JOC Article

Palladium-Catalyzed Tandem Cyclization/Suzuki Coupling of 1,6-Enynes: Reaction Scope and Mechanism

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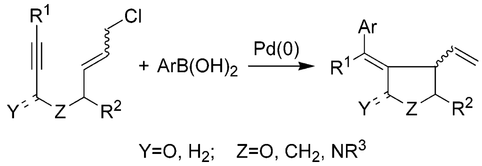

A palldium(0)-catalyzed tandem cyclization/Suzuki coupling reaction of various 1,6-enyne substrates was developed. This Pd-catalyzed enyne cyclization reaction represents a new process for the synthesis of stereodefined α-arylmethylene-γ-butyrolactones, lactams, multifunctional tetrahydrofurans, pyrrolidines, and cyclopentanes. The mechanism of the reaction was studied by the employment of different enyne isomers and boronic acids; a π-allyl palladium intermediate was suggested to explain the formation of the cyclic products. The stereochemistry of this reaction can be well explained by a chairlike transition state.

Carbocycles and heterocycles are extremely important and basic skeletons in many biologically active natural products with specific structures. The development of effective methods for the construction of ring systems is one of the most important goals which the synthetic chemist pursued. Transition metal-catalyzed carbocyclization[1] is arguably one of the most successful and straightforward methods for the construction of a ring system because it offers an efficient entryway from relatively simple precursors to cyclic compounds. Accordingly, numerous carbocyclization reactions of 1,*n*-enynes,[2] 1,*n*-diynes,[3] and 1,*n*-dienes[4] have been developed with high efficiency and selectivity.

On the other hand, increasing social needs for environmentally friendly[5] chemical processes call for the development of new processes forming several carbon−carbon and/or carbon−heteroatom bonds in one reaction. Therefore, it represents an attractive and very active field of synthetic organic chemistry because the transition metal-catalyzed process usually proceeds under mild reaction conditions. Toward this end, there has been a growing interest in the application of cascade carbopalladation processes[6] which trap the transient alkylpalladium or alkenylpalladium intermediates with al-

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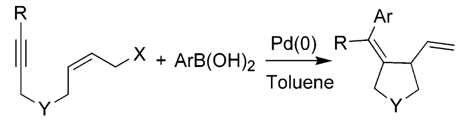
SCHEME 1. Palladium-Catalyzed Tandem Cyclization/Suzuki Coupling Reaction of 1,6-Enynes

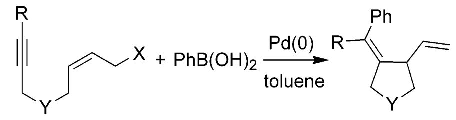


kenes,[7] alkynes,[8] CO,[1c,9] and other related unsaturated π-systems[10] or nucleophilic reagents:[11] such as the "metallo-ene" procedure,[12] and the palladium-catalyzed tandem cyclization−anion capture process,[13] etc.[14]

Pursuing our interest in developing a new enyne cyclization process,[2c,d] we developed a palladium-catalyzed tandem cyclization/Suzuki coupling reaction of 1,6-enynes, by which five-membered-ring compounds with a stereodefined exo double bond were synthesized efficiently (Scheme 1).[15]

The successful formation of five-membered products provides another example of a novel alkenylpalladium species-forming process involving a π-allylpalladium and an alkyne. Since the insertion of an alkyne into a π-allylpalladium species has been scarcely reported, further investigation into the scope and synthetic utility of this reaction was appealing.

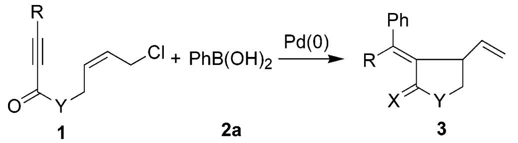
TABLE 1. Tandem Cyclization/Suzuki Coupling Reaction of Electron-Rich Enyne Substrates[a]



entry		R	Y	X	yield[b] (%)
1	**1a**	H	O	Cl	21[c]
2	**1b**	CH_3	O	Cl	90
3	**1c**	CH_3OCH_2	O	Cl	83
4	**1d**	Bu	O	Cl	84
5	**1d′**	Bu	O	Br	64
6	**1e**	Ph	O	Cl	77
7	**1e′**	Ph	O	OCO_2Et	70
8	**1f**	Bu	NTs	Cl	83
9	**1g**	CH_3	NBn	Cl	38
10	**1h**	CH_3	$C(CO_2Et)_2$	Cl	88

[a] All of the reactions were performed with **1** (0.25 mmol), **2** (0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and KF (29 mg, 0.5 mmol) in toluene (5 mL) at 60 °C. [b] Isolated yields. [c] **1a** was recovered.

TABLE 2. Tandem Cyclization/Suzuki Coupling Reaction of Electron-Poor Enyne Substrates[a]



entry		R	Y	product	yield/%[b]
1	*cis*-**1i**	Me	O	**3ia**	82
2	*trans*-**1i**	Me	O	**3ia**	81
3	**1j**	Bu	O	**3ja**	47
4	**1k**	Ph	O	**3ka**	45
5	**1l**	Ph	NBn	**3la**	88
6	**1m**	Me	NBn	**3ma**	90
7	**1n**	Me	NTs	**3na**	93

[a] All of the reactions were performed with **1** (0.25 mmol), **2** (0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and KF (29 mg, 0.5 mmol) in toluene (5 mL). [b] Isolated yields.

Results and Discussion

In our initial communication[15] we reported that the tandem cyclization/Suzuki coupling reaction of 1,6-enynes proceeded smoothly in toluene with $Pd(PPh_3)_4$ as the catalyst and KF as the base. With this result in hand, we then investigated the scope and limitation of the reaction.

Scope and Limitations. The scope and limitations of this tandem reaction have been studied by allowing a wide spectrum of enynes **1** to react with various boronic acids **2** under our optimized reaction conditions. The results are summarized in the following tables.

Electron-Rich Substrates. First, we studied the effect of different allylic groups on the reaction. We found that the substrates with different allyl groups all gave cyclic products and allyl chloride is the best among the tested allyl groups (X = Cl, OCO_2Me, Br) in terms of product yields (entries 4−7, Table 1). Then enyne substrates bearing an allyl chloride moiety and a variety of

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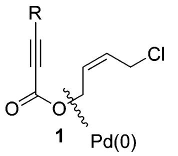
functional groups, such as alkoxy, alkyl, and aryl groups, were investigated. These substrates annulated efficiently to give the cyclized products under our standard conditions (entries 3, 4, and 6, Table 1). The tethering atoms in the enyne substrates did not seem to play a vital role in the reaction and good to excellent yields (up to 90%) were obtained with most substrates except for **1g**, which has an NBn group as the tethering group (entry 9, Table 1). However, substrate **1f**, which bears a Ts group on nitrogen, gives a good yield (entry 8, Table 1).

Electron-Deficient Substrates. When we subjected electron-poor 1,6-enyne *cis*-**1i** to the reaction condition, the cyclic product **3ia** was isolated in 82% yield. However, when other electron-poor 1,6-enynes such as **1j** and **1k** were employed as the substrates, yields descended from good to moderate (entries 3 and 4, Table 2).

We were not able to improve the yield by changing catalyst, ligands, reaction temperature, and solvents. The possible oxidative addition of palladium(0) to the carbon−oxygen bond of the allylic acetates was probably responsible for the low yields.[17] In fact, a trace of phenylalkynoic acid (<2%) resulted from the cleavage of the allyl ester by Pd(0) and some unidentified oligomers were isolated. This is also supported by the obvious improvement of yields by changing the alkynoate substrates to alkynamide substrates (entries 5−7, Table 2).



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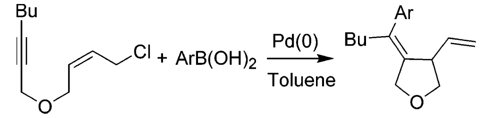
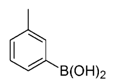
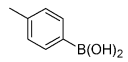
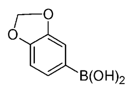
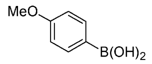
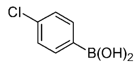
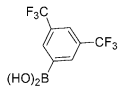
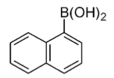
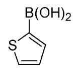
Boronic Acids. We chose **1d** as the standard enyne substrates and a variety of boronic acids to investigate the cascade cyclization−Suzuki coupling reaction; the results are summarized in Table 3.

Various aryl boronic acids, including the boronic acids bearing a heterocycle, such as **2i**, all afforded the cyclic products. When aryl boronic acids with electron-donating groups on the aromatic ring were employed, the reaction proceeded smoothly even at room temperature with good yields (entries 2−5, Table 3). However, when aryl boronic acids bearing electron-withdrawing groups were used, elevated temperatures were necessary to obtain the good yields. However, when ortho-substrated arylboronic acid was employed as substrate, the annulation reaction resulted in the formation of two rotamers (entry 8, Table 3). This was confirmed by ^{1}H NMR, GC-MS, and microanalysis.

Attempted tandem reaction of **1d** with alkenylboronic acids **2j** gave much more complex products. Only 12% cyclic product **3dj−3** was isolated, and noncyclized allylic coupling product was the major product. Similar results were obtained when other allylic substrates and alkenyl boronic acids were employed.[18]

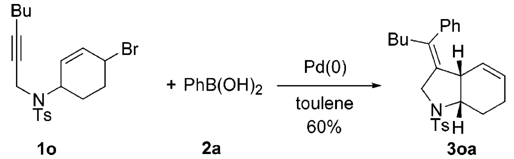
TABLE 3. Tandem Reaction of Various Boronic Acids[a]



entry	2		yield(%)[b]
1	**2a**	$PhB(OH)_2$	84
2	**2b**[d]		73
3	**2c**[d]		76
4	**2d**[d]		77
5	**2e**[d]		74
6	**2f**		87
7	**2g**		60[c]
8	**2h**		62(1/2)[e]
9	**2i**		70

[a] All of the reactions were performed with **1** (0.25 mmol), **2** (0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and KF (29 mg, 0.5 mmol) in toluene (5 mL) at 60 °C. [b] Isolated yields. [c] KOH (28 mg, 0.5 mmol) was used as a base. [d] The reaction was run at room temperature. [e] The ratio was determined by ^{1}H NMR.

Furthermore, other heterocycles, such as an indole backbone, also could be synthesized with this method efficiently. For example, enyne substrate **1o** annulated smoothly under the reaction condition to afford the cis-product exclusively, whose stereochemistry was determined by NOE spectra of **3oa**.



1o **2a** **3oa**

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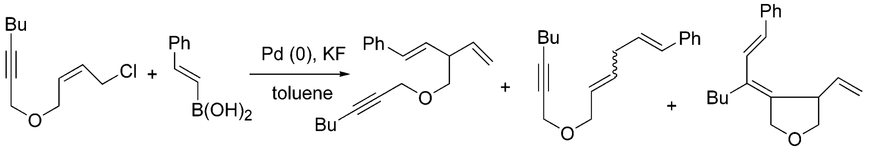
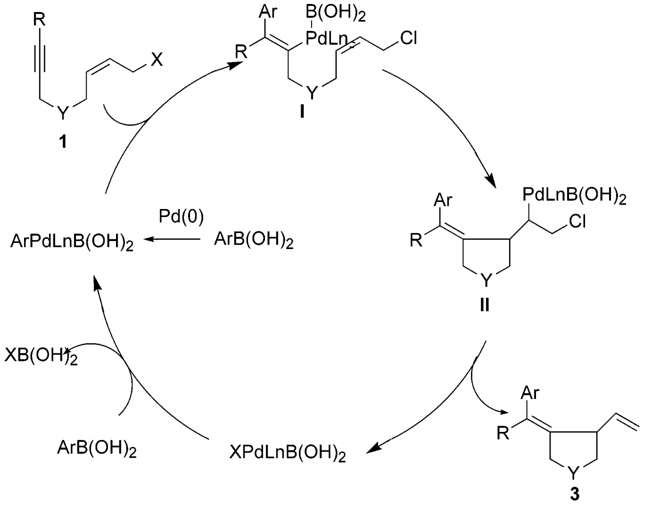
SCHEME 2. Tandem Cyclization/Suzuki Coupling Reaction of 2j



1d **2j** **3dj-1** 8% **3dj-2** 45% **3dj-3** 12%

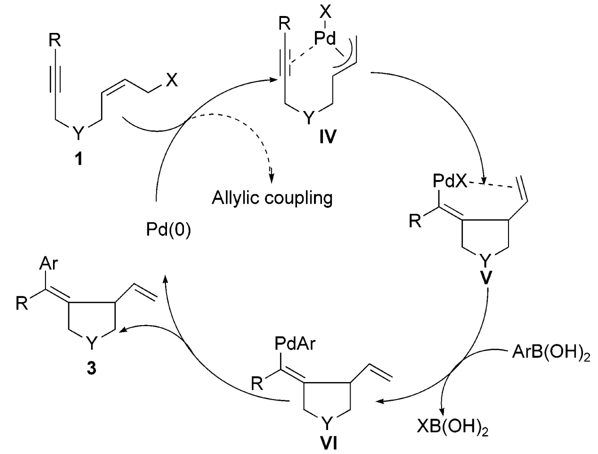
SCHEME 3. The Plausible Carbopalladation Pathway



Mechanism. Some possible mechanistic rationales[19] have been proposed for the transition metal-catalyzed carbocyclization reactions of 1,*n*-enynes. The following one is a carbopalladation process (Scheme 3). Oxidative addition of arylboronic acid to Pd(0) generates an aryl palladium species **I**,[20] followed by insertion of an alkyne to form a vinylpalladium species **II**.[21] Insertion of an alkene to vinylpalladium bond followed by β-X elimination[22] affords the product. If this is the case, initiation of the reaction with Pd(II) may also give good results since the transmetalation reaction of aryl boronic acids with Pd(II) is well documented.[23] However, when Pd(II) catalysts such as $PdCl_2$, $PdCl_2(MeCN)_2$, and $Pd(OAc)_2$ were employed, the reaction gave poor results.

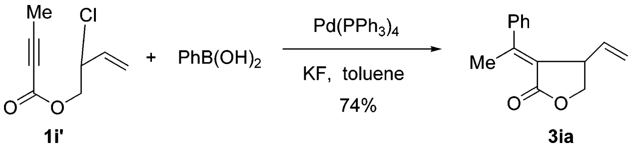
A second mechanism involving a π-allyl palladium complex as the reaction intermediate was then proposed (Scheme 4).

SCHEME 4. The Plausible Allylpalladation Pathway



Oxidative addition of Pd(0) to allyl halide or carbonate generates a π-allylpalladium intermediate **IV**. Insertion of the alkyne to the Pd allyl bond of **IV** affords **V**. Then, trapping of the transient vinylpalladium complex **V** via transmetalation with aryl boronic acids was followed by reductive elimination to give the cyclized products **3** and regenerate the Pd(0) catalyst. All these steps are well precedent in organopalladium chemistry.[6,24]

Because the reaction goes through the η^3-coordinated allyl palladium intermediate **IV**, it is reasonable that the substrates *cis*-**1i**, *trans*-**1i**, and **1i′** all afford the cyclic product in similar yields and reaction rate.



On the basis of the tandem reaction of **1**, we further studied the relative stereochemistry of the α,γ substituents in the cyclization products when 1-substiuent was introduced. The results are outlined in Table 4.

Moderate to good stereroselectivity (up to 91/9) was achieved. The major product is the cis product, which can be confirmed by the NOSEY spectra of the *cis*-**3qa** because when substrate **1q** was employed, each of the two isomers of the cyclic product could be isolated completely. The cis product can be understood by placing the allylic group and the R^2 group at equatorial orientation in the product conformation (Scheme 5).

Besides that, we also investigated the relative stereochemistry of the α,β-substituents in the cyclization

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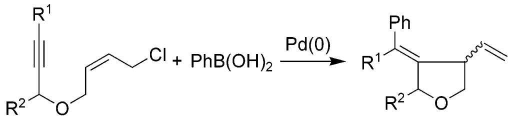
(24) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, UK, 1995.

TABLE 4. Tandem Cyclization/Suzuki Coupling Reaction of 1-Substitued Enynes[a]



s **2a** **p**

entry		R^1	R^2	product	yield/%[b] (cis/trans)[c]
1	**1p**	Bu	Ph	**3pa**	71 (87/13)
2	**1q**	Bu	4-OMe-C$_6$H$_4$	**3qa**	82 (88/12)
3	**1r**	Bu	(*E*)-CH=CHCH$_3$	**3ra**	73 (75/25)
4	**1s**	Bu	o-Cl-C$_6$H$_4$	**3sa**	78 (91/9)
5	**1t**	Ph	^{i}Pr	**3ta**	82 (85/15)

[a] All of the reactions were performed with **1** (0.25 mmol), **2a** (0.5 mmol), Pd(PPh$_3$)$_4$ (14 mg, 0.0125 mmol), and KF (29 mg, 0.5 mmol) in toluene (5 mL). [b] Isolated yields. [c] The ratio was determined by ^{1}H NMR.

SCHEME 5. The Possible Conformation Analysis of the Reaction Outcome

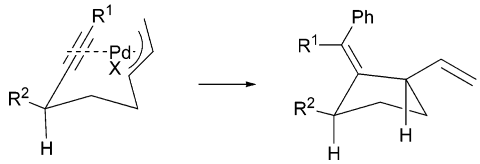
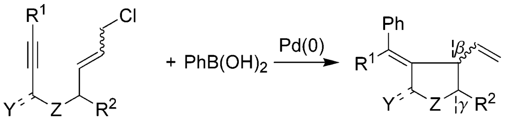


TABLE 5. Tandem Cyclization/Suzuki Coupling Reaction of 1′-Substituted Enynes



1 **2a**

entry	1	R^1	R^2	Z/E	Y	Z	yield/%[b] (trans/cis)[c]
1	**1u**	Ph	^{n}Pr	Z	H	O	96
2	**1v**	Ph	^{i}Pr	Z	H	O	86
3	**1w**	Me	^{n}Pr	E	O	O	81 (91/9)
4	**1x**	Me	^{i}Pr	Z	O	O	77 (97/3)
5	**1y**	Me	CH$_2$OBn	E	O	O	70 (70/30)
6	**1z**	Me	CH$_2$OBn	Z	H	NTs	93 (60/40)

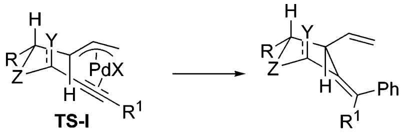
[a] All of the reactions were performed with **1** (0.25 mmol), **2a** (0.5 mmol), Pd(PPh$_3$)$_4$ (14 mg, 0.0125 mmol), and KF (29 mg, 0.5 mmol) in toluene (5 mL). [b] Isolated yields. [c] The ratio was determined by ^{1}H NMR.

products when the 1′-substituent was introduced. The results are summarized in Table 5.

As shown in Table 4, the annulations afforded β,γ-trans products with high stereoselectivity (only one trans product was isolated in some cases), which is confirmed by the NOSEY spectra of **3ua.** The steterochemistry can be understood on the basis of a chairlike conformation of the proposed reaction intermediate TS-**I** (Scheme 6).

Thus, preferential formation of trans product can be understood based upon placing the allylic group and the R group in an equatorial-like orientation in the proposed intermediate TS-**I**.Coordination[25] of a neighboring group to the allyl palladium intermediate TS-**II** may be responsible for the descending of stereochemistry when a heteroatom exists in the R fragment (entries 5 and 6, Table 5).

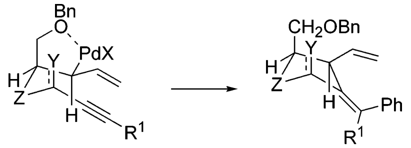
SCHEME 6. The Possible Transition State of the Reaction



TS-I

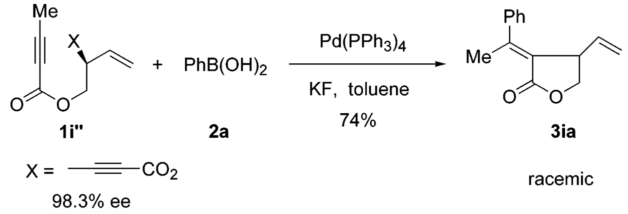
favored chair-like conformation *trans*- product

SCHEME 7. A Neighboring Group Coordinated Transition State



TS-II *cis*-product

SCHEME 8. Tandem Reaction of Chiral Substrate 1i″



The stereochemical outcome of such an intramolecular carbopalladation is influenced by the number and the nature of substituents at various positions of the acyclic molecules.[16g,26] Rather efficient chirality transfer was observed for the alkene insertion into the π-allylpalladium. Further insight into mechanistic features of oxidative addition and the alkyne insertion into the π-allylpalladium intermediate in this proposed mechanism is available from the study of the reactivity of the chiral substrate **1i″** under our reaction conditions. However, the racemic product **3ia** was isolated. Therefore, we could deduce that the insertion of alkyne into the allyl palladium bond is slower than the isomerization of the π-allylpalladium intermediate. The quick $\eta^1-\eta^3$ isomerization may cause the disappearance of the chirality of **1i″**. This also strongly favored the existence of the η^3-coordinated allyl palladium intermediate **IV**.

Conclusion

Allylpalladation of alkenes and alkynes is a powerful tool for preparing carbocycles and heterocycles. The combination of allylpalladation with intramolecular alkyne insertion, carbonylation, and transmetalation in a cascade type sequence demonstrates the high potential of these Pd-catalyzed reactions for synthesis of complex organic molecules. The cascade reaction we have developed is a highly efficient, versatile cascade reaction that

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[25] (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895.

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utilizes Pd(0)-catalyzed 1,6-enyne cyclization and Suzuki coupling reactions to give cyclic products with stereodefined exocyclic double bonds. α-Methylene-γ-butyrolactones, lactams, multifunctional tetrahydrofurans, pyrrolidine, cyclopentanes, and fused cycles, such as indole backbone, could be synthesized efficiently with this method.

Experimental Section

A. General. All reactions and manipulations were conducted in an argon-filled glovebox or with standard Schlenk techniques. Column chromatography was performed with silica gel (300−400 mesh). ^{1}H NMR and ^{13}C NMR were recorded on 300-MHz spectrometers. Chemical shifts were reported in ppm with the solvent resonance as the internal standard. MS, IR, and microanalysis were done by the State Authorized Analytical Center in the Shanghai Institute of Organic Chemistry.

B. General Method for Tandem Reaction of Enyne with Pd(PPh_3)$_4$. Under argon atmosphere, a 25 mL Schlenk tube was charged with enyne substrate (0.25 mmol), boronic acid (0.5 mmol), KF (0.5 mmol), Pd(PPh_3)$_4$ (0.0125 mmol), and toluene (5 mL). The mixture was stirred at 60 °C and the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was directly subjected to column chromatography on silica gel to give the product **3**.

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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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