9-Thiourea *Cinchona* alkaloid supported on mesoporous silica as a highly enantioselective, recyclable heterogeneous asymmetric catalyst†

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A readily recycled and regenerated heterogeneous catalyst of 9-thiourea *epi*-quinine supported on mesoporous silica exhibits enhanced enantioselectivity (up to 99.2%) in the asymmetric Friedel–Crafts reaction of imines with indoles.

The easy and perfect separation of catalysts from reaction media and subsequent facile recycling in organic catalytic processes is urgently desired given the striving for environmentally benign chemical processes or methodologies and economic benefits.[1] It is especially an extremely serious problem in the pharmaceutical industry if there is some trace of the homogeneous catalyst in the organic products at the end of the reaction because the level of purity of active pharmaceutical intermediates is strictly regulated. Herein, in addition to describing a readily recycled and regenerated heterogeneous catalyst of 9-thiourea *Cinchona* alkaloid supported on mesoporous silica, we report the enhancement of enantioselectivity resulting from the immobilization of the homogeneous catalyst on a solid support. To the best of our knowledge, this is the first report on the design of heterogeneous 9-thiourea *epi*-quinine catalysts. The nonvolatile and nontoxic characteristics upon anchoring to solid backbones and the minimization of certain deactivation by site isolation are virtues of heterogeneous catalysts.

Cinchona alkaloids have long been known as very useful and robust catalysts for many kinds of organic reactions before the recent explosion of 'organocatalysis'.[2] The first example of an asymmetric reaction catalyzed by *Cinchona* alkaloids can be dated back to 1912.[3] Since the 1960s, with the development of asymmetric phase transfer catalysts (chiral PTC),[4] and asymmetric dihydroxylation catalysts,[5] *Cinchona* alkaloid organocatalysts have drawn much more attention and have been widely used in a variety of asymmetric reactions.[6] 9-Thiourea *Cinchona* alkaloids, a unique class of bifunctional *Cinchona* organocatalysts, have been proved to be powerful chiral catalysts for a wide array of asymmetric transformations[6a] only shortly after their first application in the conjugate addition of nitromethane to chalcones in 2005.[7a] Compared with the previous traditional *Cinchona* alkaloid catalysts, one of the most noticeable features of 9-thiourea *Cinchona* alkaloid are that it bears a bulky tertiary amine moiety—the base quinuclidine—and a thiourea moiety bearing a 3,5-bis(trifluoromethyl)phenyl group at the C-9 position. Because it possesses a combination of suitably separated Lewis base and Brønsted acid functionalities attached to a fairly rigid chiral scaffold, the 9-thiourea *Cinchona* alkaloid can be utilized to initiate simultaneously the activation of both the nucleophile and electrophile, and to tune the steric conformation to achieve higher enantioselectivity in asymmetric reactions. Thus far, these bifunctional organocatalysts have been successfully applied in a wide range of nucleophilic reactions in an asymmetric manner, including conjugate addition,[7] Michael addition,[8] Mannich,[9] Friedel–Crafts,[10] aza-Henry,[11] aza-Michael,[12] and Diels–Alder reactions.[13]

SBA-15, a kind of widely recognized mesoporous silica with large and accessible channels as well as good thermal and hydrothermal stability,[14] is applied as the support for 9-thiourea *epi*-quinine in this work. The immobilization is achieved using a bottom–up approach with a mercapto group as linker. The synthetic procedure towards the catalyst is shown in Scheme 1.

SBA-15 was synthesized following the reported procedure.[14] Mercaptopropyl linkers were grafted on the walls of mesoporous silicas by treating calcined SBA-15 with $(CH_3O)_3SiCH_2CH_2CH_2SH$ in refluxing toluene. Reaction of the resulting mercaptopropyl-derived mesoporous silicas with 9-thiourea *epi*-quinine (ESI†) yielded immobilized catalyst (**1**, SBA-15-SQT). The resulting SBA-15-SQT was characterized by FT-IR spectroscopy, transmission electron microscopy (TEM), ^{13}C and ^{29}Si CP/MAS solid-state NMR spectroscopy, X-ray powder diffraction (XRD), N_2 adsorption–desorption experiments, and element analysis. The new signals at −49 ppm and −55 ppm in the ^{29}Si NMR spectrum, associated with silane silicons with two (T^2) and three (T^3) Si–O–Si linkages, respectively, indicate the grafted incorporation of the mercaptopropyl moiety. The absence of the signals at 114 ppm ($CH{=}\mathit{C}H_2$) and 141 ppm ($\mathit{C}H{=}CH_2$), and the appearance of signals at 185.6 ppm (C=S), 124.7 ppm (CF_3), and 53.2 ppm (OCH_3) from 9-thiourea *epi*-quinine in the ^{13}C NMR spectrum indicate the covalent linkage of 9-thiourea *epi*-quinine through the reaction between thiol and vinylic functions. The loading of the catalytic active site is 0.11 mmol g^{-1} calculated from the N content in SBA-15-SQT. SBA-15-SQT is found to have a surface area of 395 m^2 g^{-1} and a narrow distribution of pore size with a maximum at 5.7 nm.

The catalytic ability of SBA-15-SQT was explored in the asymmetric Friedel–Crafts reaction of indoles with imines

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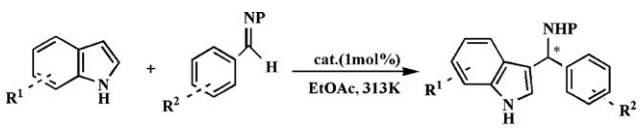
Scheme 1 Schematic representation for the preparation of the heterogeneous catalyst: (a) $(MeO)_3Si(CH_2)_3SH$, toluene, reflux; (b) 9-thiourea *epi*-quinine, AIBN, $CHCl_3$, reflux.

(ESI†). Our initial experiments were performed using indole as a model substrate with half equivalents of *N*-benzylideneben-zenesulfonamide and 1 mol% of SBA-15-SQT in ethyl acetate. It is exciting to observe that the reaction at room temperature afforded *N*-(indol-3-ylphenylmethyl)benzenesulfonamide in a 70.8% yield, 91.9% selectivity and 99.5% ee after 5 days. Further optimization reveals that the reaction could achieve a 76.8% yield, 92.5% selectivity and 99.2% ee (Table 1 entry 1), which is higher than the homogeneous counterpart observed in the literature[10c] and in our work.[15] Obviously the enantioselective inductivity of the supported 9-thiourea *epi*-quinine was better than that of pristine 9-thiourea *epi*-quinine. The immobilization of a homogeneous catalyst is generally accompanied by a decrease in activity and enantioselectivity, as observed in the enantioselective Diels–Alder cycloadditions catalyzed by polymer-supported α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol[16] and the addition of dialkylzincs to aldehydes catalyzed by alumina and amorphous silica gel-immobilized ephedrine.[17] But a few examples of enhanced enantioselectivity on heterogenization have been reported recently. The immobilization of copper complexes[18] in the bidimensional region of laponite clay increased the ee in the reaction of methyl phenyldiazoacetate with THF from virtually zero to values in the region of 40%. The ee of the allylic amination of cinnamyl acetate was enhanced from 43% to 99% by anchoring 1,1′-bis(diphenylphosphino)ferrocene[19] and from 64% to 91% by supporting rhodium(I) complex[20] in the nano-sized channels of MCM-41. The spatial effects originating from the surface figures and confinement roles of the supports are considered as the main reasons for the increases in ee values.[21]

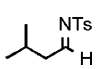
The range of substrates suitable for SBA-15-SQT catalyzed Friedel–Crafts reaction was examined in this work. The reactions of **3a**–**3e** with various indoles (**2a**–**2c**) occurred efficiently to afford the corresponding benzenesulfonamides in high enantioselectivity. Interestingly, the reaction was found to be insensitive to the electronic properties of the indole ring. Excellent enantioselectivities of the corresponding benzenesulfonamides were obtained in the reactions of **2a**–**2c** with **3a**. Compared with **2b** and **2c**, **2a** is a simpler and smaller substrate, which has easier access to the 9-thiourea *epi*-quinine active site within the channel of SBA-15. The highest yield and enantiomeric excess is observed in the reaction of **3a** and **2a**. In the reaction of **2a** with various imines (**3a**–**3e**), we found that the enantioselectivity became lower when the protecting group on N was changed from N–Bs to N–Ts. Unfortunately, the reaction did not occur when there was one electron-attracting substituent (R^2) on one aryl of aryl imines (**3c**–**3d**). The reaction also afforded a high yield and enantioselectivity when the aryl imine was changed to alkyl imine (**3e**).

The reaction of **2a** and **3a** was carried out on a simple mixture of 9-thiourea *epi*-quinine and mercaptopropyl-modified SBA-15 under the same conditions as those for entry 1 in Table 1. The corresponding benzenesulfonamide product was

Table 1 Asymmetric Friedel–Crafts reaction of indoles with imines (P = Ts or Bs (SO_2Ph)) using SBA-15-SQT[a]



2a-2c 3a-3e 4aa-4ac

Entry	2	3	Product	Selectivity [%][b]	Yield [%][b]	ee [%][c]
1	**2a**: R^1 = H	**3a**: R^2 = H, P = Bs	**4aa**	92.5 (91.8)	76.8 (76.4)	99.2 (97.5)
2	**2b**: R^1 = 6-OMe	**3a**: R^2 = H, P = Bs	**4ba**	90.6 (90.7)	68.5 (68.0)	98.9 (99.1)
3	**2c**: R^1 = 5-Me	**3a**: R^2 = H, P = Bs	**4ca**	85.7 (89.3)	65.8 (63.8)	93.2 (97.6)
4	**2a**: R^1 = H	**3b**: R^2 = H, P = Ts	**4ab**	85.3 (90.1)	68.2 (66.5)	89.5 (91.6)
5	**2a**: R^1 = H	**3c**: R^2 = 2-Cl, P = Bs	**4ac**	—	—	—
6	**2a**: R^1 = H	**3d**: R^2 = 2-NO_2, P = Bs	**4ad**	—	—	—
7	**2a**: R^1 = H	**3e**: 	**4ae**	93.1 (94.2)	79.7 (78.3)	95.6 (94.1)

[a] Reactions were carried out with **2a**–**2c** (0.2 mmol), **3a**–**3e** (0.1 mmol), and cat. (1 mol%) in 0.30 mL of solvent, at 313 K for 5 days. [b] Determined by isolated product. [c] Determined by HPLC analysis using a Chiralcel OB–H column. The values within parentheses are reproduced values. Minor errors might be caused by such processes as TLC operation or separation.

Table 2 The recycling of SBA-15-SQT as a catalyst in the asymmetric Friedel–Crafts reactions of indole (**2a**) with imine (**3a**)[a]

Recycle run	Yield [%][b]	ee [%][c]
0	76.8	99.2
1	72.3	94.4
2	64.8	96.4
3	64.0	95.8
4	55.2	84.5
5[d]	61.0	98.8

[a] Reactions were carried out with **2a** (0.2 mmol), **3a** (0.1 mmol), and cat. (1 mol%) in 0.30 mL of solvent, at 313 K for 5 days. [b] Determined by isolated product. [c] Determined by HPLC analysis using a Chiralcel OB–H column. [d] The catalyst was washed with toluene, acetone, ether and hexane before use.

afforded in 74.1% yield and in 92.0% ee, which is similar to that in the homogeneous catalytic reaction in the literature[10c] and in our work,[15] confirming that the enhancement of the yield and enantioselectivity in the Friedel–Crafts reaction of indoles with imines results from the immobilization of 9-thiourea quinine inside the nano-sized channels of the SBA-15.

The SBA-15-SQT catalyst was readily separated from the reaction mixture by simple filtration after the Friedel–Crafts reactions of indoles with imines, dried in a vacuum without any other treatment, and reused 3 times without loss of enantioselectivity (Table 2 entries 0–3), as shown in Table 2. But by the fourth recycle, the enantioselectivity was observed to fall (Table 2 entry 4). To make clear what is responsible for the change, after the fifth run the catalyst was washed with solvents. It is exciting that an ee of 98.8% was observed in the sixth run (Table 2 entry 5), which is quite comparable to the ee of the first run and the yield of the fourth run. This result illustrated the drop in the enantioselectivity in the fifth run might result mainly from the coverage of the catalytic active sites by the adsorbed reactant, product, or impurity during the reaction.

As well as the asymmetric Friedel–Crafts reactions of indoles with imines, the conjugate addition reaction of nitromethane to chalcone and the asymmetric addition of dimethyl malonate to nitroalkene were examined using SBA-15-SQT.[22] Inspiringly both of the reactions also proceeded smoothly and afforded the corresponding products in 97.8% and 84.1% ee, respectively, also exhibiting enhanced enantioselectivities compared to their homogeneous counterparts.[23]

In conclusion, for the first time, 9-thiourea *epi*-quinine was immobilized on mesoporous silica SBA-15 by covalent linkage through a linker to produce a highly enantioselective heterogeneous catalyst which could be readily recycled by simple filtration and regenerated by washing with organic solvents. The confinement effect as well as the accessibility of the nano-sized pores of the SBA-15 support, which might play roles in directing the electrophile reaction and efficiently increasing the enantiomeric excess, are under investigation in our lab by tuning the pore size of the support and tailoring the location of the active sites.

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22 *Conditions*: 0.5 mmol of nitromethane, 1.5 mmol of chalcone, and 2.5 mol% of catalytic site in 0.60 mL of solvent at 303 K for 5 days; 0.3 mmol of nitroalkene, 1.5 mmol of dimethyl malonate, and 2 mol% of catalytic site in 0.60 mL of solvent at 303 K for 5 days.
23 For the conjugate addition reaction of nitromethane to chalcone in a homogeneous system, the ee reported in the literature[7a] is 90.0%. For the homogeneous asymmetric addition of dimethyl malonate to nitroalkene, the ee is 80.6% and 88.0%, respectively, in our own work and in the literature[8c].