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Silica gel-supported bis-cinchona alkaloid: a chiral catalyst for the heterogeneous asymmetric desymmetrization of *meso*-cyclic anhydrides

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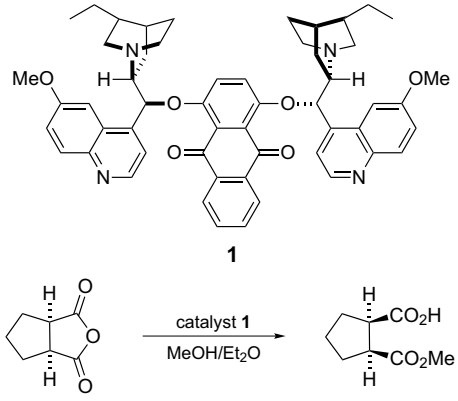
Abstract—A one-pot conversion of *meso*-cyclic anhydrides with alcoholysis in diethyl ether using SGS-$(DHQ)_2$AQN **4,** a silica gel-supported chiral catalyst, into the corresponding desymmetrized mono ester acids was achieved with enantiomeric excesses of up to 84% under mild and efficient conditions.

Enantioselective desymmetrization of *meso* compounds is 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. Examples of substrates for desymmetrization reactions include epoxides, aziridines, cyclic anhydrides, and a variety of diols.[1] The transformations utilized to desymmetrize *meso* compounds fall roughly into three major categories: transition metal-mediated, Lewis acid-mediated, and enzyme-catalyzed processes.[1] As one would expect, most of these processes use a chiral catalyst or reagent that binds to the *meso* substrate and tranforms the enantiotopic faces and groups into chemically distinct diastereotopic ones.

Recently, Deng and co-workers[2] discovered a general and highly enantioselective catalytic desymmetrization of prochiral *meso*-cyclic anhydrides using commercially available mono and bis-cinchona alkaloid derivatives as a catalyst or equivalent. Among them, 1,4-bis(dihydroquinidinyl)anthraquinone $(DHQD)_2$AQN **1**, in general afforded high enantioselectivities (up to 98% ee) with only modest catalyst loading of 8 mol% (Scheme 1).[2] For the first time, this method overcomes the frequently encountered problems of high catalyst loading when expensive cinchona alkaloid derivatives were employed. For the reutilization of catalytic ligands in consecutive asymmetric desymmetrization reactions, several attempts to recover cinchona alkaloids such as quinidine (QD) and quinine (QN) for the ring-opening of *meso*-cyclic anhydrides have been made.[3–5] However, in spite of the utility of $(DHQD)_2$AQN **1** as an excellent catalyst for the asymmetric desymmetrization of *meso*-cyclic anhydrides, there has been only one report so far about anchoring a homogeneous analogue of **1** onto the polymer-support.[6]



Scheme 1. Structure of $(DHQD)_2$AQN **1** and its use for the asymmetric desymmetrization reaction of *meso*-cyclic anhydrides with methanol.

Keywords: Catalyst immobilization; Desymmetrization; $(DHQ)_2$AQN; SGS-$(DHQ)_2$AQN; *meso*-Cyclic anhydride.
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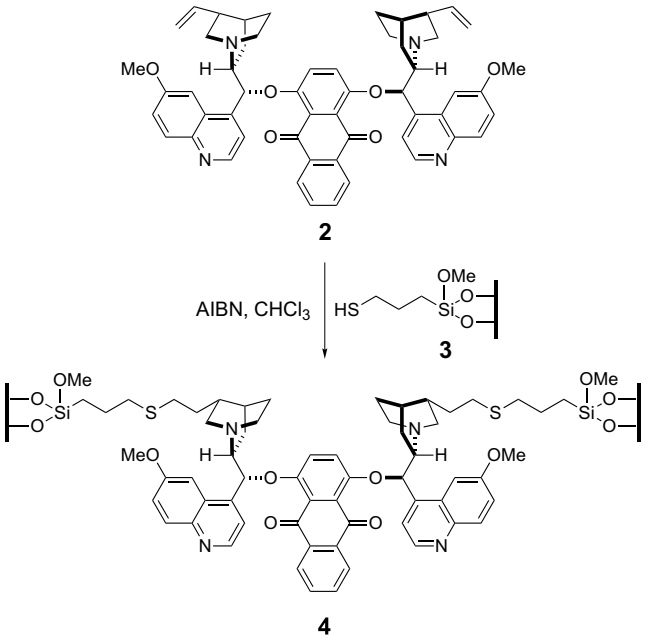


Scheme 2. Synthesis of SGS-$(DHQ)_2$AQN **4**.

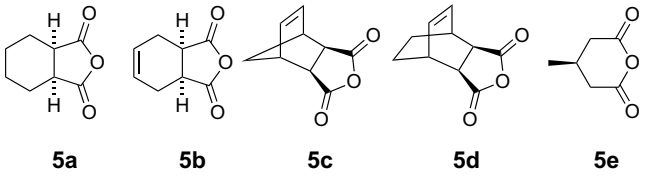
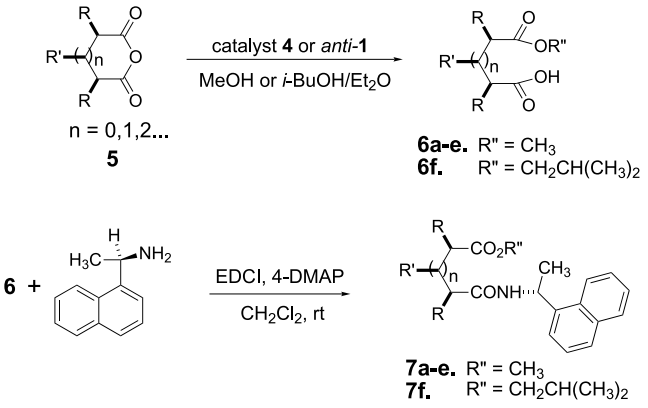


Figure 1. Various *meso*-cyclic anhydride substrates **5a**–**e**.



Scheme 3. Desymmetrization of *meso*-cyclic anhydrides **5a**–**e** with alcoholysis in diethyl ether using **4** or *anti*-**1** as a catalyst followed by conversion of the resulting hemiesters **6a**–**f** to the corresponding amide–esters **7a**–**f**.

Therefore, we became interested in the immobilization of 1,4-bis(dihydroquininyl)anthraquinone $(DHQ)_2$AQN *anti*-**1**, a homogeneous analogue of **1** onto inorganic supports to explore the possibility of its efficient reuse. Generally, inorganic materials often show higher chemical and thermal stability under catalytic conditions than cross-linked polymers. Thus, we chose commercially available silica gel (70–230 mesh) as a catalyst support.

To synthesize a suitable silica gel-supported catalyst, we started with 1,4-bis(quininyl)anthraquinone $(QN)_2$AQN **2**, a homogeneous analogue of *anti*-**1**. Alkaloid **2** was prepared by nucleophilic substitution of 1,4-difluoroanthraquinone with the lithium salt of quinine in THF at room temperature.[7,8] SGS-$(DHQ)_2$AQN **4**, a silica gel-supported bis-cinchona alkaloid $(DHQ)_2$AQN *anti*-**1**, was prepared by reacting chiral monomer **2** with mercaptopropylsilanized silica gel **3** in the presence of α,α′-azoisobutyronitrile (AIBN) as a radical initiator in $CHCl_3$ (Scheme 2).[9] The nitrogen analysis of **4** confirmed 10.7 wt % incorporation of monomeric alkaloid **2** onto silica gel (0.126 mmol/g).[10]

In a first series of experiments, we examined the desymmetrization of anhydride **5a** in diethyl ether using SGS-$(DHQ)_2$AQN **4** as a catalyst and methanol as a nucleophile under heterogeneous conditions (Fig. 1 and Scheme 3). Our results are summarized in Table 1. To optimize the experimental conditions, the influence of catalyst amount, the nucleophile to solvent ratio

Table 1. Effects of catalyst amount, the nucleophile to solvent ratio, and temperature on conversion yields and ee values in the desymmetrization reaction of *cis*-1,2-cyclohexanedicarboxylic anhydride **5a** with methanol[a]

Entry	Product[b]	Catalyst[c] (mol %)	Ratio[d]	Temperature (°C)	Conversion[e] (%)	Ee[f] (%)
1	**6a**	2	0.01:1	0	63	56
2	**6a**	2	0.01:1	−30	49	66
3	**6a**	2	0.33:1	0	94	27
4	**6a**	2	0.33:1	−30	99	39
5	**6a**	0.2	0.01:1	0	25	48
6	**6a**	0.2	0.01:1	−30	17	84
7	**6a**	0.2	0.33:1	0	95	3
8	**6a**	0.2	0.33:1	−30	65	14

[a] Reaction time (48 h).
[b] Absolute configuration (1*S*,2*R*).[3,4]
[c] SGS-$(DHQ)_2$AQN **4**.
[d] MeOH (nucleophile)/Et_2O (solvent).
[e] Determined by GC analysis of an enantiomeric mixture of **6a** using a HP-1 column (30 m × 0.32 mm × 0.25 μm).[11]
[f] Determined by HPLC analysis of a diastereomeric mixture of **7a** using a Nova-Pak® silica column (15 cm × 3.9 mm × 4 μm).[2,12]

Table 2. Desymmetrization of *meso*-cyclic anhydrides **5a–e** with alcoholysis in diethyl ether using heterogeneous catalyst **4** or homogeneous catalyst *anti*-**1**

Entry	Anhydride	Product	Catalyst[a] (mol%)	Ratio (MeOH/Et_2O)	Temperature (°C)	Time (h)	Conversion[c] (%)	Ee[d] (%)	Configuration[e]
1	**5a**	**6a**	**4** (5)	0.01:1	−20	48	73	56	1*S*,2*R*
2	**5a**	**6a**	**4** (5)	0.05:1	−30	48	85	67	1*S*,2*R*
3[2]	**5a**	**6a**	*anti*-**1** (5)	0.01:1	−20	48	84	93	1*S*,2*R*
4[2]	**5a**	**6a**	*anti*-**1** (5)	0.05:1	−30	48	99	76	1*S*,2*R*
5	**5b**	**6b**	**4** (5)	0.01:1	−20	60	56	65	1*S*,2*R*
6	**5b**	**6b**	**4** (2)	0.05:1	−10	72	77	62	1*S*,2*R*
7[2]	**5b**	**6b**	*anti*-**1** (2)	0.05:1	−10	72	96	76	1*S*,2*R*
8	**5c**	**6c**	**4** (2)	0.33:1	−30	19	78	41	2*S*,3*R*
9	**5d**	**6d**	**4** (2)	0.1:1	−30	48	18	83	2*S*,3*R*
10	**5e**	**6e**	**4** (5)	0.01:1	25	7	46	26	3*R*
11	**5a**	**6f**	**4** (5)	0.05[b]:1	0	72	76	51	1*S*,2*R*

[a] SGS-$(DHQ)_2$AQN **4** or $(DHQ)_2$AQN *anti*-**1**.
[b] 2-Methyl-1-propanol instead of MeOH as a nucleophile.
[c] Determined by GC analyses of an enantiomeric mixture of **6a–f** using a HP-1 column (30 m × 0.32 mm × 0.25 μm).[11]
[d] Determined by HPLC analyses of a diastereomeric mixture of **7a–f** using a Nova-Pak® silica column (15 cm × 3.9 mm × 4 μm).[2,12]
[e] The absolute configuration of the products **6a–f** was determined as described.[3,4]

(MeOH/ether), and temperature on the efficiency of the process was investigated, with particular regard to enantioselectivity. Interestingly, the results from Table 1 show that the conversion yields and ee values increased accordingly as the catalyst amount increased (entries 1–4 vs 5–8). In particular, as can be seen from Table 1, the conversion yields and ee values depend on the methanol to ether ratio. The more quantity of methanol as a nucleophile was used, the more the conversion yield increased, but the ee value decreased (entries 1, 2, 5, 6 vs 3, 4, 7, 8, respectively). This result was independent of reaction temperature. We observed that the higher temperature resulted in a decrease in the ee value and the lower temperature slowed down the reaction rate. As shown in entry 6 of Table 1, the catalytic amount of **4** (0.2 mol%) with respect to the reacting anhydride **5a** under heterogeneous conditions was utilized to achieve the good ee value (84% ee by carrying out the reaction in the mixture of methanol and diethyl ether at a ratio of 0.01:1 at −30 °C).

We examined the desymmetrization of *meso*-cyclic anhydrides **5a–e** with alcoholysis in diethyl ether using heterogeneous catalyst **4** or homogeneous catalyst *anti*-**1**. Our results are summarized in Table 2. Heterogeneous catalyst **4** gave similar or lower stereoselectivities compared to the corresponding homogeneous catalyst *anti*-**1** (Table 2, entries 1, 2 vs 3, 4, respectively). Interestingly, the use of a catalytic amount of silica gel-supported chiral catalyst **4** (5 or 2 mol%) produced compounds **6a** and **6b** in lower yields but with the ee values comparable to those obtained using homogeneous chiral catalyst *anti*-**1** (Table 2, entries 2, 6 vs 4, 7, respectively). Due to the negative effect of the support on the chiral microenvironment around the active centers, this immobilized chiral catalyst also suffered from moderate catalytic activity and/or enantioselectivity.

Table 3. The recyclability of heterogeneous bis-cinchona alkaloid-based catalyst **4** in the asymmetric desymmetrization reaction of **5a** with methanol[a]

Ee (%) with consecutive use of recycled catalyst **4**					
Recycle	1st	2nd	3rd	4th	5th
Ee (%)	67	67	65	62	65
Conversion (%)	85	82	73	72	68

[a] Asymmetric desymmetrization reaction using 5 mol% silica gel-supported chiral catalyst **4** was carried out in the mixture of methanol and diethyl ether at a ratio of 0.05:1 at −30 °C for 48 h.

Finally, the recyclability of the catalyst was also examined by carrying out the reaction with 5 mol% silica gel-supported chiral catalyst **4** in the mixture of methanol and diethyl ether at a ratio of 0.05:1 at −30 °C for 48 h. Enantiomeric excesses ranging from 62% to 67% were observed in several recycles of the catalytic system (Table 3). Catalyst **4** could be separated from the reaction mixture by solvent precipitation and was reused for five consecutive reactions without any significant decrease in catalytic activity and enantioselectivity. However, the catalyst was somewhat leaching from the reaction mixture. The moderate catalytic activity and enantioselectivity of silica gel-supported chiral catalyst **4** was likely attributed to its slight solubility in methanol. Although the selectivity of the reaction was moderate, this process was quite simple and efficient for catalyst immobilization.

In summary, we succeeded in a catalytic heterogeneous asymmetric methanolysis of various *meso*-cyclic anhydrides in diethyl ether using silica gel-supported chiral catalyst **4** to afford the corresponding chiral hemiesters in moderate yields and enantioselectivities. Furthermore, the process retains the ease of catalyst removal/recycling by simple filtration. The immobilized chiral catalyst could be reused several times without any significant decrease in catalytic activity and enantioselectivity. Further optimization of the reactions is currently in progress.

General procedure for the asymmetric methanolysis of meso-cyclic anhydrides **5a–e** (described for the reaction of *cis*-1,2-cyclohexanedicarboxylic anhydride **5a** in the mixture of methanol (10 equiv) and ether (5 mL per

0.1 mmol anhydride) at an approximate ratio of 0.01:1 (v/v)). After a suspension containing *cis*-1,2-cyclohexanedicarboxylic anhydride **5a** (25 mg, 0.162 mmol) and SGS-$(DHQ)_2$AQN **4** (64.3 mg, 5 mol%) in dry diethyl ether (8.1 mL) at −20 °C was stirred for 10 min, dry methanol (65.7 μL, 1.62 mmol) was added under argon atmosphere. After stirring at −20 °C for 48 h, the mixture was filtered, and then filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane = 1 : 2) to afford **6a** as a colorless oil. GC analysis of an enantiomeric mixture of **6a** for determining conversion efficiency was performed prior to work-up.[11]

General procedure for the ee determination of hemiesters **6a–f** (described for *cis*-1,2-cyclohexanedicarboxylic acid monomethyl ester **6a**). The enantiomeric excess of the product was determined by HPLC analysis of a diastereomeric mixture of the corresponding amide–ester **7a** prepared from an enantiomeric mixture of hemiester **6a** according to the literature procedure.[2,12]

To a solution containing *cis*-1,2-cyclohexanedicarboxylic acid monomethyl ester **6a** (39.8 mg, 0.214 mmol) in CH_2Cl_2 (10.7 mL) at room temperature was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 49.3 mg, 0.257 mmol). After stirring for 10 min, 4-(dimethylamino)pyridine (4-DMAP, 7.8 mg, 64.2 μmol) and (*R*)-(+)-1-(1-naphthyl)ethylamine (37.9 μL, 0.235 mmol) were added to the mixture. After stirring at room temperature for 5 h, the mixture was extracted with dichloromethane, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford **7a** as a yellow oil. HPLC analysis of a diastereomeric mixture of **7a** for determining the ee value was performed after column purification.

Acknowledgements

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8. $(QN)_2$AQN **2**. TLC ($CHCl_3$+7% MeOH+0.5% NH_4OH) $R_f = 0.23$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, $J = 4.5$ Hz, 2H), 8.27 (dd, $J = 5.8$, 3.3, 2H), 8.03 (d, $J = 9.5$, 2H), 7.79 (dd, $J = 5.5$, 3.5, 2H), 7.41 (d, $J = 4.5$, 2H), 7.38 (dd, $J = 9.0$, 2.5, 2H), 7.31 (br s, 2H), 6.60 (br s, 2H), 5.95 (br s, 2H), 5.74 (m, 2H), 4.95 (d, $J = 17.0$, 2H), 4.90 (d, $J = 10.0$, 2H), 3.92 (s, 6H), 3.25 (br s, 4H), 3.08 (dd, $J = 13.8$, 10.3, 2H), 2.68 (d, $J = 13.5$, 2H), 2.60 (td, $J = 12.0$, 3.5, 2H), 2.47 (br s, 2H), 2.27 (br s, 2H), 2.03 (br s, 2H), 1.95 (br s, 2H), 1.67 (br s, 2H), 1.44 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.74, 158.27, 151.00, 147.60, 144.59, 142.60, 141.97, 134.27, 133.34, 132.06, 126.39, 126.20, 123.39, 122.07, 120.68, 118.75 (br), 114.27, 100.56 (br), 80.08 (br), 60.13, 57.27, 55.84, 43.38, 40.04, 28.03, 27.03, 21.29 (br); HRMS (FAB+) for $C_{54}H_{53}N_4O_6$ (MH^+), calcd 853.3965; found 853.3990. $[\alpha]_D^{25} = +583.5$ ($c = 0.85$, $CHCl_3$).
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10. Element analysis (wt%) of SGS-$(DHQ)_2$AQN **4**. N 0.71, C 13.75, H 2.02, S 3.13.
11. GC analyses of an enantiomeric mixture **6a–f** were performed on a Hewlett Packard 5890A GC System using a HP-1 column (30 m × 0.32 mm × 0.25 μm) under the condition: initial temperature, 50 °C; initial time, 3 min; 15.0 °C/min gradient; final temperature, 280 °C, 17 psi. Retention time (min): **6a**, $t_R = 10.49$; **6b**, $t_R = 10.65$; **6c**, $t_R = 11.47$; **6d**, $t_R = 12.15$; **6e**, $t_R = 8.63$; **6f**, $t_R = 12.22$.
12. HPLC analyses of a diastereomeric mixture **7a–f** were performed on a Waters 600 HPLC System using a Nova-Pak® silica column (15 cm × 3.9 mm × 4 μm) under conditions: **7a**, *n*-hexane/2-propanol = 97/3, 1.0 mL/min, 280 nm, $t_R = 3.58$, $t_R = 4.24$ (major); **7b**, *n*-hexane/2-propanol = 97/3, 1.0 mL/min, 280 nm, $t_R = 3.41$, $t_R = 4.14$ (major); **7c**, *n*-hexane/2-propanol = 97/3, 1.0 mL/min, 280 nm, $t_R = 4.51$, $t_R = 5.60$ (major); **7d**, *n*-hexane/2-propanol = 97/3, 1.0 mL/min, 280 nm, $t_R = 5.58$, $t_R = 6.33$ (major); **7e**, *n*-hexane/2-propanol = 96/4, 0.9 mL/min, 280 nm, $t_R = 8.51$ (major), $t_R = 9.11$; **7f**, *n*-hexane/2-propanol = 97/3, 1.0 mL/min, 280 nm, $t_R = 3.59$, $t_R = 4.22$ (major).