[3+2] Cycloaddition Reactions of Cyclopropylmethylsilanes and α-Keto Aldehydes: Trans- and Cis-selective Formation of 2-Silylmethyltetrahydrofurans

Kohei Fuchibe, Yuji Aoki, and Takahiko Akiyama*
Department of Chemistry, Faculty of Science, Gakushuin University,
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588

(Received January 12, 2005; CL-050054)

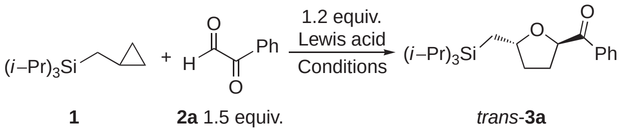
Cyclopropylmethylsilanes and α-keto aldehydes underwent novel [3+2] cycloaddition reaction to afford 2-silylmethyl substituted tetrahydrofurans in good yields. Relative stereochemistries of the products were dependent on the reaction temperatures, *trans*- and *cis*-tetrahydrofurans were obtained stereoselectively at 0 °C and at −78 °C, respectively.

Tetrahydrofuran is one of the most important structures that constitute a large family of organic heterocycles. Although a variety of synthetic methods to approach the structures have been reported so far,[1] development of more facile and efficient methods is still desired owing to a wide variety and importance of substituted tetrahydrofurans.

In order to accomplish a facile construction of the tetrahydrofuran skeletons, we have formerly got interested in cycloaddition reactions because two chemical bonds are formed in a single operation. Allylsilanes and allylgermanes were found to undergo migrative [3+2] type cycloaddition reaction with α-keto esters to afford 3-silylated tetrahydrofurans in a cis-selective manner.[2] These results clearly proved a great advantage of the cycloaddition approach for a facile and diastereoselective preparation of tetrahydrofurans and our attention was newly focused on a use of cyclopropylmethylsilanes[3] as C3 donors.[4] In this communication, we are going to describe a novel temperature-dependent trans- and cis-selective preparation of 2-silylmethylated tetrahydrofurans via [3+2] cycloaddition reactions of cyclopropylmethylsilanes with α-keto aldehydes.

Table 1 shows our general survey over Lewis acids and solvents using (cyclopropylmethyl)triisopropylsilane **1** and phenylglyoxal **2a** as substrates. It revealed that combination of $SnCl_4$ and CH_2Cl_2 is the most favorable: **1**, **2a** (1.5 equiv.), and $SnCl_4$ (1.2 equiv.) in CH_2Cl_2 gave *trans*-2-silylmethylated tetrahydrofuran **3a** in 83% yield (Table 1, Run 1)[5,6] but Lewis-basic medium such as ethers and acetonitrile resulted in low yield formation of the cycloadduct and no recovery of the starting materials (Runs 2–4). Other Lewis acids such as $TiCl_4$, $ZrCl_4$, and $BF_3 \cdot OEt_2$ gave less satisfactory results (Runs 6–8).[7,8]

Table 1. Reaction of cyclopropylmethylsilane **1** with phenylglyoxal **2a**



Run	Lewis acid	Solvent	Conditions	**3a**/% (*trans*/*cis*)[a]
1	$SnCl_4$	CH_2Cl_2	0 °C, 0.5 h	83 (>99/1)[b]
2		Et_2O	0 °C, 5 h then rt, 16 h	6 (70/30)
3		THF	0 °C, 20 h then rt, 6 h	— (—)[c]
4		CH_3CN	0 °C, 20 h then rt, 6 h	— (—)
5		Toluene	0 °C, 0.5 h	66 (83/17)
6	$TiCl_4$	CH_2Cl_2	0 °C, 0.5 h	3 (>99/1)[b]
7	$ZrCl_4$		0 °C, 24 h	8 (68/32)
8	$BF_3 \cdot OEt_2$		0 °C, 5 h then rt, 16 h	— (—)

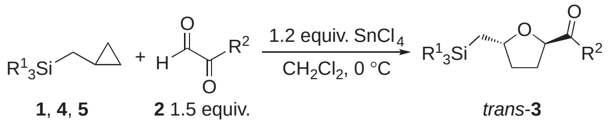
[a] Determined by integrals on ^1H NMR spectra.
[b] Only trans isomer was detected on ^1H NMR spectra.
[c] 31% of starting material **1** was recovered.

This reaction was applicable to various α-keto aldehydes: not only **2a** but also heteroaromatic glyoxals and butyl glyoxylate afforded the corresponding trans products **3** as essentially single diastereomers (Table 2, Runs 1–9).[9] Less bulky dimethylphenylsilane **6** also furnished **3** in a good yield although homoallylation product was obtained in 16% yield (Run 11).[10,11]

Interestingly, silanes **1**, **4**, **5**, and **6** reacted with aldehydes **2a**–**2h** at −78 °C to afford *cis*-**3** preferentially (Table 3, Runs 1–11). These stereochemical reversals suggested that *cis*-**3** were produced kinetically,[12] and at 0 °C, isomerized to *trans*-**3** thermodynamically. The speculation was supported by the fact that relative stereochemistry of a product was found to be trans when the reaction was carried out at −78 °C and then warmed up to 0 °C (Run 12).

These stereochemical phenomena can be rationalized by the mechanism outlined below (Scheme 1): **1** undergoes nucleophilic addition to a $SnCl_4$-activated aldehyde **2** via antiperiplanar transition state in which silylmethyl group is oriented at less hin-

Table 2. Trans-selective [3+2] cycloaddition



Run	SiR^1_3	R^2	Time/h	**3**/% (*trans*/*cis*)[a]
1	Si(*i*-Pr)$_3$ (**1**)	Ph (**2a**)	0.5	83 (**3a**) (>99/1)[b]
2		2-Naphthyl (**2b**)	0.6	72 (**3b**) (99/1)
3		2-Furyl (**2c**)	0.5	90 (**3c**) (>99/1)[b]
4		2-Thienyl (**2d**)	0.5	82 (**3d**) (>99/1)[b]
5		4-$MeOC_6H_4$ (**2e**)	0.5	76 (**3e**) (>99/1)[b]
6		4-ClC_6H_4 (**2f**)	0.5	68 (**3f**) (>99/1)[b]
7		4-MeC_6H_4 (**2g**)	0.5	84 (**3g**) (>99/1)[b]
8	Si(*i*-Pr)$_2$Ph (**4**)	CO_2*n*-Bu (**2h**)	1.0	43 (**3h**) (>99/1)[b]
9		Ph (**2a**)	1.0	84 (**3i**) (97/3)
10	Si(*t*-Bu)Ph$_2$ (**5**)	Ph (**2a**)	0.5	69 (**3j**) (59/41)
11	$SiMe_2Ph$ (**6**)	Ph (**2a**)	1.0	56 (**3k**) (>99/1)[b,c]

[a] Determined by integrals on ^1H NMR spectra.
[b] Only trans isomer was detected on ^1H NMR spectra.
[c] Homoallylation product was obtained in 16% yield.

Table 3. Cis-selective [3+2] cycloaddition[a]

Run	Silane	Aldehyde	Time/h	**3**/% (*trans*/*cis*)[b]
1	**1**	**2a**	1.5	Quant. (28/72, **3a**)
2		**2b**	1.0	89 (28/72, **3b**)
3		**2c**	1.0	87 (26/74, **3c**)
4		**2d**	1.0	57 (38/62, **3d**)
5		**2e**	2.0	66 (32/68, **3e**)
6		**2f**	1.8	71 (48/52, **3f**)
7		**2g**	1.0	85 (36/64, **3g**)
8	**4**	**2h**	18	54 (37/63, **3h**)[c]
9		**2a**	1.0	93 (32/68, **3i**)
10	**5**	**2a**	1.1	84 (33/67, **3j**)
11	**6**	**2a**	1.0	73 (31/69, **3k**)[d]
12[e]	**1**	**2a**	1.2	93 (>99/1, **3a**)[f]

[a] Silane:aldehyde:$SnCl_4$ = 1.0:1.5:1.2, CH_2Cl_2, −78 °C.

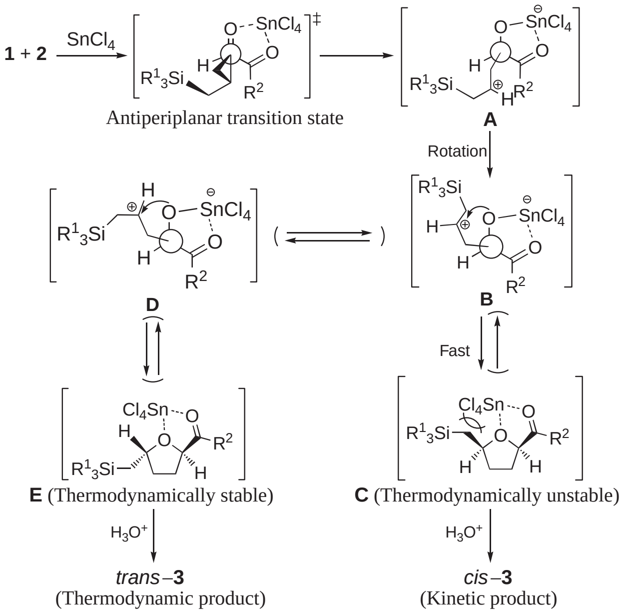
[b] Determined by integrals on ^1H NMR spectra.

[c] Approximately 0.4 equiv. of **4** was recovered.

[d] Homoallylation product was not obtained.

[e] After confirming that **1** was consumed completely by a TLC analysis, temperature was raised up to 0 °C.

[f] Only trans isomer was detected on ^1H NMR spectra.



Scheme 1. Plausible mechanism.

dered position. The resulting β-silyl cation intermediate **A** undergoes rotation and subsequent ring closure of the resulting rotamer **B** gives a *cis*-**3**/$SnCl_4$ complex **C** kinetically. Hydrolysis of **C** affords *cis*-**3**.

On the other hand, the kinetically formed intermediate **C** possesses bulky silylmethyl group on its concave face, and therefore, thermodynamically unstable. When the reaction was carried out at 0 °C or the temperature was raised up to 0 °C, thermodynamically unstable **C** thus undergoes ring opening and rotation to give **D**. Re-closing of **D** gives thermodynamically stable *trans*-complex **E** and hydrolysis of **E** affords *trans*-**3**.

In summary, we could develop novel [3+2] cycloaddition reaction of cyclopropylmethylsilanes with aldehydes. Relative stereochemistries of the products were dependent on the reaction temperatures: trans and cis diastereomers were obtained preferentially at 0 °C and −78 °C, respectively.

References and Notes

1 For reviews, see: a) M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2301. b) J.-C. Harmange and B. Figadère, *Tetrahedron: Asymmetry*, **4**, 1711 (1993).

2 a) T. Akiyama, K. Ishikawa, and S. Ozaki, *Chem. Lett.*, **1994**, 627. b) T. Akiyama, T. Yasusa, K. Ishikawa, and S. Ozaki, *Tetrahedron Lett.*, **35**, 8401 (1994). c) T. Akiyama and M. Suzuki, *Chem. Commun.*, **1997**, 2357. See for cycloaddition reactions with α,β-unsaturated carbonyls: d) T. Akiyama, E. Hoshi, and S. Fujiyoshi, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2121. e) T. Akiyama and M. Yamanaka, *Tetrahedron Lett.*, **39**, 7885 (1998). For reviews, see: f) C. E. Masse and J. S. Panek, *Chem. Rev.*, **95**, 1293 (1995). g) H.-J. Knölker, *J. Prakt. Chem.*, **339**, 304 (1997).

3 Cyclopropylmethylsilanes react with carbon electrophiles although examples are relatively scarce: a) M. Grignon-Dubois and J. Dunoguès, *J. Organomet. Chem.*, **309**, 35 (1986). b) M. Grignon-Dubois, J. Dunoguès, and R. Calas, *Can. J. Chem.*, **59**, 802 (1981). c) D. C. Braddock, D. M. Badine, T. Gottschalk, A. Matsuno, and M. Rodriguez-Lens, *Synlett*, **2003**, 345.

4 V. K. Yadav and his coworkers have recently reported cycloaddition reaction of acceptor-substituted cyclopropylmethylsilanes. See: a) V. K. Yadav and N. V. Kumar, *J. Am. Chem. Soc.*, **126**, 8652 (2004). b) V. K. Yadav and V. Sriramurthy, *Angew. Chem., Int. Ed.*, **43**, 2669 (2004). c) V. K. Yadav and V. Sriramurthy, *Org. Lett.*, **6**, 4495 (2004).

5 Relative stereochemistry of **3a** was determined by NOE experiment. Relative stereochemistries of other products except **3a** were determined by analogy on their ^1H NMR spectra.

6 This reaction requires stoichiometric amounts of $SnCl_4$. Run with 0.3 equiv. of $SnCl_4$ resulted in 38% yield of **3a** (*cis*/*trans* = 3/7) and 51% recovery of **1** (CH_2Cl_2, 0 °C, 2 h).

7 None of homoallylation product was obtained in all the cases described in Table 1.

8 This reaction did not proceed by the act of HCl that is prepared from acetyl chloride and methanol in CH_2Cl_2 (**1**:**2a**:HCl = 1.0:1.0:1.2, CH_2Cl_2, 0 °C, 0.5 h then rt, 1.0 h. 80% recovery of **1**). HCl that was possibly generated from $SnCl_4$ is thus neglectable for the reaction course.

9 *tert*-Butyl(diphenyl)silane **5** exceptionally gave the corresponding product of approximately 6:4 diastereomer ratio. The reason is not clear but we suspect that it is due to eletronic effect of two phenyl groups on silicon atom.

10 Allylphenyldimethylsilane has the similar trend when reacted with α-keto esters. See Ref. 2a.

11 Unfortunately, reactions with other carbonyl compounds such as benzaldehyde, 3-benzyloxypropionaldehyde, ethyl 2-oxo-2-phenylacetate, and 2,3-butanedione gave complex mixture. Fast metal exchange of cyclopropylmethylsilanes and $SnCl_4$ may be responsible: I. Ryu, H. Suzuki, S. Murai, and N. Sonoda, *Organometallics*, **6**, 212 (1987).

12 Reaction of **1** and **2a** at −100 °C gave a diastereomeric mixture of **3a** with essentially the same diastereomer ratio (**1**:**2a**:$SnCl_4$ = 1.0:3.0:1.2, CH_2Cl_2, −100 °C, 6 h. 69% yield, *trans*/*cis* = 26/74). This result suggests that the ratio of 3/7 reflects the ratio of kinetic constants of *trans*-cyclization and *cis*-cyclization.

Published on the web (Advance View) March 12, 2005; DOI 10.1246/cl.2005.538