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Stereoselective Synthesis of Multisubstituted Alkenes via Conformationally Labile Alkenyllithium Species

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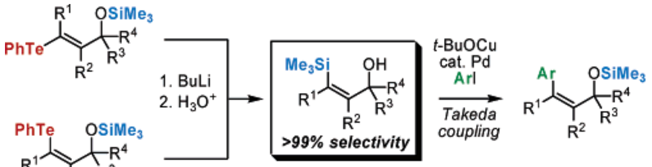
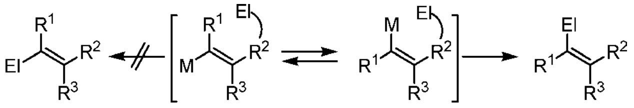
ABSTRACT



Stereoselective synthesis of tri- and tetrasubstituted alkenylsilanes has been realized by the selective intramolecular silicon migration in the rapidly equilibrating alkenyllithium species. Subsequent copper- and palladium-mediated coupling with allyl and aryl halides provides tri- and tetrasubstituted alkenes possessing all different carbon-substituents with complete stereoselectivity.

Alkenylmetal species play crucial roles in the stereoselective synthesis of multisubstituted alkenes, which are ubiquitous and essential structural constituents in organic molecules.[1] Since the stereochemical outcome of the alkenes depends critically on the stereochemistry of alkenylmetal species, its isomerization usually results in the loss of stereochemical purity. Therefore, configurationally labile alkenylmetal species have not been considered as important synthetic precursors for stereochemically defined multisubstituted alkenes,[2] because reactivity of (*E*)- and (*Z*)-isomers of alkenylmetals are almost identical. We, however, are interested in the possibility to use rapidly equilibrating alkenylmetal species for stereoselective synthesis of multisubstituted alkenes. We envisaged that discrimination of the reactivity between (*E*)- and (*Z*)-isomers of alkenylmetal species becomes possible if one isomer could selectively react with an electrophile by intramolecular reaction (Scheme 1). We report here the highly efficient synthesis of multisubstituted alkenes based on this new synthetic strategy. Although one example for the stereoselective synthesis of trisubstituted homoallyl

Scheme 1



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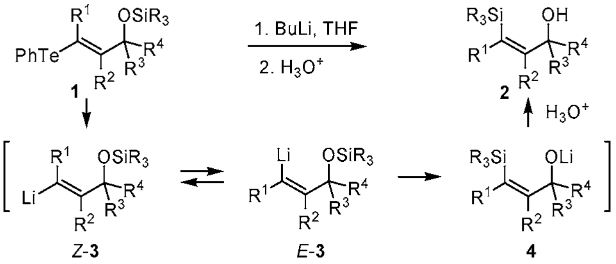
alcohol through alkene isomerization has been reported,[3] its synthetic scope as well as explicit mechanism have not been clarified. We now demonstrate that the current strategy provides a powerful route for varieties of tri- and tetrasubstituted alkenes with defined stereochemistry.[4,5]

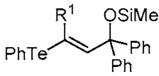
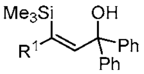
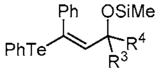
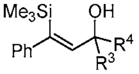
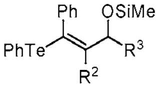
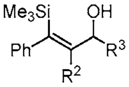
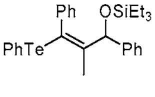
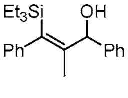
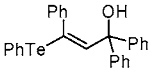
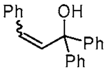
Our initial finding for the stereoselective synthesis of multisubstituted alkenes was obtained when *E*-**1a** ($R^1 = R^3 = R^4 = \text{Ph}$, $R^2 = \text{H}$, 96% *E*)[5b] was treated with butyllithium (1.1 equiv) in THF at −72 to 0 °C for 0.5 h (Scheme 2).[6]

Scheme 2



After usual hydrolytic workup, we isolated alkenylsilane (*Z*)-**2a** as an exclusive isomer in almost quantitative yield (Table 1, entry 1). The structure of **1a** and **2a** was confirmed by X-ray crystallographic analysis[5b] and by NMR analysis based on NOE, respectively, revealing that olefin isomerization as well as silicon migration from oxygen to carbon took place. As transmetalation from tellurium to lithium takes place with retention of stereochemistry through a hypervalent tellurium intermediate,[7] the result could be explained by the initial formation of (*Z*)-alkenyllithium (*Z*)-**3**, which subsequently isomerized to the (*E*)-isomer,[8] followed by the silicon migration from oxygen to carbon to **4** (Scheme 2).[9] Transmetalation to the corresponding alkenylcopper species by the reaction of **1a** with $Me_2Cu(CN)Li_2$[10] or Me_2CuLi

Table 1. Synthesis of Tri- and Tetrasubstituted Alkenylsilanes[a]

entry	substrate (*Z*:*E*)	product	yield (%)	*Z*:*E*
				
1	R^1 = Ph [**1a**] (4:96)	*Z*-**2a**	94	>99:1
2	R^1 = 3-pyridyl (1:99)		84	>99:1
3	R^1 = 4-BrC_6H_4 (1:99)		40	>99:1
				
4	R^3 = Ph, R^4 = H (28:72)		91	>99:1
5	R^3 = *c*-C_6H_{11}, R^4 = H (33:67)		84	>99:1
6	R^3, R^4 = -$(CH_2)_3$- (13:87)		60	>99:1
				
7	$R^2 = R^3$ = Me [**1b**] (51:49)	*Z*-**2b**	87	>99:1
8	R^2 = Me, R^3 = Ph (85:15)		91	>99:1
9	R^2 = Me, R^3 = H (46:54)		62	>99:1
10	R^2 = Ph, R^3 = Me (43:57)		97	>99:1
11	 (51:49) **1c**	 ***Z*-2c**	85	>99:1
12[b]	 (1:>99) **5**	 **6**	99	83:17

[a] Butyllithium (1.1−1.2 equiv) was added to a THF solution of **1** (ca. 0.5 M solution) at −72 °C, and the resulting solution was slowly warmed to 0 °C over 0.5 h. [b] Performed with 2.2 equiv of buthyllithium.

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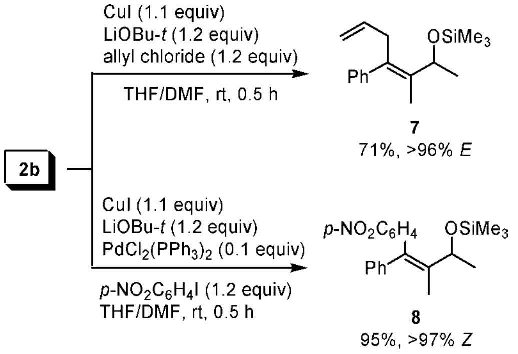
reagents[6d,11] in Et_2O also afforded (Z)-**2a** as an exclusive product in 74 and 81% yields, respectively.

The present reaction is generally applicable to alkenyltelluride **1** bearing different R^1, R^2, R^3, and R^4 groups and afforded the resulting (Z)-alkenylsilane **2** in good to excellent yields (Table 1).[12] Most notably, (Z)-isomers of both tri- and tetrasubstituted alkenes were exclusively formed regardless of the geometrical purity of the starting alkenyltellurides in all cases, indicating that both the (E)- and (Z)-isomers of alkenyllithium species generated from **1** gave the same product. The reaction also tolerates a variety of R^3 and R^4 groups to give the secondary and tertially alcohols efficiently. Although hydroxyl group-directed carbometalation of propargyl alcohol derivatives has been widely used for the stereoselective synthesis of multisubstituted alkenes,[13] the applicability of this method is limited to primary alcohols. Therefore, the current method provides a stereoselective synthetic route to highly substituted allyl alcohols with defined alkene geometry. The current reaction exhibited high functional group selectivities, and arylbromide function was retained to the product (entry 3). We could also utilize a variety of silyl groups, and **2c** also formed upon starting from **1c** (entry 11).

Several control experiments further supported the reaction pathway as depicted in Scheme 1. First, isomerization of alkenyllithium species was ascertained by the experiments using **5** (>99% E), which resulted in the formation of an 83:17 mixture of (E)- and (Z)-isomers of **6**[14] upon treatment of butyllithium followed by hydrolysis. The result is consistent with the fact that α-aryl-substituted alkenyllithiums isomerize at low temperature in a polar solvent such as THF[8] and clearly indicates the role of the silicon migration as the stereochemistry-determining step. Second, intramolecular silicon migration is ascertained by the scrambling experiments. Thus, treatment of an equimolar amount of **1b** and **1c** with butyllithium resulted in the selective formation of (Z)-**2b** (59%) and (Z)-**2c** (64%), and no silicon-scrambled products were detected. Therefore, selective intramolecular silyl group migration from (E)-**3** to **4** shifts the equilibrium between (Z)- and (E)-isomers of **3**, thus providing **2** as a single stereoisomer regardless of the stereochemistry of **1**.[15]

The virtue of the current method is the ease of the transformation of silyl groups to other functionalities (Scheme 3). We are pleased to find that the coupling reaction developed by Takeda could be nicely applied to this system.[16] Thus, alkenylsilane **2b** was transformed directly to skipped diene **7** upon transmetalation from silicon to copper followed by the treatment with allyl chloride. Further transformation from copper to palladium also enabled alkenyl-aryl coupling reaction to give vicinally aryl-substituted alkene **8** in excellent yield. In both transformations, the stereochemistry of the alkenyl carbon was retained in the products. Therefore, the stereoselective synthesis of *tetrasubstituted alkenes possessing all different carbon substituents* could be easily achieved.[4a]

Scheme 3



In summary, we have developed a new stereoselective synthesis of tri- and tetrasubstituted alkenes using conformationally labile alkenyllithium species. Furthermore, silyl group in the products serves as useful surrogate of reactive alkenylmetal species with defined structure for further synthetic transformations. Because alkenyllithiums are also prepared by the transmetalation from alkenylstannanes or alkenyliodides, or carbometalation, a variety of synthetic routes would be feasible. In addition, an internal electrophile would not be limited to the silyl groups. Exploration of such possibilities is now in progress.

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Supporting Information Available: Preparations and reactions of alkenyltellurides and transformation of alkenylsilanes. This material is available free of charge via the Internet at http://pubs.acs.org.

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