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A REVIEW

ORGANOPALLADIUM CATALYZED HETEROANNULATIONS: APPLICATION OF ORGANOPALLADIUM REAGENTS IN THE 'SYNTHESIS OF BENZOFURANS'

KIRAN RAO and D. KISHORE*

Department of Chemistry, Banasthali Vidyapith, BANASTHALI – 304022 (Raj) INDIA
e–mail: kishoredharma@yahoo.co.in

ABSTRACT

The present review gives an overview of the application of organopalladium reagents in synthesis of benzo[b]furans.

Key words : Organopalladium, Benzo[b]furan, Heteroannulation

INTRODUCTION

The broad spectrum of medicinal properties[1–10] associated with benzofuran nucleus has triggered the development of a variety of methods for the synthesis of these molecules and has led to an impressive armoury of synthetic strategies[11–14] to be devised in the literature for the synthesis of this class of compounds.

As the chemists have been now turning their attention towards "**organometallic assisted**" organic syntheses, the present review gives an overview of this technique to the synthesis of benzo[b]furans. The **use of organometallic reagents** offer unprecedented opportunities to the organic chemists in synthesis. There are many reasons for this. Virtually every organic functional group coordinates to some transition metal and upon coordination, the reactivity of that functional group is often dramatically altered. Electrophilic species can become nucleophilic and vice–versa. Stable compounds may become reactive and highly reactive compounds may become stabilized. Normal reactivity patterns of functional groups can be inverted and unconventional (impossible under normal conditions) transformations can be achieved with facility. Highly reactive, normally unavailable reaction intermediates can be generated, stabilized and used as efficient reagents in synthesis. Most of the organometallic reactions are highly specific, able to discriminate between structurally similar sites, thus reducing the need for bothersome "protection–deprotection" sequences that plague conventional organic synthesis. Finally, by careful selection of substrate and metal, multistep cascade sequences can be generated to form several bonds in a single process in which the metal "stitches together" the substrate.

One of the fastest growing area in the field of organometallic chemistry is the **use of organopalladium reagents** in organic synthesis.

The **"Palladium chemistry"** involving heterocycles has its own unique characteristics due to its different structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds which leads to a new and unconventional synthetic application. It is because of this reason that organopalladium complexes have found wide spread applications in organic syntheses. The tardy acceptance of these complexes are due to the following reasons:

(i) The real synthetic utility lies in the very wide range of organic transformations promoted by palladium catalysts and in the specificity[15] and functional group tolerance in most of these processes.

(ii) They permit unconventional transformations and give the chemist a wide latitude in the selection of starting materials.

(iii) Palladium complexes are among the most readily available, easily prepared and easily handled of transition metal complexes.

(iv) The rich reaction chemistry that palladium complexes display is due to the facile redox interchange between the two oxidation states viz +2 state and zero valent (metallic state) which palladium enjoys. Each oxidation state has its own unique chemistry.

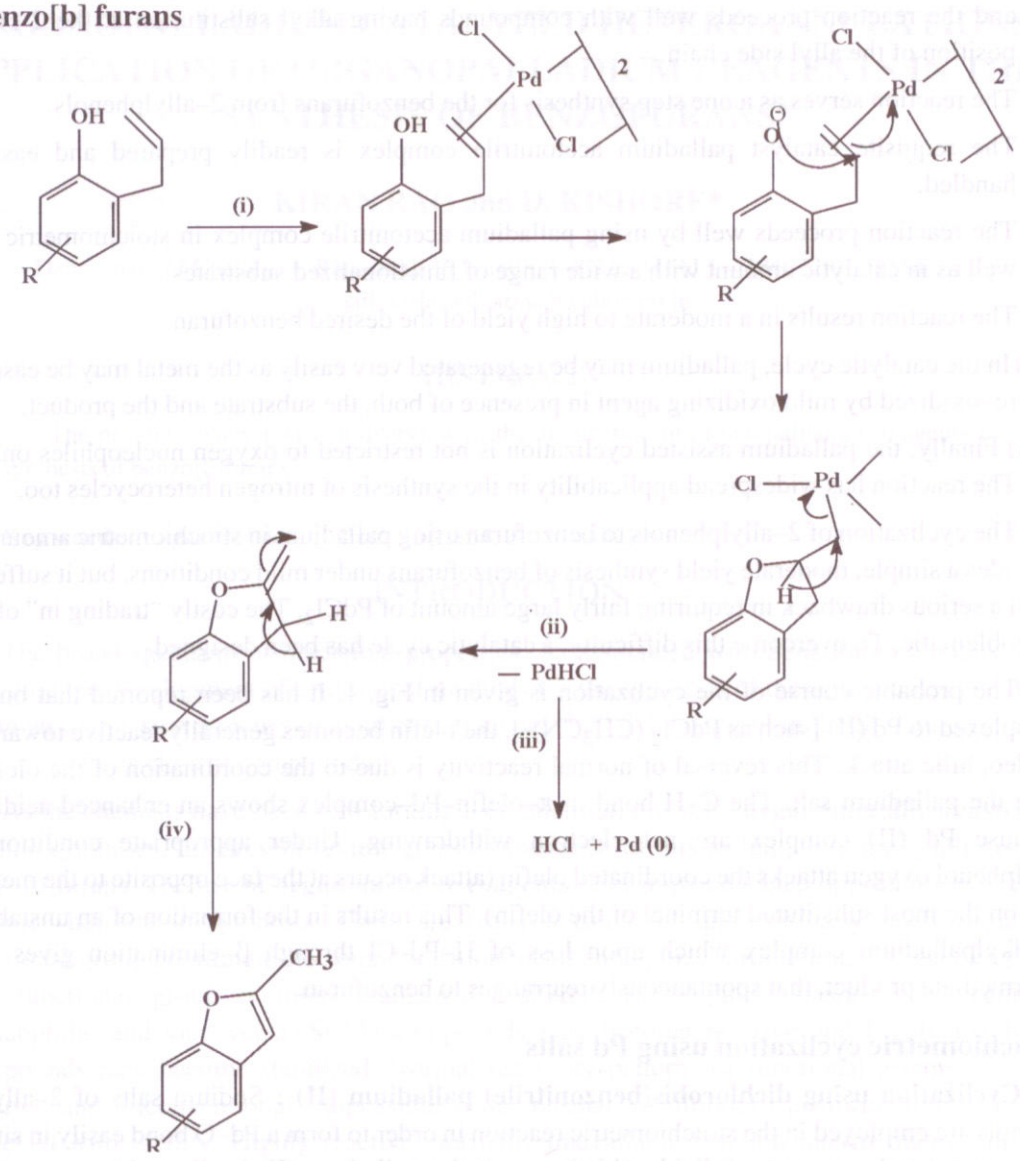
(v) Several methods are available in the literature for the detachment of the metal from the product. The exposure of σ–alkyl palladium complex to hydrogen, at temperature above -20^0 C results in an easy detachment of the metal from the product.[16] This point is very important in organic synthesis since, the metal is normally not desired in the final product.

A large number of palladium assisted heterocyclization processes have been reported in the literature[17]. Benzofurans are the focus of many recent reports on transition metal–mediated heteroannulation especially alkyne–based palladium catalyzed reactions.[18–22] For these reactions, either o–alkynylphenols or o–iodophenols are the starting substrates and the reactions are carried out using a palladium catalyst and a copper salt[23] as co–catalyst in the presence of amine base in an organic solvent. However , this single step coupling–cyclization was found to be less efficient when the starting o–iodophenols contain additional substituents[24,25] especially base labile nitro groups.

Out of the several different novel synthetic methods, which have been developed in the literature, the most practical one appears to be the palladium assisted synthesis of benzofurans and its derivatives from 2–allylphenols. The palladium assisted heteroannulation of 2–allyl-phenols provides a highly innovative and convenient synthetic entry into the benzofuran nucleus. The intriguing features of this strategy are:

(i) It required allyl aryl ether substrate and the intramolecular cyclization proceeded readily and in high yield with 2–allylphenol.

Mechanism of palladium induced heterocyclization of 2–allylphenols to benzo[b] furans



R = Br, Cl, Me, NO_2, OMe, COOMe, COOEt, CHO groups may be present on different positions in the carbocylclic ring.

(i) $PdCl_2 (CH_3 CN)_2$ (ii) β–elimination

(iii) Reductive elimination (iv) Rearrangement

Fig. 1

(ii) The reaction is compatible with a wide range of functional groups on the phenol nucleus and the reaction proceeds well with compounds having alkyl substitution at the 2 or 3 position of the allyl side chain.

(iii) The reaction serves as a one step synthesis for the benzofurans from 2–allylphenols.

(iv) The requisite catalyst palladium acetonitrile complex is readily prepared and easily handled.

(v) The reaction proceeds well by using palladium acetonitrile complex in stoichiometric as well as in catalytic amount with a wide range of functionalized substrates.

(vi) The reaction results in a moderate to high yield of the desired benzofuran.

(vii) In the catalytic cycle, palladium may be regenerated very easily as the metal may be easily re–oxidized by mild oxidizing agent in presence of both, the substrate and the product.

(viii) Finally, the palladium assisted cyclization is not restricted to oxygen nucleophiles only. The reaction has widespread applicability in the synthesis of nitrogen heterocycles too.

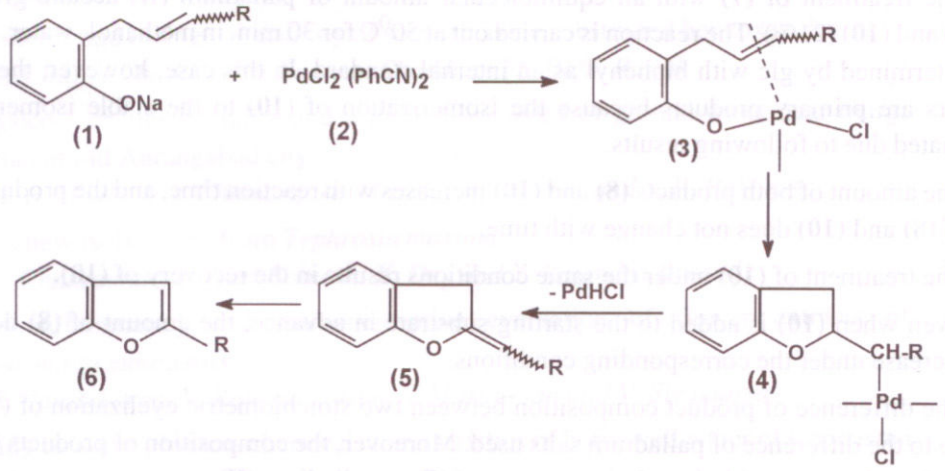
The cyclization of 2–allylphenols to benzofuran using palladium in stiochiometric amounts provides a simple, moderate yield synthesis of benzofurans under mild conditions, but it suffers from a serious drawback in requiring fairly large amount of $PdCl_2$. The costly "trading in" of it is problematic. To overcome this difficulty, a catalytic cycle has been designed.

The probable course of the cyclization is given in Fig. 1. It has been reported that once complexed to Pd (II) [such as $PdCl_2$ $(CH_3CN)_2$], the olefin becomes generally reactive towards nucleophilic attack. This reversal of normal reactivity is due to the coordination of the olefin with the palladium salt. The C–H bond in π–olefin–Pd–complex shows an enhanced acidity because Pd (II) complex are net electron withdrawing. Under appropriate conditions, allylphenol oxygen attacks the coordinated olefin (attack occurs at the face opposite to the metal and on the most substituted terminal of the olefin). This results in the formation of an unstable σ–alkylpalladium complex which upon loss of H–Pd–Cl through β–elimination gives an intermediate product, that spontaneously rearranges to benzofuran.

Stoichiometric cyclization using Pd salts

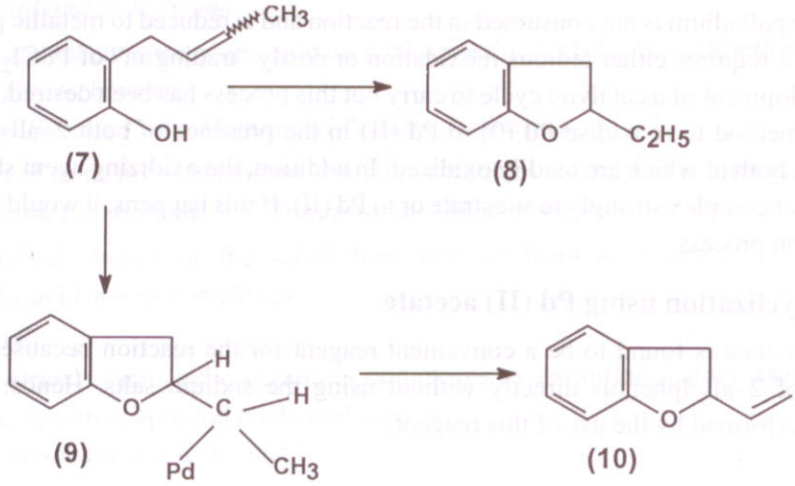
(a) Cyclization using dichlorobis(benzonitrile) palladium (II) : Sodium salts of 2–allyl-phenols are employed in the stoichiometric reaction in order to form a Pd–O bond easily in situ. An equimolecular amount of dichlorobis(benzonitrile) palladium (II) is allowed to react with the sodium salts in the presence of THF, which produces a homogeneous solution, that deposits a white precipitate after 30–60 min. Treatment of either the solution or the suspension with triethylamine produces a light yellow, homogeneous solution, which deposites metallic palladium over a course of 2–4 h. Filteration followed by evaporation gives the crude benzofuran, often as the sole organic product.

It has been reported that the treatment of 2–allylphenol with palladium on charcoal at 500–800^{0}C gives 2–methylbenzofuran.[26] Compared with this, the present method provides a very convenient synthetic method for 2–substituted benzofurans.



The formation of 2–substituted benzofurans (**6**) from sodium salt of 2–allylphenols (**1**) using dichlorobis(benzonitrile) palladium (II) (**2**), is elucidated in Scheme –1. It involves intramolecular oxypalladation of (**3**) to give the intermediate (**4**) followed by β–elimination of PdHCl species[27] to give (**6**).

In the oxypalladation intermediate (**4**), where R = H or Ph, the hydrogen from the C–2 carbon (β–hydrogen) is eliminated with palladium. The elimination gives exo–methylbenzofuran (**5**) which eventually isomerizes to the thermodynamically stable 2–substituted benzofuran (**6**).



(b) Cyclization using palladium (II) acetate : Palladium (II) acetate has been found to cause the cyclization of 2–allylphenols (**7**).

The treatment of (**7**) with an equimolecular amount of palladium (II) acetate gives (**8**) (20%) and (**10**) (21%). The reaction is carried out at 50^0C for 30 min. in methanol–water. Yields are determined by glc with biphenyl as an internal standard. In this case, however, these two isomers are primary products because the isomerization of (**10**) to the stable isomer (**8**) is eliminated due to following results.

(i) The amount of both products (**8**) and (**10**) increases with reaction time, and the product ratio of (**8**) and (**10**) does not change with time.

(ii) The treatment of (**10**) under the same conditions results in the recovery of (**10**).

(iii) Even when (**10**) is added to the starting substrate in advance, the amount of (**8**) does not increase under the corresponding conditions.

The difference of product composition between two stoichiometric cyclization of (**7**) may be due to the difference of palladium salts used. Moreover, the composition of products (**8**) and (**10**) is found to vary with the relative amount of (**7**) to palladium (II) acetate.

Although the stoichiometric cyclization reaction tolerates a wide range of functional groups in the phenol substrate but gives a low yield of the cyclized products, while catalytic cyclization (vide infra) produces a much better yield of the cyclized products. So, catalytic cyclization is preferred more than stoichiometric cyclization.

Catalytic cyclization

Although the stoichiometric cyclization provides a simple and convenient synthetic entry into the benzofuran nucleus under mild conditions but it suffers from the requirement of one mole equivalent (the stoichiometric amount) of fairly expensive palladium chloride reagent. Although the palladium is not consumed in the reaction and is reduced to metallic palladium but recycling of it requires either tedious reoxidation or costly "trading in" of $PdCl_2$ salt. For this reason, development of a catalytic cycle to carry out this process has been desired. The problem is to find a method to reoxidise Pd (0) to Pd (II) in the presence of both 2–allylphenols and benzofurans, both of which are readily oxidized. In addition, the oxidizing agent should be such that it does not complex strongly to substrate or to Pd (II). If this happens, it would interfere with the cyclization process.

Catalytic cyclization using Pd (II) acetate

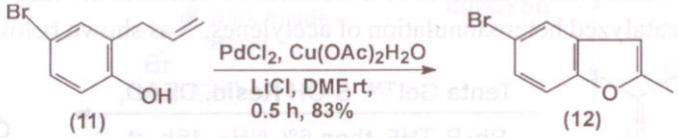
Pd (II) acetate is found to be a convenient reagent for the reaction because it causes the cyclization of 2–allylphenols directly without using the sodium salts. Hence, the catalytic reaction is performed by the use of this reagent.

By considering the fact that reduced palladium metal is readily reoxidized with cupric salt and molecular oxygen as is well known in the Wacker process,[28] the reaction of 2–allylphenols (10 m mol) is carried out in methanol–water solvent in the presence of a catalytic amount of Pd (II) acetate (0.2 m mol) and cupric acetate (5 m mol) under oxygen atmosphere. The reaction gives 2–substituted benzofurans catalytically with palladium (II) acetate.

Instead of Pd (II) acetate the heteroannulation of 2–allylphenols may also be carried out by using $PdCl_2$ $(CH_3CN)_2$ under nitrogen atmosphere. This reaction also gives satisfactory results.

Application of organopalladium reagents in the synthesis of benzofurans

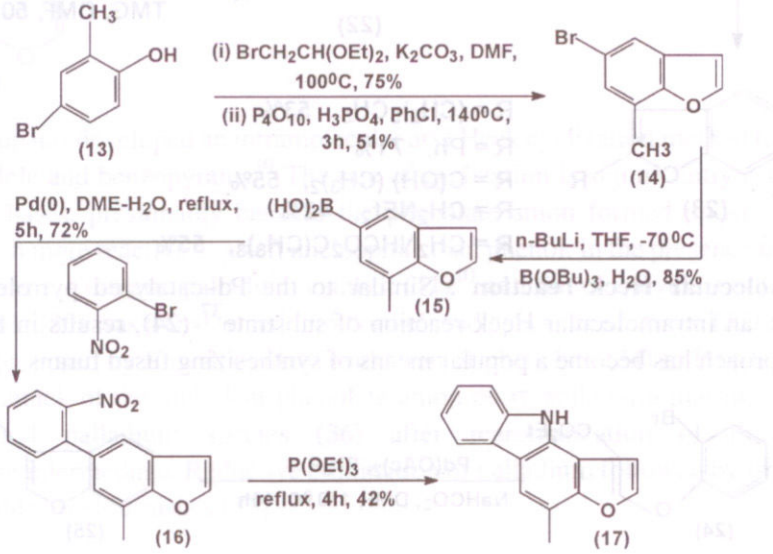
(a) Oxidative coupling / cyclization : The oxidative couplings of furan or benzo[b]furan with olefins suffers from inefficiency.[29] These reactions consume at least one equivalent of expensive palladium acetate[30] and are therefore, of limited synthetic utility.



The phenolic oxygen on 2–allyl–4–bromophenol (**11**) readily undergoes oxypalladation using a catalytic amount of $PdCl_2$ and three equivalents of $Cu(OAc)_2$, to give the corresponding benzofuran (**12**).

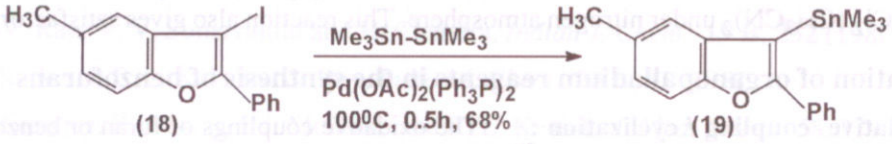
b) Suzuki coupling

(i) Furans as electrophiles : Timari's total synthesis of (**17**) commenced with alkylation of bromocresol (**13**) with bromoacetaldehyde diethyl acetal and P_4O_{10} promoted cyclization to furnish 5–bromo–7–methyl benzofuran[31] (**14**), by the sequence of reactions shown below.

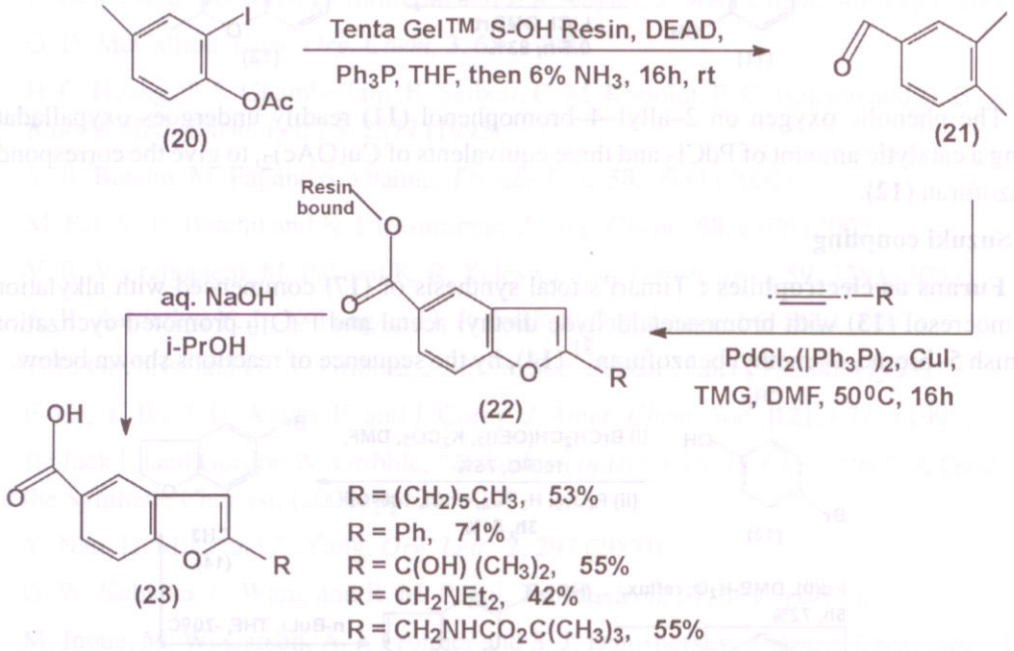


The Suzuki coupling of boronic acid (**15**), derived from (**14**), on reaction with o–bromonitrobenzene yield biaryl (**16**). Nitrene generation achieved via deoxgenation of nitro compound (**16**) using triethyl phosphate, is followed by cyclization to frostifoline (**17**).

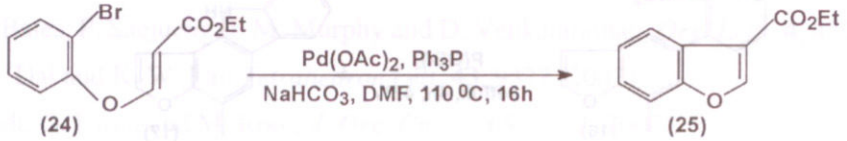
(c) Stille Coupling : This method is more suitable to base–sensitive substrate. Pd–catalyzed coupling of a halofuran or halobenzofuran (**18**) with hexabutylditin[32] give (**19**).



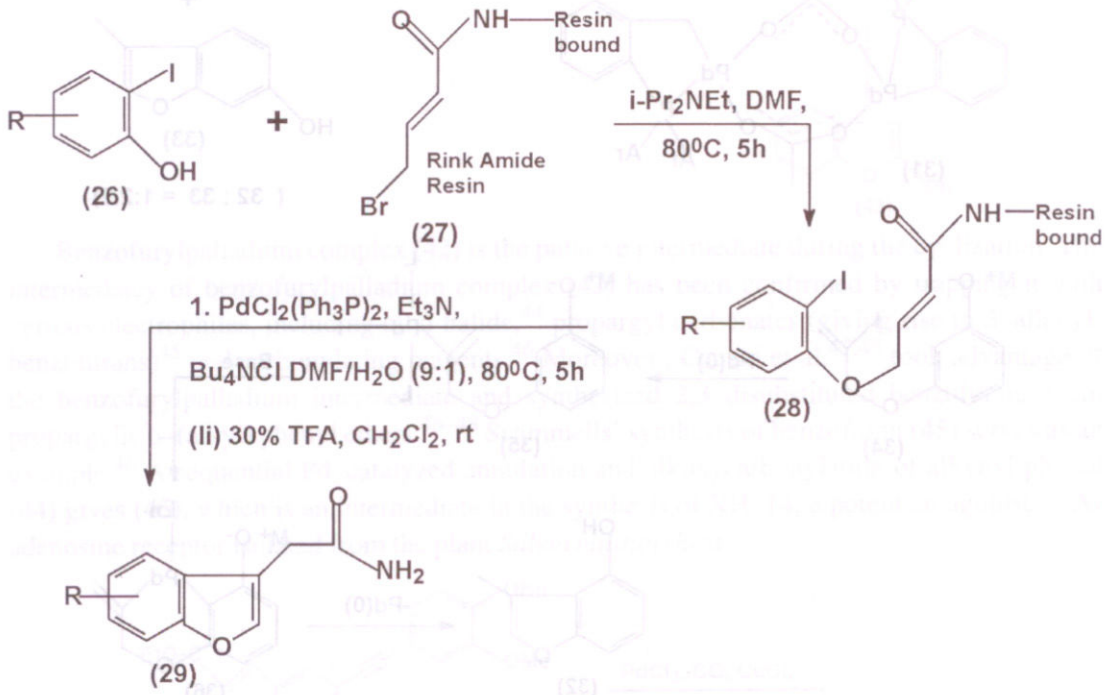
(d) Sonogashira reaction : Adapting the well–established Sonogashira solution phase reaction conditions,[33–35] a solid phase synthesis of 2–substituted benzofurans (**23**) was accomplished from (**22**) via Pd–catalyzed heteroannulation of acetylenes,[36] as shown below:



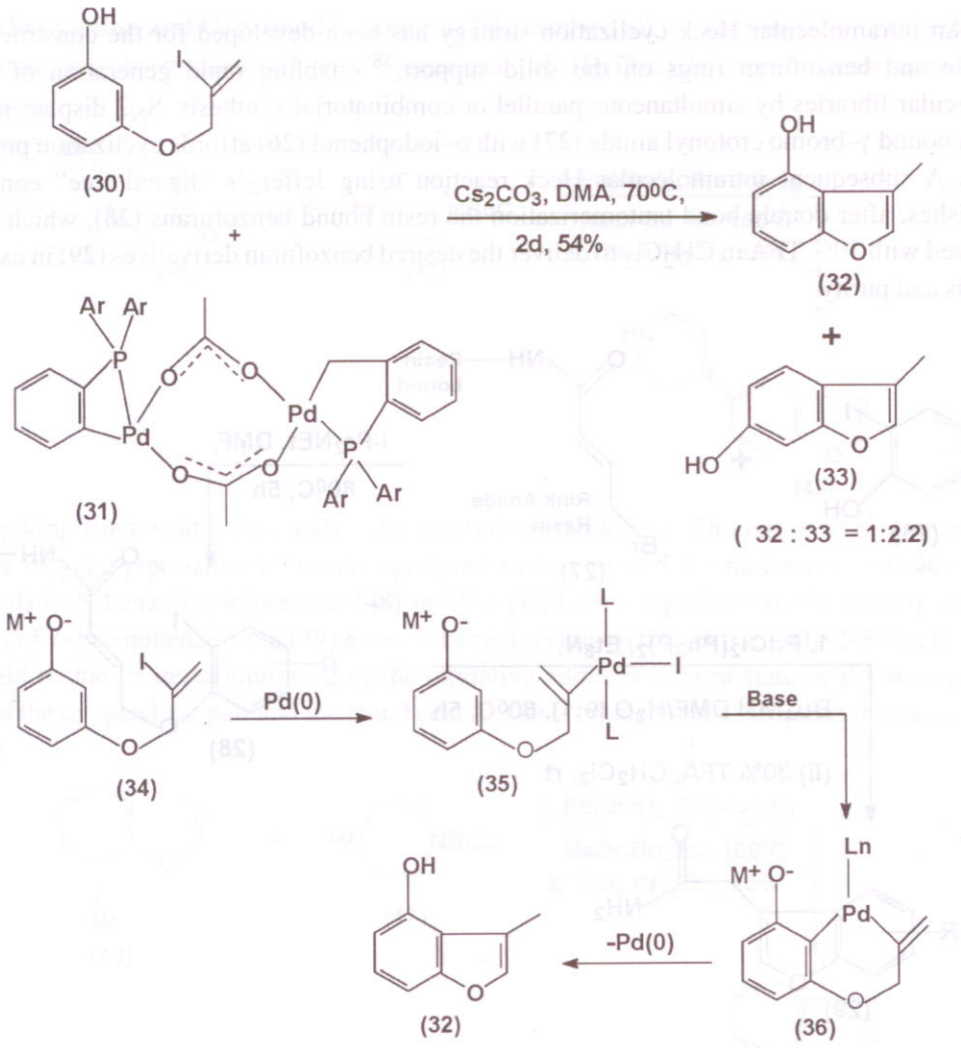
(e) Intramolecular Heck reaction : Similar to the Pd–catalyzed pyrrole and thiophene annulations, an intramolecular Heck reaction of substrate[37] (**24**), results in benzofuran (**25**). Such an approach has become a popular means of synthesizing fused furans.



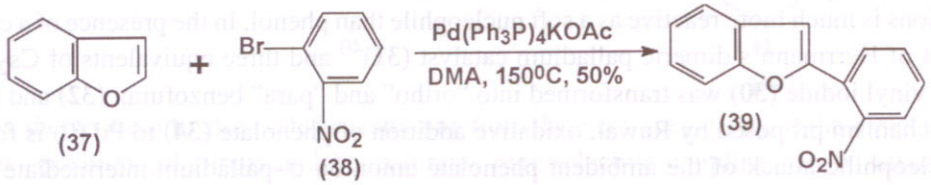
An intramolecular Heck cyclization strategy has been developed for the construction of indole and benzofuran rings on the solid support,[38] enabling rapid generation of small–molecular libraries by simultaneous parallel or combinatorial synthesis. S_N2 displacement of resin bound γ–bromo crotonyl amide (**27**) with o–iodophenol (**26**) affords cyclization precursor (**28**). A subsequent intramolecular Heck reaction using Jeffery's "ligand free" conditions furnishes, after double bond tautomerization the resin bound benzofurans (**28**), which is then cleaved with 30% TFA in CH_2Cl_2 to deliver the desired benzofuran derivatives (**29**) in excellent yields and purity.



Rawal's group has developed an intramolecular aryl Heck cyclization method to synthesize benzofurans, indole and benzopyrans.[39] The rate of cyclization is significantly accelerated in the presence of bases, presumably because the phenolate anion formed under the reaction conditions is much more reactive as a soft nucleophile than phenol. In the presence of a catalytic amount of Herrmann's dimeric palladium catalyst (**31**)[40] and three equivalents of Cs_2CO_3 in DMA, vinyl iodide (**30**) was transformed into "ortho" and "para" benzofuran (**32**) and (**33**). In the mechanism proposed by Rawal, oxidative addition of phenolate (**34**) to Pd (0) is followed by nucleophilic attack of the ambident phenolate anion on σ–palladium intermediate (**35**) to afford aryl vinyl palladium species (**36**) after rearomatization of the presumed cyclohexadienone intermediate. Reductive elimination of palladium followed by isomerization of exocyclic double bond furnishes (**32**).

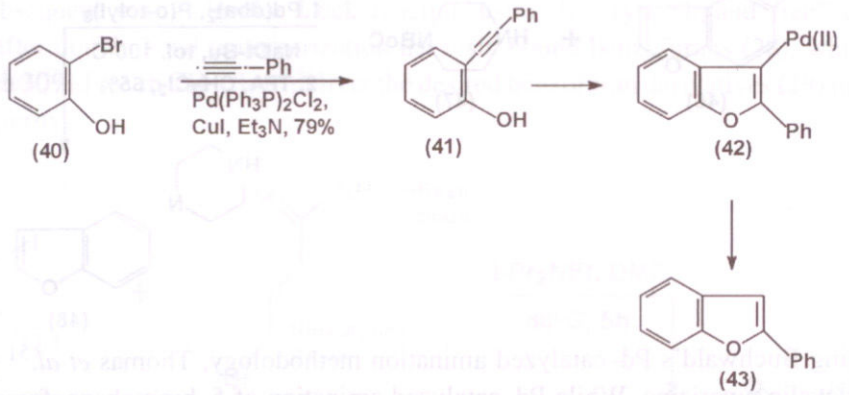


(f) Heteroaryl Heck reaction : Ohta's group has coupled aryl bromides such as 2–bromonitrobenzene (**38**) with benzofuran (**37**)[41] to form the substituted benzofuran (**39**).

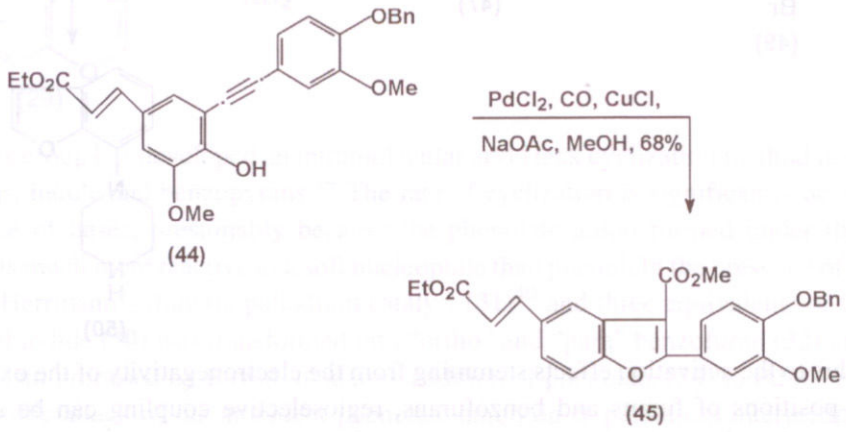


The heteroaryl Heck reaction takes place at the more electron rich C(2) position of benzofuran. Later on, heteroaryl Heck reactions to chloropyrazines with both furan and benzofuran have been developed[42].

(g) Alkynols : Analogous to the annulation of the Sonogashira adducts, a spontaneous cyclization via the intramolecular alkoxylation of alkyne (**41**) (the coupling adduct of o–bromophenol and phenyl acetylene) takes place under the reaction conditions to give 2–phenylbenzofuran (**43**).[43]

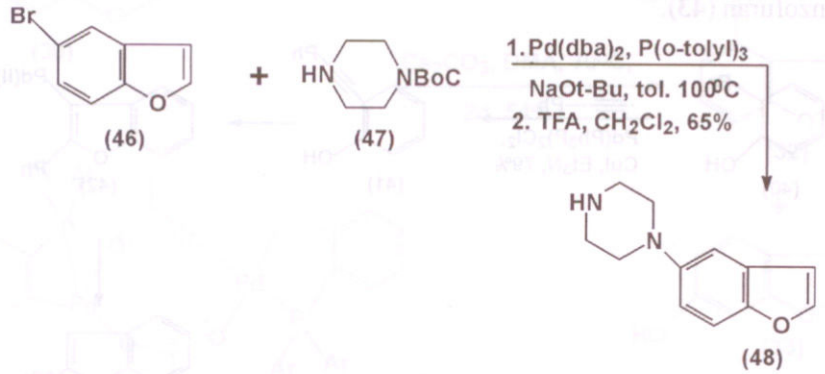


Benzofurylpalladium complex (**42**) is the putative intermediate during the cyclization. The intermediacy of benzofurylpalladium complex (**42**) has been confirmed by trapping it with various electrophiles, including allyl halide,[44] propargyl carbonates (giving rise to 3–allenyl-benzofurans)[45] and carbonylating reagents.[46] Moreover , Cacchi et al.[47,48] took advantage of the benzofurylpalladium intermediate and synthesized 2,3–disubstituted benzofurans from propargylic o–(alkyl) phenyl ethers.[46–48] Scammells' synthesis of benzofuran (**45**) serves as an example.[46] A sequential Pd–catalyzed annulation and alkoxycarbonylation of alkynyl phenol (**44**) gives (**45**), which is an intermediate in the synthesis of XH–14, a potent antagonist of A_1 adenosine receptor isolated from the plant *Salvia militiorrhiza.*

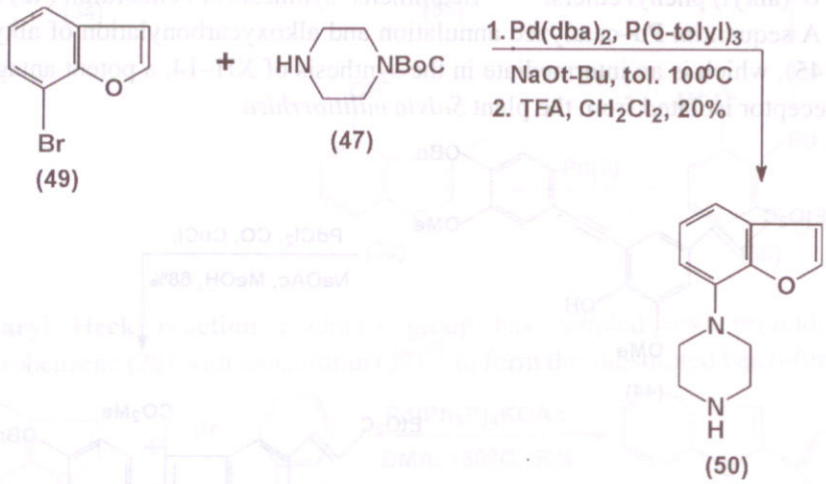


In addition, 3–hydroxy alkylbenzo[b]furans has been prepared by Bishop *et al.*[49] via a Pd catalyzed heteroannulation of silyl–protected alkynols with 2–iodophenol in a fashion akin to the Larock synthesis.

(h) Carbonylation and C–N bond formation: Pd catalyzed alkoxycarbonylation of furan and benzofuran has been achieved in the presence of $Hg(O_2CCF_3)_2$ in ethanol with low efficiency.[50]



Applying Buchwald's Pd–catalyzed amination methodology, Thomas *et al.*[51] prepared a range of bicyclic piperizine. While Pd–catalyzed amination of 5–bromobenzofuran (**46**) with (**47**) leads to 5–benzofurylpiperizine (**48**) in 65% yield after deprotection, the corresponding reaction of 7–bromobenzofuran (**49**) gives 7–benzofurylpiperizine (**50**) in only 20% yield. The low yield is due to steric hindrance of the oxidative addition intermediate or the interaction between the oxygen lone pair and the metal centre. The brominated benzofuran is the major by–product.



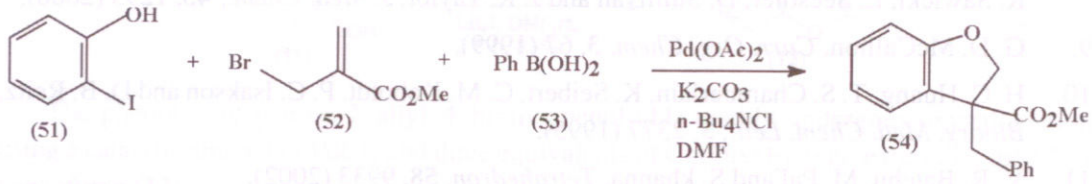
Thus, due to the activation effects stemming from the electronegativity of the oxygen atom on the α –positions of furans and benzofurans, regioselective coupling can be attained in palladium– catalyzed reactions.

(i) Pd/C catalyzed C–C bond formation : Recently, palladium catalyzed reactions in aqueous media[52–56] have attracted the attention of the chemists. These water based synthetic processes

are inherently safer as well as inexpensive. So, the use of water–soluble catalysts[57] and water–soluble phosphine ligands, e.g. sulfonated phosphines[58,59] have been explored successfully.

When compared to the most frequently used expensive palladium catalysts [e.g. Pd $(PPh_3)_4$, $(PPh_3)_2PdCl_2$ etc.], Pd/C–based methods have an economic advantage and hence remain attractive in large or industrial scale preparations. These Pd–catalyzed reactions are usually carried out in an aqueous–organic media and a co–solvent such as acetonitrile or DME is often required for these coupling reactions.[60]

Thus, palladium catalyzed reactions have promoted an interest to develop a mild and efficient method for the synthesis of 2–substituted benzo[b]furans via Pd/C catalyzed C–C bond formation reaction in water[61] in the presence of prolinol. Prolinol possesses better miscibility with water and therefore facilitated the coupling reaction affording better yields of products.[62–64]



Palladium–catalyzed processes have also come to the foreground of transition metal–promoted multi–component reactions.[65,66] Recently, a new Pd catalyzed multi–component reaction involving a Pd–catalyzed allylation of o–iodophenol (**51**) with methyl bromomethylacrylate (**52**) proceeds by a Heck reaction on the substituted acrylate, has demonstrated that (**52**) could participate in a one– pot substitution/carbopalladation reaction.[67] A new three–component reaction involving (**52**) to give dihydrobenzofuran skeleton (**54**) is shown below.

It has been found that the combination of Pd $(OAc)_2$ with n–Bu_4NCl in the presence of a base generated colloidal palladium nanoparticles which are involved in the catalytic cycle.[68,69] However, only a few examples of Pd–catalyzed allylations combined with another Pd–catalyzed process, making use of a unique catalytic system are known in the literature.[70–72] The process has been categorized as Pd–catalyzed pseudo–domino reaction (Pd–PDOM).[73] Recently, it has been reported that allenes[74,75] are also being involved in a Pd catalyzed MCR (multi–component reactions).

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