Asymmetric Organocatalysis

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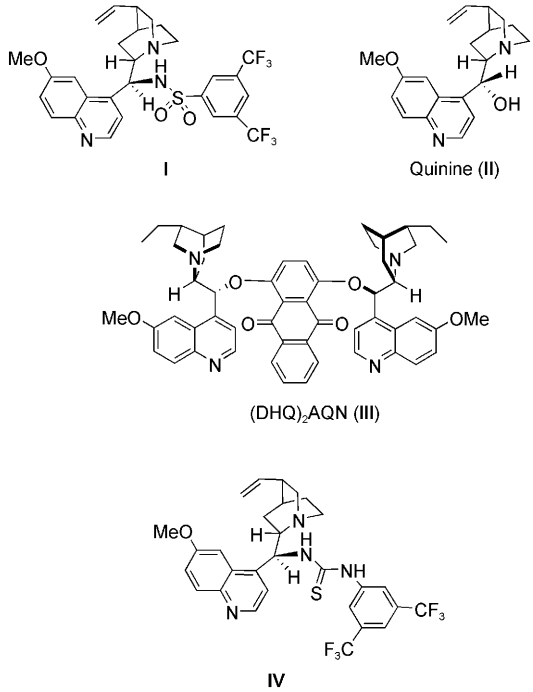
A Highly Reactive and Enantioselective Bifunctional Organocatalyst for the Methanolytic Desymmetrization of Cyclic Anhydrides: Prevention of Catalyst Aggregation**

Sang Ho Oh, Ho Sik Rho, Ji Woong Lee, Je Eun Lee, Sung Hoon Youk, Jik Chin, and Choong Eui Song**

At present, there is much interest in organocatalysts, as they tend to be less toxic and more environmentally friendly than traditional metal-based catalysts.[1] Although much progress has been made,[2] the development of chiral organocatalysts that are as reactive and stereoselective as some of the best transition-metal catalysts remains a considerable challenge. To attain reasonable reaction rates and stereoselectivity with organocatalysts, a large catalyst loading is often required. One way to address this difficulty is to design bifunctional or multifunctional organocatalysts[3] with functional groups that work cooperatively to stabilize the transition state and accelerate the rate of the reaction. It has been shown that urea- or thiourea-based bifunctional organocatalysts are effective in facilitating a variety of useful organic reactions,[4] including the methanolytic desymmetrization of cyclic anhydrides.[5,6] However, we showed recently that urea- and thiourea-based organocatalysts can form hydrogen-bonded aggregates, which results in a strong dependence of reactivity and enantioselectivity on concentration and temperature.[5] X-ray crystal structures of monofunctional and bifunctional (thio)urea derivatives show that they form aggregates through hydrogen bonding between the (thio)urea NH groups and the (thio)urea sulfur or oxygen atom in an intermolecular fashion.[7] A recent NMR spectroscopic study also showed that the thiourea **IV** exists as a dimer, even in solution.[8] Furthermore, thiourea groups tend to degrade under thermal conditions.[9]

Herein we present a thermally robust sulfonamide-based bifunctional organocatalyst **I** (Scheme 1),[10] which shows unprecedented catalytic activity and excellent enantioselectivity in the methanolytic desymmetrization[11] of *meso* cyclic anhydrides. A detailed mechanistic and computational approach to the design of **I** resulted in a catalyst that does not self-aggregate to any appreciable extent. To the best of our knowledge, **I** is the first quinine- and sulfonamide-based bifunctional organocatalyst. The quinuclidine group of **I** may be able to function as a general-base catalyst to activate the nucleophile,[12] and the sulfonamide group[13] may be able to activate the electrophile simultaneously by hydrogen bonding.



Scheme 1. Structures of cinchona-alkaloid-based organocatalysts.

To investigate the catalytic activity and enantioselectivity of the cinchona-alkaloid-based sulfonamide catalyst **I**, we examined the asymmetric methanolysis of *cis*-1,2-cyclohexanedicarboxylic anhydride (**1a**) in Et_2O with various amounts of **I** at ambient temperature. The results are summarized in Table 1, together with the results obtained with other cinchona-alkaloid-based catalysts (quinine (**II**), $(DHQ)_2AQN$ (**III**), and the quinine-based thiourea catalyst **IV**; Scheme 1). The desymmetrization of **1a** with **I** (10 mol%) proceeded surprisingly fast; the reaction was complete within 1 h to

[*] Prof. J. Chin
Department of Chemistry, University of Toronto
80 St. George Street, Toronto, ON M5S 3H6 (Canada)
E-mail: jchin@chem.utoronto.ca
S. H. Oh, J. W. Lee, J. E. Lee, S. H. Youk, Prof. C. E. Song
Department of Chemistry, Sungkyunkwan University
300 Cheoncheon, Jangan, Suwon, Gyeonggi, 440-746 (Korea)
Fax: (+82) 31-290-7075
E-mail: s1673@skku.edu
H. S. Rho
R&D center, AmorePacific Corporation
Yongin 446-729 (Korea)

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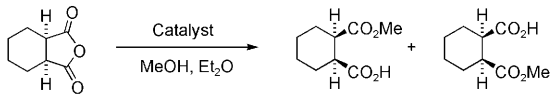
Table 1: Catalytic enantioselective ring opening of the cyclic anhydride **1a** with MeOH.[a]



1a **2a** *ent*-**2a**

Entry	Catalyst	*T* [°C]	*t* [h]	Major isomer	Yield[b] [%]	*ee*[c] [%]
1	**I** (10 mol%)	20	1	**2a**	91	96
2	**I** (5 mol%)	20	2	**2a**	92	95
3	**I** (1 mol%)	20	6	**2a**	92	95
4[d]	**I** (0.5 mol%)	20	20	**2a**	89	93
5[e]	**II** (110 mol%)	−55	60	**2a**	91	87
6[f]	**III** (5 mol%)	−20	48	**2a**	95	93
7[g]	**IV** (10 mol%)	20	10	**2a**	85	96

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.5 mmol), methanol (10 equiv, 5 mmol), and the catalyst in Et_2O (5 mL) at room temperature. [b] Yield of the isolated product after chromatographic purification. [c] Determined by HPLC (see the Supporting Information). [d] MeOH was added with a syringe pump over 20 h to minimize the uncatalyzed reaction. [e] From reference [14a] (with 3 equivalents of MeOH). [f] From reference [14b] (with 10 equivalents of MeOH). [g] From ref. [5] (with 10 equivalents of MeOH).

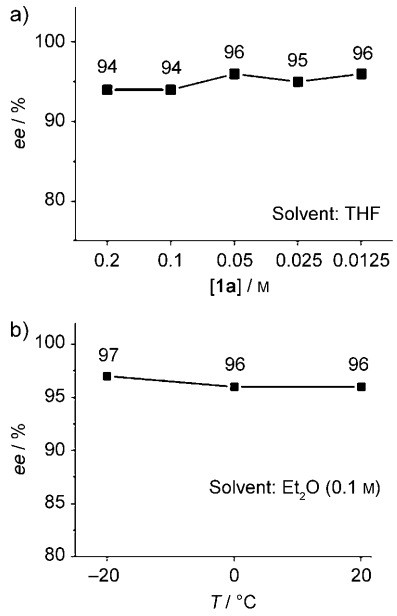
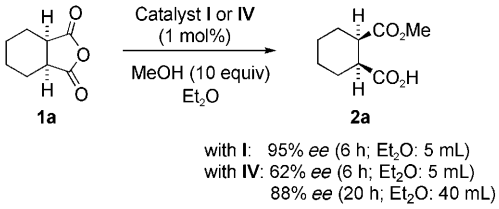


Figure 1. Effect of a) concentration and b) temperature on the enantioselectivity of **I** in the methanolysis of **1a**.



Scheme 2. Methanolytic desymmetrization of **1a** with catalysts **I** and **IV**.

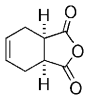
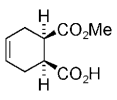
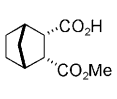
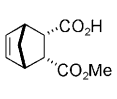
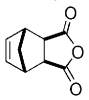
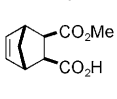
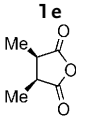
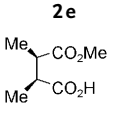
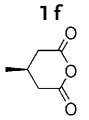
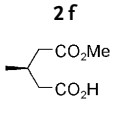
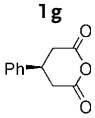
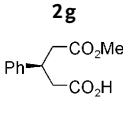
afford the chiral hemiester **2a** with excellent enantioselectivity (96% *ee*; Table 1, entry 1). A lower catalyst loading of 0.5 mol% still resulted in excellent catalytic activity and enantioselectivity (93% *ee*; Table 1, entry 4). Previously reported cinchona-alkaloid-based catalysts require much longer reaction times (Table 1, entries 5–7).[5,14] To the best of our knowledge, the sulfonamide-based catalyst **I** is the most active catalyst reported to date for the alcoholytic desymmetrization of *meso* cyclic anhydrides.

The methanolysis of **1a** with the catalyst **I** was examined under various experimental conditions. We observed the highest enantioselectivities (>94%) with aprotic, hydrogen-bond-accepting solvents, such as Et_2O (96% *ee*), THF (94% *ee*), and dioxane (95% *ee*), whereas the lowest enantioselectivities were observed with protic solvents, such as methanol (44%). (For more experimental results, see Table S-1 in the Supporting Information). More interestingly, the stereoselectivity of the sulfonamide catalyst **I** does not show a significant dependence on concentration (Figure 1A) or the reaction temperature (Figure 1B), in contrast to the thiourea-based catalyst **IV**.[5] On the basis of these experimental results, it is clear that the self-association phenomenon is not as significant in the methanolysis of cyclic anhydrides with the bifunctional sulfonamide catalyst **I** as it is in the process catalyzed by **IV**. The comparative data in Scheme 2 highlight the superior catalytic efficiency of the sulfonamide **I** relative to the thiourea catalyst **IV**. Under the same reaction conditions (**1a** (0.5 mmol), MeOH (5 mmol), Et_2O (5 mL), catalyst (1 mol%)), excellent enantioselectivity was observed with the sulfonamide catalyst **I** (95% *ee*; Table 1, entry 3) and only moderate enantioselectivity (62% *ee*) with the thiourea catalyst **IV**. The stereoselectivity of **IV** could be increased under conditions of high dilution to give the product with up to 88% *ee*, but with a sacrifice in reactivity.

We investigated the generality of the reaction under optimized reaction conditions. The methanolysis of monocyclic (Table 2, entries 5–7), bicyclic (entry 1), and tricyclic anhydrides (entries 2–4) in the presence of **I** proceeded rapidly. All reactions were complete within a few hours to give the corresponding hemiesters in excellent yields with high *ee* values.

We showed recently that DFT computation can be used to explain the observed sense of stereoselectivity for the methanolytic desymmetrization of *meso* anhydrides with the bifunctional thiourea-based organocatalyst **IV**.[5] Herein we show that the computational approach[15] can also be used to explain the observed sense of stereoselectivity for the reaction catalyzed by the bifunctional sulfonamide **I**. In this computational approach, two zwitterionic transition-state analogues for the methanolysis reaction, **3** and *ent*-**3** (Scheme 3a), are considered for their ability to bind to the catalyst **I** by hydrogen bonding. It is well known that the mechanism for many hydrolysis and alcoholysis reactions involves the formation of high-energy tetrahedral intermediates, such as **3** and *ent*-**3**.[16] As the quinuclidine group is expected to act as a general base, it is used to accept a hydrogen bond from the methanol group of the transition-state analogues. The sulfonamide group is expected to

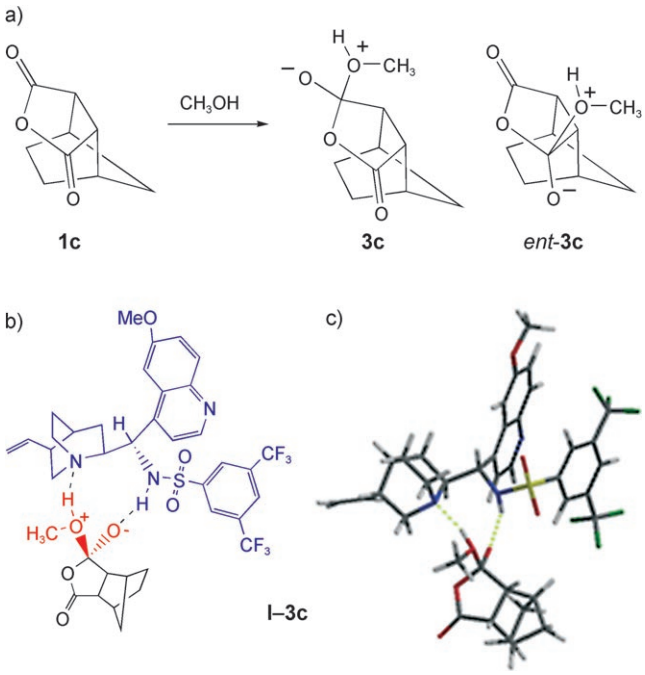
Table 2: Enantioselective methanolysis of the mono-, bi-, and tricyclic *meso* anhydrides **1b–h** with catalyst **I**.[a]

Entry	Anhydride	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	 **1b**	 **2b**	1.5	92	96
2	 **1c**	 **2c**	4.5	90	96
3	 **1d**	 **2d**	5	90	94
4	 **1e**	 **2e**	6	88	95
5[d]	 **1f**	 **2f**	5	95	98
6[e]	 **1g**	 **2g**	4	95	91
7[f]	 **1h**	 **2h**	4	97	94

[a] Reactions were carried out with **1b–e** (0.5 mmol), methanol (10 equiv, 5 mmol), and **I** (5 mol%) in Et_2O (5 mL) at room temperature. [b] Yield of the isolated product after chromatographic purification. [c] Determined by HPLC (see the Supporting Information). [d] The reaction was carried out with **1f** (0.5 mmol), methanol (10 equiv, 5 mmol), and **I** (10 mol%) in methyl *tert*-butyl ether (MTBE; 20 mL) at −20°C. [e] The reaction was carried out with **1g** (0.5 mmol), methanol (10 equiv, 5 mmol), and **I** (10 mol%) in MTBE (5 mL) at −20°C. [f] The reaction was carried out with **1h** (0.5 mmol), methanol (10 equiv, 5 mmol), and **I** (10 mol%) in MTBE (15 mL) at −20°C.

stabilize the oxyanionic group of the transition-state analogues by acting as a hydrogen-bond donor (Scheme 3b). According to the Hammond postulate, high-energy intermediates, such as **I–3** and **I**–*ent*-**3**, should resemble the actual transition states. The agreement between the observed and computed sense of stereoselectivity for the desymmetrization reaction with two different catalysts and several different substrates supports our mechanism-based computational approach (see Tables S-2 and S-3 in the Supporting Information).

Urea or thiourea-based bifunctional organocatalysts, such as **IV**, are of broad interest, as they have been shown to catalyze a wide range of organic reactions. Although they are excellent first-generation catalysts, they suffer from self-aggregation, which results in lower reactivity and a strong



Scheme 3. a) Transition-state analogues **3c** and *ent*-**3c** for the non-catalyzed methanolysis reaction. b) Schematic representation of the catalyst–transition-state-analogue complex **I–3c**, which gives the major product. c) Computed structure of **I–3c**.[15]

dependence of enantioselectivity on concentration and temperature. We have developed a thermally robust sulfonamide-based bifunctional organocatalyst **I**, which shows unprecedented catalytic activity and excellent enantioselectivity in the methanolytic desymmetrization of a variety of *meso* cyclic anhydrides. No appreciable effects of concentration and temperature on reactivity and enantioselectivity were observed with this catalyst. DFT computational studies provided detailed insight into the observed sense of enantioselectivity in the methanolysis of cyclic anhydrides in the presence of **I**. We are currently investigating applications of catalyst **I** to other asymmetric catalytic reactions.

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