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An Efficient Preparation of Optically Active α-Eurfuryl Amide by Kinetic Resolution Using the Modified Sharpless Asymmetric Epoxidation Reagent

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Abstract: Kinetic resolution of α -furfuryl amide was first carried out by using the modified Sharpless asymmetric epoxidation reagent to give the slow-reacting enantiomers, (S)-la-f and (R)-lb,f in high enantioselectivity (90-100% e.c) and high chemical yield (45-50%).

Kinetic resolution of secondary allylic alcohols by Sharpless asymmetric epoxidation using tert-butyl hydroperoxide (TBHP) in the presence of chiral titanium-tartrate catalyst, has been widely used in the synthesis of chiral natural products. This asymmetric epoxidation reaction is applicable to the kinetic resolution of other substrates, such as β -hydroxyamine, 2-thiophenyl carbinol, and α -furyl carbinol, which afford a hydroxyl group for coordination to the metal centre and a proximate site capable of accepting an oxygen atom. On the basis of this study, we started to investigate the possibility of the kinetic resolution of α -furfuryl amide la-f using the modified Sharpless reagent. These compounds are characterized by the presence of a furyl group on the amino-bearing carbon atom and their optically active form could be of interest to organic chemists. Herein we describe our finding that the kinetic resolution of α -furfuryl amides proceeds highly efficiently, thus providing a general method for the synthesis of homochiral la-f (Scheme 1).



of the oxidation of 1, in which substituent R is a primary or secondary alkyl group, are summarized in Table 1.

Table 1 Results of Kinetic Resolution of 1 by Modified Sharpless Reagent

<u>Substrate 1</u>			Slow-reacting enantiomers					Yield
	R	Ligand	Time(d)	Yield(%)	[α] D	e.e.(%)	ab.config.	of 2(%)
a	Me	Г-(+)-рть.	2	50	-7.6°	90	5	8
b	Et	и	2	47	-5.0°	93.3	S	45
с	Pr	и	2	45.7	-5.3"	94.7	S	47
d	n-Bu	н	2	46	-5.0°	90	S	41
e	i-Bu	n	2	46.5	-7.4°	90,7	S	43
£	n-Hex	н	3	45	-4.3°	100	S	46
b	Et	D-(-)-DIPT	3	50	+5.0°	93.5	R	46
f	n-liex	n	3.5	49.5	+4.40	100	R	48

a. The reaction was carried out in CH Cl_using Ti(OiPr) (1.0eq), L-(+)- or D-(-)-DIPT(1.2eq), 5-10mol% of CaH_, 10-15mol% of silica gel, and TBHP(2.5eq) at r.t. b.Unless otherwise noted, isolated yield based on racemic 1 after chromatography on silica gel. c. Optical rotations were measured on a Autopol spectrometerIII automatic polarimeter. The solvent is ethanol and the concentration range is between 1 and 3. d.Determined by ¹H NMR analysis of the corresponding MTPA amides of α -furfuryl amines, which were obtained from the cleavage of tosyl group of 1 by using naphthyl sodium in DME at -78 °C². c. Absolute configuration was proved by correlation of the products of oxidation of 1a, e by RuO₄ with the corresponding (S)-N-tosyl- α -amino acids (Scheme 3). f. On treat -ment with aqueous NaOH, 2a decomposed mostly into a highly water soluble and unidentified product. The presence of tosyl substituent on the nitrogen atom could avoid the N-oxide formation . It can be seen from Table 1 that kinetic resolution occurs in high enantioselectivity (90-100% e.e) and high chemical yield (45-50%). All the α -furfuryl amides show the following reactivity feature: When L-(+)-DIPT is used, the fast-reacting enantiomers are the one related to the R enantiomers of la-f; when D-(-)-DIPT is used, the fast-reacting enantiomers are the S enantiomers of 1b,f. This is just opposite to the empirical selectivity rule given by Sharpless and his coworkers and this reversed sense of enantioselection may be attributed to the steric hindrance of the bulky tosyl group on the nitrogen atom. An alternative explanation for the reversed sense of enantioselection is probably due to the different character of nitrogen atom from the rowsgen leading to a different coordination fashion of nitrogen to Ti(IV).

In these reactions, when using 0.6 eq. of TBHP, no reaction was observed, whereas when the TBHP was increased to 2.0-2.5 eq., the reaction proceeded smoothly to about 50-55% conversion.

In all cases the oxidation products 2a-f are readily separated by column chromatography on silica gel, since (S) or (R)-1 and 2 have quite different R values on silica gel. Compounds 2 can also be readily obtained from (S) or (R) -1 by oxidation with MCPBA in high yield (Scheme 2). Thus, the present kinetic



resolution reaction also serves as a very efficient method for the preparation of various optically active 2, which are also recognized as important chiral building blocks.

The furan ring can be converted into a carboxylic acid by ozonolysis $\frac{6}{7}$ or oxidation using RuCl /NaIO 1.1t is evident that the combination of the present kinetic resolution of α -furfuryl amides (Scheme 1) and oxidative cleavage of the furan ring (Scheme 3) provides a general and practical method for the synthesis of amino acids (Scheme 3).

Scheme 3

(S)-1a.e <u>O3. CH2Cl2</u> HO2C R HNTs (S)-3a. The starting racemic α -furfury) amides la-f could be readily prepared from the reaction of N-furfuryl-p-toluene-sulfonylimine with alkyllithium at -70 °C in 75-80% yield.

In summary, the present method for the preparation of chiral 1 and 2 is operationally simple and highly efficient and both of them can be used as chiral building blocks for the synthesis of natural products.

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