ORGANOMETALLICS

Article

Cite This: Organometallics XXXX, XXX, XXX−XXX

pubs.acs.org/Organometallics

Application of Polysaccharide-Based Chiral HPLC Columns for Separation of Nonenantiomeric Isomeric Mixtures of Organometallic Compounds

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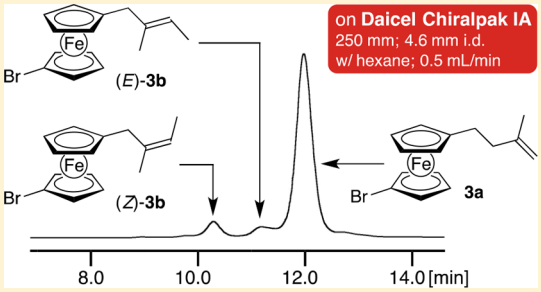
Supporting Information

ABSTRACT: A series of polysaccharide-based chiral stationary phase (CSP) columns, Daicel Chiralpak IA, IB, and IC, were applied in the separation of the nonenantiomeric isomers of various organometallic compounds and were found to be highly effective in recognizing isomers of minor structural differences. The CSP columns have succeeded to separate the double-bond regioisomers in bridged (η^5-formylcyclopentadienyl)manganese(I) dicarbonyl complexes **1a**/**1b**, the structural isomers of methylbutenylferrocene derivatives in **2a**/**2b** and **3a**/**3b**, and the geometrical isomers of the (2-methyl-2-butenyl)-ferrocenes in (*Z*)/(*E*)-**3b**. Due to the close similarity of the isomeric compounds in these mixtures, separations of the components are extremely difficult and could not be attained by conventional methods such as silica gel column chromatography, silica gel HPLC, recrystallization, distillation/sublimation, etc. Clearly, the polysaccharide-based CSP columns have unique advantages in separation/purification technology, and this study has shown potential usefulness of the CSP columns in separation of not only enantiomeric but also nonenantiomeric mixtures.



INTRODUCTION

Organometallic reagents/catalysts are powerful tools for making carbon−carbon bonds and have been utilized in various transformations in modern organic synthesis. Although the metal-mediated/catalyzed reactions have enhanced efficiency of organic synthesis, an apparent drawback of their use is the occasional formation of undesirable isomerized side-products. Unfortunately, however, these isomerized side-products are chemically/structurally/functionally very similar to the main products in many cases, and thus, their removal (separation) from the target compounds are often problematic.

"High-performance liquid chromatography with chiral stationary phase (HPLC−CSP)" is a modern chromatographic technology rapidly developing for enantiomeric resolution of racemic (or scalemic) chiral compounds.[1,2] Whereas the supply of chiral compounds in enantiomerically pure forms has been highly desirable in fine chemical industries, the HPLC−CSP technique has played an integral role in the enantiomeric purification of racemic/scalemic mixtures. Among various CSP reported so far, polysaccharide-based CSP columns are one of the most successful CSP families in the chiral HPLC and show excellent performance in enantiomeric resolution of a wide range of chiral molecules.[3,4] During the course of our studies on various asymmetric reactions, we have experienced that the polysaccharide-based CSP columns are good at recognizing not only enantiomeric pairs in chiral molecules but also *closely related nonenantiomeric isomers of minor structural differences*.[5,6] Indeed, it was found that the isomeric mixtures of organometallic complexes shown in Figure 1 could be efficiently separated/purified by the use of

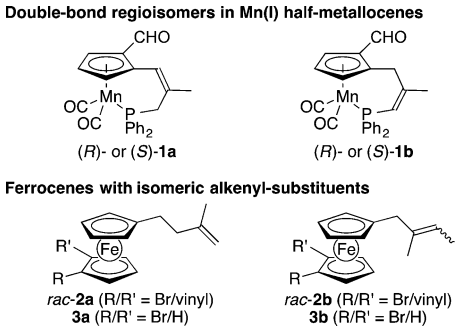


Figure 1. Nonenantiomeric isomeric pairs of organometallic complexes **1a**/**1b**, **2a**/**2b**, and **3a**/**3b** examined in this report.

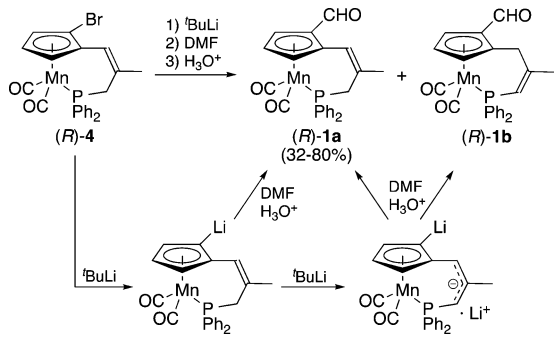
Received: November 6, 2018

the polysaccharide-based CSP columns developed by Daicel Corporation.[7] It is worth noting that separations of isomeric pairs **1a**/**1b**, **2a**/**2b**, and **3a**/**3b** by rather classical methods, such as silica gel column chromatography, silica gel HPLC, recrystallization, distillation/sublimation, etc., have been nearly impossible due to the close similarity between the main and the side products. Here we report details of the three examples of the uses of the HPLC−CSP systems for purification of the organometallic compounds contaminated with the non-enantiomeric isomers. This report demonstrates the potential usefulness of the polysaccharide-based HPLC−CSP in purification/separation processes beyond the enantiomeric resolution.

■ RESULTS AND DISCUSSION

Example 1: Separation of Double-Bond Regioisomers 1a and 1b in Bridged (η^5-Formylcyclopentadienyl)-manganese(I) Complexes. In 2017, we reported the synthesis of planar-chiral bridged (η^5-formylcyclopentadienyl)-manganese(I) dicarbonyl complex (*R*)-**1a** by the reaction shown in Scheme 1.[8] The bromo-substituent in (*R*)-**4** was

Scheme 1. Preparation of (*R*)-1a with Plausible Pathways to Contaminant (*R*)-1b



lithiated by the lithium−bromine exchange reaction using ^{t}BuLi, and a following reaction with DMF provided (*R*)-**1a** in variable yield ranging 32−80%. The variable yield in this reaction could be partly ascribed to the formation of undesirable double-bond regioisomer (*R*)-**1b**. The methylene hydrogens in the bridging $Ph_2PCH_2CMe{=}CH$-moiety in (*R*)-**4** are somewhat acidic, and an isomerization of the C=C double bond to an adjacent position took place under the basic conditions via a deprotonation/protonation sequence to give (*R*)-**1b** as a contaminant (Scheme 1). The mixture of (*S*)-**1a** and (*S*)-**1b** was prepared from (*S*)-**4** in the same way.

Removal of (*R*)-**1b** from crude (*R*)-**1a** was found to be very difficult. The two compounds are isomeric to each other with very similar three-dimensional structures. Both (*R*)-**1a** and (*R*)-**1b** also possess identical sets of polar functional groups including formyl, diphenylphosphino, and manganese(I) dicarbonyl groups. Classical chromatographic methods such as silica gel column chromatography, HPLC with a silica gel stationary phase, and preparative gel permeation chromatography, are all ineffective in separating the two compounds. Recrystallization of the crude mixture of (*R*)-**1a** and (*R*)-**1b** from hexane/ethyl acetate afforded yellow solid in which the two compounds cocrystallized, and isolation of pure (*R*)-**1a** could not be attained.

It was found that the polysaccharide-based CSP columns were highly effective in separating the two compounds. Figure 2 shows the HPLC chromatograms of the mixture of (*R*)-**1a** and (*R*)-**1b** on Daicel Chiralpak IA, IB, or IC using hexane/

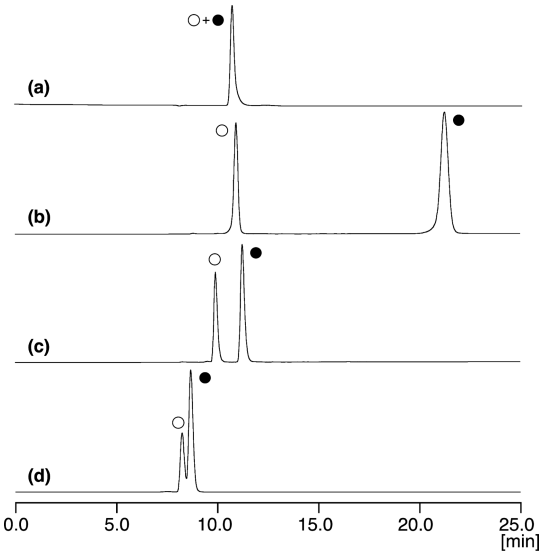


Figure 2. HPLC traces for the mixture of (*R*)-**1a** (●) and (*R*)-**1b** (○) on silica gel column (a), Daicel Chiralpak IA (b), Daicel Chiralpak IB (c), and Daicel Chiralpak IC (d) using hexane/ethyl acetate = 2/1 as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL.

ethyl acetate (2/1) as an eluent. An HPLC chromatogram on a standard silica gel column (Tosoh TSKgel Silica-150) is also displayed for comparison. The silica gel stationary phase did not recognize the structural difference between (*R*)-**1a** and (*R*)-**1b**, and the analysis of the mixture on it showed a single sharp peak as in Figure 2(a). Among the three chiral columns examined, Chiralpak IA showed the most effective separation of the two compounds (Figure 2(b)). Under the analysis conditions (column length: 250 mm; column i.d.: 4.6 mm; eluent: hexane/ethyl acetate = 2/1; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL), (*R*)-**1a** and (*R*)-**1b** were detected at 21.3 and 10.9 min, respectively, and the resolution factor (Rs)[9] for this analysis reached to 19.0. The mixture of (*R*)-**1a** and (*R*)-**1b** was also well-recognized on Chiralpak IB, and clear separation of the two components was realized with the Rs value of 3.88 (Figure 2(c)). Chiralpak IC also gave the two peaks on the HPLC analysis of the mixture; however, only the partial separation could be attained under the given conditions (Rs = 1.07).

The HPLC separation of (*R*)-**1a** and (*R*)-**1b** could be conducted on a semimacro scale as well. A sample of the mixture of (*R*)-**1a** and (*R*)-**1b** (**1a**/**1b** = 3/1; ca. 25 mg in 2 mL of the hexane/ethyl acetate eluent) was separated cleanly on Chiralpak IA (250 mm × 20 mm i.d.). The mixture of (*R*)-**1a** and (*R*)-**1b** (**1a**/**1b** = 3/1; 106 mg) was divided into five aliquots, and each aliquot was subjected to the HPLC−CSP separation on Chiralpak IA as above. After the five-time HPLC−CSP runs, (*R*)-**1a** (72 mg; 68%) and (*R*)-**1b** (23 mg; 22%) were obtained in pure forms.

It should be noted that the amount of the sample injection was regulated by the solubility of the mixture in the eluent (the injected solution was already saturated in the present eluent), and sample loading may be increased by the use of a proper (i.e., more soluble) solvent.

DOI: 10.1021/acs.organomet.8b00819
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Whereas complexes **1a**/**1b** are planar-chiral, the HPLC separation of the **1a**/**1b** mixture of the enantiomeric antipodes, that is the mixture of (*S*)-**1a** and (*S*)-**1b**, on the CSP columns was also examined. The results are summarized in Figure 3

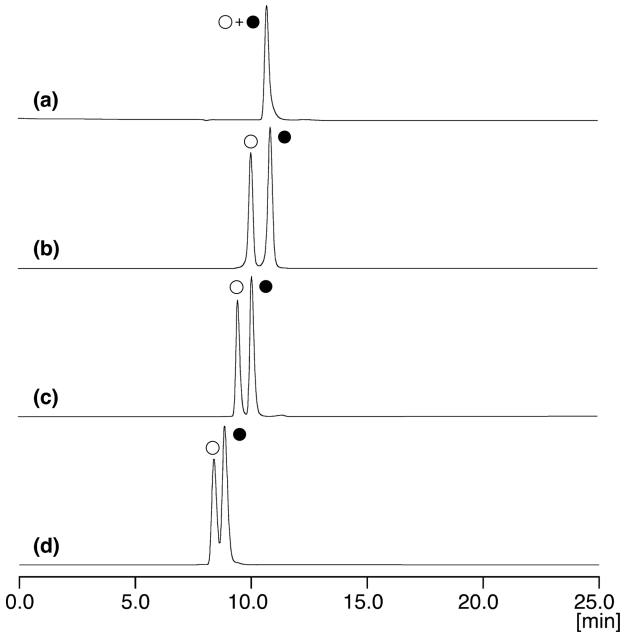
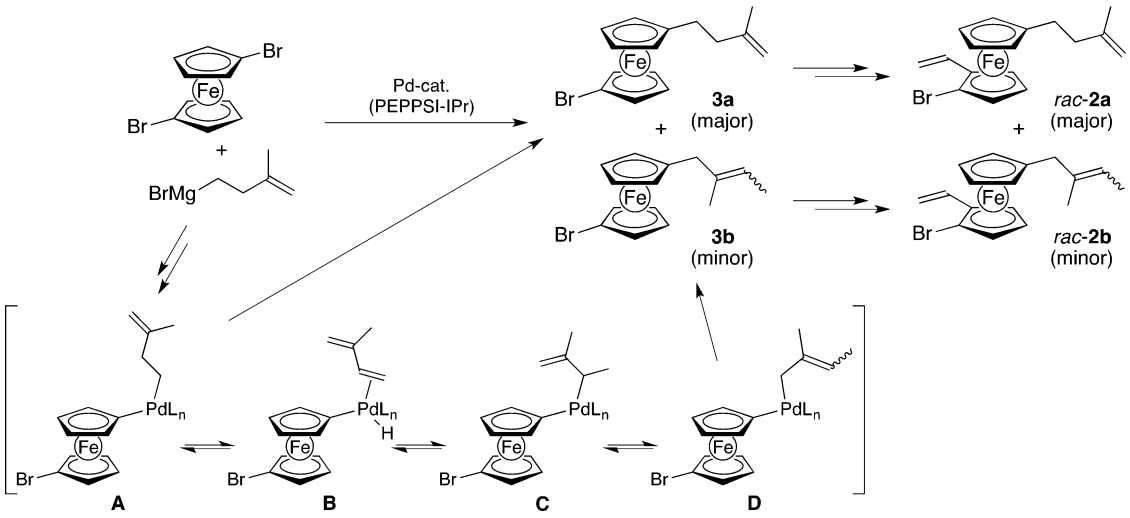


Figure 3. HPLC traces for the mixture of (*S*)-**1a** (●) and (*S*)-**1b** (○) on silica gel column (a), Daicel Chiralpak IA (b), Daicel Chiralpak IB (c), and Daicel Chiralpak IC (d) using hexane/ethyl acetate = 2/1 as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL.

with an HPLC chromatogram on the silica gel column for comparison. Daicel Chiralpak IA, IB, and IC all showed good to fair recognition between (*S*)-**1a** and (*S*)-**1b** with the Rs values of 2.37, 1.87, and 1.08, respectively. The separation of (*S*)-**1a** and (*S*)-**1b** are, however, relatively less effective than that of the (*R*)-isomers on Chiralpak IA or Chiralpak IB, because these two CSP columns recognize not only double-bond regioisomers **1a**/**1b** but also the planar-chiral enantiomeric pairs in **1a** and **1b** as well. As envisaged by the results shown in Figures 2 and 3, the HPLC−CSP traces for the mixture of *rac*-**1a** and *rac*-**1b** showed the partially overlapped four or three peaks by the simultaneous enantiomeric resolution of the respective planar-chiral enantiomers and the isomeric separation (see Supporting Information). Nevertheless, these results clearly demonstrate the potential usefulness of the polysaccharide-based CSP columns for the separation of the double-bond regioisomers.

Examples 2 and 3: Separation of Ferrocene Derivatives 2a/2b and 3a/3b Having Isomeric Methylbutenyl Substituents. Reaction between 1,1′-dibromoferrocene and excess (3-methyl-3-butenyl)magnesium bromide was conducted in the presence of PEPPSI-IPr[10] catalyst (5.0 mol %). The Kumada−Tamao−Corriu coupling of the ferrocene-electrophile was fairly slow, and monoalkenylated species **3a** was obtained predominantly together with minor side-products **3b** and recovered 1,1′-dibromoferrocene. Due to the slowness of the coupling reaction, the formation of 1,1′-dialkenylferrocene was very minor. The structures of **3b** could not be determined at this stage, because **3b** was inseparable from **3a** by standard silica gel column chromatography. The crude mixture of **3a** and **3b** was used in the subsequent reactions without separation, and they were converted into *rac*-**2a** and *rac*-**2b**, respectively (see, Experimental Section for details). Whereas the mixture of *rac*-**2a** and *rac*-**2b** was also inseparable by the classical methods (silica gel-based chromatography, GPC, etc.), the HPLC−CSP systems were examined in the separation of the two species. And indeed, they were found to be quite powerful (vide infra). After the separation of *rac*-**2b** from *rac*-**2a**, the identity of *rac*-**2b** was clarified to be a mixture of (*Z*)- and (*E*)-1-bromo-1′-(2-methyl-2-butenyl)ferrocene by the ^{1}H and ^{13}C NMR measurements as well as by the MS analysis (Figure 1 and Scheme 2). And eventually, the structure of **3b** was determined as depicted. It is worth mentioning that the observed "3-methyl-3-butenyl" to "2-methyl-2-butenyl" isomerization in the palladium-catalyzed cross-coupling reaction is unique to the bromoferrocene electrophile; an analogous reaction between bromobenzene and (3-methyl-3-butenyl)magnesium bromide provided (3-methyl-3-butenyl)benzene exclusively under otherwise identical conditions and isomerized products were not detected.

Scheme 2. Preparation of *rac*-2a and *rac*-2b with Plausible Pathways to 3b



DOI: 10.1021/acs.organomet.8b00819
Organometallics XXXX, XXX, XXX−XXX

The formation of **3b** is rationalized as shown in Scheme 2. Palladium intermediate **A**, which is formed via the oxidative addition of 1,1′-dibromoferrocene to the Pd(0) species followed by the transmetalation with the Grignard reagent, undergoes two modes of transformations. One is the direct reductive elimination to give **3a** (the major pathway), and the other is isomerization to intermediate **C** by the β-hydride elimination of 3-methyl-3-butenyl substituent and the following reverse insertion of generated η^2-isoprene to the palladium(II)-hydride bond in intermediate **B**. Subsequently, an allylic rearrangement from **C** to **D** followed by the reductive elimination from **D** gives the mixture of (*Z*)- and (*E*)-**3b** as the side-products.[11]

Compounds *rac*-**2a**/*rac*-**2b** are liquid and noncrystalline, and thus they could not be purified by recrystallization. Rather classical chromatographic methods, which included silica gel column chromatography, HPLC with a silica gel stationary phase, and preparative GPC, all failed to separate *rac*-**2b** from *rac*-**2a**. On the other hand, the polysaccharide-based CSP columns showed good recognition between *rac*-**2a** and *rac*-**2b**. Figure 4 shows the HPLC chromatograms of the mixture of *rac*-**2a** and *rac*-**2b**. While the mixture was detected as a single broad peak on the silica gel stationary phase as shown in Figure 4(a), Chiralpak IA and IB could separate *rac*-**2b** from *rac*-**2a** (Figure 4(b,c)). The smaller "bimodal" peaks in Figure 4(b,c), which were fast-eluting and detected at 11.2 min and at 13.0 min, respectively, were assigned to the (*E*)/(*Z*)-mixture of *rac*-**2b**. The bimodal shape of the smaller peaks may be ascribed to incomplete separation of the (*E*)- and (*Z*)-isomers on these CSP columns. Alternatively, it can be explained as partial enantiomeric resolution of planar-chiral and racemic *rac*-**2b** by the chiral stationary phases in Chiralpak IA and IB. The main component in the sample, *rac*-**2a**, is also planar-chiral and racemic; however, the chiral recognition of the enantiomeric pair in *rac*-**2a** by Chiralpak IA and IB was negligible under the employed conditions, and their enantiomeric resolution was not practical with these columns. On the other hand, Chiralpak IC gave the partially overlapped four peaks on the HPLC analysis of the *rac*-**2a**/*rac*-**2b** mixture, which could be ascribed to the concurrent enantiomeric resolution of planar-chiral *rac*-**2a**/*rac*-**2b** and the isomeric separation between the two. The crude mixture of *rac*-**2a** and *rac*-**2b** (**2a**/**2b** = ca. 85/15; 83.5 mg in 2 mL of hexane) was separated on semimacro scale Chiralpak IA (250 mm × 20 mm i.d.), and *rac*-**2a** (64.0 mg; 76.6%) and *rac*-**2b** (10.4 mg; 12.5%) were obtained.

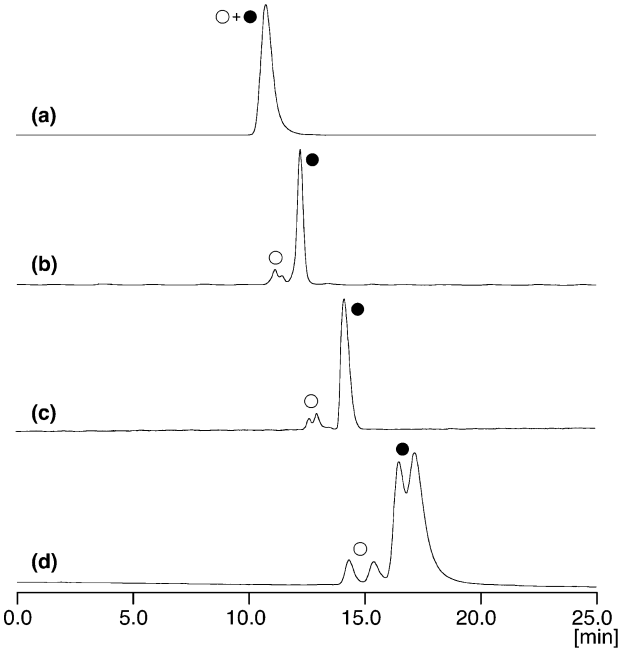


Figure 4. HPLC traces for the mixture of *rac*-**2a** (●) and *rac*-**2b** (○) on silica gel column (a), Daicel Chiralpak IA (b), Daicel Chiralpak IB (c), and Daicel Chiralpak IC (d) using hexane/ethyl acetate = 2/1 (for the silica gel column) or hexane (for the CSP columns) as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL.

After the successful removal of *rac*-**2b** from *rac*-**2a**, validity of the chiral HPLC columns for the separation of **3a** and **3b** was also examined. Ferrocene derivatives **3a** and **3b** are both liquid and could not be purified by recrystallization. While the classical chromatographic methods (silica gel column chromatography, HPLC with a silica gel stationary phase, and preparative GPC) were all ineffective in separating **3a** and **3b**, Daicel Chiralpak IA, IB, and IC all showed good to fair recognition between **3a** and **3b**. Figure 5 shows the HPLC chromatograms of the mixture of **3a** and **3b** on Daicel Chiralpak IA, IB, or IC using hexane as an eluent. An HPLC chromatogram on the silica gel column is also shown for comparison (Figure 5(a)). While Chiralpak IB could achieve only partial separation of **3a** and **3b** (Figure 5(c)), both Chiralpak IA and IC succeeded in separating the mixture. Chiralpak IC gave the two peaks on the HPLC analysis of the **3a**/**3b** mixture (Rs = 1.14; Figure 5(d)), and the fast-eluting smaller peak at 12.5 min was found to be a mixture of (*Z*)- and (*E*)-**3b**. On the other hand, the analysis on Chiralpak IA provided three peaks at 10.4, 11.2, and 12.0 min, respectively,

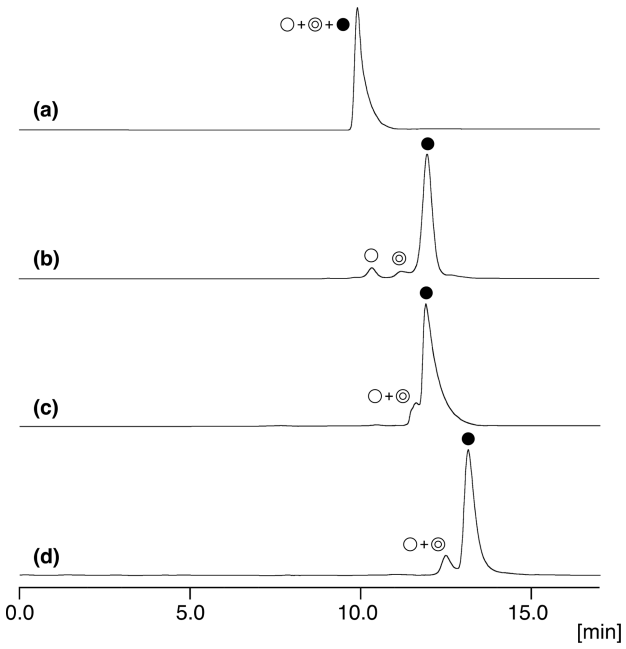


Figure 5. HPLC traces for the mixture of **3a** (●), (*Z*)-**3b** (○), and (*E*)-**3b** (◎) on silica gel column (a), Daicel Chiralpak IA (b), Daicel Chiralpak IB (c), and Daicel Chiralpak IC (d) using hexane/ethyl acetate = 2/1 (for the silica gel column) or hexane (for the CSP columns) as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL.

DOI: 10.1021/acs.organomet.8b00819
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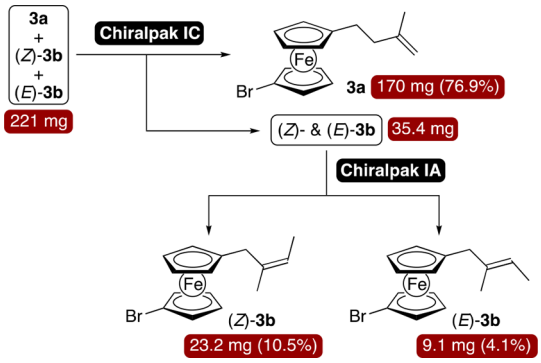
and the second and the third peaks overlapped partially (Figure 5(b)).

The identity of the three peaks in Figure 5(b) was clarified to be (*Z*)-**3b**, (*E*)-**3b**, and **3a**, respectively, by the two successive HPLC−CSP separations of the mixture and the ^{1}H and ^{13}C NMR/LR-MS measurements of the separated fractions (Scheme 3). The semimacro scale preparative HPLC of the **3a**/**3b** mixture on Chiralpak IC (250 mm × 20 mm i.d.) afforded pure **3a** in 76.9% and the mixture of (*Z*)- and (*E*)-**3b**, and the latter was further separated into the two components in 10.5% and 4.1%, respectively, by the preparative HPLC on Chiralpak IA (250 mm × 20 mm i.d.). Figure 6 shows the HPLC chromatograms of the mixture of (*Z*)- and (*E*)-**3b** on the silica gel column and on Chiralpak IA, IB, and IC. Contrary to Chiralpak IA, both Chiralpak IB and IC failed in separating (*Z*)- and (*E*)-**3b**.

Scheme 3. Separation of 3a, (*Z*)-3b, and (*E*)-3b by Successive Preparative HPLC on Chiralpak IC and Chiralpak IA



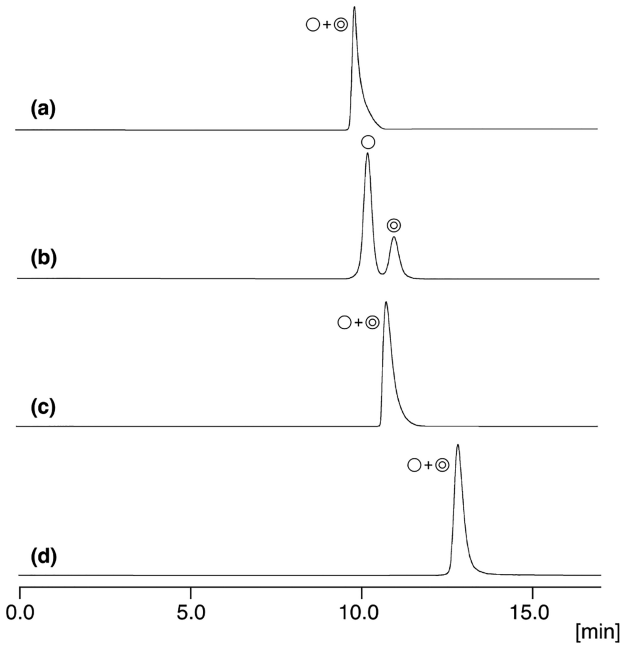


Figure 6. HPLC traces for the mixture of (*Z*)-**3b** (○) and (*E*)-**3b** (◎) on silica gel column (a) and Daicel Chiralpak IA (b), Daicel Chiralpak IB (c), and Daicel Chiralpak IC (d) using hexane/ethyl acetate = 2/1 (for the silica gel column) or hexane (for the CSP columns) as an eluent. Column length: 250 mm; column i.d.: 4.6 mm; flow rate: 0.5 mL/min; injection: ca. 10 μg in 10 μL.

CONCLUSIONS

In this article, we have demonstrated that the polysaccharide-based CSP columns, namely Daicel Chiralpak IA, IB, and IC, are highly effective in separating closely related nonenantiomeric isomers. The CSP columns have succeeded to recognize the double-bond regioisomers in **1a**/**1b**, the structural-isomeric methylbutenyl side-arms in **2a**/**2b** and **3a**/**3b**, and the geometrical isomers in (*Z*)/(*E*)-**3b**. Due to the close similarity of the isomeric compounds in these mixtures, separations of the components are extremely difficult and could not be attained by the rather classical methods such as silica gel column chromatography, silica gel HPLC, recrystallization, distillation/sublimation, etc. Clearly, the polysaccharide-based CSP columns have unique advantages in separation/purification technology, and this study has shown potential usefulness of the CSP columns in separation of not only enantiomeric but also nonenantiomeric mixtures.

The "first-generation" polysaccharide-based CSPs, which have been on the market since the 1980s, are prepared by coating the polysaccharide derivatives on a macroporous silica gel. The coated-type CSPs have severe limitations in the selection of eluents. In general, hexane, ethanol, 2-propanol, and their mixtures are the only solvents applicable on the normal phase coated-type CSP columns (the reverse phase CSP columns, which can be used with water/methanol/acetonitrile, are also available from Daicel Corporation). On the other hand, the polysaccharide derivatives are immobilized on a silica gel support in the CSP columns used in this study.[3e] The immobilized-type CSP columns, which have been commercialized since 2004, are much more durable and can be used with various eluents.[12] 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. ^{31}P NMR (at 162 MHz) chemical shifts are externally referenced to 85% H_3PO_4. Tetrahydrofuran was distilled from benzophenone-ketyl under nitrogen prior to use. (*R*)- or (*S*)-[(η^5-1-Bromo-2-(3-diphenylphosphino-2-methylpropenyl)-cyclopentadienyl-*P*)]manganese(I) dicarbonyl ((*R*)- or (*S*)-**4**),[8] 1,1′-dibromoferrocene,[13] and 4-bromo-2-methylbutene[14] were 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).[12] 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 0.5 mL/min (on the analytical columns; 250 mm-length/4.6 mm-i.d.) or 9.5 mL/min (on the semimacro scale columns; 250 mm-length/20 mm-i.d.), and the detection wavelength was 254 nm.

Preparation of 1a/1b Mixture. To a solution of (*R*)-(−)-**4** (94.1 mg, 0.191 mmol) in THF (2 mL) was added ^{t}BuLi (1.62 M in

DOI: 10.1021/acs.organomet.8b00819
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pentane, 0.30 mL, 0.486 mmol) dropwise at −78 °C. After stirring the solution for 1 h at −78 °C, DMF (21 mg, 0.29 mmol) was added dropwise, then the resulting mixture was gradually warmed to room temperature. The resulting solution was quenched with aqueous NH_4Cl solution and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtrated and concentrated under reduced pressure. The residue was purified by a silica gel chromatography (hexane/EtOAc = 3/1) to give a mixture of (*R*)-**1a** and (*R*)-**1b** as a yellow solid (70.1 mg, 0.159 mmol, 83%). The molar ratio between the two isomers was determined to be (*R*)-**1a**/(*R*)-**1b** = 3/1 by the ^{31}P NMR measurement. The mixture of (*S*)-**1a** and (*S*)-**1b** was prepared in the same way starting with (*S*)-(+)-**4**. The (*R*)- or (*S*)-**1a**/**1b** mixtures were used for the HPLC−CSP studies without further purifications.

*(R)-(+)-[(η^5-1-(3-Diphenylphosphino-2-methyl-1-propenyl)-cyclopentadienyl-2-formyl-P)]manganese(I) Dicarbonyl (**1a**).* ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H), 2.91−2.97 (m, 1H), 3.01−3.07 (m, 1H), 4.36 (br, 1H), 5.00 (br, 1H), 5.21 (br, 1H), 6.16 (br, 1H), 7.36−7.44 (m, 10H), 9.43 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 27.3 (d, J_{PC} = 4.2 Hz), 34.7 (d, J_{PC} = 20.3 Hz), 80.4 (s), 80.8 (s), 83.7 (s), 87.2 (s), 103.3 (s), 115.6 (d, J_{PC} = 12.0 Hz), 128.3 (d, J_{PC} = 8.9 Hz), 128.4 (d, J_{PC} = 8.8 Hz), 129.8 (s), 130.0 (s), 131.4 (d, J_{PC} = 9.8 Hz), 131.7 (d, J_{PC} = 10.2 Hz), 136.8 (d, J_{PC} = 41.3 Hz), 137.5 (d, J_{PC} = 42.8 Hz), 138.8 (s), 189.7 (s), 228.1 (d, J_{PC} = 21.8 Hz), 229.3 (d, J_{PC} = 20.8 Hz). ^{31}P{1H} NMR ($CDCl_3$) δ 103.3 (s). ES-HRMS calcd for $C_{24}H_{20}MnO_3P$ 442.0531, found 442.0538. $[\alpha]_D^{12}$ +344 (*c* 1.01, $CHCl_3$).

*(R)-(+)-[(η^5-1-(3-Diphenylphosphino-2-methyl-2-propenyl)-cyclopentadienyl-2-formyl-P)]manganese(I) Dicarbonyl (**1b**).* ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.85−2.89 (m, 1H), 3.36−3.40 (m, 1H), 4.50 (br, 1H), 4.75 (br, 1H), 5.13 (br, 1H), 6.26 (br, 1H), 7.36−7.45 (m, 10H), 9.40 (s). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 28.1(s), 29.3 (s), 79.9 (s), 82.9 (s), 84.5 (s), 85.9 (s), 102.6 (s), 117.8 (d, J_{PC} = 40.9 Hz), 128.3 (d, J_{PC} = 10.2 Hz, 2C), 129.3 (s), 129.5 (s), 131.5 (d, J_{PC} = 10.8 Hz), 131.8 (d, J_{PC} = 10.7 Hz), 138.5 (d, J_{PC} = 48.2 Hz), 139.3 (d, J_{PC} = 47.7 Hz), 155.5 (d, J_{PC} = 13.0 Hz), 189.3 (s), 228.4 (d, J_{PC} = 22.0 Hz), 229.4 (d, J_{PC} = 23.4 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$) δ 74.4 (s). ES-HRMS calcd for $C_{24}H_{20}MnO_3P$ 442.0531, found 442.0535. $[\alpha]_D^{23}$ +38.5 (*c* 0.50, $CHCl_3$).

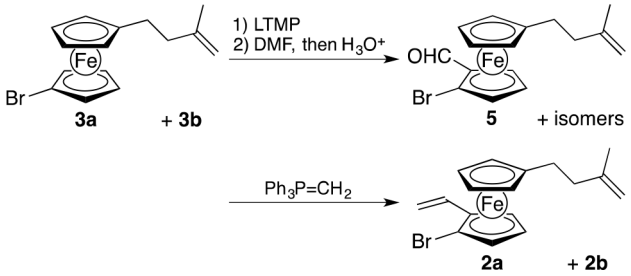
Preparation of 3a/3b Mixture. To a solution of 1,1′-dibromoferrocene (1.00 g, 2.91 mmol) and PEPPSI-IPr (99.0 mg; 0.146 mmol; 5 mol %) in THF (3 mL) was added a THF solution of (3-methyl-4-butenyl)magnesium bromide, which was prepared from 4-bromo-2-methylbutene (1.73 g; 11.6 mmol) and magnesium powder (290 mg; 11.9 mmol) in THF (5 mL), and the mixture was stirred for 20 h at 40 °C. The reaction mixture was quenched with a small amount of water at 0 °C, then the mixture was evaporated to dryness under reduced pressure. The residue was filtered through a short pad of silica gel using hexane as an eluent. After removal of the solvent, the crude material was chromatographed on silica gel (eluent: hexane) to give a mixture of **3a** and **3b** (210 mg; 0.631 mmol; 22%) as an orange oil together with recovered 1,1′-dibromoferrocene (420 mg, 1.22 mmol; 42%). The mixture of **3a** and **3b** was used for the preparation of **2a**/**2b** as well as for the HPLC−CSP studies without further purifications.

*1-Bromo-1′-(3-methyl-3-butenyl)ferrocene (**3a**).* ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 2.22−2.26 (m, 2H), 2.47−2.51 (m, 2H), 4.04−4.05 (m, 2H), 4.08−4.09 (m, 2H), 4.11−4.12 (m, 2H), 4.30−4.31 (m, 2H), 4.70−4.71 (m, 1H), 4.73−4.74 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 22.8, 27.2, 39.2, 67.7, 69.9, 70.7, 70.8, 78.3, 90.8, 110.2, 145.7. ES-HRMS calcd for $C_{15}H_{17}BrFe$: 331.9865, found 331.9869.

*(E)-1-Bromo-1′-(2-methyl-2-butenyl)ferrocene ((E)-**3b**).* ^{1}H NMR ($CDCl_3$) δ 1.54 (d, *J* = 6.7 Hz, 3H), 1.56 (br s, 3H), 3.04(s, 2H), 4.04−4.05 (m, 2H), 4.07−4.08 (m, 2H), 4.12−4.13 (m, 2H), 4.30−4.31 (m, 2H), 5.17 (qq, *J* = 6.7 and 1.3 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.5, 16.0, 39.4, 67.8, 70.1, 70.9, 71.7, 78.4, 89.1, 119.1, 135.9. ES-HRMS calcd for $C_{15}H_{17}BrFe$ 331.9865, found 331.9866.

*(Z)-1-Bromo-1′-(2-methyl-2-butenyl)ferrocene ((Z)-**3b**).* ^{1}H NMR ($CDCl_3$) δ 1.61−1.62 (m, 3H), 1.67 (d, *J* = 6.87 Hz, 3H), 3.10 (s, 2H), 4.06−4.07 (m, 2H), 4.09−4.10 (m, 2H), 4.11−4.12 (m, 2H), 4.32−4.33 (m, 2H), 5.20 (q, *J* = 6.87 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.7, 23.5, 31.0, 67.9, 70.0, 70.9, 71.5, 78.4, 89.3, 119.3, 135.6. ES-HRMS calcd for $C_{15}H_{17}BrFe$ 331.9865, found 331.9870.

Preparation of 2a/2b Mixture. The mixture of **2a**/**2b** was prepared from the **3a**/**3b** mixture by the two-step sequence as outlined below.



A solution of **3a**/**3b** mixture (854 mg, 2.56 mmol) in THF (2 mL) was cooled to −30 °C, and to this was added a THF solution of LTMP, which was prepared from 2,2,6,6-tetramethylpipperidine (400 mg, 2.83 mmol) and ″BuLi (1.64 mol/L in hexane, 1.6 mL, 2.62 mmol) in THF (2 mL) at 0 °C, dropwise via a cannula. After stirring the solution for 3 h at −30 °C, DMF (300 μL, 283 mg, 3.87 mmol) was added using a syringe. The solution was warmed to room temperature and stirred for 6 h. The reaction was quenched with water, and then the products were extracted with dichloromethane. The dichloromethane solution was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (hexane/ethyl acetate = 10/1) to give a mixture of the formyl species **5** as a dark yellow oil. Yield: 491 mg (1.36 mmol, 53%). *rac*-1-Bromo-2-formyl-1′-(3-methyl-3-butenyl)ferrocene (**5**). ^{1}H NMR (C_6D_6) δ 1.62 (s, 3H), 2.00−2.04 (m, 2H), 2.21−2.25 (m, 2H), 3.82−3.89 (m, 5H), 4.26 (br, 1H), 4.62 (br, 1H), 4.75 (br, 1H), 4.78 (br, 1H), 10.23 (s, 1H). ^{13}C{^{1}H} NMR (C_6D_6) δ 22.6, 26.6, 39.0, 67.4, 71.52, 71.55, 71.8, 71.98, 72.01, 75.3, 76.6, 80.9, 92.5, 110.9, 144.9, 191.6. ES-HRMS calcd for $C_{16}H_{17}BrFeNaO$ (M + Na) 382.9710, found 382.9713.

A solution of $Ph_3PMe{\cdot}Br$ (298 mg, 0.834 mmol) in THF (1 mL) was cooled to 0 °C, and to this was added ″BuLi (1.64 mol/L in hexane, 0.51 mL, 0.836 mmol) using a syringe. After stirring the solution for 30 min at 0 °C, a THF (1.5 mL) solution of **5** (200 mg, 0.556 mmol) was added via a cannula. The solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with aqueous $NaHCO_3$, then the products were extracted with ether. The ether solution was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (hexane/ether = 20/1) to give a mixture of **2a** and **2b** as a dark yellow oil. Yield: 189 mg (0.526 mmol, 95%). The **2a**/**2b** mixture was used for the HPLC−CSP studies without further purifications.

*rac-1-Bromo-1′-(3-methyl-3-butenyl)-2-vinylferrocene (rac-**2a**).* ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 2.18−2.21 (m, 2H), 2.40−2.45 (m, 2H), 3.98−3.99 (m, 2H), 4.04−4.06 (m, 2H), 4.17−4.18 (m, 1H), 4.38−4.39 (m, 1H), 4.41−4.42 (m, 1H), 4.69−4.70 (m, 1H), 4.72−4.73 (m, 1H), 5.21 (dd, *J* = 11.0 and 1.4 Hz, 1H), 5.45 (dd, *J* = 17.9 and 1.4 Hz, 1H), 6.56 (dd, *J* = 17.9 and 11.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 22.7, 26.4, 38.9, 63.6, 67.4, 71.0, 71.1, 71.30, 71.31, 71.7, 80.1, 81.7, 90.9, 110.0, 113.0, 132.0, 145.6. ES-HRMS calcd for $C_{17}H_{20}BrFe$ (M + 1) 359.0098, found 359.0099.

*rac-(E/Z)-1-Bromo-1′-(2-methyl-2-butenyl)-2-vinylferrocene (rac-(E/Z)-**2b**).* ^{1}H NMR ($CDCl_3$) δ 1.53 (d, *J* = 6.2 Hz, 3H of *E*-isomer), 1.54 (s, 3H of *E*-isomer), 1.58−1.59 (m, 3H of *Z*-isomer), 1.65−1.67 (m, 3H of *Z*-isomer), 2.94 (br, 2H of *E*-isomer), 3.01 (br, 2H of *Z*-isomer), 3.96−3.98 (m, 2H of both isomers), 4.03−4.08 (m, 2H of both isomers), 4.16−4.17 (m, 1H of *Z*-isomer), 4.18−4.19 (m, 1H of *E*-isomer), 4.37−4.43 (m, 2H of both isomers), 5.12−5.20 (m, 1H of both isomers), 5.22 (dd, *J* = 10.5 and 1.4 Hz, 1H of *Z*-isomer), 5.23 (dd, *J* = 10.5 and 1.4 Hz, 1H of *E*-isomer), 5.45 (dd, *J* = 17.4 and

DOI: 10.1021/acs.organomet.8b00819
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1.4 Hz, 1H of *Z*-isomer), 5.48 (dd, *J* = 17.5 and 1.4 Hz, 1H of *E*-isomer), 6.55 (dd, *J* = 17.4 and 10.5 Hz, 1H of *Z*-isomer), 6.58 (dd, *J* = 17.5 and 10.5 Hz, 1H of *E*-isomer). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.5, 13.7, 15.9, 23.4, 30.4, 38.8, 63.81, 63.84, 67.66, 67.70, 71.16, 71.24, 71.3, 71.4, 71.5, 71.6, 72.2, 72.4, 72.7, 72.9, 80.20, 80.25, 81.88 (overlap of two peaks), 89.3, 89.5, 113.1, 113.2, 119.1, 119.2, 132.20, 132.22, 135.6, 135.9. ES-HRMS calcd for $C_{17}H_{20}BrFe$ (M + 1) 359.0098, found 359.0102.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00819.

NMR spectra (^1H, ^{13}C and ^{31}P) for all the new compounds and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (B) to M.O. (Grant #18H01979) from MEXT, Japan.

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