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Atom-Economic Synthesis of Optically Active Warfarin Anticoagulant over a Chiral MOF Organocatalyst

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Abstract: A novel chiral metal-organic framework (MOF) organocatalyst has been developed, based on readily available MIL-101 and the chiral primary diamine (1*R*,2*R*)-1,2-diphenylethylenediamine, by the post-synthetic modification. Over the developed chiral heterogeneous catalyst the asymmetric synthesis of (*S*)-warfarin with high enantioselectivity can be fulfilled on a gram-scale (2.8 g) with excellent yield (92%) at low cost, making the synthesis method an ideal alternative to existing methods.

Keywords: asymmetric synthesis; catalyst design; heterogeneous catalysis; Michael addition; warfarin

The enantiomers of optically active drugs usually differ, sometimes more than 1000-fold, in their affinity to their biological receptor sites. Furthermore, such enantiomers may be metabolized at different rates in the human body, with important clinical consequences. Therefore, optically active drugs are becoming increasingly important for the treatment of diseases in patients, markets for single-isomer drugs continue to blossom, and both fine chemicals companies and academic chemists are prospecting for new enantioselective technologies to produce single-isomer drugs. An important and ultimate goal for asymmetric catalysis is to develop new reactions that afford optically active compounds that have importantly biological and pharmaceutical activities from easily available starting materials and catalysts in one step. Warfarin has been prescribed as a racemate for more than 40 years. However, the anticoagulant activity of its *S* enantiomer is about 5–8 times higher than that of its *R* enantiomer and the enantiomers are metabolized by different pathways, reflected by the different half-lives in the human body, 21–43 h and 37–89 h, for (*S*)- and (*R*)-warfarin, respectively.[1] Due to these very different anticoagulant activities and half-lives, racemic warfarin often leads to many clinical consequences, such as internal hemorrhages. Different approaches towards the synthesis of optically active warfarin have been reported.[2–5] However, most of the reported methods have one or more of the following drawbacks: tedious separation and recycling of expensive catalysts, low yields of the product, low enantiomeric excess, and multiple-step synthesis.

Asymmetric reactions catalyzed by homogeneous organocatalysts have been used as an efficient tool for the synthesis of enantiopure compounds under mild, environmentally benign conditions in the past decades.[6] Recently, Halland et al.[3] reported pioneering work on the one-step synthesis of optically active warfarin from 4-hydroxycoumarin and benzylideneacetone in the presence of imidazolidine catalysts. However, the the nature of the homogeneous catalysis makes the separation of the used catalysts from the reaction medium difficult. Subsequently, the groups of Chin[4] and Chen[5] prepared the optically active warfarin using primary organic amines as homogeneous catalysts but the gram-scale synthesis of the desired product and the reusability of the used catalysts were not conducted.

Presently, metal organic frameworks (MOFs) have attracted growing attention from both academia and industry owing to their outstanding features and thus specific applications, such as luminescence,[7] magnetic properties,[8] gas storage and adsorptive separation,[9] and catalytic properties.[10] Functionalized MOF materials can be easily achieved by assembly of designed molecular building blocks or post-synthetic modification (PSM),[11] and MOFs offer great potential in heterogeneous catalysis because of their many catalysis-friendly features, such as large surface areas, extensive porosity, well-defined cavities and portals, and chemical and composition tunability.[10g,12] In particular,

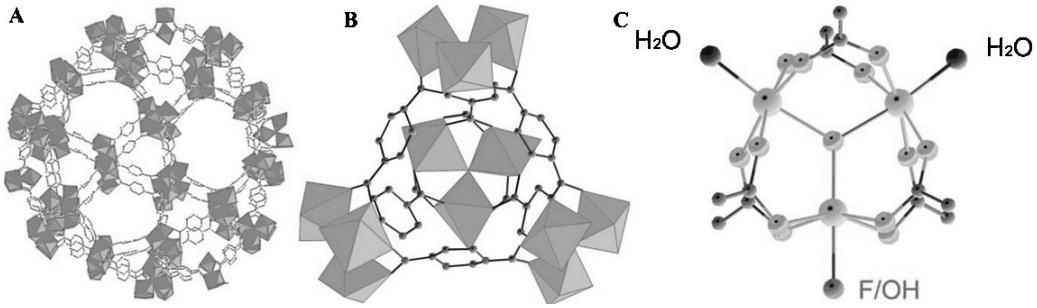


Figure 1. Schematic representation of the large cage of MIL-101 delimited by the vertex sharing of the super tetrahedron (ST) (A), the ST cage drawn in polyhedron mode (B), and the μ^3-O bridged trimeric secondary building unit (SBU) chelated by six carboxylates (C).

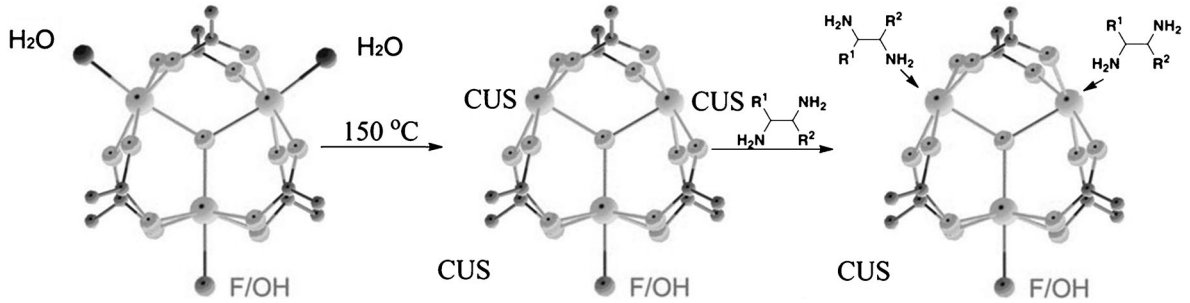


Figure 2. Evolution of the coordinatively unsaturated sites from chromium trimers in the mesoporous cages of MIL-101 after vacuum treatment at 150 °C for 12 h and functionalization of the dehydrated MIL-101 through the selective grafting of the diamine molecules onto the coordinatively unsaturated sites.

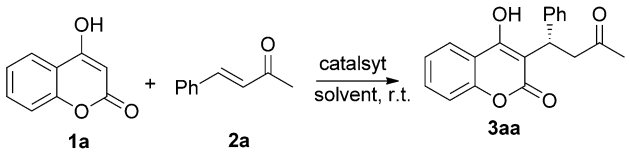
there has been increasing interest in creating chiral porous MOFs for asymmetric heterogeneous catalysis.[12e,13] Recently, a new synthetic strategy for catalytically active chiral MOFs, *via* introduction of privileged organocatalyst units into achiral frameworks by PSM, was demonstrated by Kim and co-workers,[14] but unfortunately, their reported *ee* values (52–81% *ee*) were not highly satisfactory in their asymmetric aldol reactions. Herein we have developed a series of novel chiral porous MOF organocatalysts that effectively catalyze the Michael reaction of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones with good yields and high enantioselectivities. Notably, a chiral anticoagulant drug, (*S*)-warfarin, was directly prepared in 83% *ee*, and a number of important optically, biologically, and pharmaceutically active compounds were also obtained on a gram-scale (up to 2.8 g) with high enantioselectivities (82–90% *ee*).

MIL-101 (Figure 1) is an ideal MOF for application in heterogeneous catalysis due to the following reasons:[15,16] on the one hand, its high chemical stability provides a feasibility for ligand PSM; on the other hand, MIL-101 can be coordinately modified by various groups such as amino or pyridyl groups to introduce NH_2 or L-proline catalytic sites as illustrated by the groups of Ferey,[17] Chang,[18a] Kim,[14] and Shi.[18b] In addition, chiral primary amines are an important class of asymmetric organocatalysts for a range of chiral transformations through LUMO-lowering activation.[19] These facts suggest that the incorporation of a primary amine unit into MIL-101 can create an efficient heterogeneous catalyst for organic C–C bond forming reactions by activation of carbonyl compounds through the formation of imine intermediates. Vicinal diamines were proven to be effective grafting reagents due to their multifunctional chelating groups – two amino groups.[16] As illustrated in Figure 2, if one amine group of a diamine is coordinated to the open metal coordination site chromium(III) of MIL-101 by direct ligation, the other amine group can act as an immobilized base catalyst. Therefore, (1*R*,2*R*)-1,2-cyclohexanediamine [(1*R*,2*R*)-CHDN] and (1*R*,2*R*)-1,2-diphenylethylenediamine [(1*R*,2*R*)-DPEN] were chosen as chiral organic ligands. The chiral MIL-101 organocatalysts were obtained by PSM according to the following two-step procedure (Figure 2). Firstly, MIL-101 was prepared in a similar manner as described by Férey et al.[14] with some modification. Then the dehydrated MIL-101 was treated with the chiral ligand (1*R*,2*R*)-CHDN or (1*R*,2*R*)-DPEN in refluxing anhydrous toluene for 12 h, followed by filtration. The solid was washed with ethanol and dried at room temperature to afford chiral MIL-101-based catalysts CDMIL-1 and

CDMIL-2 incorporating (1*R*,2*R*)-CHDN in different amounts and CDMIL-3 and CDMIL-4 incorporating (1*R*,2*R*)-DPEN in different amounts. All the prepared MIL-101-based organocatalysts were characterized by various techniques, including FT-IR, powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA), nitrogen adsorption, and elemental analysis, see the Supporting Information for details. The elemental analysis indicated (Supporting Information, Table S1) that 1.7 and 1.9 or 1.5 and 1.6 mmol of (1*R*,2*R*)-CHDN or (1*R*,2*R*)-DPEN per gram of the sample were incorporated for CDMIL-1 and CDMIL-2 or CDMIL-3 and CDMIL-4, respectively. The PXRD patterns (Supporting Information, Figure S2) show that almost all the characteristic peaks of the chiral MIL-101 organocatalysts are maintained but with some slight variations in the Bragg intensities, clearly indicating that the structure of the materials is unchanged during the PSM process. The occurrence of the characteristic IR absorption bands for all the MIL-101 organocatalysts demonstrates that Lewis base sites (NH_2) can be retained after following the PSM process (Supporting Information, Figure S4).

The catalytic performance of CDMILs was firstly evaluated using the asymmetric Michael addition between hydroxycoumarin (**1a**) and benzylideneacetone (**2a**) in tetrahydrofuran (THF) at room temperature. As shown in Table 1, MIL-101 was inactive in the reaction (Table 1, entry 1). All CDMILs were found to be highly active at room temperature and clean product (*S*)-warfarin **3aa** was obtained with good yield and enantioselectivity (Table 1, entries 2–5), and the yield increased with increases in the incorporated amount of the chiral organic ligand. Heterogeneous catalyst CDMIL-4 incorporating (1*R*,2*R*)-DPEN was identified as the best catalyst and a 69% *ee* value was attained (Table 1, entry 5), although the origin of the observed difference in the catalytic activity and enantioselectivity between the two incorporated chiral organic ligands (1*R*,2*R*)-CHDN and (1*R*,2*R*)-DPEN is unclear. The yield and *ee* value were decreased when the loading of CDMIL-4 in the reaction system was reduced (Table 1, entry 6). The solvents were screened as well, and THF turned out to be optimal to give the product in higher enantioselectivities and yields (Table 1, entries 5, 7 and 8). By lowering the reaction temperature to 10 °C, over CDMIL-4 the yield was only slightly decreased while a higher enantioselectivity (83% *ee*) was obtained when the reaction time was extended from 2 to 4 days (Table 1, entry 9). However, when the reaction temperature was lowered to 0 °C, the yield was significantly decreased with a slight decrease in enantioselectivity (Table 1, entry 10). Notably, the yield was dramatically increased up to 94% [1.16 g of (*S*)-warfarin **3aa** was obtained] when the Michael addition between hydroxycoumarin (**1a**) and benzylideneacetone (**2a**) was scaled up by 40 times (Table 1, entry 11), probably ascribed to the enhanced utilization efficiency of the catalyst loaded in the reactor with stirring when scaled up.

Table 1. Screening studies of the Michael addition between hydroxycoumarin (**1a**) and benzylideneacetone (**2a**).[a]



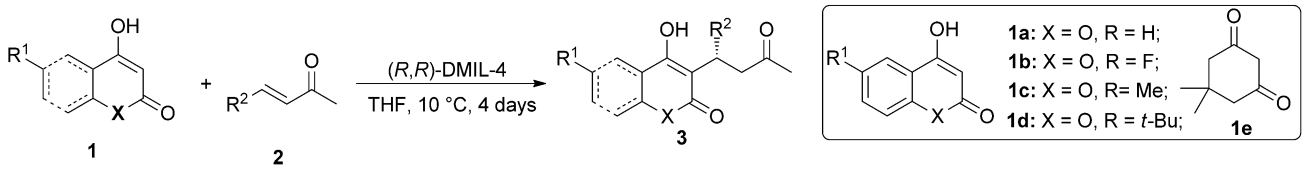
1a 2a 3aa

Entry	Solvent	Catalyst	Yield[b] [%]	*ee*[c] [%]
1	THF	MIL-101	–	–
2	THF	CDMIL-1	66	68
3	THF	CDMIL-2	69	63
4	THF	CDMIL-3	68	65
5	THF	CDMIL-4	78	69
6[d]	THF	CDMIL-4	63	61
7	toluene	CDMIL-4	52	40
8	$CHCl_3$	CDMIL-4	54	42
9[e]	THF	CDMIL-4	70	83
10[f]	THF	CDMIL-4	25	77
11[g]	THF	CDMIL-4	94	83

[a] Otherwise noted, the reactions were performed with 0.10 mmol of **1a**, 0.15 mmol of **2a**, 12 mg of catalyst in 1 mL of solvent at room temperature for 2 d.
[b] Isolated yield.
[c] Determined by the chiral HPLC analysis.
[d] 6 mg of CDMIL-4 were added.
[e] At 10 °C for 4 d.
[f] At 0 °C for 4 d.
[g] The reaction was performed with 4.0 mmol of **1a**, 6.0 mmol of **2a**, 480 mg of catalyst in 40 mL of tetrahydrofuran (THF) at 10 °C for 4 d.

With the optimal reaction conditions and the screened catalyst in hand, the catalytic activities of heterogeneous catalyst CDMIL-4 and the corresponding homogeneous catalyst (1*R*,2*R*)-DPEN were further assessed in the asymmetric Michael addition between various cyclic 1,3-dicarbonyl compounds and α,β-unsaturated ketones under the same conditions. Table 2 shows the catalytic results of the asymmetric Michael addition in the presence of CDMIL-4 or (1*R*,2*R*)-DPEN in THF at 10 °C, from which the major conclusions can be drawn as follows: (i) the asymmetric synthesis of chiral drug (*S*)-warfarin **3aa** and the related pharmaceutically active compounds with high yield and enantioselectivity can be fulfilled on a gram-scale (>1 g) at low cost, making the synthesis method an ideal alternative to existing methods; (ii) heterogeneous catalyst CDMIL-4 showed remarkable catalytic activities in the asymmetric Michael reactions and the Michael adducts were obtained with much higher enantiomeric excesses, compared to those using the corresponding homogeneous

Table 2. Asymmetric Michael additions of cyclic 1,3-dicarbonyl compounds (**1**) to α,β-unsaturated ketones (**2**).



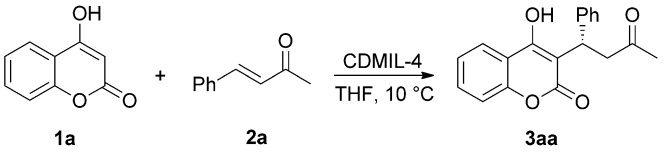
Entry	1	Ar (2)	3	CDMIL-4[a] yield [%][c]/*ee*[d,e] [%]	DPEN[b] yield [%][c]/*ee*[d,e] [%]
1	**1a**	Ph (**2a**)	**3aa**	94/83	94/69
2	**1a**	*p*-F-C_6H_4 (**2b**)	**3ab**	86/82	85/71
3	**1a**	*p*-Cl-C_6H_4 (**2c**)	**3ac**	91/82	86/70
4	**1a**	*m*-Cl-C_6H_4 (**2d**)	**3ad**	88/83	97/68
5	**1a**	*p*-Br-C_6H_4 (**2e**)	**3ae**	86/90	88/70
6	**1a**	*p*-Me-C_6H_4 (**2f**)	**3af**	81/82	87/72
7	**1a**	furyl (**2g**)	**3ag**	83/85	83/78
8	**1b**	*p*-Br-C_6H_4 (**2e**)	**3be**	87/88	89/74
9	**1c**	*p*-Br-C_6H_4 (**2e**)	**3ce**	86/87	85/70
10	**1d**	*p*-Br-C_6H_4 (**2e**)	**3de**	83/85	88/75
11	**1e**	*p*-Br-C_6H_4 (**2e**)	**3ee**	80/89	76/79
12	**1b**	Ph (**2a**)	**3ba**	91/82	83/67
13	**1e**	Ph (**2a**)	**3ea**	78/86	71/63

[a] The reactions were performed with 4.0 mmol of **1**, 6.0 mmol of **2**, 480 mg of CDMIL-4 in 40 mL of THF at 10 °C for 4 d.
[b] The reactions performed with 4.0 mmol of **1**, 6.0 mmol of **2**, 0.8 mmol of (1*R*,2*R*)-DPEN in 40 mL of THF at 10 °C for 4 d.
[c] Isolated yield.
[d] Determined by the chiral HPLC analysis.
[e] The absolute configuration was determined to be (*S*) by the X-ray analysis of **3ac**, see the Supporting Information, and other adducts were assigned accordingly.

catalyst (1*R*,2*R*)-DPEN in all cases (Table 2, entries 1–12), and the better enantioselectivity in the case of the heterogeneous catalyst may originate from the restricted movement of the substrates in the confined microporous systems in combination with multiple chiral induction; (iii) it appeared that the substituents' electronics had a minimal impact on the yields (78–94%) and enantioselectivities (82–90% *ee*); and (iv) the reaction scope was to be quite broad with respect to Michael adducts under the applied conditions. Excellent results were achieved with α,β-unsaturated ketones bearing various β-aryl or heteroaryl substitutions (Table 2, entries 2–7). A few 4-hydroxycoumarin derivatives **1b**–**1d** with different substitutions were investigated and remarkable enantioselectivities were achieved (Table 2, entries 8–10). A high *ee* value was also received in the case of 5,5-dimethylcyclohexane-1,3-dione **(1e)** (Table 2, entries 11 and 13).

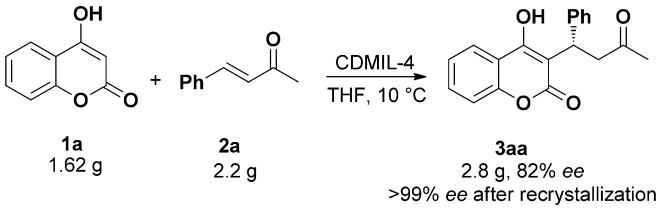
As heterogeneous catalysis in nature, the catalyst should be reusable. Therefore, the reusability of chiral heterogeneous catalyst CDMIL-4 was investigated. The catalyst can be reused for the asymmetric Michael addition up to three times without significant loss of the enantioselectivity (Table 3). Notably, the yields were excellent (94% and 88%) for the first two runs. In addition, to improve the enantiomeric purity of the Michael adduct, a single recrystallization from a water/acetone mixture provided enantiopure (> 99% *ee*) warfarin **3aa** when starting from a sample with 79% *ee*. Furthermore, the PXRD data (Supporting Information, Figure S2) implied that the used chiral catalyst after the fourth run maintained the

Table 3. Reusability of catalyst CDMIL-4 in the asymmetric Michael addition of hydroxycoumarin (**1a**) and benzylideneacetone (**2a**).[a]



Entry	Yield [%]	*ee* [%]	N content in the catalyst (mmol g^{-1})
1	94	83	3.17 (1.58)[b]
2	88	82	2.98 (1.49)[b]
3	60 (89)[c]	79	2.73 (1.37)[b]
4	31 (93)[c]	73	1.67 (0.84)[b]

[a] The reactions were performed with 4.0 mmol of **1a**, 6.0 mmol of **2a**, 480 mg of CDMIL-4 in 40 mL of THF at 10 °C for 4 d.
[b] Numbers in parentheses denote the content of free amino groups available for the reaction.
[c] Yields in parentheses calculated, based on the recovered **1a**.



Scheme 1. Asymmetric Michael addition over CDMIL-4 was scaled up by 2.5 times with respect to the reaction shown in Table 2, entry 1.

ssame tructure as that for the fresh catalyst and the elemental analysis (Table 3) of the used catalyst also confirmed the retention of the (1*R*,2*R*)-DPEN grafted on MIL-101, although the amount of the grafted (1*R*,2*R*)-DPEN was slightly decreased after the third run and significantly decreased from the third to fourth run.

Finally, in order to investigate the scalability of the synthesis of (*S*)-warfarin **3aa** over CDMIL-4, as an example, the asymmetric Michael addition of hydroxycoumarin (**1a**) and benzylideneacetone (**2a**) was also scaled up by 2.5 times with respect to the reaction shown in Table 2, entry 1 (Scheme 1). The reaction proceeded effectively and conveniently to prepare (*S*)-warfarin **3aa** on a gram-scale (up to 2.8 g) with excellent yield (92%) and enantioselectivity (82% *ee*).

In summary, a series of novel MOF-based organocatalysts CDMILs, which were found to be highly active in the asymmetric Michael additions, were developed, based on readily available MIL-101 and chiral primary diamines [(1*R*,2*R*)-CHDN and (1*R*,2*R*)-DPEN]. Among CDMILs, heterogeneous catalyst CDMIL-4 showed remarkable catalytic activities in the asymmetric Michael reactions and the Michael adducts were obtained with much higher enantiomeric excesses than those using the corresponding homogeneous catalyst (1*R*,2*R*)-DPEN in all cases. The present development leads to a catalytic enantioselective one-step procedure for the formation of one of the most widely used anticoagulants, warfarin, and related important compounds. CDMIL-4 can be reused in the asymmetric Michael addition between hydroxycoumarin (**1a**) and benzylideneacetone (**2a**) up to three times without significant change of the enantioselectivity. Notably, the asymmetric synthesis of chiral drug (*S*)-warfarin **3aa** and the related pharmaceutically active compounds with high enantioselectivity can be fulfilled on a gram-scale (>1 g) at low cost, making the synthesis method an ideal alternative to existing methods. In addition, the asymmetric Michael addition of hydroxycoumarin (**1a**) and benzylideneacetone (**2a**) was scalable and (*S*)-warfarin **3aa** was obtained on a gram-scale (>2 g) with excellent yield (92%). Furthermore, it was demonstrated that enantiopure (*S*)-warfarin could be obtained by a single recrystallization. We believe that the strategy applied in this work may lead to the design and application of heterogeneous aminocatalysts in other asymmetric transformations of α,β-unsaturated ketones as well, which is under way.

Experimental Section

Typical Procedures

MIL-101(Cr) was initially prepared from the hydrothermal reaction of terephthalic acid with $Cr(NO_3)_3{\cdot}9H_2O$, HF, and H_2O at 220 °C for 8 h. The as-synthesized MIL-101 was further purified by a three-step process using filtration, hot ethanol, and aqueous NH_4F solutions. CDMIL-1, CDMIL-2, CDMIL-3, and CDMIL-4 were prepared as follows. In a typical procedure for preparing CDMIL-4, 0.5 g of the dehydrated MIL-101 sample at 150 °C for 12 h was suspended in 30 mL of anhydrous toluene. To this suspension, 3.0 mmol of (1*R*,2*R*)-DPEN were added and the mixture was stirred with heating to reflux for 12 h. Product CDMIL-4 was recovered by filtration and washed with ethanol, and then dried at room temperature for 12 h in an oven to remove residual water. For CDMIL-1, CDMIL-2, and CDMIL-3, 1.5 and 3.0 mmol of (1*R*,2*R*)-CHDN and 1.5 mmol of (1*R*,2*R*)-DPEN, respectively, were used, but the other preparation conditions were the same. The detailed methods for the characterization and the textural and physicochemical properties of the synthesized samples are presented in the Supporting Information.

Before the asymmetric Michael additions, the MIL-101-based catalysts were treated at 120 °C for 12 h in an oven to remove residual water in the samples. All the catalytic measurements for the asymmetric Michael additions were carried out in a glass tube (20 mL) or flask (50 mL or 250 mL), depending on the total volume of the reaction medium, equipped with a magnetic stirrer. The reactor was placed in a low constant-temperature trough. After the reaction, the catalyst was separated by centrifugation. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (10% ethyl acetate/petroleum ether) to give solid product **3**. The Michael addition products were found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. Therefore, no pseudo-diastereomer was observed during HPLC analysis using the mixture of hexane/2-propanol containing 0.1% triflouroacetic acid (TFA) as the eluent. The detailed methods for the catalytic measurements and product analysis are described in the Supporting Information.

Crystal data for 3ac: $C_{19}H_{15}ClO_4$ (342.76), orthorhombic, space group P2(1)2(1)2(1), $a=10.408(3)$ Å, $b=10.566(4)$ Å, $c=14.982(5)$ Å, $U=1647.6(9)$ Å^3, $Z=4$, specimen $0.254\times0.0177\times0.123$ mm^3, $T=296(2)$ K, SIEMENS P4 diffractometer, absorption coefficient 0.251 mm^{-1}, reflections collected 11144, independent 3782 [R(int)=0.1032], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3782/0/219, goodness-of-fit on $F^2=1.032$, final R indices [$I>2\sigma(I)$] $R1=0.0444$, $wR2=0.1144$, R indices (all data) $R1=0.0594$, $wR2=0.1206$, largest diff. peak and hole 0.368 and −0.172 Å^{-3}. CCDC 943369 contains the supplementary crys-

tallographic data for this paper (**3ac**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax.: (internat.) (+44)-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Experimental procedures and characterization data are available in the Supporting Information in detail.

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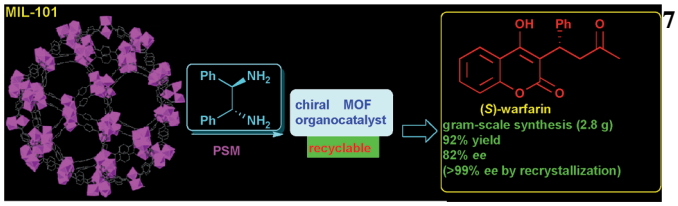

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