Organic & Biomolecular Chemistry

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 6767

Recent advances in heterobimetallic palladium(II)/copper(II) catalyzed domino difunctionalization of carbon–carbon multiple bonds

Egle M. Beccalli,[a] Gianluigi Broggini,*[b] Silvia Gazzola[b] and Alberto Mazza[a]

Received 21st March 2014,
Accepted 14th July 2014

DOI: 10.1039/c4ob00610k

www.rsc.org/obc

The double functionalization of carbon–carbon multiple bonds in one-pot processes has emerged in recent years as a fruitful tool for the rapid synthesis of complex molecular scaffolds. This review covers the advances in domino reactions promoted by the couple palladium(II)/copper(II), which was proven to be an excellent catalytic system for the functionalization of substrates.

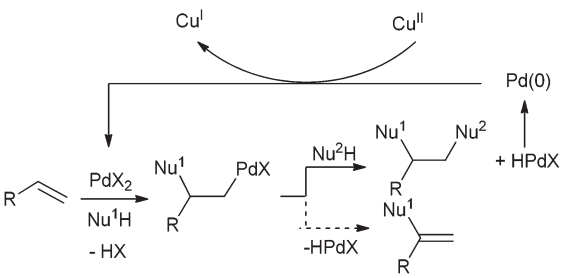
1. Introduction

The development of catalytic systems for the functionalization of unactivated carbon–carbon multiple bonds as well as aryl derivatives with nucleophiles remains one of the main interests for the chemical and pharmaceutical industries, providing economical and clean methods for variously functionalized molecular systems.[1] At the same time, the addition of carbon atoms or heteroatoms across the unsaturated molecules can be performed with 100% atom efficiency, fulfilling the requirements of atom economy. In this context, the contemporary double nucleophilic functionalization of unactivated alkenes and alkynes is a challenging strategy for the construction of substituted (hetero)aromatic systems.[2] These reactions imply the concept of the domino process as an effective tool which allows the formation of complex systems starting from simple substrates in a single transformation, often in a regio and stereocontrolled manner.[3]

The usefulness of domino reactions is highlighted in obtaining highly complex structures due to the number of bonds formed in one sequence, following the concept of bond-forming efficiency. Looking at the general applicability of the method, domino processes such as carboaminations, diaminations and aminohalogenations enable easy access to (poly)-functionalized acyclic and cyclic compounds as well as bicyclic or polycyclic ring systems.[4] As a consequence, the development of selective and tailored procedures based on new combinations of various kinds of bonds constitutes an improvement that justifies ongoing efforts in this field.

Palladium-catalyzed reactions continue to play a relevant role, allowing selective transformations that would be either difficult or impossible to obtain by conventional organic chemistry. Among the different species of palladium complexes or salts, palladium(II)-complexes act as electrophiles easily reacting with π-nucleophiles such as olefins, alkynes and aryls.[5] Looking at the reaction mechanism, an important step to pursue difunctionalized products is the formation of the intermediate σ-alkyl palladium-complex more prone to undergo a second nucleophilic addition, both in inter- or intramolecular reaction, than to give β-hydride elimination (Scheme 1). In some cases, the use of heterobimetallic catalytic species favours domino processes by slowing down the β-hydride elimination rate and assisting the second nucleophilic addition.

In these processes, the key event is the production of palladium(0) in the final elimination step; then, the presence of an oxidant in a stoichiometric amount is required to reconvert palladium(0) to palladium(II). The nature of different oxidant agents often plays a pivotal role. Among them, copper salts have been highlighted in the cross-coupling reactions (such as Sonogashira[6] or Stille[7]) and in direct arylation of heterocycles.[8]



Scheme 1

[a]*DISFARM, Sezione Chimica Generale Organica "A. Marchesini", Via Venezian 21, 20133 Milano, Italy. E-mail: egle.beccalli@unimi.it; Fax: (+39)-(0)2-50314476; Tel: (+39)-(0)2-50314479*
[b]*Dipartimento di Scienza e Alta Tecnologia, Università dell'Insubria, via Valleggio 11, 22100 Como, Italy. E-mail: gianluigi.broggini@uninsubria.it; Fax: (+39)-(0)31-238-6449; Tel: (+39)-(0)31-238-6443*

Other processes where copper(II) functions as the terminal oxidant are intramolecular oxidative couplings[9] and aminations[10] for the construction of heterocycles. In this context it is worth mentioning the Wacker process, the most economical and highly active industrial process exploiting the heterobimetallic palladium/copper catalytic system for the conversion of alkenes to aldehydes or ketones.[11]

This review gives an account of the recent domino reactions catalyzed by the palladium(II)/copper(II) heterobimetallic system, involving formation of two or more new bonds through C_{sp^2}–H or C_{sp}–H functionalization. The copper salt acts as an oxidative agent or as a co-catalyst in either intermolecular–intramolecular (or *vice versa*) or doubly intramolecular sequences. The examples reported have been grouped on the basis of the different kinds of bonds formed by the domino process, *i.e.* C–C, C–N, C–O, C–X, variously combined.

2. Carboaminations

Synthetic strategies aimed at the nitrogenated heteropolycyclic systems took advantage of domino processes such as carboamination reactions that involve C–C and C–N bond formation. In particular, several indole derivatives have been synthesized following this process.

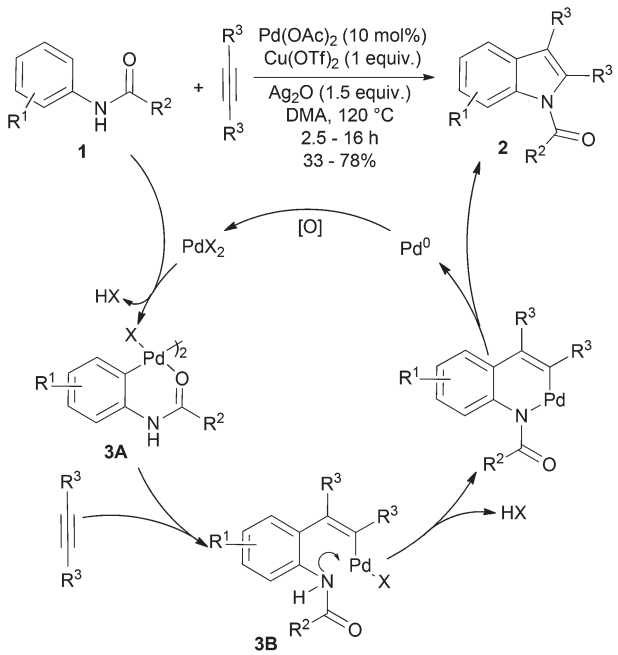
The coupling between anilides **1** and symmetrical disubstituted alkynes in the presence of Ag_2O and DMA as the solvent was proposed as an unexplored pathway to obtain indole skeleton **2** (Scheme 2).[12] A plausible mechanism is based on the assistance of the acetylamino group to generate the six-membered palladacycle **3A** which underwent insertion of an alkyne, affording a vinylic palladium(II) intermediate **3B**. The expected indole product resulted by the reductive elimination of palladium(0). The presence of electron-donating groups in the *meta*-position of the aryl ring may facilitate the C–H activation step.

Analogously, the *ortho* C–H activation of *N*-aryl-2-aminopyridines **4** and the subsequent oxidative coupling with disubstituted alkynes were exploited for the formation of *N*-pyridyl indoles **5** (Scheme 3).[13] Both electron-donating and withdrawing groups on the *N*-aryl ring could be tolerated. The reaction was regioselective and sensitive to the steric bulk around the pyridine nitrogen.

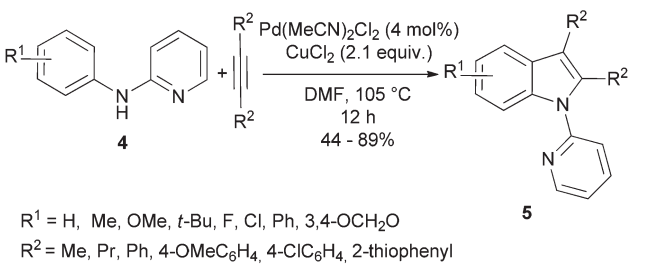
Diarylacetylenes **6** and aniline provided 2,3-diarylindoles **7** or pentaarylpyrroles **8**, the divergent outcome depending on the use of different solvents such as DMF or dioxane (Scheme 4).[14] Aryl acetylenes gave better results than aliphatic ones, nevertheless no regioselectivity was observed with unsymmetrical diarylacetylenes.

The mechanism shows the nucleophilic addition of the aniline to the palladium π-complex **9A**, furnishing the vinyl palladium complex **9B** (Scheme 5). The use of DMF as the solvent determines an electrophilic aromatic palladation yielding the indole ring, while dioxane favours the insertion of a second molecule of diarylacetylene resulting in pyrrole ring formation.

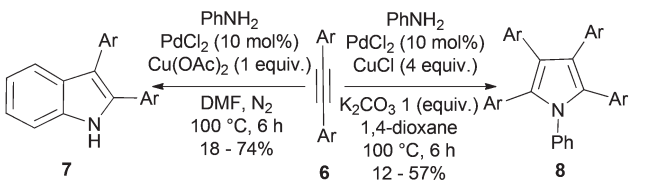
Oxidative cyclization/C–H bond functionalization of two different substituted alkynes was exploited to synthesize benzo-carbazole derivatives **10** (Scheme 6).[15] Starting from *N*,*N*-dimethyl-2-(phenylethynyl)aniline the reaction carried out with $CuCl_2$ as a co-oxidant and molecular oxygen as a terminal oxidant in the presence of a base led to the desired product. The use of tetrabutylammonium bromide and pivalic acid as additives considerably increased the yield. The suggested



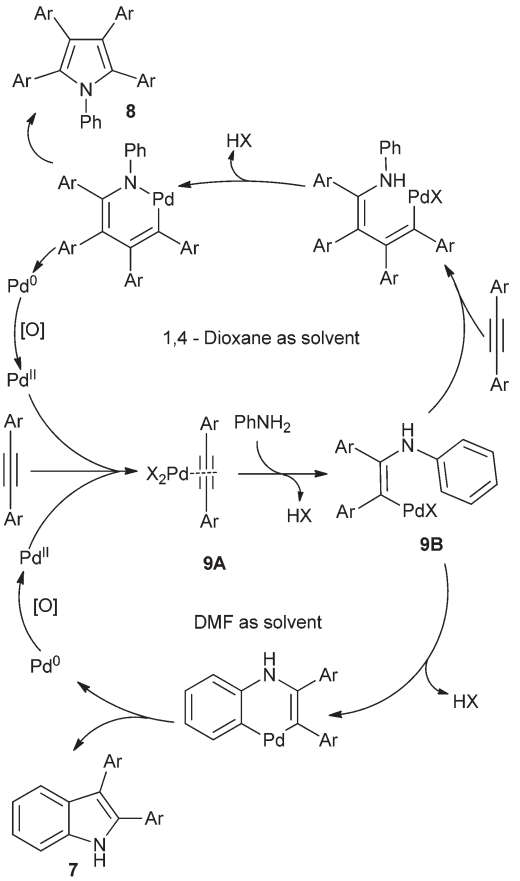
Scheme 2



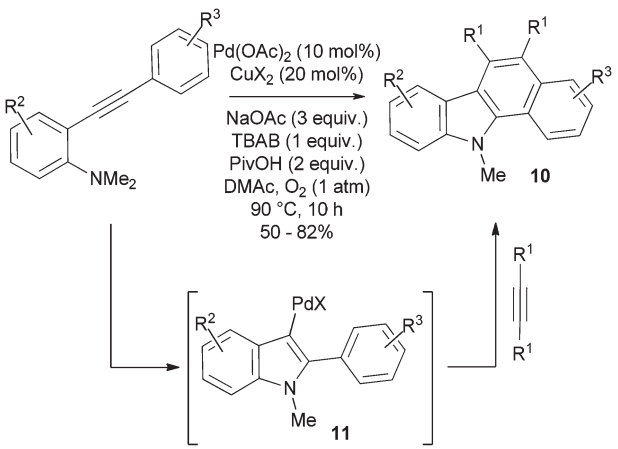
Scheme 3



Scheme 4

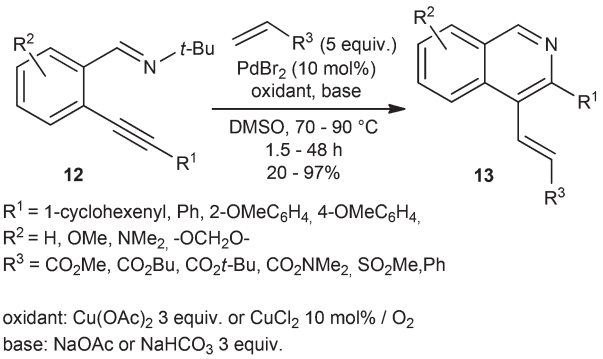


Scheme 5



Scheme 6

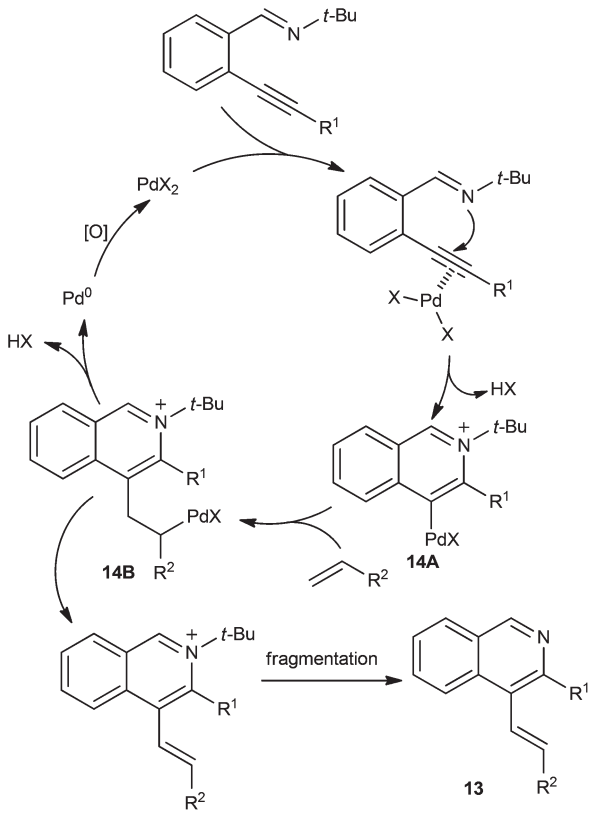
mechanism involves an intramolecular *anti*-addition of the *N*,*N*-dimethylaniline tethered to the triple bond through a formal 5-*endo*-dig mode affording an intermediate **11**. The latter inserts intermolecularly the second alkyne suitable for base-promoted aromatic palladation and subsequent formation of the tetracyclic fused-ring product.



Scheme 7

The intramolecular amination of benzaldimines **12** bearing an alkynyl group in the *ortho* position, followed by intermolecular coupling with electron-poor alkenes, was an efficient method to synthesize 4-alkenyl-3-arylisoquinolines **13** (Scheme 7).[16] Electron-donating groups on the arylaldimines improved the product yields.

The addition of alkenes *via* an Heck-type domino process on the first formed cyclic palladium-complex **14A** affords the 4-alkyl isoquinolinium-palladium(II) intermediate **14B** (Scheme 8). The β-hydride elimination of which and the subsequent *tert*-butyl group fragmentation generates the products **13**.



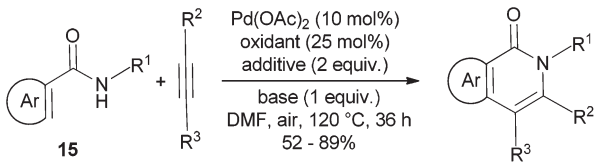
Scheme 8

Starting from *N*-alkyl- and *N*-(hetero)aryl-benzamides **15** and diaryl acetylenes, isoquinolone derivatives **16** were obtained using $Pd(OAc)_2$ and a sub-stoichiometric amount of Cu salt as a co-oxidant, atmospheric oxygen being the real oxidant for the regeneration of palladium(II) (Scheme 9).[17] On the other hand the excessive amount of $Cu(OAc)_2$ accelerated side reactions. Diphenylacetylene as well as unsymmetrical alkynes worked well, but the reaction proceeded without regioselectivity forming both regioisomers.

Intermolecular coupling of tosylated allylamines **17** with butyl vinyl ether or styrene afforded the pyrrolidines **18**. The first step consists of the aminopalladation of the vinyl ether or styrene, followed by alkene insertion of the allylamine (Scheme 10).[18] The reaction was performed at room temperature also with air as the O_2 source. The presence of additives as catechol or methyl acrylate improved the yield, presumably through the palladium(0)-intermediate stabilization, enhancing its re-oxidation rate.

Li's group reported the synthesis of phenantridines **20** starting from 2-amino-biaryls **19** and terminal alkenes, through a tandem C–H oxidative olefination/carboamination involving an unreported C–C bond cleavage process (Scheme 11).[19] With respect to previous conditions reported by Miura and co-workers for the formation of *N*-Ts phenantridines-6-acetate,[20] different reaction conditions such as the use of 3 equivalents of alkenes, the absence of a base, and the increase of reaction temperature allowed the C–C bond cleavage and the isolation of compounds **20**. In this pathway the first formed C–H functionalized intermediate **21A** arising from alkene insertion gave vinylated intermediate **21B**. The subsequent complexation with Pd(II) through carboamination step yields σ-alkyl palladium complex **21C** on which the intervention of oxygen and copper acetate gave the elimination of leaving groups with the formation of products. It must be highlighted that **20** cannot arise from substituted phenantridines by elimination steps. $PdCl_2$ was more effective than $Pd(OAc)_2$ as a catalyst. The role of the protective group R^3 as the leaving group is essential to obtain the final product.

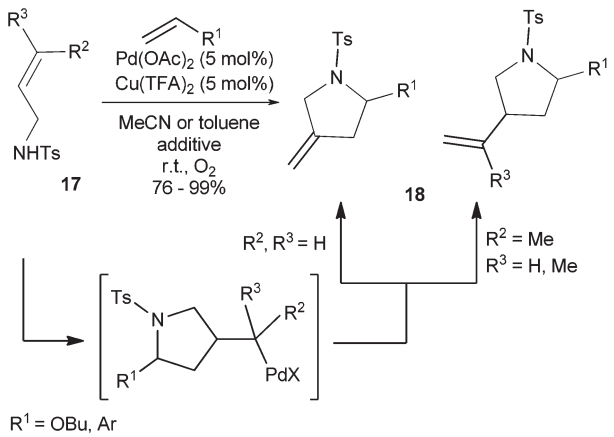
A very recent paper reported the formation of pyrrolizidine derivatives **23** starting from *N*-4,6-dienyl β-ketoamides **22**, through an entirely intramolecular aminoalkylation process.[21] The reaction was catalyzed by the couple $Pd(TFA)_2/Cu(OTf)_2$. The replacing of the oxidant with other copper salts was detrimental for the coupling, indicating the double role of $Cu(OTf)_2$ as a co-oxidant and Lewis acid. The proposed mechanism involves a palladium(II)/copper(II) bimetallic complex generated through the enol form. Then, the amide portion acts as a two-fold nucleophile responsible for C–N and C–C bond



R^1 = Me, $(CH_2)_2OMe$, Ph, Bn, 4-$OMeC_6H_4$, pyridyl
R^2 = Ph, 4-$CO_2MeC_6H_4$
R^3 = Et, Ph

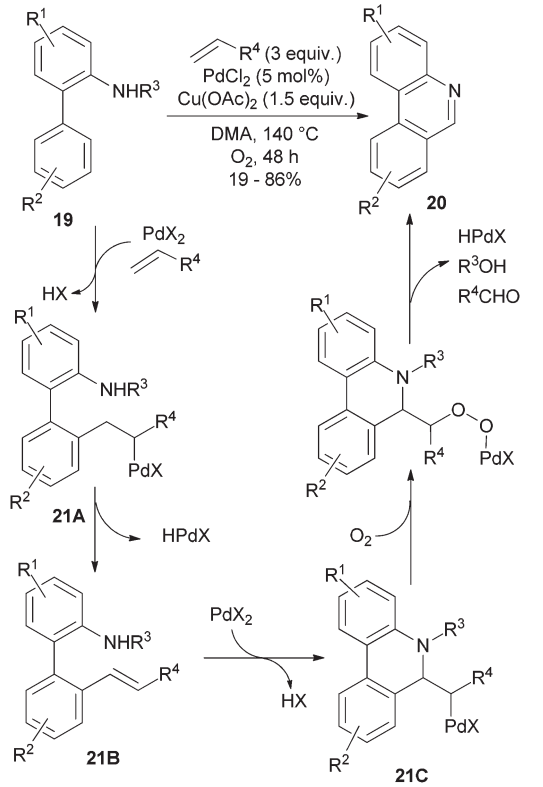
R^1 = Alk → oxidant: $Cu(OAc)_2$; additive: $NaI{\cdot}2H_2O$; base: K_2CO_3
R^1 = Ar → oxidant: $CuCl_2{\cdot}2H_2O$; additive: NaBr; base: KOH

Scheme 9



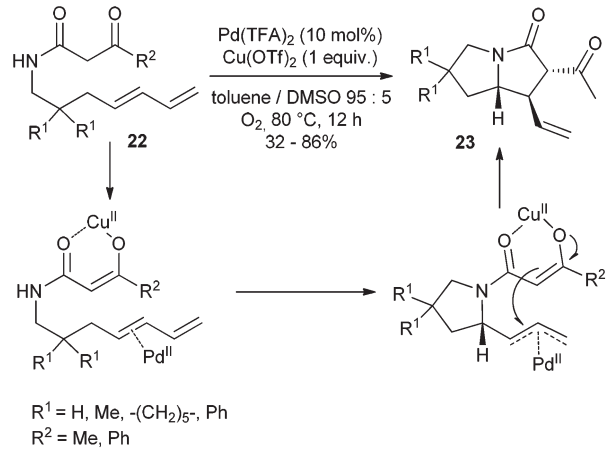
R^1 = OBu, Ar

Scheme 10

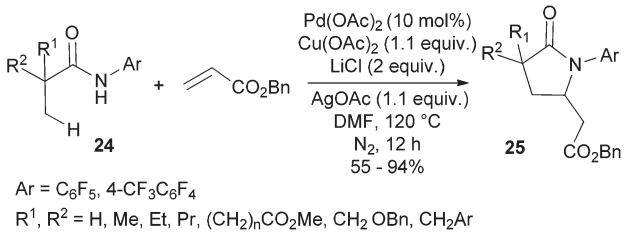


R^1 = H, Me, F, Cl, CO_2Me
R^2 = H, Me, Cl, OMe, COMe, -OCH_2O-, $CH{=}CH_2$
R^3 = Ts, Boc, H, Me, Ac, Bn, $CH_2CH{=}CH_2$
R^4 = CN, OAc, CO_2Bu, 4-$OMeC_6H_4$, $Si(OMe)_3$, SOPh, 2-naphthyl

Scheme 11



Scheme 12



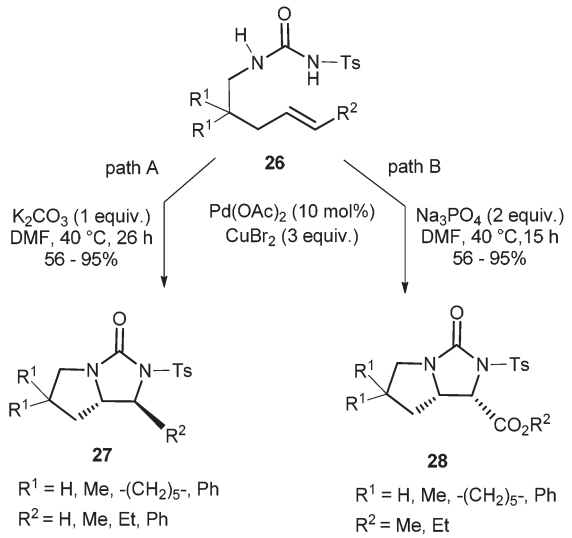
Scheme 13

formation, giving the diastereoselective cyclization in 20 : 1 ratio (Scheme 12).

A direct olefination of sp^3 β-C–H bonds of amides **24** with benzyl acrylate was performed using conditions which include $Pd(OAc)_2$ and $Cu(OAc)_2$ as catalysts, AgOAc in DMF with LiCl as an additive (Scheme 13).[22] The functionalized γ-lactams **25** were formed *via* olefin insertion followed by intramolecular 1,4-addition of the amide to the inserted acrylate. The reaction was enhanced by electron-withdrawing substituents on the *N*-aryl group. The presence of LiCl increased the yield as the chloride anions prevent the precipitation of Pd-black and induce the *in situ* formation of a chloro-bridging complex. Critical points were also the choice of polar solvents and the use of N_2 instead of air.

3. Diaminations

Domino processes involving intramolecular double C–N bond formation have also been shown to be effective at accessing bicyclic systems containing two nitrogen atoms. Ureas, guanidines and sulfamides tethered to alkenes are suitable candidates for this purpose.[23] In the case of ureas **26** as nitrogen sources, the intramolecular diamination performed with $CuBr_2$ as a terminal oxidant afforded the bicyclic products **27** or **28** (Scheme 14). The mechanism in the initial step was proven to proceed by a *syn* aminopalladation for both terminal and internal alkenes. In the case of internal alkenes, the

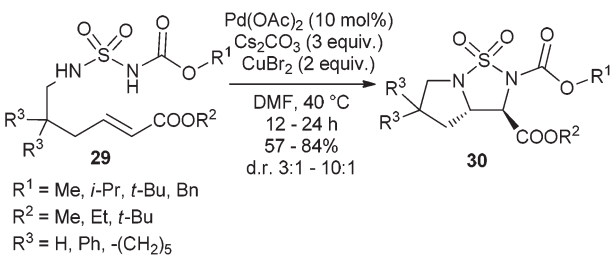


Scheme 14

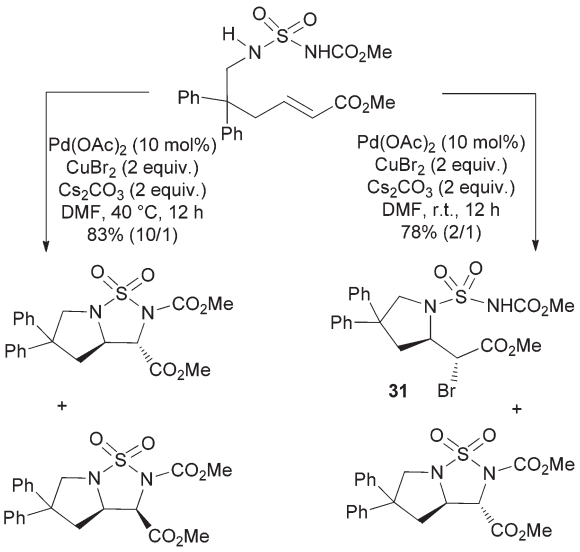
stereochemical course in the subsequent C–N bond formation differs depending on the substrates. The phenyl and alkyl-substituted alkenes provided *anti*-stereoisomer **27** (Scheme 14, path A), for ester-substituted alkenes the *syn*-3-oxo-hexahydropyrrolo[1,2-*c*]imidazole carboxylates **28** were observed (Scheme 14, path B).[24] Two important points in the mechanistic processes must be highlighted: (a) palladium(II) salts alone are unable to induce product formation; (b) $CuBr_2$ must be involved in the final C–N bond formation through a heterobimetallic complex intermediate. To demonstrate the versatility of the diamination, the process was applied in the formation of the pyrrolo[1,2-*c*]imidazole scaffold as a stereoselective pathway for the preparation of the absouline alkaloid.[23]

Subsequent studies using sulfamates **29** as nitrogen sources gave bicyclic products **30** with relative *trans*-stereochemistry with acrylate derivatives also (Scheme 15).[25] The resulting 2,3-diamino carboxylic acids serve as building blocks for the synthesis of amino acid derivatives, and the process could be applied in peptide chemistry. In fact, the treatment of **30** with KOH in THF-methanol solution led to the removal of the carbamate and the ester groups. Coupling of the free acid to the free amine group of an aminoester such as glycine methyl ester furnished a dipeptide.

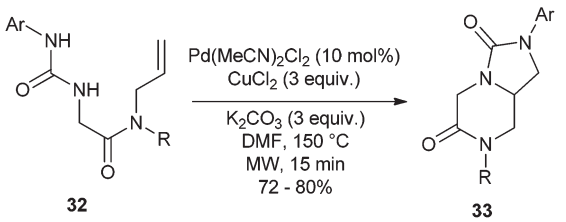
Studies directed at shedding light on the mechanism performed on the *gem*-diphenyl sulfamate revealed that the reac-



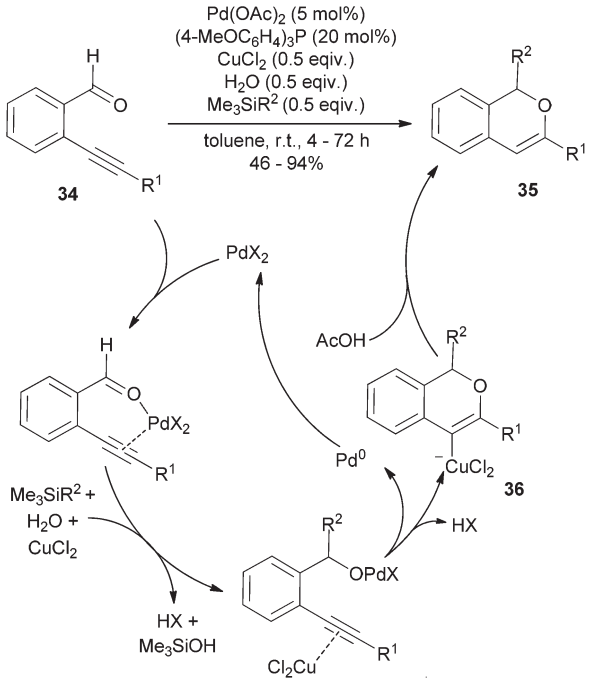
Scheme 15



Scheme 16



Scheme 17



Scheme 18

tion performed at 40 °C furnished a mixture of a 1 : 10 *syn*/*anti* cyclized product (Scheme 16). When the reaction was carried out at room temperature, the monocyclized aminobrominated compound **31** was isolated as the precursor of the bicyclic *anti*-product, arising from a second inversion of configuration.

Following the same reaction conditions, guanidine tethered to alkenes yielded bicyclic 3-imino-tetrahydro-pyrrolo[1,2-*c*]imidazoles with complete *syn*-diastereoselectivity.[23b]

Efficient and selective intramolecular diamination reactions of alkenylureas **32** were realized under microwave irradiation, providing the bicyclic products **33** containing a piperazinone ring in one step (Scheme 17).[26] A pivotal factor in obtaining this product was the presence of a base, the best of which was K_2CO_3. The omission of the base caused the formation of a divergent product arising from an aminooxygenation process, as shown in the specific paragraph.

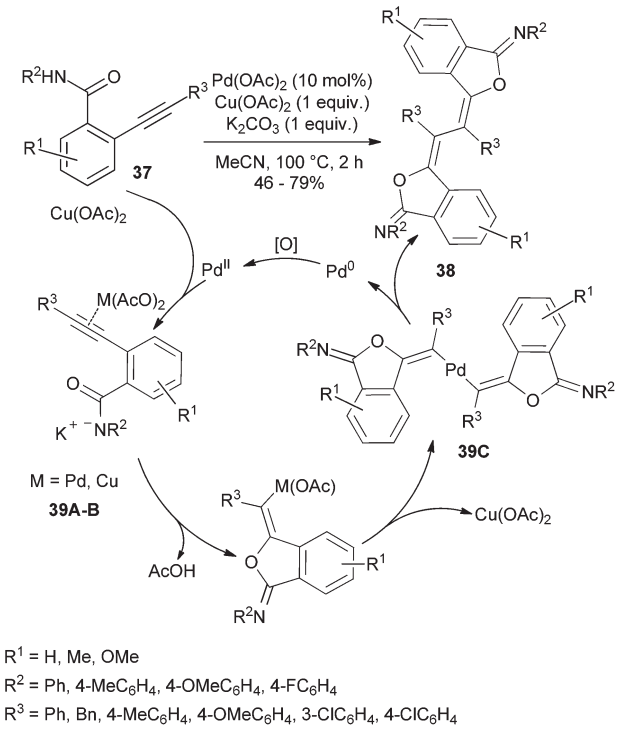
4. Carbooxygenations

Carbon–carbon and carbon–oxygen bond formation was reported in intermolecular and intramolecular domino processes, particularly applied to the synthesis of oxygen-containing heterocycles.

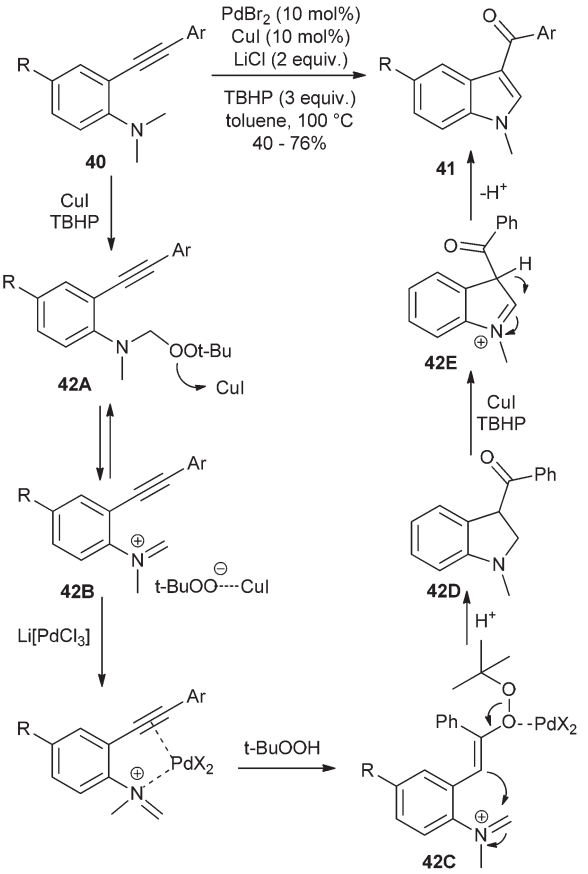
The one-pot reaction of *o*-alkynylated benzaldehydes **34** with trimethylsilyl derivatives is an efficient method for the synthesis of 1-allyl or 1-cyano-3-substituted isochromenes **35** (Scheme 18). The key step is the coordination of the palladium to the carbonyl oxygen and the triple bond that facilitates the nucleophilic attack of the silyl derivative to the carbonyl group. The acetic acid generated during the insertion of the nucleophile promoted the formation of the final product from the intermediate **36**.[27] No reaction occurred in the presence of BQ instead of $CuCl_2$, confirming that the latter did not work only as an oxidising agent.

A particular cyclizative dimerization process of *o*-(1-alkynyl)-benzamides **37** led to the formation of dimeric imino benzoisofurans **38**.[28] The hypothesized mechanism shows the formation of vinylpalladium and vinylcopper species (**39A** and **39B**, respectively), both of which afforded concurrently the divinylpalladium intermediate **39C** which upon reductive elimination would provide the final dibenzoisofuran-1,3-diene. According to this mechanism, copper(II) has two distinct roles: as a catalyst participating in the formation of C–O and C–C bonds and as an oxidant to regenerate the palladium(II) species (Scheme 19).

Starting from *N*,*N*-dimethyl-2-(phenylethynyl)anilines **40** a rare oxidative coupling of the sp^3 C–H bond adjacent to amine with alkynes was reported (Scheme 20).[29] The reaction was performed with the couple palladium–copper as co-catalysts and *tert*-butyl hydroperoxide (TBHP), acting as an oxidant as well



Scheme 19



Scheme 20

as an oxygen source. The mechanism proposed, supported by the labelling experiment and ESI/MS analysis, involves an initial copper-catalyzed reaction between the substrate **40** and two molecules of TBHP to generate peroxide **42A** which is in equilibrium with the iminium intermediate **42B**. Nucleophilic attack of TBHP on the palladium-coordinated alkyne **42B** under palladium catalysis forms the intermediate **42C**. The latter underwent intramolecular cyclization to produce 3-acylindoline **42D** which, after oxidation to the intermediate **42E**, underwent deprotonation to yield the product **41**.

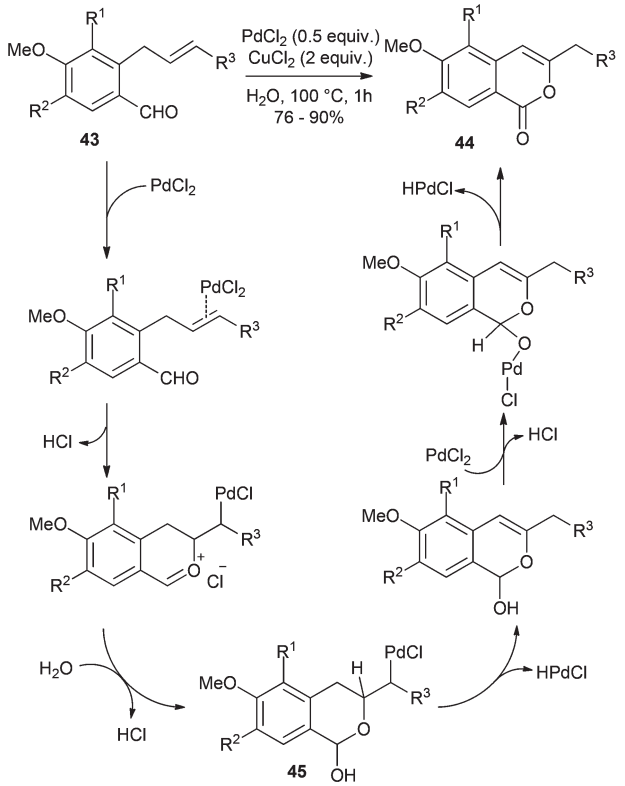
The carbooxygenation process of *o*-allylbenzaldehydes **43**, carried out in water, resulted in the formation of new substituted isocoumarins **44** (Scheme 21).[30] The domino sequence involved the 6-*exo*-trig cyclization through the nucleophilic addition of the formyl oxygen on the palladium-complexed double bond. Subsequent addition of water produced the transient hemiacetal **45** and the reductive elimination of palladium(0) and HCl afforded the final product.

Starting from lactams bearing α-allenols (as oxindoles and 2-pyrrolidinones **46**), the formation of oxygenated spirocyclic systems **47** could be rationalized in terms of a domino sequence of cyclization–alkenylation or cyclization–cross-coupling (Scheme 22).[31] The suggested mechanism is based on the initial palladium-complexation of the allene followed by the intramolecular attack of the hydroxyl group to give a spirocyclic vinylic palladium species. The subsequent cross-coupling led to the final product. The sequence was carried out also on β-lactam-tethered allenols obtaining the corresponding spirocyclic derivatives.

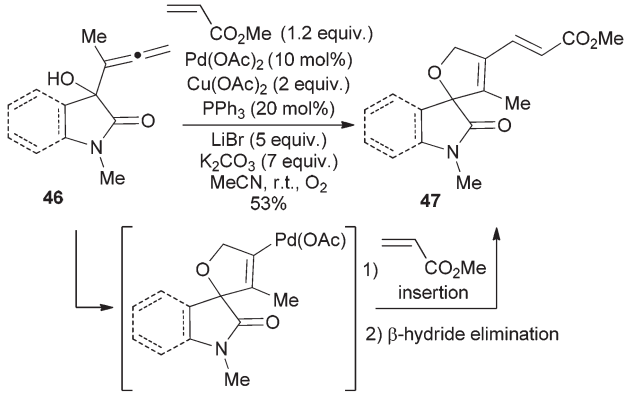
2-Furyl-carbaldehyde derivatives **49** were prepared starting from 1,3-dicarbonyl compounds **48** and propargyl alcohols (Scheme 23).[32] The key step actually consists of an intramolecular Pd-catalyzed reaction on the propargyl ether generated by the intervention of the iron as a catalyst.

Using alkynamides **50** and alkenes as efficient precursors, intermolecular carbooxygenation processes afforded functionalized α,β-unsaturated ketones **51** (Scheme 24).[33] The mechanism for the formation of the σ-alkyl Pd species **52B** involves the hydration of the first formed cyclic oxypalladation intermediate **52A** and the reaction of the alkene in a Heck-like step. The β-hydride elimination and the double bond migration to the α,β position gave the final product **51**. This last step may also be assisted by a palladium catalyst.

Coupling of allylic alcohols **53** with vinyl ethers through an initial intermolecular oxypalladation of the enol ether followed by the intramolecular alkene insertion, provided the cyclic acetals **54** (Scheme 25).[34] In this case, the allylic alcohol provided both the oxygen and the carbon nucleophiles. A similar reaction was reported by Morken as an efficient method to access vinyl substituted cyclic acetals in a diastereoselective manner.[35]



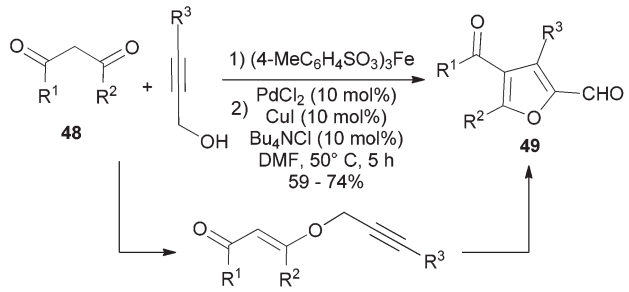
Scheme 21



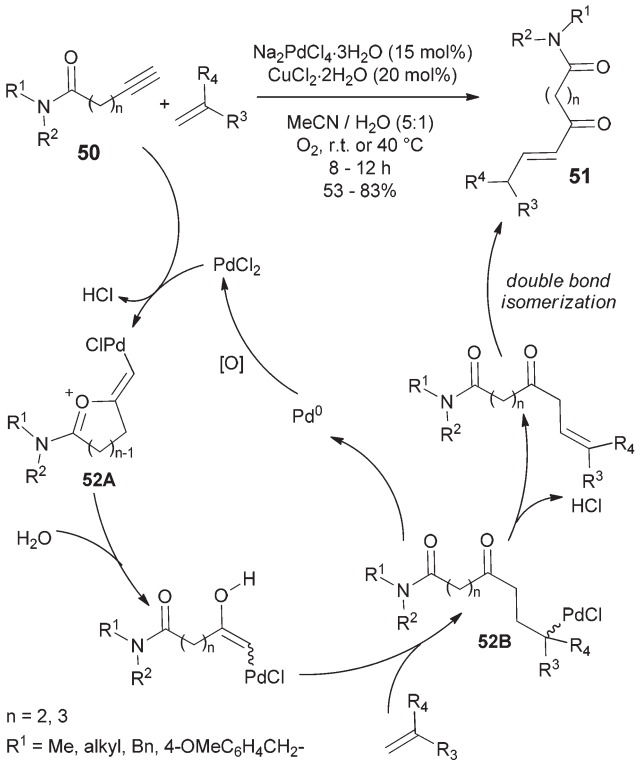
Scheme 22

Cyclization between acrylic acid and terminal alkenes produces α-methylene-γ-butyrolactone derivatives **55** (Scheme 26).[36] In order to suppress the deposition of palladium black and to overcome the drawback of using acrylic acid as the substrate, a determinant role is entrusted to the ligands. The proposed mechanism involves the nucleophilic attack of the α,β-unsaturated carboxylic acid on the palladium-coordinated alkenes with generation of the key-intermediate **56**.

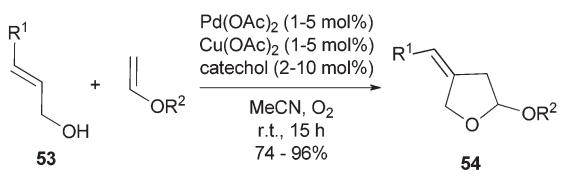
A series of 1-acetoxy-1,3-dienes **59** was synthesized in a regio- and stereoselective manner starting from electron-rich



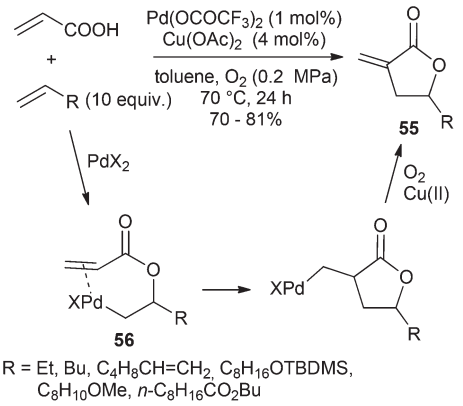
Scheme 23



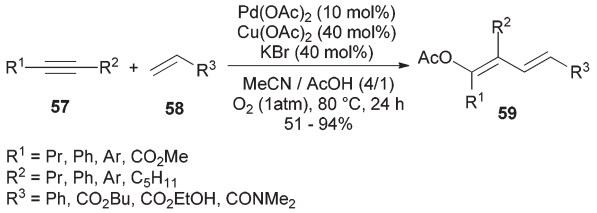
Scheme 24



Scheme 25



Scheme 26



Scheme 27

alkynes **57** and electron-poor alkenes **58** by an acetoxy-palladation/Heck-type process, using $Cu(OAc)_2$ as a co-catalyst and oxygen as a terminal oxidant (Scheme 27).[37]

5. Dioxygenations

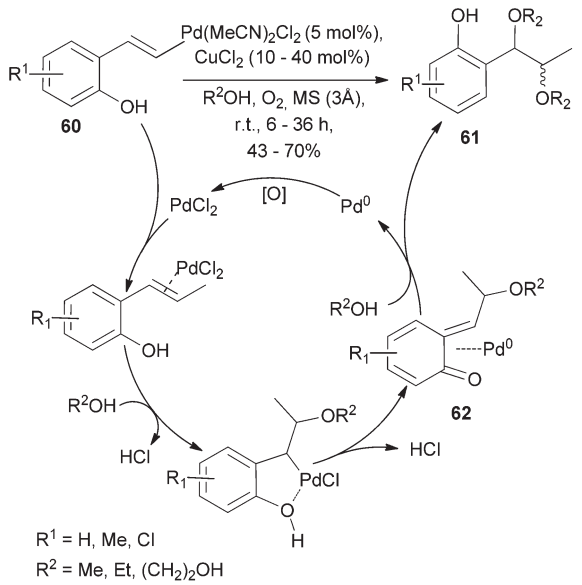
Processes involving double oxygenation are usually obtained through intermolecular dialkoxylation of alkenes by alcohols or through intramolecular reactions of polyols.

The dialkoxylation of 2-propenyl phenols **60** afforded products **61** by addition of two equivalents of MeOH (Scheme 28).[38] The key step was the formation of the quinone methide species **62** revealing the crucial role of the *o*-hydroxy group in hampering the β-hydride elimination.

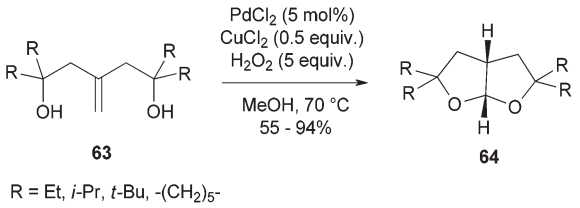
Wacker-type intramolecular acetalization of readily accessible 3-methylidene-1,5-diols **63** was an efficient method to prepare perhydrofuro[2,3-*b*]furans **64** in only three-steps, using $CuCl_2$ and H_2O_2 as co-oxidants (Scheme 29).[39] An enantiomerically pure perhydrofuro[2,3-*b*]furan has also been successfully obtained in this manner from (−)-menthone.

An intermolecular version of this procedure led to the formation of acetals as a result of the alcohol addition to alkenes.[40] Analogously the conversion of substituted styrenes to the corresponding Markovnikov dialkyl acetals was achieved exploiting the catalytic system Pd(sparteine)Cl_2 and $CuCl_2$ in the presence of O_2.[41]

The palladium(II)-catalyzed domino reactions involving double intramolecular C–O bond formation were studied by Gracza and co-workers on the sugar-derived unsaturated

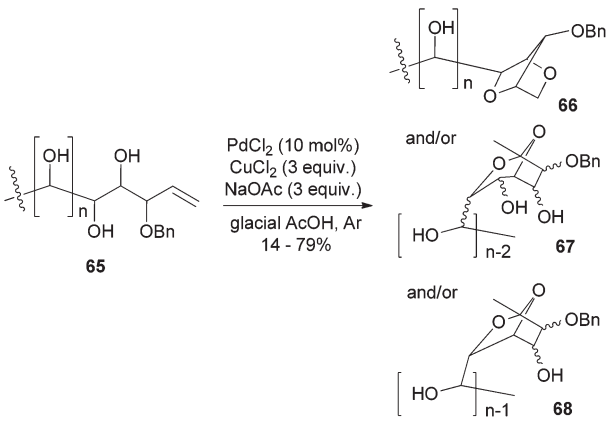


Scheme 28



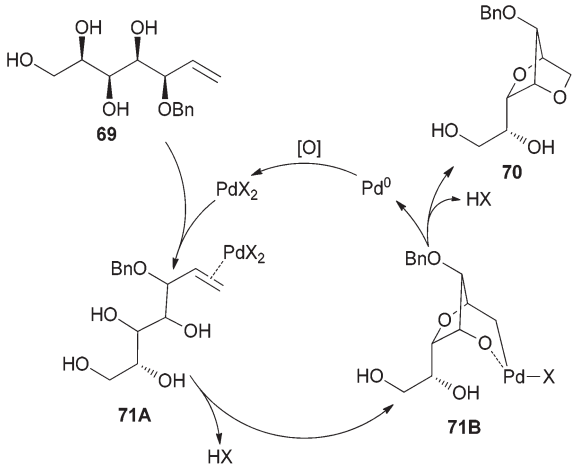
Scheme 29

polyols **65**, affording three different bicyclic oxygenated systems **66–68** (Scheme 30).[42] In fact, the chemoselectivity of the reaction is directly correlated with the relative configuration of substrates: polyols with all-*syn* configuration on C3, C4,C5-atoms led to the corresponding bicyclic structures of type **66**. From all other diastereomeric substrates, bicyclic acetals of types **67** and/or **68** were formed.

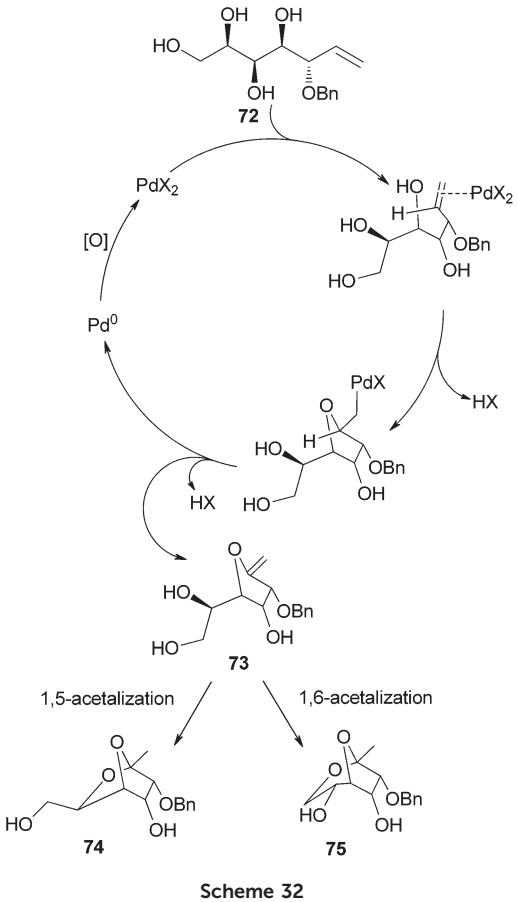


Scheme 30

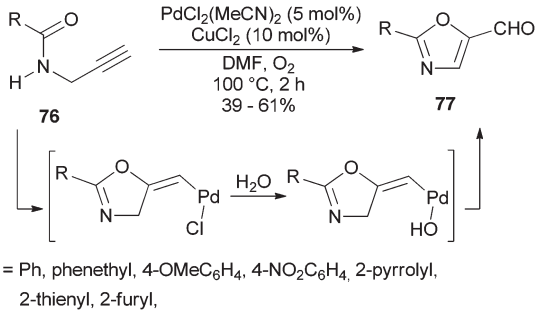
A specific example of the formation of product **66** was reported in Scheme 31. The $PdCl_2/CuCl_2$-catalyzed bicyclization of the unsaturated polyol **69** afforded the product **70**. The reaction can be mechanistically rationalized as follows: intramolecular nucleophilic attack of the 5-OH substituent on the palladium(II)-activated terminal C=C bond in π-complex **71A** leads to σ-palladium intermediate **71B**. The coplanar spatial arrangement of C-1 C-2 and 4-OPd bonds of **71B** allows the subsequent reductive elimination giving the bicyclic product. The reoxidation of palladium(0) with an oxidant other than $CuCl_2$ has a detrimental effect on bicyclization.



Scheme 31



Scheme 32



R = Ph, phenethyl, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 2-pyrrolyl, 2-thienyl, 2-furyl,

Scheme 33

On the other hand, the formation of bicyclic acetals such as **67** and/or **68** is explained in Scheme 32. Starting from **72**, a cascade process involving two steps gives the common intermediate **73** which undergoes an acid catalyzed 1,5- and/or 1,6-acetalization, giving the final products **74** and/or **75**.[42]

The reaction conditions described above allowed the cyclization of equimolar diastereomeric D-*erythro*-/D-*threo*-1-pentenitols with formation of bridged products, which on regioselective ring-opening provided trisubstituted tetrahydrofurans.[43]

This method was applied to the synthesis of natural and unnatural enantiomers of goniofufurone and its 7-epimers, starting from D-glucose,[44] as well as to the total synthesis of natural (+)-varitriol, starting from D-glucose and dimethyl L-tartrate.[45]

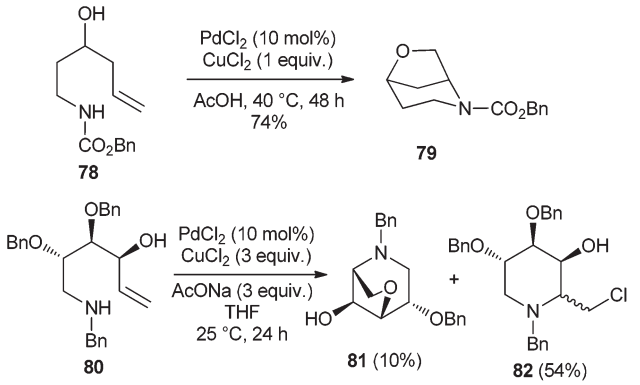
Wacker-type cyclization was also exploited for the formation of oxygenated bicyclic system affording the total synthesis of (+)-buergerinin F.[46]

A particular and straightforward synthesis of 2-substituted 5-oxazolecarbaldehydes **77** was performed by the treatment of propargylamides **76** with palladium(II)-salts and $CuCl_2/O_2$ as reoxidant agents (Scheme 33).[47] The determinant role of the copper salt was supported by the isolation of the addition product of the chloride ion as a nucleophile.

6. Aminooxygenations

The double carbon–heteroatom bond formation was highlighted as a strategy to access particular polyheterosubstituted ring systems.

The 6-oxa-2-azabicyclo[3.2.1]octane **79** was obtained by bicyclization of the 1-(benzyloxycarbonylamino)-hex-5-en-3-ol **78** (Scheme 34).[48] In general this process afforded bicyclic systems through *N*,*O*-bicyclization starting from the commercially available methyl-α-D-gluco- and methyl-α-D-galactopyranoside. The mechanism is analogous to that above reported for the two-fold C–O bond formation in Schemes 31 and 32. Exploiting as a substrate the 1-benzylamino-2,3-dibenzyloxy-5-hexen-4-ol **80** and using an excess of $CuCl_2$ (3 equiv.),



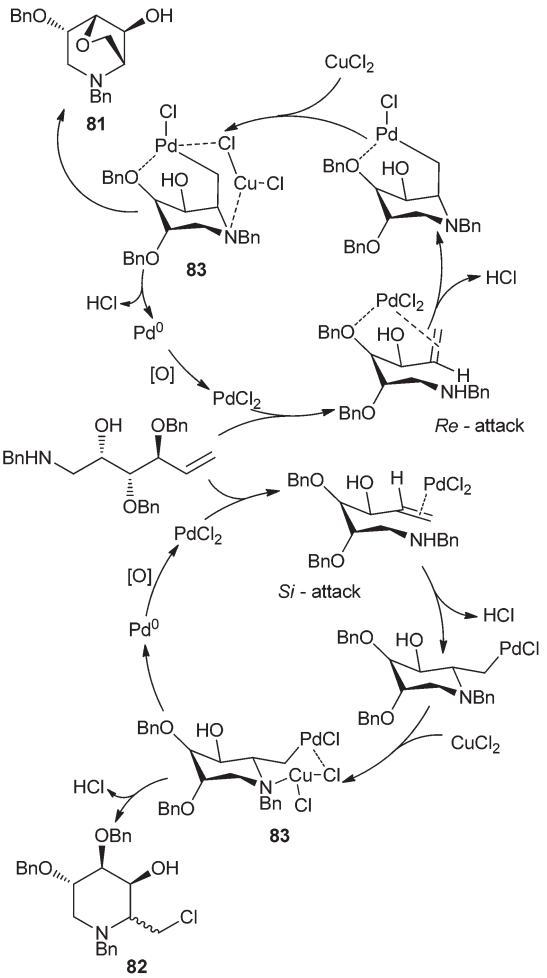
Scheme 34

the C-6 chlorinated monocyclic azasugar **82** was obtained besides the bicyclic derivative **81**. The prevalence of the chloro-substituted piperidinol **82** was observed in particular with DMF or THF as solvents and in the presence of AcONa.

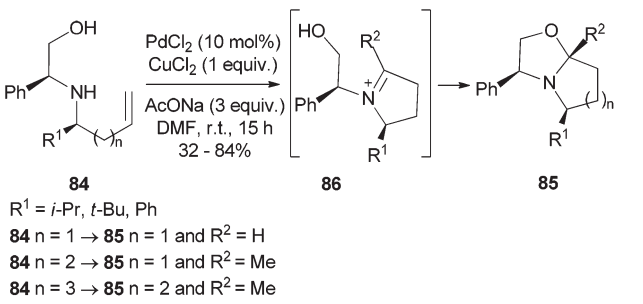
The presence of $CuCl_2$, crucial for the success of the bicyclization, may force the formation of a heterobimetallic σ-complex **83** (Scheme 35). The replacement of $CuCl_2$ by other oxidants (BQ or $Cu(OAc)_2$) was detrimental to the result and only a complex mixture of unidentified products was obtained. The isolation of the chloroderivative **82** resulted from the intramolecular nucleophilic attack from the *Si*-face of the amine to the Pd-activated double bond.[48b]

Unsaturated β-amino alcohols **84** were the suitable substrates to afford enantiopure bicyclic oxazolidines **85** with total regio- and stereo-control under Wacker-type conditions (Scheme 36).[49] The results showed the importance of a substituent on the unsaturated amine-chain for stereoselectivity. When the R^1 is an alkyl or aryl group, the bicyclic oxazolidines were obtained as single diastereomers. For n = 2, 3 in **84**, the reaction gave in good yields the bicyclic oxazolidines 5/5 and 5/6 containing an angular methyl group. The cyclizations occurred with total stereoselectivity: all the substituents are in the *cis*-position. A route involving the formation of an iminium ion **86** was hypothesized to account for the regio- and stereoselectivity of the cyclization.

Analogous bicyclic oxazolidinones **88** were formed starting from easily available allylamides of *N*-alkoxycarbonyl-protected α-amino acids **87** through a domino aminocarboxylation process (Scheme 37).[50] A key role was played by the amount of $CuCl_2$ present as an oxidant agent. More specifically, a divergent route to simple amination or domino aminocarboxylation reaction can be selected depending on the catalytic or stoichiometric amount of the copper salt. In the last case, the direct intervention of the carbamate oxygen, after the initial Pd-pro-

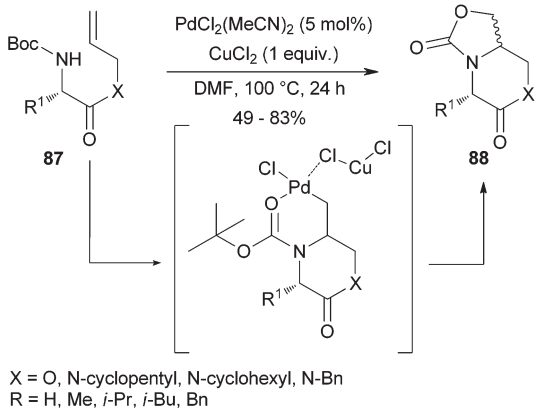


Scheme 35



R^1 = *i*-Pr, *t*-Bu, Ph
84 n = 1 → **85** n = 1 and R^2 = H
84 n = 2 → **85** n = 1 and R^2 = Me
84 n = 3 → **85** n = 2 and R^2 = Me

Scheme 36



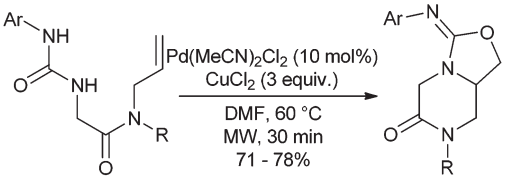
X = O, N-cyclopentyl, N-cyclohexyl, N-Bn
R = H, Me, *i*-Pr, *i*-Bu, Bn

Scheme 37

moted transfer of the nitrogen atom on the C=C double bond, resulted in the formation of the oxazolidinone ring. The stoichiometric presence of $CuCl_2$ inhibits the β-hydride elimination and the formation of the monocyclic amination product.

Alkenylureas **32**, previously reported for a diamination process (see Scheme 17), provided the 3-arylimino-oxazolo[3,4-*a*]pyrazin-6-ones **89** by an intramolecular aminooxygenation sequence (Scheme 38).[26]

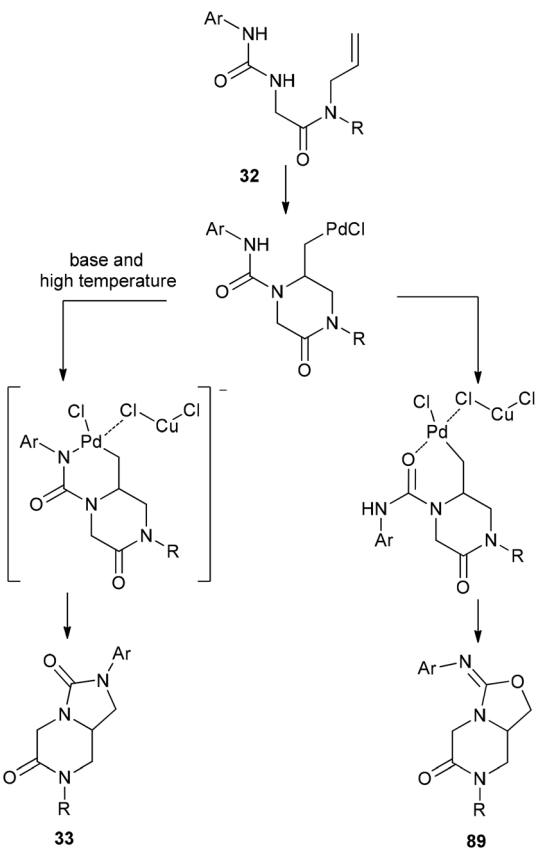
From the mechanistic point of view, in both pathways $CuCl_2$ would inhibit the common palladium β-hydride elimination of the palladium species through the formation of a heterobimetallic σ-palladium/copper complex, with the subsequent formation of the second heterocycle, imidazole in the case of basic conditions and higher temperatures (compound **33**), or oxazole working at 60 °C (compound **89**) (Scheme 39).



32 **89**

R = Cy, Bn
Ar = Ph, 4-$OMeC_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4

Scheme 38



32 **33** **89**

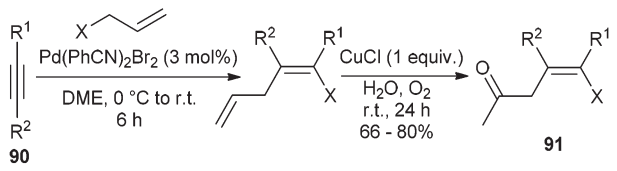
Scheme 39

7. Reactions involving C–halogen bond formation

Several very recent papers, exploiting the palladium–copper catalytic system, report domino processes involving formation of a carbon–halogen bond. The remaining step may consist of C–C, C–O or C–N bond formation resulting in the acyclic or cyclic products containing a halogen atom.

Alkynes **90** and allyl halides were the useful substrates for the synthesis of functionalized methyl ketones **91**, exploiting a particular tandem haloallylation-Wacker–Tsuji oxidation (Scheme 40).[51] The haloallylated alkenyl derivative initially generated under an oxygen atmosphere gave functionalized methyl ketone as a final product. The terminal aromatic alkyne did not afford methyl ketones. Thus, starting from phenylacetylene, 1-phenylpenten-2-en-1,4-dione was isolated in high yield.

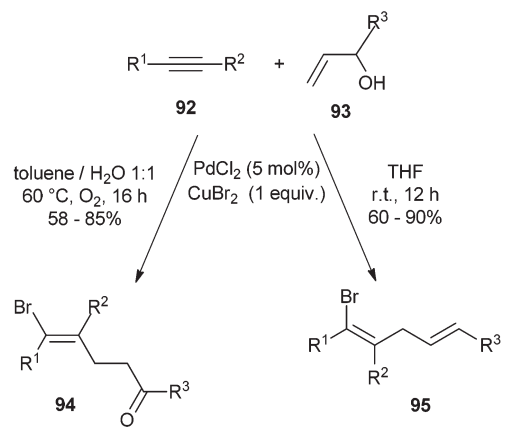
Analogous reaction with electron-poor alkynes **92** and allylic alcohols **93** in the presence of $CuBr_2$ afforded δ-bromo-γ,δ-unsaturated carbonyl compounds **94** (Scheme 41).[52] The mechanism involving Br-palladation of the alkyne followed by



90 **91**

X = Cl, Br
R^1 = H, Pr, Bu, CH_2OTBS
R^2 = H, Me, Pr, CO_2Me

Scheme 40



92 **93** **94** **95**

R^1 = Me, alkyl, CH_2Cl, Ar
R^2 = H, CH_2Cl, CO_2Me, CO_2Et
R^3 = H, alkyl, aryl

Scheme 41

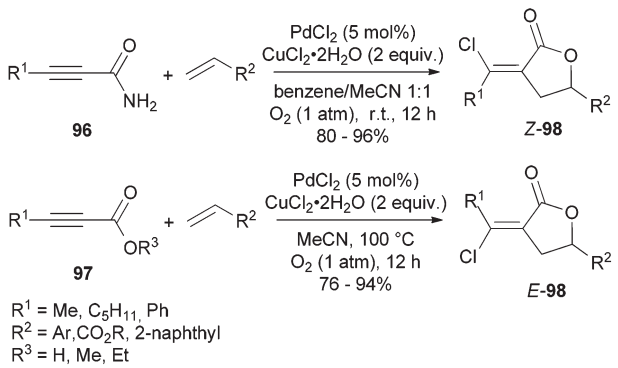
insertion of allylic alcohol was dependent on the solvent used. In fact, the substitution of the 1 : 1 mixture of toluene–H_2O with THF afforded 1-bromo-1,4-dienes **95**.

A general method to construct α-methylene-γ-lactones consisted of carboesterification of alkynamides **96** and alkenes treated with $PdCl_2$ (5 mol%) and $CuCl_2{\cdot}2H_2O$ (2 equiv.) in acetonitrile and oxygen atmosphere at room temperature. In particular, the α-halo-α-methylene-γ-lactones **98** were obtained with 98 : 2 *Z*/*E* selectivity (Scheme 42).[53] Alternatively, the *E* isomers of products **98** can be obtained by conversion of the alkynoates **97** with the same catalytic system at 100 °C. Due to the impossible mutual conversion of the *Z*/*E* isomers, it seems plausible that their formation follows different reaction pathways.

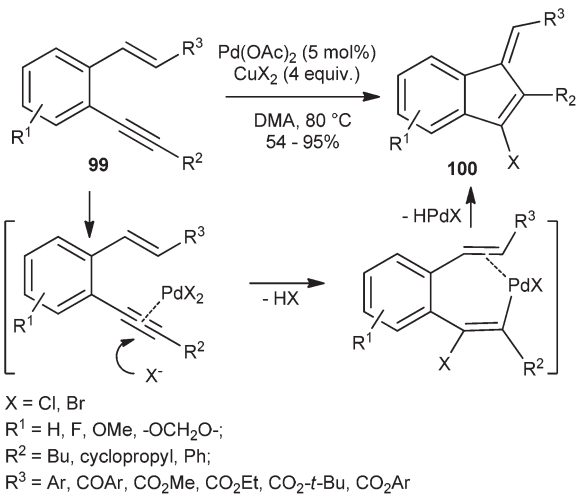
Starting from 2-alkenylphenylacetylenes **99**, sequential carbohalogenation–cyclization gave 1-methylene-indene derivatives **100** in good yields (Scheme 43).[54] The proposed mechanism involves the palladium activation of the triple bond and the nucleophilic addition of the halide anion, followed by the double bond insertion. No reaction occurred in the absence of the palladium catalyst. The products so obtained have been further elaborated through palladium-catalyzed cross-coupling reactions with arylboronic acids.

Two alkynes tethered to the same aryl substrate **101** provided substituted benzo[*a*]carbazoles **102** through a double domino addition/insertion (Scheme 44).[55] The suggested mechanism shows the formation of the intermediate 3-haloindole derivative **103**, isolated carrying out the reaction with the copper catalyst alone.

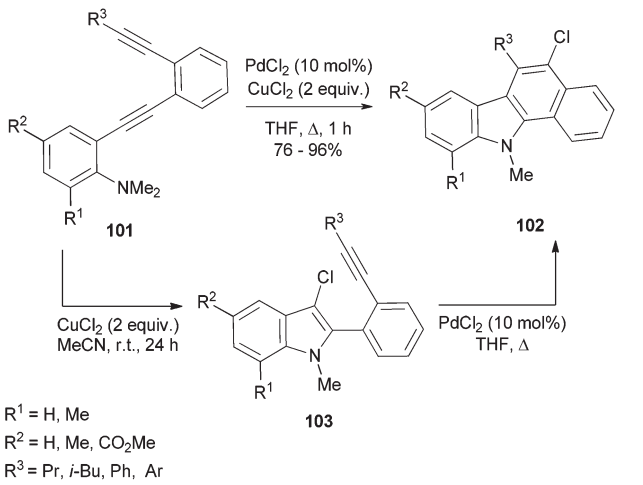
The carboamination–halogenation sequence was applied to the synthesis of halo-substituted indoles **105** and isoquinolines **106**, starting from 2-alkynyl aryl azides or 2-alkynyl benzyl azides **104** (Scheme 45).[56] 3-Haloindoles and 4-haloisoquinolines could be obtained working with PdX_2 and CuX_2 in the presence of dicyclohexyl ammonium chlorhydrate or LiBr as additives. As previously suggested, the halopalladation of alkyne was the key intermediate to support the subsequent cyclization.



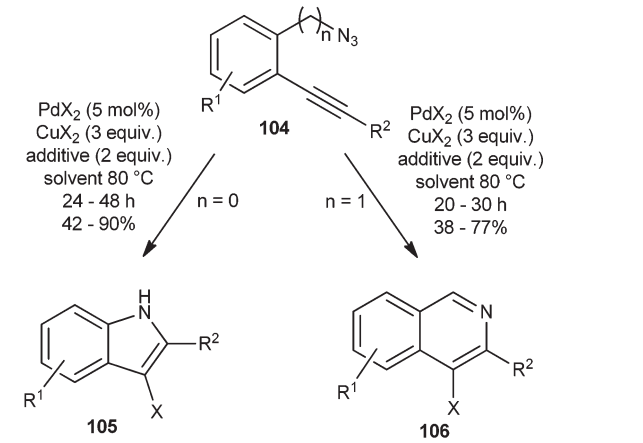
Scheme 42



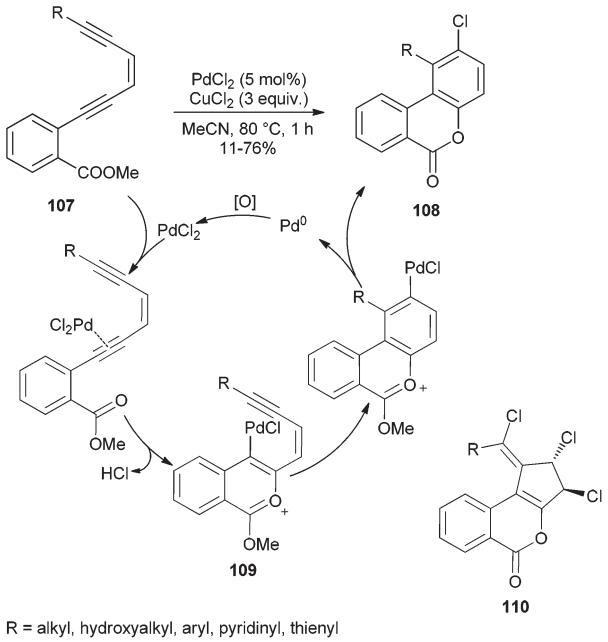
Scheme 43



Scheme 44



Scheme 45



Scheme 46

The treatment of the methyl benzoates **107** bearing an enediyne moiety in the *ortho* position with catalytic $PdCl_2$ and 3 equiv. of $CuCl_2$ gave the tricyclic products **108** (Scheme 46).[57] The proposed sequence involved the nucleophilic attack of the carbonyl oxygen of the ester functionality on the internal alkyne to give the intermediate oxonium ion **109**, followed by the 6-*endo* cyclization and displacement of the methyl group with the assistance of the chloride ion. If a bulky substituent is present at the 6-position of the chain, the 5-*exo*-dig cyclization compound **110** is also obtained as a minor product.

Starting from the propiolic acid derivatives **111**, the tricyclic compounds **112** were achieved by sequential halogenation of the triple bond and intramolecular carboesterification of the olefin (Scheme 47).[58]

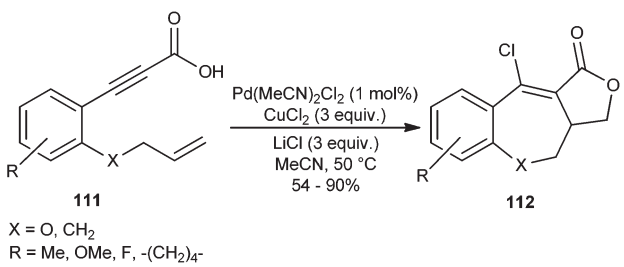
The treatment of 2- and 3-indolyl allylamides with the couple $PdCl_2(CH_3CN)_2$ and CuX_2 provided the variously substituted β-carbolinones **113** by arylation/halogenation, or arylation/esterification processes (Scheme 48).[59] The carboesterification process is the result of an unknown path that involves DMF or DMA used as solvents through a palladium(II) mechanism. The outcome of the reactions on the 3-indolyl allylamides arises from a totally selective 1,2-migration of the acyl group on the supposed spiro intermediates **114** formed by the nucleophilic attack of the C-3 indole position. On the other hand, an unusual aminohalogenation/halogenation sequence performed on 2-indolyl allylamides gave rise to the pyrazino[1,2-*a*]indole products **115**. The same tricyclic pyrazino[1,2-*a*]indole skeleton was successfully obtained by oxidative palladium(II)-catalyzed reactions starting from 1-allyl-2-indolecarboxamides.[60]

Using the same catalytic system in DMF as the solvent, the bicyclic (3*S*,4a*R*)-pyrido[1,2-*c*]pyrimidone was prepared in 90% ee by chloroamination of the corresponding (*R*)-2-allyl piperidine.[61]

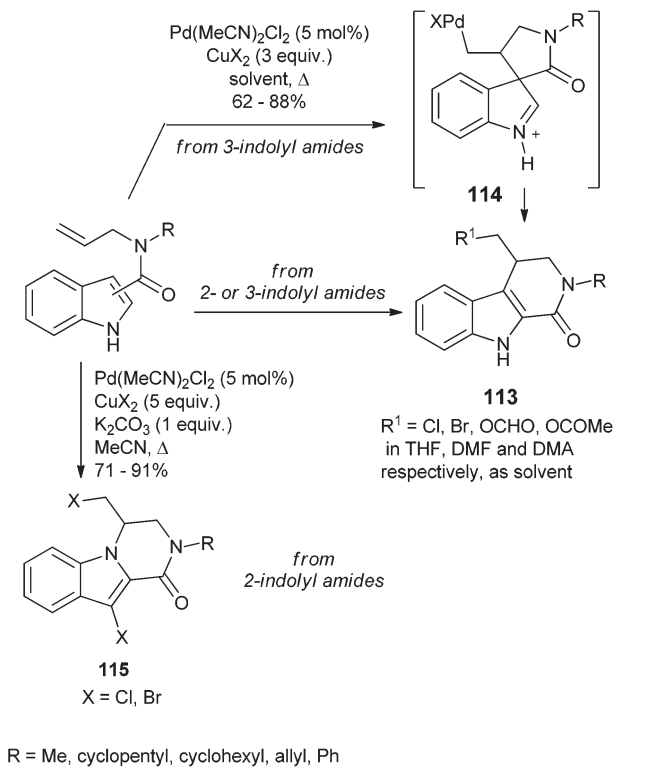
Chemoselective haloamination was also exploited in the formation of oxazolidinones and imidazolinones **117**, starting respectively from allylic alcohols or amines **116** and *p*-toluenesulfonyl isocyanate (Scheme 49).[62] The excess of halide ions probably hampered the β-hydride elimination step and permitted access to the halo-substituted heterocyclic product.

Aminohalogenation of trichloroacetyl protected allyl carbamates **118** provided the oxazolidinones **119** (Scheme 50).[63] LiCl was proven to be essential for the formation of the product. The reaction did not proceed with primary carbamates and, in the absence of the copper salt, the rearranged allyl amides were obtained. The reaction was stereoselective in favour of the *trans*-isomer, which was attributed to the 1,3-allylic strain in the transition state.

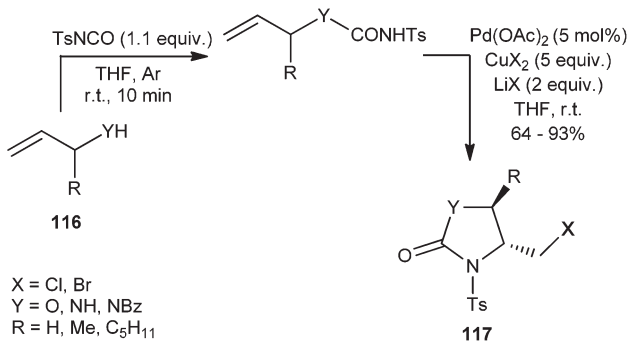
Intramolecular domino C–O/C–X or C–N/C–X bond formation allowed the conversion of allenyl alcohols, amides,



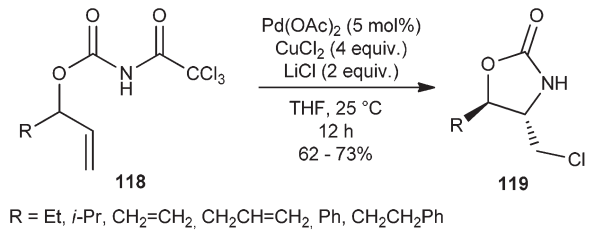
Scheme 47



Scheme 48

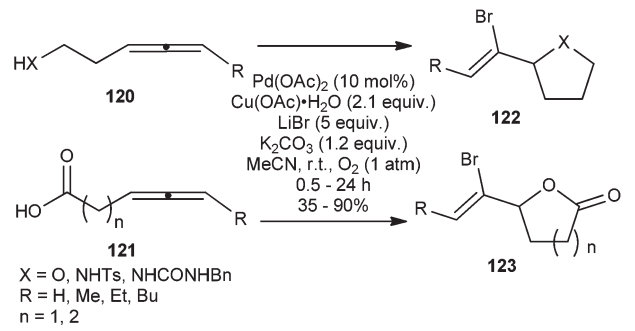


Scheme 49

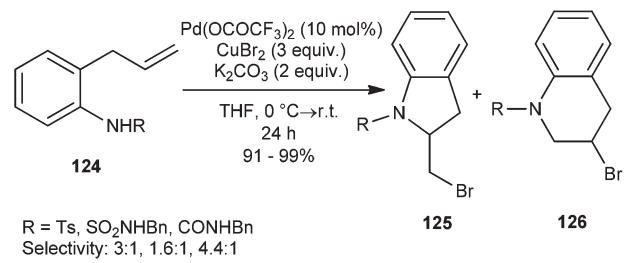


Scheme 50

carbamates **120** and carboxylic acids **121** into tetrahydrofurans, pyrrolidines, oxazolidinones **122** and lactones **123** (Scheme 51).[64] The reaction proceeds *via* the π-allyl intermediate formed by the external attack of halide on the allene coordinated to palladium, followed by the second internal nucleophilic attack to give the product.



Scheme 51



Scheme 52

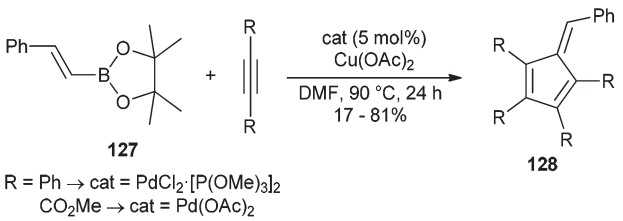
Intramolecular aminohalogenation of *ortho*-allylanilines **124** was reported to give a mixture of benzofused five- and six-membered rings **125** and **126**, the regioselectivity of which was dependent on the structure of the substrate (Scheme 52).[65] The suggested mechanism indicates the assistance of copper (II) in the reductive elimination. Solvent and reaction temperature were also determinants for the product formation.

8. Reactions involving three C–C bond formation

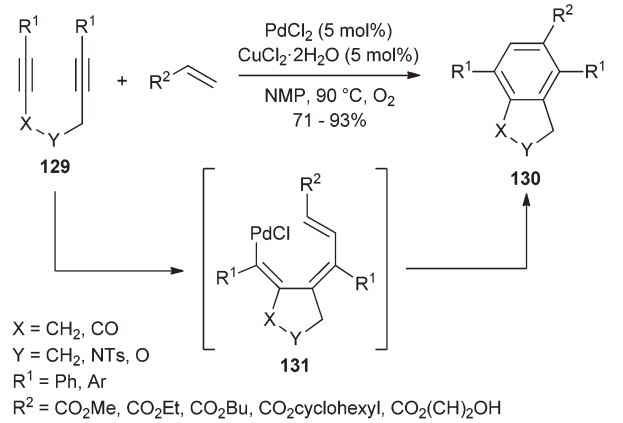
A particular domino process involving more than two C–C bonds was reported as a pathway in the formation of cyclic systems.

Starting from diphenylacetylene or dimethyl acetylenedicarboxylate and alkenyl boronic ester **127**, tetrasubstituted fulvenes **128** were achieved involving three C–C bond formation (Scheme 53).[66]

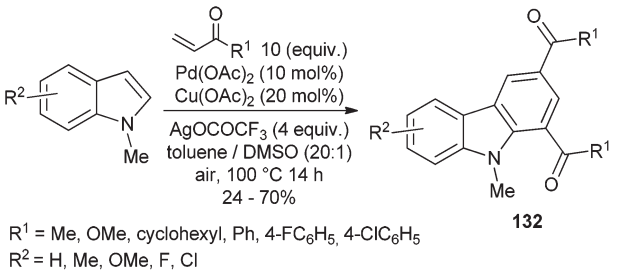
More recently, a particular [2 + 2 + 2] cyclization of 1,6-diynes **129** and acrylates afforded the polysubstituted aromatic (hetero)cyclic systems **130** through a domino process (Scheme 54).[67] This methodology was proven to be valuable for the synthesis of substituted aromatic carbocycles and heterocycles. The chloropalladation of diyne and intermolecular Heck reaction with acrylate afforded the triene **131**. The oxidative addition of palladium(0) and a subsequent intramolecular Heck reaction generated the final product. The isolation of



Scheme 53



Scheme 54



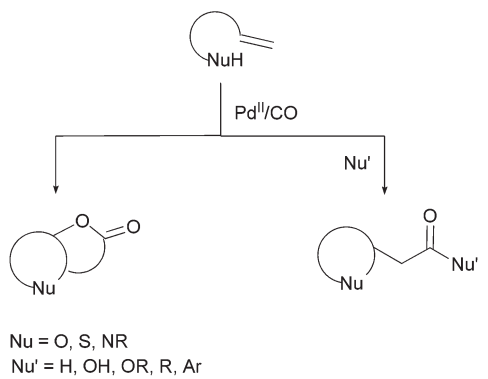
Scheme 55

the monocyclic chloroderivative intermediate **131** strengthens the suggested mechanism.

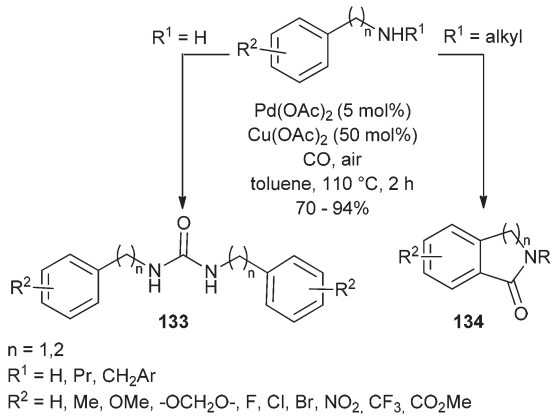
The reaction between *N*-methyl indoles and electron-deficient alkenes in the presence of trimetallic system palladium–copper–silver provided the conversion of the substrates into carbazoles **132**, through a one-pot sequence C–H alkenylation/Diels–Alder reaction (Scheme 55).[68] The reaction was performed at 100 °C in toluene–DMSO under air as an oxidant. The couple palladium–copper acts as the catalyst for the alkenylation step, while the silver salt is the promoter for the Diels–Alder cycloaddition and dehydrogenative aromatization. An example of application concerns the synthesis of a granulatimide analogue, a class of well-known Chk1 kinase inhibitors. Moreover, this procedure was used to develop alternative synthesis of various aromatic systems.

9. Carbonylations

Carbonylation chemistry by oxidative palladium(II) catalysis represents an intriguing platform for multicatalytic design. Oxidative carbonylations, developed by Semmelhack and Hegedus at the beginning of 1980, are attractive transformations because they engender rapid increases in molecular complexity by the conversion of simple unsaturated alcohol or amine substrates to complex heterocyclic products (Scheme 56). In several cases, the final step of the oxidative carbonylations involves the intervention of an alcohol (usually as a solvent) as a nucleophile to generate carboxylic ester products.



Scheme 56



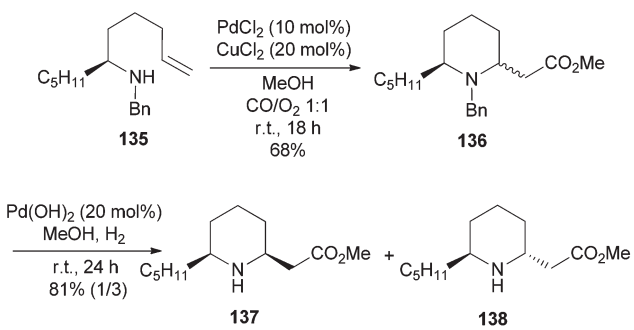
Scheme 57

Most of carbonylation domino processes involved primary amines producing symmetrical dialkylureas **133** (Scheme 57).[69] Secondary amines did not give tetraalkylureas but trialkylureas were selectively formed by addition of a secondary amine to the primary ones. Moreover phenethylamines and *N*-monoalkylated benzylic amines afforded benzolactams **134** by a direct aromatic carbonylation. Also carbonylation of 1,2-amino-alcohols resulted in the formation of oxazolidinones.

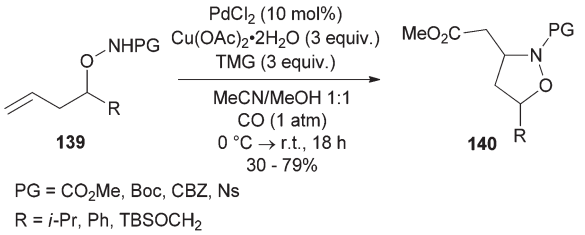
9.1 Cyclization–methoxycarbonylations

The cyclization/esterification domino process is of interest due to the facility of its incorporation into the multitransformation processes.

The aminocyclization–methoxycarbonylation sequence of alkenylamine **135** performed by catalytic $PdCl_2$ and $CuCl_2$ in MeOH under the CO/O_2 atmosphere provided an inseparable mixture of the piperidines **136** in the 68% yield (Scheme 58).[70] The final catalytic debenzylation of methylesters gave an easily separable mixture of the target piperidines **137** and **138** in 81% combined yield and in a 1 : 3 ratio in favour of the 2,6-*trans*-configured compound **136**, which is the most challenging between the two diastereoisomeric 2,6-disubstituted



Scheme 58



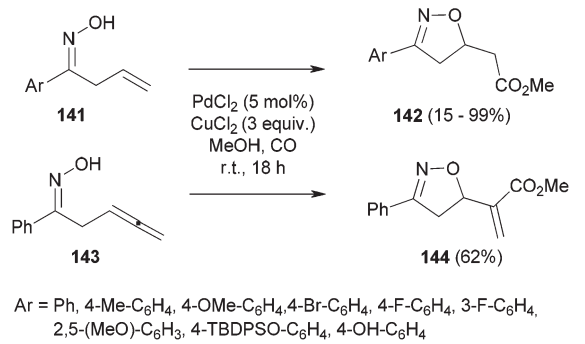
Scheme 59

piperidine alkaloids isolated from ladybird beetles of the genus *Calvia*.

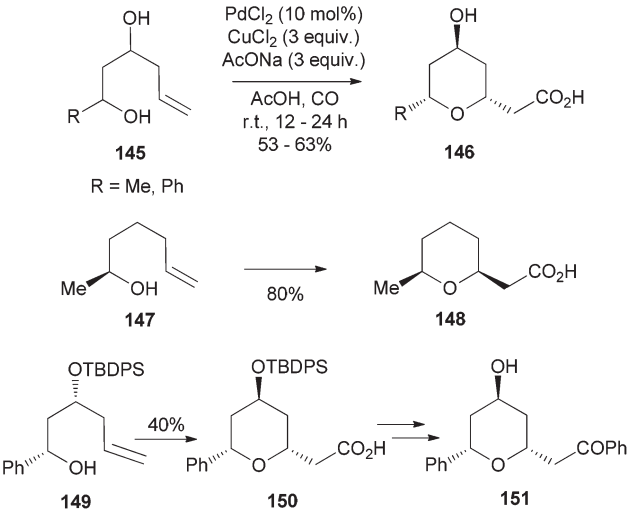
The oxidative carbonylative cyclization has been fruitfully used to synthesize methoxycarbonyl-substituted tetrahydroisoxazole derivatives. The treatment of *O*-homoallylhydroxylamines **139** with $PdCl_2$ and a copper(II) salt in the presence of a base, MeOH and carbon monoxide resulted in the formation of isoxazolidines **140** (Scheme 59).[71] Although both $CuCl_2$ and $Cu(OAc)_2$ allowed the formation of the product, the latter furnished the product in higher yield (79% with tetramethylguanidine as the base). In all cases, an electron-withdrawing substituent on the nitrogen was essential for the success of the reaction.

The 3-aryl-5-(methoxycarbonyl)methyl-substituted 4,5-dihydroisoxazoles **142** were obtained by amination/methoxycarbonylation of the alkenyloximes **141** (Scheme 60).[72] Performing this procedure on the mixture of *syn* and *anti* oxime, isoxazolines **142** were produced in racemic form in 15–99% yield. Starting from the 3,4-pentadienyloxime **143**, the (4,5-dihydroisoxazolyl) acrylate **144** was isolated in 62% yield.

The classical catalytic system ($PdCl_2$ 10 mol%, $CuCl_2$ in stoichiometric amounts and AcONa) in AcOH as the solvent was proven to be suitable to promote the intramolecular hydroxycarbonylation of alken(di)ols.[73] This domino alkoxylation/carbonylation/hydroxylation reaction provided an innovative synthetic tool for the stereoselective synthesis of 2,6-*cis*-tetrahydropyranyl acetic acids. Starting from alkendiols **145**, a range of tetrahydropyranyl acetic acids **146** were obtained (Scheme 61). The effectiveness of such a domino procedure has been demonstrated in the short and efficient synthesis of two natural products, the civet cat (+)-2-[(2*S*,6*S*)-(6-methyltetrahydro-2*H*-pyran-2-yl)]acetic acid **148** from the (2*S*)-hept-6-en-2-ol (**147**), and the diospongin A **151** from the alkendiol **149** through the key-intermediate **150**.



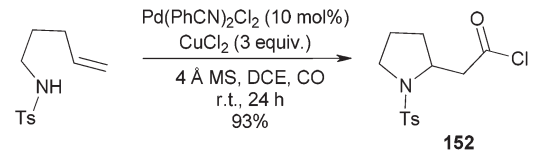
Scheme 60



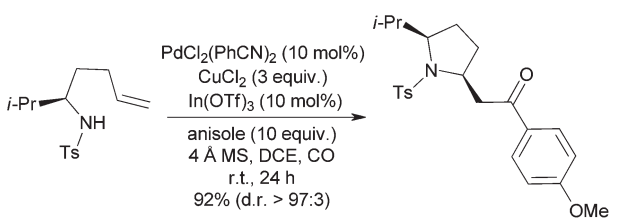
Scheme 61

Subjecting alkenylamines to standard palladium(II)/copper(II)-catalytic conditions in dichloroethane as the solvent, the reaction resulted in the formation of heterocyclic acid chlorides. When *N*-tosylpentenamine was treated with $Pd(PhCN)_2Cl_2$ (10 mol%) and $CuCl_2$ (3 equiv.) in dichloroethane under a carbon monoxide atmosphere, acid chloride **152** was isolated in 93% yield (Scheme 62).[74]

This aminochlorocarbonylative reaction was successfully incorporated in a multicatalytic process by combination with a Friedel–Crafts acylation. Working in the presence of $In(OTf)_3$ as the best Lewis acid, a variety of electron-rich aromatic nucleophiles (including aryl ether, aryl bromide, pyrrole, thiophene, and indole motifs) easily gives β-pyrrolidinyl ketone products in good to high yields and excellent diastereoselectivities. The best example is shown in Scheme 63.



Scheme 62

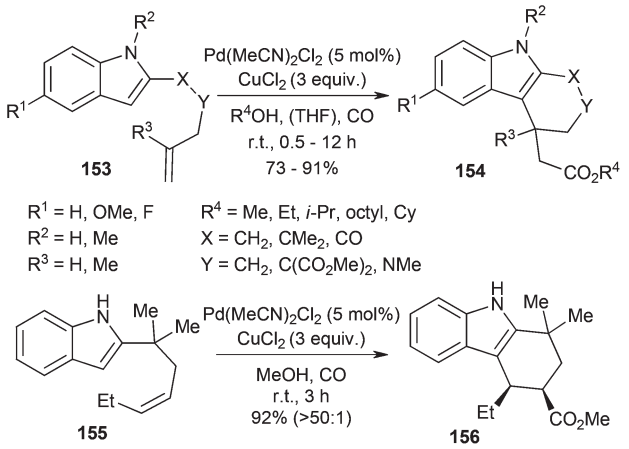


Scheme 63

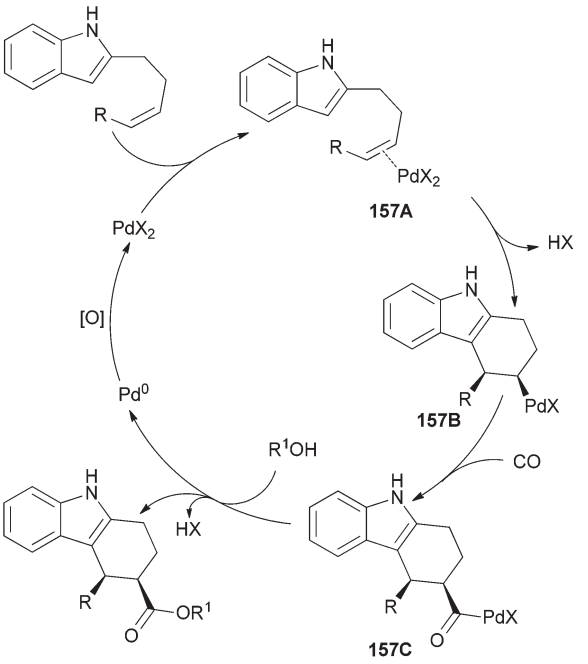
The catalytic system suitable to the cyclization/carboalkoxylation involving a heteroatom nucleophile, *i.e.* a palladium(II)-complex and $CuCl_2$ in stoichiometric amounts in MeOH under a CO atmosphere, was also successfully used by Widenhoefer to perform the addition of a carbon nucleophile and a carbonyl group across a C=C bond.[75] As shown in Scheme 64, alkenyl indoles **153** underwent cyclization/carboalkoxylation with the C-3 indolyl carbon as a nucleophile to form the corresponding tricyclic systems **154** with excellent regioselectivity. In particular, whereas the conversion of the 4-alkenylindoles features an initial 6-*exo*-trig process, the cyclization of the 3-alkenylindoles **155** occurs in a 6-*endo* manner, giving stereospecifically *cis* and *trans* tetrahydrocarbazoles **156** from *Z*- and *E*-isomer substrates. Moreover, the cyclization/carboalkoxylation of the 2-(4-pentenyl)indole was also satisfactorily performed in THF as the solvent in the presence of a number of primary and secondary alcohols.

The mechanism of the reaction involves an outer-sphere attack of the indole on the palladium-olefin complex **157A**, generating the alkylpalladium intermediate **157B** with a loss of HCl (Scheme 65). α-Migratory insertion of CO into the Pd–C bond of **157B** with retention of stereochemistry would form the acyl palladium complex **157C**, which could undergo methanolysis to release the tetrahydrocarbazole product with formation of a palladium(0). Oxidation of this latter with $CuCl_2$ would then regenerate the active palladium(II)-species. As shown for the conversion of the (*Z*)-derivative **155** into the *cis*-product **156**, the reaction occurs in a stereospecific manner.

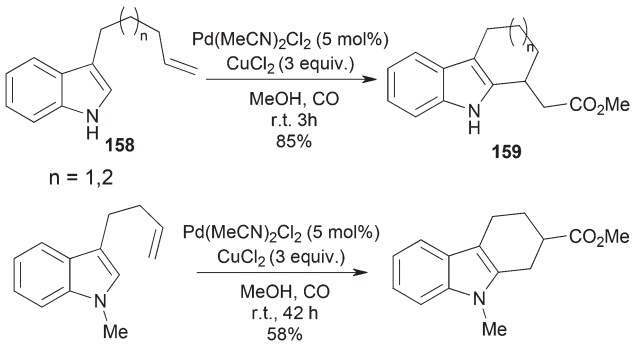
The cyclization/carboalkoxylation strategy was applied also to 3-alkenyl indoles. The compounds **158** effectively underwent 6-*exo*- or 6-*endo*-cyclization, depending on the size of the alkenyl pendant, to yield the tetrahydrocarbazole products **159** (Scheme 66). Experiments carried out on deuterium-substituted substrates seem to be in agreement with the *anti* addition of the indole and the carbomethoxy group across the olefin bond and evidenced a mechanism involving an outer-sphere nucleophilic attack of the C-2 position of the indole on a palladium-complexed olefin. However, the intervention of the indolyl C-3 position generating a spirocyclic-intermediate cannot be ruled out.



Scheme 64



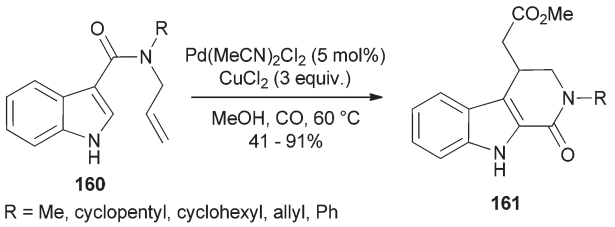
Scheme 65



Scheme 66

Besides the investigation on the 3-substituted indoles bearing the olefin moiety through an alkyl chain, the 3-indolecarboxylic acid allylamides **160** were submitted to the well-established catalytic system for the cyclization/carboalkoxylation process (Scheme 67).[59] Interestingly, the intramolecular reaction led to the formation of acetates **161**, whose β-carboline structure was unambiguously determined by X-ray diffraction analysis. In this case, the 6-*exo*-trig cyclization reasonably proceeds through the before mentioned spirocyclic iminium ion intermediate **114**, arising from the nucleophilic activity of the indolyl C-3 position despite its substitution with an electron-withdrawing functional group, followed by 1,2-migration of the acyl moiety to give the final product.

The same catalytic system allowed the intermolecular arylation/carboalkoxylation of vinyl arenes with indoles.[75b] Elec-



Scheme 67

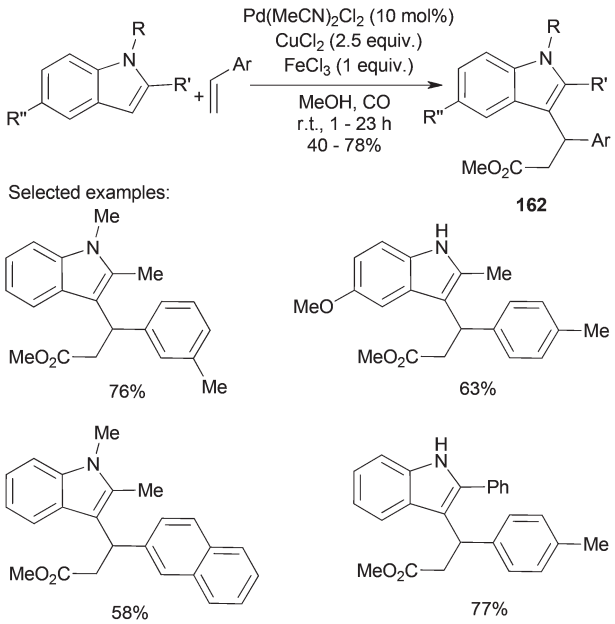
tron-rich and electron-poor vinyl arenes and 2-substituted indoles furnished regioselective compounds **162** in moderate to good yields (Scheme 68). Although ineffective as a sole stoichiometric oxidant, $FeCl_3$ increased the formation of **162** when combined with $CuCl_2$. The substitution at the C-2 position of the indole nucleus was essential to have the arylation/carboalkoxylation process.

Acyclic diesters **164** were formed through C–C bond cleavage of cyclic ketones **163** after the alkoxycarbonylation process in the presence of MeOH under a CO atmosphere (Scheme 69).[76] A side-product observed consisted of the terminal chloro-substituted monoesters **165.**

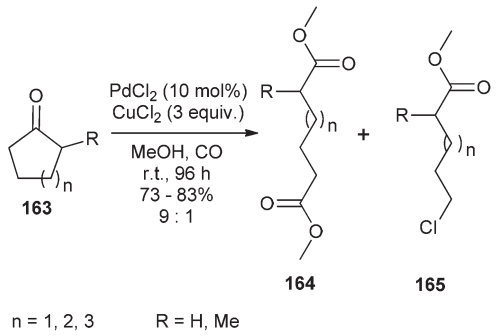
9.2 Cyclization–lactonization

Domino reactions providing bicyclic fused lactones can be performed by insertion of carbon monoxide in the second cyclization step. Thus, the lactonization, which leads to differently sized rings, occurs on the palladium intermediate arising from an initial intramolecular amination or alkoxylation.

The amino/amidocarbonylation of N-protected 1-amino-pent-4-ene-3-ols has been proven to be useful tools to build *cis*-fused pyrrolidine-γ-lactones.[77] Compared to these substrates, the homologous 6-amino-hex-2-ene-3-ols are much less



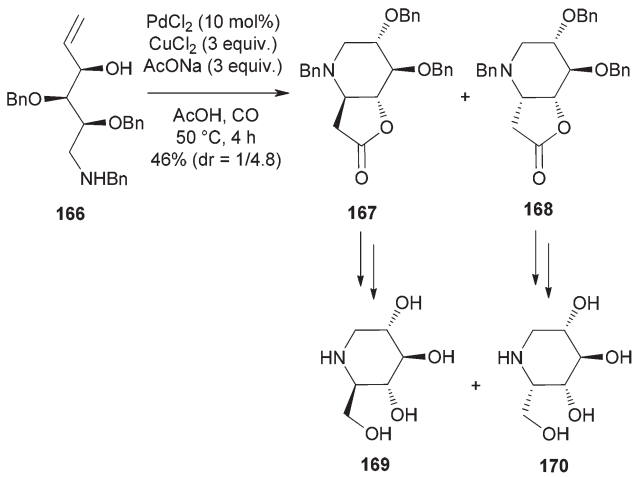
Scheme 68



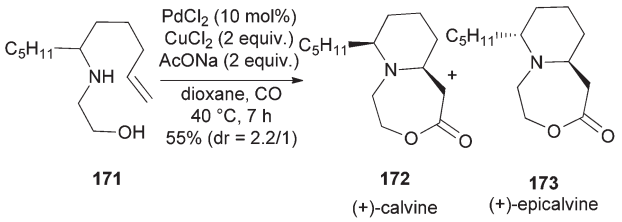
Scheme 69

reactive towards palladium(II)-catalyzed aminocarbonylations. However, the treatment of the highly substituted *N*-benzyl-4-hydroxy-hex-5-enylamine **166** in the typical carbonylative conditions ($PdCl_2$–$CuCl_2$, in the presence of AcONa, in AcOH under a CO atmosphere) yielded the piperidine lactones **167** and **168** (in a 1 : 4.8 mixture), which are direct precursors of the C-6 homologues of 1-deoxynojirimycin **169** and 5-*epi*-1-deoxyidonojirimycin **170** (Scheme 70).[78] Notably, the reaction works on the benzyl-protected amino group, while analogous procedures usually require electron withdrawing protecting groups (tosyl, carbamate, and amide).

The diastereoselective intramolecular carbonylation of the aminoalkenol **171** was used as a key step in the short synthesis of the ladybird beetle alkaloids (+)-calvine **172** and (+)-epicalvine **173** (Scheme 71).[70,79] After the initial aminocyclization to determine the piperidine ring, the lactonization step provided the seven-membered ring of the bicyclic fused products. The diastereoisomeric ratio depends on the applied catalytic conditions. Thus, using $PdCl_2$ as a catalyst and excess $CuCl_2$ as a reoxidant, compound **172** was obtained as a major product in a diastereoisomeric ratio of 2.2 : 1 and 55% yield. On the other hand, the combination of molecular oxygen (1 atm) with catalytic copper afforded the (+)-epicalvine **173** as a major product in a ratio of 7 : 3 and 53% yield.



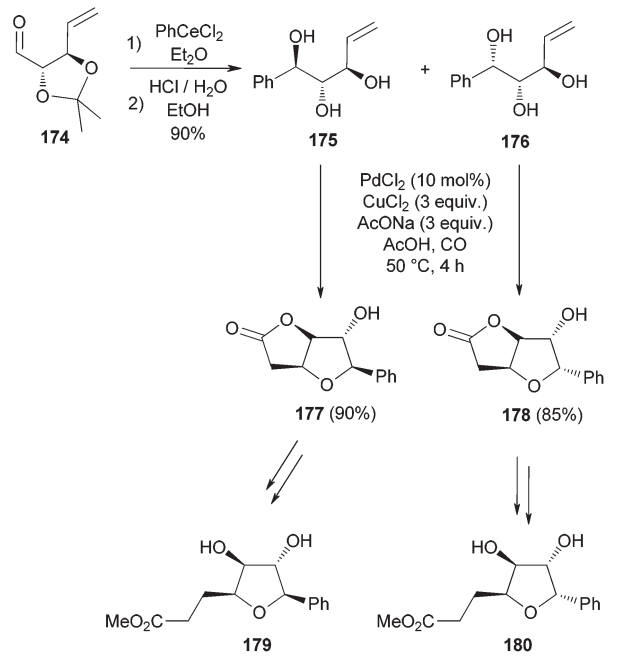
Scheme 70



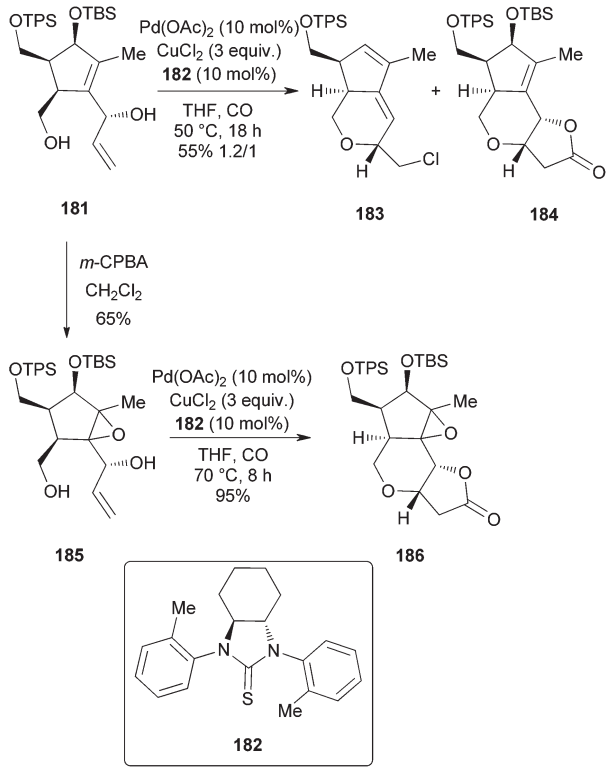
Scheme 71

Intramolecular oxycarbonylation of polyols with carbon monoxide insertion into the σ-type C–Pd bond of the σ-alkylpalladium(II) intermediate has also been reported. The bicyclization of the triols **175** and **176**, obtained by diastereoselective addition of $PhCeCl_2$ to aldose **174**, furnished lactones **177** and **178** with high regio- and *cis*-selectivity in 90 and 85% yield, respectively (Scheme 72).[80] These latter are the key compounds for the construction of the polyhydroxylated tetrahydrofuran skeleton of goniothalesdiol (**179**) and 7-*epi*-goniothalesdiol (**180**). It is noteworthy that the silyl-protection of the α-hydroxy group of the triols inferred a different regiochemistry in the cyclization.[81]

The carbonylative annulation has been used as a key step for an efficient synthesis of a tricyclic portion of micrandilactone A, isolated from a medicinal plant traditionally used in China for the treatment of rheumatic lumbago and related diseases. Standard catalytic system applied on compound **181** led only to a decomposition material. A determinant role to achieve annulation products was played by the thioureas **182**, used as a ligand in 10 mol% (Scheme 73).[82] Thus, working with $Pd(OAc)_2$ as a catalyst, $CuCl_2$, thioureas **182** under a carbon monoxide atmosphere in THF as a solvent, a mixture



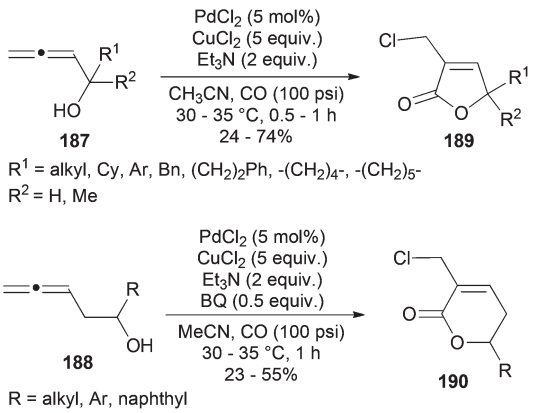
Scheme 72



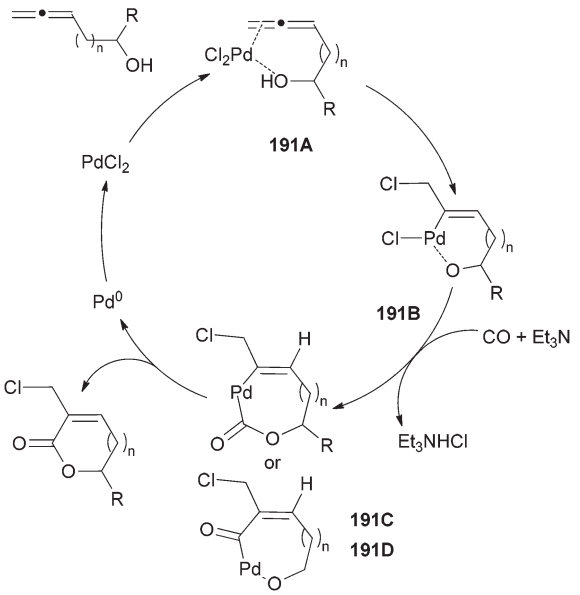
Scheme 73

of chloroderivative **183** and lactone **184** was obtained. The application of the same conditions to compound **185**, prepared by regioselective epoxidation of the alkene **181**, yielded selectively the tetracyclic product **186**.

An interesting procedure for the synthesis of 3-chloromethyl-2(5*H*)-furanones (**189**) and 3-chloromethyl-5,6-dihydropyran-2-ones (**190**) involving a chlorocyclocarbonylation in the presence of triethylamine as a base and acetonitrile as a solvent under pressure of carbon monoxide was successfully developed from 2,3- or 3,4-allenols (**187, 188**) (Scheme 74).[83]



Scheme 74



Scheme 75

The reaction plausibly proceeds by selective coordination of the terminal double bond of the substrates giving the intermediate **191A**, which is followed by the highly regioselective chloropalladation to generate the cyclic vinyl-palladium intermediate **191B** (Scheme 75). Subsequent coordination and insertion of CO afford palladacyclic intermediates **191C** or **191D**, which lead to the heterocyclic product by reductive elimination. Palladium(0) species finally regenerated by $CuCl_2$ to palladium(II) restarts a new catalytic cycle.

10. Conclusions

The present overview gives an account of the progress made in the area of the palladium(II)/copper(II) catalyzed domino reactions involving carbon–carbon and carbon–heteroatom bonds. The different typologies of procedures here discussed show the usefulness of this heterobimetallic catalytic system, which leads to the use of mild reaction conditions compatible with air and moisture, avoiding the need for reactant preactivation. The effectiveness of the dual metal catalytic system relies on the role of the copper salt, which often acts as a reoxidant agent. Moreover, the functionalization of the carbon–carbon multiple bonds is generally regioselective and the catalytic system can tolerate a broad range of functional groups.

Although great progress has been achieved, some challenges still remain for a wider applicability of the palladium(II)/copper(II) catalytic system. The improvement of enantioselective transformations should open new perspectives in organic synthesis and medicinal chemistry. On the other hand, the development of processes based on the use of co-catalytic amounts of copper(II) salts in the presence of environmentally friendly molecular oxygen as the terminal oxidant should be a benefit for pharmaceutical industries.

Acknowledgements

We thank Insubria and Milan Universities as well as MIUR (project PRIN 2010–2011 prot. 20109Z2XRJ) for the financial support.

Notes and references

1 (*a*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077–1101; (*b*) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (*c*) M. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2243–2270; (*d*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (*e*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*f*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780–1824; (*g*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292.

2 (*a*) K. H. Jensen and M. S. Sigman, *Org. Biomol. Chem.*, 2008, **6**, 4083–4088; (*b*) G. Broggini, E. M. Beccalli, A. Fasana and S. Gazzola, *Beilstein J. Org. Chem.*, 2012, **8**, 1730–1746; (*c*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068–5083.

3 (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136; (*b*) G. Poli, G. Giambastiani and A. Heumann, *Tetrahedron*, 2000, **56**, 5959–5989; (*c*) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442–524; (*d*) H. Clavier and H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 3347–3404; (*e*) S. F. Mayer, W. Kroutil and K. Faber, *Chem. Soc. Rev.*, 2001, **30**, 332–339; (*f*) T. Vlaar, E. Ruijter and V. A. Orru, *Adv. Synth. Catal.*, 2011, **353**, 809–841.

4 (*a*) J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571–582; (*b*) J. P. Wolfe, *Synlett*, 2008, 2913–2937; (*c*) F. Cardona and A. Goti, *Nat. Chem.*, 2009, 269–275; (*d*) G. Li, S. R. S. S. Kotti and C. Timmons, *Eur. J. Org. Chem.*, 2007, 2745–2758.

5 (*a*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318–5365; (*b*) J. Le Bras and J. Muzart, *Chem. Rev.*, 2011, **111**, 1170–1214; (*c*) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981–3019.

6 (*a*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922; (*b*) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46–49.

7 V. Farina, S. Kapadia, B. Krishnan, C. Wang and L. S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 5905–5911.

8 (*a*) F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2006, 1379–1382; (*b*) F. Besselievre, F. Mahuteau-Betzer, D. S. Grierson and S. Piguel, *J. Org. Chem.*, 2008, **73**, 3278–3280; (*c*) S. De Ornellas, T. E. Storr, T. J. Williams, C. G. Baumann and U. J. S. Fairlamb, *Curr. Org. Synth.*, 2011, **8**, 79–101.

9 S. Wurtz, S. Rakshit, J. J. Neumman, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230–7233.

10 (*a*) W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560–14561; (*b*) E. M. Beccalli,

E. Borsini, G. Broggini, M. Rigamonti and S. Sottocornola, *Synlett*, 2008, 1053–1057.
11 (*a*) T. Punniyamurthy, S. Velusamy and J. Iqba, *Chem. Rev.*, 2005, **105**, 2329–2363; (*b*) J. A. Keith and P. M. Henry, *Angew. Chem., Int. Ed.*, 2009, **48**, 9038–9049.
12 F. Zhou, X. Han and X. Lu, *Tetrahedron Lett.*, 2011, **52**, 4681–4685.
13 J. Chen, Q. Pang, Y. Sun and X. Li, *J. Org. Chem.*, 2011, **76**, 3523–3526.
14 X. Chen, X. Li, N. Wang, J. Jin, P. Lu and Y. Wang, *Eur. J. Org. Chem.*, 2012, 4380–4386.
15 X. F. Xia, N. Wang, L. L. Zhang, X. R. Song, X. Y. Liu and Y. M. Liang, *J. Org. Chem.*, 2012, **77**, 9163–9170.
16 Q. Huang and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 980–988.
17 N. Zhang, B. Li, H. Zhong and J. Huang, *Org. Biol. Chem.*, 2012, **10**, 9429–9439.
18 C. C. Scarborough and S. S. Stahl, *Org. Lett.*, 2006, **8**, 3251–3254.
19 Y. Y. Liu, R. J. Song, C. Y. Wu, L. B. Gong, M. Hu, Z. Q. Wang, Y.-X. Xie and J. H. Li, *Adv. Synth. Catal.*, 2012, **354**, 347–353.
20 M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211–5215.
21 D. Xing and D. Yang, *Org. Lett.*, 2013, **15**, 4370–4373.
22 M. Wasa, K. M. Engle and J. Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3680–3681.
23 (*a*) K. Muniz, C. H. Hovelmann, E. Campos-Gomez, J. Barluenga, J. M. Gonzalez, J. Streuff and M. Nieger, *Chem. – Asian J.*, 2008, **3**, 776–788; (*b*) C. H. Hoevelmann, J. Streuff, L. Brelot and K. Muniz, *Chem. Commun.*, 2008, 2334–2336.
24 K. Muniz, J. Streuff, P. Chavez and C. H. Hovelmann, *Chem. – Asian J.*, 2008, **3**, 1248–1255.
25 P. Chavez, J. Kirsch, J. Streuff and K. Muniz, *J. Org. Chem.*, 2012, **77**, 1922–1930.
26 G. Broggini, V. Barbera, E. M. Beccalli, U. Chiacchio, A. Fasana, S. Galli and S. Gazzola, *Adv. Synth. Catal.*, 2013, **355**, 1640–1648.
27 N. Asao, C. S. Chan, K. Takahashi and Y. Yamamoto, *Tetrahedron*, 2005, **61**, 11322–11326.
28 B. Yao, C. Jaccoud, Q. Wang and J. Zhu, *Chem. – Eur. J.*, 2012, **18**, 5864–5868.
29 X.-F. Xia, L.-L. Zhang, X.-R. Song, Y.-N. Niu, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 1410–1412.
30 P.-Y. Chen, K.-S. Huang, C.-C. Tsai, T.-P. Wang and E.-C. Wang, *Org. Lett.*, 2012, **14**, 4930–4933.
31 (*a*) B. Alcaide, P. Almendros and R. Rodriguez-Acebes, *Chem. – Eur. J.*, 2005, **11**, 5708–5712; (*b*) B. Alcaide, P. Almendros and R. Rodriguez-Acebes, *J. Org. Chem.*, 2006, **71**, 2346–2351.
32 H. Cao, H. F. Jiang, H. W. Huang and J. W. Zhao, *Org. Biomol. Chem.*, 2011, **9**, 7313–7317.
33 N. Momiyama, M. W. Kanan and D. R. Liu, *J. Am. Chem. Soc.*, 2007, **129**, 2230–2231.
34 (*a*) K. Minami, Y. Kawamura, K. Koga and T. Hosokawa, *Org. Lett.*, 2005, **7**, 5689–5692; (*b*) Y. Kawamura, T. Imai and T. Hosokawa, *Synlett*, 2006, 3110–3115.
35 M. A. Evans and J. P. Morken, *Org. Lett.*, 2005, **7**, 3367–3370.
36 K. Yonehara, Y. Miyoshi, A. Tsukajiama, T. Akatsuka and M. Saito, *Adv. Synth. Catal.*, 2011, **353**, 1071.
37 P. Zhou, H. Jiang, L. Huang and X. Li, *Chem. Commun.*, 2011, **47**, 1003–1005.
38 M. J. Schultz and M. S. Sigman, *J. Am. Chem. Soc.*, 2006, **128**, 1460–1461.
39 F. Alonso, D. Sanchez, T. Soler and M. Yus, *Adv. Synth. Catal.*, 2008, **350**, 2118–2126.
40 Z.-Y. Wang, H.-F. Jiang, X.-Y. Ouyang, C.-R. Qi and S.-R. Yang, *Tetrahedron*, 2006, **62**, 9846–9854.
41 A. M. Balija, K. J. Stowers, M. J. Schultz and M. S. Sigman, *Org. Lett.*, 2006, **8**, 1121–1124.
42 M. Babjak, L. Remen, P. Szolcsanyi, P. Zalupsky, D. Miklos and T. Gracza, *J. Organomet. Chem.*, 2006, **691**, 928–940.
43 M. Babjak, L. Remen, O. Karlubikova and T. Gracza, *Synlett*, 2005, 1609–1611.
44 T. Gracza and V. Jaeger, *Synthesis*, 1994, 1359–1367.
45 (*a*) M. Palik, O. Karlubikova, A. Lasikova, J. Kozisek and T. Gracza, *Eur. J. Org. Chem.*, 2009, 709–715; (*b*) M. Palík, O. Karlubikova, D. Lackovicova, A. Lasikova and T. Gracza, *Tetrahedron*, 2010, **66**, 5244–5249.
46 I. Shiina, Y. I. Kawakita, R. Ibuka, K. Yokoyama and Y. S. Yamai, *Chem. Commun.*, 2005, 4062–4064.
47 E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano and S. Sottocornola, *J. Org. Chem.*, 2008, **73**, 4746–4749.
48 (*a*) P. Szolcsanyi and T. Gracza, *Chem. Commun.*, 2005, 3948–3950; (*b*) P. Szolcsanyi and T. Gracza, *Tetrahedron*, 2006, **62**, 8498–8502.
49 J. Alladoum, E. Vrancken, P. Mangeney, S. Roland and C. Kadouri-Puchot, *Org. Lett.*, 2009, **11**, 3746–3749.
50 E. Borsini, G. Broggini, A. Fasana, S. Galli, M. Khansaa, U. Piarulli and M. Rigamonti, *Adv. Synth. Catal.*, 2011, **353**, 985–994.
51 A. N. Thadani and V. H. Rawal, *Org. Lett.*, 2002, **4**, 4321–4323.
52 (*a*) Y. Wen, L. Huang, H. Jiang and H. Chen, *J. Org. Chem.*, 2012, **77**, 2029–2034; (*b*) Y. Wen and H. Jiang, *Tetrahedron Lett.*, 2013, **54**, 4034–4037.
53 L. Huang, Q. Wang, X. Liu and H. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 5696–5700.
54 S. Ye, K. Gao, H. Zhou, X. Yang and J. Wu, *Chem. Commun.*, 2009, 5406–5408.
55 C.-C. Chen, L.-Y. Chin, S.-C. Yang and M.-J. Wu, *Org. Lett.*, 2010, **12**, 5652–5655.
56 H.-P. Zhang, S.-C. Yu, Y. Liang, P. Peng, B.-X. Tang and J.-H. Li, *Synlett*, 2011, 982–988.
57 W. R. Chang, Y. H. Lo, C. Y. Lee and M. J. Wu, *Adv. Synth. Catal.*, 2008, **350**, 1248–1252.
58 Y. Li, K. J. Jardine, R. Tan, D. Song and V. M. Dong, *Angew. Chem., Int. Ed.*, 2009, **48**, 9690–9692.
59 G. Broggini, V. Barbera, E. M. Beccalli, E. Borsini, S. Galli, G. Lanza and G. Zecchi, *Adv. Synth. Catal.*, 2012, **354**, 159–170.

60 G. Abbiati, E. M. Beccalli, G. Broggini, M. Martinelli and G. Paladino, *Synlett*, 2006, 73–76.
61 E. Borsini, G. Broggini, F. Colombo, M. Khansaa, A. Fasana, S. Galli, D. Passarella, E. Riva and S. Riva, *Tetrahedron: Asymmetry*, 2011, **22**, 264–269.
62 A. Lei, X. Lu and G. Liu, *Tetrahedron Lett.*, 2004, **45**, 1785–1788.
63 S. D. R. Christie, A. D. Warrington and C. J. Lunniss, *Synthesis*, 2009, 148–154.
64 (*a*) C. Jonasson, A. Horvàth and J. E. Bäckvall, *J. Am. Chem. Soc.*, 2000, **122**, 9600–9609; (*b*) C. Jonasson, W. F. J. Karstens, H. Hiemstra and J. E. Bäckvall, *Tetrahedron Lett.*, 2000, **41**, 1619–1622.
65 M. R. Manzoni, T. P. Zabawa, D. Kasi and S. R. Chemler, *Organometallics*, 2004, **23**, 5618–5621.
66 X. Du, M. Suguro, K. Hirabayashi and A. Mori, *Org. Lett.*, 2001, **3**, 3313–3316.
67 P. Zhou, M. Zheng, H. Jiang, X. Li and C. Qi, *J. Org. Chem.*, 2011, **76**, 4759–4763.
68 K. Ozaki, H. Zhang, H. Ito, A. Lei and K. Itami, *Chem. Sci.*, 2013, **4**, 3416–3420.
69 (*a*) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki and M. Tokuda, *J. Org. Chem.*, 2006, **71**, 5951–5958; (*b*) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342–14343.
70 P. Kubizna, I. Spanik, J. Kozisek and P. Szolcsanyi, *Tetrahedron*, 2010, **66**, 2351–2355.
71 R. W. Bates and K. Sa-Ei, *Org. Lett.*, 2002, **4**, 4225–4227.
72 M. D. Mosher, L. G. Emmerich, K. S. Frost and B. Anderson, *J. Heterocycl. Chem.*, 2006, **43**, 535–539.
73 O. Karlubikova, M. Babjak and T. Gracza, *Tetrahedron*, 2011, **67**, 4980–4987.
74 T. A. Cernak and T. H. Lambert, *J. Am. Chem. Soc.*, 2009, **131**, 3124–3125.
75 (*a*) C. Liu and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 10250–10251; (*b*) C. Liu and R. A. Widenhoefer, *Chem. – Eur. J.*, 2006, **12**, 2371–2382.
76 (*a*) O. Hamed, A. El-Qisairi and P. M. Henry, *Tetrahedron Lett.*, 2000, **41**, 3021–3024; (*b*) O. Hamed, A. El-Qisairi and P. M. Henry, *J. Org. Chem.*, 2001, **66**, 180–185.
77 (*a*) V. Jäger and W. Hümmer, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1171–1173; (*b*) Y. Tamaru, T. Kobayashi, S.-I. Kawamura, H. Hochiai and Z.-I. Yoshida, *Tetrahedron Lett.*, 1985, **26**, 4479–4482; (*c*) Y. Tamaru, M. Hoyo and Z.-I. Yoshida, *J. Org. Chem.*, 1988, **53**, 5731–5741.
78 (*a*) P. Szolcsanyi, T. Gracza, M. Koman, N. Pronayova and T. Liptaj, *Chem. Commun.*, 2000, 471–472; (*b*) P. Szolcsanyi, T. Gracza, M. Koman, N. Pronayova and T. Liptaj, *Tetrahedron: Asymmetry*, 2000, **11**, 2579–2597.
79 P. Szolcsanyi, T. Gracza and I. Spanik, *Tetrahedron Lett.*, 2008, **49**, 1357–1360.
80 M. Babjak, P. Kapitan and T. Gracza, *Tetrahedron*, 2005, **61**, 2471–2479.
81 M. Babjak, P. Zalupsky and T. Gracza, *ARKIVOC*, 2005, **v**, 45–37.
82 Y. Tang, Y. Zhang, M. Dai, T. Luo, L. Deng, J. Chen and Z. Yang, *Org. Lett.*, 2005, **7**, 885–888.
83 X. Cheng, X. Jiang, Y. Yu and S. Ma, *J. Org. Chem.*, 2008, **73**, 8960–8965.