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Highly Diastereoselective Preparation of (*E*)-Alkenylsilanes Bearing an α-Chiral Center

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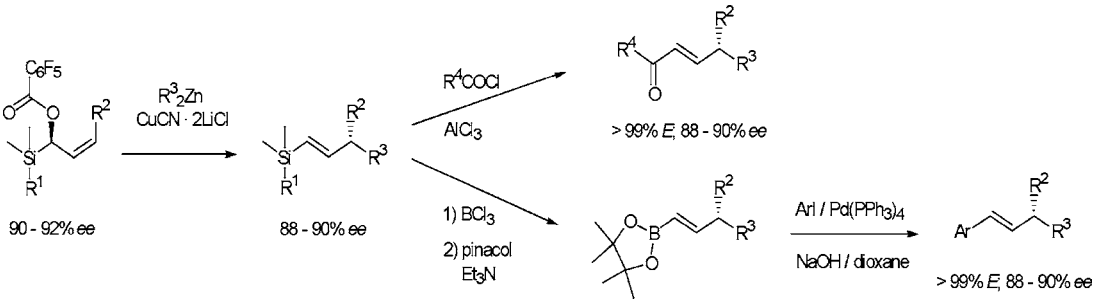
ABSTRACT



The copper(I)-mediated *anti*-S_N2' allylic substitution allows a highly stereoselective preparation of alkenylsilanes bearing a chiral center in the α-position with high transfer of chirality. These alkenylsilanes were converted into α,β-unsaturated ketones or into the corresponding boronic esters without loss of the chiral information.

Organosilicon chemistry[1] has a broad impact on organic methodology and total synthesis. Alkenylsilanes have been particularly used in palladium-catalyzed cross-coupling reactions since the pioneering work of Hiyama.[2] In recent years, this reaction has been increasingly investigated.[3,4] The preparation of alkenylsilanes remains a challenging task, and there have been only a few reports of alkenylsilanes containing an adjacent carbon stereogenic center.

We have recently reported an efficient *anti*-S_N2' allylic substitution[5,6] with almost complete transfer of the chiral information.[7] This method can be applied to the asymmetric synthesis of tertiary alcohols or amines[8] and for the preparation of ketones bearing an α-chiral center.[9] Herein, we report the diastereoselective preparation of (*E*)-alkenylsilanes containing an α-stereogenic center of type **1** via *anti*-S_N2' allylic

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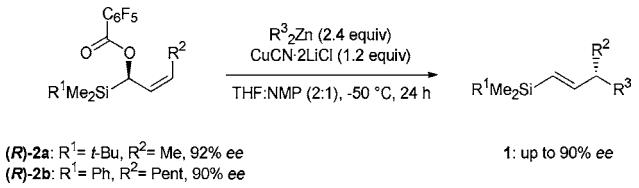
substitution reactions with diorganozinc reagents mediated by Cu(I) salt.

As the substituents at silicon may influence the reactivity of the resulting alkenylsilanes,[3] two different allylic substrates were prepared: **2a** (*t*-BuMe$_2$Si residue) and **2b** (PhMe$_2$Si residue). These allylic silanes undergo highly stereoselective S$_N$2′ substitutions as shown in Scheme 1. The allylic silane

Scheme 1. Diastereoselective *anti*-S$_N$2′ Allylic Substitution on Allylic Silanes of Type **2**

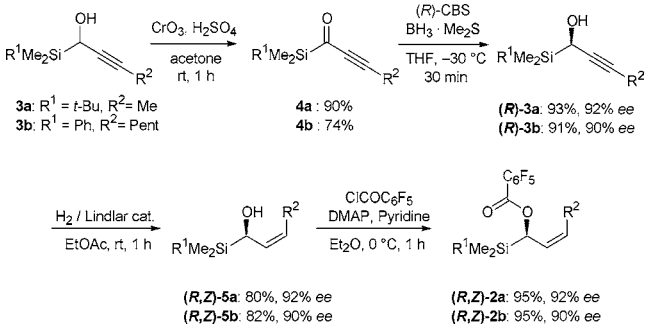


(*R*)-**2a**: R^1= *t*-Bu, R^2= Me, 92% *ee*
(*R*)-**2b**: R^1= Ph, R^2= Pent, 90% *ee*

1: up to 90% *ee*

2a was prepared starting from the α-hydroxysilane **3a**, which was obtained via a retro-Brook rearrangement reaction starting from 2-butyn-1-ol[10] (Scheme 2). Subsequent Jones

Scheme 2. Synthesis of (*R*,*Z*)-Allylic Pentafluorobenzoyl Silanes **2a** and **2b**



3a: R^1 = *t*-Bu, R^2= Me
3b: R^1 = Ph, R^2= Pent

4a : 90%
4b : 74%

(*R*)-**3a**: 93%, 92% *ee*
(*R*)-**3b**: 91%, 90% *ee*

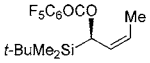
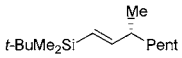
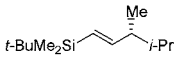
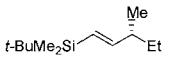
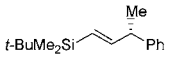
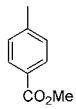
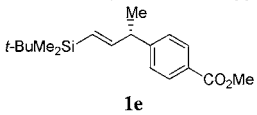
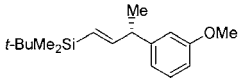
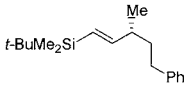
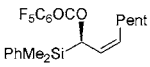
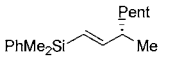
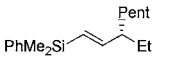
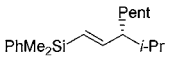
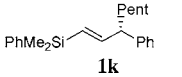
(*R*,*Z*)-**5a**: 80%, 92% *ee*
(*R*,*Z*)-**5b**: 82%, 90% *ee*

(*R*,*Z*)-**2a**: 95%, 92% *ee*
(*R*,*Z*)-**2b**: 95%, 90% *ee*

oxidation gave the silyl ketone **4a** (90%) whose enantioselective reduction with BH$_3$·Me$_2$S in the presence of (*R*)-2-methyl-CBS-oxazaborolidine[11] led to the alcohol (+)-(*R*)-**3a** in 92% yield and 92% ee.[12] The (*Z*)-hydroxyalkenylsilane (*R*)-**5a** was obtained by selective hydrogenation using a Lindlar catalyst[10] (>95% *Z* isomer, 80%). Finally, the reaction with pentafluorobenzoyl chloride in the presence of pyridine and a catalytic amount of DMAP gave the pentafluorobenzoyl allylic silane (*R*,*Z*)-**2a** in 95% yield. The allylic silanes (*R*,*Z*)-**2b** was prepared in a similar way in 90% ee (Scheme 2).

In a typical procedure, (*Z*)-pentafluorobenzoate **2a** (92% ee, entry 1 of Table 1) was treated with Pent$_2$Zn (2.4 equiv) in the presence of CuCN·2LiCl (1.2 equiv) in a mixture of THF and NMP (2:1), and after 24 h at −50 °C afforded the expected *anti*-S$_N$2′ substituted product **1a** (81%, 90% ee) with excellent transfer of chirality. A secondary diorganozinc such as *i*-Pr$_2$Zn (entry 2) reacts also with high S$_N$2′ regioselectivity (no S$_N$2 product observed). The corresponding alkenylsilane **1b** was obtained in 90% yield and 90% ee. Et$_2$Zn led to the

Table 1. Preparation of (*E*)-Alkenylsilanes of Type **1** by Copper(I)-Mediated *anti*-S$_N$2′ Substitution of Allylic Silanes **2**

entry	allyl substrate *ee* (%)[a]	R$_2$Zn (R)	(*E*)-alkenylsilane	yield (%)[b]	*ee* (%)[a]
					
1	**2a** (92)	Pent	**1a**	81	90
					
2	**2a**	*i*-Pr	**1b**	90	90
					
3	**2a**	Et	**1c**	89	88
					
4	**2a**	Ph	**1d**	86	89
					
5	**2a**		**1e**	65	89
					
6	**2a**		**1f**	60	90
					
7	**2a**	Ph(CH$_2$)$_2$	**1g**	60	84
					
8	**2b** (90)	Me	**1h**	95	89
					
9	**2b**	Et	**1i**	86	89
					
10	**2b**	*i*-Pr	**1j**	89	87
					
11	**2b**	Ph	**1k**	93	89

[a] The enantiomeric excess was determined by HPLC or GC analysis on product **1**, **2**, or derivatives. In each case the racemic product was used for calibration. [b] Isolated yield of analytically pure product.

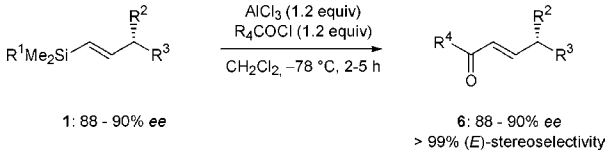
expected product **1c** (89%, 88% ee, entry 3). The substitution not only was limited to alkylzinc reagents but also proceeded well with diarylzincs. Thus, Ph$_2$Zn reacted smoothly with **3a** in the presence of CuCN·2LiCl to afford **1d** (86%, 89% ee, entry 4). More interestingly, functionalized diarylzinc reagents[13] reacted similarly, providing the corresponding methyl benzoate derivative **1e** (65%, 89% ee, entry 5) and *o*-methoxy benzene derivative **1f** (60%, 90% ee, entry 6).

A zinc reagent such as [Ph(CH$_2$)$_2$]$_2$Zn led to moderate results as a result of its lower reactivity and therefore higher required temperature (−30 °C to room temperature, 24 h, 60%, 84% ee, entry 7). Modification of the substituents on the silicon atom did not affect the level of the transfer of

chirality. Thus, Me_2Zn (2.4 equiv) reacted smoothly with (*Z*)-pentafluorobenzoate **2b** (entry 8) in the presence of CuCN·2LiCl (1.2 equiv) at −30 °C for 16 h and afforded the expected substituted product **1h** with almost no loss of the enantiomeric excess (89% ee) and in 95% yield. Et_2Zn (entry 9, 86%, 89% ee), *i*-Pr_2Zn (entry 10, 89%, 87% ee), and Ph_2Zn (entry 11, 93%, 89% ee) gave excellent results, although the addition of *i*-Pr_2Zn showed a poorer transfer (87% ee recovered) probably due to steric hindrance.

Alkenylsilanes of type **1** underwent Friedel−Crafts acylation-type reactions,[14] providing a synthesis of α,β-unsaturated ketones of type **6** (Scheme 3). Thus, the alkenylsilane

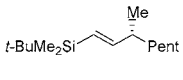
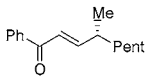
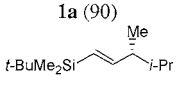
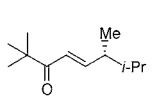
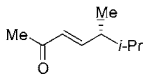
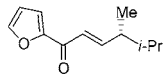
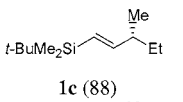
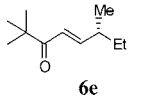
Scheme 3. Stereoselective Friedel−Crafts Acylation of Alkenylsilanes of Type **1**



1a (entry 1 of Table 2) was treated with $AlCl_3$ (1.1 equiv) and benzoyl chloride (1.1 equiv) in CH_2Cl_2 (−78 °C, 3 h, 25 °C) and afforded the corresponding (*E*)-α,β-unsaturated ketone **6a** with full retention of the chiral information (65%, 90% ee). Various acid chlorides could be similarly reacted. For example, aliphatic acid chlorides such as the bulky pivaloyl chloride (entry 2) or acetyl chloride (entry 3) were added with retention of the (*E*)-stereochemistry (90% ee, respectively, for **6b** and **6c**).

Interestingly substituted α,β-unsaturated furyl ketone **6d** (entry 4) could be easily prepared with high enantioselectivity

Table 2. Preparation of (*E*)-α,β-Unsaturated Ketone **6** by Stereoselective Friedel−Crafts Acylation on Alkenylsilanes **1**

entry	(*E*)-alkenylsilane *ee* (%)	(*E*)-α,β-unsaturated ketone	yield (%)[a]	*ee* (%)[b]
				
1	**1a** (90)	**6a**	65	90
				
2	**1b** (90)	**6b**	62	90
				
3	**1b** (90)	**6c**	68	90
				
4	**1b** (90)	**6d**	66	90
				
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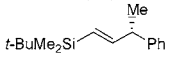
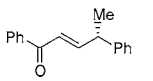
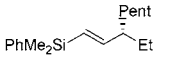
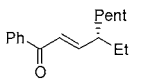
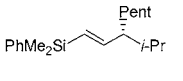
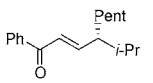
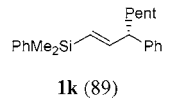
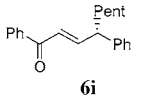
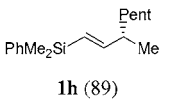
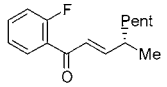
				
6	**1d** (89)	**6f**	71	89
				
7	**1i** (89)	**6g**	80	89
				
8	**1j** (87)	**6h**	86	87
				
9	**1k** (89)	**6i**	75	89
				
10	**1h** (89)	**6j**	68	89

[a] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic product was used for calibration. [b] Isolated yield of analytically pure product.

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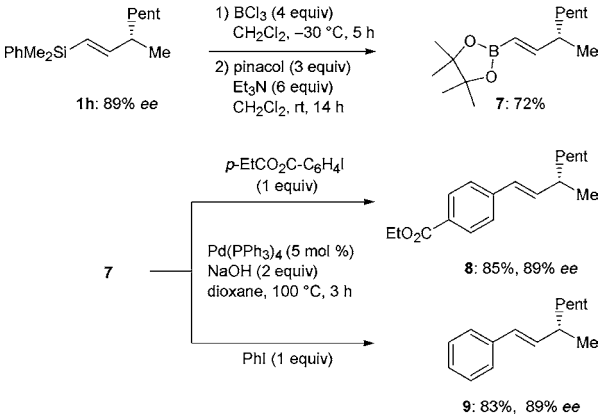
(66% yield, 90% ee) by this method. Similarly, alkenylsilanes **1i**−**k** furnished the corresponding α,β-unsaturated ketones **6g** (80%, 89% ee, entry 7), **6h** (86%, 87% ee, entry 8), and **6i** (75%, 89% ee, entry 9) when treated with $AlCl_3$ and benzoyl chloride with full retention of the stereochemical information. Interestingly the fluoro-substituted α,β-unsaturated ketone **6j** (entry 10) was prepared in high enantioselectivity by this method (68% yield, 89% ee).

Furthermore, chiral alkenylsilanes of type **1** could be successfully borodesilylated.[15] Thus, the treatment of alkenylsilane **1h** with BCl_3 (5 h at −30 °C) in CH_2Cl_2 followed by derivatization with pinacol in the presence of triethylamine (one pot) afforded the alkenyl boronopinacolate **7** in 72% yield and 89% ee (Scheme 4).

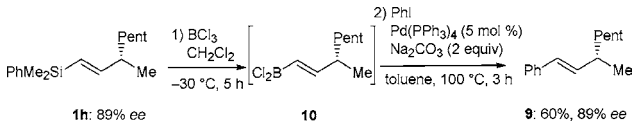
Scheme 4. *ipso*-Borodesilylation of **1h** and Successive Suzuki−Miyaura Cross-Coupling



The boronate **7** was first reacted with *p*-ethyl iodobenzoate in the presence $Pd(PPh_3)_4$ (5 mol %, 3 h at reflux in dioxane) to give the aryl-substituted alkene **8** in 85% yield and 89% ee with retention of the stereochemistry (Scheme 4).[16] The cross-coupling occurs under similar conditions when reacted with PhI and gave the phenyl-substituted alkene **9** in 83% yield and 89% ee.

In addition, an in situ *ipso*-borodesilylation−cross-coupling procedure[15] was performed in a one-pot operation. Thus, in the presence of BCl_3 (5 h, −30 °C), the alkenylsilane **7** was converted into the intermediate dichloroborane **10**, which reacted in the typical Suzuki−Miyaura conditions with PhI and $Pd(PPh_3)_4$ (5 mol %) to afford the expected disubstituted alkene **9** in 60% yield and 89% ee (Scheme 5).

Scheme 5. Sequential *ipso*-Borodesilylation Followed by in Situ Suzuki−Miyaura Cross-Coupling under Pd-Catalyzed Conditions



In summary, we have developed a highly diastereoselective method for the preparation of (*E*)-alkenylsilanes bearing an α-chiral center. These compounds are versatile intermediates and could be readily converted into α,β-unsaturated ketones by a Friedel−Crafts-type acylation or into the corresponding alkenylboronates by an *ipso*-borodesilylation and then undergo cross-coupling reactions. Further applications are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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