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Palladium-Catalyzed Tandem Cyclization/Suzuki Coupling Reaction of 1,2,7-Trienes

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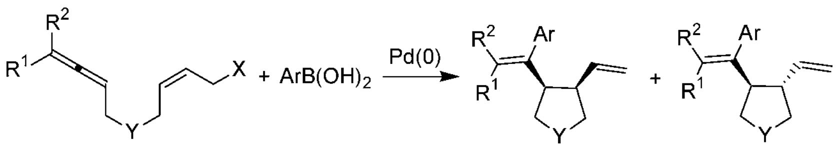
ABSTRACT



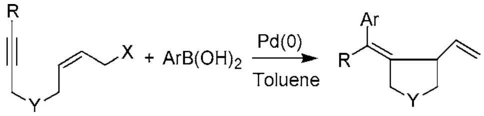
1 2 *cis*-3 *trans*-3

A Pd(0)-catalyzed 1,2,7-triene cyclization/arylation cascade reaction was realized via π-allylpalladium intermediate formation and a subsequent Suzuki coupling reaction to preferentially give a five-membered ring product with a stereodefined exocyclic double bond. Excellent cis/trans selectivity was achieved (only *cis*-3 was isolated) with heteroatom-tethered 1,2,7-triene substrates.

Transition metal-catalyzed carbocyclization[1] is a versatile method for the construction of ring systems because it offers an efficient entryway to cyclic compounds from readily available acyclic substrates. [2] Numerous carbocyclization reactions of 1,*n*-enynes,[3] 1,*n*-diynes,[4] and 1,*n*-dienes[5] have been widely investigated with various transition metal catalysts. However, carbocyclizations involving allenes have received less attention,[7] although many transformations of allenes are known.[6] To the best of our knowledge, there have only been a few reports on transition metal-catalyzed carbocyclization reactions of 1,2,7-trienes.[8]

We have recently reported a palladium-catalyzed tandem cyclization/Suzuki coupling reaction of 1,6-enynes, with which a five-membered ring compound with stereodefined exocyclic double bond was synthesized efficiently (Scheme 1).[9]

Scheme 1. Palladium-Catalyzed Tandem Cyclization/Suzuki Coupling Reaction of 1,6-Enynes



Pursuing our interest in developing new cascade carbopalladation reactions, it became highly desirable to investigate

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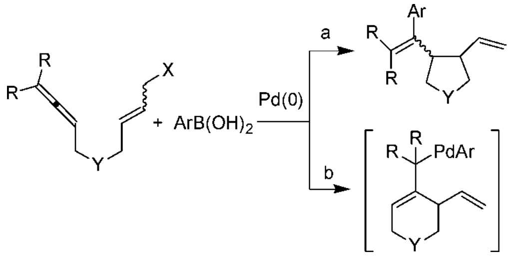
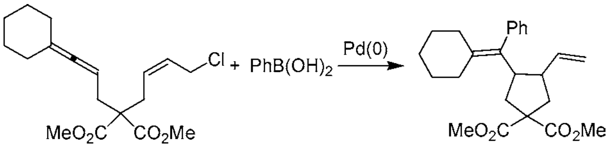
a new tandem cyclization/Suzuki coupling reaction of 1,2,7-triene substrates. This reaction of 1,2,7-triene substrates was envisioned to have more than one possible reaction pathway: a five-membered or six-membered ring product might be formed (Scheme 2).

Scheme 2. Possible Reaction Pathways of a Palladium-Catalyzed 1,2,7-Triene/Aryl Boronic Acid Cascade Reaction



To explore the proposed cyclization/Suzuki coupling reaction, a 1,2,7-triene substrate **1a** and phenyl boronic acid **2a** were chosen to screen reaction conditions. Under atmospheric argon, a Schlenk reaction tube was charged with **1a** (85 mg, 0.25 mmol), **2a** (61 mg, 0.5 mmol), KF (29 mg, 0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and THF (5 mL). After the mixture was heated at 50 °C for 4 h with stirring, the five-membered ring product **3aa** was isolated in 49% yield (entry 1, Table 1).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

entry	base	solv.	temp. (°C)	time (h)	yield (%)[b]
1	KF	THF	50	4	49
2	KF	CH_3CN	50	4	60
3	KF	DCE	80	12	nr
4	KF	EtOH	50	4	40
5	KF	toluene	50	4	88
6	K_2CO_3	toluene	50	4	89
7	K_3PO_4[c]	toluene	50	4	95
8	K_3PO_4[c]	toluene	25	18	87
9	K_3PO_4[c,d]	toluene	50	4	68
10	K_3PO_4[c,e]	toluene	50	4	52

[a] All reactions were conducted with **1a** (85 mg, 0.25 mmol), **2a** (61 mg, 0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and base (0.5 mmol). [b] Combined yields of cis and trans isomers. [c] Actually, $K_3PO_4 \cdot 3H_2O$ was employed. [d] $Pd(dba)_2$ (7 mg, 0.0135 mmol) and PPh_3 (7 mg, 0.027 mmol) were used. [e] $Pd(dba)_2$ (7 mg, 0.0135 mmol) and dppb (6 mg, 0.0135 mmol) were used.

Through extensive screening, we found that the reaction proceeded in a variety of solvents. Of all the solvents tested, toluene was the best. Both $Pd_2(dba)_3 \cdot CHCl_3$ and $Pd(PPh_3)_4$ served as convenient sources of palladium(0). $K_3PO_4 \cdot 3H_2O$ proved to be the best base, while several other bases such as KF and K_2CO_3 were effective as well (entries 5−7, Table 1).

Although the reaction proceeded at room temperature to give a comparable yield, a longer reaction time was needed than when the reaction was run at 50 °C (entry 8 vs entry 7, Table 1). Therefore, for our standard conditions, we chose 50 °C as the reaction temperature, $K_3PO_4 \cdot 3H_2O$ as the base, $Pd(PPh_3)_4$ as the Pd(0) source, and toluene as the solvent.

For 1,2,7-triene substrate **1a**, the cyclic product was obtained in high yield (95%) and fair selectivity (cis/trans = 85/15). The successful formation of a five-membered ring product **3aa** provides another example of a novel alkenylpalladium species-forming process from a π-allyl palladium and an allene.[10] Compared to the widely reported intermolecular carbopalladation of allenes[6g,11] that has been shown to give allyl palladium species, preferential formation of alkenyl palladium species has received very little attention.[6g,10b,12] For this reason, further investigation into the scope and synthetic utility of this reaction is appealing.

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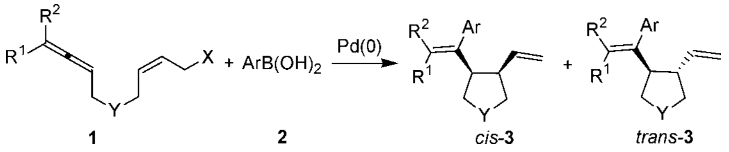
Table 2. Various 1,2,7-Triene Substrates Coupled with Arylboronic Acids



entry	substrate	R^1	R^2	Ar	Y	X	yield **3**[b] (%)[c]
1	**1a**	$-(CH_2)_5-$		Ph (**2a**)	$C(CO_2Me)_2$	Cl	**3aa** 95(85/15)
2	**1b**	H	H	Ph	$C(CO_2Me)_2$	Cl	**3ba** 83(85/15)
3	**1c**	H	H	Ph	$C(CO_2Me)_2$	Br	**3ba** 71(83/17)
4	**1d**[d]	H	H	Ph	$C(CO_2Me)_2$	OAc	0[e]
5	**1e**	Ph	H	Ph	$C(CO_2Me)_2$	Cl	**3ea** 17(80/20)
6	**1f**	^{n}Pr	H	Ph	$C(CO_2Me)_2$	Cl	**3fa** 85(91/9)
7	**1g**	^{i}Pr	H	Ph	$C(CO_2Et)_2$	Cl	**3ga** 91(91/10)
8	**1h**	H	H	Ph	NTs	Cl	**3ha** 66[f]
9	**1i**	H	H	Ph	NTs	OCO_2Me	**3ha** 65
10	**1j**	^{n}Pr	H	Ph	NTs	Cl	**3ja** 77
11	**1j**	^{n}Pr	H	*p*-OMe-C_6H_4 (**2b**)	NTs	Cl	**3jb** 82
12	**1j**	^{n}Pr	H	*p*-Cl−C_6H_4 (**2c**)	NTs	Cl	**3jc** 84
13	**1k**	^{i}Pr	H	Ph	NTs	Cl	**3ka** 84
14	**1l**	^{i}Pr	H	Ph	O	Br	**3la** 59
15	**1m**	H	H	Ph	O	Br	**3ma** 42

[a] All reactions were run with **1** (0.25 mmol), aryl boronic acid (0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and $K_3PO_4{\cdot}3H_2O$ (133 mg, 0.5 mmol) in toluene (5 mL) at 50 °C for 4 h. [b] Isolated yield. [c] Cis/trans ratios in parentheses were determined by ^{1}H NMR. [d] *Z*/*E*=2.2:1. [e] Reaction was also run in MeCN with 2 equiv of LiCl under reflux, and only some unidentified oligomers were formed. [f] Only *cis*-**3** was isolated.

The results obtained are summarized in Table 2. First, we studied the effect of different allylic groups on the cascade reaction. Of the tested groups, we found that allyl chloride, allyl carbonate, and allyl bromide (X = Cl, OCO_2Me, Br) gave similar results in terms of product yields and stereoselectivity (entries 2, 3, 8, and 9, Table 2). However, when a chloride group was replaced with an acetate group, we were unable to obtain the cyclic product. It has been reported that with a halide ligand on palladium in the π-allyl palladium complex, double-bond insertion of the allene into the allyl palladium bond occurs.[10d] Therefore, we also tried the reaction in acetonitrile with an excess of LiCl under reflux. However, the substrate was consumed completely; only some unidentified oligomers were isolated. Good to excellent yields (up to 95%) were obtained with most substrates except for **1e**, which has an aryl group on the terminus of the allene (entry 5, Table 2). This may be attributed to the conjugation of the phenyl group, which could activate the allene fragment leading to the polymerization of substrates.[13] When the tethered atom was changed from a carbon atom to an oxygen atom, the yield declined from excellent to moderate (entries 14 and 15 in Table 2). This could be ascribed to the possible decomposition of oxygen-tethered 1,2,7-triene substrates in the presence of a low-oxidative state transition metal (in fact, the oxygen-tethered 1,2,7-triene substrates **1l** and **1m** show obvious decomposition within 2 weeks even in refrigerated conditions). When we employed 1,2,7-triene substrates with a terminal allene moiety, the yield decreased (entry 15, Table 2). As reported in the literature, an additional alkyl group on the terminus of the allene may slow the decomposition of the starting material,[10e] thereby, increasing the overall yield. This is evident by comparing entry 14 with entry 15 in Table 2.

From Table 2, we also found that the tethering atoms in the 1,2,7-triene substrates play a vital role in the reaction. Compared to carbon-tethered substrates, nitrogen- and oxygen-tethered substrates (entries 8, 9, and 15) led to the isolation of only one product, cis-cyclic product **3**. The stereochemistry was determined by NOESY spectra of the products. Apparently, a tethered heteroatom is favorable to the intramolecular cyclization process with high stereoselectivity.

Under the optimized reaction conditions, we also tested the reaction with several other aryl boronic acids. With various aryl boronic acids, bearing either an electron-donating group or an electron-withdrawing group, the reaction proceeded smoothly to give cyclic products with good yields and stereoselectivities (entries 11 and 12, Table 2).

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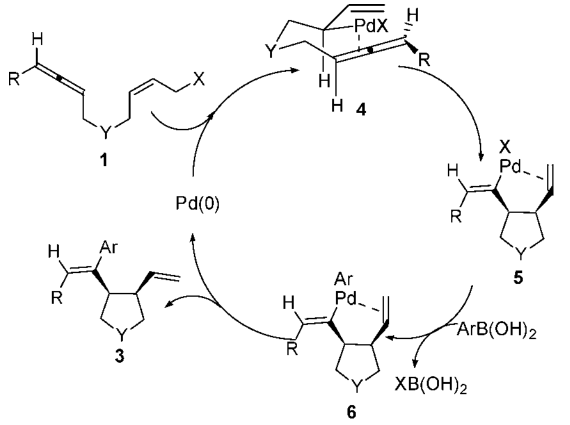
A similar mechanism for this reaction may be postulated on the basis of our results and past work (Scheme 3).[9]

Scheme 3. Plausible Mechanism of the Reaction



Oxidative addition of an allyl halide or carbonate to Pd(0) first generates a π-allyl palladium intermediate **4**. Insertion of the proximal (internal) allenic π-bond rather than the distal (terminal) allenic π-bond forms a five-membered ring intermediate with a σ-vinyl palladium bond (species **5**). Then, trapping of the transient σ-vinylpalladium complex **5** via transmetalation with aryl boronic acids followed by reductive elimination gives the cyclized products **3** and regenerates the Pd(0) catalyst.

The cis stereochemistry can be understood on the basis of a chairlike conformation of the reactive intermediate **4**. Thus, preferential formation of *cis*-**3** can be understood by placing the allene fragments and allyl group in an equatorial-like orientation in the proposed intermediate **4**. The (*E*)-form configuration of the exocyclic double bond, which was determined by NOESY spectra of the product, may be attributed to the small steric repulsion between the π-allyl palladium fragment and allenic fragment in the reaction intermediate **4**.

In summary, we have developed a highly efficient, versatile cascade reaction that utilizes a Pd(0)-catalyzed 1,2,7-triene cyclization and a Suzuki coupling reaction to give cyclic products with high selectivity. To our knowledge, the regioselective, intramolecular carbopalladation to the allene moiety giving a vinyl palladium intermediate has received little attention. Further elucidation of the reaction mechanism and development of an asymmetric version of the reaction are currently underway.

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Supporting Information Available: Experimental details, NMR spectra, and analytical data for the starting materials and the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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