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Kinetic Resolution of 3-tButyl and 3-Phenyl Cyclobutylidenethanols through Lipase-catalyzed Acylation with Succinic Anhydride.

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Key words: Lipase-catalyzed resolution; axially chiral allylic alcohols; succinic anhydride.

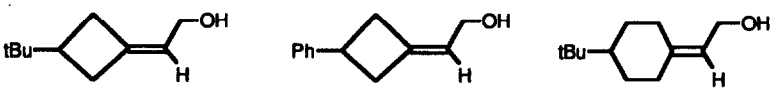
***Abstract**: Optically enriched (3-t-butyl) and (3-phenylcyclobutylidene)ethanols were readily obtained through kinetic resolution of the racemates by lipase-catalyzed acylation with succinic anhydride; the procedure is of practical use and does not require a chromatographic separation.*

The preparation of optically active alcohols by enantioselective lipase-catalyzed acylation of racemic material in organic solvents is well documented and has been widely used.[1] The efficiency (in terms of stereoselectivity, expressed as the E value[2]) of the resolution is often dependent upon the nature of the lipase and the acylating agent involved. The usual strategy to carry out such a resolution is to screen for an efficient enzyme / acylating agent couple.

For some substrates however, the recorded E values are small (typically < 5) whatever the investigated couple is. This is frequently the case for primary alcohols, where the hydroxyl group is remote from the chiral center. These alcohols may be needed optically active, even in moderate enantiomeric excess, for example to carry out stereochemical correlations (enantiomeric excesses, absolute configuration).

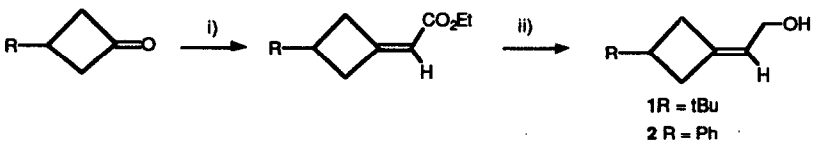
Theoretical treatment of the kinetic resolution process[2] indicates that, even though E is low, moderate to high enantiomeric purity in the unreacted substrate may be obtained provided the conversion level is high enough (typically c > 0.8), at the expense of low amounts of the amount of material recovered. A drawback of this strategy is the difficulty encountered for the separation of the desired, unreacted alcohol substrate from the ester produced in the reaction mixture. This separation is only rarely feasible by crystallization[3] or distillation[4] and is usually carried out by column chromatography.

A procedure using a cyclic anhydride (namely succinic anhydride) as an acylating agent has been described[5] and overcomes this latter difficulty. The ester produced is acidic and thus can be readily separated from the unreacted alcohol by simple base aqueous extraction. Moreover, it can be directly saponified in the aqueous phase and the enantiomeric alcohol hence isolated by solvent extraction. Although this method was originally reported for resolutions displaying high E values, we found the procedure very convenient for the easy production of alcohols having moderate to high ee, even though the E value for the resolution is small, due to the ready separation (liquid/liquid extraction) of the small amount of the unreacted alcohol from the large quantity of hemiester produced.

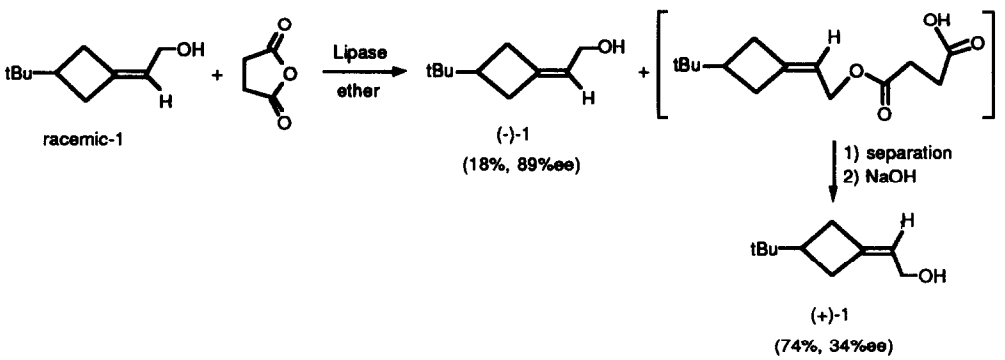


1 2 3

Only a few axially chiral hydroxylic compounds have been resolved through lipase-catalyzed hydrolysis or acylation.[6] Optically active (3-t-butylcyclobutylidene)ethanol **1** and (3-phenylcyclobutylidene)ethanol **2** were not known. We prepared racemic **1** and **2** as outlined in scheme 1. Determination of the enantiomeric excesses of **1** and **2** by ^1H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ or by ^1H NMR and hplc after derivatization to Mosher's esters[7] or 1-(1-naphthyl)ethyl carbamates[8] failed in our hands. Ee's could however nicely and accurately be measured by the use of analytical glc with modified cyclodextrin phases.[9]



Scheme 1. Preparation of 3-substituted (cyclobutylidene)ethanols.
i) NaH, $(EtO)_2(O)PCH_2CO_2Et$; ii) $LiAlH_4$ / $AlCl_3$.



Scheme 2. PFL-catalyzed acylation of **1** with succinic anhydride.

Acylations of **1** and **2** with vinyl acetate in the presence of various lipases (CCL, PPL, PFL)[10] displayed low E values. Racemic **1** and **2** were subjected to a succinic anhydride resolution performed to high conversion. A representative experiment (scheme 2) is: to 0.77g (5mmol) of racemic alcohol **1** dissolved in ether (25mL) were added 0.5 g (5mmol) of succinic anhydride and the lipase. The resulting suspension was shaken at room temperature. Conversion was monitored by glc analysis of aliquots at regular intervals (internal standard added). At the required conversion level, the enzyme was removed by filtration through a celite plug, washed with ether and the combined ether fractions extracted with 2M Na_2CO_3 (5 mL). The organic layer was washed with water, dried ($MgSO_4$) and the solvent removed to give (-)-**1** (0.14g, 18%, 89%ee). To the combined basic aqueous extracts was added 1M NaOH (10mL) and the resulting solution stirred for 3h at room

temperature. Ether extraction afforded (+)-**1** (0.57g, 74%, 34%ee). The procedure was also applied to the preparation of optically active (3-t-butylcyclohexylidene)ethanol **3**.[11] Results are collected in the Table. For comparison, CCL and RGL[12]-catalyzed acylation of **3** with vinyl acetate showed E values of 2.

For run 4 and 6, the E values calculated from the ee's of the alcohol obtained after saponification of the hemiester are higher (2 and 4, respectively) than those (1.5 and 2) reported in the Table, which are calculated from ee's of the unreacted alcohol. These discrepancies could be explained by a partial hydrolysis of the hemiester during the carbonate extraction, reducing the ee of the unreacted alcohol and hence the corresponding calculated E value.

Table. Enantioselective Lipase-catalyzed Acylation of Alcohols **1**,**2** and **3** by Succinic Anhydride.

Run	Substrate	Lipase [a] (mg)	Reaction time	Conv.	Recovered alcohol			Alcohol obtained after saponification			E[b]
			(h)	(%)	$[\alpha]_D^{20}$	ee (%)	Yield	$[\alpha]_D^{20}$	ee (%)	Yield	
1	**1**	PFL (50)	64	77	-5.3	89[c]	18	+2.01	34[d]	74	4
2	**1**	RGL (77)	60	70	+0.47	8[d]	25	-0.27	4[d]	45	1.1
3	**2**	PFL (50)	60	80	-7.7	34[d]	19	+1.88	8[d]	75	1.5
4	**2**	RGL (50)	60	80	-8.95	40[c]	31	+3.3	15[d]	49	1.5
5	**3**	PFL (50)	6	28	-1.05	12[d]	66	+2.7	31[d]	25	2
6	**3**	PFL (50)	36	79	-5.1	58[d]	20	+1.3	15[d]	72	2
7	**3**	RGL (90)	18	59	+4.2	48[d]	40	-2.8	32[d]	57	3

a) see ref 10,12.
b) Calculated using $E = \mathrm{Log}[(1-c)(1-ee)] / \mathrm{Log}[(1-c)(1+ee)]$; $(0 < c < 1; 0 < ee < 1)$.[2]
c) Measured by chiral glc on a modified cyclodextrin capillary column.[9]
d) Calculated from the estimated maximum optical rotation for optically pure compound: **1** $[\alpha]_D^{20}$ 6.0° ± 0.2 (c 2, ethanol); **2** $[\alpha]_D^{20}$ 22.5° ± 0.5 (c 2, toluene); **3** $[\alpha]_{578}^{25}$ 8.81° ± 0.34 (c 1.45, ethanol).[11]

(3-Phenylcyclobutylidene)ethanol **2** and (3-t-butylcyclohexylidene)ethanol **3** can be prepared in moderate ee's (40% and 58%, respectively) and yields (31% and 20%), in resolutions where the E values were low (E = 1.5 and 2, run 4 and 6). At low conversion (c = 0.28), (*S*)-(+)-**3** was isolated with 31%ee in 25% yield.

For a given lipase, the E value displayed in acylation of **1**, **2**, or **3** by either vinyl acetate or succinic anhydride are not significantly different. The lipase-catalyzed acylation method using succinic anhydride as an acylating agent and performed to high conversion proves however of practical use for the resolution of racemic alcohols displaying such low E values. This method avoids also lengthy, time-consuming screening of all commercially available lipases in the search for high E value. It allowed us to perform the first preparation of (cyclobutylidene)ethanols **1** and **2** in optically active form.

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