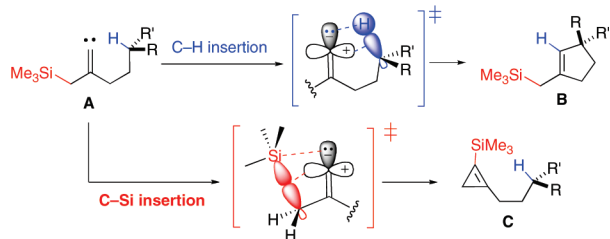


Cyclopropanation of Alkylidene Carbenes Derived from α -Silyl KetonesJingwei Li,[†] Chunrui Sun,[†] and Daesung Lee*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

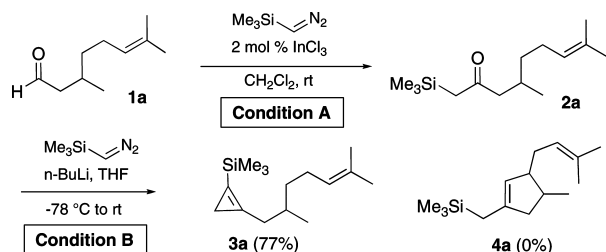
Received March 9, 2010; E-mail: dsunglee@uic.edu

Insertion of alkylidene carbenes into C–H bonds is a powerful tool for constructing carbocycles containing quaternary carbon centers with defined stereochemistry.¹ We envisioned that the prowess of this C–H insertion reaction can be extended to the silyl-substituted alkylidene carbene **A**, which should constitute an effective entry into the synthesis of functionalized cyclopentene derivatives of type **B**. In a preliminary study, however, we found that alkylidene carbene **A** preferentially provided cyclopropene **C** instead of cyclopentene derivative **B**, except for substrates with strongly activated γ –H bonds.² This is probably due to a more favorable interaction of the empty p orbital of the carbenic carbon with the nearby C–Si bond than with the rather remote γ –H bond. Since cyclopropenes are unusual yet versatile substrates for a variety of synthetic transformations,³ the development of efficient methods for their preparation is highly desirable. Herein we report a new cyclopropanation that involves selective insertion into the α –Si bond of α -silyl ketones.



Our investigation commenced with a search for an efficient method for the preparation of α -silyl ketones.⁴ We found that the indium chloride-catalyzed reaction between trimethylsilyldiazomethane and aldehydes provided an efficient preparation of α -silyl ketones (condition A in Scheme 1).⁵ With this secure method, citronellal **1a** was converted into **2a**, which was then treated with lithiated trimethylsilyldiazomethane⁶ without purification (condition B in Scheme 1), delivering a product in 77% yield. To our surprise, the identity of this compound was established to be silylcyclopropene **3a**,⁷ and the expected cyclopentene derivative **4a** was not detected.

Scheme 1. Selective Insertion into the α –Si Bond Rather Than the γ –H Bond



The generality of cyclopropene formation via α –Si insertion was further examined using a variety of aldehydes with γ,δ -

Table 1. Formation of Cyclopropenes via α –Si Bond Insertion of Alkylidene Carbenes Derived from α -Silyl Ketones^a

entry	aldehyde	cyclopropene	yield (%) ^b
1			81
2			78
3			71
4			69
5			75
6			81
7			54
8			65
9			51
10			82
11			71
12			75

^a Conditions A and B are shown in Scheme 1. ^b Isolated yield.

unsaturation (**1b–i**) and branched chains (**1j–m**) with electronic and steric variation (Table 1). Both *cis*- and *trans*-dodecenal (**1b** and **1c**) afforded the corresponding cyclopropenes **3b** and **3c** in 81 and 78% yield (entries 1 and 2). Symmetrical *cis*-dialdehyde⁸ **1d** also gave the corresponding biscyclopropene **3d** in good yield (entry 3). Aldehydes **1e–g** with trisubstituted γ,δ -double bonds behaved similarly, affording cyclopropenes **3e–g** in good yields (entries 4–6). An alkyne or aromatic substituent at this position in **1h** and **1i** did not interfere with the α –Si insertion, which provided **3h** and **3i** in 54 and 65% yield, respectively. Although the addition of alkylidene carbenes to γ,δ -double bonds is well-precedented,⁹ the addition reaction was not observed with these systems. The

[†] These authors contributed equally.

selectivity of insertion into the C γ –H bond versus the C α –Si bond was also examined with aldehydes **1j**–**m**¹⁰ containing methylene and methine protons as well as an oxygen atom at the C γ position.^{1c} Quite surprisingly, no competing insertion into the C γ –H protons or oxygen moiety¹¹ was observed, and only cyclopropenes **3j**–**m** were isolated in good yields.

Next, a variety of substrates carrying more strongly activated C γ –H bonds were explored (Table 2). Because of the especially strong activating role of the α -oxygen in the tether for C γ –H insertion,^{1c} the formation of both cyclopropene **3** via C α –Si bond insertion and dihydrofuran **4** via C γ –H insertion were expected. When subjected to condition A followed by condition B, aldehyde **1n** with C γ -methylene protons provided a mixture of cyclopropene **3n** and allylic silane-containing dihydrofuran **4n** in a 1.2:1 ratio in 75% yield (entry 1). Similarly, aldehyde **1o** afforded a mixture of cyclopropene **3o** and C–H insertion product **4o** in a slightly higher ratio (2.4:1) in 84% yield (entry 2). Surprisingly, aldehyde **1p** with allylic methylene protons yielded cyclopropene **3p** and C–H insertion product **4p** in only a 2:1 ratio, despite the fact that allylic C–H bonds are generally more activated toward carbene insertion (entry 3). The effect of an alkyl substituent was examined using methine-proton-containing substrate **1q**, which, contrary to our expectation, provided an even higher ratio (3.2:1) of cyclopropene **3q** to C–H insertion product **4q** (entry 4). Substrate **1r** containing a methine proton on a six-membered ring provided cyclopropane **3r** and a slightly increased relative amount of insertion product **4r** (**3r**/**4r** ratio of 1.5:1) in 69% yield (entry 5).

Table 2. Selectivity for Cyclopropenation of α -Silyl Ketones Containing Activated Protons at the C γ Position^a

entry	aldehyde	cyclopropene / insertion product ^b	yield (%) ^c	
1		1.2 : 1	75	
2		2.4 : 1	84	
3		2 : 1	83	
4		3.2 : 1	75	
5		1.5 : 1	69	

^a Conditions A and B are shown in Scheme 1. ^b Ratio determined by ¹H NMR analysis of the crude products. ^c Combined isolated yield of products **3** and **4**. ^d A pure sample of **4q** could not be obtained for full characterization.

In conclusion, we have developed a new cyclopropenation reaction involving C α –Si bond insertion of alkylidene carbenes derived from α -silyl ketones. This unprecedented alkylidene carbene

reactivity features an excellent selectivity for C α –Si bond insertion rather than C γ –H bond insertion or addition to γ,δ -double or -triple bonds. The selectivity trend in Table 2 clearly indicates that the α -oxygen in the tether significantly promotes C γ –H insertion, although the C α –Si bond insertion still competes effectively. It is noteworthy that the reactivity of the C–H bond toward carbene insertion depends intricately on electronic and steric factors and cannot be predicted by the simple additive effect of contributing factors.

Acknowledgment. We thank UIC and the donors of American Chemical Society Petroleum Research Fund for financial support of this work. The mass spectrometry facility at UIUC and Mr. Furong Sun are greatly acknowledged.

Supporting Information Available: General procedures and characterization data for representative compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Taber, D. F. In *Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Ed.; Georg Thieme Verlag: New York, 1995; Vol. E21, p 1127. (b) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795. (c) Yun, S. Y.; Zheng, J.-C.; Lee, D. J. *Am. Chem. Soc.* **2009**, *131*, 8413, and references cited therein.
- (2) For a related carbene insertion into a C α –H bond starting from a ketone, see: Taber, D. F.; Yu, H. J. *Org. Chem.* **1997**, *62*, 1687.
- (3) Reviews of cyclopropene chemistry: (a) Marek, I.; Simaan, S.; Masariva, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719. (d) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271. Most recent references: (e) Miede, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 248. (f) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382. (g) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378. (h) Magnus, P.; Littich, R. *Org. Lett.* **2009**, *11*, 3938. (i) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956. (j) Alnasleh, B. K.; Sherrill, W. M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231. (k) Singh, G.; Schrock, R. R. *Macromolecules* **2008**, *41*, 2990. (l) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405.
- (4) For preparation of α -silyl ketones, see: (a) Hosomi, A.; Hayashida, H.; Tominaga, Y. *J. Org. Chem.* **1989**, *54*, 3254. (b) Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228.
- (5) The α -silyl ketones prepared with a catalytic amount of indium chloride were quite pure, so additional purification steps were unnecessary. The scope of this method will be reported elsewhere. Related examples with MgBr₂ were reported previously (see ref 4b).
- (6) (a) Akiyama, M.; Isoda, Y.; Nishimoto, M.; Narazaki, M.; Oka, H.; Kuboki, A.; Ohira, S. *Tetrahedron Lett.* **2006**, *47*, 2287. (b) Akiyama, M.; Awamura, T.; Kimura, K.; Hosomi, Y.; Kobayashi, A.; Tsuji, K.; Kuboki, A.; Ohira, S. *Tetrahedron Lett.* **2004**, *45*, 7133. (c) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300. (d) Shioiri, T.; Aoyama, T. *Synth. Org. Chem. Jpn.* **1996**, *54*, 918. (e) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.
- (7) For alternative methods of preparing silylated cyclopropenes, see: (a) Stoll, A. T.; Negishi, E. *Tetrahedron Lett.* **1985**, *26*, 5671. (b) Fordyce, E. A. F.; Wang, Y.; Luebbbers, T.; Lam, H. W. *Chem. Commun.* **2008**, 1124. (c) Buchholz, H. A.; Prakash, G. K. S.; Deffieux, D.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 10003. (d) Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, 796. For the chemistry of silylated cyclopropenes, see: (e) Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868. (f) Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593. (g) Kirms, M. A.; Salcido, S. L.; Kirms, L. M. *Tetrahedron Lett.* **1995**, *36*, 7979. (h) Lee, G.-A.; Chang, C.-Y. *Tetrahedron Lett.* **1998**, *39*, 3013. (i) Branan, B. M.; Wang, X.; Jankowski, P.; Wicha, J.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 6874.
- (8) Aldehyde **1d** was prepared from cyclooctadiene via epoxidation and NaIO₄-mediated cleavage. See: Binder, C. M.; Dixon, D. D.; Almaraz, E.; Tius, M. A.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 2764.
- (9) (a) Rule, M.; Salinaro, R. F.; Pratt, D. R.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2223. (b) Salinaro, R. F.; Berson, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 7094.
- (10) For the preparation of **1k** and **1m**, see the Supporting Information and: Tan, J.; Zhang, Z.; Wang, Z. *Org. Biomol. Chem.* **2008**, *6*, 1344.
- (11) (a) Hari, Y.; Kondo, R.; Date, K.; Aoyama, T. *Tetrahedron* **2009**, *65*, 8708. (b) Feldman, K. S.; Wroblewski, M. L. *Org. Lett.* **2000**, *2*, 2603. (c) Feldman, K. S.; Wroblewski, M. L. *J. Org. Chem.* **2000**, *65*, 8659. (d) Ito, Y.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1163. (e) Sueda, T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141. (f) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1995**, *36*, 4845.

JA101998W