Pd-Assisted Multicomponent Synthesis of Heterocycles

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This review highlights some remarkable recently made achievements in the application of palladium-mediated processes to the design of multicomponent one-pot syntheses of heterocyclic compounds. Palladium-catalysed cascade reactions are surveyed, together with processes based on sequential, one-pot performance of individual transformations in which at least one is catalysed by palladium.

1. Introduction

The development of new chemical processes designed to produce elaborate heterocyclic structures in a rapid, environmentally friendly way has become an important area of research in organic chemistry. Such processes are highly desirable for the rapid generation of libraries of small molecules for high through-put screening in searches for new drug candidates. Multicomponent processes are at a premium for the achievement of high levels of diversity and brevity, as they allow three or more simple and flexible building blocks to be combined in practical, one-pot oper-

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Emmanuel Bossharth (left) was born in 1975 in Colmar, France. He studied chemistry at the ''Ecole Nationale Supérieure de Chimie de Montpellier'', where he obtained his ''diplôme d'ingénieur''. He is currently a third year PhD student at the University of Lyon in the research group of Dr G. Balme, working on the synthesis of funiculosine analogues and the development of new palladium-catalysed multicomponent reactions. His main interests are in the field of organometallic chemistry and multi-step synthesis.

Nuno Monteiro (centre) 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 in research on new palladium-mediated cyclisation processes. Following a one-year period as ''A.T.E.R.'' (Attaché Temporaire d'Enseignement et de Recherche) at the same university, in the autumn of 1993 he joined 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.

Geneviève Balme (right) 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 PhD degrees at the same University (Doctorat de 3ième cycle-1979: supervisors Pr. Jacques Goré and Dr Max Malacria; Doctorat d'état-1983: supervisor Pr. 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.

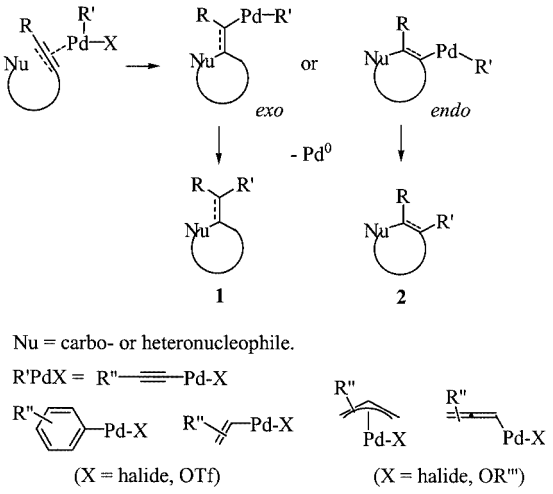
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

ations.[1] The outstanding potential of palladium-catalysed processes for the development of multicomponent reactions lies in the diversity of bond-forming processes available, the high levels of chemo-, regio-, and stereoselectivity generally observed, and their functional group tolerance.[2] In addition, concomitant incorporation of carbon monoxide into the final products may contribute in increasing the diversity of accessible compounds in many ways.[3,4] It is therefore not surprising that many efforts are being devoted to this new area of research. Ideal multicomponent syntheses allow the simultaneous addition of all reactants, reagents, and catalysts at the onset of the reaction, which requires that all reactants combine in a unique ordered manner under the same reaction conditions. However, the design of efficient novel reactions that satisfy such requirements is fraught with difficulties, as the problems one may have to face in avoiding side reactions are numerous. Palladium-mediated cascade reactions proceeding through non-isolable intermediates, such as catalytic organometallic species, may contribute to the discovery of such systems. Occasionally, the addition of certain reactants, reagents or catalysts can be delayed, so as to increase efficiency. This may occur in the case of multicomponent condensations based on sequences of individual transformations combined into a one-pot process designed to avoid isolation of intermediates. Adjustment of the reaction parameters may also be made during the course of these multiple-reaction chemical processes. The sequential addition strategy may apply to sequences of independent, consecutive Pd-catalysed processes, but combinations of Pd-catalysed reactions with other common organic transformations may also be considered. The focus of this review is to discuss recent achievements in the design of palladium-based multicomponent syntheses of heterocycles through a selection of examples from our laboratories as well as contributions from other groups, with a special emphasis on synthetic strategies. It is essentially concerned with reactions involving at least three potentially variable reactants. As a consequence, a number of processes based on the use of carbon monoxide have not been considered. Particular attention is also given to procedures in which the newly formed heterocyclic ring incorporates at least two components.

2. Cyclisation of Alkyne (or Alkene) Containing Nucleophiles

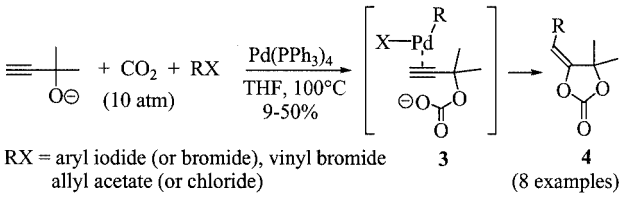
The palladium-catalysed reaction between nucleophiles bearing a tethered double or triple bond and organic halides has been developed by our group and by others into a versatile and efficient method by which to access diversely substituted carbo- and heterocyclic systems of types **1** and **2**. In this Wacker-related process, oxidative addition of an organic halide to the Pd^0 catalyst generates an organopalladium reagent, which activates the unsaturated moiety towards nucleophilic attack (Scheme 1).[5]

The wide range of available organopalladium reagents and the simplicity of the procedures make this process



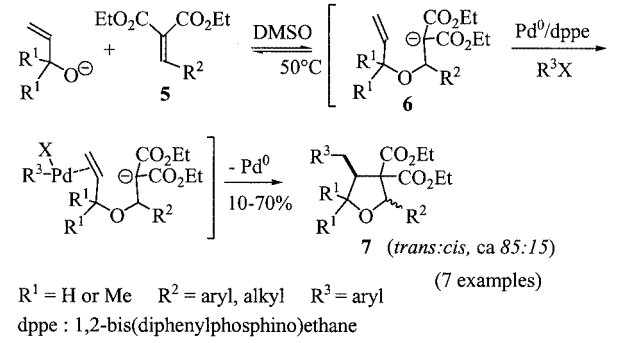
Scheme 1

highly attractive for the design of multicomponent reactions. The principal strategy toward this end has consisted of finding ways of generating the alkyne (or alkene) tethered nucleophilic precursor in situ through some reaction between two readily available reactants. The first procedure based on this strategy was developed by Inoue and co-workers in 1990, to access cyclic vinylidene carbonates **4** in low to moderate yields. The reaction involves cyclisation of a monoalkylcarbonate **3** generated by treatment of a propargylic alkoxide with carbon dioxide (10 atm). However, the process proved rather limited as the organic halide was found to be the sole flexible reactant (Scheme 2).[6]



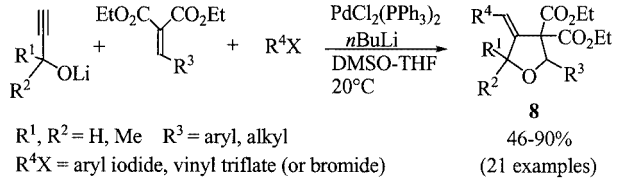
Scheme 2

In recent years our group has been developing similar strategies based on the conjugate addition of allylic (or propargylic) nucleophiles to electron-deficient olefins. For instance, addition of allylic alkoxides to diethyl arylidenemalonates (or alkylidenemalonates) **5**, easily prepared from the corresponding aldehydes by Knoevenagel reactions, generates intermediates **6**, which may undergo cyclisation-coupling reactions with various aryl iodides to yield highly substituted 3-benzyltetrahydrofurans **7** (*trans*/*cis* 85:15). This cascade process needed all reactants to be present in the reaction vessel at the same time, due to the reversibility of the conjugate addition step (Scheme 3). The use of slow addition techniques for the introduction of the allylic alkoxide partner proved necessary in order to avoid side reactions. The reaction proceeded well in DMSO at 50 °C in the presence of 5 mol % Pd^0/dppe, and the best results were obtained with potassium allylic alkoxides and with KH as base.[7]



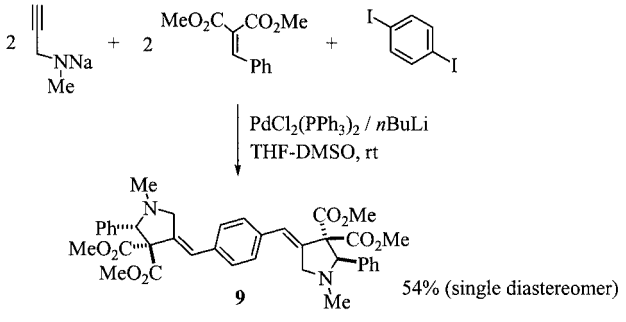
Scheme 3

The strategy was then applied to propargyl alkoxides, which proved much more reactive, allowing all components to be introduced simultaneously at the onset of the reaction with no side reaction occurring. Thus, equimolar amounts of lithium propargylic alkoxides (generated by treatment of the corresponding alcohols with *n*BuLi), conjugate acceptors and various organic halides (and triflates) were allowed to react in DMSO/THF at room temperature in the presence of 1 to 5 mol % of a Pd^0 catalyst obtained by reduction of $[PdCl_2(PPh_3)_2]$ with *n*BuLi, to afford stereodefined 3-arylidene (and alkenylidene) tetrahydrofurans **8** as single products in high yields and with short reaction times (Scheme 4).[8]



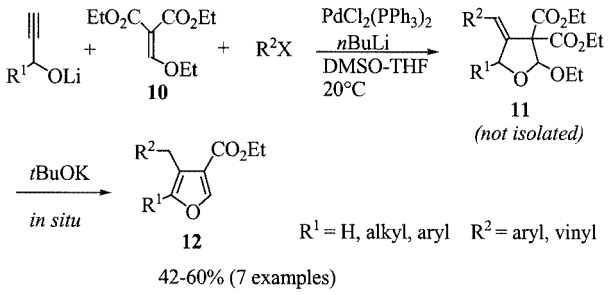
Scheme 4

The analogous pyrrolidines were also accessible under similar conditions, sodium amides, however, giving better results than the corresponding lithium salts. For instance, assembly of five reactants was successfully achieved through the use of 1,4-diodobenzene as a bis-coupling partner, producing the symmetrical bis(pyrrolidine) **9** as a single diastereomer in 54% isolated yield. Overall, four carbon−carbon bonds, two carbon−nitrogen bonds, and two cyclic systems were formed in a single operation (Scheme 5).[9]

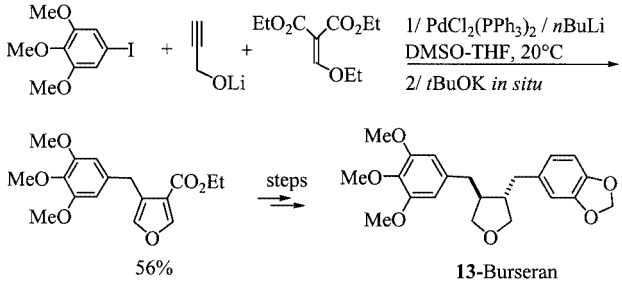


Scheme 5

An interesting extension of this chemistry to the one-pot preparation of furan derivatives **12** has been achieved by integration of the cyclisation reaction of the commercially available diethyl ethoxymethylenemalonate **10** with the eliminative decarboxylation of the resulting tetrahydrofuran **11**, effected in situ through the addition of a slight excess of *t*BuOK (Scheme 6). The entire process involved a sequence of a conjugate addition, a palladium-catalysed cyclisation-coupling reaction, an alkoxide-induced eliminative decarboxylation and, finally, a double bond isomerisation. A formal synthesis of the lignan antitumor Burseran **13** with this process as a key step illustrated the potential utility of this concept for the synthesis of important natural products of the lignan family (Scheme 7).[10]

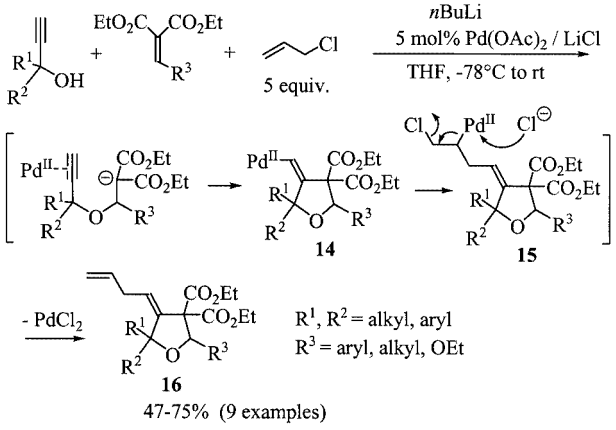


Scheme 6



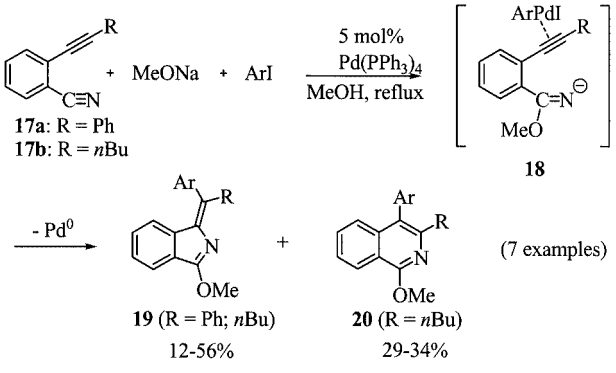
Scheme 7

More recently, Lu and Liu have also utilised the hetero-Michael addition of lithium propargylic alkoxides to alkylidene malonates in a synthesis of allylidene tetrahydrofurans **16**, based on the use of allyl chloride as a coupling partner. The reaction is initiated by addition of a catalytic amount of $Pd(OAc)_2$ and proceeds in THF at room temperature. In contrast with the previous reactions, the suggested mechanism does not involve activation of the triple bond by an organopalladium complex, in this case a (π-allyl)Pd species. Nucleophilic attack of the stabilised carbanion onto the alkyne to give vinylpalladium **14** is thought to be assisted by a Pd^{II} salt. Subsequent coupling of this with allyl chloride furnishes intermediate **15**, which undergoes β-Cl elimination in the presence of an excess of lithium chloride to give the desired heterocycle and to regenerate the Pd^{II} catalyst (Scheme 8).[11]



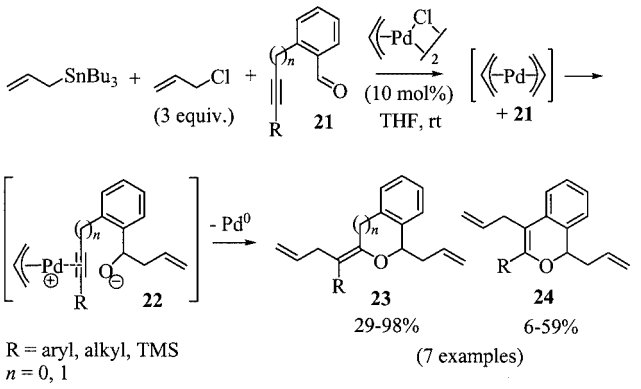
Scheme 8

Wu and co-workers developed a synthesis of benzannulated nitrogen heterocycles **19** and **20** based on the addition of sodium methoxide to 2-alkynylbenzonitriles **17** in methanol, followed by the $Pd(PPh_3)_4$-catalysed heteroannulation of the ketimine intermediate **18** with phenyl iodide, or with other aryl iodides bearing electron-donating substituents. The mode of cyclisation − 5-*exo* or 6-*endo*, resulting in isoindoles **19** or isoquinolines **20**, respectively − proved to be dependent on the nature of the substituent on the terminal alkyne carbon. 2-(2-Phenylethynyl) benzonitrile **17a** underwent exclusive 5-*exo* cyclisation, whereas 2-(1-hexynyl)benzonitrile **17b** gave mixtures of isomers with a marked preference for the 6-*endo* mode of cyclisation. This *endo*/*exo* balance was attributed to steric interactions between the entering group and the substituent on the terminal alkyne carbon (Scheme 9).[12]



Scheme 9

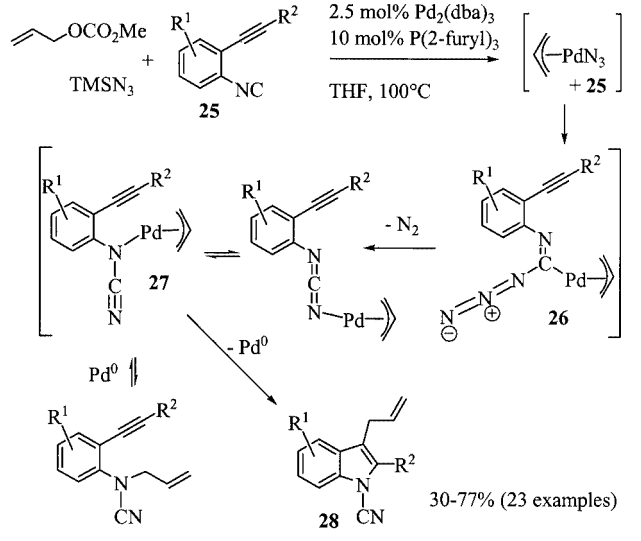
Yamamoto and co-workers described the palladium-catalysed reaction of alkynylaldehydes **21** with allyl chloride and allyltributylstannane to yield cyclic ethers **23** and **24**. The reaction is based on the generation of a nucleophilic bis(π-allyl)Pd complex in situ. This reacts with aldehydes **21** to produce benzyloxide intermediates **22**. Cyclisation of these furnishes the corresponding *exo* products **23** and/or their *endo* isomers **24**, depending on the structure of the starting alkynylaldehyde (Scheme 10). In this communication the alkynylaldehyde was the sole flexible reactant.[13]



Scheme 10

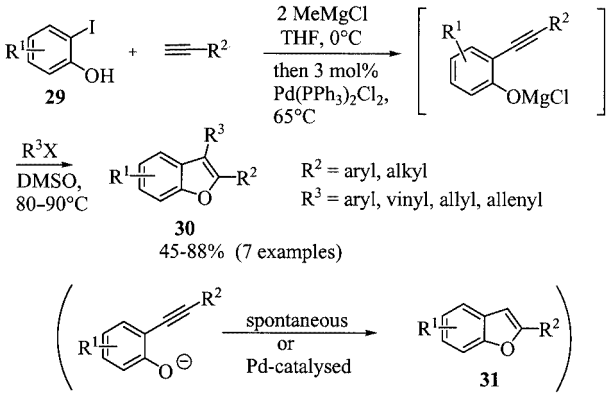
The same authors have also reported the three-component synthesis of *N*-cyanoindoles **28** based on the generation in situ of a (π-allyl)Pd aryl cyanamide complex **27**, the result of a Curtius-like rearrangement and isomerisation of intermediate **26** (Scheme 11). The reaction takes place between 2-alkynylisocyanobenzenes **25**, allyl methyl carbonate and trimethylsilylazide in the presence of catalytic $[Pd_2(dba)_3]$, with tris(2-furyl)phosphane as ligand, at 100 °C in THF. Good yields were generally obtained independently of the substitution pattern on the aryl ring.[14] This process is an interesting extension of a new Pd-catalysed reaction previously developed by the same authors for the preparation of allyl aryl cyanamides.[15] It is worth noting that the palladium-catalysed heteroannulation reaction between *o*-alkynylanilines and allylic carbonates had previously been reported by Cacchi[16] as another method by which to access 3-allylindoles.

These cyclisation processes of alkynyl compounds also represent valuable tools for the design of one-pot sequential condensation reactions in which the same palladium catalyst intervenes in more than one individual step. Indeed, new multicomponent approaches toward bicyclic heterocyclic systems based on the one-pot execution of Pd-cata-



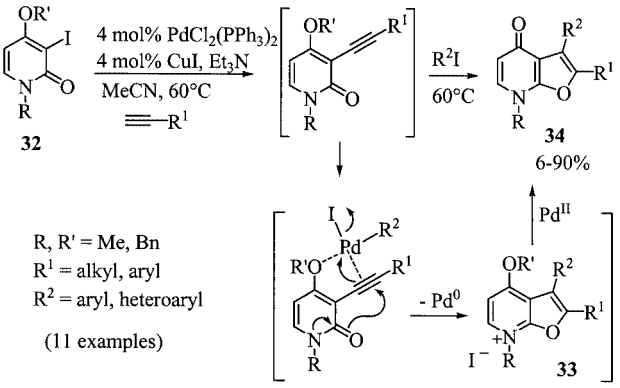
Scheme 11

lysed Sonogashira coupling reactions between terminal alkynes and organic halides[17] and Pd-based cyclisation-coupling processes have been developed. A central requirement for the development of such sequential processes is that the terminal alkyne must be consumed before the introduction of the organic halide, in order to avoid undesired side reactions. Flynn reported a practical procedure for the preparation of 2,3-disubstituted benzo[*b*]furans **30** from *o*-iodophenols **29**, terminal alkynes and organic halides (or triflates). Initial deprotonation of a mixture of **29** and terminal alkyne with two equivalents of MeMgCl in THF was followed by Sonogashira coupling, affording *o*-alkynylphenoxide intermediates. In situ addition of a DMSO solution of the organic triflate or halide furnished the corresponding benzo[*b*]furans in good yields. In addition to the simplification of the experimental procedures, the advantage of the one-pot process over the stepwise synthesis lies in the fact that it overcomes the formation of simple 2-substituted benzo[*b*]furans **31** as side products. Indeed, *o*-alkynylphenols have a propensity to undergo direct *endo*-dig cyclisation, particularly in the presence of a palladium catalyst. This may occur not only during the heteroannulative process but also during the initial coupling of the *o*-iodophenols with the terminal alkynes. Previous stepwise syntheses reported by Cacchi's group required additional protection and deprotection steps for the phenolic hydroxy group (Scheme 12).[18] The chemistry has also been applied to the synthesis of indole derivatives. In addition, insertion of carbon monoxide may be achieved, to yield 3-aroyl benzo[*b*]furan- and indole-based tubulin polymerisation inhibitors.[19]



Scheme 12

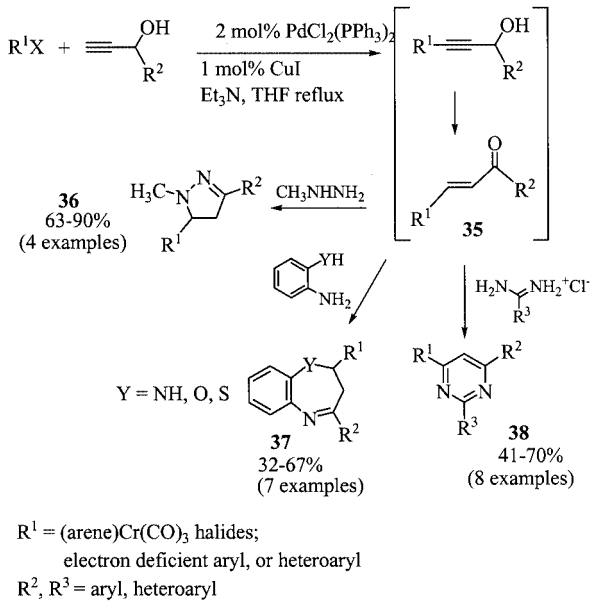
A similar strategy has been developed in our laboratories for the preparation of diversely substituted furo[2,3-*b*]pyridones **34** from 3-iodo-2-pyridones **32**. These underwent Sonogashira coupling with terminal alkynes in the presence of 4 mol % $[PdCl_2(PPh_3)_2]$ and 4 mol % CuI, in a mixture of MeCN/Et_3N at 60 °C, after which aryl halides were added to effect the heteroannulation. This produces furopyridinium salts **33**, which collapse to form the desired pyridones through subsequent cleavage of the oxygen protecting group, apparently mediated by a Pd^{II} species. Remarkably, a single palladium catalyst intervenes in three different transformations in this process, acting alternatively as an organometallic reagent or as a Lewis acid (Scheme 13).[20]



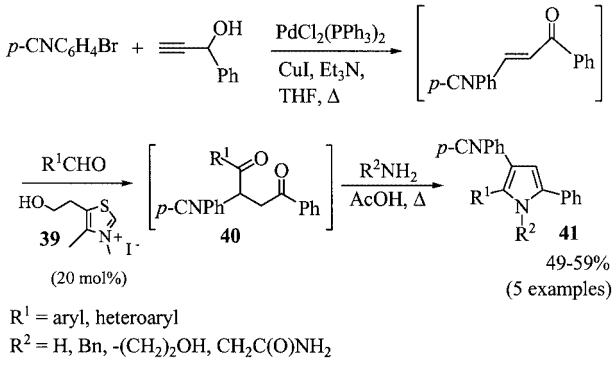
Scheme 13

3. Cross-Coupling between Terminal Alkynes and Organic Halides

As demonstrated in the previous examples, coupling reactions between unsaturated halides and terminal alkynes (Sonogashira process) may be used to generate diverse cyclisation-prone substrates in situ. Another interesting application of this process to the design of multicomponent reactions resulted from the discovery that Sonogashira coupling between terminal propargylic alcohols and sufficiently electron-poor sp^2-hybridized halogen compounds was followed by a base-catalysed isomerisation of the coupling products to afford the corresponding *trans*-configured enones.[21,22] Building on these findings, Müller and co-workers have developed various one-pot procedures for heterocycle synthesis based on the reactivity of the newly generated enones toward a selection of reagents found to be compatible with the reaction conditions. Thus, various electron-deficient π-systems and terminal propargyl alcohols were heated in THF in the presence of Et_3N and catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI. The resulting enones **35** were then alternatively treated in situ with *N*-methylhydrazine,[22] 2-amino- (or hydroxy-, or mercapto-) anilines[23] or amidinium salts[24] to produce pyrazolines **36**, 1,5-benzoheteroazepines **37** or pyrimidines **38**, respectively, upon heating (Scheme 14). The same authors have also reported a four-component system for the preparation of highly substituted pyrroles **41** by combining the coupling-isomerisation process with a Stetter reaction, to generate the 1,4-diketone intermediates **40**, and a subsequent Paal−Knorr cyclocondensation. The one-pot sequential addition procedure was set up as follows. The coupling-isomerisation of (*p*-CN)phenyl bromide with 1-phenyl-2-propyn-1-ol was conducted under the previously described conditions, after which the corresponding enone was treated with an aldehyde and heated in the presence of 20 mol % of thiazolium salt **39** to furnish the intermediate diketone. An excess of a primary amine and acetic acid were then added to the reaction mixture, which yielded the desired pyrrole upon heating (Scheme 15).[25]



Scheme 14

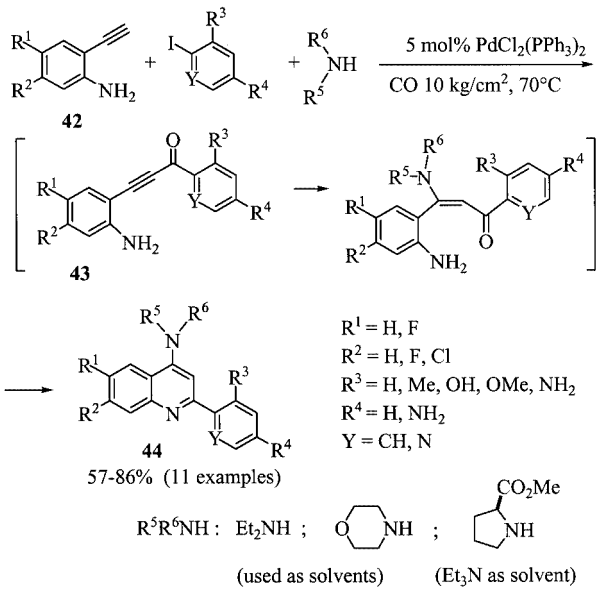


Scheme 15

Carbonylative coupling between terminal alkynes and aryl (and heteroaryl) halides offers a different approach to α,β-unsaturated ketones potentially utilisable as hetero-Michael acceptors. Torii and co-workers, for instance, reported a flexible method for the preparation of 2-aryl-4-*N*,*N*-dialkylaminoquinolines **44** based on the conjugate addition of dialkylamines to acetylenic ketones **43** − generated in situ from *o*-alkynylanilines **42** − followed by cyclocondensation between the carbonyl group and the internal arylamine (Scheme 16). The reaction proceeds in the presence of catalytic amounts of [$PdCl_2(PPh_3)_2$] under a carbon monoxide atmosphere, with the requisite dialkylamine generally used as solvent. The reaction was found not to be as effective with primary amines, which gave rise to competitive coupling reactions with the aryl iodide partner, generating benzamides as side products.[26]

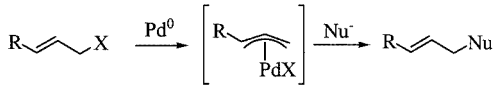
4. Nucleophilic Substitution of Allylic Compounds

The nucleophilic displacement of allylic compounds via π-allylpalladium complexes is a well established reaction



Scheme 16

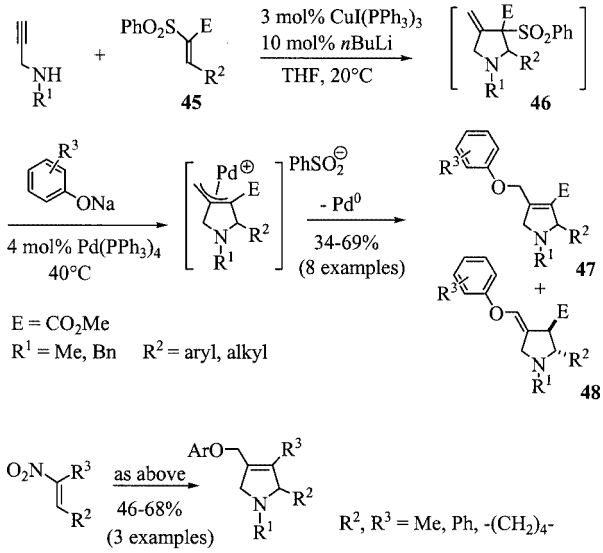
that allows the allylic alkylation of carbo- and heteronucleophiles with high levels of regio- and steroselectivity. A wide range of allylic substrates have been used as precursors of catalytic (π-allyl)Pd intermediates, amongst which allylic esters and carbonates have been by far the most widely employed. Nucleophilic attack generally occurs at the less hindered terminus of the π-allylpalladium species (Scheme 17).[27]



Scheme 17

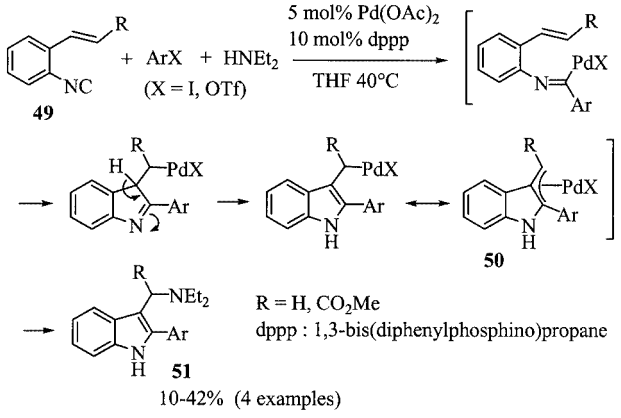
Applications of this chemistry to organic synthesis have been numerous and are still developing rapidly. The broad scope of the reaction should also offer great potential in the area of multicomponent heterocycle synthesis. For instance, a one-pot procedure for the preparation of substituted five-membered nitrogen heterocycles, based on a sequence of two metal-catalysed reactions, has been developed in our laboratories. The first step involves Cu-catalysed cycloaddition between propargylic nucleophiles and electron-deficient olefins, which gives access to *exo*-methylene heterocycles.[28,29,30] When applied to vinyl sulfones **45**, the corresponding heterocyclic allylic sulfones **46** may undergo a subsequent [$Pd(PPh_3)_4$]-catalysed sulfinate displacement by various phenolic derivatives in situ to yield 3(4)-phenoxymethyl pyrrolines **47** and their isomeric pyrrolidines **48**. This sequence exploits the dual reactivity of sulfones, which may act either as nucleophiles, through stabilization of an adjacent carbanion, or as leaving groups. In line with this, nitroolefins were also found to be very effective and ex-

panded the scope of this methodology further (Scheme 18).[31]



Scheme 18

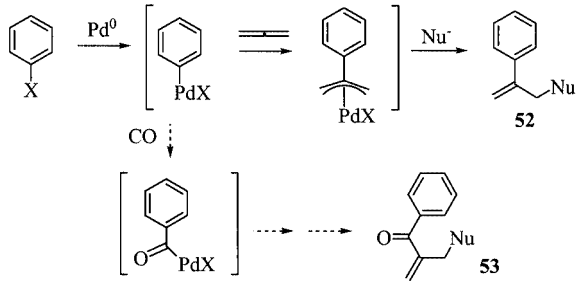
As can be seen in the next sections, in addition to the oxidative addition of allylic compounds to Pd^0 there are other well documented ways through which catalytic (π-allyl)Pd intermediates may be generated. Takahashi and co-workers have suggested that (indolylmethyl)palladium complexes of type **50** may be generated by coupling between *o*-alkenylphenyl isocyanides **49** and aryl iodides by an unusual pathway as depicted in Scheme 19. Oxidative addition of the aryl iodide to Pd^0 and successive insertions of the isocyano and alkene groups is followed by 1,3-migration of hydrogen to form the (π-allyl)Pd complex. Intermolecular trapping of this with diethylamine allows 2,3-disubstituted indoles **51** to be obtained in poor to moderate yields.[32]



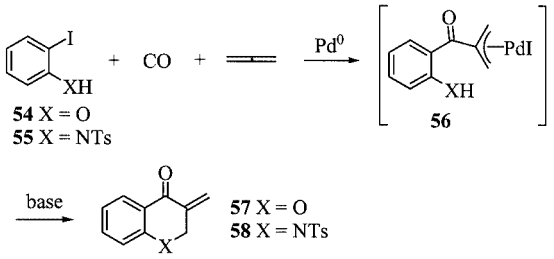
Scheme 19

5. Carbopalladation of Allenes

The carbopalladation of allenes with aryl halides represents a well known method for generation of catalytic (π-allyl)Pd species.[33] In this process, addition of an arylPd^{II} species, originating from oxidative addition of the aryl halide bond to Pd^0, to the allene occurs at the central carbon atom. The (π-allyl)Pd intermediate may then be trapped by a nucleophilic partner to yield styryl derivatives **52** (Scheme 20). In the presence of carbon monoxide, insertion of CO generates an aroylPd^{II} intermediate, which follows the same pathway to furnish chalcogen derivatives **53**. Grigg and co-workers have based many of their ingenious multicomponent reactions, the so-called "cascade molecular queuing processes", on intra- and intermolecular variations of this concept, which proved ideally suited for the synthesis of heterocycles.[34] Coupling of these cascade multicomponent processes with other consecutive transformations in the same pot is a way of increasing the diversity of the accessible compounds further. For instance, Grigg and co-workers[35] have prepared chroman-4-ones **57** and quinol-4-ones **58** from *o*-iodophenols **54** and *N*-tosyl *o*-iodoanilines **55**, respectively, based on a strategy previously developed by Alper.[36] Treatment of the aryl iodide with allene (1 atm) and carbon monoxide (1 atm) results in the formation of (π-allyl)Pd intermediate **56**, which undergoes intramolecular trapping by the heteronucleophile (Scheme 21). Generally, the reaction takes place in toluene with [$Pd(PPh_3)_4$] as catalyst and K_2CO_3 as base.

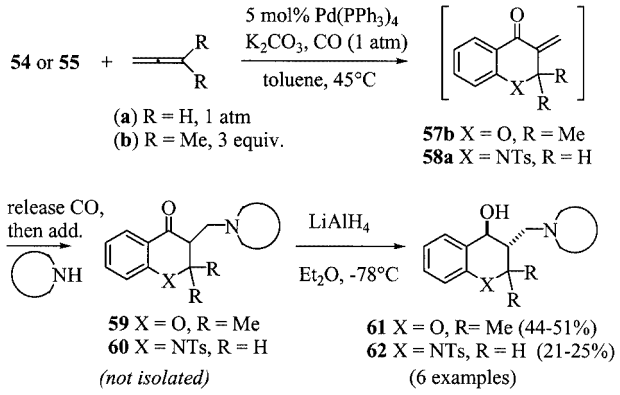


Scheme 20



Scheme 21

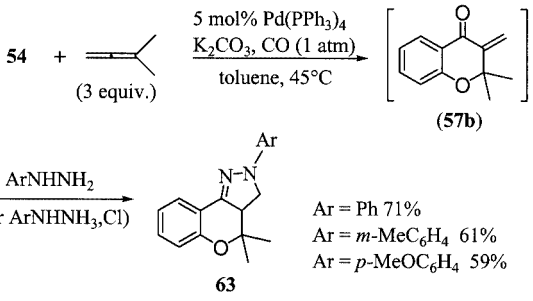
These heterocycles could be further elaborated by taking advantage of the enone system, which gave rise to a series of new one-pot procedures, as demonstrated in the following examples. γ-Amino alcohols **61**−**62** were prepared by conjugate addition of various cyclic amines to the enone intermediates **57b**−**58a**, followed by reduction of the unstable chroman-4-ones **59** and quinol-4-ones **60** with $LiAlH_4$ in



Cyclic amine: pyrrolidine, imidazole, morpholine, 1,2,4-triazole

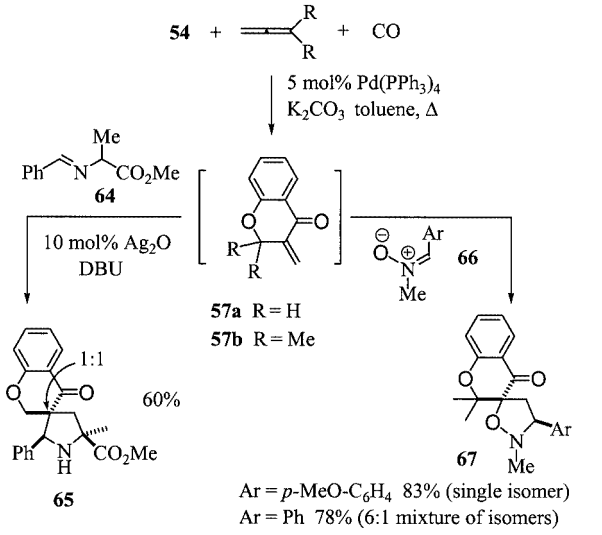
Scheme 22

diethyl ether at low temperature (Scheme 22).[35] Arylhydrazines were also shown to react with **57b** to afford 2-pyrazoline derivatives **63** (Scheme 23).[37] 1,3-Dipolar cycloadditions using the methylenechroman-4-ones **57** as 2π-components have been developed. The reaction in situ between **57a** and imine **64** in the presence of 10 mol % Ag_2O and DBU yielded the corresponding pyrrolidine derivatives **65** as a 1:1 mixture of *exo* and *endo* cycloadducts in 60% yield. The Ag_2O/base catalytic system used in this metallo-azomethine ylide cycloaddition had been developed previously by the same group. Similarly, the uncatalysed cycloaddition reaction between **57b** and aldonitrones **66** yielded isoxazolidines **67** (Scheme 24).[37]

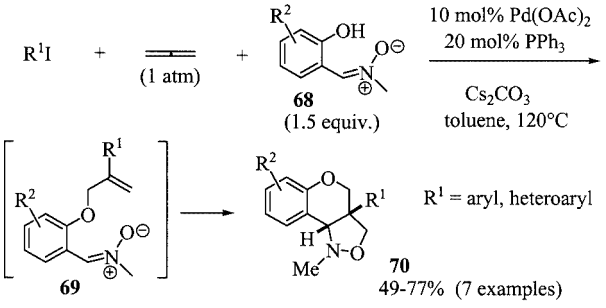


Scheme 23

Fused isoxazolidines of type **70** may be obtained through the intramolecular 1,3-cycloaddition reaction of nitrones **69**.[38] Grigg and co-workers have developed an elegant three-component cascade process that allows these nitrone intermediates to be generated and cyclised in a single operation. Here, the catalytic π-allylpalladium species generated from the carbopalladation of allenes with aryl (or heteroaryl) iodides were captured by an external phenolic nucleophile **68** bearing the required nitrone moiety (Scheme 25). The reactions were conducted under an atmosphere of allene in boiling toluene, with $Pd(OAc)_2/PPh_3$ as catalytic system and caesium carbonate as base. The highest yields were obtained with electron-rich aryl iodides.[39]



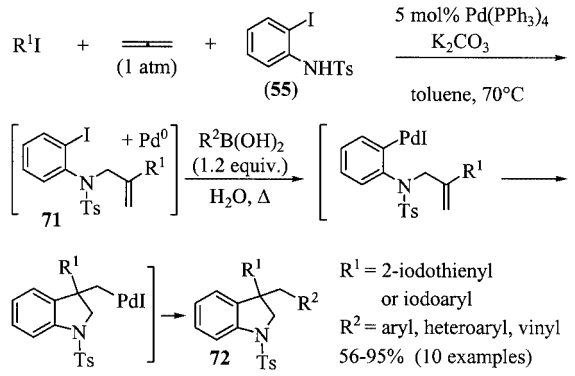
Scheme 24



Scheme 25

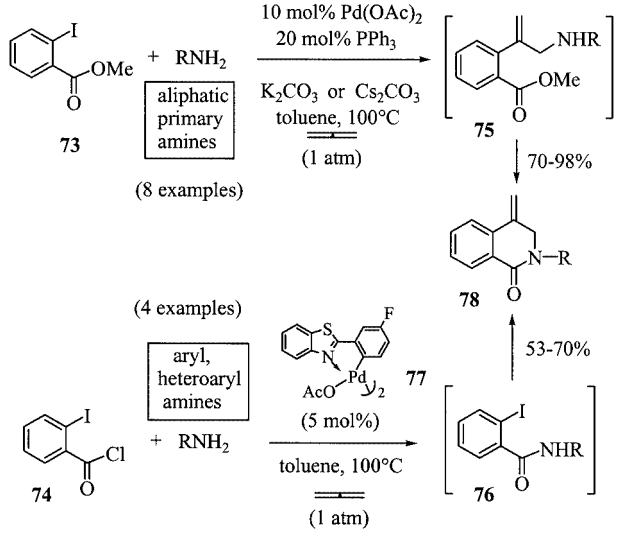
The same group has also reported efficient heterocycle syntheses based on the intermolecular palladium-catalysed amination of allenes, a process developed by Tsuji in the mid-1980s.[40] Coupling between aryl (or heteroaryl) iodides and allene and *N*-tosyl *o*-iodoanilines (**55**), for instance, furnished *N*-allyl(2-iodo)aniline intermediates **71**. These underwent Pd-catalysed *exo*-trig cyclisation in situ, terminated by cross-coupling reactions with various boronic acids – a process previously developed by the same authors[41] – to furnish 3,3-disubstituted indolines **72**. The selective reaction of allene with the aryl (or heteroaryl) iodides rather than with the iodoaniline was essential to the success of this process. 2-Iodothiophene was found to be particularly selective. The reaction takes place in toluene with $[Pd(PPh_3)_4]$ as catalyst and K_2CO_3 as base. It is essentially limited to simple allene but may be applied to 2-iodophenols to yield the analogous 2,3-dihydrobenzofurans. This four-component reaction constitutes another rare example of two consecutive, independent Pd-catalysed reactions proceeding with the same Pd catalyst over the whole integrated process (Scheme 26).[42]

In another interesting combination, Grigg and co-workers reported the preparation of *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolin-1-ones **78** by treatment of either methyl 2-iodobenzoate **73** or 2-iodobenzoyl chloride **74** with allene and various primary amines, including chiral



Scheme 26

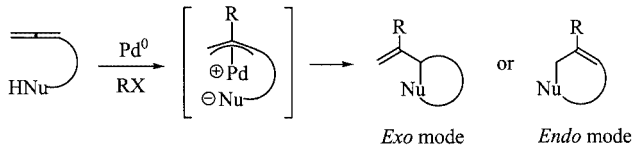
ones. Mechanistically, two pathways are proposed, depending on the starting iodobenzene derivative. Methyl 2-iodobenzoate follows the usual intermolecular carbopalladation-anion capture pathway to give intermediate **75**, which undergoes heteroannulation under classical reaction conditions. In contrast, 2-iodobenzoyl chloride first reacts with the primary amine to afford the corresponding 2-iodobenzamide **76**, which enters into the Pd-catalysed addition process and subsequent intramolecular capture of the π-allyl species by the internal amide group. In this case, catalyst **77** was found to be more effective (Scheme 27). The two methods proved complementary, as aryl and heteroarylamines were shown to give better results when starting from 2-iodobenzoyl chloride.[43]



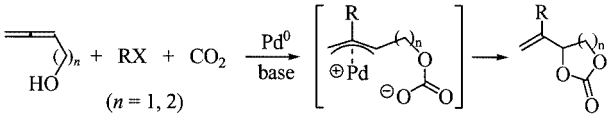
Scheme 27

Pd-mediated cyclisations between allenes bearing internal nucleophiles and organic halides are also well documented.[44] These allow regioselective syntheses of carbo- and heterocyclic rings of various sizes (Scheme 28).

For instance, as an extension of their previous work on Pd-catalysed cyclisations of carbonates generated by treatment of alkoxides with CO_2 (see Scheme 2), Inoue and co-workers have reported the preparation of five- and six-membered ring carbonates based on the carbopalladation

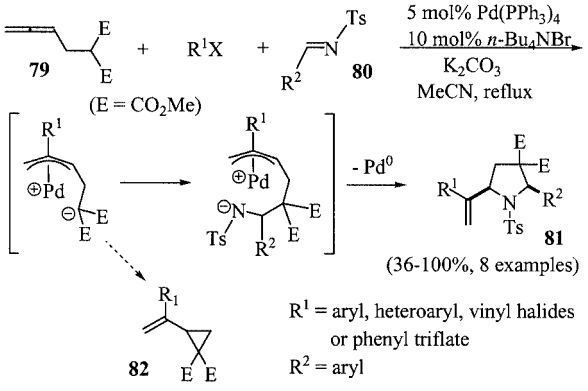


Scheme 28



Scheme 29

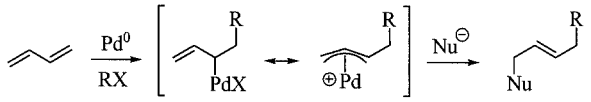
of allenols (Scheme 29).[45] Recently, Ma and co-workers[46] have developed a remarkable three-component reaction based on a conceptually related strategy utilising three potentially variable starting materials (Scheme 30). Beginning with δ-allenic malonate **79** they succeeded in intercepting the internal carbonucleophile with *N*-tosylimines **80**, acting as electrophilic relay, before ring-closure took place, which allowed for the formation of functionalised pyrrolidines **81** with high regio- and stereoselectivities. The reaction takes place in boiling MeCN in the presence of 5 mol % $[Pd(PPh_3)_4]$ and 10 mol % nBu_4NBr, with a variety of organic halides, including phenyl bromide, as well as phenyl triflate participating as coupling partners. On some rare occasions, however, the premature three-membered cycle **82**, normally obtained in the absence of imine,[47,48] is isolated as side product.



Scheme 30

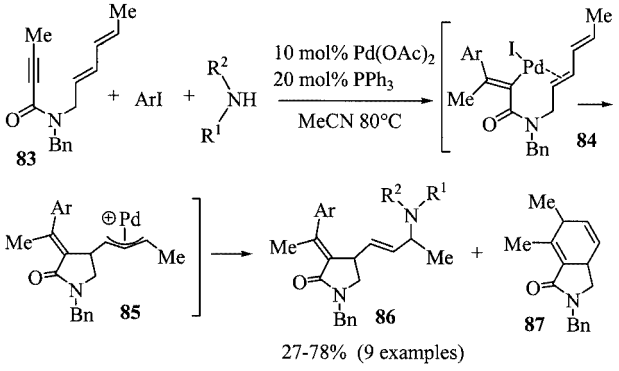
6. Carbopalladation of Conjugated Dienes

The carbopalladation of dienes with organic halides has been used for many years as a way of generating (π-allyl)Pd species. Reaction with a nucleophile present in the reaction medium allows for an overall difunctionalisation of the diene moiety.[49] It is actually one of the first Pd-catalysed multicomponent process found in the literature, and should offer great opportunities for the development of heterocycle syntheses in the future (Scheme 31).



Scheme 31

Lu and Xie have recently reported an elegant intramolecular version of this strategy, providing α-alkylidene-γ-lactams **86**. Treatment of *N*-(2′,4′-dienyl)alkynamide **83** with an aryl iodide affords a σ-vinylPd intermediate **84** through regioselective insertion of the active arylPdX species into the triple bond. Subsequent intramolecular carbopalladation of the diene as seen before affords (π-allyl)Pd intermediate **85**, which undergoes nucleophilic attack by a primary (isobutylamine, benzylamine, aniline) or secondary (piperidine, morpholine, pyrrolidine) amine at the less hindered terminus. The reaction proceeds in boiling MeCN in the presence of $Pd(OAc)_2/PPh_3$ as catalyst system (Scheme 32).[50] It should be mentioned that the competitive intramolecular Diels−Alder reaction affords bicyclic lactams **87** as side product under these conditions. This was particularly the case when aryl iodides bearing electron-withdrawing groups were employed, and with anilines as nucleophilic partners.



Scheme 32

7. Concluding Remarks

Since Ugi's pioneering work in the early 1960s,[1e] the design of novel multicomponent syntheses of heterocyclic compounds has essentially exploited the reactivity of archetypal functional groups such as isocyanides. The recent advent of high-throughput screening of compounds for biological activity, combined with increasing environmental pressures on the chemical industries, has spurred renewed activity in the development of practical one-pot procedures with high combinatorial potential. As demonstrated in this review, important contributions to this area may be achieved through applications of highly selective palladium-catalysed processes to the assembly of properly designed, easily available building blocks. These new methodologies offer straightforward routes to a wide range of polyfunctionalised heterocyclic compounds that may not be easily obtainable by other means. It is to be expected that further combinations of fundamental Pd-catalysed carbon−carbon and carbon−heteroatom bond-forming processes will be investigated toward this goal in the near future. New developments should also continue to benefit from recent innovations made in the field of palladium catalysis and should in return contribute to some extent to a better understanding of these catalytic processes.

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