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Divergent Synthesis of Chiral Covalent Organic Frameworks

Li-Ke Wang, Jing-Jing Zhou, Yu-Bao Lan, San-Yuan Ding, Wei Yu, and Wei Wang*

ABSTRACT: Featuring the simultaneous generation of a library of compounds from certain intermediate, divergent synthesis has found increasing applications in the construction of nature products and potential medicines. Inspired by this approach, we present herein a general strategy to introduce functionality, in a divergent manner, into covalent organic frameworks (COFs). This modular protocol includes two stages of covalent assembly, through which a number of functional COFs can be constructed through three-step transformation of a key platform molecule, such as 4,7-dibromo-2-chloro-1*H*-benzo[*d*]imidazole (**DBCBI**). We constructed herein four types of chiral COFs (CCOFs) from **DBCBI** via nucleophilic substitution, Suzuki coupling, and imine formation. The unique array of eight isoframework CCOFs further allowed us to compare their catalytic performance and study the structure-activity relationship in many important transformations, such as asymmetric amination reaction.

Inspired with the diversity created by nature, organic chemists have been using the divergent strategy to improve the synthetic efficiency of nature products.[1] In difference from the target-oriented synthesis (Figure 1a), the divergent synthesis is conceptually featured in the designed construction of a series of compounds from certain intermediate (Figure 1b). This strategy is extremely advantageous when the follow-up applications involve high-throughput screening processes[2], such as in drug discovery or catalyst development. Many biomacromolecules, such as DNA and proteins, are also divergently synthesized naturally or artificially from limited kinds of nucleotides and amino acids.[3] However, the powerfulness of divergent synthesis in the field of functional materials[4] is yet to be illustrated. We establish herein a divergent strategy (Figure 1c) to obtain a combinatorial library of functional covalent organic frameworks (COFs).

The research area of COFs[5] has gained rapid progress in the past decade. The identity of a crystalline COF involves its framework topology, the mortise-and-tenon joint, and the functional moiety. Many novel COFs have been ingeniously constructed with the diversity in structures or covalent joints.[5,6] In this context, further construction of COFs with embedded functional moieties[7] still remains challenging: the target-oriented synthesis has to meet all the requirements of crystallinity, porosity, and functionality. For example, although being promising in asymmetric catalysis and enantioselective recognition/separation, only a handful of chiral COFs (CCOFs) have been successfully synthesized.[8-14] In 2016, we targeted at the direct synthesis of a secondary-amine CCOF with a chiral pyrrolidine building block.[10] However, the lack of its combinatorial library makes the further high-throughput screening and structure-activity investigation impossible. Because our original synthetic route is only suitable for the special target,[10] we develop herein an updated strategy to construct a series of CCOFs for parallel evaluation of their catalytic performance. This effort may present a general protocol for the bottom-up introducing of designed functionality into COFs.

Figure 1. The divergent synthetic strategy to construct functional COFs via two-stage covalent assembly.

The key concern for divergent synthesis is that the designed route should be concise and universally robust so as to prepare the diversified targets in efficient, simultaneous, and combinatorial fashion.[1] We start with the rational design of a modular covalent-assembly protocol based on a suitable platform molecule. This molecule should be structurally rigid and symmetric, easily available, and readily installed with (chiral) functionality and connectivity via reliable transformation. Ideally, as depicted in Figure 1c, only two stages of covalent assembly from this platform molecule are necessary. The concise chemistry we envisioned for this protocol has been exemplified in Figure 2. As the first attempt, we designed 4,7-dibromo-2-chloro-1*H*-benzo[*d*]imidazole (**DBCBI**) as the platform molecule, based on which eight CCOFs (categorized into four different types) were facilely produced via nucleophilic substitution, Suzuki coupling, and imine formation.

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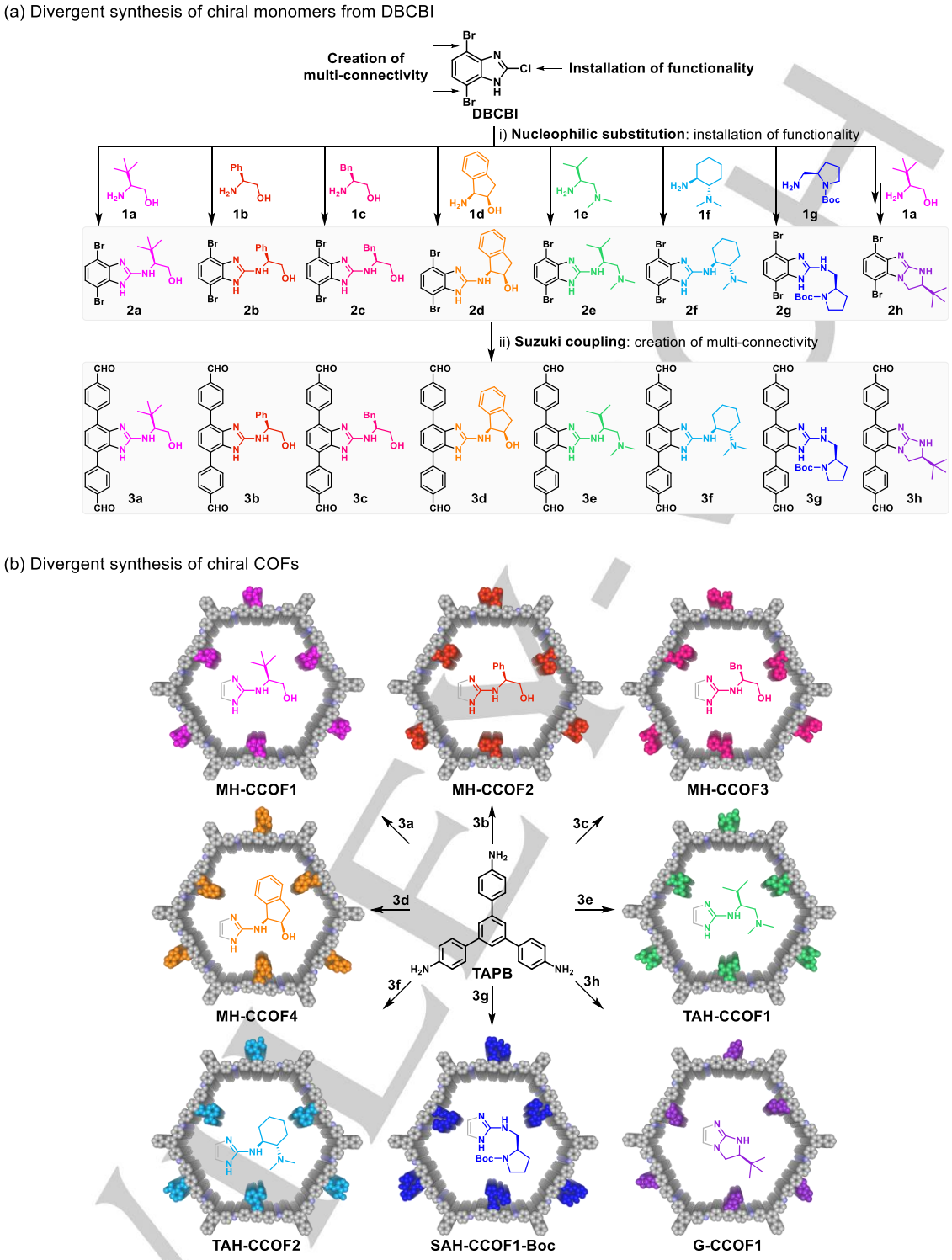

Figure 2. Two-stage divergent strategy to construct multifarious chiral COFs: a) the first stage is the divergent synthesis of chiral monomers via nucleophilic substitution and Suzuki coupling; b) the second stage is the divergent synthesis of chiral COFs via imine formation. Except for G-CCOF1 (a four-step transformation), the chiral COFs have been constructed via a three-step transformation from **DBCBI**.

In difference from the target-oriented route[10], the use of **DBCBI** as the platform molecule is crucial: (i) **DBCBI** can be synthesized in three steps with the total yield of 86% on a large scale: 500-gram of **DBCBI** with the chemical purity of 96% can be routinely obtained without any column purification in our laboratory. (ii) **DBCBI** can be facilely installed with various functional groups via classical transformations. For example, the monomers (**3a-h**) with chiral functionality have been obtained via nucleophilic substitution and Suzuki coupling reactions. Specifically, the workup of nucleophilic substitution for introducing functionality is free of solvent and of extraction, meeting the demands for green chemistry. Meanwhile, the mild

conditions for Suzuki coupling reaction guarantee the installation of terminal connectivity (such as aldehyde or amino groups) with high functional group tolerance. (iii) The synthesized monomers **3a-h** possess the functional diversity, structural symmetry, and extendable connectivity, all of which are essential for further construction of CCOFs.

We further applied the divergent strategy to construct a library of chiral COFs via dynamic covalent assembly between **3a-h** and a given structural monomer, such as 1,3,5-tris(4-aminophenyl)-benzene (**TAPB**). The optimal solvothermal condition has been established as: crystallization at 120 °C for 72 h in ethanol/mesitylene (1:1 v/v) as mixed solvents and with aqueous acetic acid (3 M) as the catalyst. As shown in Figure 2b, a series of COFs could be made with identical framework structure but with diverse functionality: MH-CCOF1, MH-CCOF2, MH-CCOF3, and MH-CCOF4 include multiple hydrogen-bonding sites; TAH-CCOF1 and TAH-CCOF2 include both tertiary-amine and hydrogen-bond sites; SAH-CCOF1-Boc contains both secondary-amine and hydrogen-bonding sites; while G-CCOF1 contains the unique guanidine moieties. Moreover, via this synthetic design, hydrogen-bond donor, Brønsted acidic and basic sites have been integrated into each CCOF catalyst, the catalytic model of which perfectly mimics those of (thio)urea and squaramide catalysts being frequently used in homogeneous organocatalysis.[15] Meanwhile, by eliminating the uncertain effects brought from different frameworks, these “isoframework” CCOFs provide a unique platform for investigation on the structure-activity relationship involved in heterogeneous asymmetric catalysis (*vide infra*). Note that this strategy may also be extended to construct "isofunctional" COFs when the structural monomer is changed.

The synthesized CCOFs were thoroughly characterized by powder X-ray diffraction, Fourier transform infrared spectroscopy, solid-state ^{13}C magic-angle-spinning (MAS) NMR, nitrogen adsorption-desorption experiments, thermogravimetric analysis, scanning electron microscopy, and transmission electron microscopy (see SI for details). Being isoframework in nature, these CCOFs possessed very similar PXRD patterns (Figure S1). Their nitrogen adsorption and desorption curves (Figure S2) all displayed type-IV isotherms, which are characteristic for mesoporous materials. The Brunauer–Emmett–Teller (BET) surface areas were determined as 215 to 809 $m^2\ g^{-1}$. The nonlocal density functional theory (NLDFT) gave rise to the pore-size distribution with the average pore width ranging from 2.7 to 2.9 nm (Figure S3). Presented in Figure 3, the ^{13}C cross-polarization (CP) MAS NMR spectra showed very similar NMR signals in the low-field region (ca. 110–150 ppm), indicating again the isoframework nature. Notably, the ^{13}C NMR signals in the high-field region (10–80 ppm) are distinct, which directly reflects the diversity in chiral functionality. The typical assignments for the ^{13}C NMR signals of the chiral moieties have been shown in each case and the full assignments have been provided in the SI.

With these CCOFs catalysts in hand, we were able to systematically investigate their structure-activity relationship in catalyzing many important transformations. The asymmetric amination reaction of ethyl 2-oxocyclopentane-1-carboxylate (**4**) with di-*tert*-butylazodicarboxilate (**5**) was first selected.[16] Having never been catalyzed with any CCOF catalysts, this reaction is however fundamentally important towards the construction of optically active nitrogen-containing molecules with excellent bio-

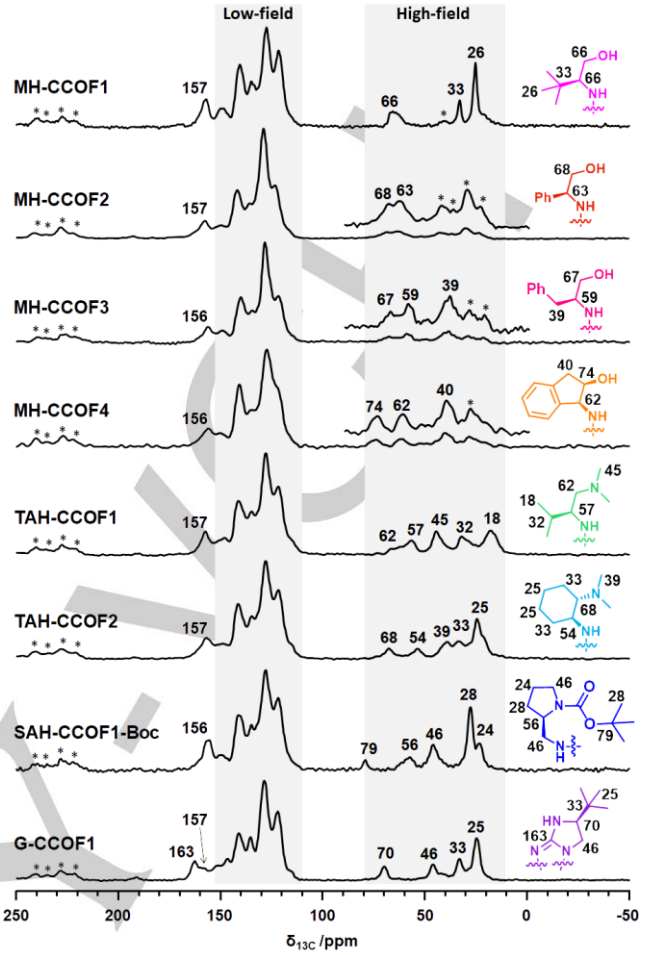

Figure 3. ^{13}C CP/MAS NMR spectra of CCOFs. The similar signals at 110–150 ppm indicate their isoframework nature, while the distinct signals at 10–80 ppm reflect the diversity in chiral functionality. The signal at 156–157 ppm in each spectrum verifies the successful –C=N– formation. The signal at 163 ppm in G-CCOF1 case is characteristic for the guanidine carbons. The asterisks denote the spinning sidebands.

logical activity and potential pharmaceutical applications.[16] Our screening results indicated that, possessing tertiary amine and hydrogen-bonding sites, TAH-CCOF1 and TAH-CCOF2 displayed better activity and enantioselectivity than other candidates. Excellent yield (96%) and steric control (99% *ee*) have been obtained when the reaction was performed in dichloromethane (DCM) at –78 °C with TAH-CCOF2 as the catalyst (entry 6). Note that this performance is superior to those (entries 9 and 10[17]) of homogeneous counterparts. We further investigated the mechanistic reason for this phenomenon. Comparison of the single-crystal structures of **7** and the model catalyst of TAH-CCOF2 revealed that the existence of steric hindrance moieties has weakened the intermolecular hydrogen bonding by enlarging their distance from 2.073 Å (Figure S103) to 5.093 Å (Figure S104). Similarly, reticulation of the chiral and hydrogen-bonding sites into the π-conjugated TAH-CCOF2 framework may further weaken the hydrogen-bonding interactions and therefore improve[18] the steric control and catalytic activity. Our control experiments have provided additional evidence to support this conclusion (SI).

Based on this finding, the substrate generality was further demonstrated by the reactions of other *β*-keto esters with **5** (SI).

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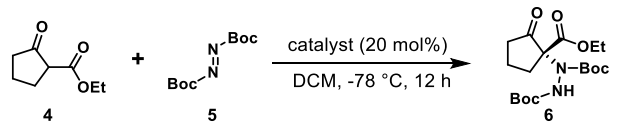
The desired amination products were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 91% *ee*). Moreover, the TAH-CCOF2 catalyst could be readily recovered by centrifugation and reused at least for seven times without any obvious loss of activity and enantioselectivity (Table S11). The crystallinity and covalent connection for the recycled TAH-CCOF2 were maintained, as evidenced by the recorded PXRD (Figure S106) and ^{13}C CP/MAS NMR (Figure S107).

Table 1. Systematic screening of CCOFs catalysts in asymmetric amination of *β*-ketoesters.[a]



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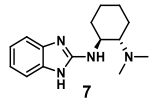
entry	catalyst	yield (%)[b]	*ee* (%)[c]
1	MH-CCOF1	81	12
2	MH-CCOF2	72	8
3	MH-CCOF3	70	9
4	MH-CCOF4	65	5
5	TAH-CCOF1	94	89
6	TAH-CCOF2	96	99
7	SAH-CCOF1-Boc	67	27
8	G-CCOF1	61	3
9	 7	78	92
10[d]		40	90[17]

[a] General conditions: in the presence of the catalyst (0.04 mmol), the reaction was carried out in DCM (2.0 mL) at –78 °C with **4** (0.20 mmol) and **5** (0.24 mmol) as the reactants. [b] Isolated yield. [c] Enantiomeric excess (*ee*) was determined by HPLC with Daicel chiral OD-H column at 210 nm (hexane/*i*-PrOH = 95/5, flow rate: 0.6 mL/min). [d] The reaction was carried out in DCM (1.0 mL) at 25 °C with **4** (0.10 mmol), **5** (0.15 mmol), and catalyst **7** (0.01 mmol) for 10 h.

The spirit in classic organic synthesis is the precise and efficient covalent-assembly.[19] For example, the MacMillan group used the divergent strategy to synthesize six indole alkaloids (categorized into three families) from the same tetracyclic intermediate.[20] Being a new member of organic family, COFs are structurally featured as crystalline and porous macromolecules organized via covalent assembly.[5] In light of the divergent concept, we produced eight CCOFs (categorized into four different types) via a three-step transformation of a key platform molecule, **DBCBI**. This simple and general strategy may not only fulfil the critical demands for diversity in the COF synthesis, but also integrate the efficiency and precision of classic organic synthesis. By realizing the fine-tuning of COF properties at the atom/molecular level, this approach provides a combinatorial library of functional COF materials for further high-throughput screening and structure-activity investigation. This purpose has also been achieved by screening out TAH-CCOF2 catalyst as the best candidate reported for the asymmetric amination reaction. We therefore expect that this contribution set up a combinatorial procedure to produce diversified functional COFs.

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Keywords: divergent synthesis • covalent organic frameworks • functionality • chiral • asymmetric catalysis

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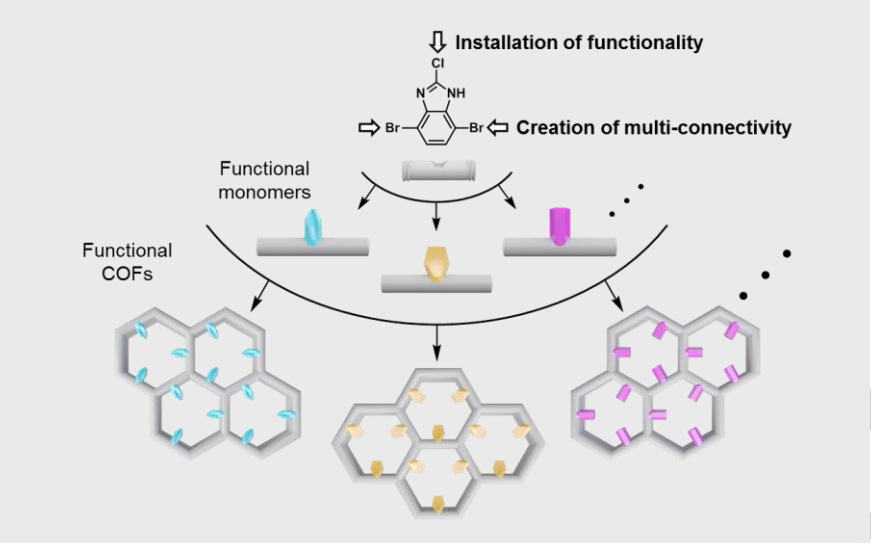

*Li-Ke Wang, Jing-Jing Zhou, Yu-Bao Lan, San-Yuan Ding, Wei Yu, and Wei Wang**

Page No. – Page No.

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A divergent strategy has been proposed to construct a combinatorial library of functional covalent organic frameworks (COFs) from a platform molecule, **DBCBI**.