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Enantioselective Alcoholysis of *meso*-Glutaric Anhydrides Catalyzed by *Cinchona*-Based Sulfonamide Catalysts

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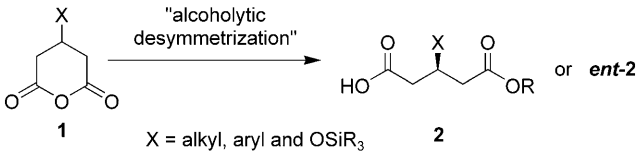
Abstract: The bifunctional *Cinchona*-based sulfonamide catalysts showed the highest levels of enantioselectivity reported to date in the alcoholytic desymmetrization of *meso*-glutaric anhydrides. Density functional theory (DFT) computational studies provide detailed insight into the observed sense of enantioselectivity. Moreover, detailed experimental studies and single crystal X-ray analysis confirmed that these bifunctional organocatalysts **3** do not form H-bonded self-aggregates in both solution and solid state. The synthetic utility of this methodology was also demonstrated in the synthesis of pharmaceutically important γ-amino acids, such as (*S*)-pregabalin. Of the many asymmetric syntheses of enantiomerically pure (*S*)-pregabalin reported to date, our synthesis requires the least number of and the simplest steps.

Keywords: asymmetric organocatalysis; bifunctional catalysis; catalyst self-association; *Cinchona*-based sulfonamide catalysts; desymmetrization; pregabalin

Introduction

There has been considerable interest in the stereoselective ring opening of *meso*-cyclic anhydrides, since the resulting hemiesters are used as versatile intermediates in the construction of many bioactive compounds.[1] Especially, the chiral 3-substituted glutaric acid monoesters **2** produced by the alcoholysis of *meso*-glutaric anhydrides **1** (Scheme 1) are used as key intermediates for the synthesis of a variety of industrially interesting pharmaceutical compounds, e.g., the 3-alkyl/arylglutaric acid monoesters **2** are used as key intermediates for the synthesis of γ-aminobutyric acid (GABA) analogues[2] (e.g., baclofen·HCl[2d,e] and pregabalin[2f]), selective serotonin receptor antagonists (e.g., paroxetin·HCl),[3] and potent P2X7 receptor antagonists[4] while silyl-protected 3-hydroxyglutaric hemiesters **2** can also be used as chiral synthons[5] in the preparation of HMG-CoA reductase inhibitors called "statins" which have inhibitory activity that allows them to suppress the biosynthesis of cholesterol (Figure 1). Much effort has, therefore, been made to develop efficient enzymatic and non-enzymatic catalytic systems for the alcoholysis of the *meso*-glutaric anhydrides **1**.[1] However, the results obtained with *meso*-glutaric anhydrides as substrates are still unsatisfactory for practical use, whereas alcoholysis with other types of *meso*-anhydrides, such as bi-, tricyclic and succinic anhydrides, usually gives excellent results. All of the approaches involving the use of *meso*-glutaric anhydrides as substrates suffer from either a narrow substrate scope and/or very long reaction time and unsatisfactory enantioselectivity.



Scheme 1.

Cooperative catalysis,[6] the simultaneous binding and activation of reacting partners resulting in both pre-organization of the substrates and stabilization of the transition state structures, is a fundamental principle in enzymatic catalysis. Therefore, recently, much effort has focused on the development of efficient bifunctional organocatalysts that effectively orient sub-

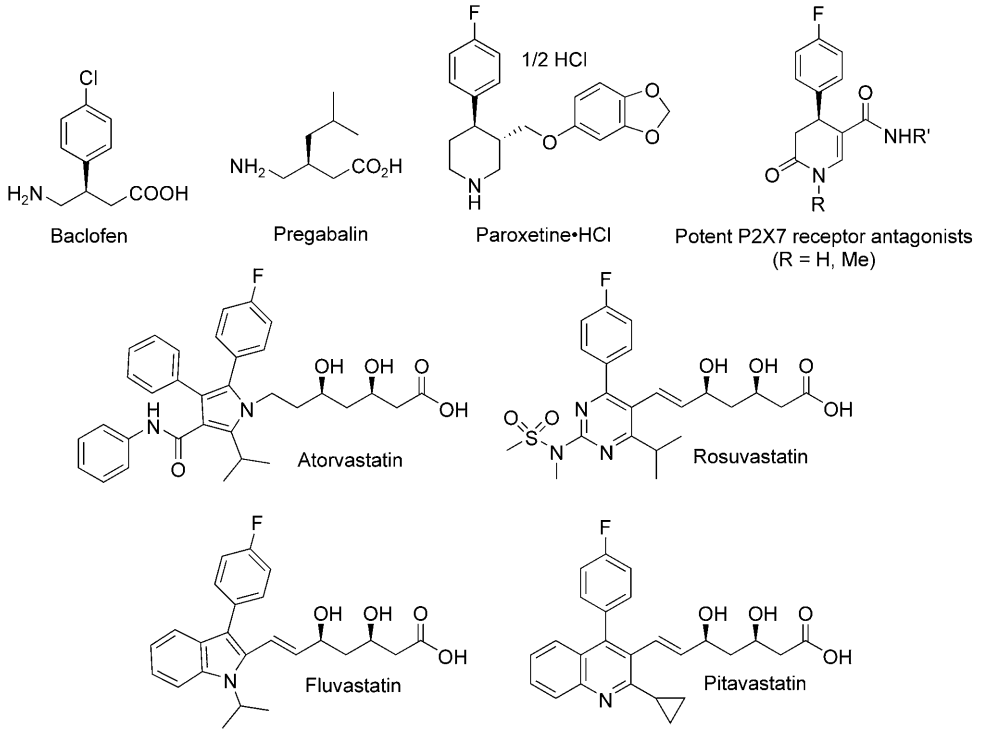


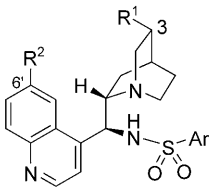
Figure 1. Examples of some pharmaceuticals which can be prepared from chiral 3-substituted glutaric acid monoesters.

strates in an enzyme-like manner.[7] Recently, we[8] and another research group[9] employed bifunctional *Cinchona*-based thioureas as organic chiral catalysts for the alcoholytic desymmetrization of *meso*-glutaric anhydrides. However, their enantioselectivity was still unsatisfactory for the synthetic use. Moreover, it is known that the bifunctional organocatalysts such as thiourea-based catalysts can form H-bonded self-aggregates in both solid[10] and solution states,[11] due to their bifunctional H-donating and accepting nature, resulting in the strong dependency of the reactivity and enantioselectivity on the concentration and temperature. Due to the self-association phenomena of this type of catalysts, the enantioselectivity generally decreases with increasing concentration or decreasing temperature,[8] which can hamper their practical use. We[12] have recently reported that *Cinchona*-based sulfonamide **3a** is highly enantioselective for the methanolytic desymmetrization of *meso*-bicyclic and tricyclic anhydrides[13] and, moreover, the self-association phenomenon is not as significant in the methanolysis of *meso*-anhydrides with the bifunctional sulfonamide catalyst **3a** as it is in the process catalyzed by **4** or **5**. Thus, we decided to optimize the catalyst structure and reaction conditions for alcoholysis of *meso*-glutaric anhydrides using the sulfonamide-type catalysts **3**.

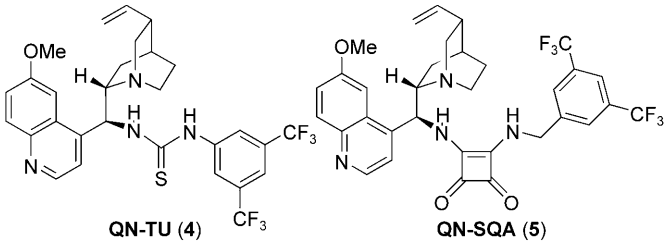
We have now completed an extensive screening of a variety of chiral sulfonamide catalysts and report here that bifunctional *Cinchona*-based sulfonamide organocatalysts **3** show the highest levels of enantioselectivity reported to date in the alcoholytic desymmetrization of *meso*-glutaric anhydrides. DFT computational studies provide detailed insight into the observed sense of enantioselectivity. Moreover, detailed experimental studies and single crystal X-ray analysis confirm that these bifunctional organocatalysts **3** do not form H-bonded self-aggregates even in solid state.

Results and Discussion

To optimize the catalyst structure, we synthesized a variety of sulfonamide catalysts **3a–k** (Figure 2) simply by the reaction of the 9-amino-(9-deoxy)-epi-*Cinchona* alkaloid[14] with an arenesulfonyl chloride (Ar) in the presence of triethylamine,[12] and examined their catalytic efficiency for the asymmetric methanolysis of 3-OTBDPS glutaric anhydride (**1a**) as a model substrate in presence of the catalyst (10 mol%) and MeOH (10 equiv.) in MTBE[15] at room temperature. The results are depicted in Table 1, with the data obtained using the thiourea and squaramide catalyst, **4** and **5**, respectively. As shown in Table 1, regardless of the substituent at the C-3 and C-6′ positions of alkaloids **3a–d**, the methanolysis of **1a** proceeded fast, with the reaction being completed within 3–4 h affording the corresponding hemiester **2a** in nearly quantitative yields and excellent *ee* values (92–93% *ee*) (Table 1, entries 1–4). The aryl substituents of the sulfonamide moiety of **3a** and **3e–3k** were



QN-SA (**3a**): R^1 = vinyl, R^2 = OMe, Ar= 3,5-$(CF_3)_2C_6H_3$
HQN-SA (**3b**): R^1 = ethyl, R^2 = OMe, Ar= 3,5-$(CF_3)_2C_6H_3$
CD-SA (**3c**): R^1 = vinyl, R^2 = H, Ar= 3,5-$(CF_3)_2C_6H_3$
HCD-SA (**3d**): R^1 = ethyl, R^2 = H, Ar= 3,5-$(CF_3)_2C_6H_3$
QN-Ph-SA (**3e**): R^1 = vinyl, R^2 = OMe, Ar= Ph
QN-1-Np-SA (**3f**): R^1 = vinyl, R^2 = OMe, Ar= 1-Np
QN-2-Np-SA (**3g**): R^1 = vinyl, R^2 = OMe, Ar= 2-Np
QN-*o*-Tolyl-SA (**3h**): R^1 = vinyl, R^2 = OMe, Ar= *o*-tolyl
QN-*m*-Tolyl-SA (**3i**): R^1 = vinyl, R^2 = OMe, Ar= *m*-tolyl
QN-*p*-Tolyl-SA (**3j**): R^1 = vinyl, R^2 = OMe, Ar= *p*-tolyl
QN-*m*-Xylyl-SA (**3k**): R^1 = vinyl, R^2 = OMe, Ar= *m*-xylyl

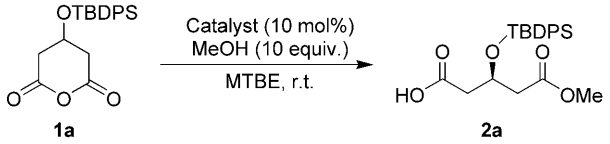


QN-TU (**4**) **QN-SQA** (**5**)

Figure 2. Structures of different *Cinchona* alkaloid organocatalysts examined in this study (QN = quinine; HQN = hydroquinine; CD = cinchonidine; HCD = hydrocinchonidine).

also relatively insensitive to the enantioselectivity (Table 1, entries 1 and 5–11). Even simple phenyl-substituted sulfonamide catalyst **3e** also exhibited comparable reactivity and enantioselectivity with **3a** (entry 5). Only *ortho*-substituted aryl substituents gave slightly lower enantioselectivity (Table 1, entries 6 and 8). Moreover, the enantioselectivities of sulfonamide catalysts **3** are higher compared with those of other type of catalysts **4** and **5** (Table 1, entries 12 and 13). Much more interestingly, however, the enantioselectivity of sulfonamide catalyst **3a** increases slightly on decreasing the reaction temperature from 20 °C to −20 °C (92% *ee* to 96% *ee*) (Figure 3). In contrast to these results, using other type of catalysts such as **QN-TU** (**4**)[14,16] and **QN-SQA** (**5**),[17] the enantioselectivity decreases significantly on decreasing the reaction temperature (e.g., 80% *ee* at −20 °C using **5**) (Figure 3 and Supporting Information, Table S1). On the basis of these experimental results, it is clear that the self-association phenomenon is not as significant in the methanolysis of glutaric anhydrides with the bifunctional sulfonamide catalyst **3a** as it is in the process catalyzed by **4** or **5**. Furthermore, the single crystal X-ray structure of **QN-SA** (**3a**) revealed that this type of catalysts

Table 1. Catalytic enantioselective ring opening of **1a** with MeOH in the presence of different catalysts.[a]



1a **2a**

Entry	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	QN-SA (**3a**)	4	97	92
2	HQN-SA (**3b**)	4	96	92
3	CD-SA (**3c**)	4	94	93
4	HCD-SA (**3d**)	3	94	92
5	QN-Ph-SA (**3e**)	8	96	91
6	QN-1-Np-SA (**3f**)	12	92	90
7	QN-2-Np-SA (**3g**)	6	91	91
8	QN-*o*-Tolyl-SA (**3h**)	8	96	90
9	QN-*m*-Tolyl-SA (**3i**)	8	99	91
10	QN-*p*-Tolyl-SA (**3j**)	8	89	91
11	QN-*m*-Xylyl-SA (**3k**)	7	87	91
12	QN-TU (**4**)	6	95	89
13	QN-SQA (**5**)	5	96	85

[a] Reactions were carried out with **1a** (0.5 mmol), 10 equiv. of MeOH and catalysts (10 mol%), in MTBE (10 mL) at room temperature.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC (see Supporting Information).

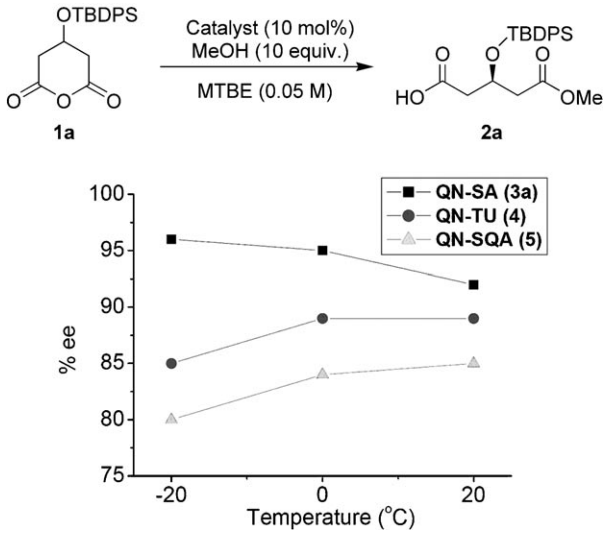


Figure 3. Effect of reaction temperature on the enantioselectivity in the methanolytic desymmetrization of **1a**.

cannot form H-bonded self-aggregates even in the solid state.[18] As shown in Figure 4, there is no intermolecular H-bond interaction between the sulfonamide NH group and the sulfone group (SO_2). In contrast to these results, X-ray crystal structures of bifunctional thiourea derivatives[10] and cinchonine-

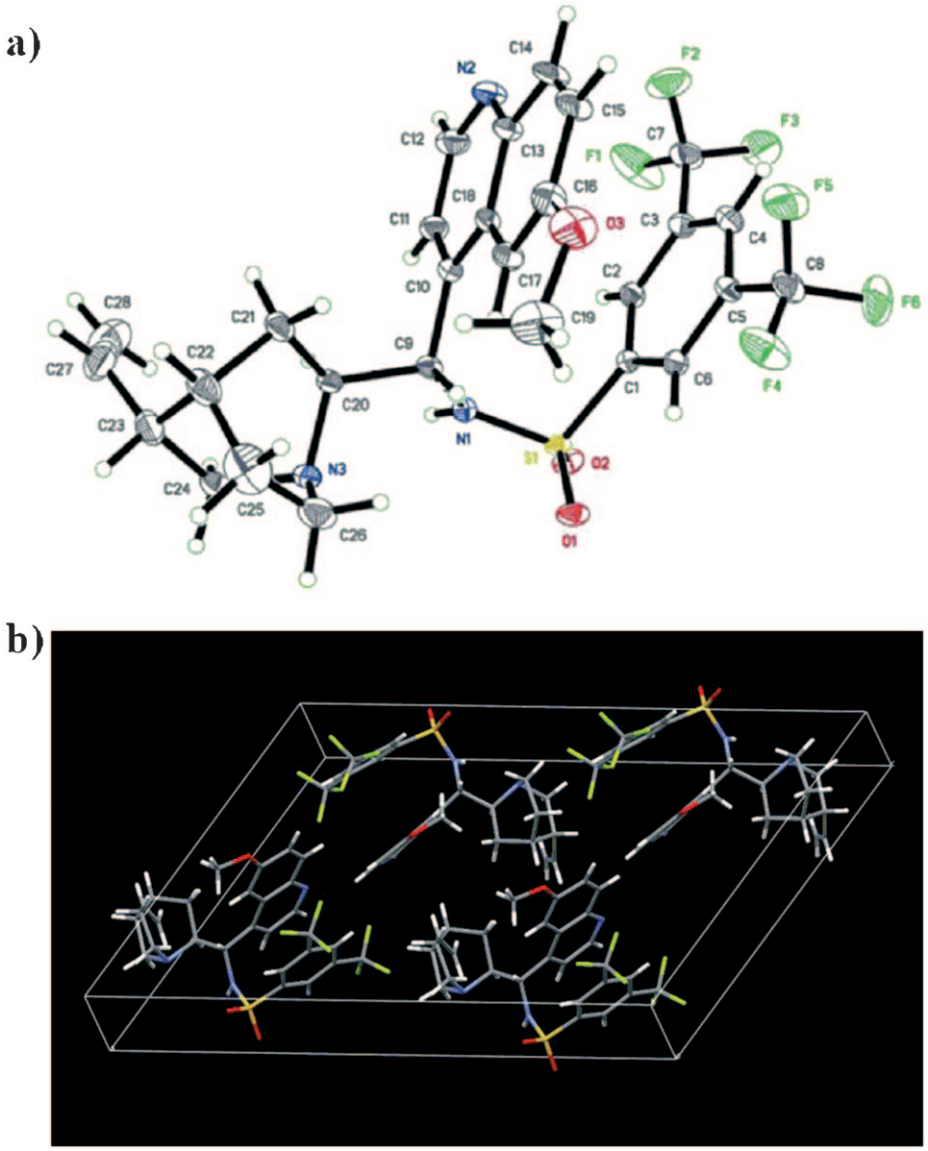
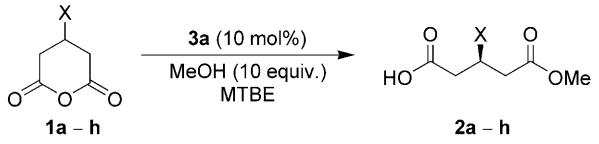


Figure 4. a) ORTEP diagram of QN-SA (**3a**). **b**) Schematic drawing of the crystal packing in **3a**.

based squaramide[19] show that they form aggregates through intermolecular bifurcate H-bonding of NH groups of the thiourea or squaramide moiety to the thiourea sulfur or the squaramide oxygen atoms, respectively.

Having established that the sulfonamides **3** act as highly enantioselective and self-association-free catalysts, we undertook to explore the scope of the substrate under the optimized reaction conditions. As shown in Table 2, a variety of *meso*-glutaric anhydrides **1a–h**, regardless of their substitution patterns at the 3-position of **1** (3-alkyl, 3-aryl and 3-silyl-protected hydroxy groups), were smoothly converted into the corresponding hemiester products **2a–h** with excellent enantioselectivity (90–96% *ee*). The strength and scope of our methodology is further demonstrated in the alcoholysis of the anhydride **1a** with different alcohols (Table 3). Almost independently of the steric demand of the alcohol, high enantioselectivity was also obtained in all cases (entries 2–5). The exceptionally high *ee* value (98% *ee*) obtained with benzyl alcohol is particularly noteworthy.[20] To the best of our knowledge, this level of reactivity and enantioselectivity is unprecedented in the alcoholytic desymmetrization of the *meso*-glutaric anhydrides **1a**. Even enzymatic processes gave much lower enantioselectivities (e.g., ~14% *ee*[21d] in the case of **2f**).[21] The observed sense of stereoselectivity is in agreement with our computation-based transition state models for the desymmetrization of the *meso*-anhydrides.[8,12a] According to the computational results (B3LYP at 6-31G* level), the transition structure (Figure 5 b and Figure 5 c) leading to the major enantiomer **2c** is favored relative to that leading to the

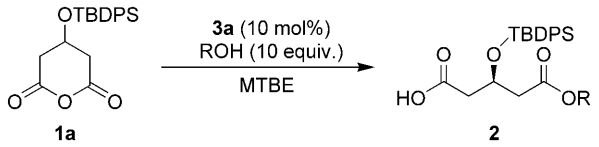
Table 2. Enantioselective methanolysis of various glutaric anhydrides **1a**–**h**.[a]



Entry	Substrate (X=)	*T* [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a** (OTBDPS)	0	11	96	95
2	**1a** (OTBDPS)	−20	28	87	96
3	**1b** (OTBDMS)	0	11	97	92
4	**1b** (OTBDMS)	−20	28	98	93
5	**1c** (Me)	−20	12	95	90
6	**1d** (*i*-Bu)[23]	0	6	95	91
7	**1d** (*i*-Bu)[23]	−20	14	96	92
8	**1e** (4-Ph)	0	6	88	92
9	**1e** (4-Ph)	−20	17	91	95
10	**1f** (4-F-C_6H_4)	20	1	92	91
11	**1f** (4-F-C_6H_4)	−20	19	81	93
12	**1g** (4-Cl-C_6H_4)	20	1	92	92
13	**1g** (4-Cl-C_6H_4)	−20	18	87	92
14	**1h** (3,4-Cl-C_6H_3)	−20	19	91	92

[a] Reactions were carried out with **1a**–**h** (0.5 mmol), 10 equiv. of MeOH and catalysts **3a** (10 mol%) in MTBE (10 mL) at 20 °C, 0 °C or −20 °C.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC (see Supporting Information).

Table 3. Asymmetric alcoholysis of cyclic anhydride **1a** with different alcohols.[a]



Entry	ROH	Main isomer	*T* [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	MeOH	**2a**	20	4	96	92
2	Allyl-OH	**2i**	20	20	92	91
3	BnOH	**2j**	20	8	90	96
4	BnOH	**2j**	0	15	98	97
5	BnOH	**2j**	−20	4.5 d	93	98

[a] Reactions were carried out with **1a** (0.5 mmol), 10 equiv. of ROH and catalysts **3a** (10 mol%) in MTBE (10 mL) at 20 °C, 0 °C or −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC (see Supporting Information).

minor enantiomer *ent*-**2c** by 4.3 kcal/mol (see Supporting Information, Table S3 for further details).[22]

To illustrate the synthetic utility of our methodology, a short and practical synthesis of (*S*)-3-amino-methyl-5-methylhexanoic acid (pregabalin), an anticonvulsant drug used for neuropathic pain treatment, was developed starting from the hemiester (*R*)-**7j** *via* the Curtius rearrangement (Scheme 2). The sequential addition of diphenylphosphoryl azide (DPPA) and NEt_3 to the hemiester (*R*)-**7j** (90% *ee*), followed by benzyl alcohol furnished the benzyl carbamate **8j** in 88% yield. The benzyl carbamate **8j** was then deprotected by hydrogenation with Pd/C to provide (*S*)-pregabalin in 100% yield with 90% *ee*. One recrystallization from aqueous *i*-PrOH afforded enantiomerically pure (*S*)-pregabalin. In fact, of the many asymmetric syntheses[2f,24] of enantiomerically pure (*S*)-pregabalin reported to date, our synthesis requires the least number of steps as well as the simplest steps.

Conclusions

In summary, we describe the alcoholytic desymmetrization of a variety of *meso*-glutaric anhydrides with unprecedentedly high enantioselectivity using self-association-free *Cinchona*-based sulfonamide catalysts. Alcohols other than methanol were effective nucleophiles in the desymmetrization reaction and also provided excellent enantiomeric excesses. In addition, the synthetic utility of this methodology was demonstrated in the synthesis of pharmaceutically important γ-amino acids such as (*S*)-pregabalin. Of the many asymmetric syntheses of enantiomerically pure (*S*)-pregabalin reported to date, our synthesis requires the least number of steps as well as the simplest steps.

Experimental Section

General Procedure for the Preparation of the Sulfonamide Catalysts 3a–k

To a solution of 9-amino(9-deoxy)-epi-*Cinchona* alkaloid[14] (3.54 g, 10.94 mmol) and arenesulfonyl chloride (10.94 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (1.52 mL, 10.94 mmol) at room temperature. The mixture was stirred at room temperature under an argon atmosphere overnight. After the addition of 50 mL of water, the reaction mixture was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$, filtrated, and then the filtrate was evaporated under vacuum. The residue was purified by column chromatography on a silica gel column with EtOAc-MeOH (20:1) to afford the sulfonamide catalyst **3** (usually above than 85% yield) as a white amorphous solid. Characterization data for **3a**–**k**, see Supporting Information.

General Procedure for Alcoholytic Desymmetrization of *meso*-Glutaric Anhydrides

Alcohol (5 mmol) was added to a stirred solution of the anhydrides (0.5 mmol) and catalyst (10 mol%) in MTBE (10 mL, 0.05 M) at the temperatures indicated in Table 1,

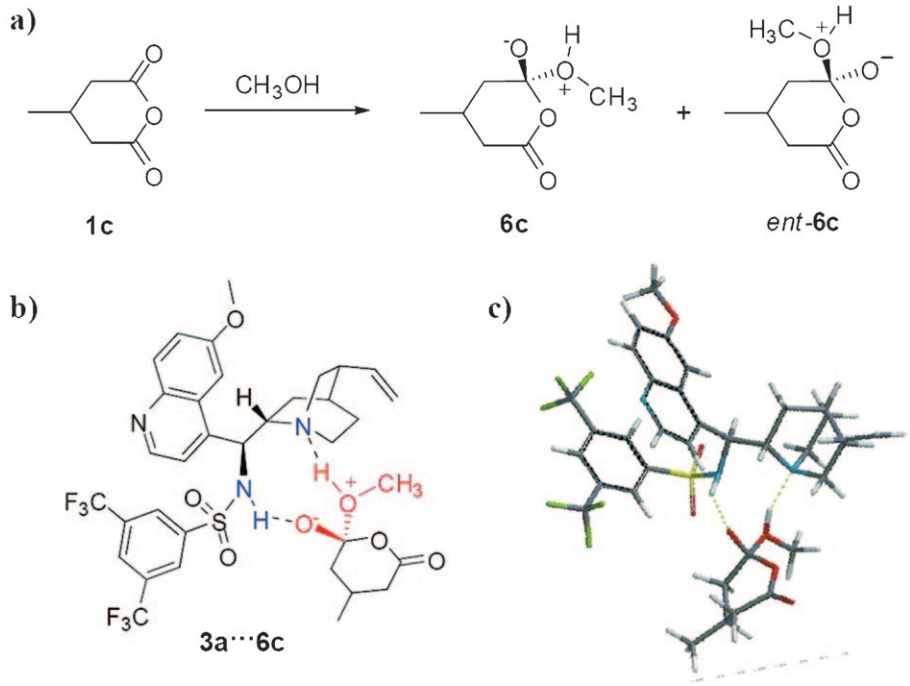
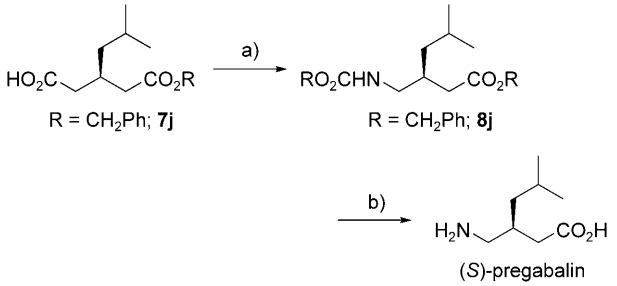


Figure 5. a) Transition-state analogues **6c** and *ent*-**6c** for the non-catalyzed methanolysis reaction. **b**) Schematic representation of the catalyst-transition-state-analogue complex **3a**···**6c**, which gives the major product. **c**) Computed structure of **3a**···**6c**



Scheme 2. Synthesis of (*S*)-pregabalin. *Reagents and conditions:* (a) DPPA, NEt_3, ROH, 88%; (b) R = $PhCH_2$, Pd/C, H_2, 15 h, > 99%.

Table 2, Table 3 and Figure 3. The reaction was stirred until the starting material was consumed as indicated by TLC analysis. Purification by column chromatography (EtOAc: hexane = 1:4–1:10) gave the hemiester product. The enantiomeric excess (*ee*) was determined by HPLC analysis of a diastereomeric mixture of the corresponding amide ester prepared from the hemiester according to the literature procedure[25] (see Supporting Information).

Acknowledgements

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