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Highly enantioselective desymmetrizations of *meso*-anhydrides☆

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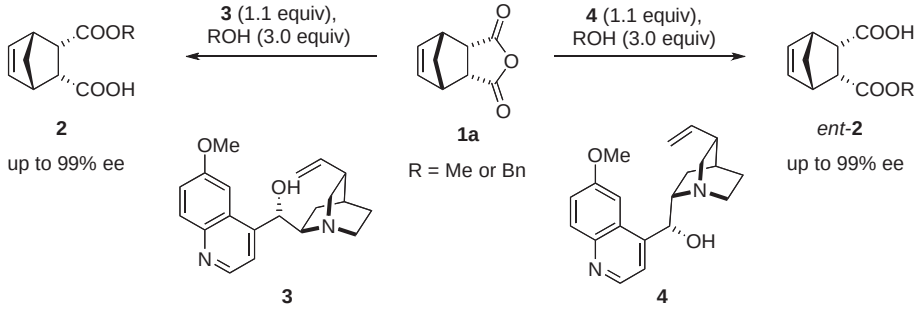
ABSTRACT

Readily available, low molecular cyclohexane-based organocatalysts promote highly enantioselective desymmetrizations of cyclic *meso*-anhydrides applying alcohols and benzyl mercaptan as nucleophiles. Both succinic and glutaric anhydrides furnished the corresponding products with up to 96% ee in mostly quantitative yields.

1. Introduction

The enantioselective desymmetrization of cyclic *meso*-anhydrides offers access to optically active compounds, which represent important chiral intermediates in the synthesis of many natural products and biologically active substances.[1] In most cases, an achiral alcohol is combined with an enantiopure base. Since the initial discoveries by Oda[2] and Aitken,[3] the use of cinchona alkaloids in asymmetric alcoholyses of *meso*-anhydrides became most common. Both the stoichiometric protocols developed by Bolm[4] (Scheme 1) and the catalytic methods using cinchona alkaloid ether derivatives introduced by Deng[5] lead to products with acceptable reactivities and enantioselectivities. Although recently, cinchona-derived thioureas[6] and sulfonamides[7] have been shown to catalyze highly enantioselective alcoholyses at ambient temperature and with low catalyst loadings, it is remarkable how often the stoichiometric protocol has found application in complex total synthesis.[8] Apparently, the advantage of having large quantities of natural cinchona alkaloids, which can even be recovered and reused, commercially available at low cost, overrides the desire to use modern catalytic versions of this synthetically highly valuable transformation.

Only a few non-alkaloid-based catalysts for enantioselective alcoholyses have recently been described.[9] Furthermore, the



Scheme 1. Asymmetric alcoholysis of *meso*-anhydrides by Bolm.

excellent enantioselectivities in high yields. Despite these advances, it should also be noted that mostly high catalyst loadings, low temperatures, and long reaction times are required for organocatalytic conversion of *meso*-anhydrides with other nucleophiles is less common.[10] The finding of novel catalysts and new protocols for reactions with diverse nucleophiles still remains challenging.

Here, we are presenting the application of several easily accessible, low molecular organocatalysts, which are effective in both enantioselective alcoholyses and asymmetric thiolyses of cyclic *meso*-anhydrides.

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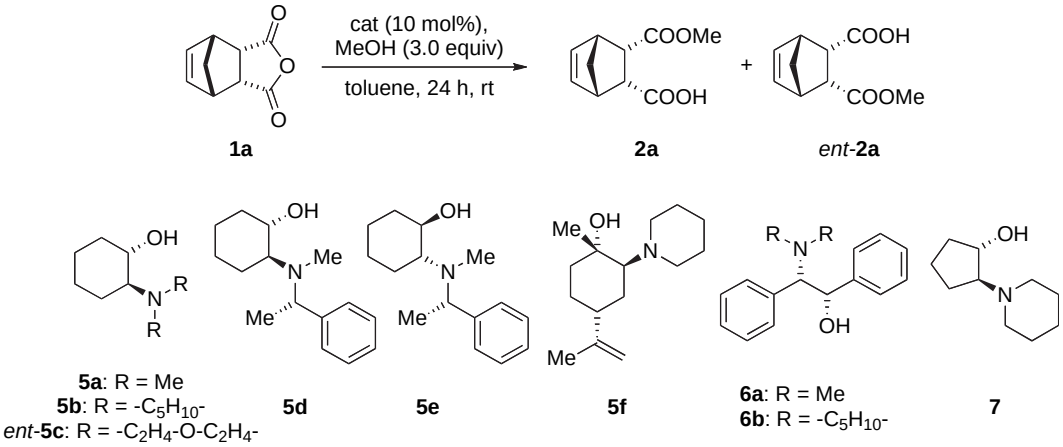
2. Results and discussion

2.1. Methanolysis of *meso*-anhydrides

Cinchona alkaloids, which are efficient mediators in the enantioselective methanolyis of *meso*-anhydrides, possess a β-aminoalcohol core structure. Assuming that this structural element played a significant role in the catalysis, several low molecular *trans*-cyclohexane-based β-aminoalcohol derivatives were synthesized[11] and tested in the methanolysis of anhydride **1a**. In these experiments, 10 mol % of the catalyst and toluene as the solvent were applied.[12] The results are summarized in Table 1.

Table 1
Screening of β-aminoalcohols as organocatalysts for the asymmetric methanolysis of anhydride **1a**[a]



Entry	Aminoalcohol	Product	% Yield[b]	% ee[c]
1	**5a**	**2a**	98	33
2	**5b**	**2a**	99	72
3	*ent*-**5c**	*ent*-**2a**	98	71
4	**5d**	**2a**	95	17
5	**5e**	*ent*-**2a**	97	10
6	**5f**	**2a**	92	16
7	**6a**	**2a**	99	16
8	**6b**	**2a**	97	57
9	**7**	**2a**	96	31

[a] The reactions were carried out using anhydride **1a** (1.0 mmol), 10 mol % of the catalyst, and 3.0 equiv of methanol in toluene (5 mL) for 24 h at room temperature.
[b] Yield of isolated product after extraction.
[c] Determined by GC analysis of the corresponding lactone using a chiral column. For details see Experimental section.

All β-aminoalcohol derivatives were highly active organocatalysts. The products could be isolated without requiring column chromatography in excellent yields.[13] Both the scaffold as well as the substitution pattern of the β-aminoalcohol core significantly influenced the selectivity of the reaction (Table 1). Piperidinyl- and morpholinyl-substituted cyclohexane-based catalysts **5b** and **5c** were the most selective and furnished product **2a** with 72 and 71% ee, respectively (Table 1, entries 2 and 3). As already observed in catalyses with cinchona alkaloids,[2] the stereochemistry of the hydroxyl-bearing carbon atom determined the absolute configuration of the product, resulting in the (*S*)-hemiester **2a** employing (1*S*)-2-aminocyclohexanol derivatives (Table 1, entries 1, 2, 4, and 6).[12]

Guided on these results and with the goal to find alternative low molecular weight catalysts with improved properties, various cyclohexane-based diamines and derivatives thereof were synthesized next. For their preparations, well-established routes starting from enantiopure 1,2-diamino cyclohexane could be utilized.[14] These compounds were then applied in catalytic anhydride openings of **1a** using toluene as solvent.[15] In Table 2 the results are summarized.

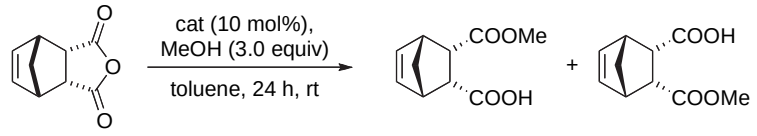
Also here, the catalyst properties were strongly affected by the substitution pattern of the amino group, and among imine derivatives **8** and **9** the highest enantioselectivity (82% ee for *ent*-**2a**) was observed when **8a** having a piperidinyl substituent was applied (Table 2, entry 1). Surprisingly, use of the corresponding *N*,*N*-dimethyl derivative led to *ent*-**2a** with only 20% ee (entry 2), and the quinidine-derived **9** proved inefficient affording *ent*-**2a** with 39% ee (entry 3). In all cases the yields were high (ranging from 89 to 94%). As observed in catalyses with β-aminoalcohols the stereochemistry of the imine-bearing carbon atom determined the absolute configuration of the product.

To introduce a better hydrogen bond donor into the catalyst, sulfonamides **10** and thioureas **11** were synthesized. To our disappointment, all derivatives showed only low to moderate enantioselectivities in the asymmetric opening of **1a**. Noteworthy in this context is a recent report on the use of a sulfonamide with a *N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine scaffold, which led to very high enantioselectivities.[9b] Compared to the catalytic behavior of the cyclohexane-derived sulfonamides reported here (Table 2, entries 4 and 5), those results were by far superior.

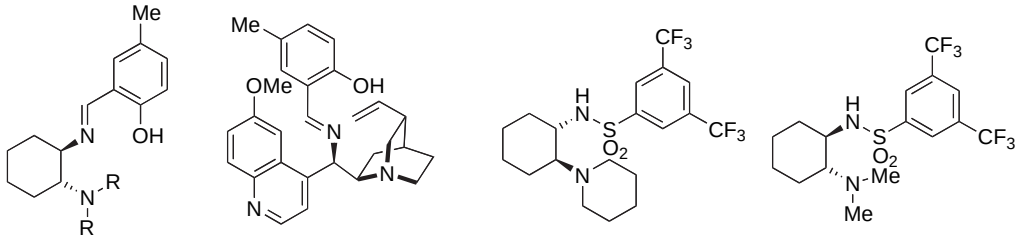
Surprising effects were observed in catalyses with thioureas **11**. There, phenyl-substituted derivative **11d** gave the best result (Table 2, entry 9). This was unexpected because in previous reports,[16] catalysts with 3,5-bis(trifluoromethyl)-substituted phenyl groups appeared to be advantageous over their phenyl analogues. Furthermore, compared with other *N*-substituents, a dimethylamino group in the thioureas (as in **11c** and **11d**) was beneficial for the enantioselectivity (Table 2, entries 8 and 9). This was in accord with observations made with sulfonamides **10** (Table 2, entry 4 vs entry 5), but it contrasted the catalytic results obtained with β-aminoalcohol dervatives **5a**–**c**, where the dimethylamino-substituted compound **5a** led to **2a** with the lowest ee (Table 1, entries 1–3).

Furthermore, sulfonamide and thiourea analogues of the corresponding aminoalcohols and imines generated the opposite enantiomer of the product (Table 1, entry 1 and Table 2, entry 1 vs

Table 2
Screening of β-diamino derivatives as organocatalysts for the asymmetric methanolysis of anhydride **1a**[a]

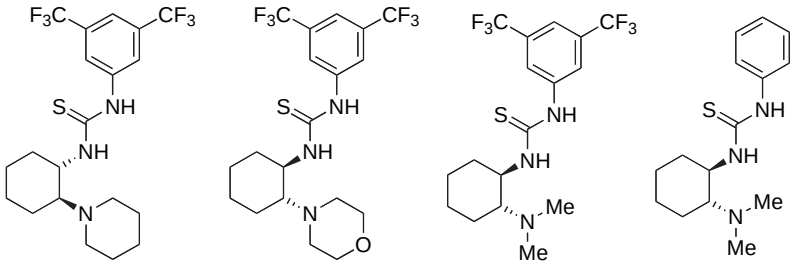


1a **2a** *ent*-**2a**



8a: R= -C_5H_{10}-
8b: R= Me

9 **10a** **10b**



11a **11b** **11c** **11d**

Entry	Catalyst	Product	% Yield[b]	% ee[c]
1	**8a**	*ent*-**2a**	91	82
2	**8b**	*ent*-**2a**	94	20
3	**9**	*ent*-**2a**	89	39
4	**10a**	*ent*-**2a**	96	15
5	**10b**	**2a**	99	45
6	**11a**	*ent*-**2a**	75[d]	10
7	**11b**	**2a**	77[d]	28
8	**11c**	**2a**	75[d]	39
9	**11d**	**2a**	98	45

[a] The reactions were carried out using anhydride **1a** (1.0 mmol), 10 mol % of the catalyst, and 3.0 equiv of methanol in toluene (5 mL) for 24 h at room temperature.
[b] Yield of isolated product after extraction.
[c] Determined by GC analysis of the corresponding lactone using a chiral column. For details see Experimental section.
[d] Yield of isolated product after column chromatography.

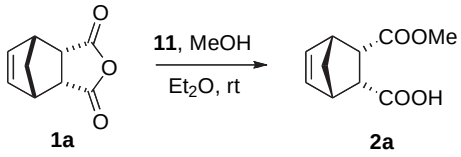
Table 2, entries 4 and 6). From this observation we concluded that depending on the nature of the catalyst either two very distinct reaction mechanisms were operating, or other factors played a decisive role.

As observed in other anhydride openings,[6,9a] thioureas can form inactive dimers, which lower the enantioselectivities. In order to study if such effects were also important here, catalyses with thioureas **11c** and **11d** were performed at various concentrations (Table 3). Again, anhydride **1a** served as substrate, and this time, diethyl ether, which proved superior to toluene (Table 2, entry 9 vs Table 3, entry 1), was used as solvent.

As the data in Table 3 reveal, the reaction showed a very strong dilution effect. Decreasing the concentration of the anhydride in a catalysis with (10 mol % of) thiourea **11d** from 0.2 mol L^{-1} to 0.025 mol L^{-1} led to a significant increase in enantioselectivity and **2a** was obtained with 90 instead of 65% ee (entries 1 and 2). At 0.0125 mol L^{-1} the ee of **2a** was even 93% (entry 3). Both phenyl- as well as bis(trifluoromethyl) phenyl-substituted catalysts **11d** and **11c**, respectively, performed well under diluted conditions. In terms of reactivity, **11d** appeared to be less active than **11c** giving **2a** in slightly lower yields after the same reaction time. The enantioselectivities, however, were superior with phenyl-substituted **11d** in most cases, and taking into account the cost for catalyst preparation, the subsequent study of the substrate scope was done with this catalyst. Thus, the conditions were as follows: use of 0.1 equiv of **11d** in a 0.0125 M solution of diethyl ether with 10 equiv of methanol.[17]

Various substituted succinic anhydrides afforded products with enantioselectivities ranging from 90 to 94% ee in very high yield (up to 99%; Table 4, entries 1–5). Openings of 3-substituted glutaric anhydrides proved less enantioselective, and products **2f** and **2g** were obtained with only 81 and 80% ee, respectively (entries 6 and 7). Bicyclic glutaric anhydrides **1h** and **1i** reacted very well leading to the corresponding hemiesters with 96 and 94% ee, respectively (entries 8 and 9).[18] In contrast, oxygen-bridged **2j**, which was obtained by asymmetric opening of anhydride **1j**, had only 72% ee (entry 10), indicating that the oxygen atom had a negative effect on the enantioselectivity. The lower ee of **2j** was mirrored by the moderate yield of this product (65%), which contrasted the excellent yields achieved in the openings of substrates **1h** and **1i** (97 and

Table 3
Optimization of the reaction conditions in the asymmetric anhydride opening of anhydride **1a** (in diethyl ether at room temperature) with organocatalysts **11** to give hemiester **2a**



1a **2a**

Entry	Catalyst (equiv)	Concentration (mol L^{-1})[a]	MeOH (equiv)	Time (h)	% Yield[b]	% ee[c]
1	**11d** (0.10)	0.2000	3	24	96	65
2	**11d** (0.10)	0.0250	10	24	99	90
3	**11d** (0.10)	0.0125	10	24	89	93
4	**11c** (0.10)	0.0125	10	24	95	92
5	**11c** (0.05)	0.0125	10	48	89	92
6	**11c** (0.01)	0.0125	10	96	75	90
7	**11d** (0.01)	0.0125	10	96	64	93
8	**11d** (0.05)	0.0250	5	48	90	92
9	**11c** (0.05)	0.0125	5	72	81	93
10	**11d** (0.05)	0.0125	5	72	79	94

[a] Concentration of anhydride **1a** in diethyl ether.
[b] Yield of isolated product after extraction.
[c] Determined by GC analysis of the corresponding lactone using a chiral column. For details see Experimental section.

96%, respectively). Noteworthy, to the best of our knowledge, there is only one other report[9d] on enantioselective openings of such type of bicyclic glutaric anhydrides.

Recently, *Rawal* applied organocatalysts with a squaramide scaffold as effective hydrogen bond donors.[19] Testing **12**, as representative catalyst of this class, in the methanolysis of **1a** under the standard conditions shown in Scheme 2 (right), the enantioselectivity was only moderate and **2a** had 62% ee. However, applying the optimized dilution conditions described above (Scheme 2, left) changed the picture, and **2a** was now obtained with 94% ee. This value compared well with the one achieved in the catalysis with thiourea **11d** (93% ee). Hence we conclude that squaramide **12** is also a highly suitable catalyst for the enantioselective methanolysis of *meso*-anhydrides.

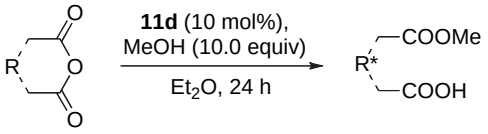
2.2. Thiolysis of *meso*-anhydrides

Next, we focused our attention on the development of suitable conditions for the less common catalytic asymmetric thiolysis. Because the natural cinchona alkaloids performed so well in the enantioselective alcoholysis and since they have not been yet applied in the thiolysis, they were tested first. To our surprise, the usual test substrate **1a** did not react with benzyl mercaptan to the desired thioester, and thus, anhydride **1c** was chosen as starting material for this study. The reactions were performed in diethyl ether and terminated by the addition of $TMSCHN_2$ and methanol. This treatment led to an in situ derivatization of the intermediately formed labile hemithioester and afforded thioester **13c** as stable product.

The application of 1 mol % of quinidine (**3**) as catalyst led to **13c** with a moderate ee of 39%. With the goal to improve the enantioselectivity, the alkaloid loading was increased (to 1.1 equiv), and to our surprise, a product with much lower ee resulted (7%). Furthermore, *ent*-**13c**, the other enantiomer of thioester **13c**, was formed in preference. Hence, the ee as well as the absolute configuration of the product were strongly dependent on the catalyst loading. Figure 1 illustrates this effect showing data from various catalyses.

These observations were in accord with those recently made in the alcoholysis of 3-substituted *meso*-glutaric anhydrides by Ivesic and Hamersak,[20] who noticed a change in the absolute product

Table 4
Enantioselective methanolysis of various *meso*-anhydrides using catalyst **11d**[a]



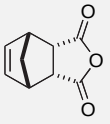
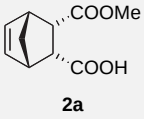
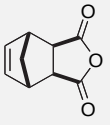
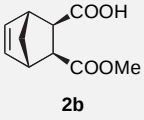
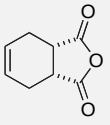
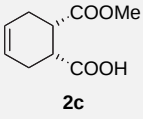
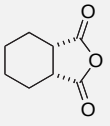
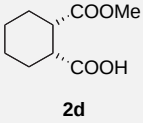
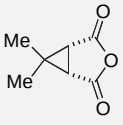
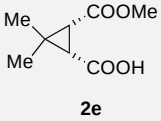
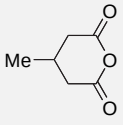
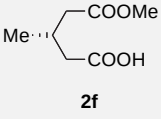
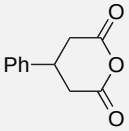
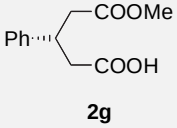
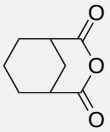
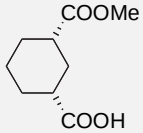
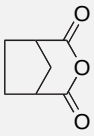
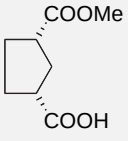
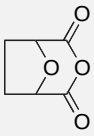
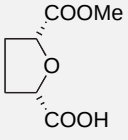
Entry	Anhydride	Product	% Yield[b]	% ee[c]
1	 **1a**	 **2a**	89	93
2	 **1b**	 **2b**	99	94
3	 **1c**	 **2c**	99	90
4	 **1d**	 **2d**	99	91
5	 **1e**	 **2e**	77	93
6	 **1f**	 **2f**	95	81
7	 **1g**	 **2g**	94	80
8	 **1h**	 **2h**	97	96

Table 4 (*continued*)

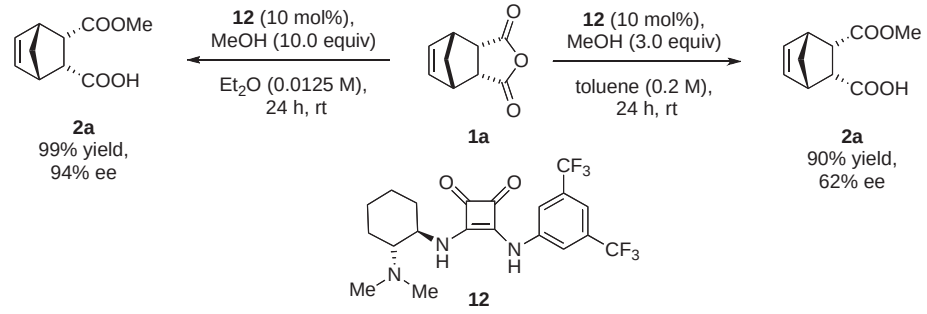
Entry	Anhydride	Product	% Yield[b]	% ee[c]
9	 **1i**	 **2i**	96	94
10	 **1j**	 **2j**	65	72

[a] The reactions were carried out using the anhydride (0.5 mmol), catalyst **11d** (10 mol %), and MeOH (10.0 equiv) in diethyl ether (40 mL) for 24 h at room temperature.
[b] Yield of isolated product after extraction.
[c] Determined by HPLC or GC analysis using chiral columns.

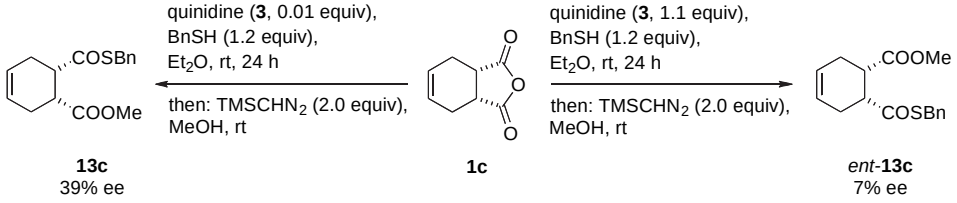
configuration when increasing the quinine loading from 0.1 to 1.6 equiv.[21] Applying those substrates (represented by glutaric anhydride **1f** and bicyclic substrate **1h**) in the quinidine-accelerated ring opening reported here showed that the thiolysis was much less affected by the catalyst loading. While the yields remained almost the same, the enantioselectivities increased (up to 77% ee) when the quinidine loadings were reduced. The best results were achieved in catalyses with only 1 mol % of quinidine (Table 5, entries 1 and 4).

Next, the low molecular cyclohexane-based catalysts were tested in the catalyzed asymmetric thiolysis of anhydride **1c** with benzyl mercaptan (Table 6). In this screening, 5 mol % of the catalyst was applied, and diethyl ether served as solvent.[22] As before, product isolation and ee analysis followed an in situ derivatization with $TMSCHN_2$ and methanol.

Both aminoalcohol **5b** and imine **8b** led to products with low ee values (Table 6, entries 1 and 2). In contrast, sulfonamides **10** and thioureas **11** performed better, yielding products with enantioselectivities in the range of 43–65% ee (Table 6, entries 3–7). Among the latter catalysts, compounds **10a**, **11a**, and **11b** having piperidinyl or morpholinyl substituents, respectively, gave higher ee's than dimethylamino-substituted **10b** or **11c**. This is particularly noteworthy, because it contrasted the behavior of those



Scheme 2. Squareamide catalyst **12** in the methanolysis of **1a**.



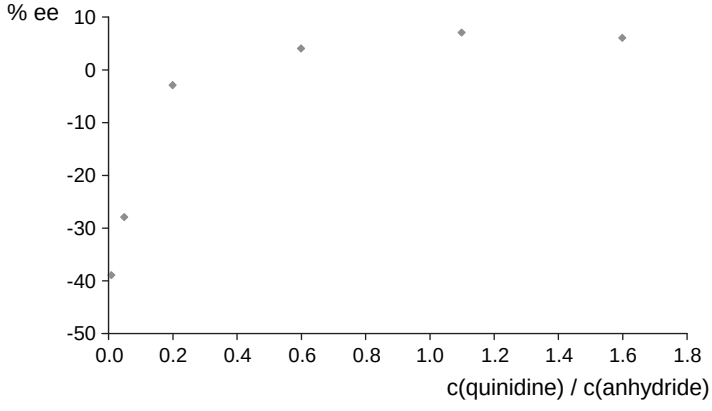
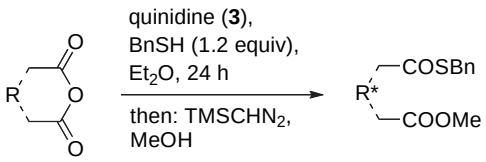
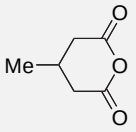
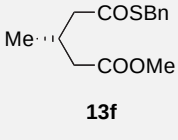
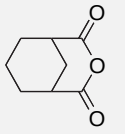
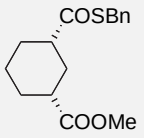


Figure 1. Dependence of the absolute product configuration on the catalyst loading in the quinidine-accelerated thiolysis of **1c**.

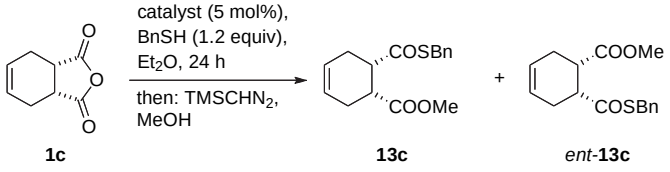
Table 5
Quinidine-accelerated thiolysis of glutaric anhydrides[a]



Entry	Cat. (equiv)	Anhydride	Product	% Yield[b]	% ee[c]
1	0.01			83	64
2	0.05			84	64
3	1.10			85	57
		1f	**13f**		
4	0.01			85	77
5	0.05			90	75
6	1.10			88	68
		1h	**13h**		

[a] The reactions were carried out using the anhydride (1.0 mmol), quinidine (**3**), and benzyl mercaptan (1.2 equiv) in diethyl ether (10 mL) for 24 h at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis using a chiral column.

Table 6
Catalyst screening for the asymmetric thiolysis of anhydride **1c**[a]



1c **13c** *ent*-**13c**

Entry	Catalyst	% Yield[b]	% ee[c]	Product
1	**5b**	59	11	**13c**
2	**8b**	80	23	*ent*-**13c**
3	**10a**	81	64	*ent*-**13c**
4	**10b**	71	59	**13c**
5	**11a**	80	50	*ent*-**13c**
6	**11b**	79	65	**13c**
7	**11c**	75	43	**13c**

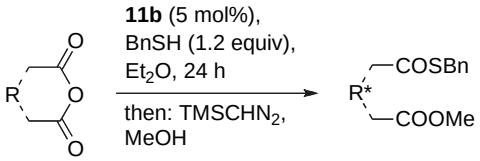
[a] The reactions were carried out using anhydride **1c** (1.0 mmol), the catalyst (5 mol %) and benzyl mercaptan (1.2 equiv) in diethyl ether (10 mL) for 24 h at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis using a chiral column.

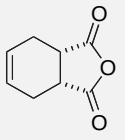
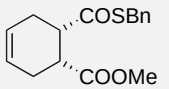
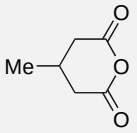
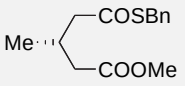
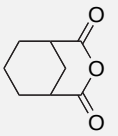
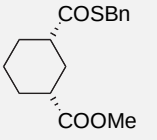
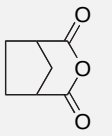
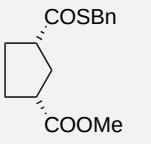
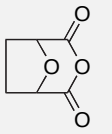
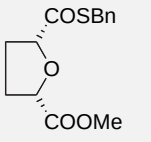
compounds in the methanolysis (comp. Table 6, entries 3–7 with Table 2, entries 4–8).

Attempts to apply thiourea catalyst **11b** at high dilution did not improve the results, and thus, the subsequent substrate screening was done under the standard thiolysis conditions (with 5 mol % of catalyst in diethyl ether). The results are summarized in Table 7.

All reactions proceeded well, and in most cases the yields were in the 90% range. The only exceptions were transformations of anhydrides **1c** and **1j**, which gave the corresponding products in only 79 and 48% yield, respectively (Table 7, entries 1 and 5). Also here, the oxygen atom in the bridging core of **1j** appeared to hamper the catalysis. Interestingly, yields and enantioselectivities went in parallel, and thus, the best enantioselectivities (up to 90% ee for **13h**) were achieved in conversions of glutaric anhydrides **1f**, **1h**, and **1i** (Table 7, entries 2–4).

Table 7
Enantioselective thiolysis of various *meso*-anhydrides catalyzed by thiourea **11b**[a]



Entry	Anhydride	Product	% Yield[b]	% ee[c]
1			79	65
	1c	**13c**		
2			88	85
	1f	**13f**		
3			93	90
	1h	**13h**		
4			94	89
	1i	**13i**		
5			48	49
	1j	**13j**		

[a] The reactions were carried out using the anhydride (1.0 mmol), thiourea **11b** (5 mol %), and benzyl mercaptan (1.2 equiv) in diethyl ether (10 mL) for 24 h at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis using a chiral column.

3. Conclusion

Various low molecular cyclohexane-based organocatalysts have been applied in the desymmetrization of cyclic *meso*-anhydrides. Using alcohols or benzyl mercaptan as nucleophiles readily available β-aminoalcohols, imines, sulfonamides, and thioureas led to the corresponding ring-opened products in high yields. The most selective catalyst was a (Takemoto type) thiourea, which furnished hemiesters in enantioselective alcoholyses of succinic and glutaric anhydrides in up to 96% ee. A related catalyst gave products with up to 90% ee in catalytic asymmetric thiolyses of glutaric anhydrides.

4. Experimental

4.1. General information

All reactions were carried out under argon using standard Schlenk and vacuum line techniques. Before use the solvents

were dried and freshly distilled under argon according to standard procedures. Anhydrides **1g**–**1j** were prepared from the corresponding diacids by dehydration with trifluoroactic anhydride. All other reagents were obtained from commercial sources and used as received. Column chromatography was done on silica gel 60 (40–63 μm) from Merck as stationary phase. TLC was performed using precoated aluminum plates (Merck silica gel 60 F_{254}). Detection was done either using UV light (254 nm) or $KMnO_4$ stain. NMR spectra were recorded on a Varian Inova 400 (400 MHz) or Mercury 300 (300 MHz) instrument. Chemical shifts are given in parts per million relative to TMS (δ=0 ppm) or solvent residual peaks as internal standards. Mass spectra were recorded on a Finnigan SSQ 7000 system (EI, 70 eV). Elemental analyses were measured on an Elementar Vario EL instrument. IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer. Optical rotations were measured on a Perkin–Elmer Model P241 instrument using a light frequency of 589 nm. Concentration *c* is listed in g/100 mL. Melting points were determined on a Büchi B-450 apparatus in open capillaries and are uncorrected.

4.2. Preparation of catalysts

Aminoalcohols **5a**–**5e**,[11] **5f**,[23] **7**,[11] and thioureas **11c** and **11d**[16] were prepared according to the literature procedures. Compounds **6a** and **6b** were obtained by alkylations of the commercial available (*S*,*S*)-(−)-2-amino-1,2-diphenylethanol. All enantiopure cyclohexane-based diamine derivatives, imines **8**,[14a] sulfonamides **10**,[10a] thioureas **11**, and squareamide **12**[19] were prepared from the corresponding enantiopure 1,2-cyclohexane diamine.[14] Imine **9**[24] was obtained from 9-*epi*-aminoquinidine following literature procedures.

*4.2.1. (1S,2S)-trans-2-(Piperidin-1′-yl)-cyclopentanol (**7**).* White solid; mp 49–51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.49 (m, 3H), 1.49–1.72 (m, 7H), 1.78–1.95 (m, 2H), 2.41–2.54 (m, 5H), 2.84 (br s, 1H), 4.07–4.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 24.6, 26.1, 27.1, 34.4, 52.4, 74.9, 75.5; IR (KBr) ν 3140, 2930, 2083, 1448, 1332, 1255, 1175, 1108, 1038, 987, 903, 872, 805, 739, 661 cm^{-1}; MS (EI, 70 eV) *m*/*z* 169 ([M$^+$], 24%), 124 (100%), 110 (44%), 98 (22%). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.32; H, 11.66; N, 8.27; $[\alpha]_D^{21}$ +43.3 (*c* 2.95, $CHCl_3$).

*4.2.2. 4-Methyl-2-({[(1R,2R)-2-(piperidin-1-yl)cyclohexyl]imino}methyl)phenol (**8a**).* Yellow solid; mp 76–77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.48 (m, 9H), 1.54–1.67 (m, 1H), 1.69–1.95 (m, 4H), 2.29 (s, 3H), 2.34–2.45 (m, 3H), 3.17 (dt, *J*=10.4, 4.4 Hz, 1H), 6.86 (d, *J*=8.5 Hz, 1H), 7.03 (d, *J*=1.6 Hz, 1H), 7.09 (dd, *J*=8.5, 2.2 Hz, 1H), 8.16 (s, 1H), 13.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 24.6, 24.8, 25.0, 25.5, 26.7, 34.3, 50.0, 67.9, 67.9, 116.7, 118.4, 126.8, 130.8, 132.4, 159.5, 163.2; IR (KBr) ν 2931, 2850, 2792, 1626, 1589, 1494, 1445, 1282, 1157, 828, 774, 671, 575 cm^{-1}; MS (EI, 70 eV) *m*/*z* 300 ([M$^+$], 35%), 217 (100%), 165 (30%), 150 (89%), 136 (26%), 124 (46%), 98 (29%), 84 (53%). Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 76.10; H, 9.43; N, 9.64; $[\alpha]_D^{21}$ −157.7 (*c* 3.02, $CHCl_3$).

*4.2.3. 2-({[(1R,2R)-2-(Dimethylamino)cyclohexyl]imino}methyl)-4-methylphenol (**8b**).* Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.39 (m, 3H), 1.52–1.68 (m, 1H), 1.68–1.92 (m, 4H), 2.26 (s, 6H), 2.28 (s, 3H), 2.50–2.62 (m, 1H), 3.20 (dt, *J*=10.2, 4.2 Hz, 1H), 6.85 (d, *J*=8.2 Hz, 1H), 7.02 (d, *J*=2.2 Hz, 1H), 7.09 (dd, *J*=8.4, 2.2 Hz, 1H), 8.24 (s, 1H), 13.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2, 20.3, 23.9, 24.6, 25.2, 34.7, 40.8, 66.9, 69.3, 116.8, 118.7, 127.2, 131.1, 132.7, 159.4, 163.0; IR (capillary) ν 2929, 1634, 1493, 1278, 1157, 1033, 947, 819, 673 cm^{-1}; HRMS calcd for $C_{16}H_{24}N_2O$ ([M$^+$]) 260.1883. Found: 260.1883; $[\alpha]_D^{21}$ −134.3 (*c* 1.34, $CHCl_3$).

*4.2.4. 2-{[(9-epi-Aminoquinidin-9-yl)imino]methyl}-4-methylphenol (**9**).* Yellow solid; mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99–1.06 (m, 1H), 1.16–1.28 (m, 1H), 1.49–1.58 (m, 2H), 1.60–1.67 (m, 1H), 2.24 (s, 3H), 2.26–1.34 (m, 1H), 2.82–3.10 (m, 4H), 3.44 (q, *J*=9.4 Hz, 1H), 4.01 (s, 3H), 4.92 (d, *J*=9.7 Hz, 1H), 5.05 (dt, *J*=5.7, 1.5 Hz, 1H), 5.08–5.12 (m, 1H), 5.82–5.95 (m, 1H), 6.82 (d, *J*=8.2 Hz, 1H), 7.00–7.10 (m, 2H), 7.40 (dd, *J*=9.2, 2.7 Hz, 1H), 7.49 (d, *J*=4.5 Hz, 1H), 7.57 (d, *J*=2.5 Hz, 1H), 8.03 (d, *J*=9.2 Hz, 1H), 8.33 (s, 1H), 8.76 (d, *J*=4.5 Hz, 1H), 13.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3, 24.9, 26.5, 27.8, 39.5, 47.6, 49.6, 55.6, 61.0, 70.5, 101.6, 114.6, 116.6, 118.5, 121.2, 121.8, 127.7, 131.8, 132.1, 133.2, 140.5, 144.5, 145.0, 147.7, 157.9, 158.7, 165.5; IR (KBr) ν 2934, 2108, 1626, 1493, 1221, 1029, 914, 821, 714, 666 cm^{-1}; HRMS calcd for $C_{28}H_{31}N_3O_2$ ([M$^+$]) 441.2411. Found: 441.2424; $[\alpha]_D^{21}$ +137.7 (*c* 1.10, $CHCl_3$).

*4.2.5. N-[(1S,2S)-2-(Piperidin-1-yl)cyclohexyl]3,5-bis(trifluoromethyl)benzenesulfonamide (**10a**).* White solid; mp 110–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00–1.27 (m, 4H), 1.28–1.56 (m, 6H), 1.62–1.70 (m, 1H), 1.73–1.86 (m, 2H), 2.10–2.36 (m, 6H), 2.75–2.86 (m, 1H), 6.20 (br s, 1H), 8.05 (s, 1H), 8.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 24.2, 24.5, 25.3, 26.5, 32.6, 49.2, 53.9, 67.3, 122.5 (q, *J*=272.8 Hz), 125.9, 127.3, 132.7 (q, *J*=34.3 Hz), 143.3; IR (KBr) ν 3149, 2933, 1740, 1452, 1354, 1278, 1136, 964, 900, 843, 680 cm^{-1}; MS (EI, 70 eV) *m*/*z* 459 ([M+H]$^+$, 9%), 439 (9%), 213 (18%), 181 (100%), 164 (13%), 96 (11%), 84 (13). Anal. Calcd for $C_{19}H_{24}F_6N_2O_2S$: C, 49.78; H, 5.25; N, 6.11. Found: C, 49.66; H, 5.23; N, 6.06; $[\alpha]_D^{22}$ +60.1 (*c* 1.39, $CHCl_3$).

*4.2.6. N-[(1R,2R)-2-(Dimethylamino)cyclohexyl]3,5-bis(trifluoromethyl)benzenesulfonamide (**10b**).* White solid; mp 80–81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95–1.24 (m, 4H), 1.60–1.67 (m, 1H), 1.71–1.80 (m, 2H), 1.98 (s, 6H), 2.13–2.21 (m, 1H), 2.21–2.28 (m, 1H), 2.69–2.78 (m, 1H), 8.03 (s, 1H), 8.32 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 24.2, 25.0, 39.7, 54.5, 66.3, 122.5 (q, *J*=272.9 Hz), 125.8, 127.5, 132.6 (q, *J*=34.3 Hz), 143.5; IR (KBr) ν 3095, 2945, 1739, 1454, 1353, 1274, 1109, 970, 900, 844, 729, 680 cm^{-1}; MS (EI, 70 eV) *m*/*z* 418 ([M], 9%), 399 (16%), 213 (40%), 141 (100%), 124 (55%), 96 (52%), 84 (21%), 70 (22%). Anal. Calcd for $C_{16}H_{20}F_6N_2O_2S$: C, 45.93; H, 4.82; N, 6.70. Found: C, 46.18; H, 4.73; N, 6.77; $[\alpha]_D^{22}$ −65.9 (*c* 1.28, $CHCl_3$).

*4.2.7. 1-[3,5-Bis(trifluoromethyl)phenyl-3-[(1S,2S)-2-(piperidin-1-yl)cyclohexyl]thiourea (**11a**).* White solid; mp 79–81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07–1.42 (m, 10H), 1.68–1.96 (m, 3H), 2.27–2.40 (m, 3H), 2.53–2.65 (m, 3H), 3.68–3.82 (m, 1H), 7.70 (s, 1H), 7.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 24.3, 24.5, 25.3, 26.3, 32.6, 49.6, 56.2, 68.9, 119.1, 122.9 (q, *J*=273.4 Hz), 124.7, 132.8 (q, *J*=33.5 Hz), 139.8, 187.1; IR (KBr) ν 3249, 2935, 1533, 1471, 1381, 1274, 1172, 1128, 967, 884, 702, 680 cm^{-1}; MS (EI, 70 eV) *m*/*z* 453 ([M$^+$], 23%), 165 (100%), 124 (51%), 86 (52%). Anal. Calcd for $C_{20}H_{25}F_6N_3S$: C, 52.97; H, 5.56; N, 9.27. Found: C, 52.99; H, 5.53; N, 9.09; $[\alpha]_D^{21}$ +13.4 (*c* 0.96, $CHCl_3$).

*4.2.8. 1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1R,2R)-2-morpholinocyclohexyl]thiourea (**11b**).* White solid; mp 176–177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05–1.42 (m, 4H), 1.69–1.99 (m, 3H), 2.30–2.41 (m, 3H), 2.61–2.74 (m, 3H), 3.47–3.60 (m, 4H), 3.95–4.07 (m, 1H), 6.71 (br s, 1H), 7.72 (s, 1H), 7.81 (s, 2H), 8.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 24.6, 25.3, 32.5, 48.5, 55.8, 67.4, 68.0, 119.1, 122.7 (q, *J*=272.6 Hz), 123.6, 133.2 (q, *J*=33.8 Hz), 138.9, 179.9; IR (KBr) ν 3247, 2939, 1740, 1542, 1462, 1381, 1272, 1218, 1171, 1130, 1017, 971, 894, 849, 704, 681 cm^{-1}; MS (EI, 70 eV) *m*/*z* 455 ([M$^+$],

15%), 368 (56%), 167 (100%), 126 (69%), 88 (43%). Anal. Calcd for $C_{19}H_{23}F_6N_3OS$: C, 50.10; H, 5.09; N, 9.23. Found: C, 50.09; H, 4.96; N, 9.22; $[\alpha]_D^{21}$ −66.7 (*c* 1.00, $CHCl_3$).

4.3. General procedure for the enantioselective methanolysis of *meso*-anhydrides

Anhydride (0.5 mmol) and thiourea **11d** (13.9 mg, 0.05 mmol) were dissolved in dry diethyl ether (40 mL) under Ar. The reaction was started by addition of methanol (203 μL, 5.0 mmol), and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuum (to dryness), and the resulting residue was dissolved in ethyl acetate. The solution was extracted with a saturated solution of sodium carbonate (3×3 mL). The combined aqueous phases were acidified with concd HCl, extracted with ethyl acetate, and the organic phase was dried over $MgSO_4$, filtered, and concentrated providing the corresponding hemiester without any further purification.

The analytic data for **2a**–**2j** were in agreement with those reported in literature.

The ee of the hemiester was determined either by GC analysis using a chiral column after conversion into the corresponding lactone (for **2a**–**2e**)[4b] or HPLC analysis using a chiral column after conversion to the corresponding thioester with benzyl mercaptan (for **2f**–**2j**). The absolute product configurations were determined comparing the measured optical rotations to literature values.

4.4. General procedure for the enantioselective thiolysis of *meso*-anhydrides

Anhydride (1.0 mmol) and thiourea **11b** (22.8 mg, 0.05 mmol) were dissolved in dry diethyl ether (10 mL) under Ar. The reaction was started by addition of benzyl mercaptan (0.141 mL, 1.2 mmol), and the mixture was then stirred at room temperature for 24 h. Next, methanol (1 mL) and a solution of $TMSCHN_2$ (2.0 M in hexane, 1 mL, 2.0 mmol) was added and stirring for 15 min was followed by addition of 2 M HCl and extraction with diethyl ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated providing the corresponding product, which was purified by column chromatography.

The analytic data for **13c**–**13h** were in agreement with those reported in literature.

*4.4.1. (1R,3S)-Methyl-3-[(benzylthio)carbonyl]cyclopentanecarboxylate (**13i**).* Colorless oil; 89% ee; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82–1.98 (m, 4H), 2.01–2.22 (m, 2H), 2.68–2.78 (m, 1H), 2.90–3.01 (m, 1H), 3.60 (s, 3H), 4.05 (s, 2H), 7.13–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.2, 29.8, 33.3, 33.8, 43.9, 51.9, 52.7, 127.2, 128.6, 128.8, 137.5, 171.2, 200.5; IR (capillary) ν 2951, 1734, 1685, 1451, 1205, 999, 918, 878, 770, 703 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ([M^+], 5%), 247 (8%), 155 (100%), 127 (23%), 95 (33%), 91 (31%), 67 (31%). Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C, 64.78; H, 6.52; $[\alpha]_D^{21}$ −8.6 (*c* 1.16, $CHCl_3$); HPLC (Chiralcel AD-H, 20 °C, 210 nm, 99/1 heptane/*i*-PrOH, 0.5 mL/min): t_{R1}=47.9 min, t_{R2}=51.4 min (major).

*4.4.2. (2S,5R)-Methyl-5-[(benzylthio)carbonyl]tetrahydrofuran-2-carboxylate (**13j**).* Colorless oil; 49% ee; ^1H NMR (CDCl3, 300 MHz) δ 2.05–2.33 (m, 4H), 3.69 (s, 3H), 3.98–4.12 (m, 2H), 4.49–4.59 (m, 2H), 7.15–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.1, 30.3, 32.7, 52.1, 78.8, 84.8, 127.2, 128.5, 128.9, 137.4, 171.6, 200.9; IR (capillary) ν 2952, 1741, 1679, 1450, 1287, 1212, 1090, 923, 706 cm^{-1}; MS (EI, 70 eV) *m*/*z* 280 ([M^+], 37%), 129 (44%), 101 (100%), 91 (44%), 69 (30%). Anal. Calcd for $C_{14}H_{16}O_4S$: C, 60.08; H, 5.78. Found: C, 59.98; H, 5.75; $[\alpha]_D^{21}$ +18.63 (*c* 1.01, $CHCl_3$); HPLC (Chiralcel AD-H, 20 °C, 210 nm, 95/5 heptane/*i*-PrOH, 1.0 mL/min): t_{R1}=17.8 min (major), t_{R2}=19.0 min.

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