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Resolution of racemic 1-azido-3-aryloxy-2-propanols by lipase-catalyzed enantioselective acetylation

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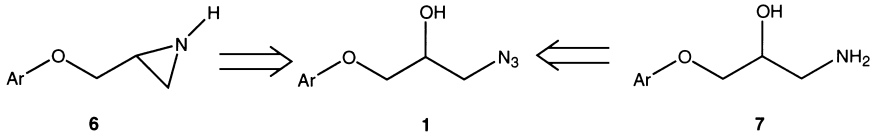
Abstract

Kinetic resolution of racemic 1-azido-3-aryloxy-2-propanols **1a**–**g** was performed using supported lipase of *Candida antarctica-B* (Novozym® SP 435) in toluene at 4°C with isopropenyl acetate as the acyl donor to afford the optically active (*S*)-alcohols **2a**–**g** and their corresponding (*R*)-acetates **3a**–**g** with *E* values from 56 to 72.

1. Introduction

During the course of our investigations dealing with bioconversions,[1] we have been interested particularly in the kinetic resolution of 1-azido-3-aryloxy-2-propanols **1** by transesterification to obtain the pure enantiomers for synthesis. These alcohols are, for instance, direct precursors of *N*–H aziridines **6** using triphenylphosphine as the cyclizing reagent[2] and of 1-amino-3-aryloxy-2-propanols **7** by reduction of the azido group[2] (Fig. 1).



6 **1** **7**

Figure 1.

This last structure is present in numerous biologically active compounds such as β-adrenolytic drugs (β-blockers), which are widely used for the treatment of angina pectoris, hypertension and

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other cardiac diseases.[3] Most of these β-blockers are still prepared and commercialized as racemates.[4] However, in numerous cases, the adrenolytic activity was found to be strongly dependent on the configuration, as for instance in propranolol (Ar = 1-naphthyl) where the (*S*)-enantiomer is much more active than the (*R*)-enantiomer which presents moreover a contraceptive activity.[5] In connection with the importance of this class of compounds, several methods have been reported for their synthesis.[6] Among the alternative routes to pure (*R*)- and (*S*)-**7**, a special interest has been devoted to direct reduction of azido moiety in 1-azido-3-aryloxy-2-propanols **1**.

The growing importance of functionalized aziridines in organic synthesis[7] and their presence in bioactive molecules[8] has created a need for synthesizing optically active aziridines. At the present time they are used as antitumor and radiation sensitizers,[9] antidiabetic compounds,[10] enzyme inhibitors,[11] chiral auxiliaries in combination with $LiAlH_4$[12] and precursors in the synthesis of several enantiopure amide-containing surfactants.[13]

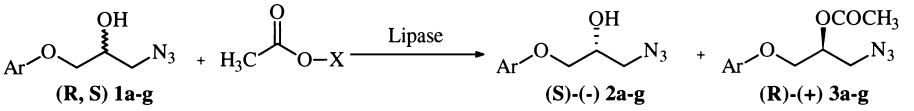
Few chemical methods have been reported for the synthesis of homochiral azido alcohols. They concern either ring-opening of epoxides[14] or the conversion of β-diols via cyclic sulphates[15] or sulphites.[16] Presently the only direct method is the one described by Matteson et al.[17] involving a great number of steps starting from homochiral pinanediol boronic esters and resulting in a low overall yield.

The enzymatic methods employed so far for their syntheses consist of:

(i) the asymmetric ring-opening of oxiranes [e.g. (*RS*) 2-methyl-2-pentyl oxirane] by azide anion with a crude immobilized enzyme preparation derived from *Rhodococcus* sp. (Novo SP 409)[18] which exhibits epoxide–hydrolase activity;
(ii) the microbiological reduction of α-azidoketones with appropriate choice of the micro-organism[2,19] such as yeasts (e.g. *Saccharomyces cerevisiae*), fungi (e.g. *Aspergillus niger*) or bacteria (e.g. *Lactobacillus kefir*);
(iii) the kinetic resolution by hydrolysis of racemic cyclic azido alcohol esters,[20] butanoates of racemic acyclic 2-azidoalkanols[21] as well as the 2-acetoxy-3-azido propanal diethyl acetal[22] with lipases from *Candida cylindracea*, *Pseudomonas fluorescens* and *Pseudomonas cepacia* (LP-80), respectively.

Surprisingly, to our knowledge, there exist only three reports on the enzymatic resolution of racemic 1-azido-3-aryloxy-2-propanols **1** and their corresponding acetates. Ader and Schneider[23] resolved racemic 1-azido-3-phenoxy-2-propanol by lipase from *Pseudomonas cepacia*-catalyzed acylation or hydrolysis of the acetate with enantiomeric ratios (*E*) of 21 and 51, respectively. 1-Azido-3-(4-*tert*-octyl)phenoxy-2-propanol[24] was similarly acylated with moderate enantioselectivity ($E = 29$). Recently,[1a] our group reported the preparation of various ring-substituted racemic azido alcohols **1** as well as their kinetic resolution by acylation using lipase from *Pseudomonas fluorescens* (Amano AK). However, only poor enantioselectivities ($E = 5$–14) were obtained, except for Ar = 1-naphthyl ($E = 41$).

Although some of the azido alcohols **1** have already been resolved by lipase-catalyzed acetylation, these cases constitute only isolated examples which demonstrate the potentiality of lipases for the preparation of such optically active compounds. To establish the general scope and applicability of this biocatalytic method, we undertook the present detailed study of the kinetic resolution by transesterification of a larger range of racemic azido alcohols **1a**–**g** (Scheme 1), investigating the influence of several parameters in order to improve the enantioselectivity described in our previous paper.[1a]

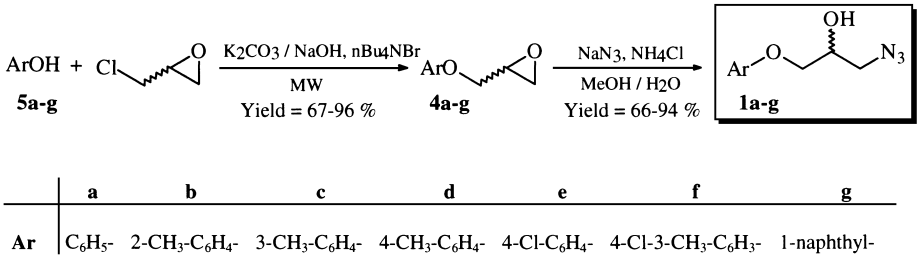


Scheme 1.

2. Results and discussion

2.1. 1-Azido-3-aryloxy-2-propanol synthesis

The racemic 1-azido-3-aryloxy-2-propanols **1a**–**g** were obtained by ring-opening of appropriate arylglycidyl ethers **4a**–**g** with sodium azide in the presence of ammonium chloride in a MeOH:H_2O (8:1 v/v) solution.[25] The latter were prepared in high yields by the Williamson reaction from the corresponding phenols **5a**–**g** and epichlorhydrin under solvent-free phase transfer catalysis coupled with microwave (MW) activation.[26] (Scheme 2)



	a	b	c	d	e	f	g
Ar	C_6H_5-	2-CH_3-C_6H_4-	3-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-Cl-C_6H_4-	4-Cl-3-CH_3-C_6H_3-	1-naphthyl-

Scheme 2.

2.2. Screening of different lipases

In a first series of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of chiral azido alcohols **1** was investigated. For this purpose, racemic **1a** and **1e** taken as model substrates, were treated at room temperature (ca. 22°C) with three equivalents of isopropenyl acetate in *tert*-butyl methyl ether in the presence of a microbial lipase. In control experiments, it was shown that the reaction did not proceed in the absence of enzyme. Generally, enzyme-catalyzed transesterifications were stopped at roughly 50% conversion by removing the enzyme by filtration. Then the acetates **3a** and **3e** and unreacted alcohols **2a** and **2e** were separated by silica gel column chromatography. The enantiomeric excess of **2a**, **2e** and **3a**, **3e** was assessed by chiral gas chromatography. In all cases the unreacted alcohols **2a**, **2e** and their acetates **3a**, **3e** had the (*S*)-(–) and (*R*)-(+) configuration, respectively.

The absolute configurations of alcohol **2a** and acetate **3a** were determined by comparison of their chiroptical and chromatographic properties with those of samples of known configuration, prepared using the method described by Ader and Schneider.[23] The main results are given in Table 1.

Table 1
Lipase-catalyzed kinetic resolutions of *rac*-**1a** and *rac*-**1e** by transesterification[a)]

Lipases	Substrate (*rac*-**1**)	Time (h)	Conv. (%)[b)]	Alcohol **(S)-(-)-2** ee_s (%)[c)]	Ester **(R)-(+)-3** ee_p (%)[c)]	E[b)]
Pseudomonas fluorescens	**a**	44	35	42	77	12
(Amano AK)	**e**	25	63	72	43	5
Pseudomonas fluorescens	**a**	24	39	54	86	23
(Amano AK-20)	**e**	26	65	66	35	4
Pseudomonas cepacia	**a**	60	47	76	85	28
(Amano PS)	**e**	120	68	99	47	13
Pseudomonas cepacia	**a**	51	41	60	86	25
(Amano P)	**e**	90	62	96	58	14
Candida rugosa	**a**	66	28	21	57	5
(Sigma L1754)	**e**	70	27	19	52	4
Candida antarctica-B	**a**	**17**	**54**	**93**	**80**	**30**
(Novozym® SP 435)	**e**	**17**	**47**	**78**	**88**	**36**
Candida antarctica-B	**a**	**20**	**52**	**87**	**81**	**28**
(Chirazyme® L-2, c.-f., C2, lyo.)	**e**	**22**	**54**	**93**	**80**	**30**

a) Conditions : 1 mmol of (±)-**1**, 3 mmol of isopropenyl acetate, 150 mg of lipase or 500 mg of immobilized lipase (Novozym® SP 435 or Chirazyme® L-2, c.-f., C2, lyo.) and 5 mL of *tert*-butyl methyl ether at 22 °C.
b) Conversions and *E*-values were calculated from the enantiomeric excess of substrate **2** (ee_s) and of product **3** (ee_p) using the usual formula : $E = \mathrm{Ln}\,[(1-ee_s)(ee_p/(ee_s+ee_p))]/\mathrm{Ln}\,[(1+ee_s)(ee_p/(ee_s+ee_p))]$, Conv. = $ee_s/(ee_s + ee_p)$. according to ref. 27.
c) Determined by chiral gc analysis using Lipodex-D (25m) column.

It is obvious from Table 1 that the best results ($E = 28$–36) were obtained with immobilized lipase from *Candida antarctica*, fraction *B* [Novozym® SP 435 and Chirazyme® L-2, c.-f., C2, lyo.]. Similar enantioselectivities for **1a** ($E = 23$–28) were obtained with lipase from *Pseudomonas fluorescens* (Amano AK-20) and *Pseudomonas cepacia* (Amano PS, Amano P), but the reactions proceeded slowly (41–47% conversion after 51–60 h). The other examined lipases showed no reaction after 5–15 days [lipase from porcine pancreas (Sigma Type II), *Rhizomucor javanicus* (Amano M), *Rhizomucor miehei* (Lipozyme®)] or poor selectivities [*Candida rugosa* (Sigma L1754), $E = 4$–5].

2.3. Solvent effect

It is known that solvent variation in many cases of lipase-catalyzed kinetic resolutions can influence the enantiomeric or enantiotopic selectivity as well as the reaction rate.[28] The effect of the solvent on substrate specificity as well as on efficiency of various enzymes is well-documented in the literature.[29] Attempts have been made to get correlations between enantioselectivity and any physicochemical characteristics of the solvent such as hydrophobicity or dielectric constant.[30]

Acetylation of *rac*-**1a** with isopropenyl acetate at 22°C in the presence of Novozym® SP 435 was performed in various non-polar organic solvents. The results reported in Table 2 show that the activity of Novozym® SP 435 in transesterification of **1a** is higher in solvents of low polarity as judged by their log P[29a] (the logarithm of the partition coefficient of a given solvent between 1-octanol and water).

With *n*-hexane, *n*-pentane, toluene, benzene and *tert*-butyl methyl ether (log P = 1.3–3.5), the reaction rates were similar in all cases and generally higher than for isopropenyl acetate, THF, acetone or dioxane (log P = –1.1–0.6). In general, enzyme selectivity was good enough for pratical use in all the tested solvents ($E = 26$–43) excepted acetone ($E = 9$) and isopropenyl acetate ($E = 16$) which acts both as acylating agent and solvent. Benzene and toluene showed the best results with

Table 2
Transesterification of *rac*-**1a** and *rac*-**1e** with isopropenyl acetate in various solvents[a)]

Entry	Substrate (rac-1)	Enzyme[a)]	Solvent	Log P	Time (h)	Conv.[b)] (%)	Alcohol **(S)-(-)-2** ee_s (%)[c)]	Ester **(R)-(+)-3** ee_p (%)[c)]	E[b)]
1	a	A	none	-	17	49	72	76	16
2	a	A	*n*-hexane	3.5	16	59	98	67	26
3	a	A	*n*-pentane	3.1	17	51	86	84	32
4	**a**	**A**	**toluene**	**2.5**	**21**	**50**	**88**	**88**	**43**
5	a	B	"	2.5	20	41	60	88	30
6	**a**	**A**	**benzene**	**2.0**	**17**	**42**	**65**	**91**	**42**
7	a	B	"	2.0	20	43	65	88	31
8	a	A	tBuOMe	1.3	17	54	93	80	30
9	a	B	"	1.3	20	52	87	81	26
10	a	A	isopropenyl acetate	0.6	192	31	37	83	16
11	a	A	THF	0.49	89	49	79	84	28
12	a	A	acetone	-0.23	92	53	70	62	9
13	**a**	**A**	**dioxane**	**-1.1**	**48**	**37**	**55**	**93**	**48**
14	**e**	**A**	**toluene**	**2.5**	**18**	**37**	**55**	**93**	**48**
15	e	B	"	2.5	20	36	48	88	26

a) Conditions : 1 mmol of (±)-**1**, 3 mmol of isopropenyl acetate, 500 mg of Novozym® SP 435 (A) or Chirazyme® L-2, c.-f., C2, lyo. (B) and 5 mL of solvent at 22 °C.
b), c) See Table 1.

$E = 42$, 43 within 17, 21 h for 42 and 50% of conversion, respectively. Enantioselectivity in dioxane was slightly higher ($E = 48$) but the reaction proceeded with a significantly slower reaction rate (37% of conversion within 48 h). Changing the enzyme from Novozym® SP 435 to Chirazyme® L-2, c.-f., C2, lyo. in the transesterification of **1a** and **1e** in toluene (Entries 4, 5, 14 and 15) as well as in benzene (Entries 6 and 7) did not alter the reaction rate considerably but led to a noticeable decrease in the enantioselectivity. With **1a** in *tert*-butyl methyl ether a lower decrease of selectivity was also noticed going from Novozym® SP 435 to Chirazyme® L-2, c.-f., C2. (This fact is highly surprising as these two enzyme preparations are identical according to the provider.) Concerning compound **1e**, no noticeable differences for enantioselectivity ($E = 48$) and reaction rate (18 h for 37% of conversion) were observed on comparison with **1a** when the reaction was performed in toluene with Novozym® SP 435 (Table 2, Entries 4 and 14).

The amount of enzyme used in all assays was changed when performed in toluene in the range 50–500 mg/mmol of substrate. A good conversion rate was provided in reasonable times (not optimized) without any modification in enantioselectivity (Table 3).

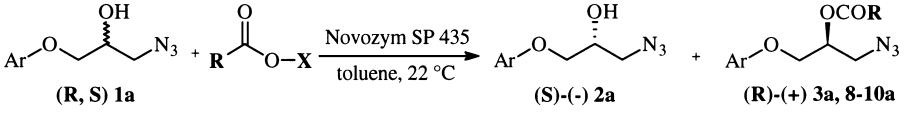
Table 3
Influence of the amount of Chirazyme® L-2, c.-f., C2, lyo. on the transesterification of *rac*-**1a**[a)]

Amount of enzyme	Time (h)	Temp. (°C)	Conv. (%)[b)]	Alcohol **(S)-(-)-2a** ee_s (%)[c)]	Ester **(R)-(+)-3a** ee_p (%)[c)]	E[b)]
500	20	22	52	87	81	28
200	18	25	51	84	81	25
100	26	25	44	68	89	27
50	26	25	40	59	87	26

a) Conditions : 1 mmol of (±)-**1a**, 3 mmol of isopropenyl acetate, Chirazyme® L-2, c.-f., C2, lyo. and 5 mL of toluene at 22 °C.
b), c) See Table 1.

2.4. Acyl donor influence

The influence of the acyl donor nature on the enantioselectivity of lipase-catalyzed transesterification reaction has been well documented by Ema et al.[31] Consequently, the influence of various acyl donors was screened for the Novozym® SP 435-catalyzed transesterification of *rac*-**1a** in toluene at 22°C (Scheme 3) and the results are reported in Table 4.



Scheme 3.

Table 4
Novozym® SP 435-catalyzed transesterification of *rac*-**1a** by use of various acylating agents[a)]

Entry	Acyl donor	R	X	Time (h)	Conv.[b)] (%)	Alcohol (S)-(-)-2a ee$_s$ (%)[c)]	Ester (R)-(+)-3a	ee$_p$ (%)[c)]	E[b)]
1	vinyl acetate	CH_3	$CH{=}CH_2$	15	56	96	**3a**	76	28
2	vinyl pentanoate	C_4H_9	$CH{=}CH_2$	31	51	85	**8a**	81	26
3	vinyl hexanoate	C_5H_{11}	$CH{=}CH_2$	42	51	83	**9a**	80	23
4	**isopropenyl acetate**	**CH_3**	**$C(CH_3){=}CH_2$**	**21**	**50**	**88**	**3a**	**88**	**43**
5	ethyl acetate	CH_3	C_2H_5	160	44	62	**3a**	78	15
6	O-isobutyryl-acetoxime	$CH(CH_3)_2$	$N{=}C(CH_3)_2$	30	52	82	**10a**	77	19

a) Conditions : 1 mmol of (±)-**1a**, 3 mmol of acylating agent, 500 mg of Novozym® SP 435 and 5 mL of toluene at 22 °C.
b), c) See Table 1.

The use of enol esters (Table 4, Entries 1–4) results in higher enantioselectivity ($E = 23$–43) when compared to ethyl acetate ($E = 15$) and *O*-isobutyryl-acetoxime ($E = 19$). It is interesting to note that lengthening in the alkyl chain of vinyl esters produces a decrease in the reaction rate, but only a marginal effect on the enantioselectivity of this reaction [enantiomeric ratio (E) ranging from 23 to 28]. The higher enantioselectivity was observed for the transesterification with isopropenyl acetate ($E = 43$). The decrease in enantioselectivity in the case of vinyl acetate may be attributed to a deactivation of the enzyme by the acetaldehyde generated in this reaction.[32] Therefore, in the next investigation, isopropenyl acetate was selected as the acylating agent.

2.5. Temperature effect

We disclosed from Sakai et al.[33] that a lipase from *Pseudomonas cepacia* (Amano PS) exerts its function at a very low temperature with markedly enhanced enantioselectivity. The thermostability of the lipase in organic solvent allows the reaction over a large range of temperatures.[34] Novozym® SP 435 (immobilized lipase from *Candida antarctica*, fraction *B*) is thermostable with a maximum activity in the range of 70–90°C.[35] The reaction of *rac*-**1a** was carried out with Novozym® SP 435 under the same conditions as described in Table 4 at temperatures ranging from 4 to 80°C (Table 5). Moreover, we examined the possible effect of microwave irradiation[37–44] on

Novozym® SP 435-catalyzed transesterification of *rac*-**1a** with isopropenyl acetate at 70 and 80°C in toluene[44] as well as in solvent-free conditions.[40] For the sake of comparison, reactions were also performed in a thermostated oil bath at the same temperature for the same time with heating profiles as close as possible (Table 5).

Table 5
Temperature influence in the Novozym® SP 435-catalyzed transesterification of *rac*-**1a**[a)]

Entry	Solvent	Activation mode[d)]	Temp. (°C)	Time	Conv.[b)] (%)	Alcohol (**S**)-(-)-**2a** ee_s (%)[c)]	Ester (**R**)-(+)-**3a** ee_p (%)[c)]	E[b)]
1	**toluene**	Δ	**4**	**50 h**	**51**	**93**	**91**	**72**
2	"	"	18	23 h	51	92	87	48
3	"	"	22	21 h	50	88	88	43
4	"	"	40	3 h 30 min.	53	92	82	33
5	"	"	70	40 min.	35	46	84	18
7	"	MW 180 W	"	"	36	48	85	20
8	none	Δ	"	"	40	50	74	11
9	"	MW 90 W	"	"	41	53	76	12
10	toluene	Δ	80	40 min.	41	53	78	14
11	none	Δ	"	10 min.	22	22	78	10
12	"	MW 240 W	"	"	23	23	78	10

a) Conditions : 1 mmol of (±)-**1a**, 3 mmol of isopropenyl acetate, 500 mg of Novozym® SP 435 and 5 mL of toluene.
b), c) See Table 1.
d) MW = microwave irradiation, Δ = classical heating.

For this reaction, a decrease of the temperature was found to have a beneficial effect on enzyme enantioselectivity. In fact, at 4°C the *E*-value was markedly increased and reached 72 for 51% of conversion within 50 h (Table 5, Entry 1). When the temperature was increased up to 40°C, the reaction time decreased to 3 h 30 min but the enantiomeric ratio decreased to 33; however, sufficiently enough for practical use. Further elevations in the temperature induced considerable decreases in enantiomeric ratio ($E=18$ and $E=14$ at 70 and 80°C, respectively). The results listed in Table 5 are used to plot ln *E* as a function of 1/T (K^{-1}) (Fig. 2). The observed straight line of this correlation was in agreement with the theoretical calculation: $\ln E = \Delta\Delta S^{\ddagger}/R - \Delta\Delta H^{\ddagger}/(RT)$.[36]

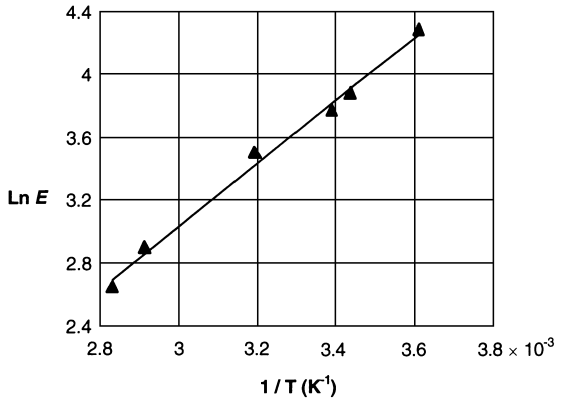


Figure 2. Correlation between ln *E* versus the inverse of temperature for the Novozym® SP 435-catalyzed transesterification of *rac*-**1a**

It is obvious from Table 5, that we cannot observe any advantages of microwave irradiation either in terms of reaction rates or enantioselectivity when compared to classical heating. As it is one of the most important problems in manufacturing process, it is interesting to note that the re-use of Novozym® SP 435 either under microvave irradiation or classical heating up to seven cycles revealed no modification in its original efficiency.

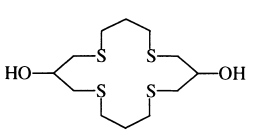
2.6. Effect of additives

The influence of triethylamine,[45] crown ethers[46,47] (15-crown-5, 18-crown-6), thiacrown ethers[48] (TTCTD, TTCHD) as well as TDA-1[47b] were studied in the lipase from *Candida antarctica*-catalyzed transesterification of *rac*-**1a** with isopropenyl acetate. Main results using Novozym® SP 435 or Chirazyme® L-2, c.-f., C2, lyo are given in Table 6.

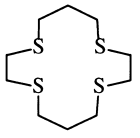
Table 6
Additive effects on the transesterification of *rac*-**1a** using Novozym® SP 435 (A) or Chirazyme® L-2, c.-f., C2, lyo. (B)[a)]

Entry	Additive	Enzyme	Temp. (°C)	Time	Conv. (%)[b)]	Alcohol **(S)-(-)-2a** ee_s (%)[c)]	Ester **(R)-(+)-3a** ee_p (%)[c)]	E[b)]
1	none	A	22	21 h	50	88	88	43
2	**NEt_3**	**A**	**22**	**1 h**	**42**	**61**	**85**	**23**
3	"	A	22	2 h	57	91	71	18
4	"	A	22	7 h	64	100	58	16
5	"	A	40	35 min.	46	66	79	17
6	"	A	70	30 min.	53	76	68	12
7	none	B	22	20 h	41	60	88	30
8	"	B	40	3 h 20 min.	49	50	89	28
9	15-crown-5	B	40	4 h	35	46	87	23
10	18-crown-6	B	40	4 h 20 min.	26	32	90	26
11	TTCTD[d)]	B	22	15 h	41	62	90	36
12	"	B	40	4 h 20min.	52	94	80	32
13	**TTCHD-D[d)]**	**B**	**22**	**15 h**	**44**	**71**	**90**	**41**
14	"	**B**	**40**	**4 h 20 min.**	**49**	**85**	**92**	**50**
15	TDA-1[d)]	B	40	4 h	45	68	85	25

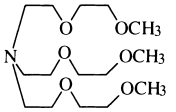
a) Conditions : 1 mmol of (±)-**1a**, 3 mmol of isopropenyl acetate, 500 mg of immobilized lipase, 14 mol. % of triethylamine or 5 mol % additive and 5 mL of toluene.
b), c) See Table 1.
d) TTCTD (1,4,8,11-Tetrathiacyclotetradecane), TTCHD-D (1,5,9,13-Tetrathiacyclohexadecane-3,11-diol), TDA-1 (Tris-(3,6-dioxa-heptyl)-amine).



TTCHD-D



TTCTD



TDA-1

It is obvious from Table 6 that only TTCHD-D (Entries 13 and 14) was found to have a beneficial effect on enzyme enantioselectivity and reaction time. The addition of triethylamine (14 mol%) at 22°C by using Novozym® SP 435 induces acceleration of the reaction rate (42% of conversion within 1 h), but the enantiomeric ratio (*E*) was markedly decreased (Entry 2). It is interesting to note that if the conversion of *rac*-**1a** in this reaction is increased up to 64%, the enantiomeric

ratio (E) of this reaction decreased to 16 (Entry 4). Although the function of triethylamine was uncertain, the same acceleration effect was also observed in kinetic resolutions of certain substrates using the same lipase Novozym® SP 435.[45d] Finally, the highest enantioselectivities ($E=41$ at 22°C, $E=50$ at 40°C) were recorded when the transesterification of *rac*-**1a** by using Chirazyme® L-2, c.-f., C2, lyo. was carried out in the presence of 5 mol% of TTCHD-D (Entry 14). Only a slight increase in enantioselectivity was observed at 22°C as well as at 40°C using TTCTD as the additive (Entries 11 and 12). On the other hand, when this transesterification was performed at 40°C, addition of 15-crown-5, 18-crown-6 and TDA-1 significantly increased the reaction time but produced only a marginal effect on enantioselectivity ($E=23$, 26, 25, respectively).

2.7. Effect of the aromatic substituents

In order to investigate the influence of the aromatic substituent (Ar), all transesterifications of *rac*-**1a–g** were carried out in toluene with isopropenyl acetate by using Novozym® SP 435 at 4°C which is the best compromise in terms of enantioselectivity and reaction rate. To our knowledge, no data are available for the absolute configurations of **2b–g** or **3b–g** or of any derivatives. For these compounds the absolute configurations were assigned by comparison of the sign of the specific rotation with the reported data for (*S*)-(–)-**2a** and (*R*)-(+)-**3a**.[1a] The results are collected in Table 7.

Table 7
Transesterification of *rac*-**1a–g** with isopropenyl acetate using Novozym® SP 435 in toluene at 4°C[a)]

Entry	Substrate rac-**1**	Ar	Time (h)	Conv. (%)[b)]	Alcohol (**S**)-(-)-**2** ee_s (%)[c)]	Ester (**R**)-(+)-**3** ee_p (%)[c)]	E[b)]
1	**a**	C_6H_5-	50	51	93	91	72
2	**b**	2-CH_3-C_6H_4-	60	44	73	93	60
3	**c**	3-CH_3-C_6H_4-	52	50	91	91	67
4	**d**	4-CH_3-C_6H_4-	45	42	68	93	56
5	**e**	4-Cl-C_6H_4-	65	49	88	92	70
6	**f**	3-CH_3-4-Cl-C_6H_3-	60	50	91	90	60
7	**g**	1-naphthyl-[d)]	49	38	58	95	70

a) Conditions : 1 mmol of (±)-**1a**, 3 mmol of isopropenyl acetate, 500 mg of Novozym® SP 435 and 5 mL of toluene at 4 °C.
b), c) See Table 1.
d) Enantiomeric excess of **2g** and **3g** were determined by chiral HPLC analysis using Chiracel OD-H column.

It appears clearly from Table 7 that it is possible to run transesterification of 1-azido-3-aryloxy-2-propanols **1a–g** with good enantioselectivities ($E=56$–72) whatever the substituents on the phenyl ring are.

3. Conclusion

We have presented a general method to realize enantioselective acetylations of 1-azido-3-aryloxy-2-propanols **2a–g** whatever the aromatic substituents are. High enantioselectivities ($E=56$–72) were obtained using Novozym® SP 435 and isopropenyl acetate in toluene at 4°C.

4. Experimental

4.1. General

Lipases from *Pseudomonas cepacia* (Amano P, Amano PS), *Pseudomonas fluorescens* (Amano AK, Amano AK-20) and *Rhizomucor javanicus* (Amano M) were purchased from Amano Pharmaceutical Co. Ltd. (Nagoya, Japan). Novozym® SP 435 (immobilized *Candida antarctica-B* lipase) and Lipozyme® (immobilized *Mucor miehei* lipase) were kindly given by Novo Nordisk (Bagsvaerd, Denmark). Lipases from *Candida rugosa* (Sigma L1754) and porcine pancreas (Sigma Type II) were obtained from Sigma (Deisenhofen, Germany). Chirazyme® L2, c.-f. C2, lyo. was kindly given by Roche Molecular Biochemicals (Mannheim, Germany). All the commercially available chemicals were obtained from Aldrich and Fluka. Solvents were of analytical-grade quality and were obtained from Lab Scan Ltd. and Aldrich. The racemic azido alcohols **1a**–**g** were prepared using previously described methods.[1a,25] The racemic acetates, as well as the other esters, were synthesized from the corresponding alcohols and chloride or anhydride according to the usual procedures [e.g. 10 mmol of *rac*-**1a**–**g**, 15 mmol of acetyl chloride, 15 mmol of pyridine in CH_2Cl_2 (30 mL) at 22°C].

4.2. Analytical methods

Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS, Gif sur Yvette, France. ^1H (200 or 250 MHz) and ^{13}C (62.9 MHz) NMR spectra were recorded on Bruker AC-200 or 250 spectrometers in $CDCl_3$ with TMS as the internal standard. Chemical shifts (δ) are quoted in ppm. Optical rotation measurements were recorded on a DiP-370 JASCO polarimeter. Gas chromatographic analyses were run on a 6000 Vega Series instrument equipped with a FID detector and Spectra-Physics SP 4290 integrator. Optical purities of unreacted azido alcohols **2a**–**f** and their acetates **3a**–**f** were controlled by GC analysis on a capillary chiral column Lipodex D (25 m) and directly determined using racemic compounds as references. The conditions were: detector and injector temperature 250°C, column temperature was 145°C (0.8 bar) in the cases of **2**–**3a**–**d**, **f** and 170°C (0.9 bar) for **2**–**3e**. The following retention times (t_r/min) were: **2a**: 79.4 (*R*), 81.3 (*S*); **3a**: 59.6 (*S*), 60.7 (*R*); **2b**: 102.3 (*R*), 103.4 (*S*); **3b**: 82.1 (*S*), 83.3 (*R*); **2c**: 112.1 (*R*), 114.0 (*S*); **3c**: 88.0 (*S*), 80.4 (*R*); **2d**: 104.2 (*R*), 105.1 (*S*); **3d**: 83.0 (*S*), 84.3 (*R*); **2e**: 85.4 (*R*), 87.0 (*S*); **3e**: 54.0 (*S*), 55.0 (*R*); **2f**: 112.3 (*R*), 114.2 (*S*); **3f**: 74.8 (*S*), 77.5 (*R*). HPLC analyses for the determination of enantiomeric purities of **2g** and **3g** were performed on a Thermo-Separation Products P-100 instrument and Chiracel OD-H column (*n*-hexane:*iso*-propanol = 90:10, 1 mL/min, 43 bar, 254 nm, 22°C) using racemic compounds as references. The following retention times (t_r/min) were 57.0 (*R*), 62.7 (*S*) for **2g** and 48.2 (*S*), 55.3 (*R*) for **3g**. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC was carried out using glass sheets pre-coated with silica gel 60 F_{254} prepared by Merck. The reaction under microwave irradiations were performed in a monomode microwave reactor (Synthewave 402 from Prolabo), fitted with a stirring system and an IR temperature detector which indicates the surface temperature. Reaction conditions were controlled using the algorithm *tout ou peu* which allows temperature control at the given value during the reaction time by modulating the power between an adequate value and 20 W (to operate under electromagnetic field all along the reaction).

4.3. Typical transesterification procedure for rac-***1a–g*** *by using Novozym® SP 435 in toluene at 4°C*

Isopropenyl acetate (3 mmol) and 500 mg of immobilized lipase from *Candida antarctica-B* (Novozym® SP 435) were added to a solution of the racemic azido alcohol **1a–g** (1 mmol) in 5 mL of toluene. The mixture was stirred at 4°C and followed by TLC. After the appropriate time (Table 6), the reaction was stopped by filtering off the solid enzyme and the solvent was evaporated under reduced pressure. The crude mixture of acetate (*R*)-(+)-**3a–g** and unreacted alcohol (*S*)-(–)-**2a–g** was separated by flash chromatography on silica gel with hexane:ethyl acetate (15:1) as the eluent. In the case of **2a–f** and **3a–f** determination of enantiomeric excess was possible by means of a chiral GC column [Lipodex-D (25 m)], while for **2g** and **3g** by chiral HPLC analysis using a Chiracel OD-H column. Optical rotation values in all cases of compounds were in accordance with the literature data.[1a] ^{1}H NMR spectras of enantiomeric azido alcohols **2a–g** were identical with those of the racemic compounds as described in the literature[1a,23,25] and their ^{13}C NMR spectras are reported below:

2a: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 53.15 (*C*H_2N_3), 68.72 (*C*H_2O), 69.01 (*C*H), 114.29, 121.17, 129.38, 157.96 (*C*–Ar);
2b: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 16.09 (*C*H_3–Ar), 53.43 (*C*H_2N_3), 68.79 (*C*H_2O), 69.90 (*C*H), 110.99, 120.99, 126.54, 126.81, 130.72, 156.10 (*C*–Ar);
2c: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 21.42 (*C*H_3–Ar), 53.35 (*C*H_2N_3), 68.89 (*C*H_2O), 69.27 (*C*H), 111.37, 115.33, 122.21, 129.26, 139.63, 158.17 (*C*–Ar);
2d: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 21.09 (*C*H_3–Ar), 53.28 (*C*H_2N_3), 68.80 (*C*H_2O), 69.30 (*C*H), 114.32, 129.39, 130.22, 157.97 (*C*–Ar);
2e: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 53.24 (*C*H_2N_3), 69.12 (*C*H_2O), 69.25 (*C*H), 115.72, 126.25, 129.38, 156.71 (*C*–Ar);
2f: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.19 (*C*H_3–Ar), 53.22 (*C*H_2N_3), 69.14 (*C*H_2O, *C*H), 112.98, 116.93, 126.41, 129.57, 137.09, 156.59 (*C*–Ar);
2g: ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 53.54 (*C*H_2N_3), 69.24 (*C*H_2O, *C*H), 105.05, 120.90, 121.45, 125.29, 125.62, 126.39, 127.47, 134.42, 153,76 (*C*–Ar).

^{1}H and ^{13}C NMR spectra, IR data, and microanalysis of acetates **3a–f** are reported below:

3a: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ 2.08 (s, 3H, $COCH_3$), 3.55 (d, J = 5.13 Hz, 2H, CH_2N_3), 4.06 (d, J = 5.23 Hz, 2H, OCH_2), 5.19–5.29 (m, 1H, chiral CH), 6.80–7.01 (m, 3H, aromatic CH), 7.20–7.31 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.73 ($COCH_3$), 50.55 (*C*H_2N_3), 65.76 (*C*H_2O), 70.56 (*C*H), 114.32, 121.58, 129.39, 157.97 (*C*–Ar), 170.05 (*C*=O); IR (neat, cm^{-1}) 2060 (N_3), 1710 (C=O); anal. calcd for $C_{11}H_{13}O_3N_3$ (235): C, 56.17; H, 5.53; N, 17.87. Found: C, 56.23; H, 5.49; N, 17.91.
3b: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ 2.12 (s, 3H, $COCH_3$), 2.21 (s, 3H, aromatic CH_3), 3.62 (d, J = 5.13 Hz, 2H, CH_2N_3), 4.10 (d, J = 5.24 Hz, 2H, OCH_2), 5.26–5.40 (m, 1H, chiral CH), 6.78–6.96 (m, 2H, aromatic CH), 7.12–7.21 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 16.06 (*C*H_3–Ar) 20.85 ($COCH_3$), 50.80 (*C*H_2N_3), 65.95 (*C*H_2O), 70.74 (*C*H), 110.87, 121.05, 126.81, 130.77, 156,07 (*C*–Ar), 174.50 (*C*=O); IR (neat, cm^{-1}) 2060 (N_3), 1710 (C=O); anal. calcd for $C_{12}H_{15}O_3N_3$ (249): C, 57.83; H, 6.02; N, 16.87. Found: C, 57.78; H, 5.97; N, 16.92.

3c: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ 2.13 (s, 3H, $COCH_3$), 2.33 (s, 3H, aromatic CH_3), 3.61 (d, J = 5.14 Hz, 2H, CH_2N_3), 4.09 (d, J = 5.21 Hz, 2H, OCH_2), 5.24–5.36 (m, 1H, chiral CH), 6.68–6.89 (m, 3H, aromatic CH), 7.12–7.24 (m, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.87 ($CO\mathit{C}H_3$), 21.41 ($\mathit{C}H_3$–Ar), 50.73 ($\mathit{C}H_2N_3$), 65.85 ($\mathit{C}H_2O$), 70.73 ($\mathit{C}H$), 111.32, 115.35, 122.21, 129.23, 139.60, 158.07 (C–Ar), 170.16 (C=O); IR (neat, cm^{-1}) 2060 (N_3), 1710 (C=O); anal. calcd for $C_{12}H_{15}O_3N_3$ (249): C, 57.83; H, 6.02; N, 16.87. Found: C, 57.80; H, 6.10; N, 16.80.

3d: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ 2.12 (s, 3H, $COCH_3$), 2.21 (s, 3H, aromatic CH_3), 3.61 (d, J = 5.12 Hz, 2H, CH_2N_3), 4.09 (d, J = 5.20 Hz, 2H, OCH_2), 5.23–5.35 (m, 1H, chiral CH), 6.65–6.89 (m, 2H, aromatic CH), 7.10–7.24 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.50 ($CO\mathit{C}H_3$), 21.10 ($\mathit{C}H_3$–Ar), 50.65 ($\mathit{C}H_2N_3$), 65.25 ($\mathit{C}H_2O$), 70.60 ($\mathit{C}H$), 114.38, 129.21, 130.40, 158.07 (C–Ar), 170.01 (C=O); IR (neat, cm^{-1}) 2060 (N_3), 1710 (C=O); anal. calcd for $C_{12}H_{15}O_3N_3$ (249): C, 57.83; H, 6.02; N, 16.87. Found: C, 57.86; H, 5.94; N, 16.76.

3e: ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ 2.13 (s, 3H, $COCH_3$), 3.61 (d, J = 5.11 Hz, 2H, CH_2N_3), 4.08 (d, J = 5.14 Hz, 2H, OCH_2), 5.20–5.36 (m, 1H, chiral CH), 6.78–6.90 (m, 2H, aromatic CH), 7.19–7.30 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.85 ($CO\mathit{C}H_3$), 50.63 ($\mathit{C}H_2N_3$), 66.28 ($\mathit{C}H_2O$), 70.50 ($\mathit{C}H$), 115.81, 126.39, 129.39, 156.67 (C–Ar), 170.11 (C=O); IR (neat, cm^{-1}) 2190 (N_3), 1720 (C=O); anal. calcd for $C_{11}H_{12}O_3N_3Cl$ (269.5): C, 48.98; H, 4.45; N, 15.58. Found: C, 48.86; H, 4.38; N, 15.62.

3f: ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ 2.13 (s, 3H, $COCH_3$), 2.33 (s, 3H, aromatic CH_3), 3.60 (d, J = 5.02 Hz, 2H, CH_2N_3), 4.07 (d, J = 5.10 Hz, 2H, OCH_2), 5.16–5.34 (m, 1H, chiral CH), 6.60–6.75 (m, 1H, aromatic CH), 6.75–6.87 (m,1H, aromatic CH), 7.13–7.30 (m, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.22 ($\mathit{C}H_3$–Ar), 20.84 ($CO\mathit{C}H_3$), 50.64 ($\mathit{C}H_2N_3$), 66.20 ($\mathit{C}H_2O$), 70.55 ($\mathit{C}H$), 113.07, 117.09, 126.55, 129.63, 137.15, 156.58 (C–Ar), 170.09 (C=O); IR (neat, cm^{-1}) 2160 (N_3), 1760 (C=O); anal. calcd for $C_{12}H_{14}O_3N_3Cl$ (283.5): C, 50.79; H, 4.94; N, 14.81. Found: C, 50.72; H, 4.86; N, 14.76.

3g: ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ 2.09 (s, 3H, $COCH_3$), 3.64 (d, J = 5.10 Hz, 2H, CH_2N_3), 4.10 (d, J = 5.25 Hz, 2H, OCH_2), 5.20–5.36 (m, 1H, chiral CH), 6.78 (d, J = 7.3 Hz, 1H, aromatic CH), 7.25–7.69 (m, 4H, aromatic CH), 7.73–7.88 (m, 1H, aromatic CH), 8.20–8.27 (m, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm) δ 20.97 ($CO\mathit{C}H_3$), 50.70 ($\mathit{C}H_2N_3$), 65.76 ($\mathit{C}H_2O$), 70.64 ($\mathit{C}H$), 105.00, 120.65, 121.21, 125.23, 125.40, 126.20, 127.33, 134.60, 153.90 (C–Ar), 169.76 (C=O); IR (neat, cm^{-1}) 2060 (N_3), 1710 (C=O); anal. calcd for $C_{15}H_{15}O_3N_3$ (285): C, 63.16; H, 5.26; N, 14.74. Found: C, 63.00; H, 5.17; N, 14.66.

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