Catalysis of the Asymmetric Desymmetrization of Cyclic Anhydrides by Nucleophilic Ring-Opening with Alcohols**

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The asymmetric desymmetrization (ADS) of *meso* compounds by enzymatic[1] and nonenzymatic[2] methods has proven to be a versatile and powerful strategy in asymmetric synthesis. ADS of *meso* compounds is particularly valuable because it allows many stereocenters to be established in a single symmetry breaking transformation. "Late-stage" ADS of topologically complex *meso* intermediates prepared by using simultaneous two-directional synthesis illustrates the power of the approach in target-oriented synthesis.[3] However, although there is aesthetic appeal in simultaneous multiple stereocenter genesis, it is only useful for targets possessing a high degree of latent or real symmetry. In contrast, ADS of relatively simple *meso* compounds can provide highly expedient access to a wide variety of usefully functionalized chiral building blocks for the asymmetric synthesis of innumerable targets.[4] A good example is the ADS of *meso* cyclic anhydrides by selective ring-opening at one of the enantiotopic carbonyls.[5] This type of ADS has attracted considerable attention over the years because many *meso* cyclic anhydrides are readily available, for example, through Diels–Alder reactions of maleic anhydride, and because the desymmetrized products, which contain chemically differentiated carboxy functions, provide a plethora of possibilities for further elaboration. In this Highlight we examine recent advances in the development of nonenzymatic catalysts, particularly chiral tertiary amines, for the ADS of *meso* cyclic anhydrides by alcoholytic ring-opening; these advances should pave the way for more widespread exploitation of this powerful approach. Moreover, we discuss some mechanistic aspects of the catalysis that may have implications for other asymmetric processes mediated by tertiary amines.

The ADS of *meso* cyclic anhydrides by direct ring-opening with enantiomerically pure alcohols, amines, and other nucleophiles has been shown to proceed with high levels of diastereoselectivity in a number of instances.[6] While this strategy is undoubtedly of synthetic value, it is limited in that stoichiometric quantities of the chiral nucleophile are required. Unless this "chiral auxiliary" is to be incorporated into the target molecule, this is clearly inefficient as additional chemical steps will be required for its removal.

Therefore, processes involving addition of achiral nucleophiles mediated by chiral catalysts are more desirable. The first enzyme-catalyzed processes were described by Oda and co-workers in 1988 who found that the lipase Amano P catalyzed the ADS of several 3-substituted glutaric anhydrides with primary alcohols in toluene or $i\mathrm{Pr_2O}$ at room temperature over 6–48 hours.[7] The corresponding hemiesters were obtained in 67–94 % yield and 60–91 % *ee*, which compares favourably with the syntheses of the same products by enzymatic ADS of the corresponding diesters.[8] Since then a number of related enzymatic protocols for the ADS of *meso* cyclic anhydrides have been reported giving high levels of enantioselectivity in many cases.[8]

The first nonenzymatic, catalytic process was reported by Oda and co-workers in 1985 who found that cinchona alkaloids catalyzed the methanolytic ADS of the *cis*-dimethylglutaric anhydride **1** with 4–20 equivalents of MeOH in toluene at room temperature over 1–12 days (Scheme 1).[9] Cinchonine (10 mol %) was the most enantioselective catalyst and gave hemiester **2** in > 95 % yield and 70 % *ee*. Cinchonidine, the diastereomer of cinchonine with the opposite enantiomeric configurations at C-8 and C-9, provided the antipodal hemiester in 64 % *ee*.

Shortly thereafter, Aitken and co-workers published details of a similar procedure catalyzed by quinine (50 mol %) in which *meso* epoxy anhydride **3** was converted into lactone **4** in 57 % yield and 76 % *ee* with 3 equivalents of MeOH in toluene at room temperature within 2 hours (Scheme 1).[10] Under these conditions, the methanolytic ADS is followed by intramolecular epoxide opening to form **4**. In this case, quinidine, the diastereomer of quinine with the opposite enantiomeric configurations at C-8 and C-9, provided the antipodal product with significantly lower enantioselectivity.

Two chiral Lewis acid-based protocols for the ADS of *meso* cyclic anhydrides were also developed during the 1990s by the groups of Fujisawa[11] and Seebach,[12] who utilized a cinchonidine:$\mathrm{Et_2Zn}$ complex and diisopropoxytitanium TADDOLates, respectively (Scheme 2). As these are mechanistically distinct from the amine-catalyzed systems, discussion of these lies outside the scope of this Highlight. It is, however, worth

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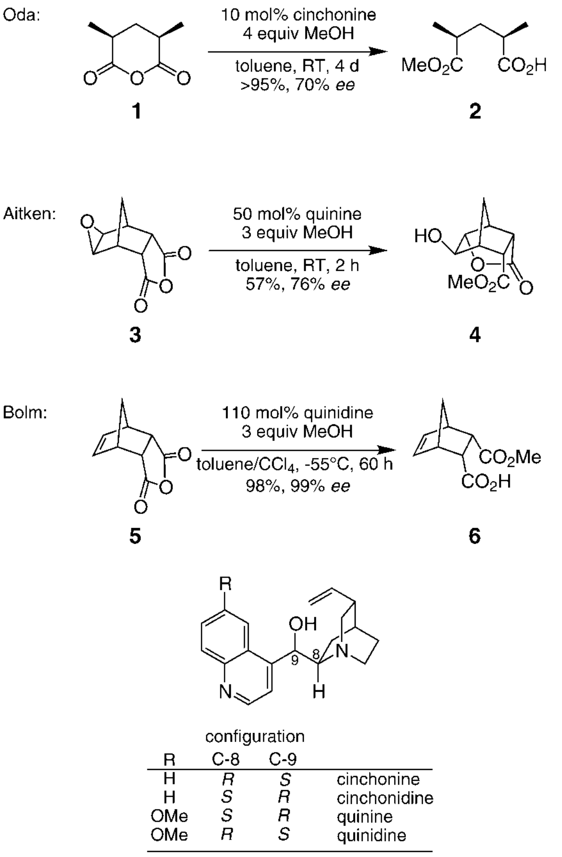
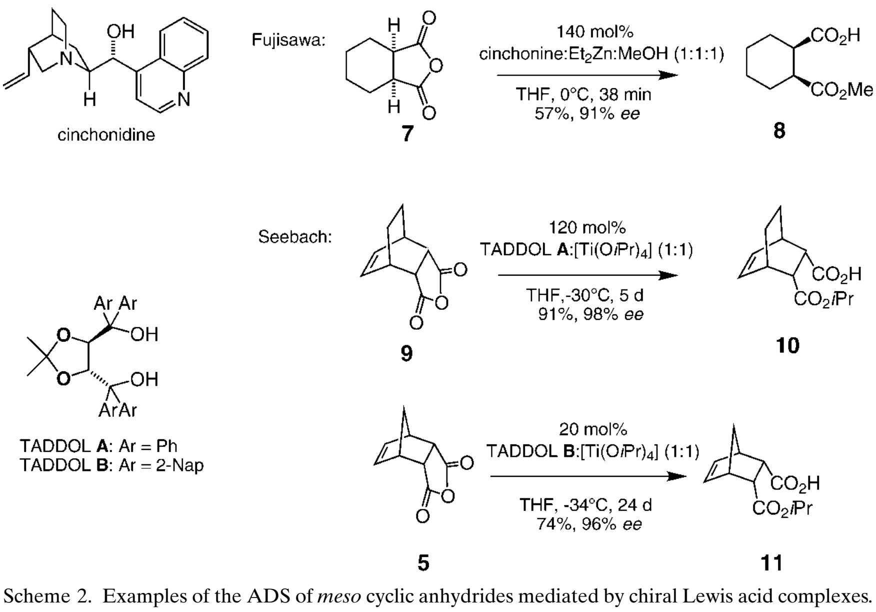


R	configuration C-8	configuration C-9	
H	*R*	*S*	cinchonine
H	*S*	*R*	cinchonidine
OMe	*S*	*R*	quinine
OMe	*R*	*S*	quinidine

Scheme 1. Examples of the ADS of *meso* cyclic anhydrides mediated by cinchona alkaloids.



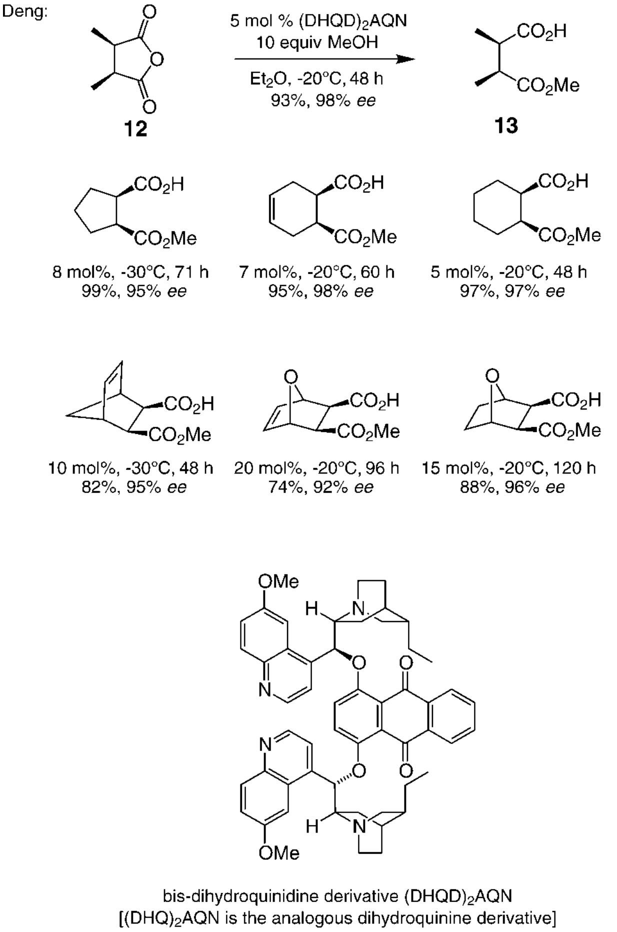
Scheme 2. Examples of the ADS of *meso* cyclic anhydrides mediated by chiral Lewis acid complexes. 2-Nap = 2-naphthyl.

noting that the method of Seebach and co-workers, which is the more selective and extensively investigated of the two, suffers from extended reaction times, particularly in catalytic mode.

In 1999, Bolm and co-workers built upon the findings reported by the groups of Oda and Aitken to develop a more enantioselective methanolysis protocol mediated by quinidine (110 mol%).[13] A range of *meso* cyclic anhydrides underwent ADS to give methyl hemiesters in 61–99% yield and 85–99% *ee* with 3 equivalents of MeOH in toluene:CCl_4 (1:1) at −55°C within 60 hours (Scheme 1). Under these conditions, quinine provided the antipodal products with comparable enantioselectivities (75–99% *ee*). The use of just catalytic quantities of the quinidine (10 mol%) resulted in lower yields and dramatic loss of enantioselectivity (for example, 50% yield and 35% *ee* for anhydride **5**). However, the catalytic protocol could be improved significantly by the addition of one equivalent of 1,2,2,6,6-pentamethylpiperidine, which allowed the ADS of anhydride **5** in 98% yield and 90% *ee*, albeit after 6 days at −55°C.

In the light of the above, a recent report by Deng and co-workers describing the methanolytic ADS of various *meso* cyclic anhydrides catalyzed by modified bis-cinchona alkaloids appears to constitute a significant breakthrough in this area.[14] As the result of screening known bis-cinchona derivatives, developed by Sharpless et al. as chiral ligands for OsO_4-catalyzed asymmetric dihydroxylation reactions, Deng and co-workers found that dihydroquinidine-based catalyst $(DHQD)_2AQN$ (5–20 mol%) mediated the formation of methyl hemiesters in 70–99% yield and 90–98% *ee* with 10 equivalents of MeOH in Et_2O at between −20°C and −40°C over 48–120 hours (Scheme 3). The corresponding dihydroquinine-based catalyst $(DHQ)_2AQN$ provided the antipodal products with comparable enantioselectivities (82–98% *ee*). No achiral base is required in the process and the use of highly toxic CCl_4 as solvent is avoided (compare with the protocol of Bolm et al.). Furthermore, the process retains the ease of catalyst removal/recycling by simple acid extraction that is a feature of all the alkaloid-catalyzed processes (in contrast to, for example, the TADDOLates of Seebach and co-workers). The ability to deliver either enantiomer of product simply by switching catalyst diastereomer is also of significant practical importance and constitutes a clear advantage over enzymatic processes.

This is not to say that the process could not be rendered more convenient: Maintaining a reaction at approximately −20°C for several days is not attractive on process scale. So what are the prospects for the development of more efficient processes? Given that all amine catalysts described so far have been based on cinchona alkaloids it seems likely that screening or rational design (or a combination of the two) could lead to the discovery of better catalysts. Indeed, the first paper describing the use of noncinchona-based catalysts (a series of chiral hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolones) for ADS of *cis*-hexahydrophthalic anhydride in up to 89% *ee* has recently appeared.[15] Comparison with the related field of acylative kinetic resolution (KR) of secondary alcohols catalyzed by nucleophilic amines (and phosphines) lends credence to the hypothesis that such efforts should bear fruit. Until just five years

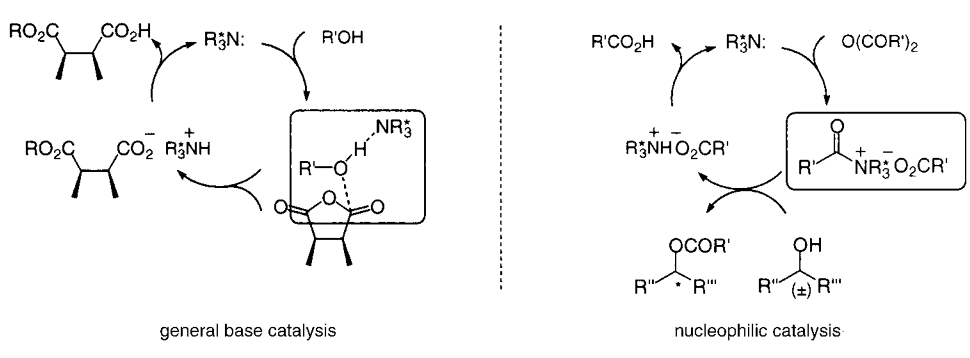


Scheme 3. Examples of the ADS of *meso* cyclic anhydrides mediated by bis-cinchona derivatives. Yields and *ee*'s in parenthesis refer to catalysis by (DHQ)$_2$AQN to give the opposite enantiomer to that shown.

ago, the alkaloid brucine constituted a state-of-the-art catalyst for these KR processes, but since then spectacular progress has been made by the introduction of "designer" chiral nucleophilic amine/phosphine catalysts, developments pioneered by the groups of Vedejs, Fu, and Oriyama.[16]

Although acylative KR of secondary alcohols and alcoholytic ADS of *meso* cyclic anhydrides can both be catalyzed by chiral amines, there appear to be significant mechanistic differences between the two modes of catalysis. Amine catalysis of the former almost certainly involves nucleophilic attack by the amine nitrogen on the anhydride to afford a reactive chiral acylammonium salt. Nucleophilic attack on this salt by the secondary alcohol gives the ester product and regenerates the amine (that is, nucleophilic catalysis; Scheme 4). An equimolar amount of an achiral and nonnucleophilic base (for example, Et$_3$N) is generally present in these reactions to ensure that the chiral amine remains unprotonated to continue the catalytic cycle. The same mechanism may, as discussed by the groups of Aitken and Bolm, also operate for cyclic anhydride ring-opening. However, neither the quinoline nor the α-substituted quinuclidine nitrogens of cinchona alkaloids are expected to be very nucleophilic, as nucleophilicity is strongly attenuated by steric factors.[17] Furthermore, for cyclic anhydrides the leaving carboxylate group has a high effective molarity (EM = 10^4 M), which makes the equilibrium between anhydride and acylammonium salt very unfavorable towards the latter.[18] Taken in combination with the fact that in nonpolar solvents, as used in the cinchona-catalyzed reactions, even the position of the equilibrium between the highly nucleophilic amine 4-dimethylaminopyridine (DMAP) and the acyclic anhydride Ac$_2$O is unfavorable,[19] this suggests that, at best, an extremely low concentration of acylammonium salt will be present and it is unlikely to be kinetically useful. Oda and co-workers have therefore proposed that cinchona-catalyzed ring-opening of *meso* anhydrides involves the quinuclidine nitrogen acting as a chiral general base rather than a nucleophile.[9] This is in line with the mechanism proposed by Wynberg for cinchona alkaloid mediated asymmetric conjugate addition reactions of thiols to enones.[20] In support of general base catalysis Oda and co-workers found that the cinchonine-catalyzed (10 mol%) ring-opening of *cis*-2,4-dimethylglutaric anhydride by methanol (20 equivalents) in toluene displayed a kinetic isotope effect (k_{MeOH}/k_{MeOD}) of 2.3. This value is probably greater than would be expected for nucleophilic catalysis even if proton transfer prior to final C–N bond cleavage were to be rate-determining.[21] The fact that the nonnucleophilic base Et$_3$N is an effective achiral catalyst for alcoholytic ring-opening of *meso* anhydrides but not for acylation of secondary alcohols also militates against the former involving nucleophilic catalysis.[9] The two contrasting mechanisms are shown in Scheme 4 although it should be stressed that, particularly in the case of Deng and co-workers' dimeric catalysts, a synergistic combination of the two mechanisms cannot be ruled out.

Irrespective of the mechanistic details, the catalytic ADS reaction of Deng and co-workers is notable on two accounts: Firstly because (DHQD)$_2$AQN is a bis-ether derivative, and secondly because no stoichiometric base is employed. Previous workers have noted that ether derivatives impart diminished enantioselectivities relative to the parent alkaloids although no specific role for the hydroxy group, either in



Scheme 4. Comparison of possible mechanisms of amine-catalyzed acylative kinetic resolution of secondary alcohols and alcoholytic ADS of *meso* cyclic anhydrides.

catalysis or in conformational control of the alkaloid, has been suggested. Indeed ab initio calculations suggest that overall the dipole moment, rather than hydrogen-bond interactions, is important in determining the conformation of monomeric cinchona alkaloids and that neither protonation nor the formation of simple ether derivatives perturbs this situation.[22] It seems likely therefore that in Deng and co-workers' dimeric structures additional $\pi-\pi$ ordering interactions are operational at least during catalysis (compare with those implicated as being significant during asymmetric dihydroxylation with this type of dimer as a ligand).[23] The absence of a stoichiometric achiral base in the protocol of Deng's group (and Oda's) suggests either that both protonated and unprotonated forms of $(DHQD)_2AQN$ mediate enantioselective ring-opening, or that the equilibrium concentration of unprotonated alkaloid is sufficient for the catalysis. The latter scenario seems more likely as Et_3N and quinuclidine, which are monobasic, are also catalytically active.[9] Indeed it is plausible that NR_3H^+ is more acidic than RCO_2H in toluene, which would make the unprotonated alkaloid the major species at equilibrium.[24] Since the groups of Aitken and Bolm have noted that protonated cinchona alkaloids (presumably protonated on the more basic quinuclidine nitrogen) are catalysts but give very poor asymmetric induction, the unprotonated and protonated forms of the catalysts used by Deng's group must show a significant activity differential. Deng and co-workers do not speculate on the mechanism of catalysis beyond describing their catalysts as "chiral Lewis bases" and do not report on the effect of added stoichiometric achiral base.

In line with all workers in this field, Deng and co-workers note that the stereochemical sense of ring-opening is predictable irrespective of the anhydride structure. This implicates the anhydride motif itself as being the primary recognition element for the alkaloid catalyst. The noncovalent interactions responsible for this recognition are clearly critically dependent on the alkaloid configuration at C-8 and C-9 and must lead to a complex in which one of the enantiotopic carbonyl groups is activated to attack. Once the precise form of this activation can be more closely defined (for example, general base/nucleophilic catalysis or some other mechanism) the prospects for rational design of more rapid and selective catalysts will be greatly improved. Given that this type of catalysis has many elements in common with enzyme catalysis and indeed with many "enzyme-like" processes, including a number of other synthetically important asymmetric processes mediated by low molecular weight organic catalysts,[25] significant further progress can be expected in the not too distant future.

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