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Silylene-mediated Polarity Reversal of Dienoates: Additions of Dienoates to Aldehydes at the δ-Position to form *trans*-Dioxasilacyclononenes

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Abstract

Silylene transfer to α,β,γ,δ-unsaturated carbonyl compounds produced oxasilacyclopentenes that underwent thermal additions to aldehydes to produce *trans*-dioxasilacyclononenes as single stereoisomers. This reaction, which converts the δ-position 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, chair-like 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 oxasilacyclopentenes. Functionalization of the resulting trans-cycloalkene occurred with complete stereoselectively.

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 dienoates at the δ-carbon. Silylene transfer to a dienoate forms a vinyl oxasilacyclopentene in which the δ-carbon becomes the nucleophilic site. These intermediates undergo nucleophilic addition to aldehydes, forming *trans*-dioxasilacyclononenes stereoselectively and stereospecifically.

The one-flask conversion of dienoate **1** and benzaldehyde to the protected adduct **5** illustrates this transformation. Silver-catalyzed silylene transfer[7] to dienoate **1** afforded vinyl oxasilacyclopentene **3** cleanly. Heating strained[8] 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]

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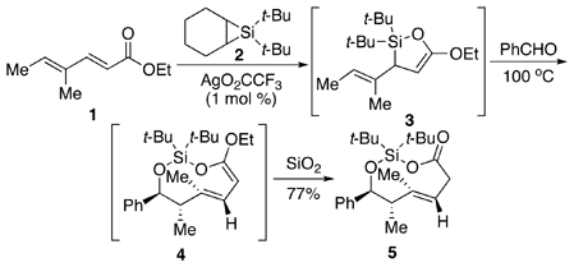
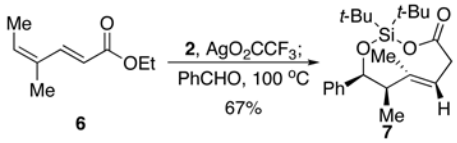
Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data for the products (PDF,CIF). This information is available free of charge via the internet at http://pubs.acs.org.



(1)

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 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

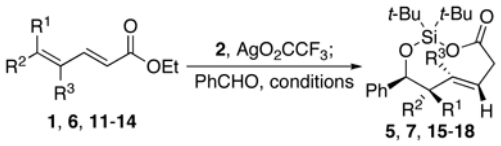
The stereospecificity of the addition reaction also indicates that it proceeds through a closed transition state.16 The product obtained from the *Z*-dienoate **6** was the syn isomer of the *trans*-dioxasilacyclononene (**7**, eq 2).9 The relative configuration of *trans*-dioxasilacyclononene **7**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



(2)

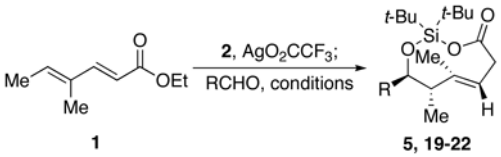
The *trans*-cyclononene products can be formed with control of absolute stereochemistry. The chiral auxiliary of dienimide **8** controlled the silylene transfer reaction, resulting in stereoselective formation of intermediate **9** (Scheme 1). Heating this silane with benzaldehyde promoted diastereoselective 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 dienoates is general for a number of unsaturated esters. 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 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.



(3)

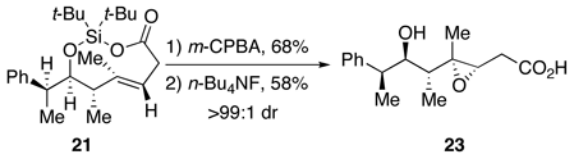
A number of aldehydes participated in the addition reaction. Reactions of sterically hindered aldehydes required longer reaction times (Table 2, entries 3 and 4). A Lewis acid catalyzed the allylation, leading to faster reactions, even at room temperature (entry 4). The relative stereochemistry of the products formed by the Lewis acid-catalyzed process was again consistent with a closed, chair-like 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



(4)

Stereochemically homogeneous products can be made by kinetic resolution. Addition to 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, chair-like transition state where the vinyl oxasilacyclopentene approached the chiral aldehyde on a Felkin trajectory.19 This result suggests that the use of chiral, non-racemic 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



(5)

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Seebach D. Angew Chem, Int Ed Engl. 1979; 18:239–258.
2. Evans DA, Nelson JV, Taber TR. Top Stereochem. 1982; 13:1–115.
3. Casiraghi G, Zanardi F, Appendino G, Rassu G. Chem Rev. 200; 100:1929–1972. [PubMed: 11749280]
4. For a recent review of 1,4-additions, see: (a) Alexakis A, Bäckvall JE, Krause N, Pàmies O, Diéguez M. Chem Rev. 2008; 108:2796–2823. [PubMed: 18671436] For references of 1,6-additions to enoates, see: (b) Fukuhara K, Urabe H. Tetrahedron Lett. 2005; 46:603–606.and references therein
5. Nair V, Vellalath S, Babu BP. Chem Soc Rev. 2008; 37:2691–2698. [PubMed: 19020682]
6. The dissolving metal reduction of a dienone resulted in protonation at the δ-position: (a) Grimm K, Venkataramani PS, Reusch W. J Am Chem Soc. 1971; 93:270–271.Crotylsilanes bearing carbonyl groups also give products that resemble electrophilic addition at the δ-position: (b) Jain NF, Takenaka N, Panek JS. J Am Chem Soc. 1996; 118:12475–12476.
7. Calad SA, Woerpel KA. J Am Chem Soc. 2005; 127:2046–2047. [PubMed: 15713073]
8. Kinnaird JWA, Ng PY, Kubota K, Wang X, Leighton JL. J Am Chem Soc. 2002; 124:7920–7921. [PubMed: 12095334]
9. The relative configuration of cyclononenes **5** and **7** was determined by nOe correlations.
10. Zimmerman HE, Traxler MD. J Am Chem Soc. 1957; 79:1920–1923.
11. For reviews see: (a) Masse CE, Panek JS. Chem Rev. 1995; 95:1293–1316. (b) Denmark SE, Almstead NG. J Mex Chem Soc. 2009; 53:174–192.
12. Denmark, SE.; Almstead, NG. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 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 KA. J Am Chem Soc. 2009; 131:14182–14183. [PubMed: 19769355] (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; 7:959–969.
14. Mukaiyama T, Banno K, Narasaka K. J Am Chem Soc. 1974; 96:7503–7509.
15. Mayr H, Kempf B, Ofial AR. Acc Chem Res. 2003; 36:66–77. [PubMed: 12534306]
16. Mukaiyama, T. Organic Reactions. Dauben, WG., editor. Vol. 28. Wiley-VCH: Weinheim; 1982. p. 203-331.
17. The relative configuration of cyclononenes **10** and **21** was determined by X-ray crystallography.
18. Allylborations can also be accelerated by Lewis acids: (a) Kennedy JWJ, Hall DG. J Am Chem Soc. 2002; 124:11586–11587. [PubMed: 12296710] (b) Ishiyama T, Ahiko T-a, Miyaura N. J Am Chem Soc. 2002; 124:12414–12415. [PubMed: 12381174]
19. Roush WR. J Org Chem. 1991; 56:4151–4160.

20. Deiters A, Mück-Lichtenfeld C, Fröhlich R, Hoppe D. Org Lett. 2000; 2:2415–2418. [PubMed: 10956510]

21. Carreira, EM.; Kvaerno, L. Classics in Stereoselective Synthesis. Wiley-VCH; Weinheim: 2009.

22. (a) Su Q, Beeler AB, Lobkovsky E, John A, Porco J, Panek JS. Org Lett. 2003; 5:2149–2152. [PubMed: 12790551] (b) Fleury E, Lannou MI, Bistri O, Sautel F, Massiot G, Pancrazi A, Ardisson J. J Org Chem. 2009; 74:7034–7045. [PubMed: 19694414]

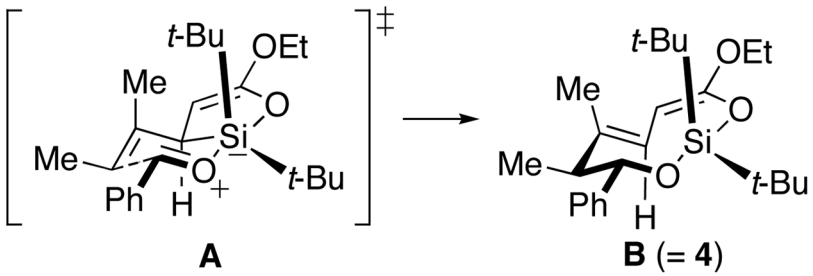
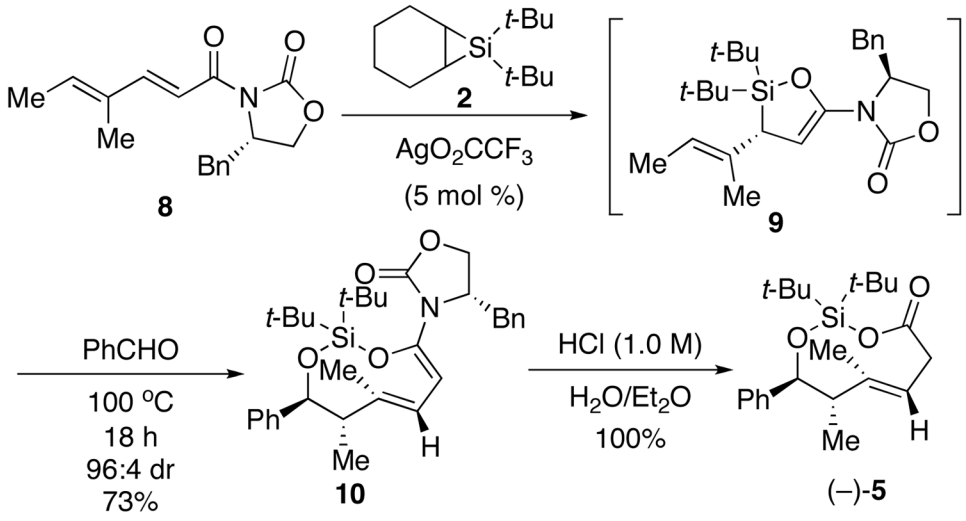


Figure 1.



Scheme 1.
Asymmetric Formation of *trans*-Dioxasilacyclononene

Table 1

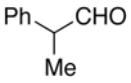
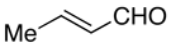
Dienoate Scope in Formation of *trans*-Dioxasilacyclononenes

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%

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

Table 2

Aldehyde Scope

entry	RCHO	Conditions, yield		Product
		Thermal	$SnBr_4$ (10 mol %), rt	
1	PhCHO	100 °C, 18 h, 77%	3 h, 37%	**5**
2	*n*-BuCHO	100 °C, 18 h, 72%	3 h, 37%	**19**
3	*i*-PrCHO	130 °C, 3 d, 73%	18 h, 40%	**20**
4		130 °C, 5 d, 72%	18 h, 94%	**21**
5		100 °C, 18 h, 80%	decomposition	**22**

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