Enantioselective Esterification of Cyclic Dicarboxylic Anhydrides Using Chiral Amino Alcohols as Auxiliaries

Makoto SHIMIZU, Kohzoh MATSUKAWA, and Tamotsu FUJISAWA*
Department of Chemistry for Materials, Mie University, Tsu, Mie 514
(Received March 1, 1993)

Synopsis. Cyclic dicarboxylic anhydrides were enantioselectively esterified with the complex formed from cinchonidine, diethylzinc, and methanol, and the half-esters obtained were readily transformed into lactones via reduction and dehydration.

Discrimination of two identical functionalities in *meso* compounds leads to a creation of more than two asymmetric carbons, and subsequent manipulations of functional groups can lead to straightforward approach to both enantiomers. Therefore, this methodology has been utilized as a convenient tool for the selective synthesis of both enantiomers starting from a single compound. Enzymatic methods involving esterification[1] and hydrolysis[2] of *meso* cyclic dicarboxylic anhydrides or the analogous diols have been utilized to effect such transformations in which the substrate specificity constitutes a major drawback, whereas those using chemical processes involve two major strategies; the diastereofacial discrimination[3] or the enantiofacial counterpart.[4]

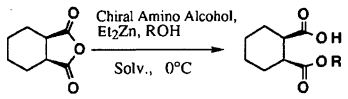
Recent progress in the diastereofacial discrimination has led to the development of various highly selective asymmetric reactions by employing chiral substrates, but the need for the removal of the chiral source attached to the starting material makes this approach rather tedious. On the other hand, enantiofacial and/or enantiotopic discrimination has several advantages due to the ready procedure without the need for the introduction and the removal of a chiral auxiliary. However, there are only a few examples that deal with desymmetrization using enantiotopic discrimination, involving the reduction[4d] or esterification[4e] of *meso* 1,2-dicarboxylic anhydrides. The latter procedure using a catalytic amount of a cinchona alkaloid as chiral auxiliary is quite effective for 2,4-dimethylglutaric anhydride. However, application of this procedure to *cis*-1, 2-cyclohexanedicarboxylic anhydride did not meet with a satisfactory discrimination, and the half-ester was obtained in less than 8% ee. In an effort to find an efficient system for the asymmetric esterification, a series of complexes formed from amino alcohol, diethylzinc, and alcohol was investigated, in which the rigid zinc metallocycles would effect the high discrimination. Herein we wish to describe an efficient method for the asymmetric synthesis of half-ester starting from *meso* dicarboxylic anhydride.

The esterification reaction was carried out by adding a solution of 1,2-cyclohexanedicarboxylic anhydride to a complex prepared from an amino alcohol, diethylzinc, and an alcohol, and the results are summarized in Table 1 (Scheme 1).

The use of (−)-ephedrine as an auxiliary did not show a satisfactory selectivity, whereas cinchona alkaloids effected a good to excellent diastereofacial discrimination, in which the bicyclic system forms a rigid metallocycle and creates a proper environment for chiral induction. Among cinchona alkaloids (−)-quinine and (−)-cinchonidine gave a good selectivity, and the half-ester was obtained in 17—91% ee. On the other hand, (+)-cinchonine and (+)-quinidine did not effect the present esterification with good selectivity. The reaction solvent and the alcohol were crucial for the success of the high enantiotopic discrimination, and the use of methanol in THF recorded the best result. This may be due to the proper solubility of the chiral auxiliary and the reactivity of the intermediate zinc alkoxide.

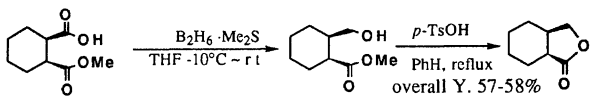
The absolute configurations of the half-esters obtained using cinchonidine were determined to be (1*S*, 2*R*) by comparison with the optical rotation value of the half-esters reported in the literature.[2c] These half-esters were readily converted into optically active lactones[5] via selective reduction of the acid with borane-dimethyl sulfide complex followed by lactonization in refluxing benzene in the presence of a catalytic amount of *p*-TsOH. The optical purities of the products in Table 1 were determined based on the optical rotation values of the corresponding γ-lactones thus transformed (Scheme 2).

The present asymmetric esterification is sensitive to the structure of the substrate, and moderate chiral induction was observed for 1,2-cyclohexenedicarboxylic anhydride **5**[6,7] *cis*-1,3-dibenzyl-2-oxoimidazoline-4,5-dicarboxylic anhydride **6**[8] and 7-oxabicyclo-[2.2.1]heptane-2,3-dicarboxylic anhydride **7**(Scheme 3).[9]



1 2

Scheme 1.



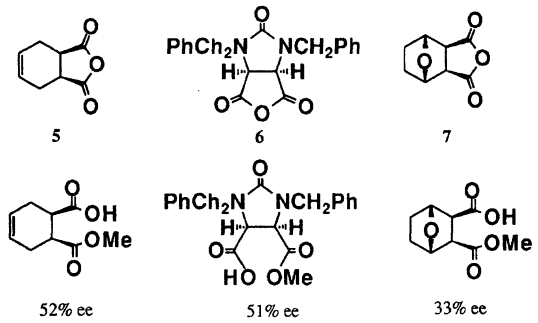
2 3 4

Scheme 2.

Table 1. Enantioselective Esterification of 1,2-Cyclohexanedicarboxylic Anhydride **1**[a)]

Entry	Amino alcohol	Solvent	Temp/°C	Alcohol	Half-ester **2** Yield[b)]/%	ee[c)]/%	Confg[d)]
1	(−)-Ephedrine	THF	0	MeOH	26	35	(1*S*,2*R*)
2	(+)-Cinchonine	THF	0	MeOH	42	30	(1*R*,2*S*)
3	(−)-Cinchonidine	THF	0	MeOH	57	91	(1*S*,2*R*)
4	(−)-Cinchonidine	$CHCl_3$	0	MeOH	72	23	(1*S*,2*R*)
5	(−)-Cinchonidine	Et_2O	0	MeOH	34	45	(1*S*,2*R*)
6	(−)-Cinchonidine	1,4-Dioxane	12	MeOH	7	23	(1*S*,2*R*)
7	(−)-Cinchonidine	THF	0	EtOH	26	17[e)]	(1*S*,2*R*)
8	(−)-Cinchonidine	THF	0—r.t.	$PhCH_2OH$	34	35[e)]	(1*S*,2*R*)
9	(+)-Quinidine	THF	0	MeOH	28	32	(1*R*,2*S*)
10	(−)-Quinine	THF	0	MeOH	10	57	(1*S*,2*R*)

a) The reaction was carried out according to the typical experimental procedure. b) Isolated yield by preparative TLC. c) Determined by the optical rotation value of the corresponding lactone. d) Determine by the sign of the optical rotation of the half-ester and/or the corresponding lactone. e) Determined by ^{1}H NMR analysis with the aid of Eu(hfc)$_3$ of the corresponding methyl ester converted by diazomethane.



Scheme 3.

These observations imply that the subtle conformational change of the anhydride by introducing an unsaturation, an oxa bridge, or an oxo group would considerably influence the enantiotopic selectivity of the present system. We are currently investigating several systems to elucidate the possible transition state.

Asymmetric esterification of cyclic dicarboxylic anhydride studied here provides a simple procedure for chiral half ester, in which the rigid metallocycle formed from cinchonidine and diethylzinc is crucial for the better discrimination. Since the chiral auxiliary is readily available and the experimental procedures are not tedious, this method offers a useful addition to the existing methodologies.

Experimental

Infrared spectra of neat liquid film samples (unless otherwise noted) were determined on a JASCO IR-810 spectrometer. ^{1}H NMR spectra were taken on a JEOL JNM-RMX 60si and EX-270 spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured with a Union PM-101 polarimeter. Mass spectra were taken on a Shimadzu QP1000 spectrometer. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium diphenylketyl immediately before use. 1,4-Dioxane was distilled from CaH_2 and stored over sodium. Chloroform was purified by passing through a pad of Al_2O_3. Preparative TLC plates were prepared with Wakogel B-5F. Column Chromatography was carried out with Wakogel C-300.

General Procedure for the Esterification of Dicarboxylic Anhydrides: The following is a typical experimental procedure. In an ordinary glassware vessel to cinchonidine (412 mg, 1.4 mmol) was added THF (4 ml) under an argon atmosphere at 0 °C. A hexane solution of diethylzinc (0.69 ml, 1.4 mmol) was added and the mixture was stirred for 15 min at 0 °C, and allowed to warm to room temperature. After an addition of a THF (2.0 ml) solution of methanol (56 μl, 1.4 mmol), a solution of *cis*-1,2-cyclohexanedicarboxylic anhydride (154.1 mg, 1.0 mmol) in THF (2.0 ml) was added dropwise by syringe pump over 30 min and the entire mixture was stirred for 38 min at 0 °C. Then 3 M-HCl (2.5 ml) was added, and the mixtures extracted with ethyl acetate (1 M=1 mol dm^{-3}). The combined extracts were dried Na_2SO_4 and concentrated to leave an oil, which was purified by silica gel TLC (hexane : ethyl acetate=1 : 1) to give 1-methyl hydrogen (1*S*,2*R*)-1,2-cyclohexanedicarboxylate (106 mg 57%) as a colorless oil. The spectroscopic properties were identical with the reported data.[2b)] IR (neat) 2960, 2925, 1740, 1440, 1415, 1360, 1180, 1030, 925, 730, and 620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.35—1.63 (4H, m), 1.70—1.87 (2H, m), 1.93—2.11 (2H, m), 2.85 (2H, s), and 3.67 (3H, s); $[\alpha]_D^{23}$ +3.7° (*c* 2.12, $CHCl_3$).

1-Ethyl Hydrogen (1*S*,2*R*)-1,2-Cyclohexanedicarboxylate:[10)] IR (neat) 3500, 2920, 2850, 1730, 1455, 1420, 1295, 1205, 1180, and 1030 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.13—1.27 (3H, t, *J*=6.9 Hz), 1.30—1.60 (4H, m), 1.60—2.10 (4H, m), 3.65 (3H, s), 3.90—4.33 (2H, q, *J*=6.9 Hz); $[\alpha]_D^{23}$ +1.5° (*c* 1.04, $CHCl_3$).

1-Benzyl Hydrogen (1*S*,2*R*)-1,2-Cyclohexanedicarboxylate: IR (neat) 3425, 3030, 2950, 1740, 1455, 1200, 1040, 750, and 705 cm^{-1}; ^{1}H NMR (CCl_4) δ= 1.37—1.52 (4H, m), 1.79—1.88 (2H, m), 2.03—2.11 (2H, m), 2.87—2.90 (2H, m), 5.01—5.18 (2H, dd, *J*=6.6 and 12.5 Hz), 7.15—7.40 (5H, m), and for the corresponding methyl ester converted by diazomethane: $[\alpha]_D^{23}$ +2.3° (*c* 0.62, $CHCl_3$); MS *m/z* (rel intensity in %) 170 (M^+−106, 4), 169 (M^+−107, 4), 141 (5), 125 (2), 122 (4), 107 (31), 91 (100),

82 (45), 78 (28), 77 (91), and 56 (39).

1-Methyl Hydrogen (1*S*,2*R*)-4-Cyclohexene-1,2-dicarboxylate:[6,7] IR (neat) 3025, 2940, 1750, 1728, 1663, 1450, 1205, 950, and 672 cm^{-1}; ^1H NMR (CCl_4) δ=2.21—2.60 (4H, m), 2.75—3.18 (2H, m), 3.64 (3H, s), and 5.65 (2H, s); $[\alpha]_D^{23}$ +1.4° (*c* 1.32, $CHCl_3$).

4-Methyl Hydrogen (4*R*,5*S*)-1,3-Dibenzyl-2-oxoimidazolidine-4,5-dicarboxylate:[8] IR (KBr disk) 1780, 1705, 1440, 1420, 1210, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.78—4.12 (4H, m), 4.41 (2H, q, *J*=15 Hz), 4.63 (2H, q, *J*=15 Hz), and 7.25 (10H, m), $[\alpha]_D^{23}$ +30.0° (*c* 0.02, Benzene).

1-Methyl Hydrogen (1*R*,2*S*)-7-Oxabicyclo[2.2.1]-heptane-1,2-dicarboxylate:[9] IR (neat) 2990, 1730, 1660, 1610, 1190, 990, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56—1.96 (4H, m), 3.10 (2H, s), 3.69 (3H, s), and 4.97—5.10 (2H, m); $[\alpha]_D^{23}$ +2.5° (*c* 0.51, $CHCl_3$).

(1*R*,6*S*)-8-Oxabicyclo[4.3.0]nonan-7-one:[5] To a solution of 1-methyl hydrogen (1*S*,2*R*)-1,2-cyclohexanedicarboxylate (93.7 mg, 0.50 mmol) in THF (3.0 ml) was added borane-dimethyl sulfide complex at −10 °C, and the reaction mixture was stirred at room temperature for 11 h. Methanol (1.5 ml) was added and the mixture was concentrated to leave an oil. This treatment was repeated three times and the crude oil was dissolved in benzene (10 ml) and then heated at reflux for 8 h. The normal workup followed by purification by silica-gel column chromatography gave (1*R*, 6*S*)-8-oxabicyclo[4.3.0]nonan-7-one (40 mg, 58%). IR (neat) 2900, 2825, 1760, 1440, 1203, 1180, 1155, and 1120 cm^{-1}; ^1H NMR (CCl_4) δ=0.98—2.80 (10H, m) and 3.70—4.28 (2H, m), $[\alpha]_D^{23}$ +30.1° (*c* 0.51, $CHCl_3$).

References

1) Y. Terao, M. Murata, and K. K. Achiwa, *Tetrahedron Lett.*, **29**, 5173 (1988).

2) a) F.-C. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Capsi, and C. R. Eck, *J. Am. Chem. Soc.*, **97**, 4144 (1975); b) P. Mohr, N. W.-Sarcevic, and C. Tamm, *Helv. Chim. Acta*, **66**, 2501 (1983); c) G. Sabbioni, and J. B. Jones, *J. Org. Chem.*, **52**, 4565 (1987); d) M. Ohno and M. Otsuka, *Org. React.,(N. Y.)*, **37**, 1 (1989), and the references cited therein.

3) a) M. C. Carreno, J. L. G. Ruano, M. Garrido, M. P. Ruiz, and G. Solladie, *Tetrahedron Lett.*, **31**, 6653 (1990); b) Y. Nagao, T. Ikeda, M. Yagi, and E. Fujita, *J. Am. Chem. Soc.*, **104**, 2079 (1982); c) Y. Nagao, T. Inoue, and E. Fujita, *J. Org. Chem.*, **48**, 132 (1983); d) Y. Nagao, T. Ikeda, T. Inoue, M. Yagi, M. Shiro, and E. Fujita, *J. Org. Chem.*, **50**, 4072 (1985); e) T. Harada, Y. Ikemura, H. Nakajima, T. Onishi, and A. Oku, *Chem. Lett.*, **1990**, 1441; f) T. Harada, I. Wada, J. Uchimura, A. Inoue, S. Tanaka, and A. Oku, *Tetrahedron Lett.*, **32**, 1219 (1991); g) T. Momose, N. Toyooka, and Y. Hirai, *Chem. Lett.*, **1990**, 1319; h) M. Yoshikawa, T. Sugimura, and A. Tai, *Chem. Lett.*, **1990**, 1003; i) T. Mukaiyama, H. Yamashita, and M. Asami, *Chem. Lett.*, **1983**, 385; j) M. Ohshima and T. Mukaiyama, *Chem. Lett.*, **1987**, 377.

4) a) K. Osakada, M. Obana, T. Ikariya, M. Saburi, and S. Yoshikawa, *Tetrahedron Lett.*, **22**, 4297 (1981); b) Y. Kawakami, J. Hiratake, Y. Yamamoto, and J. Oda, *J. Chem. Soc., Chem. Commun.*, **1984**, 779; c) Y. Ishii, K. Osakada, T. Ikariya, M. Saburi, and S. Yoshikawa, *Chem. Lett.*, **1982**, 1179; d) K. Matsuki, H. Inoue, and M. Takeda, *Tetrahedron Lett.*, **34**, 1167 (1993); e) J. Hiratake, Y. Yamamoto, and J. Oda, *J. Chem. Soc., Chem. Commun.*, **1985**, 1717.

5) G. Sabbioni, M. L. Shea, and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, **1984**, 236.

6) H.-J. Gais and K. L. Lukas, *Angew. Chem., Int. Ed. Engl.*, **23**, 142 (1984).

7) S. Kobayashi, K. Kamiyama, T. Iimori, and M. Ohno, *Tetrahedron Lett.*, **25**, 2557 (1984).

8) S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, **46**, 1907 (1982).

9) R. Bloch, E. G-Jampel, and C. Girard, *Tetrahedron Lett.*, **26**, 4087 (1985).

10) S. Takeishi, H. Doi, and H. Matsuda, *Nippon Kagaku Kaishi*, **10**, 1719 (1988).