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Review

Recent Advances in Separation and Analysis of Chiral Compounds

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Cite This: *Anal. Chem.* 2023, 95, 304−318

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This biennial review summarizes the development in the separation and analysis of chiral compounds from September 2020 to September 2022. Only some parts of quality studies were representatively discussed due to the limitation of the policy of *Analytical Chemistry*. The separation and analysis of chiral compounds exhibit great significance for the industries of chemistry, pharmaceutics, food, and agriculture. On the basis of the publications from the past two years, chromatography, electrophoresis, and membrane separation continue to be typical technologies for chiral separation and analysis. The exploration of new chiral stationary phases (CSPs) and new chiral selectors is the main direction of chiral chromatography, electrophoresis, and membrane separation. Mass spectrometry (MS) is a complementary technique to chromatography. Direct MS has attracted much attention in the past two years for direct chiral detection, while related derivatization and complexing reagents as well as specially designed MS instruments have emerged for enantiomer discrimination. Along with the idea of rapid analysis, chiral sensing is a significant direction toward separation-free chiral discrimination, represented by optical and electrochemical sensing. Accordingly, the development of more chiral sensors is crucial for chiral analysis.

CHROMATOGRAPHY

High-performance liquid chromatography (HPLC), gas chromatography (GC), and supercritical fluid chromatography (SFC) are still the primary means for the separation and analysis of chiral compounds during this review period. Although chromatography has become a fully fledged commercial technology of separation after decades of development, the development of CSPs presents significant room for improving chiral separation. In addition to the modified typical CSPs of cyclodextrin (CD), macrocyclic antibiotics, and polysaccharide,[1−3] many novel functional crystalline porous material based CSPs, including covalent−organic frameworks (COFs), metal−organic frameworks (MOFs), and porous organic cages (POCs) have started to show their up-and-coming brilliance for chromatographic separation of enantiomers.[4−7]

High-Performance Liquid Chromatography. As the most popular separation technology, HPLC was widely studied in the innovation of CSPs to promote its enantio-separation performance in this review period. CD derivatives drew great concern as both chiral mobile-phase additive and CSPs in chiral HPLC separation due to their special inclusion interaction in chiral recognition. Chiral mobile-phase additive can avoid the utilization of a costly chiral column to develop efficient enantio-separation methods. For example, 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and carboxy methyl-β-cyclodextrin (CM-β-CD) served as mobile-phase additives for baseline separation of mandelic acid derivatives and basic drug enantiomers on achiral C18 HPLC column, respectively.[8,9] More CD derivative-based composites were fabricated as CSPs for chiral HPLC. Compared with the additive of 2,6-di-O-methyl-β-CD, the CSP of 2,6-di-O-methyl-β-CD gave better HPLC enantio-separation performance for four phenethylamine enantiomers, indicating the greater efficiency of CSP in chiral HPLC.[10] 3,5-Dichloro-phenylcarbamated mono-6-ethylenediamine-β-CD was covalently anchored on silica particles to achieve HPLC enantio-separation of proton pump inhibitors.[11] To reduce the steps for the preparation of CD-based CSPs, Wang et al.[12] developed a simple one-pot

Special Issue: Fundamental and Applied Reviews in Analytical Chemistry 2023

Published: January 10, 2023

https://doi.org/10.1021/acs.analchem.2c04371
Anal. Chem. 2023, 95, 304−318

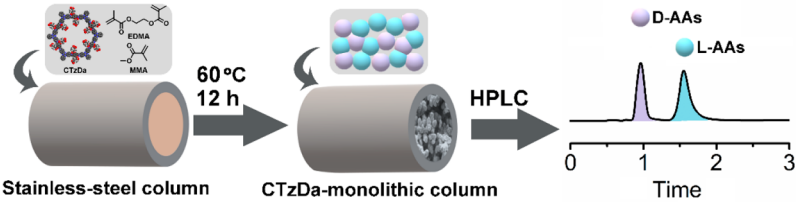

Figure 1. Fabrication of chiral COF-monolith as CSP for enantiomeric HPLC separation of AAs. Reproduced with permission from Qian, H.-L.; Liu, F.; Liu, X.; Yang, C.; Yan, X.-P. Chiral covalent organic framework-monolith as stationary phase for high-performance liquid chromatographic enantioseparation of selected amino acids. *Anal. Bioanal. Chem.* **2022**, *414*, 5255−5262 (ref 5). Copyright 2022 Springer Nature.

strategy to prepare anhydride-linked β-CD-bonded silica as the CSP for HPLC and obtained baseline separation of 17 kinds of enantiomers. A supramolecular dimer called bridged bis(CD) prepared from two single CD units is also promising in chiral molecular recognition. However, bridged bis(CD) has been rarely studied as HPLC CSPs for enantio-separation. Zhang et al.[13] reported the preparation of a new bridged bis(β-CD) via thiol−ene click reaction of allyl-ureido-β-CD and 4-4′-thiobisthiophenol. The obtained bridged bis(β-CD)-based column gave excellent resolution of 1.50−4.48 for 19 enantiomers under synergistic interactions of inclusion effect, hydrogen bonding, and $\pi-\pi$ interaction.[13]

Polysaccharide derivatives are also promising candidates for HPLC CSPs.[14−19] A series of amylose derivatives including amylose tris-[(S)-α-methylbenzylcarbamate], 2,3-bis(3,5-dimethylphenylcarbamate)-amylose, and amylose tris(3,5-dimethylphenylcarbamate) were covalently bound on silica particles and further packed into a stainless steel column for HPLC separation of α-lipoic acid/α-dihydrolipoic acid, chiral drugs, and nonsteroidal anti-inflammatory drugs, respectively.[20−22] Mixed-mode HPLC shows potential in the separation of complex analytes owing to its multiple separation mechanisms. In this regard, a C18 ionic liquid and cellulose cofunctionalized silica packed column was prepared for mixed-mode (reverse-phase/chiral) HPLC separation of hydrophobic and ionic compounds as well as racemates, including warfarin, 1-phenyl-1-propanol, ketoprofen, and styrene oxide, indicating the great potential of cellulose derivative-based multimode CSPs in chiral separation.[23] Generally, the valid content of polysaccharide-based CSPs is always within 20%, greatly limiting the performance of chiral separation. The condensation of cellulose tris(3,5-dimethylphenylcarbamates) and tetraethyl orthosilicate can give the cellulose derivative-based hybrid bead-type CSP with more than 20% valid chirality. The chiral separation ability of the hybrid bead-type CSP was better than that of a commercial cellulose tris(3,5-dimethylphenylcarbamate)-based column.[24] The chiral chondroitin sulfate A (CSA) was also covalently immobilized into a monolithic matrix to obtain CSA-based CSP for chiral HPLC separation of amlodipine and verapamil. The baseline resolution (R > 3.0) of the selected analytes was achieved on the CSA-based monolithic column within 7 min.[25]

Although the application of crystalline porous frameworks including COFs, MOFs, and POCs as CSPs for HPLC is still in its infancy, the remarkable potential of these materials in chiral HPLC separation is hard to ignore. The porous, ordered, and crystalline properties make COFs excellent candidates for CSPs, but the irregularity and nonuniform size of COF particles blocked the applications for HPLC. For these reasons, Xie et al.[4,26] prepared two core−shell chiral COF-functionalized SiO_2 composites (chiral COF@SiO_2), which overcame the limitations of the low column efficiency and high column backpressure of irregular COF-based HPLC columns. The prepared chiral COF@SiO_2 packed HPLC column successfully separated various racemates of alcohols, ketones, acids, esters, and olefins. In addition, mono-6-O-(p-toluenesulfonyl)-β-cyclodextrin (CD-Ts) was reacted with COF functionalized SiO_2 to form the CSP of COF@CD@SiO_2 for HPLC. A rapid and efficient chiral resolution of six racemates on COF@CD@SiO_2 packed column was also described.[27] The fabrication of COF-monolithic column is another available method to achieve the application of COF for chiral HPLC. A chiral COF (CTzDa) was incorporated into the permeable monolith, consisting of ethylene dimethacrylatemethyl and methacrylate, to fabricate CTzDa-monolithic column for efficient enantio-separation of selected amino acids with better resolution than commercial Poroshell 120 chiral-T column (Figure 1).[5]

The small particle size of MOFs greatly restricts MOF as HPLC CSPs. The 5 μm-sized spherical crystalline MOF (Co-MOF-74) was prepared via controlling the synthetic conditions, including temperature, concentration of reactants, and synthetic route. Then, L-tyrosine (L-Tyr) was functionalized on Co-MOF-74 to prepare the HPLC CSP of Co-MOF-74-L-Tyr to give superior enantio-resolution of eight chiral drugs or intermediates.[6] The combination of MOFs and organic polymers can efficiently enhance the ability of molecular recognition and separation. Therefore, a core−shell chiral polyaniline@MIL-101 composite (MIL-101@c-PANI) was fabricated for chiral HPLC separation. The results showed the MIL-101@c-PANI-based packed column separated more chiral compounds than the commercial tris(3,5-dimethylphenylcarbamoyl) amylose-packed column.[28]

POCs are soluble porous materials linked with cage-like monomers.[29] The formed inherent cavities are of benefit to the host−guest interaction and chiral recognition, but the exploration of POCs as HPLC CSPs is rare. Yuan et al.[7] immobilized a chiral POC (NC1-R), consisting of 3,3′,5,5′-tetraformyl-4,4′-biphenyldiol and (1*R*,2*R*)-cyclohexanediamine, on uniform silica particles to prepare NC1-R@silica as CSP. The prepared NC1-R@silica-based column gave better chiral separation than commercial Chiralpak AD-H and Chiralcel OD-H columns, demonstrating the potential of chiral POCs in HPLC enantioseparation.[7]

Chiral mesostructured inorganic materials with hierarchical chiral structures are emerging CSPs. Li et al.[30] fabricated the composites of chiral mesostructured hydroxide zinc carbonate with three levels of hierarchical chirality and silica (CMHzC@S). The prepared CMHzC@S-based HPLC column exhibited good enantio-separation of α-phenylethylamine,1-phenyl-1,2-ethanediol, and 2-chloropro-pionic acid.

Instead of exploring novel CSPs, developing two-dimensional LC can improve the chiral HPLC performance. Three

https://doi.org/10.1021/acs.analchem.2c04371
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polysaccharide (amylose/cellulose) chiral columns as the first-dimension in conjunction with a C18 or phenyl−butyl silica column as the second-dimension successfully achieved baseline separation of multiple chiral pesticides in a single-run analysis.[31]

Gas Chromatography. Like HPLC, the development of novel CSPs is also the main direction of chiral GC separation in the last two years. Functional COFs, hydrogen-bonded organic frameworks (HOFs), and POCs were devoted as CSPs for GC.[32−38] The excellent thermal stability and porosity make COFs promising as GC CSPs. Guo et al. developed a "thiol−ene" click approach to prepare an S-N-(2-mercaptoethyl)-2-phenylpropanamide functionalized COF (CTzDva).[33] The obtained chiral COF was then dynamically coated on the inner wall of a fused silica capillary. The prepared CTzDva-based capillary column gave better GC enantio-separation of the racemates of fenchone and citronellal than two commercial chiral capillary columns (Cyclosil-B and CP-Chirasil Dex CB). Moreover, β-CD-modified COF (β-CD-COF) was prepared and dynamically covered on a capillary. The fabricated β-CD-COF-capillary exhibited great GC resolution for the enantiomers of alcohols, aldehydes, ethers, and amino acid derivatives.[34]

Since both GC and HPLC have potential in the field of chiral separation, it is of great significance to prepare CSPs for simultaneously serving GC and HPLC. Two new highly stable olefin-linked COFs with chiral crown ether groups were designed and prepared as CSPs for both GC and HPLC.[37] The olefin-linked chiral COFs CSP showed excellent enantio-separation of amino acids, esters, lactones, alcohols, and drugs in GC as well as normal-phase or reversed-phase HPLC mode (Figure 2).[37]

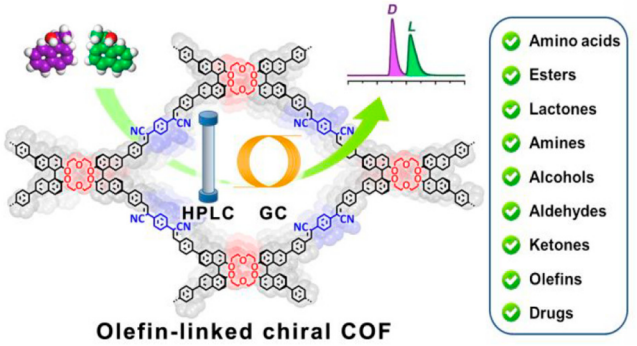

Figure 2. Preparation of olefin-linked chiral COF as CSP for HPLC or GC of chiral compounds. Reproduced with permission from Yuan, C.; Jia, W.; Yu, Z.; Li, Y.; Zi, M.; Yuan, L.-M.; Cui, Y. Are highly stable covalent organic frameworks the key to universal chiral stationary phases for liquid and gas chromatographic separations? *J. Am. Chem. Soc.* **2022**, *144*, 891−900 (ref 37). Copyright 2022 American Chemical Society.

The good solubility of POCs with an inherent cavity makes POCs easily coated on the inner wall of a capillary. The homochiral NC1-R was successfully dissolved in dichloromethane and polysiloxane OV-1701, then covered on a capillary to give an NC1-R coated capillary.[35] Good resolution of racemates (alcohols, esters, ethers, etc.) which cannot be separated on a commercial β-DEX 120 column was achieved on the NC1-R coated capillary, indicating the high potential of POCs as GC CSP.[35] In addition, a chiral metal organic cage (MOC-PA) prepared from 1,4,5,8-naphthalenetetracarboxylic-dianhydride, L-phenylalanine, and $Cu(NO_3)_2{\cdot}3H_2O$ was also reported as CSP for GC separation of various enantiomers including ethers, esters, and amino acid derivatives.[32,39]

HOFs are crystalline porous materials constructed with organic monomer via hydrogen bond rather than covalent bond. The rich hydrogen bonding interactions in HOFs promote the ability of the enantio-separation. An HOF-2 prepared with R-1,1′-bi-2-naphthol derivative and 2,4-diaminotriazinyl was coated on a capillary to give a chiral HOF-2-based capillary for GC separation of enantiomers. Although the enantio-separation performance of HOF-2-based capillary is a little unsatisfactory, this work offers a preliminary example for HOFs as CSPs in GC.[38]

Commercial GC CSPs still play a major role in developing available analytical methods for significant chiral compounds.[40] Terpenoid enantiomers exhibit great difference in odor. Chandan et al.[41] developed a simple and sensitive chiral GC method for terpenoid enantiomers with various commercial CD-based CSPs, including 2,3-disubstituted ethyl- and acetyl-CD, and permethylated CD. The developed method achieved baseline separation for selected enantiomers with the selectivity of 1.004−1.050 in essential oils.[41] The cyclic secondary amino acid enantiomers with rigid conformation are significance for the structure of protein. An economical GC-MS analytical method based on a commercial Chirasil-L-Val capillary column was developed for secondary amino acid enantiomers and successfully applied in the analysis of chiral proline and collagen in human biofluids.[42]

Supercritical Fluid Chromatography. Different from the development of novel CSPs in HPLC and GC, chiral separation by SFC mainly focuses on the establishment of efficient methods for the chiral analysis of significant compounds including bioanalytes, drugs, and pesticides with commercial chiral columns. A supercritical fluid extraction-SFC-triple quadrupole MS (SFE-SFC-QQQMS) was developed for the determination of chiral metholaxin, benzoyl, and dimethylamine in hemp seeds with the LODs of 0.04−0.41 μg kg^{-1} on a commercial ChromegaChiral Column (Merck Life Science).[43] In addition, chiral pesticides of mefentrifluconazole, *N*′-nitrosonicotine, and fluindapyr were successfully separated and determined by SFC on commercial vancomycin (VancoShell), Chiralpak (Illkirch Cedex), and Chiralcel (Daiecl) columns.[44−47] SFC is an ideal technology for the separation and purification of chiral drugs owing to its short separation time and high sample throughput. Hayes et al.[48] built a microscale SFC-based purification platform via the alteration of fluid channel and introduction of gas−liquid separators for the discovery and analysis of pharmaceuticals on ChiralPak Column (Westchester). More drug racemates of β2-agonist of terbutaline, β-blockers, antidepressant drug of paroxetine hydrochloride, and borneol lipid (candidate drug for cerebrovascular disease) were also efficiently resolved by SFC.[49−54] The coupling of different chiral columns can provide great opportunity to increase the separation efficiency of SFC.[55] A two-dimensional chiral SFC based on two different CSPs of amylose tri-(3,5-dimethylphenylcarbamate) and cellulose tris (4-methyl-benzoate) was applied to chiral separation of aliphatic acid derivatives.[56]

Besides HPLC, GC, and SFC, high-speed counter-current chromatography with HP-β-CD as chiral selector was reported for enantiomeric separation of α-substituted propionic acid.[57] Simulated moving bed chromatography with chiral stationary

https://doi.org/10.1021/acs.analchem.2c04371
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phase of amylose tris(5-chloro-2-methylphenylcarbamate) was also applied for chiral separation of amide *N*-(2-methylbenzyl-phenylglycinamide).[58] Moreover, the nanocomposites of β-CD and 3D graphene were introduced into silica slurry for thin-layer chromatography (TLC) separation of fluoxetine enantiomers.[59] Similarly, the racemate of acetylbutanol was separated by TLC with colistin sulfate as the chiral selector.[60]

CAPILLARY ELECTROPHORESIS

Capillary electrophoresis (CE) remains a popular technique for the enantio-separation of biologically active compounds. The majority of studies for chiral CE in this review period involve the application of stable, soluble, and ionizable CDs as chiral selectors for enantio-separation. In addition to the commercial chiral selectors of CDs derivates (CM-β-CD and native β-CD),[61−68] several novel functional CDs were prepared for the chiral CE analysis of significant compounds. HP-β-CD was applied as chiral selector to develop a CE-MS method for enantio-separation of botanical drugs. The method enabled direct determination of the enantiomers of tetrahydropalmatine and canadine in the complex samples of Corydalis Rhizoma with low LOD of 0.017 μg g^{-1} and good recovery of 89.1%−110.0%.[66] Sulfated-β-CD (S-β-CD) and sulfobuthylether-β-CD sodium (SBE-β-CD) were used in chiral CE separation of racemic bioactive ferrocene-modified azoles and chiral fluoroquinolones, respectively.[69,70] Ionic liquid modified SBE-β-CD was also prepared to give a superior CE enantio-separation for racemic drugs to original SBE-β-CD.[71] Sulfated-γ-CD (HS-γ-CD) was employed as CE chiral selector to investigate the enantioselective biodegradation of citalopram and verapamil.[72] A series of positively charged *N*-heterocyclic CD derivatives were prepared for enantio-separation of 22 ionic model analytes. Compared to native β-CD and acyclic amino modified β-CD, chiral *N*-heterocyclic CD derivatives were good at chiral CE separation of selected negatively charged and zwitterionic racemates.[73]

Chiral ionic liquid (CIL) is another class of important chiral selectors for CE owing to its good stability and water solubility as well as low volatility. A series of tetraalkylammonium-L-tartrate ionic liquids (TAA-L-TT) were prepared as the chiral selector, and they achieved better CE enantio-separation of model enantiomers than TT ester-type chiral selectors.[74] Moreover, Zhang et al.[75] designed and synthesized alkylphosphonium, alkylpiperidinium, and alkylpyrrolidinium-type CILs as the CE chiral selectors. This work not only offered an efficient CE method for chiral amino alcohols but also enriched the chiral selectors of CILs for CE.

The mixture of different chiral selectors was further applied in CE analysis to enhance chiral separation. The dual chiral−achiral selector complex of HP-β-CD and 5,10,15,20-tetrakis-(4-tydroxyphenyl) porphyrin was employed in CE analysis of chiral aminoalkanol derivatives (anticancer agent). The proposed CE method gave the LODs of 65.1−65.7 ng mL^{-1} and recoveries of 94.9%−99.9%.[76] The combination of multiple chiral additives is still the main direction. Chiral crown ether (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (18C6) in conjunction with α/β-CD was used in CE separation of three racemates of amino acids. The combination of β-CD/18C6 allowed baseline enantio-separation of phenylalanine and tyrosine, which cannot be achieved with only β-CD or 18C6.[77] The synergism of (2-hydroxy-3-N,N,N-trimethylamino)propyl-γ-CD and CM-β-CD successfully resolved short chiral oligonucleotide in CE.[78] The combination of amino acids-derived CIL with β-CD/HP-β-CD resulted in concentration-dependent promotion in the enantio-separation of dipeptides.[79] The dual chiral selectors of trifluoroacetatehydroxyproline/glucosyl-β-CD (Glu-β-CD) gave the best chiral CE separation of model drug enantiomers among single Glu-β-CD, nitric acid hydroxyproline/Glu-β-CD, and trifluoroacetate-L-threonine/Glu-β-CD, indicating that chiral performance was largely related to the type of amino acid.[80] The tetrabutylammonium bromide/L-arginine/β-CD-based CE methods showed great resolution of 4.78−9.84 for methionine, valine, serine, and threonine.[81] The application of the mixture of three chiral selectors consisting of vancomycin/tryptophan/Hp-β-CD was also investigated for chiral CE separation of pharmaceutical compounds.[82]

CAPILLARY ELECTROCHROMATOGRAPHY

Capillary electrochromatography (CEC) is an efficient and fast technique for the analysis and separation of chiral compounds owing to the equipment of the stationary phase on the capillary compared with typical CE. Thus, the main investigation of chiral CEC in this review period is to fabricate a chiral open-tubular column or monolithic column with novel CSPs. The most popular CSPs in CEC are still CD derivatives. Various functional CD derivatives including HP-γ-CD, β-CD, ethanediamine-β-CD, CE-β-CD, and SBE-β-CD were applied to enantio-separation of chiral drug, dansyl-amino acids, etc.[83−89] In addition, porous organic materials, enzymes, and antibiotic-based CSPs are also promising.[90−93]

CD derivatives were incorporated with other chiral CSPs to promote the enantio-resolution performance of CEC. The dual CSPs of β-CD and bovine serum albumin (BSA) were synthesized for chiral CEC separation of proton-pump inhibitors with high resolutions of 4.75−7.11. More than ten racemates were separated on the dual CSPs-based column, which cannot be realized on a single CSP of β-CD or BSA-based column.[94] β-CD and L-phenylalanine (L-Phe) were also coupled with zeolite silica nanoparticles as the CSP of open-tubular capillary column for CEC. The developed method gave low LODs of 0.015−0.90 μg mL^{-1} and good recovery of 80.6%−117.3% for the enantiomers of catechu herbs and salbutamol in real sample matrixes.[95]

CD derivatives were also used as the chiral functionality units to modify other achiral materials to obtain novel CSPs for CEC. Sulfydryl-β-CD was functionalized onto the gold nanoparticles−graphitic carbon nitride to obtain chiral CSP (CD-GNPs-*g*-C_3N_4). The column efficiency of the CD-GNPs-*g*-C_3N_4-based open tubular capillary reached 1.2×10^5 plates m^{-1} for model chiral drugs.[96] A CEC-ESI-MS method for the enantiomers of amino acids was developed with a thiol β-CD modified three-dimensional porous layer as CSP. Baseline separation of 15 racemates of amino acids on the prepared CSP was achieved (resolutions of 1.51−10.0) with column efficiencies of 5.6×10^4−1.8×10^6 plates m^{-1}.[97]

Other conspicuous CSPs in CEC are chiral MOFs. The histidine functionalized zeolitic imidazolate framework (His-ZIF-67) was anchored on the inner wall of the capillary and further modified with NH_2-β-CD. The obtained NH_2-β-CD@His-ZIF-67-based capillary column gave baseline enantio-separation of amlodipine (R = 1.7) and metoprolol (R = 1.7).[98] L-His was also incorporated with zeolitic imidazolate framework (ZIF-8) to give a homochiral L-His-ZIF-8-based open-tubular column for CEC.[99] The proposed chiral analytical method was successfully applied for the determi-

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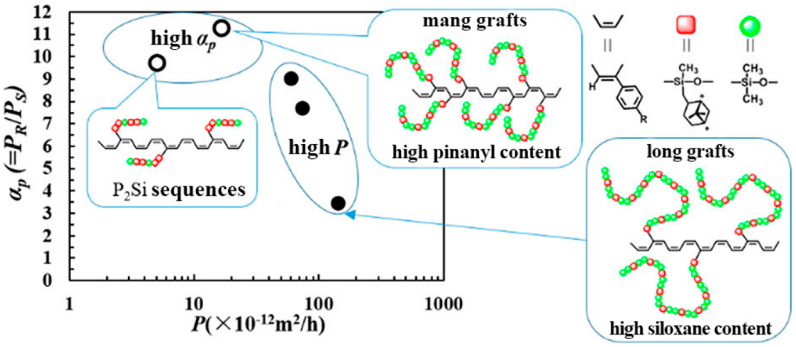

Figure 3. Preparation of a series of chiral graft copolymers with flexible chiral oligomethylpinanylsiloxane grafts and a rigid poly(phenylacetylene) backbone for chiral membrane separation. Reproduced with permission from Zang, Y.; Aoki, T.; Teraguchi, M.; Kaneko, T.; Ma, L. Q.; Jia, H. G.; Miao, F. J. Synthesis of well-defined chiral oligopinanylsiloxane graft copoly(phenylacetylene)s using the macromonomer method and their enantioselective permeability. *ACS Appl. Polym. Mater.* **2020**, *2*, 853−861 (ref 129). Copyright 2020 American Chemical Society.

nation of salbutamol aerosol in real samples with the LOD of 0.9 μg mL^{-1} and recovery of 80.4%−82.7%.[99] Other homochiral L-His-modified MOF (L-His-NH-MIL-53) and L-cysteine (L-Cys) functionalized MOF (L-Cys-PCN-222) based capillaries were also efficient for CEC enantio-separation of chiral amino acids.[100,101] The water instability dominantly limits the development of chiral CD MOFs as CSPs in CEC. Thus, Fe^{3+} was introduced to assemble with γ-CD for the synthesis of a homochiral iron-based γ-CD MOF (Fe-CD-MOF). The high charge density of Fe^{3+} was a benefit for the coordination of MOFs and γ-CD, rendering the high water-stability of Fe-CD-MOF.[102] The novel homochiral Fe-CD-MOF was also successfully applied in the CEC separation of chiral drugs. In addition to the open-tubular capillary column, the chiral MOF-based monolithic column is also practicable. Pepsin bonded MOF-5 and cellulase functionalized UiO-66-NH_2 were incorporated to an organic monolithic matrix to form the chiral MOF-monolithic capillary column for CEC separation of chiral drugs.[103,104]

Chiral COFs as the CSPs for CEC are still in their infancy. A novel chiral COF CB-DA COF, consisting of (S)-1,3,5-tri(4-aminophenyl)-2-(2-methylbutoxy)benzene (CB) and 2,5-dimethoxyterephthalaldehyde (DA), was covalently bound on amino or epoxy group functionalized silica capillary. The prepared CB-DA-COF-based capillary exhibited great enantio-resolution of chiral drugs including terbutaline, propranolol, phenylephrine, verapamil, norepinephrine, and isoprenaline.[105,106] Diphenylmethane diisocyanate-β-CD (MDI-β-CD) modified 1,3,5-triformylphloroglucinol was condensed with p-phenylenediamine to produce a chiral COF of MDI-β-CD-COF. The excellent chiral recognition of MDI-β-CD in conjunction with the unique structure of COF provided MDI-β-CD-COF superior enantioselectivity for atenolol and amlodipine besylate. The prepared CEC method obtained low LODs of 0.55−0.98 mg L^{-1} for the targets.[107]

Molecularly imprinted polymers (MIPs) are also ideal CSPs owing to their tailor-made selectivity. HP-β-CD was employed as the template to prepare chiral MIP as the coating of the capillary for efficient CEC separation of chiral drugs and amino acids.[108] Moreover, an S-citalopram MIP-based monolithic column was synthesized with the template of S-citalopram, the monomer of N-methacryloyl-(L)-phenylalanine methyl ester, and the cross-linker of ethylene dimethacrylate. The prepared monolithic CEC column gave a selectivity factor of 2.08 for the racemates of citalopram.[109]

The incorporation of a chiral selector into the achiral stationary phase is also an efficient approach for CEC enantio-separation.[110,111] Nanoparticles of poly(glycidyl methacrylate) (PGMA NP) were coated on the capillary to increase the separation efficiency of the chiral selector. The obtained PGMA NP-based column with azithromycin lactobionate and clindamycin phosphate as the chiral selector gave a high column efficiency of the selected drugs (1.2 × 10^5 plates m^{-1}).[112] The MOF-like metal organic polymer 4,5-IMD-Zn prepared from imidazole-4,5-dicarboxylic acid and $Zn(NO_3)_2$ was covalently bonded on the capillary for enantio-separation of chiral drugs with CM-β-CD as the chiral selector.[113]

MEMBRANE SEPARATION

Membranes with enantioselective permeability are another common separation media. Compared with chromatographic separation techniques that are usually performed in an analytical scale, membrane separation has greater potential for large preparative scale separation (more than kilogram level) in pharmaceutical and chemical engineering fields.[114,115] Conventional chiral membranes are prepared from polysaccharides (chitosan and cellulose), sodium alginate, poly(substituted acetylene), poly(amino acids), and lipids.[116−119] Industrial application for most chiral membranes is still difficult because of insufficient enantioselectivity under high flux following the facilitated transport mechanism. Because the performance of membranes essentially depends on different interactions between enantiomers and chiral discriminating units of membranes during transport process, the exploration of new chiral materials with high selectivity, excellent permeability, good stability, and long-time operation has been the main focus in recent years, represented by improved polymers, porous crystalline materials, carbon nanomaterials, and micro/nanochannels.[120−125] These up-to-date membrane materials have continued to grow for chiral separation in the past two years. Furthermore, the transport from facilitated mechanism to retarded mechanism has been discussed based on new materials.[126]

Graft copolymers[127] and conjugated microporous polymers (CMPs)[128] have received much attention in recent years. These materials contribute to more intrinsic and controllable chiral pores in polymer membranes to improve both selectivity and permeability. Graft copolymers possess superior adsorption chiral selectivity, diffusivity, strength, and durability. A series of chiral graft copolymers were prepared with flexible

https://doi.org/10.1021/acs.analchem.2c04371
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chiral oligomethylpinanylsiloxane grafts and a rigid poly(phenylacetylene) backbone by Zang and Aoki et al. (Figure 3).[129] The copolymer with the highest amount of grafts presented the highest selectivity value for the separation of racemic mandelic acid, and the permeability was 100 times higher than that of the chiral homopolymer. Triptycene-based polyimides are also popular materials with high porosity and intrinsic chirality. Zhang and Wang et al. employed R,R-2,6-diaminotriptycene and S,S-2,6-diaminotriptycene as monomers to synthesize a couple of chiral porous polyimides and porous membranes. These membranes exhibited high permeability and high e.e. value of 96.3% for *rac*-Binol.[130] CMPs are organic porous polymers with abundant permanent nanoporous structures, large surface area, and low density. Multiple aromatic structures in CMPs make them suitable for the separation of chiral aromatic compounds. For example, Huang et al.[131] combined a thin film of chiral CMPs with porous SiO_2 support layer, providing a simple method for improving permeability (2.07×10^{-5} m^2 h^{-1}) and selectivity (94.1% e.e. for racemic phenylalanine).

Nanofibers that provide chiral void spaces are promising to prepare chiral membranes, while electrospinning has become the breakthrough technique for the preparation of nanofibers.[132] The membranes of nonwoven texiles formed from the electrospun fibers with the diameters ranging from several nanometers to a few micrometers distinctly offer about 200-fold larger specific surface area than typical porous polymer membranes.[133] In addition to peptides, preparing chiral nanofibers was tried with celluloses. Otsuka et al.[134] used cellulose tris(3,5-dimethylphenylcarbamate) to fabricate nanofiber-based nonwoven textile with a specific surface area of 5.6 m^2 g^{-1} for the enantioselective permeation of the racemic mixture (R,S)-1-(1-naphthyl)ethanol via fast vacuum filtration. Furthermore, composite materials containing chiral polymetric nanoparticles based on leucine, phenylalanine amino acids, or polysulfone were used to prepare interwined electrospun membranes for the separation of leucine.[135] These nanofiber-based membranes are easily prepared and have potential for large-scale preparation, but the enantioselectivity is still not satisfied with e.e. values from 10% to 30%.

Various chiral recognition molecules, also called chiral selectors similar to CSPs, such as CDs and their derivatives,[136−140] and Pirkle-type molecules,[141] are important components for many chiral polymer membranes. Chiral selectors can be grafted to the membrane network or copolymerized with polymer materials. Positively charged β-CD derivatives and cationic CD derivatives were ionically bound to nafion membranes.[136,137] Ke et al.[139] reported an interfacial polymerization method by using diethylamino-β-CD monomer and trimesoyl chloride to form a composite polyamide membrane. α-CD was also mixed with m-phenylenediamine monomer for interfacial polymerization.[138] With the increase in the content of chiral selectors in the membrane, the transport mechanism in the membrane changed from facilitated to retarded transport due to the increased strength of binding interactions between selectant and chiral selectors. Membranes with retarded transport mechanism theoretically have no inverse relationship between permeability and selectivity, thus affording high flux. The polyamide membrane maintained acceptable chiral separation performance under a high water permeate flux of 35.7 L m^{-2} h^{-1}.[139]

Porous crystalline materials, such as zeolites,[142] chiral MOFs,[143] and chiral COFs,[144] expand the scope of membrane materials for chiral separation. Their large specific surface area, well-defined pore size, and adjustable chiral functional sites help to achieve both high selectivity and permeation. Membranes based on porous materials provided 1−2 orders of magnitude higher flux than traditional polymer membranes.[121] Since these crystalline materials are difficult to form into a macroscopic defect-free membrane, the mixed matrix membranes (MMMs) and thin-film nanocomposite membranes (TFNs) are two types of membranes with porous crystalline materials.

Enantioselective MMMs mixed achiral polymer matrix and homochiral porous fillers to provide the advantages of both solution-processability of polymeric matrix and high enantioselectivity and permeability of porous fillers.[120] Choi et al.[145] reported an MMM fabricated by mixing L-His-ZIF-8 and Torlon for the chiral separation of 1-phenylethanol. The fabricated membrane had much larger permeability of 53.84×10^{-6} L m^2 h bar^{-1} (25 wt % MMM) than Torlon dense membrane with the permeance of 4.52×10^{-6} L m^2 h bar^{-1}. The 25 wt % membrane had the smallest interfacial void among the casted MMMs but gave the optimal e.e. value of only 3.63%.

CD-MOF and CD-COF were also introduced to MMMs. A new strategy was developed to prepare MMMs using homochiral porous fillers and common membrane polymers.[146] A 20 wt % CD-MOF loading was tested to achieve a stable and high enantioselectivity for the separation of one enantiomer of 1-phenylethanol from the racemic mixture. Luo et al.[147] used β-CD COF as the chiral selector to fabricate β-CD COF MMM with cellulose acetate. The solute flux using the β-CD COF MMM was about 40 nmol cm^{-2} h^{-1}, and the e.e. varied in the range of 34.0%−36.6%.

Enantioselective TFNs are composed of porous polycrystalline thin films on substrate membranes, usually prepared by one-pot solvothermal film on the substrate or a layer-by-layer synthesis based on liquid-phase-epitaxy.[148] Compared to MMMs that might suffer from the block of chiral pores and the formation of achiral pores, TFNs can achieve a chiral recognition thin film with less chiral pore defects and a better selectivity. Luo et al.[147] also prepared the β-CD COF TFN and compared it with β-CD COF MMM. β-CD COF TFN achieved an optimal enantioselectivity of D,L-tryptophan (e.e. = 100%), but the flux β-CD COF TFN was only 1.9−5.4 nmol cm^{-2} h^{-1}. Chiral covalent triazine frameworks are a novel type of COFs. Chen et al. prepared novel two-dimensional chiral covalent triazine framework membrane by an "in situ growth" method on porous quartz fiber membrane. This membrane enabled the high-flux enantiomer separation of drug intermediates and drug, such as R/S-1-phenylethanol (e.e. = 21.7%).[149] It seems that either MMMs or TFNs are difficult to achieve both high selectivity and permeability. These types of membranes obviously cannot meet the requirements of industrial production and need to be further optimized from membrane fabrication to improve the selectivity, permeability, and other mechanical properties.

Carbon nanomaterials, including fullerene, graphene/graphene oxide (GO)/reduced graphene oxide (rGO), carbon nanotubes (CNTs), and graphene quantum dots (GQDs), are a promising category of membrane materials. Compared to conventional polymer membranes, carbon-based materials have exceptional atomic thickness, lamellar 2D structure, high thermal and chemical stability, antifouling property, and high tensile strength for better chiral separation perform-

https://doi.org/10.1021/acs.analchem.2c04371
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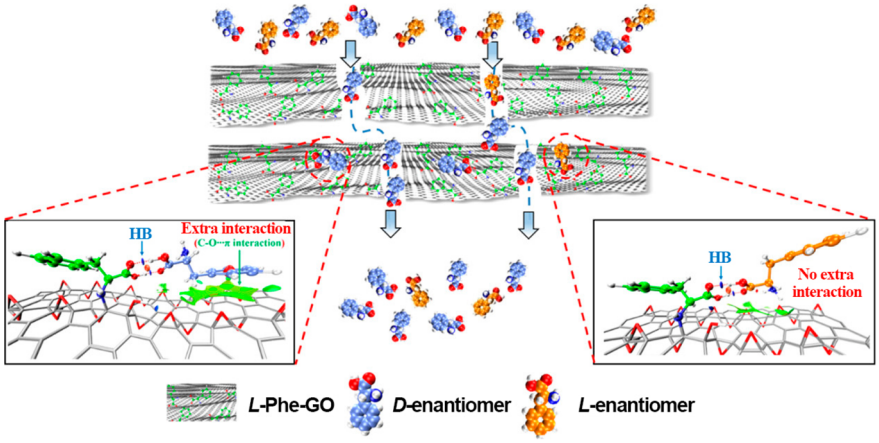

Figure 4. Interaction between enantiomers and chiral amino acid modified graphene oxide membranes. Reproduced with permission from Meng, C. C.; Zhang, S. Z.; Chen, Q. B.; Li, X. X.; Liu, H. L. Influence of host−guest interaction between chiral selectors and probes on the enantioseparation properties of graphene oxide membranes. *ACS Appl. Mater. Interfaces* **2020**, *12*, 10893−10901 (ref 156). Copyright 2020 American Chemical Society.

ance.[122] Most carbon materials work as the achiral supporting membrane, especially GO[150−152] and rGO,[153] and the abundant functional groups can be modified with chiral selectors, such as CDs, chiral amino acids, peptides, and other chiral compounds. Ethylenediamine-β-CD modified GO membrane exhibited extraordinary enantioselectivity with high percent e.e. of tryptophan (100.00%) and propranolol (75.34%). Because GO nanosheets have a multilayer structure and an interlayer spacing, it not only provided binding site in the membrane but also improved permeation flux to 3.3 L m^{-2} h^{-1} bar^{-1} for water.[154] The dipeptide-modified GO membranes exhibited a maximum separation factor of 1.85 with a 1−3 orders of magnitude improved flux compared to conventional chiral separation membranes.[155] Besides chiral selectors, achiral GO substrates further provide nonstereoselective interactions between chiral molecules and the GO surface to improve the enantioselectivity of GO-based membranes (Figure 4).[156] Many recent works presented an interesting reversal for transport mechanism of GO membranes from facilitated to retarded.[157−159] That is one of the reasons GO-based membranes get the most attention. Interlayer distances and size are two significant graphene-related parameters for membrane separation. Decreasing the interlayer distance resulted in a conversion from the facilitated to retarded mechanism at a medium external force, while both the large and small driving forces only led to the appearance of the retarded transport for preferential enantiomer.[160] Lateral size of GOs also play a dominant role in the enantioselectivity of membrane separation. Compared with smaller-size GO sheets (about 60−650 nm), larger GO sheets (about 4100 nm) achieved much better selectivity (α > 1.5) with a slightly decreased flux.[161]

Besides as substrates, direct chiral construction on carbon nanomaterials was tried as a simple and highly efficient way to obtain chiral carbon membranes. A new strategy was reported by Tan et al.[162,163] to fabricate a chiral porous graphene membrane from nonchiral porous graphene. The porous graphene with controlled and nanosized pores was immobilized on an ultrafiltration membrane for enantioselective separation of D/L-amino acids, achieving high separation factor of 4.76 for D/L-phenylalanine. CNTs have also been functionalized with chiral selectors and used as substrates to achieve chiral separation.[153,164,165] Chiral CNTs were synthesized as a unique type of chiral nanomaterial,[166,167] but they were never applied for chiral membranes because of the difficulty of obtaining pure chiral CNTs.

Micro/nanochannel membranes based on polymer and inorganic materials were prepared on a large scale as separation membranes. These materials have abundant ordered channels with diameters ranging from nano- to micrometers.[168,169] Microchannel membranes with relatively large channel size are adapted to high flux, but the enantioselective separation in the channels need specific design. Feng and Zhang et al.[170] incorporated chiral gold nanoparticles into a microchannel polycarbonate membrane to astringe the large pores and improve the enantioselectivity. The chiral Au NP-coated microchannel membrane showed a selectivity of 5.40 for R-phenylglycinol and a flux of 140.35 nmol cm^{-2} h^{-1}. Nanochannel membranes with nano size channels and chiral selectors provide a small restricted space to obtain high selectivity. Zhang and Chen et al.[171] prepared a β-CD-self-assembled nanochannel membrane that showed chiral transport of S-naproxen and achieved the chiral separation of racemic drugs. Zhang et al.[172] recently reported a proposal to pack chiral COF into nanochannels of polyethylene terephthalate membrane to improve the enantioselectivity of the nanochannel membrane. This L-Tyr-COF packed membrane maintained the large flux of 133 nmol cm^{-2} h^{-1} for large-scale separation of naproxen enantiomers with an e.e. value up to 94.2%. However, large-scale preparation and mechanical properties are still problems for micro/nanochannel-based membranes.

Several other materials, including MIPs,[173,174] hollow fibers,[175] and the composite of multiple materials,[176−180] were also applied for chiral membrane separation. The chiral membrane separation has been rapidly improved in its scale as well as purity toward large-scale industrial use.

MASS SPECTROMETRY

MS is a powerful technique for molecular qualitative and structural analysis. In general, MS identification of molecules by m/z values is unable to discriminate isomers. Even by tandem MS with commonly used fragmentation modes, enantiomers are also difficult to discriminate.[181,182] Never-

https://doi.org/10.1021/acs.analchem.2c04371
Anal. Chem. 2023, 95, 304−318

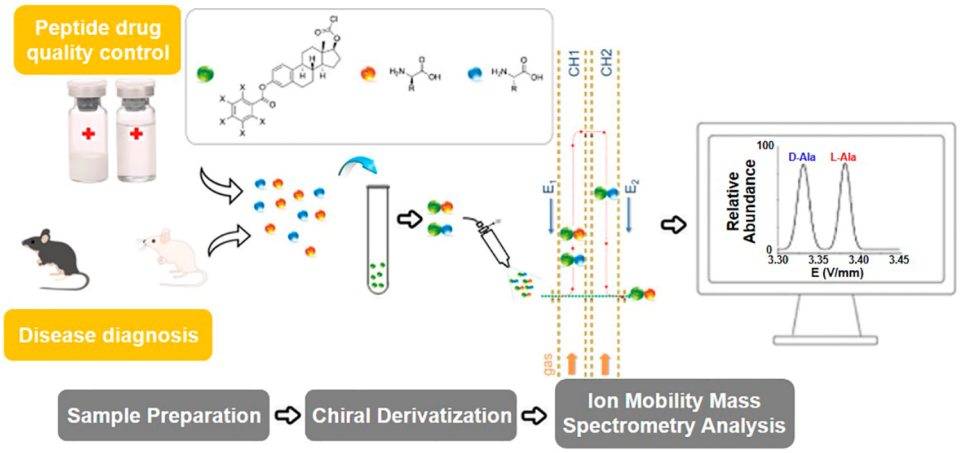

Figure 5. Derivatization of α-hydroxy/amino acids by chiral estradiol-3-benzoate-17β-chloroformates for ion mobility mass spectrometry analysis. Reproduced with permission from Li, Y. L.; Zhou, B. W.; Wang, K. K.; Zhang, J.; Sun, W. J.; Zhang, L.; Guo, Y. L. Powerful steroid-based chiral selector for high-throughput enantiomeric separation of alpha-amino acids utilizing ion mobility-mass spectrometry. *Anal. Chem.* **2021**, *93*, 13589−13596 (ref 89). Copyright 2021 American Chemical Society.

theless, several emerging MS methods, including chemical derivatization, kinetic method, ion mobility-mass spectrometry (IM-MS), and circular dichroism−laser MS, are employed to directly detect enantiomers without the combination of separation techniques. These methods are appropriate for an analysis system incompatible with the separation process, such as samples with a small volume or compounds with a short life.

Chemical derivatization is an important strategy for MS discrimination of enantiomers. It is mostly used to analyze chiral compounds via LC-MS, GC-MS, and CE-MS by transforming enantiomers to diastereomers for easier separation by chromatography.[183,184] However, typical derivatization reagents are normally not capable of selectively labeling enantiomers or bringing weight difference between enantiomers, so direct enantiomer discrimination by MS is difficult to achieve.[185] Therefore, specific derivatization reactions leading to different m/z values of parent ions or product ions for enantiomers are needed for chiral compounds by direct MS detection. Recently, Li et al.[186] used D-α-hydroxy acid dehydrogenase as a special derivatization reagent to specifically recognize and dehydrogenate D-α-hydroxy acids and developed an on-probe enzymatic dehydrogenation derivatization method for chiral analysis of α-hydroxy acids. This method enabled efficient characterization of D-lactate that shared the same mass but had much lower amounts compared with L-lactate in complex single-cell matrixes. Other special derivatization reagents and reactions are still limited for chiral discrimination.

The kinetic method is another major approach to discriminate enantiomers. Generally, it utilizes different signal abundance of diastereomers or their product ions for enantiomer discrimination.[182,187,188] Unlike special m/z values, difference in signal abundance is more easily achieved because most diastereomer pairs present different reaction rates during their formation or fragmentation. So, universal methods to transform enantiomers to diastereomers are necessary for the kinetic method. Many traditional organic derivatization reagents can covalently bind chiral molecules to form diastereomers.[185,189] Metal ion-bound cluster ions are also the reagents of choice in kinetic methods. In this case, R/S-enantiomers and a chiral reference compound are complexed with a transition-metal ion to generate trimeric complex diastereomers. Especially, the chiral reference compound is the key component in complex diastereomers for quantitative measurements. Modified amino acids,[190] fluorodeoxynucleoside,[191] and dipeptides[192] are commonly used as reference compounds. Huang et al.[193] recently demonstrated disaccharides as new reference compounds. With disaccharides and Cu^{2+}, tyrosine and naproxen enantiomers were observed to show the best chiral selectivity and good linearity between the logarithm of intensity ratio against the e.e. value. Nakakoji et al.[194−196] developed two deuterium-labeled and unlabeled chiral copper(II) complexes for chiral amino acid measurement. The intensity excess value based on the two complexes was quantitatively against the e.e. value of amino acids. These kinetic methods enabled rapid, sensitive determination of e.e. values for multiple chiral compounds in a short measurement time at a small scale.

IM-MS is an efficient improvement of MS to discriminate enantiomers via the combination of ion mobility spectrometry (IMS) with MS. IM-MS can rapidly separate molecular ions before MS detector based on ion collision cross section (CCS) values that reflect the special size, shape, and charge state of molecular ions in the gas phase.[197−199] However, enantiomers show only little CCS differences under typical IM-MS analysis. Using chiral buffer gas in an ion mobility tube is an ideal way to directly separate enantiomers.[200] In fact, a chiral buffer gas is very difficult to find. Thus, converting enantiomers to diastereomers by derivatization is an alternative method of high-resolution enantiomer separation as diastereomers are highly possible to be baseline-separated by IM-MS with the typical buffer gas.[201,202] Chiral reference-metal ion complexes are the most commonly used derivatization reagents. Different chiral reference compounds (e.g., α-, β-, γ-CD, rifamycin and natamycin)[203,204] and metal ions (e.g., Cr^{3+}, Ba^{2+}, Sr^{2+}, Ca^{2+}, and Mn^{2+})[205,206] were reported to achieve satisfactory separation factors. Furthermore, rigid structures in derivatization reagents or analytes are beneficial for high peak-to-peak resolution ($R_{p\text{-}p}$). For example, R/S-1,1,2-triphenyl-1,2-ethanediol (TPED) were separated with high resolution ($R_{p\text{-}p}$ = 2.08) after forming [natamycin + TPED + Ba−H]$^+$,[203] while R/S-pregabalin obtained high separation resolution ($R_{p\text{-}p}$ = 2.20) after forming [2β-CD + pregabalin + Sr]$^{2+}$.[205] Li et al.[89] used estradiol-3-benzoate-17β-chloroformate for the derivati-

https://doi.org/10.1021/acs.analchem.2c04371
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zation of amino acids (Figure 5) to achieve good enantiomer separation of 19 chiral amino acids in a single analytical run (~2 s). Cooper-Shepherd et al.[207] introduced an interesting method to form diastereomer dimers with aromatic analytes for IM-MS separation. The enantiomers of tryptophan and propanolol were efficiently separated without the need for an extra chiral modifier.

The combination of circular dichroism with laser MS is a specific technique to discriminate enantiomers. In this technique, a polarized femtosecond laser is employed as a type of laser ionization source, and the circular dichroism in ion yield is determined based on MS analyzer to discriminate different conformers of a chiral species.[208,209] However, the measured anisotropies of enantiomers in this way are generally weak considering measurement errors. Witte et al.[210] further improved the circular dichroism-laser MS method by adding a common path optical setup to generate a pair of counter-rotating laser foci in the interaction region before the MS analyzer. The twin-peak ion source led to well-separated and sufficiently resolved mass peaks individually for in situ correction of experimental fluctuations. This robust optical setup produced reliable and reproducible results for the conformer discrimination of 3-methyl-cyclopentanone.

MS-based techniques have been used for direct chiral discrimination, taking advantage of high speed, no need for sample separation, and low sample consumption. However, these techniques rely on specific instruments and are still in the early stage. Elements of a more general workflow, such as universal derivatization reagents and calculation methods, are still on the way.

SENSING

Chiral sensing refers to a large class of chiral analysis techniques for rapid and sensitive discrimination, usually via simple instruments without sample separation in complex matrixes.[126,211] Optical and electrochemical sensing are two main techniques for chiral sensing.

Optical Sensing. Various optical techniques, including electronic circular dichroism (ECD) spectroscopy, fluorescence spectroscopy, and surface enhanced Raman spectroscopy (SERS), are employed for chiral sensing. These sensing techniques are principally based on the host−guest interaction between chiral or achiral selectors and chiral compounds.[212,213] Selectors binding to chiral analytes are constructed to show recognizable and enhanced differential optical signals for enantiomers.

Selectors with chiral rigid structures can effectively enhance the circular dichroism signal of enantiomers for ECD sensing. Acyclic cucurbit[n]urils,[214] molecular tweezers,[214] functionalized helicenoids,[215] pillar[n]arenes,[216] chiral helicates,[217] chiral organic cages,[218] and anionic cages[219] were applied as selectors for ECD sensing. These selectors are efficient chirality selectors for aromatic compounds, but small and polar chiral organic molecules without large aromatic group are challenging to analyze. Naphthotube-based chirality sensors were thus reported with an unprecedented wide scope for the optical sensing of molecules containing no large aromatic group.[220,221] Furthermore, the self-assembled metal nanoparticles with chiral structures, such as magneto plasmonic nanoparticles,[222] gold nanorods[223] and silver nanowires,[224] were also explored as selectors. Interestingly, many metal nanoparticle-based selectors provided chiral plasmonic enhancement up to 100-fold depending on the designed size, shape, and structure of the plasmonic arrays. As a result, these nanomaterial-enhanced chirality sensors gave detection limits as low as attomolar concentration.[225]

Selectors with fluorescent signals are good for fluorescence chiral sensing. Various fluorescent nanomaterials based on single-wall carbon nanotubes,[226] MOFs,[227−229] and quantum dots[230,231] were employed for chiral discrimination in solution phase. Special topological structures of these nanomaterials with analytes contribute to the chiral sensing. For example, a fluorescent, chiral coordination polymer was synthesized with a novel topology for differential interaction with chiral Mosher's acids to provide a special quenching-based fluorescent signal.[232]

Active nanostructures or nanomaterials are also attractive selectors for SERS-based chiral sensing. Compared with other optical techniques, SERS is unique for single-molecule-level sensitivity and information-rich and label-free chiral discrimination.[233] A versatile and chiral-label-free SERS-based chiral discrimination sensing system was established using mixed-thiol self-assembled monolayers and vertically aligned Au nanorod arrays for the chiral sensing of small aromatic compounds including chiral aromatic amines, alcohols, and acids with high molecular fingerprint specificity.[234] Asymmetric nanoporous gold bowl nanoparticles were prepared to achieve direct, label-free SERS sensing of biologically important enantiomers with enantiospecific molecular fingerprints.[235]

Naked-eye recognition of enantiomers with colorimetric chirality sensors is an important development direction for chiral sensing. It displays the obvious advantages of a facile process, quick response, and low requirement for instruments. Rhombic dodecahedron shaped gold nanoparticles,[236] MoO_3 nanoparticles,[237] and fluorescein-substituted polydiacetylene vesicles[238] are newly developed colorimetric sensing materials for the chiral discrimination of chiral carboxylic acids, amino acids, etc. Such methods provided good anti-interference performance in complex matrixes for the enantiomer concentrations from mmol/L to a limit of nmol/L.

Electrochemical Sensing. Electrochemical sensing has obvious advantages of ultrasensitivity, fast response, and specific recognition along with simple and portable setup. Typical electrochemical modes, including linear sweep voltammetry,[239] differential pulse voltammetry,[240] cyclic voltammetry,[241] and electrochemical impedance spetroscopy,[242] were commonly used for chiral discrimination with chiral functionalized electrodes in this review period. Materials with chirality recognition ability and good electrical conductivity are necessary to modify electrodes. Electrically conducting oligomers,[243] chiral MOFs,[244] chiral COFs,[239] helicoid Au nanoparticles,[245] and various composite/hybrid materials are popular to form a chiral recognition layer on electrodes.

The nanopore/nanochannel-based electrochemical sensing technique is popular for chiral sensing with high sensitivity (single molecule[246]) and minimal equipment. The approaches for chiral nanopore/nanochannel construction can refer to the preparation of chiral nanochannel-based membranes. The differential flux of enantiomers through nanopores/nanochannels generates remarkable difference in the transmembrane ion flux, and the ionic transport behavior can be monitored by measuring the $I-V$ property. Asymmetric nanochannels, such as hourglass-shaped nanochannels and cone-shape nanochannels, can enhance the sensitivity for sensing. Zhang et al.[247] developed D/L-tyrosine-incorporated

https://doi.org/10.1021/acs.analchem.2c04371
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hourglass-shaped nanochannels to discriminate naproxen enantiomers with an extremely high enantioselectivity coefficient of 524.

Other techniques, such as quartz crystal microbalance (QCM),[248] scanning probe microscopy (SPM),[249] and atomic force microscopy (AFM),[250] were developed for chiral sensing in this review period. Up to now, various chiral selectors and nanopores/nanochannels have emerged and combined with optical and electrochemical analytical techniques as advanced approaches for chiral sensing. High sensitivity, high selectivity, fast response, and easy operation pursued by the recent sensing methods are still the future direction of chiral sensing techniques.

CONCLUSIONS AND PERSPECTIVES

The separation and analysis technologies for chiral compounds have achieved great progress in the last two years. The exploration of novel porous materials or modification of typical CDs, macrocyclic antibiotics, and polysaccharide as CSPs/chiral selectors has resulted in many enantiomers in pharmaceutics, agriculture, chemistry, and life science being well separated and identified. However, the investigation of chiral separation mechanisms remains insufficient. The development of novel CSPs/chiral selectors is still challenging and significant, particularly for universal chiral separation. Moreover, the cooperation of two-dimensional CSPs/chiral selectors to promote the chiral separation needs urgent and deep study.

From analytical scale to large preparative scale, various chiral membranes, including porous polymers, porous crystalline materials, carbon materials, and composite materials, have been developed for chiral separation in the last two years. Defects in permeability and selectivity for conventional chiral membranes have been improved by using these burgeoning membrane materials. High permeability (1−2 orders of magnitude in comparison to conventional polymer membranes) and selectivity have been achieved for rapid chiral separation of amino acids, racemic drugs, and so on. Besides, important transport mechanism reversal has been demonstrated for GO membranes from facilitated transport to retarded transport, providing new design ideas for chiral membranes. However, most of the exciting chiral membranes are still limited for practical use in pharmaceutical and chemical engineering fields. Large-scale preparation of membranes without defects and limited mechanical properties are the two main problems. In this regard, future development will mainly focus on the improvement of chiral building units and membrane preparation techniques. The composition of an easily prepared matrix and efficient chiral selective absorption materials is promising to meet most aspects of these requirements. In addition, nonwoven textile prepared by nanofibers is another efficient type of large-scale membrane which has high potential for practical use, and the construction of chiral nanofibers with single or multiple units is popular for future chiral membrane development.

Separation-free techniques, such as MS, optical spectroscopy, and electrochemistry, have been applied for rapid chiral detection and sensing. The development of chiral selectors contributes to fast and accurate chiral resolution. Transition-metal trimeric complex, chiral small molecules, nanoparticles with chiral structures, and chiral micro/nano channels have been popular for chiral detection and sensing in recent years. Techniques with these efficient selectors have been explored for many specific applications, such as small-volume samples, short-life compounds, rapid screening, and on-site analysis. High sensitivity and selectivity, low matrix interference, fast response, and easy operation are pursued by all of these techniques for future development. Moreover, measurements based on these techniques have their own further requirements. Universal efficient derivatization reagents are necessary for the simultaneous quantification of multiple chiral pairs in complex matrixes to make full use of MS's advantage of rich information. Optical sensing techniques have great prospects for ultrasensitive sensing down to the single-molecule level with sensitive chiral sensors. Besides, naked-eye recognition is the main development direction of optical sensing for on-site rapid screening, and chiral sensors with sensitive visual color change need to be specially designed. Last but not least, chiral sensors with good stability, good reproducibility, and miniature device size are needed for on-site electrochemical sensing to rapidly achieve semiquantified results.

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Notes

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https://doi.org/10.1021/acs.analchem.2c04371
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■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Nos. 22176073, 22076066, and 22104044) and the Natural Science Foundation of Jiangsu Province (No. BK20210448).

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https://doi.org/10.1021/acs.analchem.2c04371
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https://doi.org/10.1021/acs.analchem.2c04371
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