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# PALLADIUM CATALYSIS IN THE CONSTRUCTION OF THE BENZO[*b*]FURAN AND FURAN RINGS FROM ALKYNES AND ORGANIC HALIDES OR TRIFLATES

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**Abstract –** Three general processes leading to the construction of functionalized benzo[*b*]furan and furan rings are reviewed: 1) *the coupling-cyclization methodology*, involving the palladium-catalyzed coupling of terminal alkynes with *o*-iodophenols, or the alternative palladium-catalyzed coupling of terminal alkynes containing proximate oxygen nucleophiles with aryl and vinyl halides or triflates, followed by the cyclization of the resultant coupling intermediates; 2) *the oxypalladation-reductive elimination domino reaction*, based on the trans addition of the oxygen and an organopalladium complex across the carbon-carbon triple bond, followed by a reductive elimination step; 3) *the carbopalladation-cyclization reaction*, based on the *syn* addition of an organopalladium complex, containing an oxygen nucleophile, to the carbon-carbon triple bond, followed by the cyclization of the resultant carbopalladation adduct.

The benzo[*b*]furan and furan nuclei are structural subunits that are observed in diverse natural products[1,2] and biologically active compounds.[3,4] Furans can be found in a variety of flavor and fragrance compounds,[5] in commercially important pharmaceuticals,[6] and have also been employed as synthetic intermediates.[7] Numerous approaches to these compounds have been described[8] and palladium catalysis, which has taken a prominent role in organic synthesis due to its unique versatility,[9] has been widely employed in the synthesis of benzo[*b*]furan and furan derivatives.[10] In particular, the palladium-based construction of the benzo[*b*]furan and furan ring system from acyclic precursors has been a very active area in the last few years. Many of the most versatile and efficient benzo[*b*]furan and furan ring-forming reactions rely on the utilization of terminal and internal alkynes. The present review is aimed at surveying this chemistry.

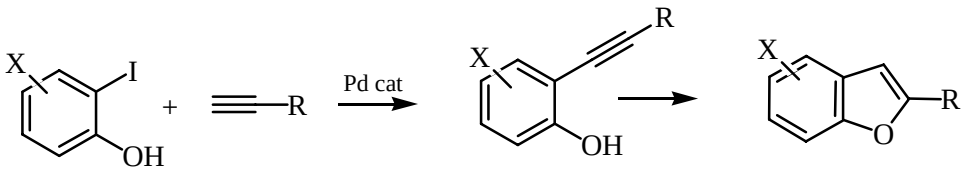
The following basic methodologies will be discussed, all involving the reaction of alkynes with aryl and vinyl halides or triflates in the presence of a palladium catalyst and C-O bond formation at the key step of the heterocyclic ring construction:

- 1. The coupling-cyclization methodology
- 2. The oxypalladation-reductive elimination domino reaction
- 3. The carbopalladation-cyclization reaction

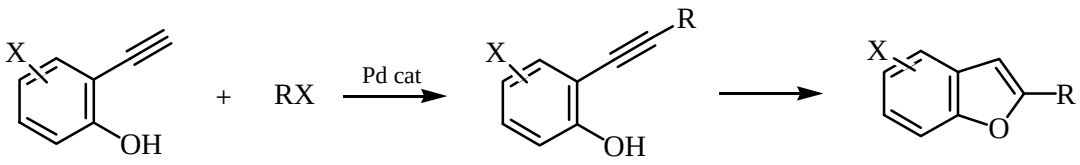
**1. The coupling-cyclization methodology**

*1.1 Construction of the of benzo[b]furan ring*

This methodoly is based on the palladium-catalyzed coupling of terminal alkynes with *o*-iodophenols, followed by the cyclization of the resultant coupling intermediates that most often occurs *in situ*, under coupling conditions, and that does not seem to require transition metals (Scheme 1). The coupling reaction is best carried out under Sonogashira conditions.[11] Alternatively, benzo[*b*]furans can be prepared through the palladium-catalyzed coupling of *o*-ethynylphenols with aryl and vinyl halides or triflates (Scheme 2).




**Scheme 1**

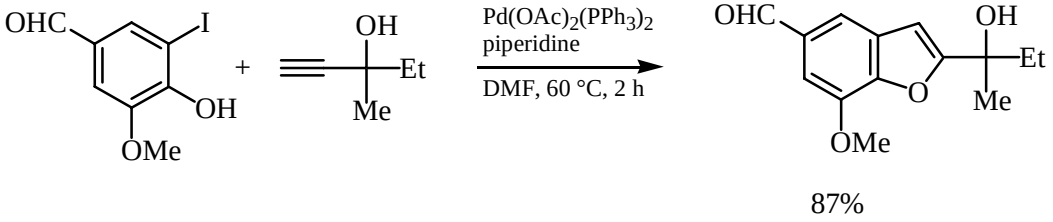



R = aryl, vinyl
X = I, Br, OTf

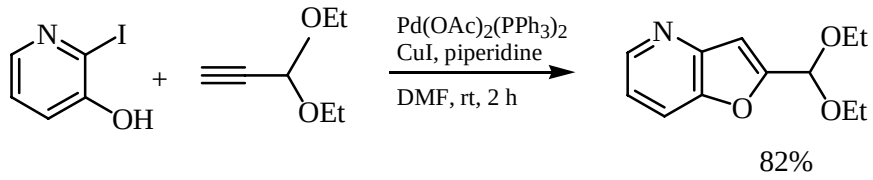
**Scheme 2**

The first example of the former methodology dates back to our palladium-catalyzed reaction of *o*-iodophenols with terminal alkynes to give 2-substituted benzo[*b*]furans (Scheme 3).[12,13] This simple and versatile procedure allows for channeling the copper-mediated synthetic approach,[14] usually requiring strong conditions (reactions are usually carried out at 110-120 °C) and stoichiometric amounts of a previously prepared Cu-acetylide reagent, into a mild procedure (reactions are typically carried out at 25-60 °C) that can accommodate a variety of functional groups.

Heteroaromatic systems can also be employed as “phenolic” components of the reaction. For example, 2-substituted furo[3,2-*b*]pyridines have been prepared from 2-halo-3-pyridinols (Scheme 4).[12]

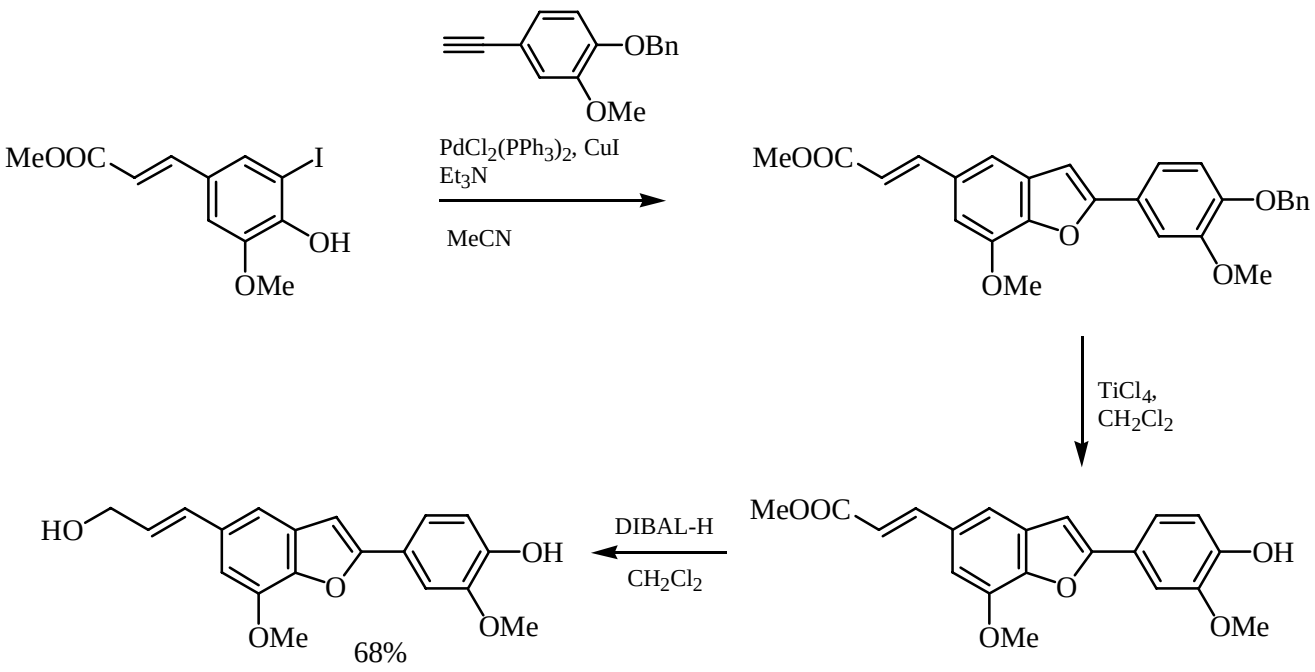



**Scheme 3**

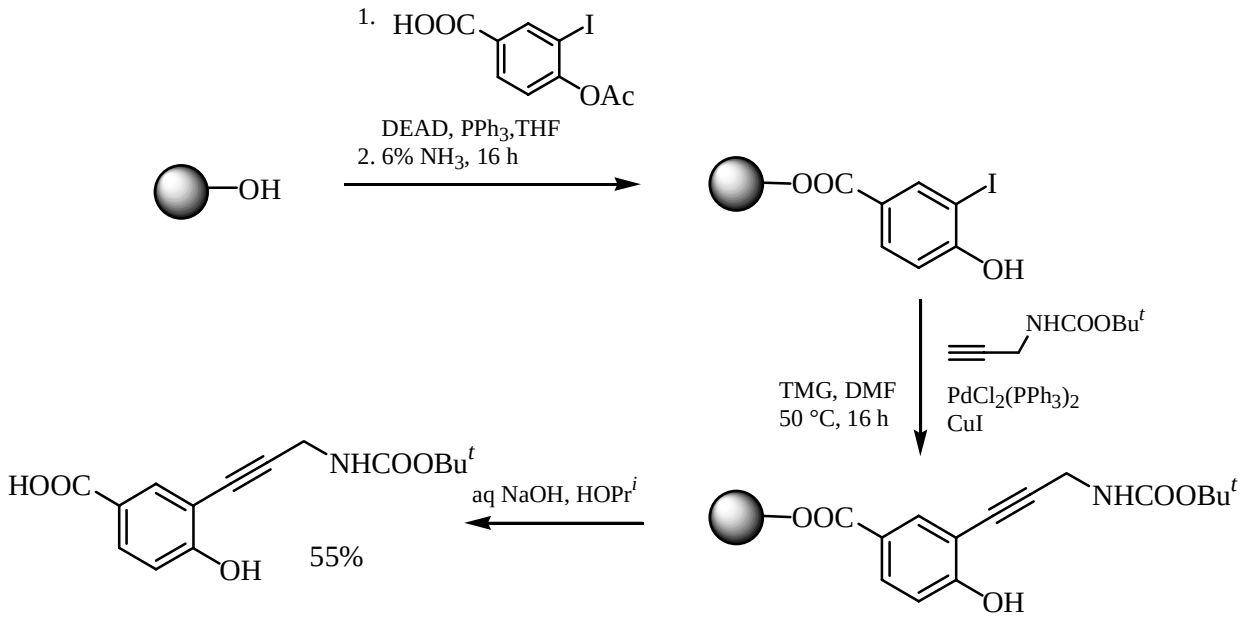



**Scheme 4**

Since then, the reaction has been widely applied to the synthesis of benzofuran derivatives, sometimes using slightly modified conditions.[15] $Pd(OAc)_2PPh_3)_2$ and $PdCl_2(PPh_3)_2$ have been usually employed as precursors of the catalyst species and piperidine, 1,1,3,3-tetramethylguanidine (TMG), and $Et_3N$ have been used as bases. For example, the naturally occurring ailanthoidol was prepared[15d] according to Scheme 5; the procedure has been adapted to a solid phase synthesis (Scheme 6);[15g] application to a homogeneous acetonitrile-water system employing $Pd(OAc)_2$, $Et_3N$, and sulfonated triphenylphosphine P(*m*-$NaSO_3$-$C_6H_4)_3$ (TPPTS) has also been described.[15c]

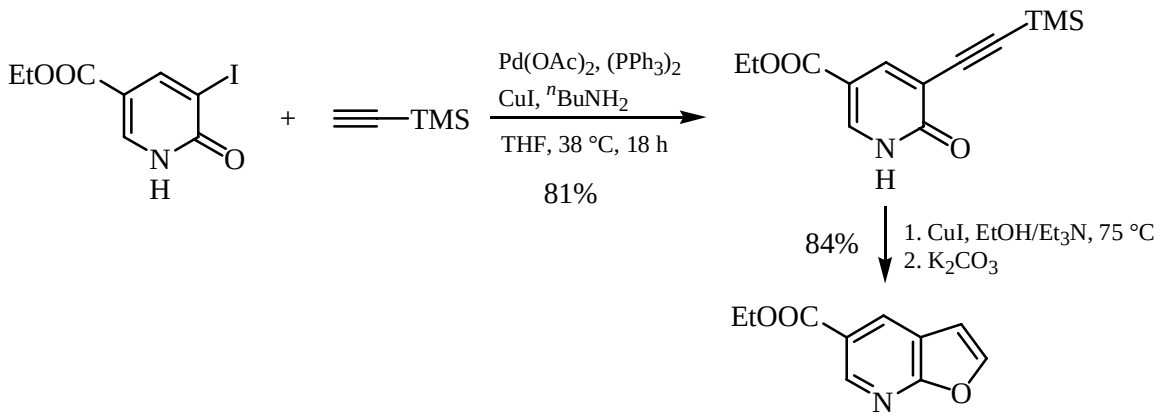



**Scheme 5**



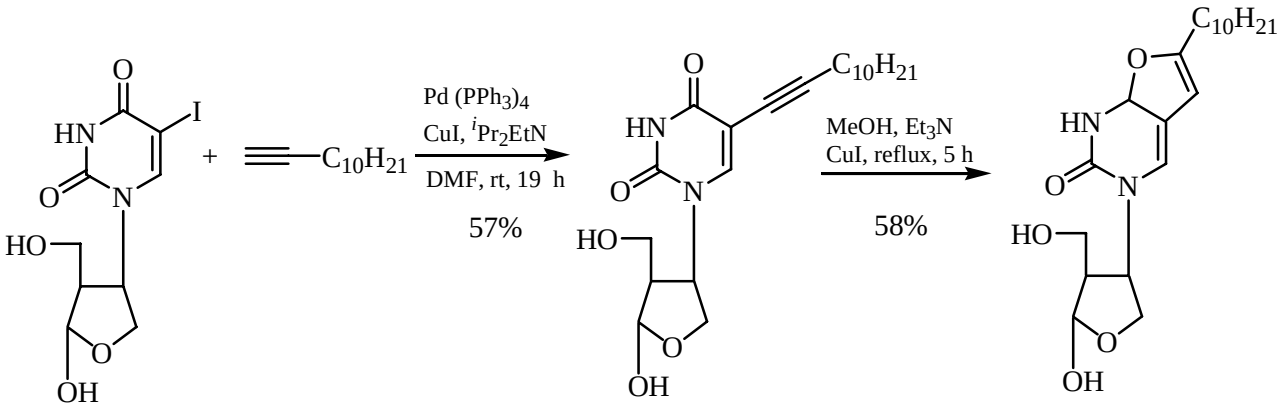

**Scheme 6**

The methodology has been employed to prepare functionalized furo[2,3-*b*]pyridines from iodopyridones and terminal alkynes.[16] With trimethylsilylacetylene the target compound is obtained through a two-step procedure that involves the isolation of the coupling intermediate and its subsequent cyclization (Scheme 7). The reaction rate of the coupling step, in THF, decreases in the order $^{n}BuNH_2$ > $Et_3N$ > $^{i}Pr_2EtN$ > $K_2CO_3$. In addition, the amount of both Pd and Cu catalysts can be reduced to acceptable levels when $^{n}BuNH_2$ is used as the base. With a variety of other terminal acetylenes, however, the coupling product has been found to cyclize under the reaction conditions used for the coupling step upon heating of the initial mixture to 40-60 °C.



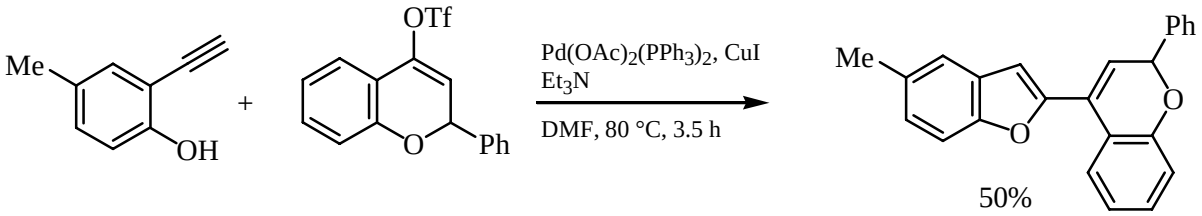

**Scheme 7**

Analogously, deoxynucleoside analogues with unusual bicyclic base moieties, recognized to be potent and selective inhibitors of varicella-zoster virus *in vivo*, have been prepared from 5-iodo nucleosides (Scheme 8).[17]




**Scheme 8**

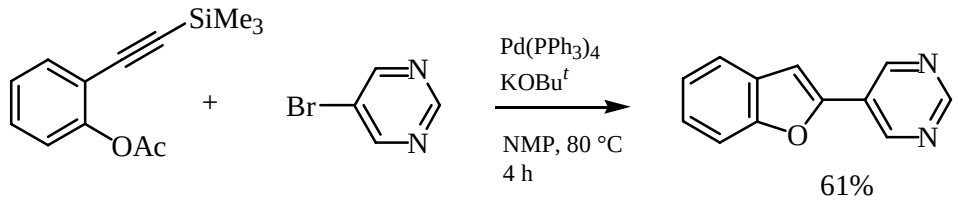
Subsequently, an alternative procedure, based on the palladium-catalyzed coupling of *o*-ethynylphenols with aryl and vinyl halides or triflates, has been developed (Scheme 2).[18] The coupling-cyclization of terminal alkynes with *o*-iodophenols (Scheme 1), in fact, involves the utilization of a specific acetylenic building block for each benzo[*b*]furan, and this may sometimes limit its scope. Coupling of *o*-ethynylphenols with appropriate $C_{sp^2}$ donors allows instead for the synthesis of several 2-vinyl- and arylbenzo[*b*]furans from the same acetylenic building block (Scheme 9).




**Scheme 9**

2,3-Disubstituted benzo[*b*]furans, most probably generated through the competitive oxypalladation-reductive elimination domino mechanism (*vide infra*), have been isolated in some cases. For example, subjection of *o*-ethynylphenol to 5-bromopyrimidine under coupling-cyclization conditions produced 2,3-bis(5-pyrimidyl)benzo[*b*]furan in 33% yield, while the desired 2-(5-pyrimidyl)benzo[*b*]furan was isolated in only 20% yield.

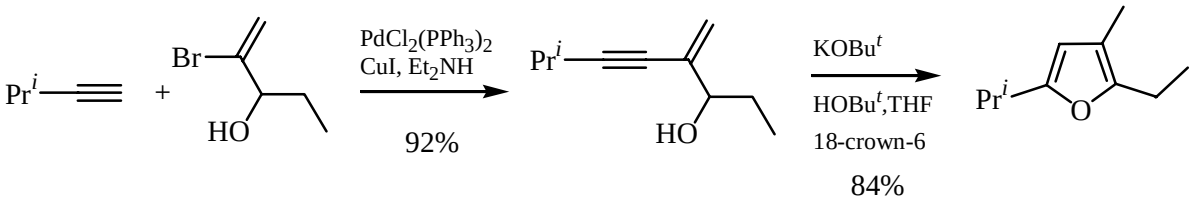
Formation of 2,3-disubstituted benzo[*b*]furans can be prevented by using *o*-[(trimethylsilyl)ethynyl]phenyl acetates as the starting alkynes (Scheme 10). The reaction has been carried out in the presence of $Pd(PPh_3)_4$ and $KOBu^t$, in 1-methyl-2-pyrrolidone (NMP), and involves the following basic steps: a) palladium-catalyzed coupling of *o*-[(trimethylsilyl)ethynyl]aryl acetates with aryl and vinyl halides or triflates, b) deprotection of the hydroxy group of the resultant *o*-alkynylaryl acetates, and c) cyclization. This approach has even the advantage of shortening the synthetic process since *o*-[(trimethylsilyl)ethynyl]aryl acetates are intermediates in the preparation of *o*-ethynylphenols.



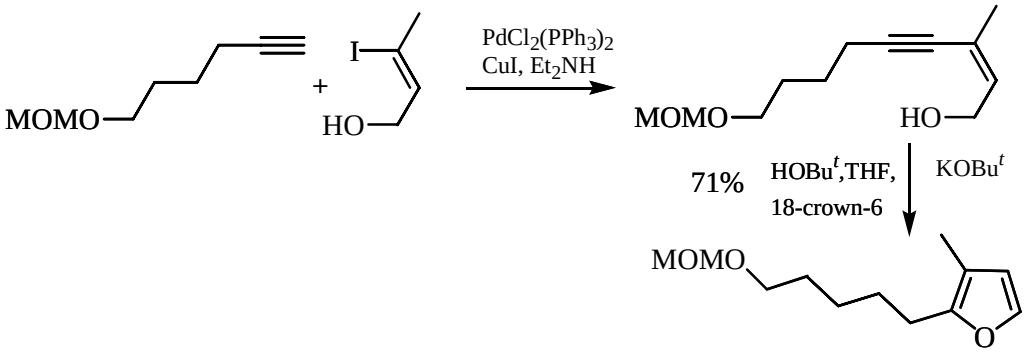

**Scheme 10**

*1.2 Construction of the furan ring*

The same coupling-cyclization methodology can be used for the construction of the furan ring. Unlike the procedure described for the preparation of the benzo[*b*]furan ring, however, coupling intermediates are usually isolated and a strong base is required to allow for the cyclization step. Examples[19] of this chemistry are given by the synthesis of substituted furan derivatives from β-alkynyl allylic alcohols (Scheme 11) and γ-alkynyl allylic alcohols (Scheme 12), available *via* palladium-catalyzed coupling of appropriate terminal alkynes and vinyl halides.



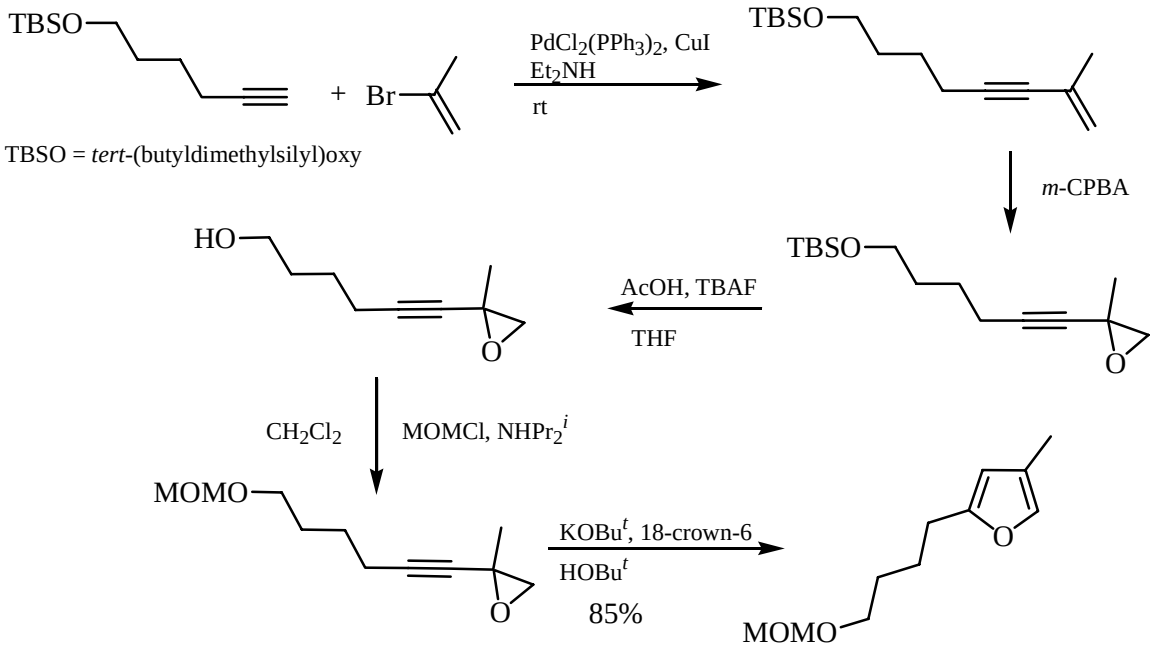

**Scheme 11**



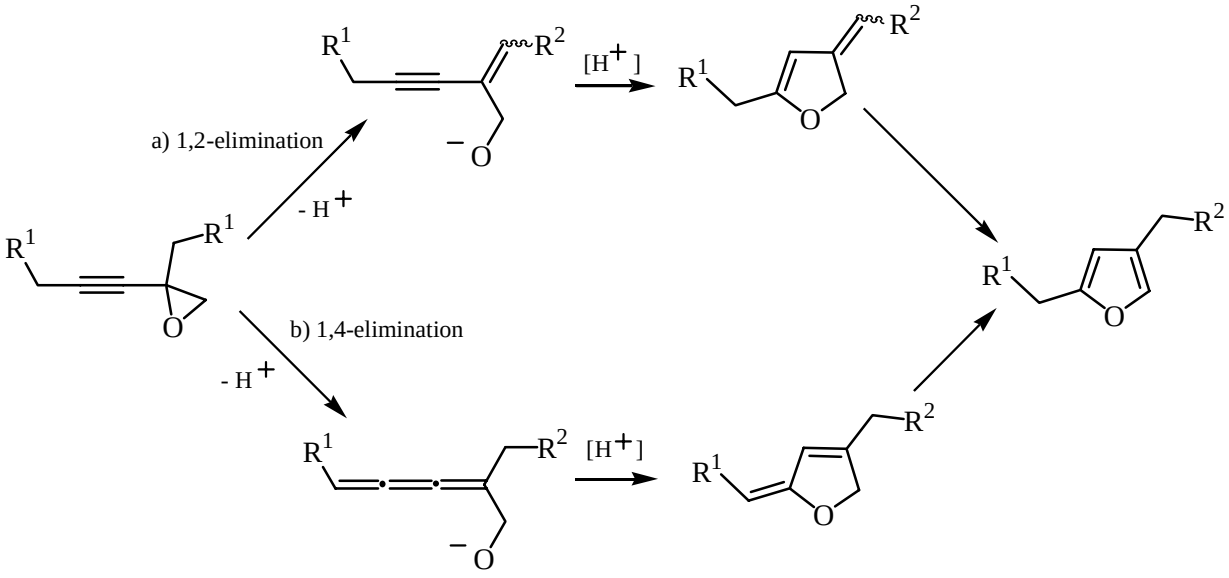

**Scheme 12**

Substituted furan derivatives have also been prepared from terminal alkynes and vinyl halides[20] according to Scheme 13. In this case, the oxygen (pro)nucleophile necessary for the cyclization step is introduced in the acetylenic compound after the coupling step, *via* epoxidation.

Deuterium-labeling studies have shown that the furan ring formation from the acetylenic epoxide proceeds through initial 1,2- and 1,4-elimination, followed by anionic cyclization of the resultant vinylacetylene and cumulene alkoxides, which subsequently isomerize to the furan products (Scheme 14).




**Scheme 13**

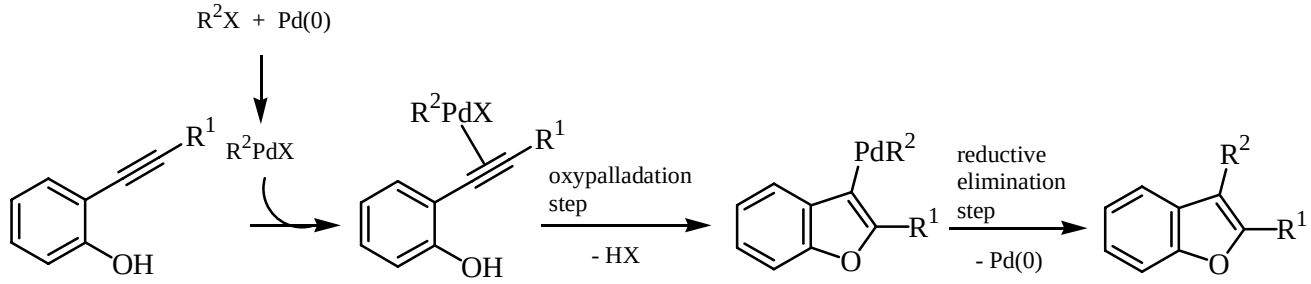



**Scheme 14**

## 2. The oxypalladation-reductive elimination domino reaction

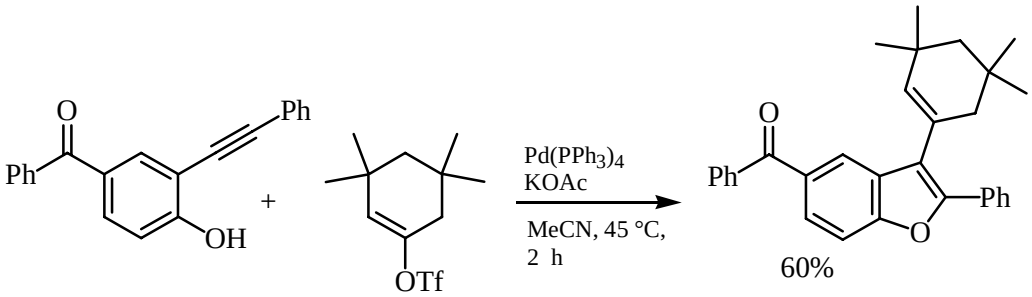
### *2.1 Construction of the benzo[b]furan ring*

This approach to the construction of the benzo[*b*]furan ring, which may provide a remarkable tool for combining the construction of the heterocyclic ring with the creation of significant molecular complexity, is based on (1) the coordination of an *o*-alkynylphenol to an organopalladium complex (formed *in situ* from a palladium catalyst and an appropriate organic precursor) to give an $\eta^3$-alkyne-organopalladium complex, (2) the *trans* addition of the phenolic oxygen and palladium across the carbon-carbon triple bond, (3) the reductive elimination that produces the benzo[*b*]furan derivative and regenerates the active palladium species (Scheme 15).



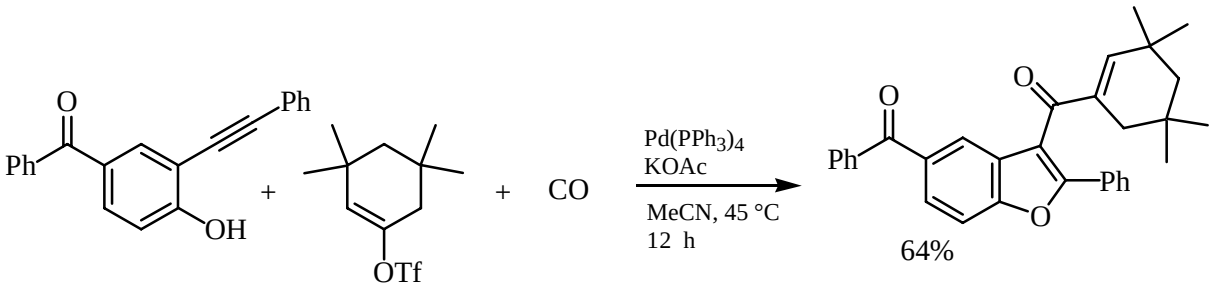

**Scheme 15**

Accordingly, 2,3-disubstituted benzo[*b*]furans have been prepared from *o*-alkynylphenols and vinyl triflates (Scheme 16).[8]



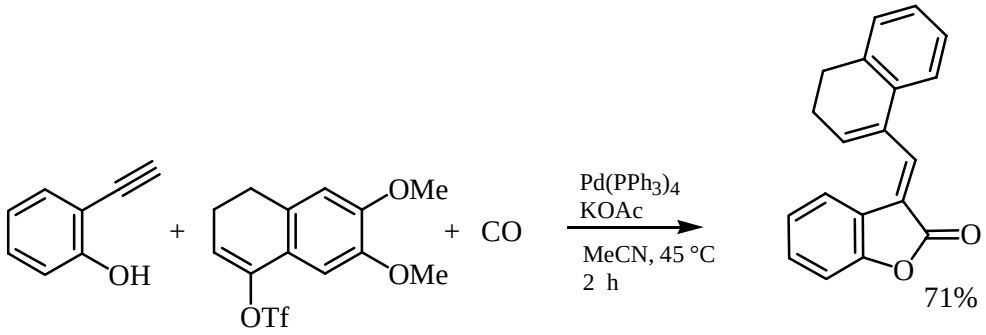

**Scheme 16**

In the presence of carbon monoxide the reaction produces 2-substituted 3-acylbenzo[*b*]furans (Scheme 17).[8]




**Scheme 17**

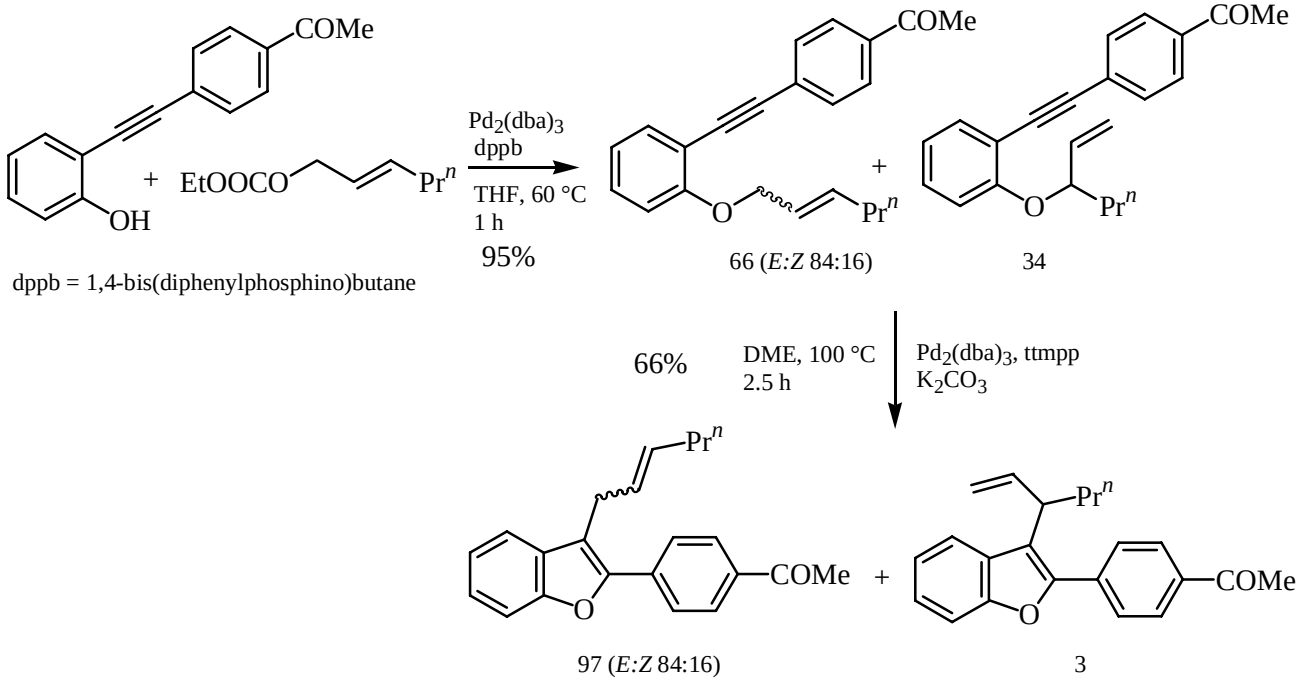
Interestingly, when *o*-ethynylphenols are subjected to the same conditions instead of *o*-alkynylphenols, a divergent behavior is observed and 3-alkylidene-2-coumaranones are isolated in good yield instead of the expected 2-unsubstituted 3-acylbenzo[*b*]furans (Scheme 18).[21] Apparently, the substitution pattern of the acetylenic moiety plays a key role in the product selectivity. A combination of steric and electronic affects could account for this. Depending on the nature of the vinyl triflate, stereoisomeric mixture of 3-alkylidene-2-coumaranones have been obtained.




**Scheme 18**

The oxypalladation-reductive elimination domino reaction has been extended to form 2-substituted 3-allylbenzo[*b*]furans from *o*-alkynylphenols and allyl carbonates. Particularly, 2-substituted 3-allylbenzo[*b*]furans have been prepared through a *palladium-catalyzed O-allylation/oxypalladation/ reductive elimination* sequence.[22] Two basic experimental protocols have been developed: a stepwise method (procedure A), based on the isolation of *o*-alkynylphenyl allyl ethers, prepared through the palladium-catalyzed reaction of *o*-alkynylphenols with allyl carbonates, and their subsequent palladium-catalyzed cyclization; a one-pot procedure (procedure B) that omits the isolation of the *O*-allyl intermediate.

Procedure A appears to be the method of choice when steric differences between the two allylic termini are small (Scheme 19). The cyclization of *O*-allyl ethers in the presence of the electron rich sterically encumbered ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) exhibits remarkable regioselectivity and almost exclusive formation of 3-allylbenzo[*b*]furans with the benzofuryl unit bound to the less substituted allyl terminus is usually observed.

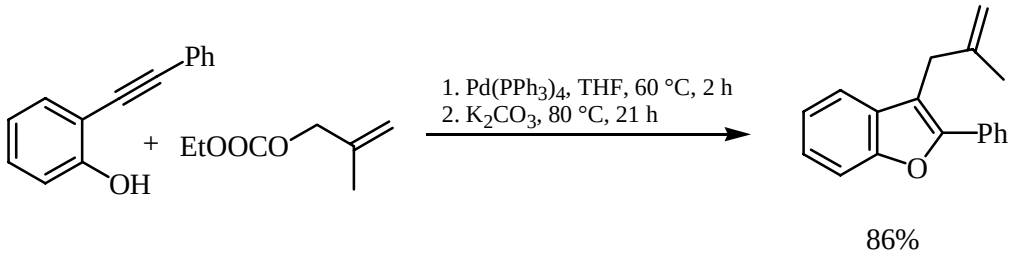



dppb = 1,4-bis(diphenylphosphino)butane

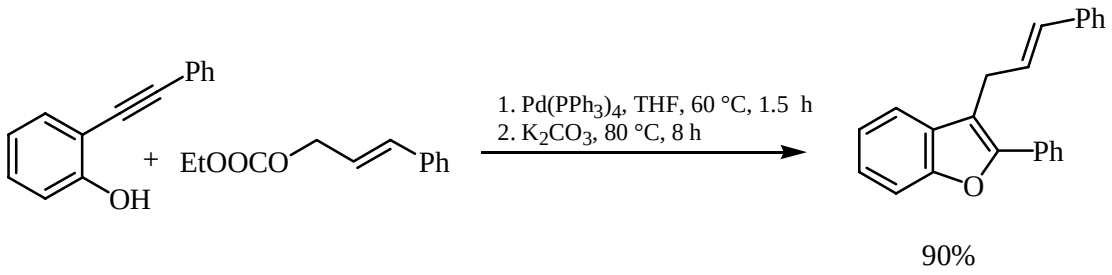
**Scheme 19**

Depending on the nature of allyl carbonates, the *O*-allylation step may afford mixtures of regio- and stereoisomeric *O*-allyl derivatives. However, this does not pose any problem. The regiochemistry of the carbon-carbon bond formed in the cyclization step as well as the stereochemistry of the olefin fragment of 3-allylbenzo[*b*]furans has been found to be almost independent of the regio- and stereochemistry of the *O*-allyl intermediates.

Procedure B has been successfully employed when the reaction proceeds through symmetric $\eta^3$-allylpalladium complexes (Scheme 20) or when the two allylic termini are markedly different from a steric point of view (Scheme 21).

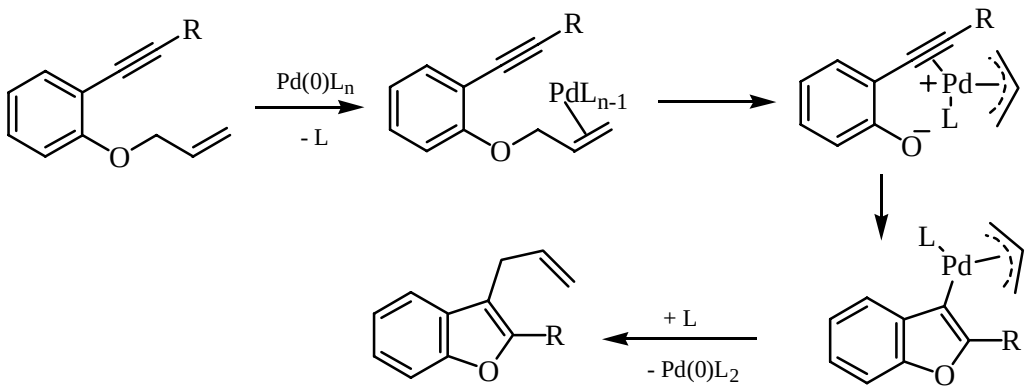



**Scheme 20**



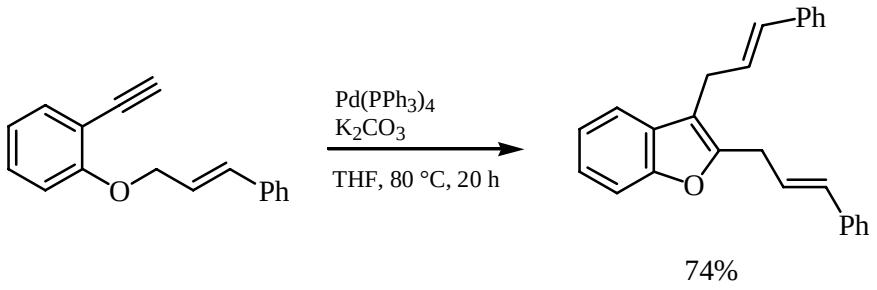

**Scheme 21**

Most probably, the cyclization of *O*-allyl ethers proceeds through the basic steps outlined in Scheme 22 for the parent *O*-allyl ether.




**Scheme 22**

With *O*-allyl ethers derived from *o*-ethynylphenol the reaction fails to give the corresponding 2-unsubstituted 3-allylbenzo[*b*]furans under standard conditions. Competitive palladium-catalyzed allylation of the acetylenic moiety[23] may account for this. Such a competitive reaction may explain the formation of 2,3-dicinnamylbenzo[*b*]furan upon subjection of (*o*-ethynylphenyl)cinnamyl ether to $Pd(PPh_3)_4$ and $K_2CO_3$ (Scheme 23).[24]

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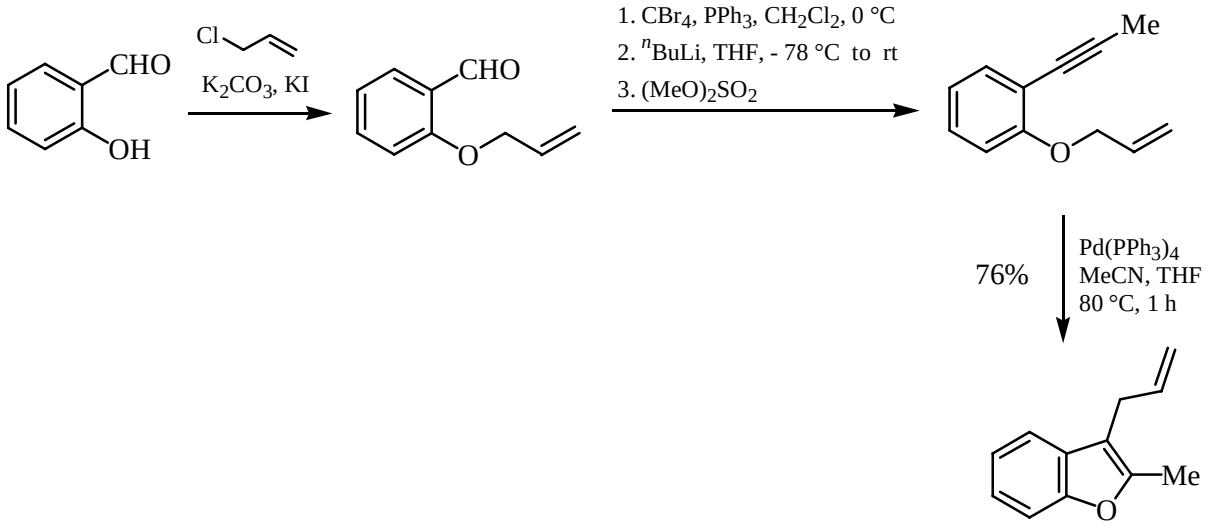
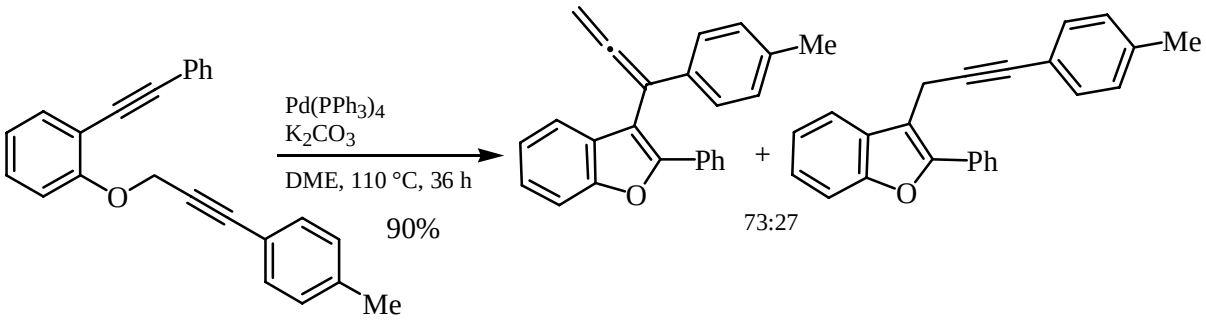
**Scheme 23**

The starting *o*-alkynylphenyl allyl ethers necessary for the palladium-catalyzed synthesis of 2-substituted 3-allylbenzo[*b*]furans can also be prepared from *o*-hydroxybenzaldehyde (Scheme 24).[25]




**Scheme 24**

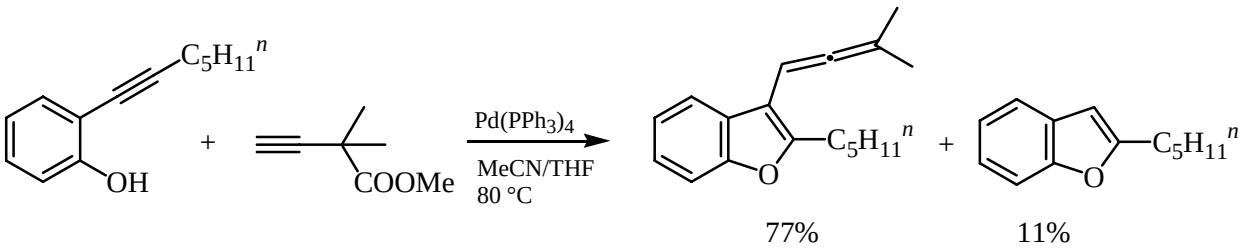
A reaction similar to that of *o*-alkynylphenyl allyl ethers has been applied to propargylic *o*-alkynyl phenyl ethers. The reaction affords 2-substituted 3-allenylbenzo[*b*]furans as the main products.[26] Formation of isomeric 3-propargyl derivatives has been in some cases observed (Scheme 25). The reaction is considered to involve the intermediacy of $\eta^3$-alkyne-σ-allenyl- and $\eta^3$-alkyne-σ-propargylpalladium complexes.




**Scheme 25**

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

2-Substituted 3-allenylbenzo[*b*]furans have been prepared even through the palladium-catalyzed reaction of *o*-alkynylphenols with propargyl carbonates (Scheme 26).[27] Satisfactory results have been obtained with tertiary propargylic carbonates, whereas with secondary propargyl carbonates the desired allenyl derivatives have been isolated in low yield and with primary propargyl carbonates no stable products have been obtained. Formation of significant amount of the parent benzo[*b*]furan product derived from direct cyclization of the starting phenol which does not require palladium catalysis has been observed.

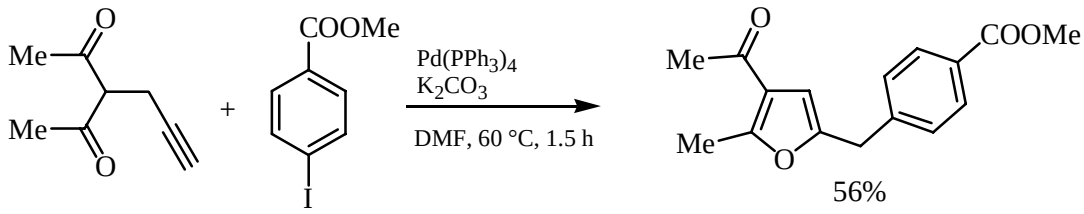



**Scheme 26**

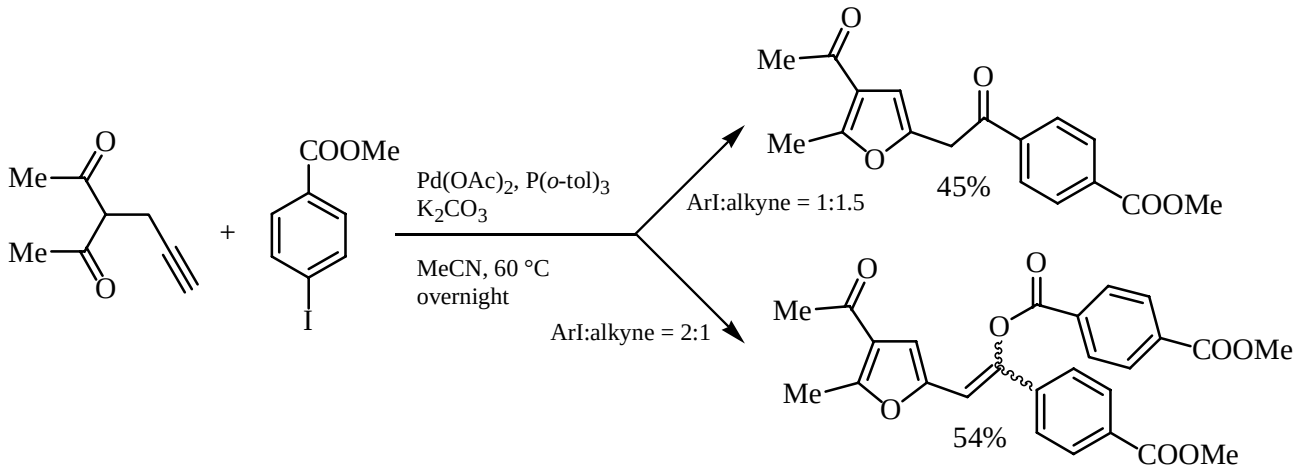
It is worth emphasizing that the procedure described in Scheme 26 affords 3-allenylbenzo[*b*]furans containing the benzofuryl unit linked to the less substituted terminus of the allenyl system, while 3-allenylbenzo[*b*]furans prepared from propargylic *o*-alkynyl phenyl ethers (Scheme 25) contain the benzofuryl unit linked to the more substituted terminus of the allenyl system.

*2.2 Construction of the furan ring*

A variety of substituted furans have been prepared from 1,3-dicarbonyl compounds with a carbon-carbon triple bond close to the enolizable part of the molecule through the oxypalladation-reductive elimination domino process. 2-Propargyl-1,3-dicarbonyl compounds have been employed to develop a straightforward synthesis of 2,3,5-trisubstituted furans (Scheme 27).[28] In the presence of carbon monoxide, the reaction produces 2,3,5-trisubstituted furans containing a 5-acylmethyl group or its enol ester depending on the aryl iodide to alkyne ratio (Scheme 28).[29]

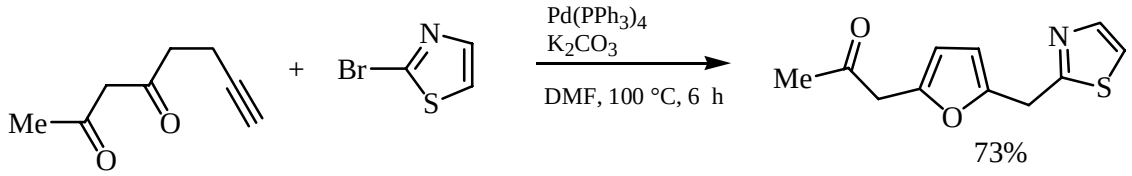



**Scheme 27**




**Scheme 28**

Alkyl 3-oxo-6-heptynoates have been used in this alkyne cyclization chemistry to synthesize 2,5-disubstituted furans (Scheme 29).[30] The reaction has been found to be highly chemoselective. No evidence has been obtained of carboannulation products. The reaction temperature has been proved to be crucial for the success of the methodology. The $K_2CO_3$ to alkyne ratio also affects the reaction outcome. The highest yields of furan products have been obtained with aryl halides containing electron-withdrawing substituents.




**Scheme 29**

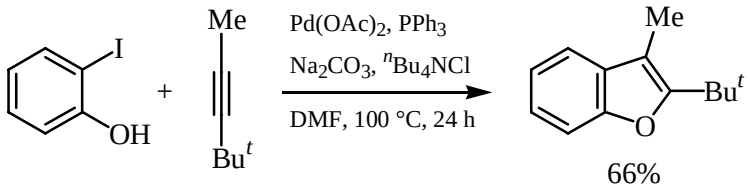
## 3. The carbopalladation-cyclization reaction

*3.1 Construction of the benzo[b]furan ring*

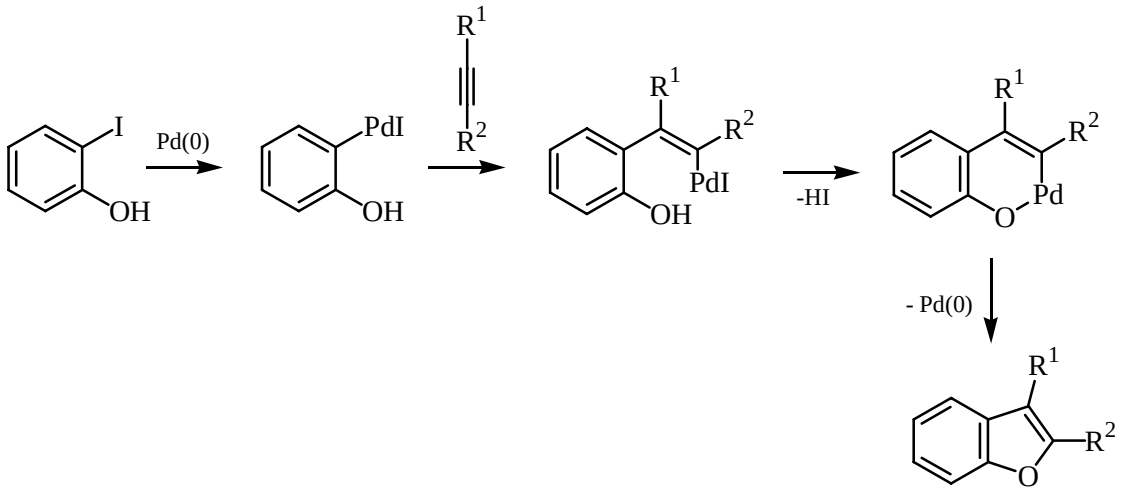
The construction of the benzo[*b*]furan ring *via* the carbopalladation-cyclization process is based on the addition of an organopalladium complex, containing an oxygen nucleophile, to the carbon-carbon triple bond of an alkyne followed by the cyclization of the resultant carbopalladation adduct.

Such an approach has been employed in the synthesis of 2,3-disubstituted benzo[*b*]furans[31] from *o*-iodophenols and internal alkynes (Scheme 30). The reaction is suggested to proceed *via* (1) oxidative addition of the aryl iodide to Pd(0), (2) *syn* addition of the resultant σ-arylpalladium complex to the carbon-carbon triple bond (the carbopalladation step),[32] (3) halide displacement by the oxygen to form a six-membered-ring oxygen-containing palladacycle, and (4) reductive elimination (Scheme 31).

The regiochemistry of the carbopalladation step follows the pattern established in the related construction of nitrogen-containing heterocycles[33] and hydroarylation and hydrovinylation reactions,[34] and is mainly controlled by steric and coordinating effects. When steric effects control the reaction, the aryl group adds preferentially to the less hindered end of the alkyne and the palladium moiety to the more hindered end. Coordinating effects control the carbopalladation step so as to direct preferentially the palladium to the acetylenic carbon close to the coordinating group and the organic fragment to the other acetylenic carbon.



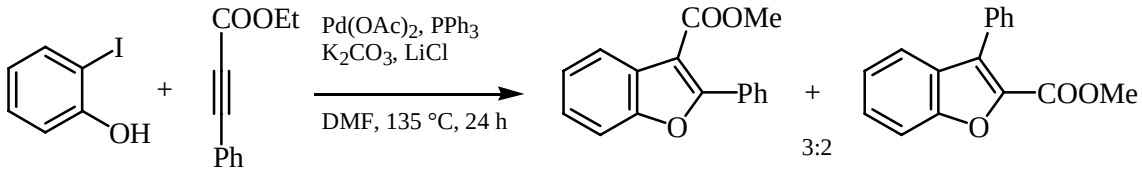

**Scheme 30**




**Scheme 31**

Hindered silylalkynes give the corresponding 2-silyl-3-substituted benzo[*b*]furans in high yields. Since the silyl-substituted benzo[*b*]furans are readily desilylated to 3-substituted benzo[*b*]furans by fluoride salts, this process nicely complements the palladium-catalyzed coupling of *o*-iodophenols with terminal alkynes[12] which affords 2-substituted benzo[*b*]furans. Sometimes, most probably because of the high reaction temperature required, reduced regioselectivity is observed (Scheme 32).

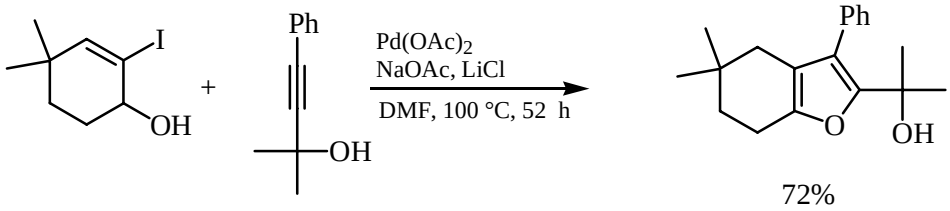
The reaction has been applied to the preparation of 3-hydroxyalkylbenzo[*b*]furans.[32]




**Scheme 32**

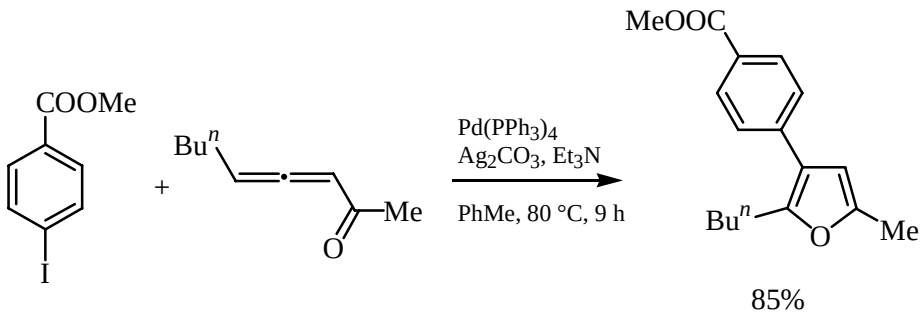
*3.2 Construction of the furan ring*

Starting from β-iodoallylic alcohols, the above procedure has been applied to the synthesis of substituted furan derivatives (Scheme 33).[33]



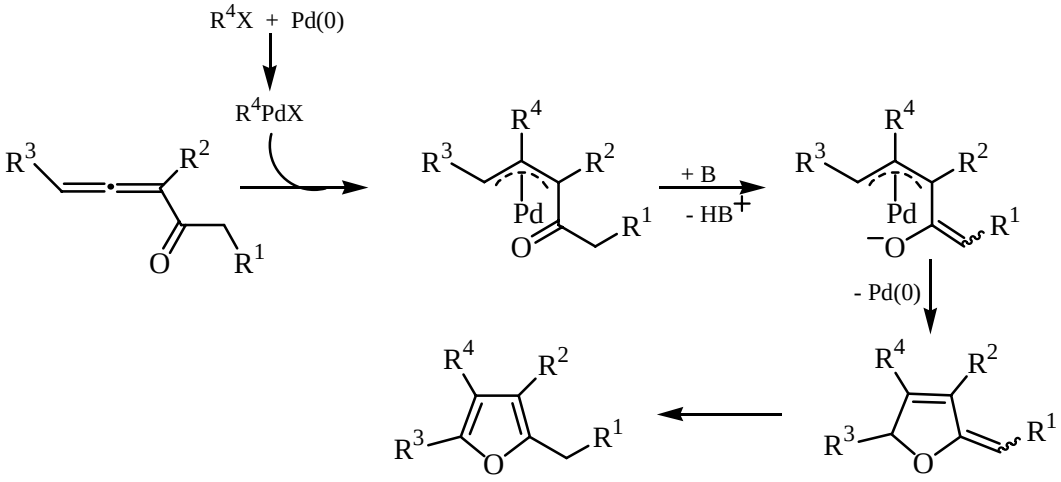

**Scheme 33**

The carbopalladation-cyclization methodology has been employed for the preparation of polysubstituted furans from 1,2-dienyl ketones and organic halides.[34] The synthesis has been carried out in the presence of $Pd(PPh_3)_4$, $Ag_2CO_3$ and $Et_3N$ (Scheme 34). A catalytic amount of $Ag_2CO_3$ (10%) is crucial to this reaction. Both electron-rich and electron-poor aryl halides can be used and, depending on the structure of allenyl ketones and organic halides, substituents at different position of the furan ring can be introduced.



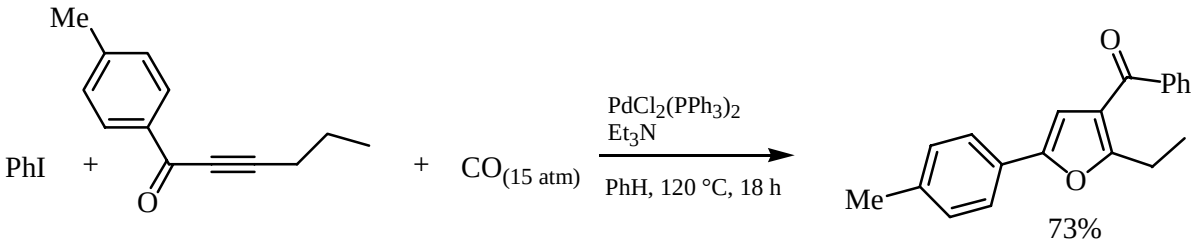

**Scheme 34**

The reaction may be envisioned to proceed according to the mechanism outlined in Scheme 35. The carbopalladation step produces an $\eta^3$-allylpalladium complex, very likely via the intermediacy of a σ-allylpalladium complex, which subsequently undergoes an intramolecular nucleophilic attack by the oxygen to give a five membered-ring heterocycle that isomerizes to the furan product.



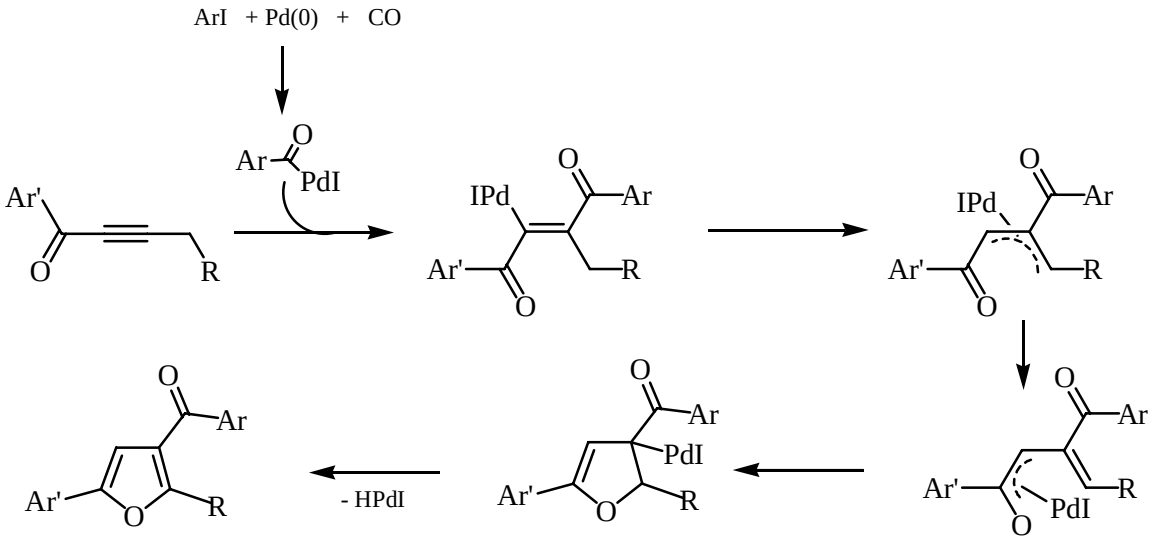

**Scheme 35**

α,β-Ynones are another class of compounds that have been subjected to the carbopalladation-cyclization approach to furans. In the presence of aryl iodides, carbon monoxide, and a palladium catalyst they have been converted into substituted furans incorporating one molecule of carbon monoxide (Scheme 36).[35]




**Scheme 36**

The reaction is suggested to proceed according to the mechanism outlined in Scheme 37.




**Scheme 37**

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