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Double Enzyme-Catalyzed One-Pot Synthesis of Enantiocomplementary Vicinal Fluoro Alcohols

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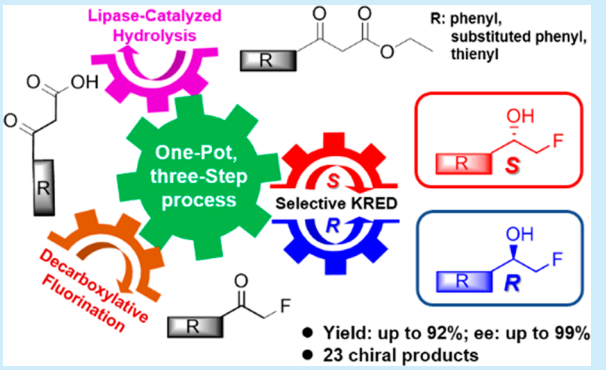
ABSTRACT: A double-enzyme-catalyzed strategy for the synthesis of enantiocomplementary vicinal fluoro alcohols through a one-pot, three-step process including lipase-catalyzed hydrolysis, spontaneous decarboxylative fluorination, and subsequent ketoreductase-catalyzed reduction was developed. With this approach, β-ketonic esters were converted to the corresponding vicinal fluoro alcohols with high isolated yields (up to 92%) and stereoselectivities (up to 99%). This new cascade process addresses some issues in comparison with traditional methods such as environmentally hazardous reaction conditions and low stereoselectivity outcome.



The incorporation of fluorine atoms into organic molecules has a profound effect on their physical, chemical, and biological properties, which play important roles in agrochemical, pharmaceutical, and materials science.[1] In particular, vicinal fluoro alcohols are an important class of fluorine compounds which can be used as the building blocks of natural product analogues or drug targets, such as steroids or carbohydrates.[2] Thus, the development of general and efficient methods to achieve fluoro alcohols has received considerable attention and significant effort in the past decades.

Traditional chemical methods to produce fluoro alcohols such as fluorination of alkenes or meso-epoxides usually exhibit limited stereoselectivity, which limits the scope of application.[3] To achieve chiral vicinal fluoro alcohols, the most effective strategy is the reduction of α-fluoro ketones by keto reductases (KRED).[4] However, the requirement of prerequisite preparation of α-fluoro ketones relies heavily on organometallic catalysts or hazardous strong oxidants, suffering from high costs and environmental pollution.[5] Deng and co-workers have developed an alternative process for the synthesis of α-fluoro ketones through the decarboxylative fluorination of β-ketonic acids catalyzed by the phase-transfer catalyst in aqueous media.[6] However, as substrates, β-ketonic acids need to be prepared just before its experimental application due to their easy decomposition into ketones.[7] Because of these limitations of existing pathways, it is highly desirable to find an efficient, general, and environment friendly strategy to achieve chiral vicinal fluoro alcohols.

Cascade reaction catalyzed by multiple enzymes or enzymes in combination with chemical catalysts is an alternative strategy to achieve chiral compounds, which has gained more attention in recent years.[8] These multistep processes have been conducted under mild reaction conditions without the isolation of intermediate compounds. For example, Turner and co-workers have developed several multienzyme cascade processes to convert alcohols into valuable products, like enantiopure amines, substituted D-tryptophans, and enantiomerically pure 2,5-disubstituted pyrrolidine alkaloids.[9] Zhao and Hartwig have reported a cascade process to generate valuable enantioenriched products combing the isomerization catalyzed by photocatalysts and the reduction of carbon−carbon double bonds by ene-reductases.[10] In this study, we describe a novel double-enzyme-catalyzed cascade reaction providing chiral vicinal fluoro alcohols from β-ketonic esters in one-pot (Scheme 1). This process consists of three steps: the β-ketonic esters are initially hydrolyzed by lipase to generate β-ketonic acids in situ. Subsequently, the β-keto acids undergo decarboxylative fluorination with Selectfluor reagent through a spontaneous process. After that, the intermediate fluoro ketones can be finally reduced by the added (*R*)- or (*S*)-selective ketoreductase respectively, to achieve chiral vicinal fluoro alcohols with high optical purity and specified configurations.

In the cascade process, the major challenge is the compatibility of enzymes and chemical catalysts. In this

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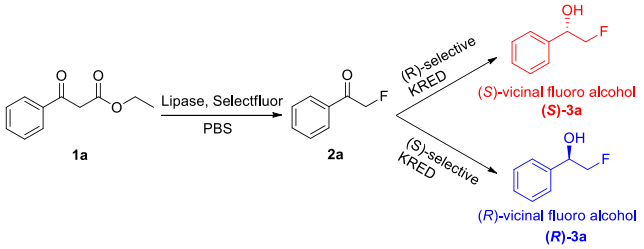
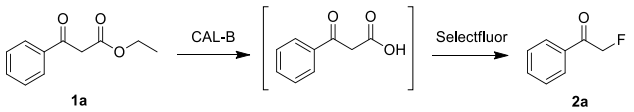
Scheme 1. Combination of Lipase and KRED in a Cascade Reaction



study, the Selectfluor reagent with strong oxidation tends to denature the enzymes through probable disruption of the tertiary protein structure.[11] Therefore, initial study was implemented to determine the feasibility of the one-pot transformation in combination of enzymatic hydrolysis and decarboxylative fluorination. We selected the decarboxylative fluorination of ethyl 3-oxo-3-phenylpropanoate (**1a**) providing 2-fluoro-1phenylethan-1-one as a model reaction. After screening various reaction parameters, we obtained the desired product **2a** in a good yield (92%) (Table 1, entry 1; see the

Table 1. Reaction Optimization for the Cascade Process Combining Enzymatic Hydrolysis and Decarboxylative Fluorination[a]



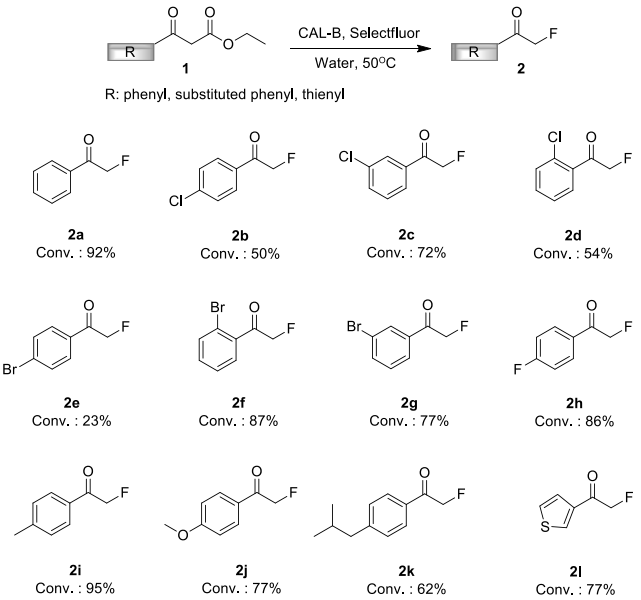
entry	variation from standard conditions	2a[b] (%)
1	none	92
2	100 mM PBS instead of 200 mM PBS	55
3	benzoyl acetic acid instead of 1a	24
4	no CAL-B	7
5	no Selectfluor	0
6	ultrapure water instead of 200 mM PBS	2
7	37 °C instead of 50 °C	48

[a]Reaction conditions: 0.05 mmol of ethyl 3-oxo-3-phenylpropanoate (**1a**) was dissolved in 2 mL of buffer (200 mM PBS, pH = 7.4), then 200 μL of CAL-B (5000 U/mL) and Selectfluor (1.2 equiv) were added to the above mixture and shaken for 12 h at 50 °C. [b]Conversions were determined by chiral GC.

Supporting Information for details). No other additives were needed in this transformation. Omission of CAL-B or Selectfluor reagent resulted in a substantial decrease of conversions (entries 4 and 5). The use of low concentration of PBS buffer (100 mM) or ultrapure water furnished a significant loss in reaction conversions or even failed to initiate the reaction (entries 2 and 6). This observation supported that the mechanism of the decarboxylative fluorination was a base-catalyzed process.[6] Lastly, experiments with different temperatures confirmed 50 °C was the best in this new cascade reaction (entry 7).

With optimal reaction conditions in hand, we next aimed to define the scope of the β-ketonic ester precursors. As illustrated in Scheme 2, the cascade reaction proceeded smoothly not only for the β-ketonic esters bearing an electron-withdrawing group on the aryl ring but also for those substrates having an electron-donating substituent. In particular, the substrates with a F, Cl, or Br substituent on the

Scheme 2. Substrate Scope of for the Lipase-Catalyzed Synthesis of α-Fluoro Ketones[a,b]



[a]Reaction conditions: 0.05 mmol of β-ketonic ester (**1**) was dissolved in 2 mL of buffer (200 mM PBS, pH = 7.4), then 200 μL of *Candida antarctica* lipase B (CAL-B, 5000 U/mL) and Selectfluor (1.2 equiv) were added into the above mixture and shaken for 12 h at 50 °C. [b]Conversions were determined by chiral GC.

aromatic ring were also tolerated in the cascade process, which could not occur in the previous study using β-ketonic acids as starting materials.[6] Heteroaromatic substituted β-ketonic esters also can be accepted to provide the corresponding α-fluoro ketones in moderate yield.

The concentration−reaction time curves of lipase-catalyzed synthesis of fluorination products were investigated and shown in Figure 1. During the whole process, the residual β-ketonic

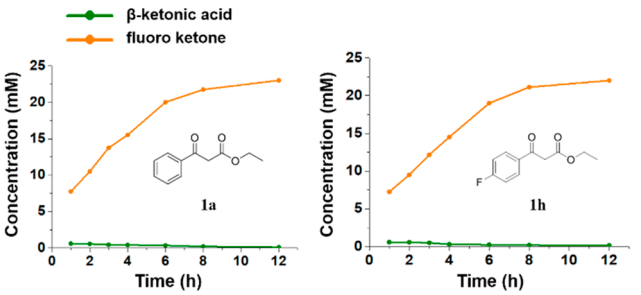


Figure 1. Reaction time curves of lipase-catalyzed synthesis of α-fluoro ketones.

acid remained at a steadily low concentration level while the yield of **2a** was increasing continuously. The same result was observed for the *p*-fluoride-substituted substrate (**1h**). Therefore, during the reaction, the concentration of Selectfluor reagent remained in large excess in comparison with β-ketonic acid. The excess Selectfluor reagent might shift the equilibrium to the right and promote the formation of fluorination products, especially for those products with an electron-withdrawing substituent on the aromatic ring which cannot be obtained in the previous reported decarboxylative fluorination of β-ketoacids.[6]

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Next step was to implement the feasibility of reduction by KRED in this one-pot protocol. Carbonyl reductase from *Kluyveromyces thermotolerans* (KtCR) was first chosen as a model enzyme for the optimization of the cascade reaction, which was identified with satisfactory (*R*)-selectivity for acetophenone.[12] The initial study was performed by adding KtCR and other cofactors (including $NADP^+$) in one pot after decarboxylative fluorination. Glucose dehydrogenase (GDH) was also added to recycle the cofactor. To our delight, the cascade system in one-pot was proceeded successfully with high total conversion (92%) and excellent (*S*)-stereoselectivity (ee = 99%, the *R*/*S* assignment was changed in accordance with the Cahn−Ingold−Prelog priority rules).

However, the high costs of the cofactors motivated us to seek a more economical way to carry out this transformation. The whole-cell reaction system was chosen to overcome this limitation by regenerating the NADPH intracellular.[13] Thus, we performed this whole-cell transformation (Figure 2) by

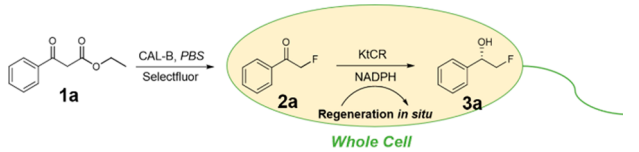


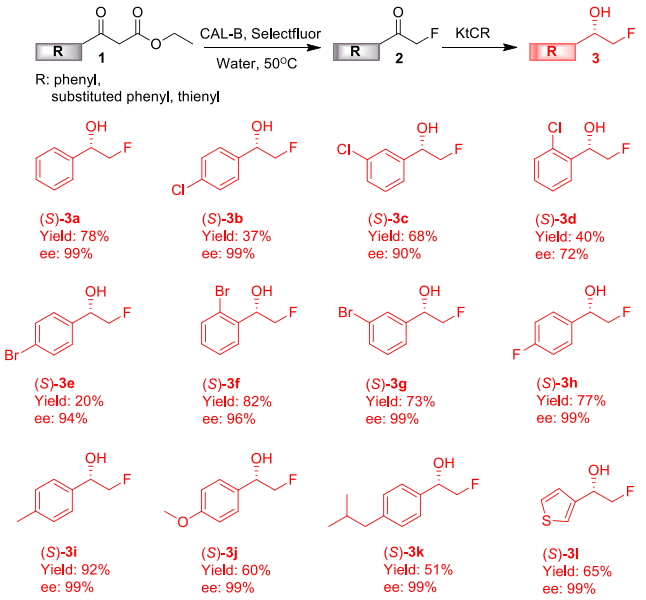
Figure 2. Whole-cell reaction system to produce chiral vicinal fluoro alcohols.

adding 10 mL of the culture medium of KtCR (OD600 ≈ 6) into the above-mentioned mixture of **1a**. As expected, **2a** was able to permeate the cell membrane, and the whole-cell one-pot reaction successfully provided the product (*R*)-**3a** in excellent total conversion (92%) and selectivity (99%).

Based on the successful one-pot process of **1a**, a range of *β*-ketonic esters were subjected to the hydrolysis, fluorination and reduction step by step to yield chiral vicinal fluoro alcohols. To assess the scalability of these cascade process, we performed 200 mg scale reactions for all tested substrates (**1a**−**1l**), and isolated yields were obtained for comparison (Scheme 3, Table S1). It can be found that both electron-donating and electron-withdrawing group substituted substrates afforded the corresponding products in acceptable isolated yields (20−92%) and high stereoselectivity (99%). Among them, **3i** gave the best result with 92% isolated yields and 99% ee, while **3e** with the lowest yield. Actually, for all tested substrates, the conversions of the second step (enzymatic reduction) were relatively high (Tables S1 and S2), while their activities in the first step of the lipase-catalyzed hydrolysis and fluorination were completely different. For example, the conversion of **1e** in the lipase-catalyzed hydrolysis and fluorination was only 23%, resulting in the lowest isolated yield (20%) for **3e**. Interestingly, the bulky *β*-ketonic esters (**1k**) and thienyl-substituted substrate (**1l**) were also tolerated with this method to give the (*S*)-isomer of **3k** and **3l** with excellent enantioselectivity (ee = 99%).

The (*S*)-selective KRED could be replaced by an (*R*)-selective KRED; thus, chiral vicinal fluoro alcohols with tailor-made steteoselectivity were achieved. By using the NADPH-dependent aldo-keto reductase from *Bacillus* sp. ECU0013 (YtbE)[14] as the KRED, most of the tested aromatic carboxylic esters could also be converted into corresponding (*R*)-alcohols with acceptable isolated yields and high ee values through the above one-pot, three-step process. The influence of substrate

Scheme 3. Substrate Scope of the Cascade Process for the Production of (*S*)-Vicinal Fluoro Alcohols[a]



[a]Reaction conditions: 1 mmol of *β*-ketonic ester (**1**) and Selectfluor (30 mM, 1.2 equiv) were dissolved in 40 mL of buffer (200 mM PBS, pH = 7.4) containing 4 mL of *Candida antarctica* lipase B (CAL-B, 5000 U/mL). The reaction mixture was shaken vigorously at 50 °C for 12 h. Then 400 mL of whole-cell culture of KtCR (resuspended in 50 mM sodium phosphate buffer, pH 6.5) with glucose (100 mmol) was added into the above mixture and shaken at 30 °C overnight. All yields are isolated yields of products. The ee values were determined by chiral GC.

structures on the CAL-B/YtBE-catalyzed cascade process was also similar to that of the CAL-B/KtCR system. Compound **1i** provided a better result than other substrates, and the isolated yield of **3e** was still the lowest because of the poor conversion in the first step of lipase-catalyzed hydrolysis and fluorination. Notably, YtbE showed the same selectivity preference for **3f** as that of KtCR, while they were opposite in the cases of other products, implying the distinct binding or recognition mechanism for **3f**. For thienyl-substituted substrate (**1l**), YtbE showed good activity, but the selectivity is very poor. These results shown in both Scheme 3 and 4 documented the synthetic utility of double enzyme-catalyzed one-pot process for the preparation of enantiocomplementary vicinal fluoro alcohols.

In summary, we have developed a one-pot, three-step cascade process combining enzymatic hydrolysis, decarboxylative fluorination, and KRED-catalyzed reduction to achieve enantiocomplementary vicinal fluoro alcohols. A series of *β*-ketonic esters can be successfully converted into the corresponding chiral vicinal fluoro alcohols with either (*R*)- or (*S*)-configuration in accordance with the selectivity of the KRED used. This one-pot cascade process was performed in the aqueous phase under moderate conditions without the separation of intermediates. A whole-cell system was implemented to regenerate NADPH in situ to make the transformation proceed in an economical way. All these advantages should enable chemoenzymatic transformations that display great potential in green synthetic chemistry and sustainable development. However, in the current scale-up reactions of double enzyme-catalyzed one-pot process, the

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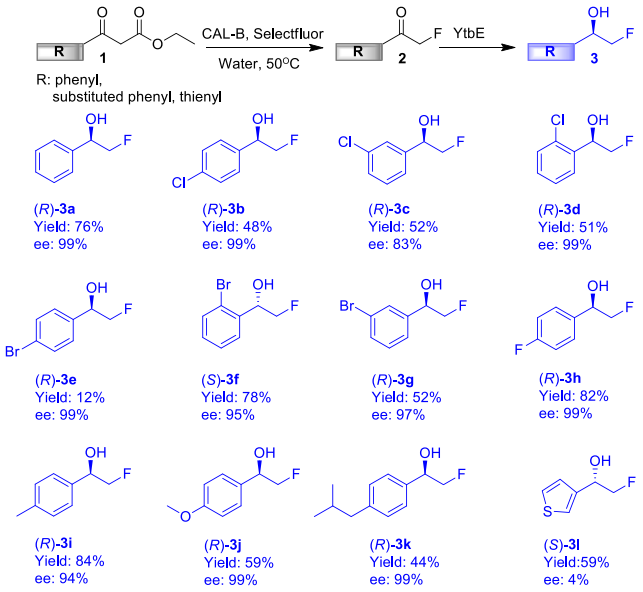
Scheme 4. Substrate Scope of the Cascade Process for the Production of (*R*)-Vicinal Fluoro Alcohols[a]



[a]Reaction conditions: 1 mmol of *β*-ketonic ester (**1**) and Selectfluor (30 mM, 1.2 equiv) were dissolved in 40 mL of buffer (200 mM PBS, pH = 7.4) containing 4 mL of *Candida antarctica* lipase B (CAL-B, 5000 U/mL). The reaction mixture was shaken vigorously at 50 °C for 12 h. Then 400 mL of whole-cell culture of YtbE (resuspended in 50 mM sodium phosphate buffer, pH 6.5) with glucose (100 mmol) was added into the above mixture and shaken at 30 °C overnight. All yields are isolated yields of products. The ee values were determined by chiral GC.

reaction concentrations are relatively dilute because of the low activity of whole-cell culture of ketoreductase. In the future, directed evolution to improve the activity of these ketoreductase or immobilization of the ketoreductase whole cells should be performed; thus, the requirement of higher reaction concentrations for potential pharmaceutical application may be satisfied.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01825.

Experimental procedures, new compounds characterization data, ^{1}H and ^{13}C NMR spectra of all products, chiral chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (b) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) Swallow, S. Fluorine in medicinal chemistry. *Prog. Med. Chem.* **2015**, *54*, 65−133. (e) Phelps, M. E. Positron emission tomography provides molecular imaging of biological processes. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 9226−9233.

(2) (a) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. Diastereodivergent hydroxyfluorination of cyclic and acyclic allylic amines: synthesis of 4-deoxy-4-fluorophytosphingosines. *J. Org. Chem.* **2012**, *77*, 7262−7281. (b) Chen, J. L.; Zheng, F.; Huang, Y.; Qing, F. L. Synthesis of gamma-monofluorinated goniothalamin analogues via regio- and stereoselective ring-opening hydrofluorination of epoxide. *J. Org. Chem.* **2011**, *76*, 6525−6533. (c) Myers, A. G.; Barbay, J. K.; Zhong, B. Asymmetric Synthesis of Chiral Organofluorine Compounds: Use of Nonracemic Fluoroiodoacetic Acid as a Practical Electrophile and Its Application to the Synthesis of Monofluoro Hydroxyethylene Dipeptide Isosteres within a Novel Series of HIV Protease Inhibitors. *J. Am. Chem. Soc.* **2001**, *123*, 7207−7219.

(3) (a) Kalow, J. A.; Doyle, A. G. Mechanistic investigations of cooperative catalysis in the enantioselective fluorination of epoxides. *J. Am. Chem. Soc.* **2011**, *133*, 16001−16012. (b) Mohanta, P. K.; Davis, T. A.; Gooch, J. R.; Flowers, R. A. Chelation-Controlled Diastereoselective Reduction of r-Fluoroketones. *J. Am. Chem. Soc.* **2005**, *127*, 11896−11897. (c) Arroyo, Y.; Sanz-Tejedor, M. A.; Parra, A.; Garcia Ruano, J. L. Asymmetric nucleophilic monofluorobenzylation of carbonyl compounds: synthesis of enantiopure vic-fluorohydrins and alpha-fluorobenzylketones. *Chem. - Eur. J.* **2012**, *18*, 5314−5318. (d) Ma, J.-A.; Cahard, D. Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev.* **2008**, *108*, PR1−PR43.

(4) (a) Matsuda, T.; Harada, T.; Nakamura, K. Alcohol dehydrogenase is active in supercritical carbon dioxide. *Chem. Commun.* **2000**, 1367−1368. (b) Borzecka, W.; Lavandera, I.; Gotor, V. Synthesis of enantiopure fluorohydrins using alcohol dehydrogenases at high substrate concentrations. *J. Org. Chem.* **2013**, *78*, 7312−7317.

https://dx.doi.org/10.1021/acs.orglett.0c01825
Org. Lett. XXXX, XXX, XXX−XXX

(5) (a) Chen, Z.; Zhu, W.; Zheng, Z.; Zou, X. One-pot α-nucleophilic fluorination of acetophenones in a deep eutectic solvent. *J. Fluorine Chem.* **2010**, *131*, 340−344. (b) Stavber, S.; Jereb, M.; Zupan, M. Solvent directing immediate fluorination of aromatic ketones using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate). *Chem. Commun.* **2000**, 1323−1324. (c) Belanger, E.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ethers. *J. Am. Chem. Soc.* **2007**, *129*, 1034−1035. (d) Jin, Z.; Hidinger, R. S.; Xu, B.; Hammond, G. B. Stereoselective synthesis of monofluoroalkyl alpha,beta-unsaturated ketones from allenyl carbinol esters mediated by gold and Selectfluor. *J. Org. Chem.* **2012**, *77*, 7725−7729.

(6) Li, J.; Li, Y.-L.; Jin, N.; Ma, A.-L.; Huang, Y.-N.; Deng, J. A Practical Synthesis of α-Fluoroketones in Aqueous Media by Decarboxylative Fluorination of β-Ketoacids. *Adv. Synth. Catal.* **2015**, *357*, 2474−2478.

(7) Zhu, T.; Ma, S. 3,4-Alkadienyl ketones via the palladium-catalyzed decarboxylative allenylation of 3-oxocarboxylic acids. *Chem. Commun.* **2017**, *53*, 6037−6040.

(8) (a) Schrittwieser, J. H.; Velikogne, S.; Hall, M.; Kroutil, W. Artificial Biocatalytic Linear Cascades for Preparation of Organic Molecules. *Chem. Rev.* **2018**, *118*, 270−348. (b) Mifsud, M.; Gargiulo, S.; Iborra, S.; Arends, I. W. C. E.; Hollmann, F.; Corma, A. Photobiocatalytic chemistry of oxidoreductases using water as the electron donor. *Nat. Commun.* **2014**, *5*, 1−6. (c) Guo, X.; Okamoto, Y.; Schreier, M. R.; Ward, T. R.; Wenger, O. S. Enantioselective synthesis of amines by combining photoredox and enzymatic catalysis in a cyclic reaction network. *Chem. Sci.* **2018**, *9*, 5052−5056. (d) Erdmann, V.; Lichman, B. R.; Zhao, J.; Simon, R. C.; Kroutil, W.; Ward, J. M.; Hailes, H. C.; Rother, D. Enzymatic and Chemoenzymatic Three-Step Cascades for the Synthesis of Stereochemically Complementary Trisubstituted Tetrahydroisoquinolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12503−12507. (e) Zawodny, W.; Montgomery, S. L.; Marshall, J. R.; Finnigan, J. D.; Turner, N. J.; Clayden, J. Chemoenzymatic Synthesis of Substituted Azepanes by Sequential Biocatalytic Reduction and Organolithium-Mediated Rearrangement. *J. Am. Chem. Soc.* **2018**, *140*, 17872−17877. (f) Ramsden, J. I.; Heath, R. S.; Derrington, S. R.; Montgomery, S. L.; Mangas-Sanchez, J.; Mulholland, K. R.; Turner, N. J. Biocatalytic N-Alkylation of Amines Using Either Primary Alcohols or Carboxylic Acids via Reductive Aminase Cascades. *J. Am. Chem. Soc.* **2019**, *141*, 1201−1206.

(9) (a) Mutti, F. G.; Knaus, T.; Scrutton, N. S.; Breuer, M.; Turner, N. J. Conversion of alcohols to enantiopure amines through dual-enzyme hydrogen-borrowing cascades. *Science* **2015**, *349*, 1525−1529. (b) Parmeggiani, F.; Rué Casamajo, A.; Walton, C. J. W.; Galman, J. L.; Turner, N. J.; Chica, R. A. One-Pot Biocatalytic Synthesis of Substituted d-Tryptophans from Indoles Enabled by an Engineered Aminotransferase. *ACS Catal.* **2019**, *9*, 3482−3486. (c) Citoler, J.; Derrington, S. R.; Galman, J. L.; Bevinakatti, H.; Turner, N. J. A biocatalytic cascade for the conversion of fatty acids to fatty amines. *Green Chem.* **2019**, *21*, 4932−4935. (d) Costa, B. Z.; Galman, J. L.; Slabu, I.; France, S. P.; Marsaioli, A. J.; Turner, N. J. Synthesis of 2,5-Disubstituted Pyrrolidine Alkaloids via A One-Pot Cascade Using Transaminase and Reductive Aminase Biocatalysts. *ChemCatChem* **2018**, *10*, 4733−4738.

(10) Litman, Z. C.; Wang, Y.; Zhao, H.; Hartwig, J. F. Cooperative asymmetric reactions combining photocatalysis and enzymatic catalysis. *Nature* **2018**, *560*, 355−359.

(11) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. Decarboxylative Fluorination of Aliphatic Carboxylic Acids via Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5654−5657.

(12) Xu, G.-C.; Yu, H.-L.; Zhang, X.-Y.; Xu, J.-H. Access to Optically Active Aryl Halohydrins Using a Substrate-Tolerant Carbonyl Reductase Discovered from Kluyveromyces thermotolerans. *ACS Catal.* **2012**, *2*, 2566−2571.

(13) (a) Both, P.; Busch, H.; Kelly, P. P.; Mutti, F. G.; Turner, N. J.; Flitsch, S. L. Whole-Cell Biocatalysts for Stereoselective C-H Amination Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 1511−1513. (b) Karasawa, M.; Stanfield, J. K.; Yanagisawa, S.; Shoji, O.; Watanabe, Y. Whole-Cell Biotransformation of Benzene to Phenol Catalysed by Intracellular Cytochrome P450BM3 Activated by External Additives. *Angew. Chem., Int. Ed.* **2018**, *57*, 12264−12269.

(14) (a) Ni, Y.; Li, C. X.; Wang, L. J.; Zhang, J.; Xu, J. H. Highly stereoselective reduction of prochiral ketones by a bacterial reductase coupled with cofactor regeneration. *Org. Biomol. Chem.* **2011**, *9*, 5463−5468. (b) Ni, Y.; Li, C. X.; Ma, H. M.; Zhang, J.; Xu, J. H. Biocatalytic properties of a recombinant aldo-keto reductase with broad substrate spectrum and excellent stereoselectivity. *Appl. Microbiol. Biotechnol.* **2011**, *89*, 1111−1118.

https://dx.doi.org/10.1021/acs.orglett.0c01825
Org. Lett. XXXX, XXX, XXX−XXX