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Palladium-Catalyzed Fluoride-Free Cross-Coupling of Intramolecularly Activated Alkenylsilanes and Alkenylgermanes: Synthesis of Tamoxifen as a Synthetic Application

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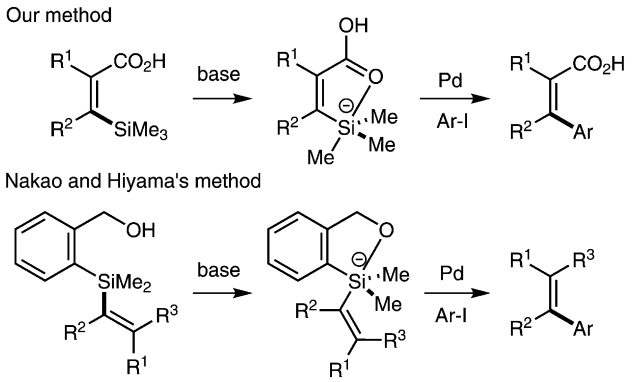
Abstract: We have demonstrated that intramolecular hypercoordination of a carboxylic acid is a powerful activation strategy for the palladium-catalyzed cross-coupling reaction of trialkyl(vinyl)silanes and trialkyl(vinyl)germanes under fluoride-free conditions. *Z*-β-Trialkylsilyl- and *Z*-β-trialkylgermylacrylic acids, synthesized stereoselectively by olefination with ynolates, are highly stable and useful reagents for cross-coupling with a variety of aryl iodides to provide tetrasubstituted olefins possessing different carbon substituents in a stereocontrolled and diversity-oriented manner. An application to a stereoselective synthesis of (*Z*)-tamoxifen is also reported.

Keywords: cross-coupling; germanium; hypervalent compounds; olefination; silicon; tamoxifen

Introduction

The transition metal-catalyzed cross-coupling reaction is one of the most important C–C bond formation methods in modern synthetic organic chemistry. Organoboron, organozinc and organostannane compounds are the reactive organometals most widely used as coupling partners for organohalides.[1] However, since some of these organometals are unstable, not easily handled, and/or not readily available, other organometal compounds have also been explored for the cross-coupling. Since they are stable and accessible, organosilicon compounds are expected to be potent organic donors in the reaction, which is known as the Hiyama coupling.[2] However, organosilanes are too stable to undergo productive coupling, unless they are activated by the formation of pentacoordinated silicates or silanolate species containing an Si–O–Pd linkage.[2d] Heteroatom substituents, such as an alkoxy and/or a hydroxy group on the silane, are essential for their efficient reactivity but these silanes tend to be labile under acidic or basic conditions.[3,4] In recent years, in order to overcome these drawbacks, highly stable all carbon-substituted silanes – with 2-pyridyl,[5] 2-thienyl,[6] benzyl,[7] phenyl,[8] allyl,[9] and silacyclobutane[10] moieties – have been developed for palladium-catalyzed cross-coupling reactions. However, a common limitation of the aforementioned silicon-based coupling reactions is the use of fluoride ion as the promoter, which would be incompatible in a complex molecule synthesis where one of the coupling partners contains silyl protective groups. And although the cross-coupling reactions of these newly developed organosilanes have been utilized for the synthesis of di- or trisubstituted olefins, they would not work well in the synthesis of tetrasubstituted olefins because of the low reactivity of the organosilanes.[11] Thus the development of a mild and convenient, non-fluoride promoted system would be highly desirable.[3c,12]

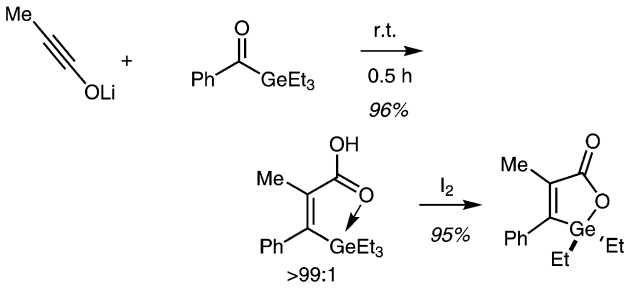
During the course of our studies on ynolates,[13] we have developed a highly stereoselective olefination of acylsilanes to afford *Z*-β-trialkylsilylacrylic acids, in which the silicon atom was found to be activated by intramolecular pentacoordination of the carbonyl oxygen atom.[14] This discovery prompted us to develop a palladium-catalyzed cross-coupling reaction of the intramolecularly activated alkenylsilanes with aryl halides to provide tetrasubstituted olefins. As far as we know, little has been reported on the synthesis of tetrasubstituted olefins *via* the Hiyama coupling so this would be a valuable contribution.[15] Furthermore, it would be even more useful if readily available trimethylsilylalkenes could be used as the substrate without the addition of activators such as fluoride in the reaction. After our preliminary publication on



Scheme 1. Palladium-catalyzed cross-coupling of intramolecularly activated organosilanes.

this cross-coupling reaction,[16] Nakao and Hiyama reported that the intramolecularly activated silicate led to the cross-coupling reaction (Scheme 1),[17] thus lending importance to our intramolecular activation concept.

To achieve higher efficiency of this type of coupling reaction, we focused our attention on germanium, which is located between silicon and tin in group 14 in the periodic table. Compared to organosilicon and organotin compounds, organogermanium compounds have attracted little attention and are not yet widely used as reagents in synthetic organic chemistry; however, they are expected to be promising coupling partners due to the fact that they are more easily handled and are less toxic than organotin compounds.[18] Since the first success of cross-coupling with carbagermatrane *via* activation of the Ge–C bond by intramolecular coordination of a tertiary amine,[19] several methods have been developed for efficient cross-coupling reactions with organogermanes bearing heteroatoms,[20] a 2-furyl group,[21] and a photoactivatable group[22] on the germanium. However, like the organosilanes, they all required strong activators, such as fluoride or hydroxide. Furthermore, no example for the synthesis of tetrasubstituted alkenes possessing all carbon substituents has, to the best of our knowledge, been reported. Recently, we have published the highly *Z*-selective olefination of acylgermanes with ynolates to provide vinylgermanes, which are intrinsically activated by the intramolecular hypercoordination of the carbonyl group (Scheme 2).[23] Thus, we were interested in seeing whether this activation methodology could be applied to the cross-coupling of organogermanes without using fluoride activators. Herein, we describe the full details of the fluoride-free palladium-catalyzed cross-coupling reaction of organosilanes and organogermanes with aryl halides resulting in multisubstituted alkenes, and an efficient synthesis of the anti-tumor drug, tamoxifen, as a synthetic application.



Scheme 2. *Z*-Selective olefination of acylgermanes with ynolates.

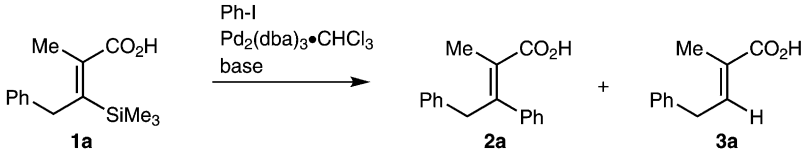
Results and Discussion

Initial investigation of the cross-coupling of (*Z*)-β-(trimethylsilyl)acrylic acid **1a**, prepared by stereoselective olefination of acylsilane with an ynolate,[14a] with iodobenzene catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ in THF did not give the desired coupling product **2a** (Table 1, entry 1). To enable the coupling reaction, LiOH was used as an additive to generate the desired product **2a** in moderate yield along with a significant amount of the protodesilylation product **3a** and the recovered starting material **1a** (entry 2). Hence, various bases were screened as the additive in this coupling reaction. While NaOH, KOH and TMSOK did not accelerate the reaction at all, Cs_2CO_3 worked well to afford the product **2a** in better yield (entry 6). Since, in the presence of water, an increased amount of the by-product **3a** was generated (entry 7), proton sources must be avoided in the reaction. As a solvent, DME was better than THF, toluene, or DMF (entries 8, 9, and 10). The ligands were next examined in the cross-coupling of **1a** with 4-chloroiodobenzene but phosphine, phosphite and arsine ligands resulted in lower yields of the coupling product **2a** [PPh_3, 7%; P(o-tolyl)$_3$, 29%; P(2-furyl)$_3$, 17%; $P(OEt)_3$, 9%; $AsPh_3$, 43%].

With the optimized reaction conditions [$Pd_2(dba)_3{\cdot}CHCl_3/Cs_2CO_3$ in DME at 60 °C] in hand, we then investigated the reaction with a variety of aryl iodides (Table 2). In most cases, the coupling products **2** were obtained in good to moderate yield along with a small amount of the protodesilylated by-products **3**. Aryl iodides possessing an electron-withdrawing group tend to give somewhat better yields than those with an electron-donating group. In several cases, the yield was slightly improved by a 10-fold dilution of the reaction with the solvent (entries 1 *vs.* 2, 3 *vs.* 4 and 7 *vs.* 8).

Under these conditions, the coupling reactions of the (*Z*)-3-aryl-3-trimethylsilylacrylic acid derivatives **1b** were attempted, with the aim of synthesizing tamoxifen-type tetrasubstituted olefins, but only the protodesilylation product **3b** was obtained (Scheme 3). Reinvestigation of various kinds of li-

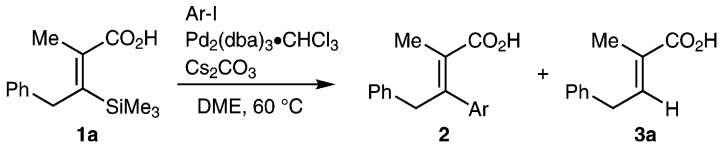
Table 1. Screening of base and solvent.[a]



Entry	Base	Solvent	Time [h]	Yield of **2a**[b] [%]	Yield of **3a**[b] [%]
1	none	THF	22	0	0
2	LiOH	THF	22	38	23
3	NaOH	THF	22	15	0
4	KOH	THF	22	34	5
5	TMSOK	THF	22	0	0
6	Cs_2CO_3	THF	9	63	8
7[c]	Cs_2CO_3	THF	18	42	42
8	Cs_2CO_3	DME	8	68	7
9	Cs_2CO_3	toluene	8	53	10
10	Cs_2CO_3	DMF	3	33	33

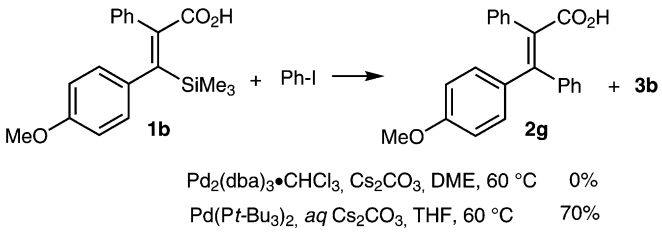
[a] *Reaction conditions:* (*Z*)-β-(trimethylsilyl)acrylic acid (**1a**, 1.0 equiv., 0.1 M), iodobenzene (1.5 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (5 mol%), base (5.0 equiv.), 60 °C.
[b] The yields were determined by ^1H NMR of the mixture of **2a** and **3a** after column chromatography.
[c] H_2O (10 equiv.) was added.

Table 2. The cross-coupling reaction of (*Z*)-β-(trimethylsilyl)acrylic acid with aryl iodides.[a]



Entry	Ar	Concentration [M]	Product **2**	Yield of **2**[b] [%]	Yield of **3a**[b] [%]
1	C_6H_5	0.1	**2a**	63	8
2	C_6H_5	0.01	**2a**	72	6
3	4-Cl-C_6H_4	0.1	**2b**	47	12
4	4-Cl-C_6H_4	0.01	**2b**	66	7
5	4-CF_3-C_6H_4	0.1	**2c**	65	3
6	4-O_2N-C_6H_4	0.1	**2d**	68	0
7	4-Me-C_6H_4	0.1	**2e**	38	10
8	4-Me-C_6H_4	0.01	**2e**	47	3
9	4-MeO-C_6H_4	0.1	**2f**	46	7

[a] *Reaction conditions:* (*Z*)-β-(trimethylsilyl)acrylic acid (**1a**, 1.0 equiv.), aryl iodide (1.5 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (5 mol%), Cs_2CO_3 (5.0 equiv.), DME, 60 °C, 22 h.
[b] The yields were determined by ^1H NMR of the mixture of **2** and **3a** after column chromatography.

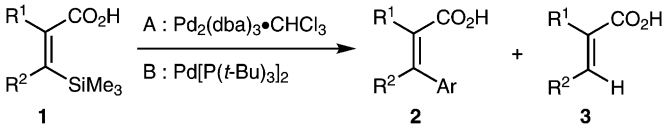


Scheme 3. Cross-coupling reaction of (*Z*)-β-(trimethylsilyl)-acrylic acid **1b** with iodobenzene.

gands on palladium revealed that most of the ligands, including combinations of PPh_3, P(*o*-Tol)$_3$, TFP, $AsPh_3$, P(biphenyl)(*t*-Bu)$_2$, dppe, and dppf with $Pd_2(dba)_3$·$CHCl_3$, and $Pd(PPh_3)_4$, resulted in generation of the protodesilylation product **3b**. Finally Pd[P(*t*-Bu)$_3$]$_2$ was found to catalyze the coupling reaction in THF with aqueous Cs_2CO_3 to afford the desired product **2g** in 70% yield with 29% of **3b**.

Using our two favorable reaction conditions (Methods A and B), we next subjected several β-silylacrylic acid derivatives **1** to the coupling reaction with aryl iodides as can be seen in Table 3, which shows the

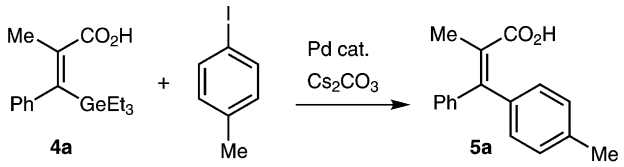
Table 3. Cross-coupling reaction of (*Z*)-β-(trimethylsilyl)acrylic acid **1** with aryl iodide.



Entry	R^1	R^2	**1**	Ar	Method[a]	Product **2**	Yield of **2**[b] [%]	Yield of **3**[b] [%]
1	Me	Bn	**1a**	C_6H_5	B	**2a**	51	15
2	Me	Bn	**1a**	4-CF_3-C_6H_4	B	**2c**	50[c]	9[c]
3	*n*-Bu	Me	**1c**	C_6H_5	A	**2h**	58	4
4	*i*-Pr	Me	**1d**	C_6H_5	A	**2i**	46	4
5	C_6H_5	Me	**1e**	C_6H_5	A	**2j**	40	15
6	C_6H_5	Me	**1e**	C_6H_5	B	**2j**	73	15
7	Me	C_6H_5	**1f**	C_6H_5	A	**2k**	34	26
8	Me	C_6H_5	**1f**	C_6H_5	B	**2k**	26	57

[a] Method A: the reactions were performed at 60 °C using **1** (1.0 equiv.), aryl halide (1.5 equiv.), Cs_2CO_3 (5.0 equiv.), and $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) in DME. Method B: the reactions were performed at 60 °C using **1** (1.0 equiv.), aryl halide (1.5 equiv.), aqueous Cs_2CO_3 (5.0 equiv.), and $Pd[P(t\text{-}Bu)_3]_2$ (5 mol%) in THF.
[b] The yields were determined by ^1H NMR of the mixture of **2** and **3** after column chromatography.
[c] The yield was determined by ^1H NMR of the crude mixture relative to an internal standard (phenanthrene).

Table 4. Optimization for cross-coupling reaction of alkenylgermanes.[a]



Entry	Pd catalyst	Solvent	Time [h]	Yield of 5a [%]
1	$Pd[P(t\text{-}Bu)_3]_2$	THF	38	35
2	$Pd[P(t\text{-}Bu)_3]_2$	toluene	38	0
3	$Pd[P(t\text{-}Bu)_3]_2$	NMP	2	78
4	$Pd(PPh_3)_4$	NMP	46	<10
5	$Pd(OAc)_2$/P(biphenyl)(t-Bu)$_2$	NMP	30	52
6	$Pd(OAc)_2$/X-phos	NMP	27	<30
7	$Pd_2(dba)_3{\cdot}CHCl_3/AsPh_3$	NMP	14	60

[a] *Reaction conditions:* (*Z*)-β-(triethylgermyl)acrylic acid (**4a**, 1.0 equiv.), 4-iodotoluene (1.5 equiv.), Pd catalyst (10 mol%), Cs_2CO_3 (3.0 equiv.), 80 °C.

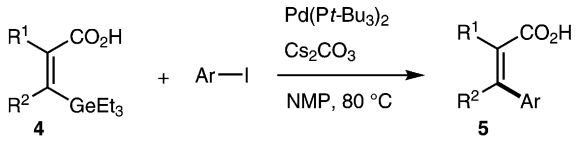
generation of the desired tetrasubstituted olefins **2** in good to modest yields. Depending on the substrate, Method B gave better yields than Method A in some cases. The generation of protodesilylation, however, could not be prevented in any case.

Fluoride-Free Cross-Coupling Reaction of Alkenylgermanes

In order to achieve generally efficient coupling reactions, and especially in order to obtain tamoxifen in good yield, we tried the reaction of the alkenylgermane **4a**, prepared by olefination of an acylgermane with an ynolate,[23] with iodotoluene in the presence of 10 mol% of the palladium catalyst and Cs_2CO_3. As shown in Table 4, among the attempted catalysts, $Pd[P(t\text{-}Bu)_3]_2$ worked very efficiently in NMP to afford the desired coupling product **5a** in 78% yield without the generation of the protonated by-products, which generally cause poor yields in this type of coupling reaction (entry 3).

Encouraged by this improved result *versus* those of the alkenylsilanes **1**, we then examined various types of aryl iodides as potential coupling partners for the intramolecularly activated alkenylgermane **4** in the coupling reaction. As shown in Table 5, iodobenzene and its derivatives bearing an electron-withdrawing substituent at the *para* position were found to afford the coupling products **5** in excellent yields (entries 1–5). It is noteworthy that this reaction did not require fluoride ion to activate the organometals. On the

Table 5. Cross-coupling reaction of alkenylgermanes **4** with aryl iodides.[a]



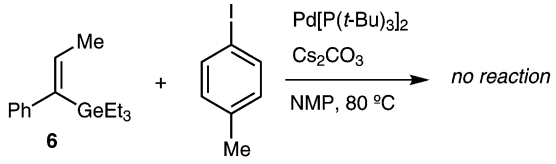
Entry	R^1	R^2	**4**	Ar	Time [h]	Product	Yield [%]
1	Me	Ph	**4a**	C_6H_5	2	**2k**	81
2	Me	Ph	**4a**	4-CF_3-C_6H_4	2	**5b**	92
3	Me	Ph	**4a**	4-Ac-C_6H_4	3	**5c**	96
4	Me	Ph	**4a**	4-EtO_2C-C_6H_4	4	**5d**	82
5	Me	Ph	**4a**	4-O_2N-C_6H_4	1	**5e**	81
6	Me	Ph	**4a**	4-MeO-C_6H_4	29	**5f**	<10
7	Me	Ph	**4a**	2-thienyl	4	**5g**	0
8	Me	Ph	**4a**	(*E*)-$C_6H_{13}CH$=CH	48	**5h**	0
9[b]	Et	Ph	**4b**	4-Ac-C_6H_4	2	**5i**	98
10	Ph	Et	**4c**	C_6H_5	2	**5j**	80

[a] *Reaction conditions:* (*Z*)-β-(triethylgermyl)acrylic acid (**4**, 1.0 equiv.), aryl iodide (1.5 equiv.), Pd[P(*t*-Bu)$_3$]$_2$ (5 mol%), Cs_2CO_3 (3.0 equiv.), NMP, 80 °C.
[b] 2 mol% Pd[P(*t*-Bu)$_3$]$_2$ was added.

other hand, this table indicates two limitations, namely that electron-donating substituents significantly inhibited the reaction (entry 6) and that iodoheteroarenes and alkenyl iodides were not coupled (entries 7 and 8). The reaction of vinylgermanes with 4-acetyliodobenzene and simple phenyl iodides afforded the tetrasubstituted olefins in excellent yields (entries 9 and 10).

Consequently, the vinylgermanes seem to be better alkenyl donors than the corresponding vinylsilanes in the palladium-catalyzed fluoride-free cross-coupling reaction, especially with electron-deficient iodobenzene derivatives as the coupling partner. This is probably because the transmetalation in the catalytic cycle with alkenylgermanes is the rate-determining step. However, electron-rich aromatic iodides were poorer substrates in comparison with the results of the reaction with the corresponding vinylsilanes, where small amounts of the coupling products were obtained (Table 2, entry 9 *vs.* Table 5, entry 6).

The simple trisubstituted vinylgermane **6** was subjected to the coupling reaction under the same conditions, but no reaction occurred. This indicated that the intramolecular activation of the germane is essential for the coupling reaction (Scheme 4).

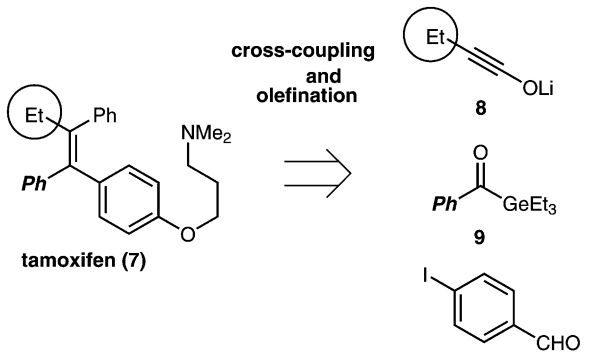


Scheme 4. Cross-coupling reaction of vinylgermane **6** with 4-iodotoluene.

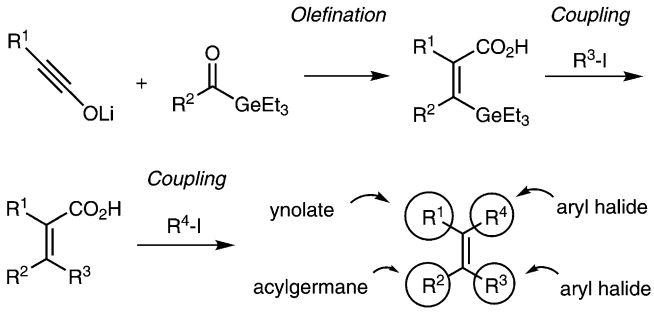
Stereoselective Synthesis of Tamoxifen

In order to show the synthetic utility of this methodology, we examined the synthesis of tamoxifen,[24] the first generation selective estrogen receptor modulator (SERM) widely used in the treatment of estrogen-dependent breast cancer.[25] Since this drug has a dissymmetric tetrasubstituted olefinic skeleton, tamoxifen and its derivatives have attracted the attention of synthetic organic chemists as a target to demonstrate the utility of a synthetic method for the construction of tetrasubstituted olefins. Almost all the successful stereoselective syntheses of tamoxifen have been based on an alkyne-carbometalation strategy;[26] however, alternative potentially successful approaches, including the highly stereoselective olefination of ketones, have not yet been reported,[27] except for our report, which involves olefination of an acylsilane, followed by palladium-catalyzed coupling in modest yield.[16] Therefore, we decided to try to achieve a more efficient synthesis of tamoxifen *via* the vinylgermane-coupling approach. The strategy is postulated in Scheme 5. The tetrasubstituted olefin would be constructed by the olefination of benzoylgermane **9**, followed by cross-coupling with 4-iodobenzaldehyde.

The benzoyltriethylgermane **9** was reacted with the ynolate **8**, prepared from ethyl 2,2-dibromobutanoate with *tert*-butyllithium, to afford the (*Z*)-vinylgermane **4b** in 98% yield as a single isomer. The palladium-catalyzed cross-coupling reaction of the vinylgermane **4b** was performed with 4-iodobenzaldehyde to give the tetrasubstituted olefin **10** in 94% yield. Next, the carboxylic acid **10** was subjected to a modified Hunsdiecker reaction with NBS to provide the bromoalkene **11**.[28] In order to convert the formyl group into



Scheme 5. Synthetic strategy for tamoxifen.



Scheme 7. The diversity-oriented synthesis of multisubstituted olefins *via* olefination of acylgermanes followed by cross-coupling reactions.

a hydroxy group, the Dakin oxidation[29] was attempted. Standard reagents such as mCPBA or hydrogen peroxide did not give good results with this substrate, but bis(trimethylsilyl) peroxide worked very well to furnish the desired hydroxy compound **12**.[30] Finally, after alkylation of the hydroxy group, the vinyl bromide was subjected to the Suzuki–Miyaura coupling to provide tamoxifen (**7**) in good yield (Scheme 6). When the Suzuki–Miyaura coupling took place prior to the Dakin oxidation, *E/Z* isomerization occurred in the Dakin oxidation step, probably due to the electron-withdrawing group on the aryl group.

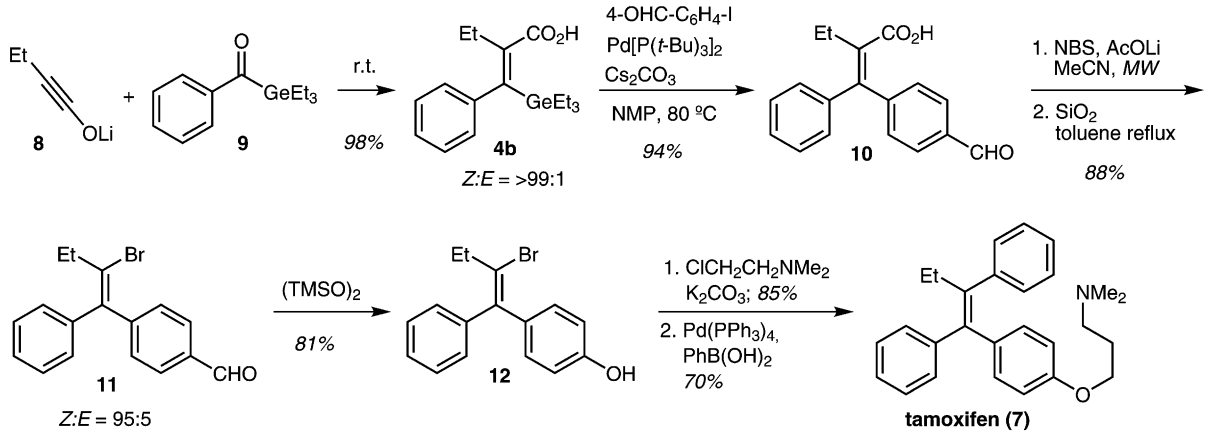
Conclusions

We have developed an efficient coupling reaction of intramolecularly activated vinylsilanes and vinylgermanes with aryl iodides. The coupling reaction using the vinylgermanes was found to be more efficient than that of the corresponding vinylsilanes, although electron-rich aryl groups are not suitable. It is noteworthy that this is the first successful synthesis of sterically condensed tetrasubstituted olefins by cross-coupling reactions using organosilanes and organogermanes. We also demonstrated the utility of this method by synthesizing tamoxifen in a stereoselective manner based on olefination of an acylgermanes/cross-coupling sequence. This synthetic protocol for the tetrasubstituted olefins can be regarded as an introduction of all four substituents separately on the olefin, namely R^1, R^2, R^3, and R^4 are derived from the ynolate, acylgermane, aryl halide, and another aryl halide, respectively (Scheme 7). Further studies will expand this approach to a general synthesis of tetrasubstituted olefins possessing four different substituents in a stereocontrolled and diversity-oriented manner.

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ solution on a JEOL JNM-AL-400 (^{1}H 400 MHz, ^{13}C 100 MHz) or a JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer using the reference standard [^{1}H 0.0 ppm (TMS), ^{13}C 77.0 ppm ($CDCl_3$)]. IR spectra were recorded on JASCO FT/IR-410 or Shimadzu FT/IR-8300 spectrophotometer. Mass spectra and high resolution mass spectra were ob-



Scheme 6. Synthesis of tamoxifen.

tained on JMS-K9, JMS-AMSUN200/300, JMS-SX102 A, or Waters LCT Premier mass spectrometers. Elemental analyses were performed with Yanaco MT-3, MT-5, MT-6 CHN-Corder. Melting points were measured with a Yanaco MP-500D apparatus and Büchi 535 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on pre-coated plates (0.25 mm, silica gel Merck $60F_{245}$). Column chromatography was performed on silica gel (Kanto Chemical Co., Inc.). All reactions were performed in oven-dried glassware under positive pressure of argon or nitrogen, unless otherwise noted. All materials were obtained from commercial suppliers and used without further purification, unless otherwise noted. *tert*-Butyllithium and *n*-butyllithium, purchased from Kanto Chemical Co., Inc., were titrated with diphenylacetic acid. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) and THF were purchased from Kanto Chemical Co., Inc.

Typical Procedure (Method A) for Cross-Coupling of (*Z*)-β-(Trimethylsilyl)acrylic Acid (Table 2, entry 2)

To a solution of **1a** (35 mg, 0.14 mmol) and Cs_2CO_3 (230 mg, 0.70 mmol) in DME (10 mL) were added sequentially iodobenzene (43 mg, 0.21 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (7 mg, 0.0070 mmol) at room temperature. After heating the mixture for 22 h at 60 °C, the solvents were evaporated to give a residue, which was diluted with CH_2Cl_2 and then acidified with 6 M aqueous HCl. The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$, filtered and concentrated under vacuum to give a crude product, which was purified by silica gel column chromatography (AcOEt/hexane, 10% to 25%) to afford 27 mg of the mixture of **2a** (72%) and **3a** (6%). After recrystallization from CCl_4-hexane, compound **2a** was isolated as colorless needles; mp 107.6–108.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 3.83 (s, 2H), 7.01–7.08 (m, 4H), 7.13–7.24 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ = 17.0 (q), 41.2 (t), 127.1 (d), 127.9 (d), 128.7 (d), 128.9 (d), 129.2 (d), 129.5 (d+s), 139.4 (s), 143.5 (s), 144.6 (s), 174.4 (s); IR ($CHCl_3$): ν = 3062, 1691 cm^{-1}; MS (EI): *m/z* = 252 (M^+), 234 (M^+-H_2O, 100%); anal. calcd. for $C_{17}H_{16}O_2$: C 80.93; H 6.39; found: C 80.98, H 6.53.

Typical Procedure (Method B) for Cross-Coupling of (*Z*)-β-(Trimethylsilyl)acrylic Acid (Table 3, entry 1)

To a solution of **1a** (30 mg, 0.12 mmol) and Cs_2CO_3 (0.12 mL, 0.60 mmol, 5.0 M in H_2O) in THF (1.5 mL) were added sequentially iodobenzene (37 mg, 0.18 mmol) and $Pd[P(t\text{-}Bu)_3]_2$ (6 mg, 0.012 mmol) at room temperature. After heating the mixture for 10 h at 60 °C, the solvent was evaporated to give a residue, which was diluted with CH_2Cl_2 and then acidified with 6 M aqueous HCl. The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated under vacuum to give a crude product, which was purified by silica gel column chromatography (AcOEt/hexane, 15% to 50%) to afford 19 mg of the mixture of **2a** (51%) and **3a** (15%).

Typical Procedure for Cross-Coupling of (*Z*)-β-(Triethylgermyl)acrylic Acid (Table 5, entry 3)

To a solution of (*Z*)-β-triethylgermylacrylic acid (**4a**, 64 mg, 0.20 mmol), 4-iodoacetophenone (59 mg, 0.24 mmol), and Cs_2CO_3 (195 mg, 0.60 mmol) in NMP (2 mL) were added sequentially molecular sieves 4 Å (90 mg) and $Pd[P(t\text{-}Bu)_3]_2$ (5 mg, 0.010 mmol) at room temperature. After heating for 3 h at 80 °C, the resulting mixture was acidified with 6 M aqueous HCl, extracted with Et_2O, and the combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The organic phase was concentrated under vacuum to give a crude product, which was purified by silica gel column chromatography (AcOEt/hexane, 20% to 70%) to afford **5c**; yield: 54 mg (96%). After recrystallization from AcOEt-hexane, compound **5c** was isolated as colorless needles; mp 157–158 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (3H, s), 2.58 (3H, s), 7.10–7.15 (2H, m), 7.23–7.38 (5H, m), 7.84–7.88 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.5 (q), 26.6 (q), 127.8 (s), 128.1 (d), 128.2 (d), 128.4 (d), 128.9 (d), 129.2 (d), 136.1 (s), 140.3 (s), 147.0 (s), 148.6 (s), 174.1 (s), 197.8 (s); IR ($CHCl_3$): ν = 3028, 1682 cm^{-1}; MS (EI): *m/z* = 280 (M^+), 265 (M^+-Me, 100%); anal. calcd. for $C_{18}H_{16}O_3$: C 77.12, H 5.75; found: C 76.89, H 5.81.

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