Versatile Synthesis of 1,1-Diaryl-1-alkenes Using Vinylboronate Ester as a Platform

Keisuke Tonogaki,[a] Kazuya Soga,[a] Kenichiro Itami,*[b] Jun-ichi Yoshida*[a]

[a] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan
Fax +81(75)3832727; E-mail: yoshida@sbchem.kyoto-u.ac.jp

[b] Research Center for Materials Science, Nagoya University, Nagoya 464-8602, Japan
E-mail: itami@chem.nagoya-u.ac.jp

Received 6 April 2005

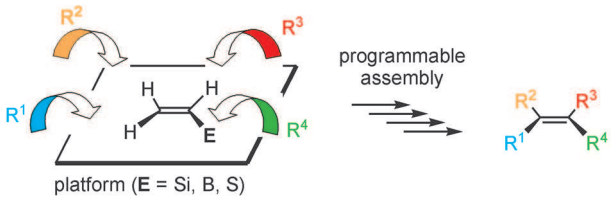
Abstract: A sequence of double Mizoroki–Heck reaction of vinylboronate pinacol ester with aryl halides followed by Suzuki–Miyaura coupling of thus-generated β,β-diarylvinylboronate esters with alkyl halides produces pharmaceutically important 1,1-diaryl-1-alkenes very efficiently. In the Pd-catalyzed Suzuki–Miyaura coupling step, the use of bulky electron-rich ligands such as P(*t*-Bu)$_2$Me and PCy$_2$(*t*-Bu) were found to be very effective.

Key words: palladium catalyst, Mizoroki–Heck reaction, Suzuki–Miyaura coupling, vinylboronate ester, alkyl halides

The regio- and stereoselective synthesis of multisubstituted olefins is one of the most important subjects in organic synthesis. In view of its synthetic challenge as well as potential application as functional materials and pharmaceuticals, we have been pursuing the chemistry (synthesis and property) of multisubstituted olefins during the last several years.[1–4] In particular, we have developed a number of programmable synthesis of multisubstituted olefins based on a sequential installation of substituents on a C=C core of an appropriate vinyl-element compound (platform, Scheme 1).[1–3]

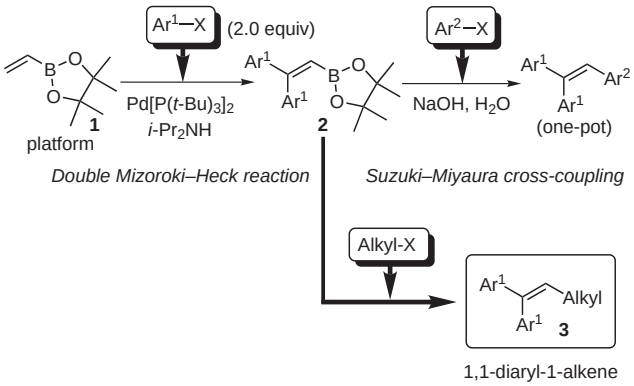
For example, we have developed a rapid synthesis of triarylethenes through the Pd-catalyzed sequential triarylation using vinylboronate ester as a platform.[2] Thus, Pd-catalyzed double Mizoroki–Heck reaction[5,6] of vinylboronate ester **1** and aryl halides produces various β,β-diarylvinylboronate esters **2** very efficiently. The thus-obtained boronate esters **2** can further undergo Suzuki–Miyaura coupling[7] with aryl halides to afford triarylethenes very rapidly (Scheme 2). From the triarylethene-based extended π-system library, we were able to find a number of interesting fluorescent materials as well as interesting photophysical properties.[1,2]

During these investigations targeting multisubstituted olefins, we became aware that pharmaceutically important 1,1-diaryl-1-alkenes **3** (Figure 1)[8,9] would be obtained straightforwardly if an efficient cross-coupling reaction of β,β-diarylvinylboronate esters **2** with alkyl halides could be developed (Scheme 2). Herein we describe an efficient and straightforward synthesis of 1,1-diaryl-1-alkenes **3** using vinylboronate ester **1** as a platform.



Scheme 1 Multisubstituted olefin synthesis using vinyl-element compounds as a platform

Since we have already established an efficient procedure for the synthesis of β,β-diarylvinylboronate esters **2** (double Mizoroki–Heck reaction of vinylboronate ester **1** and aryl halides),[2] the cross-coupling of **2** with alkyl halides was the initial focal point of this research program. In this regard, an efficient Suzuki–Miyaura cross-coupling of alkyl electrophiles with boronic acids reported recently by Fu and coworkers attracted much interest.[10] Thus, we began by simply applying the Fu's conditions [Pd(OAc)$_2$, P(*t*-Bu)$_2$Me, *t*-BuOK, *tert*-amyl alcohol] to the cross-coupling of β,β-diarylvinylboronate ester **2a** with 4-phenylbutyl bromide. Unfortunately, however, the expected 1,1-diaryl-1-alkene **3aa** was obtained only in 52% yield under their conditions (Table 1, entry 1). Therefore, we investigated various parameters of the reaction conditions for Pd-catalyzed cross-coupling of β,β-diarylvinylboronate esters with alkyl bromides.



Scheme 2 Synthetic strategy for 1,1-diaryl-1-alkenes using vinylboronate ester as a platform

SYNLETT 2005, No. 11, pp 1802–1804
Advanced online publication: 14.06.2005
DOI: 10.1055/s-2005-871539; Art ID: Y00805ST

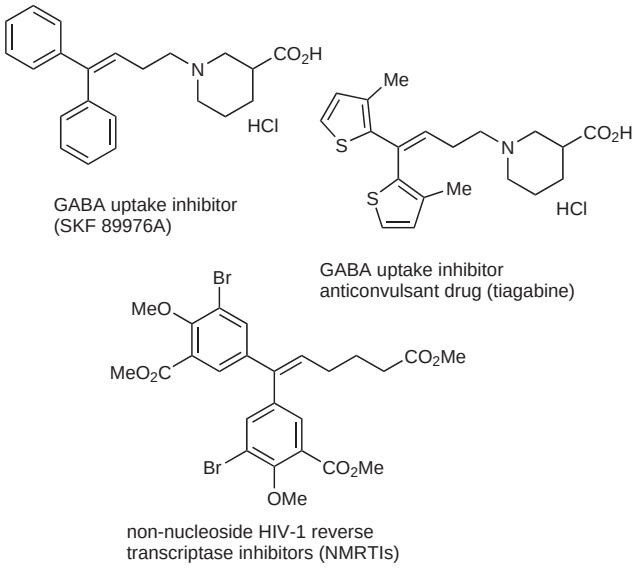
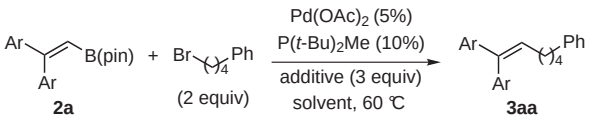


Figure 1 Examples of pharmaceutically important 1,1-diaryl-1-alkenes

We initially screened various base additives (*t*-BuOK, NaOH, K_2CO_3, Cs_2CO_3) and solvents (*tert*-amyl alcohol, toluene, dioxane; Table 1). Among various combinations examined, we found that the combination of NaOH and dioxane leads to an efficient cross-coupling of **2a** with 4-phenylbutyl bromide giving **3aa** in 80% yield (Table 1, entry 4).

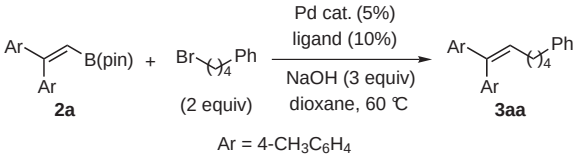
Next, we investigated Pd precursor and phosphine ligand using NaOH as an additive and dioxane as solvent that were optimized above (Table 2). When $Pd(OAc)_2$ was used as a catalyst precursor, P(*t*-Bu)$_2$Me and PCy_2(*t*-Bu) were the best among those that we examined (entries 1 and 5). It was also found that $PdCl_2$/PCy_2(*t*-Bu) system is equally effective in the cross-coupling of **2a** with alkyl bromide (entry 7).

Table 1 Examination of Additive and Solvent



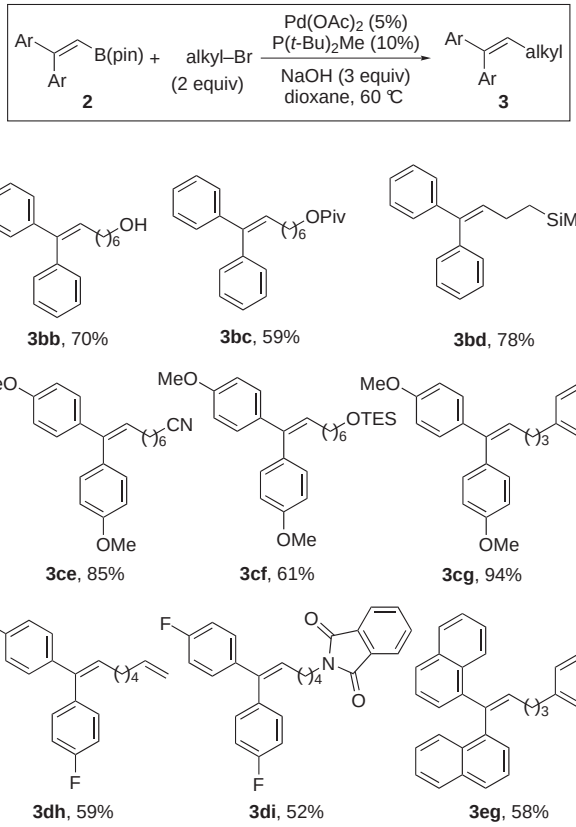
Entry	Additive	Solvent	Yield (%)
1	*t*-BuOK	*tert*-Amyl alcohol	52
2	NaOH	*tert*-Amyl alcohol	66
3	NaOH	Toluene	71
4	NaOH	Dioxane	80
5	*t*-BuOK	Dioxane	42
6	K_2CO_3	Dioxane	N.d.
7	Cs_2CO_3	Dioxane	N.d.

Table 2 Examination of Pd Precursor and Ligand



Entry	Pd	Ligand	Yield (%)
1	$Pd(OAc)_2$	P(*t*-Bu)$_2$Me	80
2	$Pd(OAc)_2$	$BiPhPCy_2$	N.d.
3	$Pd(OAc)_2$	BiPhP(*t*-Bu)$_2$	8
4	$Pd(OAc)_2$	Ad_2PBn	18
5	$Pd(OAc)_2$	PCy_2(*t*-Bu)	78
6	$Pd(OAc)_2$	PCy(*t*-Bu)$_2$	13
7	$PdCl_2$	PCy_2(*t*-Bu)	76

With improved conditions for the Pd-catalyzed Suzuki–Miyaura cross-coupling of β,β-diarylvinylboronate esters with alkyl bromides in hand, we subsequently applied these conditions to the synthesis of various 1,1-diaryl-1-alkenes (Scheme 3). Although three systems we found (Table 2, entries 1, 5, and 7) might be equally effective, we applied one of these conditions [$Pd(OAc)_2$, P(*t*-Bu)$_2$Me, NaOH, dioxane, 60 °C] in these syntheses.



Scheme 3 Synthesis of various 1,1-diaryl-1-alkenes

Gratifyingly, a wide range of functional groups was found to be intact in this cross-coupling. The use of 3-phenylpropyl bromide produced desired cross-coupling products **3cg** and **3eg** in good yields. When alkyl bromides having free hydroxyl group or triethylsilylether group were used, desired 1,1-diaryl-1-alkenes **3bb** and **3cf** were also obtained in good yields. Functional groups such as ester, nitrile, and imide were also tolerated (**3bc**, **3ce**, and **3di**). When alkyl bromide having olefinic moiety was used, desired 1,1-diaryl-1-alkene **3dh** was also obtained efficiently. When 2-(trimethylsilyl)ethyl bromide was used, the desired product **3bd** was also obtained in good yield. Moreover, various electronically and structurally diverse β,β-diarylvinylboronate esters **2b**–**e** can be applied in this reaction system to give 1,1-diaryl-1-alkenes **3** efficiently.

In summary, we have developed an efficient Pd-catalyzed cross-coupling reaction of β,β-diarylvinylboronate esters **2** with alkyl bromides. When combined with the double Mizoroki–Heck reaction of vinylboronate ester **1** with aryl halides, the present synthesis of 1,1-diaryl-1-alkenes becomes extremely versatile and flexible as a whole. All substituents on C=C core of 1,1-diaryl-1-alkenes (two aryl groups and one alkyl group) can be varied at will by simply changing the readily available organic halides in the reaction scheme. Since 1,1-diaryl-1-alkene is an important structural motif found in various pharmacologically active compounds, the present procedure should find many uses in the development of novel biofunctional small molecules.

Typical Procedure for the Suzuki–Miyaura Coupling of β,β-Diarylvinylboronate Esters with Alkyl Bromides

A mixture of $Pd(OAc)_2$ (3.4 mg, 15 μmol, 5 mol%), $P(t\text{-}Bu)_2Me$ (4.8 mg, 30 μmol, 10 mol%), NaOH (36.0 mg, 0.90 mmol), **2c** (0.30 mol, 109.9 mg), and 3-phenylpropyl bromide (0.60 mmol, 119.5 mg) in dry dioxane (1.5 mL) was stirred vigorously at 60 °C for 24 h. After cooling the reaction mixture to r.t., catalyst and salts were removed by filtration through a short silica gel pad (EtOAc). The filtrate was evaporated, and the residue was subjected to silica gel chromatography (hexane–EtOAc = 20:1) to afford **3cg** (101.6 mg, 94%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (t, *J* = 8.0 Hz, 2 H), 2.17 (td, *J* = 7.6, 7.2 Hz, 2 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 5.94 (t, *J* = 7.2 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.11–7.16 (m, 5 H), 7.23 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 32.0, 35.6, 55.27, 55.32, 113.3, 113.4, 125.5, 127.6, 128.1, 128.2, 128.3, 130.9, 132.6, 135.8, 140.8, 142.3, 158.2, 158.5. HRMS (EI): *m/z* calcd for $C_{25}H_{26}O_2$: 358.1933; found: 358.1931.

Acknowledgment

This work was financially supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. K.T. is a recipient of the JSPS Predoctoral Fellowships for Young Scientists.

References

(1) Trisubstituted olefin synthesis using vinyl(2-pyridyl)silane or vinyl(2-pyrimidyl)silane as a platform: (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (b) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3695. (c) Itami, K.; Ohashi, Y.; Yoshida, J. *J. Org. Chem.* **2005**, *70*, 2778. See also: (d) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (e) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600.

(2) Trisubstituted olefin synthesis using vinylboronate pinacol ester as a platform: Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 4093.

(3) Tetrasubstituted olefin synthesis using vinyl 2-pyrimidyl sulfide as a platform: Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778.

(4) Tetrasubstituted olefin synthesis using alkynyl(2-pyridyl)silane as a platform: (a) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (b) Kamei, T.; Itami, K.; Yoshida, J. *Adv. Synth. Catal.* **2004**, *346*, 1824.

(5) Review on Mizoroki–Heck reaction: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(6) Mizoroki–Heck reaction of vinylboronate ester: (a) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599. (b) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293. (c) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3925. (d) Hénaff, N.; Whiting, A. *Tetrahedron* **2000**, *56*, 5193. (e) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999. (f) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645.

(7) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**. (b) *Cross-Coupling Reactions*; Miyaura, N., Ed.; Springer: New York, **2002**.

(8) N'Goka, V.; Stenbøl, T. B.; Krogsgaard-Larsen, P.; Schlewer, G. *Eur. J. Med. Chem.* **2004**, 889.

(9) (a) Casimiro-Garcia, A.; Micklatcher, M.; Turpin, J. A.; Stup, T. L.; Watson, K.; Buckheit, R. W.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 4861. (b) Xu, G.; Micklatcher, M.; Silvestri, M. A.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Buckheit, R. W. Jr.; Cushman, M. *J. Med. Chem.* **2001**, *44*, 4092. (c) Silvestri, M. A.; Nagarajan, M.; Clercq, E. D.; Pannecouque, C.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 3149.

(10) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.