

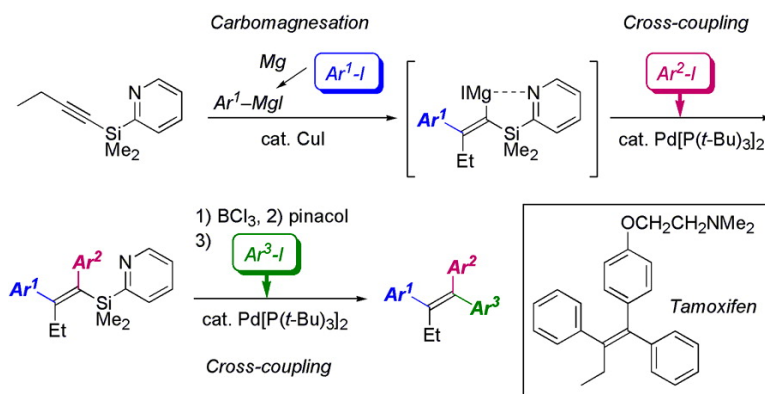
Communication

Diversity-Oriented Synthesis of Tamoxifen-type Tetrasubstituted Olefins

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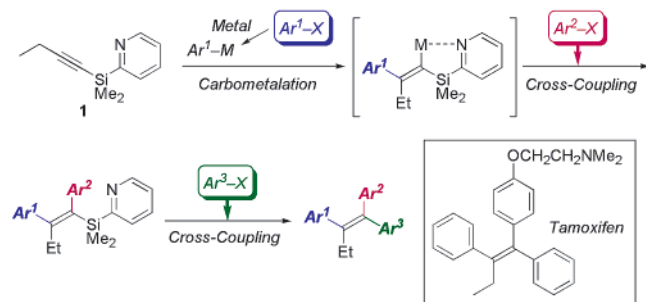
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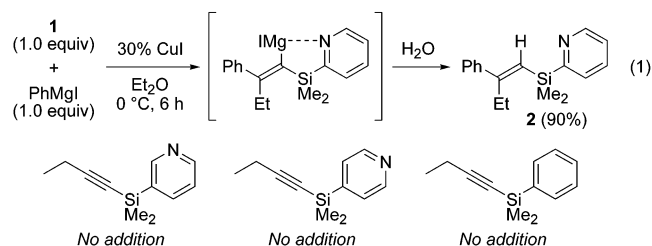
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Tamoxifen is the most important anti-breast cancer drug in clinical use and has the potential to be used as a chemopreventive breast cancer agent.¹ It is a selective estrogen receptor modulator (SERM) with anti-estrogenic properties in breast and estrogenic effects in tissues such as bone and the cardiovascular system. 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-oriented² synthetic scheme for tamoxifen-type tetrasubstituted olefins. In addition, insufficient stereoselectivity, which is often encountered with the widely used dehydration reaction³ and McMurry coupling,⁴ has been a bottleneck for rapid evaluation.⁵ As an alternative to these procedures, Miller, Cummins, Knochel, and Armstrong have developed metal-mediated synthetic methods for tamoxifen.⁶

As a part of our program aimed at the development of a general and diversity-oriented synthetic scheme for multisubstituted olefins,⁷ we have developed such a synthetic scheme for tamoxifen-type tetrasubstituted olefins utilizing our removable directing 2-pyridylsilyl group.^{8,9} We envisaged that, as an initial step of our campaign, the regio- and stereoselective addition of an arylmetal across 1-butynyldimethyl(2-pyridyl)silane (**1**) would afford a suitably substituted alkenylmetal compound through the agency of a complex-induced proximity effect of the pyridyl group on silicon. The sequential arylations at C–M and C–Si bonds (Pd-catalyzed cross-coupling reactions) of the resultant pyridylsilyl-substituted alkenylmetal compound would afford the targeted tamoxifen-type tetrasubstituted olefins. Because all aryl groups of this tetrasubstituted olefin structure stem from readily available aryl halides, the synthesis would be sufficiently diversity-oriented.



In early experiments, we found that the addition of Grignard reagents across 1-butynyldimethyl(2-pyridyl)silane (**1**) does not occur at all.¹⁰ Thus, we searched for an efficient procedure for the initial carbometallation process across **1** (eq 1). After many trials, it was found that the regio- and stereoselective addition of PhMgI (1.0 equiv) to **1** proceeded smoothly in the presence of CuI catalyst to afford **2** in 90% yield. The addition did not occur with an equimolar amount of CuI, which indicates that organocuprate might be the reactive species for this addition. The use of PhMgBr, PhMgCl, or Ph₂Mg in place of PhMgI resulted in lower addition



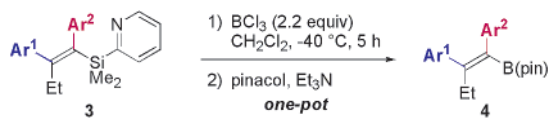
efficiency. It was also found that the Cu-catalyzed addition did not occur at all with the corresponding 3-pyridyl, 4-pyridyl, and phenylsilanes, which clearly implicates the strong directing effect (complex-induced proximity effect) of the 2-pyridyl group on silicon.¹¹

Table 1. Catalytic One-Pot Diarylation of **1**

run	Ar ¹	Ar ²	3	yield (<i>E/Z</i>)
1	C ₆ H ₅ (a)	C ₆ H ₅ (a)	3aa	80% (92/8)
2	C ₆ H ₅ (a)	4-MeOC ₆ H ₄ (b)	3ab	60% (92/8)
3	C ₆ H ₅ (a)	4-Me ₂ N(CH ₂) ₂ OC ₆ H ₄ (c)	3ac	55% (88/12)
4	C ₆ H ₅ (a)	4-CF ₃ C ₆ H ₄ (d)	3ad	75% (95/5)
5	C ₆ H ₅ (a)	4-EtOCOC ₆ H ₄ (e)	3ae	58% (94/6)
6	C ₆ H ₅ (a)	4-ClC ₆ H ₄ (f)	3af	69% (94/6)
7	3-ClC ₆ H ₄ (g)	4-Me ₂ N(CH ₂) ₂ OC ₆ H ₄ (c)	3gc	55% (92/8)
8	3-ClC ₆ H ₄ (g)	4-MeC ₆ H ₄ (h)	3gh	79% (92/8)

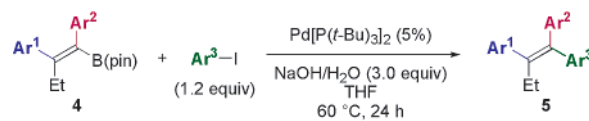
With the feasibility of an initial carbometallation process, we next examined the one-pot diarylation of **1** through the catalytic carbomagnesation/cross-coupling sequence. After extensive screening of catalyst for the cross-coupling step, Pd[P(*t*-Bu)₃]₂¹² was found to effect the Kumada–Tamao–Corriu-type cross-coupling¹³ of the resultant alkenylmagnesium compound and aryl iodide in good overall yield. Thus, by simply varying Ar¹MgI and Ar²I, we could efficiently obtain various structurally and electronically diverse alkenylsilanes **3** (Table 1).¹⁴ The two aryl groups (Ar¹ and Ar²) are introduced in a *cis* fashion, which is in accordance with syn carbometallation and retention of stereochemistry during the subsequent cross-coupling. The aryl group containing the basic side chain found in tamoxifen can be installed with ease (runs 3 and 7). Interestingly, the ester group also tolerated the conditions of this cross-coupling reaction (run 5).

With the procedure of stereoselective one-pot diarylation of **1** in hand, we investigated the cross-coupling of **3** at the C–Si bond (Hiyama cross-coupling)^{7,15} as a final step toward tamoxifen-type tetrasubstituted olefins. However, extensive screening of catalyst and activator to transfer these sterically condensed alkenyl groups

Table 2. Borodesilylation of **3**


run	3 (<i>E/Z</i>)	4	yield (<i>Z/E</i>)
1	3aa (94/6)	4aa	82% (98/2)
2 ^a	3ac (88/12)	4ac	65% (94/6)
3	3ad (95/5)	4ad	80% (99/1)
4	3ae (94/6)	4ae	64% (>99/1)
5 ^a	3gc (92/8)	4gc	77% (95/5)
6	3gh (92/8)	4gh	73% (97/3)

^a 3.3 equiv of BCl₃ was employed. After the treatment with pinacol, the mixture was treated with Cs₂CO₃ (10 equiv) in toluene (80 °C, 11 h).

Table 3. Suzuki–Miyaura Coupling of **4** with Aryl Iodides


run	4 (<i>Z/E</i>)	Ar ³	5	yield (<i>E/Z</i>)
1	4aa (97/3)	4-Me ₂ N(CH ₂) ₂ OC ₆ H ₄ (c)	5aac	95% (99/1)
2	4aa (97/3)	4-MeC ₆ H ₄ (h)	5aah	96% (99/1)
3	4ac (94/6)	C ₆ H ₅ (a)	5aca	98% (5/95)
4	4ac (94/6)	4-MeOC ₆ H ₄ (b)	5acb	95% (5/95)
5	4ac (94/6)	3-MeOC ₆ H ₄ (i)	5aci	92% (95/5)
6	4ad (99/1)	4-MeOC ₆ H ₄ (b)	5adb	97% (>99/1)
7	4ad (99/1)	4-ClC ₆ H ₄ (f)	5adf	90% (>99/1)
8	4ad (99/1)	2-MeOC ₆ H ₄ (j)	5adj	95% (>99/1)
9	4ad (99/1)	3-pyridyl (k)	5adk	67% (>99/1)
10	4gc (95/5)	4-MeOC ₆ H ₄ (b)	5gcb	80% (4/96)
11	4gc (95/5)	3-MeC ₆ H ₄ (l)	5gcl	82% (98/2)
12	4gc (97/3)	3-thienyl (m)	5gcm	87% (99/1)
13	4gh (97/3)	2-MeC ₆ H ₄ (n)	5ghn	93% (>99/1)
14	4gh (99/1)	3,5-F ₂ C ₆ H ₃ (o)	5gho	98% (>99/1)
15	4gh (99/1)	1-naphthyl (p)	5ghp	99% (>99/1)

from silicon met with no success. Thus, we turned our attention to Si/B exchange reaction borodesilylation of **3** to achieve the installation of a third aryl group (Ar³) by means of Suzuki–Miyaura coupling at the resulting C–B bond.¹⁶

The stereoselective borodesilylation¹⁷ of **3** was found to occur with BCl₃ in CH₂Cl₂ at –41 °C, and subsequent treatment of this mixture with pinacol and triethylamine (one-pot) afforded **4** in good yield with retention of stereochemistry (Table 2). For compounds bearing the tamoxifen basic side chain (Me₂NCH₂CH₂O–) such as **3ac** and **3gc**, it was necessary to treat the mixture with a base such as Cs₂CO₃ to remove a boron residue coordinated to the nitrogen. Interestingly, it was found that the isomeric purities of **4** were greater than those of the starting alkenylsilanes in all cases examined. This may be due to the reactivity difference of isomeric alkenylsilanes in borodesilylation.

Finally, the Suzuki–Miyaura coupling of **4** with aryl iodides (Ar³I) afforded the targeted tamoxifen-type tetrasubstituted olefin **5**. An extensive optimization of this final step revealed that the catalyst/base/additive combination of Pd[P(*t*-Bu)₃]₂/NaOH/H₂O (5 mol %, 3.0 equiv, 3.0 equiv) effects the desired cross-coupling in extremely high yields in THF at 60 °C (Table 3).^{12a} A variety of aryl groups including heteroaryl groups can be installed in the final tetrasubstituted olefin structure. Tamoxifen (**5aca**) and its derivatives can be prepared with ease. 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 the cross-coupling reaction.

In summary, we have established a general synthetic scheme for tamoxifen-type tetrasubstituted olefins based on the novel Cu-catalyzed carbomagnesation across alkynyl(2-pyridyl)silane. By using this synthetic scheme, we could prepare a wide array of electronically and structurally diverse tetrasubstituted olefins 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 applying order of aryl iodides into the sequence. Although we have focused our investigation on the synthesis of tamoxifen-type olefins in this study, our synthetic scheme should be easily expanded to the construction of a more general tetrasubstituted olefin structure.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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