FULL PAPER

A Straightforward Deracemisation of *sec*-Alcohols Combining Organocatalytic Oxidation and Biocatalytic Reduction

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Dedication ((optional))

Abstract: An efficient organocatalytic oxidation of racemic secondary alcohols, mediated by sodium hypochlorite (NaOCl) and 2-azaadamantane *N*-oxyl (AZADO), has been conveniently coupled with a highly stereoselective bioreduction of the intermediate ketone, catalysed by ketoreductases, in aqueous medium. The potential of this one-pot two-step deracemisation process has been proven by a large set of structurally different secondary alcohols. Reactions were carried out up to 100 mM final concentration enabling the preparation of enantiopure alcohols with very high isolated yields (up to 98%). When the protocol was applied to the stereoisomeric *rac*/*meso* mixture of diols, these were obtained with very high enantiomeric excesses and diastereomeric ratios (95% yield, >99% *ee*, >99:<1 *dr*).

Introduction

Taking the complex and efficient machinery of the living organisms as inspiration, chemists are devoting a great effort to develop artificial multi-enzymatic cascade reactions and to apply them in organic synthesis.[1] These approaches are particularly appealing because enzymes, acting in similar reaction conditions, are operationally more compatible than other types of catalysts.[2] Nevertheless, nowadays, the dividing lines between the different types of catalysis are becoming increasingly diffuse and biocatalysts are also being elegantly combined with metal-based catalysts and organocatalysts in concurrent and one-pot multi-step syntheses.[1b,3]

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 and fragrances, and pharmaceuticals.[4] The commercial availability and easy accessibility of a great variety of racemic alcohols have motivated the development of biocatalytic routes in order to get these compounds in enantiopure form. Although firstly most of these protocols were based on kinetic resolutions,[5] the maximal theoretical 50% yield for the enantiomer required as well as the need to carry out the separation of the product and the remaining substrate addressed the attention towards the need of other techniques overcoming these limitations. Thus, a variety of deracemisation approaches[6] have been successfully applied to the quantitative transformation of a racemate in an enantiopure compound, avoiding the need to discard or recycle the unwanted enantiomer.

Carbonyl reductases are in the second top position of the most used enzymes in organic synthesis due to their wide availability and high stereoselectivity.[7] Because these enzymes can promote either the selective oxidation of an alcohol or the reduction of the prochiral ketone, they have been exploited to get deracemisation by stereoinversion of secondary alcohols using two stereocomplementary enzymes.[8] Obviously, the success of the methodology is determined by a fine balance of the oxidation-reduction sequence, sometimes achieved by the specific cofactor-dependence of the two involved enzymes.[9]

Recently, a single biocatalyst, a mutant of *Thermoanaerobacter ethanolicus* secondary alcohol dehydrogenase (TeSADH), has been used to promote the deracemisation of some alcohols by means of a one-pot two-step (oxidation-reduction) protocol, in which the amount of acetone and 2-propanol was key to control the sequence.[10] However, the enantiomeric excess values obtained were, in general, moderate and only two of the five substrates investigated were isolated with *ee* >90%.

Satisfactory results were obtained when the one-pot oxidation-reduction protocol was designed combining different catalysts: the iodine/TEMPO system for the oxidation of the *sec*-alcohol followed by the bioreduction of the intermediate ketone catalysed by ADH.[11] This procedure required the use of an additive before the reduction step in order to eliminate the excess of iodine, thus enabling the preparation of some enantiopure secondary alcohols with very high yields. Even with some limitations, these methods implying different sorts of catalysts continue being a fascinating aspect of the catalysis and they still pose a challenge for chemists.[12]

Recently we have described an expedient, stereoselective and operationally simple method coupling an organocatalyst (AZADO, 2-azaadamantane *N*-oxyl) and different amino transferases to transform secondary alcohols into optically active amines.[13] The high efficiency, simplicity, and wide scope of the organocatalytic first step encouraged us to explore a new one-pot deracemisation protocol of secondary alcohols in which the non-selective AZADO-catalysed oxidation is conveniently coupled with a stereoselective reduction of the intermediate ketone mediated by a ketoreductase (KRED) (Scheme 1). The method

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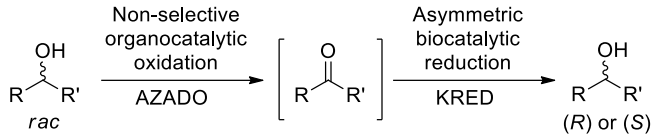
described herein has been applied to a significant series of racemic secondary alcohols as well as some diols, and the robustness of the strategy has also been shown by the high tolerance of substrate in both oxidation and reduction steps, which are carried out at 250 and up to 100 mM, respectively.



Scheme 1. Proposal of deracemisation via a catalytic oxidation-reduction sequence.

Results and Discussion

A wide series of secondary alcohols was selected in this study (Figure 1). Non-benzylic alcohols **1a** and **1b** are precursors of pharmacologically active amines such as amphetamine and fenfluramine,[14] and **1c** is a representative example of aliphatic secondary alcohol. Among benzylic alcohols, we selected **1d** and **1e**, this last being a precursor of the orally active NK1 receptor antagonist aprepitant,[15] which is used as antiemetic drug[16] and has promising antitumor activity.[17] In addition, the *para*-linked biaryl alcohol **1f**, as a model of biarylic compound, as well as the *ortho*-fusionated **1g**-**1i** were also selected. The biaryl moiety forms the basic structure of many biologically active compounds[18] and is also found in electroluminiscent polymers[19] and chiral ligands.[20] The deracemisation of the *ortho*-biarylic alcohols **1g**-**1i** has an extra added-value since previous approaches based on a lipase-catalysed kinetic resolution rendered very low yields due to the high steric congestion near to the reactive centre.[21] Furthermore, the amino alcohol derivative **1j** and the azido alcohol **1k** were also incorporated in our study as representative bifunctionalised compounds. Lastly, the viability of the method to convert the three-stereosiomers mixture of diols **1l** and **1m** into one single stereoisomer was also investigated. Enantiopure C_2-symmetric diols such as **1l** and **1m** are key compounds for the synthesis of chiral ligands,[20,22] and **1l** has been also used for the preparation of optically active crown ethers[23] and other complex molecules.[24]

The organocatalyst AZADO has exhibited not only a high catalytic potential combined with chlorine bleach (aqueous solution of NaOCl), but also a great efficiency to promote the oxidation of structurally hindered secondary alcohols. These features make this system superior to others, for example using the cheaper *N*-oxyl radical TEMPO.[25] In addition to the importance of the aforementioned non-racemic alcohols, some of them as the hindered biarylic derivatives have been selected to extend the applicability of this oxidation methodology.

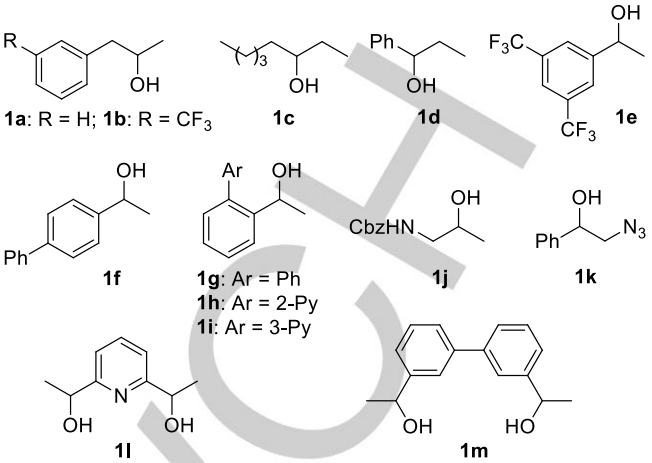


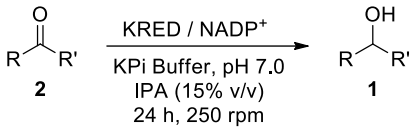
Figure 1. Racemic secondary alcohols of this study.

Similarly to the reaction conditions used in our previous contribution,[13] the alcohol oxidation step was planned by using a 0.40 M aqueous solution of sodium hypochlorite at pH 8.9, and AZADO (1.0 mol%)[26] as the catalyst, but the co-solvent α,α,α-trifluorotoluene (TFT) was changed to acetonitrile. The idea of employing this water-miscible co-solvent is to suppress or significantly lower the amount of dimethyl sulphoxide (DMSO) that would be used as co-solvent in the second step if TFT is employed.

The use of acetonitrile (5% v/v) in the oxidation step only required a slight excess of NaOCl (400 mM, 1.3 equiv) and the same amount of AZADO (1.0 mol%). The oxidation reactions were performed at different scales (1.0 – 0.15 mmol) and in all cases the starting material was totally converted into the corresponding ketone **2** after 1.5 h. Substrate concentration in this oxidation step was near to 250 mM, which was determined by the amount and concentration of the NaOCl solution used as well as the volume of co-solvent. Quantitative yields were obtained for all the ketones **2**, which were isolated in pure form by a simple extraction with ethyl acetate.

On the other hand, before carrying out the step-wise protocol, a complete screening of KREDs (from Codexis, see the Supporting Information) with the ketones **2** was performed using a range of 10-20 mM substrate concentration. Bioreductions were conducted at 30-40 ºC in 125 mM phosphate buffer (pH 7.0), with $NADP^+$ (1.0 mM) and isopropyl alcohol (IPA, 15% v/v). The most significant results are shown in Table 1. In all the cases the starting ketones (**2a**-**k**) or diketones (**2l** and **2m**) were totally transformed into the corresponding enantiopure alcohols (**1a**-**k**) or diols (**1l** and **1m**) after 24 h of reaction. In the process starting from diketones **2l** and **2m** some KREDs catalysed the formation of a mixture of mono-alcohol and diol but, in those collected in Table 1, only a trace amount of the enantiopure mono-alcohol was detected.

Table 1. Bioreduction of ketones **2a-k** and diketones **2l,m**.[a]



Ketone	Conc. (mM)	KRED[b]	*T* (ºC)	*C* (%)[b]	**1**, *ee* (%)[c]
2a	20	P2-H07	30	>99	>99 (*R*)
2b	20	P3-B03	30	>99	>99 (*S*)
2c	20	P1-A04	30	>99	>99 (*R*)
2d	20	P1-A04	30	>99	>99 (*R*)
2e	20	P1-B05	30	>99	>99 (*R*)
2f	10	P3-B03	40	>99	>99 (*S*)
2g	10	P1-B05	40	>99	>99 (*S*)
2h	20	P1-B05	40	>99	>99 (*S*)
2i	20	P1-B02	40	>99	>99 (*S*)
2j	20	P1-A04	30	>99	>99 (*R*)
2k	20	P1-A04	30	>99	>99 (*S*)
2l	20	P1-A04	30	>99	>99 (*R,R*)
2m	10	P1-A12	40	>99	>99 (*R,R*)

[a] For the structure of the ketone or diketone, see the corresponding alcohol or diol precursor **1** in Figure 1. A selection of results is here collected (see the Supporting Information for the full panel of enzymatic screenings). [b] KRED identified according to the numbering of the Screening Kit of Codexis. [c] Degree of conversion (*C*) and *ee* were determined by GC or HPLC. The absolute configuration is indicated between brackets.

To enable an efficient coupling of the oxidation and reduction reactions, some points of both steps must be considered in advance: 1) Excess of oxidant in the first step must be totally eliminated in order to preserve the labile cofactor (NADPH) and the enzyme (KRED) in the subsequent biotransformation. This issue is easily solved because the hydrogen donor –isopropyl alcohol– used in great excess in the second step quenches the remaining NaOCl in the reaction medium. Nevertheless, a compatibility proof was carried out to demonstrate that either isopropyl alcohol is an effective scavenger of NaOCl and AZADO did not affect the enzymatic activity. 2) The optimal substrate concentration for each step differs significantly. Regarding this, we posed as a major achievement to carry out the biocatalytic step up to 100 mM substrate concentration, which would be significantly higher than that used in previously reported methodologies.[10,11] As the dilution from 250 to 100 mM has to be achieved by adding phosphate buffer, and as the first step is already conducted with a high salt concentration, the feasibility of the bioreduction in such a highly saline medium should be assessed. Thus, in order to test the optimal conditions and achieve a highly efficient one-pot stepwise process, deracemisation of **1b** was selected as a benchmark reaction.

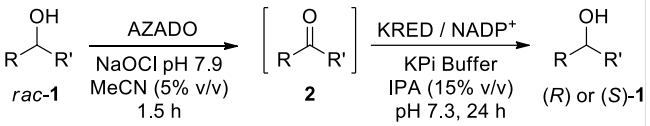
In the first attempt of oxidation-reduction sequence, and after carrying out the oxidation of **1b** (250 mM) during 1.5 h in the above mentioned conditions, IPA (15% v/v) was added and the reaction mixture stirred during five minutes. Then, each component of the second step [buffer phosphate (125 mM; pH 7.0), $MgSO_4$ (1.25 mM), and $NADP^+$ (1.0 mM)] was added to reach the target concentration of the intermediate **2b** (100 mM). In these conditions, KRED-P3-B03 retained its stereoselective activity catalysing the reduction of the ketone with total selectivity (*ee* >99%) while the conversion into (*S*)-**1b** was 79% after 24 h, and did not evolve further.

The incomplete reduction of **2b** may result from the lower solubility of this ketone in the highly saline reaction medium. Both NaCl (coming from the reacting NaOCl) and carbonate species (proceeding from $NaHCO_3$ used to reduce the pH from 9.5 to 8.9 of the commercial solution of NaOCl) contribute to increase the saline concentration in 160 and 190 mM, respectively. As a consequence, the second step is carried out in a saline concentration near to 500 mM. Accordingly, other reaction conditions were tested to lower the salt content in the bioreduction step. Thus, the addition of phosphoric acid in the second step to attain the desired phosphate concentration contributed to partially eliminating the carbonate species as carbonic acid and causing an improvement in the conversion (87%). Finally, we decided to suppress $NaHCO_3$ in the first step and lower the pH of the NaOCl solution by using of KH_2PO_4 in such amount that its concentration was 125 mM, as that required in the second step. Under these conditions, the resulting 400 mM aqueous solution of NaOCl exhibited pH 7.9 and the AZADO-catalysed oxidation of **1b** happened with total conversion after the same reaction time (1.5 h). Then, IPA (15% v/v), 125 mM phosphate buffer at pH 7.0 (containing $MgSO_4$ 2.5 mM), the KRED $NADP^+$ (1.0 mM) were successively added to reach a final 100 mM substrate concentration and pH 7.3. Upon these conditions the degree of conversion into (*S*)-**1b** (*ee* >99%) was complete after 24 h.

Once an efficient process was validated, we extended the study to the selected racemic alcohols (Figure 1) to have a broader overview of the potential of this oxidizing-reducing protocol. Therefore, after the oxidation took place, the optimized experimental procedure for the bioreduction step was applied with a selected KRED, at 100 mM substrate concentration, and 30 or 40 ºC depending on the substrate (see Table 1). Interestingly the protocol worked perfectly for a large variety of alcohols, obtaining the desired enantiopure products with complete (>99%) or very high conversion (90-93%) for ten of the thirteen substrates (Table 2). Thus, the enantiopure alcohols (*R*)-**1a**, (*S*)-**1b**, and (*R*)-**1e**, which are precursors of valuable biologically active compounds, were isolated with very high yields (90-98%). Also remarkable were the results obtained for the bifunctional amino alcohol derivative **1j** and the *ortho*-biarylic alcohols **1h** and **1i**. In the last two cases, the pyridine moiety contributed to increase the solubility of these alcohols in the reaction medium, thereby allowing a 100 mM concentration in the bioreduction step. However, with the analogous biphenylic alcohols **1f** and **1g** as

well as with the *meta*-biphenylic diol **1m** very low degree of conversions (<10%) were attained upon analogous reaction conditions. Regarding the pyridine-2,6-diethanol **1l**, the reaction happened with total conversion at 100 mM (see Table 2) and KRED-P1-A04 displayed a perfect stereoselectivity to provide the enantiopure diol (1*R*,1'*R*)-**1l** as the sole product with >99:<1 *dr*.

Table 2. One-pot two-step deracemisation of alcohols and diol **1l** at a 100 mM final concentration.[a]



Substrate	KRED	*C* (%)[b]	*ee* (%)[b]	yield (%)[c]
1a	P2-H07	>99	>99 (*R*)	93
1b	P3-B03	>99	>99 (*S*)	90
1c	P1-A04	92	>99 (*R*)	76
1d	P1-A04	90	>99 (*R*)	87
1e	P1-B05	>99	>99 (*R*)	98
1h	P1-B05	>99	>99 (*S*)	92
1i	P1-B02	>99	>99 (*S*)	90
1j	P1-A04	>99	>99 (*R*)	90
1k	P1-A04	93	>99 (*S*)	82
1l	P1-A04	>99	>99 (*R,R*)	95

[a] Reaction conditions. Oxidation step: AZADO (1.0 mol%), 250 mM substrate concentration, except for **1l** (130 mM), room temperature except for **1a** (5 ºC); reduction step was performed at 100 mM substrate concentration, at 30 ºC except for reactions starting from **1h** and **1i** (40 ºC). [b] Degree of conversion (*C*) and *ee* were determined by GC or HPLC. [c] Isolated yield after purification by column chromatography.

In order to improve the unsuccessful results achieved in some cases and reach perfect conversion for the bioreduction of the intermediate ketones, we decided to lower the concentration of the second step at 50 mM, also reducing the amount of $NADP^+$ to 0.50 mM. Gratifyingly, the reactions using racemic **1c**, **1d**, and **1k** proceeded effectively and the corresponding enantiopure alcohols were achieved with complete conversion (Table 3). On the contrary the biarylic alcohols **1f**, **1g**, and diol **1m** remained challenging, despite a slight improvement in the conversion values (up to 65% for **1f**). Pleasantly, complete conversion of these substrates could be finally reached by lowering the concentration to 25 mM and adding DMSO (10% v/v) as co-solvent. It should be noted that, despite the low concentration of the bioreduction step, the enantiopure alcohols were isolated in very high yields (90-95%). Likewise, it worth noting that KRED-P1-A12 exhibited total selectivity catalysing the formation of the diol (1*R*,1'*R*)-**1m** with >99:<1 *dr* and >99% *ee*.

Table 3. One-pot oxidation-reduction of alcohols and diol **1m** at 50 mM and 25 mM final concentration.[a]

Substrate	KRED	*C* (%)[d]	*ee* (%)[d]	yield (%)[e]
1c[b]	P1-A04	>99	>99 (*R*)	87
1d[b]	P1-A04	>99	>99 (*R*)	92
1f[b]	P3-B03	65	>99 (*S*)	61
1f[c]	P3-B03	>99	>99 (*S*)	90
1g[c]	P1-B05	>99	>99 (*S*)	92
1k[b]	P1-A04	>99	>99 (*S*)	90
1m[c]	P1-A12	>99	>99 (*R,R*)	95

[a] Oxidation step as indicated in Table 2. Reduction step was carried out at 30 ºC (for **1c**, **1d**, and **1k**) or 40 ºC (for **1f**, **1g**, and **1m**). [b] Reduction step performed at 50 mM. [c] Reduction step performed at 25 mM. [d] Determined by GC or HPLC. [e] Isolated yield after purification by column chromatography.

Conclusions

In conclusion, a new and straightforward protocol for deracemisation of alcohols has been described. The aqueous medium represented the link for two different catalytic worlds, such as organocatalysis and biocatalysis, working perfectly in a sequential fashion.

The oxidation of the racemates, mediated by NaOCl and AZADO (1.0 mol%), was easily coupled with the enzymatic reduction of the intermediate ketones in the same medium up to 100 mM concentration. Fine tuning the oxidation conditions and adequate biocatalyst selection provided a set of synthetically and pharmacologically interesting alcohols with high overall yields (up to 98%) and >99% *ee*. The efficiency of the strategy was also demonstrated for the conversion of *rac*/*meso*-diols into only one enantiomer.

Experimental Section

General Remarks

^{1}H-NMR and proton-decoupled ^{13}C-NMR spectra ($CDCl_3$) were obtained using a Bruker DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometer using the δ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent or the residual non-deuterated solvent (^{13}C: $CDCl_3$, 77.16; ^{1}H: $CHCl_3$, 7.26). Degree of conversions (*C*), *dr*, and *ee* were determined by HPLC or GC analyses. Optical rotations were

measured using a Perkin-Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Codex® KRED screening kit was purchased from Codexis.

General procedure for oxidation of racemic alcohols

To a sample of commercially available NaOCl solution (1.95 M, such as it was determined by titration),[27] KH_2PO_4 and water were added in such amount that the resulting solution was 125 mM in phosphate and 400 mM in NaOCl (pH = 7.9). Then, the corresponding amount of this NaOCl solution (1.2-1.3 equiv) was added to a solution of racemic alcohol (150 µmol) and AZADO (1.5 µmol)[28] in MeCN (150 µL). The mixture was vigorously stirred (magnetic stirring) at room temperature in all cases except for reaction with **1a**, which was conducted at 5 ºC. Once the starting material disappeared (1.5 h, TLC control using hexane-ethyl acetate 3:1 as eluent), the reaction mixture was extracted with ethyl acetate (3 × 600 µL). The organic layers were combined, dried over Na_2SO_4 and evaporated under vacuum. The ^{1}H-NMR analysis of the crude product (>95% yield) showed the corresponding ketone in pure state for synthetic purposes.

Enzymatic screening for the reduction of ketones

In a 2.0 mL eppendorf tube, ketone **2** (20 mM, except 10 mM for **2f**, **2g**, and **2m**), KRED (same weight as the ketone), and IPA (190 µL) were added to 900 µL of 125 mM phosphate buffer, pH 7.0. This buffer also contains $MgSO_4$ (1.25 mM) and the cofactor $NADP^+$ (1.0 mM). For ketones **2f-i** and **2m**, DMSO (100 µL) was also added. The resulting reaction mixture was shaken at 250 rpm and 30 or 40 °C (see Table 1) for 24 h. After this time, a 10 µL aliquot was removed by the determination of the degree of conversion by HPLC or GC analysis (see Supporting Information (SI)). Then, the mixture was extracted with ethyl acetate (2 × 500 µL), the organic layers were separated by centrifugation (90 s, 13000 rpm), combined, and finally dried over Na_2SO_4. The diastereomeric ratio (if applicable) and enantiomeric excess of the corresponding alcohol was determined by chiral HPLC or GC (see SI).

General procedure for the one-pot two-step process at a final 100 mM substrate concentration

Reactions were carried out in a 2.0 mL eppendorf tube using 10.0 mg of the starting alcohol **1** except for compound **1e**, for which the reaction was conducted at 50.0 mg scale.[29] Firstly, the oxidation was carried out following the general procedure. Once the oxidation was complete (1.5 h), IPA (15% v/v), 125 mM phosphate buffer at pH 7.0 (containing $MgSO_4$ 2.5 mM), the corresponding KRED (10.0 mg except 50.0 mg for **1e**) and the cofactor $NADP^+$ (1.0 mM) were added in order to reach a final concentration of 100 mM. For biarylic compounds, DMSO (10% v/v) was also added. The reaction mixture was incubated during 24 h at 30 or 40 °C and 250 rpm (see SI). After this time, the mixture was extracted with ethyl acetate (2 × 1.0 mL), the organic layers separated by centrifugation (90 s, 13000 rpm), combined, and finally dried over Na_2SO_4. Evaporation of the solvent yielded the crude alcohol which was purified by flash chromatography.

General procedure for the one-pot two-step process at 25 mM

Reactions were carried out in a 15.0 mL falcon centrifuge tube using 10.0 mg of the starting alcohol. Once the oxidation was complete (1.5 h), DMSO (10% v/v), IPA (15% v/v), 125 mM phosphate buffer at pH 7.0 (containing $MgSO_4$ 2.5 mM), the corresponding KRED (10.0 mg) and the cofactor $NADP^+$ (0.50 mM) were added to achieve a final concentration of 25 mM. The reaction mixture was incubated during 24 h at 40°C and 250 rpm. After this time, the mixture was extracted with ethyl acetate (2 × 2.0 mL), the organic layers were separated by centrifugation (90 s, 13000 rpm), combined, washed with brine (2 × 2.0 mL) and finally dried over Na_2SO_4. Evaporation of the solvent yielded the crude alcohol which was purified by flash chromatography.

Supporting information available: Experimental procedures, screenings for the enzymatic bioreductions, characterization data for enantiopure compounds, and copy of the HPLC chromatograms and NMR spectra.

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Keywords: Alcohols • organocatalysis • oxidation • oxidoreductases

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[29] Reactions at higher scale would be operationally viable because our methodology allows to carry out the bioreduction step at a high 100 mM substrate concentration, thus overcoming the dilution problems associated with this kind of processes. Moreover, it has been shown that the higher the scale used, the higher the yield obtained (see results for **1e** in Table 2).

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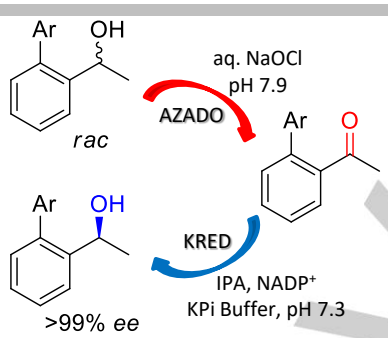
FULL PAPER

Mixed catalytic strategy: A highly efficient oxidation of a representative series of *sec*-alcohols and diols with aq. NaOCl and 2-azaadamantane *N*-oxyl (AZADO) as organocatalyst has been combined with a selective ketoreductase-catalyzed bioreduction. The sequential one-pot strategy has been performed up to 100 mM final substrate concentration allowing to obtain benzylic, non-benzylic or hindered biarylic alcohols with very high yield and >99% *ee*.



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