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Sequential Pd- and Rh-Catalyzed Three-Component Cyclization with Allenylboronate Platform

Keisuke Tonogaki,[†] Kenichiro Itami,*[,‡,§] and Jun-ichi Yoshida*[,†]

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan, and Research Center for Materials Science, Nagoya University, Nagoya 464-8602, Japan

itami@chem.nagoya-u.ac.jp; yoshida@sbchem.kyoto-u.ac.jp

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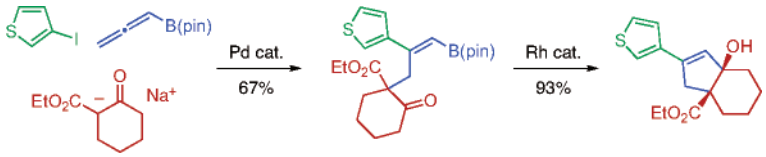
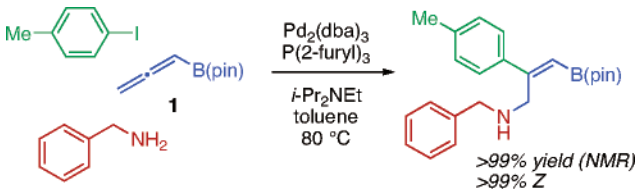
ABSTRACT



A novel three-component cyclization using allenylboronate ester is described. A three-component assembly of allenylboronate ester, aryl iodides, and stabilized carbon nucleophiles took place in the presence of palladium catalyst, furnishing functionalized alkenylboronate esters with high regio- and stereoselectivity. A Rh-catalyzed cyclization of the resultant three-component products then afforded interesting carbocyclic frameworks efficiently.

The multicomponent assembly reaction has attracted great interest of synthetic chemists as a powerful tool for rapid generation of molecular complexity and diversity.[1] In particular, multicomponent assembly based on a simple molecule bearing multiple reaction sites (platform) is a very attractive and powerful synthetic strategy.[2] As a part of our program using organoboron platforms in multicomponent assembling reactions,[3,4] we recently developed a Pd-catalyzed three-component assembly of allenylboronate pinacol ester (**1**), aryl iodides, and amines, by which highly functionalized allylic amine structures can be constructed in a regioselective, stereoselective, and diversity-oriented manner (Scheme 1).[5,6]

Scheme 1



We envisaged that the application of carbon nucleophiles having carbonyl moieties such as enolates and malonates in the three-component assembly would afford interesting compounds having potentially both nucleophilic parts (alkenylboronates)[7] and electrophilic parts (carbonyl groups)

[†] Kyoto University.
[‡] Nagoya University.
[§] PRESTO, Japan Science and Technology Agency (JST).

(1) (a) Zhu, J., Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (d) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(2) Itami, K.; Yoshida, J. *Chem. Eur. J.*, in press.

(3) (a) Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 4093. (b) Tonogaki, K.; Soga, K.; Itami, K.; Yoshida, J. *Synlett* **2005**, 1802.

(4) Selected other multicomponent assembly using organoboron platforms: (a) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152. (b) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807. (c) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (d) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 14344. (e) Petasis, N. A. In ref 1a, Chapter 7. (f) Touré, B. B.; Hall, D. G. In ref 1a, Chapter 12.

(5) Tonogaki, K.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 1464.

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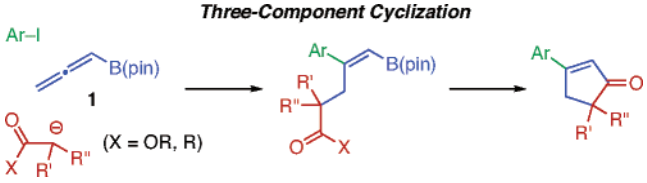
Scheme 2

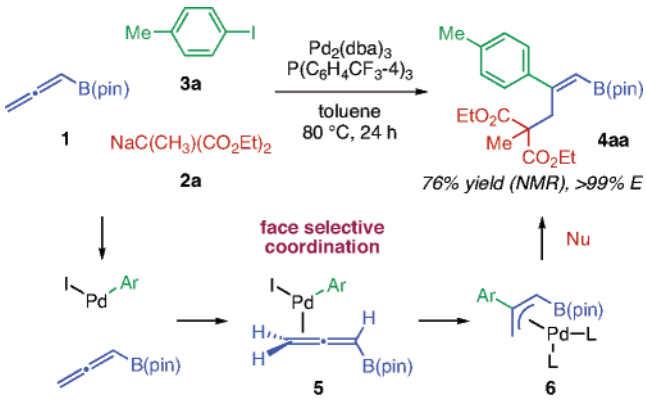
Three-Component Cyclization



(Scheme 2). Subsequent cyclization through appropriate catalysis (such as recently emerging rhodium catalysis)[8] connecting these two moieties would then furnish interesting and useful carbocyclic frameworks such as cyclopentenones. We herein report such a three-component cyclization through palladium and rhodium catalysis.

Allenylboronate pinacol ester (**1**: 1.2 equiv) was treated with $NaC(CH_3)(CO_2Et)_2$ (**2a**: 1.2 equiv) and 4-iodotoluene (**3a**: 1.0 equiv) in the presence of $Pd_2(dba)_3$ (2.5 mol %) and $P(C_6H_4CF_3\text{-}4)_3$ (10 mol %) in toluene at 80 °C for 24 h. A three-component assembling reaction took place to afford alkenylboronate **4aa** in 76% yield with virtually complete regio- and stereoselectivity (Scheme 3).[9] The *E* stereochemistry of **4aa** was determined by the NOESY experiments. The choice of supporting ligand on palladium was found to be important in this reaction. For example, the use of $P(C_6H_5)_3$ furnished **4aa** in 56% yield. The results using other representative phosphine ligands are depicted in Scheme 3. The effect of solvent employed was even more dramatic. For example, **4aa** was obtained only in 16% yield when the reaction was carried out in dioxane.

Scheme 3[a]

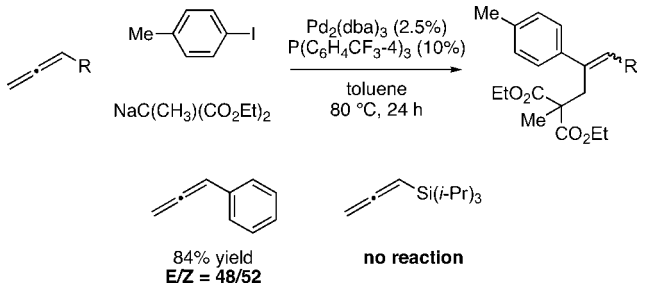


[a] Effect of Ligands: $P(C_6H_5)_3$ (56%), $P(C_6H_4OMe\text{-}4)_3$ (52%), $P(C_6H_4F\text{-}4)_3$ (55%), $P(C_6H_4CF_3\text{-}4)_3$ (76%), $P(C_6F_5)_3$ (22%), $P(2\text{-furyl})_3$ (50%), and $P(OC_6H_5)_3$ (46%).

The selective production of *E*-alkenylboronate **4aa** in this three-component assembly can be explained by assuming the following mechanism (Scheme 3). The terminal C═C bond of **1** coordinates to an arylpalladium complex, formed by **3a** and Pd(0), at the face opposite to the pinacolatoboryl group to avoid steric congestion (**5**). The subsequent arylpalladation across C═C bond leads to a π-allyl complex **6** with a boryl group anti to the aryl group due to steric congestion. Then, nucleophile **2a** attacks **6**, presumably at the unsubstituted terminal carbon of allyl ligand, to give **4aa** with the regeneration of Pd(0) catalyst. The *anti* stereochemistry of π-allyl intermediate **6** accounts for the *E* stereochemistry of **4aa**.[5]

The boryl group acts not only as a useful group that can trigger cyclization afterward but also as a stereochemical controller in the generation of key (π-allyl)palladium intermediates.[5] For example, when phenylallene was subjected to the conditions for three-component assembling reaction [$Pd_2(dba)_3$, $P(C_6H_4CF_3\text{-}4)_3$, toluene, 80 °C, 24 h], the corresponding three-component product was obtained with almost no control over stereoselectivity (Scheme 4). More interestingly, we found that the reaction did not take place with triisopropylsilylallene, attesting to a unique promoting effect of boryl group in this reaction (Scheme 4).

Scheme 4



With an efficient protocol for the three-component assembly based on allenylboronate platform **1** in hand, we subsequently applied these conditions to various stabilized carbon nucleophiles **2** and aryl iodides **3** (Table 1). The reaction proceeded efficiently with electronically and structurally diverse aryl and heteroaryl iodides to afford various *E*-alkenylboronates **4** with virtually complete regio- and stereoselectivity. Functional groups such as nitrile and chloride on the aromatic ring tolerated the reaction conditions (entries 3 and 7). Various carbon nucleophiles such as sodium ethyl 2-methylacetoacetate (**2b**), sodium ethyl 2-cyclohexanonecarboxylate (**2c**), and sodium ethyl 2-cyanopropionate (**2d**) could also be applied to this reaction (entries 4, 5, and 6). Three-component products were selectively obtained even

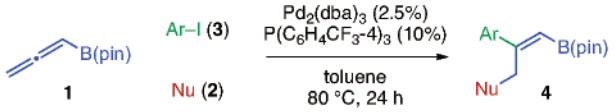
(6) Selected recent examples of catalytic multicomponent assembly using allenes: (a) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320. (b) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221. (c) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576. For reviews, see: (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.

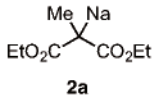
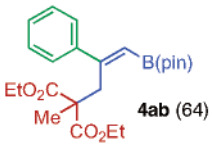
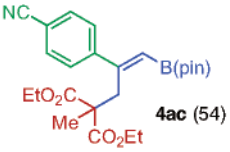
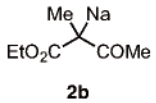
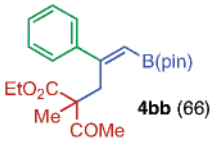
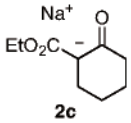
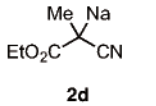
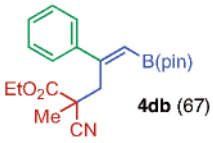
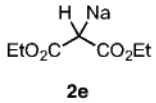
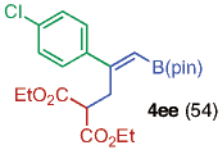
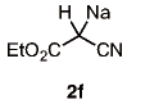
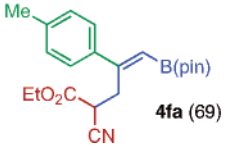
(7) Hall, D. G., Ed. *Boronic Acids*; Wiley-VCH: Weinheim, 2005.

(8) Reviews on Rh-catalyzed carbon−carbon bond-forming reactions: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(9) (a) Ahmar, M.; Gazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 4505. (b) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 513. (c) Friess, B.; Gazes, B.; Gore, J. *Tetrahedron Lett.* **1988**, *29*, 4089. (d) Gazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867.

Table 1. Three-Component Assembly of Allenylboronate Pinacol Ester (**1**), Carbon Nucleophiles (**2**), and Aryl Iodides (**3**)[a]



entry	nucleophile (**2**)	Ar-I (**3**)	**4** (yield, %)[b]
1	 **2a**	4-MeC$_6$H$_4$-I (**3a**)	 **4aa** (59)
2	**2a**	C$_6$H$_5$-I (**3b**)	 **4ab** (64)
3	**2a**	4-NCC$_6$H$_4$-I (**3c**)	 **4ac** (54)
4	 **2b**	**3b**	 **4bb** (66)
5	 **2c**	3-iodothiophene (**3d**)	 **4cd** (67)
6	 **2d**	**3b**	 **4db** (67)
7	 **2e**	4-ClC$_6$H$_4$-I (**3e**)	 **4ee** (54)
8	 **2f**	**3a**	 **4fa** (69)

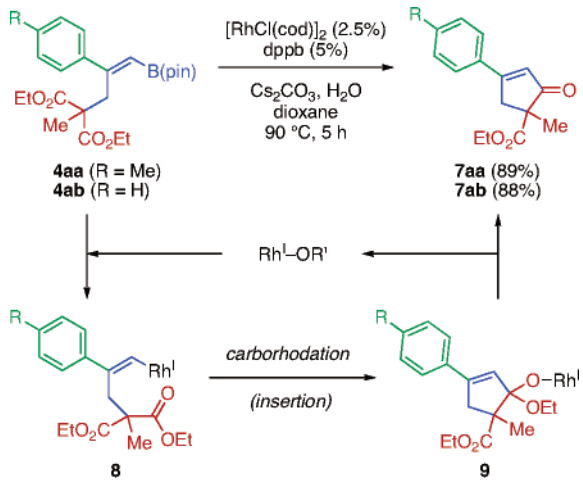
[a] Reaction conditions: **1** (0.60 mmol), **2** (0.60 mmol), **3** (0.30 mmol), $Pd_2(dba)_3$ (2.5 mol %), $P(C_6H_4CF_3\text{-}4)_3$ (10 mol %), toluene (2.0 mL), 80 °C, 24 h. [b] Isolated yield.

using nucleophiles, such as **2e** and **2f**, having acidic hydrogen atom; diallylated products were not obtained (entries 7 and 8). Unfortunately, however, the use of aryl bromides and chlorides gave three-component products in extremely low yields (<5% yield).

With the regio- and stereoselective tandem three-component assembly in hand, we subsequently examined conditions to connect nucleophilic alkenylboronate moieties and electrophilic carbonyl moieties in the resultant three-component products **4**. Very recently, Hayashi and Murakami independently reported that the intramolecular addition/substitution of organorhodium(I) species to ester group can take place to afford interesting cyclic compounds.[8,10] We envisaged that similar Rh-catalyzed cyclization might take place with our three-component products **4** having alkenylboronate and carbonyl moieties to achieve novel three-component cyclization.

Gratifyingly, the treatment of three-component products bearing diester groups (**4aa** and **4ab**) in the presence of $[RhCl(cod)]_2$ (2.5 mol %), dppb (5 mol %), Cs_2CO_3 (3 equiv), and H_2O (3 equiv) in dioxane (90 °C, 5 h) afforded highly functionalized cyclopentenones (**7aa** and **7ab**) in high yields (Scheme 5). We assume the following reaction mechanism:

Scheme 5

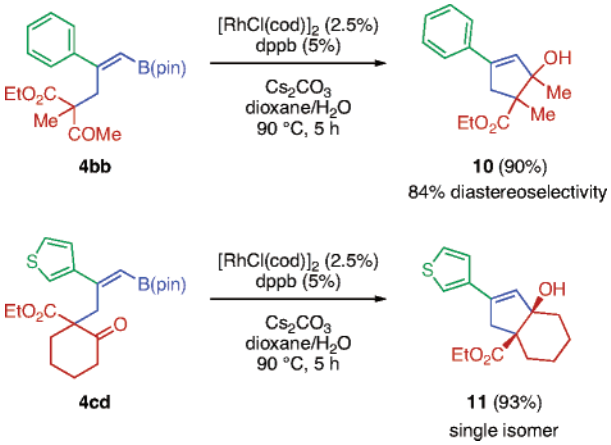


(i) the addition (carborhodation) of alkenylrhodium(I) species **8**, generated by the transmetalation of rhodium(I) complex with **4**, to the intramolecular C═O bond of ester group to afford cyclic intermediate **9**, and (ii) the β-alkoxy elimination from **9** to afford cyclopentenone **7** with the liberation of rhodium(I) alkoxide, which can reenter into the catalytic cycle (Scheme 5).

Interestingly, when **4bb** bearing ketoester moieties was subjected to Rh/dppb catalyst, selective addition to the C═O bond of the ketone group was found to proceed, furnishing highly functionalized cyclopentenol **10** as a mixture of diastereomers (major/minor = 84/16) in 90% yield (Scheme 6).[11] This product (**10**) was most likely formed through hydrolysis of the alkoxyrhodium species generated

(10) Addition of organorhodium species to esters: (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (b) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390.

Scheme 6



by intramolecular carborhodation across the C═O bond of ketone group.[11] More interestingly, when **4cd** was used as a substrate, interesting bicyclic tertiary alcohol **11** was isolated in 93% yield as a single isomer (Scheme 6). Such hydroindenol structures can be seen in a number of biofunctional molecules with interesting properties.[12]

In summary, we have developed a novel three-component cyclization using allenylboronate platform. A palladium complex catalyzed the three-component assembly of allenylboronate ester, aryl iodides, and stabilized carbon nucleophiles to produce functionalized alkenylboronate esters with virtually complete regio- and stereoselectivity. Control experiments revealed that the boryl group clearly enhanced the stereoselectivity of this three-component assembly. We also established a Rh-catalyzed cyclization of the resultant three-component products to give interesting carbocyclic frameworks very efficiently. In view of the remarkable progress utilizing organoboron compounds in C−C bond forming reactions,[7,8] the present three-component cyclization strategy should find many uses in the synthesis of previously unexplored cyclic frameworks of significant interests. Further work is in progress to explore the scope of multicomponent assembly (cyclization) based on allenylboronate platform.

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

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(11) Addition of organorhodium species to aldehydes and ketones: (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (c) Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *4*, *343*, 343. (d) Moreau, C.; Hague, C.; Weller, A. S.; Frost, C. G. *Tetrahedron Lett.* **2001**, *42*, 6957. (e) Takezawa, A.; Yamaguchi, K.; Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Synlett* **2002**, 1733. (f) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (g) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6*, 1257. (h) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667. (i) Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294. (j) Matsuda, T.; Makino, M.; Murakami, M. *Chem. Lett.* **2005**, *34*, 1416. (k) Reference 10a.

(12) For examples, see: Cerri, A.; Almirante, N.; Barassi, P.; Benicchio, A.; De Munari, S.; Marazzi, G.; Molinari, I.; Serra, F.; Melloni, P. *J. Med. Chem.* **2002**, *45*, 189 and references therein.