CHEMISTRY LETTERS, pp. 1187-1190, 1989.

Kinetic Resolution of α-Arylcarboxylic Acid Derivatives by a Catalytic Use of a Chiral Titanium Alkoxide

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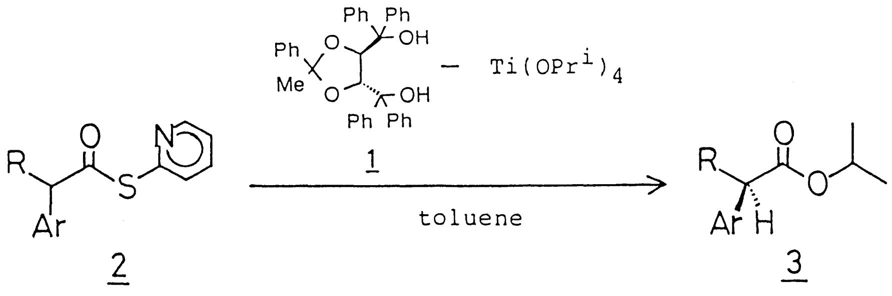
Kinetic resolution of racemic α-arylcarboxylic acids is successfully achieved by a catalytic use of titanium tetraisopropoxide and a chiral 1,4-diol in the reaction of the corresponding 2-pyridinethiol esters and isopropyl alcohol.

Development of chiral catalysts for organic synthesis has attracted considerable interest in recent years.1) In the previous papers, we reported the asymmetric Diels-Alder,2) [2+2] cycloaddition,3) ene4) and hydrocyanation5) reactions by employing a chiral titanium reagent generated from titanium dichloride diisopropoxide and a chiral 1,4-diol 1 which is derived from dimethyl tartrate. We considered that titanium tetraalkoxide having the chiral 1,4-diol moiety could be utilized effectively as a chiral metal alkoxide for asymmetric induction and the application to asymmetric esterification of racemic carboxylic acid derivatives was investigated.

The chiral titanium alkoxide was prepared in situ by mixing equimolar amounts of the chiral 1,4-diol 1 and titanium tetraisopropoxide ($Ti(OPr^i)_4$) at 0 °C in toluene.6) At first, transformation of acid chloride, acid anhydride, and various active esters of (±)-2-phenylbutanoic acid to the isopropyl ester was investigated by treatment with a half molar amount of the chiral titanium alkoxide in toluene. And the 2-pyridinethiol ester 2a was found to react with the chiral titanium alkoxide at -78 °C and the isopropyl ester 3a was obtained in 69% yield with high (91% ee) optical purity. The reaction of 2a with $Ti(OPr^i)_4$ alone or with a mixture of $Ti(OPr^i)_4$ and isopropyl alcohol, however, proceeded very slowly at -78 °C, and these evidences revealed that the nucleophilicity of isopropoxide is increased significantly by the introduction of the 1,4-diol moiety in the titanium alkoxide.

Good to high asymmetric induction was also observed in the esterification of several 2-pyridinethiol esters 27) of α-arylcarboxylic acids by applying the above method, and the (R)-isopropyl esters 3 were obtained preferentially when the (R)-1,4-diol was employed.(Eq. 1, Table 1)

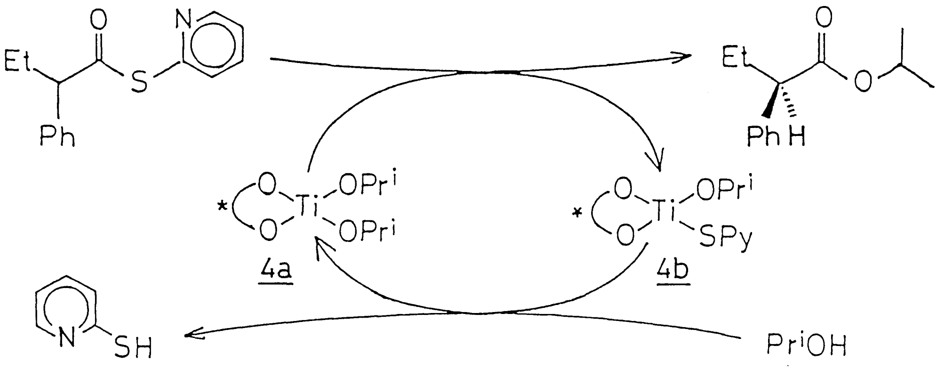


(1)

Table 1. The Reaction of 2 with the Chiral Titanium Alkoxide

	R	Ar	Temp/°C	Yield/%8)	ee/%9)	k_R/k_S10)
2a	Et	Ph	-78	69	91	34
2b	Me	Ph	-78	86	74	12
2c	Pr^i	Ph	-45	56	90	27
2d	Pr^i	p-Cl-C_6H_4	-45	49	91	28
2e	Bu^i	Ph	-78	88	92	52

Although the reaction between 2a and the chiral titanium isopropoxide proceeded at -78 °C, the reaction of equimolar amounts of 2a and isopropyl alcohol was not accelerated effectively at this low temperature with a catalytic amount of the chiral titanium isopropoxide (10% mol). These results indicate that, in the catalytic process in the following scheme, regeneration of the chiral titanium isopropoxide 4a from titanium 2-pyridinethiolate 4b and isopropyl alcohol does not take place smoothly at the low temperature. At higher temperature (0 °C), the isopropyl ester 3a was produced in good yield even with a catalytic amount of the chiral titanium alkoxide but in lower enantioselectivity. In order to facilitate the regeneration of the chiral titanium isopropoxide 4a even at low temperature, the catalytic reaction was performed in the presence of excess amounts (5 molar amounts) of isopropyl alcohol and Molecular Sieves 4A.11) In fact, the catalytic reaction proceeded smoothly at -78 °C to afford the (R)-isopropyl ester 3a in high optical purity (69% yield, 92% ee; k_R/k_S= ca. 39).



The experimental procedure is as follows: To a toluene (9 mL) solution of the (R)-chiral diol 1 (60.6 mg, 0.115 mmol) was added a 1.00 mol/L toluene solution of $Ti(OPr^i)_4$ (0.10 mL, 0.10 mmol) at 0 °C in the presence of Molecular Sieves 4A (200 mg) under an argon atmosphere, and the mixture was stirred for 1 h. At -78 °C isopropyl alcohol (0.38 mL, 5.0 mmol) and then a toluene (4.5 mL) solution of racemic 2-(2-phenylbutanoyl)thiopyridine (2a) (261.9 mg, 1.02 mmol) was added dropwise and the mixture was stirred for 90 h at this temperature. The reaction was quenched with pH 7 phosphate buffer, and the organic layer was extracted with dichloromethane and the extracts were dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by preparative TLC to afford the isopropyl ester 3a (72.9 mg, 0.353 mmol).

The above catalytic procedure found a general application to the catalytic kinetic resolution of various α-arylcarboxylic acids. As summarized in Table 2, 2-pyridinethiol esters were successfully resolved to the corresponding optically active esters in high ratios of rates of esterification of the two enantiomers (k_R/k_S). Concerning kinetic resolution of α-arylcarboxylic acids, few methods which involve the enantioselective esterification of the acid anhydrides with chiral alcohols have been reported.$^{12)}$ On the other hand, by employing the chiral catalyst the kinetic resolution proceeds using an achiral nucleophile (isopropyl alcohol), giving isopropyl esters in high optical purity. Consequently the present procedure will provide a practical method for resolution of racemic α-arylcarboxylic acids.

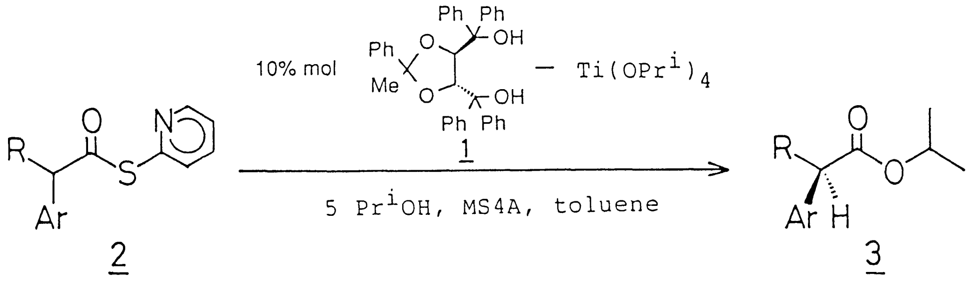


Table 2. The Catalytic Kinetic Resolution of Various α-Arylcarboxylic Acids

	R	Ar	Temp/°C	Yield/%$^{8)}$	ee/%$^{9)}$	$k_R/k_S$$^{10)}$
2a	Et	Ph	-78	69	92	39
2b	Me	Ph	-78	81	88	29
2c	Pr^i	Ph	-45	43	94	42
2d	Pr^i	p-Cl-C_6H_4	-45	37	91	26
2e	Bu^i	Ph	-78	78	91	38

This work is partially supported by a Grant in Aid for Scientific Research No. 63470012 from the Ministry of Education, Science and Culture.

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6) In ^{1}H-NMR study of the mixture of equimolar amounts of 1 and $Ti(OPr^i)_4$ in toluene-d_8, two sets of the signals corresponding to 1 are observed, indicating the presence of a 1-titanium complex and the free 1 in the ratio of 3 to 1.

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8) Based on a half molar amount of a 2-pyridinethiol ester.

9) The isopropyl esters were converted to the alcohols and the optical purity was determined by the Mosher´s method.13) In the cases of 3a,3b, and 3c, the absolute stereochemistry was determined by comparison of the optical rotations of the alcohols with those of the literatures.14-16) The absolute configuration of 3d was determined by comparison of the optical rotation of the alcohol ($[\alpha]_D^{24}$ -11.0° (c 1.44, CH_2Cl_2)) with that of the alcohol derived from the (S)-carboxylic acid kindly provided by Sumitomo Chemical Company Limited. The absolute stereochemistry of 3e is not determined.

10) k_R/k_S exhibits the relative rate, the ratio of the rates of esterification of the (R) and (S)-enantiomers.

11) Since the Diels-Alder reaction catalyzed by the chiral titanium reagent proceeds in higher enantioselectivity when Molecular Sieves 4A is present,17) this resolution reaction was examined in the presence or in the absence of Molecular Sieves 4A. The ester 3a was obtained in better chemical and optical yields by the combined use of Molecular Sieves 4A.

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(Received April 18, 1989)