Cascade Reaction by Chemo- and Biocatalytic Approaches to Obtain Chiral Hydroxy Ketones and anti 1,3-Diols

Raffaella Gandolfi\textsuperscript{a}, Giorgio Facchetti\textsuperscript{a}, Michael S. Christodoulou\textsuperscript{a}, Marco Fusè\textsuperscript{b}, Fiorella Meneghetti\textsuperscript{a} and Isabella Rimoldi\textsuperscript{a}\textsuperscript{[*]}

A chemo- and biocatalytic cascade approach was applied for the stereoselective synthesis of hydroxy ketones and the corresponding 1,3-diols. A new class of tridentate N,N,O ligands was used with copper(II) complexes for the asymmetric \(\beta\)-borylation of \(\alpha,\beta\)-unsaturated compounds. The complex containing ligand L5 emerged as the best performer, and it gave the organoborane derivatives with good ee values. The corresponding keto–alcohol compounds were then bioreduced by yeasts. The biotransformation set up with \textit{Rhodotorula rubra} allowed (R)-keto–alcohols and (S,S)-diols to be obtained with up to 99\% ee and up to 99\% de in favor of the anti enantiomers.

1. Introduction

Asymmetric transition-metal catalysts and enzymes have emerged as the most effective synthetic tools for the stereoselective preparation of many chiral compounds. The possibility to exploit different catalytic approaches for enantio- and diastereoselective catalysis is a challenging topic in chemical synthesis, especially if control of multiple stereoenergetic centers is involved\textsuperscript{[3]}.

Furthermore, the development of improved procedures by means of using less expensive, easy-to-handle, and more sustainable catalyst systems still remains an elusive goal.

Herein, we report a simple, inexpensive, and efficient catalyst system for simultaneous 1,4-conjugate addition and reduction steps on \(\alpha,\beta\)-unsaturated carbonyl compounds through base-controlled transition-metal catalysis or/and by using yeasts under mild conditions at room temperature. In our case, a cascade reaction allowed the asymmetric synthesis of differently substituted diols through the formation of the corresponding chiral keto–alcohols and diols by bioreduction. The first step is based on enriched keto–alcohol formation through Cu\textsuperscript{II}-catalyzed asymmetric boron conjugate addition to \(\alpha,\beta\)-unsaturated carbonyl compounds\textsuperscript{[2]}. In contrast to popular protocols involving the use of chiral Cu\textsuperscript{II} for the enantioselective \(\beta\)-borylation of \(\alpha,\beta\)-unsaturated acceptors, those involving the use of chiral Cu\textsuperscript{II} catalysts have been investigated only recently.

In particular, the complexation of Schiff base bidentate ligands with copper has been shown to result in compounds with interesting catalytic properties. On the other hand, organoboranes are known as extremely useful and versatile synthetic intermediates for organic synthesis\textsuperscript{[5]} that can also display biological activities. Here, for 1,4-conjugate addition to carbon–carbon double bonds, we used bis(pinacolato)diboron \([\text{B}_2(\text{pin})_2]\), which is one of the most practical tools for the establishment of new C–B bonds through transition-metal catalysis\textsuperscript{[6]}.

To enhance the catalytic performance of asymmetric catalytic boron conjugate addition, tripodal ligands\textsuperscript{[5]} based on the tetrahydroquinoline or quinolone scaffold, were incorporated into the Cu\textsuperscript{II} complexes. This successful combination led to keto–alcohol derivatives in an enantiomerically enriched form. A subsequent bioreduction step involving the use of different whole cells allowed the reduction of the keto–alcohol substrates to the corresponding enriched chiral diols\textsuperscript{[4,6]} leaving the other isomer unreacted (Scheme 1). The obtained substrates are important building blocks in the synthesis of diverse organic molecules that are versatile elements in the pharmaceutical field\textsuperscript{[7]}.

\footnotesize{\textsuperscript{[a]} Prof. R. Gandolfi,\textsuperscript{b} Dr. G. Facchetti,\textsuperscript{a} Dr. M. S. Christodoulou, Dr. F. Meneghetti, Dr. I. Rimoldi
Dipartimento di Scienze Farmaceutiche
Università degli Studi di Milano
Via Venezian 21, 20133 Milano (Italia)
E-mail: isabella.rimoldi@unimi.it

[b] Dr. M. Fusè
Scuola Normale Superiore
Piazza dei Cavalieri 7, 56126 Pisa (Italia)

[*] These authors contributed equally to this work

\textsuperscript{©} 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

\textsuperscript{https://doi.org/10.1002/open.201800056}
2. Results and Discussion

Considering the use of Schiff bases and their corresponding reduced amines as ligands in copper complexes for the asymmetric β-borylation of α,β-unsaturated carbonyl compounds, the tridentate ligands were easily synthesized starting from 8-aminoquinoline and its chiral derivatives by condensation with salicylaldehyde in EtOH at room temperature for 5 h. Then, the corresponding amines were obtained by reduction with NaBH₄ in a mixture of THF/MEOH at 0 °C for 1 h (Scheme 2). Chiral 8-aminoquinoline derivatives were previously synthesized and studied in our research group as ligands in metal complexes and were used as catalysts in the asymmetric transfer hydrogennation (ATH) of different ketones with good results.²⁶

![Scheme 2. Synthesis of ligands. Reagents and conditions: i) EtOH, RT, 5 h; ii) NaBH₄, THF/CH₂Cl₂, 0 °C, 1 h.](image)

In the case of ligand L1, reduction to the corresponding amine did not proceed in the presence of different amounts of NaBH₄ or by using Pd/C (1, 5, or 10% molar equivalents) under a H₂ atmosphere pressure, probably because of the extensive double-bond conjugation of the substrate.

The copper(II)/L complexes, obtained by treating the ligand with Cu(OAc)₂ in EtOH for 3 h at room temperature, were completely characterized. Crystals of the copper complex bearing ligand L1 suitable for X-ray structure analysis were obtained by slow evaporation of a 33% water/aceton solution at room temperature. The complex crystallized in the centrosymmetric P1 space group, with five molecules of water and one molecule of aceton, depicted as an ORTEP view in Figure 1. The complex is monomeric, and the central Cu⁰ atom is coordinated by two nitrogen donor atoms, one hydroxyl oxygen atom, and one oxygen atom from aceton in a square-planar arrangement. The bond lengths and angles are within the expected ranges. Ligand L1 is nearly planar with a maximum deviation of 0.026(3) Å for the O1 atom. The crystal structure is consolidated by an extensive network of water contacts, and this leads to the formation of supramolecular chains running along the a axis perpendicular to the ligands. In addition, weak C₆-H···Owater intermolecular interactions contribute to stabilize the crystal packing.

![Figure 1. ORTEP view of the asymmetric unit with an arbitrary atom-numbering scheme (ellipsoids are drawn at 40% probability). H atoms are shown as spheres of arbitrary radii.](image)

Catalytic asymmetric β-borylation was conducted starting from different α,β-unsaturated carbonyl compounds. Different reaction solvents (Et₂O, MeOH, EtOH, toluene, water, dichloromethane, acetonitrile, and THF) were evaluated in the presence of variable amounts of MeOH as a hydrogen donor (20–150 equivalents). With all catalysts, good yields were observed within 18 h by using 1,3-diphenyl-2-propenone as a standard substrate. Catalytic experiments showed that the best results were obtained by using Et₂O with 50 equivalents of MeOH at room temperature (Table 1).

![Table 1. Screening of the copper-catalyzed β-borylation of the standard substrate.](image)

| Entry | Ligand | Conversion [%] | ee [%] |
|-------|--------|----------------|--------|
| 1     | L1     | 99.9           | -      |
| 2     | L2     | 99.9           | rac    |
| 3     | L3     | 99.9           | 12     |
| 4     | L4     | 99.9           | 21     |
| 5     | L5     | 99.9           | 45     |

[a] All reactions were performed for 18 h by using the Cu complex (5 mol%) in diethyl ether; [b] (substrate)₊H₂O = 28 mmol; [c] (catalyst)₊H₂O = 1.4 mmol. Conversion was determined by ¹H NMR spectroscopy. [d] Data were compared by taking the average of three independent experiments. Enantiomeric excess was determined by HPLC with a chiral column (see the Experimental Section).

The enantiomeric excess was evaluated directly on the organoborane compounds by HPLC analysis. Assignment of the configuration was achieved by comparison with the corresponding β-hydroxy keto derivatives reported in the literature after deprotecting the organoborane compounds with NaBO₂·H₂O in THF/water for 1 h. Considering that the best results were obtained upon using L5 as the ligand (Table 1, entry 5), the β-borylation reaction was extended under the same reaction conditions to other α,β-unsaturated carbonyl compounds (Table 2).

For all the chalcone derivatives (Table 1, entries 5–12), the β-borylation reaction products gave very appreciable outcomes...
The proposed reaction mechanism is shown in Scheme 3. In this mechanism, the asymmetric β-borylation with a copper catalyst bearing a ligand (S)-L3 leads to the desired product. The reaction involves the formation of a chiral center through the borylation step, which is followed by deprotection to yield the final product.

The data show that good results were obtained for the biocatalytic reduction upon using whole cells of Rhodotorula rubra, Pichi etchellsii, Torulopsis magnoliae, and Torulopsis moschiana (Table 3, entries 1, 5, 11, and 12) as biocatalysts. As good outcomes ensued by employing Rhodotorula rubra either in the enantioselective reduction of the carbonyl moiety (97% ee, 91% de, 23% yield; Table 3, entry 1) or in the bioreduction of the hydroxy ketone substrate (65% ee), this yeast seemed to be the best candidate as a biocatalyst in the reduction reaction of different racemic 3-hydroxy ketones, which were eventually obtained by β-borylation and deprotection of the substrates reported in Table 2 by using a copper catalyst containing achiral ligand L1 (Table 4).

Upon using methyl aryl hydroxy ketones, the results in terms of stereoselectivity were modest both in the formation of the diols and in the resolution of the hydroxy ketone compounds (Table 4, entries 1–4). In the case of biaryl hydroxy ketones, the best results were obtained with para-substituted compounds in terms of molar conversion, whereas if the substituent was in the meta position, the yield decreased; the product was undetectable for substrates with ortho substituents. This behavior could be correlated to a change in steric hindrance of the substrate, as access to the active catalytic site could become challenging if the substituents on the phenyl ring were in a certain unfavorable position. The stereoselective control observed with the yeast seemed to confirm this hypothesis. In fact, the predominance of one configuration of the enantiomers changed between the para- and meta-substituted substrates: in the first case, the dominant (S,S)-diol underlined that the yeast followed the Prelog rule, whereas in the presence of meta-substituted substrates, (R,R)-diols were formed (ante-Prelog rule) (Table 4, entries 6–8, 10, and 13 vs. entries 9, 11, and 14). Excellent results in terms of stereoselectivity were obtained with 4-H, 4-Cl, and 4-CH$_3$ substituents for biocatalytic ketone reduction (Table 4, entries 5, 8, and 13).

A cascade reaction was then set up taking into consideration the good results obtained with the biocatalysis approach as regards the molar conversion. Thus, compounds with or without a substituent in the para position of the phenyl ring were evaluated. The cascade reaction involved first β-borylation/deprotection and then bioreduction. Although the enantioselectivity of the first step (chemocatalysis) was modest, this was an indispensable condition for bypassing the issue of negligible molar...
Table 3. Screening results for the bioreduction of 3-hydroxy-1,3-diphenylpropan-1-one by yeasts.

| Entry | Yeast | ee (%) | Diol conversion (%) | ee (%) | de (%) |
|-------|-------|--------|---------------------|--------|--------|
| 1     | Rhodotorula rubra MIM 147 | 65 | 23 | 97 | 91 (ant) |
| 2     | Saccharomyces cerevisiae | 2 | 8 | 20 | 92 (meso) |
| 3     | Saccharomyces cerevisiae zeus | 4 | 12 | 25 | 42 (meso) |
| 4     | Pichia henricii CBS 5765 | rac | 10 | -84 | 66 (anti) |
| 5     | Pichia etchellsii MIM | 55 | 19 | 99 | 85 (anti) |
| 6     | Pichia pastoris CBS 2612 | 34 | 8 | 70 | 97 (anti) |
| 7     | Pichia glucozyma CBS 5766 | 8 | 10 | 56 | 74 (anti) |
| 8     | Pachysolen tannaphylus CBS 4044 | 5 | 89 | 29 | 74 (anti) |
| 9     | Kluyveromyces marxianus var. lactis CL69 | 24 | 7 | 87 | 96 (anti) |
| 10    | Kluyveromyces marxianus CBS 1553 | 16 | 10 | 93 | 78 (anti) |
| 11    | Torulopsis magnoliae MIM 42 | 74 | 28 | 74 | 90 (anti) |
| 12    | Torulopsis molischiana CBS 837 | 67 | 24 | 82 | 91 (anti) |
| 13    | Torulopsis castelli MIM 1705 | 39 | 7 | 36 | 42 (meso) |
| 14    | Torulopsis pinus 207 | 8 | 11 | -15 | 58 (meso) |
| 15    | Sporobolomyces salmonicolor MIM | 21 | 8 | 67 | 95 (anti) |
| 16    | Lindnera fabiani CBS 5640 | 7 | 9 | 77 | 91 (anti) |

(a) The ee value was determined by HPLC with a chiral column (see the Experimental Section). (b) Molar conversion and de were calculated by $^1$H NMR spectroscopy.

Table 4. Biotransformation of different 3-hydroxy ketones with Rhodotorula rubra.

| Entry | R | R' | ee (%) Hydroxy ketone | ee (%) Diol | de (%) Diols |
|-------|---|---|-----------------------|------------|-------------|
| 1     | H | CH$_3$ | rac | 55 (R,S) | 64 (anti) |
| 2     | 3-Cl | CH$_3$ | 70 (S) | 84 (R,S) | 28 (anti) |
| 3     | 4-Cl | CH$_3$ | 47 (S) | 22 (R,S) | 75 (anti) |
| 4     | 4-NO$_2$ | CH$_3$ | 10 (S) | 43 (R,S) | 46 (anti) |
| 5     | H | C$_6$H$_5$ | 65 (R) | 97 (S,S) | 91 (anti) |
| 6     | H | 4-CNC$_6$H$_4$ | 88 (R) | rac | 61 (anti) |
| 7     | H | 4-CF$_2$C$_6$H$_4$ | 85 (R) | 82 (S,S) | 44 (anti) |
| 8     | H | 4-CIC$_6$H$_4$ | 75 (R) | 96 (S,S) | 98 (anti) |
| 9     | H | 3-CIC$_6$H$_4$ | 44 (S) | 37 (R,R) | 89 (anti) |
| 10    | H | 4-CH$_2$OC$_6$H$_4$ | 44 (R) | 99 (S,S) | 93 (anti) |
| 11    | H | 3-CH$_2$OC$_6$H$_4$ | 53 (S) | 52 (R,R) | 75 (anti) |
| 12    | H | 2-CH$_2$OC$_6$H$_4$ | - | - | - |
| 13    | H | 4-CH$_2$C$_6$H$_4$ | 72 (R) | 97 (S,S) | 85 (anti) |
| 14    | H | 3-CH$_2$C$_6$H$_4$ | 10 (S) | 98 (R,R) | 95 (anti) |
| 15    | H | 2-CH$_2$C$_6$H$_4$ | - | - | - |

[a] Substrate concentration was 2 mg mL$^{-1}$. [b] The ee value was determined by HPLC with a chiral column (see the Experimental Section). [c] The de was calculated by $^1$H NMR spectroscopy.

catalyzed by a complex bearing ligand L5 led to the organoborane compound with the $R$ configuration and variable enantiomeric excess values (7–51% ee). Subsequently, the solvent was removed in vacuo and NaBO$_2$·H$_2$O (3 equiv.) in THF/H$_2$O (1:3, 50 mg substrate/1 mL) was added. After 1 h, phosphate buffer (0.1 M, pH 7.5, 50 mL), glucose (50 g L$^{-1}$), and Rhodotorula rubra whole cells were added to the previous untreated solution to work with a final substrate concentration of 1 mg mL$^{-1}$ for 48 h (Table 5).

From the data reported in Table 5, it was observed that in the presence of electron-donating groups or hydrogen as a substituent, (S)-diols were provided with high enantiomeric excess values (Table 5, entries 1, 2, and 6). Excellent ee values were also obtained for (R)-hydroxy ketones, although in the

Table 5. Cascade reactions.

| Entry | ee (%) | ee (%) | ee (%) | ee (%) | de (%) | Yield (%) |
|-------|--------|--------|--------|--------|--------|-----------|
| 1     | H | 45 | 65 | 96 | 99 (S,S) | 95 (anti) | 96 |
| 2     | CH$_3$ | 51 | 72 | 99 | 99 (S,S) | 98 (anti) | 98 |
| 3     | CN | 4 | 88 | 90 | 7 (S,S) | 63 (anti) | 78 |
| 4     | CF$_3$ | 13 | 85 | 88 | 83 (S,S) | 46 (anti) | 75 |
| 5     | CI | 11 | 75 | 85 | 96 (S,S) | 99 (anti) | 98 |
| 6     | OCH$_3$ | 7 | 44 | 46 | 99 (S,S) | 94 (anti) | 95 |

[a] After catalytic β-borylation/deprotection. [b] After bioreduction by yeast starting from racemic hydroxy ketone. [c] Cascade reaction.
case of the substrate with a para-OCH₃ substituent, we believe that the average ee value is due to steric hindrance generated by the lone pair of electrons of the methoxy substituent in the pocket of the yeast. Regarding the results obtained with electron-withdrawing substituents, only low enantiomeric excess values were achieved in the reduction of (S,S)-dilns and in the resolution of (R)-hydroxy ketones (Table 5, entries 3–5). In this case, it is conceivable that erosion of the biocatalyst performance is a result of the low enantioselectivity of the chemo-reaction.

3. Conclusions

In conclusion, a cascade reaction combining transition-metal complexes with biocatalysts was set up for the enantioselective synthesis of keto–alcohols and the corresponding 1,3-diols. A new class of tridentate N,N,O pyridine-based ligands was used for the first time in the β–borylation reaction with copper(II) complexes to afford, in the case of ligand LS, keto–alcohols in enriched form with up to 91 % ee, which was crucial for setting up the subsequent biotransformation. Rhodotorula rubra, under optimized condition reactions, gave (S,S)-dilns (up to 99 % ee) and the S enantiomer of the keto–alcohol was consumed completely (up to 99 % ee for the unreacted R enantiomer) with both excellent enantio- and diastereoselectivities.

Experimental Section

Synthetic Procedures

General

1H NMR and 13C NMR spectra were recorded in CDCl₃ by using a Bruker DRX Avance (300 and 75 MHz) spectrometer equipped with a nonresonant probe. Chemical shifts [ppm] are referenced to the residual solvent proton/carbon signal. Polarimetry analyses were performed with a PerkinElmer 343 Plus equipped with Na/Hal lamp. MS analyses were performed by using a Thermo Finnigan (MA, USA) LCQ Advantage system MS spectrometer with an electrospray ionization source and an ion-trap mass analyzer. Mass spectra were obtained by direct infusion of a sample solution in MeOH under ESI−. Catalytic reactions were monitored by HPLC analysis with a Merck-Hitachi L-7100 equipped with Detector UV6000LP and a chiral column (AD, OD-H Chiralcel, Lux Cellulose-4, Lux Cellulose-2 or Lux Amylose-2).

General Procedure for the Synthesis of Ligands L1–L3

8-Aminoquinoline (1.2 equiv.) was dissolved in EtOH (10 mL), and salicylaldehyde (1 equiv.) was added at room temperature. The mixture was stirred for 5 h and then water (5 mL) was added. The organic layer was extracted with CH₂Cl₂ (3 × 10 mL). Anhydrous Na₂SO₄ was added, the mixture was filtered, and the solvent was removed in vacuo. The obtained product did not need further purification.

(€)-2-[(5,6,7,8-Tetrahydroquinolin-8-yl)iminomethyl]phenol (L2): S isomer: [α]D^25 = −42.13 (c = 1.1 in CHCl₃); R isomer: [α]D^25 = +42.05 (c = 0.7 in CHCl₃); 1H NMR (300 MHz, CDCl₃): δ = 8.63 (s, 1H), 3.93 (d, J = 4.67 Hz, 1H), 7.43 (d, J = 7.69 Hz, 1H), 7.32–7.24 (m, 2H), 7.12–7.08 (m, 1H), 6.97–6.83 (m, 2H), 4.56 (t, J = 3.85 Hz, 1H), 2.94–2.76 (m, 2H), 2.15–2.04 (m, 3H), 1.94–1.89 ppm (m, 1H); 13C NMR (75 MHz, CDCl₃): δ = 164.62, 161.32, 155.02, 147.72, 137.58, 132.81, 132.35, 131.92, 122.84, 119.27, 118.77, 117.07, 68.19, 31.30, 28.82, 18.84 ppm; FTR (NaCl): ν = 3436, 3046, 2927, 1964, 1629, 1262, 1088, 1031, 803 cm⁻¹; MS (ESI): m/z = 294.27 [M+H]+.

(€)-2-[(5,6,7,8-Tetrahydroquinolin-8-yl)iminomethyl]phenol (L3): R isomer: [α]D^25 = −53.4 (c = 0.4 in CHCl₃); S isomer: [α]D^25 = +59.9 (c = 0.5 in CHCl₃); 1H NMR (300 MHz, CDCl₃): δ = 13.60 (s, 1H), 8.60 (s, 1H), 7.33–7.25 (m, 3H), 7.04–6.84 (m, 3H), 4.56 (s, 1H), 2.88–2.63 (m, 2H), 2.24–2.04 (m, 3H), 1.94–1.87 ppm (m, 1H); 13C NMR (75 MHz, CDCl₃): δ = 164.48, 161.43, 156.18, 153.95, 137.83, 132.26, 131.81, 129.50, 122.64, 119.37, 118.68, 117.10, 67.62, 31.31, 28.35, 24.24, 18.68 ppm; FTR (NaCl): ν = 3056, 2930, 2864, 2733, 2665, 1731, 1627, 1472, 1416, 1081, 757 cm⁻¹; MS (ESI): m/z = 267.21 [M+H]+.

General Procedure for the Synthesis of Ligands L4 and L5

The ligand (1 equiv.) was dissolved in MeOH/THF (1:1, 5 mL), and the mixture was cooled to 0 °C. NaBH₄ (0.5 equiv.) was added, and the mixture was stirred at room temperature for 1 h. The solution was quenched with saturated NH₄Cl solution (4 mL) and was extracted with CH₂Cl₂ (3 × 8 mL). The combined organic layer was dried (Na₂SO₄), and the solvent was evaporated. The obtained product did not need further purification.

2-[(5,6,7,8-Tetrahydroquinolin-8-yl)aminomethyl]phenol (L4): S isomer: [α]D^25 = +20 (c = 0.1 in CHCl₃); R isomer: [α]D^25 = −24.2 (c = 0.1 in CHCl₃); 1H NMR (300 MHz, CDCl₃): δ = −8.39 (d, J = 3.96 Hz, 1H), 7.42 (d, J = 7.62 Hz, 1H), 7.18–7.03 (m, 3H), 6.84–6.76 (m, 2H), 4.14 (s, 2H), 3.86 (t, J = 6.15 Hz, 1H), 2.89–2.63 (m, 2H), 2.22–2.15 (m, 2H), 2.02–1.73 (m, 3H), 1.25 ppm (s, 1H); 13C NMR (75 MHz, CDCl₃): δ = 158.01, 155.95, 146.87, 137.24, 132.63, 128.68, 128.33, 123.61, 123.88, 119.05, 116.49, 57.99, 50.79, 28.75, 28.44, 19.74 ppm; FTR (NaCl): ν = 3282, 2924, 2924, 1690, 1589, 1456, 1259, 1037, 754 cm⁻¹; MS (ESI): m/z = 256.1 [M+H]+.

2-[(2-Methyl-5,6,7,8-tetrahydroquinolin-8-yl)aminomethyl]phenol (L5): S isomer: [α]D^25 = −39.1 (c = 0.6 in CHCl₃); R isomer: [α]D^25 = +32.9 (c = 0.3 in CHCl₃); 1H NMR (300 MHz, CDCl₃): δ = 7.31 (d, J = 8.2 Hz, 1H), 7.13 (m, 1H), 6.96 (d, J = 7.9 Hz, 2H), 6.83 (m, 2H), 4.14 (m, 3H), 2.47 (s, 4H), 1.86 ppm (m, 4H); 13C NMR (75 MHz, CDCl₃): δ = 155.7, 155.1, 137.5, 129.1, 128.9, 128.8, 128.0, 123.7, 121.9, 116.2, 57.9, 50.7, 28.7, 28.2, 20.4, 19.8 ppm; FTR (NaCl): ν = 3281, 2925, 2858, 1597, 1499, 1471, 1258, 1091, 1035, 816 cm⁻¹; MS (ESI): m/z = 269.15 [M+H]+.

Synthesis of α,β-Unsaturated Ketones

An aqueous solution of sodium hydroxide (30 %, 25 mL) was slowly added to a methanol solution (30 mL) of the appropriate acetophenone (1 equiv.). The solution was cooled to room temperature, and the appropriate benzaldehyde (1.2 equiv.) was added. The mixture was stirred at room temperature overnight and was then
poured into water (100 mL). The obtained solid was filtered, washed with water until neutral pH, and recrystallized (ethanol). The chemical structure was confirmed on the basis of previously reported data.3,4

General Procedure for Asymmetric Boron Conjugate Addition

A mixture of Cu(OAc)₂ (5 % mol), chiral ligand L1-L5 (6 % mol), and B₃(pin) (1.2 equiv) in Et₂O (7.5 mL) was stirred at room temperature for 1 h under a nitrogen atmosphere. A mixture of the αβ-unsaturated carbonyl compound (1 equiv) and MeOH (50 equiv) in Et₂O (2.5 mL) was added, and the mixture was stirred at room temperature for 15 h. The mixture was concentrated in vacuo, the residue was dissolved in THF/H₂O (1.5:1, 4 mL), and NaBO₃·H₂O was added. The mixture was stirred for 2 h and then filtered. The aqueous layer was washed with EtOAc (2×5 mL), and the combined organic layer was dried (Na₂SO₄). The solvent was evaporated, and the enantiomeric excess of the product was checked by HPLC analysis.

The ¹H NMR and ¹³C NMR spectra of 4-hydroxy-4-phenylbutan-2-one, 4-(3-chlorophenyl)-4-hydroxybutan-2-one, 4-(4-chlorophenyl)-4-hydroxybutan-2-one, 4-(4-nitrophenyl)-4-hydroxybutan-2-one, 3-phenyl-1,3-diphenylpropan-1-one, 3-phenyl-1-(p-tolyl)propan-1-one, 3-(3-chlorophenyl)-3-hydroxy-1-phenylpropan-1-one, 3-(3-chlorophenyl)-3-hydroxy-1-(p-tolyl)propan-1-one, 3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one, 3-hydroxy-1-(2-methylphenyl)-3-phenylpropan-1-one, 3-hydroxy-1-(3-methylphenyl)-3-phenylpropan-1-one, and 3-hydroxy-1-(2-methylphenyl)-3-phenylpropan-1-one correspond to those reported in the literature.⁴,¹¹

3-Hydroxy-1-(3-methylphenyl)-3-phenylpropan-1-one: ¹H NMR (300 MHz, CDCl₃); δ = 7.58–7.25 (m, 8 H), 7.12 (d, J = 8.2 Hz, 1H), 5.35–5.31 (m, 1H), 3.87 (s, 3H), 3.37–3.34 ppm (m, 2H); ¹³C NMR (75 MHz, CDCl₃); δ = 159.8, 144.8, 143.0, 137.9, 129.7, 128.5, 127.6, 125.7, 120.8, 120.1, 112.3, 55.4, 47.5, 24.5 ppm; MS (ESI): m/z = 279.1 [M+Na]+.

1-Phenyl-3-[4-(trifluoromethyl)phenyl]propane-1,3-diol: ¹H NMR (300 MHz, CDCl₃); δ = 7.61–7.57 (m, 2H), 7.52–7.46 (m, 2H), 7.39–7.25 (m, 5H), 5.29–5.05 (m, 2H, syn), 4.99–4.50 (m, 2H, anti), 2.22–2.15 (m, 2H, anti), 2.05–1.88 ppm (2H, syn); ¹³C NMR (75 MHz, CDCl₃); δ = 159.4, 143.8, 128.9, 128.6, 128.5, 125.7, 125.6, 125.5, 75.2 (anti), 74.2 (anti), 71.7 (syn), 71.1 (syn), 47.6 (anti), 46.4 (syn), 28.3 ppm; MS (ESI): m/z = 319.0 [M+Na]+.

Analytical Conditions

The products were analyzed by ¹H NMR spectroscopy to determine the molar conversion, whereas the diastereomeric and enantiomeric excess values were evaluated by HPLC analysis.

4-Hydroxy-4-phenylbutan-2-one: S isomer: t₁/₂ = 21 min, R isomer: t₁/₂ = 18.7 min; 1-phenylbutane-1,3-diol (anti form) S,R isomer: t₁/₂ = 16 min, R,S isomer: t₁/₂ = 17 min, (syn form) R,R isomer: t₁/₂ = 19.7 min, S,S isomer: t₁/₂ = 21 min; column: Lux cellulose-4, eluent: 2-propanol.

ChemistryOpen 2018, 7, 393 – 400 www.chemistryopen.org 398 © 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
isomer: 2-propanol/hexane = 15:85, flow = 0.5 mL min⁻¹, λ = 216 nm.

3-Hydroxy-1-(2-methoxyphenyl)-3-phenylpropan-1-one: S isomer: t<sub>R</sub> = 12 min, R isomer: t<sub>R</sub> = 19 min; column: AD CHIRALCEL, eluent: 2-propanol/hexane = 10:90, flow = 1.0 mL min⁻¹, λ = 220 nm.

3-Hydroxy-3-phenyl-1-(p-tolyl)propan-1-one: R isomer: t<sub>R</sub> = 13.5 min, S isomer: t<sub>R</sub> = 20.5 min; benzoyl-(4′-methylbenzoyl)me-thane: (anti form) S,S isomer: t<sub>R</sub> = 11 min, R,R isomer: t<sub>R</sub> = 17 min; column: Lux cellulose-4, eluent: ethanol/hexane = 10:90, flow = 1.0 mL min⁻¹, λ = 216 nm.

3-Hydroxy-1-(3-methylphenyl)-3-phenylpropan-1-one: S isomer: t<sub>R</sub> = 14 min, R isomer: t<sub>R</sub> = 11 min; 1-phenyl-3-(m-tolyl)propylene-1,3-di-ol: (anti form) S,S isomer: t<sub>R</sub> = 6 min, R,R isomer: t<sub>R</sub> = 10 min; column: Lux cellulose-4, eluent: 2-propanol/hexane = 10:90, flow = 0.8 mL min⁻¹, λ = 220 nm.

Cascade Reaction Procedure

A mixture of Cu(OAc)<sub>2</sub> (5 % mol), chiral ligand L5 (6 % mol), and B<sub>2</sub>(pin) (1.2 equiv) in Et<sub>2</sub>O (7.5 mL) was stirred at room temperature for 1 h under a nitrogen atmosphere. A mixture of the uCo(I)-unsaturated ketone (1 equiv) and MeOH (50 equiv) in Et<sub>2</sub>O (2.5 mL) was added, and the mixtures were stirred at room temperature for 15 h. The mixture was concentrated in vacuo, the residue was dissolved in THF/H<sub>2</sub>O (1:3, 50 mg substrate/1 mL), and NaBO<sub>3</sub>·H<sub>2</sub>O (5 equiv) was added. The mixture was stirred for 1 h. *Rhodotorula rubra* was then added to 0.1 M phosphate buffer (pH 7, 50 mL) containing glucose (50 g L⁻¹) to work at a final substrate concentration of 1 mg mL⁻¹. The mixture was magnetically stirred at 28 °C for 48 h. The mixture was extracted with diethyl ether (2 x 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo.

Material and Methods

**Microorganisms: Culture Conditions**

Strains from official collections or from our collection were routinely maintained on a malt extract (8 g L⁻¹ agar 15 g L⁻¹, pH 5.5). To obtain cells for the biocatalytic activity tests, the microorganisms were grown on solid medium at 28 °C for 72 h, and then they were cultured in 1000 mL Erlenmeyer flasks containing the medium (100 mL, OD<sub>600</sub>=0.5 mL⁻¹ 0.1 at t<sub>0</sub>). The microorganisms were incubated at 28 °C for 48 h on a reciprocal shaker (100 rpm). The yeasts were grown on malt extract with 5 g L⁻¹ Difco yeast extract, pH 5.6. Fresh cells from submerged cultures were centrifuged (4000 x g for 15 min at 4 °C) and washed with tap water before using. The cells used in the screening biotransformations were concentrated in a ratio of 1:2.

**Crystallography**

Diffraction data for the crystal of complex L1<sup>106</sup> were collected by means of a Enraf–Nonius CAD4 four circle diffractometer working at ambient temperature with graphite-monochromated MoKα X-radiation (λ = 0.71073 Å). X-ray diffraction data in the 2θ range of 4 to 60° and in the (hkl) range ± h ± k ± l were collected by using a
probed θ-scan mode with scan angles of (1.2 + 0.35 tan θ°) and prescan speed of 4.12 min−1. Accurate unit-cell parameters were obtained by a least-squares fit of the 2θ values for 25 reflections in the 2θ range of 30 to 40°. Data reductions (including intensity integration, background, Lorentz, and polarization corrections) were performed with the WinGX package.[13] Absorption effects were evaluated with the psi-scan method,[14] and absorption correction was applied to the data (min/max transmission factors were 0.808/0.924). The structure was solved by direct methods (SIR-97)[17] and were completed by iterative cycles of full-matrix least-squares refinement on F2 and ΔF synthesis by using the SHELXL-97[16] program (WinGX suite). All non-hydrogen atoms were refined anisotropically. The positions of the H atoms were detected in a difference Fourier and were refined with isotropic thermal factors or were introduced in calculated positions in their described geometries and allowed to ride on the attached carbon atom with fixed isotropic thermal parameters.

Conflicts of Interest

The authors declare no conflict of interest.

Keywords: biocatalysis • borylation • copper • reduction • yeast

[1] a) G. Rulli, N. Duangdee, W. Hummel, A. Berkessel, H. Gröger, Eur. J. Org. Chem. 2017, 812 – 817; b) S. Sonoike, T. Itakura, M. Kitamura, S. Aoki, Chem. Asian J. 2012, 7, 64 – 74; c) P. Vitale, F. M. Perna, G. Agrimi, A. Scilimati, A. Salomone, C. Cardellicchio, V. Capriati, Org. Biomol. Chem. 2016, 14, 11458 – 11465; d) M. T. El Ghani, J. M. J. Williams, Curr. Opin. Chem. Biol. 1999, 3, 11 – 15.
[2] a) A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers, V. K. Aggarwal, Angew. Chem. Int. Ed. 2016, 55, 14663 – 14667; Angew. Chem. 2016, 128, 14883 – 14887; b) A. Pujol, A. Whiting, J. Chem. 2017, 82, 7265 – 7279.
[3] P. Kaur, G. L. Khatik, S. K. Nayak, Curr. Org. Synth. 2017, 14, 665 – 682.
[4] a) Q.-Q. Wang, J.-M. Yang, D. Fang, J. Ren, B. Dong, B. Zhou, B.-B. Zeng, Tetrahedron Lett. 2016, 57, 2587 – 2590; b) J.-B. Xie, S. Lin, S. Qin, G. Li, Org. Lett. 2016, 18, 3926 – 3929; c) J.-B. Xie, S. Lin, J. Luo, J. Wu, T. R. Winn, G. Li, Org. Chem. Front. 2015, 2, 42 – 46; d) L. Zhu, T. Kitanoono, P. Xu, S. Kobayashi, Chem. Commun. 2015, 51, 11685 – 11688; e) L. Wang, Z. Chen, M. Ma, W. Duan, C. Song, Y. Ma, Org. Biomol. Chem. 2015, 13, 10691 – 10698.
[5] S. Pellegrotino, G. Facchetti, R. Gandolfi, M. Fusè, E. Erba, I. Rimoldi, Can. J. Chem. 2017, 95, 40 – 43.
[6] a) J. Merad, P. Borkar, F. Caijo, J.-M. Pons, J.-L. Parrain, O. Chuzel, C. Bressy, Angew. Chem. Int. Ed. 2017, 56, 16052 – 16056; Angew. Chem. 2017, 129, 16268 – 16272; b) Y. Nakamura, H. Egami, K. Matsumoto, T. Uchida, T. Katsuki, Tetrahedron 2007, 63, 6383 – 6387.
[7] J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, Angew. Chem. Int. Ed. 2010, 49, 9052 – 9067; Angew. Chem. 2010, 122, 9236 – 9251.
[8] a) I. Rimoldi, G. Facchetti, E. Cesarotti, M. Pellizzoni, M. Fuse, D. Zerla,Curr. Org. Chem. 2012, 16, 2982 – 2988; b) D. Zerla, G. Facchetti, M. Fuse, M. Pellizzoni, C. Castellano, E. Cesarotti, R. Gandolfi, I. Rimoldi, Tetrahedron: Asymmetry 2014, 25, 1031 – 1037; c) D. S. Zerna, I. Rimoldi, E. Cesarotti, G. Facchetti, M. Pellizzoni, M. Fuse, J. Organomet. Chem. 2014, 771, 2 – 8; d) L. Ricciardi, M. La Deda, A. Ionescu, N. Godbert, I. Aiello, M. Ghedini, M. Fusè, I. Rimoldi, E. Cesarotti, J. Lumin. 2016, 170, 812 – 819.
[9] L. J. Farrugia, ONTEP for Windows, University of Glasgow, Scotland, 1997.
[10] a) T. Kitanosono, P. Xu, S. Ishihiki, L. Zhu, S. Kobayashi, Chem. Commun. 2014, 50, 9336 – 9339; b) M. Isegawa, W. M. C. Sameera, A. K. Sharma, T. Kitanosono, M. Kato, S. Kobayashi, K. Morokuma, ACS Catal. 2017, 7, 5370 – 5380; c) T. Kitanosono, L. Zhu, C. Liu, P. Xu, S. Kobayashi, J. Am. Chem. Soc. 2015, 137, 15422 – 15425.
[11] a) I. Rimoldi, G. Facchetti, D. Nava, M. L. Contente, R. Gandolfi, Tetrahedron: Asymmetry 2016, 27, 389 – 396; b) G. Facchetti, R. Gandolfi, M. Fuse, D. Zerla, E. Cesarotti, M. Pellizzoni, I. Rimoldi, New J. Chem. 2015, 39, 3792 – 3800; c) I. Rimoldi, M. Pellizzoni, G. Facchetti, F. Molinari, D. Zerla, R. Gandolfi, Tetrahedron: Asymmetry 2011, 22, 2110 – 2116.
[12] A. Schiano Moriello, L. Luongo, F. Guida, M. Christodoulou, S. D. Perdicchia, S. Maione, D. Passarella, V. Di Marzo, L. De Petrocellis, CNS Neurol. Drug Targets 2016, 15, 987 – 994.
[13] a) H.-J. Xu, Y.-C. Liu, Y. Fu, Y.-D. Wu, Org. Lett. 2006, 8, 3449 – 3451; b) M. Heidlinemann, A. Berkessel, H. Gröger, ChemCatChem 2017, 9, 1383 – 1388; c) O. Illa, O. Porcar-Tost, C. Robledillo, C. Elvira, P. Nolis, O. Reiser, V. Branchadell, R. M. Ortuño, J. Org. Chem. 2018, 83, 350 – 363; d) W.-C. Yang, S.-S. Wang, A. Ramasamy, G. Rajeshwaran, Y.-Y. Liao, C.-T. Chen, Org. Biomol. Chem. 2015, 13, 2385 – 2392; e) K. Toribatake, L. Zhou, A. Tsunuta, H. Nishiyama, Tetrahedron 2013, 69, 3551 – 3560; f) Q. Huang, J.-W. Wu, H.-J. Xu, Tetrahedron Lett. 2013, 54, 3877 – 3881.
[14] A. Kiliç, M. Stephan, B. Mohar, Adv. Synth. Catal. 2015, 357, 2540 – 2546; b) A. Hu, W. Lin, Org. Lett. 2005, 7, 455 – 458; c) Y. Hua, H. H. Nguyen, W. R. Scaggs, J. Jeon, Org. Lett. 2013, 15, 3412 – 3415.
[15] L. Farrugia, J. Appl. Crystallogr. 2012, 45, 849 – 854.
[16] A. C. T. North, D. C. Phillips, F. S. Mathews, Acta Crystallogr. Sect. A. 1968, 24, 351 – 359.
[17] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Molteni, G. Polidori, R. Spagna, J. Appl. Crystallogr. 1999, 32, 115 – 119.
[18] G. M. Sheldrick, SHELX97—Programs for Crystal Structure Analysis (Release 97 – 92), University of Göttingen, Germany, 1998.
[19] CCDC 1818501 (Cu–I complex) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.