Journal Pre-proof

Mechanistic investigation on the remote stereocontrol in the chiral Lewis base-catalyzed, $SiCl_4$-promoted kinetic resolution of chlorinated *cis*-vinyl epoxides

Jungi Jung, Mugeon Song, Jun-Ho Choi, Won-jin Chung

PII: S0040-4020(20)30998-4

DOI: https://doi.org/10.1016/j.tet.2020.131763

Reference: TET 131763

To appear in: *Tetrahedron*

Received Date: 17 July 2020

Revised Date: 22 October 2020

Accepted Date: 8 November 2020

Please cite this article as: Jung J, Song M, Choi J-H, Chung W-j, Mechanistic investigation on the remote stereocontrol in the chiral Lewis base-catalyzed, $SiCl_4$-promoted kinetic resolution of chlorinated *cis*-vinyl epoxides, *Tetrahedron*, https://doi.org/10.1016/j.tet.2020.131763.

Mechanistic investigation on the remote stereocontrol in the chiral Lewis base-catalyzed, $SiCl_4$-promoted kinetic resolution of chlorinated *cis*-vinyl epoxides

Jungi Jung, Mugeon Song, Jun-Ho Choi,* and Won-jin Chung*

Department of Chemistry, Gwangju Institute of Science and Technology, 123 Cheomdan-gwagi-ro, Buk-gu, Gwangju 61005, Republic of Korea.

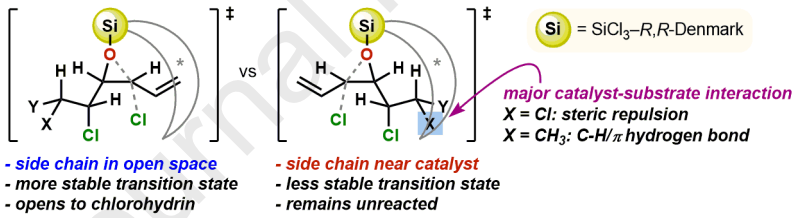
Submitted to *Tetrahedron*

Corresponding authors

Tel.: +82-62-715-4626; fax: +82-62-715-2866; e-mail: junhochoi@gist.ac.kr (J.-H. Choi)

Tel.: +82-62-715-2847; fax: +82-62-715-2866; e-mail: wjchung@gist.ac.kr (W.-j. Chung)

Abstract



It has been known that the enantioselectivity of the chiral Lewis base-catalyzed, $SiCl_4$-promoted kinetic resolution of α,β-dichloro *cis*-vinyl epoxide is highly influenced by the configuration of the distal β-chlorine-bearing stereocenter. In this report, the precise nature of this unusual remote stereocontrol was investigated both experimentally and theoretically. Upon examination of a substrate that has an alkyl group in place of the β-chlorine substituent, the spatial location of major catalyst-substrate interaction was determined. Subsequently, through computational analysis of transition states, the steric repulsion by the β-substituents as well as the additional C–H/π hydrogen bond by the alkyl substituent were proposed as the crucial stereo-determining factors.

Keywords

epoxide opening; kinetic resolution; Lewis base catalysis; silicon tetrachloride; C–H/π hydrogen bond

1. Introduction

Epoxide is one of the most versatile functional groups in organic synthesis, and thus a number of synthetic methods have been developed for the enantioselective formation of chiral epoxide [1]. Enantioenrichment can also be achieved by the enantioselective opening of optically inactive epoxide via either desymmetrization of *meso*-epoxide [2] or kinetic resolution of racemic epoxide [3], typically in the presence of chiral Lewis acid. Denmark and coworkers developed a chiral Lewis base catalysis for the generation of highly active chiral silicon Lewis acids by taking advantage of Lewis base activation of Lewis acids phenomenon [4], and the utility of such catalytic system was demonstrated in the desymmetrization of *meso*-epoxide with chiral phosphoramide catalyst and silicon tetrachloride [5]. Since this seminal report, various types of chiral Lewis base including *N*-oxide [6], phosphines [7], and phosphine oxides [8] were developed by several research groups, and highly selective epoxide desymmetrization was accomplished, illustrating the efficiency of the Lewis base-$SiCl_4$ system [9]. Later, the scope of Denmark's chiral phosphoramide-catalyzed, enantioselective epoxide opening has been successfully extended to the kinetic resolution of racemic *cis*-vinyl epoxide (**1**) by Vanderwal and coworkers during the enantioselective total synthesis of chlorosulfolipids (Fig. 1A) [10]. In this case, the dimeric bisphosphoramide **2** performed better than the monomeric catalyst even though it was an inferior catalyst for desymmetrization. Interestingly, the selectivity of the kinetic resolution is highly affected by the configuration of a relatively remote β-stereocenter. Under the identical catalytic conditions with **2**, *anti*-α,β-dichloride (R = *n*-C_6H_{13}) was resolved much more effectively than the related *syn*-α,β-dichloride (R = *n*-C_8H_{17}). Recently, a preliminary mechanistic study on the stereo-controlling effect of these chlorine-bearing stereocenters was reported by our group (Fig. 1B) [11]. Through a systematic examination of α- or β-monochlorinated substrates **4**–**6**, we have demonstrated that both α- and β-chlorine substituents are required for the high level of enantio-differentiation. In addition, computational analysis was performed for the aliphatic side chain conformation of α,β-dichlorinated vinyl epoxide in order to rationalize the cooperative action of the two stereocenters. It was suggested that the allylic 1,3-like strain at the α-stereocenter as well as the preferred gauche conformation between the α- and β-chlorine-bearing carbons result in a fairly well-defined spatial arrangement of the substituents. Then, upon examination of the ground state of a representative catalyst-substrate complex, it was proposed that the dichloroalkyl side chain could be placed near the chiral

catalyst pocket depending on the epoxide configuration, and the conformationally rigid α-center would direct the aliphatic residue toward the catalyst. Thus, the enantiomer with its alkyl side chain in a less crowded space (***i***) is likely to be activated preferentially to result in the selective epoxide opening whereas the other enantiomer-catalyst complex (***ii***) is energetically less favorable because of the destabilizing steric interaction between the β-substituents of the side chain and the catalyst. The degree of such interaction appears to be finely controlled by the position and property of the substituents at the β-center. In the current study, the influence of the remote site was further evaluated by employing a substrate with two β-alkyl groups (Fig. 1C). This type of substrate can be considered as an alkyl analog of α,β-dichloro *cis*-vinyl epoxide, in which the β-chlorine is replaced by an alkyl group. Then, a more precise computational analysis was conducted via transition state calculation to support our stereochemical model and to rationalize the observed remote configuration-dependency. Herein, we describe the results from these mechanistic investigations that led to a plausible proposal on the nature of the catalyst-substrate interaction.

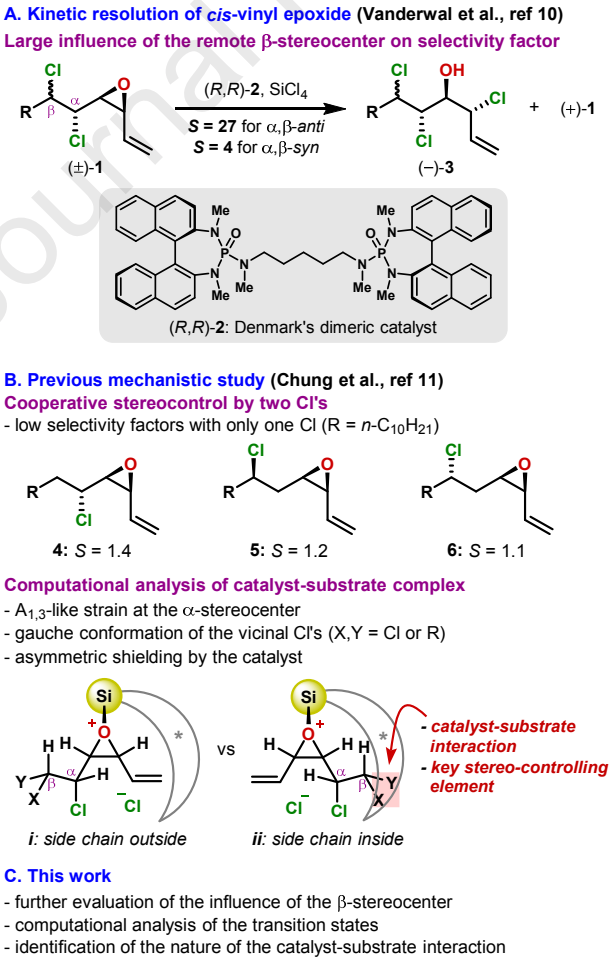
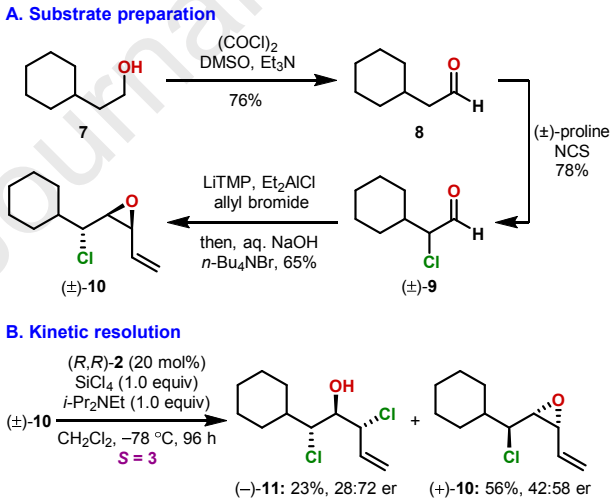


Fig. 1. Chiral Lewis base-catalyzed kinetic resolution of chlorinated c*is*-vinyl epoxide.

2. Results and discussion

2.1. Kinetic resolution of α-chloro *cis*-vinyl epoxide with two β-alkyl substituents

To probe the role of the β-substituents, two alkyl moieties were installed at the β-position of α-chloro *cis*-vinyl epoxide (Scheme 1A). A cyclohexyl group was employed in order to avoid the creation of an additional stereocenter as well as to increase the molecular weight for convenient handling. First, commercially available 2-cyclohexylethanol (**7**) was oxidized to aldehyde **8** via the Swern oxidation [12]. Then, α-chlorination was accomplished with the combination of NCS and (±)-proline to give (±)-**9** [13]. At this point, a sequence of diastereoselective bromoallylation and ring closure afforded the desired racemic *cis*-vinyl epoxide (±)-**10** [14]. The kinetic resolution of (±)-**10** was performed under the previously reported conditions (Scheme 1B) [10]. In the presence of 20 mol% of (*R*,*R*)-**2**, (±)-**10** was slowly resolved at –78 °C with moderate selectivity (*S* = 3, $\Delta\Delta G^{\ddagger}$ = 0.4 kcal/mol).



Scheme 1. Preparation and evaluation of a *cis*-vinyl epoxide substrate with two alkyl substituents at the β-position.

This result is compared with the literature data from the kinetic resolution of *syn*- and *anti*-α,β-dichloro *cis*-vinyl epoxides (Fig. 2) [10]. The illustration depicts the catalyst/substrate interaction in the transition structure of the less reactive enantiomer, which is thought to be responsible for the energy difference between the two diastereomeric transition states. The similar selectivity factors obtained with **10** and α,β-*syn*-**1** (*S* = 4, $\Delta\Delta G^{\ddagger}$ =

0.5 kcal/mol) indicate that the β-chlorine substituent of α,β-*syn*-**1** is essentially uninfluential and thus not in close contact with the catalyst. On the other hand, it appears that the β-chlorine substituent of α,β-*anti*-**1** has a significant impact on the selectivity (S = 27, $\Delta\Delta G^{\ddagger}$ = 1.3 kcal/mol). Therefore, it is highly probable that this position (highlighted in blue) is the site of important catalyst-substrate interaction (X of ***ii*** in Fig 1B). Among these three structures, only α,β-*anti*-**1** has a different substituent (Cl) at that position, and thus the noticeably high selectivity of this substrate can be rationalized by invoking a destabilizing interaction between the chlorine and the catalyst.

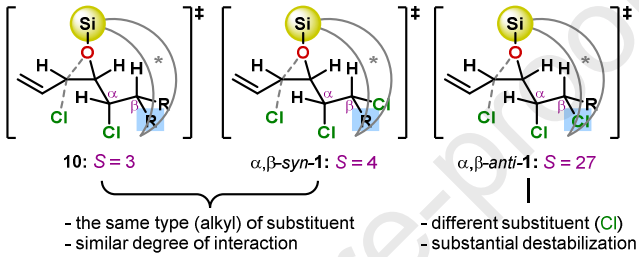


Fig. 2. Comparison of catalyst/substrate interactions.

In addition, the differential activation parameters were obtained experimentally by performing the kinetic resolution of (±)-**10** at various temperatures ranging from –80 to –20 °C (See the SI for details). Each data point was duplicated, and the average values of selectivity factor were used for the plot. During the course of this study, the experimental results often suffered from irreproducibility, probably caused by the adventitious moisture even though the reactions were conducted in the presence of *i*-Pr_2NEt as an acid scavenger [15,16]. Gratifyingly, the addition of molecular sieve alleviated this problem without affecting the stereoselectivity. From the differential Eyring plot with these data, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ were determined to be –1.1 kcal/mol and –3.8 cal/molK, respectively (Fig 3). The differential enthalpy and entropy contribute to the differential Gibbs free energy in comparable degrees ($-T\cdot\Delta\Delta S^{\ddagger}$ = 0.7 kcal/mol at –78 °C) but in the opposite directions. Thus, in theory, the reversal of enantioselection can be observed at high temperature [17]. Unfortunately, the estimated selectivity factor is only 2 even at 200 °C ($\Delta\Delta G^{\ddagger}$ = 0.7 kcal/mol favoring the other enantiomer), which is far from being practical.

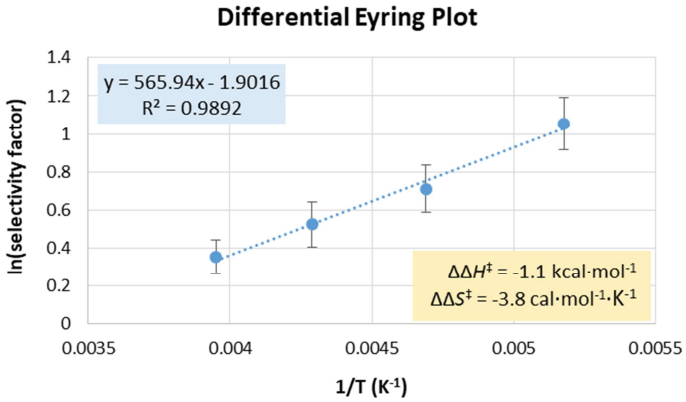


Fig. 3. Differential Eyring plot for kinetic resolution of (±)-**10**.

2.2. Computational analysis

2.2.1. Computational method

Approximate coordinates for transition states were obtained by the PM3 semi-empirical method using MOPAC 2016 [18], and then those were optimized sequentially by ab initio calculation at the HF/6-31G(d) then 6-31G(d,p) level of theory with Grimme's dispersion correction (D3) [19] using the GAMESS(US) software package [20]. The resulting structures were further refined by density functional theory (DFT) calculation at the B3LYP-D3/6-31G(d,p) level of theory [21] using the Gaussian 16 suite of programs [22]. For the solvation effect of CH_2Cl_2, the polarizable continuum model (PCM) was employed [23]. The validity of the resulting transition structures was supported by the presence of a single negative frequency that corresponds to the epoxide opening as well as the formation of reactant and product from the Intrinsic Reaction Coordinate (IRC) calculation at the same level of theory. The single point energies were obtained by DFT calculation at the B3LYP-D3/6-311++G(d,p) level of theory. The 3-D illustrations were produced using CYLview [24].

2.2.2. Transition state calculation for kinetic resolution of chlorinated *cis*-vinyl epoxides

Through an extensive mechanistic study on the complexation between (*R*,*R*)-**2** and $SiCl_4$ by Denmark and coworkers, it was revealed that the tethered bisphosphoramide Lewis base forms *cis*-chelation around the silicon center in the catalytically active species [25]. The subsequent coordination of an electrophile would generate an octahedral species [26], in which the position of electrophile, epoxide in our case, has two

possibilities, *trans* to either phosphoramide or chloride (Fig. 4). The relative stability of two isomers was estimated computationally at the inexpensive HF/6-31G(d) level of theory using a simple *cis*-dimethyl epoxide prior to the transition state calculation. After a systematic analysis of the conformation around the Si-O(epoxide) bond in each isomer, it was found that the epoxide prefers to occupy the *trans* position to phosphoramide (ΔG = 1.2 kcal/mol). This result is consistent with the orbital analysis of hypervalent octahedral silicon complexes, which has been previously done for chiral Lewis base-catalyzed, enantioselective aldol addition of trichlorosilyl ketene acetal [27]. According to the analysis, two electronegative chlorine atoms favor to constitute a hypervalent 3-center-4-electron bond (blue) and thus maintain a *trans* relationship, leaving the epoxide no choice but to be placed at the position *trans* to phosphoramide. An important consequence of this ligand arrangement is the electrophilic activation of epoxide by the formation of a dative bond to silicon through an electron-withdrawing *sp*-orbital (red).

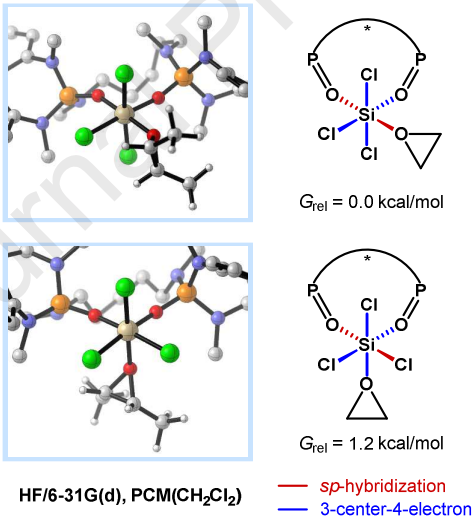


Fig. 4. Analysis of [(*R*,*R*)-**2**·$SiCl_3$·epoxide]$^+$ complex structure with respect to the position of epoxide. (Hydrogens of the catalyst are omitted for clarity.)

Using the geometry of the most stable conformer as a starting point, transition states for the (*R*,*R*)-**2**-catalyzed opening of each enantiomer of *anti*- and *syn*-α,β-dichloro *cis*-vinyl epoxides were calculated (Fig. 5). To simplify the computation process, the long aliphatic group at the side chain was replaced by a methyl group. In the complexes of (α*S*,β*R*)-*anti*- and (α*S*,β*S*)-*syn*-dichlorides (**TS-1** and **TS-3**), the α,β-dichlorinated alkyl

side chains are exposed to vacant space without experiencing meaningful interaction with the catalyst. In contrast, the side chains of (α*R*,β*S*)-*anti*- and (α*R*,β*R*)-*syn*-dichlorides (**TS-2** and **TS-4**) are located near the catalyst pocket, causing steric destabilization. These results are consistent with the simple stereochemical model from our previous study (Fig. 1B), and the computational analysis of transition states correctly predicts the absolute sense of enantioselection. The preferential activation of (–)-(α*S*,β*R*)-*anti*- and (–)-(α*S*,β*S*)-*syn*-dichlorides by (*R*,*R*)-**2**-$SiCl_3^+$ will lead to the selective consumption of these reactive enantiomers via epoxide opening. Consequently, (+)-(α*R*,β*S*)-*anti*- and (+)-(α*R*,β*R*)-*syn*-dichlorides will be left unreacted in an enantioenriched form. Furthermore, the structural characteristics and the relative single point energy values of these diastereomeric transition states can account for the different behavior of *syn*- and *anti*-dichloro *cis*-vinyl epoxides in the kinetic resolution. As alluded to earlier, the degree of interaction between the substrate and the catalyst is significantly altered by the configuration change of the β-stereocenter (**TS-2** vs **TS-4)**, which is embedded in the most crowded area. In addition, the computationally estimated $\Delta\Delta G^{\ddagger}$ values correspond well with the experimentally obtained *S* factors as $\Delta\Delta G^{\ddagger}$ = 1.2 and 0.4 kcal/mol correspond to *S* = ca. 22 and 3 at 195 K, respectively.

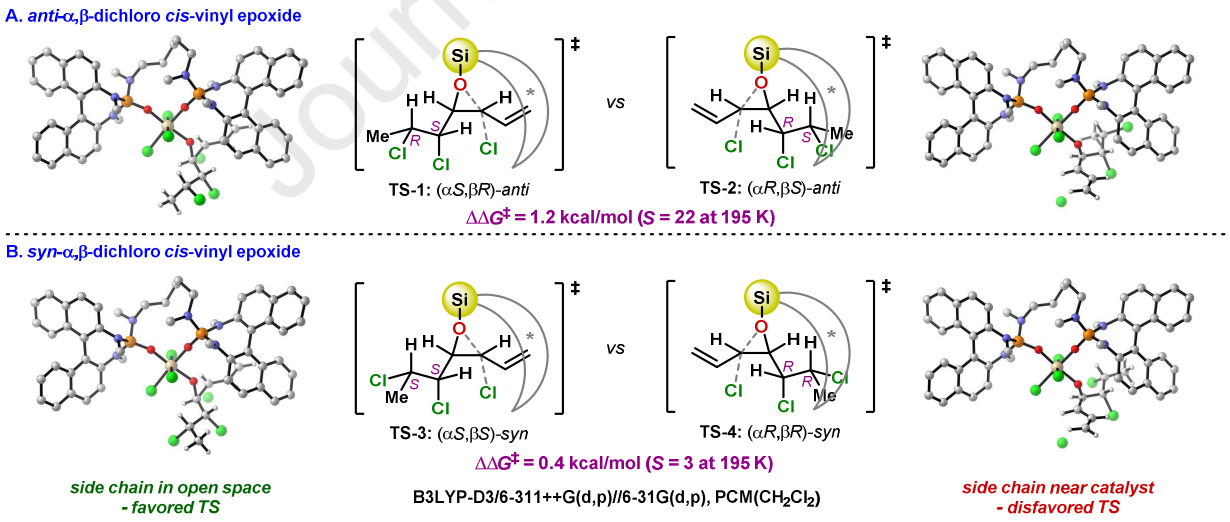


Fig. 5. Transition state calculation for each enantiomer of *anti*- and *syn*-α,β-dichloro *cis*-vinyl epoxides. (Hydrogens of the catalyst are omitted for clarity.)

To elucidate the precise nature of the catalyst-substrate interaction, the transition structures with the side chain in the catalyst pocket were carefully inspected (Fig. 6). It was found that the β-chlorine substituent in **TS-2** is

in close contact with a naphthyl ring of the catalyst, and the distance to the center of the arene ring (3.58 Å) is only slightly longer than the sum of the van der Waals radii (1.75 Å for Cl, 1.70 Å for C). Therefore, the repulsive steric hindrance between the chlorine and the catalyst must be responsible for the destabilization of **TS-2** as expected. On the other hand, the β-methyl group in **TS-4** appears to engage in a C–H hydrogen bond with the neighboring aromatic π system [28]. A C–H bond is pointing toward a naphthyl ring in roughly perpendicular orientation, and the distance between the proton and the center of the arene ring (2.75 Å) is shorter than the sum of the van der Walls radii (1.20 Å for H, 1.70 Å for C), indicating that there is a bonding interaction. The computed C–H/arene distance is in good agreement with the experimentally measured range of sp^3 C–H/arene distances [28h]. The nearby electron-withdrawing chlorine substituents could also assist this interaction by enhancing the C–H acidity. We propose that this weakly stabilizing C–H/π interaction attenuates the degree of destabilization of **TS-4** to a lesser extent. Consequently, the energy difference between the competing TS's (**TS-3** and **TS-4**) becomes smaller, thus resulting in a lower selectivity factor for *syn*-dichloride.

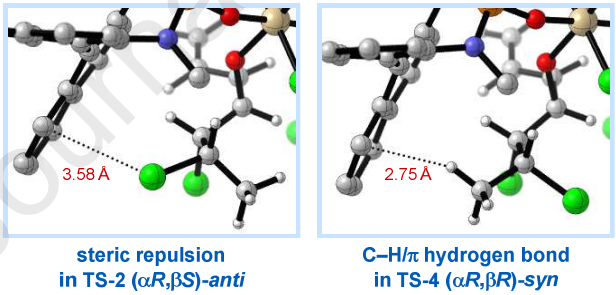


Fig. 6. Alteration of catalyst-substrate interaction by β-stereocenter: steric repulsion (**TS-2**) vs C–H/π hydrogen bond (**TS-4**). (Hydrogens of the catalyst are omitted for clarity. The distances to the center of the arene ring are shown.)

A transition state calculation was also performed for the opening of the simplest β-*gem*-dimethyl analog to account for the kinetic resolution result with (±)-**10** (Fig. 7). It was revealed that the catalyst-substrate interaction is similar to that of *syn*-α,β-dichloro *cis*-vinyl epoxide (**TS-4** vs **TS-6**). The distance between the β-methyl proton and the nearby arene ring (2.71 Å) implies that the degree of C–H/π hydrogen bond in **TS-6** is roughly equivalent to that in **TS-4**. Thus, the comparable level of enantioselection for the *syn*-α,β-dichloride

(*S* = 4) and (±)-**10** (*S* = 3) could be rationalized. Moreover, the calculated $\Delta\Delta G^{\ddagger}$ value (0.6 kcal/mol, *S* = 5 at 195 K) correlates reasonably well with the observed selectivity factor.

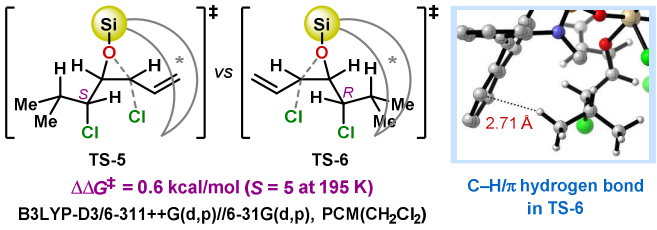


Fig. 7. Transition state calculation for a simple β,β-dialkyl analog. (Hydrogens of the catalyst are omitted for clarity. The distance to the center of the arene ring is shown.)

3. Conclusions

In summary, we have conducted experimental and theoretical mechanistic investigations on the kinetic resolution of chlorinated *cis*-vinyl epoxides to elucidate the origin of the remarkable stereo-controlling effect of the remote β-stereocenter, which has been observed with α,β-dichloro *cis*-vinyl epoxides. Through a control experiment with a β,β-dialkyl analog, the site of predominant catalyst-substrate interaction was identified (X in Fig. 1B). Furthermore, DFT calculation of the transition states suggests the presence of a weakly stabilizing C–H/π hydrogen bond between a proton of a β-alkyl group and an arene ring of the catalyst, which was presumed to be responsible for the attenuated performance of *syn*-α,β-dichloro *cis*-vinyl epoxide compared to the corresponding *anti*-dichloride. These calculation data also account for the absolute sense of enantioselection and support the stereochemical model that has been previously proposed by our group.

4. Experimental section

4.1. General experimental

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Purification of solvents and reagents are described in the Electronic Supporting Information. Filtration and column chromatography were performed using Merck silica gel (SiO_2) 60 Å (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F_{254} TLC plates. Visualization was accomplished with UV (254 nm) as well as $KMnO_4$ and *p*-

anisaldehyde staining solutions. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECS400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) spectrometer and referenced to residual chloroform (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C). Chemical shifts are reported in ppm, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Coupling constants, *J*, are reported in Hertz. Analytical chiral stationary phase gas chromatography (CSP-GC) was performed on an Agilent Technologies 7890B gas chromatograph equipped with a flame ionization detector (FID) and a B-DM (Agilent, ϕ = 0.250 mm, l = 30 m) capillary column. EI-HRMS was performed on a JEOL JMS-700 MStation mass spectrometer with magnetic sector-electric sector double focusing mass analyzer at Korea Basic Science Institute (KBSI), Daegu Center. Data are reported in the form of *m*/*z*. Optical rotation was measured on a JASCO P-2000 WI digital polarimeter at Functional Organic Molecules Synthesis Laboratory, Gwangju Institute of Science and Technology. Data are reported as follows: concentration and solvent.

4.2. Preparation of (±)-10

4.2.1. 2-Cyclohexylethanal (8) [12]

To a stirred solution of oxalyl chloride (1.0 mL, 12 mmol) in CH_2Cl_2 (40 mL) was added DMSO (1.4 mL, 20 mmol) at –78 °C under Ar. After 10 minutes, 2-cyclohexylethanol (**7**, 1.4 mL, 10 mmol) was added dropwise. After 30 minutes, triethylamine (5.6 mL, 40 mmol) was added over 25 minutes. The reaction mixture was warmed to 0 °C and stirred for 90 minutes. The reaction was quenched with sat. aq $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:hexanes = 1:40, R_f = 0.2, $KMnO_4$) to give **8** (960 mg, 76%) as a colorless oil. **8** was used for the next reaction without further purification because of its high volatility. Data for **8** [8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.4, 1H), 2.29 (dd, *J* = 6.8, 2.4, 2H), 1.89 (m, 1H), 1.76–1.62 (m, 5H), 1.35–1.23 (m, 2H), 1.22–1.10 (m, 1H), 1.06–0.94 (m, 2H).

4.2.2. 2-Chloro-2-cyclohexylethanal ((±)-9) [13b]

To a stirred solution of **8** (960 mg, 7.6 mmol) and (±)-proline (89 mg, 0.76 mmol) in CH_2Cl_2 (15 mL) was added NCS (1.3 g, 9.9 mmol) at 0 °C. After 5 minutes, the ice bath was removed. After 18.5 hours, the

reaction was quenched with sat. aq Na_2SO_3 (20 ml) and H_2O (40 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (60 ml × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:hexanes = 1:40, R_f = 0.2, $KMnO_4$) to give (±)-**9** (990 mg, 78%) as a colorless oil ((±)-**9**/dichloro aldehyde = 93/7). Data for (±)-**9** [9a]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 3.2, 1H), 3.97 (dd, *J* = 6.2, 3.4, 2H), 1.97 (m, 1H), 1.86–1.75 (m, 3H), 1.73–1.65 (m, 2H) 1.34–1.14 (m, 5H).

4.2.3. (±)-(3*S*,4*R*,5*S*)-5-Chloro-5-cyclohexyl-3,4-epoxy-1-pentene ((±)-10) [10a]

To a stirred solution of TMP (2.3 mL, 14 mmol) in THF (18 mL) was added *n*-BuLi (7.9 mL, 13 mmol) dropwise over 6 minutes at –78 °C under Ar. After 1 hour, the LiTMP solution was cannulated into a solution of allyl bromide (1.2 mL, 13 mmol) and Et_2AlCl (1.0 M in hexanes, 25 mL, 25 mmol) in THF (18 mL) at –78 °C. After 10 minutes, (±)-**9** (990 mg, 6.2 mmol) in THF (3.0 mL) was added. After 4 hours, the reaction mixture was poured into an ice-cold 5 M aq NaOH (50 mL) solution. *n*-Bu_4NBr (20 mg, 0.060 mmol) was added, and the biphasic mixture was vigorously stirred at room temperature. After 1 hour, the mixture was diluted with hexanes. The organic layer was separated, and the aqueous layer was extracted with hexanes (50 mL × 3). The combined organic layers were washed with brine (100 mL) and sat. aq NH_4Cl (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:hexanes = 1:40, R_f = 0.2, *p*-anisaldehyde) to give (±)-**10** (802 mg, 65%) as a colorless oil. Data for (±)-**10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.2, 10.8, 6.0, 1H), 5.49 (ddd, *J* = 17.2, 1.6, 0.8, 1H), 5.42 (ddd, *J* = 10.4, 1.6, 0.8, 1H), 3.53 (m, 1H), 3.42 (dd, *J* = 9.6, 6.8, 1H) 3.30 (dd, *J* = 9.6, 4.0, 1H), 2.00–1.92 (m, 1H), 1.87–1.75 (m, 4H), 1.72–1.64 (m, 1H), 1.34–1.12 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.8, 121.0, 63.3, 59.0, 56.6, 43.6, 29.8, 28.6, 26.2, 26.0, 25.8. HRMS (EI) calcd for $C_{11}H_{17}{}^{35}ClO$ $[M]^+$ 200.0968, found 200.0965. $[\alpha]_D^{25}$ = 2.6 (*c* 0.53, $CHCl_3$).

4.3. Kinetic resolution of (±)-10 [10a]

To a stirred solution of (±)-**10** (110 mg, 0.50 mmol) and (*R*,*R*)-**2** (85 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) were added *i*-Pr_2NEt (90 μL, 0.50 mmol) and silicon tetrachloride (60 μL, 0.50 mmol) at –78 °C under Ar. After 96 hours, propylene oxide (530 μL, 7.5 mmol) was added. After 1 minute, a solution of MeOH/Et_3N/CH_2Cl_2

(1/2/5, 4 mL) was quickly added to the reaction mixture. The resulting solution was vigorously stirred with a 1:1 mixture of sat. aq $NaHCO_3$ (20 mL) and sat. aq KF (20 mL) solution for 2 hours prior to filtration. The organic layer was separated, and the aquous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. (*R,R*)-**2** was removed by filtration through a short pad of silica gel, and the residue was purified by column chromatography (SiO_2, EtOAc:hexanes = 1:20, *p*-anisaldehyde) to give (+)-**10** (R_f = 0.6, 56 mg, 56%, 42:58 *er*) and (+)-**11** (R_f = 0.4, 28 mg, 23%, 28:72 *er*). Data for (+)-**10**: CSP-GC (B-DM, 34 psi, 70 °C) t_R 115 min (42%), 122 min (58%). Data for (+)-**11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (ddd, *J* = 17.0, 10.2, 7.8, 1H), 5.46 (ddd, *J* = 16.8, 1.2, 1.2, 1H), 5.31 (ddd, *J* = 10.0, 10.0, 1.0, 1H), 5.11 (dd, *J* = 7.6, 0.8, 1H), 3.91 (dd, *J* = 9.8, 2.2, 1H), 3.81 (ddd, *J* = 9.9, 1.4, 1.3, 1H), 2.14–2.06 (m, 1H), 2.02 (dd, *J* = 5.0, 1.2, 1 H), 1.82–1.77 (m, 2H), 1.70–1.67 (m, 2H), 1.57–1.43 (m, 2H), 1.34–1.25 (m, 3H), 1.24–1.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 118.9, 73.7, 67.7, 65.6, 38.2, 31.1, 26.4, 26.2, 25.8, 25.4. HRMS (EI) calcd for $C_{11}H_{18}{}^{35}Cl_2O$ $[M]^+$ 236.0735, found 236.0732. CSP-GC (B-DM, 34 psi, 120 °C) t_R 43 min (28%), 52 min (72%). $[\alpha]_D^{25}$ = 8.9 (*c* 0.21, $CHCl_3$).

4.4. Kinetic resolution at various temperatures for the Eyring plot

The kinetic resolutions for the Eyring plot were performed in a similar manner employing (±)-**10** (50 mg, 0.25 mmol), (*R,R*)-**2** (42 mg, 0.050 mmol), 3 Å molecular sieve (100 mg, powder), *i*-Pr_2NEt (5 μL, 0.03 mmol), and silicon tetrachloride (30 μL, 0.25 mmol) in CH_2Cl_2 (2.5 mL) at –20, –40, –60, and –80 °C for 1, 2, 3, and 4 days, respectively. The result from each experiment is given in the Supporting Information.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science & ICT (NRF-2020R1F1A1076028) and by "GIST Research Institute (GRI)" grant funded by the GIST in 2020.

Supporting Information

Kinetic resolution data at various temperatures, computation data, and copies of NMR spectra for all new compounds (PDF).

References

[1] Reviews: a) T. Sawano, H. Yamamoto, Eur. J. Org. Chem. 2020 (2020) 2369–2378; b) K.P. Bryliakov, Chem. Rev. 117 (2017) 11406–11459; c) O. Cussó, X. Ribas, M. Costas, Chem. Commun. 51 (2015) 14285–14298; d) C. Wang, H. Yamamoto, Chem. Asian J. 10 (2015) 2056–2068; e) R.L. Davis, J. Stiller, T. Naicker, H. Jiang, K.A. Jørgensen, Angew. Chem. Int. Ed. 53 (2014) 7406–7426; f) Y. Zhu, Q. Wang, R.G. Cornwall, Y. Shi, Chem. Rev. 114 (2014) 8199–8256; g) K.M. Weiβ, S.B. Tsogoeva, Chem. Rec. 11 (2011) 18–39; h) G. De Faveri, G. Ilyashenko, M. Watkinson, Chem. Soc. Rev. 40 (2011) 1722–1760; i) O.A. Wong, Y. Shi, Chem. Rev. 108 (2008) 3958–3987; j) D. Chatterjee, Coord. Chem. Rev. 252 (2008) 176–198; k) E.M. McGarrigle, D.G. Gilheany, Chem. Rev. 105 (2005) 1563–1602; l) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, Chem. Rev. 105 (2005) 1603–1662; m) T. Katsuki, V.S. Martin, Org. React. 48 (1996) 1− 299; n) K.A. Jørgensen, Chem. Rev. 89 (1989) 431–458.

[2] a) S. Meninno, A. Lattanzi, Chem. Eur. J. 22 (2016) 3632–3642; b) P.A. Wang, Beilstein J. Org. Chem. 9 (2013) 1677–1695; c) S. Matsunaga, Comprehensive Chirality 5 (2012) 534–580; d) M. Pineschi, Eur. J. Org. Chem. 2006 (2006) 4979–4988; e) C. Schneider, Synthesis (2006) 3919–3944; f) A. Magnus, S.K. Bertilssona, P.G. Andersson, Chem. Soc. Rev. 31 (2002) 223–229; g) E.N. Jacobsen, Acc. Chem. Res. 33 (2000) 421–431.

[3] a) J.M. Keith, J.F. Larrow, E.N. Jacobsen, Adv. Synth. Catal. 343 (2001) 5–26; (b) E. Vedejs, M. Jure, Angew. Chem. Int. Ed. 44 (2005) 3974–4001.

[4] S.E. Denmark, G.L. Beutner, Angew. Chem. Int. Ed. 47 (2008) 1560–1638.

[5] a) S.E. Denmark, P.A. Barsanti, K.-T. Wong, R.A. Stavenger, J. Org. Chem. 63 (1998) 2428–2429; b) S.E. Denmark, P.A. Barsanti, G.L. Beutner, T.W. Wilson, Adv. Synth. Catal. 349 (2007) 567–582; c) T.W. Wilson, S.E. Denmark, in Lewis Base Catalysis in Organic Synthesis (Eds: E. Vedejs, S. E. Denmark), Wiley-VCH, Weinheim, 2016, Vol. 3, chapter 23, pp.1113–1151.

[6] a) B. Tao, M.M.-C. Lo, G.C. Fu, J. Am. Chem. Soc. 123 (2001) 353–354; b) M. Nakajima, M. Saito, M. Uemura, S. Hashimoto, Tetrahedron Lett. 43 (2002) 8827–8829; c) G. Chelucci, S. Baldino, G.A. Pinna, M. Benaglia, L. Buffa, S. Guizzetti, Tetrahedron 64 (2008) 7574–7582; d) N. Takenaka, R.S. Sarangthem, B. Captain, Angew. Chem. Int. Ed. 47 (2008), 9708–9710; e) A.V. Malkov, M.R. Gordon, S. Stončius, J. Hussain, P. Kočovský, Org. Lett. 11 (2009), 5390–5393.

[7] a) G.E. Garrett, G.C. Fu, J. Org. Chem. 62 (1997) 4534–4535; b) S.H. Paek, S.C. Shim, C.S. Cho, T.-J. Kim, Synlett (2003) 849–851.

[8] a) E. Tokuoka, S. Kotani, H. Matsunaga, T. Ishizuka, S. Hashimoto, M. Nakajima, Tetrahedron: Asymmetry 16 (2005) 2391–2392; b) V. Simonini, M. Benaglia, T. Benincori, Adv. Synth. Catal. 350 (2008) 561–564; c) X. Pu, X. Qi, J.M. Ready, J. Am. Chem. Soc. 131 (2009) 10364–10365; d) S. Kotani, H. Furusho, M. Sugiura, M. Nakajima, Tetrahedron 69 (2013) 3075–3081; e) M. Ogasawara, S. Kotani, H. Nakajima, H. Furusho, M. Miyasaka, Y. Shimoda, W. Wu, M. Sugiura, T. Takahashi, M. Nakajima, Angew. Chem. Int. Ed. 52 (2013) 13798–13802.

[9] For a review on $SiCl_4$-catalyzed organic reactions: S. Rossi, M. Benaglia, A. Genoni, Tetrahedron 70 (2014) 2065–2080.

[10] a) W.-j. Chung, J.S. Carlson, D.K. Bedke, C.D. Vanderwal, Angew. Chem. Int. Ed. 52 (2013) 10052–10055; b) W.-j. Chung, J.S. Carlson, C.D. Vanderwal, J. Org. Chem. 79 (2014) 2226–2241; c) W.-j. Chung, C.D. Vanderwal, Acc. Chem. Res. 47 (2014) 718–728.

[11] J. Jung, J.H. Kim, H. Kim, S. Lee, J.□H. Choi, W.□j. Chung, Bull. Korean Chem. Soc. 40 (2019) 835–838.

[12] F. Buckingham, A.K. Kirjavainen, S. Forsback, A. Krzyczmonik, T. Keller, I.M. Newington, M. Glaser, S.K. Luthra, O. Solin, V. Gouverneur, Angew. Chem. Int. Ed. 54 (2015) 13366–13369.

[13] a) M.P. Brochu, S.P. Brown, D.W.C. MacMillan, J. Am. Chem. Soc. 126 (2004) 4108–4109; b) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K.A. Jørgensen, J. Am. Chem. Soc. 126 (2004) 4790–4791.

[14] A. Hosomi, S. Kohra, Y. Tominaga, M. Ando, H. Sakurai, Chem. Pharm. Bull. 35 (1987) 3058–3061.

[15] The extreme moisture-sensitivity of the Lewis base-$SiCl_4$ system has been noted previously during the kinetic study by Denmark and coworkers (ref 5b).

[16] The catalyst turnover assisting role of *i*-Pr_2NEt has been proposed in the enantioselective allylation with allyltrichlorosilane. a) M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, J. Am. Chem. Soc. 120 (1998) 6419–6420; b) S.E. Denmark, J. Fu, J. Am. Chem. Soc. 122 (2000) 12021–12022; c) T. Oyama, H. Yoshioka, M. Tomoi, Chem. Commun. (2005) 1857–1859.

[17] R. Saito, S. Naruse, K. Takano, K. Fukuda, A. Katoh, Y. Inoue, Org. Lett. 8 (2006) 2067–2070.

[18] Molecular Orbital PACkage 2016, http://openmopac.net/, J.J.P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA.

[19] a) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys. 132 (2010) 154104; b) R. Peverati, K.K. Baldridge, J. Chem. Theory Comput. 4 (2008) 2030–2048.

[20] a) M.W. Schmidt, K.K. Baldridge, J.A. Boatz, S.T. Elbert, M.S. Gordon, J.H. Jensen, S. Koseki, N. Matsunaga, K.A. Nguyen, S. Su, T.L. Windus, M. Dupuis, J.A. Montgomery, J. Comput. Chem. 14 (1993) 1347–1363; b) M.S. Gordon, M.W. Schmidt, Advances in Electronic Structure Theory: Gamess a Decade Later; Elsevier: Amsterdam, 2005.

[21] a) A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652; b) C. Lee, W. Yang, R.G. Parr, Phys. Rev. B: Condens. Matter 37 (1988) 785–789.

[22] Gaussian 16, Revision C.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, G.A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A.V. Marenich, J. Bloino, B.G. Janesko, R. Gomperts, B. Mennucci, H.P. Hratchian, J.V. Ortiz, A.F. Izmaylov, J.L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V.G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M.J. Bearpark, J.J. Heyd, E.N. Brothers, K.N. Kudin, V.N. Staroverov, T.A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A.P. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, J.M. Millam, M. Klene, C. Adamo, R. Cammi, J.W. Ochterski, R.L. Martin, K. Morokuma, O. Farkas, J.B. Foresman, D.J. Fox, Gaussian, Inc., Wallingford CT, 2019.

[23] a) S. Miertuš, E. Scrocco, J. Tomasi, Chem. Phys. 55 (1981) 117–129; b) J.L. Pascual-Ahuir, E. Silla, I. Tuñón, J. Comput. Chem. 15 (1994) 1127–1138; c) V. Barone, M. Cossi, J. Phys. Chem. A 102 (1998) 1995–2001.

[24] C.Y. Legault, CYLview 1.0b, Université de Sherbrooke, 2009 (http://www.cylview.org)

[25] a) S.E. Denmark, B.M. Eklov, P.J. Yao, M.D. Eastgate, J. Am. Chem. Soc. 131 (2009) 11770–11787; b) S.E. Denmark, B.M. Eklov, Chem. Eur. J. 14 (2008) 234–239.

[26] On the basis of the mechanistic study with a monomeric Lewis base catalyst (HMPA), Denmark and coworkers discussed potential involvement of 1:1 or 2:1 Lewis base-silicon complexes (ref 5b). However, in our case, the two Lewis basic sites of the dimeric catalyst are likely to chelate the same silicon, leading to the formation of a hexacoordinate octahedral silicon species upon binding of epoxide (see ref 25a).

[27] a) S.E. Denmark, Y. Fan, M.D. Eastgate, J. Org. Chem. 70 (2005) 5235–5248; b) S.N. Tandura, M.G. Voronkov, N.V. Alekseev, Top. Curr. Chem. 113 (1986) 99–189; c) O.J. Curnow, J. Chem. Educ. 75 (1998) 910–915; d) S. Rossi, S.E. Denmark, Lewis Base Activation of Silicon Lewis Acids in Organosilicon Chemistry: Novel Approaches and Reactions (Eds: T. Hiyama, M. Oestreich), Wiley-VCH Verlag GmbH & Co, 2019, chapter 10, pp.333–415.

[28] a) M. Nishio, M. Hirota, Tetrahedron 45 (1989) 7201–7245; b) M. Nishio, Y. Umezawa, M. Hirota, Y. Takeuchi, Tetrahedron 51 (1995) 8665–8701; c) Y. Umezawa, S. Tsuboyama, K. Honda, J. Uzawa, M. Nishio, Bull. Chem. Soc. Jpn. 71 (1998) 1207–1213; d) Y. Umezawa, S. Tsuboyama, H. Takahashi, J. Uzawa, M. Nishio, Tetrahedron 55 (1999) 10047–10056; e) M. Nishio, CrystEngComm 6 (2004) 130–158; f) M. Nishio, Tetrahedron 61 (2005) 6923–6950; g) O. Takahashi, Y. Kohno, M. Nishio, Chem. Rev. 110 (2010) 6049–6076; h) M. Nishio, Phys. Chem. Chem. Phys. 13 (2011) 13873–13900; i) R.K. Raju, J.W.G. Bloom, Y. An, S.E. Wheeler, ChemPhysChem 12 (2011) 3116–3130; j) S. Karthikeyan, V. Ramanathan, B.K. Mishra, J. Phys. Chem. A 117 (2013) 6687–6694; k) M. Nishio, Y. Umezawa, J. Fantini, M.S. Weiss, P. Chakrabarti, Phys. Chem. Chem. Phys. 16 (2014) 12648–12683.

- The remote stereocontrol in the kinetic resolution of chlorinated vinyl epoxide was investigated
- The role of the β-chlorine-bearing stereocenter has been elucidated by DFT calculation of transition state.
- Non-covalent interactions including C–H/π hydrogen bonding are proposed as key stereodetermining factors.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: