ARTICLE

Highly efficient asymmetric bioreduction of 1-aryl-2-(azaaryl)ethanones. Chemoenzymatic synthesis of lanicemine.

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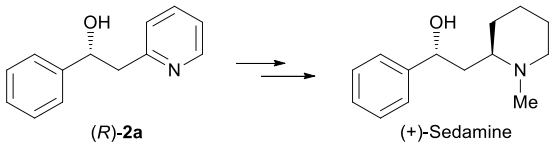
Different ketoreductases (KREDs) have been used to promote a highly selective reduction of several 1-aryl-2-(azaaryl)ethanones (azaaryl = pyridinyl, quinolin-2-yl), the corresponding secondary alcohols being obtained with very high yields and enantiomeric excesses (*ee* > 99%). The absolute configuration of each optically active alcohol has been assigned by means of modified Mosher and Kelly methods, two shielding effects being evaluated: (1) the Mosher phenyl ring effect on the azaaryl protons and (2) the one of the azaaryl ring on the Mosher methoxy group. In addition, the biologically active amine lanicemine has been synthesized from (*R*)-1-phenyl-2-(pyridin-2-yl)ethanol, thus proving the utility of the secondary alcohols here prepared.

Introduction

Enantiopure alcohols are highly valuable compounds due to their prevalent presence in natural products and to their utility as building blocks in the synthesis of a wide range of agrochemicals, flavours, fragrances, and pharmaceuticals.[1] In addition, those containing a pyridine group in their structure have numerous applications as ligands in asymmetric metal catalysis,[2] as resolving agents[3] or as starting materials for the preparation of more advanced chiral ligands.[4] Moreover, the involvement of enantiopure pyridyl alcohols or their derivatives in biologically active compounds[5] is also of great interest. For instance, optically active 1-phenyl-2-(pyridin-2-yl)ethanol **2a** (Scheme 1) has been used in the synthesis of sedamine,[6] a piperidine alkaloid[7] being effective in the treatment of cognitive disorders,[8] and both piperidine and quinoline units are present in the structure of the antimalarial drug mefloquine.[9]



Scheme 1

Several methods have previously been applied to the synthesis of optically active **2a** with varied efficiency.[10] Whereas some non-enzymatic kinetic resolution (KR) protocols were applied to racemic **2a** with moderate[11] or low selectivity,[12] the porcine pancreatic lipase (PPL)-catalysed hydrolysis of its acetyl derivative afforded the product (*R*)-**2a** with 40% degree of conversion (*C*) and 96% of enantiomeric excess (*ee*).[6b] Nevertheless, the KR methodology suffers of some limitations such as the maximal theoretical 50% yield of the required enantiomer and the need to carry out the separation of the product and the remaining substrate. Dynamic kinetic resolution (DKR) offers a noticeable improvement but, although a lipase-mediated DKR has been applied to several 1,2-diarylethanols analogues, no examples with azaaryl substituents have been reported.[13]

Taking the easy accessibility of the ketone precursors into account, a highly selective asymmetric reduction of the prochiral carbonyl group would be desirable. For this purpose, carbonyl reductases mediated reactions have many inherent merits such as environmental compatibility, high enantioselectivity, and mild reaction conditions.[14] Regarding this methodology, we have recently demonstrated the utility of KREDs (from Codexis®) to catalyse the reduction of a series of aryl methyl (or ethyl) ketones, some of them bearing a sterically bulky aryl moiety. For this reason, we thought it would be interesting to test the potential of these KREDs to promote the reduction of 1-aryl-2-(azaaryl)ethanones **1** in which a pyridine or quinoline ring is present. It is of note that the attempts to enantioselectively reduce substrate **1a** with Baker's yeast were unsuccessful.[15]

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Results and discussion

A series of ketones **1a**-**f** (Figure 1) were prepared in high yields by treatment of pyridinylmethyl- or quinolin-2-ylmethyllithium with the appropriate *N*,*N*-diethylarenecarboxamide.[16] Although these ketones have been presented in their keto forms in Figure 1, the ^{1}H-NMR spectra ($CDCl_3$) of all these compounds revealed the presence of the enol or enaminone forms in different percentages. Thus, the enol form was present in a 13-37% for **1a**-**c** and less of 5% for **1d** and **1e**. However, for the quinoline derivative **1f** only 3% of keto structure was observed, the major component (97%) being not the enol but the enaminone tautomer[17] (Scheme S1†).

The bioreduction of each compound **1a**-**f** was tested using ketoreductases from the Codexis® KRED Screening Kit and employing 17.5% v/v of isopropyl alcohol (IPA) for cofactor recycling and as a co-solvent. The screenings were performed under the standard conditions at pH 7.0 and a detailed collection of the results is included in Tables S1-S6 (ESI†). Here, separated in two tables for (*S*)- (Table 1) and (*R*)-selective bioreductions (Table 2), we have included a selection of the most significant results, that is, those of the reactions in which both the degree of conversion (*C*) and enantiomeric excess (*ee*) obtained were higher than 90%. For ketones **1a,b,d,e** both enantiomers of the corresponding alcohol **2** can be achieved by choosing the adequate KRED, the *R* enantiomer being obtained in all the cases with KRED-P2-G03. In general, 3- and 4-pyridinyl derivatives were the best substrates for the KREDs collection as a whole. Satisfactory results in the bioreductions of **1c** and **1f** were only achieved for one enantiomer (*R* and *S*, respectively) and, although several KREDs shown a moderate or very high efficacy in the reduction of **1c** (Table 2, entries 3 and 4; Table S3†), only KRED-P1-B02 was efficient to enantioselectively reduce **1f** (Table 1, entry 12; Table S6†).

Once checked the activity of KREDs, preparative bioreductions of **1** were carried out at 20-50 mM substrate concentration and with significant lowering of the KRED/ketone ratio. Thus, the amount of KRED of the screening was lowered to 25%, enough to totally convert the corresponding ketone (at a 20 mM concentration) into the optically active alcohol (*ee* ≥ 98%). In all the cases, alcohols were isolated with very high yields (90–95%) after a simple purification by column chromatography (CC).

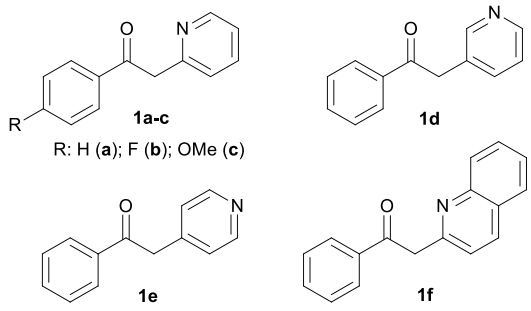
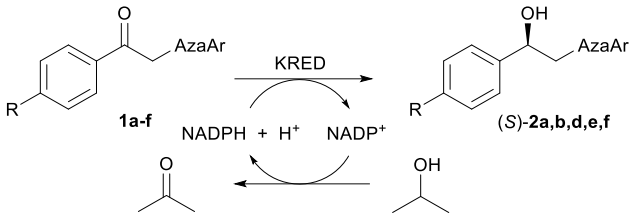


Figure 1 1-Aryl-2-(azaaryl)ethanones **1a-f** of this study.

Table 1 (*S*)-Selective KRED-catalyzed bioreductions of ketones **1**.[a]



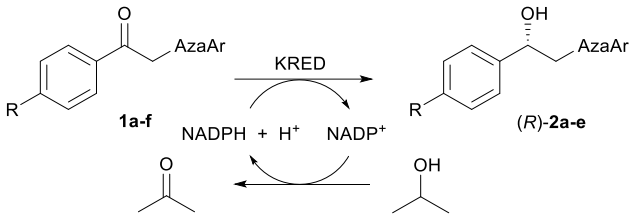
Entry	Ketone	R	AzaAr[b]	KRED[c]	Alcohol[d]	*ee* (%)[e]
1	**1a**	H	2-Py	P1-B10	(*S*)-**2a**	>99
2	**1a**	H	2-Py	P1-B12	(*S*)-**2a**	>99
3	**1b**	F	2-Py	P1-B12	(*S*)-**2b**	>99
4	**1d**	H	3-Py	P1-B02	(*S*)-**2d**	>99
5	**1d**	H	3-Py	P1-B10	(*S*)-**2d**	>99
6	**1d**	H	3-Py	P1-B12	(*S*)-**2d**	>99
7	**1d**	H	3-Py	P2-D11	(*S*)-**2d**	>99
8	**1e**	H	4-Py	P1-B02	(*S*)-**2e**	>99
9	**1e**	H	4-Py	P1-B10	(*S*)-**2e**	>99
10	**1e**	H	4-Py	P1-B12	(*S*)-**2e**	>99
11	**1e**	H	4-Py	P2-D11	(*S*)-**2e**	98
12	**1f**	H	2-Q	P1-B02	(*S*)-**2f**	>99

[a] Reactions were carried out in 125 mM phosphate buffer pH 7.0 (also containing 1.25 mM $MgSO_4$) using the corresponding ketone **1** (11 μmol, 20 mM), KRED (2 mg), $NADP^+$ (1.0 mM), and propan-2-ol (17.5% v/v) as described in ESI†. [b] Py = pyridinyl; 2-Q = quinolin-2-yl. [c] KRED identified according to the nomenclature of the Screening Kit of Codexis. [d] Degree of conversion (*C*) higher than 99% were obtained in all the cases except in entry 3 (*C* = 95%). [e] The *ee* was determined by HPLC (see ESI† for details).

Assignment of the absolute configurations

The *R* assignment for (+)-**2a** has previously been made by chemical correlation with (+)-sedamine.[6a] An identical assignment (*R*)-(+) was proposed for optically active **2c,f** by

Table 2 (*R*)-Selective KRED-catalyzed bioreductions of ketones **1**.[a]



Entry	Ketone	R	AzaAr	KRED	Alcohol[b]	*ee* (%)[c]
1	**1a**	H	2-Py	P2-G03	(*R*)-**2a**	>99
2	**1b**	F	2-Py	P2-G03	(*R*)-**2b**	>99
3	**1c**	OMe	2-Py	P2-C02	(*R*)-**2c**	>99
4	**1c**	OMe	2-Py	P2-G03	(*R*)-**2c**	>99
5	**1d**	H	3-Py	P2-G03	(*R*)-**2d**	94
6	**1e**	H	4-Py	P2-G03	(*R*)-**2e**	91

[a] Reactions conditions as indicated in Table 1. [b] Degree of conversion (*C*) higher than 99% were obtained in all the cases. [c] The *ee* was determined by HPLC (see ESI† for details).

analogy with **2a**, after having carried out the KR of racemic **2a,c,f** by means of a dehydrogenative Si-O coupling with an identical silicon-stereogenic silane.[18] However, perhaps due to a misprint, the assignment (*R*)-(–) was also proposed for optically active **2f**, when this alcohol was produced by a similar KR using an achiral silane and an optically active ligand.[19]

In our case, the specific rotation of **2a** [obtained with KRED-P2-G03, Table 1, entry 3; $[\alpha]_D^{20}$ = +37.1 (*c* 0.73, $CHCl_3$)] allowed us to assign the *R* configuration to this alcohol,[6a] and therefore to know the selectivity of all the active KREDs towards the ketone **1a**. Thus, by assuming that each specific KRED shows the same stereopreference towards all the tested ketones **1**, the absolute configuration of the other optically active alcohols **2b-f** could also tentatively be assigned. However, the diverse aryl rings of **1a-c**, the different nitrogen location in the pyridine rings of **1d,e**, and the structurally different quinoline heterocycle present in **1f** could alter the accommodation of the ketone substrates **1** in the active site of the KRED, and could originate changes in the enzyme stereopreference. In fact, such inversions of stereopreference have been observed in the bioreductions carried out with some of the KREDs (ESI†), the most significant being the results attained with KRED-P1-B05. This enzyme catalysed the formation of (*S*)-**2a,d,e** (all bearing a phenyl substituent) with *C* and *ee* up to >99% and 98%, respectively (Tables S1, S4, and S5†), but it promoted the formation of (*R*)-**1b,c** with similar high *C* and *ee* values (Tables S2 and S3†).

As a consequence, we took the decision to search for an unambiguous absolute configuration assignment of **2b-f**. For it, we decided to apply modified versions of the known methods of Mosher[20] and Kelly[21] to the (*R*)-MTPA ester derivatives of the alcohols **2**. Related to the Mosher's method, and since the absolute configuration of **2a** is unambiguously known,[6a] we chose this alcohol to test the validity of our methodology. Racemic alcohol (±)-**2a**, prepared by $NaBH_4$ reduction of **1a**, was treated with (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride [(*S*)-MTPA-Cl], and the resulting diastereomeric mixture of (*R*)-MTPA ester derivatives **3a** (Figure 2) analysed by ^{1}H-NMR.

In the Mosher method, the so-called working models for the MTPA-esters [as those shown in figure 2 for the diastereomeric esters (*R,R*)- an (*R,S*)- **3a**] are analysed in the light of the well-known global shielding effect that the phenyl group belonging to the acyl region of the ester exerts on the *syn*-placed aliphatic protons of the alcohol moiety.[22] Thus, analysing the δ values for the signals of the protons in adjacent carbons to the chiral centre in both diastereomeric esters, the configuration of the alcohol is established. For the diastereomeric mixture **3a**, these *syn*-positioned aliphatic protons correspond to the CH_2 grouping, whose diastereotopicity leads to overlapped signals that advises against their use for this purpose. However, the most deshielded pyridine proton (*i. e.*, H_{Py}-6) of both Mosher esters (*R*,*R*)- and (*R*,*S*)-**3a** resonate in a clean region of the spectrum and they appear as two well separated signals at 8.53 and 8.61 ppm (Figure 2). Taking the mentioned shielding effect of the phenyl group into account, the lowest δ value (8.53 ppm) has to be assigned to (*R*,*R*)-**3a**, with the *syn*-placed H_{Py}-6.

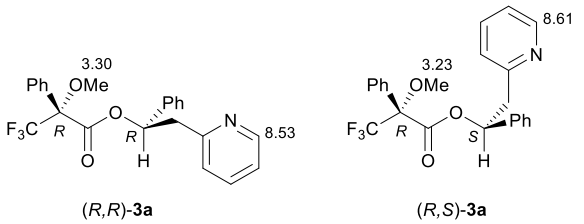


Figure 2 Working models of the diastereomeric (*R*)-MTPA esters **3a** and ^{1}H-NMR chemical shift (δ, ppm) of some selected signals.

Effectively, when the enantiopure alcohol (*R*)-**2a** was treated with (*S*)-MTPA-Cl and the resulting MTPA ester (*R*,*R*)-**3a** was analysed by ^{1}H-NMR, only the signal at 8.53 ppm was observed. This fact proves that our proposed modification of the Mosher method works well for assigning the previously reported absolute configuration of **2a**,[6a] and that this rationale could be applied to the other alcohols provided that two well separated groups of signals are observed in their spectra.

As expected, very similar ^{1}H-NMR spectra to those of **3a** were obtained for the MTPA esters **3b,c** derived from the other 2-Py alcohols **2b,c**, so that analogous analyses also allowed us to assign their absolute configurations (section 7, ESI†). In addition, the absolute configuration of the 4-Py alcohol **2e** was assigned by focusing on the equivalent, most deshielded H_{Py}-2 and -6 protons: two well resolved signals at 8.39 and 8.51 ppm were observed in the ^{1}H-NMR spectrum of the diastereomeric mixture of esters **3e**, the former being assigned to (*R,R*)-**3e**. For the MTPA ester derivatives **3d**,**f** (Figure 3), a partial overlapping was observed for some azaaryl signals in the ^{1}H-NMR spectrum of the diastereomeric mixtures. However, a series of selective-1D TOCSY experiments allowed us to distinguish and assign the signals of all the protons of the pyridine ring in the derivative **3d**, as well as three out of the six quinoline protons for **3f**. Comparison of the two set of signals newly enabled us to assign the lower δ set to the (*R,R*) diastereomer.

After this study, the most important result is that the azaaryl protons of all the (*R,R*)-MTPA esters are more shielded than those of their (*R,S*)-counterparts, thus validating our method for establishing the absolute configurations of all the alcohols **2**.

Regarding the Kelly's method,[21] which focusses on the shielding effect that suffers the methoxy group of the MTPA ester by a *syn*-placed aryl group of the alcohol region, an inspection of Figures 2 and 3 reveals that its application to our alcohols could be conflictive, since in all cases two aromatic rings, aryl and azaaryl, are present in the alcohol region. Nevertheless, the analysis of the δ_{OMe} values collected in the Figures 2 and 3, as well as the inspection of these δ_{OMe} values for **3b,c,e** (ESI†), indicate that the shielding effect of the azaarylmethyl substituent is higher than the one exerted by the aryl ring. This trend, common for all these derivatives, represents an additional confirmation of our absolute configuration assignment and, subject to further experimental data, could be used for other complicated assignments.

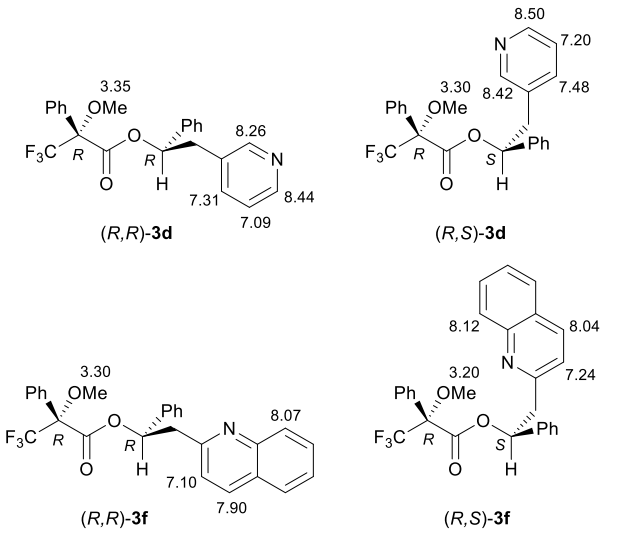


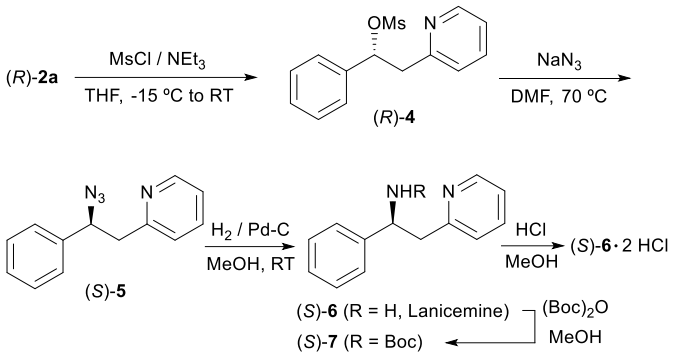
Figure 3 Diastereomeric (*R*)-MTPA esters **3d** and **3f** and chemical shift (δ, ppm) of some selected signals.

Finally, by comparing the above results with the information contained in Table 1, it is concluded that most of the highly efficient KREDs showed the same stereopreference towards all the ketone substrates **1**, which also reinforces our strategy for the absolute configuration assignment of alcohols **2**.

Chemoenzymatic synthesis of lanicemine

In addition to the already mentioned utility of this kind of optically active alcohols in the synthesis of the biologically active sedamine or other piperidine alkaloids, they also can be useful precursors of their amine analogues by applying a very simple strategy (*vide infra*). In order to prove the viability of this transformation, we have planned the synthesis of lanicemine [(*S*)-**6**, Scheme 2] from the optically active (*R*)-1-phenyl-2-(pyridin-2-yl)ethanol, (*R*)-**2a**. Lanicemine (AZD-6765) is a low-trapping *N*-methyl-D-aspartate receptor (NMDAR) antagonist with clinical relevance in a range of therapeutic areas including pain management, epilepsy, neurodegenerative disease and depression.[23]

The strategy, indicated in Scheme 2, consisted of three steps: (1) mesylation of the optically active alcohol (*R*)-**2a** (*ee* > 99%); (2) S_N2 displacement of the mesylate group in (*R*)-**4** with sodium azide; and (3) reduction of the azide (*S*)-**5**. In addition, to facilitate the storage of lanicemine, it could be converted into its dihydrochloride salt [(*S*)-**6** · 2 HCl] or, by means of *tert*-butoxycarbonylation, into its *N*-Boc derivative (*S*)-**7**. The first step –mesylation of **2a**– was carried out with mesyl chloride starting at −15 °C and allowing the reaction to reach the room temperature very slowly (12 h). This temperature control was necessary to avoid the formation of 2-(2-chloro-2-phenylethyl)pyridine as a side product. This chlorinated derivative was observed when the reaction started at room temperature. As this compound is formed from **4** by a nucleophilic substitution reaction with anion chloride, its presence in the reaction crude and the subsequent treatment with NaN_3 would lead to an azide compound **5** with a lowered enantiomeric excess. Once mesyl derivative (*R*)-**4** was isolated



Scheme 2 Synthesis of lanicemine **6** from (*R*)-**2a**.

as the only reaction product in very high yield, different reaction conditions were checked by the following reaction with NaN_3. Thus, when the process was carried out at 40 °C in *N*,*N*-dimethylformamide (DMF) as solvent, equimolar amounts of azide **5** and 2-(2-phenylethenyl)pyridine [Ph-CH=CH-(2-Py), which proceeded from a competitive elimination reaction] was formed. Moreover, the azidolysis reaction was accompanied by a high degree of racemization, judged by the low *ee* (34%) of the obtained azide **5**. This means that both bi- and unimolecular mechanisms are acting in the substitution process. Furthermore, the alkene is likely to mainly be produced by the unimolecular mechanism taking the poor basicity of the anion azide into account. When the temperature was increased to 52 °C, the amount of alkene diminished and the azide **5** was isolated with 89% ee, higher than in the previous experiment but still with a significant loss of *ee*. Keeping in mind that the higher temperature is favouring the bimolecular mechanism, the azidolysis was finally conducted at 70 °C. Under these conditions a low amount (5%) of alkene continued appearing, but the azide (*S*)-**5** was isolated with a high 97% *ee* and 88% yield after purification by CC, consequently demonstrating the efficacy of this process.

Reduction of the azide group in (*S*)-**5** was also checked under different conditions. The Staudinger protocol with PPh_3 was unsuccessful. The reduction with $LiAlH_4$ proceeded smoothly at room temperature, the reaction crude consisting of the amine (*S*)-**6** with a very small amount of impurities. Finally, the best results were obtained by hydrogenation with H_2 and Pd/C as catalyst, which led to lanicemine in 98% yield. The subsequent treatment with HCl in methanol gave the lanicemine dihydrochloride (*S*)-**6** · 2 HCl, which can be recrystallized from a methanol-ethyl acetate mixture. As the synthesis of the *N*-Boc derivative is necessary to analyse the *ee* of both its amine precursor and the azide, the crude lanicemine was also converted into the *N*-Boc derivative (*S*)-**7**, which was isolated with very high yield (90%, after CC purification) and 97% *ee*.

The same protocol was also applied to the synthesis of (*R*)-**6** and (*R*)-**7** (ee = 97%) starting from enantiopure (*S*)-**2a**.

Experimental

General experimental procedures (synthesis of ketones, racemic samples, and Mosher's ester derivatives) and

screenings for the enzymatic bioreductions are described in ESI† along with copies of the chiral HPLC chromatograms and NMR spectra.

General procedure for the preparative bioreduction of ketones 1

Reactions were carried out in 5 or 10 mL glass vials which were initially charged with 20.0 mg of the corresponding ketone **1**. Then propan-2-ol (17.5% v/v), DMSO (if necessary to completely dissolve **1**, up to a maximum of 3.5% v/v), 125 mM phosphate buffer at pH 7.0 (containing 1.25 mM $MgSO_4$), the corresponding KRED (20 mg) and the cofactor $NADP^+$ (1 mM) were added to achieve a final 20 – 50 mM concentration of **1**. The reaction mixture was incubated during 24 h (96 h for **1f**) at 30°C and 250 rpm. After this time, the mixture was extracted with ethyl acetate (4 × 4 mL), the organic layers were separated by centrifugation (5 min, 4700 rpm) after each extraction, combined, washed with brine (8 mL) and finally dried over anh. Na_2SO_4. Evaporation of the solvent yielded the crude alcohol which was purified by flash column chromatography (hexane-ethyl acetate as eluent). By this procedure the following optically active alcohols **2** were obtained:[24]

(*R*)-1-Phenyl-2-(pyridin-2-yl)ethanol (2a). The reaction was carried out with 50 mM **1a**, without DMSO and with KRED-P2-G03. **2a** was obtained as a white crystalline solid with 95% yield (after flash chromatography; 19.2 mg, 96.3 µmol). M.p. = 131.6-133.0 °C (lit.,[6a] 122-124 °C). $[\alpha]_D^{20}$ = +38.1 (*c* 0.72, $CHCl_3$), *ee* > 99% [lit.,[6a] $[\alpha]_D^{20}$ = +42 (*c* 1, $CHCl_3$), *ee* > 96%; lit.,[19] $[\alpha]_D^{20}$ = +25.6 (*c* 0.65, $CHCl_3$), *ee* = 88%]. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.54 (ddd, *J* = 0.9, 1.6, and 5.1 Hz, 1H, H_{Py}-6), 7.63 [dt, *J* = 1.6 (d) and 7.7 (t) Hz, 1H, H_{Py}-4], 7.47-7.16 (several m, 6H), 7.11 (d, *J* = 7.7 Hz, 1H, H_{Py}-3), 5.17 (dd, *J* = 4.6 and 7.5 Hz, 1H, H-1), 5.0-4.2 (br s, 1H, OH), 3.22-3.07 (m, AB signals of an ABX system, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 159.5 (C), 148.4 (CH), 143.9 (C), 136.7 (CH), 128.2 (CH), 127.1 (CH), 125.7 (CH), 123.7 (CH), 121.6 (CH), 73.2 (CH), 45.6 (CH_2). These NMR data are in agreement with literature data.[18b]

(*R*)-1-(4-Fluorophenyl)-2-(pyridin-2-yl)ethanol (2b). [This compound was not described as optically active in the literature]. The reaction was carried out with 30 mM **1b**, with DMSO (1.75% v/v) and with KRED-P2-G03. **2b** was obtained as a white crystalline solid with 92% yield (after flash chromatography; 18.6 mg, 85.5 µmol). M.p. = 142.8-144.5 °C. $[\alpha]_D^{20}$ = +40.1 (*c* 0.95, $CHCl_3$), *ee* > 99%. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.52 (br d, *J* = 4.9 Hz, 1H, H_{Py}-6), 7.63 [dt, *J* = 1.8 (d) and 7.5 (t) Hz, 1H, H_{Py}-4], 7.38 (m, 2H), 7.20 (dd, *J* = 5.3 and 7.5 Hz, 1H, H_{Py}-5), 7.10 (d, *J* = 7.8 Hz, 1H, H_{Py}-3), 5.4-4.6 (br s, 1H, OH), 5.14 (dd, *J* = 4.6 and 7.5 Hz, 1H, H-1), 3.22-3.00 (m, AB signals of an ABX system, 2H, CH_2). These ^{1}H-NMR data are in agreement with literature data[25] for the racemic compound. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 161.9 (d, $^1J_{C,F}$ = 244,5 Hz, C), 159.3 (C), 148.3 (CH), 139.7 (d, $^4J_{C,F}$ = 3.0 Hz, CH), 137.0 (CH), 127.4 (d, $^3J_{C,F}$ = 8.1 Hz, CH), 123.8 (CH), 121.8 (CH), 115.0 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 72.6 (CH), 45.5 (CH_2).

(*R*)-1-(4-Methoxyphenyl)-2-(pyridin-2-yl)ethanol (2c). The reaction was carried out with 20 mM **1c**, without DMSO and with KRED-P2-G03. **2c** was obtained as a white crystalline solid with 91% yield (after flash chromatography; 18.4 mg, 80.1 µmol). M.p. = 124.6-126.4 °C. $[\alpha]_D^{20}$ = +18.6 (*c* 1.2, $CHCl_3$), *ee* > 99% [lit.,[18b] $[\alpha]_D^{20}$ = +13.4 (*c* 0.38, $CHCl_3$), *ee* = 92%]. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.51 (br d, *J* = 4.7 Hz, 1H, H_{Py}-6), 7.61 [dt, *J* = 1.9 (d) and 7.7 (t) Hz, 1H, H_{Py}-4], 7.33 (d, *J* = 8.6 Hz, 2H), 7.17 (bdd, *J* = 5.2 and 7.0 Hz, 1H, H_{Py}-5), 7.10 (d, *J* = 7.7 Hz, 1H, H_{Py}-3), 6.87 (d, *J* = 8.6 Hz, 2H), 5.4-4.6 (br s, 1H, OH), 5.11 (dd, *J* = 3.6 and 8.7 Hz, 1H, H-1), 3.22-3.02 (AB signals of an ABX system, $^3J_{A,X}$ = 3.6, $^3J_{B,X}$ = 8.7, and $|^2J_{A,B}|$ = 14.9 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 159.6 (C), 158.7 (C), 148.3 (CH), 136.8 (CH), 136.2 (C), 126.9 (CH), 123.8 (CH), 121.6 (CH), 113.6 (CH), 72.8 (CH), 55.2 (CH_3), 45.7 (CH_2). These NMR data are in agreement with literature data.[19]

(*S*)-1-Phenyl-2-(pyridin-3-yl)ethanol (2d). [This compound was not described as optically active in the literature]. The reaction was carried out with 50 mM **1d**, without DMSO and with KRED-P2-D11. **2d** was obtained as a white solid with 90% yield (after flash chromatography; 18.2 mg, 91.3 µmol). M.p. = 123.7-125.1 °C. $[\alpha]_D^{20}$ = –13.8 (*c* 0.85, $CHCl_3$), *ee* > 99%. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.30 (br d, *J* = 4.9 Hz, 1H, H_{Py}-6), 8.26 (br s, 1H, H_{Py}-2), 7.43 [dt, *J* = 2.0 (t) and 7.9 (d) Hz, 1H, H_{Py}-4], 7.38-7.20 (m, 5H), 7.13 (dd, *J* = 4.9 and 7.9 Hz, 1H, H_{Py}-5), 4.85 (dd, *J* = 5.6 and 7.5 Hz, 1H, H-1), 3.5-3.0 (br s, 1H, OH), 3.06-2.90 (AB signals of an ABX system, $^3J_{A,X}$ = 5.6, $^3J_{B,X}$ = 7.5, and $|^2J_{A,B}|$ = 13.8 Hz, 2H, CH_2). These ^{1}H-NMR data are in agreement with literature data[26] for the racemic compound. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 150.3 (CH), 147.3 (CH), 143.6 (C), 137.4 (CH), 133.9 (C), 128.4 (CH), 127.7 (CH), 125.8 (CH), 123.1 (CH), 74.7 (CH), 42.8 (CH_2).

(*S*)-1-Phenyl-2-(pyridin-4-yl)ethanol (2e). [This compound was not described as optically active in the literature]. The reaction was carried out with 50 mM **1e**, without DMSO and with KRED-P1-B12. **2e** was obtained as a white solid with 90% yield (after flash chromatography; 18.3 mg, 91.3 µmol). M.p. = 107.8-109.5 °C. $[\alpha]_D^{20}$ = –16.1 (*c* 0.83, $CHCl_3$), *ee* > 99%. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.29 (br d, 2H, H_{Py}-2/6), 7.39-7.20 (m, 5H) 7.06 (d, *J* = 5.5 Hz, 2H, H_{Py}-3/5), 4.90 (dd, *J* = 5.3 and 7.7 Hz, 1H, H-1), 3.61 (br s, 1H, OH), 3.09-2.89 (AB signals of an ABX system, $^3J_{A,X}$ = 5.3, $^3J_{B,X}$ = 7.7, and $|^2J_{A,B}|$ = 13.5 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 148.9 (CH), 147.8 (C), 143.6 (C), 128.4 (CH), 127.7 (CH), 125.8 (CH), 125.0 (CH), 74.1 (CH), 45.1 (CH_2). These ^{1}H- and ^{13}C-NMR data are in agreement with literature data for the racemic compound.[27]

(*S*)-1-Phenyl-2-(quinolin-2-yl)ethanol (2f). The reaction was carried out with 20 mM **1f**, with DMSO (3.5% v/v) and with KRED-P1-B02. **2f** was obtained as a yelow solid with 91% yield (after flash chromatography; 18.3 mg, 73.6 µmol). M.p. = 122.1-123.7 °C (lit.,[18b] 115-117 °C for a sample with *ee* = 82%). $[\alpha]_D^{20}$ = –79.4 (*c* 0.90, $CHCl_3$), *ee* > 99% [lit.,[18b] $[\alpha]_D^{20}$ = –59.0 (*c* 0.99, $CHCl_3$), *ee* = 82%]. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.13-8.05 [two partially overlapped doublets centered at 8.10 (*J* = 8.3 Hz) and 8.08 (*J* = 8.5 Hz) ppm, 2H], 7.81 (br d, *J* = 8.1 Hz, 1H), 7.73 (dd, *J* = 1.4, 6.9, and 8.4 Hz, 1H), 7.58-7.45 (several m, 3H), 7.42-7.25 (several m, 3H), 6.20 (br s, 1H, OH), 5.34 (dd, *J* = 4.5 and 7.7 Hz, 1H, H-1), 3.41-3.25 (m, AB signals of an ABX system, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 160.4 (C), 146.8 (C), 143.8 (C), 136.8 (CH), 129.8 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 126.8 (C), 126.2 (CH), 125.8 (CH), 122.0 (CH),

72.9 (CH), 46.0 (CH_2). These ^{1}H- and ^{13}C-NMR data are in agreement with literature data.[18b]

(*S*)-2-(2-Azido-2-phenylethyl)pyridine 5

A solution of alcohol (*R*)-**2a** (54.0 mg, 0.271 mmol, *ee* > 99%) and triethylamine (100 μL, 0.72 mmol) in anhydrous THF (1.0 mL) was treated with mesyl chloride (41.9 μL, 0.542 mmol) at −15 °C and the reaction was allowed to slowly reach room temperature. After 12 h, ethyl acetate was added and the organic solution was successively washed with saturated aq. $NaHCO_3$ and water. After drying the organic layer on anh. Na_2SO_4, the solvent was eliminated and the crude consisting of the mesyl derivative (*R*)-**4** (such it was deduced from its ^{1}H NMR spectrum) was used in the next step without purification. Thus, the crude (*R*)-**4** was dissolved in anh. DMF (1.1 mL) and NaN_3 (88 mg, 1.35 mmol) was added. The mixture was heated at 70 °C during 5 h (TLC control, hexane:ethyl acetate 3:1; R_f for the azide, 0.26). Then, ethyl acetate and water were added, the organic phase was separated and the aqueous layer extracted with ethyl acetate (2 × 6 mL). The joined organic layers were washed with water and dried on anh. Na_2SO_4. Evaporation of the solvent yielded the azide (*S*)-**5** which was purified by flash column chromatography (hexane:ethyl acetate 9:1). Light yellow oil (53,5 mg, 88% yield); $[\alpha]_D^{20}$ = −94.4 (*c* 1.8, $CHCl_3$), *ee* = 97%. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.59 (ddd, *J* = 0.9, 1.9, and 4.9 Hz, 1H, H_{Py}-6), 7.57 [dt, *J* = 1.9 (d) and 7.7 (t) Hz, 1H, H_{Py}-4], 7.43-7.23 (m, 5H, Ph), 7.15 (ddd, *J* = 1.2, 4.9, and 7.6 Hz, 1H, H_{Py}-5), 7.09 (dt, *J* = 1.1 (t), 7.8 (d) Hz, 1H, H_{Py}-3), 5.09 (dd, *J* = 5.9 and 8.8 Hz, 1H, H-1), 3.28-3.12 (AB signals of an ABX system, $^3J_{A,X}$ = 5.9, $^3J_{B,X}$ = 8.8, and $|^2J_{A,B}|$ = 13.8 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 157.4 (C), 149.3 (CH), 139.3 (C), 136.3 (CH), 128.7 (CH), 128.2 (CH), 126.7 (CH), 124.1 (CH), 121.7 (CH), 65.8 (CH), 45.1 (CH_2). HRMS-ESI$^+$ calcd. for $[C_{13}H_{13}N_4]^+$ $(M+H)^+$ 225.1135 *m/z*, found 225.1137.

(*S*)-1-phenyl-2-(pyridin-2-yl)ethanamine (*S*)-6 and its dihydrochloride salt (*S*)-6·2HCl

To a solution of (*S*)-**5** (52,0 mg, 0.232 mmol) in methanol (9.0 mL), palladium on carbon (Pd/C, 45 mg, 10% w/w) was added and the reaction mixture was stirred under a H_2 atmosphere at room temperature for 45 min. Then, the suspension was filtered through a celite® pad. The organic solution was concentrated to give the crude lanicemine, (*S*)-**6** (45 mg, 98% yield); ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.58 (ddd, *J* = 0.9, 1.7, and 4.9 Hz, 1H, H_{Py}-6), 7.56 [dt, *J* = 1.9 (d) and 7.7 (t) Hz, 1H, H_{Py}-4], 7.42-7.19 (several m, 5H), 7.13 (ddd, *J* = 1.1, 4.9, and 7.5 Hz, 1H, H_{Py}-5), 7.05 (br d, *J* = 7.8 Hz, 1H, H_{Py}-3) 4.48 (dd, *J* = 4.9 and 9.0 Hz, 1H, H-1), 3.20-2.96 (AB signals of an ABX system, $^3J_{A,X}$ = 4.9, $^3J_{B,X}$ = 9.0, and $|^2J_{A,B}|$ = 13.6 Hz, 2H, CH_2), 2.0-1.5 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 159.3 (C), 149.3 (CH), 145.6 (C), 136.2 (CH), 128.4 (CH), 127.0 (CH), 126.3 (CH), 124.0 (CH), 121.3 (CH), 56.0 (CH), 48.2 (CH_2). The crude amine (*S*)-**6** (25.0 mg, 0.126 mmol) was redissolved in methanol (4.0 mL) and trimethylsilyl chloride (TMSCl, 240 μL 1.89 mmol) was added. After 6 hours at room temperature, the solvent was eliminated under reduced pressure and the residue was successively washed with small portions of THF (4 × 1.5 mL), obtaining the lanicemine hydrochloride (*S*)-**6** · 2HCl as a white solid (34 mg, >99% yield); $[\alpha]_D^{20}$ = +81.0 (*c* 1.2, MeOH), *ee* = 97% [Lit.[28] $[\alpha]_D^{20}$ = +87.1 (*c* 1.1, MeOH), *ee* > 99%]. The dihydrochloride salt, (*S*)-**6** · 2HCl, can be recrystallyzed from a mixture of methanol-ethyl acetate; m.p. 200.4-202.5 °C (dec.); ^{1}H NMR (MeOH-d_4, 300.13 MHz) δ (ppm): 8.75 (ddd, *J* = 0.8, 1.6, and 5.8 Hz, 1H, H_{Py}-6), 8.50 [dt, *J* = 1.6 (d) and 7.9 (t) Hz, 1H, H_{Py}-4], 8.00-7.90 (m, 2H, H_{Py}-5 and H_{Py}-3), 7.55-7.38 (m, 5H, Ph), 4.98 (dd, *J* = 6.3 and 9.7 Hz, 1H, H-1), 3.98 and 3.78 (AB signals of an ABX system, $^3J_{A,X}$ = 6.3, $^3J_{B,X}$ = 9.7, and $|^2J_{A,B}|$ = 14.3 Hz, 2H, CH_2). These ^{1}H-NMR data are in agreement with literature[29] data. ^{13}C NMR (MeOH-d_4, 75.5 MHz) δ (ppm): 152.3 (C), 148.1 (CH), 143.3 (CH), 135.9 (C), 131.1 (CH), 130.7 (CH), 129.8 (CH), 128.6 (CH), 127.3 (CH), 55.6 (CH), 39.0 (CH_2).

***tert*-Butyl [(*S*)-1-phenyl-2-(pyridin-2-yl)ethyl]carbamate (*S*)-7**

To a solution of crude lanicemine (*S*)-**6** (20.0 mg, 0.101 mmol) in methanol (1.0 mL), di-*tert*-butyl dicarbonate (44 mg, 0.20 mmol) was added. The mixture was maintained at room temperature during 4 h. Then, solvents were removed and the residue subjected to flash column chromatography (hexane:ethyl acetate 5:1) to give pure (*S*)-**7** (27 mg, 90% yield) as a white solid. M.p. = 133.2-134.8 °C. $[\alpha]_D^{20}$ = –49.8 (*c* 1.1, $CHCl_3$), *ee* = 97%. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ (ppm): 8.53 (br d, *J* = 4.6 Hz, 1H, H_{Py}-6), 7.50 [dt, *J* = 1.8 (d) and 7.7 (t) Hz, 1H, H_{Py}-4], 7.33-7.15 (m, 5H, Ph), 7.11 (ddd, *J* = 1.0, 5.0, and 7.6 Hz, 1H, H_{Py}-5), 6.94 (br d, *J* = 7.8 Hz, 1H, H_{Py}-3), 5.98 (br s, 1H, NH), 5.08 (br s, 1H, H-1), 3.38-3.00 (m, 2H, CH_2), 1.35 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 158.0 (C), 155.1 (C), 148.9 (CH), 142.2 (C), 136.3 (CH), 128.2 (CH), 126.9 (CH), 126.0 (CH), 123.9 (CH), 121.5 (CH), 79.2 (C), 54.8 (CH), 44.6 (CH_2), 28.2 (CH_3). HRMS-ESI$^+$ calcd. for $[C_{18}H_{23}N_2O_2]^+$ $(M+H)^+$ 299.1754 *m/z*, found 299.1758.

Conclusions

The utility of several commercially available ketoreductases has been proved in the asymmetric reduction of different prochiral aromatic ketones which also bear an (azaryl)methyl grouping. In most of the cases, (*R*)- and (*S*)-selective KREDs were found, thus allowing the preparation of both enantiomers of the alcohol with *ee* > 99%. The assignment of the absolute configuration of each optically active secondary alcohol here prepared has been established using modified Mosher and Kelly methods. These findings could be applied in the absolute configuration assignment of other more complex alcohols. Finally, as a proof of the usefulness of this kind of compounds, one of them has been transformed into the biologically active lanicemine by means of a very simple and efficient strategy.

Conflicts of interest

There are no conflicts to declare.

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