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CRITICAL REVIEW

Recent advances in enantioselective organocatalyzed anhydride desymmetrization and its application to the synthesis of valuable enantiopure compounds

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Recent years have witnessed increasing interest in the field of asymmetric organocatalysis. In particular, efforts in this field have been devoted to the use of small organic molecules in asymmetric processes based on enantiotopic face discrimination and, only recently, efforts have also been devoted to asymmetric organocatalytic desymmetrization of prochiral substrates—a process based on enantiotopic group discrimination. This *critical review* documents the advances in the use of organocatalysis for the enantioselective desymmetrization of achiral and *meso* anhydrides and its application to the synthesis of valuable compounds as reported until 2010 (134 references).

1. Introduction

Desymmetrization reactions of achiral or *meso* compounds constitute a powerful and useful methodology that allows enantiomerically enriched or enantiomerically pure compounds to be obtained.[1] In this synthetic approach enantiotopic functional group differentiation results in breaking of the molecular symmetry and chiral compounds are obtained with different levels of enantioselectivity. Originally most of these transformations were mediated by enzymes[2–4] but very rapidly the use of chiral metal complexes bearing enantiomerically pure ancillary ligands gained an important role in desymmetrization processes.[5–9] In this field asymmetric organocatalysis had been underexplored and only recently has it emerged as a valuable complement and/or alternative to existing well-established enzymatic and metal-based methodologies used in desymmetrization reactions.

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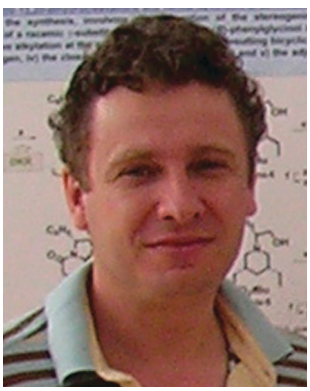
María D. Díaz de Villegas

María Dolores Díaz de Villegas graduated in Chemistry from the University of Zaragoza in 1981. In 1985 she received her PhD (PhD Thesis Award) from the University of Zaragoza, Spain. After a period (1986–1988) as Assistant Professor at the University of Zaragoza, in 1989 she joined the Spanish Council for Scientific Research (CSIC) as Tenured Scientist. In 2001, she was promoted to a position of CSIC Research Scientist. Her research interests focus on the development of new methodologies in stereoselective synthesis and enantioselective organocatalysis and its applications.



José A. Gálvez

José Antonio Gálvez was born in La Paul (Huesca), Spain in 1963. He studied chemistry at the University of Zaragoza where he obtained his PhD degree in 1990. After a two-year period at the University of La Rioja as Assistant Professor, he returned to the University of Zaragoza in 1993 where he was appointed Senior Lecturer in 1997. His current research interests focus on the asymmetric synthesis of biologically active compounds (alkaloids with a piperidine or pyrrolidine skeleton, azasugars, amino alcohols and amino acids) and the design of new organocatalysts and axially chiral ligands and their applications in asymmetric catalysis.

Asymmetric organocatalysis offers several advantages over homogeneous organometallic catalysis and enzymatic catalysis. Organocatalysts are usually inexpensive organic molecules that are readily available and are also non-toxic and bench-stable. Reactions can usually be performed without the exclusion of water under aerobic conditions and without the risk of metal contamination. As organocatalysis can be considered an environmentally benign synthetic protocol, in recent years there has been increasing interest in asymmetric organocatalyzed variants of other well-established synthetic methodologies for the asymmetric synthesis of chiral compounds. This interest has resulted in several book reviews,[10–13] special issues,[14–17] and review articles[18–28] concerning the most recent breakthroughs in this field as they continue to emerge in the literature.

Pablo Etayo

Pablo Etayo was born in Pamplona, Spain, in 1980. He graduated in Chemistry with Honors from the University of Zaragoza in 2003. In 2008 he received his PhD (PhD Thesis Award) from the same University. Then he spent around one year as a postdoctoral fellow of the University Institute of Research in Homogeneous Catalysis (IUCH). In October 2009, he was appointed to his present position at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain, where he joined Prof. A. Vidal's group as a postdoctoral researcher. His research interests focus on both metal-mediated and organocatalyzed enantioselective processes and their applications to the asymmetric synthesis of industrially and biologically relevant enantiomerically pure compounds.

As part of the trend outlined above, in recent years asymmetric organocatalytic versions of several desymmetrization reactions have appeared in the literature. These reactions include asymmetric desymmetrization of cyclic achiral and *meso* anhydrides by direct enantioselective nucleophilic ring-opening (Fig. 1)—a strategy with an undoubted synthetic value. A wide range of highly functionalized enantiopure building blocks for the asymmetric synthesis of innumerable and valuable chiral nonracemic targets can be easily obtained by using this efficient synthetic approach.[29–33]

This review is focused on developed methods for the enantioselective organocatalyzed desymmetrization of cyclic anhydrides. Firstly we discuss the development of synthetic strategies using organocatalysts with different structural features—cinchona alkaloid derivatives, amines and amino alcohols, bifunctional urea and thiourea derivatives, bifunctional sulfonamide or phosphoramide derivatives—and finally we bring into focus the application of these new synthetic strategies in the preparation of valuable enantiomerically pure compounds.

2. Cinchona alkaloid derivatives

Cinchona alkaloids have found extensive application as catalysts[34–37] in enantioselective synthesis due to their interesting structure and architecture, which harbours a unique combination of polar and lipophilic groups.[38,39] Cinchona alkaloids and their derivatives are the main chiral Lewis bases used as organocatalysts in the desymmetrization of cyclic anhydrides by nucleophilic ring-opening. The first approaches were reported by Oda and Aitken's groups in the late 1980s. Oda and co-workers[40,41] described the nucleophilic ring-opening of several cyclic anhydrides by methanol in the presence of 10 mol% of a cinchona alkaloid. The naturally occurring bases quinine (**1**), cinchonidine (**2**), quinidine (**3**) and cinchonine (**4**) (Fig. 2) showed high catalytic activity in the methanolysis of six-membered cyclic anhydrides, providing the corresponding

Ramón Badorrey

Ramón Badorrey received his PhD in 2000 from the University of Zaragoza. In 1998 he took a predoctoral position at the Centro de Investigación y Desarrollo de Barcelona under the supervision of Prof. G. Valencia. In 2003 he undertook a postdoctoral stay in the Stratingh Institute at the University of Groningen under the supervision of Prof. B. L. Feringa and in 2004 he joined the Dipartimento di Chimica G. Ciamician at the Bologna University under the supervision of Prof. A. Umani-Ronchi. He is a Senior Lecturer at the University of Zaragoza and investigates the development of enantiopure nitrogen compounds that are easily tuneable for their evaluation as chiral organocatalysts in different enantioselective processes.

Pilar López-Ram-de-Víu

Pilar López-Ram-de-Viu, BS in chemistry at the University of Zaragoza (1987), received her PhD (PhD Thesis Award) from the same University in 1991. Between 1992–1993 she took a postdoctoral position at the Conservatoire National des Arts et Métiers (CNAM) of Paris under the supervision of Dr L. Oliveros. After this period she joined the Department of Organic Chemistry at the University of Zaragoza, where she carried out teaching and research activities, first as Assistant Professor and later as Senior Lecturer. Her research interests focus on the synthesis of optically active compounds with potential biological activity in an enantiomerically pure form, combining the use of different stereoselective synthetic strategies and resolution techniques.

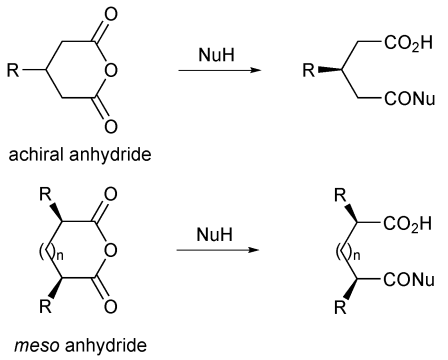


Fig. 1 Asymmetric desymmetrization of cyclic achiral and *meso* anhydrides by direct enantioselective nucleophilic ring-opening.

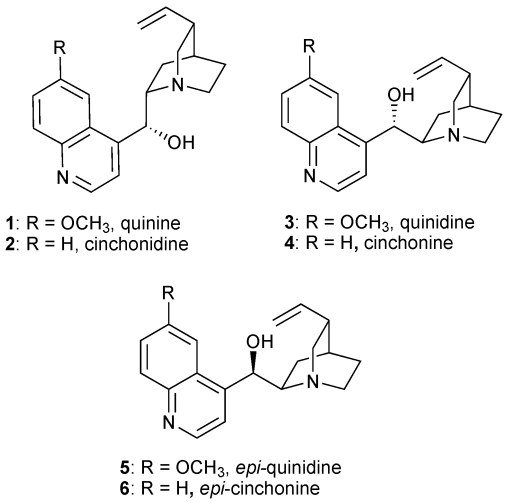


Fig. 2 Structures of cinchona alkaloids **1–6** used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.

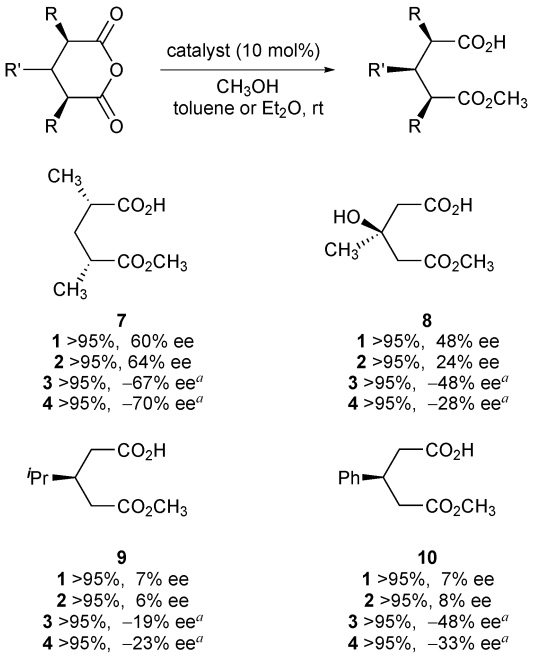
hemiester in very high yield (>95%) but only moderate enantiomeric excess (Scheme 1).

The stereochemical course of the reaction depends on the configuration at C8 and C9 of the alkaloid. Quinidine and cinchonine, bases with an 8*R*,9*S* configuration, gave hemiesters of opposite absolute configuration to that provided by quinine and cinchonidine, bases with an 8*S*,9*R* configuration, with comparable levels of enantioselectivity.

epi-Quinidine (**5**) and *epi*-cinchonine (**6**) (Fig. 2) were more selective than quinidine and cinchonine for the enantioselective methanolysis of five-membered cyclic anhydrides (Scheme 2), usually providing the hemiesters of opposite configuration and with a better enantioselectivity. Investigation of the reaction mechanism led to the conclusion that the quinuclidine ring is responsible for the base catalysis.

Polymer-supported quinine derivatives were found to catalyze the methanolysis of *cis*-2,4-dimethylglutaric anhydride, although the enantioselectivity of the desymmetrization reaction decreased to some extent.[42]

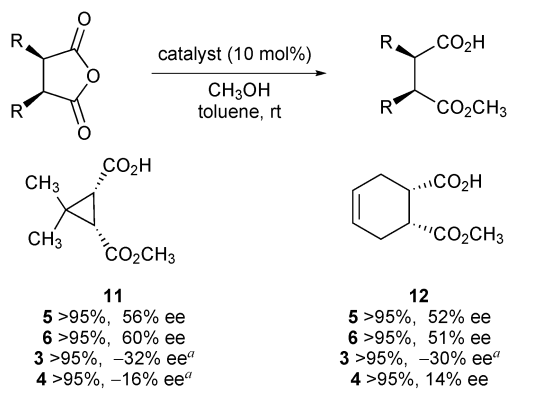
Aitken and co-workers[43,44] studied the cinchona alkaloid-catalyzed methanolysis of cyclic anhydrides (Scheme 3). The use of 10 mol% of organocatalyst gave quite low enantioselectivities, with quinine being the most effective catalyst for



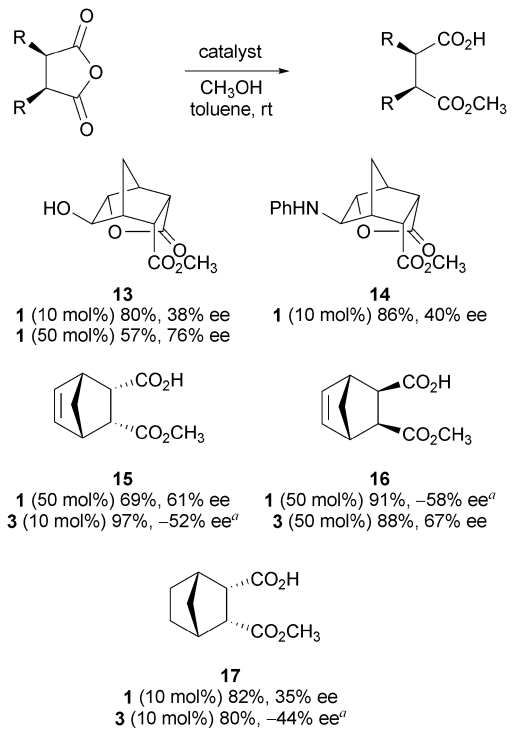
Scheme 1 Oda's cinchona alkaloid-catalyzed opening of six-membered cyclic anhydrides with methanol.

the preparation of compound **13**. In this case enantioselectivities improved significantly on increasing the catalyst loading. The authors suggested a possible explanation for this fact based on the observation that the monohydrochloride salt of quinine catalyzed the non-enantioselective methanolysis of the anhydride. Variations in other parameters, such as reaction temperature, alcohol used as a nucleophile or polarity of the solvent, did not increase the enantioselectivity of the reaction.

In the late 1990s, Bolm and co-workers[45,46] developed a new protocol for the desymmetrization of a wide variety of cyclic anhydrides in which a stoichiometric amount of a cinchona alkaloid was used to promote the enantioselective methanolysis. Lowering the temperature and solvent polarity had a beneficial effect on the enantioselectivity and when



Scheme 2 Oda's cinchona alkaloid-catalyzed opening of five-membered cyclic anhydrides with methanol.



Scheme 3 Aitken's cinchona alkaloid-catalyzed opening of cyclic anhydrides with methanol.

desymmetrization was carried out at −55 °C in a 1 : 1 toluene/CCl_4 mixture the resulting methyl hemiester products were obtained in moderate to very good yields and with high to excellent enantiomeric excesses (Scheme 4).

The stereochemical outcome of the reaction was uniform (Fig. 3), meaning that quinine- and quinidine-mediated ring-opening of cyclic anhydrides generated methyl hemiesters of

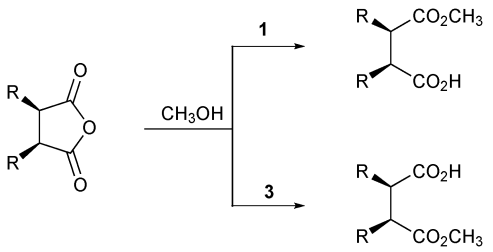
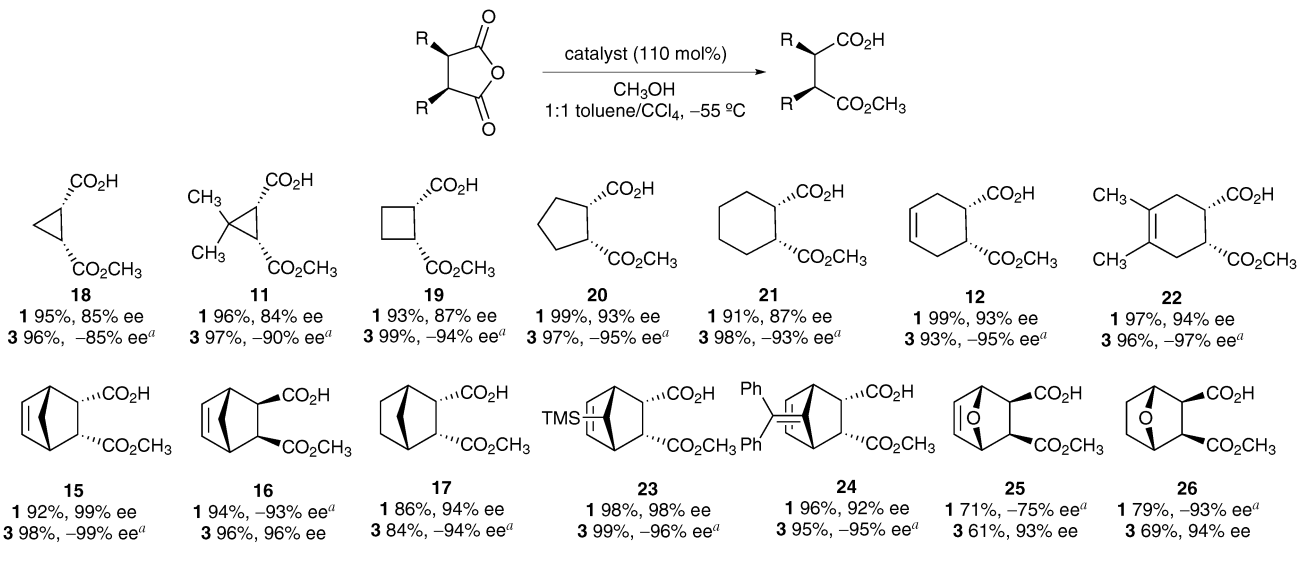


Fig. 3 Stereochemical outcome of Bolm's cinchona alkaloid-promoted desymmetrization of cyclic anhydrides.

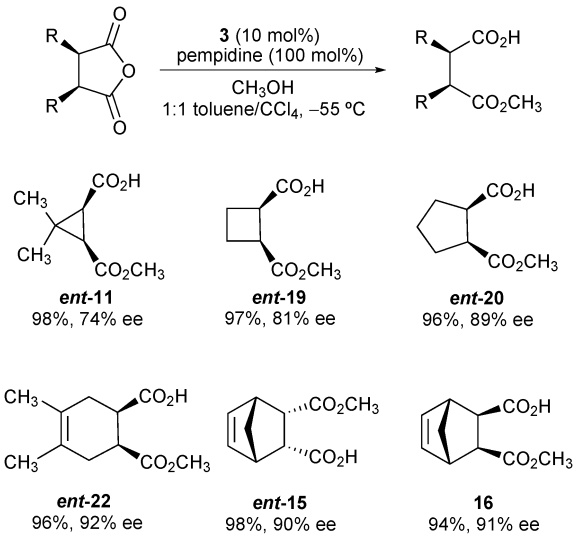
opposite absolute configuration in most cases with comparable enantiomeric excess. Sterically hindered five-membered cyclic anhydrides did not react at all and methanolysis of the only tested monocyclic anhydride—*cis*-2,3-dimethylsuccinic anhydride—led to an inseparable mixture of epimeric compounds.

The use of a catalytic amount of the cinchona alkaloid (10 mol%) led to a dramatic decrease in the enantioselectivity of the reaction. This finding has been attributed to the catalytic activity of the protonated cinchona alkaloid in the desymmetrization process promoting the formation of the racemic methyl hemiester.

The presence of a stoichiometric amount of a second achiral base capable of regenerating the unprotonated cinchona alkaloid minimized the erosion in enantioselectivity caused by this undesired competitive reaction, thus allowing the use of a catalytic amount of the alkaloid.[46] Among the achiral bases screened as additives, 1,2,2,6,6-pentamethylpiperidine (pempidine) was the most effective and allowed methyl hemiester ***ent*-15** to be obtained in 98% yield and 90% ee by enantioselective methanolysis of the corresponding anhydride using 10 mol% of quinidine and one equivalent of 1,2,2,6,6-pentamethylpiperidine. This behaviour is not general and in some cases significantly worse results are obtained with the catalytic protocol (Scheme 5).



Scheme 4 Bolm's cinchona alkaloid-catalyzed opening of cyclic anhydrides with methanol.



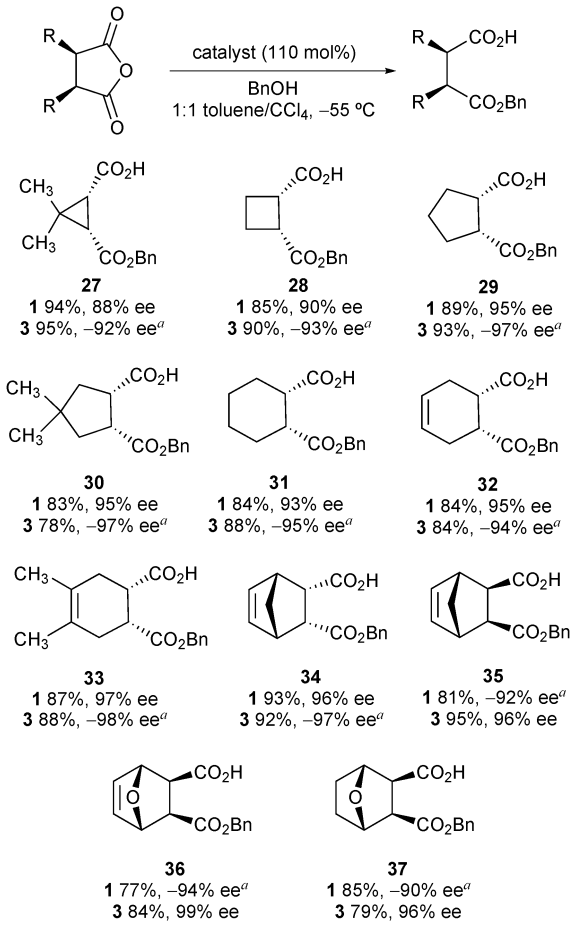
Scheme 5 Bolm's cinchona alkaloid-catalyzed opening of cyclic anhydrides with methanol using a catalytic amount of quinidine.

Carloni *et al.*[47] studied the quinidine-mediated methanolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride using 10 mol% of quinidine at −25 °C. It was observed that the enantioselectivity of the reaction depended on the solvent polarity, with THF found to be the best one in terms of asymmetric induction. Under these conditions the presence of ethyldiisopropylamine (DIPEA) as the additive increased the reaction rate but was detrimental for the enantiopurity of the resulting product. Increasing the reaction time from 16 h to 36 h gave the hemiester ***ent*-12** in 96% yield and 85% ee. Under the same reaction conditions quinine afforded the hemiester **12** with a lower enantioselectivity (65% ee). Anchoring of quinidine to siliceous supports through a thioether linker led to immobilized catalysts, which have been used as heterogeneous and reusable organocatalysts in this reaction to obtain the hemiester ***ent*-12** with enantioselectivities ranging from 52% to 65% ee.

Other alcohols have also been examined as nucleophiles[48] in the stoichiometric cinchona alkaloid-mediated anhydride ring-opening. Among the screened nucleophiles, benzyl alcohol was the most appealing in terms of yield, enantioselectivity and subsequent workup. Cinchona alkaloid-mediated opening with benzyl alcohol is applicable to a variety of structurally different substrates (Scheme 6) and the resulting benzyl hemiester products, once appropriately derivatized, can easily be cleaved by simple catalytic hydrogenation, which broadens their applicability for further synthetic transformations.

Organocatalysts can be recovered in nearly quantitative yields without loss of enantioselectivity, and the use of toxic CCl_4 can be avoided for most starting anhydrides with only a slight decrease in the enantioselectivity of the desymmetrization reaction.[46,48] The stoichiometric approach is then suitable for multigram scale reactions, which led to the corresponding hemiesters in even greater yields and selectivities.[49]

Recently these reactions have been performed at room temperature in the absence of solvent using the ball milling technique.[50,51] Among the various alcohols tested as nucleophiles, *p*-methyl- and *o*-bromobenzyl alcohol gave the best



Scheme 6 Bolm's cinchona alkaloid-catalyzed opening of cyclic anhydrides with benzyl alcohol.

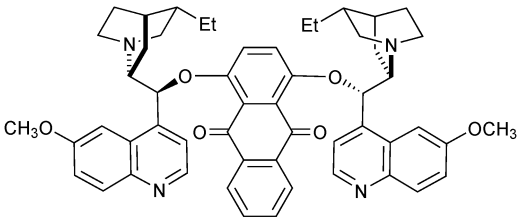
results in the quinidine-mediated enantioselective desymmetrization of cyclic anhydrides. The reaction can be performed with only equimolar amounts of anhydride and alcohol, which simplifies workup, without loss of reaction yield or enantioselectivity. This technique has been used to obtain hemiesters in high yields but with moderate enantioselectivities (up to 64% ee).

In the early 1990s Deng *et al.* used commercially available modified cinchona alkaloids $(DHQD)_2AQN$ (**38**) and $(DHQ)_2AQN$ (**39**) (Fig. 4) as organocatalysts in the desymmetrization of cyclic anhydrides.[52,53]

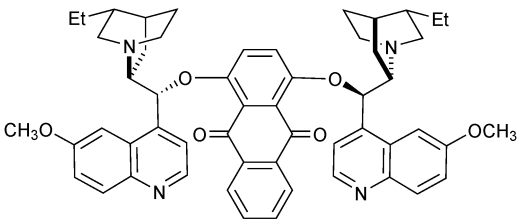
Methanolysis of succinic and glutaric anhydrides in the presence of catalytic amounts of the organocatalyst (5–30 mol%) provided the corresponding hemiesters with very good to excellent enantioselectivities on using diethyl ether as solvent at low temperature (−20 °C to −40 °C) (Scheme 7).[52,53]

The stereochemical outcome of the reaction was highly predictable[53] (Fig. 5) and opposite enantiomers were obtained when **38** and **39** were used to promote the methanolysis of cyclic anhydrides.

Other modified mono- and bis-cinchona alkaloids have been obtained and efficiently used in the desymmetrization of cyclic anhydrides.[54–59] Among them, quinidine-derived organocatalysts **42–48** (bearing alkyl-*O*-acetate side chains), **49–50**

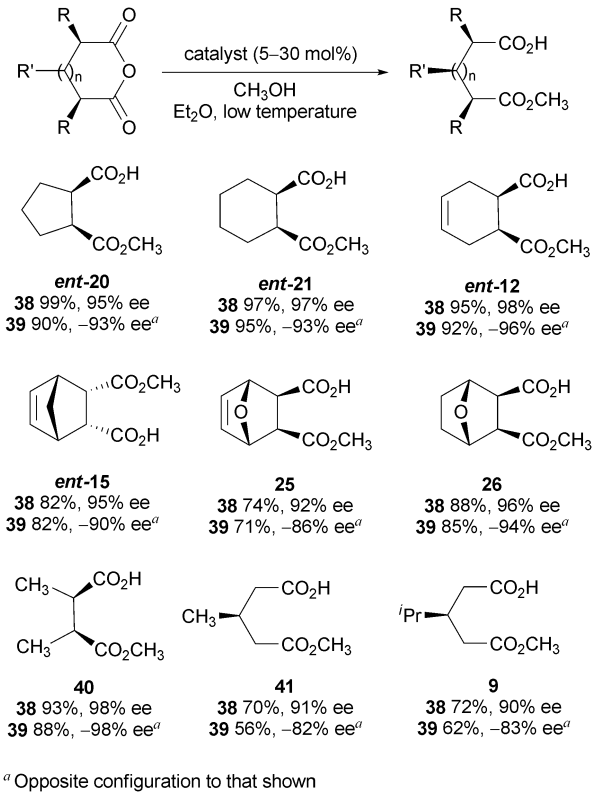


38: $(DHQD)_2AQN$



39: $(DHQ)_2AQN$

Fig. 4 Structures of modified cinchona alkaloids **38** and **39** used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.



[a] Opposite configuration to that shown

Scheme 7 Deng's modified cinchona alkaloid-catalyzed opening of cyclic anhydrides with methanol.

(bearing propargyl side chains) and dihydroquinidine derived organocatalyst **51** (bearing a 9-phenanthrenyl side chain) (Fig. 6) showed activities and enantioselectivities comparable or superior to **38** when the methanolysis of *cis*-2,3-dimethylsuccinic anhydride was performed in the presence of 20 mol% of organocatalyst in diethyl ether at room temperature with a 0.02 M substrate concentration.[56–58]

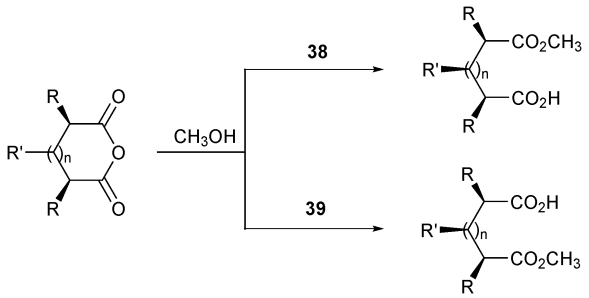
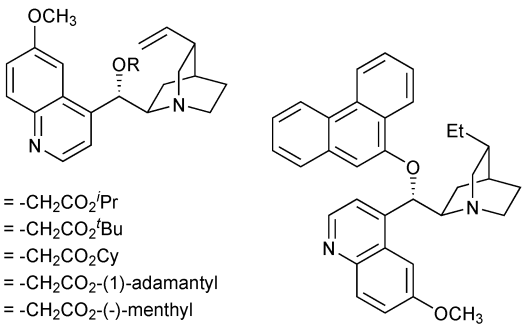


Fig. 5 Stereochemical outcome of Deng's modified cinchona alkaloid-promoted desymmetrization of cyclic anhydrides.

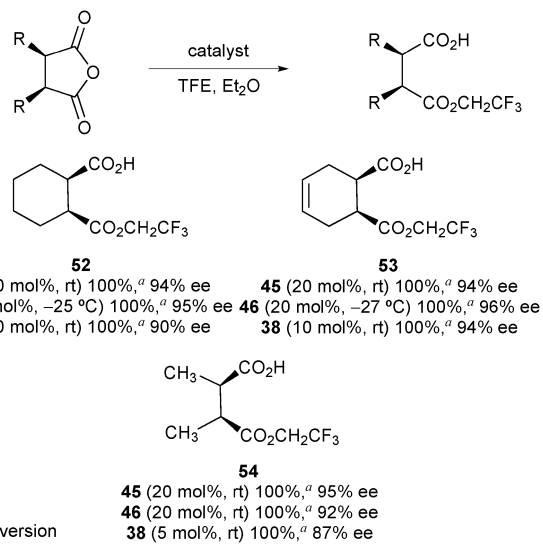


42: R = $-CH_2CO_2{}^iPr$
43: R = $-CH_2CO_2{}^tBu$
44: R = $-CH_2CO_2Cy$
45: R = $-CH_2CO_2$-(1)-adamantyl
46: R = $-CH_2CO_2$-(-)-menthyl
47: R = $-CH_2CO_2$-isobornyl
48: R = $-CH_2CO_2$-*endo*-(1*R*)-(+)-fenchyl
49: R = $-CH_2C{\equiv}CH$
50: R = $-CH_2C{\equiv}C$-(4-CH_3O-C_6H_4)

51

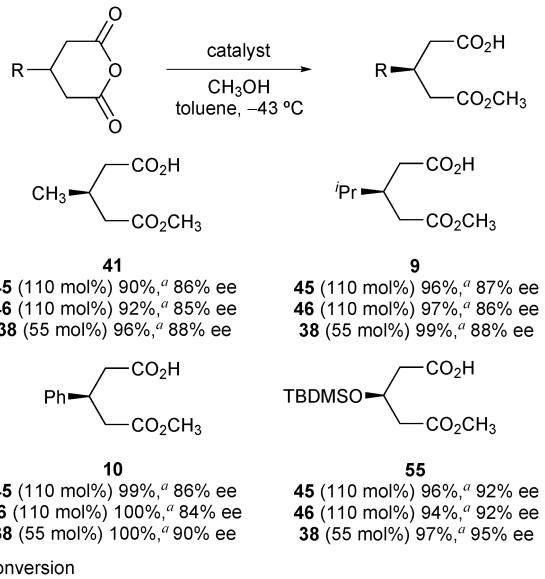
Fig. 6 Structures of modified mono-cinchona alkaloids **42–51** used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.

Cinchona alkaloid derivatives **45** and **46** are remarkably efficient when trifluoroethanol (TFE) is used for asymmetric alcoholysis. Indeed these compounds are superior to **38** in the trifluoroethanolysis of succinic anhydrides.[56] Selected results are shown in Scheme 8, working at 0.02 M substrate concentration in diethyl ether as solvent at low or room temperature.



[a] Conversion

Scheme 8 Modified cinchona alkaloid organocatalyzed opening of cyclic anhydrides with trifluoroethanol.

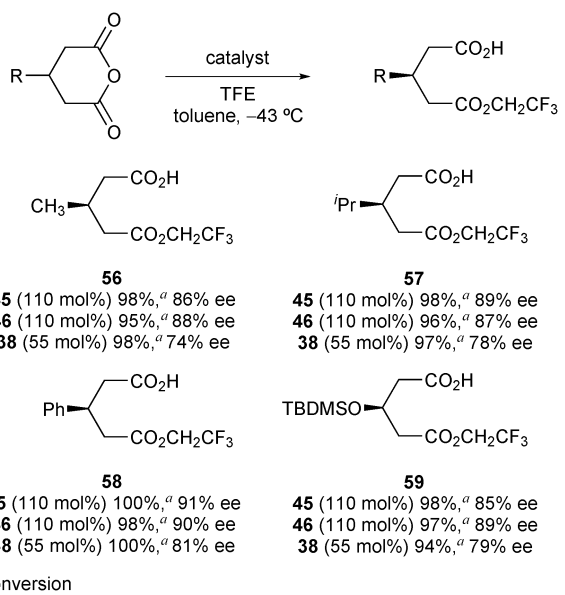


Scheme 9 Modified cinchona alkaloid-catalyzed methanolysis of 3-substituted glutaric anhydrides.

Full conversion of the corresponding starting anhydride was attained in all cases.

Desymmetrization of 3-substituted glutaric anhydrides, which are challenging substrates for alcoholysis due to their low activity and more severe product inhibition of the catalysts, has also been investigated. Monomeric alkaloids **45** and **46** proved to have a remarkable catalytic performance in the methanolysis (Scheme 9) and trifluoroethanolysis (Scheme 10) of 3-substituted glutaric anhydrides on working in toluene as solvent at −43 °C and a 0.2 M substrate concentration.[56]

Compared to **38** under the same conditions, **45** and **46** showed comparable enantioselectivity and a slightly lower catalytic activity. In addition, an organocatalyst loading of 100–110 mol% instead of 55 mol% was necessary to reach



Scheme 10 Modified cinchona alkaloid-catalyzed opening of 3-substituted glutaric anhydrides with trifluoroethanol.

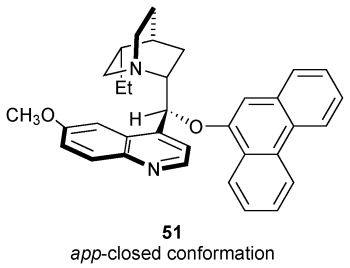


Fig. 7 *app*-Closed conformation of the modified mono-cinchona alkaloid organocatalyst **51**.

similar conversion levels. In any case, considering both the cost and catalytic properties, these modified monomeric cinchona alkaloids are superior to the dimeric organocatalyst.

Recent studies[59] on the mechanism of the cinchona alkaloid-derived organocatalyzed desymmetrization of cyclic anhydrides by asymmetric alcoholysis indicate that this reaction proceeds through a general base catalysis mechanism in which the cinchona alkaloid first forms an amine alcohol hydrogen-bonded complex. The activated alcohol then reacts selectively with one of the enantiotopic carbonyl groups of the anhydride. The *app*-closed conformation has been identified as the active conformation of the modified mono-cinchona alkaloid organocatalyst **51** (Fig. 7) in the enantioselective methanolysis of *cis*-2,3-dimethylsuccinic anhydride, and a model consistent with the observed sense of asymmetric induction has been proposed.

It is worth mentioning that the organocatalyst **46** can be easily prepared on a multigram scale (53% overall yield) from readily available and inexpensive starting materials.[59] In addition, this catalyst is sufficiently stable to acids to be readily recovered in high yield by using a simple extraction protocol.[56]

Bis-cinchona alkaloids **38** and **39** have been supported on silica gel and used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides with the aim of exploring the possibility of efficient reuse.[60,61]Among the different catalysts tested, silica gel-supported $(DHQD)_2AQN$ organocatalysts led to better enantioselectivities than silica gel-supported $(DHQ)_2AQN$ organocatalysts, and those more rigid organocatalysts were superior in terms of enantioselectivity and stability, with **60** (Fig. 8) proving to be the best catalytic system to perform efficiently the enantioselective desymmetrization of several succinic and glutaric anhydrides.

These silica gel-supported organocatalysts could be reused several times in the enantioselective methanolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride without significant decreases in catalytic activity or enantioselectivity.[61]

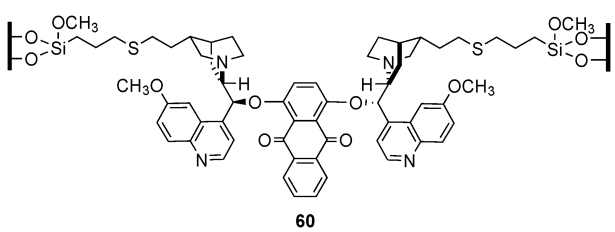
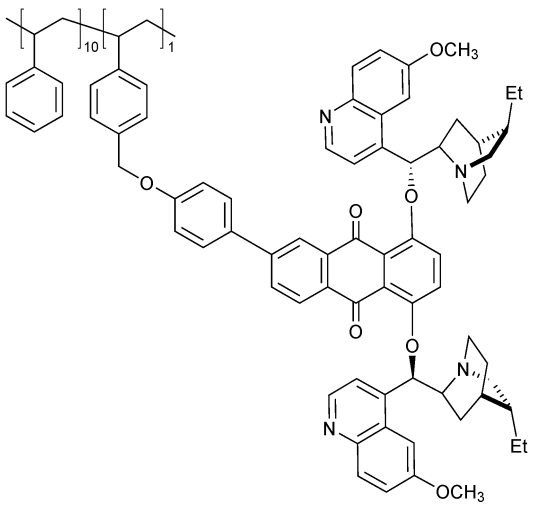


Fig. 8 Structure of the silica gel-supported organocatalyst **60**.



61

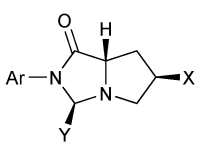
Fig. 9 Structure of the polystyrene-supported organocatalyst **61**.

The organocatalyst **38** has also been anchored to linear polystyrene (Fig. 9) and its application in membrane reactors to perform enantioselective desymmetrization of cyclic anhydrides has been tested.[62,63] The use of the polymer-supported organocatalyst **61** in the methanolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride gave complete conversion in 1 h at room temperature and the resulting hemiester **12** was obtained with *ca.* 80% ee. Nevertheless, conversion and enantioselectivity decreased during a continuous reaction due to product inhibition of the catalyst. In a repetitive batch system conversion remained high for several cycles but enantioselectivity declined to 40% or 60% ee after 6 cycles depending on the workup after each run.

3. Amines, amino alcohols and diamines

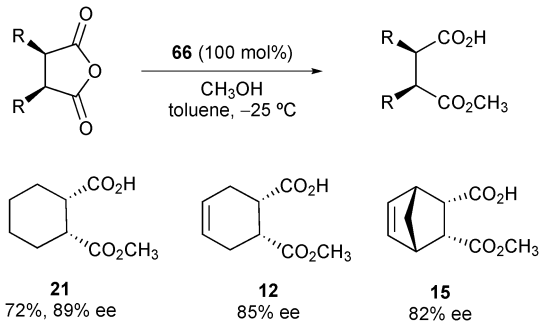
Enantiomerically pure non-alkaloid tertiary amines have also been used as chiral organocatalysts in the enantioselective desymmetrization of cyclic anhydrides. In this context several hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-ones derived from proline and 4-hydroxyproline (Fig. 10) were examined for the enantioselective methanolysis of *cis*-cyclohexane-1,2-dicarboxylic anhydride.[64]

The reaction was performed in toluene at −25 °C in the presence of 10 mol% of the organocatalyst. On using 4-hydroxyproline-derived amines **63** or **66**, the hemiester **21** was



62: Ar = Ph, X = Y = H
63: Ar = Ph, X = OH, Y = H
64: Ar = Ph, X = OTBDMS, Y = H
65: Ar = Ph, X = OH, Y = Ph
66: Ar = 4-*n*-C_8H_{17}-C_6H_4, X = OH, Y = H

Fig. 10 Structures of hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-ones **62–66** tested as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.



21 72%, 89% ee
12 85% ee
15 82% ee

Scheme 11 Enantioselective methanolysis of cyclic anhydrides using hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one **66** as the organocatalyst.

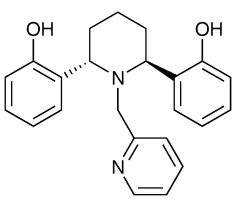
obtained with moderate yield (33–40%) and enantioselectivity (*ca.* 65% ee). Results were improved when 100 mol% of organocatalyst **66** was used. Under these conditions several cyclic anhydrides were desymmetrized with high enantiomeric excesses (Scheme 11).

Tripodal tertiary amine **67** (Fig. 11) behaves as an efficient organocatalyst in the desymmetrization of cyclic anhydrides.[65] A catalyst loading as low as 5 mol% of this amine was enough to perform enantioselective methanolysis of different cyclic anhydrides, some of which were difficult substrates in the cinchona alkaloid-mediated ring-opening.

Working in toluene as solvent at room temperature and using an excess of methanol the corresponding methyl hemiesters were obtained with moderate to good enantioselectivities and in high isolated yields (Scheme 12). At 0 °C the methanolysis reaction proceeded with slightly higher enantioselectivity but in some cases a dramatic decrease in yield was observed.

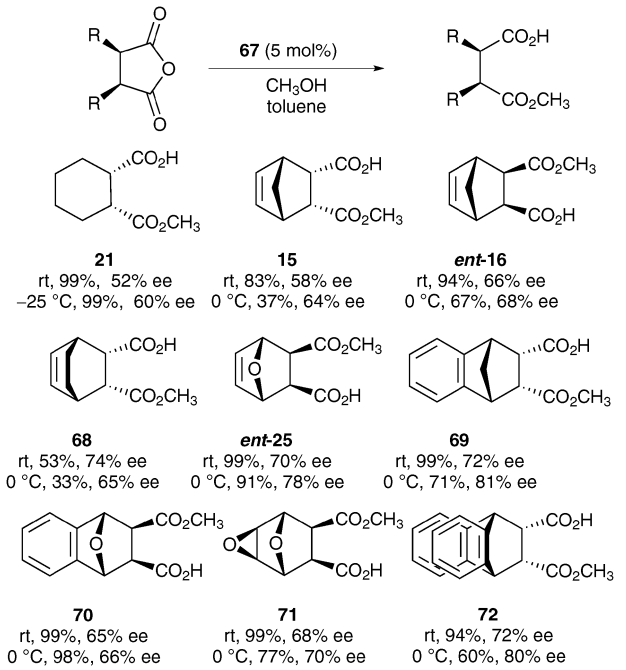
Several enantiomerically pure β-amino alcohol derivatives (Fig. 12) have recently been tested as alternative chiral organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.[66]

The efficiency of these organocatalysts has been explored in the enantioselective methanolysis of tricyclic anhydride **82** by using 10 mol% of the β-amino alcohol derivative in toluene as solvent at room temperature. The activity of all catalysts was excellent, but the enantioselectivity strongly depended on the organocatalyst backbone and the enantiomeric excesses varied from 16% to 72%, with piperidinyl- and morpholinyl-substituted compounds **74** and **75** being the most efficient organocatalysts. On using these amino alcohol derivatives methyl hemiesters ***ent*-15** and **15** were obtained, respectively, in 72% and 71% ee (Scheme 13).



67

Fig. 11 Structure of the tripodal 2,6-*trans*-trisubstituted piperidine **67** tested as an organocatalyst in the enantioselective desymmetrization of cyclic anhydrides.



Scheme 12 Enantioselective methanolysis of cyclic anhydrides using 2,6-*trans*-trisubstituted piperidine **67** as the organocatalyst.

Recent mechanistic studies on the desymmetrization of cyclic anhydride **82** using the enantiomer of the chiral amino alcohol **74** as organocatalyst clearly indicate that a general base-catalysis pathway is energetically favoured over a nucleophilic mechanism for this methanol-induced enantioselective ring-opening.[67]

The enantiomerically pure 1,2-diamine derivatives shown in Fig. 13 also promote the enantioselective methanolysis of anhydride **82** under the previous reaction conditions.[66] In this case, piperidinyl-substituted derivative **83** was the most efficient organocatalyst and this provided the methyl hemiester **15** in 91% yield and with 82% ee.

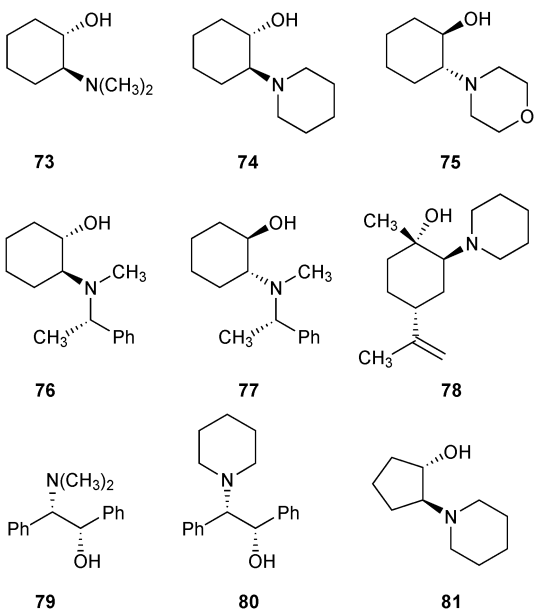
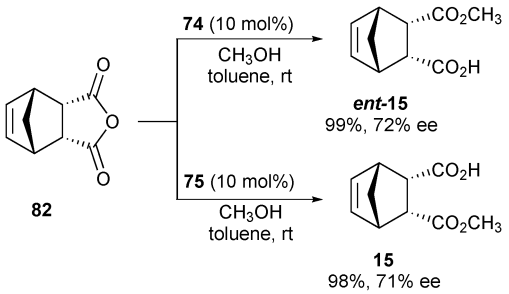


Fig. 12 Structures of β-amino alcohol derivatives **73–81** tested as organocatalysts in the enantioselective desymmetrization of anhydride **82**.



Scheme 13 Enantioselective methanolysis of anhydride **82** using β-amino alcohol derivatives **74** and **75** as organocatalysts.

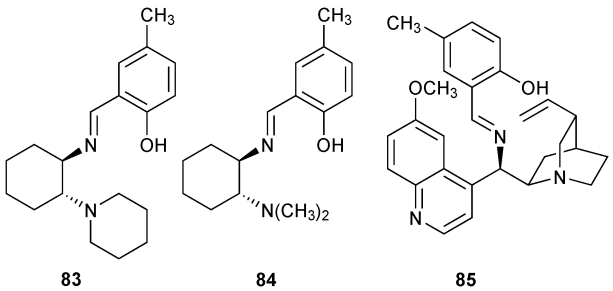


Fig. 13 Structures of 1,2-diamine derivatives **83–85** tested as organocatalysts in enantioselective desymmetrization of the anhydride **82**.

All attempts to use the amino alcohol derivative **74** or the diamine **83** as the organocatalyst in the enantioselective thiolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride with benzyl mercaptan led to disappointing results.[66]

4. Urea and thiourea derivatives

In recent years new chiral bifunctional organic molecules containing a urea or a thiourea moiety have emerged as very efficient organocatalysts for a wide range of synthetically useful asymmetric transformations[68–79] involving the addition of an acidic pronucleophile to an electrophile incorporating hydrogen-bond accepting functionalities.

Connon *et al.* tested some bifunctional cinchona alkaloid-derived ureas and thioureas (Fig. 14) as organocatalysts for the nucleophilic ring-opening of cyclic anhydrides.[80]

Among the compounds investigated, bifunctional thiourea-quinine alkaloid **86** behaved as a highly efficient organocatalyst in desymmetrization reactions of cyclic anhydrides. Indeed, loadings as low as 1 mol% of the thiourea derivative **86** were sufficient to reach high levels of conversion in the enantioselective methanolysis of cyclic anhydride **82**. The enantioselectivity depended on the solvent and concentration of anhydride in the solvent. The methyl hemiester **15** was obtained in 93% to 96% ee on working at room temperature in methyl *tert*-butyl ether (MTBE) as solvent at concentrations between 0.025 M and 0.015 M. Urea-quinine alkaloid **87** and thiourea-dihydroquinine alkaloid **88** also behaved as highly efficient organocatalysts under the same reaction conditions. Thiourea-quinidine alkaloid **89** gave the hemiester ***ent*-15** with

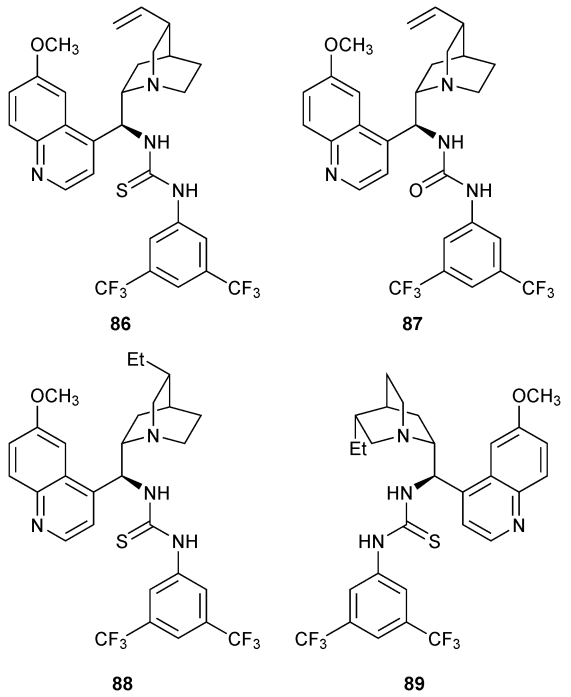


Fig. 14 Structures of bifunctional urea- and thiourea-based alkaloids **86–89** used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.

the opposite absolute configuration but the enantioselectivity was significantly lower (77% ee).

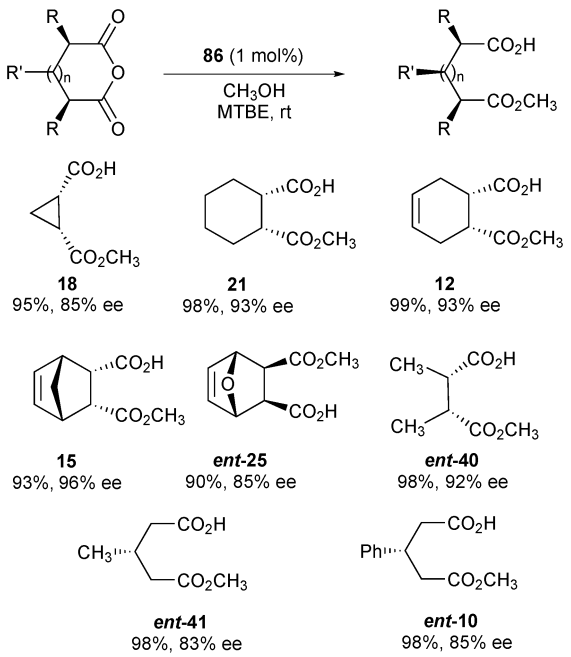
The same protocol was applied to the enantioselective methanolysis of a variety of succinic and glutaric anhydride derivatives, with excellent levels of enantioselectivity achieved on employing an organocatalyst loading as low as 1 mol% (Scheme 14). The optical purity of glutaric acid methyl hemiesters could be increased up to *ca*. 90% ee on working at 0 °C without increasing the catalyst loading.

A one-pot sequence consisting of desymmetrization by alcoholysis of *cis*-cyclohexane-1,2-dicarboxylic anhydride with allyl alcohol followed by esterification with methanol and deprotection allowed the synthesis of ***ent*-15** with excellent enantioselectivity while avoiding the use of a *pseudo*-enantiomeric organocatalyst.[80]

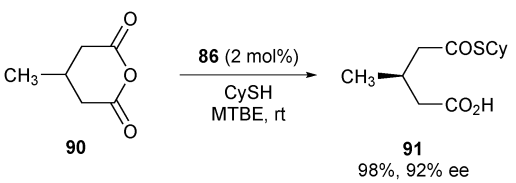
The same protocol was evaluated for the enantioselective thiolytic desymmetrization of cyclic anhydrides by using benzyl mercaptan and cyclohexanethiol as nucleophiles.[81] The reaction of 3-methylglutaric anhydride (**90**) with cyclohexanethiol in the presence of 2 mol% of the thiourea derivative **86** afforded the hemithioester **91** in excellent yield and with high enantioselectivity (Scheme 15).

Independently, Song *et al*.[82] reported that the methanolytic desymmetrization of cyclic anhydrides with 10 mol% of the thiourea derivative **86** proceeded smoothly at room temperature in dioxane to afford the corresponding methyl hemiester with excellent enantioselectivity (Scheme 16).

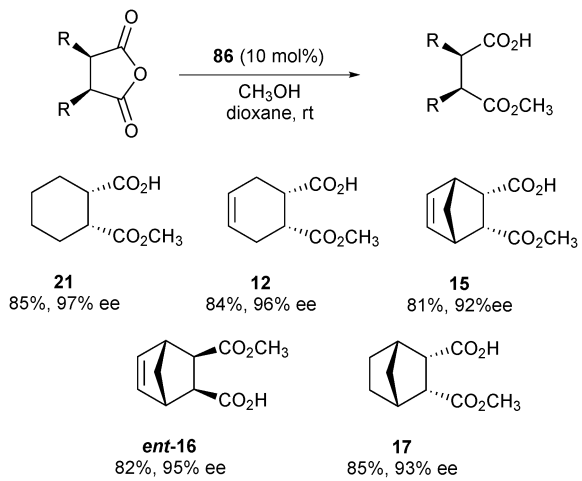
The enantioselectivity of the desymmetrization reaction in THF as solvent increased on dilution of the reaction mixture. Enantiomeric excess generally showed a slight increase on raising the reaction temperature from −20 °C to 25 °C. The reaction in aprotic, hydrogen-bond accepting solvents gave the highest ee values while protic solvents like methanol gave the lowest ee values. These unusual effects of concentration, temperature, and solvent on the reaction enantioselectivity were explained in terms of a mechanism involving monomer–dimer equilibration of the organocatalyst.[82]



Scheme 14 Connon's enantioselective methanolysis of cyclic anhydrides using the thiourea derivative **86** as organocatalyst.



Scheme 15 Enantioselective thiolysis of 3-methylglutaric anhydride (**90**) using the thiourea derivative **86** as organocatalyst.



Scheme 16 Song's enantioselective methanolysis of cyclic anhydrides using the thiourea derivative **86** as organocatalyst.

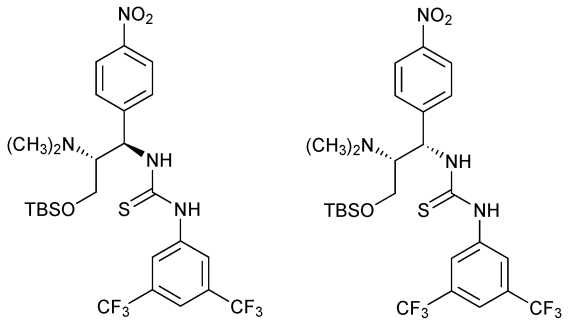


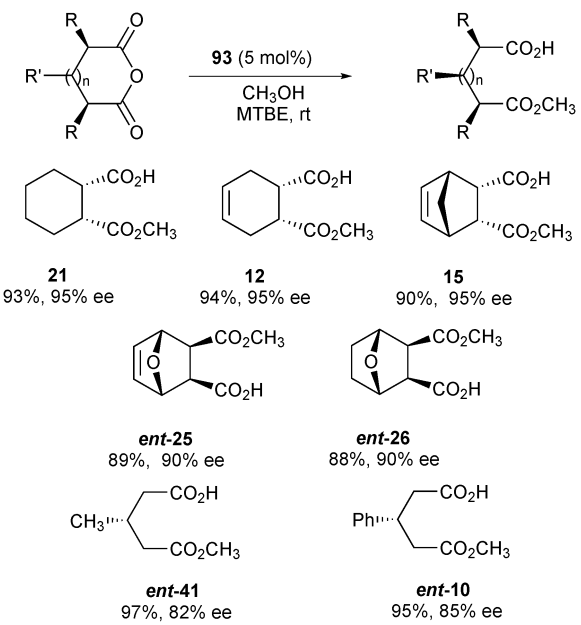
Fig. 15 Structures of thiourea-based bifunctional organocatalysts **92** and **93** derived from (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol.

Novel thiourea-based bifunctional organocatalysts **92** and **93**, derived from inexpensive (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)-propane-1,3-diol (Fig. 15), have recently been developed for the enantioselective alcoholysis of cyclic anhydrides.[83] Both organocatalysts led to the formation of the corresponding hemiester with identical absolute configuration but with different levels of enantioselectivity, with the thiourea derivative **93** being the most effective one.

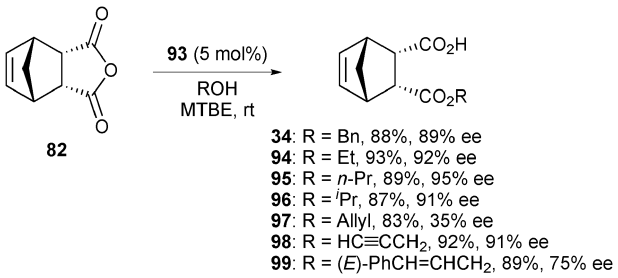
Optimal results were obtained when the reactions were carried out in MTBE as solvent at room temperature using 5 mol% of the thiourea derivative **93** as the organocatalyst with an anhydride concentration of 0.0125 M (Scheme 17).

High enantiomeric excesses were also obtained in most cases when alcohols other than methanol were used as nucleophiles in the enantioselective organocatalyzed desymmetrization of the cyclic anhydride **82** (Scheme 18).[83]

Urea **100** and thioureas **101**, ***ent*-101** and **102**, derived from (*S*)- or (*R*)-3-methylbutane-1,2-diamine (Fig. 16), behave as very efficient organocatalysts in the enantioselective alcoholytic desymmetrization of different cyclic anhydrides.[84]



Scheme 17 Enantioselective methanolysis of cyclic anhydrides using the thiourea derivative **93** as organocatalyst.



Scheme 18 Thiourea derivative **93** organocatalyzed nucleophilic ring-opening of the anhydride **82** using various alcohols as nucleophiles.

Optimal results in the enantioselective methanolysis of cyclic anhydride **82** using thiourea derivative **101** as the organocatalyst were obtained when the reactions were carried out at room temperature with an anhydride concentration of 0.015 M in MTBE as solvent and employing 10 equivalents of methanol and 5 mol% of the organocatalyst. Under these conditions the methyl hemiester **15** was obtained with 82% conversion and 96% ee after 18 h. Similar results were obtained on using urea derivative **100** as the organocatalyst. The use of allyl or benzyl alcohol as nucleophiles gave hemiesters **97** and **34** in 96% yield/96% ee and 90% yield/74% ee, respectively, on using the thiourea derivative **101** as the organocatalyst under optimized reaction conditions.

Enantioselective methanolysis of a variety of cyclic anhydrides was performed by using thiourea **101** as the organocatalyst (Scheme 19). These reactions gave the corresponding methyl hemiesters with usually excellent levels of enantioselectivity. The use of the enantiomeric thiourea ***ent*-101** (Fig. 16) as organocatalyst gave methyl hemiesters of opposite absolute configuration with similar enantioselectivity levels.

Thioureas derived from *trans*-cyclohexane-1,2-diamine (Fig. 17) have also been tested as organocatalysts for the enantioselective

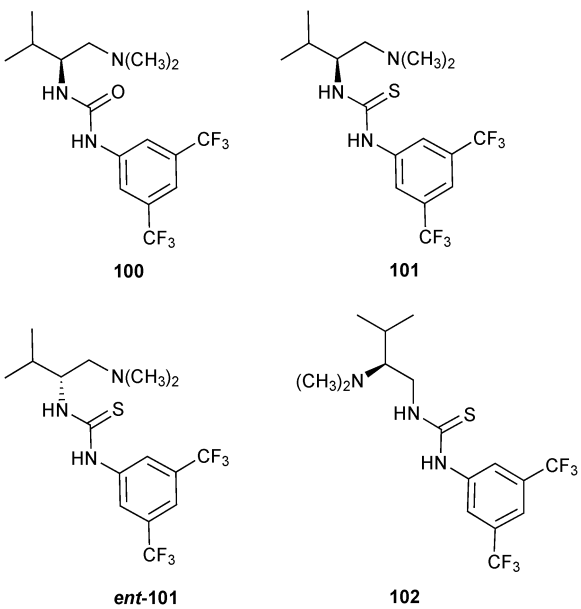
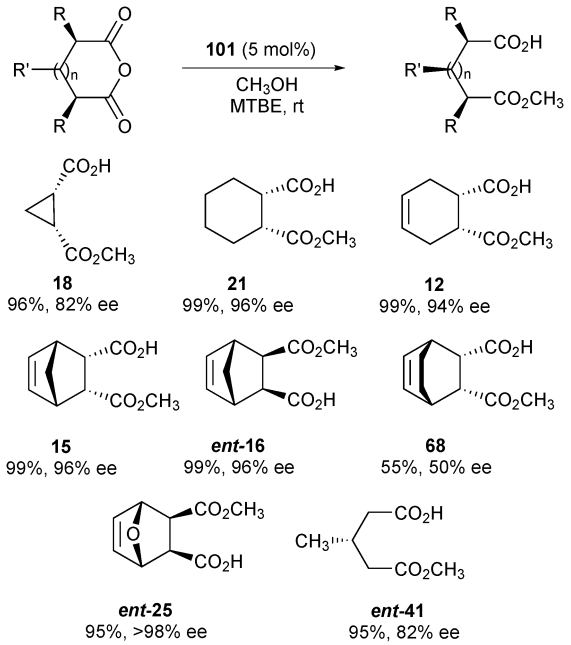


Fig. 16 Structures of bifunctional urea- and thiourea-based organocatalysts **100–102** and ***ent*-101** derived from (*S*)- or (*R*)-3-methylbutane-1,2-diamine.



Scheme 19 Enantioselective methanolysis of cyclic anhydrides using thiourea **101** as organocatalyst.

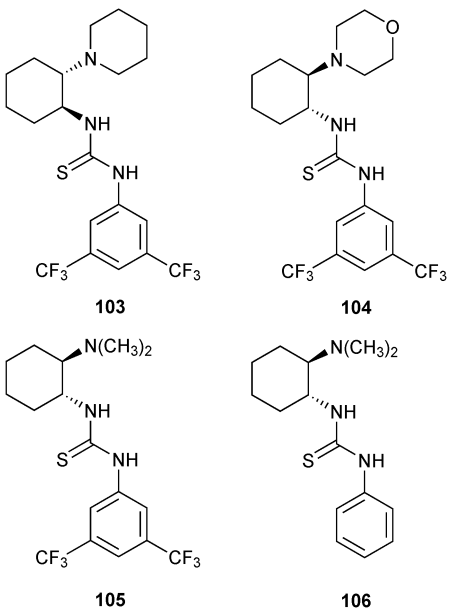
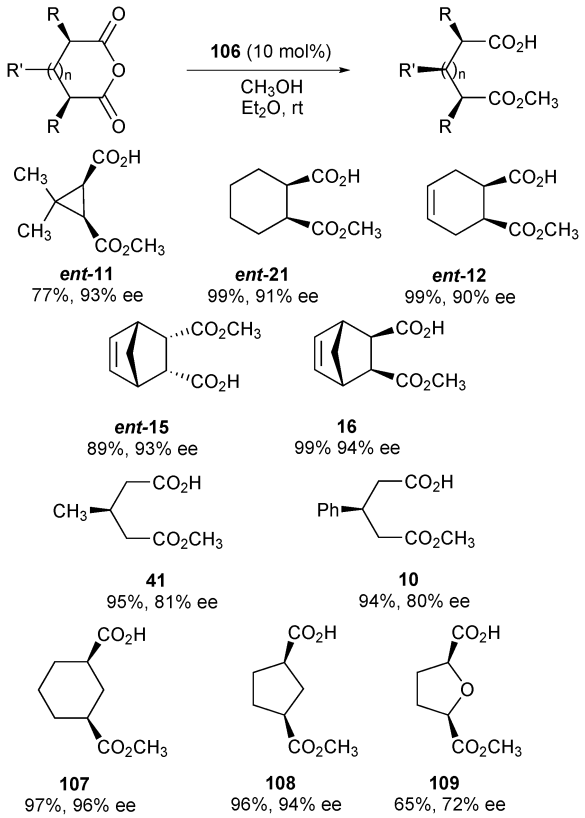


Fig. 17 Structures of thiourea-based bifunctional organocatalysts **103–106** derived from *trans*-cyclohexane-1,2-diamine.

methanolysis of the cyclic anhydride **82**.[66] In this case the presence of a dimethylamino group in the structure was beneficial, with thioureas **105** and **106** being the most effective organocatalysts for this transformation. The enantioselectivity of the methanolysis reaction of cyclic anhydride **82** with these organocatalysts strongly depended on dilution and, on working at anhydride concentrations of 0.025 M or lower, enantioselectivities were greater than 90% ee.

The efficient enantioselective methanolysis of a variety of cyclic anhydrides as 0.0125 M ethereal solutions was performed at



Scheme 20 Enantioselective methanolysis of cyclic anhydrides using the thiourea derivative **106** as organocatalyst.

room temperature using 10 mol% of the thiourea derivative **106** as the organocatalyst (Scheme 20).[66]

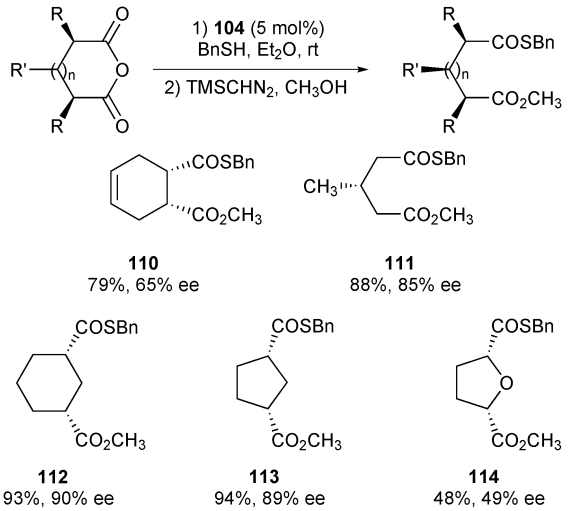
Piperidinyl- and morpholinyl-substituted thioureas **103** and **104** were more effective organocatalysts than the dimethylamino-substituted thiourea **105** in the enantioselective thiolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride with benzyl mercaptan as the nucleophile.[66] In this case, the use of high dilution conditions did not improve the results.

Thiourea **104** was chosen as an organocatalyst for the enantioselective thiolysis of other cyclic anhydrides with benzyl mercaptan. The *in situ* methylation of the initially obtained hemithioesters afforded stable thioesters with enantioselectivities that depended on the starting cyclic anhydride (Scheme 21).

5. Sulfonamide and phosphoramide derivatives

Enantiomerically pure sulfonamide and phosphoramide derivatives have emerged as promising new bifunctional chiral organocatalysts for use in asymmetric organic synthesis.[85–87]

In this context, Song *et al.*[88–90] developed a new chiral bifunctional sulfonamide-based alkaloid organocatalyst **115** (Fig. 18) for the enantioselective methanolysis of cyclic anhydrides. This catalyst shows unprecedented catalytic activity and excellent enantioselectivity. An advantage of this new organocatalyst is that it does not suffer from self-aggregation and thus the reactivity and enantioselectivity does not depend on the reaction concentration and temperature. Sulfonamide **115** is the most active organocatalyst reported to date for the alcoholytic desymmetrization of cyclic anhydrides.



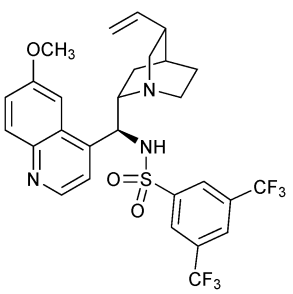
Scheme 21 Enantioselective thiolysis of cyclic anhydrides using thiourea derivative **104** as organocatalyst.

For example, a reaction time of 1 h was sufficient to complete the enantioselective methanolysis of *cis*-cyclohexane-1,2-dicarboxylic anhydride in diethyl ether as solvent at room temperature using 10 mol% of sulfonamide **115**. Under these reaction conditions the methyl hemiester **21** was isolated in 91% yield and 96% ee. The organocatalyst loading could be reduced to an unprecedented level and catalytic activity and enantioselectivity remained excellent. After 20 h at room temperature the hemiester **21** was isolated in 89% yield and 93% ee with an organocatalyst loading as low as 0.5 mol%.[88]

This behaviour is general and methanolysis of a range of succinic anhydrides under optimized reaction conditions—diethyl ether as solvent at room temperature in the presence of 5 mol% of sulfonamide **115**—was complete within a few hours to give the corresponding methyl hemiesters in excellent yields and with high enantioselectivity (Scheme 22).[88,89]

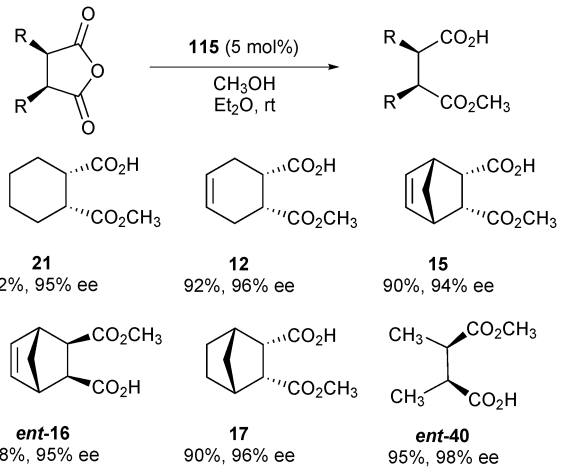
Methanolysis of glutaric anhydrides in MTBE as solvent using 10 mol% of sulfonamide **115** as the organocatalyst led to high enantiomeric excesses regardless of the substitution pattern at the 3-position of the glutaric anhydride (Scheme 23).[90] A slight decrease in the temperature led to an increase in the enantioselectivity of the desymmetrization reaction but in some cases the isolated yield decreased significantly.

High enantioselectivities were also observed when alcohols other than methanol were used as nucleophiles in the desymmetrization of 3-(*tert*-butyldiphenylsilyloxy)glutaric



115

Fig. 18 Structure of the sulfonamide-based organocatalyst **115**.

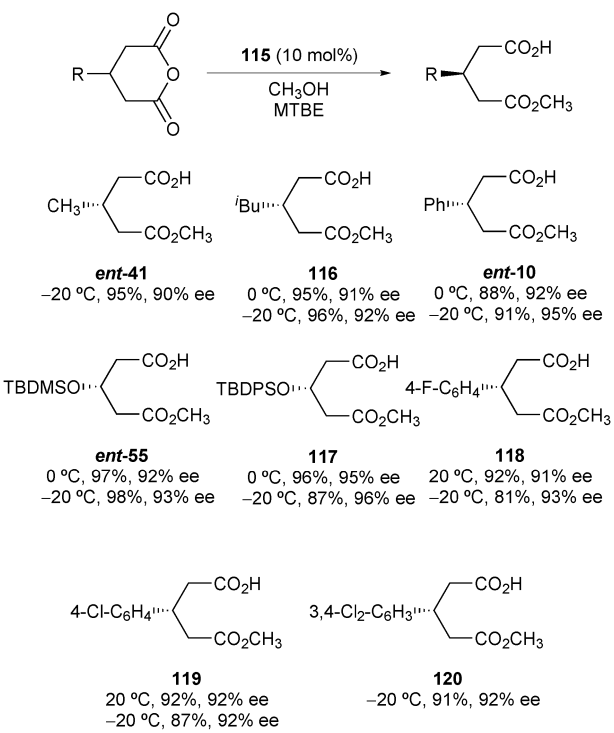


Scheme 22 Enantioselective methanolysis of succinic anhydrides using sulfonamide **115** as organocatalyst.

anhydride. The use of allyl or benzyl alcohols as nucleophiles at room temperature in MTBE as solvent and with 10 mol% of sulfonamide **115** as organocatalyst gave the corresponding allyl and benzyl hemiesters in 92% yield/91% ee and 90% yield/96% ee, respectively.[90]

Other chiral bifunctional sulfonamide-based alkaloids with different substitution patterns (**121–131**, Fig. 19) were also excellent organocatalysts for the enantioselective desymmetrization of cyclic anhydrides.[89,90]

Enantioselective methanolysis of *cis*-cyclohexane-1,2-dicarboxylic anhydride in diethyl or diisopropyl ether as solvent at room temperature in the presence of 5 mol% of organocatalysts **121**, **122**, **127** or **128** led to the methyl hemiester **21**,



Scheme 23 Enantioselective methanolysis of glutaric anhydrides using sulfonamide **115** as organocatalyst.

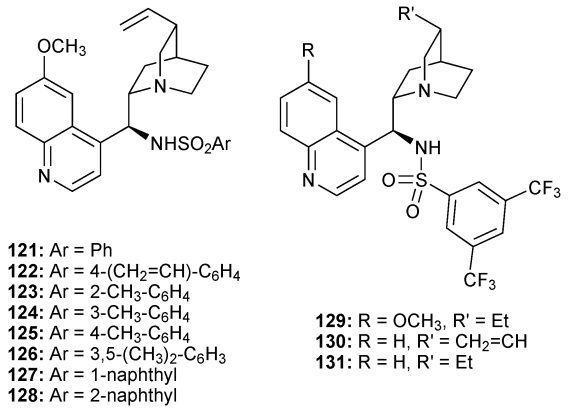
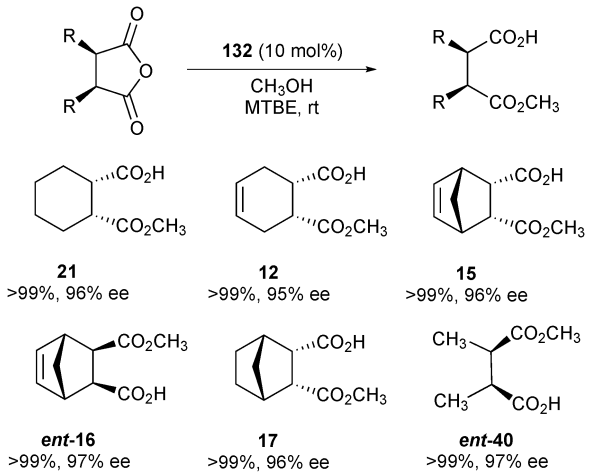


Fig. 19 Structure of sulfonamide-based organocatalysts **121–131**.



Scheme 24 Enantioselective methanolysis of cyclic anhydrides using the polymer-supported organocatalyst **132**.

which was isolated in greater than 95% yield and with enantioselectivities in the range 92–96% ee.[89]

Enantioselective methanolysis of 3-(*tert*-butyldiphenylsilyloxy)glutaric anhydride in MTBE as solvent at room temperature in the presence of 10 mol% of organocatalyst **121** or **123–131** led to the methyl hemiester **117**, which was isolated in 87% to 99% yield and with enantioselectivities of 90% to 93% ee.[90]

A polymer-supported chiral sulfonamide-based bifunctional organocatalyst **132** (Fig. 20) has been designed and its catalytic performance has been assessed.[91]

Enantioselective methanolysis of succinic anhydrides in MTBE as solvent at room temperature and in the presence of 10 mol% of the polymeric organocatalyst **132** proceeded in a few hours to give the corresponding methyl hemiesters in quantitative yields and with excellent enantioselectivities (Scheme 24). The organocatalyst loading could be reduced to levels as low as 1 mol% while maintaining excellent catalytic activity and enantioselectivity for the methanolysis of *cis*-cyclohexane-1,2-dicarboxylic anhydride. All of the products were easily isolated by simple filtration to remove the polymer followed by evaporation.

Non-alkaloid based sulfonamides have also been used as organocatalysts in the enantioselective desymmetrization of cyclic anhydrides.

Sulfonamide **133**, derived from (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine (Fig. 21), has been used as an organocatalyst in the nucleophilic ring-opening of cyclic anhydrides with benzyl alcohol.[92] The reaction was performed at room temperature in diethyl ether as solvent and using 5 mol% of catalyst. The resulting benzyl hemiesters were submitted to methylation to afford the corresponding diesters with high yields and enantioselectivities (Scheme 25).

Chiral sulfonamide **133** also catalyzed the enantioselective thiolysis of cyclic anhydrides with benzyl mercaptan under the same reaction conditions (Scheme 26).[93]

Enantiomerically pure sulfonamides **147** and **148** derived from *trans*-cyclohexane-1,2-diamines (Fig. 22) have also been tested as organocatalysts in the enantioselective methanolysis of cyclic anhydride **82** and thiolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride.[66]

Although these compounds performed rather well in terms of reactivity, the enantiomeric excesses were quite low in the methanolysis reaction and only moderate in the thiolysis reaction. Sulfonamides **147** and **148** promoted the preferential formation of methyl hemiesters or hemithioesters of opposite absolute configuration.

Very recently, List developed new phosphoramide and thiophosphoramide organocatalysts **149** and **150** derived from BINOL-phosphoric or thiophosphoric acids respectively (Fig. 23). These compounds behave as bifunctional Brønsted acid/base organocatalysts due to the presence of both the pyridine ring and the phosphoramide functionality.[94]

Enantioselective methanolysis of cyclic *cis*-cyclohexane-1,2-dicarboxylic anhydride in toluene as solvent at room temperature and in the presence of 10 mol% of phosphoramide **149**

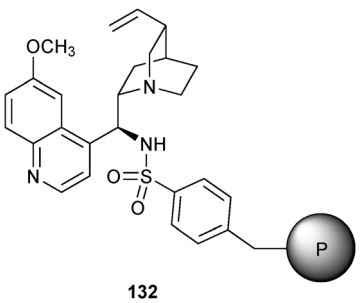


Fig. 20 Structure of the polymer-supported sulfonamide-based bifunctional organocatalyst **132**.

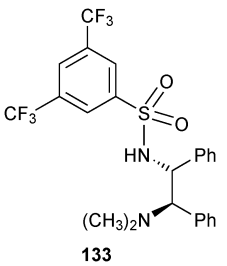
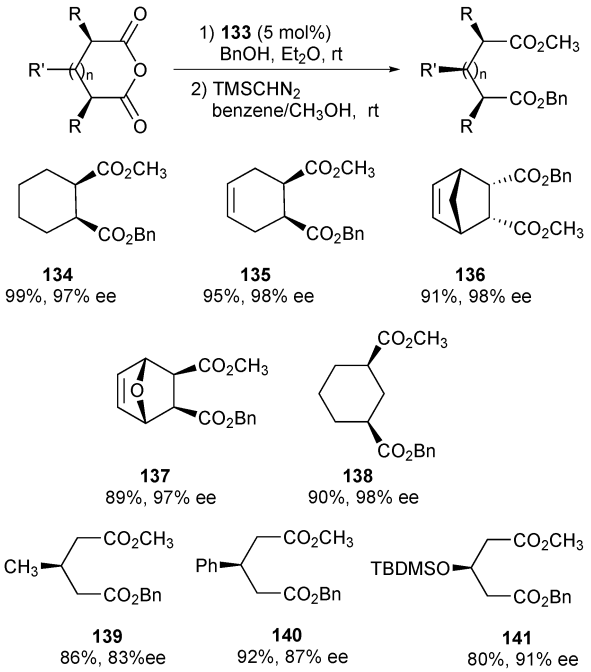
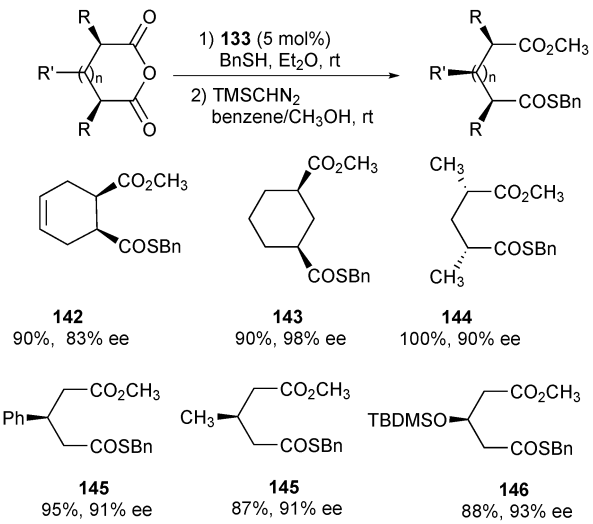


Fig. 21 Structure of the sulfonamide-based organocatalyst **133** derived from (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine.



Scheme 25 Sulfonamide **133** organocatalyzed opening of cyclic anhydrides using benzyl alcohol as the nucleophile.



Scheme 26 Sulfonamide **133** organocatalyzed opening of cyclic anhydrides using benzyl mercaptan as the nucleophile.

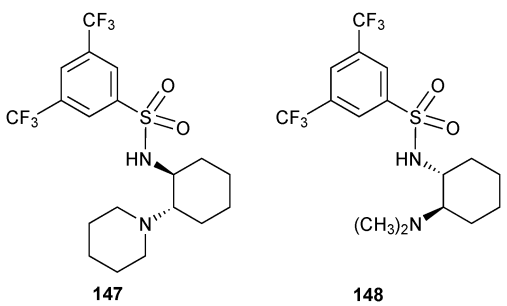


Fig. 22 Structure of sulfonamide-based organocatalysts **147** and **148** derived from *trans*-cyclohexane-1,2-diamines.

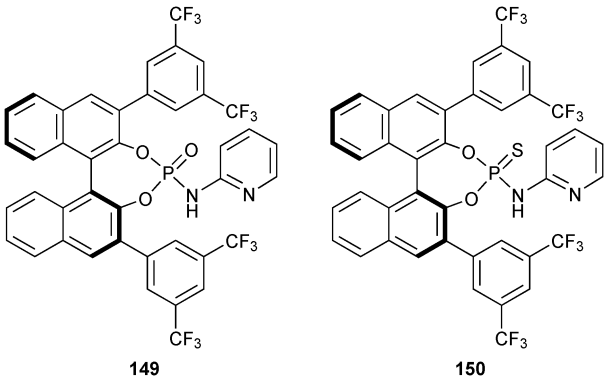
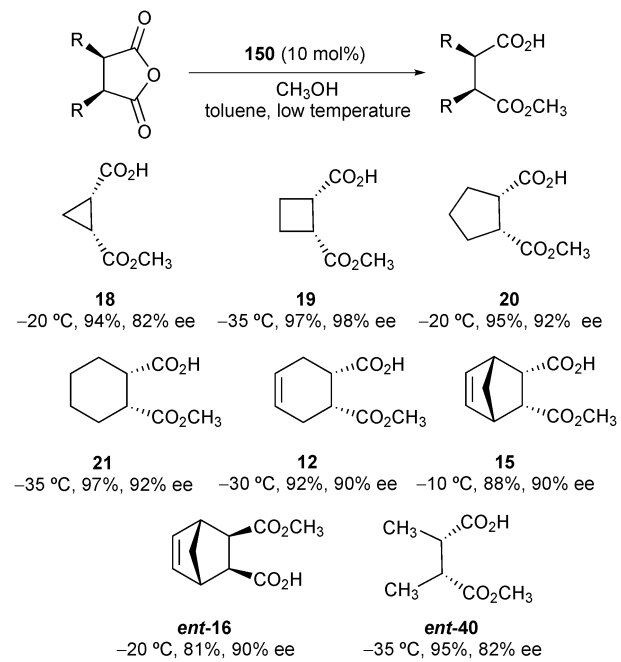


Fig. 23 Structures of phosphoramide and thiophosphoramide organocatalysts **149** and **150** derived from BINOL-phosphoric or thiophosphoric acid.

gave the corresponding methyl hemiester **21** with a good enantioselectivity (80% ee). A change in the position of the nitrogen or the presence of an additional basic site in the pyridine ring was detrimental for the enantioselectivity. On the other hand, enantioselective ring-opening of *cis*-cyclohexane-1,2-dicarboxylic anhydride under the same reaction conditions and in the presence of 10 mol% of thiophosphoramide **150** gave the methyl hemiester **21** with the same enantioselectivity, which was further increased to 92% ee on working at low temperature (−35 °C).

High yields and enantioselectivities were obtained under optimized reaction conditions using various cyclic anhydrides as substrates[94] (Scheme 27). The procedure is amenable to the use of other alcohols as nucleophiles and high enantioselectivities (94% to 96% ee) were also achieved even with sterically more demanding alcohols.



Scheme 27 Thiophosphoramide **150** organocatalyzed methanolysis of cyclic anhydrides.

6. Synthetic applications

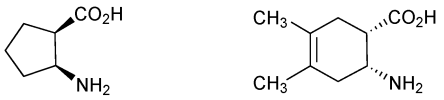
Enantioselective organocatalyzed anhydride desymmetrization has provided efficient access to chiral intermediates for the synthesis of valuable enantiopure compounds and this area is covered in the present section of this review. The use of hemiester derivatives previously obtained by using organocatalytic enantioselective desymmetrization of cyclic anhydrides as intermediates for the synthesis of valuable enantiomerically pure compounds is described first. Subsequently we discuss the development of synthetic strategies that use organocatalytic enantioselective desymmetrization of specific cyclic anhydrides synthesized *ad hoc* as the key step in the synthesis of different enantiomerically pure compounds. The organocatalytic key step for every synthesis is emphasized and, where appropriate, further synthetic transformations are detailed.

Bolm *et al*. developed a general strategy for the synthesis of β-amino acids from chiral benzyl and methyl hemiesters obtained by enantioselective anhydride desymmetrization.[48,95] The hemiester was converted to the corresponding acyl azide and this was submitted to Curtius rearrangement (Scheme 28). Isocyanate intermediates reacted smoothly with several alcohols to allow the introduction of different N-protecting groups, which can be removed by hydrogenolysis (R′ = Bn), acid catalyzed hydrolysis (R′ = CH_3O-$C_6H_4CH_2$), photolytic cleavage (R′ = 2-NO_2-$C_6H_4CH_2$), or hydrogen transfer (R′ = $PhCH_2CH_2$). In this way structurally diverse β-amino acid derivatives were obtained with high overall yields. Competitive retro-Diels–Alder reaction during the Curtius rearrangement of ***ent*-36** containing a 7-oxabicyclo[2.2.1]hept-2-ene ring was avoided by protecting the double bond through bromine addition.[96]

Some chiral β-amino acids obtained in this way have proven to be versatile intermediates in the asymmetric synthesis of biologically active compounds such as CCR2 antagonists[97] and hepatitis C virus NS5B polymerase inhibitors,[98,99] or poly-β-amino acid derivatives.[100]

Relevant examples of the application of this synthetic protocol include the synthesis of the antifungal antibiotic (1*R*,2*S*)-cispentacin **151**, starting from the methyl hemiester **20**[95] or the benzyl hemiester **29**,[48] and the synthesis of the β-amino acid **152**—an *in vivo* inhibitor of the growth of *candida albicans*—starting from methyl hemiester ***ent*-22**[95] (Fig. 24).

In addition to β-amino acids, other relevant chiral compounds have been synthesized starting from hemiesters previously obtained by using Bolm's methodology for the enantioselective desymmetrization of cyclic anhydrides. Both enantiomers of *trans*-4-cyclohexene-1,2-dicarboxylic were obtained from **12** and ***ent*-12** by selective epimerization.[101]



151 152

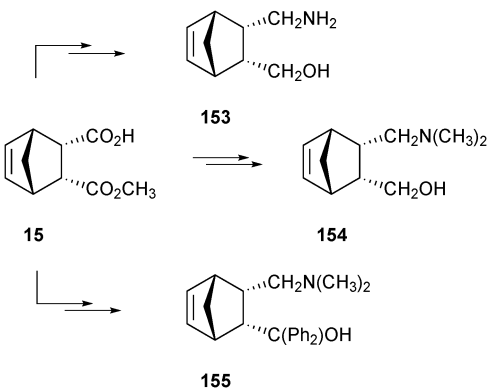
Fig. 24 Structures of cispentacin **151** and β-amino acid **152** obtained according to Bolm's methodology.

cis-1,4-Amino alcohol ligands with a norbornene skeleton, for use in the asymmetric diethylzinc addition to benzaldehyde, were obtained in an enantiomerically pure form starting from **15**[102] (Scheme 29).

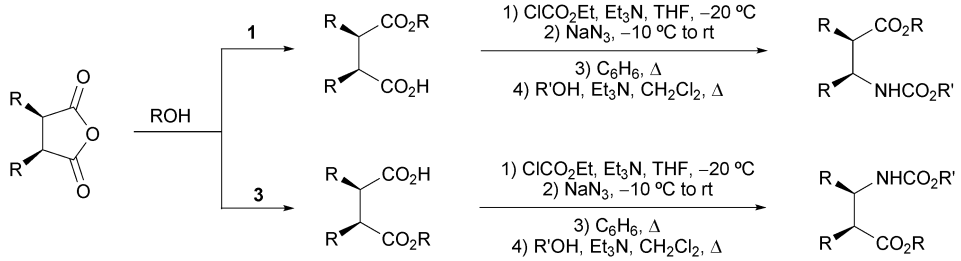
Chiral *trans*-norbornane 1,2-diamine derivatives **157**, **158**, and **159**, salen analogues **160** and **161**, and *trans*-norbornane 1,4-diamine **162** were prepared from methyl hemiester ***ent*-15** after selective epimerization (Scheme 30).[103,104]

The methyl hemiester ***ent*-15** was also used to obtain daphniacetal A **163** (Fig. 25)—a new oxa-cage natural product isolated from the fruit of *Daphniphyllum macropodum*—for the determination of its absolute configuration.[105]

Hemiesters **15** and ***ent*-15** were starting materials in the synthesis of chiral monomers **164** and **165** (Scheme 31) or their diastereoisomers to be used in the preparation of polymeric chiral catalysts for enantioselective C–C-bond formation by ring-opening metathesis polymerization (ROMP).[106]



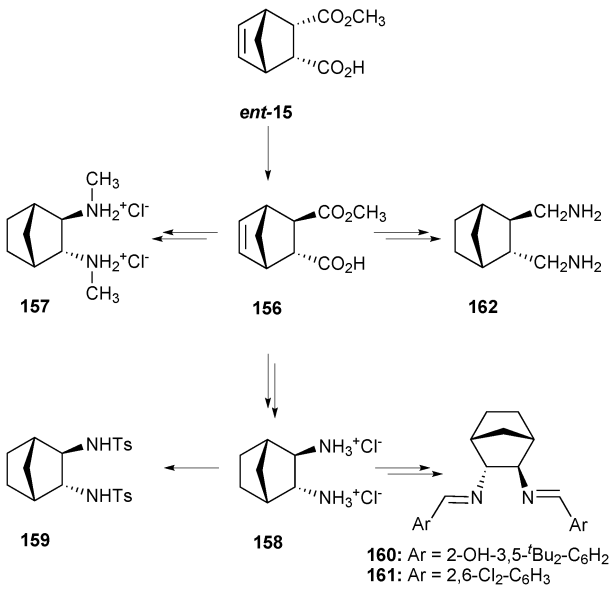
Scheme 29 *cis*-1,4-Amino alcohol ligands obtained from hemiester **15**.



R = CH_3, Bn

R' = Bn, CH_3O-$C_6H_4CH_2$, 2-NO_2-$C_6H_4CH_2$, $PhCH_2CH_2$

Scheme 28 General scheme of Bolm's methodology for the enantioselective synthesis of β-amino acids from cyclic anhydrides.



Scheme 30 *trans*-Norbornanediamines and salen analogues obtained from the hemiester ***ent*-15**.

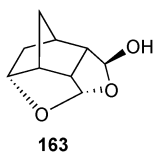
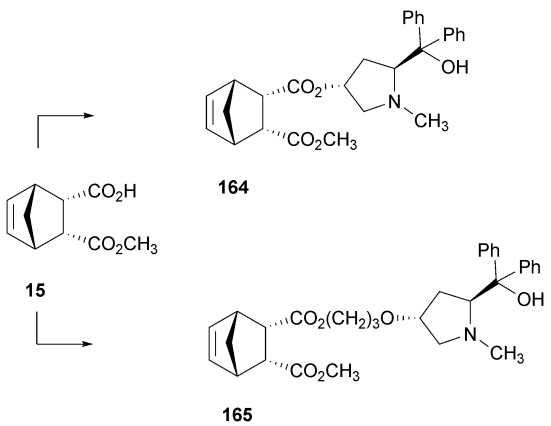


Fig. 25 Structure of daphniacetal A obtained from the hemiester ***ent*-15**.

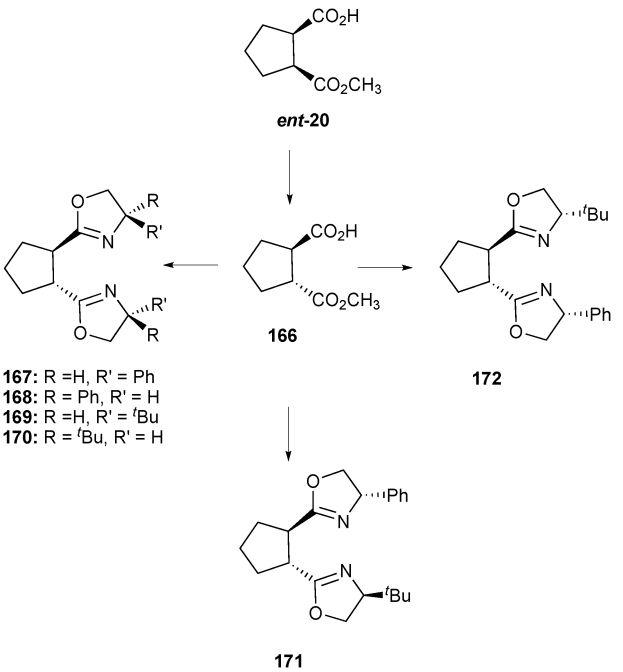
Benzyl hemiesters **31**, ***ent*-31** and ***ent*-34** were suitable s tarting materials to prepare peptidic structures containing *endo-cis*-norbornenedicarboxylate and *cis*-cyclohexane-1,2-dicarboxylate scaffolds as diacid linkers that promote well-defined secondary structures.[107,108]

New valuable C_2- and C_1-symmetric chiral bisoxazoline ligands **167–172** with a rigid cyclic backbone were prepared after selective epimerization of the methyl hemiester ***ent*-20** (Scheme 32).[109]

Guingant's synthesis of (+)-brefeldin C **173** (Fig. 26), one of the ultimate intermediates in the biosynthetic pathway to the



Scheme 31 Chiral monomers obtained from the hemiester **15**.



Scheme 32 Bisoxazoline ligands obtained from the hemiester ***ent*-20**.

naturally occurring macrolide antibiotic brefeldin A, also made use of the hemiester ***ent*-20** as a synthetic precursor.[110,111]

Fukuyama *et al*. reported a total synthesis of (−)-huperzine A **174** (Fig. 27), a naturally occurring sesquiterpene alkaloid effective in counteracting the effects of neurodegeneration, starting from the benzyl hemiester ***ent*-36**.[112]

Benzyl cyclobutanecarboxylates deuterium-labelled at C2 have recently been prepared from the hemiester ***ent*-28**.[113]

***Ent*-12**, obtained by enantioselective methanolysis of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride according to Deng's methodology, was the chiral substrate used in the asymmetric synthesis of the bridged tricyclic enone **175**—a key advanced intermediate in the total synthesis of the antibiotic platencin **176** (Scheme 33).[114]

Hemiester **19**, obtained by Wakchaure and List in 98% ee by using the bifunctional organocatalyst **150**, was transformed

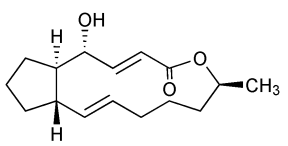


Fig. 26 Structure of (+)-brefeldin C obtained from the hemiester ***ent*-20**.

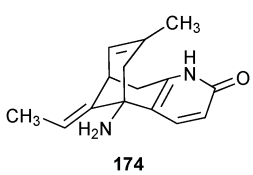
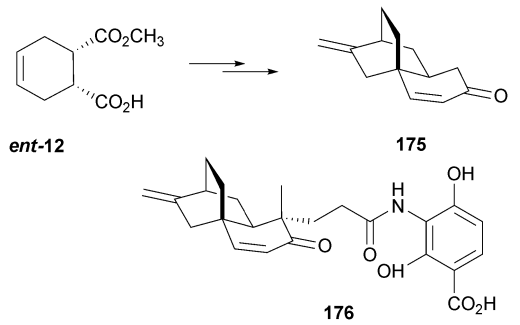
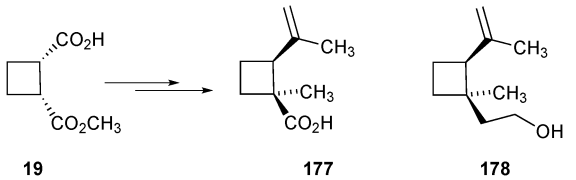


Fig. 27 Structure of (−)-huperzine A obtained from the hemiester ***ent*-36**.



Scheme 33 Key intermediate for platencin obtained from the hemiester ***ent*-12**.

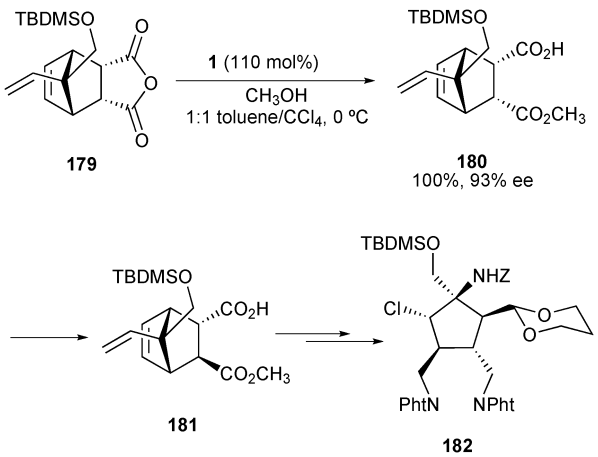


Scheme 34 Key intermediate of (+)-grandisol obtained from hemiester **19**.

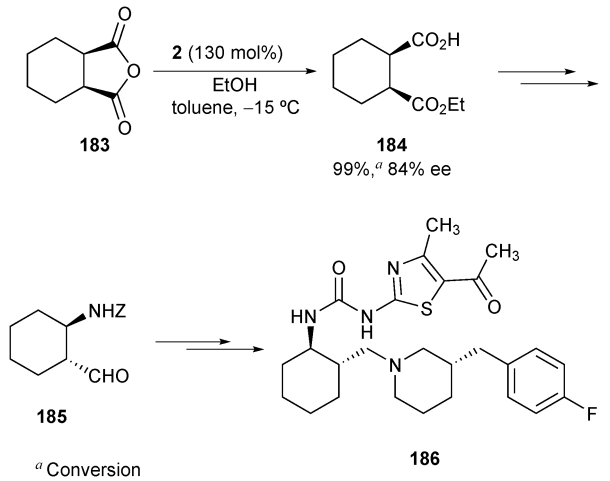
into compound **177** (Scheme 34).[94] This constitutes a formal synthesis of (+)-grandisol **178**, the main component of the sex pheromone of the cotton boll weevil used to protect cotton crops by capturing and killing populations of the insect.

Bolm's methodology for the enantioselective desymmetrization of appropriate cyclic anhydrides using a stoichiometric amount of a cinchona alkaloid has been used as the key step in the asymmetric synthesis of several chiral compounds. Enantioselective methanolysis of the cyclic anhydride **179** in the presence of quinine (110 mol%) in a 1 : 1 toluene/CCl_4 mixture of solvents at 0 °C gave methyl hemiester **180** in quantitative yield and 93% ee. The hemiester **181**, obtained by selective epimerization of **180**, was transformed into the cyclopentyl core **182** found in axinellamines A–D, which are bisguanidine alkaloids with bactericidal activity (Scheme 35).[115]

Enantioselective ring-opening of the cyclic anhydride **183** by ethanol in the presence of quinidine (130 mol%) afforded the



Scheme 35 Approach for the synthesis of the cyclopentyl core **182** found in axinellamines A–D starting from cyclic anhydride **179**.

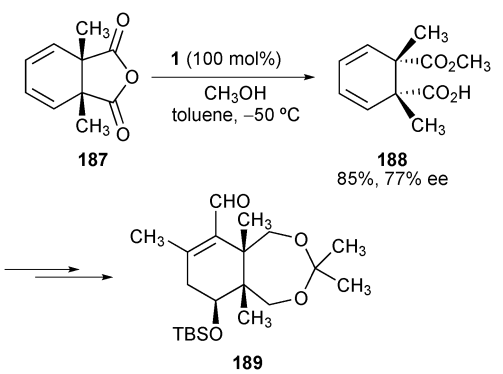


Scheme 36 Approach for the synthesis of the CCR3 antagonist **186** starting from anhydride **183**.

hemiester **184** with 99% conversion and in 84% ee. This constitutes an effective alternative to tackle the asymmetric synthesis of the amino aldehyde **185**,[116] a key fragment for the convergent multikilogram scale synthesis of the CCR3 antagonist **186** (Scheme 36). Base-promoted epimerization of the methyl hemiester **184** led to improved enantiopurity to greater than 99% ee by isolation of the corresponding (*R*)-phenylethylamine salt.

Zoanthenol is an aromatic member of the zoanthamine alkaloid family with potent anti-platelet activity for human platelet aggregation. A new approach to the synthesis of the zoanthenol C ring chiral synthon **189** uses enantioselective methanolysis of the cyclic anhydride **187** with two vicinal all carbon quaternary centres in the presence of a stoichiometric amount of quinine (100 mol%).[117] The enantioselectivity at room temperature was low (50% ee) but could be improved up to 77% ee on working at −50 °C (Scheme 37). Enantioselective methanolysis of the anhydride **187** using 10 mol% of quinidine and one equivalent of the achiral base 1,2,2,6,6-pentamethylpiperidine afforded the methyl hemiester **188** in 88% yield and with 70% ee.

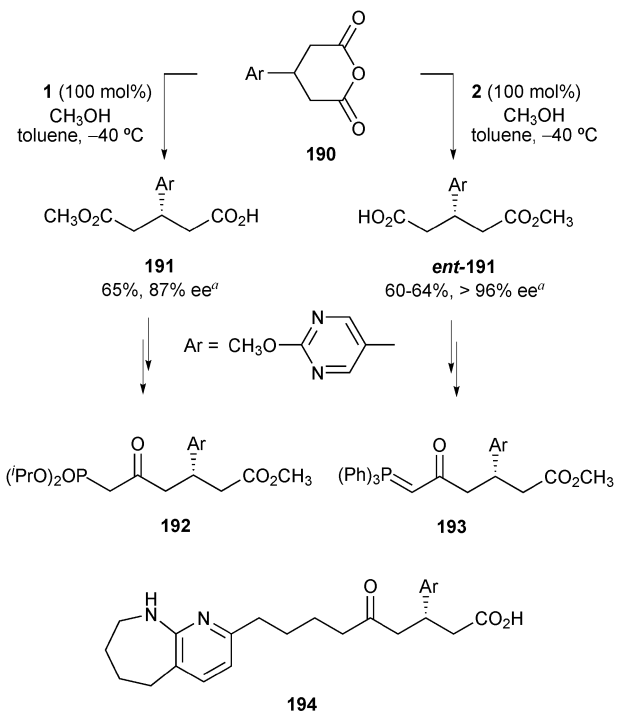
3-Arylpentanedioic acid hemiesters **191** and ***ent*-191** were used in Keen's synthesis of phosphonate **192** and phosphorane **193** and tested as key fragments in the convergent synthesis of



Scheme 37 Approach for the synthesis of the zoanthenol C ring chiral synthon **189** starting from cyclic anhydride **187**.

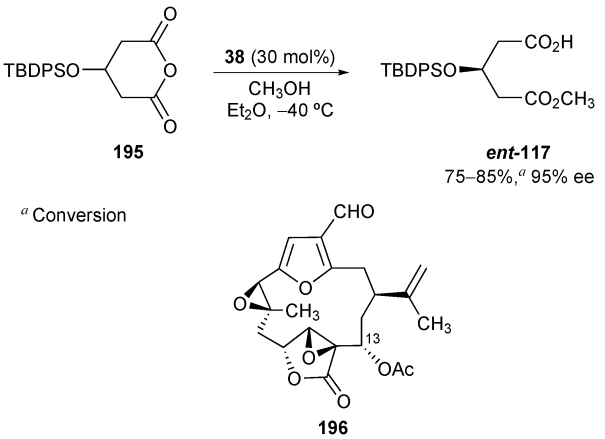
$\alpha_v\beta_3$ antagonist **194**. These hemiesters were prepared using alkaloid-mediated enantioselective methanolysis of the glutaric anhydride **190**.[118] Among the different organocatalysts and conditions tested, the best results were obtained on using stoichiometric amounts of quinine or quinidine in toluene as solvent at −40 °C. Under these conditions methanolysis of **190** afforded **191** in 58% ee or ***ent*-191** in 62% ee depending on the alkaloid used as the organocatalyst (Scheme 38). The quinine salt of **191** was filtered off at the end of the reaction and the hemiester **191** was isolated in 65% yield and with 87% ee. On the other hand, crystallization of hemiester ***ent*-191** from aqueous HCl was accompanied by an increase in enantiopurity to >96% ee for the isolated product (60–64% yield). Phosphorane **193** was a better intermediate to complete the convergent synthesis of **194** as the Wittig coupling with the corresponding aldehyde occurred in significantly higher yield than the Horner–Wadsworth–Emmons olefination reaction with phosphonate **192**.

Deng's methodology has also been applied in the asymmetric synthesis of several chiral compounds of interest. Enantioselective creation of the C13 stereocentre of the potent neuromuscular toxin lophotoxin **196** used desymmetrization of the 3-substituted glutaric anhydride **195** in the presence of a substoichiometric amount of the modified alkaloid **38** (30 mol%) (Scheme 39).[119] Working in diethyl ether as solvent at −40 °C the hemiester ***ent*-117** was obtained with very high enantioselectivity (95% ee) although conversion was not complete after 70 h. A temperature increase up to −20 °C led to compound ***ent*-117** with total conversion, albeit with lower enantiopurity (88% ee).



[a] After enantiopurity enrichment

Scheme 38 Approach for the synthesis of key chiral fragments used in the synthesis of the $\alpha_v\beta_3$ antagonist **194** starting from the anhydride **190**.

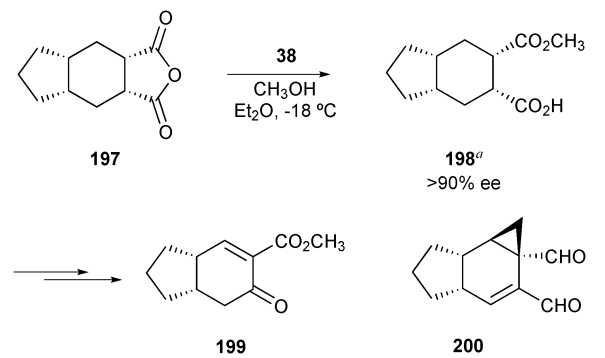


Scheme 39 Synthetic strategy for the enantioselective creation of the C13 stereocentre of lophotoxin **196** starting from the anhydride **195**.

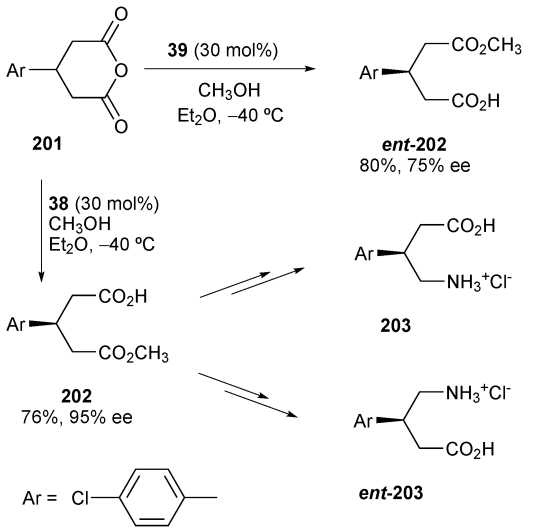
$(DHQD)_2AQN$-Catalyzed methanolysis of the cyclic anhydride **197** was the key step for asymmetric induction in the synthesis of the compound **199** (Scheme 40).[120] This compound is a formal precursor of the unsaturated 1,4-dialdehyde **200**, a synthetic analogue of the potent cytotoxic agent tridemethylisovelleral. The reaction in the presence of an undefined substoichiometric amount of **38** in diethyl ether as solvent at −18 °C afforded the hemiester **198** in more than 90% ee and a good yield.

Desymmetrization of 3-(4-chlorophenyl)glutaric anhydride **201** with methanol in diethyl ether as solvent at −40 °C using 30 mol% of **38** or **39** as the organocatalyst gave chiral hemiesters **202** and ***ent*-202** with 95% or 75% ee, respectively (Scheme 41).[121] The hemiester **202** of *S* configuration was transformed into both (*R*)-baclofen hydrochloride (**203**) and (*S*)-baclofen hydrochloride (***ent*-203**).

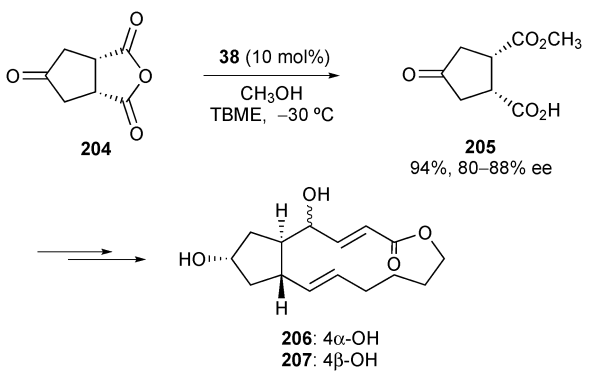
Guingant *et al.*[111,122] studied the enantioselective methanolysis of the cyclic anhydride **204** in the presence of a catalytic amount of **38** as the key step in the asymmetric total synthesis of brefeldin A analogues **206** and **207** (Scheme 42). The enantioselectivity of the anhydride methanolysis in the presence of 10 mol% of **38** according to Deng's methodology was highly dependent on the anhydride concentration, a fact that had not previously been reported. A 94% yield of the hemiester **205** with an enantiomeric excess in the range 80–88% was



Scheme 40 Approach for the synthesis of **199**, a formal precursor of the tridemethylisovelleral analogue **200**, starting from the anhydride **197**.



Scheme 41 Approach for the synthesis of (*R*)- and (*S*)-baclofen hydrochlorides (**203** and ***ent*-203**) starting from the anhydride **201**.



Scheme 42 Approach for the synthesis of brefeldin A analogues **206** and **207** starting from the anhydride **204**.

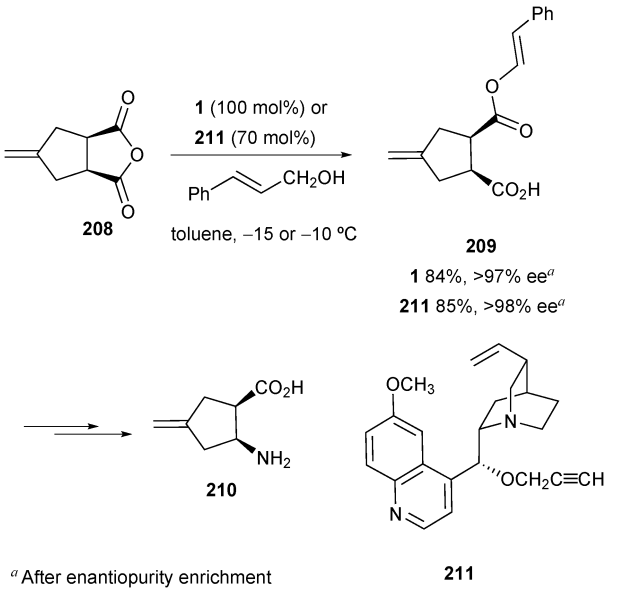
reproducibly obtained on working at −30 °C in TBME as solvent with an anhydride concentration of 0.02 M.

For some particular chiral compounds an enantioselective anhydride desymmetrization step has been performed using different organocatalysts and methodologies.

Alcoholysis of the cyclic anhydride **208** using (*E*)-cinnamyl alcohol as the nucleophile is a key step in the multikilogram scale synthesis of enantiomerically pure antifungal agent BAY 10-8888/PLD-118 **210** (Scheme 43).

The alcoholysis reaction in toluene as solvent at −15 °C and in the presence of stoichiometric amounts of quinine yielded the crude hemiester **209**, which was isolated in 84% yield and in more than 97% ee after enrichment of enantiopurity.[123,124] Attempts to perform ring-opening of the anhydride **208** with the same alcohol in diethyl ether as solvent at room temperature and using 5 mol% of organocatalyst **38** to promote the enantioselective alcoholysis afforded ***ent*-219** in 89% ee but in only 54% isolated yield.[124]

O-Propargylquinine **211**, a pseudoenantiomer of **49** (see Fig. 6), has proven to be an efficient organocatalyst for the previous enantioselective desymmetrization step.[125] Nucleophilic ring-opening of the cyclic anhydride **208** with (*E*)-cinnamyl

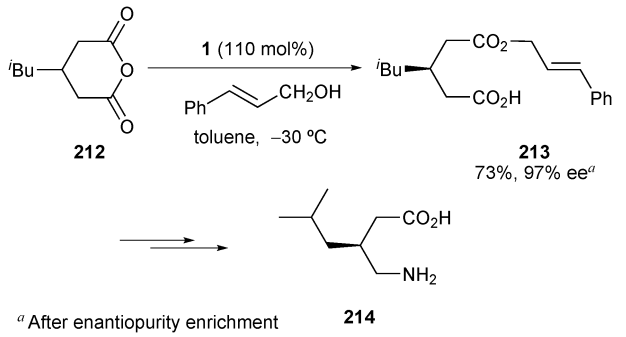


Scheme 43 Approaches for the synthesis of BAY 10-8888/PLD-118 **210** starting from cyclic anhydride **208**.

alcohol in the presence of stoichiometric amounts of **211** led to better results than those previously obtained with quinine under the same reaction conditions. In toluene as solvent at −10 °C and using 50 mol% of **211** as organocatalyst, the hemiester **209** was obtained with a yield and enantioselectivity that were comparable to those obtained with 100 mol% of quinine, but the reaction required 24 h to reach completion. The reaction time was reduced to 8 h on increasing the catalyst loading up to 70 mol% and these conditions were successfully applied on a pilot-plant scale and, after enrichment of enantiopurity, the hemiester **209** was isolated in 85% yield and more than 98% ee.

Quinine-mediated desymmetrization of 3-isobutylglutaric anhydride **212** was studied as a key step in the synthesis of (*S*)-pregabalin, an anticonvulsant drug used for the treatment of neuropathic pain.[126] After optimization of the organocatalyst loading, temperature and alcohol used as the nucleophile, the reaction on a preparative scale was performed at −30 °C in toluene as solvent with 110 mol% of quinine **1** and using (*E*)-cinnamyl alcohol as the nucleophile. Under these conditions the cinnamyl hemiester **213** was initially obtained in 72% ee. After enrichment of enantiopurity using (*S*)-phenylethylamine, the cinnamyl hemiester **213** was isolated in 73% yield and 97% ee and transformed into enantiomerically pure (*S*)-pregabalin **214** (Scheme 44).

It was observed that the stereochemical course of the enantioselective desymmetrization of 3-isobutylglutaric anhydride **212** using benzyl alcohol as the nucleophile depended on the degree of quinine loading.[127] Decreasing the organocatalyst loading from 160 mol% to 10 mol% caused an inversion of stereochemistry and the absolute configuration of the hemiester preferentially formed changed from *R* to *S*. The influence of temperature on enantioselectivity also depended on the catalyst loading. Whereas the enantioselectivity of the reaction using stoichiometric quantities of the alkaloid can be significantly improved on lowering the reaction temperature, with a low catalyst loading a decrease in



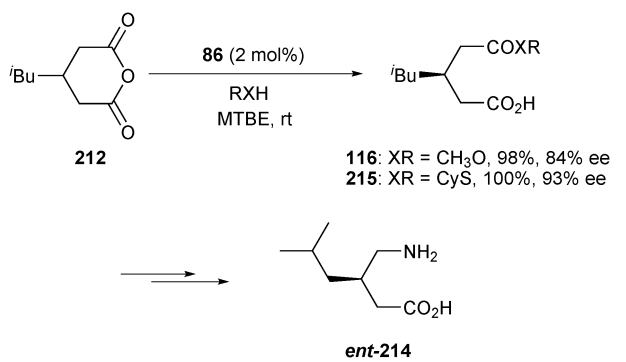
Scheme 44 Approach for the synthesis of (*S*)-pregabalin **214** starting from the anhydride **212**.

the temperature did not lead to the same improvement in enantioselectivity. On the other hand, the enantioselectivity of the reaction using 50 mol% of quinine can be increased to levels that might be of synthetic interest (63% ee) by performing the reaction in the presence of carboxylic acids as additives. In this case the influence of the acid structure was almost negligible and the stereoselectivity mainly depended on the acid pK_a.

Connon *et al.*[128] applied alkaloid-derived thioureas to the preparation of chiral key intermediates in the synthesis of both enantiomers of pregabalin. Enantioselective methanolysis of the cyclic anhydride **212** in MTBE as solvent at room temperature and in the presence of 2 mol% of thiourea-quinine alkaloid **86** yielded the methyl hemiester **116** in 98% yield and with 84% ee. Thiolysis of the anhydride with cyclohexanethiol under the same reaction conditions led to the hemithioester **215** in quantitative yield and with a better enantioselectivity (93% ee). Both methyl hemiester **116** and hemithioester **215** were transformed into the *R* enantiomer of the γ-amino acid pregabalin (Scheme 45).

Thiourea-quinidine alkaloid **216** (Fig. 28) was used to promote thiolysis of the anhydride **212** to gain access to the (*S*)-pregabalin chiral intermediate ***ent*-215**. Under the previous reaction conditions the required hemithioester was also obtained in nearly quantitative yield and with the same level of enantioselectivity (92% ee).[128]

Methanolysis of the glutaric cyclic anhydride **217** was studied as a key step in the synthesis of (*S*)-4-(4-fluorophenyl)-1,4,5,6-tetrahydro-6-oxo-3-pyridinecarboxylic acid **219**,



Scheme 45 Approaches to the synthesis of (*R*)-pregabalin ***ent*-214** starting from the anhydride **212**.

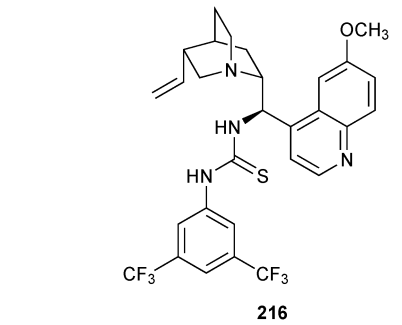
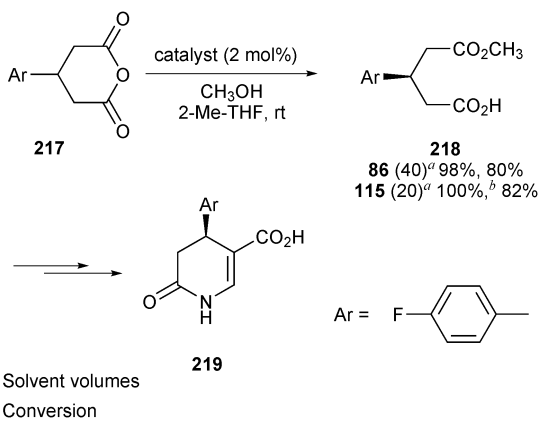


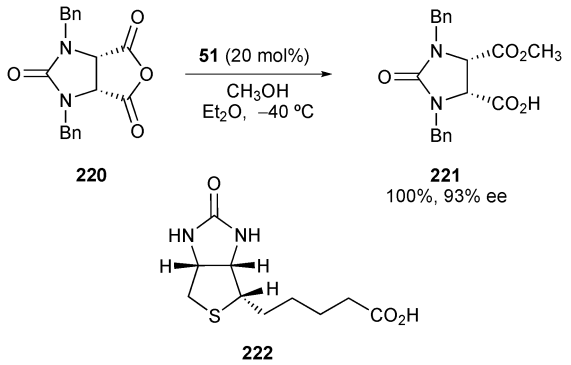
Fig. 28 Structure of the thiourea-quinidine alkaloid **216**.

the core structure of a series of $P2X_7$ antagonists. It was observed that the solvent polarity was very important to achieve good conversion and enantioselectivity levels when thiourea **86** was used to promote the reaction.[129,130] Both tetrahydrofuran and 2-methyltetrahydrofuran gave full conversion and a high enantioselectivity, with 2-methyltetrahydrofuran being the most effective reaction medium. After optimization of the anhydride concentration, the amount of methanol and the organocatalyst loading, the hemiester **218** was obtained in nearly quantitative yield and 88% ee on working at room temperature with 10 equivalents of methanol, 2 mol% of catalyst and 800 volumes of solvent. Large-scale studies were performed with 40 volumes of solvent and under these conditions the hemiester **218** was obtained in a diminished 80% ee, which could be enhanced to greater than 95% ee by treatment with a toluene/hexane mixture. In an effort to improve the enantioselectivity and reduce the solvent volume, the use of sulfonamide **115** to promote enantioselective methanolysis of the anhydride **217** was investigated.[130] Enantioselectivity was improved from 80% up to 82% ee on using half the volume of 2-methyltetrahydrofuran and working at room temperature with 10 equivalents of methanol and 2 mol% of the organocatalyst (Scheme 46).

Finally, organocatalysts derived from almost all kinds of compounds covered in this review have been tested in the enantioselective desymmetrization of commercially available cyclic anhydride **220**, directed to the synthesis of (+)-biotin **222**, one of the water-soluble B-complex vitamins. In Deng's formal synthesis of (+)-biotin some modified mono-cinchona



Scheme 46 Approaches for the synthesis of compound **219** starting from the anhydride **217**.

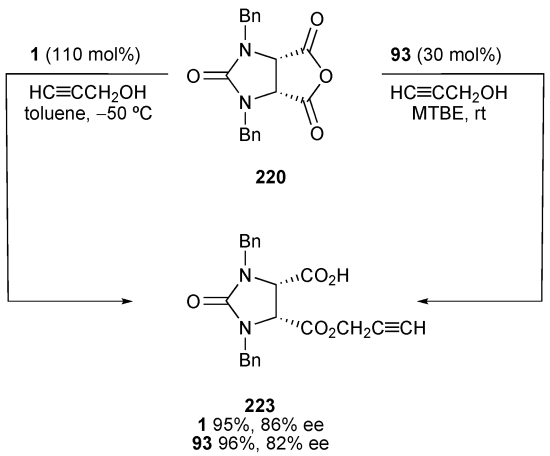


Scheme 47 Deng's approach to the synthesis of (+)-biotin **222** starting from the anhydride **220**.

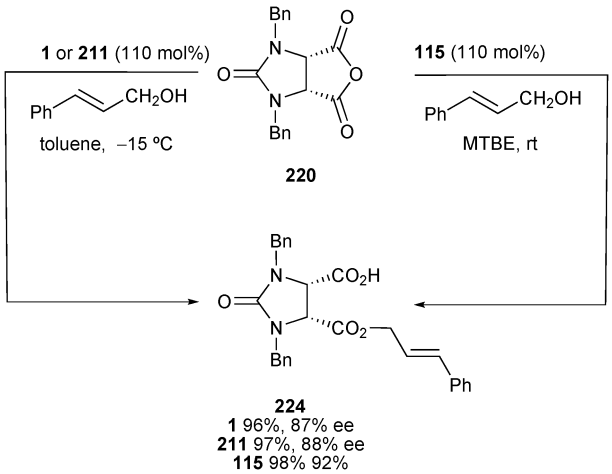
alkaloids were tested to perform the enantioselective methanolysis of anhydride **220**. Among them organocatalyst **51**, which bears a 9-phenanthrenyl side chain, led to optimal results. Working at −40 °C in diethyl ether as solvent and in the presence of 20 mol% of organocatalyst **51**, the corresponding hemiester **221** was obtained in nearly quantitative yield and 93% ee (Scheme 47).[131]

Chen *et al.*[132] optimized reaction conditions in the quinine-promoted enantioselective methanolysis of the anhydride **220**. When the reaction was performed in toluene at −50 °C and using 110 mol% of quinine **1**, the corresponding methyl hemiester was obtained in nearly quantitative yield and with good enantioselectivity (82% ee). The use of propargyl alcohol as the nucleophile enhanced the enantioselectivity of the desymmetrization reaction and the propargyl hemiester **223** was obtained in 95% yield and 86% ee (Scheme 48). When this reaction was performed in MTBE as solvent at room temperature and using 30 mol% of the thiourea derivative **93** as the organocatalyst, the hemiester **223** was obtained in 96% yield and 82% ee.[83]

The use of (*E*)-cinnamyl alcohol as the nucleophile gave excellent results in the desymmetrization of anhydride **220** on using 110 mol% of quinine **1** or *O*-propargylquinine **211**—the pseudoenantiomer of **49**—in toluene as solvent at −15 °C (Scheme 49). The yield and enantioselectivity obtained using



Scheme 48 Enantioselective alcoholysis of anhydride **220** with propargyl alcohol as the nucleophile.



Scheme 49 Enantioselective alcoholysis of anhydride **220** with (*E*)-cinnamyl alcohol.

the modified alkaloid were comparable to those obtained with quinine, *ca.* 96% yield and 87% ee, and the required reaction time was shorter.[133] Organocatalyst **211** could be easily recovered and reused without any decrease in the enantioselectivity in ten sequential reactions.

Sulfonamide-based organocatalyst **115** has also been tested in the alcoholysis of anhydride **220**.[134] Although the enantioselectivity of the methanolysis reaction in MTBE at room temperature and in the presence 10 mol% of **115** was very poor (32% ee), it could be improved using 110 mol% of organocatalyst (82% ee). This result could not be further improved on changing the solvent or the reaction temperature. The efficiency of the asymmetric alcoholysis proved to be highly dependent upon the steric properties of the nucleophile. Under optimized reaction conditions and with the use of (*E*)-cinnamyl alcohol, the corresponding cinnamyl hemiester was obtained in 98% yield and with 92% ee (Scheme 49). Further elaboration of this intermediate resulted in an improved asymmetric total synthesis of (+)-biotin that is more compatible with the industrial scale and with some advantages over previously reported syntheses.

7. Conclusions

Among the different approaches for the enantioselective synthesis of chiral compounds, asymmetric organocatalysis has started to play an important role in recent years and has quickly provided useful methodologies to perform enantioselective desymmetrization of cyclic anhydrides. Low temperatures and high catalyst loadings were usually required to obtain acceptable levels of enantioinduction for practical uses when naturally occurring alkaloids were used as organocatalysts. In the presence of a stoichiometric amount of a second achiral base the enantioselectivity remained high on using a catalytic amount of the alkaloid. The catalytic protocol was also effective in terms of yield and enantioselectivity on using modified mono- and bis-cinchona alkaloids, even at room temperature.

Recently developed bifunctional organocatalysts have proven to be highly efficient in the enantioselective desymmetrization of cyclic anhydrides. The practical use of urea- and

thiourea-based organocatalysts was hampered by the need to work at low anhydride concentrations as these organocatalysts can form hydrogen-bonded aggregates and enantioselectivity decreases with increasing concentration or decreasing temperature. Sulfonamide-based bifunctional organocatalysts did not show any dependence of reactivity and enantioselectivity on concentration and temperature. Furthermore, excellent enantioinduction was observed on working at room temperature and reducing the catalyst loadings to unprecedented levels.

Chiral hemiesters obtained by organocatalyzed enantioselective desymmetrization of cyclic anhydrides have been transformed into a variety of valuable chiral compounds. Relevant applications of this methodology have been found in the synthesis of interesting pharmaceutical compounds such as CCR3 antagonists, antifungal agent BAY 10-8888/PLD-118 and (+)-biotin on a multikilogram scale.

We believe that asymmetric organocatalysis is a valuable alternative to other methodologies previously reported to carry out anhydride desymmetrization. This augurs well for the development of new and more powerful organocatalysts for this enantioselective transformation with broader substrate scope in the near future.

Acknowledgements

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