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Enantioselective desymmetrization of *meso*-cyclic anhydrides catalyzed by hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolones

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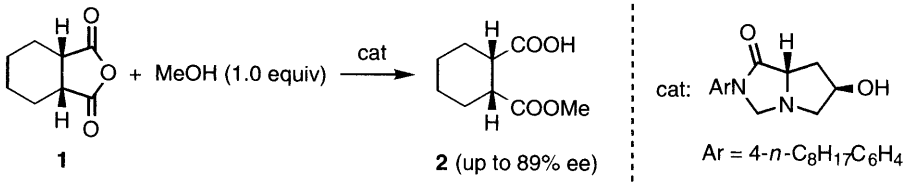
Abstract—Asymmetric methanolysis of *meso* cyclic carboxylic anhydrides including hexahydrophthalic anhydride proceeded in toluene in the presence of (6*R*,7a*S*)-(2-aryl-6-hydroxy)hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one to give the corresponding desymmetrized mono ester acids (e.g. (1*S*,2*R*)-2-(methoxycarbonyl)cyclohexane-1-carboxylic acid) with enantiomeric excesses of up to 89%. © 2001 Elsevier Science Ltd. All rights reserved.

Enantioselective desymmetrization of *meso* compounds is a powerful synthetic means of preparing enantiomerically enriched products where plural stereogenic carbon centers are generated in one-step.[1] Enantioselective ring opening of *meso* cyclic anhydrides is one of the cases.[2,3] Although much work has appeared on enantioselective nonenzymatic alcoholysis,[3] high enantioselectivity has been achieved only by use of stoichiometric amounts of unrecyclable chiral agents[4] and/or in highly toxic halogenated solvent systems,[5,6] which renders them impractical. Development of chiral nucleophilic catalysts for enantioselective acyl transfer has seen very rapid growth,[7] however, surprisingly, little attention has been paid to the use of catalysts for the enantioselective alcoholysis of *meso* cyclic anhydrides. As part of our effort to develop highly stereoselective and useful asymmetric processes, the catalytic asymmetric methanolysis of *meso* cyclic anhydrides was examined. We report herein the asymmetric methanolysis of hydrophthalic anhydride derivatives which is catalyzed by a new *N*-chiral bicyclic amine (6*R*,7a*S*)-(2-aryl-6-hydroxy)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**3**) in toluene to give the corresponding optically active mono ester acids with enantiomeric excesses of up to 89% (Scheme 1).

Various chiral tertiary amines including quinine, quinidine, sparteine, and pyrrolo[1,2-*c*]imidazolones (**3**) were examined for the enantioselective methanolysis of hexahydrophthalic anhydride **1**. The optically active amines **3** having the hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one framework have been identified as effective chiral agents from the library of *N*-chiral bicyclic tertiary amines.[8] The chiral amine library was designed and prepared with a view to using it for screening asymmetric catalysts where the target reaction is promoted by Lewis bases or nucleophiles. The bicyclic amines **3a**–**e** were readily prepared in high yields starting with anilines, prolines, and aldehydes by two sets of one-pot reactions shown in Scheme 2. Reaction of hexahydrophthalic anhydride (**1**) with methanol (2 equiv.) was performed at −25°C in toluene



1

2 (up to 89% ee)

Scheme 1.

Keywords: enantioselective desymmetrization; nucleophilic catalyst; pyrrolo[1,2-*c*]imidazolone.
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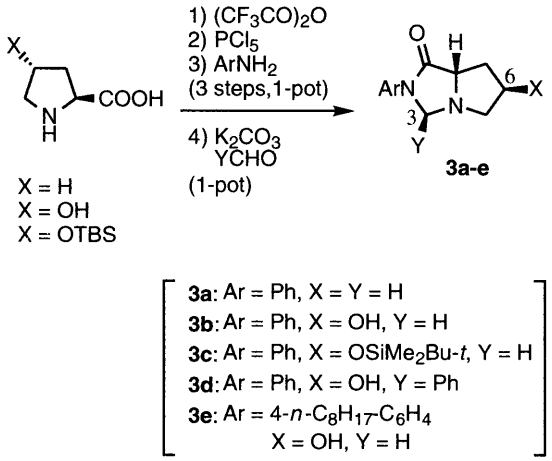


Scheme 2.

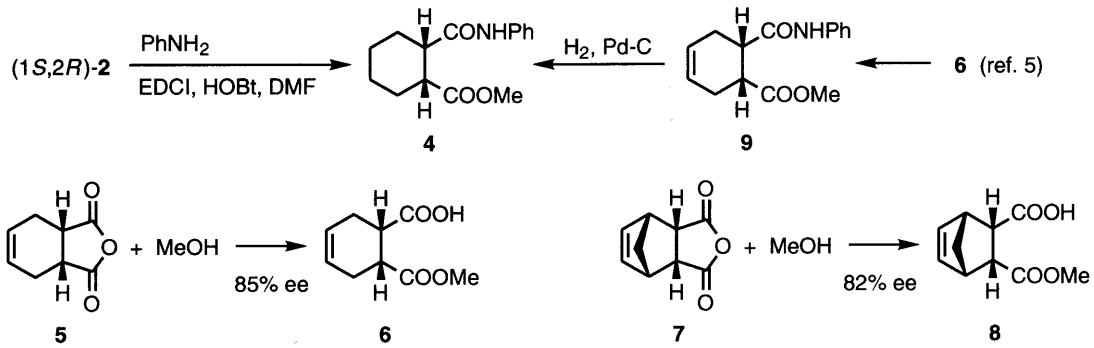
Table 1. Asymmetric methanolysis of **1** catalyzed by various chiral tertiary amines[a]

Catalyst	Yield % of **2**[b]	% ee of **2**[c]	Absolute configuration[c]
Quinine	49	27	(1*S*,2*R*)
Quinidine	61	27	(1*R*,2*S*)
Sparteine	69	<3	–
3a	26	<3	–
3b	40	65	(1*S*,2*R*)
3c	11	34	(1*R*,2*S*)
3d	<3	–	–
3e	33	65	(1*S*,2*R*)
3e[d]	72	89	(1*S*,2*R*)

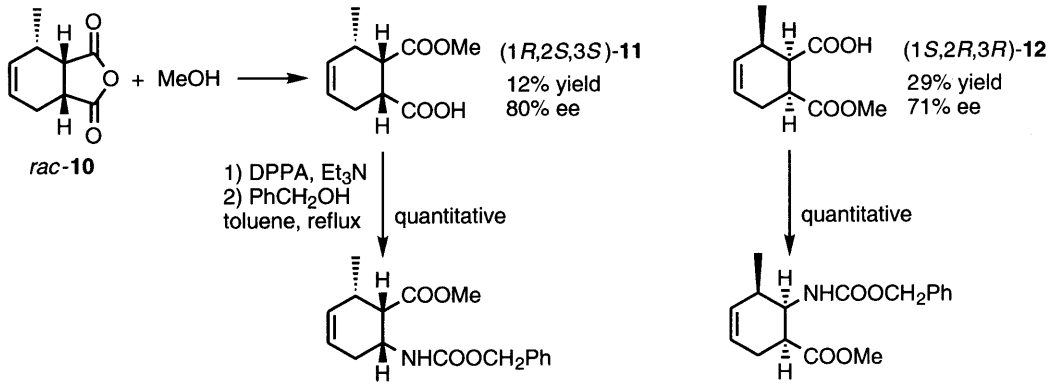
[a] All reactions were carried out in toluene (0.1 M of **1**) at −25°C for 20 h. **1**/MeOH/cat = 1.0/2.0/0.1.
[b] Without chromatographical purification.
[c] Determined by HPLC (see text).
[d] **1**/MeOH/cat = 1.0/1.0/1.0.

for 20 h in the presence of 10 mol% of the chiral tertiary amine catalyst. The desired methyl ester **2** was isolated by acid–base extraction. The resulting crude ester acid **2** was converted into the anilide **4** which was taken on to HPLC analysis with a chiral stationary phase column (Chiralcel OJ, hexane/*i*-PrOH = 4/1) without further purification. The results are summarized in Table 1. Among the tertiary amines, the (6*R*, 7a*S*)-(2-aryl-6-hydroxy)hexahydro-1*H*-pyrrolo[1,2-*c*]-imidazol-1-one (**3b** or **3e**) turned out to be the best catalyst giving the mono methyl ester (1*S*,2*R*)-**2** with high enantioselectivity. Thus, the asymmetric methanolysis catalyzed by **3b** afforded 65% ee of the ester acid (1*S*,2*R*)-**2** in 40% yield. It was found that Cinchona alkaloids, quinine and quinidine, catalyzed the methanolysis with low stereoselectivities to give (1*S*,2*R*)-**2** (27% ee) and (1*R*,2*S*)-**2** (27% ee), respectively, although it has been reported that the stoichiometric use of the Cinchona alkaloids in CCl_4 promotes desymmetrization of related *meso* anhydrides with high enantioselectivity.[5] Sparteine showed little enantioselectivity under the same reaction conditions. It is noteworthy that the stereochemical outcome of the methanolysis is strongly affected by the substituent at the C6 position of the amine **3**. The reaction using the amine **3a**, which lacks the C6 hydroxy group, was much less enantioselective giving <3% ee of the mono ester **2**. The amine **3c** having a sterically bulky silyloxy group at the C6 position gave (1*R*,2*S*)-**2**,which is the antipode of that obtained using **3b**. The pyrrolo[1,2-*c*]imidazolone **3d** having a C3-phenyl substituent showed little catalytic activity under the same reaction conditions. The phenyl substituent at the C3 position in **3d** is in close proximity to the reactive lone pair of the bridgehead nitrogen atom thereby disturbing the nucleophilic attack on the anhydride **1** (Table 1).

The highest enantioselectivity was observed when 1 equiv. of **1** to 1 equiv. of methanol and 1 equiv. of the catalyst **3e** were used. Thus, the reaction of **1** with methanol in toluene at −25°C for 20 h in the presence of **3e** (1.0 equiv.) gave 72% of (1*S*,2*R*)-**2** with 89% ee. Tetrahydrophthalic anhydride (**5**) and norbornenedicarboxylic anhydride (**7**) gave **6** and **8** with 85% ee and 82% ee, respectively, under the same reaction conditions (Scheme 3). A practical procedure is given for the methanolysis of **1** with 1 equiv. of **3e**: A toluene solution of hexahydrophthalic anhydride **1** (0.1 M soln), 1.0 equiv. of methanol, and 1.0 equiv. of **3e** was stirred at −25°C for 7 days. The reaction mixture was extracted with dil. HCl and sat. $NaHCO_3$, successively to separate the remaining **1**, **3e**, and the ester acid **2**. The catalyst **3e** was recovered from the acidic layer quantitatively. The aqueous basic layer was acidified with dil.



Scheme 3.



Scheme 4.

HCl and extracted with toluene to give the crude **2**. The crude methyl ester acid **2** was dissolved in ether/hexane (1:15) and the insoluble materials were filtered off. The filtrate was concentrated and chromatographed on silica gel to give **2** in 72% yield. The enantiomeric purity of **2** was determined by HPLC analysis of the anilide **4** to be 89% ee. The absolute configuration of **2** was assigned to be (1*S*,2*R*) by comparison of the order of retention time in the HPLC analysis of the anilide **4** to that of an authentic sample prepared from (1*S*,2*R*)-**6**.[5]

The mono ester acid **11**, which is a synthetic intermediate for (−)-PGE_1,[9] and **12** were readily obtained in their enantiomerically enriched form via asymmetric methanolysis of (3-methyl)tetrahydrophthalic anhydride **10**. A racemic mixture of **10** (*rac*-**10**) was subjected to the methanolysis catalyzed by **3e** to give 80% ee of (1*R*,2*S*,3*S*)-**11** in 12% yield and 71% ee of (1*S*,2*R*,3*R*)-**12** in 29% yield. A Curtius rearrangement of the methyl ester acids **11** and **12** gave the corresponding *N*-protected β-amino acids (Scheme 4).

Acknowledgements

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