ORGANIC LETTERS

2013
Vol. 15, No. 13
3294–3297

Synthesis of Multisubstituted Olefins through Regio- and Stereoselective Silylborylation of an Alkynylboronate/Chemoselective Cross-Coupling Sequences

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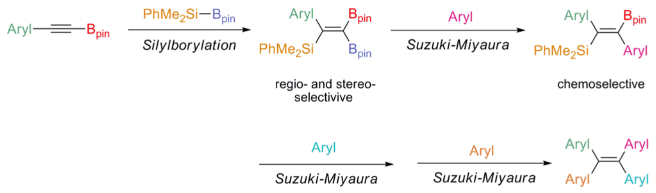
Received May 13, 2013

ABSTRACT



A highly regio- and stereoselective silylborylation of an alkynylboronate is disclosed. $PhMe_2Si{-}B_{pin}$ undergoes a $Pd(OAc)_2/^tOctNC$-catalyzed *syn*-addition to the alkynylboronate to yield 1-phenyl-1-silyl-2,2-diborylethene with high regioselectivity. The product 1-phenyl-1-silyl-2,2-diborylethene is then chemoselectively arylated by Suzuki–Miyaura coupling to afford (*Z*)-1-silyl-2-borylstilbene derivatives. This approach is extended to the synthesis of a tetraarylated olefin with four different substituents.

The regio- and stereodefined synthesis of multisubstituted olefins is one of the most challenging goals in synthetic organic chemistry. Owing to their interesting photophysical and redox properties, tetraarylethenes are interesting functional materials and their ring-substituted analogues are valuable synthetic targets in materials science.[1] Moreover, since the reported procedures are mainly limited to the preparation of symmetrical tetraarylethenes via homocoupling reactions of diaryldiazomethanes,[2] diaryldichloromethanes,[3] diaryl thioketones,[4] and diaryl ketones,[5] the development of a general method for the synthesis of unsymmetrically substituted tetraarylated olefins, preferably with four different aryl groups, has been a valuable target for organic chemists.[6]

We envisaged that a combination of transition-metal-catalyzed silylborylation[7−9] of unsymmetrical internal alkynes with cross-coupling reactions could provide a straightforward synthetic entry for various tetraarylethenes. However, silylborylation of unsymmetrical internal alkynes, e.g. 1-phenyl-1-propyne, was reported to decrease the regioselectivity obviously while the use of unsymmetrical diarylethynes[10] as the substrates is readily

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(1) For example: (a) Schultz, A.; Diele, S.; Laschat, S.; Nimtz, M. *Adv. Funct. Mater.* **2001**, *11*, 441. (b) Verkerk, U.; Fujita, M.; Dzwiniel, T. L.; McDonald, R.; Stryker, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 9988.

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(3) Hill, D. H.; Parvez, M. A.; Sen, A. *J. Am. Chem. Soc.* **1994**, *116*, 2889.

(4) Alper, H.; Ripley, S.; Prince, T. L. *J. Org. Chem.* **1983**, *48*, 250.

(5) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.

(6) Recent successful synthesis of tetraarylated olefins: (a) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765. (c) Tsuji, H.; Ueda, Y.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 11854.

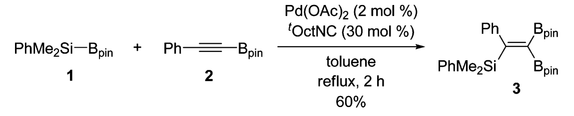
10.1021/ol401333j

anticipated to form a mixture of the regioisomers, which limits a diversity of regio- and stereospecific silylborylated olefins.[7d]

In this communication, we report a novel synthetic protocol for the preparation of tetrasubstituted olefins, especially for tetraarylated analogues with four different aryl groups, using the palladium-catalyzed silylborylation of alkynylboronates,[11] to yield 1-phenyl-1-silyl-2,2-diborylated olefins with perfect regio- and stereoselectivities, followed by chemoselective Suzuki–Miyaura coupling[12] to deliver (*Z*)-1-silyl-2-borylstilbene motifs. Because the reagents are readily available and the operations are simple, this synthetic strategy proves more selective and tolerant than those previously reported.

According to a report in 1999,[7d] in the presence of the *in situ* generated palladium(0)–isonitrile complex, the reaction of the silylborane **1** with the alkynylboronate **2** took place in refluxing toluene (Scheme 1; B_{pin} is pinacolatoboryl). A catalytic amount of $Pd(OAc)_2$ (2 mol %) and 1,1,3,3-tetramethylbutyl isonitrile (^{t}OctNC) (30 mol %) efficiently gave rise to the silylborylation product **3** in 60% yield as a single isomer. However, the reaction did not proceed smoothly at lower temperatures with decreased yields being obtained (17% yield at 50 °C). $Pd(OAc)_2$ in conjunction with cyclohexyl isonitrile (CyNC) likewise gave a poor yield (19%). In addition, phosphine and phosphite ligands could not generate an efficient Pd catalyst for the reaction.

Scheme 1. Regio- and Stereoselective Silylborylation of **2**



The stereochemistry of the adduct **3** was confirmed by X-ray crystallographic analysis.[13,14] Thus, silylborylation was found to take place regio- and stereoselectively with the silyl moiety geminal to the phenyl group. Although the similar 1,1-diboryl-1-alkenes have been prepared by *gem*-diborylation of 1,1-dibromo-1-alkenes with ^{n}BuLi/bis(pinacolato)diboron[15] or ketone addition of tris(pinacolato)borylmethyllithium,[16] to the best of our knowledge, there are no known examples of the silylated 1,1-diboryl-1-alkenes, and they would be difficult to synthesize under basic conditions due to desilylation.

A possible catalytic cycle forming **3** is proposed to explain the observed regioselectivity. This proposed cycle is presented in Scheme 2. We propose that silylborane **1** oxidatively adds to the Pd(0) catalyst to generate the Pd(II) species **A**. Intermediate **A** then undergoes migratory insertion, wherein alkynylboronate **2** inserts into the Pd–B bond (borylpalladation) to form **B**. Although the borylpalladation mechanism has been proposed as the result of theoretical studies,[8c,17] another possibility, silylpalladation, cannot be neglected. This selectivity is opposite to that observed for the analogous process with organozirconium species.[18] Finally, the adduct **3** is produced by reductive elimination, regenerating the Pd catalyst.

Since functional materials, natural products, and bioactive pharmaceuticals have all been synthesized with 1,1-diborylated olefins,[19,20] to further test the utility of this building block, compound **3** was successively subjected to Suzuki–Miyaura coupling with an equimolar amount of

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(14) CCDC-643360 (**3**), -643361 (**5a**), and -643362 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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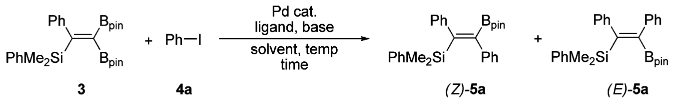
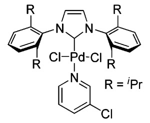
Table 1. Screening the Optimal Conditions of Chemoselective Suzuki–Miyaura Coupling[a]

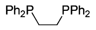


entry	Pd cat. (mol %)	ligand (mol %)	base	solvent	temp/°C	time/h	isolated yield/% (Z:E)[b]
1	$Pd(dba)_2$ (5)	$[HP^tBuMe_2]BF_4$ (20)	KOH	THF	rt	12	0
2	$Pd(PPh_3)_4$ (10)	--	KOH aq.	dioxane	70	12	24 (96:4)
3	$Pd(PPh_3)_4$ (20)	--	KOH aq.	THF	rt	12	38 (92:8)
4	PEPPSI-IPr (5)	--	KOH aq.	toluene	50	12	55 (92:8)
5	PEPPSI-IPr (10)	--	KOH aq.	THF	rt	3	59 (75:25)
6	Pd_2dba_3•$CHCl_3$ (5)	P^tBu_3 (20)	KOH aq.	THF	rt	3	76 (75:25)
7	Pd_2dba_3•$CHCl_3$ (5)	P^tBu_3 (20)	Cs_2CO_3 aq.	THF	rt	12	64 (92:8)
8	$PdCl_2(NCPh)$ (10)	dppe (20)	KOH aq.	THF	rt	12	60 (86:14)
9	$PdCl_2(NCPh)$ (10)	dppbz (20)	KOH aq.	THF	rt	12	27 (>99:1)
10	$PdCl_2(NCPh)$ (10)	1,8-dppn (20)	KOH aq.	THF	rt	12	64 (85:15)
11	$PdCl_2(NCPh)$ (10)	Xantphos (20)	KOH aq.	THF	rt	12	41 (86:14)
12	**$PdCl_2(dppf)$ (5)**	**--**	**KOH aq.**	**THF**	**rt**	**3**	**85 (88:12)**

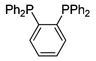
[a] Reaction conditions: **3** (0.1 mmol), **4a** (0.1 mmol), Pd cat./ligand, base (0.3 mmol), solvent (1 mL). [b] Isolated yield of the isomeric mixture, the Z:E ratios were determined by the ^1H NMR spectra.



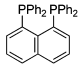
PEPPSI-IPr



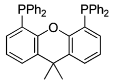
dppe



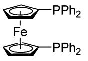
dppbz



1,8-dppn

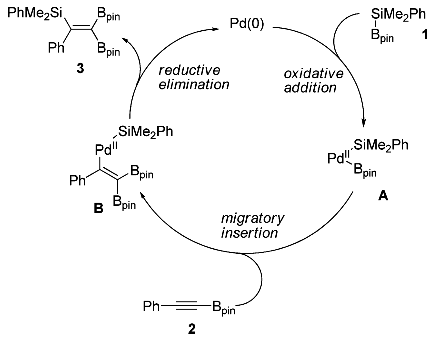


Xantphos



dppf

Scheme 2. A Plausible Mechanism of Silylborylation of an Alkynylboronate **2**



iodobenzene (**4a**) to ascertain whether the first coupling would be chemoselective. Various palladium catalysts and ligands were tested, and the results obtained are listed in Table 1. A combination of $Pd(dba)_2$ with the $[HP^tBuMe_2]BF_4$ salt, which had proven to be the best catalyst for the Suzuki–Miyaura coupling reaction of alkenylboronates with alkyl bromides,[12b] was found to be suboptimal for the present reaction due to desilylation of **3**. $Pd(PPh_3)_4$ also exhibited lower reactivity (entries 2 and 3). PEPPSI-IPr[21] and $Pd_2dba_3\cdot CHCl_3/P^tBu_3$ proved more reactive and afforded a relatively higher yield, albeit with reduced chemoselectivity (entries 4 and 5). An initial survey demonstrated that aqueous KOH accelerated the reaction. Palladium catalysts with monodentate ligands were not particularly efficient.

Therefore, several representative bidentate ligands were examined (entries 8–12). We were delighted to find that $PdCl_2(dppf)$[22] performed significantly better (entry 12). Although all the examined catalysts gave rise to the coupling product **5a** as a mixture of stereoisomers, the isomeric mixture was separated by silica gel column chromatography. The *Z*-geometry of the major isomer of product **5a** was confirmed by X-ray crystallographic analysis.[13,14] An authentic product (*E*)-**5a** was synthesized by silylborylation of diphenylethyne to provide comparator NMR data,[13] and this was indeed distinct from that of (*Z*)-**5a**. This observed chemoselectivity is consistent with that reported by Shimizu and Hiyama,[15a] wherein the C–C bond formation at the cis position of the alkyl groups was observed in the reaction of 1,1-diboryl-1-alkene with aryl iodides. The C–C bond at the cis position of the $SiMe_2Ph$ group was formed with moderate discrimination of two geminal boryl groups in **3**. Considering the conformational energies (*A*-values) of the Ph (2.8) and $SiMe_2Ph$ (2.5–2.8) groups,[23] the chemoselectivity cannot be explained simply by a steric effect. From the viewpoint of electronic demands, the ^{11}B NMR spectrum of **3** showed an overlapped signal at 29.9 ppm, indicating that the two boryl groups are electronically similar. Thus, at present, the reason why the two boryl groups in **3** are discriminated remains unclear.

After optimizing the reaction conditions for the chemoselective Suzuki–Miyaura coupling of **3**, a series of aryl

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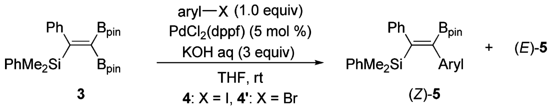
Table 2. Chemoselective Suzuki–Miyaura Coupling of **3** with Aryl Iodides **4** or Aryl Bromides **4′**[a]



entry	aryl–X	**5**	yield (Z/E)[b]
1	Ph-I (**4a**)	**5a**	85 (88:12)
2[c]	Ph-Br (**4a′**)	**5a**	78 (87:13)
3	4-$MeOC_6H_4$-I (**4b**)	**5b**	87 (89:11)
4	2-$MeOC_6H_4$-I (**4c**)	**5c**	57 (92:8)
5	3-$MeOC_6H_4$-I (**4d**)	**5d**	83 (89:11)
6	4-MeC_6H_4-I (**4e**)	**5e**	92 (88:12)
7	4-$CF_3C_6H_4$-I (**4f**)	**5f**	57 (87:13)
8[c]	4-$CF_3C_6H_4$-Br (**4f′**)	**5f**	59 (85:15)
9	4- ClC_6H_4-I (**4g**)	**5g**	92 (88:12)
10	4- $EtO_2CC_6H_4$-I (**4h**)	**5h**	70 (86:14)

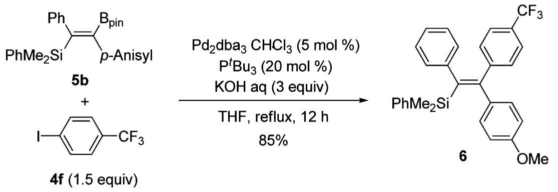
[a] Reaction conditions: **3** (245 mg, 0.5 mmol), **4** or **4′** (0.5 mmol), $PdCl_2$(dppf) (18 mg, 5 mol %), 3 M KOH solution (1.5 mmol, 0.5 mL) in THF (5 mL). [b] Isolated yields after silica gel column chromatography; Z/E ratios were determined by the ^1H NMR spectra. [c] The reaction time was 18 h.

iodides **4** were subjected to survey the reaction scope. 2-Iodoanisole (**4c**) afforded the desired product **5c** in moderate yield that we ascribe to a steric effect (entry 4). As shown in Table 2, it is noteworthy that some aryl bromides **4′** also gave moderate to good yields when the reaction time was extended to 18 h (entries 2 and 8). It is also notable that a chloro group in the substrate **4g** remained intact during the reaction with no trace of side product observed. Synthesis of compounds **5** would be impracticable via *anti*-silylborylation[7k] of unsymmetrical diarylethynes because the regioselectivity of the addition would not be controllable.

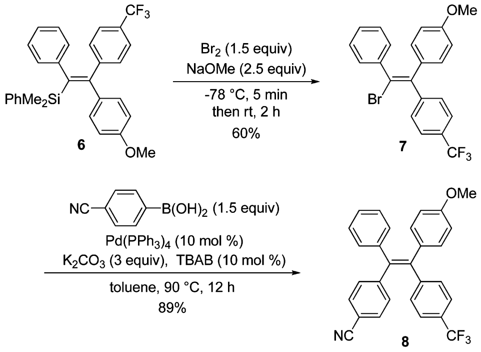
With a diverse range of reagents **5** in hand, we sequentially introduced an additional aryl group by Suzuki–Miyaura coupling of the remaining boron moiety. The triarylated alkenylsilane **6** was synthesized successfully by the reaction of (*Z*)-**5b** with **4f** in the presence of $Pd_2dba_3\cdot CHCl_3/P^tBu_3$ as the catalyst (Scheme 3).

Finally, we addressed the synthesis of a tetraarylated olefin **8** with four different aryl groups through sequential cross-couplings by utilizing the remaining silyl moiety. With Br_2 and NaOMe in MeOH,[24] the silyl group in **6** was successfully transformed to the corresponding bromide **7** along an inversion of stereochemistry. A sequential Suzuki–Miyaura coupling of **7** with 4-cyanophenylboronic acid then afforded the tetraarylated olefin **8** in 88% yield as a sole product whose structure was unambiguously confirmed by X-ray diffraction (Scheme 4).[13,14]

Scheme 3. Sequential Suzuki–Miyaura Coupling for Synthesis of Triarylated Alkenylsilane **6**



Scheme 4. Synthesis of Tetraarylated Olefin **8**



In summary, we have successfully developed a synthesis of tetraarylated olefins featuring a perfectly regio- and stereoselective silylborylation of the alkynylboronate and sequential chemoselective Suzuki–Miyaura couplings. This protocol can be applicable to a variety of functional groups on the aryl moieties, including those not compatible with the organolithium reagents required in previous approaches. Further studies to clarify the factors for the selectivity and to expand this synthetic method to a more general approach to the complicated π-conjugated molecules are in progress.

Acknowledgment. The authors gratefully thank Prof. Michinori Suginome (Kyoto University) for valuable discussions; Ms. Megumi Kosaka and Mr. Motonari Kobayashi at the Department of Instrumental Analysis, Advanced Science Research Center, Okayama University for the measurements of elemental analyses; and the SC-NMR Laboratory of Okayama University for the NMR measurements. Y.N. also acknowledges The Sumitomo Foundation.

Supporting Information Available. Copies of ^1H NMR and $^{13}C\{^1H\}$ NMR spectra for all the new compounds, as well as details on experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.