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Asymmetric Synthesis of Tetrahydrofurans by Diastereoselective [3+2] Cycloaddition of Allylsilanes with α-Keto Esters Bearing an Optically Active Cyclitol as a Chiral Auxiliary

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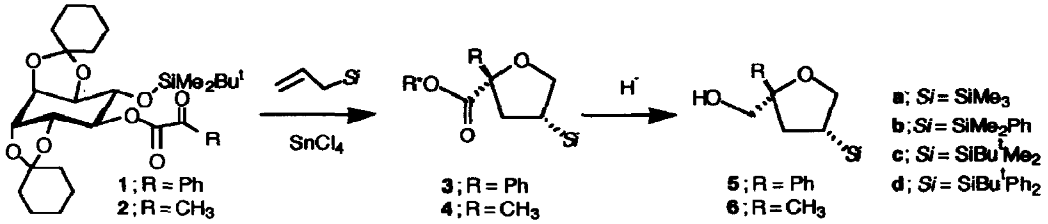
Abstract: **Tin (IV) chloride mediated [3+2] cycloadditions of allylsilanes with optically active α-keto esters derived from L-quebrachitol afforded tetrahydrofuran derivatives via 1,2-silyl migration with high level of diastereoselectivity. Removal of the chiral auxiliary gave silyl-substituted tetrahydrofurans of excellent optical purity.**

Natural compounds containing chiral tetrahydrofurans have been of special interest due to their wide spread occurrence and their intriguing biological activities.[2] Numerous methods for the preparation of optically active tetrahydrofurans have been developed.[3] We have recently reported that tin (IV) chloride promoted [3+2] cycloaddition of allylsilanes and α-keto esters afforded silyl-substituted tetrahydrofurans of excellent diastereoselectivity via 1,2-silyl migration.[4] Thus, allylsilanes represent very useful synthetic equivalents of 2-silyl-substituted 1,3-dipoles.[5-8]

In the course of investigating the utility of L-quebrachitol (1L-(–)-2-*O*-methyl-*chiro*-inositol), which is a naturally occurring optically active cyclitol obtained from an exudate of the rubber tree,[9,10] we have demonstrated that chiral cyclitols derived from L-quebrachitol were excellent chiral auxiliaries.[11-14]

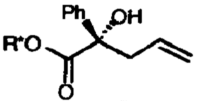


We wish to report here highly selective asymmetric synthesis of 2,2-disubstituted tetrahydrofurans, which employs tin (IV) chloride mediated diastereoselective [3+2] cycloaddition of allylsilanes with chiral α-keto esters (**1** and **2**) those are derived from L-quebrachitol.[8] Although Panek have recently reported Lewis acid promoted diastereoselective addition of chiral crotylsilanes to aldehydes leading to optically active tetrahydrofurans,[5] ready availability of the chiral α-keto esters provide an advantage of our strategy over Panek's protocol, in which less accessible chiral allylsilanes were employed.

Table 1. Results of the tin (IV) chloride promoted cycloaddition of allylsilane with 1 in CH_2Cl_2[a)]

Entry	*Si*	Reaction conditions	Yield 3/%	7/%	5/%	De of 5/%	Ee of 5/%
1	$SiMe_3$	r.t. 5 min	72	22	85[b)]	>98	95
2	$SiPhMe_2$	r.t. 5 min	78	20	72[c)]	>98	>98
3	$SiMe_2Bu^t$	-78°C, 10 min	83	2	78[c)]	>98	96
4	$SiPh_2Bu^t$	r.t. 25 min	85	0	73[b)]	>98	98

a) 1.1 equiv of tin (IV) chloride and 1.2 equiv of allylsilane were employed. b) Reduction with $LiBH_4$. c) Reduction with $LiAlH_4$.



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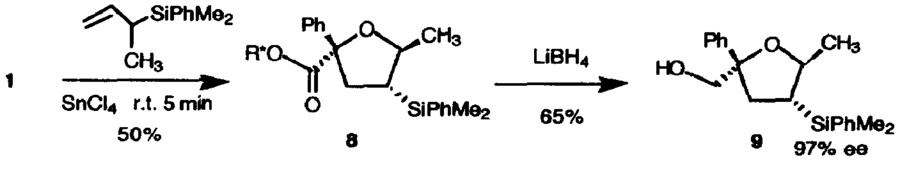
α-Keto esters 1 and 2 were readily prepared from L-quebrachitol.[11b] As reported previously, highly diastereoselective allylation of 1 with allyltrimethylsilane took place by use of tin (IV) chloride, affording exclusively 7 in 92% yield with >98% de.[12] While studying the allylation of 1, we found that a tetrahydrofuran **3a** was best obtained in 72% yield by addition of a diluted solution of tin (IV) chloride (1.1 equiv) in CH_2Cl_2 to a mixture of 1 and allyltrimethylsilane (1.2 equiv) in CH_2Cl_2 at room temperature for 5 min (Table 1, Entry 1). Reductive removal of the chiral auxiliary with $LiBH_4$ gave a chiral tetrahydrofuran **5a** as a single diastereomer in 85% yield. The cycloannulation proceeded successively with other allylsilanes, resulting in the formation of tetrahydrofurans (**5b**, **c**, **d**) of excellent optical purity (Entries 2, 3, and 4). *t*-Butyl substituted allylsilanes had higher propensity to form 5-membered rings. Optical purity of **5a**-**5d** was determined by chiral HPLC analysis (CHIRAL CELL OD, Daicel chemical Co., Ltd.) of their acetates.

Table 2. Results of the tin (IV) chloride promoted cycloaddition of allylsilanes with 2 in CH_2Cl_2[a)]

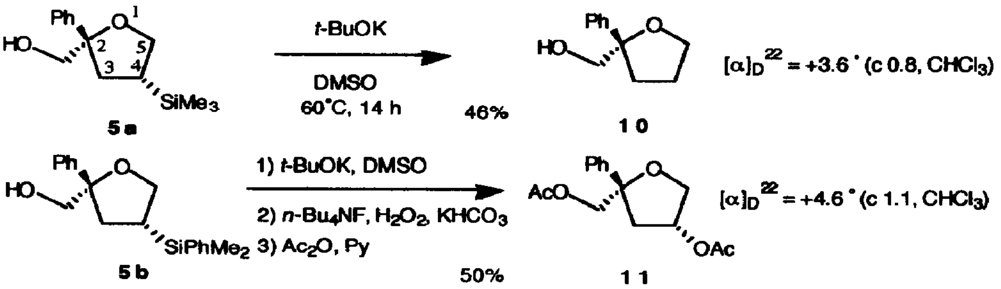
Entry	*Si*	Yield 4/%	6/%	De of 6/%	Ee of 6/%[b)]
1	$SiMe_3$	66	60[c)]	>95	>96
2	$SiPhMe_2$	48	70[d)]	90	>98
3	$SiPh_2Bu^t$	71	100[c)]	66	84

a) Reactions were carried out at room temperature for 5 min with 1.1 equiv of tin (IV) chloride and 1.2 equiv of allylsilane. b) E.e. of the major diastereomer of 6. c) Reduction with $LiBH_4$. d) Reduction with $LiAlH_4$.

Tin (IV) chloride catalyzed cycloaddition of allyltrimethylsilane with 2 also afforded a tetrahydrofuran **4a** in 66% yield. (Table 2, Entry 1) Reductive removal of the chiral auxiliary with $LiBH_4$ furnished **6a** as a single diastereomer in >96% ee, which was determined by 270 MHz ^1H NMR analysis as its MTPA ester. A *t*-butyl substituted allylsilane showed lower diastereoselectivity (Entry 3).



The cycloaddition of **1** with α-methyl substituted allylsilane (2 equiv) followed by reduction led to a 2,2,4,5-substituted tetrahydrofuran **9** as a single diastereomer with 97% ee.



Finally transformation of the silyl moieties was examined. Removal of a trimethylsilyl group of **5a** by means of *t*-BuOK afforded a 2,2-disubstituted tetrahydrofuran (**10**).[15] Although Panek had demonstrated that dimethylphenylsilyl group of tetrahydrofuran could be transformed to hydroxyl group by use of Hg salt with retention of the configuration,[5b,16] it was found that this transformation was achieved without heavy metal salt; successive treatment of **5b** with *t*-BuOK-DMSO, *n*-Bu_4NF-H_2O_2-MeOH-$KHCO_3$,[17] and Ac_2O-Py gave an optically pure 4-hydroxy-tetrahydrofuran as its diacetate (**11**).

Relative stereochemistries of **5a** and **9** were confirmed by chemical correlation of the tetrahydrofurans whose structures had been established by the NOE study in our previous report.[4,18] Those of other tetrahydrofurans were deduced by analogy.

The establishment of the absolute configuration at C(2) in **5a** was made as follows: $BF_3 \cdot OEt_2$ mediated ring opening of **3a** followed by hydrolysis afforded (S)-2-hydroxy-2-phenyl-4-pentenoic acid ($[\alpha]_D^{22}$ +26 ° (c 0.47, $CHCl_3$) (lit.[19] $[\alpha]_D^{22}$ +29° (c 1, $CHCl_3$)). This result revealed that the present diastereofacial selectivity was same as those of the $SnCl_4$ promoted addition of allylsilanes and silyl enol ethers to **1**.[12,13] The absolute stereochemical assignment of other tetrahydrofurans was based on the diastereofacial selectivity observed for **5a**.

A typical experimental procedure for the preparation of **3a** is described (Entry 1, Table 1). To a solution of **1** (153 mg, 0.261 mmol) and allyltrimethylsilane (50 μL, 0.54 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise a 0.2 mol/L solution of tin (IV) chloride in CH_2Cl_2 (1.7 mL, 0.29 mmol) at room temperature. After being stirred at the temperature for 5 min, the reaction mixture was quenched by addition of triethylamine (0.1 mL) followed by H_2O (5 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO_2, hexane: ethyl acetate = 10:1, v/v, developed twice) gave **3a** (131 mg, 72%) and **7** (35 mg, 22%).

In summary, we have developed a novel method for the preparation of optically active tetrahydrofurans taking advantage of the [3+2] cycloaddition of allylsilanes with α-keto esters derived from a chiral cyclitol.

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