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ORIGINAL CONTRIBUTION

Intramolecular palladium-catalyzed reaction β-H elimination or C–H activation: A general method for the synthesis of fused pyran rings

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ABSTRACT

Pyrans constitute an important class of 6-member heterocycles with one oxygen atom. Together with its benzo derivatives, pyrans can formulate a prevalent verity of natural and synthetic products in industrial applications. This is an important core molecule having versatile use with its derivatives in pharmaceuticals, dye industry, catalysis, agrochemicals and many more. Several methods for the preparation of pyranderivatives have been reported earlier. In this mini review we have developed of some efficient method for the construction of a fused pyran ring by intramolecular Heck reaction followed by β-H elimination from O-allylated ether.

KEYWORDS: Fused pyran; Intermolecular Heck; Regioselective; C–H bond functionalization; Alkyl palladium complex.

1. INTRODUCTION

Palladium is a member of the nickel triad in the periodic table. Palladium complexes exist in three oxidation states, Pd(0), Pd(II), and Pd(IV). The facile inter conversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry, since each oxidation state exhibits different chemistries. Pd(0) complexes are fairly nucleophilic and rather labile and are also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic, or allylic halides or triflates to Pd(0). This chemistry can be very useful for the synthesis of heterocycles and carbocycles.

Palladium(II) complexes are extremely important in organopalladium chemistry. They are typically electrophilic, soluble in most common organic solvents, and stable to air. Thus, they are easily stored and handled. The most common organic substrates for Pd(II) are electron-rich species, such as olefins, alkynes, and arenes. Some of the most useful Pd (II) chemistry is based on the fast and reversible formation of Pd(II) complexes with olefins and alkynes, which undergo subsequent attack by nucleophiles. That chemistry has recently been reviewed elsewhere. Numerous Pd(II) complexes of the type L_2PdCl_2 are easily formed from $PdCl_2$ and the appropriate ligand L. The most useful Pd(II) complexes are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2(RCN)_2$. Pd(II) complexes are often added to reactions as pre catalysts, since they are readily reduced by various species to Pd(0), which then catalyzes the desired process.

Cyclization by palladium-catalyzed oxidative addition/ reductive elimination is a powerful method for the construction of heterocycles. This process generally involves the addition of a covalent molecule to a Pd(0) complex, with cleavage of the covalent bond and oxidation of Pd(0) to Pd(II), to afford a organopalladium(II) halide or triflate complex. The σ-bonded species, once formed, generally undergoes rapid insertion of an unsaturated species or other reactions as outlined in **Scheme 1**. Subsequent reductive elimination affords the desired heterocycle and Pd(0), which reenters the catalytic cycle directly, in contrast to Pd(II)- catalyzed reactions, which usually require an additional

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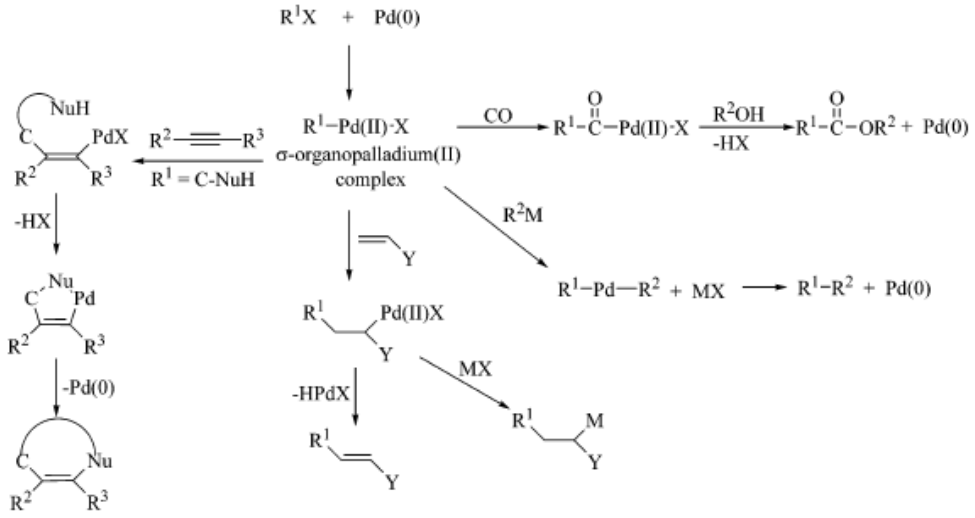
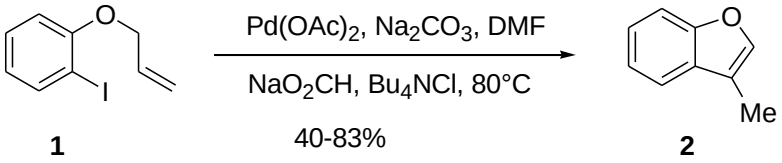
reoxidation step. The mechanistic details of these processes have been reviewed.[1-7] The palladium-catalyzed cyclization of vinylic/aryl halides or triflates containing neighboring alkenes, dienes, alkynes, and arenes via oxidative addition/reductive elimination reactions provides a very valuable approach to a wide range of heterocycles.[8-26]



Scheme 1

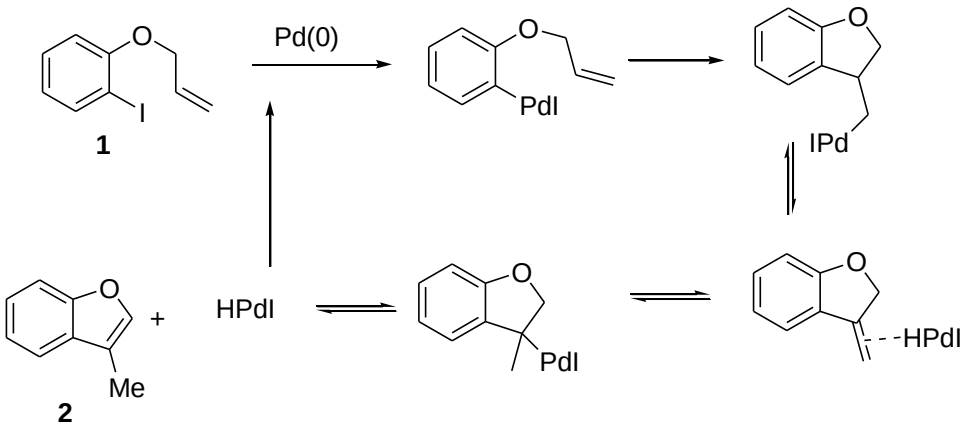
Intramolecular Heck reactions have become a versatile tool in heterocyclic synthesis. Larock have reported the use of *o*-iodoaryl allylethers **1** as starting material in the preparation of benzofurans **2** via intramolecular Heck cyclization (Scheme 2).[27]



1 **2**

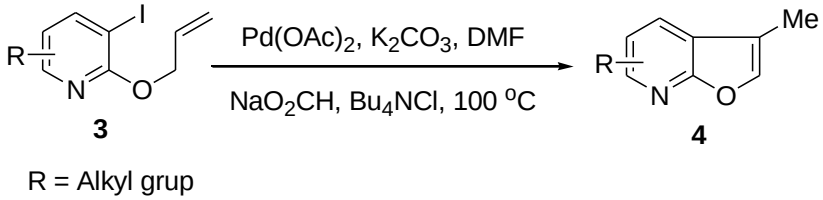
Scheme 2

This cyclization proceeds under mild conditions and in reasonably good isolated yields when catalytic amounts of $Pd(OAc)_2$, Na_2CO_3, HCO_2Na, and Bu_4NCl in DMF are employed at 80 ^oC. Mechanistically, these reactions appear to proceed as indicated in Scheme 3. The addition of HCO_2Na improves the overall yields of benzofurans.



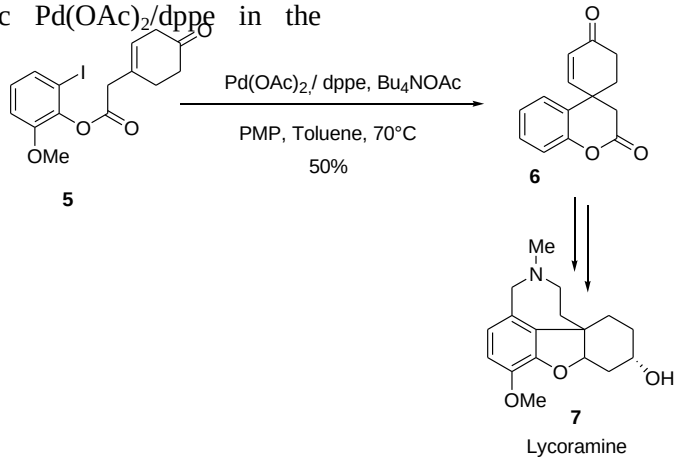
Scheme 3

Yum and co-workers also used sodium formate in their preparation of 3-alkylfuropyridines **4** from iodopyridinyl allyl ethers **3** (Scheme 4).[28] Allylic ethers **3** with longer side chains and 2-cyanopyridyl allyl ether provided lower yields of the desired products.



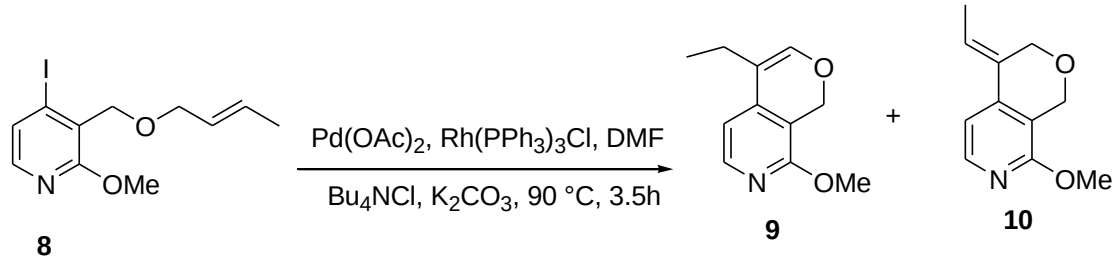
Scheme-4

Guillou and co-workers utilized an intramolecular Heck cyclization to prepare a benzopyran ring in their synthesis of the alkaloid lycoramine (Scheme 5).[29] The tricyclic benzopyran **6** was obtained from iodide **5** in 50% yield using catalytic $Pd(OAc)_2$/dppe in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP), tetrabutylammonium acetate, and toluene as the solvent. In the absence of Bu_4NOAc or when $Pd(OAc)_2$ and MeCN were used at reflux, the product **6** was isolated in lower yields.



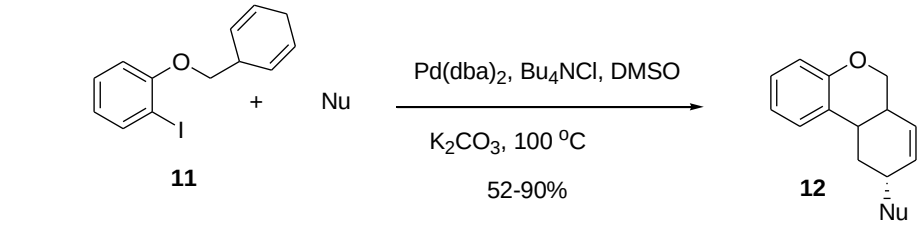
Scheme-5

The use of a catalytic couple composed of Rh(I) and Pd(II)to prepare enol ether **9** and allylic ether **10** has been described by Bankston and co-workers (Scheme 6).[30] They found that a catalyst consisting of Rh(I) and Pd(II) gives the desired product in better yields than the use of Pd(II) alone. In the presence of Rh(I) *endo* cyclization was preferred. Other parameters, such as dilution, temperature and the palladium ligand can also effect the rate and selectivity.



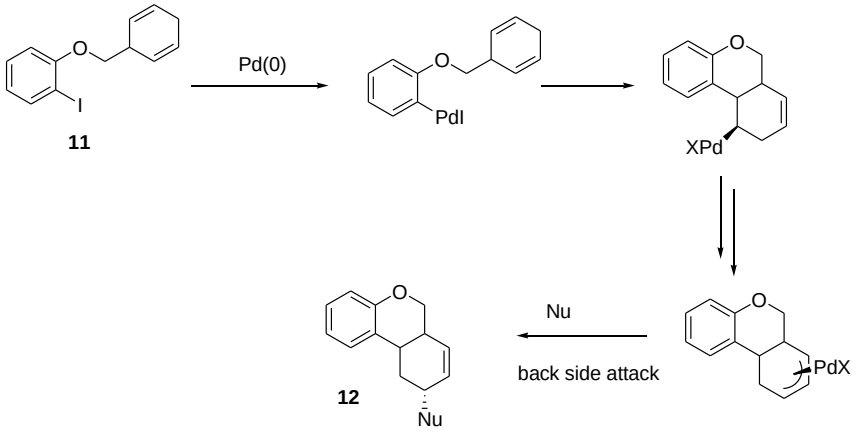
Scheme-6

Larock utilized the intramolecular Heck cyclization of 2,5-cyclohexadienyl-substituted aryl iodides to prepare functionalized heterocycles (Scheme 7).[31] the reaction of a variety of carbon, nitrogen, oxygen, and sulfur nucleophiles with aryl iodides, such as **11**, in the presence of catalytic $Pd(dba)_2$ in DMSO at 100 □C afforded the heterocyclic compounds **12** in good yields and high diastereoselectivity. The reaction is believed to proceed via (1) Oxidative addition of the aryl halide to Pd(0), (2) Organopalladium addition to one of the carbon-carbon double bonds, (3) Palladium migration along the carbon chain on the same face of the ring to form a *σ*-allyl palladium intermediate, and (4) Nucleophilic displacement of the resulting *σ*-allyl palladium species (Scheme 8).



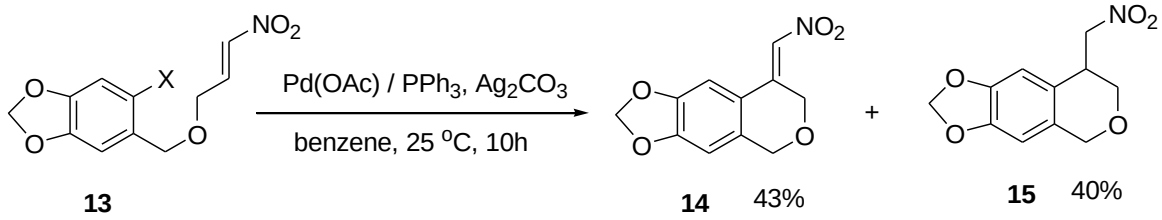
Nu = $CH(CO_2Et)_2$, $TsNCH_2Ph$, $HC(CO_2\text{-}t\text{-}Bu)_2$, NHPh, SO_2Ph, OAc, OPh

Scheme 7



Scheme 8

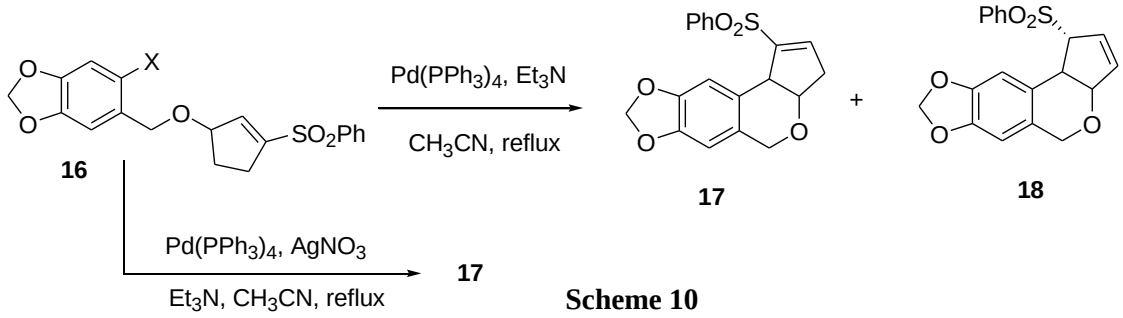
Iodoarene **13** was found by Denmark and Schnute to undergo Pd-catalyzed intramolecular Heck cyclization in the presence of stoichiometric amounts of $Pd(OAc)_2$ and PPh_3 at room temperature to afford *exo* cyclic pyran derivative **14** (Scheme 9).[32] The use of Ag_2CO_3 as a base and the nonpolar solvent benzene are crucial for the success of the reaction. The product was obtained as a single geometrical isomer along with the corresponding saturated nitroalkane **15**.



13 **14** 43% **15** 40%

Scheme 9

The intramolecular Heck reaction of vinylic sulfones by catalytic Pd(0) in the presence of $AgNO_3$ generates polycyclic sulfones (Scheme 10).[33] The vinylic sulfone **16** bearing an iodide provides a much higher yield of the cyclization product than the corresponding bromide. The absence of $AgNO_3$ afforded the cyclic product **17** accompanied by the allylic isomer **18**.

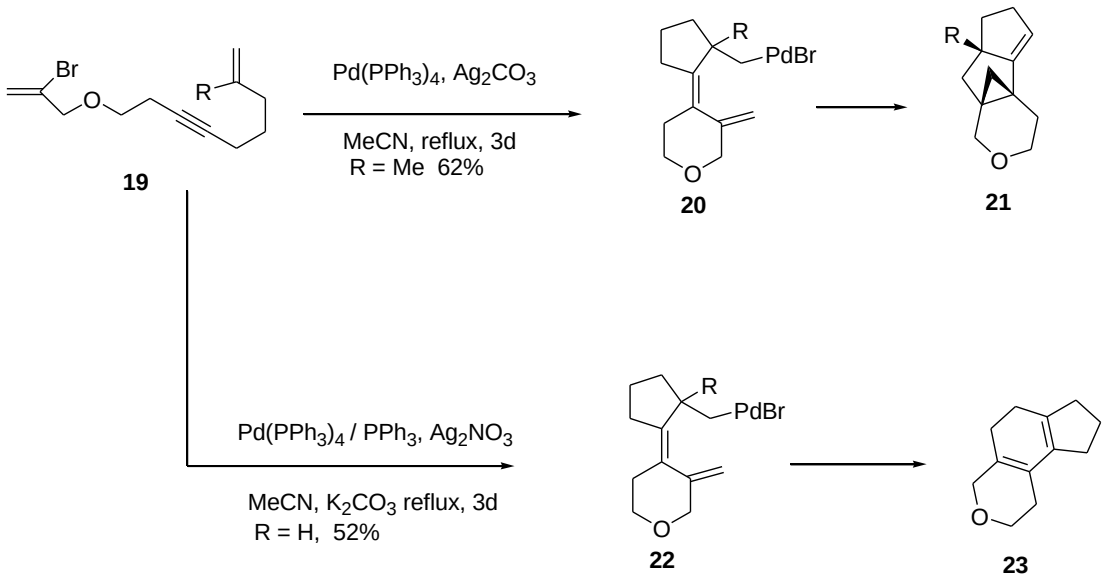


16 **17** **18** **17**

Scheme 10

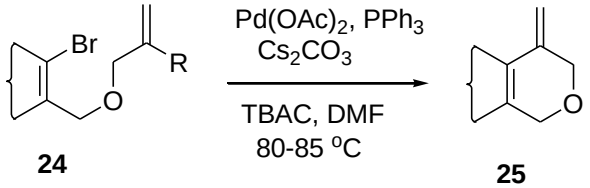
The intramolecular Heck cyclization of the dienyne **19** with a methyl substituent provided the tetracyclic product **21** in good yield via 5-*exo-trig* cyclization of intermediate **20** and eventual *β*-hydride elimination (Scheme11).[34]

On the other hand, when the hydrogen-substituted dienyne **19** was cyclized, it afforded tricyclic diene **23** in 52% yield via *endo* cyclization of **22** and subsequent *β*-hydride elimination.



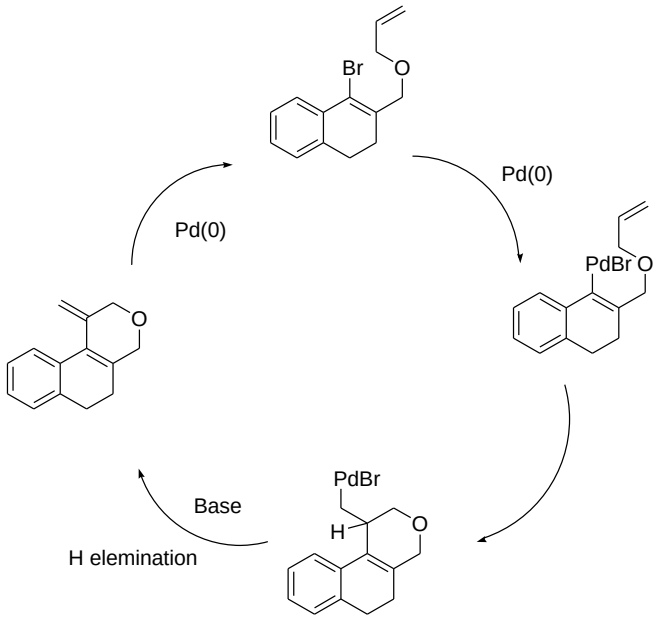
Scheme-11

We also developed a general method for the synthesis of pyran ring and tetracyclic pyran ring by palladium catalyzed *β*-H elimination or by C-H activation[35-38]. The intramolecular Heck reaction was then performed with *O*-allylated **24** in the presence of $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and TBAC (tetrabutylammoniumchloride) in DMF at 80-85 °C to afford pyran derivatives **25.**



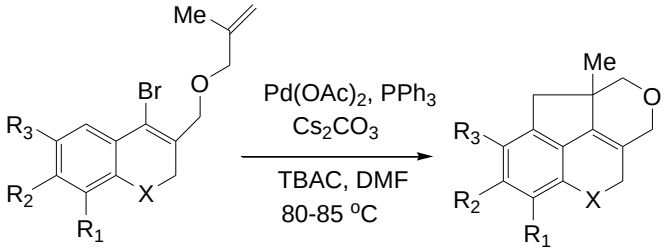
Scheme 12

The mechanism of this reaction is very simple. Initially an alkenyl palladium(II) intermediate was generated by oxidative addition of Pd(0) to the sp^2 C–Br bond which undergoes addition to the unactivated double bond to produce an alkylpalladium which underwent *β*-H elimination reaction to afford pyran ring which is shown below (Scheme 13).



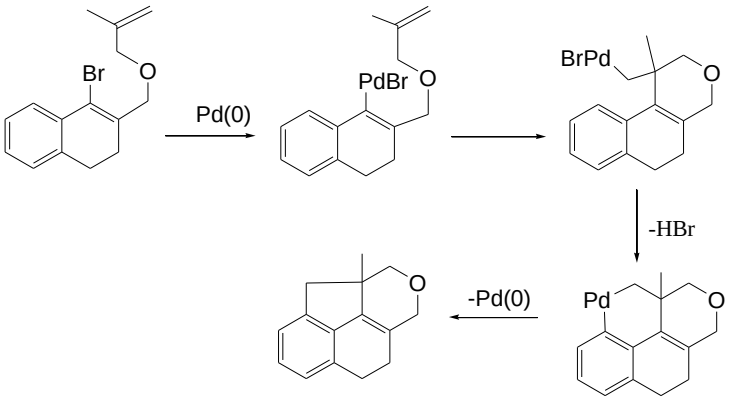
Scheme 13

During our studies, an interesting result was observed (Scheme 14). *O*-Methallylated compounds **26** were subjected to intramolecular Heck reaction under the same conditions to afford tetracyclic pyrans **27**.



26 **Scheme 14** **27**

A plausible mechanism for the above reaction is shown in Scheme 16. Initially an alkenyl palladium (II) intermediate was generated by oxidative addition of Pd(0) to the sp^2 C–Br bond which undergoes addition to the unactivated double bond to produce an alkyl palladium which underwent cyclization with the aromatic ring through C–H activation. Since no elimination is possible due to the absence of a *β*-H in the alkyl palladium intermediates, C–H activation is facilitated (Scheme 15).



Scheme 15

2. **CONCLUSION**

In conclusion, we have developed a method for the synthesis of fused pyran rings by intramolecular Heck reaction and tetracyclic pyran formation by intramolecular Heck reaction and regioselective C–H activation. It is possible to utilize this method for the synthesis of benzopyran systems and in this review we have discussed some different strategies for the synthesis of some pyran based natural product.

REFERENCES

[1] Maitlis, P. M. *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vols. 1 and 2.

[2] Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: New York, 1980.

[3] Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

[4] Larock, R. C. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: London, 1994; Vol. V, Chapter 3.

[5] Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley and Sons: New York, 1995.

[6] Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000.

[7] Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley and Sons: New York, 2002; Vols. 1 and 2.

[8] Imbos, R.; Minnaard, A. J.; Feringa, B. L. A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand. *J. Am. Chem. Soc*. 2002, *124*, 184.

[9] Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. Palladium-Catalyzed Cross-Coupling of Unsaturated Phenols with Vinylic Halides and Triflates. *Tetrahedron Lett*. 1998, *39*, 237.

[10] Larock, R. C.; Yang, H.; Pace. P.; Narayanan, K.; Russell, C. E.; Cacchi, S.; Fabrizi, G. Synthesis of Oxygen Heterocycles via Pd-catalyzed Cross-coupling of Unsaturated phenols and Vinylic halides or triflates. *Tetrahedron* 1998, *54*, 7343.

[11] Ma, S.; Negishi, E. Palladium-Catalyzed Cyclization of -Haloallenes. A New General Route to Common, Medium, and Large Ring Compounds via Cyclic Carbopalladation. *J. Am. Chem. Soc.* 1995, *117*, 6345.

[12] Ma, S.; Duan, D.; Shi, Z. Palladium(0)-Catalyzed Cyclization Reaction of Polymer-Supported Aryl Iodides with 1,2-Allenyl Carboxylic Acids: A Facile Solid-Phase Synthesis of Butenolides. *Org. Lett.* 2000, *2*, 1419.

[13] Ma, S.; Yu, Z. Efficient Synthesis of Bibutenolide Derivatives through Oxidative Dimeric Cyclization-Coupling Reaction of 2, 3-Allenoic Acids. *Org. Lett.* 2003, *5*, 1507.

[14] Rozhkov, R. V.; Larock, R. C. An Efficient Approach to Dihydrofurocoumarins via Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxycoumarins. *J. Org. Chem.* 2003, *68*, 6314.

[15] Rozhkov, R. V.; Larock, R. C. Synthesis of Dihydrofurocoumarins viaPalladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxycoumarins. *Org. Lett*. 2003, *5*, 797.

[16] Larock, R. C.; Doty, M. J.; Han, X. Palladium-Catalyzed Heteroannulation of Internal Alkynes by Vinylic Halides. *Tetrahedron Lett.* 1998, *39*, 5143.

[17] Larock, R. C.; Han, X.; Doty, M. J. Synthesis of α-Pyrones via Palladium-Catalyzed Annulation of Internal Alkynes. *Tetrahedron Lett.* 1998, *39*, 5713.

[18] Roesch, K. R.; Zhang, H.; Larock, R. C. Synthesis of Isoquinolines and Pyridines by the Palladium-Catalyzed Iminoannulation of Internal Alkynes. *J. Org. Chem.* 2001, *66*, 8042.

[19] Dai, G.; Larock, R. C. Synthesis of 3,4-Disubstituted Isoquinolines via Palladium-Catalyzed Cross-Coupling of *o*-(1-Alkynyl)benzaldimines and Organic Halides. *Org. Lett*. 2001, *3*, 4035.

[20] Dai, G.; Larock, R. C. Synthesis of 3,4-Disubstituted Isoquinolines via Palladium-Catalyzed Cross-Coupling of 2-(1-Alkynyl)benzaldimines and Organic Halides. *J. Org. Chem*. 2003, *68*, 920.

[21] Roesch, K. R.; Larock, R. C. Synthesis of Isoindolo[2,1-*a*]indoles by the Palladium-Catalyzed Annulation of Internal Alkynes. *Org. Lett.* 1999, *1*, 1551.

[22] Roesch, K. R.; Larock, R. C. Synthesis of Isoindolo[2,1-*a*]indoles by the Palladium-Catalyzed Annulation of Internal Acetylenes. *J. Org. Chem.* 2001, *66*, 412.

[23] Zhang, H.; Larock, R. C. Synthesis of *β*- and *γ*-Carbolines by the Palladium-Catalyzed Iminoannulation of Internal Alkynes. *Org. Lett.* 2001, *3*, 3083.

[24] Zhang, H.; Larock, R. C. Synthesis of *β*- and *γ*- Carbolines by the Palladium-Catalyzed Iminoannulation of Alkynes. *J. Org. Chem*. 2002, *67*, 9318.

[25] Zhang, H.; Larock, R. C. Synthesis of Annulated *γ*-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation. *Org. Lett.* 2002, *4*, 3035.

[26] Zhang,H.; Larock, R. C. Synthesis of Annulated *γ* -Carbolines and Heteropolycycles by the Palladium-Catalyzed Intramolecular Annulation of Alkynes. *J. Org. Chem*. 2003, *68*, 5132.

[27] Larock, R. C.; Stinn, D. E. Synthesis of Benzofurans via Palladium-promoted Cyclization of Ortho-substituted Aryl allyl ethers. *Tetrahedron Lett*. 1988, *29*, 4687.

[28] Cho, S. Y.; Kim, S. S.; Park, K.-H.; Kang, S. K.; Choi, J.-K.; Yum,E. K. Synthesis of 3-Alkylfuropyridines via Palladium-catalyzed Cyclization of Iodopyridinyl Allyl Ethers. *Heterocycles* 1996, *43*, 1641.

[29] Gras, E.; Guillou, C.; Thal, C. A Formal Synthesis of (±) Lycoramine via an Intramolecular Heck reaction. *Tetrahedron Lett*. 1999, *40*, 9243.

[30] Bankston, D.; Fang, F.; Huie, E.; Xie, S. Palladium(II) Acetate-Tris(triphenylphosphine)rhodium(I)Chloride: A Novel Catalytic Couple for the Intramolecular Heck Reaction. *J. Org. Chem*. 1999, *64*, 3461.

[31] Larock, R. C.; Han, X. Palladium-Catalyzed Cross-Coupling of 2, 5-Cyclohexadienyl-Substituted Aryl or Vinylic Iodides and Carbon or Heteroatom Nucleophiles. *J. Org. Chem*. 1999, *64*, 1875.

[32] Denmark, S. E.; Schnute, M. E. Palladium-Promoted Intramolecular Addition of an Aryl Iodide to a Nitroalkene. *J. Org. Chem.* 1995, *60*, 1013.

[33] Jin, Z.; Fuchs, P. L. Regiospecific Silver[I] Promoted, Palladium(0)-Catalyzed Intramolecular Addition of Aryl iodides to Vinyl sulfones. *Tetrahedron Lett*. 1993, *34*, 5205.

[34] Meyer, F. E.; Parsons, P. J.; de Meijere, A. Palladium-Catalyzed Polycyclization of Dienynes: Surprisingly Facile Formation of Tetracyclic Systems Containing a Three-Membered Ring. *J. Org. Chem*. 1991, *56*, 6487.

[35] Jana, R.; Samanta, S.; Ray,K.J, Substrate dependent intramolecular palladium-catalysed cyclisation and subsequentb-H elimination or C–H activation: a genera method for the synthesis of fused pyran rings. *Tetrahedron Letters* 49 (2008) 851–854

[36] Jana, R.; Chaterjee, I.; Samanta, S.; Ray,k.J, Novel and Rapid Palladium-Assisted 6π

[37] Electrocyclic Reaction Affording 9,10-Dihydrophenanthrene and Its

[38] Analogue. *Organic Lettere*, 2008 Vol. 10, No. 21, 4795-4797

[39] Jana, R.; Dewan, M.; Roymahapatra,G. Synthesis of fused pyran and tetracyclicpyran rings by intramolecular palladium-catalyzed β-H elimination and C-H bond Functionalization. ES Materials & Manufacturing 2021, 13, 40-52

[40] Jana, R.; Dewan, M.; Roymahapatra,G. Synthesis of 9,10 –Dihydrophenanthrine, phenanthrine, mono and Dialkyl Phenanthrine and Octa-hydro Phenanthrine by Palladium catalyzed Heck reaction. ES Materials & Manufacturing 2021, 14, 51-58