Palladium-Catalyzed Novel Cycloisomerization: An Unprecedented Domino Oxidative Cyclization towards Substituted Carbocycles

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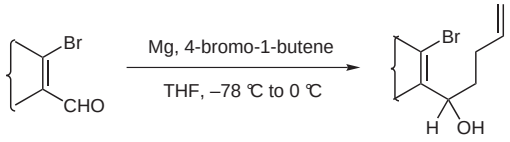
Received 8 April 2005

Abstract: Efficient Pd-catalyzed cyclization of homoallylated β-bromo-vinylalcohols via a domino process to carbocycle derivatives in presence of different bases is reported. An unexpected and novel palladium-mediated Heck-type intramolecular oxidative cyclization of 1-bromohexa-1-ene-5-yn-3-ol derivatives is also described.

Key words: Heck reaction, palladacycles, tandem reactions, oxidation, isomerization

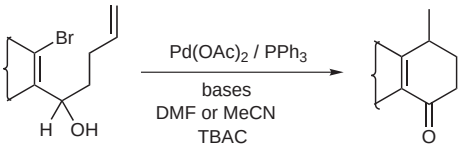
The formation of carbon–carbon bonds using in situ generated organometallic reagents is of fundamental importance in organic synthesis.[1] Palladium catalysts have emerged as extremely powerful tools for the construction of carbon–carbon bonds.[2] Their popularity stems in part from their capability to oxidize,[3a,b] reduce,[3c,d] isomerize[3e,f] as well as to form new bonds. Substituted carbocycles represent a common structural component of naturally occurring and biologically active molecules.[4] The cyclization of unsaturated substrates using an intramolecular Heck reaction promoted by organopalladium complexes is of fundamental importance for the construction of a vast array of mono- and polycarbocyclic and also polyheterocyclic systems[5] and is therefore a highly attractive feature in the synthesis of cyclic natural products.[5e] In this context, we have recently reported[6] a new palladium-promoted domino C–C cyclopalladation sequence allowing the facile one-pot synthesis to cyclopentenones with promising synthetic value. The 1-bromohexa-1,5-diene-3-ol derivatives underwent Pd-catalyzed oxidative cyclization to functionalized cyclopentenones in very good yields. In this communication we wish to report the reactivity of new sensitive substrates towards palladium-catalyzed intramolecular Heck reaction, which provides an efficient route to cyclopentenones and cyclohexenones.

The starting materials were synthesized by addition of the Grignard reagents derived from 4-bromo-1-butene and Mg to bromoaldehydes (Scheme 1) in tetrahydrofuran (THF) to afford bromo alcohols (**1a**–**6a**, Table 1) in good yield.



Scheme 1

Applying Heck reaction to the compounds **1a**–**6a** under standard conditions,[7] produced substituted cyclohexenones (Scheme 2) exclusively through 6-*exo*-*trig* cyclization pathways.



Scheme 2

In our previous communication, we opted for HCOONa as the base, but later, we performed the reaction with other bases (Na_2CO_3, K_2CO_3, NaOAc, Et_3N) and acetonitrile as solvent. In all these cases we successfully isolated the cyclized products. To improve the yield further, we incorporated tetrabutyl ammonium chloride as additive, which was found to be effective in all cases (Table 2).

The structure of **6b** was unambiguously determined by X-ray crystallographic analysis (Figure 1).

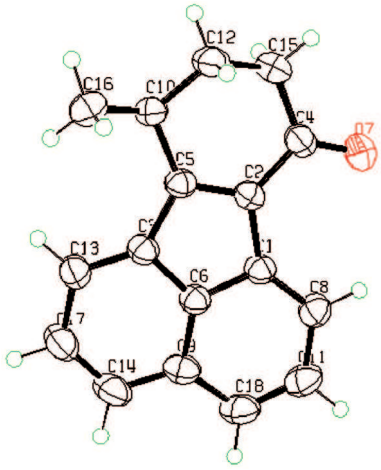
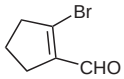
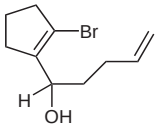
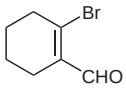
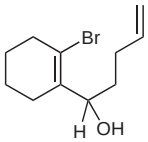
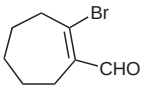
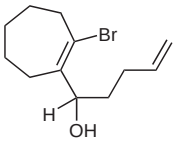
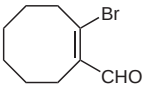
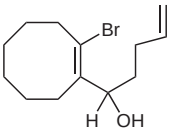
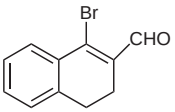
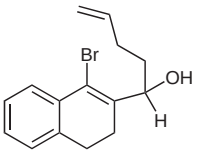
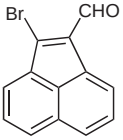
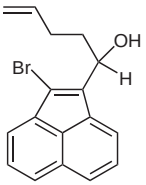


Figure 1 ORTEP view of the structure **6b**

As we could not isolate any intermediate for this reaction, we speculate that the mechanism follows the sequence in Scheme 3. During the search for an intermediate, we synthesized compound **I** by O-alkylation of 1-(2-bromo-

SYNLETT 2005, No. 14, pp 2135–2140
Advanced online publication: 22.07.2005
DOI: 10.1055/s-2005-872241; Art ID: D09305ST

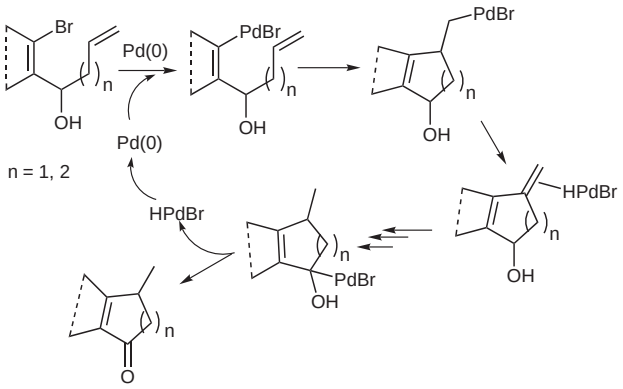
Table 1 Homoallylation of the β-Bromo-vinylaldehydes Using Mg/4-Bromo-1-butene[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1		 **1a**	6.0	69
2		 **2a**	5.5	63
3		 **3a**	5.5	64
4		 **4a**	6.5	61
5		 **5a**	5.5	72
6		 **6a**	5.5	75

[a] *Reagents and conditions*: β-bromo-vinylaldehydes (1 mmol), 4-bromo-1-butene (1.3 mmol), THF (6–8 mL), Mg metal (1.2 mmol), stirred at –78 °C.
[b] Yields are of isolated product.

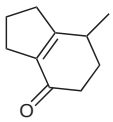
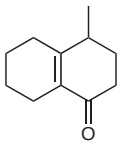
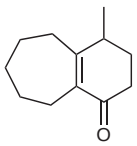
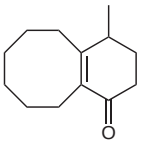
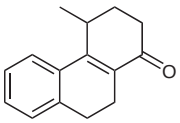
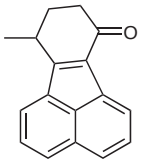
acenaphthylen-1-yl)-but-3-en-1-ol with methyl iodide in presence of sodium hydride in 67% yield. Heck reaction of **I** (Scheme 4), under identical conditions, produced compound **II** in 54% yield, which readily underwent isomerization and afforded ketone **III** in presence of mild acid in 45% yield. This may be considered as partial evidence in favor of the cyclization followed by isomerization.

Our continuing interest was then focused towards the successive coupling of 1-bromo-hexa-1-ene-5-yn-3-ol derivatives via novel palladium-catalyzed oxidative cyclization and isomerization. Attempted Heck reaction of substrates (entries **1c**–**8c**, Table 3) did not produce the anticipated cyclopentanoid moiety containing an exocyclic double

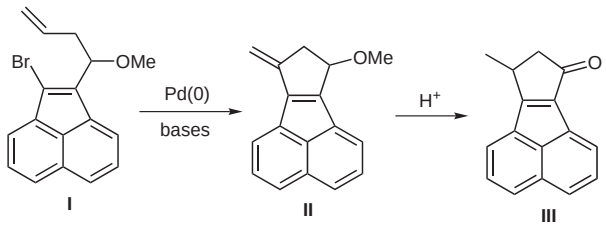


Scheme 3 The plausible mechanism

Table 2 Palladium-Catalyzed Cyclization

Substrate	Product	Yield (%)[a]
1a	 **1b**	44
2a	 **2b**	38
3a	 **3b**	51
4a	 **4b**	51
5a	 **5b**	53
6a	 **6b**	65

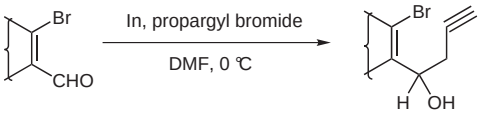
[a] Yield refers to isolated yield. All of the compounds gave satisfactory ^{1}H NMR, ^{13}C NMR spectroscopic and MS spectrometric data.[11]



Scheme 4

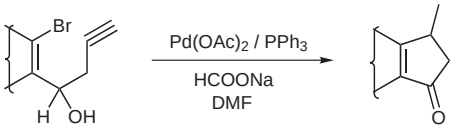
bond but we found the 3-methyl cyclopentenone as the only isolable product. Attempts to perform the reaction using other bases like K_2CO_3, Na_2CO_3, Et_3N, were all unsuccessful resulting in polymeric materials.

The 1-bromohexa-1-ene-5-yn-3-ol derivatives were synthesized from substituted β-bromovinylaldehydes by indium-mediated propargylation[8] with propargyl bromide (Scheme 5). The propargyl indium reagent generated in situ readily underwent regioselective addition to the carbonyl group of bromo-vinylaldehyde at 0 °C.



Scheme 5

When we subjected the appropriate propargylated β-bromo-vinylalcohols to $Pd(OAc)_2$ (10 mol%), PPh_3 (0.25 equiv), HCOONa (1 equiv) and DMF, we found the same 3-methyl cyclopentenones (Scheme 6, **1d**–**8d**) as the only isolable products (Table 4).



Scheme 6

It has been previously reported[9a] that the alkyne insertion reactions are terminated by anion capture. In this case, the alkynyl-palladium[9b] intermediate formed by intramolecular insertion of the unactivated triple bonds could be terminated by hydrogenolysis with formic acid to generate the terminal alkene, which undergoes isomerization to thermodynamically stable ketone. All these substrates (entries **1c**–**8c**) underwent cyclization through the 5-*exo*-*dig* pathway and were reduced through isomerization under the reaction conditions.[7] As the Pd(0)-catalyzed isomerization is unusual, it may proceed through a Pd(II) intermediate.[10]

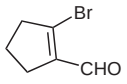
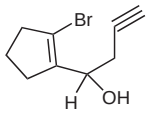
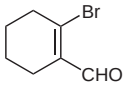
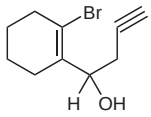
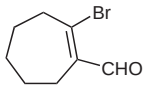
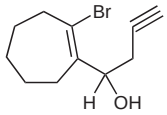
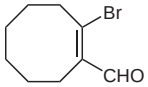
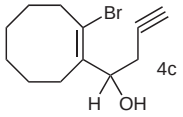
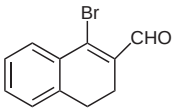
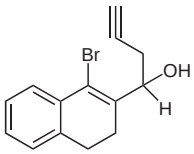
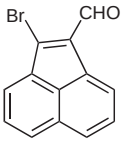
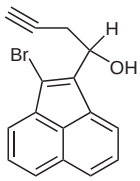
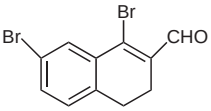
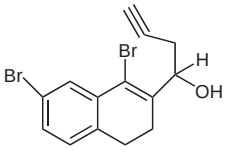
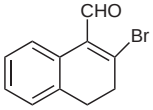
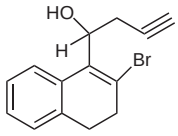
We obtained the reduced cyclopentenone as the only isolable product. However, the cyclization of 1-(1,7-dibromo-3,4-dihydro-naphthalen-2-yl)-but-3-yn-1-ol (entry **7c**) failed under the same reaction conditions and we obtained a complex mixture of products.

In conclusion, we have outlined a palladium-catalyzed cycloisomerization towards the synthesis of fused carbocycles. The developed methodology serves an effective transition metal-catalyzed protocol for the cyclization of unactivated alkenes, alkynes via a tandem process. The palladium acetate–HCOONa protocol could be used for intramolecular Heck reactions, though the mechanistic aspects are not yet fully understood. Our efforts are currently directed towards further exploitation of this procedure for sequential allylations and cyclizations.

Acknowledgment

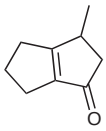
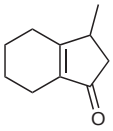
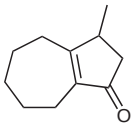
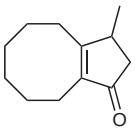
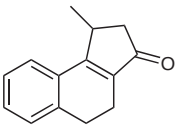
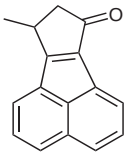
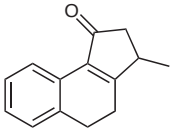
Financial support from DST (New Delhi) and CSIR (New Delhi) (for fellowship to S.M) is gratefully acknowledged. We are also thankful to Dr. Manish Bhattacharya, IIT-Kharagpur, India for the crystal structure.

Table 3 Propargylation of the β-Bromo-vinylaldehydes Using In/Propargyl Bromide[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1		 **1c**	4.5	80
2		 **2c**	5.5	78
3		 **3c**	4.0	75
4		 **4c**	5.0	74
5		 **5c**	5.0	79
6		 **6c**	5.0	82
7		 **7c**	5.5	75
8		 **8c**	5.0	78

[a] *Reagents and conditions*: β-bromo-vinylaldehydes (1 mmol), propargyl bromide (1.3 mmol), DMF, In metal (1.2 mmol), stirred at 0 °C.
[b] Yields are isolated yield.

Table 4 Pd-Catalyzed Cyclization

Substrate	Product	Yield (%)[a]
1c	 **1d**	40
2c	 **2d**	38
3c	 **3d**	48
4c	 **4d**	42
5c	 **5d**	34
6c	 **6d**	40
7c	Messy mixture (**7d**)	–
8c	 **8d**	35

[a] Yields refers to isolated yield. All of the compounds gave satisfactory ^{1}H NMR, ^{13}C NMR spectroscopic and MS spectrometric data.[11] The structure of **6d** was unambiguously determined by X-ray crystallographic analysis.

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(7) **General Procedure for the Palladium-Catalyzed Cyclization.**
The appropriate homoallylated or propargylated β-bromo-vinylalcohols, $Pd(OAc)_2$ (10 mol%), PPh_3 (0.25 equiv), base (1 equiv)[HCOONa (1 equiv) for propargylated compound only] and DMF (6–8 mL) were placed in a two-neck round-bottom flask. After degassing with N_2 the mixture was heated to 70 °C for 4 h. After cooling, the reaction mixture was diluted with cold H_2O and extracted with Et_2O (4 × 25 mL), and dried (Na_2SO_4). The solvent was evaporated, and the product was isolated by column chromatography (PE–EtOAc 9:1).

(8) **General Procedure for Propargylation.**
A mixture of β-bromo vinylaldehyde (1 mmol), propargyl bromide (1.3 mmol), indium metal (SRL, India) (1.2 mmol), NaI (3 mmol) in DMF (4–5 mL) was stirred at 0 °C until completion of the reaction (checked by TLC). The reaction mixture was quenched with aq NH_4Cl solution diluted with H_2O and extracted with Et_2O (3 × 25 mL). The solvent was removed at r.t. under vacuum.

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(11) **Spectral Data of Representative Compounds.**

7-Methoxy-9-methylene-8,9-dihydro-7*H*-cyclopenta[*a*]acenaphthylene (II):
^{1}H NMR (200 MHz, C_6D_6): δ = 3.01–3.16 (m, 2 H), 3.20 (s, 3 H), 4.48 (dd, 1 H, *J* = 2.87 Hz, *J* = 2.96 Hz), 5.02 (br s, 1 H), 5.49 (br s, 1 H), 7.20–7.31 (m, 3 H), 7.45–7.60 (m, 3 H). Anal Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 88.25; H, 5.92.

3-Methyl-3,4,5,6,7,8-hexahydro-2*H*-azulen-1-one (3d):
IR ($CHCl_3$): ν_{max} = 1685 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (d, 3 H, *J* = 6.96 Hz), 1.42–1.67 (m, 6 H), 1.73–1.83 (m, 4 H), 2.26–2.58 (m, 2 H), 2.67–2.7 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.98, 23,09, 26.33, 26.50, 31.13, 31.42, 37.04, 43.13, 141.72, 181.02, 208.11. MS (EI, 70 eV): *m/z* = 164 [M$^+$]. Anal Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.65; H, 9.62.

10-Methyl-9,10-dihydro-8*H*-fluoranthen-7-one (6b):
IR ($CHCl_3$): ν_{max} = 1660 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55 (d, 3 H, *J* = 7.12 Hz), 2.06–2.09 (m, 1 H), 2.39–2.78 (m, 3 H), 3.39–3.45 (m, 1 H), 7.53 (m, 2 H), 7.79 (d, 1 H, *J* = 8.20 Hz), 7.92–7.98 (m, 2 H), 8.26 (d, 1 H, *J* = 6.79 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.38, 29.19, 31.32, 35.68, 126.11, 126.21, 126.96, 127.54, 128.41, 128.66, 130.86, 136.81, 161.66, 196.89. MS (EI, 70 eV): *m/z* = 234 [M$^+$]. Anal Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.92; H, 5.93.