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Formal [3 + 2] and [3 + 3] Additions of Acceptor-Substituted Cyclopropylmethylsilanes to Allenylsilanes

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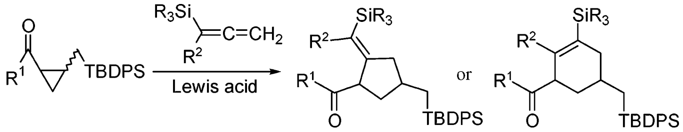
ABSTRACT



1,3-Dipolar synthons formed from vicinal TBDPS-substituted cyclopropyl alkyl/phenyl ketones on treatment with Lewis acids such as $TiCl_4$ and Et_2AlCl reacted with allenylsilanes to furnish [3 + 2] and [3 + 3] adducts with high regio- and stereocontrol.

The endeavor of carbon−carbon bond formation becomes attractive when more than one bond is formed in a single maneuver. Lewis acid promoted reactions of allenylsilanes with 1,2- and 1,3-dipoles provide easy access to five- and six-membered carbo- and heterocyclic rings where the allenylsilane functions as the synthetic equivalent of a silyl-substituted 1,2- and/or 1, 3-dipole.[1] To explore the synthetic applications of cyclopropylmethylsilanes,[2] we have previously shown cyclopropyl ketones bearing a vicinal *tert*-butyldiphenylsilylmethyl group to serve as excellent 1,3-dipolar synthons under Lewis acid conditions to enable formal [3 + 2] cycloadditions of arylacetylenes in a regio- and stereoselective manner.[2d] To our knowledge, dipolar additions of donor−acceptor substituted cyclopropanes to allenylsilanes are hitherto unknown.[1,3] However, allylation and cycloaddition reactions of activated cylopropanes with allylsilanes have been reported.[3b,4] Herein, we report the first application of allenylsilanes for cycloaddition with *tert*-butyldiphenylsilylmethyl-substituted cyclopropyl ketones, leading to the formation of [3 + 2] and [3 + 3] adducts. The course of the reaction was modulated by both the reaction temperature and the substitution profile of the allenylsilane.

In principle, the donor−acceptor substituted cyclopropane of type **1** could react first either a nucleophile through the silicon-stabilized positive end of the dipole or with an electrophile through the negative end, i.e., the enolate.[3d] The reaction outlined in Scheme 1 falls under the former domain. The vinyl cation **A** may rearrange to the vinyl cation **B** entailing 1,2-migration of the allenylsilicon function.[1,5] The

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(1) (a) Miura, K.; Hosomi, A. *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 409−501. (b) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (c) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (d) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389. (e) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407. (f) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1991**, *32*, 2327. (g) Evans, D. A.; Sweeny, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (h) Denmark, S. E.; Gomez, L. *Heterocycles* **2002**, *58*, 129.

(2) (a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717. (b) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (c) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281. (d) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669. (e) Yadav, V. K.; Vijaya Kumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652.

(3) (a) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099. (b) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 4639. (c) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (f) Yu, M.; Pantos, G. D.; Sessler, J. L.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057. (g) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139.

(4) (a) Bambal, R.; Kemmett, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734. (b) Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657. (c) Bohm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955.

10.1021/ol047991w CCC: $27.50

Scheme 1. Working Mechanism for [3 + 2] and [3 + 3] Additions

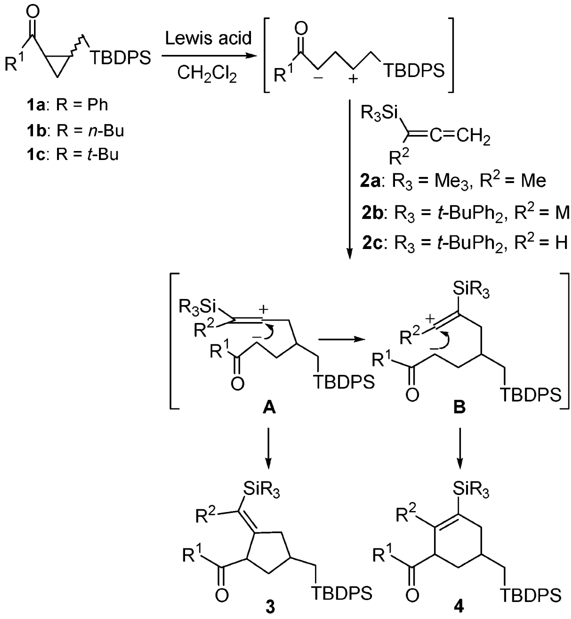
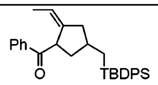
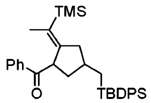
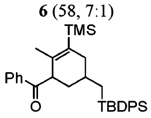
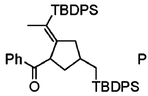
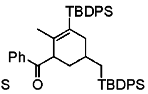
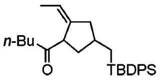
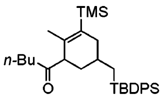
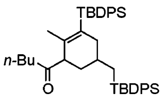
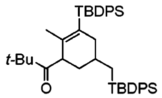


Table 1. [3 + 2] and [3 + 3] Additions of **1a**−**c** with Allenylsilanes

Entry	silane	allenylsilane	Lewis acid	Product (yield %, *cis:trans*)	
1	**1a** (*cis/trans*)	**2a**	$TiCl_4$	 **5** (90, 3.2:1)	
2[a]	**1a** (*cis/trans*)	**2a**	$TiCl_4$	 **6** (58, 7:1)	
3	**1a** (*cis/trans*)	**2a**	Et_2AlCl	 **7** (65, 100:0)	
4	**1a** (*cis/trans*)	**2b**	$TiCl_4$	 **8** (53, 95:5)	 **9** (32, 100:0)
5[b]	**1a** (*cis/trans*)	**2b**	$TiCl_4$	**8** (15, 95:5)	**9** (45, 100:0)
6	**1a** (*cis/trans*)	**2b**	Et_2AlCl	**9** (60, 100:0)	
7	**1b** (*cis/trans*)	**2a**	$TiCl_4$	 **10** (75, 1.9:1)	
8	**1b** (*cis/trans*)	**2a**	Et_2AlCl	 **11** (65, 100:0)	
9	**1b** (*cis/trans*)	**2b**	Et_2AlCl	 **12** (55, 100:0)	
10	**1c** (*cis/trans*)	**2b**	$TiCl_4$	 **13** (65, 100:0)	

[a] Reaction was conducted using both $TiCl_4$ and Et_2AlCl, 1.3 equiv each. [b] Reaction was conducted at −20 °C.

intramolecular capture of the cations **A** and **B** by the enolate will then culminate in the formation of the five- and six-membered carbocycles, **3** and **4**, respectively. The olefin geometry in **3** is likely to be controlled by the steric effects arising from the terminal substituents on the olefinic bonds in the allenylsilane and the enolate and also by the stereoelectronic effects arising from the allenyl silicon during the ring closure.

The phenyl ketone **1a**[6] underwent smooth ring opening with $TiCl_4$ in CH_2Cl_2 at − 78 °C and reacted subsequently with the allene **2a** to afford the [3 + 2] adduct **5** (Table 1, entry 1). In contrast to the previous reports,[1] the allenyl trimethylsilicon was lost. Employment of Et_2AlCl along with $TiCl_4$ (1.3 molar equiv each) at − 78 °C prevented this loss (entry 2). The loss of the trimethylsilyl group under only $TiCl_4$ conditions must, therefore, be due to protodesilylation caused by the adventitious HCl. Since Et_2AlCl is an efficient scavenger of protons,[7] its application terminated the protodesilylation channel completely. Application of anhydrous K_2CO_3 as a suspension was not successful at preventing the loss of the trimethylsilicon function, probably because of the heterogeneous nature of the reaction mixture.

We studied next the effect of temperature on the mode of addition arising from the migration of the allenyl silicon. When the above reaction was conducted at 25 °C under $TiCl_4$ conditions, the reaction was vigorous, resulting in a mixture of several products. However, Et_2AlCl worked very well at 25 °C, and interestingly, only the [3 + 3] adduct was formed (Table 1, entry 3). The allenyl trimethylsilicon function was retained in the product to arm it with the synthetically useful vinylsilane motif.[8] Bulky substituents on the silicon in allenylsilane[1c] will also be expected to prevent its loss under the $TiCl_4$ condition. Indeed, when **1a** was reacted with the allenylsilane **2b** at − 78 °C, both the [3 + 2] and [3 + 3] adducts had formed in a 1.7:1 ratio (Table 1, entry 4). Further, when the same reaction was conducted at − 20 °C, significant migration of the allenyl silicon occurred to furnish [3 + 2] and [3 + 3] adducts in a 1:3 ratio (Table 1, entry 5). A complete silicon migration was noted when the reaction was conducted at 25 °C using Et_2AlCl (Table 1, entry 6). The opening of the cyclopropane ring with Et_2AlCl pro-

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(5) For discussions on silyl-stabilized β-carbocations, see: (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; p 81. (b) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2627. (c) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res*. 1999, *32*, 183.

(6) Cyclopropane derivatives **1a**−**c**, **16**, and **20** were prepared from a rhodium-catalyzed carbene insertion reaction of the corresponding diazocompound with allyl *tert*-butyldiphenylsilane.

(7) Snider, B. B.; Rodini, David J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

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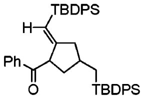
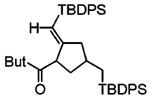
ceeded poorly at temperatures below 25 °C. Thus, the silicon migration appears to be facile at higher temperatures.

The results from other cyclopropane derivatives are also collected in Table 1. The reaction of the alleneylsilane **2a** with the *n*-butyl ketone **1b** (entry 7) was similar to the reaction with the phenyl ketone **1a**. However, the *cis*:*trans* selectivity had reduced from 3.2:1 to 1.9:1. Unlike the reaction of the phenyl ketone **1a** (entry 4), the *tert*-butyl ketone **1c** reacted with the allenylsilane **2b** under $TiCl_4$ conditions to afford the [3 + 3] adduct exclusively (entry 10). The relative stereochemistry of the substituents and the geometry of the olefinic bond in the products were ascertained from NOE measurements.

In partial support of the reaction proceeding through discrete vinyl cations as outlined in Scheme 1, we considered studying reactions of the allenylsilane **2c**. The transition state corresponding to **B** (Scheme 1, $R^2 = H$) will be expected to be higher in energy than the transition state corresponding to **A** (Scheme 1, $R^2 = H$) as a result of the difference in the substitution profile of the cationic center. Thus, one would expect the [3 + 2] adduct to form in preference to the [3 + 3] adduct, irrespective of the reaction temperature and the Lewis acid employed. The results are collected in Table 2.

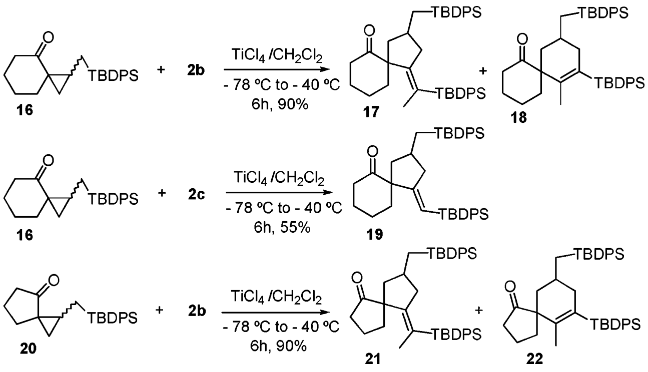
Table 2. [3 + 2] Additions of **1a** and **1c** with Allenylsilane **2c**

Entry	silane	allenylsilane	Lewis acid	Product (yield %, *cis*:*trans*)
1	**1a** (*cis*/*trans*)	**2c**	$TiCl_4$	 **14** (62, 2.8:1)
2	**1a** (*cis*/*trans*)	**2c**	Et_2AlCl	**14** (40, 2.3:1)
3	**1c** (*cis*/*trans*)	**2c**	$TiCl_4$	 **15** (60, 5.8:1)

In the event that the reactions were conducted under the standard conditions, the [3 + 2] adducts formed exclusively. The alternate silirenium ion formation is unable to explain the exclusive attack of the enolate on the internal allenic carbon. The silirenium pathway cannot explain the observed dependence of product distribution on temperature either. As above, the relative stereochemistry of the substituents and the geometry of the olefinic bond in the products were ascertained from NOE measurements.

The [4.4]-, [4.5]-, and [5.5]-spiro skeletons[9] were also generated in good to excellent yields (Scheme 2). *trans*-**16**[6] and *cis*-**16**[6] reacted with the allenylsilane **2b** to generate a 2:1 mixture of **17** and **18**, each as a single diastereomer, and with the allenylsilane **2c** to generate **19** exclusively, again as a single diastereomer. Likewise, *trans*-**20**[6] and *cis*-**20**[6] reacted with the allenylsilane **2b** to generate a 1:1.1 mixture of **21** and **22**, each as a single diastereomer.[10]

Scheme 2. Construction of [4.4]-, [4.5]-, and [5.5]-Spiro Skeletons



The predominant *cis*-selectivity could be explained from a consideration of the possible transition state structures for the addition. Two transition structures, TS-I and TS-II (Figure 1), could be constructed for the [3 + 3] addition. TS-I, leading to the *trans*-product, will be higher in energy than TS-II for the steric interactions as shown. The *cis*-product will therefore predominate. Likewise, two transition state structures, TS-III and TS-IV, could be constructed for the [3 + 2] addition. Since TS-III, leading to the *trans*-product, will be higher in energy than TS-IV for the *pseudo*-1,3-diaxial interaction as shown, TS-IV will generate the *cis*-product predominantly.

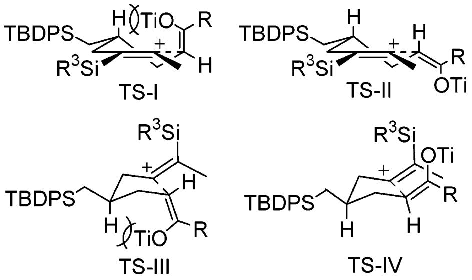


Figure 1. Transition states for [3 + 2] and [3 + 3] additions.

It is easy to see for the *E*-enolate as well that the transition states corresponding to TS-I and TS-III will be higher in energy than the transition states corresponding to TS-II and TS-IV, respectively, for the steric interactions arising from R and the axial hydrogen on the carbon bearing the silylmethyl function. The *cis*-product must therefore predominate again. The exclusive [3 + 3] addition in entry 10

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(9) (a) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903. (b) Sannigrahi, M. Tetrahedron **1999**, *55*, 9007. (c) Knoelker, H.-J.; Baum, E.; Graf, R.; Jones, P. G.; Spieb, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 2583. (d) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (e) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901.

(10) The assignment of the relative stereochemistry of **17**−**19**, **21**, and **22** by NOE measurements was difficult because of the crowded nature of the spectrum. Efforts are being made to secure the same through derivatization and crystal structure illucidation.

(Table 1) could be explained through TS-IV wherein the steric interactions of R (= *t*-Bu) with the methyl group of the allenyl reactant in the *Z*-enolate or the silicon function of the allenyl reactant in the corresponding *E*-enolate retarded the five-ring closure. This allowed the silicon to migrate to attain the strain-free six-membered ring transition structure TS-II.

In summary, vicinal *tert*-butyldiphenylsilylmethyl substituted cyclopropyl ketones reacted with allenylsilanes in the presence of Lewis acids such as $TiCl_4$[11] and Et_2AlCl [12] to form five- and six-membered carbocycles via formal [3 + 2] and [3 + 3] additions with high regio- and stereocontrol. The reaction with Et_2AlCl at 25 °C generates the six-membered ring product exclusively. The present protocol has potential to find applications in the synthesis of carbocyclic natural products and carbocyclic nucleosides.[13]

Acknowledgment. Authors thank DST, Government of India, for financial support. This work is dedicated to Professor R. P. Gandhi, a true inspirer.

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **General Procedure for the $TiCl_4$-Assisted Reaction.** A solution of freshly distilled $TiCl_4$ (61 mg, 0.326 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added slowly under N_2 to the stirred solution of a cylopropylmethylsilane (0.251 mmol) and an allenylsilane (0.326 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at −78 °C. The reaction mixture turned deep red. After stirring for 3 h at −78 °C, it was warmed slowly over 1 h to −40 °C. The stirring was continued at this temperature for 2 h, and the reaction mixture was taken up in Et_2O (10 mL). The ethereal solution was washed with water (1 × 7 mL). The aqueous washing was extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine, dried, and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/hexanes) furnished the pure product(s). The separation of the *cis*- and *trans*-isomers was achieved by radial chromatography over silica gel (EtOAc/hexanes).

(12) **General Procedure for the Et_2AlCl-Assisted Reaction.** A solution of Et_2AlCl (54 mg, 0.375 mmol) in toluene (0.208 mL) was added slowly under N_2 to the stirred solution of a cylopropylmethylsilane (0.251 mmol) and an allenylsilane (0.326 mmol) in anhydrous CH_2Cl_2 (1.3 mL) at 25 °C when the reaction mixture turned pale yellow. After stirring for 6 h, the reaction mixture was quenched with water at 0 °C and diluted with Et_2O (10 mL). The ethereal solution was washed with water (7 mL). The aqueous washing was extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine, dried, and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/hexanes) furnished the pure product.

(13) (a) Huldlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (c) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947. (d) Gurjar, M. K.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552. (e) Moon, H. R.; Kim, H. O.; Lee, K. M.; Chun, M. W.; Kim, J. H.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 3501. (f) Hong, J. H.; Shim, M. J.; Ro, B. O.; Ko, O. H. *J. Org. Chem.* **2002**, *67*, 6837.