Tetrahedron: Asymmetry Vol. 1, No. 12, pp. 851-854, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

KINETIC RESOLUTION OF RACEMIC ALCOHOLS WITH CHIRAL CARBOXYLIC ACIDS AND DICYCLOHEXYLCARBODIIMIDE†

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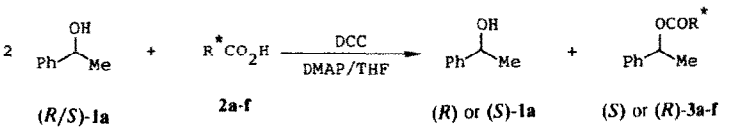
(*Received* 17 *October* 1990)

Abstract: The DCC-esterification method has been used to kinetically resolve racemic mixtures of alcohols. With simple chiral carboxylic acids, such as *O*-aryl lactic acids, in the presence of various basic catalysts, mixtures of the enantiomerically enriched alcohols (e.e. <50%) and the corresponding esters (d.e.<70%) have been obtained.

Most of the known methods for efficient kinetic resolution are based on biochemical processes.[1] In the case of alcohols chemical kinetic resolution is known by means of optically active anhydrides; however, this procedure is of little preparative value and has been used only for the prediction of absolute configurations.[2] For allylic alcohols, the kinetic resolution by epoxidation[3a] or catalytic hydrogenation[3b] has been described. We report here for the first time a method that allows kinetic resolution of racemic alcohols using chiral acids and dicyclohexylcarbodiimide (DCC).

The reaction of a racemic mixture of 1-phenylethanol (**1a**) with different chiral carboxylic acids **2** (2:1 molar ratio) in the presence of DCC and a catalytic amount of 4-(dimethylamino)pyridine (DMAP)[4] in THF at room temperature led to a mixture of the corresponding ester **3** and the remaining alcohol **1a** (both diastereoselectively and enantioselectively enriched, respectively), the process taking place through a kinetic resolution (Scheme 1 and Table 1). We found that among the various carboxylic acids tried, the corresponding *O*-aryl-substituted (*R*)-lactic acid (**2c, 2d**) gave the best results[5] (Table 1, entries 3 and 4). On the other hand, the separation of both reaction products was easily carried out with a short column of silica gel.



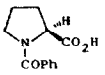
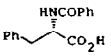
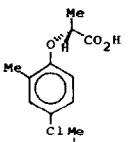
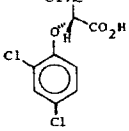
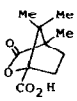
(*R/S*)-**1a** **2a-f** (*R*) or (*S*)-**1a** (*S*) or (*R*)-**3a-f**

Scheme 1

Taking into account the results summarized in Table 1 we applied this kinetic resolution to different alcohols **1** using the acid **2d** under comparable reaction conditions (Scheme 2 and Table 2).

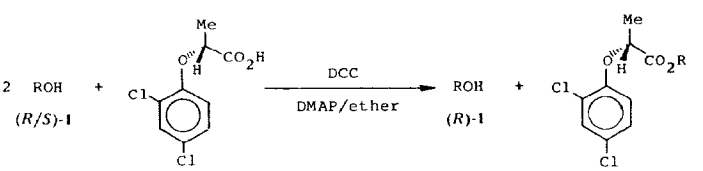
† Dedicated to the memory of Dr. Seppo K. Juntunen

Table 1. Esterification of **1a** with chiral carboxylic acids **2** in THF.

Entry	Acid		Reaction time (h)	Alcohol **1a**			Ester **3a-f**	
	no.	formula		yield (%)[a]	e.e.(%)[b]	config.[c]	yield (%)[a]	d.e.(%)[d]
1	**2a**		3	80	19	*R*	81	35
2	**2b**		3	80	2	*R*	94	2
3	**2c**		6	80	41	*R*	85	52
4	**2d**		5[e]	89	43	*R*	80	50
5	**2e**		4.5	75	30	*R*	95	39
6	**2f**		5	93	20	*S*	71	35

[a] Based on the starting carboxylic acid **2**. [b] From the $[\alpha]_D^{25}$ value in comparison with the literature data: $[\alpha]_D^{23}$ -52.5 (c=2.27, CH_2Cl_2) (Ref. 6). [c] See ref. 6. [d] From 300 MHz ^1H n.m.r. [e] In ether.

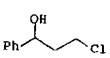
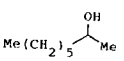
Once more, appreciable chiral discrimination has been found for each alcohol that has been submitted to the esterification. It is noteworthy that in all cases the configuration of the isolated alcohol was *R* and consequently the corresponding *S*-isomer was preferentially esterified to give the product **3d.**



Scheme 2

In the next part of this study, we considered the influence of the reaction conditions (solvent, catalyst, temperature) on the process. Thus, we observed that the process can be carried out in different solvents (Et_2O, Pr^i_2O, hexane, heptane, THF) and with various amines as catalysts; in general most of the e.e. (alcohol) and d.e. (ester) values are in the range of 40-60% (Table 3). The low induction with HMTA (25-27%) as well as the obtention of a 85:15 mixture of ester **3** (d.e. 70%) in the case of 1-dimethylamino-2-propanol as catalyst clearly demonstrate the important role of the base during the

Table 2: Esterification of racemic alcohols **1** with (*R*)-**2d** in ether

Entry	Alcohol **1**		Reaction time (h)	Alcohol **1**			Ester **3d**	
	no.	formula		Yield (%)[a]	e.e.(%)[b]	config.[c]	Yield (%)[a]	d.e.(%)[d]
1	**1a**		5	89	43[e]	*R*	80	50
2	**1b**		4.5	86	[f]	*R*[g]	92	31
3	**1c**		5.5	88	50[h]	*R*	94	55
4	**1d**		5	81	48[i]	*R*	90	52
5	**1e**		3	82	32[j]	*R*	85	40
6	**1f**		5	82	39[k]	*R*	86	43
7	**1g**		5	85	19[l]	*R*	83	26

[a] Based on the starting carboxylic acid **2c**. [b] From the $[\alpha]_D^{25}$ value in comparison with the literature data. [c] See references 6-12. [d] From 300 MHz ^{1}H n.m.r. [e] Lit.[6] $[\alpha]_D^{23}$ -52.5 (c=2.27, CH_2Cl_2). [f] $[\alpha]_D^{25}$ -1.5 (c=2.4, $CHCl_3$); no data found. [g] Lit.[7]. [h] Lit.[8] $[\alpha]_D^{20}$ +7.8 ($CHCl_3$). [i] Lit.[9] $[\alpha]_D^{21}$ -48.6 (c=5, $CHCl_3$). [j] Lit.[10] $[\alpha]_D^{20}$ +16.13 (EtOH). [k] Lit.[11] $[\alpha]_D^{23}$ +24.0 (c=1, $CHCl_3$). [l] Lit.[12] $[\alpha]_D^{20}$ +9.9 (EtOH).

asymmetric recognition step.[13] On the other hand, when the reaction was performed at lower temperature (-40°C) than the ambient (Table 3, entry 3) a slight increase in the e.e. (for **1a**) and d.e. (for **3d**) took place. Finally we have studied the increment of both diastereomeric and enantiomeric excess when the process is repeated. Thus, the ester obtained from **1a** and **2c** (Table 3, entry 6; 51% d.e.) was hydrolyzed (methanolic potassium hydroxide) yielding *S*-**1a** and optically pure **2c** (both in >90% yield). When this alcohol was used as starting material for the same process as above, we obtained the corresponding *S*-**1a**-containing ester (80% yield; 70% d.e.) and *R*-**1a** (84% yield; 10% e.e.). On the other hand, when *R*-**1a** (Table 3, entry 6; 44% e.e.) was allowed to react with **2c** under the same conditions as above the expected alcohol *R*-**1a** (94% yield; 61% e.e.) and the *S*-**1a**-containing ester (81% yield; 25% e.e.) were isolated. So, we have found that a second process improves by about 20% d.e. (51% – 70%) or e.e. (44% – 61%) the results of the first one.

In conclusion, we describe in this paper that the esterification with chiral acids constitutes an easy, cheap and rapid method for kinetic resolution of racemic alcohols. It is not yet clear which factors are crucial for the size of the asymmetric discrimination in these reactions, since every parameter seems important: the solvent, the base, the structure of the chiral acid and the racemic alcohol. On the other

Table 3: Esterification of **1a** with **2c** and **2d** under different reaction conditions

Entry	Acid	Reaction conditions			Alcohol **1a**		Ester **3c** or **3d**	
		base (cat.)[a]	solvent	time (h)	yield (%)[b]	e.e.(%)[c]	yield (%)[b]	d.e.(%)[d]
1	**2d**	DMAP	Et_2O	5	89	43	80	50
2	**2c**	DMAP	Et_2O	3.5	95	39	72	45
3	**2c**	DMAP	Et_2O	3[e]	93	44	85	51
4	**2c**	DMAP	hexane	6	90	38	94	44
5	**2c**	DMAP	THF	6	80	41	82	52
6	**2c**	PP	Et_2O	3.5	88	44	86	51
7	**2d**	collidine	Et_2O	3	90	41	86	51
8	**2d**	HMTA	Et_2O	7	95	25	53	27
9	**2c**	brucine	heptane	2.5	85	50	91	56
10	**2c**	nicotine	Et_2O	3	79	45	78	56
11	**2c**	DMAPR	Pr^i_2O	3	98	39	51	70
12	**2c**	ME	Pr^i_2O	4	95	44	62	60

[a] DMAP: 4-(dimethylamino)pyridine; PP: 4-pyrrolidinopyridine; HMTA: hexamethylenetetraamine; DMAPR: 1-dimethylamino-2-propanol; ME: *N*-methylephedrine. [b] From the $[\alpha]_D^{25}$ value in comparison with the literature data: $[\alpha]_D^{23}$ -52.5 (c=2.27, CH_2Cl_2) (Ref. 6). [c] See ref. 6. [d] From 300 MHz ^1H n.m.r. [e] Performed at -40°C.

hand these observations tend to anticipate that this simple (resolution) method may become complementary to (usually used) biochemical procedures.[14]

References and Notes

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5. These derivatives were prepared by the Mitsunobu method (*Synthesis* **1981**, 1) starting from the corresponding (*S*)-ethyl lactate: A. Heumann, unpublished results. We thank the BASF Company, Ludwigshafen, Germany, for a generous gift of these two acids.
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13. It is clear from these results that DMAP as a base should be avoided when complete reaction between the acid and the alcohol is desired: esterification with MTPA (**2e**) for the determination of enantiomeric purity by NMR methods for example. Bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) give good chemical yields and low chiral discrimination in DCC esterification reactions.
14. This work was supported by DGICYT (no. PB88-0287) Spain, and by Asociacion Hispano Francesa (no. HF-023/90)-Actions Intégrées Franco Espagnoles 1990 (no. 56).