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C–C Coupling

Palladium-Based Catalytic Systems for the Synthesis of Conjugated Enynes by Sonogashira Reactions and Related Alkynylations

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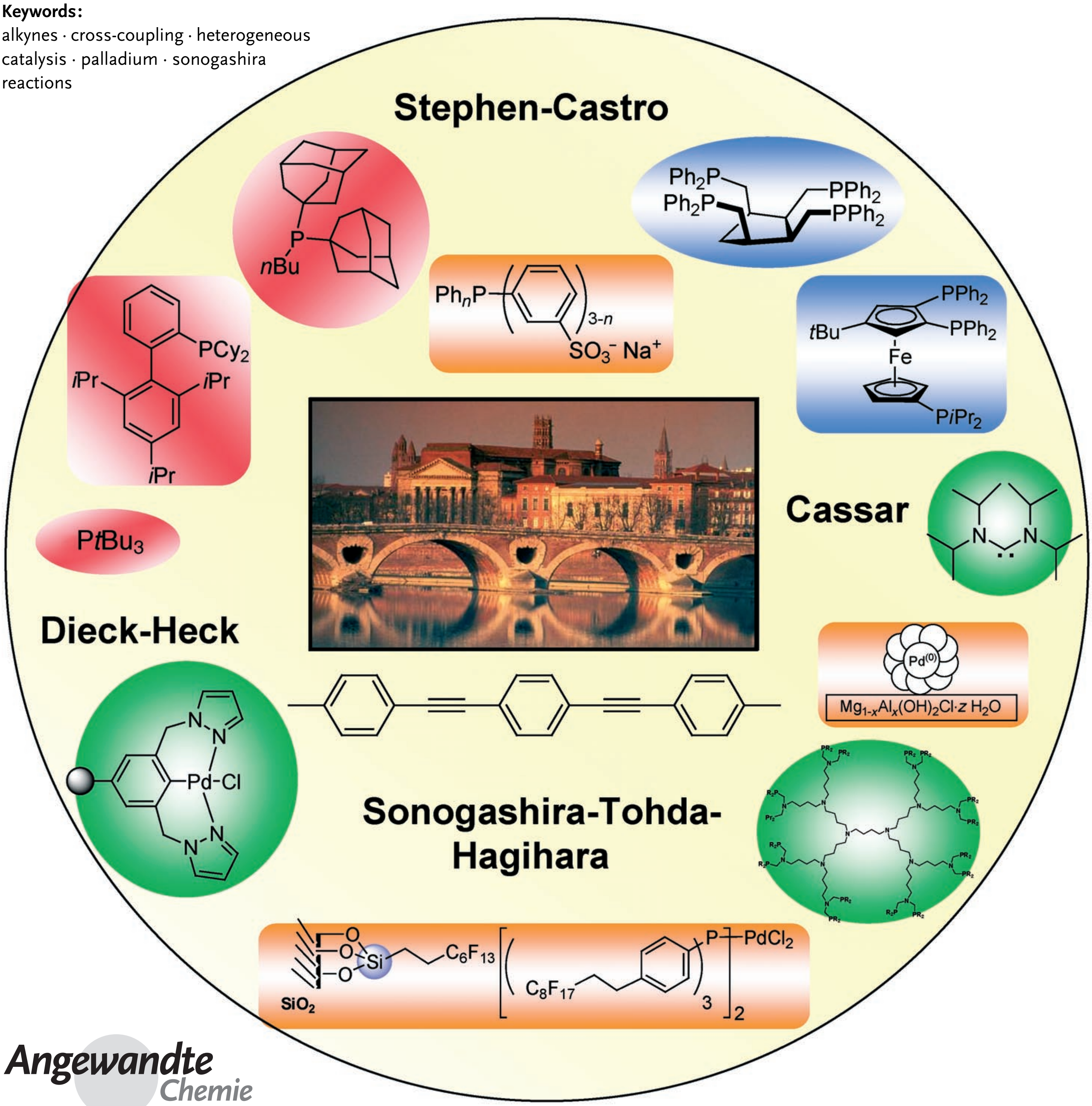
Keywords:
alkynes · cross-coupling · heterogeneous catalysis · palladium · sonogashira reactions



Conjugated alkynes are recurring building blocks in natural products, a wide range of industrial intermediates, pharmaceuticals and agrochemicals, and molecular materials for optics and electronics. The palladium-catalyzed cross-coupling between sp^2-hybridized carbon atoms of aryl, heteroaryl, and vinyl halides with sp-hybridized carbon atoms of terminal acetylenes is one of the most important developments in the field of alkyne chemistry over the past 50 years. The seminal work of the 1970s has initiated an intense search for more general and reliable reaction conditions. The interest in the catalytic activation of demanding substrates, the need to minimize the consumption of depletive resources, and the search for easy access to an increased variety of functionalized enynes has led to the current generations of high-turnover catalysts. This Review gives an overview of the highly efficient palladium catalyst systems for the direct alkynylation of $C(sp^2)$ halides with terminal alkynes, both in homogeneous and heterogeneous phases.

From the Contents

1. Introduction

The palladium-catalyzed cross-coupling between sp^2-hybridized carbon atoms ($C(sp^2)$) aryl, heteroaryl, and vinyl halides and sp-hybridized carbon atoms of terminal acetylenes (C(sp)) pertains to the family of modern and extremely powerful synthetic methods for the synthesis of important organic intermediates. The conjugated π systems resulting from alkynylation reactions—conducted either with alkynylmetal reagents or directly with terminal alkynes—are building blocks often encountered within natural products, pharmaceutical molecules, synthetic agrochemicals, and molecular materials. The palladium/copper co-catalyzed alkynylation of aryl and vinyl halides is probably the most widely employed methodology to yield enynes; a simpler version of the reaction requires exclusively a palladium catalyst (widely known as copper-free alkynylation).

Collectively, the seminal works by Stephens and Castro (1963),[1] Dieck and Heck (1975),[2] Cassar (1975),[3] and Sonogashira, Tohda, and Hagihara (1975)[4] have initiated an outstanding number of studies in the fields of organic chemistry, organometallic chemistry and catalysis, total synthesis, and material science.[5–8] The original reactions and their experimental conditions, as disclosed by the pioneering authors (Scheme 1), reveal both a straightforward applicability and a very large substrate range, which is probably at the origin of their success.

Sonogashira and related alkynylation reactions have been covered in the last few years by several relevant reviews, in which the authors focused in general on their own areas of research.[5–19] Table 1 lists these and other pertinent review articles related to the palladium-catalyzed synthesis of conjugated enynes and the various applications of these reactions. In 2006 Tykwinski and Shi Shun reviewed the synthetic efforts directed towards the synthesis of polyyne natural products, together with a highlight of the natural sources and biological relevance of some selected examples.[9] The important role of palladium-catalyzed alkynylations in total synthesis has been covered in a recent review by Nicolaou et al.[7]

The performances of the current palladium catalysts with the highest turnover numbers (TONs) or turnover frequencies (TOFs) in homogeneous phase cross-coupling, including Sonogashira and related reactions, were critically examined by Farina in 2003;[10] Fu and Littke had previously covered the palladium-catalytic systems able to activate the relatively inert chloride substrates.[11] Several reviews have surveyed the results obtained for alkynylation reactions carried out in the presence of carbene ligands[12–15] or palladacyle complexes.[13,16] Conceptual advances by Tykwinski,[17] cross-coupling in water by Genêt and Savignac,[18] and advances on mechanistic aspects by Jutand[19] have also been covered. In light of these recent reviews it appears that a critical discussion specifically devoted to all the different classes of catalytic systems proposed to date for homogenous and

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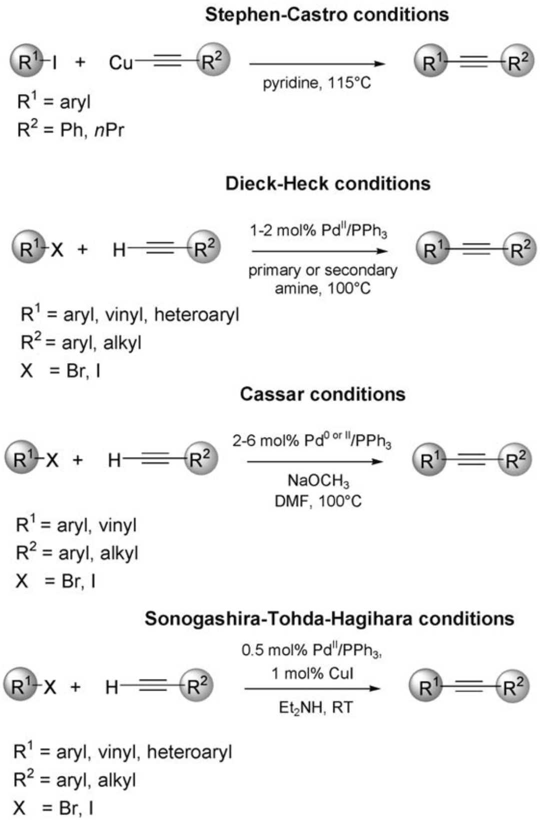


Scheme 1. Original conditions reported in pioneering works on alkynylation reactions of $C(sp^2)$ halides.

heterogeneous Sonogashira–Heck alkynylation reactions would be timely and useful.

Herein we compare the highly efficient palladium catalyst systems reported for the direct alkynylation of $C(sp^2)$ halides with terminal alkynes in the presence (Sonogashira—Tohda–Hagihara reaction) and without (Dieck–Heck–Cassar alkynylation) a copper co-catalyst. The advantages of the reactions being carried out in a homogeneous phase are covered in the first part, notably: 1) high turnover numbers, 2) the coupling of the widely available and low-cost aryl chlorides, 3) milder reaction conditions and the minimization of the consumption of depletive resources. The second part is devoted to the recyclable catalytic systems both in homogeneous and heterogeneous phases: 1) biphasic (and/or thermomorphic) systems, 2) colloidal and solid-supported catalysts, and 3) systems using unusual solvents, such as ionic liquids. The last part is a discussion on other closely related research in this field, especially: 1) new activation processes (microwaves and sonication), 2) catalytic systems using other metals and the so-called "metal-free" systems, and 3) recently disclosed unusual coupling partners. The remaining challenges in the field as well as the desirable developments are outlined in the conclusion. In this Review, the literature cut-off on this very productive topic in organic chemistry and catalysis was the beginning of 2006.

2. Sonogashira–Heck Alkynylations in the Homogeneous Phase

In the last three decades a large number of palladium–ligand complexes (and even ligand-free catalytic systems) have been tested on homogeneous-phase Sonogashira–Heck–Cassar reactions. These studies have shown that virtually any palladium source is capable of reaching high TONs for facile reactions—such as the coupling of aryl iodides with phenylacetylene—provided appropriate reaction conditions are found. On the other hand, with less-reactive substrates—such as electron-rich or sterically congested aryl bromides, aryl chlorides, propargyl alcohols, or propargylamines—much lower TONs are generally obtained, and the ligands have a large influence on the outcome of the reactions. Therefore, the systematic study of TONs in palladium-catalyzed C–C bond-formation processes is an important area of research for future industrial applications. For this reason the focus herein is placed upon the TONs of the reactions rather than on the yields, which are generally high.

The factors that affect the rates of the Sonogashira reaction are not completely understood, however, the steric and electronic properties of the ligands and catalysts are determining parameters. In the following, we discuss successively the results of studies carried out on systems incorporating either monophosphanes, carbenes, and di-, tri-, and tetradentate ligands, as well as palladacycles; herein emphasis is placed upon the alkynylation reactions which employed vinyl and aryl bromides or chloride substrates.

Henri Doucet was born in Paris in 1967. He received his PhD in chemistry with Prof. P. H. Dixneuf and Dr. C. Bruneau at Rennes University. After postdoctoral positions at Oxford University (J. M. Brown) and Nagoya University (R. Noyori), he moved to the University of Marseille as a CNRS researcher. His research interests include organic synthesis by metal-catalyzed processes and ligand synthesis. At the end of 2006 he joined Rennes University.

Jean-Cyrille Hierso was born in Toulouse in 1971. He studied physical chemistry at the Université P. Sabatier, where he worked on Pd nanochemistry (MS 1994, Dr. B. Chaudret, LCC-CNRS) and on CVD for heterogeneous catalysis (PhD 1997, Prof. P. Kalck). After postdoctoral research on scorpionate organometallic complexes (Prof. M. Etienne, LCC) and paints chemistry (Prof. J. Reedijk, Netherlands), in 2001 he was appointed Maître de Conférences in Dijon. In 2006 he was awarded his Habilitation on the synthesis of ferrocenyl polyphosphanes and their application in homogeneous catalysis.

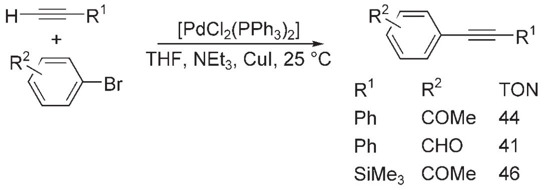
Table 1: Review articles relating to the synthesis and application of enynes and polyynes, as well as to the catalytic systems developed for the alkynylation of halides (published after 1999).

Title	Authors	Ref.
Synthesis of Naturally Occurring Polyynes	R. R. Tykwinski, A. L. K. Shi Shun	[9]
Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis	K. C. Nicolaou, P. G. Bulger, D. Sarlah	[7]
High-Turnover Palladium Catalysts in Cross-Coupling and Heck Chemistry: A Critical Overview	V. Farina	[10]
Recent homogeneous catalytic applications of chelate and pincer *N*-heterocyclic carbenes	E. Peris, R.-H. Crabtree	[12]
Dual role of nucleophiles in palladium-catalyzed Heck, Stille, and Sonogashira reactions	A. Jutand	[19]
Palladium-Catalyzed Alkynylation	E.-I. Negishi, L. Anastasia	[6]
Evolution in the Palladium-Catalyzed Cross-Coupling of sp- and sp^2-Hybridized Carbon Atoms	R. R. Tykwinski	[17]
Phospha-palladacycles and N-heterocyclic carbenes palladium complexes: efficient catalysts for C–C coupling reactions	W. A. Herrmann, K. Öfele, D. von Preysing, S. K. Schneider	[13]
N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis	W. A. Herrmann	[14]
Palladium-Catalyzed Coupling Reactions of Aryl Chlorides	A. F. Littke, G. C. Fu	[11]
Catalytic cross-coupling reactions mediated by palladium/nucleophilic carbene systems	S. Nolan et al.	[15]
Development of Pd/Cu-catalyzed cross-coupling of terminal acetylenes with sp^2 carbon halides	K. Sonogashira	[5]
Poly(arylethynylene)s: Syntheses, Properties, Structures, and Applications	U. H. F. Bunz	[8]
Application of palladacycles in Heck-type reactions	W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger	[16]
Recent developments of palladium(0) catalyzed reactions in aqueous medium	J.-P. Genêt, M. Savignac	[18]

2.1. High-Turnover Palladium–Ligand Catalyst Systems

2.1.1. Palladium–Monophosphane Systems

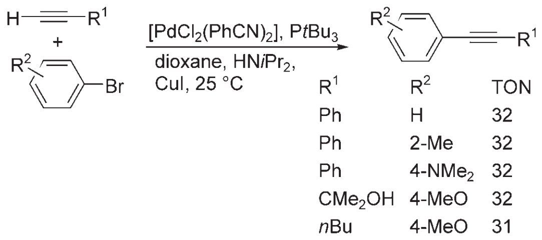
The Sonogashira–Heck coupling was originally carried out using amines as solvents. Thorand and Krause found that good yields were obtained when this reaction was carried out using 2 mol% $[PdCl_2(PPh_3)_2]$, 4 mol% CuI, and 1.5 equivalents of triethylamine in THF (Scheme 2). For example, 4-bromobenzaldehyde or 4-bromoacetophenone gave the expected products with yields of 99% and 92%, respectively, when trimethylsilylacetylene was used. Moreover, these reactions were performed at room temperature.[20]



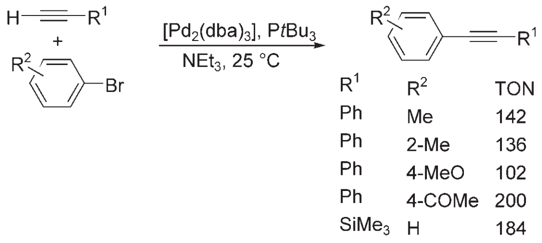
Scheme 2. Alkynylations of aryl bromides in THF.

Two years later, Fu, Buchwald, and co-workers determined that $[PdCl_2(PhCN)_2]/P(tBu)_3$ serves as an efficient and a versatile catalyst for a wide range of Sonogashira reactions of electron-poor or electron-rich aryl bromides at room temperature (Scheme 3): 4-bromoanisole couples with high efficiency, even the very electron-rich 4-bromo-*N*,*N*-dimethylaniline reacts cleanly at room temperature, and Sonogashira couplings of sterically hindered aryl bromides can be achieved at room temperature. This study provided evidence of the usefulness of bulky, electron-rich phosphanes in palladium-catalyzed Sonogashira reactions.[21]

The efficiency of the $[Pd_2(dba)_3]/PtBu_3$ system in the absence of a copper co-catalyst was reported concomitantly by Böhm and Herrmann (Scheme 4).[22] This system promotes the alkynylation of electron-rich, electron-poor, and sterically congested aryl bromides equally at room temperature, without the need for a CuI co-catalyst. This catalyst is highly active—only 0.5 mol% palladium and ligand are required. Both Et_3N and THF can be employed as the solvent; Et_3N plays an additional role of an organic base.

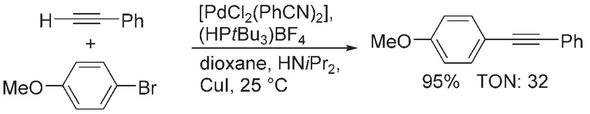


Scheme 3. Sonogashira coupling of aryl bromides using a Pd/P*t*Bu_3 system.



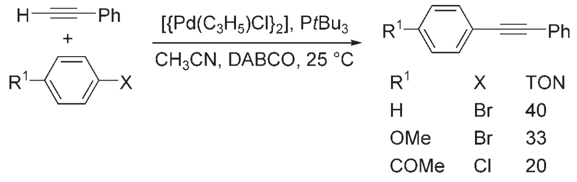
Scheme 4. Heck coupling (copper-free) of aryl bromides using a Pd/P*t*Bu_3 system. dba = *trans*,*trans*-dibenzylideneacetone.

The practical utility of trialkylphosphanes such as $PtBu_3$ can be compromised by their sensitivity to oxidation, which can render them difficult to handle. To address this problem, Netherton and Fu examined the conversion of air-sensitive trialkylphosphanes into storable, air-stable phosphonium salts by protonation of the phosphorus atom (Scheme 5). The authors demonstrated that these robust salts can serve as direct alternatives to the corresponding phosphanes: a simple deprotonation by a Brønsted base under the reaction conditions releases the trialkylphosphane.[23]



Scheme 5. Air-stable phosphonium salts used in Sonogashira alkynylations of aryl bromides.

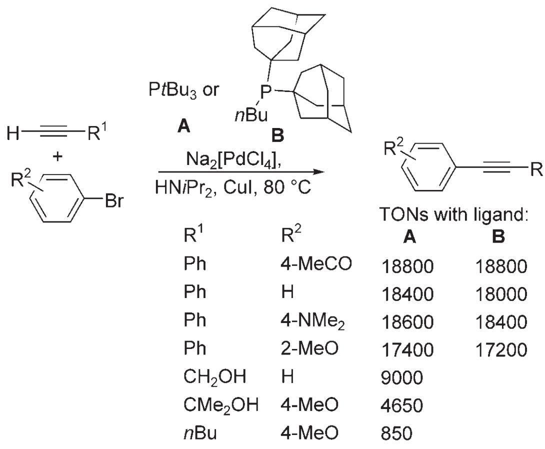
Following the reports by Fu, Buchwald, and Herrmann (Schemes 3 and 4) Soheili et al. developed a copper-free alkynylation procedure for aryl bromides with PtBu$_3$ at room temperature (Scheme 6). With acetonitrile as the solvent and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base, the reaction of activated and electron-rich aryl bromides with aromatic and aliphatic acetylenes proceeded in good yields. A lower conversion was obtained using 4-chloroacetophenone.[24]



R^1	X	TON
H	Br	40
OMe	Br	33
COMe	Cl	20

Scheme 6. Heck alkynylation of aryl bromides and chlorides using a Pd/PtBu$_3$ system.

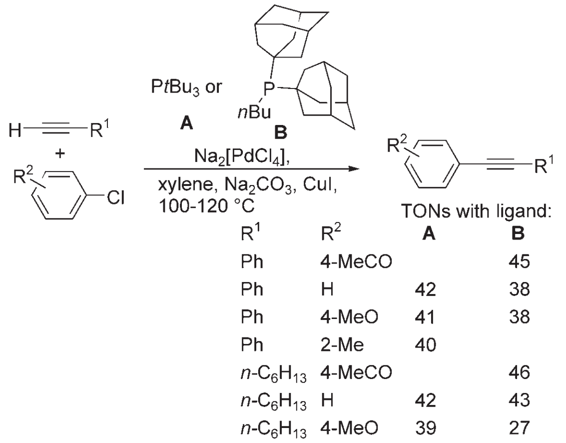
The efficiency of bulky, electron-rich phosphane ligands was also developed by Köllhofer and Plenio. They obtained high TONs for the alkynylation of a wide variety of aryl bromides at higher temperatures than those employed before; $Na_2[PdCl_4]$/PtBu$_3$ was used as the catalyst while HNiPr$_2$ was used as the solvent and the base (Scheme 7). For example, a TON of 18600 was obtained for the reaction of the deactivated aryl bromide *N*,*N*-dimethyl-4-bromoaniline with phenylacetylene at 80 °C.[25] By using this catalytic system, the sterically congested 1-bromo-2,6-dimethylbenzene reacted with phenylacetylene to give the expected product with a TON of 16800. They also explored the potential of (1-Ad)$_2$PBn (1-Ad = 1-adamantyl) as the ligand for this coupling instead of PtBu$_3$. The coupling of various aryl bromides with phenylacetylene at catalyst loadings as low as 0.005 mol% occurred in excellent yields; PtBu$_3$ was found to be the superior ligand for most of the substrate combinations.



R^1	R^2	A	B
Ph	4-MeCO	18800	18800
Ph	H	18400	18000
Ph	4-NMe$_2$	18600	18400
Ph	2-MeO	17400	17200
CH_2OH	H	9000	
CMe_2OH	4-MeO	4650	
*n*Bu	4-MeO	850	

Scheme 7. Sonogashira coupling of aryl bromides using Pd/PtBu$_3$ and Pd/(1-Ad)$_2$PBn systems.

These two sterically hindered and electron-rich phosphane ligands were also found to be efficient for the coupling of aryl chlorides (Scheme 8). A variety of electron-poor, electron-rich, and sterically congested aryl chlorides were successfully alkynylated in good yields and TONs using 2 mol% of the catalyst. The choice of the base was decisive for the success of this reaction. While alkynes and aryl bromides couple efficiently in the presence of HNiPr$_2$, reactions with aryl chlorides were troublesome. The best solvents were toluene, xylene, and DMSO, and the best base Na_2CO_3.[26] The recycling possibilities using modified ligands of this kind has also been examined (see Section 3.1.1).[27–31]

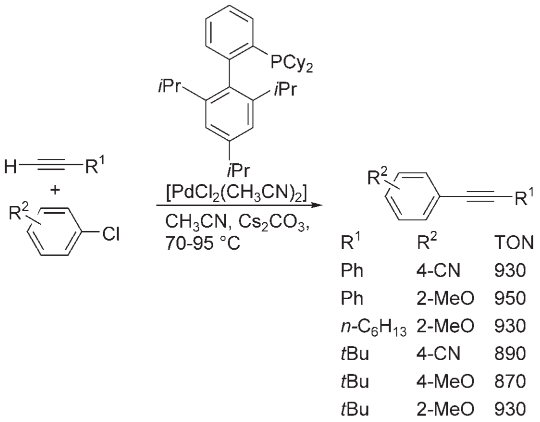


R^1	R^2	A	B
Ph	4-MeCO		45
Ph	H	42	38
Ph	4-MeO	41	38
Ph	2-Me	40	
n-C_6H_{13}	4-MeCO		46
n-C_6H_{13}	H	42	43
n-C_6H_{13}	4-MeO	39	27

Scheme 8. Sonogashira alkynylation of aryl chlorides using Pd/PtBu$_3$ and Pd/(1-Ad)$_2$PBn systems.

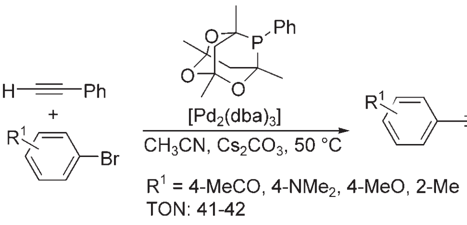
Probably the most impressive results for the activation of aryl chlorides have been reported by Gelman and Buchwald using dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphane as the ligand. They have developed a general protocol for the coupling of aryl chlorides and alkynes using a low catalyst loading in the presence of this sterically congested electron-rich ligand (Scheme 9). This method requires only 0.1 mol% catalyst, moderate temperatures (70–95 °C), and tolerates electron-rich, electron-poor, and sterically congested aryl chlorides. They have also observed that the addition of CuI as a co-catalyst can inhibit the coupling reaction or lead to a decrease in the yield. A good functional group compatibility and a broad range of compatible alkynes characterize this new catalytic system.[32] For example, the reaction of 2-chloroanisole with phenylacetylene gave the coupling product with a TON of 950 and in 95% yield. A sulfonated version of this ligand for a Sonogashira reaction in water has also been described (see Section 2.3).[33]

A few other bulky and electron-rich phosphane ligands have been prepared and tested in the Sonogashira reaction. A palladium complex of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane has been shown to be an



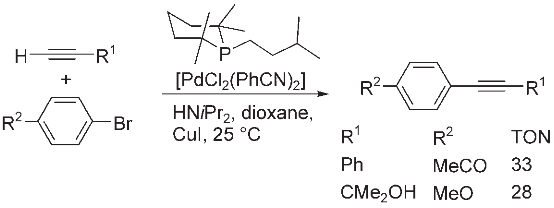
Scheme 9. Heck alkynylation (copper-free) of aryl chlorides using a Pd/PCy$_2$(triisopropylbiphenylyl) system.

effective catalyst for the alkynylation of aryl bromides, including electron-rich or sterically congested ones (Scheme 10).[34]



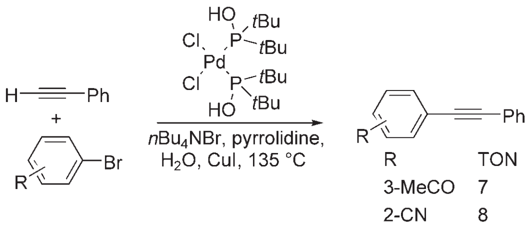
Scheme 10. Heck alkynylation of aryl bromides using a Pd/phospha-adamantane system.

Capretta and co-workers have also demonstrated that the phosphorinane family of trialkylphosphane ligands can be used in the Sonogashira reaction of aryl bromides (Scheme 11).[35] The reactions were performed at room temperature in dioxane with HN(iPr)$_2$ as the base and CuI as the co-catalyst.



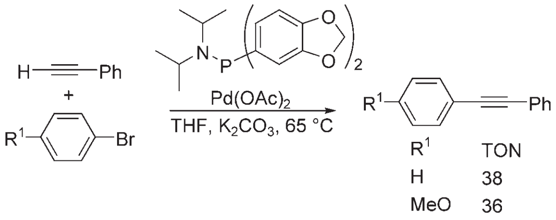
Scheme 11. Sonogashira coupling of aryl bromides using a Pd/phosphorinane system.

Wolf and Lerebours developed a combination of a palladium source and a phosphinous acid as the catalyst for a Sonogashira reaction that proceeds in water and in air without the need for an organic cosolvent (Scheme 12, see also Section 2.3). Disubstituted alkynes have been prepared in up to 91 % yield by the coupling of various aryl halides in the presence of tetrabutylammonium bromide and pyrrolidine or NaOH using 10 mol % catalyst.[36]



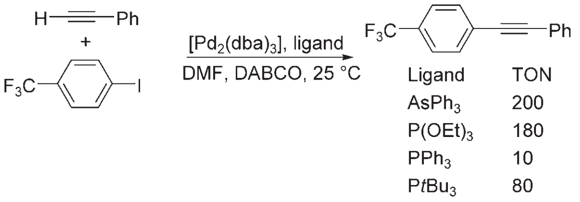
Scheme 12. Alkynylation in water employing a palladium–phosphinous acid complex as catalyst.

Zhang and co-workers have developed a copper- and amine-free Sonogashira reaction using readily prepared, air-stable aminophosphane ligands. The mild reaction conditions and the utilization of an inorganic base are the most attractive features of this reaction (Scheme 13). The use of electron-rich and bulky ligands might make both the oxidative addition and the reductive elimination steps easier. However, these ligands have not yet been tested in the activation of aryl chlorides.[37]



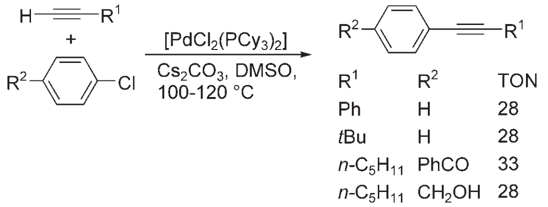
Scheme 13. Palladium/aminophosphane-catalyzed alkynylation of aryl bromides.

Martensson and co-workers have attempted to optimize the copper-free alkynylation reaction through careful choice of the solvent and base. Several reactions were conducted using 4-trifluoromethyliodobenzene to examine the dependence of the alkynylation on the solvent, base, and ligand (such as AsPh$_3$ or P(OEt)$_3$, Scheme 14; see also Section 4.3).[38]



Scheme 14. Coupling of an aryl iodide using Pd/AsPh$_3$ and Pd/P(OEt)$_3$ systems.

[PdCl$_2$(PCy$_3$)$_2$] showed high catalytic activity in the cross-coupling of aryl chlorides with a variety of terminal alkynes in DMSO at 100–120 °C under copper-free conditions and with Cs$_2$CO$_3$ as the base (Scheme 15). The advantages of this copper-free procedure include the availability and ease of handling of the catalyst, and a high catalytic activity for both



Scheme 15. Copper-free alkynylation of aryl chlorides using the complex $[PdCl_2(PCy_3)_2]$. Cy = cyclohexyl.

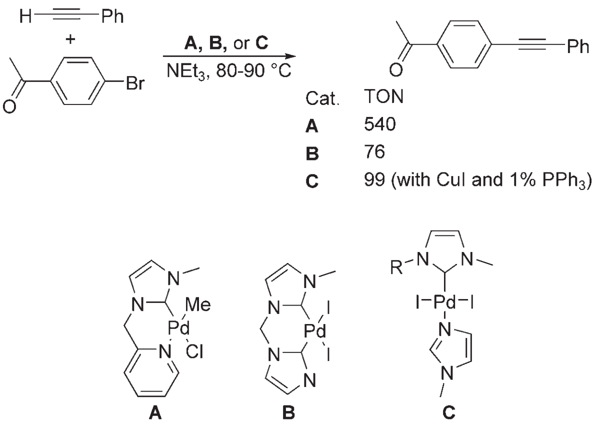
electron-poor and electron-rich aryl chlorides.[39] A variety of functional groups including alcohols, esters, and ketones were tolerated under these conditions.

Of the relevant useful procedures, a low temperature (−20 °C) Sonogashira reaction of aryl iodides has also been described in which tris(2,4,6-trimethylphenyl)phosphane was used as the ligand.[40]

Catalytic protocols involving a combination of a palladium source and monophosphane ligands emerged as very powerful systems in the Sonogashira–Heck–Cassar alkynylation reactions of demanding aryl bromide and chlorides. Some of the ligands in this category, especially the sterically congested and electron-rich $PtBu_3$, $(1\text{-}Ad)_2PBn$, dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphane, and PCy_3 have led to reactions with impressive TONs, even with deactivated aryl bromides or aryl chlorides. These palladium catalysts will likely play a leading role in the development of Sonogashira–Heck alkynylation reactions in the coming years; particularly if properties such as air- and moisture-insensitivity are developed, they could replace traditional systems with PPh_3 ligands.

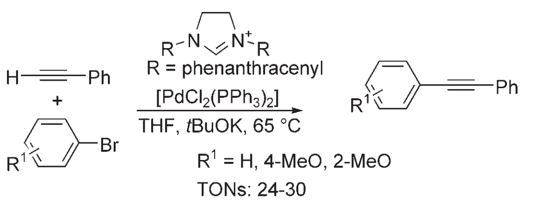
2.1.2. Systems Incorporating Carbenes

Carbene ligands have also been employed for homogeneous-phase Sonogashira–Heck reactions (Schemes 16-18).[41–48] In all cases the alkynylation products were obtained, however, generally with low TON values. The highest TON of 540 was reported by McGuiness and Cavell using a carbene–pyridine ligand for the coupling of 4-bromoacetophenone with phenylacetylene (complex **A** in Scheme 16).[41]



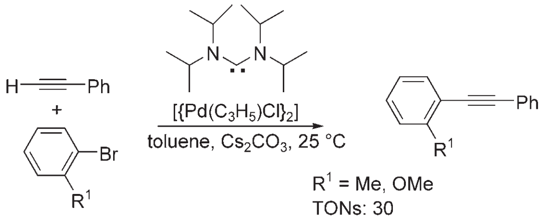
Scheme 16. Alkynylation reactions of 4-bromoacetophenone using Pd/carbene systems.

Bulky phenanthracenyl-substituted imidazolium-derived carbene ligands have been investigated for the copper-free alkynylation of aryl bromides and iodides (Scheme 17). A remarkable dependence on the size of the ligand was found.[44]



Scheme 17. Phenanthracenylimidazolium-derived carbene ligands for the Heck alkynylation of aryl bromides.

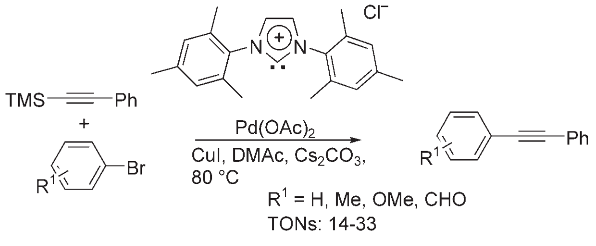
Palladium complexes of acyclic diaminocarbenes ligands were also found to catalyze the alkynylation of aryl bromides such as 2-bromotoluene or 2-bromoanisole in high yields (Scheme 18).[45]



Scheme 18. Heck alkynylation of *ortho*-substituted bromoarenes with a Pd/diaminocarbene acyclic ligand.

A palladium/imidazolium chloride system has been used to mediate the coupling reaction of aryl halides with alkynylsilanes. The combination of 3 mol% $Pd(OAc)_2$ and 6 mol% imidazolium chloride in the presence of Cs_2CO_3 as the base proved to be an efficient system for the coupling of *para*- and *ortho*-substituted aryl bromides with alkynylsilanes in high yields and with TONs of 14 to 33 (Scheme 19).[46]

It is noteworthy that the coupling of primary and secondary alkyl bromides with terminal alkynes using palladium–carbene complexes as catalysts has also recently been described (see Section 4.3).[47,48]

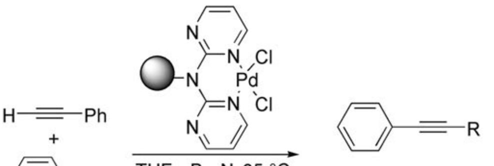


Scheme 19. A palladium/imidazolium chloride system for the coupling of aryl bromides and alkynylsilanes.

To date, carbene ligands do not appear to be highly efficient catalysts for the coupling of aryl chlorides. In addition, more mechanistic studies are needed to reach a better understanding of the only moderate efficiency of these catalytic systems for aryl alkynylation reactions.

2.1.3. Chelating Diphosphanes, Diamines, and P,N Ligands

Didentate ligands such as diphosphanes or diamines are also efficient at catalyzing Sonogashira–Heck alkynylation reactions. A polymer-supported copper-free system with a bispyrimidine ligand resulted in the efficient alkynylation of aryl iodides with high TONs (Scheme 20). The use of the less reactive bromobenzene gave a satisfactory yield of up to 85 %, even with Pd amounts as low as 0.006 mol %. The reaction of chlorobenzene can be accelerated effectively by the addition of $n\mathrm{Bu_4NBr}$ to the reaction mixture. Under these conditions the TON was similar to those obtained with iodo- or bromobenzene.[49]

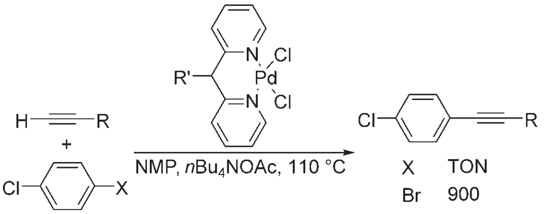


X	TON
Cl	14800*
Br	15500
I	22300

* Addition of $\mathrm{Bu_4NBr}$

Scheme 20. Coupling of aryl halides to phenylacetylene using a supported palladium–bispyrimidine complex.

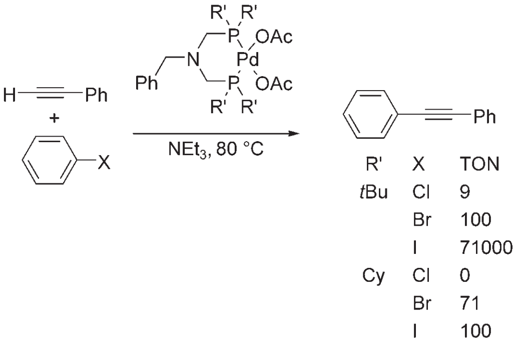
A di(pyridin-2-ylmethyl)amine-derived palladium chloride complex is also an efficient catalyst for the coupling of aryl iodides or bromides with alkynes (Scheme 21, see also Section 2.3). With this catalyst, the alkynylation can be performed under copper-free conditions in *N*-methylpyrrolidine (NMP), with TONs up to 200 000 and TOFs up to 67 000 for aryl iodides, and TONs up to 900 for aryl bromides.[50,51] The coupling of 2-bromothiophene with phenylacetylene in the presence of 0.1 mol % catalyst led to the product in 90 % yield. This ligand was also anchored to a polymer for heterogeneous catalysis studies (see Section 3.2.2).[51,52]



X	TON
Br	900
I	200000

Scheme 21. Alkynylation of aryl halides using a palladium–bispyridine complex.

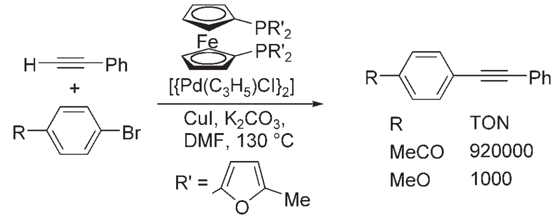
The efficiency of bulky electron-rich diphosphane ligands for Sonogashira reactions with iodobenzene, bromobenzene, or activated aryl chlorides has been investigated by Astruc and co-workers (Scheme 22). A TON of 100 was obtained for the reaction of bromobenzene with phenylacetylene. However, these catalysts gave low TONs of 0–15 and yields of 0–30 % with aryl chlorides. A bis(*tert*-butylphosphane) was generally found to be more efficient than a bis(cyclohexylphosphane) ligand.[53] The efficiency of a dendrimer derivative of this catalyst and a resin-supported bis(diphenylphosphanylmethyl)aminopolystyrene complex have also been tested (see Section 3.1.1).[54,55]



R'	X	TON
*t*Bu	Cl	9
	Br	100
	I	71000
Cy	Cl	0
	Br	71
	I	100

Scheme 22. Alkynylations of aryl halides using palladium and an electron-rich aminobisphosphane.

Among the ligands used for Sonogashira–Heck alkynylations, bulky phosphanes with poor σ-donating ability have attracted much less attention. Their efficiency is a pleasant surprise since poor σ-donor ligands would not be expected to facilitate the oxidative addition step, but rather would be assumed to be powerful inhibitors. The didentate ligand 1,1′-bis[di(5-methyl-2-furyl)phosphanyl]ferrocene catalyzed the arylation of phenylacetylene efficiently (Scheme 23). 4-Bromoacetophenone and 4-bromoanisole were employed as the activated and deactivated substrates, respectively. The reaction of 4-bromoacetophenone in the presence of 10^{-4} mol % catalyst gave a TON of 920 000, which is among the highest reported TONs for aryl bromides. 4-Bromoanisole was also quantitatively converted, but with a lower TON of 1000.[56]

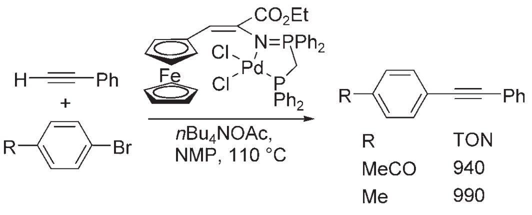


R	TON
MeCO	920000
MeO	1000

Scheme 23. A Pd/[bis(furyl)phosphanyl]ferrocene system for the alkynylation of aryl bromides at low concentration.

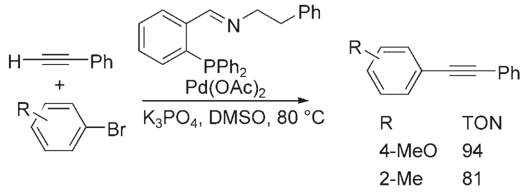
As the authors noted, a decisive advantage of the ferrocenylphosphane ligands such as 1,1′-bis[di(5-methyl-2-furyl)phosphanyl]ferrocene is their robustness towards air, moisture (no phosphorus oxidation), and elevated reaction temperatures, which allows them to be used in substantially lower concentration.

The palladium(II) complex of a ferrocene-based phosphinimine-phosphane ligand was also applied to the amine- and copper-free Sonogashira coupling of aryl iodides and aryl bromides with terminal alkynes by using one equivalent of tetrabutylammonium acetate as an activator (Scheme 24). The corresponding disubstituted alkynes were obtained in high yields and good TONs by using 0.1 mol % of the Pd catalyst.[57]



Scheme 24. A ferrocene-based phosphinimine-phosphane ligand for the copper-free alkynylation of aryl bromides.

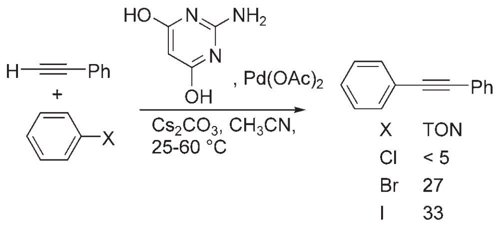
The combination of an iminophosphane ligand and Pd(OAc)$_2$ was found to be more effective than a Pd(OAc)$_2$/PPh$_3$ complex for the coupling of some aryl bromides with alkynes (Scheme 25).[58]



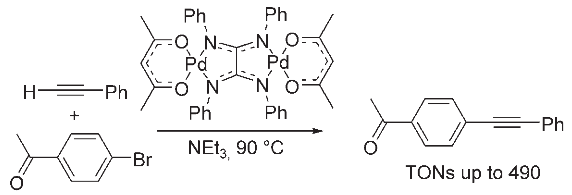
Scheme 25. Coupling of aryl bromides to phenylacetylene using a Pd/iminophosphane system.

The efficiency of a Pd(OAc)$_2$/pyrimidine catalyst has also been evaluated (Scheme 26). This system gave satisfactory results in terms of yields of product, however, low TONs were reported.[59]

A dinuclear palladium–tetraphenyl oxalic amidinate complex has been used as a precatalyst in the copper-free Sonogashira reaction of 4-bromoacetophenone with phenylacetylene, and gave moderate TONs (Scheme 27).[60]



Scheme 26. Coupling of aryl halides to phenylacetylene using a palladium–pyrimidine system.



Scheme 27. Coupling of 4-bromoacetophenone to phenylacetylene using a dinuclear [Pd(acac)] complex.

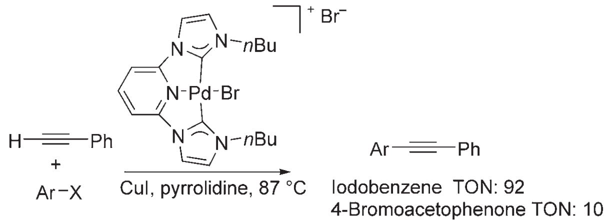
Yoshifuji and co-workers have reported the use of didentate P,P[61] and P,S ligands[62] with 1,3-diphosphapropene skeletons for the coupling of iodobenzene with phenylacetylene using 2.5 mol % catalyst. The P,P ligand was inactive for the coupling of bromobenzene.

Several didentate ligands provided efficient catalytic systems for the alkynylation of aryl substrates. Three of them led to very good TONs: 22300 (bispyrimidine ligand, Scheme 20), 200000 (bipyridine ligand, Scheme 21), and 71000 (bis-*tert*-butylphosphane ligand, Scheme 22) in the coupling of simple aryl iodide substrates. Some were even efficient at activating more demanding aryl bromides: the bispyrimidine and bipyridine ligands (Schemes 20 and 21) allow the coupling of aryl bromides (TONs of 15500 and 700, respectively), while the ferrocene-based didentate ligands (Schemes 23 and 24) gave the arylated alkynes in fairly good to remarkably high TONs (920000 and 990, respectively). Conversely, most of these ligands were found to be less efficient in the activation of aryl chlorides.

2.1.4. Tri- and Tetradentate Ligands

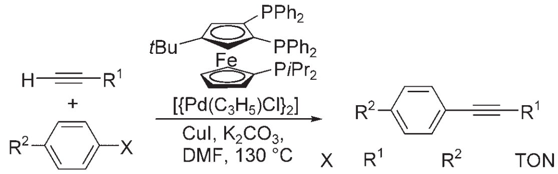
Only a few multidentate ligands (tri-, tetradentate, or more) have been tested for Sonogashira–Heck alkynylations. This is all the more surprising since, most of the time, a threefold or more excess of the monodentate ligands are used under conventional conditions. Thus, multidentate ligands might be of great interest in the future development of catalytic alkynylations.

The potential of a tridentate C,N,C-dicarbene pincer ligand has been evaluated in the reaction of iodobenzene and 4-bromoacetophenone with phenylacetylene (Scheme 28). Iodobenzene and phenylacetylene can be coupled in 92 % yield in pyrrolidine using 1 mol % of this catalyst and CuI as a promoter. On the other hand, a 10 % yield was obtained after 19 h from 4-bromoacetophenone.[63] Recently, this complex has been immobilized onto clays (see Section 3.2.3).[64]



Scheme 28. Sonogashira alkynylation with the palladium complex of a tridentate C,N,C-dicarbene pincer ligand.

The scope and limitations of a system combining palladium with a tridentate ferrocenylphosphane ligand for the coupling of a variety of aryl bromides with alkynes has also been described (Scheme 29).[65] High reaction rates were observed when activating groups are present on the aryl bromide. For example, the coupling of 4-fluorobromobenzene, 4-bromoacetophenone, and 4-bromobenzonitrile with phenylacetylene using 0.001 mol% of the palladium complex led to the coupling products with TONs of 20000, 250000, and 46000, respectively. The quantitative conversion of the strongly deactivated 4-bromoanisole requires a higher catalyst loading (0.4 mol%) and resulted in a lower TON of 520. Reactions with activated aryl chlorides such as 4-chlorobenzonitrile and 4-chloroacetophenone using 0.4 mol% of the catalyst, but in the absence of copper promoter, led to the desired products in TONs of 540 and 205, respectively, and in very good yields. Aliphatic alkynes such as 1-decyne and 1-butyn-4-ol were coupled to 4-bromoacetophenone, with good TONs of 620 and 460, respectively.

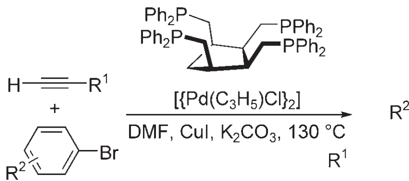


X	R^1	R^2	TON
Br	Ph	MeCO	250000
Br	Ph	F	20000
Br	Ph	MeO	520
Cl	Ph	MeCO	205*
Cl	Ph	CN	540*
Br	n-C_8H_{17}	MeCO	620

* Reactions performed without CuI

Scheme 29. A tridentate ferrocenylphosphane ligand for the coupling of aryl bromides and chlorides with high TON.

The tetraphosphane ligand tedicyp (Scheme 30) combined with $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ catalyzed the coupling of aryl bromides with alkynes in good yields under highly dilute conditions. High reaction rates were observed when electron-withdrawing activating groups were present on the aryl bromide. A TON of 2800000 was obtained for the coupling of 3,5-bis(trifluoromethyl)bromobenzene with phenylacetylene.[66] The best results were usually obtained with K_2CO_3 as the base and CuI as the co-catalyst in DMF at 130°C. The system was efficient for the alkynylation of *ortho*-substituted aryl bromides, even if lower reaction rates were observed with these sterically hindered substrates. Thus, the coupling of 9-bromoanthracene or 2,4,6-triisopropylbromobenzene to phenylacetylene proceeded in good yields.[67]

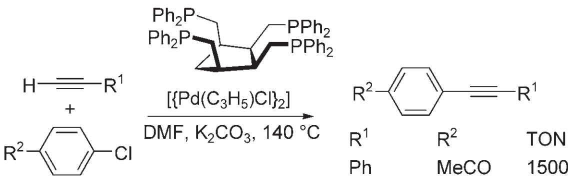


R^1	R^2	TON
Ph	4-MeCO	700000
Ph	4-CN	870000
Ph	H	8200
Ph	4-NMe_2	5000
Ph	2-Me	4000
CH_2OH	4-CN	96
$(CH_2)_2OH$	4-CN	5000
$(CH_2)_3OH$	4-CN	60000
$CH_2N$$n$$Pr_2$	4-CN	1000
$CH(OEt)_2$	4-MeCO	95000
$CH(OEt)_2$	4-MeO	8200

Scheme 30. Sonogashira coupling of aryl bromides with a Pd/tetradentate polyphosphane (tedicyp) catalyst.

The tedicyp/palladium system was also a convenient catalyst for the cross-coupling of a variety of heteroaryl halides with various alkynes.[68] Heteroarenes such as pyridines, quinolines, and indoles or thiophenes gave the alkynylated adducts in good yields. The coupling reactions of aryl halides with a variety of alkynols also proceeded efficiently (Scheme 30).[69] Higher reaction rates were observed with 1-butyn-4-ol, 1-pentyn-5-ol, and 1-hexyn-6-ol as substrates than with propargyl alcohol. The coupling reaction of propargylamine derivatives with substituted aryl bromides has also been examined.[70] The substituents on the nitrogen atom of the propargylamine derivatives have an important influence on the reaction rates: *N*,*N*-dialkylpropargylamines such as *N*,*N*-diethylpropargyl amine are more reactive than *N*-methylpropargylamines. The lowest TONs were observed in the presence of propargylamine. With this alkyne, 5 mol% of the catalyst precursor had to be used to achieve satisfactory coupling. The reaction of several aryl substrates with *N*,*N*-dialkylpropargylamines can be performed with as little as 0.1 mol% Pd/ligand. The coupling of aryl bromides with propiolaldehyde diethyl acetal also proceeded efficiently with the Pd/tedicyp catalytic system.[71] This reaction can be performed on most of the aryl bromides with 0.01 mol% of the catalyst precursor.

Lower TONs were obtained for the reactions of aryl chlorides in the presence of the Pd/tedicyp catalyst (Scheme 31).[72] However, a variety of substrates such as 4-chloroacetophenone, 4-chlorobenzonitrile, and 4-chloroanisole can be successfully activated. These reactions gave better results in the absence of copper iodide: Addition of copper iodide often led to the formation of side products such as the dimerization of the alkynes (Glaser–Hay homocoupling). The electronic properties of the aryl chlorides have an important effect on the reaction rates: Electron-poor aryl chlorides are

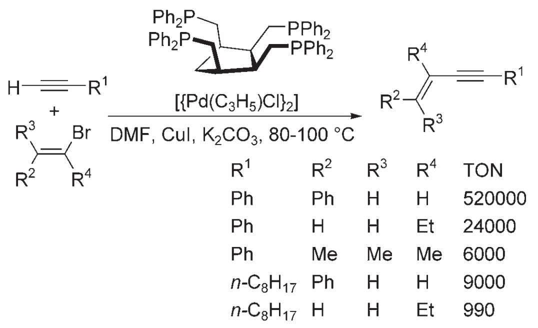


R^1	R^2	TON
Ph	MeCO	1500
Ph	CN	16000
Ph	F	217
Ph	MeO	155
n-C_8H_{17}	MeCO	390
n-C_8H_{17}	CN	620

Scheme 31. Heck alkynylation of aryl chlorides with Pd/tedicyp.

more reactive than electron-rich ones, but even 4-chloroanisole led to the desired alkynylated product in good yield.

Sonogashira reactions of several vinyl bromides, including sterically demanding ones, with a variety of terminal alkynes has also been performed with 0.1–0.0001 mol% Pd/tedicyp as the catalyst system (Scheme 32).[73] The most reactive vinyl bromide was β-bromostyrene, even though α-substituted vinyl bromides, such as 1-bromo-1-propene and 2-bromo-1-butene, also gave the coupling adducts in high TONs. This system can also be used at a low catalyst loading for the reactions of sterically hindered vinyl bromides, such as 2-bromo-1,1,2-triphenylethylene and 2-bromo-3-methyl-2-butene. The highest TONs for vinyl bromides were obtained with phenylacetylene, 1-decyne, 3-butyn-1-ol, 4-pentyn-1-ol, 3,3-diethoxy-1-propyne, and 1,1-dipropyl-2-propynylamine.



R^1	R^2	R^3	R^4	TON
Ph	Ph	H	H	520000
Ph	H	H	Et	24000
Ph	Me	Me	Me	6000
n-C_8H_{17}	Ph	H	H	9000
n-C_8H_{17}	H	H	Et	990

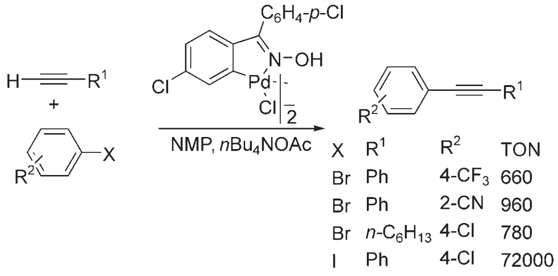
Scheme 32. Vinylation of terminal alkynes with high TON using Pd/tedicyp.

The use of multidentate ligands afforded some of the highest TONs observed in Sonogashira–Heck–Cassar cross-coupling. Demanding substrates such as deactivated aryl bromides and aryl chlorides have been coupled with excellent TONs by using different multidentate ligands. Relatively high reaction temperatures were required to obtain TONs greater than 10000. Under these conditions the use of multidentate ligands might help to stabilize the catalytic species. In addition, these ligands might also have a positive influence in accelerating the reductive elimination step of the catalytic cycle (step of releasing the product) by steric pressure on the active palladium center. Mechanistic studies of these postulates are necessary,[74] and should certainly provide clues for the future development of multidentate ligands for resource-economic catalysis.

2.1.5. *Palladacycles*

Palladacycles, which are highly stabilized palladium complexes, have been reported to be useful ligands for homogenous Sonagashira–Heck cross-coupling alkynylation reactions. The way these compounds generally operate in cross-coupling reactions has been the subject of controversy (molecular catalysts or sources of reactive "naked" palladium(0) species upon degradation?) and alkynylation reactions are no exception. Nevertheless, the catalytic efficiency of the palladacycles has led to great interest.

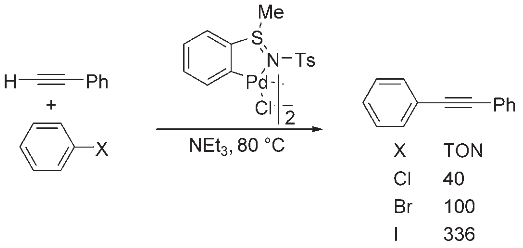
Nájera and co-workers have disclosed that a cyclopalladated oxime complex (Scheme 33) is an efficient catalyst for phosphane-, copper-, and amine-free alkynylations conducted in NMP in the presence of nBu$_4$NOAc. TONs of 960 for the coupling of aryl bromides such as 1-bromonaphthalene and 2-bromobenzonitrile (and 72000 for an aryl iodide) have been reported.[75,76] The authors obtained lower TONs (132 to 150) for the coupling of iodobenzene using pyrrolidine as the solvent and CuI as the promoter.[77] Interestingly, all these reactions can be performed in air.



X	R^1	R^2	TON
Br	Ph	4-CF_3	660
Br	Ph	2-CN	960
Br	n-C_6H_{13}	4-Cl	780
I	Ph	4-Cl	72000

Scheme 33. An oxime–palladacycle for the efficient copper-free alkynylation of aryl halides.

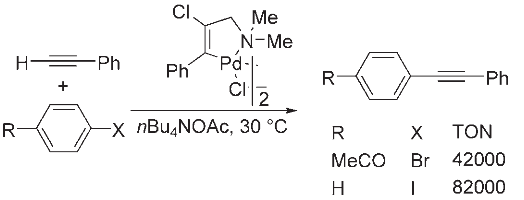
The performances of a sulfilimine palladacycle in an alkynylation reaction has also been evaluated (Scheme 34). TONs of 100 and 336 were obtained in the arylation of phenylacetylene with bromobenzene or iodobenzene at 80°C under copper-free conditions. A low yield of 10% and a TON of 40 was obtained when chlorobenzene was used.[78]



X	TON
Cl	40
Br	100
I	336

Scheme 34. A sulfilimine palladacycle for the copper-free alkynylation of aryl halides. Ts = toluene-4-sulfonyl.

The palladacycle derived from the chloropalladation of 3-(dimethylamino)-1-phenyl-1-propyne promotes the alkynylation of bromo- and iodoarenes at room temperature (Scheme 35). Turnover numbers up to 82000 have been

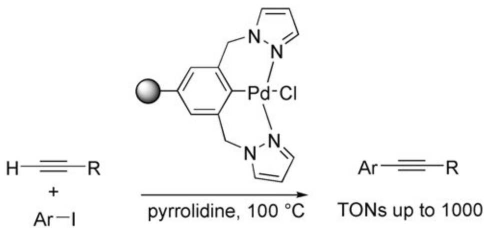


R	X	TON
MeCO	Br	42000
H	I	82000

Scheme 35. Alkynylations of activated aryl halides at room temperature by a palladacycle with high TON.

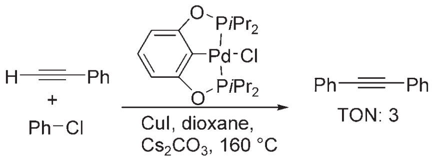
achieved with iodoarenes, and 42 000 with activated aryl bromides; for deactivated bromoarenes TONs up to 94 were obtained at higher temperatures (120 °C).[79]

The activity of some palladacycles which incorporate tridentate pincer ligands (see Section 2.1.4 for a relevant carbene example) have been explored. A polymer-supported Herrmann palladacycle has been employed for the reaction of 4-bromoacetophenone with phenylacetylene (TON 49)[80] and a polymer-supported N,C,N pincer complex comprising two pyrazole units has been employed for the copper-free coupling of aryl iodides with phenylacetylene or hex-1-yne (Scheme 36).[81]



Scheme 36. A polymer-supported N,C,N pincer palladacycle for the alkynylation of aryl iodides.

A P,C,P pincer ligand was found to be weakly active for the coupling of chlorobenzene with phenylacetylene when CuI was used as a co-catalyst at 160 °C (Scheme 37). This system led to better results when $ZnCl_2$ was used as the co-catalyst[82] (an interesting zinc catalytic version of the powerful Negishi alkynylation).[6]



Scheme 37. Test of a P,C,P pincer palladacycle complex for the alkynylation of chlorobenzene.

Palladacycles are useful catalysts for the alkynylation of aryl iodides and activated aryl bromides, although they appear in general to give only moderate TONs with deactivated aryl bromides and aryl chlorides. This finding might be linked to the catalytic pathway of these compounds, since low-coordinated (or naked) Pd^0 species have repeatedly been found to be very active for the coupling of simple substrates, but inefficient when demanding substrates are considered. The current results would thus be more consistent with the palladacycles acting as reservoirs of palladium(0) low-coordinated species, rather than precursors of defined active palladium(II) and palladium(IV) complexes. Nevertheless, further studies are still required to determine the possibilities of this kind of system, including some successful experiments on more-demanding substrates.

Different classes of homogeneous systems incorporating elaborated ligands appear to give useful catalysts for Sonogashira–Heck reactions. The efficiency of these systems in terms of TONs and yields of the coupling reactions strongly depend on the steric and electronic features of the substituents on the alkyne and aryl halides. The nature of the halide, the presence of a co-catalyst and a promoter, the nature of the solvent and of the base, and the reaction temperature are all crucial parameters. We summarize in the following the main lessons learned from the studies we reviewed on homogeneous palladium-catalyzed alkynylation of vinyl and aryl halides.

- *Solvent*: Originally, these reactions were mainly performed using amines as the solvent (pyrrolidine or NEt_3). Good results can be obtained with most aryl bromides and iodides by using amines. On the other hand, solvents such as toluene, xylene, DMF, acetonitrile, or DMSO associated with bases such as carbonates, amines, or ammonium salts seem to give higher yields and TONs for aryl chlorides.
- *Base*: Several bases have been employed with success. The use of NEt_3, $HNiPr_2$, DABCO, or K_2CO_3 generally gives high yields of products in the cross-coupling of aryl bromides. The most suitable bases for the less reactive aryl chlorides are probably the carbonates Na_2CO_3, Cs_2CO_3, and K_2CO_3.
- *Temperature*: The reactions can be performed at room temperature with aryl iodides, bromides, and even with aryl chlorides. However, the use of bulky electron-rich phosphanes appears to be necessary for the room-temperature activation of aryl chlorides. Higher reaction temperatures (70–140 °C) should be used with both aryl chlorides and bromides to obtain high TONs.
- *Copper promoter*: CuI is most often added to facilitate or accelerate the reactions. This co-catalyst is probably useful for reactions of aryl iodides and aryl bromides. Conversely, with aryl chlorides, the presence of a copper co-catalyst can lead to complete inhibition of the main palladium catalytic cycle and can result in complete consumption of the alkynes by competitive processes such as dimerization or oligomerization of the alkyne. These competitive copper-catalyzed reactions can be faster than the palladium-catalyzed arylation of alkynes, especially at elevated temperatures.
- *Alkyne*: The substituents on the alkyne exert a considerable influence on the reaction rates. The reactivity order seems to be partially related to the acidity of the alkyne and is approximately: $Ph > -(CH_2)_nCH_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(OR)_2$, $-CH_2NR_2 > -CH_2OH$, $-CH_2OCH_3$, $-CH_2OSi(CH_3)_3$, $-CH_2NHR > -CH_2NH_2$, $-C(=O)OCH_3$ with R = alkyl.
- *Aryl halide*: Aryl iodides are very reactive and their substituents generally have a minor effect on the reaction rates. Aryl bromides are less reactive and their substituents have a stronger influence on the rates and yields of the reactions. Most of the homogenous catalysts can activate electron-poor aryl bromides such as bromoacetophenone derivatives. The alkynylation of electron-rich aryl bromides such as bromoanisoles or bromoanilines is more difficult but can be performed with palladium complexes of bulky, electron-rich phosphanes, didentate ligands such as diphosphanes and diamines, or polyphosphanes using appropriate reaction conditions. Only a few catalytic systems are able to activate aryl chlorides, especially the

electron-rich ones. The most powerful ligands for the alkynylation of aryl chlorides are probably the bulky electron-rich phosphanes dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphane, P*t*Bu$_3$, PCy$_3$, or (1-Ad)$_2$PBn, a bispyrimidine ligand (Scheme 20), a tridentate ferrocenylphosphane (Scheme 29), and the tetraphosphane tedicyp (Scheme 31).

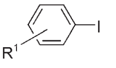
- *Ligand and catalyst*: Different family of ligands or palladium/ligands have been developed and tested. Relatively high reaction temperatures are required to obtain high TONs (> 10000), and the use of multidentate ligands might help stabilize the catalytic systems. Multidentate ligands might also accelerate the reductive elimination step of the catalytic cycle leading to the formation of the product. The leading family of ligands for the activation of aryl chlorides at low temperature is the bulky electron-rich phosphanes. Palladacycles might serve as useful reservoirs of active palladium(0) species and they are convenient catalysts for the alkynylation of aryl iodides and activated aryl bromides; however, so far, like most carbene ligands, they generally gave poor or moderate TONs with deactivated aryl bromides or aryl chlorides.

2.2. "Ligand-Free" Catalyst Systems

Successful reports of "ligand-free" versions of Sonogashira–Heck alkynylation reactions are scarce and have appeared only recently.[83–87] The development of such processes would be advantageous from an economic standpoint as a number of useful ligands are considered to be expensive, sensitive, or difficult to obtain. However, we want to distinguish in this section the "ligand-free" systems from the more commonly encountered use of precursor complexes such as [PdCl$_2$(PPh$_3$)$_2$] *in the absence of additional free ligands*, since these latter systems are not strictly "ligand-free". In addition, the term "ligand-free" generally neglects the fact that amine bases or salts that are added as promoters can weakly coordinate to a metal nucleus or particle. Therefore, the current expression "ligand-free" should be taken with caution.

Urgaonkar and Verkade have reported a procedure for a copper-, amine-, and ligand-free alkynylation of aryl iodides using Pd(OAc)$_2$ or [Pd$_2$(dba)$_3$] and tetrabutylammonium acetate (Scheme 38).[83] This base was found to be clearly superior to commonly used secondary and tertiary amines such as triethylamine, piperidine, and diisopropylamine, as well as slightly superior to NaOAc, Na$_2$CO$_3$, and Cs$_2$CO$_3$. Good to excellent conversions (68–97%) were obtained in 3 to 6 h at room temperature in DMF for the alkynylation with the aromatic alkyne phenylacetylene. The procedure has been extended with success to aliphatic terminal alkynes with a variety of functional groups (Table 2).

Table 2: Ligand-free coupling of ArI and alkynes promoted by *n*Bu$_4$NOAc.[a]

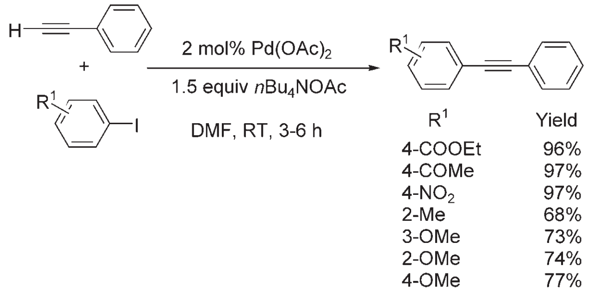
Aryl iodide  R^1	Alkyne $H-\equiv-R^2$ R^2	Yield [%][b]	*t* [h]
4-COMe	1-cyclohexenyl	90	3
	n-hexyl	94	3
4-NO$_2$	*n*-hexyl	96	3
	(CH$_2$)$_4$OH	98	3
2-OMe	1-cyclohexenyl	75	6
	(CH$_2$)$_4$OH	77	6
4-OMe	1-cyclohexenyl	76	6
	(CH$_2$)$_3$Cl	80	6
	(CH$_2$)$_4$OH	93	6

[a] Conditions: 2 mol% Pd(OAc)$_2$, 1.5 equiv *n*Bu$_4$NOAc, DMF, RT. [b] Yield of isolated cross-coupling product.

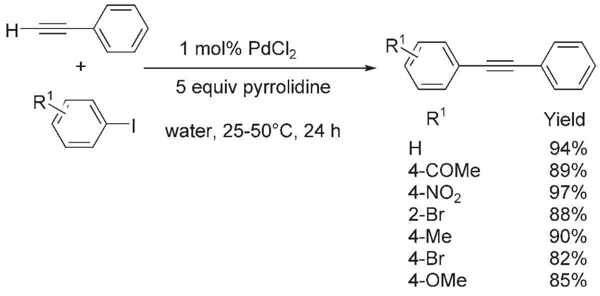
The efficiency of this system to couple aryl bromides using 4 mol% Pd was limited to activated electron-poor bromobenzenes bearing 4-keto, 4-nitro, and 4-cyano groups. The actual effect of the *n*Bu$_4$NOAc remains unclear; the authors believe that palladium nanoparticles are not involved in the homogeneous catalytic pathway.

Yang and co-workers have found that alkynylations of aryl iodides can be carried out with 1 mol% PdCl$_2$ in water at 50°C in the presence of 5 equivalents of pyrrolidine as a base under aerobic conditions (Scheme 39).[84] The scope of the reaction has been examined and the reaction tolerates various functional groups on the coupling partners (Table 3).

Li et al. have used the combination of Pd(OAc)$_2$ and DABCO under various conditions to promote copper-free and "ligand-free" alkynylation.[85–87] In their first report the authors employed DABCO in a catalytic amount (6 mol%, as a ligand according to the authors), with another inorganic base being added (3 equiv K$_2$CO$_3$ or Cs$_2$CO$_3$). Under these conditions, TONs as high as 720000 were obtained for the

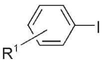
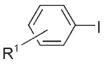


Scheme 38. "Ligand-free" palladium-catalyzed alkynylation of aryl iodides promoted by tetrabutylammonium acetate.



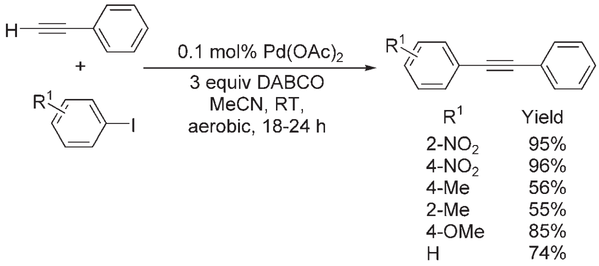
Scheme 39. "Ligand-free" palladium-catalyzed alkynylation of aryl iodides in water promoted by pyrrolidine.

Table 3: Ligand-free coupling of ArI and alkynes in water/pyrrolidine.[a]

Aryl iodide  R^1	Alkyne  R^2	Yield [%]	T [°C]
4-CN	nBu	70	25
4-NO_2	nBu	85	25
H	NMe_2	76	50
4-Me	NMe_2	70	50
4-Me	Br	68	50
4-I	H	80	50
2-iodonaphtalene	Ph	85	50
4-OMe	OMe	75	50

[a] Conditions: 1 mol% $PdCl_2$, 5 equiv pyrrolidine, 24 h.

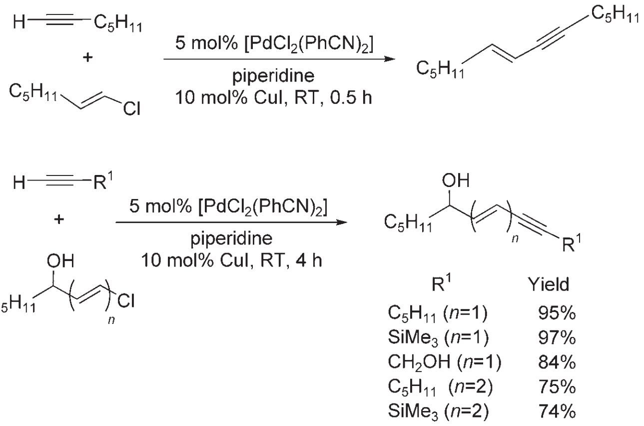
reaction of the electron-poor 4-nitroiodobenzene with phenylacetylene at room temperature in acetonitrile, with Pd$(OAc)_2$ being used at 0.0001 mol%. The limitations of the system were found with unactivated aryl bromides, which were not converted, even at 110 °C. Li et al. then reported a modification of their procedure in which DABCO was used in large excess (3 equiv) as a base (Scheme 40).[86] This system was efficient for the coupling of a number of aryl iodides to phenylacetylene; in some test reactions 2 mol% CuI had a deleterious effect. The coupling of bromide substrates was not efficient. Recently, the authors investigated the potential of $Pd(OAc)_2$/DABCO-catalyzed cross-coupling in water.[87] The use of 20 mol% poly(ethyleneglycol) 400 as a phase-transfer agent allowed the coupling of 4-nitrobromobenzene and 4-bromoanisole to phenylacetylene (yields of 80 and 35%, respectively) in the presence of 2 mol% Pd/4 mol% DABCO in water at 80 °C. These performances remained substantially inferior to the other cross-coupling reactions tested (Suzuki and Stille reactions).



Scheme 40. "Ligand-free" palladium-catalyzed alkynylation of aryl iodides promoted by DABCO.

All the "ligand-free" alkynylation reactions conducted to date clearly reached a limit in terms of substrate scope with unactivated aryl bromides. Interestingly, pioneering studies by Alami and Linstrumelle reported that vinyl chlorides react in piperidine with terminal alkynes in the presence of $[PdCl_2(PhCN)_2]$ and CuI to give conjugated enynes in good yield (Scheme 41).[88]

The reaction rate for the coupling of (E)-chloro-1-heptene to 1-heptyne was found to be very sensitive to the presence of phosphane ligands, *which slowed down the reaction*. These results, together with the high TONs reported in the presence of less than 0.01 mol% $Pd(OAc)_2$ by Li et al.,[85] might suggest that weakly coordinated palladium complexes can occasionally lead to remarkably active species. Therefore, studies concerning low-coordinated palladium species (especially in low concentration) and their reaction mechanisms remains of significant interest.

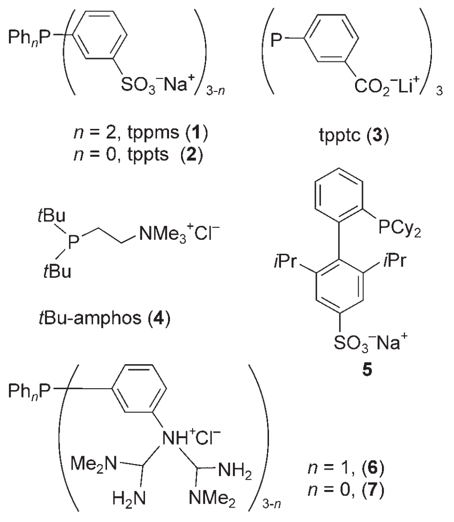


Scheme 41. "Ligand-free" alkynylation of vinyl chlorides.

2.3. Catalysis in Aqueous Solution

Sonogashira–Heck type alkynylations under aqueous conditions deserve special attention for several reasons. In addition to the widely accepted necessary effort to reduce or eliminate the industrial use of expensive, toxic, flammable, and nonrenewable organic solvents, C–C cross-coupling in water is expected to give new selectivity in various classical reactions, as well as access to the activation of hydrophilic substrates. Such substrates which are insoluble in organic solvents include many interesting pharmaceutics precursors. Moreover, chemical reactions in water-containing solutions is highly desirable for the development of modern biochemical in vivo applications, which are required to be performed under mild conditions to ensure that the fragile structure of proteins in higher organisms is not damaged. Only a few catalytic systems have been reported to be effective in neat water. In the following most of the reactions are reported in a mixed aqueous solution of water with acetonitrile, methanol, or ethanol; under these conditions the improved solubility of some organic components possibly reduce the problems arising from phase transfer processes. Furthermore, the ratio of water in the reactions appears to be a very important parameter since it has been shown that, at least in some cases, substoichiometric amounts of water can promote Sonogashira cross-coupling in organic solvents.[89] Consequently, in this section we will focus on reactions conducted in a medium (or solvent) that is at least 50 vol% water.

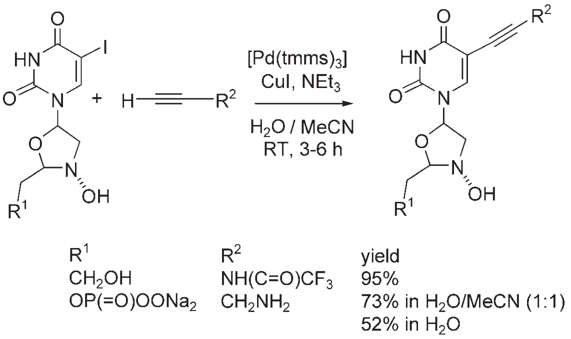
A large number of the different strategies for alkynylation reactions in water are devoted to water-soluble phosphanes (Scheme 42). The first studies on the development of a general method for palladium-catalyzed alkynylation in aqueous media used triphenylphosphane ligands modified



Scheme 42. Water-soluble phosphane ligands employed in C(sp^2) alkynylation reactions.

with hydrophilic sulfonate groups: (3-sulfonatophenyl)diphenylphosphane sodium (tppms, **1**) and tris(3-sulfonatophenyl)-phosphane trisodium (tppts, **2**; Scheme 42).[90–92]

Casalnuovo and Calabrese isolated the water-soluble complex [Pd^0(tppms)$_3$], which was employed for the alkynylation of unprotected iodonucleotides, iodonucleosides, and an iodoamino acid with propargylamine and propargyltrifluoroacetamide (Scheme 43).[90] Fairly good to excellent yields of the coupling products were obtained in water/acetonitrile solution (1:1) under mild conditions (room temperature, 2–12 h) by using 10 to 20 mol% [Pd(tppms)$_3$], NEt$_3$ (2 equiv), and substoichiometric amounts of CuI.



Scheme 43. Alkylation of nucleosides using a water-soluble palladium complex.

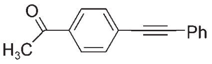
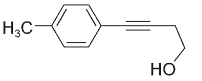
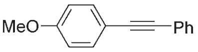
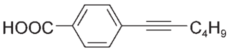
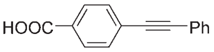
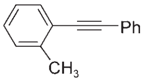
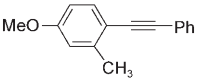
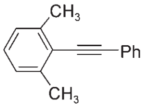
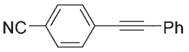
This catalytic system also allowed the quantitative coupling of 4-iodotoluene to phenylacetylene at room temperature in water/acetonitrile solution (1:9) using only 0.1 mol% of [Pd(tppms)$_3$].

Genêt et al. reported early on the use of 2.5 mol% Pd(OAc)$_2$, 5 mol% tppts, and NEt$_3$ for the coupling of aryl and vinyl iodides with terminal alkynes in aqueous acetonitrile (H$_2$O/MeCN, 1:20).[91] Mechanistic and kinetic studies on this system have demonstrated the spontaneous formation of a [Pd^0(tppts)$_2$] complex upon mixing Pd(OAc)$_2$ with four equivalents of tppts.[92] A Pd(OAc)$_2$/5 tppts combination was also used to couple peptides functionalized with aryl iodide groups to a C_3-symmetric trialkyne in water; acetylene products were obtained with molecular weights of up to 12000.[93]

Michelet, Savignac, Genêt, and co-workers synthesized the highly water-soluble ligand **3** (1100 g L^{-1}). This carboxylated analogue of tppms shows a higher basicity. The system comprising 1 mol% Pd(OAc)$_2$, 4 mol% **3**, and 2.5 equivalents of NEt$_3$ or HN*i*Pr$_2$ in water/acetonitrile (1:7) at 60 °C was efficient for the copper-free alkynylation of *ortho*-substituted aryl iodides.[94]

The electron-rich bulky water-soluble alkyl monophosphanes **4**,[95] and **5**,[33] were shown to give catalytic systems that were more efficient than the catalysts derived from sulfonated triphenylphosphane. Shaughnessy and co-workers have employed 3 mol% [Pd(OAc)$_2$(**4**)], 1 mol% CuI, and 120 mol% HN*i*Pr$_2$ in aqueous acetonitrile (1:1) to yield a set of enynes from activated or deactivated bromides in moderate to high yields (Table 4).

Table 4: Coupling products of aryl bromides and alkynes using Pd/**4**.[a]

Product	GC yield [%]
	85 50[b]
	94
	78
	84
	92
	90
	73
	30
	36[c]

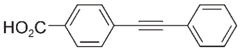
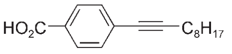
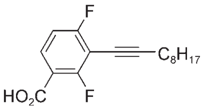
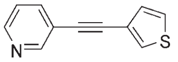
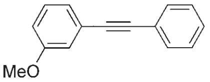
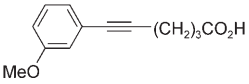
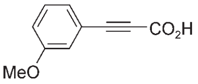
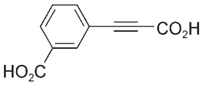
[a] Conditions: 3 mol% [Pd(OAc)$_2$/**4**], 1 mol% CuI, 1.2 equiv HN*i*Pr$_2$ in water/MeCN (1:1), 5 h, 50 °C. [b] Without CuI. [c] From the aryl chloride.

4-Bromoacetophenone and 4-bromoanisole were coupled to phenylacetylene in yields of 85 and 78%, respectively. The sterically and electronically deactivated *ortho*-substituted arenes 2-bromotoluene and 4-methoxy-2-bromotoluene were also efficiently coupled with phenylacetylene in yields of 90 and 73%, respectively, while the hindered 1-bromo-2,6-dimethylbenzene was somewhat troublesome (30% yield of the coupling product with phenylacetylene). The efficiency of the system was found to be only moderate for the activated chloride 4-chlorobenzonitrile (36% yield). Notably, attempts to carry out the Sonogashira coupling with Pd(OAc)$_2$/tBu-amphos in neat water, water/toluene, or water/ethyl acetate were unsuccessful. From computational studies, the authors have correlated the coordination chemistry and the catalytic activity of water-soluble ligands (including **4**) to their steric and electronic features.[95b] Catalyst activity increased as the cone angle of the ligands increased; catalyst activity also correlated well with some other calculated elecronic parameters, such as the HOMO–LUMO (highest occupied molecular orbital–lowest unoccupied molecular orbital) energy gap of the ligand, and the HOMO energy level of the LPd(0) species.

Anderson and Buchwald have developed reaction conditions for the coupling of activated and deactivated aryl chlorides to a variety of seldomly used alkynes in the presence of 2.5 mol% [PdCl$_2$(MeCN)$_2$], 7.5 mol% **5**, and 2.5–5 equivalents of Cs$_2$CO$_3$ in aqueous acetonitrile (1:1, Table 5).[33] Phenylacetylene and *n*-decyne were coupled to the electron-deficient 4-chlorobenzoic acid in yields of 96 and 86%, respectively. The sterically and electronically deactivated *ortho*-substituted substrate 2,6-difluoro-3-chlorobenzaldehyde was also coupled in a good yield to *n*-decyne (71%). Deactivated 3-chloroanisole was efficiently coupled to phenylacetylene (88% yield). The catalytic system gave access in excellent yields (93%) to a bis(heteroaryl) compound containing sulfur and nitrogen atoms, as well as in fairly good yields (69–70%) to functionalized aryl alkynoic acids from both electron-poor 3-bromobenzaldehyde and electron-rich 3-bromoanisole.

Compared to the reactions conditions developed by Shaughnessy and co-workers for the activation of aryl bromides with **4**, the coupling of problematic partners (deactivated chlorides or electron-poor alkynoic acids) clearly required delicate mastering of higher temperatures (60–100°C), longer reaction times (12 h), and large amounts of ligand and base (7.5 mol% **5**, 5 equiv of expensive Cs$_2$CO$_3$). Nevertheless, the alkynylation system based on the biphenylmonophosphane **5** give access to aryl propiolic acids, while propiolate esters have been found to be difficult coupling partners because of their propensity to polymerize in the presence of palladium.[33]

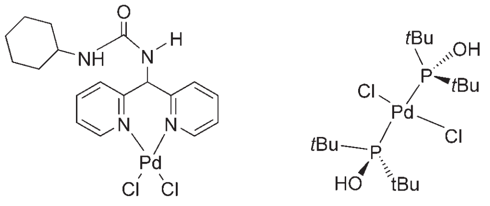
Table 5: Coupling products of aryl chlorides and alkynes using Pd/**5**.[a]

Product	Yield [%][b]
	96
	86
	71
	93
	88
	85
	70[c]
	69[c]

[a] Conditions: catalyst 2.5 mol% [PdCl$_2$(MeCN)$_2$], 7.5 mol% **5**, 2.5–5 equiv Cs$_2$CO$_3$ in water/MeCN (1:1), 8–12 h, 60–100°C. [b] Yield of isolated product. [c] From the Ar bromide; reaction at 60°C, alkyne added at 0°C.

The ionic guanidine phosphanes **6** and **7** were employed under biocompatible aqueous conditions to promote the coupling of water-soluble iodoarenes with terminal alkynes.[96] The simple cross-coupling of iodobenzoate and propiolic acid in a mixture of water/acetonitrile (7:3) at 35°C by employing 5 mol% Pd(OAc)$_2$, 25 mol% **6**, 10 mol% CuI, and 2 equivalents of NEt$_3$ afforded the expected enyne quantitatively in 45 minutes (220 min using **7**, no conversion with ligand-free Pd acetate, 75% conversion with tppts). To test the reaction in the presence of fragile biomolecules, an excess (500 wt%) of the enzyme RNAase-A was added, which remained unaltered after complete reaction as evidenced by capillary electrophoresis. On the basis of these model experiments, 4-iodobenzoate was coupled to ω-tetradecynoic acid, a long-chain terminal alkynyl fatty acid;[96a] the amount of palladium was increased to 10 mol%, because of decomposition of the catalytic system (formation of palladium black), to quantitatively functionalize the alkynyl lipid within 15 minutes.

A few well-defined precatalyst palladium complexes have been evaluated for alkynylation in neat water (Scheme 44).



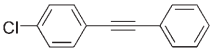
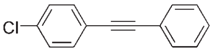
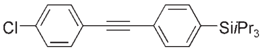
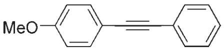
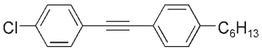
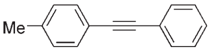
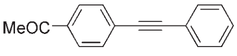
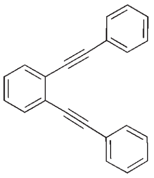
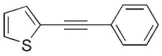
8 **9**

Scheme 44. Palladium complexes employed in water-based C(sp^2) alkynylation reactions.

Nájera and co-workers have used the chelated palladium–dipyridilmethylamine complex **8** for the cross-coupling of a wide array of aryl iodides and bromides with terminal alkynes.[50,51] The copper-free reactions were carried out in refluxing water in the presence of 0.5 to 0.01 mol% **8**, 50–100 mol% tetra-*n*-butylammonium bromide (TBAB), and 2 equivalents of pyrrolidine as base. Good TONs were obtained for these reactions, despite the recurring formation of secondary products in low yield (5 to 20%) from the homocoupling of acetylenes (Table 6).[51]

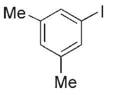
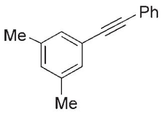
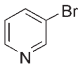
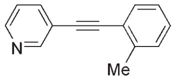
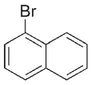
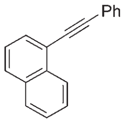
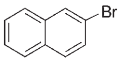
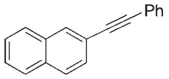
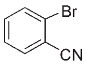
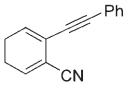
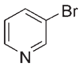
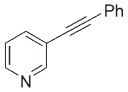
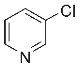
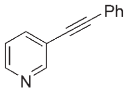
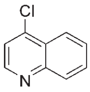
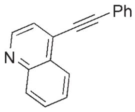
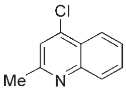
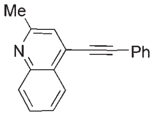
Under analogous conditions, the palladium complex **9** of a phosphinous acid was used with CuI for the coupling of various aryl halides, including activated heteroaryl chlorides (pyridines), in refluxing water in the presence of TBAB and pyrrolidine.[36] Table 7 summarizes the alkyne products

Table 6: Coupling products of aryl bromides and alkynes using the complex **8**.[a]

Product	Yield [%][b]	TON
	82	410
	93[c]	9300
	79	395
	62[c]	620
	65	325
	76	380
	81	405
	91[c]	910
	85	425

[a] Conditions: 0.2–0.01 mol% **8**, 50 mol% TBAB, 2 equiv pyrrolidine, H_2O, 100°C. [b] Yield of isolated product. [c] From the aryl iodide.

Table 7: Coupling products of aryl halides and alkynes using the complex **9**.[a]

Aryl halide	Product	Yield [%]
		90
		90
		91
		73
		81
		90
		65[b]
		71[b]
		73[b]

[a] Conditions: 10 mol% **9**/CuI, 1 equiv TBAB, 2 equiv pyrrolidine, H_2O, 100°C. [b] 0.5 M NaOH used as base.

obtained and the reaction conditions. The amount of precursor complex utilized (10 mol% **9**) is in this case substantially higher than in the case of the chelated palladium complex **8**.

Besides modified water-soluble phosphanes or palladium complexes, it has been shown that under certain reaction conditions classical triphenylphosphane complexes can be used for Sonogashira alkynylation in water. Beletskaya and co-workers reported that the reaction of terminal acetylenes with iodoarenes can be carried out in 1M aqueous K_2CO_3 in the presence of 1 mol% [$PdCl_2(PPh_3)_2$], 2 mol% CuI, and 10 mol% NBu_3; excellent yields were obtained in 1–6 h at 20°C.[97] Sinou and co-workers concomitantly reported that water-promoted coupling of aryl and vinyl halides in acetonitrile (1:10) can be carried out in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, and 2.5 equivalents of NEt_3 at room temperature without CuI, but using 1 equivalent of $n$$Bu_4NHSO_4$ as a phase-transfer reagent.[98] More recently, Bhattacharya and Sengupta disclosed that aryl iodides and activated aryl bromides can be coupled at higher temperature (70°C) with a variety of aromatic and aliphatic terminal alkynes in neat water without a phase-transfer reagent by using 0.5 mol% [$Pd(PPh_3)_4$], 1 mol% CuI, and 150 mol% $i$$Pr_2NEt$ or pyrrolidine.[99] Other reaction conditions used exclusively for the coupling of aryl iodides employed 1 mol% [$PdCl_2(PPh_3)_2$] and CuI either in aqueous ammonia,[100] or in the presence of (*S*)-prolinol as a promoter in aqueous DMF.[101] All these conditions suffer from limitations since aryl bromides and chlorides can not be used as substrates for coupling.

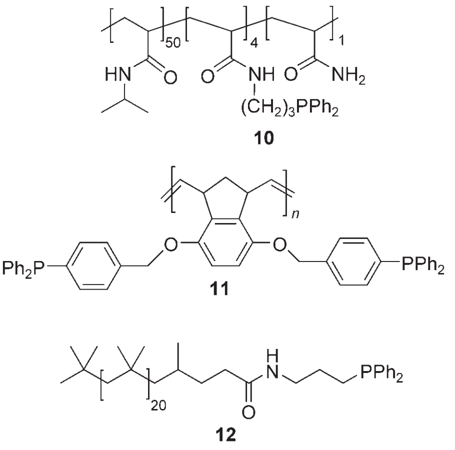
Additionally, a number of miscellaneous strategies which have employed water-based conditions are known: cross-coupling reactions catalyzed by palladium on charcoal or with palladium powder,[102–105] nickel and transition-metal-free catalysis,[106–108] supported ligands and complexes,[109–111] and ligand-free catalysis.[84] These methodologies are discussed in the corresponding sections.

3. Recyclable Systems for Sonogashira–Heck Alkynylations

3.1. Recyclable Homogeneous-Phase and Liquid Biphasic Systems

3.1.1. Soluble Polymeric and Phase-Tagged Ligands

Soluble polymer supports functionalized with phosphanes have been explored as ligands in palladium-catalyzed alkynylation reactions. The recovery of the catalyst from such systems involves a filtration process, and the soluble supports may be either precipitated from solution or isolated by membrane filtration.

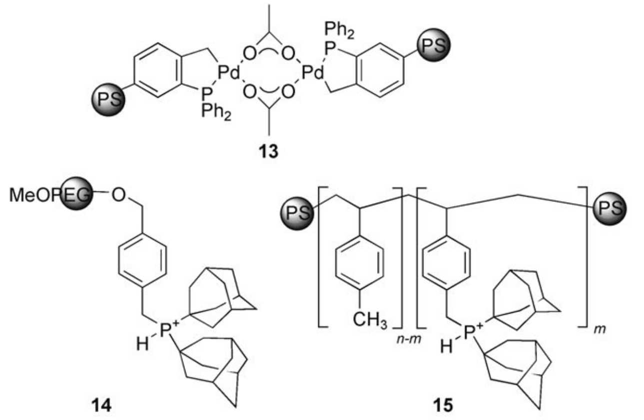


10

11

12

Scheme 45. Polymer-bound phosphane ligands employed in Sonogashira reactions.



13

14

15

Scheme 46. Polystyrene- and polyethylene glycol bound palladacycles and phosphane ligands. PS = polystyrene.

The poly(*N*-isopropylacrylamide) phosphane ligand **10** (Scheme 45) was used for the alkynylation of PhI with phenylacetylene in a thermomorphic biphasic dimethylacetamide/heptane system which is immiscible at 20 °C and miscible in all proportions at 65 °C.[112a] The polymer is also water soluble and can be used in mixed aqueous and organic phases.[112b] Diphenylacetylene was obtained in 87 % yield in the presence of 2 mol % Pd, 8 mol % **10**, and 5 mol % CuI. Unfortunately, recycling experiments were not run to assess the usefulness of the ligand in this specific reaction.

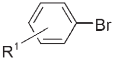
The polynorbornene-derived phosphane ligand **11** (Scheme 45) was used in 10 mol % for the coupling of phenylacetylene with the activated iodide methyl 4-iodobenzoate in the presence of 2.5 mol % $[Pd_2(dba)_3]$ and CuI.[113] A 95 % yield of the product was obtained in cycle 1 and the catalytic activity gradually fell by approximately 4–8 % in each recycle (cycle 2: 90 %, cycle 3: 86 %, cycle 4: 79 %, cycle 5: 65 %). Demanding substrates need to be tested to more accurately establish the potential of this system, which was employed under relatively harsh conditions (12 h, 90 °C).

The polyisobutylene oligomer derivative **12** (4 mol %) with 1 mol % Pd and 4 mol % CuI at 70 °C in a monophasic EtOH/heptane (9:1) mixture was equally efficient for the alkynylation of the activated 4-iodoacetophenone and the strongly deactivated 4-iodoanisole over three recycling experiments (average conversion 90 and 76 %, respectively).[114]

More readily accessible polymers (such as polystyrenes or polyethylene glycol) have been employed as supports to yield soluble recyclable palladium-containing catalytic systems. The polystyrene-supported palladacycle precatalyst **13** (Scheme 46) was synthesized and used in the alkynylation of activated 4-bromoacetophenone;[115] a quantitative conversion of an enyne was obtained after 72 h at 90 °C by employing 0.2 mol % precatalyst. The conversion of 4-bromoacetophenone can be maintained above 90 % after four recycling steps (cycle 6: 65 % yield) by using 5 mol % **13** and no copper co-catalyst.

The catalytic systems based on soluble polymer supports modified with electron-rich phosphanes allowed the range of suitable halide substrates to be enlarged. Köllhofer and Plenio have attached adamantylphosphanes to a monomethyl polyethylene glycol ether (MeOPEG) to form the polymer-supported ligand **14** (Scheme 46).[29] The resulting polymeric phosphane is soluble in water and polar solvents, such as CH_3CN or DMSO, and insoluble in alkanes. The catalytic system of 1 mol % $Na_2[PdCl_4]$, 2 mol % **14**-Br, 0.7 mol % CuI, and HN*i*Pr$_2$ as a base in DMSO at 60–75 °C allowed the alkynylation of various activated and deactivated aryl bromides (including *ortho*-substituted substrates) with phenylacetylene, 1-octyne, and (trimethyl)silyl acetylene in good to excellent yields (Table 8); the coupling of 1-octyne remained somewhat troublesome despite longer reaction times. Interestingly, the leaching of the catalyst into the *n*-heptane employed for extraction of the products appeared to be less than 0.005 %, and a constant TOF was maintained through four recycling experiments. The palladium catalytic system with **14** was superior to the analogous system with the polymer-supported phosphane MeOPEG-$OC_6H_4PPh_2$, for

Table 8: Coupling of ArBr and alkynes over five cycles with $Na_2[PdCl_4]$/2 **14**-Br$^-$ in DMSO.

Aryl bromide	Alkyne	Yield [%]		
	$H-\equiv-R^2$			
R^1	R^2	first run (crude product)	after recycling[a]	*t* [h]
H	Ph	73	94	0.5
4-COMe	Ph	36	94	0.5
4-Me	Ph	90	96	1
4-OMe	Ph	48	94	2
2-Me	Ph	94	96	3
4-COMe	SiMe$_3$	76	92	2
4-Me	SiMe$_3$	94	94	3
4-OMe	SiMe$_3$	92	93	4
2-Me	SiMe$_3$	83	81	5
4-COMe	*n*Hex	95	57	12
4-Me	*n*Hex	95	52	12
4-OMe	*n*Hex	81	37	12

[a] Overall yield of isolated product from four successive recycling experiments.

which application was limited to the activation of aryl iodides.[29]

Plenio and co-workers also investigated the performance of the phosphonium ligand supported on linear poly(*p*-methylstyrene) **15** (Scheme 46) in the Sonogashira cross-coupling of aryl bromides.[27,31] The good conversions obtained with 0.5 mol% $[PdCl_2(PhCN)_2]$, 1 mol% **15**, and 1.5 mol% CuI in toluene at 60 °C for 2–5 h in the presence of $HNiPr_2$ (80–86% average yields after 4 to 7 cycles for the coupling of 4-bromoanisole, bromobenzene, or 4-bromoacetophenone) were comparable to the ones reported for Pd/**14** (Table 8).[27] The main difference was the mode of recycling, which was based on nanofiltration with solvent-resistant poly(dimethylsiloxane)/polyacrylonitrile membranes. Under these conditions, the retention of the polymeric catalyst in the membrane was found to be greater than 99.95%. The authors also employed the polymeric phosphanes **15** and **14** under continuous-flow biphasic conditions for the alkynylation of aryl iodides (65% conversion from 4-iodoanisole/phenylacetylene) and bromides (> 98% conversion from 4-*t*Bu-bromobenzene/phenylacetylene), respectively. Two processes based on heterogeneous-catalysis fixed-bed reactors were designed (Figure 1). In these reactors the catalytic systems were solubilized either in a polar or an apolar stationary phase, while another mobile phase (nonmiscible, of inverse polarity) was employed to carry the reactants (pumped in) and the products (pumped off) through the stationary phase.[30] In this method, the tuning of the partition coefficients of the chemicals into the different phases is a key parameter.

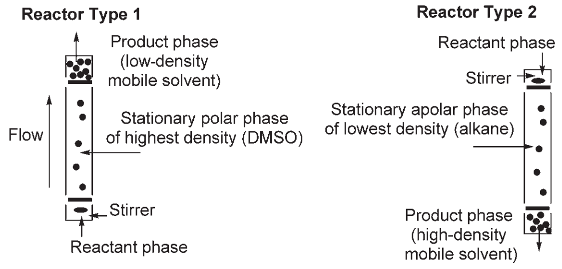
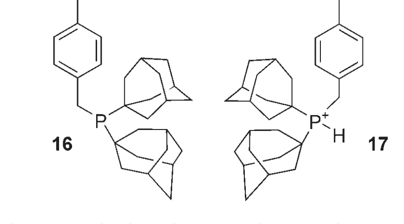


Figure 1. Reactors for continuous-flow biphasic catalysis.

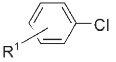
As the activation of aryl chlorides was not possible when the MeOPEG-supported ligand **14** was used,[28] Plenio and co-workers synthesized and tested two recyclable ionic ligands: the monophosphane $[Et_3N^+\text{-}CH_2\text{-}C_6H_4\text{-}P(1\text{-}Ad)_2]Br^-$ (**16**-Br) and the diphosphonium salt $[Ph_3P^+\text{-}CH_2\text{-}C_6H_4\text{-}HP^+(1\text{-}Ad)_2](Br^-)_2$ (**17**-Br_2, Scheme 47). Table 9 summarizes the performances of these ionic phosphanes in the coupling of activated and deactivated aryl chlorides using 2 mol% $Na_2[PdCl_4]$, 4 mol% ammonium- or phosphonium-functionalized ligands, 1.5 mol% CuI, and Na_2CO_3 as a base in DMSO at 120 °C.[28] Good to excellent overall yields were obtained from the coupling of activated chlorides (4-nitrobenzene and 4-bromoacetophenone), whereas electron-rich deactivated chlorides such as 4-bromotoluene or 4-bromoanisole were converted in only moderate yields. Less than 0.05% of the catalyst leached into the heptane extraction solvent; this value is, however, ten-times greater than in the case of the MeOPEG-supported ligand **14**.[29]



16 **17**

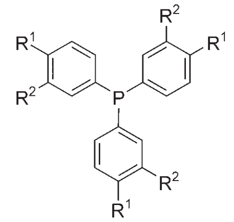
Scheme 47. Electron-rich phosphanes with ionic phase tags.

Table 9: Coupling of ArCl and alkynes using $Na_2[PdCl_4]$/**17**-Br_2 in DMSO at 120 °C after five cycles.

Aryl chloride 	Alkyne $H-\!\equiv\!-R^2$	Yield [%]		
R^1	R^2	first run (crude product)	after recycling[a]	*t* [h]
4-NO_2	Ph	35	84	6
4-COMe	Ph	46	90	8
4-Me	Ph	45	49	24
4-OMe	Ph	39	47	24
4-NO_2	iPr_3Si	40	72	14
4-COMe	iPr_3Si	63	74	14

[a] Overall yield of isolated product from four successive recycling experiments.

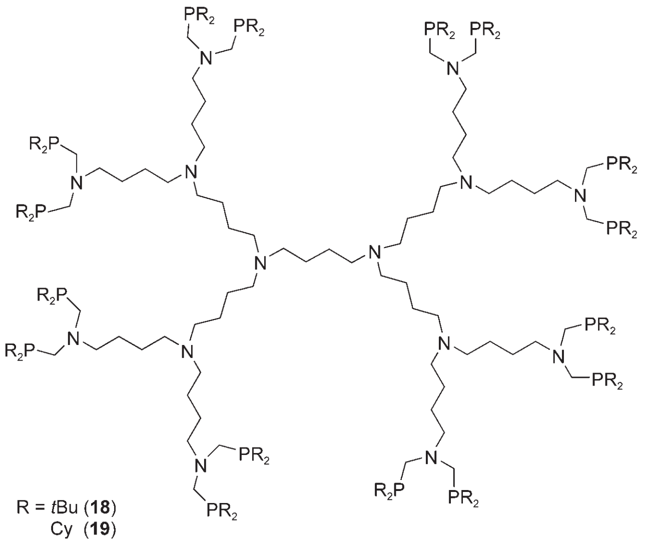
Three phosphane ligands with fluorinated side chains (Scheme 48) have been investigated in the Sonogashira cross-coupling of aryl bromides with various alkynes in a fluorous biphasic system.[116] Good to excellent conversions were observed with electronically activated bromides (NO_2-, COMe-, CO_2Et-substituted bromobenzene) and were maintained over two recycling experiments irrespective of the ligand used (2 mol% Pd/fluorinated phosphane, 5 mol% CuI, 100 °C, 4 h). The systems were inefficient for the coupling of electron-rich 4-bromoanisole.



R^1 = H and R^2= $(CH_2)_2\text{-}(CF_2)_7\text{-}CF_3$
R^1= $(CH_2)_2\text{-}(CF_2)_7\text{-}CF_3$ and R^2 = H
R^1= $OCH_2\text{-}(CF_2)_6\text{-}CF_3$ and R^2 = H

Scheme 48. Phosphane ligands with perfluorinated groups used under biphasic DMF/$(CF_3)_2C_6F_{10}$ conditions.

Besides the oligomer- and polymer-supported phosphane ligands, Heuzé, Astruc, and co-workers have described the synthesis and applications of dendrimer-supported electron-rich phosphanes.[54] Three generations of well-defined dendritic polyaminophosphane ligands (with 4, 8, and 16 pairs of chelating phosphorus atoms substituted either by two cyclohexyl or two *tert*-butyl groups, Scheme 49) were prepared. The six different dendritic ligands obtained have been treated



Scheme 49. Dendritic second-generation phosphane ligands (eight pairs of chelating P donors).

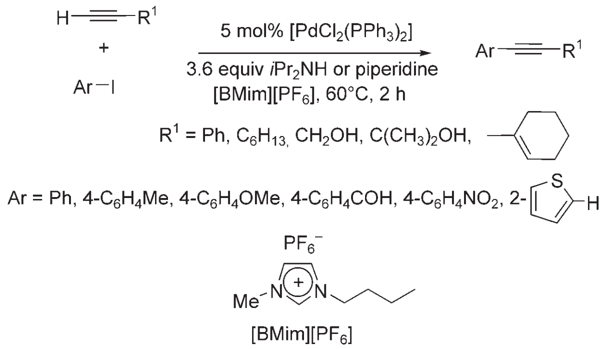
with $Pd(OAc)_2$ to form metallodendrimers with 4-, 8-, or 16-palladium nuclei which have been tested in the copper-free cross-coupling of iodobenzene and bromobenzene with phenylacetylene. The metallodendrimers incorporating *t*Bu groups (1 mol%, employed at 25 to 120 °C) were found to be efficient for the alkynylation of iodobenzene (97–100% yields) and bromobenzene (93–100%). The analogous catalysts bearing cyclohexyl groups were less efficient under similar conditions (iodobenzene conversion: 46–79%, bromobenzene conversion: 15–20%). However, these latter metallodendrimers could be recovered by multiple precipitations, while the metallodendrimers bearing *t*Bu groups were very soluble in common solvents. A negative dendritic effect was observed for the recoverable third-generation metallodendrimers; thus, only the first- and second-generation metallodendrimers bearing cyclohexyl groups (**19**, Scheme 49) combined both recovery possibilities and acceptable activities for the alkynylation of iodobenzene. These studies illustrate the difficulty that generally exists in transferring the activity of homogeneous catalysts to recoverable catalysts.

Heuzé, Astruc, and co-workers later reported the results of coupling iodobenzene with phenylacetylene over six recycling experiments by employing 2 mol% of the recoverable cyclohexyl-functionalized metallodendrimers.[55] A significant drop in the performances, which correlated with the decomposition of the dendritic catalysts, was observed after the fourth cycle.

3.1.2. *Systems with Ionic Liquids*

As demonstrated in the previous sections, the influence of the solvent on Sonogashira–Heck reactions has been a parameter that has always been thoroughly examined. While biphasic catalytic conditions (aqueous NaOH/benzene) with a phase-transfer agent (for example, benzyltriethylammonium chloride) were among the earlier solvent variations examined,[117] the latest innovation in this field concerns the direct use of ionic liquids as solvents. Most of the solvents employed as room-temperature ionic liquids are molten imidazolium salts.

Ryu and co-workers discovered that the copper-free coupling of aryl iodides and vinyl bromides with aromatic and aliphatic acetylenes could be carried out in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ($[BMim][PF_6]$) at 60 °C in the presence of 5 mol% $[PdCl_2(PPh_3)_2]$ and 3.6 equivalents of HN*i*Pr_2 or piperidine.[118] Excellent yields of the isolated coupling products were obtained (85–97%) starting from a variety of substituted terminal alkynes and aryl halides (Scheme 50). Under the same conditions, the catalyst could be recycled three times for the synthesis of diphenylacetylene with only a slight loss of activity. The authors applied their system in an ionic liquid to produce diphenylacetylene in a continuous-flow microreactor.



Scheme 50. Coupling of aryl iodides to terminal alkynes in an ionic liquid.

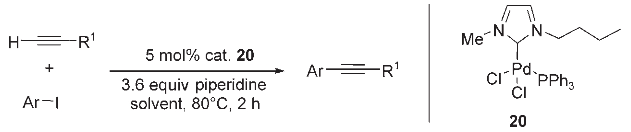
With the development of automated procedures as a goal, the same research group has employed a palladium–carbene complex for the high-throughput screening of a set of alkynylation reactions with various imidazolium salts in a 24-array parallel reactor (Table 10).[119] Their results illustrate the importance of the nature of the ionic solvent employed, and confirm the superior efficiency of $[BMim][PF_6]$.

Park and Alper used the phosphane-free palladium–bisimidazole **21** for the copper-free coupling of aryl iodides (Scheme 51).[120] The coupling of the terminal alkyne phenylacetylene gave products in moderate to excellent yield (32–98%), depending on the substituent on the aryl iodide, while the coupling of other alkynes with 4-iodoacetophenone was somewhat more difficult (28–58% yield of the isolated product).

Consistent with the studies reported by Ryu and co-workers,[118] the catalyst could be recycled three times for reactions with activated and deactivated iodide substrates, and again showed only a slight decrease in activity.[120]

Srinivasan and co-workers carried out a Heck alkynylation of aryl iodides at 30 °C under ultrasound irradiation in the liquid imidazolium salt 1,3-di-*n*-butylimidazolium tetrafluoroborate ($[BBim][BF_4]$);[121] the authors reported the in situ formation of palladium(0) nanoparticles as the possible catalyst for the reaction (see Section 3.1.3). In contrast,

Table 10: Alkynylations in various ionic liquid solvents.[a]



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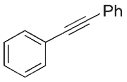
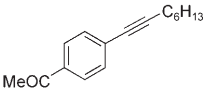
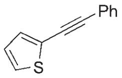
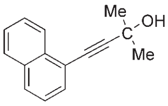
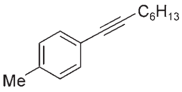
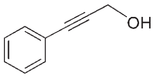
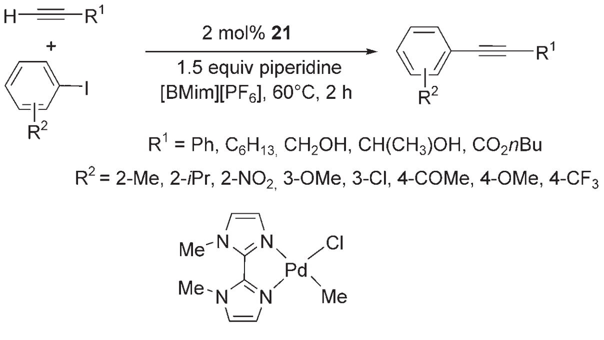
	[BMim][PF$_6$]	[BMim][BF$_4$]	[BMim][NTf$_2$]	[BMPy][BF$_4$]
	94	89	82	66
	92	89	84	48
	90	85	83	65
	85	75	35	55
	75	69	70	43
	59	38	14	14

[a] Yields determined by ^{1}H NMR spectroscopy. [BMim][BF$_4$] = 1-butyl-3-methylimidazolium tetrafluoroborate; [BMim][NTf$_2$] = 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide; [BMPy][BF$_4$] = 1-butyl-1-methylpyrrolidinium tetrafluoroborate.



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Scheme 51. Coupling of aryl iodides to terminal alkynes in an ionic liquid.

García and co-workers have reported a weak activity in the coupling of activated aryl iodides and bromides in the presence of palladium black particles, a palladium–carbene complex, or a carbapalladacycle at 120 °C in various liquid imidazolium salts (0–57 % yield).[122]

In these pioneering studies the conditions reported for the alkynylation of aryl halides were limited to iodoarenes, thus, significantly hampering the practical development of the ionic-solvent version of the reaction. Nevertheless, it was recently shown that the activation of a variety of aryl bromides is possible, including strongly electronically and sterically deactivated ones.[123] The copper-free system of 1 mol % [{Pd(η^3-C_3H_5)Cl}$_2$], 3 mol % PPh$_3$, and 1.2 equivalents of pyrrolidine in [BMim][BF$_4$] at 130 °C is efficient for the coupling of *para* and/or *ortho* mono-, di-, or trisubstituted aryl bromide substrates with phenylacetylene or long-chain aliphatic terminal acetylenes such as 1-decyne (Table 11). In addition to the quantitative conversion of 4-bromoacetophenone, good to excellent conversions were obtained in 2 to 4 h for the coupling of phenylacetylene with the electronically activated 4-bromobenzonitrile, 3,5-bis(trifluoromethyl)bromobenzene and with the unactivated bromobenzene. Electronically and/or sterically deactivated bromides such 4-bromanisole, 4-bromotoluene, and 2-bromotoluene could be coupled in excellent yields to phenylacetylene and 1-decyne by using longer reaction times.

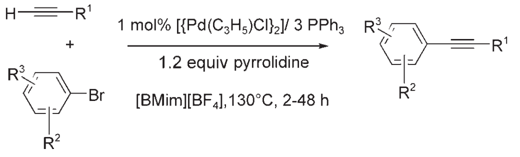
While the cross-coupling of aryl halides in which one or both of the *ortho* positions is substituted generally suffers from additional complications of steric origin, 2-bromonaphthalene and bromomesitylene were quantitatively converted into the corresponding enynes.[123] A double alkynylation was possible starting from a dibromoaryl substrate (98 % conversion in enynes, with 60 % of the monosubstituted product and 40 % of the disubstituted one). With this simple system the catalyst could be recycled three times, although a slight deactivation was noted. Attempts to activate aryl chlorides with the Pd/PPh$_3$/pyrrolidine system remained unsuccessful, and even the strongly activated 4-chloroacetophenone was not converted at high temperature.

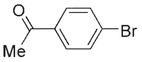
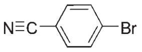
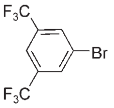
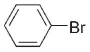
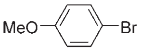
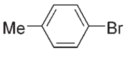
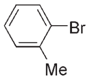
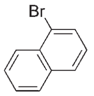
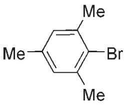
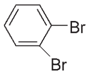
The Sonogashira–Heck coupling of aryl chlorides has so far not been successful in ionic liquids. However, such procedures remain promising in regard to the ease with which recycling can be achieved.[123b] The use of water-soluble ligands (or at least ionic ligands) should allow a better immobilization of the catalytic systems in the ionic phase. More fundamental studies are also required to identify the catalytic species truly involved in the processes (Are they molecular or colloidal species? Do they incorporate phosphane and/or carbene ligands?) and their degree of immobilization in the ionic solvent.

3.1.3. *Colloidal Catalyst Systems*

Soluble colloidal nanoparticles are commonly viewed as "semiheterogeneous" systems that might combine the advantages of homogeneous catalysts (activity and selectivity) and heterogeneous catalysis (stability and reuse). Consequently, some very recent studies were devoted to the evaluation of their performances in the alkynylation of arenes.

Table 11: Coupling of ArBr and alkynes in an ionic liquid imidazolium salt.



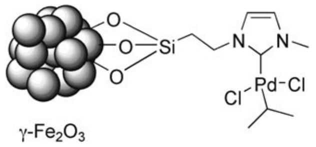
Aryl bromide	Alkyne	Yield [%][a]	*t* [h]
	HC≡CPh 1-decyne	> 99 96	2 4
	HC≡CPh	80	4
	HC≡CPh	92	4
	HC≡CPh	82	2
	HC≡CPh 1-decyne	95 76	20 20
	HC≡CPh 1-decyne	86 76	20 4
	HC≡CPh 1-decyne	99 65	20 4
	HC≡CPh	98	4
	HC≡CPh	> 99	48
	HC≡CPh	98[b]	24

[a] GC yield given; after workup, yields of the isolated products reach 90–95 % of these values. [b] 58 % of the monosubstituted product and 42 % of the disubstituted one.

Li et al. have used known palladium colloids stabilized by a polar layer of polyvinylpyrrolidone (PVP) in refluxing ethanol in the presence of K_2CO_3 for the coupling of electron-poor and electron-rich aryl iodides in very good yields.[124] Under these conditions, 1 mol % Pd/PVP nanoparticles allowed the coupling of iodobenzene in 95–90 % yield over seven recycling experiments (after each reaction the colloid was precipitated by the addition of diethyl ether and decantation). This system was found to be superior to the ligand-free $Pd(OAc)_2$ source (52 % yield), $[Pd(PPh_3)_4]$ (48 %), sub-micrometer-sized palladium powder (< 10 %), palladium sponge (0 %), and Jeffery's catalyst nBu$_4$NBr/Pd (90 %). Moderate yields were obtained with aryl bromides. The finding that the addition of PPh_3 significantly improved the results raises the question of the nature of the active species; one possibility is "naked" reactive Pd^0 atoms, where the nanoparticles mainly act as a colloidal reservoir that slowly delivers Pd atoms.

Hyeon and co-workers synthesized Ni/Pd core–shell particles stabilized by an aminooctadecene surfactant (oleylamine), and with a shell enriched with Pd atoms.[125] Their proposal was based on the concept that catalytic reactivity is due to the surface atoms and therefore the core can be formed from a less expensive metal such as nickel. Sonogashira reactions (2 mol % Pd atoms, 1 mol % CuI, HNiPr$_2$ as solvent, 80 °C, 2–18 h) and recycling were successfully conducted on aryl bromides. In these reactions 1.5 mol % PPh_3 was added, but the authors did not explain the precise role of this ligand amount with regard to the activity of the nanoparticles.

Gao and co-workers grafted a Pd/N-heterocyclic carbene complex onto the surface of soluble maghemite nanoparticles (γ-Fe_2O_3) stabilized by oleate surfactants (Scheme 52).[126]

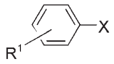


Scheme 52. A palladium–carbene immobilized on magnetic iron oxide nanoparticles.

The solubility of the particles is due to their small dimensions (11 nm ± 10 %) and organic coating. The superparamagnetism of the maghemite core allows the particles to be magnetically concentrated and re-dispersed using a small permanent magnet positioned externally.

The nanoparticles were used at 7.3 mol % palladium (about 1.5 mmol g^{-1}) in DMF at 50 °C in the presence of 15 mol % CuI and 2 equivalents of Na_2CO_3. Electron-rich and electron-poor aryl iodides and bromides were efficiently coupled (Table 12). Substrates with *ortho* substituents were also tested, and recycling of the nanoparticles was achieved by magnetic concentration, washing, and air drying, without further purification. About 97 wt % of the iron oxide–palladium nanoparticles were recovered. This system was shown to be superior to an analogous polystyrene solid-phase system; the authors attributed this to an easier access to the surface active sites.

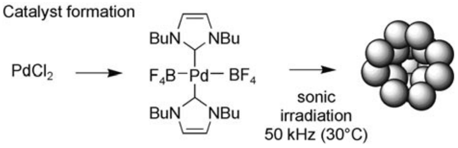
Table 12: Sonogashira cross-coupling of phenylacetylene and aryl halides with iron oxide palladium particles.

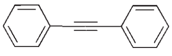
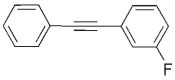
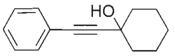
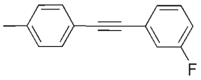
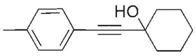
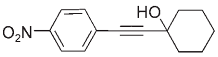
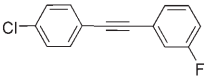
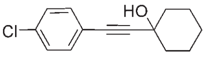
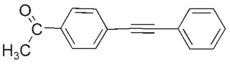
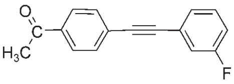
Aryl halide 		
R1	X	Yield [%][a]
2-Me	I	89[b]
2-Me	Br	91
3-OMe	I	88
3-OMe	Br	93
4-COMe	I	91

[a] Yield of isolated coupling product. [b] GC yield after recovery: 91, 90, 91, and 89 %.

Srinivasan and co-workers have reported the formation of well-defined palladium nanoparticles in acetone or in [BBim][BF_4] (average size 5 and 11 nm, respectively) from 2 mol % $PdCl_2$ and 1.5 equivalents of triethylamine under ultrasound irradiation at ambient temperature.[121] The authors assumed these species to be the active ones in the copper-free alkynylation reactions summarized in Table 13. They reported access to a number of novel enyne compounds in excellent yields in unusual solvents, with the reaction being much faster in acetone. The activation of aryl chlorides was not effective with these systems and a lower yield (65 %) was obtained for the coupling of the activated bromoacetophenone to phenylacetylene. Recycling of the catalytic system was possible in the synthesis of diphenylacetylene from iodobenzene and phenylacetylene, with only a slight loss of activity (from 93 to 85 % yield after five cycles).

Table 13: Sonogashira cross-coupling of aryl iodides and acetylenes under ultrasound irradiation.



Product	In acetone yield [%] (*t* [min])	In [BBim][BF$_4$] yield [%] (*t* [h])
	85 (15)	93 (2)
	78 (15)	89 (2)
	65 (30)	78 (2.5)
	72 (20)	84 (2)
	68 (35)	74 (2.5)
	68 (35)	72 (2.5)
	72 (15)	82 (2)
	66 (35)	72 (2.5)
	84 (15)	90 (2)
	80 (15)	86 (2)

A genuine colloidal activity is more convincing in catalytic palladium colloidal systems employed without additional strong ligand species (such as PPh$_3$ or carbenes). Indeed, in the absence of in situ evidence, it can not be totally ruled out that the colloidal solution is mainly a reservoir of unsaturated active molecular species; this is particularly the case for unproblematic substrates such as vinyl and aryl iodides or activated bromides. Much progress could be accomplished from in situ characterization (rather than characterization of the reaction product) or from any strategy that can definitely rule out any monomolecular activity. The activation of more-demanding substrates (deactivated bromides or chlorides) would also be of interest, since numerous studies have shown that these compounds are hardly converted by low-coordinated (or "naked") palladium atoms.

3.2. *Heterogeneous and Solid-Supported Systems*

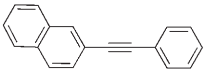
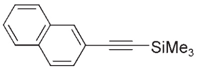
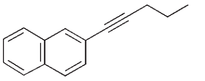
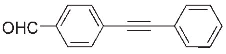
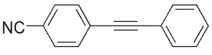
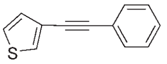
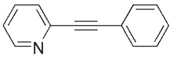
Homogeneous catalysis is a powerful tool in highly active and selective organic transformations. Nevertheless, in industry the large majority of catalytic processes are still conducted under heterogeneous conditions, since the separation of the catalysts from the product mixture is easier than in classical homogeneous systems. Therefore, besides the development of homogeneous catalysts that can be used in very low concentrations—for which the catalyst quantity is at the ppm level, and thus separation is often not necessary—efforts have been made to provide heterogeneous versions of the Sonogashira–Heck cross-coupling reaction.

3.2.1. *Palladium on Carbon*

The most readily available form of a supported palladium catalyst, that is, palladium on carbon (Pd/C),[127–134] was also the first one to be explored in the Sonogashira alkynylations of a variety of aryl- and heteroaryl bromides under heterogeneous conditions. Guzmán and co-workers reported early on that the catalytic system consisting in 4 mol % commercial Pd/C, 4 mol % CuI, and 16 mol % PPh$_3$ in NEt$_3$/acetonitrile (2:1) at 80 °C for 3 h, allowed various enynes to be produced in fairly good yields (Table 14).[127] The authors found that [Pd(PPh$_3$)$_4$] was possibly the active species in the reaction mixture, with Pd/C thus serving as a reusable inexpensive source of palladium.

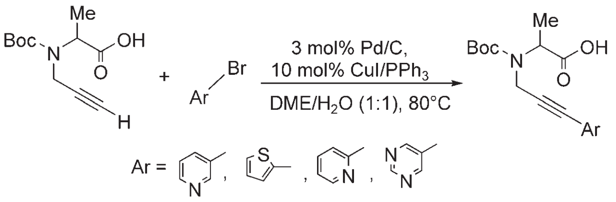
Kotschy and co-workers have updated this method recently,[128] and showed that the coupling of heteroaryl chlorides and deactivated bromides to 1-hexyne and alkynols in the presence of 5 mol % Pd/C, 10 mol % CuI and PPh$_3$, as well as 1.2 equivalents of HN*i*Pr$_2$ at reflux in aqueous dimethyl acetamide was possible in moderate yields (26–

Table 14: Sonogashira synthesis of enynes catalyzed by Pd/C.

Coupling product	Yield [%]
	53
	58
	86
	72
	64
	53
	67

54 %). A series of experiments (hot filtrations and tests on the catalytic activity of the filtrates) confirmed the hypothesis of Guzmán and co-workers that palladium leaches into the solution in an active form, thus providing a homogenous catalytic pathway for the coupling reaction.[128]

Heteroaryl bromides have also been employed in aqueous DME for cross-coupling reactions with propargylamino acids and peptides in the presence of 3 mol % Pd/C, 10 mol % CuI/PPh$_3$, and 2.5 equivalents of K_2CO_3 (Scheme 53).[129] Aryl iodides and bromides without any hydrophilic functional groups have been coupled to alkynols in water by using Pd/C in the presence of 2-aminoethanol.[103,130]

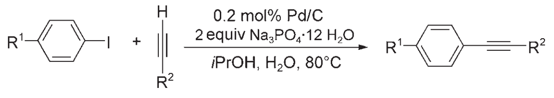


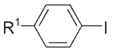
Scheme 53. Coupling of propargylamino acids and peptides to aryl bromides. Boc = *tert*-butoxycarbonyl.

Copper-free variations of alkynylation reactions with Pd/C have also been explored. Mori and Seki have found that Pd(OH)$_2$/C gives a higher yield for the coupling of 3-bromopyridine with phenylacetylene or 2-methyl-3-butyn-2-ol than classical Pd/C catalysts.[131] Zhang has successfully carried out the alkynylation of aryl iodides under copper-, amine-, and phosphane-free conditions (Table 15);[132] moderate to high yield of enynes were obtained at 80 °C within 2 to 6 h by using a small amount of palladium (0.2 mol %) and 2 equivalents of $Na_3PO_4 \cdot 12\,H_2O$ as a base in 2-propanol/water solution (1:1). No recycling experiments were described for this system.

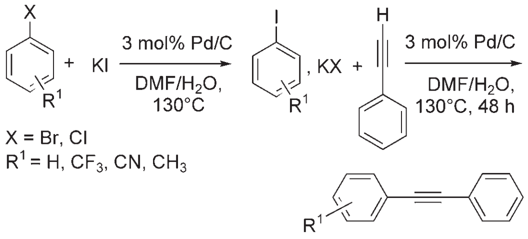
One recent innovation concerning the application of a copper-free Pd/C catalytic system for alkynylation was its use for activating aryl bromides and electron-poor aryl chlorides by a two-step process that involved first a halogen exchange reaction and then alkynylation with phenylacetylene (Scheme 54).[133] The Pd/C catalyst was reused in five further cycles for the coupling of 4-cyanochlorobenzene to phenylacetylene. Attempts to make the halogen-exchange step catalytic in KI was unfortunately unsuccessful.

Table 15: Copper-, amine-, and phosphane-free synthesis of enynes catalyzed by Pd/C.



Aryl iodide  R^1	Alkyne $H-\equiv-R^2$ R^2	Yield [%][a]	*t* [h]
NO_2	Ph	98	3
COMe	Ph	98	2
Me	Ph	67	6
OMe	Ph	60	6
NO_2	$(CH_2)_2OH$	79	2
COMe	$(CH_2)_2OH$	80	5
Me	$(CH_2)_2OH$	45	5
OMe	$(CH_2)_2OH$	37	5

[a] Yield of isolated product.



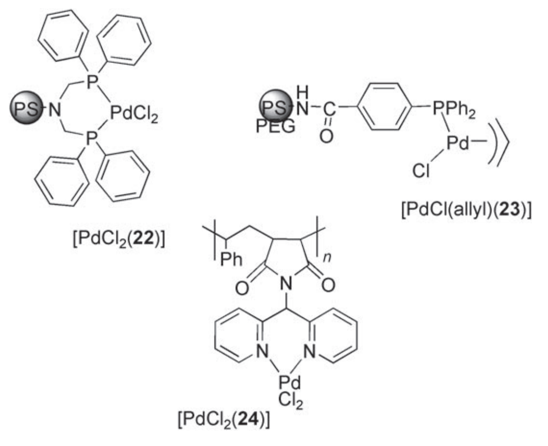
Scheme 54. One-pot cascade reaction of halogen exchange and alkynylation of bromides and activated chlorides.

The high-throughput screening of a biological sandwich immunoassay has recently identified a convenient system for the coupling of imidazole- and guaiacol-functionalized alkynes with aryl iodides;[133] The combination of Pd/C and $CuBr \cdot Me_2S$ in water/acetonitrile was the most efficient catalyst among a library of 96 systems prepared from the combination of a set of 4 homogeneous and 8 solid-supported palladium sources, as well as 8 co-catalysts (copper, silver, and gold compounds). These results show that whatever the operating mode of the Pd/C systems, they remain of practical interest for facile Sonogashira–Heck alkynylation.

3.2.2. *Catalysts Supported on Polymers and Silica*

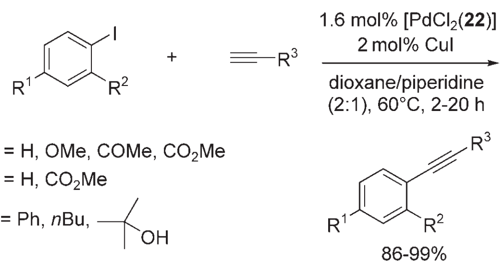
The activity and recyclability of better structurally defined polymer- or silica-supported heterogeneous catalysts have also been explored. Aminomethyl-functionalized polystyrene beads were used to form the polystyrene-supported chelating diphosphane ligand **22** (Scheme 55).[135]

The catalytic system based on 1.6 mol % [PdCl$_2$(**22**)] and 2 mol % CuI at 60 °C in dioxane/piperidine allows the coupling of a variety of aryl iodides with aromatic and



Scheme 55. Phosphanyl-, diphosphanyl-, and diimino-based resin-supported palladium catalysts.

aliphatic terminal alkynes in quantitative yield (Scheme 56). The catalyst could be recycled four times with no detectable deactivation (99% conversion) in the coupling of phenyliodide with phenylacetylene over long reaction times.

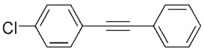
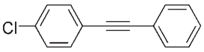
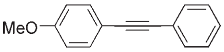
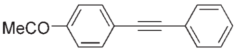
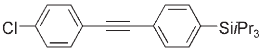
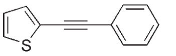


Scheme 56. Alkynylation of aryl iodides with polystyrene-bound chelating phosphane **22**.

The copper-free Heck alkynylation with 5 mol% polystyrene-polyethylene glycol (PS-PEG) supported palladium monophosphane complex [PdCl(allyl)(**23**)] (Scheme 55) and 5 equivalents of CsOH in water at 60 °C allowed various phenyl-substituted alkynecarboxylic acids to be obtained in moderate to good yields from iodobenzene.[111,136]

Nájera and co-workers have examined the cross-coupling of activated and deactivated iodides and bromides with phenylacetylene and triisopropylsilylacetylene in the presence of [PdCl$_2$(**24**)] (Scheme 55), with pyrrolidine used as a base and TBAB as an additive in refluxing water (Table 16).[52]

Table 16: Coupling products of aryl iodides and alkynes using [PdCl$_2$(**24**)].[a]

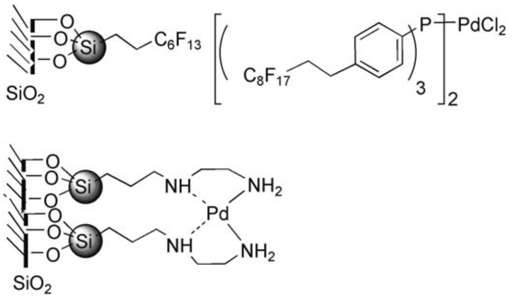
Product	Yield [%][b]	Cat. [mol%]	t [h]	TON
	99	0.001	31	99000
	99	0.1	1	990
	96	0.1	1	960
	99[c]	0.2	1.5	495
	99[c]	0.2	14	495
	92[c]	0.2	1	460

[a] Conditions: 0.2–0.001 mol% [PdCl$_2$(**24**)], 50 mol% TBAB, 2 equiv pyrrolidine. [b] Yield of product (GC). [c] From the aryl bromide.

Aryl iodides were activated with 0.1–0.001 mol% Pd and aryl bromides with 0.2 mol% Pd. In general, a better efficiency was observed with the polymeric catalyst [PdCl$_2$(**24**)] than with its corresponding mononuclear complex **8** (see Section 2.3, Scheme 44). The catalyst was recovered by filtration and could be used successfully after being recycled four times for the coupling of activated and deactivated iodides as well as 4-bromoacetophenone to phenylacetylene. Microwave heating was used to increase the rate of reaction, however the catalysts were then not reusable. No appreciable catalytic activity was detected from the filtrates during the recycling processes. A system employing a bispyrimidylamine ligand was developed for the alkynylation of aryl iodides and reached high TONs (see Section 2.1.3).[49] Other polymer-supported complexes of palladium evaluated in the alkynylation of arenes were used in studies of only limited scope.[137]

On silica supports it is possible to distinguish between catalytic systems that are immobilized either through covalent attachment or through adsorptive, electrostatic, or other weaker interactions. Less metal leaching is expected from systems immobilized through strong covalent bonding, nevertheless significant results have been obtained from catalysts immobilized by other means.

Fluorous reversed-phase silica gel (FRPSG) have been used instead of the expensive and environmentally persistent fluorous solvents to immobilize fluorinated palladium–phosphane catalysts (Scheme 57, top).[138]

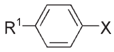


Scheme 57. Silica-immobilized palladium catalysts employed in aryl alkynylation reactions.

The cross-coupling of 4-nitrobromobenzene and phenylacetylene was achieved in satisfactory yields of 98, 97, and 71% for three successive experiments by using 2 mol% Pd/FRPSG catalysts in the presence of CuI/HNnBu$_2$ in DME at 100 °C for 14 h; however, the catalytic activity and the recyclability dropped significantly in the third cycle and also if a lower amount of catalyst (0.2–0.002 mol%) was used.[138] A study on a more diverse array of substrates would be necessary to determine the scope of these catalysts. Based on an analogous concept, catalytic Pd(OAc)$_2$/n ttpts ($n = 2$ or 5) systems have been deposited on the surface of mesoporous silica and shown to be successfull for the coupling of phenylacetylene with iodobenzene in the presence of CuI/NEt$_3$ in acetonitrile/water.[139] The authors believe that the solids behave essentially as a reservoir of highly soluble species, from which the leaching species might be a lipophilic Pd/phosphane intermediate with a C≡CPh group; thus making the system useless for recycling (see Section 3.2.3 for an example of a mesoporous silica with a "channel" structure that interferes with catalysis).

The more tightly bound inorganic/organic hybrid material aminoethyl-aminopropyl-functionalized silica gel with an immobilized palladium catalyst (Scheme 57, bottom) has been used for the coupling of a variety of aryl iodides and bromides.[140] In the absence of a copper promoter and phosphane ligand, good to excellent yields of the coupling products were obtained from iodides in EtOH at 80 °C for 6 h, and from electron-poor and electron-rich bromides in DMF at 110 °C for 8 h (Table 17).

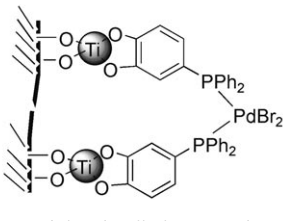
Table 17: Alkynylation with a silica-supported palladium catalyst.

Aryl halide 		Alkyne $H{-}{\equiv}{-}R^2$	Yield [%][a]
R^1	X	R^2	
OMe	I	Ph	96
H	I	Ph	94
Me	I	Ph	98
NO_2	I	Ph	98
H	I	C_8H_{17}	92
H	I	CH_2OH	90
NO_2	Br	Ph	96
Me	Br	Ph	85

[a] Yield of isolated product.

The authors indicated that after filtration and work-up procedures the silica-supported palladium was recovered and was used for 30 consecutive trials without any decreases in activity.[140] A partially analogous 3-aminopropyl-functionalized silica gel has been used to produce an immobilized palladium catalyst, which was successfully used in a series of copper-free alkynylation coupling reactions, but had a more limited scope of aryl iodides.[141]

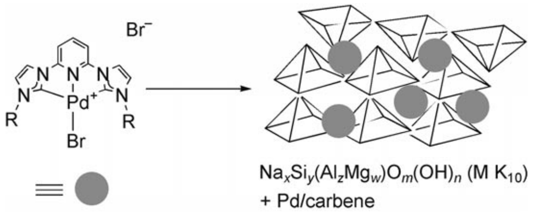
Besides SiO_2-immobilized palladium catalysts, McDonagh and co-workers have proposed the functionalization of titanium dioxide with palladium through a strongly bound catecholate ligand (Scheme 58).[142] A careful characterization of the catalytic material was conducted by solid-state ^{31}P NMR spectroscopy and diffuse-reflectance IR spectroscopy on $W(CO)_5$ derivatives. As a preliminary experiment, the coupling of the substrate 4-iodonitrobenzene proceeded to completion over a rather long time period (24 h). Deactivation of the catalyst was observed after recycling it twice by simple filtration.



Scheme 58. A TiO_2-immobilized palladium catalyst employed in aryl alkynylation reactions.

3.2.3. *Solid-Supported Catalysts on Mineral Intercalation Materials*

Less common supports such as clays, zeolites, and perovskites have also been examined.[64,143,144] Smectite clays (montmorillonite K10 and bentonites of different surface area) were used to immobilize palladium complexes incorporating a rigid tridentate C,N,C-carbene pincer ligand through adsorptive and electrostatic interactions (Scheme 59).[64] In the presence of 5 mol % CuI and a base in DMA (or pyrrolidine), the system resulted in the successful coupling of phenylacetylene with aryl iodides and three activated bromides. One recycle was reported without noticeable deactivation.



Scheme 59. A clay-immobilized palladium complex of a carbene pincer used in catalytic alkynylation reactions.

Ley and co-workers have reported that palladium- and copper-containing perovskites of general formula $LaFe_{0.57}Cu_{0.38}Pd_{0.05}O_3$ and $Nd_{2.04}Cu_{0.95}Pd_{0.05}O_4$ can promote the alkynylation of aryl iodides and of 4-nitrobromobenzene in H_2O/DMA at 120 °C, despite the low amount of palladium present (2.5 mol % perovskite in the standard procedure, thus 0.125 mol % Pd).[144]

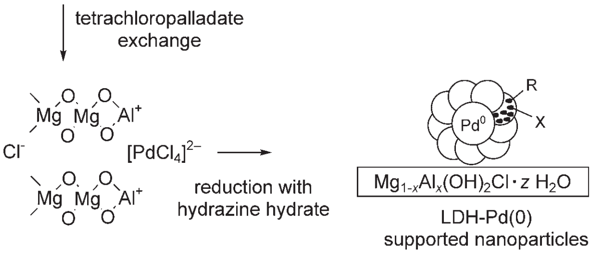
In regard to heterogeneous systems that can be used under copper-free conditions, Djakovitch and co-workers have prepared modified NaY and NH_4Y zeolites by ion exchange using a 0.1 M aqueous solution of $[Pd(NH_3)_4]Cl_2$.[143a,b] The catalysts $[Pd(NH_3)_4]^{2+}$/(Na)Y and $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ were obtained with a palladium content of 7 and 5.2 wt %, respectively, and have been used for the copper-free alkynylation of aryl iodides and bromides with 1 mol % Pd-modified zeolite. Consistent with the previously described heterogeneous catalytic systems—but in the absence of copper—electron-rich and electron-poor aryl iodides as well as activated aryl bromides gave almost quantitative yields. Conversely, unactivated aryl bromides led to only moderate yields (20 to 45 % for 4-bromoanisole and 4-bromobenzene).[143b] Nevertheless, the heterogeneous system $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ was shown to be relatively stable towards leaching—the filtrate resulting from a hot filtration was found to be almost inactive—and recyclable over five runs with constant high yields of the product; it is worth noting, however, that the initial activity of the fresh catalyst was 25-times higher than that observed in the other cycles (125 versus 5 $mmol\,min^{-1}\,g_{cat}^{-1}$).

The pore size of these microporous modified-zeolite catalysts was suggested by Dufaud, Djakovitch, and co-workers to possibly be too restricted for synthetic applications with molecules of larger size, such as those encountered in the pharmaceutical and agrochemical industries.[143c] Therefore, they prepared heterogeneous catalytic materials by immobilizing $[PdCl_2\{PPh_2(CH_2)_2SiCH_3(OCH_2CH_3)_2\}_2]$ in mesoporous SBA-15 silica (pore size 5–7 nm). The authors verified that the pore size of the supports was of crucial importance to the success of the heterogeneous catalytic alkynylation of hindered aryl halides, such as 2-bromonaphthalene and 9-bromoanthracene. The Pd/SBA-15 catalyst was found to be more active than the zeolite-supported $[Pd(NH_3)_4]^{2+}/(NH_4)Y$, which the authors ascribed to the larger aperture of the channels in the mesoporous material.[143c] The diffusion of chemicals towards and away from the active centers would be consequently substantially improved by tenfold-larger pores.

3.2.4. *Supported Nanoparticles as Catalysts*

In the field of recyclable heterogeneous systems for organic reactions, the heterogeneous catalysts based on immobilized molecular palladium species (see Section 3.2.3) have to compete with other heterogeneous species that are somewhat related to the soluble colloids and "giant clusters" and generally called "supported nanoparticles". The size and dispersion of these nanosized species determine their activity: a higher specific area (and a better activity) is expected from particles of smaller sizes.

While well-characterized supported nanoparticles for catalysis remains relatively scarce, Choudary et al. have reported that palladium nanoparticles supported on basic layered double hydroxide (LDH) are useful for copper-free alkynylations and other cross-coupling reactions (Scheme 60).[145]

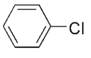
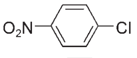
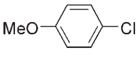


Scheme 60. Formation of palladium(0) nanoparticles supported on layered double hydroxide.

The average size of the palladium nanoparticles in fresh LDH-Pd^0 and in the catalyst used were measured by transmission electron microscopy to be 4–6 nm. The alkynylation of three aryl chlorides with phenylacetylene was conducted in THF/water (1:1) at 80°C in the presence of 1 mol% Pd supported on LDH (Table 18).

Fairly good to excellent yields were obtained for the activation of the demanding, unactivated substrates chlorobenzene and 4-chloroanisole. The unusual activity of this promising system was attributed to the influence of the basic support, which could facilitate the oxidative addition of aryl chlorides to palladium(0) particles. The LDH-Pd catalyst was reused five times and showed consistent activity and selectivity in the coupling of phenylacetylene with chlorobenzene (95%, 95%, 93%, 92%, 92%). After filtration, subsequent tests on the filtrate have shown that the palladium bound to LDH is the only active species, although 1 to 4.5% of the total palladium leached into the solution. While studies on a wider set of chloride substrates would be of great interest, the idea of electronically active supports is also an interesting concept that could be developed for heterogeneous alkynylation reactions.

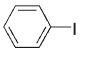
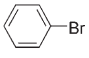
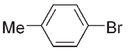
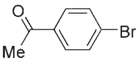
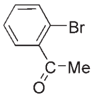
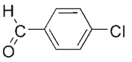
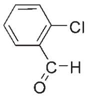
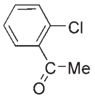
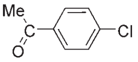
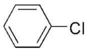
Table 18: Alkynylation of aryl chlorides with phenylacetylene using 1 mol% Pd-LDH.

Aryl chloride	*t* [h]	Yield [%]
	30	95
	48	82
	48	60

The method reported by Choudary et al., which consists of palladium–anion exchange followed by reduction with hydrazine hydrate, has been used by Hell and co-workers for MgLa mixed oxide with $Na_2[PdCl_4]$.[146] The resulting Pd/MgLa mixed oxide with a palladium content of 0.73 mmol g^{-1} was employed in the alkynylation of a range of aryl halides with various terminal alkynes (Table 19).

Consistent with the results of Choudary et al.,[145] the copper-free coupling of aryl iodides and bromides (either activated or not) was achieved in 60–90% yield. The system allowed activated chlorides, including *ortho*-substituted substrates, to be coupled. The Pd/MgLa mixed oxide gave only a poor yield (22%) of the coupling product from chloroben-

Table 19: Copper-free alkynylation of aryl halides catalyzed by Pd/MgLa.[a]

Aryl halide	H—≡—R^2 R^2	Yield [%][b]
	Ph *n*-C_5H_{11} CH_2OH	90 81 70
	Ph	64
	Ph	60
	Ph	86
	Ph	84
	Ph	68
	Ph	67
	Ph	63
	Ph	55
	Ph	22

[a] Conditions: 1.5 mol% Pd catalyst, 1.2 equiv NEt_3, DMF, 80°C, 10–24 h. [b] Yield of isolated product.

zene and phenylacetylene compared to the LDH-Pd^0 used by Choudary et al. This finding could possibly be due to a weaker basicity of the support; however, more detailed characterizations need to be obtained for certainty.

Ion exchange followed by hydrazine reduction was applied to support palladium(0) particles in a glass/polymer composite as a fixed bed for a continuous-flow reactor. The system was successfully tested for the copper-free alkynylation of the simple substrate 4-iodoacetophenone with phenylacetylene.[147]

A variety of supported-catalytic materials have been proposed for use in the heterogeneously catalyzed Sonogashira–Heck alkynylation. Besides the general recyclability observed (sometimes deactivation occurred, however!), a significant number of these systems seem to play the role of the reservoir (or source) of soluble molecularly active palladium species. These systems generally require the addition of a ligand to activate substrates more demanding than aryl iodides or activated bromides. These results underline the necessary effort needed to determine (or at least evaluate) the true origin of the catalytic effect (for example, by testing the reactivity of the filtrate, measurements of palladium leaching and the kinetics of the systems). Conversely, well-characterized, efficient palladium-supported catalytic materials on basic hydroxide supports[145] or mesoporous materials[143c] have shown interesting activity towards the alkynylation of chloroarenes and sterically hindered aryl bromides. Therefore, many more heterogeneous catalytic systems are expected in the future, especially some incorporated into continuous-flow procedures.

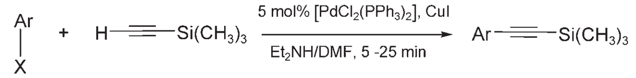
4. Miscellaneous and Connected Studies

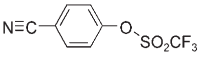
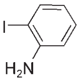
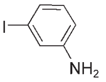
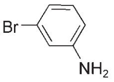
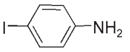
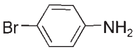
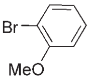
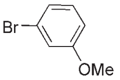
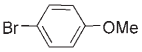
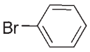
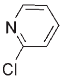
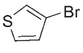
4.1. Microwave-Enhanced Catalysis

Microwave irradiation of organic reactions has gained in popularity in the last decade after it was found to significantly accelerate a wide number of transformations and improve turnover frequencies. Kabalka et al. were the first to report general conditions for the enhancement of the Sonogashira cross-coupling reaction by microwave irradiation.[148] Under solventless conditions and with efficient mixing, a variety of aryl, heteroaromatic, and vinyl iodides were efficiently coupled to terminal alkynes in the presence of palladium powder (36 mol %), CuI (35 mol %), PPh$_3$ (65 mol %), and 1 g of KF-doped alumina in a 1000-watt microwave oven for 2.5 minutes. The reaction did not occur in the absence of palladium, CuI, or triphenylphosphane; furthermore aryl bromides and chlorides did not react in this system. The authors reported that the solventless conditions and the alumina were absolutely required as a temperature moderator to avoid any uncontrollable reactions of liquids in the presence of metallic palladium.

A homogeneous version of the Sonogashira reaction enhanced by microwave heating was later developed by Erdély and Gogoll, in which they used secure special heavy-walled process vials.[149] The coupling of a range of aryl and heteroaryl halides as well as triflates with trimethylsilylacetylene was carried out in good to excellent yields (Table 20) in 5 to 25 minutes in HNEt$_2$/DMF (3:1) in the presence of 5 mol % [PdCl$_2$(PPh$_3$)$_2$] and CuI (with the less reactive halides 20 mol % of PPh$_3$ was added to stabilize the palladium catalyst).

Table 20: Sonogashira alkynylation under microwave irradiation in closed vessels (3–4 bars).



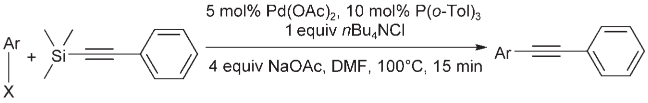
Aryl substrate	Yield [%][a]	*t* [min]
	99	5
	92	5
	99	5
	83	25
	98	5
	87	25
	87	25
	89	25
	90	25
	87	25
	97	25
	81	25

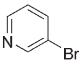
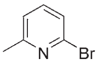
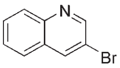
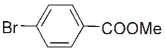
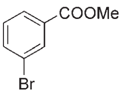
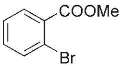
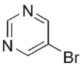
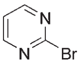
[a] Yield of coupling product.

A comparison with reported data showed that the reactions are about 20- to 100-fold faster under these microwave conditions.[149] The coupling in high yield of deactivated halides such as bromoanisole, including *ortho*-substituted substrates, with a heteroaryl chloride is a noticeable achievement. The trimethylsilyl group allows further functionalizations of the enynes, but it is certainly of interest to test this system with other terminal alkynes. The authors have subsequently reported a solid-phase microwave-promoted version of their alkynylation reaction of aryl halides attached to a polystyrene resin.[150]

Sørensen and Pombo-Villar have described a copper-free method for the direct coupling of phenyl(trimethylsilyl)acetylene to aryl and heteroaryl halides to yield diaryl acetylenes under microwave irradiation (Table 21).[151] The yields obtained in the absence of a copper promoter depended on

Table 21: Heck alkynylation of silylated alkynes under microwave irradiation (450 watt)



Aryl substrates	Yield [%] (as in the scheme)	Yield [%] (without phosphane)[a]
	71	61
	50[b]	40
	55	57
	7	7
	84	60
	85	60
	84	60
	44	37

[a] Yield of isolated product. [b] 600 W, 2.5 min.

the substrates. A phosphane-free version has also been explored.

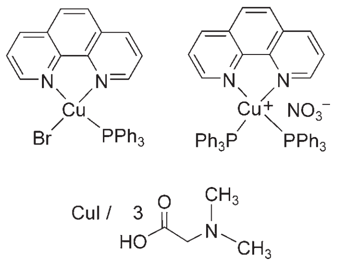
Microwave irradiation has also been applied to alkynylations with nickel powder,[152] or in the absence of any transition metal (see Section 4.2).[152] The impressive increase in the reaction rate, which is one of the foundations of catalysis, makes microwave-promoted methods very promising for future development, particularly if conditions compatible with high-efficiency catalytic auxiliaries are found.[33]

4.2. Alkynylations Catalyzed by Other Metals and Metal-Free Versions

The high cost of palladium sources has resulted in a number of studies aimed at finding a cheaper metal for the catalytic alkynylations, from which a limited number were successful. The metals mainly used to replace palladium were copper, nickel, and ruthenium. Metal-free alkynylations have also been reported.

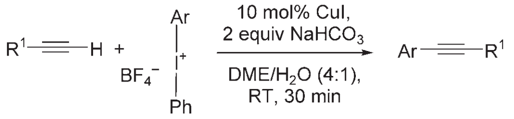
Miura and co-workers reported early on that under certain conditions (high temperature, in DMF) the reaction of various aryl and vinyl iodides with terminal alkynes proceeds efficiently in the exclusive presence of catalytic amounts of copper iodide with two equivalents of PPh_3 and a base.[154,155] A reaction mechanism involving initial formation of copper–acetylide species coordinated by PPh_3, which is essential to the reaction, was proposed.[155]

More recently, some other catalytic systems based on copper were developed (Scheme 61) which incorporated a nitrogen-containing ligand instead of triphenylphosphane;[156,157] the amount of metal (10 mol%) and the temperatures required for the coupling reactions did not make these systems superior to the catalyst prepared by Miura and co-workers for the alkynylation of aryl iodides.[155] However, a system based on CuI together with three equivalents of *N,N*-dimethylglycine (Scheme 61) allowed the coupling of a range of aryl bromides (including electron-rich bromides) in good to excellent yields.[157]



Scheme 61. Copper-based catalytic systems for the alkynylation of aryl and vinyl halides.

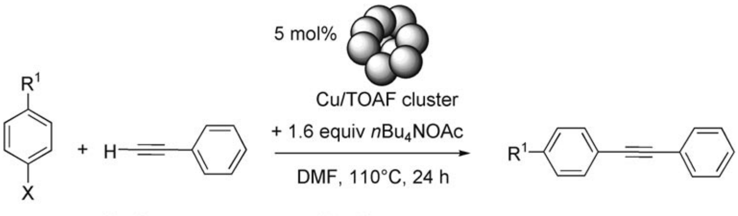
Kang et al. reported that the copper-catalyzed production of enynes from terminal alkynes and hypervalent aryl iodonium salts at room temperature occurred within 30 minutes (Scheme 62).[158] These unusual coupling partners allowed a wide variety of alkynylations to be achieved under mild conditions; nevertheless in terms of atom economy, the formation of iodide-containing co-products need to be considered.



Scheme 62. Copper-catalyzed coupling of iodonium salts with terminal alkynes. DME = 1,2-dimethoxyethane.

Copper nanoclusters stabilized by tetraoctylammonium formate (TOAF) have been successfully employed for the cross-coupling of phenylacetylene with aryl iodides and activated aryl bromides (Scheme 63).[159] The deactivated bromides were more difficult to activate, with the conversion remaining low even in the presence of 10 mol % of the copper cluster. The clusters could be reused three times when another equivalent of the reactants and base were added.

Cross-coupling alkynylation reactions conducted with nickel species as catalysts are surprisingly scarce.[106,152,160] Based on their nickel-catalyzed reaction of copper acetylides with 4-nitroiodobenzene, Beletskaya et al. were the first to disclose general conditions for the coupling of aryl iodides with terminal acetylenes in the presence of 5 mol % $[NiCl_2(PPh_3)_2]$, 10 mol% CuI, and 2 equivalents of K_2CO_3 (Scheme 64).[106]



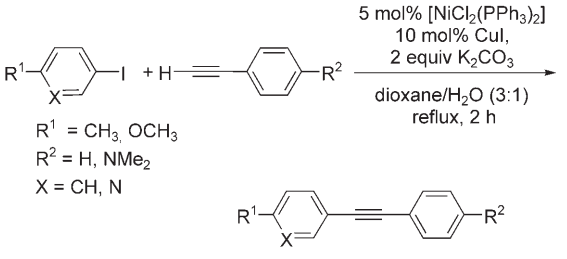
X = I

R1	Yield
H	82%
CH_3	84%
CF_3	99%
NO_2	94%
OCH_3	99%
OH	99%

X = Br

R1	Yield
CN	91%
NO_2	99%
CF_3	53%
CH_3	20%
OCH_3	16%

Scheme 63. Coupling of aryl iodides and bromides with phenylacetylene catalyzed by copper nanoclusters.



Scheme 64. Nickel-promoted Sonogashira cross-coupling.

The authors indicate that the reactions can be carried out using CuI only; however the coupling is less efficient in the absence of [NiCl$_2$(PPh$_3$)$_2$]. In contrast, the addition of PPh$_3$ retarded the reaction under the conditions studied.

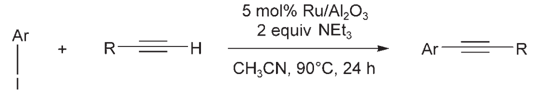
Wang et al. have reported a Sonogashira coupling catalyzed by ultrafine nickel powder: aryl and alkenyl iodides were coupled to acetylenes in good to excellent yields in the presence of 10 mol% of nickel powder (100 nm diameter), 5 mol% CuI, and 30 mol% PPh$_3$ in 2-propanol/KOH at 80 °C.[160] Modified conditions (DMF/K$_2$CO$_3$) were employed for the coupling of the activated substrates 2- and 3-bromopyridine as well as 4-cyanobromobenzene at 120 °C. Recyclability is claimed, unfortunately the nature of the active species is not disclosed in the report; the experiment conditions possibly indicate that the powder acts as a source of nickel atoms or colloids stabilized by the large excess of triphenylphosphane.

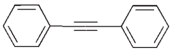
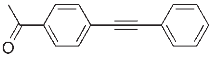
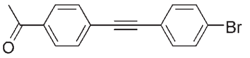
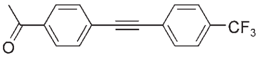
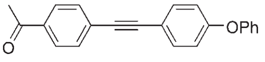
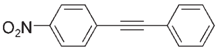
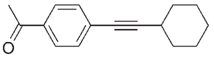
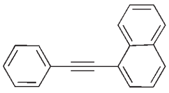
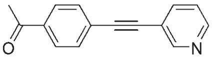
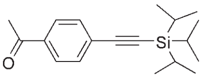
Chang and co-workers have recently found that ruthenium might be a potential catalyst for Heck alkynylations.[161] Ruthenium supported on alumina allowed the coupling of aryl iodides to terminal alkynes to proceed in good yield in the absence of a copper promoter (Table 22). Alumina was a more effective support than MgO, TiO$_2$, activated carbon, or the smectite clay montmorillonite K10. The activity remained, however, moderate and mostly activated aryl iodides were used in experiments with long reaction times (24 h) and rather high metal loadings (5 mol%).

The research groups of Leadbeater and Van der Eycken independently reported that Sonogashira–Heck alkynylations can be effected in the absence of any transition-metal compound.[153] Both methods were carried out in water with microwave irradiation, and the authors verified that transition-metal-free alkynylations did not occur under conventional heating in an oil bath above 170 °C. Tables 23 and 24 summarize the catalytic conditions and the results obtained. The microwave irradiation allows aryl iodides to be efficiently coupled to phenylacetylene in a mixture of water/polyethylene glycol and in the presence of two equivalents of NaOH, while aryl bromides were found to be more difficult substrates (Table 23). The cross-coupling reactions employing aryl iodides and the aliphatic terminal alkyne 1-hexyne were also found to be poor (> 20%).

The experimental conditions proposed by Van der Eycken et al. were slightly more harsh, with higher temperatures and longer reaction times needed, as well as the addition of the phase-transfer agent (TBAB, tetrabutylammonium bromide) and a significant amount of sodium carbonate (Table 24). Their conditions allowed the coupling of activated bromides and heteroaryl substrates, while some other iodides and bromides were unexpectedly troublesome. However, practical application of these metal-free methods remains rather limited because of: 1) the necessary use of a microwave apparatus and 2) the difficulty in anticipating which substrate will react or not (see the inconsistency in and between Tables 23 and 24). Thus, mechanistic aspects need to be investigated to clarify this

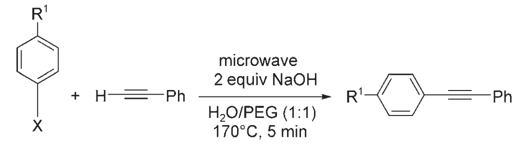
Table 22: Cross-coupling reactions catalyzed by Ru/Al$_2$O$_3$.

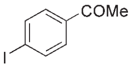
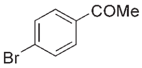
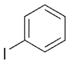
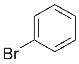
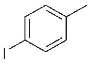
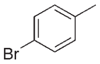
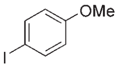
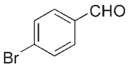


Product	Yield [%]
	85
	85
	79
	87
	71
	86
	60
	66
	97
	91

[a] Yield of isolated coupling product.

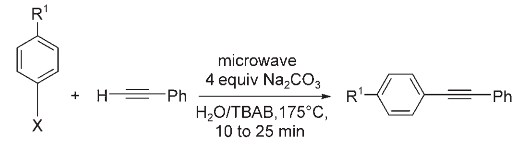
Table 23: Transition-metal-free alkynylations of aryl halides in water under microwave irradiation.[153a]

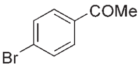
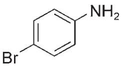
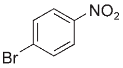
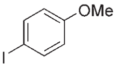
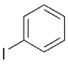
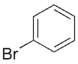
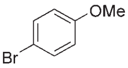
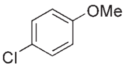
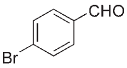
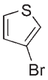
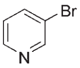
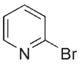


Aryl halide	Yield [%][a]
	91
	67
	83
	41
	92
	9
	43
	0

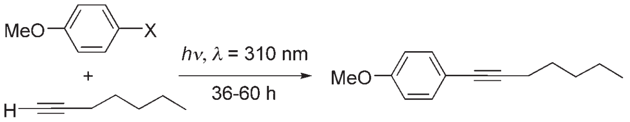
[a] Yield of isolated product.

Table 24: Transition-metal-free alkynylations of aryl halides in water under microwave irradiation.[153b]



Aryl halide	Yield [%][a]
	85
	66
	52
	78
	0
	0
	70
	0
	0
	84
	83
	0

[a] Yield of isolated product.



X	Yield	ArX conv.
Cl	62%	100%
F	60%	65%
OMes	73%	75%
OTf	83%	80%
OPO_3Et_2	90%	80%

Scheme 65. Transition-metal-free photoinduced synthesis of enynes (yields based on converted ArX). Mes = mesityl, Tf = triflate.

problem. Furthermore, the existence of a true "microwave effect" which is different from a conventional thermal activation might be established and correlated to the possible noncatalytic reaction pathways.[153c]

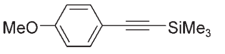
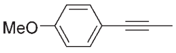
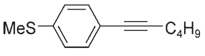
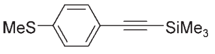
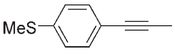
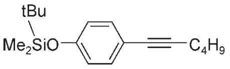
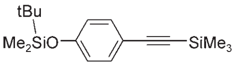
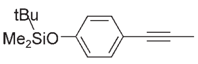
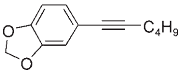
A very innovative approach has been reported by Protti, Fagnoni, and Albini for the metal-free alkynylation of aryl precursors.[162] They studied the photolysis of various precursors of the 4-methoxyphenyl cation (the corresponding aryl chloride, fluoride, mesylate, triflate, and diethylphosphate) in the presence of ten equivalents of terminal alkynes and an equimolar amount of NEt_3 in trifluoroethanol (Scheme 65). The conversion of the aryl precursors occurred in 65 to 100 %, and the yields of the isolated enynes were between 60 and 90 %. These are the first examples of an alkynylation reaction using an aryl fluoride, aryl mesylate, or aryl phosphate.

The use of electron-rich aryl chlorides under transition-metal-free photolysis allowed the enynes depicted in Table 25 to be produced in fairly good yields. This metal-free protocol proceeded via a phenyl cation formed by photoheterolysis of an aryl halide (or pseudohalide) and allowed aryl alkynes to be obtained in reasonably good yields for a reaction conducted at room temperature.[162] The use of trimethylsilylpropyne to yield silylated enynes (Table 25) is an interesting way to obtain more-sensitive derivatives that require protection, and offers an alternative reaction to the handling of some low-boiling alkynes.

Finally, it is worth noting that silver oxide[163] and indium tribromide[164] have been used as the stoichiometric reagent and catalytic promoter, respectively, in the copper-free palladium-catalyzed alkynylation of aryl iodides.

To date the methodologies aimed at substituting palladium for another metal (or even at eliminating transition metals) in Sonogashira–Heck cross-couplings are less efficient than the leading procedures in which palladium catalytic

Table 25: Photochemical synthesis of enynes from aryl chlorides.

Coupling product	ArCl conversion [%]	Yield [%][a]
	100	71
	100	51
	90	55
	80	58
	100	44
	100	51
	100	64
	100	71
	100	52

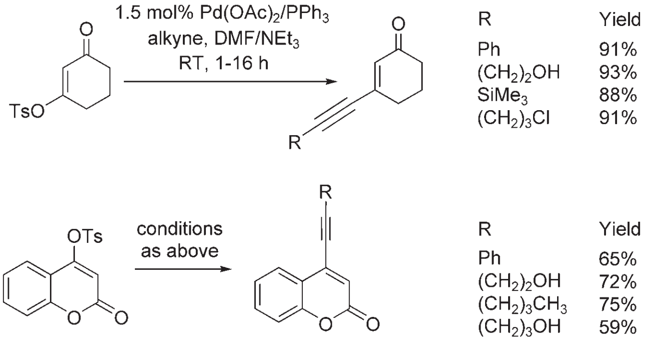
[a] Yield of isolated product, based on the conversion.

systems are employed (especially with powerful auxiliary ligands), but they still remain of substantial interest as seminal studies. Further studies remain to be done on this topic, especially regarding copper complexes stabilized by nitrogen donors and the development of nickel-based catalytic systems.

4.3. Unusual Coupling Partners

Since the discovery of the Sonogashira–Heck alkynylation in the 1970s its scope has been extended far beyond the use of iodides, bromides, chlorides, and terminal acetylenes as coupling partners. Table 26 summarizes the main unusual coupling partners reported to date: 1) aryl and vinyl substrates bearing leaving groups other than halides, 2) unusual aryl halides, 3) alkyl halides, and 4) unusual alkynes. The large number of polyfunctionalized organic molecules used as building blocks in total syntheses are not reviewed,[7] as in most cases a precise target was pursued and thus they have generally not been studied on a large array of coupling partners.

Pseudohalides such as aryl sulfonates were tested early on as an alternative to halobenzenes for the copper-free Heck alkynylation (Table 26, entry 1). In 1986 Chen and Yang showed that phenyl fluoroalkanesulfonate with electron-withdrawing or electron-donating substituents on the phenyl ring are efficient coupling partners for phenylacetylene and trimethylsilylacetylene, in the presence of 3 mol% [$PdCl_2(PPh_3)_2$] in DMF/NEt_3 (5:1) at 90 °C. The coupling products were obtained in greater than 75% in 3–17 h.[165] Alami, Ferri, and Linstrumelle subsequently observed that the coupling of vinyl triflates in pyrrolidine (or piperidine) occurred within few minutes at 25 °C in the presence of 5 mol% [$Pd(PPh_3)_4$].[166] Activated vinyl tosylates bearing functional groups have been used for copper-free Heck alkynylation with a variety of aromatic and aliphatic terminal alkynes to yield conjugated enynones in fairly good to excellent yields (59–93%, Scheme 66).[167]



Scheme 66. Heck alkynylation of functionalized vinyl tosylates.

Gelman and Buchwald have shown that the copper-free coupling of aryl tosylates with terminal alkynes, such as 1-octyne and phenylacetylene, was also possible in fairly good yield (60 to 80%) in refluxing acetonitrile in the presence of 5 mol% palladium and an electron-rich *ortho*-biphenylmonophosphane and 4.5 equivalents of Cs_2CO_3; slow addition of the alkynes was necessary to avoid oligomerization of these reactants.[32] Vogel and Dubbaka have disclosed the usefulness of arene sulfonyl chlorides as coupling partners to alkynes in Sonogashira alkynylation by employing 3 mol% [$Pd_2(dba)_3$], 10 mol% P*t*Bu_3, 15 mol% CuI, and 2.5 equivalents of K_2CO_3 as the catalytic system in boiling THF; it is noteworthy that the competing alkyne homocoupling was also reduced by the slow addition of an excess of alkyne substrate.[168]

The efficiency of the Heck reaction with unreactive aryl halides in the presence of phosphonium halides was expanded upon by Chang and co-workers when they reported on the usefulness of tetraarylphosphonium chlorides as arylating reagents in cross-coupling reactions.[169] $Ph_4P^+Cl^-$ was employed with a range of alkynes in Heck alkynylations (Table 26, entry 2). Aromatic and aliphatic terminal alkynes functionalized with silyl, hydroxy, and heteroaromatic groups were efficiently arylated by employing 3 equivalents of alkyne in the presence of 5 mol% $Pd(OAc)_2$ and 2 equivalents of NEt_3 in DMF at 100 °C for 12 h (Table 27).

The authors postulated that phosphonium species play a dual role: as an arylating agent and as a stabilizing ligand on the palladium complexes (explaining the apparent ligand-free efficiency of the system) upon release of phosphane from the phosphonium ions.[169]

The scope of the Sonogashira reaction has been extended by the use of unusual halide partners such as bromoquinolizium bromides (Table 26, entry 3) and chlorotetrazines (entry 4). Under standard Sonogashira conditions, moderate to high yields of aryl and heteroaryl ethynyl quinolizium cations were obtained, which gave access to enyne systems bearing cationic units.[170] Classical Sonogashira conditions also gave, in moderate to good yield, the first alkynyl

Table 26: Alkynylation reactions with unusual coupling partners.

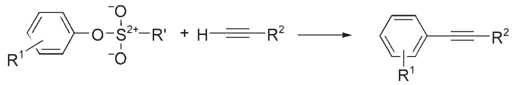
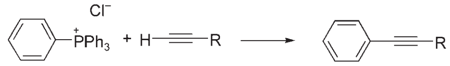
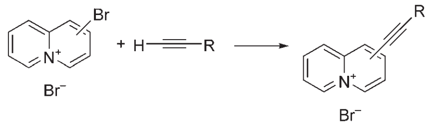
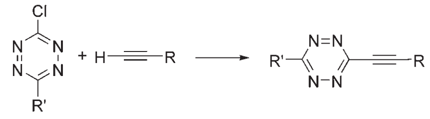
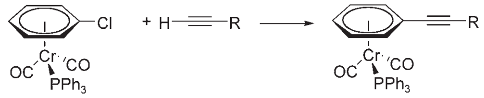
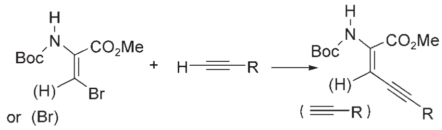
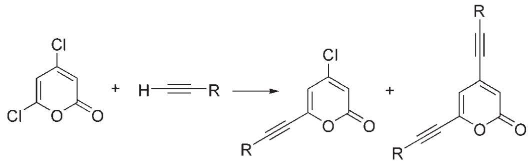
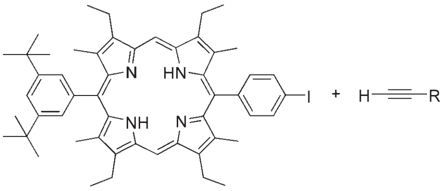
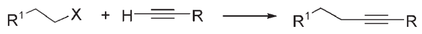
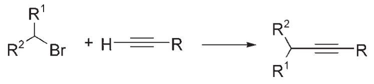
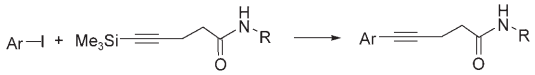
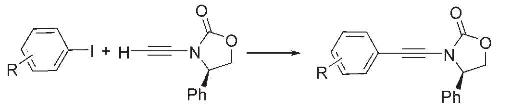
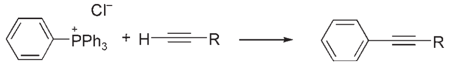
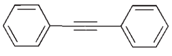
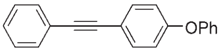
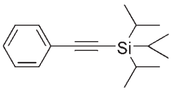
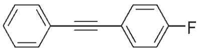
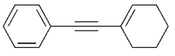
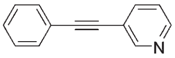
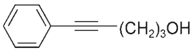
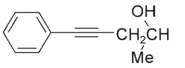
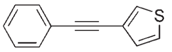
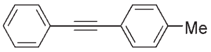
Entry	Reactions	Coupling partners (or remarks)	Ref.
unusual leaving groups on aryl and vinyl substrates			
1	 R' = -CF$_3$, -(CF$_2$)O(CF$_2$)$_2$H, -C$_6$H$_4$CH$_3$, -Cl	leaving groups are triflates (fluoroalkanesulfonates), tosylates, or arenesulfonyl chlorides	[32, 165–168]
2		leaving group is triphenylphosphonium chloride	[169]
unusual aryl halides			
3		bromoquinolizium bromides	[170]
4	 R' = morpholinyl, pyrrolidinyl, -NEt$_2$	chlorotetrazines	[171]
5		chlorobenzene–chromium complex	[172]
6		dehydroamino acid derivatives	[173]
7		dichloropyrone	[174]
8		porphyrins	[38]
alkyl halides			
9		primary alkyl bromides and iodides	[47]
10		secondary alkyl bromides	[48]
unusual alkynes			
11	$\mathrm{Ar{-}Br} + \mathrm{KF_3B{\equiv}R} \longrightarrow \mathrm{Ar{\equiv}R}$ R = -nBu, -Ph, -TMS, -nC$_8$H$_{17}$, -(CH$_2$)$_2$Ph,-(CH$_2$)$_3$Cl	trifluoroborates as leaving groups (Suzuki coupling[175b])	[175]
12	$\mathrm{Ar{-}Br} + 1/4\ \mathrm{NaAl}(\equiv\mathrm{R})_4 \longrightarrow \mathrm{Ar{\equiv}R}$ Ar = aryl, heteroaryl	tetraalkynyl aluminates	[176]
13		silylalkynylamides	[163b]
14		ynamide	[177]

Table 27: Arylation of terminal alkynes with $PPh_4^+Cl^-$.



Coupling product	Yield [%][a]
	99
	99
	99
	86
	77
	77
	64
	63
	62
	62

[a] Yield of isolated product.

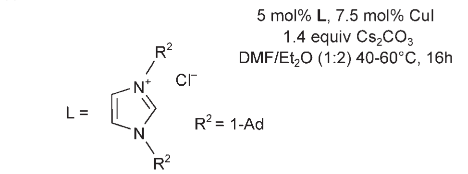
tetrazines, compounds which are potentially useful in crop protection and pyrotechnics.[171]

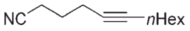
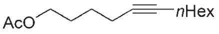
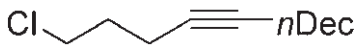
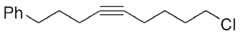
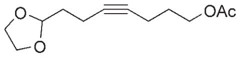
The complexation of chloroarenes activate the C(arene)–Cl bond for further reaction. Based on this idea, Ansorge and Müller successfully coupled propargyl alcohols and other terminal alkynes to a chlorobenzene–chromiumcarbonyl complex (Table 26, entry 5) under standard Sonogashira conditions.[172]

Other nontraditional bromides and chlorides substrates have been studied as coupling partners for acetylenes under the same conditions (Table 26, entries 6 and 7); even dialkynylation reactions with dibromodehydroalanine and dichloropyrone derivatives were possible.[173,174] The solubility and stability problems necessitated the use of notably modified conditions for the necessarily copper-free alkynylation of the arylic iodide moiety of porphyrins (Table 26, entry 8: 15 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 1.5 equiv $AsPh_3$ as the ligand in $NEt_3/CH_2Cl_2/MeOH$ as the basic solvent at 40 °C for 1 h).[38]

Another challenging issue recently addressed by Fu and Eckhardt as well as Glorius and co-workers is the extension of Sonogashira cross-coupling to alkyl halides (Table 26, entries 9 and 10).[47,48] The main complication encountered in the cross-coupling reactions of alkyl electrophiles bearing a β-C(sp^3)-H group is the facility for the intermediate resulting from the oxidative addition of alkyl-X to the palladium center to undergo β-hydride elimination instead of the expected palladium-mediated coupling to the alkyne. The systems proposed for the alkynylation of a large variety of unactivated primary alkyl halides,[47] and secondary alkyl bromides,[48] were based on palladium–carbene species (Tables 28 and 29, respectively).

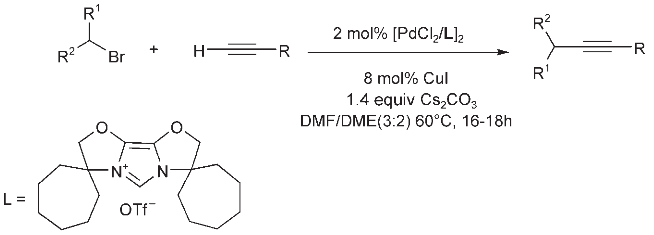
Table 28: Coupling of primary alkyl bromides to terminal alkynes.

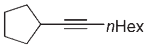
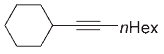
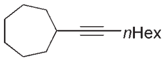
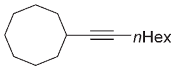
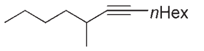
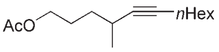
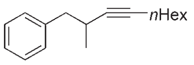


Coupling product	Yield [%][a]
	79
	71
	70
	59
	50
	74
	58

[a] Yield of isolated product.

Table 29: Coupling of secondary alkyl bromides to terminal alkynes.



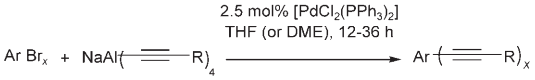
Coupling product	Yield [%][a]
	65
	71
	76
	54
	77
	63
	39

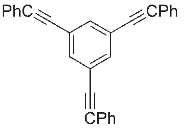
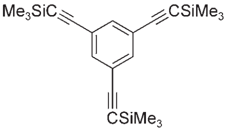
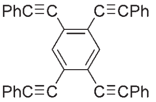
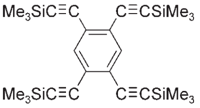
[a] Yield of isolated product.

Moderate to good yields of long-chain internal alkynes were obtained under relatively mild conditions. These studies open up the way to improve the catalytic conditions for these new reactions, and add to the list of interesting applications of imidazolium-based carbene ligands.

Modifications of terminal alkynes produced another category of innovative coupling partners for Sonogashira–Heck alkynylation reactions. The research group of Molander proposed alkynyl trifluoroborates as efficient coupling partners for functionalized aryl bromides, triflates, and heteroaryl chlorides (Table 26, entry 11).[175a] The alkynyl cross-coupling reactions were effected by employing 9 mol% $[PdCl_2dppf]\cdot CH_2Cl_2$ (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) in refluxing THF or THF/water, in the presence of 3 equivalents of Cs_2CO_3 as the base. Molander and co-workers disclosed that tetraalkynyl aluminates (Table 26, entry 12) are also suitable candidates for coupling with aryl and heteroaryl bromides, as well as with polybromoarenes (Table 30). To the best of our knowledge these specific substrates have only rarely been explored in a systematic manner.[176] All four alkynyl moieties of the reagent can take part in the coupling process, and the reported reactions are high yielding and selective, thus making these methods of high interest for the synthesis of polyalkynes.

Table 30: Synthesis of polyalkynes from the coupling of polybromoarenes with tetraalkynylaluminates.



Coupling product	Yield [%][a]
	90
	88
	92
	71

[a] Yield of isolated product.

Terminal alkynes incorporating aliphatic and cyclic amide functions have been coupled to aryl iodides: Nagasaka and co-workers used palladium-catalyzed reactions with silylalkynyl amides promoted by silver salts (Table 26, entry 13), with the loss of the trimethylsilyl group being at the origin of the consecutive arylation.[163b] Hsung and co-workers have described the coupling of alkynes bearing terminal cyclic amide groups with hindered or electronically deactivated aryl iodides under classical Sonogashira conditions (Table 26, entry 14): 10 mol% $[Pd(PPh_3)_4]$, 7 mol% CuI in $HNiPr_2$/toluene (2:1) at 65 °C.[177] Bromobenzene was unreactive under these conditions, while iodobenzene gave the coupling product in 93 % yield.

Mori and co-workers have shown that (aryl alkynyl)silanes such as (phenylethynyl)trimethylsilane react with aryl iodides, bromides, chlorides, and triflates under adapted Sonogashira conditions (5 mol% $[Pd(PPh_3)_4]$, 10 mol% CuCl in DMF at 80 °C) through loss of the silyl group;[178] the effect of substituents on the silicon atom, on the aryl alkynyl group, and on the halide or pseudohalide have been thoroughly examined. The transmetalation of the aryl alkynyl group from silicon to copper was proposed as a key step.

The various modifications in coupling partners explored for the Sonogashira–Heck–Cassar alkynylation demonstrate that this elegant process is still widely regarded as one of the most straightforward and powerful catalytic process to produce functionalized alkyne building blocks. Among the potential developments expected in this dynamic field are the more general coupling of alkyl halides as well as access to other enynes bearing ionic units.

5. Summary and Outlook

As we have attempted to demonstrate herein, an impressive diversity of palladium-based catalytic systems inspired by "Sonogashira–Heck–Cassar" alkynylation reactions have been developed during the last few years. Advances in both the homogeneous and heterogeneous catalytic synthesis of conjugated enynes have been mainly directed towards the challenge of sustainability. In an increased awareness of resource saving, atom economy, cost-cutting, and recycling, recent studies have provided for catalyzed alkynylations: 1) powerful electron-rich monophosphanes for the activation of demanding aryl chlorides, 2) efficient multidentate ligands which allow the coupling of unactivated bromide and chloride substrates with low amounts of palladium and ligand, 3) water-soluble systems of large scope and environmental utility, 4) various catalysts that are recyclable over six cycles or more. These catalytic systems will progressively supplant the still popular original protocols disclosed in the 1970s, not only in the research laboratories but also in industrial applications.

However, a number of challenges remain. Recyclable systems still do not repeatedly activate the readily available and low-cost aryl chlorides: the well-known gap between the activity of homogeneous and heterogeneous species remains untouched. Less energy intensive protocols (at room temperature or alternative methods) still have to become more efficient. The highest turnover numbers have to be achieved under industrial conditions, particularly in view of the purity of the products.

Beyond these practical points, a large number of mechanistic questions concerning the homogeneous and heterogeneous versions of these reactions have not been addressed. Determination of the origin of the activity is an issue common to palladacycle and nanoparticle catalysts; answers could then allow further improvement in terms of mildness and the scope of the reactions. In regard to the catalytic cycles and elementary steps, it is also noteworthy that several studies involving new ligands (or catalytic systems) carried out in parallel for related cross-coupling reactions (Stille or Suzuki reactions) have highlighted the fact that the systems are generally less efficient when they are used in the Sonogashira–Heck reaction.

Finally, the quest for a perfectly mastered industrial alkynylation system that allows recycling and high TONs with a wide applicability and convenience (including demanding substrates) should stimulate further studies in this field in the coming years.

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