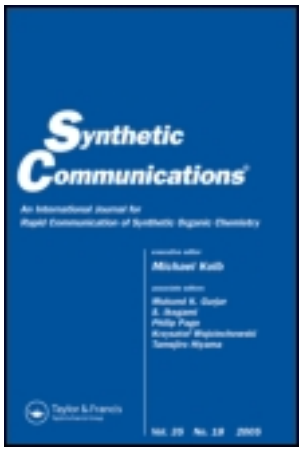

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RESOLUTION OF CHIRAL ALIPHATIC AND ARYLALKYL AMINES USING IMMOBILIZED CANDIDA ANTARCTICA LIPASE AND ISOLATION OF THEIR R- AND S-ENANTIOMERS

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RESOLUTION OF CHIRAL ALIPHATIC AND ARYLALKYL AMINES USING IMMOBILIZED *CANDIDA ANTARCTICA* LIPASE AND ISOLATION OF THEIR R- AND S-ENANTIOMERS

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ABSTRACT

The resolution of chiral aliphatic and arylalkyl amines in high enantiomeric excess (up to 97.5% ee for the R-enantiomers and up to 99.9% ee for the S-enantiomers) and good yield (50–80%) using immobilized *Candida antarctica* lipase and ethyl acetate as acyl donor has been demonstrated. A second resolution on the R-amine increased the enantiomeric excess to more than 99.5% (up to 99.9%).

In conjunction with a drug development program, a cost-effective method of obtaining the enantiomers of chiral 2-alkylamines in very high enantiomeric excess (99.0% minimum, preferably >99.5%) was required. Optically pure enantiomers of chiral amines have been prepared by a variety of methods (1), including

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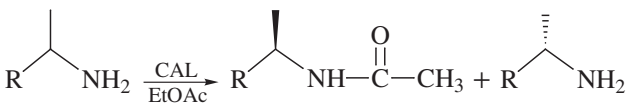
multi-step transformations starting from optically pure amino acids (2–5), the resolution of racemic mixtures via multiple fractional recrystallizations of diastereomeric complexes with chiral acids (6–9), and kinetic resolution of racemates by enzyme-catalyzed acyl transfer reactions (10–20). In addition to the numerous steps involved and the risk of racemization, transformations from optically pure amino acids suffer from the disadvantages that the starting materials, if commercially available, are usually expensive and may not be available in the required optical purity. Fractional recrystallizations of diastereomeric complexes are tedious and very inefficient. The major disadvantages of enzymatic resolutions, namely, the relatively low purity of the commercial natural enzyme preparations and their expense, have been overcome in recent years for some enzymes with the introduction of very pure, re-usable, immobilized enzymes, which function well in many organic solvents. Several enzymes have been studied for their efficiency in kinetic resolution of chiral amines, including *Pseudomonas aeruginosa* lipase (11), *subtilisin* (10,12,21) and *Candida antarctica* lipase(13–17,19,20).

Candida antarctica lipase (CAL) in an immobilized form (Novozym 435) has been demonstrated to be a versatile catalyst in acyl transfer reactions with amines in non-aqueous media using simple procedures (Scheme). It has been shown to catalyze selectively the acylation of the R-enantiomer of 2-butylamine (13,15,16), 2-pentylamine (17), 2-heptylamine (13,15,16) and 2-octylamine (14), as well as 1-phenylethylamine (13–17), utilizing a variety of acyl donors in several organic solvents, giving products in poor to moderate yields (25–75%) and good to high enantiomeric excess (up to 98%). The best results in terms of % yield and enantiomeric excess of the R-enantiomer have been obtained for 2-heptylamine (79% and >95% ee, respectively) and 1-phenylethylamine (84% and 95% ee) using methyl 3-phenylpropanoate as acyl donor and di-isopropyl ether as solvent (13). This acyl donor, however, is expensive and the excess is difficult to remove (b.p. = 238°C). Resolution of 2-pentylamine to 98% ee with ethyl acetate, which is both inexpensive and easy to remove, as acyl donor has been demonstrated, but at a conversion of only 44% (17).

None of the reported procedures met our criteria of good yield and very high enantiomeric excess of both enantiomers (in the cited papers, the S-enantiomers were not isolated), ease of work-up, and use of inexpensive reagents. In this paper we report procedures that realize these objectives.



R = ethyl, propyl, pentyl, hexyl, nonyl, phenyl

Scheme.

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Table 1. Kinetic Resolution of Racemic Aliphatic Amines (R-Enantiomers)

Amine	Solvent	Reaction Time (days)	% Yield (product)	% ee R
2-Butyl	Hexane	2	26	70.0
	Ether	2	43	67.2
2-Pentyl	Hexane	2	48	97.2
	Ether	2	58	97.2
	Et_3N	2	70	95.4
	EtOAc	1	72	92.9
2-Hexyl	Ether	2	71	94.8
	EtOAc	1	75	84.8
2-Heptyl	Hexane	2	63	96.0
	Ether	2	80	95.6
	THF	2	76	95.2
	Et_3N	1	74	95.4
	EtOAc	8 h	66	95.2
2-Octyl	Hexane	2	70	97.6
	Ether	2	99	96.2
	EtOAc	1	93	92.0
2-Undecyl	Ether	1	80	96.5
	EtOAc	16 h	86	90.4

RESOLUTION AND ISOLATION OF THE R-ENANTIOMER

Effect of Solvent and Reaction Time on Enantioselectivity and % Yield

The effect of solvent and reaction time on % yield and enantiomeric excess for the acylation of 2-heptylamine by ethyl acetate was examined for five solvents (hexane, diethyl ether, tetrahydrofuran, triethylamine, ethyl acetate) and a range of reaction times (8 hours to 7 days). Similar but less extensive experiments were carried out for the other chiral amines. Conditions for the highest % ee are summarized in Tables 1 and 2.

The possibility that non-enzymatic (and therefore non-stereoselective) acylation may occur was investigated. After 7 days at room temperature, a solution of (RS)-2-heptylamine in ethyl acetate (without Novozym 435) gave only a trace of product (<0.3%).

Increase in Enantiomeric Excess After Second Resolution

No combination of reaction conditions gave enantiomeric excesses of the R-enantiomers that met requirements. In order to enhance the % ee, a second

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Table 2. Kinetic Resolution of Racemic Arylalkyl Amines (R-Enantiomers)

Amine	Solvent	Reaction Time (days)	% Yield (product)	% ee R
1-Phenylethyl	Ether	2	71	81.4
	EtOAc	1	59	80.4
	Et_3N	1	41	86.4
1-Phenyl-2-propyl	Ether	2	66	85.8
	EtOAc	1	62	82.6
	Et_3N	31 h	56	88.9

resolution was carried out. The amide product of the first resolution was hydrolyzed to the hydrochloride salt of the primary amine, which was converted to the free base and treated again with ethyl acetate and Novozym 435. Three methods of converting the salt to the free base were investigated: (a) basification with aqueous NaOH, extraction with ether and distillation of the free amine; (b) basification with aqueous NaOH, extraction with ether, and use of the extract for the second resolution; and (c) treatment of the hydrochloride salt with triethylamine in ether, filtration of the triethylamine hydrochloride, and then use of the filtrate for the second resolution. The results for 2-heptylamine are summarized in Table 3. Method C is preferred for the isolation of the free bases of 2-butylamine, 2-pentylamine, and 2-hexylamine, the volatility and solubility in water of which markedly reduced the efficiency of methods A and B. For 2-octylamine, 2-undecylamine, and for the arylalkylamines, the simpler and faster Method B is preferred over Method C. 2-Butylamine requires a third resolution to reach an enantiomeric excess of 99.0%.

Removal of Unreacted Substrate

Unreacted substrate was removed either by oxalate precipitation or by silica gel chromatography. The precipitation of unreacted substrate as the oxalate salt was

Table 3. Effect of Second Resolution on Enantiomeric Excess for 2-Heptylamine (R-Enantiomers)

Method	Reaction Solvent	Reaction Time (h)	% ee (initial)	% ee (final)	%Yield (amide)
A	Hexane	72	90.6	99.7	65
A	Ether	72	90.6	>99.9	81
A	Et_3N	40	90.6	>99.9	81
B	Ether	48	87.3	99.6	54
C	Et_3N/ether	96	87.3	99.4	61

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used routinely for all the amines because these salts, which are essentially insoluble in ether, THF, hexane, and ethyl acetate, provide superior recovery. Excess oxalic acid was removed from the acetylated product in the filtrate during the subsequent isolation and purification of the free (R)-amine by hydrolysis, basification, and extraction.

Alternatively, if the presence of excess oxalic acid in the N-acetyl product was undesirable, the filtered reaction solution was added directly to a silica gel column. Unreacted substrate, which is retained on the column during elution of the amide product with hexane:ethyl acetate, was recovered in quite good yield (60–70% for 2-heptylamine) by elution with methanol into methanolic HCl. This method was unsuitable when reaction solvent was triethylamine; evaporation of the solvent prior to loading onto the column resulted in substantial or complete loss of substrate.

RESOLUTION AND ISOLATION OF THE S-ENANTIOMER

The effect of reaction time on % recovery and enantiomeric excess of unreacted (S-enriched)-substrates (recovered as the oxalate) was examined for two solvents, diethyl ether and ethyl acetate (Table 4). With ethyl acetate as solvent, enantiomeric excess improved with increasing reaction time such that, for example, after 14 days the R-enantiomer of 2-heptylamine was essentially undetectable.

Table 4. Kinetic Resolution of Racemic Aliphatic and Arylalkyl Amines (S-Enantiomers)

Amine	Solvent	Reaction Time (days)	Recovery (%)*	% ee (S)
2-Butyl	EtOAc	7	38	94.2
2-Pentyl	EtOAc	7	82	99.8
2-Hexyl	EtOAc	7	84	99.1
2-Heptyl	Ether	21	94	99.6
	EtOAc	5	91	99.4
	EtOAc	14	81	>99.9
2-Octyl	EtOAc	5	94	99.8
2-Undecyl	EtOAc	7	86	99.4
1-Phenylethyl	EtOAc	10	73	93.8
	EtOAc	21	46	99.0
1-Phenyl-2-propyl	EtOAc	10	72	86.7
	EtOAc	21	46	93.6

*% recovery of the theoretical amount of S-enantiomer.

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EXPERIMENTAL

Materials

Candida antarctica lipase (Novozym 435) was a gift from Novo Nordisk A/S (Denmark)/Novo Nordisk BioChem North America, Inc. Racemic 2-butylamine, 2-pentylamine, 2-heptylamine, 2-octylamine, and 1-phenylethylamine were purchased (Lancaster Synthesis, Inc.). Racemic 2-hexylamine, 2-undecylamine and 1-phenyl-2-propylamine were synthesized from 2-hexanone, 2-undecanone, and 1-phenyl-2-propanone, respectively, by lithium aluminum hydride reduction of their oximes. All solvents were reagent grade (Caledon Laboratories Ltd., Edmonton, Canada). Silica gel (70–230 mesh, 60A) and lithium aluminum hydride were purchased from the Aldrich Chemical Co.

Enantiomeric Analysis

The enantiomeric purity of the products (after hydrolysis) and of recovered substrates was determined by derivatization of the amine (R-amine hydrochloride or S-amine oxalate) with (S)-N-trifluoroacetylprolyl chloride and separation of the diastereomers by gas chromatography on a chiral column (22).

General Procedure: Resolution of (RS)-2-Alkylamines and Arylalkylamines

The (RS)-2-alkylamine or arylalkylamine (2 mmol) was dissolved in an organic solvent (5 mL) and then ethyl acetate (8 mmol, 800 uL) and Novozym 435 (100 mg) were added. The mixture was gently shaken for the specified time at room temperature (21°C). The reaction was terminated by suction filtration of the enzyme, which was washed with diethyl ether (2 × 3 mL) and ethyl acetate (2 × 3 mL). [Novozym 435 is re-usable: even after 4 uses, each for 48 h, no reduction in % yield or enantiomeric purity was observed].

The combined filtrates were loaded onto a silica gel column (4 g), and the R-amide was eluted with hexane:ethyl acetate (1:1). Unreacted substrate was then eluted with methanol into methanolic HCl. The (R)-amide was hydrolyzed by refluxing in concentrated hydrochloric acid for 48 h at 135°–140°C. After rotary evaporation, the residue was taken up in water, extracted with ethyl acetate (to remove unhydrolyzed amide), and the aqueous solution was evaporated to give the R-amine hydrochloride.

Experimental data for characterization of the isolated (R)-amine hydrochlorides (all of which are known compounds) are: observed m.p. (solvent of recrystallization); literature m.p.; MH + [MS-CI (isobutane)]: **(R)-2-butylamine. HCl:**

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153.5°–154°C (methanol/ether); 151°–152°C (24); MH^+, 74. **(R)-2-Pentylamine. HCl:** 175.5°–176°C (methanol/ether); 168°C (racemate)(23); MH^+, 88. **(R)-2-hexylamine. HCl:** 106°–107°C (methanol/ether); 102°–103°C(23); MH^+, 102. **(R)-2-heptylamine.HCl:** 100°–101°C (hexane); 81°–83°C (racemate)(23) MH^+, 116. **(R)-2-octylamine.HCl:** 89°–90°C (hexane); 90°–91°C(23); MH^+, 130. **(R)-2-undecylamine.HCl:** 85°C (hexane); 84°C (racemate)(23); MH^+, 172. **(R)-1-phenylethylamine.HCl:**171.5°–172°C (methanol/ether); 171°–173°C(25); MH^+, 122; also m/z 106, 105. **(R)-2-phenylisopropylamine.HCl:** 154°–155°C (methanol/ether); 156°C(23); MH^+, 136.

Each of the alkyl and arylalkylamines (as the trifluoroacetyl-L-prolyl derivative) and N-acetyl amides was further characterized by comparison of its gas chromatographic retention time to that of an authentic sample.

Alternatively, the filtrates were added to a solution of oxalic acid (180 mg, 2 mmol) in ether (15 mL), and the oxalate salt was filtered and washed with ether. The filtrates were rotary evaporated at 70°C, the residue was loaded onto a column of silica gel (4.0 g), and the N-acetyl amide (enriched in the R-enantiomer) was eluted with hexane:ethyl acetate (1:1) (some of the excess oxalic acid also elutes under these conditions).

Experimental data for characterization of the (S)-amine oxalates (recrystallized from methanol-ether), all of which are new compounds, are: **(S)-2-butylamine.oxalate**: 152.5°–153°C; ^{1}NMR (D_2O): δ 0.80 (t, 3H, terminal C**H**$_3$), δ 1.15 (d, 3H, α-C**H**$_3$), δ 1.48 (m, 2H, β-C**H**$_2$), δ 3.15 (m, 1H, α-C**H**). Elemental analysis: calculated (found): %C = 44.17 (44.14); %H = 8.03 (8.15); %N = 8.58 (8.38).

(S)-2-pentylamine.oxalate: 149°–150°C; ^{1}NMR (D_2O): δ 0.80 (t, 3H, terminal C**H**$_3$), δ 1.15 (d, 3H, α-C**H**$_3$), δ 1.27 (m, 2H, γ-C**H**$_2$), δ 1.41 (m, 2H, β-C**H**$_2$). δ 3.22 (m,1H, α-CH). Elemental analysis: calculated (found): %C = 47.45 (47.54); %H = 8.53 (8.76); %N = 7.90 (7.81).

(S)-2-hexylamine.oxalate: 141°–143°C; ^{1}NMR (D_2O): δ 0.78 (t, 3H, terminal C**H**$_3$), δ 1.14 (d, 3H, α-C**H**$_3$), δ 1.21 (m, 4H, γ,δ-C**H**$_2$), δ 1.47 (m, 2H, β-C**H**$_2$), δ 3.21 (m, 1H, α-C**H**). Elemental analysis: calculated (found): % C = 50.25(50.04); %H = 8.96 (8.71); % N = 7.32 (7.18).

(S)-2-heptylamine.oxalate: 103°–104°C; ^{1}NMR (D_2O): δ 0.75 (t, 3H terminal C**H**$_3$), δ 1.05–1.30 (m, 9H, α-C**H**$_3$) plus γ,δ,ϵ-C**H**$_2$), δ 1.45 (m, 2H, β-C**H**$_2$), δ 3.21 (m, 1H, α-C**H**). Elemental analysis: calculated (found): %C = 52.67 (52.30); %H = 9.33 (9.15); %N = 6.82 (6.61).

(S)-2-octylamine.oxalate: 109°–111°C; ^{1}NMR (D_2O): δ 0.74 (t, 3H, terminal C**H**$_3$), δ 1.05–130 (m, 11H, α-C**H**$_3$) plus γ,δ,ε,ϕ-C**H**$_2$,) δ 1.44 (m, 2H, β-C**H**$_2$), δ 3.19 (m, 1H, α-C**H**). Elemental analysis: calculated (found): %C = 54.77 (54.01); %H = 9.65 (9.98); %N = 6.39 (6.19).

(S)-2-undecylamine.oxalate: 103°–107°C; ^{1}NMR (D_2O): δ 0.72 (t, 3H, terminal C**H**$_3$), δ 1.05–1.30 (m, 17H, α-C**H**$_3$) plus (7 × C**H**$_2$), δ 1.48 (m, 2H,

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β-C**H**$_2$), δ 3.20 (m, 1H, α-C**H**). Elemental analysis: calculated (found): %C = 59.74 (59.10); %H = 10.41 (9.20); %N = 5.36 (5.30).

(S)-1-Phenylethylamine.oxalate (amine:oxalate 2:1): 225°–226°C; ^{1}NMR (D_2O): δ 1.52 (d, 3H, α-C**H**$_3$), δ 4.41 (q, 1H, α-C**H**), δ 7.37 (s, 5H phenyl **H**). Elemental analysis: calculated (found): %C = 65.04 (64.66); %H = 7.28 (7.48); %N = 8.43 (8.15).

(S)-1-phenylisopropylamine.oxalate: 170°–171°C; ^{1}NMR (D_2O): δ 1.20 (d, 3H, α-C**H**$_3$), δ 2.81 (d, 2H, β-C**H**$_2$), δ 3.50 (m, 1H, α-C**H**), δ 7.27 (m, 5H, phenyl **H**). Elemental analysis: calculated (found): %C = 58.66 (58.21); %H = 6.71 (7.28); % N = 6.22(6.06).

Methods for Converting the Amine Salt to the Free Amine for Second Resolution

(A) Aqueous Basification of the Amine Salt and Isolation by Distillation

The (R)-amide (200 mmol) was hydrolyzed by refluxing in concentrated hydrochloric acid (150 mL) for 48 h at 135°–140°C. After rotary evaporation, the residue was taken up in water, extracted with ethyl acetate (to remove unhydrolyzed amide), and the aqueous solution was evaporated. The residue was suspended in ether/water (300/100 mL) and stirred vigorously while adding 50% NaOH (60 mL). The mixture was shaken vigorously and the aqueous layer extracted once more with diethyl ether (70 mL). The extracts were dried over $MgSO_4$, concentrated, and distilled (for 2-heptylamine, yield 70%). The amine was then enzymatically resolved and the acyl product isolated as described in the General Procedure.

(B) Aqueous Basification of Amine Salt Without Isolation of Free Amine

The amide (2 mmol) was hydrolyzed by refluxing in concentrated hydrochloric acid (15 mL) for 48 h at 135°–140°C. After rotary evaporation, the residue was taken up in water, extracted with ethyl acetate, and then the aqueous solution was evaporated. The residue was dissolved in 50% NaoH (1 mL) and the amine was extracted by vortex mixing with diethyl ether (3 × 2 mL). The extracts were dried over $MgSO_4$, and then treated with ethyl acetate and Novozym 435; the product was purified in the usual way.

(C) In situ Basification with Triethylamine in an Organic Solvent

The R-amine hydrochloride or the S-amine oxalate (2 mmol) was neutralized in situ by gentle shaking for 3 h with an excess of triethylamine (2.5 mL) in ether

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(5 mL). The precipitated triethylamine hydrochloride (or oxalate) was filtered and washed with ether (2.5 mL). The combined filtrate was treated with ethyl acetate and Novozym 435, and the product isolated in the usual way.

CONCLUSION

Candida antarctica lipase (Novozym 435) with ethyl acetate as acyl donor in an organic solvent constitutes a simple method for the resolution of several chiral aliphatic and arylalkyl amines on both small and large scales. Conditions are described permitting both *R*- and *S*-enantiomers to be isolated in good yield with enantiomeric excess up to 99.9%.

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