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Review

Heterocycles via cyclization of alkynes promoted by organopalladium complexes☆

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Abstract

Two general classes of reactions leading to heterocycles are reviewed: the sequential hydroarylation(hydrovinylation)/cyclization of alkynes containing proximate nucleophilic and electrophilic centers, a process which combines the palladium-catalyzed *cis* addition of an aryl or vinyl unit and a hydrogen atom to the carbon–carbon triple bond with the formation of a new bond between the nucleophile and the electrophile; the palladium-catalyzed cyclization of alkynes containing proximate nucleophiles with organopalladium complexes, which is based on a *trans* heteropalladation/reductive elimination tandem reaction. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Alkynes; Catalysis; Cyclization; Heterocycles; Palladium

1. Introduction

The utilization of alkynes in the palladium-catalyzed synthesis of heterocycles represents one of the most versatile and efficient tools for the preparation of this class of compounds. A number of processes which allow the construction of a wide variety of functionalised heterocyclic rings from acetylenic building blocks have been developed, providing important new dimensions in the design of synthetic strategies. The focus of this review is on the area of palladium-catalyzed synthesis of heterocyclic compounds which involves two general classes of reactions: (1) the sequential hydroarylation(hydrovinylation)/cyclization of alkynes containing proximate nucleophilic and electrophilic centers, a process which combines the palladium-catalyzed *cis* addition of an aryl or vinyl unit and a hydrogen atom to the carbon–carbon triple bond with the formation of a new bond between the nucleophile and the electrophile (Scheme 1); (2) the palladium-catalyzed cyclization of alkynes containing proximate nucleophiles, which is based on the *trans* addition of a nucleophile and an organic fragment across the carbon–carbon triple bond (Scheme 2). *Endo–dig* (Scheme 2a) and *exo–dig* (Scheme 2b) cyclization products can be obtained depending on the number of carbon atoms in between the multiple bond and the nucleophilic center.

Basically, these reactions differ in the way the acetylenic moiety is involved in the construction of the ring. In the hydroarylation(hydrovinylation)/cyclization process the cyclization event occurs 'outside' the carbon–carbon triple bond. The carbopalladation step provides the alkyne with the structural modification required to bring the nucleophilic and the electrophilic fragments closer to each other so as to favor the formation of a new bond between them. In the *trans* addition process the carbon–carbon triple bond is in-

☆ Dedicated to Professor Richard F. Heck and Professor Jiro Tsuji.

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stead directly involved in the bond breaking and making events leading to the heterocyclic ring.

These two processes, however, have a common root in the η^2-alkyne-organopalladium complex formed initially, the first acetylenic intermediate in this chemistry. Depending on a variety of factors—the nature of the substituents close to the carbon–carbon triple bond, ligands, solvents and added salts—this intermediate can follow different reaction pathways making it possible to develop diverse synthetic processes. Since understanding the behavior of the η^2-alkyne-organopalladium complex is essential to the design and utilization of these processes in synthetic applications, this review highlights the influence of these factors on its reactivity.

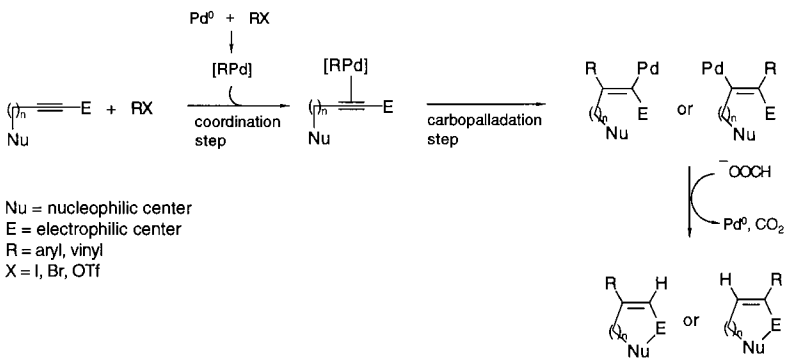
Special attention is focused upon the synthetic applications of this chemistry.

2. The hydroarylation and hydrovinylation reaction

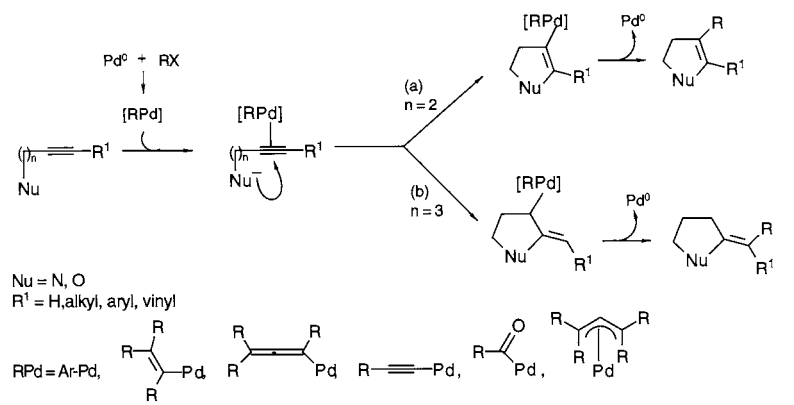
2.1. Overview

2.1.1. Mechanism

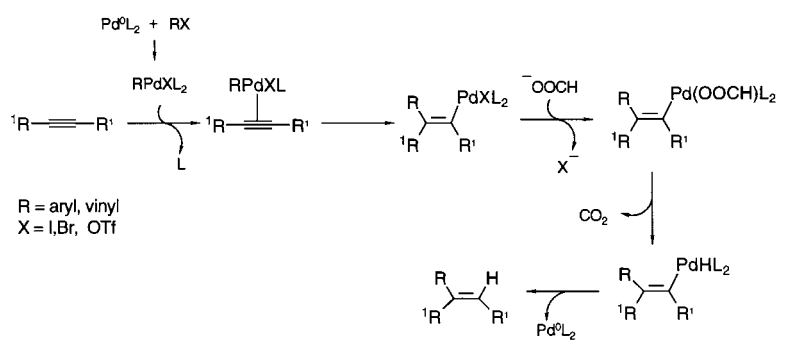
Hydroarylations and hydrovinylations of alkynes have been performed with aryl/vinyl halides or triflates. In these reactions the η^2-alkyne-σ-aryl/vinylpalladium



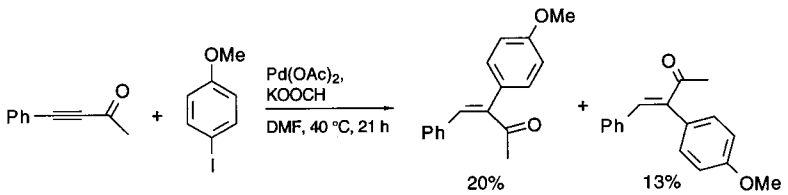
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

intermediate derived from the alkyne and the σ-aryl/vinylpalladium complex generated in situ undergoes the addition of the aryl/vinylpalladium fragment to the carbon–carbon triple bond (Scheme 3). Subsequently, the resultant σ-vinylpalladium adduct is converted into the formate derivative from which, after decarboxylation and reductive elimination of palladium(0) species, the trisubstituted olefin derivative is generated [1]. The isolation of the deuterated olefin when the reaction is carried out in the presence of monodeuterated formic acid, DCOOH, is consistent with this mechanism. The net result of the reaction is the addition of an aryl or vinyl unit on one side of the carbon–carbon triple bond and a hydrogen atom on the other side. Depending on the nature of the C_{sp^2} donor and the alkyne, coupling derivatives and/or arenes or alkenes, derived from the reduction of the σ-aryl- or σ-vinylpalladium intermediates, are generated in variable amounts. Alkenes arising from the reduction of alkynes may also be generated as minor by-products.

2.1.2. Stereoselectivity

The reaction is stereoselective and *cis* addition olefins are usually obtained [2]. The formation of significant amounts of overall *trans* derivatives has sometimes been observed (there are, however, several known examples of overall *trans* additions of transition metal–hydride or metal–alkyl fragments to acetylenic compounds [3–6]). For example, the *trans* hydroarylation product was isolated in the reaction of 4-phenyl-3-butyn-2-one with 4-iodoanisole [7] (Scheme 4).

As the observed general predominance of *cis* hydroarylation or hydrovinylation products argues against the existence of a direct *trans* addition pathway paralleling the *cis* addition pathway, the appearance of both *E* and *Z* isomers of the products following the carbopalladation step should involve the formation of a *cis* addition intermediate capable of rotation about the C=C bond. A possible rationale for this *cis–trans* isomerization of the addition intermediate could involve contributions from zwitterionic resonance forms derived from the formal donation of an electron pair by a d^8 palladium centre [8] (Fig. 1). In the hydroarylation of 4-phenyl-3-butyn-2-one (Scheme 4) the carbonyl group could play a pivotal role in lowering the C=C bond order to the point needed for the rotation that results in the formation of the *trans* addition product.

2.1.3. Regioselectivity

With unsymmetrical alkynes the regiochemistry of the hydroarylation(hydrovinylation) process is primarily controlled by steric and coordinating affects whereas electronic effects play a minor role.

2.1.3.1. Steric effects. Steric effects control the carbopalladation step so as to direct preferentially the organic fragment to the less hindered end of the carbon–carbon triple bond and the palladium to the more hindered end. This tendency has been discussed in terms of irreversible migration of the organic framework and the palladium moiety onto the coordinated acetylene, though no definitive evidence of this assumption has yet been obtained (a reversible addition step would mandate considering steric effects in the carbopalladation intermediates). According to this view, steric effects might favor transition states that minimize steric strain in the vicinity of the site involved in the formation of the shorter carbon–carbon bond (Fig. 2a) at the expense of transition states locating the organic fragment close to the bulkier terminus of the acetylenic system (Fig. 2b). Analogous regiochemistry has been observed in other reactions proceeding through the addition of organopalladium [9] and organomanganese [10] complexes to acetylenes.

Alkynes containing an aryl group on one side and a trimethylsilyl group on the other side of the acetylenic system [11] (Ar versus $SiMe_3$; Scheme 5) produce as main products olefin derivatives in which the added carbon unit is located at the carbon atom σ-bonded to the aryl group and the hydrogen atom (the palladium in the carbopalladation step) is located at the carbon atom σ-bonded to the trimethylsilyl group.

In the presence of less steric demanding groups such as acetals [7] [Ar versus $CH(OR)_2$] the aromatic ring behaves like the larger substituent and the addition of the σ-C_{sp^2}-palladium complex to the carbon–carbon triple bond proceeds preferentially through a transition

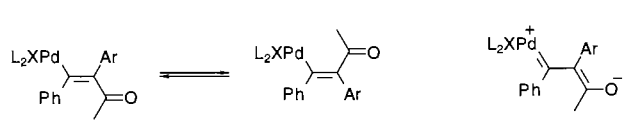


Fig. 1.

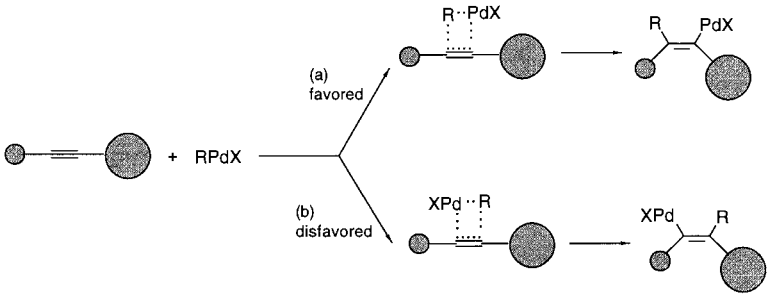
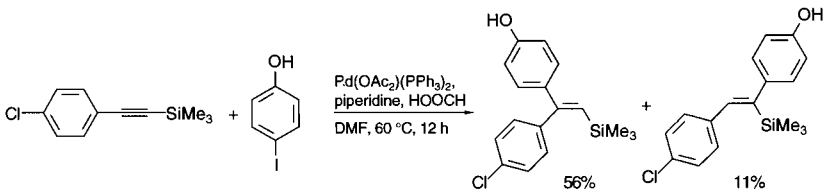
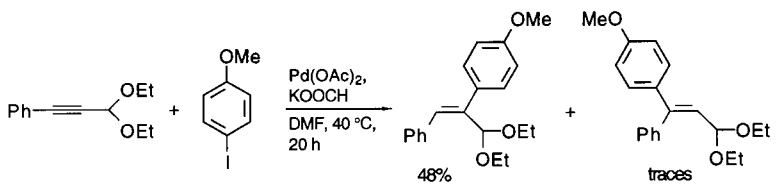


Fig. 2.



Scheme 5.



Scheme 6.

state that minimizes steric strain between the aromatic ring of the starting alkyne and the approaching unsaturated framework. Consequently, addition intermediates where the palladium is linked to the carbon far from the acetal group are favored and the reaction proceeds as shown in Scheme 6.

To account for the effect of the aromatic ring ligated to the acetylenic carbon in dictating the orientation of the carbopalladation step it has been suggested that the conversion of η^2-palladium complexes into the corresponding σ-vinylpalladium complexes occurs through transition states where steric interactions between nonbonded groups and electronic effects resemble those roughly sketched in Fig. 3 using 3,3-diethoxy-1-phenyl-1-propyne (the likely bending of acetylenic substituents is not represented). These spatial arrangements, whereby the plane of the aromatic ring is coplanar, or nearly so, to the plane containing the acetylenic carbons and the palladium atom, could benefit by some overlapping of the aromatic π-electrons with the acetylenic π-electrons orthogonal to those coordinated to palladium. At the same time, they could allow the aromatic ring to provide a steric hindrance higher than that of the acetal substituent, favoring the migration of aryl or vinyl units onto the carbon linked to the acetal substituent (Fig. 3a).

The same pronounced directing effect of the aryl group has been observed in other palladium-catalyzed additions of aryl halides to 1-phenyl-1-propyne (Ph versus Me) [9a,b,12,13], to electron-deficient alkynes (Ph versus CHO [9b,13] or COMe [13] or COOR [9b,12–14] and in the hydroarylation of methyl 3-phenylpropynoate (Ph versus COOMe) [15].

2.1.3.2. Coordinating effects. Coordination of neighboring groups to the palladium complex approaching the carbon–carbon triple bond can play a significant role in directing the addition step (Fig. 4).

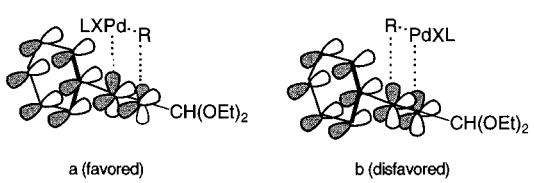


Fig. 3.

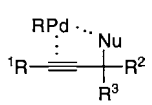
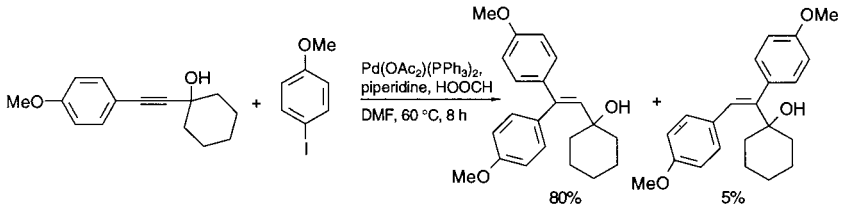
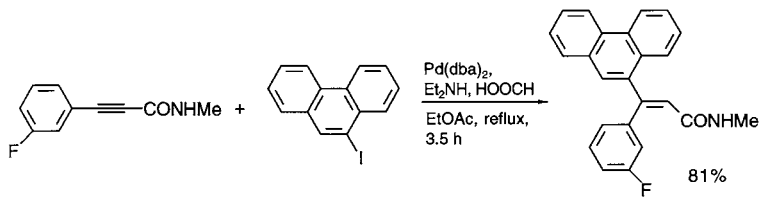


Fig. 4.



Scheme 7.



Scheme 8.

This effect has been invoked to account for the pronounced regioselectivity observed in the hydroarylation of tertiary propargylic alcohols [16] (Ar versus CR^1R^2OH) (Scheme 7).

Coordinating effects, related to the amido group, have also been suggested to account for the remarkable regiochemistry of the hydroarylation of arylpropiolamides [17] (Scheme 8). Best results have been obtained by using a phosphine-free palladium catalyst, ethyl acetate or THF as solvents and dilute solutions. The presence of phosphines ligands, highly coordinating solvents such as DMF, or a high reaction concentration appear to compete with the amide functionality for coordinating to palladium and lower the regioselectivity. For example, use of bis(triphenylphosphine)palladium diacetate, piperidine, formic acid and DMF as solvent in the reaction of 9-phenanthryl iodide with 3-(*m*-fluorophenyl)-*N*-methylpropiolamide gave a mixture of all four regio- and stereoisomeric hydroarylation products, in addition to significant amounts of the *cis*-olefin derivative of the starting alkyne and phenanthrene.

2.1.3.3. Electronic effects. Electronic effects appear to play a minor role in hydroarylation(hydrovinylation) reactions. For example, in the hydroarylation(hydrovinylation) of acetylenic acetals (Scheme 6), semiempirical calculations made on the starting alkyne have shown that the negative charge on the acetylenic carbon bearing the acetal group is more than twice as high as on the acetylenic carbon linked to the aryl substituent (Fig. 5). Therefore, to the extent that the charge distribution in the starting noncoordinated alkyne can be taken as a measure of the charge distribution in the more polarized transition state leading to the σ-vinylpalladium complex (theoretical investigations on the acetylene system have shown that no intermediate is involved in the η^2-to-σ-vinyl conversion [18]), electronic factors should favor the formation of the intermediate in which the palladium is linked to the same atom as the acetal group. The hydroarylation and the hydrovinylation of 3,3-diethoxy-1-aryl-1-propyne with aryl and vinyl halides, however, invariably gave rise to the preferential formation of olefinic derivatives generated from the palladium complex in which the palladium is linked to the carbon bearing the aryl group [7].

Further evidence suggesting that polarization of the alkyne does not significantly influence the regiochemistry of the reaction comes from the hydroarylation of unsymmetrical diaryl acetylenes such as (*p*-acetylphenyl)-2-phenylacetylene and (*p*-methoxyphenyl)-2-phenylacetylene, whereby one of the aryl groups bears a strong electron-withdrawing and electron-donating substituent: in this case, the two possible regioisomers are generated in almost equimolar amounts [1] (Scheme 9).

Even in the presence of strongly electron-withdrawing substituents conjugated to the carbon–carbon triple bond (Ar versus COR or COOR), where electronic factors would be expected to influence the hydroarylation reaction in such a way that the added aryl unit ends up far from the carbonyl function, hydroarylation or hydrovinylation products arise from sterically biased additions and main products contain the added aryl unit close to the carbonyl group. The palladium-catalysed reaction of alkyl phenylpropynoate with a

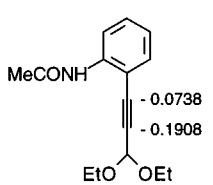
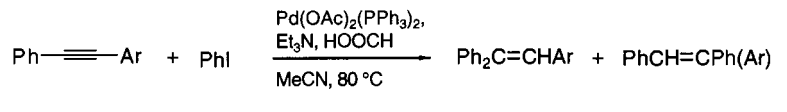
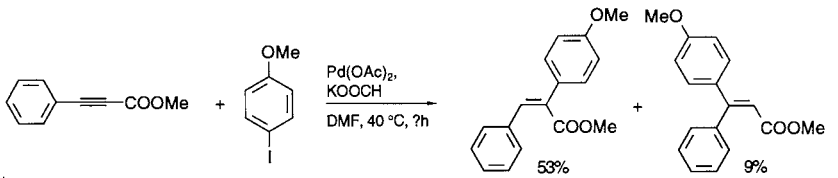


Fig. 5.

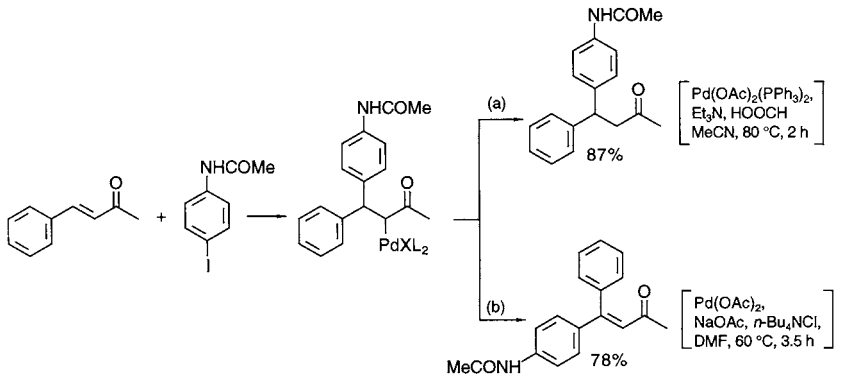


Ar = *p*-MeO-C_6H_4-	8h	(42)	(58)
Ar = *p*-MeCO-C_6H_4-	5.5h	(57)	(43)

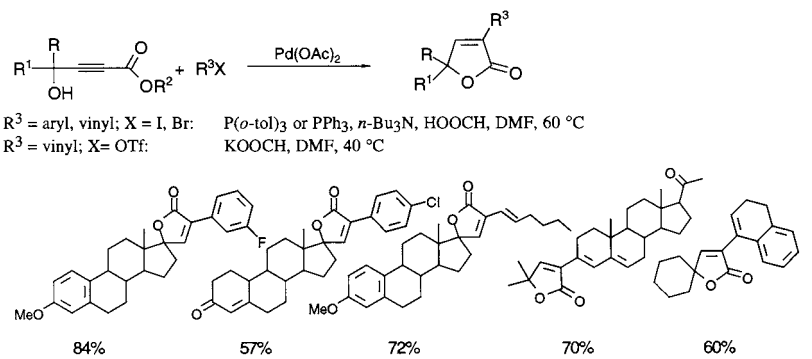
Scheme 9.



Scheme 10.



Scheme 11.



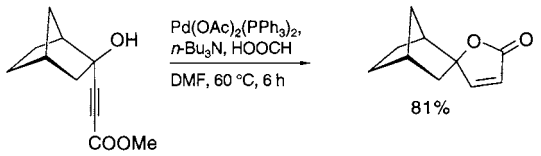
Scheme 12.

variety of aryl iodides proceeds in a regioselective fashion and affords methyl *Z*-2-arylcinnamates as the main products [15] (Scheme 10). This is in agreement with the regiochemistry of related additions of 'σ-arylpalladium halides' to electron-deficient alkynes such as 3-phenylpropynal [9b,13], 4-phenyl-3-butyn-2-one [13] and alkyl phenylpropynoate [9b,12–14].

It is worth noting that, in contrast to the mechanistic picture emerging from the carbopalladation of electron-deficient alkynes, the carbopalladation of olefins conjugated to carbonyl groups appears to be primarily controlled by electronic effects. Indeed, both the hydroarylation [19] (Scheme 11a) and the vinylic substitution [20] (Scheme 11b) of β-aryl-α,β-enones afford products arising from electronically biased addition intermediates, where the added aryl unit is linked to the β-carbon and the palladium moiety to the α-carbon.

3. Heterocycles via the hydroarylation(hydrovinylation)/cyclization sequence

Because the *cis* stereochemistry of the hydroarylation(hydrovinylation) reaction pushes the substituents of the two acetylenic carbons on the same side of the molecule, when these substituents bear suitable elec-



Scheme 13.

trophilic and nucleophilic centers the addition step may be followed, in some cases in situ, by a cyclization step and the whole process may provide a valuable entry into cyclic derivatives.

This addition/cyclization strategy has been successfully applied to the regioselective synthesis of α-aryl/vinylbutenolides from readily available alkyl 4-hydroxy-2-alkynoates and aryl/vinyl halides [21] or triflates [22] (Scheme 12). Regioisomeric β-substituted butenolides have usually been isolated in low yield. With vinyl triflates, best results have been obtained by using a phosphine-free palladium catalyst. Apparently, phosphine ligands tend to favor the reduction of σ-vinylpalladium intermediates to the corresponding alkenes [23].

When omitting aryl iodides or vinyl triflates, but otherwise keeping all the other parameters the same, the reduction of the carbon–carbon triple bond (a side reaction in the hydroarylation/hydrovinylation of alkynes) may turn out to be the main reaction pathway. Indeed, subjection of alkyl 4-hydroxy-2-alkynoates to formic acid and n-Bu_3N in the presence of a palladium catalyst produces butenolides through a hydrogenation/cyclization sequence [21a] (Scheme 13).

The remarkable directing effect of the tertiary propargyl alcohol group has been exploited to develop a regioselective synthesis of 4-substituted-2H-1-benzopyrans from *o*-acetoxy- or *o*-benzoyloxyarylethynyl carbinols [24] (Scheme 14).

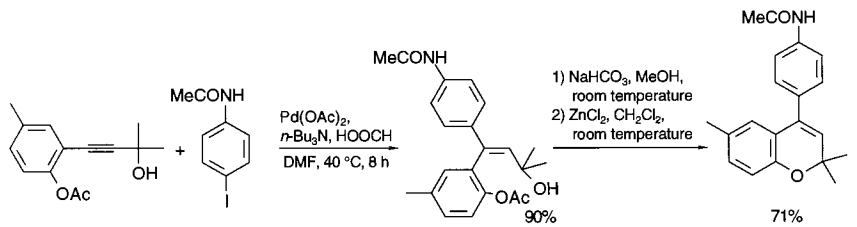
3-Substituted-quinolines have been prepared from 3,3-diethoxy-1-(*o*-acetamidophenyl)-1-propyne in good overall yield through a one-flask process, omitting the isolation of hydroarylation(hydrovinylation) intermediates [7] (Scheme 15). Regioisomeric 4-substituted-quinolines have been isolated in variable amounts (from traces, if any, to 10% yield). Poor results have been obtained by using the corresponding *o*-amino derivative. The regiochemistry of the reaction appears to be mainly controlled by the steric effect of the aryl group. The possibility that coordination of the *ortho* nitrogen atom to palladium may contribute to the regiochemistry of the carbopalladation step appears unlikely: the hydroarylation of 3,3-diethoxy-1-(*p*-acetamidophenyl)-1-propyne shows in fact the same regiochemical trend as the *o*-acetamido counterpart.

The related 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne allows an analogous reaction to form cromanols and coumarins [15] (Scheme 16). In this case too, the regiochemical outcome appears to be controlled by steric effects and the new carbon–carbon bond is formed preferentially at the carbon close to the acetal group.

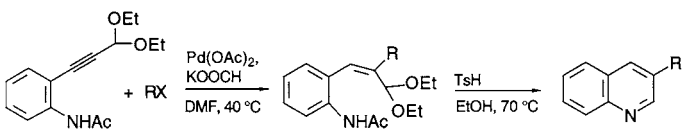
The reaction sequence leading to the formation of the coumarin product can even be conducted as a one-pot operation that omits the isolation of hydroarylation and chromenol intermediates (Scheme 17)

4. Heterocycles via intramolecular hydroarylations and hydrovinylations

Intramolecular versions of hydroarylation and hydrovinylation reactions leading to the synthesis of heterocycles have been described. In these reactions the basic concept of the intermolecular hydroarylation (hy-

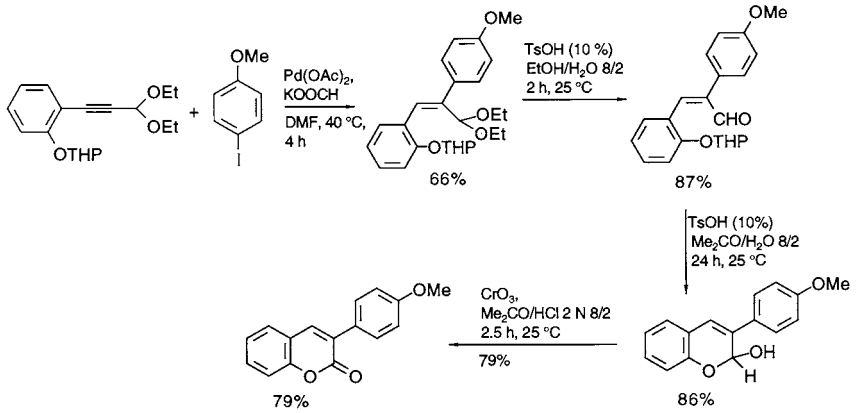


Scheme 14.

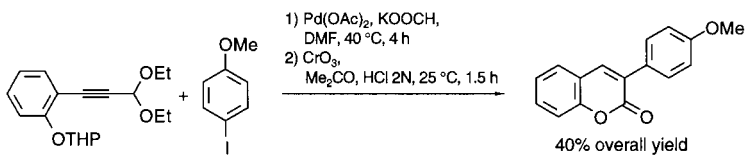


R = *p*-MeO-C_6H_4 (56%); Ph (51%); *p*-MeCO-C_6H_4 (60%); *p*-MeOCO-C_6H_4 (49%); *p*-MeCONH-C_6H_4 (50%); *m*-CF_3-C_6H_4 (52%); PhCH=CH (55%); *p*-HO-C_6H_4 (63%); *m*-$HOCH_2$-C_6H_4 (65%); *m*-F-C_6H_4 (54%); *m*-CF_3-C_6H_4 (52%)

Scheme 15.



Scheme 16.



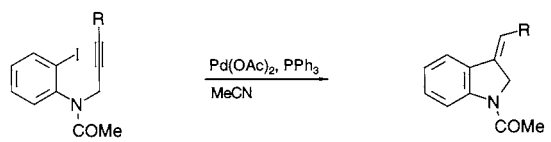
Scheme 17.

drovinylation)/cyclization methodology is reversed: the linkage between the nucleophile and the electrophile is already present in the starting alkyne and the acetylenic fragment is directly involved in the cyclization event. The realization of these reactions is based on the carbopalladation rate being significantly faster than the rate of direct formate capture (and, consequently, reduction) of the σ-aryl(vinyl)palladium intermediate formed initially. This side reaction might pose serious problems especially when the process is employed for the construction of large rings. The addition of additives such as Et_4NCl, $TlNO_3$ or Ag_2CO_3 may influence the selectivity of the process promoting the intramolecular hydroarylation(hydrovinylation) reaction at the expense of the direct reduction of the carbon–halogen bond.

Intramolecular hydroarylation reactions have been successfully applied to the construction of a variety of five- (Scheme 18), six- (Scheme 19) and seven-membered heterocyclic rings (Scheme 20) [25].

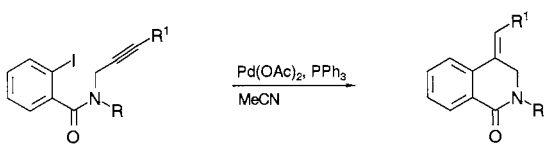
This strategy has been used in the synthesis of the conformationally restrained analogues of the combined thromboxane antagonist/synthase inhibitor GR85305 [26] (Scheme 21).

The palladium-catalyzed intramolecular hydrovinylation of a 1,1-dibromoalkene provides an approach to the core unit of the quinolizidine based diene homopumiliotoxin alkaloids with complete control of the stereochemistry of the exocyclic double bonds [27] (Scheme 22). Interestingly, the products were found to retain one bromine atom regardless of what excess of reducing agent was used.



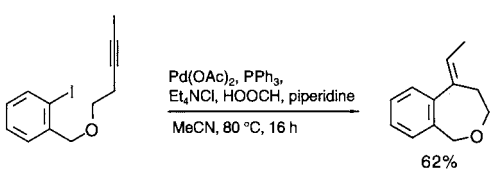
R = Me (HOOCH, Ag_2CO_3, r.t., 16 h): 60%
R = $SiMe_3$ (HOOCH, piperidine, Et_4NCl, 60 °C, 1h): 50%
R = $CH_2N(CH_2)_5$ (NaOOCH, Ag_2CO_3, 60 °C, 5 h): 54%
R = CH_2NEt_2 (NaOOCH, Ag_2CO_3, 60 °C, 15 h): 56%

Scheme 18.

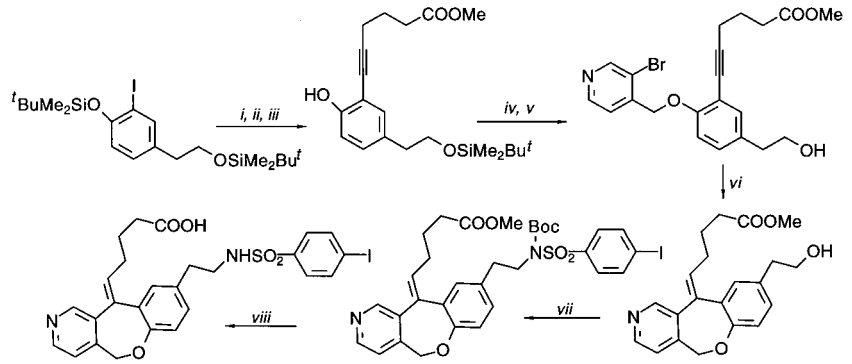


R = Me, R^1 = H (HOOCH, piperidine, 60 °C, 2 h): 60%
R = CH_2Ph, R^1 = Me (HOOCH, piperidine, 60 °C, 8 h): 50%
R = Me, R^1 = $CH_2N(CH_2)_5$ (NaOOCH, $TlNO_3$, 60 °C, 12 h): 53%

Scheme 19.

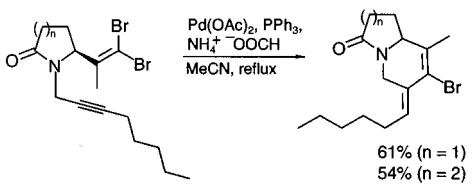


Scheme 20.



i. $Pd(PPh_3)_4$, CuI, dicyclohexylamine, MeCN, 31%; *ii.* *n*-Bu_4NF, THF, 95%; *iii.* $ClSiMe_2Bu^t$, imidazole, DMF, 99%; *iv.* 3-bromo-4-pyridinemethanol, PPh_3, DEAD, THF, 55%; *v.* *n*-Bu_4NF, THF, 94%; *vi.* $Pd(OAc)_2$, tri-*o*-tolylphosphine, HOOCH, piperidine, MeCN, 60%; *vii.* N-Boc-*p*-iodosulphonamide, PPh_3, DEAD, THF, 23%; *viii.* NaOH, MeOH, H_2O, 39%.

Scheme 21.



Scheme 22.

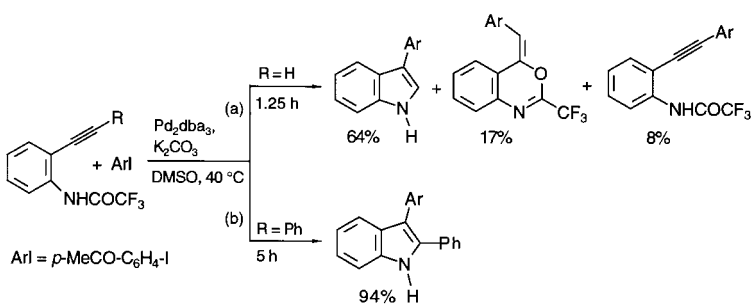
5. Heterocycles through intramolecular nucleophilic attack on η^2-alkyne-organopalladium complexes

5.1. Overview

η^2-Alkyne-organopalladium complexes generated from internal and terminal alkynes and containing nucleophilic centers close to the acetylenic moiety can undergo an intramolecular nucleophilic attack across the carbon–carbon triple bond coordinated to the organopalladium complex and give rise to the formation of cyclization products. The electronic density on the acetylenic carbons, the nature of the acetylenic moiety (internal or external), the strength of the nucleophile, the nature of phosphine ligands, additives and bases are the main factors influencing their reactivity.

The effect of the electronic density of the acetylenic carbons is well illustrated by the cyclization of *o*-ethynyl trifluoroacetanilide and *o*-phenylethynyltrifluoroacetanilide [28] (Scheme 23). Whereas *o*-ethynyl trifluoroacetanilide reacts with *p*-iodoacetophenone to afford a mixture of indole product, coupling product and *O*-cyclization product (the latter generated through the intramolecular nucleophilic attack of the oxygen end of the bidentate nucleophile—the amido group-across the carbon–carbon triple bond coordinated to palladium) (Scheme 23a), *o*-phenylethynyltrifluoroacetanilide produces the corresponding 2,3-disubstituted indole in high yield, and none of the *O*-cyclization derivative is discernible (Scheme 23b). The *O*-cyclization product becomes the main reaction product (61% yield) when the reaction is carried out in THF at 60°C for 7 h in the presence of $Pd_2(DBA)_3$ and the sterically encumbered strongly basic tris(2,4,6-trimethoxy phenyl)phosphine (TTMPP) [29].

Semiempirical calculations show that the electronic density in the starting alkynes (Scheme 23, R = H, Ph) is as outlined in Fig. 6. Assuming that the charge distribution in the transition states leading from η^2-alkyne-organopalladium complexes to the indole products reflects the charge distribution in the starting noncoordinated alkyne, electronic factors should favor the nucleophilic attack of the nitrogen atom on the carbon linked to the phenyl group in *o*-phenylethynyl-



Scheme 23.

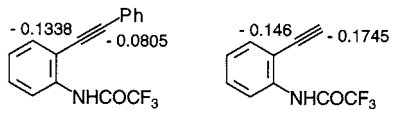


Fig. 6.

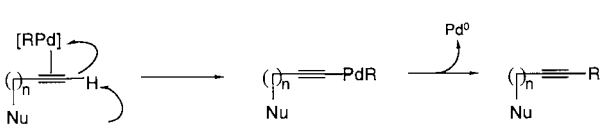
trifluoroacetanilide, where the charge difference is much higher than in *o*-ethynyltrifluoroacetanilide. The *O*-cyclization at the 'external' carbon, generating a seven-membered ring, is disfavored as compared to the formation of the five-membered nitrogen-containing ring by the size of the ring being formed [30] and the *O*-cyclization generating the six-membered ring derivative should be prevented by the lower electrophilicity of the 'internal' carbon. Conversely, when the charge difference between the two carbons decreases, like in *o*-ethynyltrifluoroacetanilide, the *O*-cyclization producing the six-membered ring product can compete more effectively.

With terminal alkynes the formation of η^2-alkyne-organopalladium complexes might even affect the tendency of the C_{sp}–H bond to dissociate. Consequently, depending on the relative strength of the nucleophile close to the alkyne moiety and of the added base, base attack on the terminal hydrogen (Scheme 24) could prevail over the intramolecular nucleophilic attack on the carbon–carbon triple bond and lead to the formation of the carbon–palladium bond between the incipient acetylide anion and the coordinated palladium. The resultant σ-alkynyl-σ-organopalladium complex [31] undergoes the reductive elimination of Pd(0) species to afford a coupling derivative.

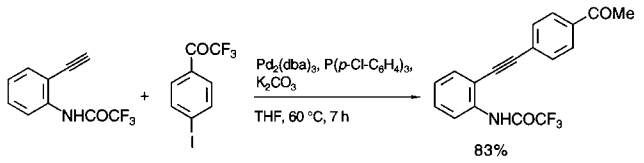
This behavior has been observed, for example, in the reaction of *o*-ethynyltrifluoroacetanilide with *p*-iodoacetophenone in the presence of $Pd_2(DBA)_3$, tris(*p*-chlorophenyl)phosphine and K_2CO_3, which gives the corresponding coupling product in 83% yield [28] (Scheme 25).

It may be pointed out, in passing, that coupling products derived from terminal alkynes containing proximate nucleophiles can be subjected to cyclization conditions, and indeed the construction of heterocyclic rings based upon the concept of palladium-catalyzed coupling/cyclization has been proved to be a useful synthetic procedure [32] (Scheme 26).

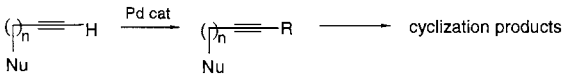
As to the strength of the nucleophile, literature data support the view that η^2-alkyne-organopalladium complexes require strong, anionic nucleophiles to afford



Scheme 24.



Scheme 25.



Scheme 26.

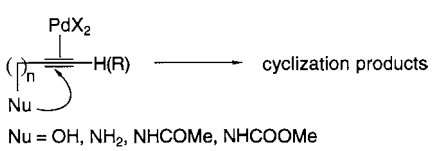
cyclization products. The possibility that in some cases proton removal from the (pro)nucleophile takes place in the transition state leading to the *trans* addition to the carbon–carbon triple bond could also be considered. Whatever the detailed mechanism for the nucleophilic attack on the activated acetylenic fragment may be, it remains that organopalladium complexes appear to be less effective than palladium dichloride or palladium diacetate as activators of the carbon–carbon triple bond toward nucleophilic attack. This is well illustrated by a variety of reactions producing heterocycles from functionalized alkynes via coordination to palladium dichloride followed by nucleophilic attack by hydroxy [33], amino [32a,33a,34] amido [34b,35] and ketonic (via the corresponding enol or hydrate forms) [36] groups (Scheme 27)

Ligands, additives and bases, the most difficult factors to fully appreciate and generalize, may cause dramatic changes in the reactivity of η^2-alkyne-organopalladium complexes. Specific examples will be shown afterwards.

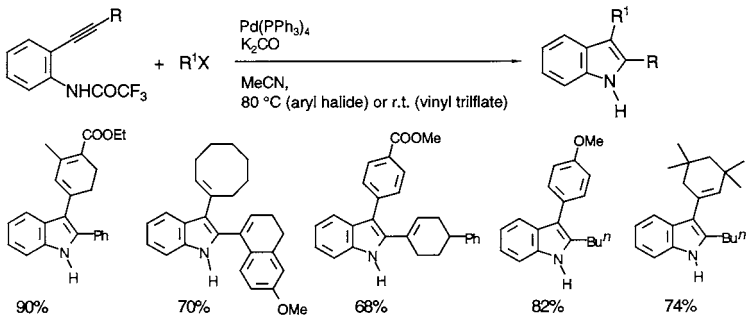
5.2. Cyclization of alkynes and aryl/vinyl halides or triflates

5.2.1. Cyclization of alkynes containing nitrogen nucleophiles

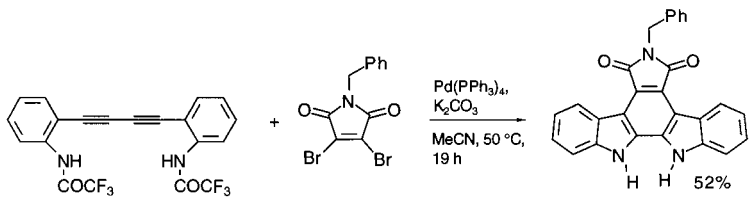
o-Alkynyltrifluoroacetanilides react with vinyl triflates or aryl halides in the presence of a palladium catalyst to afford 2,3-disubstituted-indoles [37] (Scheme 28). *o*-Phenylethynylaniline and *o*-phenylethynylacetanilide fail to produce cyclic derivatives. The nature of the base and ligand play a key role in controlling the reaction outcome. Best results have been obtained by using K_2CO_3 whereas the employment of Et_3N gives



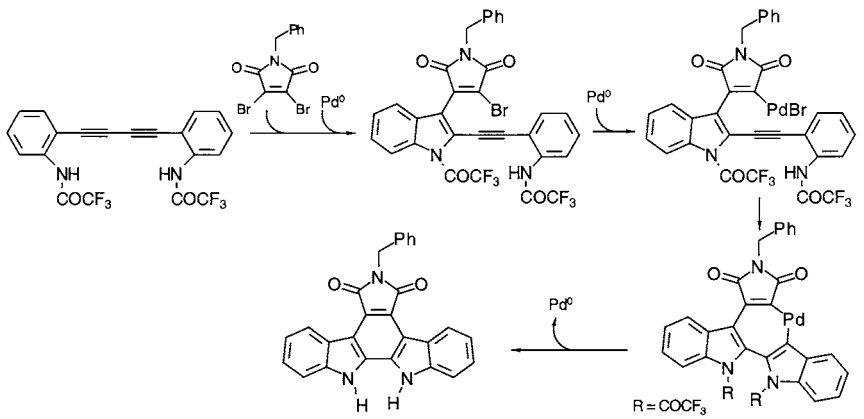
Scheme 27.



Scheme 28.



Scheme 29.



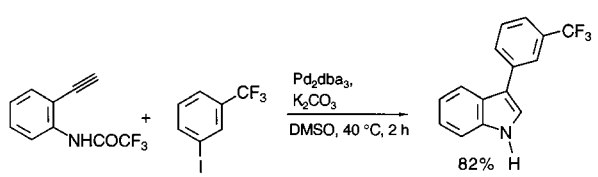
Scheme 30.

lower yields. With benzyl bromide as the organic halide a moderate yield of 3-benzylindoles is obtained, the main reaction product being the N-benzyl derivative [38]. For example, the reaction of benzyl bromide with (*o*-hex-1-ynyl)trifluoroacetanilide at 80°C gave 2-*n*-butyl-3-benzylindole in 47% yield and the *N*-benzyl derivative in 50% yield.

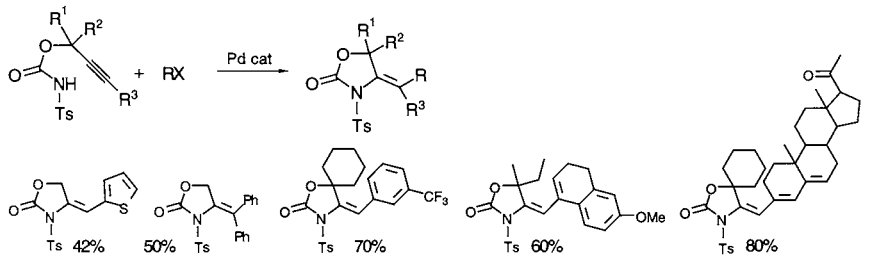
The employment of a symmetrical 1,3-diacetylene as the starting alkyne and 3,4-dibromomaleimide allows the application of the procedure to the synthesis of the indolo[2,3-a]carbazole alkaloid ring system [39] (Scheme 29), present in several active molecules such as arcyriaflavin A and the potent antitumor agent rebeccamycin.

This polyannulation reaction, wherein four bonds are generated in a single step, is assumed to proceed as outlined in Scheme 30.

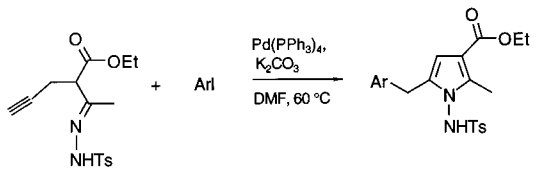
The extension of this chemistry to *o*-ethynyltrifluoroacetanilide provides access to 2-unsubstituted-3-arylindoles [28] (Scheme 31). Notably, exposure of *o*-ethynyltrifluoroacetanilide and aryl iodides to the same reaction conditions employed in the synthesis of 2,3-disubstituted indoles leads to unsatisfactory results, coupling and *O*-cyclization products being among the main by-products. Best results are obtained by using $Pd_2(DBA)_3$, DMSO and K_2CO_3 at 40°C (these condi-



Scheme 31.

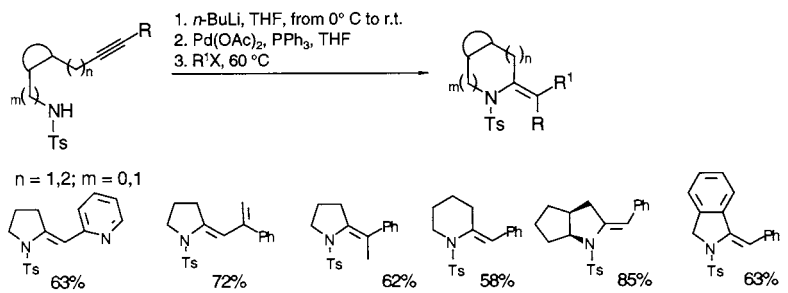


Scheme 32.



Ar = *p*-MeOOC-C_6H_4 (50%); *m*-F-C_6H_4 (65%); *p*-O_2N-C_6H_4 (63%); *m*-CF_3-C_6H_4 (48%); *p*-MeCO-C_6H_4 (60%)

Scheme 33.



Scheme 34.

tions can successfully be applied to the preparation of 2,3-disubstituted-indoles as well). Aryl bromides fail to give the corresponding 3-arylindole: indole, generated through a palladium catalyzed cyclization of *o*-ethynyltrifluoroacetanilide not involving the aryl donor, is in this case isolated in good yield.

The palladium-catalyzed reaction of propargyl tosylcarbamates with aryl halides or vinyl triflates produces regio-and stereoselectively (*E*)-4-alkylidene-3-tosyloxazolidin-2-ones in moderate to good yield (Scheme 32). The reaction can be carried out under various conditions: $Pd(PPh_3)_4$, K_2CO_3, DMF, 60°C (aryl iodides) [40]; $Pd(PPh_3)_4$, *n*-Bu_4NCl, K_2CO_3, DMF, 60°C (vinyl triflates) [41]; $Pd(OAc)_2$, tri(2-furyl)phosphine, *n*-Et_4NCl, MeCN, 25°C (aryl iodides and vinyl triflates) [41].

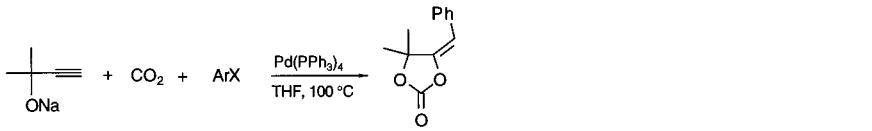
The palladium-catalyzed reaction of ethyl 2-acetyl-4-pentynoate tosylhydrazone with aryl iodides affords 1,2,3,5-tetrasubstituted pyrroles through an *exo–dig* cyclization/isomerization process [42] (Scheme 33).

Acetylenic compounds bearing less acidic N–H bonds give cyclization products in the presence of strong bases. For example, stereodefined 2-alkylidenepyrrolidines or -piperidines have been prepared exposing acetylenic tosylamides to aryl, heteroaryl or vinyl halides, $Pd(OAc)_2$ and *n*-butyllithium [43] (Scheme 34). No migration of the exocyclic double bond was observed.

5.2.2. Cyclization of alkynes containing oxygen nucleophiles

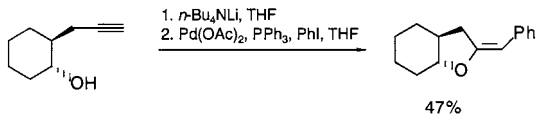
The reaction of the sodium salt of α-ethynyl tertiary alcohols (prepared from the alcohol and a slight excess of NaH) with CO_2 and aryl halides in the presence of a palladium catalyst affords cyclic vinylidene carbonates [44] (Scheme 35). None of the cyclization products are obtained with *o*-bromotoluene and *p*-bromoanisole whereas allyl acetate and chloride produce 3-butenylidene carbonate in 16 and 15% yield, respectively, when lithium alcoholate is used instead of sodium alcoholate. Internal acetylenic alcoholates such as those derived from 2-methyl-3-octyn-2-ol and 2-methyl-4-phenyl-3-butyn-2-ol fail to give the expected cyclization derivatives as do primary acetylenic alcohols such as 3-butyn-2-ol and propargyl alcohol.

Stereodefined 2-alkylidenetetrahydrofurans and pyrans have been synthesized from alkyl or aryl acetylenic alcoholates and organic halides [45]



ArX = PhI (68%); *p*-Me-C_6H_5-I (50%); PhBr (21%); *p*-Cl-C_6H_5-Br (30%); *p*-OHC-C_6H_5-Br (9%); PhCH=CHBr (32%)

Scheme 35.



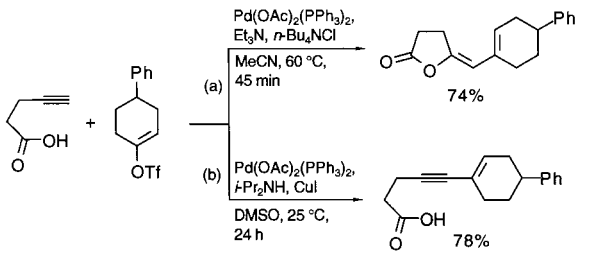
Scheme 36.

(Scheme 36). Benzylbromide and iodomethane can also be used as organic halides. Best results have been obtained with *n*-BuLi, $PdCl_2$ or $Pd(OAc)_2$ and PPh_3 in THF. Use of $NaHCO_3$ or MeONa as bases, of catalysts such as $Pd(DBA)_2$ or $PdCl_2(PPh_3)_2$/DIBAL or the employment of solvents such as DMF, $CHCl_3$, benzene or toluene gave only low yields or undetectable amounts of the desired products. The employment of zinc alkoxide also proved unsuccessful.

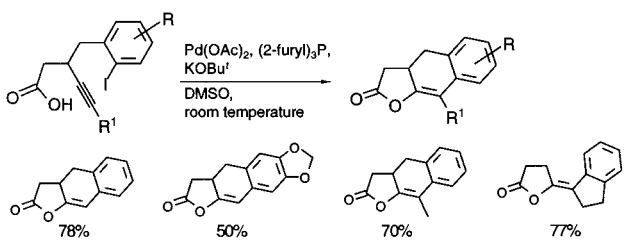
The palladium-catalyzed reaction of vinyl triflates or vinyl/aryl halides with 4-pentynoic acid, 2,2-disubstituted-4-pentynoic acids, and 5-substituted-4-pentynoic acids produces regio-and stereoselectively the corresponding (*E*)-δ-vinyl/aryl-γ-methylene-γ-butyrolactones [46] (Scheme 37). Reactions are carried out in the presence of catalytic amounts of $Pd(OAc)_2(PPh_3)_2$ or $Pd(PPh_3)_4$, Et_3N, and *n*-Bu_4NCl. The presence of chloride anions appears necessary to obtain the best results, especially with vinyl triflates.

Interestingly, by appropriate choice of additives the cyclization of terminal pentynoic acids can be diverted into a different reaction channel producing coupling derivatives [47] (Scheme 38b). Analogous control of the reactivity of the terminal carbon–carbon triple bond has been achieved with other functionalized alkynes [42,48,49].

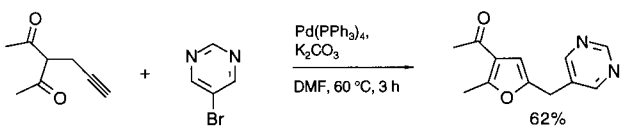
An intramolecular version of the methodology illustrated in Scheme 37 provides a straightforward approach to tricyclic γ-alkylidenebutyrolactones [50]. Best conditions are shown in Scheme 39. Replacement of



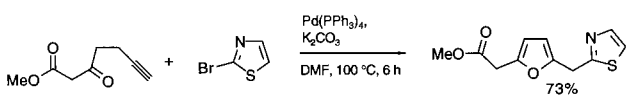
Scheme 38.



Scheme 39.



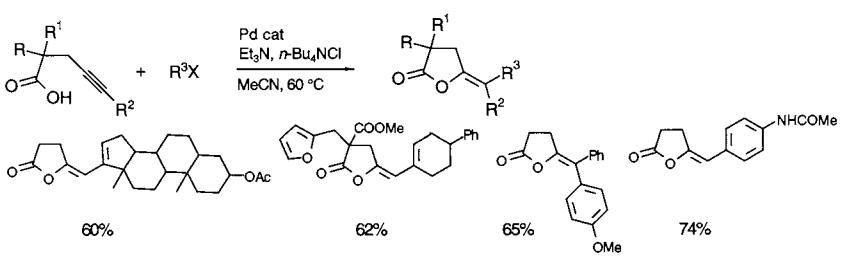
Scheme 40.



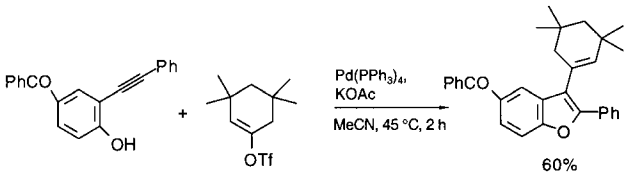
Scheme 41.

tri(2-furyl)phosphine with triphenylphosphine produces trace amounts of the lactone product.

2-Propargyl-1,3-dicarbonyl compounds and alkyl 3-oxo-6-heptynoates react with vinyl triflates or vinyl/aryl/heteroaryl halides to give 2,3,5-trisubstituted- [48] (Scheme 40) and 2,5-disubstituted- [49] (Scheme 41)



Scheme 37.



Scheme 42.

furans. In these reactions the *exo–dig* cyclization is followed by an isomerization step that proceeds under mild conditions with 2-propargyl-1,3-dicarbonyl compounds but requires higher temperature when alkyl 3-oxo-6-heptynoates are used as starting alkynes. Notably, with the latter alkynes, no evidence was attained of cyclization products arising from the nucleophilic attack of the carbon terminus of the putative enolate intermediate.

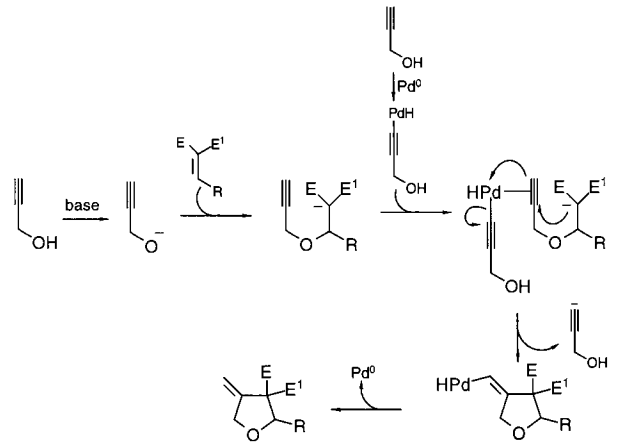
2,3-Disubstituted-benzo[*b*]furans have been prepared from *o*-alkynylphenols and vinyl triflates [32e] (Scheme 42).

5.2.3. Cyclization of alkynes containing carbon nucleophiles

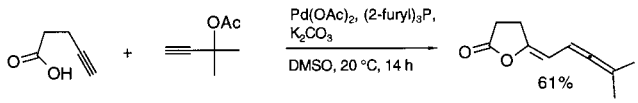
Propargyl alcohols and alkylidene or arylidenemalonates have been reacted in the presence of a palladium catalyst, under basic conditions, to afford 3-methylenetetrahydrofurans [51] (Scheme 43).

The reaction has been suggested to proceed through the conjugate addition of propargyl alcoholate to alkylidene or arylidenemalonate producing an anionic adduct which, after coordination to a palladium(II) hydride species formed through the oxidative insertion of Pd(0) into the C_{sp}–H bond of the propargyl alcohol, undergoes an intramolecular *exo–dig* cyclization to afford the 3-methylenetetrahydrofuran product (Scheme 44)

Although this synthesis of heterocycles may be considered to belong to, conceptually and mechanistically, the same reactions discussed in this section, it provides some important, distinctive features worth of emphasis: (1) the anion necessary for the nucleophilic attack across the carbon–carbon triple bond activated by the organopalladium complex is generated through a Michael reaction; (2) the organopalladium complex activating the carbon–carbon triple bond does not transfer the organic fragment to the heterocyclic ring; (3) the heteroatom–carbon bond is generated before the cyclization step takes place.



Scheme 44.



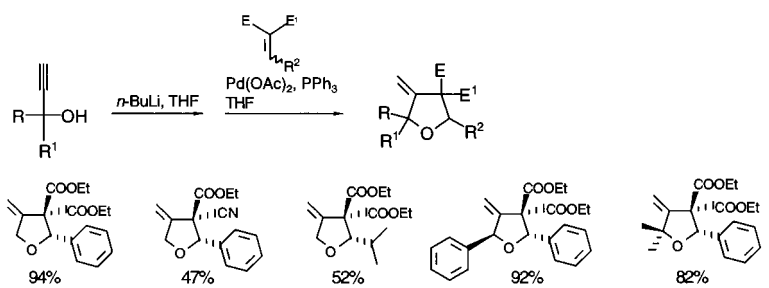
Scheme 45.

5.3. Cyclization of alkynes and propargyl esters or ethers

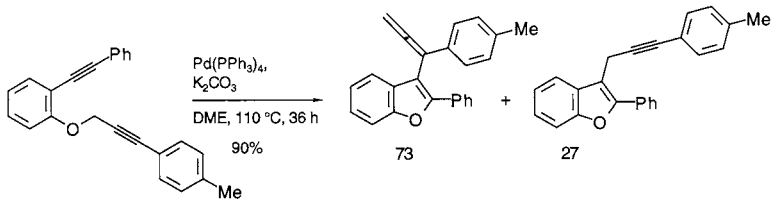
Propargyl acetates have been employed as allenyl donors in the synthesis of allenenol lactones from pentynoic acid derivatives [53] (Scheme 45). Best results have been obtained in the presence of K_2CO_3 as the base. The employment of KOBu^t produces lower yields.

The reaction of propargylic *o*-(alkynyl)phenyl ethers in the presence of $Pd(PPh_3)_4$ and K_2CO_3 affords 2-substituted-3-allenylbenzo[*b*]furans in good yields [52] (Scheme 46). Depending on the nature of the starting alkyne, variable amounts of isomeric 2-substituted-3-propargylbenzo[*b*]furans have been isolated.

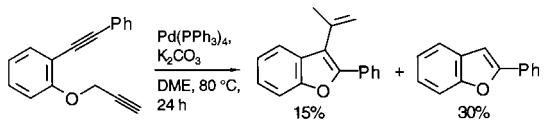
The presence of a substituent on the terminal acetylenic carbon of the propargylic fragment has been found to be crucial for the success of the reaction. For



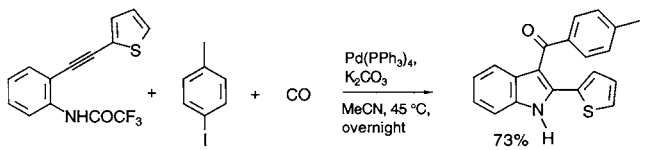
Scheme 43.



Scheme 46.



Scheme 47.



Scheme 49.

example, subjection of propargyl *o*-phenylethynyl ether to cyclization conditions resulted in the formation of a mixture of 2-phenyl- and 2-phenyl-3-(2-propenyl)benzo[*b*]furan—none of the allenyl and/or propargylic product was observed (Scheme 47).

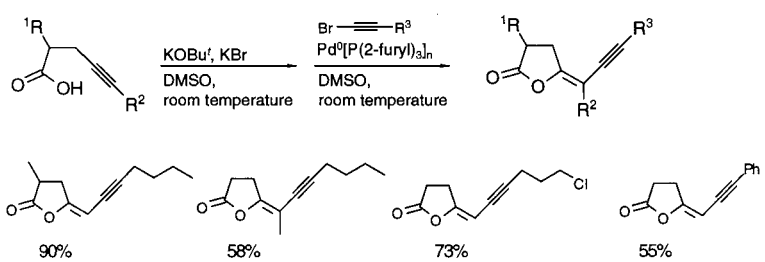
5.4. Cyclization of alkynes and 1-halo-1-alkynes

δ-(*E*)-Alkynylidene-γ-butyrolactones, a class of compounds active as suicide inhibitors of serine proteases, have been prepared from pentynoic acids and 1-bromo-1-alkynes [54] (Scheme 48). Competitive formation of δ-iodo-γ-methylene-γ-butyrolactone has been observed with 1-iodo-1-alkynes. Tri(*o*-tolyl)phosphine and tri(2-furyl)phosphine can promote an efficient transformation. However, best results have been obtained in the presence of tri(2-furyl)phosphine. The utilization of lithium, sodium and potassium carboxylates has been explored, but only the latter have been proved effective in this cyclization. The presence of KBr and the employment of DMSO as solvent consistently increase the yield.

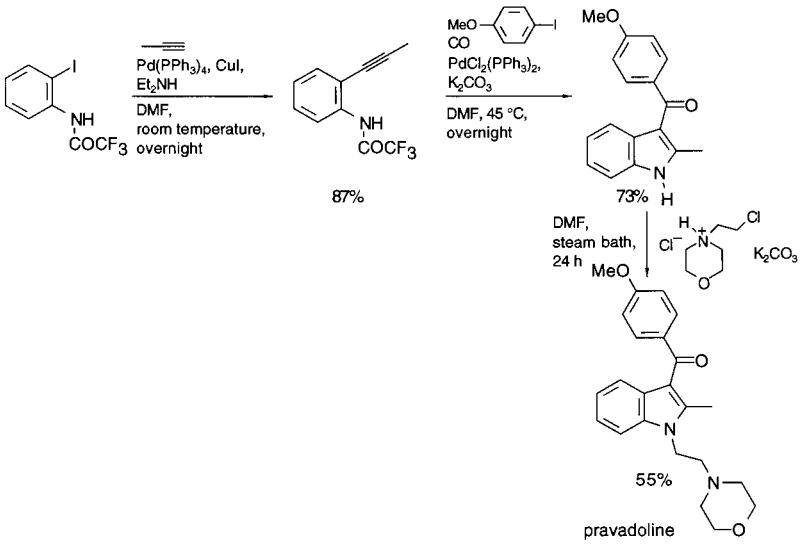
5.5. Cyclization of alkynes and aryl/vinyl halides or triflates in the presence of carbon monoxide

5.5.1. Cyclization of alkynes containing nitrogen nucleophiles

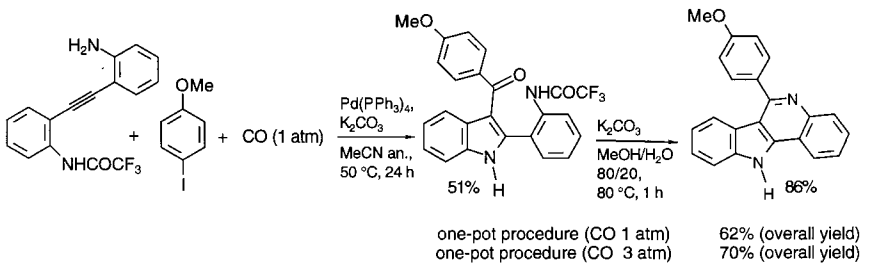
The palladium-catalyzed reaction of 2-alkynyltrifluoroacetanilides with aryl halides or vinyl triflates under a carbon monoxide atmosphere and in the presence of potassium carbonate produces 2-substituted-3-acyl indoles in fair to good yield [38]. Most probably, the reaction proceeds through the nucleophilic attack of the nitrogen on the carbon–carbon triple bond coordinated to a σ-acylpalladium complex (other reaction pathways, however, could contribute to the formation of 3-acylindole products). The use of $Pd(PPh_3)_4$ or $Pd(OAc)_2(PPh_3)_2$ in acetonitrile, under a balloon of carbon monoxide, can give good results in many cases (Scheme 49). With aryl halides containing electron-withdrawing groups, anhydrous acetonitrile and higher pressure of carbon monoxide are needed. The utilization of $Pd(DBA)_2/P(o\text{-}TOL)_3$ in acetonitrile, under a balloon of carbon monoxide, can in these cases provide an alternative, simpler procedure but its effectiveness is to be evaluated each time. Alkynes containing free amino groups fail to produce cyclic derivatives. For example, no indole derivative was isolated from the reaction of 2-phenylethynylaniline with 4-methoxyphenyl iodide or 6-methoxy-3,4-dihydro-1-naphthyl triflate. The employment of benzyl bromide as the organic halide produces low yields of the corresponding 3-acylindole product. Exposure of (*o*-hex-1-ynyl)trifluoroacetanide, benzyl bromide and carbon monoxide to cyclization conditions affords 3-phenylacetyl-2-*n*-butylindole in 32% yield. The main reaction product (61% yield) is the *N*-benzyl derivative.



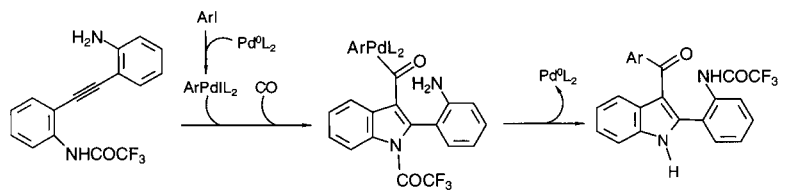
Scheme 48.



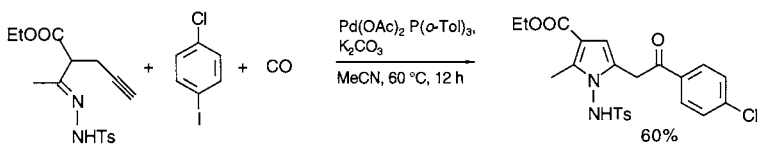
Scheme 50.



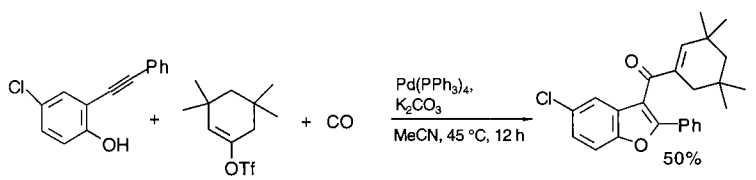
Scheme 51.



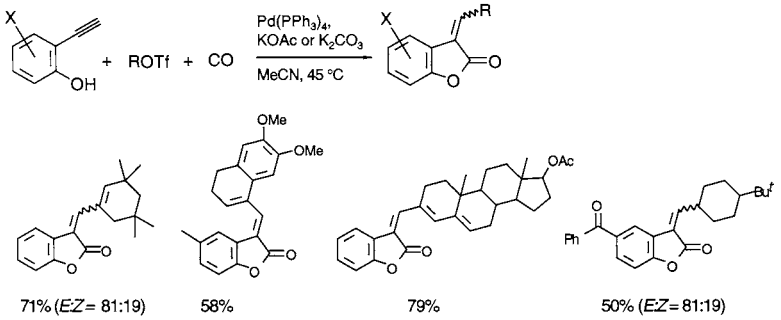
Scheme 52.



Scheme 53.



Scheme 54.



Scheme 55.

The methodology was applied to the synthesis of pravadoline, an indole derivative designed as a nonacidic analogue of non-steroidal anti-inflammatory drugs (NSAIDs) (Scheme 50).

Readily available *o*-aminophenyl,*o*-trifluoroacetamidophenylacetylene has been used in a two-step synthesis of indolo-quinolines [55] (Scheme 51). Higher yield are usually obtained when the synthesis is conducted as a one-pot process.

Most probably the palladium-catalyzed cyclization proceeds as outlined in Scheme 52.

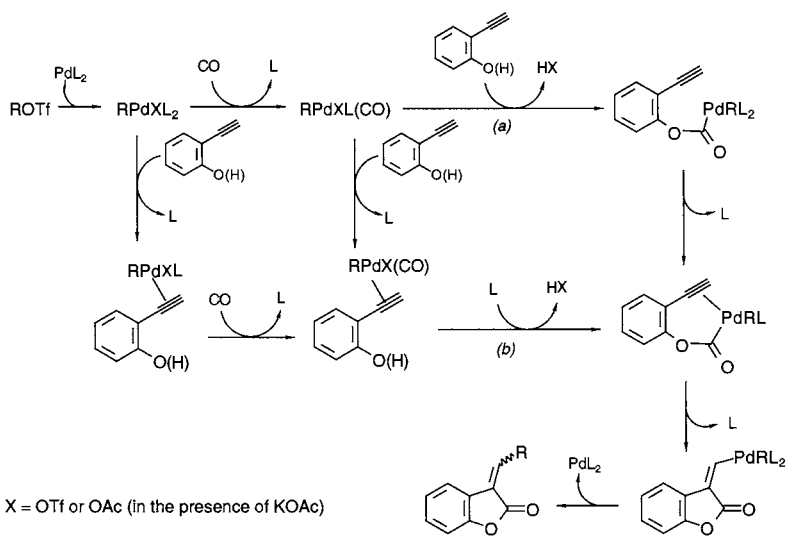
Under an atmosphere of carbon monoxide ethyl 2-acetyl-4-pentynoate tosylhydrazone and aryl iodides can produce functionalised pyrroles [42] (Scheme 53).

5.5.2. Cyclization of alkynes containing oxygen nucleophiles

The palladium-catalyzed reaction of *o*-alkynylphenols with vinyl triflates in the presence of KOAc and $Pd(PPh_3)_4$, under a balloon of carbon monoxide, produces 2-substituted-3-acyl-benzo[*b*]furans [32e] as shown in scheme Scheme 54. Best results have been achieved with *o*-alkynylphenols bearing electron-withdrawing substituents in the aromatic ring. Depending on the substitution pattern of the reagents, variable amounts of 2,3-disubstituted-benzo[*b*]furans (Scheme 42) have also been isolated and in some cases 2-substituted-benzo[*b*]furans have been obtained as the main reaction products. The presence of electron-donating substituents in the starting *o*-alkynylphenols and/or the utilization of aryl halides resulted in the preferential formation of *O*-acyl derivatives, very likely derived by the capture of acylpalladium intermediates by the phenolic oxygen.

o-Ethynylphenols and vinyl triflates, when treated under the same reaction conditions producing 2-aryl-3-acylbenzo[*b*]furans from *o*-arylethynylphenols and vinyl triflates, follow a complete different course and afford 3-alkylidene-2-coumaranones [56] (Scheme 55).

Steric and electronic effects have been invoked to account for the different behavior of *o*-ethynyl- and *o*-arylethynylphenols. The cyclization to coumaranones has been suggested to proceed according to the mechanism outlined in Scheme 56. The key step is the intramolecular *syn*-addition of the carbonyl-palladium fragment of an η^2-alkyne-σ-oxycarbonyl-σ-vinylpalla-



Scheme 56.

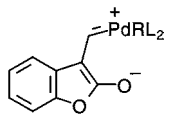


Fig. 7.

dium complex to the carbon–carbon triple bond. The resultant σ-vinylpalladium intermediate undergoes the reductive elimination of Pd(0) species to give the 2-coumaranone derivative and the active catalyst.

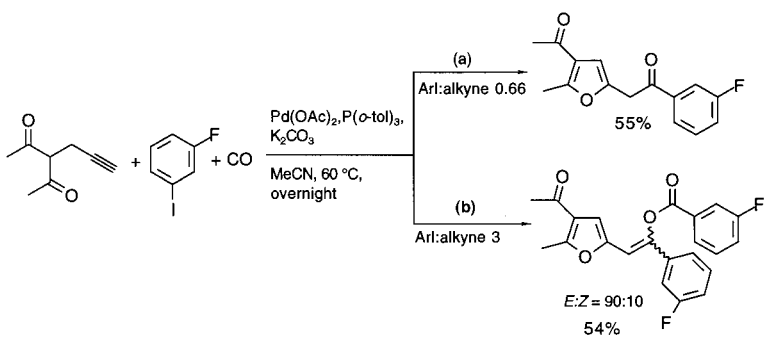
Though this mechanistic proposal supports the concept of a *syn* addition to the triple bond to produce *Z*-alkylidene coumaranone derivatives, the great majority of the examples examined give preferentially the *E*-isomers. Control experiments suggest that *E*-isomers are generated through a thermal *cis–trans* isomerization of the reductive elimination product arising from the *syn* adduct formed initially and that the observed stereochemistry is dependent on the relative thermodynamic stabilities of the *cis* and *trans* derivatives. A *cis–trans* isomerization of the vinyl ligand formed initially by a *syn*-addition, involving contributions from zwitterionic resonance form of type shown in Fig. 7, could contribute to the product distribution.

The reaction of 3-acetyl-5-hexyn-2-one with aryl iodides under a balloon of carbon monoxide affords 2,3,5-trisubstituted furans containing a 5-acylmethyl group (Scheme 57a) or its enol ester (Scheme 57b) depending on the aryl iodide to alkyne ratio [57]. The enol ester has been suggested to arise from the 5-acylmethyl product, via capture of the corresponding enolate by an acylpalladium complex.

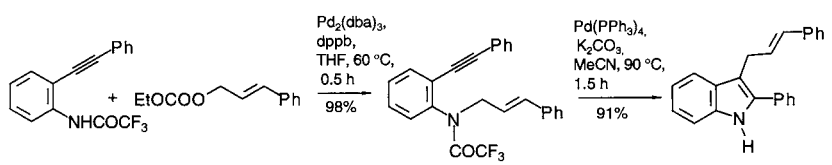
5.6. Cyclization of alkynes and allyl esters

5.6.1. Cyclization of alkynes containing nitrogen nucleophiles

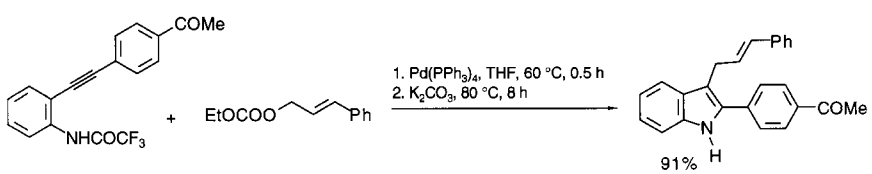
The palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilides with allyl esters leads to the regioselective formation of 3-allylindoles [58]. This method complements the synthesis of 3-allylindoles based on the cyclization of *N*-methoxycarbonyl-*o*-alkynylanilines and allyl chlorides in the presence of $PdCl_2(MeCN)_2$, which is presumed to proceed via trapping of the σ-indolylpalladium intermediate, generated in situ, with the allyl chloride (the new carbon–carbon bond is in this case generated regioselectively at the γ position in an S_N2' fashion) [34b]. Three basic procedures have been developed: a stepwise method based on the isolation of *N*-allyl derivatives (only *N*-allyl derivatives bearing the nitrogen fragment on the less substituted allyl terminus have been isolated) and their subsequent cyclization to 3-allylindoles (Scheme 58); a one-pot reaction omitting the isolation of the *N*-allyl derivatives (Scheme 59); and a procedure which generates 3-allylin-



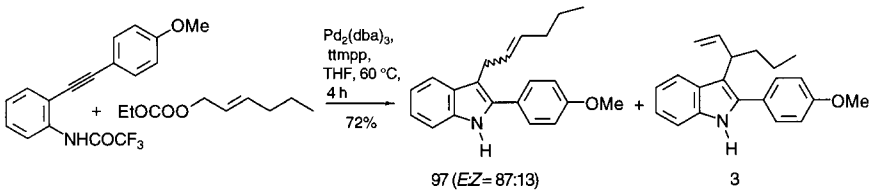
Scheme 57.



Scheme 58.



Scheme 59.



Scheme 60.

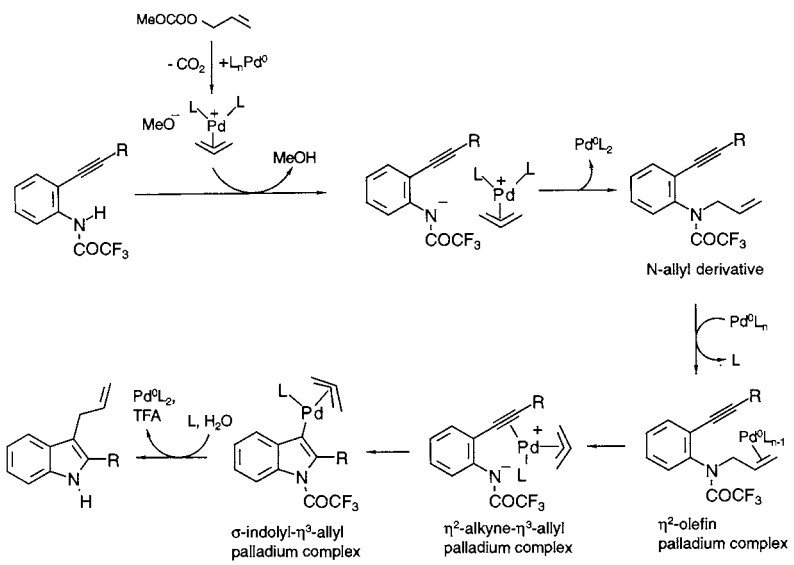
doles through a mechanism not involving the intermediacy of *N*-allyl derivatives (Scheme 60).

The presence of a substituent on the central carbon atom of the allylic system seems to be tolerated whereas substitution at both termini or sterically encumbered substituents at one end of the alkyne moiety hamper the cyclization reaction. Both electron-donating and electron-withdrawing substituents are tolerated. As to the regiochemistry of the new carbon–carbon bond, the most challenging situation is posed when steric differences between the two allylic termini are small. In these cases, remarkable regioselectivity is observed in the presence of tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) [29] and the indole unit is located preferentially, if not exclusively, on the less substituted terminus of the allylic system. The process is accompanied by some loss of olefin geometry.

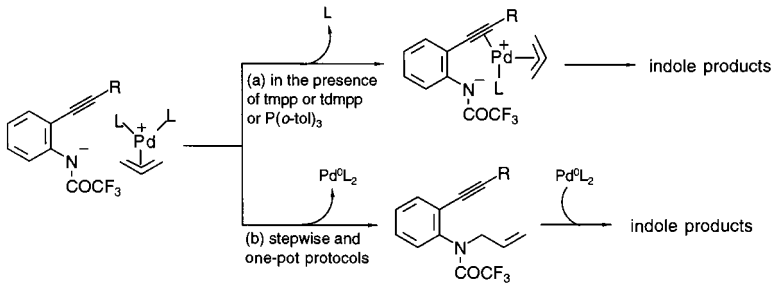
As to the reaction mechanism, stepwise and one-pot protocols are based on the basic steps illustrated in Scheme 61 using allyl carbonate: (1) the nucleophilic attack of the nitrogen atom on the allylic portion of the η^3-allylpalladium complex derived from the allyl ester to give a *N*-allyl derivative; (2) the formation of an η^2-alkyne-η^3allylpalladium complex, resulting from the ionization of an η^2-olefinpalladium complex (η^2-olefin-palladium complexes are usually believed to be the first intermediates in the palladium-catalyzed allylations [59]) and the displacement of one ligand to the palladium by the carbon–carbon triple bond (that may be favored by the proximity of the acetylenic moiety to the metal and that may also take place before ionization); (3) the intramolecular nucleophilic attack of the nitrogen atom across the activated carbon–carbon triple bond to afford a σ-indolyl-η^3-allylpalladium complex; (4) the reductive elimination of Pd(0) species through the transfer of the indolyl fragment to the allyl group in a *cis* fashion [60], which produces the indole derivative and regenerates the active catalytic species.

According to this scheme, the nitrogen atom intervenes in the process as nucleophile in the *N*-allylation step and as leaving group [61–63] in the cyclization step. The ease of the palladium-promoted dissociation of the $N-C_{allyl}$ bond, producing the η^2-alkyne-η^3-allylpalladium complex, has been attributed to the contemporary presence of the aryl and trifluoroacetyl groups on the nitrogen atom.

The procedure not involving an *N*-allylation step (Scheme 60) entails the coordination of the carbon–carbon triple bond to the palladium of the η^3-allylpalladium fragment being faster than the nucleophilic attack of the nitrogen on the allylic portion of the complex. Thus (Scheme 62a), an η^2-alkyne-η^3-allylpalladium complex is formed preferentially over the *N*-allyl derivative (Scheme 62b). Steric factors have been sug-



Scheme 61.



Scheme 62.

gested to account for this behavior. Indeed, sterically demanding ligands may create an η^3-allylpalladium complex more prone to relieving steric crowding in the coordination sphere of palladium rather than allowing a nucleophilic attack by the nitrogen atom on the allylic terminus. Consequently, in the presence of TTMPP (or even tris(2,6-dimethoxyphenyl)phosphine (TDMPP) or P(o-TOL)$_3$) the ambident electrophilic part of the η^3-allylpalladium fragment prefers to complex with the alkyne unit, generating an η^2-alkyne-η^3-allylpalladium complex, instead of undergoing the nucleophilic attack of the nitrogen on the allylic carbon.

6. Cyclization of alkynes containing oxygen nucleophiles

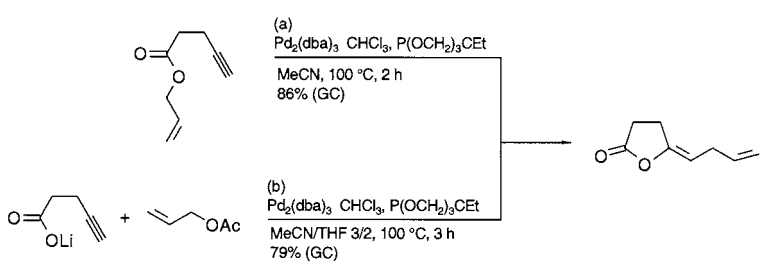
Treatment of allyl alkynoates (Scheme 63a) or lithium alkynoates and allyl acetates (Scheme 63b) with a palladium catalyst produces regio- and stereoselectively γ-(E)-alkylidene-γ-butyrolactones [64].

The formation of the lactone is influenced by the nature of the ligand and the solvent. Trimethylolpropane phosphite and triisopropyl phosphite give the best results whereas trimethyl and triphenyl phosphites are not effective. Triphenylphosphine showed a medium effect. Acetonitrile or mixed solvents containing acetonitrile are good solvents for the synthesis whereas THF or benzene proved unsuccessful. With substituted allyl units the stereochemistry of the allyl moiety in the lactone derivative is predominantly to exclusively E. The regiochemistry of the new carbon–carbon bond depends on the nature of the allyl unit: while the new carbon–carbon bond is generated exclusively at the less substituted allyl terminus with the cinnamyl unit, an approximately 1:1 regioisomeric mixture is obtained with 1- or 2-butenyl units.

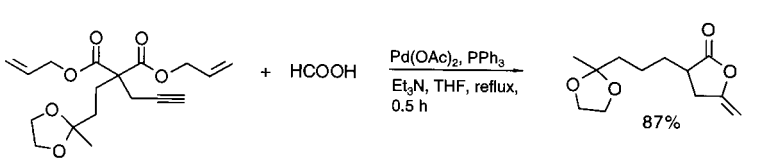
Diallyl 2-propynylmalonates have been used as building blocks for developing a simple synthetic method for the preparation of γ-methylene-γ-butyrolactones by palladium-catalyzed cyclization and hydrogenolysis with formic acid [65] (Scheme 64).

The proposed reaction mechanism is outlined in Scheme 65. The success of the reaction is based on the activation of the carbon–carbon triple bond and subsequent cyclization being faster than the hydrogenolysis of the allyl ester [66] leading to the free carboxylic acid.

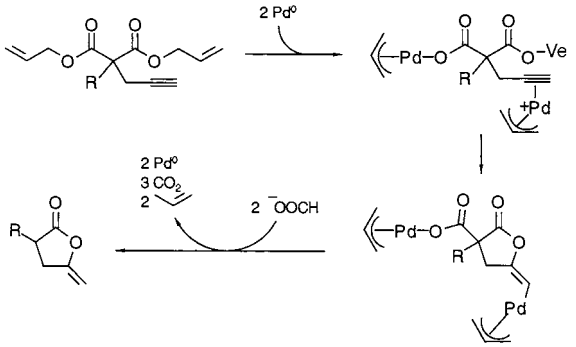
Activation of the carbon–carbon triple bond by η^3-allylpalladium complexes has been employed in the synthesis of 2-substituted-3-allylbenzo[b]furans from (o-alkynylphenyl)allyl ethers [67]. Attempts to prepare 2-unsubstituted-3-allylbenzo[b]furans from terminal acetylenes proved unsuccessful. (o-Alkynylphenyl)allyl



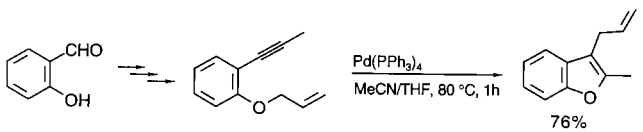
Scheme 63.



Scheme 64.



Scheme 65.



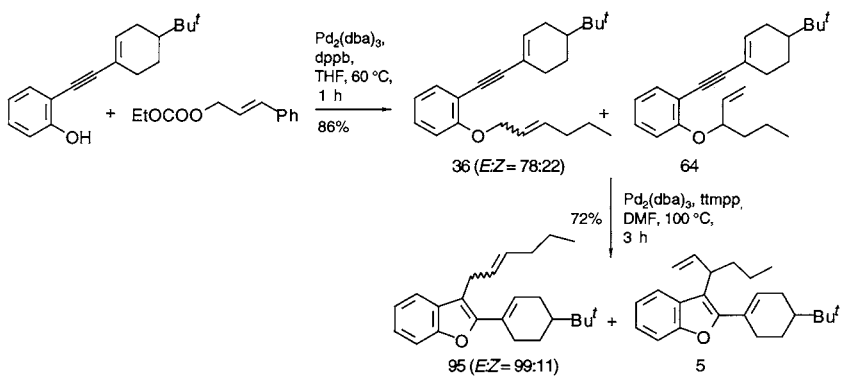
Scheme 66.

ethers can be prepared from *o*-hydroxybenzaldehyde and reacted in the presence of $Pd(PPh_3)_4$ to afford the benzo[*b*]furan derivative (Scheme 66).

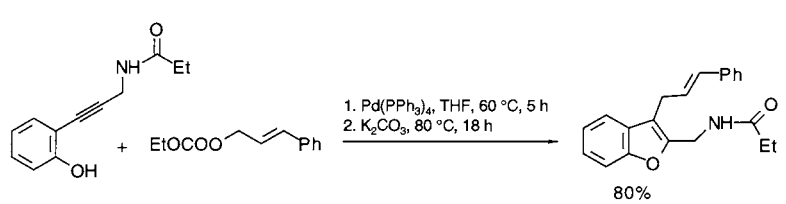
Alternatively, (*o*-alkynylphenyl)allyl ethers can be prepared through the palladium-catalyzed reaction of *o*-alkynylphenols with allyl carbonates. In this case, two different experimental protocols have been developed [68]: (1) a stepwise method, based on the preparation of stereo- and regioisomeric mixtures of (*o*-alkynylphenyl)allyl ethers and their subsequent cyclization to benzo[*b*]furans (Scheme 67), and; (2) a one-pot protocol omitting the isolation of (*o*-alkynylphenyl)allyl ethers (Scheme 68). The formation of variable amounts of regioisomeric *O*-allylation derivatives do not pose any problem. In fact, the regiochemistry of the carbon–carbon bond formed in the cyclization step and the stereochemistry of the olefin fragment of 3-allylbenzo[*b*]furans are almost independent of the regio- and stereochemistry of the *O*-allyl intermediates.

7. Conclusions

This review has highlighted many versatile, and in several cases unique, palladium-catalyzed heterocyclizations of alkynes which may provide important new dimensions in the design of synthetic strategies for the construction of heterocyclic rings. The benefit that derives from palladium chemistry in terms of selectivity and tolerance of functional groups underlines the potential of these methodologies and makes them interesting and powerful alternatives to many standard organic reactions. The possibility to influence the reaction outcome through small changes in the nature of ligands or additives increases the versatility of the procedures. In spite of the numerous successes, the full scope of this chemistry has yet not been exploited and it seems reasonable to expect further developments, especially in the preparation of complex molecules.



Scheme 67.



Scheme 68.

Acknowledgements

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