Stereoselective Anhydride Openings

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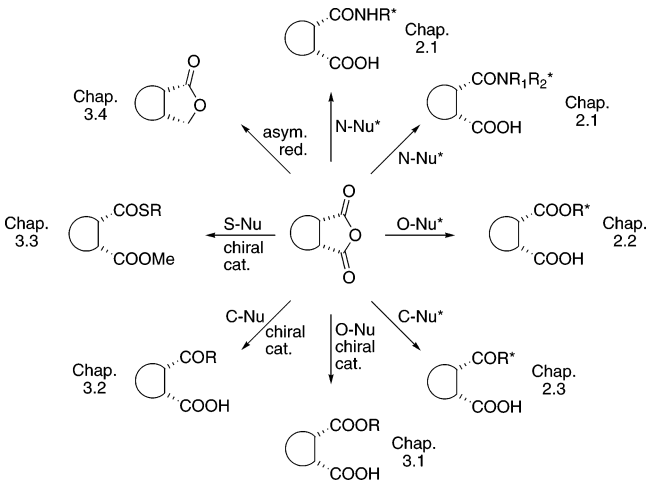
Scheme 1



1. Introduction

Desymmetrization of meso compounds to yield chiral products proved to be a powerful synthetic tool in asymmetric synthesis since it allows formation of multiple stereogenic centers in one symmetry-breaking operation.[1] In this context, considerable attention has been paid in recent years to the desymmetrization of cyclic *meso*-anhydrides,[2] leading to optically active products which are valuable building blocks particularly due to their use as intermediates in the synthesis of natural products or biologically active substances (Scheme 1). The great potential of the cyclic anhydrides as a substrate class was proven in the synthesis of chiral hemiesters, lactones, amido acids, and more recently ketoacids and thioesters. Moreover, their easy accessibility, either from commercial suppliers or by means of chemical transformations, makes them valuable for both academic as well as industrial communities.

The goal of this review is to give a comprehensive overview on well-established as well as newly developed strategies in the field of anhydride desymmetrization. In this context we will limit the discussion to the diastereo- and enantioselective desymmetrization of cyclic *meso*-anhydrides and highlight related synthetic applications. Parallel kinetic resolution of asymmetrically substituted racemic cyclic anhydrides as well as parallel and dynamic kinetic resolution of *N*- and *O*-carboxy anhydrides have recently been summarized[1c,2b,3] and are regarded as beyond the scope of this review.

2. Diastereoselective Anhydride Opening

Several attempts toward the development of a highly diastereoselective anhydride opening are described in the

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Iuliana Atodiresei was born in 1977 in Radauti (Romania). She studied chemistry at the Al. I. Cuza University of Iasi (Romania), where she received her B.Sc. and M.Sc. degrees in 1999 and 2001, respectively. During her master studies she spent 9 months at the TU Braunschweig (Germany) as a Socrates exchange student, performing research in the field of cross-conjugated compounds under the supervision of Professor Hopf. In 2001 she joined the group of Professor Bolm at the RWTH Aachen University (Germany), where she carried out her doctoral studies in the field of anhydride desymmetrization. After receiving her Ph.D. degree in 2005, she spent 18 months in the group of Professor Raabe, focusing on theoretical and computational chemistry. Since 2007 she has been working with Professor Bolm and Professor Raabe, being involved in the determination of the absolute configuration of organic molecules by means of theoretical investigations and CD spectroscopy.

Ingo Schiffers was born in 1970 in Mönchengladbach (Germany). He studied chemistry at the RWTH Aachen University (Germany), where he received his doctoral degree in 2002 under the supervision of Professor Carsten Bolm. His dissertation research involved organocatalysis and asymmetric synthesis of beta amino acids. He is currently holding a permanent researcher position in the group of Professor Bolm.

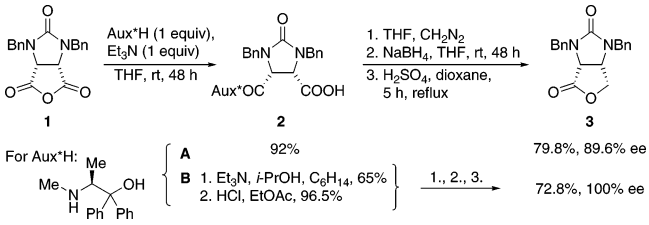
Carsten Bolm was born in Braunschweig in 1960. He studied chemistry at the TU Braunschweig (Germany) and the University of Wisconsin, Madison. In 1987 he obtained his doctorate with Professor Reetz in Marburg (Germany). After postdoctoral training with Professor Sharpless at MIT, Cambridge, MA, he worked in Basel (Switzerland) with Professor Giese to obtain his habilitation. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he has been Chair of Organic Chemistry at the RWTH Aachen (Germany). At the universities in Madison, WI, Paris (France), Florence (Italy), Milan (Italy), Namur (Belgium), and Tokyo (Japan) he held visiting professorships. His awards include the Heinz-Maier-Leibnitz prize, the ADUC-Jahrespreis for habilitands, the annual prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, the Otto-Klung prize, the Otto-Bayer award, and a fellowship of the Japan Society for the Promotion of Science and the Prix Franco-Allemand by the Société Francaise de Chimie.

literature, and chiral alcohol and amine nucleophiles are known to undergo reaction with low to excellent diastereoselectivity. The advantage of the above-mentioned technique consists in the availability of a large range of methods suitable for separation of the two diastereoisomeres. The main drawback is the requirement of stoichiometric amounts of chiral substances which are not always part of the target molecule and have to be removed after establishment of the stereogenic centers.

2.1. Diastereoselective Anhydride Opening with Nitrogen Nucleophiles

The first approach toward a diastereoselective process dates back to 1954 when Carter subjected the 3-phenylglutaric anhydride to reaction with (*S*)-1-phenylethylamine.[4] The crystalline product was isolated in 95% yield and in a 3:2 diastereomeric ratio. Despite low selectivity this is one of the first reports on a nonenzymatic desymmetrization process. Almost three decades later, in 1981, scientists at Sumitomo reported on the desymmetrization of *cis*-1,3-dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**1**) with various chiral secondary amines to yield the corresponding imidazolidin-2-one derivatives which were subsequently converted into the appropriate lactone in satisfactory overall yields and up to 89.6% ee (Scheme 2, **A**).[5] Crystallization of the amide

Scheme 2

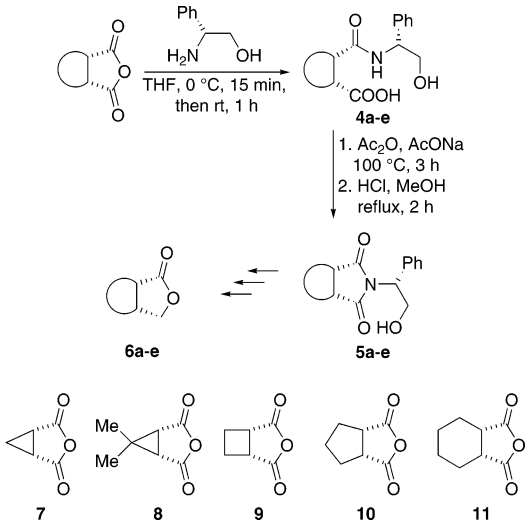


acid intermediate **2** obtained from the reaction of **1** with (*S*)-*N*-methyl-2-amino-1,1-diphenyl-1-propanol followed by esterification, reduction, and cyclization allowed formation of the desired lactone **3** in enantiomerically pure form (Scheme 2, **B**).

Mukaiyama described the opening of several bicyclic anhydrides with (*R*)-2-amino-2-phenylethanol followed by conversion of the amide acids into the corresponding chiral imides (67−90%).[6] Subsequent selective reduction, acid-catalyzed hydrolysis, and cyclization furnished the appropriate lactones with moderate to good enantioselectivities (58−88% ee) in good overall yields (60−75%) (Table 1).

Although in this particular case the reduction of imides **5a**−**e** and not the anhydride opening determines the stereochemistry of the products, it is mentioned here since the approach is of high synthetic value as illustrated by the four-

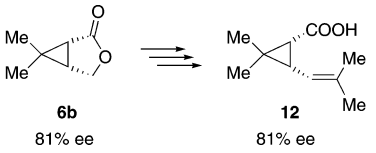
Table 1. Anhydride Desymmetrization with (*R*)-2-Amino-2-phenylethanol



entry	anhydride	imide	yield (%)	lactone	yield (%)[a]	ee (%)
1	**7**	**5a**	90	**6a**	60	58
2	**8**	**5b**	67	**6b**	64	81
3	**9**	**5c**	82	**6c**	70	69
4	**10**	**5d**	78	**6d**	71	69
5	**11**	**5e**	68	**6e**	75	88

[a] Yield over three steps, starting from imide.

step synthesis of optically active (1*R*,3*S*)-*cis*-chrysanthemic acid (**12**) starting from lactone **6b** (eq 1).



(1)

In 1984, Oda reported on the ring opening of *meso*-2,4-dimethylglutaric and 3-hydroxy-3-methylglutaric anhydrides with axially chiral binaphthyldiamine derivatives, the amide acids being obtained in good to high selectivity (60−92% de).[7] Efforts toward extending the method to other substrates were less successful, and the products were obtained with lower diastereomeric excesses (24−58% de).[8]

Nagao reacted *meso*-2,4-dimethylglutaric anhydride with two equivalents of the (4*R*)-4-methoxycarbonyl-1,3-thiazolidine-2-thione (**14**) to give the corresponding diamide **15** which, on aminolysis with piperidine, afforded the diamides **16** and **17** in 66% yield and 97.5:2.5 ratio (Scheme 3).[9] Recrystallization from CH_2Cl_2−petroleum ether afforded the major product **16** in a pure form. Furthermore, **16** was reacted with various nucleophiles, yielding enantiomerically pure products which are useful precursors in the total synthesis of several natural products. On the basis of data from X-ray crystallography the authors assumed that the piperidine nucleophile attacked predominantly the carbonyl group attached to the (*S*) stereogenic center. It should be noted that the same protocol has also been successfully applied to diverse symmetrically substituted diacids, leading to optically pure products in good overall yields.[10]

Later a direct desymmetrization process was developed, which implied use of the sodium salt of (4*S*)-4-isopropyl-1,3-thiazolidine-2-thione as nucleophile.[11] Addition of a freshly prepared THF solution of the sodium salt of the thiazolidinone **19** to a solution of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (**21**) in THF at low temperature followed by acidic workup gave the crude amide acid which was subsequently treated with diazomethane to give the corresponding amide ester **20a** in 96% yield and 86% de (Table 2, entry 1). Screening of various additives showed a strong dependence of the reaction on the nature of these additives. Although the yield decreased (80% vs 96%), the diastereomeric excess improved (94% vs 86%) using a stoichiometric amount of DMSO as additive (Table 2, entry 2). Carrying out the reaction in the presence of HMPA, 18-crown-6, or TMEDA was less efficient with respect to the yield and/or selectivity (Table 2, entries 3−5). Regarding the mechanism, it was assumed that the sodium salt attacked the pro-(*S*) site carbonyl carbon from its least hindered side, whereas approach of the pro-(*R*) site was sterically unfavored. In order to extend the substrate scope, other anhydrides were tested in the reaction described above with and without DMSO as additive, but they always occurred with lower yield and selectivity (Table 2, entries 6−11).

Ward described the desymmetrization of a *meso*-2,3-dibenzylbutanedioic acid anhydride with (*R*)-1-phenylethylamine, the corresponding amide acid being obtained as white crystals in 62% yield and 86% de.[12]

Scheme 3

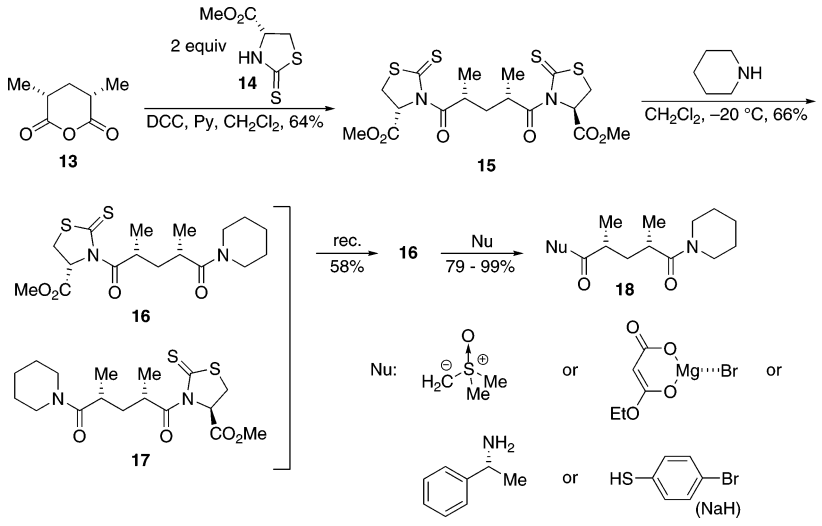
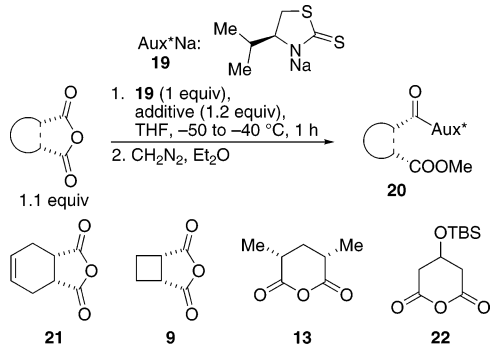


Table 2. Anhydride Desymmetrization with (4*S*)-4-Isopropyl-1,3-thiazolidine-2-thione



entry	anhydride	additive	yield (%)	de (%)
1	**21**	none	96	86
2	**21**	DMSO	80	94
3	**21**	HMPA	48	96
4	**21**	TMEDA	68	82
5	**21**	18-crown-6	6	76
6	**9**	none	81	62
7	**9**	DMSO	85	68
8	**13**	none	87	28
9	**13**	DMSO	86	46
10	**22**	none	62	40
11	**22**	DMSO	46	16

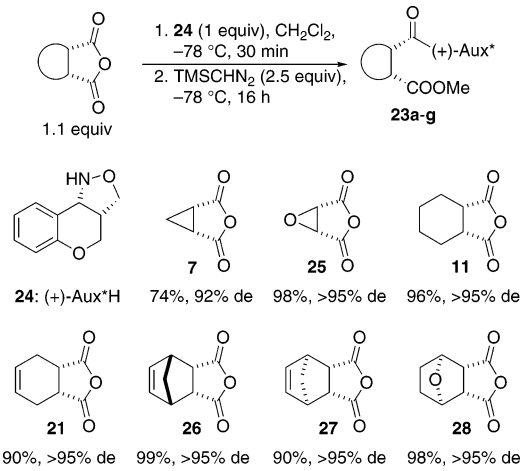
The desymmetrization of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride using proline esters as chiral nucleophiles was reported by Noth.[13] The process has been successfully applied to the synthesis of peptides and pseudopeptides incorporating an *endo*-(2*S*,3*R*)-norborn-5-ene residue.[14] Unfortunately, proline cannot be cleaved and replaced by other amino acids, so that this synthetic approach is limited to molecules containing proline at the first position of one peptide strand. In addition, the protocol suffers from strong substrate limitations in that any attempts to extend the methodology to bicyclic anhydrides resulted in poor or no asymmetric induction.[15]

Ghosh described the desymmetrization of 3-substituted glutaric and 3,4-bis-substituted adipic acid anhydrides with the lithium salt of Evans' oxazolidinones.[16] Notably, this work includes the only known example concerning the asymmetric ring opening of a seven-membered monocyclic anhydride. Although the reactions occur with low selectivity even under optimized conditions (20−34% de), the diastereomeric amide acids and their corresponding methyl, benzyl, and *tert*-butyl esters are easily separable by fractional crystallization and/or chromatographic methods. In addition, the oxazolidinones can be fully recovered in analytically pure form. Furthermore, the method has found application in the total synthesis of the antifungal agent (+)-preussin.[17]

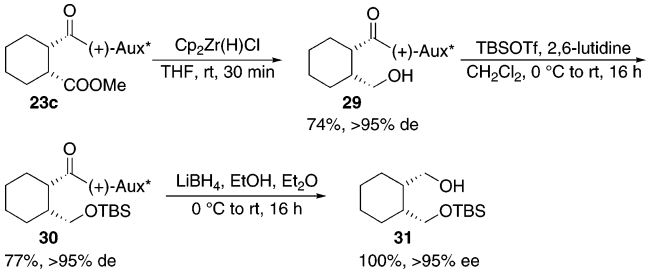
In light of these results, the desymmetrization process reported recently by Ley constitutes a significant achievement in the field.[18] As depicted in Scheme 4, upon treatment with chiral isoxazole **24** and subsequent trapping with TMS−diazomethane, various bi- and tricyclic anhydrides have been converted into the corresponding amide methyl esters **23a**−**g** in high yields (74−99%) and with high to excellent selectivities (92->95% de).

The synthetic usefulness of the method was demonstrated by conversion of the amido ester **23c** into the corresponding monoprotected 1,4-diol (Scheme 5). Selective reduction of the methyl ester moiety with Schwartz reagent followed by alcohol protection and reductive cleavage of the chiral auxiliary leads to the 1,4-monoprotected diol **31** in good overall yield and excellent enantioselectivity (> 95% ee).

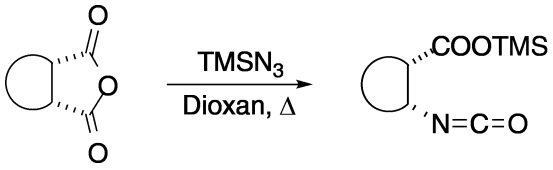
Scheme 4



Scheme 5



Although the ring opening of cyclic *meso*-anhydrides with silyl azides to yield isocyanato carboxylic acid silyl esters has been reported by several groups (eq 2),[19] an asymmetric version of this interesting transformation has yet not been provided.



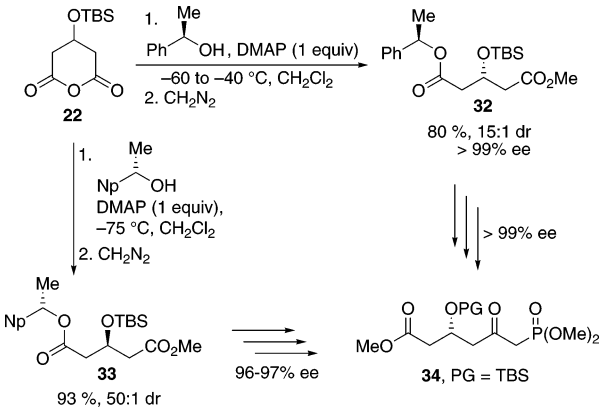
(2)

2.2. Diastereoselective Anhydride Opening with Oxygen Nucleophiles

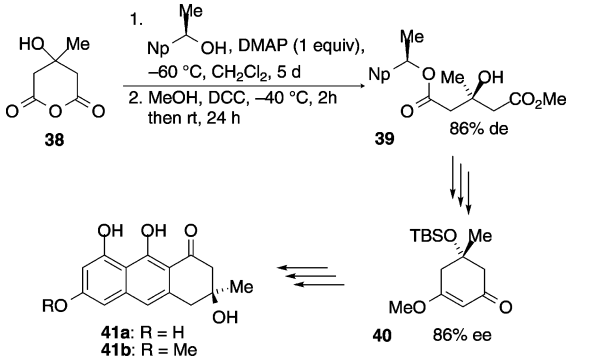
Several reports focus on addition of chiral *O*-based nucleophiles such as alcohols, diols, aminoalcohols, and hydroxyacids to *meso*-anhydrides. This reaction offers access to diastereomeric hemiesters and was explored for the first time by Cohen in the mid-1950s.[20] For this purpose 3-phenylglutaric anhydride was examined in the reaction with L-menthol, but the product was obtained with poor selectivity.

The first significant achievements in the field were reported by Heathcock.[21] In an initial study, addition of (*R*)-1-phenylethanol to 3-[(*tert*-butyldimethylsilyl)oxy]glutaric anhydride (**22**) in the presence of achiral amine bases was investigated under various conditions. Subsequent esterification with diazomethane yields the corresponding diester **32** in good overall yields. The best result (80% yield, 15:1 dr) was achieved when the opening reaction was carried out in dichloromethane at −40 °C in the presence of DMAP (1 equiv) as base (Scheme 6).[21b] The two diastereomeric diesters are easily separable by preparative HPLC and have been used

Scheme 6



Scheme 7

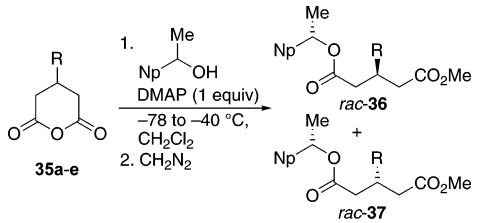


together with their corresponding enantiomers as synthons in the total synthesis of compactin and several compactin structural analogs.[21a,b] A further improvement was achieved when (*R*)-1-phenylethanol was substituted by (*S*)-1-naphthylethanol, the appropriate diester **33** being obtained in a very high yield (93%) and excellent selectivity (50:1 diastereomeric ratio) (Scheme 6).[21c]

In order to enlarge the substrate scope, several 3-substituted glutaric anhydrides **35** were tested in reactions with racemic 1-naphthylethanol to give hemiesters, which have been converted into the corresponding racemic diesters **36** and **37** by treatment with diazomethane.[22] As depicted in Table 3, the level of diastereoselectivity proved to be highly dependent on the size of the substituents and decreased considerably with increasing the steric bulk.

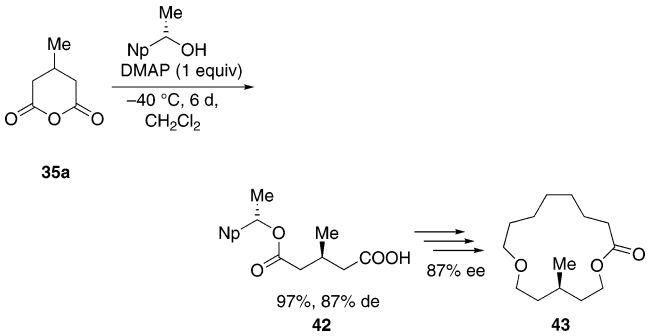
Recently, Müller extended this methodology to the desymmetrization of 3-hydroxy-3-methylglutaric anhydride (**38**)

Table 3. Diastereoselective Anhydride Desymmetrization with Racemic 1-Naphthylethanol



entry	anhydride	R	yield (%)	dr (**36**:**37**)
1	**35a**	Me	94	16:1
2	**35b**	Et	95	14:1
3	**35c**	*i*-Pr	97	7:1
4	**35d**	Ph	92	8:1
5	**35e**	*t*-Bu	91	1:3

Scheme 8



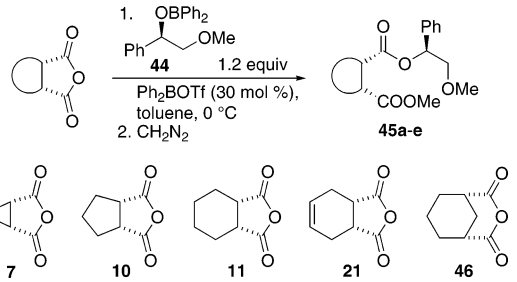
(Scheme 7).[23] The chiral diester **39** obtained in this fashion was used as precursor in the total synthesis of (*S*)-atrochrysone (**41a**) and (*S*)-torosachrysone (**41b**),[24] two key intermediates in the synthesis of dimeric pre-anthraquinone pigments which are commonly isolated from fungi and higher plants.

A de of 87% was observed in the opening of 3-methylglutaric anhydride (**35a**) with (*S*)-1-naphthylethanol, and the product was applied in the synthesis of a new powerful oxamacrolide musk odorant **43** (Scheme 8).[25]

Mukaiyama reported on a boron-catalyzed desymmetrization of bicyclic *meso*-anhydrides with (*R*)-1-phenylethanol derivatives as chiral source.[26] The strategy was based on the possibility of activating the anhydride by diphenylboryl triflate followed by selective esterification of one of the two enantiotopic carbonyl groups. With cyclohexane-1,2-dicarboxylic anhydride (**11**) as test substrate, the best results were obtained when the reaction was carried out in toluene at 0 °C and (*R*)-2-methoxy-1-phenylethanol diphenylborate was employed as nucleophile. Subsequent treatment with diazomethane afforded the corresponding diester **45c** as a single diastereomer (99% de), albeit in moderate yield (59%) (Table 4, entry 3). The yield could be considerably increased (90%) when two equivalents of **44** were used in the reaction (Table 4, entry 4). The method was successfully extended to other bicyclic anhydride substrates, the products being obtained in good yields (75−95%) and moderate to excellent diastereoselectivities (40−99% de) (Table 4, entries 1, 2, 5, and 6).

In the search for a convenient route for the synthesis of optically pure *cis*- and *trans*-hemiesters with a norbornene

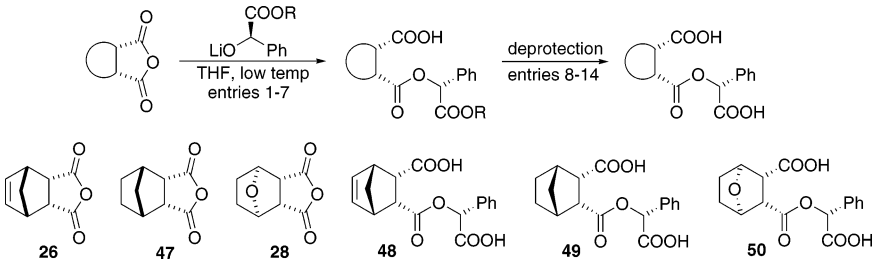
Table 4. Diphenylboryl Triflate-Catalyzed Anhydride Desymmetrization



entry	anhydride	diester	yield (%)	de (%)[a]
1	**7**	**45a**	91	40
2	**10**	**45b**	75	70
3[b]	**11**	**45c**	59	99
4	**11**	**45c**	90	99
5	**21**	**45d**	95	90
6	**46**	**45e**	90	90[c]

[a] Backbone stereochemistry: (1*S*,2*R*). [b] 1 equiv of **44** was used in the reaction. [c] Backbone stereochemistry was not determined.

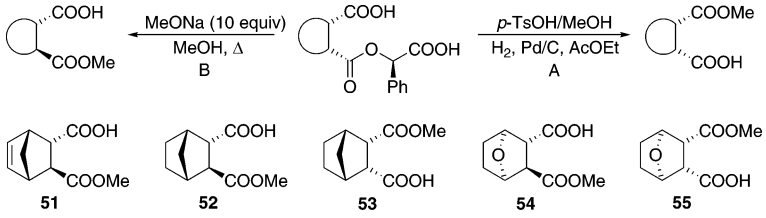
Table 5. Diastereoselective Anhydride Derivatization with Mandelic Acid Derivatives



entry	anhydride	hydroxy acid ester; R =	temp (°C)	de (%)	entry	dep.[a]	diacid[b]	yield[c] (%)	de[d] (%)
1	**26**	(*R*), PMB	−35	70	8	A	**48**-(2*R*,3*S*)	50.2	100
2	**26**	(*S*), Bh[e]	−78	48	9	B	*ent*-**48**-(2*S*,3*R*)	47.0	100
3	**26**	(*R*), Bn	−78	72	10	C	**49**-(2*R*,3*S*)	65.0	100
4	**47**	(*R*), Bn	−65	74	11	C	**49**-(2*R*,3*S*)	66.0	100
5	**47**	(*S*), PMB	−35	72	12	A	*ent*-**49**-(2*S*,3*R*)	65.5	100
6	**28**	(*R*), Bn	−65	46	13	C	**50**-(2*S*,3*R*)	66.0	97
7	**28**	(*S*), Bn	−65	48	14	C	*ent*-**50**-(2*R*,3*S*)	65.5	97

[a] Deprotection: A, conc HCl in CH_3CN; B, CF_3COOH in anisole; C, H_2 and Pd/C in MeOH. [b] Backbone stereochemistry. [c] Overall yield, after crystallization, starting from anhydride. [d] After crystallization. [e] Bh = benzhydryl.

Table 6. Efficient Synthesis of *cis*- and *trans*-Methylmonoesters



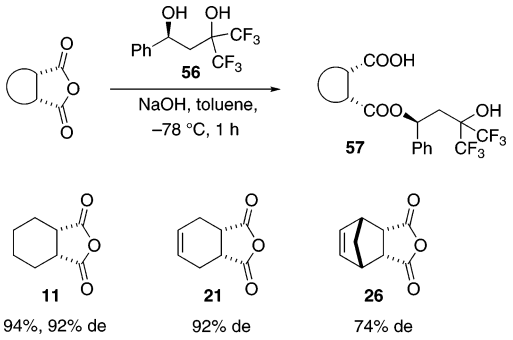
entry[a]	diacid	method	hemi-ester	yield (%)	ee (%)	entry[a]	diacid	hemi-ester	yield (%)	ee (%)
1	**48**	B	**51**	93	99.8	6	*ent*-**48**	*ent*-**51**	94	99.8
2	**49**	B	**52**	94	97.4	7	*ent*-**49**	*ent*-**52**	95	99.8
3	**49**	A	**53**	80	>99.9	8	*ent*-**49**	*ent*-**53**	88	>99.9
4	**50**	B	**54**	50	96.0	9	*ent*-**50**	*ent*-**54**	50	95.2
5	**50**	A	**55**	82	97.0	10	*ent*-**50**	*ent*-**55**	78	97.0

[a] The methods applied for the reactions listed in the entries 6−10 are the same as for the synthesis of the corresponding enantiomers, entries 1−5.

and a norbornane-type backbone, Ohtani selected several mandelic acid derivatives and tested their efficiency in the ring-opening reaction of tricyclic anhydrides.[27] As highlighted in his study, the best results were obtained upon treatment of the anhydrides with the lithium salt of benzyl, benzhydryl, or *p*-methoxybenzyl mandelate at low temperature in THF (Table 5, entries 1−7). Subsequent deprotection followed by crystallization afforded the appropriate diacids **48**−**50** in good overall yields and excellent diastereoselectivities (97−100% de) (Table 5, entries 8−14). Attempts toward extending the desymmetrization methodology to 3-substituted glutaric anhydrides remained less successful.[28]

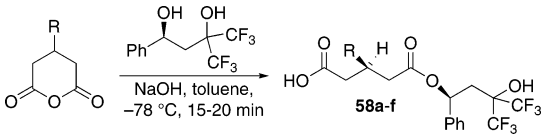
Furthermore, the diacids **48**−**50** were readily converted into the corresponding *cis*- and *trans*-hemiesters by two independent pathways. As presented in Table 6, while esterification followed by catalytic hydrogenolysis provides access to the desired *cis*-hemiesters (route A), selective epimerization and esterification in the presence of an excess amount of sodium methoxide (10 equiv) offers access to the *trans*-hemiesters without loss of selectivity (route B). It should be noted that gradual addition of an insufficient amount of sodium methoxide (2.5 equiv) to a refluxing solution (MeOH:THF = 2:1) of *cis*-diacid **49** afforded the trans product **52** in a racemic form. It is assumed that racemization takes place through an intramolecular cyclization reaction followed by a nonselective methanolysis and epimerization. Decreasing the amount of methoxide to 1.8 equiv induced no epimerization and caused total racemization of the *cis*-hemiester. However, the problem could be circumvented by dropping diacid **49** into a large excess of concentrated sodium methoxide (3−10 equiv) in refluxing methanol.

Scheme 9



Modest to high levels of asymmetric induction were attained by Taguchi in the opening of various bi- and tricyclic anhydrides (Scheme 9) and several 3-substituted glutaric anhydrides (Table 7) with the monosodium salt of 1-phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol (**56**).[29] Nonpolar sol-

Table 7. Diastereoselective Ring Opening of Glutaric Anhydrides with 1-Phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol



entry	anhydride	R	hemiester	yield (%)	de (%)
1	**22**	OTBS	**58a**	90	92
2	**35a**	Me	**58b**	90	66
3	**35c**	*i*-Pr	**58c**	94	90
4	**35d**	Ph	**58d**	95	66
5	**35f**	CF_3	**58e**	95	90
6	**35g**	Bn	**58f**	96	76

vents and the presence of the two geminally trifluoromethyl groups on the nucleophile proved to be crucial for accomplishing a clean and fast reaction.

The sense of asymmetric induction was constant in the set of monocyclic anhydrides, and higher selectivities were achieved when more sterically bulky substituents were present on the substrate (Table 7).

Kunieda achieved high diastereoselectivity in the ring opening of a variety of bi- and tricyclic anhydrides using lithium complexes generated in situ from various sterically hindered chiral *N*-sulfonylamino alcohols (Table 8).[30] A significant increase in the diastereoselectivity was observed when hexamethylphosphoric triamide (HMPA) was employed as additive. For example, the cyclohexane hemiester **59c** was obtained in 93% yield and 99% de using the lithium salt of the corresponding bulky 2,4,6-triisopropylbenzenesulfonyl amino alcohol **63** and 5 equiv of HMPA at −78 °C in THF (Table 8, entry 3). Interestingly, use of the zinc salt as nucleophile resulted in formation of the other diastereomer. Accordingly, both diastereomers could be selectively synthesized using different metal salts of the same chiral amino alcohol.

Although less selective in the case of cyclohexane-1,2-dicarboxylic anhydride (**11**) (92% de) (Table 8, entry 6), the lithium salt of the chiral *N*-TPS-aminoalcohol **62** proved highly effective for discrimination of the two carbonyl groups in the case of the tricyclic anhydrides, affording the corresponding hemiesters in high yields (84−99%) and excellent diastereomeric excess (98−99% de) (Figure 1).

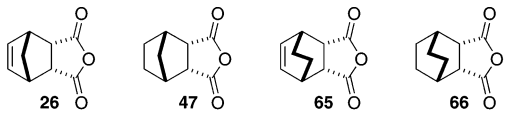
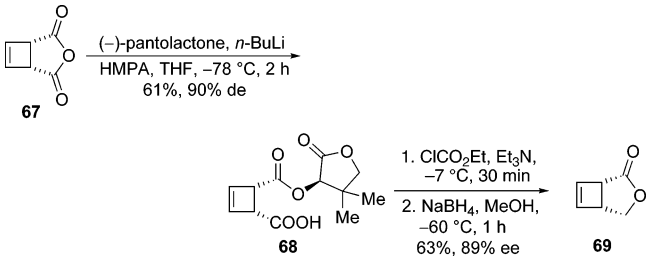


Figure 1.

An isolated example, presenting the opening of *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride (**67**) with (−)-pantolactone as a key step in a nonenzymatic alternative route to (+)-3-oxabicyclo[3.2.0]hept-6-en-2-one (**69**), was briefly described by Huet (Scheme 10).[31]

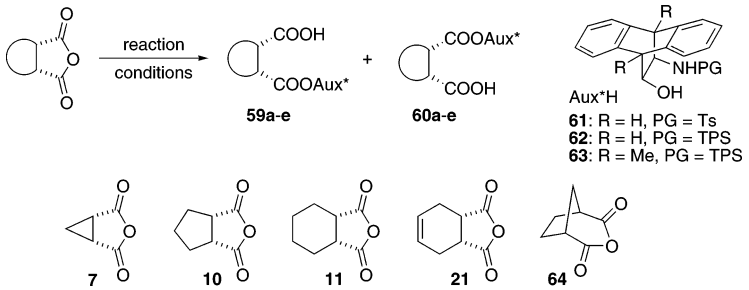
Scheme 10



In a recent study, Dai describes the synthesis of racemic 2-substituted *N*,*N*-dialkyl-1-naphthamides followed by resolution into enantiomerically pure compounds and their application in the ring opening of bicyclic anhydrides.[32]

Considerable attention has also been paid to the desymmetrization of *cis*-1,3-dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**1**) with various chiral secondary alcohols. In this context, a highly diastereoselective process has been developed by Pauling and Wehrli at Hoffmann-La Roche.[33] It was found that several (*S*)-alcohols with the general formula RMeCHOH are able to discriminate between the two anhydride carbonyl groups (Table 9), leading to the

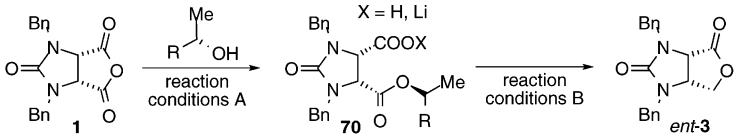
Table 8. Diastereoselective Anhydride Desymmetrization with Chiral *N*-Sulfonylamino Alcohols

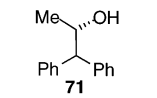
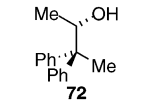
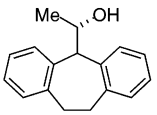
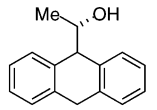
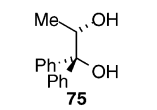


	BuLi/aminoalcohol **63** (1:1) HMPA (5 equiv), THF, −78 °C, 2 h					$ZnEt_2$/aminoalcohol **61** (1:1) no additive, CH_2Cl_2, 24 h				
entry	anhydride	hemi-ester	yield (%)	dr **59**:**60**	de (%)	hemi-ester	temp (°C)	yield (%)	dr **59**:**60**	de (%)
1	**7**	**59a**	95	500:1	>99	**60a**	reflux	85	1:1.3	13
2	**10**	**59b**	78	500:1	>99	**60b**	25	82	1:4	60
3	**11**	**59c**	93	>500:1	>99	**60c**	reflux	85	1:26[a]	93
4	**21**	**59d**	93	>500:1	>99	**60d**	25	89	1:17	89
5	**64**	**59e**	81	28:1[b]	93	**60e**	25	90	1:22	91
6	**11**	**59c**	93	22:1[c]	92	**60c**				
7	**21**	**59d**	91	20:1[c]	91	**60d**				
8	**64**	**59e**				**60e**	25		1:38[d]	95

[a] THF (1 equiv), 6 h. [b] Aminoalcohol **61**/BuLi (2 equiv) and LiCl (2 equiv) used as additive, 3 h. [c] Reaction performed in the presence of aminoalcohol **62**. [d] 2 equiv of $ZnEt_2$.

Table 9. Influence of Alcohol Structure on the Ring Opening of *cis*-1,3-Dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione



entry	alcohol	reaction conditions	lactone, ee (%)	
1	 **71**	A. Toluene, (*S*)-1,1-diphenylpropan-2-ol (1 equiv), DABCO (0.5 equiv), –10 °C, 18 h, rt, 1 h, HCl B. $LiBH_4$ (2 equiv), THF, Et_3N (1 equiv), 40 °C, 2 h HCl, 70 °C, 30 min	95.8	98.7[a]
2	 **72**	A. Toluene, (*S*)-3,3-diphenyl-2-butanol (1 equiv), reflux, 6 h, Et_3N (1 equiv), THF B. $LiBH_4$ (2.4 equiv), THF, 40 °C, 14 h 10 °C, HCl, 60 °C, 30 min	86.5	95.2[a]
3	 **73**	A. THF, (+)-10,11-dihydro-α-methyl-5H-dibenzo-[a,d]cycloheptene-5-methanol (1 equiv), Et_3N (1 equiv), rt, 18 h, HCl B. $LiBH_4$ (2.3 equiv), THF, Et_3N (1 equiv), 40 °C, 2.5 h, 10 °C, HCl, 60 °C, 30 min	85.0	95.0[a]
4	 **74**	A. THF, (+)-9,10-dihydro-α-methyl-9-anthracene-methanol (1 equiv), Et_3N (1 equiv), rt, 18 h B. $LiBH_4$ (1.9 equiv), THF, 40 °C, 2 h 10 °C, HCl, rt, 24 h	83.2	94.2[a]
5	 **75**	A. (*S*)-1,1-diphenyl-1,2-propandiol (1 equiv), toluene, –5 °C, Bu_3N (1 equiv), 0 °C, 1 h rt, 1 h, 1N LiOH, 4 h B. $LiBH_4$ (1.3 equiv), THF, 10 M H_2O in THF, 20 °C, 4h, 40 °C, 2 h, H_2O HCl, 90 °C, 1 h	98.5	

[a] After recrystallization.

corresponding chiral hemiesters which upon reduction and cyclization afforded the (3a*S*,6a*R*)-lactone *ent*-**3** in up to 95.8% ee (Table 9, entries 1−4). A single recrystallization from isopropanol raised the enantiomeric excess to 98.7% (Table 9, entry 1). Although highly diastereoselective, the process is less attractive for the large production scale since it requires several additional steps for isolation of the hemiester intermediate and involves tedious purifications, which are essential for recovery of the water-soluble amine base catalysts. A considerable improvement has been achieved by switching to water-insoluble amine base catalysts such as tributyl- or trioctylamine. This process allowed purification of the intermediates just by simple filtration and washing.[34] Accordingly, the trioctylammonium salt of the hemiester obtained in the ring opening of anhydride **1** with the chiral diol **75** was isolated as a single diastereomer (100% de) in 89% yield. Analogously, the tributylamonium salt has been obtained in 97.6% de directly after the reaction (99.8% de after isolation). In situ conversion of the tributylamonium salt into the lithium salt proceeded cleanly and afforded the product in 96% yield and 98.7% de. Subsequent ester reduction and cyclization led to the desired lactone, a key intermediate in the synthesis of (+)-biotin,[35] with excellent selectivity (98.5% ee) (Table 9, entry 5).

A similar approach has been described by scientists at Merck. They obtained the hemiesters in moderate to good selectivity when chiral β-amino alcohols were employed as auxiliaries in the reaction.[36] In the case of (−)-*N*-methylephedrine the selectivity could be increased from 78% to 98.6% de by crystallization. Subsequent reduction and cyclization, followed by recrystallization, afforded the desired lactone in good overall yield and 99.9% ee.

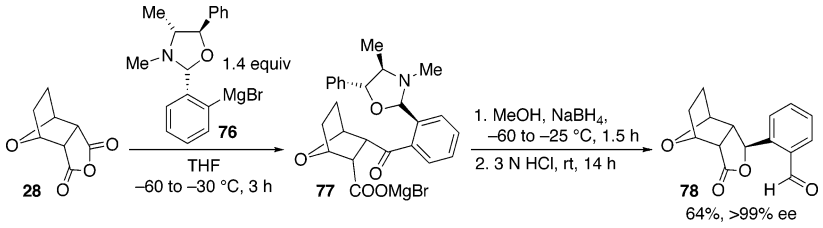
2.3. Diastereoselective Anhydride Opening with Carbon Nucleophiles

The first transformation involving carbon-based nucleophiles was reported by Real, who employed chiral Grignard reagents.[37] Addition of pseudoephedrine-derived Grignard reagent **76** to anhydride **28** produced the expected diastereomeric δ-keto acid as its corresponding salt **77**. In situ reduction and acid hydrolysis proved to be highly regioselective, delivering predominantly the desired aldehyde **78** (>99.4% de) in 64% overall yield and >99% ee. Use of the enantiomeric Grignard reagent under the same reaction conditions led to the enantiomeric aldehyde (*ent*-**78**) in 65% overall yield, >99.4% de, and 99% ee. Development of this highly substrate-specific process was the result of the demand for an efficient strategy for the synthesis of aldehyde **78**, which is a key intermediate in the synthesis of 7-oxabicycloheptane prostaglandin analogs.[38]

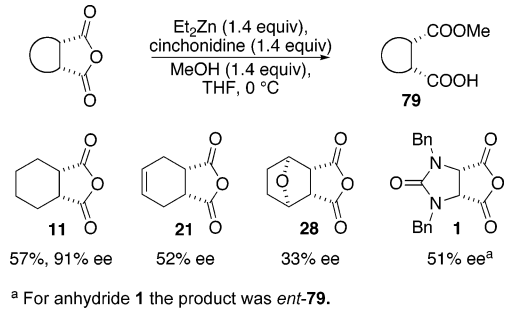
3. Enantioselective Anhydride Desymmetrization

Despite several attempts toward a highly diastereoselective process, no general protocol, with respect to anhydride structure, could be elaborated. Consequently, the enantioselective desymmetrization emerged as an attractive alternative. Unlike the previously described protocols, which give products with covalently linked chiral auxiliaries, these systems deliver directly enantiomerically enriched products. Within the past few years, several research groups have focused their attention on the development of an efficient, highly enantioselective strategy. In principle, this could be achieved by chemical or enzymatic transformations. Whereas the first approach has grown continuously in recent years, the second appears somewhat limited.

Scheme 11



Scheme 12



[a] For anhydride **1** the product was *ent*-**79**.

3.1. Enantioselective Desymmetrization with Oxygen Nucleophiles

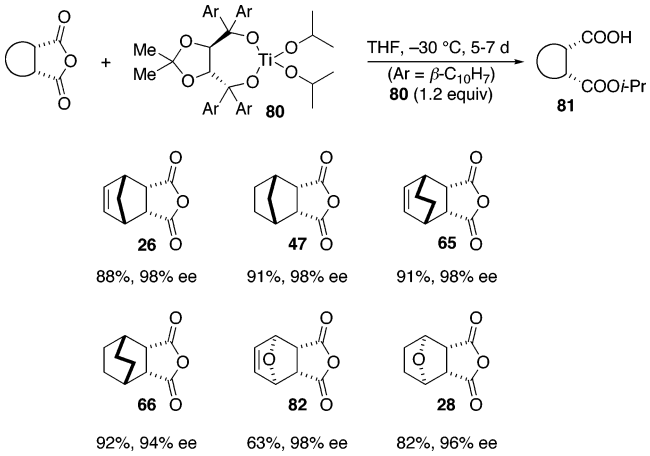
There are an increasing number of reports in the field of enantioselective desymmetrization of cyclic *meso*-anhydrides with alcohol nucleophiles. Among them, two complementary directions can be distinguished: while the first one promotes chemical transformations which make use of achiral alcohol nucleophiles in combination with either a chiral Lewis acid or a metal-free chiral mediator or catalyst, the second one relies on the power of enzymes to accomplish a selective esterification process.

3.1.1. Anhydride Opening with Chiral Lewis Acids

The first contribution in this field stems from Fujisawa, who explored the reaction of *meso*-dicarboxylic anhydrides with achiral alcohols as nucleophiles and chiral metal complexes as mediators.[39] In the optimization process, the reactions were performed by adding a solution of the cyclohexane-1,2-dicarboxylic anhydride (**11**) to a solution containing the active species generated by mixing a chiral amino alcohol with diethyl zinc and an achiral alcohol. The hypothesis that an in situ generated complex was able to promote high enantiofacial discrimination was confirmed for a metallacycle derived from cinchonidine, diethylzinc, and methanol. In this case the corresponding hemiester was isolated with 91% ee in 57% yield (Scheme 12). Attempts to extend the methodology to other substrates revealed that the process was highly sensitive with respect to the substrate structure. Thus, here the enzymatic asymmetric desymmetrization of *meso*-diesters leading to the same products appears superior.[1e−i]

A similar concept making use of the presence of both a Lewis acidic and a nucleophilic moiety within the same molecule was introduced by Seebach.[40] In this particular case, the authors investigated in detail the possibility of a Lewis acid-mediated transfer of an isopropoxy group from the chiral ligand sphere of Ti−TADDOLate to cyclic *meso*-anhydrides to afford the corresponding hemiesters. The system was optimized for the norbornene anhydride (**26**), and the best result (88%, 98% ee) was obtained at −30 °C in THF using β-naphthyltitanium TADDOLate derivative **80** as mediator.

Scheme 13



A large variety of tricyclic anhydrides have been functionalized under these conditions, affording products in high yields (82−92%) and with excellent enantiomeric excesses (94−98% ee) (Scheme 13).

Slightly higher temperatures were required in the case of less reactive bicyclic anhydrides, leading to products in good yields (59−87%) and with high enantiomeric excesses (88−96% ee). In contrast, the opening of anhydride **1** proceeded only with a low selectivity of 26% ee (Figure 2). Unfortunately, only unsatisfactory results were obtained when mono- and disubstituted glutaric anhydrides were subjected to the alcoholysis reaction.

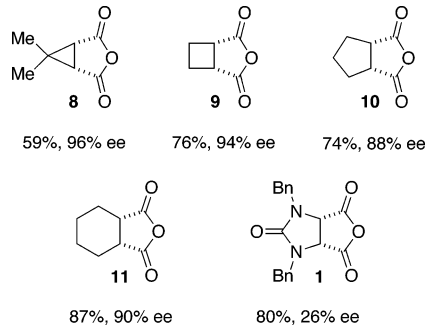
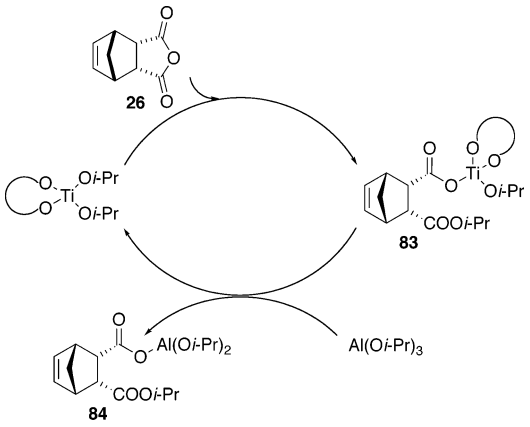


Figure 2.

In addition, a catalytic protocol which permitted the substoichiometric use of Ti−TADDOLate in the presence of stoichiometric amounts of Al(O*i*-Pr)$_3$ was developed. The proposed catalytic cycle is outlined in Scheme 14. It was assumed that if the rate of the Ti−TADDOLate-catalyzed enantioselective alcoholysis was much greater than the rate of the Al(O*i*-Pr)$_3$-catalyzed alcoholysis leading to a racemate, the ee of the hemiester could be retained while Al(O*i*-Pr)$_3$ regenerated the chiral catalyst via metal−ligand exchange. Accordingly, the appropriate hemiester was obtained in 74% yield and 96% ee using a catalytic amount of Ti−TAD-

Scheme 14



DOLate (20 mol %) and a stoichiometric amount of aluminum isopropoxide. Unfortunately, the catalytic process now required an extensive reaction time (24 days), and it was less successful when applied to other substrates.

Subsequently, the methodology was extended to the ring opening of *meso*-sulfonylimides to give the corresponding sulfonylamido isopropyl esters with up to 98% ee.[41] The Ti−TADDOLate-mediated kinetic resolution of racemic dioxolanones, azlactones, and biaryllactones leading to highly enantioenriched products was also described.[42]

3.1.2. Anhydride Opening with Chiral Lewis Bases

This field is largely dominated by the use of naturally occurring cinchona alkaloids and their derivatives as chiral Lewis bases. Only recently, reports describing the use of alternative Lewis bases for promoting an enantioselective anhydride opening reaction have appeared.

Due to their availability, stability, and low production cost, cinchona alkaloids have frequently been used not only in the chemical but also in the pharmaceutical and food industries.[43] Two of their main advantages are that they possess a (pseudo)enantiomeric counterpart and that their structure can be easily modified in order to obtain more effective catalysts (Figure 3).

The first results in the field of metal-free enantioselective anhydride opening were independently reported in the late 1980s by Oda[44] and Aitken.[45] A large variety of cyclic *meso*-anhydrides were functionalized, and the corresponding hemiesters were obtained in high yield and with moderate enantioselectivities using a catalytic amount of cinchona alkaloids. While Oda's studies dealt with the desymmetrization of mono- and bicyclic anhydrides, Aitken extended the substrate scope to more complex tri- and tetracyclic anhydrides. Oda investigated the influence of the catalyst structure on the reaction selectivity and sense of asymmetric induction.[44a,b] Glutaric and succinic anhydrides were examined in the reaction with methanol as nucleophile in the presence of 10 mol % of the cinchona alkaloid. The products were obtained in high yields but with low to moderate enantiomeric excesses. The enantioselectivity was found to be strongly dependent on specific substrate/catalyst combination, the stereochemistry being entirely controlled by the configuration at C8 and C9 of the catalyst. Generally, the naturally occurring cinchona alkaloids (erythro bases) were more active and selective than their C9-epimers (threo bases) in the desymmetrization of glutaric anhydrides, affording the products with up to 70% ee. On the other hand, the erythro bases exhibited lower asymmetric induction compared to the threo bases for the five-membered ring anhydrides (Scheme 15).

A similar reaction protocol was developed by Aitken. Room-temperature methanolysis of *meso*-epoxyanhydride **92** in the presence of 10 mol % of quinine in toluene followed by intramolecular epoxide opening led to lactone **94** with 38% ee in 80% yield.[45a] An increase in the catalyst loading to 50 mol % afforded the lactone with 76% ee (Scheme 16). In addition, a single recrystallization in the presence of quinine furnished enantiomerically pure product (>99% ee). Since lactone **94** is acid sensitive, polymer-supported cinchona alkaloids, prepared by copolymerization with acrylonitrile, were next examined in order to avoid possible difficulties, which could arise from the acidic workup. The reaction was found to be efficient but always occurred with lower selectivity compared to the one performed with nonpolymeric catalysts. The reaction was not restricted to epoxyanhydrides, and aziridine **93** reacted under similar conditions (toluene, rt, 10 mol % of QN) with methanol (3 equiv) to give **95** with 40% ee in 86% yield.

Under the same reaction conditions (10−50 mol % catalyst, 3 equiv of MeOH, rt, toluene, 24 h), several norbornane-type anhydrides afforded the corresponding methyl hemiesters with moderate enantiomeric excesses (35−67% ee) in good yields (69−97%) (Figure 4).[45b]

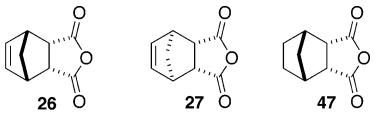


Figure 4.

Taking into account that 3-hydroxy-3-methylgluatric anhydride (**38**) possesses a free hydroxyl group, Shirahama examined the possibility of an intramolecular alcoholysis reaction.[46] Treatment of the anhydride with the lithium

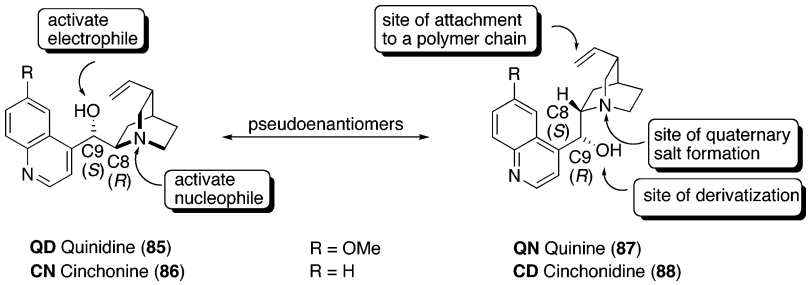
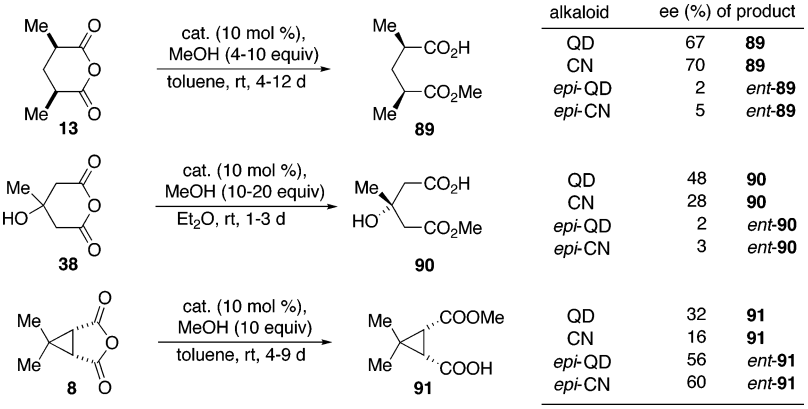


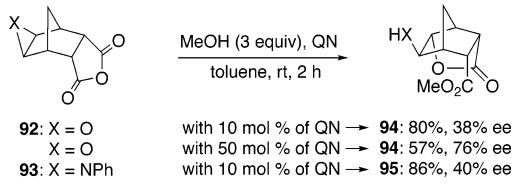
Figure 3.

Scheme 15

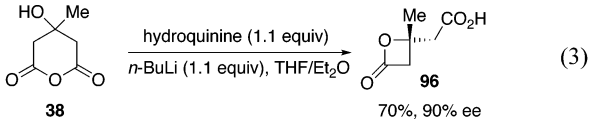


alkaloid	ee (%) of product	
QD	67	**89**
CN	70	**89**
epi-QD	2	*ent*-**89**
epi-CN	5	*ent*-**89**
QD	48	**90**
CN	28	**90**
epi-QD	2	*ent*-**90**
epi-CN	3	*ent*-**90**
QD	32	**91**
CN	16	**91**
epi-QD	56	*ent*-**91**
epi-CN	60	*ent*-**91**

Scheme 16



alkoxide of hydroquinine afforded the (*R*)-β-lactone **96** with 90% ee in 70% yield (eq 3).



(3)

On the basis of Oda's and Aitken's pioneering studies, an improved protocol was developed by Bolm which allowed a wide range of structurally diverse methyl hemiesters to be prepared with up to 99% yield and 99% ee.[47] Low temperature, an excess of methanol, and a stoichiometric amount of the inexpensive and readily available cinchona alkaloid constituted the key features for a highly efficient ring-opening reaction. Under the same reaction conditions, various bi- and tricyclic anhydrides reacted with methanol to give the corresponding hemiesters in very good yields (61−99%) and high to excellent enantioselectivities (75−99% ee). Remarkably, whereas quinidine-mediated ring-opening reaction gave rise to hemiesters of type **79**, quinine always exhibits opposite selectivity, allowing formation of enantiomeric products *ent*-**79**.

In contrast, under identical conditions, more sterically hindered anhydrides **65**, **101**, and **102** did not react at all (Figure 5). Unfortunately, only an unseparable mixture of

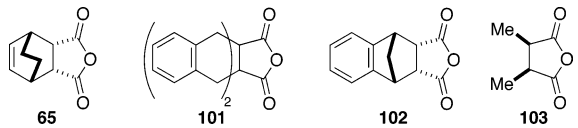


Figure 5.

the desired hemiester with its epimerization product was obtained in conversions of monocyclic *cis*-2,3-dimethylsuccinic anhydride (**103**).

Nevertheless, compared to the existing methods this new protocol proved to be very simple and more convenient to perform. After the reaction the alkaloids could be recovered quantitatively and reused without loss of selectivity. Furthermore, pure toluene proved also to be a suitable solvent, leading to equal or slightly lower selectivities (86−96% ee). In addition, a catalytic protocol which gave comparable results and involved use of 0.1 equiv of quinidine and 1 equiv of the achiral sterically hindered tertiary amine base pempidine (**104**) was also described (Scheme 18).[47b]

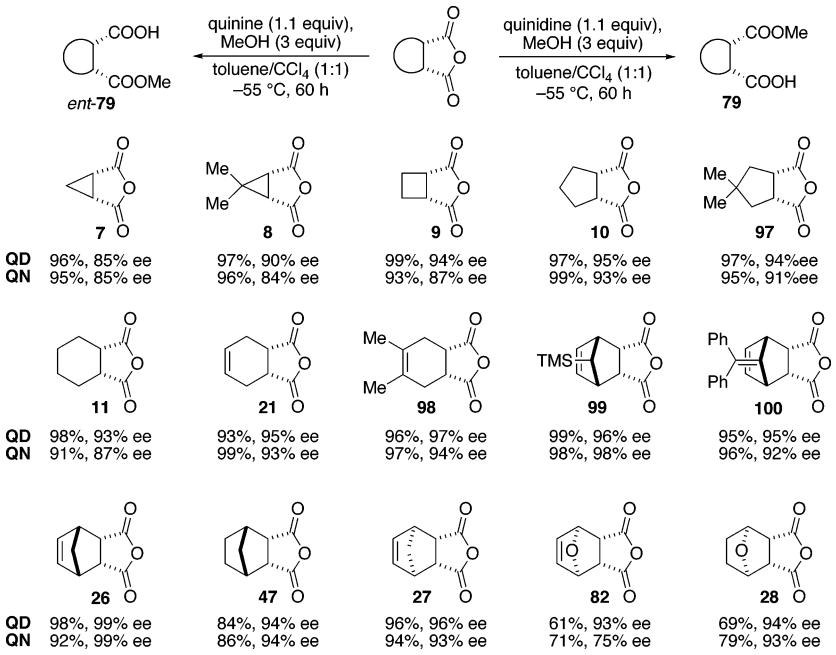
Independently, scientists at Sumitomo applied similar approaches to the ring opening of *cis*-1,3-dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**1**).[48] Methyl and benzyl hemiesters were obtained with comparable selectivities (73.3% and 73.6% ee) when stoichiometric amounts of the chiral amine base were used in the reaction. In contrast, cinchonidine-mediated ring-opening reaction afforded the benzyl hemiester with a considerable lower enantioselectivity (25.9% ee) (Table 10). Attempts to carry out the desymmetrization in the presence of a Lewis acid catalyst have also been described, the product being obtained with only moderate selectivity (23.7−55.2% ee).

An improved version of the alkaloid-mediated asymmetric anhydride opening described above resulted from systematic screening of alcohol nucleophiles.[49] In this context, benzyl alcohol appeared to satisfy all criteria required by a practical protocol. Accordingly, structurally diverse anhydrides have been converted into their corresponding benzyl hemiesters with very high enantiomeric excesses and excellent yields. A simple aqueous workup permits the isolation of the products in analytically pure form (Scheme 19).

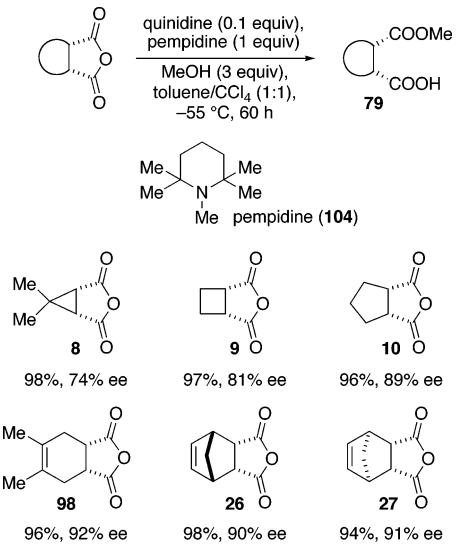
Remarkably, in most cases the benzyl hemiesters were furnished with slightly higher enantiomeric excesses compared to their methyl analogues. This effect was more pronounced for the quinine-mediated reactions, where the variation Δee (benzylester/corresponding methylester) was established between 2% and 6% for the bicyclic anhydrides. Concerning the tricyclic anhydrides the results were even more positive. This statement is best illustrated in the case of oxanorbornene anhydride **82**, where both benzyl ester enantiomers were formed in higher yields and enantioselectivities. It is a notable performance since in this particular case the corresponding methanolysis gave both stereoisomers with 18% ee difference. In addition, with benzyl alcohol as nucleophile the reactions could be performed in toluene as solvent, avoiding the use of the previously applied toxic carbon tetrachloride. The openings occurred with comparable or even better enantioselectivities and yields in pure toluene (Figure 6), the only difference being that the quinine-mediated alcoholysis required a higher concentration (0.1 M for toluene and 0.05 M for toluene/CCl_4).

Moreover, the reactions performed excellent on multigram scale, the products being obtained in even greater yields and

Scheme 17



Scheme 18



selectivities (Figure 7).[50] For example, the oxanorbornene derivative **112** was isolated in 89% yield, after column chromatography, and >99% ee. The result is even more relevant when one considers that cleavage of the oxygen bridge offers easy access to carba-sugar derivatives. This newly developed methodology is of practical utility since a wide range of benzyl hemiesters are for the first time easily available in enantiomerically enriched forms. The protocol is also net superior to the enzymatic methods since so far no enzyme has been shown to be able to hydrolyze benzyl diesters.

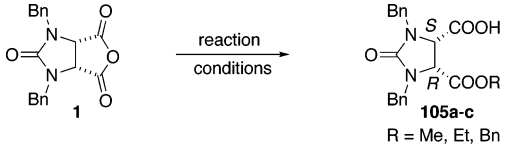
A solvent-free version[51] of the standard anhydride opening methodology was accomplished using an emerging technology, namely, ball milling.[52] The benefit of the mechanochemical technique on the alcoholysis reaction is evident since the reaction is carried out now with an equimolar amount of alcohol and the product can be purified by a simple acidic wash.

Comparable results were simultaneously obtained by Deng,[53] who found that commercially available mono- and bis-cinchona alkaloid derivatives were also capable of functioning as effective chiral Lewis base/nucleophilic organic catalysts in the ring-opening reaction. These modified cinchona alkaloids have previously been used by Sharpless as ligands in the asymmetric dihydroxylation and aminohydroxylation reaction.[54] Screening of various aryl ethers and esters of cinchona alkaloids in the room-temperature asymmetric methanolysis of *cis*-2,3-dimethylsuccinic anhydride showed that the dihydroquinidine-based catalysts, DHQD-PHN and $(DHQD)_2AQN$, possess a remarkable ability to promote a highly enantioselective reaction. A further improvement resulted from subsequent solvent screening. Accordingly, a large range of bi- and tricyclic anhydrides underwent ring-opening reaction with methanol (10 equiv) at −20 or −30 °C in ether in the presence of 5−20 mol % of $(DHQD)_2AQN$, affording the corresponding methyl hemiesters with excellent enantioselectivities (92−98% ee) in high yields (74−99%) (Table 11, entries 1−6). Notable, with $(DHQD)_2AQN$ (5−30 mol %) as catalyst, even the monocyclic anhydrides were readily converted into enantiomerically enriched (90−98% ee) acyclic hemiesters (Table 11, entries 7−9).

As already emphasized in the present section, the enantioselective ring opening of bi-, tri-, and tetracyclic anhydrides is a versatile synthetic transformation providing important synthons for organic synthesis. In contrast, the selective ring opening of monocyclic anhydrides is still considered as problematic. In this light, Deng's results described above constitute a breakthrough in the field. In order to further enlarge the substrate and nucleophile scope new quinidine derivatives **113** have been synthesized.[55] By an appropriate selection of the substituent a competitive and more efficient catalyst could be obtained. A schematic representation of these newly developed catalysts is given in Figure 8. Since they can be prepared in reasonable yields starting from relatively inexpensive starting materials, they possess significant advantages over the high-priced dimeric cinchona alkaloids.

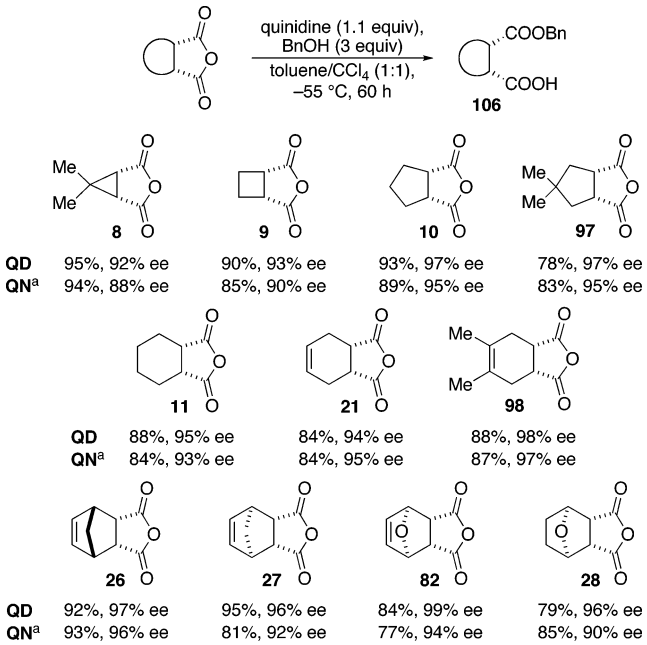
The monomeric quinidine derivatives depicted in Figure 8 were examined in the ring-opening reaction of *cis*-2,3-

Table 10. Cinchona Alkaloid-Mediated Enantioselective Ring Opening of *cis*-1,3-Dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione



entry	scale (mmol)	reaction conditions	yield (%)	ee (%)
1	0.6	5 mL of toluene, −50 °C, 0.6 mmol of quinine, 1.7 mmol of MeOH, 21 h, acidic workup	49.1	73.3
2	0.69	5 mL of toluene, −50 °C, 0.06 mmol of quinine, 0.68 mmol of pempidine, 1.7 mmol of EtOH, 21 h, acidic workup	56.0	59.8
3	0.6	2.5 mL of toluene, 2.5 mL of CCl_4, −20 °C, 0.6 mmol of quinine, 0.6 mmol of BnOH, 16 h, acidic workup	76.8	73.6
4	0.6	2.5 mL of toluene, 2.5 mL of CCl_4, −20 °C, 0.6 mmol of cinchonidine, 0.6 mmol of BnOH, 16 h, acidic workup	81.4	25.9

Scheme 19[a]



[a] For the quinine-mediated reaction, *ent*-**106** was obtained.

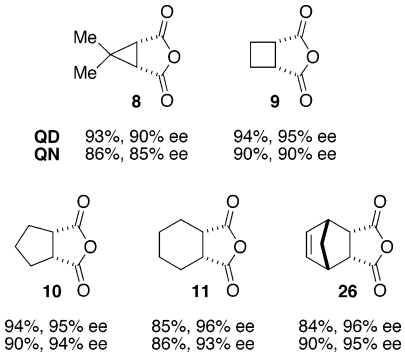
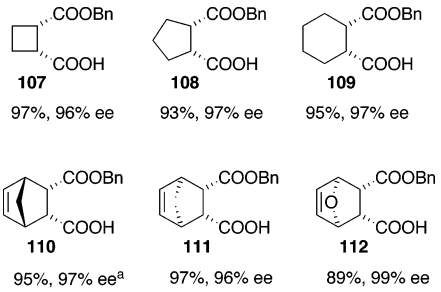


Figure 6.

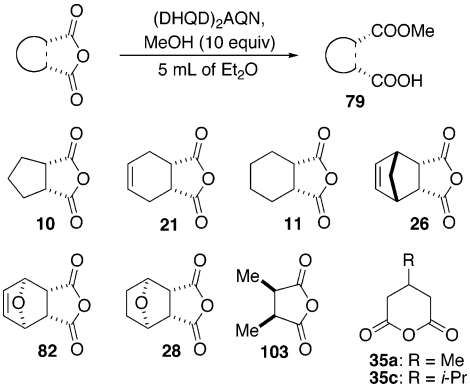
dimethylsuccinic anhydride (**103**) under various conditions. As illustrated in Table 12, containing a brief selection of the best achievements with methanol and trifluoroethanol as nucleophiles, the monomeric cinchona alkaloids QD-AD, QD-(−)-MN, QD-(+)-MN, QD-PP, QD-TB, QD-IP, and QD-PC possess comparable or superior activity and selectivity over $(DHQD)_2AQN$. The reactions were conducted on a 0.1 mmol scale and 0.02 molar concentration in diethyl ether at room temperature with 10 equiv of nucleophile. Remarkably, the monomeric alkaloids performed better in the reactions with trifluoroethanol compared to methanol, the reactions showing 100% conversion and very high selectivities.



[a] For *ent*-**112**: 94%, 97% ee.

Figure 7.

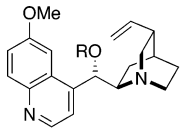
Table 11. Bis-Cinchona Alkaloid-Catalyzed Anhydride Desymmetrization



				$(DHQD)_2AQN$		$(DHQ)_2AQN$[a]	
entry	anhydride	temp (°C)	cat (mol %)	yield (%)	ee (%)	yield (%)	ee (%)
1	**10**	−30	8	99	95	90	93
2	**21**	−20	7	95	98	92	96
3	**11**	−20	5	97	97	95	93
4	**26**	−30	10	82	95	82[b]	90
5	**82**	−20	20	74	92	71	86
6	**28**	−20	15	88	96	85	94
7	**103**	−20	5	93	98	88	98
8	**35a**	−40	30	70	91	56[c]	82
9	**35c**	−40	30	72	90	62[c]	83

[a] For the $(DHQ)_2AQN$-mediated reaction the product is *ent*-**79**. [b] Reaction at −20 °C with 20 mol % of catalyst. [c] Reaction at −35 °C.

Next, various 3-substituted glutaric anhydrides were evaluated in the alcoholysis reaction. In all investigations QD-PP exhibited essentially inferior catalyst properties compared to QD-AD, QD-MN, and $(DHQD)_2AQN$. In the case of methanolysis of 3-alkyl glutaric anhydrides **35a** and **35c**, QD-AD and QD-MN featured selectivities similar to $(DHQD)_2$-AQN. Their activity appeared to be dependent on the substituent on the anhydride substrate: whereas in the case of the



quinidine-based catalysts
113

QD-CN	-CH_2—≡N
QD-PP	-CH_2—≡—H
QD-PH	-CH_2—≡—Ph
QD-AN	-CH_2—≡—*p*-MeOPh
QD-NT	-CH_2—≡—*p*-NO_2Ph

QD-(–)-MN	-CH_2COO-(–)-Menthyl	**QD-IP**	-CH_2COO*i*-Pr
QD-(+)-MN	-CH_2COO-(+)-Menthyl	**QD-TB**	-CH_2COO*t*-Bu
QD-AD	-CH_2COO-(1)-Adamantyl	**QD-CH**	-$CH_2COOC_6H_{11}$
QD-IB	-CH_2COO-Isobornyl	**QD-AC**	-CH_2COMe
QD-(+)-EF	-CH_2COO-*endo*-(1*R*)-(+)-Fenchyl	**QD-PC**	-CH_2CO*t*-Bu
QD-(–)-IPC	-CH_2COO(1*R*,2*R*,3*R*,5*S*)-(–)-Isopinocanphyl	**QD-Piv**	-CO*t*-Bu

Figure 8.

Table 12. Catalyst Screening in the Ring Opening of *cis*-2,3-Dimethylsuccinic Anhydride

		MeOH			CF_3CH_2OH		
entry[a]	catalyst	time (h)	conv (%)	ee (%)	time (h)	conv (%) (yield)	ee (%)
1	QD-AD	25	99	90	24	100	95
2	QD-(−)-MN	7	99	89	26	100 (99)	92
3[b]	QD-(+)-MN	9	96	89	21	100 (76)	94
4	QD-PP	48	93	87	53	100	89
5	QD-TB	49	95	88	13	100 (94)	92
6	QD-IP	25	99	86	25	100 (98)	90
7	QD-PC	27.5	92	86	13	100 (81)	91
8[c]	$(DHQD)_2AQN$	13	86	92	53	100	87

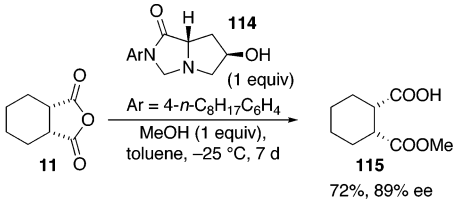
[a] Conditions: 0.1 mmol scale, 0.02 M, Et_2O, rt, catalyst (20 mol %), alcohol (10 equiv). [b] Reaction at 19 °C. [c] Catalyst (5 mol %).

isopropyl substituent they showed similar activity compared to $(DHQD)_2AQN$, longer reaction times were required in the case of methyl substitution. In addition, lowering the reaction temperature and changing the solvent from toluene to ether had only a minor effect on the enantioselectivity but influenced considerably the catalyst activity. On the other hand, in the case of trifluoroethanolysis QD-AD and QD-MN showed for both substrates higher activity as well as enantioselectivity. In addition, their efficiency was evaluated in the reaction of aryl- and OTBS-substituted glutaric anhydrides **35d** and **22**, respectively. The results indicate that $(DHQD)_2AQN$ is slightly more efficient in the case of the methanolysis but again less efficient in the case of trifluoroethanolysis. As yet, the cost and catalytic properties featured by the monomeric cinchona alkaloid derivatives render them as net superior over the dimeric catalysts. Furthermore, this new developed methodology was successfully extended also to bi- and tricyclic anhydrides.

Remarkably, the protocol developed by Deng for the desymmetrization of glutaric and succinic anhydrides has been evaluated and is in use at Daiso Co. for the large production scale of optically active hemiesters.[56] Further studies by Deng revealed that the bis-cinchona alkaloids are able to efficiently mediate the kinetic resolution of racemic cyclic anhydrides and *N*-carboxy anhydrides as well as the dynamic kinetic resolution of *N*- and *O*-carboxy anhydrides.[3,57]

A polymer-supported $(DHQD)_2AQN$ catalyst has been recently introduced and evaluated in the asymmetric ring-opening reaction of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (**21**) by Wöltinger.[58] By means of a repetitive batch system it was possible to run the reaction over 18 cycles achieving a conversion of >95% for each cycle. However, the synthetic usefulness of the process is still limited since it was only optimized for a single substrate and the ee decreased drastically, from almost 90 to 60%, during the first 5 runs. Silica gel-supported quinidine, as heterogeneous catalyst for the anhydride desymmetrization, was synthesized and optimized for the same substrate by Carloni.[59] More efficient heterogeneous chiral organocatalysts were introduced by Han,[60] who demonstrated that silica gel-supported bis-cinchona alkaloids exhibited higher catalytic activity in comparison to Carloni's system. In addition, they proved to be applicable to a wider substrate spectrum and give products with up to 92% ee.

Uozumi and more recently Bolm focused their attention on the use of non-cinchona-based catalysts for the enantioselective anhydride desymmetrization. A library of five *N*-chiral bicyclic tertiary amines was synthesized[61] and tested in the methanolysis of cyclohexane-1,2-dicarboxylic anhydride (**11**) by Uozumi.[62] The methyl hemiester **115** was obtained in poor yield (33%) and moderate selectivity (65% ee) when a catalytic amount of pyrrolo-imidazolone derivative **114** (10 mol %) was used as chiral catalyst. The yield and selectivity increased considerably (72%, 89% ee) when a stoichiometric amount of the chiral catalyst was employed. Under the same conditions, the desymmetrization of anhydrides **21** and **26** proceeds less selective, the products being obtained in 85% and 82% ee, respectively.



(4)

Although promising, the 5-step procedure for the catalyst synthesis,[61,62] the limited substrate spectrum, and the moderate reaction selectivity render the system less convenient from practical and synthetic point of view.

Recent studies by Bolm disclosed new, alternative catalysts for the anhydride desymmetrization.[63] Ordinary β-amino alcohols[64] with low molecular weight (Figure 9) were now employed as catalysts for this reaction.

In the initial stage the influence of temperature, solvent polarity, and amount of catalyst on the reaction yield and

Table 13. Enantioselective Alcoholysis of Various 3-Substituted Glutaric Anhydrides

			MeOH			CF_3CH_2OH		
entry[a]	anhydride	catalyst	time (h)	conv (%) (yield)	ee (%)	time (h)	conv (%) (yield)	ee (%)
1	**35a**	QD-AD	40	90	86	23.5	98 (88)	86
2	**35a**	QD-(−)-MN	40	92	85	23.5	95	88
3	**35a**	QD-PP	77.5	92(69)	77	70.5	93 (65)	77
4[b]	**35a**	$(DHQD)_2AQN$	17	96	88	44	97.5	74
5[c]	**35a**	QD-AD	86	98.4 (93)	87	49.5	98.5 (91)	88
6[c,d]	**35a**	QD-AD	141	86 (58)	90	94	87.6 (70)	90
7	**35c**	QD-AD	36.5	96	87	52	98 (87)	89
8	**35c**	QD-(−)-MN	42	97	86	61	96	87
9	**35c**	QD-PP	91	90.3 (72)	80	91	90.9 (70)	55
10[b]	**35c**	$(DHQD)_2AQN$	36.5	99 (86)	88	51	97	78
11	**35d**	QD-AD	24.5	99 (92)	86	35.5	100 (91)	91
12	**35d**	QD-(−)-MN	29	100 (100)	84	23.5	97.7	90
13	**35d**	QD-PP	52	91.5 (73)	79	71.5	97 (89)	81
14[b]	**35d**	$(DHQD)_2AQN$	18	100 (98)	90	44.5	100 (84)	81
15	**22**	QD-AD	56	96	92	71	98	85
16	**22**	QD-(−)-MN	42	94	92	91	97	89
17	**22**	QD-PP	105	91.5 (46)	78	105	87.4 (68)	48
18[b]	**22**	$(DHQD)_2AQN$	33.5	97	95	81	94	79

[a] Conditions: 0.1 mmol scale, 0.2 M, −43 °C, 110 mol % of catalyst, 1.5 equiv of alcohol, toluene. [b] 55 mol % of catalyst. [c] −53 °C. [d] Performed in Et_2O.

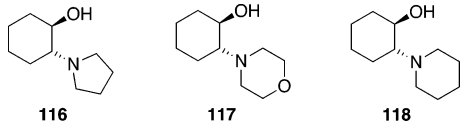
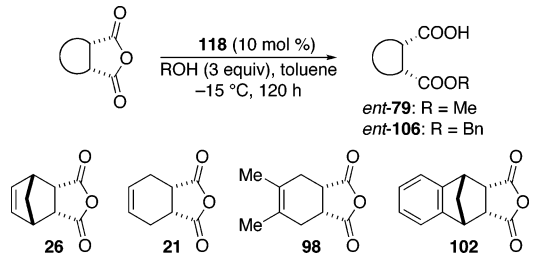


Figure 9.

Table 14. Amino Alcohol-Catalyzed Enantioselective Anhydride Alcoholysis

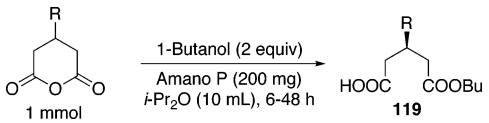


		MeOH		BnOH	
entry	anhydride	yield (%)	ee (%)	yield (%)	ee (%)
1[a]	**26**	85	56		
2[b]	**26**	81	76		
3[c]	**26**	83	82		
4	**26**	80	81	69	83
5	**21**	77	95	86	95
6	**98**	69	74	65	79
7	**102**	67	76		

[a] Reaction at rt with 10 mol % of **116** as catalyst. [b] Reaction at rt with 10 mol % of **117** as catalyst. [c] Reaction at −15 °C with 10 mol % of **117** as catalyst.

selectivity was investigated in detail. In a second phase the efficiency of various β-amino alcohols with distinct backbone templates was briefly explored in the ring opening of anhydride **26**. The investigation led to identification of an efficient catalytic system (−15 °C, toluene, 10 mol % of catalyst, and 3 equiv of alcohol as nucleophile) for the stereoselective alcoholysis reaction. Although completely inactive at low temperature (−60 °C), the *trans*-β-amino alcohol **116** with a cyclohexane backbone turned out to be a fairly efficient catalyst for the room-temperature reaction, affording the product in 85% yield and 56% ee (Table 14, entry 1). Slightly better results were obtained when the reaction was performed in the presence of β-amino alcohol **117** (81%, 76% ee) (Table 14, entry 2). The yield and selectivity were raised (83% yield, 82% ee) by lowering the temperature (−15 °C) and extending the reaction time (120 vs 72 h) (Table 14, entry 3). Comparable results were obtained when β-amino alcohol **118** was employed in the reaction (80%, 81% ee) (Table 14, entry 4). Under identical conditions several anhydrides were opened with methanol and benzyl alcohol as nucleophile to give the corresponding hemiesters with good to excellent selectivities (74−95% ee) in moderate to high yields (65−86%) (Table 14, entries 4−7).

Table 15. Lipase-Catalyzed Anhydride Desymmetrization

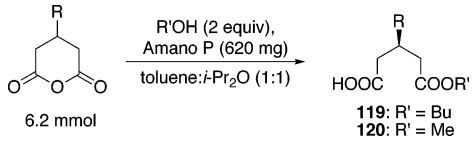


			1 mmol		10 mmol	
entry	anhydride	R	yield (%)	ee (%)	yield (%)	ee (%)
1	**35a**	Me	74	91	95	93
2	**35b**	Et	67	80	92	87
3	**35c**	*i*-Pr	85	76	85	76
4	**35h**	*n*-Pr	72	60	72	60

3.1.3. Enzymatic Processes

There are a limited number of publications dealing with the enzymatic alcoholysis of meso and prochiral anhydrides.[65] Although the results obtained by means of enzymatic processes are not at the level reached using chemical transformations, they are worth mentioning since they focus on conversions of substrates, which proved difficult to desymmetrize by chemical approaches. Oda applied Amano P lipase (from *Pseudomonas fluorescens*) as catalyst for the ring opening of 3-substituted glutaric anhydrides.[66] Enantioselectivities of up to 91% ee have been obtained when the reactions were carried out in diisopropyl ether and 1-butanol was employed as nucleophile (Table 15).[66a] Generally, the selectivity decreased with increasing steric bulk. In the case of Me and Et substituents, the yield increased considerably when the reaction was performed on a arger scale.[66b]

Table 16. Lipase-Catalyzed Asymmetric Alcoholysis

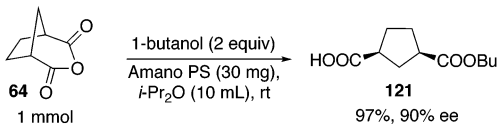


			R = Me		R[1] = Bu	
entry	anhydride	R	yield (%)	ee (%)	yield (%)	ee (%)
1	**35a**	Me[a]	92	87	74	91
2	**35i**	CH_2Cl	100	80	100	86
3	**35j**	CH_2F	100	84	100	70
4	**35k**	OMe	100	81	99	86

[a] The reactions were performed on 1 mmol scale in *i*-Pr_2O as solvent.

The methodology has also been extended to use of anhydrides bearing substituents other than simple alkyl groups.[67] Their desymmetrization is particularly significant since the products contain additional functional groups at the third position which can be exploited in further derivatization steps (Table 16).

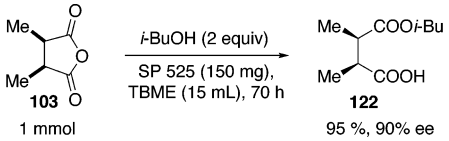
The same protocol has been applied by Chênevert[68] to the desymmetrization of bicyclic anhydride **64**, ester **121** being obtained in 81% yield and 82% ee when Amno P lipase (from *Pseudomonas fluorescens*) was used as catalyst. An improvement in both yield (97%) and selectivity (90% ee) was observed when Amano PS (from *Pseudomonas cepacia*) was employed in this reaction (eq 5).



(5)

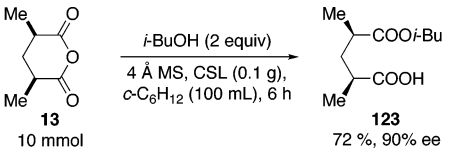
A slight modification of Oda's protocol was applied by Kurihara[69] for the esterification of 3-methyl glutaric anhydride (**35a**), and the product (80%, 86% ee) was subsequently used as starting material in the total synthesis of (−)-yellow scale pheromone.

Detailed studies on the enzymatic esterification of succinic and glutaric anhydrides stem from Ozegowski.[70] Treatment of 2,3-dimethylsuccinic anhydride (**103**) with 2-butanol in *tert*-butyl methyl ether at room temperature in the presence of lipase SP 525 and calcium sulfate hemihydrate afforded hemiester **122** with 90% ee and in 95% yield (eq 6).[70a]



(6)

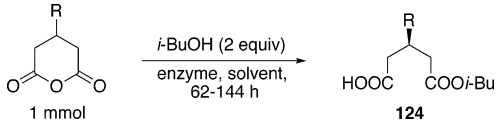
In the case of 2,4-dimethyl glutaric anhydride (**13**) the best result (72% yield and 90% ee) was attained when the esterification was performed in cyclohexane at room temperature in the presence of CSL lipase (from *Candida sp. 382*) and 4 Å molecular sieves (eq 7).[70b]



(7)

The alcoholysis of 3-hydroxy, methoxy, and acetoxy glutaric anhydrides has been explored under various conditions.[71] In this context, the efficiency of several enzymes as well as their influence on the reaction stereochemical outcome were investigated under variation of solvent and nucleophile. A careful selection of the enzyme and the reaction conditions allowed the synthesis of the 3-(*R*)-monoesters with up to 90% ee (Table 17, entries 1−3). The study revealed in most of cases a strong substrate−catalyst dependence and showed that catalysts which proved effective for certain substrates were inactive for others. For example, CSL lipase (from *Candida sp. 382*), which gave rise to the (*S*)-product in >98% ee in the case of 3-acetoxy glutaric anhydride (**35m**) (Table 17, entry 4), was completely inactive in the case of 3-hydroxy anhydride (**35l**).

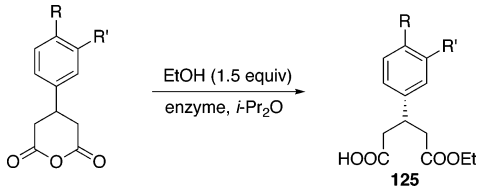
Table 17. Enzymatic Catalyzed Esterification of Glutaric Anhydrides



entry	anhydride	R	enzyme[a]	solvent	yield (%)	ee[b] (%)
1	**35l**	OH	Pan	dioxane	53	60
2	**35k**	OMe	PCL	Et_2O	80	90
3	**35m**	OAc	PCL	TBME	63	41
4	**35m**	OAc	CSL[c]	Et_2O	64	>98[d]

[a] Pan: pancreatin 0.5 g. PCL: Amano PS lipase from *Pseudomonas cepacia* 0.1 g. CSL: lipase from *Candida sp. 382* 0.1 g. [b] Absolute configuration: (*R*). [c] 4 Å MS. [d] Absolute configuration: (*S*).

Table 18. Enzymatic Alcoholysis of 3-Aryl-glutaric Anhydrides[a]

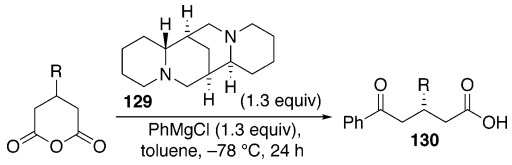


				Novozyme 435		Chirazyme L-2,C3		Amano PS-C imob	
entry	anhydride	R	R	time	ee[b] (%)	time	ee[b] (%)	time	ee[b] (%)
1	**35d**	H	H	61 h	78	19 h	83	19 h	77[c]
2	**126**	Cl	H	5 h	68	4 d	71	4 d	16
3	**127**	OMe	H	13 d	68	7 d	68	8 d	52[d]
4	**128**	Cl	Cl	4 d	60	2 d	77	2 d	44

[a] The data summarized here are taken from ref 73a. [b] Absolute configuratin: (*S*). [c] Absolute configuration: (*R*). [d] 66% ee after recrystallization.

Initially, Ostaszewski concentrated his studies on the development of a unique one-pot, two-step synthesis based on the desymmetrization of more reactive 3-aryl-substituted glutaric anhydrides and subsequent use of the products as substrates for Ugi and Passerini multicomponent condensations.[72] Later, optimization of the enzymatic process constituted an additional focus of interest.[73] Screening of various commercially available enzymes showed that the nonimmobilized enzymes were generally ineffective independent of the tested substrate. Nevertheless, this drawback could be overcome using immobilized lipases, which proved to be suitable for this type of substrates, affording the corresponding hemiesters with moderate to high selectivities (Table 18).

Table 19. (−)-Sparteine/PhMgCl-Catalyzed Anhydride Arylation



entry	anhydride	R	yield (%)	ee (%)
1[a]	**35d**	Ph	63	88
2	**35d**	Ph	91	92
3	**35g**	Bn	87	92
4	**35h**	*n*-Pr	74	90
5	**35c**	*i*-Pr	70	92
6	**35n**	*i*-Bu	76	91
7	**35e**	*t*-Bu	84	91
8	**22**	OTBS	51	87
9	**35o**	*o*-tolyl	87	8
10	**35p**	3-thiophene	74	91

[a] Reaction with 1 equiv of **129**, 1 equiv of PhMgCl.

3.2. Enantioselective Desymmetrizations with Carbon Nucleophiles

As already emphasized, interest in the development of general and selective desymmetrization methods has increased considerably in recent years, and with it, the involvement of carbon-based nucleophiles in the desymmetrization reactions has caught substantial attention. Worth noticing is that while the pioneering studies by Real, mentioned above, dealt with use of chiral Grignard reagents, the concepts newly introduced by Fu, Rovis, and Harada deal with use of achiral nucleophiles in the presence of chiral mediators or catalysts.

3.2.1. Grignard Reagents/(–)-Sparteine Anhydride Alkylation

Fu[74] focused on development of an enantioselective version of the protocol described by Real. It was found that commercially available (−)-sparteine[75] promotes an enantioselective ring-opening reaction of 3-phenyl glutaric anhydride (**35d**) by phenyl magnesium chloride (PhMgCl), leading to the corresponding δ-keto acid in 63% yield and 88% ee (Table 19, entry 1). A significant improvement in the yield (91%) and selectivity (92% ee) was observed when a slight excess of Grignard reagent/(−)-sparteine complex[76] was employed as a source of chirality (Table 19, entry 2). Under these conditions various 3-substituted glutaric anhydrides were converted into the corresponding keto acids in good yields (51−91%) and high enantioselectivities (87−92% ee) (Table 19, entries 3−10).

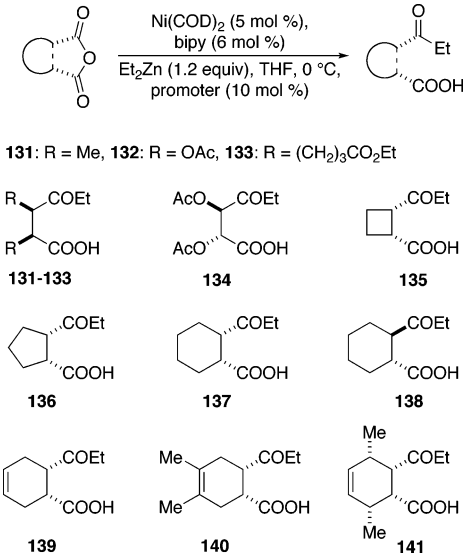
3.2.2. Metal-Catalyzed Anhydride Alkylation

Detailed studies on the alkylation of cyclic *meso*-anhydrides catalyzed by a nickel complex have been described by Rovis.[77] Initially, nonstereoselective approaches were investigated. They will be presented here since the results provided the bases for the subsequent asymmetric anhydride opening developed by the same author. 2,2′-Bipyridyl and several phosphine ligands were initially tested in combination with $Ni(COD)_2$ in the addition of diethylzinc to cyclohexane-1,2-dicarboxylic anhydride (**11**). The mechanistic pathway involves, first, an oxidative addition of the low-valent nickel complex to the electron-deficient C−O bond of the anhydride. The resulting organometallic species then undergoes transmetalation with the zinc reagent to provide the key intermediate, which upon reductive elimination affords the product and regenerates the catalyst. Use of electron-deficient olefins as promoters for the reductive elimination increased the yield and reaction rate considerably. For example, addition of $ZnEt_2$ to cyclohexane-1,2-dicarboxylic anhydride (**11**) is 250 times faster in the presence of 10 mol % of *p*-trifluoromethylstyrene and affords the product in 80% yield in less than 5 min. Concerning the influence of the ligand structure on the reaction efficiency, it was found that bidentate phosphine ligands are superior to trialkyl- and triarylmonodenate ones. The reaction is highly general with respect to the substrate, and a large variety of mono- and bicyclic succinic anhydrides have been reacted with $ZnEt_2$ to give the corresponding γ- and δ-keto acids in moderate to excellent yields (61−95%) (Table 20).[77b]

Moreover, tri- and tetracyclic succinic anhydrides undergo smooth reaction with $ZnEt_2$ leading to γ-keto acids in high yields (68−96%) (Table 21).[77b]

Surprisingly, although the bipy−nickel complex was highly effective in promoting alkylation of succinic anhydrides, glutaric anhydrides did not react at all under identical conditions. Nevertheless, alkylation of glutaric anhydrides could be successfully achieved using a pyphos-derived nickel catalyst. Accordingly, a number of monocyclic glutaric anhydrides with various substitution patterns have been alkylated, affording the products in moderate to good yields (52−85%) in a short period of time.[77b] As depicted in Table 22, alkyl- and aryl-substituted anhydrides performed well in the alkylation reaction leading to acyclic keto acids in

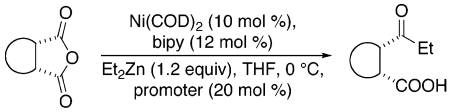
Table 20. Metal-Catalyzed Alkylation of Mono- and Bicyclic Anhydrides (nonstereoselective)

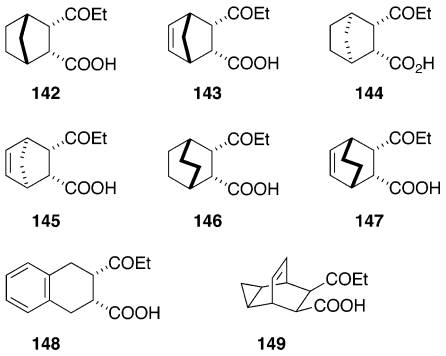


entry	promoter	ketoacid	yield (%)
1[a]	4-CF_3-sty	**131**	93
2	4-F-sty	**132**	74
3	4-F-sty	**133**	75
4[a]	4-CF_3-sty	**134**	88
5[a]	4-CF_3-sty	**135**	61
6[b]	4-F-sty	**136**	71
7[a]	4-CF_3-sty	**137**	95
8	4-F-sty	**138**	87
9[a]	4-CF_3-sty	**139**	95
10	4-F-sty	**140**	90
11[b]	4-F-sty	**141**	95

[a] Reactions performed with 10 mol % of $Ni(COD)_2$, 12 mol % of bipy, and 20 mol % of promoter. [b] Isolated as methyl ester.

Table 21. Metal-Catalyzed Alkylation of Tricyclic Anhydrides (nonstereoselective)

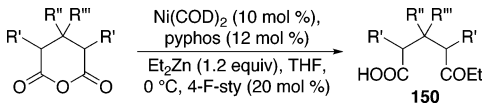




entry	promoter	ketoacid	yield (%)
1	4-CF_3-sty	**142**	88
2	4-CF_3-sty	**143**	96
3[a]	4-CF_3-sty	**144**	79
4	4-CF_3-sty	**155**	91
5[b]	4-F-sty	**146**	88
6[b]	4-F-sty	**147**	96
7[a,b]	4-F-sty	**148**	90
8[a]	4-F-sty	**149**	68

[a] Isolated as methyl ester. [b] Reactions performed with 5 mol % of $Ni(COD)_2$, 6 mol % of bipy, and 10 mol % of promoter.

Table 22. Metal-Catalyzed Alkylation of Glutaric Anhydrides (nonstereoselective)



entry	anhydride	R	R	R	yield (%)
1[a]	**35a**	H	H	Me	81
2	**35d**	H	H	Ph	77
3	**35q**	H	H	OBn	52
4[b]	**35r**	H	H	NHTs	57
5	**151**	H	OAc	Me	75
6	**13**	Me	H	H	85

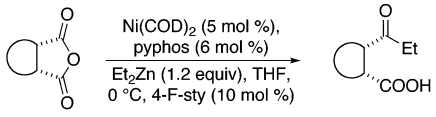
[a] 4-CF_3-sty. [b] 5 mol % of $Ni(COD)_2$, 6 mol % of pyphos, 10 mol % of 4-F-sty.

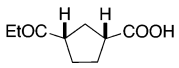
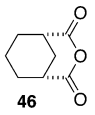
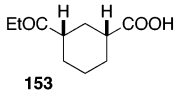
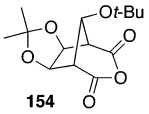
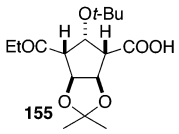
high yields (77−85%) (Table 22, entries 1, 2 and 6). Furthermore, heteroatom substituents were as well tolerated, providing *O*- and *N*-protected β-hydroxyl and β-amino acid derivatives in moderate yields (52−75%) (Table 22, entries 3−5).

Notably, alkylation of bridged bicyclic anhydrides **64** and **46** proceeds highly diastereoselectively, affording the corresponding 1,3-*syn*-cyclopentane and cyclohexane derivatives as single isomers in very high yields (90% and 88%, respectively) (Table 23, entries 1 and 2).[77b] Under similar conditions, even the labile substrate **154** undergoes clean reaction, leading to the pentasubstituted cyclopentane derivative **155** in 88% yield (Table 23, entry 3).

The methodology has also been extended to the use of nucleophilic coupling partners other than diethylzinc. In this context, diorganozinc reagents (dimethyl, diphenyl- and diisopropylzinc) as well as alkylzinc halides proved to be compatible coupling partners. Noteworthy, in situ generation

Table 23. Metal-Catalyzed Alkylation of Bridged Bicyclic Glutaric Anhydrides (nonstereoselective)

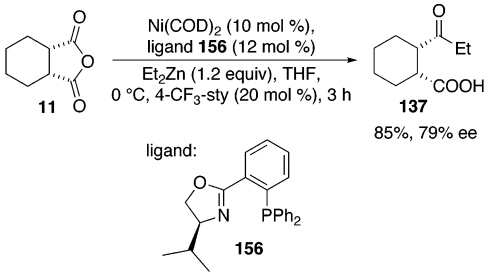


entry	anhydride	product	yield (%)
1	 **64**	 **152**	90
2	 **46**	 **153**	88
3[a]	 **154**	 **155**	88

[a] 10 mol % of $Ni(COD)_2$, 12 mol % of pyphos, 6 mol % of 4-F-sty.

of the dialkyl- and diarylzinc reagents from the appropriate lithium or Grignard reagents was also feasible and indicated that the byproducts (lithium and magnesium salts) are tolerated in the reaction mixture. Furthermore, an alternative protocol based on the use of $Ni(acac)_2$ as catalyst precursor was developed, showing that the reaction was not limited to use of highly sensitive $Ni(COD)_2$. The keto acids obtained by this methodology have been selectively reduced either by Et_3BHLi (Super Hydride) or by PhMeSiH to give the corresponding anti and syn lactones.[78]

In addition, use of Pfaltz' *N*,*P*-ligand **156** (*i*-PrPHOX) afforded an active catalyst for the enantioselective alkylation of cyclohexane-1,2-dicarboxylic anhydride (**11**) and provided the γ-keto acid **137** in 85% yield and 79% ee (eq 8).[77a]

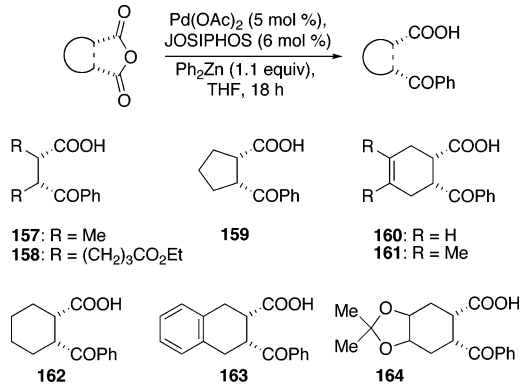


(8)

An improved protocol for this asymmetric anhydride desymmetrization has also been developed.[79] Room-temperature palladium-catalyzed diphenylzinc addition to structurally diverse cyclic anhydrides provided the corresponding keto acids in good yields (61−89%) and high enantioselectivities (89−97% ee) (Table 24).

As an extension of this work, use of mixed zinc species[80] in the Ni-catalyzed anhydride alkylation was evaluated.[81] Initial studies revealed that while in the case of parent diorganozinc reagents methyl was transferred twice as fast as ethyl and four times faster than phenyl, in the case of mixed species generated from a 1:1 mixture of the parent reagents phenyl transfer was favored over methyl and ethyl (Table 25, entries 1−3). For consistency, the transfer of bulkier isopropyl and $TMSCH_2$ groups was also investigated,

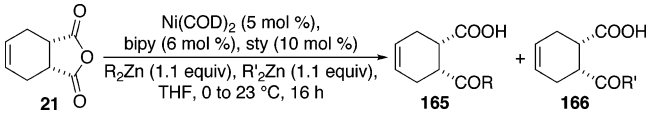
Table 24. Enantioselective Anhydride Arylation



entry	product	temp (°C)	yield (%)	ee (%)
1	**157**	80	72	92
2[a]	**158**	80	61	89
3	**159**	40	74	89
4	**160**	23	69	91
5	**161**	23	87	90
6	**162**	23	89	94
7	**163**	23	84	95
8	**164**	23	83	97

[a] The product was isolated as the methyl ester.

Table 25. Anhydride Alkylation with Mixed Zinc Reagents (nonstereoselective)



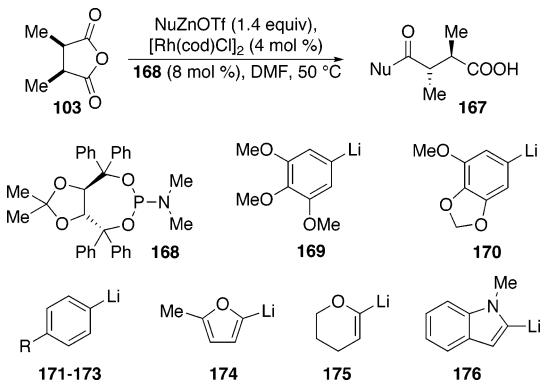
entry	R	R	product ratio **165**:**166**	yield (%)
1	Ph	Et	19:1	91
2[a]	Ph	Et	19:1	87
3	Ph	Me	9:1	89
4	Me	Et	3:1	75
5	Ph	*i*-Pr	>20:1	90
6	Me	*i*-Pr	>20:1	90
7	Et	$TMSCH_2$	>20:1	78

[a] 0.7 equiv of R_2Zn, 0.7 equiv of $R^1{}_2Zn$.

and as expected, their transfer rate was much lower compared to the transfer rate of methyl, ethyl, and phenyl groups (Table 25, entries 5−7). Furthermore, in situ generation of one of the parent diorganozinc reagents followed by subsequent metathesis to generate the mixed zinc reagents was also viable and broadened the scope of potential transferable groups. A transfer rate of 10:1 and an enantioselectivity of 75% ee were obtained when the phenylation of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (**21**) was carried out with 0.7 equiv of a 1:1 mixture of Ph_2Zn and Et_2Zn in the presence of *i*-PrPHOX ligand (**156**) as a source of chirality. It should be noted that although the transfer rate and yield of the reaction were essentially not affected, the enantioselectivity decreased considerably when the parent Ph_2Zn was in situ prepared from the corresponding phenyl bromide, *n*-butyllithium, and zinc chloride.

Another important issue, namely, the enantioselective anhydride desymmetrization with in situ generated organozinc reagents, has been successfully addressed by switching to rhodium complexes.[82] In this context, alkylation of *cis*-2,3-dimethylsuccinic anhydride (**103**) with 3,4,5-trimethoxyphenylzinc triflate, formed in situ from the appropriate arylbromide by lithium−halogen exchange and subsequent treatment with zinc triflate, performed best (85%, 87% ee) in DMF at 50 °C with a complex derived from [Rd(cod)Cl]$_2$ and phosphoramidite ligand **168** (Taddol-PNMe$_2$). Remarkably, the reaction tolerates a large range of nucleophiles, and the corresponding keto acids are obtained in good yields (74−88%) and high enantiomeric excesses (80−88% ee) (Table 26). Notably, this newly developed methodology has found application in the total synthesis of three eupomatilone lignans.[83]

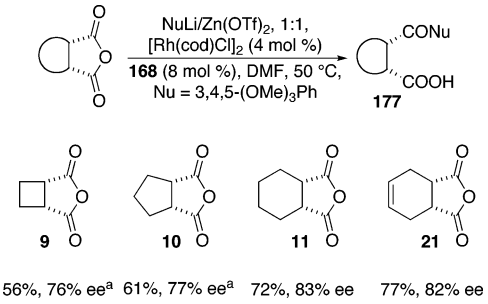
Table 26. Rhodium-Catalyzed Enantioselective Alkylation[a]



entry	nucleophile (NuLi)	yield (%)	ee (%)
1	**169**	85	87
2	**170**	88	88
3	**171**	75	85
4	**172**	74	87
5	**173**	78	87
6	**174**	82	85
7	**175**	76	80
8	**176**	84	86

[a] **171**, R = H; **172**, R = Me; **173**, R = F. NuZnOTf formed in situ from 1:1 NuLi/Zn(OTf)$_2$.

Scheme 20[a]

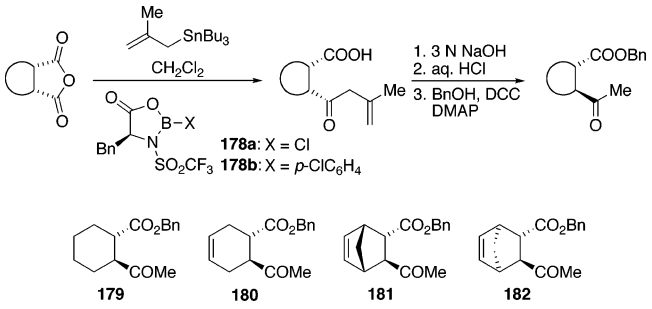


[a] Reactions run at 25 °C.

Furthermore, the reaction is not limited to *cis*-2,3-dimethylsuccinic anhydride, and under previously optimized conditions, several bicyclic anhydrides have been alkylated, leading to the desired products with slightly lower yields (56−77%) and selectivities (76−83% ee) (Scheme 20).

In addition, it was demonstrated that nickel complexes are also able to mediate the processes of decarbonylation and cross-coupling of *meso* anhydrides,[84] leading for the first time to the corresponding β- and γ-cross-coupled products in good yields (50−85%). These newly developed technologies expand the number of potential chemical transformations which are based on the derivatization of easily accessible *meso*-anhydrides.

Table 27. Oxazaborolidinone-Catalyzed Anhydride Alkylation



entry	anhydride	product	temp (°C)	yield (%)	ee (%)
1	**11**	**179**	rt	96	18
2	**11**	**179**	−20	57	30
3	**21**	**180**	rt	91	16
4	**21**	**180**	−20	49	28
5	**26**	**181**	rt	82	29
6	**26**	**181**	−40	26	53
7	**100**	**182**	rt	80	17

3.2.3. Oxazaborolidinone-Catalyzed Anhydride Alkylation

A recent report from Harada[85] showed that the widely used oxazaborolidinones (OXBs)[86] are promising Lewis acid catalysts for the ring opening of cyclic *meso*-anhydrides with 2-methylallyltributyltin. As illustrated in the general reaction scheme of Table 27 the anhydrides were treated at room temperature with 2 equiv of tributylmethallylstannane in the presence of oxazaborolidinone **178b** (30 mol %) as Lewis acid to give the corresponding alkylated products. Subsequent treatment with base led to fragmentation and epimerization, and acidic workup and esterification provided the *trans*-keto esters **179**−**182** in good overall yields (80−96%) but low selectivities (16−29% ee) (Table 27, entries 1, 3, 5, and 7). The selectivity could be slightly increased by lowering the temperature, the process being accompanied by a drastic decrease of yield (Table 27, entries 2, 4, and 6). An improvement in the selectivity was obtained by switching to alternative catalysts with enhanced Lewis acidity, which were able to promote a more selective alkylation reaction at lower temperature. For example, extended reaction (120 h) of the tricyclic anhydride **26** at −78 °C catalyzed by OXB−BCl (**178a**) afforded the enantiomeric *trans*-keto ester, *ent*-**181**, with 80% ee in 13% yield.

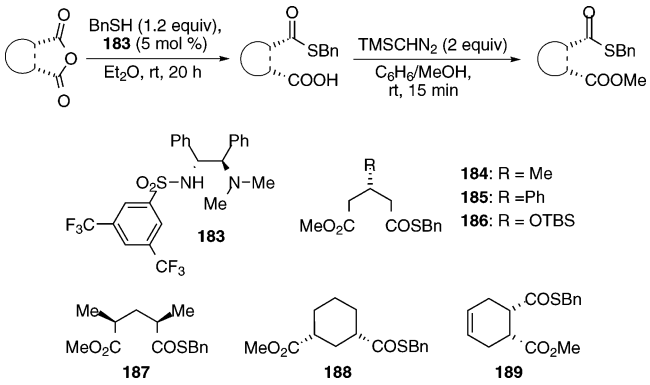
3.3. Enantioselective Desymmetrization with Sulfur Nucleophiles

The success of sulfur-based nucleophiles in the enantioselective desymmetrization of *meso*-epoxides is well acknowledged in the literature, and several excellent catalytic systems have been disclosed.[87] Recent advances in the field of desymmetrization led also to the development of new methodologies based on use of thiol nucleophiles for the asymmetric ring opening of *meso*-anhydrides[88] and newly aziridines.[89]

3.3.1. Sulfonamide-Catalyzed Anhydride Thiolysis

Although rather difficult, the breakthrough in the field of enantioselective thiolysis of *meso*-anhydrides has been achieved by Nagao.[88] Chiral bifunctional sulfonamides,[90] which recently emerged as new organocatalysts for several asymmetric processes, proved their usefulness also in this transformation.

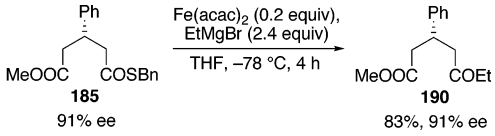
Table 28. Sulfonamide-Catalyzed Anhydride Thiolysis



entry	anhydride	product	yield (%)	ee (%)
1	**35a**	**184**	87	91
2	**35d**	**185**	95	91
3	**22**	**186**	88	93
4	**13**	**187**	100	90
5	**46**	**188**	90	98
6	**21**	**189**	90	83

Treatment of 3-phenylglutaric anhydride (**35d**) with benzyl mercaptane in the presence of a catalytic amount of sulfonamide **183** provided the corresponding benzyl thioester monocarboxylic acid, which upon methylation with TMSCHN$_2$ afforded the corresponding diester. Regarding the catalyst structure, screening of various sulfonamides accentuated the necessity of both acidic and basic functionalities within the catalyst frame in order to ensure a successful reaction. The influence of solvent, temperature, and amount of catalyst on the reaction yield and selectivity has been investigated in detail, and the best results were obtained when the reaction was performed at room temperature in diethyl ether and with 5 mol % of **183** as catalyst. Accordingly various anhydrides have been converted into the corresponding diesters in very high overall yields (87−100%) and high to excellent selectivities (83−98% ee) (Table 28).

The utility of this newly developed transformation has been proven by conversion of the diester **185** into the chiral ketoester **190** (83%, 91% ee) upon treatment with Fe(acac)$_3$ and EtMgBr in THF at low temperature (eq 9).



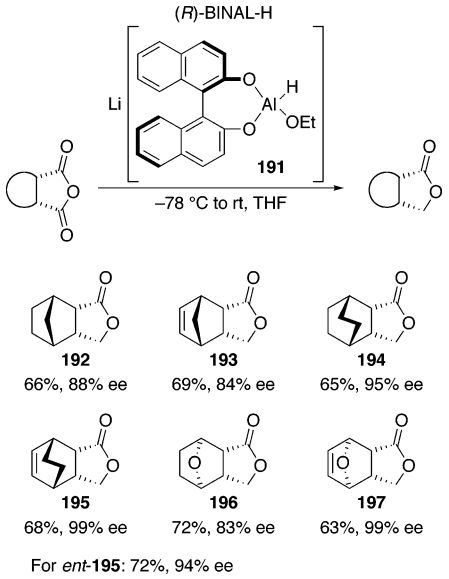
(9)

3.4. Asymmetric Reduction

Selective reduction of the cyclic *meso*-anhydrides provides direct access to the corresponding γ- and δ-lactones. In some early attempts chiral Ru(II) complexes were used to catalyze the asymmetric hydrogenation of several 3-substituted glutaric anhydrides and some bicyclic anhydrides. However, the products were obtained in moderate yields and with low selectivities.[91]

A practical protocol with a wider substrate scope was described by Matsuki[92] and involves use of the well-known BINAL-H.[93] The great efficiency of the complex derived from LiAlH$_4$, ethanol, and 1,1′-bi-2-naphthol has been previously demonstrated in the reduction of unsaturated ketones. Treatment of various tricyclic anhydrides with the in situ prepared (*R*)-BINAL-H afforded the corresponding

Scheme 21



γ-lactones with high to excellent enantioselectivities (83−99% ee) in good yields (63−72%) (Scheme 21).[92a]

Furthermore, this method has been applied to bicyclic anhydrides, and the products have been obtained in moderate to good yields (52−76%) and moderate to high selectivities (64−90% ee) (Figure 10).[92b] Reduction of anhydride **1** delivered the lactone *ent*-**3**, which is the key intermediate for the synthesis of (+)-biotin, in good yield (76%) and high selectivity (90% ee). It is assumed that (*R*)-BINAL-H preferentially attacks the carbonyl group attached to the carbon of pro-(*R*) configuration from its less hindered face (anhydrides **26**, **47**, **65**, and **66**), leading in a first stage to a hydroxylactone which is further reduced to give the final product. In addition, the corresponding enantiomeric lactones can be easily prepared by means of reduction with the easily accessible (*S*)-BINAL-H.

A recent report from Spindler describes the use of iridium-based catalysts for the asymmetric hydrogenation of mono- and bicyclic anhydrides.[94] Although good to full conversions are obtained, the selectivity is in the range of 21−87% ee even under optimized conditions.

3.5. Applications

3.5.1. Amino Acids and Derivatives

Considerable attention has been paid in recent years to the development of efficient strategies for the synthesis of optically pure β-amino acids[95] and especially cyclic ones.[96]

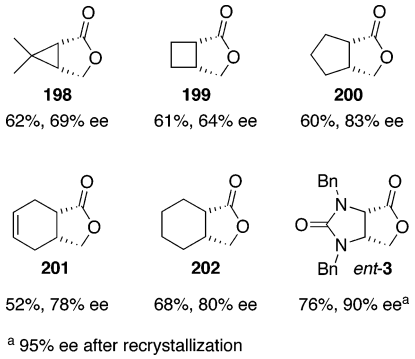
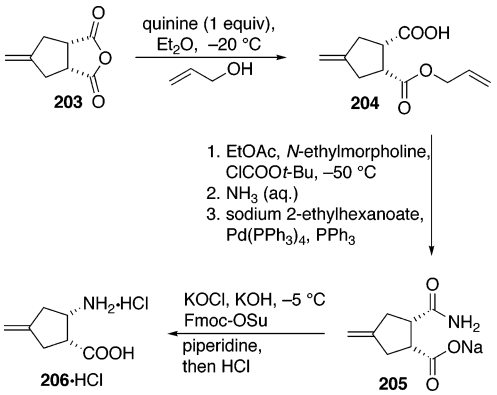
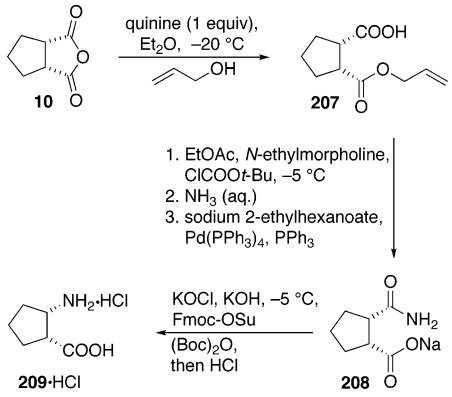


Figure 10.

Scheme 22



Scheme 23



The increasing interest in such cyclic compounds is particularly due to the bright spectrum of biological properties exhibited by many of the members of this class.[97] In addition to their usefulness as essential elements in the pharmacological and medicinal chemistry, recent studies have also been devoted to their incorporation into β-peptides with defined structure.[98]

On the basis of the results of Oda and Aitken, Mittendorf developed a straightforward procedure for the synthesis of alicyclic β-amino acids.[99] Ring opening of the 4-methylene-cyclopentane-1,2-dicarboxylic anhydride (**203**) with allyl alcohol in the presence of an equimolar amount of quinine in diethyl ether proceeded efficiently, affording the corresponding hemiester in 83.5% yield and over 99% ee after only 4 h (Scheme 22). Comparable selectivity has been attained also with propanol, butanol, and isobutanol as nucleophiles (95−98% ee). Interestingly, employment of methanol under similar reaction conditions was less successful and led to the desired methyl hemiester with a significant decrease in the selectivity (75% ee). Nevertheless, subjection of the allyl hemiester (>99% ee) to aminolysis with aqueous ammonia and subsequent cleavage of the allyl protecting group led to the corresponding amide acid in the form of its sodium salt **205**. Hofmann rearrangement with successive mild protection/deprotection steps afforded the desired amino acid hydrochloric salt **206**·HCl without epimerization.

Cispentacine hydrochloric salt **209**·HCl was obtained in a similar manner starting from cyclopentane dicarboxylic anhydride (**10**) (Scheme 23). Cispentacin (**209**), an antifungal antibiotic, which was independently isolated by two Japanese groups from *Bacillus cereus* and *Streptomyces setonii*,[100] was first prepared enantioselectively by Davies.[101] Since then several groups have focused their research toward synthesiz-

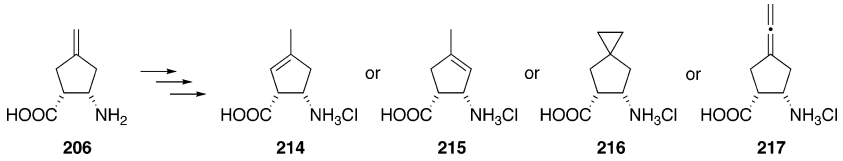
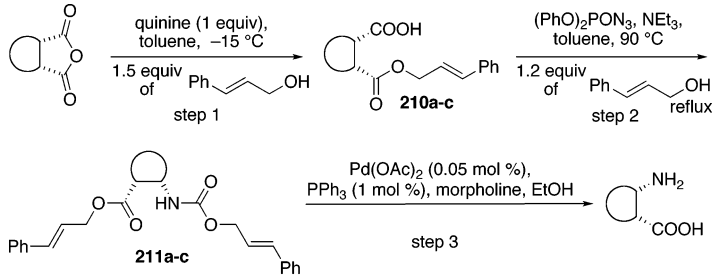


Figure 11.

Table 29. Synthesis of Various *β*-Amino Acids According to Mittendorf



entry	anhydride	aminoacid		step 1 yield (%)	step 1 ee (%)	step 2 yield (%)	step 2 ee (%)	step 3 yield (%)	step 3 ee (%)
1	**203**	**206**	A	94	85	70	>99	70	>99.5
			B[a]	85	>98	80	>99	85	>99.5
2[b]	**203**	*ent*-**206**		93	>93	79	>99	68	>99.5
3	**10**	**209**		93	>86	57	>99	66	>99.5
4[c]	**212**	**213**		-	-	-	-	-	-

[a] After crystallization. [b] Quinidine-mediated reaction. [c] Data are not provided.

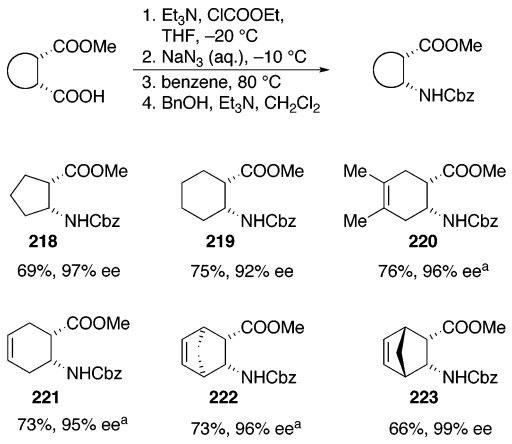
ing this valuable material.[102] Newly, besides its antifungal activity, cispentacin has attracted attention also as an efficient organocatalyst for the Hajos−Parrish−Eder−Sauer−Wiechert reaction.[103]

A substantial improvement of the synthetic path described above has been attained by making use of the same protective group for both acidic and amine functionalities.[104] This new strategy can be used to circumvent extra protection/deprotection steps which were required in the initial approach. As envisaged, the opening reaction of 4-methylene-cyclopentane-1,2-dicarboxylic anhydride (**203**) with cinnamyl alcohol proceeded selectively in the presence of quinine to give the crude hemiester **210a** in 94% yield and 85% ee. Subsequent Curtius rearrangement and trapping of the isocyanate intermediate with cinnamyl alcohol followed by crystallization afforded the protected amino acid **211a** in 70% yield and ≥98% ee. One-pot removal of the ester and carbamate protecting groups followed by recrystallization allowed the isolation of free amino acid **206** in 70% yield and over 99% ee (Table 29, entry 1 A). In addition, precipitation of the racemic form of the product obtained in the first step followed by filtration and evaporation allowed isolation of the optically active hemiester in 85% yield and with an increase in the enantiomeric excess (≥98%). Utilization of this material in the next step permitted isolation of the protected amino acid **211a** in 80% yield and ≥98% ee (Table 29, entry 1 B). Furthermore, the reactions performed well on a pilot-plant unit to produce the free amino acid on kilogram scale. The corresponding enantiomer has been selectively synthesized from the enantiomeric hemiester *ent*-**210a** obtained in the quinidine-mediated ring-opening reaction. Cispentacin (**209**) and heterocyclic amino acid **213** have been synthesized in a similar manner and tested together with the *exo*-methylen derivatives for their potential antifungal activity against *Candida albicans*. A similar approach toward synthesizing the cinnamyl ester **210a** was recently described by scientists from Daiso Co.,[57i] *O*-propargylquinine[55,57h] being now employed as catalyst in the reaction.

Other optically active cyclopentane *β*-amino acid analogs have been easily accessible starting from **206** using the *N*-Boc-protected amino acid or amino ester as key intermediates (Figure 11).

In addition, an alternative synthesis of the free amino acid **214** starting from the *meso*-anhydride **203** has been recently described by Hamersak.[105] The synthetic approach involves conversion of the *meso*-anhydride **203** into the racemic 5-methyl-4,6a-dihydro-3aH-cyclopenta[c]furan1,3-dione followed by quinine-mediated kinetic resolution and Curtius

Scheme 24[a]



[a] Over 99.7% ee after recrystallization.

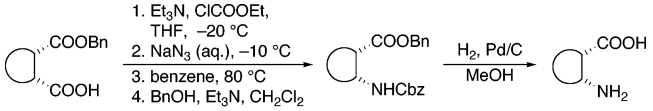
rearrangement to give a mixture of cis- and trans-protected amino acids. Purification by crystallization followed by deprotection and recrystallization allowed isolation of the free amino acid **214** in 97% ee.

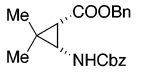
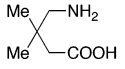
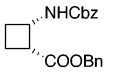
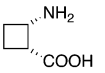
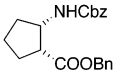
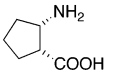
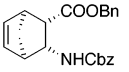
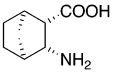
Similar strategies, which allow the synthesis of various protected as well as free cyclic β-amino acids, were independently developed by Bolm.[49,102c] The first approach[100c] used as chiral synthons the hemiesters available from the highly enantioselective methanolysis of cyclic *meso*-anhydrides.[47] Subjection of the methyl hemiesters to Curtius rearrangement and trapping of the isocyanate intermediate with benzyl alcohol afforded the corresponding *N*-Cbz-protected amino esters **218**−**223** without loss of selectivity (Scheme 24). Only conversion of the methyl hemiester (95% ee) obtained from the desymmetrization of anhydride **100** into the corresponding protected amino acid was less successful, and due to side reactions, the product was obtained in 28% yield and 27% ee. The synthetic route described above was not limited to *N*-Cbz protection, and it was shown that protecting groups like MOZ, hZ, (2-NO$_2$)-Z-, or Boc are as well tolerated. Furthermore, one-pot acidic hydrolysis of the isocyanate and ester moieties in the intermediate derived from the monoester obtained from the quinine-mediated methanolysis of anhydride **10** afforded the cispentacine hydrochloride as its hemihydrate complex (**209**·HCl·0.5 H$_2$O), an additional ion exchange chromatography being required to liberate the unprotected amino acid.[101b]

Furthermore, both *exo*- and *endo*-norbornene derivatives **222** and **223** proved to be useful monomers in the ring-opening methathesis polymerization reaction, allowing the synthesis of polymeric materials with a defined weight and chain length.[106] The *N*-Boc-protected norbornene amino acid derivative has been used as a template for the synthesis of conformationally constrained two-stranded peptides with an antiparallel orientation.[107]

Easier access to the free amino acids was facilitated by the availability of optically active benzyl monoesters.[49] In this particular case the ease of benzyl ester deprotection by simple hydrogenation was explored after the derivatization reactions. Accordingly, the *N*-Cbz-protected amino acid benzyl esters, obtained by Curtius rearrangement of the corresponding acyl azides and trapping with benzyl alcohol, were easily converted into the desired free β-amino acids (Table 30). Although the reactions were performed on a 15 mmol laboratory scale, due to the ease of all the synthetic steps and accessibility of the substrates, larger quantities would as well be easily manageable.

Table 30. Synthesis of Various β-Amino Acids According to Bolm



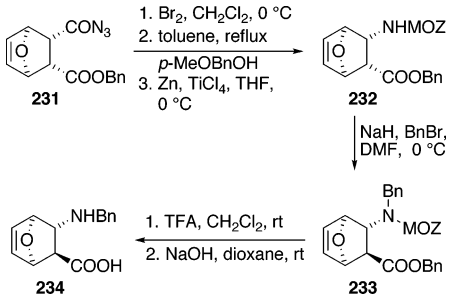
entry	protected amino acid	yield (%)	ee (%)	aminoacid	yield (%)
1	 **224**	70	19	 **225**	-
2	 **226**	74	93	 **227**	93
3	 **228**	77	94[a]	 **209**	98
4	 **229**	72	93	 **230**	97

[a] >99.7% ee after recrystallization

Application of this new protocol allowed the simplified asymmetric synthesis of cispentacin (**209**) (>99% ee) (Table 30, entry 3) and delivered for the first time the optically active saturated amino acid **230** (93% ee) (Table 30, entry 4).[108] It should be noted that in the case of cyclopropyl derivative **224** the Curtius degradation process occurred with partial racemization, which is most probably due to the presence of an open-chain intermediate which finally undergoes a stereospecific ring-closure reaction (as revealed by NMR spectroscopy). The instability of the three-membered ring was once more proven during the attempted hydrogenolytic deprotection reaction when instead of the desired cyclic product the corresponding ring-opened achiral γ-amino acid **225** was the only identified product. Considerable attention should also be paid to the deprotection of **226**. In this case, the corresponding free amino acid **227** was obtained in high yield (93%) and selectively (93% ee) only when the hydrogenation was performed under standard conditions (H$_2$, Pd/C, MeOH, 1−2 h). Extending the reaction time to 12 h led, in a test experiment, to C−C bond cleavage. Although highly sensitive,[109] the (−)-2-aminocyclobutane-1-carboxylic acid **227** is a valuable material and has been used, in a protected form, for the synthesis and structural investigation of conformationally constrained β-dipeptides.[110] In addition, an alternative strategy which allows the synthesis of both enantiomers with >97% ee has recently been described.[111]

Remarkably, with the aid of the desymmetrization protocol described by Bolm, even the synthesis of highly sensitive oxa-norbornene derivatives has successfully been addressed (Scheme 25).[112] Regarding the overall synthetic strategy, additional protection/deprotection steps are required since the substrate is prone to decompose during the conventional Curtius degradation. In this context, protection of the double bond in the acyl azide **231** obtained according to Bolm followed by rearrangement and double-bond deprotection furnished the protected *cis*-β-amino acid **232**. *N*-Benzylation with simultaneous epimerization and subsequent deprotection afforded the appropriate *trans*-β-amino acid **234**, which was

Scheme 25



used in an Ugi multicomponent reaction. Subjection of the Ugi adducts to retro-Diels−Alder reaction and several deprotection steps allowed, as a result, the synthesis of various (*S*)-α-amino acid derivatives in a highly efficient manner. The corresponding enantiomer *ent*-**234** and, with it, controlled access to (*R*)-α-amino acid derivatives is easily provided just by using quinidine in the initial desymmetrization reaction.

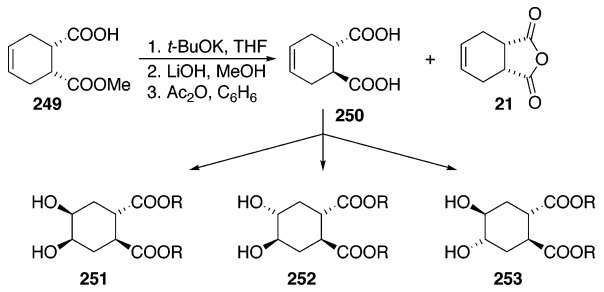
A slightly modified protocol has been used by scientists at Bristol-Myers Squibb for the pilot-plant production of *trans*-*β*-amino acid **237**,[113] which is a valuable intermediate in the synthesis of **242**, a selective CCR3 antagonist (Scheme 26).[114] The enantioselectivity of 87% ee observed in the desymmetrization step has been retained during the selective ester epimerization reaction and could be significantly increased (>99% ee) by crystallizing the salt obtained when treating the *trans*-hemiester with (*R*)-1-phenylethylamine.

Recently, the synthesis of proline derivative **248**,[115] a key intermediate for the synthesis of a Hepatitis C virus protease inhibitor,[116] has been accomplished by starting from cyclopropane *meso*-anhydride **8**. Aminolysis of the allyl half-ester **243** followed by reduction afforded the appropriate 1,4-amino alcohol **245**, which was easily converted into the *N*-Cbz-protected *γ*-amino aldehyde **246**. The α-hydroxypyrrolidine derivative obtained by cyclization was subsequently converted into the desired proline derivative **248**.

3.5.2. Toward the Synthesis of Glycomimetics

Another synthetic approach, which relies on the protocol developed by Bolm, was described by Bernardi, who applied the anhydride desymmetrization as a key step in the synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid (**250**).[117] The (1*S*,2*S*) enantiomer obtained according to the route depicted in Scheme 28 was used as a synthon in

Scheme 28

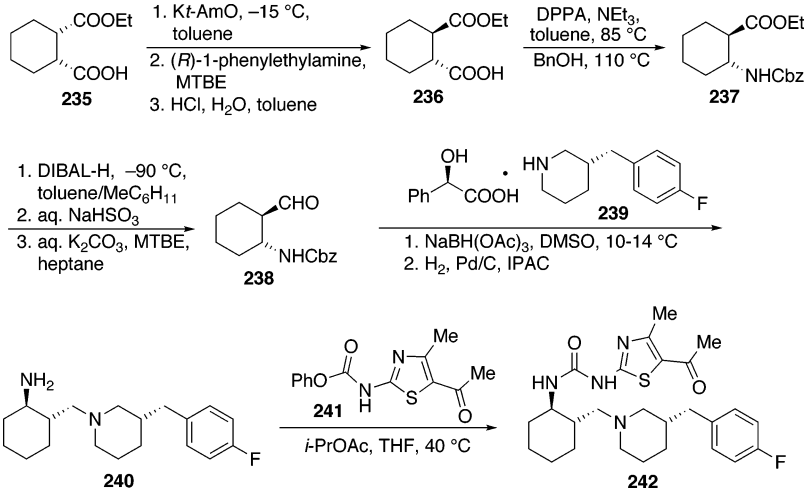


the synthesis of conformationally constrained cyclohexanediols of type **251**−**253**, which are useful building blocks for the preparation of glycomimetics,[118] as promising therapeutic agents.[119]

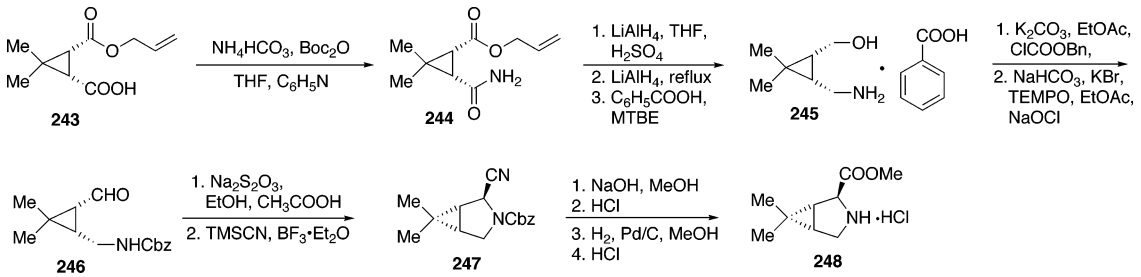
3.5.3. Asymmetric Synthesis of the Cyclopentyl Core of Axinellamines

Axinellamines (**258**)[120] are bis-guanidine alkaloids which received increasing attention after their isolation from the

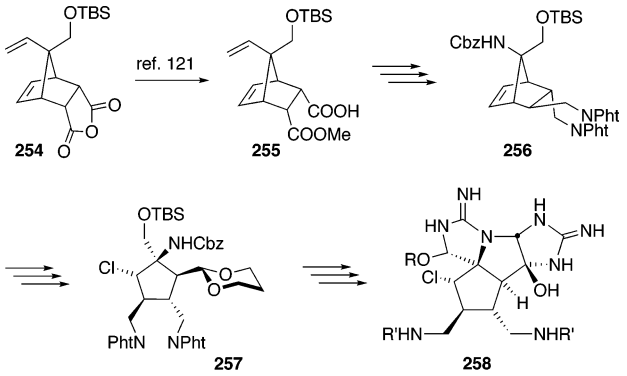
Scheme 26



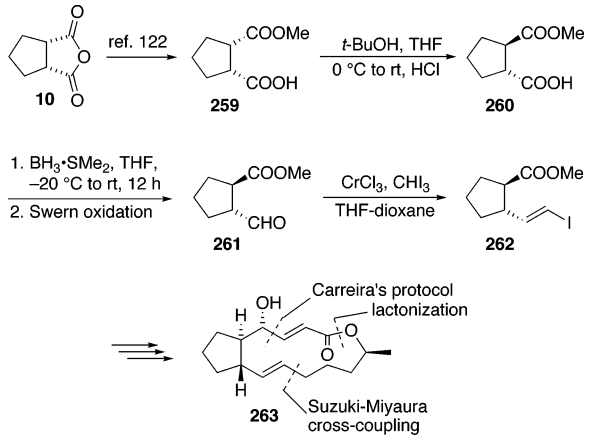
Scheme 27



Scheme 29



Scheme 30



marine sponge Axinella sp., particularly due to their activity against the Gram-negative bacterium *Helicobacter pylori*. Development of efficient methodologies for their stereoselective synthesis was therefore demanded. In this context, Carreira described an approach toward synthesizing the cyclopentyl core of these natural products in a stereocontrolled manner.[121] As illustrated in Scheme 29, the overall synthetic strategy takes advantage at an early stage of the anhydride desymmetrization methodology in order to introduce asymmetry into the *meso*-substrate. The fully functionalized cyclopentyl core **257** was obtained by following a suitable synthetic path and proper selection of the reaction conditions.

3.5.4. Total Synthesis of Brefeldin C

Anhydride desymmetrization and subsequent selective epimerization were also used in order to introduce the stereochemistry into the main fragment required for the total synthesis of naturally occurring biologically active (+)-brefeldin C (**263**).[122] This compound is the precursor for (+)-brefeldin A,[123] a naturally occurring macrolide which, as previously demonstrated, possesses unique biological activities.

3.5.5. Synthesis of a $\alpha_v\beta_3$ Antagonist

A slight modification of the desymmetrization procedure reported by Bolm has been applied by scientists at Merck for the ring opening of monocyclic anhydride **264** (Scheme 31).[124] Accordingly, both methyl hemiester enantiomers, (*S*)-**265** and (*R*)-**265**, could be easily synthesized on kilogram scale. Subsequently, they were converted into phosphorane **266** and phosphonate **267**, respectively, having the same absolute configuration (*S*). At this stage, their different reactivity coupled with the advantageous purification of phosphorane **266** by crystallization favored its use for further derivatization. Hence, the synthesis proceeded by coupling of phosphorane **266** with aldehyde **268**, and subsequent functionalizations afforded the desired $\alpha_v\beta_3$ antagonist **281**, a potential candidate for the treatment of osteoporosis.

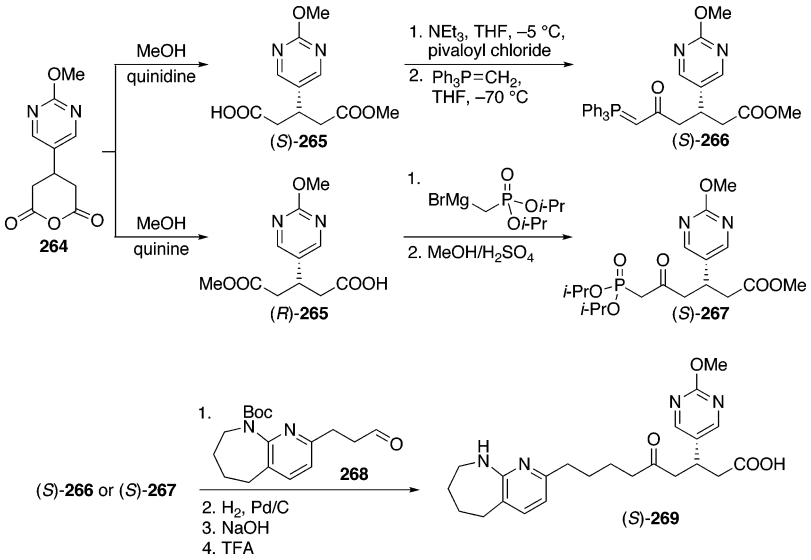
3.5.6. Toward the Synthesis of Biotin

As highlighted in the previous sections, the diastereoselective anhydride desymmetrization has frequently been used as a supporting tool for the synthesis of lactone *ent*-**3**, a key intermediate in the total synthesis of biotin.[35] Concerning the enantioselective ring opening of *cis*-1,3-dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**1**), despite several attempts so far the best results were achieved by Deng when employing the mono-cinchona alkaloid DHQD-PHN as catalyst in the reaction. Selective acid reduction of *ent*-**105a** followed by cyclization allowed formation of the desired lactone *ent*-**3** without any decrease of the enantiomeric excess (Scheme 32).[125]

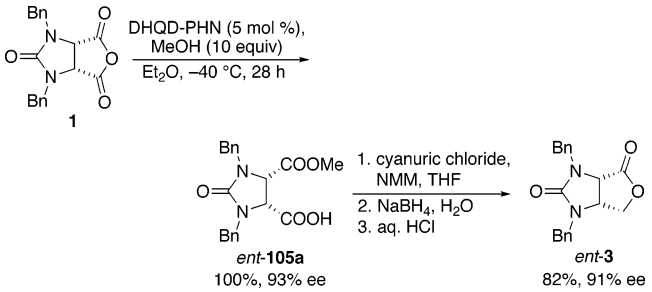
3.5.7. Toward the Synthesis of Lophotoxin

Deng's desymmetrization protocol has also been successfully applied to the ring opening of 3-OTBDPS-substituted

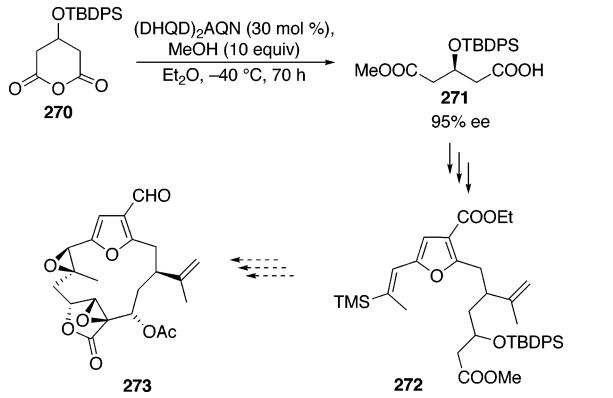
Scheme 31



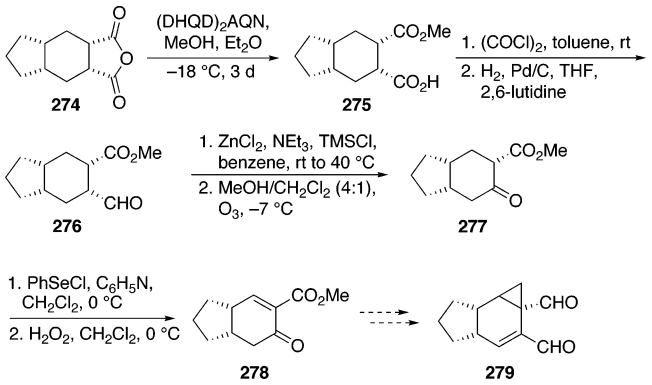
Scheme 32



Scheme 33



Scheme 34



glutaric anhydride (**270**)[126] to give the methyl hemiester **271** (95% ee), which was, after intensive optimization processes, converted into the furan derivative **272**, a potential precursor for the synthesis of lophotoxin (**273**) (Scheme 33).[127]

3.5.8. Toward the Synthesis of an Isovelleral Analog

The bis-cinchona alkaloid-catalyzed ring-opening reaction constituted the key for successful transformation of the *meso*-anhydride **274** into the optically active α,β-unsaturated β-keto ester **278** (90% ee).[128] The latter compound is an intermediate in the synthesis of tridemethylisovelleral (**279**), an analogue of the biologically active isovelleral. Since the conversion of *rac*-**278** into the (±)-dialdehyde **279** has already been accomplished,[129] the synthesis of optically pure material constitutes a complex but not difficult task. Notably, racemic tridemethylisovelleral displayed higher cytostatic activity toward cancer cells when compared to (+)-isovelleral.

Apart from the impressive applications described above, the desymmetrization methodology has also found utilization in the synthesis of chiral diamines,[130,131] aminoalocols,[132,133] and more recently C_2- and C_1-symmetric bis-oxazolines.[134] Whereas Bolm described the synthesis of norbornane-type vicinal diamines,[130] Tanyeli presented the synthesis of a 1,4-analog.[131] Furthermore, synthesis of 1,3-amino alcohols with a norbornane backbone[132] and 1,4-amino alcohols with an unsaturated framework[133] has also been addressed, and the products have been tested as chiral ligands in the asymmetric addition to aldehydes.

4. Conclusions

The anhydride desymmetrization has extensively been investigated over the past few years, and along with well-established methods involving the use of oxygen- and nitrogen-based nucleophiles, new concepts making use of carbon and sulfur nucleophiles have recently been introduced. As stated above, both diastereo- as well as enantioselective approaches furnished reliable and practical synthetic protocols, which have received increasing attention and widespread applications for the preparation of biologically active compounds on lab- as well as large-scale synthesis. Regarding the enantioselective ring opening, a couple of methods are particularly noteworthy since both enantiomers of a given product are easily available in optically active from the same substrate just by careful selection of the reaction conditions. Furthermore, as a result of the development of new methods in the field of anhydride desymmetrization, even the synthesis of challenging substrates can now be successfully addressed.

5. Abbreviations

Ac	acetyl
Acac	acetylacetonate
t-Am	*tert*-amyl
Aux	auxiliary
AQN	anthraquinone
BINAL-H	reagent prepared from 1,1′-binaphthol, $LiAlH_4$, and ethanol
bipy	2,2′-bipyridyl
Bh	benzhydryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
Cat	catalyst
Cbz	benzyloxycarbonyl
CD	cinchonidine
CN	cinchonine
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DIBAL-H	diisobutyl aluminum hydride
DHQD	dihydroquinidinyl
DHQ	dihydroquinyl
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
Et	ethyl
Fmoc-OSu	*N*-(9-fluorenylmethoxycarbonyloxy)succinimide
HMPA	hexamethylphosphoramide
Josiphos	(*R*)-(−)-1-[(*S*)-2(diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine
Me	methyl
MOZ	*p*-methoxybenzyloxycarbonyl
MTBE	methyl *tert*-butyl ether
NMM	*N*-methylmorpholine
MS	molecular sieves
Np	naphthyl

NPht	phthalimido
Nu	nucleophile
QD	quinidine
QN	quinine
pempidine	1,2,2,6,6-pentamethylpiperidine
PG	protecting group
Ph	phenyl
PHN	9-phenantryl
Pyphos	(2-diphenylphosphino)ethylpyridine
PMB	*p*-methoxybenzyl
i-Pr	isopropyl
n-Pr	*n*-propyl
Py	pyridine
i-PrPHOX	(4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole
$[Rh(cod)Cl]_2$	bis(1,5-cyclooctadiene)dirhodium(I) dichloride
Sty	styrene
TADDOL	α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
o-tolyl	*o*-methylphenyl
TPS	triisopropylbenzenesulfonyl
Ts	*p*-toluenesulfonyl
hZ	phenethyloxycarbonyl
$(2\text{-}NO_2)$-Z-	*o*-nitrobenzyloxycarbonyl

6. Acknowledgment

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7. Addendum

This review covers the literature until June 2007. During the submission and review period of this article a few new publications related to this topic have appeared.[135−139]

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