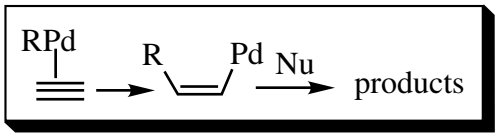

IV.2.5 Carbopalladation of Alkynes Followed by Trapping with Nucleophilic Reagents

SANDRO CACCHI and GIANCARLO FABRIZI

A. INTRODUCTION

The Pd-catalyzed addition of a carbon residue on one side of the carbon–carbon triple bond and a hydrogen atom or a carbon, oxygen, or nitrogen nucleophile on the other side is one of the most versatile and efficient tools for the funtionalization of alkynes. This methodology is of great value because the required palladium complexes are readily available from a variety of precursors, a vast array of acetylenes can be employed, and the reaction can tolerate a wide range of functional groups. It has been used to develop a number of synthetic processes, providing new important perspectives in the design of synthetic strategies. Most of this chemistry has been performed employing aryl and alkenyl halides or triflates as starter species, though the utilization of allyl acetates has also been described. The reaction is generally considered to involve the initial coordination of the alkyne to the organopalladium(II) complex (generated *in situ* from a suitable precursor) to form an η^2-alkyne-organopalladium intermediate (**Figure 1**).

The fate of this η^2-alkyne-organopalladium intermediate has been found to depend on a number of reaction variables. For example, in the presence of a nucleophile close to the carbon–carbon triple bond, it can enter the carbopalladation–,[1],[2] oxypalladation–,[3]–[6] or aminopalladation–[7],[8] reductive elimination domino reaction path or, when the reaction is carried out with a terminal alkyne, it can produce coupling products.[9]

The focus of this section is on the processes that proceed through the following basic steps: (i) conversion of η^2-alkyne-organopalladium intermediates—which may be formed via intermolecular (**Scheme 1**) or intramolecular (**Scheme 2**) coordination of the alkyne to palladium—to the corresponding σ-alkenylpalladium adducts (the insertion of carbon–carbon triple bond into the carbon–palladium bond is known as the carbopalladation step); (ii) trapping of these intermediates with nucleophiles such as hydrogen donors (usually formate anions), organometals, carbon monoxide, and nitrogen and oxygen nucleophiles (trapping with alkenes, alkynes, aromatics, and heteroaromatics are not considered in this section); and (iii) reductive elimination of a palladium(0) species, which affords the addition product and regenerates the catalyst. When aryl and alkenyl halides or triflates contain a nucleophilic center in a location that allows it to attack the palladium atom once the carbopalladation adduct is formed (**Scheme 1b**), intramolecular halide or triflate

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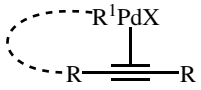
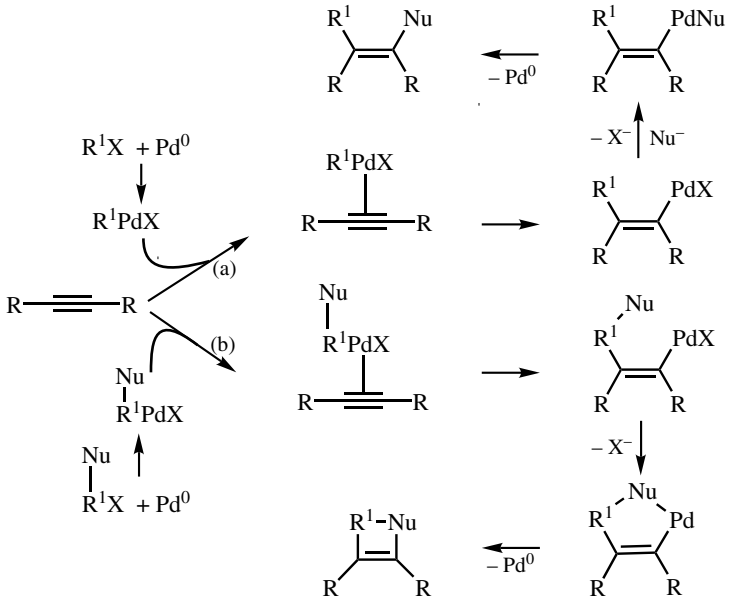
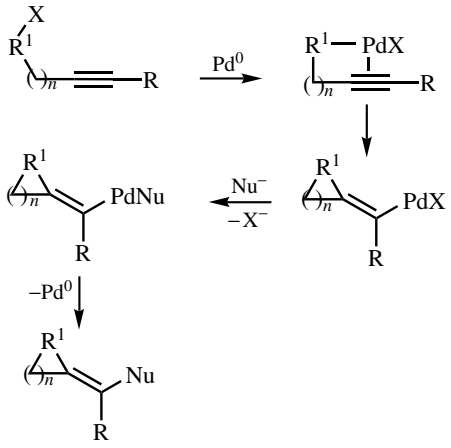


Figure 1



Scheme 1



Scheme 2

displacement from the palladium can occur to form a heteroatom-containing palladacycle, which subsequently affords an annelation product via a reductive elimination step.

Performing the reaction under an atmosphere of carbon monoxide may further widen the scope of the methodology, making it possible to prepare organic compounds that have incorporated a molecule of carbon monoxide.

The success of such a cascade carbopalladation–trapping methodology depends on the trapping of the carbopalladation adducts being sufficiently faster than the direct trapping of the organopalladium intermediates formed in the oxidative insertion step, so as to permit the desired carbopalladation to be completed. Premature termination via nucleophilic trapping of organopalladium species formed in the oxidative insertion step may pose serious problems to the process, particularly when it involves an intermolecular carbopalladation step or when the intramolecular carbopalladation generates large rings.

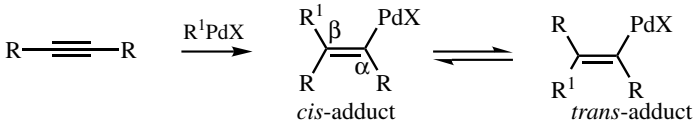
B. THE CARBOPALLADATION STEP

The carbopalladation step is crucial to the stereo- and regiochemical outcome of these reactions, and an understanding of the effects governing the addition of the carbon–palladium bond to the carbon–carbon triple bond is essential to the design and utilization of the methodology in the synthesis of complex organic molecules. This step has usually been discussed in terms of irreversible addition, though no definitive evidence of this assumption has yet been obtained (a reversible reaction would mandate considering the relative stabilities of the stereo- and regioisomeric addition intermediates and the influence of the reaction conditions on their stability). According to this view, interpretations of experimental data have been based on the evaluation of factors controlling the migration of the organic residue and the palladium moiety onto the coordinated carbon–carbon triple bond. Mechanistic rationalizations are often difficult due to the interplay of many factors. Reaction variables such as the nature of the carbon donor, the substitution pattern of the alkyne, the added salt, base, and solvent, the absence or presence of phosphine ligands, as well as the combination of them exert a strong influence on the reaction outcome, and moving from a given set of reaction conditions to another may often cause remarkable changes. Nonetheless, a few notable facets of orientation appear to arise from available data and they are briefly discussed in the next two paragraphs.

B.i. Stereochemistry

The observed general predominance of *cis* addition products following the carbopalladation step (**Schemes 1a** and **2**) and the formation of cyclic derivatives (**Scheme 1b**) appear to argue in favor of a mechanism involving a *syn* addition of the organic residue and the palladium moiety to the carbon–carbon triple bond. The appearance of final products as *trans* derivatives is more likely to indicate the intermediacy of *cis*-adducts capable of isomerization to the *trans*-adducts (**Scheme 3**) rather than the existence of a direct *trans* addition paralleling the *cis* addition pathway.

A possible rationale for this *cis–trans* isomerization of addition intermediates considers rotation about the C_α—C_β bond involving contributions from zwitterionic resonance forms **i** or **ii** (depending on the nature of the substituents at the acetylenic carbons) as shown in **Figure 2**. A variety of Pd-catalyzed reactions producing both *cis*- and



Scheme 3

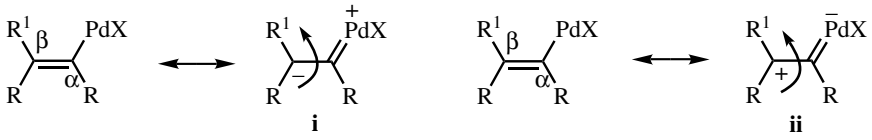
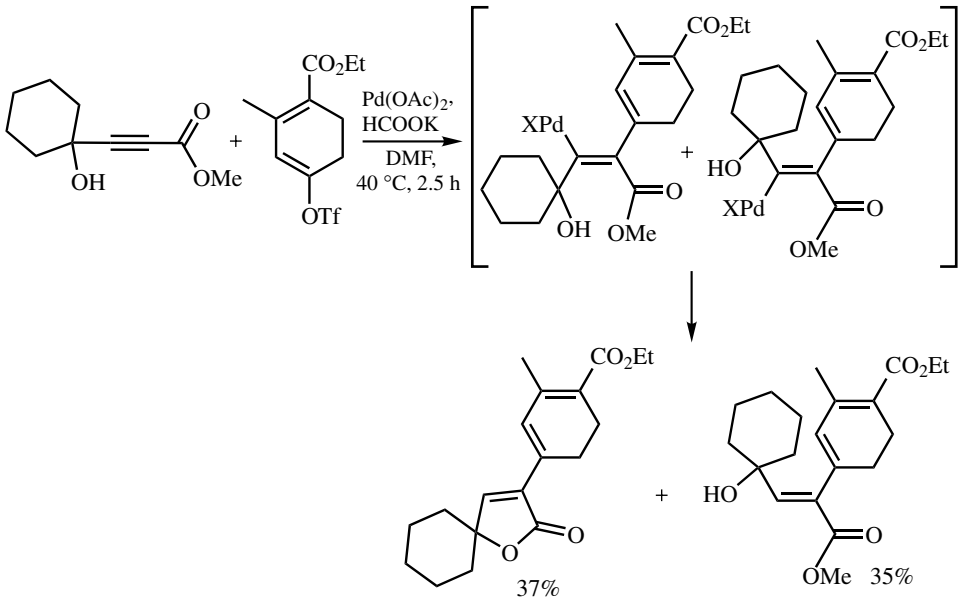


Figure 2

trans-isomers of the products following the carbopalladation step have been discussed on the basis of this *cis–trans* isomerization postulate.[10]–[15] However, no systematic work has yet been done to shed some light on the factors influencing the *cis–trans* isomerization of carbopalladation adducts. Electronic effects might exert an influence. For example, the formation of the *trans* addition derivative in the reaction of 4-carbethoxy-3-methyl-1,3-cyclohexadienyl triflate with methyl 3 (hydroxycyclohexyl)prop-2-ynoate[16] (**Scheme 4**) could be ascribed to the combined electron-withdrawing effect of the two ester groups, which might play a pivotal role in lowering the C_{α}—C_{β} bond order of the *cis*-σ-alkenylpalladium adduct to the point needed for rotation. The nature of the base and the C_{sp^2} donor also appear to exert an influence on the stereochemistry (as well as on the regiochemistry) of the carbopalladation step. However, further work is needed before a comprehensive general rationale is provided.



Scheme 4

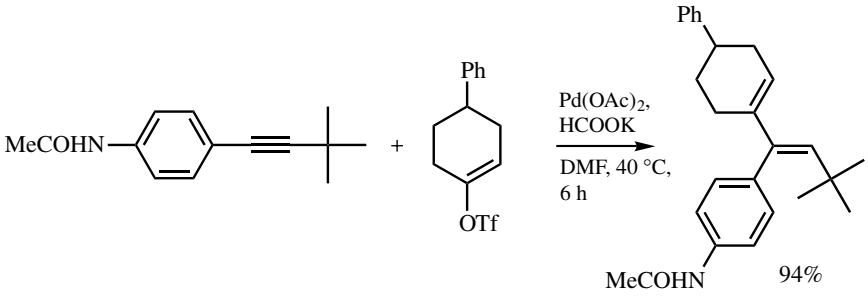
B.ii. Regiochemistry

The regiochemistry of the carbopalladation step is considered to be controlled primarily by steric and coordination effects, whereas electronic effects appear to be less important.

As to steric effects, the currently available data argue in favor of the idea that they control the conversion of the η^2-alkyne-organopalladium intermediate into the

σ-alkenylpalladium adduct so as to direct the organic residue preferentially to the less hindered end of the carbon–carbon triple bond and the palladium moiety to the more hindered end. In practice, steric effects might favor transition states with minimized steric strain in the vicinity of the site involved in the formation of the new carbon–carbon bond (**Figure 3a**) at the expense of transition states locating the organic residue close to the bulkier terminus of the acetylenic system (**Figure 3b**).

Examples of this trend are numerous.[15]–[26] For instance, steric effects appear to be responsible for the remarkable regioselectivity observed in the Pd-catalyzed hydroalkenylation of 4-phenylcyclohex-1-enyl triflate with 1-(*p*-acetamidophenyl)-3,3-dimethyl-1-propyne in the presence of potassium formate[16] (**Scheme 5**). In this reaction, which is also highly stereoselective, the added alkenyl group is placed regioselectively on the less sterically encumbered end of the carbon–carbon triple bond and the hydrogen (the palladium moiety in the carbopalladation adduct) on the more sterically congested end.



Scheme 5

Coordination of neighboring groups to palladium can play a significant role in directing the conversion of an η^2-alkyne-organopalladium intermediate into the carbopalladation adduct.[16],[21],[24]–[38] In essence, they tend to influence the formation of vinylic adducts in such a way that the added palladium ends up close to the coordinating group (**Figure 4**). Such an effect has been invoked to account for the strong directing effect of tertiary hydroxyl groups (**Schemes 6** and **7**) and the amido group (**Scheme 8**). The presence of phosphine ligands, the coordinating ability of solvents, and the concentration may interfere with the directing ability of coordinating groups.

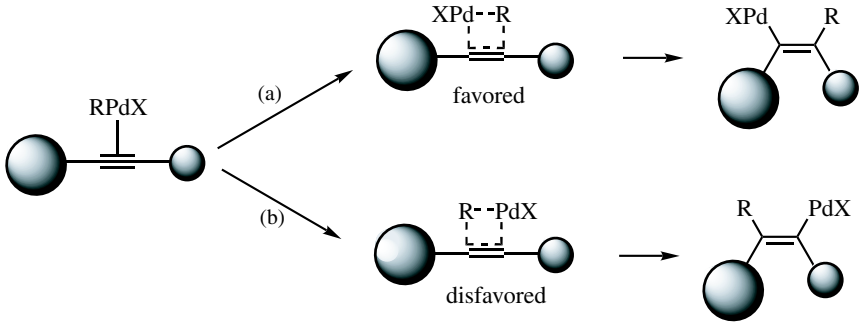


Figure 3

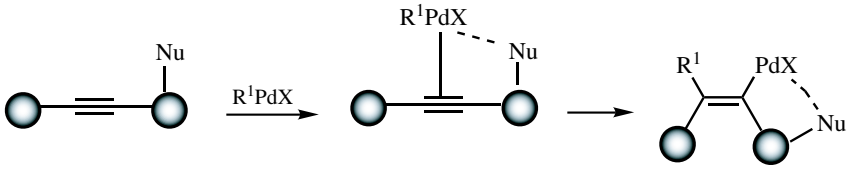
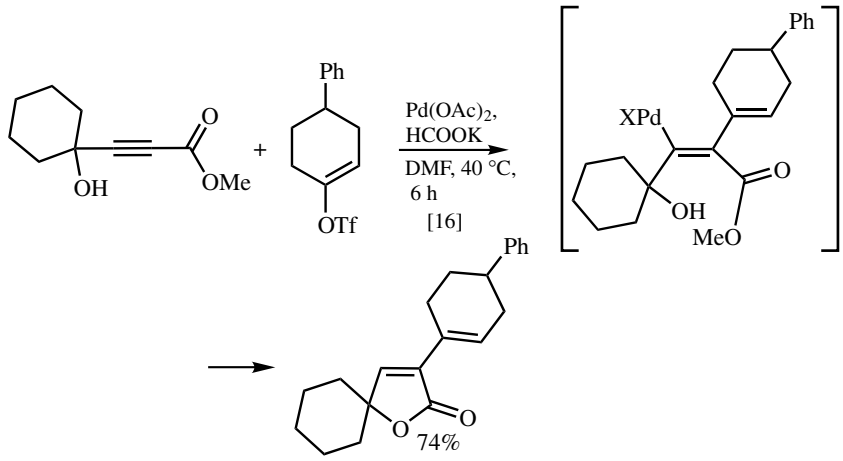
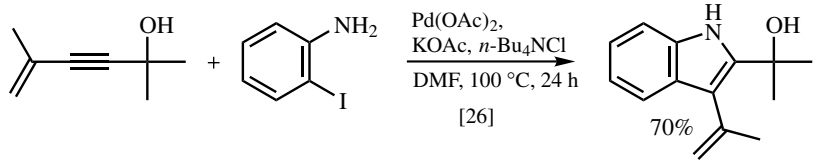


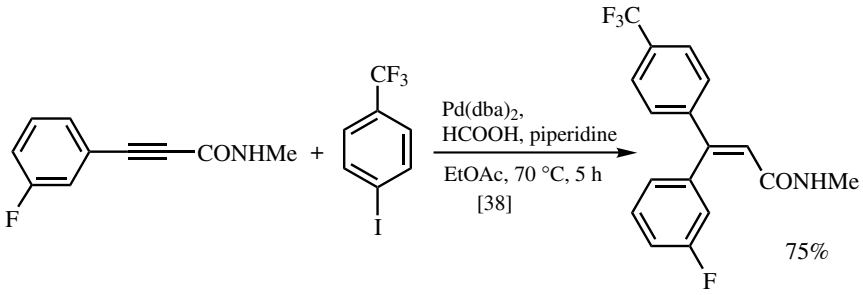
Figure 4



Scheme 6



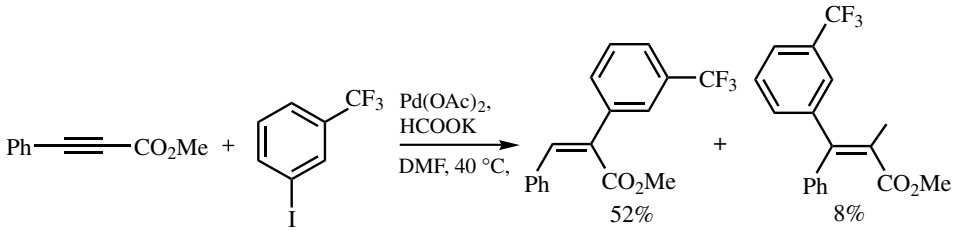
Scheme 7



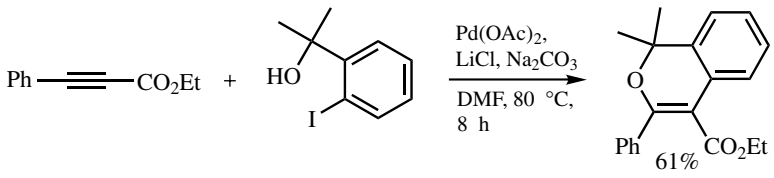
Scheme 8

As to the electronic effects, in general they appear to play a minor role. For example, the hydroarylations and hydroalkenylations of unsymmetrical diarylacetylenes bearing an electron-withdrawing group on an aromatic ring and an electron-donating group on the

other—whereby the acetylenic carbons should be differentiated only by the electronic effects of the substituents—proceeded with only modest to low regioselectivity.[39] Furthermore, several reactions involving the intermediacy of "σ-aryl- or σ-alkenylpalladium halides and triflates" support the view that when steric and/or coordinating factors have opposite directing effects as compared to electronic factors, the former tend to prevail. This tendency is well illustrated by the hydroarylation of methyl 3-phenylpropynoate[40] (**Scheme 9**) or by the annelation of ethyl phenylpropynoate[21] (**Scheme 10**). In these reactions electronic factors would be expected to influence the regioselectivity in such a way that added aryl units take up the position far from the carbonyl functionality. On the contrary, the carbopalladation step appears to be primarily governed by the directing effect of the phenyl group and the entering carbon unit ends up close to the carbonyl functionality.

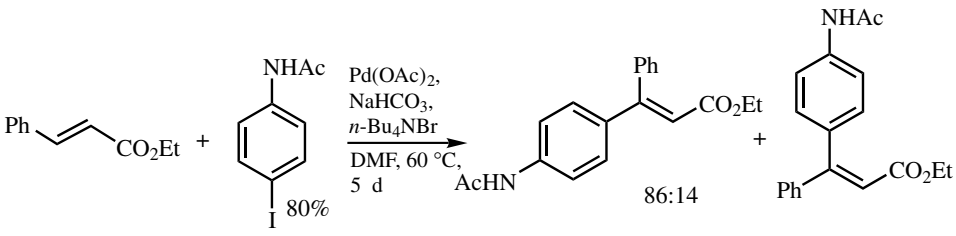


Scheme 9



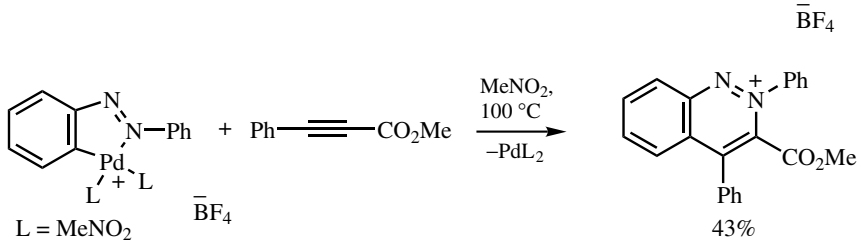
Scheme 10

This is in sharp contrast with the mechanistic picture emerging for the carbopalladation of electron-deficient alkenes, which appears to be controlled primarily by electronic factors. For example, electronically biased carbopalladation adducts are most probably involved in the Pd-catalyzed reaction of methyl cinnamate with aryl iodides. This reaction in fact produces vinylic substitution products containing the added aryl unit exclusively attached to the β-carbon (**Scheme 11**).[41] The same trend has been observed in the vinylic substitution[42]–[44] and hydroarylation[45]–[48] of β-substituted-α, β-enones.



Scheme 11

There are, however, indications that electronic effects may in some cases control the carbopalladation step. For example, the reaction of methyl 3-phenylpropynoate with an ionic cyclopalladated azobenzene tetrafluoroborate complex gives rise to the formation of the 2,4-diphenyl isomer of the cinnolinium salt[49] (**Scheme 12**). In this case, the conjugating effect of the ester group apparently exerts more influence in directing the carbopalladation than the phenyl does.

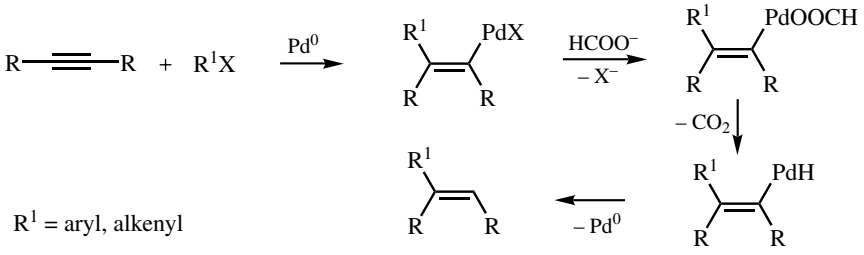


Scheme 12

C. INTERMOLECULAR CARBOPALLADATION

C. i. Trapping with Formate Anions: Hydroarylation and Hydroalkenylation Reactions

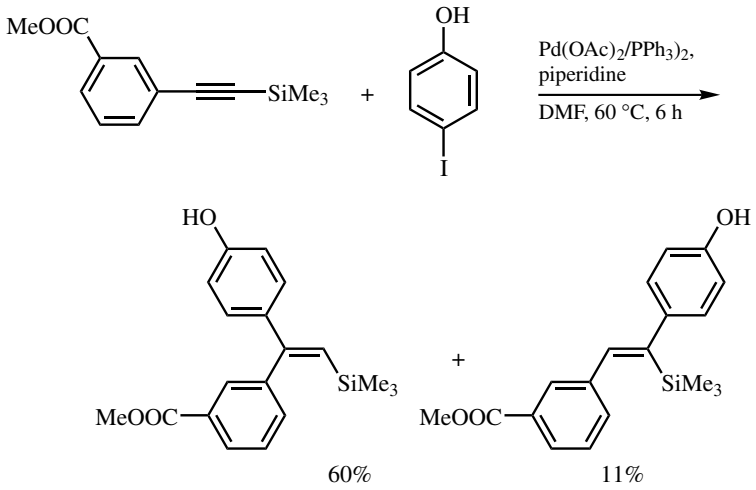
The reaction of alkynes with aryl and alkenyl halides or triflates in the presence of formate anions, one of the first reactions based on the concept of trapping carbopalladation adducts with a nucleophile, affords alkene products through the formation of a carbon–hydrogen bond at one of the acetylenic carbons and a carbon–carbon bond with an aryl or alkenyl unit at the other.[39] This hydroarylation or hydroalkenylation process most probably proceeds by conversion of carbopalladation adducts into the corresponding formate derivatives via trapping with formate anions (usually generated *in situ* from formic acid and an amine base or added as sodium or potassium salts). Subsequent decarboxylation and reductive elimination gives organic compounds and regenerates the catalyst (**Scheme 13**). The formation of deuterated alkenes when the reaction is carried out in the presence of DCOOH argues in favor of this mechanism. Depending on the nature of the C_{sp2} donors and the starting alkynes, variable amounts of arenes or alkenes derived from premature reduction of σ-aryl- and σ-alkenylpalladium intermediates, and/or alkenes derived from reduction of the starting alkynes, and/or coupling derivatives may be formed as side products.



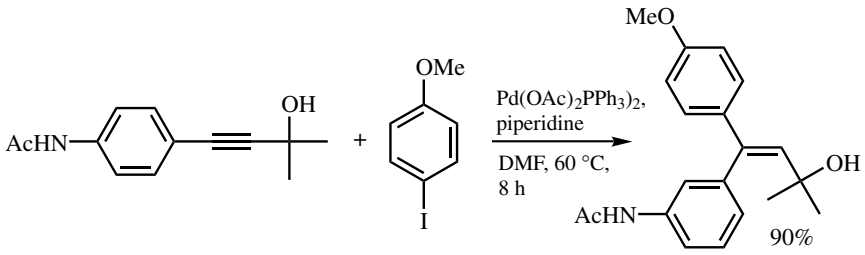
Scheme 13

Several terminal and internal acetylenes have been subjected to hydroarylation and hydroalkenylation conditions. With terminal acetylenes[39] trisubstituted alkenes are obtained. Most of the hydroarylation and hydroalkenylation chemistry, however, has been performed with variously substituted internal acetylenes.

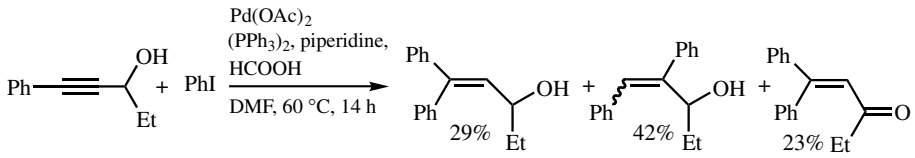
Arylethynylsilanes afford preferentially 2,2-disubstituted alkenylsilanes[17] (**Scheme 14**), although mixtures of regioisomers have occasionally been observed. Desilylation of hydroarylation products may occur during the reaction. Treatment after filtration through a column of silica gel of the crude hydroarylation mixture with iodine in benzene/water at 75 °C affords 1,1-disubstituted alkenes usually in high overall yield. Arylpropargyl alcohols containing tertiary hydroxy groups produce regioselectively γ,γ-disubstituted allylic alcohols[34] (**Scheme 15**). Secondary propargyl alcohols appear to be less effective in directing the carbopalladation step, and mixtures of allylic alcohols with carbonyl derivatives are formed (**Scheme 16**). The latter very likely derive from the *syn*-β-elimination of a HPd species from the alkenylpalladium adducts bearing palladium on the carbon close to the secondary alcoholic group. Alkyl arylpropynoates give hydroarylation products with the added aryl unit located preferentially at the carbon bearing the ester group[40] (**Scheme 17**). With 3,3-dialkoxy-1-aryl-1-propynes the regiochemistry of addition is controlled by the directing effect of the aryl group and the added aryl unit ends up at the carbon next to the acetal substituent[15] (**Scheme 18**). The hydroarylation of arylpropiolamides with aryl iodides has best been carried out using dilute solutions, low-coordinating solvents, and a phosphine-free palladium(0) catalyst.[38] Employing these conditions results in a highly regio- and stereoselective reaction (**Scheme 19**). Highly coordinating solvents, or phosphine ligands, or a high concentration has proved to lower the regioselectivity, most probably because of the competition with the amide functionality for coordination to palladium. For example, when 3-(*m*-fluorophenyl)-*N*-methylpropionamide was treated with 6-iodo-4-(isopropylsulfonyl)-1*H*-benzimidazol-2-ylamine in the presence of bis(triphenylphosphine)palladium diacetate, piperidine, and formic acid in DMF, a mixture of all four regio- and stereoisomeric hydroarylation products was obtained in low yield, along with the *cis*-alkene derived from the starting alkyne and dehalogenated benzimidazole.



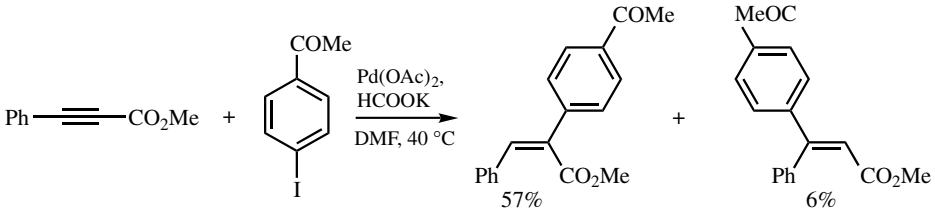
Scheme 14



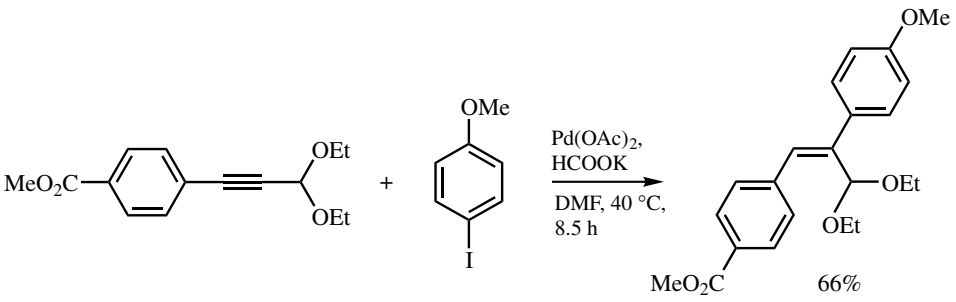
Scheme 15



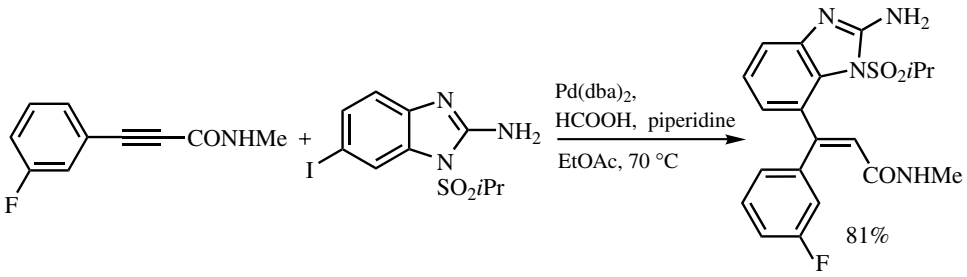
Scheme 16



Scheme 17

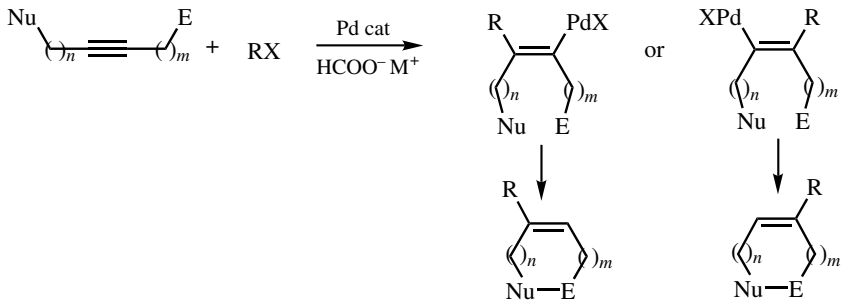


Scheme 18



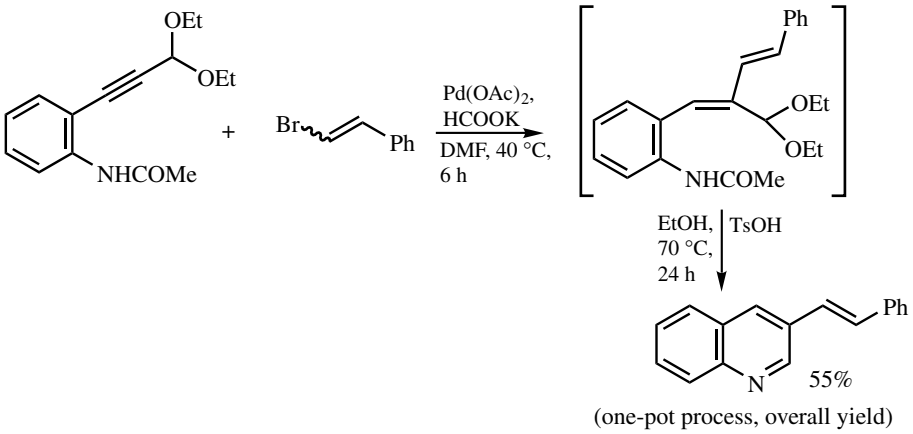
Scheme 19

C.i.a. ***Sequential Hydroarylation (Hydroalkenylation)/Cyclization.*** Since the *cis* stereochemistry of addition pushes the substituents of the acetylenic moiety to the same side of the olefinic double bond, a cyclization reaction can follow the addition step when these substituents bear suitable nucleophilic and electrophilic centers, and the whole process resembles a valuable straightforward methodology for the preparation of cyclic compounds (**Scheme 20**). Cyclization can occur under hydroarylation(hydroalkenylation) conditions—either before or after the substitution of the carbon-hydrogen bond for the carbon-palladium bond—or by subjecting the isolated hydroarylation(hydroalkenylation) product to suitable reaction conditions. This strategy has been employed successfully to develop new routes to various heterocycles.



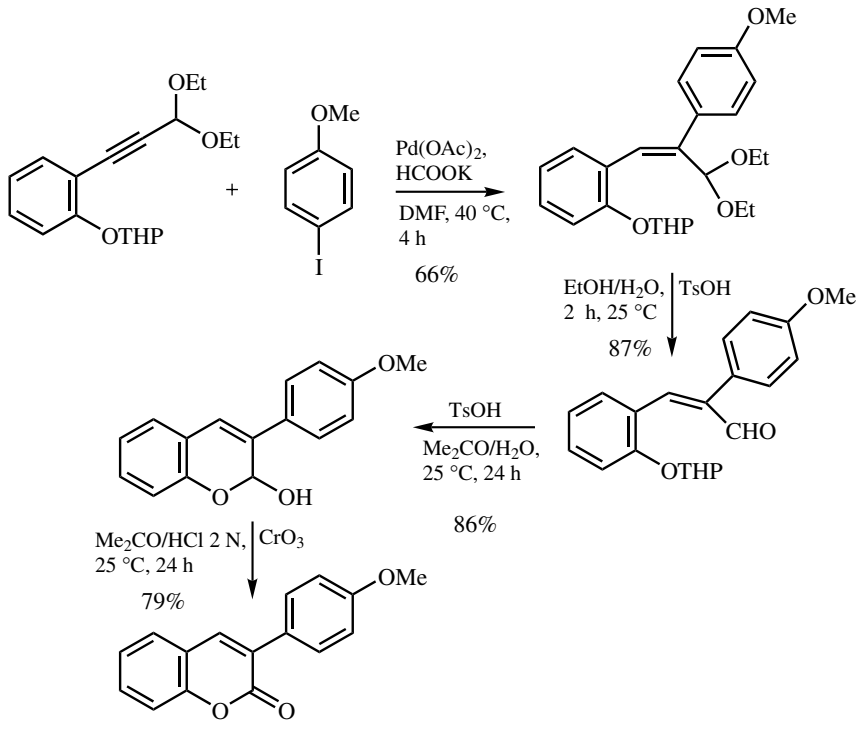
Scheme 20

3-Aryl- and 3-alkenyl-quinolines have been prepared from 3,3-diethoxy-1-(*o*-acetamido phenyl)-1-propyne[15] (**Scheme 21**). The regiochemistry of the carbopalladation step is controlled by the directing effect of the aryl group joined to the acetylenic carbon and the new carbon–carbon bond is formed preferentially at the carbon close to the acetal group. The existence of a directing effect of the *o*-amido substituent, involving coordination of palladium, seems unlikely in view of the fact that the *p*-amido derivative affords a similar mixture of regioisomers. Minor amounts of the regioisomeric 4-substituted quinolines have occasionally been isolated. The reaction can best be carried out as a one-flask process, omitting the isolation of hydroarylation or hydroalkenylation products.



Scheme 21

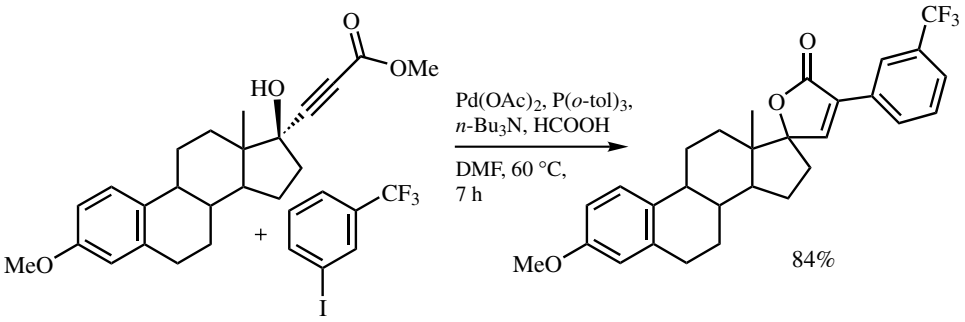
Extension of this alkyne cyclization chemistry to 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne has provided a new route to substituted cromanols and coumarins[40] (**Scheme 22**). Here again the aryl group attached to the acetylenic carbon appears to exert a strong directing effect on the regiochemistry of the process. Utilization of the corresponding *o*-hydroxy- and *o*-acetoxyphenyl propynes has proved unsatisfactory. Coumarins can be obtained through a one-pot process without the isolation of hydroarylation, oxidation, and cyclization intermediates. Using this procedure, the reaction of 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne with 4-iodoanisole gave the corresponding coumarin derivative in 40% overall yield.



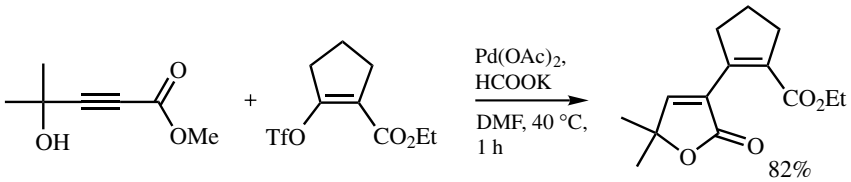
Scheme 22

The scope of this sequential hydroarylation(hydroalkenylation)/cyclization methodology has been extended to the synthesis of α-aryl-[36] (**Scheme 23**) and α-vinylbutenolides[16],[37] (**Scheme 24**). These compounds have been prepared by reaction of alkyl 4-hydroxy-2-butynoates with aryl and alkenyl halides or triflates. The tertiary hydroxy group appears to exert more influence on the direction of the carbopalladation than the ester group does. With aryl iodides the new carbon–carbon bond is formed preferentially at the carbon next to the ester group, and regioisomeric β-substituted butenolides have occasionally been isolated in low yield. When alkenyl triflates are employed, the reaction is highly regioselective and α-alkenylbutenolides are formed almost exclusively. The best results in terms of yield have been obtained by using phosphine-free catalysts. Apparently, phosphine ligands favor the premature reduction to alkenes of the σ-alkenylpalladium intermediates generated in the oxidative addition step. Premature reduction of σ-aryl- or σ-alkenylpalladiums may be observed

even with aryl or alkenyl halides. However, excess aryl or alkenyl halide can often be used in these cases. With alkenyl triflates, equimolar amounts of alkyne and alkenyl donor are used because of the high cost of the latter.



Scheme 23

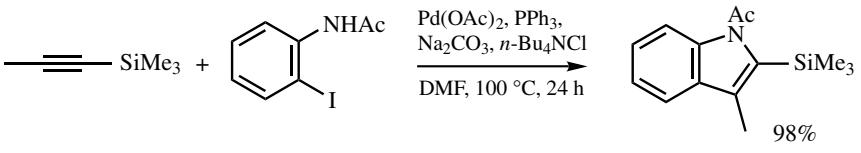


Scheme 24

C.ii. Intramolecular Trapping of Carbopalladation Adducts

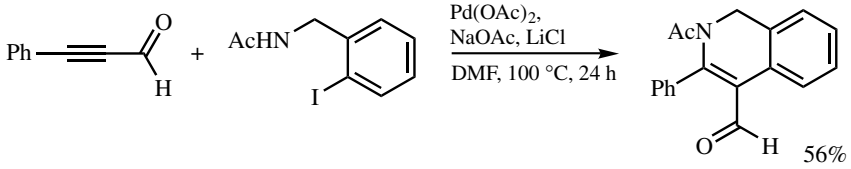
This type of reaction has been developed by employing aryl and alkenyl halides or triflates containing proximate nitrogen or oxygen nucleophiles and internal acetylenes.

o-Iodoaniline and the corresponding *N*-methyl, -acetyl, and -tosyl derivatives have been utilized as aryl donors with a variety of internal alkynes to provide 2,3-disubstituted indoles.[26]–[30] Excess alkyne, LiCl or *n*-Bu_4NCl, sodium or potassium acetate or carbonate as a base, and occasionally PPh_3 have been employed to obtain the best results. The reaction is quite regioselective. The aryl group is placed on the carbon far from the coordinating or more sterically encumbered substituent of the carbon–carbon triple bond and the nitrogen moiety on the carbon close to the coordinating or more sterically encumbered substituent (**Scheme 25**). This methodology has been employed to develop new routes to pyrrolopyrimidines,[31] pyrrolopyridines,[31] thienopyrroles,[31] and 5-, 6-, and 7-azaindoles.[32],[33]



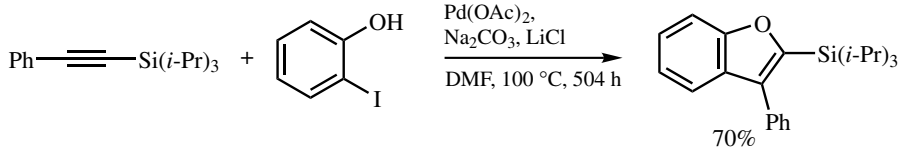
Scheme 25

The extension of this annelation chemistry to *o*-iodobenzylamine has proved sluggish. By employing the corresponding acetamide a variety of 1,2-dihydroquinolines have been prepared.[21] Alkynes containing aryl or carbonyl groups have given the best results and proved to react in a highly regioselective manner (**Scheme 26**).

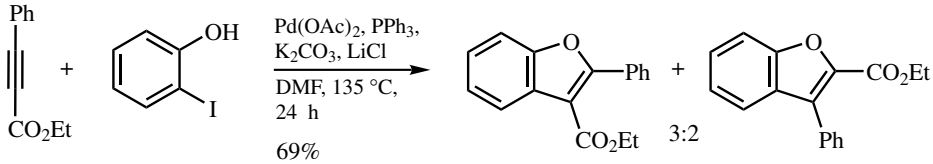


Scheme 26

Heteroannelation employing *o*-iodophenol has proved more difficult than analogous reactions with *o*-iodoaniline. The process appears to be limited to sterically encumbered alkyl acetylenes or acetylenes bearing aryl, carbonyl, or silyl groups, and higher temperatures are generally required[21] (**Scheme 27**). At the higher temperatures required, reduced regioselectivity is sometimes observed (**Scheme 28**).

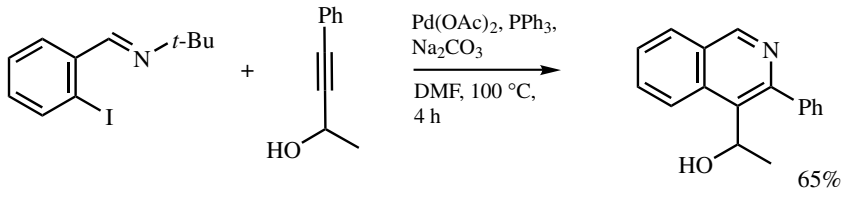


Scheme 27



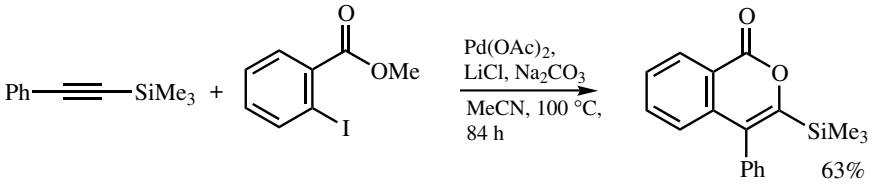
Scheme 28

Isoquinoline derivatives have been prepared from the *tert*-butylimines of *o*-iodobenzaldehydes[50] (**Scheme 29**). Methyl-, isopropyl-, allyl-, benzyl-, and α-methylbenzylimines either failed to produce any of the desired isoquinoline product or gave it in low yield. Employment of vinylic *tert*-butylimines affords pyridine derivatives.

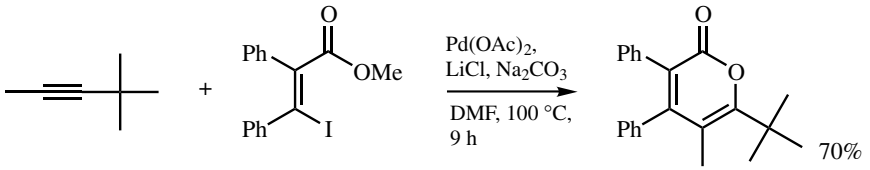


Scheme 29

o-Iodobenzoates[21],[51] (**Scheme 30**) and acyclic as well as cyclic alkyl (*Z*)-3-iodo-, (*Z*)-3-bromo-, and (*Z*)-3-[(trifluoromethyl)sulfonyloxy]-2-propenoates[25] (**Scheme 31**) have been employed as C_{sp^2} donors to give, respectively, isocoumarins and α-pyrones. Most probably these annelation processes proceed though intramolecular nucleophilic attack of the carbonyl oxygen on the alkenylpalladium adduct to form a seven-membered palladacyclic salt from which the product is obtained through reductive elimination. Loss of the ester alkyl group may occur—via a nucleophilic substitution process—either during the reaction itself or during the aqueous workup. These annelations are generally regioselective, although mixtures of regioisomers have occasionally been observed.



Scheme 30



Scheme 31

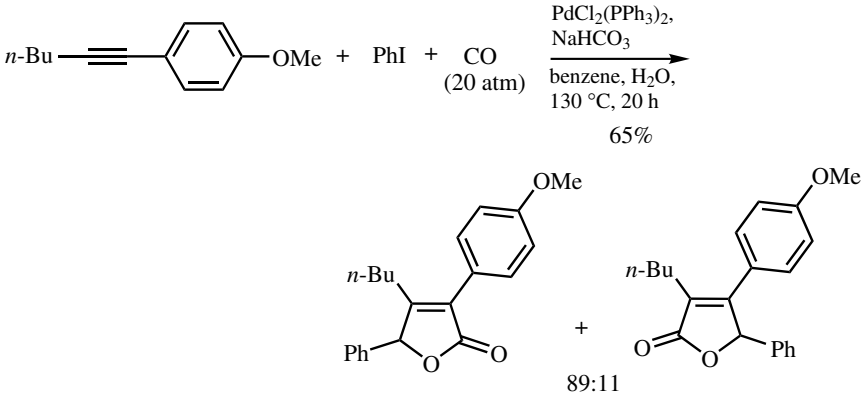
A variety of other heterocycles have been synthesized regioselectively by treating appropriate functionally substituted alkenyl halides with internal alkynes.[52],[53]

C.iii. Acylpalladation–Carbonylation–Trapping with Nucleophiles

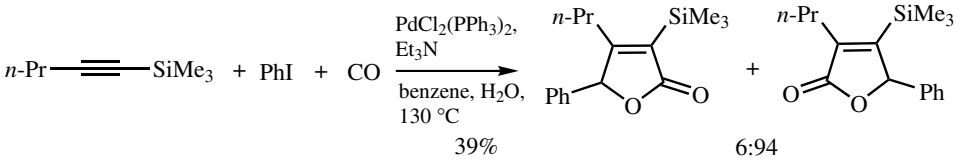
In the presence of carbon monoxide, the reaction of aryl or alkenyl halides and triflates with alkynes may involve an acylpalladation step. Organopalladiums derived from C_{sp^2} donors may in fact be interconverted to relatively stable acylpalladium intermediates. These can subsequently react with alkynes to form acylpalladation adducts from which organic compounds may be generated (upon reaction with a terminating agent or with another molecule of carbon monoxide followed by trapping with a terminating agent) along with palladium complexes that can enter new catalytic cycles.

Such a process has been performed with internal alkynes and aryl iodides under a pressure of 20 atm of carbon monoxide.[54] The fate of the acylpalladation adducts generated under these conditions has been found to depend on the substrate structure and the particular reaction conditions. Those substrates that are convertible to (*Z*)-γ-oxo-α,β-unsaturated acylpalladiums lacking δ-hydrogens are converted to the corresponding butenolides in the presence of water, which serves as a hydrogen donor (**Schemes 32** and **33**). Carbon monoxide most probably is the source of two electrons. The reaction is regioselective and one of the regioisomeric butenolides is formed preferentially. The mechanism of this butenolide formation is likely to involve the addition of

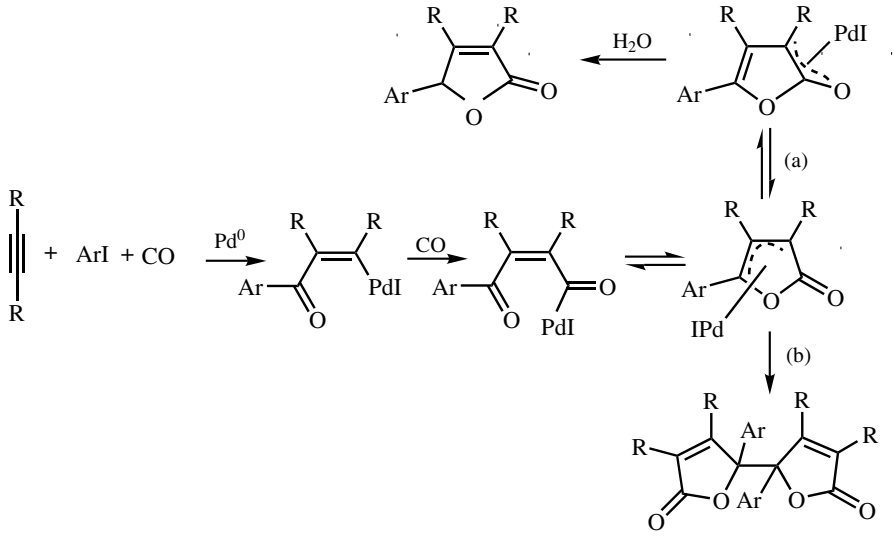
an acyl and a palladium fragment to the carbon–carbon triple bond, trapping of the resultant acylpalladation adduct with carbon monoxide, intramolecular oxygen displacement of palladium to give a π-allylpalladium complex, isomerization to an oxo-π-allylpalladium complex, and termination via hydrogen transfer (**Scheme 34a**). In the absence of a suitable proton source or in the presence of factors that can disfavor the butenolide formation, the reaction affords a dimeric derivative (**Scheme 34b**).



Scheme 32



Scheme 33

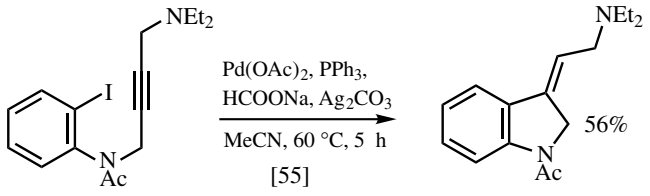


Scheme 34

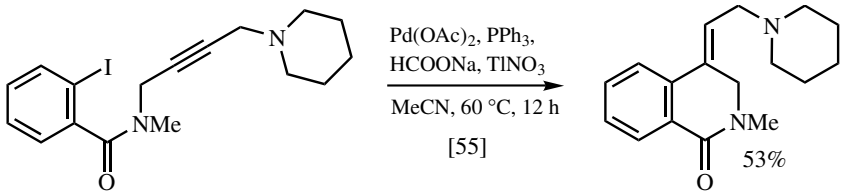
D. INTRAMOLECULAR CARBOPALLADATION

D.i. Trapping with Formate Anions: Hydroarylation and Hydroalkenylation Reactions

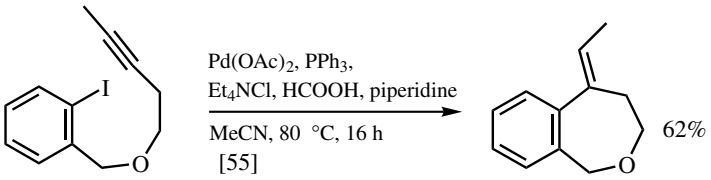
The intramolecular version of the hydroarylation and hydroalkenylation protocol has been developed as a useful approach to a variety of five- (**Scheme 35**), six- (**Scheme 36**), and seven- (**Schemes 37** and **38**) membered heterocycles.[55]–[57] Alkynes containing a C_{sp^2}–halogen bond or a C_{sp^2}–triflyloxy bond close to the acetylenic fragment have usually been employed. The utilization of additives such as Ag_2CO_3, Et_4NCl, or $TlNO_3$ has been reported[55] to favor the intramolecular hydroarylation or hydroalkenylation path at the expense of the direct reduction of the initially formed oxidative addition intermediate. This



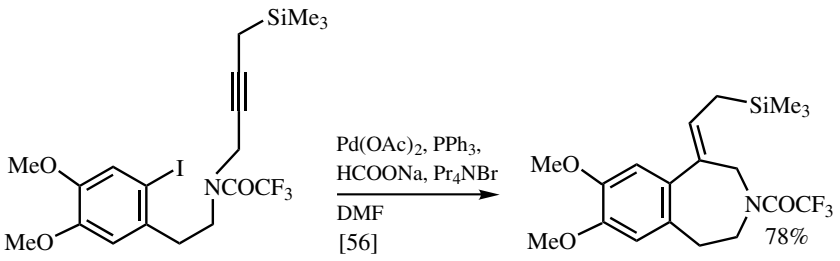
Scheme 35



Scheme 36



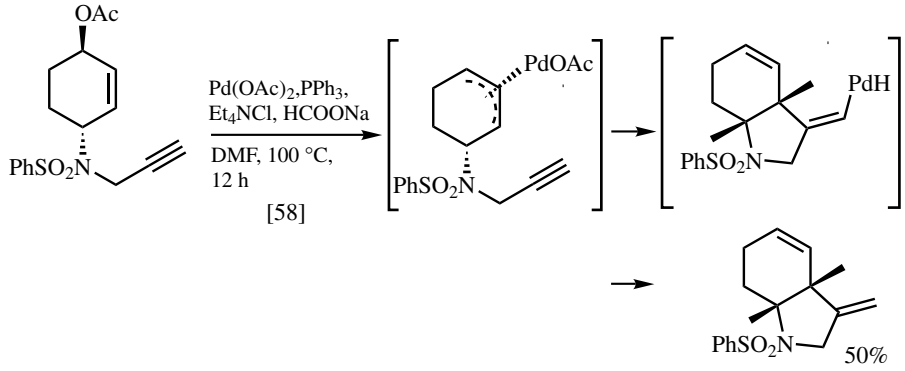
Scheme 37



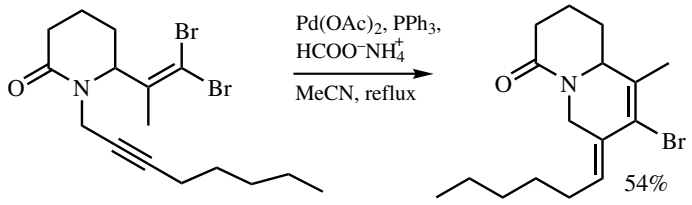
Scheme 38

is particularly useful when the carbopalladation of the carbon–carbon triple bond generates large rings. The employment of alkynes containing proximate allylic acetate units has also been described.[58] The process outlined in **Scheme 39** is regio- and stereospecific and no double bond isomerization is observed in the product

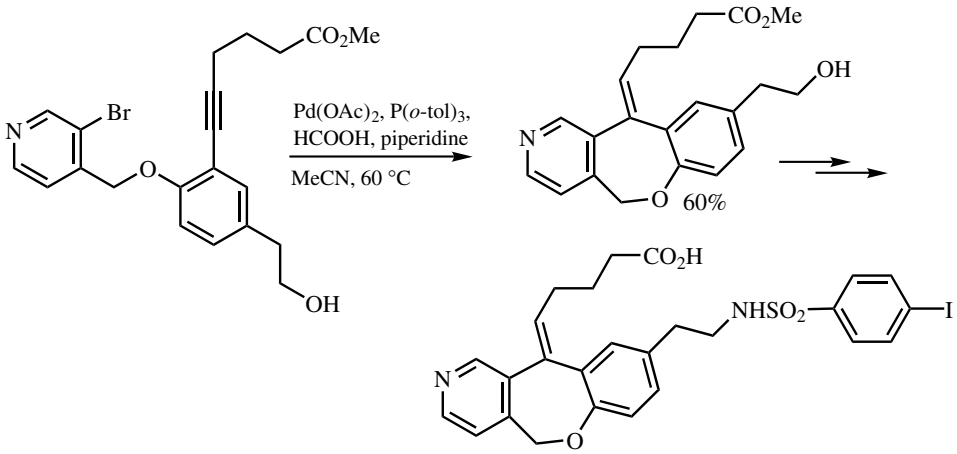
The intramolecular hydroarylaion and hydroalkenylation methodology has provided novel routes to the core unit of the quinolizidine-based homopumiliotoxin alkaloids[59] (**Scheme 40**) and the conformationally restrained analogs of the combined thromboxane antagonist/synthase inhibitor GR85305[60] (**Scheme 41**).



Scheme 39



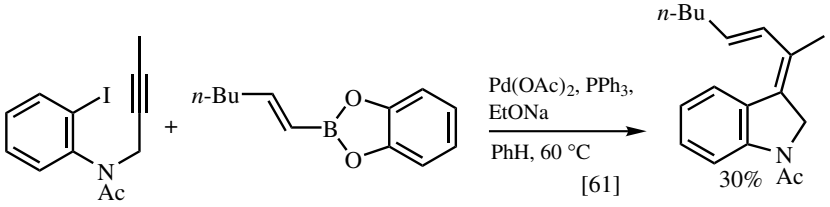
Scheme 40



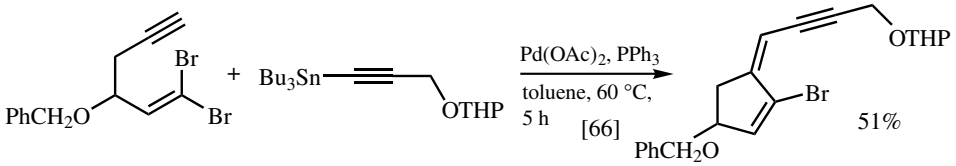
Scheme 41

D.ii. Trapping with Organometals

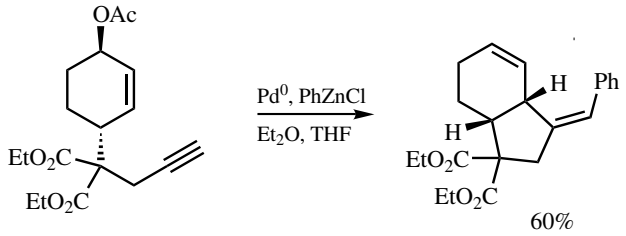
Trapping of carbopalladation adducts via cross-coupling with organometals leads to the substitution of the carbon–palladium bond with a carbon–carbon bond. Alkynes bearing proximate aryl[61]–[65] (**Scheme 42**) and alkenyl[66]–[68] (**Scheme 43**), halide fragments or allyl acetate groups[58] (**Scheme 44**) and a variety of organometals can be used for such a transformation.



Scheme 42



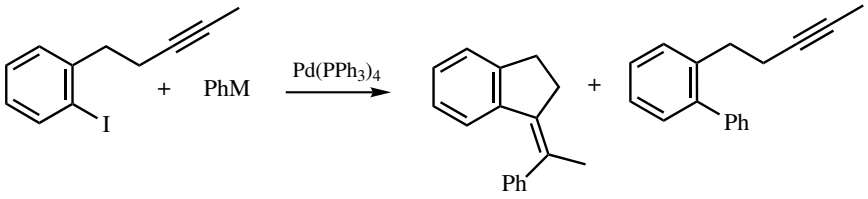
Scheme 43



Scheme 44

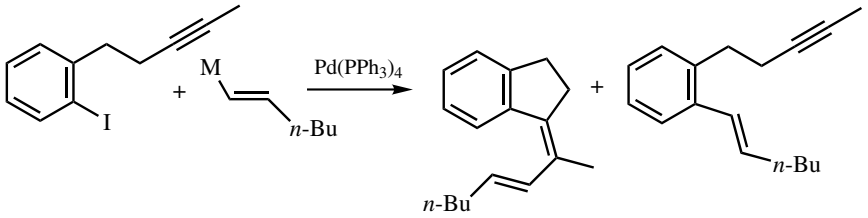
Organozinc compounds have widely been employed in this chemistry.[58],[61],[63]–[65] However, it has been shown[69] that the utilization of these very reactive organometals is generally less satisfactory than other organometals. This is due to the tendency of organozinc compounds to react with σ-organopalladium intermediates formed in the oxidative addition step before the carbopalladation step takes place. Specific examples of cyclizing carbopalladation–arylation, carbopalladation–alkenylation, and carbopalladation–alkynylation reactions are provided in **Schemes 45–47**. In these cases, highly satisfactory results have been obtained by employing organometals containing aluminum for carbopalladation–arylation, tin and zirconium for carbopalladation–alkenylation, and tin for carbopalladation–alkynylation sequences.

This carbopalladation–cross-coupling methodology has been used successfully for access to neocarzinostatine model compounds[66]–[68] (**Scheme 48**) and ellipticine derivatives[70] (**Scheme 49**).



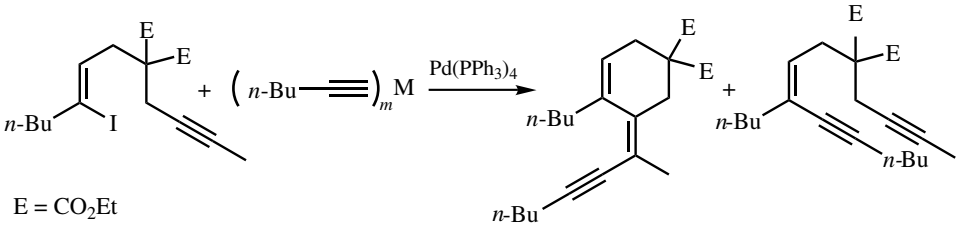
M = ZnCl	34%	7%
M = $AlPh_2$	93%	<2%

Scheme 45



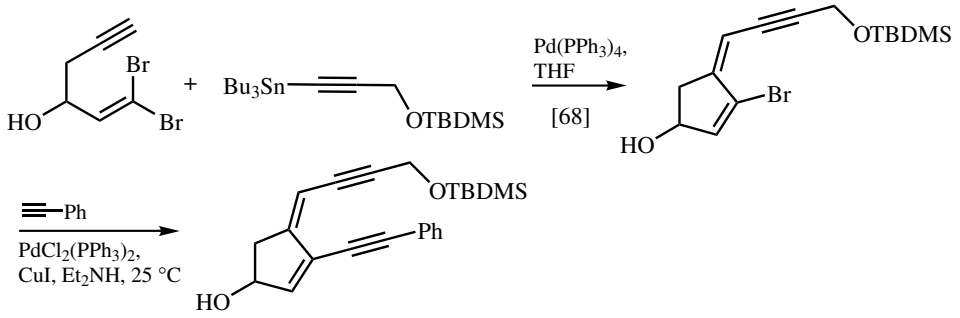
M = ZnCl	19%	68%
M = $ZrCp_2Cl$	84%	<3%
M = $SnMe_3$	69%	<4%
M = catecholborane	41%	<4%
M = $AlBu_2$	57%	32%

Scheme 46

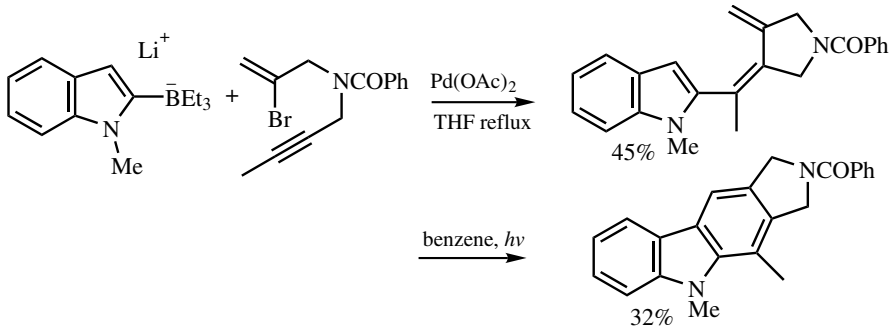


M = Zn; m = 2	8%	75%
M = $SnMe_3$; m = 1	73%	5%

Scheme 47



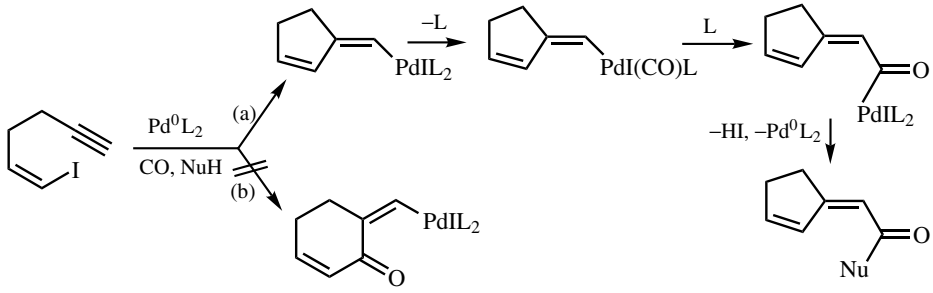
Scheme 48



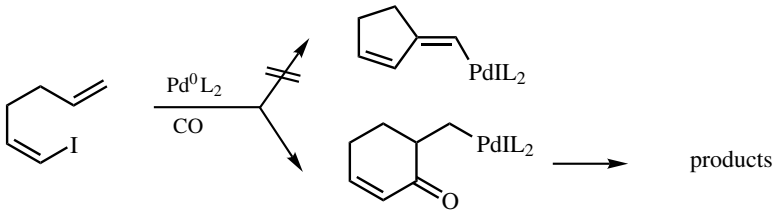
Scheme 49

D.iii. Trapping with Carbon Monoxide and a Nucleophile

When the Pd-catalyzed reaction of alkynes bearing proximate aryl or alkenyl halide groups is carried out in the presence of carbon monoxide, cyclizing aryl- or alkenylpalladation of the carbon–carbon triple bond occurs without premature incorporation of carbon monoxide (**Scheme 50a**), which would produce acylpalladation adducts (**Scheme 50b**). Subsequently, the resultant aryl- or vinylpalladation adducts are converted into the corresponding acylpalladiums that in turn can be trapped by external (as shown in **Scheme 50a**) or internal nucleophiles to afford organic products incorporating a molecule of carbon monoxide. This result appears to suggest that cyclizing aryl- or alkenylpalladation producing a five- or six-membered ring is strongly favored over the cyclizing acylpalladation giving rise to a five-, six-, or seven-membered ring ketone. Such behavior is in contrast to the corresponding alkene reaction proceeding preferentially through a cyclizing acylpalladation[71]–[74] (**Scheme 51**).

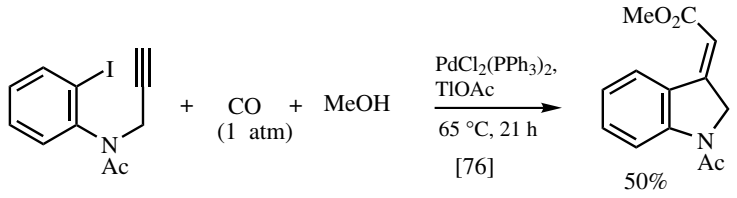


Scheme 50

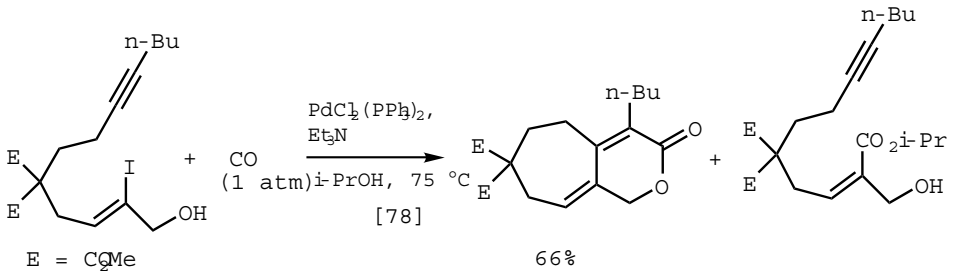


Scheme 51

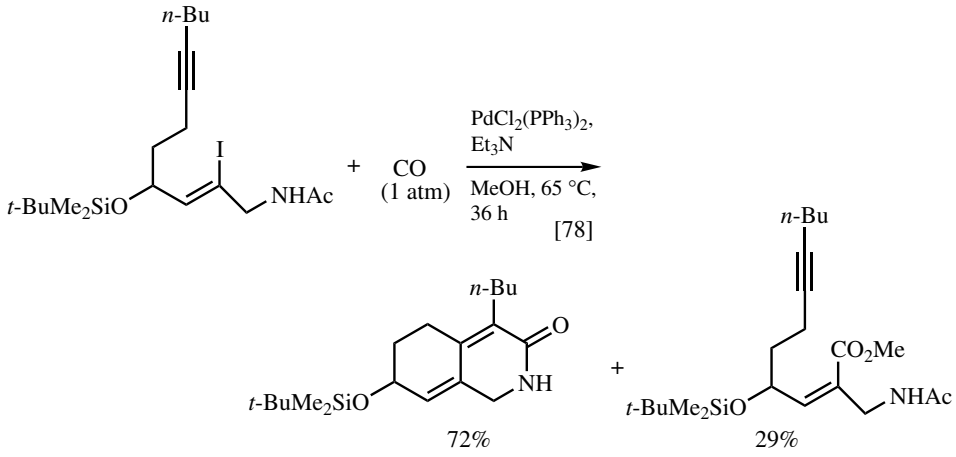
Examples of cyclizing aryl- and alkenylpalladation followed by carbonylation and trapping by external or internal nucleophiles[75]–[78] to give esters, lactones, and lactames are illustrated in **Schemes 52–54**. Formation of lactames has been more satisfactorily carried out with iodoenynes containing ω-carboxamido or ω-sulfonamido groups than with substrates containing ω-amino groups.



Scheme 52



Scheme 53



Scheme 54

E. SUMMARY

Over the last fifteen years or so the domino process involving the intermolecular and intramolecular carbopalladation of alkynes followed by trapping of the resultant

σ-alkenylpalladium adducts with nucleophiles has been shown to be a very versatile methodology that has provided a number of novel and selective ways to functionalize the carbon–carbon triple bond.

A number of acyclic and cyclic derivatives have been prepared. Aryl and alkenyl halides or triflates have most frequently been employed as the starter substrates. The utilization of allylic acetates has also been described. Hydrogen donors (usually formate anions), organometals, nitrogen and oxygen nucleophiles, and carbon monoxide (and an oxygen or nitrogen nucleophile) have been utilized as trapping agents. As to the acetylene component, most of this chemistry has been performed using internal alkynes, especially in the intermolecular processes. Terminal alkynes have usually been employed in reactions proceeding through intramolecular carbopalladation.

Available data provide a basic rationale in terms of stereo- and regioselectivity that can be achieved, but further work in this direction, to attain a better understanding of the factors influencing the crucial carbopalladation step, may be anticipated.

The process can tolerate a wide range of important functionalities, both in the starter substrate and in the acetylenic reaction partner. This makes applications to the synthesis of complex molecules especially promising and will undoubtedly bring new opportunities for the preparation of biologically active compounds.

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