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Dynamic Kinetic Resolution of Benzoins by Lipase−Metal Combo Catalysis

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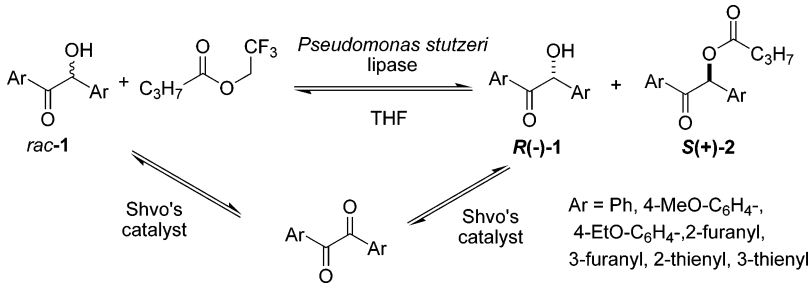

The synthesis of some noncommercial racemic 1,2-diaryl-2-hydroxyethanones (benzoins) is described, optimizing the previously reported methodologies. In a further step, the kinetic resolution of these substrates is reported, obtaining conversions of around 50% and ee_p higher than 99% in very short reaction times. As enzymatic catalyst, after screening of several enzymes, the lipase TL (from *Pseudomonas stutzeri*) was the most efficient, working in an organic solvent with a very low log *P* value, such as THF. Finally, the dynamic−kinetic resolution of different benzoins using a lipase−ruthenium-catalyzed transesterification in organic solvents is described for the first time, obtaining conversions up to 90% maintaining the excellent enantioselectivity in all cases.

Introduction

Optically pure α-hydroxy ketones are important structural units for many drugs and natural products, such as the antidepressant bupropion and its metabolites,[1] a component of indinavir (inhibitor of HIV protease[2]), some antitumoral antibiotics such as olivomycin A and chromomycin A_3,[3] or some inhibitors of amyloid-β protein production, useful in the treatment of Alzheimer's disease.[4]

Benzoins (1,2-diaryl-2-hydroxyethanone structures) are particularly useful as urease inhibitors[5] or as building blocks for the synthesis of different heterocycles.[6] These compounds are generally obtained through benzoin condensation, one of the most traditional C−C bond-forming reactions in organic chemistry, which uses a nonchiral catalyst such as cyanide,[7] thiamine,[8] or other chiral thiazolium and triazolium salts in a biomimetic manner.[9] Chiral benzoins can also be obtained enzymatically by the enantioselective benzoin or acyloin condensation catalyzed by thiamine diphosphate dependent enzymes:[10] pyruvate decarboxylase (PDC), benzoylformate decarboxylase (BFD), and

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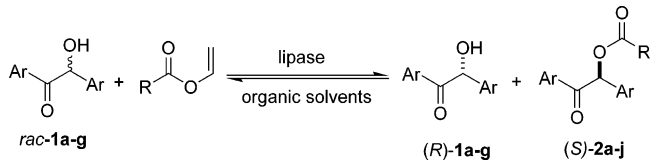
TABLE 1. Substrates of the Enzymatic Kinetic Resolution



substrates			products
1a	Ar = Ph	(*R*)-(−)-**1a**	(*S*)-(+)-**2a**: Ar = Ph; R = $-CH_3$
			(*S*)-(+)-**2b**: Ar = Ph; R = $-C_3H_7$
1b	Ar = 2-furanyl	(*R*)-(−)-**1b**	(*S*)-(+)-**2c**: Ar = 2-furanyl; R = $-CH_3$
			(*S*)-(+)-**2d**: Ar = 2-furanyl; R = $-C_3H_7$
1c	Ar = 3-furanyl	(*R*)-(−)-**1c**	(*S*)-(+)-**2e**: Ar = 3-furanyl; R = $-CH_3$
1d	Ar = 2-thienyl	(*R*)-(−)-**1d**	(*S*)-(+)-**2f**: Ar = 2-thienyl; R = $-CH_3$
			(*S*)-(+)-**2g**: Ar = 2-thienyl; R = $-C_3H_7$
1e	Ar = 3-thienyl	(*R*)-(−)-**1e**	(*S*)-(+)-**2h**: Ar = 3-thienyl; R = $-C_3H_7$
1f	Ar = 4-$MeOC_6H_4$	(*R*)-(−)-**1f**	(*S*)-(+)-**2i**: Ar = 4-$MeOC_6H_4$−; R = $-C_3H_7$
1g	Ar = 4-$EtOC_6H_4$	(*R*)-(−)-**1g**	(*S*)-(+)-**2j**: Ar = 4-$EtOC_6H_4$−; R = $-C_3H_7$

benzaldehyde lyase (BAL). Other biocatalytical methods for the synthesis of enantiomerically pure benzoins are the enantioselective reduction of α-diketones[11] and the fungal deracemization[12] or lipase-catalyzed kinetic resolution of racemic benzoin.[13]

Despite the progress in asymmetric synthesis, the dominant production method to obtain a single enantiomer in industrial synthesis is based on the kinetic resolution of racemates.[14] However, an important drawback of kinetic resolutions (KR) is the intrinsic limitation of the maximum theoretical yield at 50%. Under some circumstances, it is possible to obtain a yield of 100% by carrying out substrate racemization under the resolution conditions in a dynamic kinetic resolution (DKR) process.[15] For this purpose, one of the best methods to obtain enantiomerically pure secondary alcohols is to combine an enzymatic resolution with a transition-metal-mediated catalyzed racemization via hydrogen transfer.[16] Nevertheless, the first basic requirement for an efficient DKR is to identify an effective KR. Thus, in this work we report both a convenient enzymatic kinetic resolution of racemic benzoins by means of a lipase-catalyzed enantioselective acylation, as well as the combination of this process with a ruthenium-catalyzed substrate racemization, obtaining the homochiral acylated products in higher yields through a DKR process.

Results and Discussion

Some of the substrates employed in the enzymatic resolution (shown in Table 1), such as benzoin (**1a**), 2-furoin (**1b**), and 4,4′-dimethoxybenzoin (**1f)**, are commercially available. 3-Furoin (**1c**) and 4,4′-diethoxybenzoin (**1g**) were synthesized following the methodology previously described by our group.[10e] 2,2′-Thenoin (**1d**) and 3,3′-thenoin (**1e**) were also synthesized following a classical benzoin condensation through a more simple procedure than that described by Roberts−Bleming et al.,[17] reaching similar yields as those described but employing a much easier workup protocol, as described in the Experimental Section.

The racemic acylated products were also chemically synthesized in order to identify the kinetic resolution products by comparison with their HPLC retention times and UV spectra, except those esters of 3-furoin (**1c**), as their extreme lability, as described,[10e] avoids the preparation of the standards.

Various commercial lipase preparations, either immobilized or crude enzyme powder, were tested for the transesterification process, using racemic benzoin **1a** as the standard substrate. The lipases were tested using different solvents and temperatures, and vinyl acetate as acyl donor, following the methodology described by Aoyagi et al.[13b] Because of the low solubility of **1a** in the low polarity organic solvents usually employed in lipase-catalyzed transesterifications, some different lipase preparations (immobilized lipases from *Candida antarctica* B, *Thermomyces laenuginosus*, and *Rhizomucor miehei*, lipase from *Pseudomonas cepacia*, and Lipase TL from *Pseudomonas stutzeri*) were tested in ^{t}BuOMe, chloroform, and THF, solvents with a low value of log *P* (lower than 2), which are generally considered harmful for the lipase catalysis.[18]

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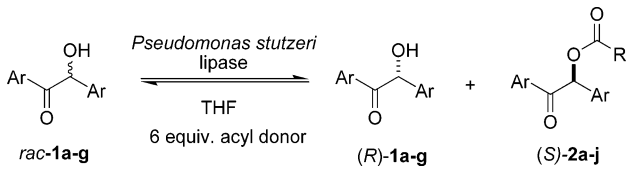
TABLE 2. ***Ps. stutzeri*** **Lipase-Catalyzed Kinetic Resolution of Different Benzoins**[a]



entry	substrate	acyl donor	*T* (°C)	conv[b] (%)	reaction time (h)	ee_p [b] (%)	*E*
1	**1a**	vinyl acetate	rt	50	30	>99	>200
2	**1a**	vinyl butyrate	rt	45	24	>99	>200
3	**1a**	vinyl butyrate	37	49	24	>99	>200
4	**1a**	vinyl acetate	50	49	4	>99	>200
5	**1a**	vinyl butyrate	50	50	4	>99	>200
6	**1b**	vinyl acetate	rt	45	24	95	92
7	**1b**	vinyl butyrate	rt	48	24	95	113
8	**1b**	vinyl butyrate	37	49	24	95	125
9	**1c**	vinyl acetate	rt	43	24	51	4
11	**1d**	vinyl acetate	rt	27	24	84	15
12	**1d**	vinyl butyrate	37	29	24	94	47
13	**1d**	vinyl butyrate	50	43	6	>99	>200
14	**1e**	vinyl butyrate	rt	42	24	94	66
15	**1e**	vinyl butyrate	50	49	6	>99	>200
16	**1f**	vinyl butyrate	50	49	6	>99	>200
17	**1g**	vinyl butyrate	50	49	6	>99	>200
18	**1a**	trifluoroethyl butyrate	50	35	24	>99	>200

[a] Reaction conditions: 0.47 mmol of **1** was dissolved in 5 mL of THF, and Lipase TL (20 mg/mL) and the acyl donor (6 equiv) were added under inert atmosphere. [b] Determined by HPLC analysis using Chiralcel OD column.

Only Lipase TL showed activity in this process, as was described by Aoyagi et al.,[13b] and no conversion was detected for the other enzymatic preparations. Lipase from *Pseudomonas stutzeri* has been frequently included in previous screenings for searching the best catalyst in the resolution of different compounds,[19] but very few papers describe this uncommon enzyme as the best for transesterification processes.[13a,b,20] The kinetic resolution of **1a** catalyzed by Lipase TL in THF was carried out under different experimental conditions, as shown in Table 2 (entries 1−5).

Although the resolution in entry 1 is much better than that published by Aoyagi et al.[13b] (only a 40% yield after 42 h, no ee_p data reported), it is necessary to further improve the efficiency of the KR in order to have an optimal starting point for an ulterior DKR. As it has been shown that the structure of the acyl donor influences the catalytic efficiency of the lipase,[21,22] vinyl butyrate was tested as acyl donor, and this gave an excellent behavior at a slightly lower reaction time (24 h, Table 2, entry 2). Furthermore, the reaction product ((*S*)-2-oxo-1,2-diphenylethyl butyrate, Table 1, **2b**) was much easier to purify from the reaction mixture by column chromatography. These findings suggest that vinyl butyrate is the most convenient acyl donor.

In a second step, the effect of temperature on the KR of **1a** was studied. The results in Table 2 (entries 3−5) show that the conversion rate increased when the reaction temperature was raised, maintaining in all cases the excellent enantioselectivity observed. The most favorable temperature for this substrate was 50 °C because of the highest yield and ee_p values obtained at a really short reaction time (4 h). This optimal temperature value agrees with the one provided by the supplier,[23] although when the enzyme stability at 50 °C was tested by incubation in the reaction medium a moderate decrease in the lipase activity was observed after 4 h (data not shown).

The KR of some other racemic benzoins (**1b**−**1g**, Table 1) was carried out in a similar way, and different acylating agents and temperatures were tested in each case. The results in Table 2 (entries 6−17) show excellent conversions and enantioselectivity, except for the kinetic resolution of 3,3′-furoin (**1c**), which once again showed a remarkable tendency toward racemization.[10e] In fact, it is well-known that benzoins are prone to suffer from auto-oxidation process leading to the corresponding dicarbonyl compounds.[24] This process is favored by the presence of bases because the enediolate intermediate is more sensitive to oxidation.[25] On the other hand, this side reaction is even more severe for substrates possessing electron-rich aromatic rings,[26] which are very easily oxidized, particularly at high temperatures. In some cases, e.g., for **1b** and **1c**, although the enzyme activity is higher at 50 °C, this temperature should not be used as a greater percentage of substrate is oxidized. Nevertheless, in most cases, the exceptional catalytic behavior of Lipase TL at high temperature made possible the kinetic resolution at a reaction rate which is higher than that of the collateral oxidation, so that excellent conversions and enantioselectivities were reached in a very short reaction time (4−6 h).

After reaching the maximum conversion for each case, the optically pure products **2a**−**c**,**g**−**j** were purified by silica gel column chromatography, and the optical rotations were measured. The absolute configurations of the acylated product of **1a** (**2a** and **2b**), **1b** (**2c**), **1d** (**2g**), and **1f** (**2i**) were assigned to be *S*, according to a correlation of the positive optical rotations values of the benzoins with data from the literature[10c,27] and to HPLC data of the standards. Consequently, the absolute configuration of **2h** and **2j** was assigned assuming a uniform reaction mechanism.

For this substrate, according to Kazlauskas' rule,[28] which predicts the enantiomer that will be preferentially converted by

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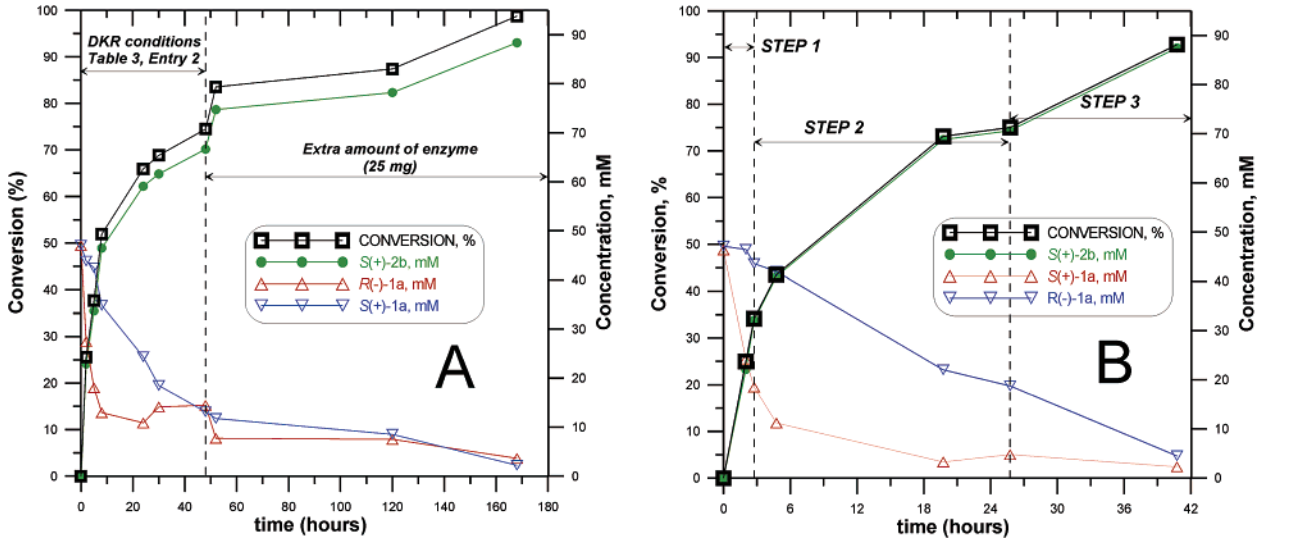
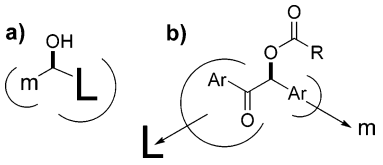


FIGURE 1. (A) DKR of **1a** adding fresh enzyme after 48 h; (B) sequential DKR of **1a**.

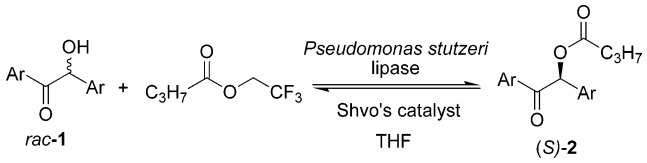
SCHEME 1. (a) Preferred Enantiomer According to Kazlauskas' Rule.[28] (b) *S*-(+) Enantiomer of Acylated Benzoins



most of lipases depending on the relative size of substituents (*m* = medium, L = large) around the stereocenter, as depicted in Scheme 1, the *R*-enantiomer was expected to be preferentially recognized by the lipase. In this case, special enzymatic substrate recognition was observed, and unexpectedly the *S*-enantiomer was acylated by the lipase. As had been previously pointed out by Martín-Matute and Bäckvall[29] for lipase B from *C. antarctica*, the keto group of benzoin could bond to the enzyme in the active site, and in this way it will behave like a small group instead as a large group.

To carry out the DKR, the lipase−metal combo catalysis[16] was followed. In this methodology, the DKR is obtained in a one-pot methodology by coupling the enzymatic KR with an in situ ruthenium-based racemization process. Thus, the DKR of benzoin was carried out using Shvo's catalyst[30] (1-hydroxytetraphenylcyclopentadienyl (tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyldiruthenium) at 50 °C. The use of vinyl esters as acyl donors in the lipase-catalyzed KR results in the formation of acetaldehyde, which can interfere with the hydrogen transfer catalyst employed in the DKR.[16c] Thus, an activated ester (trifluoroethyl butyrate) was chosen as the acylating agent because, according to literature data,[16a,b] the isolation of products is easier when using this kind of activated esters compared to aryl esters, also decribed for DKR. In a previous experiment, benzoin KR was carried out with this acyl donor (Table 2, entry 18), resulting in a lower reaction rate than that obtained using vinyl butyrate. In any case, different

TABLE 3. One-Pot Dynamic Kinetic Resolution of Different Benzoins[a]



entry	substrate	lipase amt (mg)	Shvo's catalyst (equiv)	*T* (°C)	conv[b] (%)	reaction time (h)	ee$_p$ [b] (%)
1	**1a**	25	0.05	50	68	48	>99
2	**1a**	50	0.05	50	71	48	>99
3	**1a**	75	0.05	50	84	48	>99
4	**1a**	100	0.05	50	40	48	>99
5	**1a**	50	0.1	50	52	48	>99
6	**1a**	50	0.05	40	87	55	>99
7	**1b**	50	0.05	50	78	72	>99
8	**1e**	50	0.05	50	76	72	>99

[a] Reaction conditions: 0.011 mmol of Shvo's catalyst, Lipase TL (20 mg/mL), 0.235 mmol of **1** in 2.5 mL of THF, trifluoroethyl butyrate (1.32 mmol), at 50°C under inert atmosphere. [b] Determined by HPLC analysis using Chiralcell OD column.

experimental conditions (relative amounts of enzyme and metal catalyst) were tested in order to optimize the DKR with this acyl donor. The results are summarized in Table 3 (entries 1−5). As can be seen, conversions as high as 84%, with excellent enantioselectivity, are described for the first time in the acylation of benzoin. However, due to the lower enzymatic activity with trifluoroethyl butyrate, longer reaction time (48 h) is required for the process, so that the side oxidation to the dicarbonyl compound is increased. The conversion was slightly improved by lowering the reaction temperature to 40 °C and leaving the reaction time up to 55 h (entry 6).

Two other substrates were tested, **1b** and **1e**, which gave similar conversion values (around 80%), not detecting any trace of the other enantiomer of the corresponding esters. Thus, the excellent enzymatic enantioselectivity is not altered by the metal catalyst.

Nevertheless, to improve the results, we tried a different sequential strategy: as mentioned before, the enzyme suffers from a moderate deactivation when incubated at 50 °C, so an extra amount of enzyme was added to the reaction media after

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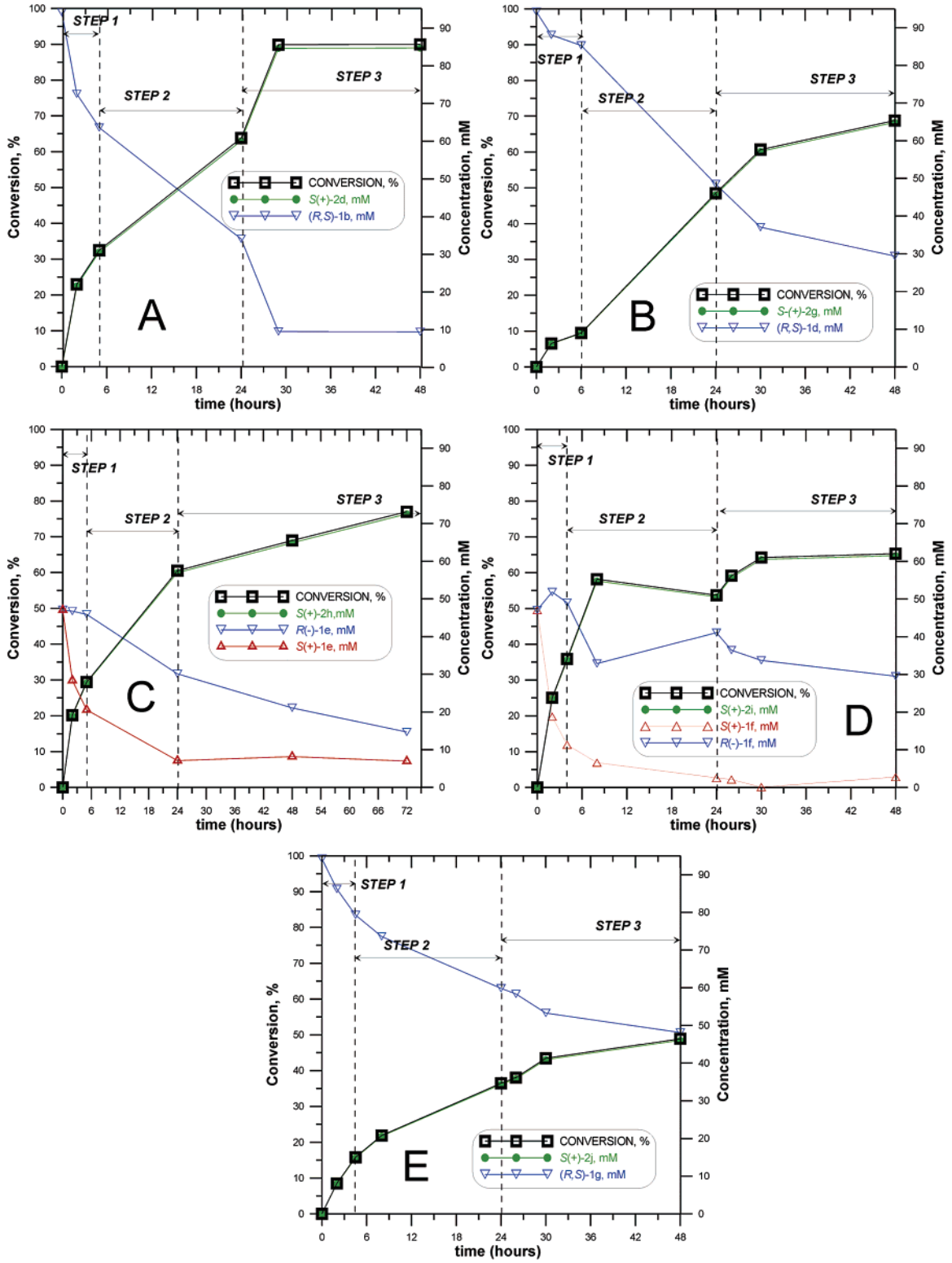

FIGURE 2. Sequential DKR of different benzoins: (A) DKR of **1b**; (B) DKR of **1d**; (C) DKR of **1e**; (D) DKR of **1f**; (E) DKR of **1g**.

48 h in order to compensate the decrease of enzymatic activity. The results are shown in Figure 1A. As can be seen, the conversion was increased up to 93% with an ee_p value higher than 99%, although the reaction time had to be extended up to 168 h.

To the best of our knowledge, these are the best results described for the DKR of benzoin, but a large increase in the reaction time was demanded as a consequence of the slow acylation capability of the lipase with trifluoroethyl butyrate, so that another strategy was followed: thus, in a first step, vinyl butyrate (much better acyl donor, but unsuited for DKR[16c]) and a small amount of lipase was used for a quick KR; after evaporating the remnant acyl donor, Shvo's catalyst, trifluoroethyl butyrate, and a new amount of fresh lipase were added (second step). Finally, to compensate the previously mentioned enzymatic deactivation, in a third step, a new portion of enzyme

was added. The results obtained are depicted in Figure 1B, yielding 92% of conversion of enantiopure (*S*)-(+)-**2b** at a much shorter reaction time (only 48 h vs 168 h in Figure 1A).

These conditions were adopted for testing the lipase capability in the DKR of some other benzoins, as shown in Figure 2. As can be seen, the DKRs applying this sequential methodology lead to good conversion values (between 50 and 90%) for the different substrates tested, maintaining for all cases the excellent optical purity of the products at reduced reaction times (48−72 h).

Through this DKR, it would be possible to obtain the *S*-enantiomer of benzoins in very good yield and enantiopurity by a further mild basic hydrolysis of *S*-esters as described,[13b] while by using BAL-mediated condensation[10] the enantiomer obtained is the antipode *R*-benzoin, so that the significance of this lipase−metal combo catalysis is even higher. This is another example on the use of different enzymes to obtain complementary enantiomers,[31] which can be particularly useful in the synthesis of chiral building blocks. Further experiments are being conducted in our laboratory (use of second-generation ruthenium catalysts) to improve the DKR methodology and to apply it to new benzoins.

Conclusions

In this paper, the first case of dynamic kinetic resolution of benzoin-type substrates is described by employing a kinetic resolution of racemic substrates (lipase-catalyzed enantioselective acylation) combined with an in situ ruthenium-catalyzed substrate racemization, proficiently obtaining the homochiral *S*-acylated products (yields up to 90%, with enantiomeric excess values higher than 99%). In all cases, the particular stereobias of the lipase toward the racemic substrates allows the production of the opposite enantiomer of that one described through a different enzymatic methodology.

Experimental Section

General Procedure for the Synthesis of Thenoins: 2-Thenoin (1d). Thiamine hydrochloride (1.686 g, 5 mmol) was dissolved in absolute ethanol (30 mL), and triethylamine (4.2 mL, 30 mmol) and 2-thiophenecarboxaldehyde (8.9 mL, 100 mmol) were added. The mixture was stirred at room temperature under argon. After 24 h, the product started to precipitate. It was filtered, and the white solid collected (**1d**) (10.75 g, 48 mmol) was washed with cold ethanol (48% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.79 (1H, dd, J = 3.8, 1.0 Hz), 7.75 (1H, dd, J = 4.9, 1.1 Hz), 7.34 (1H, dd, J = 5.9, 1.1 Hz), 7.15 (1H, dd, J = 4.9 Hz), 7.13 (1H, dddd, J = 3.5, 1.2, 0.6 Hz), 7.01 (1H, dd, J = 5.1, 3.5 Hz), 6.07 (1H, s), 4.41 (1H, 2d, J = 1.4, 0.8 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 190.3, 142.4, 139.6, 135.8, 134.7, 128.8, 127.6, 127.3, 127.2, 71.3.

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General Procedure for the Synthesis of the Racemic Acylated Products (2a−j): Synthesis of 2-Oxo-1,2-diphenylethyl Butyrate (2b). Compound **1a** (212.25 mg, 1 mmol) was dissolved in dichloromethane (3 mL), and triethylamine (1.1 mmol) and butyryl chloride (1.5 mmol) were added. The mixture was stirred at room temperature for 15 h. Purification by column chromatography (SiO_2, *n*-hexane/ethyl acetate, 5:1) yielded **2b** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.97 (2H, dd, J = 8.3, 2.0 Hz), 7.96 (2H, dd, J = 8.3, 1.5 Hz), 7.57 (1H, t, J = 1.3 Hz), 7.54 (1H, t, J = 2.4 Hz), 7.51 (1H, m), 7.48 (1H, d, J = 1.9 Hz), 7.45 (1H, dd, J = 1.4, 2.0 Hz), 7.42 (1H, m), 7.39 (1H, dd, J = 1.9, 2.0 Hz), 7.37 (1H, d, J = 1.9 Hz), 6.89 (1H, s), 2.54 (1H, c, J = 7.6 Hz), 2.42 (1H, c, J = 7.6 Hz), 1.74 (2H, sex, J = 7.4 Hz), 1.0 (3H, t, J = 7.4 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ 194.3, 173.6, 135.1, 134.1, 133.8, 129.6, 129.5, 129.5, 112.8, 76.9, 36.2, 18.8, 14.0.

General Procedure for the Kinetic Resolution of Benzoins. Compound **1a** (100 mg, 0.47 mmol) was dissolved in 5 mL of THF, and lipase from *Ps. stutzeri* (20 mg/mL) and vinyl butyrate (358 μL, 2.82 mmol) were added. The mixture was stirred at 50 °C under argon for 4 h. Conversion (50%) and enantiomeric excess (>99%) were determined by HPLC analysis (*n*-hexane/2-propanol, 90:10). The product (*S*)-**2b** was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 5:1). NMR data of (*S*)-**2b** are similar to those of *rac*-**2b**. $[\alpha]^{20}_D$: +117.8 (*c* 3.5 $CHCl_3$).

General Procedure for "One-Pot" Dynamic Kinetic Resolution of Benzoin Compounds. Shvo's catalyst (12 mg, 0.011 mmol) and lipase from *Ps. stutzeri* (50 mg) were added to a 5 mL flask. *rac*-**1a** (50 mg, 0.235 mmol), anhydrous THF (2.5 mL), and trifluoroethyl butyrate (200 μL, 1.32 mmol) were added, and the mixture was stirred at 50 °C under argon. Conversion and enantiomeric excess were determined by HPLC analysis (*n*-hexane/2-propanol, 90:10).

General Procedure for "Sequential" Dynamic Kinetic Resolution of Benzoin Compounds. First Step (Quick KR). Compound **1a** (50 mg, 0.235 mmol) was dissolved in 2.5 mL of anhydrous THF, and lipase from *Ps. stutzeri* (25 mg) and vinyl butyrate (300 μL, 2.36 mmol) were added. The mixture was stirred at 50 °C under argon until 30% conversion was reached (2.75 h). **Second Step (DKR).** The mixture was filtered, and THF and the remnant acyl donor were evaporated. The solid was resolved in 2.5 mL of THF, and Shvo's catalyst (6 mg, 0.0055 mmol) and trifluoroethyl butyrate (200 μL, 1.32 mmol) were added. The new reaction mixture was stirred at 50 °C under argon. **Third Step.** After 17 h, 25 mg of fresh enzyme was added, and the mixture was stirred at 50 °C under argon until no remnant substrate was detected by HPLC analysis (*n*-hexane/2-propanol, 90:10).

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Supporting Information Available: General experimental procedure, full spectroscopic data for all new compounds, and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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