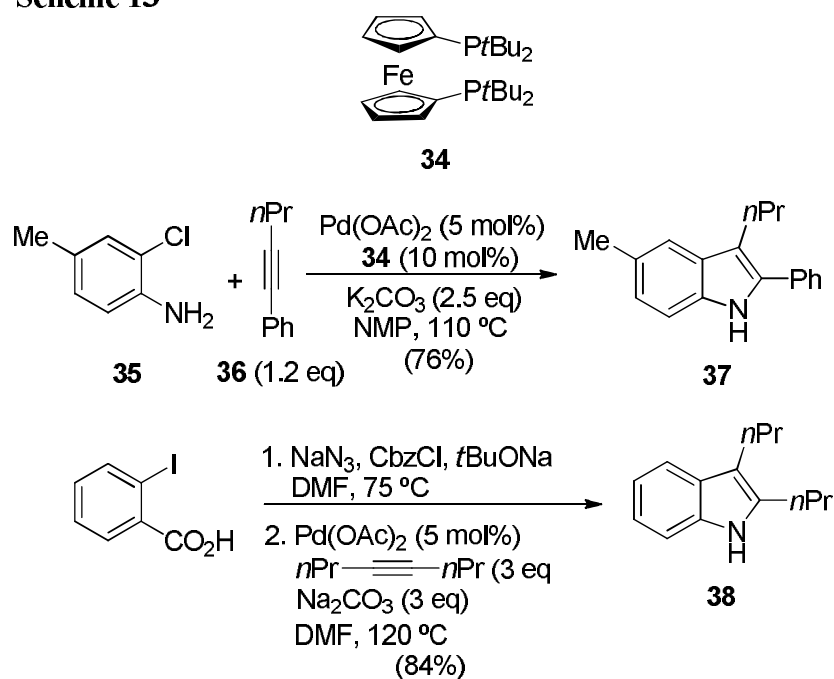
Scheme 12



Different procedures which enable the use of less reactive halogenated aniline derivatives or other halogenated systems as precursors in the former Larock indole synthesis have been developed.^{32e,f} Thus, *o*-bromo- or even *o*-chloroanilines, such as **35**, have been used in the intramolecular formal addition to internal alkynes, such as **36**, leading to indoles, such as **37** (91:9 regioisomer ratio), in a process catalyzed by a combination of Pd(OAc)₂ and the ferrocene-derived ligand **34** in the presence of potassium carbonate in NMP as solvent at 110 or 130 °C (Scheme 13).³⁶ In addition, an

example of other halogenated systems employed for this indole synthesis is the use of *o*-iodobenzoic acid, which has also been used as precursor in this type of reaction, following a one-pot Curtius rearrangement/palladium-catalyzed indolization with internal alkynes.³⁷ This methodology involves the reaction of *o*-iodobenzoic acid with sodium azide in the presence of benzyl chloroformate and sodium *tert*-butoxide, followed by reaction with the internal alkyne, such as oct-4-yne, under Pd(OAc)₂ catalysis (5 mol%), to give disubstituted indole **38** (Scheme 13). Moreover, indoles can also be obtained by the intermolecular reaction of simple non-halogenated anilines with electron-deficient alkynes by means of Pd(OAc)₂-catalyzed C-H activation using molecular oxygen as oxidant.³⁸

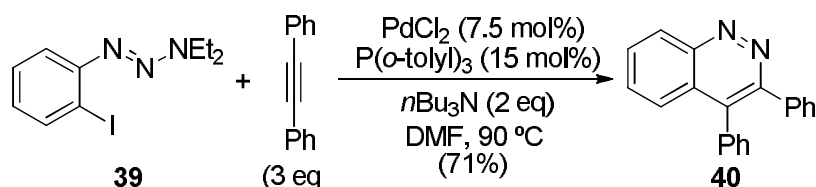
Scheme 13



Other more complex heterocycles have been obtained recently following this annulation scheme. Thus, pyrrole[1,2-*a*]quinolines have been obtained by palladium-catalyzed cyclization of iodopyranoquinolines and internal alkynes,³⁹ and cyclopentacarbazolones have been prepared from the annulation of 2-bromo-3-formylcarbazoles and internal alkynes under Pd(OAc)₂ catalysis.⁴⁰ In addition, 3,4-substituted cinnolines such as **40** have been obtained by annulation of 2-iodophenyltriazene **39** with diphenylacetylene, the reaction being catalyzed by a

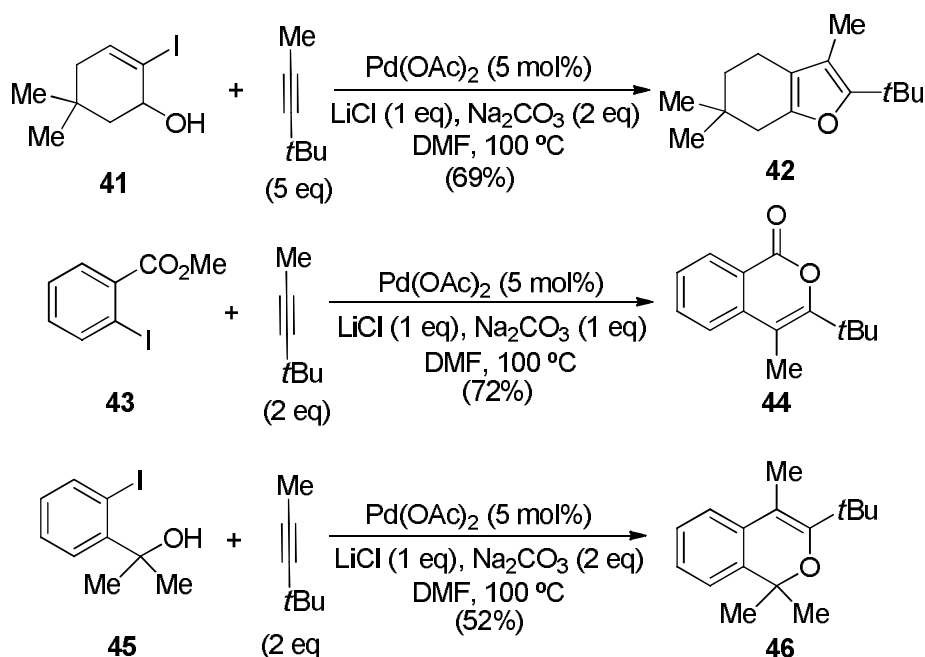
combination of PdCl₂ (7.5 mol%) and P(*o*-tolyl)₃ (15 mol%) in the presence of tri-*n*-butylamine as base in DMF at 90 °C (Scheme 14).⁴¹

Scheme 14



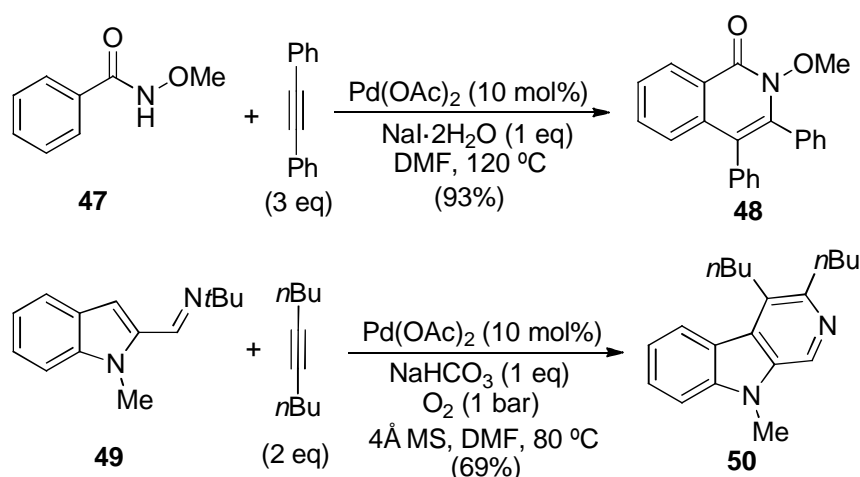
Oxygenated heterocycles can also be obtained using this intermolecular palladium-catalyzed coupling annulation strategy. For instance, the palladium-catalyzed heteroannulation of internal alkynes such as (3,3-dimethylbut-1-yn-1-yl)benzene by hydroxy-containing vinylic halides such as iodocyclohexenol **41** give rise to furan **42** after double bond isomerization, the process being carried out using a catalytic amount of Pd(OAc)₂ (5 mol%) in the presence of lithium chloride and sodium carbonate, in DMF at 100 °C (Scheme 15).⁴² This strategy, when performed using *o*-halogenated phenols and internal alkynes affords 2,3-disubstituted benzofurans,⁴³ as in the case of the above mentioned synthesis of indoles, although the process is more difficult and usually higher temperatures are required. Under these reaction conditions, 3,4-disubstituted isocoumarins and polysubstituted α -pyrones can be prepared regioselectively in good yields by treating halogen- or triflate-containing aromatic and α,β -unsaturated esters, respectively, with internal alkynes in the presence of a palladium catalyst,⁴⁴ as illustrated in Scheme 15 with the preparation of isocoumarin **44** by the reaction of *o*-iodinated benzoate **45** with 4,4-dimethylpent-2-yne. In addition, 1*H*-isochromenes such as **46** can be prepared from *o*-iodobenzyl alcohols such as **45** and an internal alkyne, using the same reaction conditions (Scheme 15).^{43a}

Scheme 15



Isoquinolinones can be prepared from *N*-methoxy- or *N*-isopropoxybenzamides and internal alkynes via a ligand-free palladium-catalyzed C-H and N-H activation.⁴⁵ The procedure is performed using $\text{Pd}(\text{OAc})_2$ as catalyst (10 mol%) in the presence of dihydrated sodium iodide as additive, in DMF at $120\text{ }^\circ\text{C}$, as illustrated in Scheme 16 with the synthesis of isoquinolinone **48** by reaction of benzamide **47** and diphenylacetylene. In addition, carbolines have been obtained by palladium-catalyzed iminoannulation of internal alkynes, using oxygen as the oxidant, as in the case of the synthesis of carboline **50** from the annulation of the *tert*-butylimine of *N*-substituted indole-2-carboxaldehyde **49** and dec-5-yne, promoted by $\text{Pd}(\text{OAc})_2$ (10 mol%) in the presence of sodium bicarbonate as base and TBAB in DMF at $80\text{ }^\circ\text{C}$, in the presence of molecular sieves (MS) and under an atmospheric pressure of oxygen (Scheme 16).⁴⁶ Similarly, β - and γ -carbolinones have been obtained by palladium-catalyzed direct dehydrogenative annulation of indolecarboxamides with internal alkynes using air as oxidant,⁴⁷ and benzazepines have been obtained by palladium-catalyzed oxidative cyclization of isatins and alkynes.⁴⁸

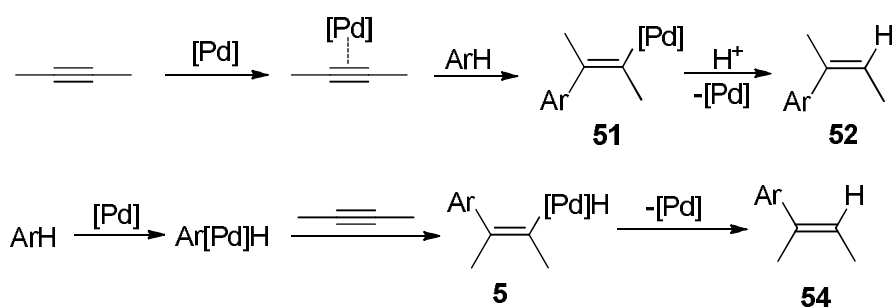
Scheme 16



2.3. Vinyl Arenes

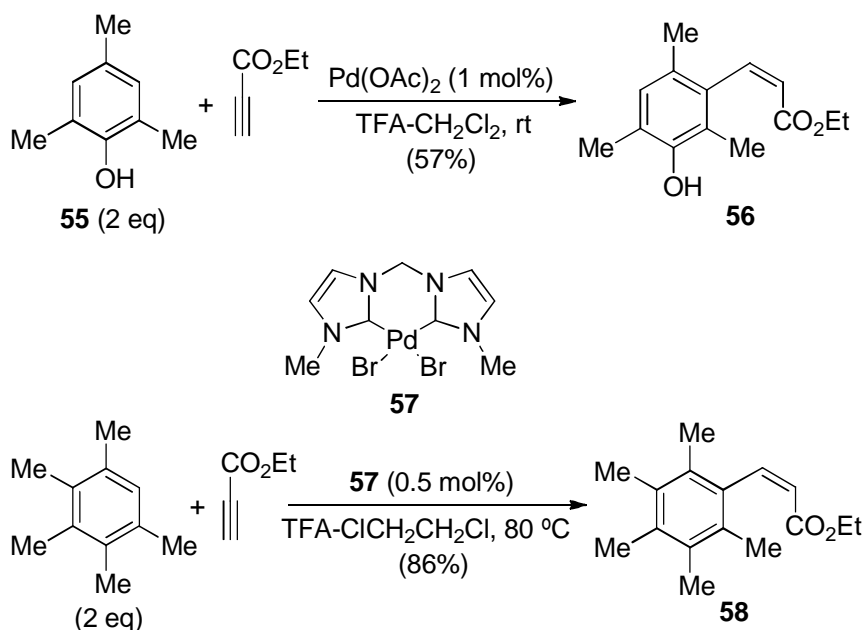
The direct hydroarylation of alkynes catalyzed by a transition metal such as palladium can formally be regarded as a reaction in which both aryl and hydrogen moieties add across a triple bond, providing a direct approach to the preparation of derivatives of styrene, stilbene, chalcone, cinnamic acid and related olefinic derivatives.⁴⁹ The procedure is, in principle, simpler than those based on Heck reactions or cross-coupling methods, which require the use of haloarenes or other arene electrophiles. The reaction is considered to occur through activation of the triple bond by coordination with a cationic palladium, thus undergoing an electrophilic substitution with an electron-rich arene to form the arylvinylmetal complex **51**, which is subsequently protonated to form the aryl-alkene **52** (Scheme 17). Another possible mechanism would arise when the palladium complex activates a C-H (or C-X) bond of the arene by oxidative addition, forming an arylvinylmetal **53**, which affords the aryl-alkene **54** after reductive elimination. The regioselectivity in the palladium-catalyzed intermolecular reactions of alkynes with arenes is dictated by the substitution pattern of the alkyne, and the addition proceeds in most cases in an electrophilic manner following a Markovnikov rule.⁵⁰

Scheme 17



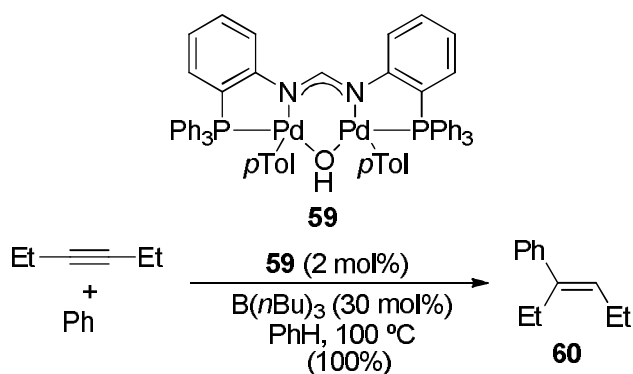
An example of the pioneering hydroarylation reaction employing $\text{Pd}(\text{OAc})_2$ (1 mol%) as catalyst under strong acidic conditions (TFA), is shown in Scheme 18 with the formation of vinyated alkene **56** from arene **55** and ethyl propiolate,⁵¹ the mechanism proceeding through the palladium-activated alkyne pathway.⁵² Good results have also been obtained in this reaction when preparing (*Z*)-cinnamic ester derivatives by coupling of arenes to propiolic acid esters, using palladium(II)-*N*-heterocyclic carbene (NHC) complexes as catalysts.⁵³ A recent example of this hydroarylation is shown in Scheme 18, where the dinuclear palladium(II)-NHC complex **57** is used as catalyst (0.5 mol%) in the presence of TFA for the hydroarylation of ethyl propiolate with pentamethylbenzene giving the (*Z*)-product **58**, the reaction being carried out in 1,2-dichloroethane as solvent at 80 °C.^{53b} A closely related palladium(II)-NHC complex bearing trifluoroacetates instead of bromides has been used as catalyst (0.1 mol%) for performing this reaction in the ionic liquid $[\textit{n}\text{BuMe}_3\text{N}][\text{NTf}_2]$ in the presence of TFA as acid and co-solvent. Although the final yields were moderate to low, recovery of the palladium species in the ionic liquid was possible.^{53c} In addition, heterocycles such as pyrroles and indoles have also been used for this hydroarylation reaction of alkynes.⁵⁴

Scheme 18



Dinuclear palladium complexes have shown to catalyze the *syn*-hydroarylation of alkynes with arenes.⁵⁵ Thus, the reaction between hex-3-yne and benzene in the presence of $\text{Pd}_2p\text{Tol}_2(\mu\text{-OH})(\mu\text{-dpfam})$ {dpfam = *N,N'*-bis[2-(diphenylphosphanyl)phenyl]formamidinate} (**59**, 2 mol%) and $\text{B}(n\text{Bu})_3$ (30 mol%) at 100 °C afforded quantitatively (*E*)-3-phenylhex-3-ene (**60**) (Scheme 19), the reaction proceeding through arene activation.

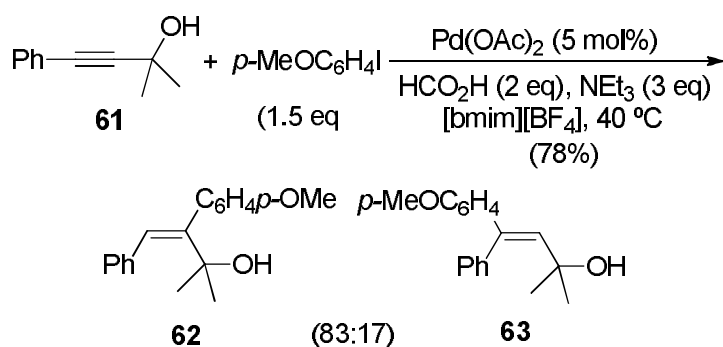
Scheme 19



The palladium-catalyzed hydroarylation of alkynes carried out using aryl iodides and triflates is a known procedure which allows the formation of vinyl arenes with *cis*-selectivity through activation of the arene.⁵⁶ The reaction is performed using

$\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as catalyst in the presence of an ammonium formate salt and shows a certain lack of regioselectivity, unless a bulky end is present on one side of the carbon-carbon triple bond. This methodology could be converted into a phosphine ligand-free process using $\text{Pd}(\text{OAc})_2$ as the catalyst in the presence of potassium formate in DMF as solvent at 40 °C, for the hydroarylation of 3,3-dialkoxy-1-aryl-1-propynes with aryl iodides.⁵⁷ More recently, this ligandless methodology has been used for the hydroarylation of propargylic alcohols at room temperature in ionic liquids.⁵⁸ Under these reaction conditions, aryl iodides are used in the hydroarylation of propargylic alcohols, such as **61**, using $\text{Pd}(\text{OAc})_2$ (5 mol%) in the presence of triethylammonium formate in the ionic liquid $[\text{bmim}][\text{BF}_4]$ (bmim: 1-butyl-3-methylimidazolium) at 40 °C, to afford regioselectively the corresponding arylated allyl alcohols **62** and **63** in good yield (Scheme 20). The mechanism of this phosphine-free hydroarylation reaction of alkynes has been investigated theoretically, explaining the unusual anti-Michael selectivity when α,β -acetylenic carbonyl substrates are used.⁵⁹

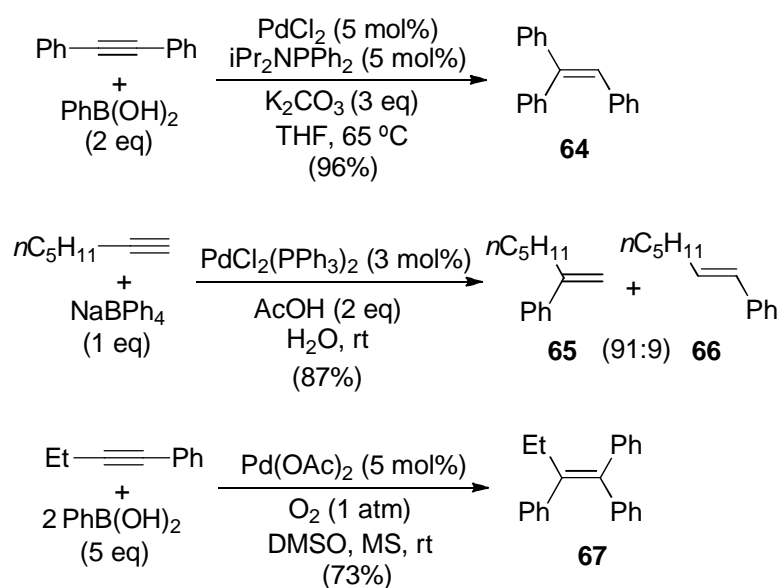
Scheme 20



Arylboronic acids⁶⁰ and also sodium tetraphenylborate⁶¹ have been used in palladium-catalyzed hydroarylation reactions of alkynes, affording trisubstituted alkenes in a *syn*-addition fashion. Thus, if a heteroatom-bearing directing group is present, as in the case of propargylic amines, the arylation takes place closer to that group,^{60d} whereas typical terminal alkynes favor branched-type olefins,^{60a} internal unsymmetrical ones afford regioisomeric mixtures favoring the less hindered position,^{60b} and propiolates favor Michael-type olefins.^{60a-c} Some examples of these reactions can be seen in Scheme 21, where diphenylacetylene is hydroarylated using phenylboronic acid, in a process catalyzed by the combination PdCl_2 (5 mol%)/ $i\text{Pr}_2\text{NPPH}_2$ (5 mol%), in the presence of potassium carbonate as base, in THF as solvent at 65 °C, to yield

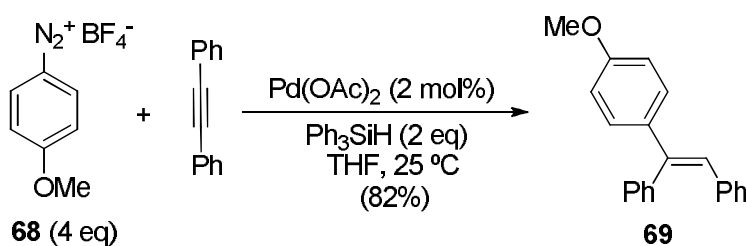
triphenylethylene (**64**).^{60e} An example of the use of sodium tetraphenylborate as hydrophenylating agent is the transformation of hept-1-yne in a process carried out using $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%) in aqueous acetic acid at room temperature, yielding geminal- and (*E*)-olefins **65** and **66**, the former being the major regioisomer (Scheme 21).⁶¹ In addition, arylboronic acids have also been used for the preparation of tetrasubstituted olefins via palladium-catalyzed double arylation of internal alkynes, as shown in the preparation of tetrasubstituted olefin **67** from addition of two equivalents of phenylboronic acid to ethylphenylacetylene (Scheme 21).⁶² The reaction involves the *syn* addition of two equivalents of an arylboronic acid to opposite ends on the triple bond, and is carried out using $\text{Pd}(\text{OAc})_2$ (5 mol%) in DMSO as solvent in the presence of molecular sieves and using molecular oxygen as oxidant.

Scheme 21



Arenediazonium tetrafluoroborates have also been used as aryl sources for the palladium-catalyzed hydroarylation of internal alkynes.⁶³ The methodology employs $\text{Pd}(\text{OAc})_2$ (2 mol%) as catalyst in the presence of triphenylsilane in THF at room temperature, as illustrated in Scheme 22 for the hydroarylation of diphenylacetylene with arenediazonium tetrafluoroborate **68** to give olefin **69**. Unsymmetrical alkynes gave very low regioselectivities, whereas the reaction with ethyl phenylpropionate afforded regio- and diastereoselectively ethyl (*Z*)-2-arylcinnamates (*E/Z* > 99:1).

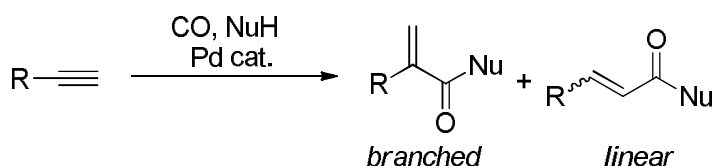
Scheme 22



2.4. Acrylic Acids, Esters and Amides

The three-component reaction which converts unsaturated hydrocarbons, carbon monoxide and a nucleophilic heteroatom-bearing donor, such as water, alcohols and amines, into saturated or unsaturated acids or its corresponding derivatives, using group VIII transition metal catalysts is generally known as the Reppe carbonylation, palladium being one of the most frequent metals employed.⁶⁴ Thus, the palladium-catalyzed carbonylation of terminal alkynes with water, alcohols or amines normally produces mixtures of linear and branched α,β -unsaturated acids, esters or amides, respectively (Scheme 23), with a ratio largely depending on the catalytic system, the reaction conditions, the substrate used and the nucleophile.^{64b,65}

Scheme 2

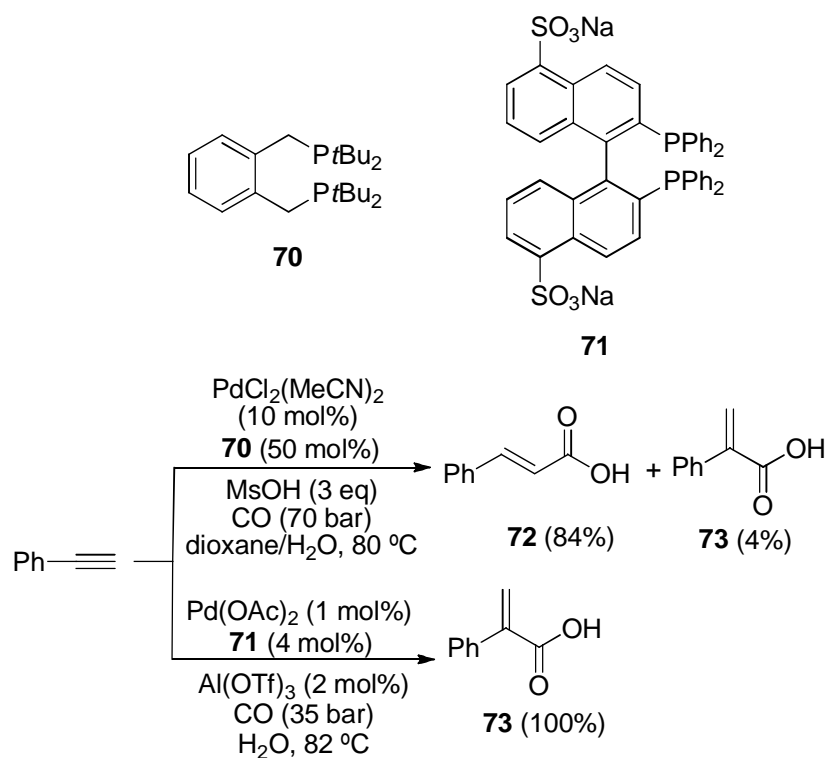


Among these palladium-catalyzed Reppe reactions with alkynes, the reaction using carbon monoxide and water leading to carboxylic acids (hydrocarboxylation) has been much less frequent than the reaction with alcohols (hydroesterification or hydroalkoxycarbonylation) and amines (aminocarbonylation).^{64b,65} Hydrocarboxylation reactions are usually slower than, for instance, methoxycarbonylation reactions, resulting in some catalytic deactivation.^{64a} Particularly, the hydrocarboxylation of the most simple alkyne, acetylene, leading to acrylic acid, is very rare,^{64b,65} although there are recent studies about the hydrocarboxylation of acetylene using a catalytic system containing $Pd(OAc)_2$, phosphines such as diphenyl(2-pyridyl)phosphine (2-PyPPh₂) and

acids such as trifluoromethanesulfonic acid (TfOH) under CO pressure (7-50 bar) and temperatures of 40/50 °C.⁶⁶ Under these conditions, 88% conversion of acetylene and 99% selectivity towards acrylic acid was achieved, factors such as amount of water and initial partial pressure of CO having great influence on the catalytic activity.

Preference for the linear unsaturated acid has been observed in the hydrocarboxylation of phenylacetylene when using as catalytic combination a mixture of Pd(MeCN)₂Cl₂ (10 mol%) and diphosphine **70** (50 mol%), in the presence of methanesulfonic acid (MsOH) under a CO pressure of 70 bar and at 80 °C (Scheme 24). Under these reaction conditions, (*E*)-cinnamic acid (**72**) was obtained as the major product, whereas the branched 2-phenylacrylic acid (**73**) was obtained in only a 4% yield, small amounts of saturated 3-phenylpropanoic and 2-phenylsuccinic acids from hydrogenation and secondary hydrocarboxylation, respectively, being also detected.⁶⁷ On the contrary, the branched 2-phenylacrylic acid (**73**) was exclusively observed when using as catalyst a combination of Pd(OAc)₂ (1 mol%) and sulfonated Binap diphosphine **71** (4 mol%) in the presence of Al(OTf)₃ (2 mol%) under a CO pressure of 35 bar and at 82 °C, using as solvent MeOH/H₂O (1:2), neat H₂O or H₂O/DME (1:1) (Scheme 24).⁶⁸

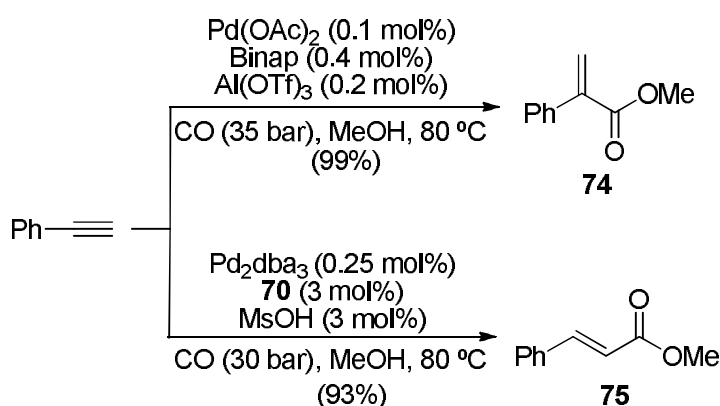
Scheme 24



The most efficient palladium catalyst for the methoxycarbonylation of alkynes was developed in the 1990s by combining Pd(OAc)₂ and the already mentioned ligand 2-PyPPh₂, together with methanesulfonic acid, a mixture that achieved the methoxycarbonylation of propyne with extremely high efficiency.⁶⁹ Thus, 40.000 TON and 99.95% selectivity towards methyl methacrylate (MMA) was obtained at 60 bar CO and 45-60 °C. The success of this 2-PyPPh₂ ligand inspired its use in other carbonylation reactions of alkynes (as above mentioned), for instance in a recent methoxycarbonylation of acetylene leading to methyl acrylate.⁷⁰ In addition, other heterocycle-containing phosphines were prepared for related uses,^{64b,65} as 2,6-bis-(biphenylphosphino)pyridine, which was employed by the Shell company, combined to Pd(OAc)₂, in a commercial synthesis of methyl methacrylate by a highly branched-selective methoxycarbonylation of propyne.^{64a,71}

The methoxycarbonylation of alkynes usually displays certain preference for the branched regioselectivity,^{64b,65} as is exemplified in Scheme 25, which shows the highly selective and quantitative preparation of methyl 2-phenylacrylate (**74**) (methyl atropate) from phenylacetylene (99:1 branched/linear) when using as a catalytic system a mixture of Pd(OAc)₂ (0.1 mol%)/Binap (0.4 mol%) and Al(OTf)₃ (0.2 mol%), in methanol as solvent and under a CO pressure of 35 bar and at 80 °C reaction temperature.⁶⁸ However, the mentioned crucial influence of the catalytic system in the regioselectivity of these Reppe reactions can clearly be seen in Scheme 25, where the linear methoxycarbonylation product of phenylacetylene, methyl (*E*)-cinnamate (**75**), is obtained (99:1 branched/linear regioselectivity) using a mixture of Pd₂(dba)₃ (0.25 mol%)/**70** (3 mol%) as catalyst and the presence of MsOH (3 mol%), working under CO pressure (30 bar) in methanol as solvent at 80 °C.⁶⁷ The uncommon regiochemistry of this last reaction is explained by a hydride mechanism involving sterically-induced addition of a created palladium hydride onto the alkyne leading to a linear vinyl palladium species, followed by CO insertion and methanolysis.

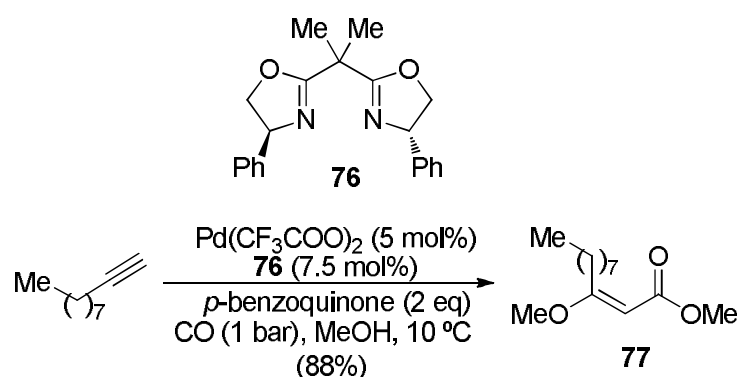
Scheme 25



This mentioned influence of the reaction conditions in the regioselectivity of these carbonylation processes has been explored in extension, as in the model methoxycarbonylation of phenylacetylene using $\text{Pd}(\text{OAc})_2$ as palladium source, dppb as ligand [dppb = bis(diphenylphosphino)butane] and *p*-toluenesulfonic as acid additive, in the presence of methanol under CO pressure (6.9 bar) in acetonitrile at 110 °C.⁷² These conditions afforded the linear methyl (*E*)-cinnamate (**75**) as the main compound. However, a change in the palladium source from $\text{Pd}(\text{OAc})_2$ to $\text{PdCl}_2(\text{PPh}_3)_2$ changed the selectivity from the linear acrylate **75** to the branched ester **74**, whereas a change in the ligand from dppb to 1,1'-bis(diphenylphosphino)ferrocene (dppf) has the same effect. In addition, exchanging acetonitrile by DMF or DMSO also led to the branched ester as the major regioisomer.

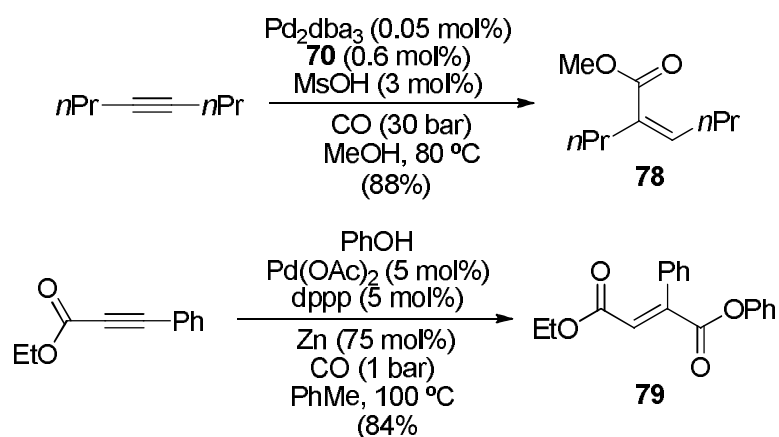
Methyl β -methoxyacrylates such as **77** have been obtained by reaction of terminal alkynes, such as dec-1-yne, with CO (1 bar) in methanol at 10 °C, the process being catalyzed by combining palladium(II) trifluoroacetate [$\text{Pd}(\text{CF}_3\text{COO})_2$] (5 mol%) and the bis-oxazoline ligand (*S*)-PhBox (**76**) (7.5 mol%) in the presence of *p*-benzoquinone (Scheme 26).⁷³

Scheme 26



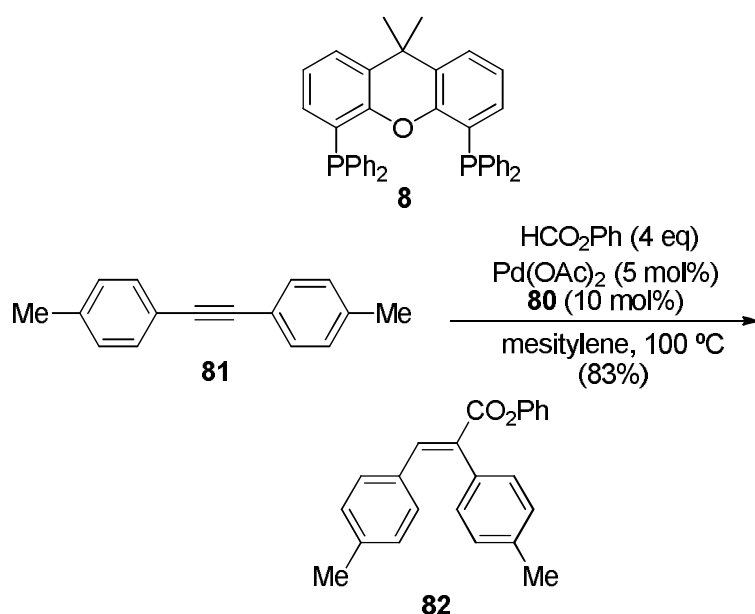
Internal alkynes have been less common substrates than terminal ones for these types of carbonylation reactions, as regioselectivity is a frequent problem.^{64b,65} However, when symmetrical alkynes are employed, carbonylation reactions can be synthetically useful, as shown in Scheme 27, where the reaction conditions employed in the preparation of methyl (*E*)-cinnamate are used for the methoxycarbonylation of oct-4-yne, leading to the α,β -unsaturated methyl ester **78**.⁶⁷ In addition, depending of the substrate, even unsymmetrical alkynes can be regioselectively hydroesterified, as can be seen in Scheme 27. Thus, ethyl phenylpropiolate is hydrophenoxycarbonylated to diester **79** using as catalyst a mixture of $\text{Pd}(\text{OAc})_2$ (5 mol%) and 1,3-bis(diphenylphosphino)propane (dppp, 5 mol%) in the presence of zinc (75 mol%) as additive and phenol, under an atmosphere of CO (1 bar) in toluene as solvent at 100 °C.⁷⁴

Scheme 27



The use of CO in these hydroesterification reactions can be avoided using other carbonyl sources, such as formate or oxalate esters.^{64b, 65} For instance, aryl formates have been used as a CO source in the hydroesterification of internal alkynes, such as **81**, using Pd(OAc)₂ (5 mol%) as palladium source, Xantphos (**80**) as ligand (10 mol%), in mesitylene as solvent at 100 °C, to give the corresponding unsaturated phenyl ester **82** with total (*E*)-stereoselectivity (Scheme 28).⁷⁵ This methodology has also been applied to terminal alkynes, affording almost exclusively the corresponding branched regioisomers.

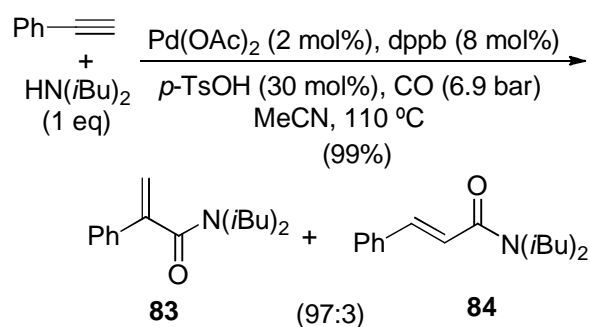
Scheme 28



The synthesis of α,β -unsaturated amides from alkynes has been performed similarly to the alkoxy carbonylation process, but using primary or secondary amines instead of water, alcohols or phenols.^{64b,65} For example, the aminocarbonylation of phenylacetylene has been achieved in the presence of diisobutylamine, using Pd(OAc)₂ as palladium source (2 mol%), dppb as ligand (8 mol%) and *p*-toluenesulfonic acid (*p*-TsOH) as additive (30 mol%), in the presence of methanol under CO pressure (6.9 bar) in acetonitrile at 110 °C. Under these conditions, the corresponding branched amide **83** was almost exclusively obtained, a negligible amount of the linear cinamide **84** being observed (Scheme 29).⁷² It is remarkable that under exactly the same reaction conditions, but in the presence of methanol, the corresponding linear methyl cinamate was the main product (12:88 branched/linear ratio), as above commented.⁷² This

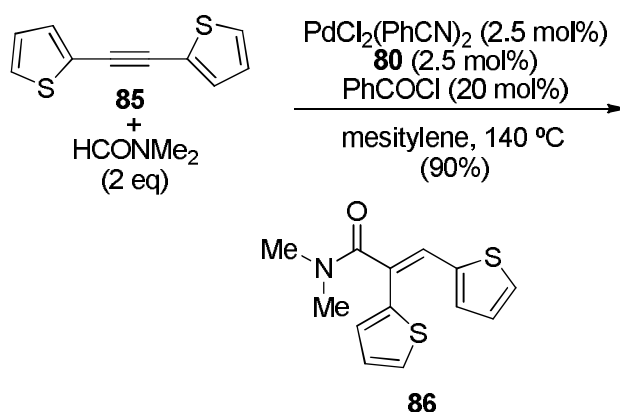
indicated that not only the palladium source, ligand, additive or solvent exert an influence in the regioselectivity of these carbonylation reactions, but also that the nucleophile exerts a strong control. All these data reveal a complex mechanism still not fully understood, as well as different catalytic cycles governing alkoxy carbonylation and aminocarbonylation processes.⁷⁶

Scheme 29



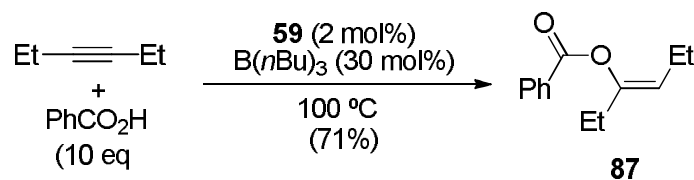
The use of CO has also been avoided in the case of the aminocarbonylation reaction, for instance, by using formamides. Thus, the reaction of formamides with internal alkynes in the presence of a $\text{PdCl}_2(\text{PhCN})_2$ (2.5 mol%), Xantphos (**80**) (2.5 mol%) and benzoyl chloride (20 mol%) as an in situ HCl-forming additive, in mesitylene at 140 °C, afforded (*E*)- α,β -unsaturated amides regio- and stereoselectively, as shown in Scheme 30. Thus, the aminocarbonylation of 1,2-di(thiophen-2-yl)ethyne (**852**) with *N,N*-dimethylformamide afforded the unsaturated amide **86** in a 99:1 *E/Z* diastereoselectivity.⁷⁷ These conditions were also used for the aminocarbonylation of terminal alkynes, affording the corresponding branched amides as the major products in regioselectivities higher than 81/19 branched/linear ratio.⁷⁷ Control experiments revealed that in this catalytic reaction, formamide reacts directly with the alkyne, not by decomposition of the formamide to CO and the amine and subsequent conventional aminocarbonylation.

Scheme 30



The transition metal-catalyzed addition of carboxylic acid to alkynes (hydrooxycarbonylation) is a process suitable for the preparation of vinyl carboxylates, some of them of paramount industrial importance as is the case of vinyl acetate, and also used heavily in intramolecular reactions.^{30a} However, the examples of palladium-catalyzed intermolecular addition of carboxylic acids to alkynes is restricted to few old examples.^{30a} The most recent study is the use of dinuclear palladium complexes such as **59** (2 mol%), which have shown suitable to induce stereoselectively the hydrocarboxylation of alkynes such as hex-3-yne using carboxylic acids, such as benzoic acid, in the presence of Lewis acids, such as $\text{B}(n\text{Bu})_3$ (30 mol%), as additives at 100 °C (Scheme 31).⁷⁸ The resulting vinyl benzoate **87** is obtained as the (*Z*)-isomer, this stereoselectivity being generally the major one in this process.

Scheme 31

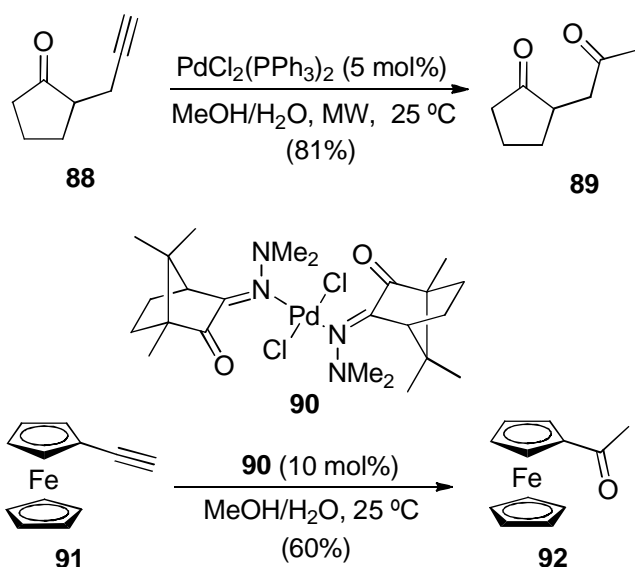


2.5. Ketones

The addition of heteroatom-hydrogen bonds (including N-H, O-H, S-H, Se-H, and P-H) across the carbon-carbon triple bond catalyzed by transition-metal species is an important process from a synthetic point of view as it leads to a diverse array of different functionalities and, in principle, can be performed with 100 % atom economy a requirement of ‘green chemistry’.^{30a,50}

Among these processes, the palladium-catalyzed addition of water to alkynes (hydration) can be an easy way of generating ketones from alkynes,⁷⁹ although anchimeric assistance (neighboring group participation) has been sometimes necessary. Thus, PdCl₂(MeCN)₂ in aqueous acetonitrile under microwave irradiation was used in the hydration of ketone **88** as it leads to 1,4-diketone **89** (Scheme 32).⁸⁰ Modified conditions have been the use of a phase-transfer agent in a two-phase system in the case of the hydration of a hydroxylated alkyne⁸¹ or the use of a Nafion/palladium(II) resin in aqueous ethanol for the hydration of 2-methylbut-3-yn-2-ol to 3-hydroxy-3-methylbutan-2-one.⁸² However, there are isolated examples where carbonyl or hydroxy-related anchimeric assistance have not been necessary in particular cases, as the Markovnikov hydration of ethynylferrocene (**91**) to acetylferrocene (**92**) catalyzed by camphor hydrazone-derived palladium(II) complex **90** (10-25%) in aqueous methanol at room temperature (Scheme 32), although related alkynes such as 1-ferrocenylprop-1-yne or simple terminal acetylenes such as oct-1-yne or several ethynylbenzenes were not affected or polymerized.⁸³

Scheme 32

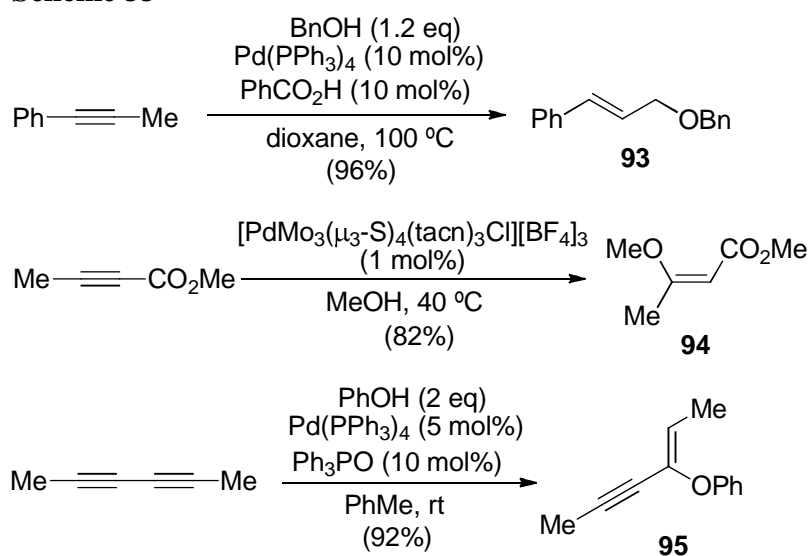


2.6. Allyl and Vinyl Ethers

The intermolecular addition of alcohols to alkynes (hydroalkoxylation), which leads to alkenylated ethers, is a more difficult process to accomplish than its intramolecular version, therefore few and not very recent reports can be found.^{30a,50} An example of a simple and good-yielding hydroalkoxylation of a simple internal alkyne such as 1-phenyl-1-propyne with alcohols, such as benzyl alcohol, yielding the cinnamyl ether **93** is shown in Scheme 33.⁸⁴ The reaction takes place with (*E*)-stereoselectivity through the corresponding allene intermediate and was performed using $\text{Pd}(\text{PPh}_3)_4$ (10 mol%) as catalyst and benzoic acid as additive (10 mol%) in dioxane as solvent at 100 °C. When the hydroalkoxylation process is intended to achieve vinylylated ethers, activated alkynes such as propiolic acid esters were used as starting materials. Thus, a polynuclear transition-metal-sulfur complex,⁸⁵ such as the single-cubane-type cluster $[\text{PdMo}_3(\mu_3\text{-S})_4(\text{tacz})_3\text{Cl}][\text{BF}_4]_3$ (*tacz* = 1,4,7-triazacyclononane), was used as catalyst (1 mol%) in the hydroalkoxylation of different propiolic acid esters following a *trans*-addition. This is the case of the hydromethoxylation of methyl but-2-ynoate to give the corresponding β -methoxylated unsaturated ester **94**, the reaction being carried out in methanol at 40 °C and monoarylated acetylenes remaining unreactive (Scheme 33).⁸⁶ When related bimetallic cluster $[(\text{Cp}^*\text{Ir})_2(\mu_3\text{-S})_2\text{PdCl}_2]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) were used for the hydroalkoxylation of a series of nonactivated arylacetylenes, the

regioselectively formed Markovnikov-type vinyl ethers were in situ transformed into diacetals after a second hydroalkoxylation reaction.⁸⁷ In addition, diynes have been hydroaryloxyated in an ‘anti-Wacker’-type process catalyzed by Pd(PPh₃)₄ (5 mol%) in the presence of triphenylphosphine oxide (10 mol%) in toluene at room temperature, as shown in Scheme 30, where hexa-2,4-diyne is transformed into the phenoxyated enyne **95**.⁸⁸

Scheme 33

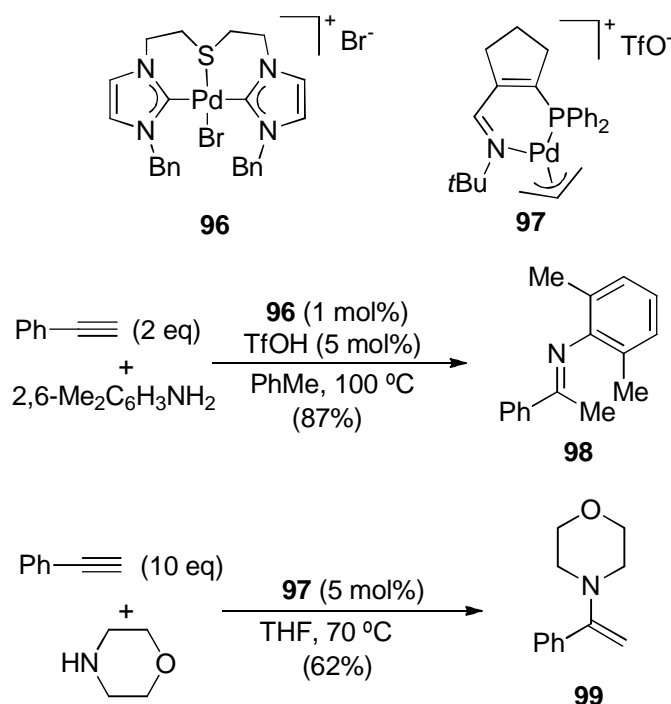


2.7. Enamines, Imines and Allylamines

The palladium-catalyzed addition of amines to alkynes (hydroamination) leads to an enamine which, according to the nature of the amine, can remain or evolve as an imine (or can be hydrolyzed to a ketone). This methodology has experienced a considerable research and success in the case of the intramolecular version, as many nitrogen-containing heterocyclic systems, as indoles, can be obtained in this way (see Section 3.2), its intermolecular counterpart being however much less explored.^{30a,50,89} Recent uses of palladium complexes for the intermolecular preparation of these nitrogenated systems can be seen in Scheme 34 in the synthesis of acetophenone imines, such as **98**, by reaction of aromatic amines, such as 2,6-dimethylaniline, with phenylacetylene. This reaction is catalyzed by the CSC-pincer palladium complex **96** (1 mol%) in the presence of triflic acid (5 mol%) as additive in toluene as solvent at 100

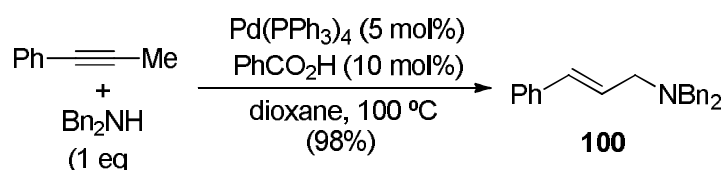
°C.⁹⁰ Acetophenone imines have also been prepared by using as catalyst a palladium(II) 4-iminophosphine complex **97**, working in THF at 70 °C, the use of cyclic secondary amines, such as morpholine, under these reaction conditions allowing the preparation of the corresponding enamine **99** (Scheme 34).⁹¹

Scheme 34



Allylic amines have been prepared from internal phenyl acetylenes and secondary amines following a hydroamination protocol consisting of using simple $\text{Pd}(\text{PPh}_3)_4$ as catalyst (5 mol%) in the presence of a substoichiometric amount of benzoic acid (10 mol%) in dioxane as solvent at 100 °C.⁹² According to this procedure, allylamines such as **100** were prepared by reaction of dibenzylamine with prop-1-yn-1-ylbenzene with total stereoselectivity, the process taking place through the allene intermediate (Scheme 35).

Scheme 35

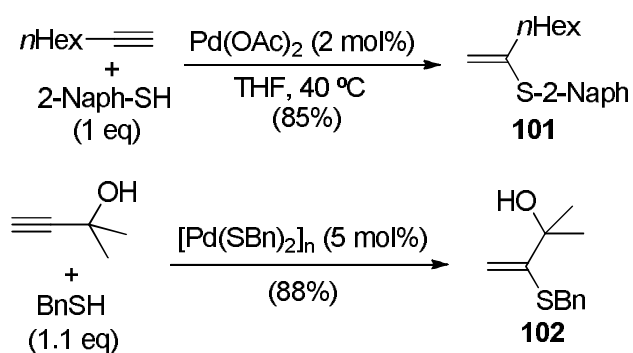


2.8. Vinyl Sulfides and Selenides

The transition-metal-catalyzed addition of thiols or selenols to alkynes (hydrothiolation or hydroselenation) was a process that did not receive much attention, probably due to the prejudice that these types of compounds can act as a catalyst poison. However, in the last ten years, considerable research has been carried out in this area^{30a,93} due to the interest of vinyl sulfides and selenides in synthesis and in material sciences.

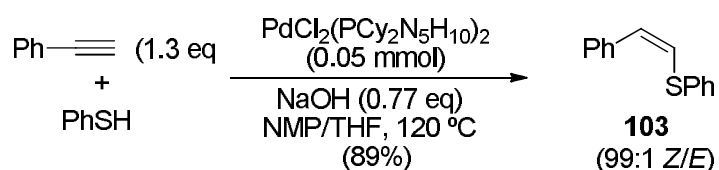
The intermolecular palladium-catalyzed addition of thiols and selenols has been usually carried out on terminal alkynes, achieving mainly the corresponding branched Markovnikov-type vinyl chalcogenides, contrary to the regiochemistry resulting from the classical radical addition reaction.^{30a,93} A typical example of palladium catalyzed addition of thiols to alkynes is the pioneering use of simple Pd(OAc)₂ as catalyst. Thus, terminal alkynes such as oct-1-yne reacted with naphthalene-2-thiol using this palladium salt as catalyst (2 mol%) in THF at 40 °C to give the branched vinyl sulfide **101** (Scheme 36), internal alkynes giving mixtures of regio- and (*E/Z*)-stereoisomers.⁹⁴ The use of other palladium(II) catalysts such as PdCl₂(PPh₃)₂ required higher temperatures leading to certain isomerization, whereas Pd(PPh₃)₄ showed lower reactivity. When using two equivalents of thiols and Pd(OAc)₂ as catalysts in water as solvent, a second hydrothiolation of the branched vinyl sulfide took place leading to ketone thioacetals.⁹⁵ A more recent hydrothiolation of alkynes has been carried out using shape-controlled PdNPs of the type [Pd(SR)₂]_n, generated by dissolving the Pd(OAc)₂ (5 mol%) in the alkyne and adding the thiol. This methodology afforded high yields and regioselectivity in the hydrothiolation of terminal alkynes,⁹⁶ as shown in Scheme 36 for the formation of vinyl sulfide **102** from 2-methylbut-3-yn-2-ol and phenylmethanethiol. In addition, heterogeneous palladium ‘nanosalts’ have shown high efficiency and regioselectivity in these hydrothiolation (and hydroselenation) of terminal alkynes.⁹⁷

Scheme 36



The uncommon preferential anti-Markovnikov-type addition of thiols to terminal alkynes has been achieved recently using as catalyst a dichlorobis(aminophosphine) complex of palladium.⁹⁸ Thus, $\text{PdCl}_2(\text{PCy}_2\text{NC}_5\text{H}_{10})_2$, in the presence of sodium hydroxide in NMP/THF as solvent 120 °C, has been employed as a very reactive catalyst (0.05 mol%) in the hydrothiolation of terminal aromatic alkynes with aromatic thiols. This procedure achieved total regioselectivity of the anti-Markovnikov-type linear vinyl sulfide in high yields and with high (*Z*)-diastereoselectivity, as in the case of the preparation of vinyl sulfide **103** from the hydrothiolation of phenylacetylene with benzenethiol (Scheme 37). Terminal aliphatic alkynes afforded however the Markovnikov-type branched vinyl sulfide as the major product, although with not so high regioselectivity than before, whereas internal alkynes gave *Z/E* mixtures of isomers.

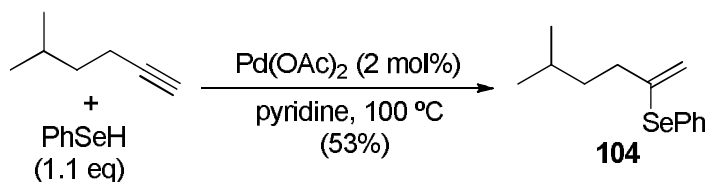
Scheme 37



The use of Pd(OAc)_2 (2 mol%) showed to catalyze the hydroselenation of terminal alkynes with benzeneselenol in benzene as solvent at 80 °C, leading to branched vinyl selenides.⁹⁹ However, small amounts of byproducts from double hydroselenation and isomerization are formed under these conditions, the selectivity to

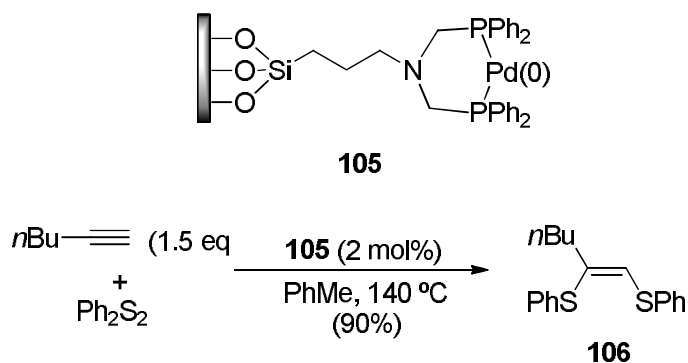
the final terminal alkene being achieved totally by using pyridine as solvent as exemplified in Scheme 38 with the preparation of **104** from 5-methylhex-1-yne.¹⁰⁰

Scheme 38



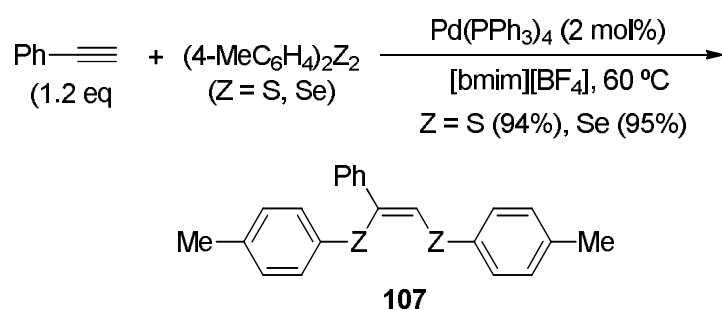
The palladium-catalyzed addition of diaryl or dialkyl-1,2-disulfides and 1,2-diselenides to terminal alkynes, affords the corresponding vinyl 1,2-disulfides or 1,2-diselenides mainly with (*Z*)-stereoselectivity.⁹³ This was demonstrated in the pioneering work that showed that Ph₂S₂ and Ar₂Se₂ add to terminal alkynes under Pd(PPh₃)₄-catalyzed conditions giving the *Z*-isomer, except in the case of phenylacetylene which afforded significant amounts of the *E*-isomer.¹⁰¹ Since then, other palladium species and reaction conditions have been attempted to improve yields and stereoselectivities for this process.⁹³ As an example of using a recyclable supported catalyst, (*Z*)-1,2-bis(arylsulfanyl)-substituted alkenes such as **106** have been synthesized by the stereoselective addition of diaryl disulfides to terminal alkynes catalyzed by a mobil crystalline material MCM-41-supported bidentate phosphine palladium(0) complex **105**, as is the case of the addition of diphenyldisulfide to hex-1-yne (Scheme 39).¹⁰² The catalyst was reused up to five times keeping its activity.

Scheme 39



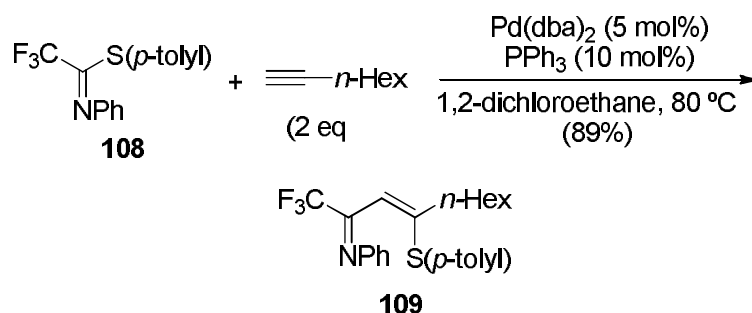
The ionic liquid [bmim][BF₄] has been used as solvent for the highly regioselective addition of Ar₂Z₂ (Z = S, Se) to terminal alkynes catalyzed by Pd(PPh₃)₄ (2 mol%), as shown in the case of the preparation of (*Z*)-1,2-disulfide and 1,2-diselenide **107** from phenylacetylene, no traces of the *E*-isomer being observed (Scheme 40).¹⁰³ The ionic liquid containing the catalyst was recycled two times in the case of the addition of Ph₂Se₂ to hex-1-yne, showing identical yield of the final 1,2-diselenide. Moreover, examples can be found about the cyanochalcogenation of terminal alkynes with PhZCN (Z = S, Se) catalyzed by Pd(PPh₃)₄ (10 mol%), the corresponding (*Z*)-olefins bearing the cyano group at the terminal position.¹⁰⁴

Scheme 40



More exotic examples of addition of sulfur-bearing species to alkynes can also be found, as exemplified in the reaction of iminosulfides such as **108** to oct-1-yne to give the iminothiolation product **109** with good *E/Z* stereoselectivity (18:82) (Scheme 41).¹⁰⁵ The process is catalyzed by the combination Pd(dba)₂ (5 mol%)/PPh₃ (10 mol%), using 1,2-dichloroethane as solvent at 80 °C. Another example would be the synthesis of 2,3-dihydrothiopyran-4-one derivatives by the PdCl₂ (1 mol%)/CuI (10 mol%)-catalyzed reaction between α,β-unsaturated thioesters and propargyl alcohols in the presence of bases, the addition to the triple bond taking place after both carbon-sulfur bonds cleavage.¹⁰⁶

Scheme 41

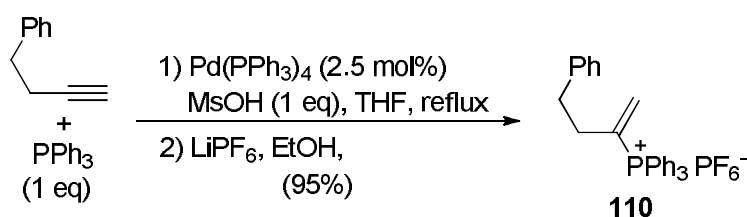


2.9. Vinyl Phosphines, Phosphine Oxides, Phosphinates and Phosphonates

The formation of C-P bonds by the transition-metal-catalyzed addition of P-H species to alkynes is a methodology that has received strong interest in the last years due to the increasing importance of phosphorus-related chemicals in the synthesis of compounds with biological activity.^{30a,107} Among these transformations, the intermolecular palladium-catalyzed addition of species containing P(III)-H or P(V)-H bonds to alkynes has been carried out mainly on terminal acetylenes, leading to a preference for the branched/linear final product depending on the nature of the palladium species, the nature and geometrical arrangement of the phosphorus group being also crucial.¹⁰⁸

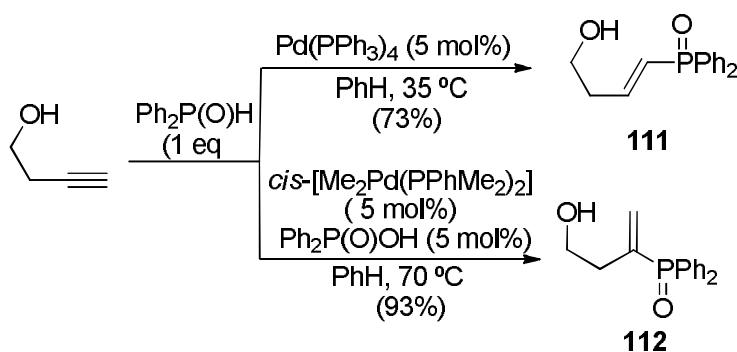
Alkenylated phosphines have been very scarcely prepared following this hydrophosphination methodology. Thus, the palladium-catalyzed [Pd(PPh₃)₄, Pd₂(dba)₃, Pd(OAc)₂] addition of diphenylphosphine to terminal alkynes allowed the preparation of mixtures of the linear alkenylphosphine accompanied of the branched product, the proportions strongly depending on the reaction conditions.¹⁰⁹ In addition, particularly remarkable is the regioselective addition of triphenylphosphine to terminal alkynes catalyzed by Pd(PPh₃)₄ (0.1 mol%) in the presence of methanesulfonic acid in refluxing THF affording Markovnikov-type vinyl phosphonium salts such as **110**, obtained after reaction with but-3-yn-1-ylbenzene and anion exchange (Scheme 42). Under these conditions, functionalities such as alcohols, nitriles or esters remained unaltered, the use of other phosphines giving no reaction.¹¹⁰

Scheme 42



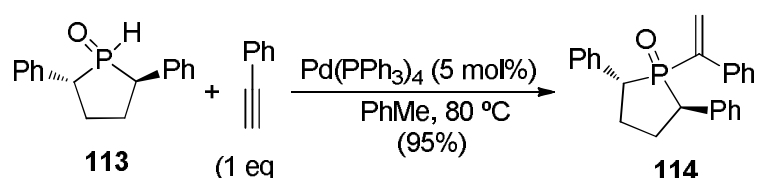
Vinylated phosphine oxides have been obtained by palladium-catalyzed addition of dialkylated or diarylated phosphine oxides to alkynes. Thus, a very effective hydrophosphinylation of terminal alkynes following this methodology has been achieved by using diphenylphosphine oxide and $\text{Pd(PPh}_3)_4$ as catalyst (5 mol%) in benzene at 35 °C. Under these conditions, terminal alkynes (except 1-ethynylcyclohex-1-ene) afforded regio- and diastereoselectively the anti-Markovnikov-type linear alkenylphosphine oxide with (*E*)-stereochemistry, as in the case of the reaction of oct-1-yne, affording the phosphine oxide **111** (Scheme 43).¹¹¹ The regioselectivity of this reaction has been reversed totally by using as catalyst the complex *cis*- $[\text{Me}_2\text{Pd(PPhMe}_2)_2]$ (4 mol%) in the presence of trace amounts of diphenylphosphinic acid (5 mol%), which afforded the corresponding Markovnikov-type branched alkenylphosphine oxide **112** (94% regioselectivity) (Scheme 43).¹¹² The authors justify the formation of this branched regioisomer by formation of a new reactive $\text{Ph}_2\text{P(O)-Pd(L}_2\text{)-OP(O)Ph}_2$ complex, insertion of the Pd-P(O)Ph_2 bond into the carbon-carbon triple bond (phosphinylpalladation) with formation of an alkynylpalladium species, and subsequent protonolysis with $\text{Ph}_2\text{P(O)H}$.

Scheme 43



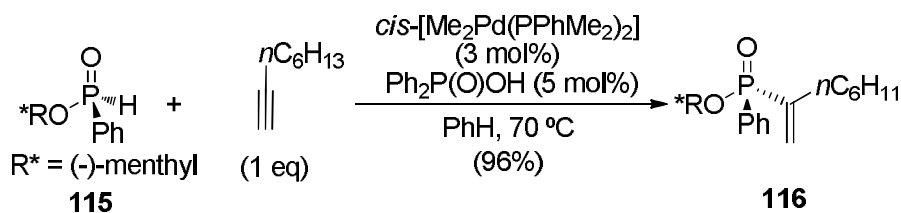
A recent example of the synthesis of C₂-symmetric vinylphosphine oxides with regioselectivity towards the branched vinylphosphine oxide is shown in Scheme 40, where terminal alkynes such as phenylacetylene reacted with (2*R*,5*R*)-2,5-diphenylphospholane 1-oxide (**113**) in the presence of Pd(PPh₃)₄ (5 mol%) in toluene as solvent at 80 °C, to give enantiomerically pure branched-type vinylphosphine oxide **114** (Scheme 44).¹¹³ In addition, examples can be found of Markovnikov-type addition of diphenylphosphine oxide to terminal alkynes catalyzed by Pd(OAc)₂ (5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe, 8 mol%) in propionitrile as solvent at 100 °C,¹¹⁴ as well as the use of a diphosphine-hydrosilane binary systems that allows the regioselective synthesis of branched vinylphosphine oxides from terminal alkynes under Pd(PPh₃)₄ catalysis (5 mol%).¹¹⁵ Moreover, tetraphenyldiphosphine has been used in the hydrophosphinylation reaction of terminal alkynes catalyzed by Pd(OAc)₂ (5 mol%), leading to branched vinylated phosphine oxides after air-oxidation during work-up,¹¹⁶ and diphenylphosphine oxide has been used in a double addition to oct-1-yne using a Zr (or Hf)-Pd heterobinuclear system as catalyst, the preliminary branched and linear vinylated phosphine oxides being intermediates.¹¹⁷

Scheme 44



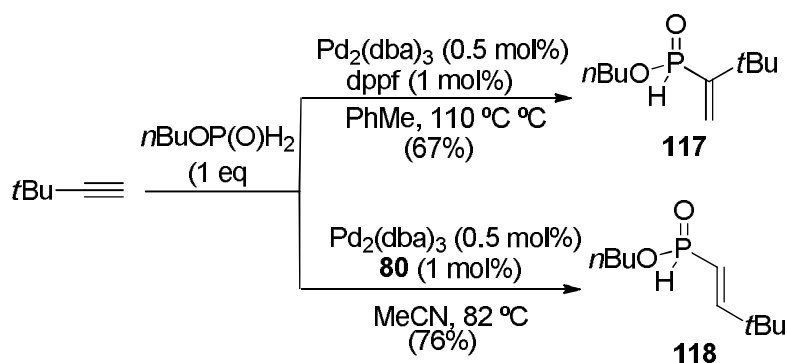
Enantiomerically pure Markovnikov-type vinylphosphinates, such as **116**, have been regioselectively prepared (>95% selectivity) by the hydrophosphinylation reaction of terminal alkynes, such as oct-1-yne, with (-)-menthyl *H*-phosphinate **115** catalyzed by the former combination *cis*-[Me₂Pd(PPhMe₂)₂] (3 mol%)-Ph₂P(O)OH (5 mol%) (Scheme 45).¹¹⁸ Under these conditions, trimethylsilylacetylene afforded the linear (*E*)-isomer, probably for steric interactions, whereas an internal alkyne such as diphenylacetylene afforded the corresponding chiral phosphinate product of the *syn*-addition.

Scheme 45



Ethyl phenylphosphinate has been used in the regioselective hydrophosphonylation of terminal alkynes catalyzed by the combination Pd(OAc)₂ (5 mol%)/dppe (7.5 mol%) in toluene at 100 °C, the branched Markovnikov-type branched vinylphosphinates obtained with regioselectivities generally higher than 94%.¹¹⁹ In addition, hypophosphorous compounds ROP(O)H₂ have been shown to add to terminal alkynes with a regioselectivity strongly dependent to the ligand in the catalytic palladium species.¹²⁰ Thus, the use of PdCl₂(PPh₃)₂¹²¹ or Pd₂(dba)₃/dppf¹²² favors the branched isomer, whereas the presence of the Xantphos ligand (**80**) favors the linear one with (*E*)-stereoselectivity.^{121,122} This is the case of the hydrophosphonylation of 3,3-dimethylbut-1-yne with *n*BuOP(O)H₂, which gave a reversal of the regioselectivity by changing the ligand, from branched phosphinate **117** (2.6/1 branched/linear ratio) to the linear one **118** (1/6.7 branched/linear ratio) (Scheme 46).¹²² These results have been justified by the different bite angle of the ligand in the palladium catalyst, as well as by stereoelectronic effects.

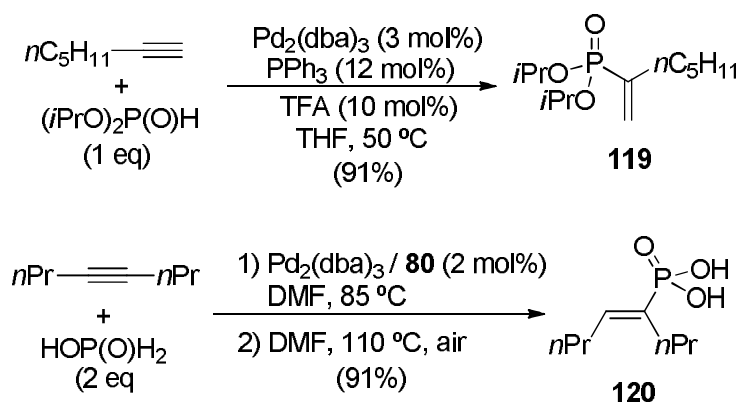
Scheme 46



Alkenylphosphonates have been obtained by using the above mentioned palladium complex cis -[Me₂Pd(PPhMe₂)₂] as catalyst (3 mol%) in the addition of dimethylphosphonate to terminal alkynes (hydrophosphonylation) leading

regioselectively to the branched vinylphosphonates.¹²³ This procedure was improved by using commercial Pd₂(dba)₃ as catalyst in the presence of triphenylphosphine,¹²⁴ as exemplified in Scheme 47, where terminal alkynes, such as hept-1-yne, reacted with dialkylphosphonates, such as diisopropylphosphonate, under Pd₂(dba)₃ (3 mol%)/PPh₃ (12 mol%) catalysis in the presence of TFA (10 mol%) in THF at 50 °C, to give the corresponding vinylphosphonate **119**.^{124b} Following this procedure, an internal alkyne, such as hex-3-yne, gave the corresponding hydrophosphonylated compound with *syn*-addition, whereas trimethylsilylacetylene gave the linear (*E*)-phosphonate.^{124b} In addition, the combination Pd₂(dba)₃/Xantphos (**80**) (2 mol%) has been used as catalyst for the hydrophosphonylation of an internal alkyne such as oct-4-yne with hypophosphorous acid affording vinylated phosphonic acid **120** (Scheme 47).¹²⁵ The process is a two-step procedure consisting of an initial hydrophosphinylation followed by oxidation by air.

Scheme 47



3. Chemicals by Palladium-Catalyzed Intramolecular Additions to Alkynes

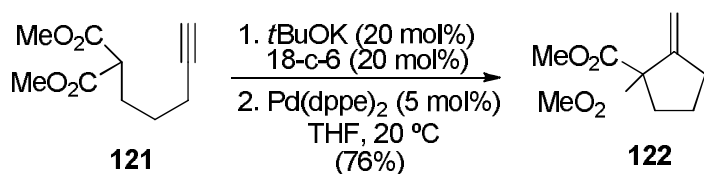
The intramolecular reaction of carbon and heteroatom nucleophiles to alkynes catalyzed by palladium species is a practical way of obtaining carbo- and hetero-cycles, respectively. Thus, if an alkyne contains an internal nucleophile, the coordination of the organopalladium species to the carbon-carbon triple bond, followed by cyclization produce a cyclic vinylpalladium adduct. Both *endo* and *exo* cyclization adducts can be obtained depending on the number of carbon atoms between the triple bond and the nucleophilic center. Reductive elimination produces the heterocyclic or carbocyclic

product regenerating the catalyst. This approach is particularly important in the case of the palladium-catalyzed internal cycloaddition of heteroatoms to acetylenic systems, a huge array of heterocyclic systems being prepared in this way. In this section, examples of these internal cyclizations leading to carbo- and heterocycles will be shown.

3.1. Carbocycles

The intramolecular addition of enolates to alkynes under transition metal catalysis is a powerful tool to construct five-membered carbocyclic compounds bearing an olefinic moiety.¹²⁶ The cyclization usually proceeds in a *5-exo-dig* mode to provide methylenecyclopentanes starting from ϵ,ζ -alkynyl carbonyl compounds, as exemplified in seminal works where compounds such as malonate-derived alkyne **121** are deprotonated with a substoichiometric amount of potassium *tert*-butoxide in the presence of a crown ether, and subsequently cyclized in the presence of a catalytic amount of Pd(dppe)₂ (5 mol%) in THF at 20 °C to give cyclopentane **122** (Scheme 48).¹²⁷

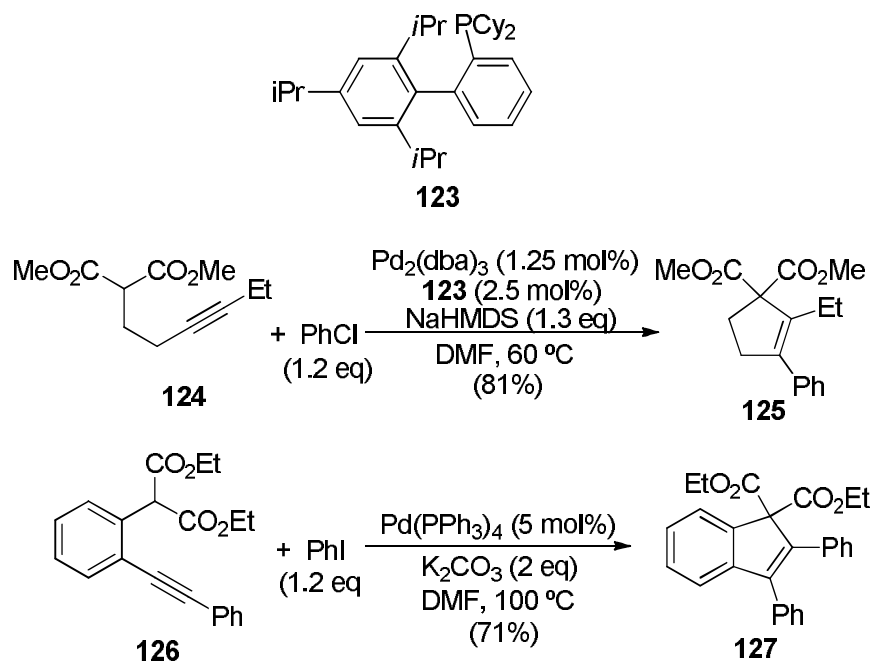
Scheme 48



More recently, the use as catalyst of a combination of Pd₂(dba)₃ (1.25 mol%) and the ligand XPhos (**123**) (2.5 mol%) in the presence of sodium hexamethyldisilazide and an organic halide, has allowed the *5-endo-dig* cyclization of homopropargyl-substituted dicarbonyl compounds leading to 1,2-disubstituted cyclopentenes, as in the case of the preparation of cyclic system **125** from alkyne **124** and phenyl chloride (Scheme 49).¹²⁸ In addition, this type of *5-endo-dig* carboannulation is observed in arylative cyclizations leading to indenenes, with structurally limited substrates activated by the conjugation of the aromatic ring.¹²⁹ An example of this last process is represented in Scheme 49, where 2-[2-(2-phenylethynyl)phenyl]malonate (**126**) is cyclized in the

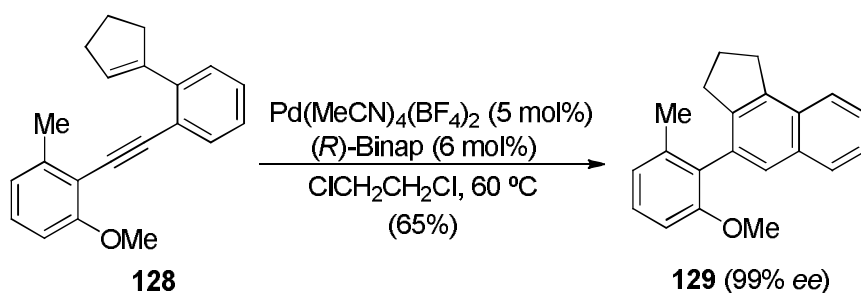
presence of an aryl or vinyl halide such as phenyl iodide under $\text{Pd}(\text{PPh}_3)_4$ catalysis (5 mol%) and potassium carbonate as base in DMF at 100 °C, affording indene **127**.¹³⁰

Scheme 49



The intramolecular palladium(II)-catalyzed asymmetric cycloisomerization of enynes can be used for the synthesis of biaryls, which can be enantioselectively obtained when chiral ligands are employed. Thus, the use of (*R*)-Binap (6 mol%) as ligand combined to $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ (5 mol%) as palladium source in dichloroethane as solvent at 60 °C gave axially chiral biaryls with up to 99% *ee*, the reactivity and enantioselectivity depending on the nature and position of substituent of the arene ring.¹³¹ Particularly, the enynes with an aryl group substituted by an *o*-methoxy group at alkyne terminus gave chiral biaryls with good enantioselectivity, as exemplified in the preparation of enantiomerically pure biaryl **129** from the cyclization of **128** (Scheme 50).

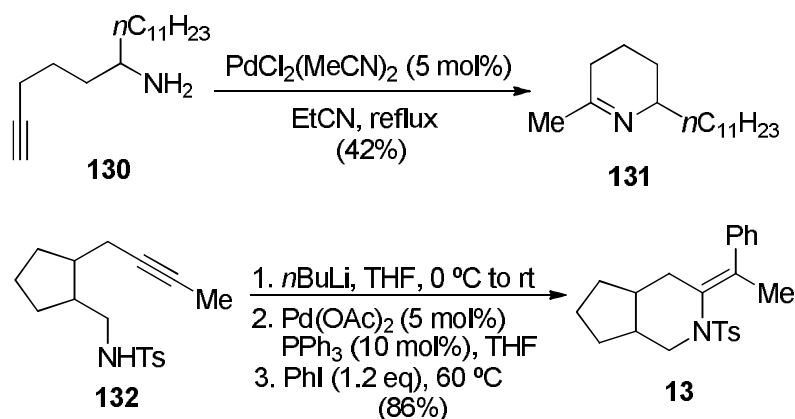
Scheme 50



3.2. Heterocycles

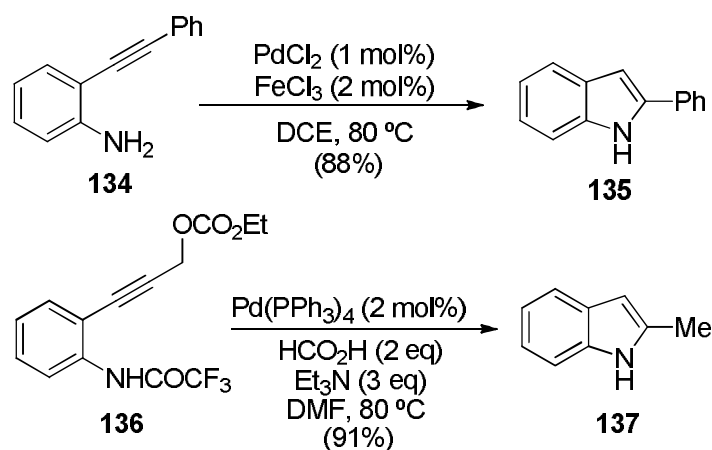
The palladium-catalyzed cyclization of alkynes bearing a heteronucleophile has proven extraordinarily useful for the synthesis of a wide variety of heterocycles,^{30,32c,d,32f,89c,129} the process proceeding by coordination of the palladium species to the C-C triple bond, followed by cyclization and reductive elimination. Both *endo* and *exo* cyclization products can be obtained depending on the number of carbon atoms between the triple bond and the nucleophilic center. Classic examples of this heterocyclic-leading process are the synthesis of five- and six-membered nitrogen-containing heterocycles by internal hydroamination,^{30a,89c,132} as in the intramolecular *exo-dig* aminopalladation of alkynylamines which gave intermediary alkenylpalladium compounds that hydrolyzed and isomerized to thermodynamically stable cyclic imines.¹³³ Thus, treatment of 3-alkynylamines with a catalytic amount of $\text{PdCl}_2(\text{MeCN})_2$ (5 mol%) gave exclusively 1-pyrrolines in good yields, whereas 5-alkynylamines afforded 2,3,4,5-tetrahydropyridines, as shown in Scheme 51 with the preparation of tetrahydropyridine **131** from alkynylamine **130**, after isomerization of the *exo* double bond.^{133a} When 1-amino-3-alkyn-2-ols were cyclized under PdCl_2 or $\text{Pd}(\text{OAc})_2$ catalysis (5 mol%) in refluxing DMF, pyrroles were obtained upon cyclization and dehydration.¹³⁴ This procedure can be made more versatile considering that it is possible to trap the intermediate alkenylpalladium species resulting from the intramolecular hydroamination with organic halides, in a tandem intramolecular aminopalladation/ cross-coupling reaction. This is the case of the stereodefined synthesis of 2-(alkylidene) piperidine **133**, which was synthesized by treatment of acetylenic tosylated amine **132** with *n*BuLi, followed by addition of a catalytic amount of $\text{Pd}(\text{OAc})_2$ (5 mol%) and triphenylphosphine (10 mol%) in THF and, finally, phenyl iodide (Scheme 51).¹³⁵

Scheme 51



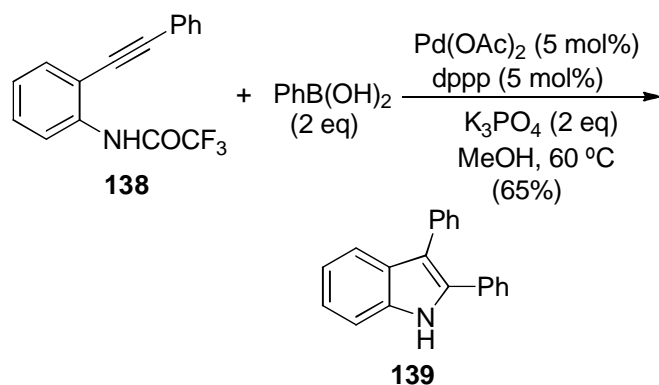
This intramolecular cyclization reaction to an alkyne has been one of the most frequently employed palladium-catalyzed methodologies for the synthesis of the already mentioned important indole system (see Section 3.2).^{30b,30d,32c-f,129} Thus, the palladium-catalyzed intramolecular cyclization of *o*-alkynylated anilines allows the synthesis of the indole ring, an example being the preparation of 2-phenylindole (**135**) from *o*-alkynylated aniline **134** after treatment in open air with a catalytic combination of PdCl₂ (1 mol%) and FeCl₃ (2 mol%), as reoxidant of the formed palladium(0) to palladium(II), in dichloroethane (DCE) as solvent at 80 °C (Scheme 52).¹³⁶ The internal cyclization with unprotected anilines can also be achieved using solid-supported palladium catalysts.¹³⁷ However, the use of unprotected anilines for this reaction is not so common, as usually lower conversions and high catalyst loadings are required.¹³⁸ More frequent has been the use of *N*-protected systems as starting materials, for instance in the form of trifluoroacetanilides, as exemplified in the synthesis of 2-methylindole (**137**) from *o*-alkynylated trifluoroacetanilide **136** (Scheme 52). This reaction was catalyzed by Pd(PPh₃)₄ (2 mol%) in the presence of a formate as reducing agent and takes place through an allenyl/propargylpalladium complex.¹³⁹ Interestingly, when two nitrogenated functionalities are conveniently situated to both sides of the alkyne system, a palladium-catalyzed double cyclization has been observed.¹⁴⁰

Scheme 52



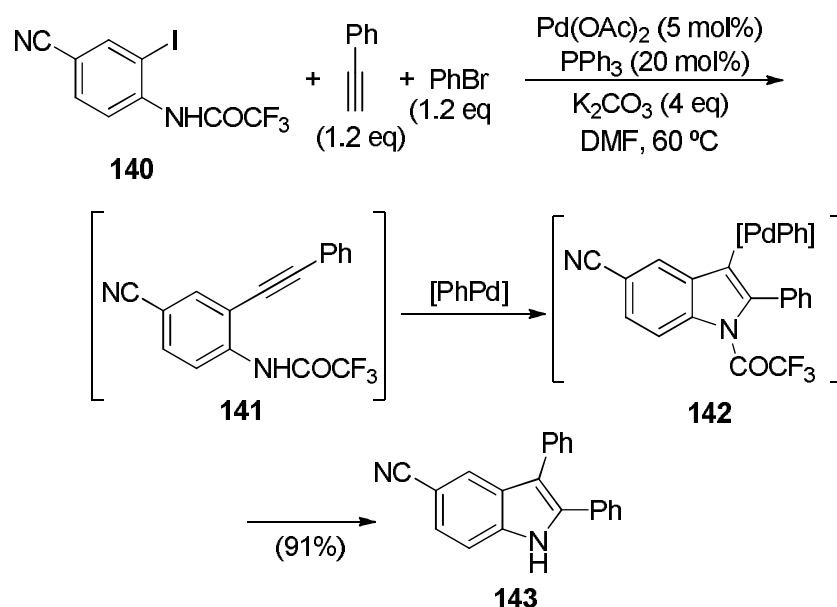
Furthermore, the indoles produced can be subsequently substituted at the 3-position by trapping the intermediate cyclic alkenylpalladium complex, formed after the cyclization, with an organic electrophile. Examples of the use of this useful methodology with aryl/heteroaryl,¹⁴¹ alkyl,¹⁴² and alkynyl halides,¹⁴³ α -iodoenones,¹⁴⁴ aryl^{141d} and vinyl triflates,^{141a,c,e} arenediazonium tetrafluoroborates,¹⁴⁵ and allyl esters¹⁴⁶ as electrophiles can be found. Arylboronic acids have also been employed, as in the case of the synthesis of 2,3-diphenylindole (**139**), which was obtained by cyclization of 2-alkynyltrifluoroacetanilide **138** catalyzed by Pd(OAc)₂ (5 mol%)/dppp (5 mol%) followed by an in situ cross-coupling with phenylboronic acid, the process being performed in the presence of potassium phosphate under an atmospheric pressure of oxygen, in methanol at 60 °C (Scheme 53).¹⁴⁷ Recently, even allylic alcohols have been used for the incorporation of allyl moieties to the 3-position of 2-substituted indoles when using this 5-*endo-dig* cyclization.¹⁴⁸

Scheme 53



The starting *o*-alkynylated aniline derivatives for these palladium-catalyzed indole syntheses are frequently prepared from terminal alkynes using the well-known palladium-catalyzed Sonogashira reaction (see Section 6.1). Therefore, it is suitable to in situ generate the *o*-alkynylated system from a terminal alkyne and an *o*-halogenated aniline derivative, and further perform the cyclization reaction. An example of the use of this indole synthesis is shown in Scheme 54, where *o*-iodinated trifluoroacetanilide **140** is converted into the intermediate alkynylated system **141** in the presence of phenylacetylene and a catalytic system formed by Pd(OAc)₂ (5 mol%) and triphenylphosphine (20 mol%). This species cyclizes forming the alkenylpalladium **142**, which gives 2,3-disubstituted indole **143** after reductive elimination.¹⁴⁹ Recent examples of the preparation of more complex heterocycles using this strategy can be found, as in the case of the preparation of pyrrolo[3,2-*c*]quinoline derivatives by palladium-catalyzed alkylation/cyclization of 3-iodo-4(phenylamino)quinolines.¹⁵⁰

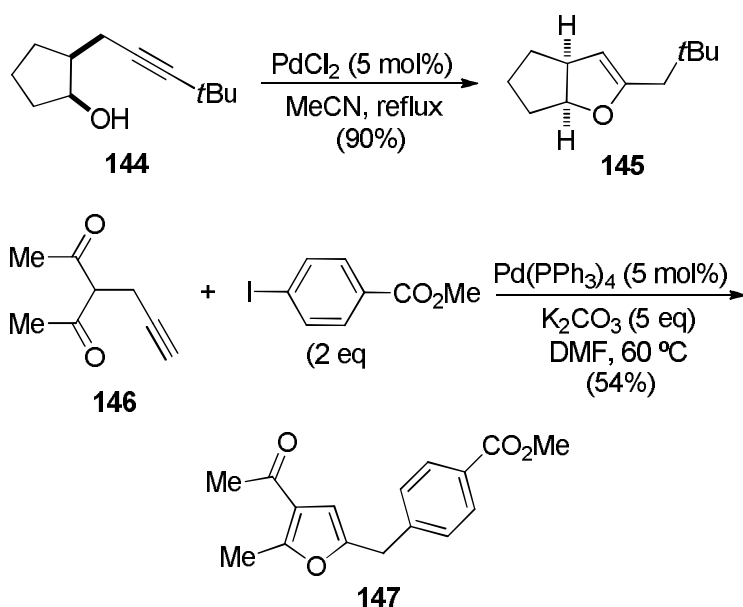
Scheme 54



The intramolecular hydroalkoxylation reaction of alkynes with a close OH group has been more deeply studied than the intermolecular version (see Section 3.2). This reaction provides a straightforward methodology for the construction of oxygen-containing heterocycles.^{30,129} Thus, a seminal work on this topic is the synthesis of bicyclic 2,3-dihydrofuran **145** by intramolecular hydroalkoxylation of alkynol **144**, a process catalyzed by PdCl₂ (5 mol%) in refluxing acetonitrile (Scheme 55).¹³² However,

3-, 4- and 5-alkyn-1-ols led to mixtures of the expected dihydrofurans and dihydropyrans and ketones resulting from the hydration of the triple bond. A similar procedure when applied to β,γ -acetylenic ketones or 2-methoxy-3-alkyn-1-ols afforded the corresponding furans in good yields.¹³² Other examples of the synthesis of furans are the palladium-catalyzed internal cyclization of (*Z*)-2-en-4-ynol,¹⁵¹ and the cyclization of 2-propargyl-1,3-dicarbonyl compounds such as **146** with vinyl and aryl triflates or halides, such as methyl *p*-iodobenzoate, under $\text{Pd}(\text{PPh}_3)_4$ catalysis (5 mol%) in the presence of potassium carbonate as base, which gave the 2,3,5-substituted furan **147** (Scheme 55).¹⁵²

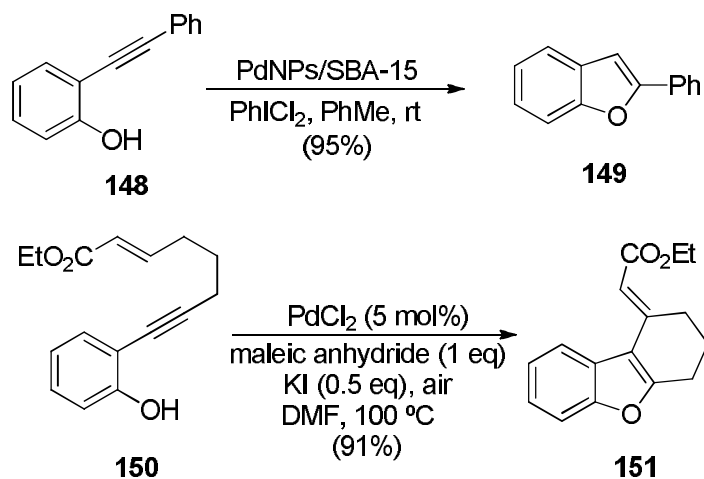
Scheme 55



When *o*-alkynylated phenols are involved as starting materials, the corresponding benzofurans are obtained after a palladium-catalyzed intramolecular hydroalkoxylation. A recent example can be seen in Scheme 52, where 2-benzofuran (**149**) is obtained from *o*-alkynylated phenol **148** in a cyclization carried out in a flow reactor and catalyzed by PdNPs immobilized on mesoporous silica SBA-15, in the presence of iodobenzene dichloride as an oxidant, in toluene at room temperature (Scheme 56).¹⁵³ In addition, an example of a further extension of this strategy to the synthesis of more complex systems is the preparation of tetrahydrodibenzofuran **151** by the usual intramolecular cyclization of alkynylated phenol **150** followed by an oxidative Heck reaction, this cascade process being catalyzed by PdCl_2 (5 mol%) in the presence

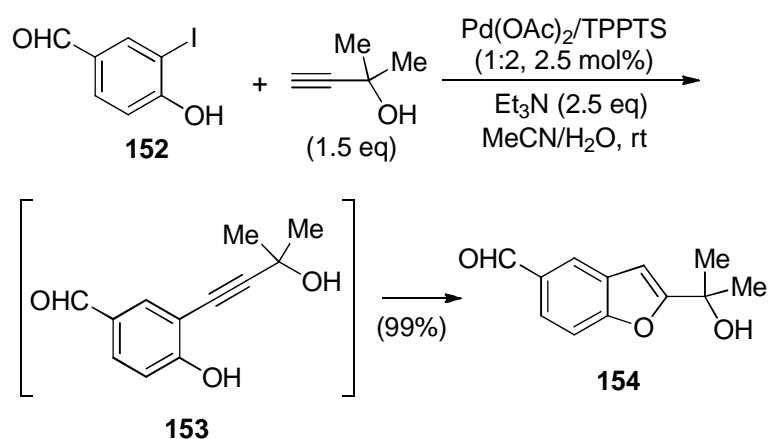
of maleic anhydride as additive and potassium iodide in DMF at 100 °C in air (Scheme 56).¹⁵⁴ Moreover, similarly than in the case of the synthesis of 2,3-disubstituted indoles, 2,3-disubstituted benzofurans can be prepared by cyclization of *o*-alkynylated phenols following by trapping the alkenylpalladium intermediate with unsaturated halides or triflates.¹⁵⁵

Scheme 56



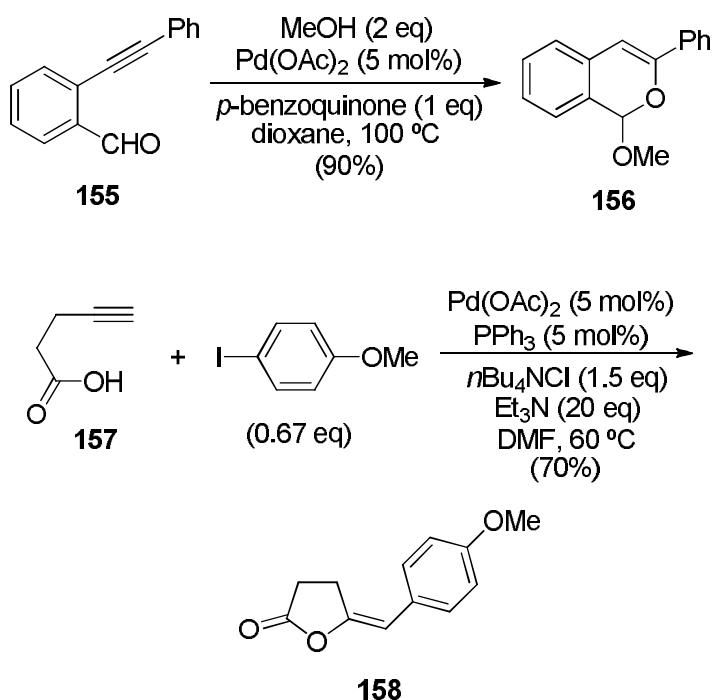
However, it has been more frequent to prepare these kind of benzocondensed systems from *o*-iodinated phenols and terminal alkynes by the above mentioned in situ palladium-catalyzed Sonogashira coupling (see Section 6.1) followed by intramolecular cyclization.^{155,156} An example is the preparation of benzofuran **154** by in situ formation of alkynylphenol intermediate **153** from iodophenol **152** and 2-methylbut-3-yn-2-ol under Sonogashira conditions, followed by intramolecular cyclization. The process is catalyzed by a combination of Pd(OAc)₂ and a water-soluble phosphine such as 3,3',3''-phosphinidynetris(benzenesulfonic acid) (TPPTS), in the presence of triethylamine as base in aqueous acetonitrile as solvent at room temperature (Scheme 57).¹⁵⁷ In addition, the use of a ligand and an amine can be avoided, using tetra-*n*-butyl acetate as base in acetonitrile as solvent under ultrasound irradiation.¹⁵⁸ When this two-step Sonogashira-cyclization methodology is performed starting from *o*-iodobenzoic acids, phthalide isobenzofuranones¹⁵⁹ and 3-substituted isocoumarins¹⁶⁰ have been obtained.

Scheme 57



1*H*-Isochromenes have been prepared from *o*-alkynylated benzaldehydes in a process catalyzed by Pd(OAc)₂ (5 mol%) in the presence of *p*-benzoquinone and an alcohol, in dioxane as solvent, as in the case of the synthesis of isochromene **156** from alkynylbenzaldehyde **155** (Scheme 58).¹⁶¹ This process has also been performed via the in situ Sonogashira/cyclization strategy, without isolation of the disubstituted alkyne intermediate, starting from 2-chloro-3-formylquinolines and leading to pyrano[4,3-*b*]quinolines.¹⁶² In addition, indoles has been used as nucleophiles, instead of alcohols for this reaction.¹⁶³ Moreover, 4-alkynoic acids can be transformed regio- and stereoselectively into (*E*)-butyrolactones by reaction with aryl or vinyl halides or triflates.¹⁶⁴ The reaction is catalyzed by a combination of Pd(OAc)₂ (5 mol%) and triphenylphosphine (5 mol%) in the presence of tetra-*n*-butylammonium chloride (TBAC) and triethylamine in DMF at 60 °C, as shown in Scheme 58 with the preparation of butyrolactone **158** from pent-4-ynoic acid (**157**) and *p*-iodoanisole. Other more complex oxygenated systems, such as chromene quinoxalines have been recently prepared by alkylation of phenol-containing 2-chlorinated quinoxalines with terminal alkynes under palladium-on-charcoal catalysis.¹⁶⁵

Scheme 58



4. Chemicals by Palladium-Catalyzed Oxidation of Alkynes

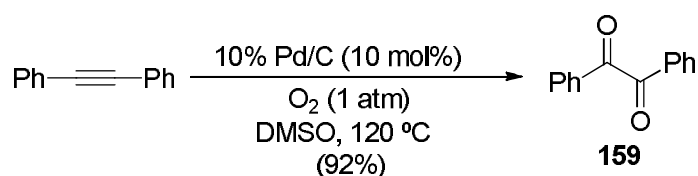
The carbon-carbon triple bond can be oxidized under palladium-catalyzed conditions,¹⁶⁶ although this is a procedure much less explored than the corresponding oxidation of alkenes. The reactivity and selectivity of the reaction depends on the substitution of the triple bond, 1,2-diarylethyne being the most reactive. The main oxidation products are 1,2-diketones, esters or furans, depending on both the used procedure and the substrate. However, it is known that catalytic amounts of $\text{Pd}(\text{NO}_3)_2$ and PdCl_2 in aqueous nitric acid can transform acetylene in oxalic acid and glyoxal, respectively,^{166a} although these methodologies have not found practical uses. In this section, examples of palladium-catalyzed synthetic procedures leading to the above mentioned main type of chemicals are shown.

4.1. 1,2-Diketones

The palladium-catalyzed oxidation of the carbon-carbon triple bond of internal alkynes, mainly diarylated acetylenes, leading to the corresponding 1,2-diketones has been carried out using DMSO as a solvent and an oxidant, in reactions catalyzed by

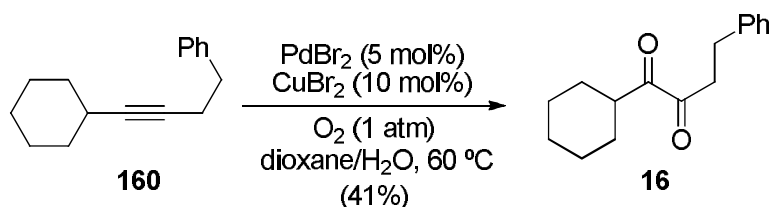
PdCl_2 ,¹⁶⁷ PdI_2 ¹⁶⁸ or the combination $\text{Pd}(\text{OAc})_2/\text{CuBr}_2$.¹⁶⁹ Other procedures that combine DMSO and molecular oxygen as dual oxidants using 10% Pd/C (10 mol%) as catalyst can be used, as shown in the typical formation of benzil (**159**) from diphenylacetylene (Scheme 59).¹⁷⁰ It is necessary to note that all these DMSO-containing oxidation procedures produce unpleasant dimethylsulfide as oxidation residue. Therefore, other oxidants have also been used, as in the recent oxidation of diarylalkynes catalyzed by 10% Pd/C (10 mol%), where pyridine *N*-oxide has been used as oxidant and solvent, the supported catalyst being recovered by filtration and reused up to five times.¹⁷¹

Scheme 59



A Wacker-type oxidation of alkynes has been developed using as catalyst the combination PdBr_2 (5 mol%)- CuBr_2 (10 mol%) using molecular oxygen as oxidant in aqueous dioxane as solvent.¹⁷² As usual, almost all the examples of alkynes reported following this procedure are diarylalkynes, although there is an example using the dialkylated acetylene **160** which is also oxidized to 1,2-diketone **161** (Scheme 60). Moreover, the mixture PdCl_2 (5 mol%)- CuCl_2 (5 mol%) has been used as catalytic mixture in the oxidation of diarylalkynes and some alkylphenylalkynes to the corresponding diketones, the reaction being performed in PEG-400 in the presence of water at room temperature.¹⁷³

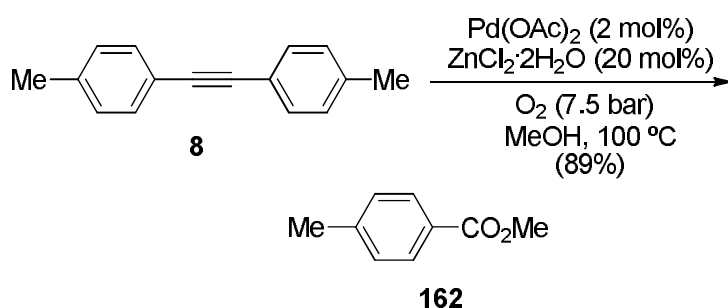
Scheme 60



4.2. Esters

Esters can be formed by oxidative cleavage of alkynes under palladium catalysis in the presence of an alcohol.¹⁷⁴ The reaction proceeds using Pd(OAc)₂ (2 mol%) as catalyst in the presence of ZnCl₂·2H₂O (20 mol%) under oxygen pressure (7.5 bar), using the alcohol as solvent at 100 °C, as in the case of the oxidative cleavage of di-*p*-tolylacetylene (**81**) in methanol, which afforded the corresponding methyl ester **162** (Scheme 61). Unsymmetrical diaryl- and alkyl aryl acetylenes gave mixtures of both esters, whereas terminal alkynes gave only esters from the substituted side.

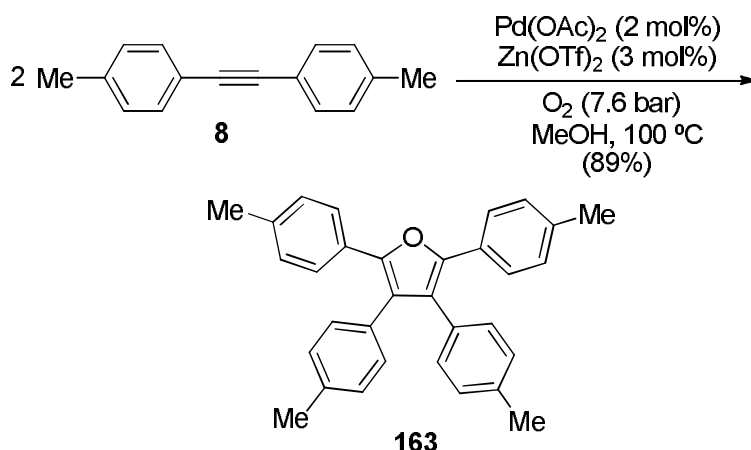
Scheme 61



4.3. Furans

Related to the oxidative cleavage of alkynes to esters,¹⁷⁴ it was discovered that under similar reaction conditions, but using zinc(II) triflate (3 mol%) as Lewis acid, diarylalkynes were transformed into tetrasubstituted furans.¹⁷⁵ The process probably takes place through formation of the corresponding 1,2-diketone, which suffers Lewis acid-promoted cyclocondensation. An example of this reaction is shown in Scheme 62, with the formation of furan **163** by oxidation-cyclocondensation of di-*p*-tolylacetylene (**81**). In addition, tetrasubstituted furans from diarylalkynes have also been obtained in a reaction catalyzed by PdCl₂ in DMA (*N,N*-dimethylacetamide)-H₂O as solvent under an oxygen atmosphere,¹⁷⁶ as well as using Pd(OAc)₂ as catalyst and a fluororous biphasic system of DMA and perfluorodecalin as solvent under oxygen.¹⁷⁷

Scheme 62



5. Olefins by Palladium-Catalyzed Reduction of Alkynes

The catalytic reduction by partial hydrogenation (semi-hydrogenation) of internal alkynes is an efficient method for the production of olefins, and palladium catalysts have been the most effective achieving this transformation.¹⁷⁸ This reaction, particularized in the case of the semi-hydrogenation of acetylene to ethylene, is applied, for instance, into the industrial polymerization of ethylene to polyethylene in order to purify the feedstock from acetylene, which would otherwise poison the polymerization catalyst.¹⁷⁹ Thus, research on new palladium species for the catalytic semi-hydrogenation of acetylene to ethylene is a subject of present industrial interest.¹⁸⁰

The semi-hydrogenation of alkynes is problematic because the reaction is often accompanied by isomerization and/or over-reduction of the alkenes formed with the same catalysts. Commonly, palladium is not employed alone. Instead the reaction is promoted by a second metal,^{179a} termed also as a co-catalysts or just as a promoter, which slightly modifies the activity, selectivity and stability of the catalyst. These promoters can be metals of group 11 (Cu, Ag, Au), sp metals or semi-metals (Pd, Sn, Bi, Ga among others), and group 1 metal ions (Na, K).¹⁸¹ In addition, a selectivity or process modifier is added, such as carbon monoxide, amines, nitriles, alkali and sulfur compounds, which are species able to coordinate the palladium modifying its reactivity.^{179a, 182} Studies of the gas-phase hydrogenation of alkynes on solid palladium catalysts have shown strong modifications in the near-surface region of palladium, in which carbon (from fragmented feed molecules) occupies interstitial lattice sites forming a palladium carbide. Much less carbon is dissolved in palladium during

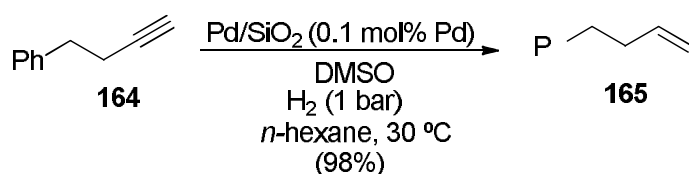
unselective, total hydrogenation, and this process proceeds on hydrogen-saturated β -hydride, whereas selective hydrogenation is only possible after decoupling bulk properties from the surface events.¹⁸³ Thus, the population of subsurface sites of palladium by either hydrogen or carbon, governs the hydrogenation events on the surface.

The Lindlar catalyst [Pd/CaCO₃ and Pb(OAc)₂, in conjunction with quinoline], is an old and effective system for the semi-hydrogenation of internal alkynes to the corresponding (Z)-alkenes,¹⁸⁴ although it has disadvantages, such as the use of environmentally unfriendly Pb(OAc)₂ during the catalyst preparation, and that generally it cannot be used for the semi-hydrogenation of terminal alkynes. Therefore, a variety of palladium-based catalyst systems, mainly heterogeneous,^{178c,d} but also homogeneous,^{178b} have been studied for this palladium-catalyzed semi-hydrogenation of acetylenes to olefins. Particularly, the development of catalytic systems based on specifically created supported PdNPs for this semi-hydrogenation reaction has been frequent in the last years, as the catalytic behavior of supported PdNPs vary considerably in terms of both the size of the particles and their interaction with the support.¹⁸⁵ For instance, it has been shown that larger particles are more selective to semi-hydrogenation.¹⁸⁶

Palladium(0) has been supported on different materials for achieving this reductive transformation. Thus, mono- and bi-metallic palladium and tungsten catalyst were supported over alumina and used in the partial hydrogenation of hept-1-yne (substrate/palladium: 1,100 molar ratio) under a hydrogen pressure of 1.5 bar in toluene at 30 °C, bimetallic PdW species affording better results.¹⁸⁷ In addition, palladium(0) supported on ZnO and a palladium-zinc alloy, have been used as catalyst in the gas-phase semi-hydrogenation of pent-1-yne, achieving suppression of the total hydrogenation to the corresponding alkane, contrary to when using palladium(0) on silica gel as catalyst.¹⁸⁸ However, it has been shown that the addition of small amounts of DMSO to a Pd/SiO₂ catalyst suppresses this over-hydrogenation and isomerization of alkenes, probably due to preferential adsorption of DMSO compared to alkene products. This supported catalyst has been then applied to both internal alkynes and terminal alkynes, as shown in the semi-hydrogenation of **164** to give alkene **165** (Scheme 63).¹⁸⁹ The catalyst was separable from the reaction mixture after the hydrogenation and reusable without loss of its high catalytic activity or selectivity. Moreover, palladium(0) has been deposited on the surface of SiO₂-Al₂O₃ in an 'eggshell' distribution through

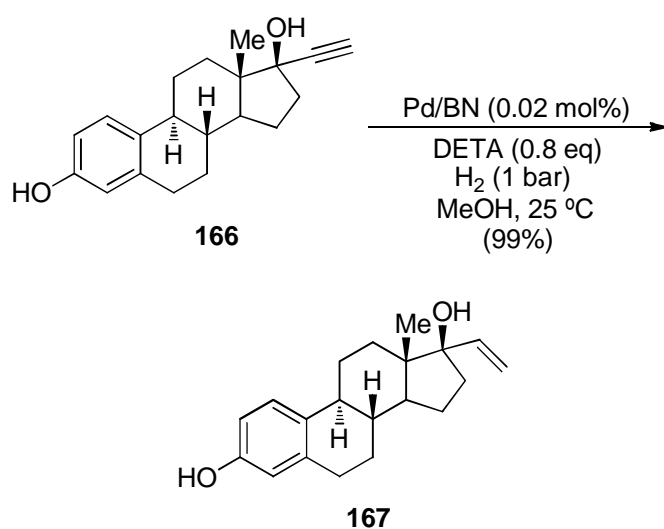
the reduction of palladium salts by solution-phase carbon monoxide.¹⁹⁰ This distribution, compared to a uniformly impregnated catalyst, had significant catalyst activity in the gas-phase partial hydrogenation of phenylacetylene, an important industrial process in polystyrene production to eliminate alkyne traces which poison the polymerization catalysts. This process has also been achieved in liquid-phase by using 1% palladium(0) supported on TiO₂, achieving moderate to high selectivity towards styrene (86-90%) at complete conversion, the process being carried out under an hydrogen pressure of 1-5 bar, in ethanol at room temperature.¹⁹¹

Scheme 63



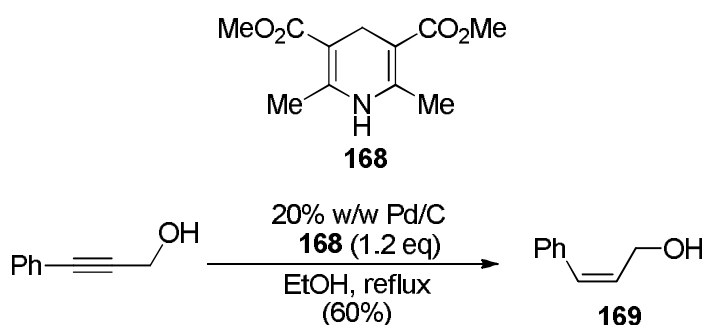
Graphite oxide has also been used as a supporting material for PdNPs of controlled crystallite size, and this material has been used as a catalyst (substrate/catalyst: 2,500-10,000 ratio) in the liquid-phase partial hydrogenation of internal alkynes (10 bar, 25 °C), affording selectivities for the *cis*-alkenes ranging from 83 to 98%. Recently, palladium(0) supported on boron nitride (Pd/BN) has been applied as catalyst in the presence of diethylenetriamine (DETA) to the semi-hydrogenation of terminal and internal alkynes to furnish the corresponding olefins, as exemplified in the very effective partial hydrogenation of estrone-derived alkyne **166** to compound **167** (Scheme 64). The reaction has been performed under an atmospheric pressure of hydrogen in methanol at room temperature and resulted in a very high *cis*-selectivity when internal alkynes were involved.¹⁹²

Scheme 64



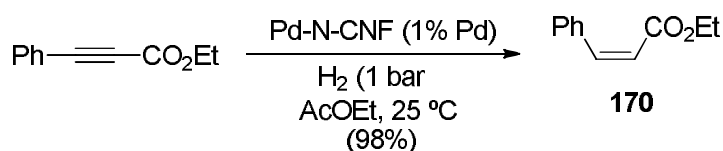
The BASF company recently developed a technology (NanoSelect™)¹⁹³ that allows the preparation of the now commercially available colloidal palladium(0) on water-wet activated carbon (NanoSelect LF 100) or titanium silicate (NanoSelect LF 200), these materials acting as catalyst for the selective hydrogenation of alkynes to alkenes, its results being comparable to the Lindlar catalyst. In addition, palladium on carbon (20% w/w) has been employed as catalyst for the partial hydrogenation of internal and terminal alkynes using the Hantzsch ester (**168**) as hydrogen donor.¹⁹⁴ The reaction was performed in refluxing ethanol as solvent, as shown in Scheme 65 in the stereoselective preparation of the (*Z*)-allylic alcohol **169** from 3-phenylprop-2-yn-1-ol, other functionalized systems such as phenylpropionic acid and its methyl ester giving also good results, although terminal alkynes gave rise to rather low yields. Furthermore, PdNPs modified with subsurface carbon via blending a glucose precursor, have been used as catalyst in the liquid-phase hydrogenation of 3-hexyn-1-ol under hydrogen (3 bar) in isopropanol at 30 °C, achieving 92% selectivity towards the corresponding alkene in a 10.8 *Z/E* ratio.¹⁹⁵ Interestingly, the use of commercial 5% Pd/C as catalyst under these conditions gave no selectivity at all towards the alkene.

Scheme 65



PdNPs have been supported on other carbonaceous materials apart from activated carbon, such as carbon black and multiwall carbon nanotubes, and have been used as recyclable catalysts for the gas-phase semi-hydrogenation of phenylacetylene, those supported on carbon nanotubes giving the highest selectivity (ca. 96%), their activity remained intact after five reuse cycles.¹⁹⁶ Carbon nanofibers (CNF) have also been employed as support for PdNPs, acting as catalyst in the liquid phase semi-hydrogenation of 1-pentyl-3-ol,¹⁹⁷ whereas when doped with nitrogen (Pd-N-CNF, 1% Pd, substrate/catalyst: 2,000) allowed the selective *cis*-hydrogenation of internal alkynes, working at atmospheric pressure of hydrogen in ethyl acetate as solvent at room temperature, as in the hydrogenation of ethyl phenylpropiolate to the corresponding (*Z*)-alkene **170** (Scheme 66).¹⁹⁸ Moreover, palladium loaded in detonation nanodiamond has been explored as catalyst in the semi-hydrogenation of diphenylacetylene under molecular hydrogen (20 bar) in methanol at 50 °C, although its selectivity *cis*-stilbene to 1,2-diphenylethane was low.¹⁹⁹

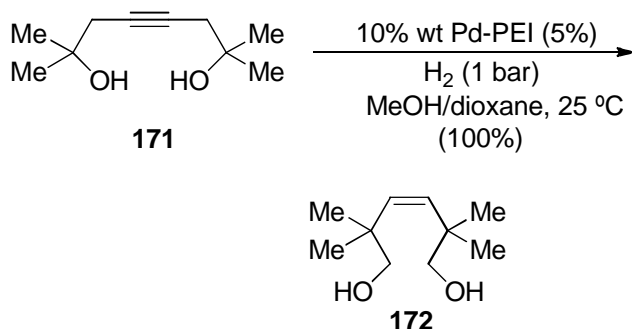
Scheme 66



Polymers have also been used for supporting PdNPs formed by impregnation of the polymer with palladium(II) salts and further reduction. For example, hypercrosslinked polystyrene-containing PdNPs has been used as catalysts in the selective hydrogenation of terminal acetylene alcohols (1 bar H₂ pressure, toluene, 25 °C), these nanocomposites

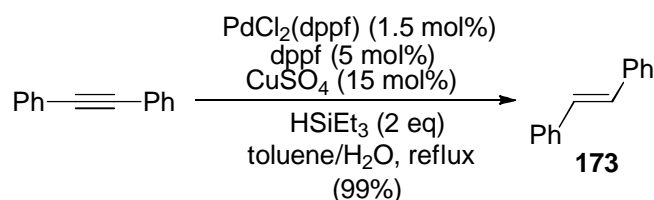
showing high selectivity (up to 98.5% at 100% conversion) towards the corresponding terminal olefins.²⁰⁰ However, more abundant examples where the polymer contains nitrogenated groups can be found, as nitrogen atoms can act as modifiers of the activity of the palladium species. Thus, PdNPs have been supported on polyaniline and employed as catalyst (1 mol%) in the hydrogenation of diphenylacetylene and ethyl phenylpropiolate, the reaction being performed under hydrogen atmosphere (1 bar) in methanol at room temperature.²⁰¹ In the former case, *Z*-stilbene was the main product (12% of 1,2-diphenylmethane byproduct is obtained), commercial 10% Pd/C affording just 1,2-diphenylethane from total hydrogenation, whereas much less selectivity was observed in the last case. In addition, PdNPs supported on polyethyleneimine (10% wt Pd-PEI) have resulted very effective and (*Z*)-selective as catalyst in the partial hydrogenation of internal and terminal alkynes, working under an atmospheric pressure of hydrogen in a 1:1 mixtures of methanol/dioxane or methanol/ethyl acetate as solvents at room temperature,²⁰² as in the case of the semi-hydrogenation of propargylated diol **171** to the corresponding dihydroxylated (*Z*)-alkene **172** (Scheme 67).^{202a} Moreover, gel-type co-polymeric resins obtained by polymerization of glycidyl methacrylate, styrene and ethylene glycol dimethacrylate, and functionalized with amine groups have been used as supports for PdNPs, acting this material as catalyst with low palladium content (0.5- 1 wt% Pd) for the partial hydrogenation of alkynes such as 2-butyne-1,4-diol or phenylacetylene, the catalyst being recycled up to four times keeping its reactivity.²⁰³ Finally, examples of nitrogenated dendron-stabilized PdNPs for the semi-hydrogenation of internal alkynes²⁰⁴, as well as PdNPs stabilized on DNA from salmon or calf for the partial hydrogenation of 3-butyne-2-ol²⁰⁵ can be found.

Scheme 67



The use of homogeneous conditions in the palladium-catalyzed *syn*-semi-hydrogenation of alkynes leading to alkenes is less frequent,^{178b} although examples of the use of bisphosphine-containing complexes of palladium employed in alkyne semi-hydrogenation reactions can be found.²⁰⁶ An uncommon (*E*)-selectivity for the corresponding olefin in the partial reduction of internal alkynes by transfer hydrogenation has been achieved with PdCl₂(dppf) (1.5 mol%) as catalyst and CuSO₄ as modifier, using HSiEt₃ as hydrogen donor in refluxing aqueous toluene. Under these conditions, the corresponding (*E*)-alkenes were the main products, as in the case of the reduction of diphenylacetylene, leading to *trans*-stilbene (**173**) (Scheme 68).²⁰⁷ Interestingly, in the absence of the CuSO₄ modifier, the *cis*-product was mainly obtained, suggesting that CuSO₄ induces isomerization of the nascent *cis*-isomer. In addition, it has been shown in a transfer semihydrogenation of alkynes catalyzed by Pd₂(dba)₃ (1 mol%)/dppb (2-4 mol%) that, by changing the hydrogen donor from formic acid to 25% aqueous formic acid in dioxane at 80 °C, the stereoselectivity of the process can be switched from *Z* to *E*, again through an in situ *Z/E* isomerization.²⁰⁸ Although both transfer hydrogenation methods mostly provide excellent *E*-selectivities and yields, their dependence on a *Z/E* isomerism largely restricts the substrate scope to internal, conjugated alkynes, nonconjugated internal alkynes giving rather poor stereoselectivity.

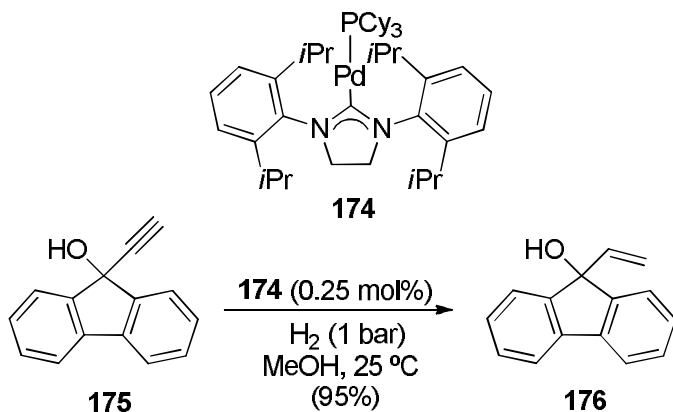
Scheme 68



Examples of the use of palladium-NHC complexes as catalysts in the semi-hydrogenation of alkynes can also be found. Thus, the NHC-complex **174** has been used as catalyst (0.25 mol%) in the reduction of diphenylacetylene to *cis*-stilbene and also in the partial hydrogenation of fluorenol-derived terminal alkyne **175** to olefin **176** (Scheme 69), the reaction being carried out under atmospheric pressure of hydrogen in MeOH at room temperature.²⁰⁹ Other examples of the use of zero-valent palladium-NHC complexes as catalysts for the transfer semi-hydrogenation of terminal²¹⁰ and internal^{210,211} alkynes, using HCO₂H as hydrogen source have been reported. Recently, even ammonia-borane has been used as hydrogen donor for the *cis*-semihydrogenation

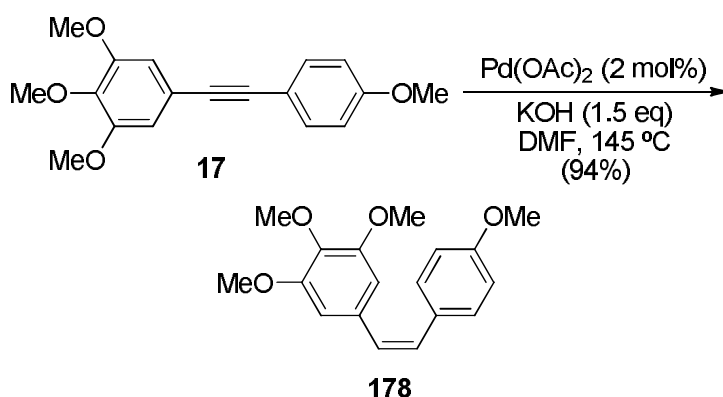
of a couple of symmetric internal alkynes, using a very low loading (0.05-0.25 mol%) of a zero-valent palladium-NHC complex as catalyst.²¹²

Scheme 69



Excellent results have been achieved in the stereoselective partial hydrogenation of internal alkynes using the simple ligand-free Pd(OAc)₂ as catalyst (2 mol%) and DMF/KOH as hydrogen source at 145 °C, a methodology applied to the synthesis of analogues of *cis*-combretastatin A-4, such as (*Z*)-alkene **178** from the reduction of diarylacetylene **177** (Scheme 70).²¹³

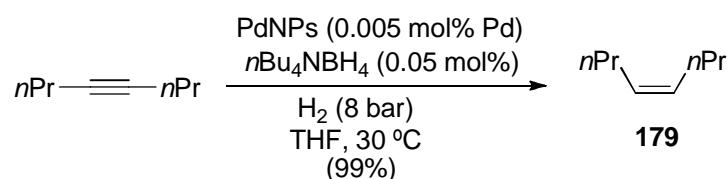
Scheme 70



Solubilized PdNPs, created from Pd(OAc)₂ and potassium *tert*-butoxide in DMF at room temperature, and stabilized by the presence of tetra-*n*-butylammonium borohydride, have been employed in the semi-hydrogenation of terminal and internal alkynes such as oct-4-yne, with a substrate/Pd ratio as high as 200,000:1 under a

hydrogen atmosphere (8 bar) in THF at 30 °C, to give (*Z*)-oct-4-ene (**179**) in >99% content and complete conversion (Scheme 71), the absence of tetra-*n*-butylammonium borohydride leading to partial over-reduction of the alkene.²¹⁴ In addition, differently shaped palladium nanocrystals with controlled size have been assayed in selective alkyne semi-hydrogenations, such as nanohexagons and nanospheres²¹⁵ or nanocubes²¹⁶ for the hydrogenation of 2-methyl-3-butyn-2-ol to the corresponding alkene, the nanocrystals shape becoming an important factor in the selectivity of the process.

Scheme 71

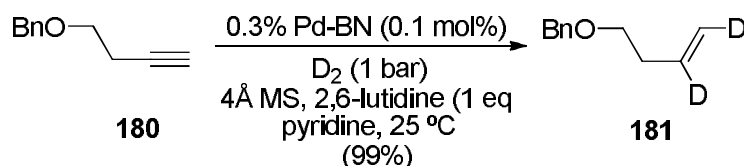


The reaction of PdCl₂ dispersed in TBAB with tri-*n*-butylamine at 120°C led to stable isolable PdNPs which have been dispersed in an ionic liquid or in methanol or used in solventless conditions for the *cis*-selective hydrogenation of 2-hexyne (2 bar of hydrogen and 20°C), the use of [bmim][BF₄] as ionic liquid allowing the recycle of the catalyst up to four times keeping the reaction rate.²¹⁷ In addition, mono-dispersed PdNPs have been prepared in ionic liquids and employed in the semi-hydrogenation of internal and terminal alkynes, the system being suitable for recycling affording similar results after four runs. Hydrogen pressure influenced strongly the selectivity towards alkanes or alkenes using this last methodology, and 1 bar hydrogen pressure yielded (*Z*)-alkenes, whereas a 4 bar hydrogen pressure afforded alkanes.²¹⁸

cis-Deuterated alkenes can be prepared by using the Lindlar catalyst for partial reductive deuteration of 1,2-disubstituted alkynes in the presence of an atmosphere of D₂. However, D₂ gas is expensive and not easily obtainable because of the usually complicated acquisition process as a consequence of its combustible nature and import restrictions, being considered as a strategic material. Thus, *cis*-deuterated alkenes have been obtained from internal alkynes, such as diphenylacetylene, using D₂ gas generated by the electrolysis of D₂O in a special flow reactor using the Lindlar catalyst.²¹⁹ Terminal alkynes cannot be transformed into the corresponding *cis*-D₂-alkenes using the Lindlar catalyst due to over-reduction, and recently they have been obtained by reaction of D₂ gas, generated by stirring Pd/C in D₂O at room temperature, with terminal alkynes

using a 0.3% palladium supported on boron nitride (Pd-BN, 0.10 mol%) as catalyst in the presence of molecular sieves and 2,6-lutidine as base in pyridine as solvent at room temperature.²²⁰ This methodology is exemplified in Scheme 72 with the reduction of terminal alkyne **180** to the *cis*-deuterated alkene **181**. In addition, *trans*-deuteration has been observed by using a combination of hexamethyldisilane and deuterium oxide as a deuterium transfer reagent in the presence of a catalytic amount of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]_2$ (5 mol%) and PPh_3 (10 mol%) in *N,N*-dimethylacetamide at 80 °C, the process taking place through the corresponding (*Z*)-isomer intermediate.²²¹

Scheme 72



6. Chemicals by Palladium-Catalyzed C-C Coupling Reactions of Alkynes

Palladium-catalyzed methodologies are probably the most effective for the formation of C(sp)-C(sp²) and C(sp)-C(sp) bonds starting from terminal alkynes and leading to an important array of conjugated systems. Thus, the palladium-catalyzed transformation of terminal alkynes into alkynylated arenes and heteroarenes, 1,3-enynes and 1,3-diynes, as well as carbonyl-containing conjugated ynones and ynamides will be presented in this section. Only examples of the use of ‘real’ alkynes as starting materials in palladium-catalyzed transformations will be commented, the use of previously prepared alkynylated species (such as alkynyl metals) being excluded.

6.1. Alkynylated Arenes

Alkynyl arenes are chemicals of high interest, for instance as intermediates in the synthesis of carbo- and heterocycles (see Section 3) or becoming part of highly conjugated systems in advanced acetylene-based materials for electrooptical

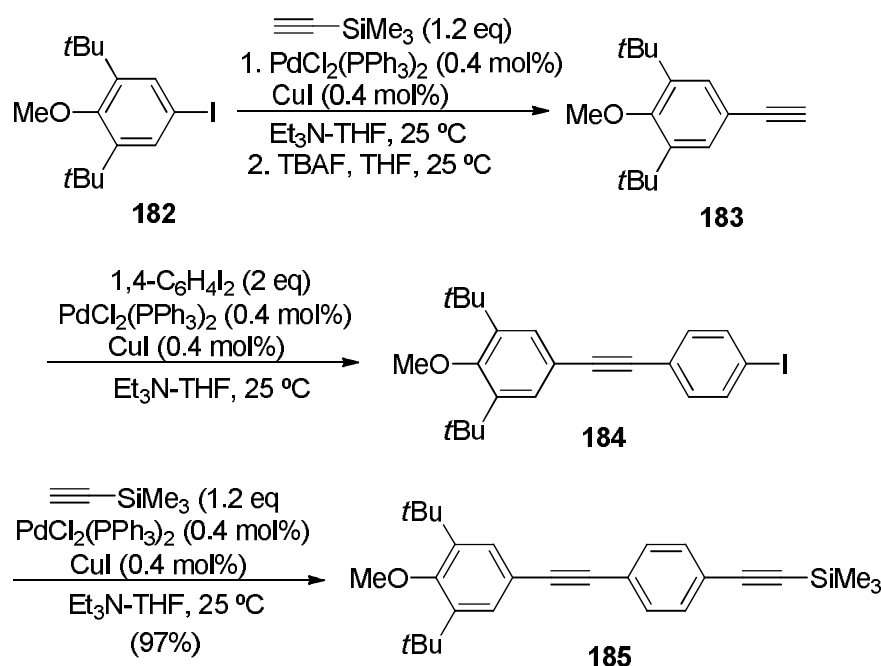
applications²²² or nanoscale architectures.²²³ Although there are limited examples of the direct palladium-catalyzed alkynylation of arene C-H bonds under oxidative conditions through chelation-assisted strategies,²²⁴ the palladium-catalyzed Sonogashira cross-coupling reaction between a terminal alkyne and an aryl halide or triflate is the main and principal way of obtaining this kind of compounds. Although there are recent ligand-free procedures involving continuous flow conditions with tubular reactors of catalytic metal inner surfaces,²²⁵ the process is typically performed using a phosphine-containing palladium complex as catalyst in the presence of a catalytic amount of a copper(I) salt and an excess of an amine (or inorganic base) under homogeneous conditions.²²⁶ The presence of the copper co-catalyst (the traditional and properly named Sonogashira reaction), although beneficial in terms of increasing the reactivity of the system, adds additional environmental problems, complicates purification of the formed alkynes and makes necessary to avoid the presence of oxygen in order to block the undesirable formation of 1,3-diynes from alkyne homocoupling through a copper-mediated Hay/Glaser reaction.²²⁷ Therefore, coupling procedures avoiding the use of copper have been developed by making the catalytic system more reactive, achieving the so-called 'copper-free' Sonogashira reaction.²²⁶ This reaction name, although very common, is a bit unfair, as Cassar²²⁸ and Heck²²⁹ pioneered this palladium-catalyzed alkynylation reaction in the absence of copper.

As in other palladium-catalyzed cross-coupling reactions, the palladium species experiences more or less easy oxidative addition to the carbon-halogen(triflate) bond depending on the type of halogen atom (or triflate) present,²³⁰ the general reactivity order of the sp^2 species being aryl iodide > aryl triflate \geq aryl bromide \gg aryl chloride. Therefore, the Sonogashira reaction with terminal alkynes usually is easier when the more unstable aryl iodides are used, whereas the use of the more stable aryl chlorides, if not strongly activated (electron-poor), still represent a challenge.²²⁶ In this section, we will present some recent examples of the use of terminal alkynes for the preparation of alkynylated arene systems by means of the palladium-catalyzed Sonogashira cross-coupling reaction, including homogeneous and heterogeneous catalytic systems as well as copper-cocatalyzed and copper-free procedures.

The most used palladium catalysts for this reaction have been $Pd(PPh_3)_4$ [sometimes formed in situ by mixing a palladium(II) salt and triphenylphosphine] and the more stable and soluble $PdCl_2(PPh_3)_2$. These two complexes continue to be nowadays by far the most frequently employed catalysts when a copper-cocatalyzed

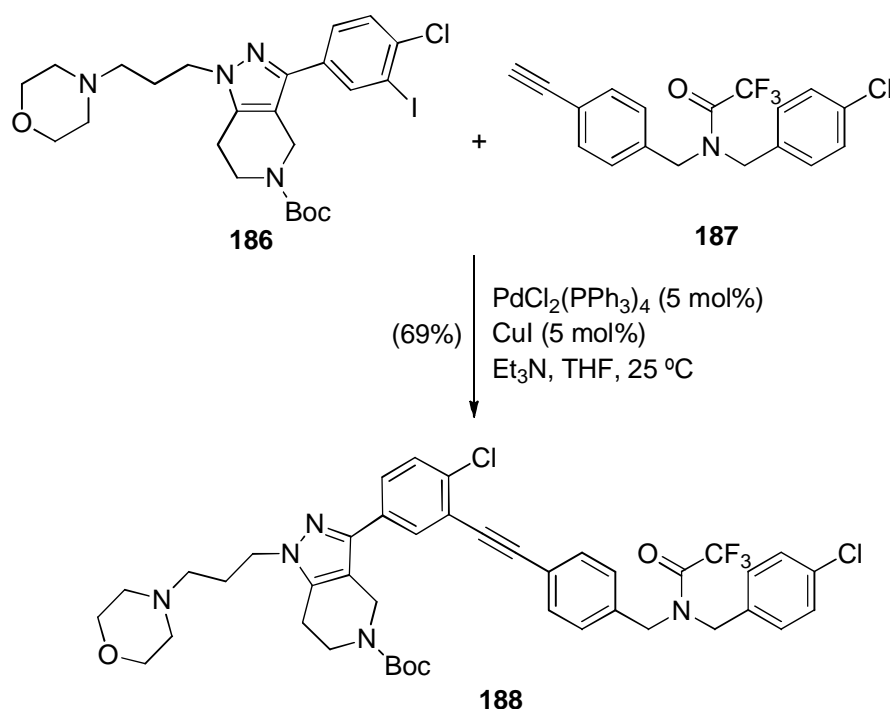
Sonogashira cross-coupling reaction is going to be used in a practical application. Example of a practical use of this typical copper-cocatalyzed Sonogashira alkynylation reaction using aryl iodides as coupling partners is the preparation of phenylene ethynylene polymers or oligomers, which are key compounds for the fabrication of electronic and optoelectronic devices.²²² Another recent example is the synthesis of a series of di-*tert*-butyl-substituted phenylene ethynylene dimer, trimer, tetramer, and pentamer, compounds with high interests as organic wires, in a stepwise process.²³¹ Thus, reaction of di-*tert*-butylated iodobenzene **182** with trimethylsilylacetylene (TMSA) (an acetylene equivalent) under the traditional Sonogashira conditions catalyzed by PdCl₂(PPh₃)₂ (0.4 mol%)/CuI (0.4 mol%) in the presence of triethylamine/THF as solvent at room temperature afforded the alkynylated compound **183**, after desilylation with tetra-*n*-butylammonium fluoride (TBAF) (Scheme 73). Subsequent Sonogashira reaction with 1,4-diiodobenzene gave iodinated alkyne **184**, which was alkynylated again with TMSA to yield dimer **185**. Obviously, this last compound can be desilylated and coupled again with 1,4-diiodobenzene and so on to give phenylene ethynylene oligomers. However, the amount of the observed homo-coupling products is increased when increasing the substituent group size on the terminal alkyne.

Scheme 73



Another recent example of the classical copper-cocatalyzed Sonogashira coupling of a terminal alkyne and an aryl iodide, now devoted to the preparation of compounds of biological interest is the synthesis of diaryl alkyne **188**, an intermediate of lysosomal cysteine protease inhibitor Cathepsin S (Scheme 74).²³² This compound has been prepared by coupling terminal alkyne **187** and aryl iodide **186** using the same reaction conditions than in the previous example, the higher reactivity of the C-I bond compared to that of C-Cl bond being demonstrated.

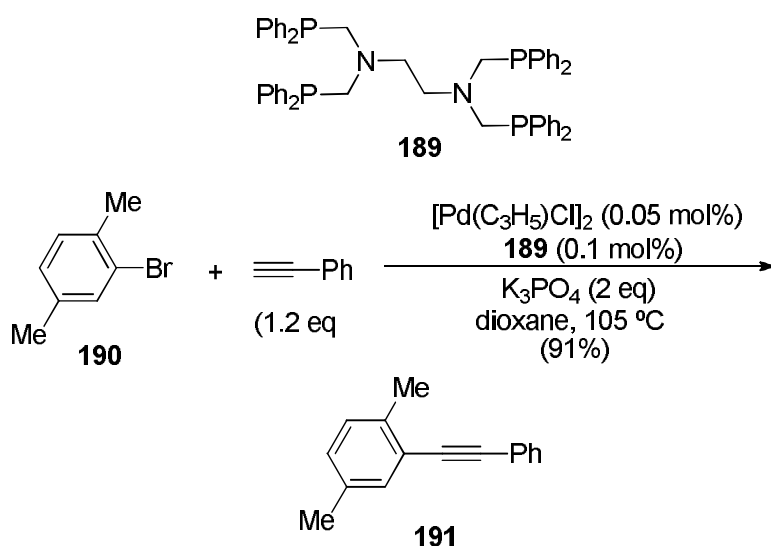
Scheme 74



Examples of the use of aryl bromides for the palladium-catalyzed coupling with terminal alkynes leading to interesting compounds are common, as in the recent synthesis of donor-acceptor tetrakis(ethynyl)pyrenes, obtained from the corresponding tetrabrominated pyrenes and terminal alkynes using the classical copper-cocatalyzed Sonogashira conditions.²³³ However, copper-free procedures are nowadays more deeply explored. Thus, aryl bromides have been coupled with terminal alkynes using as catalyst $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ (0.05 mol%) combined to the tetraphosphine **189** (0.1 mol%), using potassium phosphate as base in dioxane as solvent at 105 °C, as shown in the reaction of aryl bromide **190** and phenylacetylene to give disubstituted alkyne **191** (Scheme 75).²³⁴ Other copper-free coupling of aryl bromides and terminal alkynes have

also been recently achieved using chlorophosphine,²³⁵ biphenyl-containing bis(diphenylphosphine)²³⁶ or functionalized ionic liquid-containing phosphine-ligated ligands.²³⁷ In addition, aryl bromides have been coupled recently with terminal alkynes under continuous flow conditions.²³⁸

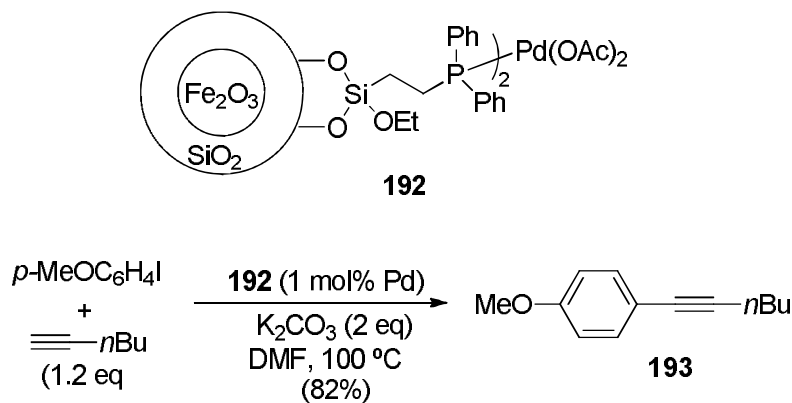
Scheme 75



Supporting the phosphine ligands on different polymers or inorganic supports allows the preparation of recoverable palladium catalysts which can be reused further, something important in large scale synthesis.^{226b,c} Recent examples of phosphine-containing supported palladium catalysts devoted to the preparation of alkynylated arenes are the magnetic nanoparticle-supported palladium complex **192**, which has been used as catalyst (1 mol% Pd) for the copper-free Sonogashira coupling of terminal alkynes and aryl iodides or aryl bromides using potassium carbonate as base in DMF at 100 °C, as in the coupling of *p*-iodotoluene with hex-1-yne to give alkyne **193** (Scheme 76).²³⁹ The catalyst was recovered by using a magnet and reused up to eight times with almost no loss of activity. Further examples of the use as catalysts of palladium(II) coordinated to diphenylphosphine-functionalized mesoporous silica,²⁴⁰ silica nanospheres,²⁴¹ or to metal-organic frameworks²⁴² can be found, although only employed in the coupling of phenylacetylene and iodobenzene. In addition, commercial polyurea-encapsulated palladium-triphenylphosphine Pd-EnCatTM TPP30 has been used as recyclable catalyst (3.5 mol% Pd) for the coupling of terminal acetylenes and aryl bromides.²⁴³ The reaction was performed in the presence of DBU as base in acetonitrile

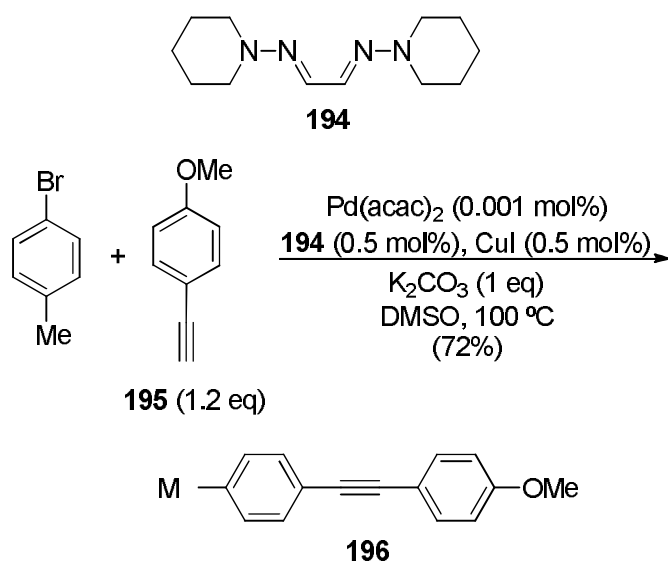
at 120 °C under microwave irradiation, the supported catalyst being recycled up to six times with only a slight decrease in the reactivity.

Scheme 76



Although phosphine ligands are the most frequently employed in the Sonogashira alkylation reaction of arene halides, many other non-phosphonated complexes has been employed, although most often only for the coupling of terminal alkynes with aryl iodides and bromides.²²⁶ A recent example is the use a nitrogenated ligand such as hydrazone **194**, which when combined (0.5 mol%) to $Pd(acac)_2$ (acac = acetylacetonate) at a very low loading (0.001 mol%) in the presence of CuI (0.5 mol%) allowed the cross-coupling of terminal alkynes and aryl bromides, as in the case of the synthesis of alkyne **196** from the alkylation of *p*-bromotoluene with terminal alkyne **195** (Scheme 77).²⁴⁴

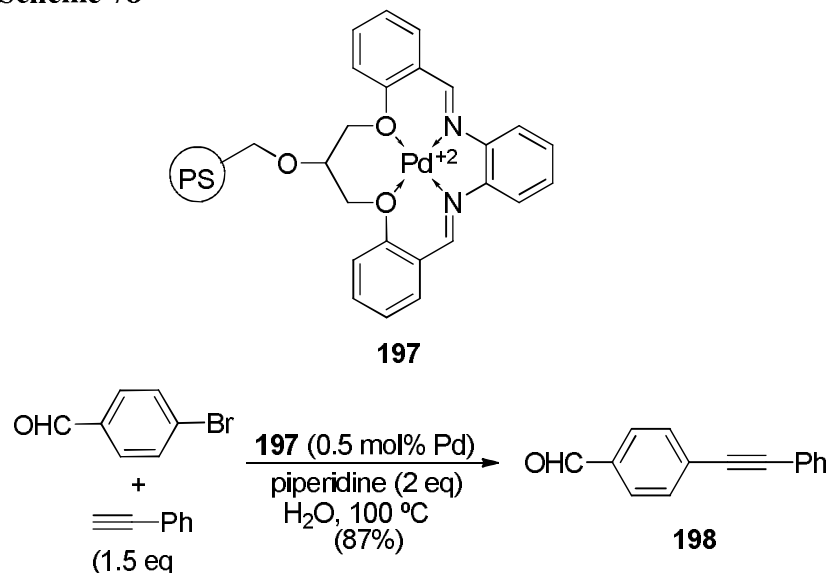
Scheme 77



Non-phosphanated palladium complexes have also been immobilized on different materials in order to achieve recoverable and reusable systems. Recent examples include the use of polystyrene-anchored palladium(II)-salophen complex **197** as catalyst (0.5 mol% Pd) for the coupling of aryl iodides and activated aryl bromides with phenylacetylene in water, as shown in Scheme 78 with the coupling of *p*-bromobenzaldehyde and phenylacetylene to give alkyne **198**, the catalyst being recovered by filtration and reused up to 5 times with a 10% loss of activity.²⁴⁵ Water has also been used as solvent when a polystyrene-supported terpyridine palladium complex has been used as catalyst (5 mol% Pd) in the coupling of phenylacetylene and aryl iodides.²⁴⁶ In addition, polystyrene has also been used to anchor a palladium(II) phenyldithiocarbamate complex which has been used as catalyst (0.01 mol% Pd) in the coupling of aryl iodides and bromides with terminal acetylenes, reuse up to five times being possible.²⁴⁷ Moreover, a palladium(II)-salophen complex has been immobilized on diatomite and has been found suitable to catalyze (0.003 mmol%) the copper-free Sonogashira coupling of terminal alkynes and aryl iodides and bromides in triethylamine at room temperature, reusing up to three runs being possible.²⁴⁸ Furthermore, examples of the use of superparamagnetic nanoparticles-supported palladium(II) complexes with Schiff-base bidentate ligands,²⁴⁹ metallodendritic palladium catalysts containing 2-pyridyl-1,2,3-triazole moieties as ligands,²⁵⁰ mesoporous organosilica palladium(II) complexes containing a phloroglucinol-diimine

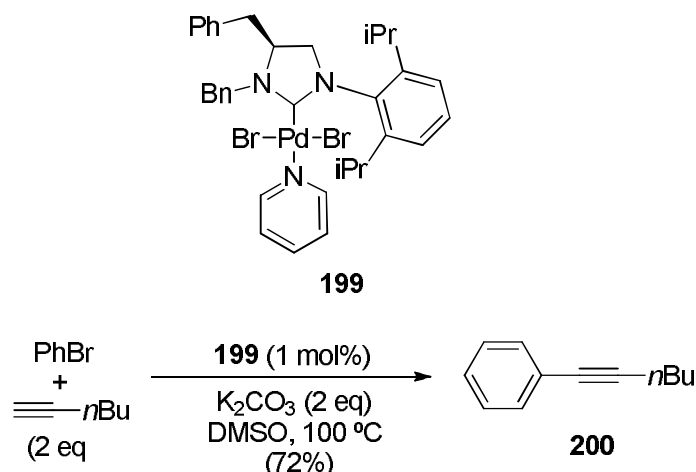
moiety as ligand,²⁵¹ as well as carbon nanotubes with thiol-containing ligands for palladium²⁵² can be found, although synthetically limited to the use of aryl iodides.

Scheme 78



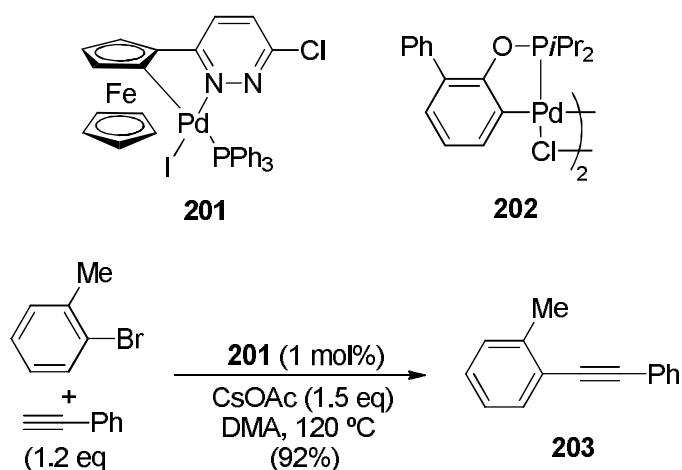
NHC-palladium complexes are gaining popularity as catalysts in Sonogashira alkyne-arylation reactions due to their enhanced catalytic activity, thus allowing copper-free couplings.^{226b,c} A recent example of their use as catalysts in the formation of alkyne-arylated arenes is the chiral complex **199**, which has been employed (1 mol%) in the copper-free alkyne-arylation of aryl bromides in the presence of potassium carbonate as base in DMSO as solvent at 100 °C, as shown in the preparation of alkyne-arylated arene **200** from phenyl bromide and hex-1-yne (Scheme 79).²⁵³ Other abnormally bonded NHC-palladium complexes have been used as catalysts in the copper-free Sonogashira alkyne-arylation of aryl halides,²⁵⁴ whereas thiol-functionalized NHC-palladium complexes have also been used as catalysts, although the presence of copper(I) iodide resulted necessary.²⁵⁵

Scheme 79



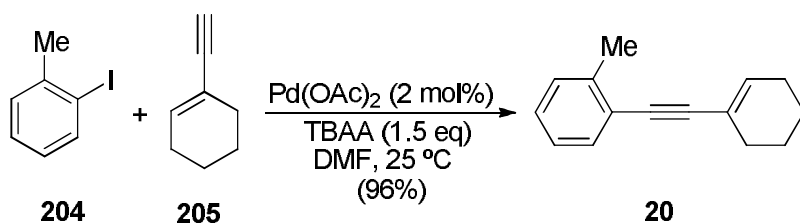
Palladacycles are palladium compounds that usually show high catalytic activity and high stability, being precursors of active PdNPs²⁵⁶ which can act as catalysts in the copper-free Sonogashira reaction.^{226b} Recent examples of their use in the copper-free Sonogashira alkyne arylation are the cyclopalladated ferrocenylpyridazine palladium complex **201**, which has been used as catalyst (0.1-2 mol%) in the reaction of terminal alkynes with aryl bromides, using cesium acetate as base, in *N,N*-dimethylacetamide (DMA) as solvent at 120 °C.²⁵⁷ An example of the use of this methodology is the preparation of alkyne **203** from the reaction of *o*-bromotoluene and phenylacetylene (Scheme 60). Aryl bromides afforded high yields, although aryl chlorides gave rise to moderate yields only when bearing electron-withdrawing groups. In addition, aqueous solvents at 40 °C have been employed in the alkyne arylation of aryl iodides using as catalyst (0.25 mol%) the palladacycle **202**.²⁵⁸ Other recent examples involve the use of an *ortho*-palladated complex of homoveratrylamine using aryl iodides and bromides²⁵⁹ or recyclable palladacycle systems using ionic liquids as solvents, although working only with aryl iodides as coupling partners.²⁶⁰ In addition, recent examples of coupling of aryl iodides and bromides with terminal alkynes using polystyrene-anchored Schiff-based palladacycles as catalysts can be found.²⁶¹ Moreover, aryl iodides²⁶² and bromides^{262a} have also been coupled to terminal acetylenes using palladium-containing pincer complexes as catalysts.

Scheme 80



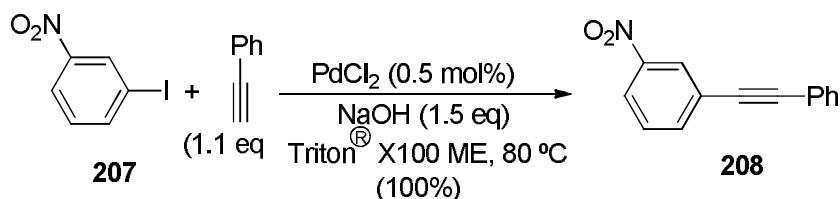
Palladium salts, deprived of any ligand, can be used as catalysts in the Sonogashira coupling of terminal alkynes and aryl halides, mainly iodides and bromides. For instance, terminal alkynes, such as **205**, have been cross-coupled with aryl iodides, such as **204**, affording the corresponding alkyne **206**, in a reaction catalyzed by Pd(OAc)₂ (2 mol%) in the presence of a tetra-*n*-butylammonium acetate (TBAA) as a probable nanoparticle stabilizer, the process being performed in DMF as solvent at room temperature (Scheme 81).²⁶³ Another recent example is the use of formate-based room temperature ionic liquids as solvents at 100 °C for the coupling of phenylacetylene and aryl iodides and bromides, low loadings of PdCl₂ being used as catalyst (0.02 mol%).²⁶⁴ In addition, two commercially available recyclable polyurea-encapsulated Pd-EnCatTM, deprived of any phosphine ligand, have been used in copper-free Sonogashira couplings. Thus, Pd EnCat 30 (1 mol%) have been employed as catalyst in the coupling of aryl iodides with terminal alkynes, piperidine being used as base in aqueous acetonitrile (1 : 1) at 40 °C, the catalyst being recovered and reused up to three times with slight decrease in the final yield of the cross-coupled product.²⁶⁵ The less porous Pd-EnCat 40 has been reported to perform (0.1–0.01 mol% Pd) the coupling of aryl iodides and a few aryl bromides using pyrrolidine as solvent at 85 °C, microwave irradiation accelerating the process.²⁶⁶

Scheme 81



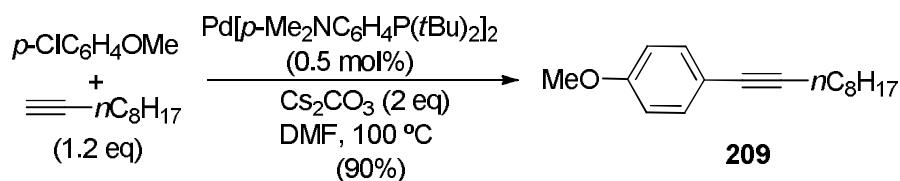
The use of PdNPs as catalysts in the Sonogashira cross-coupling reaction has found rising interest,^{226b, c, 267} as evidence has shown that PdNPs can in fact be the real catalyst in many Sonogashira processes as a consequence of decomposition of the original palladium salt or complex. One of the reasons for the rapidly developing field of nanoparticle research is the distinctly differing physicochemical properties presented by metal nanoparticles compared to their bulk counterparts due to their large surface-to-volume ratio, providing many highly active metal uncoordinated sites. An example of their use in this alkynylation reaction as catalysts is the in situ generation of PdNPs by combining PdCl₂ (0.5 mol%) and sodium hydroxide, which are stabilized by oil-in-water microemulsions (ME) formed by the mixture Triton[®] X100/*n*-heptane/*n*-butanol/water/PEG at 80 °C.²⁶⁸ These conditions have allowed to couple aryl iodides, such as **207**, with phenylacetylene yielding the corresponding alkyne **208** (Scheme 82). Other examples of this disubstituted alkyne synthesis catalyzed by PdNPs,²⁶⁹ even Pd-Cu bimetallic and specifically fabricated tripodal-shaped nanoparticles,²⁷⁰ using water as solvent can be found. In addition, differently immobilized PdNPs have been employed as recyclable catalysts in Sonogashira couplings,^{226b, c} recent examples being PdNPs stabilized on linear polystyrene,²⁷¹ poly(vinyl alcohol) nanofiber mats,²⁷² polypyrrole globules,²⁷³ agarose,²⁷⁴ synthetic adsorbent resins,²⁷⁵ graphite²⁷⁶ and graphene²⁷⁷ oxides and silicate base materials²⁷⁸ as well as dendrimers.²⁷⁹ However, the use of PdNPs as catalyst is mostly limited to the coupling of terminal alkynes with reactive aryl iodides or activated aryl bromides.^{226b, c}

Scheme 82



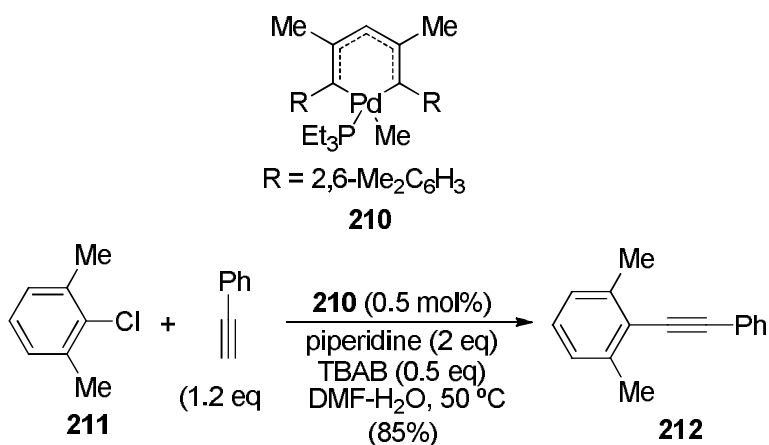
As mentioned, not only the desire of avoiding the presence of a copper(I) co-catalyst, but also the necessity of coupling terminal alkynes with the less reactive aryl chlorides has boosted the development of more reactive palladium-containing catalytic systems based, for instance, in the presence of bulky electron-rich phosphine ligands. For example, the Ad₂P(*n*-Bu) (Ad = adamantyl) (4 mol%) ligand showed its usefulness years ago in the coupling of aryl chlorides with selected alkynes in the presence of Na₂PdCl₄ (2 mol%) as palladium catalyst precursor and CuI (1.5 mol%) as co-catalyst, electron-deficient aryl chlorides affording very high yields but electron-neutral and electron-rich chlorides giving lower yields.²⁸⁰ Under these conditions, the use of *t*Bu₃P gave slightly better yields with electron-rich systems. This last ligand, combined to PdCl₂(PPh₃)₂ (2 mol%) and DBU resulted also efficient in the copper-free coupling of aryl chlorides and terminal alkynes under microwave irradiation.²⁸¹ In addition, another copper-free Sonogashira coupling protocol for the coupling of activated or not aryl chlorides and tosylates using Xphos (**123**) (3 mol%) combined to PdCl₂(MeCN)₂ (1 mol%) was also developed,²⁸² as well as a copper-free procedure for the use of aryl chlorides catalyzed by PdCl₂(PCy₃)₂ (3 mol%) in the presence of cesium carbonate as base in DMSO at 100-150 °C.²⁸³ Very recently, palladium(0) and (II) complexes with the *p*-Me₂NC₆H₄P(*t*Bu)₂ ligand have been shown as effective catalysts (0.5-1.5 mol%) for the copper-free coupling of aryl chlorides and terminal acetylenes, cesium carbonate being used as base and DMF as solvent at 90-110 °C.²⁸⁴ An example employing Pd[*p*-Me₂NC₆H₄P(*t*Bu)₂]₂ (0.5 mol%) as catalyst is shown in Scheme 83, with the coupling of a deactivated aryl chloride such as *p*-chloroanisole with dec-1-yne, yielding disubstituted acetylene **209**.

Scheme 83



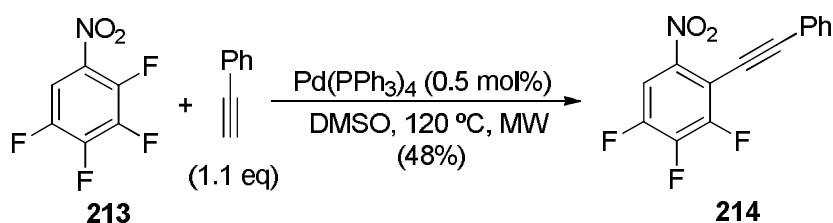
Some phosphine-free catalytic systems have also been used for the successful coupling of terminal alkynes and aryl chlorides.^{226c} For example, low loadings (0.5 mol%) of the β -di-ketiminatophosphine palladium complex **210** have shown to catalyze efficiently the copper-free Sonogashira coupling of aryl chlorides with terminal alkynes, as illustrated in the coupling of the hindered chloride **211** with phenylacetylene to give disubstituted alkyne **212** (Scheme 84).²⁸⁵ The reaction is carried out in the presence of piperidine as base and TBAB in aqueous DMF at only 50 °C.

Scheme 84



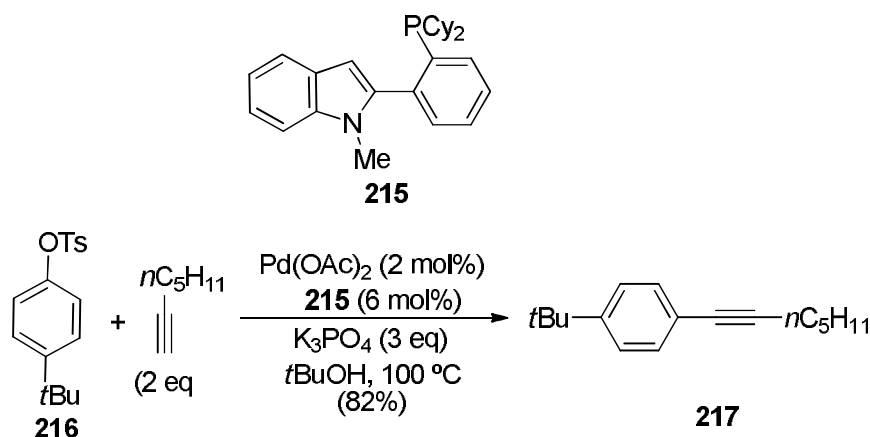
Recently, even highly electron-poor polyfluoroaryls have been employed in palladium-catalyzed Sonogashira-type couplings with terminal alkynes, although with moderate yields of the final alkyne.²⁸⁶ The procedure has been carried out using highly fluorinated nitrobenzene systems (pentafluoronitrobenzene and tetrafluoronitrobenzenes) and phenylacetylene or 2-methylbut-3-yn-2-ol as coupling partners, $\text{Pd}(\text{PPh}_3)_4$ (0.05 mol%) as catalyst and DMSO as solvent at 120 °C under microwave irradiation. An example is shown in Scheme 85 with the coupling of tetrafluoronitrobenzene **213** and phenylacetylene to give disubstituted alkyne **214**.

Scheme 85



Aryl tosylates²⁸⁷ and mesylates^{287b} are obtained easily from phenols and can be employed as the coupling partners of terminal alkynes in Sonogashira cross-coupling reactions leading to alkynyl arenes. An example is the cross-coupling of tosylate **216**, which has been alkynylated with a terminal alkyne such as hept-1-yne using as catalytic system a combination of Pd(OAc)₂ (2 mol%) and the CM-Phos (**215**) ligand (6 mol%) using potassium phosphate as base and *tert*-butanol as solvent at 100 °C, to give internal alkyne **217** (Scheme 86).^{287b}

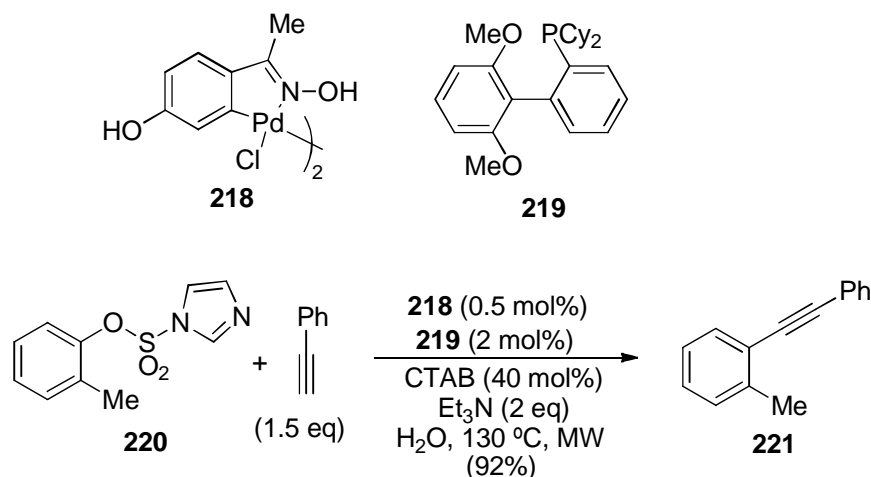
Scheme 86



Similarly to aryl tosylates, aryl imidazol-1-ylsulfonates, also prepared from the corresponding phenols, can be coupled with terminal alkynes using a palladium-catalyzed copper-free Sonogashira-like procedure, using Pd(OAc) (0.1 mol%) as palladium source in the presence of Xphos as ligand (0.2 mol%), potassium phosphate as base and DMSO as solvent at 65 °C.²⁸⁸ This copper-free coupling has also been performed very recently in neat water at 110 °C assisted by microwave irradiation using the oxime palladacycle **218** as precatalyst (0.5 mol%), Sphos (**219**) (2 mol%) as ligand, hexadecyltrimethylammonium bromide (CTAB) as additive and triethylamine as base,

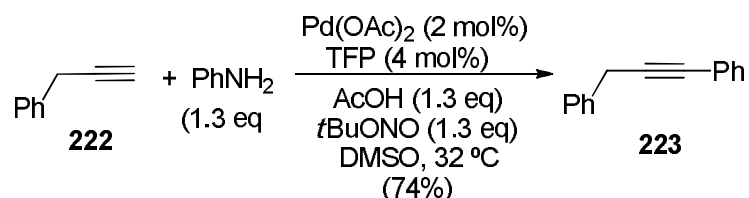
as in the case of the coupling of phenyl imidazylate **220** with phenylacetylene to give disubstituted alkyne **221** (Scheme 87).²⁸⁹

Scheme 87



Arenediazonium salts (from the corresponding anilines) have also been used as coupling partners of terminal alkynes in palladium-catalyzed Sonogashira reactions in the presence of copper co-catalysis.²⁹⁰ This coupling can also be performed starting directly from anilines, using in situ generated arenediazonium salts by means of *tert*-butyl nitrite. This is a copper-free procedure based on the use of the mixture Pd(OAc)₂ (2 mol%)/tri-(2-furyl)phosphine (TFP) (4 mol%) as catalytic combination in DMSO as solvent at 32 °C, as in the case of the coupling of aniline with terminal acetylene **222** to give internal alkyne **223** (Scheme 88).²⁹¹

Scheme 88



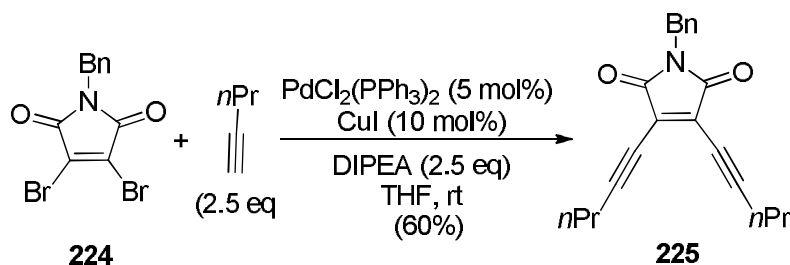
6.2. Alkynylated Heterocycles

The Sonogashira cross-coupling reaction between halogenated heterocyclic systems and terminal alkynes is the most evident strategy to follow when the preparation of

alkynylated heteroarenes is intended.^{226b} As in carbocyclic systems (see Section 6.1), the alkylation of aromatic heterocyclic systems by means of a transition-metal-catalyzed reaction is governed by the higher or lower electrophilicity of the carbon atom at the heterocycle. In the oxidative addition step, Pd(0) acts as a nucleophile and will preferentially attack the most electron-deficient position. Thus, cross-coupling reactions for which the oxidative addition is rate determining, i.e. the Sonogashira cross-coupling, often show a high preference in favor of the most electrophilic position.²⁹² In this section, some examples of the introduction of an alkyne moiety into heterocyclic systems, using the ‘typical’ copper-cocatalyzed Sonogashira reaction, as well as employing the ‘copper-free’ procedure, and also examples of the not very common direct oxidative coupling of terminal alkynes and heterocycles, will be shown.

The traditional Sonogashira reaction has been used for the alkylation of five-membered heterocycles such as maleimides.²⁹³ Thus, using PdCl₂(PPh₃)₂ as catalysts (5 mol%) in the presence of CuI as cocatalyst (10 mol%) and diisopropylethylamine (DIPEA) as base, dibrominated maleimide **224** has been dialkynylated with terminal alkynes, such as pent-1-yne, to give dialkynylated maleimide **225**, the reaction being performed in THF as solvent at room temperature (Scheme 89).

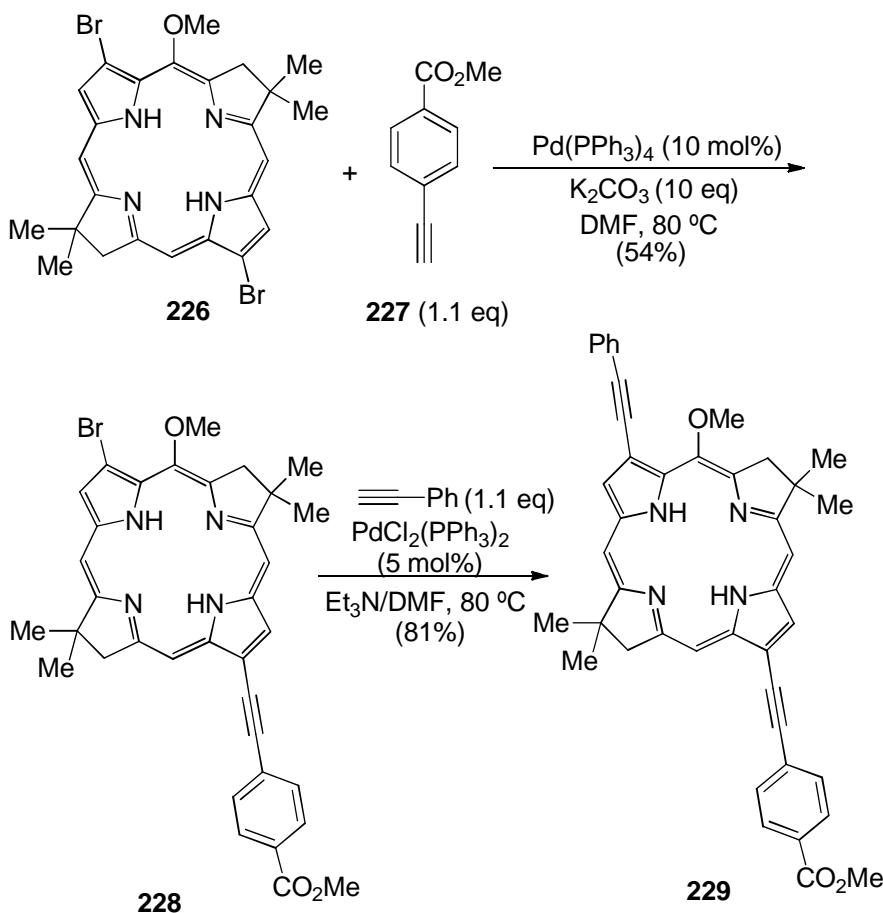
Scheme 89



Terminal alkynes can alkynylate a pyrrole unit bearing an appropriate halide under Sonogashira conditions, even copper-free when reactive enough species are involved. An example is the selective alkylation of 3,13-dibromo-5-methoxybacteriochlorin (**226**) for biomedical applications.²⁹⁴ Thus, **226** can be monoalkynylated with terminal alkyne **227** under copper-free Sonogashira conditions using Pd(PPh₃)₄ (10 mol%) as catalyst and potassium carbonate as base in DMF at 80 °C as solvent, to give bacteriochlorin **228** (Scheme 90). Subsequent alkylation with terminal alkynes, such as phenylacetylene, also under copper-free conditions using now PdCl₂(PPh₃)₂ (5 mol%)

as catalyst in DMF/triethylamine at 80 °C afforded dialkynylated nonsymmetrical bacteriochlorin **229**.

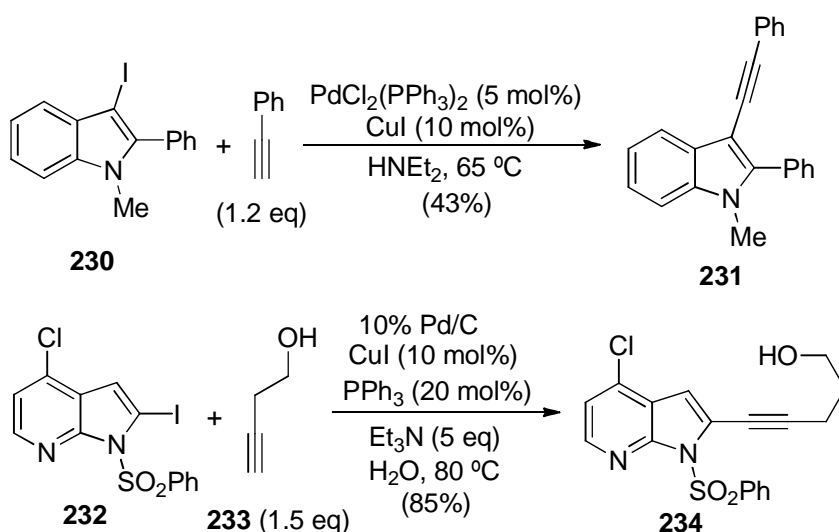
Scheme 90



The alkylation of the structurally important indole has been performed on systems bearing an halogen or even a triflate leaving group under the typical Sonogashira conditions,^{32a,e} an example being the synthesis of a library of 3-alkynylated indoles, in solution and on a solid support, obtained from 3-iodinated indoles and terminal alkynes.²⁹⁵ The synthesis has been carried out using the combination $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%)/ CuI (10 mol%) as catalyst, in diethylamine at 65 °C, as in the case of the preparation of 3-alkynyl indole **231** from iodinated indole **230** and phenylacetylene (Scheme 91). In addition, alkylnated azaindoles can also be obtained, as exemplified in the preparation of compounds such as **234**, obtained by copper-cocatalyzed Sonogashira coupling of terminal alkynes, such as **233**, to 2-iodinated azaindole **232** (Scheme 91).²⁹⁶ The palladium source in this transformation was 10%

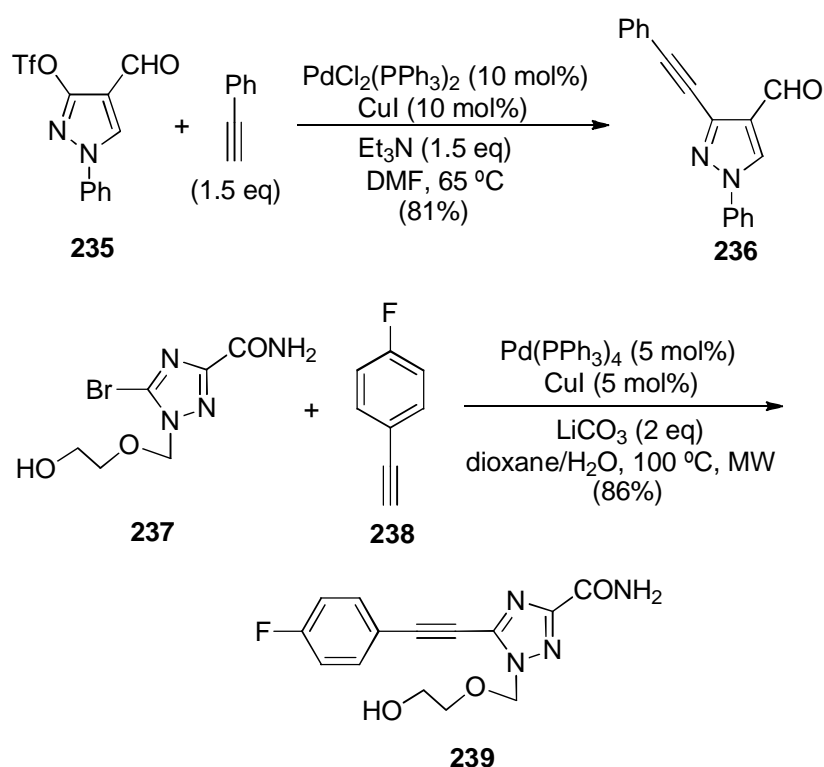
palladium on charcoal, a frequently employed palladium catalyst for the alkylation of heteraryl halides.²⁹⁷ In this case, triethylamine was used as base and water at 80 °C as solvent, although the addition of triphenylphosphine was required. Other halogenated dinuclear five-six-membered nitrogenated heterocycles, such as imidazo[1,2-a]pyridines,²⁹⁸ and imidazo[1,2-b]pyridazines²⁹⁹ have been alkynylated with terminal alkynes under copper-cocatalyzed Sonogashira conditions, using $\text{PdCl}_2(\text{PPh}_3)_2$ as palladium source.

Scheme 91



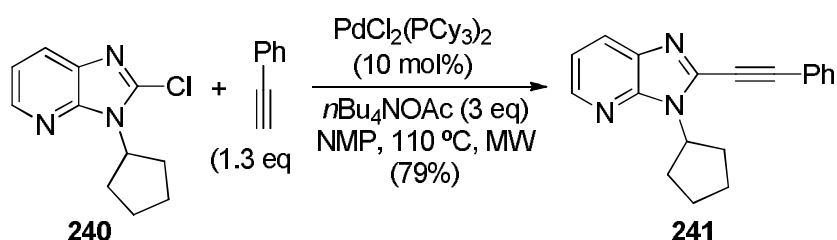
The pyrazole ring has also been alkynylated using the Sonogashira reaction conditions, as exemplified in Scheme 92 with the preparation of 3-alkynylated pyrazole-4-carbaldehyde **236** from pyrazole **235**, bearing a triflate as leaving group, and phenylacetylene.³⁰⁰ The process is catalyzed using large amounts of the catalytic combination $\text{PdCl}_2(\text{PPh}_3)$ (10 mol%)/ CuI (10 mol%), using triethylamine as base in DMF at 65 °C. An example of alkylation of an halogenated aryltriazole can also be seen in Scheme 92, where 5-brominated triazole **237** is alkynylated with terminal alkynes, such as **238**, under usual Sonogashira reaction conditions and microwave irradiation, to give arylethynyltriazole acyclonucleoside derivative **239**, which has been found to inhibit hepatitis C virus replication.³⁰¹

Scheme 92



2-Halo-3-alkyl imidazo[4,5-b]pyridines have been recently found as appropriate substrates to experience a 2-alkynylation with terminal alkynes under copper- and amine-free Sonogashira conditions, using $\text{PdCl}_2(\text{PCy}_3)_2$ (10 mol%) as catalyst in the presence of tetra-*n*-butylammonium acetate and NMP as solvent under microwave irradiation.³⁰² Under these conditions, iodo-, bromo- and chloro-substituted systems such as **240** have been alkynylated with a terminal alkyne such phenylacetylene, to give imidazopyridine **241** (Scheme 93).

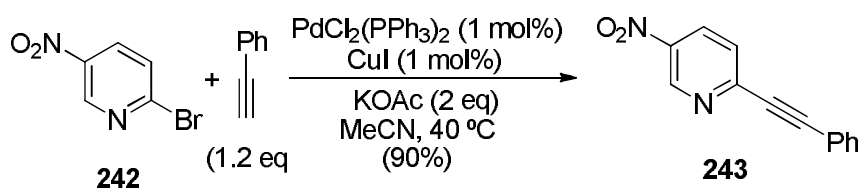
Scheme 93



Halogenated pyridines can be alkynylated under the typical Sonogashira reaction conditions, the 2-position being the most reactive. For instance, 2-bromo-5-

nitropyridine (**242**) has been 2-alkynylated with a terminal alkyne such as phenylacetylene, to give pyridine **243**, in a process catalyzed by the combination PdCl₂(PPh₃)₂ (1 mol%)/CuI (1 mol%), in the presence of potassium acetate as base using acetonitrile as solvent at a reaction temperature of 40 °C (Scheme 94).³⁰³ Similarly, phenylacetylene has been used for the alkylation of 2-bromonicotinaldehyde, using Pd(OAc)₂ as palladium source, CuI as co-catalyst and triphenylphosphine as external ligand, in triethylamine.³⁰⁴ In addition, pyridines bearing a chloro and a bromo substituent have shown to be monoalkynylated always at the carbon bearing the bromo atom when using the typical copper-cocatalyzed Sonogashira conditions.³⁰⁵ Moreover, 2- and 3-bromopyridines have been alkynylated with terminal alkynes using as catalyst a nanosized MCM-41 anchored palladium bipyridyl complex in the presence of CuI as co-catalyst and triphenylphosphine, using triethylamine as base and solvent at 90 °C, the anchored catalyst being suitable for reusing with a slight loss of activity after three runs.³⁰⁶

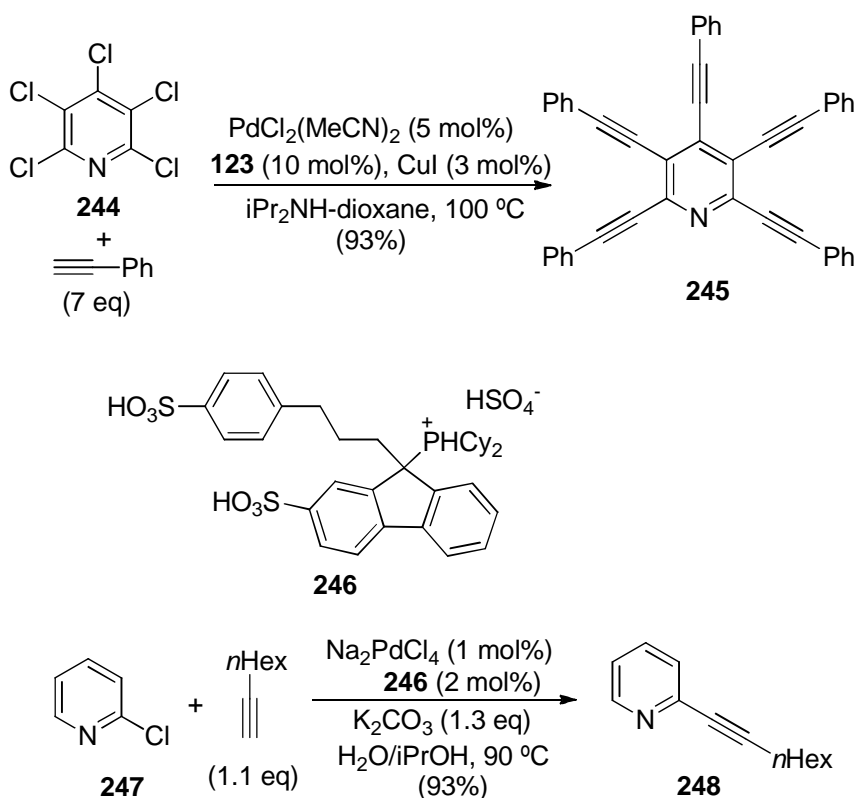
Scheme 94



As mentioned, the addition of electron-rich phosphines as ligands improves the reactivity of the catalyst thus, allowing the use of less reactive substrates and sometimes copper-free conditions. An example is the difficult but high-yielding penta-alkynylation of pentachloropyridine (**244**) with phenylacetylene to give **245**, using as catalyst a combination of PdCl₂(MeCN)₂ (5 mol%), Xphos (**123**) (10 mol%) and CuI (3 mol%), in a mixture of *i*Pr₂NH and dioxane at 100 °C as solvent (Scheme 95).³⁰⁷ Another example of the use of an electron-rich phosphine ligand, this time in a copper-free Sonogashira procedure is the alkylation of 2-, and 3-chloropyridines and electron-rich 2-amino-5-bromopyridines with terminal alkynes in high yields in aqueous isopropanol at 90 °C, using as catalyst a combination of Na₂PdCl₄ (1 mol%) and the electron-rich water-soluble protonated phosphine **246** (2 mol%). 2-Chloropyridine (**247**) has been alkynylated with oct-1-yne under these conditions to give the pyridine derivative **248**

(Scheme 95).³⁰⁸ In addition, copper-free Sonogashira conditions using $\text{PdCl}_2(\text{PPh}_3)_2$ and DABCO as the base under microwave irradiation in acetonitrile or water as solvents, have been employed for the coupling reaction of terminal alkynes with a pyridinium *N*-heteroarylamidine such as *N*-(5-iodopyridin-2-yl)amidine.³⁰⁹

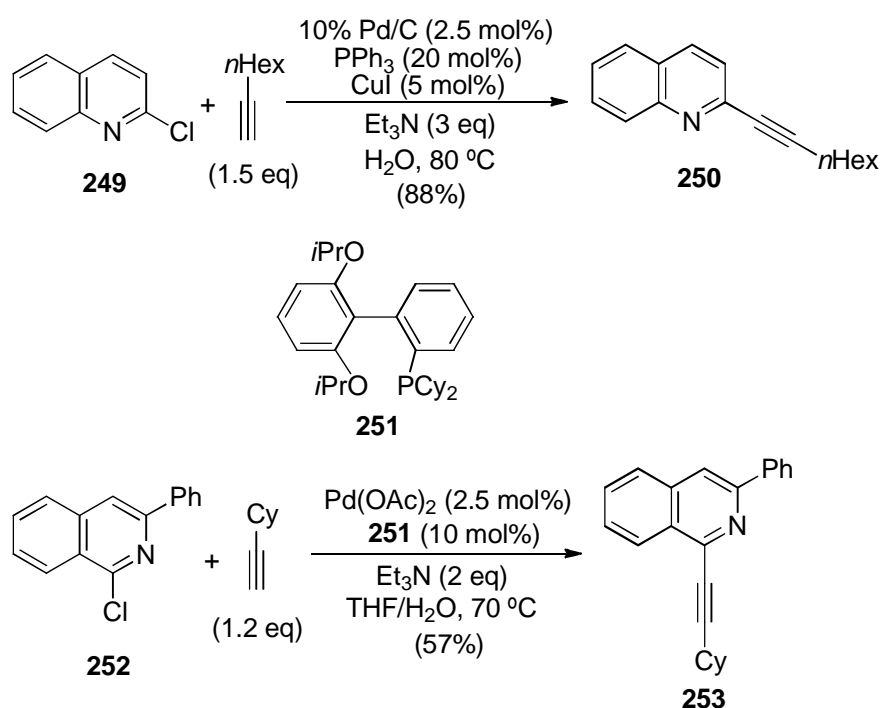
Scheme 95



2-Alkynylquinolines have been prepared from 2-chloroquinolines and terminal alkynes using a copper co-catalyzed Sonogashira cross-coupling reaction promoted by 10% palladium-on-charcoal combined to triphenylphosphine and using water at 80 °C as solvent, as exemplified in the preparation of alkynylated quinoline **250** from 2-chloroquinoline (**249**) and oct-1-yne, triethylamine being used as base (Scheme 96).³¹⁰ Under these reaction conditions, the Sonogashira reaction of 2,4-dichloroquinoline afforded exclusively the 2-alkynylated product, as a result of the being the more activated position.³¹⁰ When iodo or chloro substituents are present on the quinoline nucleus, the alkylation takes place at the more reactive iodo-bearing position, as shown in the reaction of 4-chloro-3-iodoquinolines with terminal alkynes under the typical Sonogashira conditions.³¹¹ In addition, 2-, 3-, and 4-chlorinated [2,3-*b*]indoles can be alkynylated with terminal alkynes by means of the copper-cocatalyzed

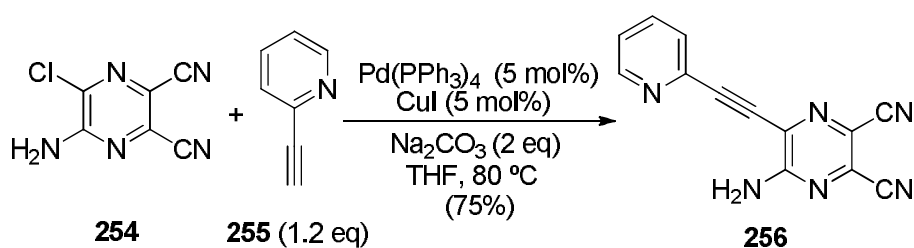
Sonogashira reaction.³¹² Moreover, 4-terminal alkynes have been used for the alkylation of 1-chloroisoquinolines, but under copper-free Sonogashira conditions, using as catalyst a combination of Pd(OAc)₂ (2.5 mol%) and the electron-rich phosphine Ruphos (**251**), triethylamine as base and aqueous THF at 70 °C as solvent, as exemplified in the preparation of 1-alkynylated isoquinoline **253** from 1-chloroisoquinoline **252** and cyclohexylacetylene (Scheme 96).³¹³

Scheme 96



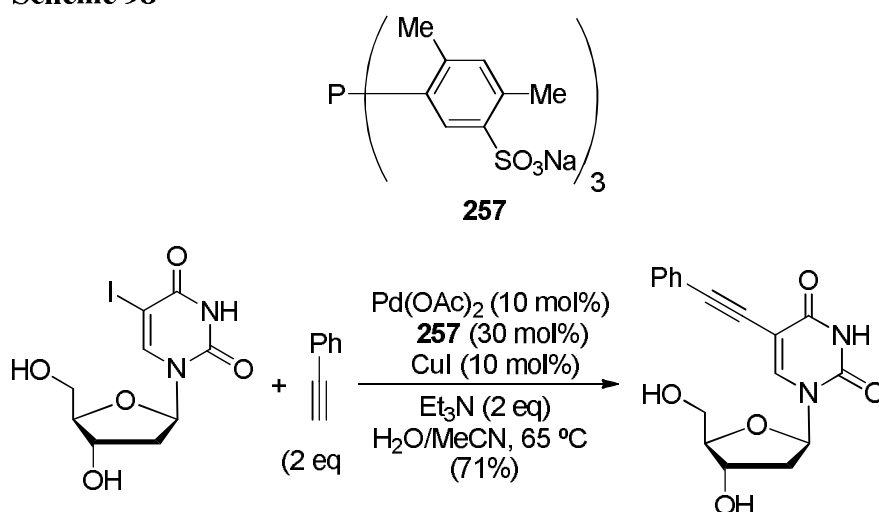
Pyrazines are activated substrates that, even bearing relatively unreacting carbon-chlorine bonds, can be alkylation reacting with terminal alkynes under the typical Sonogashira conditions. An example is the reaction of chlorinated pyrazine **254**, which reacts with alkyne **255** under Pd(PPh₃)₄ catalysis and CuI co-catalysis, in the presence of sodium carbonate in THF at 80 °C as solvent, affording the corresponding alkylation system **256** (Scheme 97), employed as precursor of aza-phthalocyanines dyes with well-defined spectral properties.³¹⁴ Recent examples of alkylation of chlorinated pyrazin-2-(1*H*)-ones³¹⁵ or pyrido[2,3-*d*]pyridazines³¹⁶ under this copper-cocatalyzed conditions can also be found.

Scheme 97



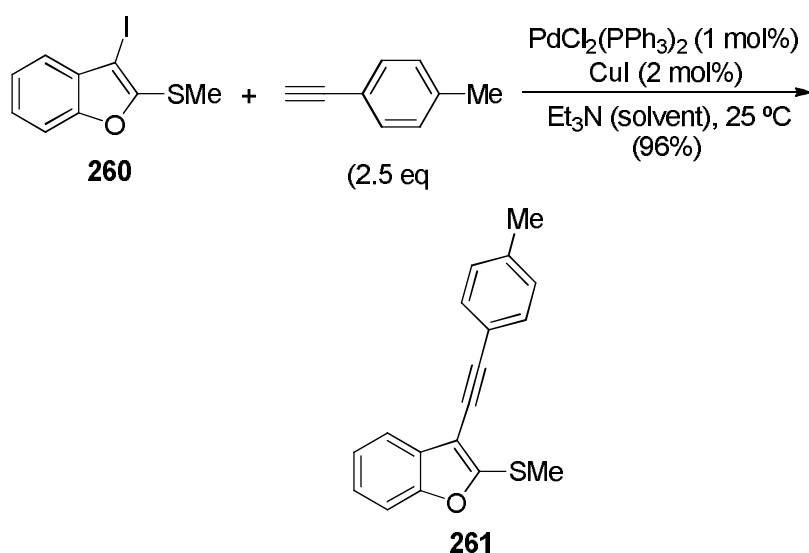
The alkylation of the nucleobases of nucleosides allows the synthesis of non-natural systems with interesting biological properties, and the Sonogashira reaction has been particularly useful for achieving this purpose.^{226b,c} An interesting example of this palladium-catalyzed transformation is shown in Scheme 98, where unprotected 5-iodouridine **258** reacts with terminal alkynes such as phenylacetylene under copper-cocatalyzed Sonogashira conditions to give alkynylated system **259**.³¹⁷ This methodology, which has also been applied to the alkylation of 8-bromopurines, is carried out using Pd(OAc)_2 (10 mol%) as palladium source, CuI as co-catalyst (10 mol%) and TXPTS [trisodium tri(2,4-dimethyl-5-sulfonatophenyl)phosphine] (**257**) as water-soluble ligand, allowing to perform the reaction in aqueous acetonitrile at 65 °C as solvent. In addition, 5-iodo uracil-morpholino monomers have been recently 5-alkynylated with different terminal alkynes using $\text{Pd(PPh}_3)_4$ (10 mol%) as catalyst under copper-cocatalyzed reaction conditions.³¹⁸

Scheme 98



An example of the alkylation of halogen-bearing oxygenated heterocycles using the ‘typical’ copper-cocatalyzed Sonogashira conditions is the reaction of methylsulfanyl-containing iodinated benzofuran **260**, which was alkynylated with terminal alkynes, such as *p*-tolylacetylene, using PdCl₂(PPh₃)₂ (1 mol%)/CuI (2 mol%) as catalytic mixture, in triethylamine at room temperature, yielding 3-alkynylated benzofuran **261** (Scheme 99).³¹⁹ In addition, 4-(1-alkynyl)-2-(5*H*)-furanones have been obtained from β-tetronic acid bromide and terminal acetylenes under palladium/copper catalysis,³²⁰

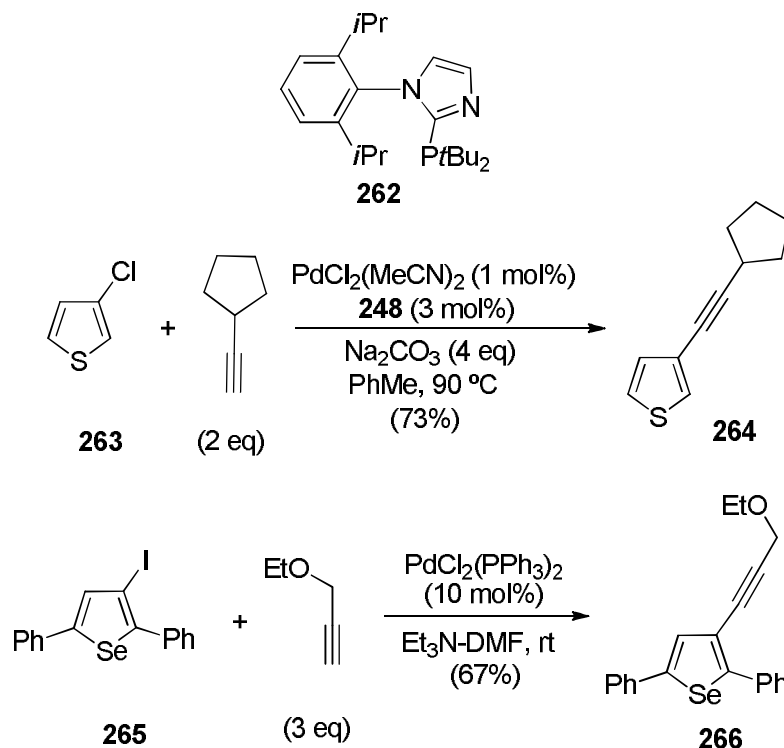
Scheme 99



An application of the use of electron-rich phosphines as ligands for the copper-free Sonogashira coupling of difficult chlorinated substrates, when applied to sulfur-containing heterocycles is, for instance, the alkylation of 3-chlorothiophene (**263**) with terminal alkynes. This reaction is suitable to be performed in a copper-free fashion using the ‘Buchwald-type’ ligand **262** (3 mol%) combined to PdCl₂(MeCN)₂ (1 mol%) as palladium source, using sodium carbonate as base in toluene at 90 °C. An application of this methodology is shown in the preparation of alkynylated thiophene **264** using cyclopentylacetylene (Scheme 100).³²¹ In addition, a copper-free Sonogashira procedure has also been used for the cross-coupling reaction of terminal alkynes with 3-iodoselenophenes.³²² In this case, PdCl₂(PPh₃)₂ was used as palladium catalyst, although in high loading (10 mol%), and triethylamine as base in DMF at room temperature, an example being the synthesis of 3-alkynylselenophene **266** from iodoselenophene **265**

and 3-ethoxyprop-1-yne (Scheme 100). However, alkynyldihydroselenophene derivatives have been obtained from 3-iododihydroselenophenes by alkylation with terminal alkynes under $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mol %) catalysis in the presence of CuI (2 mol %).³²³

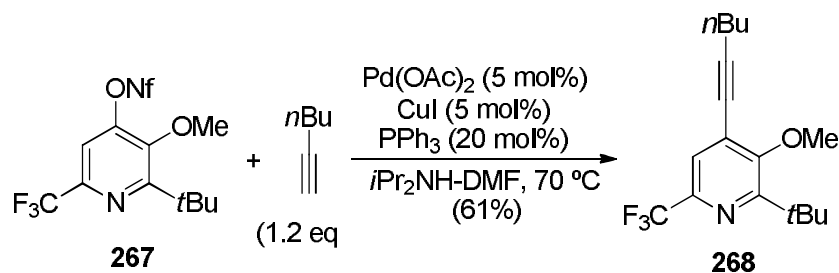
Scheme 100



When the palladium-catalyzed alkylation reaction is intended to be performed at a carbon bearing a hydroxy group, instead of a halogen, a solution is to transform the hydroxyl group in a better leaving one, such as a triflate. This has been carried out in situ in the case of 4-hydroxycoumarins, which have been 4-alkynylated with terminal alkynes under copper-free Sonogashira conditions [$\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), ethyldiisopropylamine, acetonitrile as solvent at 60 °C] when the reaction is performed in the presence of *p*-toluenesulfonyl chloride.³²⁴ The nonafluorobutanesulfonate (Nf) group (obtained from the corresponding hydroxyl group) has been used as a leaving group in the copper-cocatalyzed Sonogashira alkylation of pyridines.³²⁵ An example of this transformation is the alkylation of pyridine **267** with hex-1-yne to give compound **268**, using $\text{Pd}(\text{OAc})_2$ as catalyst (5 mol%), CuI as co-catalyst (5 mol%) and adding triphenylphosphine (20 mol%), diisopropylamine being used as base and solvent combined to DMF at 70 °C (Scheme 101). Moreover, tautomerizable heterocycles can

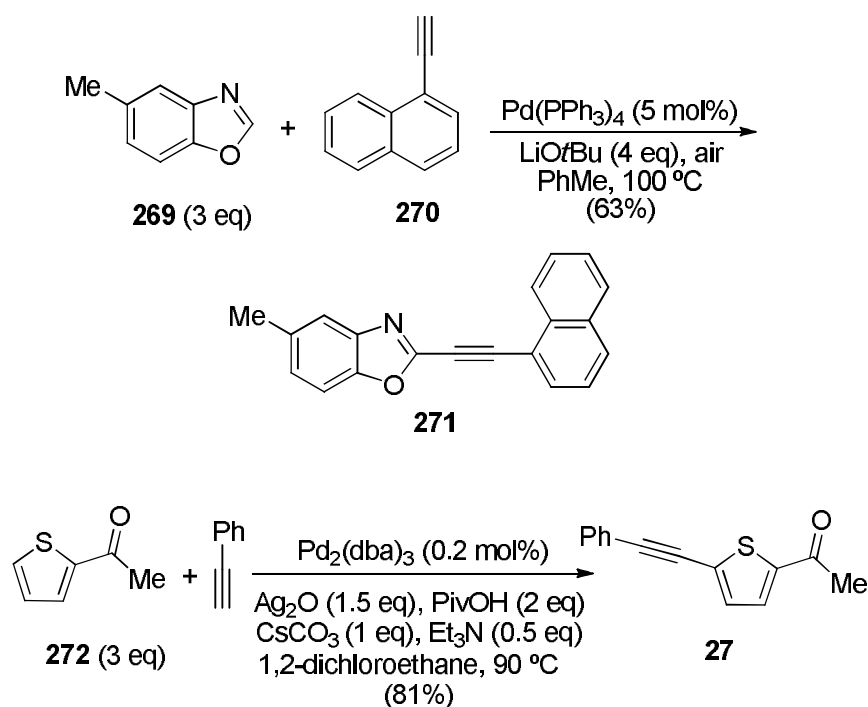
be alkynylated with terminal alkynes via in situ C-OH activation with the peptide coupling reagent bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP), followed by Sonogashira coupling using as catalyst a copper-free system formed by $\text{PdCl}_2(\text{MeCN})_2$ (5 mol%) and 2-(dicyclohexylphosphino)biphenyl (2-PhC₆H₄PCy₂) (15 mol%).³²⁶

Scheme 101



The direct oxidative alkylation of some 5-membered heteroarenes with terminal alkynes has been achieved under palladium catalysis. Concerning atom economy, this process can be potentially superior to the Sonogashira coupling. Thus, *N*-alkylated 3-methylindoles have been alkynylated at C-2 with terminal alkynes in a process catalyzed by K_2PdCl_4 (10 mol%) using cesium carbonate as base and oxygen (1 bar) and pivalic acid as oxidants, in DMSO as solvent at 80 °C.³²⁷ Another more simple oxidative 2-alkynylation of oxazoles and thiazoles has been performed using $\text{Pd}(\text{PPh}_3)_4$ as catalyst (5 mol%) and lithium *tert*-butoxide as base, using air as oxidant in toluene at 100 °C,³²⁸ as is the case of the reaction of benzo[*d*]oxazole **269** with alkyne **270** to give the alkynylated heterocycle **271** (Scheme 102). In addition, azole derivatives containing two different alkynyl groups have been prepared by direct oxidative alkylation using as catalyst $\text{Pd}(\text{OAc})_2$ (2.5 mol%) in the presence of silver carbonate and acetic acid, working in a mixture of DMF-DMSO as solvent at 120 °C.³²⁹ Furthermore, another five-membered heterocycles, particularly thiophenes, have been alkynylated with terminal acetylenes using as catalyst $\text{Pd}_2(\text{dba})_3$ (0.2 mol%) and Ag_2O as oxidant, in the presence of pivalic acid (PivOH), cesium carbonate and triethylamine, in 1,2-dimethoxyethane as solvent at 90 °C, leading to interesting 2-alkynylated systems.³³⁰ An example this last methodology can be seen in Scheme 102, where 2-alkynylated thiophene **273** has been obtained from the direct oxidative coupling of 2-acylthiophene (**272**) and phenylacetylene.

Scheme 102



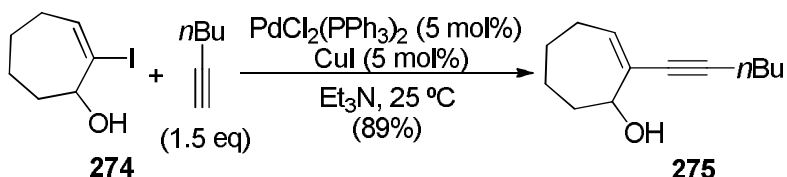
6.3. 1,3-Enynes

The conjugated 1,3-enyne moiety is a structure of high interest due to its presence in many natural products and biologically active substrates as well as in new functional materials, and its preparation by the cross-coupling of terminal alkynes and vinylic systems is straightforward by using a configuration-retention stereospecific procedure such as the palladium-catalyzed Sonogashira methodology.²²⁶ In this section, mainly examples of recent synthesis of the 1,3-enyne system by using this copper-cocatalyzed and copper-free alkylation procedure with different catalytic systems will be shown. Other less used palladium-catalyzed synthesis of enynes, such as alkyne dimerization or direct coupling of alkynes and alkenes will also be shown.

The typical copper-cocatalyzed Sonogashira reaction has been employed for the preparation of conjugated enynes using as coupling partners the ‘easy’ vinyl iodides, as exemplified in Scheme 103, which shows the use of $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%) combined to CuI (5 mol%) as catalytic combination for the coupling of hex-1-yne with cyclic vinyl iodide **274** affording enyne **275**, the reaction being performed in triethylamine as solvent at room temperature.³³¹ In addition, water has been used as solvent in the coupling of terminal alkynes with vinyl iodides under $\text{Pd(PPh}_3)_4$ (2 mol%)/ CuI (4

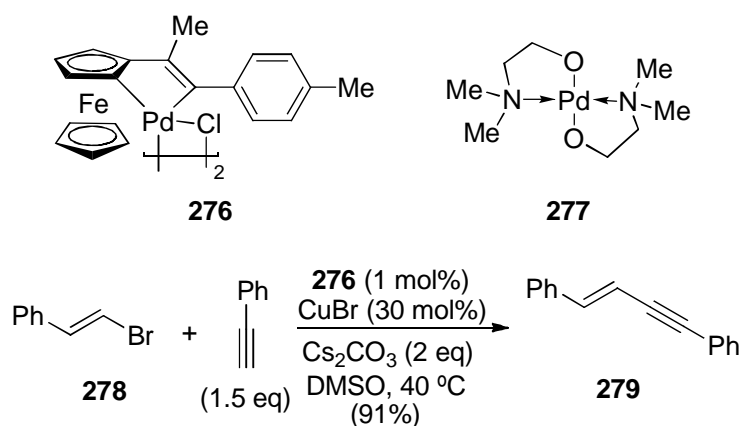
mol%) catalysis using pyrrolidine as base.³³² Other functionalized vinyl iodides have also been used for the coupling with terminal alkynes, leading to enynes under this classical Sonogashira reaction, such as (*E*)-2-iodovinyl sulfones³³³ and (*E*)-1-iodovinyl-1-tributylstannanes.³³⁴

Scheme 103



A recent example of the use of vinyl bromides as the coupling partners of terminal alkynes for the synthesis of 1,3-enynes via the copper-cocatalyzed Sonogashira reaction is the process promoted by palladacycle **276** (1 mol%) combined to CuBr (20 mol%).³³⁵ Using this catalytic combination, (*E*)- β -bromostyrene (**278**) has been coupled to phenylacetylene to give enyne **279**, cesium carbonate being used as base and DMSO as solvent at 40 °C (Scheme 104). This reaction has also been carried out under copper-free conditions using as catalyst the palladium(II) complex based on *N,N*-dimethylethanolamine **277** (1 mol%), cesium carbonate as base and DMF as solvent at room temperature.³³⁶

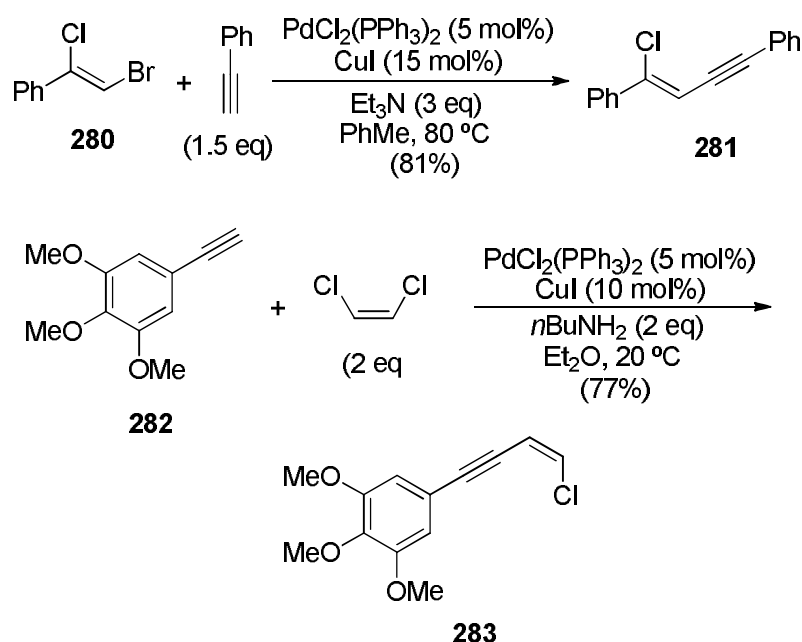
Scheme 104



Vinyl chlorides, similarly to aryl chlorides (see Section 6.1), are less reactive towards the coupling with terminal alkynes by means of the Sonogashira reaction than

their corresponding iodides or bromides, therefore their applicability for this cross-coupling process has been less frequent. For instance, when a chlorine and bromine atoms are on an alkene system, as in the case of **280**, the Sonogashira reaction takes place on the C-Br bond, as shown in the synthesis of enyne **281** after reaction of **280** with phenylacetylene catalyzed by $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%) and CuI (15 mol%) in the presence of triethylamine as base in toluene at 80 °C (Scheme 105).³³⁷ The more reactive (*Z*)-1,2-dichloroethylene has been used under the classical Sonogashira reaction conditions catalyzed by $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%)/ CuI (10 mol%), giving rise to enynes and dienynes, as in the case of its reaction with monoarylated alkyne **282**, using *n*-butylamine as base in ether as solvent at 20 °C. Chlorinated enyne **283**, an intermediate in the synthesis of anticancer Combrestatin analogues, was obtained under these conditions (Scheme 105).³³⁸ In addition, (*Z*)-1,2-dichloroethylene has also been used for the coupling with amino acid-containing terminal alkynes, in reaction catalyzed by $\text{PdCl}_2(\text{PhCN})_2$ (0.05 mol%) and CuI (0.05 mol%).³³⁹ Moreover, activated (*E*)-2-chlorovinyl sulfones have also been used for the coupling with terminal acetylenes.³⁴⁰

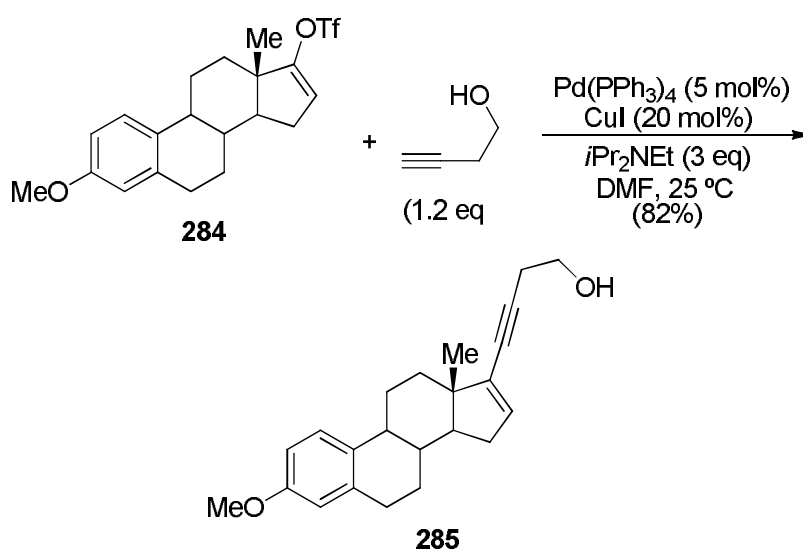
Scheme 105



Vinyl triflates, prepared easily by trapping the corresponding enolate from ketones, can also be used for the palladium-catalyzed Sonogashira coupling with terminal alkynes, giving rise to conjugated enynes. A useful example of this

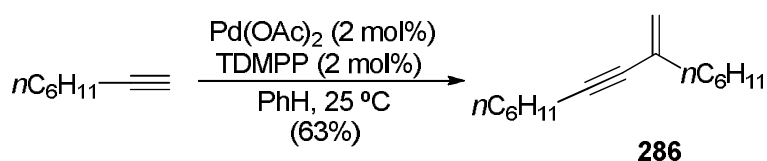
methodology is the cross-coupling of 17-steroidal triflates, such as **284**, and terminal alkynes, such as but-3-yn-1-ol, to give 17-alkynylsteroids such as **285** (Scheme 106).³⁴¹ The process was catalyzed by the combination of Pd(PPh₃)₄ (5 mol%)/CuI (20 mol%) in the presence of diisopropylethylamine and in DMF as solvent at room temperature, although it was observed that the use of silver acetate as cocatalyst instead of CuI gave rise to higher yields.

Scheme 106



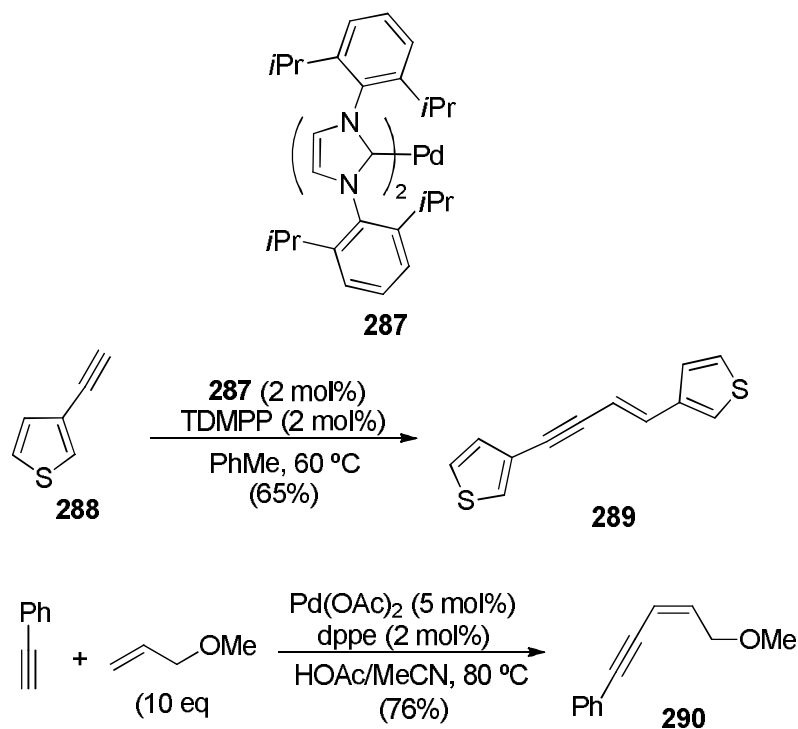
Apart from the Sonogashira cross-coupling reaction, other less-frequently employed methodologies for the synthesis of 1,3-enynes have been used. Thus, inactivated alkenes have been coupled with ethynyl bromides under Pd(OAc)₂ catalysis (5 mol%) in a ‘reverse’ Sonogashira reaction.³⁴² However, the direct palladium-catalyzed dimerization of alkynes is a more atom-economical approach towards conjugated enynes. The highly selective head-to-tail palladium-catalyzed dimerization of terminal alkynes was developed some time ago, using as catalytic system a combination of Pd(OAc)₂ (2 mol%) and the electron-rich and bulky ligand tris(2,6-dimethoxyphenyl)phosphine (TDMPP) (2 mol%),³⁴³ as in the case of the dimerization of oct-1-yne to yield enyne **286** (Scheme 107).^{343a} However, when using a Pd(OAc)₂/imidazolium chloride catalytic system, mixtures of regio- and stereoisomeric enynes were obtained.³⁴⁴

Scheme 107

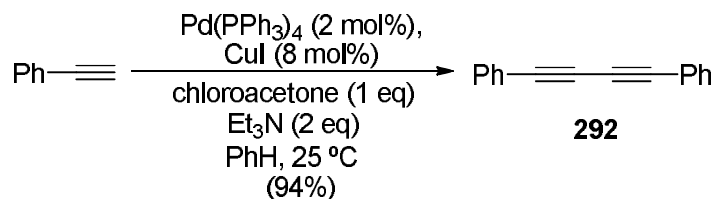


The head-to-head palladium-catalyzed dimerization of terminal alkynes has been achieved with high regio- and (*E*)-stereoselectivity, using as catalyst $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3/\text{TDMPP}$, although the method is limited to terminal aryl acetylenes bearing a requisite *ortho*-H atom, as agostic interactions are involved.³⁴⁵ More recently, a very selective head-to-head dimerization has been achieved using as catalyst the bis-*N*-heterocyclic carbene palladium complex **287** (2 mol%) in the presence of TDMPP (2 mol%) in toluene at 60 °C, as in the dimerization of 3-ethynylthiophene (**288**) to give enyne **289** (Scheme 108).³⁴⁶ In addition, (*Z*)-1,3-enynes have been obtained by dehydrogenative olefination of terminal arylalkynes with allylic ethers, as exemplified in the coupling of phenylacetylene and allyl methyl ether to yield compound **290** (Scheme 108), the process being catalyzed by $\text{Pd}(\text{OAc})_2$ (5 mol%)/*dppe* (2 mol%) in acetic acid/acetonitrile as solvent at 80 °C.³⁴⁷

Scheme 108

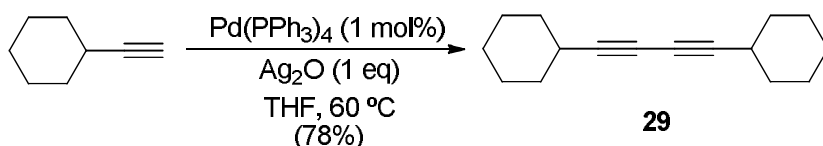


Scheme 110



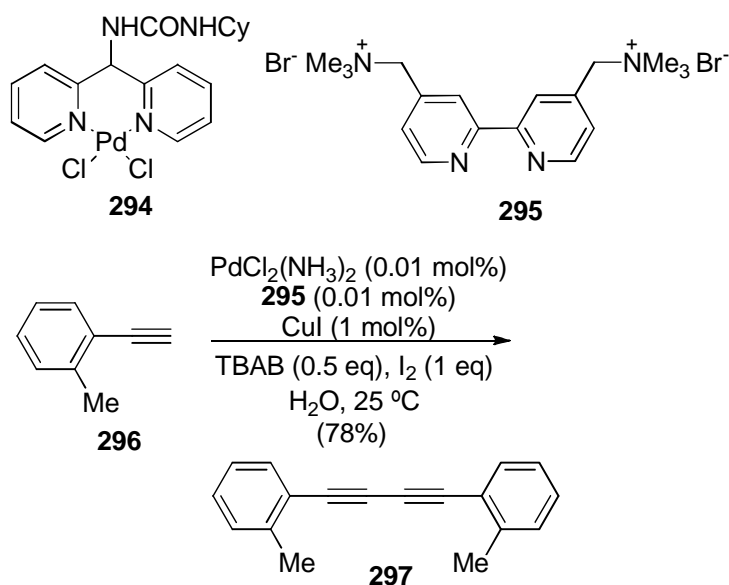
Other oxidants, combined with a catalytic mixture of a commercial palladium complex or salt and CuI, have been employed to achieve the homocoupling or terminal alkynes, as is the case of 4-iodo-2-nitroresorcinol or DMSO [with PdCl₂(PPh₃)₂],³⁵⁶ iodine [with PdCl₂(PPh₃)₂],³⁵⁷ ethyl bromoacetate [with PdCl₂(PPh₃)₂],³⁵⁸ air [with Pd(OAc)₂],³⁵⁹ triethylamine oxide [with PdCl₂],³⁶⁰ *p*-chloranyl [with Pd(PPh₃)₄],³⁶¹ (diacetoxyiodo)benzene [with PdCl₂],³⁶² (diacetoxyiodo)benzene and iodosylbenzene [with PdCl₂ + PPh₃].³⁶³ Silver(II) oxide has also been used recently as an oxidant combined to a rather low loading of Pd(PPh₃)₄ as catalyst (1 mol%) in the copper-free homocoupling of aryl and alkylacetylenes, the reaction being performed in THF as solvent at 60 °C, as in the case of the homocoupling of cyclohexylacetylene to give 1,3-diyne **293** (Scheme 111).³⁶⁴ In addition, there are examples where no stoichiometric oxidant has been added to achieve the homocoupling using the combination PdCl₂(PPh₃)₂ (3 mol%)/CuI (3 mol%) as catalyst, the addition of more triphenylphosphine (9 mol%) being sufficient.³⁶⁵ This is the case of the homocoupling of propargyl glycosides, although large amounts of PdCl₂(PPh₃)₂ (10 mol%) and 1 equivalent of CuI have been necessary.³⁶⁶ Moreover, water-soluble phosphines have also been used combined to Pd(OAc)₂ in a homogeneous acetonitrile-water system, with³⁶⁷ and without¹⁵⁷ Cu(I) promotor, affording diynes with moderate yields, whereas Pd₂(dba)₃ (5 mol%) has been used for the homocoupling of terminal alkynes in the presence of allyl bromide and TBAB, in CH₂Cl₂/50% aq NaOH under phase-transfer conditions.³⁶⁸

Scheme 111



Palladium complexes bearing pyridine rings as ligands have been employed as catalyst in this homocoupling reaction, as shown in the case of complex **294** which has proved successful acting as catalyst at a very low loadings (0.05-0.5 mol%) in the homocoupling of phenylacetylene.³⁶⁹ The reaction was carried out in the presence of CuI as co-catalyst (5 mol%), using pyrrolidine or tetra-*n*-butylammonium acetate (TBAA) as base, in NMP as solvent at 110 °C and without any additional oxidant. In addition, the cationic bipyridine ligand **295** has been used combined to a very low loading of the palladium complex PdCl₂(NH₃)₂ (0.001-1 mol%) and CuI (1 mol%) to generate a catalytic system that allows the coupling of terminal alkynes in water as solvent at room temperature, working in the presence of TBAB and with or without iodine as oxidant in open air. An example of the use of this methodology is the coupling of acetylene **296** to furnish 1,3-diyne **297** (Scheme 112).³⁷⁰ In this case, the water-soluble catalyst system was separated from the organic products by extraction and the residual aqueous solution was active for reuse for several cycles without a significant decrease in activity.

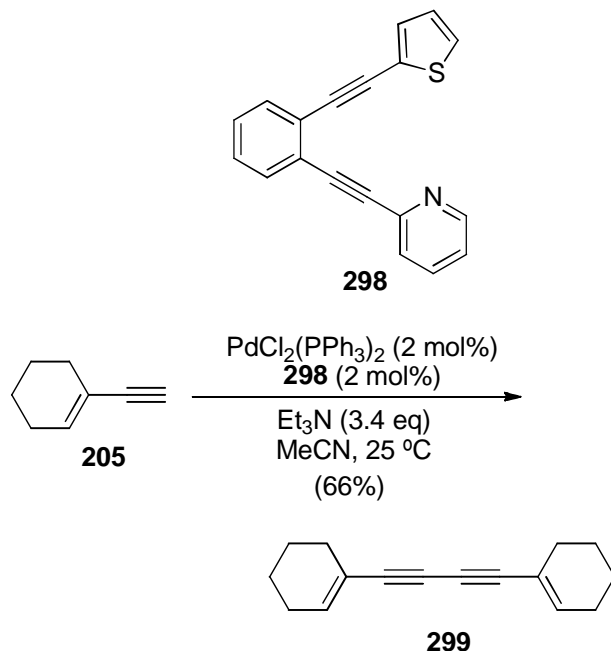
Scheme 112



In the presence of dialkynylated bis-heterocycle **298** as ligand (2 mol%), PdCl₂(PPh₃)₂ (2 mol%) has shown to catalyze the copper-free homocoupling of aromatic and aliphatic terminal alkynes in the presence of triethylamine as base, in

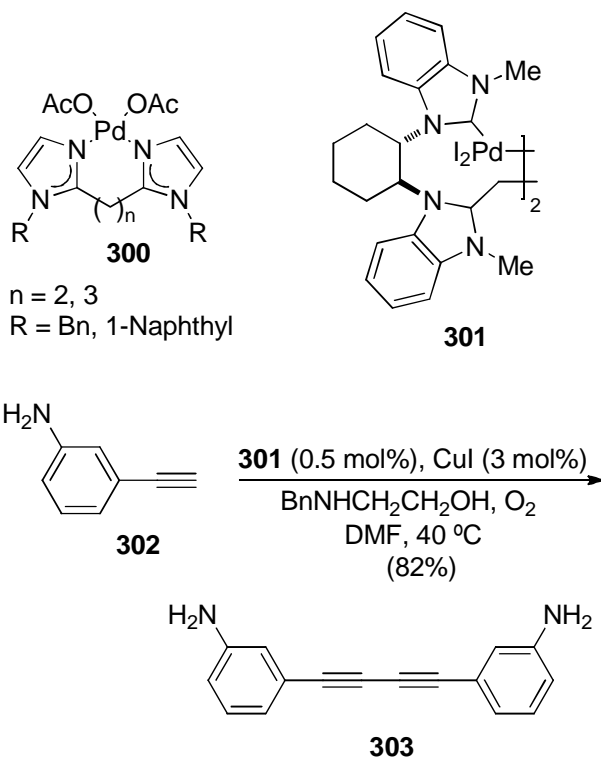
acetonitrile at 40 °C or room temperature in air, as in the case of the homocoupling of enyne **205** to diyne **299** (Scheme 113).³⁷¹

Scheme 113



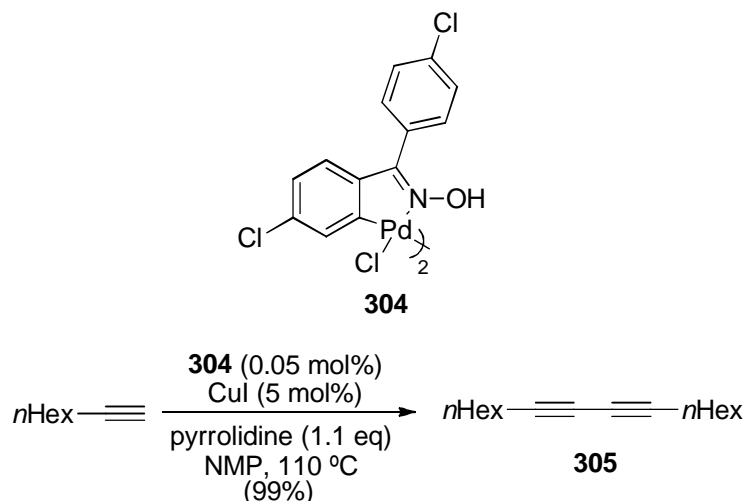
There are a few examples where NHC-palladium complexes have been used as catalysts in the homocoupling of terminal alkynes, as is the case of complexes **300** which have been used as catalysts (0.3 mol%) in the homocoupling of arylacetylenes, working in the presence of benzoquinone as oxidant in acetonitrile as solvent at 70 °C, although the conversions were low to moderate.³⁷² In addition, NHC-palladium complexes such as **301** has been used as catalyst (0.5 mol%) in the presence of CuI as co-catalyst (3 mol%) and 2-(benzylamino)ethanol as base under molecular oxygen in DMF at room temperature to give homocoupled products from terminal acetylenes, as is the case of the coupling of alkynylated aniline **302** to give 1,3-diyne **303** (Scheme 114).³⁷³ Furthermore, the use of NHC macrocyclic palladium pincer complexes for this homocoupling reaction has also been reported.³⁷⁴

Scheme 114



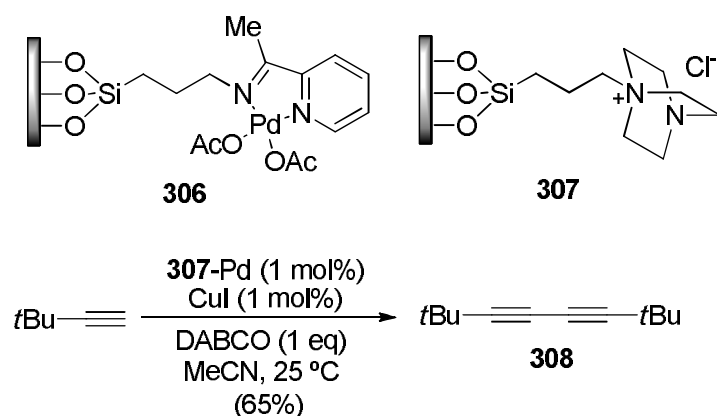
Palladacycles have also been employed as catalysts in the homocoupling of terminal alkynes in the absence of oxidants. Thus, there are examples where palladacycles from ferrocenylimines (2.5 mol%) combined to CuI (2.5 mol%) catalyze the homocoupling of aromatic and aliphatic terminal alkynes leading to diynes.³⁷⁵ However, better results were achieved employing as catalyst the oxime-derived palladacycle **304**, which at very low loadings (0.05-0.5 mol%) and combined to CuI (5 mol%) was able to catalyze the homocoupling of aromatic and aliphatic terminal alkynes, as illustrated in Scheme 115 with the formation of diyne **305** from oct-1-yne, the reaction being carried out in the presence of pyrrolidine as base in NMP at 110 °C.³⁷⁶

Scheme 115



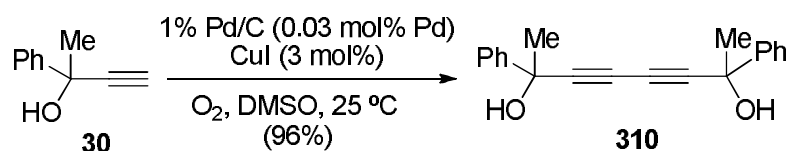
The use of supported palladium species for achieving this homocoupling reaction has also been explored.^{352c} Examples are the use of a polystyrene-PEG400-PPh₂ as a supported phosphine ligand combined to PdCl₂ (3 mol%) and in the presence of CuI (3 mol%). The reaction was carried out in acetonitrile/water with sodium percarbonate as both an oxidant and a base at room temperature, and the catalyst was recovered by filtration and reused up to five times with a certain decrease in its activity.³⁷⁷ In addition, the palladium complex anchored to mesoporous silica **306** (1 mol%) promotes the homocoupling of phenylacetylene.³⁷⁸ The reaction proceeds in the presence of 4-iodophenol which acts as oxidizer and triethylamine as base at 70 °C, no reusing experiments being performed. Moreover, Pd(0) and Pd(II) nanoparticles have been supported on a 1,4-diazabicyclo[2.2.2]octane (DABCO)-functionalized mesoporous silica SBA-15 **307** after heating Pd(OAc)₂ and the support in refluxing acetone. The resulting anchored palladium species **307**-Pd has been used as catalyst (1 mol%) in the homocoupling of aromatic and aliphatic terminal alkynes at room temperature.³⁷⁹ However, the presence of 1 equivalent of DABCO and CuI (1 mol%) was necessary. The catalysts was recovered by centrifugation and reused up to four times keeping its activity. An example of the use of this methodology is the synthesis of diyne **308** from *tert*-butylacetylene (Scheme 116).

Scheme 116



Low loading of 1% Pd/C (0.01-0.03 mol% Pd) combined to CuI (3 mol%) have been employed as a catalytic mixture in the homocoupling of aromatic and aliphatic terminal alkynes leading to 1,3-diynes in good yields, using oxygen as oxidant in DMSO as solvent at room temperature, no attempts for recycling being made.³⁸⁰ An example of the application of this methodology is the homocoupling of propargyl alcohol **309** to furnish diyne **310** (Scheme 117).

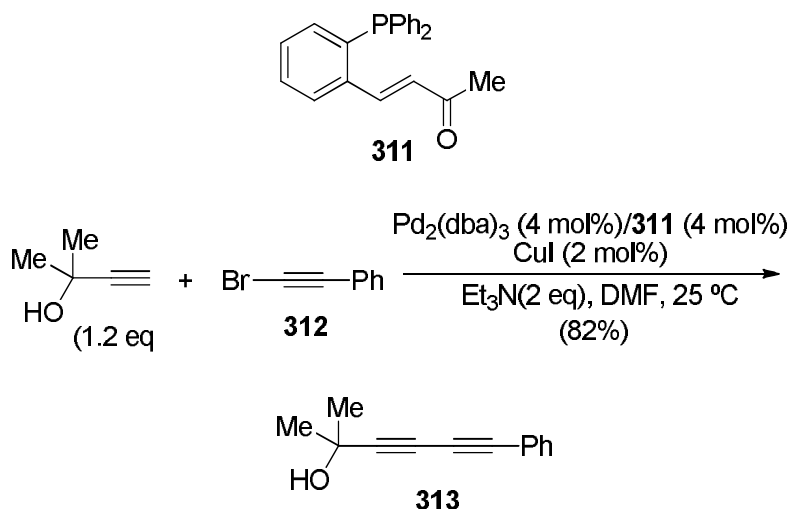
Scheme 117



All the above mentioned procedures for the synthesis of 1,3-diynes are limited to the preparation of symmetrically substituted systems, as they are all dealing with the palladium-catalyzed homocoupling of terminal alkynes. However, there are also procedures which allow the formation of unsymmetrically substituted 1,3-diynes through palladium-catalysis, one of them being the direct coupling of terminal alkynes and 1-haloalkynes. This process was demonstrated as possible, using the Pd/Cu Sonogashira reaction conditions, employing 1-iodoalkynes³⁸¹ or 1-bromoalkynes³⁸² as terminal alkyne counterparts. In addition, the catalytic combination of Pd(OAc)₂/TPPTS (1/2, 5 mol%) has been used for the heterocoupling of terminal alkynes and 1-iodoalkynes under aqueous conditions, although certain amounts of the homocoupling product were observed.¹⁵⁷ However, good results have been obtained using a

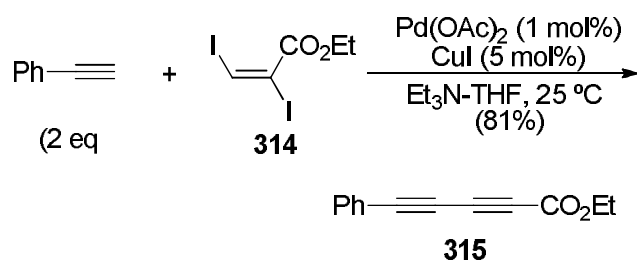
combination of the phosphine ligand **311** and $\text{Pd}_2(\text{dba})_3$ to generate a catalyst (4 mol%) employed in the coupling of terminal alkynes and 1-bromoalkynes, the process being cocatalyzed by CuI (2 mol%) in the presence of triethylamine as base in DMF as solvent at room temperature.³⁸³ An example of this process is the cross-coupling of 2-methylbut-3-yn-2-ol to (bromoethynyl)benzene (**312**) to give unsymmetrically substituted 1,3-diyne **313** (Scheme 118). This process has also been carried out using low loadings of $\text{Pd}(\text{OAc})_2$ (0.01 mol%) as catalyst and CuI (0.2-2 mol%) as cocatalyst, in the presence of TBAB and using diisopropylamine as base and solvent at 70 °C, PdNPs being involved in the catalysis.³⁸⁴ In addition, this procedure has also been performed using as catalyst PdNPs (2 mol%) supported on the (DABCO)-functionalized mesoporous silica SBA-15 **307**.³⁸⁵ In this case, the reaction was achieved using CuI as cocatalyst (2 mol%) triethylamine as base in DMF as solvent at room temperature, and the catalyst was recovered by filtration and reused up to three times, a certain loss of activity observed in the third run.

Scheme 118



The preparation of unsymmetrical 1,3-diyne has also been carried out by the palladium-catalyzed coupling of terminal alkynes with (*E*)-1,2-diiodoalkenes followed by an in situ dehydroiodination.³⁸⁶ The process was performed using the combination of $\text{Pd}(\text{OAc})_2$ (1 mol%) and CuI (5 mol%) as catalyst, and a mixture of triethylamine and THF as basic solvent at room temperature, as shown in Scheme 119 with the coupling of phenylacetylene with diiodoacrylate **314** to give 1,3-diyne **315**.

Scheme 119

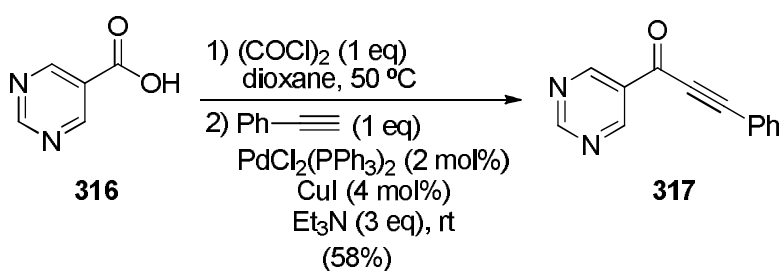


6.5. Ynones

Alkynylated ketones (ynones) are important structural motifs found in many biologically interesting compounds,³⁸⁷ and also are multipurpose intermediates in the synthesis of natural products³⁸⁸ and in the formation of several heterocycles.³⁸⁹ Suitable synthetic methods for the preparation of conjugated ynones utilize palladium catalysts for the coupling of terminal alkynes with an acid chloride (acyl Sonogashira reactions)^{226b,c} or with organic halides in the presence of carbon monoxide (carbonylative Sonogashira reactions).^{226b,c,390}

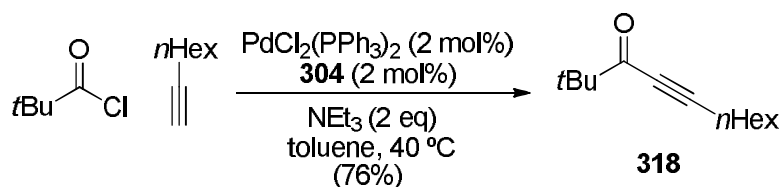
The acyl Sonogashira reaction has been frequently performed by combining a terminal alkyne and acyl chloride under the typical palladium-copper cocatalyzed reaction conditions.^{226b,c} However, some difficulties are often encountered and related to instability of the necessary acyl chlorides are prompting modifications in this old synthetic methodology. Thus, carboxylic acids from heterocyclic systems can be activated in situ with oxalyl chloride, a subsequent one-pot copper-cocatalyzed Sonogashira coupling with terminal alkynes under the usual conditions leading to ynones.³⁹¹ An example of this methodology which avoids the isolation of unstable heterocyclic acyl chlorides is shown in Scheme 120, where pyrimidine-5-carboxylic acid (**316**) is transformed into its unstable acyl chloride and reacts in cross-coupled in situ with phenylacetylene to give ynone (**317**).

Scheme 120



The formation of undesirable diynes as byproducts is another of the known problems of using the typical copper cocatalyzed Sonogashira reaction conditions in the formation of ynones. Therefore, the use of copper-free procedures by using more reactive palladium species is receiving special interest.^{226b,c} Thus, the common palladium complex $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mol%), in the presence of the former dialkynylated bis-heterocycle **298** as ligand (2 mol%), catalyzes the acyl Sonogashira reaction of aryloyl and alkylloyl chlorides and terminal alkynes to give the corresponding ynones, the reaction being performed in the presence of triethylamine as base, in toluene at $40\text{ }^\circ\text{C}$.³⁹² An example of this methodology is the coupling of pivaloyl chloride with oct-1-yne to give ynone **318** (Scheme 121). In addition, the oxime-derived palladacycle **304** has been used as low-loading catalyst (0.001 mol%) for the copper-free acylation of terminal alkynes with carboxylic acid chlorides, in the presence of triethylamine as base in toluene at $110\text{ }^\circ\text{C}$.³⁹³ Furthermore, recent examples employing as catalysts other less common palladium complexes³⁹⁴ as well as recyclable supported palladium complexes³⁹⁵ or nanoparticles³⁹⁶ able to perform this copper-free ynone formation reaction can also be found.³⁹⁷

Scheme 121

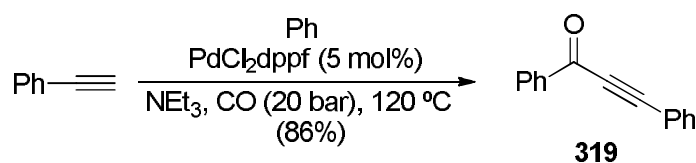


According to the sometimes limited stability of the respective acid chlorides and to a certain lack of functional tolerance of this acyl Sonogashira methodology, the carbonylative Sonogashira coupling of terminal alkynes and aryl halides (mostly

iodides) in the presence of carbon monoxide represents the most straightforward way to prepare ynones.^{226b,c,390a,b} In addition, is a useful procedure for the generation of non-isolated ynone intermediates for the synthesis of heterocycles.^{390b} such as 2-aryl phenyl-4*H*-chromen-4-ones by in situ cyclization of ynones from 2-iodophenols,³⁹⁸ or 1,2,3-(NH)-triazoles by reaction of ynone intermediates with sodium azide.³⁹⁹

The first carbonylative Sonogashira reaction was reported more than thirty years ago using PdCl₂dppf as catalyst (5 mol%).⁴⁰⁰ Aryl iodides, such as phenyl iodide, were coupled with terminal acetylenes, such as phenylacetylene, in triethylamine under CO at pressures up to 80 bar and a temperature of 120 °C giving ynones such as **319** (Scheme 122). Since then, many palladium catalysts, unsupported and supported, as well as many reaction conditions have been reported attempting to achieve this transformation using more active palladium species, lower CO pressures, lower temperatures, environmentally-friendly solvents and so on.^{390b} For instance, using recyclable PdNPs supported on polymers as catalyst (0.5 mol%) and water as solvent (CO pressure: 30 bar, 130 °C),⁴⁰¹ or avoiding the use of CO using CO-releasing molecules such as silacarboxylic acids.⁴⁰²

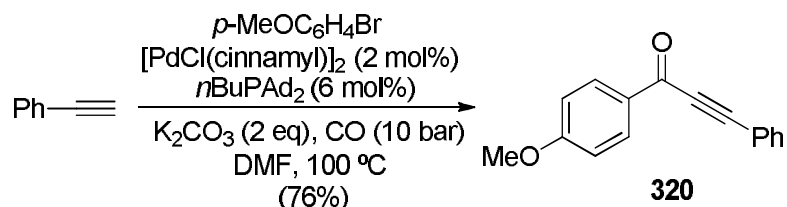
Scheme 122



However, although there are examples of the use of vinyl triflates as alkyne counterpart in this process,⁴⁰³ almost all the examples of carbonylative Sonogashira reactions have been carried out using aryl iodides, which is somehow a shortcoming of the methodology.^{390b} Therefore, recent research has been done in order to overcome this limitation, allowing the use other substrates. Thus, aryl bromides have been used in the carbonylative Sonogashira reaction of arylacetylenes, using as catalyst a combination of [PdCl(cinnamyl)]₂ (2 mol%) and *n*BuPAd₂ (Ad = adamantyl) (6 mol%) in the presence of potassium hydroxide as base under an atmosphere of CO (10 bar) in DMF at 100 °C, as in the case of the synthesis of ynone **320** from phenylacetylene and 4-bromoanisole (Scheme 123).⁴⁰⁴ In addition aryl triflates have also been used as coupling partners,

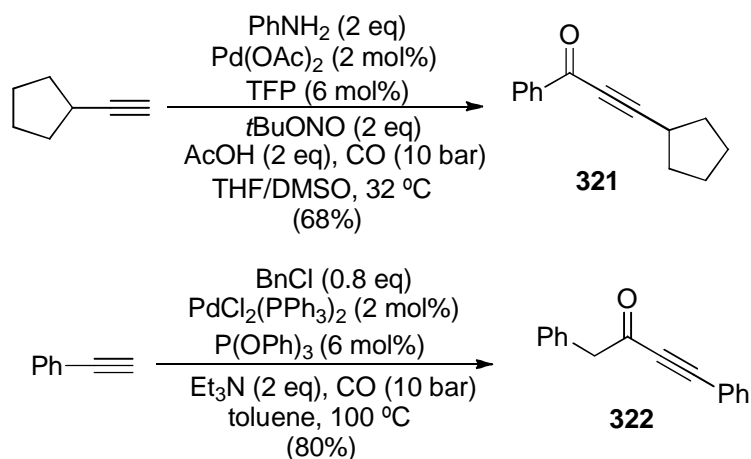
using the former palladium source (1 mol%) and Xantphos (**80**) as ligand (2 mol%), triethylamine as base under CO (10 bar) in toluene as solvent at 110 °C.⁴⁰⁵

Scheme 123



Aryl amines can also be used in this carbonylative reaction with alkynes, after an in situ formation of the corresponding arenediazonium salts with *tert*-butyl nitrite and a carbonylative coupling with terminal alkynes catalyzed by Pd(OAc)₂ (2 mol%)-TFP (6 mol%) [TFP = tri(2-furyl)phosphine] under CO (10 bar) in THF/DMSO at 32 °C, as shown in Scheme 124 in the formation of ynone **321** from ethynylcyclopentane and aniline.⁴⁰⁶ In addition, benzyl chlorides have been employed in the carbonylative Sonogashira reaction of arylacetylenes, using as catalyst PdCl₂(PPh₃)₂ (2 mol%) accompanied of P(OPh)₃ (6 mol%), in the presence of triethylamine under CO (10 bar) in toluene as solvent at 100 °C, as in the case of the preparation of ynone **322** from benzyl chloride and phenylacetylene (Scheme 124).⁴⁰⁷ Moreover, there are recent examples of the synthesis of 3-alkylidenefuran-2-ones using a palladium-catalyzed multicomponent reaction between aryl bromides or triflates, terminal acetylenes and CO, the process taking place through carbonylation of the ynone intermediate.⁴⁰⁸

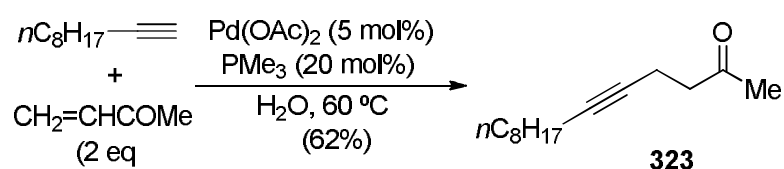
Scheme 124



Examples of the use of recyclable supported catalysts for this reaction can also be found, although then the most reactive iodides must be used as coupling counterparts. Thus, the MCM-41-supported bidentate phosphine palladium(0) complex **105** has been used as catalyst (0.05 mol%) in the heterogeneous carbonylative Sonogashira coupling reaction of terminal alkynes with aryl iodides under CO (1 bar).⁴⁰⁹ This polymeric palladium catalyst was reused up to ten times without any decrease in activity.

Non-conjugated ynones, such as β -alkynyl ketones can be obtained by palladium-catalyzed conjugate addition of terminal alkynes to enones. Thus, reaction of a monosubstituted acetylene such as dec-1-yne with β -unsubstituted acyclic enones such as methyl vinyl ketone has allowed to obtain alkynylated ketone **323**, in a process catalyzed by Pd(OAc)₂ (5 mol%) and PMe₃ (20 mol%) in water or acetone as solvent at 60 °C (Scheme 125).⁴¹⁰ β -Substituted acyclic and cyclic enones have also been employed more recently in this conjugate addition reaction, using as catalyst the combination Pd₂(dba)₃ (5 mol%)/(2,4-*t*BuC₆H₃O)₃P (10 mol%), in dioxane at 90 °C.⁴¹¹

Scheme 125



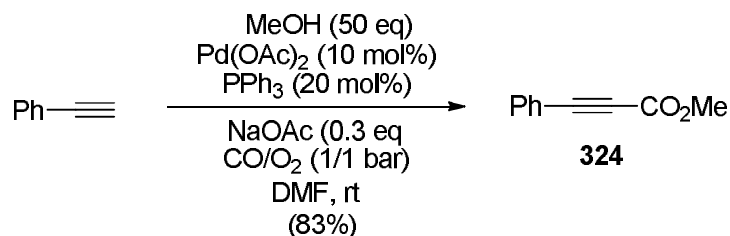
6.6. Ynoates and Ynamides

The transition metal-catalyzed oxidative carbonylation is a convenient way of introducing carboxyl-derived functionalities in hydrocarbons acting as nucleophiles.⁴¹² When the oxidative carbonylation is carried out on the terminal C-H of monosubstituted alkynes in the presence of alcohols or amides under palladium catalysis, substituted 2-ynoates and 2-ynamides, respectively, are obtained.

The first oxidative carbonylation of terminal alkynes in the presence of an alcohol leading to 2-alkynoates was developed more than thirty years ago,⁴¹³ the process being carried out using PdCl₂ (5 mol%) as catalyst and CuCl₂ as reoxidant in the presence of sodium acetate as base under an atmospheric pressure of CO at room

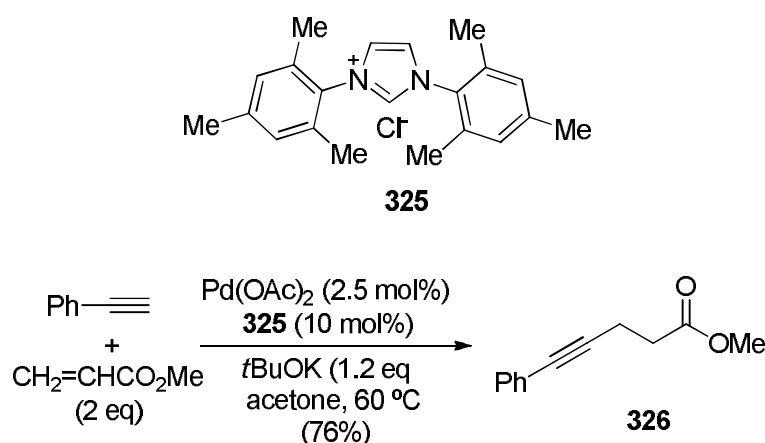
temperature. Lately, other more convenient procedures based on the use of oxygen as the final oxidant were developed, as in the case of the synthesis of methyl aryl- and alkyl-2-ynoates using of a multicatalytic system consisting of Pd(OAc)₂ (5 mol%)-chlorohydroquinone-molybdovanadophosphate in the presence of methanesulfonic acid in methanol as solvent at room temperature and under a mixed atmosphere of CO/O₂.⁴¹⁴ A more simple procedure was developed, although with higher catalyst loading, based on the use of PdCl₂ (10 mol%) and PPh₃ (20 mol%) as catalyst, in the presence of sodium acetate as base and working under an atmospheric pressure of CO/O₂ in DMF as solvent at room temperature.⁴¹⁵ Employing these reaction conditions, terminal alkynes such as phenylacetylene was converted into ynoates such as methyl phenylpropiolate (**324**) (Scheme 126). In addition, on the basis of the findings on this homogeneous catalytic system, a heterogeneous catalytic one using 10% Pd/C (0.05 mol%) was also developed and applied to formation of methyl phenylpropiolate, although high pressures of CO (50 bar) and O₂ (7.5 bar) were needed and no attempts of catalyst recovery were made.⁴¹⁵

Scheme 126



Non-conjugated ynoates, such as β -alkynylated esters, have been obtained by palladium-catalyzed conjugate addition of terminal alkynes to methyl or *tert*-butyl acrylate, following a similar procedure than the above mentioned for the preparation of alkynylated ketones, although using now a NHC ligand generated from **325**.^{410b} An example of this methodology is illustrated in Scheme 127, where phenylacetylene adds to methyl acrylate to give β -alkynylated ester **326**.

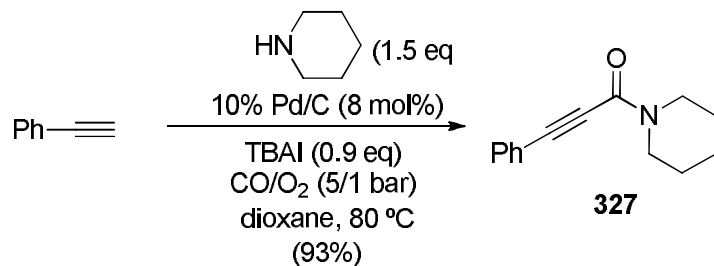
Scheme 127



Although some conjugated ynamides have been prepared by Sonogashira-type palladium-catalyzed coupling of terminal alkynes with carbamoyl chlorides,⁴¹⁶ a more direct synthetic procedure is the palladium-catalyzed oxidative carbonylation using amines. However, this process is not as easy as in the case of the preparation of ynoates, as a reaction between phenylacetylene and diethylamine under the above mentioned pioneering procedure for the preparation of ynoates using PdCl₂/CuCl₂/AcONa, gave only 5% yield of the corresponding diethylamine of phenylpropionic acid.⁴¹³ Thus, the first successful procedure for this transformation was the conversion of alkyl- and arylacetylenes into 2-ynamides catalyzed by a mixture of PdI₂ (0.2 mol%) and KI (2 mol%), the process being carried out in the presence of secondary amines under CO/air in dioxane at 100 °C.⁴¹⁷ The reaction afforded better results with aryl acetylenes, as alkylacetylenes afforded small amounts of products from diaminocarbonylation of the triple bond, and the use of secondary amines was necessary, primary amines being unreactive or affording complex mixtures. This catalytic system has been used in other carbonylation reactions of functionalized terminal alkynes, the corresponding products leading to heterocyclic systems after cyclization.⁴¹⁸ In addition, 10% Pd/C (8 mol%) can be used as catalyst in a ligand-free oxidative aminocarbonylation of terminal alkynes, the reaction being carried out with secondary amines in the presence of tetra-*n*-butylammonium iodide (TBAI) under CO/O₂ in dioxane at 80 °C.⁴¹⁹ When using arylacetylenes the reaction afforded high yields of the corresponding ynamides, as exemplified in the preparation of ynamide **327** from phenylacetylene and piperidine (Scheme 128), the use of an alkyl acetylene such as hex-1-yne affording 55% yield for the same reaction. The catalyst was recycled and reused up to four times without loss of

activity, no significant palladium leaching being detected by inductively coupled plasma atomic emission spectroscopy (ICP-AES).

Scheme 128



7. Conclusions

This review has intended to illustrate how the familiar alkynes, combined to the powerful catalytic properties of palladium species, can be converted into very versatile starting materials for the preparation of an enormous variety of compounds of interest. The development over the last few years of more reactive palladium catalysts, apart from the traditional phosphine-containing complexes, as well as new reaction conditions has broadened the reaction possibilities of alkynes, from the traditional addition reactions of heteronucleophiles, to many synthetically important carbon-carbon bond formation reactions. Particular attention has been devoted in the past ten years to the use of supported palladium catalysts suitable to being recovered and reused once the transformation of the alkyne has been achieved, something especially convenient when industrially useful processes are intended, although sometimes their reactivity was lower compared to homogeneous systems. Similarly, the use of palladium nanoparticles as catalysts is a topic making rapid progress in the last years and their use for the transformation of alkynes in interesting chemicals is no exception. In addition, the present environmental worries have also been shown with examples of the use of friendly solvents, such as water, for carrying out the synthesis of different chemicals from alkynes. However, in spite of all these developments, plenty of work is still ahead in order to achieve low loadings of catalytic systems, supported or not, applicable to the reaction of alkynes, functionalized or not, with synthetic counterparts bearing any functionality, under mild and environmentally friendly reaction conditions. There is no

doubt that alkynes still will continue showing more and more synthetic possibilities in the near future.

8. Acknowledgments

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