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Article

Application of Polysaccharide-Based Chiral High-Performance Liquid Chromatography Columns for the Separation of Regio-, *E*/*Z*-, and Enantio−Isomeric Mixtures of Allylic Compounds

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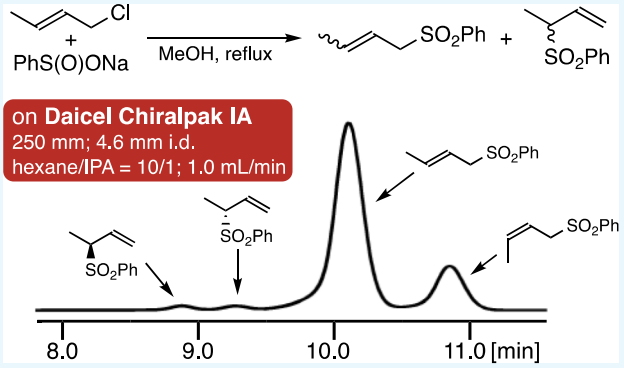
ABSTRACT: Daicel Chiralpak IA, IB, and IC, which are the polysaccharide-based chiral stationary phase (CSP) columns for high-performance liquid chromatography (HPLC), were applied in the separation of the non-enantiomeric isomeric mixtures obtained by the various allylation reactions and were highly effective in separating the regio- and (*E*)/(*Z*)-isomers in the allylation products. Due to the close structural similarity of the isomeric allylic compounds in the reaction mixtures, separations of the isomers are laborious and could not be accomplished by the conventional methods such as silica gel column chromatography, silica gel HPLC, preparative GPC, distillation, and so forth. This study has shown potential advantages of using the polysaccharide-based CSP columns in the separation of not only enantiomeric but also non-enantiomeric isomeric mixtures.



INTRODUCTION

Development of novel regio- and stereoselective reactions is one of the most important objectives in modern organic synthesis. Although various highly selective transformations have been reported so far, the reactions of "perfect" selectivity (in a practical sense, the reactions giving less than detectable minor products) has been rare, and the vast majority of regio- and stereoselective reactions provide a mixture of a main product (usually the target compound) and minor side products. In many cases, the side products (regio- and/or stereoisomers of the main product) are chemically/structurally/functionally similar to the main product, and thus, their removal (separation) from the target compound is not always easy. For this reason, development of efficient separation (purification) protocols is as equally important as of the stereoselective reactions themselves.

"High-performance liquid chromatography with the chiral stationary phase (HPLC−CSP)" is a chromatographic technique developed for the separation of the two enantiomers in a racemic (or scalemic) chiral compound.[1,2] The supply of chiral compounds in enantiomerically pure forms has been highly important in fine chemical/pharmaceutical industries, especially with the "chiral switch" policy. Since the chromatographic enantiomeric separation can be performed without loss of chiral solutes under the ideal conditions, HPLC−CSP has been used in not only analytical but also preparative scales for supplying enantiomerically pure chiral compounds. Among various CSP known to date, polysaccharide-based CSP columns are one of the most universal CSPs in the chiral HPLC.[3,4] Although the primal purpose of developing the CSPs is the application to enantiomeric resolution of chiral compounds, the CSPs have also been demonstrated to be good at recognizing closely related non-enantiomeric isomers of minor structural differences.[5−7] We recently described that the polysaccharide-based CSP columns, namely, Daicel Chiralpak IA, IB, and IC,[8] showed excellent performance in separating structurally similar non-enantiomeric isomeric mixtures of organometallic complexes (see, Figure 1).[7] It should be emphasized that, because of the close similarity of the isomeric compounds in these mixtures, separations of the components are practically unattainable by the rather classical methods such as silica gel column chromatography, silica gel HPLC, recrystallization, distillation, etc.

The allylation reaction is essential and important transformations in organic synthesis because allyl moieties can be converted into various functional groups and are omnipresent in a range of natural products and pharmaceuticals. Hence, various procedures of introducing allylic substituents have been developed, which include thermally driven or catalytic processes as well as the reactions of allylic nucleophiles,[9] electrophiles,[10] or radicals.[11] In a reaction with an unsym-

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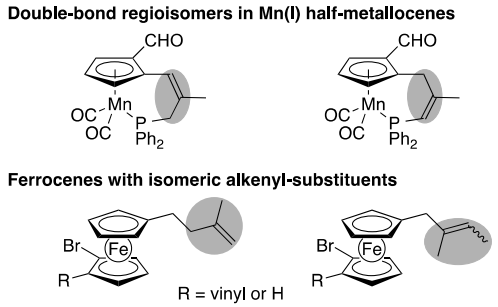
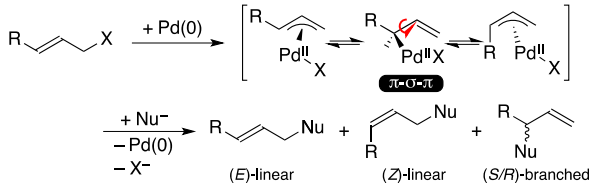


Figure 1. Non-enantiomeric isomeric pairs of organometallic complexes separated by the polysaccharide-based HPLC−CSP.[7]

metrically substituted allylic reagent, the two rection modes, that is, α- and γ-substitutions, compete in many cases producing a mixture of regio, E/Z, and enantiomeric isomers. An example of the selectivity issue is depicted in Scheme 1 in

Scheme 1. Possible Isomeric Allylation Products by the Palladium-Catalyzed Tsuji−Trost Reaction



the case of the palladium-catalyzed substitution of an allyl electrophile with a soft nucleophile via a π-allylpalladium intermediate (the Tsuji−Trost reaction).[10] Analogous α- versus γ-selectivities are commonly observed in the nucleophilic and the radical allylation processes as well. It should be pointed out that the isomeric products cogenerated through the allylation processes are not always easily separated from each other.

In this article, we have examined the application of the HPLC−CSP systems for the purification of various allylation products which consist of the corresponding isomers, as shown in Scheme 1. This report demonstrates the potential usefulness of the polysaccharide-based HPLC−CSP in purification/separation processes beyond the enantiomeric resolution.

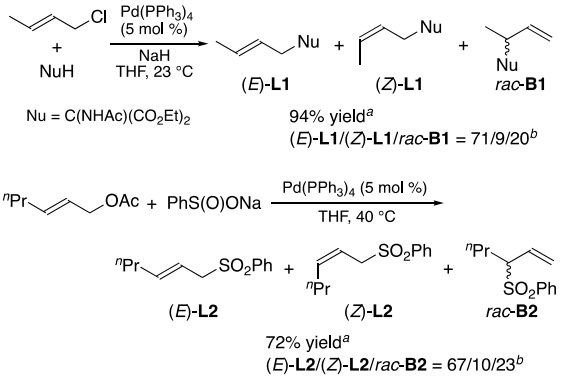
RESULTS AND DISCUSSION

Separation of Isomeric Mixtures Obtained by the Palladium-Catalyzed Allylation of a Soft Nucleophile with an Allylic Electrophile (the Tsuji−Trost Reaction). Palladium-catalyzed allylic substitution (the Tsuji−Trost reaction)[10] is one of the most widely and the most frequently used metal-catalyzed reactions, which proceeds via a π-allylpalladium(II) intermediate. The π-allylpalladium species undergoes isomerization via a so-called $\pi-\sigma-\pi$ process, and the stereochemical outcome of the catalytic reaction is highly dependent on the stereochemical structure of the π-allylpalladium(II) intermediate (Scheme 1).

Two representative examples of the Tsuji−Trost reactions were conducted in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), as summarized in Scheme 2. In both cases, the reactions gave the corresponding allylation products in good yields as mixtures of isomers.

As expected, separation of the isomers in **L1**/**B1** ("**L**" and "**B**" represent *linear* and *branched*, respectively) was very

Scheme 2. Palladium-Catalyzed Tsuji−Trost Allylic Substitution Reactions and the Product Distribution



[a] isolated yield by silica gel chromatography.
[b] determined by ^{1}H NMR.

difficult due to their close similarity. Both standard silica gel column chromatography and preparative gel permeation chromatography are ineffective in separating the isomers. Preparative HPLC with a silica gel stationary phase was also useless for the separation of the mixture. It was found that certain polysaccharide-based CSP columns were much more effective in separating the isomers in **L1**/**B1**. Figure 1 displays the HPLC chromatograms of the mixture of (*E*)-**L1**, (*Z*)-**L1**, and *rac*-**B1** on Daicel Chiralpak IA, IB, or IC using hexane/2-propanol (10/1) as an eluent. An HPLC chromatogram on a standard silica gel column (Tosoh TSKgel Silica-150) is also shown for comparison. The silica gel stationary phase scarcely recognized the isomers in **L1**/**B1**, and the analysis of the mixture on it showed a shouldered single peak. While Chiralpak IB was also ineffective with a single broad peak for the analysis of the mixture, both Chiralpak IA and IC succeeded in separating all the isomers (including the two enantiomers in *rac*-**B1**) in the mixture showing four peaks. Chiralpak IC displayed better separation than Chiralpak IA (Figure 2, bottom). Under the analysis conditions (column length: 250 mm; column i.d.: 4.6 mm; eluent: hexane/2-propanol = 10/1; flow rate: 1.0 mL/min; injection: ca. 10 μg in

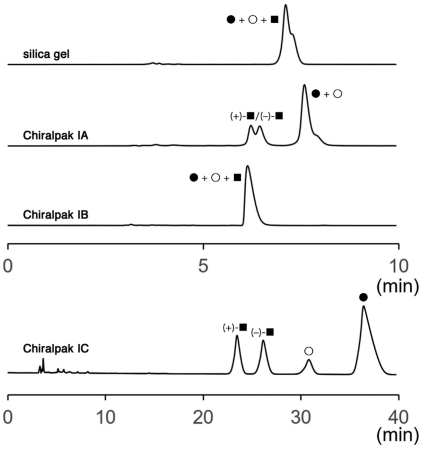


Figure 2. HPLC traces for the mixture of (*E*)-**L1** (●), (*Z*)-**L1** (○), and **B1** (■) on a silica gel column, Daicel Chiralpak IA, Daicel Chiralpak IB, and Daicel Chiralpak IC using hexane/2-propanol = 10/1 as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 1.0 mL/min; injection: ca. 10 μg in 10 μL.

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10 μL), (+)-**B1**, (−)-**B1**, (*Z*)-**L1**, and (*E*)-**L1** were detected at 23.6, 26.3, 31.0, and 36.7 min, respectively, and the resolution factors (Rs)[12] for this analysis were ranging from 2.50 to 3.85.

The HPLC separation of the isomers in **L1**/**B1** could be carried out on a semimacro scale in the same way. A sample of the **L1**/**B1** mixture ((*E*)-**L1**/(*Z*)-**L1**/*rac*-**B1** = 71/9/20 determined by the ^{1}H NMR analysis; 40.0 mg in 2 mL of hexane/2-propanol = 10/1) could be separated cleanly on Chiralpak IC (250 mm × 20 mm i.d.), and all the four isomers, namely, (*E*)-**L1** (28.0 mg, 70.0%), (*Z*)-**L1** (3.0 mg, 7.5%), (+)-**L2** (3.8 mg, 9.5%), and (−)-**L2** (4.2 mg, 11%), were obtained in pure forms.

The mixture of **L2** and **B2** was also inseparable by the classical methods (silica gel-based chromatography, GPC, etc.), and therefore the HPLC−CSP systems were examined in the separation of the isomeric sulfones. Indeed, the polysaccharide-based CSP columns showed good recognition between (*E*)-**L2**, (*Z*)-**L2**, and **B2**. Figure 3 shows the HPLC

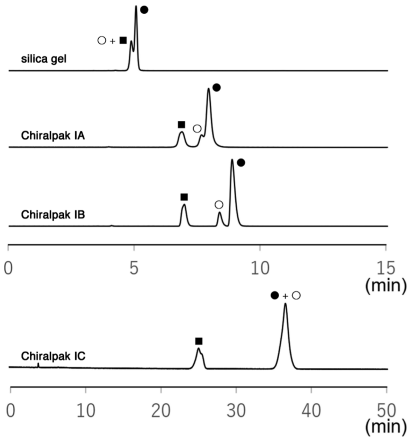


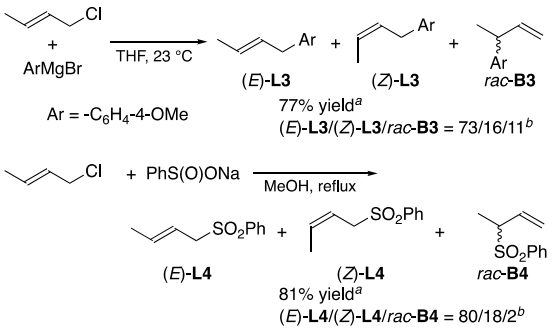
Figure 3. HPLC traces for the mixture of (*E*)-**L2** (●), (*Z*)-**L2** (○), and **B2** (■) on a silica gel column, Daicel Chiralpak IA, Daicel Chiralpak IB, and Daicel Chiralpak IC using hexane/2-propanol = 10/1 as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 1.0 mL/min; injection: ca. 10 μg in 2 μL.

chromatograms of the mixture of (*E*/*Z*)-**L2** and *rac*-**B2**. The mixture was detected as incompletely separated two peaks on the silica gel stationary phase. While Chiralpak IA showed the three peaks, the two peaks, assigned to (*Z*)-**L2** and (*E*)-**L2**, were partially overlapped. Among the HPLC columns examined, Chiralpak IB displayed the best performance showing the clearly separated three peaks which were assigned to **B2**, (*Z*)-**L2**, and (*E*)-**L2**, respectively. The resolution factors (Rs)[12] for this analysis were 4.46 and 1.65, respectively. Chiralpak IC showed the clearly separated two peaks on the HPLC analysis of the mixture. The fast-eluting peak detected at 25.1 min had a bimodal shape, which was ascribed to incomplete separation of the two enantiomers in **B2**. The slow-eluting peak at 36.5 min was clarified to be a mixture of (*E*)- and (*Z*)-**L2** by the ^{1}H NMR analyses.

The mixture of (*E*)-**L2**, (*Z*)-**L2**, and **B2** ((*E*)-**L2**/(*Z*)-**L2**/**B2** = 67/10/23; 36.9 mg in 2 mL of hexane/2-propanol = 10/1) was separated on semimacro scale Chiralpak IB (250 mm × 20 mm i.d.), and (*E*)-**L2** (22.9 mg; 62.1%), (*Z*)-**L2** (4.1 mg; 11%), and *rac*-**B2** (9.1 mg; 25%) were obtained in pure forms.

Separation of Isomeric Mixtures Obtained by Thermally Driven Nucleophilic Substitution of Allylic Electrophiles. In many thermally driven nucleophilic substitution reactions between a nucleophile and an allylic electrophile, the competitive two reaction pathways, namely, S_N2 and S_N2' processes, are operating to produce an isomeric mixture of the allylation products. The two nucleophiles were applied in the reactions with crotyl chloride, and the results are summarized in Scheme 3. In both cases, (*E*)-linear

Scheme 3. Thermally Driven Nucleophilic Allylic Substitution Reactions and the Product Distribution



[a] isolated yield by silica gel chromatography.
[b] determined by ^{1}H NMR.

compounds, (*E*)-**L3** and (*E*)-**L4**, are the major products, but certain amounts of (*Z*)-linear species, (*Z*)-**L3** and (*Z*)-**L4**, as well as branched species, **B3** and **B4**, were obtained as the minor products concomitantly.

Once again, separation of the isomeric components in these product mixtures was problematic. While both standard silica gel column chromatography and the silica gel HPLC did not work for this purpose, the HPLC−CSP systems showed much better performance of recognizing the isomeric compounds. The results of the HPLC analyses of the mixture of (*E*)- and (*Z*)-**L3**/*rac*-**B3** are integrated in Figure 4. As mentioned above,

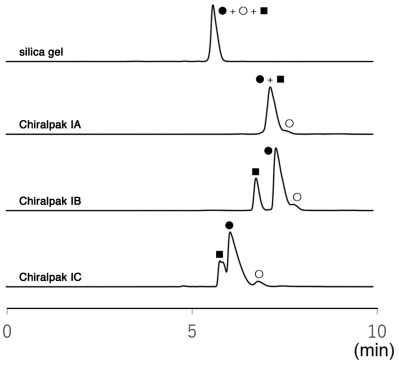


Figure 4. HPLC traces for the mixture of (*E*)-**L3** (●), (*Z*)-**L3** (○), and **B3** (■) on a silica gel column, Daicel Chiralpak IA, Daicel Chiralpak IB, and Daicel Chiralpak IC using hexane as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 1.0 mL/min; injection: ca. 10 μg in 10 μL.

the mixture was detected as a single peak on the silica gel stationary phase. Among the three CSP columns examined, Chiralpak IB and IC were capable of separating all the three isomers simultaneously. On Chiralpak IB, **B3** was the fastest-eluting isomer and clearly separated from the other two which were partially overlapped. On the other hand, (*Z*)-**3L** was the slowest-eluting and clearly separated from incompletely separated **B3** and (*E*)-**3L** on Chiralpak IC. The bimodal

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shape of the first peak on Chiralpak IC is ascribed to incomplete separation of the two enantiomers in **B3**.

The semimacro scale separation of the isomers in the **L3**/**B3** mixture could be realized by the use of the two CSP columns successively. The semimacro scale preparative HPLC of the mixture (32.0 mg in 2 mL of hexane) on Chiralpak IB (250 mm × 20 mm i.d.) afforded pure **B3** in 9.6% (3.1 mg) and the mixture of (*Z*)- and (*E*)-**L3**, then the latter was subjected to the second preparative HPLC on Chiralpak IC (250 mm × 20 mm i.d.) to give pure (*E*)- and (*Z*)-**L3** in 75.3% (24.1 mg) and 13% (4.3 mg), respectively.

The HPLC−CSP systems revealed the high capability to resolve into the isomeric components in **L4**/**B4** as well. While the HPLC with the silica gel stationary phase showed a single peak for the mixture, the HPLC−CSP systems gave the multiple peaks for the analyses of the **L4**/**B4** mixture as shown in Figure 5. Among the three CSP columns examined,

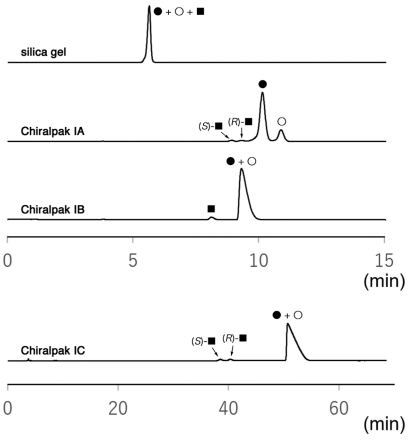


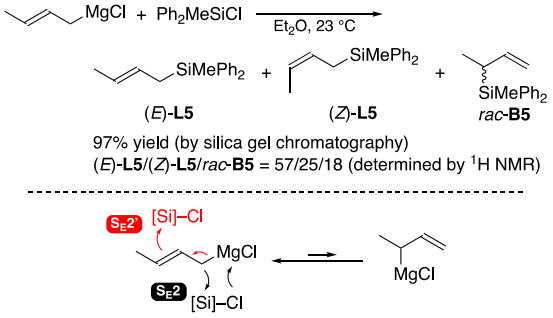
Figure 5. HPLC traces for the mixture of (*E*)-**L4** (●), (*Z*)-**L4** (○), and **B4** (■) on a silica gel column, Daicel Chiralpak IA, Daicel Chiralpak IB, and Daicel Chiralpak IC using hexane/2-propanol = 10/1 as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 1.0 mL/min; injection: ca. 10 μg in 10 μL.

Chiralpak IA displayed the best performance of separating the isomers in **L4**/**B4**, and near baseline-separation of all the four isomers (including the two enantiomers in **B4**) was achieved on this CSP. Under the analysis conditions (column length: 250 mm; column i.d.: 4.6 mm; eluent: hexane/2-propanol = 10/1; flow rate: 1.0 mL/min; injection: ca. 10 μg in 10 μL), (+)-(*S*)−**B4**, (−)-(*R*)-**B4**, (*E*)-**L4**, and (*Z*)-**L4** were detected at 8.9, 9.3, 10.1, and 10.9 min, respectively, and the resolution factors (Rs)[12] for this analysis were ranging from 1.17 to 2.19.

The semimacro scale HPLC separation of the isomers in the **L4**/**B4** mixture was achieved by the use of Chiralpak IA (250 mm × 20 mm i.d.) as follows. The **L4**/**B4** mixture (a sample obtained by the Pd-catalyzed reaction, of which isomeric distribution was (*E*)-**L4**/(*Z*)-**L4**/*rac*-**B4** = 35/8/57, was used for the semimacro scale experiment; 55 mg in 2 mL of hexane/2-propanol = 10/1) could be separated cleanly on Chiralpak IA (250 mm × 20 mm i.d.), and all the four isomers, namely (*E*)-**L4** (18 mg, 33%), (*Z*)-**L4** (3.2 mg, 5.8%), (+)-(*S*)-**L4** (15 mg, 27%), and (−)-(*R*)-**L4** (15 mg, 27%), were obtained in pure forms.

Separation of Allylsilanes Prepared from Nucleophilic Crotyl Grignard Reagent and Chlorosilane. An unsymmetric allyl-metal reagent reacts with a nucleophile either at the α-carbon or the γ-carbon of the allylic moiety in many cases. For example, the reaction between crotylmagnesium chloride and chloromethyldiphenylsilane provided a mixture of (*E*)-/(*Z*)-**L5** and **B5** in 57:25:18 molar ratio (Scheme 4). This selectivity issue is usually rationalized as

Scheme 4. Reaction of Crotyl Grignard Reagent with a Chlorosilane and the Product Distribution



competitive operation of the S_E2 and the S_E2' processes.[13] In addition, the Grignard reagent was suggested to exist as the rapidly equilibrating two species,[14] which also contributed to the product distribution to a certain extent.

Separation of the **L5**/**B5** mixture was difficult due in part to their low polarity. Even with the HPLC−CSP systems, complete separation of the three isomers could not be attained. The HPLC analyses using the silica gel stationary phase, Chiralpak IA, or IB all failed to separate the mixture showing the single sharp peaks as shown in Figure 6. The best

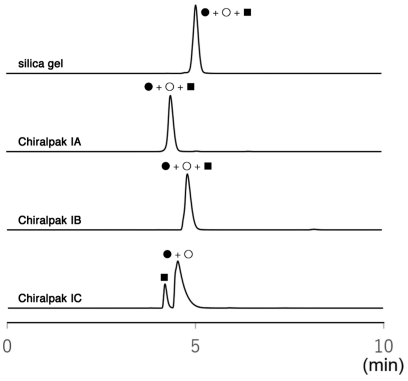


Figure 6. HPLC traces for the mixture of (*E*)-**L5** (●), (*Z*)-**L5** (○), and **B5** (■) on a silica gel column, Daicel Chiralpak IA, Daicel Chiralpak IB, and Daicel Chiralpak IC using hexane as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 1.0 mL/min; injection: ca. 20 μg in 5 μL.

result was achieved on Chiralpak IC, and the complete separation of **B5** from (*E*)- and (*Z*)-**L5** was realized. The slow-eluting peak, assigned to the (*E*)- and (*Z*)-**L5** mixture, has the bimodal shape due to the incomplete separation of the two isomers.

The semimacro scale preparative HPLC of the **L5**/**B5** mixture (35.2 mg in 2 mL of hexane) on Chiralpak IC (250 mm × 20 mm i.d.) afforded pure **B5** in 17% (6.0 mg) and the mixture of (*E*)- and (*Z*)-**L5** in 81.3% (28.6 mg), respectively.

Effect of Eluents on the HPLC−CSP Separation. Eluents were screened for the two representative HPLC−CSP separations of the allylation products mixtures, namely,

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the **L1**/**B1** mixture on Chiralpak IC and the **L4**/**B4** mixture on Chiralpak IA. The eluent compositions examined were hexane/2-propanol, hexane/ethanol, methyl *tert*-butyl ether (*Mt*BE), or hexane/dichloromethane, and the results are integrated in the Supporting Information (see, pages S35 and S36). For the **L1**/**B1** mixture on Chiralpak IC, hexane/2-propanol and hexane/ethanol were the two best eluent compositions and gave very similar chromatograms. The other two eluents showed much poorer separation. For the **L4**/**B4** mixture on Chiralpak IA, hexane/2-propanol was the best eluent among the four examined. While all the four isomers (including the two enantiomers in **B4**) were clearly separated using hexane/2-propanol, the other three eluent compositions gave partially overlapped three peaks. It should be pointed out that the elution order of the isomeric components of the allylic compound mixtures depends on the choice of eluents. For example, the elution order of the **L4**/**B4** mixture on Chiralpak IA using hexane/ethanol is **B4**, (*E*)-**L4**, and then (*Z*)-**L4**. On the other hand, the order changed to **B4**, (*Z*)-**L4**, and then (*E*)-**L4** with MtBE.

CONCLUSIONS

Through the experiments reported in this article, we have revealed that the polysaccharide-based CSP columns, namely, Daicel Chiralpak IA, IB, and IC, are useful in separating the chemically/structurally/functionally similar non-enantiomeric isomers in the allylated species. The CSP columns have succeeded to recognize the regio- and geometric isomers cogenerated by the various allylation processes. Because of the close similarity of the isomeric compounds in these allylation products, separations of the isomers are troublesome and the rather classical purification methods such as silica gel column chromatography, silica gel HPLC, recrystallization, distillation/sublimation, and so forth do not work in many cases. Allylation is an important transformation in organic synthesis; however, highly stereoselective allylations using unsymmetric allylation reagents are still challenging and the concomitant formation of undesired isomers is difficult to avoid. Clearly, the polysaccharide-based CSP columns have a great prospect in the separation/purification of isomeric allylic compounds. This study has demonstrated potential usefulness of the CSP columns in the separation of not only enantiomeric but also non-enantiomeric mixtures. The polysaccharide derivatives are immobilized on a silica gel support in the CSP columns used in this study.[3e] These CSP columns are fairly durable and can be used with various eluents.[15] The robustness of the immobilized-type CSP columns makes them more user-friendly and should enhance their uses beyond the enantiomeric separation.

EXPERIMENTAL SECTION

General Information. All anaerobic and/or moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. Tetrahydrofuran and diethyl ether were distilled from benzophenone-ketyl under nitrogen prior to use. Tetrakis(triphenylphosphine)-palladium(0)[16] was prepared according to the reported methods. All the other chemicals were obtained from commercial sources and used as received unless otherwise noted. The CSP columns (Chiralpak IA, IB, and IC) were purchased from Daicel Corporation (Tokyo, Japan).[15] The silica gel column (TSKgel Silica-150) was purchased from Tosoh Corporation (Tokyo, Japan).

Instrumentation and HPLC−CSP Conditions. Chromatographic studies on the CSPs were performed with a JASCO PU-2086 (pump)/UV-2075 (UV detector) system at room temperature. The eluents were specified in the legends of the chromatograms (Figures 2−6). The flow rate was 1.0 mL/min (on the analytical columns; 250 mm-length/4.6 mm-i.d.) or 20 mL/min (on the semimacro scale columns; 250 mm-length/20 mm-i.d.), and the detection wavelength was 254 nm.

Palladium-Catalyzed Allylic Substitution Reactions: General Procedure (Scheme 2). To a solution of a nucleophile (ca. 3.8 mmol; 1.5 equiv to the allyl electrophile) and $Pd(PPh_3)_4$ (5 mol %) in THF (ca. 5.0 mL) was added an allyl electrophile (ca. 2.5 mmol) by means of a syringe at room temperature. The solution was stirred at the indicated temperature overnight, leading the complete consumption of the electrophile. The resulting solution was quenched with aqueous $NaHCO_3$ solution, and the mixture was extracted with chloroform. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give an isomeric mixture of the allylation products. The molar ratio between the isomers was determined by the ^{1}H NMR measurement. The obtained isomeric mixtures, **L1**/**B1** and **L2**/**B2**, were used for the HPLC−CSP studies. The characterization data of the purified compounds are listed below.

*(+)- and (−)-Diethyl 2-Acetamido-2-(3-buten-2-yl)-propanedioate (**B1**).* ^{1}H NMR ($CDCl_3$): δ 1.13 (d, J = 6.9 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.26 (t, J = 6.8 Hz, 3H), 2.04 (s, 3H), 3.30 (dq, J = 8.5 and 6.9 Hz, 1H), 4.19−4.31 (m, 4H), 5.02−5.10 (m, 2H), 5.78 (ddd, J = 17.0, 10.1, and 8.5 Hz, 1H), 6.54 (br, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 14.11, 14.13, 15.8, 23.3, 43.3, 62.3, 62.6, 68.5, 116.6, 138.1, 167.3, 168.1, 169.2. $[\alpha]_D^{21.2}$ +18.5 (c 0.38, $CHCl_3$), $[\alpha]_D^{21.3}$ −12.4 (c 0.47, $CHCl_3$). EI-HRMS calcd for $C_{13}H_{21}NO_5Na$ (M + Na), 294.1317; found, 294.1317.

(E)-Diethyl 2-Acetamido-2-(2-butenyl)propanedioate ((E)-L1).[17] ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 6H), 1.64 (d, J = 6.5 Hz, 3H), 2.04 (s, 3H), 2.99 (d, J = 7.4 Hz, 2H), 4.19−4.30 (m, 4H), 5.18 (dt, J = 15.3 and 7.4 Hz, 1H), 5.53 (dq, J = 15.3 and 6.5 Hz, 1H), 6.74 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 14.1, 18.2, 23.1, 35.9, 62.6, 66.5, 123.6, 130.7, 167.9, 169.0.

(Z)-Diethyl 2-Acetamido-2-(2-butenyl)propanedioate ((Z)-L1).[17] ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.3 Hz, 6H), 1.59 (d, J = 6.9 Hz, 3H), 2.02 (s, 3H), 3.10 (d, J = 7.8 Hz, 2H), 4.20−4.28 (m, 4H), 5.15 (dt, J = 10.9 and 7.8 Hz, 1H), 5.63 (dq, J = 10.9 and 6.9 Hz, 1H), 6.75 (br, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 13.1, 14.1, 23.2, 30.2, 62.7, 66.2, 122.5, 129.3, 168.0, 169.1.

*rac-(1-Hexen-3-ylsulfonyl)benzene (**B2**).*[18] ^{1}H NMR ($CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 3H), 1.19−1.33 (m, 1H), 1.38−1.51 (m, 1H), 1.62−1.71 (m, 1H), 2.02−2.11 (m, 1H), 3.47−3.53 (m, 1H), 5.03 (d, J = 17.1 Hz, 1H), 5.28 (d, J = 10.1 Hz, 1H), 5.61 (ddd, J = 17.1, 10.1, and 9.2 Hz, 1H), 7.51−7.55 (m, 2H), 7.61−7.65 (m, 1H), 7.83−7.85 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 13.7, 19.9, 28.9, 69.9, 123.6, 128.9, 129.4, 130.5, 133.7, 137.6.

(E)-(2-Hexenylsulfonyl)benzene ((E)-L2).[19] ^{1}H NMR ($CDCl_3$): δ 0.81 (t, J = 7.4 Hz, 3H), 1.25−1.34 (m, 2H), 1.95−2.00 (m, 2H), 3.75 (d, J = 7.2 Hz, 2H), 5.40 (dt, J = 14.2

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and 7.2 Hz, 1H), 5.51 (dt, J = 14.2 and 6.6 Hz, 1H), 7.51−7.57 (m, 2H), 7.62−7.66 (m, 1H), 7.83−7.88 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 13.6, 22.0, 34.7, 60.3, 116.1, 128.6, 129.1, 133.7, 138.5, 141.8.

(Z)-(2-Hexenylsulfonyl)benzene ((Z)-L2).[19] ^1H NMR ($CDCl_3$): δ 0.75 (t, J = 7.4 Hz, 3H), 1.10−1.12 (m, 2H), 1.67−1.73 (m, 2H), 3.85 (d, J = 7.8 Hz, 2H), 5.42 (dt, J = 10.9 and 7.8 Hz, 1H), 5.72 (dt, J = 10.9 and 7.4 Hz, 1H), 7.53−7.58 (m, 2H), 7.62−7.66 (m, 1H), 7.88−7.91 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 13.7, 22.2, 29.4, 55.4, 115.5, 128.7, 129.2, 133.8, 138.7, 139.6.

Thermal Nucleophilic Allylic Substitution Reactions: General Procedure (Scheme 3). To a solution of a nucleophile (ca. 7.5 mmol; 1.5 equiv to the allyl electrophile) in an appropriate solvent (ca. 5 mL) was added an allyl electrophile (ca. 5 mmol) by means of a syringe at room temperature. The solution was stirred at the indicated temperature overnight, leading the complete consumption of the electrophile. The resulting solution was quenched with aqueous $NaHCO_3$ solution, and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give an isomeric mixture of the allylation products. The molar ratio between the isomers was determined by the ^1H NMR measurement. The obtained isomeric mixtures, **L3**/**B3** and **L4**/**B4**, were used for the HPLC−CSP studies. The characterization data of the purified compounds are listed below.

*rac-1-(3-Buten-2-yl)-4-methoxybenzene (**B3**).*[20] ^1H NMR ($CDCl_3$): δ 1.34 (d, J = 7.0 Hz, 3H), 3.42 (qd, J = 7.0 and 6.4 Hz, 1H), 3.79 (s, 3H), 4.99−5.10 (m, 2H), 5.98 (ddd, J = 16.9, 10.3, and 6.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.0, 42.2, 55.4, 112.9, 113.9, 128.3, 137.8, 143.7, 158.0.

(E)-1-(2-Butenyl)-4-methoxybenzene ((E)-L3).[21] ^1H NMR ($CDCl_3$): δ 1.68 (br d, J = 6.4 Hz, 3H), 3.26 (d, J = 6.4 Hz, 2H), 3.79 (s, 3H), 5.44−5.62 (m, 2H), 6.83 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 18.0, 38.3, 55.4, 113.9, 126.1, 129.5, 130.6, 133.6, 158.0.

(Z)-1-(2-Butenyl)-4-methoxybenzene ((Z)-L3).[21b] ^1H NMR ($CDCl_3$): δ 1.72 (d, J = 5.2 Hz, 3H), 3.34 (d, J = 4.8 Hz, 2H), 3.79 (s, 3H), 5.53−5.61 (m, 2H), 6.84 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 12.9, 32.3, 55.4, 114.0, 124.6, 129.3, 129.6, 133.4, 158.0.

(+)-(*S*)- and (−)-(*R*)-(3-Buten-2-ylsulfonyl)benzene (B4).[22] ^1H NMR ($CDCl_3$): δ 1.45 (d, J = 7.0 Hz, 3H), 3.72 (dq, J = 8.0 and 7.0 Hz 1H), 5.10 (d, J = 17.1 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 5.83 (ddd, J = 17.1, 10.3, and 8.0 Hz 1H), 7.52−7.57 (m, 2H), 7.62−7.67 (m, 1H), 7.84−7.87 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 13.1, 64.3, 122.0, 128.9, 129.5, 131.4, 133.8, 137.0. $[\alpha]_D^{22.2}$ +11.4 (c 1.39, $CHCl_3$, *S*-enantiomer), $[\alpha]_D^{22.5}$ −11.6 (c 1.37, $CHCl_3$, *R*-enantiomer; lit.[22a] $[\alpha]_D^{25}$ −18.0 (c 1.2, EtOH)).

(*E*)-(2-Buenylsulfonyl)benzene ((*E*)-L4).[22b] ^1H NMR ($CDCl_3$): δ 1.68 (d, J = 6.6 Hz, 3H), 3.73 (d, J = 7.2 Hz, 2H), 5.43 (dt, J = 15.2 and 7.2 Hz, 1H), 5.56 (dq, J = 15.2 and 6.6 Hz, 1H), 7.54−7.57 (m, 2H), 7.63−7.67 (m, 1H), 7.85−7.87 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 18.3, 60.2, 117.1, 128.6, 129.1, 133.7, 136.7, 138.6.

(*Z*)-(2-Buenylsulfonyl)benzene ((*Z*)-L4).[22b] ^1H NMR ($CDCl_3$): δ 1.35 (d, J = 7.0 Hz, 3H), 3.86 (d, J = 8.0 Hz, 2H), 5.43 (dt, J = 10.7 and 8.0 Hz, 1H), 5.83 (dq, J = 10.7 and 7.0 Hz, 1H), 7.53−7.57 (m, 2H), 7.63−7.67 (m, 1H), 7.88−7.91 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 12.9, 55.0, 116.4, 128.7, 129.2, 133.8, 134.1, 138.7.

Reaction of Crotylmagnesium Chloride with Chloromethyldiphenylsilane (Scheme 4). To a solution of crotylmagnesium chloride, which was prepared from crotyl chloride (756 mg, 8.31 mmol) and magnesium (210 mg, 8.50 mmol) in diethyl ether (15 mL) at 0 °C, was added a solution of chloromethyldiphenylsilane (920 mg, 3.95 mmol) in diethyl ether (2.0 mL) at 0 °C. The solution was stirred at room temperature overnight. The resulting solution was quenched with aqueous NH_4Cl solution, and the mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/benzene = 8/1) to give an isomeric mixture of the silanes as a colorless oil. Yield: 0.97 g (97%). The molar ratio between the isomers was determined to be (*E*)-**L5**/(*Z*)-**L5**/**B5** = 57/25/18 by the ^1H NMR measurement. The obtained isomeric mixture was used for the HPLC−CSP studies. The characterization data of the separated compounds are listed below.

rac-(3-Buten-2-yl)methyldiphenylsilane (B5).[23] ^1H NMR ($CDCl_3$): δ 0.53 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 2.29 (qd, J = 7.2 and 7.0 Hz, 1H), 4.82−4.91 (m, 2H), 5.92 (ddd, J = 17.1, 10.1, and 7.0 Hz, 1H). 7.32−7.40 (m, 6H), 7.53−7.55 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ −6.5, 13.4, 25.7, 111.5, 127.86, 127.91, 129.4 (2C), 135.02, 135.07, 135.96, 135.97, 140.9.

(E/Z)-(2-Butenyl)methyldiphenylsilane ((E/Z)-L5).[24] ^1H NMR ($CDCl_3$): δ 0.53 (s, 3H of *E*-isomer), 0.54 (s, 3H of *Z*-isomer), 1.47 (br d, J = 6.0 Hz, 3H of *Z*-isomer), 1.59 (br d, J = 6.0 Hz, 3H of *E*-isomer), 1.97 (d, J = 7.6 Hz, 2H of *E*-isomer), 2.03 (d, J = 8.0 Hz, 2H of *Z*-isomer), 5.27−5.49 (m, 2H of both isomers), 7.30−7.39 (m, 6H of both isomers), 7.49−7.55 (m, 4H of both isomers). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ −4.55 (*E*-isomer), −4.52 (*Z*-isomer), 12.8 (*Z*-isomer), 15.7 (*Z*-isomer), 18.2 (*E*-isomer), 20.2 (*E*-isomer), 122.9 (*Z*-isomer), 125.0 (*E*-isomer), 125.3 (*Z*-isomer), 125.9 (*E*-isomer), 127.90 (*E*-isomer), 127.92 (*Z*-isomer), 129.31 (*E*-isomer), 129.37 (*Z*-isomer), 134.65 (*Z*-isomer), 134.70 (*E*-isomer), 137.0 (*Z*-isomer), 137.1 (*E*-isomer).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06187.

NMR spectra (^1H and ^{13}C) for all the allylic compounds and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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