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A polymer-supported *Cinchona*-based bifunctional sulfonamide catalyst: a highly enantioselective, recyclable heterogeneous organocatalyst†

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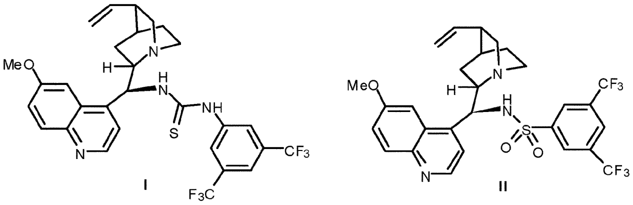
The design, synthesis, and catalytic application of a highly enantioselective and indefinitely stable polymer-supported *Cinchona*-based bifunctional sulfonamide is reported.

Currently, there is much interest in organocatalysts, as they tend to be less toxic and more environmentally friendly than traditional metal-based catalysts.[1] They can be used with a wider range of substrates than enzymes, as well as in various organic solvents. Although much progress has been made, developing chiral organocatalysts that are as reactive and stereoselective as some of the best transition metal-based catalysts or enzymes still remains a significant challenge. In order to obtain reasonable reaction rates and stereoselectivities with organocatalysts, a large catalyst loading is often required. One way to address this difficulty is to design bifunctional or multifunctional organocatalysts, with functional groups that work cooperatively to stabilize the transition state and accelerate the rate of the reaction.[2] It has been shown that *Cinchona*-based bifunctional thiourea **I**[3] or sulfonamide **II**[4] (Fig. 1) organocatalysts are highly effective in facilitating a variety of useful asymmetric reactions.

However, in spite of the versatility of this class of bifunctional organocatalyst, these homogeneous catalysts still provide relatively low turnover numbers and are costly to prepare. Moreover, a tedious work-up procedure is often required to purify the product. The possible contamination of the product by the catalyst may also restrict their use in large-scale applications. Thus, it would be highly desirable to develop heterogeneous analogues of soluble organocatalysts **I** or **II** that could simplify the work-up procedure required for purification of the product, and allow for easy recovery of the catalyst and its potential recycling. It has been reported that thiourea catalysts tend to degrade under thermal conditions.[5] In fact, we also observed during our ongoing study[6] on thiourea-based organocatalysts that **I** can be rapidly decomposed under radical polymerization conditions (*e.g.*, 110 °C in chlorobenzene; see the ESI†). Thus, we decided to prepare a polymeric analogue of the thermally robust sulfonamide catalyst, **II**. Herein, we report the design, synthesis and catalytic application of the polymer-supported *Cinchona*-based sulfonamide, **IV**.

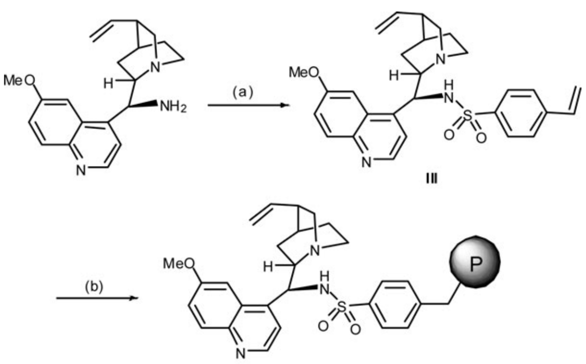
Polymeric catalyst **IV** was designed with the following criteria: (1) the monomeric moiety should mimic the structure of **II**; (2) the polymerization site should be located far enough from the catalytic sites (acidic sulfonamide proton and quinuclidine base) to minimize the detrimental changes in the conformational preference of the reactant–catalyst intermediates; and (3) the morphology of the resin should be such that no limitation on mass transfer arises, with all of its active sites being freely accessible.

Polymeric catalyst **IV** was simply prepared, as depicted in Scheme 1, by the reaction of 9-amino-(9-deoxy)-epiquinine[5] with 4-vinylbenzylsulfonyl chloride[7] in the presence of triethylamine, affording the monomeric moiety, **III**, followed by suspension copolymerization of **III** with styrene and



I II

Fig. 1 *Cinchona*-based bifunctional thiourea and sulfonamide organocatalysts **I** and **II**.



IV (0.4 10 mmol of sulfonamide moiety per g)

Scheme 1 The synthesis of polymer-supported sulfonamide catalyst **IV**: (a) 4-vinylbenzene sulfonyl chloride, NEt_3, CH_2Cl_2, RT, 2 h, 79% yield; (b) styrene, 1,4-divinylbenzene (2 mol%), AIBN (2 mol%), chlorobenzene–H_2O, 110 °C, 12 h.

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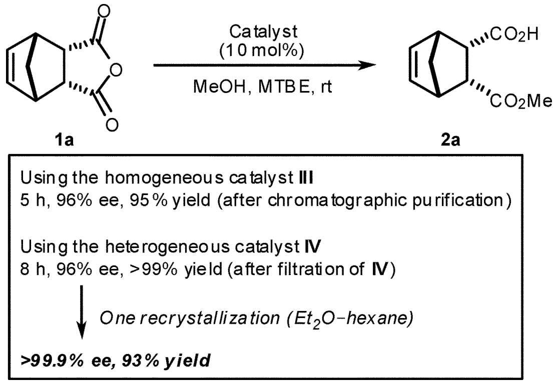


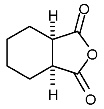
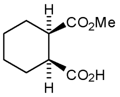
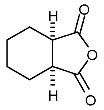
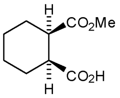
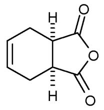
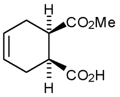
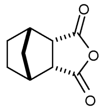
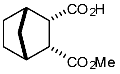
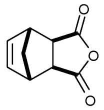
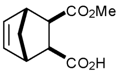
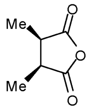
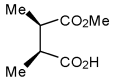
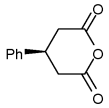
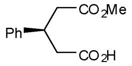
Scheme 2 The methanolytic desymmetrization of **1a** under homogeneous and heterogeneous conditions.

1,4-divinylbenzene (2%) in the presence of the radical initiator, AIBN (see the ESI†).[8] The resulting white-colored resin **IV** was fully characterized by FT-IR spectroscopy, ^{13}C CP/MAS solid-state NMR spectroscopy and elemental analysis (see the ESI†). The loading of the catalytic site was 0.410 mmol g^{-1}, as calculated from the N and S contents of polymer **IV**.

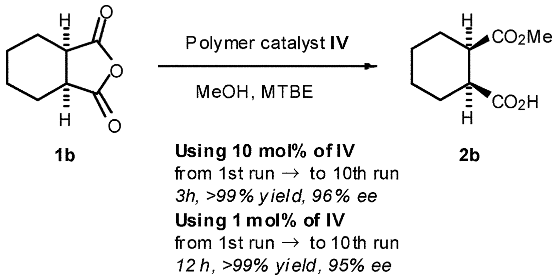
Cinchona-based sulfonamide catalysts such as **II** have proven to be extremely useful in the methanolytic desymmetrization of cyclic anhydrides.[4,9] Thus, the catalytic ability of the insoluble polymer **IV** was explored in the same reaction. To compare its catalytic efficiency with that of its soluble counterpart, the catalytic activity and enantioselectivity of monomeric analogue **III** and polymeric catalyst **IV** were first examined in the methanolysis (10 equiv. of MeOH) of *cis*-5-norbornene-endo-2,3-dicarboxylic anhydride (**1a**) (0.5 mmol) in MTBE (10 mL) with 10 mol% of catalyst at ambient temperature. As shown in Scheme 2, the polymeric catalyst, **IV**, exhibited the same level of enantioselectivity (96% ee) as that obtained with its homogeneous analogue, **III**, although a slightly longer reaction time was required. It is noteworthy that hemiester **2a** was obtained in its pure form after simple filtration of the polymeric catalyst, followed by evaporation of the volatiles. Moreover, the enantiomerically pure (>99.9% ee) hemiester **2a** could be easily obtained after a single crystallization from Et$_2$O–hexane.

Next, the substrate scope was investigated. As shown in Table 1, the methanolysis of monocyclic (entries 6 and 7), bicyclic (entries 1–3) and tricyclic (entries 4 and 5) anhydrides catalyzed by resin **IV** proceeded rapidly. All reactions were completed within a few hours to give the corresponding hemiesters in quantitative yields and excellent ee's (up to 97% ee). A lower catalyst loading of 1 mol% still resulted in excellent catalytic activity and enantioselectivity (>99% yield, 95% ee, 12 h; Table 1, entry 2). Here again, all of the products were obtained in their pure form by the simple filtration of resin **IV**, followed by evaporation of the volatiles.

Table 1 The enantioselective methanolysis of mono-, bi- and tricyclic *meso*-anhydrides **1b–1h**[a]

Entry	Anhydride	Product	Time/h	Yield (%)[b]	Ee (%)[c]
1	 **1b**	 **2b**	3	>99	96
2[d]	 **1b**	 **2b**	12	>99	95
3	 **1c**	 **2c**	3	>99	95
4	 **1d**	 **2d**	7	>99	96
5	 **1e**	 **2e**	7	>99	97
6[e]	 **1f**	 **2f**	7	>99	97
7[e]	 **1g**	 **2g**	9	>99	89

[a] The reactions were carried out with **1b–1e** (0.5 mmol), 10 equiv. of methanol (5 mmol) and polymer catalyst **IV** (10 mol%) in MTBE (10 mL) at RT. [b] Isolated yields. [c] Determined by HPLC (see the ESI). [d] 1 mol% of polymer catalyst **IV** was used. [e] The reactions were carried out with **1f** or **1g** (0.5 mmol), 10 equiv. of methanol (5 mmol) and polymer catalyst **IV** (50 mol%) in MTBE (10 mL) at 0 °C.



Scheme 3 Catalyst recycling experiments.

Finally, the recyclability of the catalysts was also examined. Resin **IV** was readily recovered from the reaction mixture by simple filtration after the methanolytic ring opening reaction of **1b**, followed by washing with MTBE and drying in a vacuum. Surprisingly, the polymeric catalyst exhibited indefinite stability under catalytic conditions and, thus, the recovered catalyst was able to be recycled ten times without any loss in the turnover time or enantioselectivity (**using 10 mol% of catalyst:** >99% yield, 3 h, 96% ee's; **using 1 mol% of catalyst:** >99% yield, 12 h, 95% ee's) (Scheme 3). The FT-IR and ^{13}C CP/MAS solid-state

NMR spectra of the catalyst recovered after ten runs showed exactly the same peaks as those of the resin **IV** before use (see the ESI†). To the best of our knowledge, this is the most successful work to date on the heterogeneous methanolytic desymmetrization of *meso*-cyclic anhydrides.[10]

In conclusion, we have developed a promising polymer-supported bifunctional *Cinchona*-based sulfonamide organocatalyst **IV**. The heterogeneous catalyst, **IV**, showed excellent activity and enantioselectivity (up to 97% ee) in the methanolytic desymmetrization of *meso*-cyclic anhydrides. Moreover, its long-term stability under catalytic conditions allowed for its repeated recycling without any loss of turnover time or enantioselectivity. Thus, we believe that this catalytic process, which is appealing in terms of its simplicity, practicability, environmental friendliness and cost-effectiveness, is adjustable for industrial use. We are currently investigating the application of polymeric catalyst **IV** to other heterogeneous asymmetric catalytic reactions. Further research into related polymer-supported catalysts is also in progress.

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Notes and references

1 (*a*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; (*b*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2005; (*c*) *Chem. Rev.*, ed. B. List, 2007, **107**, 5413–5883 (special issue on organocatalysis); (*d*) *Acc. Chem. Res.*, ed. K. N. Houk and B. List, 2004, **37**, 487–631 (special issue on asymmetric organocatalysis).

2 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175; (*b*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520–1543.

3 Review: S. J. Connon, *Chem. Commun.*, 2008, 2499–2510.

4 S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin and C. E. Song, *Angew. Chem., Int. Ed.*, 2008, **47**, 7872–7875.

5 B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967–1969.

6 H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin and C. E. Song, *Chem. Commun.*, 2008, 1208–1210.

7 D. J. Berrisford, P. A. Lovell, N. R. Suliman and A. Whiting, *Chem. Commun.*, 2005, 5904–5906.

8 It is well known that simple allylic double bonds, such as the olefin moiety at the C10′ and C11′ positions of quinine, do not participate in free radical polymerization; L. Canali, C. E. Song and D. C. Sherrington, *Tetrahedron: Asymmetry*, 1998, **9**, 1029–1034.

9 Reviews: (*a*) I. Atodiresei, I. Schiffers and C. Bolm, *Chem. Rev.*, 2007, **107**, 5683–5712; (*b*) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid and L. Deng, *Acc. Chem. Res.*, 2004, **37**, 621–631.

10 (*a*) F. Bigi, S. Carloni, R. Maggi, A. Mazzacani, G. Sartori and G. Tanzi, *J. Mol. Catal. A: Chem.*, 2002, **182**, 533–539; (*b*) Y. M. Song, J. S. Choi, J. W. Yang and H. Han, *Tetrahedron Lett.*, 2004, **45**, 3301–3304; (*c*) H. S. Kim, Y. M. Song, J. S. Choi, J. W. Yang and H. Han, *Tetrahedron*, 2004, **60**, 12051–12057.