Asymmetric Alcoholysis of Cyclic Anhydrides

Yonggang Chen, Paul McDaid, and Li Deng*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

Received February 27, 2003

Contents

1. Introduction

Asymmetric dihydroxylation of simple olefins,[1,2] epoxidation of olefins,[3,4] and the asymmetric hydrogenation and reduction of ketones[5] are all mediated by small molecule catalysts and are among the most useful asymmetric transformations in organic synthesis. In addition to high enantioselectivity, other common features shared by these reactions are their accessibility to the chemist in terms of ease of use, generality and availability of substrate, accessibility of catalyst and reagents, and inherent value of the chiral product. These reactions set a benchmark by which all new asymmetric reactions are judged.

These reactions involve the chiral recognition of two enantiotopic faces of a ubiquitous planar functional group. Powerful catalytic asymmetric transformations that involve the discrimination of enantiotopic functional groups via desymmetrization or the differentiation of racemates via kinetic resolution are less common. However, desymmetrizations and kinetic resolutions benefit from the availability of a wide variety of meso, prochiral, and racemic substrates, the possibility of employing virtually any chemical transformation, and the opportunity to establish the absolute configurations of multiple stereogenic centers in a single step. Consequently, chemists who wish to develop new and powerful asymmetric transformations using these synthetic strategies have a wealth of reactions and substrates to choose from. Recently, an increasing amount of effort has been devoted to the development of efficient catalytic desymmetrizations and kinetic resolutions.[6] This review focuses on the desymmetrizations and kinetic resolutions via enantioselective alcoholytic ring opening (ARO) of a wide range of readily available meso, prochiral, and racemic cyclic anhydrides.[7] These asymmetric alcoholyses have recently emerged as promising reactions that may be applicable to both research and industrial scale asymmetric synthesis of a broad range of important chiral building blocks such as hemiesters, α-amino acids, and α-hydroxy acids. Because of the very limited number of examples, enzyme-mediated alcoholysis of meso cyclic anhydrides will not be discussed in this review.[8]

2. Desymmetrization of Meso and Prochiral Cyclic Anhydrides

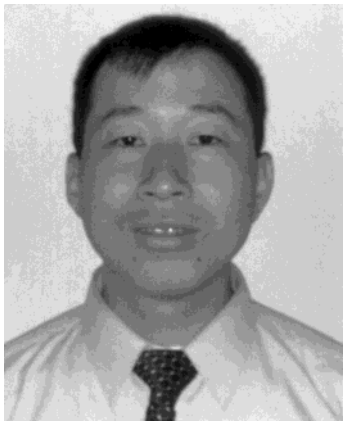
A wide range of meso and prochiral cyclic anhydrides, including those containing multiple rings and multiple stereogenic centers, are readily accessible. Desymmetrization of such a symmetric cyclic anhydride via enantioselective alcoholysis generates the corresponding hemiester, a highly functionalized chiral product with one or more stereogenic centers. The desymmetrization creates chirality by breaking the symmetry of the meso compound. Consequently, the absolute configuration of numerous stereogenic centers can be established in a single chemical step. The two chemically differentiated functional groups of the hemiester provide handles for further synthetic elaboration. This is a value-added transformation that utilizes a cheap reagent, an alcohol, to convert a ubiquitous structural motif to a remarkably valuable chiral building block. Not surprisingly, a considerable amount of effort has been devoted to the development of general and highly enantioselective variants of this desymmetrization over the past 20 years.

2.1. Diastereoselective Alcoholysis Using Chiral Nucleophiles

The reaction of a meso or prochiral cyclic anhydride with a chiral alcohol produces the corresponding

* Author to whom correspondence should be addressed [fax (781) 736-2516; e-mail deng@brandeis.edu].

10.1021/cr020037x CCC: $44.00
Published on Web 07/29/2003

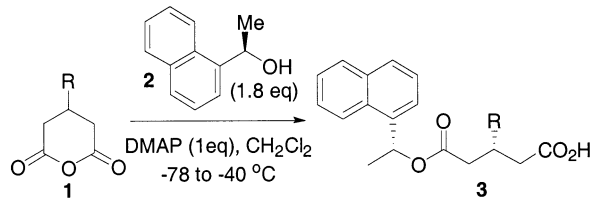


Yonggang Chen was born in Dunhuang, China, in 1973. He obtained both his B.S. and M.S. degrees from Lanzhou University under the supervision of Professor Yulin Li. He recieved his Ph.D. in chemistry from Brandeis University in 2003 with Professor Li Deng. He is currently an American Heart Association Postdoctoral Fellow with Professor Eric N. Jacobsen at Harvard University. Dr. Chen's research interests involve the development of new reactions in organic synthesis and the synthesis of bioactive molecules.

Paul McDaid was born in 1975 in Dublin, Ireland. He received his B.S. in chemistry in 1997 from University College Dublin. Since 1998 he has been a graduate student at Brandeis University in the laboratory of Professor Li Deng, where he is involved in the study of catalytic asymmetric reactions.

Li Deng received his B.S. degree from Tsing Hua University in Beijing, China, his M.S. degree with James M. Cook from the University of Wisconsin—Milwaukee, and his Ph.D. in chemistry with Eric N. Jacobsen from Harvard University. After an American Cancer Society postdoctoral fellowship with Professors Gregory L. Verdine and George M. Whitesides at Harvard University, he joined the faculty at Brandeis University in 1998, where he is now Associate Professor of chemistry. He has held an Alfred P. Sloan Foundation Fellowship. His current interests lie in the development of new synthetic reactions and asymmetric synthesis.

Table 1. Desymmetrization of Meso 3-Substituted Glutaric Anhydrides Using a Chiral Alcohol as Nucleophile



entry	anhydride	R	time (days)	temp (°C)	yield (%)	ds
1	**1a**	OTBS	9	−75	92	50:1
2	**1b**	Me	2	−40	94	16:1
3	**1c**	Et	3	−40	95	14:1
4	**1d**	*i*-Pr	4	−40	97	7:1
5	**1e**	Ph	3	−40	92	8:1
6	**1f**	*t*-Bu	16	−40	91	1:3

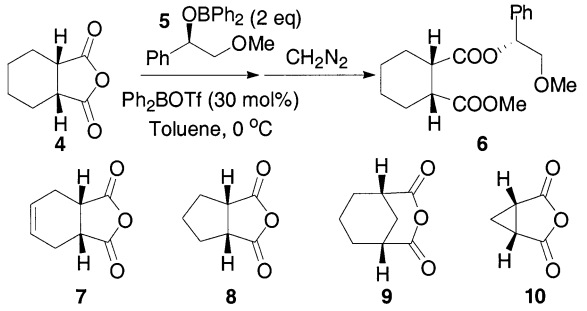
hemiester as two distereomers. This approach was first applied in 1956 by Cohen to desymmetrize a prochiral anhydride, 3-phenyl glutaric anhydride, using menthol as the stoichiometric nucleophile.[9] However, the two diastereomers were generated in a close to 1:1 ratio. In 1985, Heathcock first demonstrated that synthetically useful selectivity could be attained for the desymmetrization of cyclic anhydrides with a chiral alcohol.[10] The highest diastereoselectivity was obtained with (*R*)-1-(1′-naphthyl)-ethanol (**2**) as the chiral nucleophile in the desymmetrization of 3-[(*tert*-butyldimethylsilyl)oxy] glutaric anhydride (**1a**) (Table 1).[11] The diastereoselectivity was lower with simple alkyl or aryl substituents and decreased as the atom of the substituent attached to the anhydride ring became increasingly substituted.

Mukaiyama used (*R*)-2-methoxy-1-phenylethanol diphenylborate (**5**) as the nucleophile, in the presence of a catalytic amount of diphenylboryl triflate, to effect the diastereoselective desymmetrization of a number of meso bicyclic anhydrides, forming the corresponding hemiesters in moderate to excellent diastereoselectivities (40−99% de) and good to excellent yields (75−95%) (Table 2).[12] The best results were obtained for succinic and glutaric anhydrides fused with a six-membered ring. Replacement of the six-membered ring with a ring of smaller size led to a decrease in the diastereoselectivity.

The diastereoselective alcoholysis approach was also explored with metal salts of chiral diols and chiral amino alcohols. Taguchi reported that modest to excellent selectivities could be achieved for the ring opening of both meso succinic anhydrides and prochiral 3-substituted glutaric anhydrides **1** using the monosodium salt of diol **11** (Table 3).[13]

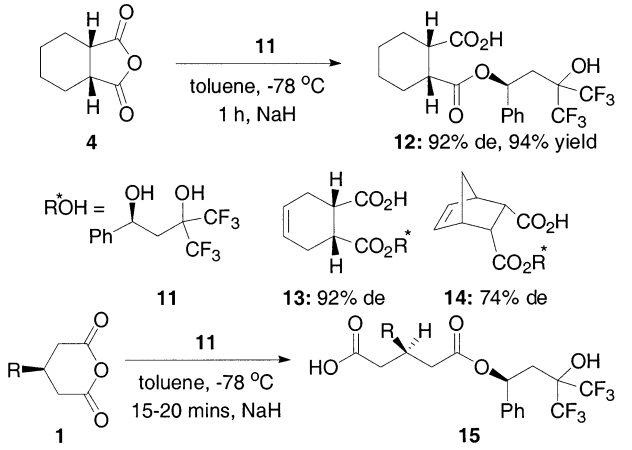
More recently, Kunieda attained extraordinarily high diastereoselectivity in the ring opening of a variety of bi- and tricyclic succinic anhydrides with the lithium or zinc salts of rigid chiral *N*-sulfonyl amino alcohols (Table 4).[14] The steric bulk of the sulfonyl group, the metal species used, and the use of additives all play a crucial role in determining the stereoselectivity. The highest diastereoselectivities were achieved using the lithium salts of the bulky

Table 2. Asymmetric Desymmetrization of Meso Cyclic Anhydrides Catalyzed by Diphenylboryl Triflate



entry	anhydride	time (h)	yield (%)	de (%)
1	**4**	61	90	99
2	**7**	94.5	95	90
3	**8**	229	75	70
4	**9**	116	90	90
5	**10**	61	91	40

Table 3. Diastereoselective Alcoholysis of Meso Cyclic Anhydrides Using 1-Phenyl-3,3-bis(trifluoromethyl)propane-1,3-diol



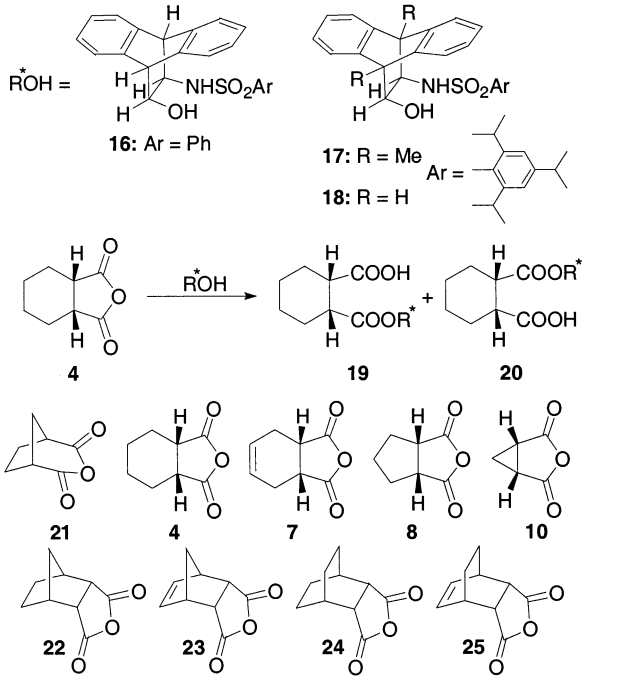
entry	anhydride	R	yield (%)	de (%)
1	**1a**	TBSO	90	92
2	**1b**	Me	90	66
3	**1d**	*i*-Pr	94	90
4	**1e**	Ph	95	66
5	**1g**	CF_3	95	90
6	**1h**	$PhCH_2$	96	76

amino alcohols **17** and **18** in the presence of 5 equiv of HMPA (Table 4, entries 3, 5, 7, 9, and 11−14). The selecitivities were not as high with the lithium salt of chiral *N*-tosyl alcohol **16**. However, when the zinc salt of **16** was used as the nucleophile (Table 4, entry 2) the sense of asymmetric induction was found to be opposite to that obtained using the corresponding lithium salt (Table 4, entry1). Consequently, either diastereomer of the product could be obtained using alcohol **16**, depending on the metal species used in the reaction. The mechanism for the reversal of the diastereoselection remains unclear.

As summarized in Scheme 1, Shirahama carried out the desymmetrization of 3-hydroxy-3-methyl glutaric anhydride (**27**) via an intramolecular alcoholysis. When treated with the lithium alkoxide of hydroquinine (1.1 equiv), the (*R*)-enantiomer of β-lactone **26** was formed in >90% ee and 70% yield.[15] With hydroquinidine, the (*S*)-enantiomer **28** was obtained in similar ee and yield.

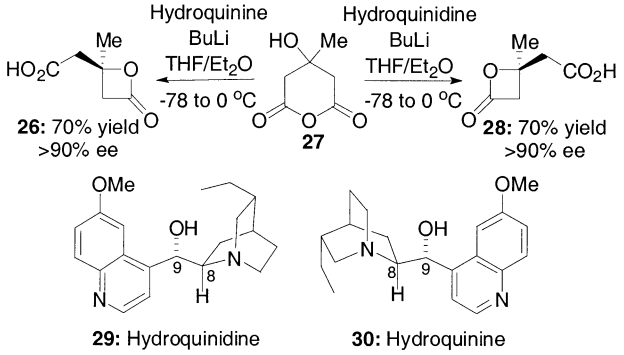
In addition to chiral alcohols,[16] other chiral nucleophiles, such as chiral amines[17] and oxazolidinones[18] have also been used in the highly diastereoselective desymmetrization of various meso cyclic anhydrides.

Table 4. Diastereodifferentiation of Meso Cyclic Anhydrides Using Sterically Congested Chiral *N*-Sulfonylamino Alcohols



entry	anhydride	reagents	additive (equiv)	solvent	temp (°C)	yield (%)	**19**:**20** (de)
1	**21**	**16**/BuLi	LiCl (2.0)	THF	−78	81	28:1
2	**21**	**16**/$ZnEt_2$		$CHCl_2$	25	90	1:22
3	**4**	**17**/BuLi	HMPA (5.0)	THF	−78	93	500:1
4	**4**	**16**/$ZnEt_2$	THF (1.0)	$CHCl_2$	reflux	85	1:26
5	**7**	**17**/BuLi	HMPA (5.0)	THF	−78	90	500:1
6	**7**	**16**/$ZnEt_2$		$CHCl_2$	25	89	1:17
7	**8**	**17**/BuLi	HMPA (5.0)	THF	−78	78	500:1
8	**8**	**16**/$ZnEt_2$		$CHCl_2$	25	82	1:4
9	**10**	**17**/BuLi	HMPA (5.0)	THF	−78	95	500:1
10	**10**	**16**/$ZnEt_2$		$CHCl_2$	reflux	85	1:1.3
11	**22**	**18**/BuLi	HMPA 5.0)	THF	−78	99	150:1
12	**23**	**18**/BuLi	HMPA (5.0)	THF	−78	86	99:1
13	**24**	**18**/BuLi	HMPA (5.0)	THF	−78	90	160:1
14	**25**	**18**/BuLi	HMPA (5.0)	THF	−78	84	140:1

Scheme 1. Asymmetric Desymmetrization of HMGA



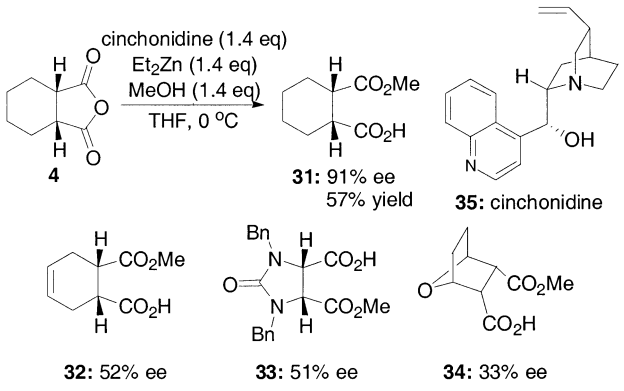
Although high diastereoselectivities can be achieved using chiral alcohols or their corresponding sodium or lithium salts as the nucleophile, this chiral auxiliary approach has a number of inherent disadvantages. Initially obtaining stoichiometric amounts of the chiral alcohol can be costly and time-consuming. The removal and subsequent recovery of the chiral auxiliary from the resulting hemiester is also not as straightforward as desired. Another drawback is the lack of generality observed in these transformations. Subtle changes in the structure of the cyclic anhydride often have a deleterious effect on the selectivity of its reaction with a given chiral alcohol. Consequently, reliably achieving synthetically useful levels of asymmetric induction for a wide range of meso cyclic anhydrides using a single and easily accessible chiral reagent, even in a stoichiometric amount, remains a significant challenge.

As a nucleophile−electrophile reaction, the alcoholysis of anhydrides can be promoted by either a Lewis acid or a Lewis base. Conceivably, many of the limitations associated with the chiral auxiliary approach can be overcome via an efficient chiral Lewis acid-catalyzed or chiral Lewis base-catalyzed alcoholysis. The most tantalizing prospect is, without question, the realization of a highly enantioselective and reliable desymmetrization using a catalytic amount of chiral Lewis acid or Lewis base while employing a cheap alcohol as the stoichiometric nucleophile.

2.2. Enantioselective Alcoholysis with Chiral Lewis Acids

In 1993, Fujisawa and co-workers reported a Zn-mediated desymmetrization of *cis*-1,2-cyclohexane dicarboxylic anhydride (**4**).[19] Addition of a solution of the anhydride (1.0 equiv) at 0 °C to a pre-prepared THF solution containing methanol (1.4 equiv), a natural cinchona alkaloid (1.4 equiv), and diethyl zinc (1.4 equiv) led to the formation of the corresponding hemiester in enantiomerically enriched form (Scheme 2).

Scheme 2. Enantioselective Desymmetrization of Meso Cyclic Anhydrides



This transformation was explored using a variety of combinations of chiral amino alcohols, solvents, and alcohols. The best results were obtained using cinchonidine as ligand. *cis*-1,2-Cyclohexane dicarboxylic anhydride (**4**) was converted to its corresponding hemiester **31** in 91% ee and 57% yield under the optimized conditions shown in Scheme 2. This was the first example of the use of a metal-based reagent to mediate a highly enantioselective desymmetrization of a meso cyclic anhydride with a common achiral alcohol. However, the enantioselectivity was very sensitive to the structure of the substrate. Under the same reaction conditions, desymmetrization of anhydrides **4** and **7** afforded the corresponding hemiesters **31** and **32** in 91 and 52% ee, respectively.

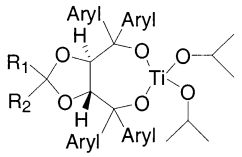


Figure 1. Ti-TADDOLates (*R*, *R*).

Oda had previously discovered that cinchona alkaloids catalyzed the methanolysis of anhydrides in the absence of a metal.[20] The dramatically different enantioselectivities obtained in Fujisawa's and Oda's studies (vide infra) employing the same cinchona alkaloid (cinchonidine) in the asymmetric alcoholysis of anhydride **7** (52 vs 18% ee, respectively) indicated that Zn played an important role in Fujisawa's system. Fujisawa suggested that the cinchona alkaloid and diethyl zinc form a rigid metallocycle, which activates the anhydrides and effects the discrimination of the enantiotopic functional groups.

In 1995, Seebach and co-workers reported a dramatic advancement in the development of a chiral Lewis acid-promoted alcoholytic desymmetrization of meso anhydrides.[21] Seebach's previous success using chiral titanates to promote a variety of enantioselective reactions[22] had prompted him to explore the possibility of using these chiral Lewis acids in the asymmetric alcoholysis of meso cyclic anhydrides. The chiral titanates **36** shown in Figure 1 (the diisopropoxytitanuim TADDOLates) contain both a Lewis acidic moiety and a nucleophilic isopropoxide moiety within the same molecule. It was envisioned that the alcoholysis of cyclic meso anhydrides could be carried out via the transfer of an alkoxide from the chiral ligand sphere of the titanate to the Lewis acid-activated anhydride. This desymmetrization reaction was initially examined using *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**23**; Figure 2). Under optimized reaction conditions, treatment of the anhydride **23** with 1.20 equiv of the Ti-TADDOLate **36d** in THF at −30 °C gave the corresponding chiral hemiester **44** in 98% ee and 88% yield (Table 5). Both the ligand and the product were purified via a convenient extractive procedure.

One outstanding feature of this reaction is the unprecedented substrate scope, with excellent ee values (90−98%) obtained for an array of bi- and tricyclic succinic anhydrides. The ring opening of monocyclic *cis*-2,3-dimethyl succinic anhydride (**42**) occurred in 96% ee and 73% yield. However, the reaction is not effective for highly functionalized and bulky succinic anhydrides. The desymmetrization of **41**, an intermediate in the Goldberg−Sternbach synthesis of biotin,[23] proceeded with low enantioselectivity (26% ee). The enantioselectivities were also

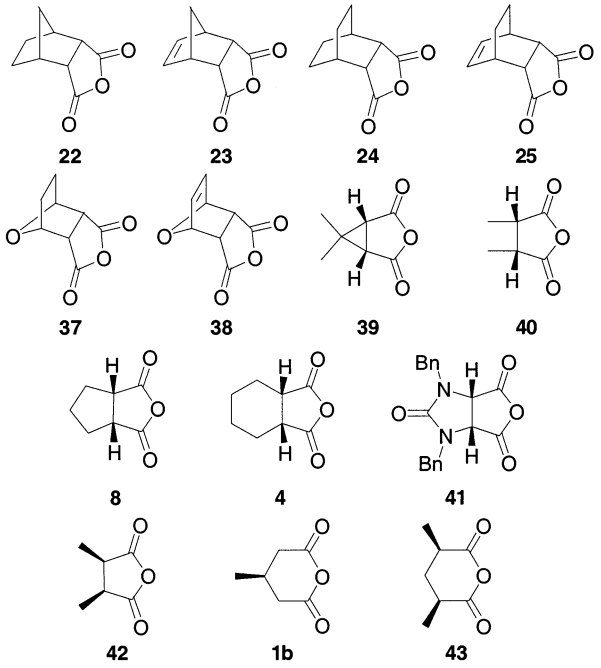
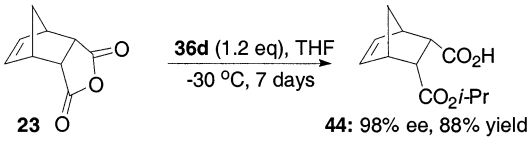


Figure 2.

Table 5. Asymmetric Ring Opening of Meso Cylic Anhydrides with Ti-TADDOLates[a]



entry	anhydride	time (days)	temp (°C)	yield (%)	ee (%)
1	**22**	6	−30	91	98
2	**23**	7	−30	88	98
3	**24**	5	−30	92	94
4	**25**	5	−30	91	98
5	**37**	6	−30	82	96
6	**38**	6	−30	63	98
7	**39**	5	−15	59	96
8	**40**	5	−15	76	94
9	**8**	5	−15	74	88
10	**4**	5	−15	87	>90
11	**41**	9	−20	80	26
12	**42**	5	−18	73	96
13	**1b**	5	−15	64	50
14	**43**	9/4	−20/0	99	0

[a] Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395.

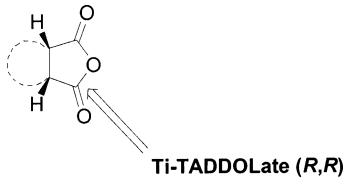


Figure 3. Stereochemical projection for desymmetrization of prochiral meso cyclic anhydrides using Ti-TADDOLate **36d**.

unsatisfactory for the relatively unreactive glutaric anhydrides. Desymmetrization of 3-methylglutaric anhydride **1b** and 2,4-dimethylglutaric anhydride **43** produced the corresponding hemiesters in 50 and 0% ee, respectively. With either the succinic or glutaric anhydrides, the sense of asymmetric induction in relation to the absolute configuration of the TADDOL ligand is consistently predictable using the projection illustrated in Figure 3.

Scheme 3

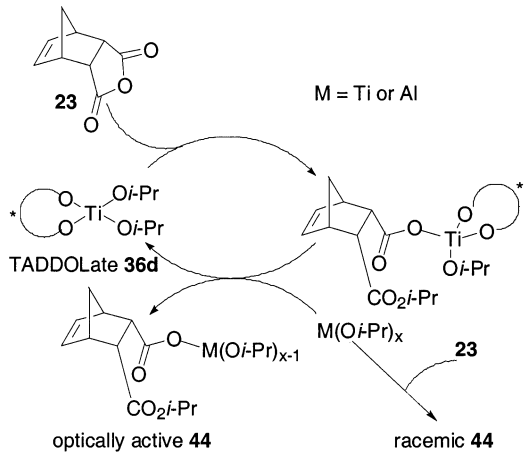
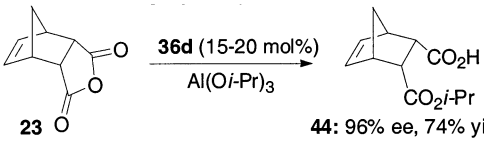


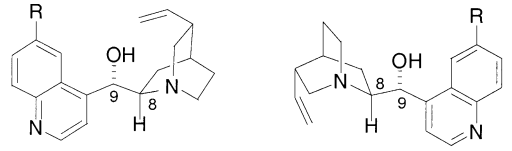
Table 6. Substoichiometric Use of Ti-TADDOLate 36d for the Enantioselective Ring Opening of Meso Cyclic Anhydrides



entry	anhydride	**36d** (mol %)	$Al(O\textit{i}\text{-}Pr)_3$ (mol %)	time (days)	temp (°C)	yield (%)	ee (%)
1	**23**	15	80[a]	20	−30	80	34
2	**23**	20	80	24	−34	74	96
3	**38**	20	80	24	−34	83	52
4	**40**	20	80	24	−15	78	78
5	**42**	20	80	24	−15	84	72

[a] $Ti(O\textit{i}\text{-}Pr)_4$ was used instead of $Al(O\textit{i}\text{-}Pr)_3$.

Previous work by Seebach and co-workers on the Ti-TADDOLate-catalyzed addition of dialkylzinc or alkyltitanium to aldehydes demonstrated dramatic ligand acceleration.[22a−d,24] Seebach hoped to observe the same phenomenon in the alcoholysis of cyclic meso anhydrides. This could enable the development of an efficient catalytic variant of the highly enantioselective alcoholysis with Ti-TADDOLate. As outlined by Seebach in the catalytic cycle shown in Scheme 3, if the ligand acceleration was large enough, that is, if the rate of the Ti-TADDOLate-catalyzed enantioselective alcoholysis was much greater than the rate of the $Ti(O\textit{i}\text{-}Pr)_4$-catalyzed racemic alcoholysis, then the high ee of the hemiester could be retained while the $Ti(O\textit{i}\text{-}Pr)_4$ regenerated the Ti-TADDOLate through a metal−ligand exchange. Consequently, a catalytic amount of TADDOL ligand would be sufficient to mediate a highly enantioselective alcoholysis. The desymmetrization of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**23**) was carried out using Ti-TADDOLate **36d** (15 mol %) and $Ti(O\textit{i}\text{-}Pr)_4$ (80 mol %) and resulted in the formation of the hemiester **44** in 34% ee and 80% yield (Table 6, entry 1). From this result it was apparent that the degree of ligand acceleration was not large enough. The competing racemic alcoholysis, catalyzed by $Ti(O\textit{i}\text{-}Pr)_4$, led to a significant deterioration in the optical purity of the hemiester. When $Al(O\textit{i}\text{-}Pr)_3$ was



45: Quindine R = OMe
46: Cinchonine R = H
47: Quinine R = OMe
35: Cinchonidine R = H

Figure 4. Structures of cinchona alkaloids.

used instead of Ti(O*i*-Pr)$_4$, the hemiester was produced in 96% ee and 74% yield. Despite the reaction taking 24 days to proceed, these results provided the first example of a highly enantioselective catalytic desymmetrization of meso cyclic anhydrides.

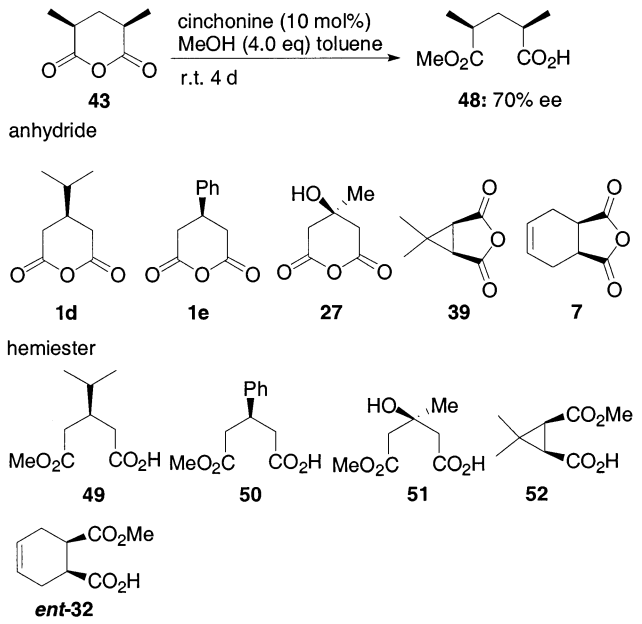
Unfortunately, the high ee obtained with **23** could not be extended to other meso anhydrides. When compared with the results obtained from the corresponding stoichiometric reactions, the desymmetrization of anhydrides via this substoichiometric method generally resulted in the formation of the corresponding hemiesters with significantly lower enantiomeric excess. Nevertheless, by combining high enantioselectivity with a broad substrate scope, Seebach's Ti-TADDOLates-promoted alcoholysis remains the benchmark for the desymmetrization of meso cyclic anhydrides using a chiral Lewis acid approach.

2.3. Enantioselective Alcoholysis with Chiral Lewis Bases

In principle, a chiral Lewis base, such as a chiral amine, can promote enantioselective alcoholysis of anhydrides by activating the nucleophilic alcohol via a general base catalysis mechanism or by activating the electrophilic anhydride via a nucleophilic catalysis mechanism. At first glance, the development of an efficient base-catalyzed enantioselective ARO of meso anhydrides seems to be a hopeless approach. The most obvious obstacle is the incompatibility of the acidic hemiester with a chiral amine catalyst. It is therefore striking to see that the first nonenzymatic catalytic alcoholysis of meso and prochiral cyclic anhydrides, reported by Oda and co-workers in 1985, was realized with a chiral amine catalyst.[20a] The employment of 10 mol % of a cinchona alkaloid (Figure 4) is sufficient to catalyze a clean and complete alcoholysis of anhydride **43**, generating the corresponding hemiester **48** in quantitative yield (Table 7). Subsequently, Oda showed that the cinchona alkaloids remained catalytically effective for meso bicyclic succinic anhydrides and other glutaric anhydrides.[20b]

Oda examined the catalyst structure/selectivity relationship using natural cinchona alkaloids and their corresponding C9-epimers. The enantioselectivity of the reaction was low to moderate and was found to be dependent on specific combinations of catalyst and substrate. The highest enantioselectivity attained for each cyclic anhydride investigated by Oda is summarized in Table 7. In general, the natural cinchona alkaloids were more active and selective catalysts for the desymmetrization of glutaric anhydrides than their C9-epimers. However, the natural cinchona alkaloids were less efficient than their C9-epimers with succinic anhydrides such as **39** and **7**.

Table 7. Cinchona Alkaloid Catalyzed ARO of Cyclic Anhydrides[a]



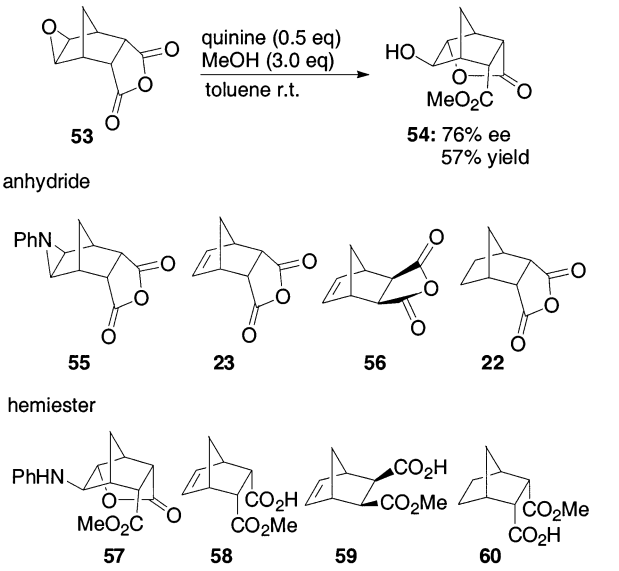
entry	anhydride	hemiester	catalyst (10 mol %)	MeOH (equiv)	time (days)	ee (%)
1	**43**	**48**	cinchonine	4.0	4	70
2	**43**	**48**	quinidine	4.0	4	67
3	**1d**	**49**	cinchonine	10.0	1	23
4	**1d**	**49**	quinidine	10.0	1	19
5	**1e**	**50**	cinchonine	10.0	1	33
6	**1e**	**50**	quinidine	10.0	1	48
7	**27**	**51**	cinchonine	20.0	1	28
8	**27**	**51**	quinidine	20.0	1	48
9	**39**	**52**	epicinchonine	10.0	9	60
10	**7**	*ent*-**32**	epiquinidine	10.0	7	52

[a] The chemical yield was quantiative or >95%.

Aitken and co-workers later extended the substrate scope of the natural cinchona alkaloid-catalyzed alcoholysis to include more functionalized complex tricyclic succinic anhydrides (Table 8).[25] Modest enantioselectivity was also observed in Aitken's quinine-catalyzed asymmetric methanolysis of tricyclic anhydrides (Table 8). However, Aitken made the important observation that increasing the catalyst loading led to a significant increase in the ee of the hemiester. For example, when the amount of quinine was increased from 0.1 to 0.5 equiv, the enantioselectivity of lactone **54** improved from 38 to 76% ee. Aitken also investigated the effect of temperature on the enantioselectivity of the reaction. Using a catalytic amount of quinine, Aitken and co-workers did not observe an increase in selectivity when the temperature of the reaction was reduced from room temperature to −30 °C.

To identify the active basic moiety of the catalyst, Oda compared the rate constants of methanolysis of anhydride **43** when catalyzed by cinchonine, quinuclidine, and quinoline, respectively. Whereas quinuclidine catalyzed the reaction as effectively as cinchonine, the quinoline-catalyzed reaction was nearly 60 times slower than the other two reactions. This suggested that the quinuclidine nitrogen was the active site of the catalyst. This notion received further

Table 8. Cinchona Alkaloid Catalyzed ARO of Cyclic Anhydrides



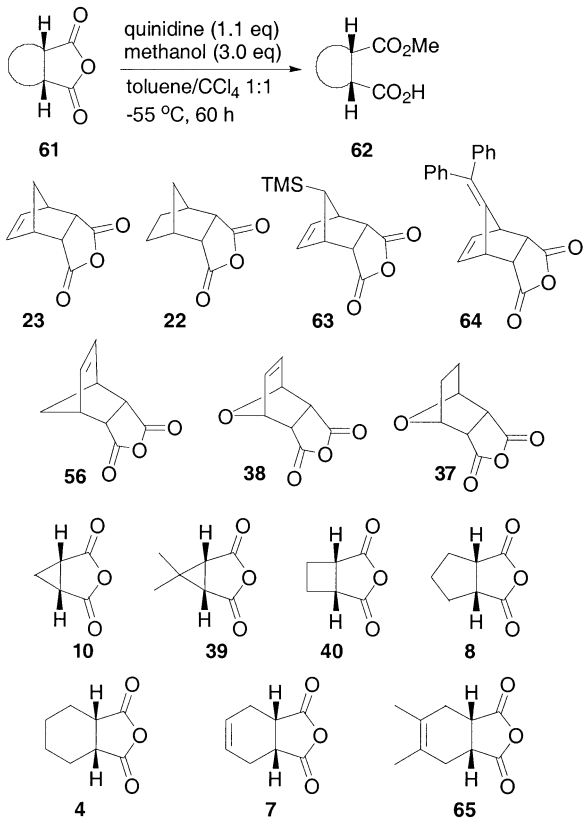
entry	anhydride	hemiester	catalyst (equiv)	yield (%)	ee (%)
1	**55**	**57**	quinine (0.1)	86	40
2	**23**	**58**	quinine (0.5)	69	61
3	**56**	**59**	quinidine (0.5)	88	67
4	**22**	**60**	quinidine (0.1)	80	44

support from Aitken's demonstration that only racemic product was obtained from methanolysis of a meso anhydride when a monohydrochloride salt of quinine was used as catalyst.[25]

Oda's and Aitken's studies not only established the first catalytic enantioselective alcoholysis of meso anhydrides employing a metal-free catalyst of remarkably general activity but also provided strong evidence to indicate that the basic quinuclidine nitrogen was the active site of the catalyst. These results pointed out a promising strategy for the development of an efficient catalytic enantioselective alcoholytic desymmetrization of meso anhydrides. Given that chiral amine-catalyzed alcoholysis was not revisited until almost 10 years later, it appears that the most important lessons to be learned from Oda's and Aitken's studies were initially overlooked, perhaps due to the unsatisfactory ee values.

In 1999, Bolm and co-workers reported a highly enantioselective protocol for the desymmetrization of meso anhydrides promoted by a stoichiometric amount of quinidine or quinine.[26] The key difference between Bolm's protocol and those of Oda and Aitken is the employment of 1.1 equiv, instead of a catalytic amount, of the cinchona alkaloid. Bolm also carried out the alcoholysis at a low temperature, instead of room temperature. The best results were obtained by performing the reaction in a 1:1 toluene/CCl_4 solvent system at −55 °C. A wide variety of bicyclic and tricyclic succinic anhydrides were converted to the corresponding hemiesters in 61−99% yield and 85−99% ee (Table 9). Whereas quinidine-mediated reactions give hemiester **62** as the major enantiomer, quinine-catalyzed reactions give hemiester *ent*-**62** as the major enantiomer with equal, or slightly lower,

Table 9. Quinidine- and Quinine-Mediated ARO of Cyclic Anhydrides



		quinidine-mediated		quinine-mediated[a]	
entry	anhydride	ee (%)	yield (%)	ee (%)	yield (%)
1	**23**	99	98	99	92
2	**22**	94	84	94	86
3	**63**	96	99	98	98
4	**64**	95	95	92	96
5	**56**	96	96	93	94
6	**38**	93	61	75	71
7	**37**	94	69	93	79
8	**10**	85	96	85	95
9	**39**	90	97	84	96
10	**40**	94	99	87	93
11	**8**	95	97	93	99
12	**4**	93	98	87	91
13	**7**	95	93	93	99
14	**65**	97	96	94	97

[a] For quinine-catalyzed reaction, *ent*-**62** are obtained as major products.

enantiomeric excess. The reaction generally goes to completion within 60 h. The cinchona alkaloids can be easily recycled quantitatively using a simple extractive procedure. Use of the toxic CCl_4 can be avoided by performing the reaction in toluene, although a slight deterioration in enantiomeric excess and yield is observed. These practical features render Bolm's protocol one of the most reliable and attractive among existing procedures for alcoholytic desymmetrization of cyclic anhydrides. However, attempted desymmetrization of the dimethyl succinic anhydride **42** (Figure 5) generated an inseparable mixture of the corresponding hemiester and 14% of the epimerization product. Some sterically bulky succinic anhydrides (**66**, **67**, and **25**) did not react at all under these conditions. The desymmetrization of meso 2,4-

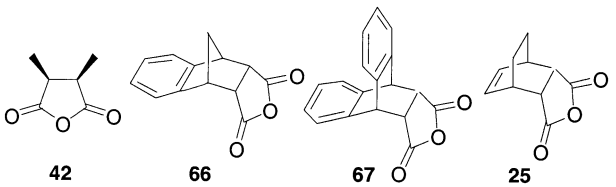
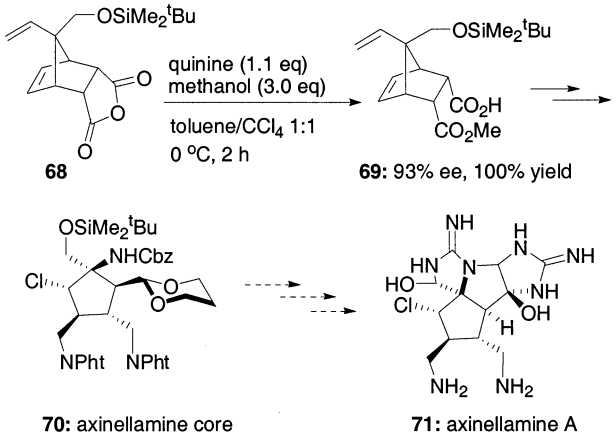


Figure 5.

disubstituted or prochiral 3-substituted glutaric anhydrides was not described.

Bolm's method has already been applied by Carreira and co-workers in the enantioselective synthesis of the cyclopentyl core of the axinellamines.[27] Asymmetric methanolysis of meso cyclic anhydride **68** gave the corresponding hemiester **69** in 93% ee and quantitative yield (Scheme 4). The hemiester was

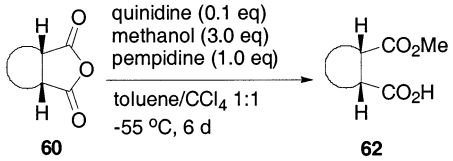
Scheme 4. Enantioselective Synthesis of the Cyclopentyl Core of the Axinellamines



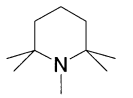
subsequently transformed into the axinellamine core **70** via a very efficient synthetic route. Bolm's method was also used by Bernardi and co-workers in a multigram scale synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid.[28] Further examples of the application of Bolm's method can be found in the literature.[29]

In addition to offering a highly attractive protocol for desymmetrization of meso anhydrides, Bolm's results also provided new and important insights into the origin of the low enantioselectivity with catalytic amounts of cinchona alkaloids as described by Oda and Aitken. The dramatically different enantioselectivities obtained when stoichiometric and catalytic amounts of cinchona alkaloids were employed to mediate the reaction could be explained by the role played by a protonated cinchona alkaloid. This protonated species is the expected product of a reaction between the acidic hemiester and the basic cinchona alkaloid. As shown earlier by Aitken,[25a] the HCl salt of quinine is still catalytically active and produces racemic product. For both Oda's and Aitken's protocols, as the alcoholysis proceeds to high conversion, the increasing amount of hemiester generated by the alcoholysis will, in turn, lead to an increase in the amount of protonated cinchona alkaloid and a decrease in, or even disappearance of, free alkaloid. Consequently, the racemic alcoholysis promoted by the protonated species will become increasingly

Table 10. Catalytic Use of Quinidine in the Presence of Pempidine (72) in the ARO of Cyclic Anhydrides



		hemiester	
entry	anhydride	ee (%)	yield (%)
1	**23**	90	98
2	**56**	91	94
3	**39**	74	98
4	**40**	81	97
5	**8**	89	96
6	**65**	92	96



72: pempidine

competitive, resulting in a significant deterioration in the optical purity of the hemiester. In Bolm's protocol, the use of a stoichiometric amount of cinchona alkaloid ensures the presence of unprotonated alkaloid throughout the reaction. This minimizes the deterioration in optical purity caused by the protonated cinchona alkaloid. These results indicate that if the cinchona alkaloid could be regenerated via conversion of the undesirable ammonium salt to the corresponding free amine, only a catalytic amount of the alkaloid would be required to realize a highly enantioselective alcoholysis.

Bolm reasoned that a second achiral base could be used to regenerate quinidine and experimentally validated the concept. Bolm screened a series of sterically hindered tertiary amine additives for their ability to trap the acidic hemiester without promoting a competitive racemic alcoholysis.[30] 1,2,2,6,6-Pentamethylpiperidine (pempidine, **72**) was identified as the most effective additive. Enantioselective methanolysis of succinic anhydride **23** was achieved in 90% ee and 98% yield with a catalytic amount of quinidine (0.1 equiv) and a stoichiometric amount of pempidine (**72**). However, pempidine is more expensive than quinidine, and the alcoholysis requires an extended reaction time (6 days) to obtain complete conversion when this protocol is employed. In general, the enantioselectivity of the catalytic protocol is lower than that of the stoichiometric protocol. The degree of ee erosion is small for some anhydrides (**8**, **56**, and **65**) but is significant for a number of others (**23**, **39**, and **40**) (Table 10).

In parallel with Bolm's studies, Deng and coworkers developed an exceptionally general and highly enantioselective catalytic alcoholysis of meso and prochiral cyclic anhydrides with commercially available modified cinchona alkaloids (Figure 6).[31] These modified cinchona alkaloids were originally developed by Sharpless and co-workers as chiral ligands for the Os-catalyzed asymmetric dihydroxylation of simple olefins.[2] Although these alkaloids were widely known and subsequently made commercially available, they had never been applied as metal-free organic catalysts for other asymmetric reactions. Deng and co-workers discovered that the biscinchona alkaloid $(DHQD)_2AQN$ and the monocinchona alkaloid DHQD-PHN were highly effective

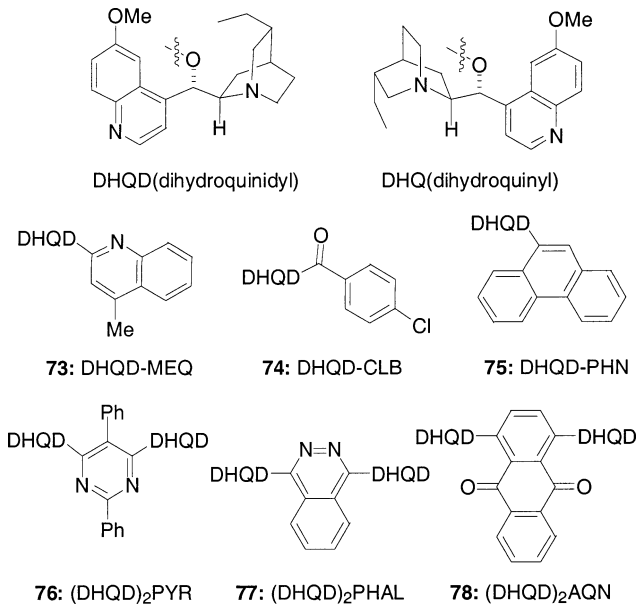
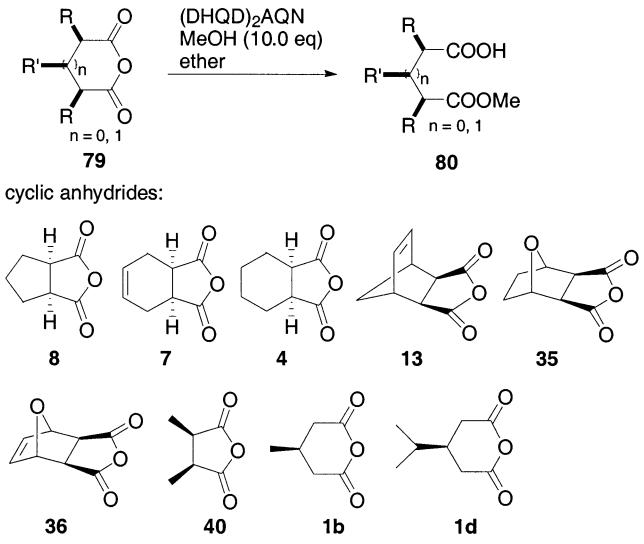


Figure 6. Structures of modified cinchona alkaloids.

Table 11. $(DHQD)_2AQN$- and $(DHQ)_2AQN$-Catalyzed ARO of Cyclic Anhydrides



entry	anhydride	catalyst[a] (mol %)	temp[a] (°C)	hemiester[a] yield (%)	hemiester[a] ee (%)
1	**8**	8 (8)	−30 (−30)	99 (90)	95 (93)
2	**7**	7 (7)	−20 (−20)	95 (92)	98 (96)
3	**4**	5 (5)	−20 (−20)	97 (95)	97 (93)
4	**13**	10 (20)	−30 (−20)	82 (82)	95 (90)
5	**35**	15 (15)	−20 (−20)	88 (85)	96 (94)
6	**36**	20 (20)	−20 (−20)	74 (71)	92 (86)
7	**40**	5 (5)	−20 (−20)	93 (88)	98 (98)
8	**1b**	30 (30)	−40 (−35)	70 (56)	91 (82)
9	**1d**	30 (30)	−40 (−35)	72 (62)	90 (83)

[a] $(DHQD)_2AQN$-catalyzed reaction; data in parentheses are obtained with $(DHQ)_2AQN$ as catalyst, and *ent*-**80** are major products.

catalysts for the desymmetrization of a wide variety of cyclic anhydrides.

As summarized in Table 11, using 5−30 mol % of the cinchona alkaloids, excellent enantioselectivities (90−98% ee) were obtained in the desymmetrization of monocyclic, bicyclic, and tricyclic succinic anhydrides, as well as glutaric anhydrides. The desymmetrization of meso cyclic anhydrides is carried out at −30 to −20 °C in ether and typically takes 24−72 h to go to completion, generating the corresponding hemiesters in good to excellent yields. The reaction is most effective for bicyclic succinic anhydrides. Even with low catalyst loading (5−8 mol %), the alcoholysis of these bicyclic substrates can be achieved in nearly quantitative yields and in >95% ee. The reaction is also highly effective for monocyclic succinic anhydrides such as dimethyl succinic anhydride **42**. Although attained with a high loading of $(DHQD)_2AQN$, the excellent enantioselectivity in the desymmetrization of 3-substituted glutaric anhydrides (**1b** and **1d**) is particularly noteworthy. Even with Seebach's alcoholytic desymmetrization protocol, mediated by a stoichiometric amount of Ti-TADDOLate, desymmetrization of **1b** proceeded with only 50% ee.

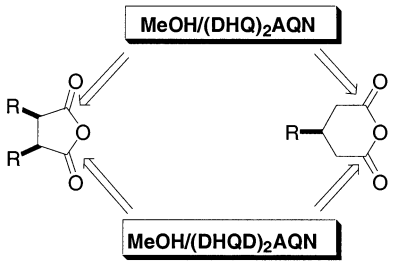
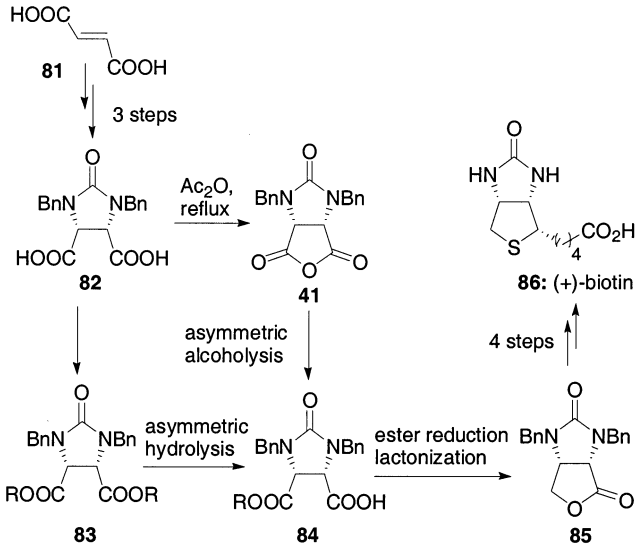


Figure 7. Stereochemical projection for desymmetrization of cyclic anhydrides.

The stereochemical outcome of the desymmetrization is highly predictable and follows the stereoselection rule illustrated in Figure 7. Whereas $(DHQD)_2$-AQN-catalyzed reactions give hemiesters **80** in high yield and excellent enantiomeric excess, *ent*-**80** can be obtained in similar yield and equal or slightly lower enantiomeric excess using $(DHQ)_2AQN$. Several practical features of this reaction are also noteworthy. Catalyst recovery and product purification can be carried out using a simple extractive procedure instead of chromatographic purification. The recovered catalyst can be reused without any loss of efficiency in terms of yield and enantioselectivity.

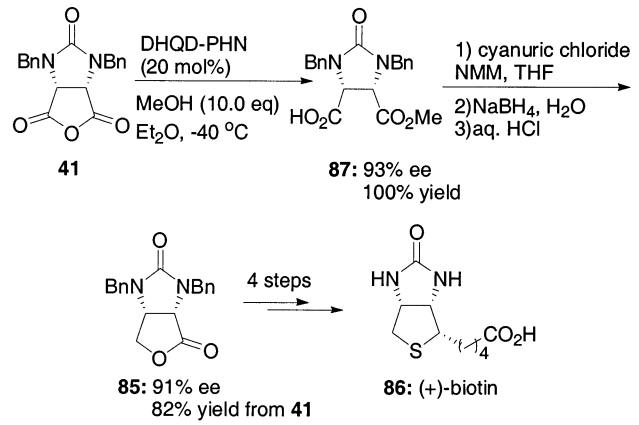
Deng and co-workers have applied this method in a formal catalytic asymmetric total synthesis of (+)-biotin.[32] Although Goldberg and Sternbach reported the first total synthesis of biotin more than 50 years ago, their route is still regarded as one of the best (Scheme 5).[23,33] The potential of this approach had not been fully realized due to the lack of an efficient catalytic method for the desymmetrization of the meso intermediates anhydride **41** and diester **83**. Meso intermediates **41** and **83**, due to their bulky size and the presence of multiple polar and basic functionalities, proved to be very difficult to desymmetrize successfully using existing catalytic asymmetric methods. Both the attempted enzymatic hydrolysis of diester **83** (75% ee)[34] and the Ti-TADDOLates-promoted alcoholysis of anhydride **41** (26% ee)[21b] were unsatisfactory. In contrast, modified cinchona alkaloid-catalyzed desymmetrization of anhydride **41** proved to be very effective (Scheme 6). With 20 mol % DHQD-PHN, anhydride **41** was readily desymmetrized to give the corresponding hemiester **87** in 93% ee and quantitative yield. $NaBH_4$ reduction of **87,** followed by ring cyclization, gave lactone **85** in 91%

Scheme 5[a]



[a] Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737.

Scheme 6. Formal Catalytic Asymmetric Synthesis of (+)-Biotin with Modified Cinchona Alkaloids[a]



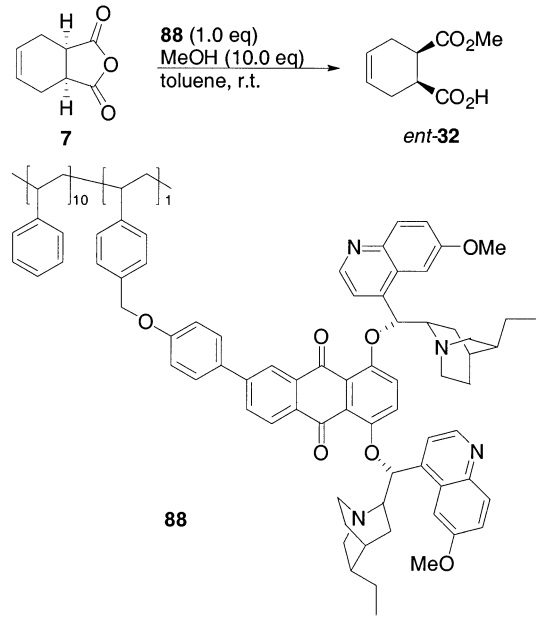
[a] Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737.

ee and 82% yield. Lactone **85** had been previously converted to biotin.[33]

The studies carried out by Deng and co-workers establish the modified cinchona alkaloids, $(DHQD)_2$-AQN and DHQD-PHN, as the most efficient catalysts so far for the desymmetrization of cyclic anhydrides. Deng's studies are also notable for the use of a catalytic amount of a chiral amine, in the absence of a stoichiometric base, to realize the alcoholysis of anhydrides, generating an acidic hemiester in nearly quantitative yield and in up to 98% ee. Understanding the origin of the significantly enhanced catalytic activity and selectivity of the modified cinchona alkaloids relative to those of the natural cinchona alkaloids such as quinidine should be an important goal of future studies. These studies could provide valuable insights into the design and development of a new generation of catalysts that are more efficient and practical.

Recently, Wöltinger and co-workers investigated the activity of a polymer-bound AQN catalyst **88** for the asymmetric ring opening of cyclic anhydride **7** (Scheme 7).[35] By using a repetitive batch system, ARO of anhydride **7** with a stoichiometric amount of

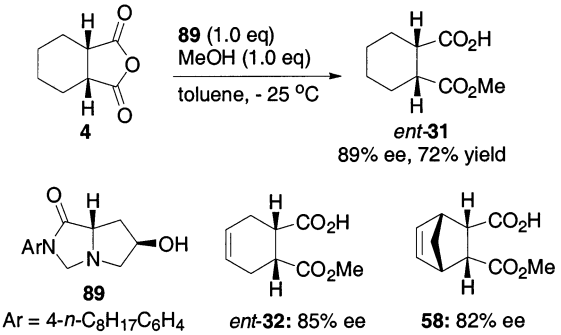
Scheme 7



88 was carried out over 18 cycles in toluene at room temperature with >99% conversion for each cycle. The ee of hemiester *ent*-**32** dropped from almost 90 to 60% during the first 5 runs and then stabilized at 60% for the last 13 runs.

This recent progress with modified cinchona alkaloids should encourage further exploration of other chiral amines as catalysts for enantioselective alcoholysis reactions. Notable progress has already been made in this direction. In 2001, Uozumi and co-workers reported that enantioselective alcoholysis of cyclic anhydrides could be attained using chiral tertiary amine **89**.[36] In the presence of 1.0 equiv of **89**, methanolysis of anhydride **4** at −25 °C in toluene gave hemiester *ent*-**31** in 89% ee and 72% yield (Scheme 8). Using 10 mol % instead of 1.0 equiv of **89**, hemiester *ent*-**31** was obtained in only 65% ee and 33% yield.

Scheme 8



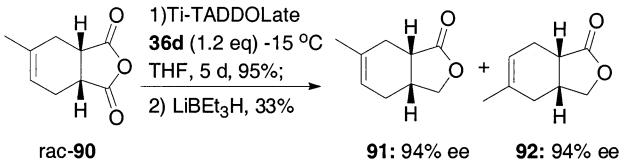
3. Kinetic Resolution of Racemic Cyclic Anhydrides

At first glance, the kinetic resolution of racemic cyclic anhydrides via ARO is not very appealing. Even with ideal enantioselectivity, ARO of racemic anhydrides will produce a mixture of two regioisomeric hemiesters and the enantiomerically enriched cyclic anhydrides. Optically active cyclic anhydrides

do not appear to be useful building blocks because it is not obvious how to address the issue of regioselectivity in the further elaboration of these compounds. Not surprisingly, only four kinetic resolutions of racemic cyclic anhydrides have been reported. Only one is catalytic in nature. However, these reports contain interesting observations and synthetically useful findings.

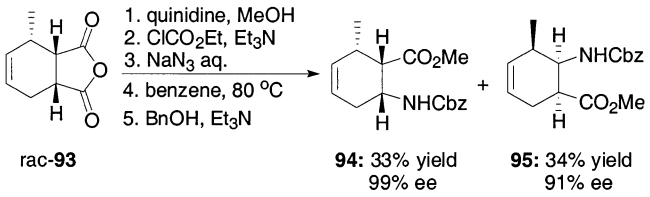
Various chiral Lewis acids and bases that are effective stoichiometric mediators for the desymmetrization of meso anhydrides have also been examined for their ability to promote kinetic resolutions of racemic bicyclic anhydrides (**90** and **93**). These bicyclic anhydrides closely resemble the parent unsubstituted meso bicyclic anhydride *cis*-1,2-cyclohexanedicarboxylic anhydride (**4**). In 1997, Seebach and co-workers reported that the Ti-TADDOLate-mediated kinetic resolution of racemic anhydride **90**, followed by reduction and cyclization, gave a 1:1 inseparable mixture of hemiesters **91** and **92**, both of which were obtained in very high enantiomeric excess (Scheme 9).[37] Bolm and co-workers reported

Scheme 9



that a quinidine (1.1 equiv)-mediated kinetic resolution of racemic **93**, followed by a four-step reaction sequence, gave two isomeric N-protected β-aminoesters, **94** and **95**, in very high enantiomeric excess (Scheme 10).[38] Uozumi and co-workers also reported

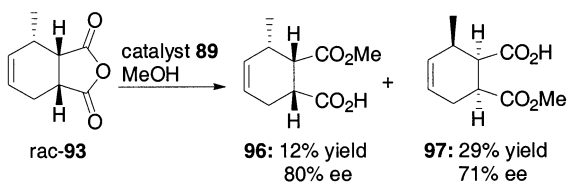
Scheme 10[a]



[a] Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrère, L.; Gerlach, A.; Raabe, G. *Synthesis* **2001**, 1719.

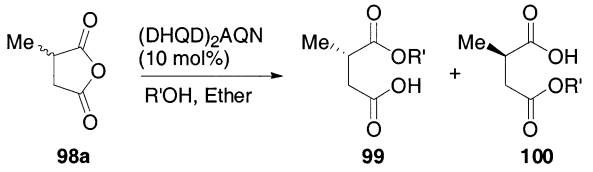
that a stoichiometric amount of the chiral tertiary amine **89** mediated a kinetic resolution of the racemic anhydride **93**, affording hemiesters **96** and **97** in enantiomerically enriched form (Scheme 11).[36]

Scheme 11



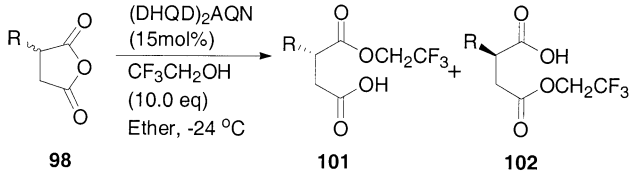
Deng and Chen recently reported a general and highly enantioselective catalytic kinetic resolution of racemic monosubstituted succinic anhydrides via $(DHQD)_2AQN$-catalyzed ARO.[39] In initial model studies with 2-methyl succinic anhydride, they found that

Table 12.



					% ee	
entry	R′OH	temp (°C)	conv (%)	**99**/**100**	**99**	**100**
1	MeOH	25	100	39/61	74	67
2	EtOH	25	100	49/51	82	67
3	*n*-PrOH	25	100	45/55	81	72
4	CF_3CH_2OH	25	100	49/51	85	72
5	CF_3CH_2OH	−25	100	44/56	91	80

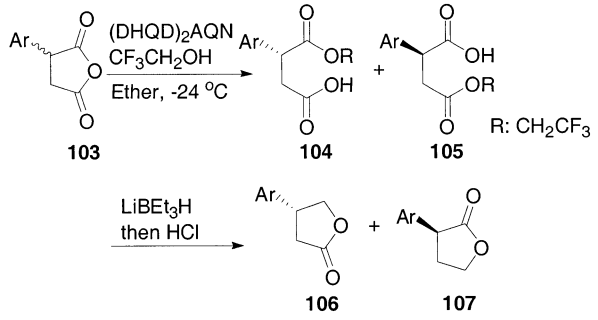
Table 13. $(DHQD)_2AQN$-Catalyzed Parallel Kinetic Resolution of 2-Alkyl Succinic Anhydrides



			% ee		% yield	
entry	substrate	**101**/**102**	**101**	**102**	**101**	**102**
1[a]	**98a**: R = −Me	44/55	93	80	36	41
2	**98b**: R = −Et	40/60	91	70	38	50
3	**98c**: R = $-n$-C_8H_{17}	42/56	98	66	38	41
4	**98d**: R = $-CH_2CH{=}CH_2$	46/53	96	82	40	49

[a] 20 mol % catalyst was used.

Table 14. Asymmetric Synthesis of β-Aryl-γ-lactones (106) via Parallel Kinetic Resolution of 2-Aryl Succinic Anhydrides (103)



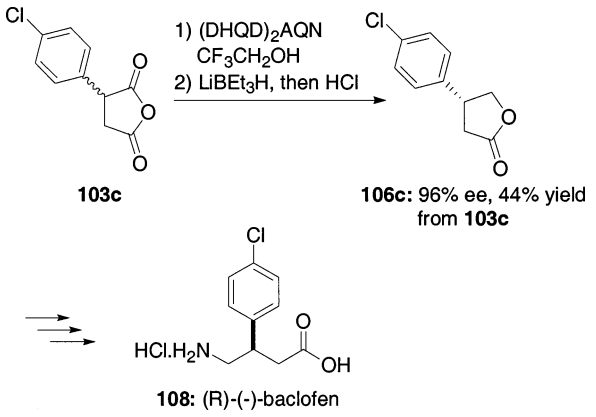
		% ee		% ee (yield, %)	
entry	substrate	**106**	**107**	**106**	**107**
1[a]	**105a**: Ar = Ph	95	87	95 (44)	82 (32)
2	**105b**: Ar = 3-MeO−C_6H_4	96	83	95 (45)	83 (30)
3	**105c**: Ar = 4−Cl−C_6H_4	96	76	96 (44)	63 (29)

[a] Using $(DHQ)_2AQN$ as catalyst, *ent*-**106a** was obtained in 44% yield and 88% ee.

the structure of the alcohol has a significant impact on the enantioselectivity. Increasing the size of the alcohol from methanol to ethanol resulted in increased enantioselectivity but reduced reaction rate. 2,2,2-Trifluoroethanol was identified as the alcohol of choice (Table 12). This catalytic kinetic resolution was also remarkable in terms of its substrate scope. A wide variety of 2-alkyl (Table 13) and 2-aryl (Table 14) succinic anhydrides were effectively resolved. The

two regioisomers of the alkyl hemiesters were separable using normal chromatographic separation. Although not separable from each other, aryl succinates **104** and **105** can be readily converted to other important and separable chiral building blocks, such as the β- and α-aryl-γ-butyrolactones. It should be noted that optically active 3- and 2-aryl succinate hemiesters are not accessible in a straightforward manner by other catalytic asymmetric approaches. The synthetic utility of this catalytic kinetic resolution was demonstrated in a formal total synthesis of baclofen, an effective GABA receptor agonist, which is used as a therapeutic reagent for muscle spasticity (Scheme 12). Using the highly efficient catalytic kinetic resolution of racemic **103c** as the key step, Deng and Chen prepared lactone **106c** in 96% ee and 44% overall yield. This lactone had been previously converted to Baclofen.[40]

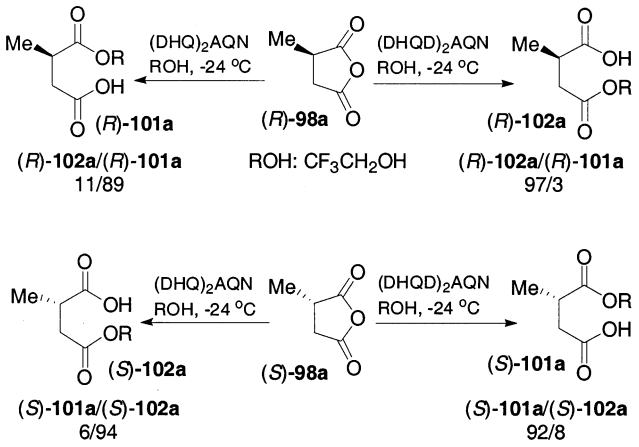
Scheme 12. Formal Total Synthesis of (*R*)-(−)-Baclofen (108)



The kinetic resolutions discussed above are unusual in that two highly enantiomerically enriched hemiesters are generated from the complete consumption of the racemic starting anhydrides. These two optically active hemiesters are most likely generated by two simultaneous enantioselective and regioselective alcholyses of the two enantiomers of the anhydrides. Such a special kinetic resolution process is called a parallel kinetic resolution (PKR).[41−43] In the resolution of **98a**, Deng and Chen observed that hemiesters **99** and **100** were generated in a close to 1:1 ratio throughout the reaction process. Deng and Chen further demonstrated the divergent regioselective alcoholysis experimentally by the $(DHQ)_2AQN$ and $(DHQD)_2AQN$-catalyzed alcoholysis of optically pure (*R*)- and (*S*)-2-methyl succinic anhydride (Scheme 13). These results unambiguously established the modified cinchona alkaloid-catalyzed alcoholysis of racemic monosubstituted succinic anhydrides as a PKR process. This is the first catalytic PKR realized with an organic catalyst.

These PKRs are very effective in converting a racemic starting material into two optically active products, such as hemiesters, in very high ee. The two regioisomers of the hemiester are, however, often difficult to separate from each other and, in some cases, are inseparable. However, both Deng and Bolm have shown that they can be converted to valuable chiral building blocks that are less polar and, thus, more amenable to chromatographic purification. These PKRs of racemic anhydrides provide attractive routes for the synthesis of chiral building blocks that are difficult to obtain using other methods. The efficient PKR of monosubstituted succinic anhydrides reported by Deng and Chen is particular noteworthy, as it demonstrates that even the removal of one of the two substitutents of the meso succinic anhydride does not change how the $(DHQD)_2AQN$-catalyzed alcoholysis recognizes the cyclic anhydride (Figure 8). This result provided Deng and co-workers with new insights for the development of new and synthetically important catalytic asymmetric alcoholyses.

Scheme 13. Reagent-Controlled Highly Regioselective Alcoholysis of (*R*)- and (*S*)-Methyl Succinic Anhydrides with Modified Cinchona Alkaloids



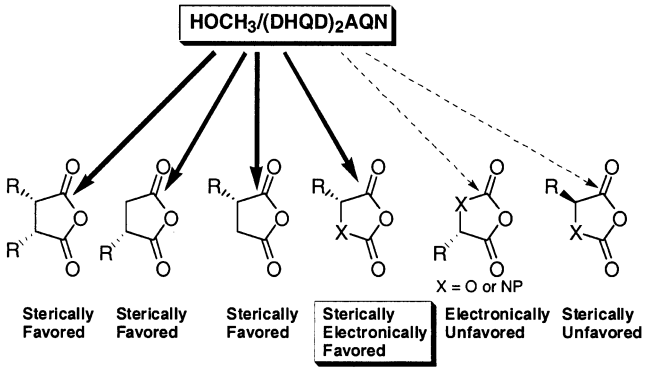


Figure 8.

4. Kinetic Resolution and Dynamic Kinetic Resolution of N- and O-Carboxy Cyclic Anhydrides

4.1. Kinetic Resolution of *N*- and *O*-Carboxy Cyclic Anhydrides

Having established the efficient and general PKR of monosubstituted succinic anhydrides, Deng and co-workers reasoned that the modified cinchona alkaloid-catalyzed asymmetric alcoholysis might also be able to efficiently recognize the two enantiomers of the cyclic *N*- and *O*-carboxyanhydrides (Figure 8). Consequently, Deng and co-workers first tested this hypothesis by attempting a kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCAs).[44]

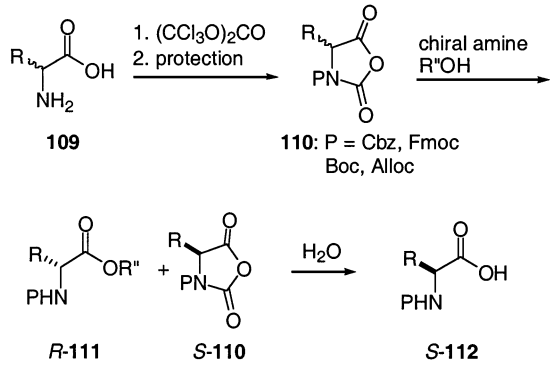
Table 15. Kinetic Resolution of UNCA (110) via Modified Cinchona Alkaloid-Catalyzed Alcoholysis[a]

	UNCA **110**						ee (yield, %)		
entry		R	P	temp (°C)	time (h)	conv (%)	(*S*)-**112**	(*R*)-**111**	*s*
1	**a**	$PhCH_2$	Cbz	−60	17	51	98 (48)	93 (48)	114
2	**b**	4-F−$C_6H_4CH_2$	Cbz	−78	31	50	93 (42)	92 (48)	79
3	**c**	4-Cl−$C_6H_4CH_2$	Cbz	−60	18	52	97 (43)	88 (52)	59
4	**d**	4-Br−$C_6H_4CH_2$	Cbz	−78	45	51	92 (39)	87 (51)	45
5	**e**	2-thienylmethyl	Cbz	−78	25	50	95 (47)	94 (49)	115
6	**f**	$CH_3(CH_2)_5$	Cbz	−60	37	51	94 (42)	91 (49)	78
7	**g**	$BnOCH_2$	Cbz	−78	72	52	96 (44)	89 (49)	69
8	**h**	*i*-Pr[b]	Cbz	0	22	59	96 (40)	67 (58)	19
9	**i**	Ph[c]	Cbz	−78	16	46	84 (46)	97 (45)	170
10	**j**	4-MeO−C_6H_4[c]	Cbz	−78	85	56	95 (43)	74 (56)	23
11	**k**	$PhCH_2$	Fmoc	−78	46	51	96 (47)	92 (50)	93
12	**l**	$PhCH_2$	Boc	−40	15	59	98 (41)	67 (56)	19
13	**m**	$PhCH_2$	Alloc	−60	15	50	91 (45)	91 (45)	67
14	**n**	$PhCH_2CH_2$	Alloc	−60	36	54	96 (41)	81 (53)	35

[a] Unless noted, the reaction was performed by treatment of **110** with $(DHQD)_2AQN$ (10 mol %) and methanol in ether (7.0 mL). [b] The reaction employed DHQD-PHN (20 mol %). [c] Ethanol was used as the nucleophile.

UNCAs (**110**) can be easily prepared in high yields from the corresponding readily available racemic α-amino acids (**109**, Scheme 14).[45] ARO of UNCA

Scheme 14



generates the carbamate-protected amino ester **111**. It was envisioned that an efficient kinetic resolution would give the carbamate-protected amino ester **111** and unreacted UNCA (**110**) in high ee. The latter could be further hydrolyzed to the corresponding carbamate-protected amino acid **112**. Simple extractive procedures could then be utilized for facile purification of acidic amino acid **112** and neutral amino ester **111** and recovery of the basic amine catalyst. An efficient catalytic kinetic resolution of UNCA **110**, therefore, could provide a highly attractive route for the synthesis of suitably protected optically active amino acids from the corresponding racemic amino acids.

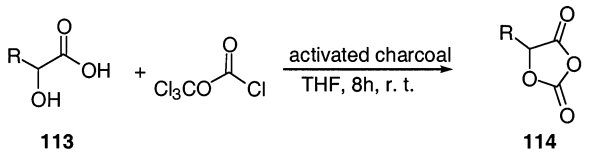
Indeed, the best catalyst for the asymmetric alcoholysis of meso and racemic anhydrides, $(DHQD)_2$-AQN, was also the most effective catalyst for the resolution of UNCA. Kinetic resolution of UNCA **110a** with $(DHQD)_2AQN$ proceeded with extremely high enantioselectivity ($S = 114$). It should be noted, however, that the monomeric catalysts DHQD-PHN and quinidine were also very effective, affording selectivity factors of 47 and 27, respectively, under the same conditions. The kinetic resolution of UNCAs was found to be remarkably general (Table 15). At −78 to 0 °C in ether, a broad range of UNCAs bearing a wide variety of alkyl and aryl substituents were resolved cleanly with exceedingly high enantioselectivities (with selectivity factors of up to 170) and in excellent yields (90−99%). Furthermore, the kinetic resolution tolerated all commonly used carbamate-protecting groups. The purification of the optically active amino esters and acids, as well as the quantitative recovery of the catalyst, was achieved using an extractive procedure.

Having achieved efficient kinetic resolution of *N*-carboxyanhydrides, Deng and Tang attempted to extend the use of modified cinchona alkaloids as catalysts to the resolution of the 1,3-dioxolane-2,4-diones (**114**).[46] An efficient kinetic resolution of these *O*-carboxyanhydrides would provide a new, straightforward catalytic approach to optically active α-hydroxy acids, if these racemic *O*-carboxyanhydrides could be easily prepared from the readily available racemic α-hydroxy acids.

Condensations of α-hydroxy acids (**113**) with phosgene or one of its equivalents appeared to be a straightforward route for the preparation of **114**. However, few such examples were reported. In the procedure reported by Toyooka, *O*-carboxyanhydrides were prepared from the reaction of the corresponding α-hydroxy acids with diphosgene in refluxing THF.[47] However, a significant amount of the byproduct, 4-chlorobutyl chloroformate, was also obtained and further purification was required, resulting in only moderate isolated yields of the anhydrides **114** (46−78%). Deng and Tang found that the use of charcoal as an additive allowed the condensation to be carried out at room temperature, resulting in a clean, high-yielding reaction. Using this modified procedure, Deng and Tang were able to prepare a wide variety of *O*-carboxyanhydrides (**114**) from the corresponding α-hydroxy acids (**113**) in 90−100% yield (Table 16).

Once again, modified cinchona alkaloids were found to be very effective catalysts for the kinetic resolution of these *O*-carboxyanhydrides, with $(DHQD)_2$-AQN identified as the best catalyst for this transformation. 5-Alkyl-1,3-dioxolane-2,4-diones undergo a highly enantioselective alcoholysis to give both (*S*)-**114** and (*R*)-**115** in high optical purity (Table 17). Hydrolysis of the reaction mixture gives acid **113** and ester **115**, both of which can be obtained in excellent

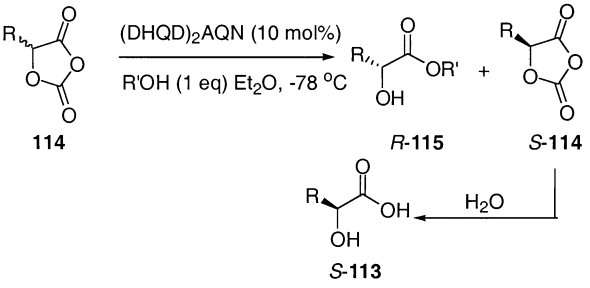
Table 16. Preparation of 5-Substituted 1,3-Dioxolane-2,4-diones



113 114

entry	R	yield (%)	entry	R	yield (%)
1	**a** C_6H_5	100	8	**h** 1-naphthyl	100
2	**b** 4-Cl−C_6H_4	100	9	**i** 2-Cl−C_6H_4	100
3	**c** 4-Br−C_6H_4	100	10	**j** 2-Me-C_6H_4	95
4	**d** 4-F−C_6H_4	100	11	**k** $C_6H_5CH_2$	95
5	**e** 4-CF_3−C_6H_4	100	12	**l** $C_6H_5CH_2CH_2$	97
6	**f** 4-^{i}Pr−C_6H_4	100	13	**m** $CH_3(CH_2)_3$	92
7	**g** 3,4-F_2−C_6H_3	100	14	**n** $(CH_3)_2CH$	90

Table 17. Kinetic Resolution of 5-Alkyl 1,3-Dioxolane-2,4-diones



114 *R*-115 *S*-114 *S*-113

				ee (yield, %)		
entry	R	R′	time (h)	(*S*)-**113**	(*R*)-**115**	*s*
1	**k** $PhCH_2$	Et	12	95 (39)	96 (47)	133
2	**l** $PhCH_2CH_2$	Et	24	85 (40)	93 (46)	67
3	**m** *n*-Bu	Et	36	95 (36)	92 (46)	57
4	**n** *i*-Pr	allyl	6	93 (32)	90 (48)	49

ee and good yield following a facile extractive purification procedure.

4.2. Dynamic Kinetic Resolution (DKR) of *N*- and *O*-Carboxy Cyclic Anhydrides

DKR represents the most desirable form of kinetic resolution.[48] It synergistically combines a racemization with a kinetic resolution of a racemic mixture to convert both enantiomers of the racemic starting material into a single, highly enantiomerically enriched product. However, the development of an efficient DKR represents one of the most challenging endeavors in asymmetric catalysis. In addition to a highly enantioselective kinetic resolution, a fast racemization of the starting material relative to the kinetic resolution needs to be established, under conditions that must not cause racemization of the product. Efficient nonenzymatic DKRs with a general substrate scope are extremely rare. Recognizing that UNCAs and dioxolanediones are more susceptible to base-catalyzed racemization than amino esters and hydroxy esters, Deng and co-workers began to develop experimentally simple yet efficient DKRs of these readily accessible *N*- and *O*-carboxyanhydrides.[46,49] It was envisioned that the modified cinchona alkaloid could perform a dual-function catalytic role, promoting both the highly enantioselective

Scheme 15

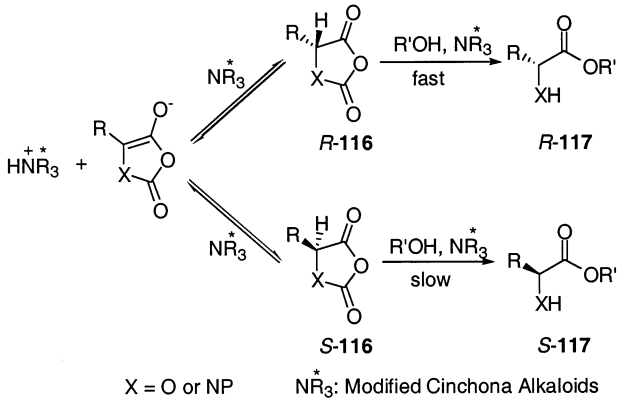
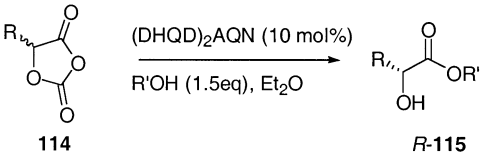


Table 18. Dynamic Kinetic Resolution of 5-Aryl-1,3-dioxolane-2,4-diones



114 *R*-115

entry	R	R′OH	temp (°C)	time (h)	yield (%)	ee (%)
1	**a** C_6H_5	EtOH	−78	24	71	95
2	**b** 4-Cl−C_6H_4	EtOH	−78	24	70	96
3	**c** 4-Br−C_6H_4	EtOH	−78	24	80	96
4	**d** 4-F−C_6H_4	EtOH	−78	24	65	95
5	**e** 4-CF_3−C_6H_4	EtOH	−78	24	85	93
6	**f** 4-^{i}Pr−C_6H_4	EtOH	−20	8	68	91
7	**g** 3,4-F_2−C_6H_3	EtOH	−78	24	65	94
8	**h** 1-naphthyl[a]	^{n}PrOH	−40	14	74	91
9	**i** 2-Cl−C_6H_4	EtOH	−60	10	66	62
10	**j** 2-Me-C_6H_4	EtOH	−20	4	61	60

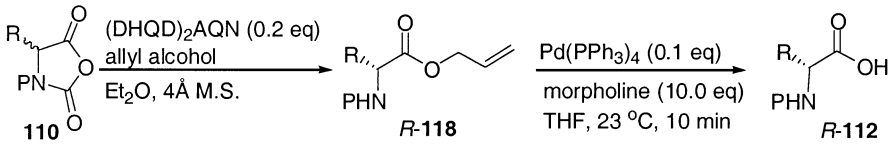
[a] This reaction was performed in THF.

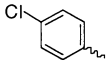
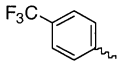
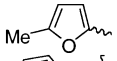
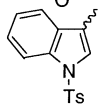
kinetic resolution and the fast racemization of UNCAs and dioxolanediones (Scheme 15). Such a single-catalyst-mediated efficient DKR was first realized with α-aryl dioxolanediones **114** as substrates.

A variety of 5-aryl-dioxolanediones (**114a**−**h**, Table 18) undergo highly efficient DKR with $(DHQD)_2AQN$ in ether at −78 to −20 °C, affording esters **115a**−**h** in excellent ee (91−96% ee) and yield (65−85%). The efficiency of the DKR was reduced with substrates bearing an ortho-substituted benzene ring. The ee of esters **115i**,**j** was found to be high at low conversion, but decreased gradually from 90 to 62% and from 85 to 60%, respectively, as the reaction proceeded to completion. The initially high ee indicates that the alcoholyses of **114i**,**j** are still highly enantioselective. The reduced efficiency of the DKR is therefore caused by the slow racemization of **114i**,**j** relative to their alcoholysis.

Deng and co-workers extended the scope of this dual-function catalysis of modified cinchona alkaloids, realizing an efficient, rapid, and nearly quantitative DKR of α-aryl UNCAs at room temperature. The substrate scope of the DKR of α-aryl UNCAs was found to be very general. Both α-aryl and α-heteroaryl UNCAs were resolved in high yield and excellent ee (Table 19). Allyl alcohol was found to be

Table 19. Dynamic Kinetic Resolution of UNCA 110 with Alcoholysis by $(DHQD)_2AQN$ and $(DHQ)_2AQN$[a]



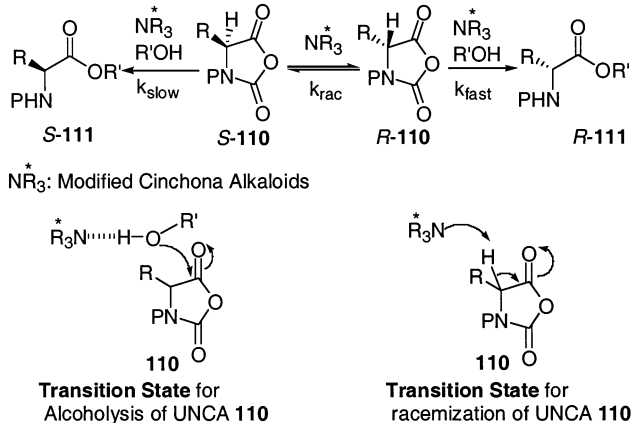
entry	R		P	temp (°C)	time (h)	118 %ee	118 %yield	112 %ee	112 %yield
1		**i**	Cbz	23 (34)	1 (1)	91 (83)	97 (96)	90	91
2		**o**	Cbz	23	1	90	96	90	93
3		**p**	Cbz	23	1	92	97	92	92
4		**q**	Cbz	23	1	90	95	90	88
5		**r**	Cbz	-30	2	92	93	92	93
6		**s**	Cbz	23 (23)	1 (2)	91 (84)	95 (95)	91	94
7		**t**	Cbz	23 (-30)	0.5 (1)	91 (92)	98 (91)	89	86
8		**u**	Cbz	23 (0)	0.5 (0.5)	93 (92)	97 (93)	91	92
9		**v**	Cbz	0 (34)	1.5 (0.5)	90 (82)	95 (93)	89	95
10		**w**	Fmoc	23	1	90	98	90	92

[a] Results in parentheses were obtained from reactions with $(DHQ)_2AQN$, which afforded (*S*)-**118**.

the best reagent for the alcoholysis, allowing the generation of the corresponding allyl amino esters in excellent ee. In most cases the optically active allylamino esters could be converted to the α-aryl and heteroaryl amino acids in excellent yields and without any deterioration in optical purity via a room temperature Pd-catalyzed deallylation. Consequently, this DKR constitutes a general, mild, and high-yielding method for the catalytic asymmetric synthesis of α-aryl amino acids.

A conceptually interesting result from Deng and co-workers' studies of the DKR of UNCAs is the demonstration that a normal kinetic resolution can be converted to an efficient DKR, simply by exploiting the temperature effect. Deng's previous studies showed that at −78 °C, the alcoholysis of α-aryl UNCAs with $(DHQD)_2AQN$ is a normal kinetic resolution. The results of mechanistic studies by Deng and co-workers indicate a general base catalysis mechanism for the modified cinchona alkaloid-catalyzed alcoholysis.[44] The rate-determining step of this mechanism has a termolecular transition state (Scheme 16). On the other hand, the epimerization of UNCA catalyzed by the modified cinchona alkaloid involves a bimolecular transition state. It was envisioned and subsequently shown that the epimerization, a reaction of lower order than the alcoholysis, could be

Scheme 16



accelerated dramatically relative to the alcoholysis by raising the reaction temperature from −78 to 23 °C. This development in turn enabled Deng and co-workers to fulfill a critically important condition required for an efficient DKR, namely, the establishment of a racemization that is faster than the enantioselective alcoholysis ($k_{rac} \gg k_{fast}$, k_{slow}). Because catalytic kinetic resolutions are often of higher order than racemizations, this temperature effect can be explored as an experimentally simple approach for the development and optimization of new DKRs.

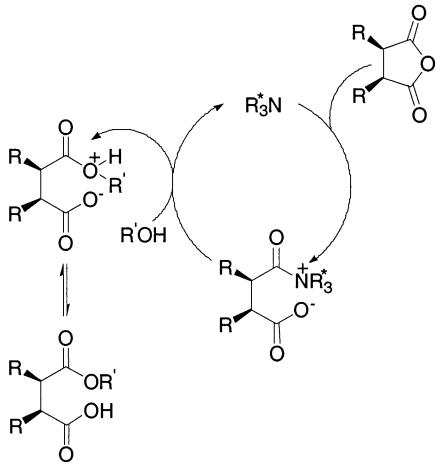
The kinetic resolution of *N*- and *O*-carboxyanhydrides via asymmetric alcoholysis constitutes a notable new development in the study of asymmetric alcoholysis of anhydrides. It has significantly expanded the synthetic scope and value of this transformation. These KR and DKR processes, based on modified cinchona alkaloid-catalyzed asymmetric alcoholysis, represent highly enantioselective, mild, and reliable methods for the asymmetric synthesis of amino acids and hydroxy acids. Especially noteworthy is the high-yield access to a wide range of aryl and heteroaryl amino acids provided by the highly enantioselective, rapid, and nearly quantitative DKR of α-aryl UNCAs at room temperature. Utilizing cheap reagents, including readily accessible and fully recyclable catalysts, these experimentally simple and efficient kinetic resolutions are promising methods for even industrial scale asymmetric synthesis.

5. Mechanistic Studies

In this section, our discussion will focus on the kinetic data obtained so far and what these data tell us about the mechanism of catalytic asymmetric alcoholysis. Aitkin has demonstrated that the HCl salt of quinine is catalytically active but promotes racemic alcoholysis, so the enantioselective alcoholysis is highly unlikely to proceed via a mechanism involving a chiral ammonium salt as the catalyst.[25a] Nucleophilic catalysis and general base catalysis are two plausible mechanistic pathways for the cinchona alkaloid-catalyzed asymmetric ring opening of cyclic anhydrides.

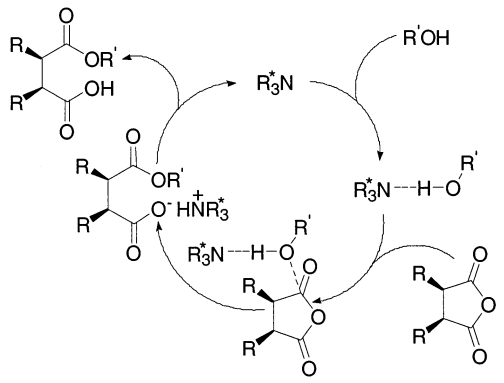
Nucleophilic Catalysis Mechanism (Scheme 17). The first step in the nucleophilic catalysis mechanism involves nucleophilic attack by the chiral amine nitrogen on the anhydride, forming an acylammonium salt. This is followed by nucleophilic attack by the alcohol on this acylammonium salt, giving the hemiester product and regenerating the amine.

Scheme 17. Nucleophilic Catalysis Mechanism



General Base Catalysis Mechanism (Scheme 18). The first step in the general base catalysis mechanism is the formation of a hydrogen-bonding complex between the chiral amine and the alcohol. This activates the alcohol, enabling it to attack the anhydride. The resulting ion pair undergoes proton transfer, forming the hemiester product and regenerating the chiral amine catalyst.

Scheme 18. General Base Catalysis Mechanism

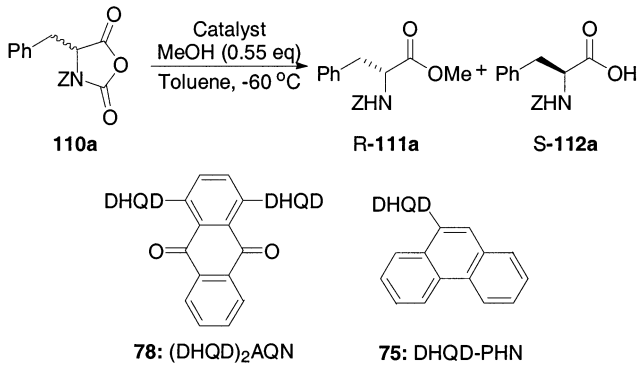


Limited mechanistic studies have been carried out to date on cinchona alkaloid-catalyzed alcoholysis. However, some important insights into the fundamental chemical mechanism of asymmetric alcoholysis have been gained. Oda and co-workers carried out the first study.[20a] Oda carried out the desymmetrization of meso cyclic anhydrides using both quinuclidine and quinoline as catalysts. Quinuclidine catalyzed the reaction at the same rate as cinchonine, Oda's best catalyst, whereas when quinoline was employed as catalyst, the rate of the alcoholysis was 60 times slower, almost the same rate as the background reaction. From these results, Oda deduced that the quinuclidine moiety of cinchonine was responsible for its catalytic activity. The desymmetrization of *cis*-2,4-dimethyl glutaric anhydride was then carried out under pseudo-first-order conditions, using cinchonine as catalyst, to determine the kinetic isotope effect (KIE) with MeOD. Pseudo-first-order conditions were achieved by reacting the anhydride with 20 equiv of MeOH (or MeOD). A KIE (k_{MeOH}/k_{MeOD}) of 2.3 was detected. This KIE was similar in value to the KIE of ∼3 observed in base-catalyzed hydrolysis of acetic anhydride, a reaction that is known to proceed via a general base catalysis mechanism.[50]

The second mechanistic study, carried out by Deng and co-workers, examined the modified cinchona alkaloid catalyzed kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCAs).[44] Kinetic studies were carried out on the methanolysis of phenylalanine UNCA in toluene at −60 °C using DHQD-PHN and $(DHQD)_2AQN$ as catalysts (Scheme 19). With either the mono- or biscinchona alkaloid as catalyst at low concentration, the reaction exhibited a first-order dependence on alcohol, UNCA, and the catalyst. A kinetic isotope effect of 1.3 (k_{MeOH}/k_{MeOD}) was detected under pseudo-first-order conditions.

Both Oda and Deng observed a first-order dependence of the rate of the alcoholysis on alcohol and also a KIE when MeOD was used as the nucleophile. Oda also observed that 2,2,2-trifluoroethanol was more reactive than ethanol. These results are consistent with a general base catalysis mechanism in which ring opening is the rate-limiting step. If nucleophilic catalysis were occurring with ring open-

Scheme 19



ing as the rate-limiting step, the rate of the reaction should not exhibit a dependence on alcohol. If the acyl transfer step in a nucleophilic catalysis mechanism is rate limiting, one would expect the observed rate with 2,2,2-trifluoroethanol to be slower than with ethanol, because trifluoroethanol, due to the electron-withdrawing character of the fluorine atoms on the 2-position, is less nucleophilic than ethanol. However, in the transition state for the ring-opening step of the general base catalysis mechanism the electron-withdrawing trifluoromethyl group can stabilize the developing negative charge on the oxygen atom of the alcohol, thereby rendering alcoholysis with trifluoroethanol a faster reaction than that with ethanol.

When one considers that a carboxylic acid is, in general, >6 orders of magnitude more acidic in water than a protonated amine, the proton transfer from the ammonium salt to the carboxylate in the general base catalysis mechanism seems to be a highly unfavorable step. However, it is plausible that the ammonium salt becomes more acidic than the carboxylic acid in a nonpolar organic solvent such as ether or toluene.[7,51] It is not so surprising that the thermodynamic stability of the salt relative to the free acid and base depends so much on solvent. The carboxylate ammonium salt is most likely to exist as a tight ion pair complex in ether or toluene, whereas in water both the carboxylate and the ammonium ions are most likely to be surrounded by water molecules. However, as clearly shown in Bolm's studies, the neutralization of quinidine by the hemiester is a major obstacle to the use of a catalytic amount of quinidine for the enantioselective ARO of cyclic anhydrides.[30] Neutralization of $(DHQD)_2AQN$ and DHQD-PHN by the hemiester appears to occur to a lesser extent, yet these modified cinchona alkaloids are kinetically more active than quinidine. Understanding why, relative to quinidine, $(DHQD)_2AQN$ and DHQD-PHN perform as kinetically more potent base catalysts but thermodynamically weaker bases could provide critical insights into the design and development of a significantly improved chiral Lewis base catalyst for asymmetric alcoholysis of cyclic anhydrides.

Deng and co-workers also observed that DHQD-PHN and $(DHQD)_2AQN$ catalyzed the kinetic resolution of phenylalanine UNCA with similar rates and similar levels of enantioselectivity (selectivity factor = 50 and 41, respectively).[44] Because the alcoholysis shows a first-order dependence for both catalysts, the similar rates and selectivities obtained with the mono- and biscinchona alkaloids strongly indicate that, in both cases, the ring opening of UNCA is mediated by a single DHQD group. It is highly unlikely that any cooperative catalysis, where one DHQD moiety activates the alcohol and another activates the anhydride, is occurring in the cinchona alkaloid-catalyzed asymmetric alcoholysis of cyclic anhydrides.

The results from both Oda's and Deng's mechanistic studies point to a general base catalysis mechanism for the cinchona alkaloid-catalyzed alcoholysis. Deng and co-workers have used this mechanistic insight to develop a highly efficient DKR of α-aryl UNCAs via modified cinchona alkaloid-catalyzed alcoholysis. However, these corresponding results should not be taken as evidence of a mechanistic trend for asymmetric alcoholysis of anhydrides with other chiral amines or even with cinchona alkaloids under reaction conditions that differ from those in Oda's or Deng's studies. In addition, it certainly does not rule out the possibility of other chiral base-catalyzed ring opening reactions of cyclic anhydrides occurring via a nucleophilic catalysis mechanism. Carrying out careful kinetic studies of asymmetric reactions very often reveals unexpected mechanistic scenarios.[52] Consequently, it remains necessary to determine the mechanisms of other chiral amine catalyzed alcoholyses of cyclic anhydrides on a case-by-case basis.

6. Conclusions

A number of approaches toward highly enantioselective alcoholysis of cyclic anhydrides have been developed over the past few years, with readily accessible and easily recyclable organic catalysts based on the cinchona alkaloid skeleton showing the most promise at present. In terms of enantioselectivity and yield, generality of substrate scope, accessibility of the substrates, reagents, and catalysts, and ease of product purification, the most efficient catalytic asymmetric alcoholysis of cyclic anhydrides has begun to fulfill many of the critical requirements that define a powerful catalytic asymmetric reaction. Nonetheless, enormous challenges remain to be met to fully realize the potential of this remarkable transformation. A certainly challenging and desirable goal is the development of a new generation of catalysts that cost substantially less to produce, yet are capable of affording improved enantioselectivity and activity at room temperature. Even more challenging is the discovery of new catalysts that allow significant expansion of the current substrate scope to include, for example, 2,4-dialkyl glutaric anhydrides.[53] To meet these challenges, future efforts directed toward the elucidation of the mechanistic basis of the currently most efficient catalysts and the continuing exploration of a diverse range of catalysts are indispensable.

7. Acknowledgment

We thank NIH (GM-61591), the Research Corporation (RI-0311), the Harcourt General Charitable Foundation, and Daiso Inc. for financial support.

8. References

(1) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(2) (a) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000; p 357. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Kolb, H. C.; Sharpless, K. B. *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, p 219. (d) Marko, I.; Svendsen, J. S. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 20. (e) Bolm, C.; Hildebrand, J. P.; Muniz, K. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; p 399.

(3) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (c) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000; p 231.

(4) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2. (d) Jacobsen, E. N.; Wu, M. H. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 18.2.

(5) (a) Noyori, R. *Science* **1990**, *248*, 1194. (b) Ohkuma, T.; Noyori, R. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 6.1. (c) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (d) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(6) For excellent recent reviews see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N.; *Adv. Synth. Catal.* **2001**, *343*, 5. (b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (c) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1765. (d) Jacobsen, E. N.; Wu, M. H. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 35. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(7) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131.

(8) For enzyme-catalyzed alcoholysis of meso anhydrides see: (a) Yamamoto, K.; Nishioka, T.; Oda, J.; Yamamoto, Y. *Tetrahedron Lett.* **1988**, *29*, 1717. (b) Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087. (c) Ozegowski, R.; Kunath, A.; Schick, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1191.

(9) Altschul, R.; Bernstein, P.; Cohen, S. G. *J. Am. Chem. Soc.* **1956**, *78*, 5091.

(10) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731.

(11) (a) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142. (b) Thiesen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

(12) Ohshima, M.; Mukaiyama, T. *Chem. Lett.* **1987**, 377.

(13) Suda, Y.; Yago, S.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1992**, 389.

(14) (a) Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1995**, *36*, 931. (b) Hashimoto, N.; Kawamura, S.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1996**, *37*, 9237.

(15) Hashimato, K.; Kitaguchi, J.; Mizuno, Y.; Kobayashi, T.; Shirahama, H. *Tetrahedron Lett.* **1996,** *37*, 2275.

(16) (a) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849. (b) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 4120. (c) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 2122.

(17) (a) Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1984**, 779. (b) Nagao, Y.; Inoue, T.; Fujita, E.; Terada, S.; Shiro, M. *Tetrahedron* **1984**, *40*, 1215. (c) Ward, R. S.; Pelter, A.; Edwards, M. I.; Gilmore, J. *Tetrahedron: Asymmetry* **1995**, *6*, 843. (d) North, M.; Zagotto, G. *Synlett* **1995**, 639. (e) Albers, T.; Biagini, S. C. G.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A.; North, M.; Uriarte, E.; Zagotto, G. *Synthesis* **1996**, 393. (f) Ward, R. S.; Pelter, A.; Edwards, M. I.; Gilmore, J. *Tetrahedron* **1996**, *52*, 12799. (g) Jones, I. G.; Jones, W.; North, M.; Teijeira, M.; Uriarte, E. *Tetrahedron Lett.* **1997**, *38*, 889. (h) Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *J. Org. Chem.* **1999**, *64*, 5413.

(18) Verma, R.; Mithran, S.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 257.

(19) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128.

(20) (a) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1717. (b) Hiratake, J.; Inagaki M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053.

(21) (a) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395. (b) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190.

(22) (a) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99. (c) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321. (d) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363. (e) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473. (f) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuehnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.

(23) (a) Goldberg, M. W.; Sternbach, L. H. U.S. Patent 2,489,232, 1949; *Chem. Abstr.* **1951**, *45*, 184. (b) Goldberg, M. W.; Sternbach, L. H. U.S. Patent 2,489,235, 1949; *Chem. Abstr.* **1951**, *45*, 186a. (c) Goldberg, M. W.; Sternbach, L. H. U.S. Patent 2,489,-238, 1949; *Chem. Abstr.* **1951**, *45*, 186h.

(24) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohác, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071.

(25) (a) Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 632. (b) Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 513.

(26) (a) Bolm, C.; Gerlach A.; Dinter, C. L. *Synlett* **1999**, 195. (b) Bolm, C.; Dinter, C. L.; Seger, A.; Höecker, H.; Brozio, J. *J. Org. Chem.* **1999**, *64*, 5730.

(27) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793.

(28) Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. *Tetrahedron: Asymmetry* **1999**, *10*, 3403.

(29) (a) Bolm, C.; Dinter, C. L.; Schiffers, I.; Defrère, L. *Synlett* **2001**, *12*, 1875. (b) Bolm, C.; Tanyeli, C.; Grenz, A.; Dinter, C. L. *Adv. Synth. Catal.* **2002**, *344*, 649. (c) Bolm, C.; Schiffers, I.; Atodiresei, I.; Ozcubukcu, S.; Raabe, G. *New J. Chem.* **2003**, *27*, 14. (d) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K. H. *Synthesis* **2003**, *1*, 136.

(30) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

(31) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

(32) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737.

(33) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.

(34) Iriuchijima, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907.

(35) Wöltinger, J.; Krimmer, H.-P.; Drauz, K. *Tetrahedron Lett.* **2002**, *43*, 8531.

(36) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S.-i. *Tetrahedron Lett.* **2001**, *42*, 411.

(37) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539.

(38) Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrère, L.; Gerlach, A.; Raabe, G. *Synthesis* **2001**, 1719.

(39) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302.

(40) (a) Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1997**, *38*, 1195. (b) Schoenfelder, A.; Mann, A.; Coz, S. L. *Synlett* **1993**, 63.

(41) For reviews on parallel kinetic resolution see: (b) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (b) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. (c) Kagan, H. *Croat. Chem. Acta* **1996**, *69*, 669.

(42) For other examples of parallel kinetic resolutions see: (a) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930. (b) Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428. (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584. (c) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (d) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383. (c) Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commum.* **1995**, 1247. (e) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493.

(43) For enzyme-catalyzed parallel kinetic resolutions see: (a) Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann.* **1995**, 1699. (b) Mischitz, M.; Faber, K. *Tetrahedron Lett.* **1994**, *35*, 81. (c) Petit, F.; Furstoss, R. *Tetrahedron: Asymmetry* **1993**, *4*, 1341. (d) Alphand, V.; Furstoss, R. *J. Org. Chem.* **1992**, *57*, 1306.

(44) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696.

(45) (a) Fuller, W. D.; Goodman, M.; Naider, F. R.; Zhu, Y. F. *Biopolymers* **1996**, *40*, 183. (b) Daly, W. H.; Poché, D. *Tetrahedron Lett.* **1988**, *29*, 5859.

(46) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.

(47) Toyooka, K.; Takeuchi, Y.; Kubota, S. *Heterocycles* **1989**, *29*, 975.

(48) For reviews on dynamic kinetic resolution see: (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (b) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447. (d) Ward, R. S.; *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (e) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(49) Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321.

(50) Talbot, R. J. E. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, The Netherlands, 1972; p 286.
(51) Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.
(52) One recent example is Jacobsen's elucidation, through rigorous kinetic study, of an unexpected cooperative catalysis mechanism for the Co−Salen-catalyzed hydrolytic ring opening of epoxides, which involves simultaneous activation of both the nucleophile and the electrophile by two molecules of the catalyst. (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780. (c) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.
(53) Racemic and meso cyclic anhydrides should be interesting substrates for other asymmetric ring opening reactions. For recent examples see: (a) Ostendorf, M.; Romagnoli, R.; Cabeza Pereiro, I.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174. (c) Shintani, R.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057.

CR020037X