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REVIEW ARTICLE

Application of chiral materials in electrochemical sensors

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Abstract

Chirality is a universal phenomenon in nature and an essential attribute of life systems. Chiral recognition has very important research value in many fields. Amino acids and other chiral molecules are the basic components of human body. Understanding the configuration of chiral molecules is beneficial not only to the development of life science, but also to the development of chiral recognition. Compared with other traditional chiral recognition methods, electrochemical methods have the advantages of rapid detection, simple operation, low price, and high sensitivity, which has been widely concerned. In this review, we present an overview of chiral materials in a view of various chiral selectors, including amino acids and their derivatives, proteins, polysaccharides, chiral ligand exchange compounds, chiral cavity compounds (such as cyclodextrin, cucurbituril, calixarene, crown ether), and chiral ionic liquids, which were applied for the recognition of chiral molecules. Besides the chiral recognition mechanisms, some critical challenges and outlooks in the field of electrochemical chiral sensing interfaces are also discussed.

Keywords Chiral materials · Chiral selectors · Chiral electrochemical sensor · Carbon-based materials · Chiral recognition mechanism

Introduction

Chirality is a universal phenomenon in living systems. Chiral molecules are widely found in medicines, food additives, pesticides, humans, and the environment. There is a growing demand for effective methods to produce pure enantiomeric compounds due to each enantiomer has different or even opposite pharmacology and biology activity [1]. One of the enantiomers is effective; the other is ineffective or even toxic, which makes chiral separation a great challenge [2]. Chiral resolution or separation has become one of the most effective methods to obtain a certain configuration of pure enantiomers [3]. Therefore, the development of effective analytical methods for the identification and detection of individual enantiomers is of great practical significance in the field of food, medical science, clinical analysis, and other fields [4].

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In 1848, Louis Pasteur manually separated two mirror images of crystalline sodium ammonium tartrate. In 1858, Pasteur pointed out that his interest in molecular chirality came from biological research. In 1893, Lord Kelvin first defined chirality. He pointed out that "any geometric figure, or a group of points, has chirality if it cannot coincide with itself on a plane mirror" [5]. The shocking "thalidomide incident" that occurred in the 1960s was because pregnant women did not distinguish between R-thalidomide and S-thalidomide in the treatment of pregnancy reactions. Later studies showed that only R-thalidomide has the effect of treating pregnancy reaction, and S-thalidomide has teratogenic effect [6]. The painful lesson of the "Sea Leopard Incident" tells us that chiral recognition is very important. Therefore, more and more researchers have begun to explore efficient and convenient chiral separation and recognition methods for the sensitive recognition of chiral molecules. However, circular dichroism exhibits low sensitivity [7]. Instrumental analysis needs expensive equipment and analysis cost [8]. Fluorescence detection is easily interfered by other molecules, which leads to fluorescence quenching [9]. The detection speed of high-phase liquid chromatography is slow and the operation is complicated [10]. Alternatively, the electrochemical devices have become increasingly common in the recognition of chiral molecules due to the advantages of high selectivity, sensitivity, low

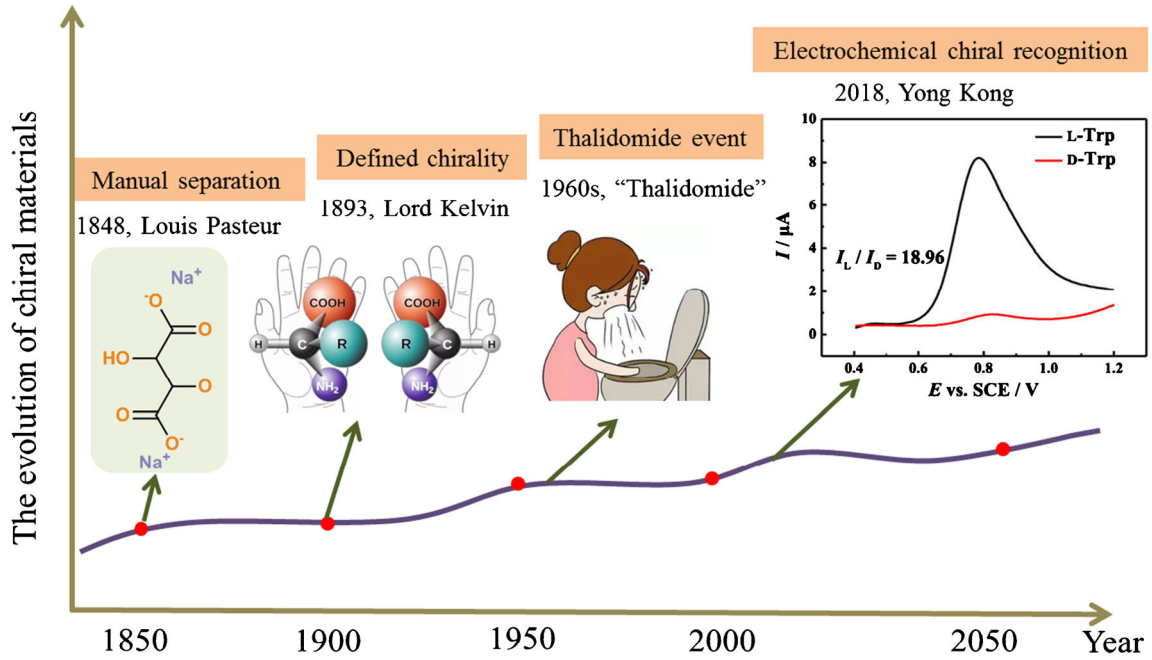

Fig. 1 The development of chirality

price, and fast detection [11]. Figure 1 shows the development of chirality.

The chiral sensing interface must have a chiral microenvironment or chiral center to perform chiral recognition, and the chiral microenvironment or chiral center is provided by a chiral selector [12]. Most chiral selectors are not conductive except for some conductive chiral ionic liquids. Therefore, when the chiral selector is modified simply on the electrode to construct an electrochemical chiral sensor, its poor conductivity will hinder the transmission of electrochemical signals, and may not obtain the optimal recognition result. Carbon-based materials, such as graphene and carbon nanotubes, have been widely used in the electrochemical field due to their excellent electrochemical performance, good electrical conductivity, large specific surface area, and biocompatibility [13]. In addition, carbon nanotubes and graphene can also provide a good electrochemical sensing platform for chiral selectors, thereby expanding electrochemical signals and increasing detection sensitivity [14, 15]. Various proposal of electrochemical measurement had been used during the past several years. Many literature have been reported on the synthesis of chiral materials based on different chiral selectors, such as amino acids and their derivatives [16], proteins [17], polysaccharides [18], chiral metal structures [19], chiral cavity (such as cyclodextrin, calixarene, crown ether) [20], chiral ionic liquids [21], and chiral polymers [22] (as shown in Fig. 2). Based on this perspective, this review will comprehensively introduce the latest progress in the construction of electrochemical chiral sensing interfaces based on different chiral materials, and further discuss some mechanisms and prospects in the field of electrochemical chiral recognition.

Common chiral selectors in electrochemical sensors

Chiral selectors can provide chiral microenvironment for the identified enantiomers, which renders the chiral guest molecules and chiral selectors have specific effects. Therefore, chiral selectors used to construct electrochemical sensors must meet the following conditions. (i) Chiral selectors must provide different chiral microenvironments for chiral guest molecules. In short, chiral selectors have chirality or chiral selectors can produce different chiral microenvironments for different configuration of chiral molecules. (ii) Chiral selectors can generate intermolecular forces with chiral molecules (such as electrostatic attraction, electrostatic repulsion, hydrogen bonding, hydrophobic interaction, π-π force, etc). (iii) No matter how the chiral guest molecule rotates, it can produce a different force with the chiral selector. (iiii) Electrochemical chiral sensors have certain requirements for the conductivity, film-forming properties, and biocompatibility of chiral composite materials. According to previous reports, many chiral selectors used to construct electrochemical chiral sensing interfaces have been developed, including chiral amino acids and their derivatives, proteins, polysaccharides, chiral ligand exchange compounds, chiral cavity (such as cyclodextrin, calixarene, crown ether), chiral ionic liquids, etc.

Chiral materials based on amino acids and its derivatives

Amino acids are the basic components of proteins (biologically functional macromolecular) [23]. Amino acids can be

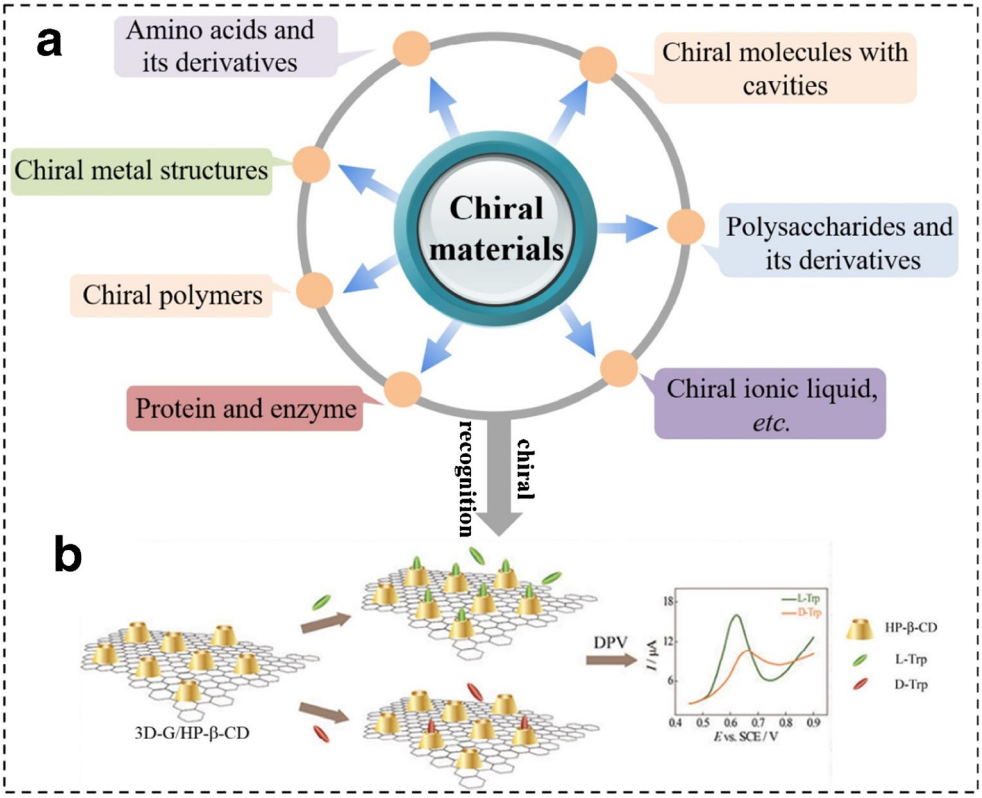

Fig. 2 **a** Chiral materials based on several kinds of chiral selectors used in electrochemical field. **b** The construction of electrochemical chiral sensing interface and its chiral recognition [20]

named α-amino acids, β-amino acids, γ-amino acids...w-amino acids according to the position of the amino group. But, α-amino acids are the products of protein hydrolysis, and there are more than 20 kinds of α-amino acids after hydrolysis. Except for glycine, the α-carbon atoms of other amino acids are all optically active. Amino acids and their derivatives are often used as chiral selectors to synthesize chiral recognition materials, and provide chiral environment for chiral guest molecules to construct electrochemical chiral sensing interfaces during the process of constructing electrochemical chiral sensors [24]. The forces generated between amino acids (used as chiral selector) and the chiral guest molecules are generally a hydrogen bond, electrostatic interaction, and π-π interaction. The recognition mechanism is usually a three-point force model [25]. The chiral selectors based on amino acids and their derivatives in electrochemical sensors mainly include phenylalanine, lysine, tryptophan, etc. [26]. In addition to the abovementioned amino acids, cysteine (Cys) is also a common chiral selector in electrochemical chiral recognition. Similar to other amino acids, cysteine also has amino and carboxyl groups. Besides, cysteine also has a sulfhydryl group, which changes the electron cloud density of cysteine. The excellent activity of weakly acidic sulfhydryl group on cysteine renders it is easily oxidized and easy to self-assemble with gold nanoparticles or other metal cations. Researchers have usually prepared various electrochemical chiral sensing interfaces based on Cys. Shi et al. (Fig. 3a) have prepared chiral selector-functionalized magnetic nanoparticles by self-assembly L-cysteine (L-Cys) on the Au/Fe_3O_4 nanocomposites via a facile reduction process. The as-prepared L-Cys-Au/Fe_3O_4 magnetic nanoparticles (MNPs) were used to construct a novel magnetic electrochemical chiral sensor (MECS), which was used to differentiate the tyrosine (Tyr) enantiomers. Under the synergic advantages of the magnetic Fe_3O_4 NPs and the chiral feature of L-Cys functionalized AuNPs, a linear regression between the concentration of the two Tyr enantiomers and the peak current was obtained over the range of 1–125 mM, with the LOD of 0.021 mM and 0.084 mM for L-Tyr and D-Tyr, respectively [27]. Guo et al. have synthesized an urchin-like chiral metal organic framework/reduced graphene oxide (urchin-CMOF/rGO) nanocomposite, which was used for the construction of the electrochemical sensing interface to high-efficient discriminate the tryptophan (Trp) enantiomers, as shown in Fig. 3 b [28]. Meanwhile, Zhu's group have developed an effective electrochemical chiral sensing interface for the recognition of Trp enantiomers, which was constructed via electrodepositing L-Cys on the surface of glass carbon electrode (GCE) modified with carbon black (CB). The sequential steps are shown in Fig. 3 c [29]. In addition to the abovementioned electrochemical chiral sensors with substrate materials, Cys can also directly self-assemble with Au nanoparticles and modified on GCE to identify the enantiomers. Besides, chiral electrochemical recognition has potential advantage for the detection of chiral molecules. But,

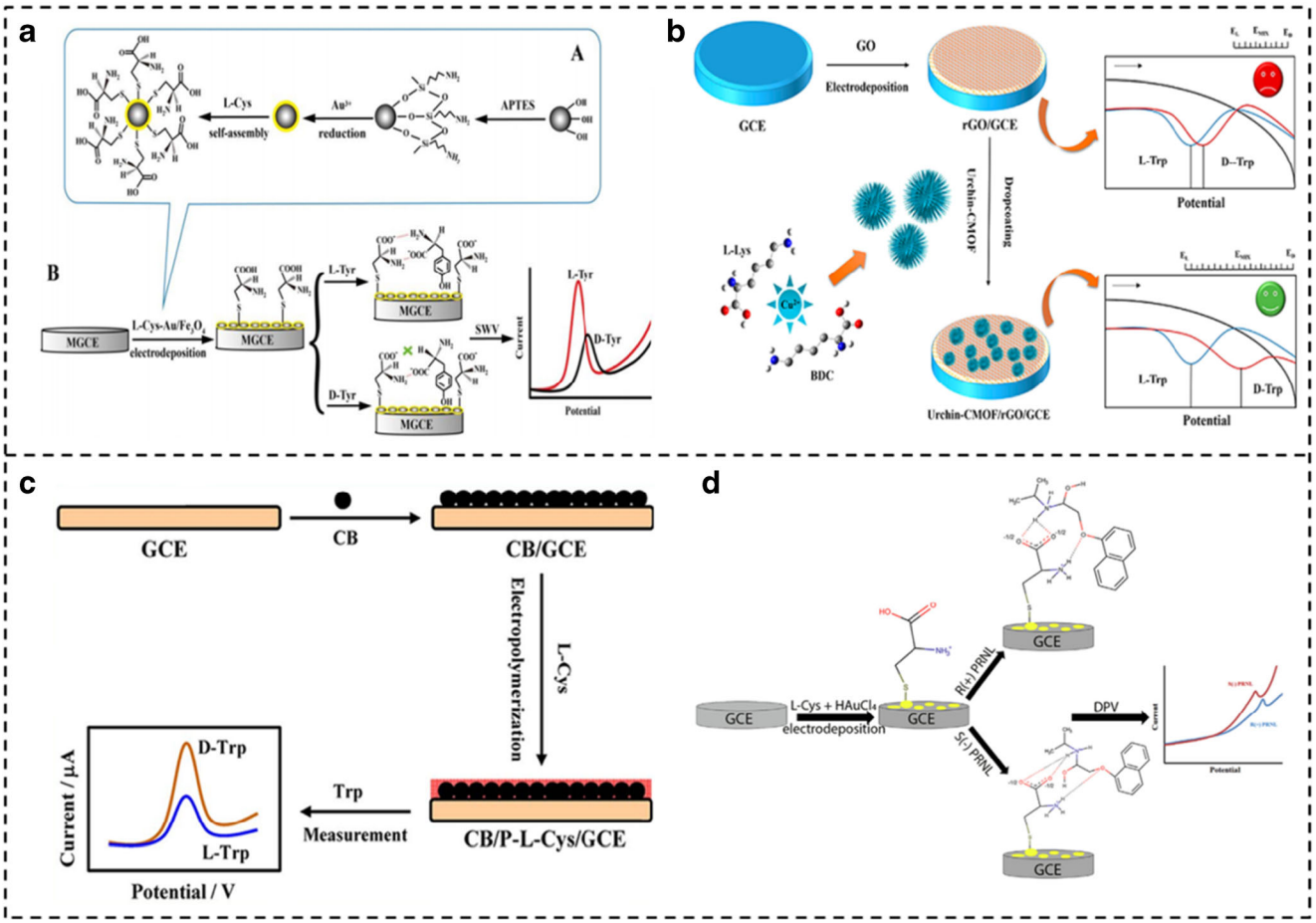

Fig. 3 **a** Schematic diagram for preparing MECS [27]. **b** Schematic illustration of urchin-CMOF/rGO/GCE for recognition of D/L-Trp [28]. **c** Schematic illustration for constructing CB/P-L-Cys/GCE [29]. **d** Schematic representation of the development of L-Cys AuNPs [30]

few studies have been committed to the clear mechanism related to the chiral recognition. Stoian et al. have paid great effort to investigate the recognition mechanism of the propranolol (PRNL) enantiomers via differential pulse voltammetry (DPV), electrochemical impedance spectroscopy (EIS), and computational modeling (molecular dynamics simulations). The electrochemical sensing interface was constructed via anchoring L-cysteine (L-Cys) on GCE modified by gold nanoparticles. Molecular dynamics simulations indicated that the H-bond donor and acceptor atoms of both the L-Cys and guest molecules (R-PRNL and S-PRNL) was related to chiral recognition signal (Fig. 3d) [30].

Chiral materials based on polysaccharides and its derivatives

Polysaccharides are polymers formed by the polymerization of monosaccharides, which are mainly composed of plant polysaccharides and animal polysaccharides. The structure of polysaccharides is different due to the different composition and molecular weight, which leads to the diversity of properties. Natural polysaccharides have been widely used in various fields because of their low price, non-toxic, good biocompatibility, and wide sources [31]. The polysaccharides used in chiral recognition mainly include cellulose, starch, chitosan, cyclodextrin (natural cyclic oligosaccharides), alginate, and its derivative sodium alginate [32]. Most polysaccharides contain active groups such as hydroxyl, amino, and carboxyl groups, which can provide active sites for the recognition of chiral guest molecules.

Chitosan (CS) is obtained by deacetylation of chitin. There are six glucose residues in each helix plane of chitosan. Chitosan is usually insoluble in water, but soluble in acid solution. CS has a double helix structure, which plays an important role in chiral recognition [33]. There are three common material models when polysaccharides are used as chiral selectors, which are electrodeposition, self-assembly, and covalent crosslinking, respectively. Inspired by the double helix structure of DNA, Gu et al. have reported a facile chiral differentiation system via electrodepositing CS on a GCE, which was constructed for electrochemical chiral recognition Trp enantiomers. This chiral recognition may be resulted from the H-bonds formed selectively between CS and chiral molecule from the perspective of supramolecular, which was

further confirmed by chiral recognition of Trp with sulfonated CS (SCS) (Fig. 4a) [34]. Although electrodeposition the CS directly on the surface of the GCE is simple, the morphology of the single polysaccharide is irregular. Therefore, combining two polysaccharides via self-assembly is also an ideal model for constructing electrochemical chiral sensors [37]. As shown in Fig. 4 b, a facile system based on a highly ordered framework was constructed via self-assembling the ammonia-ethanol cotreated chitosan (ae-CS) on Cu^{2+}-modified β-cyclodextrin (Cu-β-CD). The highly ordered self-assembly structure was formed during the "regrowth" process of the ae-CS films. Trp enantiomers were well distinguished by the self-assembled ae-CS/Cu-β-CD framework via DPV [35].

Cellulose is also a kind of polysaccharide in plants, which is a linear natural polymer formed by D-glucose units. Because the basic unit (D-glucose unit) of cellulose has optical activity and the single helix structure of cellulose, cellulose and its derivatives can be used as chiral selectors to construct electrochemical chiral sensing platform to recognize chiral molecules due to the optical activity of D-glucose unit and its single helix structure. Lu's research group modified 2, 2, 6, 6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized cellulose nanocrystals (TOCNCs) and L-cysteine (L-Cys) on the gold electrode (TOCNC/L-Cys/Au), and used it to identify the enantiomers of phenylalanine, leucine, and valine enantiomers. The results showed that the adsorption capacity of TOCNCs for D-amino acids was stronger than that for L-amino acids, so there was a significant difference in peak current between L-and D-amino acids [38]. However, compared with self-assembly, integrating two polysaccharides together via covalent bonding may render a better microstructure. Bao et al. integrated two kinds of polysaccharides of sodium carboxymethyl cellulose (CMC) and CS together via covalent crosslinking. The covalently crosslinked polysaccharides (CMC-CS) with a mass ratio of 1:1 showed a three-dimensional (3D) network microstructure, which made a significantly increased hydrophility due to the external exposure of polar groups. Then, the chiral electrochemical sensor was fabricated with the covalently crosslinked

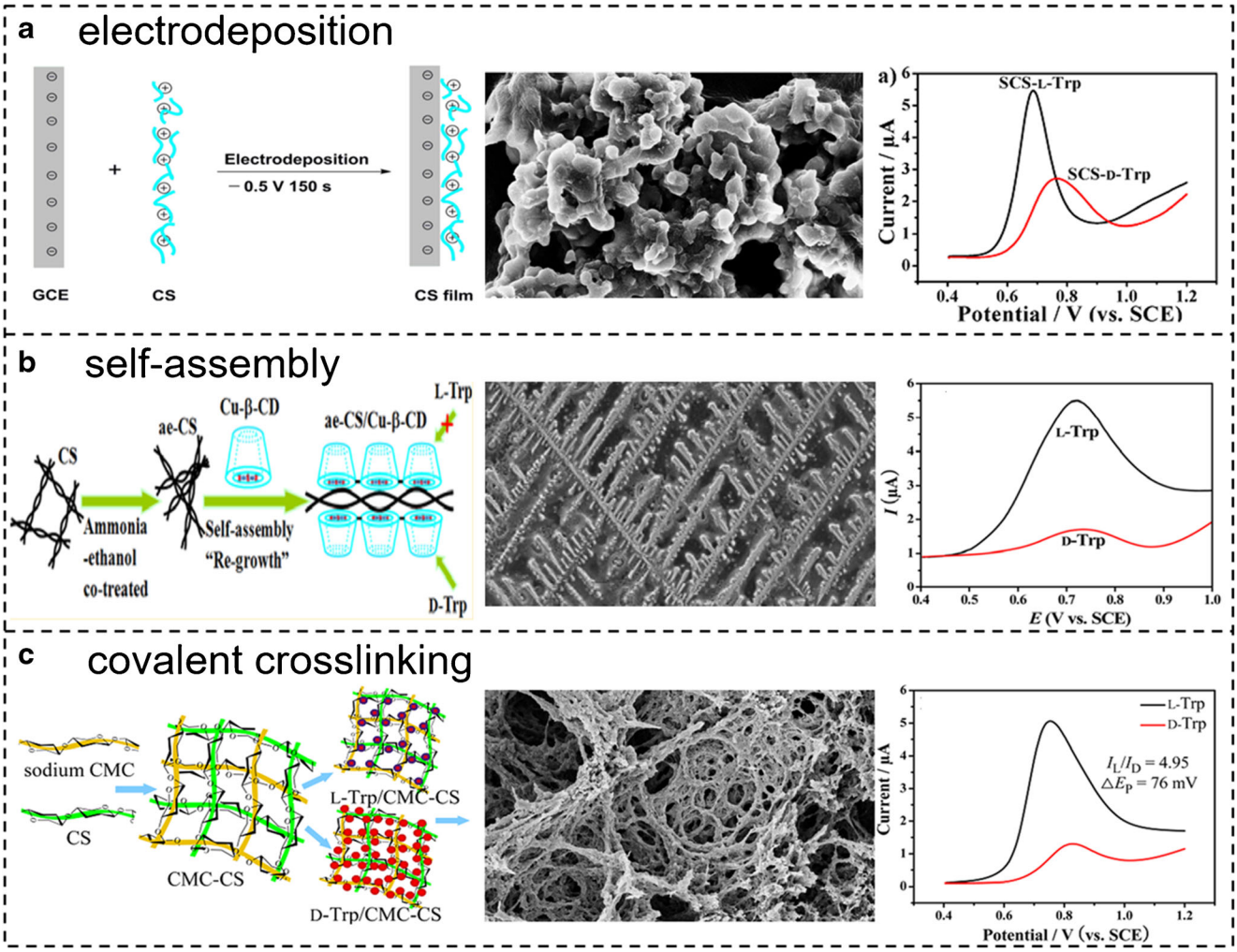

Fig. 4 **a** Electrodeposition of CS on the GCE, the SEM of CS/GCE, and DPV of SCS-L-Trp and SCS-D-Trp [34]. **b** Schematic illustration of the preparation of ae-CS/Cu-β-CD, the SEM of ae-CS/Cu-β-CD, and DPV of ae-CS/Cu-β-CD/GCE in L- and D-Trp [35]. **c** Formation of 3D structure of CMC-CS, the SEM of CMC-CS, and the DPV of CMC-CS/GCE in L- and D-Trp [36]

polysaccharides and applied it for chiral recognition of Trp isomers (Fig. 4c) [36].

Starch is a polysaccharide composed of only one kind of glucose. According to the composition of glucose units, starch includes amylose and amylopectin. Amylose is composed of about two hundred glucose units, and has the spiral spatial configuration. Amylopectin has high molecular weight and poor water solubility, which is composed of thousands of glucose residues. Since starch has many hydroxyl groups, when it is used as a chiral selector, it can generate intermolecular hydrogen bonds with chiral guest molecules to achieve recognition effect. Zou et al. have fabricated an electrochemical chiral sensor based on soluble starch (SS) and CS, which was applied to recognize tyrosine (Tyr) enantiomers via electrochemical measurement [39]. Bao et al. self-assembled potato starch (PS) on poly (glutamic acid) (P-L-Glu), and selected the tryptophan enantiomers as the guest molecule for chiral recognition. The results show that the affinity of PS/P-L-Glu for D-Trp is higher than that for L-Trp, which is due to the formation of intermolecular hydrogen bonds between PS and D-Trp. However, when using hydroxypropyl PS (H-PS) instead of PS, the recognition efficiency will be reduced [40].

Chiral materials based on protein

Protein is one or more biological macromolecules composed of α-amino acid residues, which are the component of all cells and tissues, and the main undertaker of life activities. Living organisms mainly exist in the chiral environment composed of biomolecules. The receptors and enzymes in living organisms are always affected by stereoselectivity. The subunit of protein (L-amino acid) has chiral properties, which can specifically recognize small biological molecules. Proteins have different levels of structure, namely primary structure, secondary structure, tertiary structure, and quaternary structure. Its unique stereoscopic structure makes proteins have three-dimensional structure, which can provide chiral sites and forces for chiral guest molecules. The performance of each protein is quite different, so the specific recognition mechanism cannot be explained clearly. Glutathione (GSH) is a tripeptide containing γ-amide bond and sulfhydryl, which is composed of glutamic acid, cysteine and glycine. It exists in almost every cell of the body. Glutathione can help maintain normal immune system function, and has antioxidant and integrated detoxification effects. The enantioselective recognition system was constructed by combining the advantages of GSH and α-cyclodextrin (α-CD) [41]. Ye et al. used Cu, Pt, and Cu-Pt NPs to decorated GSH (GSH-Cu/Pt). Then, the GSH-Cu/Pt was used for electrochemical recognition of tyrosine isomers (Fig. 5a) [42]. Chiral peptide is also an organic compound, which is dehydrated from chiral amino acids and contains carboxyl and amino groups. Multiple peptides can be folded to form a protein molecule. Proteins are sometimes referred to as "polypeptides." Sun et al. have constructed an electrochemical chiral sensor based on achiral polyethyleneimine (PEI) and chiral peptide (D-BGAc) via self-assembly technology, which was used to differentiate Trp enantiomers (Fig. 5b) [43].

In the process of chiral recognition, hydrophobic channel and polar group of protein tertiary structure can produce hydrophobic interaction, hydrogen bond interaction, and electrostatic interaction, thus forming diastereomer between protein and chiral guest molecule and producing chiral recognition. When protein is used for chiral recognition, the pH and temperature of the system are required to ensure the invariance of protein. There are several types of protein based chiral selectors. (i) Five heteropolysaccharide units and one peptide chain constitute the structure of α-acid glycoprotein. The isoelectric point of α-acid glycoprotein is between 2.7 and 3.2. When α-acid glycoprotein is used as a chiral selector to recognize chiral molecules, the recognized chiral guest molecules should have hydrogen bonding functional groups, the interaction points between aromatic functional groups and hydrogen bonded functional groups should be less than three, and the chiral center atom should be adjacent to the aromatic functional groups. (ii) γ-globulin and ovomucin. Yingzi Fu et al. fixed γ-globulin on the surface of gold nanoparticles modified glassy carbon electrode, and used it to identify mandelic acid enantiomers. Electrochemical method (differential pulse voltammetry), quartz crystal microbalance, UV-Vis spectrum, and atomic force microscope all showed that the electrode had good recognition ability for R-mandelic acid. Ovalbumins contain O-glycoside linked sugar chains, which are also used to recognize chiral molecules [45]. (iii) Serum protein is the most widespread protein in the biological circulatory system. It is the carrier of drugs and some biomolecules, and has the function of buffering blood concentration and maintaining osmotic pressure in life activities. The serum proteins used for chiral selector are mainly human serum albumin (HAS) and bovine serum albumin (BSA). The isoelectric point of HAS is 4.7. It contains 585 α-amino acid residues, of which only one tryptophan is located at position 214. The isoelectric point of BSA is also 4.7, it contains 585 α-amino acid residues, and its structure contains two tryptophans located at positions 212 and 134, respectively. Human serum protein as a chiral selector is mainly used to detect neutral and weakly acidic chiral molecules [46, 47]. The bovine serum albumin is mainly used to identify neutral compounds, anionic chiral substances, and amino acid compounds [48]. Yingzi Fu group used BSA functionalized toluidine blue and reduced graphene oxide (BSA)/TBO@rGO) to construct an electrochemical chiral sensing platform to recognize naproxen (Nap) enantiomers. The electrochemical recognition results show that the signal of R-Nap and chiral sensing platform is strong than that of S-Nap. Quartz crystal microbalance further proves that BSA and R-Nap have strong affinity (Fig. 5c) [44].

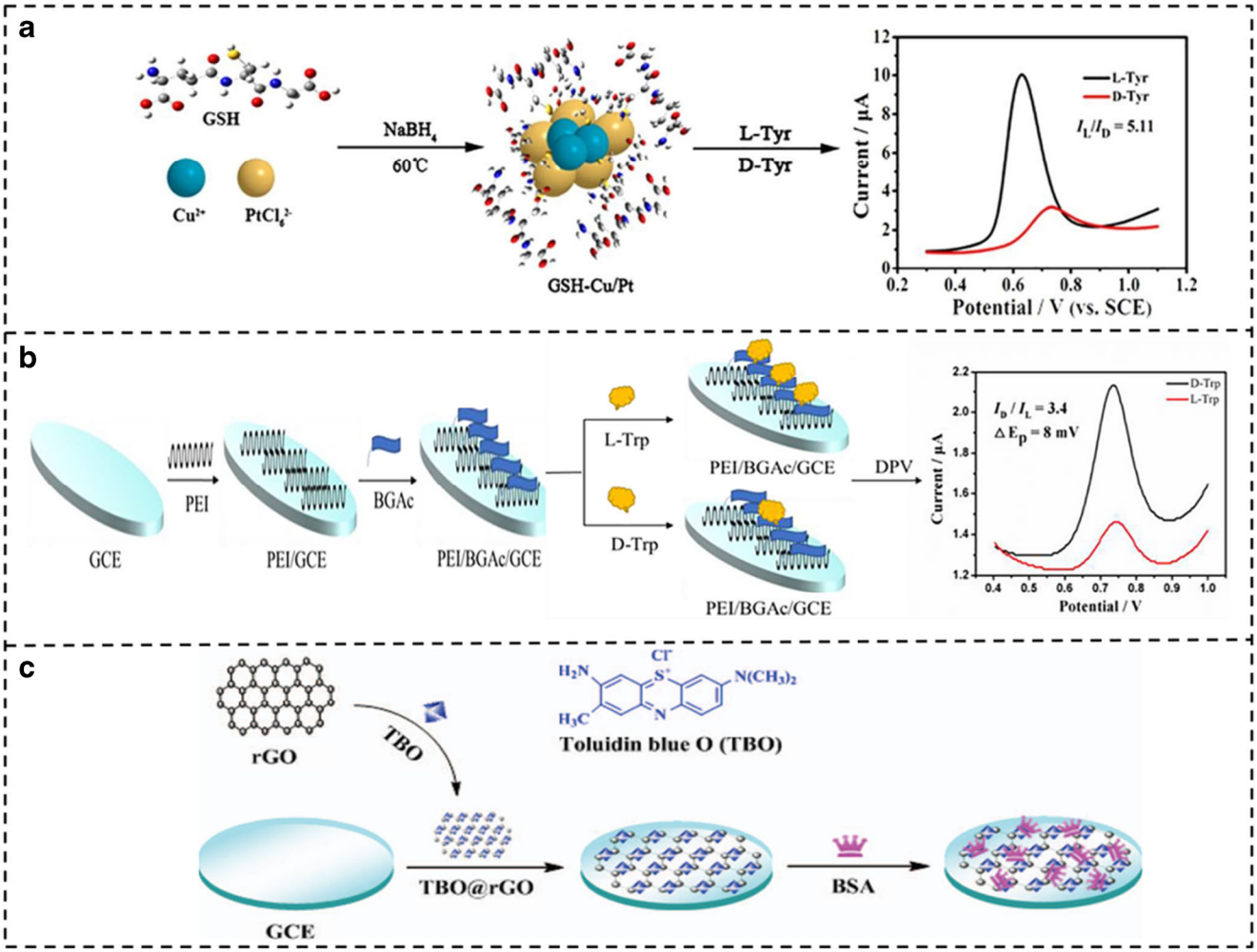

Fig. 5 **a** Schematic illustration of the preparation of GSH-Cu/Pt and its recognition response [42]. **b** Fabrication of PEI/D-BGAc/GCE and the electrochemical recognition of Trp enantiomer [43]. **c** The construction of BSA)/TBO@rGO/GCE [44]

Chiral materials based on chiral cavities

Chiral cavities based on supramolecular are also commonly used as chiral selectors in electrochemical sensors. These chiral cavities mainly include crown ethers, cucurbituril, calixarenes, and cyclodextrins and so on, which are commonly used for chiral recognition. Crown ether is a cyclic polyether with a cavity-like structure. The inner cavity of the ring is heteroatoms with strong electronegativity, such as oxygen, sulfur, and nitrogen, and the outer edge of the ring is lipophilic. Since Pederson synthesized crown ethers in 1967, crown ethers have been used to separate chiral compounds in high-performance liquid chromatography [49, 50]. However, crown ethers have no chirality, so it is necessary to introduce chiral microenvironment into crown ethers to recognize chiral molecules. According to the chiral microenvironment introduced into crown ethers, the main categories of chiral crown ethers are as follows: (i) Crown ether is modified with chiral tartaric acid molecule. (ii) Polysaccharide molecule is introduced into crown ethers as chiral microenvironment. (iii) Chiral crown ethers were synthesized by introducing naphthalene monomer into crown ethers.

Cucurbituril (CB) is a kind of oligomeric compound hosts. The cyclic urea monomers are bridged by methylene groups. With the development of science, the family of cucurbitacin has expanded [51, 52]. One type of CB can be divided into two main branches: double-bridge and single-bridge CB. The inner cavity of all cucurbitacins is hydrophobic. However, the electronic binding properties of single-bridge and double-bridge cucurbitacins are different. So far, the chemical properties of cucurbitacin have been reported in previous literature [53]. The cucurbituril hosts have excellent symmetry, but there are some ways to destroy this symmetry. So, the cucurbituril can be used in chiral recognition [54]. The challenges associated with chiral induction in achiral hosts were previously reported by Aoyama et al. [55], and the detail was further studied by Borovkov et al. [56].

Calixarene is a kind of cyclic condensation compounds obtained by the reaction of formaldehyde and p-substituted phenol in alkaline condition. Calixarene has a cavity structure

similar to that of crown ethers. The inner cavity is a highly concentrated part of the electron cloud of aromatic groups. The opening of one edge of calixarene is small, and the edge of calixarene is distributed with strong polar hydroxyl groups. The other edge of calixarene is hydrocarbon group, which is lipophilic. The structure of calixarene mainly has the following four characteristics. (i) The cavity size of calixarene can be adjusted according to the reaction conditions. (ii) The calixarene is easy to derivatize, and the phenolic hydroxyl substituent of the calixarene and the p-substituent of the benzene ring are easy to derivatize, thus introducing the required functional group to obtain a highly selective chiral selector. (iii) Calixarene has good thermal stability, low toxicity, and good flexibility. Mao et al. have synthesized a novel calixarene derivative and used it for electrochemical chiral recognition. In this process, R-mandelic acid was grafted onto the surface of calix[4]arene (FC4D), and then the calix[4]arene grafted by R-mandelic acid underwent a click reaction with graphene. R-mandelic acid will provide chiral recognition ability for calixarene derivatives through hydrogen bonding as a chiral auxiliary. At the same time, two chiral units will be bound to the upper edge of calixarene. Due to the synergy effect, it can better recognize enantiomers. It is worth noting that the prepared FC4D-G has extremely high sensitivity and selectivity for the recognition of aminopropanol enantiomers by using the dual advantages of functional calixarene and graphene [57].

Cyclodextrin is the most common chiral holes selector in electrochemical chiral sensors. Cyclodextrins include α-, β-, and γ-cyclodextrins, which are oligosaccharides composed of six, seven, and eight glucose units, respectively. Cyclodextrin is cavity-shaped. Cyclodextrin has a hydrophilic outer cavity (due to the primary and secondary hydroxyl groups distributed on the edge of the cavity) and a hydrophobic inner cavity (glycoside oxygen bridges and hydrogen atoms of the hydroxyl group). The hydrophobic inner cavity of cyclodextrin enables it to include many guest molecules such as organic molecules, inorganic molecules, metal complexes, and biological molecules to form host-guest inclusion compounds [58, 59]. Because each glucose unit constituting the cyclodextrin has five chiral centers, it can provide a good host chiral environment for the recognition of chiral guest molecules, and form host-guest inclusion compounds with chiral guest molecules. Therefore, cyclodextrin can be used as a chiral selector to combine with a variety of materials (such as graphene, carbon nanotubes, and graphene quantum dots) to generate chiral recognition capabilities for chiral guest molecules in electrochemical chiral sensors [60, 61]. The use of cyclodextrin-like chiral cavity substances for chiral recognition must meet the following conditions: (i) Chiral guest molecules should be able to complexate with chiral cavities materials (cyclodextrins). (ii) The size of the hydrophobic part of the chiral guest molecule should exactly match the size of the cavity. If the volume of the chiral guest molecule is small, the two configurations of chiral molecules are easy to move in the chiral hole, and are in the average environment of the chiral hole, resulting in a small recognition difference. (iii) The chiral center of the chiral guest molecule or the functional group connected with the chiral center can interact with the group at the edge of the hole.

It is not ideal to use only the chiral cavities molecule as a chiral selector to directly modify the glassy carbon electrode without the base material. Electrochemical chiral sensors need not only to distinguish chiral enantiomers, but also to improve electrochemical signals. The combination of enantioselectivity and electrochemical properties gives the composite many interesting properties for use as a sensing device. Carbon nanotubes wrapped with reduced graphene oxide CNTs@rGO can be used as an ideal substrate material for the construction of electrochemical chiral sensors. Yi et al. have constructed sensitive electrochemical sensing interface for chiral recognition by combining advantage of CNTs@rGO and β-CD (CNTs@rGO as ideal substrate material and β-CD as chiral selector). A double signal electrochemical sensor was designed, which can reflect the differential binding affinity of β-CD and guest molecules to the electrochemical signal (Fig. 6a) [62]. With the transformation of prototypes in their synthesis and function, charged alkanes have attracted more and more attention. Wu et al. reported a proposal which interlock mechanically β-cyclodextrin and ionic liquid with each other to form charged alkanes through ionic hydrogen bonds. It will quickly generate a blue precipitate when the charged alkane reacted with Cu (II) ions. Considering that the synthesized molecule has good electrical activity and stability, it can be modified on the bare GCE and further used as a probe. The oxidation peak current response of the probe has obvious chiral difference for four isomers (tryptophan, tyrosine, cysteine, and malic acid). The L-configuration has a higher oxidation peak current, but it is difficult to observe the electrochemical signal of the D-configuration. More interestingly, the recognition ability between the L-configuration and the D-configuration of tryptophan can be reversed in buffer solutions with different pH. These results indicate that the steric hindrance dynamic conversion process based on alkanes can expand the chiral difference (Fig. 6b) [63]. Metal organic frameworks (MOFs) are a kind of organic-inorganic hybrid materials, which are composed of organic ligands and inorganic metal units. Generally, it has variable topological structure and physical and chemical properties. Chiral metal organic frameworks (MOFs) have great potential in the field of chiral recognition. Upadhyay et al. have synthesized copper metal organic framework (CD-CuMOF) based on β-CD, which was used for the recognition of ethambutol (ETB) isomers. The mechanism of the complex formed between CD-CuMOF and ETB (Fig. 6c) and CD-CuMOF pathway for ETB are shown in Fig. 6d [64].

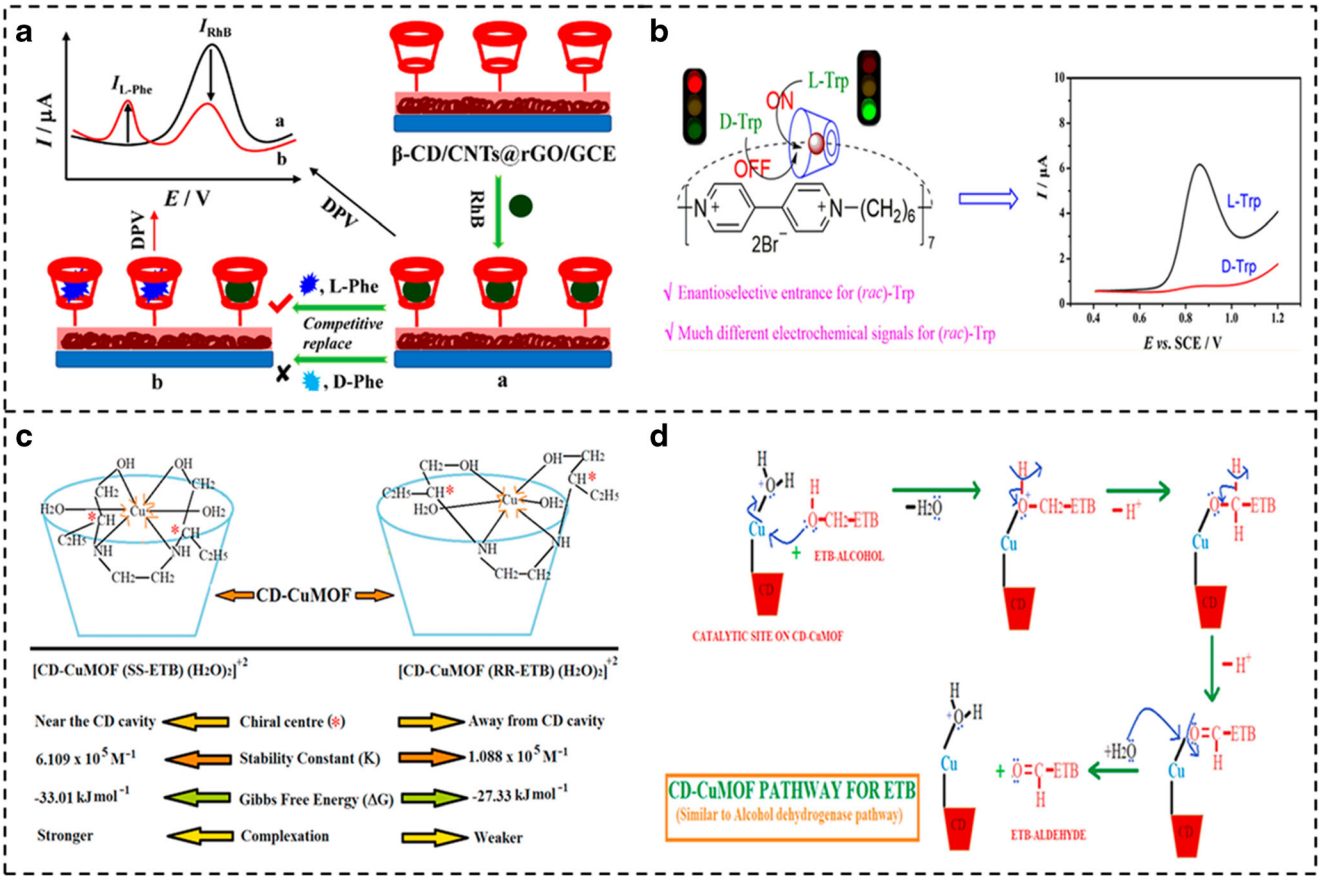

Fig. 6 **a** Schematic diagram of the dual-signaling electrochemical chiral sensor for Phe enantiomers [62]. **b** Stereoselectivitive entrance and different electrochemical signals for (*rac*)-Trp [63]. **c** Mechanism of complex formed between isomers of ETB and CD-CuMOF, **d** CD-CuMOF pathway for ETB [64]

Chiral materials based on chiral ligand exchange compounds

In 1961, Helfferich first proposed the principle of ligand exchange [65], and then Davankov further developed and applied the principle of chiral ligand exchange [66]. Chiral ligand exchange principle combines ion exchange technology and coordination chemistry to distinguish chiral molecules. The main principle of using chiral ligand exchange compounds as chiral selectors to recognize chiral molecules is the principle of ligand exchange. The ligands commonly used in electrochemical chiral recognition are polysaccharides, amino acids, and its derivatives. Since most amino acids and their derivatives have active groups that can coordinate, such as amino and carboxyl groups, and the distance between the active groups is moderate, amino acids and their derivatives can easily interact with metal ions (such as Cu^{2+}, Zn^{2+}, Fe^{2+}). The most common coordination ions used for chiral ligands are Cu^{2+} and Zn^{2+}. Many researchers have combined the principle of ligand exchange with electrochemical measurement to identify enantiomers with the increasing development of the electrochemical field [67]. Bao et al. used sodium alginate as a chiral selector via electrodeposition on the surface of glassy carbon electrode. It can form a complex with tyrosine, [(SA)Zn(II)(L-Tyr)] and [(SA)Zn(II)(D-Tyr)], when Zn^{2+} exists. The chiral selector preferentially recognizes D-Tyr due to the difference in steric hindrance during the formation of these two complexes (Fig. 7a) [68]. Electroactive nanoparticles have attracted great attention due to its good catalytic ability, biological microenvironment, and electronic conductivity. Electroactive nanoparticles can cause significant DPV peak current due to its easy oxidation. Compared with the single metal nanoparticles, the core-shell metal nanoparticles have enhanced electrochemical signal and stability. Zhao et al. have reported a novel proposal for the electrochemical recognition of Trp enantiomers by using electroactive core-shell Au@Ag NPs as electroactive tags. Compared with L-Trp, the large binding constant of D-Trp on Au@Ag NPs and the strong coordination ability between D-Trp and Cu^{2+} leads to the assembly of electroactive Au@Ag NPs on the electrode, thus generating a strong electrochemical (DPV) signal (Fig. 7b) [69]. Chen et al. have reported a chiral electrochemical sensor based on a ligand exchange compound (Fig. 7c), which was modified on the surface of a glassy carbon electrode. The enantioselective interface of a molecularly imprinted sol-gel (MIS) membrane with an imprinted cavity was prepared by

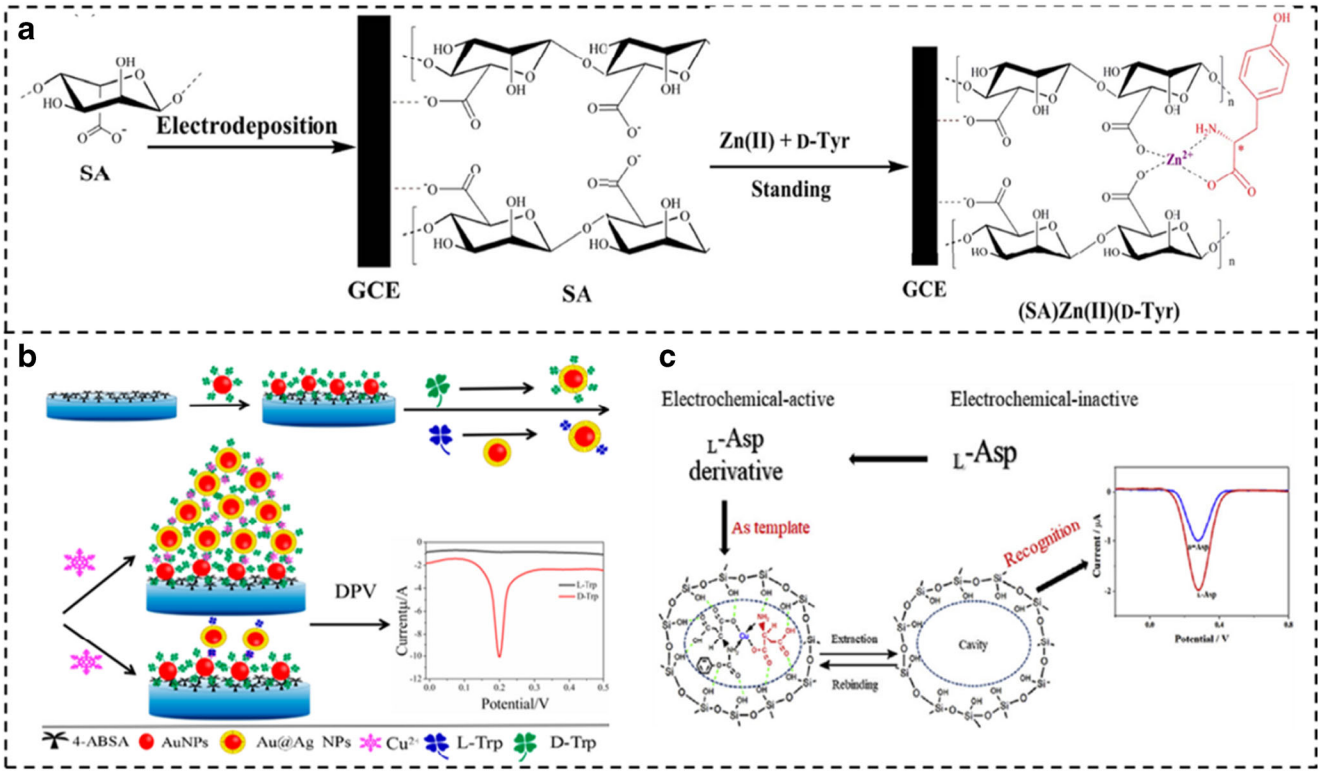

Fig. 7 **a** Schematic illustration of the construction of [(SA)Zn(II)(L-Tyr)] or [(SA)Zn(II)(D-Tyr)] modified GCE [68]. **b** The construction of electrochemical chiral sensing interface and electrochemical recognition [69]. **c** The elution and rebinding of MIS [70]

combining a sol-gel process with molecular imprinting technology. To obtain the electrochemical response of the enantiomers of L-aspartic acid, the ternary derivative complex of L-aspartic acid (L-Aspartic acid) Cu^{2+} (N-carbobenzoxy-L-aspartic acid) was used as a template to fabricate imprinted cavities [70]. According to the above discussion, it can be found that electrochemical chiral sensors based on metal complexes accelerated the development of chiral electrochemical recognition. However, the metal ions in the electrochemical chiral sensor based on the principle of ligand exchange of chiral metal complexes not only can interact with the chiral selector, but also interact with the chiral guest to quickly form a diastereomeric complex compound. Therefore, there is a gap between the force of metal ions and chiral selectors, and that of chiral guest molecules when chiral recognition occurs based on the principle of chiral ligand exchange. However, both the chiral guest molecule itself and the chiral selector itself can form complexes with metal ions in this system, which render the recognition process more complicated.

Chiral materials based on chiral ionic liquid

Chiral ionic liquids mainly include chiral cationic liquids and chiral anionic liquids. The common cationic chiral ionic liquids are imidazole chiral ionic liquids, pyridine chiral ionic liquids, and ammonium salt chiral ionic liquids. Anionic chiral ionic liquids mainly include lactic acid chiral ionic liquids, amino acid chiral ionic liquids, and camphor chiral ionic liquids. At present, chiral ionic liquids also have some related applications in the field of electrochemical sensors [71, 72]. Wu et al. have prepared a new chiral ionic liquid (CIL) and used it as an electrolyte to further functionalize graphene sheets (GO-(S, S)-CIL) (Fig. 8a), and GO-(S, S)-CIL was used to differentiate L−/D-tryptophan, R-/S-mandelic acid, R-/S-malic acid, and L−/D-tyrosine. For tryptophan isomers, the peak potential of the L-Trp is more negative than that of the D-Trp, and the peak-to-peak potential difference is close to 72 mV [73]. Besides, the morphology of the exfoliated GO-(S,S)-CIL is laminas, as shown in SEM image [76]. Polymeric chiral ionic liquids are synthesized via polymerization of anionic or cationic liquid monomers. Kong et al. have synthesized a novel chiral poly (ionic liquid)-metal complex (S, S)-PCIL-5-Cu(II), which was used as modifier to construct electrochemical chiral sensor for the first time. By comparing the difference between the oxidation peak potential (E_P) and the peak current (I_P), it is shown that the chiral sensor can be used to identify various amino acids. It is remarkable that the L or (S) form showed a higher I_P, compared with the D or (R) form. For example, the peak current ratio (I_L/I_D) of malic acid is 24.8. However, the E_P of D-malic acid is negative relative to L-malic acid. The peak-to-peak potential is 88 mV (Fig. 8b) [74]. Conductive materials are excellent carriers and are widely used in electrochemical identification. In another report, Wu et al. have prepared a mesoporous organosilica sphere

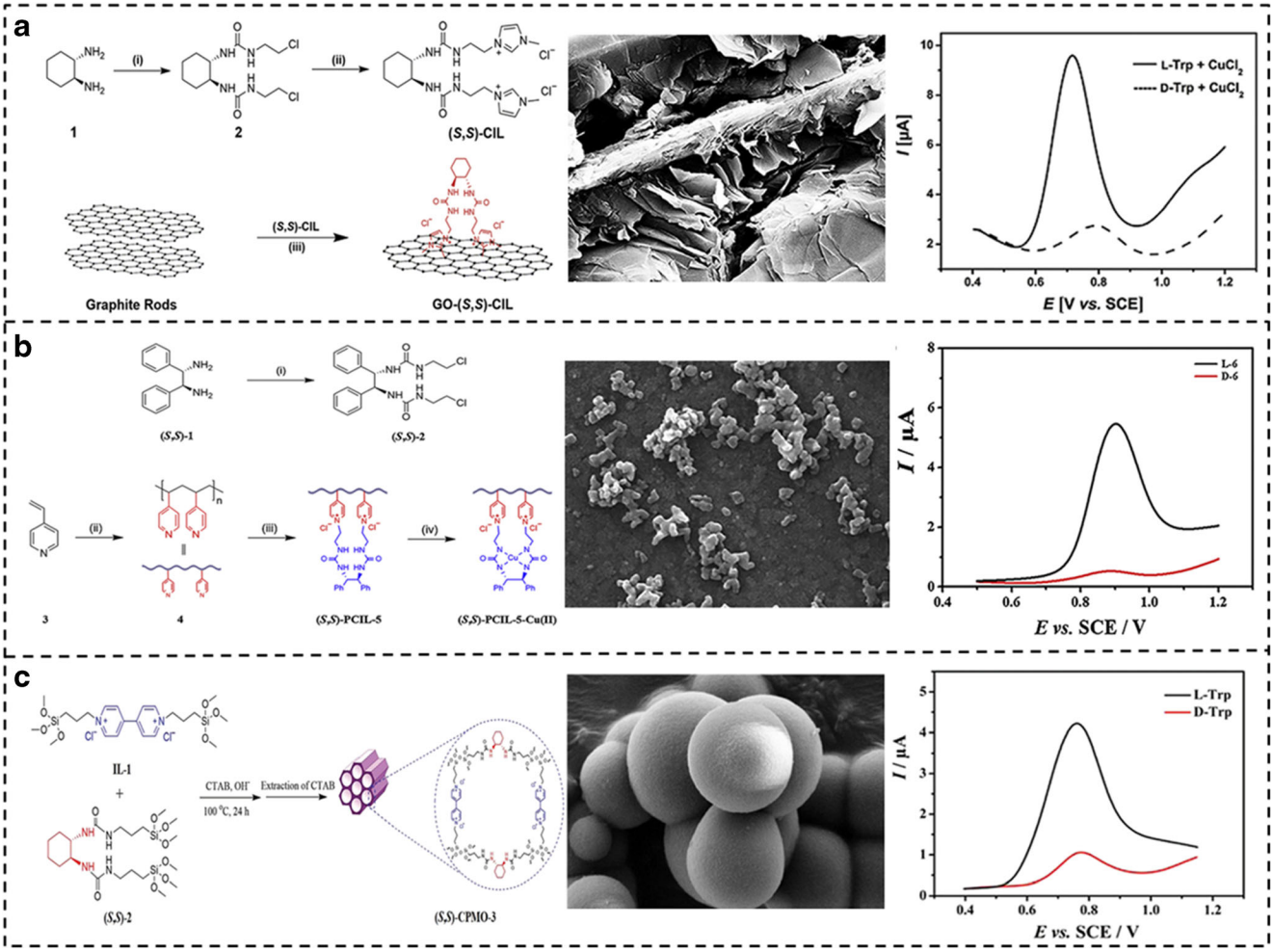

Fig. 8 **a** The synthesis process of GO-(S, S)-CIL, the SEM of GO-(S, S)-CIL, and DPV of GO-(S, S)-CIL/GCE in L- and D-Trp [73]. **b** The synthesis illustration of (S, S)-PCIL-5-Cu (II), the SEM of (S, S)-PCIL-5-Cu (II), and DPV of (S, S)-PCIL-5-Cu(II)/GCE in L-6 and D-6 [74]. **c** Schematic illustration of the preparation of (S, S)-CPMO-3-GCE, the SEM of (S, S)-CPMO-3, and DPV of (S, S)-CPMO-3/GCE in L-Trp and D-Trp [75]

(S, S)-CPMO-3 with the chiral sites and electrochemical performance. The mesoporous organosilica consist of free ions in ionic liquids and chiral centers of (1S, 2S)-1, 2-diaminocyclohexane. Then, an electrochemical chiral sensing interface was fabricated based on (S, S)-CPMO-3. The result showed that the (S, S)-CPMO-3-GCE exhibited ideal chiral recognition to various amino acids. Taking L-Trp and D-Trp as an example, the peak current ratio value of I_L/I_D was 13.84, and the potential difference was close to 48 mV (Fig. 8c) [75].

Application of carbon-based materials in chiral electrochemical sensors

Graphene is a two-dimensional material with a honeycomb monoatomic layer composed of sp^2 carbon atoms. The discovery of graphene fills the gap in two-dimensional carbon nanomaterials. Carbon nanotubes can be formed by rolling graphene, fullerene can be formed by warping graphene, and graphite is the result of ordered stacking of graphene. Therefore, graphene is the basis for the formation of other carbon nanomaterials. Initially, few or single-layer graphene nanosheets were obtained by mechanical exfoliation and epitaxial chemical vapor deposition [77]. Graphene has a very thin sheet structure, showing a certain wrinkle structure. The folding structure is a special structure of single-layer graphene sheet to reduce the transition from planar to three-dimensional morphology, which is a necessary condition for the stable existence of graphene. Graphene has been widely used in many fields due to its special properties, such as nanoelectronics [78], nanocomposite materials [79], solar cells [80], and supercapacitors [81]. In addition, graphene is considered to be a potential application for sensor electrode modification materials due to it can be easily chemically modified by other groups and molecules. Although graphene has excellent electrical conductivity and biocompatibility, it has

no chiral center and chiral site, so it cannot be directly used for chiral recognition. Chiral selectors, such as chitosan, cyclodextrin, cellulose, amino acids, and their derivatives, have poor electrical conductivity. If they are directly modified on the electrode to recognize chiral molecules, it may hinder electrochemical signals. Graphene-based materials can provide an effective electrochemical chiral sensing platform for chiral selectors. If the advantages of chiral selectors and carbon-based materials are combined, it will not only provide chiral centers for the sensing platform, but also expand the recognition signal and increase the recognition efficiency. Graphene can be combined with chiral selectors through covalent interaction and non-covalent interaction to form new chiral composite materials, which not only promote the application of non-conductive chiral selectors in the field of electrochemical sensors, but also increase the application range of carbon-based materials. Yang et al. synthesized rGO-PDA-L-Lys-Cu by Michael addition/Schiff base reaction between polydopamine functionalized graphene (rGO-PDA) and L-lysine copper (L-Lys-Cu). The chiral composite (rGO-PDA-L-Lys) was obtained via removing the copper on rGO-PDA-L-Lys-Cu by EDTA, which was used for electrochemical identification of tryptophan isomers. The recognition results show that the chiral sensing platform had a strong affinity to D-Trp [82]. Wang et al. have synthesized highly ordered nanostructures of reduced graphene oxide (RGO) covalently functionalized with sodium carboxymethyl cellulose (CMC) using ethylenediamine (EDA) as bridging group, which was used for electrochemical chiral recognition. The recognition mechanism is hydrogen bonding between hydroxyl group on CMC and amino or carboxyl group on tryptophan [83]. From the above discussion, it can be seen that graphene has been widely used as a substrate in the field of electrochemical chiral sensing, but the obvious agglomeration of two-dimensional graphene and the low loading of chiral molecules make its application limited. Therefore, three-dimensional graphene as a base material is also a development direction in the construction of electrochemical chiral sensors [84].

In the late twentieth century, Li Jima from Japan has reported a nanocarbon structure with a multilayer tube for the first time, namely carbon nanotubes (CNTs) [85]. According to the number of layers constituting carbon nanotubes, carbon nanotubes can be divided into multi-wall carbon nanotubes and single-wall carbon nanotubes. Carbon nanotubes can be used as substrate materials and combined chiral selectors to form chiral composites, which was also widely used in the construction of electrochemical sensors. However, the agglomeration effect of carbon nanotubes limits its application to a certain extent. The traditional method to increase its dispersion is to use mixed acid to treat CNTs to carboxylate them. Although carboxylation can solve the problem of agglomeration, it destroys the structure of CNTs and affects their performance and structural integrity. Therefore, many researchers have carried out in-depth discussion to improve the performance of carbon nanotubes [86]. Due to its excellent electrochemical performance, carbon nanotubes have been widely used in electrochemical chiral recognition as the base material of chiral composite materials. Zhang et al. have constructed an electrochemical chiral sensing platform based on the natural right-handed chirality of cellulose nanocrystals (CNCs) and MWCNTs, and it was used for rapid and sensitive recognition of tryptophan enantiomers [87]. Single-walled carbon nanotubes (SWCNTs), composed of single-layer graphite seamlessly packaged in cylindrical shape, are widely used as base material for electrochemical sensors [88]. Chiral SWCNTs have unique optical properties, and each chiral carbon nanotube has its own unique absorption spectrum, which is an ideal choice for applications such as electrochemical chiral recognition and solar cells [89, 90]. As shown in Fig. 9 a, Zhu et al. have designed a novel strategy for the construction of v-SWCNTs. The v-SWCNTs array was successfully modified on GCE by simple cyclic voltammetry (CV). The carboxylated SWCNTs were ordered by carboxyethylenediamine (EDA) as a double peptide bond linker, attaching to the oxidized surface of the GCE to form a single-layer SWCNT array. Then, as a model molecule, D- and L-DOPA were distinguished to verify the chiral recognition ability of the chiral v-SWCNTs array modified GCE [91]. As shown in Fig. 9 b, He et al. have proposed a novel strategy of electrochemical measurement for the investigation of chirality recognition of (7, 6) and (6, 5) SWNTs with DNA-(6, 5) and DNA-(7, 6). The result showed that the length and sequence composition of the DNA chain significantly affect the interaction between chiral SWNT and DNA [92].

Although the separation of single-walled carbon nanotubes based on the helicity and habituality of single-helical carbon nanotubes has recently attracted great interest, the exploration of left-handed and right-handed SWCNTs enantiomers (defined as “M” and “P”) to conduct chiral sensing is still in its early stages. Pu et al. have separated the enantiomers from (6, 5) single-chirality SWCNTs via a mixed surfactant multicolumn gel chromatography, and then the left-handed (M-(6,5)) or right-handed (P-(6,5)) SWCNTs was modified on GCE to realize enantioselectivity, which were used for electrochemical chiral recognition of DOPA enantiomers by differential pulse voltammetry (DPV) (Fig. 9c) [93]. In addition to graphene and carbon nanotubes, graphene quantum dots are also a kind of chiral substrates in the field of electrochemical chiral recognition [2, 94].

Chiral recognition mechanism

According to previous studies, the most pivotal step for chiral recognition is the formation of diastereomeric complexes between the chiral selector and the enantiomers [95]. The result of electrochemical chiral recognition is caused by the different Gibbs free energy of the diastereomeric complex formed

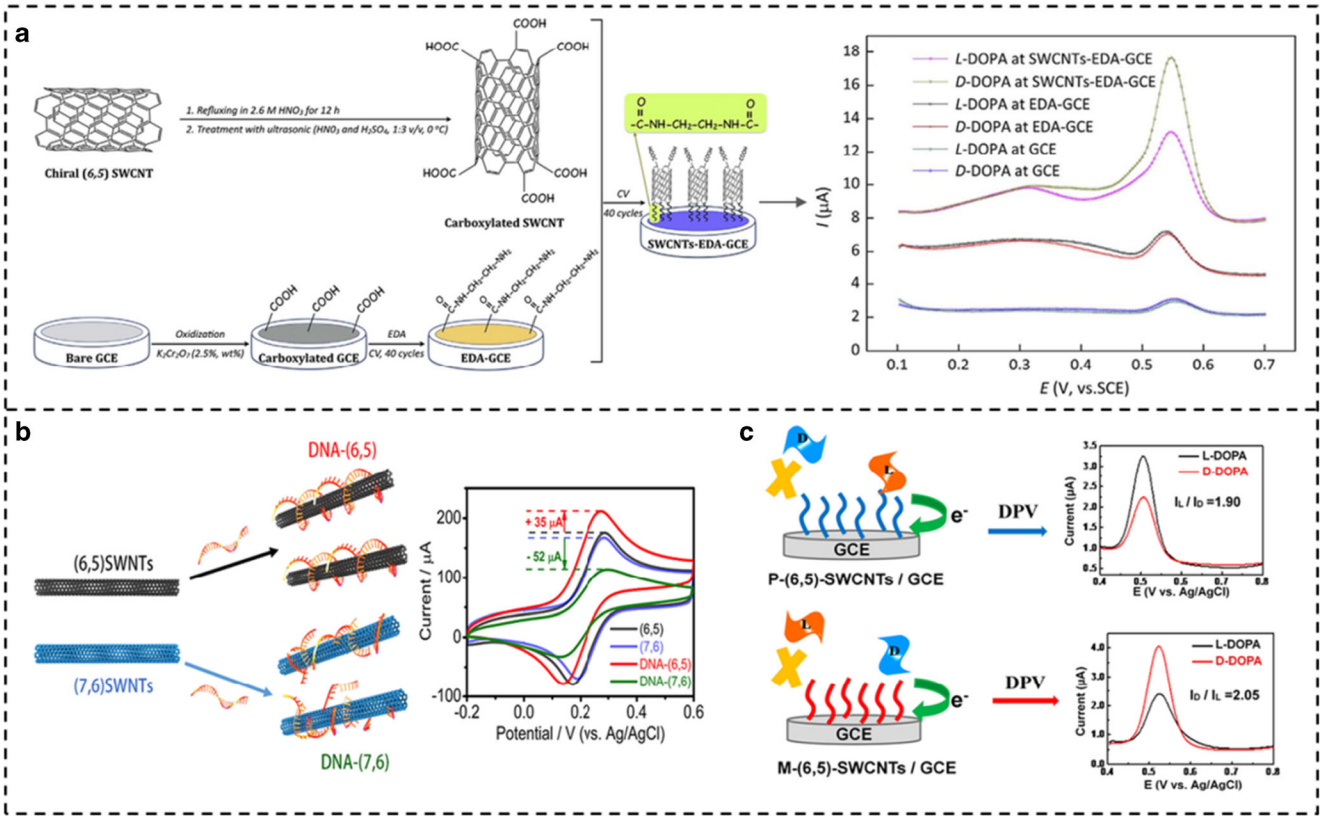

Fig. 9 **a** Schematic illustration of the modification of v-SWCNTs on GCE and its electrochemical recognition for DOPA enantiomers [91]. **b** The investigation on chirality selection of (7, 6) and (6, 5) SWCNTs with various DNA sequences and its electrochemical response [92]. **c** Schematic illustration of the formation of P-(6,5) SWCNTs/GCE and M-(6,5) SWCNTs/GCE and its electrochemical recognition [93]

between the two enantiomers and the chiral selector, converting it into visible electrochemical signal. The three-point force model [96–98] and the principle of chiral ligand exchange [99, 100] are often used to illustrate the mechanism of chiral recognition. In the three-point force recognition model, hydrogen bonding is very strong because negative sites can be very close to hydrogen atoms, which will exhaust any remaining repulsive electrons [101]. The steric hindrance is generated by the inherent space required by each atom or atom on the functional group, which is repulsive and very strong in a short distance [102]. The principle of chiral ligand exchange is based on diastereomeric ternary coordination compounds formed by analytes, metal ions, and chiral selectors [103]. According to the differences in the structural stability of the ternary metal complexes formed by the enantiomers of different configurations, they can be reflected on electrochemical signals to selectively identify the chiral enantiomers [104].

Molecular imprinting technology (MIT) is a potential method for the synthesis of polymers which has highly selective chiral recognition abilities for chiral molecules and use as separation media. Compared with traditional chiral recognition systems, chiral molecular imprinting of polymers has various merits, such as easy to operate, low cost, and flexibility to construct several self-supporting form. Molecular imprinting technology generates chiral recognition by creating a three-dimensional cavity with specific recognition. Günter Wulff first used molecularly imprinted polymers for chiral recognition in 1978 [105]. To prepare molecularly imprinted polymer (MIP), the system must contain the pure enantiomer (chiral template molecule), functional monomer, crosslinker, and initiator [106]. The template molecules were eluted with appropriate solvent to obtain the three-dimensional cavity of chiral molecular imprinting after successful imprinting [107]. Knowing how to prepare molecularly imprinted polymers can easily determine the affinity strength of the enantiomers used as templates. Chiral recognition based on molecular imprinting is mainly steric hindrance and size matching. The vital characteristic of chiral molecular recognition by molecular imprinting technology is its strong recognition specificity, which cannot play an important role in enantiomeric separation [108]. In addition, the stability of chiral molecularly imprinted polymers is easily affected by the change of external environment [109]. As shown in Fig. 10, Wattanakit et al. have reported the construction of chiral imprinted mesoporous platinum via the electrochemical reduction in the existence of a liquid crystal phase and DOPA molecules. Chiral imprinted mesoporous platinum obtained via the electrochemical reduction showed large specific surface area due to its mesoporosity, and also exhibited

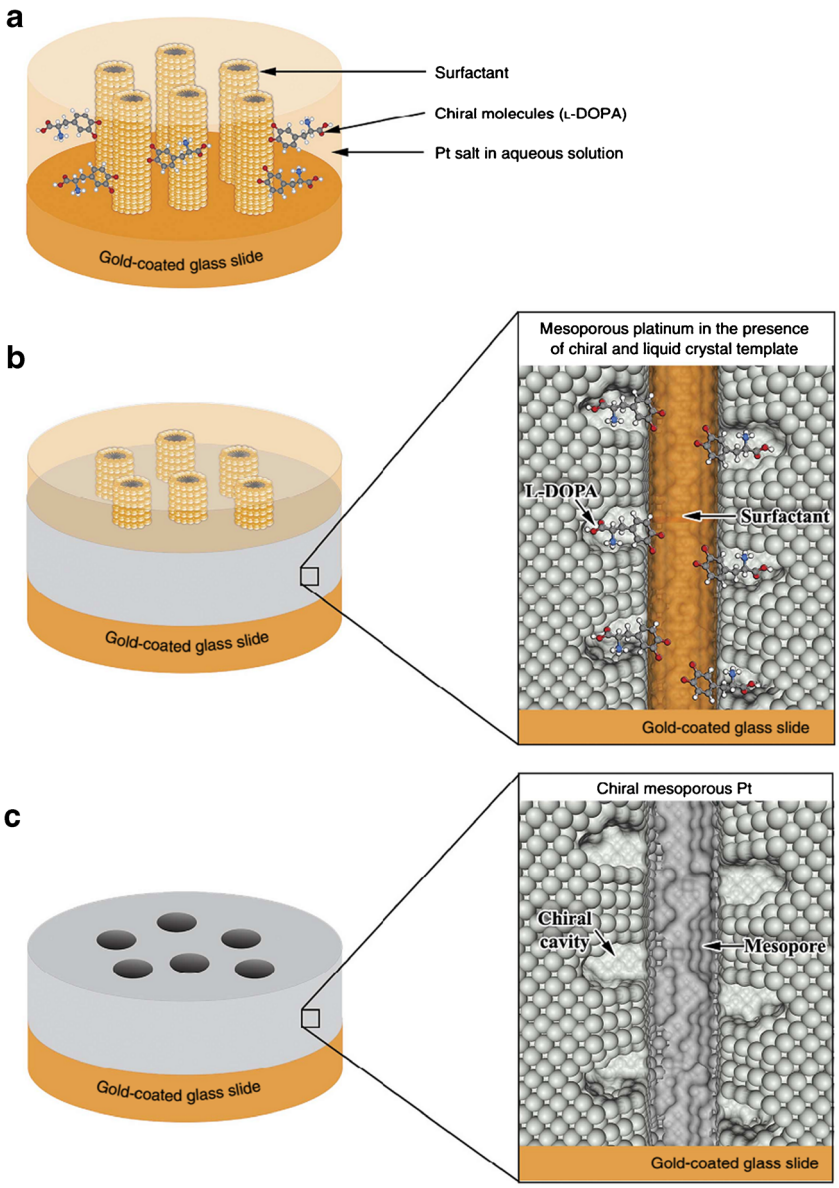

Fig. 10 **a** Interaction of the liquid crystal phase with the template molecules. **b** Electrodeposition of platinum around the self-assembled structure. **c** Structure of after template elution [110]

chiral recognition ability between L-DOPA and D-DOPA enantiomers [110].

Conclusion and outlook

Electrochemical chiral recognition is an efficient and sensitive detection method, which has attracted wide attention of researchers. The effect of chirality on biology and chemistry is well known. Effective methods are needed to quantitatively and qualitatively determine enantiomers with the increasing demand for chiral compounds in various fields, which of great significance to the future development of biotechnology due to most chiral molecules are biomolecules. The review exhibited the development of electrochemical chiral sensing interface in the past several years based on the chiral selectors, substrate material, and common mechanisms in the field of electrochemical recognition. The most important step to construct an electrochemical chiral sensing interface is to introduce chiral centers on the chiral interface. Proteins, polysaccharides, chiral ligand exchange compounds, chiral cavity (such as cyclodextrin, calixarene, and crown ether), chiral ionic liquids, amino acids, and their derivatives can provide chiral sites for chiral platforms. Carbon-based materials have excellent electrical conductivity, larger specific surface area, and better biocompatibility, which can provide a good sensing platform for electrochemical sensors, thereby improving detection sensitivity. Although many electrochemical chiral platforms have been developed, and have important guiding significance for the development of chiral recognition, there are still some prospects for the construction of practical electrochemical chiral sensors. (i) Researchers still need to design

and synthesize chiral composite materials with orderly structure and definite loading capacity to realize precise identification of chiral molecules and improve the efficiency of chiral recognition. (ii) The explanation of the chiral recognition mechanism needs to be supplemented in the field of electrochemical chiral sensors. The mechanism is clear when the chiral molecule with definite structure is used as chiral selector. However, the specific mechanism of is not clear due to the structure of macromolecular derivatives and polymers is uncertain. Therefore, the chiral recognition mechanism in the field of electrochemical chiral sensors still needs further study. (iii) Researchers still need to construct electrochemical chiral sensing platforms with specific recognition capabilities, and design a chiral drug separation equipment to realize batch separation of chiral drugs in industrial production.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing of interests.

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