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Graphical Abstract

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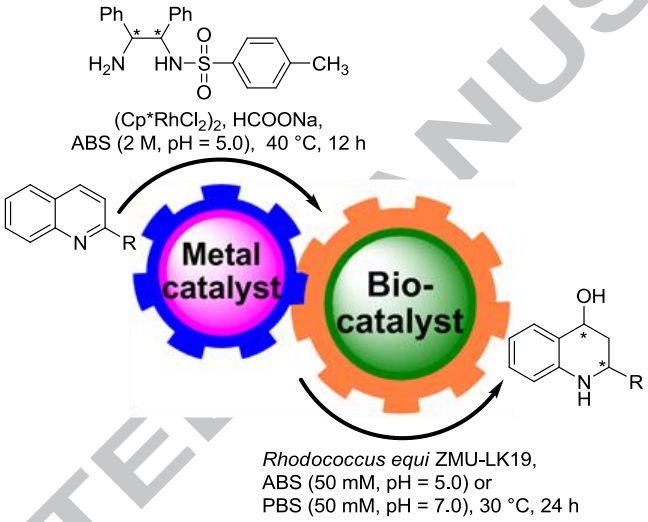

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Asymmetric combinational "metal-biocatalytic system": one approach to chiral 2-subsituted-tetrahydroquinoline-4-ols towards two-step one-pot processes in aqueous media

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ABSTRACT

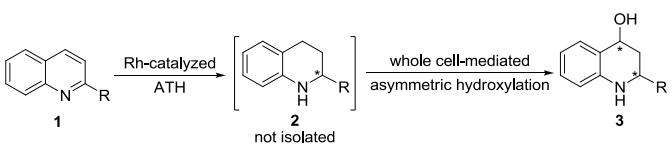
A novel asymmetric "metal-biocatalytic system", involving Rh-catalyzed asymmetric transfer hydrogenation and whole cell mediated asymmetric hydroxylation in aqueous buffer, has been achieved. The methodology gives access to 2-subsituted-tetrahydroquinoline-4-ols bearing two stereocenters from 2-subsituted-quinolines in moderate to excellent results (up to 47% yield, 99:1 dr, and >99% ee).

1. Introduction

Combinational catalysis as one of the most powerful strategies in asymmetric synthesis has been attracting considerable interest because of its great potential in the construction of chiral compounds.[1] Obviously, metal catalysis combined with organocatalysis, organocatalysis combined with biocatalysis as well as metal catalysis combined with biocatalysis are common strategies in combinational catalysis.[2] In general, biocatalysts are inactive among the chem-biocatalytic system, which is attributed to enzymes in biocatalysts are deactivated by chemicals.[2] Therefore, the development of highly efficient and compatible catalytic system between chemical catalysts, especially metal catalysts, and biocatalysts is a challenge. In the past decade, asymmetric combinational "metal-biocatalytic system", including Wacker oxidation/reduction,[3] aldol reaction/reduction,[4] Heck/reduction,[5] olefinmetathesis/epoxidation,[6] Suzuki reaction/reduction,[7] allylic alcohol isomerisation/bioamination,[8] amination/Suzuki reaction,[9] hydrogenation/hydrolysis,[10] have been developed. Remarkably, metal-biocatalytic asymmetric reaction has been served as an extra ordinary tool for synthesis of new chiral compounds which are difficult to obtain by conventional means.

Transition metal complexes catalyzed asymmetric transfer hydrogenation (ATH) has emerged as a powerful and practical technology for synthesis of optically active compounds, which was attributed to its high enantioselectivity, operational simplicity and broad substrate scope.[11] Additionally, biocatalyzed asymmetric hydroxylation accessing to chiral *sec*-alcohols by C–H bond oxidation has been also developed.[12] Given that these two different reactions could be carried out in aqueous medium, so it's possible that two successive chemical reactions in one-pot would be realized by combination of transfer hydrogenation with hydroxylation. Such step-economic transformations are desirable and valuable.

As a continuation of our ongoing interests in the metal catalysis and biocatalysis,[13] herein we disclose an unprecedented catalytic strategy combining Rh-catalyzed ATH with whole cell mediated asymmetric hydroxylation for the construction of a series of chiral 2-subsituted-tetrahydroquinoline-4-ols (Scheme 1).



Scheme 1. Asymmetric synthesis of 2-subsituted-tetrahydroquinoline-4-ols through a combinational catalytic process.

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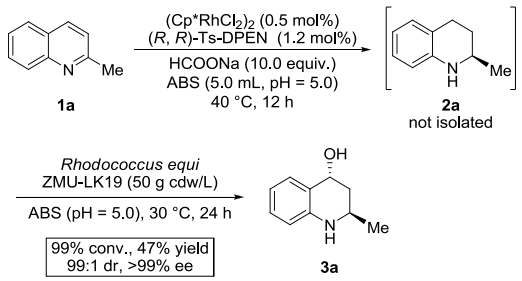
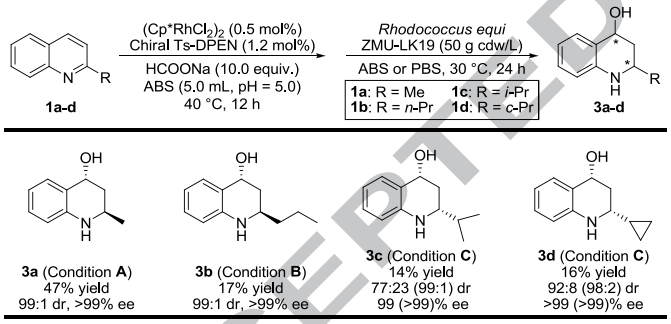
2. Results and discussion



Scheme 2. Enantioselective synthesis of **3a**.

Our studies began with the Rh-catalyzed asymmetric transfer hydrogenation. 10 mol% of metal-complex prepared via treating (*R*, *R*)-Ts-DPEN and $(Cp^*RhCl_2)_2$ in situ was applied to catalyze the ATH of **1a** (0.5 mmol, 100 mM). As a result, excellent conversion (98%) and enantioselectivity (97%) were obtained using HCO_2Na (10.0 equiv.) as hydrogen source in pH 5.0 with the HOAc/NaOAc system (ABS, 2 M, 5.0 mL) at 40 ºC for 12 h (Scheme 2).[14] After that this mixture was diluted to 83.3 mL using ABS buffer (50 mM, pH = 5.0), and then the diluted mixture (83.3 mL) was divided equally into seventeen portions. Subsequently, cell of *Rhodococcus equi* ZMU-LK19 prepared via cell growth and cultivation was suspended in each portion of mixture (4.9 mL) to a cell density of 50 g dcw/L and the mixture was incubated at 30 ºC for 24 h.[13k] To our delight, compound **3a** was obtained in excellent results (99% conv., 47% yield, 99:1 dr and >99% ee). The absolute configuration of **3a** was determined to be (C2*R*, C4*R*) configuration by comparing the HPLC spectra with the literature known compound.[13k]



Scheme 3. Substrate Scope. For the reaction conditions, see the supporting information. The yield was determined by HPLC analysis of the crude reaction mixture using external standard, the ee value and dr value were determined by chiral HPLC analysis. The result in parentheses was obtained after recrystallization from a mixture of petroleum ether and ethyl acetate.

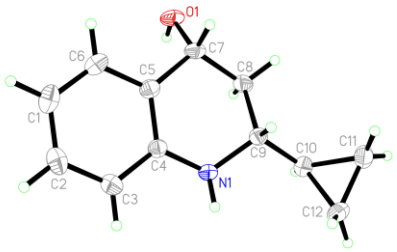
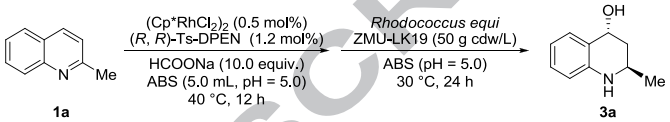


Fig.1. The X-ray structure of compound **3d**.

Under the similar reaction conditions, the generality of this one pot two-step synthesis was subsequently investigated. As shown in Scheme 3, when R was *n*-propyl, the reaction proceeded smoothly and gave the corresponding product **3b** in 17% yield with excellent diastereo- and enantioselectivity (99:1 dr, >99% ee). However, compound **1c** with *i*-Pr group at the C2-position of the quinoline wasn't a good substrate, affording **3c** in moderate results (14% yield, 77:23 dr and 99% ee). Interestingly, the method was compatible with compound **1d**, in which R was represented by cyclopropyl, leading the corresponding chiral tetrahydroquinoline **3d** in 16% yield with 92:8 dr and >99% ee. To our delight, the diastereo- and enantioselectivity of **3c** and **3d** could be further improved after one recrystallization. The absolute configuration of the product **3d** was unambiguously determined as (C2*R*, C4*R*) by X-ray crystallographic analysis with CuKα radiation= 1.54184 Å (Fig. 1),[15] compound **3c** in Scheme 3 was tentatively assigned by analogy.



Scheme **4.**"Metal-Biocatalytic System" on a large scale quantity.

To examine the utility of the asymmetric "metal-biocatalytic system", large scale quantity of **1a** (0.5 mmol, 100 mM) was carried out with 10 mol% of metal-complex in 5.0 mL ABS buffer (2 M, pH = 5.0) at 40 °C for 12 h (Scheme 4). Afterwards, the reaction system was diluted to 83.3 mL using ABS buffer (50 mM, pH = 5.0), and then the diluted mixture (83.3 mL) was directly conducted on *Rhodococcus equi* ZMU-LK19 mediated biotransformation. Delightfully, the corresponding product **3a** also could be obtained in an improved yield up to 73% without any loss of diastereo- (99:1 dr) and enantioselectivity (>99% ee).

3. Conclusions

In conclusion, we have developed a novel combinational catalyzed asymmetric transfer hydrogenation/regio- and enantioselective hydroxylation process with 2-substitute quinolines (**1**), providing chiral 2-subsituted-tetrahydroquinoline-4-ols (**3**) in moderate to excellent results (14-47% yield, 77:23-99:1 dr and 99->99% ee). Satisfactorily, the diastereo- and enantioselectivity of some products could be further improved after recrystallization. The current methodology not only provides a new approach to chiral 2-subsituted-tetrahydroquinoline-4-ols, which are contained in numerous biologically important molecules, but also further illustrates the potentiality of chemoenzymatic multistep one-pot processes. We expect that insights gained from our present study are helpful for opening new opportunities to access chiral 2-subsituted-tetrahydroquinoline-4-ols.

Acknowledgments

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15. See supporting information for the details of X-ray structure of **3d**.

Supplementary Material

Supplementary data for this article can be found in a separate electronic file, including detailed experimental procedures, characterization data, copies of NMR (**1b-d**, **2a**, **3a-d**) and HPLC (**2a**, **3a-d**) as well as the X-ray crystallographic data of **3d**.

Highlights

- Asymmetric “metal-biocatalytic system”.
- One-pot conversion of 2-subsituted-quinolines to 2-subsituted-tetrahydroquinoline-4-ols.
- Synthesis of chiral 2-subsituted-tetrahydroquinoline-4-ols in moderate to excellent results.
- Further illustrates the potentiality of chemoenzymatic multistep one-pot processes.