

Cationic Pd(II)-Catalyzed Enantioselective Cyclization of Arylmethyl 2-Alkynoates Initiated by Carbopalladation of Alkynes with Arylboronic Acids

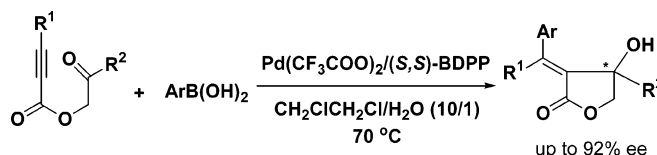
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ABSTRACT



A cationic palladium(II)-catalyzed enantioselective intramolecular addition of vinylpalladium species to ketones initiated by the carbopalladation of alkynoates under mild conditions without a Pd(II)/Pd(0) redox system was developed with high yield and enantioselectivity. This cascade reaction provides an efficient method for the construction of optically active hydroxylactones.

Suffering from the less nucleophilic properties of the organopalladium species, the addition of carbon–palladium bond toward carbon–heteroatom multiple bonds has received scant attention compared with the numerous reports on the insertion of carbon–carbon multiple bonds.¹ Although, some reactions catalyzed by Rh,² Ni,³ and others have been reported in this area, there were only a few examples on the addition of the organopalladium species to carbon–hetero-

atom multiple bonds.^{4–7} Even so, most of them were catalyzed by Pd(0) species which involved a Pd(II)/Pd(0) redox system.^{4,5}

In our earlier work, we reported a Pd(II)-catalyzed addition of a carbon–palladium species initiated by the acetoxypal-

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(1) For general reviews on palladium chemistry, see: (a) Tsuji, J., Ed. *Palladium in Organic Synthesis*; Springer: New York, 2005. (b) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002.

(2) (a) Fagnou, K.; Lartens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667. (c) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (d) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (e) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (f) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821. (g) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.

(3) (a) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 1682. (b) Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371. (c) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (d) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181.

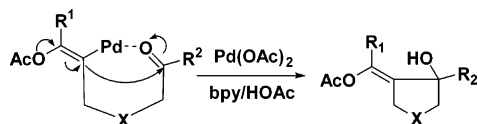
(4) For recent papers on the nucleophilic attack by palladium species, see: (a) Yamamoto, Y.; Nakamura, I. *Top. Organomet. Chem.* **2005**, *14*, 211 and references therein. (b) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735. (c) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026. (d) Solin, N.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2005**, *7*, 689. (e) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, *12*, 2539.

(5) (a) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551. (c) Suzuki, K.; Arao, T.; Ishii, S.; Maeda, Y.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 5789. (d) Hopkins, C. D.; Guan, L.; Malinakova, H. C. *J. Org. Chem.* **2005**, *70*, 6848.

(6) (a) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765. (b) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987.

laddation of alkynes to a carbonyl group.⁸ In the course of the reaction, vinylpalladium intermediates were generated by the acetoxypalladation of alkynes. The presence of the acetoxo group in the olefinic bond made the formed vinylpalladium species relatively more nucleophilic, and the nucleophilic addition to the carbonyl group became possible (Scheme 1). The question arises if this addition reaction is

Scheme 1. Addition of 2-Acetoxyvinylpalladium Species to the Ketone Group

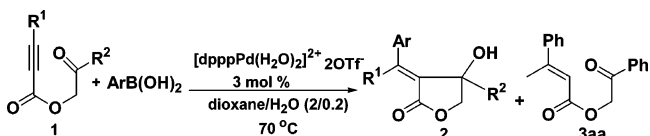


still possible when the reaction is initiated by carbopalladation of an alkyne.

Organoboronic acids have been well-used in transition-metal-catalyzed carbon–carbon bond-forming reactions.⁹ The carbopalladation of alkynes triggered by the addition of arylboronic acids is a promising way to generate vinylpalladium intermediates.¹⁰ On the other hand, we have reported the addition of arylboronic acids to nitriles⁶ and the intramolecular addition to ketones⁷ catalyzed by cationic Pd complexes recently. It occurred to us that the cationic Pd catalyst may favor the addition of the vinylpalladium species to carbon–heteroatom bonds. Compared to the neutral Pd(II) species, there are two advantages for cationic Pd(II) species:^{11,12} vacant coordination sites and stronger Lewis acidity. Herein, we wish to describe an unprecedented asymmetric cascade reaction which consists of the intermolecular carbopalladation of the alkynoates using arylboronic acids and subsequent intramolecular addition of vinylpalladium intermediates to the ketone group catalyzed by cationic Pd(II) complexes.

Our initial studies started by employing benzoylmethyl 2-butynoate as a model substrate in combination with PhB(OH)₂ to examine the reaction activity in the presence of different Pd(II) catalyst. When the neutral catalyst Pd(OAc)₂/dppp was employed, the protonolysis product **3aa** was obtained in 41% yield (Table 1, entry 1). Using [(dppp)-Pd(H₂O)₂](OTf)₂^{13a} as the catalyst, the reaction afforded **2aa** in 89% yield (Table 1, entry 4). However, the transformation was sluggish when the reaction was catalyzed by the two

Table 1. Cationic Pd(II)-Catalyzed Cyclization of Arylmethyl 2-Alkynoates^a



entry	1	R ¹	R ²	Ar	2	yield (%) ^b
1 ^c	1a	CH ₃	Ph	Ph	2aa	
2 ^d	1a	CH ₃	Ph	Ph	2aa	39
3 ^e	1a	CH ₃	Ph	Ph	2aa	30
4	1a	CH ₃	Ph	Ph	2aa	89
5	1a	CH ₃	Ph	4-MeOC ₆ H ₄	2ab	92
6	1a	CH ₃	Ph	4-MeC ₆ H ₄	2ac	90
7	1a	CH ₃	Ph	4-FC ₆ H ₄	2ad	94
8	1a	CH ₃	Ph	3-NO ₂ C ₆ H ₄	2ae	96
9	1a	CH ₃	Ph	3-MeOC ₆ H ₄	2af	85
10	1a	CH ₃	Ph	2-naphthyl	2ag	88
11	1b	<i>n</i> -C ₃ H ₇	Ph	Ph	2ba	81
12	1c	<i>n</i> -C ₇ H ₁₅	Ph	Ph	2ca	79
13	1d	Ph	Ph	Ph	2da	84
14	1e	CH ₃	4-MeOC ₆ H ₄	Ph	2ea	82
15	1f	CH ₃	4-ClC ₆ H ₄	Ph	2fa	90
16	1g	CH ₃	4-BrC ₆ H ₄	Ph	2ga	89
17	1h	CH ₃	CH ₃	Ph	2ha	76

^a Reaction conditions: Substrate (0.2 mmol), arylboronic acid (0.3 mmol) [(dppp)Pd(H₂O)₂](OTf)₂ (0.006 mmol) in dioxane/H₂O (2 mL/0.2 mL) at 70 °C. ^b Isolated yield. ^c Catalyzed by Pd(OAc)₂/dppp. ^d Catalyzed by [(bpy)Pd(OH)₂](OTf)₂; **3aa** was obtained also in 33% yield. ^e Catalyzed by [(dppe)Pd(H₂O)₂](OTf)₂; **3aa** was obtained also in 21% yield.

other cationic Pd catalysts [(bpy)Pd(OH)₂](OTf)₂^{6,13b} and [(dppe)Pd(H₂O)₂](OTf)₂^{13c} (Table 1, entries 2 and 3). These results indicated that the acetoxo group is crucial in the addition of vinylpalladium species to ketones under neutral Pd(II) catalyst conditions. Meanwhile, the higher Lewis acidity of the cationic Pd(II) species might be the another reason for the success of the reaction.

A series of α -alkylidene- β -hydroxy- γ -lactones were obtained in good to excellent yields (Table 1, entries 4–17) when a variety of arylboronic acids and arylmethyl 2-alkynoates were employed. However, ortho-substituted arylboronic acid gave no cyclization product probably because of the steric hindrance. The stereochemistry of the exocyclic double bond in products **2** was assigned as (*E*)-configuration on the basis of the lower field chemical shift

Scheme 2. Chiral Bidentate Phosphorus Ligands Screened in the Asymmetric Cyclization of Arylmethyl 2-Alkynoates

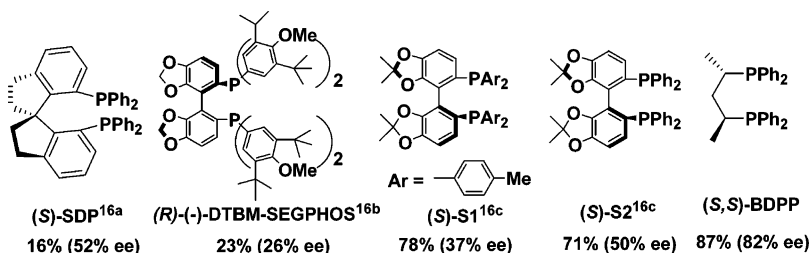


Table 2. Asymmetric Cyclization of Arylmethyl 2-Alkynoates under the Catalysis of $\text{Pd}(\text{CF}_3\text{COO})_2/(\text{S}, \text{S})\text{-BDPP}^a$

entry	product	yield (%) ^b	ee (%) ^c
1		87	82 (+)
2		87	74 (+)
3		87	78 (+)
4		83	92 (-)
5		92	81 (+)
6		85	89 (+)
7		83	83 (+)
8		82	62 (+)
9		65	79 (+)
10		90	75 (+)
11		85	76 (+)
12		82	84 (-)

^a Reaction conditions: Substrate (0.2 mmol), arylboronic acid (0.5 mmol), $\text{Pd}(\text{CF}_3\text{COO})_2$ (0.006 mmol), $(\text{S}, \text{S})\text{-BDPP}$ (0.006 mmol) in $\text{CH}_2\text{ClCH}_2\text{Cl}/\text{H}_2\text{O}$ (2 mL/0.2 mL) at 70 °C. ^b Isolated yield. ^c The ee values were determined by chiral HPLC. The sign of optical rotation was indicated in parentheses (for details see Supporting Information).

of the methyl or alkyl group for the *E* isomer in ^1H NMR spectra¹⁴ and compared with the data in the literature.¹⁵ Again, the structure of **2af** was confirmed by X-ray crystallography.

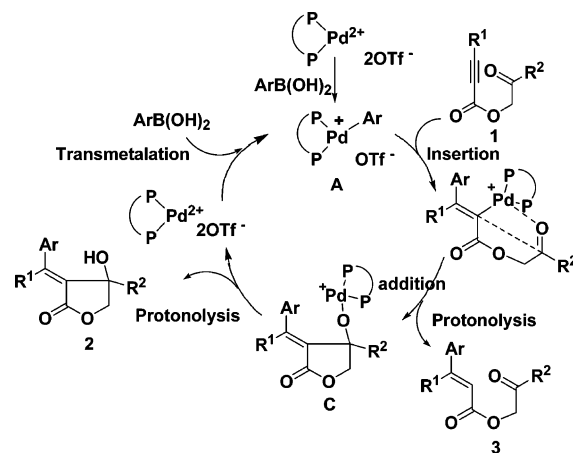
(7) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, 128, 16504.

(8) Zhao, L.; Lu, X. *Angew. Chem. Int. Ed.* **2002**, 41, 4343.

Subsequently, the asymmetric version of this cascade cyclization was studied. Unexpectedly, $[(R)\text{-(binap)Pd}(\text{H}_2\text{O})_2]\text{-(OTf)}_2$ which was effective in cationic palladium-catalyzed intramolecular addition of arylboronic acid to ketones⁷ showed low reactivity in the present reaction in dioxane (25% yield). Although the yield was improved to 71% in CH_3NO_2 , low enantioselectivity (34% ee) was still observed. Some other chiral bidentate phosphorus ligands¹⁶ also gave negative results (Scheme 2). Fortunately, enlightened by the structure of dppp, $(\text{S}, \text{S})\text{-BDPP}^{16d}$ was tested, and good yields with moderate to excellent ee values were obtained (Table 2). It is important to note here that to simplify the experimental manipulation, $\text{Pd}(\text{CF}_3\text{COO})_2/(\text{S}, \text{S})\text{-BDPP}$ was used directly in the reaction to generate cationic palladium-(II) species in situ.¹⁷

The possible mechanism is proposed as shown in Scheme 3.¹⁸ First, arylpalladium species **A** is formed by transmeta-

Scheme 3. Proposed Mechanism of the Asymmetric Cyclization of Arylmethyl 2-Alkynoates under the Catalysis of Cationic Palladium(II) Initiated by Carbopalladation



lation of the cationic $\text{Pd}(\text{II})$ species with arylboronic acids. Regioselective insertion of **1** to **A** affords vinylpalladium intermediate **B** (carbopalladation). High Lewis acidity of the

(9) (a) Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. (b) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995. (c) Suzuki, A. *Organoboranes in Organic Syntheses*; Hokkaido University: Sapporo, Japan, 2004. (d) Hall, D. C. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005.

(10) (a) Oh, C. H.; Ryu, J. H. *Bull. Korean Chem. Soc.* **2003**, 24, 1563. (b) Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim, N. *Angew. Chem., Int. Ed.* **2003**, 42, 805. (c) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, 43, 5063. (d) Oh, C. H.; Park, S. J.; Ryu, J. H.; Gupta, A. K. *Tetrahedron Lett.* **2004**, 45, 7093. (e) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, 7, 259. (f) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 3184.

(11) For reactions catalyzed by cationic palladium species, see: (a) Yamamoto, A. *J. Organomet. Chem.* **1995**, 500, 337. (b) Coates, G. W. *Chem. Rev.* **2000**, 100, 1223. (c) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, 35, 905. (d) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, 78, 941. (e) Mikami, K.; Hatano, M.; Akiyama, K. *Top. Organomet. Chem.* **2005**, 14, 279 and references therein.

(12) For the cationic palladium catalyzed reactions of arylboronic acids, see: (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, 42, 2768. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, 23, 4317.

Pd center in cationic species **B** may activate the carbonyl group by coordination to the unshared electron pairs on the oxygen atom, facilitating the formation of the intermediate **C**.^{11e} It is also proposed that this coordinated intermediate **B** is helpful to the enantioface discrimination of ketones resulting in high ee values.¹⁹ A competitive reaction is the protonolysis of the vinyl palladium species producing byproduct **3**. After the addition of the Csp² carbon to the activated carbonyl group in **B** generates **C**, the product **2** is

(13) (a) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110. (b) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *Organometallics* **1996**, *15*, 3509. (c) Fallis, S.; Anderson, G. K.; Rath, N. P. *Organometallics* **1991**, *10*, 3180.

(14) (a) Minami, T.; Niki, I.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3236. (b) Tanaka, K.; Tamura, N.; Kaji, A. *Chem. Lett.* **1980**, 595.

(15) (a) Torabi, H.; Evans, R. L.; Stavely, H. E. *J. Org. Chem.* **1969**, *34*, 3792. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (c) Ma, S.; Zhu, G.; Lu, X. *J. Org. Chem.* **1993**, *58*, 3692. (d) Xie, X.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 8415. (e) Zhu, G.; Tong, X.; Cheng, J.; Sun, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1712.

(16) (a) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (c) Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2185. (d) Purchased from Strem Chemicals Co.

(17) Gini, F.; Hessen, B.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309.

(18) (a) Maassarani, F.; Pfeffer, M.; Spencer, J.; Wehman, E. *J. Organomet. Chem.* **1994**, *466*, 265. (b) Vicente, J.; Abad, J. A.; López-Peláez, B.; Martínez-Viviente, E. *Organometallics* **2002**, *21*, 58.

(19) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284.

formed by protonolysis of the palladium alkoxide intermediate **C** with regeneration of the palladium species to make the catalytic cycle possible. Of course, another pathway to form intermediate **C** by the insertion of carbonyl group coordinated to palladium via the π -electrons to carbon–palladium bond in **B** could not be excluded.

In summary, we have developed a cationic palladium(II)-catalyzed enantioselective addition of vinylpalladium species to ketones initiated by carbopalladation of the alkynes without a Pd(II)/Pd(0) redox system. This cascade reaction provided an efficient way for the construction of optically active hydroxylactones.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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