Novel Insights into the Combination of Metal- and Biocatalysis: Cascade One-Pot Synthesis of Enantiomerically Pure Biaryl Alcohols in Deep Eutectic Solvents

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One of the pioneering examples of chemoenzymatic cascades in water such as the palladium-catalysed Suzuki-cross coupling followed by an enzymatic reduction has been revisited by the employment of a medium containing Deep Eutectic Solvents (DESs) for the catalytic performance. Thus, the unique properties of these neoteric solvents enabled to reach high substrate concentration for the overall process. Moreover, both isolated enzymes and whole cells exhibited excellent activities which allowed to obtain a set of chiral biaryl alcohols in good yields and very high enantiomeric excess (> 99%).

Introduction

As stated by the burgeoning number of articles, the combination of chemo- and biocatalysts has turned into a pivotal research topic in the catalysis field. [1] Thus, this interest has spurred the development of new methodologies to merge the practical and economic advantages of both catalytic worlds. [2]

In this context, one of the pioneering examples combining metal- and enzyme-catalysed transformations in aqueous medium is a sequence consisting of an initial Suzuki cross coupling of halogenated acetophenones followed by an ADH (alcohol dehydrogenase)-mediated reduction. The original report, dated in 2008, efficiently yielded an enantiopure biary alcohol when operating at 33 mM and 70 °C during the coupling reaction, and 25 mM at room temperature for the biotransformation. [3] Further improvements enabled to conduct the first step at room temperature by the use of water-soluble palladium catalysts and a high percent of propan-2-ol (50% v/v) as co-solvent, although proceeding at a low substrate concentration (up to 40 mM). [4] Alternatively, a biphasic solvent system consisting of water and an ionic liquid (IL) allowed to obtain a set of chiral biaryl alcohols in good yields and very high enantiomeric excess (> 99%).

With these precedents in mind, we turned our attention towards a new class of biorenewable solvents, namely Deep Eutectic Solvents (DESs), which have been demonstrated as a valuable alternative to volatile organic compounds from the standpoint of sustainability. [5] These solvents are natural mixtures of low-cost biodegradable components such as quaternary ammonium salts (e.g., choline chloride) and uncharged hydrogen-bond donors (HBD) (such as urea, carboxylic acids or polyols), thereby forming an extensive H-bond network throughout the solvent which stabilizes liquid configurations and results in lower melting points than those of their individual components. DESs share many unique IL-like solvent properties such as thermal stability, low vapour pressure, non-flammability, easy recycling and high solubility of organic compounds. Furthermore, they are cheaper, readily available, do not require further purification, offer high tunability, and are considered to be less toxic compared to ILs given the nature of its components. [6]

As part of our ongoing interest in the study of chemoenzymatic cascades, [7] we investigated the viability of the abovementioned cascade process, namely the Suzuki cross coupling followed by bioreduction in a one-pot two-step fashion in mixtures of DESs and aqueous buffers (Scheme 1). To the best of our knowledge, there exists only one example of a chemoenzymatic cascade developed in parallel in these neo-

Scheme 1. Devised chemoenzymatic cascade towards chiral biaryl alcohols in DES-buffer medium.
teric solvents, which is the combination of a ruthenium-catalysed isomerisation with an enzymatic reduction. [19]

**Results and Discussion**

Over the past decade DESs have found applications in several chemical sciences and technologies such as electrochemistry and metal processing, material chemistry, nanotechnology, photosynthesis and energy technology, separations processes, and stabilisation of DNA. With respect to synthetic purposes, DESs have provided examples of improved activity and selectivity in: i) organometallic-mediated stoichiometric transformations, [20] and ii) metal-, [21] enzyme-, [22] or organo-catalysed reactions. [23] In this sense, processes traditionally restricted to anhydrous solvents such as polar organometallic chemistry could be conducted in DESs, establishing a new bridge between main group chemistry and green solvents. [24] Regarding biocatalysis, [25] DESs have been successfully implemented as a reaction medium for enzymes such as lipases, epoxide hydrolases, proteases, peroxidases and oxidoreductases so far. [26]

Very recently, several palladium-catalysed cross-coupling reactions (Suzuki-Miyaura, Sonogashira or Heck couplings) were efficiently accomplished in neat DESs by using cationic pyridinophosphine ligands in association with PdCl$_2$. [27] Accordingly, and considering the cationic nature of the ligand to be critical, we set out to investigate the feasibility of the Suzuki coupling in eutectic mixtures by using our previous water-soluble palladium-catalyst system: PdCl$_2$/TPPTS [tris (3-sulfonatophenyl) phosphine hydrate, sodium salt]. [3] Thus, the coupling between 4'-bromoacetophenone (1) and phenylboronic acid (2) to yield 4'-phenolacetophenone (5a) was selected as a benchmark reaction, and four chloride boronate (ChCl)-based eutectic mixtures, namely 1ChCl/2Gly (Gly = glycercoll), 1ChCl/2H$_2$O, 1ChCl/15or (or = sorbitol) and 1ChCl/2Urea, were utilized in this study (Table 1). The reaction medium also contained 20% (v/v) of an buffer solution pH = 8.5 to accomplish the required basic conditions as described in previous reports. [25, 26] Preliminary attempts performed according to the reported conditions (40 mM of 1 and 2, 4 mol% PdCl$_2$, 5 mol% TPPTS, temperature, 24 h) unveiled 1ChCl/2Gly as the optimal DES, leading to a conversion of 92% (entry 4). On the other hand, the reaction did not work in 1ChCl/2Urea (entry 2) while 1ChCl/2H$_2$O and 1ChCl/15or displayed conversions higher than 80% (entries 1 and 3). Next, we focused on 1ChCl/2Gly and explored the effect of parameters such as temperature and catalyst loading. By heating at 70 °C enabled quantitative conversion towards 5a (>99%, entry 5). Remarkably, an identical result was obtained at this temperature when using a decreased catalyst loading of only 1 mol% PdCl$_2$ and 3 mol% TPPTS (entry 6). Next, to get more insight into the process, we tested higher substrate concentrations which fit better in an industrial setting (entries 7–11). Thus, it was found that concentrations of 100 mM or greater demanded heating to 100 °C in the 1ChCl/2Gly-buffer mixture to reach complete conversion, with the upper limit being 200 mM (entry 8). On the contrary, upon these conditions the analogue mixtures based on 1ChCl/15or and 1ChCl/2H$_2$O led to poor conversions (<40%, entries 9–10) which made to discard these DESs for further optimization. Finally, the parametrization was also extended to other aryl halides. Thus, the aryl chloride turned out to be less reactive (conversion = 65%, entry 12) meanwhile the iodine derivative enabled complete conversion at 200 mM and 100 °C (entry 13). Based on the results described in the above cited report about cationic phosphine ligands in DESs, [25] the reactions with bromine and iodine reagents were essayed with a catalyst load reduced tenfold (entries 14–15). In the case of the aryl iodide the process worked efficiently (entry 14), and despite a slight decrease conversion, the low required catalyst loading could be interesting from an economic point of view for large-scale reactions.

| Table 1. Parametrisation of the Suzuki cross-coupling reaction of 1 and 2 in DES-buffer (4:1) medium catalysed by PdCl$_2$/TPPTS. 
| Entry | X | DES | [Pd]/ligand [mol%] | T [°C] | [1] [mM] | Conv. [%] |
|-------|---|-----|-------------------|-------|---------|-----------|
| 1     | Br | 1ChCl/15Or | 4/5 | rt | 40 | 82 |
| 2     | Br | 1ChCl/2Urea | 4/5 | rt | 40 | 0 |
| 3     | Br | 1ChCl/2H$_2$O | 4/5 | rt | 40 | 80 |
| 4     | Br | 1ChCl/2Gly | 4/5 | rt | 40 | 92 |
| 5     | Br | 1ChCl/2Gly | 4/5 | 70 | 40 | >99 |
| 6     | Br | 1ChCl/2Gly | 1/3 | 70 | 40 | >99 |
| 7     | Br | 1ChCl/2Gly | 1/3 | 70 | 100 | 99 |
| 8     | Br | 1ChCl/2Gly | 1/3 | 100 | 200 | >99 |
| 9     | Br | 1ChCl/15or | 1/3 | 100 | 200 | 40 |
| 10    | Br | 1ChCl/2H$_2$O | 1/3 | 100 | 200 | 35 |
| 11    | Br | 1ChCl/2Gly | 1/3 | 100 | 300 | 60 |
| 12    | Cl | 1ChCl/2Gly | 1/3 | 100 | 200 | 65 |
| 13    | I | 1ChCl/2Gly | 0.1/0.3 | 100 | 200 | 92 |
| 14    | I | 1ChCl/2Gly | 0.1/0.3 | 100 | 200 | 40 |

[a] Reaction conditions (40 mM): A solution of PdCl$_2$ and TPPTS (previously stirred in 1.0 mL of KPi buffer pH 8.5 during 30 min) was added to a mixture of 1 (0.389 mmol), 2 (0.389 mmol), DES (8.0 mL), KPi buffer pH 8.5 (1.0 mL). Then, the pH was adjusted to 8.5 with aq 3 N NaOH and the mixture vigorously stirred at the specified temperature during 24 h; [b] Determined by HPLC.
and iii) arylpyridine ketones (5c–e). First, the fluorinated derivatives reached conversions in the range of 90–95 % at room temperature and 40 mM due to the high reactivity of the boronic acids 2 bearing such electron-withdrawing groups. Further heating to 70 °C enabled quantitative conversion at 200 mM. Similarly, biaryl ketones 5a,b,j,l underwent quantitative conversion at 200 mM and 70 °C. Conversely, the pyridine derivatives demanded more drastic conditions since the conversions were lower than 60 % at 40 mM and 70 °C. Thus, a temperature of 100 °C improved the process dramatically and led to complete conversion at 200 mM. In all the cases, the resulting biaryl ketones were easily recovered from the reaction medium by adding saturated aqueous NH₄Cl and further extraction with cyclopentyl methyl ether (90–> 95 %).

Once assessed the conditions for the Suzuki coupling as the first step of the cascade, next we focused on the reduction of the formed ketones (5a–j) by using a commercial kit of KREDs and two ADHs overexpressed in E. coli with opposite enantioselectivity. In the last years, DESs have proved to be an excellent reaction medium for performing bioreductions with whole cells overexpressing oxidoreductases, and very applications with purified KREDs were reported as well. Likewise, a fine tuning of the ratio DES/water enabled remarkable enhancements of enantioselectivity and even switching the stereochemical outcome. With these premises, the biaryl ketone 5a was initially tested with a set of engineered KREDs from Codexis (Table 2). In a typical experiment, 5a (5 mM) was incubated in the presence of a KRED (200 % w/w) at 30 °C and 250 rpm in a mixture of 1ChCl/2Gly-buffer 1:1.5 (containing 1.25 mM MgSO₄ and 1 mM NADP⁺) supplemented with isopropanol (i-PrOH, 10 % v/v) for cofactor recycling. The choice of this reaction medium, which contains about 35 % (v/v) of DES, was based to preserve the stability of the enzymes. Actually, most of purified KREDs considered in this study and the ADH from L. kefir were recently reported to display good stability in the bioreduction of propiophenone at 50 % DES for 1ChCl/2Gly and 1ChCl/1Sorb while only a few ones were active at 80 % DES. From the series of KREDs of the kit, most of the biocatalysts rendered biphenylethan-1-ol (6a) in quantitative conversion and perfect enantioselectivity (> 99 % ee, entries 1–17). Likewise, the two enzymes overexpressed in E. coli, namely the (R)-selective ADH from Lactobacillus kefir DSM 20587 (NAD⁺ dependent) and the (S)-selective ADH from Rhodococcus ruber DSM 44541 (NAD⁺ dependent), worked efficiently in this reaction medium, forming both enantiomers of 6a in enantiomerically pure form (entries 18–19). Seeing as the excellent enantioselectivities exhibited by the enzymes at this DES-buffer ratio, a further medium engineering optimisation by increasing the percent of DES was discarded.

Next, on the basis of the established enzymatic conditions in Table 2, the reduction of ketones 5b–j was screened with the overexpressed ADHs from L. kefir DSM 20587 and R. ruber DSM 44541 as well as with four purified enzymes from the Codexis’ kit, namely the (R)-selective KRED–P1-A04 and KRED–P2-H07 and the (S)-selective KRED–P2-G09 and KRED–P3-H12. The choice of these four biocatalysts was based on the results

### Table 2. ADH-catalysed reduction of 1-(biphenyl-4-yl) ethanone (5a) in DES-buffer medium[a]

| Entry | Enzyme            | Conv[b] [%] | ee[b] [%] |
|-------|-------------------|-------------|-----------|
| 1     | P1-A04            | > 99        | > 99 (R)  |
| 2     | P1-B02            | > 99        | 99 (R)    |
| 3     | P1-B05            | > 99        | > 99 (R)  |
| 4     | P1-B10            | > 99        | > 99 (R)  |
| 5     | P1-H08            | > 99        | 98 (R)    |
| 6     | P2-G09            | > 99        | > 99 (S)  |
| 7     | P2-B02            | > 99        | 63 (S)    |
| 8     | P2-C02            | > 99        | > 99 (S)  |
| 9     | P2-C11            | > 99        | 90 (S)    |
| 10    | P2-D03            | > 99        | > 99 (R)  |
| 11    | P2-D11            | > 99        | 95 (R)    |
| 12    | P2-D12            | > 99        | > 99 (R)  |
| 13    | P2-G03            | > 99        | > 99 (R)  |
| 14    | P2-H07            | > 99        | > 99 (R)  |
| 15    | P3-B03            | > 99        | > 99 (S)  |
| 16    | P1-A12            | > 99        | > 99 (R)  |
| 17    | P3-H12            | 95          | 98 (S)    |
| 18    | L. kefir DSM 20587| > 99        | > 99 (R)  |
| 19    | R. ruber DSM 44541| > 99        | > 99 (S)  |

[a] Reaction conditions: KRED (1.0 mg) and 5a (5 mM) were added in a 1ChCl/2Gly (215 µL)/ KPi buffer 125 mM pH 7.0 (325 µL) mixture (1.25 mM MgSO₄, 1 mM NADP⁺), and i-PrOH (60 µL) and shaken at 30 °C and 250 rpm for 24 h. For R. ruber reactions, 5 U were added in a 1ChCl/2Gly (215 µL)/ KPi buffer 50 mM pH 7.0 (325 µL) mixture (1 mM NAD⁺), and i-PrOH (60 µL); For L. kefir reactions, 15 U were added in a 1ChCl/2Gly (215 µL)/ KPi buffer 50 mM pH 7.0 (325 µL) mixture (1 mM MgCl₂, 1 mM NADP⁺), and i-PrOH (60 µL). [b] Measured by HPLC; [c] Measured by chiral HPLC.

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## Scheme 2. Scope of the Suzuki cross-coupling reaction in DES-buffer medium under the optimised reaction conditions [200 mM substrate concentration, 1ChCl/2Gly-KPi buffer pH 8.5 (4:1), PdCl₂ (1 mol%), TPPTS (3 mol%), 70 °C or 100 °C, 24 h].
 afforded in Table 2 with 5a and also the good activity recently reported on the bioreduction of propiophenone in DES-buffer 1:1 mixtures. As depicted in Table 3, which contains some selected examples of the screening, it was possible to access the coupling step but using the complementary ADH from DSM 44541 for the bioreduction, (R)-6j was formed with 99% ee (entry 20). Once the coupling was complete (HPLC analysis), the reaction mixture was diluted to 75 mM with the aqueous buffer and MgCl₂) and fed with the ADH from L. kefir DSM 20587 and i-ProOH. Thus, the bioreduction of the formed ketone intermediate took place smoothly, (R)-6a being obtained with good conversion (78%) and >99% ee (entry 1). Following an analogous procedure for the coupling step but using the complementary ADH from R. ruber DSM 44541 for the bioreduction, (S)-6a was formed with both high conversion and optical purity (entry 2). Next, similar cascades were established with this couple of enzymes and the required substrates to produce the biarylic alcohols 6d, 6e and 6g. The ADH from L. kefir DSM 20587 led to the formation of the corresponding (R)-enantiomer of these alcohols with >99% ee and conversions of up to 91% (entries 3 and 5). Meanwhile, selected examples of the screening, it was possible to access alternatively both enantiomers of the target alcohols after 24 h with very high conversion (>99%) and enantioselectivity (99–>99% ee). The only exception was the sterically hindered ortho-biaryl ketone 5j, which led to enantiopure (R)-6j but with very low conversion (26%, entry 19; see also Table S11 in the SI). Exceptionally, the bioreduction of 5j was also assayed with a different KRED from the kit, namely P1-B02, which was recently found to be very active towards 5j in aqueous medium. Pleasantly, this biocatalyst enabled to reach (S)-6j with complete conversion and >99% ee (entry 20).

Interestingly, both ADHs overexpressed in E. coli (L. kefir and R. ruber) were very efficient in terms of reactivity and selectivity towards some of the substrates (ε >99%, ee >99%). This makes these biocatalysts especially attractive for a hypothetical gram-scale process in comparison with the commercial purified ones due to their high cost (for the full panel of enzymatic screenings, see Tables S3–S11 in the SI). A further goal of the project was to enhance the substrate concentration in the biocatalytic step, which could meet the parameters of a manufacture setting. Pleasantly, the good solubilising properties of the DESs (being used in an amount of close to 35% v/v) ensured a homogeneous reaction mixture for some selected bioreductions at 75 mM substrate concentration, enabling comparable results to those obtained in the screening at 5 mM.

Table 3. Selection of ADH-catalysed reductions of biaryl ketones 5a–j in DES-buffer medium.

| Entry | Ketone | Enzyme   | Alcohol | Conv[a] [%] | ε[e] [%] |
|-------|--------|----------|---------|-------------|---------|
| 1     | 5a     | L. kefir | 6a-PrOH | >99         | >99 (R) |
| 2     | 5a     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 3     | 5b     | P1-A04   | 6a-PrOH | >99         | >99 (R) |
| 4     | 5b     | P3-H12   | 6a-PrOH | >99         | >99 (R) |
| 5     | 5c     | P1-A04   | 6a-PrOH | >99         | >99 (S) |
| 6     | 5c     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 7     | 5d     | L. kefir | 6a-PrOH | >99         | >99 (S) |
| 8     | 5d     | L. kefir | 6a-PrOH | >99         | >99 (S) |
| 9     | 5e     | L. kefir | 6a-PrOH | >99         | >99 (R) |
| 10    | 5e     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 11    | 5f     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 12    | 5f     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 13    | 5g     | L. kefir | 6a-PrOH | >99         | >99 (S) |
| 14    | 5g     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 15    | 5h     | P1-A04   | 6a-PrOH | >99         | >99 (R) |
| 16    | 5h     | P2-G09   | 6a-PrOH | >99         | >99 (S) |
| 17    | 5i     | P1-A04   | 6a-PrOH | >99         | >99 (R) |
| 18    | 5i     | R. ruber | 6a-PrOH | >99         | >99 (S) |
| 19    | 5j     | P2-H07   | 6a-PrOH | 26          | >99 (R) |
| 20    | 5j     | P1-B02   | 6a-PrOH | >99         | >99 (S) |

[a] Reaction conditions: 5a–j (5 mM) and KRED (1 mg) in 1ChCl:2Gly (215 µL)/ KPi buffer 125 mM pH 7.0 (325 µL) mixture (1.25 mM MgCl₂ and 1 mM NADP⁺), and i-ProOH (60 µL). The mixture was stirred for 24 h at 250 rpm and 30 °C. For L. kefir reactions, 15 U and KPi buffer 50 mM pH 7.0 were used, the mixture containing 1 mM MgCl₂, and 1 mM NADP⁺; For R. ruber reactions, 5 U and KPi buffer 50 mM pH 7.0 were used, the mixture containing 1 mM NAD⁺; [b] Determined by HPLC; [c] Determined by chiral HPLC.
the ADH from *R. ruber DSM 44541* gave access to the (S)-counterparts with conversions >90% (entries 4, 6 and 7). In all cases, after filtration through silica the target biaryl alcohols were isolated in high yields (>80% with the exception of entry 1). It is worth noting that despite being a stepwise process, the overall methodology is operationally simple and the media coming from the metal-catalysed reaction was used directly to feed the enzymatic bioreduction, resulting in simplified downstream operations relative to classical multistep reactions with tedious isolation and purification of intermediates.

**Conclusions**

A chemoenzymatic cascade consisting on a palladium-catalysed Suzuki cross-coupling followed by an enzymatic reduction mediated by alcohol dehydrogenases has been efficiently implemented in *ad hoc* mixtures of DESs and aqueous media. The two catalytic steps took place efficiently and the excellent enantioselectivity displayed by the biocatalysts enabled the preparation of both enantiomers of several chiral biarylic alcohols in enantiomerically pure form. Likewise, the presence of the neoteric solvent in the medium enabled to tackle the solubility hurdles of the substrates, the biotransformation being executed at 75 mM concentration. In summary, this report underlines the advantages of DESs for their utilization in the fields of chemocatalysis and biocatalysis and will open up new perspectives for further exploration of chemoenzymatic one-pot processes in these reaction media.

**Experimental Section**

**General Procedure for the Suzuki Cross-Coupling Reaction in DES-Buffer Medium**

At first, a suspension of PdCl$_2$ (3.5 mg; 0.02 mmol; 1 mol%) and TPPTS (34 mg; 0.06 mmol; 3 mol%) in 1 mL of phosphate buffer 150 mM pH 8.5 was prepared. After 30 min the resulting catalyst solution was added to a mixture, consisting of arylbromide (1.945 mmol; 1 eq, 200 mM), boronic acid (1.945 mmol; 1 eq, 200 mM), DES (8 mL) and phosphate buffer 150 mM pH 8.5 (1 mL). The pH was adjusted to 8.5 by dropwise addition of aq 3 N NaOH. After cooling at rt, KPi buffer 150 mM pH 8.5 (6.05 mL), i-PrOH (1.95 mL), NADP$^+$ (1 mM), MgCl$_2$ (1 mM) and ADH from *L. kefir DSM 20587* (690 U) were added and the mixture stirred for 24 h at 30 ºC. For entries 2, 4, 6 and 7, after cooling at rt, KPi buffer pH 8.5 (6.05 mL), i-PrOH (1.95 mL), NAD$^+$ (1 mM) and ADH from *R. ruber DSM 44541* (360 U) were added and the mixture stirred for 24 h at 30 ºC.

**General Procedure for the Bioreduction of Biarylketones 5–j in DES-Buffer Medium**

In a 2.0 mL Eppendorf tube, ketone (5 mM) and purified KRED (1.0 mg) were added to a 1ChCl2Gly (215 µL)/125 mM KH$_2$PO$_4$ buffer pH 7.0 (325 µL) mixture (containing 1.25 mM MgSO$_4$, 1 mM NADP$^+$), and i-PrOH (60 µL, 10% v/v). For *L. kefir* reactions, 15 U of ADH and KPi buffer 50 mM pH 7.0 were used, the mixture containing 1 mM MgCl$_2$ and 1 mM NADP$^+$; for *R. ruber* reactions, 5 U of ADH and KPi buffer 50 mM pH 7.0 were used, the mixture containing 1 mM NAD$.^+$ In all the cases, the reaction mixture was shaken at 30 ºC and 250 rpm for 24 h. To determine the conversion, 10 µL of the mixture were diluted with 90 µL of Milli-Q water and analysed by achiral reverse phase. The mixture was then extracted with AcOEt (2x 500 µL) and aq saturated NH$_4$Cl (110 µL), the organic layers separated by centrifugation (120 sec, 1300 rpm), combined and dried over Na$_2$SO$_4$. The enantiomeric excess of alcohols was measured by chiral HPLC.
Preparative-Scale Synthesis of (S)-1-(4-(Pyridin-3-yl) Phenyl) Ethanol (S)-6d in a One-Pot Sequential Process

A suspension of PdCl₂ (3.5 mg; 0.02 mmol; 1 mol %) and TPPTS (34 mg; 0.06 mmol; 3 mol %) in 1 mL of phosphate buffer 150 mM pH 8.5 was prepared. After 30 min the resulting catalyst solution was added to a mixture, consisting of 3-bromopyridine (1.945 mmol), (4-acetylphenyl) boronic acid (1.945 mmol), 1H-ChiC6G7H (8 mL) and phosphate buffer 150 mM pH 8.5 (1 mL). Then, the pH was adjusted to 8.5 by dropwise addition of aq 3 N NaOH and the reaction mixture was stirred at 100 °C for 24 h. After cooling to rt, phosphate buffer 150 mM pH 8.5 (6.05 mL), i-PrOH (1.95 mL, 11 % v/v), NAD⁺ (1 mM) and ADH from Rhodococcus ruber DSM 44541[18] (360 U) were added. After stirring for another 24 h at 30 °C, aq saturated NH₄Cl (25 mL) was added and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to provide as a yellowish oil (85 %).

Preparative-Scale Synthesis of (R)-1-(4-(Pyridin-4-yl) Phenyl) Ethanol (R)-6e in a One-Pot Sequential Process

A suspension of PdCl₂ (3.5 mg; 0.02 mmol; 1 mol %) and TPPTS (34 mg; 0.06 mmol; 3 mol %) in 1 mL of phosphate buffer 150 mM pH 8.5 was prepared. After 30 min the resulting catalyst solution was added to a mixture, consisting of 4-bromopyridine (1.945 mmol), (4-acetylphenyl) boronic acid (1.945 mmol), 1H-ChiC6G7H (8 mL) and phosphate buffer 150 mM pH 8.5 (1 mL). Then, the pH was adjusted to 8.5 by dropwise addition of aq 3 N NaOH and the reaction mixture was stirred at 100 °C for 24 h. After cooling to rt, phosphate buffer 150 mM pH 8.5 (6.05 mL), i-PrOH (1.95 mL, 11 % v/v), NAD⁺ (1 mM) and ADH from Rhodococcus ruber DSM 44541[18] (360 U) were added. After stirring for another 24 h at 30 °C, aq saturated NH₄Cl (25 mL) was added and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to provide as a white solid (80 %).

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Conflict of Interest

The authors declare no conflict of interest.

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