Prayogik Rasayan

Palladium Catalyzed Intramolecular Cyclization and C-H Activation Reaction Interesting Tool for the Synthesis of Some Exquisite Molecules

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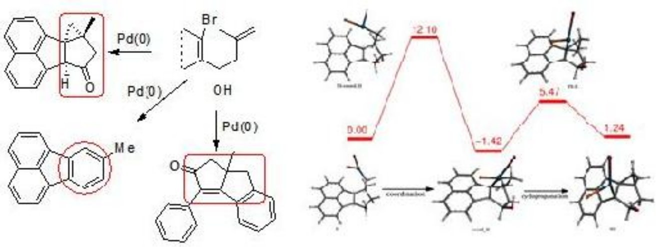
Abstract

We have successfully investigated the palladium catalyzed cyclization in diene system to the formation of three unusual products. By varying the reaction conditions, we observed the formation of fused cyclopentane-cyclopropane rings, fused cyclopentane-cyclopentane rings or benzene ring formation from similar types of diene substrates. The most unexpected and unusual step, the formation of cyclopropane, was studied using density functional theory based calculations.



Formation of carbon-carbon bond using *in-situ* generated organometallic reagents has great fundamental importance in organic synthesis.[1-9] In the field of synthetic chemistry, the search for new and more efficient methods of carbon–carbon bond formation for application in the total synthesis of complex molecules, particularly of cyclic compounds, continue to be a major goal. Over the last two decades, an important area of investigation towards this end has involved transition metal mediated and catalyzed reactions.[10-16] Transition metal-based methods often increase synthetic efficiency by forming several carbon–carbon bonds, with high selectivity, in a single reaction.

Palladium complexes emerged as extremely powerful tools for the construction of carbon-carbon bond forming reactions because palladium (II) intermediates generated by oxidative addition of organic electrophiles to palladium (0) complexes can be utilized widely for transmetallation and insertion into unsaturated bonds.[17, 18] The ready accessibility of two stable oxidation states, *i.e.*, 0 and +2, its interconversion between the two oxidation states as well as the ready availability of palladium-containing species having simultaneously one or more empty and filled nonbonding orbitals are a few of the important factors that are responsible for the versatility and usefulness of Pd complexes as catalysts. The extraordinary utility of palladium in organic synthesis in recent years is due to its unique ability to form carbon-carbon bonds without protecting most important functional groups. The popularity of the palladium complexes increases in part from their capability to oxidize, reduce, isomerize[19] as well as to form new bonds.

In the intramolecular reactions, entropic factors become absolute dominant. In the majority of studied cases, this reaction proceeds in the *exo-trig* mode, as this way is by far less sterically demanding. The intramolecular palladium-catalyzed cyclization nearly always favours the *5-exo-trig*[3] pathway in those cases where competition between *6-endo-* and *5-exo-trig* closures is possible. The *endo*[20] mode is favoured for electronic reasons. Palladium catalyzed cycloisomerization is well precedented now a days.

Substituted carbocycles represent a common structural component of naturally occurring and biologically active molecules, including pharmaceuticals. Among the carbocycles, cyclopentenone ring systems are often embedded in a wide array of natural and unnatural organic products and are interesting drug targets. Cyclopentanoid natural products, such as jasmonates and prostaglandins, are a diverse and biologically significant class.[9] A lot of research has been underway using different organic compounds, polymers and small molecular drugs for applications in diverse fields[5, 21-40].

Palladium catalyst has extraordinary ability to construct carbon-carbon bonds for the synthesis of complex molecules from simple precursors. The palladium catalyzed formation of oligocyclic compounds via tandem cyclization of suitably substituted polyenes/enynes is an important synthetic strategy in last two decades. However, formation of cyclopropane fused cyclopentanone ring system synthesis is not so simple. A few cases for the formation of fused three member rings through palladium catalyzed Heck reactions are known in literature.[11, 17, 18] Meijere and coworkers have reported an unprecedented palladium catalyzed domino polycyclization of dienynes leading to a new type of tetracyclic skeleton containing a cyclopropane ring.[19] Herein we report an unprecedented palladium catalyzed cyclization leading to the formation of a cyclopropane fused cyclopentanone ring in acenaphthene skeleton.
We have recently achieved the carbo and hetero cyclic frame works from bromo vinyl aldehydes[1] by sequential use of Ullmann Cross coupling and McMurry coupling reactions. Annulated bromovinyl aldehydes were converted to 5-7

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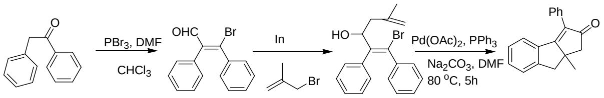
member cyclic ketones by Heck-type reaction.[1, 4, 16, 20, 23, 33] Shortest synthesis of Cuparene from bromoaldehydes has also been achieved.[9, 20]

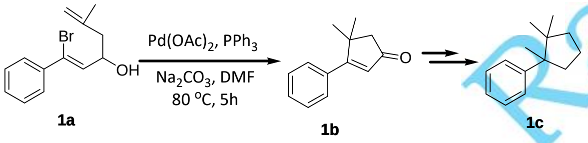
The Heck reaction was performed with 2-allyloxy compound to produce pentalongin and its derivatives, whereas the same reaction with 2-methylallyloxy compound interestingly yielded two different compounds, depending on the reaction conditions. Mechanistic investigation showed that the compound with an annulated *O*-containing 7-membered ring formed via *7-endo trig* cyclization and the other one with a fused furan and pyran moiety formed via *6-exo trig* cyclization followed by the participation of the oxygen lone pair. The improvement of yield by nano Palladium and C-H activation is the extra bonus of this study.



Halo vinyl aldehydes have also been converted to polycyclic aza and thiaarenes including oxidative metabolites and their relevance to chemical carcinogenesis have been established.

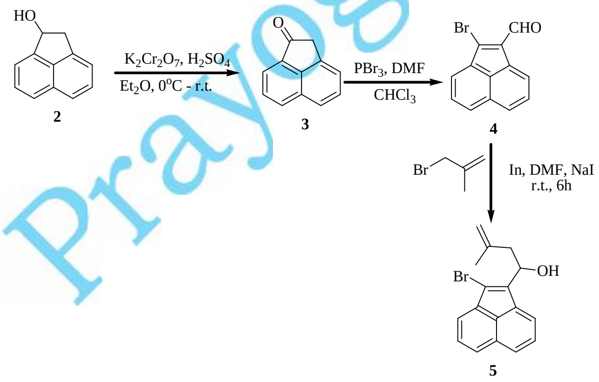
The cyclization of unsaturated substrates using intramolecular Heck reaction is of fundamental importance for the synthesis of various natural products. Recently, we have synthesized the natural product β-cuparenone *via* palladium catalysed tandem Heck cyclization of 1-Bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ol derivatives (Scheme 1).[9]

Scheme 1: Synthetic background

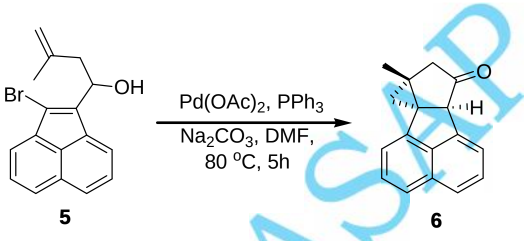


In continuation with our previous work, we were curious about the results of tandem intra-molecular Heck reaction in condensed ring system and for that we have synthesized our scaffold starting from acenaphthene (Scheme 2).

Scheme 2: Synthesis of scaffold



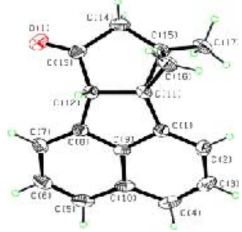
Once we got our synthetic scaffold 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (**5**), we employed it in the intramolecular Heck reaction using the previously screened reaction conditions. Unlike the previous case, here we got a three member ring containing carbocycle (**6**) involving a series of transformations in one –pot , intramolecular 5-*exo*-trig cyclization, cyclopropanation with exclusive *cis* stereochemistry of the 5,3 ring system and also oxidation of secondary alcohol to ketone. Synthesis of this type of ring systems will be very difficult in traditional way leaving aside the unique one-pot conversion (Scheme 3).[41-43]



Scheme 3: Intramolecular Heck cyclization

From the crystal structure of the product (**6,** CCDC No: 1829095), it has been established that the cyclopropane is *cis* to the hydrogen that is bonded to C(12). This synthetic method opens up new one pot protocol for multifunctional transformations (Figure 1).

Figure 1: ORTEP view of compound **6**



When we reacted the substrate **5** with Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$ in DMF at different temperature, we observed the formation of a new product 8-methylfluoranthene (**7**) which was formed as the sole product at 140 °C in 68% yield (Scheme 7). The results are shown in Table 1.

Scheme 4: Reaction of 5 at higher temp

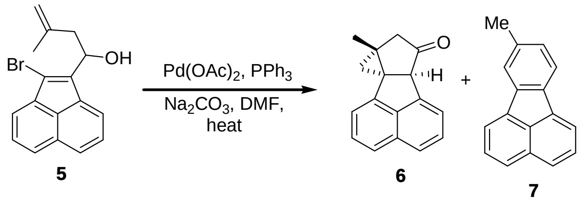


Table 1: The reaction of **5** at different temperature

Sl. No.	Temp. (°C)	Yield of **6**	Yield of **7**
1	60	Trace	00
2	70	35	00

3	80	72	00
4	100	46	Trace
5	120	Trace	41
6	140	00	68
7	150	00	63

In conclusion, we have developed simple protocol for complex multi ring systems with defined stereochemistry. Several uses in cancer fields are also documented in recent years[12].

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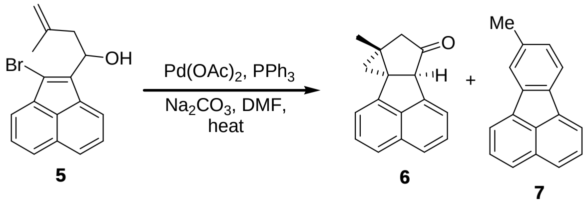
Scheme 5: Reaction of 5 at higher temperature



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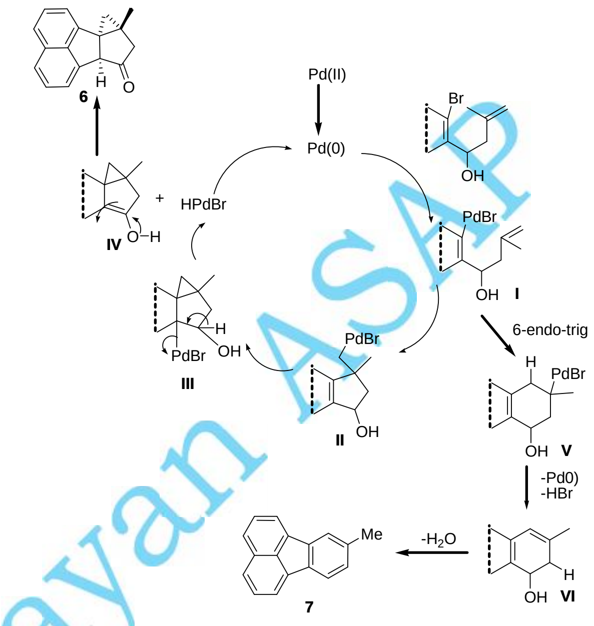
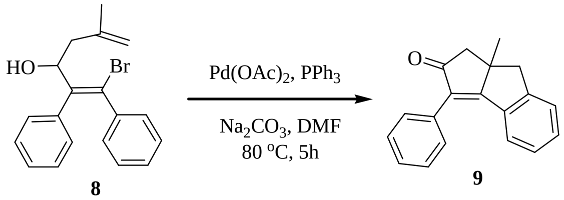
The mechanistic pathway for our reaction has been outlined below (Scheme 5). In one of the possible pathways, the intermediate (**I**) initially was cyclized to afford **II.** Pd in the intermediate II further attacked the inactivated double bond present in the ring junction resulting in the formation of a three membered ring. The intermediate (**III**) underwent β-elimination followed by keto-enol tautomerization to afford the cyclized keto product fused with a cyclopropane ring. Here a number of processes occurred sequentially. Cyclization occurred initially followed by cyclopropanation and then addition to the inactivated double bond followed by keto-enol tautomerization. Hence, we are able to obtain the compound (**6**) by carrying out the Heck reaction with 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (**5**). In another pathway, if the intermediate **I** undergo 6-*endo*-trig cyclization, it forms the six membered ring containing intermediate **V**. Then the intermediate **V** undergoes *β*-hydride elimination followed by dehydroxylation gives the fully aromatized product 8-methylfluoranthene (**7**).

Scheme 6: Plausible reaction mechanism for the formation of **6** and **7**.



After getting these exciting results, we employed the reaction conditions on the 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (**5**) analogue (Z)-1-bromo-5-methyl-1,2-diphenylhexa-1,5-dien-3-ol **8** and in this case we got another exciting product 8a-methyl-3-phenyl-8,8a-dihydrocyclopenta[a]inden-2(1H)-one (**9**) in 67% yield, the formation of two fused cyclopentane rings *via* C-H activation at the adjacent phenyl ring (Scheme 6). No other product was observed on changing the temperature like in previous case.

Scheme 7: Intramolecular Heck reaction in deoxybenzoin system



We have described a plausible mechanism for the formation of two five membered rings in scheme 6. At first Pd(0) undergoes oxidative addition with C-Br bond in substrate 7 to form **8a**. Then intramolecular Heck cyclization occurs with the C=C double bond *via* 5-*exo*-trig pathway to construct first cyclopentane ring (**8b**). Then a C-H activation occur at *ortho*-position of phenyl ring adjacent to PdBr to form the intermediate **8c**. The reductive elimination of Pd(II) constructs the second cyclopentane ring (**8d**) *via* the regeneration of Pd(0). Then the compound **7d** undergoes Pd mediated oxidation to give the final product [8]

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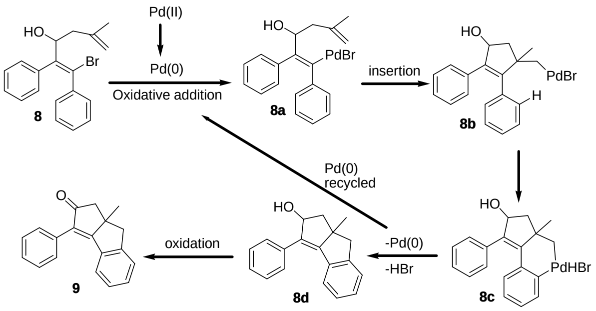

Scheme 8: Plausible mechanism for the formation of two cyclopentane rings

Experimental

3-step reactions from commercially available ketones have been described.

1. Preparation of bromoaldehyde

In a two-neck r.b 3 mmol of Dimethylformamaide and chloroform was taken and stirred in an ice bath. To this 2.7 mmol of Phosphoroustribromide was added drop wise using a needle syringe. The mixture was stirred for half an hour at room temperature until a solid complex was formed. Then a solution of the ketone in chloroform was added drop wise using a needle syringe. This was stirred in an ice bath for 12hrs.

After checking the TLC spot, the reaction was quenched with water, sodium bicarbonate added to neutralize the acid formed and the compound was extracted with dichloromethane solvent.

2. Allyllation of the bromoaldehyde

In a two neck r.b 3 mmol of ally/methallyl bromide, 4 mmol of sodium iodide was taken in DMF solvent and to this 1.2 mmol of indium metal was added and stirred in room temperature for one hr. To this the solution of the bromoaldehyde in DMF was added dropwise to the metal complex. It was stirred at room temperature for 8 hours.

After checking the TLC spot, the reaction was quenched with water, and the compound was extracted with dichloromethane solvent. It was then purified by column chromatography.

3. Cyclisation of the allylated product

The allylated product was taken in two neck rb and 0.3 mmol Triphenylphosphine and 1 mmol Sodium formate was added. Then TBAC was added followed catalytic amount of palladium. Then the air inside the rb was removed using vacuum pump. The vacuum was released in an argon atmosphere and degassing was done for twenty minutes. The reaction was stirred at 60^{O} C for 8 hrs.

After checking the TLC spot, the reaction was quenched with water, and the compound was extracted with diethyl ether solvent.

The compound was purified by column chromatography using 25:1 pet ether, ethyl acetate solvent.

All compounds are in consistent with the structures proposed by MS, NMR and other spectral data.

The mechanism of the unexpected cyclopropanation was analyzed with density functional calculations at B3LYP-D3-BJ/def2-SVP//BP86-D3-BJ/def2-SVP[16,41-45] level of theory using TURBOMOLE V 6.5 package. The intermediate **II** (Scheme 5) has nearly T –shaped geometry at Pd(II) center, i. e., square planar geometry with three sites occupied by bromine, phosphine and terminal carbon(C4) leaving an empty site. The usual β-hydrogen elimination will not procced from this intermediate due to lack of β-hydrogens. Hence the double bond (C1-C2) in the ring junction of complex (**II**) gets coordinated to the vacant site in II to form the intermediate complex (**coord_II**). The coordination requires an activation energy 12.10 kcal/mol and is exergonic by -1.42 kcal/mol. The transition state for the cyclopropanation from intermediate (**coord_II**) was identified, and the activation free energy was found to be 6.89 kcal/mol. The intermediate (**III**) with a fused cyclopropane ring is shown in Figure 2. The cyclopropane and Pd(II) are in the same side of the five-membered ring.

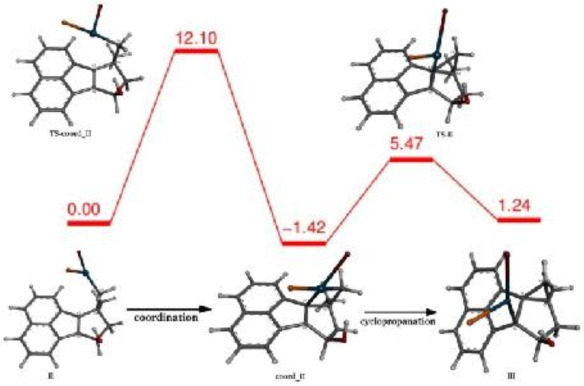

Figure 2: Reaction profile for the cyclopropanation step (Scheme 5) . The energies are in kcal/mol from B3LYP-D3-BJ/def2-SVP//BP86-D3-BJ/def2-SVP level of theory. The optimized geometries are shown.

We have successfully investigated the palladium catalyzed cyclization in diene system to the formation of three unusual products. By varying the reaction conditions, we observed the formation of fused cyclopentane-cyclopropane rings, fused cyclopentane-cyclopentane rings or benzene ring formation from similar types of diene substrates. The most unexpected and unusal step, the formation of cyclopropane, was studied using density functional theory based calculations.

Summary of this work is depicted below.:

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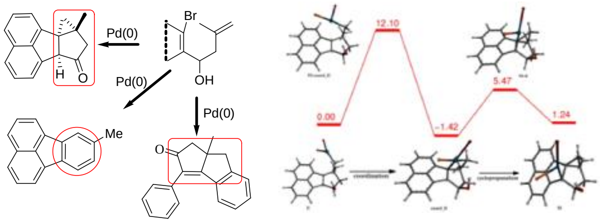

4. Acknowledgment

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