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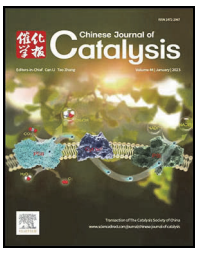

Article

Enzyme-metal-single-atom hybrid catalysts for one-pot chemoenzymatic reactions

Xiaoyang Li [a], Yufei Cao [b], Jiarong Xiong [b], Jun Li [c], Hai Xiao [c,*], Xinyang Li [d], Qingqiang Gou [d], Jun Ge [b,e,f,*]

[a] *State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Nanchang University, Nanchang 330047, Jiangxi, China*
[b] *Key Laboratory for Industrial Biocatalysis, Ministry of Education, Department of Chemical Engineering, Tsinghua University, Beijing 100084, China*
[c] *Department of Chemistry, Tsinghua University, Beijing 100084, China*
[d] *SINOPEC (Beijing) Research Institute of Chemical Industry Co., Ltd., Beijing 122000, China*
[e] *Institute of Biopharmaceutical and Health Engineering, Tsinghua Shenzhen International Graduate School, Shenzhen 518055, Guangdong, China*
[f] *Institute of Biomedical Health Technology and Engineering, Shenzhen Bay Laboratory, Shenzhen 518107, Guangdong, China*

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ABSTRACT

Combining enzymatic and single-metal-atom catalysis is a promising approach for green chemical synthesis. We herein report a one-pot chemoenzymatic cascade reaction to asymmetric synthesize (*R*)-1-(4-biphenyl) ethanol by using the highly active and selective enzyme-metal-single-atom hybrid as the catalyst. We demonstrate that the Pd single atoms anchored lipase (Pd_1/CALB-P) can efficiently drive one-pot cascade reactions in aqueous solution at 30 °C to achieve facile synthesis of chiral biaryl alcohols, which are important pharmaceutical intermediates that traditionally require complex synthesis procedures. The rate of (*R*)-1-(4-biphenyl) ethanol formation catalyzed by Pd_1/CALB-P is more than 30-fold higher than that of the combination of commercial palladium on carbon (Pd/C) and lipase-pluronic conjugate (CALB-P). The enzyme-metal-single-atom hybrid catalyst provides a promising strategy for effectively merging the enzymatic and single-atom catalysis.

1. Introduction

The merging of different types of catalysis including enzymatic, homogeneous, and heterogeneous catalysis is fundamentally important for both understanding catalysis at the atom level and the design of novel hybrid catalysts. The latter points to a direction toward the ideal catalyst that can drive complex tandem reactions efficiently in one-pot manner, and simplify the whole chemical production and separation process [1–4]. Artificial enzymes that merge enzymatic, homogeneous, and heterogeneous catalysis provide such a promising platform for developing novel hybrid catalysts that can operate to achieve the above goal efficiently under ambient conditions.

Directed evolution has been applied to tailor the active site of an enzyme with high efficiency [5,6], and artificial metalloenzymes have been generated by replacing the original metal atom at the active site by a new one [7–13]. These methods are successful but usually only engineer the original active sites of enzymes, and this implies that the engineered enzyme may still be limited to catalyzing a single reaction. Inspired by the atom-

* Corresponding author. E-mail: junge@mail.tsinghua.edu.cn (J. Ge), haixiao@tsinghua.edu.cn (H. Xiao).
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ically dispersed metal catalysts [14–16] that make a bridge between the homogeneous and heterogeneous catalysis, we proposed that anchoring the metal single atoms to the nonactive sites of an enzyme can lead to an artificial enzyme with both its original active site and the new active sites of metal single atoms, merging the enzymatic and single-atom catalysis.

In this study, we report an one-pot reaction to asymmetric synthesize (*R*)-1-(4-biphenyl)ethanol from racemic 1-(4-bromophenyl)ethyl acetate by using the Pd-anchored lipase (Pd_1/CALB-P) as the catalyst. The enzyme-metal-single-atom hybrid catalyst was constructed by a photochemical approach. In the one-pot reaction, the lipase-catalyzed stereo-selective hydrolysis and the Pd-catalyzed C-C coupling were carried out concurrently. The Pd_1/CALB-P catalyst exhibits extremely high activity and stability for the C-C coupling reactions, with the turnover frequency (TOF) for the Sonogashira coupling of iodobenzene and phenylacetylene to be 3.5-fold and 2.3-fold of the heterogeneous Pd nanoparticles (NPs) (Pd/C and PdNPs/CALB-P, respectively), and also surpassing the homogeneous catalyst $Pd(PPh_3)_4$. More importantly, the Pd_1/CALB-P hybrid catalyst delivered the one-pot asymmetric synthesis of chiral biphenyl alcohols in aqueous solution at 30 °C efficiently. The rate for producing (*R*)-1-(4-biphenyl)ethanol catalyzed by Pd_1/CALB-P is more than 30-fold higher than that catalyzed by the commercial Pd/C and CALB-P. This demonstrates that the enzyme-metal-single-atom hybrid catalyst is promising for effectively merging the enzymatic and single-atom catalysis.

2. Experimental

2.1. Catalyst preparation

The Pd-anchored lipase was fabricated using the method reported previously [17]. To prepare the Pd_1/CALB-P (4.0 wt% Pd, 10% CALB), Pd chloride ($PdCl_2$, 22.18 mg, 125 μmol) was first dissolved in dimethyl sulfoxide (5 mL). The CALB-P conjugate (50 mg) was dispersed in dry toluene (5 mL). Benzophenone (30 mmol, 54.7 mg) was added to the CALB-P solution under magnetic stirring at 25 °C. The mixture was then subjected to the removal of dissolved oxygen by bubbling argon for 30 min. To generate free radicals, the CALB-P and BP mixture was irradiated under a xenon lamp with a UV filter (250–380 nm, 27.9 mW cm^{-2}, PLS-SXE300CUV). After 2 min of the UV irradiation, the $PdCl_2$ solution (500 μL) was added dropwise to the mixture for the preparation of Pd_1/CALB-P. The UV irradiation continued for 18 min. The photoexcited benzophenone readily abstracted H from the methylene group of pluronic. The alkyl radicals from pluronic then reacted with $PdCl_2$ to stabilize the Pd single atoms on enzyme [17]. The Pd_1/CALB-P was collected by centrifugation at 4 °C, 10000 r/min for 5 min. After washing with toluene (5 mL × 3), the precipitated Pd_1/CALB-P was then washed by ethanol (5 mL × 3) and resuspended in deionized water (5 mL). The powder of the Pd_1/enzyme-P was obtained by lyophilization and stored at 4 °C.

2.2. Sonogashira coupling reaction catalyzed by Pd_1/CALB-P

Pd_1/CALB-P (0.014 mmol Pd), aryl halide (1.0 mmol), deionized water (2.5 mL) and pyrrolidine (415 μL, 5 mmol) were added to a 5-mL vial. The mixture was stirred at 50 °C for 5 min. Phenylcetylene (1.2 mmol) was subsequently added to this solution and the reaction mixture was stirred at 50 °C. The reaction mixture was then extracted with EtOAc (7.5 mL). For the reuse of Pd_1/CALB-P, the precipitate was separated by centrifugation at 10000 r/min at 4 °C for 5 min. After washing with deionized water (2.5 mL × 3), the precipitate was transferred to a 5-ml vial and resuspended in deionized water (2.5 mL) by magnetic stirring to carry out the next run of catalysis. 1,4-Diphenylbutadiyne could form as the byproduct due to the self-coupling of phenylacetylene in the Sonogashira coupling reactions. The yield and selectivity were determined by GC-MS analysis.

2.3. Synthesis of (R)-1-(4-biphenyl)ethanol by coupling the lipase-catalyzed selective hydrolysis reaction and the Pd-catalyzed Suzuki reaction

4–Dimethylaminopyridine (74.7 mg, 0.611 mmol) and triethylamine (0.062 mL, 0.448 mmol) were added to a stirred solution of racemic 1-(4-bromophenyl)ethanol (82 mg, 0.408 mmol) in dichloromethane (2 mL) at 0 °C under argon atmosphere. Then acetic anhydride (45.8 mg, 0.448 mmol) was added slowly. The mixture was stirred at 0 °C for 2 h and then purified by silica gel column chromatography. The collected fractions were concentrated under vacuum to afford racemic 1-(4-bromophenyl)ethyl acetate. Pd_1/CALB-P (0.48 mg Pd, 6 U CALB), racemic 1-(4-bromophenyl)ethyl acetate (14.6 mg, 0.2 mmol) and potassium carbonate (83 mg, 0.6 mmol) were dissolved in deionized water (2 mL). Conversion of 1 μmol of

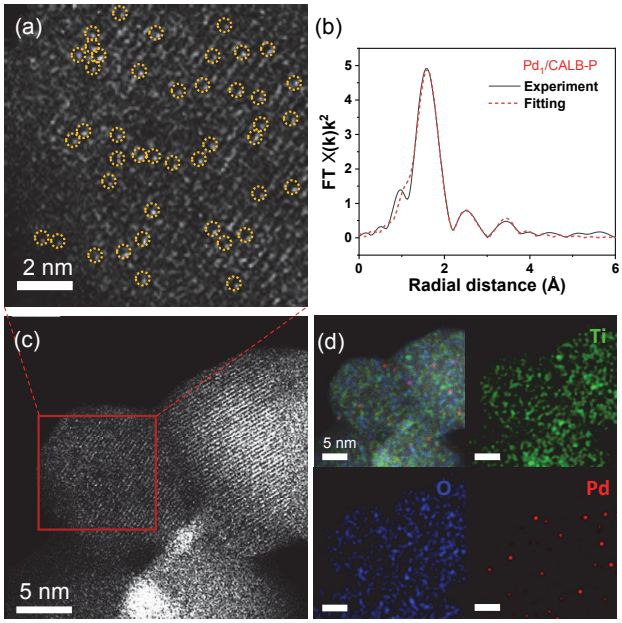


Fig. 1. Characterizations of Pd_1/CALB-P. (a) Magnified AC-STEM image of Pd_1/CALB-P; (b) Comparison of Fourier transforms and fitting results for EXAFS of Pd_1/CALB-P; AC-STEM image of Pd_1/CALB-P (c) and the corresponding elemental mapping (d) for Pd, Ti and O. Pd_1/CALB-P was adsorbed on TiO_2 and then calcined in air at 250 °C for better contrast.

p-NPB per minute in the assay at 25 °C was defined as one enzyme activity (U). The mixture was vigorously stirred at 30 °C for 5 min. To initiate the reaction, phenylcetylene (1.2 mmol) was subsequently added to this solution and the reaction mixture was stirred at 30 °C. The reaction was quenched with HCl solution (1.5 mol/L, 2 mL) and then the product was separated by extraction with ethyl acetate. The byproducts that may formed in this reaction is shown in Fig. S10. The yield and selectivity were determined by GC-MS analysis. The *ee* value of (*R*)-1-(4-biphenyl) ethanol was calculated by chiral HPLC analysis. The condition was as follows, column: CHIRALCEL® OD 250 × 4.6 mm, *Φ* 10 μm; flow: 0.5 mL/min; *λ*: 254 nm; mobile phase: 10% (*v*/*v*) isopropanol in hexane and temperature: 25 °C.

3. Results and discussion

The Pd_1/CALB-P was synthesized by anchoring Pd single atoms on the lipase-pluronic conjugate (CALB-P) *via* a photochemical method. In a typical synthesis, the carbon radicals were produced on the polymer chain under ultraviolet light (UV) treatment, which bind to the Pd atoms together with amino acids of enzyme surface to form a stable structure. As shown in Fig. 1(a), the brighter dots of the aberration-corrected scanning transmission electron microscopy (AC-STEM) image of Pd_1/CALB-P represent Pd atoms. And no obvious Pd clusters or nanoparticles was observed, demonstrating that the Pd atoms were highly dispersed on the CALB-P conjugate (Figs. 1(a), 1(c)). The uniform distribution of Pd atoms over the carrier was confirmed by the elemental mapping (Fig. 1(d)). The extended X-ray absorption fine structure spectroscopy (EXAFS) (Fig. 1(b)) and the corresponding simulation data (Table S1) showed that there was a notable peak at ~1.6 Å from the Pd–O or Pd–C coordination and no Pd–Pd bond was detected in Pd_1/CALB-P. The possible sites for anchoring Pd single atoms on enzyme were investigated by density functional theory (DFT) calculations and molecular dynamics (MD) simulation, showing that Asp223 is the most possible residue that anchors the Pd single atom on the active site of lipase [17]. The estimated distance between the Pd single atom and active site (Ser105) was around 1.3 nm.

The activity of Pd on the enzyme-metal-single-atom hybrid

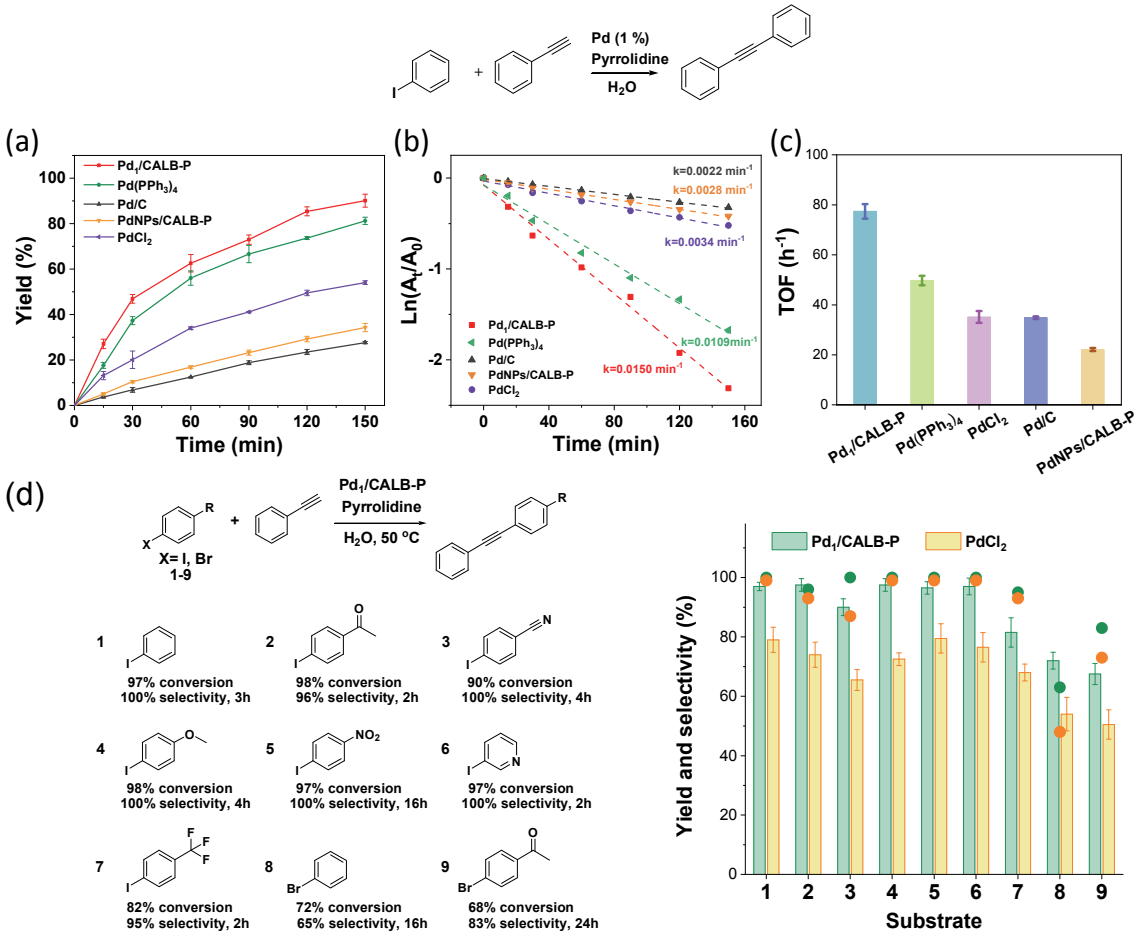


Fig. 2. Catalytic performance of Pd in C–C coupling reactions. (a) Conversion versus reaction time. (b) $\ln(A_t/A_0)$ versus reaction time, A_t and A_0 stand for the concentration of iodobenzene at the intervals and at the initial stage; (c) Comparison of TOF for the Pd_1/CALB-P, $PdCl_2$, Pd/C, $Pd(PPh_3)_4$ and PdNPs/CALB-P in the Sonogashira reactions using iodobenzene and phenylacetylene as the substrates. (d) Reaction scheme and the performance of Pd_1/CALB-P in the Sonogashira coupling of phenylacetylene and aryl halides. Yields (bars) and selectivities (circles) of products in Sonogashira couplings by using aryl halides (entries 1–9) as the substrates. Green color: Pd_1/CALB-P, orange color: $PdCl_2$. Each data point and error bar represent the mean and standard deviation from at least three independent measurements.

catalyst was evaluated in the C–C coupling reaction. The Sonogashira coupling of iodobenzene with phenylacetylene was first tested in aqueous solution at 50 °C using pyrrolidine as the base. The turnover frequency (TOF) of Pd_1/CALB-P (Pd mass loading is 4.0%) displayed 2.3-fold, 3.5-fold and 2.2-fold of the heterogeneous catalysts Pd/C, PdNPs/CALB-P and the precursor $PdCl_2$, respectively (Fig. 2(c)). The activity of Pd_1/CALB-P in aqueous solution even surpassed the homogeneous catalyst $Pd(PPh_3)_4$ under the optimized condition. The Pd_1/CALB-P proved to be a very efficient catalyst, giving a reaction rate constant (k) of 0.015 min^{-1} towards diphenylacetylene (Fig. 2(b)). And the conversion of iodobenzene was 97% after 3 h at 50 °C. In contrast, $PdCl_2$ displayed a low reaction rate (k = 0.0034 min^{-1}, 79% conversion after 3 h at 50 °C) (Fig. 2(d) and Table S4). The Pd_1/CALB-P exhibited excellent reusability as well, still giving 95% conversion of iodobenzene and remained more than 93% residual activity after ten batches of reuse (Fig. S4). In contrast, only 60% conversion of iodobenzene was obtained after ten batches of reusing the $PdCl_2$/CALB-P mixture.

To further demonstrate the high efficiency of the Pd-anchored hybrid enzymes in Sonogashira coupling reactions, the board scope of substrates was examined and shown in Fig. 2(d) and Table S4. For aryl iodides bearing an electron-withdrawing group, such as $-COCH_3$, $-CN$, $-NO_2$, $-CF_3$, Pd_1/CALB-P afforded good yields to the desired products (81.5%–97.5%) within 2–16 h, which outperformed the $PdCl_2$ counterpart under the same condition. It is noteworthy that for the aryl iodide with an electron-donating group $-OCH_3$, Pd_1/CALB-P also gave an excellent yield of 97.5% within 4 h. In the case of the heteroaromatic compound, 97% yield was obtained within 2 h. We further tested the coupling of aryl bromides which are more difficult to be activated for the Sonogashira coupling reactions compared to the aryl iodides. To our delight, Pd_1/CALB-P gave 72% yield within 16 h and 67.5% yield within 24 h in the reactions using bromobenzene and 4'-bromoacetophenone as the substrates, respectively.

The mechanism for the Sonogashira reaction catalyzed by Pd_1/CALB-P was investigated by DFT calculations with a model catalyst (for more details of model construction, see supporting information). Although the copper-free Sonogashira cross-coupling has been extensively used to form *sp*(2)-*sp* carbon-carbon bond in organic synthesis, its mechanism remains elusive and debatable [18]. We speculate that the Pd^{II}/Pd^{IV} redox manifold is plausible in the catalytic process. As shown in Fig. 3, Complex **1** undergoes substitution of PhI for an oxygen on the carboxyl group to form **2**, which brings the Ph–I bond into contact with the Pd^{II} center to facilitate the ensuing oxidative addition (OA). The OA step takes place through the transition state **3-ts**, leading to a six-coordinate Pd^{IV} complex with an activation free energy of 16.60 kcal/mol. Subsequently, phenylacetylene substitutes iodide through the π-system of its H–C≡C group. This substitution facilitates the deprotonation by pyrrolidine to form the precursor **7** of reductive elimination. Direct deprotonation of phenylacetylene is unattainable with a high free energy increase (Fig. S7). Complex **7** then undergoes reductive elimination at the Pd^{IV} center via transition state **8-ts** to form a new carbon–carbon bond, and the catalytic species **1** recovers. The energy barriers and energy changes of each step of the reaction were reasonable. This overall free energy landscape was similar to the prior reports of Pd catalyzed C–C coupling reactions [19]. Similar Pd^{II}/Pd^{IV} mechanism has been proposed in organometallic reactions [20, 21]. A previous theoretical study also showed the Pd^{II}/Pd^{IV} redox manifold in a Pd-catalyzed C–C coupling reaction [22].

Due to the high activity of atomically distributed Pd active centers on the enzyme-polymer conjugate, the hybrid enzyme with two types of different active sites can be utilized to drive traditional multi-step chemo-enzymatic reactions in one-pot manner. For example, chiral biaryl alcohols are valuable building blocks for the construction of enantiomerically pure pharmaceuticals, which are generally synthesized by multi-step chemical [23] or chemoenzymatic process [24]. By using Pd_1/CALB-P hybrid enzyme as the catalyst, we achieved a new one-pot reaction to produce (*R*)-1-(4-biphenyl)ethanol from racemic 1-(4-bromophenyl)ethyl acetate (Scheme 1). In this process, the lipase-catalyzed stereo-selective hydrolysis reac-

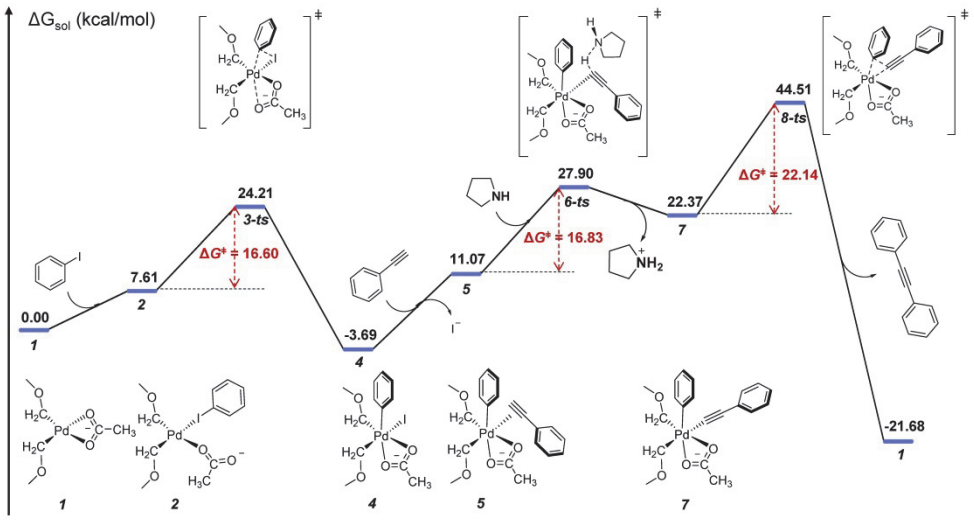
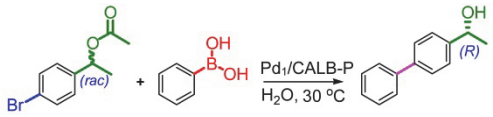


Fig. 3. Calculated free energy profile of the Sonogashira reaction pathway catalyzed by the model catalyst for Pd_1/CALB-P.



Scheme 1. Synthesis of (*R*)-1-(4-biphenyl)ethanol by one-pot chemoenzymatic reaction.

Table 1
Productivity and selectivity of Pd_1/CALB-P for the synthesis of (*R*)-1-(4-biphenyl)ethanol.

Catalyst	Yield (%)	Selectivity (%)	*ee* (%)	Rate [d]
Pd_1/CALB-P [a]	48	96	99.7	25
$Pd(PPh_3)_4$+CALB-P [a]	3	95	98.5	1.7
PdNPs/CALB-P [a]	6	90	99.5	3.1
Pd/C+CALB-P [a]	1.2	92	99.9	0.8
PdNPs/CALB-P [b]	14	84	99.5	3.6
Pd/C+CALB-P [c]	8	69	98.4	1.2

Conditions: Pd_1/CALB-P (0.48 mg Pd, 6 U CALB), racemic 1-(4-bromophenyl)ethyl acetate (0.2 mmol), potassium carbonate (0.6 mmol), and phenylcetylene (1.2 mmol) in water at 30 °C for 4 h. The amounts of Pd used in the reactions were [a] 2.3 μmol, [b] 4.6 μmol, and [c] 6.9 μmol. [d] Rate of (*R*)-1-(4-biphenyl)ethanol formation per gram of Pd.

tion (Figs. S13 and S14) and the Pd-catalyzed C–C coupling reaction were carried out concurrently. Within 4 hours, the Pd_1/CALB-P-catalyzed reaction reached 48% yield of (*R*)-1-(4-biphenyl)ethanol, 96% selectivity and an enantiomeric excess (*ee*) value of 99.7%, at the substrate concentration of 100 mmol/L. Hot-filtration is an efficient way to confirm whether the catalysis follow a homogeneous or heterogeneous pathway. The Pd_1/CALB-P catalyst was separated from the reaction mixture follow 4 h of the chemoenzymatic reaction. The filtrate showed that only 0.05 ppm Pd had leached into the solution and the reaction did not proceed when a new batch of substrates was added to the filtrate, indicating that the reaction was intrinsically catalyzed by a heterogeneous catalyst of Pd_1/CALB-P. In contrast, only yields of 3% and 6%, selectivity of 95% and 90% were obtained when using the combination of $Pd(PPh_3)_4$ and CALB-P, and PdNPs/CALB-P as the catalyst. In the case of using the combination of Pd/C and CALB-P, the C–C coupling reactions can hardly occur at the same condition of 2.3 μmol Pd amount (condition a in Table 1), due to the low activity of Pd/C. Increasing the amount of Pd catalysts (conditions b, c in Table 1) can result in some extent of reaction but still unsatisfactory reaction rate. The rate of product formation when using Pd_1/CALB-P as the catalyst was 25 mmol h^{-1} g_{Pd}^{-1}, which is 13.7-fold, 30.3-fold and 7.0-fold higher than that of the combination of $Pd(PPh_3)_4$ and CALB-P, Pd/C and CALB-P, and PdNPs/CALB-P, respectively (Table 1). The superior catalytic performance and selectivity of the Pd_1/CALB-P is contributed to the atomically dispersed form of Pd and the neighboring of enzymatic and single-Pd-atom active sites in the hybrid enzyme. Since the short distance between the Pd single atom and active site (around 1.3 nm), Pd single atom and the active site of lipase is expected to generate proximity effect. The increase in the local concentration of intermediates may lead to the high activity of Pd_1/CALB-P in the chemoenzymatic cascade reaction.

4. Conclusions

In summary, we have developed a new one-pot reaction to asymmetric synthesize (*R*)-1-(4-biphenyl)ethanol by using the Pd-anchored lipase in which Pd atoms uniformly dispersed on the lipase-pluronic conjugat as the catalyst. The Pd_1/CALB-P catalyst delivers a TOF 3.5-fold of commercial Pd/C for the Sonogashira C–C coupling reaction, and no decay in activity was observed for 10 cycles of reuse. DFT calculations revealed a Pd^{II}/Pd^{IV} catalytic cycle in the mechanism for the Sonogashira reaction catalyzed by Pd_1/CALB-P. More importantly, this hybrid enzyme Pd_1/CALB-P can efficiently catalyze a new one-pot cascade reaction at 30 °C in aqueous solution to synthesize the chiral biaryl alcohols, and the production rate exceeds that catalyzed by the commercial Pd/C and CALB-P by a factor of 30. The enzyme-metal-single-atom hybrids make a bridge between the enzymatic and single-atom catalysis and have a wide range of applications in organic synthesis.

Notes

The authors declare no competing interests.

Electronic supporting information

Supporting information is available in the online version of this article.

References

[1] A. Wang, J. Li, T. Zhang, *Nat. Rev. Chem.,* **2018**, 2, 65–81.
[2] Z. C. Litman, Y. Wang, H. Zhao, J. F. Hartwig, *Nature,* **2018**, 560, 355–359.
[3] R. Ye, J. Zhao, B. B. Wickemeyer, F. D. Toste, G. A. Somorjai, *Nat. Catal.,* **2018**, 1, 318–325.
[4] K. K. Sakimoto, A. B. Wong, P. Yang, *Science,* **2016**, 351, 74–77.
[5] F. H. Arnold, *Acc. Chem. Res.,* **1998**, 31, 125–131.
[6] F. H. Arnold, A. A. Volkov, *Curr. Opin. Chem. Biol.,* **1999**, 3, 54–59.
[7] P. Dydio, H. M. Key, A. Nazarenko, J. Y.–E. Rha, V. Seyedkazemi, D. S. Clark, J. F. Hartwig, *Science,* **2016**, 354, 102–106.
[8] E. N. Mirts, I. D. Petrik, P. Hosseinzadeh, M. J. Nilges, Y. Lu, *Science,* **2018**, 361, 1098–1101.
[9] S. Studer, D. A. Hansen, Z. L. Pianowski, P. R. E. Mittl, A. Debon, S. L. Guffy, B. S. Der, B. Kuhlman, D. Hilvert, *Science,* **2018**, 362, 1285–1288.
[10] T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science,* **2012**, 338, 500–503.
[11] W. J. Song, F. A. Tezcan, *Science,* **2014**, 346, 1525–1528.
[12] O. Pàmies, M. Dieguez, J. E. Bäckvall, *Adv. Synth. Catal.,* **2015**, 357, 1567–1586.
[13] I. Willner, R. Baron, B. Willner, *Adv. Mater.,* **2006**, 18, 1109–1120.
[14] B. Qiao, A. Wang, X. Yang, L. F. Allard, Z. Jiang, Y. Cui, J. Liu, J. Li, T. Zhang, *Nat. Chem.,* **2011**, 3, 634–641.
[15] L. Liu, A. Corma, *Chem. Rev.,* **2018**, 118, 4981–5079.
[16] P. Liu, Y. Zhao, R. Qin, S. Mo, G. Chen, L. Gu, D. M. Chevrier, P. Zhang, Q. Guo, D. Zang, B. Wu, G. Fu, N. Zheng, *Science,* **2016**, 352, 797–800.

Graphical Abstract

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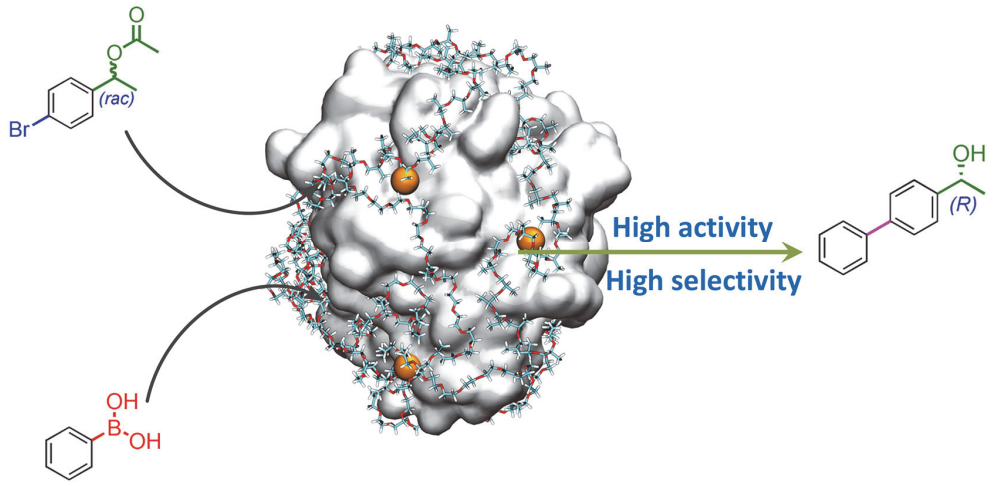
Enzyme-metal-single-atom hybrid catalysts for one-pot chemoenzymatic reactions

Xiaoyang Li, Yufei Cao, Jiarong Xiong, Jun Li, Hai Xiao *, Xinyang Li, Qingqiang Gou, Jun Ge *
Nanchang University; Tsinghua University;
SINOPEC (Beijing) Research Institute of Chemical Industry Co., Ltd.; Shenzhen Bay Laboratory ;



An one-pot chemoenzymatic cascade reaction to synthesize chiral alcohol realized by using the highly active and selective enzyme-metal-single-atom hybrid as the catalyst. The enzyme-metal-single-atom hybrid catalyst provides a promising strategy for effectively merging the enzymatic and single-atom catalysis.

[17] X. Li, Y. Cao, K. Luo, L. Zhang, Y. Bai, J. Xiong, R. N. Zare, J. Ge, *Nat. Commun.*, **2022**, 13, 2189.
[18] R. Chinchilla, C. Nájera, *Chem. Soc. Rev.*, **2011**, 40, 5084–5121.
[19] Z. Chen, E. Vorobyeva, S. Mitchell, E. Fako, M. A. Ortuño, N. López,S. M. Collins, P. A. Midgley, S. Richard, Gianvito Vilé, J. Pérez-Ramírez, *Nat. Nanotechnol.*, **2018**, 13, 702–707.
[20] X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.*, **2009**, 48, 5094–5115.
[21] G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.*, **2013**, 52, 11726–11743.
[22] Y. Dang, S. Qu, J. W. Nelson, H. D. Pham, Z. X. Wang, *J. Am. Chem. Soc.*, **2015**, 137, 2006–2014.
[23] X. Dong, A. Weickgenannt, M. Oestreich, *Nat. Commun.*, **2017**, 8, 15547.
[24] E. Burda, W. Hummel, H. Groeger, *Angew. Chem. Int. Ed.*, **2008**, 47, 9551–9554.

酶-金属单原子复合催化剂在一锅法生物-化学反应的应用

黎晓阳[a], 曹宇飞[b], 熊佳容[b], 李 隽[c], 肖 海[c,*], 李昕阳[d], 苟清强[d], 戈 钧[b,e,f,*]
[a]南昌大学食品学院, 食品科学与技术国家重点实验室, 江西南昌330047
[b]清华大学化工系, 工业生物催化教育部重点实验室, 北京100084
[c]清华大学化学系, 北京100084
[d]中石化(北京)化工研究院有限公司, 北京122000
[e]清华深圳国际研究生院生物医药与健康工程研究所, 广东深圳518055
[f]深圳湾实验室生物医药健康技术与工程研究所, 广东深圳518107

摘要: 酶催化与金属单原子催化结合, 理论上可开发众多新的绿色化学合成反应, 是催化科学的一个重要研究前沿方向. 酶-金属单原子复合催化剂兼具酶和金属单原子催化剂的高效、高立体选择性等优点. 目前已成功构建的单原子分散金属催化剂的载体一般为刚性的无机载体, 利用柔性蛋白分子作为载体制备单原子分散金属催化剂的技术瓶颈问题在于蛋白分子具有柔性、构象易变的特点, 并且氨基酸残基与金属原子之间的相互作用力较弱, 蛋白分子表面的氨基酸残基难以与金属单原子稳定结合. 针对这样一个关键技术瓶颈问题, 我们建立了酶-金属单原子复合催化剂的光化学合成方法.

本文研究酶-金属单原子复合催化剂在生物-化学一锅级联反应合成联苯类手性醇中的催化性能. 联苯类手性醇是手性药物的重要中间体, 通常通过多步化学法或生物-化学级联法制备. 相比于多步化学法, 利用生物-化学级联反应制备联苯类手性化合物具有反应条件温和、选择性高、环境友好等优点. 采用光化学法合成脂肪酶-钯单原子复合催化剂(Pd_1/CALB-Pluronic), 通过球差矫正扫描透射电镜和扩展X射线吸收精细结构表征复合催化剂的形貌. 首先研究了Pd_1/CALB-Pluronic复合催化剂中单原子分散Pd催化的C–C偶联反应催化效率, 然后考察了它在生物-化学一锅级联反应中的催化性能; 发现该催化剂在C–C偶联反应中具有比常用的Pd均相催化剂和Pd非均相催化剂更好的活性. 在碘苯和苯乙炔的Sonogashira反应中, Pd_1/CALB-Pluronic的TOF值大于均相催化剂$Pd(PPh_3)_4$, 是多相商业催化剂Pd/C的3.5倍. Pd_1/CALB-Pluronic重复使用10次后, 活性仍保留97%, 具有很好的稳定性. 通过DFT计算分析催化反应路径, 提出了Pd_1/CALB-Pluronic复合催化剂的2价Pd单原子在Sonogashira反应中可能存在Pd^{II}/Pd^{IV}催化机理.

本文开发了(*R*)-1-(4-联苯)乙醇的生物-化学一锅级联反应合成新路线: Pd_1/CALB-Pluronic复合催化剂在30 °C的水溶液中催化(±)-1-(4-溴苯基)乙酸乙酯和苯硼酸反应生成(*R*)-1-(4-联苯)乙醇. 在该过程中, CALB催化的立体选择性水解反应和Pd单原子催化的C–C偶联反应同时进行. 其中, CALB催化(±)-1-(4-溴苯基)乙酸乙酯中的*R*型异构体水解为(*R*)-1-(4-溴苯基)乙醇, Pd单原子催化(*R*)-1-(4-溴苯基)乙醇与苯硼酸进行Suzuki反应生成(*R*)-1-(4-联苯)乙醇. Pd_1/CALB-Pluronic复合催化剂在30 °C下催化生物-化学一锅级联反应合成(*R*)-1-(4-联苯)乙醇, 其催化效率是商业催化剂Pd/C和CALB-Pluronic催化剂组合的31.3倍.

关键词: 化学-酶催化反应; 酶-金属复合催化剂; 单原子催化剂; 协同催化; 手性醇

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*通讯联系人. 电子信箱: junge@mail.tsinghua.edu.cn (戈钧), haixiao@tsinghua.edu.cn (肖海).

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