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Substrate dependent intramolecular palladium-catalysed cyclisation and subsequent β-H elimination or C–H activation: a general method for the synthesis of fused pyran rings

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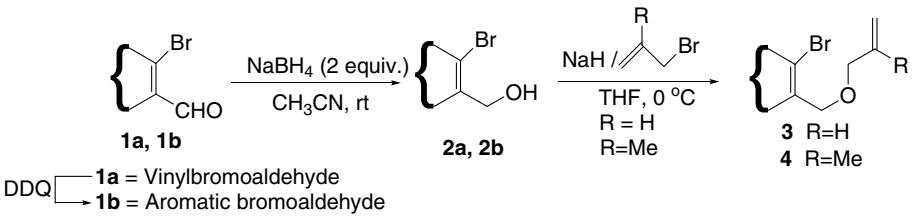
Abstract

An efficient and convenient method for the synthesis of fused pyran rings via intramolecular palladium-catalysed cyclisation followed by β-H elimination or C–H activation has been developed. It is possible to utilise this method for the synthesis of benzopyran systems.

Keywords: C–H activation; Benzopyran; Tetracyclic pyran ring; Heterocycles

1. Introduction

Intramolecular palladium-catalysed oxidative cyclisation is a powerful method for the construction of heterocycles.[1] This method has been extended for the synthesis of many natural products such as the phenanthridone alkaloid, (+)-pancratistin and its analogs.[2] Diospongines A and B also possess a six-membered cyclic ether core unit with two aromatic side chains.[3] Carbohydrate derivatives bearing fused pyran or furan rings have also been prepared by intramolecular Heck cyclisation.[4] Guillou and co-workers utilised an intramolecular Heck cyclisation to prepare a benzopyran ring during the synthesis of the alkaloid lycoramine.[5] Based on a previous report utilising a pyran ring system as the subunit of natural products, we proposed a method for the development of these ring systems via palladium-catalysed intramolecular[6–8] reaction of substituted cyclic derivatives of 3-allyloxy-1-bromopropene and 3-(3-bromo-allyloxy)-2-methylpropene. Attention was first focused on the construction of the starting materials for the Heck reaction by O-allylation and O-methallylation of bromoalcohols. Thus, vinyl bromoaldehydes **1** were first reduced to vinyl bromoalcohols **2a** with sodium borohydride in CH_3CN (Scheme 1).



Scheme 1. Preparation and O-allylation/methallylation of bromovinyl alcohol.

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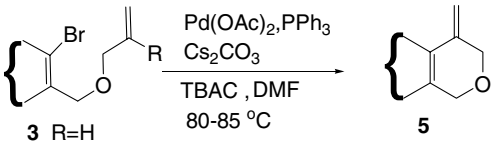
Vinyl bromoaldehydes **1a** were also aromatised with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to produce aromatic bromoaldehydes **1b**, which on sodium borohydride reduction yielded aromatic bromoalcohols **2b**. Alcohols **2a** and **2b** were converted to O-allylated/methallylated products **3** and **4** (for structures, see Table 1) by reaction with allyl bromide/methallyl bromide in the presence of sodium hydride in THF at 0 °C. The intramolecular Heck reaction was performed with O-allylated **3** in the presence of $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and TBAC (tetrabutylammonium chloride) in DMF at 80 °C to afford pyran derivatives **5a**–**f** (Table 1, entries 1–6, Scheme 2). With compound **3g**, however, products **5g** and **5h** were formed in a 65:10 ratio.

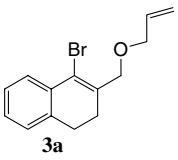
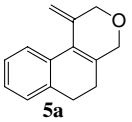
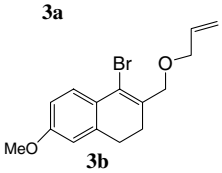
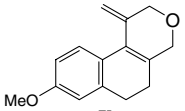
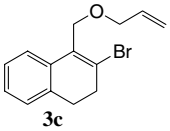
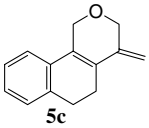
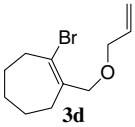
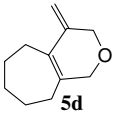
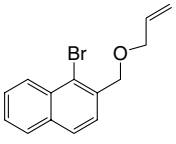
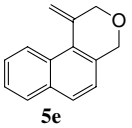
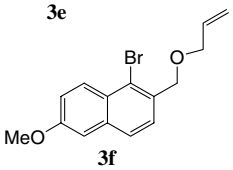
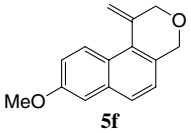
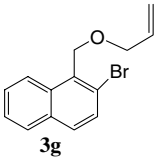
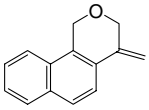
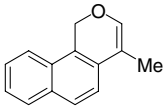
During our studies, an interesting result was observed (Scheme 3). O-Methallylated compounds **4a**–**c** and aromatised compounds **4d**, **4e** were subjected to intramolecular Heck reaction under the same conditions to afford pyrans **6a**–**e**, while compounds **4f** and **4g** afforded *gem*-dimethyl products due to the difficulty of formation of a four-membered ring through C–H activation.



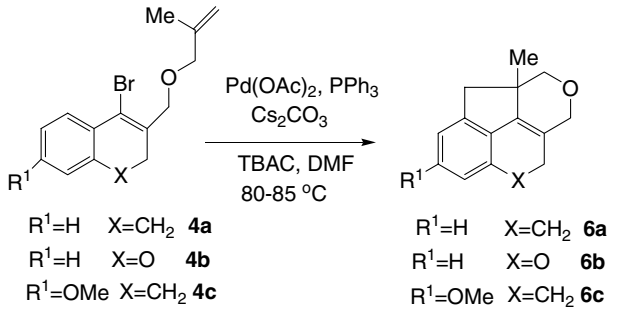
Scheme 2. Pd-catalysed intramolecular cyclisation of O-allylated derivatives.

The formation of products **6a**–**e** can be explained through C–H activation[9] of the cyclic organopalladium addition intermediates, formed by addition to the unactivated double bond. (see Table 2).

Table 1
Palladium-catalysed intramolecular cyclisation of O-allylated derivatives of bromoalcohols

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **3a**	 **5a**	6	75
2	 **3b**	 **5b**	5	72
3	 **3c**	 **5c**	5	70
4	 **3d**	 **5d**	6	65
5	 **3e**	 **5e**	6	70
6	 **3f**	 **5f**	5	72
7	 **3g**	 **5g**  **5h**	6	65 + 10

Reagents and conditions: **3a**–**g** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1 equiv), TBAC (1.5 equiv), DMF, 80–85 °C.



Scheme 3. Pd-catalysed intramolecular cyclisation of O-methallylated derivatives.

A plausible mechanism for the above reaction is shown in Scheme 4. Initially an alkenyl palladium(II) intermediate was generated by oxidative addition of Pd(0) to the sp^2 C–Br bond which undergoes addition to the unactivated double bond to produce an alkylpalladium which underwent cyclisation with the aromatic ring through C–H activation. Since no elimination is possible due to the absence of a β-H in the alkylpalladium intermediates, C–H activation is facilitated.

In conclusion, we have developed a method for the synthesis of fused pyran rings by intramolecular Heck reaction and tetracyclic pyran formation by intramolecular Heck reaction and regioselective C–H activation.

Table 2
Palladium catalysed intramolecular cyclisation of O-methallylated bromoalcohols

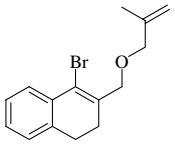
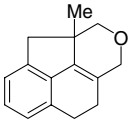
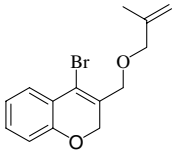
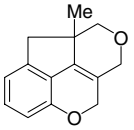
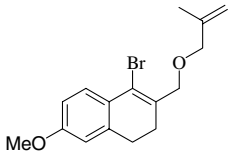
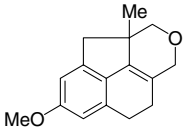
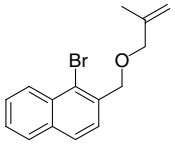
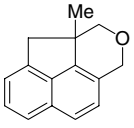
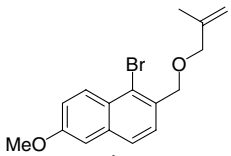
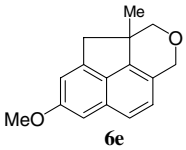
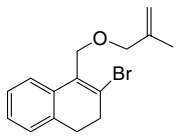
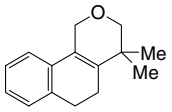
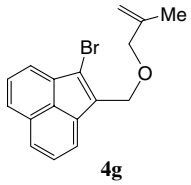
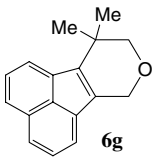
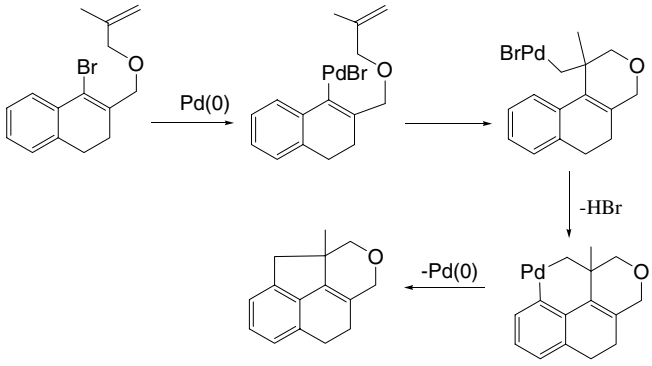
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **4a**	 **6a**	5	65
2	 **4b**	 **6b**	6	55
3	 **4c**	 **6c**	5	63
4	 **4d**	 **6d**	5	65
5	 **4e**	 **6e**	6	60

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)
6	 **4f**	 **6f**	5	55
7	 **4g**	 **6g**	5	50

Reagents and conditions: **4a–g** (1 equiv) $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1 equiv), TBAC (1.5 equiv), DMF, 80–85 °C.



Scheme 4. A plausible mechanism for the Pd-catalysed cyclisation.

2. Typical experimental procedure for the Heck reaction

Compounds **3** or **4** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1 equiv) and DMF (6 mL) were placed in a two neck round bottom flask. After degassing with N_2, the mixture was heated at 80–85 °C for 4 h. After cooling, the reaction mixture was diluted with cold water and extracted with ether (20 mL × 3) and the combined organics dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by preparative thin layer chromatography.

2.1. Spectral data of representative compounds

Compound **5b**: White solid, mp 80–82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.09 (t, 2H, $J = 7.2$ Hz), 2.70 (t, 2H, $J = 7.2$ Hz), 3.81 (s, 3H), 4.31 (s, 2H), 4.36 (s, 2H), 5.10 (s, 1H), 5.37 (s, 1H), 6.72–6.75 (m, 2H), 7.47 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.07, 28.34, 55.28, 69.24, 71.36, 110.16, 110.79, 113.78, 125.31, 126.26, 127.08, 134.07, 136.98, 138.78, 158.13, MS-ESI: $m/z = 229.1557$ (100%) [M^++H].

Compound **6c**: White solid, mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (s, 3H) 2.09–2.22 (m, 2H), 2.68–2.92 (m, 4H), 3.29 (d, 1H, $J = 10.0$ Hz), 3.77 (s, 3H), 3.93 (d, 1H, $J = 10.0$ Hz), 3.97 (d, 1H, $J = 16.0$ Hz), 4.42 (d, 1H, $J = 16.0$ Hz), 6.60 (s, 1H), 6.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.45, 25.34, 26.57, 43.27, 46.53, 55.57, 67.09, 73.87, 108.42, 110.40, 110.76, 111.57, 122.43, 131.98, 139.04, 160.70. MS-ESI: $m/z = 243.1367$ (100%), [M^++H]. HRMS calcd for $C_{16}H_{19}O_2$ [M^++H]: 243.1385; found: 243.1367.

Acknowledgement

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