Kinetic Resolution of 1-Biaryl- and 1-(Pyridylphenyl)alkan-1-ols Catalysed by the Lipase B from *Candida antarctica*

Robert Kourist, Javier González-Sabín, Ramón Liz, Francisca Rebolledo*

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33071 Oviedo, Spain
Fax: (+34)-98-510-3448, e-mail: FRV@fq.uniovi.es

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Abstract: Lipase B from *Candida antarctica* (CAL-B) catalyses the highly enantioselective ($E > 200$) transesterification of some 1-biaryl-2-yl-, -3-yl-, and -4-ylethanols and -propan-1-ols, as well as 1-(*o*-, *m*-, and *p*-pyridylphenyl)ethanols, **6**, with vinyl acetate, Kazlauskas' rule being obeyed in all cases. *meta* and *para*-Substituted substrates were transformed within several hours (conversion degree ranging from 23–50%), reaction rates for propan-1-ol derivatives being slower than those for ethanol derivatives. Transesterifications of *ortho*-substituted alcohols took several days and were accompanied by a chemoenzymatic side reaction: the formation of another acetate derived from the hemiacetal between **6** and acetaldehyde coming from vinyl acetate. This side reaction was suppressed in the presence of isopropenyl acetate as acyl donor, conversion degrees for transesterification ranging from 20–40% after ten days ($E > 200$). The usefulness of (*R*)-**6p** as ligand in the asymmetric addition of diethylzinc to benzaldehyde was also demonstrated.

Keywords: alcohols; enantioselectivity; enzyme catalysis; hemiacetal esters; transesterification

Introduction

Synthesis of optically active 1-(het)arylalkan-1-ols is an area of continuous interest in organic chemistry. These compounds can be easily transformed into other compounds such as amines, sulphur or phosphorus derivatives, and have been used for the preparation of chiral drugs and ligands.[1] Furthermore, fluorine-containing optically active alcohols are also of great value due to their potential use as ferroelectric liquid crystals and drugs.[2]

Among the diversity of methods to obtain optically active alcohols,[3] the lipase-catalysed kinetic resolution of racemic alcohols has become a popular methodology, a great variety of enantioenriched alcohols and derivatives being prepared by means of hydrolysis, esterification and transesterification reactions.[4] The mild reaction conditions of these processes, the availability of lipases, the high values of the chemo- and stereoselectivities often exhibited by these enzymes as well as their compatibility with other non-enzymatic catalysts[5] have contributed to stimulating the interest of organic chemists towards these catalysts.

In this paper we present the synthesis and resolution of a variety of 1-biaryl-2-yl-, -3-yl-, and -4-ylethanols and -propan-1-ols, as well as 1-(*o*-, *m*-, and *p*-pyridylphenyl)ethanols, **6**, by means of transesterification reactions catalysed by lipase B from *Candida antarctica* (CAL-B). Several reasons prompted us to choose these substrates. Biaryls and arylpyridines form the basic structure of many biologically active compounds[6] and also are found in new materials such as electroluminiscent conjugated polymers[7] and semiconductors.[8] Moreover, optically active biaryl compounds have found widespread application as ligands in catalytic asymmetric synthesis.[9] On the other hand, our goal is also to investigate the catalytic activity and enantioselectivity of CAL-B towards substrates **6**. Substrate mapping studies have shown that secondary alcohols bearing a medium-sized substituent such as a methyl or ethyl group are successfully resolved by CAL-B. However, substrates bearing biaryl groups as the large-sized substituent have not been investigated. We also focused our interest on the study of the influence of both steric and electronic effects of the biaryl substituents on enzyme activity. We accordingly investigated seventeen different substrates **6**, including examples of *ortho*-, *meta*- and *para*-isomers, as well as those with methyl, methoxy and fluoro substituents on the ring that does not bear the alcohol chain.

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Results and Discussion

Synthesis of Racemic Alcohols 6

The preparation of alcohols *rac*-**6** was accomplished by $NaBH_4$ reduction of the corresponding ketones **5** which, in turn, were obtained *via* Suzuki–Miyaura cross-coupling reactions between appropriate aryl bromides and arylboronic acids.[10] Acetyl or propionyl groups were previously present in the aryl bromides, except for the synthesis of methyl pyridylphenyl ketones, which were prepared from bromopyridines and acetylphenylboronic acids (Scheme 1). The synthesized alcohols *rac*-**6a–q** are shown in Figure 1.

Enzymatic Resolution of Racemic *para*- and *meta*-Substituted Alcohols 6a–n

The resolution of alcohols *rac*-**6a–n** was carried out by transesterification reactions catalysed by CAL-B (Novozym 435) using vinyl acetate as acyl donor and *tert*-butyl methyl ether as solvent.[11] In all cases, the acyl donor was employed in a three-fold molar excess with respect to the substrate, 4 Å molecular sieves being added to ensure a low water activity in the reaction medium. The obtained results are shown in Table 1.

In spite of the variety of substrates used, the enantioselectivity values (E)[12] were very high in almost all cases, thus allowing the isolation of acetates (*R*)-**7** in enantiopure form or with ee > 99%. In those cases where reactions were stopped at a 50% conversion value (Table 1, entries 1, 9, 11 and 13), both products (*R*)-**7a**,**i**,**k**,**m** and remaining substrates (*S*)-**6a**,**i**,**k**,**m** were obtained with very high ee (> 97%).

As regards the influence of the substrate structure on enzyme activity, all the ethanol substrates **6a–c**, **i–m** were transformed with similar enantioselectivities and, especially, reaction rates. Thus, irrespective of the *para* or *meta* geometry, of the phenyl or pyridyl nature of the ring remote from the ethanol chain, and of the presence or absence of substituents in this latter ring, all of these substrates were transformed at average reaction rates ranging from 7.1 to 16.7 mmol L^{-1} h^{-1}. However, propan-1-ol substrates **6d–h**, **n** were clearly acetylated more slowly (average reaction rates range, 1.2–2.9 mmol L^{-1} h^{-1}). Interestingly, the lowest E value was observed for the slower substrate, **6n**.

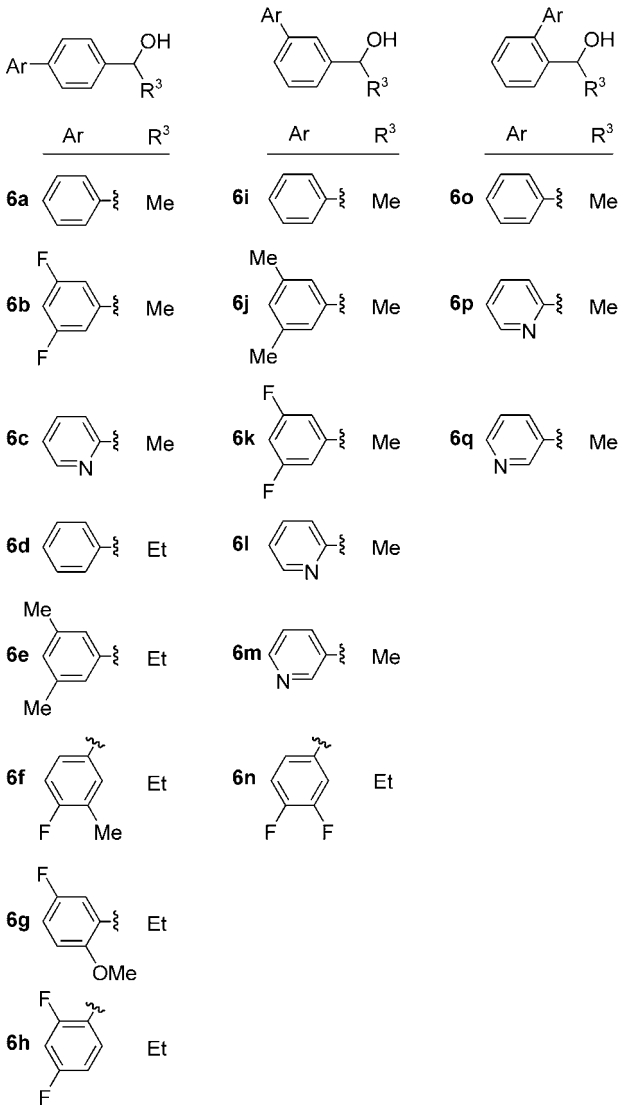
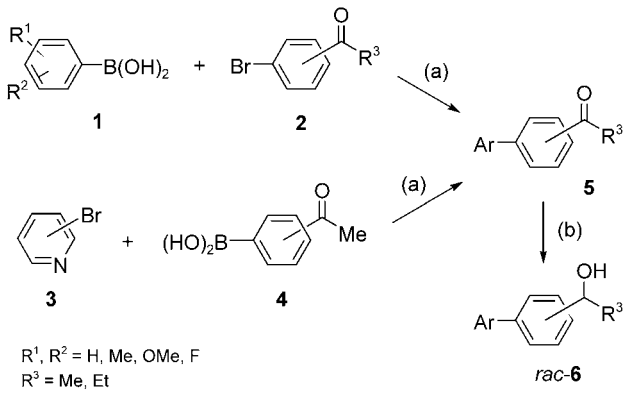


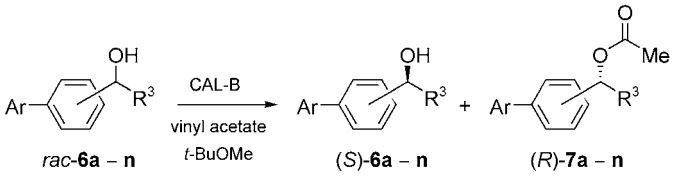
Figure 1. Racemic alcohols prepared according Scheme 1.



Scheme 1. Reagents: (a) $Pd(OAc)_2$, Ph_3P, aqueous Na_2CO_3, propan-1-ol; (b) $NaBH_4$, ethanol.

In the reaction of *rac*-**6a**, the *S*-configuration for the remaining alcohol **6a** was assigned after comparison of its specific rotation with that reported.[13] This means that CAL-B follows Kazlauskas' rule,[14] i.e., the *R*-enantiomer of the substrate is preferentially transformed. The same stereochemical preference was deduced from the reactions of *para*-substituted *rac*-**6e,g** and *meta*- substituted *rac*-**6i,j** by applying Kelly's empirical method[15] as described below. In Figure 2 are shown

Table 1. Enzymatic resolution of *para*- and *meta*-biaryl alcohols *rac*-**6a–h** and *rac*-**6i–n**.[a]



Entry	Substrate	R^3	Time [h]	(*S*)-**6**		(*R*)-**7**		*c* [%][c]	*E*[c]
				Yield [%][b]	ee_S [%]	Yield [%][b]	ee_P [%]		
1	**6a**	Me	4.0	41	>99	50	>99	50	>200
2	**6b**	Me	2.3	50	93	48	>99	48	>200
3	**6c**	Me	2.0	51	93	44	>99	48	>200
4	**6d**	Et	9.0	71	36	26	>99	26	>200
5	**6e**	Et	9.0	65	37	28	99	27	>200
6	**6f**	Et	8.3	60	49	33	enantiopure	33	>200
7	**6 g**	Et	9.0	78	29	21	>99	23	>200
8	**6 h**	Et	5.8	58	38	24	99	28	>200
9	**6i**	Me	1.8	45	98	42	99	50	>200
10	**6j**	Me	2.5	51	72	37	99	42	>200
11	**6k**	Me	4.2	47	98	46	>99	50	>200
12	**6 l**	Me	2.5	38	90	39	>99	48	>200
13	**6 m**	Me	2.6	41	>99	43	enantiopure	50	>200
14	**6n**	Et	17	59	50	34	96	34	90

[a] All the reactions were carried out at 28 °C and 200 rpm.
[b] Isolated yields after flash chromatography.
[c] Determined from ee of the remaining substrate (ee_s) and ee of the product (ee_P) as in ref.[12]

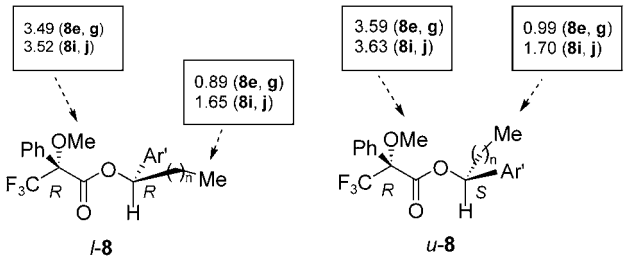


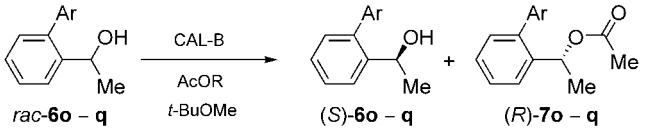
Figure 2. (*R*)-MTPA esters **8e**, **g** (n=1) and **8i**, **j** (n=0). Chemical shifts (δ, ppm) of methoxy and methyl groups (^{1}H NMR, $CDCl_3$) (Ar′=biaryl substituent).

the usual working models for the (*R*)-MTPA esters *l*- and *u*-**8e, g, i, j** derived from *rac*-**6e, g, i, j**, as well as the δ values (^{1}H NMR) for their methoxy and methyl groups. The δ values were assigned taking into account the fact that biaryl (Ar′) substituents shield the methoxy group in *l*-diastereomers, but they do not do so in *u*-diastereomers. Likewise, methyl groups in *l*-diastereomers are shielded by the phenyl group of the Mosher moiety. Chemical shifts for both methoxy and methyl groups of the (*R*)-MTPA esters derived from the optically active alcohols **6e, g, i, j**, obtained after saponification of the enzymatically produced esters **7e, g, i, j**, are identical to those of the *l*-diastereomers, thus establishing the *R*-configuration for **7e, g, i, j**. Bearing in mind these results, as well as the structural analogy of all the substrates investigated here, we have assigned the *S*-configuration to all unreacted alcohols (*S*)-**6** and the *R*-configuration to all products (*R*)-**7**.

Enzymatic Resolution of Racemic *ortho*-Substituted Alcohols 6o–q

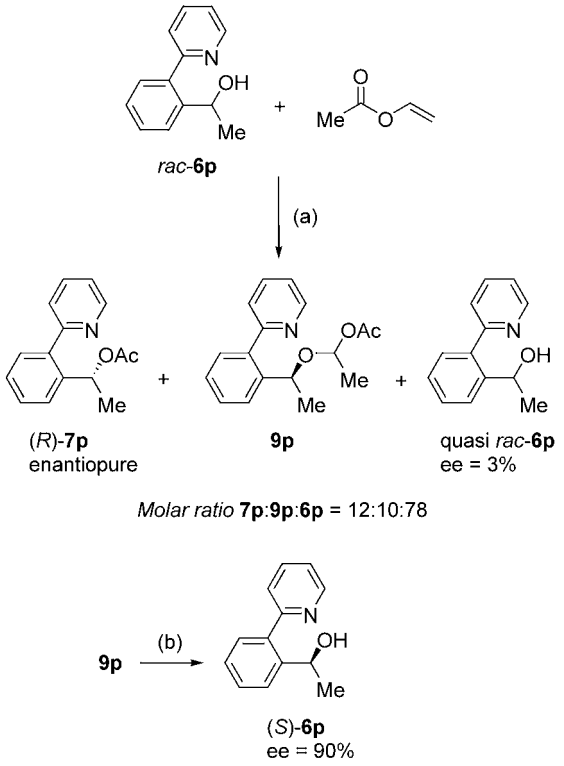
First, we assayed the transesterifications of alcohols *rac*-**6o** and *rac*-**6p** under the same reaction conditions as for *para*- and *meta*-substrates. The enzyme showed a very high enantioselectivity, esters (*R*)-**7o** and (*R*)-**7p** being obtained with an ee>99%. However, reactions were notoriously slower and very low conversion degrees were attained after five days of reaction. The results are shown in Table 2 (entries 1 and 2). Surprisingly, along with the corresponding ester **7o** (or **7p**), another product also bearing an acetate function, **9o** (or **9p**), was formed. Scheme 2 shows the compounds of these reactions, exemplified for that of *rac*-**6p**, including the ratio among them and their ee values. Although all attempts at separating the two esters **7** and **9** by flash column chromatography failed, the structure of **9** could be easily determined from the ^{1}H and ^{13}C NMR spectra of the esters mixtures. Moreover, a small amount of pure **9p** was isolated by semi-preparative HPLC, and its hemiacetal acetate structure was corroborated. To the best

Table 2. Enzymatic resolution of *ortho*-biaryl alcohols *rac*-**6o – q**.[a]



Entry	Substrate	Acyl donor AcOR	Time [days]	(*S*)-**6** ee_S [%]	(*R*)-**7** ee_p [%]	*c* [%]	*E*
1	**6o**	vinyl acetate	5	31	enantiopure	32[b]	>200[c]
2	**6p**	vinyl acetate	5	3	>99	12[b]	>200[c]
3	**6o**	1-(ethoxy)vinyl acetate	8	25	77	24[d]	10[d]
4	**6o**	isopropenyl acetate	10	45	>99	31[d]	>200[d]
5	**6p**	isopropenyl acetate	10	24	enantiopure	20[d]	>200[d]
6	**6q**	isopropenyl acetate	10	67	enantiopure	40[d]	>200[d]

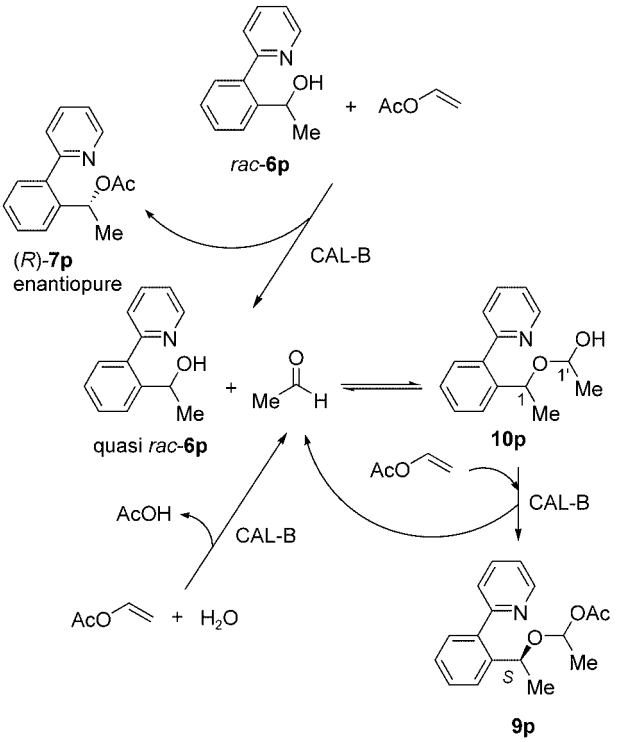
[a] All the reactions were carried out at 28 °C and 200 rpm.
[b] Conversion degree determined by ^{1}H NMR of the reaction crude considering ester **7** as the only product of the reaction.
[c] Determined from ee_P and *c* as in ref.[12]
[d] Determined from ee of the remaining substrate (ee_s) and ee of the product (ee_P) as in ref.[12]



Scheme 2. Reagents and conditions: (a) CAL-B, *t*-BuOMe, 120 h, 28 °C, 200 rpm; (b) 1 N NaOH, MeOH, RT.

of our knowledge, only one previous report exists in which the formation of analogous hemiacetal esters has been described, namely, in lipase-catalysed transesterifications with vinyl acetate of some sterically hindered alicyclic secondary alcohols.[16] However, the enantiomeric purity of the resulting products was determined in the aforementioned study in only one case, for which a very low ee was reported.

The formation of the highly non-racemic **9** involves several steps, as exemplified for **9p** in Scheme 3. Although the route is similar to that published,[16] we consider it of interest to make a number of remarks about this route. Acetaldehyde is actually produced not only during the enzymatic transesterification of **6**, but also as a consequence of a side enzymatic hydrolysis of vinyl acetate. The involvement of this side reaction was demonstrated by the presence of pyridinium acetate salts in



Scheme 3. Steps involved in the enzymatic reaction of *rac*-**6p** with vinyl acetate.

the crude reaction mixture by analysis of its ^{1}H NMR spectrum. Bearing in mind that acetic acid salts were formed in larger amounts than ester **7p**, we think that the main source of acetaldehyde in these processes was the side hydrolysis reaction. Acetaldehyde and substrate **6p** are in equilibrium with the hemiacetal **10p**, this step probably being catalysed by the acid present in the medium. As indicated in Schemes 2 and 3, **6p** is quasi-racemic during all the process to judge by the slow, similar formation rates of **7p** and **9p** (see molar ratio in Scheme 2), as well as by their opposite configurations at the C1 chiral centre. Thus, a final CAL-B-catalysed acetylation of the hemiacetal **10p** would explain the high ee shown by the hemiacetal acetate **9p** (see below). No product **9p** was detected in the absence of the enzyme, even when acetaldehyde was added.

As can be appreciated, hemiacetal **10p** and its acetyl derivative **9p** contain two chiral centres (C1 and C1′), and thus a mixture of four stereoisomers could be formed. We did not investigate the stereoisomeric ratio of **9p**, but only the enantiomeric excess of the alcohol **6p** resulting from its basic hydrolysis. As can be seen in Scheme 2, this alcohol **6p** presents a high ee (90%) and the *S*-configuration, as determined by ^{1}H NMR analysis of its Mosher ester derivative. In the reaction of *rac*-**6o**, the mixture of (*R*)-**7o** (ee > 99%) and **9o** cannot be resolved, but the *S*-configuration for **9o** can be deduced after basic hydrolysis of a 65:35 **7o**:**9o** mixture, which yielded the alcohol (*R*)-**6o** with a very diminished ee (34%). From this result an ee = 91% can be estimated for the alcohol (*S*)-**6o** resulting from the hydrolysis of **9o**. Overall, the enzyme showed an opposite enantiopreference towards the chiral centre C1 in the reactions with **6o**, **p** and **10o**, **p**. This opposite (*S*)-enantiopreference towards **10o**, **p**, where the chiral centre is somewhat distant from the reactive site, has also been observed in the lipase-catalysed transesterification of some *N*-hydroxymethyl-β-lactams.[17]

To avoid the formation of acetaldehyde, other acyl donors such as 1-ethoxyvinyl and isopropenyl acetates were used in the resolution of *ortho*-substituted alcohols. These new acyl donors are activated esters but their respective leaving groups, ethyl acetate and acetone, do not interfere with the enzymatic process. Although acetone could also form a hemiacetal with **6**, the hydroxy group of this compound would be analogous to that of a tertiary alcohol, with CAL-B not showing any transesterification activity towards this kind of substrate.[18] When 1-ethoxyvinyl acetate[19] was employed as acyl donor in the reaction with *rac*-**6o** (Table 2, entry 3), no side products were detected, but the reaction was slower and less enantioselective than when vinyl acetate was used. This lower enantioselectivity may be due to a competitive, non-enzymatic acylation of the alcohol as a consequence of the long reaction time.[20] We thus assayed the reaction of *rac*-**6o** with isopropenyl acetate (entry 4). The reaction was also slower than that with vinyl acetate, but CAL-B showed a very high enantioselectivity, (*R*)-**7o** being obtained as the only product with a very high ee. When these conditions were applied to the other *ortho*-substituted substrates, *rac*-**6p** and *rac*-**6q**, the enzyme also catalysed the reactions with very high enantioselectivities, enantiopure (*R*)-**7p** and (*R*)-**7q** being obtained (entries 5 and 6).

It should be noted that **6p** is the slowest of the three *ortho*-substituted substrates **6o**–**q** investigated here. On the basis of the accepted mechanism by which lipases operate,[21] we consider the lower reactivity of 1-[*o*-(2-pyridyl)phenyl]ethanol (**6p**) to be due to the presence of an intramolecular hydrogen bond between the hydroxy group and the pyridine nitrogen atom. This hydrogen bond may be responsible for (a) a less efficient activation of **6p** by the imidazole of the His-224, which acts as a basic catalyst (Figure 3), and (b) a more rigid structure for **6p**, thus hindering its adequate accommodation in the active site of CAL-B. Additional evidence of this hydrogen bond is the high chemical shift for the hydroxy proton of **6p** (δ = 6.47 ppm) when compared with those of the other *ortho*-substituted substrates [δ = 2.10 (**6o**) and 4.46 (**6q**) ppm], all the ^{1}H NMR spectra being measured in similarly concentrated $CDCl_3$ solutions.

This intramolecular hydrogen bond in **6p** forces both benzene and pyridine rings to lie far from coplanarity. Thus, when the geometry of **6p** was optimized at the HF/6–31G* level of theory, a minimum was found having a N–C2′–C2–C1 dihedral angle (see Fig. 3) of 51°, and a hydrogen bond between the nitrogen of the pyridine ring and the hydroxy group. This geometry precludes the deshielding of the H-3 proton due to the strong –R effect of the 2-pyridyl substituent, which is clearly confirmed by comparison of the ^{1}H NMR spectra of a set of 2-phenylpyridinic compounds. Thus, whereas 2-phenylpyridine and products **6c** and **6 l**, which lack intramolecular hydrogen bond, display chemical shifts ranging from 7.9 to 8.0 ppm for their protons in *ortho* to the pyridine ring, H-3 of product **6p** resonates at 7.40–7.47 ppm (superimposed to H-5).

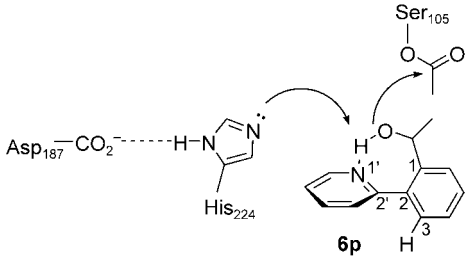
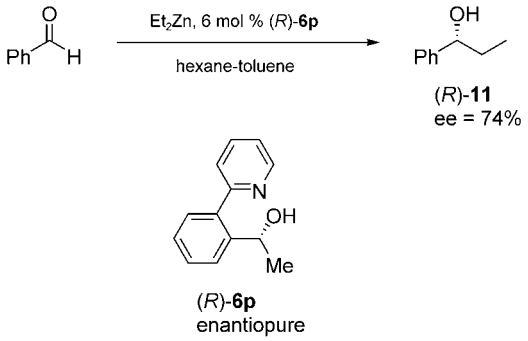


Figure 3. Schematic representation of the attack of **6p** to the acyl enzyme intermediate.

Application of Some Optically Active Biaryl Alcohols

Optically active acetyl derivatives (*R*)-**7c**, **l**, **m**, **p**, **q**, all bearing a pyridine ring and obtained with an ee > 99%, were hydrolysed and the resulting alcohols (*R*)-**6c**, **l**, **m**, **p**, **q** examined as chiral promoters in the addition of diethylzinc to benzaldehyde. Pyridine-containing alcohols were chosen because chiral ligands with the pyridine sp^2 nitrogen donor play an important role in homogeneous catalytic asymmetric reactions.[3a] Reactions were performed at 20 ^{0}C with 2.0 equivs. of Et_2Zn in a 2:1 hexane-toluene mixture, in the presence of 6.0 mol % of alcohol (*R*)-**6**, according to a reported procedure.[22] After 24 h of reaction, benzaldehyde was completely consumed, and the produced 1-phenylpropan-1-ol (**11**) isolated with moderate to high yield (70–92%). Reactions with ligands (*R*)-**6c**, **l**, **m**, **q** were not enantioselective and *rac*-**11** was isolated in all cases. In these ligands, the hydroxy group is far away from the pyridine nitrogen, which prevents the formation of a chelate zinc complex. However, when the addition was carried out with ligand (*R*)-**6p** (Scheme 4), alcohol (*R*)-**11** was isolated with a high yield (92%) and moderate ee (74%). In this case, the hydroxy group is nearer to the pyridine nitrogen, thus facilitating the formation of a chelate zinc complex, as may be anticipated from inspection of the hydrogen bond existing between the hydroxy group and the nitrogen atom.



Scheme 4.

Conclusion

We have demonstrated that CAL-B is a very efficient catalyst for the resolution of a variety of 1-biarylethanols, 1-biarylpropan-1-ols and 1-(pyridylphenyl)ethanols. In almost all cases very high enantioselectivities were obtained in the transesterification with vinyl acetate, although the reactivity was highly influenced by the kind of alcohol and by the geometry of the biaryl or pyridylphenyl ring. Reactions with *para*- and *meta*-substituted 1-biarylpropan-1-ols were slower than those with the analogous ethanols, even though the most significant differences were found with *ortho*-substituted alcohols. Reactions with these substrates and vinyl acetate were so slow that a competitive side reaction took place, i.e., the formation of hemiacetal esters as a consequence of the initial formation of a hemiacetal between the alcohol and the enzymatically produced acetaldehyde and a subsequent enzymatic transesterification of this hemiacetal. Resolutions were efficiently achieved in these cases using isopropenyl acetate as acyl donor. Furthermore, the applicability of 1-(pyridylphenyl)alkan-1-ols as ligands in the asymmetric addition of diethylzinc to benzaldehyde has been tested. The high yield and moderate ee achieved by using (*R*)-1-[2-(2-pyridyl)-phenyl]ethanol, (*R*)-**6p**, may be the starting point for the development of new optically active pyridylphenylalkanols in order to obtain more efficient asymmetric ligands.

Experimental Section

General Remarks

Thin-layer chromatography was performed on precoated TLC plates of Merck silica gel $60F_{254}$, using potassium permanganate as developing reagent. For column chromatography, Merck silica gel 60 (particle size, 40–63 μm) was used. Melting points were taken using a Stuart SMP3 apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 343 polarimeter. Mass spectra were recorded on a Hewlett-Packard 5897 A (electron impact, 70 eV) and a Hewlett-Packard 1100 HPLC/MS (electrospray) instruments. The C, H, N analyses were performed on a Perkin-Elmer 2400 analyzer. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were obtained with a Bruker AC-200 spectrometer (200.13 MHz for the ^{1}H and 50.3 MHz for the ^{13}C nuclei), using the δ scale (ppm) for chemical shifts; calibration was made on the $CDCl_3$ (^{13}C; 76.95 ppm) or the residual $CHCl_3$ (^{1}H; 7.26 ppm) signals; ^{13}C NMR spectra were edited using DEPT techniques. The assignments of the ^{1}H and ^{13}C NMR spectra of compound **6p** were deduced by analysis of its COSY, HSQC and HMBC spectra (Bruker AMX-400 spectrometer; 400.13 MHz for the ^{1}H and 100.61 MHz for the ^{13}C nuclei). COSY, HSQC and HMBC experiments were carried out using standard Bruker software. For the determination of some enantiomeric excess values, ^{19}F NMR spectra of the corresponding diastereomeric pair of Mosher's esters were obtained with a Bruker AV-300 spectrometer (282.38 MHz); the diastereomeric ratio was determined from the inverse-gated proton-decoupled ^{19}F NMR spectra of the crude reaction mixture, using a pulse width of 15°, a relaxation delay of 10 s and an accumulation of 240–4096 scans. Most of the enantiomeric excesses were determined with an LC-10AD Shimadzu high performance liquid chromatograph, using Chiralcel OD or OB-H columns (Daicel).

Preparation of the Biaryl Ketones 5

Ketones **5** were prepared (Scheme 1) by means of the Suzuki–Miyaura cross-coupling reaction[10] by adapting a previously

described procedure.[23] Ar and R^3 substituents in ketones **5** are the same as for the corresponding alcohols *rac*-**6** (Figure 1). All reactions were carried out under a nitrogen atmosphere in Schlenk-type glassware. The appropriate aryl bromide **2** (or bromopyridine **3**) (2.50 mmol) and arylboronic acid **1** (or **4**) (3.15 mmol) were stirred at room temperature in propan-1-ol (6.0 mL) for 15 min. Then, palladium(II) acetate (9.70 μmol, 2.2 mg), triphenylphosphine (29.5 μmol, 7.8 mg), 2.0 M aqueous Na_2CO_3 (3.95 mmol, 1.95 mL) and distilled water (1.25 ml) were added, and the mixture was refluxed overnight. After cooling at room temperature, distilled water (5.0 mL) was added and the mixture was stirred in air for 5 min. After extracting the mixture (ethyl acetate, 2×15 mL), the organic layer was successively washed with 0.50 M aqueous Na_2CO_3 (2×6 mL) and brine (2×5 mL), and then dried with anhydrous Na_2SO_4 by stirring for 10 min in the presence of activated carbon (0.25 g). The resulting suspension was filtered through a 1 cm pad of celite and the solid residue washed with ethyl acetate. Low pressure elimination of solvent yielded the corresponding crude biaryl ketone **5**. To obtain analytical samples and to purify spectroscopically unsatisfactory crude ketones, recrystallization from ethanol or flash column chromatography (hexane:ethyl acetate as eluent) were undertaken. In the cases of methyl pyridylphenyl ketones **5c, l, m, p, q**, pure samples were easily achieved by means of two successive acid (3 N aqueous H_2SO_4) and basic (3 M aqueous NaOH) extraction processes (both with dichloromethane, 2×10 mL) to discard non-pyridine side-products.[24]

In this way, biaryl ketones **5a–q** were obtained in 70–97% isolated yields. For characterization data, see the Supporting Information.

Preparation of Racemic 1-Biarylethanols or 1-Biarylpropan-1-ols *rac*-6

The appropriate biaryl ketone **5** (1.00 mmol), dissolved in ethanol (25 mL), was stirred overnight, at room temperature, with $NaBH_4$ (0.75 mmol). [*ortho*-Ketones **5o**, **p**, **q** require 1.50 mmol of $NaBH_4$]. After low pressure elimination of ethanol, distilled water (10 mL) was added and the mixture was extracted with diethyl ether (2×15 mL). Conventional washing, drying and elimination of solvent gave the corresponding crude, essentially pure alcohol *rac*-**6**, which occasionally (or for obtaining analytical samples) had to be purified by flash column chromatography (hexane:ethyl acetate as eluent). In this way, the racemic alcohols *rac*-**6a–q** were obtained in 78–98% yields.

Enzymatic Acetylation of Racemic Alcohols *rac*-6

To a mixture of a racemic alcohol *rac*-**6a–n** (0.600 mmol), CAL-B (Novozyme 435, 60 mg) and powdered 4 Å molecular sieves (30 mg) under a nitrogen atmosphere, anhydrous *tert*-butyl methyl ether (10 mL) and vinyl acetate (1.80 mmol) were added. [*ortho*-Alcohols **6o–q** require isopropenyl acetate (1.80 mmol) as acetyl donor]. The resulting mixture was circularly shaken at 28 °C and 200 rpm for the time shown in Tables 1 and 2. The enzyme was filtered off through a 1 cm pad of celite, washed with dichloromethane and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (hexane:ethyl acetate as eluent) to obtain successively the corresponding enantioenriched acetate (*R*)-**7** and alcohol (*S*)-**6**. For characterization data, see the Supporting Information.

Preparation of an Analytical Sample of (4*S*)-2-[2-(2-Pyridyl)phenyl]-3-oxapentan-2-yl Acetate (9p)

Racemic alcohol *rac*-**6p** was submitted to an enzymatic acetylation (*vide supra*) using vinyl acetate as acetyl donor. Flash column chromatography (hexane:ethyl acetate 5:1) of the crude reaction mixture yielded a 29 mg fraction consisting of a 60:40 mixture of acetates **7p**:**9p**. Then, this mixture was submitted to semipreparative HPLC using a Kontron instrument equipped with a Kromosil 60 column (250×20 mm; silica, particle size 7 μm). Using hexane:isopropyl alcohol 97:3 as eluent at room temperature and a flow of 5 mL/min, a fraction of pure **9p** (colourless oil, 6 mg) was eluted with a retention time of 57.3 min. **9p:** ^{1}H NMR: δ = 1.29 (d, CH_3-CH, J = 5.3 Hz), 1.48 [d, CH_3-CH(Ar)-O, J = 6.6 Hz], 1.82 (s, CH_3-CO), 5.01 (q, Ar-CH-O, J = 6.6 Hz), 5.58 (q, O-CH-O, J = 5.3 Hz), 7.21–7.66 (m, H-3, H-4, H-5, H-6, H-3′, H-5′), 7.66 (dt, H-4′, J_d = 1.8, J_t = 7.7 Hz), 8.66 (bd, H-6′, J = 5.5 Hz); ^{13}C NMR: δ = 20.85, 20.97, 23.86 (3 CH_3), 71.44 (Ar-*C*H-O), 94.65 (O-CH-O), 121.74, 124.17, 126.25, 127.35, 128.88, 129.37 (C-3, C-4, C-5, C-6, C-3′, C-5′), 136.27 (C-4′), 139.91, 140.93 (C-1, C-2), 148.84 (C-6′), 159.26 (C-2′), 170.13 (C=O); HRMS: M^+ found: 285.1358 (M^+ calculated: 285.1365); MS (EI, 70 eV): *m/z* (%) = 226 [(M – CH_3CO_2)$^+$, 1], 199 (69), 198 (100), 184 (72), 182 (73), 180 (92), 167 (55), 156 (76), 80 (52); anal. calcd. for $C_{17}H_{19}NO_3$ (285.3): C 71.56, H 6.71, N 4.91; found: C 71.43, H 6.99, N 5.15.

Determination of Enantiomeric Excesses

Enantiomeric excesses of alcohols (*S*)-**6** were determined by chiral HPLC or by the Mosher's method in those cases where HPLC failed. To determine the ee of the acetates (*R*)-**7**, these were previously saponified (15 equivs. of 1 M methanolic NaOH, room temperature, overnight, > 95% yield) to their corresponding alcohols (*R*)-**6**. In addition, enantiomeric excess of (*R*)-1-phenylpropan-1-ol[25] [(*R*)-**11**] was determined by chiral HPLC.

HPLC method: A Chiralcel OD column was used, except for **6f**, which required a Chiralcel OB-H column. Hexane:isopropyl alcohol (H:iPA) mixtures were employed as eluents, with a flow value of 0.8 mL/min. **6a**: H:iPA 95:5; T = 25 °C; t_R = 15.31 (*S*) and 17.72 (*R*) min; R_S = 1.2. **6b**: H:iPA 92:8; T = 20 °C; t_R = 9.59 (*R*) and 10.72 (*S*) min; R_S = 1.1. **6c**: H:iPA 75:25; T = 30 °C; t_R = 9.02 (*S*) and 13.72 (*R*) min; R_S = 4.2. **6d**: H:iPA 97:3; T = 20 °C; t_R = 24,45 (*S*) and 27.27 (*R*) min; R_S = 1.2. **6f**: H:iPA 98:2; T = 20 °C; t_R = 17.86 (*R*) and 19.64 (*S*) min; R_S = 1.0. **6h**: H:iPA 97:3; T = 20 °C; t_R = 15.42 (*R*) and 16.96 (*S*) min; R_S = 1.1. **6k**: H:iPA 95:5; T = 25 °C; t_R = 12.10 (*R*) and 15.35 (*S*) min; R_S = 1.9. **6 l**: H:iPA 75:25; T = 30 °C; t_R = 17.10 (*R*) and 22.55 (*S*) min; R_S = 3.0. **6m**: H:iPA 85:15; T = 35 °C; t_R = 11.57 (*S*) and 18.27 (*R*) min; R_S = 4.1. **6n**: H:iPA 90:10; T = 30 °C; t_R = 7.27 (*R*) and 9.06 (*S*) min; R_S = 2.0. **6o**: H:iPA 99:1; T = 20 °C; t_R = 9.38 (*R*) and 13.70 (*S*) min; R_S = 3.9. **6p**: H:iPA 90:10; T = 20 °C; t_R = 11.93 (*S*) and

15.64 (*R*) min; $R_S = 3.0$. **6q**: H:iPA 90:10; $T = 20\,^{\circ}C$; $t_R = 10.86$ (*S*) and 12.49 (*R*) min; $R_S = 1.3$. **11**: H:iPA 97:3; $T = 20\,^{0}C$; $t_R = 14.21$ (*R*) and 15.72 (*S*) min; $R_S = 2.1$.

Mosher's method: Alcohols (*S*)- and (*R*)-**6e, g, i, j** were converted into their pairs of diastereomeric Mosher's esters.[26] Then the ^{19}F NMR spectra of the pairs of Mosher's esters were acquired in such conditions (see General Remarks section) that the corresponding enantiomeric excesses can be expressed with an error lesser than 0.5%.[27] Chemical shifts of the trifluoromethyl group resonances, whose integral values allow us to determine the enantiomeric excesses, are the following (the corresponding diastereomers are indicated in brackets). **6e**: −71.67 (*R,R*) and −71.96 (*R,S*) ppm; **6g**: −71.72 (*R,R*) and −72.02 (*R,S*) ppm; **6i**: −71.77 (*R,R*) and −72.02 (*R,S*) ppm; **6j**: −71.74 (*R,R*) and −72.00 (*R,S*) ppm.

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