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Medium-Ring Compounds

Diastereoselective Synthesis of Eight-Membered-Ring Allenes from Propargylic Epoxides and Aldehydes by Silylene Insertion into Carbon–Oxygen Bonds**

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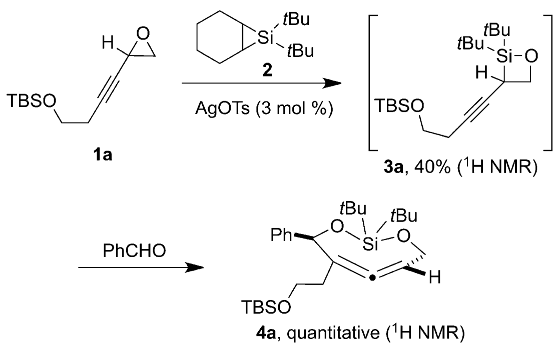
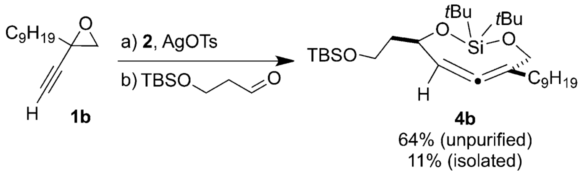
The synthesis of eight-membered-ring allenes is limited by the difficulty of constraining cumulated double bonds within a medium-sized ring. Forcing the allene functionality into a medium-sized ring puts significant strain on the ring and distorts the allene from its optimal bond and torsional angles.[1] As a result, eight-membered-ring allenes are either reactive intermediates[2,3] or require bulky substituents to stabilize them.[4,5] Introducing elements with longer atomic radii such as sulfur, selenium, phosphorus, or silicon reduces the ring strain of cyclic allenes sufficiently in some cases to permit isolation.[6–9] For example, six-, seven-, and eight-membered-ring allenes containing three silicon atoms have been isolated.[10–12] Most cyclic allenes contain carbon–heteroatom bonds directly on the allene, which impart stability by polarizing the allene functionality to favor charge-separated resonance forms.[13] For example, four- and five-membered-ring allenes have been reported that rely on π-donor substituents to stabilize the highly distorted allene functional group.[14,15]

Herein, we report the two-step, one-flask diastereoselective synthesis of eight-membered-ring allenes. An X-ray crystal structure revealed significant deviations from the optimal bond and torsional angles as compared to unconstrained allenes.[16] Deprotection of these cyclic allenes provided tetrasubstituted allenes with control of the relative configurations between the carbon stereocenter and the axis of chirality.[17,18]

The synthesis of eight-membered-ring allenes relies on the unique reactivity of silylenes and strained cyclic silanes. Treatment of the epoxide **1a** with a catalytic amount of a silver salt at −20 °C for three hours provided the silaoxetane **3a** (Scheme 1). The uncatalyzed[19] addition of an aldehyde to this strained propargylic silane formed the eight-membered-ring allene as a single diastereomer (Scheme 1). When the epoxide **1b** was used, a similar allene was obtained [Eq. (1)]. The trisubstituted allenes **4a** and **4b**, however, were not stable to isolation: they were so reactive that they decomposed readily even when stored under a nitrogen atmosphere.



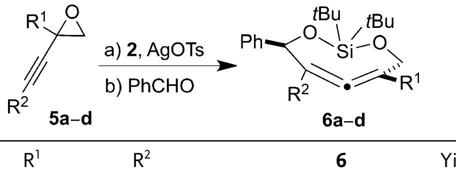
Scheme 1. Insertion of a silylene into a propargylic carbon–oxygen bond and subsequent aldehyde addition. TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.



(1)

By contrast, tetrasubstituted allenes derived from more substituted propargylic epoxides were isolable and stable to silica gel chromatography. This reaction sequence was general for a variety of propargylic epoxides (Table 1) and aldehydes (Table 2), thus yielding tetrasubstituted allenes as single diastereomers. The epoxide **5c** provided the allene **6c** in lower yield, probably because of steric congestion at the atom undergoing insertion. The yield of **7d** is lower than those of the other allenes because of the difficulty with purification,

Table 1: Formation of eight-membered-ring cyclic allenes.



Entry	R1	R2	**6**	Yield [%][a]
1	Me	C_6H_{13}	**6a**	71
2	Me	CH_2CH_2OTBS	**6b**	58
3	*i*Pr	C_6H_{13}	**6c**	35
4	Me	$SiMe_3$	**6d**	66

[a] Yield of isolated product from reaction run on a preparative scale (1 mmol).

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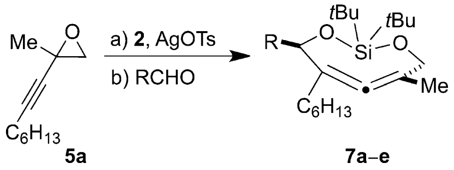
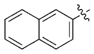
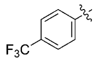
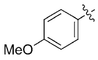
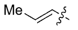
Table 2: Aldehyde scope for allene synthesis.

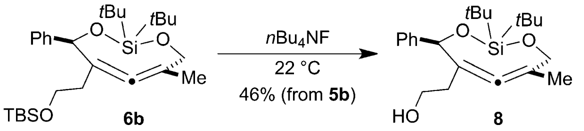


Entry	RCHO	7	Yield [%][a]
1		**7a**	60
2		**7b**	54
3		**7c**	49
4		**7d**	21
5	*i*Pr	**7e**	53

[a] Yield of product isolated from reaction run on a preparative scale (1 mmol).

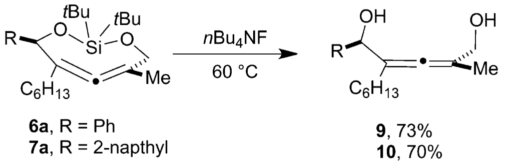
thus suggesting that this crotonaldehyde-derived allene is more reactive. The observation that only tetrasubstituted allenes could be isolated and purified demonstrates that the allene is strained, thus requiring steric hinderance to prevent undesired decomposition reactions.[4,20]

These cyclic allenes could be deprotected to provide either homoallylic alcohols or linear allene diols depending on reaction conditions. The allene **6b** containing a primary silyl ether could be selectively deprotected to provide the allene **8** [Eq. (2)]. More forcing conditions were required to remove the di-*tert*-butylsilyl group [Eq. (3)]. When the allenes **6a** and **7a** were heated with a solution of $n\mathrm{Bu_4NF}$ that had been dried over 3 Å molecular sieves, the di-*tert*-butylsilyl group was removed. In contrast, the allene was not compatible with standard acidic conditions for deprotection.[21]



(2)

X-ray crystallography revealed significant deviations of both the bond and torsion angles of the allene, thus indicating that these allenes are strained (Figure 1).[22] The C2-C3-C4 bond angle is bent from linearity by 16°.[23] Comparison of other bond angles in similar eight-membered-ring systems reveals that this 164° bond angle is among the smallest bond angles reported for cyclic allenes.[24] The average of the torsion angles around the allene is 81.6°, as compared to 90°, thus indicating that the ends of the allene are not perpendicular to each other.[25]



(3)

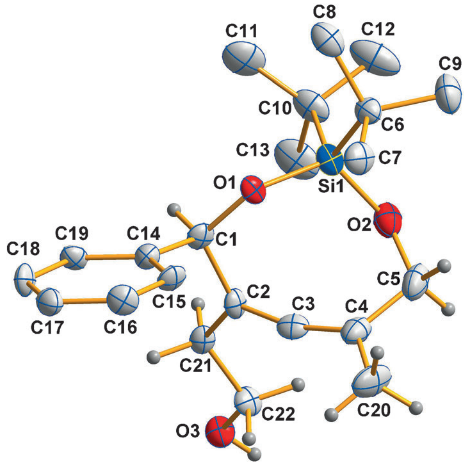


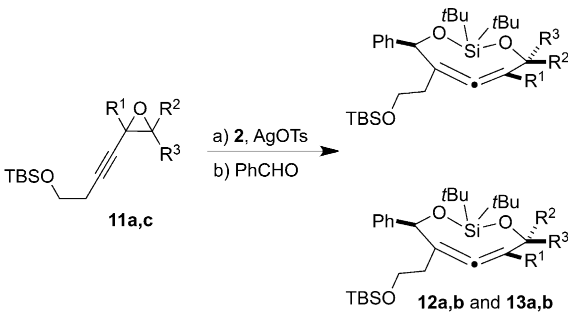
Figure 1. Molecular structure of **8** (ellipsoids set at 50% probability). Hydrogen atoms on the phenyl ring and *tert*-butyl groups are emitted for clarity. Selected bond lengths [Å] and angles [°]: C2–C3 1.300(7), C3–C4 1.321(8), O1–Si1 1.648(4), O2–Si1 1.637(4); C2-C3-C4 164.0(6), O1-Si1-O2 116.7(2).[38]

Because the strained allene is not stabilized by a heteroatom substituent, the bond angle and torsional angle distortions are not likely the result of electronic effects. Heteroatoms in other cyclic allenes stabilize the cumulated bonds by donating electron density into the allene antibonding π* orbitals, thus leading to charge-separated resonance forms.[13] This electronic interaction results in twisting of the ends of an allene towards a coplanar orientation and lengthening of the allene carbon–carbon bonds. In one example, a five-membered ring allene with four heteroatom substituents has coplanar allene substituents, and the allene carbon–carbon bond lengths are dramatically lengthened (1.370 and 1.386 Å).[14] By contrast, a seven-membered-ring allene with one silicon atom connected to the allene is twisted by 30°, but the allene carbon–carbon bond lengths are closer to their unconstrained values (1.307 and 1.293 Å compared to 1.31 Å).[12] Because the bond distances in **8** do not deviate considerably from the optimal bond length for allenes (1.31 Å)[26] and the allene is not highly twisted, the deviations from optimal bond angle and torsional angles in **8** most likely result from strain induced by the ring.[17]

Experiments with substituted propargylic epoxides revealed that carbon–carbon bond formation is stereospecific, but silylene transfer is not. Silylene transfer to the diastereomeric propargyl epoxides **11a** and **11b** provided diastereomeric silaoxetanes, although some erosion of stereochemistry occurred (Table 3).[27] Upon addition of benzaldehyde, diastereomeric allenes were formed with product ratios matching those of the silaoxetane mixtures.[28] Similar observations were made when the epoxide **11c** was employed.

The loss of stereochemistry during insertion of the silylene (Table 3) into the carbon–oxygen bond suggests that insertion proceeds through a ring-opened intermediate such as diradical **B** (Scheme 2).[29,30] After coordination of a silver silylene

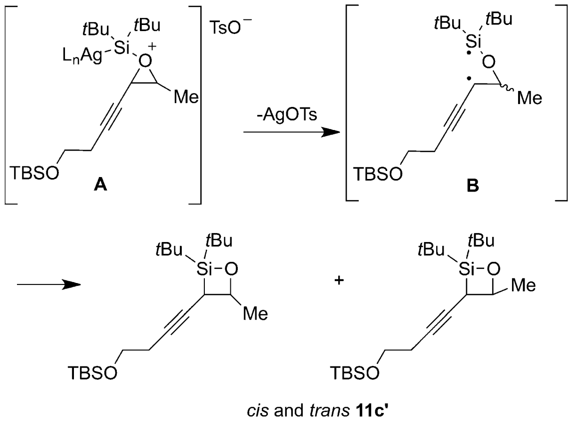
Table 3: Synthesis of diastereomeric allenes.



Entry	11	R¹	R²	R³	%	d.r.[c]
1	**11a**	Me	H	H	49[a]	71:29 (71:29)
2	**11b**	H	Me	H	46[b]	37:63 (33:67)
3	**11c**	H	H	Me	32[b]	73:27 (70:30)

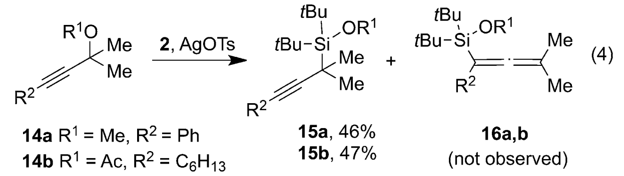
[a] Yield determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [b] Yield of product isolated after removal of the TBS group. [c] Determined using ^{1}H NMR spectroscopy. Values within parentheses are for the silaoxetane intermediates.

intermediate to the epoxide oxygen atom (intermediate **A**), homolytic cleavage of the propargylic carbon–oxygen bond would afford the intermediate **B**. If carbon–carbon bond rotation were competitive with radical ring closure, then scrambling of stereochemistry would be expected.[31,32] Stabilization of a radical by an adjacent alkynyl group supports this mechanism and explains the observed regioselectivity of silaoxetane formation.[33]



Scheme 2. Insertions of silylenes into propargylic carbon–oxygen bonds.

Insertions of silylenes into carbon–oxygen bonds do not require release of ring strain from an epoxide.[34,35] Silylene transfer to the acyclic propargyl ethers **14a**,**b** provided propargyl silanes **15a**,**b** as single regioisomers [Eq. (4)]. The allenes **16a**,**b**, which would result from transposition of the π bond, were not observed. By contrast, insertions of silylenes into allylic carbon–oxygen bonds are accompanied by allylic transposition.[27,31,32,36]



The relative configurations of the axis of chirality and the point of chirality of the cyclic allene are established in the transition state for aldehyde addition (Figure 2). Coordination of the carbonyl group to the Lewis-acidic silicon atom[37] of the strained four-membered-ring silane forms the adduct **C** in which the aldehyde is activated for carbon–carbon bond formation.[27] This pentacoordinate silicon atom adopts a geometry in which the *tert*-butyl groups are placed in basal positions to avoid steric interactions with each other.[27,36] The cyclic transition-state **D** accounts for how the point chirality of the starting material is translated to both the point chirality and axial chirality of the product.

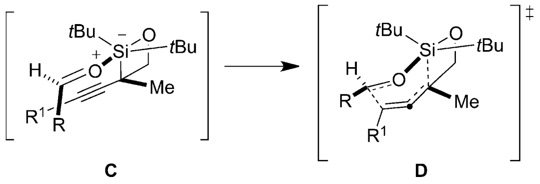


Figure 2. Transition state for aldehyde addition.

In conclusion, allenes embedded within the constraints of an eight-membered ring can be synthesized as single diastereomers by inserting a silylene into a propargylic carbon–oxygen bond followed by aldehyde addition. These tetrasubstituted cyclic allenes are stable to ambient conditions and do not require any special handling. Examination of the X-ray crystal structure revealed that the allene is bent significantly from linearity by the strain caused by incorporation of this functional group into a medium-sized ring.

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[1] K. J. Daoust, S. M. Hernandez, K. M. Konrad, I. D. Mackie, J. Winstanley, R. P. Johnson, *J. Org. Chem.* **2006**, *71*, 5708–5714.
[2] D. Rodríguez, M. F. Martínez-Esperón, A. Navarro-Vázquez, L. Castedo, D. Domínguez, C. Saá, *J. Org. Chem.* **2004**, *69*, 3842–3848.
[3] T. Mahlokozera, J. B. Goods, A. M. Childs, D. M. Thamattoor, *Org. Lett.* **2009**, *11*, 5095–5097.
[4] J. D. Price, R. P. Johnson, *J. Org. Chem.* **1991**, *56*, 6372–6376.
[5] Larger nine- and ten-membered-ring allenes, however, which can accommodate the requisite allene geometry, are readily isolated. See, for example: a) M. Ogasawara, A. Okada, K. Nakajima, T. Takahashi, *Org. Lett.* **2009**, *11*, 177–180; b) C. Chiappe, A. De Rubertis, H. Detert, D. Lenoir, C. S. Wannere, P. von R. Schleyer, *Chem. Eur. J.* **2002**, *8*, 967–978; c) M. Perscheid, D. Schollmeyer, U. Nubbemeyer, *Eur. J. Org. Chem.*

2011, 5250–5253; d) J. L. Luche, J. C. Damiano, C. Cohen-Addad, *J. Am. Chem. Soc.* **1980**, *102*, 5370–5374.

[6] X. Zhao, Z. Zhong, L. Peng, W. Zhang, J. Wang, *Chem. Commun.* **2009**, 2535–2537.

[7] T. Shimizu, D. Miyasaka, N. Kamigata, *J. Org. Chem.* **2001**, *66*, 1787–1794.

[8] a) C. M. Mömming, G. Kehr, B. Wibbeling, R. Fröhlich, B. Schirmer, S. Grimme, G. Erker, *Angew. Chem.* **2010**, *122*, 2464–2467; *Angew. Chem. Int. Ed.* **2010**, *49*, 2414–2417.

[9] a) B.-H. Xu, G. Kehr, R. Fröhlich, B. Wibbeling, B. Schirmer, S. Grimme, G. Erker, *Angew. Chem.* **2011**, *123*, 7321–7324; *Angew. Chem. Int. Ed.* **2011**, *50*, 7183–7186.

[10] T. Shimizu, F. Hojo, W. Ando, *J. Am. Chem. Soc.* **1993**, *115*, 3111–3115.

[11] Y. Pang, S. A. Petrich, V. G. Young, Jr., M. S. Gordon, T. J. Barton, *J. Am. Chem. Soc.* **1993**, *115*, 2534–2536.

[12] S. E. Gottschling, K. K. Milnes, M. C. Jennings, K. M. Baines, *Organometallics* **2005**, *24*, 3811–3814.

[13] M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem.* **2010**, *122*, 8992–9032; *Angew. Chem. Int. Ed.* **2010**, *49*, 8810–8849.

[14] V. Lavallo, C. A. Dyker, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5491–5494; *Angew. Chem. Int. Ed.* **2008**, *47*, 5411–5414.

[15] M. Melaimi, P. Parameswaran, B. Donnadieu, G. Frenking, G. Bertrand, *Angew. Chem.* **2009**, *121*, 4886–4889; *Angew. Chem. Int. Ed.* **2009**, *48*, 4792–4795.

[16] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.

[17] J. A. Marshall, Y. Tang, *J. Org. Chem.* **1993**, *58*, 3233–3234.

[18] J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180–7184.

[19] Aldehyde addition occurred in the absence of a silver catalyst. A control experiment in which the silver catalyst was sequestered using *N*,*N*-tetramethylethylenediamine prior to addition of the aldehyde demonstrated that silver is not required for aldehyde addition. For uncatalyzed allylation of carbonyl compounds using silacyclobutanes, see: K. Matsumoto, K. Oshima, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 7152–7155.

[20] For examples of low reactivity of tetrasubstituted allenes, see: a) C. Mukai, N. Kuroda, R. Ukon, R. Itoh, *J. Org. Chem.* **2005**, *70*, 6282–6290; b) Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079–2081.

[21] For methods to remove the silylene protecting group to form diols, see: T. D. Nelson, R. D. Crouch, *Synthesis* **2000**, 1031–1069.

[22] P. W. Dillon, G. R. Underwood, *J. Am. Chem. Soc.* **1974**, *96*, 779–787.

[23] The experimentally determined bond angle at the central carbon atom of the allene was slightly smaller than the 166.5° value calculated by ab initio methods (HF/6-311G*). Details are provided in the Supporting Information.

[24] A 1,3-bisthio eight-membered-ring allene, for example, contains a 162.50° bond angle, while its selenium counterpart contains a larger angle of 166.5°. See Refs. [6] and [7].

[25] The ^{13}C NMR shifts of the central allene carbon did not change appreciably upon removal of the di-*tert*-butylsilyl group.

[26] J. Ye et al., *Org. Lett.* **2012**, *14*, 1346–1349, see the Supporting Information.

[27] M. Prévost, K. A. Woerpel, *J. Am. Chem. Soc.* **2009**, *131*, 14182–14183.

[28] Variable-temperature NMR spectroscopy experiments confirmed that **12a** and **12b** are distinct diastereomers rather than atropisomers.

[29] S. S. Kostina, W. J. Leigh, *J. Am. Chem. Soc.* **2011**, *133*, 4377–4388.

[30] It is also possible that zwitterionic intermediates are involved in this stepwise silylene insertion.

[31] L. E. Bourque, P. A. Cleary, K. A. Woerpel, *J. Am. Chem. Soc.* **2007**, *129*, 12602–12603.

[32] L. E. Bourque, P. A. Haile, J. M. N. Loy, K. A. Woerpel, *Tetrahedron* **2009**, *65*, 5608–5613.

[33] D. J. Henry, C. J. Parkinson, P. M. Mayer, L. Radom, *J. Phys. Chem. A* **2001**, *105*, 6750–6756.

[34] J. L. Wolk, T. Hoz, H. Basch, S. Hoz, *J. Org. Chem.* **2001**, *66*, 915–918.

[35] J. L. Wolk, M. Sprecher, H. Basch, S. Hoz, *Org. Biomol. Chem.* **2004**, *2*, 1065–1069.

[36] M. Prévost, J. W. Ziller, K. A. Woerpel, *Dalton Trans.* **2010**, *39*, 9275–9281.

[37] S. A. Sullivan, C. H. DePuy, R. Damrauer, *J. Am. Chem. Soc.* **1981**, *103*, 480–481.

[38] CCDC 950159 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.