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One-step hydrothermal synthesis of chiral carbon dots with high asymmetric catalytic activity for an enantioselective direct aldol reaction†

Shuang Liu,‡[ab] Yu He,‡[ab] Yu Liu,[b] Shuaibin Wang,[ab] Yajun Jian,[b] Baoxin Li[abc] and Chunli Xu*[ab]

Chiral carbon dots are prepared by a simple and one-step hydrothermal reaction at 180 °C for 2 h using citric acid and D-proline as precursors, which show high asymmetric catalytic activity for enantioselective direct aldol condensation. This work provides a hint for the simple preparation of heterogeneous chiral catalysts.

Chirality is a fundamental property of nature. In recent years, the demand for chiral compounds and chiral materials has promoted the development of asymmetric synthesis. The synthesis of chiral substances provides the scientific basis and material support for the research and development of chiral medicines, chiral pesticides and chiral materials.[1–3] Asymmetric catalytic synthesis requires only a small amount of chiral catalysts to convert a large number of pre-chiral substrates into chiral products, and is one of the most effective ways to obtain pure chiral substances. So far, successful asymmetric catalytic reactions have been usually homogeneous catalysis. Homogeneous chiral catalysts used in asymmetric catalytic reactions are divided into three types of compounds, including small organic molecules (such as amino acids and their derivatives, natural alkaloids and their derivatives, and chiral phosphoric acid),[4,5] metal–organic complexes (chiral salen–metal complexes, chiral naphthalene–diphenyl phosphate complexes, and chiral metal–oxazoline),[6,7] and enzymes (*e.g.*, hydrolase and redox enzyme).[8] In homogeneous catalysis, catalysts are homogeneously dispersed in a reaction system, which is beneficial to improve the catalytic activity of the catalysts, but not easy to separate from the reaction mixture after the reaction. So, it is difficult to recycle the expensive chiral catalyst, and the cost of production is increased. Furthermore, the purity of the product is affected by the catalyst.

Heterogeneous chiral catalysis can avoid the disadvantage of homogeneous catalysis and is beneficial for the industrial production of asymmetric synthesis.[7,9,10] Generally, there are no intrinsic chiral sites on the surface of heterogeneous catalysts. The chiral sites on the surface of heterogeneous catalysts are generated by the post-synthesis modification of chiral compounds. Chiral compounds (chiral ligands or chiral small organic molecules) are supported on the surface of pre-synthesized heterogeneous catalysts through physical adsorption,[10–12] encapsulation,[13] electrostatic interactions,[14] or chemical bonding,[15,16] to prepare heterogeneous chiral catalysts. Physical adsorption, encapsulation and electrostatic interactions, as non-chemical bonding methods, have the advantages of simple operation, but due to the weak force between the small chiral molecules and the heterogeneous catalysts, the chiral molecules can easily fall off, which is not conducive to the reuse of the catalysts. For chemical bonding modification, small chiral molecules are covalently attached to solid catalysts, and the heterogeneous chiral catalysts obtained were stable in structure and could be used many times. Chemical bonding modification generally requires modification of the supports, as well as the appropriate derivation of small chiral molecules (such as the addition of connecting arms), and then the chiral compounds are "anchored" to the surface of the supports through interface chemical reactions.[10,15,16] The chemical modification or derivation of supports and small chiral molecules generally requires multi-step organic chemical reactions, and the formation of the covalent bonding between supports and chiral compounds also has the problem of slow reaction speed and time consumption. These procedures are complicated and time consuming, and hereby increase the cost of catalyst preparation.[10,15,16] If the multi-step post-synthesis modification of the covalent bond process is substituted by a one-step method, the achieved heterogeneous chiral catalysts not only have the advantages of stability, but also can avoid the disadvantages of complicated and time-consuming procedures.

[a] *Key Laboratory of Applied Surface and Colloid Chemistry (Shaanxi Normal University), Ministry of Education, Xi'an, 710119, P. R. China. E-mail: xuchunli@snnu.edu.cn*
[b] *School of Chemistry and Chemical Engineering, Shaanxi Normal University, Chang'an West Street 620, Xi'an 710119, P. R. China*
[c] *Key Laboratory of Analytical Chemistry for Life Science of Shaanxi Province (Shaanxi Normal University), Xi'an 710119, P. R. China*

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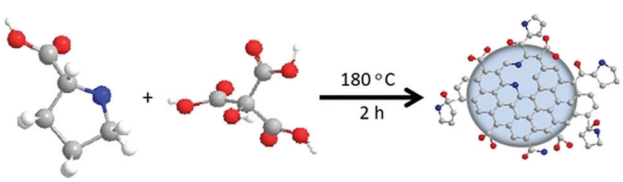
‡ Co-first author.

As a new kind of metal-free nanomaterial, carbon quantum dots (CQDs, carbon dots) have attracted extensive attention from researchers in the fields of physics, chemistry, and biology due to their strong quantum confinement effects and stable fluorescence properties.[17–19] Since CQDs were first discovered in 2004, researchers have developed a number of synthesis methods.[20] The solvo-thermal synthesis method can produce CQDs in one-step, and the process is very simple. The exact structure of the resulting CQDs is still disputed, but the surface functional groups of the CQDs are generally believed to be covalently attached to the carbon nucleus.[18,19,21] Recently, researchers have found a very interesting phenomenon that the active structure of the precursor molecules can be retained on the surface of the carbon dots. So, the carbon dots can have some characteristics of the precursor molecules.[22] For example, carbon dots prepared by the hydrothermal method using folic acid as a precursor retains folic acid characteristics and can recognize folic acid receptors on the surface of cancer cells.[23] With ciprofloxacin as the precursor, the carbon dots prepared by the hydrothermal method retained the antibacterial properties of ciprofloxacin, and could effectively inhibit the growth of *Staphylococcus aureus* and *Escherichia coli*.[24] The researchers refer to the ability of carbon dots to retain the molecular properties of their precursors as the "memory effect".[22,25] In 2019, Zammataro *et al.* prepared the carbon dots and then fixed the chiral complex Mn-Salen-OH to the carbon dots by the covalent bonding mode, and studied their catalytic performance in the enantioselective epoxidation of olefins.[26] This study preliminarily proved the feasibility of using carbon dots as catalyst supports and the possibility of using chiral carbon dots for asymmetric catalysis. However, the traditional post-covalent bond loading method has the disadvantages of complex and time-consuming operation.

A direct asymmetric aldol reaction is one important reaction in biosynthesis, which can increase the carbon chain, and its products are widely used in biomedicine and other fields.[27] Han *et al.* found that carbon quantum dots display photo-enhanced hydrogen-bond catalytic ability in aldol condensation.[28] In this work, chiral carbon dots (CA-D$_P$-CQDs) are prepared by a one-step hydrothermal reaction at 180 °C for 2 h (Scheme 1). In this method, citric acid (CA, carbon source) and D-proline (D-Pro, chiral source) were used as the precursors for CA-D$_P$-CQDs. The obtained carbon dots were used to catalyze the aldol condensation reaction. Unexpectedly, we found that the one-step prepared CA-D$_P$-CQDs had a chiral catalytic activity. The carbon dots could catalyze the aldol condensation reaction of *P*-nitrobenzaldehyde and cyclohexanone, with a yield of 98% (^{1}H NMR results) and 73% ee. For comparison, carbon dots were also similarly prepared using



Scheme 1 The schematic illustration for the synthesis of CA-D$_P$-CQDs.

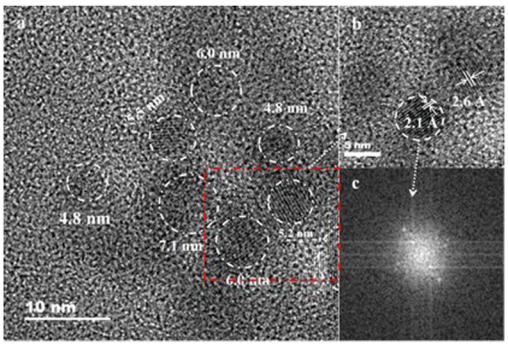


Fig. 1 Electron microscopy images and the inverse Fourier transform diffraction pattern of CA-D$_P$-CQDs. (a and b) HRTEM and (c) the inverse Fourier transform electron diffraction pattern of a single carbon dot in the selected area of (b).

single CA or D-Pro as raw materials. The obtained carbon dots were named CA-CQDs with single CA as the raw material and D$_P$-CQDs with single D-Pro as the raw material, respectively.

Fig. 1a shows the HRTEM image of CA-D$_P$-CQDs taken under a 10 nm ruler. It can be seen that CA-D$_P$-CQDs are uniformly dispersed and the mean particle size is 5.5 ± 1.5 nm. The lattice spacings of 2.6 Å and 2.1 Å in Fig. 1b, which respectively correspond to the (100) and (002) crystal planes of graphene, are observed.[29] The lattice fringes of CA-D$_P$-CQDs are similar to those of carbon dots synthesized by the carbonization of citric acid alone in the literature.[30] Fig. 1c displays the inverse Fourier transform diffraction pattern of a single carbon dot. Two pairs of apertures are observed, which correspond to 2.6 Å and 2.1 Å diffraction spots. This indicated that CA-D$_P$-CQDs are composed of a graphite core.

FT-IR spectrum of CA-D$_P$-CQDs (Fig. 2) displays the inheritance from the characteristic peaks of raw materials and new characteristic peaks. The broad peak at 3460 cm^{-1} is assigned to O–H and N–H stretching vibrations inherited from the carboxylic acid and amine groups in CA and D-Pro.[31,32] The small dump at 2969 cm^{-1} may be caused by the C–H stretching vibration, which inherits from D-Pro. The absorption signals at 1729 cm^{-1} and 1440 cm^{-1} are attributed to C=O stretching vibration peaks inherited from the characteristic peaks of COO$^-$ in CA or D-Pro.

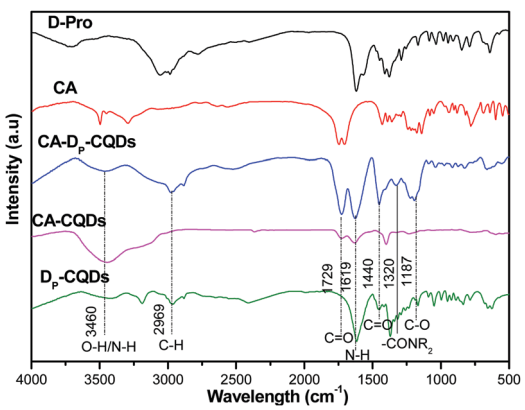


Fig. 2 FTIR spectra of CA-CQDs, D$_P$-CQDs, CA-D$_P$-CQDs, and the raw materials of CA and D-Pro.

The peaks at 1619 cm^{-1} are assigned to the asymmetric bending vibration of the amino group from D-Pro.[33] The adsorption signals at 1187 cm^{-1} are attributed to C–O stretching vibration peaks inherited from the characteristic peaks of CA or D-Pro, which are stronger in intensity than those of C–O in CA-CQDs and D_P-CQDs. In contrast with the FTIR spectra of raw materials (D-Pro and CA) and carbon dots (CA-CQDs and D_P-CQDs) from single raw materials, CA-D_P-CQDs display a new peak at 1320 cm^{-1} assigned to $-CONR_2$. The difference in the FTIR spectra indicates that CA-D_P-CQDs result from not the physical mixture of CA-CQDs and D_P-CQDs, but that D-Pro and CA react with each other and undergo dehydration polymerization to form new chemical bonds of $-CONR_2$ and more C–O bonds on the carbon skeleton.[34] FT-IR analysis indicates that CA-D_P-CQDs have both the inheritance properties and new properties.

As shown in Fig. 3a, the circular dichroism (CD) signal of D-Pro appears at 212 nm. Compared with the D-Pro raw material, the CD signal of CA-D_P-CQDs at 208 nm in Fig. 3b should be the inheritance of the chiral signal of D-Pro, while the new chiral peak at 220 nm may be caused by the π–π^* conjugation of sp^2-hybridized carbon in the carbonized core of CA-D_P-CQDs.[34] The CD signals of CA-D_P-CQDs indicate that the synthesized carbon quantum dots have chirality. As shown in Fig. 3b, the effect of hydrothermal time on the chirality of synthesized carbon quantum dots was explored. With the increase of hydrothermal time, the inherited chiral signal at 208 nm gradually weakens, and a new chiral signal at 220 nm appears at 6 h hydrothermal time. The intensity of the new chiral signal increases with hydrothermal time, and it reaches the strongest at 8 h. Above 8 h, the intensity decreases. The results indicate that the chirality of CA-D_P-CQDs is inherited from their precursor D-Pro and affected by hydrothermal time.

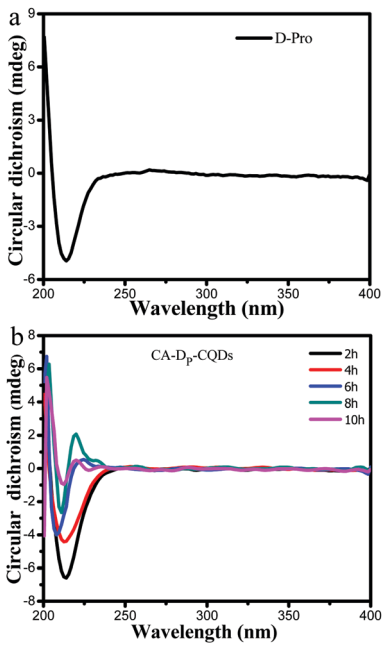


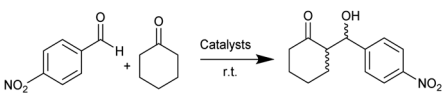
Fig. 3 CD spectra of D-Pro (a) and CA-D_P-CQDs with different hydrothermal times (b).

The direct aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone was chosen as the model reaction to evaluate the asymmetric catalytic activity of the obtained CQDs. As shown in Table 1, CA-D_P-CQDs prepared under 2 h (or 4 h) hydrothermal time were an excellent catalyst, furnishing the corresponding aldol product in 98% yield with >95% De and >71% ee (Table 1, entries 5 and 9). The asymmetric catalytic activity of CA-D_P-CQDs was also higher than those of both CA-CQDs (entry 3) and D_P-CQDs (entry 4). Under the same reaction conditions, CA-CQDs provided no products, and D_P-CQDs furnished the corresponding aldol product in 58% yield. This indicates that the asymmetric catalytic performance of the carbon dots prepared by binary materials is higher than those prepared by single materials. The reusability of CA-D_P-CQDs is tested (Table 1, entries 5–8). It shows similar asymmetric activity in the first three times. In the fourth time, the reaction time lasts longer than the former, but the enantioselectivity remains unchanged.

The structural analysis by TEM, FTIR, and CD indicates that CA-D_P-CQDs are chiral and composed of a carbon core and surface functional groups. The asymmetric structure may result in the intrinsic asymmetric catalytic activity of CA-D_P-CQDs. Since the D-Pro precursor of CA-D_P-CQDs is also chiral and has asymmetric catalytic activity, the asymmetric catalytic activity of CA-D_P-CQDs may have resulted from either their intrinsic structure or the residual uncarbonized D-Pro precursor.

In order to ensure that the asymmetric catalytic activity of CA-D_P-CQDs comes from their own structure and not from the remaining uncarbonized raw materials of D-Pro, a controlled experiment is carried out. D-Pro furnishes the corresponding aldol product in 96% yield with >95% de and 93% ee (Table 1, entry 1), which is consistent with ref. 35. However, D-Pro after

Table 1 Direct aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone in the presence of catalysts[a]



Entry	Catalysts	Hydrothermal time (h)	Reaction time (h)	Yield	De (anti)[b] (%)	ee% (S)
1	D-Pro[c]	—	24	96	95	93
2	The dialyzed D-Pro[d]	—	48	n.a.[e]	n.a.	n.a.
3	CA-CQDs	4	48	n.a	n.a.	n.a.
4	Dp-CQDs	4	24	58	94	81
5	CA-Dp-CQDs^{1st}	2	24	98	96	71
6	CA-Dp-CQDs^{2nd}	2	24	98	96	65
7	CA-Dp-CQDs^{3rd}	2	24	98	96	65
8	CA-Dp-CQDs^{4th}	2	32	98	96	65
9	CA-Dp-CQDs	4	24	98	95	73

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.5 mmol, 75.5 mg), cyclohexanone (5 mmol), catalyst in 2 mL of DMSO/H_2O (3 : 1). The reactions were carried out at room temperature. [b] Diastereomeric excess (De) = anti-diastereomers/(anti-diastereomers + syn-diastereomers), which is determined by ^1H NMR (400 Hz). [c] Directly catalyzed by the raw material of D-Pro, the amount added is 20% mol of the substrate. [d] 0.6600 g of D-Pro was dialyzed for three days. [e] n.a. = not applicable.

dialysis for 3 days shows no asymmetric catalytic activity (Table 1, entry 2). This indicates that dialysis could remove all the liquid D-Pro. Dialysis is also a common method to purify carbon dots reported in literature studies.[36,37] Since the dialysis conditions of CA-D_P-CQDs are the same as those of D-Pro, even if there are residues of D-Pro that are not carbonized, they can be removed by dialysis. Therefore, the asymmetric catalytic activity of CA-D_P-CQDs should come from their asymmetric structure, and not from the remaining uncarbonized raw materials of D-Pro. Hereby, the asymmetric structure provides the intrinsic asymmetric catalytic activity of CA-D_P-CQDs. Since CA-D_P-CQDs were prepared by a one-step hydrothermal method from citric acid and chiral D-Pro with asymmetric catalytic activity, the intrinsic catalytic activity of carbon dots indicates that they had a chiral catalytic memory effect.

In summary, a CA-D_P-CQD catalyst is prepared by a one-step hydrothermal method using D-Pro and citric acid as raw materials. It is composed of a graphite core with a mean size of 5.5 nm and surface functional groups of N–H, C–H, C═O, C–O, and –$CONR_2$. CA-D_P-CQDs display chiral character and show high asymmetric catalytic performance in direct aldol reactions. When the hydrothermal time is 2 h (or 4 h), the obtained CA-D_P-CQDs display high asymmetric catalytic activity for the direct aldol condensation of *P*-nitrobenzaldehyde and cyclohexanone, as shown by a yield of 98% (^{1}H NMR results) and an ee% of >71%. Furthermore, CA-D_P-CQDs are reusable and can be used 4 times. This work demonstrates that chiral CQDs have the memory effect of asymmetric catalytic activity. The present work opens a new way to prepare heterogeneous chiral catalysts.

Shuang Liu: data curation, and writing – original draft. Yu He: data curation. Yu Liu: data curation. Shuaibin Wang: data curation. Yajun Jian: writing – review and editing. Baoxin Li: writing – review and editing. Chunli Xu: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, and writing – review and editing.

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Conflicts of interest

There are no conflicts to declare.

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