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Control of Chemo-, Regio-, and Stereoselectivities in Ligand-Free Pd-Catalyzed Oxidative Heck Reactions of Arylboronic Acids or Alkenylboronate with Allyl Esters

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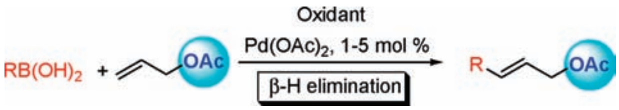
ABSTRACT



A ligand-free Pd-catalyzed highly selective oxidative Heck reaction of organoboronic acids with allyl esters was developed. β-H elimination is highly chemoselectively controlled, leading to γ-substituted allyl esters, which is contrary to the traditional Heck-type reactions of allyl esters. Moreover, the regio- and stereoselectivities are also high due to the chelation between O and Pd atoms.

Allyl esters have been widely applied in the syntheses of natural products and pharmaceuticals.[1] Among these, Pd(0)-catalyzed allylic alkylations of allyl acetates and organic halides present a powerful tool to construct C−C bonds.[2] Compared to organic halides, organoboronic acids are attractive due to their ease of handling, stability, and low toxicity. Although Pd-catalyzed oxidative Heck reaction of organoboronic acids and olefins had been well-studied,[3,4] Pd(II)-catalyzed coupling of boronic acids with allyl esters is rarely achieved due to the complicated selectivities (internal vs terminal; β-H vs β-OAc elimination; styrenyl vs allylic, Scheme 1). Significantly, Sawamura and co-workers[5a] realized the γ-regioselective allyl−aryl coupling via β-OAc elimination[6] of allyl acetates and arylboronic acids (path a, Scheme 1). In contrast, control of β-H elimination in this kind of oxidative Heck reaction is rarely achieved. White's group[7] reported a Pd(II)/phenyl bis-sulfoxide-catalyzed Heck-type reaction of 3-acetoxy-1-dodecene and

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[1] For leading reviews, see: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163–3185. (b) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181–1196.

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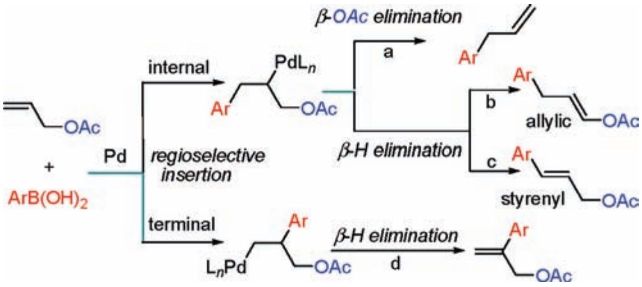
[3] For leading reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1133; (c) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 2004; (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.

[4] For some recent examples of oxidative Heck reactions, see: (a) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393. (b) Crowley, J. D.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12092–12093. (c) Lindh, J.; Enquist, P.-A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957–7962. (d) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933–3935. (e) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462–9465. (f) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144–6148. (g) Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 1484–1485. (h) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709–1712.

10.1021/ol9009865 CCC: $40.75

Scheme 1. Complicated Selectivities in the Oxidative Heck Reaction of Allyl Esters and Boronic Acids

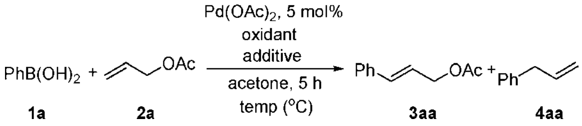


phenylboronic acids through β-H elimination for the first case, which was also achieved by Xiao and co-workers[8] employing Pd(OAc)$_2$/dppp as catalysts but with low regioselectivity. Despite these achievements, the substrate scope is limited, and ligand is required in the above methods. Hence, the development of an efficient method for β-H elimination is important for continued advancements in this area. Herein, we demonstrate a ligand-free Pd-catalyzed method to highly selectively control the β-H elimination in the oxidative Heck reaction of organoboronic acids with allyl esters (path c, Scheme 1).

We previously developed a ligand free Pd-catalyzed Heck reaction of aryl iodide with allyl esters, in which Ag$^+$ exhibited an important role to promote β-H elimination, leading selectively to the retention of traditional leaving groups such as OAc and OCOOMe.[9] It is well-known that Ag$^+$ can serve as an excellent oxidant in the Pd(II)/oxidant agent catalytic system[10a] and also can be used to control the double-bond position in Heck reactions.[10b,c] Thus, we hypothesized that an oxidative Heck-type reaction of allyl acetates and arylboronic acids via β-H elimination could be realized by the use of Ag oxidant under proper conditions (path c, Scheme 1).

On the basis of our previous studies, we initiated this project by investigating the reaction of phenylboronic acid **1a** and allyl acetate **2a** catalyzed by Pd(OAc)$_2$. When AgOAc was used as oxidant in this reaction, the expected product **3aa** was successfully produced in 30% yield (entry 1, Table 1). Although **4aa** was also obtained, the regioselectivities were very high (**3aa**: internal/terminal >20:1, styrenyl/allylic >20:1). Other general oxidants such as Cu(OAc)$_2$, Ag$_2$CO$_3$, AgOTf, AgF, or BQ (benzoqinone) presented low efficiency. It is noteworthy that when Pd(II)/phenyl bis-sulfoxide was used as catalyst, the reaction carried out in dioxane using BQ as oxidant[11] only gave **3aa** in 18% yield (entry 2, Table 1). The yield of **3aa** increased to 48% when Cu(OAc)$_2$ was used as cooxidant (entry 3, Table 1). It was reported that fluoride ion could promote Suzuki−Miyaura coupling reactions.[12] The presence of KF facilitates this transformation to 55% yield (cf. entries 3 and 4, Table 1). The use of CsF instead of KF decreased the efficiency of the transformation (cf. entries 7 and 8, Table 1). The efficiencies were low when the reaction was carried out in other solvents such as DMF, DMSO, toluene, or 2-pentanone. Moreover, the yield increased when the reaction was stirred at 85 °C using acetone as solvent in a sealed tube (cf. entries 4 and 6, Table 1, also see the Supporting Information). After various screenings on different reaction parameters, we finally reached the optimal reaction conditions: Pd(OAc)$_2$ (5 mol %), AgOAc (2.0 equiv), CuF$_2$ (1.0 equiv), and KHF$_2$ (2.0 equiv) in

Table 1. Pd(OAc)$_2$-Catalyzed Oxidative Heck Reaction between Phenylboronic Acid **1a** and Allyl Acetate **2a**[a]



entry	oxidant (equiv)	additive (equiv)	T (°C)	yield (%)[b] 3aa	yield (%)[b] 4aa
1	AgOAc (2.0)		reflux	30	3
2[c]	BQ (2.0)	AcOH (4.0)	45	18	0
3	AgOAc (2.0) Cu(OAc)$_2$·H$_2$O (1.0)		reflux	48	3
4	AgOAc (2.0) Cu(OAc)$_2$·H$_2$O (1.0)	KF (2.0)	reflux	55	4
5		KF (2.0)	reflux	4	2
6	AgOAc (2.0) Cu(OAc)$_2$·H$_2$O (1.0)	KF (2.0)	85	74	6
7	AgOAc (2.0) CuF$_2$ (1.0)	KF (2.0)	85	73	5
8	AgOAc (2.0) CuF$_2$ (1.0)	CsF (2.0)	85	19	9
9	AgOAc (2.0) CuF$_2$ (1.0)	KHF$_2$ (2.0)	85	92 (91)[d]	2
10	AgF (2.0) CuF$_2$ (1.0)	KHF$_2$ (2.0)	85	12	2
11	Ag$_2$SO$_4$ (2.0) CuF$_2$ (1.0)	KHF$_2$ (2.0)	85	15	5
12[e]	AgOAc (2.0) CuF$_2$ (1.0)	KHF$_2$ (2.0)	85	78 (78)[d]	2

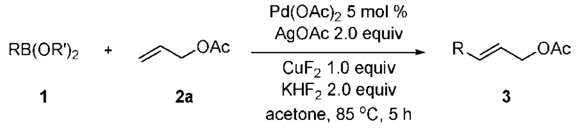
[a] **1a** (0.5 mmol), **2a** (1.0 mmol), Pd(OAc)$_2$ (0.025 mmol), additive, acetone (2.5 mL) were heated in a sealed tube. [b] GC yields using *n*-dodecane as an internal standard. [c] This reaction was carried out under the similar conditions developed by White and co-workers,[6] but employed 5 mol % Pd-catalyst: **1a** (0.75 mmol), **2a** (0.5 mmol), Pd(II)/phenyl bis-sulfoxide (0.025 mmol), BQ (1.0 mmol), AcOH (2.0 mmol), dioxane (3.0 mL), at 45 °C for 24 h. [d] Isolated yield, ***E*-3aa**/***Z*-3aa** = 20:1. [e] 1 mol % of Pd(OAc)$_2$ was used.

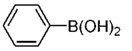
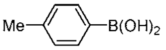
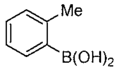
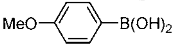
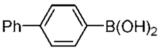
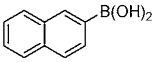
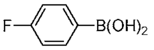
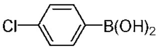
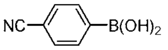
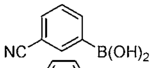
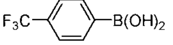
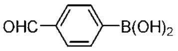
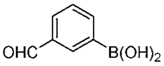
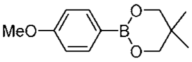
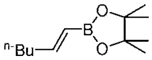
acetone at 85 °C. Under this conditions, 91% of **3aa** was isolated with high chemo-, regio-, and stereoselectivities (**3aa**/**4aa** = 98:2; **3aa**: internal/terminal >20:1, styrenyl/allylic >20:1, ***E*-3aa**/***Z*-3aa** = 20:1) (entry 9, Table 1). Gratifyingly, 78% of **3aa** was formed when only 1 mol % of Pd(OAc)$_2$ was employed (entry 12, Table 1).

With the optimal reaction conditions in hand, we examined the scope of the Pd(OAc)$_2$-catalyzed oxidative Heck reaction in the absence of ligand. A range of arylboronic acids with electron-withdrawing or electron-donating groups proceeded efficiently with good to excellent yields of the expected arylated allyl acetates (Table 2). All reactions exhibited excellent regioselectivities (internal/terminal >20:1, styrenyl/allylic >20:1); no or only traces of allyl arene products **4** were observed in these transformations. Furthermore, the stereoselectivities in some cases had been selectively controlled (⩾20:1) for **3ca**, **3da**, **3ga**, **3ha**, **3ja**, and **3oa**. When the arylboronic acids were substituted at the ortho position, the yield was low due to the steric hindrance effect (entry 3, Table 2). It is noteworthy that arylboronic acids with substituents such as chlorides, nitriles, and aldehydes survived well (entries 8−10, 12, and 13, Table 2). Their functional groups could thus be used for further transformations. Furthermore, arylboronic ester **1n** smoothly provided **3da** in 80% yield with high regioselectivities and stereoselectivity (entry 14). Notably, (2*E*,4*E*)-2,4-nonadienyl acetate **3oa** was obtained in 37% yield when alkenylboronic ester **1o** was employed in this transformation (entry 15, Table 2).

The scope of the ligand-free Pd(OAc)$_2$-catalyzed highly selective Heck reaction was further expanded to a variety of substituted allyl esters **2** (Table 3). These results indicate that the reaction is tolerant of a wide range of allyl acetates substituted at the α- and β-positions. The regioselectivities were also controlled in these transformations (internal/terminal >20:1, styrenyl/allylic >20:1). Notably, allyl acetates bearing H, Et, and pentyl groups, respectively, at the α-position were efficiently performed with phenylboronic acid (Table 2; entries 4 and 5, Table 3), despite the low yield of α-methyl allyl acetate (entry 3, Table 3). Furthermore, the stereoselectivities of these transformations with α-substituted allyl acetate were very high (only *E*-isomers were observed, see entries 3−6). However, when the 2-position of the substrate was substituted, the stereoselectivity became worse due to the steric hindrance (entries 1 and 2, Table 3). It is interesting to find that allyl benzoate **2h** reacted with **1l** to give **3lh** in 75% yield (entry 7). Moreover, ***E*-3ai** was formed in 45% yield as the sole product when relatively

Table 2. Pd(OAc)$_2$-Catalyzed Oxidative Heck Reaction of Allyl Acetate **2a** with Different Organoboronic Acids **1**[a]



entry	1	*E*-3/*Z*-3[b]	yield of 3 (%)[c]
1	 (**1a**)	20/1	91 (**3aa**)
2	 (**1b**)	>20/1	92 (**3ba**)
3	 (**1c**)	16/1	37 (**3ca**)
4	 (**1d**)	13/1	69 (**3da**)
5	 (**1e**)	20/1	45 (**3ea**)
6	 (**1f**)	>20/1	75 (**3fa**)
7	 (**1g**)	14/1	87 (**3ga**)
8	 (**1h**)	13/1	86 (**3ha**)
9	 (**1i**)	20/1	84 (**3ia**)
10	 (**1j**)	17/1	70 (**3ja**)
11	 (**1k**)	>20/1	76 (**3ka**)
12	 (**1l**)	>20/1	80 (**3la**)
13	 (**1m**)	20/1	81 (**3ma**)
14	 (**1n**)	20/1	80 (**3da**)
15	 (**1o**)	6/1	37 (**3oa**)

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Pd(OAc)$_2$ (0.025 mmol), AgOAc (1.0 mmol), CuF$_2$ (0.5 mmol), KHF$_2$ (1.0 mmol), acetone (2.5 mL), in sealed tube, at 85 °C, 5 h. [b] *E*/*Z* determined by ^{1}H NMR. [c] Isolated yield.

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(5) (a) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277. For other oxidative Heck reactions of allyl esters via β-OAc elimination, see: (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384–3388. (c) Miyaura, N.; Yamada, K.; Suginome, Suzuli, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980. (d) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015. (e) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453–7456. (f) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445–2448. For Heck reactions of allyl esters with aryl iodides via β-OAc elimination, see: (g) Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72–73. (h) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747.

(6) (a) Cheng, J. C.-Y.; Daves, G. D., Jr. *Organometallics* **1986**, *5*, 1753–1755. (b) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899–4904. (c) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604–7605. (d) Lu, X. *Top. Catal.* **2005**, *35*, 73–86.

(7) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076–15077.

(8) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425.

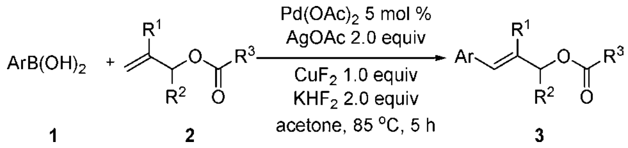
(9) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732.

(10) (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (b) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–3900. (c) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859–4862.

(11) This reaction was carried out under similar conditions developed by White and co-workers (see ref 6) but employed 5 mol % of Pd(II)/phenyl bis-sulfoxide as catalyst.

(12) (a) Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961–964. (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561. (f) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (g) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103.

Table 3. Pd(OAc)$_2$-Catalyzed Oxidative Heck Reaction of Boronic Acid **1** with Different Allyl Esters **2**[a]



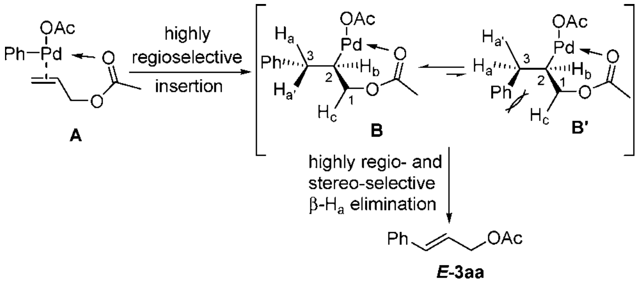
entry	Ar (**1**)	R^1	R^2	R^3	**2**	***E*-3/*Z*-3**[b]	yield of **3** (%)[c]
1	Ph (**1a**)	Me	H	Me	**2b**	6/1	65 (**3ab**)[13]
2	4-CHO-C$_6$H$_4$ (**1l**)	Ph	H	Me	**2c**	6/1	72 (**3lc**)
3	Ph (**1a**)	H	Me	Me	**2d**	only *E*	41 (**3ad**)
4	Ph (**1a**)	H	Et	Me	**2e**	only *E*	82 (**3ae**)
5	Ph (**1a**)	H	*n*-C$_5$H$_{11}$	Me	**2f**	only *E*	85[d] (**3af**)
6	Ph (**1a**)	H	Ph	Me	**2g**	only *E*	20 (**3ag**)
7	4-CHO-C$_6$H$_4$ (**1l**)	H	H	Ph	**2h**	13/1	75 (**3lh**)
8	Ph (**1a**)	H	H	OMe	**2i**	only *E*	45[d] (**3ai**)

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Pd(OAc)$_2$ (0.025 mmol), AgOAc (1.0 mmol), CuF$_2$ (0.5 mmol), KHF$_2$ (1.0 mmol), acetone (2.5 mL), in sealed tube, at 85 °C, 5 h. [b] *E*/*Z* determined by ^{1}H NMR. [c] Isolated yield. [d] **1** (0.75 mmol), **2a** (0.5 mmol), AgOAc (2.5 equiv), CuF$_2$ (1.25 equiv), and KHF$_2$ (3.0 equiv) were used.

active allyl methyl carbonate **2i** was employed in this oxidative Heck reaction (entry 8, Table 3).

The high regioselectivities observed in these transformations are due to the chelation between O and Pd atoms as reported.[9,14] After the highly regioselective insertion, intermediate **B** was favored to form due to the steric hindrance effect between Ph and H$_c$ (Scheme 2). Furthermore, the rotation of the C$_1$−C$_2$ bond was impeded due to this chelation. Therefore, H$_a$ finally regio- and stereoselectively reached the syn relationship with Pd for subsequent β-H elimination leading to ***E*-3aa**.

Scheme 2. Possible Pathways for the High Regio- and Stereoselectivity



In summary, we have developed a ligand-free, Pd-catalyzed, highly selective oxidative Heck reaction of organoboronic acids with allyl esters. Simple and commercially available Pd(OAc)$_2$ is employed in the absence of ligand in this transformation. β-H elimination is highly chemoselectively controlled, leading to γ-substituted allyl esters, which is contrary to the traditional Heck-type reactions of allyl esters. Moreover, the regio- and stereoselectivities are also high due to the chelation between O and Pd atoms. Further studies on the scope and synthetic applications are ongoing in our laboratory.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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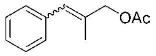
(13) The ratio of isomer



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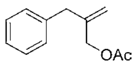

is 4.2:1.

(14) (a) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073–3076. (b) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604–2605. (c) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271.