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# Palladium-catalyzed tandem oxidative cyclization of 1-bromohexa-1,5-dien-3-ols: easy access to cyclopentenones

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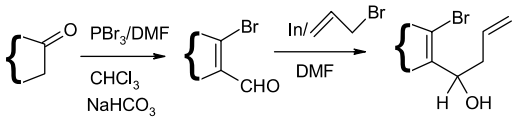
**Abstract**—The novel Pd-catalyzed tandem cyclization of 1-bromohexa-1,5-dien-3-ols, prepared from the corresponding β-bromovinylaldehydes to cyclopentenone derivatives has been developed.


Palladium complexes are powerful catalysts for carbon–carbon bond forming reactions because Pd(II) intermediates generated by oxidative addition of organic electrophiles to Pd(0) complexes can be utilized widely for transmetallation and insertion into unsaturated bonds.[1] Cyclopentenones are building blocks for the development of biologically active compounds[2] and are major structural features of numerous natural products.[3] Because of the importance of cyclopentenones[4] several methods for their preparation have been developed. The most convergent synthesis of cyclopentenones is the Pauson–Khand reaction, which consists of the co-cycloaddition of alkynes, alkenes and carbon monoxide.[5] Recently Larock and co-workers[6a,b] and also Negishi et al.[7] have extensively explored palladium-catalyzed cyclization reactions via migratory insertion of CO. There are also reports of palladium-catalyzed oxidations of secondary alcohols to ketones in the absence[8a] or presence of molecular oxygen as an oxidant.[8b,c] We wish to report here a novel palladium-catalyzed oxidative cyclization of 1-bromohexa-1,5-dien-3-ol derivatives, which provides a highly efficient and novel route to cyclopentenones. The 1-bromohexa-1,5-dien-3-ol derivatives were synthesized using $PBr_3$/DMF followed by indium-mediated allylation (Scheme 1).




**Scheme 1.**

Recently we reported[9] the indium-mediated Barbier-type allylation of chlorovinyl aldehydes. We found that an allyl indium reagent generated in situ readily undergoes regioselective addition to the carbonyl group of β-bromovinylaldehydes (Table 1) (synthesized by the reaction of ketomethylene compounds with $PBr_3$/DMF[10]).

We now describe the optimized catalyst system for the Pd(0) cyclization[11] (Table 2). It is reported that the 1-bromohexa-1,5-dien-3-ol derivatives (entries 1–10), which could cyclize via either 5-*exo* or 6-*endo* pathways, cyclize exclusively *exo* rather than *endo* when subjected to these reaction conditions (Scheme 2).

As we could not isolate any intermediate in this reaction, there are many reasonable possibilities. We proposed the mechanism (Scheme 3) for this annulation includes (1) $Pd(OAc)_2$ reduction to the active palladium(0) catalysts, (2) oxidative addition of the organic halide to Pd(0), (3) hydride transfer to form the palladium hydride intermediate, (4) oxidation, (5) cyclopalladation with the unactivated olefin and reductive elimination. The compound **8a**, which contains a large group failed to cyclize to the desired product presumably due to the steric interaction between the bromine and the palladium intermediate.

Another reasonable possibility[12] is that, formate normally serves as a hydride source, but the competing reaction is β-elimination followed by alkene isomerization, which

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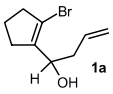
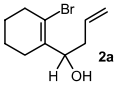
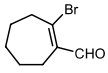
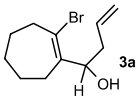
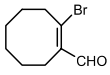
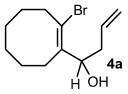
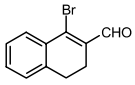
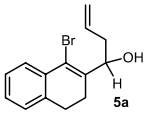
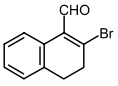
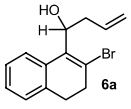
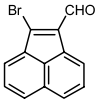
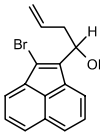
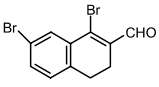
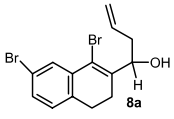
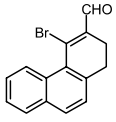
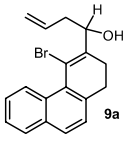
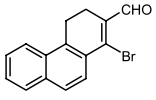
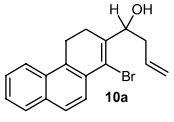
**Table 1.** Allylation of the β-bromo-vinylaldehydes using In/allyl bromide

| Entry no. | Substrate | Products | Time (h) | Yield (%) |
|---|---|---|---|---|
| **1** |  |  | 4 | 73 |
| **2** |  |  | 3 | 61 |
| **3** |  |  | 3.5 | 72 |
| **4** |  |  | 4.5 | 76 |
| **5** |  |  | 3.5 | 73 |
| **6** |  |  | 3.5 | 76 |
| **7** |  |  | 4 | 81 |
| **8** |  |  | 3.5 | 72 |
| **9** |  |  | 4.5 | 64 |
| **10** |  |  | 5 | 61 |

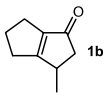
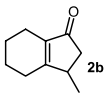
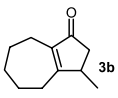
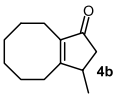
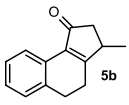
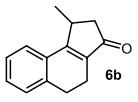
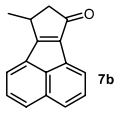
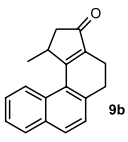
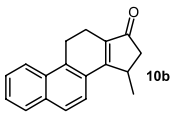
Reagents and conditions: β-bromo-vinylaldehydes (1 mmol), allyl bromide (3 mmol), DMF, In metal (1.2 mmol), stirred at 25 °C.

would lead ultimately to the thermodynamically favored ketone (Scheme 4).

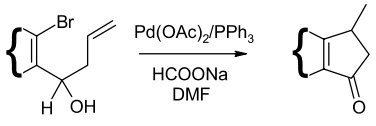
The structures of the products were supported by analysis and spectral data,[13] in one case **7b** X-ray data confirmed the depicted structure[14] (Fig. 1).

In summary we have developed an effective transition metal-catalyzed protocol for the cyclization of an unactivated olefin via a tandem process. Cyclopentenones have been successfully synthesized in good yield by the palladium-catalyzed oxidative cyclization of 1-bromohexa-1,5-dien-3-ol derivatives. Cyclopentenones containing 5,5; 6,5; 7,5 and 8,5 fused rings have been prepared. Our efforts are currently directed towards expanding the utility of the methods to other substrates.

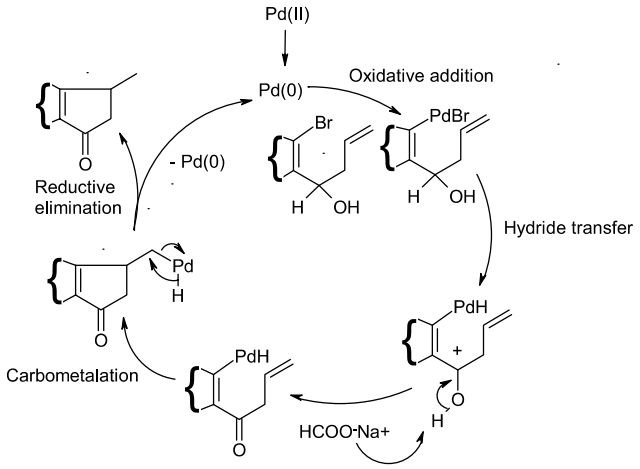
**Table 2.** Cyclization using Pd(0)

| Substrate no. | Products | Yield (%) |
|---|---|---|
| **1a** |  | 58 |
| **2a** |  | 61 |
| **3a** |  | 60 |
| **4a** |  | 63 |
| **5a** |  | 61 |
| **6a** |  | 62 |
| **7a** |  | 71 |
| **9a** |  | 34 |
| **10a** |  | 36 |

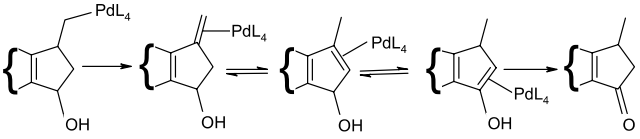
Reagents and conditions: 10 mol% of $Pd(OAc)_2$, 0.25 equiv of $PPh_3$, 1 equiv of HCOONa, a reaction temperature of 80 °C and DMF as solvent.




**Scheme 2.**




**Scheme 3.** A proposed mechanism for the cyclization.




**Scheme 4.** Another proposed mechanism.

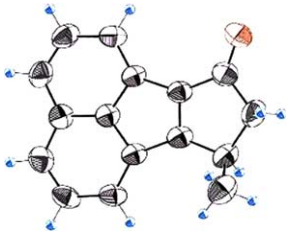


**Figure 1.** ORTEP view of the structure **7b**.

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11. General procedure for the palladium-catalyzed cyclization: The appropriate allylated β-bromo-vinylaldehyde, $Pd(OAc)_2$ (10 mol%), $PPh_3$ (0.25 equiv), HCOONa (1 equiv) and DMF were placed in a two neck round bottom flask. After degassing with $N_2$ it was heated to 80 °C for 8 h. After cooling, the reaction mixture was diluted with cold water and extracted with diethyl ether, and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and was isolated by column chromatography.
12. Authors are thankful to the referee for proposing the alternative mechanism.
13. Selected data for **7b**: IR (KBr) 1679, 1628 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.56 (d, 3H, $J = 7$ Hz), 2.56, 2.65 (dd, 1H, $J_{cis} = 2.0$ Hz, $J_{gem} = 18.0$ Hz), 3.23, 3.32 (dd, 1H, $J_{trans} = 6.16$ Hz, $J_{gem} = 18.0$ Hz), 3.60–3.68 (m, 1H), 7.55–7.69 (m, 2H), 7.82–8.02 (m, 4H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 20.87, 31.49, 50.36, 124.63, 126.14, 127.58, 127.64, 128.15, 129.47, 130.60, 131.19, 133.11, 133.74, 142.79, 181.14, 200.17. Anal. Calcd for $C_{16}H_{12}O$: C, 87.27; H, 5.45. Found: C, 87.54; H, 5.36. MS (EI, 70 eV) $m/z$ 220 ($M^+$).
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