Cyclization Reactions

DOI: 10.1002/anie.200803424

An Efficient Approach to Substituted 1,5,7,8,9-Pentahydrocyclopenta-[*h*]-2-Benzopyran-3-one Derivatives by a Palladium-Catalyzed Tandem Reaction of 2,7-Alkadiynylic Carbonates with 2,3-Allenoic Acids**

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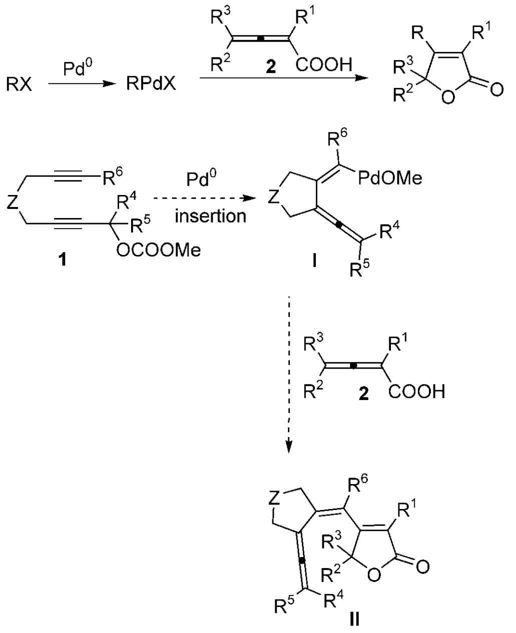
Transition-metal-catalyzed cyclization reactions of functionalized allenes in the presence of organic halides have become powerful tools for the synthesis of cyclic compounds.[1–5] Based on this approach, we envisioned that a 1,3,4-trienyl palladium intermediate **I**, which is formed from the oxidative addition and cyclic carbopalladation of 2,7-alkadiynylic carbonates,[6] might act similarly to the aryl/alkenyl palladium intermediates formed from the oxidative addition of organic halides with palladium(0) to trigger the cyclization of 2,3-allenoic acids **2** to afford butenolides with a 1,3,4-trienyl unit at the β position (Scheme 1).[7] However, our preliminary study showed that the reaction of 2,7-alkadiynylic carbonate **1a** and 2,3-allenoic acid **2a** in the presence of [Pd(PPh$_3$)$_4$] (5 mol %) in acetonitrile at 60 °C for one hour failed to afford the **II**-type product. Instead, an interesting and unexpected new product was formed and isolated cleanly (Table 1, entry 1). The structure of this product was unambiguously established as the tricyclic product **3a** by X-ray diffraction analysis (Figure 1).[8] Herein, we report our recent observations in this area.

An assortment of palladium catalysts and solvents were screened for the transformation (Table 1). When [Pd(PPh$_3$)$_4$] was used as the catalyst, the reaction proceeded smoothly in DMSO, DCE, and MeNO$_2$ (Table 1, entries 2–4). Among them MeNO$_2$ was shown to be the best solvent with **3a** isolated in 87 % yield (Table 1, entry 4). Other solvents such as THF, DMF, *N*-methyl-2-pyrrolidone, and toluene, were ineffective (Table 1, entries 5–8). Whereas better results were not observed by using catalyst systems with Pd(OAc)$_2$/phosphrous-containing ligand (Table 1, entries 9 and 10). Bidentate ligands such as dppe and binap resulted in trace amount of product as determined by TLC analysis (Table 1, entries 11 and 12).



Scheme 1. Palladium(0)-catalyzed reaction of 2,3-allenoic acids with aryl or alkenyl halides (above) vs 2,7-alkadiynylic carbonates (below). X = halide, Z = tether.

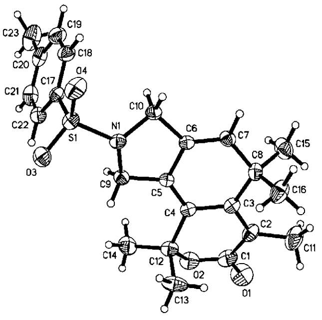


Figure 1. ORTEP plot of **3a** shown with ellipsoids at the 30 % probability level.

Next, the substrate scope of 2,3-allenoic acids **2** and 2,7-alkadiynylic carbonates **1** (which are N tethered) were surveyed under the optimized reaction conditions (Table 2, entries 1-9). Fully decorated 2,3-allenoic acids may be alkyl (Table 2, entry 1), allyl (Table 2, entry 2), or aryl (Table 2, entries 3 and 4) substituted. The carbon–carbon triple bond at the 7 position may be either terminal (Table 2, entries 1–8 and 11) or nonterminal (Table 2, entries 9 and 10). The reaction

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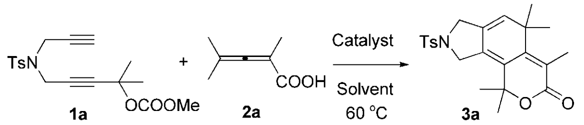
[**] Financial support from the State Key Basic Research & Development Program (2006CB806105) and the National Natural Science Foundation of China (20732005) are greatly appreciated. We also thank J. Chen for reproducing the results presented in Table 2, entries 2 and 8, and Scheme 2.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803424.

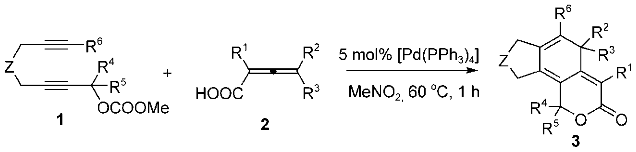
Table 1: Effect of solvent and catalyst on the cyclization reaction of 2,7-alkadiynylic carbonate **1a** with 2,3-allenoic acid **2a**.[a]

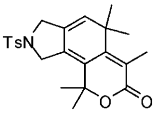
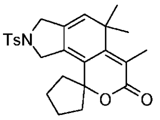
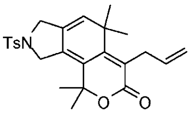
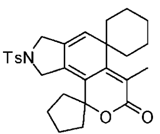
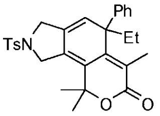
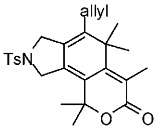
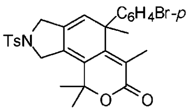
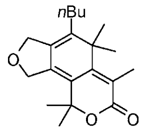
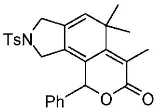
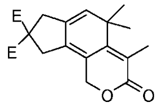
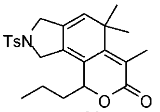


Entry	Solvent	Catalyst	Yield [%][b] (%)[c]
1	MeCN	[Pd(PPh$_3$)$_4$]	100 (76)
2	DMSO	[Pd(PPh$_3$)$_4$]	100 (75)
3	DCE	[Pd(PPh$_3$)$_4$]	92
4	MeNO$_2$	[Pd(PPh$_3$)$_4$]	100 (87)
5	THF	[Pd(PPh$_3$)$_4$]	25
6	DMF	[Pd(PPh$_3$)$_4$]	42
7	NMP	[Pd(PPh$_3$)$_4$]	23
8	toluene	[Pd(PPh$_3$)$_4$]	11
9	MeNO$_2$	Pd(OAc)$_2$, 10 mol% tfp	100 (71)
10	MeNO$_2$	Pd(OAc)$_2$, 10 mol% Ph$_3$P	83 (66)
11	MeNO$_2$	Pd(OAc)$_2$, 5 mol% dppe	trace
12	MeNO$_2$	Pd(OAc)$_2$, 5 mol% binap	trace

[a] Under argon, a mixture of **1a** (0.3 mmol), **2a** (0.33 mmol), palladium complex (5 mol%), and ligand in solvent (3 mL) was stirred at 60°C for 1 h. [b] Determined by ^{1}H NMR spectroscopy with CH$_2$Br$_2$ as the internal standard. [c] Yield of isolated product. binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, dppe = 1,2-bis(diphenylphosphino)ethane, NMP = *N*-methyl-2-pyrrolidone, tfp = tri(futan-2-yl)phosphine, Ts = 4-toluenesulfonyl.

Table 2: Palladium-catalyzed cyclization reaction of 2,7-alkadiynylic carbonates **1** with 2,3-allenoic acids **2**.[a]



Entry	Products	Yield [%][b]	Entry	Products	Yield [%][b]
1	 **3a**	87	7	 **3g**	74
2	 **3b**	74	8	 **3h**	70
3	 **3c**	75	9	 **3i**	61
4	 **3d**	73	10	 **3j**	75
5	 **3e**	86	11	 **3k**	54
6	 **3f**	80			

[a] The reaction was carried out under argon in a Schlenk tube using **1** (0.3 mmol), **2** (0.33 mmol), and [Pd(PPh$_3$)$_4$] (5 mol%) in MeNO$_2$ (3 mL) at 60°C for 1 h. [b] Yield of isolated product. E = COOEt.

proceeded smoothly with primary (Table 2, entry 11), secondary (Table 2, entries 5 and 6), and tertiary (Table 2, entries 1–4 and 7–10) 2,7-diynylic carbonates. The method is also applicable to oxygen tethered (Table 2, entry 10) or carbon tethered (Table 2, entry 11) 2,7-alkadiynylic carbonates to form the corresponding tricyclic compounds **3j** and **3k**.

When optically active 2,7-diynylic tosylamide *R*-(+)-**1h**, which was prepared readily from propionaldehyde in four steps (Scheme 2, see the Supporting Information for experimental details),[9] was used, its cyclization with **2a** under the standard reaction conditions afforded the optically active product *R*-(−)-**3l** in 73% yield with greater than 99% *ee*.

In addition, it was observed that when 4-monosubstituted 2,3-allenoic acids **2f** and **2g** were used, the reaction yielded the aromatized tricyclic products **4** (Scheme 3). The structure of **4b** was also confirmed by X-ray diffraction analysis (Figure 2).[10]

A rationale is proposed for the above transformation (Scheme 4). Instead of triggering the normal cyclization to afford the expected product **II** (see Scheme 1), the carbon–carbon double bond at the 4 position of the 1,3,4-trienyl palladium species **I** would undergo highly regioselective intermolecular oxypalladation with 2,3-allenoic acid **2** to form an ester C–O bond to yield the palladabicyclic intermediate **III**. Regioselective intramolecular carbopalladation of the relatively electron-rich carbon–carbon double bond in the allenoic moiety in **III** would form the six-membered lactone ring and the seven-membered palladacycle. Subsequent reductive elimination of intermediate **IV** would form tricyclic product **3** and regenerate the catalytically

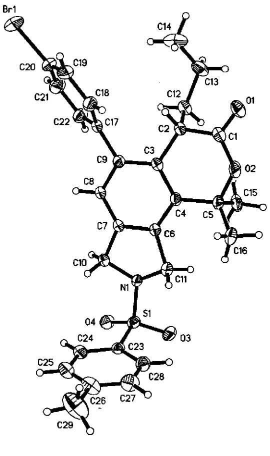
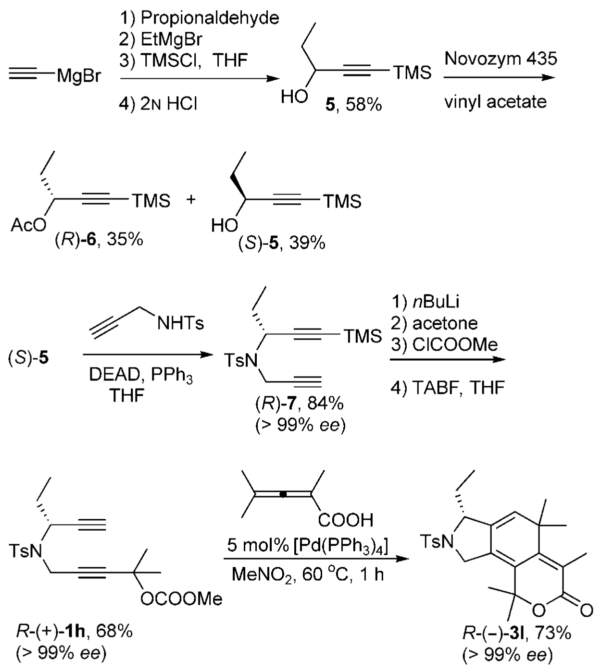
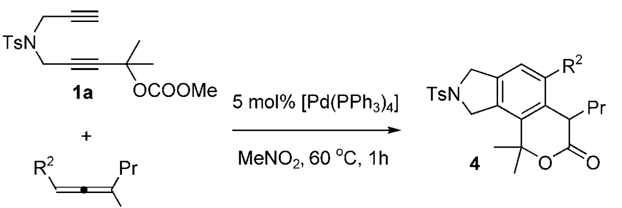


Figure 2. ORTEP plot of **4b** shown with ellipsoids at the 30% probability level.



Scheme 2. Synthesis and cyclization of an optically active substrate. DEAD = diethyl azodicarboxylate, TBAF = *tetra-n*-butylammonium fluoride, TMS = trimethylsilyl.



R^2	Yield (%)
1-Naphthyl-(**2f**)	69 (**4a**)
4-BrC$_6$H$_4$-(**2g**)	59 (**4b**)

Scheme 3. Cyclization reaction of 2,7-alkadiynylic carbonate **1a** with 4-monosubstituted 2,3-allenoic acids **2**.

active palladium(0). For a 4-monosubstituted 2,3-allenoic acid, **3** may readily further aromatize to give the tricyclic **4** with a benzene ring in the center of the molecule.

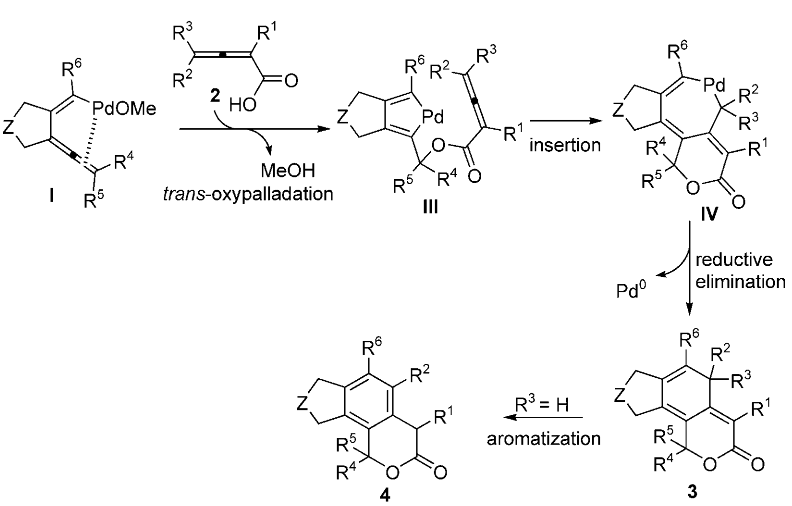
In conclusion, we have developed an efficient methodology for the synthesis of 1,5,7,9-pentahydrocyclopenta[*h*]-2-benzopyran-3-one skeletons from easily available 2,3-allenoic acids[2b,c,11] and 2,7-alkadiynylic carbonates.[6b,c] Owing to the importance of this versatile skeleton,[12,13] the reaction will be potentially useful in organic synthesis and medicinal chemistry. Furthermore, the transformation revealed here involves the formation of four bonds within one synthetic operation.

Experimental Section

A typical procedure for the preparation of **3a**: 2,3-allenoic acid (**2a**, 42 mg, 0.33 mmol), [Pd(PPh$_3$)$_4$] (17 mg, 0.015 mmol, 5 mol%), 2,7-alkadiynoic carbonate (**1a**, 110 mg, 0.3 mmol), and MeNO$_2$ (3 mL) were sequentially added to a dried and degassed Schlenk tube under Ar. The resulting reaction mixture was stirred at 60 °C for 1 h. When the reaction was complete (as evident by TLC), removal of the solvent by evaporation and purification by column chromatography on silica gel (eluent: CH$_2$Cl$_2$) afforded the pure **3a** (109 mg, 87%) as a colorless solid, m. p. 172–173 °C (acetone/diethyl ether 1:10). ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.71$ (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 5.40 (s, 1H), 4.16 (s, 2H), 3.93 (s, 2H), 2.43 (s, 3H), 2.24 (s, 3H), 1.53 (s, 6H), 1.34 ppm (s, 6H); ^{13}C NMR (75.4 MHz, CDCl$_3$): $\delta = 16.7$, 21.4, 26.6, 28.0, 38.6, 50.0, 52.3, 79.8, 122.8, 126.9, 127.6, 127.9, 129.8, 131.5, 132.2, 132.6, 144.1, 150.8, 165.4 ppm; EIMS: m/z (%): 413 (M^+, 15.07), 398 ($M^+ - CH_3$, 4.05), 91 (100); IR (thin film): $\tilde{\nu} = 1783$, 1698, 1597, 1347, 1163 cm^{-1}; elemental analysis calcd for C$_{23}$H$_{27}$NO$_4$S: C 66.80, H 6.58, N 3.39; found, C 66.78, H 6.47, N 3.31.

Received: July 15, 2008

Keywords: allenoic acids · cyclization · palladium · tandem reactions



Scheme 4. A possible mechanism for the cyclization reaction of 2,7-alkadiynylic carbonates with 2,3-allenoic acids catalyzed by [Pd(PPh$_3$)$_4$].

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[8] Crystal data for **3a**: Recrystallization from acetone/diethyl ether (1:10), $C_{23}H_{27}NO_4S$, MW = 413.52, Monoclinic, space group *P*21/*c*, Mo_K, final *R* indices $[I > 2\sigma(I)]$, $R1 = 0.0633$, $wR2 = 0.1486$, *R* indices (all data): $R1 = 0.0963$, $wR2 = 0.1647$; $a = 12.6156(17)$ Å, $b = 7.5890(11)$ Å, $c = 23.006(3)$ Å, $\alpha = 90$, $\beta = 100.518(3)$, $\gamma = 90°$, $V = 2165.6(5)$ Å^3, $T = 293(2)$ K, wavelength: 0.71073 Å, $Z = 4$, reflections collected/unique 12125/4704 ($R_{int} = 0.1281$), number of observation $[I > 2\sigma(I)]$ 2980, parameters 268. CCDC 675814 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[10] Crystal data for **4b**: Recrystallization from acetone/diethyl ether (1:10), $C_{29}H_{30}BrNO_4S$, MW = 568.51, Monoclinic, space group *P*21/*n*, Mo_K, final *R* indices $[I > 2\sigma(I)]$, $R1 = 0.0424$, $wR2 = 0.0778$, *R* indices (all data): $R1 = 0.0984$, $wR2 = 0.0868$; $a = 17.4190(17)$ Å, $b = 9.6103(10)$ Å, $c = 31.794(3)$ Å, $\alpha = 90°$, $\beta = 93.815(2)°$, $\gamma = 90°$, $V = 5310.5(9)$ Å^3, $T = 293(2)$ K, wavelength: 0.71073 Å, $Z = 8$, reflections collected/unique 27183/9845 ($R_{int} = 0.0900$), number of observation $[I > 2\sigma(I)]$ 4485, parameters 657. CCDC 675815 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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