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STEREOSELECTIVE SYNTHESIS OF TETRAHYDROFURAN BY DIASTEROSELECTIVE [3+2] CYCLOADDITION REACTION OF CHIRAL ALLYLSILANE WITH α-KETO ESTER

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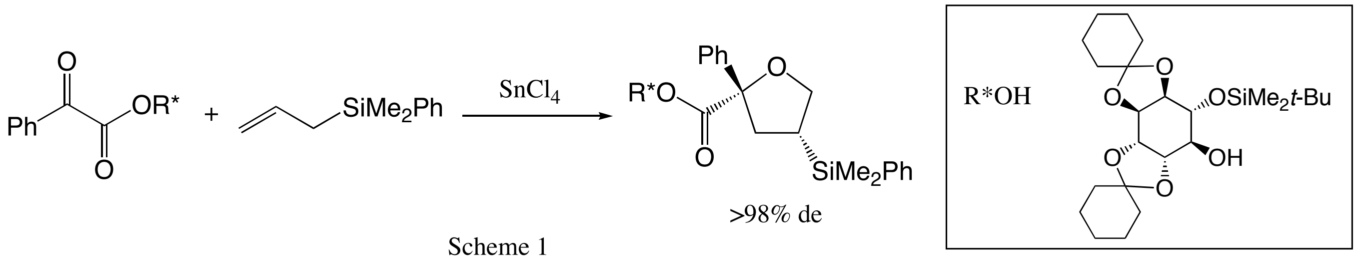
Abstract –Lewis acid mediated [3+2] cycloaddition reaction of chiral allylsilane, bearing a stereogenic center on the silyl substituents, with α-keto ester gave silyl-substituted tetrahydrofurans with good to high stereoselectivity.

INTRODUCTION

Tetrahydrofuran is one of the most important core heterocyclic structures, which exist abundantly in nature. Development of novel method for the preparation of the tetrahydrofuran structure continues to be a challenging task.[1] Lewis acid mediated [3+2] cycloaddition reactions of allylsilane with carbonyl compounds provide useful method for the construction of the tetrahydrofuran derivatives.[2] Although chiral Lewis acid-catalyzed [3+2] cycloaddition reaction of allylsilane with carbonyl compounds has not been reported so far, diastereoselective [3+2] cycloaddition reactions have been reported to give tetrahydrofuran derivatives in optically active form. Two kinds of the combination of alylsilane and carbonyl compounds may be taken into account. One is the combination of achiral allylsilane and chiral carbonyl compounds. We already reported diastereoselective [3+2] cycloaddition reaction of allylsilane with optically active α-keto ester (Scheme 1).[3] The other is the combination of chiral allylsilane with achiral carbonyl compounds. The [3+2] cycloaddition of chiral allylsilane bearing a stereogenic center at allylic carbon attached silicon, represented as **1**, has been extensively employed for the preparation of chiral tetrahydrofurans, by Panek,[4] and Roush.[5] We focused on the chiral allylsilane bearing a stereogenic center at α-silyl group, represented as **2**, and studied diastereoselective [3+2] cycloaddition of **3**[6] with α-keto ester.[7]



Scheme 1

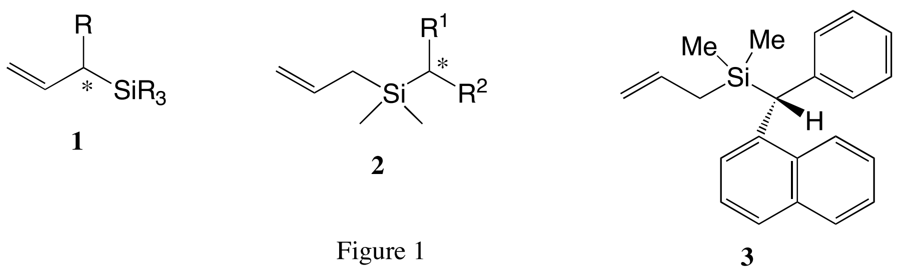


Figure 1

RESULTS AND DISCUSSION

Chiral allylsilane (**3**) was prepared starting from (*R*)-chlorodimethyl[(1-naphthyl)phenylmethyl]silane[6,8] with allyl Grignard reagent. Initial study of the $SnCl_4$-mediated [3+2] cycloaddition reaction of allylsilane with α-keto ester (**4a**) (R=Me) furnished silyl-substituted tetrahydrofuran in a good yield with moderate diastereoselectivity (Table 1, Entry 1). Changing the ester substituent of **4** had beneficial effect on the diastereoselectivity. Use of an ethyl ester (**4b**) (R=Et) improved the de to 70%. Increasing the size of the ester substituents increased the de. The best result was obtained by use of **4e** (R= *t*-butyl) to give the corresponding silyl-substituted tetrahydrofuran (**5e**) in 85% de, which was determined by chiral HPLC analysis.

The silyl group of **5e** was transformed into hydroxy group by the Tamao oxidation[9] to give hydroxy-substituted tetrahydrofuran (**6**) in optically active form (Scheme 2).

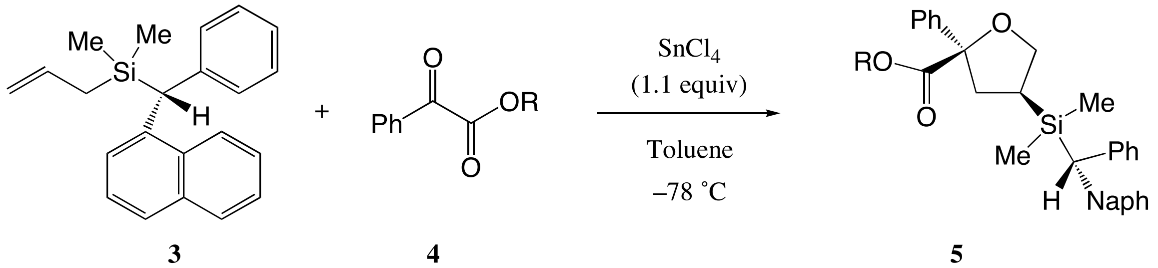
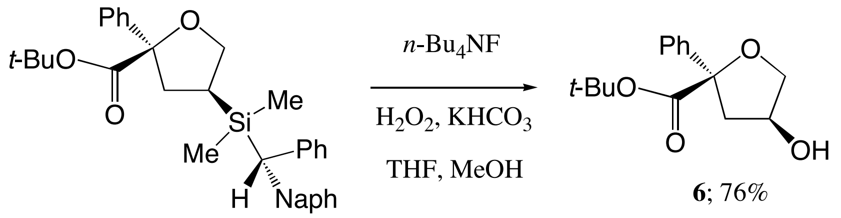


Table 1. Results of the [3+2] cycloaddition reaction

Entry	R	Product	Yield /%	de/%
1	Me	**5a**	89	55
2	Et	**5b**	93	70
3	*i*-Pr	**5c**	92	71
4	C_6H_{11}	**5d**	88	80
5	*t*-Bu	**5e**	94	85

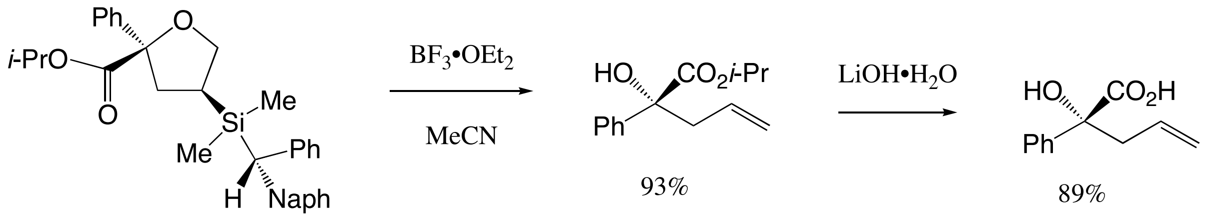


5e

6; 76%

Scheme 2

The establishment of the absolute configuration at C(2) of **5** was made as follows; BF_3•OEt_2-mediated ring opening of **5c** and subsequent hydrolysis to give (*R*)-2-hydroxy-2-phenyl-4-pentenoic acid ($[\alpha]_D^{22}$ −16.1° (c 0.96, $CHCl_3$), lit.,[10] (*S*-isomer) ($[\alpha]_D^{22}$ +29° (c 1, $CHCl_3$)) (Scheme 3). The absolute stereochemistry of other tetrahydrofurans was considered to be same as that of **5c**.



5c 67% ee

93%

89%

Scheme 3

$[\alpha]_D^{22}$ −16.1° (c 0.96, $CHCl_3$)

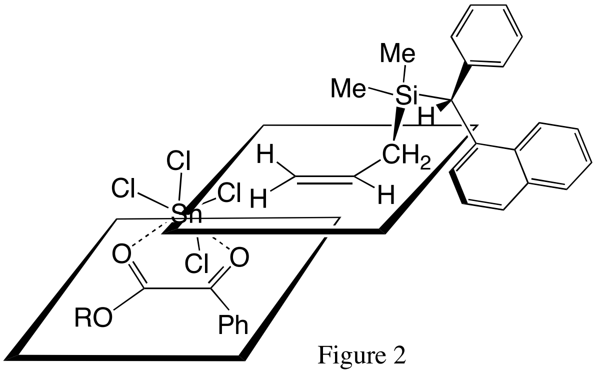


Figure 2

The stereochemical outcome can be rationalized by the plausible synclinal transition state model[3a] as shown in Figure 2. α-Keto ester forms chelate complex and the allylsilane attacks the si-face of the chelated carbonyl. Bulky ester functionality favors this conformation. The conformation of allylsilane shown above derives from the enery-minimized structure by molecular mechanics.[11]

In summary, we have developed diastereoselective [3+2] cycloaddition reaction of optically active allylsilane bearing a stereogenic center on silyl group with α-keto esters. Diastereoselectivity of the cycloaddition reaction is dependent on the ester substituent of α-keto ester.

This paper is dedicated to Professor Barry Trost in celebration of his 65th birthday.

EXPERIMENTAL

Diastereoselective [3+2] cycloaddition of **3** with **4e** (Table 1, Entry 5) is described.

To a solution of **3** (75.0 mg, 0.237 mmol) and **4e** (R= *t*-Bu) (40.7 mg, 0.197 mmol) in toluene (0.4 mL) was added a toluene solution of $SnCl_4$ (0.22 mL, 0.22 mmol, 1.0 mol/L toluene solution) at –78 ˚C. After being stirred at –78˚C for 1 h, the reaction mixture was quenched by addition of sat. $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to leave crude material, which was purified by thin layer chromatography (SiO_2, ethyl acetate : hexane = 1 : 5 / v:v) to afford **5e** (96.5 mg, 0.185 mmol) in 94 %. The diastereomeric excess was determined by chiral HPLC analysis to be 85% de. (ChiralCel OD-H, hexane/ethanol = 150:1, Flow rate =0.5 mL/min, UV=234 nm)

R_f= 0.5 (hexane:ethyl acetate= 5:1/v:v)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10-8.08 (m, 1H), 7.82-7.80 (m, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=7.3 Hz, 1H), 7.44-7.35 (m, 3H), 7.30-7.17 (m, 9H), 7.10-7.06 (m, 1H), 4.33 (s, 1H), 3.86 (dd, *J*=8.5, 8.5 Hz, 1H), 3.66 (dd, *J*=12.1, 8.5 Hz, 1H), 2.26 (t, *J*=12.8 Hz, 1H), 2.12 (dd, *J*=12.8, 7.4 Hz, 1H), 1.50-1.41 (m, 1H), 1.34 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.9, 141.4, 138.0, 134.4, 132.5, 128.9, 128.4, 128.2, 127.9, 127.4, 127.0, 126.8, 126.0, 125.5, 125.4, 125.3, 125.0, 123.8, 87.1, 84.5, 71.4, 68.8, 40.0, 39.0, 25.1, 21.5, -3.7, -4.8; IR ($CHCl_3$) 1725, 1221 cm^{-1}.

Oxidative cleavage of the carbon-silicon bond.

To a solution of 1M *n*-Bu_4NF in THF (0.43 mL, 0.43 mmol) was added a solution of **5e** (140.7 mg, 0.269 mmol, 84% de) in THF (3.0 mL) at 0 ˚C. The mixture was allowed to warm to rt and stirred for 30 min. To the mixture were added successively $KHCO_3$ (40.4 mg, 0.404 mmol), H_2O_2 (35%, 0.32 mL, 2.69 mmol), and methanol (1.2 mL). After being stirred at –78˚C for 24 h, the reaction mixture was diluted with CH_2Cl_2 and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were successively washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4.

The solvent was evaporated in vacuo to leave crude material, which was purified by thin layer chromatography (SiO_2, ethyl acetate : hexane = 2 : 3 / v:v) to afford **6** (53.9 mg, 0.204 mmol) in 76 %. The enantiomeric excess was determined by chiral HPLC analysis to be 83%. (ChiralCel OD-H, hexane/ethanol = 50:1, Flow rate =0.5 mL/min, UV=234 nm).

R_f= 0.4 (hexane:ethyl acetate= 3:2/ v:v)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, *J*=8.2 Hz, 2H), 7.35-7.25 (m, 3H), 4.51 (br s, 1H), 4.11 (d, *J*=3.1 Hz, 2H), 2.93 (d, *J*=13.9 Hz, 1H), 2.59 (d, *J*=6.2 Hz, 1H), 2.28 (dd, *J*=13.9, 5.3 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 142.2, 128.7, 128.2, 125.1, 87.7, 84.4, 76.2, 69.3, 45.2, 25.9, 21.8; MS (EI) m/z (%) 163(100), 145(18), 105(50), 77(28), 56(45); IR ($CHCl_3$) 3469, 1726, 1220 cm^{-1}; $[\alpha]_D^{26}$ +14.4° (c 1.1, $CHCl_3$, 83% ee).

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