Chapter 10

Hybrid Organic-Inorganic Materials Containing a Nanocellulose Derivative as Chiral Selector

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Abstract

Hybrid organic-inorganic materials (HOIM), with high mechanical stability, large surface area, tailored pore size, controlled morphology, and organic loading have shown superior chiral separation performance. In this chapter, the preparation of hybrid organic-inorganic materials of core-shell silica microspheres by a layer-by-layer self-assembly method is described. The enantioseparation performance by high-performance liquid chromatography is illustrated by various types of chiral compounds under normal- and reversed-phase elution conditions. The chiral selector of nanocrystalline cellulose derivative hybrid organic-inorganic materials showed good performance in the separation of enantiomers.

Key words Chiral selectors, Hybrid organic-inorganic materials, Nanocellulose, Enantioseparation, High-performance liquid chromatography

1 Introduction

Chirality is an essential property of nature. When enantiomers were taken up by the human body or the ecological environment, there are significant differences in their pharmacological activities, metabolic processes and toxicity, and some may even have the opposite effect [1]. Thus far, chiral separations still remain one of the most significant issues in the field of analytical science. Over the last few decades, various analytical techniques have been developed for chiral separations including gas chromatography, high-performance liquid chromatography, capillary electrochromatography, and capillary liquid chromatography [2]. Compared to many methods, high-performance liquid chromatography using chiral stationary phases (CSPs) is considered one of the most effective methods to separate enantiomers because of the high separation efficiency and the general applicability [3, 4]. Therefore, the exploitation of new types of chiral selectors is still a research topic in the field of enantioseparation.

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Emerging hybrid organic-inorganic materials (HOIM) with both organic and inorganic components have attracted a lot of attention because the integrative design, which is expected to provide excellent and unique properties [5–7]. Compared with conventional materials, HOIMs obtained by simultaneous reaction of organic molecules and inorganic components have abundant and homogeneously distributed organic functional groups within the whole framework instead of simply modifying the surface of inorganic oxides. Weak bonds still exist between organic and inorganic phases in such materials [8, 9]. HOIMs were endowed with new functions and features owing to the tunable functional organic groups in the pore walls or channels, which can achieve chromatographic separations not only on the surface of the materials but also at the inner part of the material. Moreover, the loading amount of chiral selectors in HOIMs and uniformly distributed organic functional groups can be tailored through controlling the ratio of chiral precursors over inorganic precursors in the preparation process. This makes HOIMs to have a great prospect as chiral stationary phases. In 2008, Okamoto and coworkers reported a novel method for synthesizing organic-inorganic hybrid materials using cellulose tris(3,5-dimethylphenylcarbamate) (CDMPC) and tetraethyl orthosilicate [10]. The proposed silica hybrid spheres exhibited similar chiral recognition and possessed a higher loading capacity compared to a commercial chromatographic column coated with the same chiral selector. Therefore, HOIMs are emerging in chiral analysis due to their superiority as separation materials.

Important results of hybrid organic-inorganic materials used as chiral stationary phases have been achieved in the last 10 years. In 2007, Yang and coworkers synthesized bifunctionalized mesoporous organosilica spheres with *trans*-(1*R*,2*R*)-diaminocyclohexane in the pores and applied these as chiral stationary phase in high-performance liquid chromatography (HPLC). The column packed with the bifunctionalized mesoporous organosilica spheres exhibits higher selectivity and resolution for racemic amino acids than a column packed with *trans*-(1*R*,2*R*)-diaminocyclohexane (DACH)-SiO_2 prepared by the conventional post-synthesis grafting method [11]. In 2008, Yang and coworkers prepared a new mesoporous organic-inorganic sphere with *trans*-(1*R*,2*R*)-bis-(ureido)-cyclohexane covalently bridged in the pore wall by co-condensation of *N*,*N*′-bis-[(triethoxysilyl)propyl]-*trans*-(1*R*,2*R*)-bis-(ureido)-cyclohexane and 1,2-bis(trimethoxysilyl)ethane through a hierarchical double templating method. The hybrid material was employed as a novel kind of chiral stationary phase in HPLC. The column packed with the hybrid material efficiently separated the enantiomer of *R*/*S*-1,10-bis-2-naphthol even at a high sample load and at high flow rates because of the high chiral selector loading and high surface area of the material [12]. In 2012, Di and coworkers synthesized

mesoporous organosilicas with both *R*-(+)-1,1′-binaphthyl-2,2′-diamine and ethane moieties bridging in the framework. They used C18TMACl as structural directing agent, one-step co-condensation of *N*,*N*′-bis-[(triethoxysilyl)propyl]-(*R*)-bis-(ureido)-binaphthyl and 1,2-bis(triethoxysilyl)ethane [13]. The column packed with these organosilica spheres exhibited greater selectivity for *R*/*S*-1,1′-bi-2,2′-naphthol. In 2013, Di and coworkers used a layer-by-layer method for the synthesis of novel chiral core-shell silica microspheres with a DACH moiety bridged in the mesoporous shell. The functionalized core-shell silica microspheres were characterized and tested as chiral stationary phases in HPLC. *R*/*S*-1,1′-bi-2,2′-naphthol, *R*/*S*-6,6′-dibromo-1,1′-bi-2-naphthol, and *R*/*S*-1,1′-bi-2,2′-phenanthrol were enantioseparated rapidly on the column packed with the DACH core-shell silica particles [14]. In 2014, Bao and coworkers synthesized a hybrid of CDMPC as chiral stationary phase (organic/inorganic: 70/30, w/w) via the sol-gel method [15]. Compared to a commercial Chiralpak IB column, better enantioseparation was achieved on this material for pindolol, metoprolol, propranolol, bisoprolol, and atenolol. In 2015, Zhao and coworkers fabricated a β-cyclodextrin-based periodic mesoporous organosilica (PMO) CSP via one-step copolymerization of silanized monochlorotriazinyl β-cyclodextrin and *N*-benzoyl-L-tyrosine ethyl ester (BTEE) in the presence of cetyltrimethylammonium bromide (CTAB) as template [16]. Functional groups such as β-cyclodextrin, triazinyl, and ethyl were introduced in the pore channels and pore walls of the hybrid material, respectively, which made this hybrid material a multifunctional stationary phase including groups for enantioresolution, anion exchange, and achiral separations.

Among the various chiral separation materials, cellulose derivatives are the most commonly used chiral selectors for CSPs because of their ability to enantioseparate a large number of chiral compounds [17–20]. In 2007, Ikai and coworkers reported an efficient immobilization of polysaccharide derivatives onto silica gel via intermolecular polycondensation of triethoxysilyl groups, specifically using the 3-(triethoxysilyl)propyl group as cross-linker [21]. On this basis, the group reported the synthesis of organic-inorganic hybrid materials using CDMPC bearing a small amount of 3-(triethoxysilyl)propyl residues and tetraethyl orthosilicate as a CSP for HPLC [10]. Nanocrystalline cellulose (NCC) not only retains the major properties of cellulose, but has also some unique characteristics such as a high surface area and optical properties. This makes NCC a promising material for the preparation of CSPs. Recent data show that NCC suspensions can form a chiral nematic liquid-crystalline phase, which consequently can be utilized as a template to prepare chiral ordered materials. These have been applied as new chiral separation materials [22, 23].

Based on the merits of hybrid cellulose-based CSPs as well as the selective chiral discrimination properties, nanocellulose hybrid organic-inorganic core-shell CSPs for HPLC were designed by coating NCC derivatives on silica gel to further study the applications of nanocellulose in chiral separation. By using layer-by-layer and sol-gel methods, a nanocellulose derivative was introduced into the hybrid porous shell by the copolymerization reaction of organosilica precursors [24, 25]. These NCC-based CSPs showed better peak shape and higher column efficiency compared to a cellulose-based CSP, which indicated that NCC is an attractive material for CSPs. NCC derivative-based chiral selectors followed typical normal-phase HPLC behavior in hydrocarbon-alcohol mobile phases. Several examples of deviation from this behavior have been recently reported [26, 27]. In aqueous organic mobile phases, polysaccharide derivative-based CSPs are known to follow atypical reversed-phase behavior. In some cases even up to 30% water (v/v) could be used especially in combination with aprotic organic solvents such as acetonitrile [28–31].

This chapter describes the synthesis of a NCC-based CSP and its application to enantioseparations in the normal-phase and the reversed-phase elution mode. The synthesis of the material is outlined in Fig. 1.

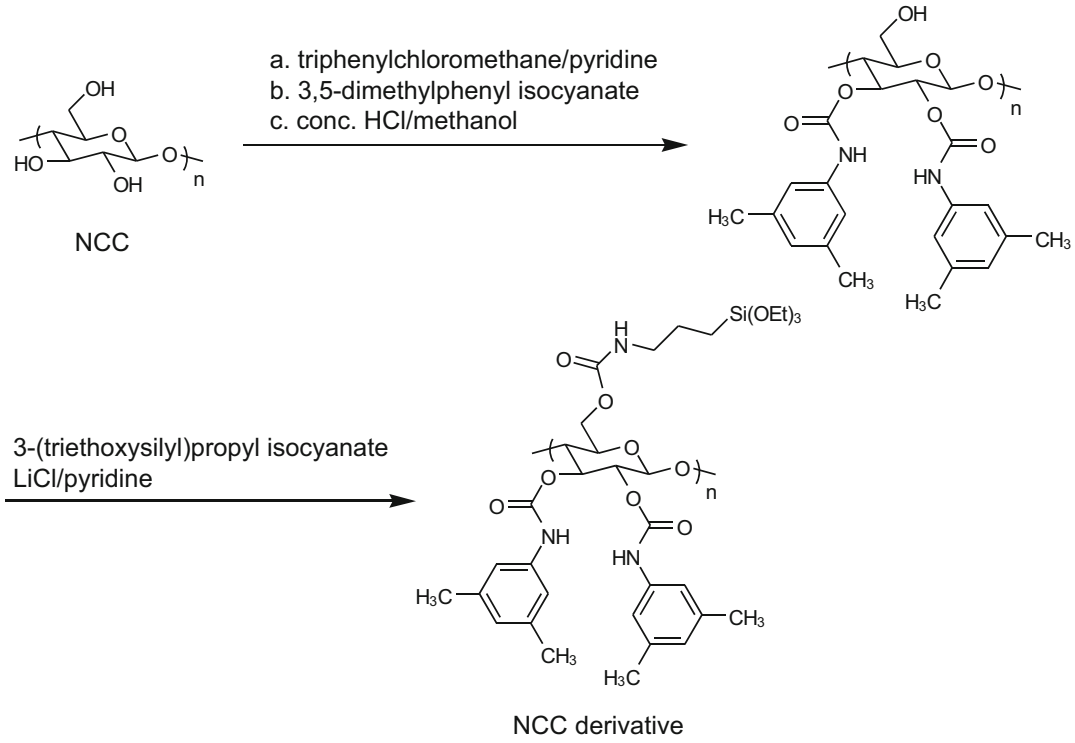

Fig. 1 Scheme of the preparation of hybrid organic-inorganic materials as chiral selectors for HPLC enantioseparations

2 Materials

2.1 Instrumentation and Materials

1. A commercial HPLC instrument with a UV detector: In the present study, a Waters HPLC System (Waters, Milford MA, USA) composed of a Waters 515 HPLC pump, a Waters 2487 UV detector, and a Rheodyne 7725i injector with a 20 μL sample loop.
2. A commercial column slurry packing apparatus: An Alltech 95551U HPLC slurry packing instrument (Alltech, Nicholasville, KY, USA) is suitable.
3. A commercial pH meter.
4. A commercial sonication bath for sonicating samples and degassing mobile phases.
5. A laboratory centrifuge capable of centrifuging a volume of 100–200 mL.
6. A commercial lyophilizer for freeze-drying samples.
7. A Soxhlet extraction apparatus for purification of the hybrid organic-inorganic material.
8. Dialysis tube membranes with a molecular weight cutoff of 7500.

2.2 Mobile Phases and Solutions

Use HPLC-grade organic solvents. Use ultrapure water (18.25 MΩ·cm at 25 °C) prepared by a suitable water purification system. All reagents should be of analytical grade.

1. *Sample solutions*: Dissolve analytes at a concentration of 1 mg/mL in the respective mobile phase.
2. *Mobile phases for separations under normal-phase conditions:* Mix the appropriate amounts of n-hexane and an alcohol. In the experiments described below, the following mobile phases were applied depending on the analyte: n-hexane-isopropanol (99.5/0.5, v/v), n-hexane-isopropanol (97/3, v/v), n-hexane-ethanol (97/3, v/v), and n-hexane-isopropanol-chloroform (70/15/15). Filter through 0.45 μm filters and sonicate for 10 min before use.
3. *Mobile phases for separations under reversed-phase conditions:* Mix the appropriate volumes of acetonitrile and water. In the experiments described below, the following mobile phases were applied depending on the analyte: acetonitrile/water (15/85, v/v), acetonitrile/water (20/80, v/v), and acetonitrile/water (30/70, v/v). Filter through 0.45 μm filters and sonicate for 10 min before use.

3 Methods

Carry out all procedures at room temperature unless otherwise specified. Perform chemical reactions in a well-ventilated hood. Chemicals may be hazardous to human health; thus, observe safety precautions when handling chemicals and wear protective gear if applicable.

3.1 Synthesis of NCC

1. Disperse 5.0 g microcrystalline cellulose (*see* **Note 1**) in 50 mL sodium hypochlorite solution (*see* **Note 2**) for 12 h at room temperature.
2. Sonicate suspension of 30 min.
3. Dilute with 200 mL ultrapure water to stop the reaction.
4. After letting the suspension settle, decant supernatant and centrifuge for 10 min at 10,000 × *g*.
5. Wash residue repeatedly with ultrapure water. A colloidal suspension of NCC is obtained.
6. Place colloidal suspension in 50 mL portions in dialysis membrane tubings (cutoff 7500) with the aid of a 100 mL graduated cylinder. Place five of these tubings in 10 L of deionized water. Replace 5 L of water every day for 3 days until the pH of the suspension becomes neutral (*see* **Note 3**).
7. Lyophilize the suspension to obtain dry NCC material.

3.2 Synthesis of NCC 3,5-Dimethylphenyl Carbamate Derivative

The synthesis of the material is outlined in Fig. 1.

1. Place 1.0 g freeze-dried NCC in a round-bottom flask equipped with a magnetic stir bar and a reflux condenser closed with a drying tube containing calcium hydroxide. Add 50 mL dry pyridine (*see* **Note 4**) and stir for 24 h at 80 °C.
2. Add 3.5 g triphenylchloromethane (trityl chloride) and stir for 12 h at 80 °C.
3. Ad 4.0 mL 3,5-dimethylphenyl isocyanate to the mixture and stir for 24 h at 80 °C.
4. Let the reaction mixture cool to room temperature and pour the solution into 200 mL methanol while stirring. A white precipitate is formed.
5. Collect product by filtration and wash with methanol.
6. Suspend the solid in 2% (v/v) hydrochloric acid in methanol (*see* **Note 5**) and stir for 24 h at room temperature.
7. Collect the white solid by filtration and wash with 30 mL methanol. Dry at 60 °C under vacuum for 24 h.
8. Dissolve 1.5 g of the dried solid in 60 mL pyridine (*see* **Note 4**) containing 1.5 g anhydrous lithium chloride in a round-

bottom flask equipped with a magnetic stir bar and a reflux condenser closed with a drying tube containing calcium hydroxide. Stir for 2 h at room temperature.

9. Add 1.2 mL 3-(triethoxysilyl)propyl isocyanate and stir the mixture for 16 h at 80 °C.
10. Let the mixture cool to room temperature and pour into 200 mL. Collect the precipitated NCC 3,5-dimethylphenyl carbamate derivative by filtration. Wash the product with methanol and dry at 60 °C for 24 h under vacuum.

3.3 Preparation of Hybrid Organic-Inorganic Material

1. Disperse 3.0 g activated 5 μm silica gel particles (*see* **Note 6**) in 100 mL of a 0.025 M cetyltrimethylammonium bromide (CTAB) solution (*see* **Note 7**) and sonicate for 30 min. Let stand for another 1 h.
2. Collect the silica gel particles by filtration, wash with 50 mL ultrapure water, and dry at 60 °C for 12 h under vacuum.
3. Dissolve 0.05 g NCC 3,5-dimethylphenyl carbamate derivative obtained according to Subheading 3.2 in 25 mL pyridine (*see* **Note 4**) in a 100 mL round-bottom flask equipped with a condenser closed by a calcium hydroxide drying tube and a magnetic stir bar at room temperature.
4. Add 3 mL of tetraethyl orthosilicate (TEOS) and 2 mL of ethanol and continue stirring at room temperature.
5. In a separate flask, dissolve 0.1 g CTAB in 1.0 mL of 0.037 g/mL aqueous hydrofluoric acid solution and add 0.5 mL concentrated hydrochloric acid.
6. After complete dissolution of CTAB, add this solution to the mixture prepared in **step 4**.
7. Cool the mixture to 15 °C and stir the mixture for 4 h to form a stable hybrid silica sol.
8. Place the 3.0 g CTAB-silica obtained in **steps 1–2** in the hybrid silica sol and let stand for 1.5 h.
9. Centrifuge the solution to collect the particles. Wash the silica particles repeatedly with ultrapure water.
10. Dry the particles at 60 °C under vacuum for 12 h.
11. Repeat **steps 3–10** five times if required and combine products to obtain sufficient quantities of the material.
12. Extract excessive CTAB by Soxhlet extraction using 50% aqueous ethanol to obtain the pure hybrid organic-inorganic material. Dry under vacuum for 12 h at 60 °C.

3.4 Column Packing

1. Connect the stainless steel column (150 × 4.6 mm) to the slurry packing apparatus.
2. Suspend 2.0 g hybrid organic-inorganic material in a mixture of 25 mL dioxane and 25 mL chloroform and sonicate for 2 min.

3. Place the slurry in the slurry reservoir of the packing apparatus and pack into the column at a pressure of 50 MPa.
4. Use *n*-hexane as displacement solvent for the packing.

3.5 Example 1: Enantioseparations in the Normal-Phase Mode

1. Install the hybrid organic-inorganic CSP column in the HPLC instrument.
2. Place the respective mobile phase (*see* **Note 8**) in the solvent reservoir and equilibrate column at a flow rate of 1.0 mL/min until a stable baseline is obtained.
3. Set detection wavelength to 254 nm.
4. Inject sample solution (20 μL) and record chromatogram.

Examples of enantioseparations in the normal-phase mode on the hybrid organic-inorganic CSP are shown in Fig. 2 (*see* **Note 9**).

3.6 Example 2: Enantioseparations in the Reversed-Phase Mode

1. Install the hybrid organic-inorganic CSP column in the HPLC instrument.
2. Place the respective mobile phase (*see* **Note 10**) in the solvent reservoir and equilibrate column at a flow rate of 1.0 mL/min until a stable baseline is obtained.
3. Set detection wavelength to 254 nm.
4. Inject sample solution (20 μL) and record chromatogram.

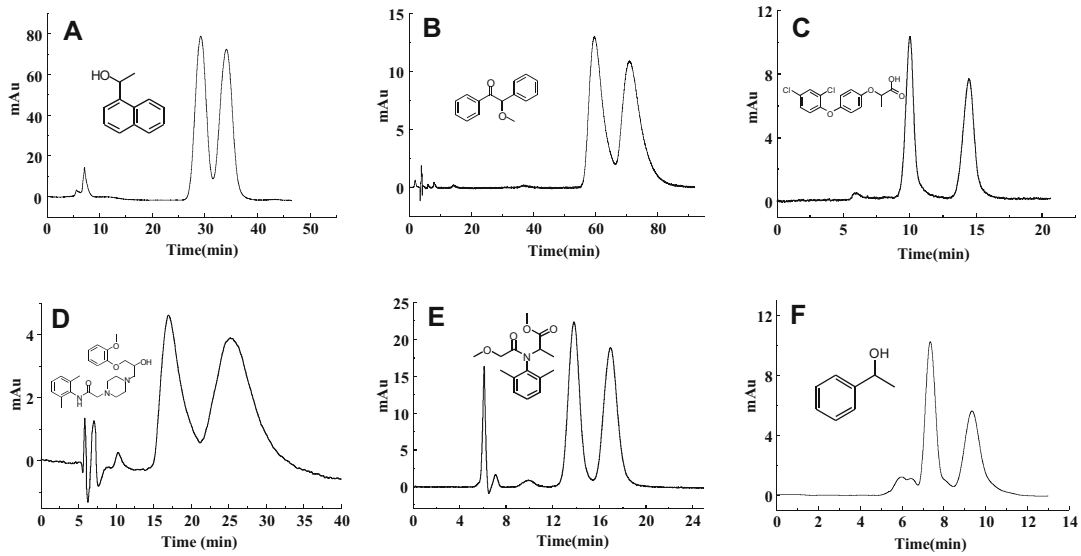

Fig. 2 Chromatograms of enantioseparations on the hybrid organic-inorganic material under normal-phase elution mode. The separations were obtained at a flow rate of 1.0 mL/min with the following mobile-phase compositions: (**a**–**c**) *n*-hexane-isopropanol (99.5:0.5, v/v); (**d**) *n*-hexane-isopropanol (97:3, v/v); (**e**) *n*-hexane-ethanol (97:3, v/v); (**f**) *n*-hexane-isopropanol-chloroform (70:15:15, v/v/v)

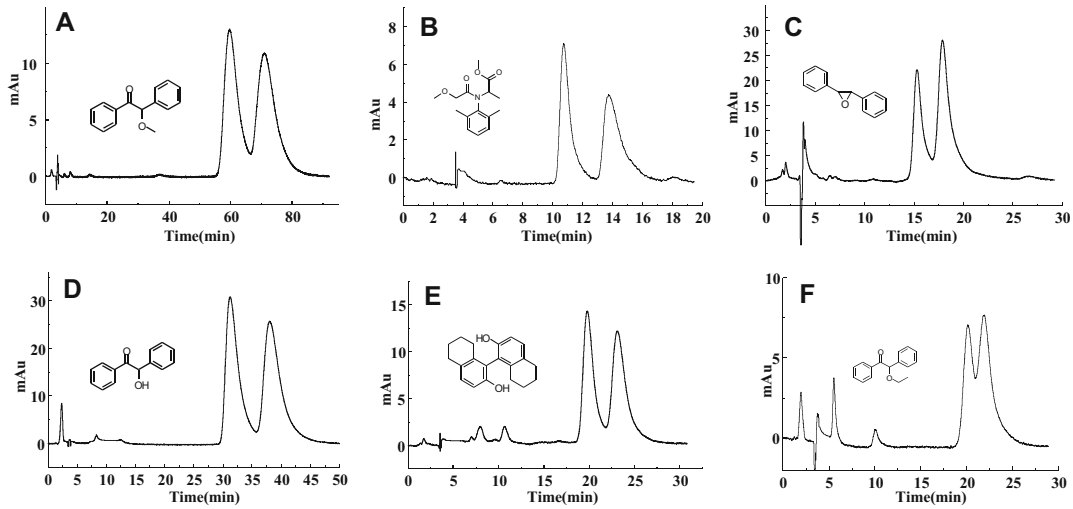

Fig. 3 Chromatograms of enantioseparations on the hybrid organic-inorganic material under reversed-phase elution mode. The separations were obtained at a flow rate of 1.0 mL/min with the following mobile-phase compositions: (**a**, **d**, **f**) acetonitrile:water (15:85, v/v); (**b**, **c**) acetonitrile:water (20:80, v/v); (**e**) acetonitrile: water (30:70)

Examples of enantioseparations in the reversed-phase mode on the hybrid organic-inorganic CSP are shown in Fig. 3 (*see* **Note 9**).

4 Notes

1. Microcrystalline cellulose from Merck KG (Darmstadt, Germany) gave best results in our hands but materials from other commercial sources may be suitable as well.
2. The sodium hypochlorite solution should contain an active chlorine content of not less than 10%. Wear protective gloves, protective clothing, and eye protection when handling the solution.
3. Dialysis is performed to remove the excess of acid.
4. Pyridine is toxic. Wear protective gear and operate in a well-ventilated hood.
5. 1000 g of a 2% HCl solution in methanol can be prepared from 46.0 mL concentrated hydrochloric acid and 946 g methanol.
6. For silica gel activation, place 3 g silica gel (5 μm particle size) in 50 mL concentrated hydrochloric acid and leave at room temperature for 24 h. Filter and wash with ultrapure water until the pH of the filtered solution is neutral. Dry at 80 °C under vacuum for 24 h.
7. A 0.025 M cetyltrimethylammonium bromide (CTAB) solution is prepared by dissolution of 0.92 g of CATB in 100.0 mL ultrapure water.

8. The amount of the alcohol content in n-hexane increases the polarity of the mobile phase. An increase will result in shorter elution times due to the weakening of interactions such as hydrogen bonds between the analyte and the chiral selector. The concentration of the alcohol should be studied during method optimization.
9. HPLC instruments from different companies as well as different instruments from the same supplier may yield slightly different results even when using identical experimental conditions. Thus, the variables may require slight changes when transferring a certain analytical method from one instrument to another; instruments from different manufacturers may have different operation conditions.
10. Mobile-phase additives such as THF and $CHCl_3$ can be used in enantioseparations on the hybrid organic-inorganic CSP to improve peak shape and separation performance.

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