BIOCATALYSIS

# Stereodivergent atom-transfer radical cyclization by engineered cytochromes P450

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Naturally occurring enzymes can be a source of unnatural reactivity that can be molded by directed evolution to generate efficient biocatalysts with valuable activities. Owing to the lack of exploitable stereocontrol elements in synthetic systems, steering the absolute and relative stereochemistry of free-radical processes is notoriously difficult in asymmetric catalysis. Inspired by the innate redox properties of first-row transition-metal cofactors, we repurposed cytochromes P450 to catalyze stereoselective atom-transfer radical cyclization. A set of metalloenzymes was engineered to impose substantial stereocontrol over the radical addition step and the halogen rebound step in these unnatural processes, allowing enantio- and diastereodivergent radical catalysis. This evolvable metalloenzyme platform represents a promising solution to tame fleeting radical intermediates for asymmetric catalysis.

As nature's privileged catalysts, enzymes are well known for their ability to exert exquisite control over the stereochemical outcome of chemical reactions (*1*). Over the past three decades, the advent of directed evolution (*2*, *3*) has enabled the rapid development of customized enzymes to generate excellent activity and stereoselectivity, which are often complementary to those of traditional small-molecule catalysts (*4*). However, until recently, the catalytic repertoire of enzymes has been mostly limited to reactions found in nature, posing constraints on the types of products available from enzyme catalysis. To merge the excellent tunability and stereocontrol of biocatalysts with the synthetic versatility of abiotic systems, the discovery and development of new-to-nature enzymatic activity are widely recognized as preeminent objectives at the interface of modern biocatalysis and organic synthesis (*5*, *6*).

Our group initiated a research program to repurpose naturally occurring metalloenzymes to catalyze unnatural radical reactions in a stereocontrolled fashion. Owing to the reactive nature of radical intermediates and the lack of synthetically achievable stereoinduction strategies, imposing enantio- and diastereocontrol over free-radical–mediated bond forming processes has remained a daunting challenge in asymmetric catalysis (*7*, *8*). On the other hand, natural enzymes (*9*), such as radical *S*-adenosylmethionine enzymes (*10*), facilitate radical reactions with excellent chemo-, regio-, and stereoselectivity. However, most natural radical enzymes display a narrow substrate scope. We propose that repurposing widely used, biotechnologically important enzymes to catalyze new-to-nature radical reactions may allow a diverse array of easily available substrates to be converted with operational simplicity. In this respect, recent notable contributions from the Hyster and Zhao laboratories (*11*) demonstrated the use of visible light to unveil excited-state activities of ketoreductases (*12*) and ene reductases (*13*–*18*), allowing for a range of stereoselective hydrogen-transfer transformations to be developed.

Small-molecule complexes of first-row transition metals are reported to catalyze unselective radical reactions via ground-state single-electron transfer between the metal center and the substrate, and we envisioned a powerful strategy to control the stereoselectivity of these radical reactions by engaging enzymes bearing a redox-active metallocofactor in these

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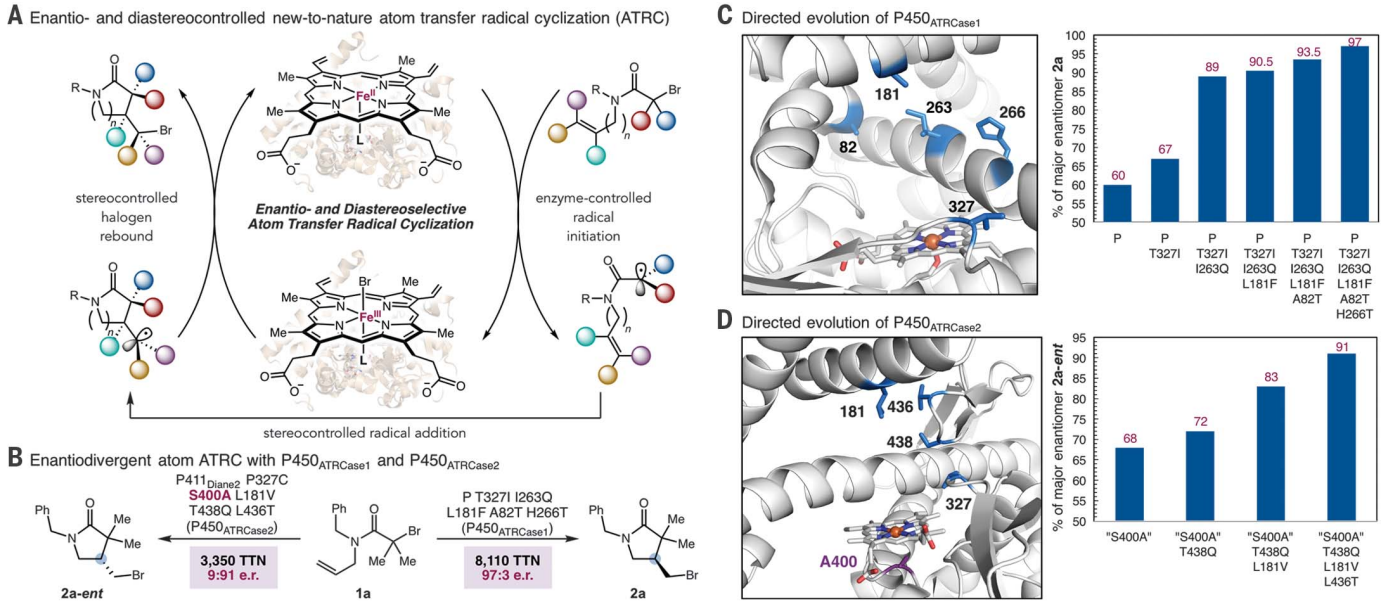


**Fig. 1. New-to-nature biocatalytic ATRC.** (**A**) Enantio- and diastereocontrolled ATRC. R, alkyl; Me, methyl; L, Fe-coordinating amino acid residue. (**B**) Enantiodivergent ATRC using $P450_{ATRCase1}$ and $P450_{ATRCase2}$. Ph, phenyl. (**C**) Directed evolution of $P450_{ATRCase1}$. The illustration at left was created on the basis of the crystal structure of a closely related P450 variant [Protein Data Bank identifier (PDB ID): 4H23]. "P" denotes P411-CIS T438S. (**D**) Directed evolution of $P450_{ATRCase2}$. The illustration at left was created on the basis of the crystal structure of a closely related P450 variant (PDB ID: 5UCW). "S400A" denotes $P411_{Diane2}$ with P327C and S400A. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; Y, Tyr.

unnatural processes. By fine-tuning the interaction between the reactive radical intermediate and the metalloprotein scaffold by means of directed evolution, these metalloenzyme catalysts could be engineered to achieve levels of enantio- and diastereocontrol that are unmatched by small-molecule catalysts. With this strategy, a diverse array of unnatural radical metalloenzymes could potentially be developed, as metalloredox couples that span a wide range of potentials—including Fe(II)/Fe(III) (*19*, *20*), Co(I)/Co(II) (*21*), and Cu(I)/Cu(II) (*22*)—are readily available in a myriad of native metalloenzymes. In particular, inspired by polymer chemists' research in employing heme-based systems to generate radical species for polymerization (*23*, *24*), we saw numerous opportunities for leveraging heme proteins as a general platform for asymmetric radical transformations. Previous important work from Arnold, Fasan, and others demonstrated that heme proteins can be repurposed to catalyze unnatural carbene and nitrene transfers analogous to the natural oxene transfer observed in heme oxygenases (*25*–*30*). Thus, the highly promiscuous and evolvable nature of heme proteins makes them particularly promising for the development of stereocontrolled metalloredox radical chemistry.

We envisioned a family of unnatural biocatalytic reactions—namely, stereoselective atom-transfer radical cyclization (ATRC) (*31*, *32*)—to be advanced with metalloenzymes. In our proposed ATRC catalyzed by Fe-dependent enzymes (Fig. 1A), the metalloprotein catalyst in its ferrous state undergoes single-electron transfer with an organic halide, producing a transient radical intermediate in the active site. Rapid addition of the nascent radical species to an unsaturated system would afford a product radical, which would subsequently react with the ferric halide to produce the product and regenerate the metalloenzyme catalyst. The envisioned ATRC simultaneously installs an alkyl group and a halogen atom across the C=C double bond of an olefin substrate, thereby generating valuable products with added stereochemical complexity (*31*). Despite the extensive study and widespread utility of ATRC reactions, the development of general methods for stereocontrolled ATRC presents substantial hurdles for small-molecule catalysts (*7*, *33*, *34*). Because it is difficult to maintain a tight association between the chiral catalyst and the radical intermediate, general catalytic strategies to exert enantiocontrol over the C–C bond forming radical addition step remain unavailable. Imposing catalyst-controlled diastereoselectivity in the subsequent halogen-rebound step is similarly challenging. Herein, we describe the development of metalloprotein catalysts that provide excellent enantio- and diastereocontrol for this daunting problem in asymmetric catalysis. Notably, our protein engineering efforts allow for development of a toolbox of stereocomplementary catalysts, granting enantio- and diastereodivergent access to ATRC products.

In the present study, we evaluated both heme (P450s, globins, and cytochromes *c*) and nonheme Fe-dependent proteins for the targeted transformation (table S1). ATRC of substrate **1a** was selected as the model reaction, because $FeCl_2$ was known to facilitate these processes (*35*) and the corresponding enantioenriched lactams derived from these cyclization processes are ubiquitous in medicinally relevant scaffold (*36*). The utility of Fe enzymes in our library was evaluated in the form of purified proteins, cell-free lysates, and whole-cell catalysts. Although several metalloproteins were found to promote the desired radical cyclization (table S1), among all of the metalloprotein catalysts we examined, a serine-ligated variant of *Bacillus megaterium* P450 (CYP102A1) (*37*)—known as "P" (*38*)—furnished a measurable enantiomeric excess [60:40 enantiomeric ratio (e.r.)] and the highest activity. Notably, the activity of intact *Escherichia coli* cells harboring P was an order of magnitude higher than that of the purified protein catalyst with identical enantioselectivity (tables S4 and S5). The ability to use whole bacterial cells as catalysts without further manipulation substantially accelerated this protein engineering campaign.

To further improve the enantioselectivity of this radical cyclization process, we next performed directed evolution through iterative cycles of site-saturation mutagenesis (SSM) and screening (Fig. 1, B and C). In each round of engineering, 90 clones were screened. By

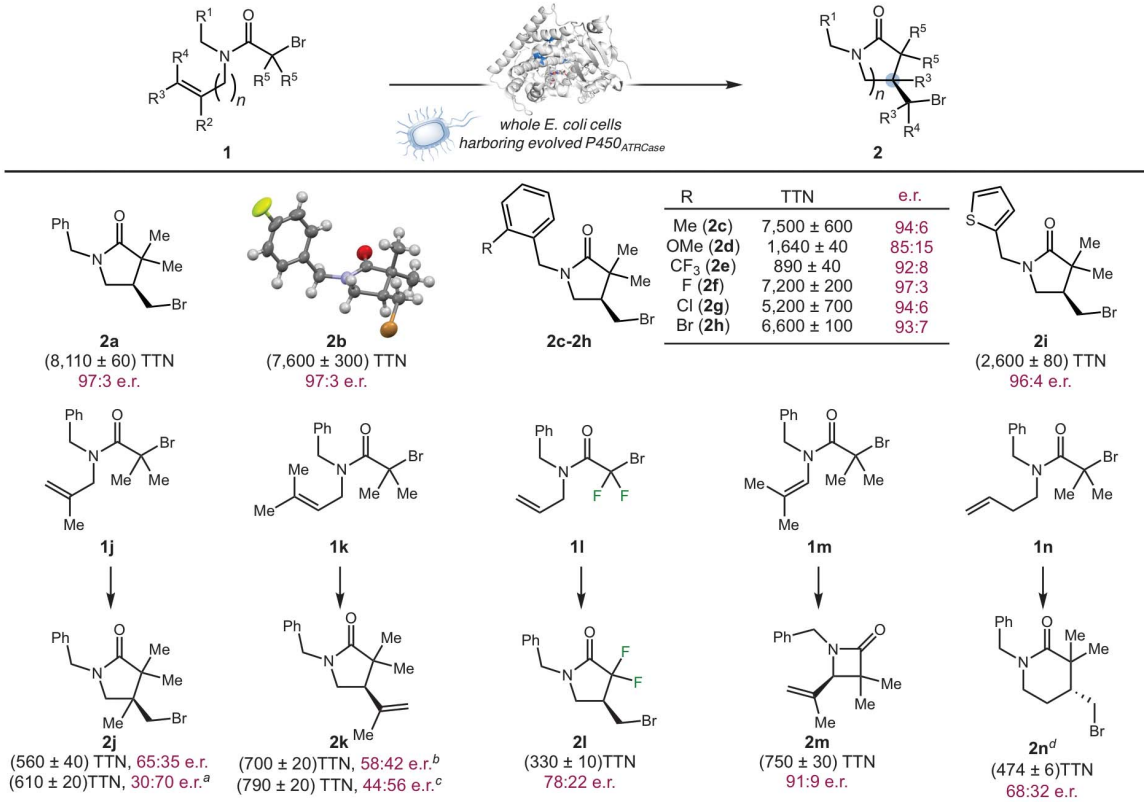


**Fig. 2. Substrate scope of new-to-nature enantioselective ATRC.** [a]Variant P′ was used. [b]P with T327I and I263Q was used. [c]$P450_{ATRCase1}$ (P with T327I, I263Q, L181F, A82T, and H266T) was used. [d]$P450_{ATRCase2}$ with A330K was used. Whole-cell reactions were carried out at $OD_{600}$ (optical density at 600 nm) = 5 to 30. The variation of e.r. values is ≤1%. See the supplementary materials for details.

targeting active-site residues proximal to the heme cofactor—including residues 327, 263, 181, 82, and 266—through five rounds of protein engineering, the e.r. of the desired product (**2a**) could be rapidly enhanced. With our final metalloenzyme variant, $P450_{ATRCase1}$ (P with T327I, I263Q, L181F, A82T, and H266T), the desired product formed with excellent yield and enantioselectivity [89% yield, a total turnover number (TTN) of 8110, and 97:3 e.r.]. By further decreasing the catalyst loading, a TTN of 20,000 was achieved without affecting the enantioselectivity.

During the course of this study, we also found that another serine-ligated P450 variant ($P411_{Diane2}$) that we previously engineered for enantioselective C–H amidation (*39*) was also active for this ATRC, with inverted enantiopreference (Fig. 1B). $P411_{Diane2}$ was further evolved via recursive SSM and screening (Fig. 1D). An axial ligand effect was investigated in this unnatural metalloredox radical chemistry. Notably, the "S400A" variant lacking a coordinating axial ligand (here,"S400A" indicates $P411_{Diane2}$ with the P327C and S400A mutations) facilitated the unnatural radical reaction with a 1.4-fold improvement in TTN relative to the S400 variant, without affecting the enantioselectivity (from 1160 TTN and 32:68 e.r. to 1590 TTN and 32:68 e.r.; table S7). By targeting other active-site residues, including 327, 181, 438, and 436, we arrived at $P450_{ATRCase2}$ ($P411_{Diane2}$ with P327C, S400A, L181V, T438Q, and L436T) with substantially enhanced activity and enantioselectivity (3350 TTN, 91:9 e.r.).

We next surveyed the substrate scope of the ATRC process (Fig. 2). A range of functional groups on the nitrogen substituent was readily tolerated, providing the corresponding γ-lactam in excellent TTN and enantioselectivity (**2a** to **2i**). Chloro- (**2g**) and bromo- (**2h**) substituents were also compatible, providing a valuable functional group handle for further derivatization. Substrates bearing a heterocycle, such as thiophene (**2i**), were also transformed with excellent enantiocontrol. Substituted olefins (**1j** and **1k**) as well as α,α-difluorinated (**1l**) substrates could also be converted into the desired γ-lactam products, including **2j** bearing contiguous quaternary-quaternary stereocenters. The absolute configuration of **2b** was ascertained by x-ray crystallography. Using these engineered metalloenzyme catalysts, β- and δ-lactams (**2m** and **2n**) readily formed in an enantioselective fashion, indicating the potential of this biocatalytic platform to access a diverse array of enantioenriched lactam products. Products **2k** and **2m** were derived from dehydrohalogenation of the ATRC product.

Given the success of engineered metalloenzymes in exerting stereocontrol over the C–C bond forming step, we questioned whether we could further leverage this metalloredox biocatalytic platform to control the relative stereochemistry in the C–Br bond forming halogen rebound event (Fig. 3A). To this end, we re-examined all of the P450 variants we accumulated in this protein engineering effort. We identified two hits, $P450_{ATRCase}$ gen-4 (P with T327I, I263Q, L181F, and A82T) and P′ (P with L181V, L437F, and S438Q), giving rise to promising levels of opposite diastereopreferences. Through iterative rounds of SSM

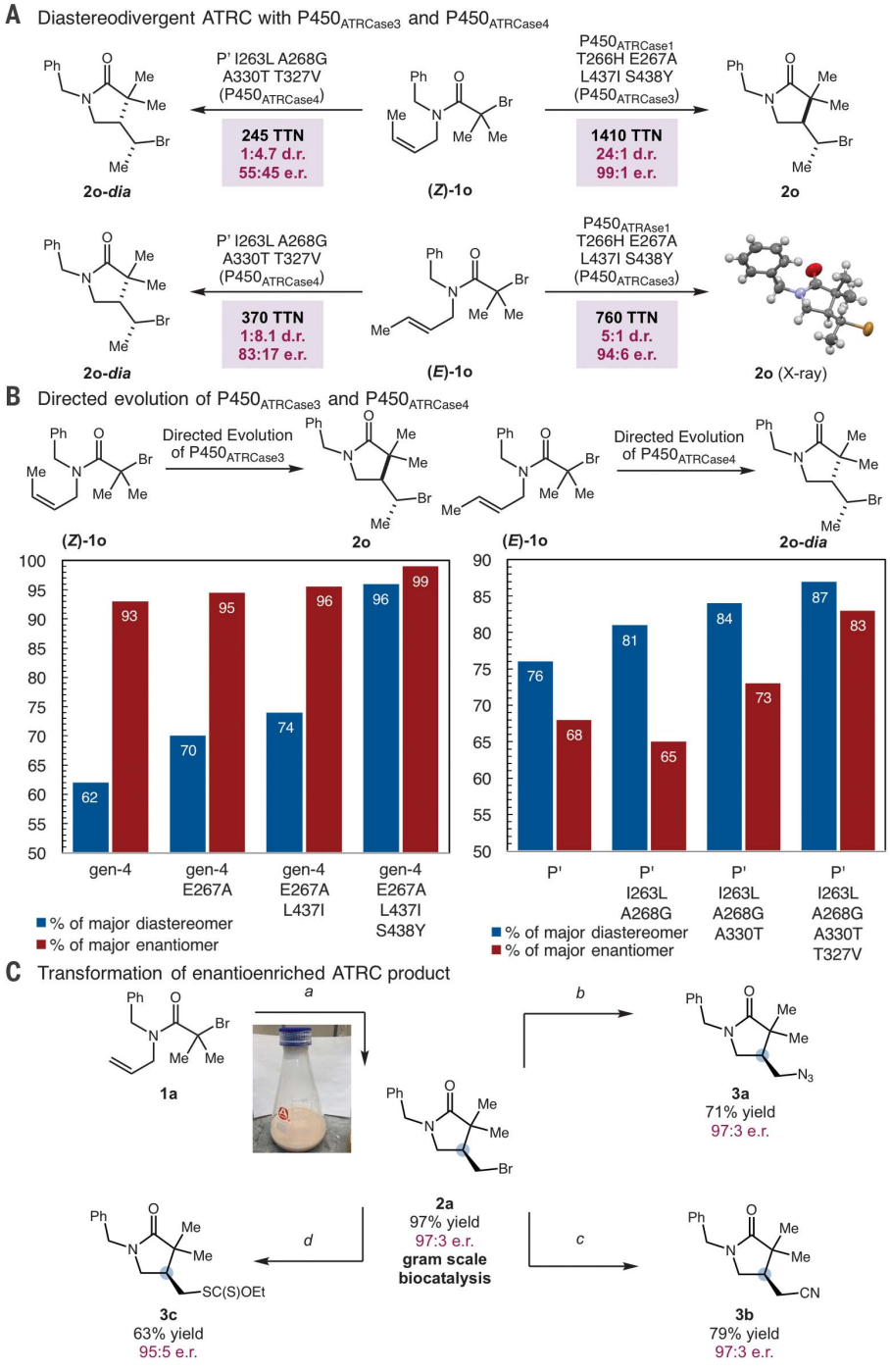


**Fig. 3. Further development and application of new-to-nature ATRC.** (**A**) Diastereodivergent new-to-nature ATRC with $P450_{ATRCase3}$ and $P450_{ATRCase4}$. (**B**) Directed evolution of $P450_{ATRCase3}$ and $P450_{ATRCase4}$. (**C**) Transformation of enantioenriched ATRC product. Conditions: *a*. Whole-cell biotransformation using *E. coli* cells resuspended in M9-N buffer (pH = 7.4) at room temperature (RT) for 12 hours, 97% yield, 97:3 e.r.; *b*. $NaN_3$, NaI, dimethylformamide (DMF)/$H_2O$, 60°C, 16 hours, 79% yield, 97:3 e.r.; *c*. NaCN, NaI, DMF/$H_2O$, 60°C, 16 hours, 71% yield, 97:3 e.r.; and *d*. KSC(S)OEt, acetone, RT, 12 hours, 63% yield, 95:5 e.r..

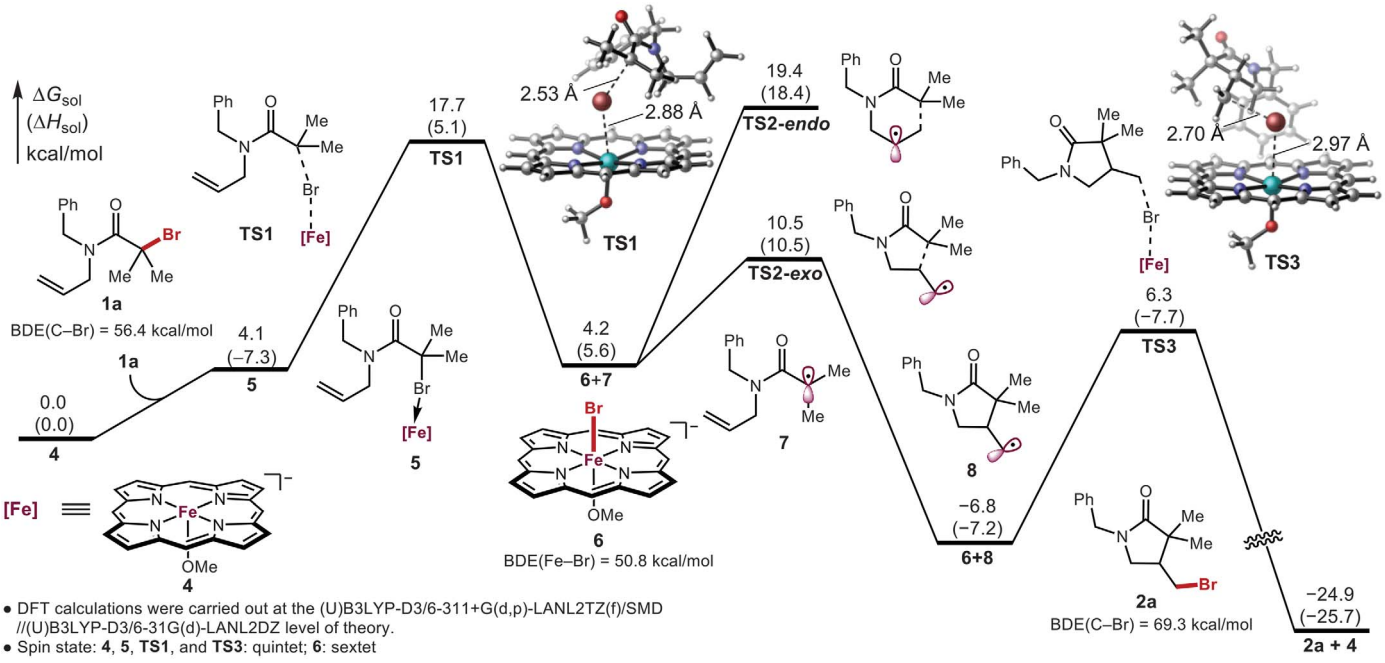


**Fig. 4. Reaction energy profile of the current biocatalytic atom-transfer radical addition using a model system for the axial serine-ligated Fe-porphyrin catalyst.** A methoxy-bound Fe porphyrin was used as the model system for serine-ligated P450 (*39*). $\Delta G_{sol}$, Gibbs free energy; $\Delta H_{sol}$, enthalpy; BDE, bond dissociation enthalpy.

and screening, we engineered an orthogonal set of highly selective biocatalysts, including $P450_{ATRCase3}$ and $P450_{ATRCase4}$, allowing for the diastereodivergent synthesis of either **2o** or **2o-*dia*** (Fig. 3B). For comparison, the use of the traditional tris(2-pyridylmethyl)amine copper(I) catalyst for ATRC (*40*) produced **2o** and **2o-*dia*** with low diastereoselectivity [1:1.6 and 2.1:1 diastereomeric ratio from (*E*)- and (*Z*)-**1o**, respectively; see the supplementary materials for details]. Moreover, with $P450_{ATRCase3}$ and $P450_{ATRCase4}$, (*E*)- and (*Z*)-**1o** provided the same major diastereomer (see the supplementary materials). Thus, starting from easily accessible mixtures of (*E*)- and (*Z*)-**1o**, the diastereoconvergent biocatalytic transformation with $P450_{ATRCase3}$ or $P450_{ATRCase4}$ delivered the corresponding γ-lactam product in good diastereoselectivity. The relative stereochemistry of **2o** was determined by x-ray diffraction analysis (see the supplementary materials for details).

To further demonstrate the synthetic utility of engineered radical metalloenzymes, we performed this whole-cell biotransformation on a gram scale (Fig. 3C). Excellent yield and enantioselectivity were observed, showcasing the practicality of this new-to-nature biocatalytic reaction. Furthermore, the presence of a bromine functional group in enantioenriched ATRC products allowed for a range of diversification reactions to be conveniently carried out. $S_N2$-type (i.e., second order) nucleophilic substitution with a range of nucleophiles generated synthetically versatile azide (**3a**), cyanide (**3b**), and xanthate (**3c**) products in good yields while maintaining stereochemical purity. Combined with the enantioselective biocatalytic ATRC, these derivatization reactions allowed a range of formal enantioselective carbofunctionalization reactions, including carboazidation (**3a**), carbocyanation (**3b**), and carboxanthation (**3c**), to be achieved.

Consistent with our initial hypothesis, our radical clock experiments with hemin as the catalyst led to ring-opening products (see the supplementary materials for details), indicating that radical intermediates are involved in this process. To gain further insight into the reaction mechanism, we performed density functional theory (DFT) calculations using a model system (*39*) for the axial serine-ligated P450 catalyst (Fig. 4; see the supplementary materials for details). DFT calculations showed that the Fe porphyrin catalyst remains high-spin throughout the catalytic cycle in this biocatalytic ATRC process. This finding is not consistent with the previously studied native oxene transfer (*41*) and analogous nitrene transfer (*39*) chemistry of P450 enzymes, wherein spin crossover is involved. With the model system, the radical initiation step (**TS1**) has a relatively low activation barrier ($\Delta G^{\ddagger}$) of 17.7 kcal/mol. Considering that the enzyme environment may further facilitate this process by promoting substrate binding to form complex **5**, this Fe-catalyzed radical initiation is expected to be kinetically facile. The electron-rich nature of the Fe center allows for the facile single-electron reduction of the substrate, as evidenced by the substantial electron transfer (0.44 $e^-$) from **4** to **1a** in **TS1**. After the selective 5-*exo*-trig cyclization (**TS2-exo**) to form the primary carbon radical **8**, the bromine rebound step (**TS3**) is highly exergonic, with a low activation barrier of 13.1 kcal/mol. The fast trapping of the carbon radical via bromine atom transfer renders the C–C bond formation step irreversible and enables kinetic control of reaction stereochemistry. The bromine rebound reactivity is promoted by the conversion of a weaker Fe–Br bond in the ferric bromide species (**6**) to a stronger primary $C(sp^3)$–Br bond in **2a**. Therefore, the ability of the Fe porphyrin system to promote both radical initiation and bromine rebound steps makes it an effective ATRC biocatalyst.

## REFERENCES AND NOTES


1. U. T. Bornscheuer *et al.*, *Nature* **485**, 185–194 (2012).
2. J. D. Bloom, F. H. Arnold, *Proc. Natl. Acad. Sci. U.S.A.* **106** (suppl. 1), 9995–10000 (2009).
3. U. T. Bornscheuer, B. Hauer, K. E. Jaeger, U. Schwaneberg, *Angew. Chem. Int. Ed.* **58**, 36–40 (2019).
4. M. T. Reetz, *Angew. Chem. Int. Ed.* **50**, 138–174 (2011).
5. H. Renata, Z. J. Wang, F. H. Arnold, *Angew. Chem. Int. Ed.* **54**, 3351–3367 (2015).
6. K. Chen, F. H. Arnold, *Nat. Catal.* **3**, 203–213 (2020).
7. M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **103**, 3263–3296 (2003).
8. R. S. J. Proctor, A. C. Colgan, R. J. Phipps, *Nat. Chem.* **12**, 990–1004 (2020).
9. C. M. Jäger, A. K. Croft, *ChemBioEng Rev.* **5**, 143–162 (2018).
10. J. B. Broderick, B. R. Duffus, K. S. Duschene, E. M. Shepard, *Chem. Rev.* **114**, 4229–4317 (2014).
11. B. A. Sandoval, T. K. Hyster, *Curr. Opin. Chem. Biol.* **55**, 45–51 (2020).
12. M. A. Emmanuel, N. R. Greenberg, D. G. Oblinsky, T. K. Hyster, *Nature* **540**, 414–417 (2016).

13. B. A. Sandoval, A. J. Meichan, T. K. Hyster, *J. Am. Chem. Soc.* **139**, 11313–11316 (2017).
14. K. F. Biegasiewicz *et al*., *Science* **364**, 1166–1169 (2019).
15. P. D. Clayman, T. K. Hyster, *J. Am. Chem. Soc.* **142**, 15673–15677 (2020).
16. M. J. Black *et al*., *Nat. Chem.* **12**, 71–75 (2020).
17. X. Huang *et al*., *Nature* **584**, 69–74 (2020).
18. C. G. Page *et al*., *J. Am. Chem. Soc.* **143**, 97–102 (2021).
19. E. G. Kovaleva, J. D. Lipscomb, *Nat. Chem. Biol.* **4**, 186–193 (2008).
20. I. G. Denisov, T. M. Makris, S. G. Sligar, I. Schlichting, *Chem. Rev.* **105**, 2253–2277 (2005).
21. K. L. Brown, *Chem. Rev.* **105**, 2075–2149 (2005).
22. E. I. Solomon *et al*., *Chem. Rev.* **114**, 3659–3853 (2014).
23. K. J. Rodriguez *et al*., *ACS Macro Lett.* **7**, 1111–1119 (2018).
24. A. Simakova, M. Mackenzie, S. E. Averick, S. Park, K. Matyjaszewski, *Angew. Chem. Int. Ed.* **52**, 12148–12151 (2013).
25. Y. Yang, F. H. Arnold, *Acc. Chem. Res.* **54**, 1209–1225 (2021).
26. O. F. Brandenberg, R. Fasan, F. H. Arnold, *Curr. Opin. Biotechnol.* **47**, 102–111 (2017).
27. T. Hayashi *et al*., *Nat. Catal.* **1**, 578–584 (2018).
28. H. M. Key, P. Dydio, D. S. Clark, J. F. Hartwig, *Nature* **534**, 534–537 (2016).
29. P. Dydio *et al*., *Science* **354**, 102–106 (2016).
30. D. M. Carminati, R. Fasan, *ACS Catal.* **9**, 9683–9697 (2019).
31. W. T. Eckenhoff, T. Pintauer, *Catal. Rev., Sci. Eng.* **52**, 1–59 (2010).
32. A. J. Clark, *Eur. J. Org. Chem.* **2016**, 2231–2243 (2016).
33. B. Chen, C. Fang, P. Liu, J. M. Ready, *Angew. Chem. Int. Ed.* **56**, 8780–8784 (2017).
34. D. Yang, S. Gu, Y.-L. Yan, N.-Y. Zhu, K.-K. Cheung, *J. Am. Chem. Soc.* **123**, 8612–8613 (2001).
35. C. K. Tseng, E. G. Teach, R. W. Simons, *Synth. Commun.* **14**, 1027–1031 (1984).
36. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **57**, 10257–10274 (2014).
37. C. J. C. Whitehouse, S. G. Bell, L.-L. Wong, *Chem. Soc. Rev.* **41**, 1218–1260 (2012).
38. J. A. McIntosh *et al*., *Angew. Chem. Int. Ed.* **52**, 9309–9312 (2013).
39. Y. Yang, I. Cho, X. Qi, P. Liu, F. H. Arnold, *Nat. Chem.* **11**, 987–993 (2019).
40. C. Schumacher, J. G. Hernández, C. Bolm, *Angew. Chem. Int. Ed.* **59**, 16357–16360 (2020).
41. S. Shaik, D. Kumar, S. P. de Visser, A. Altun, W. Thiel, *Chem. Rev.* **105**, 2279–2328 (2005).

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## SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.abk1603
Materials and Methods
Figs. S1 to S6
Tables S1 to S17
References (*42*–*102*)

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Science

# Stereodivergent atom-transfer radical cyclization by engineered cytochromes P450

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**Radical cyclization made easy**

Metalloenzymes contain metal cofactors that can sometimes be exploited to catalyze reactions distinct from their natural function. Drawing on inspiration from heme-based radical polymerizations, Zhou *et al*. screened a panel of metalloproteins for candidates that could catalyze an atom-transfer radical cyclization, producing a lactam from an amide substrate bearing bromoalkyl and alkene functional groups (see the Perspective by Zhang and Dydio). Cytochrome P-450 derivatives were effective catalysts, and a series of enzyme variants were generated by directed evolution to access the full range of enantiomer and diastereomer products for model substrates. Such biocatalysts are valuable additions to the synthetic chemistry toolkit and reiterate the potential of metalloenzymes in catalyzing useful unnatural reactions. —MAF







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