Cyclisations Involving Attack of Carbo- and Heteronucleophiles on Carbon-Carbon $\pi$-Bonds Activated by Organopalladium Complexes

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Dedicated to Professor Jacques Goré on the occasion of his 65th birthday with warm thanks for a fruitful collaboration over many years.

Abstract: In the late 1980’s, a new process based on an intramolecular palladium-mediated cyclisation coupled with a carbon-carbon bond forming reaction appeared in the literature. Since the first report, many novel ring systems have been synthesized using this methodology. The aim of this present review article is to summarise a number of synthetic applications of this new process developed over the last fifteen years.

1 Introduction

The cyclisation of unsaturated substrates bearing a carbo- or heteronucleophile promoted by organopalladium complexes is now well established as a powerful method for the preparation of a vast array of mono- and polycyclic systems. This annulation proceeds in a completely stereoselective trans manner since it involves an attack of the nucleophile onto the unsaturated bond from the opposite side of the activating $\sigma$-unsaturated palladium species. The latter is in most cases generated in situ from oxidative addition of the palladium(0) complex to an unsaturated halide or triflate. A reductive elimination gives the cyclisation product and regenerates the catalyst (Scheme 1). Since its discovery, in the late 80’s, numerous transformations involving alkenes, alkynes, allenes having carbon, oxygen and nitrogen nucleophiles have been reported. The purpose of this review is to summarise the work developed in this area over the past decade from this and other laboratories. This article is divided into sections relating to the nature of the ring formed during the cyclisation reaction with a special emphasis on recent synthetic applications.

2 Carbocycles

2.1 Cyclisation of Unactivated Olefins

In 1987, Goré and Balme1 described the palladium-mediated reaction of alkylidenecyclopropanes 1 bearing a stabilized carbon nucleophile with phenyl iodide that yielded the bicyclic compound 2 (Scheme 2). Although the mechanism of the cyclisation process was not clear at that time, this was certainly the first reported example of an intramolecular nucleophilic attack on an unsaturated electrophile activated by an organopalladium species, a hitherto unknown phenomenon. Indeed, unactivated olefins are inert towards attack of nucleophiles. When complexed to palladium(II) salts, it is well known that stabilized carbanions may react with these olefin palladium(II) complexes to generate $\sigma$-alkylpalladium complexes.2 In this new cyclisation reaction, an organopalladium(II) halide, not a palladium(II) salt, acts as the electrophilic partner of the cyclisation. Therefore, this reaction, which only requires catalytic quantities of the metal, results in overall difunctionalisation of the olefinic substrate.
This new cyclisation method was then applied to linear δ-ethylenic stabilized carbon nucleophiles 3, which gave rise to the expected carbocyclic derivatives 4 in good yields (Scheme 3). These studies showed the importance of the nature of the base as the reaction proceeds under mild reaction conditions when the softer potassium malonates are involved, the corresponding sodium malonates requiring elevated temperatures.3,4

Scheme 2

Geneviève Balme was born in Saint Symphorien s/s Coise, a small town situated in the hills about 30 km west of Lyon. After a first academic position as a primary school teacher (2 years in France, 3 years on the Island of Reunion) she studied chemistry at the University of Lyon and received her Ph.D. degree in the same University (Doctorat de 3ième cycle-1979; supervisors Prof. Jacques Goré and Dr. Max Malacria; Doctorat d’état-1983; supervisor Prof. Jacques Goré). In 1994, she was promoted to Directeur de Recherche at the Centre National de la Recherche Scientifique. Her main research interests focus on the development of new synthetic methods using transition metal complexes such as palladium-catalysed sequential reactions, multicomponent reactions and their application to the synthesis of natural products and biologically active compounds.

Didier Bouyssi was born in Valence, France, in 1964 and studied chemistry at the University of Lyon where he obtained his Ph.D. degree in 1992 under the guidance of Prof. Jacques Goré and Dr. Geneviève Balme for research on new palladium-mediated cyclisation processes. After a one-year period as ‘ATER’ (Attaché Temporaire d’Enseignement et de Recherche) in the same university, he was appointed by University of Lyon as a ‘Maître de Conférences’ in the group of Geneviève Balme. His current research interests cover the development of organic synthetic methods using transition metal complexes as catalytic reagents, multi-components reactions and the synthesis of natural or unnatural bioactive compounds.

Thierry Lomberget was born in 1973 in Bourg-en-Bresse, France. He received his Ph.D. degree from the University Claude Bernard of Lyon in 2002 under the supervision of Dr. G. Balme for research on palladium-catalysed cyclisation reactions of conjugated enynes. He is currently a post-doctoral fellow at the University of Geneva in the research group of Prof. E. P. Kündig, working on the desymmetrisation of arene chromium tricarbonyl complexes. His main interests are in the field of organometallic chemistry, pericyclic reactions and asymmetric synthesis.

Nuno Monteiro was born in Marinha Grande, Portugal, in 1965 and grew up in France. He studied chemistry at the University of Lyon where he obtained his Ph.D. degree in 1992 under the guidance of Prof. Jacques Goré and Dr. Geneviève Balme for research on new palladium-mediated cyclisation processes. Following a one-year period as ‘A.T.E.R.’ (Attaché Temporaire d’Enseignement et de Recherche) in the same university, he joined in the fall of 1993 the team of Prof. Varinder K. Aggarwal (University of Sheffield, U.K.) as a Marie Curie post-doctoral fellow to work on the synthesis of carbocyclic analogues of polyoxins and nikkomycins, a family of nucleoside-like antibiotics. In 1996 he returned to Lyon where he was appointed by the CNRS as a ‘Chargé de Recherches’ in the group of Geneviève Balme. His current research interests concern the use of transition metal complexes as catalytic reagents in organic synthesis, the development of diversity-oriented synthetic methods directed toward heterocycles, and the synthesis of bioactive natural products and structural analogues.
The stereochemical course of this reaction has been probed with functionalised cyclopentenes \(5\). When these substrates were treated by an aryl halide under the reaction conditions depicted in Scheme 4, single diastereoisomers \(6\) were isolated. The stereocontrol observed during the formation of the newly formed stereocenter confirms the idea that this reaction proceeds via a Wacker-type mechanism in which the organopalladium halide is an electrophilic partner in this cyclisation reaction.\(^5,6\)

By using the intramolecular version of this strategy, the stereocontrolled synthesis of the fused tricyclooctanoid \(8\) was achieved. The total synthesis of \(\pm\)-capnellene, a marine natural product, has been carried out by applying the palladium-mediated carbocyclisation to the internal vinyl iodide \(7\) as the key step. The reaction took place at room temperature in THF, in the presence of potassium hydride as base and Pd(OAc)\(_2\)/dppe as catalytic system leading to triquinane \(8\) in 70% yield which was converted into capnellene by standard methods (Scheme 5).\(^7\)

However, under the same conditions, the analogous substrate \(9a\) lacking the angular methyl group yielded the bicyclic product \(10\) predominantly. The reaction failed due to a competition between the insertion of the vinyl Pd(II) complex into the alkene (classical Heck reaction) and the expected bis-cyclisation reaction. The course of this palladium-mediated reaction was found to be strongly dependent on the nature of both the base and the halide. The triquinane \(11\) could be selectively obtained in good yield by switching to a more reactive nucleophile such as the methyl cyanoacetate and using a vinyl bromide instead of the corresponding iodide (\(9b\)) (Scheme 6).\(^8\)

While the methodology for the preparation of cyclopentane derivatives has been well established, the construction of cyclohexane homologues proved to be more difficult. For instance, dimethyl 5-hexenylmalonate showed a strong tendency to give a direct coupling reaction of the alkene with the aryl halide (classical Heck reaction). However, the cyclisation/Heck reaction balance here was also strongly affected by the nature of the nucleophilic part of the precursors \(12\).

When one or both of the malonate esters were substituted for a nitrile, exclusive formation of cyclisation products \(13\) was observed (Scheme 7).\(^9\)

This duality (Heck reaction versus cyclisation process) may be controlled to change the course of the reaction. Indeed, the same starting material \(14\) selectively gave rise to compounds resulting from a Heck process or from the pal-
ladium mediated bis-cyclisation process by simple alterations to the reaction conditions. The most effective change to be made concerned the strength of the carbonucleophile, which depended on the nature of the base (Scheme 8). A strong anionic nucleophile (KH as base) gave rise to the trans-hydrindane system 15 exclusively, while a weaker nucleophile (use of carbonate bases) afforded the Heck products 16 and 17.\(^{10}\)

This tandem cyclisation reaction was also applied to the linear substrates (E)-18a and (E)-18b and it was shown that the bulkiness of the nucleophile was the determining factor controlling the cyclisation selectivity: the 5-exo-cyclisation process leading to cyclopentane derivatives 19 was observed when the sterically encumbered malonate was involved. This was due to strong interaction between the bulky nucleophile and one of the allylic hydrogens of the linear substrate. endo-Cyclisation leading to trans-octahydrophenanthrene 20 was the only reaction observed with a less sterically demanding nucleophile (Scheme 9).\(^{11}\)

Moreover, the remarkable influence of the double bond geometry of the starting material on the stereochemistry of the product was also demonstrated. The syntheses of these tricyclic compounds occurred with concomitant stereocontrol of the two newly formed adjacent carbon centers since these cyclisations proceed in a completely stereoselective trans manner. The reaction was then stereospecific, the stereochemistry being defined by that of the double bond in the linear cyclisation precursor. The relative configuration of the indane substrates was hereby controlled (Scheme 10).\(^{12}\)

### 2.2 Cyclisation of Unactivated Alkynes

This new cyclopentannulation method was applied to the acetylenic homologues 21 and it must be emphasised that stereodefined exocyclic double bonds were formed even in the case of substituted alkynes (R\(^1\) ≠ H), the carbonucleophile and the organopalladium species adding in a trans fashion across the unsaturated bond. Unfortunately, for acetylenic compounds, the palladium-catalysed tandem cyclisation/coupling reaction remains limited to the formation of five membered rings 22. By using substrates 23 with one carbon more in the side chain, some severe limitations were observed: the palladium mediated reaction led to the formation of the desired stereodefined arylidene cyclohexane compound 24 accompanied by the linear coupling product 25 resulting of the classical Sonogashira type reaction (Scheme 11).\(^{13-15}\)

Recently, this strategy was extended to the formation of stereodefined functionalised 1,3-bis-exocyclic dienes by cyclisation of conjugated enynes having a stabilised carbon nucleophile. The moderate yields obtained with substrates of type 26 are presumably due to steric interaction of the two adjacent methylene groups and the geminal diesters in the rigid coplanar system 27. It is worth noting that the reaction performed in the presence of aryl iodides gave rise to the formation of two cyclisation products, the expected product 27 and the dienic substrate 28 which resulted from a decarboxylative reaction of 27 (Scheme 12).
However, higher homologues of type 29 gave rise to the formation of stereodefined functionalised 1,3-bis-exocyclic dienes 30 or conjugated trienes 31 in good yields depending on the nature of the coupling partner (aryl iodide; vinyl triflate or bromide). When heated in refluxing toluene the trienes underwent electrocyclic rearrangement to give cyclohexadienes as demonstrated on hexatriene 31b. A one-pot cyclisation/coupling/electrocyclisation transformation was devised so as to produce the bicyclic system 32 (60% yield) without isolation of intermediate 31b (Scheme 13).

A practical and efficient strategy for the synthesis of either cis- or trans-hexahydro-1H-benz[f]indene 35 and 37 was developed starting from the common acetylenic precursor 33 (Scheme 14). This compound was involved in a palladium-catalysed cascade bis-cyclisation process leading to the unsaturated tricyclic substrate 34. The optimal conditions for this cyclisation were found to be Pd(OAc)$_2$ (0.05 equiv), dppe (0.05 equiv), and potassium hydride (1.1 equiv) in 1-methyl-2-pyrrolidinone at 55 °C. Catalytic hydrogenation of 34 over Pd/C at atmospheric pressure occurred with complete selectivity from the least hindered face to afford the cis-hexahydro-1H-benz[f]indene 35 in essentially quantitative yield. By changing the order of the two preceding steps, only the trans-hexahydro-1H-benz[f]indene structure 37 was obtained. Indeed, the selective hydrogenation of the acetylenic substrate 33 over Lindlar’s catalyst gave 36, which was subjected to the palladium-mediated cyclisation reaction (same conditions as above but using THF in place of NMP). The stereochemical control of this reaction may be explained if it were to pass through a transition state in which the benzylic substituent lies in a pseudoequatorial orientation.$^{17}$

### Scheme 11

\[
\begin{align*}
R & = \text{Ar}\text{yl} \\
Z & = \text{CO}_2\text{Me}, \text{CN}, \text{SO}_2\text{Ph} \\
Z' & = \text{CO}_2\text{Me}, \text{CN} \\
R & = \text{aryl}, \text{vinyl}, \text{alkynyl} \\
R_1 & = \text{H, Me, } (\text{CH}_2)_4\text{OThP} \\
\end{align*}
\]

### Scheme 12

\[
\begin{align*}
\text{Pd(dba)$_2$, dppe, RX} \\
\text{t-BuOK, THF, r.t.} \\
\text{Ar} \\
\text{Z} = \text{CO}_2\text{Me}, \text{CN, SO}_2\text{Ph} \\
\text{Z} = \text{CO}_2\text{Me, CN} \\
\text{RX} = \text{aryl, vinyl} \\
\end{align*}
\]

### Scheme 13

\[
\begin{align*}
\text{Pd(dba)$_2$, dppe, RX} \\
\text{t-BuOK, THF, r.t.} \\
\text{Ar} \\
\text{Z} = \text{CO}_2\text{Me, CN, SO}_2\text{Ph} \\
\text{Z} = \text{CO}_2\text{Me, CN} \\
\text{RX} = \text{aryl, vinyl} \\
\end{align*}
\]

### Scheme 14

\[
\begin{align*}
Pd(dppe) \\
\text{KH, NMP} \\
\text{H}_2, \text{Lindlar’s catalyst} \\
\end{align*}
\]
have been synthesized by attack of oxygen\textsuperscript{18} or nitrogen\textsuperscript{19} nucleophiles on alkenes coordinated by palladium salts such as palladium chloride or palladium acetate (Scheme 15).

In marked contrast, various electrophilic organopalladium complexes are able to trigger the intramolecular nucleophilic attack of a heteronucleophile on alkynes through coordination, and a variety of heterocyclic systems have been elaborated using this strategy. However, a competitive reaction may arise when terminal alkynes are involved, i.e. the direct coupling reaction of the alkyne with the unsaturated halide or triflate (Scheme 16).

### 3.1 Oxygen Heterocycles

The first example of a cyclisation of an acetylenic heteronucleophile catalysed by organopalladium species was developed by Tsuda and Seagusa in 1988 on allyl 4-pentynoates \textsuperscript{38} (Scheme 17).\textsuperscript{20} Oxidative addition of the palladium(0) complex to \textsuperscript{38} generates a $\pi$-allyl palladium cation and an alkyanoate. This catalytic species activates the carbon-carbon triple bond towards the intramolecular nucleophilic attack of the carboxylate to produce, after reductive elimination, the substituted unsaturated lactones \textsuperscript{39} regio- and stereoselectively. A related system, involving lithium alkynoates \textsuperscript{40} and allylic acetates \textsuperscript{41}, was also studied by the same group.

The preparation of exocyclic enol lactones \textsuperscript{43} by palladium-mediated coupling of unsaturated halides and triflates with 4-pentynoic acids \textsuperscript{42} was later reported by Cacchi.\textsuperscript{21} Reactions were carried out in the presence of Et\textsubscript{3}N, $n$-Bu\textsubscript{4}NCl and catalytic amounts of Pd(OAc)\textsubscript{2} or Pd(PPh\textsubscript{3})\textsubscript{2}. The presence of chloride anions was necessary to obtain optimum results (Scheme 18).

Simultaneously to this work, the transformation of the same pentynoates to the biologically active ynenol lactones \textsuperscript{45}, under the influence of $\sigma$-ethynylpalladium complexes generated from alkynyl bromides \textsuperscript{44}, was reported by Balme and co-workers (Scheme 19). The reaction, here, was only effective with the potassium carboxylates (prepared from the corresponding carboxylic acids with $t$-BuOK in DMSO). The nature of the phosphine ligand was also found to influence the cyclisation process, best results being achieved with tri(2-furyl)phosphine (TFP).\textsuperscript{22}
A similar procedure in which σ-allenylpalladium complexes issued from propargyl acetates \( \text{46} \) activate the carbon-carbon triple bond was then developed to yield potentially bioactive new unsaturated exo-enol lactones \( \text{47} \) (Scheme 20).\(^{23}\)

Using the same conditions [tris(2-furyl)phosphine as a palladium ligand, \( t\)-BuOK in DMSO] Rossi and co-workers prepared \( 5H\)-furan-2-ones \( \text{49} \) by intramolecular palladium-mediated \( 5\)-endo cyclisation of \( 3\)-ynoic acids \( \text{48} \) in the presence of unsaturated halides (Scheme 21). This reaction was however limited to internal \( 3\)-ynoic acids substituted by an alkyl group.\(^{24}\)

EnantiomERICally pure acetylene-containing \( N \)-protected \( \alpha \)-aminoacids \( \text{50} \) were also cyclised to obtain five- or six-membered lactones \( \text{51} \). The cyclisation/coupling reaction took place with phtalimide-protected amino acids, using \( \text{Pd(PPh}_3\text{)}_4, \text{Et}_3\text{N, tetrabutylammonium chloride (TBAC) in MeCN at 60 °C in the presence of two equivalents of iodobenzene or } p\text{-iodoanisole.} \)

In the reaction of \( 2\)-(1-alkynyl)benzoic acids \( \text{52} \) with aryl halides, a mixture of 3-substituted 4-arylisoquoramin \( \text{53} \) and 3-[(1,1-unsymmetrically dissubstituted)methylene]-isobenzofuran-1\((3H)\)-ones \( \text{54} \) was obtained with the latter compounds being formed as the major products (Scheme 23).\(^{27}\) The chemoselectivity for the formation of \( \text{53} \) and \( \text{54} \) seems to be dependent on the mode of substitution of the acetylenic moiety. The reaction was performed in acetonitrile, using \( \text{K}_2\text{CO}_3 \) as base and catalytic amounts of \( \text{Pd(PPh}_3\text{)}_4 \).

The palladium-mediated coupling/cyclisation reaction of alkynoic acids was recently extended by Jacobi and co-workers\(^{28}\) to the preparation of meso-substituted semicormins, as an approach towards the synthesis of Corrin derivatives such as Cobyric acid (Scheme 24). For instance, when the 4-alkynoic acid \( \text{56} \) was reacted with iminoyl chlorides \( \text{55} \), in the presence of the reagent system \( \text{Pd(PPh}_3\text{)}_4/\text{BnN(C}_2\text{H}_5\text{)}_3\text{Cl/Et}_3\text{N, the corresponding enol-lactones } \text{57} \) were obtained as a mixture of \( E \)- and \( Z \)-isomers, this ratio reflects the steric interactions. Aminolysis of \( \text{57} \) followed by dehydration yielded the desired semicormins \( \text{58} \) obtained as the \( Z \)-isomers exclusively due to internal hydrogen bonding. It is worth noting that the corresponding alkyne amides were found to be inert toward the \( \text{Pd(0)-mediated coupling reaction with iminoyl chlorides.} \)

A similar strategy was used for the synthesis of compounds of the Chlorin family.\(^{29}\) As an example, reaction of alkyne acid \( \text{59} \) with iodopyrrole \( \text{60} \) yielded the enol-lactone \( \text{61} \), which was obtained exclusively as the \( Z \)-isomer in 96% yield. Again, this unexpected result may be explained by rapid isomerisation of the initial \( E \)-enol lactone giving (\( Z \))-\( 60 \), which is stabilized by internal hydrogen bonding. It is noteworthy that this reaction was performed on a 20 g scale. The synthesis of Chlorin \( \text{61} \) was achieved from this intermediate in a six-step sequence (Scheme 25).

(2R)- and (2S)-phytochromobilin dimethyl esters have also been prepared by the same group in enantiomERICally pure form by reaction of the chiral alkyne acid \( \text{62} \) with iodopyrrole \( \text{63} \). This reaction gave exclusively the enol-lac-
as a single geometric isomer, which was further transformed into amide (Scheme 26). 30

An intramolecular version of the cyclisation/coupling reaction of alkynoic acids was developed by Balme and co-workers31,32 for the synthesis of various benzo-annulated enol lactones (Scheme 27). Treatment of pentynoic acids 66 under the conditions previously developed for the intermolecular version (see Scheme 19) gave the best results. This bis-cyclisation reaction proved to be dependent on the nature of the reactant. When aryl iodides were used as precursors of arylpalladium complexes, the expected bis-annulated products 67 were synthesised in excellent yields, whereas the use of aryl bromides afforded mixtures of compounds 67 and 68, resulting from bis- and mono-cyclisation reactions, respectively. Using this approach, a formal synthesis of anti-ulcer agent U-68,215 was developed from a known enol lactone intermediate (67a).

This intramolecular bis-cyclisation reaction has also been applied to the construction of the 3-(1'-indanylidene) phthalide nucleus, a known precursor of the core of the antitumor antibiotic Fredericamycin A, a natural product isolated from Streptomyces griseus. Indeed, one of the
ways by which the spirocycle is generated, is the transformation of ylidene phtalides 70 into spirocyclic diketones 71 by a DIBAL reduction of the enol lactone followed by in situ aldol condensation. The intramolecular bis-cyclisation reaction of 69 took place in DMSO, at room temperature, using inorganic bases such as potassium or cesium carbonates. Pd(OAc)$_2$ reduced by NaBH$_4$ in the presence of 2 equivalents of tris(2-furyl)phosphine or triphenylphosphine was used as the catalyst. The oxidative addition to the aryl iodide was followed by the regioselective intramolecular attack of the carboxylate in a 5-exo-process to give the expected phthalide unit 70 (Scheme 28).$^{33}$

![chemical structures](image)

**Scheme 28**

A wide range of stereodefined 2-alkylidene or arylidene tetrahydrofurans and pyrans 73 can be prepared by treatment of alkyl or aryl acetylenic lithium alkoxides 72 in THF with various organic halides in the presence of a palladium catalytic system (Scheme 29). Use of n-BuLi as base was crucial to the success of the cyclisation and only Pd(OAc)$_2$ and PdCl$_2$, with triphenylphosphine as ligand, were found to be effective catalysts.$^{34}$

![chemical structures](image)

**Scheme 29**

In palladium-mediated reactions of unsaturated halides with allenes 74 bearing an oxygen nucleophile, generally, the organic part of the electrophile is introduced to the central carbon of the allene (Scheme 30).

This may be explained by insertion of one of the allenic bonds into the organopalladium bond to form a π-allyl palladium complex 75 (path a). This intermediate may lead to the formation of α,β-unsaturated ketones 76$^{40}$ by β-hydride elimination (n = 0), or may undergo internal nucleophilic attack to produce aryl or alkynyl substituted heterocycles 77 and/or 78 depending on the regioselectivity of this attack. However, the alternative mechanism related to the above-mentioned cyclisation reactions that involves attack of the heteronucleophile onto one of the double bonds of the allene activated by coordination of the electrophilic organopalladium species (path b or c) cannot be totally ruled out and is often suggested by the authors.$^{36-38}$ These two plausible mechanisms were also considered in palladium-mediated cyclisations of allenylcarboxylic acids$^{36,38}$ or amines (see section 3.3). These two possible modes of reaction$^{39}$ seem to be dependent on the strength of the heteronucleophile: a strong anionic nucleophile probably favours the nucleophilic attack on one of the sp$^3$-carbons of the allene while a soft nucleophile allows allene insertion into the palladium-carbon bond of the organopalladium complex before attack of the internal nucleophile may occur.

However, in sharp contrast with the preceding results, an unusual reaction in which the oxygen nucleophile attacks the central carbon atom of the allene was recently reported by Ma and co-workers (Scheme 31).$^{40}$ This result was observed during the palladium-mediated cyclisation of 3,4-allenols 79 with electron-donating or electron-withdrawing aryl iodides that led to the formation of 2,3-dihydrofurans 80. The yields of this Pd(0)-catalysed cyclisation/coupling reaction were strongly dependent on the nature of the base, the highest yields of furan derivatives being obtained with Cs$_2$CO$_3$ as base. Only traces of the cyclised products were isolated in the presence of Na$_2$CO$_3$.

Polysubstituted 3-allyl furans 84 could be synthesized via reaction of allenyl ketone 81 with allylic bromide 82.$^{41}$ The reaction occurred using Pd$_2$(db)(dba)$_2$CHCl$_3$ as the catalyst. Here, a π-allyl palladium species promoted the cyclisation to give π-allyl 3-furanyl palladium species 83 via a highly regioselective coupling reaction. Subsequent isomerisation of the exocyclic double bond gave the expected furans (Scheme 32).

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A synthesis of tetrasubstituted furans 87 was developed using a one-pot, two-step sequence. It involved first a SmI2-promoted reduction of 4,5-epoxyalk-2-ynyl ester 85 in THF that generates 2,3,4-trien-1-ol 86. After removal of the solvent, 86 was treated with an aryl halide or triflate in the presence of Pd(PPh3)4 and Et3N in wet DMF at 60–80 °C. This resulted in an attack of the oxygen nucleophile on the central double bond of the triene to give the corresponding heterocycles in moderate yields (Scheme 33).42

Phenolic oxygen can also participate in this oxypalladation process catalysed by organopalladium species. Reaction of o-alkynylphenols 88 with a variety of vinyl (and aryl) triflates gave rise to the benzo[b]furan skeleton 89 found in numerous natural compounds as well as man-made substances having remarkable biological properties. The reaction took place in the presence of potassium acetate using Pd(PPh3)4 in acetonitrile. Due to a tendency of these o-alkynylphenols to undergo a direct endo-dig cyclisation to simple 2-substituted benzo[b]furans 90, the latter compounds were usually obtained as side products in small amounts (Scheme 34).43

This competing side reaction could be avoided by using a one-pot three-component coupling process recently developed by Flynn and co-workers.44 In this reaction, the possibility of direct cyclisation was prevented by initial deprotonation of a mixture of o-iodophenols 91 and terminal alkynes 92 with MeMgCl in THF. This was followed by a palladium-catalysed coupling reaction leading to o-alkynylphenoxide intermediate 93. In situ addition of the unsaturated triflate (or halide) in solution in DMSO permitted a direct access to the benzo[b]furans in good yields (Scheme 35).

Arcadi and Cacchi performed the cyclisation reaction of o-ethynylphenols with vinyl triflates under carbon monoxide. Different products were obtained depending on the substitution pattern of the alkyne in the starting phenol (Scheme 36). With internal alkyne, CO insertion into aryl or alkynyl palladium complexes was followed by the heteroannulative coupling reaction to give the corresponding 3-acyl-2-arylbenzo[b]furans 94. In marked contrast, under the same conditions, the reaction with terminal alkyne followed a completely different course. Indeed, capture of the acylpalladium intermediate by the phenolic oxygen followed by an intramolecular carbopalladation reaction led to 3-alkylidene-2-coumaranones 95.
in good yields. The authors suggested a combination of electronic and steric effects to explain this difference of behaviour. The use of \textit{aryl iodides} in place of \textit{vinyl triflates} resulted in the preferential formation of $\alpha$-acyl derivatives \textsuperscript{96,43,45} Recently, Fathi and Yang succeeded in applying this methodology to a selection of aryl iodides, and best results were obtained with $\alpha$-ethynylphenols bearing electron-withdrawing substituents on the aromatic ring.\textsuperscript{46} The three-component reaction developed by Flynn and co-workers\textsuperscript{47} (Scheme 35) has also been performed under CO to access potent tubulin polymerisation inhibitors.

2-Substituted-3-alloybenzo[b]furans \textsuperscript{98} were obtained in a complete neutral medium by starting from $\alpha$-alkynylallyloxybenzenes \textsuperscript{97} easily prepared from $\alpha$-hydroxybenzaldehyde (Scheme 37). The heteroannulation process here was promoted by a $\eta^1$-allyl palladium complex formed in situ by oxidative addition of the palladium(0) complex to the starting allyl aryl ether. The reaction was limited to the cyclisation of internal alkynes, the terminal analogues giving rise to complex mixtures of products.\textsuperscript{48} $\alpha$-Alkynylallyloxybenzenes of type \textsuperscript{97} may also be prepared from palladium-catalysed reaction of $\alpha$-alkynylphenols with allyl carbonates \textsuperscript{99}.\textsuperscript{49} They may be isolated as stereo- and regiosomeric mixtures and be subsequently cyclised using Pd$_2$(dba)$_3$ and an electron-rich sterically encumbered ligand such as tris(2,4,6-trimethylphenyl)phosphine (ttmpp) (Scheme 38). When non-symmetric $\pi$-allylpalladium complexes are involved as promoting species, such a catalyst system resulted in complete regioselectivity toward the formation of 3-allylbenzofuran in which the benzofuryl unit is bound to the less substituted allyl terminus. Alternatively, a one-pot protocol omitting isolation of the $\alpha$-alkynylallyloxybenzenes was developed using Pd(PPh$_3$)$_3$ as catalyst.

This methodology was then applied to propargylic $\alpha$-(alkynyl)phenyl ethers \textsuperscript{100}. The reaction occurred in DME, at 110 °C, in the presence of Pd(PPh$_3$)$_3$ and K$_2$CO$_3$, and led to the expected 2-substituted-3-allyl-benzofuran \textsuperscript{101}, which were in some cases, accompanied by their isomeric 2-substituted-3-propargylbenzofuran \textsuperscript{102} (Scheme 39). The presence of an aryl substituent on the terminal acetylenic carbon of the propargyl fragment in \textsuperscript{100} was found to be crucial for the success of the reaction. The reaction proceeds either via $\sigma$-allyl or $\sigma$-propargyl palladium intermediates formed by oxidative addition of the propargyl $\alpha$-(alkynyl)phenyl ethers to Pd(0). These two intermediates can then undergo nucleophilic attack of the phenoxide on the activated triple bond. The ratio of the two isomeric products were shown to be dependent on the nature of the starting alkyne.\textsuperscript{50}

2-Substituted-3-allylbenzo[b]furans were also prepared from $\alpha$-alkynylphenols using a procedure where the activating allylpalladium species was issued from the reaction of propargyl carbonates \textsuperscript{103} with Pd(0) (Scheme 40). In this case, formation of the isomeric propargylic benzo-furans was not observed. Instead, as previously observed for similar reactions (see Scheme 34), small amounts of 2-substituted benzo-furans were produced as side products. This procedure allowed the preparation of diversely substituted allyl compounds.\textsuperscript{51}
Deoxynucleoside analogues 105, a series of inhibitors of varicella-zoster virus, have been synthesized from the corresponding alkynyl deoxyuridines 104 in moderate to good yields (40–75%). The construction of the furo[2,3-d]pyrimidin-2-one nucleus has been achieved using Pd(PPh₃)₄ as catalyst and Et₃N as base in DMF at 60–70 °C (Scheme 41).

A sequential palladium-catalysed cyclisation reaction of 3-acetyl-5-hexyn-2-one 106a,53 ethyl 2-acetyl-4-pentynoate 106b,53 or alkyl 3-oxo-6-heptynoate 108 with various unsaturated halides and triflates in the presence of Pd(PPh₃)₄ and K₂CO₃ provided valuable routes to substituted furans (107a, 107b, or 109, respectively) (Schemes 42 and 43). Trans addition of the oxygen nucleophile and the organopalladium complex across the triple bond was followed by isomerisation of the exo-cyclic double bond to furnish the corresponding aromatised furan derivatives. When 106a was reacted under a carbon monoxide atmosphere, 2,3,5-substituted furans 110 or enol esters 111 were formed depending on the alkyne/aryl iodide ratio (Scheme 44). The formation of the enol esters arose from further reaction of 110 with the acylpalladium intermediate when an excess of unsaturated halide was used in the basic medium.55

Scheme 40

Scheme 41

Scheme 42

Scheme 43

Scheme 44

The development of multicomponent condensation reactions based on these new palladium-mediated cyclisation processes allowed resulted in the preparation of highly functionalised tetrahydrofurans in a single step from sim-
Activated olefins have been reacted with allylic alcohols and unsaturated halides in the presence of a palladium catalyst and a base to give 4-benzyltetrahydrofuran-3,3-dicarboxylates. The methodology was based on a domino reaction in which the enolate resulting from an initial 1,4-addition of the propargyl alkoxide to the conjugate acceptor was followed by the palladium-mediated cyclisation reaction involving the unsaturated halide. However, it was necessary to use slow addition techniques in order to avoid undesirable side-reactions.

Substitution of allylic alcohols for their propargylic analogues produced a new class of stereodefined arylidene (or alkenylidene) tetrahydrofurans in high yields. In this case, due to higher reactivity of these unsaturated alcohols, it was possible to obtain a great variety of substituted tetrahydrofurans by simply mixing equal amounts of each of the three components in THF–DMSO at room temperature in the presence of a palladium(0) catalyst. The efficiency of this palladium-mediated three-component reaction has been shown to be strongly influenced by the nature of the catalyst system and a palladium(0) catalyst generated in situ by reduction of PdCl₂(PPh₃)₂ with n-butyllithium has been found particularly effective.

A novel one-pot, two-step synthetic entry into functionalised 4-benzylfuran derivatives of type was then developed by extending this strategy to the commercially available diethyl ethoxymethylene malonate as conjugate acceptor. It successively involved a conjugate addition, a palladium-catalysed cyclisation/coupling reaction, an alkoxide-induced decarboxylative elimination, and finally, a double bond isomerisation. A formal synthesis of the lignan anti-tumor Burseran employed this process as a key step illustrating the potential utility of this concept in the synthesis of important natural products of the lignan family.

Two other examples of multicomponent reactions leading to oxygen heterocycles should be mentioned. The combination of sodium 2-methyl-3-butyn-2-olate, aryl halides and carbon dioxide to afford the cyclic vinylidene carbonates (9–68% yields) was reported by Inoue and co-workers in 1990. This reaction was restricted to terminal acetylenic tertiary alcohols and worked well in the presence of iodobenzene and p-iodotoluene, arylbromides and allyl acetate (or chloride) giving poor results (9–32%). The reaction proceeds through formation of a monoalkylcarbonate generated by reaction of the propargyl alkoxide with CO₂. This is followed by the attack of the newly formed oxygen nucleophile onto the triple bond activated by the arylpalladium species.

More recently, Yamamoto and co-workers described the palladium-catalysed reaction of alkynylaldehydes with allyl chloride and allyltributylstannane to yield cyclic ethers and carbon dioxide to afford the cyclic vinylidene carbonates.
cyclisation of the latter furnishes the corresponding exo-products 118 and/or their endo-isomers 119 depending on the structure of the starting alkylnaldehyde (Scheme 49).

Scheme 49

3.2 Nitrogen Heterocycles

The intramolecular trans addition of alkenyl or aryl groups and amines to internal or terminal alkynes has been shown to be an efficient route to various nitrogen heterocycles.61 This strategy has been applied to the construction of stereodefined 2-alkylidenepyrrolidine or piperidine derivatives 121. These compounds have been prepared by treatment of acetylenic tosylamines 120 with n-BuLi (1.1 equiv) followed by addition of phenyl iodide (3 equiv), heteroaryl iodides or alkenyl bromides in the presence of Pd(OAc)$_2$ (0.05 equiv), PPh$_3$ (0.1 equiv). The reaction took place at 60 °C in THF (Scheme 50).

Scheme 50

This strategy was used for the construction of hexahydropyrrins 124, in a study directed toward the construction of Corrins, a class of natural products having interesting biological activities, in particular a potential utility in photodynamic therapy (PDT) (Scheme 51).62,63 In this approach, the terminal alkyne amine 122b ($R^1 = Me$) the cyclisation required heating in MeCN at 80 °C and the most effective catalytic system was in this case Pd$_2$dba$_3$/TFP/BnN(Et)$_3$Cl.

Scheme 51

The synthesis of stereodefined 4-arylidene-3-tosyloxazolidin-2-ones 126 starting from propargyl tosylcarbamates 125 has been simultaneously reported by Arcadi64 and Balme65 (Scheme 52). Both electron-rich and electron-poor aryl iodides and vinyl triflates took part in the reaction and, generally, gave good yields. The addition of quaternary ammonium salts such as tetrabutyl or benzyltriethylammonium chloride was important to avoid competitive side reactions. These reactions can be either carried out in DMF at 60 °C using the K$_2$CO$_3$/Pd(PPh$_3$)$_4$ system64 or in MeCN at room temperature using the alternative t-BuOK/Pd(OAc)$_2$/TFP system.65 Depending on the substitution at the propargylic position, a direct exo-dig cyclisation leading to simple 4-methylene-3-tosyloxazolidin-2-ones as by-products was sometimes observed.

Scheme 52

The cyclisation reaction of o-alkynyltrifluoroacetanilides 127 promoted by various organopalladium complexes generated in situ from C$_2$ donors such as aryl and vinyl halides (or triflates),66 as well as allyl esters 99,67 and alkyl halides 128 have been thoroughly developed by Cacchi. It allowed for the preparation of a large variety of functionalised indole derivatives 129–131. The reactions

worked well with internal acetylenes bearing alkyl, vinyl, and aryl groups and with terminal acetylenes (Scheme 53). Concerning this last case, when o-ethynyltrifluoroacetanilide 127a was cyclised in the presence of aryl halides, the expected indoles were accompanied by their isomeric six-membered ring derivatives 132 that resulted from the O-cyclisation of the ambident nucleophile generated from the trifluoroacetamido group. The N-/O-cyclisation ratio was found to be highly dependent on the nature of both the solvent and the catalytic system (Scheme 54).69 The palladium-catalysed solid-phase synthesis of these indole derivatives was also recently reported.70

For the preparation of Arcyriaflavin A and Rebeccamycin, an indolo[2,3-a]carbazole ring system 135, the palladium-catalysed polyanannulation of diacetylene 133 with N-benzyl-3,4-dibromomaleimide (134), wherein two carbon-carbon, and two nitrogen-carbon bonds were formed in a single step (Scheme 55).71

A new route to the interesting class of 2-substituted-3-acylindoles of type (Scheme 56) was also developed by carrying out the cyclisation reaction of the o-alkynyltrifluoroacetanilides in the presence of carbon monoxide.72 This methodology was applied to the synthesis of Pravalodine, a biologically active molecule designed as an analogue of non-steroidal anti-inflammatory drugs (NSAIDS) (Scheme 56).

When the carbonylation of aryl iodides was performed in the presence of o-(o-aminophenyl) trifluoroacetanilide 137, the palladium-catalysed carbonylate cyclative cyclisation was followed by the intramolecular reaction of the amino group on the 3-acylindole intermediate 138 to afford 6-aryl-11H-indolo[3,2-c]quinolines 139 in moderate to
good yields (Scheme 57). The reaction was catalysed by Pd(PPh₃)₄ and took place in anhydrous MeCN at 50 °C using K₂CO₃ as base under 3 atm of carbon monoxide.⁷³

Interestingly, the same reaction developed on bis(o-trifluoroacetamidophenyl)acetylene 140 led to the formation 12-acylindolo[1,2-c]quinazolines 142, via the intermediate indole 141, by intramolecular nucleophilic attack of the ortho nitrogen to the carbonyl of the indole trifluoroacetyl group (Scheme 58). Aryl iodides and vinyl triflates (or bromides) were shown to be excellent coupling partners and the acylindoloquinazoline derivatives were obtained in good yields.⁷⁴ In the absence of CO, the reaction follows the same pathway to give the corresponding 12-aryl-(or alkenyl)indolo[1,2-c]quinazolines.⁷⁵

Various 3,4-disubstituted isoquinolines 144 have recently been prepared via an intramolecular cyclisation of N-tert-butyl-o-(1-alkynyl)-benzaldimines 143 promoted by vinyl-, aryl-, allyl- or alkynylpalladium complexes (Scheme 59). The cyclisation took place in DMF at 100 °C using 0.05 equivalent of Pd(PPh₃)₄ in the presence of K₂CO₃ as base. The cyclisation/coupling reaction was followed by in situ cleavage of the tert-butyl group from the nitrogen. The reaction yields were strongly dependent on the electronic nature of the substituents on the aryl iodide. When an electron-donating group was present, competition between the desired product and the direct cyclisation process producing 3-monosubstituted products occurred. Higher yields were obtained with aryl iodides bearing an electron-withdrawing group in the para- or ortho-position. This is due to a stronger coordination of the corresponding arylpalladium intermediate to the alkylene triple bond.⁷⁶ When the same reaction was performed under an atmosphere of carbon monoxide or alternatively in the presence of acyl halides, the intramolecular cyclisation reaction was promoted by an acylpalladium intermediate (ArCOPdX) leading to 3-substituted-4-arylisooquinolines 145. The yields were strongly dependent on the base employed, organic bases such as tri-n-butylamine and triethylamine giving the best results.⁷⁷,⁷⁸

The reaction of 2-alkynylbenzonitriles 146 with sodium methoxide and phenyl iodide, or other aryl iodides bearing electron-donating substituents, was developed using Pd(PPh₃)₄ as catalyst for the formation of five- or and six-membered ring heterocycles, namely the isoindoles 147 and isoquinolines 148, respectively. The product distribution was shown to be dependent on the nature of the substituent on the terminal alkyne carbon (Scheme 60). Mechanistically, the reaction was supposed to proceed through the formation of an iminium anion by addition of methoxide to the nitrile group, which underwent an intramolecular attack onto the activated carbon-carbon triple bond by either 5-exo or 6-endo mode of cyclisation. 2-(2-Phenylethynyl) benzonitrile (146a, R = Ph) underwent an exclusive 5-exo cyclisation process to afford 3-diarylmetalidenesoindoles 147. In sharp contrast, under the same reaction conditions, 2-(1-hexynyl)benzonitrile (146b, R = n-Bu) led to the formation of isoquinolines 148 as main products (29–34%) along with the corresponding isoindoles (12–25%). This endo/exo balance might be attributed to steric interactions between the entering group and the substituent on the terminal alkyne carbon.⁷⁹

Ethyl 2-acetyl-4-pentynoate tosylhydrazone 149 also reacted with various aryl halides to yield polyfunctionalised 1-tosylaminopyrroles 150 in quite good yields (Scheme 61). These compounds resulted in chemoselec-
The cyclisation/coupling reaction of enantiomerically pure Ts- and Ns-protected amino acids (R)-152a and (R)-152b with aryl halides and unsaturated triflates has been investigated by Rutjes and co-workers25,26 (Scheme 62). The reaction must be carried out in MeCN, at 60–80 °C, using 0.1 equivalent of Pd(PPh3)4 and 5 equivalents of K2CO3. The presence of n-Bu4NCl was critical for the coupling reaction to proceed efficiently and furnish the desired pyrrolidines 153. Indeed, in its absence, the carbon-carbon coupling did not take place and instead, the undesired non-arylated product 154 was isolated. It is noteworthy that no racemisation occurred during the reaction, the enantiopurity of the starting material being retained in the cyclised product.

However, in contrast with the preceding results, an unusual regiochemical outcome for the cyclisation reaction in which the nitrogen nucleophile attacks the central carbon atom of the allene was reported by Hiemstra’s group (Scheme 64).93 This unprecedented observation was made during the palladium-mediated cyclisation of ω-(2,3-butenyldienyl)lactams 158 with aryl halides using reaction conditions developed by Gallagher and co-workers.84 Generally, a mixture of two regiosomeric cyclisation products 159 and 160 was obtained, resulting from the ac-
tivation of either the terminal or the internal double bond of the allene by the organopalladium species. In this case, the reaction mechanism proposed by Tsuji91 for heteronucleophiles and by Goré and Cazes92 for carbonucleophiles could be ruled out since such a mechanism would have led to the formation of bicyclic allylamides via insertion of the allene into the palladium-bond followed by a 4-exo-trig or 6-endo-trig cyclisation mode on the π-allylpalladium intermediate.

The same reaction was then developed on enantiopure allenic oxazolidinones 161 and lactams 162 easily prepared from (S)-pyroglutamic acid and L-serine, respectively (Scheme 65). These substrates when subjected to the previous cyclisation reactions afforded enantiopure bicyclic enamides 163 and 164 in good yields. However, the dimethyl-substituted allene 162a showed interesting behaviour. The expected cyclic product 164a was formed in poor yield (16%), as it was accompanied by a mixture of non-cyclised dienic compounds 165 and 166 isolated in 65% combined yield. Apparently, here, the classical insertion of the phenyl group to the central carbon of the allene competed with the cyclisation/coupling reaction. This was explained by the steric crowding on the terminal allene carbon that slows down attack of the nitrogen nucleophile on the (σ-aryl)Pd-coordinated allene, therefore allowing for competitive reactions to take place.94

A three-component synthesis of stereodefined 4-benzylidene-(or alkanyliden)-pyrrolidines 167 based on a cascade conjugate addition-carbopalladation sequence has been reported.95 The procedure combines propargylamines with gem-diactivated olefins and unsaturated halides (or triflates) at room temperature using PdCl₂(PPh₃)₂ reduced by n-BuLi as the catalyst (Scheme 66). Assembling five reactants was also successfully achieved by using 1,4-diodobenzene as a bis-coupling partner, which produced bis-pyrrolidine 168 as a single diastereomer. Overall, four carbon-carbon bonds, two carbon-nitrogen bonds, and two cycles were formed in a single operation.

4 Conclusion

During the past fifteen years the present cyclisation/coupling reaction of unsaturated substrates bearing a pendant nucleophile with organic halides and triflates has become a powerful tool for the preparation of complex carbon- and heterocyclic compounds. The method allows the creation...
of several bonds and rings in a single, practical operation with high control of regio- and stereochemistry. It has shown wide flexibility with respect to the nature of the nucleophilic partner and that of the organopalladium precursors. These features make them also highly attractive for the development of new multicomponent reactions, which combine complexity with diversity. We are confident that many new applications of this reaction will be reported in the future.

References

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(17) Coudanne, I.; Balme, G. Synlett 1998, 998.
(38) A similar duality (Heck reaction versus cyclisation reaction) depending on the strength of the nucleophile was also observed in a palladium mediated cyclisation of olefins (see Scheme 8).