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Highly Efficient Asymmetric Esterification of Cyclic meso-Dicarboxylic Anhydrides Catalyzed by Diphenylboryl Triflate

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In the presence of a catalytic amount of diphenylboryl triflate, cyclic meso-dicarboxylic anhydrides are esterified by diphenylboric ester of (R)-2-methoxy-1-phenylethanol in a highly stereoselective manner, and, after the treatment with diazomethane, the chiral diesters are obtained with high diastereomeric excess.

In the field of asymmetric syntheses, differentiation of two identical functional groups in a symmetrical molecule is one of the most effective methods, because in the chiral product thus obtained the two functional groups are chemically distinguishable. Therefore, the product could be converted into both enantiomeric series of useful intermediates by the selective transformations of these functional groups.[1)]

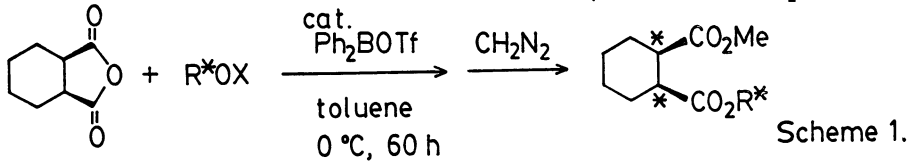
The preparations of optically active compounds from symmetrical dicarboxylic acids or their derivatives have been studied for recent years, and especially selective hydrolysis of meso and prochiral diesters by enzymes or microorganisms has been extensively investigated.[2)] Although there have been several reports on the asymmetric syntheses by chemical procedures,[3-8)] only a few methods have been reported for the asymmetric opening of symmetrical dicarboxylic anhydrides. In these reactions discrimination between two enantiotopic carbonyl groups was effected by the chiral binaphthyldiamine derivatives,[6)] (R)-1-phenylethanol,[7)] and chinchona alkaloids as chiral catalysts.[8)] However, in the first case the chiral sources were synthesized with some difficulties and in the second and the third cases the selectivities were not so good yet. Therefore, a convenient and efficient method for the preparation of optically active compounds from symmetrical dicarboxylic anhydrides is still desired.

In this communication, we wish to report that, in the presence of a catalytic amount of diphenylboryl triflate, cyclic meso-dicarboxylic anhydrides are esterified with diphenylboric ester of (R)-2-methoxy-1-phenylethanol stereoselectively, and, after the treatment with diazomethane, the chiral diesters are obtained with high stereoselectivities.

In our continuous effort on creating chiral compounds from symmetrical molecules,[3,9)] and our recent study on new synthetic reactions using diphenylboryl triflate as a catalyst,[10)] it was expected that a cyclic meso-dicarboxylic anhydride would be activated by diphenylboryl triflate, and one of two enantiotopic carbonyl groups in the activated anhydride is selectively esterified with a chiral alcohol.

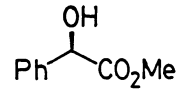
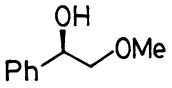
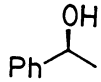
At first, the reaction conditions such as solvent and temperature were investigated and it was found that the highest chemical yield was achieved when the reaction was carried out in toluene at 0 °C.

Next, we screened various chiral alcohols and their derivatives in detail to increase the stereoselectivity. As shown in Table 1, diphenylboric ester of (R)-2-methoxy-1-phenylethanol[11] gave the best result and only one diastereomer was obtained exclusively (entry 6). The yield was increased by using two equivalents of the chiral source (entry 7), and excess chiral alcohols could be easily recovered without racemization. In this reaction, it is also pointed out that,



Scheme 1.

Table 1. The screening of the chiral sources

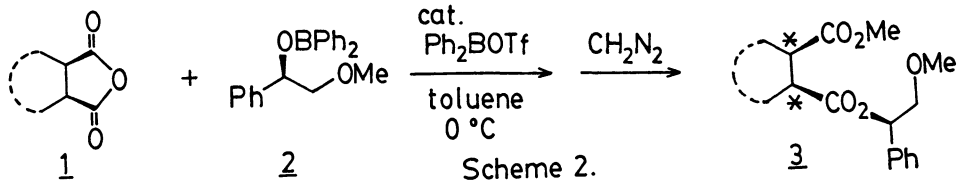
Entry	R*OH	X	Yield/%	d.e./%[a]	Config.[b]
1		H	85	58	1R,2S
2		$SiMe_3$	43	49	1R,2S
3		BPh_2	61[c]	80	1S,2R
4		H	33	51	1S,2R
5		$SiMe_3$	81	72	1S,2R
6		BPh_2	59	99	1S,2R
7		BPh_2	90[c]	99	1S,2R
8		BPh_2	46[c]	d)	

a) Determined by HPLC. b) Determined by comparison of the optical rotation value of 1-methyl hydrogen cis-1,2-cyclohexanedicarboxylate reported in Ref. 12, after the removal of the chiral source by catalytic hydrogenation. c) Two equivalents of the chiral source were used. d) Not determined.

using (R)-methyl mandelate as the chiral source, the absolute configuration of the diester derived from free alcohol or its trimethylsilyl ether was opposit to that of the diester from the diphenylboric ester (entries 1-3). This reversal is very intriguing though the interpretation of the result is obscure so far.

In the reaction using diphenylboric ester of (R)-2-methoxy-1-phenylethanol, it is assumed that oxygen atom of the methoxy group coordinate to boron atom to form the rigid five-membered ring structure, which leads to the effective chiral induction.

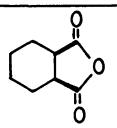
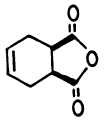
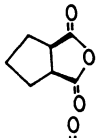
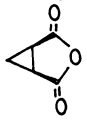
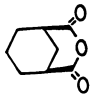
Next, we tried to apply this method to various cyclic meso-dicarboxylic anhydrides, and the results are summarized in Table 2. According to this method, the chiral diesters (3) were synthesized with high diastereomeric excess except in the case of cis-cyclopropanedicarboxylic anhydride. It is noted that the reaction of cis-cyclopentanedicarboxylic anhydride proceeded with good stereoselectivity (entry 3), whereas enzymatic hydrolysis of dimethyl cis-cyclopentanedicarboxylate gave the poor stereoselectivety (10% e.e.).[13,14] As shown in the present



1 2 3

Scheme 2.

Table 2. The asymmetric esterification of cyclic meso-dicarboxylic anhydrides[a)]

Entry	Anhydride	Reaction time/h	Yield/%	d.e./%[b)]	Config.
1		61	90	99	1S,2R[c)]
2		94.5	95	90[c)]	1S,2R[c)]
3		229	75	70	1S,2R[d)]
4		61	91	40[d)]	1S,2R[d)]
5		116	90	90	e)

a) Molar ratio of 1 : 2 = 1.0 : 2.0. b) Determined by HPLC unless otherwise noted. c) Determined by comparison of the optical rotation value of 1-methyl hydrogen cis-1,2-cyclohexanedicarboxylate reported in Ref.12, after the removal of the chiral source by catalytic hydrogenation. d) Determined by comparison of the optical rotation value of the half ester reported in Ref. 13, after the removal of the chiral source by catalytic hydrogenation. e) Not determined.

asymmetric esterification catalyzed by diphenylboryl triflate, the chemical method has an advantage over the biological process in some cases. The absolute configurations of the diesters (3) were determined to be (1S, 2R), therefore it is noted that the diphenylboric ester (2) preferentially attacks to the pro-S carbonyl groups of cyclic meso-dicarboxylic anhydrides (1). The chiral diesters were readily converted into the optically active half-esters, versatile starting materials for natural products syntheses, by catalytic hydrogenation.

The following example is representative: Under argon atmosphere, to a toluene (2 cm^3) solution of silver triflate (0.45 mmol) was added diphenylchloroborane (0.45 mmol) in toluene (2 cm^3) at 0 °C. After stirring for 1h, cis-1,2-cyclohexanedicarboxylic anhydride (1.5 mmol) in toluene (6 cm^3) was added. In another flask, to a toluene (3 cm^3) solution of (R)-2-methoxy-1-phenylethanol (3.0 mmol) was added n-BuLi in hexane (1.8 cm^3, 3.0 mmol) at 0 °C. Stirring was continued for 10 min, and diphenylchloroborane (3.0 mmol) in toluene (4 cm^3) was added. The resulting mixture was added to the above-mentioned solution of Ph_2BOTf and the anhydride by a cannula at 0 °C. The reaction mixture was stirred for 61 h, then the reaction was quenched with 1 mol dm^{-3} HCl. After the usual work-up, the half-ester was isolated. Excess (R)-2-methoxy-1-phenylethanol were also recovered [169

mg, 37%, $[\alpha]_D^{27}$ -47.0 ° (c 1.68, CH_2Cl_2)]. The treatment of this half-esters with diazomethane afforded the corresponding diester [433 mg, 90%, $[\alpha]_D^{26}$ -73.6 ° (c 2.58 , CH_2Cl_2)].

According to this reaction, chiral diesters, versatile building blocks for natural products syntheses, are conveniently synthesized with high diastereomeric excess. In addition, the present study shows that, in the presence of a catalytic amount of diphenylboryl triflate, diphenylboric ester of (R)-2-methoxy-1-phenylethanol, readily accessible chiral alcohol, makes it possible to differenciate two enantiotopic carbonyl groups in symmetrical dicarboxylic anhydrides in a highly stereoselective manner. The application of this reaction to the kinetic resolution of racemic symmetrical dicarboxylic anhydrides is now in progress.

References

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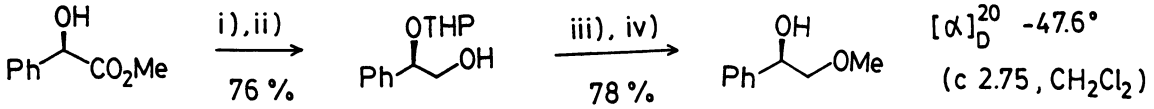
11) (R)-2-Methoxy-1-phenylethanol was easily synthesized from commercially available (R)-methyl mandelate according to the following scheme. And it was apparent that the alcohol was optically pure by HPLC analysis of its MTPA ester.



i) DHP/cat.TsOH ii) $LiAlH_4$ iii) NaH then MeI iv) MeOH/cat.TsOH

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