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Asymmetric Catalytic Alkylation of 4-Chlorophenylacetic Acid

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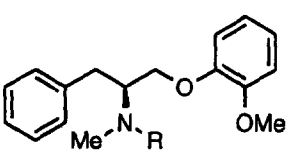
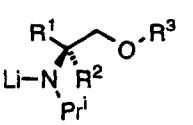
Abstract: Using N-(monoalkyl)-α,β-diphenyl-β-hydroxy ethylamine as chiral ligands, 46.2% enantiomeric excess was obtained in the asymmetric catalytic alkylation of 4-chlorophenyl acetic acid.

It is well known that asymmetric catalytic alkylation is a very difficult problem in synthetic organic chemistry, if you want to get a high e.e. of the alkylated products in the reactions. Several years ago, Tomioka et.al.[1] reported that for the asymmetric alkylation of cyclohexanone using benzyl halide as alkylating agents and amino ether (1) as the chiral ligand, the e.e. values of the products were between 23 - 51%. Lower values of 2-24% e.e. were obtained by Ando and Shioiri[2] in the alkylation of the acid with compound (II) as the chiral induction agent.



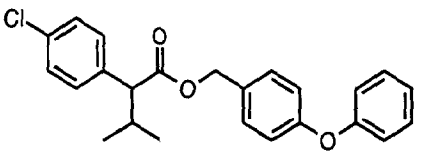
I



II

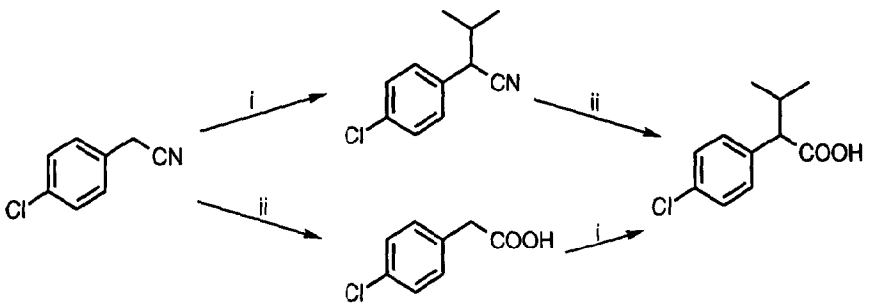
Recently, O'Donnell and Wu utilized a chiral phase transfer catalyst in the alkylation reaction. The e.e. values obtained were between 16% and 50%.[3] From these three examples, we see that induction with a single stereogenic centre is not effective in this asymmetric alkylation. So Jiang et. al.[4] obtained high e.e. (up to 98%) via double chiral induction.

In the synthesis of Fanvalerate (III), α-isopropyl-4-chlorophenylacetic acid is an important intermediate. When its configuration is S-(+), the insecticidal activity is higher than that of R-(-)enantiomer. The non-racemic α-isopropyl-4-chlorophenylacetic acid usually comes from resolution of racemic acid. Herein we put forward a new asymmetric synthesis method.



III

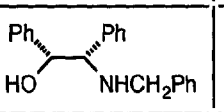
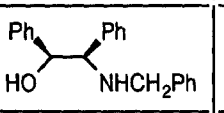
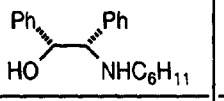
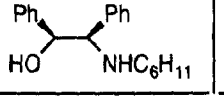
Using 2-iodopropane as the alkylating reagent, we studied the alkylation of 4-chlorophenylacetic acid and 4-chlorophenyl acetonitrile under the influence of chiral amino alcohol ligands. The e.e. values were 2-46.2% and the routes are as follows:



Scheme: Reagents i) ligand, ^{i}PrI, nBuLi, THF; ii) H_2SO_4, Δ, CH_3COOH

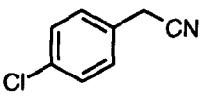
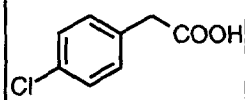
Four chiral amino alcohol ligands, which were prepared by literature methods, were used in these alkylations.[5] They also can be recovered from the reactions and their optical activities are maintained. Their specific rotations and recovery yields are summarized in Table 1. The results of the reactions can be found in Table 2.

Table 1: Specific rotations and recovery yields of the four ligands

Number	Ligand	$[\alpha]_D^{20}$ (c, CH_2Cl_2)	configuration	recovery yield (%)	$[\alpha]_D^{20}$ (c, CH_2Cl_2)[a]
1		+13.25 (0.8)	D/1R,2S	84	+13.25 (0.6)
2		-13.05 (0.78)	L/1S,2R	71	-12.7 (0.6)
3		+37.15 (0.37)	D/1R,2S	/[b]	/[b]
4		-35.25 (0.40)	L/1S,2R	71	-34.8 (0.88)

a. After recovery; b. Ligand **3** was not recovered

Table 2: Results of asymmetric alkylations

Reactant[a]	ligand	Reaction conditions[b]	C.Y.[d](%)	$[\alpha]_D^{20}$ (c, C_6H_6)[f]	e.e.[e] (%)	configu-ration
	2	-50°C, 48hrs	24.7	+9.8 (0.52)	19.2	S
	3	-50°C, 48hrs	41.2	+5.9 (1.4)	11.5	S
	4	-70°C, 64hrs	23.5	+3.9 (1.2)	7.6	S
	1	-60°C, 64hrs r.t.,[c]	60	+1 (1.5)	2.0	S
	2	-60°C, 64hrs r.t., 32hrs	44.7	+15 (1.2)	29.4	S
	3	-60°C, 64hrs r.t., 32hrs	33	+6.1 (0.75)	11.9	S
	4	-70°C, 64hrs	49.6	+23.6 (0.68)	46.2	S

a. The molar ratio of reactant: ligand: n-BuLi is 1:1.2:2.4 for reactant 4-chlorophenyl acetonitrile and it is 1:2:4 for 4-chlorophenyl acetic acid.

b. All reactions are run in THF pretreated by refluxing over Na and diphenyl ketone protected by high purity N_2.

c. The room temperature is about 15°C.

d. When reactant is 4-chlorophenyl acetonitrile, the chemical yields are overall yields of two steps, both alkylation and hydrolysis, but for the others, they are yields only of alkylations.

e. Calculated by comparison of the values of specific rotations with known data $[\alpha]_D^{20} = 47$ (e.e. = 92%).[6]

f. The optical rotations were determined after recrystallization.

Experimental

Melting points were measured on a digital electrothermal melting point apparatus. Infrared spectra were recorded on a Microlab 620 MX spectrometer, ^1H NMR spectra were recorded by using a Varian FT-80 and a Bruker-200 NMR spectrometer, chemical shifts were measured in ppm relative to TMS as an internal standard. The elemental analyses were obtained on a Carlo Erba-1106 automatic analyzer. The optical rotations were determined on a Perkin-Elmer 241 automatic polarimeter.

General procedure for the alkylation.

Chiral amino alcohol ligand was dissolved in dry THF, stirred for a few minutes under N_2 atmosphere, then n-BuLi was added before cooling to -30°C. The mixture was stirred for 3 hrs at -30°C before cooling to -78°C, adding 4-chlorophenyl acetic acid or 4-chlorophenylacetonitrile both as solutions in THF. Stirring for 2 hrs 2-iodopropane was added. When the reaction was finished, the mixture was quenched with 10% NH_4Cl aqueous solution and stirred for 1 hr, then the ligand was precipitated and filtered. The filtrate was extracted with ether. The combined organic extracts were washed with 2N HCl aqueous, followed by H_2O to neutral. The solution was dried (Na_2SO_4) and evaporated under reduced pressure. The light yellow solid was obtained and recrystallized from benzene.

The hydrolysis of 4-chlorophenyl acetonitrile and 2-(4-chlorophenyl)-3-methyl butylnitrile can be carried using methods.

4-chlorophenyl acetic acid: C.Y. 86.7%, m.p. 107.5 - 109.5°C: I.R. 3200 - 2600 cm^{-1} (-OH), 1700 cm^{-1} (S): ^1H NMR 8.8 ppm (br, 1H), 7.3 ppm (m, 4H), 4.9 ppm (S, 2H).

α-isopropyl-4-chlorophenyl acetonitrile: IR. 2960 - 2860 cm^{-1}, 1380 cm^{-1}: ^1H NMR. 7.2 ppm (m, 4H), 3.1 ppm (d, 1H), 2.05 ppm (m, 1H), 1.0 ppm (d, 6H).

α-isopropyl-4-chlorophenyl acetic acid: m.p. 87.5 - 89.5°C: IR. 2600 -3200 cm^{-1} (-OH), 1700 cm^{-1} (S): ^1H NMR 8.7 ppm (br, 1H), 7.2 ppm (m, 4H), 3.15 ppm (d, 1H), 2.25 ppm (m, 1H), 1.05 ppm (d, 3H), 0.7 ppm (d, 3H): MS (m/z). 212 (M^+), 170 (100%), 125: Anal. Calcd for $C_{11}H_{13}O_2Cl$: C%, 62.12; H%, 6.16 found C%, 62.23; H%, 5.96.

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