Tetrahedron Letters,Vol.30,No.21,pp 2825-2828,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

BINAPHTHOL AS A CHIRAL AUXILIARY. ASYMMETRIC ALKYLATION OF ARYLACETIC ACID

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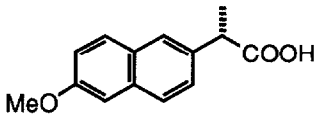
Abstract: Binaphthyl esters of substituted and unsubstituted phenylacetic acids were alkylated with a high diastereoselectivity.

Optically active 2-arylalkanoic acids are regarded as an important class of compounds in view of their biological activity.[1] Representative among these is (*S*)-naproxen (**1**),[2] which has been widely used as an analgesic-antipyretic and anti-inflammatory drug, while (*S*)-2-(4-chlorophenyl)-3-methyl butyric acid (**2**) is a counterpart of a synthetic pyrethroid in commercial use.[3] A number of approaches have been published for asymmetric synthesis of these molecules.[4] Recently, catalytic methods including asymmetric hydrogenation[5,6] of the corresponding arylalkenoic acid and asymmetric hydroformylation[7] of olefins were reported. Surprisingly, however, there has been no report so far on asymmetric alkylation of arylacetic acid with high enantiomeric excess.[8] Here, we describe an efficient synthesis of optically active 2-arylalkanoic acid *via* diastereoselective alkylation of binaphthyl esters of arylacetic acid.



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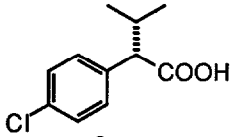

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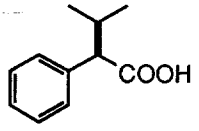


3

A solution of (*R*)-binaphthyl ester **4** (X = H, 0.5 mmol) in tetrahydrofuran (THF, 4 ml) was added at -78 °C to a solution of lithium diisopropylamide (LDA, 2.1 eq.) in THF (2 ml) and hexamethylphosphoric triamide (HMPA, 10 eq.) within 20 min. The mixture was stirred at -78 °C for 30 min.; isopropyl iodide (40 eq.) was added, and stirring continued for 4 h. During the period of the reaction, the temperature was gradually raised to -30 °C. Usual extractive workup afforded a 97% yield of a diastereomeric mixture **5** (R' = *i*-Pr, X = H) and **6** (R' = *i*-Pr, X = H) in an approximate ratio of 9:1. A single recrystallization from ether-hexane gave **5** (R' = *i*-Pr, X = H) with 98% purity judging from the 400 MHz ^{1}H NMR spectrum. Acid hydrolysis of **5** (R' = *i*-Pr, X = H) with aqueous sulfuric acid provided (*R*)-3-

Table I . Alkylation of Binaphthyl Phenylacetate **4**.

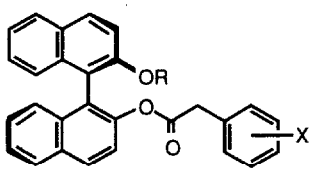
		alkylating	reaction conditions			product	
run	X	agent	temp. °C	time, h	yield, %	ratio, **5** : **6**	(R' =)
1[a,b]	H	MeI	-78	1.0	35	86 : 14	(Me)
2[a]	H	MeI	-78	0.3	85	77 : 23	(Me)
3[c]	H	MeI	-78	0.2	71	76 : 24	(Me)
4[a,b,d]	H	MeI	-78~-40	2.5	12	86 : 14	(Me)
5[a]	H	EtI	-78	0.3	70[e]	78 : 22	(Et)
6[a]	H	*n*-PrI	-78	1.0	83	78 : 22	(*n*-Pr)
7[a]	H	*n*-BuI	-78	2.5	90	78 : 22	(*n*-Bu)
8[a]	H	$PhCh_2Br$	-78	0.3	86	78 : 22	(Ph CH_2)
9[a]	H	CH_2=$CHCH_2Br$	-78	0.3	84	82 : 18	(CH_2=$CHCH_2$)
10[a]	H	*i*-PrI	-78~-40	3.5	95	92 : 8	(*i*-Pr)
11[c]	H	*i*-PrI	-78~-30	4.0	97	89 : 11	(*i*-Pr)
12[a]	H	*i*-BuI	-78~-50	4.0	76	96 : 4	(*i*-Bu)
13[f]	*p*-OMe	MeI	-78	2.5	85	53 : 47	(Me)
14[f]	*p*-OMe	EtI	-78	3.0	85	68 : 32	(Et)
15[f]	*p*-OMe	*n*-PrI	-78	8.0	81	85 : 15	(*n*-Pr)
16[f]	*p*-OMe	*i*-PrI	-78~-65	8.0	91	98 : 2	(*i*-Pr)
17[f]	*p*-OMe	*i*-BuI	-78~-65	10.5	84	100 : 0	(*i*-Bu)
18[f]	*o*-OMe	*i*-PrI	-78	8.0	65[g]	99 : 1	(*i*-Pr)
19[f]	*o*-OMe	*i*-BuI	-78~-55	9.5	62[h]	99 : 1	(*i*-Bu)
20[f]	*p*-Me	*i*-PrI	-78~-70	10.0	84	93 : 7	(*i*-Pr)
21[f]	*p*-Cl	*i*-PrI	-78~-50	8.5	83	91 : 9	(*i*-Pr)

[a] *dl*-Binaphthol ester. [b] Without HMPA. [c] (*R*)-Binaphthyl ester. [d] Dimethoxyethane as a solvent. [e] A 19% of the starting material was recovered. [f] (*S*)-Binaphthyl ester. [g] A 31% of the starting material was recovered. [h] A 28% of starting material was recovered.

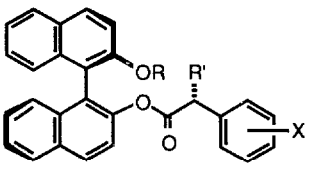
methyl-2-phenylbutyric acid (**3**) {$[a]_D$ -57.4° (chloroform), lit.[9] $[a]_D$ +62.5° (chloroform)} with a slight loss of optical purity.

Table I lists the results of the alkylation of binaphthyl esters of substituted and unsubstituted phenylacetic acids. Note that the (*R*)-binaphthyl esters always

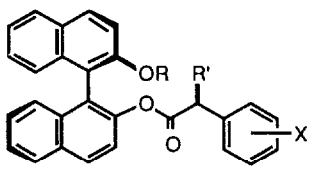
introduce *R*-configuration as the chiral center newly created and *vice versa*. The bulkiness of alkylating agents exerts a remarkable influence on stereoselectivity. Thus, 90 - 100 % selectivity was observed when isopropyl or isobutyl iodide was used as an electrophile (runs 10-12, 16-21). Chemical yield was very low without HMPA as a cosolvent though the diastereomeric ratio was improved (runs 1, 4).



4, R = H
7, R = Me, X = H



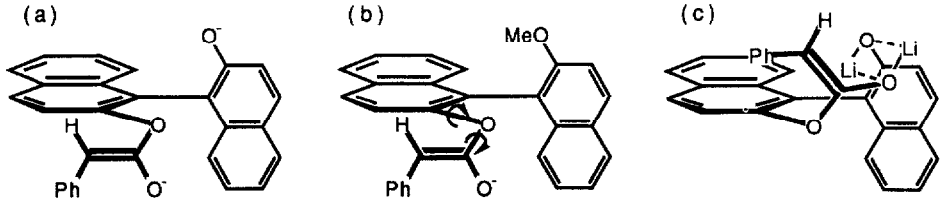
5, R = H
8, R = Me, X = H



6, R = H
9, R = Me, X = H

The phenolic hydroxyl group appeared to be indispensable for high diastereoselectivity. Thus, isopropylation of racemic methyl ether **7** afforded an approximately 1 : 1 mixture of **8** (R' = *i*-Pr) and **9** (R' = *i*-Pr) in 70% yield. The diastereomeric ratio again increased without HMPA even in methylation [**8** (R' = Me) : **9** (R' = Me) = 83 : 17], though the yield was low. The relative configuration of the major product was proved to be the same as that of **5**, because demethylation of the product mixture with a combination reagent of aluminum chloride and ethanethiol[10] afforded a mixture of **5** (R = Me) and **6** (R = Me), rich in the former.

Figure 1. Possible conformations of enolates.



Although the detailed mechanism remains to be studied, the conformation of the intermediate enol as shown in Figure 1a explains the observed stereoselectivities for alkylation. The exclusive formation of (Z)-enolate from esters on deprotonation by LDA in THF-HMPA is well established.[11] In this conformation, two naphthyl rings bisect each other at a torsional angle of about 90° due to the steric reason, and electrostatic repulsion keeps the two negatively charged oxygens maximally apart. Thus, the *re*-face of the nucleophilic carbon is more open than the *si*-face which is hindered by the attaching naphthyl ring,

when (*R*)-binaphthol is used as a chiral auxiliary. In the case of the methyl ether **7**, discrimination between the *re*- and the *si*-face is less operative, because easier rotation about the two C-O bonds, indicated by an arrow, is expected as a result of decrease in repulsive interaction between the enolate oxygen and the oxygen in the methoxyl group (Figure 1b). Figure 1c shows a plausible intermediate from **4** without HMPA as a cosolvent, in which the *si*-face of the (*E*)-enolate[11,12] is blocked sterically because of the chelation. The enhanced diastereoselectivity in methylation of **7** without HMPA can be explained by a chelated model of a similar type.

Scope, limitations, and the detailed mechanism of this reaction are currently under investigation.

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(Received in Japan 29 March 1989)