

Silylene-Mediated Polarity Reversal of Dienoates: Additions of Dienoates to Aldehydes at the δ -Position To Form *trans*-Dioxasilacyclononenes

Christian C. Ventocilla and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States, and
Department of Chemistry, New York University, New York, New York 10003, United States

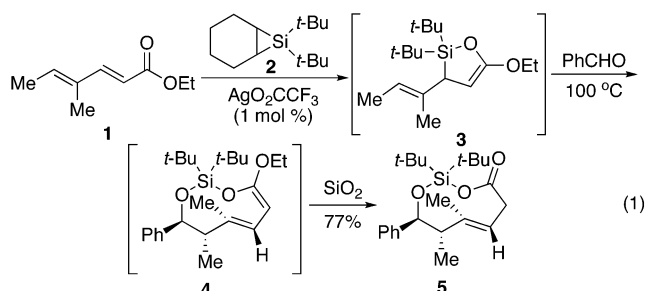
Received October 26, 2010; E-mail: kwoerpel@nyu.edu

Abstract: Silylene transfer to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds produced oxasilacyclopentenones that underwent thermal additions to aldehydes to produce *trans*-dioxasilacyclononenes as single stereoisomers. This reaction, which converts the δ -position of the unsaturated carbonyl compound into a nucleophilic center, represents an inversion of polarity from the normal pattern of reactivity. The stereospecificity of the reaction suggests that the addition to aldehydes occurred through a closed, chairlike six-membered transition state. This reaction can be used to prepare enantiomerically pure materials by the use of chiral auxiliaries to control the formation of the oxasilacyclopentenones. Functionalization of the resulting *trans*-cycloalkene occurred with complete stereoselectivity.

The different positions of unsaturated carbonyl compounds exhibit predictable patterns of reactivity. While the α - and γ -positions are donor sites, the β - and δ -positions are acceptors.¹ For example, the aldol reaction, in which the α -position is nucleophilic, is a common transformation,² and the vinylogous aldol reaction uses the γ -position as a nucleophile.³ Conjugate addition reactions capitalize on the electrophilicity of the β - and δ -positions.⁴ The polarity of these positions can be reversed in some cases. For example, formal homoaldol reactions employ the β -position as a nucleophilic site.⁵ Umpolung reactivity where the δ -position is nucleophilic, on the other hand, is uncommon.⁶

In this communication, we present a method for addition of aldehydes to dienotes at the δ -carbon. Silylene transfer to a dienote forms a vinyl oxasilacyclopentene in which the δ -carbon becomes the nucleophilic site. These intermediates undergo nucleophilic additions to aldehydes, forming *trans*-dioxasilacyclononenes stereoselectively and stereospecifically.

The one-flask conversion of dienote **1** and benzaldehyde to the protected adduct **5** illustrates this transformation. Silver-catalyzed silylene transfer⁷ to dienote **1** afforded vinyl oxasilacyclopentene **3** cleanly. Heating strained⁸ vinyl oxasilacyclopentene **3** with benzaldehyde produced the dienol ether **4** as a single diastereomer. Filtration through silica gel hydrolyzed the silyl ketene acetal to provide the corresponding *trans*-dioxasilacyclononene **5** as one diastereomer.⁹



The anti configuration of the addition product **4** is likely established through a Zimmerman–Traxler-like¹⁰ transition state in which the aldehyde is activated by coordination to the silicon center (A, Figure 1). Although *E*-allylic silanes typically react with

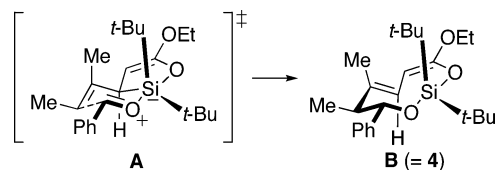
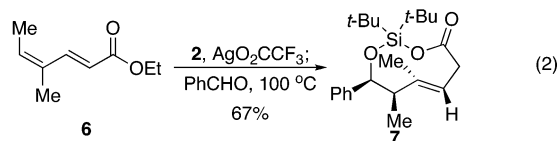


Figure 1

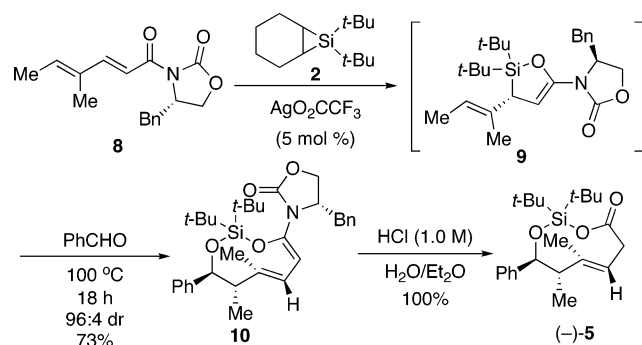
aldehydes in the presence of Lewis acids through open transition states to give syn products,^{11,12} allylic silanes can react through closed transition states if the silicon atom is particularly Lewis acidic.^{8,13} Three facts support the closed transition state for the formation of adduct **4**: (1) an external Lewis acid was not required to activate the addition of silane **3** to an aldehyde; (2) the *E*-allylic silane gave the anti product, not the syn product; and (3) no Mukaiyama¹⁴ α -aldol products were formed by reaction of the more nucleophilic silyl ketene acetal moiety.¹⁵

The stereospecificity of the addition reaction also indicates that it proceeds through a closed transition state.¹⁶ The product obtained from the *Z*-dienote **6** was the syn isomer of the *trans*-dioxasilacyclononene (**7**, eq 2).⁹ The relative configuration of *trans*-dioxasilacyclononene **7** is also consistent with its formation through a closed, chairlike transition state.^{11,12}

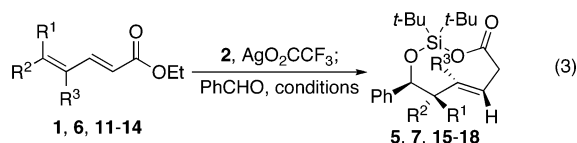


The *trans*-cyclononene products can be formed with control of absolute stereochemistry. The chiral auxiliary of dienimide **8** controlled the silylene transfer reaction, resulting in stereoselective formation of intermediate **9** (Scheme 1). Heating this silane with benzaldehyde promoted the diastereoselective formation of *trans*-dioxasilacyclononadiene **10**.¹⁷ Treatment of diene **10** with acid under biphasic conditions removed the chiral auxiliary, providing enantioenriched *trans*-dioxasilacyclononene (–)-**5**.

The addition of aldehydes at the δ -position of dienotes is general for a number of unsaturated esters (eq 3). Reaction times, however, depend upon the nucleophilicity of the allylic silane formed after silylene transfer. Substrates that possessed a methyl substituent at the γ -position (Table 1, entries 1, 2, and 4) produced methallyl silanes that underwent faster addition relative to substrates that only had a hydrogen atom at that position.¹⁵

Scheme 1. Asymmetric Formation of *trans*-Dioxasilacyclononene

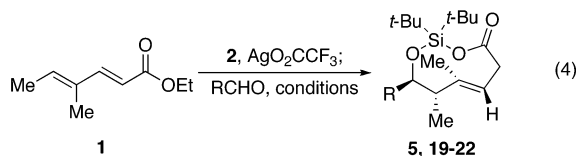
The longer reaction times of the substrates that only had a hydrogen atom at the γ -position led to more decomposition products and lower yields.

**Table 1.** Dienoate Scope in Formation of *trans*-Dioxasilacyclononenes (eq 3)^a

entry	Dienoate	R ¹	R ²	R ³	Conditions	Product	Yield
1	1	H	Me	Me	100 °C, 18 h	5	77%
2	6	Me	H	Me	100 °C, 18 h	7	67%
3	11	H	Me	H	100 °C, 5 d	15	59%
4	12	H	H	Me	100 °C, 2 d	16	53%
5	13	Me	Me	H	100 °C, 10 d	17	38%
6	14	H	H	H	100 °C, 5 d	18	37%

^a Products were formed as one isomer as determined by ¹H NMR spectroscopy and GCMS. Yields reported are isolated yields.

A number of aldehydes participated in the addition reaction (eq 4). Reactions of sterically hindered aldehydes required longer reaction times (Table 2, entries 3 and 4). A Lewis acid catalyzed the allylation, leading to faster reactions, even at room temperature (entry 4). The relative stereochemistry of the products

**Table 2.** Aldehyde Scope (eq 4)^a

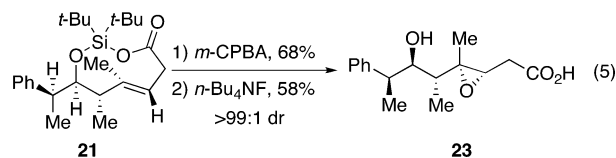
entry	RCHO	Conditions, yield		Product
		Thermal	SnBr ₄ (10 mol %), rt	
1	PhCHO	100 °C, 18 h, 77%	3 h, 37%	5
2	<i>n</i> -BuCHO	100 °C, 18 h, 72%	3 h, 37%	19
3	<i>i</i> -PrCHO	130 °C, 3 d, 73%	18 h, 40%	20
4	Ph-CHO	130 °C, 5 d, 72%	18 h, 94%	21
5	Me-CHO	100 °C, 18 h, 80%	decomposition	22

^a Products were formed as one isomer as determined by ¹H NMR spectroscopy and GCMS. Yields reported are isolated yields.

formed by the Lewis acid catalyzed process was again consistent with a closed, chairlike transition state. The Lewis acid likely coordinated to the oxygen atom of the O–Si bond of the vinyl oxasilacyclopentene **3**, increasing the electrophilicity of the silicon center.¹⁸

Stereochemically homogeneous products can be made by kinetic resolution. Addition to a chiral aldehyde (Table 2, entry 4) produced the adduct as a single diastereomer.¹⁷ The relative stereochemistry of *trans*-dioxasilacyclononene **21** is consistent with a closed, chairlike transition state where the vinyl oxasilacyclopentene approached the chiral aldehyde on a Felkin trajectory.¹⁹ This result suggests that the use of chiral, nonracemic aldehydes would give enantioenriched products.

Because substituted *trans*-cyclononenes adopt specific conformations and are slow to isomerize,²⁰ functionalization of the carbon–carbon double bond only occurred on the outside face. Treatment of *trans*-dioxasilacyclononene **21** with *m*-CPBA followed by deprotection afforded epoxide **23** as a single diastereomer. This selectivity is noteworthy because epoxidations of acyclic alkenes with *m*-CPBA in which the faces of the alkene are only differentiated by A_{1,2} strain are generally not diastereoselective.²¹ In addition, hydroxyl-directed epoxidation of free alcohols with structures analogous to cyclononene **21** would give epoxides with the opposite relative configuration compared to epoxide **23**.²¹



In summary, silylene transfer to dienoates afforded intermediates that function as δ -enolate equivalents that react with aldehydes to form addition products stereoselectively and stereospecifically. Enantiopure products can be synthesized by employing a chiral auxiliary to control silylene transfer. Further functionalization of the *trans*-cycloalkene occurred diastereoselectively. This methodology has potential application for the synthesis of polypropionate natural products and related structures.²²

Acknowledgment. This project was supported by the National Institute of General Medical Sciences of the National Institutes of Health (GM-54909). C.C.V. thanks the NIGMS for a predoctoral fellowship (F31GM080157). K.A.W. thanks Amgen and Lilly for awards to support research. We thank Dr. Phil Dennison (UCI) for assistance with NMR spectroscopy, Dr. Joseph W. Ziller (UCI) for X-ray crystallography, and Dr. John Greaves and Ms. Shirin Sorooshian (UCI) for mass spectrometry.

Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data for the products (PDF,CIF). This information is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.
- (2) Evans, D. A.; Nelson, J. N.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115.
- (3) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.
- (4) (a) For a recent review of 1,4-additions, see: Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (b) For a recent review of 1,6-additions to enoates, see: Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603–606, and references therein.
- (5) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698.
- (6) (a) The dissolving metal reduction of a dienone resulted in protonation at the δ -position: Grimm, K.; Venkataramani, P. S.; Reusch, W. J. *Am. Chem. Soc.*

- 1971, 93, 270–271. (b) Crotylsilanes bearing carbonyl groups also give products that resemble electrophilic addition at the δ -position: Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475–12476.
- (7) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046–2047.
- (8) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921.
- (9) The relative configurations of cyclononenes **5** and **7** were determined by NOE correlations.
- (10) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
- (11) For reviews, see: (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (b) Denmark, S. E.; Almstead, N. G. *J. Mex. Chem. Soc.* **2009**, *53*, 174–192.
- (12) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 299–402.
- (13) For different methods for activation of silicon centers, see: (a) Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152–7155. (b) Prévost, M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 14182–14183. (c) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620–6628. (d) Sakurai, H. *Synlett* **1989**, 1–8. (e) Shibato, A.; Itagaki, Y.; Tayama, E.; Hokke, Y.; Asao, N.; Maruoka, K. *Tetrahedron* **2000**, *56*, 5373–5382. (f) Fürstner, A.; Voigtländer, D. *Synthesis* **2000**, 959–969.
- (14) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
- (15) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.
- (16) Mukaiyama, T. In *Organic Reactions*; Dauben, W. G. Ed.; Wiley-VCH: Weinheim, 1982; Vol. 28, pp 203–331.
- (17) The relative configurations of cyclononenes **10** and **21** were determined by X-ray crystallography.
- (18) Allylboration can also be accelerated by Lewis acids: (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587. (b) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415.
- (19) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4160.
- (20) Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2000**, *2*, 2415–2418.
- (21) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009.
- (22) (a) Su, Q.; Beeler, A. B.; Lobkovsky, E.; John, A.; Porco, J.; Panek, J. S. *Org. Lett.* **2003**, *5*, 2149–2152. (b) Fleury, E.; Lannou, M.-I.; Bistri, O.; Sautel, F.; Massiot, G.; Pancrazi, A.; Ardisson, J. *J. Org. Chem.* **2009**, *74*, 7034–7045.

JA109631Z