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Chemoenzymatic synthesis of optically active 2-(2′- or 4′-substituted-1*H*-imidazol-1-yl)cycloalkanols: chiral additives for (L)-proline†

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Enantiopure substituted imidazoles obtained by enzymatic kinetic resolution can be promising candidates as co-catalysts for aldol reactions catalysed by (L)-proline. These additives seem to form supramolecular complexes with the catalyst through the formation of H-bonds, leading to significant improvement in both the reaction rates and selectivity of the reaction. Herein, we present our results on the use of these substituted *trans*-2-imidazoyl-cycloalkanols as additives for the (L)-proline catalyzed direct aldol reaction between ketones and aromatic aldehydes.

Introduction

Organocatalysis is gaining importance as an environmentally friendly alternative to well established asymmetric transformations based on metal-containing catalysts.[1] Thus, it is becoming a common tool in synthetic organic chemistry. From the toolbox of small organocatalysts, proline is by far one of the most popular ones, as it is cheap, readily available in both enantiomeric forms and can be used for a wide range of synthetic transformations.[2] Among them the direct catalytic aldol reaction is a well-studied and broadly applicable C–C bond-forming reaction, which provides enantiomerically enriched β-hydroxy carbonyl compounds.[3] However, (L)-proline itself presents some major drawbacks, presenting a poor solubility and reactivity in non-polar organic solvents, and can lead to parasitic side reactions that significantly reduce the selective conversion of the aldehyde into the corresponding aldol, requiring high catalyst loadings in order to achieve acceptable yields.[4] Therefore, much effort has been devoted to the development of new organocatalysts based on structurally modified (L)-prolines.[5] The design and synthesis of these new organocatalysts does not only allow modifying their physical properties but also may lead, in some cases, to more efficient and enantioselective processes. Different synthetic strategies have been assayed to achieve this goal, but, in general, all of them required the re-design, re-synthesis, and re-selection of efficient organocatalysts, limiting, to some extent, the scope of this approach. A simpler alternative is the use of different types of additives, whose addition to the reaction containing the (L)-proline will help to modify its outcome in terms of yield and selectivity. This allows a fast design and evaluation of a new series of catalytic systems by simply tuning the nature of the selected additive. Thus, different additives[6] such as alcohols,[7] ureas and thioureas,[8] guanidinium salts,[9] amine bases[10] or the simple addition of water[11] have been reported to accelerate the reaction rate and to increase its diastereo- and enantioselectivity.

We have recently reported a general chemoenzymatic methodology to produce optically active *trans*-2-imidazoyl-cycloalkanols.[12] These functionalised chiral imidazole derivatives may interact with the organocatalyst through H-bonding and/or by acid–base mechanisms leading to the formation of the corresponding chiral salts. This may provide mechanisms allowing us to fine-tune the catalytic properties of (L)-proline. Herein, we present our results on the use of these substituted *trans*-2-imidazoyl-cycloalkanols as additives for the (L)-proline catalyzed direct aldol reaction between ketones and aromatic aldehydes.

Results and discussion

Synthesis of the substituted *trans*-2-imidazoyl-cycloalkanols

Firstly, the nucleophilic opening of cycloalkene oxides **1a–b** with different substituted imidazoles (**2a–e**) was performed obtaining the corresponding racemic cyclopentanols **3a–e** and cyclohexanols **4a–e** using refluxing 1,4-dioxane as solvent (Table 1).

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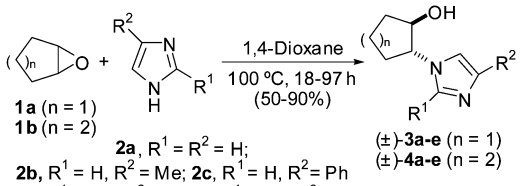
Table 1 Synthesis of racemic alcohols **3a–e** and **4a–e**



Entry	Oxide	Imidazole	*t* (h)	Yield (%)
1	**1a**	**2a**	18	88[a]
2	**1b**	**2a**	24	86[a]
3	**1a**	**2b**	23	89[b]
4	**1b**	**2b**	24	78[b]
5	**1a**	**2c**	23	50[b]
6	**1b**	**2c**	24	56[b]
7	**1a**	**2d**	23	62[b]
8	**1b**	**2d**	24	71[b]
9	**1a**	**2e**	97	71[b]
10	**1b**	**2e**	94	90[b]

[a] Reaction performed with 2 M imidazole. [b] Reaction performed with 5 M imidazole.

In all cases, the ring opening afforded exclusively the *trans*-alcohol isomers, the formation of the *cis*-analogues not being observed. The most hindered imidazoles (R^1 or R^2 = Me, Ph) were less reactive than the unsubstituted ones (R^1 and R^2 = H). For that reason, more concentrated solutions (5 M) were used for the substituted imidazoles **2b–e** (in comparison to 2 M for **2a**).

The effect of the steric congestion on the proximity of the reactive nitrogen atom is especially remarkable in the case of 2-phenylimidazole (**2e**) requiring 4 days to achieve high conversions of the corresponding racemic alcohols **3e** and **4e** (Table 1, entries 9 and 10). All the final products were isolated in high purity after flash chromatography and an additional washing of the resulting colour solids with hot diethyl ether. For 4-methylimidazole (**2b**) two isomers were detected corresponding to the two possible nucleophilic attacks involving the non-equivalent nitrogen atoms of the imidazole ring, isolating **3b** and **4b** as a mixture of the 4-methyl and the 5-methyl isomers in 4 : 1 and 7 : 1 ratio respectively.

For the enzymatic kinetic resolution of the corresponding racemic alcohols, *Candida antarctica* lipase B (CAL-B) and *Pseudomonas cepacia* lipase (PSL-C I, currently known as *Burkholderia cepacia* lipase) were selected as the possible biocatalysts for the acetylation reaction. A three-fold excess of vinyl acetate (VinOAc, **7**), a commonly employed activated ester for the kinetic resolution of alcohols, was used as the acyl donor. Tetrahydrofuran, an organic solvent usually applied in lipase-catalyzed kinetic resolutions, was used as the solvent (Table 2).

The asymmetric *O*-acylation of related six membered ring alcohols has been previously reported using *tert*-butyl methyl ether (TBME), PSL-C from Amano Pharmaceuticals and at 45 °C yielding the acetate (*R,R*)-**6a** and the alcohol (*S,S*)-**4a** in enantiopure form and good yields (entries 1–4).[12] Accordingly, PSL-C was selected for the biotransformation of the six-membered ring substituted imidazole derivatives (±)-**4b–e**. Optimal kinetic resolutions were attained for the 4-substituted derivatives (**4b**) and (**4c**) after 13 h at 30 °C (Table 2, entries 5 and 6). However, lower reactivities, although maintaining high enantioselectivities, were noticed for (**4d**) and (**4e**) having substituents close to the alcohol group. An increase in the temperature to 45 °C was required to achieve 50% conversion in 67 h for **4d** (entries 7 and 8). Lower conversions were observed for the more sterically demanding substrate **4e** even at 60 °C (entries 9 and 10).

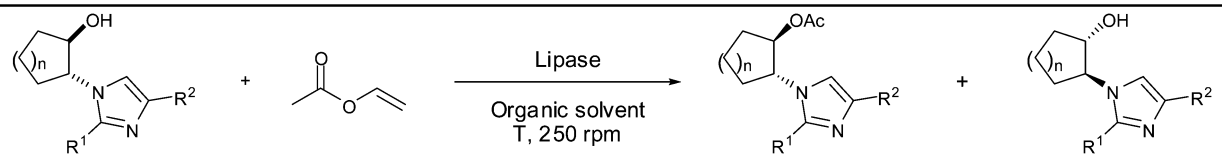
Similarly the five-membered ring imidazoles were efficiently resolved using PSL-C Amano, CAL-B or PSL-C I, depending on the substrate structure. Short reaction times and 30 °C were appropriate for the non-substituted imidazole **3a** or the 4-phenyl derivative **3c** (entries 11–13, 16 and 17) while slightly longer times were needed for the 4-methylated compound **3b** (entries 14 and 15). Best results for the 2-substituted analogues **3d** and **e** were attained at 60 °C and using CAL-B, providing in both cases the (*S,S*)-alcohols in enantiomerically pure form (entries 18–21).

Ion-pairing formation *vs.* H-bond interaction

In principle, these chiral imidazoles could form the corresponding salts with (L)-proline by a simple acid–base reaction. This was checked by adding a methanolic solution of the corresponding imidazole to a solution containing one equivalent of (L)-proline. After removing the solvent, the crude mixtures were analyzed by ^{1}H-NMR, FT-IR ATR and DSC. The ^{1}H-RMN did not show any trend that could reveal the formation of the corresponding imidazolium salt, which suggests that the substituted imidazoles are not basic enough for this purpose. Only slight shifts were observed, in particular for the signal corresponding to the α-CH proton of the (L)-proline (see Fig. S1 at ESI†). For an equimolecular mixture of (L)-proline and **4d** this signal is shifted from 3.62 to 3.67 ppm. This indicates a certain degree of interaction between the imidazole and (L)-proline even when a polar solvent (DMSO) was used. The FT-IR ATR of the solid mixture also suggests the presence of some interaction between both components. Thus, for the imidazole:(L)-proline mixture, a red-shift in the C=O stretching frequency (from 1550.5 to 1557.7 cm^{-1}, see Fig. S2 at ESI†) is observed, accompanied by a reduction of the band intensity in comparison with the pure (L)-proline. The H-bonded OH stretch also confirms this trend. In the mixture, the intensity of the OH stretching band is reduced, being shifted from 3048.4 to 3061.9 cm^{-1} suggesting a weaker H-bond network than in pure (L)-proline (see Fig. S2 at ESI†).

This situation is also supported by DSC studies of different combinations of the imidazole **4a** (mp = 88 °C) and (L)-proline (mp = 222 °C). The results showed that the addition of imidazole resulted in dramatic reductions in the melting point of (L)-proline (see Fig. S3 and Table S1 at ESI†). Thus, a mixture with only 0.17 molar equiv. of **4a** led to a melting point reduction of *ca.* 30 °C. For the **4a**:(L)-proline equimolecular mixture, the melting point was 168 °C, while the excess of **4a** (5 molar equiv., X_{4a} = 0.83) further reduced the temperature to 155 °C (see Fig. S4 at ESI†). This behaviour is reminiscent of the one reported for salicylic acid–salicylate mixtures.[14] The melting point of the imidazole is also affected. For the equimolecular mixture, a reduction of the melting point from 88 °C to 68 °C was found (onset temperature, see Table S1 at ESI†). Hence, supramolecular interactions *via* hydrogen bonding between the

Table 2 Lipase catalyzed kinetic resolution of racemic alcohols *trans*-**3a–e** and *trans*-**4a–e**



(±)-**3a-e** (n = 1)
(±)-**4a-e** (n = 2)

(1*R*,2*R*)-**5a-e**
(1*R*,2*R*)-**6a-e**

(1*S*,2*S*)-**3a-e**
(1*S*,2*S*)-**4a-e**

Entry	Alcohol	Enzyme	Solvent	T (°C)	t (h)	ee_S[a] (%)	ee_P[a] (%)	c[b] (%)	E[c]
1	**4a**	CAL-B	THF	30	39	93	98	49	>200
2	**4a**	PSL-C Amano	THF	30	14	97	98	48	>200
3	**4a**	PSL-C Amano	TBME	30	13	33	>99	25	>200
4	**4a**	PSL-C Amano	TBME	45	15	>99 (88)	>99 (91)	50	>200
5	**4b**	PSL-C Amano	THF	30	13	95 (92)	>99 (91)	48	>200
6	**4c**	PSL-C Amano	THF	30	13	99 (92)	>99 (94)	50	>200
7	**4d**	PSL-C Amano	THF	30	92	92	>99	48	>200
8	**4d**	PSL-C Amano	THF	45	67	99 (88)	>99 (91)	50	>200
9	**4e**	PSL-C Amano	THF	45	136	23	>99	19	>200
10	**4e**	PSL-C Amano	THF	60	72	26	>99	21	>200
11	**3a**	CAL-B	THF	30	14	99 (92)	>99 (91)	50	>200
12	**3a**	PSL-C Amano	THF	30	14	97 (88)	>99 (91)	49	>200
13	**3a**	PSL-C I	THF	30	14	>99 (92)	>99 (94)	50	>200
14	**3b**	CAL-B	THF	30	48	99 (92)	>99 (94)	50	>200
15	**3b**	PSL-C I	THF	30	48	94 (88)	>99 (94)	49	>200
16	**3c**	CAL-B	THF	30	15	>99 (80)	>99 (93)	50	>200
17	**3c**	PSL-C I	THF	30	15	74 (90)	>99 (96)	43	>200
18	**3d**	CAL-B	THF	30	92	66 (73)	99 (84)	38	>200
19	**3d**	CAL-B	THF	60	60	>99 (94)	95 (91)	51	>200
20	**3e**	CAL-B	THF	60	55	>99 (90)	96 (91)	51	>200
21	**3e**	PSL-C I	THF	60	55	60 (90)	>99 (87)	38	>200

[a] Enantiomeric excesses determined by HPLC; isolated yields in brackets refer to the corresponding conversion value. [b] Conversion values: $c = ee_S/(ee_S + ee_P)$. [c] Enantiomeric ratio: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[13]

carboxyl group of proline and both nitrogen atoms (preferentially the unsubstituted one) and the –OH group of the imidazole seem to be established and one possible model is shown in Fig. 1. Such interactions should be weaker than those found in pure (L)-proline but compete with proline–proline interactions reducing the melting point in the solid mixtures. Similar trends can be found for mixtures of (L)-proline with other imidazoles (see Table S2 at ESI†). Thus, such proline–chiral imidazole interactions can provide an opportunity for the fine tuning of the catalytic performance of (L)-proline.[15]

The impact of substituted *trans*-2-imidazoyl-cycloalkanols on the (L)-proline catalytic efficiency

In order to elucidate the potential use of *trans*-2-imidazoyl-cycloalkanols as additives for aldol reactions catalyzed by (L)-proline, the neat reaction between *p*-nitrobenzaldehyde and acetone was studied inside an NMR tube using deuterated acetone. Initially, the reactions were performed at 25 °C with a 40 mol% of proline, and at a 0.14 M concentration of aldehyde in the presence and absence of one equivalent of the imidazole **4a**. Fig. 2 depicts the profile of aldol formed *vs.* reaction time for the reaction with and without **4a**. It seems clear that the presence of **4a** as an additive substantially increases the reaction rate. Thus, after four hours *ca.* 90% of aldol is obtained in the presence of **4a**, while the reaction catalyzed just by (L)-proline led to less than 20% yield. Therefore, the additive has a significant positive effect on the activity. It is worth mentioning that the (L)-proline presents a low solubility in acetone. Indeed, the NMR spectrum indicates that only around 10% of added (L)-proline is solubilised in acetone, leading to a 5.7 mM concentration instead of the expected 57 mM. The presence of **4a** produces a twofold enhancement of the solubility of (L)-proline in acetone (from 5.7 to 11.4 mM). Thus, as the imidazole is completely soluble, the actual molar ratio of **4a**:(L)-proline in the solution is 5:1, even when an equimolecular solid mixture of both of them was added to the reaction.

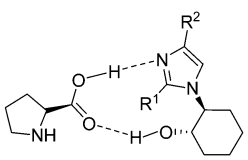


Fig. 1 Possible hydrogen bonding interactions for the imidazole–proline system.

Important changes in the enantioselectivity of the reaction were also produced by the presence of imidazoles as co-catalysts. In order to identify the structural factors affecting the stereoselectivity of the process the model reaction was carried out with an equivalent amount of different substituted imidazoles. The results are summarized in Table 3.

In the case of **4a**, the corresponding aldol was obtained with only a moderate enantiomeric excess (31% ee, Table 3, entry 3).

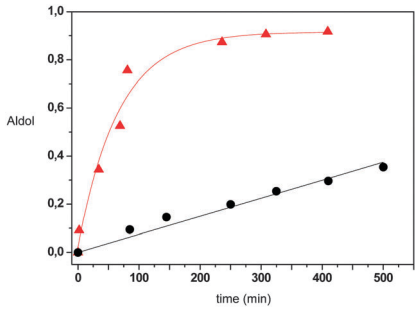


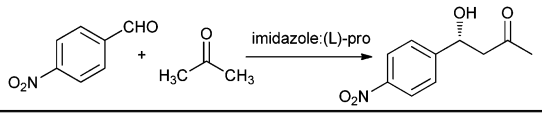
Fig. 2 Kinetic profile for the aldol reaction (a) red triangles: 1 : 1 ratio **4a** : L-proline; (b) black dots: absence of **4a**. 1 : 0.4 RCHO : cat ratio, 25 °C, 1.36 M in d_6-acetone.

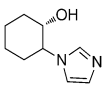
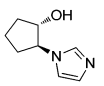
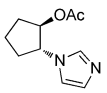
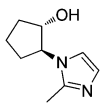
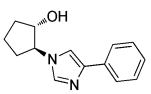
When just *N*-methyl imidazole was used, the ee found was higher than that obtained for **4a** and similar to that of the reference system (50% ee, Table 3, entry 2).

As the enantioselectivity achieved by cyclopentyl imidazole derivatives was higher (51% ee for **3a**) than that for cyclohexyl derivatives (31% ee for **4a**, Table 3, entries 3 and 4) the corresponding substituted cyclopentyl imidazoles were tested as co-catalysts. The acetylation of the hydroxyl group resulted in higher asymmetric inductions (65% ee for (*R*,*R*)-*trans*-β-OAc-cyclohexylimidazole and ~50% ee for (*S*,*S*)-*trans*-β-OH-cyclohexylimidazole, Table 3, entries 4 and 5). The same trend was observed for imidazole derivatives methylated at C2 (55% ee for the acetylated compound *vs.* 37% ee for the alcohol, Table 3, entries 6 and 7). Note that replacement of the proton by a methyl group at C2 reduced in both cases the asymmetric induction (Table 3, entry 4 *vs.* 6 and entry 5 *vs.* 7). The presence of a relatively bulky group in C4, such as phenyl, did not result in a significant change in the enantioselectivity of the aldol (Table 3, entries 4 *vs.* 8). Thus, a greater asymmetric induction was achieved with imidazoles not substituted at the C2 position and the acetylated hydroxyl group. Indeed, the level of enantioselection achieved in the presence of the additive, especially for **5a**, can be as good as that found for the reaction catalyzed by L-proline in the absence of any imidazole (entry 1, Table 2) but with the enhancement in catalytic activity.

Additionally, the same imidazole:L-proline mixtures were also tested for the neat reaction between *p*-nitrobenzaldehyde and cyclohexanone. The results obtained are summarized in Table 4.

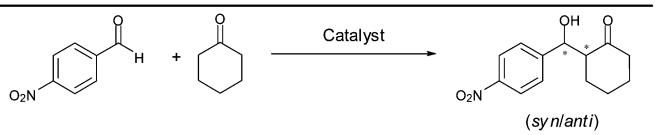
Table 3 Aldol reaction between *p*-nitrobenzaldehyde and acetone[a]

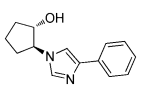


Entry	Imidazole derivative	Conversion[b] (%)	Selectivity[c] (%)	ee[d] (%)
1	—	>99	99	65
2		>99	99	50
3		>99	90	31
4		>99	95	51
5		>99	99	65
6		>99	90	37
7		>99	99	55
8		>99	98	53

[a] RCHO : acetone : complex (imidazole-L-proline) 1 : 10 : 0.4, at room temperature for 24 hours; imidazole-L-proline molar ratio 1 : 1 and aldehyde concentration 1.36 M. [b] Conversion calculated by ^{1}H-NMR in the crude of the reaction. [c] Selectivity calculated by ^{1}H-NMR in the crude of the reaction. Selectivity refers to the ratio between aldol products and side products, being those dehydration products or formed through parasite reactions (ref. 16). [d] Enantiomeric excess calculated by HPLC for the enantiomer *R* (major peak) [ee = (peak area (*R*) − peak area (*S*)) × 100/total area (*R* + *S*)].

Table 4 Aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone[a]



Entry	Imidazole derivative	Yield[b] (%)	Selectivity *anti* : *syn*[c] (%)	ee$_{anti}$[g] (%)	ee$_{syn}$[d] (%)
1	—	99	50 : 50	7	97[f]
2		98	70 : 30	65	60[f]
3		99	70 : 30	78	65[f]
4		99	70 : 30	72	41[f]
5		99	69 : 31	79	13[f]
6		99	67 : 33	77	23[e]
7		99	67 : 33	84	84[f]

[a] RCHO : cyclohexanone : cat 1 : 10 : 0.4, (1 : 1) imidazole-L-proline, at room temperature for 24 hours and aldehyde concentration: 0.96 M. [b] Yield calculated by ^{1}H-NMR in the crude of the reaction. [c] Selectivity calculated by ^{1}H-NMR in the crude of the reaction for the *anti* diastereomer. [d] Enantiomeric excess calculated by HPLC for each diastereoisomer [ee = (major peak area − minor peak area) × 100/total area]. [e] First major peak of the two peaks of *syn* diastereoisomers in the HPLC. [f] Second major peak of the two peaks of *syn* diastereoisomers in the HPLC. [g] Enantiomeric excess calculated by HPLC for the enantiomer 2′*R*,1′*S* (major peak) of the *anti* diastereoisomer.

All mixtures tested were active, leading to the corresponding aldol with excellent yields. The diastereoselectivity of the process was similar for the different imidazoles tested with an *anti* : *syn* ratio of 70 : 30. These diastereoselectivity values are higher than those for L-proline alone under the same experimental conditions (50 : 50 *anti* : *syn*). In terms of enantioselectivity, similar trends to those described above for the reaction with acetone were obtained in most cases. In general, acetylated derivatives produced an asymmetric induction higher than the non-acetylated ones (Table 4, entry 3 *vs.* 4 and entry 5 *vs.* 6). The methylation of the C2 position is reflected in a reduction of the enantioselectivity for the *syn* aldol, keeping it at a level similar to that of the *anti* aldol. This reduction in enantioselectivity, in the case of the acetylated co-catalysts, was about 50%. Noteworthily, for the C2 methylated imidazoles a topicity inversion could be observed when comparing the acetylated and non-acetylated derivatives (Table 4, entry 4 *vs.* 6). For this reaction, the presence of a 4-phenyl group at the imidazole ring slightly improved the enantiomeric excess obtained, reaching a 84% ee for both the *anti* and *syn* isomers. Hence, all results show that the substitution pattern of the imidazole used as the additive appears to be essential to determine the asymmetric induction.

Conclusions

In summary, we have shown that enantiopure substituted imidazoles obtained by enzymatic kinetic resolution can be promising candidates as co-catalysts for aldol reactions catalysed by L-proline. These additives seem to form supramolecular complexes with the catalyst through the formation of H-bonds, leading to a significant improvement in both the reaction rates and the selectivity of the reaction. The stereoselectivity of the process is highly influenced by the structural parameters of the imidazole. The systems tested reveal the importance of the substitution pattern at the C2 position, the size of the cycloalkyl ring attached to one of the nitrogen atoms of the imidazole and the presence of a hydroxyl group or its acetylated counterpart as key parameters to optimize the enantioselectivity. We are currently exploring other classes of azole-based systems that can benefit from being programmed to interact as complementary co-catalysts and will report in due course.

Experimental section

Candida antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU g^{-1}) was a gift from Novozymes. *Pseudomonas cepacia* lipase was purchased from Amano Pharmaceuticals (PSL-C Amano, 1019 U g^{-1}) or Sigma-Aldrich (PSL-C I, 1638 U g^{-1}). All other reagents were purchased from Aldrich and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatography was performed using silica gel 60 (230–240 mesh). High performance liquid chromatography (HPLC) analyses were carried out at 20 °C in a Hewlett Packard 1100 chromatograph under the conditions specified for each substrate and with UV monitoring at 210 nm or 254 nm. IR spectra were recorded either on NaCl plates or KBr pellets in a Perkin-Elmer 1720-X FT or on a MIRacle Single Reflection Diamond/ZnSe ATR in a Jasco FT-IR 6200. ^{1}H, ^{13}C NMR, DEPT, and ^{1}H–^{13}C heteronuclear experiments were performed using AV-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) Bruker spectrometers or Varian INOVA 500. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). A HP1100 chromatograph mass detector was used to record mass spectra experiments (MS) through $APCI^+$ or ESI^+ experiments. Measurement of the optical rotation was done in a Perkin-Elmer 241 polarimeter.

General procedure for the synthesis of racemic alcohols

A solution of oxide **1a–b** (15.63 mmol) and the corresponding imidazole derivative **2a–e** (12.50 mmol) in 1,4-dioxane (2.50 mL) was stirred at 100 °C for 18–97 h and then the mixture was cooled to room temperature. After this time, the solvent was evaporated under reduced pressure and the resulting crude purified by flash chromatography on silica gel (10% MeOH/CH_2Cl_2) yielding (±)-*trans*-**3a–e** or (±)-*trans*-**4a–e** (50–90%) as white solids. For additional data see Table 1.

General procedure for the synthesis of racemic acetates

To a solution of (±)-*trans*-**3a–b** (0.32 mmol) or (±)-*trans*-**4a–b** in dry CH_2Cl_2 (3.2 mL), Et_3N (133 μL, 0.95 mmol), DMAP (12.8 mg, 0.10 mmol) and Ac_2O (60 μL, 0.62 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred at room temperature for 4 h until complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$) yielding (±)-*trans*-**5a–e** and *trans*-**6a–d** as pale yellow oils, or *trans*-**6e** as a white solid (78–98% yield).

General procedure for the enzymatic kinetic resolution of imidazole derivatives

To a suspension of racemic alcohol *trans*-**3a–e** or *trans*-**4a–e** (0.60 mmol) and the corresponding enzyme (CAL-B or PSL-C I in 1 : 1 weight ratio relative to the alcohol) in dry THF (6.0 mL), vinyl acetate (166 μL, 1.80 mmol) was added under a nitrogen atmosphere at 30–60 °C. The reaction was shaken for the appropriate time at different temperatures and 250 rpm. Aliquots were regularly analyzed by HPLC until around 50% conversion was reached. The reaction was stopped and the enzyme filtered off using CH_2Cl_2 (3 × 5 mL), the solvent evaporated under reduced pressure and the reaction crude purified by flash chromatography on silica gel (5–10% MeOH/$CHCl_3$) affording the corresponding optically enriched acetates and alcohols. For additional data see Table 2.

General procedure for the formation of the imidazole:L-proline complex

To a solution of the corresponding substituted imidazole (0.27 mmol) in MeOH (5 mL) L-proline (32.1 mg, 0.27 mmol) was added. The resulting mixture was stirred at room temperature for 24 h. After this time, the solvent was removed by

distillation under reduced pressure to obtain the corresponding complex.

General procedure for the aldol reaction

Over a mixture of the corresponding imidazole : (L)-proline complex (1 : 1) (0.4 mmol) and acetone or cyclohexanone (10 mmol), *p*-nitrobenzaldehyde (1 mmol) was added. The resulting mixture was stirred for 24 h at room temperature, following the reaction by TLC (33% EtOAc/hexane). After that time, chloroform (10 mL) was added and the mixture was washed with deionized water (3 × 5 mL). The organic phase was dried with anhydrous magnesium sulphate and the solvent evaporated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel (33% EtOAc/hexane).

4-Hydroxy-4-(4-nitrophenyl)butan-2-one

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.10 (s, 3H, CH_3), 2.78 (dd, 2H, J = 3.3, 6.6 Hz, CH_2), 3.94 (s, 1H, OH), 5.17 (dt, 1H, J = 3.8, 7.7 Hz, CH), 7.44 (d, 2H, Ph), 8.02 (d, 2H, J = 8.9 Hz, Ph). R_f: 0.25 (33% EtOAc/hexane). HPLC: 36.2 min (*R*) and 41.1 min (*S*) (Chiralcel OJ, Hex/IPA (90 : 10), flow: 0.75 mL min^{-1}, T: 30 °C, λ: 254 nm).

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.32–1.78 (m, 5H), 2.26–2.53 (m, 4H), 4.02 (s, 1H, OH), 4.83 (d, 1H, J = 8.3 Hz, CH, *anti*), 5.41 (s, 1H, CH, *syn*), 7.44 (d, 2H, J = 8.5 Hz, Ph), 8.13 (d, 1H, J = 8.5 Hz, Ph). R_f: 0.27 (33% EtOAc/hexane). HPLC: 16.2 min and 20.6 min (*syn*); 22.3 min (2*S*,1′*R*) and 29.6 min (2*R*,1′*S*) (*anti*) (Chiralpak AD, Hex/IPA (90 : 10), flow: 1 mL min^{-1}, T: 30 °C, λ: 254 nm).

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