ChemPubSoc Europe
DOI: 10.1002/chem.201402434
CHEMISTRY
A European Journal
Communication

Chiral Alkenes

Planar Chiral Dialkoxysilane: Introduction of Inherent Chirality and High Reactivity in Conventional Achiral Alkene

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Abstract: A simple eight-membered dialkoxysilane (*E*)-**1** prepared from 2-pentene-1,5-diol, showed remarkably stable planar chirality along with high reactivity toward epoxidation, Diels–Alder reaction, and cycloaddition reaction with azide.

Functionalization of alkenes with discrimination of the stereotopic faces is one of the most fundamental and efficient approaches in asymmetric synthesis, and hence, numerous diastereoselective and enantioselective methods have been developed so far.[1] Basically, an alkene has no chiral element; therefore, introduction of an external chiral element such as an sp^3 carbon chirality into the adjacent position of the alkene or into the reagent is necessary to discriminate between the stereotopic faces of the alkene. In contrast, if an alkene having inherent chirality is available, unique and efficient asymmetric synthesis can be performed without the aid of external chiral element.[2,3]

To create an "inherent chiral alkene," we envisioned the transformation of a conventional achiral alkene **i** into a medium-sized cyclic molecule **ii** via ring formation with a detachable "buckle **Z**" (Figure 1). The resulting **ii** should have planar chirality because of its conformational constraint.

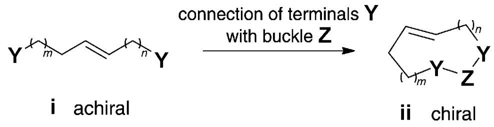


Figure 1. Introduction of chirality and high reactivity in achiral alkene **i**.

To realize this concept, we designed new eight-membered olefinic dialkoxysilanes (*E*)-**1** (≡**ii**, m and $n=1$, Y=O, Z=SiR_2), in which silicon acts as the buckle to connect both side of 1,5-diol.[4] Conformational analysis by DFT (density functional theory) calculation suggests that the alkene moiety of (*E*)-**1** forms stereogenic planes in the most stable conformation, as shown in Figure 2.[5] Furthermore, estimated barrier to racemization is high enough to isolate an enantiomer (see below). Herein, we describe the detailed synthesis, stereochemical behavior, and reaction of dialkoxysilanes (*E*)-**1**.[6,7]

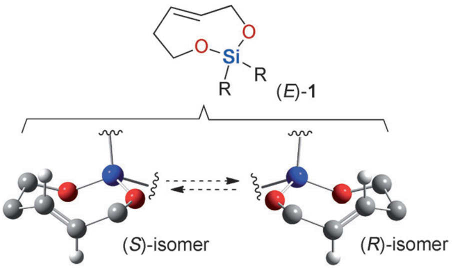
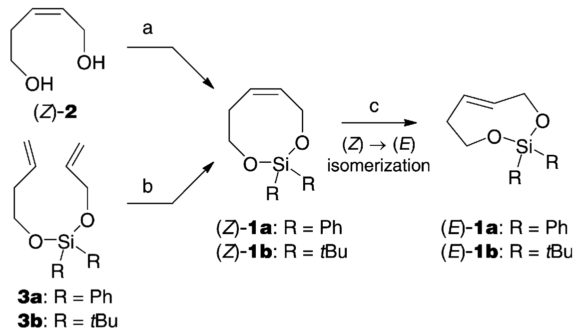


Figure 2. Most stable conformers of (*E*)-**1**.

An ideal approach to (*E*)-**1** is assembling achiral diol (*E*)-2-pentene-1,5-diol [(*E*)-**2**] and dichlorosilane, however, the entropically unfavorable cyclization of (*E*)-**2** might be difficult. Therefore, we carried out a detour-route synthesis involving the photochemical isomerization of (*Z*)-**1**, as illustrated in Scheme 1. At the outset, we prepared (*Z*)-**1a** (R=Ph) and (*Z*)-**1b** (R=*t*Bu) from (*Z*)-**2** and commercially available dichlorosilanes. The reaction of (*Z*)-**2** and R_2SiCl_2 (R=Ph or *t*Bu) in the



Scheme 1. Synthesis of (*E*)-**1a**,**b**. Reagents and conditions: a) R_2SiCl_2, $AgNO_3$, *N*,*N*-dimethylformamide, 0 °C, (*Z*)-**1a**: 71 %, (*Z*)-**1b**: 77 %. b) Grubbs' 1st generation catalyst (5 mol %), CH_2Cl_2, RT, (*Z*)-**1a**: 87 %, (*Z*)-**1b**: 72 %. c) dimethyl isophthalate (20 mol %), $h\nu$: 280 nm, CH_3CN, RT, (*E*)-**1a**: 25 %, (*E*)-**1b**: 31 %.

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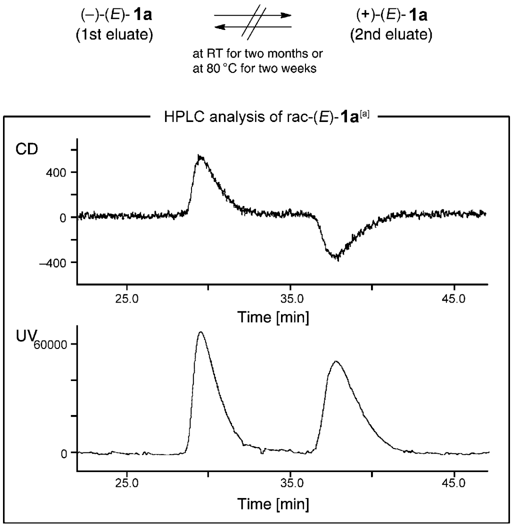
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402434.

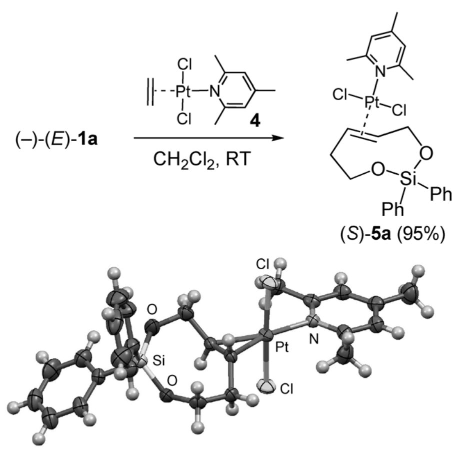
presence of $AgNO_3$ under high-dilution conditions afforded (*Z*)-**1a** and (*Z*)-**1b** in 71% and 77% yields, respectively.[8]

An alternative approach, the RCM (ring-closing olefin metathesis) of **3a** and **3b**, was also efficient, and (*Z*)-**1a** and (*Z*)-**1b** were obtained in 87% and 72% yields, respectively.[9,10] Photochemical isomerization of (*Z*)-**1a,b** was performed by irradiation with 280 nm UV light in the presence of dimethyl isophthalate (sensitizer) in acetonitrile, and **1a** and **1b** were obtained as 25:75 and 33:67 *E/Z* mixtures, respectively.[11] Pure (*E*)-**1a,b** were successfully isolated by $AgNO_3$-impregnated silica gel chromatography.[12,13] The existence of isolable enantiomers of (*E*)-**1a** was revealed by HPLC analysis using a chiral stationary column equipped with a CD (circular dichroism) detector. As shown in Scheme 2, both enantiomers of (*E*)-**1a** were separated: the first eluate was the (−)-isomer ($[\alpha]_D^{20} = -65.4$, *c* 1.66, $CHCl_3$) and the second eluate was the (+)-isomer ($[\alpha]_D^{21} = +63.6$, *c* 1.61, $CHCl_3$).[14] Further, the remarkable stereochemical stability of (*E*)-**1a** was revealed. Namely, the enantiopurity of the isolated enantiomer of (*E*)-**1a** was almost unchanged in toluene solution at ambient temperature for two months or at 80 °C for at least two weeks.

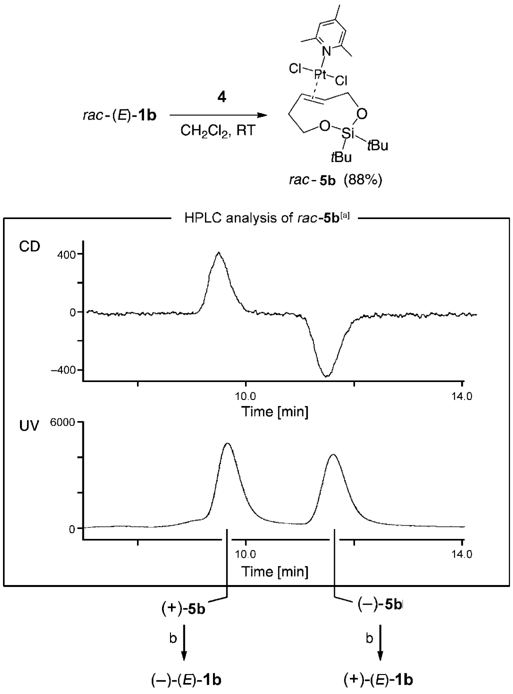


Scheme 2. Stereochemical behavior of (*E*)-**1a**. [a] CHIRALCEL OJ-H (4.6×250 mm), hexane/*i*PrOH = 90:10, flow rate: 0.5 mL min^{-1}, CD 254 nm, UV: 254 nm.

Because straightforward determination of the absolute configuration of non-crystalline (*E*)-**1a** was difficult, we decided to prepare Pt-complexes of the enantiomers by our previously developed method.[15] Reaction of (−)-(*E*)-**1a** with $PtCl_2$(2,4,6-trimethylpyridine)($CH_2{=}CH_2$) (**4**) in CH_2Cl_2 at RT afforded the desired **5a** in 95% yield, as crystals suitable for X-ray analysis. The analysis results showed that the absolute configuration of (−)-(*E*)-**1a** is (*S*) (Scheme 3).[16]



Scheme 3. Synthesis and X-ray analysis of (*E*)-**5a** and ORTEP drawing of (*S*)-**5a** (50% probability ellipsoids).



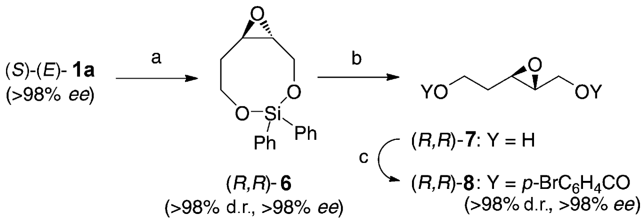
Scheme 4. Transformation of (*E*)-**1b** into **5b** and separation of the enantiomers. [a] CHIRALPAK AD-H (4.6×250 mm), hexane/*i*PrOH = 95:5, flow rate: 0.5 mL min^{-1}, CD: 254 nm, UV: 300 nm. Reagents and conditions: a) semi-preparative HPLC: CHIRALPAK AD-H (25×250 mm), hexane/*i*PrOH = 95:5, flow rate: 4.0 mL min^{-1}, UV: 300 nm, b) PPh_3, CH_2Cl_2, 0 °C, (−)-(*E*)-**1b**: 57%, (+)-(*E*)-**1b**: 90%.

In contrast to the case of (*E*)-**1a**, direct separation of the enantiomers of (*E*)-**1b** using a chiral stationary column was unsuccessful. Hence, we examined for the Pt-complex derivatization method. As shown in Scheme 4, Pt-complex **5b** was prepared in racemic form from *rac*-(*E*)-**1b** and **4**, and both enantiomers of **5b** were successfully separated by HPLC using a chiral stationary column. Removal of the Pt moiety from (+)-and (−)-**5b** using PPh_3 afforded (−)-(*E*)- and (+)-(*E*)-**1b**, respectively.[17] The enantiopurity of the isolated enantiomers of **1b** was almost unchanged in toluene at 80 °C for two weeks.

Elucidation of the detailed stereochemical stability of (*E*)-**1a** and (*E*)-**1b** by measuring the change in the optical purity is difficult owing to their remarkable reactivity of the *E*-alkene moiety.[18] Therefore, we estimated the racemization energy by

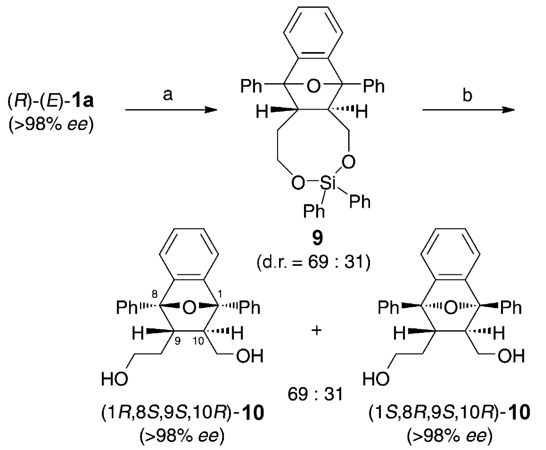
DFT calculations: (*E*)-**1a** is much more stable than (*E*)-**1b** [$\Delta E^{\ddagger}_{(298\ K)}$ = 32.6 and 28.7 kcal mol^{-1} for (*E*)-**1a** and (*E*)-**1b**, respectively].[5] From these data, the half-lives of the optical activity ($t_{1/2}$) of (*E*)-**1a** and (*E*)-**1b** at 25 °C were calculated as 1,375 years and 1.9 years, respectively. These results mean that the synthesis of remarkably stable planar chiral alkene was realized by the simple transformation of acyclic olefinic diol into cyclic dialkoxysilane and that the stereochemical stability of the resulting (*E*)-**1** can be adjusted by appropriate choice of the substituent R on the silylbuckle **Z**.

The obtained (*E*)-**1** is unique in that it is a highly reactive chiral alkene. As shown in Scheme 5, the reaction of (*S*)-(*E*)-**1a** with *m*CPBA (1.2 equiv) in CH_2Cl_2 at 0 °C proceeded to completion within 1 h to afford epoxide (*R*,*R*)-**6** quantitatively in a stereospecific manner (> 98 % d.r., > 98 % *ee*).[19] In general, a conventional (*Z*)-alkene is more reactive toward epoxidation than is an (*E*)-alkene.[20] However, a similar epoxidation reaction of (*Z*)-**1** was rather slow, taking approximately 24 h for completion. The observed significantly high reactivity of (*E*)-**1** would be attributable to the distorted structure of the olefinic bond. The silyl buckle moiety could be removed from **6** by treatment with TBAF to quantitatively afford epoxide **7** having an acyclic skeleton. The stereochemical purity of **7** (> 98 % d.r., > 98 % *ee*) was reconfirmed by HPLC analysis of bromobenzoate derivative **8** using a chiral stationary column.

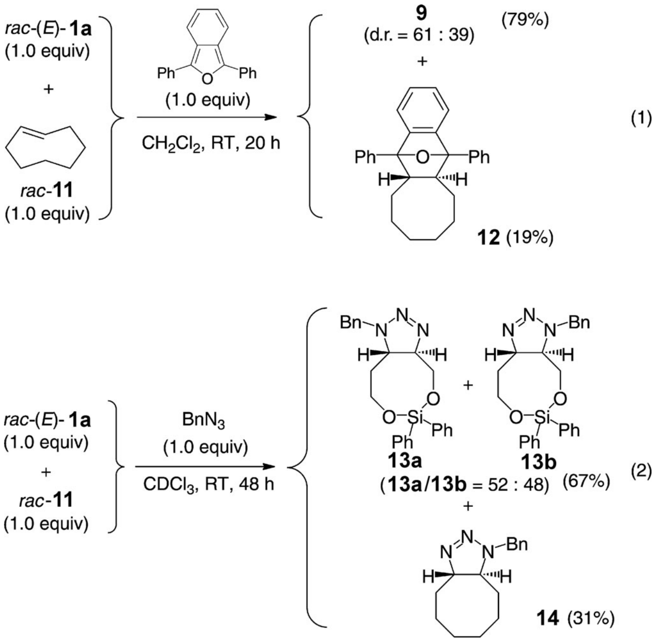


Scheme 5. Epoxidation of enantioenriched (*E*)-**1a**. Reagents and conditions: a) *m*CPBA (1.2 equiv), CH_2Cl_2, 0 °C, 1 h, quant.; b) TBAF, THF, RT, quant.; c) $p\mathrm{BrC_6H_4COCl}$, Et_3N, *N*,*N*-dimethyl-4-dimethylaminopyridine (cat.), CH_2Cl_2, 0 °C, 97 %. *m*CPBA = *meta*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride.

(*E*)-**1a** showed very high reactivity for Diels–Alder reactions as well. The reaction of (*R*)-(*E*)-**1a** with 1,3-diphenyl isobenzofuran proceeded to completion within 2.5 h even at RT to afford the cycloaddition product **9** in 90 % yield as a diastereomeric mixture (d.r. = 69:31), as shown in Scheme 6.[21] The stereochemistry of the diastereomers of **9** was unambiguously determined as (1*R*,8*S*,9*S*,10*R*) and (1*S*,8*R*,9*S*,10*R*) by X-ray analysis.[16] Optically pure diols (1*R*,8*S*,9*S*,10*R*)-**10** and (1*S*,8*R*,9*S*,10*R*)-**10** were afforded from **9** by removal of the silyl buckle moiety. In sharp contrast, a similar reaction of (*Z*)-**1a** did not proceed under the similar conditions:[22] the reaction of an equimolar mixture of (*E*)-**1a**, (*Z*)-**1a**, and excess 1,3-diphenyl isobenzofuran at RT for 4 h gave only **9** (quant.), and (*Z*)-**1a** was recovered almost intact (94 %).



Scheme 6. Diels–Alder reaction of (*E*)-**1a** and 1,3-diphenyl isobenzofuran. Reagents and conditions: a) 1,3-diphenylisobenzofuran (1.5 equiv), toluene, RT, 2.5 h, 90 %; b) TBAF, THF, 0 °C, 75 %.



Scheme 7. Competitive reactions of (*E*)-**1a** and *trans*-cyclooctene (**11**).

The Diels–Alder reactivity of (*E*)-**1a** was higher than that of *trans*-cyclooctene (**11**), which is the well-known highly strained and reactive alkene.[23] As shown in Scheme 7-(1), the reaction of an equimolar mixture of *rac*-(*E*)-**1a**, *rac*-**11**, and 1,3-diphenyl isobenzofuran at RT for 20 h provided **9** (d.r. = 61:39) and **12** in 79 % and 19 % yields, respectively; this result meant that (*E*)-**1a** has 4.2 times greater reactivity than does **11**.[24] Furthermore, (*E*)-**1a** showed greater reactivity than did **11** for the [3+2] cycloaddition reaction [Scheme 7-(2)].[25] Namely, a similar competitive reaction of (*E*)-**1a** and **11** with benzyl azide at RT for 48 h afforded **13** (**13a**/**13b** = 52:48) and **14** in 67 % and 31 % yields, respectively.[26–29]

In conclusion, we have developed a simple and efficient approach to introduce chirality and enhance reactivity to conventional achiral alkenes. The resulting novel alkene shows remarkably stable chirality as well as high reactivity toward epoxidation, Diels–Alder reaction, and cycloaddition reaction with azides. Further studies to extend the concept of introducing chirality and reactivity in alkenes, along with investigations of the synthetic applications of the inherent chiral alkene, are in progress.

Acknowledgements

This research was supported by the JSPS KAKENHI, Grant Number Nos. 22350019, 24106734, and 24350048; the Global COE Program (Kyushu Univ.), the MEXT Project of Integrated Research on Chemical Synthesis, and the Nagase Science and Technology Foundation. We thank Y. Tokito and K. Ideta (Kyushu Univ.) for assistance in the HRMS measurements and NMR analysis, respectively.

Keywords: alkenes · chirality · cyclic molecules · dialkoxysilanes · stereoselective transformations

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[14] The specific rotation value of the enantiopure (−)-isomer was estimated from the value of the (−)-isomer with 94% *ee* ($[\alpha]_D^{20} = -61.5$, *c* 1.66, $CHCl_3$).

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[16] Selected crystallographic data are provided in Supporting Information along with the CCDC numbers.

[17] The absolute stereochemistry of (*E*)-**1b** was not determined, yet.

[18] An attempt to perform kinetic studies of racemization at high temperature failed because of the concomitant *E-Z* isomerization. Detailed study on the observed unusual thermal isomerization of alkene is now underway.

[19] Woerpel and colleagues reported the highly diastereoselective epoxidation of eight-membered olefinic dialkoxysilane having a chiral carbon by use of *m*CPBA. See the ref. [7].

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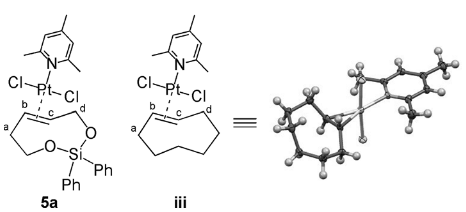
[22] The reaction of (*Z*)-**1a** and 1,3-diphenyl isobenzofuran at 80 °C for 75 h gave another diastereomer of **9** (>95% d.r.) in only 29% yield, along with a significant amount of a recovered (*Z*)-**1a** (71%).

[23] The high reactivity of (*E*)-cyclooctene in the Diels–Alder reaction has been reported. See the references [21a], [21b].

[24] To clarify the correlation between the structure and reactivity of alkenes, we compared the structures of the alkene moieties of (*E*)-**1a** and **11**. Because straightforward comparison of the structures of non-crystalline (*E*)-**1a** and **11** was difficult, we compared the X-ray structures of the corresponding Pt-complexes **5a** and **iii**. However, the no significant trend was observed: as shown in below, **5a** and **iii** show approximately the same length of the olefinic double bond $C_b{=}C_c$ [**5a**: 1.387(8) Å, **iii**: 1.380(6) Å] and torsional angle of the alkene plane $\angle C_aC_bC_cC_d$ [**5a**: 130.5(6)°, **iii**: 130.2(5)°].



5a **iii**

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Received: March 1, 2014