One-Pot Syntheses

Novel Three-Component Reactions Based on a Heck Carbopalladation/Cyclization Domino Reaction**

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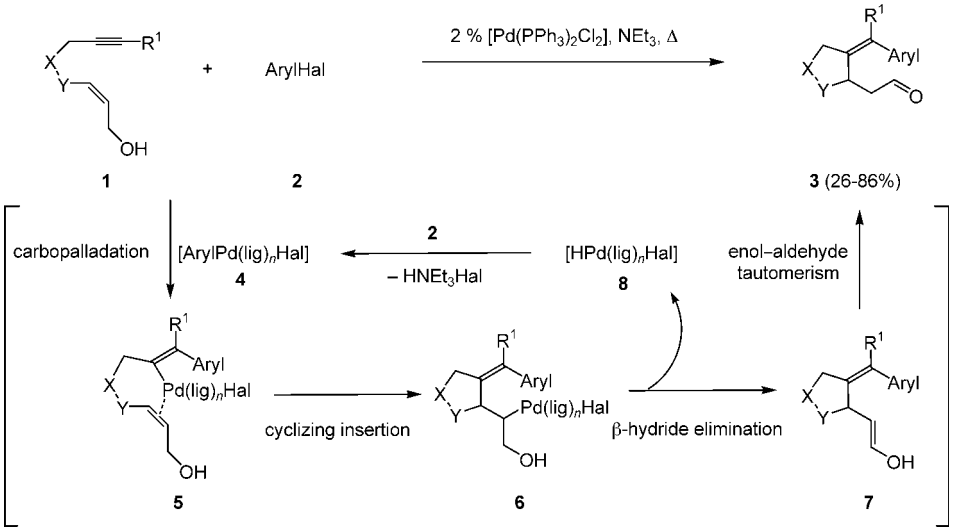
Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday

Palladium-catalyzed domino reactions based on sequences of insertions of organopalladium species into multiple bonds (carbopalladation) have fundamentally revolutionized synthetic concepts for the formation of carbo- and heterocyclic systems.[1,2] These transformations proceed under exceptionally mild reaction conditions and are highly compatible with polar functional groups. Conceptually, multicomponent reactions[3] initiated by palladium-catalyzed carbon–carbon bond-forming reactions[2,4] address very fundamental principles of synthetic efficiency and reaction design and, therefore, they have recently attracted considerable and steadily increasing academic, economic, and ecological interest. Besides, the prospect of extending one-pot reactions for combinatorial and solid-phase applications[3c,5] promises manifold opportunities for developing novel lead structures for pharmaceuticals, catalysts, and even novel molecule-based materials. Therefore, mastering unusual combinations of elementary organic reactions is a major conceptual challenge in engineering novel types of sequences. As part of our program directed toward developing new one-pot sequences and domino processes based upon transition-metal-catalyzed in situ activation of alkynes by cross coupling[6] or cycloisomerization,[7] we report herein on the first Heck carbopalladation/cyclization sequence of ynallyl alcohols and aryl halides to give γ,δ-enals. Two novel consecutive three-component reactions initiated by this new domino reaction serve as illustrations.

Although intramolecular Heck reactions[8] have a broad range of applications culminating in domino sequences like the impressive Negishi zipper reactions,[1a] and since the use of enynes as relays for Heck carbopalladation/cyclization sequences has been thoroughly studied,[9,10] the transformation of ynallyl alcohols that could furnish γ,δ-enals has remained unexplored to date. However, the generation of an aldehyde functionality en route could enormously enhance the degree of molecular diversity possible in multicomponent reactions.

The reaction of alkynylallyl alcohols **1**[11] and aryl halides **2** in the presence of 2 mol% of $[Pd(PPh_3)_2Cl_2]$ in boiling triethylamine under Heck reaction conditions furnished the cyclized γ,δ-enals **3** (the tetrahydrofuran derivatives **3a–i** and chromane derivatives **3k–m**) in moderate to good yields (Scheme 1, Table 1).[12]



Scheme 1. The palladium-catalyzed Heck carbopalladation/cyclization sequence for the conversion of ynallyl alcohols **1** into γ,δ-enals **3**.

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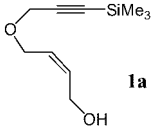
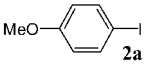
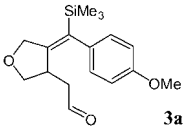
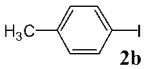
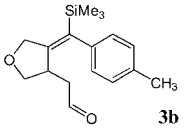
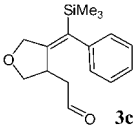
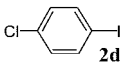
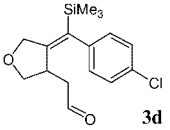
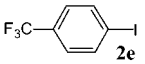
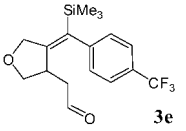
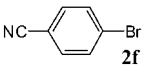
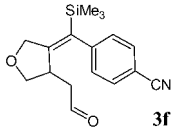
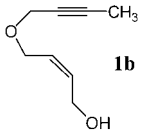
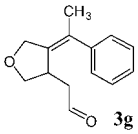
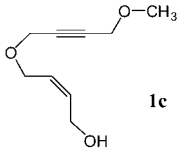
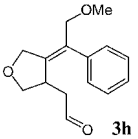
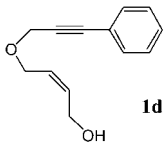
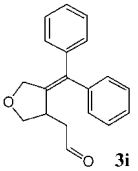
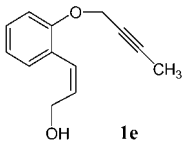
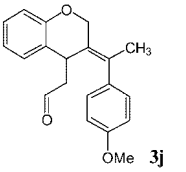
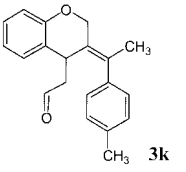
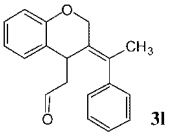
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 623), the Fonds der Chemischen Industrie, and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged. The authors also cordially thank the BASF AG for the generous donation of chemicals.

The structures of the ethylidenetetrahydrofuranyl and ethylidenechromanyl acetaldehydes **3** were supported unambiguously by spectroscopic analyses (^1H, ^{13}C and DEPT, COSY, NOESY, HETCOR, and HMBC NMR experiments, IR, UV/Vis, mass spectrometry). The configuration of the tetrasubstituted double bonds can be deduced unequivocally from the appearance of significant cross peaks (between the signals of the exocyclic trimethylsilyl, methyl, and methylene substituents and endocyclic methylene proton resonances in α-position to the ether bridge) in the NOESY spectra.

 DOI: 10.1002/anie.200461134

Table 1: Palladium-catalyzed Heck carbopalladation/cyclization of ynallyl alcohols **1** to give γ,δ-enals **3**.[a]

Entry	Ynallyl alcohol **1**	Aryl halide **2**	*t* [h]	γ,δ-Enal **3**	Yield [%][b]
1	 **1a**	 **2a**	5	 **3a**	65
2	**1a**	 **2b**	2.5	 **3b**	85
3	**1a**	 **2c**	5	 **3c**	86
4	**1a**	 **2d**	2	 **3d**	76
5	**1a**	 **2e**	15	 **3e**	66
6[c]	**1a**	 **2f**	0.5	 **3f**	85
7	 **1b**	**2c**	4.5	 **3g**	47
8[d]	 **1c**	**2c**	24	 **3h**	29
9[d]	 **1d**	**2c**	28	 **3i**	26
10	 **1e**	**2a**	6	 **3j**	58
11	**1e**	**2b**	5	 **3k**	60
12	**1e**	**2c**	6	 **3l**	65

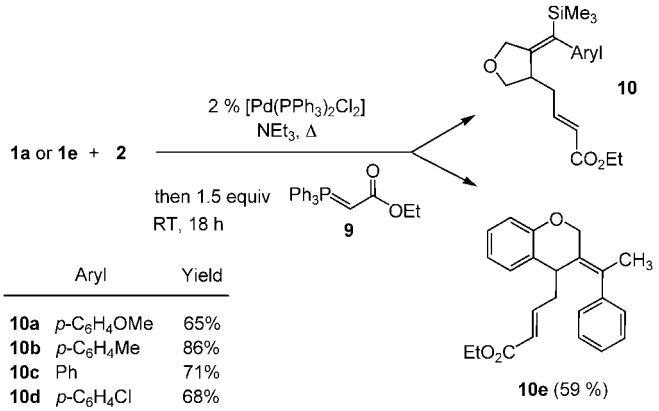
For footnotes, see next page.

This new palladium-catalyzed domino reaction has precedence in its elementary steps, such as intramolecular insertion of tethered alkynes and alkenes,[1a] and the Heck reaction of allyl alcohols to furnish 3-arylpropanals,[13] and can therefore be rationalized as follows (Scheme 1): After the oxidative addition of the aryl halide **2** to the in situ generated Pd^0 species, the arylpalladium halide **4** coordinates and the triple bond of the ynallyl alcohol **1** is inserted by means of a *syn* carbopalladation to furnish the vinylpalladium species **5** in a stereospecific fashion. Coordination and cyclizing insertion of the allyl alcohol fragment generates the alkylpalladium species **6** which then undergoes a β-hydride elimination to give the dienol **7**. Instantaneously tautomerization of **7** gives the enal product **3**, and the hydridopalladium halide species **8**, which reductively eliminates hydrogen halide with base assistance to regenerate the Pd^0 species. After the oxidative addition of **2** the catalytic cycle starts again. Interestingly, the reaction with the trimethylsilyl-substituted alkynylallyl alcohol **1a** gives considerably higher yields (Table 1, entries 1–6 and entries 7–9). The rigidified phenylene-bridged ynallyl alcohol **1e** readily participates in the sequence furnishing chromanylacetaldehyde derivatives in reasonable yields (entries 10–12). Since the Heck carbopalladation/cyclization sequence is considerably hampered with electron-deficient aryl halides—as reflected by either the longer reaction times or, alternatively, microwave irradiation to achieve complete conversion (entries 5 and 6)—the arylpalladium species exerts a strong electronic effect in the carbopalladation step.

This new Heck carbopalladation/cyclization domino sequence of alkynylallyl alcohols to give γ,δ-enals forms the basis for sequential one-pot three-component reactions that are compatible with the mild reaction conditions of the initial Pd-catalyzed process. The newly formed aldehyde functionality is perfectly suited for a subsequent Wittig olefination. Thus, the reaction of alkynylallyl alcohols **1a** and **1e** with the aryl halides **2** in the presence of a catalytic amount of $[Pd(PPh_3)_2Cl_2]$ in boiling triethylamine followed by addition of a stabilized phosphorus ylide of type **9** at room temperature furnishes the 2,3,6,7-diene esters **10** in moderate to good yields (Scheme 2).[12]

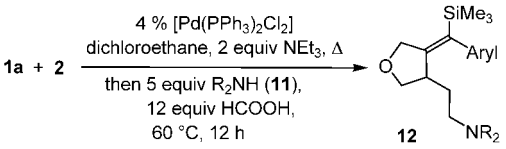
Additionally, upon reducing the amount of triethylamine to only two equivalents, the new Heck carbopalladation/cyclization sequence can serve as an entry for a subsequent reductive amination under Leuckart–Wallach conditions[14] in a sequential one-pot reaction. Thus, the reaction of alkynylallyl alcohol **1a** in the presence of a catalytic amount of $[Pd(PPh_3)_2Cl_2]$ and 2 equiv of triethylamine in boiling 1,2-dichloroethane followed by addition of various secondary amines **11** and formic acid at 60 °C results in the formation of β-aminoethylalkylidenetetrahydrofurans **12** in moderate to excellent yields (Scheme 3).[12]

In conclusion, we have developed a Heck carbopalladation/cyclization domino reaction starting from ynallyl alcohols **1** and aryl halides to give γ,δ-enals **3**. This new domino process was readily elaborated into two consecutive one-pot three-component sequences in which a Heck carbopalladation/cyclization/Wittig sequence and a Heck carbopalladation/cyclization/reductive amination sequence give rise to heterocyclic 2,3,6,7-diene esters and β-aminoethylalkylidenetetrahydrofurans, respectively. Studies addressing the scope of these novel sequences and related sequential transformations to enhance molecular diversity in pharmaceutically interesting targets are currently under investigation.



	Aryl	Yield
10a	*p*-C_6H_4OMe	65%
10b	*p*-C_6H_4Me	86%
10c	Ph	71%
10d	*p*-C_6H_4Cl	68%

Scheme 2. The palladium-catalyzed Heck carbopalladation/cyclization/Wittig sequence giving 2,3,6,7-diene carbonyl compounds **10**.



	Aryl	NR_2	Yield
12a	Ph	NEt_2	69%
12b	Ph	$N(CH_2)_4$	79%
12c	Ph	$N(CH_2)_6$	65%
12d	*p*-$C_6H_4CH_3$	$N(CH_2)_6$	62%
12e	Ph	$N(CH_2CH_2)_2O$	69%
12f	Ph	$N(CH_2CH_2)_2NCH_3$	59%

Scheme 3. The palladium-catalyzed Heck carbopalladation/cyclization/reductive amination sequence yielding β-ethylaminobenzylidene tetrahydrofurans **12**.

Experimental Section

Heck carbopalladation/cyclization sequence (**3b**): In a 50-mL screw-top pressure vessel $[Pd(PPh_3)_2Cl_2]$ (15 mg, 0.02 mmol) was dissolved in degassed triethylamine (10 mL). Then, **1a** (198 mg, 1.00 mmol) and **2b** (240 mg, 1.10 mmol) were added successively to the solution. The

Table 1: [a] Reaction conditions: 1.0 equiv ynallyl alcohol **1**, 1.1 equiv aryl halide **2** (0.1 M in triethylamine), and 0.02 equiv $[Pd(PPh_3)_2Cl_2]$ were heated at reflux for 2–28 h. [b] Yields refer to yields of isolated compounds **3** after flash chromatography on silica gel; purity was estimated to be ≥95% by NMR spectroscopy and elemental analysis and/or HRMS. [c] The reaction was performed in a microwave oven (0.50 mmol **1a**, 0.55 mmol **2f**, 2 mol% $[Pd(PPh_3)_2Cl_2]$; heating rate: 160 s with 300 W to 150 °C, 30 min of reaction time at 150 °C, cooling rate: 240 s to 45 °C). [d] $[Pd(PPh_3)_4]$ as a catalyst.

reaction mixture was heated at reflux for 2.5 h then allowed to cool to room temperature before diethyl ether (150 mL) was added, and the resulting precipitate was filtered. The solvents were removed from the filtrate in vacuo, and the residue was flash chromatographed on silica gel to give analytically pure **3b** (239 mg, 85% yield) as a pale yellow oil, $R_f = 0.59$ (hexane/diethyl ether 1:1). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = -0.17$ (s, 9H), 2.34 (s, 3H), 2.50–2.55 (m, 1H), 2.76–2.81 (m, 1H), 2.93 (ddd, $J = 1.6$, 9.7, 17.8 Hz, 1H), 3.68–3.72 (m, 1H), 3.81 (dd, $J = 1.6$, 11.3 Hz, 1H), 4.08 (d, $J = 17.1$ Hz, 1H), 4.20 (dd, $J = 2.3$, 17.2 Hz, 1H), 6.97–7.01 (m, 2H), 7.10–7.14 (m, 2H), 9.86–9.87 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 0.2$ (CH_3), 21.1 (CH_3), 31.2 (CH), 46.8 (CH_2), 67.3 (CH_2), 70.6 (CH_2), 128.5 (CH), 128.7 (CH), 133.8 ($C_{quat.}$), 137.2 ($C_{quat.}$), 137.4 ($C_{quat.}$), 149.5 ($C_{quat.}$), 201.5 ppm (CH); HRMS calcd for $C_{17}H_{24}O_2Si$: 288.1546, found: 288.1543; Elemental analysis calcd for $C_{17}H_{24}O_2Si$ (288.5): C 70.78, H 8.39; found: C 70.61, H 8.43.

Heck carbopalladation/cyclization/Wittig sequence (**10b**): In a 50-mL screw-top pressure vessel [$Pd(PPh_3)_2Cl_2$] (14 mg, 0.02 mmol) was dissolved in degassed triethylamine (10 mL). Then, **1a** (198 mg, 1.00 mmol) and **2b** (241 mg, 1.10 mmol) were added successively to the solution. The reaction mixture was heated at reflux for 2.5 h then allowed to cool to room temperature before THF (5 mL) and **9** (523 mg, 1.50 mmol) were added successively, and the reaction mixture was stirred at room temperature for 18 h. The precipitates were removed by filtration, the solvents were removed from the filtrate in vacuo, and the residue was flash chromatographed on silica gel to give the analytically pure **10b** (301 mg, 86%) as a yellow oil, $R_f = 0.72$ (hexane/diethyl ether 1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = -0.16$ (s, 9H), 1.30 (t, $J = 7.1$ Hz, 3H), 2.23–2.61 (m, 6H), 3.58–3.66 (m, 1H), 3.81 (dd, $J = 1.9$, 11.2 Hz, 1H), 4.02–4.26 (m, 4H), 5.92 (dt, $J = 1.4$, 15.6 Hz, 1H), 6.91–7.15 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 0.4$ (CH_3), 14.2 (CH_3), 21.1 (CH_3), 35.2 (CH_2), 36.0 (CH), 60.1 (CH_2), 66.0 (CH_2), 70.5 (CH_2), 122.8 (CH), 128.6 (CH), 128.7 (CH), 134.5 ($C_{quat.}$), 137.1 ($C_{quat.}$), 137.6 ($C_{quat.}$), 147.1 (CH), 149.2 ($C_{quat.}$), 166.4 ppm ($C_{quat.}$); HRMS calcd for $C_{21}H_{30}O_3Si$: 358.1964, found: 358.1950; Elemental analysis calcd for $C_{21}H_{30}O_3Si$ (358.6): C 70.35, H 8.43; found: C 70.31, H 8.42.

Heck carbopalladation/cyclization/reductive amination sequence (**12b**): In a 50-mL screw-top pressure vessel [$Pd(PPh_3)_2Cl_2$] (28 mg, 0.04 mmol) was dissolved in a mixture of degassed 1,2-dichloroethane (10 mL) and triethylamine (202 mg, 2.00 mmol). Then, **1a** (198 mg, 1.00 mmol) and **2c** (240 mg, 1.10 mmol) were added successively to the solution. The reaction mixture was heated at reflux for 3 h then allowed to cool to room temperature before formic acid (552 mg, 12.0 mmol) and pyrrolidine (**11b**) (356 mg, 5.00 mmol) were added successively, and the reaction mixture was heated to 60°C for 12 h. The reaction mixture was allowed to cool to room temperature, diethyl ether (150 mL) and anhydrous potassium carbonate were added, and the precipitates were removed by filtration. The solvents were removed from the filtrate in vacuo, and the residue was flash chromatographed on basic alumina (Brockmann activity IV) to give the analytically pure **12b** (261 mg, 79%) as a yellow-red oil, $R_f = 0.31$ (hexane/diethyl ether 1:2). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = -0.22$ (s, 9H), 1.67–1.85 (m, 6H), 2.09–2.18 (m, 1H), 2.42–2.60 (m, 6H), 3.60–3.67 (m, 1H), 3.83 (dd, $J = 2.2$, 11.0 Hz, 1H), 4.04 (d, $J = 16.9$ Hz, 1H), 4.20 (dd, $J = 2.2$, 16.9 Hz, 1H), 7.04–7.11 (m, 2H), 7.20–7.30 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 0.4$ (CH_3), 23.4 (CH_2), 31.5 (CH_2), 35.3 (CH), 54.3 (CH_2), 54.9 (CH_2), 66.8 (CH_2), 70.4 (CH_2), 127.2 (CH), 127.9 (CH), 128.8 (CH), 135.8 ($C_{quat.}$), 141.0 ($C_{quat.}$), 148.2 ppm ($C_{quat.}$); HRMS calcd for $C_{20}H_{31}NOSi$: 329.2175, found: 329.2167; Elemental analysis calcd for $C_{20}H_{31}NOSi$ (329.56): C 72.89, H 9.48, N 4.25; found: C 73.36, H 9.71, N 3.91.

Received: June 30, 2004

Keywords: amination · C–C coupling · domino reactions · multicomponent reactions · olefination

[1] For excellent reviews, see for example, a) E.-I. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365; b) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; c) S. Bräse, A. de Meijere in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**, p. 99.

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