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Lipase TL®-mediated kinetic resolution of benzoin: facile synthesis of (1*R*,2*S*)-*erythro*-2-amino-1,2-diphenylethanol

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Abstract

The lipase TL®-mediated kinetic resolution of (±)-benzoin (**1**) proceeded to give the corresponding optically pure benzoin (*R*)-**1**. On the other hand, (*S*)-benzoin-*O*-acetate (**5**) could be hydrolyzed without epimerization to give (*S*)-benzoin (*S*)-**1**, under alkaline conditions. Further, (*R*)-**1** was converted to (1*R*,2*S*)-2-amino-1,2-diphenylethanol (99:1 er) according to the procedure reported previously.

The preparation of *erythro*-2-amino-1,2-diphenylethanol in optically pure form has recently received widespread attention due to the use of these amino alcohols as chiral auxiliaries in asymmetric synthesis,[1] chiral stationary phases for HPLC applications[2] and as ligands in asymmetric catalysis.[3] Several methods have been reported in the literature for the synthesis of both antipodes of *erythro*-2-amino-1,2-diphenylethanol. The classical synthesis of these substances involves the resolution of racemic *erythro*-2-amino-1,2-diphenylethanol, obtained by the hydrogenation of benzoin oxime (**2**), with L-glutamate as reported by Tishler et al. in 1951 (Scheme 1).[4] More recently, the asymmetric dihydroxylation of *trans*-stilbene, followed by amination has been described by Sharpless et al.[5] Fujisawa et al. reported the asymmetric reduction of 1,2-diaryl-2-benzyloxyiminoethanones[6] and Davis et al. reported an asymmetric synthesis of benzoin oxime by the asymmetric enolate oxidation of deoxybenzoin.[7] Despite the existence of these procedures, there remains a need for a practical and convenient preparation of optically pure benzoin from which a host of important optically active compounds, including the *erythro*-2-amino-1,2-diphenylethanols, can be accessed. In our own work, we have extensively demonstrated that (5*S*,6*R*)- and (5*R*,6*S*)-4-CBz and *t*-BOC-5,6-diphenyl-2,3,5,6-tetra-

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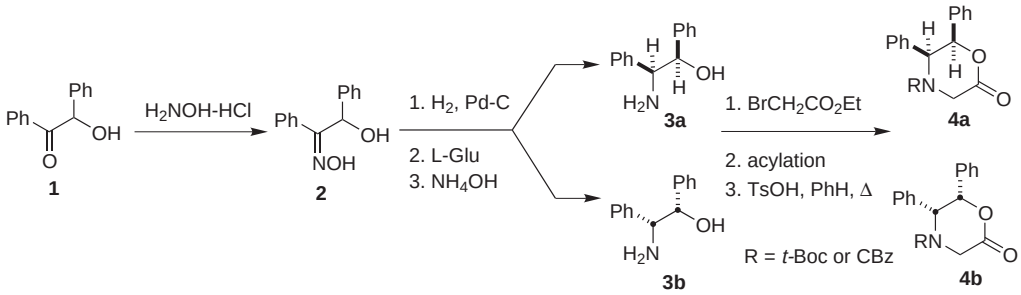


Scheme 1.

hydro-4*H*-1,4-oxazin-2-ones, are useful as a chiral, non-racemic glycine templates for the synthesis of structurally diverse α-amino acids.[1] Thus far, the commercial synthesis of these compounds (Scheme 1) has employed the classical Tishler procedure,[4] which involves a rather time-consuming crystallization procedure that has limited large (>10 kg) throughput. This limitation has prompted us to investigate an alternative approach. We would like to report here the enzymatic optical resolution of benzoin and the preparation of optically pure (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethanol.

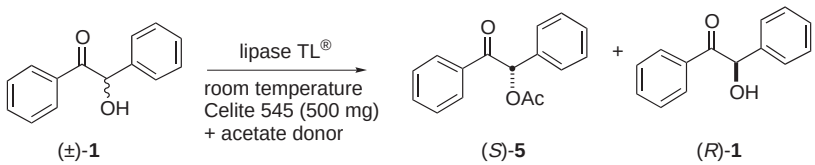
Initially, we examined the kinetic resolution of (±)-benzoin (**1**) in the presence of various commercially available lipases including, PPL, Amano PS®, Amano I®, Amano II®, Lipase MY®, UL®, TL®, SC®, AL®, OF®, and QL® in a mixture of vinyl acetate and THF at room temperature. Among these lipases, Lipase TL® was found to be the most effective (conversion rate up to 50%). Next, the reaction parameters were varied including the acyl donor, reaction time, and solvent; the results are shown in Table 1. The best results were obtained when the

Table 1
Kinetic resolution of (±)-benzoin **1**

Entry	Lipase TL® (mg)[a]	Solvent[b]	Acyl donor[d]	Reaction time (h)	(*S*)-**5**		(*R*)-**1**	
					Yield (%)	Er[g]	Yield (%)	Er[g]
1	10	THF[b]	VA	20	9	–	79	–
2	50	THF[b]	VA	20	29	–	35	–
3	100	THF[b]	VA	42	40	–	53	–
4	250	THF[b]	VA	20	52	–	46	–
5	100	EtOAc[b]	VA	20	2	–	95	–
6	100	Benzene[b]	VA	20	18	–	69	–
7	100	THF[b]	IA	43	3	–	88	–
8[e]	1250	THF[c]	VA	20	42	>99:1	40	97:3
9[e,f]	1250	THF[c]	VA	20	46	>99:1	48	96:4

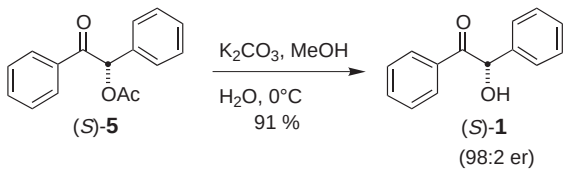
[a] Reaction scale = 100 mg of racemic benzoin.
[b] 5 mL of solvent was used.
[c] 25 mL of solvent was used.
[d] VA: vinyl acetate, IA: isopentenyl acetate; 12 equiv. of the acyl donor was employed.
[e] Reaction scale = 500 mg of racemic benzoin.
[f] Reaction in the absence of Celite®.
[g] The enantiomeric ratios (er's) were determined by HPLC using Chiralcel OD®.

reaction was conducted in a mixture of THF as a solvent and vinyl acetate as an acyl donor at room temperature (entry 4). The products were easily separated by flash column chromatography on silica gel. On the basis of these results, the conditions employed in entry 4 were scaled to 500 mg of racemic benzoin both in the presence and absence of Celite®. The best results obtained (Table 1, entry 9) gave (*R*)-**1** in 48% yield and 96:4 er plus (*S*)-**2** in 46% yield and >99:1 er.[8] The enantiomeric ratios of benzoin acetate and the recovered benzoin were determined by using chiral HPLC analysis (Chiralcel OD®).[9] When the kinetic resolution of benzoin was conducted in the presence of a recovered Lipase TL®, the same product ratios were obtained within experimental error. Thus, although a 2.5 g/g excess of enzyme was found to be optimal, it can be easily recovered and re-used without loss of enzymatic activity (Scheme 2).



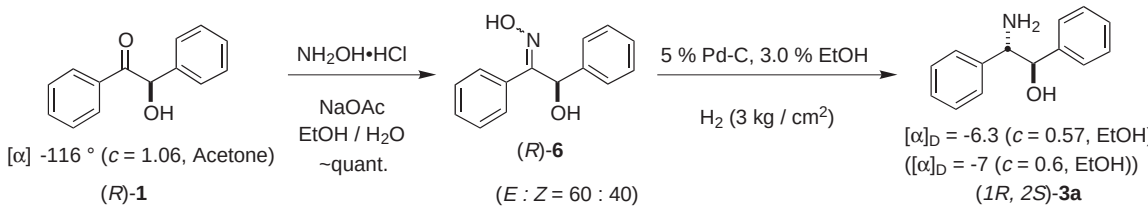
Scheme 2.

The antipode (*S*)-**1**, was obtained from (*S*)-**5** by saponification with potassium carbonate in methanol–water at 0°C to give the corresponding benzoin (*S*)-**1**, in 91% yield and 98:2 er (Scheme 3).[10]



Scheme 3.

The transformation of (*R*)-benzoin to (1*R*,2*S*)-*erythro*-2-amino-1,2-diphenylethanol (**3a**) via the corresponding oxime was performed to confirm that the optical integrity of the benzoin can be maintained. Treatment of (*R*)-**1** with hydroxylamine hydrochloride in a mixture of EtOH and H_2O gave the corresponding oxime (obtained and used as 60:40 mixture of *E* and *Z* isomers) in quantitative yield (**6**, Scheme 4). Catalytic hydrogenation of the *E*-*Z* mixture of oxime **6** proceeded stereoselectively to give the *erythro*-amino alcohol **3a** in high yield. The enantiomeric purity of **3a** was determined to be 99:1 by chiral HPLC analysis (Chiral CD-Ph®).[9]



Scheme 4.

Since the optically active amino alcohols **3** have previously been converted to the oxazinones **4** in high yield without the need for chromatographic separation, the present procedure constitutes an alternative for the practical synthesis of both antipodes of the glycinates (**4a** and **4b**).[1] Further, since highly optically enriched benzoin can be employed as an important intermediate for the synthesis of other optically active substances, the procedure reported here employing recyclable lipase-mediated kinetic resolution may enjoy additional utility. The application of this procedure for the production of other substituted benzoin derivatives in optically active form is under investigation in these laboratories.

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7. Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem*. **1989**, *54*, 2021–2024. This procedure reports a 0.32 g scale in five steps from deoxybenzoin in >96% optical purity.
8. Kinetic resolution of benzoin (**1**): a mixture of benzoin **1** (100 mg, 0.47 mmol), THF (5 mL), and vinyl acetate (0.5 mL, 5.64 mmol) was stirred at room temperature for 15 h. After filtration, the filtrate was concentrated in vacuo to give a residue. The residue was purified via flash column silica gel chromatography (eluted with hexane–EtOAc) to give (*S*)-acetate **5** and recovered (*R*)-benzoin **1**.
9. Determination of enantiomeric ratios of benzoin (**1**) and benzoin acetate (**5**) by use of HPLC. Column: Daicel Chiralcel OD® column (4.6×250 mm). Solvent: hexane: ^{i}PrOH = 9: 1. UV wave length: 270 nm. Flow rate: 1.0 mL/min. Pressure: 20 kg/cm^2.
10. Hydrolysis of (*S*)-benzoin acetate (**5**): A mixture of (*S*)-acetate **5** (100 mg, 0.39 mmol), MeOH (30 mL), H_2O (30 mL) and K_2CO_3 (54 mg, 0.39 mmol) was stirred at 0°C for 4 h. After adding H_2O (150 mL) to the reaction mixture, the aqueous solution was extracted with EtOAc (50 mL×3). The organic layer was washed with sat. NaCl (50 mL×3), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a residue that was purified by flash column chromatography (hexane–AcOEt = 6:1) to give a (*S*)-benzoin. The er of the product was determined by HPLC method mentioned above.