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

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ABSTRACT
A simple and facile approach for the synthesis of various structurally different tricyclic bent oxepine frameworks from a 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.

GRAPHICAL ABSTRACT

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Introduction
Seven-membered oxacycles have been a topic of recent interest because of their occurrence in natural products and use in polymers and pharmacological applications. [1] The benz[ b] oxepine ring system both medicinally and pharmacogenically is important because of its antimycrobacterial, 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] A few more examples are gathered in Fig. 1. Another biologically active compound, pacharin, was isolated from the plant Bauhinia purpurea which shows significant inhibition to cancer cell growth. [4] A similar type of natural active compound radulanins H and E isolated from Radula perrottetii also consists of an 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 designing of a vast array of cyclic natural products.\[7\] Oh et al. 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 coworkers.\[9\] 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 unfavorable entropy and enthalpy.\[11\]

**Results and discussion**

Based on the previous reports,\[1–10\] 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 a preceding communication, we have described the synthesis of a fused pyran ring system by intramolecular Heck reaction (Scheme 1).\[12\] Recently, our group synthesized pentalogin and its related natural product using a similar methodology (Scheme 1).\[13\] We now communicate our findings about the formation of oxepine derivatives from O-homoallylated derivatives of bromo alcohol.

Initially, we targeted synthesis of O-homoallylated derivatives by treatment with bromo alcohol and 4-bromobutene but we were unable to get the Heck precursor of oxepine derivatives. We changed our strategy by converting bromoalcholos \(3\) to bromomethylvinyl bromide derivatives \(4\), which on treatment with but-3-en-1-ol and sodium hydride in tetrahydrofuran (THF) at 0 °C to produce O-homoallylated derivatives \(5\) (Scheme 2).

![Biologically active compounds of oxepine ring system.](image1.png)

**Figure 1.** Biologically active compounds of oxepine ring system.

![Synthesis of different oxacycles by Heck reaction.](image2.png)

**Scheme 1.** Synthesis of different oxacycles by Heck reaction.
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 °C.

The pivotal roles of catalyst, base, and ligand on the Heck reaction have been well explored in the literature.\cite{14} To standardize the reaction condition, experiments were performed without PPh 3.

**Table 1.** Intramolecular Heck cyclization of O-homoallylated derivative by using different type of bases, catalysts, and solvent.\textsuperscript{a}

| Entry | Catalyst | Base | Time (h) | Yield (%) of 7a |
|-------|----------|------|----------|-----------------|
| 1     | Pd(OAc)\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 5         | 80              |
| 2     | Pd(OAc)\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 6         | 63\textsuperscript{b} |
| 3     | Pd(OAc)\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 12        | 0\textsuperscript{c} |
| 4     | PdCl\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 10        | 48              |
| 5     | PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 12        | 55\textsuperscript{d} |
| 6     | Pd(PPh\textsubscript{3})\textsubscript{4} | Cs\textsubscript{2}CO\textsubscript{3} | 12        | 33\textsuperscript{d} |
| 7     | Pd(dba)\textsubscript{2} | Cs\textsubscript{2}CO\textsubscript{3} | 10        | 39\textsuperscript{d} |
| 8     | Pd(OAc)\textsubscript{2} | Na\textsubscript{2}CO\textsubscript{3} | 8         | 45              |
| 9     | Pd(OAc)\textsubscript{2} | K\textsubscript{2}CO\textsubscript{3} | 8         | 47              |
| 10    | Pd(OAc)\textsubscript{2} | Et\textsubscript{3}N | 9         | 50              |

\textsuperscript{a}Reagent and conditions: substrate (1 equiv.), catalyst (10 mol %), base (1.2 equiv.), PPh\textsubscript{3} (0.25 equiv.), TBAC (1.5 equiv.), DMF, 80 °C.

\textsuperscript{b}Dioxane solvent.

\textsuperscript{c}Acetonitrile solvent.

\textsuperscript{d}Reaction was performed without PPh\textsubscript{3}.
performed in which the reaction parameters such as catalyst, base, and 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, PdCl₂, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, and Pd₂(dba)₃ (Table 1, entries 1–10). In the absence of external ligand PPh₃, the yield was decreased substantially (Table 1, entries 5–7), whereas Pd(OAc)₂ with added PPh₃ 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 PPh₃. Moreover, the yield of Heck reaction was also studied by varying bases. We have investigated the role of different bases such as Cs₂CO₃, Na₂CO₃, K₂CO₃, and Et₃N (Table 1, entries 1 and 6–8) for this cyclization process. Among the carbonate bases, the cesium salt is a stronger base and has greater solubility in dimethylformamide (DMF). Consequently, β-H elimination in catalytic cycle in the Heck reaction becomes more promising in the presence of cesium carbonate and should provide much greater yield than other carbonate bases. This explanation was supported by the experimental observation where the intramolecular Heck cyclization in presence of Cs₂CO₃ afforded a good yield of oxepine derivative with higher rate compared to sodium and potassium carbonate. On the other hand, Et₃N gave very poor yields in the presence of Pd(OAc)₂ because of the sterically hindered transition state during β-H elimination. Alternatively, commonly used solvents in the Heck reaction are DMF,

![Scheme 3](image-url)

**Scheme 3.** Synthesis of oxepine derivatives via Pd-catalyzed intramolecular Heck coupling. Notes: 

| Reagent and conditions: Reactant 5a–5k (1 equiv.), Pd(OAc)₂ (10 mol%), Cs₂CO₃ (1.2 equiv.), PPh₃ (0.25 equiv.), TBAC (1.5 equiv.), DMF, 80 °C, 4 h; ²5 h were required; ³12 h were required. |
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 not useful for cyclization of \(5a\) even after 12 h of heating at 80 °C (entry 3). Hence, the optimum condition for the reaction was \(\text{Pd(OAc)}_2\), \(\text{PPh}_3\), \(\text{Cs}_2\text{CO}_3\), and \(\text{TBAC}\) (tetrabutylammonium chloride) in DMF at 80 °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 the substituted benzene ring. The more electron-rich aromatic ring afforded oxepine derivative in lower yield as oxidative addition of \(\text{Pd}(0)\) to C-Br bond becomes more difficult and as a result \(Z=\text{H}\) precursors (\(5a\) and \(5g\)) produce better yield than the substituted derivatives (\(5b–5f\) and \(5h–5l\)). Beside the electron-donating substituent, we have also tested this cyclization for electron-withdrawing substituent to aromatic ring. The \(Z=\text{-NO}_2\) group did not furnish any cyclized product whereas \(Z=\text{-Br}\) 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 derivative formation in the presence of electron-donating or electron-withdrawing substituent on aryl ring depends either on stabilization of \(\text{Ar-Pd(II)-X}\) complex or insertion of alkene system in the catalytic cycle of Heck reaction.\[^{[15]}\]\(^{[15]}\) However, in the case of compound \(5j\) only one isomeric product \(7j\) was obtained in 60% yield (Scheme 3).

The mechanism for oxepine derivative formation via intramolecular Heck reaction is well documented in the literature.\[^{[16]}\]\(^{[16]}\) This process involves initial oxidative addition of a \(\text{L}_2\text{Pd}(0)\) catalyst to afford a \(\sigma\text{-arylpalladium(II)}\) complex of \(5a\). Intramolecular coordination

![Scheme 4. Proposed mechanism of oxepine derivative formation.](image)
of an alkene and subsequent formation of carbon–carbon bond by syn addition provide an σ-alkylpalladium(II) intermediate, which readily undergoes β-hydride elimination to release the oxepine derivative 7a (Scheme 4). Conversion of the hydridopalladium(II) complex to the active L₂Pd(0) catalyst by a 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 5). 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 minimize steric interaction in substrates 7a′–e′, 7g′–h′, and 7k′ compared to 7j′. Additionally, similar type substrate 7f′ does not enjoy steric interaction as the Sp³ 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 the less crowded 7j′′ intermediate, which obtains the thermodynamically stable isomeric product 7j.

In a previous report we have successfully prepared tetracyclic 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 conditions, we did not get the desired product 8 as shown in Scheme 6. This can be explained by the formation of strained five-membered ring during C-H activation (Scheme 6).

**Conclusion**

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

**Experimental**

**Typical experimental procedure for Heck reaction (7)**

Compound 5 (1 equiv.), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (0.25 equiv.), Cs$_2$CO$_3$ (1.2 equiv.), and DMF (6 mL) were placed in a two-necked, round-bottomed flask. After degassing with N$_2$, the mixture was heated to 80–85°C for 4–5 h. 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 (TLC).

**1-Methylene-5,6,7,9,10,11-hexahydro-8-oxa-cyclohepta[a]naphthalene (7a)**

Colorless liquid.$^1$H NMR (CDCl$_3$, 400 MHz) δ: 2.22 (t, 2H, $J = 8.0$ Hz), 2.62 (t, 2H, $J = 6.0$ Hz), 2.76 (t, 2H, $J = 8.0$ Hz), 3.90 (t, 2H, $J = 6.0$ Hz), 4.30 (s, 2H), 5.00 (s, 1H), 5.35 (s, 1H), 7.12–7.18 (m, 3H), 7.36 (d, 1H, $J = 6.8$ Hz). $^{13}$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.

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