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Diversity-Oriented Synthesis of Tamoxifen-type Tetrasubstituted Olefins

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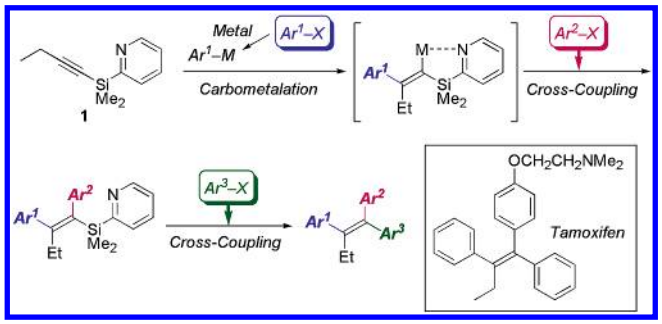
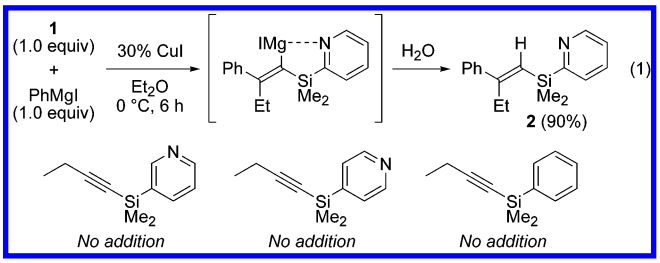
Tamoxifen is the most important anti-breast cancer drug in clinical use and has the potential to be used as a chemopreventive breast cancer agent.[1] It is a selective estrogen receptor modulator (SERM) with anti-estrogenic properties in breast and estrogenic effects in tissues such as bone and the cardiovascular 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-oriented[2] synthetic scheme for tamoxifen-type tetrasubstituted olefins. In addition, insufficient stereoselectivity, which is often encountered with the widely used dehydration reaction[3] 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.

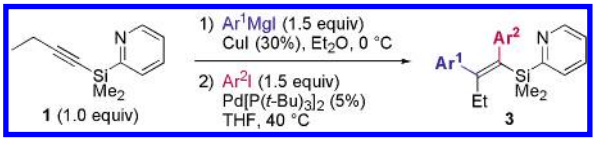


In early experiments, we found that the addition of Grignard reagents across 1-butynyldimethyl(2-pyridyl)silane (**1**) does not occur at all.[10] Thus, we searched for an efficient procedure for the initial carbometalation process across **1** (eq 1). After many trials, it was found that the regio- 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 Ph_2Mg 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 (*E*/*Z*)
1	C_6H_5 (**a**)	C_6H_5 (**a**)	**3aa**	80% (92/8)
2	C_6H_5 (**a**)	4-$MeOC_6H_4$ (**b**)	**3ab**	60% (92/8)
3	C_6H_5 (**a**)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**3ac**	55% (88/12)
4	C_6H_5 (**a**)	4-$CF_3C_6H_4$ (**d**)	**3ad**	75% (95/5)
5	C_6H_5 (**a**)	4-$EtOCOC_6H_4$ (**e**)	**3ae**	58% (94/6)
6	C_6H_5 (**a**)	4-ClC_6H_4 (**f**)	**3af**	69% (94/6)
7	3-ClC_6H_4 (**g**)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**3gc**	55% (92/8)
8	3-ClC_6H_4 (**g**)	4-MeC_6H_4 (**h**)	**3gh**	79% (92/8)

With the feasibility of an initial carbometalation 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, $Pd[P(t\text{-}Bu)_3]_2$[12] was found to effect the Kumada−Tamao−Corriu-type cross-coupling[13] of the resultant alkenylmagnesium compound and aryl iodide in good overall yield. Thus, by simply varying Ar^1MgI and Ar^2I, we could efficiently obtain various structurally and electronically diverse alkenylsilanes **3** (Table 1).[14] The two aryl groups (Ar^1 and Ar^2) are introduced in a cis fashion, which is in accordance with syn carbometalation 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

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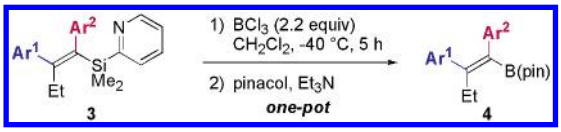
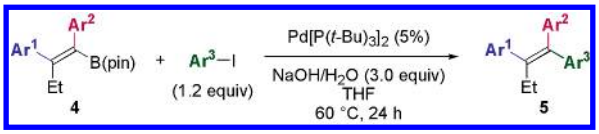
Table 2. Borodesilylation of **3**



run	**3** (*E*/*Z*)	**4**	yield (*Z*/*E*)
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 BCl_3 was employed. After the treatment with pinacol, the mixture was treated with Cs_2CO_3 (10 equiv) in toluene (80 °C, 11 h).

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



run	**4** (*Z*/*E*)	Ar^3	**5**	yield (*E*/*Z*)
1	**4aa** (97/3)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**5aac**	95% (99/1)
2	**4aa** (97/3)	4-MeC_6H_4 (**h**)	**5aah**	96% (99/1)
3	**4ac** (94/6)	C_6H_5 (**a**)	**5aca**	98% (5/95)
4	**4ac** (94/6)	4-$MeOC_6H_4$ (**b**)	**5acb**	95% (5/95)
5	**4ac** (94/6)	3-$MeOC_6H_4$ (**i**)	**5aci**	92% (95/5)
6	**4ad** (99/1)	4-$MeOC_6H_4$ (**b**)	**5adb**	97% (>99/1)
7	**4ad** (99/1)	4-ClC_6H_4 (**f**)	**5adf**	90% (>99/1)
8	**4ad** (99/1)	2-$MeOC_6H_4$ (**j**)	**5adj**	95% (>99/1)
9	**4ad** (99/1)	3-pyridyl (**k**)	**5adk**	67% (>99/1)
10	**4gc** (95/5)	4-$MeOC_6H_4$ (**b**)	**5gcb**	80% (4/96)
11	**4gc** (95/5)	3-MeC_6H_4 (**l**)	**5gcl**	82% (98/2)
12	**4gc** (97/3)	3-thienyl (**m**)	**5gcm**	87% (99/1)
13	**4gh** (97/3)	2-MeC_6H_4 (**n**)	**5ghn**	93% (>99/1)
14	**4gh** (99/1)	3,5-$F_2C_6H_3$ (**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 (Ar^3) by means of Suzuki−Miyaura coupling at the resulting C−B bond.[16]

The stereoselective borodesilylation[17] of **3** was found to occur with BCl_3 in CH_2Cl_2 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 ($Me_2NCH_2CH_2O$−) such as **3ac** and **3gc**, it was necessary to treat the mixture with a base such as Cs_2CO_3 to remove a boron residue coordinated to the nitrogen. Interestingly, it was found that the isomeric purities of **4** were greater that 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 (Ar^3I) afforded the targeted tamoxifen-type tetrasubstituted olefin **5**. An extensive optimization of this final step revealed that the catalyst/base/additive combination of $Pd[P(t\text{-}Bu)_3]_2$/NaOH/H_2O (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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