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Communication

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Catalytic Asymmetric Synthesis of Chiral Covalent Organic Frameworks from Prochiral Monomers for Heterogeneous Asymmetric Catalysis

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ABSTRACT: Direct synthesis, post-synthetic modification and chiral induction have been recognized as three powerful methods to synthesize chiral covalent organic frameworks (CCOFs). However, catalytic asymmetric methodology, as the most important and effective synthetic approach to access chiral organics, has not been enabled for CCOFs synthesis thus far. Herein we report, for the first time, the construction of CCOFs from prochiral monomers via catalytic asymmetric polymerization. The obtained propargylamine-linked CCOFs can be the highly reusable chiral catalysts to promote asymmetric Michael addition reactions. The concept of catalytic asymmetric polymerization might open a new route for constructing the CCOFs that are not possible with the existing CCOF synthetic methods.

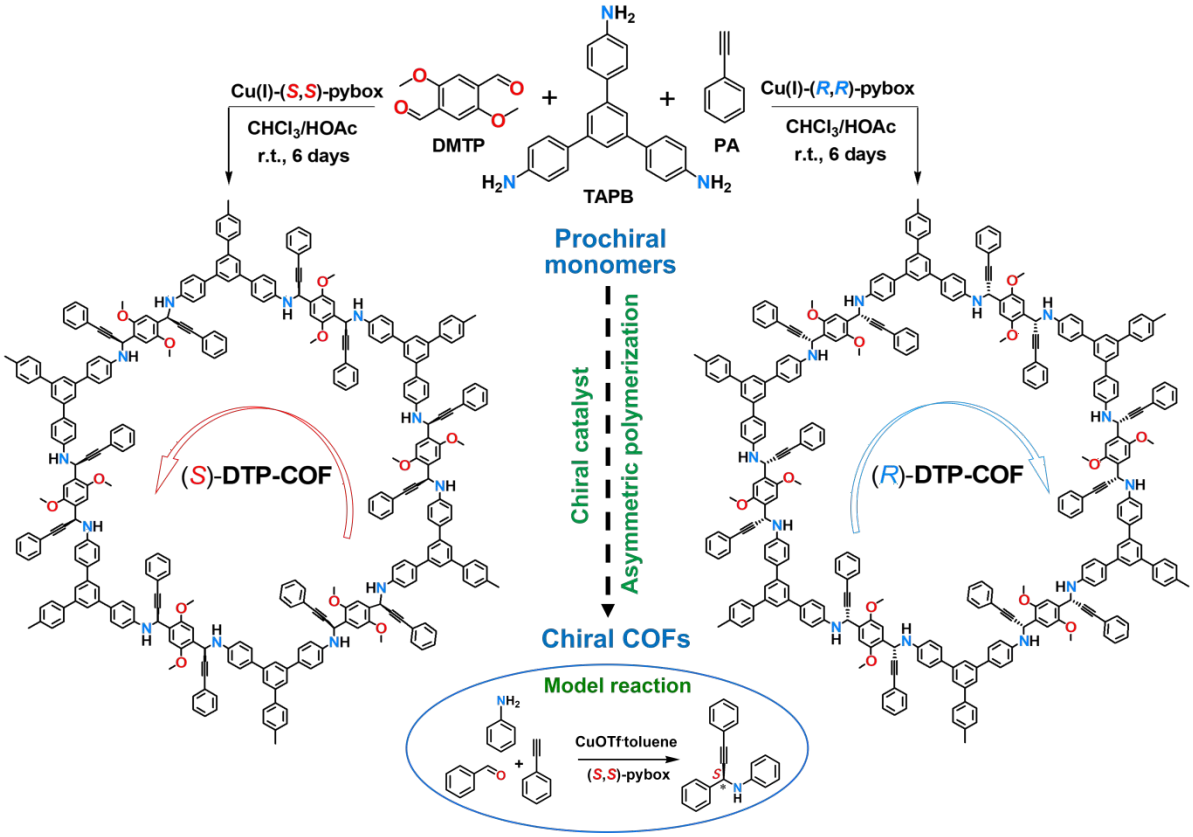
Since Yaghi et al. reported the first example of covalent organic framework (COF) in 2005,[1] COF-chemistry has grown at a breathtaking pace. In addition to adsorption/separation,[2] sensing,[3] and biomedical[4] uses, a surge of interest has occurred in COF-based catalysis.[5] Compared with the vigorous development of achiral COF synthesis and their symmetric catalysis, the chiral covalent organic framework (CCOF) synthesis and CCOF-based asymmetric catalysis, however, has drawn much less attention.[6] Nevertheless, as new appointee in asymmetric catalysis, the CCOF-based catalysts are walking into the sight field of chemists. For example, several recent reports show that the organocatalysts,[7] metal nano particles,[8] and metal-ion[9] loaded CCOFs can efficiently promote asymmetric organic transformations in heterogeneous way. Therein, the highly ordered arrangement of chiral entity in the well-defined inner channels, together with the rigid COF skeleton, can endow CCOFs with the tenacious chiral confined space, consequently, ensures the optical purity of the products under the reaction conditions.

To date, the reasonable synthetic approaches for CCOFs have been known as direct synthesis (direct polymerization of the chiral organic monomers), post-synthetic modification (PSM, decoration of the established COFs by chiral species) and chiral induction methods (chiral additives involved polymerization).[6] As the most powerful and efficient synthetic strategy to access chiral organics, asymmetric catalysis,[10] however, has not yet debuted. We anticipate that the conversion of prochiral monomers to the CCOFs via asymmetric catalysis would not only provide a new dimension to the design and synthesis of CCOFs, but could allow the CCOFs synthesis to be more powerful.

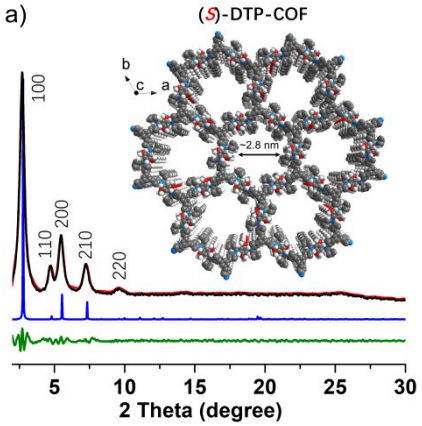
Inspired by the large library of asymmetric organic reactions, we surmise that CCOFs can also be prepared by catalytic asymmetric polymerization of the prochiral monomers with the aid of chiral catalysts. To test the possibility, we chose to employ the multicomponent one-pot *in situ*[11] catalytic asymmetric polymerization of divergent achiral dialdehyde, triamine with terminal aryl alkyne to prepare the propargylamine-linked CCOFs. As we know, the chiral pyridine-2,6-bis(oxzolines)-Cu(I)[12] complexes are highly efficient catalysts for the synthesis of chiral propargylamines from prochiral aldehydes, amines, and alkynes under mild conditions via A^3-coupling reactions.[13]

As shown in Scheme 1, the model reaction among benzaldehyde, aniline and phenylacetylene afforded model compound of *N*-((*S*)-1,3-diphenylprop-2-ynyl)benzenamine (*N*-(*S*)-DPPYBA) in 92% yield with 99% ee in the presence of CuOTf·toulene/(*S*, *S*)-2,6-bis(4-phenyl-2-oxazolinyl)pyridine ((*S*, *S*)-pybox) at room temperature (Figure S1). Based on this, we performed the catalytic asymmetric synthesis of CCOF from the corresponding prochiral monomers. As a result, the chiral propargylamine-linked (*S*)-**DTP-COF** was successfully synthesized via catalytic asymmetric polymerization of 2,5-dimethoxyterephthaldehyde (DMTP), 1,3,5-tris(4-aminophenyl)benzene (TAPB) and phenylacetylene (PA) in 61% yield as dark red crystalline solids with the assistance of CuOTf·toluene/(*S*, *S*)-pydox (Scheme 1). Of note, the optimized conditions were established as crystallization at room temperature for six days in $CHCl_3$ with HOAc. Unlike conventional COF synthesis, this approach did not require any vigorous reaction conditions, such as solvothermal at high temperature and high pressure.

Scheme 1. Synthesis of (*S*)- and (*R*)-DTP-COFs via Catalytic Asymmetric Polymerization, with the Corresponding Model Reaction in the Inset



The measured powder X-ray diffraction (PXRD) pattern of (*S*)-**DTP-COF** (Figure 1a, black) indicated that it was microcrystalline material, and a series of observed peaks at 2.7°, 4.7°, 5.4°, 7.2° and 9.6° were assigned to the (100), (110), (200), (210) and (220) facets, respectively. Simulation of its PXRD pattern with Materials Studio[14] suggested that it possessed the most probable structure with 2D eclipsed (AA) stacking, and the Pawley refinement showed a negligible difference between the simulated and experimental PXRD pattern (Figure 1a, red). (*S*)-**DTP-COF** was assigned to the chiral space group *P*6 with optimized parameters of $a = b = 36.83$ Å, $c = 4.70$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, residuals w*R*p = 9.81% and *R*p = 7.61% (Table S1).



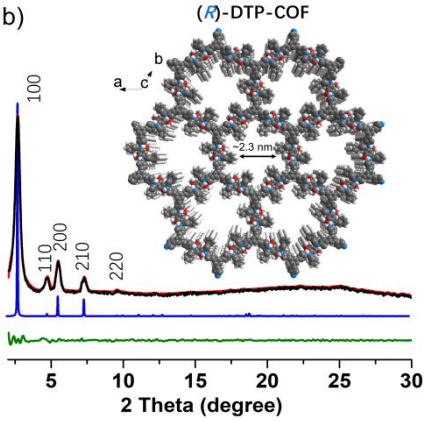


Figure 1. Indexed experimental (black), Pawley-refined (red), and simulated (blue) PXRD patterns of (*S*)-**DTP-COF** (a) and (*R*)-**DTP-COF** (b). The difference plots are presented in green. Eclipsed structures proposed for (*S*)- and (*R*)-**DTP-COF** are shown as top insets (C, dark gray; N, blue; O, red; H, white).

Formation of the propargylamine linkage was confirmed by FT-IR and ^{13}C CP-MAS solid-state NMR spectroscopy. The FT-IR spectra showed typical bands for C≡C-H at 3293 cm^{-1} in PA, NH_2 at 3434 and 3454 cm^{-1} in TAPB, and CHO at 1670 cm^{-1} in DMTP basically disappeared, meanwhile the characteristic peaks at 3377 (NH), and 1286 cm^{-1} (C-N) appeared after polymerization (Figure S2a). The observed

carbon resonances in ^{13}C NMR showed that (*S*)-**DTP-COF** contains methoxyl (~56 ppm) and aromatic (~109–128 ppm) species. Furthermore, the weak peaks at approximately 49 and 74 ppm respectively attributed to the -*C*NH- and -*C*≡*C*- species unambiguously verified the formation of propargylamine linkage (Figure S2b). All these assignments were determined according to the chemical shifts of corresponding carbons on model compound and literature reports.

The porosity of (*S*)-**DTP-COF** was examined by gas adsorption–desorption measurement, and its sorption profile can be described as a type IV isotherm, which is characteristic of mesoporous materials. N_2 adsorption at 77 K revealed absorption of 282 cm^3/g for (*S*)-**DTP-COF** (Figure S2c), and its surface area calculated on the basis of the BET model was determined to be 684 m^2/g. The pore size distribution curves, calculated via nonlocal density functional theory (NLDFT) analysis (Figure S2c inset), showed that the pore width of (*S*)-**DTP-COF** is centered at ~2.9 nm, which is in good agreement with its simulated structure. (*S*)-**DTP-COF** is stable against organic (THF, DMSO, DMF, EtOH, $CHCl_3$), water, basic (NaOH aqueous solution, 12M) and acidic (HCl aqueous solution, 2M) media (Figure S2d).

Scanning electron microscopy (SEM) image indicated that (*S*)-**DTP-COF** was nanometer-scale material (Figure S2e), and no different morphology was observed, further indicating that it was obtained in single phase. Its transmission electron microscope (TEM) image again evidenced its high crystalline nature (Figure S2f). Thermogravimetric analysis (TGA) suggested that it is thermally stable up to ~300 °C (Figure S2g).

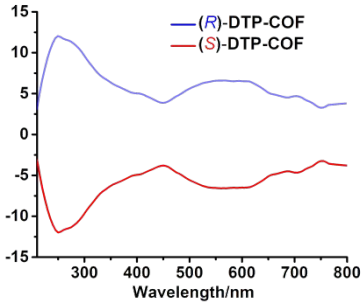
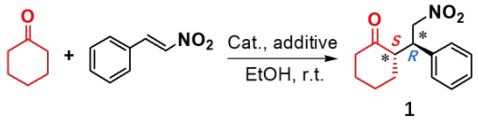


Figure 2. CD spectra showing that the pairs of (*S*)- and (*R*)-**DTP-COF** are mirror images of one another.

The chiral nature of (*S*)-**DTP-COF** was proved by its circular dichroism (CD) spectrum. As shown in Figure 2, (*S*)-**DTP-COF** is optically active and displayed negative Cotton effect at ca. 250, 580 and 704 nm, and positive dichroic signals at ca. 450 and 753 nm in its CD spectrum.

As shown above, (*S*)-**DTP-COF** is an amino-enriched chiral porous material, so we envision that it could be the asymmetric organic catalyst to promote aminocatalytic reactions,[15] such as Michael addition, in a heterogeneous way. We then chose the reaction of cyclohexanone with 1-((*E*)-2-nitrovinyl)benzene as a model Michael addition reaction to optimize the reaction conditions. The yield, diastereomeric ratio (dr), and enantiomeric excess (ee) for the (*S*)-**DTP-COF**-catalyzed Michael addition, together with a series of control experiments, are displayed in Table 1 (entries 1-8). The best result was obtained when the reaction was performed in EtOH with (*S*)-**DTP-COF** (5 mg, 3.3 mol % based on NH) and *p*-TsOH at room temperature for 13 h (entry 1). The desired *γ*-nitroketone of **1** was generated in 97% yield with 96% ee and 72:28 dr (TON = 29.4, TOF = 2.7 h^{-1}). Without acid (entry 2) or with other kinds of acids (entries 3-5), the reactions afforded the desired product in much lower yields (13-78%). In the absence of (*S*)-**DTP-COF**, no conversion was observed under the same conditions (entry 6). In addition, when the reaction was carried out with a lower catalyst loading, 2.0 mol % instead of 3.3 mol %, the desired product was isolated in a slightly lower 92% yield but with excellent ee (95%) and dr (72:28) values (entry 7). Also, more CCOF loading (4.5 mol%) could not substantially enhance the yield (97%), ee (96%) and dr (72:28) values (entry 8). In comparison with the reported $[(S)\text{-Py}]_{0.17}$-TPB-DMTP-COF[7b] and Tfp2-COF,[7d] (*S*)-**DTP-COF** provided better yield and ee values, but with worse anti/syn ratio for the synthesis of **1**.

Table 1. Optimization of Reaction Conditions for the Model Asymmetric Michael Addition Catalyzed by (*S*)-DTP-COF[a]



1

EN	cat.	additive	yield (%)[b]	dr[c]	ee (%)[c]
1	**(*S*)-DTP-COF**	***p*-TsOH**	**97**	**72:28**	**96**
2	(*S*)-**DTP-COF**	-	33	76:24	86
3	(*S*)-**DTP-COF**	CH_3CO_2H	35	75:25	95
4	(*S*)-**DTP-COF**	CF_3SO_3H	78	73:27	94
5	(*S*)-**DTP-COF**	$PhCO_2H$	13	74:26	95
6	-	*p*-TsOH	-	-	-
7[d]	(*S*)-**DTP-COF**	*p*-TsOH	92	72:28	95
8[e]	(*S*)-**DTP-COF**	*p*-TsOH	97	72:28	96
9	*N*-(*S*)-DPPYBA	*p*-TsOH	21	55:45	74

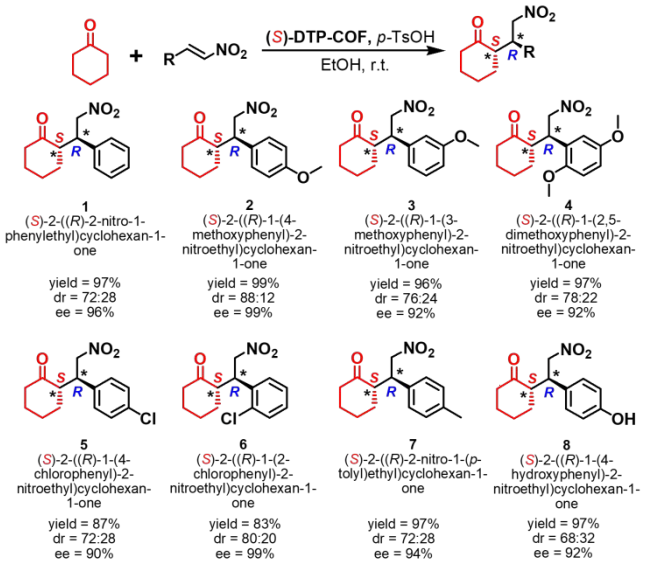
[a]Reaction conditions: cyclohexanone (10 mmol), 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol), additive (20% mol), acid (0.05 M), EtOH (2 mL), catalyst (5 mg, 3.3 mol % based on NH), 13h. [b]Isolated yield. [c]The dr and ee values were determined by chiral HPLC (Figure S3). [d](*S*)-**DTP-COF** (2.0 mol %). [e](*S*)-**DTP-COF** (4.5 mol %).

In contrast, the synthesis of **1** catalyzed by molecular model compound of *N*-(*S*)-DPPYBA only provided 21% yield with 55:45 dr and 74% ee in a homogeneous way (Table 1, entry 9), indicating that the (*S*)-**DTP-COF** displayed much better activity and chiral templating effect to its homogeneous control.

The hot leaching test confirmed that (*S*)-**DTP-COF** is a typical heterogeneous catalyst (Figure S4a), and it could be reused and gave a 96% yield with 72:28 dr and 95% ee at the tenth catalytic run (Figure S4b). The slightly decreased yield and ee value might result from a modestly reduced

surface area (Figure S4c) although no detectable morphology (Figure S4d) and crystallinity (Figure S4e) changes were observed after ten catalytic cycles.

Table 2. Scope of the Michael Addition Reactions Catalyzed by (*S*)-DTP-COF[a]



[a]Reaction conditions: cyclohexanone (10 mmol), aromatic nitroolefin (0.5 mmol), *p*-TsOH (20% mol, 0.05M), EtOH (2 mL), (*S*)-**DTP-COF** (5 mg, 3.3 mol % based on NH), 13 h. Isolated yield. Compounds **1**-**8** were characterized by ^{1}H NMR, ^{13}C NMR and MS spectra, and their dr and ee values were determined by chiral HPLC (Figure S5).

The generality of this CCOF-catalyzed Michael addition was also verified. As shown in Table 2, the Michael addition reactions of cyclohexanone with -OCH_3, -Cl, -CH_3 and -OH substituted *β*-nitrostyrenes at different positions proceeded smoothly under the optimal conditions, and provided 82-99% yields with dr = 68:32-88:12 and 90-99% ee values, respectively (Figure S5). However, the larger-sized β-tetralone with 9-(2-nitrovinyl)anthracene could not afford the desired product (yield, ∠1%), suggesting that (*S*)-**DTP-COF** possesses substrate size effect. Besides, we are pleased that this (*S*)-**DTP-COF**-catalyzed Michael addition can be readily scaled up. For example, **1** was generated in 93% yield (1.6 g) with 96% ee and 72:28 dr via gram-scale reaction under the given conditions (Figure S6).

The absolute configuration of Michael addition product was determined by the single-crystal analysis. For example, **2** crystallizes in a chiral orthorhombic crystal system with space group $P2_12_12_1$ (No. 19, CCDC 2015687) (Figure 3, Tables S2). The absolute configuration of the chiral centers is as follows: C9 (*S*), C8 (*R*), which is further supported by the positive (~250 nm) and negative dichroic signals (~294 nm) in its CD spectrum (Figure 3).

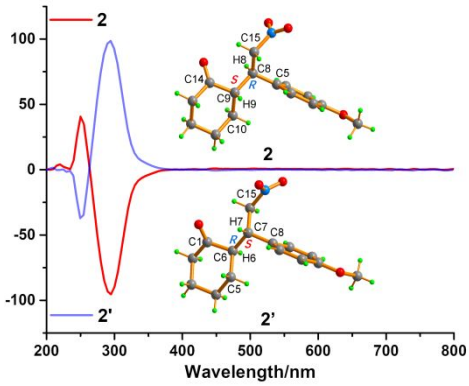


Figure 3. X-ray single-crystal crystal structures (insets) and CD spectra indicating the pair of **2** and **2'** are mirror images of each other.

Moreover, we performed the same catalytic asymmetric polymerization for **DTP-COF** synthesis, but with (*R*, *R*)-pybox instead of (*S*, *S*)-pybox. As expected, the (*R*)-**DTP-COF** was readily generated (Scheme 1, Figure S7). Simulation of its PXRD pattern with Materials Studio indicated that it features the same eclipsed 2D structure as (*S*)-**DTP-COF** (Figure 1b, Table S3), but with the opposite chirality (Figure 2). With the aid of (*R*)-**DTP-COF**, compound **2'**, a mirror-image isomer of **2** (Figure 3), was legitimately obtained in 99% yield with dr = 87:13 and 99% ee under the same reaction conditions (Figure S8). Its absolute configuration was once again confirmed by the single-crystal analysis (Figure 3, Table S4, CCDC 2015688). The result revealed that the chiral **DTP-COF** herein possessed a powerful chiral confinement effect which could regulate the product enantioselectivity by expediently tuning the CCOF chirality.

The excellent catalytic stereoselectivity of both (*S*)- and (*R*)-**DTP-COFs** clearly resulted from their high-optical purity (93% ee) (Figure S9, Table S5). Worth noting is that non-optically active COF could be obtained by using racemic pybox than chiral one (Figure S10, Table S5). Additionally, the generality of asymmetric polymerization methodology for CCOF synthesis was further demonstrated via the same asymmetric A^3-coupling reactions with different monomers (Figure S11-S15, Supporting Information).

In conclusion, we have successfully designed and synthesized a series of propargylamine-linked CCOFs via asymmetric catalysis from prochiral monomers under ambient conditions. Catalytic asymmetric polymerization herein convincingly complements the existing approaches of CCOFs synthesis. In addition, the obtained chiral propargylamine-linked DTP-COFs can be the highly active reusable catalysts to promote asymmetric Michael addition reactions (Table S6), even at a gram-scale level. We believe that the concept of catalytic asymmetric polymerization is general, moreover, significantly broadens the scope of CCOFs synthesis.

ASSOCIATED CONTENT

Supporting Information. Instruments and methods; synthesis and additional characterization of CCOFs; catalytic procedure;

catalytic products characterization; crystallographic information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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