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Chiral hydrogen-bonded frameworks featuring proline motifs as heterogeneous catalysts for the enantioselective synthesis of warfarin

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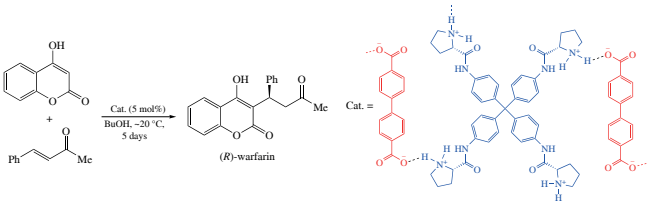
Chiral hydrogen-bonded organic frameworks incorporating proline motifs were synthesized from tetrakis-, bis- or monoprolinamide precursors and di- or tetracarboxylic or sulfonic acids. Their testing as heterogeneous catalysts for the synthesis of warfarin provided product yields of up to 84% with *ee* values of up to 45%.



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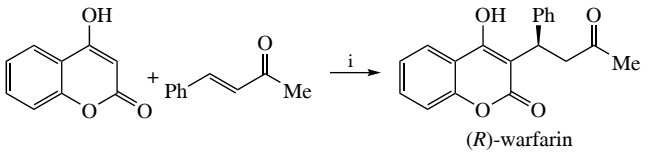
Homogeneous catalysis is an extremely important area in modern chemistry. However, the inherent challenge of catalyst recovery and regeneration from the reaction mixture limits its applicability in large-scale industrial processes. For this reason, heterogeneous catalysts dominate approximately 80% of multi-tonnage industrial production, owing to their ease of separation and recyclability.[1] Despite these advantages, heterogeneous systems often suffer from low selectivity, primarily due to the non-uniform distribution of active sites on solid supports. It seemed that this problem could be solved by immobilizing homogeneous catalysts on polymeric solid carriers, yet the high cost and limited operational stability of such systems have hindered their widespread industrial adoption.[2] Recent advances in crystalline framework materials, such as metal–organic frameworks (MOFs) and covalent-bonded organic frameworks (COFs), have demonstrated catalytic performance that rivals or even surpasses that of their homogeneous counterparts.[3,4] However, such catalysts are expensive due to high cost of initial substances.[5,6]

Recently, hydrogen-bonded organic frameworks (HOFs) have emerged as a promising solution offering significant advantages over MOFs and COFs.[7–9] These materials do not contain metals and can be easily synthesized, which makes them significantly cheaper than their analogs. Moreover, their structural flexibility improves the diffusion of the substance inside the framework. The reversible nature of hydrogen bonding should allow easy regeneration of such catalysts, which may simplify the integration of these systems into industrial processes.[10]

This study reports the preparation of novel class of chiral HOFs and their use as heterogeneous catalysts for the production of the vital anticoagulant drug warfarin.[11,12] The use of HOFs as catalysts for asymmetric reaction should involve the presence of chiral catalytic fragments derived from the structure-determining part of the framework. In this research, modification of the framework with L-proline fragments was employed since the moiety secures high efficiency and selectivity as asymmetric homogeneous catalysts for a wide variety of reactions, according to literature data.[13] The synthesis of the important anticoagulant pharmaceutical warfarin has been selected as a target model reaction (Scheme 1).

The basic tecton of the chiral HOFs was prepared by the condensation of tetrakis(4-aminophenyl)methane with L-proline, which afforded tetrakisprolinamide **TPA**[14,15] (Figure 1). Bisprolinamide-functionalized *o*-phenylenediamine **DPA** was also employed in this study.

The frameworks were synthesized *via* a straightforward mixing of aqueous solutions of trifluoroacetate derivatives of **TPA** or **DPA** with sodium salts of acids **1**–**5** (see Figure 1). The resulting solid frameworks, **TPA**·**(1–5)** and **DPA**·**(1–5)**, were isolated by filtration, thoroughly washed and dried.[†] The obtained systems were subsequently tested as catalysts in a model reaction of warfarin synthesis (see Scheme 1). The catalysts derived from sulfonic acids (**TPA**·**1**, **TPA**·**2**, **DPA**·**1**



Scheme 1 *Reagents and conditions*: i, catalyst (5 mol%), BuOH, room temperature, 5 days.

[†] Codes consisting of abbreviations **TPA**, **DPA** or **MPA** multiplied at digits **1**–**5** reflect only the nature of bases and acids and do not take into account their stoichiometry.

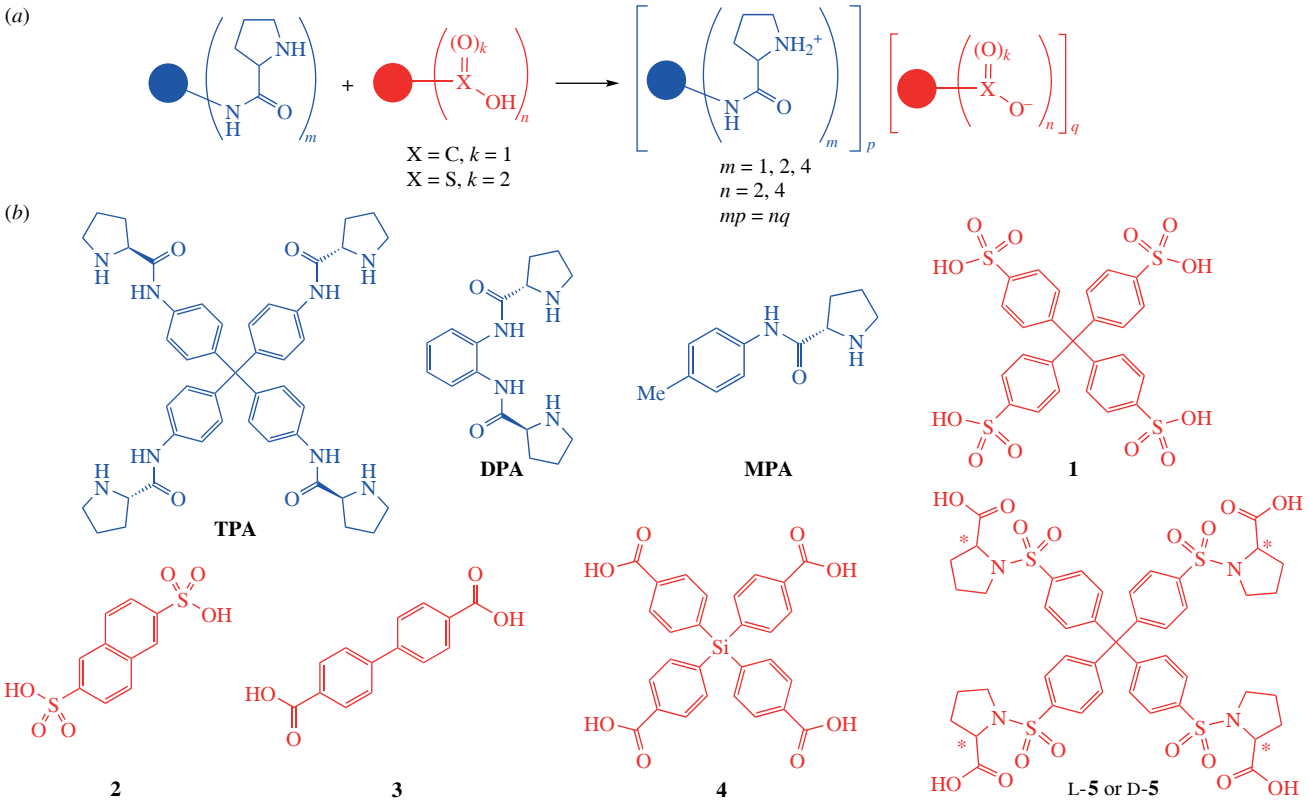


Figure 1 (*a*) General methodology for obtaining frameworks. (*b*) Structural formulas of the components used to produce frameworks.

Table 1 Catalytic activity of frameworks in the synthesis of warfarin.[a]

Entry	Catalyst	Yield (%)[b]	*ee* (%) (*R*)[c]
1	**TPA**·**1**	0	–
2	**TPA**·**2**	0	–
3	**TPA**·**3**	71	45
4	**TPA**·**4**	44	24
5	**TPA**·[L-**5**]	16	13
6	**TPA**·[D-**5**]	19	18
7	**DPA**·**1**	0	–
8	**DPA**·**2**	0	–
9	**DPA**·**3**	84	72
10	**DPA**·**4**	60	61
11[d]	**MPA**·**3**	28	24

[a]4-Hydroxycoumarin (0.1 mmol), benzylideneacetone (0.15 mmol), catalyst (5 mol%), BuOH (1.0 ml), room temperature, 5 days. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column. [d]Homogeneous model reaction, 20 mol% of **MPA**·**3** was used.

and **DPA**·**2**) exhibited no catalytic activity (Table 1, runs 1, 2). Evidently, the amino groups of **TPA** become completely protonated, which inhibits their ability to activate the ketone substrate. Furthermore, the low basicity of the sulfonate anion is insufficient to deprotonate 4-hydroxycoumarin, thereby hindering its activation as a nucleophile in the reaction.

The dicarboxylate-based framework **TPA**·**3** with biphenyl-4,4′-dicarboxylic acid **3** demonstrated significant catalytic activity affording the product in 71% yield and with 45% *ee*. Surprisingly, more structurally stable framework **TPA**·**4**, derived from tetrakis(4-carboxyphenyl)silane **4**,[16] exhibited relatively low yield and reduced enantioselectivity compared to **TPA**·**3** (see Table 1, entry 3 *vs*. entry 6).

The influence of chiral acid on catalytic activity was tested by preparing tetraacid **5** *via* modification of tetrasulfonic acid **1** with an L- or D-proline moieties. The **TPA**·[L-**5**] and **TPA**·[D-**5**] frameworks exhibited very low activity (see Table 1, runs 5, 6). However, when a mixture of **TPA** and **5** was used as the catalyst, a notable enhancement in efficiency was observed. The mixture of **TPA** and L-**5** afforded warfarin in 53% yield with 47% *ee*, while mixture of **TPA** and D-**5** gave 44% yield with 50% *ee*. Notably, the catalytic performance showed minimal dependence on the absolute configuration of the proline moiety, as evidenced by the comparable results obtained with both enantiomers. The observed activity difference between these catalytic systems can be attributed to partial framework formation when using mixed components. In such cases, a portion of the **TPA** remains in a non-framework state and participates in catalysis independently. This dual-phase behavior when both framework and non-framework species coexist leads to modified catalytic performance compared to fully formed HOF systems.

The highest efficiency among the studied catalysts is shown by framework **TPA**·**3**, providing a yield of 71% and *ee* of 45%. Optimization of the reaction conditions using framework **TPA**·**3** was carried out (Table 2). The reaction did not proceed in dichloromethane and showed limited activity in acetonitrile, isopropyl alcohol, and ethyl acetate. The best results were

Table 2 Catalytic activity of framework **TPA**·**3** in the synthesis of warfarin in different solvents.[a]

Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	BuOH	71	45
2[d]	BuOH	60	25
3	CH_2Cl_2	0	–
4	MeCN	29	23
5	THF	76	27
6	EtOH	60	0
7	MeOH	57	41
8	Pr^iOH	31	36
9	EtOAc	17	21

[a]4-Hydroxycoumarin (0.1 mmol), benzylideneacetone (0.15 mmol), catalyst (5 mol%), solvent (1.0 ml), room temperature, 5 days. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column. [d]At 40 °C for 12 h.

obtained in THF and *n*-butanol. Although the product yield is higher in THF than in *n*-butanol, enantioselectivity in THF is lower. Thus, *n*-butanol was identified as the optimal solvent, balancing both reaction efficiency and selectivity. Heating resulted in reduced performance for both yield and enantioselectivity compared to room temperature. The influence of water is ambiguous. The yield initially increased with small amounts of water but decreased beyond a certain threshold, while enantioselectivity consistently declined with increasing water content (see Online Supplementary Materials).

A heterogeneity test for the **TPA**·**3** catalyst was conducted using a 'teapot' protocol. The reaction was allowed to proceed for 1 day, after which the catalyst was removed by centrifugation, and the reaction mixture was left for an additional 4 days. The final outcome was compared with two control experiments: one running for 1 day and the other for 5 days. The results demonstrated that the reaction stopped upon removal of the catalyst, confirming the heterogeneous nature of **TPA**·**3** (see Online Supplementary Materials).

The homogeneous analogue of **TPA**·**3**, consisting of the L-prolinamide derivative of 4-methylaniline **MPA**[17] and **3** forming salt **MPA**·**3**, was synthesized. Unlike **TPA**·**3**, **MPA**·**3** does not form framework structure and is soluble in *n*-butanol. When tested as a homogeneous catalyst under identical proline loading conditions to **TPA**·**3**, **MPA**·**3** afforded warfarin in only 28% yield with 24% *ee*. These results demonstrate significantly lower catalytic performance compared to the HOF system, suggesting that the framework structure itself may exert a beneficial effect on catalytic activity.

The use of amine **DPA** as a structure-forming component presented challenges in the formation of stable solid frameworks. While frameworks **DPA**·**1** and **DPA**·**2**, obtained from **DPA** and sulfonic acids **1** or **2**, showed the highest stability, they demonstrated no catalytic activity. Attempts to synthesize frameworks using carboxylic acids resulted in either metastable solids (**DPA**·**3** and **DPA**·**4**) or complete failure to form a framework. Specifically, no precipitation was observed when trifluoroacetate **DPA** was mixed with the sodium salts of L-**5** or D-**5**.

During the warfarin synthesis, **DPA**·**3** and **DPA**·**4** were destroyed by acidic 4-hydroxycoumarin temporarily forming a salt with **DPA**. As a result, the framework structure in the reaction mixture disintegrated into free amine **DPA**, soluble in *n*-butanol, and acid **3** or **4**. Their catalytic activity was the same as with a mixture of components providing yields of 60–84% and *ee* of 61–72% (see Online Supplementary Materials).

Heterogeneity test performed with **DPA**·**3** revealed that the reaction continued even after catalyst removal, indicating the breakdown of the framework structure. This suggests that **DPA**·**3** operates in a homogeneous manner after its structural integrity is compromised, and thus cannot be classified as a true heterogeneous catalyst.

On the basis of the presented data an inverse dependence of the catalytic activity of the framework on its structure can be observed.

To conclude, the preparation and characterization of novel class of chiral HOFs as asymmetric catalysts for the synthesis of the vital pharmaceutical warfarin have been accomplished. The successful application of these HOFs suggests their potential applicability to a broader range of carbonyl transformations, representing a promising direction for future research.[18–21] The structure of the frameworks was shown to have a paramount importance for their catalytic performance.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7796.

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