Catalytic Carbometalation/Cross-Coupling Sequence across Alkynyl(2-pyridyl)silanes Leading to a Diversity-Oriented Synthesis of Tamoxifen-Type Tetrasubstituted Olefins

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Received: July 10, 2004; Accepted: October 15, 2004

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A general synthetic scheme for tamoxifen-type tetrasubstituted olefins based on the novel Cu-catalyzed carbomagnesation across alkynyl(2-pyridyl)silane has been developed. A wide array of electronically and structurally diverse tetrasubstituted olefins can be prepared in a regiocontrolled, stereocontrolled, and diversity-oriented manner. Noteworthy features are that (i) the three aryl groups, which are believed to be important (essential) for anti-estrogenic activity, can be varied at will because they all stem from readily available aryl iodides, and (ii) any stereo- and regioisomers can, in principle, be prepared by simply changing the order use of the aryl iodides in the sequence.

Keywords: carbomagnesation; cross-coupling; directing effect; diversity-oriented synthesis; synthesis design; tamoxifen

Introduction

The regio- and stereoselective synthesis of multisubstituted olefins is one of the most challenging subjects in organic synthesis.[1] Since multisubstituted olefins are widespread found in pharmacologically important molecules, a general and diversity-oriented approach[2] toward such class of compounds is highly called for.[1f] Among such multisubstituted olefins, we have been particularly interested in tamoxifen (Figure 1) and its derivatives.[3] Tamoxifen is the most important anti-breast cancer drug in clinical use and has the potential to be used as a chemopreventive breast cancer agent. It is a selective estrogen receptor modulator (SERM) with anti-estrogenic properties in the breast and estrogenic effects in tissues such as bone and the cardiovascular system. Its SERM profile makes it a valuable alternative to hormone replacement therapy, especially for women at high risk of endometrial cancer.

Although these aspects of tamoxifen have stimulated research for a superior and ideal SERM, rapid and systematic screenings have been hampered by the lack of a general and diversity-oriented synthetic scheme for tamoxifen-type tetrasubstituted olefins. In addition, insufficient stereoselectivity, which is often encountered with the widely used dehydration reaction[4] and McMurry coupling,[5] has been a bottleneck for rapid evaluation.[6] Alternative to these procedures, Miller has developed a stereoselective synthesis of tamoxifen (9 steps) using alkyne carbometalation as a key step.[7] Knochel has developed a similar carbometalation-based synthesis.[8] Armstrong has developed an alkyne diboration/cross-coupling sequence for the synthesis of tamoxifen derivatives.[9] However, new synthetic schemes that allow more flexible structural modifications of the aryl groups, which are believed to be important (essential) for anti-estrogenic activity, are still in high demand.

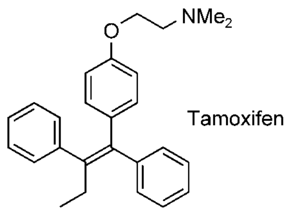
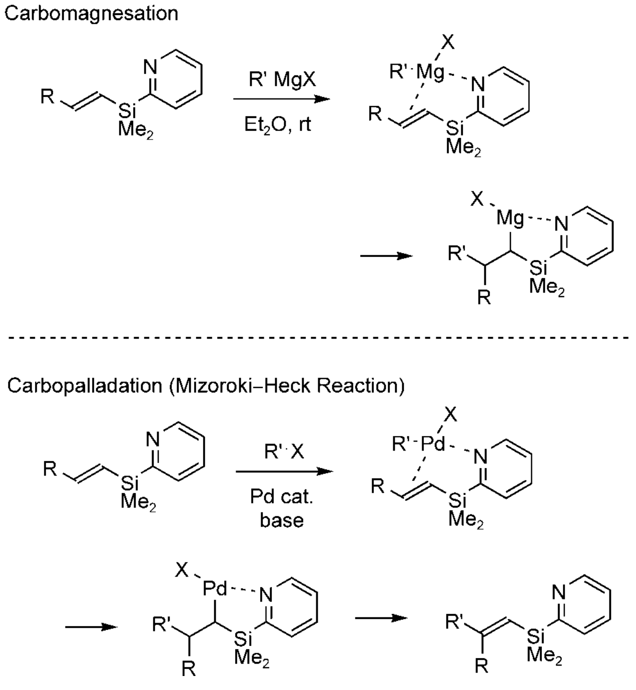


Figure 1. Structure of tamoxifen.

Background: Pyridylsilyl-Directed Organometallic Reactions

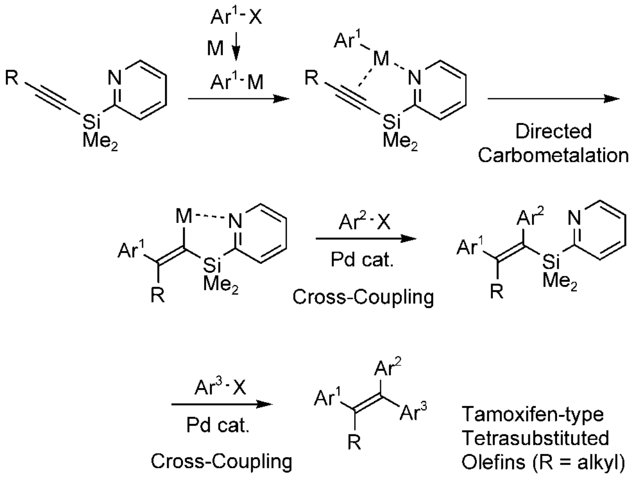
During the last few years, we have been particularly interested in the utilization of the dimethyl(2-pyridyl)silyl group (2-PyMe$_2$Si group) as a "removable directing

DOI: 10.1002/adsc.200404220



Scheme 1. Directed carbomagnesation and carbopalladation across alkenyl(2-pyridyl)silanes.

group" in metal-catalyzed[10] and -mediated[11] processes for enhancing the total efficiency of chemical reactions.[12,13] In such a strategy, a range of reactions can be directed through the agency of the complex-induced proximity effect (CIPE),[14] yet the initial product can still be transformed into a variety of products with the removal of the directing group. In particular, our findings that a number of previously difficult carbometalation reactions could be achieved by utilizing alkenyl(2-pyridyl)silanes are of great interest (Scheme 1). For example, the addition of Grignard reagents (carbomagnesation) was found to proceed at room temperature.[11c] The facile addition of primary alkyl Grignard reagents to alkenylsilanes was realized for the first time. We also found that the Mizoroki–Heck reaction, which includes carbopalladation as a key elemental step, of alkenylsilanes is also facilitated by the pyridyl group on silicon.[10a] A "hard-to-achieve" double Mizoroki–Heck reaction was also realized by using vinyl(2-pyridyl)silane.[1f] A number of control experiments and X-ray crystal structure analysis supported our supposition that extremely facile and regioselective carbometalations are due to the strong complex-induced proximity effect of the pyridyl group on silicon, together with the inherent silicon α effect. In addition to its utility as a removable directing group, 2-PyMe$_2$Si group can also be used as a "phase tag"[15] and a "removable hydrophilic group"[16] enabling easy purification (acid/base extraction) and aqueous reaction, respectively.



Scheme 2. Our synthetic strategy for tamoxifen-type tetrasubstituted olefins using a directed carbometalation across alkynyl(2-pyridyl)silanes as a key step.

Directed Carbometalation Across Alkynyl(2-pyridyl)silanes: A Key Step Toward a Diversity-Oriented Synthesis of Tamoxifen-type Tetrasubstituted Olefins

As an extension of carbometalation across alkenyl(2-pyridyl)silanes and as a key step toward the development of a diversity-oriented synthesis of tamoxifen-type tetrasubstituted olefins, we envisaged that the addition of arylmetal compounds (Ar^1–M) across alkynyl(2-pyridyl)silanes would afford alkenylmetal compounds suitable for further transformations. We expected this addition to be regio- and stereoselective as in the cases using alkenyl(2-pyridyl)silanes through the agency of the complex-induced proximity effect of the pyridyl group on silicon. The sequential arylations at the C–M and C–Si bonds of the resultant pyridylsilyl-substituted alkenylmetal compound utilizing Pd-catalyzed cross-coupling reactions with aryl halides (Ar^2–X and Ar^3–X) would afford the targeted tamoxifen-type tetrasubstituted olefins. Since three aryl groups (Ar^1, Ar^2, and Ar^3), which are believed to be important (essential) for anti-estrogenic activity,[3] stem from readily available aryl halides, the synthesis would be sufficiently diversity-oriented. Moreover, any stereo- and regioisomers can, in principle, be prepared by simply changing the order of application of the aryl halides in the sequence.[17]

Results and Discussion

Aryl Groups Installed into Tamoxifen-Type Tetrasubstituted Olefin Structure in this Study

By following the synthetic sequence described in Scheme 2, we succeeded in installing a number of aryl

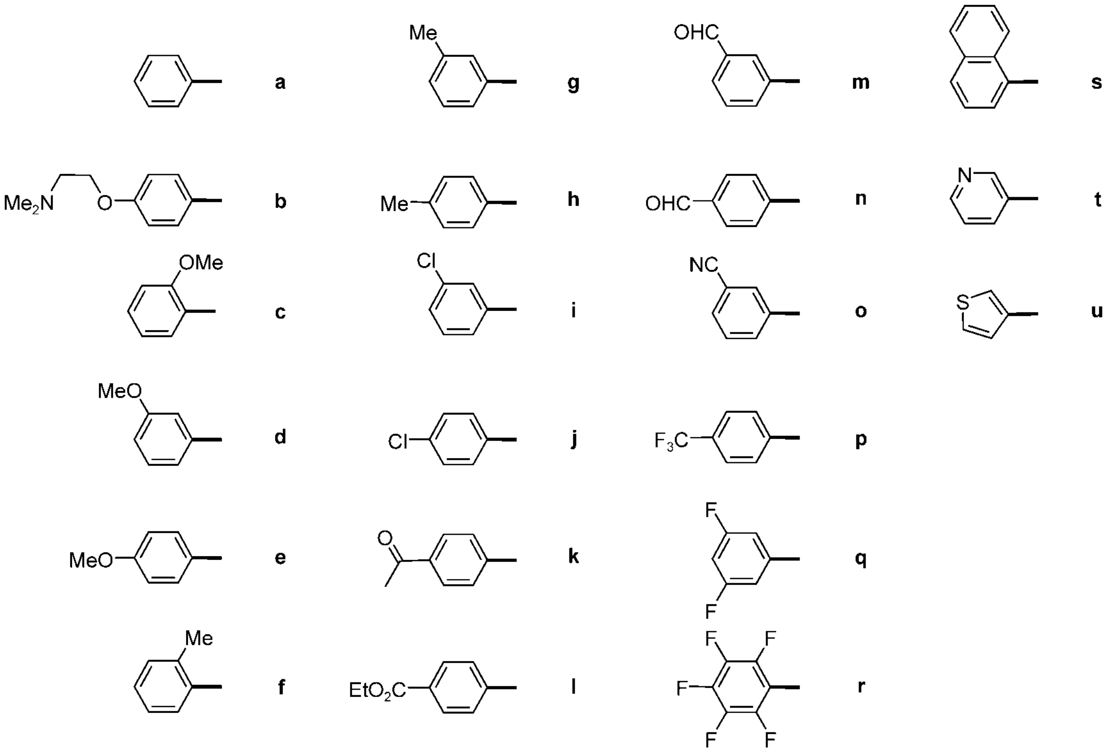


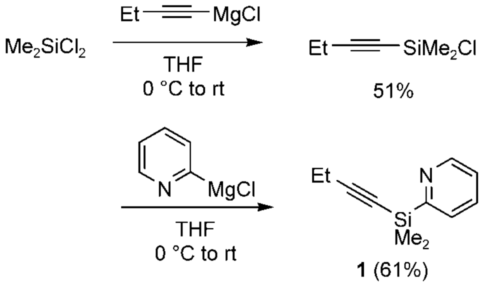
Figure 2. Aryl and heteroaryl groups used in this study.

and heteroaryl groups in the targeted tamoxifen-type tetrasubstituted olefin structure. The following 21 groups were successfully installed in this study (Figure 2). For simplicity, we assigned them alphabetically as follows and used them in compound assignment.

Copper-Catalyzed Carbomagnesation across Alkynyl(2-pyridyl)silanes

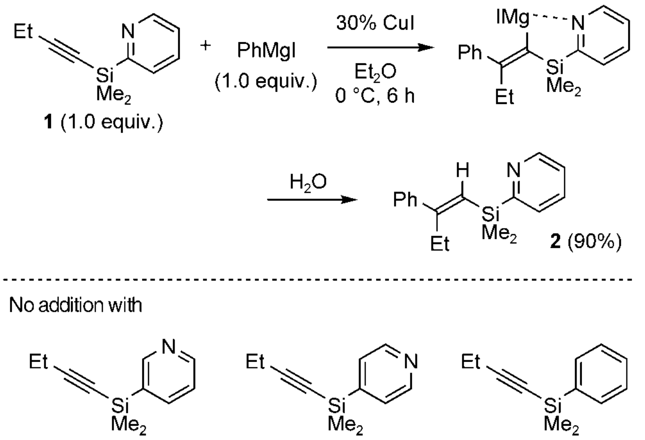
As an alkynylsilane platform for the tamoxifen-type tetrasubstituted olefin synthesis, we selected (1-butynyl)dimethyl(2-pyridyl)silane (**1**) which can be prepared by the consecutive treatment of 1-butynylmagnesium chloride and 2-pyridylmagnesium chloride with dichlorodimethylsilane (Scheme 3). This method can be used for the synthesis of other alkynyl(2-pyridyl)silanes in the synthesis of tamoxifen-type tetrasubstituted olefins bearing various alkyl side chains.

With the requisite platform in hand, we examined the addition of organometallic reagents (carbometalation) to (1-butynyl)dimethyl(2-pyridyl)silane (**1**). To our surprise, however, representative organometallic reagents including Grignard reagents and organozinc reagents did not give the corresponding addition products.[18] Therefore, we screened various organometallics and metal catalysts that accomplish a carbometalation across **1** and found that the use of PhMgI in combination with CuI catalyst effects the desired transformation.[19] Thus, in the presence of a catalytic amount of CuI (30 mol %), the regio- and stereoselective addition of PhMgI (1.0 equiv.) to **1** (1.0 equiv.) took place at 0 °C in Et_2O to afford **2** in 90% yield after aqueous workup (Scheme 4). The use of PhMgBr, PhMgCl, or Ph_2Mg in place of PhMgI resulted in a lower efficiency of the addition.[20] In addition, we found that the use of 3-pyridyl-, 4-pyridyl-, and phenyl(1-butynyl)silanes instead of **1** resulted in no addition. These results clearly implicate the strong directing effect (complex-induced proximity effect) of the 2-pyridyl group on silicon in the alkynylsilane structure to achieve this Cu-catalyzed carbomagnesation reaction (Scheme 4).[21]



Scheme 3. Synthesis of (1-butynyl)dimethyl(2-pyridyl)silane (**1**).

During these investigations, we found that the amount of CuI employed has a substantial influence on the efficiency of carbomagnesation. The results using varied amounts of CuI (0 ~ 100 mol %) in the reaction of **1**



Scheme 4. Cu-catalyzed carbomagnesation across (1-butynyl)dimethyl(2-pyridyl)silane (**1**).

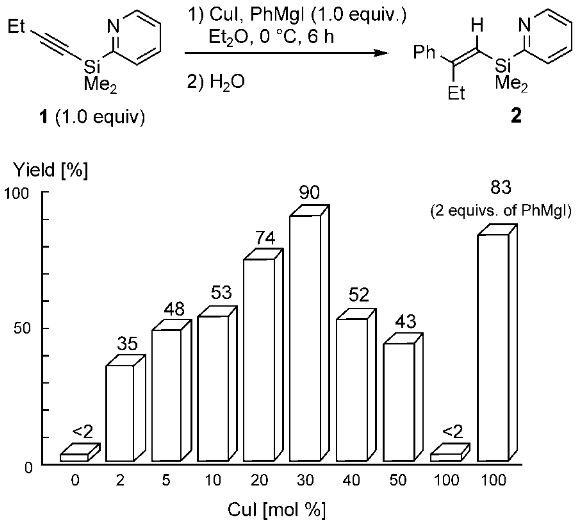


Figure 3. The effect of catalyst loading of CuI.

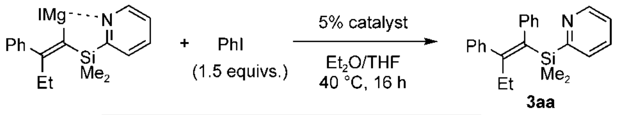
(1.0 equiv.) and PhMgI (1.0 equiv.) are shown in Figure 3. The addition did not occur in the absence of CuI as already mentioned. The yield of **2** increased with increasing amount of CuI, reaching a maximum yield (90%) when employing 30 mol % based on **1** and PhMgI. However, further increases of employed CuI resulted in lower yields of **2**. In particular, the reaction using an equimolar amount of CuI resulted in no addition, which suggests that the carbometalation does not proceed through organocopper species but rather through organocuprate species. In line with this assumption, the adduct **2** was obtained in 83% yield even when using an equimolar amount of CuI when 2.0 equivs. of PhMgI were employed.

Pd-Catalyzed Cross-Coupling Reaction of Carbomagnesation Products with Aryl Halides

With the feasibility of an initial carbometalation process, we next examined the one-pot diarylation of **1** through the catalytic carbomagnesation/cross-coupling sequence. Thus, the Tamao–Kumada–Corriu-type[22] cross-coupling reaction of an alkenylmagnesium compound (carbomagnesation product derived from **1** and PhMgI) with iodobenzene was first examined using various Ni and Pd complexes (Table 1). All reactions were performed by adding a THF solution of catalyst (5 mol %) and iodobenzene (1.5 equivs.) to a solution of the alkenylmagnesium compound obtained by the CuI-catalyzed reaction of **1** and PhMgI, and the resultant mixture was stirred at 40 °C for 16 h unless otherwise stated. The use of $NiCl_2(PPh_3)_2$ resulted in the production of the diphenylated compound **3aa** in good yield (76%), but the stereoselectivity ($E/Z = 81/19$) was somewhat disappointing (run 1). The two phenyl groups are introduced in a *cis* fashion, which is in accordance with *syn* carbometalation and retention of stereochemistry during the subsequent cross-coupling. Currently, we assume that the *Z* isomer of **3aa**, which is formed as a minor product, is derived from the isomerization of alkenylmagnesium intermediate.[23] Interestingly, $NiCl_2$(dppe) was found not to promote this cross-coupling presumably reflecting the steric hindrance of the alkenylmagnesium compound (run 2). Palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ also promoted the cross-coupling, but the yield and stereoselectivity were somewhat lower than those achieved with the nickel catalyst (runs 3 and 4). After further investigation, it was found that $Pd[P(t\text{-Bu})_3]_2$[24] was the most effective catalyst for this cross-coupling to afford **3aa** in high yield and stereoselectivity (80% yield, $E/Z = 92/8$) (run 5). Although **3aa** could be obtained with virtually complete stereoselectivity ($E/Z = >99/1$) when the cross-coupling step was performed at room temperature with this catalyst, the low chemical yield (52%) became problematic (run 6). Thus, we set the conditions described in run 5 as the standard conditions for the catalytic one-pot diarylation of **1**.

The beneficial effect of $P(t\text{-Bu})_3$ ligand may be worthy of note. Recently, there have been numerous reports that the use of the $P(t\text{-Bu})_3$ ligand gives rise to beneficial effects in Pd-catalyzed cross-coupling reactions, in which the electron-richness and steric-bulkiness of $P(t\text{-Bu})_3$ are believed to accelerate the oxidative addition step and the reductive elimination step, respectively.[24,25] However, we assume that the beneficial effect of the $P(t\text{-Bu})_3$ ligand observed here is somewhat different from those mentioned above. We suppose that the steric-bulkiness of $P(t\text{-Bu})_3$ ligand should render its dissociation from palladium in the Ph–Pd–I intermediate so as to make a coordination site required for the subsequent transmetalation (with sterically congested alkenylmagnesium compound) more easily. In this context, the use of bulky heterocyclic carbene ligands should shed some light because they are also known as elec-

Table 1. The effect of catalyst in Tamao–Kumada–Corriu-type cross-coupling of an alkenylmagnesium compound with iodobenzene.



Run	Catalyst	Yield (*E/Z*)
1	$NiCl_2(PPh_3)_2$	76% (81/19)
2	$NiCl_2(dppe)$	no reaction
3	$Pd(PPh_3)_4$	55% (62/38)
4	$PdCl_2(PPh_3)_2$	57% (81/19)
5	$Pd[P(t\text{-}Bu)_3]_2$	80% (92/8)
6[a]	$Pd[P(t\text{-}Bu)_3]_2$	52% (>99/1)
7	$Pd(OAc)_2$/IMes·HCl[b]	32% (94/6)

[a] The reaction was performed at room temperature.

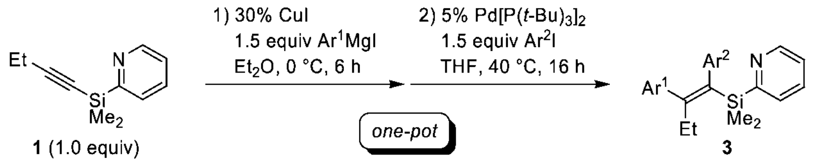
[b] IMes·HCl = *N,N'*-bis(2,4,6-trimethylphenyl)imidazoyl chloride.

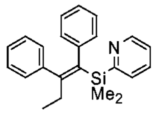
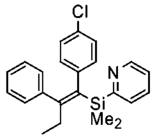
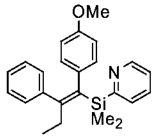
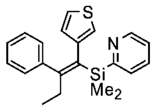
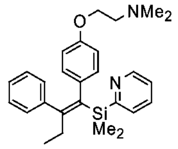
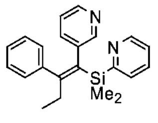
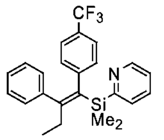
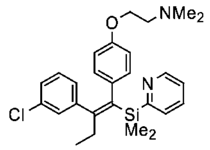
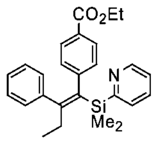
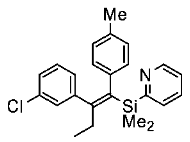
tron-rich and bulky ligands but are known not to dissociate from the metal easily.[26] We found that the use of the bulky carbene ligand IMes resulted in a substantial decrease in the coupling efficiency (run 7), which is in line with our assumption that the ligand dissociation is a key factor in this cross-coupling. The detrimental effect of a bidentate ligand (DPPE) also supports this notion.

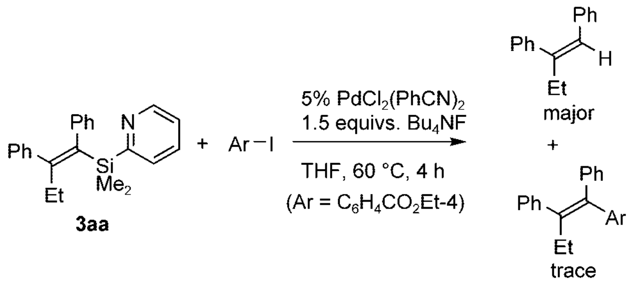
Catalytic One-Pot Diarylation of 1 with Arylmagnesium Iodides and Aryl Halides

With efficient catalysts for both carbomagnesation and cross-coupling in hand, we subsequently examined the synthesis of 1,2-diaryl-1-butenyl(2-pyridyl)silanes **3** through one-pot diarylation of **1** (Table 2). Thus, by simply varying Ar^1–MgI and Ar^2–I, we could obtain various structurally and electronically diverse alkenylsilanes **3**. In all cases examined, the stereoselectivities were high

Table 2. Synthesis of **3** by one-pot carbomagnesation/cross-coupling reaction of **1**..



run	Ar1	Ar2	product	3 yield (*E/Z*)	run	Ar1	Ar2	product	3 yield (*E/Z*)
1	a	a		**3aa** 80% (92/8)	6	a	j		**3aj** 69% (94/6)
2	a	e		**3ae** 60% (92/8)	7	a	u		**3au** 26% (96/4)
3	a	b		**3ab** 55% (88/12)	8	a	t		**3at** 31% (88/12)
4	a	p		**3ap** 75% (95/5)	9	i	b		**3ib** 55% (92/8)
5	a	l		**3al** 58% (94/6)	10	i	h		**3ih** 79% (92/8)



Scheme 5. The attempted installation of the third aryl group *via* Hiyama-type cross-coupling reaction of **3aa** with aryl halide.

($E/Z = 88/12 \sim 96/4$). The cross-coupling occurred efficiently with Ar^2–I having both electron-donating and -withdrawing groups. The aryl group containing the basic side chain found in tamoxifen can also be installed with ease (runs 3 and 9). Interestingly, the ester group in Ar^2–I also tolerated the conditions of this cross-coupling reaction (run 5). Unfortunately, heteroaromatic substrates, such as 3-iodopyridine and 3-iodothiophene, were found to be poor substrates in this reaction (runs 7 and 8).

Attempted Synthesis of Tetrasubstituted Olefins by Hiyama-Type Cross-coupling Reactions

Having established the procedure of stereoselective one-pot diarylation of **1**, the C–Si arylation of the resultant **3** has remained as a final transformation toward tamoxifen-type tetrasubstituted olefins. Because we have already reported that the 2-pyridylsilyl group on C=C can be transformed into aryl groups by Hiyama-type silicon-based cross-coupling reactions[1f,10b,27] with aryl halides in the presence of a palladium catalyst and tetrabutylammonium fluoride, **3aa** and 4-iodobenzoic acid ethyl ester was subjected to our standard conditions [$PdCl_2(PhCN)_2$, Bu_4NF, THF, 60 °C]. Unfortunately, however, the reaction exclusively afforded the protodesilylation product of **3aa** with only a trace amount of the desired coupling product (Scheme 5). Since extensive screening of catalyst and activator to transfer these sterically condensed alkenyl groups from silicon met with no success, we turned our attention to the Si/B exchange reaction (borodesilylation) of **3** to achieve the installation of the third aryl group (Ar^3) by means of Suzuki–Miyaura coupling at the resulting C–B bond.[28]

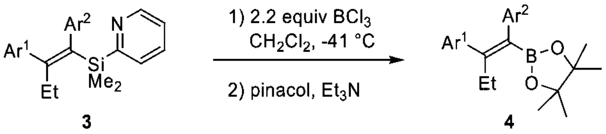
Synthesis of Alkenylboronate Esters 4 by the Borodesilylation of Alkenylsilanes 3

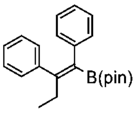
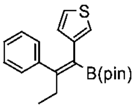
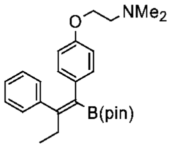
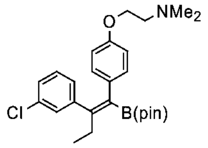
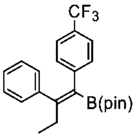
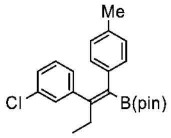
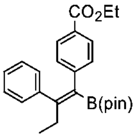
The stereoselective borodesilylation[29] was found to occur by treating alkenyl(2-pyridyl)silanes **3** with BCl_3 (2.2 equivs.) in CH_2Cl_2 at −41 °C, and subsequent treatment of this mixture with pinacol and triethylamine (one-pot) afforded alkenylboronate esters **4** in good yield with retention of stereochemistry (Table 3). For compounds bearing the tamoxifen basic side chain ($Me_2NCH_2CH_2O$-) such as **3ab** and **3ib**, it was necessary to add 3.3 equivs. of BCl_3 for borodesilylation and to treat the resultant mixture (after quenching with pinacol) with a base such as Cs_2CO_3 to remove a boron residue coordinated to the nitrogen (runs 2 and 6). Interestingly it was found that the isomeric purities of **4** were greater than those of the starting alkenylsilanes in all cases examined except the reaction of **3au** ($96/4 \rightarrow 95/5$). This may be due to the reactivity differences of isomeric alkenylsilanes in borodesilylation.

Synthesis of Tamoxifen-Type Tetrasubstituted Olefins 5 by Suzuki–Miyaura Coupling of 4 and Aryl Halide

Finally, the Suzuki–Miyaura coupling of alkenylboronate esters **4** with aryl halides was investigated for the synthesis of targeted tamoxifen-type tetrasubstituted olefin **5**. At the outset, the examination of catalyst and additive was performed using **4aa** and 4-iodotoluene as model substrates (Table 4, runs 1–4). When these substrates were subjected to $Pd(PPh_3)_4$ and K_3PO_4 in THF at 60 °C, the tetrasubstituted olefin **5aah** was obtained in 66% yield together with the protodeboration product **6** (32%) (run 1). After extensive screening of Pd catalysts, the use of $Pd[P(t\text{-}Bu)_3]_2$, which was demonstrated as a good catalyst for Suzuki–Miyaura coupling by Fu,[24a] in combination with K_3PO_4 or Cs_2CO_3 resulted in efficient coupling to afford **5aah** in 92% yield (runs 2 and 3). However, the use of KF, which was reported to be an efficient additive in combination with $Pd[P(t\text{-}Bu)_3]_2$,[24a] did not give the desired coupling product (run 4). Because it was found that the $Pd[P(t\text{-}Bu)_3]_2/Cs_2CO_3$ system gave tamoxifen (**5aba**) in much lower yield (54%) along with considerable amounts of the protodeboration product **6ab** (run 5), we reinvestigated additives suitable for compounds bearing the tamoxifen basic side chain ($Me_2NCH_2CH_2O$-) such as **4ab**. For these investigations, we initially used **4ab** with a *Z/E* ratio of 90/10 (runs 5–8). As is usual practice in Suzuki–Miyaura coupling chemistry, the addition of H_2O substantially improved the coupling efficiency (run 6). This may be due to the generation an Ar–Pd–OH intermediate that has been suggested to possess high reactivity toward subsequent transmetalation with an alkenylboronate ester.[28] The use of NaOH (with or without H_2O) in place of Cs_2CO_3 also resulted in improved coupling efficiency giving tamoxifen (**5aba**) in high yields and high stereoselectivities (runs 7 and 8). The protodeboration product **6ab** was not observed under these conditions. When **4ab** with *Z/E* ratio of 94/6 was subjected to the conditions described in run 8, tamoxifen (**5aba**) was obtained in 98% yield with 95% stereoselectivity

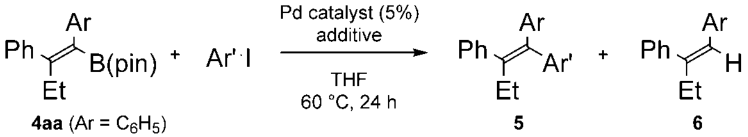
Table 3. Synthesis of alkenylboronate esters **4** by borodesilylation of alkenyl(2-pyridyl)silane **3**.



run	**3** (*E*/*Z*)	product	**4** yield (*Z*/*E*)	run	**3** (*E*/*Z*)	product	**4** yield (*Z*/*E*)
1	**3aa** (92/8)		**4aa** 82% (98/2)	5	**3au** (96/4)		**4au** 75% (95/5)
2[a]	**3ab** (88/12)		**4ab** 65% (94/6)	6[a]	**3ib** (92/8)		**4ib** 77% (95/5)
3	**3ap** (95/5)		**4ap** 80% (99/1)	7	**3ih** (92/8)		**4ih** 73% (97/3)
4	**3ae** (94/6)		**4ae** 64% (>99/1)				

[a] 3.3 equivs. of BCl_3 were employed. After the treatment with pinacol, the mixture was treated with Cs_2CO_3 (10 equivs.) in toluene (80 °C, 11 h).

Table 4. Screening of Pd catalyst and additives in Suzuki–Miyaura coupling of 1,2-diarylated alkenylboronate pinacol esters **4aa** and **4ab**.

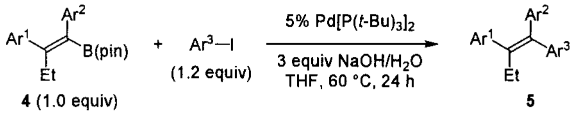


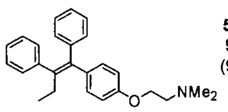
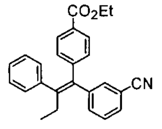
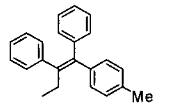
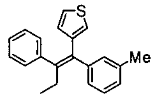
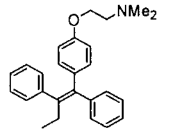
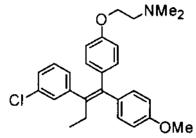
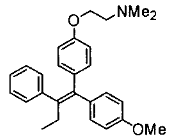
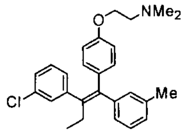
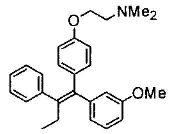
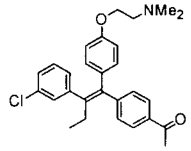
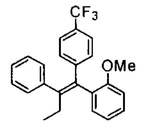
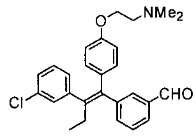
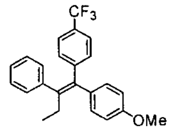
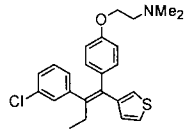
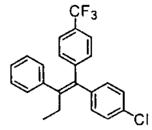
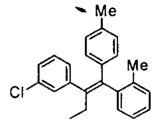
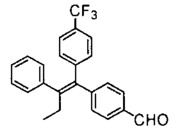
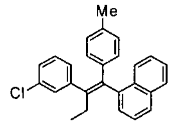
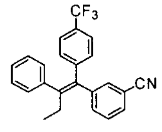
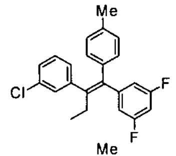
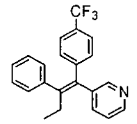
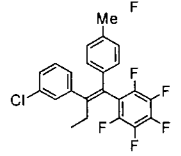
4aa (Ar = C_6H_5)
4ab (Ar = $C_6H_4OCH_2CH_2NMe_2$-4)
Ar' = C_6H_4Me-4 (for **4aa**), C_6H_5 (for **4ab**)

run	**4** (*Z*/*E*)	Pd catalyst	additive[a]	**5**	yield (*Z*/*E*)
1	**4aa** (98/2)	$Pd(PPh_3)_4$	K_3PO_4	**5aah**	66% (<1/99)[b]
2	**4aa** (98/2)	$Pd[P(t\text{-}Bu)_3]_2$	K_3PO_4	**5aah**	92% (<1/99)
3	**4aa** (98/2)	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3	**5aah**	92% (<1/99)
4	**4aa** (98/2)	$Pd[P(t\text{-}Bu)_3]_2$	KF	**5aah**	<2% (-)
5	**4ab** (90/10)	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3	**5aba**	54% (88/12)[c]
6	**4ab** (90/10)	$Pd[P(t\text{-}Bu)_3]_2$	Cs_2CO_3/H_2O	**5aba**	85% (91/9)
7	**4ab** (90/10)	$Pd[P(t\text{-}Bu)_3]_2$	NaOH	**5aba**	80% (91/9)
8	**4ab** (90/10)	$Pd[P(t\text{-}Bu)_3]_2$	$NaOH/H_2O$	**5aba**	86% (92/8)
9	**4ab** (94/6)	$Pd[P(t\text{-}Bu)_3]_2$	$NaOH/H_2O$	**5aba**	98% (95/5)

[a] 3.0 equivs. of additive were employed.
[b] **6aa** was obtained in 33% yield (*Z*/*E* = >99/1).
[c] **6ab** was obtained in 16% yield (*Z*/*E* = >99/1).

Table 5. Synthesis of tamoxifen-type tetrasubstituted olefins **5** by Suzuki–Miyaura coupling reaction of alkenylboronate esters **4** with aryl iodides.



run	4 (Z/E)	Ar3	product	5 yield (E/Z)	run	4 (Z/E)	Ar3	product	5 yield (E/Z)
1	**4aa** (97/3)	**b**		**5aab** 95% (99/1)	12	**4al** (>99/1)	**o**		**5alo** 35% (>99/1)
2	**4aa** (97/3)	**h**		**5aah** 96% (99/1)	13	**4au** (95/5)	**g**		**5aug** 97% (<1/99)
3	**4ab** (94/6)	**a**		**5aba** 98% (5/95)	14	**4ib** (95/5)	**e**		**5ibe** 80% (4/96)
4	**4ab** (94/6)	**e**		**5abe** 95% (5/95)	15	**4ib** (95/5)	**g**		**5ibg** 82% (98/2)
5	**4ab** (94/6)	**d**		**5abd** 92% (95/5)	16	**4ib** (95/5)	**k**		**5ibk** 42% (<1/99)
6	**4ap** (99/1)	**c**		**5apc** 95% (>99/1)	17	**4ib** (95/5)	**m**		**5ibm** 50% (96/4)
7	**4ap** (99/1)	**e**		**5ape** 97% (>99/1)	18	**4ib** (95/5)	**u**		**5ibu** 87% (99/1)
8	**4ap** (99/1)	**j**		**5apj** 90% (>99/1)	19	**4ih** (97/3)	**f**		**5ihf** 93% (>99/1)
9	**4ap** (99/1)	**n**		**5apn** 59% (>99/1)	20	**4ih** (99/1)	**s**		**5ihs** 99% (>99/1)
10	**4ap** (99/1)	**o**		**5apo** 56% (>99/1)	21	**4ih** (99/1)	**q**		**5ihq** 98% (>99/1)
11	**4ap** (99/1)	**t**		**5apt** 67% (>99/1)	22	**4ih** (97/3)	**r**		**5ihr** 45% (93/7)

(run 9). Thus, we set the conditions described in run 9 as the standard conditions for the final Suzuki–Miyaura coupling of alkenylboronate esters **4**.

With optimized conditions for the final Suzuki–Miyaura coupling in hand, the alkenylboronate esters **4** prepared were cross-coupled with various aryl iodides (Table 5). Although aryl bromides can also be employed in this cross-coupling, we used aryl iodides in this study because they usually gave better results in our system. Thus, in the presence of $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), NaOH (3.0 equivs.), and H_2O (3.0 equivs.), the cross-coupling of alkenylboronate esters **4** (1.0 equiv.) proceeded with aryl iodides (1.2 equivs.) in THF at 60 °C to afford tamoxifen-type tetrasubstituted olefins **5**. The yields are generally very high and a variety of aryl groups including heteroaryl groups can be installed in the final tetrasubstituted olefin structure with ease. Unfortunately, however, the cross-couplings using aryl iodides bearing functional groups sensitive to strong base were somewhat low-yielding (runs 9, 10, 12, 16, and 17). It should also be mentioned that this final cross-coupling step also helped to increase the isomeric purities of the final olefins **5** (> 99% in most cases) presumably because of the reactivity difference of isomeric **4** in cross-coupling reaction.

Conclusion

In conclusion, we have established a general synthetic scheme for tamoxifen-type tetrasubstituted olefins based on a catalytic carbometalation/cross-coupling sequence across alkynyl(2-pyridyl)silanes. Copper catalysis as well as the strong directing effect of the 2-pyridyl group on silicon were revealed in the initial alkyne carbomagnesation. By employing a Pd catalyst and aryl iodides in the solution of alkenylmagnesium compounds generated by the Cu-catalyzed carbomagnesation of 1-butynyldimethyl(2-pyridyl)silane (**1**), a regio- and stereoselective installation of two aryl groups onto **1** was achieved in one-pot (**1** → **3**). Although direct C–Si arylation of the resultant alkenylsilanes **3** was not feasible, we developed a borodesilylation/cross-coupling sequence of **3** to achieve the installation of the third aryl group at C–Si bonds yielding the targeted tamoxifen-type tetrasubstituted olefins **5**. With this synthetic scheme in hand, a wide array of electronically and structurally diverse tetrasubstituted olefins can be prepared in a regiocontrolled, stereocontrolled, and diversity-oriented manner. Noteworthy features of our synthesis are that (i) the three aryl groups, which are believed to be important (essential) for anti-estrogenic activity, can be varied at will because they all stem from readily available aryl iodides, and (ii) any stereo- and regioisomers can, in principle, be prepared by simply changing the order of application of the aryl iodides in the sequence. Although we have focused our investigation on the synthesis of tamoxifen-type olefins in this study, our synthetic scheme should be easily expandable to the construction of more general tetrasubstituted olefin structures.

Experimental Section

General Remarks

^1H and ^{13}C NMR spectra were recorded on Varian GEMINI-2000 (^1H 300 MHz, ^{13}C 75 MHz), Varian MERCURY plus (^1H 400 MHz, ^{13}C 100 MHz), and JEOL A-500 (^1H 500 MHz, ^{13}C 125 MHz) spectrometers in $CDCl_3$. EI mass spectra were recorded on a JMS-SX102A spectrometer. FAB mass spectra were recorded on a JMS-HX110A spectrometer. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. $Pd[P(t\text{-}Bu)_3]_2$ was purchased from Strem Chemicals, Inc. and used as received. The characterization data for compounds **3**, **4**, and **5** are described in the Supporting Information.

1-Butynyldimethyl(2-pyridyl)silane (1)

To a solution of dichlorodimethylsilane (25.9 g, 200 mmol) in dry Et_2O (200 mL) was added a solution of 1-butynylmagnesium chloride (100 mmol, 1.18 M) in THF at 0 °C. After stirring the mixture at room temperature for 12 h, dry hexane (100 mL) was added. Filtration, removal of solvents, and subsequent distillation afforded 1-butynyl(chloro)dimethylsilane as a colorless liquid; yield: 7.53 g (51%); bp 67–68 °C/55 mmHg. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.53$ (s, 6H), 1.15 (t, $J = 7.2$ Hz, 3H), 2.27 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 3.8$, 13.2, 13.5, 80.0, 111.6; IR (neat): $\nu = 2979$, 2180, 1314, 1256, 1044 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_6H_{11}SiCl$: 146.0319; found: 146.0316.

To a solution of 2-bromopyridine (15.8 g, 100 mmol) in dry THF (100 mL) was added a solution of isopropylmagnesium chloride (100 mmol, 1.88 M) in THF at room temperature, and the mixture was stirred for 3 h. The resultant solution of 2-pyridylmagnesium chloride was added to a solution of 1-butynyl(chloro)dimethylsilane (15.1 g, 103 mmol) in THF (100 mL) at 0 °C. After stirring the mixture at room temperature for 15 h, saturated aqueous $NaHCO_3$ (50 mL) was added to the mixture. The organic phase was separated and the aqueous phase was extracted with Et_2O (100 mL × 3). The combined organic phase was dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation afforded **1** as a colorless liquid; yield: 11.6 g (61%); bp 101–104 °C/7.0 mmHg. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.41$ (s, 6H), 1.15 (t, $J = 7.5$ Hz, 3H), 2.27 (q, $J = 7.5$ Hz, 2H), 7.17 (ddd, $J = 7.5$, 4.8, 1.5 Hz, 1H), 7.57 (td, $J = 7.5$, 1.5 Hz, 1H), 7.72 (dt, $J = 7.5$, 1.2 Hz, 1H), 8.73 (ddd, $J = 4.8$, 1.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -1.5$, 13.6 (two carbons), 80.8, 111.2, 122.9, 129.4, 134.1, 150.0, 165.4; IR (neat): $\nu = 2979$, 2176, 1576, 1417 cm^{-1}; HRMS (FAB): *m/z* calcd. for $C_{11}H_{16}NSi$ (MH^+): 190.1052; found: 190.1051.

1-Butynyldimethyl(3-pyridyl)silane

The title compound was prepared according to the procedure used for the preparation of **1**. Yield: 69%; bp 130–132 °C/6.4 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.42$ (s, 6H), 1.19 (t, $J = 7.5$ Hz, 3H), 2.30 (q, $J = 7.5$ Hz, 2H), 7.28 (ddd, $J = 7.5$, 4.8, 1.2 Hz, 1H), 7.91 (dt, $J = 7.5$, 1.8 Hz, 1H), 8.61 (dd, $J = 4.8$, 1.8 Hz, 1H), 8.80 (dd, $J = 1.8$, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -0.9$, 13.5, 13.6, 80.2, 111.8, 123.1, 132.5, 141.3, 150.2, 154.1; IR (neat): $\nu = 2979$, 2176, 1574, 1559, 1395 cm^{-1}; HRMS (EI): *m*/*z* calcd. for $C_{11}H_{15}NSi$: 189.0974; found: 189.0974.

1-Butynyldimethyl(4-pyridyl)silane

The title compound was prepared according to the procedure used for the preparation of **1**. Yield: 16%; bp 103–105 °C/2.4 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.39$ (s, 6H), 1.18 (t, $J = 7.5$ Hz, 3H), 2.29 (q, $J = 7.5$ Hz, 2H), 7.49 (dm, $J = 4.8$ Hz, 2H), 8.58 (dm, $J = 4.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -1.3$, 13.58, 13.61, 79.8, 112.0, 128.3, 147.6, 148.7; IR (neat): $\nu = 3054$, 2178, 1578, 1404 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{11}H_{15}NSi$: 189.0974; found: 189.0976.

1-Butynyldimethylphenylsilane

To a solution of chlorodimethylphenylsilane (5.1 g, 30 mmol) in dry THF (30 mL) was added a solution of 1-butynylmagnesium chloride (33 mmol, 2.00 M) in THF at 0 °C. After stirring the mixture at room temperature for 17 h and then at 70 °C (reflux) for 7 h, H_2O (20 mL) was added. The organic phase was separated and aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic phase was dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation afforded the title compound as a colorless liquid; yield: 3.74 g (66%); bp 97–99 °C/6.5 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.41$ (s, 6H), 1.20 (t, $J = 7.5$ Hz, 3H), 2.31 (q, $J = 7.5$ Hz, 2H), 7.35–7.42 (m, 3H), 7.62–7.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -0.6$, 13.6, 13.8, 81.4, 110.9, 127.8, 129.2, 133.6, 137.6; IR (neat): $\nu = 2979$, 2176, 1429 cm^{-1}; HRMS (EI): *m*/*z* calcd. for $C_{12}H_{16}Si$: 188.1021; found: 188.1020.

Typical Procedure of Cu-Catalyzed Carbomagnesation across 1 (Scheme 4)

To a suspension of 1-butynyldimethyl(2-pyridyl)silane (**1**; 66.6 mg, 0.35 mmol) and CuI (17.2 mg, 0.09 mmol) in dry Et_2O (0.6 mL) was added a solution of phenylmagnesium iodide (0.30 mmol, 1.20 M) in Et_2O at 0 °C. After stirring the mixture at 0 °C for 6 h, H_2O (1 mL) and 28% aqueous NH_3 (1 mL) were added to the mixture. The organic phase was separated and aqueous phase was extracted with EtOAc (2 mL × 3). Removal of the solvent under reduced pressure afforded the crude **2**. The yield was determined to be 90% by ^{1}H NMR analysis using 1,2-dichloroethene as an internal standard. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.52$ (s, 6H), 0.85 (t, $J = 7.5$ Hz, 3H), 2.60 (q, $J = 7.5$ Hz, 2H), 5.94 (s, 1H), 7.18–7.23 (m, 1H), 7.25–7.35 (m, 3H), 7.44 (dm, $J = 8.1$ Hz, 2H), 7.60 (dm, $J = 3.6$ Hz, 2H), 8.81 (ddd, $J = 4.5$, 1.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -1.6$, 13.7, 28.4, 122.7, 123.9, 126.3, 127.4, 128.1, 129.4, 134.0, 142.8, 150.1, 161.1, 167.7; IR (neat): $\nu = 2967$, 1593, 1574, 1418, 1246 cm^{-1}; HRMS (EI): *m*/*z* calcd. for $C_{17}H_{21}NSi$: 267.1443; found: 267.1442.

Typical Procedure of Catalytic One-Pot Diarylation of 1 (Table 2)

To a suspension of 1-butynyldimethyl(2-pyridyl)silane (**1**; 190.5 mg, 1.01 mmol) and CuI (57.0 mg, 0.30 mmol) in dry Et_2O (2 mL) was added a solution of phenylmagnesium iodide (Ar^1MgI; 1.50 mmol, 1.93 M) in Et_2O at 0 °C. After stirring the mixture for 6 h, a solution of 4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl iodide (Ar^2I; 435.8 mg, 1.50 mmol) and Pd[P(*t*-Bu)$_3$]$_2$ (25.2 mg, 0.05 mmol) in dry THF (2 mL) was added to the mixture. The resultant mixture was stirred at 40 °C for 16 h. After cooling the reaction mixture to room temperature, H_2O (*ca.* 10 mL) was added. The organic phase was separated and aqueous phase was extracted with $CHCl_3$ (10 mL × 3). The combined organic phase was washed with H_2O (10 mL × 2) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent silica gel chromatography ($CHCl_3$/MeOH/Et_3N = 100/10/1) afforded **3ab** as a pale yellow oil; yield: 236.1 mg (55%). The stereochemistry was determined to be 88% *E* by ^{1}H NMR analysis.

Typical Procedure of Borodesilylation of 3 (Table 3, Runs 1, 3, 4, 5, and 7).

To a solution of **3aa** (68.8 mg, 0.20 mmol, 92% *E*) in dry CH_2Cl_2 (0.5 mL) was added a solution of BCl_3 (0.44 mmol, 1.0 M) in CH_2Cl_2 at −41 °C. After stirring the mixture at −41 °C for 5 h, a solution of pinacol (136.9 mg, 1.16 mmol) and Et_3N (0.5 mL) in dry CH_2Cl_2 (0.5 mL) was added. After stirring the mixture at room temperature for 14 h, saturated aqueous $NaHCO_3$ (*ca.* 2 mL) was added to the mixture. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL × 3). The combined organic phase was dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent silica gel chromatography (hexane/EtOAc = 20/1) afforded **4aa** as a white solid; yield: 54.8 mg (82%). The stereochemistry was determined to be 98% *Z* by ^{1}H NMR analysis.

Typical Procedure of Borodesilylation of 3 Bearing the Aminoethoxy Side Chain (Table 3, Runs 2 and 6).

To a solution of **3ab** (1.26 g, 2.93 mmol, 88% *E*) in dry CH_2Cl_2 (10 mL) was added a solution of BCl_3 (9.90 mmol, 1.0 M) in CH_2Cl_2 at −41 °C. After stirring the mixture at −41 °C for 5 h, a solution of pinacol (3.65 g, 30.9 mmol) and Et_3N (5 mL) in dry CH_2Cl_2 (5 mL) was added. After stirring the mixture at room temperature for 3 h, Cs_2CO_3 (5.90 g, 18.1 mmol) and dry toluene (6 mL) were added to the mixture. The resultant mixture was stirred at 80 °C for 13 h. After cooling the mixture to room temperature, saturated aqueous $NaHCO_3$ (*ca.* 20 mL) was added to the mixture. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was dried over

$MgSO_4$. Removal of the solvent under reduced pressure and subsequent silica gel chromatography ($CHCl_3$/MeOH/Et_3N = 100/10/1) afforded **4ab** as a pale yellow oil; yield: 800.7 mg (65%). The stereochemistry was determined to be 94% *Z* by ^1H NMR analysis.

Typical Procedure of Suzuki–Miyaura Coupling of 4 with Aryl Iodide (Table 5).

To a solution of Pd[P(*t*-Bu)$_3$]$_2$ (5.2 mg, 0.01 mmol) in dry THF (0.2 mL) were added iodobenzene (Ar^3I; 49.0 mg, 0.24 mmol), a solution of **4ab** (84.3 mg, 0.20 mmol) in dry THF (0.4 mL), NaOH (24.5 mg, 0.61 mmol), H_2O (10.8 mg, 0.60 mmol), and dry THF (0.1 mL) at room temperature. The mixture was stirred at 60 °C for 24 h. After cooling the reaction mixture to room temperature, H_2O (*ca.* 1 mL) was added. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (2 mL × 3). The combined organic phase was dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent silica gel chromatography ($CHCl_3$/MeOH/Et_3N = 100/10/1) afforded **5aba** as a white solid; yield: 72.3 mg (98%). The stereochemistry was determined to be 95% *Z* by ^1H NMR analysis.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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[20] The followings are the yields of **2** obtained by the reactions of **1** (1.0 equiv.) and PhMgX (2.0 equivs.) in the presence of CuI (10 mol%) in Et_2O at 0 °C: PhMgI (74%), PhMgBr (27%), PhMgCl (0%), Ph_2Mg (0%). For low-yielding reactions, a considerable amount of the starting material **1** was recovered. At the moment, we cannot provide a reasonable rationale for the dramatic difference of counterions on PhMgX.

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