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Pd(0) catalyzed intramolecular Heck reaction: a versatile route for the synthesis of 2-aryl substituted 5-, 6-, and 7-membered O-containing heterocycles

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ABSTRACT

An efficient and convenient method for the synthesis of 2-aryl substituted tetrahydropyran, tetrahydrofuran, and oxepine derivatives via intramolecular palladium catalyzed cyclization is developed. The two *exo*-cyclic double bonds at adjacent carbon atoms in these ring systems could serve as potential dienes for cycloaddition reactions.

1. Introduction

The intramolecular Heck reaction is a very useful approach for the synthesis of various heterocyclic and carbocyclic rings.[1] This reaction is also important for the synthesis of natural products. Substituted pyran, furan, and oxepine rings are common structural components found in many natural products such as mycalamide,[2] (+)-trans-kumasyne,[3] and roglolenyne.[4] Laulimide, a novel cancer-therapy agent which contains two pyran rings can be synthesized by nucleophilic attack on a carbopalladium complex.[5] Morphine contains a fused furan ring and has been synthesized via intramolecular Heck reaction.[6] Alternatively, an intermolecular Heck reaction is used for the synthesis of (−)-strychnine, which contains an oxepine subunit.[7] These ring systems have been prepared by various methods including radical cyclization,[8] olefin metathesis[9] and metal catalyzed cyclization.[10,11] Among these, palladium catalyzed cyclization is a very powerful method due to its tolerance of a wide variety of functional groups, thus neatly avoiding protection group chemistry. Based on previous reports utilizing pyran, furan, and oxepine ring systems as the subunit of many natural products, we propose a general method for the synthesis of these ring systems via palladium catalyzed intramolecular Heck reaction.[12–15]

In this context, we describe the intramolecular Heck cyclization of 4-(2-bromoallyloxy)-4-arylbut-1-ene, 4-(2-bromoallyloxy)-2-methyl-4-arylbut-1-ene and 3-(2-bromoallyloxy)-3-arylprop-1-ene which yields the corresponding tetrahydropyran, oxepine, and tetrahydrofuran, respectively. Herein, we report two modes of cyclization, one being the *exo* mode leading to substituted tetrahydropyran and tetrahydrofurans and the other being the *endo* mode that leads to the substituted oxepines. The main feature of the 2-aryl substituted tetrahyropyran and tetrahyrofuran rings prepared herein is the presence of two adjacent double bonds that can be utilized in cycloaddition reactions leading to 2-aryl substituted fused pyran and furan rings.[16]

First, the starting materials for the Heck reaction were prepared by *O*-2-bromo-allylation of 1-arylbut-3-en-1-ol (**2**), 1-arylbut-3-methyl-3-en-1-ol (**3**), and 1-arylprop-2-ene-1-ol (**4**). The alcohols **2** and **3** were synthesized by treating the appropriate aryl aldehyde **1** with indium metal, sodium iodide, and allyl bromide or methallyl bromide in dimethylformamide at room temperature. The alcohols **4** were synthesized by treating aryl aldehydes with vinylmagnesium bromide in tetrahydrofuran at 0 °C followed by stirring at room temperature (25–30 °C). Alcohols **2**, **3**, and **4** were reacted with 2,3-dibromopropene in the presence of sodium hydride in THF at 0 °C to give 4-(2-bromoallyloxy)-4-arylbut-1-ene (**5**), 4-(2-bromoallyloxy)-2-methyl-4-arylbut-1-ene (**6**), and 3-(2-bromoallyloxy)-3-arylprop-1-ene (**7**), respectively, as the precursors for the intramolecular Heck reaction, (Scheme 1).

Heck reaction precursors **5, 6**, and **7** (1 mmol) with $Pd(OAc)_2$ (5 mol %), PPh_3 (0.5 equiv) and Cs_2CO_3 (1.2 equiv) in dimethylformamide (8 ml) at 80–85 °C yielded the desired 4,5-dimethylene-2-aryl-tetrahydropyrans **8a–h** (Table 1, entries 1–8), 4-methyl6-methylene-2-aryl-2,3,6,7-tetrahydro-oxepines **9a–e**

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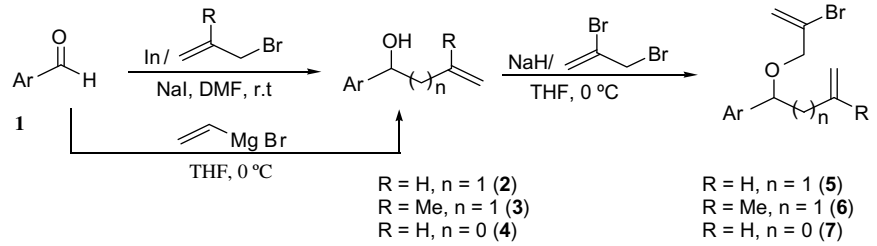


Scheme 1. Preparation of *O*-2-bromo-allylated derivatives.

Table 1
Pd-catalyzed cyclization of various 2-bromo-allylated derivatives[a]

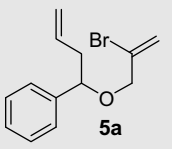
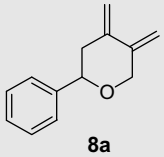
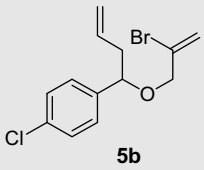
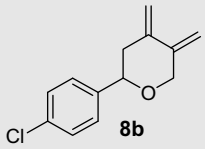
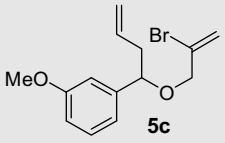
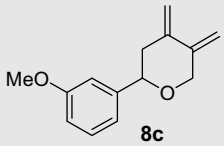
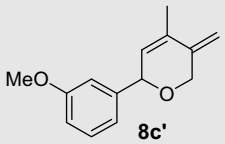
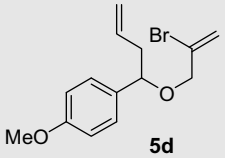
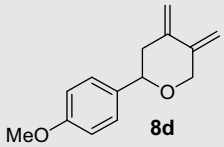
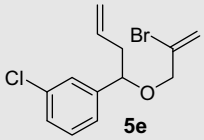
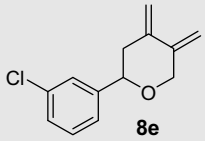
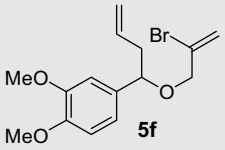
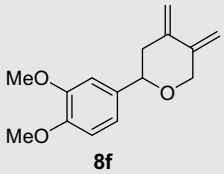
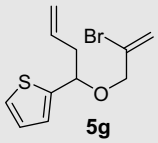
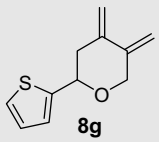
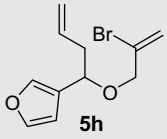
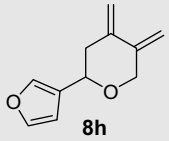
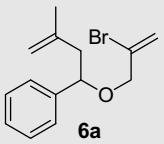
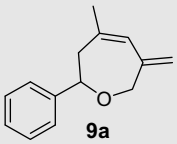
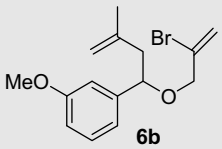
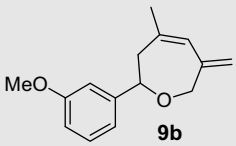
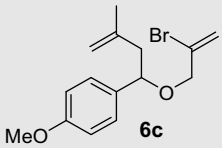
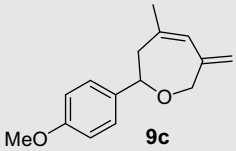
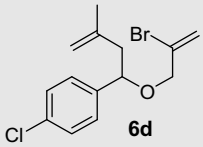
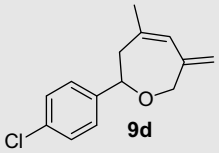
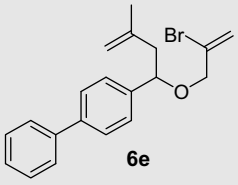
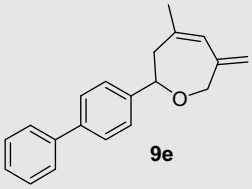
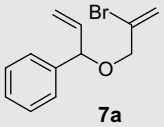
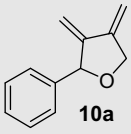
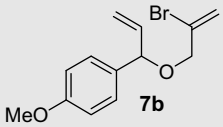
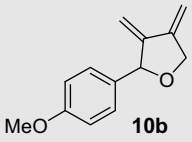
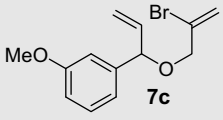
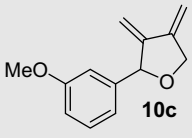
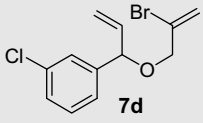
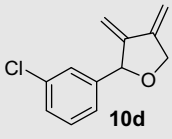
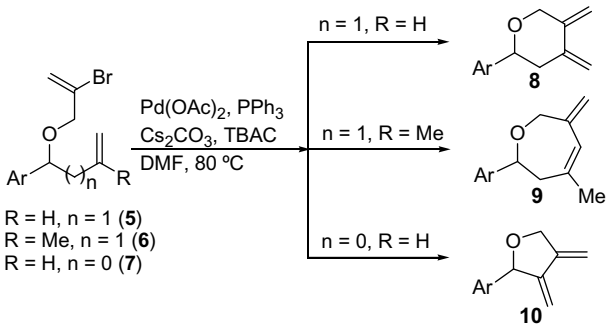
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **5a**	 **8a**	1.83	80
2	 **5b**	 **8b**	1.75	70
3	 **5c**	 **8c**  **8c'**	1.5	65 + 10
4	 **5d**	 **8d**	2.0	78
5	 **5e**	 **8e**	1.5	72
6	 **5f**	 **8f**	1.5	70
7	 **5g**	 **8g**	1.5	82
8	 **5h**	 **8h**	2.0	65

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)
9	 **6a**	 **9a**	1.0	80
10	 **6b**	 **9b**	1.5	75
11	 **6c**	 **9c**	1.2	68
12	 **6d**	 **9d**	1.4	70
13	 **6e**	 **9e**	2	60
14	 **7a**	 **10a**	1.0	80
15	 **7b**	 **10b**	1.30	72
16	 **7c**	 **10c**	1.0	70
17	 **7d**	 **10d**	1.5	75

[a] Reagents and conditions: **5a–h**, **6a–e**, **7a–d** (1 equiv), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (1.2 equiv), PPh_3 (0.5 equiv), TBAC (1.5 equiv), DMF, 80–85 °C.

(Table 1, entries 9–13), and 3,4-dimethylene-2-aryl-tetrahydrofurans **10a–d** (Table 1, entries 14–17) in moderate to good yields (Scheme 2). *Exo*-trig cyclization was observed with all the substrates **5** and **7**, yielding products with two adjacent exocyclic double bonds, except in the case of **5c** where two products **8c** and **8c′** were obtained, one having an exocyclic double bond and the other an endocyclic double bond due to isomerization. In the case of compounds **6,** *endo*-trig cyclization was observed to yield oxepine



Scheme 2. Pd-catalyzed cyclization of 2-bromo-allylated derivatives.

derivatives in good yields. The reactions are suitable for substrates possessing both electron donating and electron withdrawing substituents, except nitro groups. The reaction was also successful using acetonitrile as solvent and K_2CO_3 as base.

In conclusion, we have developed a method for the synthesis of various substituted tetrahydropyran, tetrahydrofuran, and oxepine derivatives via palladium catalyzed intramolecular Heck reaction. We expect that the two adjacent exocyclic double bonds in the tetrahydropyrans and tetrahydrofurans can be utilized in cycloaddition reactions leading to various substituted fused pyran and furan derivatives.

2. Typical experimental procedure for the Heck reaction

Compound **5, 6**, or **7** (1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (0.5 equiv), Cs_2CO_3 (1.2 equiv), tetrabutylammonium chloride (1.5 equiv), and DMF (8 mL) were placed in a two-necked round-bottomed flask. After degassing with N_2, the mixture was heated at 80–85 °C for 2 h. After cooling, the reaction mixture was diluted with cold water and extracted with ether. The combined organics were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by preparative thin layer chromatography.

2.1. Spectral data of representative compounds[†]

Compound **8c**: Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.48–2.62 (m, 2H), 3.81 (s, 3H), 4.22 (d, 1H, J = 12.8 Hz) 4.47 (d, 2H, J = 12.8 Hz), 4.84 (s, 1H) 4.86 (s, 1H), 5.18 (s, 1H), 5.20 (s, 1H), 6.81–6.83 (m, 1H), 6.94–6.95 (m, 2H), 7.24–7.28 (m, 1H). ^{13}CNMR ($CDCl_3$, 50 MHz) δ: 42.43, 55.27, 72.17, 79.64, 109.02, 110.04, 111.19, 113.44, 118.20, 129.45, 143.50, 143.68, 143.71, 159.17. MS-ESI: m/z = 217.1197 (100%) [M^++H]. HRMS calcd for $C_{14}H_{17}O_2$ [M^+ +H]: 217.123; found: 217.1197.

Compound **9b**: Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.81 (3H, s), 2.50–2.74 (m, 2H), 3.81 (s, 3H) 4.39, 4.43, 4.60, 4.64 (AB-q, 2H, J = 14.4 Hz), 4.76–4.82 (m,1H), 4.91 (s, 1H), 4.92 (s, 1H), 6.08 (s, 1H), 6.79–6.81 (m, 1H), 6.91–6.93 (m, 2H), 7.22–7.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 27.10, 44.10, 55.25, 73.50, 81.51, 110.14, 112.95, 114.00, 118.08, 127.33, 129.36, 136.90, 145.19, 145.70, 159.70. MS-ESI: m/z = 253.1181 (100%) [M^++Na]. HRMS calcd for $C_{15}H_{18}O_2Na$ [M^+ +Na]: 253.1207, found: 253.1181.

Compound **10d**: Colorless liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.56, 4.53, 4.66, 4.69 (AB-q, 2H, J = 13.2 Hz), 4.71 (s, 1H), 5.03 (s, 1H) 5.34 (s, 1H) 5.48 (s, 1H) 5.53 (s, 1H) 7.24–7.29 (m, 1H) 7.34 (s, 1H) 7.54–7.51 (m, 1H) 7.69–7.71 (m, 1H). ^{13}CNMR ($CDCl_3$, 50 MHz) δ: 71.56, 83.75, 103.18, 105.86, 125.39, 127.28, 128.13, 128.73, 128.78, 129.64, 130.83, 132.38.

Acknowledgment

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[†] The substituted tetrahydrofuran derivatives were very unstable, as a result mass spectra and CHN analysis could not be obtained.