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Kinetic Resolution of Racemic Carboxylic Acids and Alcohols with Homochiral Alcohols and Carboxylic Acids, Respectively, and the Mukaiyama or Palomo Reagents

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Abstract: *The Mukaiyama and Palomo reagents have been used for the kinetic resolution of racemic carboxylic acids or alcohols with homochiral alcohols or carboxylic acids, respectively, in the presence of triethylamine. Thus, enantiomerically enriched carboxylic acids (e.e.<68%), alcohols (e.e.<41%) or diastereoisomerically enriched esters (d.e.<84%) are obtained.*

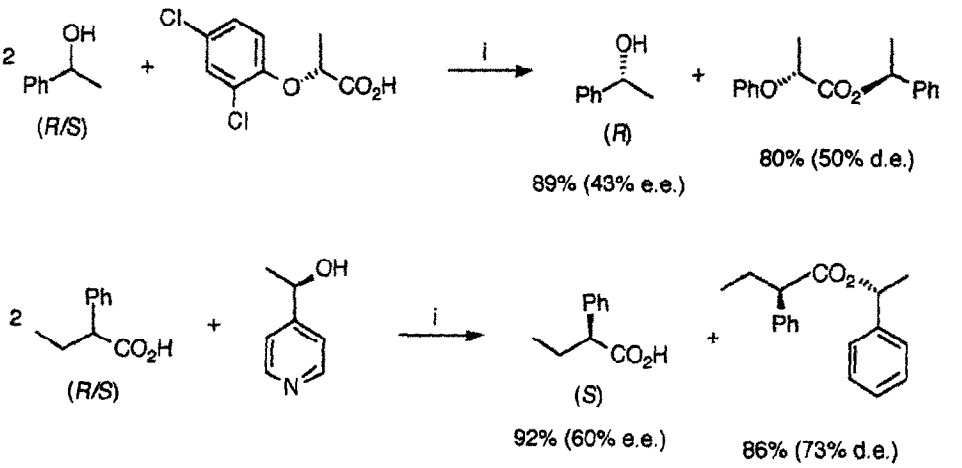
Introduction

Kinetic resolution is a very efficient method for obtaining chiral molecules above all in biochemical processes[1]. In the case of alcohols the most useful kinetic resolutions have been applied on allylic derivatives by epoxidation[2] or catalytic hydrogenation[3]. For carboxylic acids, the kinetic resolution of the corresponding anhydrides by means of homochiral alcohols has been described[4], the Horeau method being the most known application of this reaction[5]. We have recently reported the use of dicyclohexylcarbodiimide (DCC) for the kinetic resolution of racemic alcohols[6] or carboxylic acids[7] with homochiral carboxylic acids or alcohols, respectively. Two examples of these last reactions are included in the Scheme 1. In this paper we study the kinetic resolution of racemic carboxylic acids and alcohols with homochiral alcohols and carboxylic acids, respectively, by means of the Mukaiyama[8] or Palomo[9] reagents as condensation agents.

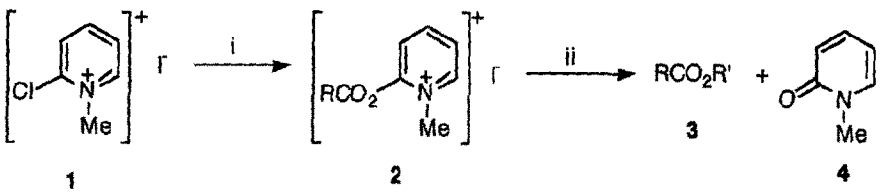
Results and Discussion

1.- Kinetic Resolution of Racemic Carboxylic Acids and Alcohols with the Mukaiyama Reagent

The general mechanism for the condensation reactions using the Mukaiyama reagent **1** is described in the Scheme 2[8]: in the first step the formation of the intermediate **2** takes place, activating the carbonyl group of the ester functionality for the nucleophilic attack of the alcohol, so the corresponding ester **3** is formed together with 2-pyridone **4.**



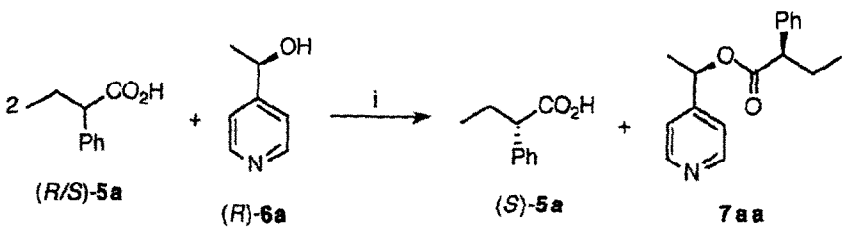
Scheme 1. *Reagent*: i, DCC/DMAP, THF or PhMe.



Scheme 2. *Reagent*: i, RCO_2H, Bu^n_3N; ii, R'OH.

1.1.-Kinetic Resolution of Carboxylic Acids

We first studied the best reaction conditions for carrying out the process, starting from (*R/S*)-2-phenylbutyric acid (**5a**) and (*R*)-1-(4-pyridyl)ethanol (**6a**)[10]; these reagents were chosen because they gave good results in the DCC-method[7] (Scheme 3 and Table 1).



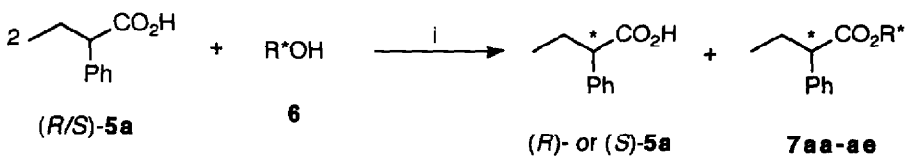
Scheme 3. *Reagent*: i, **1**, Et_3N-solvent (Table 1).

Table 1. Kinetic resolution of racemic **5a** with (*R*)-**6a** and the Mukaiyama reagent **1** under different reaction conditions

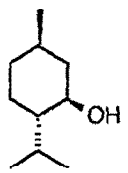
	Reaction conditions		Acid (*S*)-**5a**			Ester **7aa**	
Entry	solvent	time (d)	yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	yield (%)[a]	d.e. (%)[c]
1	CH_2Cl_2	4	111	+22	24	43	44
2	THF	2	113	+18	19	38	66
3	PhMe	1	62	+33	36	50	74
4	Et_2O	1	81	+26	28	27	49
5[d]	PhMe	1	84	+31	34	58	68
6[e]	PhMe	-	78	+29	31	81	75

[a] Isolated yield based on the starting alcohol (*R*)-**6a**. [b] Calculated from the $[\alpha]_D^{20}$ value in comparison with the literature data measured under the same conditions (ref. 11): (*S*)-**5a** (99%) $[\alpha]_D^{19}$ +92 (c=0.9, toluene). [c] Deduced from the ^1H and ^{13}C NMR (300 and 75 MHz, respectively). [d] The reaction temperature was 60°C. [e] The corresponding anhydride was previously formed (1d) and then the alcohol (*R*)-**6a** was added.

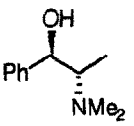
The best results were obtained with toluene as solvent at room temperature and using a 2:1:1.2 molar ratio of **5a**:(*R*)-**6a**:**1**. Then we studied the kinetic resolution of racemic **5a** using different homochiral alcohols **6** under the above described reaction conditions, finding that the best yields were obtained using the alcohol (*R*)-**6a** (Scheme 4 and Table 2, entry 1). When methyl (*S*)-2-hydroxypropanoate [(*S*)-**6d**] was used as the alcoholic component the esterification did not take place, the corresponding anhydride of **5a** being the only reaction product isolated (Table 2, entry 4). As in the case of the DCC-induced kinetic resolution of racemic carboxylic acids[7], the alcohol (*S*)-**6a** was the best one when using the Mukaiyama reagent. Thus, this alcohol was tested for the kinetic resolution of different racemic carboxylic acids **5** (Scheme 5 and Table 3).



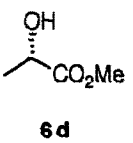
Scheme 4. *Reagent*: i, **1**, Et_3N, toluene.



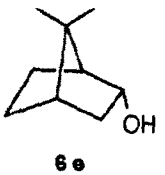
6b



6c



6d

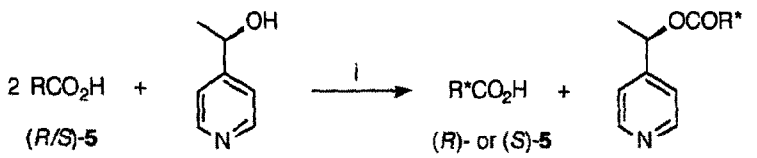


6e

Table 2. Kinetic resolution of 2-phenylbutyric acid (**5a**) with homochiral alcohols **6** and the Mukaiyama reagent (**1**) in toluene.

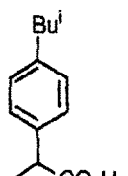
Entry	Alcohol **6**	Reaction time (d)	Carboxylic acid **5a** yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	Ester **7** no.	yield (%)[a]	d.e. (%)[c]
1	**6a**	1	62	+33	36	**7aa**	50	74
2	**6b**	14	84	+8	9	**7ab**	60	35
3	**6c**	2	87	-0.5	~1	**7ac**	69	20
4[d]	**6d**	1	-	-	-	-	-	-
5	**6e**	7	53	+0.5	~1	**7ae**	73	0

[a] Isolated yield based on the starting alcohol **6**. [b,c] See footnotes b and c, respectively, in Table 1. [d] The corresponding anhydride was the only reaction product isolated (>90%).

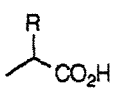


(*R*)-**6a** **7aa-7ha**

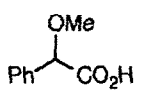
Scheme 5. *Reagent*: i, **1**, Et_3N, toluene.



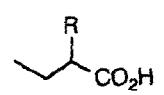
5b



5c : R=Ph
5d : R=OPh
5f : R=Cl



5e



5g : R=Cl
5h : R=Me

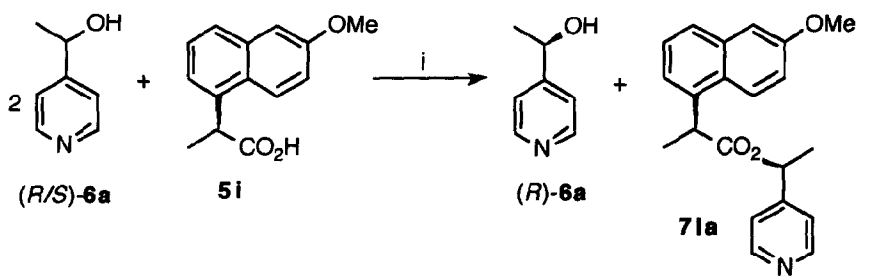
Table 3. Kinetic resolution of carboxylic acids **5** with the alcohol **6a** and the Mukaiyama reagent (**1**) in toluene.

Entry	Reaction time (d)	Carboxylic acid **5**				Ester		
		no.	yield (%)[a]	$[\alpha]_D^{20}$[b]	e.e. (%)[c]	no.	yield (%)[a]	d.e. (%)[d]
1	1	**5a**	62	+33	36[e]	**7aa**	50	74
2	1	**5b**	69	+20	33[f]	**7ba**	98	72
3	1	**5c**	78	+33	45[g]	**7ca**	94	65
4	5	**5d**	83	+16	40[h]	**7da**	67	49
5	1	**5e**	83	+28	19[i]	**7ea**	58	35
6	4	**5f**	103	-1	10[j]	**7fa**	19	51
7	1	**5g**	83	+6	55[k]	**7ga**	65	50
8	5	**5h**	28	+1	5[l]	**7ha**	80	0

[a] Isolated yield based on the starting alcohol **6a**. [b] Measured under the same conditions than those described in the literature. [c] Calculated from the $[\alpha]_D$ values in comparison with the literature data. [d] See footnote c in Table 1. [e] Ref. 11: $[\alpha]_D^{19}$ +92 (c=0.9, toluene). [f] Ref. 12: $[\alpha]_D^{25}$ +60 (95% ethanol). [g] Ref. 11: $[\alpha]_D^{20}$ +72 (c=1.6, chloroform). [h] Ref. 13: $[\alpha]_D^{22}$ +39.3 (c=2.5, ethanol). [i] Ref. 11: $[\alpha]_D^{17}$ +150 (c=1, ethanol). [j] Ref. 11: $[\alpha]_D^{25}$ -9.1 (c=2.17, water). [k] Ref. 14: $[\alpha]_D^{27}$ -9.7 (methanol). [l] Ref. 15: $[\alpha]_D^{20}$ -24 (c=0.9, water).

1.2.-Kinetic Resolution of Alcohols

As in the former part we first studied the best reaction conditions varying the solvent for a standard process between the racemic alcohol **6a** and naproxen (**5i**), both commercially available (Scheme 6 and Table 4).



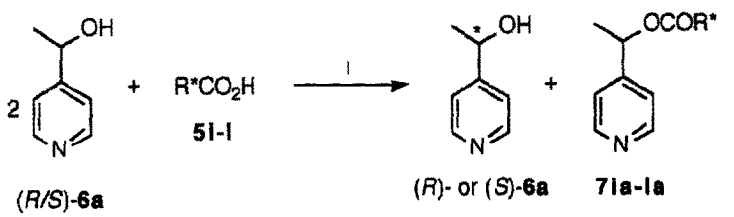
Scheme 6. *Reagent*: i, **1**, Et_3N, solvent (Table 4).

In this case we took diethyl ether as solvent in order to investigate the kinetic resolution of carboxylic acids **5**, using a similar stoichiometry as in the case of the resolution of carboxylic acids: **6a**:**5**:**1**=2:1:1.2 (Scheme 7 and Table 5). The best results were obtained with naproxen (Table 5, entry 1).

Table 4. Kinetic resolution of racemic **6a** with naproxen (**5l**) and the Mukaiyama reagent **1** under different reaction conditions

	Reaction conditions		Alcohol (*R*)-**6a**			Ester **7la**	
Entry	solvent	time (h)	yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	yield (%)[a]	d.e. (%)[c]
1	Et_2O	3	32	+16	29	75	60
2	PhMe	1	20	+18	31	71	50
3	CH_2Cl_2	4	41	+4	7	49	33
4	THF	1	33	+6	11	47	45

[a] Isolated yield based on the starting naproxen **5l**. [b] Calculated from the $[\alpha]_D^{20}$ value in comparison with the literature data (ref. 16): $[\alpha]_D^{20}$ +56±3 (c=1, chloroform). [c] See footnote c in Table 1.

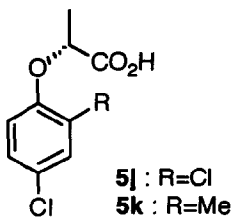


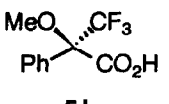
Scheme 7. *Reagent*: i, **1**, Et_3N, diethyl ether.

Table 5. Kinetic resolution of the alcohol **6a** with homochiral carboxylic acids **5** and the Mukaiyama reagent (**1**) in diethyl ether.

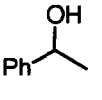
			Alcohol **6a**			Ester **7**		
Entry	Carboxylic acid **5**	Reaction time (h)	yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	no.	yield (%)[a]	d.e. (%)[c]
1	**5i**	3	32	+16	29	**7ia**	75	60
2	**5j**	1.5	23	+14	25	**7ja**	71	50
3	**5k**	16	51	+5	9	**7ka**	99	52
4	**5l**	15	90	+19	33	**7la**	89	42

[a] Isolated yield based on the starting carboxylic acid **5**. [b,c] See footnotes b and c, respectively, in Table 4.

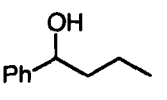




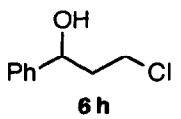
5l



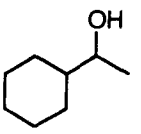
6f



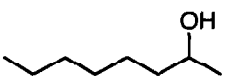
6g



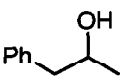
6h



6l



6j

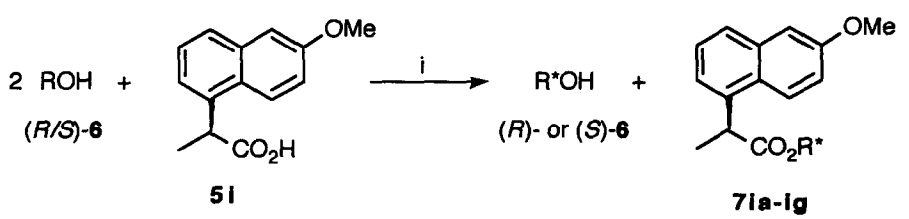


6k

Table 6. Kinetic resolution of alcohols **6** with naproxen (**5i**) and the Mukaiyama reagent (**1**) in diethyl ether.

Entry	Reaction time	Alcohol **6**				Ester **7**		
		no.	yield (%)[a]	$[\alpha]_D^{20}$[b]	e.e. (%)[c]	no.	yield (%)[a]	d.e. (%)[d]
1	3 h	**6a**	32	+16	29[e]	**7ia**	75	60
2	14 h	**6f**	91	+1.5	3[f]	**7if**	29	39
3	3 d	**6g**	90	+0.5	1[g]	**7ig**	56	41
4	6 d	**6h**	91	+1	4[h]	**7ih**	55	55
5	3 d	**6i**	73	-[i]	-[i]	**7ii**	29	48
6	3 d	**6j**	80	0	0[i]	**7ij**	43	12
7	3 d	**6k**	100	+1.5	8[k]	**7ik**	40	37

[a] Isolated yield based on the starting carboxylic acid **5i**. [b-d] See footnotes b-d, respectively, in Table 3. [e] See footnote b in Table 4. [f] Ref. 17: $[\alpha]_D^{23}$ -52.5 (c=2.27, dichloromethane). [g] Ref. 11: $[\alpha]_D^{21}$ -48.6 (c=5, chloroform). [h] Ref. 18: $[\alpha]_D^{23}$ +24.0 (c=1, chloroform). [i] $[\alpha]_D^{20}$ +3 (c=1.67, chloroform); ref. 6: no data found. [j] Ref. 15: $[\alpha]_D^{20}$ +9.9 (neat). [k] Ref. 19: $[\alpha]_D^{20}$ +16.13 (ethanol).

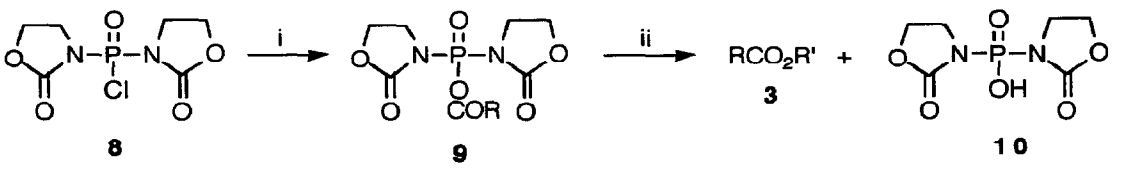


Scheme 8. *Reagent:* i, **1**, Et_3N, diethyl ether.

We then studied the kinetic resolution of different racemic alcohols **6** with naproxen as the homochiral carboxylic acid, the Mukaiyama reagent as the condensation agent, and diethyl ether as solvent (Scheme 8). The obtained results are summarized in the Table 6: as it can be seen the chemical and optical yields are, in general, poorer than in the case of the kinetic resolution of carboxylic acids shown above.

2.- Kinetic Resolution of Racemic Carboxylic Acids and Alcohols with the Palomo Reagent

The Palomo reagent **8** [bis(2-oxo-3-oxazolidinyl)phosphinic chloride] has been employed in esterification processes[9]; the proposed mechanism involves the mixed anhydride **9**, which suffers a S_N reaction with the alcohol to give the corresponding ester **3** and the phosphoric diamide **10** (Scheme 9).



Scheme 9. *Reagent*: i, RCO_2H, Et_3N; ii, R'OH.

2.1.- Kinetic Resolution of Carboxylic Acids

The study with the Palomo reagent was parallel to that carried out in the former part 1. Thus, the racemic carboxylic acid **5a** was reacted with the alcohol (*R*)-**6a** as was described in the Scheme 1, but using the condensation agent **8** instead of **1**, and with the same stoichiometry. The results are summarized in Table 7: as it can be seen, the best results were obtained with toluene (Table 7, entry 4), as in the case of the Mukaiyama reagent. In one run the intermediate anhydride was first prepared and then allowed to react with the alcohol in a two-step reaction: the results were not better than in the direct process (compare in Table 7,, entries 4 and 5).

Table 7. Kinetic resolution of racemic **5a** with (*R*)-**6a** and the Palomo reagent **8** under different reaction conditions

	Reaction conditions		Carboxylic acid (*S*)-**5a**			Ester **7aa**	
Entry	solvent	time	yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	yield (%)[a]	d.e. (%)[c]
1	CH_2Cl_2	3 h	61	+12	12	60	56
2	Et_2O	4 d	84	+36	38	64	72
3	THF	4 d	102	+25	27	80	70
4	PhMe	2 d	72	+57	61	99	68
5[d]	PhMe	3 d	75	+22	24	76	84

[a-c] See footnotes a-c, respectively, in Table 1. [d] The corresponding anhydride was formed (1h) prior to the addition of the alcohol (*R*)-**6a**.

With these results in hand we studied the kinetic resolution of the racemic acid **5a** with different alcohols (Scheme 4, with i, **8**, Et_3N, toluene, and Table 8) and the kinetic resolution of racemic acids **5** with the best alcohol (*R*)-**6a** (Scheme 5 with i, **8**, Et_3N, ,toluene, and Table 9).

Table 8. Kinetic resolution of 2-phenylbutyric acid (**5a**) with homochiral alcohols **6** and the Palomo reagent (**8**) in toluene.

Entry	Alcohol **6**	Reaction time (d)	Carboxylic acid **5a**			Ester **7**		
			yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	no.	yield (%)[a]	d.e. (%)[c]
1	**6a**	2	72	+57	61	**7aa**	98	68
2	**6c**	14	35	+9	10	**7ab**	95	34
3	**6d**	3	98	-2	2	**7ac**	74	36

[a-c] See footnotes a-c, respectively, in Table 2.

Table 9. Kinetic resolution of carboxylic acids **5** with the alcohol **6a** and the Palomo reagent (**8**) in toluene.

Entry	Reaction time (d)	Carboxylic acid **5**				Ester **7**		
		no.	yield (%)[a]	$[\alpha]_D^{20}$[b]	e.e. (%)[c]	no.	yield (%)[a]	d.e. (%)[d]
1	2	**5a**	72	+57	61[e]	**7aa**	98	68
2	3	**5b**	79	+33	55[f]	**7ba**	98	69
3	5	**5c**	84	+46	68[g]	**7ca**	98	67
4	5	**5d**	98	+18	45[h]	**7da**	97	57
5	2	**5e**	96	-22	15[i]	**7ea**	67	25
6	3	**5f**	33	+2	24[j]	**7fa**	23	64
7	3	**5g**	61	+2.5	25[k]	**7ga**	64	65
8	5	**5h**	62	+0.5	1[l]	**7ha**	65	16

[a-l] See footnotes a-l, respectively, in Table 3.

As in the case of the Mukaiyama reagent, the best results were obtained with the alcohol **6a** (Tables 8 and 9, entries 1); in general, the Palomo reagent works better than the Mukaiyama one (compared Tables 2 and 3 with 8 and 9).

2.2.- Kinetic Resolution of Alcohols

Following the same strategy as before we first studied the reaction conditions for one standard process: in this case we took the couple formed by (*R/S*)-1-phenylethanol (**6f**) and naproxen (**5l**) and the same stoichiometry as always: however, the results were very bad (e.e<1% and d.e.<51%). Thus, we used again the alcohol **6a** for studying its kinetic resolution with different homochiral carboxylic acids (Scheme 7, with **i**, **8**, Et_3N, diethyl ether, and Table 10) and naproxen (Scheme 8, with **i**, **8**, Et_3N, diethyl ether, and Table 11) or the acid **5j** (Scheme 10 and Table 12) for the kinetic resolution of different racemic alcohols, using in all cases the Palomo reagent (**8**).

Table 10. Kinetic resolution of the alcohol **6a** with homochiral carboxylic acids **5** and the Palomo reagent (**8**) in diethyl ether.

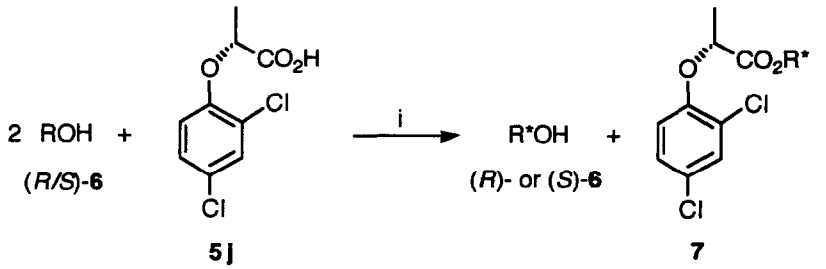
			Alcohol **6a**			Ester **7**		
Entry	Carboxylic acid **5**	Reaction time (h)	yield (%)[a]	$[\alpha]_D^{20}$	e.e. (%)[b]	no.	yield (%)[a]	d.e. (%)[c]
1	**5l**	6	95	+10	17	**7la**	47	38
2	**5j**	16	87	+24	41	**7ja**	92	64
3	**5k**	16	98	+21	38	**7ka**	95	64
4	**5l**	19	98	-15	27	**7la**	82	43

[a-c] See footnotes a-c, respectively, in Table 5.

Table 11. Kinetic resolution of alcohols **6** with naproxen (**5l**) and the Palomo reagent (**8**) in diethyl ether.

		Alcohol **6**				Ester **7**		
Entry	Reaction time	no.	yield (%)[a]	$[\alpha]_D^{20}$[b]	e.e. (%)[c]	no.	yield (%)[a]	d.e. (%)[d]
1	6 h	**6a**	95	+9.5	17[e]	**7ia**	47	38
2	20 h	**6f**	78	-0.5	1[f]	**7if**	33	51
3	6 d	**6g**	138	+0.5	1[g]	**7ig**	20	68
4	6 d	**6h**	87	+0.5	2[h]	**7ih**	15	42
5	6 h	**6i**	82	+0.5	-[i]	**7ii**	11	69
6	6 d	**6j**	96	<+0.5	1[j]	**7ij**	20	3

[a-j] See footnotes a-j, respectively,in Table 6.



Scheme 10. *Reagent*: i, **8**, Et_3N, diethyl ether.

Table 12. Kinetic resolution of alcohols **6** with the carboxylic acid **5j** and the Palomo reagent (**8**) in diethyl ether.

Entry	Reaction time	Alcohol **6**				Ester **7**		
		no.	yield (%)[a]	$[\alpha]_D^{20}$[b]	e.e. (%)[c]	no.	yield (%)[a]	d.e. (%)[d]
1	16 h	**6a**	87	+24	41[e]	**7ja**	92	64
2	26 h	**6f**	50	-3	6[f]	**7jf**	57	11
3	8 d	**6g**	90	+0.5	1[g]	**7jg**	16	1
4	4 d	**6h**	92	-1	4[h]	**7jh**	58	20
5	1 d	**6j**	71	-0.5	6[i]	**7jj**	58	3

[a-h] See footnotes a-h, respectively, in Table 11. [i] See footnote j in Table 11.

In general, Palomo's reagent works slight better than the Mukaiyama one in the kinetic resolution of racemic carboxylic acids, but worst in the case of the kinetic resolution of racemic alcohols.

Experimental Part

General.- ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer with $SiMe_4$ as internal standard and using $CDCl_3$ as solvent. $[\alpha]_D$ values were measured with an Optical Activity AA-10 Automatic Digital Polarimeter. Chromatographic analysis (GLC) for monitoring reactions were determined with a Hewlet Packard HP-5890 instrument equipped with a 25 m WCOT capillary column (0.22 mm diam., 0.2 μm film thickness OV-101 stationary phase) using nitrogen (2 ml/min) as the carrier gas, $T_{injector}$=270°C, T_{column}=60°C (3 min), and 60-248 (15 °C/min). Thin layer chromatography (TLC) was carried out on aluminum backed plates coated with a 0.2 mm layer of silica gel 60H, using a mixture of hexane/ethyl acetate as eluant, and

revealed, in general, with an UV lamp. Column chromatography was performed using silica gel 60 of 70-270 mesh and hexane/ethyl acetate as eluant. All starting materials were commercially available (Aldrich, Fluka) of the best grade and were used without further purification. Solvents were dried as usually. The reactions were performed under an argon atmosphere.

Kinetic Resolution of Racemic Carboxylic Acids (5) using the Mukaiyama or the Palomo Reagents.- A mixture ot the racemic carboxylic acid **5** (1 mmol), the homochiral alcohol **6** (0.5 mmol), the condensation reagent **1** or **8** (0.6 mmol) and triethylamine (1.2 mmol) in the corresponding solvent (5 ml; see Tables 1-3 and 7-9) was stirred under argon till the process finished (monitored by GLC or TLC). Then, diethyl ether (10 ml) and 0.5 M sodium hydroxide (10 ml) were added to the resulting mixture. The aqueous layer was neutralyzed with hydrochloric acid, dried over anhydrous sodium sulfate and evaporated (15 Torr) to yield the crude carboxylic acids **5**. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr) to give the crude alcohols **6**. Both crude products were purified by column chromatography (silica gel, hexane/ethyl acetate). Reaction times, yields, $[\alpha]_D$ values, e.e and d.e. percentages are collected in Tables 1-3 and 7-9.

Kinetic Resolution of Racemic Alcohols 6 using the Mukaiyama or the Palomo Reagents,- A mixture of the racemic alcohol **6** (1 mmol), the chiral carboxylic acid (0.5 mmol), the condensation reagent **1** or **8** (0.6 mmol) and triethylamine (1.2 mmol) in the corresponding solvent (5 ml; see Tables 4-6 and 10-12) was stirred under argon till the process finished (monitored by GLC or TLC). To the resulting mixture was added diethyl ether (10 ml) and a 0.5 sodium hydroxide solution (10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was then chromatographied (silica gel, hexane/ethyl acetate) to give the corresponding alcohols **6** and the esters **7**. Reaction times, yields, $[\alpha]_D$ values, e.e and d.e. percentages are collected in Tables 4-6 and 10-12[20].

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