# A Highly Enantioselective Catalytic Desymmetrization of Cyclic Anhydrides with Modified Cinchona Alkaloids

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Enantioselective opening of readily accessible prochiral cyclic anhydrides generates enantiomerically enriched chiral hemiesters containing one or multiple stereogenic centers and two chemically differentiated carbonyl functionalities (eq 1). These optically active
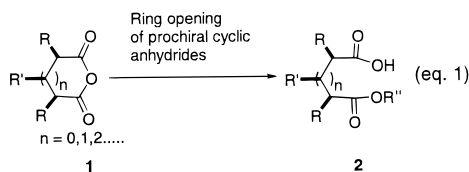

bifunctional hemiesters are versatile chiral building blocks for asymmetric synthesis.[1−9] Due to its considerable potential in organic synthesis, the development of enantioselective desymmetrization of prochiral cyclic anhydrides has drawn much attention.[10−15] Despite considerable effort,[12b,13−15] the development of an effective catalytic desymmetrization of prochiral cyclic anhydrides remains a highly desirable yet elusive goal. In this paper we wish to report a significant advance toward achieving this goal.

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Table 1. Desymmetrization of 2,3-Dimethylsuccinic Anhydride (**3**)
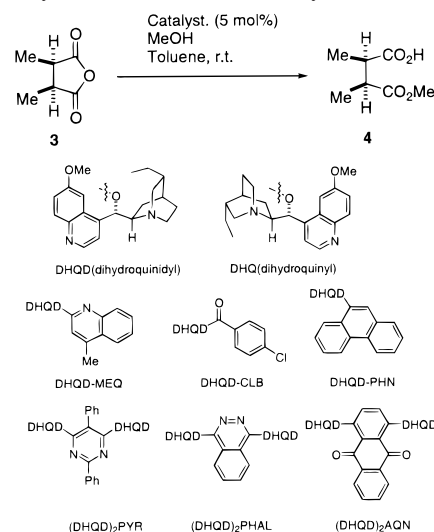
entry	catalyst	ee, %[a]	entry	catalyst	ee, %[a]
1	quinidine	64	5	(DHQD)$_2$PYR	13
2	DHQD−MEQ	31	6	(DHQD)$_2$PHAL	18
3	DHQD−CLB	32	7	(DHQD)$_2$AQN	85
4	DHQD−PHN	81			

[a] ee is determined by chiral GC (see Supporting Information).

Oda and Aitken reported respectively that cinchona alkaloids catalyze asymmetric methanolysis of various mono-, bi-, and tricyclic anhydrides to afford the corresponding chiral hemiesters in good to excellent yields and in moderate ee (up to 76% ee).[13,14,16] In searching for a more effective chiral amine catalyst for the desymmetrization of cyclic anhydrides, we were attracted to a number of readily available ethers of cinchona alkaloids that were developed by Sharpless and co-workers in their landmark investigations of the asymmetric dihydroxylation of simple olefins.[17] The exceptional effectiveness of these amine ligands in the promotion of osmium-catalyzed asymmetric oxidation reactions is attributed to their capability to form an enzyme-like chiral pocket.[18,19] We hypothesized that the same feature in principle could make these chiral amines effective chiral Lewis base catalysts for asymmetric nucleophile−electrophile reactions. With these considerations in mind and using 2,3-dimethylsuccinic anhydride (**3**) as the model substrate, we screened a variety of commercially available aryl ethers and esters of cinchona alkaloids for their ability to catalyze enantioselective alcoholysis of prochiral cyclic anhydrides.

The results of our screening study are presented in Table 1.

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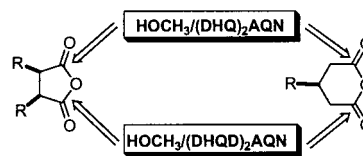
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Table 2. Desymmetrization of Representative Cyclic Anhydrides with Methanolysis Catalyzed by (DHQD)₂AQN and (DHQ)₂AQN[a,b]

Entry	Anhydride	Products[c]	Temp.[b] (°C)	Yield %[b,d]	ee%[b,e]	Catalyst (mol %)[b]
1			-30	99 (90)	95(93)	8 (8)
2			-20	95 (92)	98 (96)	7 (7)
3			-20	97 (95)	97 (93)	5 (5)
4			-30 (-20)	82 (82)	95 (90)	10 (20)
5			-20	88 (85)	96 (94)	15 (15)
6			-20	74 (71)	92 (86)	20 (20)
7			-20	93 (88)	98 (98)	5 (5)
8			-40 (-35)	70 (56)	91 (82)	30 (30)
9			-40 (-35)	72 (62)	90 (83)	30 (30)

a The reaction was performed by treatment of the cyclic anhydride (0.1 mmol) with methanol (10 equivalent) in the presence of (DHQD)₂AQN under the indicated reaction conditions in ether (5.0 mL). *b* The results in parentheses are obtained with (DHQ)₂AQN as the catalyst and the hemiesters of the opposite absolute stereoconfiguration as shown are obtained. *c* For detailed descriptions of determination of absolute configuration of hemiesters as shown, see Supporting Information. *d* Isolated yields. *e* ee is determined by chiral GC, HPLC, and ¹H NMR analysis as described in the Supporting Information.[12]

The structure of the ether or ester substituent of the modified cinchona alkaloids was found to have a pronounced effect on the selectivity of the catalyst. Most significantly, very good enantioselectivity was observed in reactions mediated by two readily available aryl ethers of cinchona alkaloids. Reaction of 1 equiv of anhydride **3** with 10 equiv of methanol in toluene in the presence of 5 mol % of either DHQD−PHN or (DHQD)₂AQN as the catalyst resulted in complete consumption of **3** after 2 h at room temperature to give hemiester **4** in 81% and 85% ee, respectively (entries 4 and 7). While the modified monomeric cinchona alkaloid, DHQD−PHN, is a very effective catalyst, the biscinchona alkaloid, (DHQD)₂AQN, in general afforded higher enantioselectivities, so we selected this catalyst for further optimization. A significant improvement in enantioselectivity (from 85% to 91% ee) was obtained by replacing toluene with ether as the solvent of the reaction at room temperature. Exceptionally high enantioselectivity (98% ee) could be attained by decreasing the temperature of the reaction to −20 °C.

The scope of the reaction was found to be very general, with excellent enantioselectivity obtained in the desymmetrization of monocyclic, bicyclic, and tricyclic prochiral and meso anhydrides (Table 2). Exceptionally high enantioselectivity is generally observed in the ring opening of bicyclic anhydrides to provide monocyclic hemiesters containing two stereogenic centers (entries 1−3). The high enantioselectivity for the ring opening of *cis*-

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Figure 1. Stereochemical projection for desymmetrization of prochiral cyclic anhydrides.

cyclopentane-1,2-dicarboxylic acid anhydride (95% ee, entry 1) is particularly noteworthy when compared with results obtained by the best method employing stoichiometric amounts of chiral promoters such as chiral Ti-TADDOLates (88% ee).[12] Furthermore, the same hemiester is obtained in very low ee (17%) from enzyme-catalyzed hydrolysis of the corresponding diester.[20] Sterically bulky tricyclic anhydrides including those containing heterocyclic rings other than the cyclic anhydride are readily converted into bicyclic chiral hemiesters in high enantioselectivity (entries 4−6). For example, the *endo*-bicyclo[2.2.1]heptene hemiester (entry 4), which is not accessible through enzyme-catalyzed hydrolysis of the corresponding diester,[20] is prepared in excellent ee. Excellent to outstanding enantioselectivities are also obtained with monocyclic anhydrides (entries 7−9) to generate synthetically versatile acyclic chiral building blocks possessing one or two stereogenic centers. As summarized in Table 2, the opposite enantiomer of the hemiester was obtained in similar enantiomeric excess and yield when (DHQ)₂AQN was employed as the catalyst. Furthermore, the stereochemical outcome of the desymmetrization was found to be highly predictable by following the stereoselection rule illustrated in Figure 1.

We have performed a preparative scale reaction to demonstrate the practical features of the catalytic desymmetrization. With 5 mol % (DHQD)₂AQN, *cis*-cyclohexane-1,2-dicarboxylic acid anhydride was transformed on a 5.0 mmol scale to the corresponding hemiester in 97% ee and nearly quantitative yield (97%). When the starting material was consumed, a simple extraction of the reaction mixture with aqueous HCl (1 N) effectively separated the catalyst from the product. Evaporation of the organic solvent provided the desired product in high purity (no detectable impurities by NMR). The catalyst was easily recovered quantitatively by basifying the aqueous phase followed by extraction of the alkaline aqueous solution with EtOAc and removal of the organic solvent. The recovered catalyst, pure as determined by NMR, could be used for another preparative scale reaction to give a new batch of the desired product with consistently high ee and yield.

In summary, we have developed the first nonenzymatic catalytic method for the preparation of chiral hemiesters in synthetically useful optical purity. The reaction provides straightforward access toward either enantiomer of the chiral hemiester of interest with a predictable stereochemical outcome. Importantly, the catalyst can be easily recovered in quantitative yield. These features should render the reaction not only a highly attractive alternative to synthetic routes employing hydrolytic enzymes,[20] but also the most desirable method for the preparation of many optically active chiral hemiesters. The study described herein also provides the first example of the remarkable effectiveness of readily available modified biscinchona alkaloids as chiral Lewis base catalysts for asymmetric nucleophile−electrophile reactions.

Supporting Information Available: Complete experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.