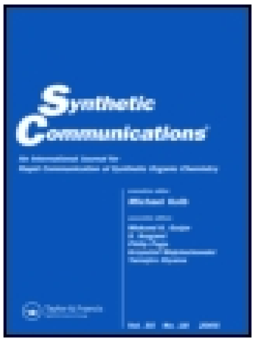

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Pd(0) catalyzed intramolecular Heck reaction: A general route for fused oxepine derivatives Pd(0) Catalyzed intramolecular Heck reaction

Arup Kumar Adak[1], Arabinda Mandal[1], Susanta Kumar Manna[1], Suresh Kumar Mondal[1], Akash Jana[1], Dipesh Ghosh[2], Debasish Kundu[3], Shubhankar Samanta[1], Jayanta K. Ray[4]

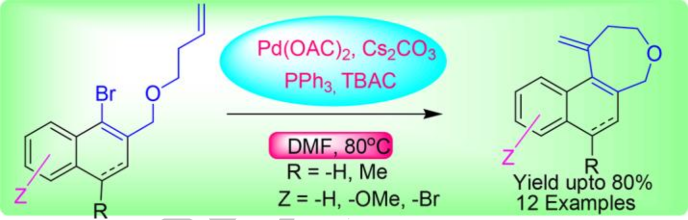
[1]Department of Chemistry, Haldia Government College, Haldia, India [2]Vivekananda Mission Mahavidyalaya, Haldia, India [3]Department of Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata, India [4]Department of Chemistry, Indian Institute of Technology, Kharagpur, India

Corresponding author Shubhankar Samanta , E-mail: chemshubha@gmail.com, Jayanta K. Ray E-mail: jkray@chem.iitkgp.ernet.in

Supplemental data for this article can be accessed on the publisher's website.

Abstract

A simple and facile approach for the synthesis of various structurally different tricyclic bent oxepine frameworks from readily accessible precursor has been introduced. The synthesis of substituted oxepine derivative involved Pd (0) catalyzed Heck reaction. This methodology enriches the literature for the large ring formation.



KEYWORDS: oxepine, Heck reaction, large ring, *exo-trig*, cyclization

INTRODUCTION

Seven-membered oxacycles has been the topic of recent interest because of their occurrence in natural products, used in polymers, and pharmacological applications.[1]

The benz[b]oxepine ring system both medicinally and pharmacogenically are important due to their anti-mycrobacterial, antifungal and anticancer activity.[2] Examples of naturally occurring natural products are monocyclic zoapatanol, tricyclic bent ptaeroxylin and linear oxepino[3,2-*g*]chromone.[3] Few more examples are gathered in Fig. 1. Another biologically active compound pacharin was isolated from plant *Bauhinia purpurea* which shows significant inhibition to cancer cell growth.[4] Similar type of natural active compound radulanins H and E isolated from *Radula perrottetii* also consist of oxepine subunit.[4] The oxepine ring has been prepared through C-C bond formation or via the coupling with a heteroatom which proceeds through the C-Y bond formation.[5] Among them palladium catalyzed intramolecular C-C bond formation is the versatile method for the synthesis of heterocyclic and carbocyclic molecules.[6] The cyclization of unsaturated substrate using an intramolecular Heck reaction promoted by palladium species is of fundamental importance for the designing of vast array of cyclic natural products.[7] Oh et al. has been synthesized oxacycles from haloene-ynes using palladium catalyst reductive cyclization.[8] A platinum-catalyzed medium size ring formation with significant yield was described by Dyker and co-workers.[9] Alternative routes have also been developed for these ring systems based on ring expansion, ring closing metathesis, reductive intramolecular cyclization with SmI_2, and several other methods.[10] Although numerous methods have been developed by several groups over the years, synthetic methods for the construction of medium-sized carbocycles and heterocycles are still challenging and deserve further exploration because of the unfavourable entropy and enthalpic reasons. [11]

RESULT AND DISCUSSION

Based on the previous report, [1-10] utilizing an oxepine ring system as the subunit of natural products, we have developed a new method via palladium-catalyzed intramolecular reaction of *O*-homoallylated derivatives of bromo alcohol. In preceding communication, we have described the synthesis of fused pyran ring system by intramolecular Heck reaction (Scheme 1).[12] Recently, our group synthesized pentalogin and its related natural product using similar methodology (Scheme 1).[13] In this connection, we wish to communicate our findings for the formation of oxepine derivatives from *O*-homoallylated derivatives of bromo alcohol.

Initially, we targeted to synthesize *O*-homoallylated derivatives by treating with bromo alcohol with 4-bromobutene but we were unable to get the Heck precursor of oxepine derivatives. Changing our strategy by converting bromoalcholos **3** to bromomethylvinyl bromide derivatives **4**, which on treatment with but-3-en-1-ol and sodium hydride in THF at 0°C to produce *O*-homoallylated derivatives **5** (Scheme 2). Similarly the *O*-homomethyl allylated compound **6** was synthesized by the reaction of 3-Methyl-but-3-en-1-ol with bromomethyl vinyl bromide in the presence of sodium hydride in THF at 0 ^{0}C.

Pivotal role of catalyst, base and ligand on the heck reaction has been well explored in the literature.[14] To standardized the reaction condition, experiments were performed in which the reaction parameters such as catalyst, base, solvents were varied for model substrate **5a** (Schematic representation in Table 1). The *exo-trig* cyclization takes place in the presence of $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ (Table 1, entries 1-10). In absence of external ligand PPh_3 the yield was decreased substantially (Table 1, entries 5-7) whereas $Pd(OAc)_2$ with added PPh_3 increased the yield to 80% (Table 1, entry 1). This is because of oxidative addition of C-Br bond to the Pd(0) complex facilitated by exogenous PPh_3. Moreover, the yield of Heck reaction was also studied by varying bases. We have investigated the role of different bases such as Cs_2CO_3, Na_2CO_3, K_2CO_3 and Et_3N (Table 1, entries1, 6-8) for this cyclization process. Among the carbonate bases, the cesium salt is stronger base and has a higher solubility in DMF. Consequently, β-H elimination in catalytic cycle in Heck reaction becomes more promising in presence of cesium carbonate and should provide much higher yield than other carbonate bases. This explanation was supported by the experimental observation where the intramolecular Heck cyclisation in presence of Cs_2CO_3 afforded a good yield of oxepine derivative with higher rate compared to sodium and potassium carbonate. On the other hand, Et_3N gave very poor yield in presence of $Pd(OAc)_2$ because of sterically hindered transition state during β-H elimination. Alternatively, commonly used solvents in heck reaction are DMF, acetonitrile and dioxane. Among the solvents, dioxane, instead of DMF, failed to produce satisfactory yield of **7a** under this condition (entry 2). Unfortunately, acetonitrile as solvent was incompetent for cyclisation of **5a** even after 12 h heating at 80 ^{0}C (entry 3). Hence the optimum condition for the reaction was $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and TBAC (tetrabutylammonium chloride) in DMF at 80 ^{o}C (Table 1).

Using optimum condition (Table 1, entry 1), the intramolecular Heck reaction was performed with *O*-homoallylated products to afford fused seven member oxacycles with excocyclic double bond **7** in 43-80 % yield. The reaction works well with both aromatic and vinyl system and can tolerate substituted benzene ring. The more electron rich aromatic ring afforded oxepine derivative in lower yield as oxidative addition of Pd(0) to C-Br bond becomes more difficult and as a result Z = H precursors (**5a** and **5g**) produce better yield than the substituted derivatives (**5b-5f** and **5h-5l**). Beside electron donating substituent, we have also tested this cyclization for electron withdrawing substituent to aromatic ring. The Z = -NO_2 group did not furnish any cyclised product whereas Z = -Br provided our desired product **7l** with noticeable influence on yield (43%) and reaction time. Here, difficulty in solubility was responsible for significantly lower yield of cyclized product. The ease of oxepine derivatives formation in presence of electron donating or electron withdrawing substituent on aryl ring depends either by stabilization of Ar-Pd(II)-X complex or insertion of alkene system in the catalytic cycle of Heck reaction.[15] However, in case of compound **5j** only one isomeric product **7j** was obtained in 60% yield (Table 2).

The mechanism for oxepine derivative formation via intramolecular Heck rection is well documented in literature.[16] This process involves initial oxidative addition of a $L_2Pd(0)$ catalyst to afford a σ-arylpalladium(II) complex of **5a**. Intramolecular coordination of an alkene and subsequent formation of carbon-carbon bond by syn addition provide a σ-alkylpalladium(II) intermediate, which readily undergoes *β*-hydride elimination to release the oxepine derivative **7a**. Conversion of the hydridopalladium(II) complex to the active $L_2Pd(0)$ catalyst by base completes the catalytic cycle.

The isomeric product for 7j can be explained from the mechanistic point of view in the *β*-H elimination step of intramolecular Heck reaction (Scheme 4). Steric influence plays a crucial in the reductive elimination of HBr from alkyl Pd (II) complex.[17] The distance between large Pd (II) complex and Ar-H atom is significant to minimised steric interaction in substrates **7a-e, 7g-h & 7k** compared to **7j**. Additionally, similar type substrate **7f** does not enjoy steric interaction as Sp^3 C-H and Pd (II) complex adopts a preferred conformation by which it gives normal Heck product **7f**. Therefore, **7j** undergoes syn rearrangement to produce less crowded **7j"** intermediate which obtained thermodynamically stable isomeric product **7j**.

In previous report we have successfully prepared tetrcyclic derivatives via palladium catalyzed C-H activation process from *O*-methylallyted derivatives of **3**.[12] To obtain such type of C-H activation product, when the substrate **6** was subjected to Heck reaction under identical condition, we did not get the desired product **8** as shown in Scheme 5. This can be explained by the formation of strained five membered ring during C-H activation (Scheme 5).

CONCLUSION

In summary, we have developed a general methodology for the synthesis of oxepine derivatives via intramolecular Heck reaction which will enrich the literature for large ring formation. Further studies are underway to synthesis of bioactive molecules bearing oxepine units for future communication.

EXPERIMENTAL

Typical Experimental Procedure For Heck Reaction (7)

Compounds (**7**, 1equiv.), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (0.25 equiv.), Cs$_2$CO$_3$ (1.2 equiv.), DMF (6 mL) were placed in a two neck round bottom flask. After degassing with N$_2$, the mixture was heated to 80-85 ^{o}C for 4-5h. After cooling the reaction mixture was diluted with cold water and extracted with ether (20 mL x 3) and dried (Na$_2$SO$_4$). The solvent was evaporated and the crude product was purified by preparative thin layer chromatography.

1-Methylene-5, 6, 7, 9, 10, 11-Hexahydro-8-Oxa-Cyclohepta[A]Naphthalene (7a)

Colourless Liquid, ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.22 (t, 2H, *J* = 8.0Hz), 2.62 (t, 2H, *J* = 6.0Hz,), 2.76 (t, 2H, *J* = 8.0Hz), 3.90 (t, 2H, *J* = 6.0Hz), 4.30 (s, 2H), 5.00 (s, 1H), 5.35 (s, 1H), 7.12-7.18 (m, 3H), 7.36 (d, 1H, *J* = 6.8Hz). ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 27.8, 28.3, 39.4, 71.5, 74.4, 116.8, 125.3, 126.1, 126.5, 127.1, 134.3, 135.6, 135.9, 135.9, 144.4. IR ν_{max} (CHCl$_3$, cm^{-1}) 2985, 2844, 1625, 1540. HRMS calcd for C$_{15}$H$_{16}$O [M$^+$+H]: 213.1281, found: 213.1285.

SUPPORTING INFORMATION

Electronic supplementary information (ESI) (1H and 13C spectra of representative compounds) for this article and can be accessed on the publisher's website.

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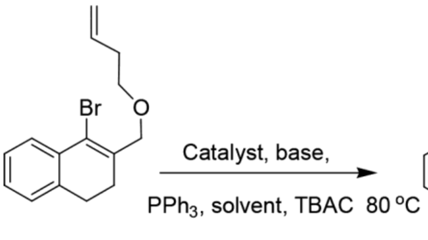
Table 1 Intramolecular Heck cyclization of *O*-homoallylated derivative by using different type of bases, catalysts and solvent[a]

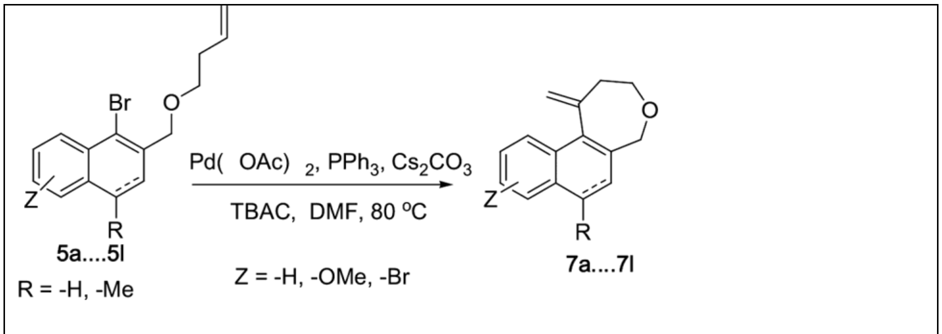


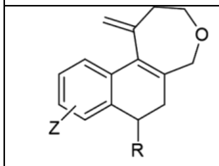
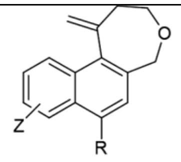
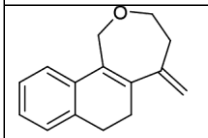
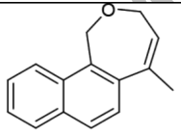
5a 7a

Entry	Catalyst	Base	Time	Yield (%) of **7a**
1.	**$Pd(OAc)_2$**	**Cs_2CO_3**	**5**	**80**
2.	$Pd(OAc)_2$	Cs_2CO_3	6	63[b]
3.	$Pd(OAc)_2$	Cs_2CO_3	12	0[c]
4.	$PdCl_2$	Cs_2CO_3	10	48
5.	$PdCl_2(PPh_3)_2$	Cs_2CO_3	12	55[d]
6.	$Pd(PPh_3)_4$	Cs_2CO_3	12	33[d]
7.	$Pd_2(dba)_3$	Cs_2CO_3	10	39[d]
8.	$Pd(OAc)_2$	Na_2CO_3	8	45
9.	$Pd(OAc)_2$	K_2CO_3	8	47
10.	$Pd(OAc)_2$	Et_3N	9	50

[a]**Reagent and conditions**: Substrate (1 equiv.), Catalyst (10 mol %), Base (1.2 equiv.), PPh_3 (0.25 equiv.), TBAC (1.5 equiv.), DMF, 80 °C; [b]Dioxane solvent; [c]Acetonitrile solvent; [d]Reaction was performed without PPh_3.

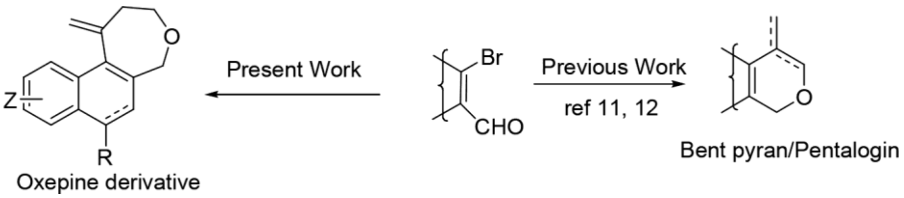
Table 2 Synthesis of oxepine derivatives *via* Pd-catalyzed intramolecular heck coupling[a]



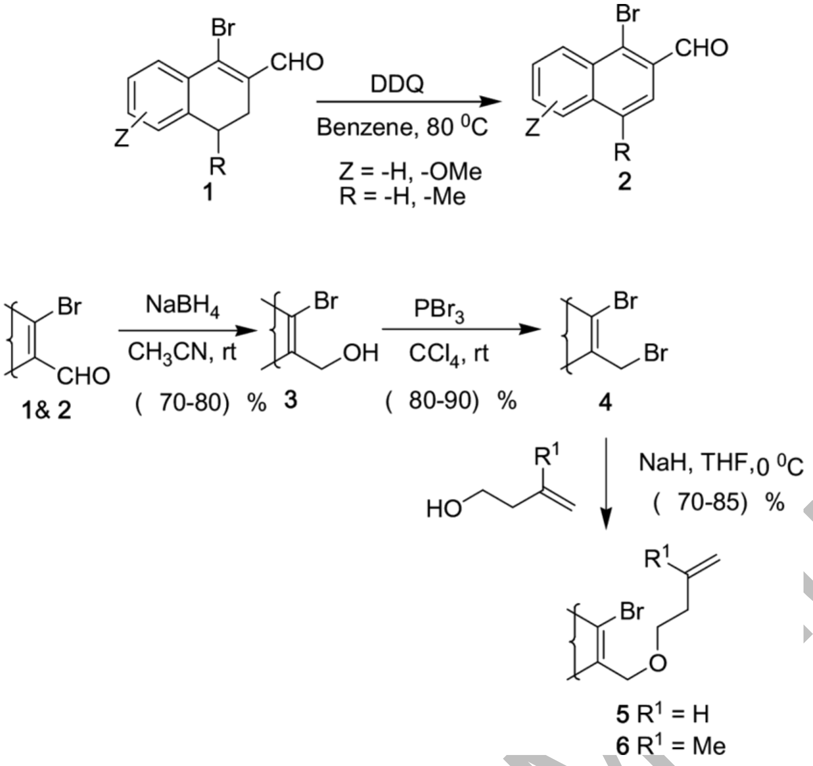
 **7a** (R = H, Z = H), 80 % **7b** (R = H, Z = 5-OMe), 69% **7c** (R = H, Z = 6-OMe), 72%[b] **7d** (R = H, Z = 7-OMe), 67%[b] **7e** (R = Me, Z = H), 73% 7l (R = H, Z = Br), 43%[c]	 7g (R = H, Z = H), 76% 7h (R = H, Z = 7-OMe), 63%[b] 7i (R = Me, Z = H), 71%[b] 7k (R = H, Z = 6-OMe), 65%[b]
 7f (R = H, Z = H), 66%[b]	 7j (R = H, Z = H), 60%[b]

[a] **Reagent and conditions**: Reactant 5a-5k (1 equiv.), Pd(OAc)$_2$ (10 mol %), Cs$_2$CO$_3$ (1.2 equiv.), PPh$_3$ (0.25 equiv.), TBAC (1.5 equiv.), DMF, 80 ^{0}C, 4hrs; [b] 5 hrs time was required; [c] 12 hrs time was required.

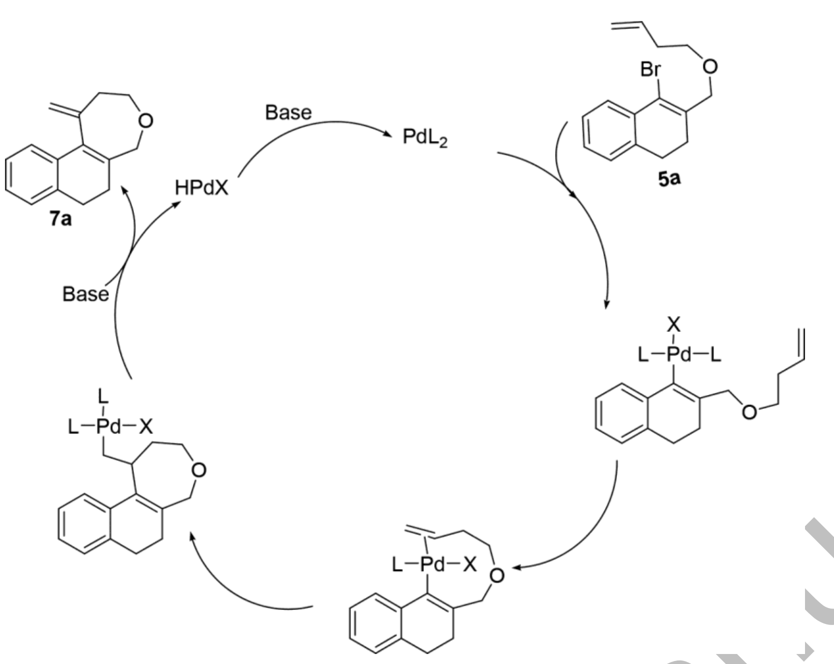
Scheme 1. Synthesis of different oxacycles by Heck reaction



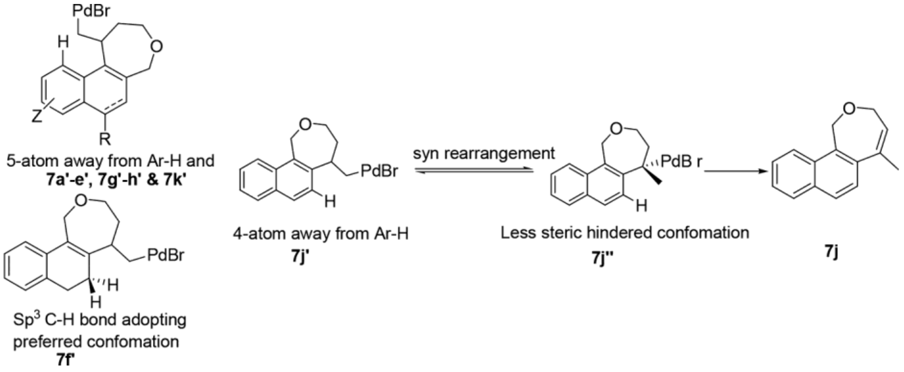
Scheme 2. Preparation of intramolecular Heck precursor



Scheme 3. Proposed mechanism of oxepine derivative formation



Scheme 4. Mechanistic overview for isomerisation in Heck reaction.



Scheme 5. Pd (0) catalyzed C-H activation

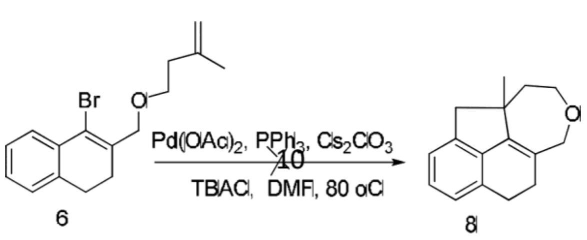
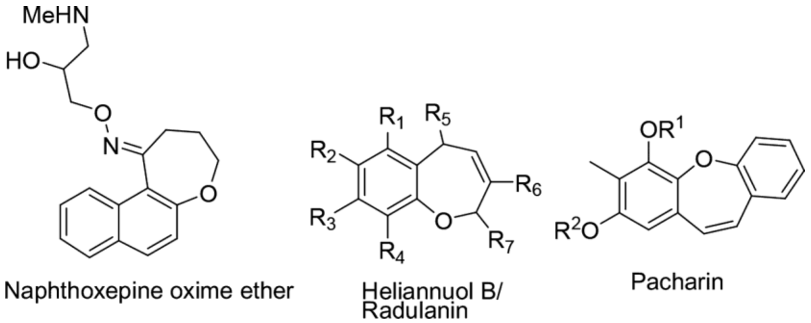


Figure 1. Biologically active compounds of oxepine ring system



Naphthoxepine oxime ether

Heliannuol B/
Radulanin

Pacharin