ChemPubSoc Europe
DOI: 10.1002/chem.201402996
CHEMISTRY
A European Journal
Communication

Asymmetric Oxidation

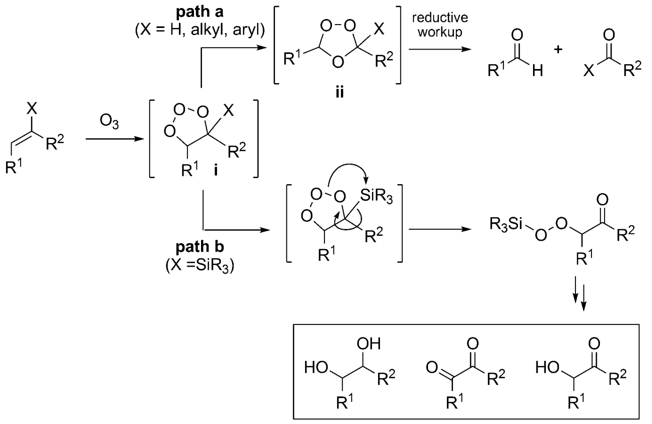
Asymmetric Ozone Oxidation of Silylalkene Using a C_2-Symmetrical Dialkoxysilyl Group as a Chiral Auxiliary

Kazunobu Igawa,[a] Yuuya Kawasaki,[a] Kosuke Nishino,[b] Naoto Mitsuda,[b] and Katsuhiko Tomooka*[a]

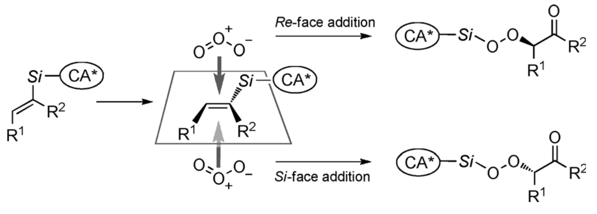
Abstract: Ozone oxidation of silyl-substituted alkenes, namely silylalkenes, proceeds in an addition-type manner to afford α-silylperoxy carbonyl compounds in good to excellent yields, without the formation of normal ozonolysis products. Herein the ozone oxidation of chiral alkenylsilanes prepared from alkynes and a newly designed chiral hydrosilane is reported. The reaction affords silylperoxides with high diastereoselectivity (up to 94% d.r.). The silylperoxides are convertible into enantioenriched chiral acyloins in a stereospecific manner.

Stereoselective oxidation of alkenes is one of the most important and widely utilized methods in asymmetric synthesis.[1] However, handling explosive peroxides or highly toxic transition-metal reagents is a fundamental problem in these reactions. On the other hand, ozone is a prominent oxidant that can be easily prepared from and is re-convertible to safe and clean oxygen. Despite this substantial advantage, ozone has not been applied to the asymmetric oxidation of alkenes, because the reactions generally involve the cleavage of a carbon–carbon double bond to afford achiral carbonyl compounds, which is widely known as "ozonolysis" (**path a** in Scheme 1).[2]

To this end, we recently found that ozone oxidation of silyl-substituted alkenes, namely silylalkenes, proceeds in an addition-type manner to afford α-silylperoxy carbonyl compounds in good to excellent yields, without the formation of normal ozonolysis products (**path b** in Scheme 1).[3,4] The key step in this unique oxidation is the migration of the silyl group from carbon to oxygen in the primary ozonide **i**, which prevents 1,3-dipolar cycloelimination, including C–C bond cleavage to form secondary ozonide **ii**. The resulting α-silylperoxy carbonyl compounds are easily and efficiently convertible into synthetically valuable acyloins, 1,2-diketones, 1,2-diols, and so on.[3] The reaction mechanism clearly suggests that the stereochemistry of the newly generated α-carbonyl stereogenic center is determined in the 1,3-dipolar cycloaddition step to form ozonide **i**. Thus, we envisioned that asymmetric ozone oxidation would be realized by attaching the appropriately chosen chiral auxiliary to a silylalkene.[5–7] We planned the introduction of a chiral auxiliary (CA*) on the silyl group to efficiently construct a chiral environment around the alkene moiety that is easily removed from the oxidation product (Scheme 2). The details are provided below.



Scheme 1. Ozonolysis and addition-type ozone oxidation of alkene.



Scheme 2. Concept of asymmetric ozone oxidation.

At the outset, we designed silylalkenes **2** having a chiral alkoxy moiety on silicon.[8] These silylalkenes were prepared by the reaction of chlorosilane **1** and a variety of chiral alcohols, in good to excellent yields (85–98%), as shown in Scheme 3. Ozone oxidation of **2** was performed as per our standard procedure: bubbling about 1.2 v/v% O_3/O_2 gas in AcOEt at −78 °C.[3] The reactions of **2a–c** afforded the corresponding α-silylperoxy ketones **3a–c** in quantitative yields, although the

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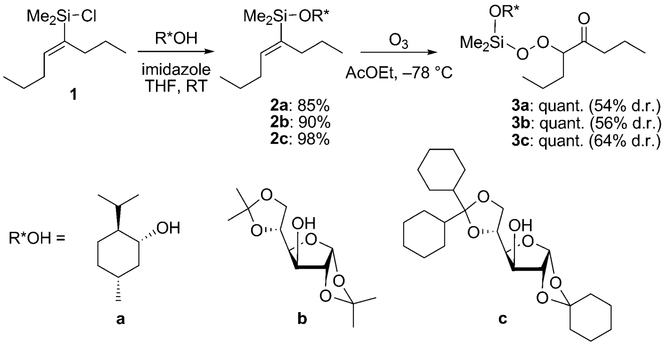
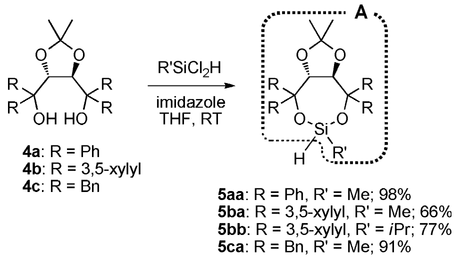
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402996.



Scheme 3. Preparation and ozone oxidation of chiral silylalkene **2**.

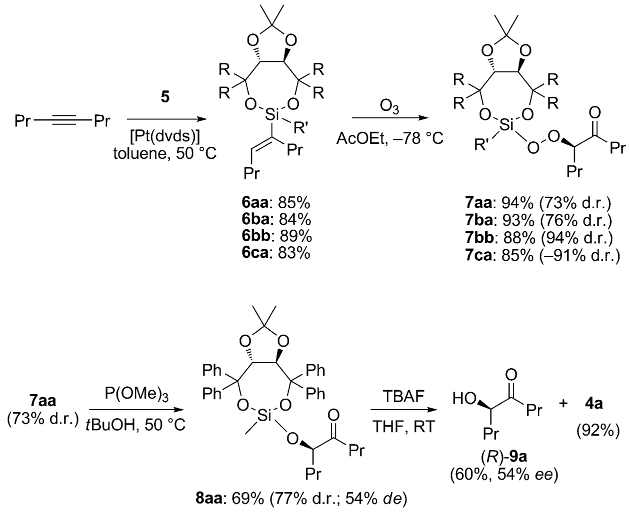
migrating silyl groups were bulky. However, the diastereoselectivity of the reactions, which is our main concern, was poor (54–64 % d.r.).

Because of these disappointing results, we recognized the need to redesign the chiral auxiliary. After several attempts, we found that the novel C_2-symmetrical dialkoxysilyl group **A** is suitable for this purpose and that it can be easily introduced into alkynes by hydrosilylation with dialkoxyhydrosilane **5** prepared from α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL; **4**)[9] and R′SiCl$_2$H, in excellent yield (Scheme 4).[10,11] Notably, compound **5** is stable under the standard operation conditions, including purification by silica-gel chromatography. In particular, **5 aa** (R = Ph, R′ = Me) has good crystallinity and hence can be purified by recrystallization.



Scheme 4. Preparation of hydrosilane **5**.

The hydrosilylation of **5** and 4-octyne in the presence of 1,3-divinyl-1,1,3,3-tetramethyldisiloxaneplatinum(0)—[Pt(dvds)]—afforded **6 aa–ca** in good yields (83–89 %) with excellent *E* selectivities (> 99 % *E*) (Scheme 5).[12] Ozone oxidation of silylalkenes **6** was performed by the above-mentioned standard procedure. The reaction of **6 aa** afforded the corresponding α-silylperoxy ketone **7 aa** in 94 % yield with good diastereoselectivity (73 % d.r.). The stereochemistry of the newly generated stereogenic center of **7 aa** was determined to be *R* by transforming the compound into a stereochemically defined acyloin **9 a**, as follows.[13] The reaction of **7 aa** with P(OMe)$_3$ in *t*BuOH proceeded to afford *O*-silylated acyloin **8 aa** in 69 % yield.[14,15] The reaction of **8 aa** with tetra-*n*-butylammonium fluoride (TBAF) afforded (*R*)-**9 a** in 60 % yield without loss of enantiopurity along with a good deal of TADDOL **4 a**.[16,17]



Scheme 5. Preparation and ozone oxidation of **6**, followed by transformation to acyloin **9**.

With this promising result in hand, we focused on the influence of the structure of the dialkoxysilyl group **A** on the stereoselectivity. The stereoselectivity was slightly improved by the use of **5 ba** (R = 3,5-xylyl) as the dialkoxyhydrosilane: the oxidation of **6 ba** afforded (*R*)-**7 ba** in 76 % d.r. The highest stereoselectivity was obtained by the use of **5 bb** having bulky R and R′ groups: the oxidation of **6 bb** afforded (*R*)-**7 bb** in 94 % d.r. Interestingly, the dialkoxysilane with a benzyl group as R provided the opposite stereoselectivity: the oxidation of **6 ca** afforded (*S*)-**7 ca** in 91 % d.r.

To gain insight into the observed stereoselectivity, we computed the transition states for the 1,3-dipolar cycloaddition of ozone with a simplified silylalkene **6 d** at the RHF/6-31G(d) level of theory, in which the conformation of **5 aa** in the crystalline state, revealed by the X-ray crystallographic analysis, was used for the initial conformation of the dialkoxysilyl group of **6 d** (Figure 1).[18,19] Assuming that the ozone accesses the alkene moiety from the opposite side of the methyl group on silicon to avoid steric repulsion, we estimated four types of transition states **TS1**–**TS4** with differences in the *Re*/*Si* face selection and *endo*/*exo* modes in 1,3-dipolar cycloaddition. The calculation results showed that **TS1**, in which ozone reacts with the alkene moiety from the *Re*-face in the *endo*-cyclization mode to form a silylperoxide with *R* configuration at the carbonyl α-position, is the most favorable. Although the calculation level is too low to discuss the result in detail, the models seem to adequately show the effect of the asymmetric environment created by the chiral silyl group **A**.[20]

The present asymmetric ozone oxidation has a broad substrate scope. As shown in Scheme 6, the ozone oxidation of 3-hexyne-, 2-butyne-1,4-diol-, and 6-phenyl-2-hexyn-1-ol-derived silylalkenes (**6 e**–**6 g**, respectively) afforded the corresponding α-silylperoxy ketones in 90 (78 % d.r.), 85 (91 % d.r.), and 86 % yield (89 % d.r.), respectively.[21–23] Moreover, a similar reaction of the cyclododecyne-derived cyclic silylalkene **6 h** proceeded with good stereoselectivity (82 % d.r.).

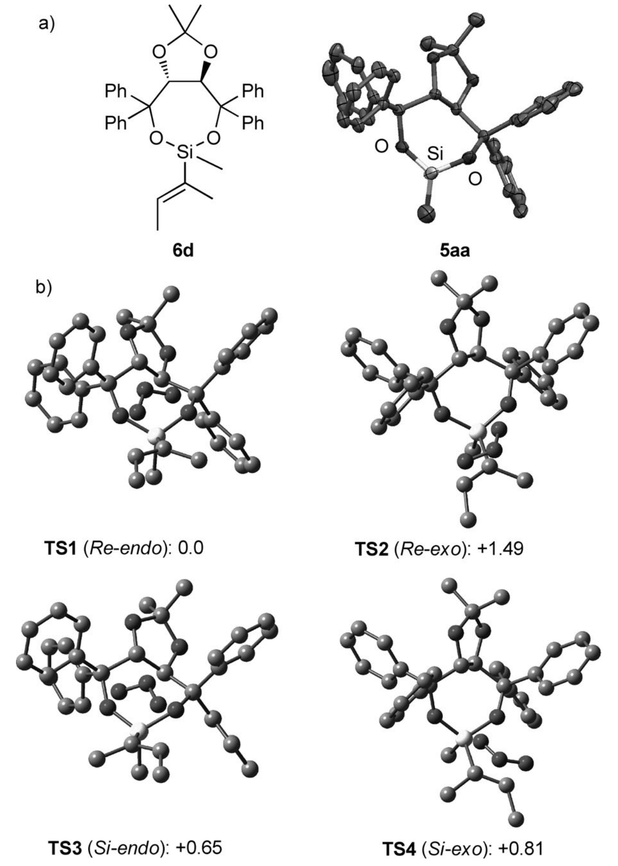
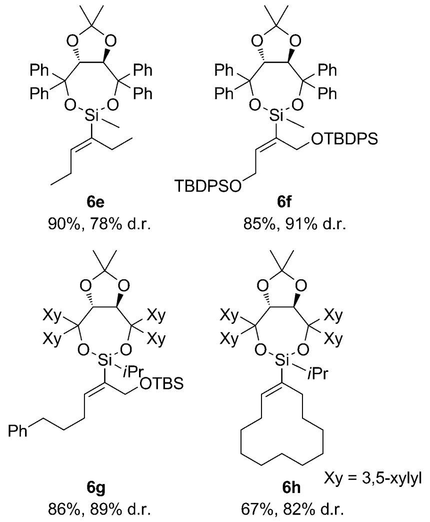


Figure 1. a) Schematic representation of **6d** and ORTEP of **5aa** (ellipsoids set at 40% probability level). b) Transition state models for the 1,3-dipolar cycloaddition of ozone with alkenylsilane **6d**. The relative zero-point vibrational energies in kcal mol^{-1}.



Scheme 6. Scope and limitation of asymmetric ozone oxidation.

In conclusion, we have developed an unprecedented asymmetric ozone oxidation of silylalkenes by using a C_2-symmetrical dialkoxysilyl group as a chiral auxiliary. Further studies to apply the asymmetric ozone oxidation to natural product synthesis, along with investigations of the synthetic applications of the C_2-symmetrical dialkoxyhydrosilane, are in progress.

Acknowledgements

This research was supported by JSPS KAKENHI (grant numbers 24106734 and 24350048) and the MEXT Project of Integrated Research on Chemical Synthesis. We thank Y. Tokito (Kyushu Univ.) for assistance in the HRMS measurements.

Keywords: acyloin · alkenes · asymmetric oxidation · ozone · silylperoxide

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[16] Enantiopurity of **9a** was determined by GLC analysis, see Supporting Information for details.

[17] Hydrogenation of silylperoxides **7** using transition metal catalysts directly affords acyloins **9**, but with loss of stereopurity. Mechanistic studies for the epimerization are now underway.

[18] Gaussian 09 program (Revision B.01), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc. Wallingford CT, **2009**.

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[20] Although the reason for the change in diastereoselectivity when using a Bn-substituted system has not been clarified, the X-ray crystallographic analysis of **5aa** and **6ca** show a substantial difference in the conformation of the dialkoxysilyl group **A**, see Supporting Information.

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[22] The absolute stereochemistries of silylperoxides **7e** and **7f** derived from **6e** and **6f** were determined to *R* at the carbonyl α-position by derivatization to authentic samples, see Supporting Information for the details.

[23] The absolute stereochemistries of silylperoxides **7g** and **7h** derived from **6g** and **6h** have not yet been determined.

Received: April 8, 2014

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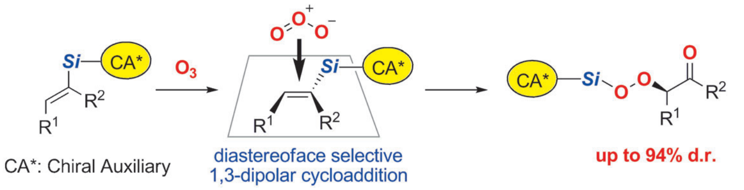

Putting ozone to work: Ozone oxidation of chiral alkenylsilanes prepared from alkynes and a newly designed chiral hydrosilane affords silylperoxides with high diastereoselectivity (up to 94% d.r.; see scheme). The silylperoxides are convertible into enantioenriched chiral acyloins in a stereospecific manner.

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