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Combined lipase-catalyzed resolution/Mitsunobu esterification for the production of enantiomerically enriched arylalkyl carbinols

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Abstract—Several arylalkyl carbinols [1-indanol, 1-tetralol, 1-phenylethanol, 1-(1-naphthyl)ethanol, 1-(2-naphthyl)ethanol, 1-(4-methoxyphenyl)ethanol, 1-acenaphthenol] were deracemized through sequential combinations of lipase-catalyzed resolution and Mitsunobu inversion. The corresponding (*R*)-acetates were obtained in 72–83% yield and 89–99% ee.
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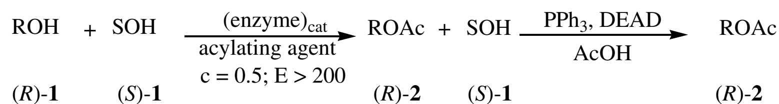
1. Introduction

Optically active secondary alcohols are useful intermediates in the preparation of bioactive compounds. Lipase-catalyzed kinetic resolution of racemic alcohols has proved to be a good method to obtain enantiomerically enriched materials.[1] One of the most popular methods is to acylate the racemic alcohol with enol acetates (vinyl or isopropenyl acetate) to give the acetylated alcohol. Even in the case where the enantioselectivity factor is high ($E > 200$), this method may have drawbacks. Indeed, at 50% conversion, the unreacted alcohol (*S*)-**1** [or (*R*)-**1**] and the produced acetate (*R*)-**2** [or (*S*)-**2**] show the same high ee. Since they show close physical properties, these compounds are usually separated through silica gel chromatography. A way to avoid this separation is to use a cyclic anhydride as an acylating agent.[2] Under these conditions, the acidic hemisuccinate formed and the neutral unreacted alcohol can be readily separated by base aqueous extraction. However, no more than 50% of the desired enantiomer is obtained (Scheme 1).

A strategy for obtaining more than 50% of one enantiomer is to carry out an enantioconvergent process, using a combination of biochemical and chemical reactions.[3] Methods based on a dynamic kinetic resolution processes combine a lipase-catalyzed kinetic resolution and a transition-metal-catalyzed racemization of the slowly reacting enantiomer.[4] Another method has been described that allows the one-pot conversion of the racemic alcohol **1** into a nearly quantitative yield of one enantiomerically enriched acetate (*R*)-**2** [or (*S*)-**2**], without the need for separation. It involves an efficient enzyme-catalyzed resolution of the racemic alcohol through lipase-catalyzed acylation followed by a stereoselective substitution of the hydroxyl group (after conversion into a good leaving group) of the unreacted alcohol with an oxygen nucleophile.[5] Alternatively, the substitution of the hydroxyl group may be achieved through a Mitsunobu reaction by a carboxylate.[4f,5a,6] Moreover, the use of acetic acid as the pronucleophile in this latter process will afford the acetate (*R*)-**2**.

2. Results and discussion

In the course of our studies on the enzymatic resolution of alkyl–aryl secondary alcohols,[2g,7] we applied the aforemen-



Scheme 1. Deracemization of an alcohol through a selective kinetic resolution/substitution sequence.

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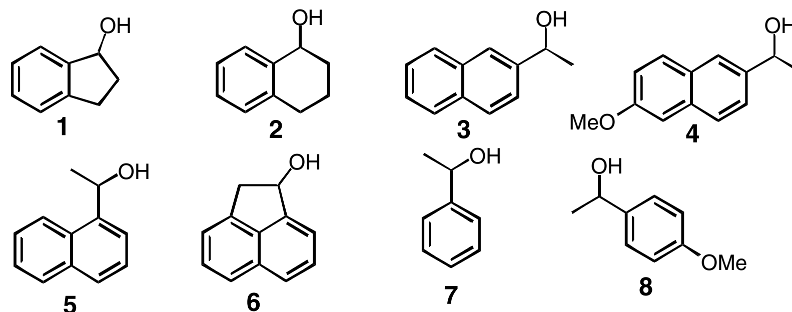

tioned Mitsunobu band procedure to obtain enantiomerically enriched acetates of arylalkyl carbinols **1**–**8** (1-arylethanols **3**, **4**, **5**, **7**, **8**, indanol **1**, tetralol **2** and acenaphthenol **6**), which are useful substrates for palladium-catalyzed coupling reactions with stabilized carbanions.[8]

Racemic alcohols **1**–**8** (2 mmol) were treated with isopropenyl acetate (4 mmol) in diethyl ether (10 mL) in the presence of *Candida antarctica* lipase B (CAL B),[9] for an appropriate time.

A short study was undertaken for substrates **1**, **5**, and **6** in order to investigate the effect of the catalyst amount with regards to the conversion and enantioselectivity after 24–30 h of reaction. The results are collected in Tables 1–3.

Table 1. CAL B catalyzed resolution of **1**

CAL B (mg)	Conversion	$ee_{alcohol}$[a]	$ee_{acetate}$[a]	*E*[b]
150	0.54	0.99	0.85	60
30	0.51	0.99	0.91	110
12	0.50	0.99	0.99	>500
6	0.47	0.88	0.99	>500

Effect of the amount of catalyst used on the conversion and ee's after 24–30 h reaction: 2 mmol substrate, 10 mL diethyl ether, room temperature.
[a] Measured by HPLC using Chiralcel OD-H column.
[b] Calculated from $ee_{alcohol}$ or $ee_{acetate}$ and conversion.[10]

Table 2. CAL B catalyzed resolution of **5**

CAL B (mg)	Conversion	$ee_{alcohol}$[a]	$ee_{acetate}$[a]	*E*[b]
150	0.50	0.99	0.99	>500
60	0.50	0.99	0.99	>500
30	0.39	0.64	0.99	380
6	0.17	0.20	0.99	240

Effect of the amount of catalyst used on the conversion and ee's after 24–30 h reaction: 2 mmol substrate, 10 mL diethyl ether, room temperature.
[a] Measured by HPLC using Chiralcel OD-H column.
[b] Calculated from $ee_{alcohol}$ or $ee_{acetate}$ and conversion.[10]

Table 3. CAL B catalyzed resolution of **6**

CAL B (mg)	Conversion	$ee_{alcohol}$[a]	$ee_{acetate}$[a]	*E*[b]
60	0.50	0.99	0.99	>500
30	0.30	0.42	0.99	300
6	0.07	0.07	0.99	200

Effect of the amount of catalyst used on the conversion and ee's after 24–30 h reaction: 2 mmol substrate, 10 mL diethyl ether, room temperature.
[a] Measured by HPLC using Chiralcel OD-H column.
[b] Calculated from $ee_{alcohol}$ or $ee_{acetate}$ and conversion.[10]

It can be seen that for alcohols **5** and **6**, both conversions and enantioselectivities go up as the catalyst amount increases. Conversely, for substrate **1**, the enantioselectivity increases by decreasing the amount of catalyst for the same conversion. Such studies allow us to choose the amount of catalyst used and the reaction time for a satisfactory enantioselectivity at ca. 50% substrate conversion (monitored by chromatography). At ca. 50% conversion, the reaction mixture was filtered (Celite) then the ee's of the ester produced and the unreacted alcohol measured (chiral chromatography). To the filtrate was added PPh_3 (2.4 mmol) and AcOH (2.4 mmol). The addition of diisopropylazodicarboxylate (DIAD) (2.4 mmol) was carried out at 0 °C to convert the unreacted (*S*)-alcohol into the (*S*)-acetate (room temperature, 24 h). The results are collected in Table 4.

At 50% conversion, both the produced acetate and the unreacted alcohol showed ee >99%, except for **8**, (91% ee at 52% conversion). The acetate isolated after Mitsunobu reaction showed either an excellent (>99% from **1**, **2**, **4** substrates) or good (89–91% from **3**, **5**, **6**, **7** substrates) enantiomeric excess. No residual alcohol was detected.

Since the unreacted alcohols showed an ee >99% after the enzymatic acylation process, the loss of enantiomeric purity of the acetate produced by the substitution step should arise from a less than fully stereoselective substitution during the Mitsunobu process. Such non-stereoselectivity has yet been reported.[11] The loss of stereoselectivity may arise from a competitive unimolecular substitution process proceeding via a benzylic carbocation. It is surprising to see that **4** afforded a stereoselective reaction, although the corresponding intermediate benzylic carbocation would have been stabilized. The proper conditions to suppress the racemization-induced process could not be found uptil now.

3. Conclusion

In conclusion, a single enantiomer of acetate of each alcohol **1**–**8** was obtained in 89–99% ee and in 70–83% yield from the corresponding racemates, through a combined lipase-catalyzed kinetic resolution followed by an in situ inversion of the unreacted alcohol by a Mitsunobu reaction.

Table 4. Deracemization of alcohols **1**–**8** through a resolution/inversion process

Substrate[a]	CAL B catalyzed resolution[b]					Mitsunobu inversion	
	CAL B (mg)	Reaction time (h)	(*S*)-Alcohol (% ee)[c]	(*R*)-Acetate (% ee)[c]	*E*[d]	(*R*)-Acetate (% ee)[c]	Yield[e] (%)
1	12	24	>99	>99	>500	>99	82
2	100	24	>99	>99	>500	>99	79
3	50	24	>99	>99	>500	91	76
4	40	24	>99	>99	>500	>99	74
5	120	30	>99	>99	>500	89	72
6	120	30	>99	>99	>500	89	83
7	40	64	>99	>99	>500	90	81
8[d]	40	24	>99	91	110	82	70

[a] 2 mmol substrate, 10 mL diethyl ether, room temperature.
[b] Conversion = 0.50.
[c] Ee determined by HPLC using CHIRALCEL OD-H or OB-H column.
[d] Calculated from $ee_{alcohol}$ and $ee_{acetate}$ and conversion $c = 0.5$[10] (except for **8**, where $c = 0.53$).
[e] Isolated yield.

4. Experimental

4.1. General

Bruker AM 250 spectrometer, operating at 250 MHz for ^{1}H, and at 62.5 MHz for ^{13}C, was used for the NMR spectra, which are referenced to the solvent as the internal standard. Optical rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature using a cell of 1 dm length and $\lambda = 589$ nm.

The enantiomeric excesses were measured by a chiral stationary phase HPLC on Chiralcel® OD-H column or a Chiralcel® OB-H column. Retention times are reported in minutes.

4.2. Typical procedure for synthesis of enantiomerically pure acetates (*R*)-1a–8a

Racemic alcohols **1**–**8** (2 mmol) were added to isopropenyl acetate (4 mmol) in 10 mL of diethyl ether in the presence of an adjusted amount of immobilized lipase from *C. antarctica* B. The mixture was stirred at room temperature for an appropriate time (see Tables 1–3) until the conversion reached ca. 50% (chiral chromatography). The reaction was stopped by filtering off the solid enzyme on Celite and the solvent evaporated under reduced pressure.

The crude mixture of the (*R*)-acetate and unreacted (*S*)-alcohol was dissolved in 4 mL of diethyl ether. To this solution were added AcOH (0.144 g, 2.4 mmol) and PPh_3 (0.628 g, 2.4 mmol). The reaction mixture was immediately cooled to 0 °C and a solution of diisopropyl azodicarboxylate (DIAD) (0.48 g, 2.4 mmol) was added dropwise, under vigorous stirring during 20 min. The mixture was allowed to warm to room temperature and stirred for 24 h. Concentration of reaction mixture in vacuo followed by silica gel column chromatographic purification of the residue using hexane and ethyl acetate (8:2) gave only the acetates (*R*)-**1a**–**8a** in 70–83% yield.

The conditions for the analysis of alcohols (*R*)-**1**–**8** are reported below:

1: (*S*)-(+)-Indan-1-ol: HPLC (Chiralcel® OD-H), $t_{(S)} = 21.3$; $t_{(R)} = 24.4$; (hexane/*i*-PrOH 98:2, flow: 0.8 mL/min).[12]
2: (*S*)-(+)-1,2,3,4-Tetrahydro-1-naphthalenol: HPLC (Chiralcel® OB-H), $t_{(S)} = 27.3$; $t_{(R)} = 48.0$; (hexane/*i*-PrOH 99:1, flow: 0.8 mL/min).[12]
3: (*S*)-(−)-1-(2-Naphthyl)ethanol: HPLC (Chiralcel® OD-H), $t_{(S)} = 35.0$; $t_{(R)} = 36.9$ (hexane/*i*-PrOH 95:5, flow: 0.5 mL/min).[13]
4: (*S*)-(−)-1-(6-Methoxy-2-naphthyl)ethanol: HPLC (Chiralcel® OD-H), $t_{(S)} = 15.0$; $t_{(R)} = 18.2$ (hexane/*i*-PrOH 90:10, flow: 1 mL/min).[12]
5: (*S*)-(−)-1-(1-Naphthyl)ethanol: HPLC (Chiralcel® OD-H), $t_{(S)} = 9.6$; $t_{(R)} = 15.0$ (hexane/*i*-PrOH 90:10, flow: 1 mL/min).[14]
6: (*S*)-(+)-1-Acenaphthenol: HPLC (Chiralcel® OD-H), $t_{(S)} = 33.2$; $t_{(R)} = 36.3$ (hexane/*i*-PrOH 97:3, flow: 1 mL/min).[14]
7: (*S*)-(−)-1-Phenylethanol: HPLC (Chiralcel® OB-H), $t_{(S)} = 7.75$; $t_{(R)} = 11.3$ (hexane/*i*-PrOH 94:6, flow: 1 mL/min).[12]
8: (*S*)-(−)-1-(4-Methoxyphenyl)ethanol: HPLC (Chiralcel® OB-H), $t_{(S)} = 31.6$; $t_{(R)} = 42.35$ (hexane/*i*-PrOH 96:4, flow: 1 mL/min).[12]

The conditions for the analysis of acetates (*R*)-**1a**–**8a** are reported below:

1a: (*R*)-(+)-Indan-1-yl acetate: HPLC (Chiralcel® OD-H), $t_{(R)} = 6.18$; $t_{(S)} = 6.69$; (hexane/*i*-PrOH 98:2, flow: 0.8 mL/min).[12]
2a: (*R*)-(+)-1,2,3,4-Tetrahydro-1-naphthalenol acetate: HPLC (Chiralcel® OB-H), $t_{(R)} = 15.6$; $t_{(S)} = 17.5$ (hexane/*i*-PrOH 99:1, flow: 0.6 mL/min).[12]
3a: (*R*)-(+)-1-(2-Naphthyl)ethyl acetate: HPLC (Chiralcel® OD-H), $t_{(R)} = 8.95$; $t_{(S)} = 10.25$ (hexane/*i*-PrOH 95:5, flow: 0.6 mL/min).[13]
4a: (*R*)-(+)-1-[2-(6-Methoxynaphthyl)]ethyl acetate: HPLC (Chiralcel® OD-H), $t_{(R)} = 9.87$; $t_{(S)} = 10.8$ (hexane/*i*-PrOH 90:10, flow: 0.6 mL/min).[12]
5a: (*R*)-(+)-1-(1-Naphthyl)ethyl acetate: HPLC (Chiralcel® OD-H), $t_{(R)} = 8.15$; $t_{(S)} = 10.2$ (hexane/*i*-PrOH 90:10, flow: 0.6 mL/min).[14]

6a: (R)-(+)-1-Acenaphthylenol-1,2-dihydro acetate: HPLC (Chiralcel® OD-H), $t_{(R)} = 11.3$; $t_{(S)} = 12.8$ (hexane/*i*-PrOH 99.3:0.7, flow: 1 mL/min).[14]

7a: (R)-(+)-1-Phenylethylacetate: HPLC (Chiralcel® OB-H), $t_{(R)} = 26.3$; $t_{(S)} = 30.8$ (hexane/*i*-PrOH 99.2:0.8, flow: 0.5 mL/min).[12]

8a: (R)-(+)-1-(4-Methoxyphenyl)ethyl acetate: HPLC (Chiralcel® OB-H), $t_{(S)} = 31.5$; $t_{(R)} = 34.7$ (hexane/*i*-PrOH 99.2:0.8, flow: 1 mL/min).[12]

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