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Palladium-catalyzed cycloheptatriene formation by [3+2+2] cocyclization of 2-substituted allylic alcohols and alkynes

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Abstract—Cycloheptatrienes were obtained by the reaction of 2-substituted allylic alcohols with alkynes in the presence of catalytic amounts of palladium complexes and *p*-toluenesulfonic acid.

Transition-metal-catalyzed cocyclizations have proved to be very useful and versatile in organic syntheses.[1] Various types of reactions have been reported to prepare cyclic compounds from simple starting materials. Whereas a large number of reactions for the synthesis of four- to six-membered rings have been reported, the preparation of seven-membered rings by cocyclization is rather limited.[1a,b] Especially, there have been few examples for catalytic [3+2+2] cocyclizations.[2–5] Recently, the nickel-catalyzed reactions using cyclopropylidene compounds as three-carbon fragments were reported by Saito and co-workers[2] and de Meijere and Zhao.[3] Alkenylated Fisher carbene complexes were also used as three-carbon fragments in the rhodium-catalyzed cocyclization with allenes.[4]

During the course of our study on the palladium-catalyzed arene formation by [2+2+2] cocyclization of alkynes and allyl tosylate,[6] we found the reaction of 2-substituted allylic compounds with alkynes gave cycloheptatrienes instead of arenes. In this Letter we report a novel palladium-catalyzed [3+2+2] cocyclization of allylic alcohols and alkynes.[5]

We previously reported that the reaction of allyl tosylate with 3-hexyne gave 1,2,3,4-tetraethyl-5-methylbenzene in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3.[6] Under the same reaction conditions, the reaction of methallyl tosylate **1a** with 3-hexyne **2a** afforded [3+2+2] cocyclization products, tetraethylmethylcycloheptatrienes **3** in 13% yield, Eq. 1. Methallyl alcohol **1b** could be also utilized as a three-carbon fragment by addition of *p*-toluenesulfonic acid or anhydride.[7] Since the direct use of allylic alcohols in catalytic processes is more desirable,[8] especially from the viewpoint of atom economy,[9] we focused on the reaction of allylic *alcohols* with alkynes. The results are summarized in Table 1.[10] In the presence of 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol % of PPh_3 and 20 mol % of *p*-toluenesulfonic acid, the reaction of **1b** with **2a** gave **3** in 9% yield (entry 1). The use of $P(OPh)_3$ and PCy_3 as ligands did not improve the yield of **3** (entries 3 and 4). Whereas 1 equiv of $P(o\text{-Tol})_3$ was not effective, the reaction with 2 equiv of $P(o\text{-Tol})_3$ afforded **3** in a better yield (entries 2 and 6). This result is in contrast with the above-mentioned [2+2+2] cocyclization, which was inhibited by more than 2 equiv of monophosphine ligands.[6] Finally, cycloheptatrienes **3** were obtained in 58% yield after the optimization of several reaction conditions such as the amounts of **2a**, 1,2-dichloroethane and the catalyst (entry 7). The ratio of **3a** and **3b** was moderate in most reactions and not significantly affected by reaction conditions. Other 2-substituted allylic alcohols such as 2-aryl-2-propen-1-ols **1c–e** and methyl 2-hydroxymethylacrylate **1f** could be used as three-carbon fragments for the [3+2+2] cocyclization, giving the corresponding cycloheptatrienes **4–7**, respectively (entries 8–11). However, no products were obtained in the reaction of 2-chloro2-propen-1-ol. The reaction of methallyl alcohol **1b** with 2-butyne **2b** gave pentamethylcycloheptatrienes **8** in 39% yield (entry 12). The reactions with diphenylacetylene, dibenzoylacetylene, dimethyl acetylenedicarboxylate, 1,4-dimethoxy-2-butyne and several terminal alkynes gave no cocyclization products.

Keywords: Cycloheptatriene; Palladium; [3+2+2] Cocyclization; Alkyne; Allylic alcohol.

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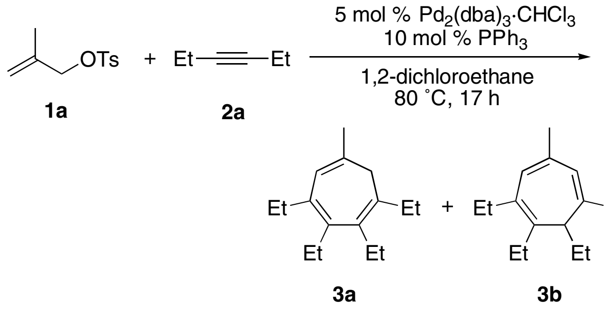
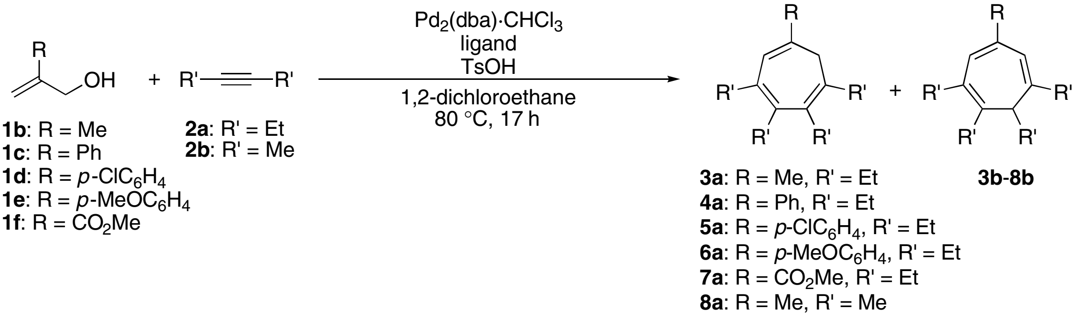


(1)



(2)

Table 1. Palladium-catalyzed [3+2+2] cocyclization between 2-substituted allyl alcohols and alkynes[a]

Entry	Alcohol	Alkyne (mmol)	$Pd_2(dba)_3·CHCl_3$ (mol %)	Ligand (P/Pd)	$ClCH_2CH_2Cl$ (ml)	Product, yield[b] (%)	Ratio[c] (**a**/**b**)
1	**1b**	**2a** (1.0)	5	PPh_3 (1)	3	**3**, 9	46:54
2	**1b**	**2a** (1.0)	5	PPh_3 (2)	3	**3**, 8	69:31
3	**1b**	**2a** (1.0)	5	$P(OPh)_3$ (1)	3	**3**, 2	nd
4	**1b**	**2a** (1.0)	5	PCy_3 (1)	3	**3**, 7	44:56
5	**1b**	**2a** (1.0)	5	P(*o*-Tol)$_3$ (1)	3	**3**, 8	6:94
6	**1b**	**2a** (1.0)	5	P(*o*-Tol)$_3$ (2)	3	**3**, 17	46:54
7	**1b**	**2a** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**3**, 58	65:35
8	**1c**	**2a** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**4**, 52[d]	30:70
9	**1d**	**2a** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**5**, 31[d]	15:85
10	**1e**	**2a** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**6**, 56[d]	21:79
11	**1f**	**2a** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**7**, 31[d]	50:50
12	**1b**	**2b** (5.0)	10	P(*o*-Tol)$_3$ (4)	1	**8**, 39[d]	81:19

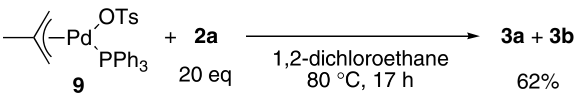
[a] A reaction mixture of an alcohol (0.5 mmol), an alkyne, $Pd_2(dba)_3·CHCl_3$, TsOH (20 mol %), and ligand in 1,2-dichloroethane was heated at 80 °C for 17 h.

[b] GC yields.

[c] Determined by ^1H NMR spectra.

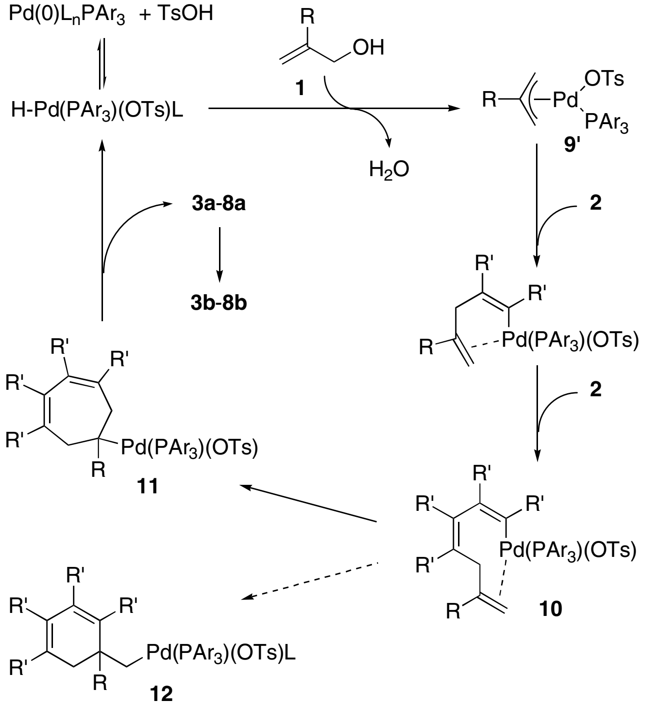
[d] Isolated yields.

To gain an insight into mechanism of the cocyclization, the reaction of (η^3-methallyl)palladium complex **9** with **2a** was conducted. Treatment of **9** with excess amounts of **2a** under similar reaction conditions resulted in the formation of **3** in 62% yield, Eq. 3. This result indicates that the [3+2+2] cocyclization proceeds via a (η^3-allyl)palladium intermediate[11] as well as the previous [2+2+2] cocyclization.[6] A plausible catalytic cycle is shown in Scheme 1. The reaction of alcohols **1** with a palladium hydride complex generated from Pd(0) and TsOH would afford (η^3-RC_3H_4)palladium complex **9′**.[12] Only one molecule of P(*o*-Tol)$_3$ probably ligates to palladium because of its bulkiness. Excess P(*o*-Tol)$_3$ might be effective for stability of Pd(0) species or β-hydride elimination of **11**. Successive insertion of two molecules of **2** into the C–Pd bond of **9′** gives alkenylpalladium complex **10**. Seven-membered ring intermediate **11** is selectively generated by 7-*endo*-*trig* cyclization.[13] The substituents R of inserting alkenes could affect the selectivity between the 7-*endo*-*trig* cyclizaion and the 6-*exo*-*trig* cyclization giving intermediate **12**,[14] which is an intermediate in the [2+2+2] cocyclization[6] of allyl tosylate and alkynes. Cycloheptatrienes **3**–**8** are obtained by β-hydride elimination of **11**.



(3)

In summary, we found a novel palladium-catalyzed [3+2+2] cocyclization, in which tetrasubstituted cycloheptatrienes were obtained from one molecule of 2-substituted allylic alcohol and two molecule of alkyne.



Scheme 1.

The direct use of allylic *alcohols* instead of other allylic compounds has important advantages such as atom economy and easy availability.

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7. Other sulfonic acids such as p-$ClC_6H_4SO_3H$, CH_3SO_3H and CSA can be used instead of TsOH. However, the product yields were lower in the reactions with stronger acids such as TfOH, or with Lewis acids such as BEt_3 and $M(OTf)_3$ (M = In, Cu, lanthanides).
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10. *Representative procedure for the [3+2+2] cocyclization.* Synthesis of **3** from **1b** and **2a**. To a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mmol, 52 mg), P(o-Tol)$_3$ (0.40 mmol, 122 mg) and TsOH (0.10 mmol, 19 mg) in 1,2-dichloroethane (1 ml) was added alcohol **1b** (0.50 mmol, 67 mg) under a nitrogen atmosphere in a pressure vial. After stirring for 10 min, alkyne **2a** (5.0 mmol, 0.57 ml) was added to a reaction mixture. After heating at 80 °C for 17 h, the mixture was filtered through a short plug of silica using ether as an eluent. Volatiles were evaporated and the residue was purified by silica gel column chromatography with hexane to give a mixture of **4a** and **4b** in 52% yield (77 mg). Anal. Calcd for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.98; H, 10.01. Cycloheptatrienes **4a** and **4b** are separable by flash chromatography. Compound **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60–7.47 (m, 2H), 7.35–7.29 (m, 2H), 7.22 (tt, $J = 7.3$, 1.2 Hz, 1H), 6.14 (s, 1H), 3.13 (d, $J = 11.8$ Hz, 1H), 2.59–1.96 (m, 8H), 2.07 (d, $J = 11.8$ Hz, 1H), 1.06 (t, $J = 7.5$ Hz, 3H), 1.03 (t, $J = 7.5$ Hz, 3H), 0.92 (t, $J = 7.5$ Hz, 3H), 0.84 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.9, 140.9, 139.2, 137.0, 134.3, 132.9, 131.6, 128.3, 126.7, 126.5, 125.6, 35.4, 27.3, 26.5, 23.3, 22.3, 15.9, 15.7, 14.9, 14.0. Compound **4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52–7.40 (m, 2H), 7.40–7.32 (m, 2H), 7.25 (tt, $J = 7.9$, 1.3 Hz, 1H), 6.57 (s, 1H), 6.06 (t, $J = 1.3$ Hz, 1H), 2.74 (dt, $J = 1.3$, 7.7 Hz, 1H), 2.37–2.07 (m, 6H), 1.31–1.14 (m, 2H), 1.16 (t, $J = 7.4$ Hz, 3H), 1.11 (t, $J = 7.5$ Hz, 3H), 1.06 (t, $J = 7.5$ Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.4, 143.9, 139.0, 136.8, 132.2, 130.0, 128.3, 126.8, 126.6, 119.4, 50.2, 33.2, 29.8, 27.2, 19.9, 15.5, 13.5, 13.0, 12.3.
11. Actually, the isolated allyl complex **9** served as a catalyst for the [3+2+2] cocyclization although the yield of **3** in the reaction with **9** was lower than in the reaction with $Pd_2(dba)_3 \cdot CHCl_3$/P(o-Tol)$_3$. Whereas η^3-methallylpalladium complexes having P(o-Tol)$_3$ and OTs^- as ligands were expected to be better catalysts for the cocyclization, those complexes could not be prepared.
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14. Although moderate yields of cycloheptatrienes could be attributed to the formation of intermediate **12**, no products including six-membered rings were detected.