Cyclisations Involving Attack of Carbo- and Heteronucleophiles on Carbon-Carbon π-Bonds Activated by Organopalladium Complexes

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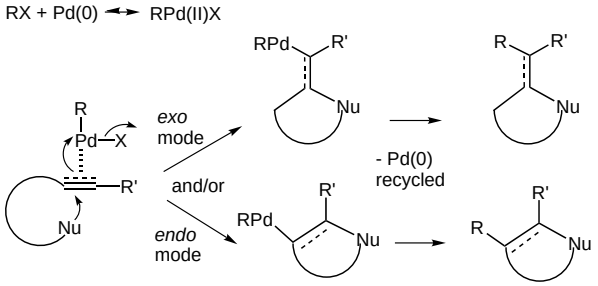
Dedicated to Professor Jacques Goré on the occasion of his 65th birthday with warm thanks for a fruitful collaboration over many years.

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.

Key words: catalysis, palladium, carbocycles, heterocycles, cyclisation



Scheme 1

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 σ-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 Balme[1] 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 σ-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.

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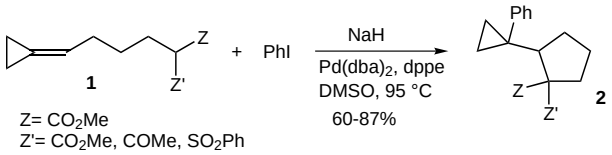
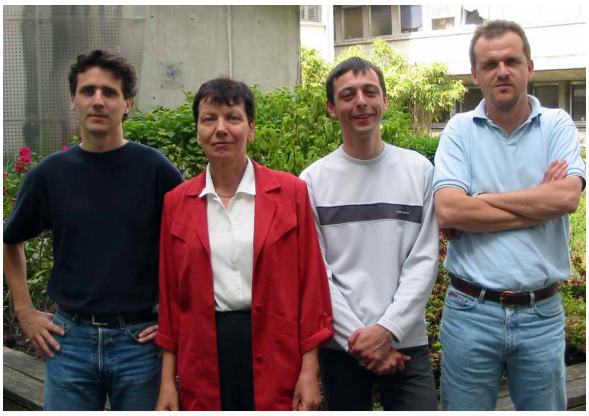


Scheme 2

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]

Biographical Sketches



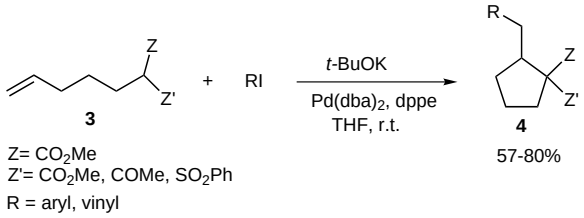
from left to right: Nuno Monteiro, Geneviève Balme, Thierry Lomberget Didier Bouyssi

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.

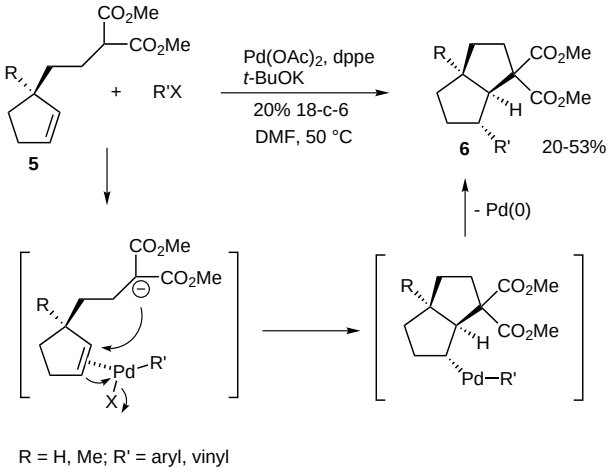
Thierry Lomberget was born in 1973 in Bourg-en-Bresse, France. He received his Ph.D. degree from the University Claude Bernard of Lyon in 2002 under the supervision of Dr. G. Balme for research on palladium-catalysed cyclisation reactions of conjugated enynes.
He is currently a post-doctoral fellow at 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.



Scheme 3

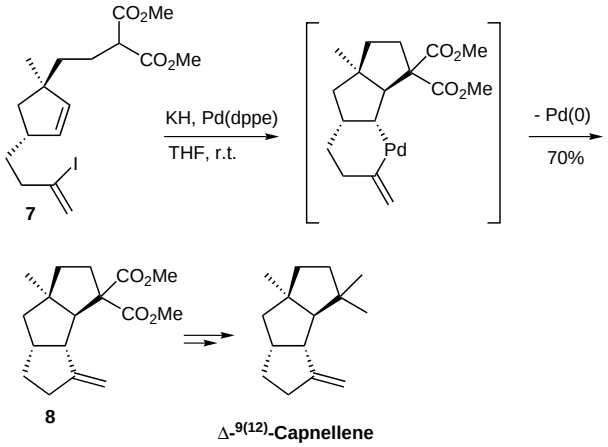
The stereochemical course of this reaction has been probed with functionalised cyclopentenes **5**. When these substrates were treated by an aryl halide under the reaction conditions depicted in Scheme 4, single diastereoisomers **6** were isolated. The stereocontrol observed during the formation of 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]



Scheme 4

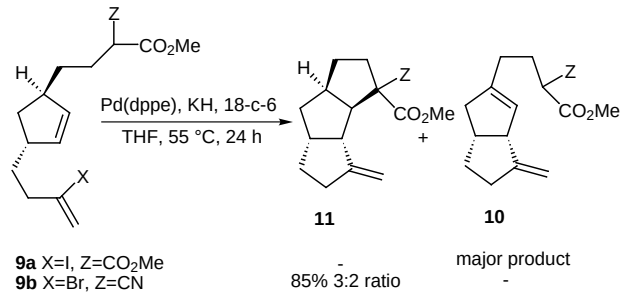
By using the intramolecular version of this strategy, the stereocontrolled synthesis of the fused tricyclopentanoid **8** was achieved. The total synthesis of (±)-capnellene, a marine natural product, has been carried out by applying the palladium-mediated carbocyclisation to the internal vinyl iodide **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



Scheme 5

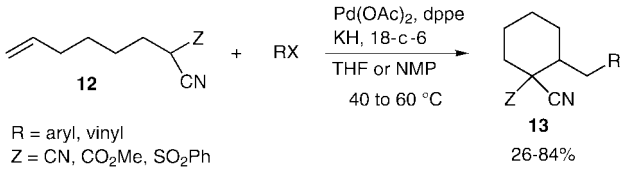
methyl cyanoacetate and using a vinyl bromide instead of the corresponding iodide (**9b**) (Scheme 6).[8]



Scheme 6

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**.

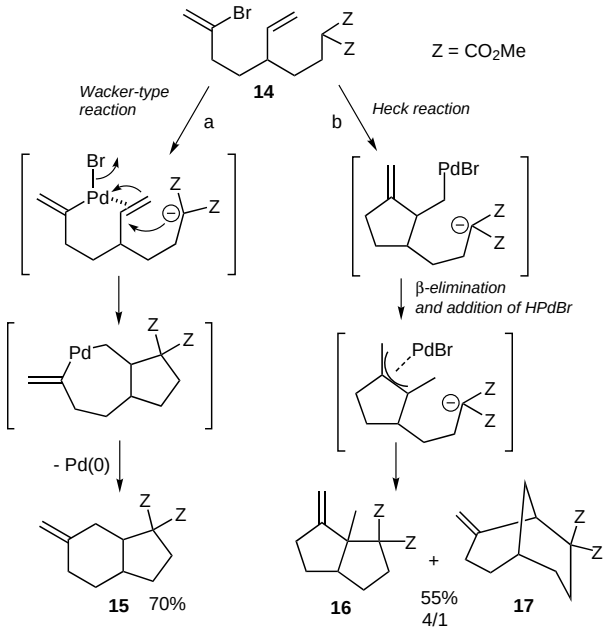
When one or both of the malonate esters were substituted for a nitrile, exclusive formation of cyclisation products **13** was observed (Scheme 7).[9]



Scheme 7

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-

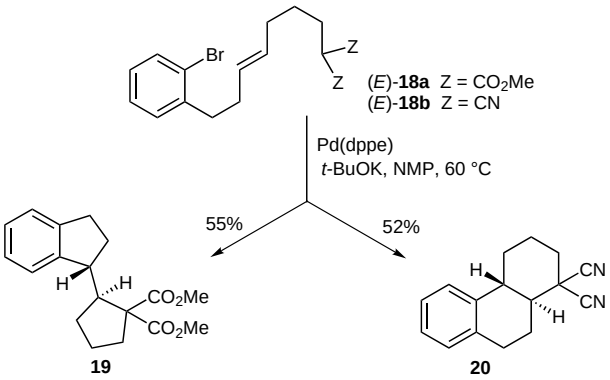
ladium mediated bis-cyclisation process by simple alterations to the reaction conditions. The most effective change to be made concerned the strength of the carbonucleophile, which depended on the nature of the base (Scheme 8). A strong anionic nucleophile (KH as base) gave rise to the *trans*-hydrindane system **15** exclusively, while a weaker nucleophile (use of carbonate bases) afforded the Heck products **16** and **17**.[10]



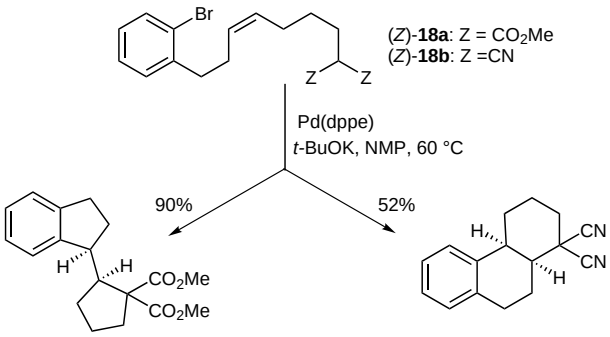
Scheme 8 *Conditions:* (a) 5% $Pd(OAc)_2$, 5% dppe, 1.1 equiv KH, THF, 55°C; (b) 5% $Pd(OAc)_2$, 10% PPh_3, 2 equiv TEBA, 2 equiv K_2CO_3, DMF, 60 °C.

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 concommitant 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]



Scheme 9

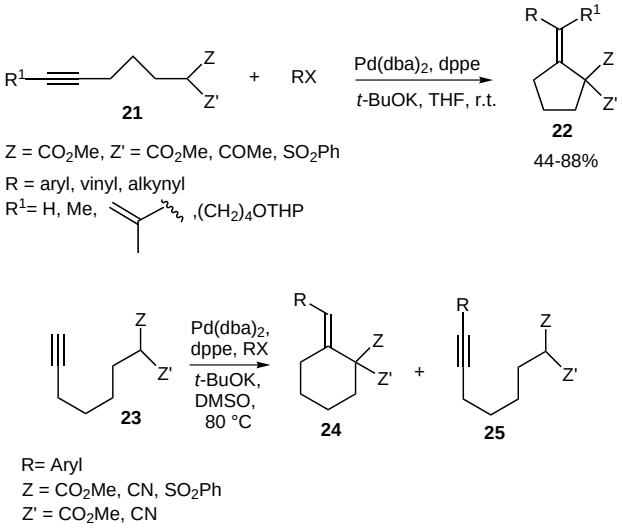


Scheme 10

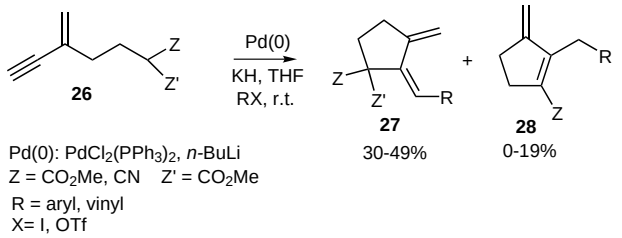
2.2 Cyclisation of Unactivated Alkynes

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 ($R^1 \neq H$), 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).



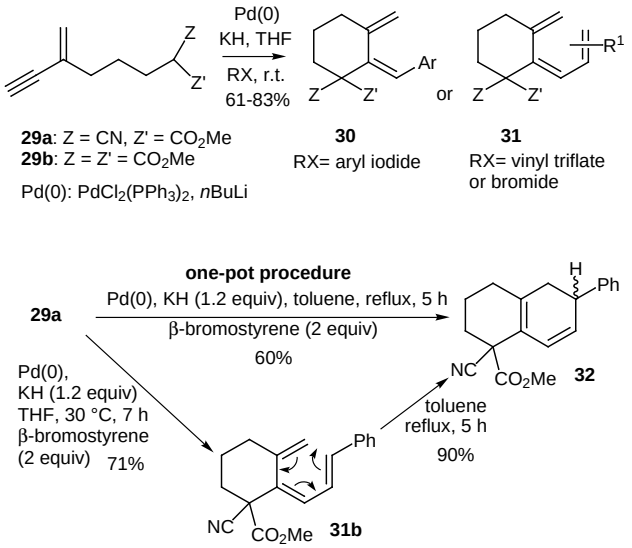
Scheme 11



Scheme 12

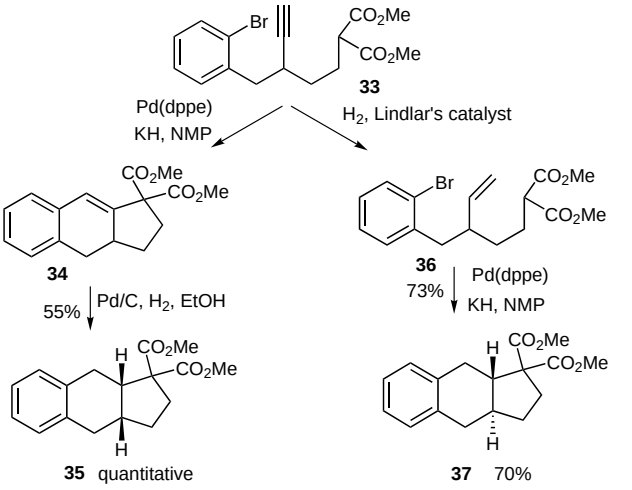
However, higher homologues of type **29** gave rise to the formation of stereodefined functionalised 1,3-bis-exocyclic dienes **30** or conjugated trienes **31** in good yields depending on the nature of the coupling partner (aryl iodide; vinyl triflate or bromide). When heated in refluxing toluene the 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).[16]

A practical and efficient strategy for the synthesis of either *cis*- or *trans*-hexahydro-1*H*-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-1*H*-benz[*f*]indene **35** in essentially quantitative yield. By changing the order of the two preceding steps, only the *trans*-hexahydro-1*H*-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 pal-



Scheme 13

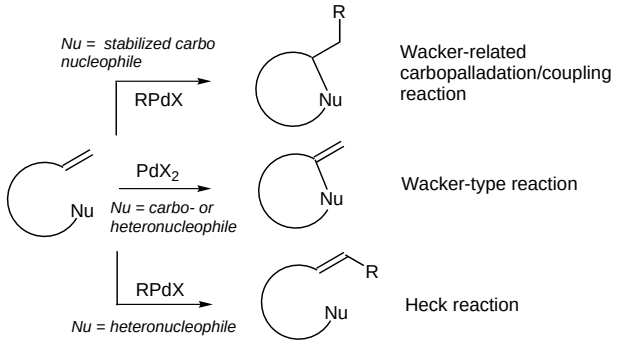
ladium-mediated cyclisation reaction (same conditions as above but using THF in place of NMP). The stereochemical control of this reaction may be explained if it were to pass through a transition state in which the benzylic substituent lies in a pseudoequatorial orientation.[17]



Scheme 14

3 Heterocycles

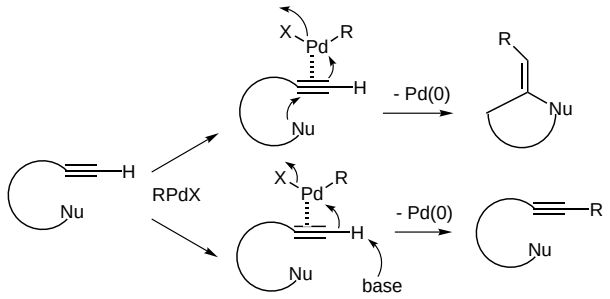
Although there are a number of examples of intramolecular reactions of soft carbonucleophiles on alkenes coordinated by organopalladium complexes, there are no examples of the same reaction realised in the presence of heteronucleophiles. In this case, the palladium-catalysed arylation of olefins (Heck reaction) prevails over the intramolecular attack of the heteronucleophile on the activated carbon-carbon double bond, leading to the linear arylated product.[4] Such difference in reactivity may be due, in part, to the higher basicity of heteronucleophiles. It is noteworthy that a variety of heterocyclic systems



Scheme 15

have been synthesized by attack of oxygen[18] or nitrogen[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).

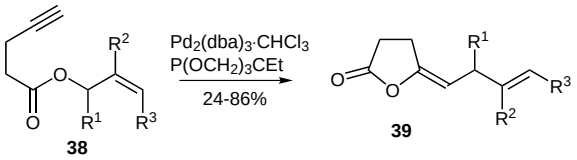


Scheme 16

3.1 Oxygen Heterocycles

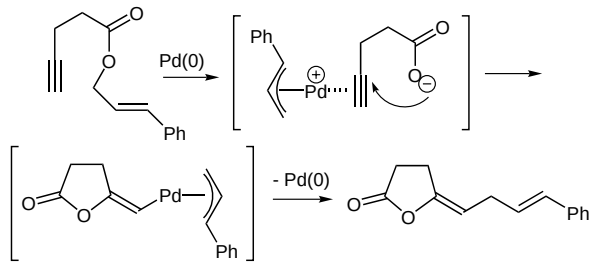
The first example of a cyclisation of an acetylenic heteronucleophile catalysed by organopalladium species was developed by Tsuda and Seagusa in 1988 on allyl 4-pentynoates **38** (Scheme 17).[20] Oxidative addition of the palladium(0) complex to **38** generates a π-allyl palladium cation and an alkynoate. 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 **39** regio- and stereoselectively. A related system, involving lithium alkynoates **40** and allylic acetates **41,** was also studied by the same group.

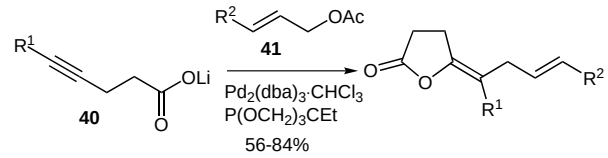
The preparation of exocyclic enol lactones **43** by palladium-mediated coupling of unsaturated halides and triflates with 4-pentynoic acids **42** was later reported by Cacchi.[21] Reactions were carried out in the presence of Et_3N,



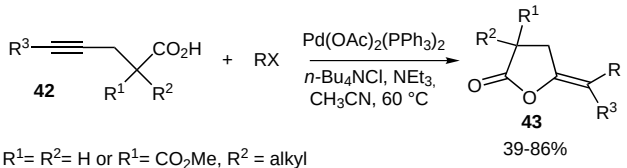
R^1, R^2, R^3 = H ; R^1= Me, R^2, R^3 = H ; R^1, R^2= H, R^3 = Ph

Mechanism:





Scheme 17

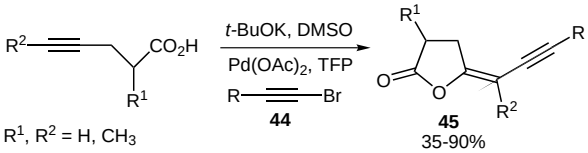


R^1= R^2= H or R^1= CO_2Me, R^2 = alkyl
R^3= aryl, alkyl
R= vinyl, aryl; X= OTf, I, Br

Scheme 18

n-Bu_4NCl and catalytic amounts of $Pd(OAc)_2$ or $Pd(PPh_3)_4$. The presence of chloride anions was necessary to obtain optimum results (Scheme 18).

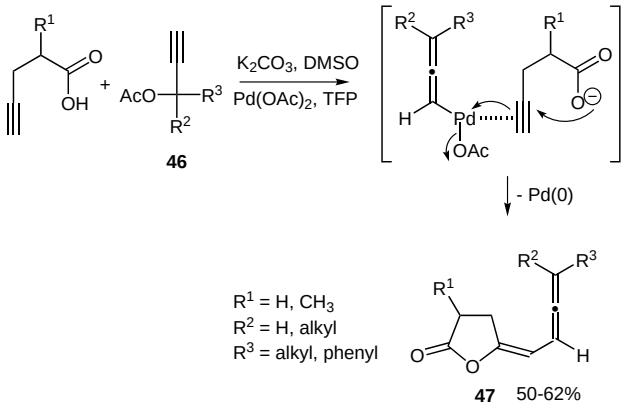
Simultaneously to this work, the transformation of the same pentynoates to the biologically active ynenol lactones **45,** under the influence of σ-ethynylpalladium complexes generated from alkynyl bromides **44**, was reported by Balme and co-workers (Scheme 19). The reaction, here, was only effective 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).[22]



R^1, R^2 = H, CH_3
R = aryl, alkyl

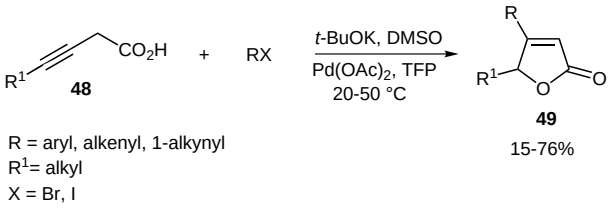
Scheme 19

A similar procedure in which σ-allenylpalladium complexes issued from propargyl acetates **46** activate the carbon-carbon triple bond was then developed to yield potentially bioactive new unsaturated *exo*-enol lactones **47** (Scheme 20).[23]



Scheme 20

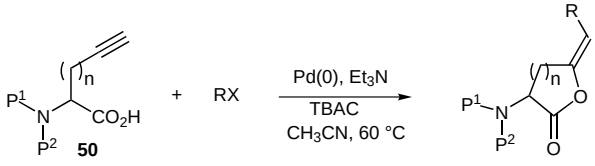
Using the same conditions [tri(2-furyl)phosphine as a palladium ligand, *t*-BuOK in DMSO] Rossi and co-workers prepared 5*H*-furan-2-ones **49** by intramolecular palladium-mediated 5-*endo* cyclisation of 3-ynoic acids **48** in the presence of unsaturated halides (Scheme 21). This reaction was however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



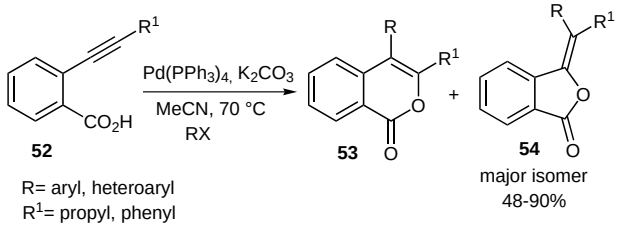
Scheme 21

Enantiomerically pure acetylene-containing *N*-protected α-aminoacids **50** were also cyclised to obtain five- or six-membered lactones **51**. The cyclisation/coupling reaction took place with phtalimide-protected amino acids, using $Pd(PPh_3)_4$, Et_3N, tetrabutylammonium chloride (TBAC) in MeCN at 60 °C in the presence of two equivalents of iodobenzene or *p*-iodoanisole. The corresponding cross-coupled lactones were obtained in moderate yields and complete racemisation occurred at the temperature required for cyclisation (Scheme 22).[25,26]

In the reaction of 2-(1-alkynyl)benzoic acids **52** with aryl halides, a mixture of 3-substituted 4-arylisocoumarins **53** and 3-[(1,1-unsymmetrically disubstituted)methylidene]-isobenzofuran-1(3*H*)-ones **54** was obtained with the latter compounds being formed as the major products (Scheme 23).[27] The chemoselectivity for the formation of **53** and **54** seems to be dependent on the mode of substitution of the acetylenic moiety. The reaction was performed



Scheme 22



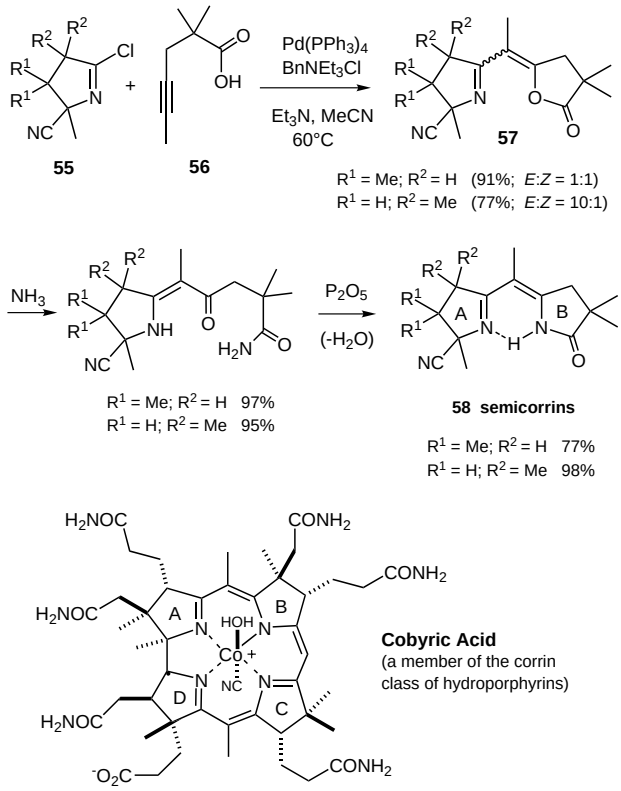
Scheme 23

in acetonitrile, using K_2CO_3 as base and catalytic amounts of $Pd(PPh_3)_4$.

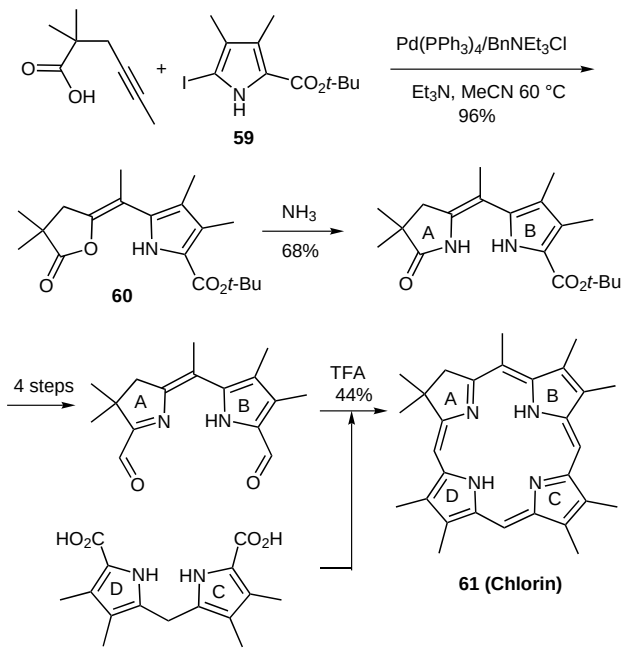
The palladium-mediated coupling/cyclisation reaction of alkynoic acids was recently extended by Jacobi and co-workers[28] to the preparation of meso-substituted semicorrins, as an approach towards the synthesis of Corrin derivatives such as Cobyric acid (Scheme 24). For instance, when the 4-alkynoic acid **56** was reacted with iminoyl chlorides **55**, in the presence of the reagent system $Pd(PPh_3)_4/BnN(C_2H_5)_3Cl/Et_3N$, the corresponding enol-lactones **57** were obtained as a mixture of *E*- and *Z*-isomers, this ratio reflects the steric interactions. Aminolysis of **57** followed by dehydration yielded the desired semicorrins **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 Pd(0)-mediated coupling reaction with iminoyl chlorides. This is due to the relatively weak nucleophilicity of amides compared to the corresponding acids.

A similar strategy was used for the synthesis of compounds of the Chlorin family.[29] As an example, reaction of alkynoic acid **56** with iodopyrrole **59** yielded the enol-lactone **60**, 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 **61** was achieved from this intermediate in a six-step sequence (Scheme 25).

(2*R*)- and (2*S*)-phytochromobilin dimethyl esters have also been prepared by the same group in enantiomerically pure form by reaction of the chiral alkyne acid **62** with iodopyrrole **63**. This reaction gave exclusively the enol-lac-



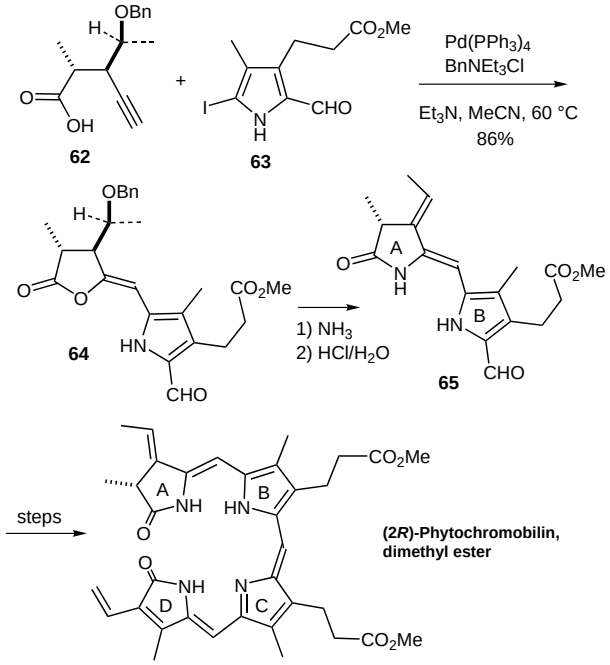
Scheme 24



Scheme 25

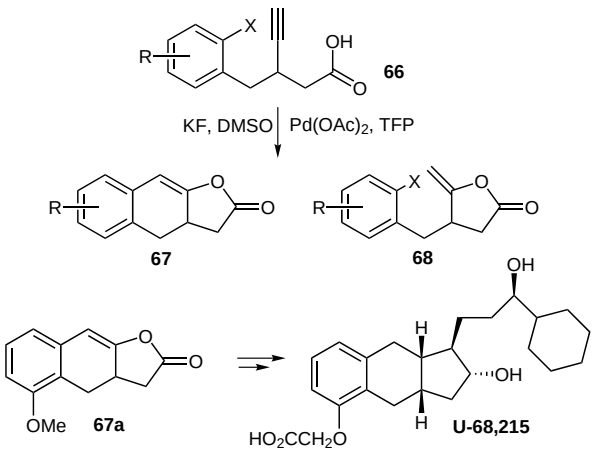
tone **64** as a single geometric isomer, which was further transformed into amide **65** (Scheme 26).[30]

An intramolecular version of the cyclisation/coupling reaction of alkynoic acids was developed by Balme and coworkers[31,32] for the synthesis of various benzo-annulated enol lactones **67** (Scheme 27). Treatment of pentynoic acids **66** under the conditions previously developed for the



Scheme 26

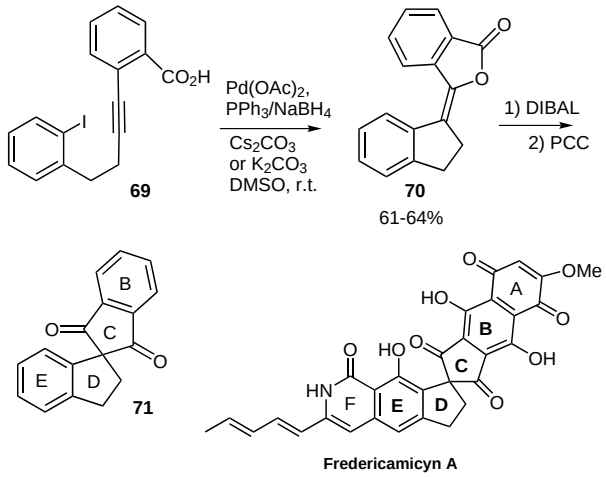
intermolecular version (see Scheme 19) gave the best results. This bis-cyclisation reaction proved to be dependent on the nature of the reactant. When aryl iodides were used as precursors of arylpalladium complexes, the expected bis-annulated products **67** were synthesised in excellent yields, whereas 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**).



Scheme 27

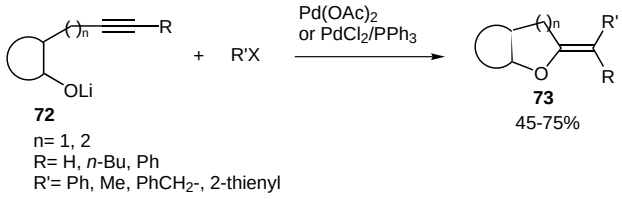
This intramolecular bis-cyclisation reaction has also been applied to the construction of the 3-(1′-indanylidene) phtalide nucleus, a known precursor of the core of the antitumor antibiotic Fredericamicyn A, a natural product isolated from *Streptomyces griseus*. Indeed, one of the

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 phtalide unit **70** (Scheme 28).[33]



Scheme 28

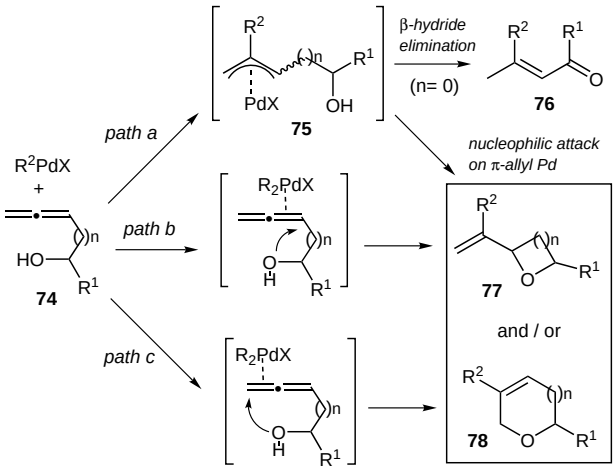
A wide range of stereodefined 2-alkylidene or arylidene tetrahydrofurans and pyrans **73** can be prepared by treatment of alkyl or aryl acetylenic lithium alkoxides **72** in THF with various organic halides in the presence of a palladium catalytic system (Scheme 29). Use of *n*-BuLi as base was crucial 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]



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**[35] by

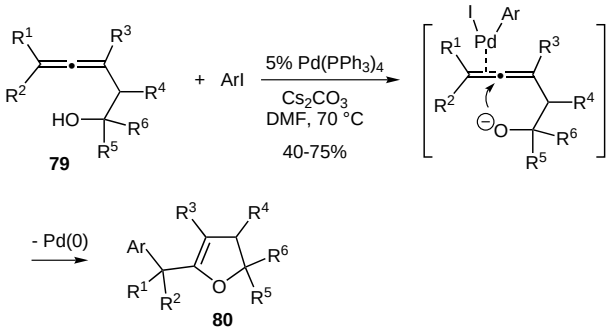


Scheme 30

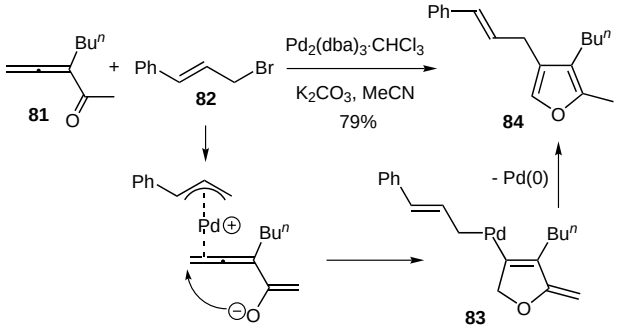
β-hydride elimination (n = 0), or may undergo internal nucleophilic attack to produce aryl or alkenyl substituted heterocycles **77** and/or **78** depending on the regioselectivity of this attack. However, the alternative mechanism related to the above-mentioned cyclisation reactions that involves attack 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^2-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_2CO_3 as base. Only traces of the cyclised products were isolated in the presence of Na_2CO_3.

Polysubstituted 3-allyl furans **84** could be synthesized via reaction of allenyl ketone **81** with allylic bromide **82**.[41] The reaction occurred using $Pd_2(dba)_3 \cdot CHCl_3$ 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).



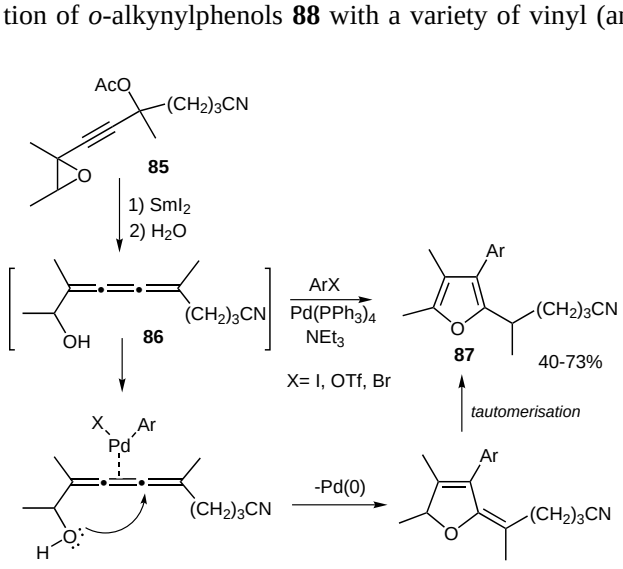
Scheme 31



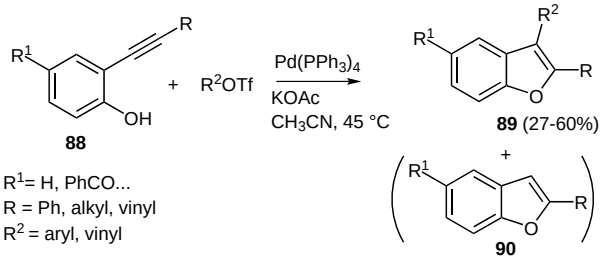
Scheme 32

A synthesis of tetrasubstituted furans **87** was developed using a one-pot, two-step sequence. It involved first a SmI_2-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 $Pd(PPh_3)_4$ and Et_3N 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 $Pd(PPh_3)_4$ 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]

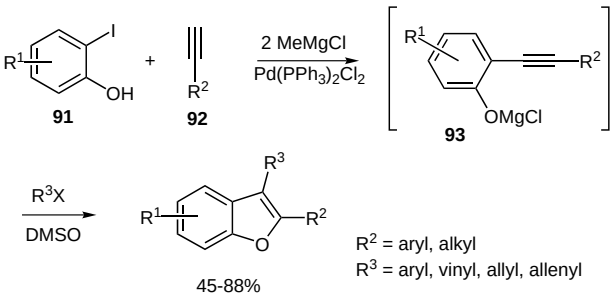


Scheme 33



Scheme 34

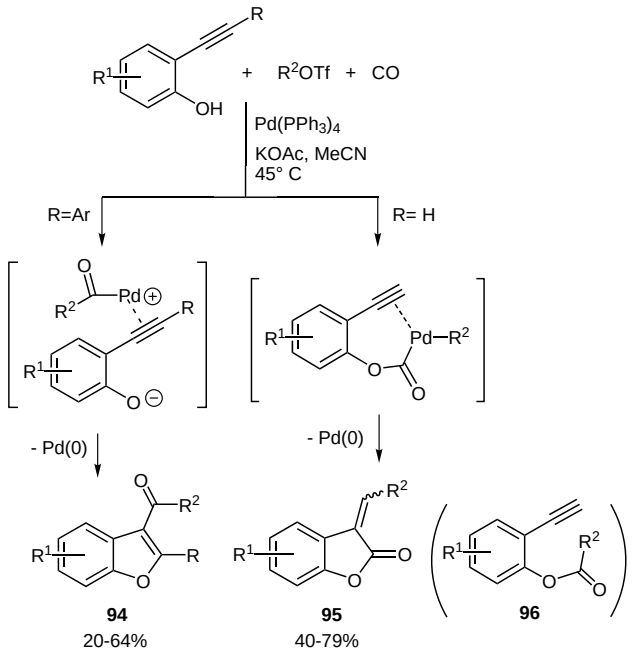
This competing side reaction could be avoided by using a one-pot three-component coupling process recently developed by Flynn and co-workers.[44] In this reaction, the possibility of direct cyclisation was prevented by initial deprotonation of a mixture of *o*-iodophenols **91** and terminal alkynes **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).



Scheme 35

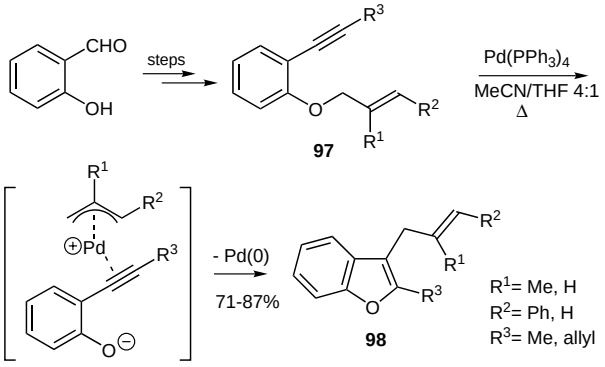
Arcadi and Cacchi performed the cyclisation reaction of *o*-ethynylphenols with vinyl triflates under carbon monoxide. Different products were obtained depending on the substitution pattern of the alkyne in the starting phenol (Scheme 36). With internal alkynes, CO insertion into aryl or alkenyl palladium 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 alkynes 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 *aryl iodides* in place of *vinyl triflates* resulted in the preferential formation of *o*-acyl derivatives **96**.[43,45] Recently, Fathi and Yang succeeded in applying this methodology to a selection of aryl iodides, and best results were obtained with *o*-ethynylphenols bearing electron-withdrawing substituents on the aromatic ring.[46] The three-component reaction developed by Flynn and co-workers[47] (Scheme 35) has also been performed under CO to access potent tubulin polymerisation inhibitors.



Scheme 36

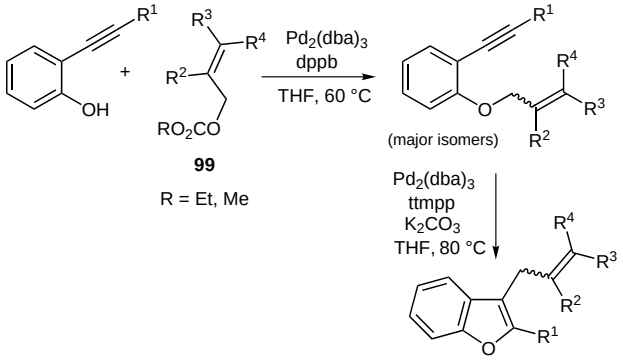
2-Substituted-3-allylbenzo[*b*]furans **98** were obtained in a complete neutral medium by starting from *o*-alkynylallyloxybenzenes **97** easily prepared from *o*-hydroxybenzaldehyde (Scheme 37). The heteroannulation process here was promoted by a η^3-allyl palladium complex formed in situ by oxidative addition of the palladium(0) complex to the starting allyl aryl ether. The reaction was limited to the



Scheme 37

cyclisation of internal alkynes, the terminal analogues giving rise to complex mixtures of products.[48]

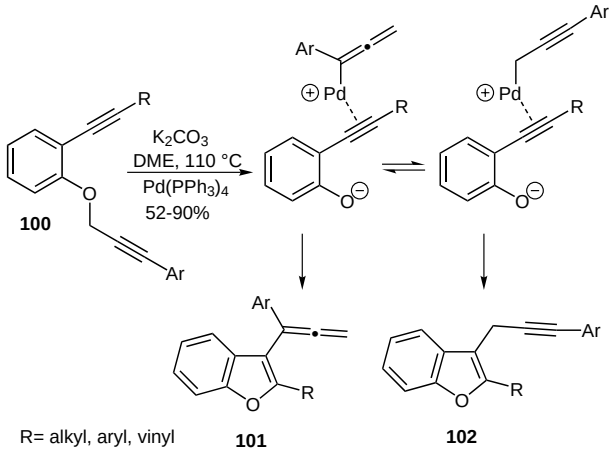
o-Alkynylallyloxybenzenes of type **97** may also be prepared from palladium-catalysed reaction of *o*-alkynylphenols with allyl carbonates **99**.[49] They may be isolated as stereo- and regioisomeric mixtures and be subsequently cyclised using $Pd_2(dba)_3$ and an electron-rich sterically encumbered ligand such as tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) (Scheme 38). When non-symmetric π-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 *o*-alkynylallyloxybenzenes was developed using $Pd(PPh_3)_4$ as catalyst.



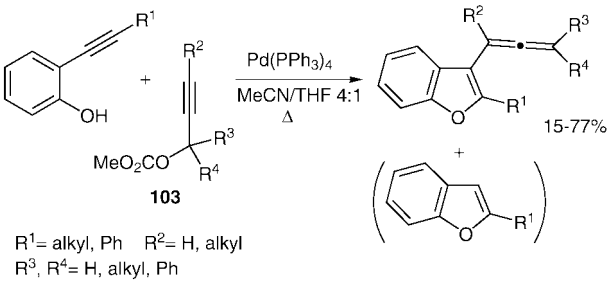
Scheme 38

This methodology was then applied to propargylic *o*-(alkynyl)phenyl ethers **100**. The reaction occurred in DME, at 110 °C, in the presence of $Pd(PPh_3)_4$ and K_2CO_3, and led to the expected 2-substituted-3-allenyl-benzo[*b*]furans **101**, which were in some cases, accompanied by their isomeric 2-substituted-3-propargylbenzo[*b*]furans **102** (Scheme 39). The presence of an aryl substituent on the terminal acetylenic carbon of the propargylic fragment in **100** was found to be crucial for the success of the reaction. The reaction proceeds either via σ-allenyl or σ-propargyl palladium intermediates formed by oxidative addition of the propargylic *o*-(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.[50]

2-Substituted-3-allenylbenzo[*b*]furans were also prepared from *o*-alkynylphenols using a procedure where the activating allenylpalladium species was issued from the reaction of propargyl carbonates **103** with Pd(0) (Scheme 40). In this case, formation of the isomeric propargylic benzofurans was not observed. Instead, as previously observed for similar reactions (see Scheme 34), small amounts of 2-substituted benzofurans were produced as side products. This procedure allowed the preparation of diversely substituted allenyl compounds.[51]



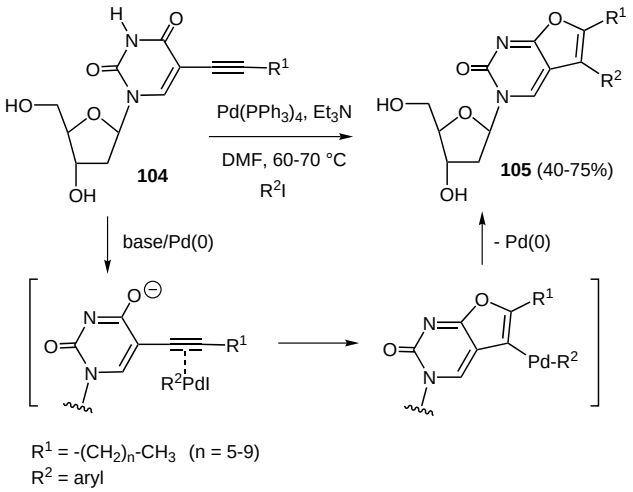
Scheme 39



Scheme 40

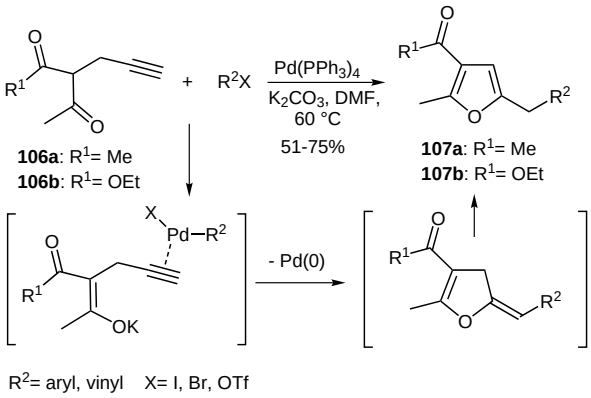
Deoxynucleoside analogues **105**, a series of inhibitors of varicella-zoster virus, have been synthesized from the corresponding alkynyl deoxyuridines **104** in moderate to good yields (40–75%).[52] The construction of the furo[2,3-*d*]pyrimidin-2-one nucleus has been achieved using $Pd(PPh_3)_4$ as catalyst and Et_3N 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**[54] with

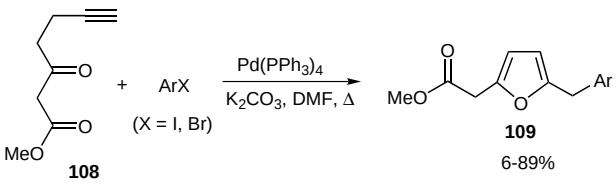


Scheme 41

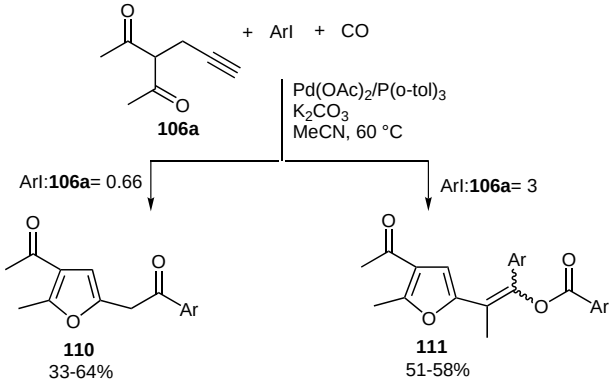
various unsaturated halides and triflates in the presence of $Pd(PPh_3)_4$ and K_2CO_3 provided valuable routes to substituted furans (**107a**, **107b**, or **109,** respectively) (Schemes 42 and 43). *Trans* addition of the oxygen nucleophile and the organopalladium complex across the triple bond was 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 arised from further reaction of **110** with the acylpalladium intermediate when an excess of unsaturated halide was used in the basic medium.[55]



Scheme 42



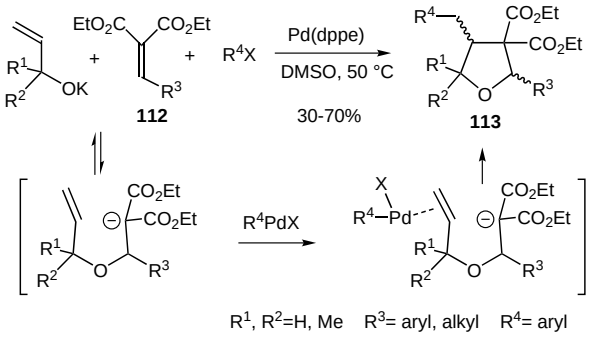
Scheme 43



Scheme 44

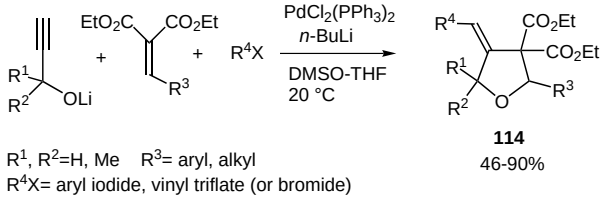
The development of multicomponent condensation reactions based on these new palladium-mediated cyclisation processes allowed resulted in the preparation of highly functionalised tetrahydrofurans in a single step from sim-

ple, readily available, and inexpensive starting materials. Activated olefins **112** 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 **113**. 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 (Scheme 45).[56]



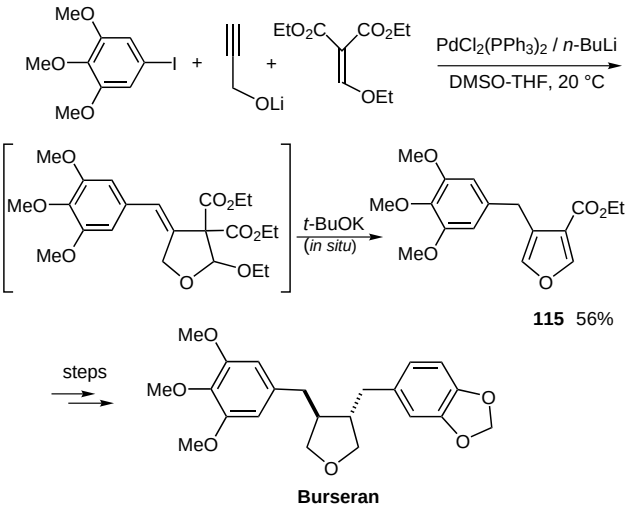
Scheme 45

Substitution of allylic alcohols for their propargylic analogues produced a new class of stereodefined arylidene (or alkenylidene) tetrahydrofurans **114** 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 $PdCl_2(PPh_3)_2$ with *n*-butyllithium has been found particularly effective (Scheme 46).[57]



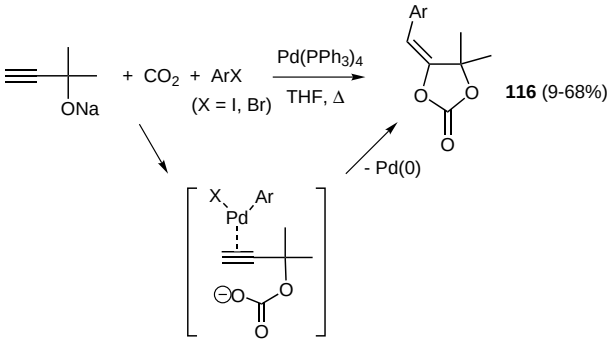
Scheme 46

A novel one-pot, two-step synthetic entry into functionalised 4-benzylfuran derivatives of type **115** was then developed by extending this strategy to the commercialy 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 (Scheme 47).[58]



Scheme 47

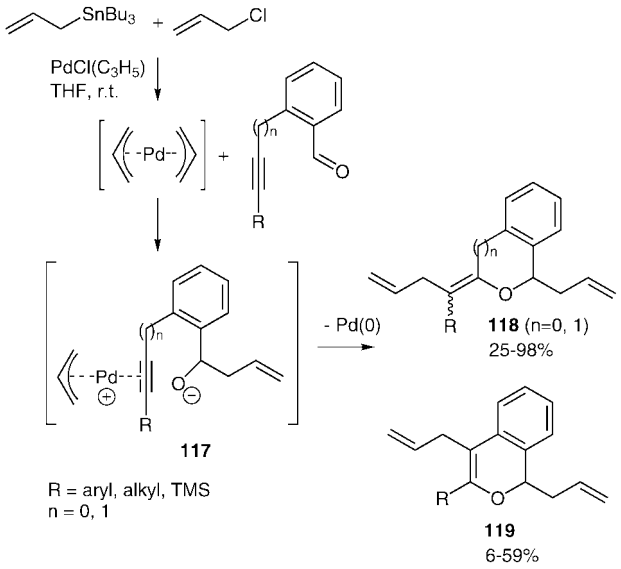
Two other examples of multicomponent reactions leading to oxygen heterocycles should be mentioned. The combination of sodium 2-methyl-3-butyn-2-olate, aryl halides and carbon dioxide to afford the cyclic vinylidene carbonates **116** (9–68% yields) was reported by Inoue and co-workers[59] in 1990. This 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 CO_2. This is followed by the attack of the newly formed oxygen nucleophile onto the triple bond activated by the arylpalladium species (Scheme 48).



Scheme 48

More recently, Yamamoto and co-workers[60] described the palladium-catalysed reaction of alkynylaldehydes with allyl chloride and allyltributylstannane to yield cyclic ethers **118** and **119**. The reaction is based on the in situ generation of a nucleophilic bis-π-allylpalladium complex that reacts with aldehydes to produce intermediates **117**. The

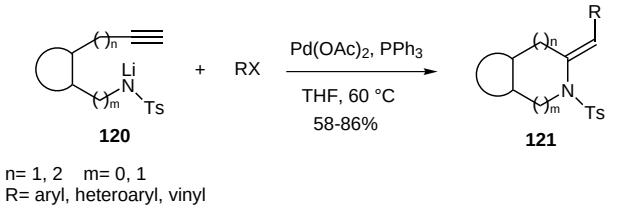
cyclisation of the latter furnishes the corresponding *exo*-products **118** and/or their *endo*-isomers **119** depending on the structure of the starting alkynylaldehyde (Scheme 49).



Scheme 49

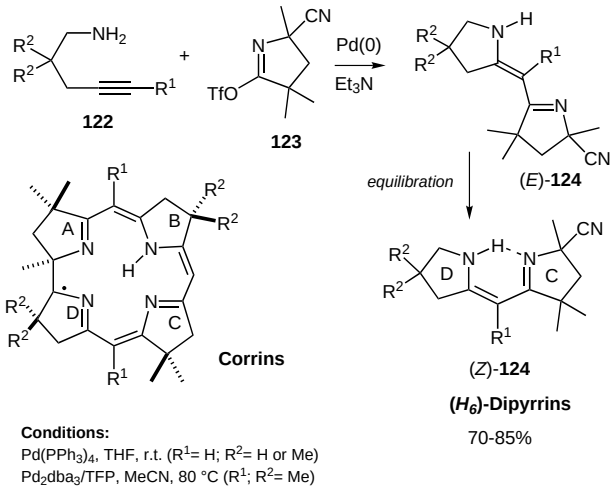
3.2 Nitrogen Heterocycles

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).



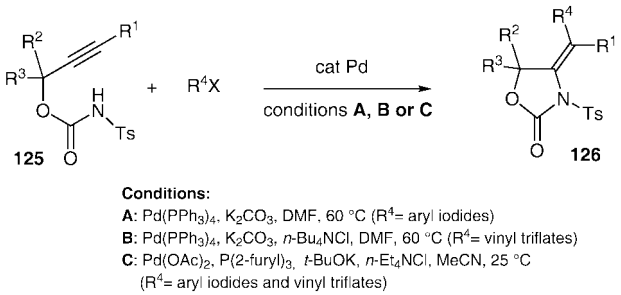
Scheme 50

This strategy was used for the construction of hexahydrodipyrrins **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 amines **122a** (R^1 = H) were subjected to the palladium-initiated cyclisation reaction with imidoyl triflate **123** as coupling partner using the reagent system $Pd(PPh_3)_4/NEt_3$/THF. This afforded the (*Z*)-(H_6)-dipyrrins **124** as a result of rapid equilibration of the initially formed *E*-isomer. For the internal 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_2dba_3/TFP/$BnN(Et)_3Cl$.



Scheme 51

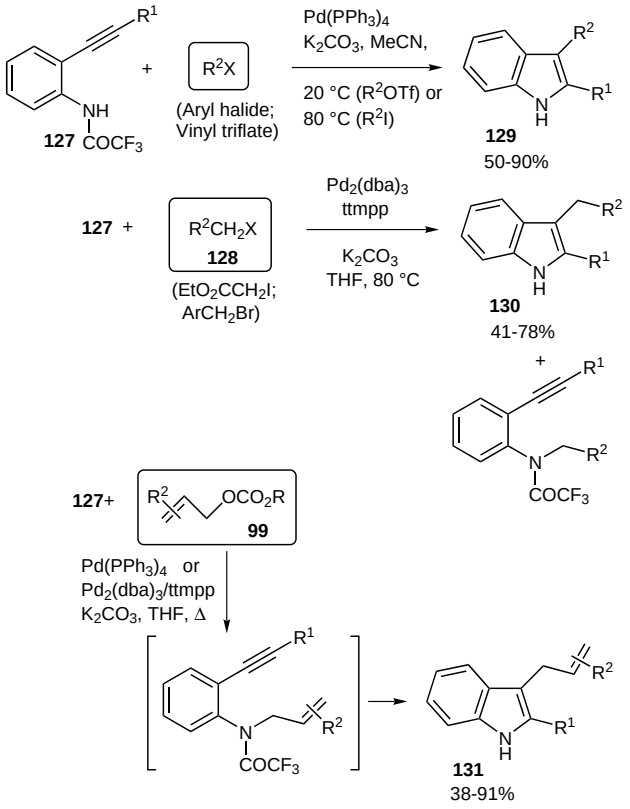
The synthesis of stereodefined 4-arylidene-3-tosyloxazolidin-2-ones **126** starting from propargyl tosylcarbamates **125** has been simultaneously reported by Arcadi[64] and Balme[65] (Scheme 52). Both electron-rich and electron-poor aryl iodides and vinyl triflates took part in the reaction and, generally, 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 $K_2CO_3/Pd(PPh_3)_4$ system[64] 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.



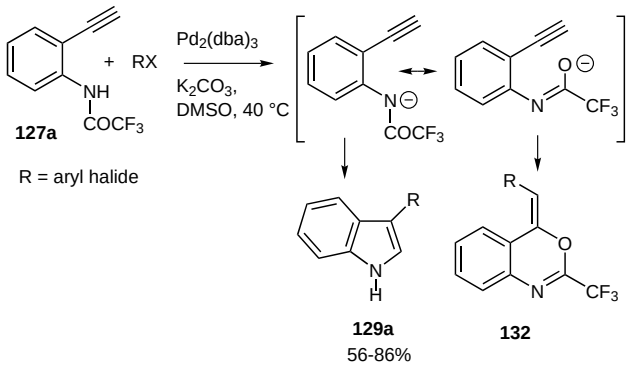
Scheme 52

The cyclisation reaction of *o*-alkynyltrifluoroacetanilides **127** promoted by various organopalladium complexes generated in situ from $C_{sp}2$ donors such as aryl and vinyl halides (or triflates),[66] as well as allyl esters **99**,[67] and alkyl halides **128**[68] 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]

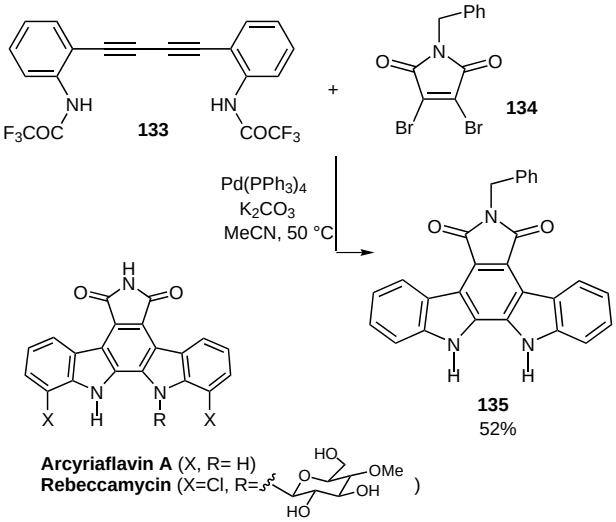


Scheme 53



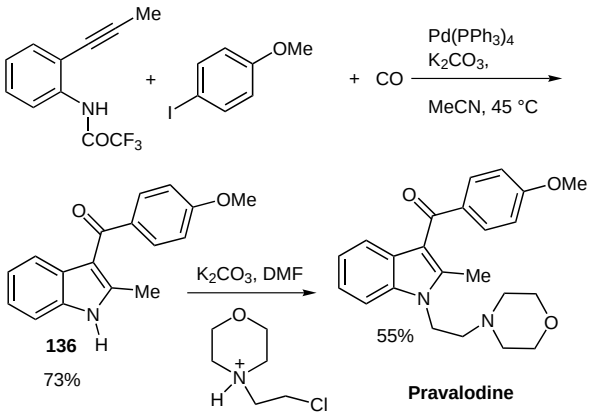
Scheme 54

Based on the same strategy, the indolo[2,3-*a*]carbazole ring system **135**, common to Arcyriaflavin A and Rebeccamycin was prepared by palladium(0)-catalysed polyannulation 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]



Scheme 55

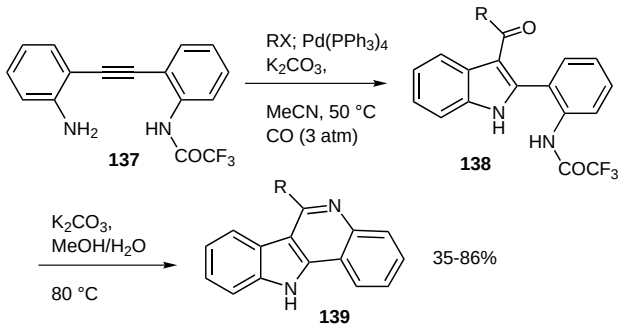
A new route to the interesting class of 2-substituted-3-acylindoles of type **136** was also developed by carrying out the cyclisation reaction of the *o*-alkynyltrifluoroacetanilides in the presence of carbon monoxide.[72] This methodology was applied to the synthesis of Pravalodine, a biologically active molecule designed as an analogue of non-steroidal anti-inflammatory drugs (NSAIDS) (Scheme 56).



Scheme 56

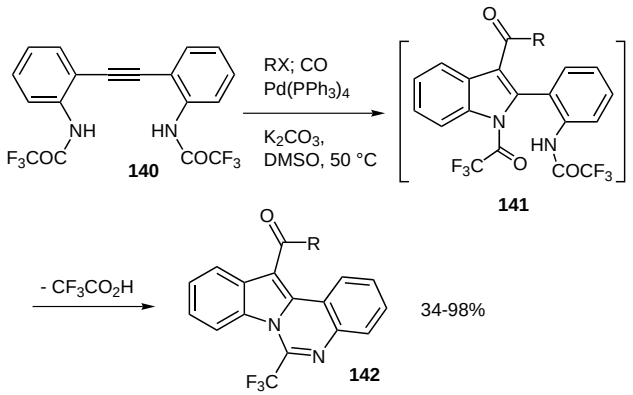
When the carbonylation of aryl iodides was performed in the presence of *o*-(*o*-aminophenyl) trifluoroacetanilide **137**, the palladium-catalysed carbonylative cyclisation was followed by the intramolecular reaction of the amino group on the 3-acylindole intermediate **138** to afford 6-aryl-11*H*-indolo[3,2-*c*]quinolines **139** in moderate to

good yields (Scheme 57). The reaction was catalysed by $Pd(PPh_3)_4$ and took place in anhydrous MeCN at 50 °C using K_2CO_3 as base under 3 atm of carbon monoxide.[73]



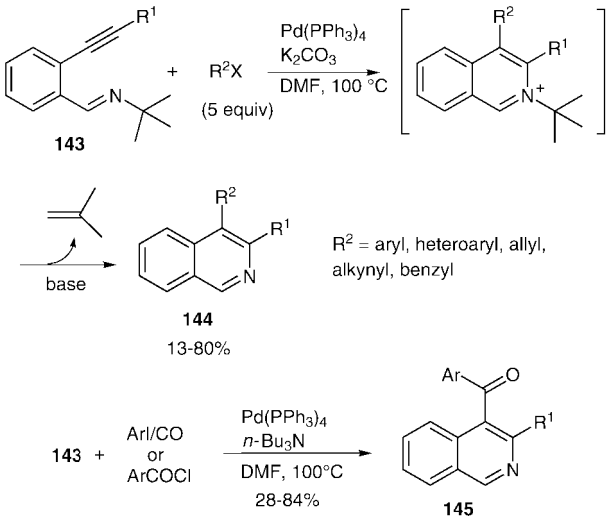
Scheme 57

Interestingly, the same reaction developed on bis(*o*-trifluoro acetamidophenyl)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]



Scheme 58

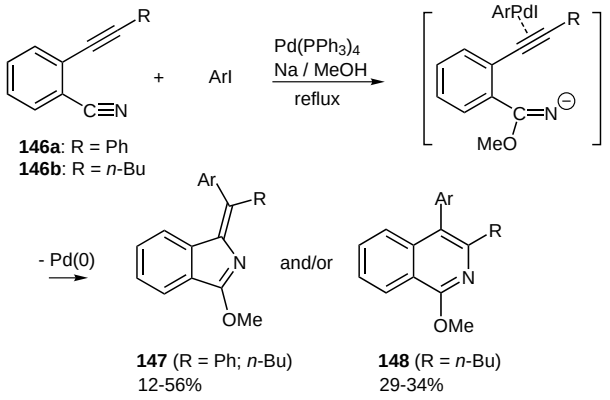
Various 3,4-disubstituted isoquinolines **144** have recently been prepared via an intramolecular cyclisation of *N*-*tert*-butyl-*o*-(1-alkynyl)-benzaldimines **143** promoted by vinyl-, aryl-, allyl- or alkynylpalladium complexes (Scheme 59). The cyclisation took place in DMF at 100 °C using 0.05 equivalent of $Pd(PPh_3)_4$ in the presence of K_2CO_3 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 alkyne 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-aroyl isoquinolines **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]



Scheme 59

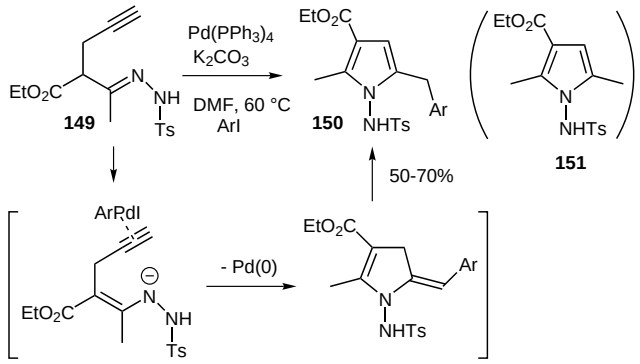
The reaction of 2-alkynylbenzonitriles **146** with sodium methoxide and phenyl iodide, or other aryl iodides bearing electron-donating substituents, was developed using $Pd(PPh_3)_4$ as catalyst for the formation of five- or/and six-membered ring heterocycles, namely the isoindoles **147** and isoquinolines **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-diarylmethylideneisoindoles **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-



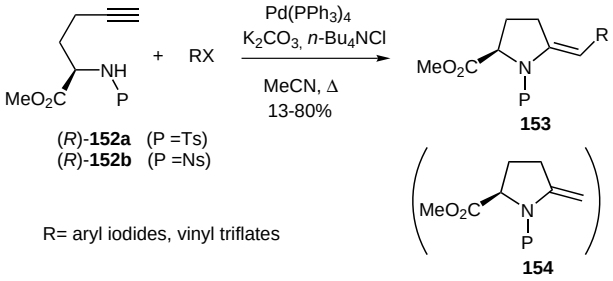
Scheme 60

tive attack of the nitrogen onto the palladium-activated triple bond. In some cases, in addition to the product, a substantial amount of pyrrole **151** issued from direct *exo-dig* cyclisation was isolated. The formation of this side product was highly dependent on the nature of the palladium catalyst and might be promoted by a σ-alkynyl-palladium(II) species generated in situ from insertion of the palladium into the C_{sp}-H bond of the starting material.[2] This competing reaction could be limited by running the reaction in DMF at 60 °C, in the presence of K_2CO_3 as base and $Pd(PPh_3)_4$ as the catalyst.[80] It should be mentioned that phosphorylated (and phosphinylated) 1-aminopyrroles have also been synthesized by another group[81,82] using a similar strategy.



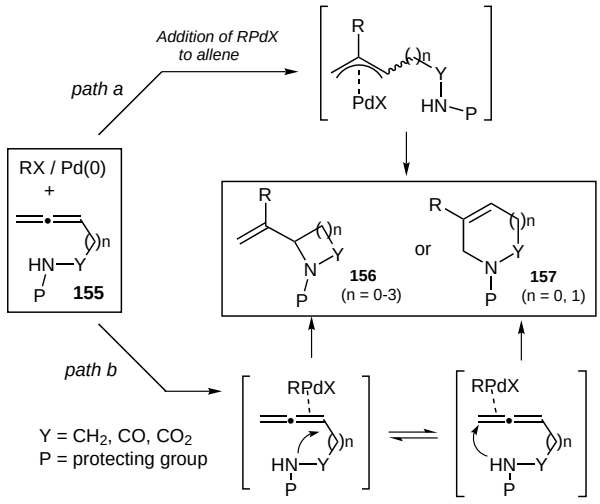
Scheme 61

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-workers[25,26] (Scheme 62). The reaction must be carried out in MeCN, at 60–80 °C, using 0.1 equivalent of $Pd(PPh_3)_4$ and 5 equivalents of K_2CO_3. The presence of *n*-Bu_4NCl 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.



Scheme 62

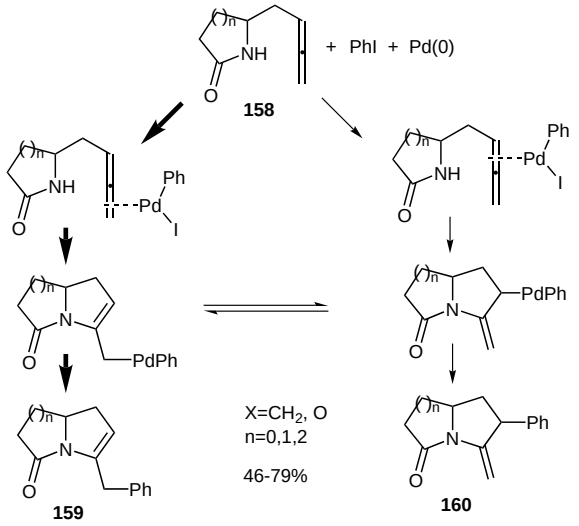
The palladium(0)-catalysed coupling reaction of unsaturated halides, triflates, hypervalent iodonium salts or allyl halides with allenes bearing an amino group separated from the carbon atom by one to four carbon atoms (**155**) has been studied by several groups.[38,83–90] These reactions have permitted the synthesis of a large variety of three to six-membered azacycles (**156**, **157**). As previously discussed in section 3.2, two plausible mechanisms may be envisaged (Scheme 63). In one case (path a), addition of the organopalladium species to the allene precedes attack of the internal nucleophile.[91,92] In the other case (path b), the intramolecular nucleophilic attack of the lactam nitrogen onto one of the double bonds of the activated allene first occurs.



Scheme 63

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-butadienyl)lactams **158** with aryl halides using reaction conditions developed by Gallagher and co-workers.[84] Generally, a mixture of two regioisomeric cyclisation products **159** and **160** was obtained, resulting from the ac-

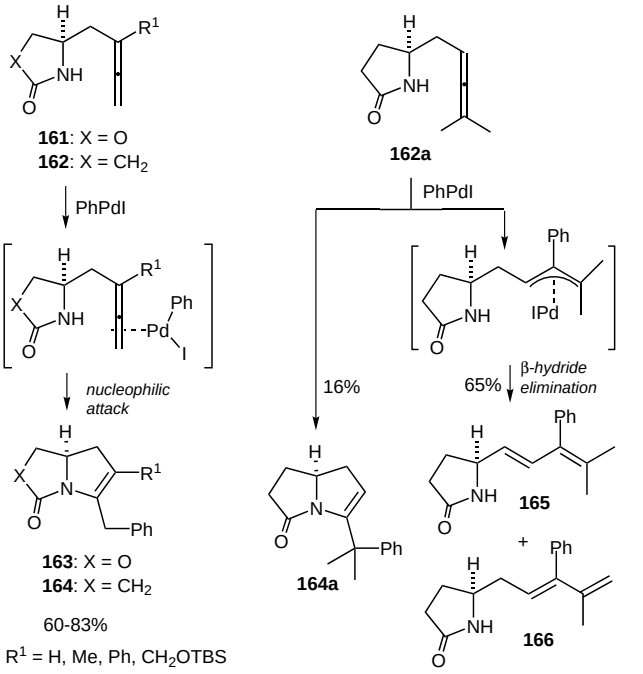
tivation of either the terminal or the internal double bond of the allene by the organopalladium species. In this case, the reaction mechanism proposed by Tsuji[91] for heteronucleophiles and by Goré and Cazes[92] for carbonucleophiles could be ruled out since such a mechanism would have led to the formation 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.



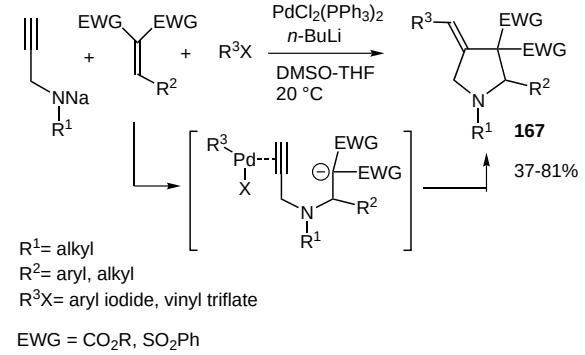
Scheme 64

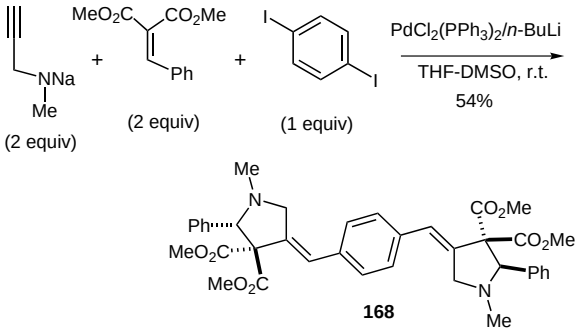
The same reaction was then developed on enantiopure allenic oxazolidinones **161** and lactams **162** easily prepared from (*S*)-pyroglutamic acid and L-serine, respectively (Scheme 65). These substrates when subjected to the previous cyclisation reactions afforded enantiopure bicyclic enamides **163** 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 alkenylidene)-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 $PdCl_2(PPh_3)_2$ 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.



Scheme 65





Scheme 66

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 carbo- 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.

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