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Preparation of Optically Active α-Pyrryl Carbinols by Kinetic Resolution Using the Modified Sharpless Asymmetric Epoxidation Reagent

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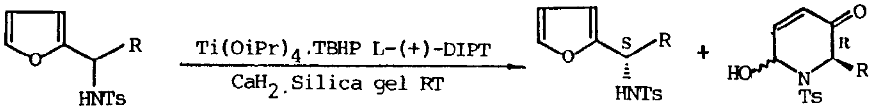
Abstract: Kinetic resolution of α-pyrryl carbinol was carried out by using the modified Sharpless asymmetric epoxidation reagent to give the slow-reacting enantiomers, (R)-3a-f and (S)-3b,d in high enantioselectivity (>90%e.e.) and high chemical yield (30-43%).

After the discovery of the highly efficient kinetic resolution of secondary allylic alcohols by Sharpless asymmetric epoxidation[1], various types of substrate having a hydroxy group at the chiral center and an adjacent site capable of accepting an oxygen atom have been investigated. The β-hydroxyamine[2],2-thiophenylcarbinol[3], and α-furylcarbinol[4] have been shown to be good subatrates for the kinetic resolution.

Recently we have found that the kinetic resolution of racemic α-furfuryl amides 1a-f, using the modified Sharpless reagent,proceeded highly efficiently, providing both the slow reacting enantiomer and the fast reacting enantiomer in high chemical and optical yields[5](Scheme 1).

Scheme 1



1a-f   (s)-1a-f   2a-f

R= Me,Et.Pr.n-Bu,i-Bu,n-Hex

Herein we report for the first time the kinetic resolution of (dl)-pyrryl carbinol using the modified Sharpless reagent(Scheme 2). These compounds are characterized by the presence of a pyrryl group on the hydroxyl-bearing carbon atom and their optically active form could be of interest to organic chemists.

Scheme 2

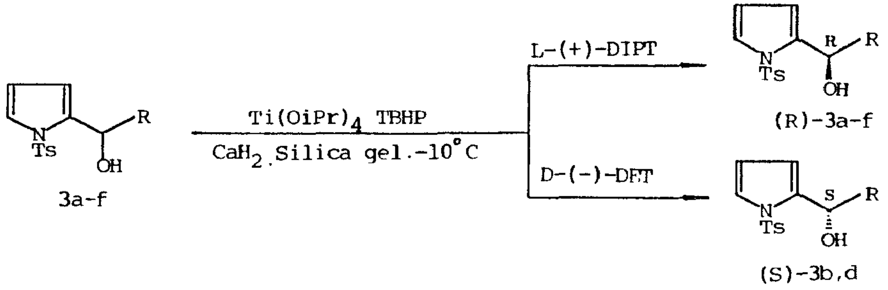


Table 1. Kinetic Resolution of **3** by Modified Sharpless Reagent[a]

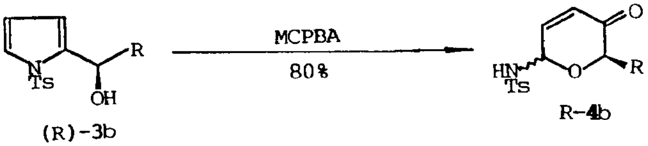
Substrate3		Slow-reacting enantiomers					
	R	Ligand	Time(hrs)	Yield(%)[b]	$[\alpha]_D$[c]	e.e.(%)[d]	ab.config.[e]
a	Me	L-(+)-DIPT	16	43	+21.5	>95	R
b	Et	"	16	38	+37.1	92	R
c	n-Bu	"	16	35	+42.6	90	R
d	n-Hex	"	16	33	+42.9	94	R
e	n-Decane	"	16	30	+38.0	90	R
f	$-CH_2CH=CH_2$	"	16	38	+65.6	>95	R
b	Et	D-(-)DET	16	40	-36.2	90	S
d	n-Hex	"	16	36	-45.5	>95	S

a. The reaction was carried out in CH_2Cl_2 using $Ti(OiPr)_4$(1.0eq),L-(+)-DIPT or D-(-)-DET(1.2eq), 5-10 mol% of CaH_2, 10-20 mol% of silica gel, and TBHP(1.0eq) at -10° C. b. Isolated yield based on racemic **3** after chromatography on silica gel. c. Optical rotations were measured on a Autopol spectrometer Ⅲ automatic polarimeter.The solvent is ethyl acetate and the concentration range is between 1.0 and 1.1. d. Determined by ^{19}F-NMR(90MHz) or ^{1}H-NMR(200MHz) analysis of the corresponding MTPA esters of α-pyrryl carbinols. e. Absolute Configuration was determined by Horeau's method.

The results of the oxidation of various 3 in which a substituent R is a primary or secondary alkyl group using TBHP(1.0eq), $Ti(OiPr)_4$(1.0eq), L-(+)DIPT or D-(-)DET(1.2eq), 5-10mol% of CaH_2 and 10-20mol% of silica gel are summarized in Table 1. The presence of a tosyl substituent on the nitrogen atom avoided N-oxide formation[6]. It can be seen from Table 1 that kinetic resolution occurs in high enantioselectivity and high chimical yield. In these reaction, when L-(+)-DIPT are used, the slow-reacting enantiomers are the one related to the R enantiomers of 3a-f, when D-(-)DET are used, the slow-reacting enantiomers are the S enantiomers of 3b,d. This is the another example of the feature of predictability to the parent process for the kinetic resolution of allylic alcohols[6].

The isolation of (R)-3a-f or (S)-3b,d can be carried out more conveniently by treating the crude reaction mixture with aqueous NaOH. In all cases, an unidentified product probably resulting from the oxidation reaction, was isolated from the alkaline extract. But compound R-**4**b can be readly obtained from (R)-3b by oxidation with MCPBA in high yield (Scheme 3).Thus,the present kinetic resolution reaction also serves as a very efficient method for the preparation of various optically active **4**b, which are also recognized as important chiral building blocks.

Scheme 3



The starting racemic α-pyrryl carbinols 3a-h can be readily prepared from the reaction of α-pyrryl carbaldehyde with a Grignard reagent or alkyl lithium.

A typical experimental procedure is represented by preparation of (R)-3d: To a solution of $Ti(OiPr)_4$ (0.43 ml, 1.5 mmol) in dried CH_2Cl_2(4 ml) was added CaH_2 (6 mg, 0.15 mmol%), silica gel (13 mg, 0.30 mmol%) and L-(+)-DIPT (0.38 ml, 1.8 mmol). After being stirred for 10 min, the solution was cooled to -20°C and racemic 3d (0.50 g, 1.5 mmol) in CH_2Cl_2 (1.5 ml) was added. The solution was stirred for an additional 10 min and TBHP (0.34 ml, 1.5 mmol, 4.4 M in benzene) was then added. The solution was placed in -10°C for 16 hours and poured into 10 ml of 10% tartaric acid. The mixture was stirred vigorously for 1 h at -10°C and 4 h at room temperature.The solution was extracted with CH_2Cl_2

(5 ml, twice).The combined CH_2Cl_2 extract was concentrated and the residual oil was dissolved in Et_2O (20 ml) and extracted with 1N NaOH (8 ml) for 30 min at 0°C with vigorous stirring. The ethereal solution was washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether:ethyl acetate= 15:1, 1% NEt_3) to give (R)-**3d** (0.165 g, 33% yield).

Application of the optically active **3** to natural product synthesis is in progress.

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