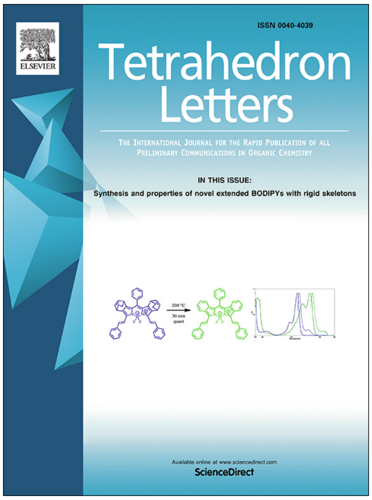

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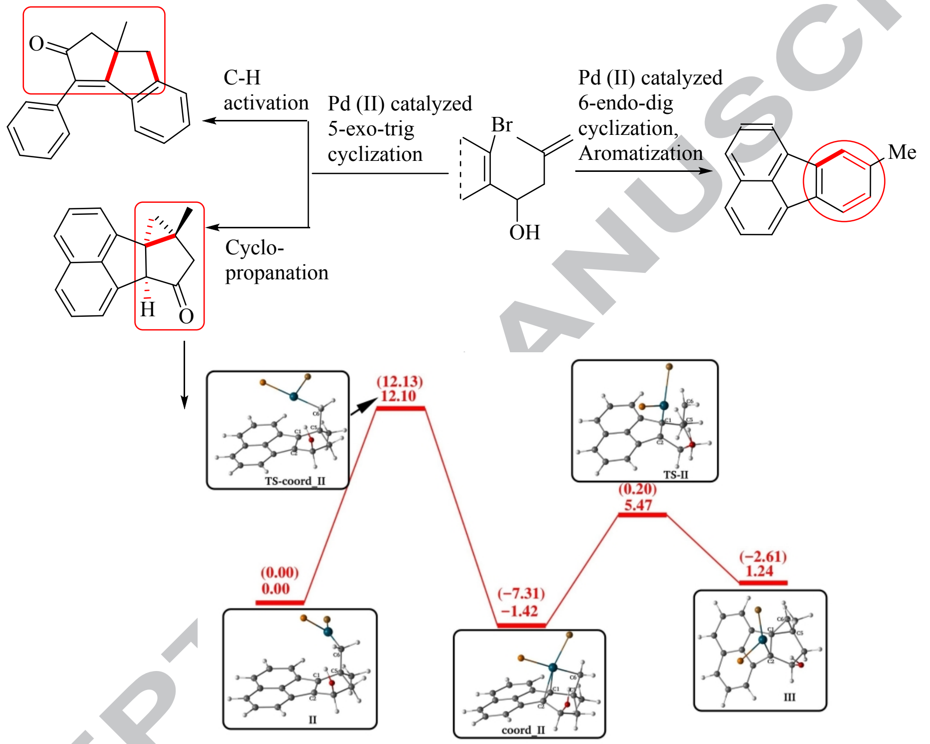

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Palladium-catalyzed expedient Heck annulations in 1-bromo-1,5-dien-3-ols: Exceptional formation of fused bicycles

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ABSTRACT

An unprecedented Pd-catalyzed intramolecular Heck cyclization has been investigated on halogenated diene scaffolds undergoing various mode of cyclization and termination leading to the formation of structurally differing fused cyclopenta(e)none and aromatic analogue. The discrimination in the fate of palladium intermediates formed in situ undergoing heck cyclization preferentially arises out of the difference in reaction temperature as well as substrate architecture. Sequential heck reaction of 1-Bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ol derivatives followed by oxidation or termination via sp^2 C-H activation in aromatic ring led to the formation of fused cyclopentanes. However, the similar reaction at elevated temperature showed predominance towards the formation of aromatic analogues via one pot cyclization and dehydroxylation. The mechanism for the formation of cyclopentanone fused with cyclopropane ring system is supported by density functional theory based calculations.

Palladium catalysts are bestowed with evolutionary capability to construct carbon-carbon bonds for the synthesis of complex framework from simple precursors.[1] The cross-coupling of unsaturated electrophilic substrates with a nucleophilic counterpart using Pd-catalyzed Heck reaction is of fundamental importance for the direct access to various natural products.[1d, 1f, 5] Recently Shang and Fu delineated an irradiation-induced intermolecular heck reaction of unactivated alkyl halides at room temperature.[3] Liu and coworkers introduced a palladium-catalyzed intramolecular 6-endo selective alkyl-heck reactions to access 5-Phenyl-1,2,3,6-tetrahydropyridine derivatives.[4] The generation of oligocyclic compounds *via* tandem cyclization of suitably substituted polyenes/enynes using these catalysts has been hallmarked as an important synthetic strategy in last two decades.[5] Nemoto and coworkers established Pd-catalyzed cascade cyclization by intramolecular Heck insertion of an allene−allylic amination sequence to access 3,4-Fused Tricyclic Indoles (Scheme 1a).[6] However, formation of fused bicyclic systems such as cyclopropane-cyclopentane rings through palladium catalyzed Heck reaction have limited popularity due to the ring strain associated with the product formation.[7] In this regard, Meijere and coworkers have advented an unprecedented palladium catalyzed domino polycyclization of dienynes leading to a new type of tetracyclic skeleton containing a cyclopropane ring.[8] In our antecedent studies, we have synthesized the sesquiterpene natural product, β-cuparenone *via* palladium catalyzed tandem Heck cyclization of 1-Bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ol derivatives (Scheme 1a).[9] In continuation with the previous work, we were keen in further exploration of tandem intra-molecular Heck reaction in condensed ring scaffold related to acenaphthenene and deoxybenzoin derivatives (Scheme 1b).

Herein we present our relevant contribution towards an unprecedented palladium-catalyzed annulation leading to diverse mode of termination resulting in the formation of fused cyclopentanone as well as aromatic analogues. The targeted synthetic scaffold 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (5), was subjected to Pd-catalyzed intramolecular Heck reaction utilizing reaction conditions developed in our prior reports.

Unlike the previous cases, here we ended up with a cyclopropane ring fused with the carbocycle (**6**) involving a series of transformations in a single pot. The amenable substrates undergoes simultaneous intramolecular 5-*exo*-trig cyclization, cyclopropanation with exclusive *cis* stereochemistry conferring 5,3 ring system followed by the oxidation of secondary alcohol to ketone. The unique pathway for one pot synthesis of these complexities involving multiple phenomenons is uncommon. Interestingly, the reaction underwent different mode of cyclization with variation in temperature (Scheme 2).

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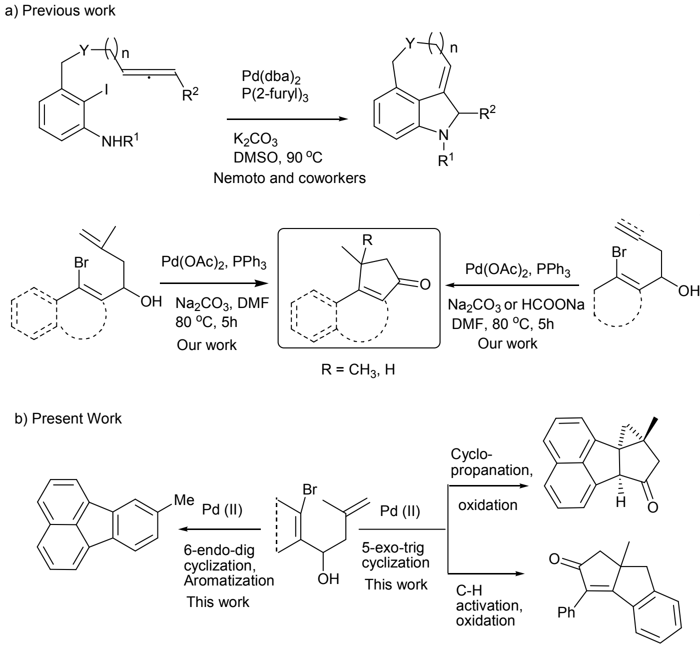
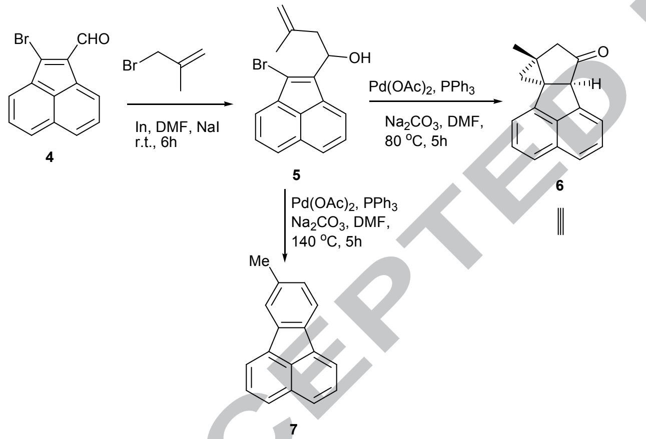


Scheme 1: Synthetic approaches for Pd-catalyzed cascade cyclization reactions



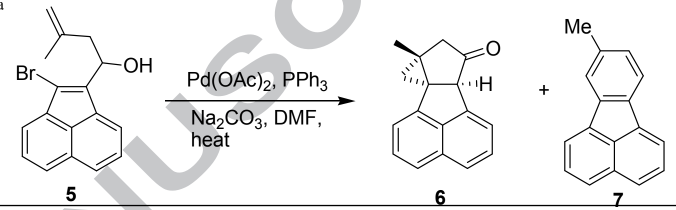
Scheme 2: Varied mode of cyclization [6] under different temperature

From the crystal structure of the product (**6**, Scheme 2, 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 avenue for one pot protocol to multifunctional transformations.

The initial screening was started by carrying out the reaction of substrate **5** with Pd(OAc)$_2$ as catalyst, PPh$_3$ as ligand and Na$_2$CO$_3$ as base in DMF at 60 °C which resulted in the formation of product (**6**) in trace amount (Table 1). Increasing the temperature till 80 °C enhanced yield of **6** to 72% as the sole product. Further increase in temperature of the reaction to 100 °C led to declination in the yield of product **6** while 8-methylfluoranthrene (**7**) started appearing as byproduct in trace amount. Attempting the reaction at 140 °C resulted in the formation of 8-methylfluoranthene as the sole product in a maximum yield of 68%. Further inclination in temperature endured with declination in yield of product. The results are shown in table 1.

A plausible mechanistic interpretation for cascade annulation has been outlined in Scheme 3. The Pd(0) catalyst obtained through *in situ* reduction of Pd(II) in presence of PPh$_3$, undergoes oxidative addition into the substrate (5) to afford the intermediate I. A dual possibility of cyclization for intermediate I *via* heck reaction arise out of either *5-exo-trig* or *6-endo-dig* pathway. *5-exo-trig* cyclization of the intermediate (I) afforded the 5-membered cyclic Pd-intermediate II which undergo cyclopropanation *via* addition to the internal double bond situated at ring junction furnishing intermediate III. The *β*-elimination of intermediate (III) followed by keto-enol tautomerization accounts for the formation of cyclopropane-fused-cyclopentanone (6) as the final product

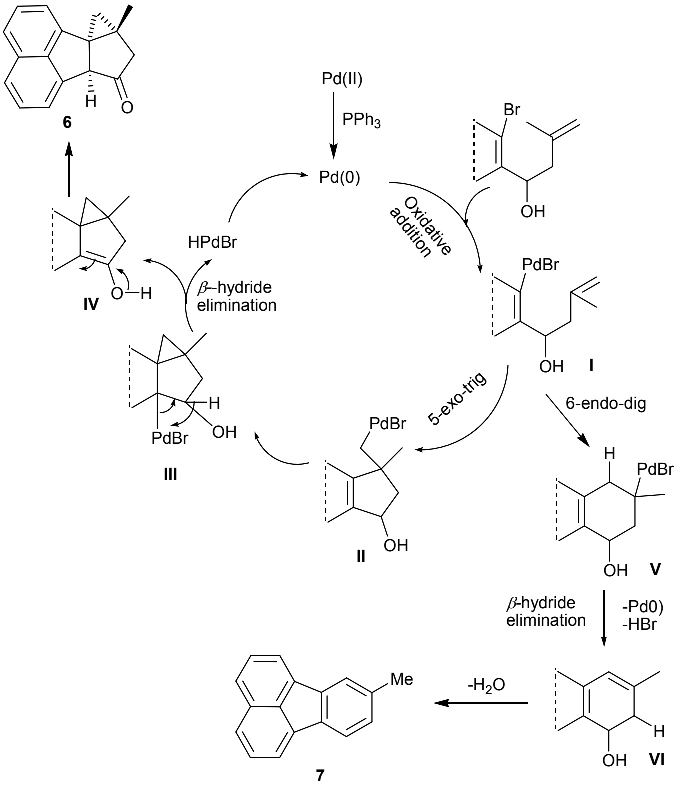
Table 1: Optimization studies for formation of products **6** and **7**[a]



Sl. No.	Temp. (°C)	Yield(%)[b]	
		6	7
1	60	Trace	0
2	70	35	0
3	80	72	0
4	100	46	Trace
5	120	Trace	41
6	140	00	68
7	150	00	63

[a] Reaction condition:

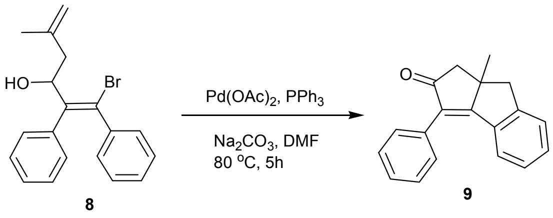
[b] Isolated yield



Scheme 3: Plausible mechanistic for the formation of **6** and **7**.

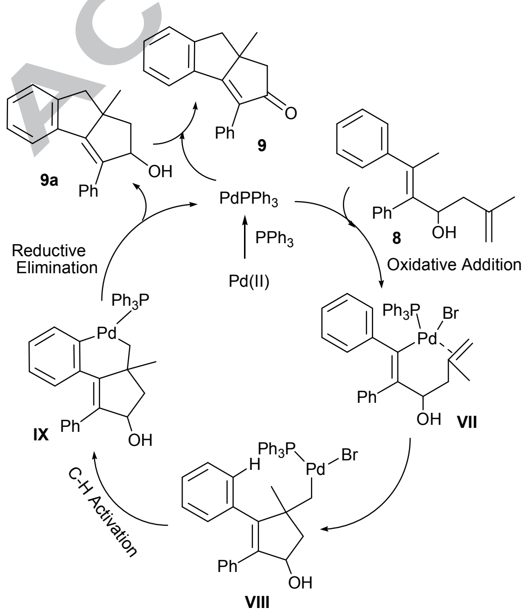
An alternative approach for cyclization encompasses *6-endo-dig* cyclization of intermediate I resulting in the formation of 6-membered Pd-intermediate V. *β*-hydride elimination of the intermediate V followed by dehydroxylation leads to aromatization of the precursor leading to 8-methylfluoranthene (7) as the sole product. Thus, in both the cases, a sequential set of Pd-catalyzed transformations for 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (**5**) leads to the formation structurally distinguished fused scaffolds.

The scope of cyclization was extended further by employing the reaction conditions on (Z)-1-bromo-5-methyl-1,2-diphenylhexa-1,5-dien-3-ol (**8**), a structural analogue to 1-(2-bromoacenaphthylene-1-yl)-3-methyl-but-3-en-1-ol (**5**). The result juxtaposes formation of prior products and encounter establishment of alternative mode of termination for the cyclized intermediate (Scheme 4). Therefore, the Pd-catalyzed cyclization of **8** ended up in the formation of 8a-methyl-3-phenyl-8,8a-dihydrocyclopenta[a]inden-2(1H)-one (**9**) as the only product in 67% yield. Notably, no side product was observed on changing the temperature unlike previous cases.



Scheme 4: Intramolecular Heck reaction in deoxybenzoin system

A related mechanism for the simultaneous formation of fused five membered rings in product **9** has been described in scheme 5. The *in situ* generated Pd(0) undergoes oxidative addition *via* migratory insertion into C-Br bond of substrate **8** to form intermediate **VII**. The intramolecular Heck cyclization with the C=C double bond *via* 5-*exo-trig* pathway constructs the Pd-intermediate containing cyclopentane ring **VIII**. Subsequent *ortho* Csp^2-H bond activation of phenyl ring accessible to PdBr results in the intermediate **IX**. Reductive elimination of Pd(II) intermediate (**IX**) generated the fused cyclopentane rings **9a** *via* the regeneration of Pd(0). The compound **9a** undergoes Pd-initiated oxidation of alcohol (**9a**) to ketone (**9**) as final product.



Scheme 5: Plausible mechanism for the formation of two cyclopentane rings

The mechanism of the unexpected cyclopropanation was analyzed with density functional calculations at B3LYP-D3-BJ/def2-SVP//BP86-D3-BJ/def2-SVP[10-14] level of theory using TURBOMOLE V 6.5[15,16] package. The intermediate II (Scheme 3) 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 cannot 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.

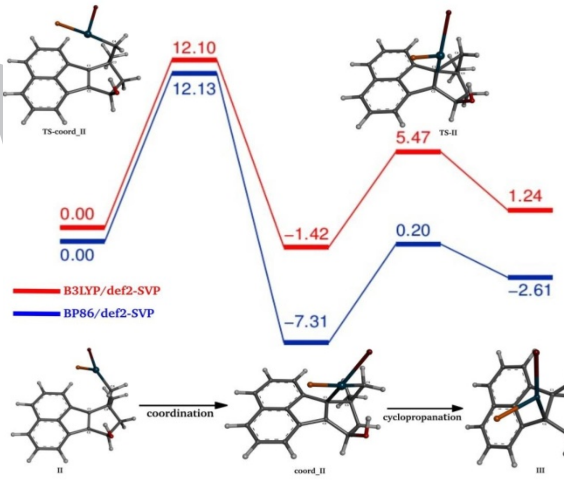


Figure 2: Reaction profile for the cyclopropanation step (Scheme 5). The energies are in kcal/mol from B3LYP-D3-BJ/def2-SVP//BP86-D3-BJ/def2-SVP level of theory. The optimized geometries are shown.

We have successfully elucidated the palladium catalyzed cascade cyclization in halogenated diene system for the formation of structurally discriminated unusual scaffolds. The variation of temperature in the reaction affected the mode of cyclization leading to the competitive predominance for fused cyclopentane-cyclopropane rings or aromatic analogue. Interestingly, the structural difference in substrate led to the variation in mode of termination ensuring the liberation of fused bicyclopentane rings as product under Pd-catalyzed reaction conditions. The formation of cyclopropane fused cyclopentane, was further justified using density functional theory based calculations.

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Notes and references

1. (a) Yamamoto, Y. *Chem. Soc. Rev.***,** **2014**, *43*, 1575; (b) Wu, X. F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.,* **2011**, *40*, 4986.; (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4442; (d) Nandi, S.; Singha, R.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* , **2012**, *53*, 2659; (e) Singha, R.; Roy, S.; Nandi, S.; Ray, P.; Ray, J. K. *Tetrahedron Lett.* **2013**, *54*, 657; (f) Nandi, S.; Singha, R.; Ray, J. K. *Tetrahedron*, **2015**, *71*, 669; (g) Ghosh, M.; Ray, J.K. *Tetrahedron* **2017**,*73*, 3731.
2. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4442.
3. Wang, G. –Z.; Shang, R.; Cheng, W. –M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307−18312.
4. X. Dong, Y. Han, F. Yan, Q. Liu, P. Wang, K. Chen, Y. Li, Z. Zhao, Y. Dong and H. Liu, *Org. Lett.*, 2016, **18**, 3774–3777.
5. (a) Zhang, Y.; Negishi, E. I. *J. Am. Chem.* Soc. **1989**, *111*, 3454. (b) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990,** *31*, 1343. (c) Wu, G.; Lamaty, F.; Negiehi, E. I. *J. Org. Chem.* **1989**, *54*, 2507; (d) Trost, B. M.; Lee, D. *C. J. Am. Chem. Soc.* **1988**, *110*, 7255; (e) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek A. L.; Hiemstra, H. *J. Organomet. Chem.* **2001**, *624***,** 244; (f) Paul, S.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2010**, *51*, 5604; (g) Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 7153.
6. Nakano, S.; Inoue, N.; Hamada, Y.; Nemoto, T. *Org. Lett.* **2015**, *17*, 2622.
7. (a) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1992**, *33*, 7965; (b) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 7661; (c) Zhang, Y.; Negeshi, E. I. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
8. Meyer, F. E.; Parsons, P. J.; Meijere, A. *J. Org. Chem*. **1991**,*56*, 6488.
9. Ray, D.; Ray, J. K. *Org. Lett.*, **2007,** *9*, 191.
10. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.*, **1988**, *37*, 785.
11. Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.*, **2011**, *32*, 1456.
12. Dieter, K. M.; Stewart, J. J. P. *J. Mol. Struct.*, **1988**, *163*, 143.
13. Schaefer, H. Horn; Ahlrichs, R. *J. Chem. Phys.*, **1992**, *97*, 2571.
14. (a) Becke, A. D. *Phys. Rev. A.,* **1988**, *38*, 3098. (a) Perdew, J. P. *Phys. Rev. B.*, ***1986***, *34*, 7406.
15. TURBOMOLE V6.5, a development of University of Karlsruhe and Forschungzentrum Karlsruhe GmbH, 19892007, TURBOMOLE GmbH since 2007.
16. Ahlrichs, R.; Br, M.; Hser, M.; Horn, H.; Khmel, C. *Chem. Phys. Lett.*, **1989**, *162***,** 165.

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Highlights

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