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# Synthesis of both Enantiomers of Hemiesters by Enantioselective Methanolysis of Meso Cyclic Anhydrides Catalyzed by α-Amino Acid-Derived Chiral Thioureas†

Rubén Manzano, José M. Andrés, María-Dolores Muruzábal, and Rafael Pedrosa*

*Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Dr. Mergelina s/n, 47011-Valladolid, Spain*

*pedrosa@qo.uva.es*

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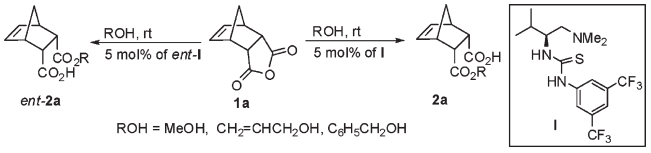


Both ureas and thioureas derived from L- or D-valine act as bifunctional organocatalysts able to induce the enantioselective alcoholysis of mono-, bi-, and tricyclic meso anhydrides. The desymmetrization occurs in near quantitative yields and excellent enantiomeric ratios (up to >99:<1) under low catalyst loading. Both enantiomers of the hemiesters can be directly obtained by changing the configuration of the catalyst.

Enantioselective desymmetrization by alcoholysis of meso anhydrides is one of the most simple methods to access chiral building blocks with either single or multiple stereocenters.[1] This reaction has attracted considerable attention, and different methodologies have been developed to get desymmetrization of meso cyclic dicarboxylic anhydrides.[2] To this end, diastereoselective desymmetrizations with chiral alcohols,[3] and enantioselective transformations with achiral alcohols promoted by cinchona alkaloids in both catalytic[4] or stoichiometric proportions[5] have been described. Homogeneous[6] or heterogeneous supported cinchona derivatives[7] and some other amines[8] have also been used in that transformation. A good level of enantioselectivity is also obtained in enzyme-catalyzed[9] enantioselective desymmetrization of anhydrides. Some of those protocols are of limited application because of the need of high catalyst loading, long reaction times, or low reaction temperature.

Recently, excellent yields and ee values have been obtained in desymmetrization of meso anhydrides by methanolysis[10] or thiolysis[11] by using bifunctional sulfonamides derived from cinchona alkaloids. Interestingly, chiral ureas and thioureas have been extensively employed as organocatalysts,[12] but their use for desymmetrization of meso anhydrides is scarcely reported. Only a few bifunctional thioureas have been recently described as excellent organocatalysts for these desymmetrizations. The number of structures of these catalysts is limited because the chiral environment is provided by quinine, dihydroquinine,[13] or chiral 2,3-diaminopropanol derivatives.[14]

It has been shown that quinidine-derived catalyst is less enantioselective and efficient than the quinine analogue, but quinine and quinidine derivatives do not behave as pseudoenantiomers in this reaction. Consequently, only one enantiomer of the final hemiester was obtained in the reactions catalyzed by thioureas derived from these alkaloids. To circumvent this problem and obtain both enantiomers, a three-step procedure

† Dedicated to Professor José Barluenga on the occasion of his 70th birthday.

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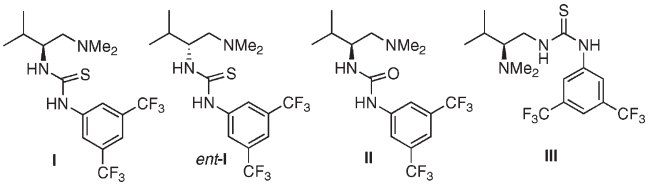


**FIGURE 1.** Bifunctional organocatalysts used for the alcoholysis of meso anhydrides.

**SCHEME 1. Methanolysis of Anhydride 1a in Different Solvents**

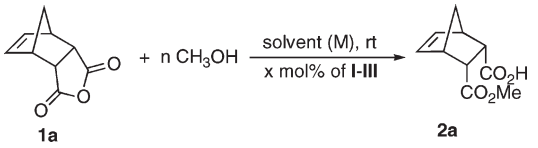


**TABLE 1. Effects of the Solvent in the Enantioselective Methanolysis of 1a Promoted by Thiourea I**[a]

| entry | solvent | time (h) | MeOH equiv (*n*) | conversion[b] (%) | er[c,d] |
|---|---|---|---|---|---|
| 1 | MeOH | 18 | | 100 | 55:45 |
| 2 | DCM | 18 | 10 | 28 | 90:10 |
| 3 | hexane | 18 | 10 | 100 | 71:29 |
| 4 | toluene | 18 | 10 | 67 | 91:9 |
| 5 | EtOAc | 18 | 10 | 35 | 96:4 |
| 6 | $Et_2O$ | 18 | 10 | 82 | 98:2 |
| 7 | THF | 18 | 10 | 29 | 96:4 |
| 8 | MTBE | 18 | 10 | 82 | 98:2 |
| 9 | MTBE | 32 | 10 | 100 | 98:2 |

[a]Reaction performed on a 0.5 mmol of anhydride (0.015M) scale with 10 equiv of methanol and 5 mol % of the catalyst **I** at rt. [b]Conversions were determined by $^1$H NMR of the reaction mixture. [c]Determined by chiral HPLC of the hemiester and of 4-bromophenyl ester derivative (see the Supporting Information). [d]Absolute configuration was determined by comparing the specific rotation of **2a** with that of the literature data.

has been described.[15] This method consists of the alcoholysis of the meso anhydride with allyl alcohol, further esterification of the hemiester with methanol, and selective hydrolysis of the allylic ester.

It was necessary to search for novel structures able to catalyze the enantioselective desymmetrization of meso anhydrides and reach either enantiomer of hemiester in a single step. We have recently described an easy and very modular synthesis[16] of novel chiral ureas and thioureas **I**−**III** (Figure 1) derived from small 1,2-diamines, readily obtained from natural and unnatural amino acids. These compounds act as excellent organocatalysts in nitro-Michael additions, and now we report on their use for the enantioselective desymmetrization of mono-, bi-, and tricyclic meso anhydrides by reaction with alcohols. These compounds could work as bifunctional organocatalysts, activating simultaneously the alcohol and the anhydride by means of hydrogen bonding with the dimethylamino group and the urea or thiourea moiety.

The solvent effects on the process were studied by taking as reaction reference the enantioselective methanolysis of tricyclic anhydride **1a** and valine-derived thiourea **I** (5 mol %) as catalyst (Scheme 1). These reactions were carried out at room temperature, in a 0.015 M solution of anhydride in the corresponding solvent for a fixed reaction time of 18 h, and the results are collected in Table 1.

**TABLE 2. Effects of the Concentration and the Loading and Nature of the Catalyst**[a]

| entry | concn (M) | catalyst (*x* mol %) | time (h) | MeOH equiv (*n*) | conversion[b] (%) | er[c,d] |
|---|---|---|---|---|---|---|
| 1 | 0.150 | **I** (5) | 18 | 10 | 100 | 88:12 |
| 2 | 0.030 | **I** (5) | 18 | 10 | 95 | 96:4 |
| 3 | 0.015 | **I** (5) | 18 | 5 | 66 | 98:2 |
| 4 | 0.005 | **I** (5) | 18 | 10 | 30 | 98:2 |
| 5 | 0.015 | **I** (5) | 18 | 10 | 82 | 98:2 |
| 6 | 0.015 | **I** (10) | 12 | 10 | 100 | 97:3 |
| 7 | 0.015 | **I** (1) | 96 | 10 | 100 | 97:3 |
| 8 | 0.015[e] | **I** (5) | 66 | 10 | 100 | 98:2 |
| 9 | 0.015 | **II** (5) | 18 | 10 | 82 | 96:4 |
| 10 | 0.015 | **III** (5) | 160 | 10 | 42 | 56:44 |

[a]Reaction performed on a 0.5 mmol of anhydride scale with *n* equiv of methanol and *x* mol % of the catalyst in MTBE at rt. [b]Conversions were determined by $^1$H NMR of the reaction mixture. [c]Determined by chiral HPLC of 4-bromophenyl ester derivative (see the Supporting Information). [d]Absolute configuration was determined by comparing the specific rotation of **2a** with that of the literature data. [e]The reaction was carried out at 4 °C.

The best results in terms of enantioselectivity were obtained by using ethereal solvents (entries 6−9 in Table 1) or EtOAc (entry 5), while the reactions in THF or EtOAc were very slow and only 29% and 35% yield of the product was obtained after 18 h (entries 5 and 7 in Table 1). The hemiester was formed in 82% yield when the reactions were carried out in diethyl ether or MTBE as solvents for the same period of time (entries 6 and 8) or quantitatively after 32 h in the last case (entry 9 in Table 1). The reaction was completed in hexane, but with low enantioselectivity (entry 3 in Table 1), whereas the stereoselection was good, albeit the yield was moderate in toluene (entry 4) or very low in DCM (entry 2). As expected, the reaction was faster, but much less selective, when methanol was used as solvent (entry 1), possibly because of the competitive formation of hydrogen bonds between the solvent and the catalyst.[17]

We next examined the influence of some other experimental parameters, such as the concentration, the temperature, the loading and the nature of the catalyst, and the quantity of methanol, and the results are collected in Table 2. Taking as a reference the conditions summarized in entry 5 of Table 2 (i.e., 0.015 M of anhydride in MTBE, 5 mol % of catalyst, and 10 equiv of MeOH), it is clear that the reaction was faster and less enantioselective at higher concentration of meso anhydride (entries 1 and 2 in Table 2). On the contrary, the enantioselection increased but the yield highly decreased in high dilution conditions (entry 4). Excellent enantioselection, albeit moderate yield, was obtained when the amount of methanol was reduced to 5 equiv (entry 3). The reaction proceeded with excellent enantioselectivity by using only 1 mol % of catalyst, although it was necessary to increase the reaction time to 96 h (entry 7), whereas an increase of the catalyst loading to 10 mol % accelerated the reaction rate, which was completed after 12 h (entry 6). Higher reaction time but no deterioration of the enantiomeric excess was observed when the reaction was run at 4 °C (entry 8).

Interestingly, only small differences were observed in the reactions catalyzed by urea **II** and thiourea **I**. In both cases the methanolysis of the anhydride occurred in very good yield, and only a slight decrease in the enantioselection was

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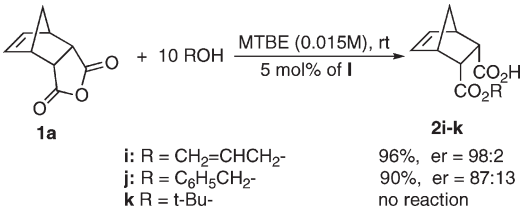
**SCHEME 2. Alcoholysis of 1a with Different Alcohols**



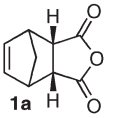
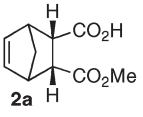
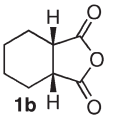
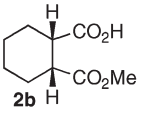
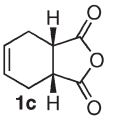
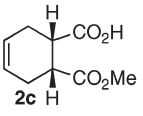

observed when **II** was used as catalyst (compare entries 5 and 9 in Table 2). On the contrary, thiourea **III**, regioisomer of **I**, was a poor catalyst for the desymmetrization of **1a**, leading to the hemiester **2a** in poor yield and enantiomeric ratio after 160 h of reaction (entry 10).

A brief study was performed with different alcohols as nucleophiles in the desymmetrization of **1a** (Scheme 2). Contrary to a previous report,[14] excellent enantioselectivity (98:2) was obtained by using allyl alcohol as alcoholysis reagent, but the enantioselection decreased to 87:13 with benzyl alcohol. The reaction did not take place with a more sterically demanding alcohol such as *tert*-butanol.

The substrate scope under the optimized reaction conditions was studied in the enantioselective methanolysis of mono-, bi-, and tricyclic anhydrides **1a**−**h**, and the results are summarized in Table 3. The methanolysis of all of them occurred quickly in excellent yields and enantioselectivity at low catalyst loading, although some differences were observed depending on the structure of the anhydride. For instance, the reaction was faster for 3-methylglutaric anhydride (**1h**) but the enantiomeric ratio decreased to 91:9 (entry 10 in Table 3). Longer reaction periods were required for the methanolysis of bi- and tricyclic succinic anhydrides, although the hemiesters were obtained with excellent enantioselection. An exception of that general behavior was the tricyclic anhydride **1e**, which led to the hemiester in moderate yield and very modest enantioselection after 120 h of reaction (entry 7). As expected, the reaction time increased when the desymmetrization was carried out at lower temperature, albeit no appreciable modifications in the yield or enantiomeric ratio were observed (compare entries 5 versus 6 or 10 versus 11 in Table 3). An important fact is that our method allows the direct preparation of both enantiomers of a given hemiester starting from the same anhydride and using either enantiomeric thioureas **I** or *ent*-**I** as catalyst (entry 2 in Table 3).

It is noteworthy that the stereochemical outcome of the reaction is independent of the relative stereochemistry of the starting meso anhydride: both, *endo* (**1a**−**e**) and *exo* tricyclic anhydrides (**1f** and **1g**) reacted by the same carbonyl group (compare entries 1, 7, 8, and 9 in Table 3). Catalysts **I** and **II**, with *S* configuration at the diamine stereocenter, promoted the reaction of the *pro-R* carbonyl group of all the anhydrides (**1g** was an exception because of the change in the priority of the substituents), whereas *ent*-**I** activated the enantiotopic *pro-S* counterpart (entry 2 in Table 3). Computational calculations on the mechanism of methanolysis of meso anhydrides catalyzed by thioureas[10a,14,17] have pointed out that the tertiary amino group of the catalyst interacts with methanol, while the thiourea moiety establishes hydrogen bonding with the anhydride. Taking these studies as a basis, the transition state analogue for the methanolysis of meso anhydrides **1a** catalyzed by thiourea **I** is proposed in Figure 2. This model rationalizes the sense of the observed enantioselection.

**TABLE 3. Enantioselective Methanolysis of Mono-, Bi-, and Tricyclic Meso Anhydrides Catalyzed by Thioureas I or *ent*-I[a]**

| Entry | Anhydride | Product | Time (h) | Yield (%)[b] | er[c,d] |
|---|---|---|---|---|---|
| 1 |  |  | 32 | 99 | 98:2 |
| 2 | 1a | 2a | 32[e] | 98 | 3:97 |
| 3 |  |  | 12 | 99 | 98:2 |
| | 1b | 2b | | | |
| 4 |  |  | 12 | 99 | 97:3 |
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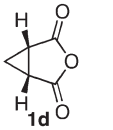
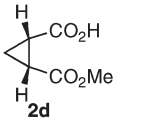
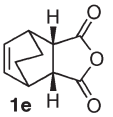
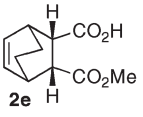
| 5 |  |  | 24 | 96 | 91:9 |
| 6 | 1d | 2d | 60[f] | 94 | 93:7 |
| 7 |  |  | 120 | 55 | 75:25 |
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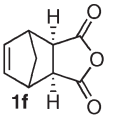
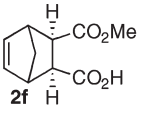
| 8 |  |  | 12 | 99 | 98:2 |
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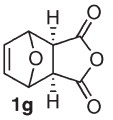
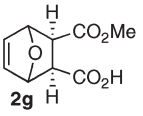
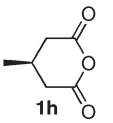
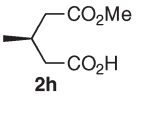
| 9 |  |  | 32 | 95 | >99:<1 |
| | 1g | 2g | | | |
| 10 |  |  | 5 | 95 | 91:9 |
| 11 | 1h | 2h | 14[f] | 95 | 92:8 |

[a]Reaction performed on a 0.5 mmol of anhydride (0.015M) scale with 10 equiv of methanol and 5 mol % of catalyst **I** in MTBE at rt. [b]Numbers refer to isolated yield. [c]Determined by chiral HPLC of the hemiester or of 4-bromophenyl ester derivative (see the Supporting Information). [d]Absolute configurations were determined by comparing the specific rotations of **2** with those of the literature data. [e]The reaction was carried out with *ent*-**I** as catalyst. [f]Reaction at 4 °C.

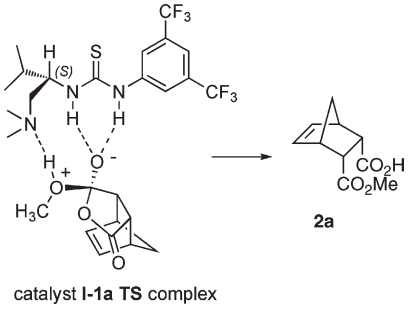



**FIGURE 2.** Schematic proposed transition state analogue for methanolysis of meso anhydrides **1a**.

In summary, we have shown that our thioureas and ureas, which are easily prepared from cheap and accessible natural and unnatural valines, behave as excellent organocatalysts in

the enantioselective alcoholic desymmetrization of cyclic meso anhydrides. Both enantiomers of the hemiesters can be prepared simply by changing the stereochemistry of the catalyst. The catalyst derived from L-valine leads to the 1*R*,2*S*-hemiesters whereas the thiourea derived from unnatural D-valine gives the antipodal desymmetrization product. These results also demonstrate that (thio)ureas bearing only one stereocenter are as enantioselective or more than those previously reported for the desymmetrization of cyclic meso anhydrides.

## Experimental Section

**General Procedure for Enantioselective Alcoholysis of Meso Anhydrides.** Methanol (203 $\mu$L, 5.0 mmol) was added dropwise to a 0.015 M solution of anhydride **1a** (85 mg, 0.5 mmol) and catalyst **I** (10.0 mg, 0.025 mmol) in MTBE (33 mL) at room temperature. The reaction mixture was stirred until the anhydride was consumed (TLC). The solvent was evaporated in vacuo and the residue was dissolved in $CH_2Cl_2$ (5 mL). The solution was extracted with saturated aqueous $Na_2CO_3$ (2 × 5 mL). The combined aqueous layers were acidified with 2 M HCl and extracted with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the pure hemiester **2a** as a white solid (98 mg, 99% yield). $[\alpha]^{25}_D$ −5.8 (*c* 2.3, $CCl_4$, 98:2 er). *ent*-**2a**: $[\alpha]^{25}_D$ +7.6 (*c* 1.9, $CCl_4$, 3:97 er). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.34 (br d, $J$ = 8.8 Hz, 1H), 1.50 (dt, $J$ = 8.8, 1.9 Hz, 1H), 3.17−3.20 (m, 2H); 3.29 (dd, $J$ = 10.2, 3.0 Hz, 1H), 3.34 (dd, $J$ = 10.2, 3.0 Hz, 1H), 3.60 (s, 3H), 6.22 (dd, $J$ = 5.5, 3.1 Hz, 1H), 6.33 (dd, $J$ = 5.6, 3.0 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 45.9 (CH), 46.4 (CH), 47.9 (CH), 48.1 (CH), 48.6 ($CH_2$), 51.4 ($CH_3$), 134.2 (CH), 135.4 (CH), 172.8 (C), 178.6 (C). HRMS calcd for $C_{10}H_{12}O_4 + Na^+$ 219.0633, found 219.0630. The er was determined by chiral HPLC analysis of the hemiester and of its 4-bromophenyl ester derivative (see the Supporting Information).

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**Supporting Information Available:** Experimental procedures, spectral data for all new compounds, copies of $^1$H NMR and $^{13}$C NMR spectra for all compounds, and copies of the HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.