LETTER

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Oxidative diversification of amino acids and peptides by small-molecule iron catalysis

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Secondary metabolites synthesized by non-ribosomal peptide synthetases display diverse and complex topologies and possess a range of biological activities[1,2]. Much of this diversity derives from a synthetic strategy that entails pre-[3] and post-assembly[2] oxidation of both the chiral amino acid building blocks and the assembled peptide scaffolds. The vancomycin biosynthetic pathway is an excellent example of the range of oxidative transformations that can be performed by the iron-containing enzymes involved in its biosynthesis[4]. However, because of the challenges associated with using such oxidative enzymes to carry out chemical transformations *in vitro*, chemical syntheses guided by these principles have not been fully realized in the laboratory[5]. Here we report that two small-molecule iron catalysts are capable of facilitating the targeted C–H oxidative modification of amino acids and peptides with preservation of α-centre chirality. Oxidation of proline to 5-hydroxyproline furnishes a versatile intermediate that can be transformed to rigid arylated derivatives or flexible linear carboxylic acids, alcohols, olefins and amines in both monomer and peptide settings. The value of this C–H oxidation strategy is demonstrated in its capacity for generating diversity: four 'chiral pool' amino acids are transformed to twenty-one chiral unnatural amino acids representing seven distinct functional group arrays; late-stage C–H functionalizations of a single proline-containing tripeptide furnish eight tripeptides, each having different unnatural amino acids. Additionally, a macrocyclic peptide containing a proline turn element is transformed via late-stage C–H oxidation to one containing a linear unnatural amino acid.

A synthetic strategy inspired by non-ribosomal peptide synthetases (NRPSs) was envisioned wherein a small-molecule-catalyst-mediated C–H oxidation of an amino acid in a monomer or peptide generates a versatile synthetic intermediate that may be transformed into numerous structural and functional group types with retained optical purity. Analogous strategies have successfully employed prefunctionalized pluripotent building blocks to generate structurally diverse compounds[6,7]. Limited examples of C–H oxidations of amino acid derivatives are known and of these few have been demonstrated in peptides[8–11]. Chelate-controlled C–H arylations are positionally limited to amino-terminal residues[9] and stoichiometric C–H hydroxylation methods suffer from operational difficulty, modest efficiency, and have no demonstrated chemoselectivity in peptide settings[10,11]. A survey of the possible products of C–H oxidation at the side chains of the proteinogenic amino acids led us to reason that targeting hydroxylation at C5 of proline would provide an excellent first example of our envisioned strategy (Fig. 1c). Oxidation of proline, a biomass chemical, to 5-hydroxyproline (**5-HP**) furnishes an intermediate having a highly synthetically versatile hemiaminal functional group that may be transformed to unnatural amino acids (UAAs) and UAA-containing peptides. **5-HP** and 5-functionalized proline derivatives are currently accessed via multistep synthetic routes from pre-functionalized glutamic acid or pyroglutamic acid derivatives[12]. Recently, methods have been developed to furnish α-aryl pyrrolidines via iron salts[13] or photoredox catalysts[14] and chiral α-nitrile pyrrolidines via biocatalysis[15]. These α-amine functionalization methods generally proceed via generation of positively charged nitrogen via quaternization or amino radical cation formation followed by decarboxylation, deprotonation or abstraction of the α-hydrogen of the homolytically and heterolytically weakest C–H bond. On a proline core, C–H abstraction may occur preferentially at the weakest α-(C2)–H (bond dissociation enthalpy of about 87 kcal mol^{-1})[16] bond versus the α-(C5)–H (bond dissociation enthalpy of about 90 kcal mol^{-1}), leading to racemization. Free hydroxyl radical oxidations[17] and photoredox-mediated arylations[14,18] of proline form 2-pyrrolidone and racemic α-arylated derivatives, respectively.

We sought a method for a direct (C5)–H hydroxylation of proline that would preserve its C2 stereocentre and those in every amino acid residue present in peptide settings. Additionally, we sought an oxidant that would be highly chemoselective for the target residue over the other amino acid side-chain C–H bonds. For these reasons, we evaluated the small-molecule non-haem iron catalysts Fe(PDP) (catalyst **1**)[19,20] and Fe(CF_3PDP) (catalyst **2**)[21] (Fig. 1b). Such bulky, electrophilic C–H oxidation catalysts do not discriminate solely on the basis of C–H bond dissociation energies, but rather select between C–H bonds on the basis of their electronic, steric and stereoelectronic properties. This, along with observations of stereoretentive oxidations of an isoleucine derivative and dipeptide, suggested that site selectivity for C5 proline oxidation was likely, given that C2 is both sterically and electronically deactivated[21]. Additionally, in complex-molecule settings, catalyst **1** was shown to oxidize hyperconjugatively activated C–H bonds (for example, ethereal C–H bonds) at faster rates than other aliphatic C–H bonds[20], suggesting that regioselectivity for α-(C5)–H proline, hyperconjugatively activated by the nitrogen lone pair, would effectively compete with C–H oxidation of aliphatic amino acid residues.

We began our investigations into this NRPS-inspired strategy with the evaluation of the oxidation reactivity of N-(4-nitrophenylsulfonyl)-(*L*)-proline methyl ester (−)-**3** with Fe(PDP) (**1**) (Fig. 2a). Subjection of (−)-**3** to reported slow addition conditions[20] with **1** (25 mol%), AcOH, and H_2O_2 at room temperature led to full oxidation at C5 of proline, affording the glutamic acid derivative (−)-**4** in 77% yield, presumably via over-oxidation of singly oxidized **5-HP** as its open-chain tautomer. We reasoned that a milder oxidation protocol may allow for selective oxidation of proline to the desired **5-HP**, and found that by lowering the reaction temperature to 0 °C and decreasing the catalyst loading (iterative addition of **1,** 15 mol%), it was possible to isolate **5-HP** in good yield (62%) (see the Supplementary Information for details). A similarly encouraging result was observed with the less rigid proline homologue pipecolic acid, affording 6-hydroxylpipecolic acid **5** in 53% yield. Interestingly, Boc-proline methyl ester (where

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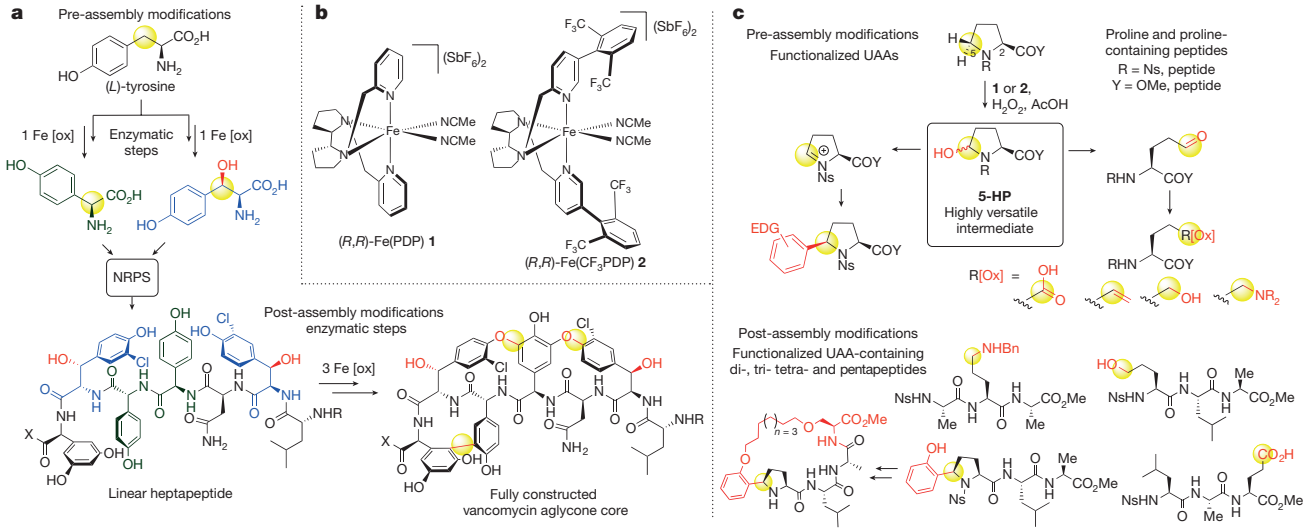

Figure 1 | NRPS-inspired strategy for iron-catalysed C–H oxidative functionalization of amino acids and peptides. a, Oxidative tailoring iron-enzyme pre- and post-assembly modifications in the biosynthesis of vancomycin. Iron enzymes diversify tyrosine into the two UAAs hydroxyphenylglycine and β-hydroxytyrosine, which are incorporated by the NRPS into a heptapeptide. Post-assembly oxidative tailoring by iron enzymes effects side-chain cross-linking to afford the vancomycin core. X = OH or the peptidyl carrier protein; R = H or methyl. **b**, The small-molecule non-haem iron C–H oxidation catalysts Fe(PDP) **1** and Fe(CF_3PDP) **2**. PDP = [*N*,*N*′-bis(2-pyridylmethyl)]-2,2′-bipyrrolidine. **c**, Iron catalysts **1** and **2** catalysed pre-assembly oxidative modification of proline to afford numerous classes of UAAs. Post-assembly oxidative modifications by **1** and **2** of proline-containing polypeptides to furnish UAA-functionalized polypeptides. Ns = 4-nitrophenylsulfonyl; Bn = benzyl; [ox], oxidation; yellow circles indicate sites of oxidative modification.

Boc = *tert*-butoxylcarbonyl) gave oxidation to Boc-pyroglutamic acid methyl ester under the same conditions as the major isolated product (see the Supplementary Information for details). Gratifyingly, these experiments resulted in conditions for C5 oxidation of proline with control of the final oxidation state. Notably, we did not observe oxidation or racemization of the C2 stereocentre, even under the forcing conditions used to generate the glutamic acid analogue (−)-**4**.

We questioned whether *in situ* derivatization of the hemiaminal functional group of **5-HP** could effect pre-assembly oxidative tailoring modifications, diversifying proline into non-proteinogenic amino acids. Arylated proline motifs are prevalent in medicinal agents[22]. Direct arylation at the 5-position of proline could be effected by a sequential proline oxidation/arylation procedure: crude **5-HP** generated by Fe(PDP) oxidation is treated with BF_3OEt_2 to afford a highly reactive *N*-sulfonyl iminium ion intermediate that undergoes diastereoselective nucleophilic attack by an electron-rich arene (Fig. 2b). We first explored phenols as arenes in this transformation: phenol and 2-naphthol adducts (+)-**6** and (−)-**7** were isolated in high yields with >20:1 *syn*-stereochemistry, and with generally high regioselectivity (3.1:1.0 ortho/para for **6**, >20:1 for **7**). Using this oxidative arylation procedure, a novel crosslink (−)-**8** between proline and tyrosine was efficiently forged, reminiscent of the side-chain crosslinks between amino acids effected by oxidative tailoring enzymes (for example, vancomycin). Additionally, the intriguing natural product–amino acid conjugate (+)-**9** was produced when the polyphenol natural product resveratrol was employed as the arene. The scope of electron-rich arenes is not limited to phenols, as high yields and selectivites were observed with heteroarenes such as anthrone, indole, and benzothiophene, affording adducts **10**–**12**. The adducts were generally formed in *syn*-stereochemistry—possibly owing to steric factors introduced by the nosyl group—confirmed by single-crystal X-ray diffraction of adducts (−)-**7**, (+)-**11**, and (+)-**12** (see the Supplementary Information for details). Interestingly, the anthrone adduct (−)-**10** was furnished as the *anti*-diastereomer. Overall, this proline oxidation/arylation procedure efficiently furnishes stereochemically enriched (>20:1 diastereomeric ratio) 5-arylproline derivatives, presenting an array of structural features and functional groups.

To complement the synthetic versatility of **5-HP** as a precursor to rigid proline derivatives, we envisioned that *in situ* transformations of the open-chain aldehyde tautomer of **5-HP** could be a second avenue to access a variety of linear UAA structures that remain difficult synthetic targets[23] (see the Supplementary Information for details). We developed a one-pot approach starting with Fe(PDP) (**1**) oxidation of (−)-**3** to **5-HP** followed by either reduction, olefination or reductive amination to furnish linear terminal hydroxyl-, olefin- or amino-containing UAAs (Fig. 2c). For example, (−)-**3** was transformed to the 5-hydroxy-*L*-norvaline derivative (+)-**13** via Fe(PDP) (**1**) hydroxylation followed by *in situ* reduction with $NaBH_4$. Alternatively, C–H hydroxylation followed by Wittig olefination of (*L*)- or (*D*)-proline furnished the chiral (*L*)-2-aminohex-5-enoic acid derivative (+)-**15** and its enantiomer (43% and 40%, respectively) (see the Supplementary Information for details). Similarly, performing this transformation on the proline homologue pipecolic acid generated the (*D*)-2-amino-6-heptenoic acid derivative (−)-**17**. The retention of stereochemistry at C2 of proline (−)-**3** over these sequences was established by synthetic derivatization and comparison of optical activity of products (−)-**4**, (+)-**13**, and (+)-**15** to known compounds (see the Supplementary Information for details).

Fe(PDP) (**1**)-catalysed C–H hydroxylation followed by reductive amination afforded a general method of installing amines to furnish valuable UAAs, such as the chiral ornithine derivative (+)-**19**. The diversity of functionalized secondary and primary amines that may be used renders this a powerful transformation; for example, using 1-(2-aminopyridyl)-piperazine, a fluorescently labelled aminopyridine conjugated UAA (−)-**21** may be directly generated in an optically active form. The backbone amine of any suitably protected amino acid may be used to furnish backbone-to-side-chain linkages such as in the tryptophan derivative (+)-**22**. Utilization of less sterically encumbered primary amines results in reductive amination followed by intramolecular cyclization to afford optically enriched 3-aminopiperidinone scaffolds like (+)-**23**. Notably, additional reactive functionality can be united with the proline-derived backbone: proline oxidation/reductive amination with propargylamine furnished alkyne-substituted (+)-**24**, which may undergo a Cu-catalysed azide-alkyne cycloaddition to

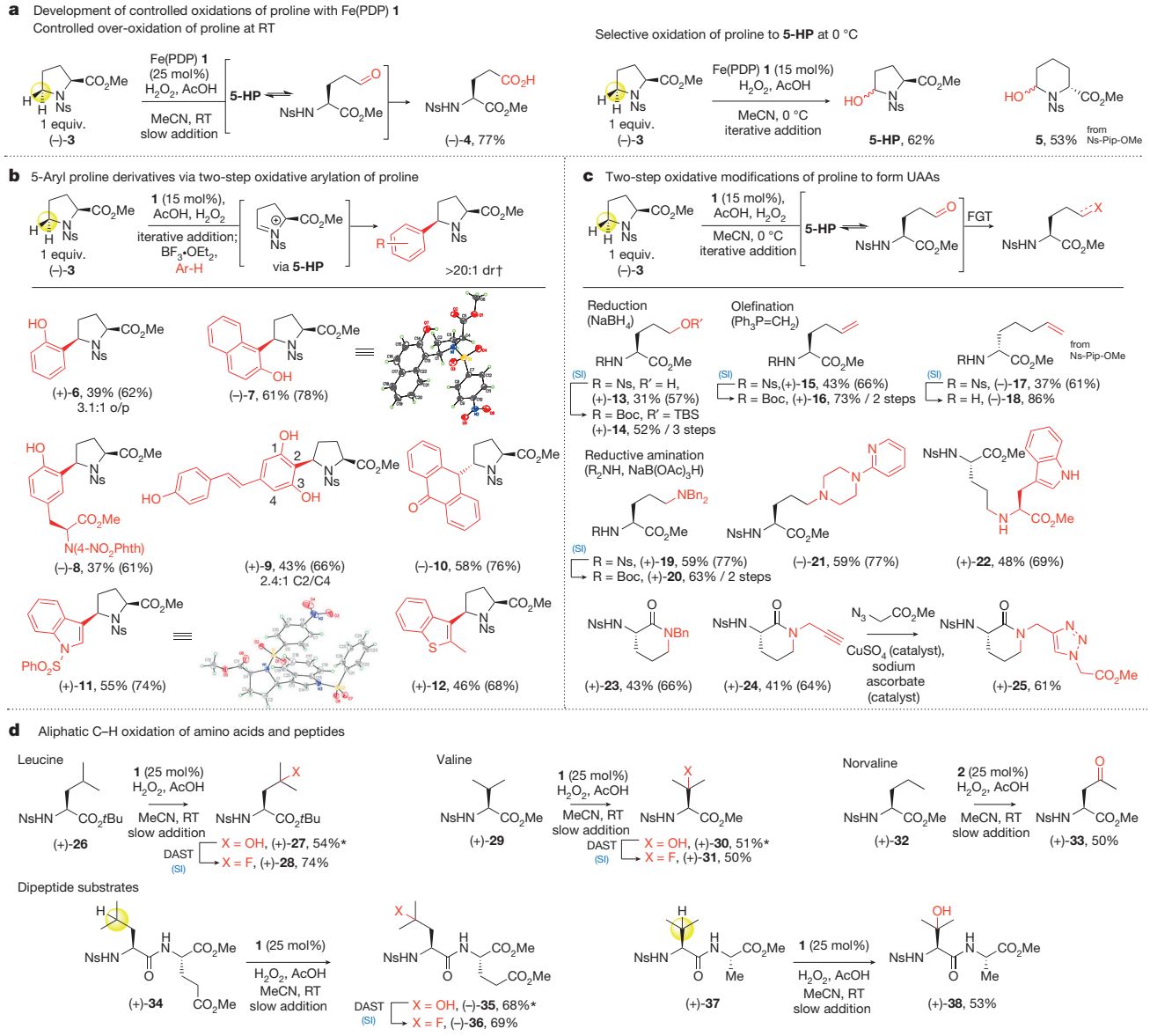

Figure 2 | Four amino acids transformed to twenty-one chiral UAAs via small-molecule iron-catalysed C–H hydroxylations. a, Oxidations to glutamic acid and **5-HP**. Slow addition was as follows: AcOH (0.5–5 equiv.) was added to a MeCN solution of (−)-**3**. **1** (0.25 equiv. in CH_3CN, 0.2 M) and H_2O_2 (5–9 equiv. in CH_3CN, 0.4–0.72 M) were added via syringe pump (75 min) simultaneously. Iterative addition: (−)-**3** in MeCN was cooled to 0 °C. **1** (5 mol%) and AcOH (0.5 equiv.) were added, followed by dropwise addition (3 min) of 0 °C MeCN solution of H_2O_2 (1.9 equiv.). The addition of **1**, AcOH and H_2O_2 was repeated twice, every 10 min. Crude **5-HP** was passed through a silica gel plug and concentrated before arylation (in **b**) or reduction, olefination, or reductive amination (in **c**). **d**, Aliphatic C–H oxidation. *Starting material recycled once. †dr, diastereomeric ratio, after isolation; o/p, ortho/para; RT, room temperature; DAST, diethylaminosulfur trifluoride; SI, Details for all methods can be found in the Supplementary Information. Yields represent the average of two experiments. Yields in parentheses are average yield per step.

afford optically enriched triazole (+)-**25**. Significantly, these UAAs can be readily denosylated under mild conditions to furnish chiral amino esters with N-protecting groups common to peptide synthesis (for example, (+)-**14**, (+)-**16**, (−)-**18**, and (+)-**20**).

Additionally, we evaluated the generality of this method for the oxidation of chiral-pool amino acids possessing oxidizable aliphatic side-chain residues with stronger tertiary and secondary C–H bonds to enable direct routes to important UAAs (Fig. 2d). For example, exposure of leucine-, valine-, and *L*-norvaline-derived substrates to the reaction conditions with either **1** (tertiary oxidation) or **2** (secondary oxidation) at room temperature resulted in efficient aliphatic C–H oxidation, affording the tertiary hydroxyl derivatives (+)-**27** and (+)-**30** and the δ-oxo derivative (+)-**33** in good yields. These chiral hydroxylated amino acids are widely used in medicinal chemistry and as synthetic intermediates[24]. Importantly, the ability of catalysts **1** and **2** to selectively oxidize aliphatic side-chain C–H bonds of amino acids was not diminished when this method was applied to dipeptides possessing these residues, as similarly efficient oxidation of a leucine and valine residue were observed in these settings, see (−)-**35** and (+)-**38**. The tertiary hydroxyl groups in (+)-**27**, (+)-**30**, and (−)-**35** were converted to the fluorinated amino acids (+)-**28** and (+)-**31** and the fluorinated peptide (−)-**36**. Collectively, these results demonstrate a small-molecule-catalysed NRPS pre-assembly modification strategy, wherein a simple proline precursor and three other amino acids prone to oxidation are converted to twenty-one chiral UAAs representing seven distinct functional group

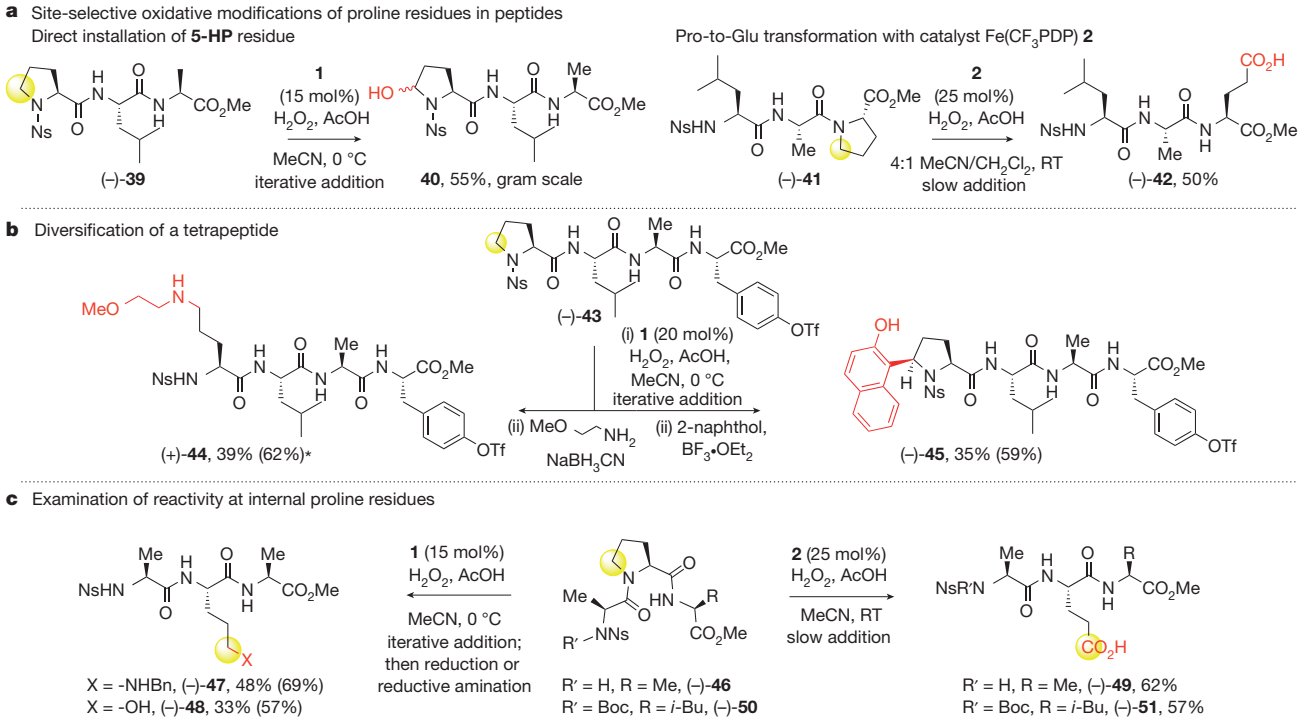

Figure 3 | Direct oxidative modification of N-terminal, C-terminal and internal proline residues in peptides by small-molecule iron-catalysed C–H hydroxylation. a, Chemoselective oxidative modifications of N-terminal and C-terminal proline-containing peptides. **b**, Diversification of a tetrapeptide via chemoselective oxidation/functionalization sequences. *Starting material recycled once. **c**, Direct oxidative opening of internal proline residues in tripeptides affords UAA- or glutamic-acid-containing tripeptides. Yields represent the average of two experiments. Yields in parentheses note the average yield per step. All slow additions were run with AcOH (0.5 equiv.)/H_2O_2 (5 equiv.).

arrays: alcohols, fluorines, aryls, carboxylates, olefins, ketones and amines.

Post-assembly oxidative tailoring modifications in the more complex setting of a peptide were possible with catalysts **1** and **2** because of high functional group tolerance for amides in peptide settings, as well as high chemoselectivity in C5 oxidation of proline preferentially over other aliphatic C–H oxidations (Fig. 3a). For example, subjecting tripeptide (−)-**39** to oxidation with **1** at 0 °C led to the direct hydroxylation of the proline residue, with no observed off-site oxidation at the leucine residue. The use of catalyst **2** for proline over-oxidation in peptides was superior to catalyst **1**, possibly owing to the increased steric bulk around the iron centre of **2**, which minimizes off-site tertiary oxidation and deleterious coordination with the peptide. Underscoring the site selectivity and chemoselectivity that can be achieved with catalyst **2**, it is noteworthy that a +4 change in oxidation state of a methylene carbon in (−)-**41** to a carboxylic acid in (−)-**42** could be effected in the presence of an oxidizable tertiary C–H bond of a nearby leucine residue.

The Fe(PDP) C–H hydroxylation/arylation and reductive amination sequences were further tested in a challenging tetrapeptide setting (−)-**43** that included potentially oxidizable leucine, alanine, and tyrosine residues (Fig. 3b). Proline oxidation occurred with high site selectivity, and functionalization proceeded to efficiently furnish the amine (+)-**44** and the naphthol adduct (−)-**45**. We additionally examined the positional flexibility of proline oxidation, and found that catalyst **2** controlled over-oxidation of tripeptides containing an internal proline and furnished the corresponding glutamic acid derivatives (−)-**49** and (−)-**51** in excellent overall yields (62% and 57% yield, respectively; Fig. 3c). The internal proline of tripeptide (−)-**46** could also be transformed to the amine-containing residue (−)-**47** and the bishomoserine residue (−)-**48** via catalyst **1** oxidation followed by either reductive amination or reduction, respectively.

We sought to test our hypothesis that the ability to selectively install **5-HP** residues into proline-containing precursor peptides with catalyst **1** or catalyst **2** would enable a small-molecule-catalysed post-assembly oxidative strategy, affording late-stage diversification of peptides to new structures containing natural or unnatural amino acids (Fig. 4a). The tripeptide (−)-**39** was subjected to the full suite of proline oxidative modification reactions to install a phenol (oxidative arylation), carboxylic acid (controlled over-oxidation with catalyst **2**), alkene (Wittig olefination), alcohol (reduction), and four different amine functionalities (reductive amination), in good overall yields (average 40%, 63% per step) without observing epimerization of α-C–H bonds (chiral amino acid analysis of (−)-**53** indicated no epimerization to *D*-configuration of any residues; see the Supplementary Information for details). Strikingly, eight novel peptide sequences (**52**–**59**) were rapidly constructed from one peptide in one to two steps, underscoring the potential for such reactions to enable efficient diversification of native residues in a preassembled peptide setting. Alternative routes to make all eight peptides would involve eight separate syntheses from the respective amino acid building blocks, including the synthesis of UAAs.

Macrocyclic peptides are highly prevalent among NRPS natural products, and are valued as therapeutic candidates relative to their linear analogues owing to their increased stability against chemical and enzymatic degradation, increased receptor selectivity, and pharmacokinetic properties[25–28]. We sought to explore how the rapid installation of new functional groups in peptides from a simple proline residue could allow for the rapid construction and elaboration of macrocycles[7]. The phenol-, carboxylic acid- and olefin-derived tripeptides (**52**–**54**, see above) could be rapidly transformed into three macrocycles containing the ethereal (−)-**60**, amide (−)-**61**, and aliphatic (−)-**62** linkers, respectively, via short synthetic sequences (Fig. 4a) (see the Supplementary Information for details). The presence of functional groups on the linkage of stapled peptide-like structures like these has been shown to modulate the biological properties of the overall product[29]. Collectively, the small library of molecules rapidly synthesized from tripeptide (−)-**39** demonstrates the breadth of functionally

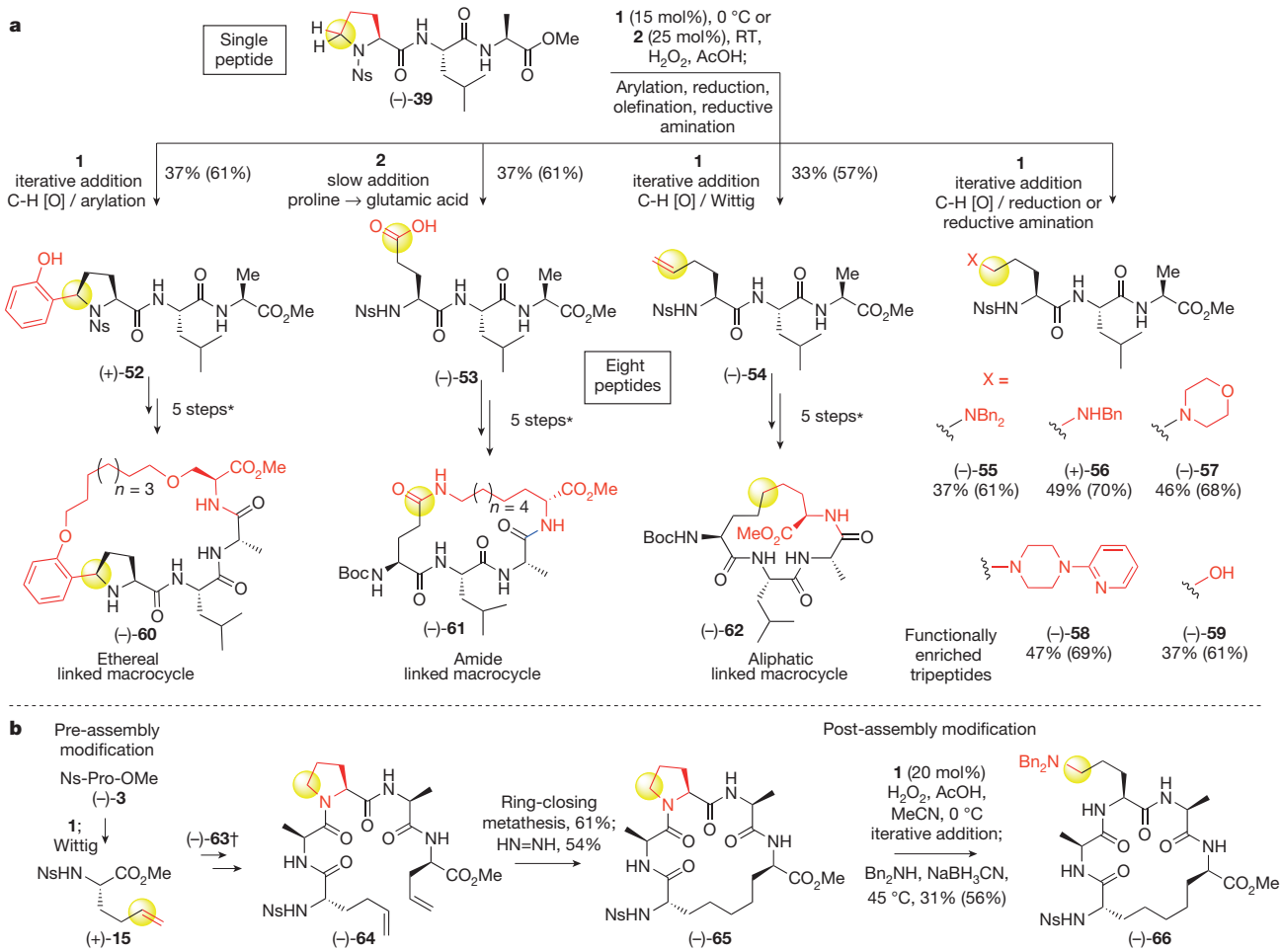

Figure 4 | Small-molecule iron-catalysed oxidative diversification of tripeptides and macrocycles. a, Fe(PDP) **1** and Fe(CF_3PDP) **2** oxidative modifications of a single tripeptide enables synthesis of eight functionally diverse UAA-containing tripeptides. Slow addition was run with AcOH (0.5 equiv.)/H_2O_2 (5 equiv.). *Macrocycles **60**–**62** were prepared from tripeptides **52**–**54** using 5-step transformations involving alkene appendage to the UAA residue, coupling of a fourth alkene-containing amino acid to the C terminus, conversion of Nosyl to a Boc group, ring-closing metathesis and hydrogenation. Individual routes vary in order. See the Supplementary Information for full details. **b**, Late-stage diversification of a proline-containing peptide macrocycle via post-assembly oxidation/reductive amination. †(—)-63 is Boc-Ala-Pro-Ala-(D)-Allylglycine-OMe. Yields generally represent the average of two experiments. Yields in parentheses indicate the average yield per step.

and structurally enriched molecules that can be accessed using our post-assembly oxidative strategy.

Proline has been used by synthetic chemists as a turning-element that helps to bring the ends of a linear peptide together to promote macrocyclizations[30]. We explored whether the NRPS-inspired C–H oxidation/functionalization strategy would enable internal proline residues, which serve as turn elements within a linear peptide sequence, to be transformed into a range of natural and unnatural acyclic amino acids. Encouraged by the high positional flexibility of proline oxidation (see above), we assembled a proline-containing linear pentapeptide (−)-**64**, using our pre-assembly modified UAA (+)-**15**, which was rapidly produced by C–H oxidation/olefination of proline (−)-**3**, and subjected it to ring-closing metathesis, which proceeded in good yield (61%) to furnish an 18-membered macrocycle. Reduction of the internal olefin with diimide provided the macrocyclic pentapeptide (−)-**65**. Application of the post-assembly C–H oxidation/functionalization with **1** to this macrocycle resulted in the late-stage conversion of the proline conformational element to a dibenzylornithine derivative (−)-**66**. This example underscores the potential for proline residues as diversifiable structural elements that may be functionally and structurally transformed at late stages in complex peptide settings.

The NRPS-inspired oxidation strategy described herein represents a powerful method for the direct diversification of amino acids and peptides via C–H oxidation. We anticipate that this strategy will benefit small-peptide therapeutics by enabling the rapid exploration of key physical properties (such as charge, polarity, and steric and stereochemical effects) and inspire the continued invention of non-directed, site-selective C–H oxidation reactions that unmask the potential for the pluripotent reactivity of C–H bonds in complex molecules.

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Supplementary Information is available in the online version of the paper.

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Author Information The crystal data have been deposited in The Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk) under accession numbers 1478939, 1478940, and 1478941. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to M.C.W. (mcwhite7@illinois.edu).