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Enantiocomplementary C-H Bond Hydroxylation Combining Photo-catalysis and Whole-Cell Biocatalysis in One-pot Cascade Process

Yongzhen Peng,[a] Danyang Li,[a] Jiajie Fan,[a] Weihua Xu,[a] Jian Xu,*[a] Huilei Yu,[b] Xianfu Lin,[a] and Qi Wu*[a]
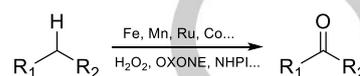
Abstract: Enantiocomplementary hydroxylation of alkyl aromatics through a one-pot photo-biocatalytic cascade reaction is described. The photoredox process is implemented in aqueous phase with O_2 as oxidant and the subsequent (R)- or (S)-selective bioreduction is performed by whole cell system without the addition of the expensive cofactor (NADPH). This mild, operationally simple protocol transforms a wide variety of readily available aromatic compounds into valuable chiral alcohols with high yield (up to 90%) and stereoselectivity (up to 99%), thereby displaying important potentials in organic synthesis.
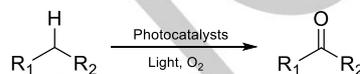
Introduction

Selective C-H oxyfunctionalization has still attracted broad interest in organic synthesis.[1] Over the past decades, transition metals such as Fe, Mn, Ru have been utilized to synthesize highly functionalized molecules by direct oxidation with hazardous strong oxidants, such as H_2O_2, oxone and NHPI, which may strongly hamper their industrial application (Scheme 1).[2] Therefore, to develop more safety and environmental-friendly approaches remains challenges.

The direct oxyfunctionalization of C-H by molecular oxygen as a sustainable oxidant is one of the so-called "dream reactions". Recently, the photocatalytic C-H oxygenation of alkyl benzenes with O_2 has been developed rapidly. For example, Wolf, Hollmann and Pasau's groups have described such approaches using different organic dyes such as riboflavin tetraacetate (RFT) and sodium anthraquinoneulfonate (SAS), respectively.[3] However, most of these approaches would oxidize alkyl benzenes to the corresponding ketones, rather than chiral alcohols.
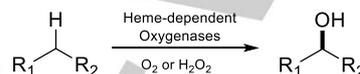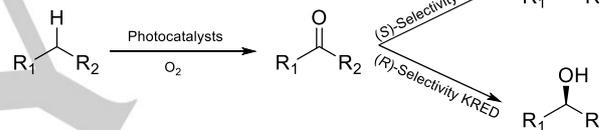

Scheme 1. Selective C-H oxyfunctionalization by different methods. a) Transition metal catalysis. b) Photocatalysis. c) Biocatalysis. d) This work combining the photocatalytic process with enzymatic reactions steps.

Stereoselective hydroxylation for producing chiral alcohols has been proved very useful in organic synthesis. Biocatalysis is an effective approach to carry out this process. Heme-dependent oxygenases, such as P450 monooxygenases are leveraged for the synthesis of chiral alcohols from inactive C-H bonds.[4] However, this type of enzyme relies on a complex and susceptible electron transport chain from flavin domain to heme active site to regenerate the active side.[5] Another example is peroxygenases, which employs H_2O_2 to recycle the heme, directly.[6] However, excess H_2O_2 also destabilizes the enzyme and reduces the activity.[7] Therefore, the above limitations of traditional biocatalysis lead us to consider an alternative approach to achieve this transformation.

Cascade reaction combining chemical catalysts and enzymes is becoming a powerful approach to achieve functional molecules.[8] These multi-step reactions have been conducted without the isolation of intermediate compounds. The most notable example is dynamic kinetic resolution of secondary alcohols and amines with metallic catalysts and lipases.[9] Subsequently, other one-pot cascade reactions have been developed to synthesize alcohols, amines, amino acids and even polymers.[10] Recently, The cascade reaction with a combination of photoredox and biocatalysis has gained increasing attentions.[11] For example, Hollmann and co-workers have discovered photocatalytic processes for the *in situ* generation of H_2O_2 to combine with peroxygenases.[5] Zhao and Hartwig have reported a cascade process to generate valuable enantioenriched product combining the isomerization catalysed by photocatalysts

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and the reduction of carbon–carbon double bonds catalysed by ene-reductases.[12] Very recently, Schmidt and co-workers have developed a novel cascade process to perform asymmetric C-H benzylic hydroxylation to achieve (R)-selective achiral alcohols combining photoredox and KRED reduction.[13] However, the reduction in the second step relies on the addition of expensive cofactors (NADP+). To overcome this limitation, herein, we develop an alternative one-pot cascade protocol in combination with the photo-catalysis and whole-cell biocatalysis for the production of enantiocomplementary alcohols. The employment of NADPH self-regeneration in whole cell system avoids the addition of NADP+, which makes it a more economical way in organic synthesis.

Results and Discussion

This type of cascade reactions suffers from two major challenges. Firstly, the photocatalysts tend to denature the enzymes through disruption of the tertiary protein structure or inactivation of the cofactors. Furthermore, most KREDs are active in aqueous phase, only extremely few can tolerate organic media.[14] Conversely, most reported photocatalysts were employed in anhydrous conditions. Therefore, the initial study was to implement the photocatalytic carbonylation of ethylbenzene in aqueous phase (25% acetonitrile as cosolvent). Based on the previous studies, RFT was first chosen to investigate the model reaction as its highly catalytic activity[3c] and biocompatibility[15]. After irradiation for 12 h with blue LED, this process was proved to be inefficient, only less than 10% yield of 2a was observed. When Fe(ClO_4)_3 was employed as a co-catalyst, the yield was increased to 60%. Nevertheless, the yield of by-product alcohol (3a) was up to 10%, which would significantly decrease the stereoselectivity of the reduction by KREDs in the second step. In order to optimize the reaction conditions and minimize side effects, other water-soluble dyes were tested as well. To our delight, by employing SAS as a photocatalyst, a moderate yield (67%) of desired product 2a was achieved with only 2% by-product (3a) after 12 h irradiation. By increasing the amount of SAS to 20 mol%, the yield of 3a successfully improved to 90% (Table 1, Entry 4). The yield declined significantly when using water as solvent independently without acetonitrile. This phenomenon was likely due to the low solubility of alkyl benzenes in pure water. Finally, control experiments were carried out, confirming the requirement of SAS, air and a blue light source in this method.

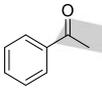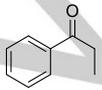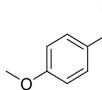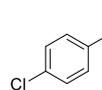**Table 1.** Reaction optimization for the photocatalytic C-H oxyfunctionalization[a].

Entry	Reaction condition	Yield of 2a/% [b]	Yield of 3a/% [b]
1	RFT	10	3
2	RFT + Fe(ClO_4)_3	60	10
3	SAS	67	2
4	SAS[c]	90	1
5	Entry 4. No CH_3CN	9	1
6	Entry 4. No air	1	0
7	Entry 4. No light	0	0
8	Entry 4. No SAS	0	0

[a] Reaction conditions: 25 mM ethylbenzene, 2 mL mixture solution containing 25 % (v/v) acetonitrile in water, with photocatalyst (2.5 mM, 10 mol%), under the irradiation with blue LEDs for 12 h at r. t. [b] Determined by chiral GC. [c] with SAS (5.0 mM, 20 mol%).

Under the optimal conditions identified in Table 1, different substituted aromatic compounds afforded the moderate to high yields of the desired carbonylation products (Table 2). Particularly, the substrate with p-methoxy substituent on the aromatic ring afforded the highest yield of the corresponding ketone (2c, 97%). Moreover, substitution o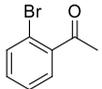f bromine or chlorine in different positions and other substrates with the structure of thiophene and indene could also be tolerated (2d-2g, 2i-2j). However, the yield of α-hydroxy-substituted alkylbenzene remarkably decreased for the reason of the α-hydroxy oxidation.

Table 2. Scope of the selective C–H bond carbonylation [a], [b].

2a
Yield: 90%

2b[c], [d]
Yield: 77%

2c
Yield: 97%

2d[c], [d]
Yield: 71%
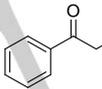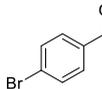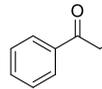
2e[c], [d]
Yield:53%

2f[c],
Yield:72%

2g[c]
Yield:50%

2h
Yield:23%
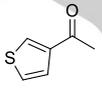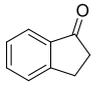
2i[c]
Yield:91%

2j[c]
Yield:82%

[a] Reaction conditions: 25 mM substrate, 2 mL mixture solution containing 25 % (v/v) acetonitrile in water, with photocatalyst (5 mM, 20 mol%), under the irradiation with blue LEDs for 12 h at r. t. [b] Determined by chiral GC. [c] Reaction for 18 h. [d] 30 % (v/v) acetonitrile in water.

Next, we focused on the reduction of acetophenone (2a) by ketoreductase to obtain chiral alcohols. Carbonyl reductase from *Kluyveromyces thermotolerans* (KtCR) was chosen as a model enzyme which was identified with satisfactory R-selectivity.[16] Initially, we performed the cascade reaction with all factors in one-pot. Unfortunately, the process was ineffective, only 5% desired chiral product (3a) was observed. We supposed that the formation of products might be supressed for three reasons: (i) Excess H_2O_2 which was accumulated along with irradiation as shown in Figure 1, had significant effects to the structure of enzymes and probably reduced their catalytic activity; (ii) Excided SAS strongly inhibited the activity of KtCR by diminishing the NADPH which was regenerated by GDH, as similar as flavin reported by Schmidt and Holloman;[11e] (iii) And the reduced alcohol product would be oxidized again by SAS (Figure S1).

Based on these results, we first extracted the crude products with MTBE, and subsequently conducted the enzymatic reduction reaction in PBS buffer. With such a straightforward two-pot cascade reaction, the KtCR-catalyzed reduction could be performed under the optimization conditions and showed the highest activity. Chiral alcohol 3a was achieved in a high yield of 96% with satisfactory stereoselectivity (ee: 99%).
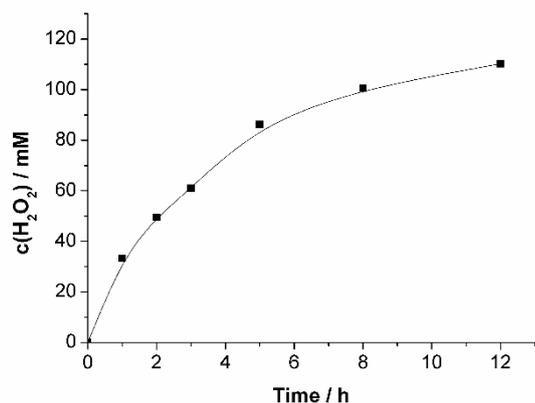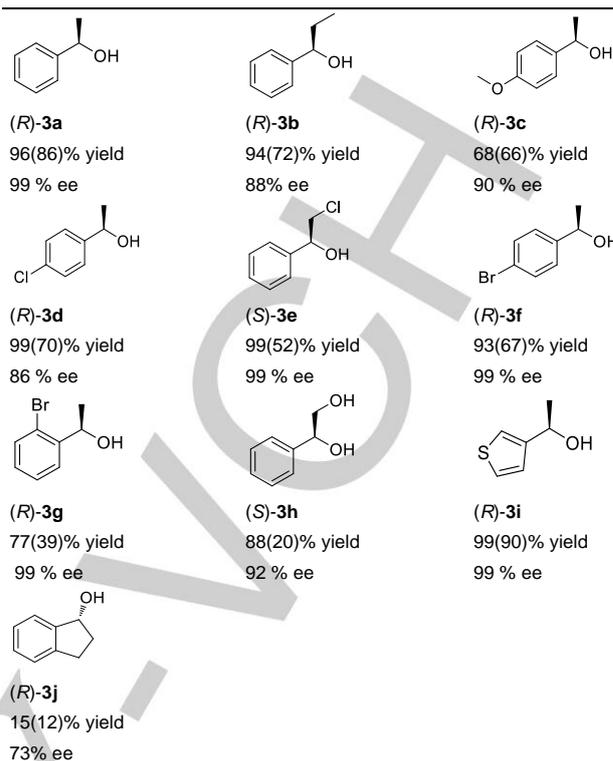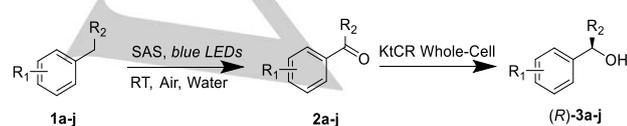
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Figure 1. The formation of H$_2$O$_2$ during the photoredox carbonylation

Although the cascade reaction of two-pot C-H stereoselective hydroxylation was achieved successfully, the extraction of intermediate products consumed large amounts of organic solvents, which suffered from the limitation of low reaction economy and environmental pollution. And the following reduction process required a stoichiometric amount of the expensive cofactor (NADPH) as an electron donor which strongly hampered the further application of this cascade process. The whole-cell reaction system, wherein the intact periplasm apparently protects enzymes from inactivation by chemical reagents[17] and recycles the expensive cofactor (NADPH) *in situ*[18], was tested to implement this process in one-pot and reduce the requirement of NADPH as well. Further simplified research was conducted in 2 mL aqueous solution containing 25 mM 1a and 20% mol SAS. After 12 h irradiation, 20 mL whole-cell culture medium of ketoreductase with 250 mM glucose were added in one-pot. The reactor was shaken at 200 rpm and 30°C for overnight, then the yields were determined by GC. To our delight, high yield (86%) and stereoselectivity (99%) of (R)-3a was obtained.

After successfully developing the one-pot system of asymmetrical C-H hydroxylation with a photocatalyst and a KRED, we next investigated the substrate scope of this method. The results by KtCR are summarized in Table 3. Aromatic substrates without substituents on the benzene ring displayed high activity and excellent enantioselectivity (3a, 3b, 3e and 3h). Various substituents on the phenyl rings such as halogen (3d, 3f-g) and methoxyl (3c) were all tolerated well. Moreover, substrates with methyl (3b), chlorine (3e) or hydroxyl (3h) substituents on the α-methyl position also displayed satisfactory yields and selectivity. Interestingly, the size of aromatic ring displayed important effect to the KtCR-catalyzed reduction. Compared with thiophene-(3i) and benzene-contained substrate, indanone (3j) might not be accepted by KtCR well leading to the low reactivity (yield = 15%).

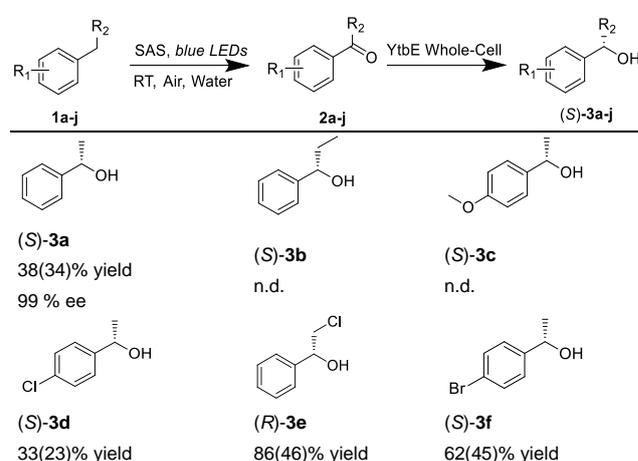**Table 3.** Substrate scope of (R)-selective reduction [a], [b], [c]

(R)-3a
96(86)% yield
99 % ee

(R)-3b
94(72)% yield
88% ee

(R)-3c
68(66)% yield
90 % ee

(R)-3d
99(70)% yield
86 % ee

(S)-3e
99(52)% yield
99 % ee

(R)-3f
93(67)% yield
99 % ee

(R)-3g
77(39)% yield
99 % ee

(S)-3h
88(20)% yield
92 % ee

(R)-3i
99(90)% yield
99 % ee

(R)-3j
15(12)% yield
73% ee

[a] The obtained photocatalyst reaction system was added to KtCR whole cell culture. [b] Yields and ee values referred to the KtCR-catalyzed reduction reactions, which were determined by chiral GC or HPLC, and the total yields of photo-enzymatic cascade reactions were given in parentheses. [c] The *R/S* assignment was changed in accordance with the Cahn-Ingold-Prelog priority rules.

The scaling-up reaction of the model reaction was also carried out, in which 85% yield and 98% ee value (100 mg scale) were successfully achieved. This process led to efficient transformation of the model substrate to the corresponding alcohols with high yield.

In order to extend the application of the cascade reaction, (S)-selective KREDs (YtbE from *Bacillus subtilis* 168) was employed to achieve (S)-alcohols.[19] In the model reaction, (S)-2a was offered by YtbE with moderate yield and excellent ee value. Same process was conducted and a variety of (S)-configured alcohols were obtained with ideal yields and ee values (Table 4).

Table 4. Substrate scope of (S)-selective reduction [a], [b], [c]

(S)-3a
38(34)% yield
99 % ee

(S)-3b
n.d.

(S)-3c
n.d.

(S)-3d
33(23)% yield

(R)-3e
86(46)% yield

(S)-3f
62(45)% yield

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99 % ee

(*R*)-**3g**
99(50)% yield

99 % ee

(*S*)-**3j**
n.d.

88 % ee

(*R*)-**3h**
52(12)% yield
91 % ee

99 % ee

(*S*)-**3i**
n.d.

[a] The obtained photocatalyst reaction system was added to YtbE whole cell culture. [b] Yields and ee values referred to the YtbE-catalyzed reduction reactions, which were determined by chiral GC or HPLC, and the total yields of photo-enzymatic cascade reactions were given in parentheses. [c] The *R/S* assignment was changed in accordance with the Cahn-Ingold-Prelog priority rules.
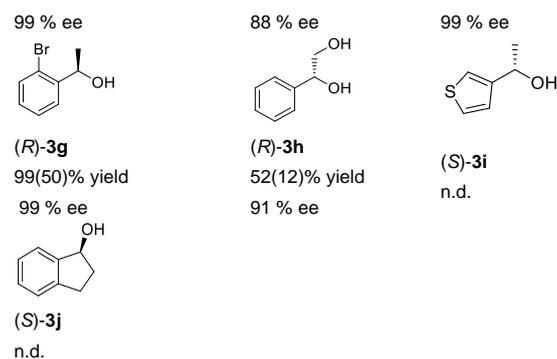
Conclusions

In summary, we have reported an enantiocomplementary C-H hydroxylation process in a one-pot cascade reaction combining photocatalysis and biocatalysis. A series of enantiocomplementary chiral alcohols are successfully achieved from readily available aromatic compounds through simple process with two types of KREDs in high yields (up to 90%) and stereoselectivity (up to 99%). This photochemo-enzymatic one-pot whole-cell C-H hydroxylation reaction is conducted in water and using O_2 as oxidant, and these advantages will contribute to the synthesis of chiral alcohols, which are highly valuable intermediates for the production of pharmaceutical drugs and bioactive compounds.

Experimental Section

General information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. The ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX400 MHz spectrometer using TMS as an internal standard in $CDCl_3$. Yields and stereoselectivity were determined by chiral GC with Agilent CP-chirasil-Dex CB column or chiral HPLC with a Chiralpak OJ-H column (250 mm×4.6 mm, n-hexane/2-propanol as the mobile phase) and a UV detector (220 nm). The power of the *LEDs* is 8 W.

Preparation of ketoreductases (KtCR and YtbE). 100 µL stored bacteria was first incubated in 5 mL LB media with Kanamycin (50 µg/mL) and then shaken at 37 ℃ for overnight. 5 mL preculture was added to 500 mL fresh LB medium with 50 µg/mL Kanamycin. The cultures were shaken at 37°C until OD_{600} at 0.6 and then cooled at 4°C for 30 min. Isopropyl β-thiogalactopyranoside (IPTG) was added to a final concentration of 0.5 mM to induce ketoreductases expression at 25 ℃. Cells were harvested by centrifugation, and resuspended in 50 mM sodium phosphate buffer (pH 6.5 for KtCR and YtbE) for reaction.

Preparation of racemic alcohols. The given ketone (2 mmol) was added into a solution of $NaBH_4$ (5 mmol) in methanol (10 mL) at room temperature (20ºC). The solution was stirred until the complete disappearance of ketone substrate indicated by TLC. The crude product was evaporated in vacuo and diluted in dichloromethane (20 mL), and then washed with water (10 mL). The organic phase was separated and dried over anhydrous magnesium sulfate, and then evaporated in vacuum.

General procedure for one-pot reaction. 2 mL mixture solution (25% v/v acetonitrile in water) containing 25 mM substrate and 5 mM SAS, was incubated under aerobic conditions at r.t. and exposed to the light of 8 W blue *LED* irradiation for 12 hours (the reaction time could be extended to ensure no residual alcohols). 20 mL cell culture of ketoreductase (resuspended in 50 mM sodium phosphate buffer, pH 6.5) with glucose (250 mM) was added into the photocatalytic mixture and shaken at 30 ℃ for overnight. The stereoselectivity and yield was determined by chiral GC or HPLC.

Scaling-up one-pot reaction catalyzed by photocatalyst and ketoreductase. The scale-up reaction was performed as follows: SAS (0.2 mmol, 20 mol%) and 1 mmol 1a was dissolved in 40 mL mixture solution of acetonitrile and water (25% v/v acetonitrile as cosolvent). The reaction mixture was irradiated with blue *LEDs* for 20 hours (the reaction time could be extended to ensure no residual alcohols). 400 mL whole-cell culture of ketoreductase (resuspended in 50 mM sodium phosphate buffer, pH 6.5) with glucose (10 mmol) was added into the photocatalytic reaction mixture and shaken at 30 ºC for overnight. The reaction solution was extracted with ethyl acetate for three times, then the organic phase was dried over anhydrous sodium sulfate and concentrated in vacuum. The obtained crude product was further separated and purified by flash column chromatography.

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Herein, we develop an alternative one-pot cascade protocol in combination with the photo-catalysis and whole-cell biocatalysis for the production of enantiocomplementary alcohols.
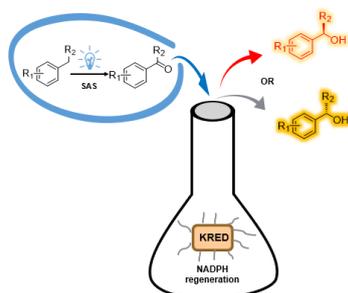
C-H bond hydroxylation, Combination photo-catalysis and whole-Cell biocatalysis *

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Enantiocomplementary C-H Bond Hydroxylation Combining Photo-catalysis and Whole-Cell Biocatalysis in One-pot Cascade Process