ORGANIC LETTERS

2003
Vol. 5, No. 20
3645−3648

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

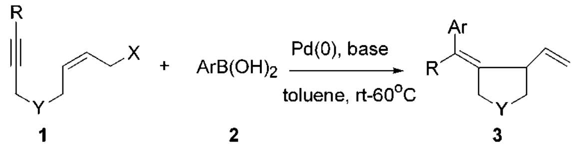
Gangguo Zhu and Zhaoguo Zhang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, China

zhaoguo@mail.sioc.ac.cn

Received July 15, 2003

ABSTRACT

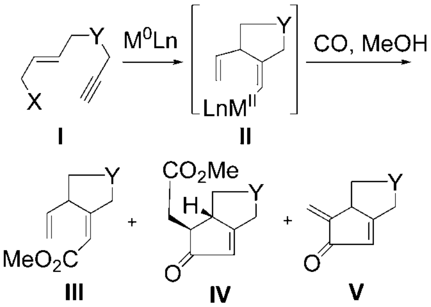


A Pd(0)-catalyzed 1,6-enyne cyclization–arylation cascade reaction was effected via π-allylpalladium intermediate formation and subsequent Suzuki coupling to give cyclic products with stereodefined exocyclic double bonds.

π-Allylpalladium chemistry is one of the most fruitful areas of organometallic catalysis.[1] However, most reactions involve nucleophilic attack to a π-allylpalladium intermediate by hard or soft nucleophiles.[1,2] The insertion of an alkyne to a π-allylpalladium species has been scarcely reported except for a dimerization−allylation reaction of terminal alkynes,[3] a benzannulation reaction of alkynes and allyl tosylates,[4] and several intramolecular reactions followed by carbonylation[5] such as the "metallo-ene" procedure Oppolzer developed.[6]

Of all of these transformations, the cyclization of 1,6-dienes has been studied more extensively than the corresponding reaction of enyne substrates.[7] Although the following enyne substrates **I** can afford "metallo-ene"-type products **III−V**, the stereoselectivity of the reaction could not be controlled, and the ratio of the products varies with different metals, ligands, and even the tethering Y atoms (Scheme 1).[6a] It is generally accepted that the reaction proceeded through a transient vinyl palladium intermediate (**II**),[6] which is thermodynamically stable, and undergoes

Scheme 1. Nickel(0)- and Palladium(0)-Catalyzed Allylation/Carbonylation Reaction



---

(1) For general reviews on allylpalladium chemistry: (a) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, UK, 2000. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 3.3. (c) Bäckvall, J.-E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998. (d) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (e) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (f) Consiglio, G.; Waymouth, R. *Chem. Rev.* **1989**, *89*, 257.

(2) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413.

(3) Inoue, Y.; Ohuchi, K.; Kawamata, T.; Ishiyama, J.-I.; Imaizumi, S. *Chem. Lett.* **1991**, 835.

(4) Tsukada, N.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2000**, *2*, 655.

(5) (a) Keese, R.; Guidetti-Grept, R.; Herzog, B. *Tetrahedron Lett.* **1992**, *33*, 1207. (b) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560. (c) Aggarwal, V. K.; Butters, M.; Davies, P. W. *Chem. Commun.* **2003**, 1046. (d) Holzapfel, C. W.; Marais, L. *Tetrahedron Lett.* **1998**, *39*, 2179. (e) Holzapfel, C. W.; Marais, L.; Toerien, F. *Tetrahedron* **1999**, 55, 3467.

(6) (a) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883. (b) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266. (c) Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38.

(7) (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 5, p 29. (b) Gómez-Bengoa, E.; Cuerva, J. M.; Echavarren, A. M.; Martorell, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 767. (c) Oppolzer, W.; Kuo, D. L.; Hutzinger, M. W.; Léger, R.; Durand, J. O.; Leslie, C. *Tetrahedron Lett.* **1997**, *38*, 6213.

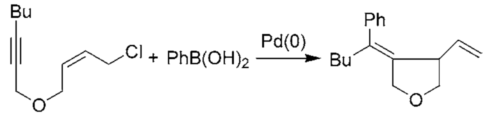
10.1021/ol035304f CCC: $25.00

further transformations to regenerate the Pd catalyst. Employing different trapping methods allowed the reaction to be developed into useful processes such as a cyclization/carbonylation cascade (Scheme 1)[5,6] and a tandem cyclization/anion capture reaction.[8]

Since organoboron reagents are nontoxic, air-stable, and easily accessible,[9] the Suzuki coupling is one of the most important ways to form a carbon−carbon bond.[10] It is worthwhile to explore the possibility of combining the cyclization and Suzuki coupling reaction. Namely, if we trap the vinyl palladium species (**II** in Scheme 1) with organoboron reagent, we may develop the reaction into a highly selective process. Herein, we report our preliminary results in the study of the cyclization−Suzuki coupling reaction of 1,6-enynes.

To explore the proposed cylization−Suzuki coupling reaction, a readily available enyne substrate **1a** and phenyl boronic acid **2a** were chosen to screen the reaction conditions. Under an argon atmosphere, a Schlenk reaction tube was charged with **1a** (50 mg, 0.25 mmol), **2a** (61 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and acetonitrile (5 mL), and after the mixture was heated at 60 °C for 4 h with stirring, the desired product **3aa** was isolated in 62% yield (entry 1, Table 1). 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). KF proved to be the best base, and several other bases such as CsF, Cs_2CO_3, and K_2CO_3 were effective as well. Although the reaction was faster at 60 °C (entry 13, Table 1), it also proceeded at a reasonable rate at room temperature to give a comparable yield (entry 14, Table 1). Therefore, we chose KF as the base, $Pd(PPh_3)_4$ as the Pd(0) source, toluene as the solvent, and room temperature as the standard reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



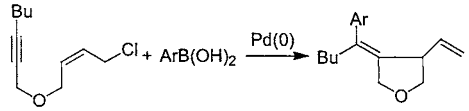
1a **2a** **3aa**

entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	K_2CO_3	CH_3CN	60	4	62
2	K_2CO_3	THF	60	2	61
3	K_2CO_3	DMF	80	2	30
4	K_2CO_3	dioxane	80	2	35
5	K_2CO_3	toluene	60	4	73
6	K_2CO_3	benzene	60	3	63
7	K_2CO_3[c]	toluene	60	3	72
8	K_2CO_3[d]	toluene	60	3	61
9	K_2CO_3[e]	toluene	60	4	73
10	Na_2CO_3	toluene	60	18	34
11	$K_3PO_4{\cdot}3H_2O$	toluene	60	36	31
12	Cs_2CO_3	toluene	60	2	73
13	KF	toluene	60	2	84
14	KF	toluene	25	6	83
15	CsF	toluene	60	2	80

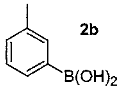
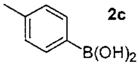
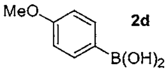
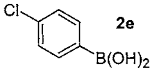
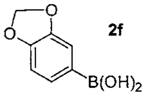
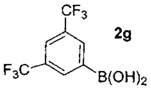
[a] All of the reactions were run with **1a** (50 mg, 0.25 mmol), **2a** (61 mg, 0.5 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0125 mmol), and base (0.5 mmol) in a specified solvent (5 mL). [b] Isolated yield. [c] $Pd_2(dba)_3{\cdot}CHCl_3$ (7 mg, 0.0063 mmol) and PPh_3 (7 mg, 0.025 mmol) were used. [d] $Pd(OAc)_2$ (3 mg, 0.0134 mmol) and PPh_3 (14 mg, 0.053 mmol) were used. [e] H_2O (45 μL, 2.5 mmol) was added.

Under the optimized reaction conditions, we then tested the reaction with a range of the aryl boronic acids, and the results are summarized in Table 2. When aryl boronic acids with electron-donating groups on the aromatic ring were employed, the reaction proceeded smoothly at room temperature in good yields. However, when aryl boronic acids bearing electron-withdrawing groups were used, the reaction proceeded sluggishly at room temperature and was not complete even after 24 h. Nevertheless, at elevated temperatures (60 and 80 °C), the reaction was finished within 3 h to give good yields (entries 4, 6, Table 2).

Table 2. Reaction of Aryl Boronic Acids with Enyne **1a**[a]



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

entry	$ArB(OH)_2$	temp. (°C)	time (h)	yield (%)[b]
1	 **2b**	25	4	**3ab**: 73
2	 **2c**	25	8	**3ac**: 76
3	 **2d**	25	8	**3ad**: 74
4	 **2e**	60	2	**3ae**: 87
5	 **2f**	25	7	**3af**: 77
6[c]	 **2g**	80	3	**3ag**: 60

[a] Reactions were performed with **1a** (50 mg, 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 yield. [c] KOH (28 mg, 0.5 mmol) was used as a base.

---

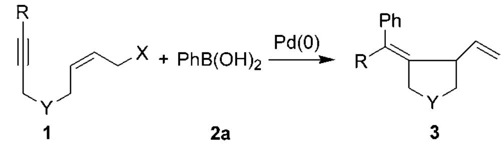
(8) (a) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325. (b) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329. (c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (d) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525. (e) Grigg, R.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 2545. (f) Griss, R. *J. Heterocycl. Chem.* **1994**, *31*, 631.

(9) *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., Wiley-VCH: Weinheim, Germany, 2001.

(10) (a) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

A variety of enyne substrates were studied in the reaction, and the results are summarized in Table 3. Under the above-mentioned standard reaction conditions except at a reaction temperature of 60 °C, all of the 1,6-enyne substrates employed afforded the desired cyclic products.

Table 3. Various Enyne Substrates Coupled with Phenylboronic Acid **2a**[a]



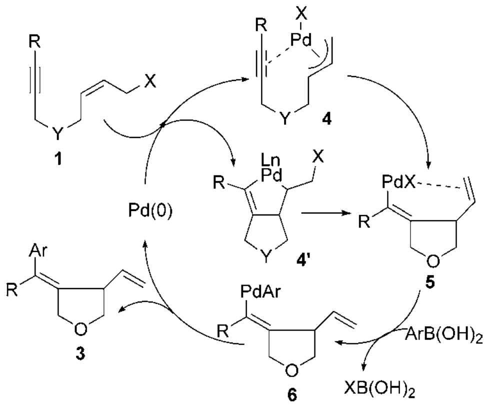
	1				
entry		R	Y	X	yield (%)[b]
1	**1a**	*n*-Bu	O	Cl	84
2	**1b**	H	O	Cl	21[c]
3	**1c**	Me	O	Cl	90
4	**1d**	Ph	O	Cl	77
5	**1e**	Ph	O	OCO_2Me	70
6	**1f**	*n*-Bu	NTs	Cl	83
7	**1g**	Me	NBn	Cl	38
8	**1h**	Me	$C(CO_2Me)_2$	Cl	88
9	**1i**	*n*-Bu	O	Br	64

[a] Reaction conditions: enyne **1** (0.25 mmol), boronic acid **2a** (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 for 3 h. [b] Isolated yields. [c] **1b** was recovered.

The tethering atoms in the enyne substrates did not seem to play a vital role in the reaction; 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 7, Table 3). Enyne substrates with a terminal alkyne moiety also gave poor yields (entry 2, Table 3).

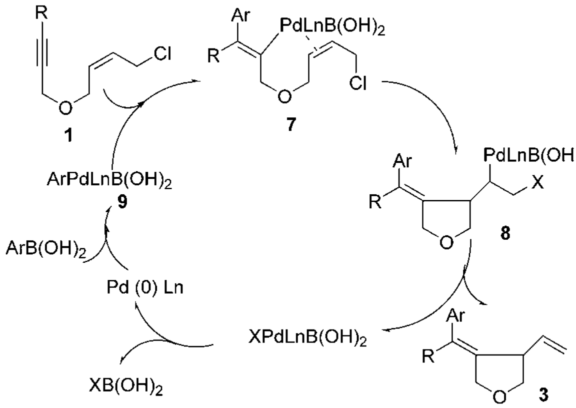
The configuration of the exocyclic double bond is exclusively in the (*E*)-form, which was determined by NOE spectra and comparison with the authentic sample[11] and further confirmed by the X-ray structure of the product **3fa**.[12] Scheme 2 shows a plausible mechanism that accounts for the stereochemistry of the reaction. Oxidative addition of allyl halide or carbonate to Pd(0) first generates a π-allylpalladium intermediate **4**. Insertion of the alkyne to the Pd-allyl bond of **4** affords **5**. Then, trapping of the transient vinyl palladium complex **5** via transmetalation with aryl boronic acids followed by reductive elimination gives the cyclized products **3** and regenerates the Pd(0) catalyst. A palladium metallocycle **4′** may also be formed under the reaction conditions,**[13]** and it could react further via β-X elimination[14] to give **5**.

Scheme 2. Plausible Mechanism of the Reaction



Another mechanism involving a carbopalladation[8f,15] pathway (Scheme 3) may also be responsible for the reaction. In this route, oxidative addition of aryl boronic acid to Pd(0) generates an aryl palladium species **9**, as was reported by Uemura and others.[16] Insertion of the triple bond to a Pd−aryl bond then affords a new vinyl palladium intermediate **7**. Subsequent insertion of the intramolecular carbon−carbon double bond into the C−Pd bond would generate **8**. β-heteroatom elimination[14] of **8** would give the cyclized products **3**. 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.[17] However, when Pd(II) catalysts such as $PdCl_2$, $PdCl_2(MeCN)_2$, and $Pd(OAc)_2$ were employed, the reaction gave poor yields with recovered starting materials.

Scheme 3. Carbopalladation Pathway



---

(11) Sample was made by Suzuki coupling reaction with 3-(1-chloropentylidene)-4-vinyl tetrahydrofuran (ref 18) and phenyl boronic acid.

(12) See Supporting Information.

(13) (a) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636. (b) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (c) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249.

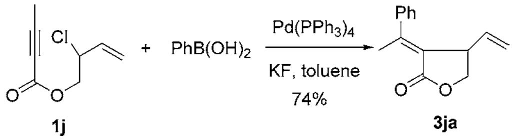
(14) (a) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (c) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115. (d) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

(15) For carbopalladation reaction of alkynes: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121. (b) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (c) Zhang, Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (d) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (e) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

(16) (a) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85. (b) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (c) Aramendía, M. A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* **1999**, *64*, 3592.

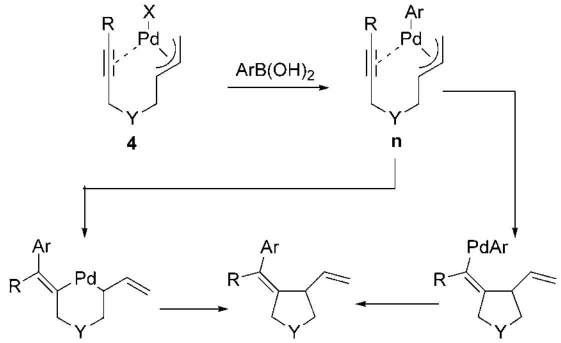
Additional important proof supporting the proposed π-allylpalladium pathway (Scheme 2) is that substrate **1j**[18] could also undergo the same reaction to afford the cyclic product **3ja** in good yield (Scheme 4). However, whether the transmetalation occurs after or prior to the insertion of the C–C triple bond into C–Pd bond (Scheme 2 vs Scheme 5) remains unclear and worthy of further investigation.

Scheme 4



In summary, we have developed a highly efficient, versatile cascade reaction that utilizes Pd(0)-catalyzed 1,6-enyne cyclization and Suzuki coupling reactions to give cyclic products with stereodefined exocyclic double bonds. Further elucidation of the reaction mechanism and development of an asymmetric version of the reaction are ongoing in our laboratory.

Scheme 5



Acknowledgment. We thank the National Natural Science Foundation of China, Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality for financial support.

Supporting Information Available: Experimental details and analytical data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035304F

---

(17) (a) Cho, C. S.; Itotani, K.; Uemura, S. *J. Organomet. Chem.* **1993**, *443*, 253. (b) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313.

(18) Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 6370.