JOC*Note*

Highly Enantioselective Desymmetrization of *Meso* Anhydrides by a Bifunctional Thiourea-Based Organocatalyst at Low Catalyst Loadings and Room Temperature

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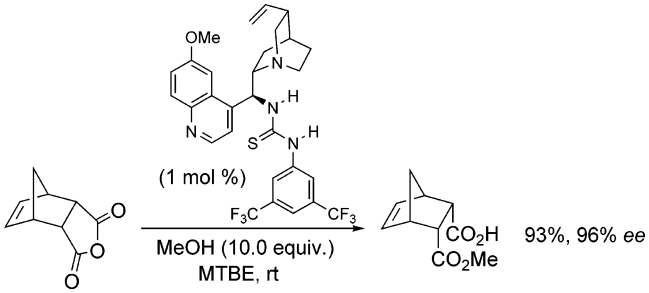
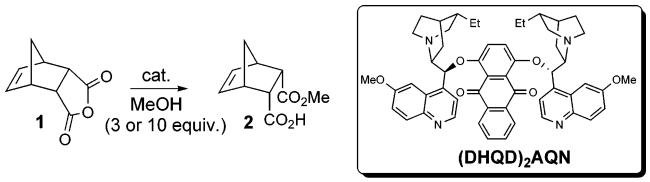


Bifunctional (thio)urea-based cinchona alkaloid derivatives have been shown to promote highly efficient enantioselective desymmetrization reactions of *meso* anhydrides. The most selective of these catalysts is capable of the enantioselective methanolysis of succinic and glutaric anhydride derivatives to form hemiester products with >90% yield and enantiomeric excess at 1 mol % loading and ambient temperature.

The catalytic asymmetric desymmetrization of *meso* anhydrides via the addition of an alcohol nucleophile represents a simple and elegant method for the preparation of synthetically pliable hemiesters with the generation of either single or multiple stereocenters with high levels of enantiocontrol.[1,2] While chiral Lewis acid-catalyzed anhydride desymmetrizations have been reported,[3] the use of chiral amine catalysts has emerged as a more effective strategy for the enantioselective promotion of these reactions.[1c−e]

Oda first reported the desymmetrization of *meso* anhydrides catalyzed by both natural and modified *cinchona* alkaloids in 1985.[4] While catalysis was efficient at 10 mol % loading, enantioselectivity was moderate (up to 70% ee). Shortly afterward Aitken obtained comparable results in a similar study and demonstrated that the alkaloid's chiral quinuclidine moiety (only when present as the free base) was responsible for the observed stereocontrol.[5] Speculating therefore that the moderate enantioselectivity of these reactions was due to the protonation of the catalyst's quinuclidine base by the product, with the result that unselective catalysis by the quinoline unit becomes dominant at high conversions, Bolm and co-workers later found that the use of 110 mol % of either quinine or quinidine (both inexpensive) allowed the desymmetrization of a variety of *meso* anhydrides by methanolysis at −55 °C with excellent enantioselectivity (Scheme 1).[6] The alkaloid could be used at 10 mol % loading in conjunction with stoichiometric amounts of a tertiary amine at −55 °C; however, low temperatures and long reaction times (6 d) were required.[6b,7]

SCHEME 1. (Modified) Cinchona Alkaloid-Derived Catalysis of Anhydride Desymmetrization by Bolm and Deng



Bolm: PhMe/CCl_4, -55 °C, 60 h
quinidine (110 mol%)
98%, 99% *ee*

Deng: Et_2O, -30 °C, 48 h
$(DHQD)_2AQN$ (10 mol%)
82%, 95% *ee*

Deng et al. later reported that the commercially available modified cinchona alkaloid Sharpless' ligand $(DHQD)_2AQN$ and its quinine-derived *pseudo*enantiomer $(DHQ)_2AQN$ could promote highly enantioselective succinic anhydride derivative alcoholysis at 5−20% loading without the need of an added stoichiometric base at temperatures of −20 to −30 °C (Scheme 1). The methanolysis of glutaric anhydrides (traditionally a more difficult class of substrate) involved the use of higher catalyst loadings of 30 mol % and reactions at −40 °C.[8−10]

Bolm's and Deng's procedures represent important milestones in this field which allow the asymmetric synthesis of useful chiral building blocks from readily available starting materials

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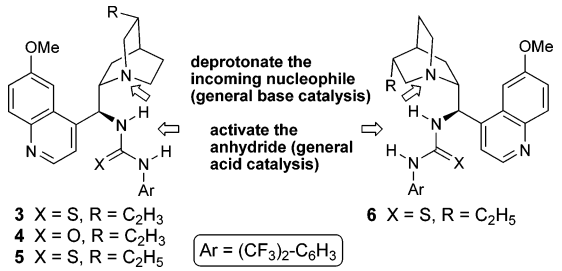

FIGURE 1. Bifunctional cinchona alkaloid-derived catalysts.

and catalysts.[7,9] As is the case with any catalytic methodology scope for further development remains: for instance, the high catalyst loadings required using difficult substrates and the maintenance of the reaction at low temperatures (−20, −30, or −55 °C) for extended periods (48−60 h) would not be optimal for industrial applications of this technology.[11,12]

We therefore became interested in the evaluation of chiral bifunctional (thio)ureas (Figure 1) as catalysts for these reactions. This catalyst class has been shown[13] to be capable of the bifunctional catalysis of a number of asymmetric addition reactions involving the addition of an acidic pronucleophile to an electrophile incorporating hydrogen bond accepting functionality; however, to the best of our knowledge these materials had not been tested as catalysts for reactions involving anhydride electrophiles.[14,15] Oda[4] detected a significant kinetic isotope effect ($k_H/k_D = 2.3$) associated with the addition of methanol to *cis*-2,4-dimethylglutaric anhydride catalyzed by quinine, which is strongly indicative of a general base catalysis mechanism for these reactions.[16] We therefore postulated that **3**−**6** held promise as efficient promoters of these reactions which could selectively bind and activate the anhydride electrophile by hydrogen bonding to the (thio)urea moiety[17,18] and subsequently encourage attack at a single anhydride carbonyl moiety through general-base catalysis mediated by the suitably positioned chiral quinuclidine base. It was envisaged that the activation of *both* nucleophilic and electrophilic reaction components in a controlled chiral environment could offer distinct advantages with respect to both rate and selectivity.

The results of our preliminary investigations to test this premise are outlined in Table 1. As a starting point we chose to study the effect of solvent polarity and reaction concentration on the asymmetric methanolysis of **1** by modified *cinchona* alkaloids **3**−**6** at ambient temperature. From a catalyst activity perspective the initial results were promising: as little as 1 mol % of the bifunctional quinine-derived thiourea catalyst **3** could promote the reaction to high levels of conversion in 1 day (entries 1−5). Methyl *tert*-butyl ether proved to be the optimumsolvent of those tested; in this medium (0.4 M concentration) **2** could be prepared in 67% ee. While this level of selectivity was disappointing, we were subsequently pleased to

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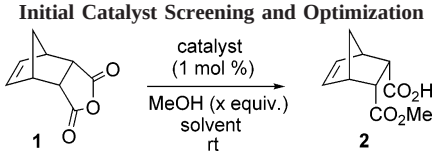
TABLE 1. Initial Catalyst Screening and Optimization



entry	cat.	solvent	concn (M)[a]	x	*t* (h)	conv (%)[b]	ee (%)[c]
1	**3**	PhMe	0.4	10	24	93	30
2	**3**	CH_2Cl_2	0.4	10	24	80	33
3	**3**	THF	0.4	10	24	73	65
4	**3**	Et_2O	0.4	10	24	86	40
5	**3**	MTBE	0.4	10	24	81	67
6	**3**	MTBE	0.125	10	48	88	85
7	**3**	MTBE	0.025	10	72	92	91
8	**3**	MTBE	0.020	10	72	91	94
9	**3**	MTBE	0.015	10	96	93	96
10	**4**	MTBE	0.015	10	96	88	89
11	**5**	MTBE	0.015	10	96	91	89
12	**6**	MTBE	0.015	10	96	74	−77
13[d]	**3**	MTBE	0.025	10	144	76	95
14	**3**	MTBE	0.125	5	72	82	92
15	**3**	MTBE	0.025	5	72	62	96
16[e]	**3**	MTBE	0.025	5	24	>98	94

[a] Refers to the concentration of the anhydride in the solvent. [b] Conversion: determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity (% ee: determined with excellent agreement by either CSP-HPLC or ^{1}H NMR after derivatization, see the Supporting Information). [d] Reaction at 0 °C with 2 mol % catalyst. [e] 5 mol % catalyst used.

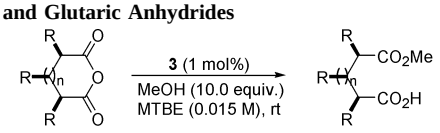
observe an increase in product enantioselectivity at lower reaction concentrations (entries 5−9), which allowed the formation of the hemiester **2** in 91−96% ee at concentrations between 0.025 and 0.015 M (entries 7−9). Under optimum conditions both urea-based catalyst **4** and the dihydroquinine-derived thiourea **5** promoted marginally less selective methanolysis than **3** (entries 10 and 11), while the quinidine-derived catalyst **6** furnished **2** as the opposite antipode to that obtained with catalyst **3**, albeit with considerably lower enantioselectivity (entry 12). A lower reaction temperature of 0 °C resulted in a slower reaction without an increase in selectivity (entry 13)

Interestingly, the use of 5 equivalents of methanol leads to more selective catalysis at the expense of reaction rate (compare entries 6−7 with 14−15);[19] however, this drawback can be circumvented by the use of increased catalyst loadings (5 mol %, entry 16) if required.

With a readily available organocatalyst and reaction conditions conducive to clean asymmetric anhydride desymmetrization at room temperature identified, attention now turned to the key question of reaction scope. Succinic anhydride derivatives **1** and **7**−**11** could be smoothly transformed into hemiesters **2** and **14**−**18** in excellent isolated yields and ee in the presence of **3** (1 mol %) at ambient temperature. As expected, glutaric anhydrides **12** and **13** underwent faster methanolysis with diminished enantioselectivity; however, we were pleased to find that at 0 °C both **19** and **20** could be prepared in excellent yield and enantiomeric excess without requiring increased catalyst loading (entries 8 and 10).

(19) We proposed that at high concentrations (e.g., 0.4 M) methanol makes a significant contribution to the overall solvent properties (14% v/v), while at lower concentrations (e.g., 0.015 M) its contribution is negligible (0.6% v/v). To test this, we repeated the reaction detailed in entry 9 of Table 1 using MTBE solvent with *t*BuOH additive (14% v/v). Under these conditions **2** was formed in 75% ee. The same reaction (0.015 M) in pure MeOH as solvent gave 9% ee.

TABLE 2. Room Temperature Asymmetric Methanolysis of Succinic and Glutaric Anhydrides



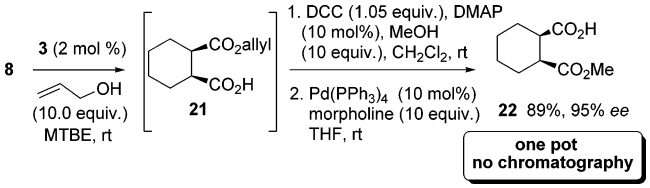
entry	anhydride	product	t (h)	yield (%)[a]	*ee* (%)[b,c]
1	**7**	**14**	40	99	93
2	**8**	**15**	30	98	93
3	**1**	**2**	100	93	96
4	**9**	**16**	14	98	92
5	**10**	**17**	96	95	85
6	**11**	**18**	130	90	85
7	**12**	**19**	18	98	83
8[d]			50	94	90
9	**13**	**20**	22	98	85
10[d]			26	95	89

[a] Isolated yield. [b] Enantioselectivity (% ee*:* determined with excellent agreement by either CSP-HPLC or ^{1}H NMR after derivatization, see the Supporting Information). [c] The absolute configurations of **2** and **14**−**20** are as indicated above. [d] Reaction at 0 °C, 0.0075 M.

Methanol can also be replaced with allyl alcohol in these reactions without compromising either efficiency or enantioselectivity. Given that the quinidine-derived catalyst **5** promotes less enantioselective alcoholysis than **3**, the use of allyl alcohol in these reactions allows the possibility of the synthesis of either hemiester enantiomer from a given *meso* anhydride in high enantiomeric excess with a single catalyst via an alcoholysis, (methyl) esterification, and deprotection sequence (Scheme 2). Using this strategy the opposite antipode of **15** (i.e., **22**) could be prepared in excellent yield and ee by using catalyst **3** in a convenient one-pot procedure without requiring chromatographic purification steps.[20]

(20) A simple base-wash, extraction, acidification, and extraction sequence furnishes pure product. See the Supporting Information.

SCHEME 2. Enantioselective Alcoholysis with Allyl Alcohol



In summary, readily available bifunctional *cinchona* alkaloid derived catalysts such as **3** have been shown to promote highly efficient, ambient-temperature, asymmetric *meso* anhydride desymmetrization reactions. Both succinic and challenging glutaric anhydride derivatives can be cleanly converted to the corresponding methyl hemiesters with excellent enantioselectivity by using an unprecedented catalyst loading of 1 mol % without requiring a stoichiometric amine additive. Allyl alcohol can also be used as the nucleophile, which allows the convenient enantioselective synthesis of either antipodal methyl hemiester product of a given *meso* anhydride with a single catalyst enantiomer.

Experimental Section

Desymmetrization of *Meso* Anhydrides into the Corresponding Methyl Hemiesters: Room Temperature Procedure (Table 2, entry 1): A 40 mL reaction vial containing a stirring bar was charged with **7** (0.30 mmol, 45.6 mg) and **3** (0.003 mmol, 1.8 mg). The reaction vial was fitted with a septum and flushed with argon. MTBE (20 mL) was added followed by dry methanol (122 μL, 3.00 mmol) in a dropwise manner via syringe and the reaction mixture was stirred at room temperature for 40 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography to provide **14** (55.0 mg, 99%) as a colorless oil. The enantiomeric excess and absolute configuration were determined as described in the Supporting Information. 93% ee $[\alpha]^{20}_{D}$ −4.9 (*c* 1.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34−2.45 (m, 2H), 2.55−2.65 (m, 2H), 3.05−3.13 (m, 2H), 3.72 (s, 3H), 5.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.3, 39.0, 39.1, 51.5, 124.6, 124.7, 173.2, 179.0.

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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