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Highly stereoselective synthesis of allylic β-lactams *via* enzymatic C(sp^3)–H amidation

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β-Lactams are versatile synthons for organic synthesis as well as valuable pharmacophores for drug development. Here, we describe a biocatalytic strategy for the enantioselective synthesis of allylic β-lactams *via* a hemoprotein-catalyzed intramolecular C(sp^3)–H amidation reaction with dioxazolone substrates. Leveraging a stepwise radical mechanism and overriding the typical reactivity of metallonitrenes, this system provides access to a variety of β-lactam products with consistently high enantioselectivity (≥99% ee) by favoring the amination of an allylic C(sp^3)-H bond over the more facile functionalization of the adjacent olefin group. This works expands the range of stereoselective strategies for C–N bond formation *via* C(sp^3)–H functionalization and demonstrates the value of new-to-nature biocatalysis to promote chemical transformations not currently accessible through chemocatalysis.

Introduction

The selective functionalization of aliphatic C(sp^3)–H bonds remains a keystone challenge in synthetic organic chemistry, especially when multiple potentially reactive functionalities coexist within a molecule. Among various C–H functionalization strategies, the direct amination of C(sp^3)–H bonds has attracted significant interest,[1–6] primarily due to the prevalence of nitrogen-containing moieties in pharmaceuticals and natural products,[7,8] as well as the intrinsic difficulty associated with integrating nitrogen into complex molecular frameworks. Among nitrogen-containing heterocycles, β-lactams represent one of the most significant pharmacophores in medicinal chemistry.[9] Since the discovery of penicillin, β-lactam scaffolds have been indeed central to the development of antimicrobial agents and enzyme inhibitors.[9] The structural rigidity, ring strain, and unique reactivity make them invaluable in both drug development as well as versatile building blocks for the synthesis of organic molecules (Fig. 1A).[10]

Because of their synthetic and pharmacological relevance, significant efforts have been devoted to the development of synthetic methods for the stereoselective synthesis of β-lactams.[11,12] State-of-the-art catalytic methods include the use of palladium-catalyzed carbonylative cycloaddition reactions,[13] copper-catalyzed Kinugasa/Michael domino reactions,[14] and copper-catalyzed C(sp^3)–C(sp^2) cross coupling reaction,[15] iron-catalyzed olefin oxyamidation,[16] among others.[11,12] The possibility to construct β-lactam rings *via* a direct, C(sp^3)–H functionalization process is particularly attractive due to the ubiquitous presence of aliphatic C–H bonds in organic molecules. In this context, current methods include carbene C–H insertion with diazoamides[17–19] and the palladium-catalyzed β-C(sp^3)–H amidation of functionalized amides bearing a directing group such as quinolines or amide protecting groups. Despite this progress, chemocatalytic methods for the stereoselective synthesis of these β-lactam compounds *via* an undirected C(sp^3)–H amination reaction are not available.

Over the past years, considerable progress has been made in the development of biocatalytic strategies for intra- and intermolecular C(sp^3)–H amination reactions *via* abiological nitrene transfer chemistry using engineered hemoproteins and other metalloenzymes.[20–33] Complementing and expanding beyond the scope of chemocatalytic nitrene transfer methods for C(sp^3)–H amination,[7,34–39] these methods have enabled the asymmetric synthesis of sultams, carbamates, sulfamide, lactams, as well as benzylic, allylic and propargylic amines with high catalyst-controlled selectivity. Relevant to the present work, we recently demonstrated the possibility to engage dioxazolone-based nitrene precursors in a hemoprotein-catalyzed intramolecular amination of benzylic C(sp^3)–H bonds for the stereoselective synthesis of β-, γ-, and δ-lactams with high activity and enantioselectivity (Fig. 1C).[32]

Building on this progress, we were interested in targeting the enantioselective synthesis of allylic β-lactams *via* an intramolecular allylic C(sp^3)–H amination process, as the resulting products combine the strained β-lactam pharmacophore with a versatile allylic functionality for further diversification. These compounds also constitute convenient precursors to allylic amines, which are valuable motifs in bioactive molecules in their own right (Fig. 1A).[40] While intermolecular allylic C–H

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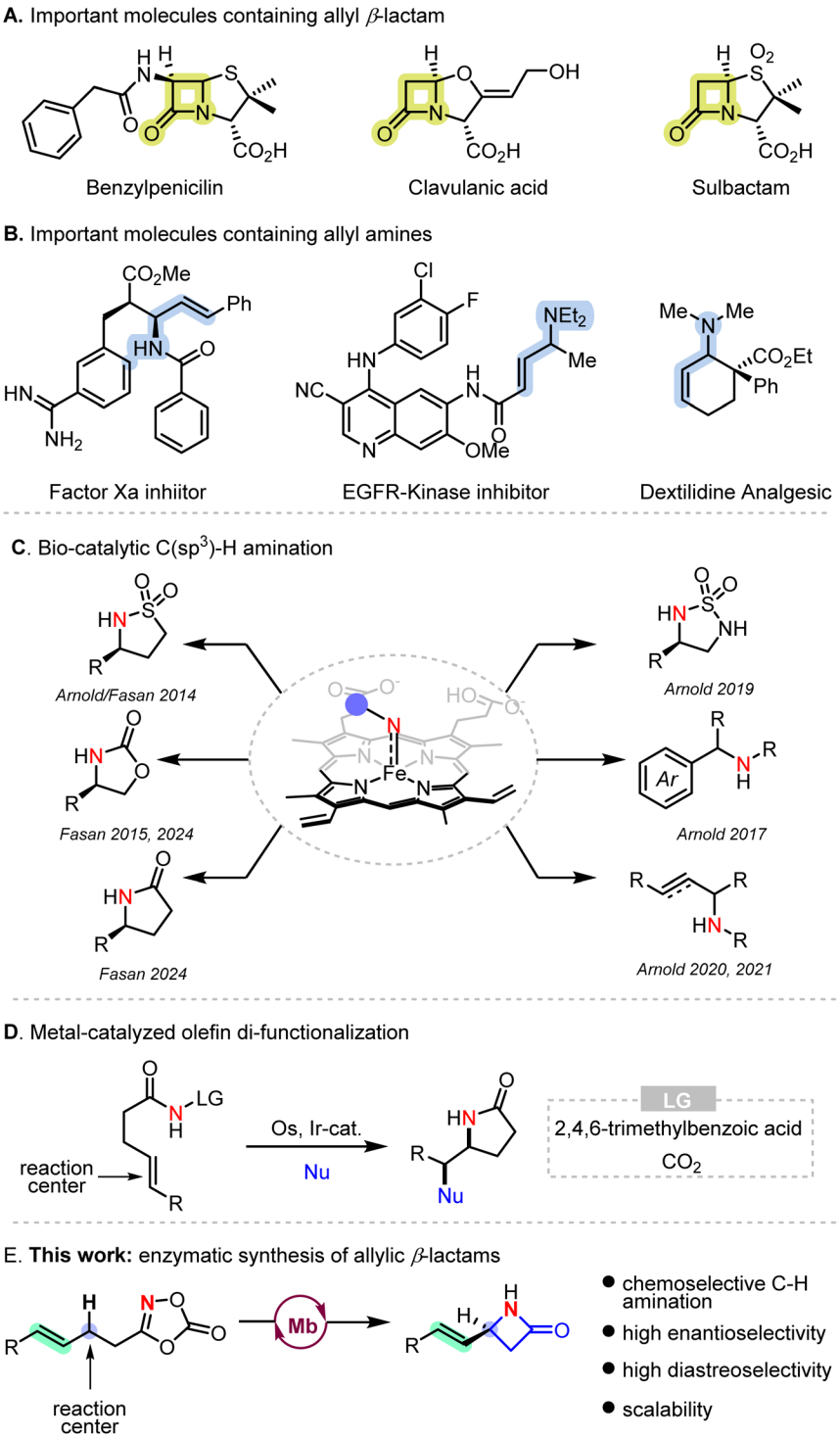
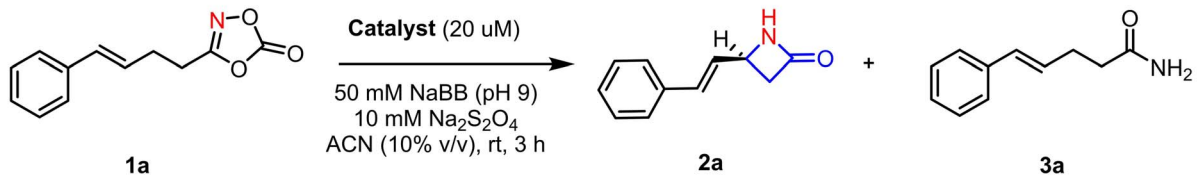


Fig. 1 Beta-lactams *via* enzyme-catalyzed allylic C–H amination (A) and (B) representative bioactive molecules β-lactam rings and allylic amines; (C) biocatalytic C–H amination reactions; (D) asymmetric γ-lactam synthesis *via* metal-catalyzed olefin di-functionalization; (E) biocatalytic β-lactam formation *via* allylic C(sp^3)–H amidation (this work).

amination have been achieved with both transition metal catalysts[5,8,34,36,41–46] and biocatalysts,[25,29] there are no reported examples of allylic C–H amination to make β-lactams. This transformation indeed presents peculiar challenges in that functionalization of the more reactive olefin group tends to outcompete functionalization of the adjacent allylic C(sp^3)–H bond in the presence of metallonitrene intermediates, in particular when the latter would lead to formation of a strained 4-membered ring.[47–55] This reactivity bias has been indeed exploited to obtain γ- (or δ)-lactams *via* a variety of olefin

A



B

Entry	Catalyst	2a (%)	3a (%)	*ee* of 2a
1	Fe(TPP)Cl	0	0	-
2	Co(TPP)	0	0	-
3	Hemin	0	0	-
4	Mb (sperm whale)	0	100	-
5	Mb (H64V)	2	98	>99%
6	Mb (H64V,V68A)	57	43	>99%
7	Mb (H64Q,V68A)	8	92	>99%
8	Mb (L29F,H64V,V68A)	34	66	>99%
9	Mb (L29A,H64V,V68A)	16	84	>99%
10	Mb(H64V,V68A,I107V)	55	45	>99%

C

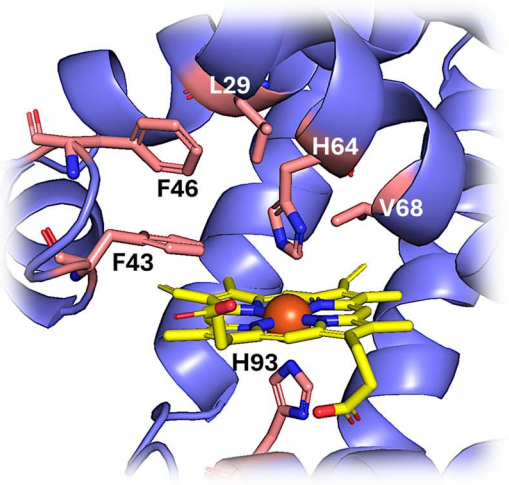


Fig. 2 Biocatalytic intramolecular C(sp^3)–H allylic amidation of dioxazolones. (A) Amidation reaction of **1a**; (B) activity and enantioselectivity of **2a** with engineered Mb variants and other porphyrin-based metal catalysts in the reaction with **1a**; (C) crystal structure of wild-type Mb (PDB: 1JW8) with the residues near the Fe center highlighted in yellow. Reaction conditions: 400 μL scale, 20 μM protein, 10 mM **1a**, 10 mM $Na_2S_2O_4$ in sodium borate buffer (50 mM, pH 7), 10% (v/v) acetonitrile, 3 h, room temperature, anaerobic conditions. The yields and product distribution were determined by GC using calibration curves of the isolated product.

difunctionalization strategies in the presence of both late and first-row transition metal catalysts (Fe, Os, Rh, Ir) (Fig. 1D).[50–55]

Herein, we demonstrate the possibility to overcome this inherent reactivity bias with the development of an enzyme-catalyzed β-lactam forming reaction *via* chemo- and stereoselective allylic C–H amination (Fig. 1E). This transformation, which is shown to proceed *via* a stepwise hydrogen atom transfer/radical rebound mechanism, enables the expeditious preparation of a variety of allylic β-lactams with high enantioselectivity from readily available starting materials.

Results and discussion

In initial studies, a diverse set of heme-containing enzymes and proteins, including myoglobin, various cytochromes P450 (*e.g.* $P450_{BM3}$, CYP119, P411–CHF[56] variants) cytochromes *c*, and others, were screened for their ability to promote the intramolecular C(sp^3)–H amination of allylic dioxazolone (**1a**) to give the desired β-lactam **2a**. However, none of the enzymes produced any detectable amount of the desired product (Table S1). Of note, the same reaction failed or gave minimal reactivity in the presence of several porphyrin-based catalysts commonly used for carbene transfer reactions such as Fe^{III}(TPP)Cl and Co^{II}(TPP) (Fig. 2). We then extended our screening to an in-house collection of purified myoglobin variants library containing a range of single to quadruple mutations at residues surrounding the heme cofactors. While the large majority of these variant showed no activity, Mb(H64V) displayed basal activity for formation of the desired product **2a** (2% yield) with high enantioselectivity (99% ee; Fig. 2). Among these proteins, Mb(H64V,V68A), which was previously found to be an effective catalyst for many carbene transfer reactions[57] as well as for intramolecular C–H amidation with dioxazolones,[32] proved to be an optimal biocatalyst for the present reaction (Fig. 2). Interestingly, the activity and selectivity of Mb variants containing alanine and/or glycine mutations at the 64 or 68 positions significantly decreased when compared to Mb(H64V,V68A), and a similar effect was seen for Mb variants incorporating additional active site mutations in the Mb(H64V,V68A) background (*e.g.* L29A/F), indicating that the enzyme's reactivity is sensitive to subtle alterations in the configuration of the active site (Fig. 2B). Based on previous studies,[32] we anticipated that the inclusion of an organic co-solvent would enhance the desired C–H amidation process by disfavoring formation of the amide byproduct **3a**, which derives from reduction and protonation of the heme-nitrene

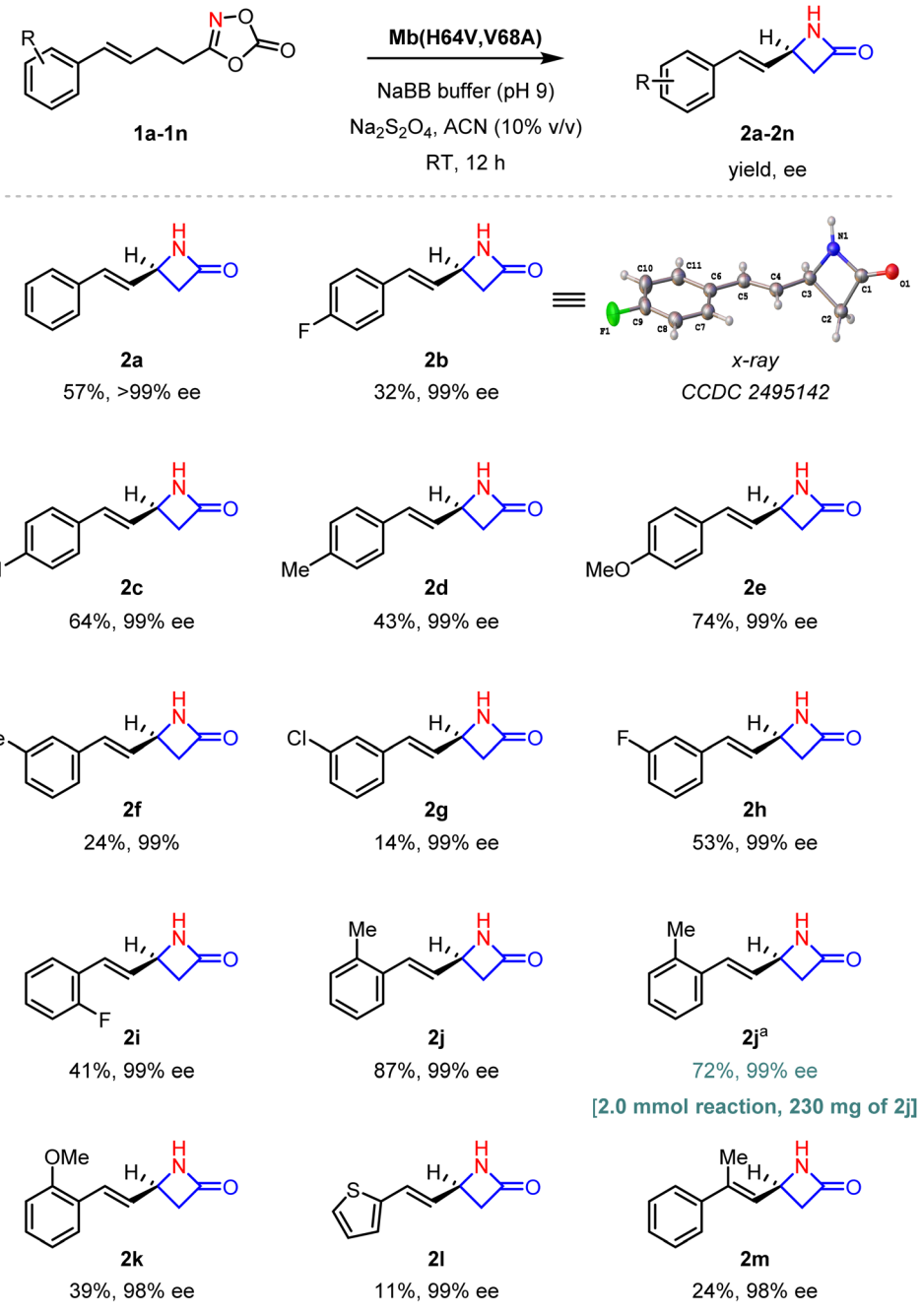


Fig. 3 Substrate scope of Mb-catalyzed intramolecular C(sp^3)–H allylic amidation of dioxazolones. Reaction conditions: 400 μL scale, 20 μM protein, 10 mM **1a**, 10 mM $Na_2S_2O_4$ in NaBB buffer (50 mM, pH 9), 10% (v/v) acetonitrile, 3 h, room temperature, anaerobic conditions. The yields and product distribution were determined by GC using calibration curves of the isolated product. [a]2.0 mmol scale reaction. The yield corresponds to isolated yield of product **2j**.

intermediate.[21] Indeed, screening showed that the use of acetonitrile (ACN) at 10% (v/v) was optimal to maximize the yield of the C–H amidation product **2a** over the byproduct **3a** (Tables S2 and S3). Additional tuning of the reaction showed that slightly alkaline (pH 9) conditions are optimal for the reaction (Table S4). Under these optimized conditions, Mb(H64V,V68A) catalyzes the formation of the allylic β-lactam product **1a** in high enantiopurity (>99% ee) in 57% yield. The configuration of the β-lactam product was determined to be *S* based on crystallographic analysis of the fluorinated analog **2b** (Table S5 and Fig. S1)

With optimized reaction conditions in hand, the Mb(H64V,V68A)-catalyzed allylic C–H amination reaction was tested against various dioxolanone substrates (Fig. 3). Notably, a range of different electron withdrawing and electron donating groups at the *ortho*, *meta* or *para* position of the phenyl ring in

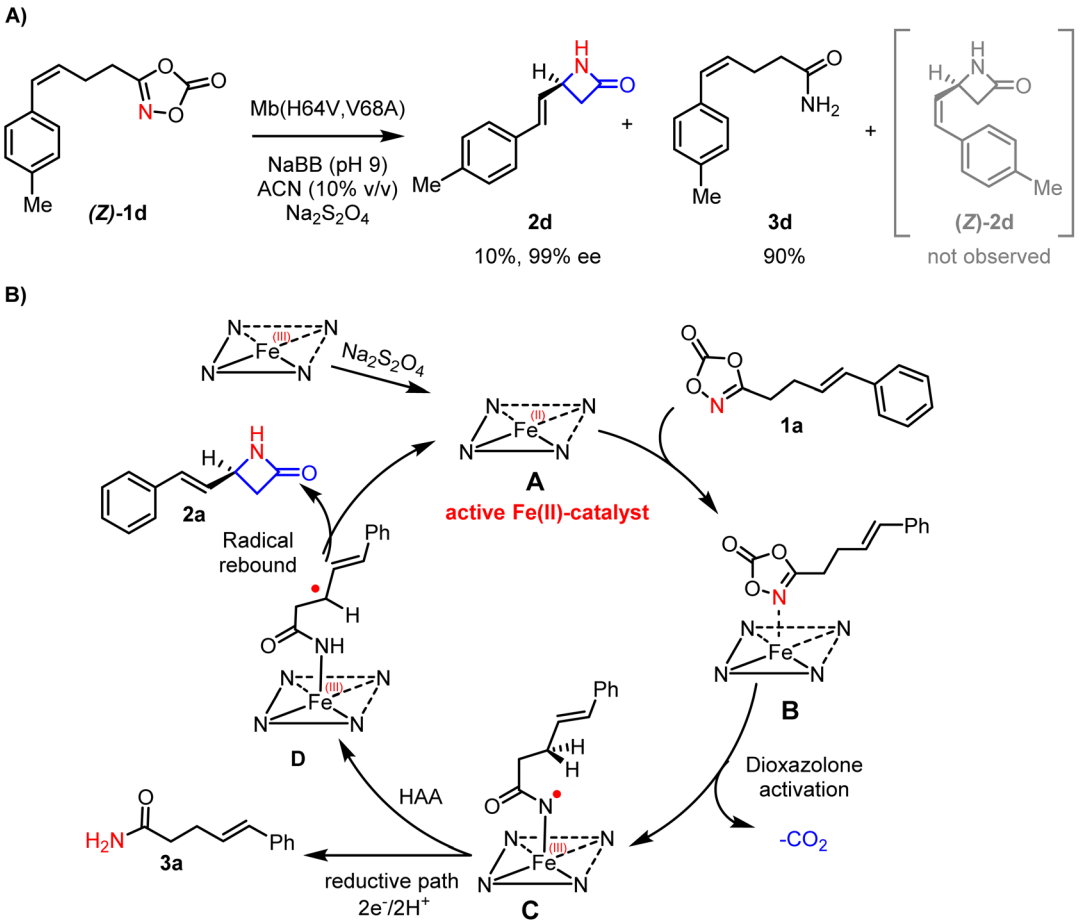


Fig. 4 Mechanistic studies and proposed reaction mechanism. (A) *Z*/*E* isomerization experiment with *cis*-dioxazolone *Z*-1D. Reaction conditions: 400 μL scale, 20 μM protein, 10 mM **1a**, 10 mM $Na_2S_2O_4$ in NaBB buffer (50 mM, pH 9), 10% (v/v) acetonitrile, 2 hours, room temperature, anaerobic conditions. (B) Proposed catalytic cycle.

the dioxazolone substrates were tolerated by the enzyme to give the desired allylic β-lactam products **2b**–**2k** in good to satisfactory yields and with consistently high enantioselectivity (99% ee). Interesting structure–activity trends could be derived from this set of reactions. For the *para*-substituted substrates, the yields of C–H aminated product was found to depend, in part, on the electronic nature of the substituent, as indicated by the significantly higher yield for the methoxy-substituted product **2e** (74% yield) compared to fluorine-containing counterpart **2b** (32% yield) (Fig. 3). For the *meta* substituted dioxazolones, on the other hand, the yield of the C–H amination product appeared to be influenced in larger part by the size of the substituent, as suggested by the higher yield of the *meta*-fluorinated product **2h** (53%) compared to the bulkier, methyl- and chloro-substituted counterparts **2f** and **2g** (24–14% yield). For the *ortho*-substituted dioxazolones, the ortho-methyl substituted substrate gave the highest yield of the β-lactam product **2j** (87%) compared to methoxy (**2k**) and fluoro-substituted analogs (**2i**), which were produced in 39–41% yields. The thiophene-containing substrate **1l** was also processed by the enzyme to give the desired β-lactam **2l** with excellent enantioselectivity, albeit in low yield (11%). Importantly, the reactions with **1m** further demonstrated that the substitution at the level of the olefin group is also compatible with the present system to afford the allylic β-lactam **2m** in moderate yields (24%) but high enantiomeric excess (98% ee). To further demonstrate the synthetic utility of the present methodology, a preparative scale reaction (2 mmol) was carried out using **1j** as the substrate, which afforded 230 mg of the β-lactam product **2j** in 72% isolated yield and high enantiopurity (99% ee) (Fig. 3). Overall, the high enantioselectivity of this scaled-up reaction along with the preserved and consistently high enantioselectivity observed across all the products in Fig. 3 highlight the generality of the Mb(H64V,V64A) catalyst and methodology for the asymmetric synthesis of allylic β-lactams.

Experiments were then carried out to investigate the mechanism of the reaction, also for *vis-a-vis* comparison with previous mechanistic studies on biocatalytic formation of γ-lactams from dioxazolones.[32] Consistent with the previous finding, transformation of the *cis* dioxazolone substrate **(*Z*)-1d** produced only the *E*-configured product **2d** (Fig. 4A), indicating full isomerization of the double bond at the level of an allylic radical intermediate prior to the C–N bond formation step. Then intramolecular kinetic isotope effect (KIE) experiments

were carried out using the monodeuterated substrate **1a–d**, which showed the absence of a positive KIE at the level of the aminated C–H bond (KIE = 1.04 ± 0.1), indicating that C–H bond cleavage is not part of the rate determining steps of the reaction (see SI). Based on these results and previous studies,[58] we propose a mechanism in which reaction of the catalytically active ferrous protein reacts with the dioxazolone substrate to form a heme–dioxazolone complex which undergoes decarboxylation to produce the acyl-nitrene intermediate **C** (Fig. 4B). The latter mediates an allylic C–H bond abstraction to the generate the allylic radical intermediate **D**, followed by C–N bond formation *via* a radical rebound process. As suggested by previous calculations,[32] and consistent with the *E*/*Z* isomerization and KIE experiments of Fig. 4, the C–N bond-forming step is believed to be the rate-limiting and enantioselectivity-determining step of the reaction.

Conclusions

In conclusion, we have reported a first example of a biocatalytic strategy for the enantioselective synthesis of allylic β-lactams *via* an intramolecular C(sp^3)–H amidation reaction. Using an engineered myoglobin variant, this approach provides access to medicinally and synthetically valuable β-lactam products with excellent enantioselectivity. Mechanistic studies support a stepwise radical pathway, where the formation of the C–N bond *via* a radical rebound mechanism plays a pivotal role in determining enantioselectivity. A most notable feature of this strategy is its exquisite biocatalyst-controlled chemoselectivity, which enables construction of a strained β-lactam ring by favoring functionalization of an allylic C(sp^3)–H bond over the more facile functionalization of the adjacent olefin group, typically observed with synthetic transition metal catalysts (Fig. 1D).[55] These results illustrate the value of new-to-nature biocatalysis not only for expanding the range of stereoselective strategies for C–N bond formation *via* direct C(sp^3)–H functionalization but also for accessing chemical transformations not currently accessible through chemocatalysis.

Author contributions

S. R. and R. F. conceptualized the study. N. Z. J. and Z. W. performed the bulk of the experiments with assistance by A. C. and S. R., under R. F. supervision. S. R., N. Z. J., Z. W. and R. F. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2495142 contains the supplementary crystallographic data for this paper.[59]

All experimental procedures and spectroscopic data can be found in the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6sc01440b.

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