Bifunctional organocatalyst for methanolytic desymmetrization of cyclic anhydrides: increasing enantioselectivity by catalyst dilution†

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Highly enantioselective methanolysis of *meso*-cyclic anhydride was achieved with bifunctional organocatalyst containing a quinine–thiourea moiety; unusual concentration, temperature and solvent effects on the enantioselectivity can be explained in terms of a mechanism involving monomer–dimer equilibration of the catalyst.

There has been considerable interest in stereoselective ring opening of *meso*-cyclic anhydrides. Stereoselective alcoholysis of these anhydrides is particularly attractive as the resulting hemiesters are used as versatile intermediates in the construction of many bioactive compounds.[1] Chiral bases derived from cinchona alkaloids[2] or proline[3] have been reported as catalysts for stereoselective alcoholysis of anhydrides. Recently, bifunctional organocatalysts have been developed for simultaneous activation of both electrophilic and nucleophilic components of various organic reactions.[4] Thus we became interested in the possible use of cinchona based thiourea catalysts[5] such as **I** and **II** for alcoholysis of anhydrides. The quinuclidine group of the catalyst may be able to function as a general base catalyst and activate the nucleophile (alcohol) while the thiourea group may be able to simultaneously activate the electrophile (anhydride) by double hydrogen bonding. We report here computational and experimental studies on the reactivity and stereoselectivity of bifunctional organocatalysts **I** and **II** for methanolysis of *meso*-cyclic anhydrides.[6]

To verify the importance of the bifunctionality of the catalyst, asymmetric methanolysis (10 equiv.) of *cis*-1,2-cyclohexane dicarboxylic anhydride **1a** in dioxane with 10 mol% of **I** or **II** was examined at ambient temperature. The results are summarized in Table 1, together with the data obtained with cinchona base catalysts (*i.e.*, quinine (**III**) and hydroquinine (**IV**)). As shown in Table 1, the desymmetrization of **1a** with bifunctional catalysts **I** and **II** proceeded smoothly; these reactions were completed within 10 h, affording the chiral hemiester **2a** with excellent ees (entries 1 and 3). Reducing the amount of catalyst to 5 mol% still resulted in excellent enantioselectivity (95% ee, entry 2). However, the monofunctional alkaloid catalysts **III** and **IV** required longer reaction time and gave poor enantioselectivities (entries 4–5). On the basis of these experimental results, it is clear that the additional thiourea moiety is essential for high reactivity and enantioselectivity.

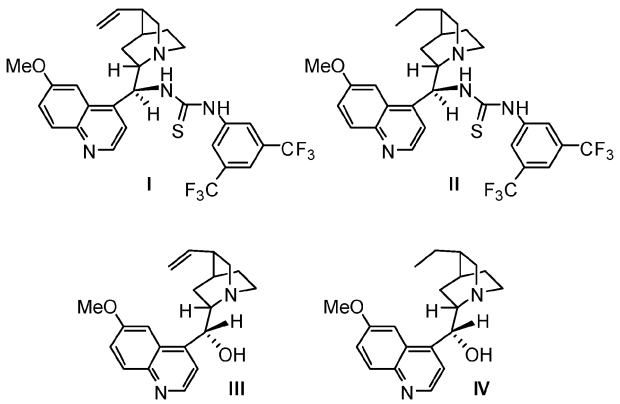
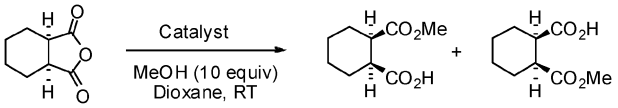


Fig. 1 Structure of organocatalysts.

Methanolysis of **1a** with the most efficient catalyst (**I**) was examined under various experimental conditions. Surprisingly, the enantioselectivity of the desymmetrization reaction increases with dilution of the reaction mixture. Thus when the amount of the reaction solvent (THF) is increased from 2.5 mL to 80 mL while keeping other conditions the same, the ee of the product increases from 82% to 96% (Fig. 2a).

Table 1 Catalytic enantioselective ring opening of **1a** with MeOH[a]



Entry	Catalyst	Time (h)	Main isomer	Yield[b]	ee (%)[c]
1	**I**	10	**2a**	85	97
2[d]	**I**	13	**2a**	82	95
3	**II**	10	**2a**	85	95
4	**III**	20	**2a**	81	55
5	**IV**	20	**2a**	82	53

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.5 mmol), 10 equiv. of MeOH (5 mmol) and catalysts **I–IV** (10 mol%) in dioxane (40 mL) at RT. [b] Isolated yields after chromatographic purification. [c] Determined by HPLC (see ESI†). [d] Reaction was carried out with 5 mol% of catalyst **I**.

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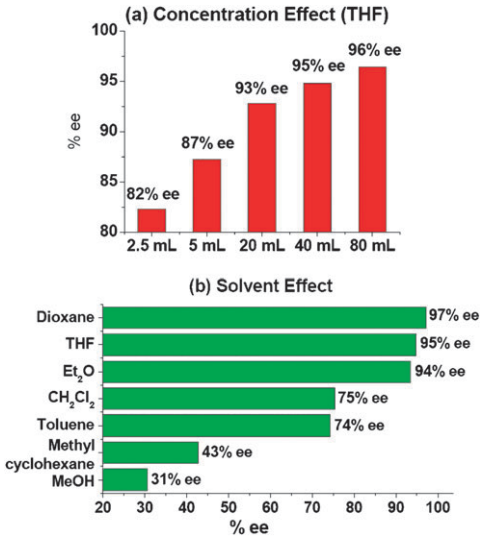


Fig. 2 Investigation of reaction conditions for enantioselective methanolysis of *meso*-cyclic anhydride **1a** in the presence of chiral catalyst **I**.

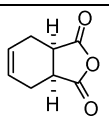
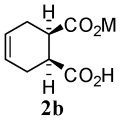
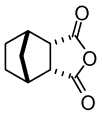
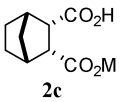
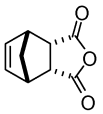
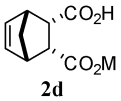
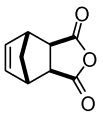
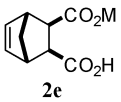
Furthermore, the enantioselectivity generally increases slightly on raising the reaction temperature from −20 °C to 25 °C (77% ee to 82% ee when 2.5 mL THF is used. See ESI†).

In addition to the rather unusual concentration and temperature effects on the enantioselectivity, there is also an interesting solvent effect for the desymmetrization reaction. The highest enantioselectivities (>94%) are obtained with aprotic, H-bond accepting solvents (Fig. 2b) while the lowest enantioselectivity is obtained with protic solvents like methanol (31%).

In light of the above experimental results, we suggest that the cinchona-based thiourea catalyst may exist mainly in the dimeric (or higher order) form by self-association at high concentrations, at low temperature and with non-coordinating solvents. On the other hand, under dilute conditions, at ambient temperature and with coordinating solvents, the catalyst could exist mainly in the monomeric form that is responsible for high enantioselectivity. It is well known that urea groups form hydrogen bonded complexes with themselves and with hydrogen bond accepting solvents like THF.[7] Thus, dimerization or aggregation of the catalyst is expected to be more favorable in toluene than in THF. Polar protic solvents like methanol that can both accept and donate hydrogen bonds are expected to weaken the hydrogen bonding interaction between the catalyst and the substrates. To confirm our hypothesis, ^{1}H NMR dilution experiments of **I** were carried out in d^8-toluene and marked concentration dependencies were observed for the chemical shift of –C(=S)N(H)–Ar proton. The chemical shift of this proton was downfield-shifted from 9.3 to 11.1 ppm upon concentration from 10 mM to 212 mM. This concentration dependency is consistent with the hydrogen-bonded self-association of **I** (See ESI†).[8]

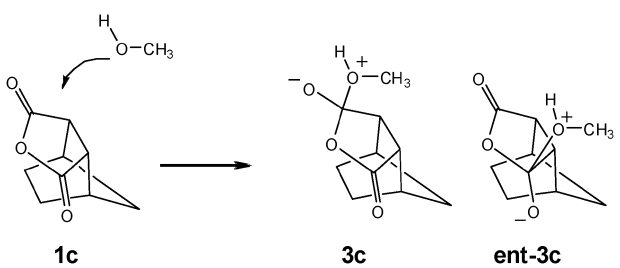
We investigated the substrate scope under optimized reaction conditions. As shown in Table 2, **I** catalyzed methanolysis of bicyclic (entry 1) and tricylcic anhydrides (entries 2–4) proceeds smoothly to give the products in high yields and

Table 2 Enantioselective methanolysis of various *meso*-cyclic anhydrides(**1b–1e**) catalysed by chiral catalyst **1**[ab]

Entry	Anhydride	Product	Time (h)	Yield (%)[c]	ee (%)[d]
1	 **1b**	 **2b**	15 (16)	84 (82)	96 (95)
2	 **1c**	 **2c**	28 (30)	85 (86)	93 (93)
3	 **1d**	 **2d**	25 (27)	81 (82)	92 (92)
4	 **1e**	 **2e**	25 (27)	82 (79)	95 (92)

[a] Reactions were carried out with **1b–1e** (0.5 mmol), 10 equiv. of methanol (5 mmol) and catalyst **I** (10 mol%) in dioxane (40 mL) at RT. [b] The results in parentheses were obtained when THF (40 mL) was used as solvent. [c] Isolated yields after chromatographic purification. [d] Determined by HPLC (see ESI†).

ees. Computation was used to investigate the observed sense of stereoselectivity in the methanolysis of **1c** (Scheme 1). Rationalizing the observed sense of stereoselectivity let alone predicting the extent of the stereoselectivity for catalytic processes can be a challenging problem. This involves not only understanding the mechanism but also the rate and enantio-determining step of the catalytic process. The mechanistic role of the tertiary amine in **I** is expected to be that of a general base rather than a nucleophile. The rate determining step for the methanolysis reaction should be general base catalyzed addition of methanol to the anhydride rather than the ring opening step since carboxylate is a better leaving group than methoxide. One of the two faces of the anhydride (**1c**) is protected by the five membered ring. Thus addition of methanol from the open side should give zwitterionic species **3c** and **ent-3c** (Scheme 1). These high energy tetrahedral intermediates may be considered transition state analogs for the uncatalysed methanolysis reaction. According to the Hammond postulate, transition states for formation of high energy intermediates (like **3c** or **ent-3c**) are expected to resemble the intermediate.



Scheme 1

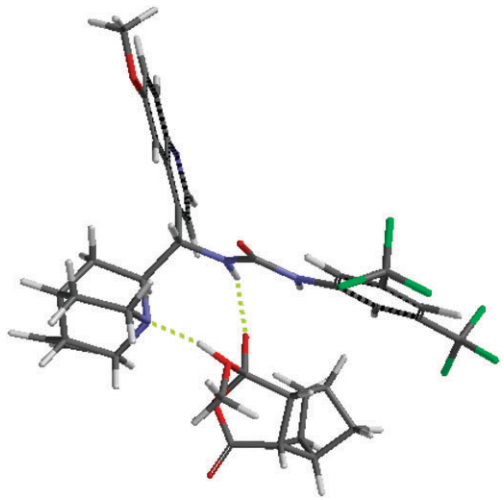


Fig. 3 Computed structure of catalyst(**I**)-**3c** complex.

Intermediate **3c** (or ent-**3c**) has both a strong hydrogen bond acceptor (oxyanion) and a strong hydrogen bond donor (protonated ether). The catalyst (**I**) also has hydrogen bond donating (thiourea) and hydrogen bond accepting (tertiary amine) groups. Thus two complementary hydrogen bonding interactions may be anticipated between the catalyst and the transition state analogs.

Molecular mechanics computation was used for initial docking of **3c** (or **ent-3c**) to **I** and DFT computation (B3LYP at 6-31G* level) was used to obtain the final energies. Computed structures of the catalyst-transition state analog complexes (**I-3c** and **I-ent-3c**) show the anticipated hydrogen bonding interactions between the thiourea and the oxyanion groups and between the tertiary amine and the protonated ether groups (See Fig. 3 for **I-3c**). These complexes may be regarded as transition state analogs for the rate and enantio-determining step of the catalytic process where the quinuclidine group is acting as a general base and the thiourea group is acting as a carbonyl group activator by hydrogen bonding. The **I-3c** complex is about 1.6 kcal mol^{-1} more stable than the **I-ent-3c** complex by computation. This is in reasonable agreement with the experimentally observed enantioselectivity (93% ee) which translates to an energy difference of about 2.0 kcal mol^{-1} for the two transition states. The computed sense of stereoselectivity for methanolysis of each of the anhydrides in Table 2 is in agreement with the experimentally observed sense (see ESI†).

In conclusion, highly enantioselective methanolysis of *meso*-cyclic anhydrides was achieved with organocatalysts **I** and **II**. Unusual concentration, temperature and solvent effects on the enantioselectivity of the desymmetrization reaction can be explained in terms of a mechanism involving monomer–dimer equilibration of the catalyst. Computation provides detailed insight into the observed sense of enantioselectivity for the methanolysis reaction.

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Notes and references

1 (*a*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005, Ch. 13; (*b*) P. I. Dalko, in *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2005, pp. 312–316; (*c*) I. Atodiresei, I. Schiffers and C. Bolm, *Chem. Rev.*, 2007, **107**, 5683.

2 (*a*) J. Hiratake, Y. Yamamoto and J.-I. Oda, *J. Chem. Soc., Chem. Commun.*, 1985, 1717; (*b*) J. Hiratake, M. Inagaki, Y. Yamamoto and J.-I. Oda, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1053; (*c*) R. A. Aitken, J. Gopal and J. Hirst, *J. Chem. Soc., Chem. Commun.*, 1988, 632; (*d*) C. Bolm, A. Gerlach and C. L. Dinter, *Synlett*, 1999, **2**, 195; (*e*) C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, *J. Org. Chem.*, 2000, **65**, 6984; (*f*) C. Bolm, I. Schiffers, I. Atodiresei and C. P. R. Hackenberger, *Tetrahedron: Asymmetry*, 2003, **14**, 3455; (*g*) C. Bolm, I. Atodiresei and I. Schiffers, *Org. Synth.*, 2005, **82**, 120; (*h*) Y. Chen, S.-K. Tian and L. Deng, *J. Am. Chem. Soc.*, 2000, **122**, 9542.

3 Y. Uozumi, K. Yasoshima, T. Miyachi and S. Nagai, *Tetrahedron Lett.*, 2001, **42**, 411.

4 For selected reviews, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520.

5 (*a*) B. Vakulya, S. Varga, A. Csapai and T. Soo, *Org. Lett.*, 2005, **7**, 1967; (*b*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*c*) T. Marcelli, R. N. S. van der Hass, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 929; (*d*) J. Song, Y. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 6048; (*e*) C. M. Bode, A. Ting and S. E. Schaus, *Tetrahedron*, 2006, **62**, 11499; (*f*) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding and Y. Wu, *Synlett*, 2005, **4**, 603.

6 Quite recently, Nagao *et al.* reported enantioselective thiolysis of prochiral cyclic anhydrides utilizing a bifunctional chiral sulfonamide catalyst: T. Honjo, S. Sano, M. Shiro and Y. Nagao, *Angew. Chem., Int. Ed.*, 2005, **44**, 5838.

7 It has been reported that thioureas can exist in oligomeric form by hydrogen-bonded self-association: M. C. Etter, Z. Urbanczyk-Lipkowska, M. Zia-Ebrahimi and T. W. Panunto, *J. Am. Chem. Soc.*, 1990, **112**, 8415.

8 (*a*) D. F. Nogales, J.-S. Ma and D. A. Lightner, *Tetrahedron*, 1993, **49**, 2361; (*b*) C. Ikeda, N. Nagahara, E. Motegi, N. Yoshioka and H. Inoue, *Chem. Commun.*, 1999, 1759.

