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Heterogeneous organocatalysis for the asymmetric desymmetrization of *meso*-cyclic anhydrides using silica gel-supported bis-cinchona alkaloids

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Abstract—The silica gel-supported bis-cinchona alkaloid **1a** was prepared and found to be an efficient heterogeneous chiral organocatalyst with high catalytic activities, enantioselectivities (up to 92% ee), and recyclability for the asymmetric desymmetrization of *meso*-cyclic anhydrides with alcoholysis.

1. Introduction

Enantioselective desymmetrization of *meso* compounds using enzymatic[1] and non-enzymatic[2] methods has proven to be a powerful synthetic means of preparing enantiomerically enriched products where multiple stereocenters can be introduced in one step, enabling the conversion of cheap starting materials into more expensive ones. The non-enzymatic method reported by Oda[3] and Aitken[4] employed a catalytic amount of inexpensive and readily available cinchona alkaloids for the asymmetric methanolysis of *meso*-cyclic anhydrides to afford chiral hemiesters in good to excellent yields and moderate enantiomeric excesses. Based on the findings of Oda and Aitken groups, Bolm and co-workers developed a more enantioselective methanolysis of *meso*-cyclic anhydrides by using a stoichiometric quantity of cinchona alkaloids.[5]

Recently, Deng and co-workers found that commercially available modified cinchona alkaloids are able to function as effective chiral Lewis-base/nucleophilic organic catalysts.[6] These organocatalysts allow desymmetrization and (dynamic) kinetic resolution of cyclic anhydrides, cyanation of ketones, and conjugate addition of thiols to cyclic enones with high enantioselectivity. Among them, a highly enantioselective organocatalytic desymmetrization of prochiral *meso*-cyclic anhydrides with methanolysis is achieved by using the commercially available bis-cinchona alkaloids such as 1,4-bis(dihydroquinidinyl)anthraquinone $(DHQD)_2AQN$ **1** (Scheme 1).[6c] For the first time, this method overcomes the frequently encountered problem of the high loading of cinchona alkaloids to obtain high enantioselectivity in such reactions.

Very recently, we reported the immobilization of the bis-cinchona alkaloid, 1,4-bis(dihydroquininyl)anthraquinone $(DHQ)_2AQN$ **2**, onto silica gel and its use for the asymmetric desymmetrization of *meso*-cyclic anhydrides (Fig. 1).[7] The resulting heterogeneous chiral organocatalyst **2a** gave moderate enantioselectivities (up to 84% ee) in those reactions. Reuse of this heterogeneous organocatalyst invariably gave a small reduction in ee values and conversions and thereby showed some stability under the reaction conditions. Although the results obtained using organocatalyst **2a** were somewhat satisfactory, a similar study using its counterpart **1a** would offer an opportunity to compare their enantioselectivity for the desymmetrization of *meso*-cyclic anhydrides and thus to observe a true diastereomeric effect stemming from the pseudo-enantiomeric alkaloid **1a**.

Here, we report the preparation of the silica gel-supported organocatalyst, SGS-$(DHQD)_2AQN$ **1a**, and its use for the asymmetric desymmetrization of *meso*-cyclic anhydrides. For comparison studies, the more flexible organocatalysts **1b** and **2b** were also prepared, where only one of dihydroquinidine (DHQD) or dihydroquinine (DHQ) moieties in **1** and **2** was tethered to silica gel by use of their derivatives **8** and **9** containing quinidine (QD) and quinine (QN),

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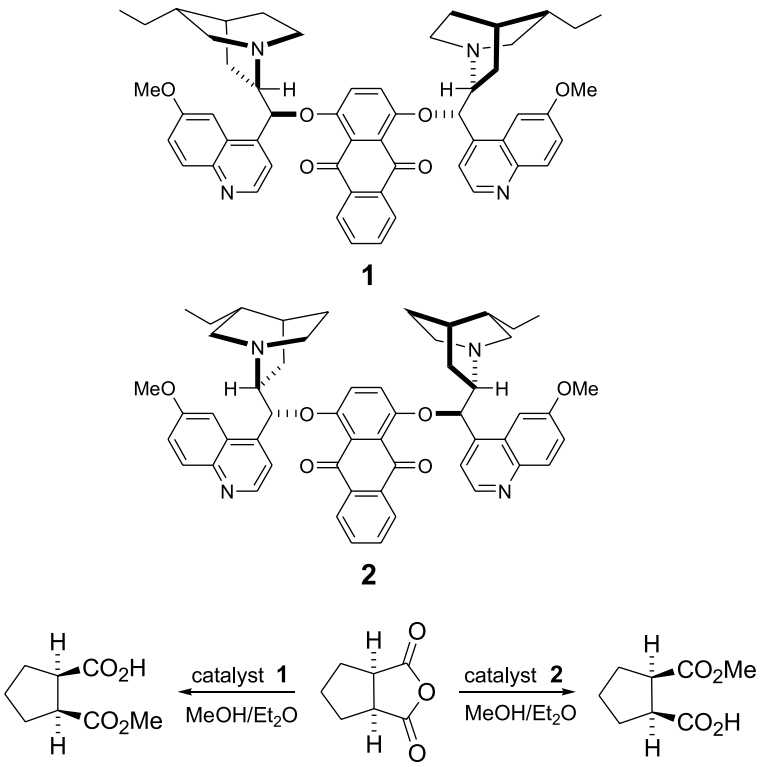


Scheme 1. Structures of the bis-cinchona alkaloids, $(DHQD)_2AQN$ **1** and $(DHQ)_2AQN$ **2**, and their use for the asymmetric desymmetrization reaction of *meso*-cyclic anhydrides with methanol.

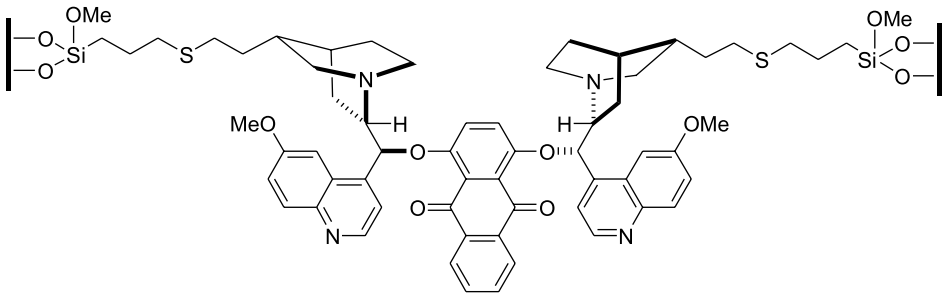
respectively. We found that **1a** showed higher enantioselectivities compared to **2a** and their flexible derivatives **1b** and **2b**. In addition, organocatalyst **1a** could be recycled five times without any significant loss of catalytic activity and enantioselectivity.

2. Results and discussion

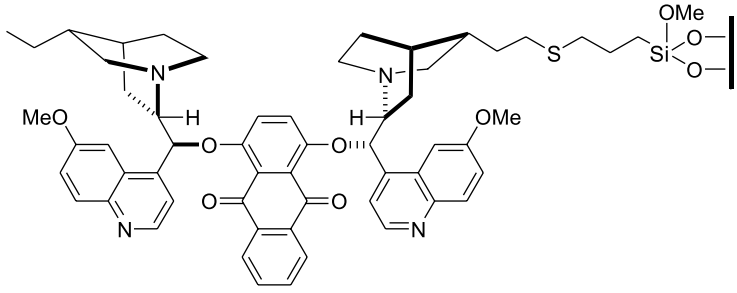
To synthesize the silica gel-supported organocatalyst **1a**, we started with 1,4-bis(quinidinyl)anthraquinone $(QD)_2AQN$ **4**, a homogeneous analogue of **1**. Alkaloid **4** was prepared by nucleophilic substitution of 1,4-difluoroanthraquinone (**3**) with the lithium salt of quinidine in THF at room temperature (Scheme 2).[8] The desired silica gel-supported bis-cinchona alkaloid **1a** was prepared by reacting chiral monomer **4** with mercaptopropylsilanized silica gel in the presence of α,α'-azoisobutyronitrile (AIBN) as a radical initiator in $CHCl_3$.[9] The nitrogen analysis of **1a** confirmed 6.09 wt% incorporation of monomeric alkaloid **4** onto silica gel (0.0711 mmol/g). Organocatalysts **1b**, **2a**, and **2b** were prepared in a similar manner.

In a first series of experiments, we examined the desymmetrization of *meso*-cyclic anhydride **10a** in various solvents using **1a** as an organocatalyst and methanol as a nucleophile under heterogeneous conditions (Scheme 3). Our results are summarized in Table 1. To optimize the reaction conditions, the influence of catalyst amount, the nucleophile to solvent ratio (MeOH/solvent), and temperature on the efficiency of the process was investigated, with particular regard to enantioselectivity. The reaction was performed at -30 °C for 72 h because the higher temperature resulted in a decrease in optical yield and the lower temperature slowed down the reaction rate. In reactions with organocatalyst **1a** (5 mol%), the best enantioselectivity (88% ee) was attained by using the 0.05:1 mixture of methanol and toluene/CCl_4 (1:1) at -30 °C (Table 1, entry 3). In particular, SGS-$(DHQD)_2AQN$ **1a** was superior to SGS-$(DHQ)_2AQN$ **2a** for the asymmetric desymmetrization of **10a** (Table 1, entries 1–3 vs 7–9). These results are consistent with those obtained by Oda,[3b] Aitken,[4b] Bolm,[5c] Bigi[10] who pointed out that diastereomeric quinidine, a pseudo-enantiomer of quinine, afforded the ring opening product with slightly higher enantioselectivity. A comparison between rigid and flexible organocatalysts (**1a**, **2a** vs **1b**, **2b**) shows that the rigidity of the active site seems to be crucial to the enantioselectivity and stability of the catalytic system (Table 1, entries 1, 7 vs 10, 11).

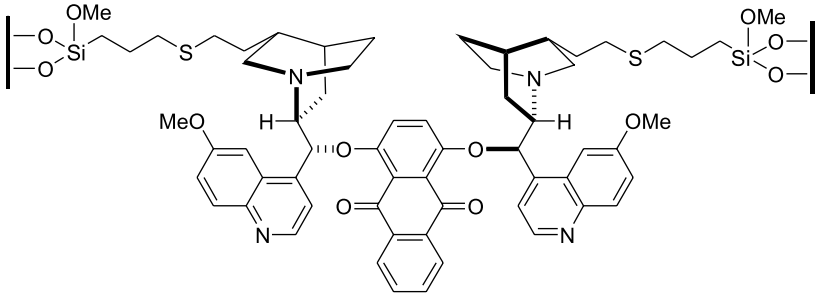
The highest enantioselectivity (92% ee) was obtained by a one-pot conversion of *meso*-cyclic anhydride **10b** with organocatalyst **1a** (20 mol%) into the corresponding desymmetrized mono ester acid **11b** in the 0.1:1 mixture of methanol and diethyl ether at -10 °C (Table 2, entry 2). In contrast, *meso*-cyclic anhydrides **10c–e** afforded very low conversions despite excellent ee values: **10c** gave **11c** in 9% conversion and 83% ee; **10d** gave **11d** in 8% conversion and 77% ee. The low reactivity of *meso*-cyclic anhydrides **10c–e** could probably be due to their steric effects in the heterogeneous asymmetric desymmetrization reactions. We also investigated the effect of various nucleophiles on the asymmetric desymmetrization reactions by replacing methanol with ethanol or 2-propanol. As a result, ethanol



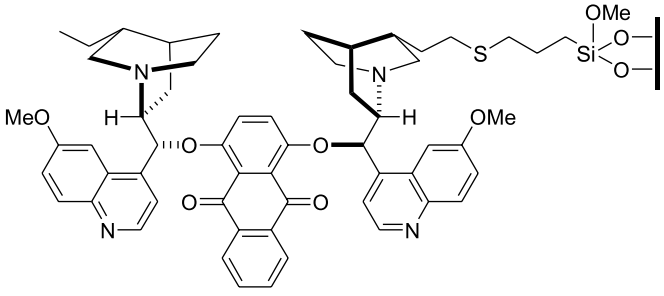
1a



1b



2a



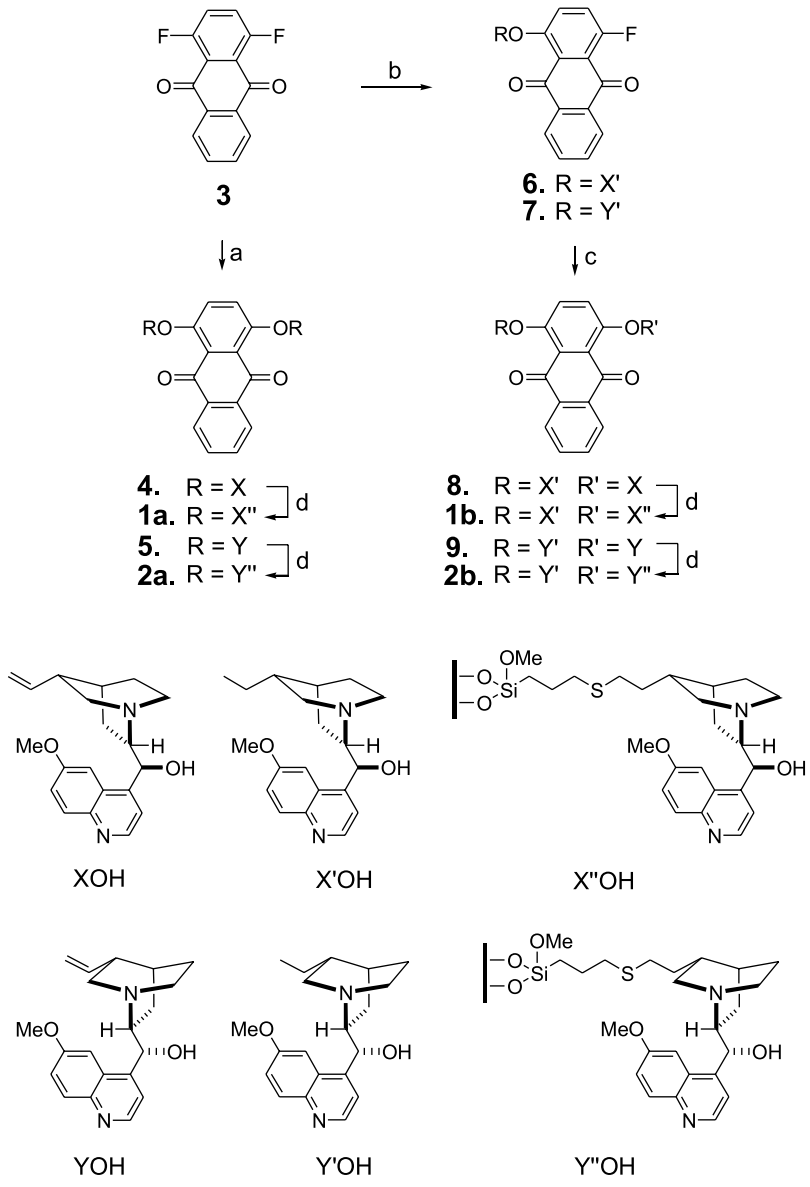
2b

Figure 1. Structures of the silica gel-supported bis-cinchona alkaloids, SGS-$(DHQD)_2$AQN **1a** and **1b** and SGS-$(DHQ)_2$AQN **2a** and **2b**.

and 2-propanol as nucleophiles exhibited lower reactivity and enantioselectivity compared to methanol (Table 2, entries 1 vs 6, 7).

Finally, the recyclability of silica gel-supported organocatalysts was also examined by carrying out the reaction with **1a** (20 mol%) in the 0.1:1 mixture of methanol and diethyl ether at -10 °C for 72 h (Table 3). To our delight, excellent enantioselectivity was retained throughout the successive recycling of organocatalysts. Organocatalyst **1a** could be separated from the reaction mixture by simple filtration and reused for five consecutive reactions without any significant decrease in enantioselectivity (92–89% ee) and catalytic activity (73–70% conversion). A gradual decrease in the enantioselectivity and catalytic activity of the silica gel-supported organocatalyst **1a** with repetitive use was likely attributed to its slight solubility in methanol and thereby somewhat leaching from the reaction mixture (ca. 1% for each cycle).

In summary, we succeeded in a heterogeneous organocatalytic asymmetric methanolysis of various *meso*-cyclic anhydrides in diethyl ether using the silica gel-supported chiral organocatalyst **1a** to afford the corresponding chiral



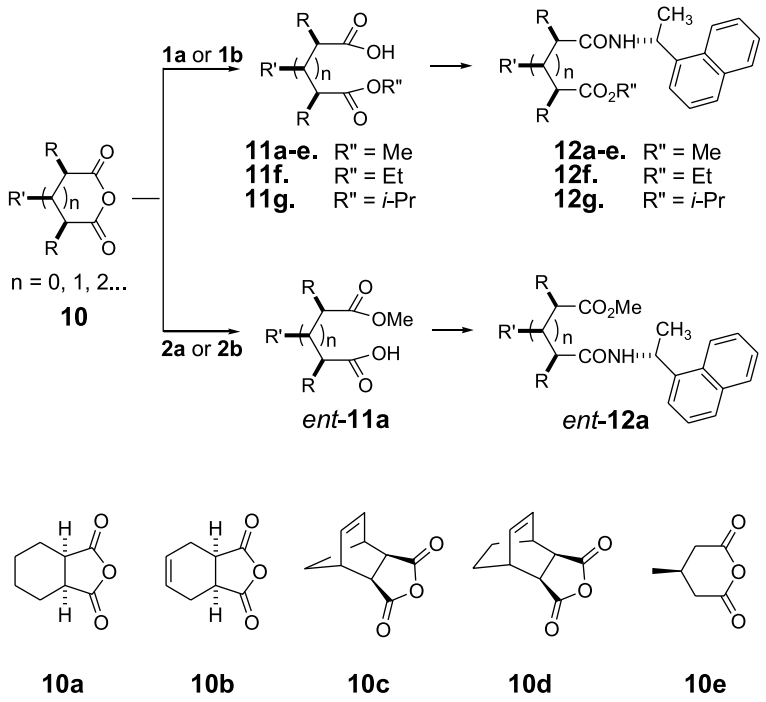
Scheme 2. Synthesis of SGS-$(DHQD)_2$AQN **1a** and **1b** and SGS-$(DHQ)_2$AQN **2a** and **2b**: (a) quinidine (XOH) or quinine (YOH), *n*-BuLi, THF, −50 °C to rt, (**4**, 71%; **5**, 76%), or XOH, NaH, DMF, rt, (**4**, 72%); (b) hydroquinidine (X′OH) or hydroquinine (Y′OH), NaH, DMF, rt, (**6**, 45%; **7**, 68%); (c) XOH or YOH, NaH, DMF, rt, (**8**, 77%; **9**, 98%); (d) mercaptopropylsilanized silica gel (SGS-SH), AIBN, $CHCl_3$, 80 °C, (**1a**, 0.0711 mmol/g; **2a**, 0.0733 mmol/g; **1b**, 0.0604 mmol/g; **2b**, 0.0630 mmol/g).

hemiesters with excellent enantioselectivities in moderate conversions. In such reactions, the rigidity of the organocatalyst appears to be an important parameter. Furthermore, the immobilized chiral organocatalyst **1a** could be reused several times without any significant decrease in catalytic activity and enantioselectivity. Our process therefore retains the ease of catalyst removal/recycling as well as the efficient reaction protocol.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 or a Varian Mercury 300 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane or solvent and coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-AM505WA mass spectrometer using a fast atom bombardment (FAB) technique. Optical rotations (α) were determined on a Rudolph AUTOPOL III automatic polarimeter. Elemental analysis was performed on a CE EA1110 elemental analyzer. GC analysis was performed on a Younglin Acme 6000 GC system. HPLC analysis was performed on a Waters 600 HPLC system equipped with a 2487 dual λ absorbance detector. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} precoated plates (0.25 mm thickness, Merck). Flash chromatography was carried out on silica gel 60 (230–400 mesh, Merck). Bis-cinchona alkaloids **4**, **5**, **8**, and **9** were prepared by



Scheme 3. Desymmetrization of *meso*-cyclic anhydrides **10a–e** with alcoholysis in diethyl ether using **1a**, **1b**, **2a**, or **2b** as a organocatalyst followed by conversion of the resulting hemiesters **11a–g** and *ent*-**11a** into the corresponding amide–esters **12a–g** and *ent*-**12a**, respectively.

Table 1. Effects of various heterogeneous organocatalysts and solvents on conversions and ee values in the desymmetrization reaction of *cis*-1,2-cyclohexanedicarboxylic anhydride **10a** with methanol[a]

Entry	Anhydride	Product	Catalyst[b] (mol%)	Solvent	Conversion[c] (%)	ee[d] (%)	Configuration[e]
1	**10a**	**11a**	**1a** (5)	Diethyl ether	76	80	1*R*,2*S*
2	**10a**	**11a**	**1a** (5)	THF	44	88	1*R*,2*S*
3	**10a**	**11a**	**1a** (5)	Toluene/CCl_4 (1:1)	78	88	1*R*,2*S*
4	**10a**	**11a**	**1a** (5)	Toluene	9	67	1*R*,2*S*
5	**10a**	**11a**	**1a** (5)	EtOAc	5	70	1*R*,2*S*
6	**10a**	**11a**	**1a** (5)	*t*-Butyl methyl ether	47	86	1*R*,2*S*
7	**10a**	*ent*-**11a**	**2a** (5)	Diethyl ether	65	64	1*S*,2*R*
8	**10a**	*ent*-**11a**	**2a** (5)	THF	16	63	1*S*,2*R*
9	**10a**	*ent*-**11a**	**2a** (5)	Toluene/CCl_4 (1:1)	67	46	1*S*,2*R*
10	**10a**	**11a**	**1b** (5)	Diethyl ether	58	67	1*R*,2*S*
11	**10a**	*ent*-**11a**	**2b** (5)	Diethyl ether	45	43	1*S*,2*R*

[a] MeOH (nucleophile)/solvent (ca. 0.05:1 (v/v)), reaction temperature (−30 °C), reaction time (72 h).
[b] SGS-$(DHQD)_2$AQN **1a** and **1b**, SGS-$(DHQ)_2$AQN **2a** and **2b**.
[c] Determined by GC analysis of an enantiomeric mixture for **11a** or *ent*-**11a** on a Chiraldex G-TA column (30 m×0.25 mm).
[d] Determined by HPLC analysis of a diastereomeric mixture for **12a** or *ent*-**12a** on a Hypersil silica column (4.6×200 mm, 5 μm).[6c,7]
[e] The absolute configuration of **11a** and *ent*-**11a** was determined as described.[5,7]

Table 2. Desymmetrization of *meso*-cyclic anhydrides **10a-e** with alcoholysis in diethyl ether using heterogeneous organocatalyst **1a**[a]

Entry	Anhydride	Product	Catalyst[b] (mol%)	Time (h)	Conversion[c,d] (%)	ee[e] (%)	Configuration[f]
1	**10a**	**11a**	**1a** (20)	48	82	89	1*R*,2*S*
2	**10b**	**11b**	**1a** (20)	72	73	92	1*R*,2*S*
3	**10c**	**11c**	**1a** (20)	72	9	83	2*R*,3*S*
4	**10d**	**11d**	**1a** (20)	72	8	77	2*R*,3*S*
5	**10e**	**11e**	**1a** (20)	72	22	43	3*S*
6	**10a**	**11f**[g]	**1a** (20)	72	7	82	1*R*,2*S*
7	**10a**	**11g**[h]	**1a** (20)	72	6	53	1*R*,2*S*

[a] MeOH (nucleophile)/Et_2O (solvent) (ca. 0.1:1 (v/v)), reaction temperature (−10 °C).
[b] SGS-$(DHQD)_2$AQN **1a**.
[c] Determined by GC analysis of an enantiomeric mixture for **11a**, **11f**, or **11g** on a Chiraldex G-TA column (30 m×0.25 mm).
[d] Determined by GC analysis of an enantiomeric mixture for each of **11b–e** on a HP-1 column (30 m×0.32 mm×0.25 μm).
[e] Determined by HPLC analysis of a diastereomeric mixture for each of **12a–g** on a Hypersil silica column (4.6×200 mm, 5 μm).[6c,7]
[f] The absolute configuration of **11a–g** was determined as described.[5,7]
[g] EtOH instead of MeOH as a nucleophile.
[h] *i*-PrOH instead of MeOH as a nucleophile.

Table 3. The recyclability of the heterogeneous bis-cinchona alkaloid-based organocatalyst **1a** in the asymmetric desymmetrization reaction of **10b** with methanol[a]

ee (%) with consecutive use of recycled organocatalyst **1a**					
Recycle	1st	2nd	3rd	4th	5th
ee (%)	92	91	93	86	89
Conversion (%)	73	72	70	71	70

[a] Asymmetric desymmetrization reaction using 20 mol% silica gel-supported chiral organocatalyst **1a** was carried out in the 0.1:1 mixture of methanol and diethyl ether at −10 °C for 72 h.

modified procedures.[8] Reagent-grade chemicals were purchased from Aldrich, Fluka, Junsei, and TCI and used as received unless otherwise specified.

3.1.1. Mercaptopropylsilanized silica gel (SGS-SH). Dried silica gel 60 (230–400 mesh, 14.0 g) was treated with (3-mercaptopropyl)trimethoxysilane (61.3 mL) in anhydrous pyridine/toluene (1:1) (59.0 mL). After stirring at 90 °C for 24 h, the slurry was cooled to room temperature, filtered, washed with MeOH and $CHCl_3$, and dried in vacuo for 24 h to afford derivatized silica gel (15.6 g) containing 3.59 wt% S, corresponding to 1.12 mmol of S per g of derivatized silica gel. Element analysis (wt%): C 6.81, H 1.60, S 3.59.

3.1.2. SGS-(DHQD)$_2$AQN 1a. To a suspension of SGS-SH (2.64 g, 2.95 mmol) in $CHCl_3$ (60 mL) was added **4** (1.20 g, 1.41 mmol) and α,α'-azoisobutyronitrile (AIBN, 120 mg, 0.731 mmol). After stirring at reflux for 48 h under Ar, the slurry was cooled to rt, filtered, exhaustively washed with MeOH and CH_2Cl_2, and dried in vacuo to give **1a** (2.74 g). Element analysis (wt%) of **1a**: C 10.00, H 1.82, N 0.40, S 3.44.

3.1.3. SGS-(DHQD)$_2$AQN 1b. To a suspension of SGS-SH (1.31 g, 1.46 mmol) in $CHCl_3$ (60 mL) was added **8** (1.50 g, 1.75 mmol) and AIBN (125 mg, 0.760 mmol). After stirring at reflux for 48 h under Ar, the slurry was cooled to rt, filtered, exhaustively washed with MeOH and CH_2Cl_2, and dried in vacuo to give **1b** (1.33 g). Element analysis (wt%) of **1b**: C 9.45, H 1.81, N 0.34, S 3.54.

3.1.4. SGS-(DHQ)$_2$AQN 2a. To a suspension of SGS-SH (2.09 g, 2.34 mmol) in $CHCl_3$ (60 mL) was added **5** (1.0 g, 1.17 mmol) and AIBN (100 mg, 0.609 mmol). After stirring at reflux for 48 h under Ar, the slurry was cooled to rt, filtered, exhaustively washed with MeOH and CH_2Cl_2, and dried in vacuo to give **2a** (2.2 g). Element analysis (wt%) of **2a**: C 10.18, H 1.69, N 0.41, S 3.44.

3.1.5. SGS-(DHQ)$_2$AQN 2b. To a suspension of SGS-SH (1.31 g, 1.46 mmol) in $CHCl_3$ (60 mL) was added **9** (1.50 g, 1.75 mmol) and AIBN (125 mg, 0.760 mmol). After stirring at reflux for 48 h under Ar, the slurry was cooled to rt, filtered, exhaustively washed with MeOH and CH_2Cl_2, and dried in vacuo to give **2b** (1.35 g). Element analysis (wt%) of **2b**: C 10.15, H 1.78, N 0.35, S 3.03.

3.2. General procedure for the asymmetric methanolysis of *meso*-cyclic anhydrides 10a–e

Described for the reaction of *cis*-1,2-cyclohexanedicarboxylic anhydride **10a** in the mixture of methanol (ca. 60 equiv) and diethyl ether (5 mL per 0.1 mmol anhydride) at an approximate ratio of ca. 0.05:1 (v/v).

After a suspension containing *cis*-1,2-cyclohexanedicarboxylic anhydride **10a** (12 mg, 0.0778 mmol) and SGS-(DHQD)$_2$AQN **1a** (54.7 mg, 5 mol%) in dry diethyl ether (3.9 mL) at −30 °C was stirred for 10 min under Ar, dry MeOH (195 μL, 4.81 mmol) was added. After stirring at −30 °C for 72 h, the reaction mixture was filtered, and then the filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography (EtOAc/*n*-hexane = 1:2) to afford an enantiomeric mixture for **11a** as a colorless oil. For determining conversion efficiency, GC analysis of an enantiomeric mixture for **11a** was performed prior to work-up. The filtrate for GC analysis was prepared by filtering the reaction mixture followed by washing with EtOAc.

GC analysis of an enantiomeric mixture for **11a**, **11f**, or **11g** obtained by use of **1a** was performed on a Chiraldex G-TA column (Advanced Separation Technology, 30 m × 0.25 mm) under the condition: initial temperature, 130 °C; initial time, 10.0 min; 2.0 °C/min gradient; final temperature, 170 °C, 17 psi. Retention time (min): **11a**, t_R = 32.44, t_R = 32.58 (major); **11f**, t_R = 30.26; **11g**, t_R = 30.27. GC analysis of an enantiomeric mixture for each of **11b–e** was performed on a HP-1 column (Hewlett Packard, 30 m × 0.32 mm × 0.25 μm) under the condition: initial temperature, 50 °C; initial time, 5.0 min; 15.0 °C/min gradient; final temperature, 170 °C, 17 psi. Retention time (min): **11b**, t_R = 9.75; **11c**, t_R = 10.78; **11d**, t_R = 10.83; **11e**, t_R = 10.77.

3.3. General procedure for the ee determination of hemiesters 11a–g (described for *cis*-1,2-cyclohexanedicarboxylic acid monomethyl ester 11a)

The enantiomeric excess of the product was determined by HPLC analysis of a diastereomeric mixture for the corresponding amide–ester **12a** prepared from an enantiomeric mixture for hemiester **11a** according to the literature procedure.[6c,7]

To a filtrate containing an enantiomeric mixture for *cis*-1,2-cyclohexanedicarboxylic acid monomethyl ester **11a** (36.4 mg, 0.195 mmol) in CH_2Cl_2 (9.8 mL) at room temperature was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI, 44.9 mg, 0.234 mmol). After stirring for 10 min, 4-(dimethylamino)pyridine (DMAP, 7.2 mg, 58.6 μmol) and (*R*)-(+)-1-(1-naphthyl)-ethylamine (34.7 μL, 0.215 mmol) were added to the mixture. After stirring at room temperature for 5 h, the reaction mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The crude residue was purified by flash chromatography (EtOAc/*n*-hexane = 1:2) to afford a diastereomeric mixture for **12a** as a yellow oil. For determining the ee value, HPLC analysis of a diastereomeric mixture for **12a** was performed prior to column

purification. The diastereomeric mixture was dissolved in EtOAc and diluted with *n*-hexane for HPLC analysis.

HPLC analysis of a diastereomeric mixture for each of **12a**–**g** was performed on a Hypersil silica column (Thermo, 4.6×200 mm, 5 μm) with UV monitoring at 280 nm and a flow rate of 1.0 mL/min under isocratic conditions: **12a**, *n*-hexane/2-propanol=97/3, t_R=8.20 (major), t_R=11.09; **12b**, *n*-hexane/2-propanol=97/3, t_R=10.74 (major), t_R=13.89; **12c**, *n*-hexane/2-propanol=97/3, t_R=16.75 (major), t_R=22.47; **12d**, *n*-hexane/2-propanol=97/3, t_R=14.86 (major), t_R=18.32; **12e**, *n*-hexane/2-propanol=96/4, t_R=24.54, t_R=26.80 (major); **12f**, *n*-hexane/2-propanol=97/3, t_R=6.98 (major), t_R=8.67; **12g**, *n*-hexane/2-propanol=97/3, t_R=8.52 (major), t_R=11.30.

Acknowledgements

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