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PAPER

Straightforward preparation of biologically active 1-aryl- and 1-heteroarylpropan-2-amines in enantioenriched form†

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Because of the importance of developing stereoselective syntheses for single enantiomers, a selected panel of racemic biologically active 1-aryl- and 1-heteroarylpropan-2-amines has been prepared, followed by a study of their behavior in enzymatic kinetic resolution (KR) processes. For this purpose, lipase B from *Candida antarctica* (CAL-B) proved to be an ideal biocatalyst allowing the preparation of the corresponding enantioenriched (*R*)-amides and (*S*)-amines by aminolysis reactions. Likewise, dynamic kinetic resolutions (DKR) have been successfully achieved combining the use of CAL-B and Shvo's catalyst. This research constitutes the first example of a lipase-catalyzed DKR process of β-substituted isopropylamines.

Introduction

The family of 1-arylpropan-2-amines represents a subclass of chiral amines with interesting pharmacological properties. Most of them show central and peripheral stimulant activity by multiple actions at serotonin (5-HT) receptor subtypes and their applications cover, for instance, the treatment of sleep disorders, depression and obesity.[1] Particularly, the isomeric 1- and 2-naphthylpropan-2-amines are efficient monoamine oxidase (MAO) inhibitors[2] and it has been proved that the 2-naphthyl analogue lacks the side effects associated with central nervous system stimulants. In addition, the 1-heteroaryl analogues such as 1-(1*H*-indol-3-yl)propan-2-amine are precursors of potent β-adrenergic receptor agonists, the activity being strongly dependent on the configuration of their stereogenic centers.[3] Among this family of amines is also found α-methylhistamine, the reference histamine H_3-receptor agonist most extensively used, whose (*R*)-enantiomer is significantly more potent than its (*S*)-counterpart.[4] In recent years, a plethora of analogues of α-methylhistamine have been synthesized by means of changing the alkyl chain, attaching substituents to the amine group and even replacing the imidazole moiety by other aromatic rings.[5] Furthermore, many prodrugs of α-methylhistamine have also appeared, such as carbamates or azomethine, to overcome pharmacokinetic problems ascribed to its insufficient oral absorption and poor brain penetration.[6]

Despite the aforementioned applications of these amines and their well established stereochemistry–activity relationship, biological studies of single stereoisomers are still scarce, probably due to their limited availability. As far as we are aware no reports of lipase-catalyzed stereoselective transformations of 1-heteroarylpropan-2-amines have been described yet. For that reason, we wish to report a simple and highly efficient chemoenzymatic approach to this class of amines with relevant therapeutic uses. The enantioselective acylation of the corresponding racemates using the *Candida antarctica* lipase type B (CAL-B) as a catalyst will be firstly investigated in order to optimize the kinetic resolution (KR) of these substrates. Dynamic kinetic resolution (DKR) processes will be also attempted to look for methods to prepare optically active amine derivatives in high yields.

Results and discussion

Racemic amines were synthesized from aldehydes **1a–e**, commercially available except **1e**, selecting two isomeric aryl (1- and 2-naphthyl) and three heteroaryl (3-indolyl, 3-pyridyl, and 4-imidazolyl) derivatives due to their pharmacological interest (Scheme 1). Thus, all selected aromatic aldehydes, except 1*H*-imidazole-4-carbaldehyde, were transformed into the corresponding amines in a two-step sequence, which involves a Henry reaction with nitroethane and ammonium acetate at 115 °C to produce the (*E*)-nitropropene intermediates **2a–d**,[7] followed by reduction using lithium aluminium hydride in refluxing THF. Racemic amines **3a–d** were isolated with overall yields ranging from 33 to 74% (Scheme 1). Specifically, moderate yields were achieved for isopropylamines (±)-**3a–c** bearing naphthyl and indolyl substituents, while a lower yield was attained for the pyridyl analogue **3d**.

This protocol failed when applied to 1*H*-imidazole-4-carbaldehyde, the protection of the imidazole ring being required

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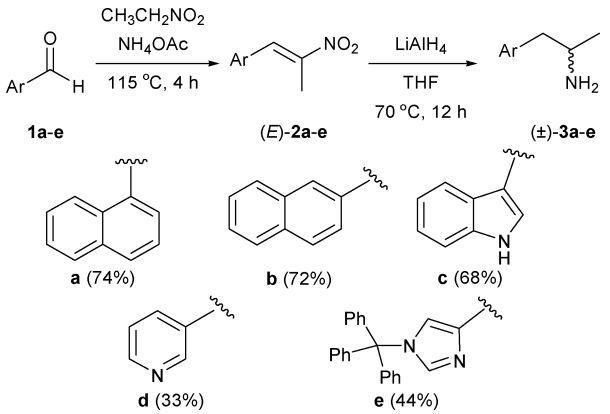


Scheme 1 Synthesis of racemic amines **3a–e**.

in this case.[8] After unsuccessful attempts with protecting groups such as benzyl or Boc (due to the formation of regioisomeric mixtures as well as the partial deprotection during the process), the trityl group turned out to be adequate to perform the complete synthetic sequence. Thus, the corresponding 1-*N*-trityl-α-methylhistamine **3e** was obtained with 44% overall yield (Scheme 1). In addition, and considering previous reports,[9] the attachment of such a bulkier group should ensure a high enantiodiscrimination by the enzyme in the subsequent KR of (±)-**3e**.

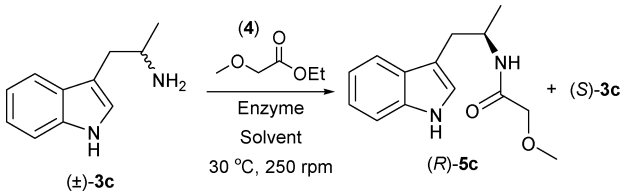
Biocatalytic processes are nowadays recognized as efficient methods for the production of enantiopure compounds.[10] In this sense, enzymatic resolutions of amines present interesting advantages over traditional diastereomeric salt resolutions. They are based on the possibility of using eco-friendly catalysts, mild reaction conditions and simple separation protocols. Transaminases and hydrolases are the most commonly used enzymes to carry out this type of transformation,[11] with some efficient examples involving chiral isopropylamines.[8,12]

We focused our attention on the lipase-catalyzed KR of (±)-**3a–e** by means of aminolysis reactions using a non-activated ester such as ethyl acetate as well as ethyl methoxyacetate (**4**), the best results in terms of reactivity and enantioselectivity being found with the last one (data not shown). This is not a surprising result as alkyl methoxyacetates have been previously found to be excellent acyl donors for the kinetic resolution of primary benzylic amines.[13]

First of all a set of lipases were tested in the stereoselective lipase-mediated acylation of the racemic 1-(1*H*-indol-3-yl)propan-2-amine (**3c**, Table 1). For most of them very low conversions were achieved although with an excellent selectivity towards the formation of methoxyacetamide (*R*)-**5c**. AK lipase (entry 1), *Pseudomonas cepacia* lipase (PSL IM, entry 2), *Rhizomucor miehei* lipase (RML, entry 3), and porcine pancreas lipase (PPL, entry 4) led to up to 7% of enantiopure (*R*)-**5c** in the corresponding reaction with 5 equiv. of **4** in THF at 30 °C after 20 h. Interestingly, *Candida antarctica* lipase type B (CAL-B, entry 5) exhibited a higher activity in a shorter span (3.5 h), yielding both amide **5c** and amine **3c** in almost enantiopure form (98% ee and >99% ee, respectively).

Kinetic resolutions were also carried out in different organic solvents such as 1,4-dioxane, *tert*-butyl methyl ether (TBME) or toluene searching for optimal conditions in the resolution of racemic amine **3c**. All of them also occurred with excellent levels of selectivity leading to the isolation of the enantiopure (*S*)-amine after 3.5 h (entries 6–8).

Table 1 Kinetic resolution of amine (±)-**3c**[a]



Entry	Enzyme	Solvent	*t* /h	Ee_P (%)[b]	Ee_S (%)[b]	*c* (%)[c]	*E*[d]
1	AK	THF	20	> 99	4	4	> 200
2	PSL IM	THF	20	> 99	< 3	< 3	> 200
3	RML	THF	20	> 99	< 3	< 3	> 200
4	PPL	THF	20	> 99	7	7	> 200
5	CAL-B	THF	3.5	98	> 99	51	> 200
6	CAL-B	Dioxane	3.5	97	> 99	51	> 200
7	CAL-B	TBME	3.5	98	> 99	51	> 200
8	CAL-B	Toluene	3.5	95	> 99	51	> 200

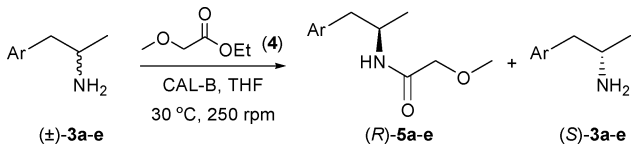
[a] Enzymatic reaction conditions: racemic amine **3c** (50 mg), lipase (50 mg), ester **4** (5 equiv.), solvent (0.10 M), 30 °C and 250 rpm. [b] Enantiomeric excess of substrate (ee_S) and enantiomeric excess of product (ee_P) values were determined by HPLC (see the Supporting Information†). [c] $c = ee_S/(ee_S + ee_P)$. [d] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[14]

Finally we decided to extend our results in the kinetic resolution of racemic amines **3a–e**. THF was selected as solvent because of the high solubility of amines in this organic solvent, and the reactions were performed using CAL-B as biocatalyst (Table 2). Biocatalytic processes were regularly analyzed by HPLC and finally stopped when conversion values reached close to 50%. Except for 1-(3-pyridyl)propan-2-amine (**3d**, entry 4), all the amines were acylated with excellent enantioselectivities. Meanwhile short reaction times were required for naphthyl **3a,b** (entries 1 and 2) and indolyl **3c** (entry 3) derivatives, one day of reaction was necessary to attain a 50% conversion with the α-methylhistamine derivative **3e**. In all cases, the remaining (*S*)-amines and the produced (*R*)-methoxyacetamides **5a–e** were isolated with high to excellent enantiomeric excesses. The (*S*)-configuration for the remaining amines **3a–e** was established by comparison of the optical rotation sign for some of them with data reported in the literature.[15] Consequently, this means that CAL-B follows Kazlauskas' rule,[16] the (*R*)-enantiomer of the amine being preferentially acylated. The lower enantioselectivity found for **3d** could be explained on the basis of the active site empirical model established for CAL-B. According to that, the higher the size differences between substituents attached to the stereocenter, the higher the enantiodiscrimination produced. Moreover, as predicted, the attachment of the trityl moiety to the imidazole ring in **3e** significantly enhanced the size of the bigger substituent, leading to an excellent enantioselectivity.[8,17]

Interestingly, it is also remarkable that our results represent a complementary approach to the one described by Gil and co-workers, allowing the production of (*R*)-amides of opposite configuration to the ones previously obtained using an alkaline protease in the KR of **3a,c**.[12]

Probably the most advantageous issue in a kinetic resolution (KR) resides in the fact that both single enantiomers can be attained starting from a racemic mixture. Unfortunately, the maximum yield in one enantiomer is limited to 50% due to the

Table 2 Kinetic resolution of amines (±)-**3a–e** catalyzed by CAL-B[a]



(±)-**3a-e** (*R*)-**5a-e** (*S*)-**3a-e**

Entry	Substrate	*t* /h	(*R*)-**5a–e** Ee$_P$ (%)[b]	(*R*)-**5a–e** Yield (%)[b]	(*S*)-**3a–e** Ee$_S$ (%)[b]	(*S*)-**3a–e** Yield (%)[b]	*c* (%)[c]	*E*[d]
1	(±)-**3a**	4	> 99	(99)	87	(81)	47	> 200
2	(±)-**3b**	5	98	(99)	91	(96)	48	> 200
3	(±)-**3c**	3.5	98	(88)	> 99	(81)	51	> 200
4	(±)-**3d**	4	85	(96)	98	(36)	54	52
5	(±)-**3e**	24	96	(83)	97	(71)	50	> 200

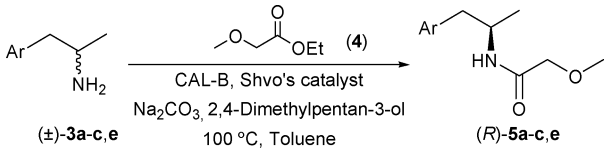
[a] Enzymatic reaction conditions: racemic amine (±)-**3a–e** (50 mg), CAL-B (50 mg), ester **4** (5 equiv.), THF (0.10 M), 30 °C and 250 rpm. [b] Ee values were determined by HPLC (see the Supporting Information†), and isolated yields were calculated taking into account the degree of conversion. [c] $c = ee_S/(ee_S + ee_P)$. [d] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$. [14]

obvious limitations of the technique. If only one enantiomer is desired, DKR provides a remarkable yield improvement by combining the action of a biocatalyst with a racemization agent, usually at high temperatures.[18] This methodology has been efficiently applied for example to secondary alcohols,[19] primary[20] and secondary amines[21] and amino acid amides.[22] However, surprisingly this methodology has not been extended to any 1-heteroarylpropan-2-amines yet. In our case and taking into account the excellent selectivities shown by CAL-B towards amines **3a–c,e** in the lipase-catalyzed kinetic resolutions, we decided to evaluate the possibility of successfully carrying out DKR processes with these substrates.

We chose commercially available dimeric ruthenium Shvo's catalyst for the development of DKR processes because of its versatility in organic synthesis.[23] The main reason for its efficient catalytic activity is based on its dissociation under thermal conditions.[24] Initially THF and toluene were selected as solvents because of the limited solubility of the organocatalyst in TBME and 1,4-dioxane.[25] Before carrying out DKR reactions, racemization experiments were performed using enantiomerically pure amine (*S*)-**3c** obtained in the CAL-B catalyzed KR reactions. Sodium carbonate was used as base and 2,4-dimethylpentan-3-ol as mild hydrogen donor, in the reactions with THF at 70 °C and toluene at 100 °C, both reaction temperatures close to the corresponding solvent boiling point. Interestingly no appreciable racemization was detected after 22 h in THF (**3c** was recovered with >95% ee) while heating in toluene led to the racemic amine, thus probing the possible applicability of the latter conditions in DKR processes.

Once the optimal conditions for the racemization of the remaining enantioenriched amine of the biocatalyzed process were found, we ensured that no background reaction occurs in the absence of biocatalyst and metal complex under these experimental conditions. For the enzymatic DKR processes, we selected racemic amines **3a–c,e**, that is, those that show the best enantioselectivity values in the CAL-B catalyzed kinetic resolutions. Ethyl methoxyacetate (**4**) was used as acyl donor, and in order to favour the racemization reaction, the relative amount of **4** was decreased in comparison with the KR experiments from 5 to 2 equiv. In addition, the load of CAL-B with respect to the amine was decreased from (1 : 1) in weight to (1 : 0.25),

Table 3 CAL-B-mediated DKR of (±)-**3a–c,e** using ethyl methoxyacetate in dry toluene and the presence of Na_2CO_3 and 2,4-dimethylpentan-3-ol at 100 °C after 24 h



(±)-**3a-c,e** (*R*)-**5a-c,e**

Entry	Substrate[a]	*c* (%)[b]	Yield (%)[c]	Ee$_P$ (%)[d]
1	(±)-**3a**	93	50	97
2	(±)-**3b**	> 99	58	93
3	(±)-**3c**	87	86	97
4	(±)-**3e**	80	74	91

[a] Amines (±)-**3a–c** and CAL-B were used in a (1 : 0.25) ratio in weight meanwhile for (±)-**3e** a ratio (1 : 1) was used. [b] Ratio calculated by GC for **3a–c** and ^{1}H NMR for **3e**. [c] Isolated yields after flash chromatography. [d] Determined by HPLC.

except for the less reactive amine, the imidazole derivative **3e** (Table 3).

Reactions starting from naphthylpropan-2-amines **3a,b** led to high or complete conversions (93->99%) after 24 h, the formation of the corresponding methoxyacetamides (*R*)-**5a,b** (93–97% ee, Table 3, entries 1 and 2) occurring with high selectivity. For the indole and the imidazole derivatives (±)-**3c,e** good conversion values were also achieved (80–87%), yielding the amides (*R*)-**5c,e** in very high optical purity (91–97% ee, entries 3 and 4). It must be mentioned that the DKR of racemic amine **3c** was also tried in THF at 70 °C. However under these conditions only a 52% conversion of amide **5c** was attained, this product (*R*)-**5c** and the corresponding amine (*S*)-**3c** being isolated with 92% and 97% ee, respectively. This result is in agreement with the previous observations in the racemization experiments. Side-products as amine dimerization species were only detected in individual cases, but in minor amounts. Although all amides were achieved with over 90% ee, the lower enantiomeric excesses in comparison with the KR processes can be explained because of

the lower enantioselectivity displayed by CAL-B in toluene at this higher reaction temperature.

Conclusions

In summary, after developing the synthesis of a panel of valuable 1-(hetero)arylpropan-2-amines with current and potential applications in medical treatments, we have taken advantage of the stereodiscrimination shown by CAL-B for the production of the corresponding (*S*)-amines and (*R*)-amides by means of KR processes. Likewise, in those enzymatic aminolysis reactions which occur with good enantiomeric ratios, we have tested the combination of bio- and chemo-catalysts for the development of DKRs, allowing the preparation of (*R*)-amides with high yields and optical purities. Thus, the DKR of β-isopropylamines has been reported for the first time taking advantage of the compatibility of CAL-B and Shvo's catalyst in the optimized reaction conditions.

Experimental

General procedure for the synthesis of racemic 1-(hetero)arylpropan-2-amines 3a–e

Nitroethane (5.9 cm^3) was added to a mixture of the corresponding aldehyde (3.0 mmol) and ammonium acetate (57 mg, 0.74 mmol), and the resulting suspension was heated to reflux for 6 h. After cooling at room temperature, the solvent was evaporated and the crude material was extracted with water (30 cm^3)—for the nitropropene derivatives **2a,b**—or with saturated aqueous solution of $NaHCO_3$ (30 cm^3)—for the nitropropene derivatives **2c–e**—and dichloromethane (3 × 30 cm^3). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the corresponding 2-nitropropene **2a–e** in quantitative yield. Spectroscopic data for **2a–e** were in good agreement with those previously published.[26] These compounds were used as crude materials in the following reduction reaction. Thus, the corresponding nitropropene **2a–e** (3.1 mmol) was dissolved in anhydrous THF (62 cm^3) and $LiAlH_4$ (0.35 g, 9.3 mmol) was added gradually under a nitrogen atmosphere. The reaction mixture was refluxed overnight. After cooling at room temperature, water was carefully added until total destruction of the hydride excess, and then, a solution of aq. 4 N NaOH was added in order to capture the aluminium salts. The resulting mixture was filtered over celite®, washed with THF, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography [$MeOH/CH_2Cl_2$ 1 : 1 for compounds **3a,b** or NH_3 (32% aq. solution)/MeOH 2 : 98 for compounds **3c–e**] to yield the corresponding amine **3a–e**.

General procedure for the enzymatic kinetic resolution of racemic amines (±)-3a–e

To a suspension of racemic amine **3** (50 mg, 0.10 M) and enzyme (CAL-B, 50 mg) in dry THF, ethyl methoxyacetate (5 equiv.) was added under a nitrogen atmosphere. The reaction was shaken at 30 °C and 250 rpm during 3.5–24 h. Then, the reaction was stopped, and the enzyme filtered and washed with THF (5 × 1 cm^3). The solvent was evaporated and both optically active amine (**3a–e**) and methoxyacetamide (**5a–e**) present in the residue were separated using different methods depending on the substrate. Compounds **5c–e** and **3c–e** were separated by flash chromatography (different mixtures of $MeOH/CH_2Cl_2$ and NH_3 (32% aq. solution)/MeOH 2 : 98, respectively). However, the mixtures of **5a,b** and **3a,b** were treated with 3 N aq. H_2SO_4 (5 cm^3) and extracted with dichloromethane (3 × 5 cm^3). The aqueous phase was treated with solid NaOH at 0 °C until basic pH was reached, and extracted with dichloromethane (5 × 5 cm^3). Both organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, affording optically active methoxyacetamides **5a,b** and amines **3a,b**. Yields for both compounds **5** and **3** were calculated taking into account the degree of conversion attained in the reaction (see Table 1). In order to determine the enantiomeric excesses of amines **3a–e**, they were treated with acetyl chloride and the resulting acetamides were analyzed by HPLC.

General procedure for the dynamic kinetic resolution of amines (±)-3a–e

A flame dried Schlenk flask was charged with the racemic amine **3** (50 mg, 0.10 M) and a magnetic stirrer, closed, evacuated and backfilled with nitrogen three times. Then, under the same inert atmosphere, Shvo's catalyst (10 mol%), toluene, CAL-B [12.5 mg for amines **3a–c** or 50 mg for amine **3e**], Na_2CO_3 (25 mg), 2,4-dimethylpentan-3-ol (0.5 equiv.) and ethyl methoxyacetate (2 equiv.) were subsequently added. The reaction mixture was stirred at 100 °C for 24 h. Then, after cooling at room temperature, the reaction was filtered over celite® and washed with methanol (5 × 2 cm^3). The solvent was removed *in vacuo* and the crude material was purified by column chromatography, yielding the corresponding methoxyacetamides **5a–c,e** (see Table 2).

Acknowledgements

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