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Palladium-catalyzed intramolecular 5-*endo–trig* oxidative Heck cyclization: a facile pathway for the synthesis of some sesquiterpene precursors

Devalina Ray, Sunanda Paul, Sulagna Brahma and Jayanta. K. Ray*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

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Abstract—An efficient and convenient method for the construction of substituted cyclopentenones via palladium-catalyzed intramolecular 5-*endo–trig* oxidative cyclization has been introduced as a powerful new strategy for the synthesis of sesquiterpenes.

1. Introduction

Transition metal-catalyzed intramolecular reactions of alkenes are representative reactions in the organic chemistry of palladium[1] which can continuously stimulate research due to their immense synthetic potential. Recently substituted cyclopentenones have been evaluated as useful synthons for the synthesis of natural[2] and unnatural[3] products. As an extension of the palladium-catalyzed intramolecular Heck cyclization for the synthesis of substituted cyclopentenones, we have already reported synthetic approaches starting from allylated,[4a] propargylated,[4b] and methallylated[4c] derivatives of a number of β-bromovinylaldehydes following different pathways. Intermolecular Heck reactions of halides with allylic alcohols[5] are widely known while the intramolecular version[6] is somewhat rare. The palladium-catalyzed alkylation of thiopene at the 3-position is accomplished by adopting the intermolecular coupling of 3-bromothiopene with substituted allyl alcohols.[7] As part of our ongoing effort to expand the synthetic utility of substituted cyclopentenones, we have been investigating palladium-catalyzed Heck reactions on substrates possessing allylic alcohols.

In this context, we describe the intramolecular palladium-catalyzed 5-*endo–trig* Heck cyclization of 1-bromopenta-1,4-dien-3-ols resulting in substituted cyclopentenones. Based on the successful use of vinyl halides or vinyl triflates as vinyl donors in palladium-catalyzed reactions with olefinic systems[8] and the known behavior of allylic alcohols in palladium-catalyzed reactions with organic halides, we thought that our method would be a viable route toward the synthesis of cyclopentenones related to natural product precursors. *endo*-Cyclizations are relatively rare in comparison to the *exo* mode of cyclization.[9] Vinylated derivatives of the β-bromovinylaldehydes were chosen as our substrate because their reactions with aromatic analogues are very sluggish and result in the formation of low yields of products.

The reactions are of preparative value for the synthesis of sesquiterpene precursors. The structural skeleton **6b** is the core structure of (±)-α-cuparenone (**6d**) and laurene (**6e**).[10] Both sesquiterpenes can be obtained from **6b**, which in turn can be prepared by our methodology (Scheme 1).

The starting materials were synthesized by the addition of vinylmagnesium bromide (1 mmol) to β-bromovinylaldehydes (1 mmol) in tetrahydrofuran (THF) at 0 °C to afford the bromo alcohols (**1a**–**9a**) (Table 1) in good yield (Scheme 2).

Treatment of the substrates (**1a**–**9a**) (1 mmol) with $Pd(OAc)_2$ (5 mol %), PPh_3 (0.5 equiv) and triethylamine (1.2 equiv) in acetonitrile (8 mL) at 80 °C yielded the cyclized keto compounds (**1b**–**9b**) (Table 2) in moderate

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* Corresponding author. Tel.: +91 3222 283326; fax: +91 3222 282252; e-mail: jkray@chem.iitkgp.ernet.in

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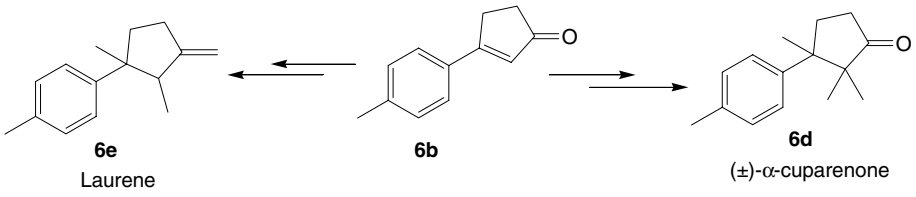
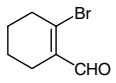
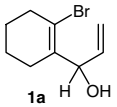
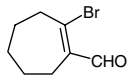
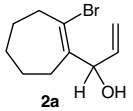
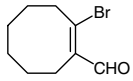
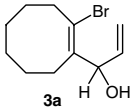
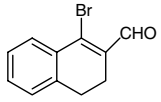
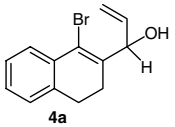
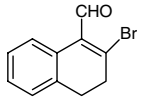
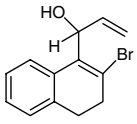
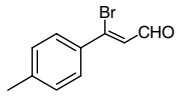
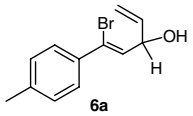
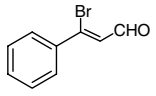
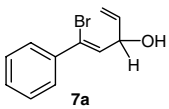
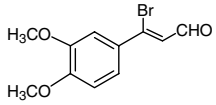
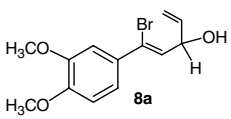
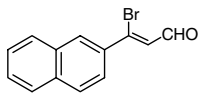
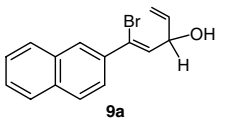
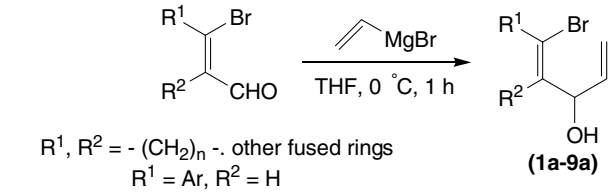


Scheme 1.

Table 1. Vinylation of β-bromovinylaldehydes using vinylmagnesium bromide[a]

Entry	Substrate	Product	Yield[b] (%)
1		 **1a**	89
2		 **2a**	90
3		 **3a**	90
4		 **4a**	85
5		 **5a**	92
6		 **6a**	89
7		 **7a**	90
8		 **8a**	90
9		 **9a**	85

[a] β-Bromovinylaldehyde (1 mmol), vinylmagnesium bromide (1 mmol), THF (8 mL) at 0 °C for 1 h.
[b] Yields refer to isolated yields.



Scheme 2.

to good yields (Scheme 3). These palladium-catalyzed cyclizations have proceeded via a 5-*endo–trig* pathway.

In an attempt to extend our methodology and apply it to the synthesis of sesquiterpenes, we prepared a precursor of (±)-α-cuparenone, which can be converted to the desired natural product in a single step[11] (Scheme 4). The precursor (**6c**) was synthesized via 1,4-addition of **6b** with Me_2CuLi.

In conclusion, we have developed a methodology for the construction of five-membered rings with α,β unsaturated keto functionality.

2. Typical experimental procedure

2.1. General procedure for the palladium-catalyzed Heck cyclization

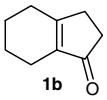
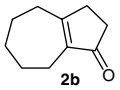
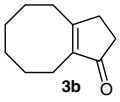
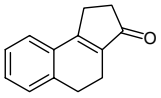
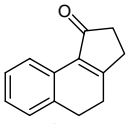
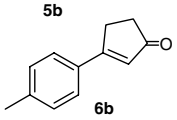
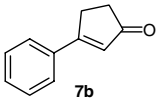
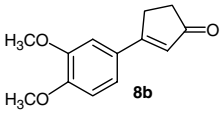
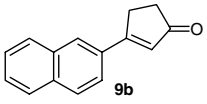
The appropriate vinylated derivative (1 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (0.5 equiv) and Et_3N (1.2 equiv) were dissolved in acetonitrile. After degassifying with argon, the solution was heated to 80 °C for 8–10 h. The reaction mixture was cooled, diluted with ice water and extracted with diethyl ether. The solvent was evaporated after drying (with Na_2SO_4) and the product was purified by silica gel (60–120 mesh) column chromatography.

2.2. Spectral data of representative compounds[†]

2.2.1. 1-(2-Bromo-cyclohex-1-enyl)prop-2-en-1-ol (1a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58–1.69 (4H, m), 1.86 (1H, br s), 1.99–2.05 (1H, m), 2.19–2.27 (1H, m), 2.50–2.51 (2H, m), 5.18 (1H, d, $J = 10.4$ Hz), 5.31 (1H, br s), 5.34 (1H, d, $J = 17.2$ Hz), 5.82–5.90 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.04, 24.67, 25.24, 36.83, 74.77, 114.82, 120.66, 135.98, 137.02. Anal. Calcd for $C_9H_{13}OBr$: C, 49.79; H, 6.03. Found: C, 48.99; H, 5.92.

[†] The substituted vinyl alcohols were unstable, so mass spectra and CHN analysis could not be obtained.

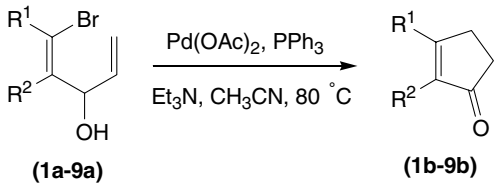
Table 2. Palladium-catalyzed intramolecular 5-*endo*–*trig* cyclization[a]

Substrate no.	Product	Yield[b] (%)
1a	 **1b**	65
2a	 **2b**	70
3a	 **3b**	73
4a	 **4b**	70
5a	 **5b**	75
6a	 **6b**	65
7a	 **7b**	70
8a	 **8b**	68
9a	 **9b**	70

[a] All the reactions were carried out with 5 mol % of $Pd(OAc)_2$, 0.5 equiv PPh_3, 1.2 equiv of Et_3N in acetonitrile (8 mL) at 80 °C for 8–10 h.

[b] Yields refer to isolated yields after purification.

2.2.2. 1-(2-Bromocyclohept-1-enyl)prop-2-en-1-ol (2a). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36–1.76 (6H, m), 2.23 (2H, d, $J = 9.1$ Hz), 2.79 (2H, d, $J = 7.9$ Hz), 5.17 (1H, d, $J = 11.0$ Hz), 5.31 (1H, br s), 5.40 (1 H, br s), 5.73–5.89 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.22, 26.50, 27.43, 31.53, 41.51, 76.11, 114.75, 123.98, 136.81, 141.17.



(1a-9a) **(1b-9b)**

R^1, R^2 = - $(CH_2)_n$ -, other fused rings

R^1 = Ar, R^2 = H

Scheme 3.

2.2.3. 1-(2-Bromocyclooct-1-enyl)prop-2-en-1-ol (3a). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (4H, m), 1.58–1.68 (4H, m), 2.21–2.28 (1H, m), 2.32–2.39 (1H, m), 2.69–2.72 (2H, m), 5.17 (1H, d, $J = 10.4$ Hz), 5.36–5.41 (2H, m), 5.84–5.92 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.52, 26.59, 27.34, 27.49, 31.29, 37.04, 75.75, 114.44, 123.03, 137.49, 138.41.

2.2.4. 1-(1-Bromo-3,4-dihydronaphthalen-2-yl)prop-2-en-1-ol (4a). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.87 (1H, br s), 2.34–2.57 (2H, m), 2.72–2.83 (2H, m), 5.23 (1H, d, $J = 10.6$ Hz), 5.44 (2H, d, $J = 17.0$ Hz), 5.61 (1H, br s), 5.88–6.02 (1H, m), 7.08–7.28 (3H, m), 7.66–7.69 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.09, 28.00, 74.77, 115.37, 119.04, 126.64, 126.89, 127.12, 128.08, 133.72, 136.48, 136.53, 139.74. IR ($CHCl_3$): ν_{max} 3378, 1615, 1234, 942, 751 cm^{-1}. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.88; H, 4.94. Found: C, 58.99; H, 4.83.

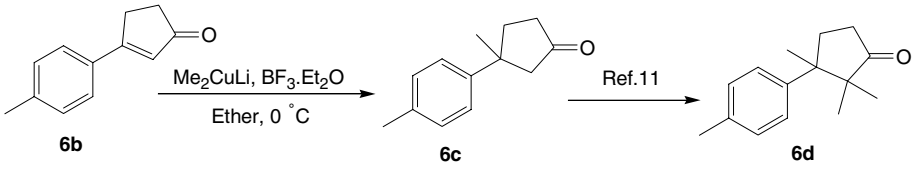
2.2.5. 1-(2-Bromo-3,4-dihydronaphthalen-1-yl)prop-2-en-1-ol (5a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68–2.86 (4H, m), 5.18 (1H, d, $J_{cis} = 11.6$ Hz), 5.37 (1H, d, $J_{trans} = 17.2$ Hz), 5.72 (1H, d, $J = 3.2$ Hz), 6.04–6.12 (1H, m), 7.04–7.09 (3H, m), 7.61–7.63 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.56, 35.97, 74.44, 115.45, 125.27, 125.48, 126.15, 127.19, 127.53, 131.93, 135.20, 135.49, 137.96. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.88; H, 4.94. Found: C, 58.34; H, 4.91.

2.2.6. 1-Bromo-1-*p*-tolylpenta-1,4-dien-3-ol (6a). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (3H, s), 5.20 (1H, br s), 5.21 (1H, d, $J = 9.8$ Hz), 5.42 (1H, d, $J = 17.1$ Hz), 5.91–6.07 (1H, m), 6.22 (1H, d, $J = 7.7$ Hz), 7.13–7.47 (AB q, 4H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.60, 73.45, 104.16, 126.66, 127.47 (2 × C), 128.68, 128.94 (2 × C), 130.63, 137.31, 139.09. IR ($CHCl_3$): ν_{max} 3367, 1610, 1224, 924, 774 cm^{-1}.

2.2.7. 1-Bromo-1-phenylpenta-1,4-dien-3-ol (7a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (1H, br s), 5.21–5.25 (1H, m), 5.24 (1H, d, $J = 10.8$), 5.44 (1H, d, $J = 17.2$ Hz), 5.95–6.04 (1H, m), 6.26 (1H, d, $J = 7.6$ Hz), 7.33–7.41 (3H, m), 7.53–7.55 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.46, 115.75, 116.08, 127.58, 128.35 (2 × C), 128.99, 129.06, 131.49, 133.95, 137.17.

2.2.8. 1-Bromo-1-(3,4-dimethoxyphenyl)penta-1,4-dien-3-ol (8a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (1H, br s), 3.90 (3H, s), 3.91 (3H, s), 5.21 (1H, br s), 5.23 (1H, d, $J = 10.4$ Hz), 5.43 (1H, d, $J = 17.2$ Hz), 5.91–6.04 (1H, m), 6.18 (1H, d, $J = 7.6$ Hz), 6.83 (1H, d, $J = 8.4$ Hz), 7.07 (1H, d, $J = 2.0$ Hz), 7.13–7.15 (1H, dd, $J = 8.4$ Hz, $J = 2.4$ Hz).

2.2.9. 1-Bromo-1-naphthalen-2-yl-penta-1,4-dien-3-ol (9a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (1H, d, $J = 10.0$ Hz), 5.16 (1H, br s), 5.39 (1H, d, $J = 17.2$ Hz), 5.91–6.00 (1H, m), 6.33 (1H, d, $J = 7.6$ Hz), 7.41–7.47 (2H, m), 7.57–7.59 (dd, 1H, $J = 8.8$ Hz, $J = 2.0$ Hz), 7.72–7.79 (3H, m), 7.97 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.56, 115.82, 124.10, 124.69, 126.59, 126.64, 126.79, 127.48 (2 × C), 127.79, 127.95, 128.39, 129.89, 131.85, 137.20.



Scheme 4.

2.2.10. 2,3,4,5-Tetrahydrocyclopenta[α]naphthalen-1-one (5b).[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59–2.69 (6H, m), 2.97 (2H, t, $J = 8.0$ Hz), 7.18–7.28 (3H, m), 8.25 (1H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.99, 27.55, 29.19, 35.82, 123.86, 126.67, 127.47, 127.75, 129.05, 134.36, 134.83, 175.05, 206.18; HRMS (ESI, 70 eV): $m/z = 185.0966$ [M^++H] (calculated mass for $C_{13}H_{12}O$: 185.0966 [M^++H]).

2.2.11. 3-(3,4-Dimethoxyphenyl)cyclopent-2-enone (8b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57–2.60 (2H, m), 3.02–3.04 (2H, m), 3.93 (3H, s), 3.94 (3H, s), 6.48 (1H, s), 6.92 (1H, d, $J = 8.4$ Hz), 7.14 (1H, d, $J = 1.6$ Hz), 7.27–7.30 (1H, dd, $J = 8.4$ Hz, $J = 2.0$ Hz). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.67; H, 6.40.

2.2.12. 3-Naphthalen-2-yl-cyclopent-2-enone (9b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65–2.67 (2H, m), 3.19–3.21 (2H, m), 6.71 (1H, s), 7.55–7.58 (2H, m), 7.75–7.77 (1H, m), 7.87–7.91 (3H, m), 8.13 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.61, 35.26, 116.09, 123.90, 126.79, 126.84, 127.69, 127.75, 127.78, 128.60, 128.89, 132.95, 134.90, 173.73, 209.45. HRMS (ESI, 70 eV): $m/z = 209.0907$ [M^++H] (calculated mass for $C_{15}H_{12}O$: 209.0922 [M^++H]).

2.2.13. 3-Methyl-3-*p*-tolylcyclopentanone (6c).[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, s), 2.14–2.40 (4H, m), 2.23 (3H, s), 2.54–2.58 (2H, d, $J = 17.6$ Hz), 7.06–7.18 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.87, 29.40, 35.86, 36.74, 43.46, 52.32, 125.32 (2 × C), 129.19 (2 × C), 135.85, 145.44, 218.83; HRMS (ESI, 70 eV): $m/z = 189.1241$ [M^++H] (calculated mass for $C_{13}H_{16}O$: 189.1235 [M^++H]).

Compounds **1b**, **2b**, **3b**, **4b**, **6b**, and **7b** are reported in the literature.[14]

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