Solid-Phase Synthesis and Asymmetric Reactions of Polymer-Supported Highly Enantioenriched Allylsilanes

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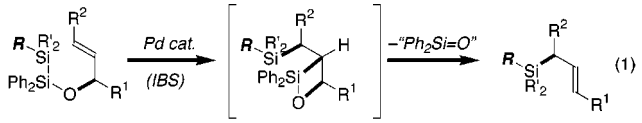
There is an increasing demand for polymer-supported reagents (PSR) in organic synthesis which enable not only the efficient synthesis of target molecules but also effective collection of a number of derivatives for chemical libraries.[1] Furthermore, chiral technologies with development of enantio-directing PSR in organic synthesis, which produces enantiopure molecules stereoselectively in reaction with achiral molecules, seems to be highly attractive and useful.[2] Enantioenriched chiral allylsilanes attached onto the polymer may be one of the most promising and attractive candidates for such enantio-directing PSR, since a high degree of chirality transfer from the silicon-bound allylic carbon to the newly created stereogenic centers in the products has been established in the solution-phase reactions.[3]

Recently, Panek and Zhu successfully demonstrated asymmetric allylation of electrophiles with a polymer-supported allylsilane, in which the allylic moiety was attached to the polymer support through an ω-hydroxy group.[4] Remarkably high yields and diastereoselectivities comparable to those for the corresponding solution-phase reaction were achieved by this strategy. However, the particular polymer-supported allylsilane may not have taken full advantage of immobilization, since the attachment through the hydroxy group may considerably limit the structural variation of the allylsilanes, and the requirement of solution-phase preparation of the enantioenriched allylsilanes bearing the hydroxy group for the attachment may detract from synthetic efficiency. With these in mind, we planned the solid-phase synthesis of new enantioenriched allylsilanes attached onto the resin through the silicon atom.[5] Herein, we report on the synthesis of new polymer-supported enantioenriched allylsilanes, of which synthetic utility is demonstrated by the new asymmetric cyclization reaction giving highly enantioenriched oxacycloheptene derivatives.

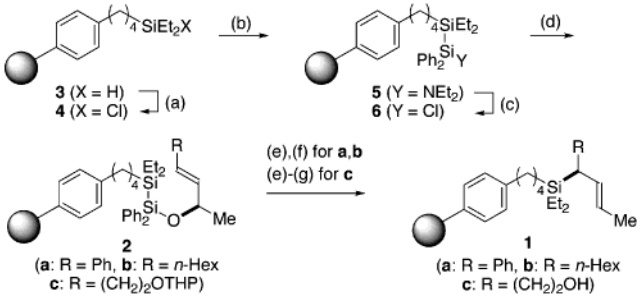
A feasible synthetic plan for the synthesis of polymer-bound enantioenriched allylsilanes is based on the transformations involving stereoselective intramolecular bis-silylation (IBS) of optically active allylic alcohols, of which the solution-phase variant has been established by us (eq 1).[6] This protocol may be



(1)

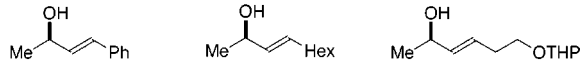
highly suitable for the application to the solid-phase synthesis (**R** = polymer support), since the stereo-determining step involves an intermolecular process (IBS), in which stereoselectivity may hardly be affected by immobilization of substrate onto the polymer support.

Scheme 1. Synthesis of Polymer-Supported Enantioenriched Allylsilanes[a]



[a] Reagents and conditions: (a) 1,3-dichloro-5,5-dimethylhydantoin, CH_2Cl_2, room temperature, 5 h; (b) $Ph_2(Et_2N)SiLi$, THF, room temperature, 10 h; (c) AcCl, THF, room temperature, 4 h; (d) **7a-c** (1 equiv), imidazole, CH_2Cl_2, room temperature, 10 h; (e) $Pd(acac)_2$ (6 mol %), 1,1,3,3-tetramethylbutyl isocyanide, toluene, 110 °C, 6 h; (f) PhLi or *n*-BuLi, THF, 0 °C, 1 h; (g) TsOH, EtOH/THF (1/2), 50 °C, 5 h.

To apply our IBS protocol, we needed to establish a preparative method for polymer-bound disilane carrying a chlorine atom on the silicon for the attachment of allylic alcohols. Commercially available PS-bound (PS: polystyrene) hydrosilane **3** (1.6 mmol/g) was chosen as a starting material, of which transformation to chlorosilane **4** has been reported already (Scheme 1).[7] Reaction of **4** with (diethylamino)diphenylsilyllithium[8] (3 equiv) was carried out at room temperature for 10 h. The reaction mixture was treated with acetyl chloride for conversion of the diethylamino group in **5** into chloride (**6**). The disilane formation was estimated to be quantitative by GC quantification of *N*,*N*-diethylacetamide formed in the chlorination step. This PS-bound chlorodisilane **6** was reacted with highly enantioenriched allylic alcohols **7a**−**c** in the presence of imidazole as a base in dichloromethane.



Fortunately, we found that only 1 equiv of optically active alcohol was needed for attaining reasonable chemical yields of **2** (ca. 80%) and that use of more equivalents did not improve the yield at all. The resulting resins **2a**−**c** were treated with a catalyst generated from $Pd(acac)_2$/1,1,3,3-tetramethylbutyl isocyanide at 110 °C in toluene.

Subsequently, the reaction mixtures were treated with PhLi (for **2a**) or *n*-BuLi (for **2b** and **2c**) at 0 °C in THF to give PS-bound allylsilanes including **1a** and **1b**. For the preparation of **1c** bearing the ω-hydroxy group on the allylic moiety, the THP protection was removed with a catalytic amount of *p*-toluenesulfonic acid in EtOH/THF at 50 °C. It is worth mentioning that the optimized condition using PPTS for the solution-phase deprotection of the

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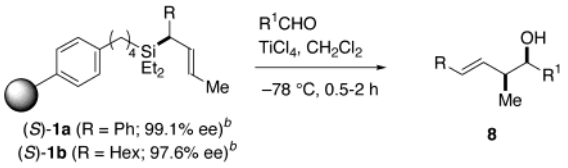
Table 1. Allylation of Aldehydes with PS-Bound Enantioenriched Allylsilanes **1a** and **1b**[a]



(*S*)-**1a** (R = Ph; 99.1% ee)[b]
(*S*)-**1b** (R = Hex; 97.6% ee)[b]

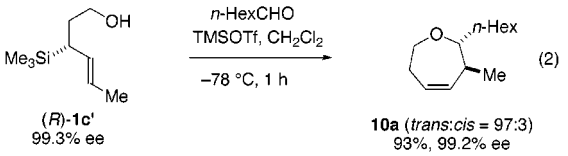
entry	allylsilane (R)	aldehyde (R^1CHO)	product (% yield)[c]	syn:anti[d]	% ee[e]
1	**1a** (Ph)	MeCHO	**8a** (54)	96:4	98.6
2	**1a**	*n*-HexCHO	**8b** (44)	93:7	99.0
3	**1a**	*i*-PrCHO	**8c** (40)	97:3	93.0
4	**1b** (*n*-Hex)	*i*-PrCHO	**8d** (34)	99:1	95.6

[a] **1**, aldehyde (2.0 (for **1a**) or 1.0 equiv (for **1b**)), and $TiCl_4$ (2.0 equiv) were stirred at −78 °C for 0.5−2 h. [b] Enantiomeric excesses determined for the starting allylic alcohols. [c] Isolated yield based on **2** (3 steps). [d] Determined by capillary GC (for entries 1, 3, and 4) or ^{1}H NMR (entry 2). [e] Determined by chiral HPLC.

THP group only resulted in sluggish removal of the protection in the solid-phase synthesis.

With these PS-bound allylsilanes **1a** and **1b** in our hands, we examined some reactions with aldehydes under the typical reaction conditions using $TiCl_4$ at −78 °C (Table 1).[9] Acetaldehyde afforded the corresponding *syn*-homoallylic alcohol **8a** with good diastereoselectivity comparable to the corresponding solution-phase reactions (entry 1). The chemical yield (54%) based on the loaded allylic alcohol **7a** on resin **2a** indicated that each of the three steps was accomplished in high yield (>80% in average). More importantly, formation of allylsilanes possessing not only high enentiopurity but also complete trans olefin geometry was unambiguously evidenced by the nearly perfect chirality transfer from the allylic alcohol. The resin **1a** was also reacted with heptanal and isobutyraldehyde under the same reaction conditions (entries 2 and 3). Although the yield decreased with the increase of the bulkiness of the aldehydes, a high level of diastereoselectivity and chirality transfer has been attained in these reactions. Resin-bound allylsilane **1b** served similarly as an enantioselective allylation reagent, giving the corresponding homoallyl alcohol **8d** with good stereoselectivity (entry 4).

Next, we examined the reactions of ω-hydroxylated allylsilane **1c** with aldehydes in the presence of TMSOTf.[10] The corresponding solution-phase reaction was tested prior to the resin-bound counterpart (eq 2). Reaction of (*R*)-**1c′** (99.3% ee) prepared from

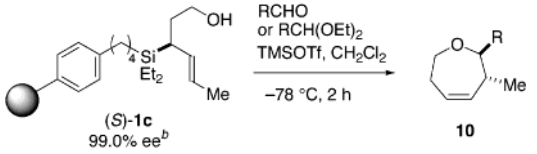


(*R*)-**1c′**
99.3% ee

10a (*trans*:*cis* = 97:3)
93%, 99.2% ee

(*S*)-**7c** with hexanal proceeded in the presence of TMSOTf at −78 °C, giving trans-disubstituted oxacycloheptene **10a** in high yield. The observed high ee (99.2%) revealed that the seven-membered-ring formation proceeded with perfect chirality transfer. Under the same reaction conditions, the resin-bound **1c** afforded **10a** in 64% yield based on the loaded alcohol **7c** (Table 2, entry 1). In addition to the high degree of chirality transfer, the high overall yield for the four steps was remarkable. The overall yield was slightly better than that for the solution-phase synthesis, which was calculated to be 60%. The corresponding diethyl acetal was similarly used as electrophile to give **10a** (entry 2). Application of this resin **1c** to the synthesis of some other oxacycloheptenes was found to be fruitful. Thus, acetaldehyde, cyclohexanecarboxaldehyde, and benzaldehyde afforded the corresponding seven-membered-ring ethers in good yields with a high degree of chirality transfer (entries 3−5). It is worth mentioning that the reactions of resin **1c** with aldehydes proceeded so selectively that essentially no byproducts derived from either the aldehydes or the resin were contained in the crude products.[11]

Table 2. Asymmetric Synthesis of Disubstituted Oxacycloheptenes **10** via Reactions of PS-Bound Enantioenriched Allylsilane **1c** with Aldehydes and Acetal[a]



(*S*)-**1c**
99.0% ee[b]

entry	electrophile	product (R)	%yield[c]	*trans*:*cis*[d]	%ee[e]
1	*n*-HexCHO	**10a** (*n*-Hex)	64	92:8	97.9
2	*n*-HexCH(OEt)$_2$	**10a**	67	93:7	97.9
3	MeCHO	**10b** (Me)	(70)	91:9	>97.2[f]
4	*c*-HexCHO	**10c** (*c*-Hex)	59	91:9	98.1
5	PhCHO	**10d** (Ph)	70	92:8	98.1

[a] **1c**, aldehyde (1.0 equiv), and TMSOTf (2.0 equiv) were stirred at −78 °C for 2 h. [b] Enantiomeric excesses determined for the starting allylic alcohols. [c] Isolated yield based on **2c** (4 steps). GC yield in parentheses. [d] Determined by capillary GC (for entries 1−4) or ^{1}H NMR (entry 5). [e] Determined by chiral GC or HPLC. [f] Incomplete separation in the chiral GC analysis.

In summary, we have demonstrated that resin-bound enantioenriched allylsilanes, which serve as convenient enantiodirecting PSR in organic synthesis, are prepared on the solid phase by the palladium-catalyzed intramolecular bis-silylation protocol. The structurally well-defined allylsilanes on the polymer support are ready not only for highly enantioselective reactions with electrophiles, but also further transformation on the solid support to more elaborated ones. Investigation along this line, as well as optimization of the polymer support, is currently underway in this laboratory

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Supporting Information Available: Experimental procedures, characterization data for the new compounds, and ^{1}H NMR charts of the crude **10** obtained in the reactions of (*S*)-**1c** with electrophiles (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See ^{1}H NMR charts in the Supporting Information.