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PHASE TRANSFER CATALYSIS USING CHIRAL CATALYSTS. V. ASYMMETRIC NUCLEOPHILIC SUBSTITUTIONS WITH C, O, N AND S-ANIONS

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Summary: Several asymmetric nucleophilic substitutions with C, N, O and S-anions have been performed under PTC conditions using chiral quaternary ammonium salts as PT catalysts.

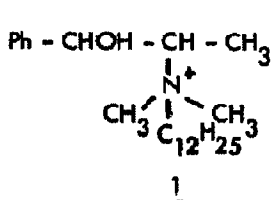
The use of chiral phase-transfer catalysts in the synthesis of optically active compounds has been a matter of interest in recent years. The application of these catalysts has been mainly reported in two areas: a) Asymmetric synthesis[1-5] and b) Kinetic resolution[6,7]. However, in spite of their synthetic interest, only three examples of asymmetric nucleophilic substitutions have been reported by these PTC methods[4,5,6].

In this paper we wish to communicate some new examples of both asymmetric synthesis and kinetic resolution in nucleophilic displacement reactions of alkyl halides by C, O, and S-anions (reactions a and b), in the presence of chiral quaternary ammonium salts derived from ephedrine (1) or china alkaloids (cinchonidine 2a, cinchonine 2b, quinine 2c).

a) $Br-CH(Y)(CH_3) + X^- \xrightarrow{cat.} X-CH(R)(CH_3) + Br^-$

$X^- = Ph-O^-,\ Ph-COO^-,\ Ph-S^-$; $Y = -COOC_2H_5,\ -C_2H_5$

b) $R_1R_2R_3CH + R-X \xrightarrow[OH^-]{cat.} R_1R_2R_3C-R + XH$



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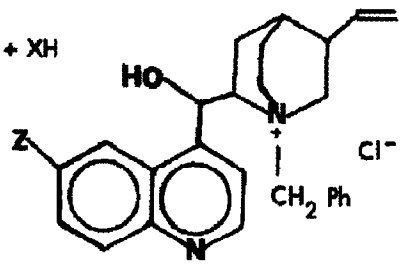


2a Z = H C_8 (S) C_9 (R)
2b Z = H C_9 (R) C_8 (S)
2c Z = OCH_3 C_8^9 (S) C_9^8 (R)

In the first set of experiments (Table 1), we essayed the reaction of (±)-ethyl 2-bromopropionate with phenoxide (exp. 1-4), benzoate (exp. 5-6) and thiophenoxide (exp. 7-9) anions. For comparative purposes, some of our previously reported[5] results of the N-alkylation of this substrate with potassium phthalimide, are included. If (±)-bromobutane is used as substrate the reaction only takes place when the nucleophile is thiophen-

oxide (Table 1, exp. 9). In these examples it must be emphasized that the nucleophilic substitution occurs at a chiral C-atom.

TABLE 1

Exp. No.	X^-	Y	Catalyst	Solvent	Yield[a,b]	α_D^{20}	O.P.(%)	Remarks
1	PhO^-	COOEt	2a	MC	10	1.055	2.4 (R)	c, g, j, l
2	PhO^-	COOEt	2a	T	36	0.158	0.36 (R)	c, g
3	PhO^-	COOEt	2b	MC	9	-1.026	2.3 (S)	c, g, k
4	PhO^-	COOEt	1	MC	10	0.013	0.03 (R)	c, g
5	$PhCOO^-$	COOEt	2a	D	8	-0.84	3.44 (R)	d, g, m
6	$PhCOO^-$	COOEt	2a	MEK	30	-0.262	1.06 (R)	d, g
7	PhS^-	COOEt	2c	B	41	1.81	1.00 (R)	e, h, n
8	PhS^-	COOEt	2c	B	50	0.54	0.30 (R)	e, n
9	PhS^-	Et	2c	B	7	1.77	-	f, i
10	$Phth^-$	COOEt	2a	T	23	-1.80	9.5 (S)	n, k
11	$Phth^-$	COOEt	2b	T	28	3.62	19.1 (R)	n, j

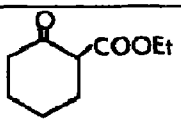
MC: methylene chloride; MEK: methyl ethyl ketone; D: dioxane; B: benzene; T: tetrahydrofuran ; $Phth^-$: Phthalimide

a) All products show physical constants, IR and ^{1}H-NMR spectra identical to those reported in the literature. Reactions were performed under S-L conditions except Exp. 7 (L-L).
b) Isolated by vacuum distillation or silicagel column chromatography.
c) 1% mol catalyst, 4 hr, reflux.
d) 2% mol catalyst, 4 hr, reflux.
e) 5% mol catalyst, 5 hr, room temperature.
f) 5% mol catalyst, 5 hr, reflux.
g) neat.
h) c = 10, MeOH.
i) c = 15, Cl_3CH.
j) prevailing enantiomer recovered (R).
k) prevailing enantiomer recovered (S).
l) α_D max 44.0 (neat)[8,9].
m) α_D^{24} max 24.4 (neat)[9].
n) o.p. determined by the acid hydrolysis to the acid 2-thiophenoxypropionic α_{max} = 170.3 (neat)[10]. This value is according to that calculated by ^{1}H-NMR spectra in the presence of $Eu(tfc)_3$ as shift reagent.

As seen from Table 1, optically active compounds have been obtained in all of the cases. The results show that these processes present the same general patterns previously observed when phthalimide anion was used[4] (exp. 10, 11). Thus, a) There is a kinetic resolution of racemic substrate induced by the chiral ion pair formed by the chiral ammonium cation and the reactant anion. This is demonstrated by the recovery of unreacted optically active substrate (exp. 1, 2, 10, 11). Moreover, the reaction occurs with partial inversion of configuration, recovered substrate and alkylated product both having the same configuration. b) The use of diastereomeric cat-

alysts (2a and 2b) determines the prevailing enantiomer (exp. 1, 3 and 10, 11). c) The catalysts derived from china alkaloids seem more stereoselective than ephedrinium salts in these type of reactions (exp. 1 and 4). d) Stereoselectivity is affected by the polarity of the solvent (exp. 1, 2, 5, 6). However, in contrast to the N-alkylation (exp. 10, 11) the enantioselectivity is of the same order in O-alkylation with phenoxide using both cinchonidinium (exp. 1) and cinchoninium catalyst (exp. 3).

TABLE 2

Exp. No.	Substrate	R-X	Catalyst (% molar ratio)	Yield[a,b]	α_D^{20}	O.P.(%)	Remarks
12	 3	$PhCH_2Cl$	2c (5%)	50	-0.926		b, e
13		$PhCH_2Cl$	1 (5%)	40	-3.558	7±3	b, c, e
14		$PhCH_2Cl$	2c (5%)	35	-4.50		b, d, e
15	$PhCH_2CN$ 4	EtBr	2c (1%)	75	0		f, g
16		EtBr	1 (10%)	84	0		f, g
17	Ph-CH-CN C_2H_5 5	$PhCH_2Cl$	2c (5%)	87	0.240		b
18		$PhCH_2Cl$	1 (5%)	69	0.453		b
19		CH_3I	1 (5%)	44	-0.051	0.7 (S)	h, i

a) All products show physical constants, IR and ^{1}H-NMR spectra identical to those reported.
b) Product isolated by silicagel column chromatography.
c) Enantiomeric excess measured by ^{1}H-NMR with Eu (tfc)$_3$.
d) Benzyl chloride in 50% molar ratio to substrate.
e) c = 5-10, Cl_3CH.
f) Isolated by vacuum distillation.
g) Neat.
h) Isolated by vacuum distillation followed by silica-gel column chromatography.
i) Determined by acid hydrolysis to phenylbutyric acid[12].

C-alkylation enables a different kind of PTC asymmetric nucleophilic displacement. Table 2 shows the results we obtained in the C-alkylation of three C-acidic compounds. Ethyl 2-oxocyclohexanecarboxilate and phenylacetonitriles were alkylated according to the general method of M. Makosza[9] using the chiral catalysts 1 or 2c. From the results some considerations should be pointed out:

a) In contrast to the former reactions, the chiral C-atom in this case is provided by the C-acidic compound and the alkyl halide is achiral. In order to know the mechanism of the asymmetric alkylations, compound 3 was used in 50% molar excess to benzyl chloride (exp. 14). Recovery of unreacted 3 without optical activity shows that there is no kinetic resolution in this reaction, but an asymmetric synthesis induced by the chiral reactant ion pair (achiral carbanion-chiral ammonium cation).

b) The differences between results of the alkylation of compounds 4 (exp. 13, 14) and 5 (exp. 15-17) are significant. C-alkylation of 5 yields optically active products in contrast to C-alkylation of 4. The latter result

can be explained by the racemization of the alkylated product (ethylphenylacetonitrile) via the remaining acidic C-H bond, in the strongly basic media.

Though the optical purity reached is low, it must be emplasized that asymmetric C-alkylations of compound 5, constitute, to the best of our knowledge, the first instance of this kind of reaction, and it may be an interesting approach to the synthesis of a large number of chiral compounds. Further work in this area is in progress.

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