Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Modification of N-Terminal α-Amine of Proteins via Biomimetic ortho-quinone-mediated Oxidation

Ping Wang (wangp1@sjtu.edu.cn)
Shanghai Jiao Tong University https://orcid.org/0000-0002-8640-1483
Siyao Wang
Shanghai Jiao Tong University
Qingqing Zhou
Shanghai Jiao Tong University
Yunxue Li
Shanghai Jiao Tong University
Xiaoping Chen
Shenzhen University
Rong-Hua Luo
Chinese Academy of Sciences
Liu-Meng Yang
Key Laboratory of Animal Models and Human Disease Mechanisms，Kunming Institute of Zoology, Chinese Academy of Sciences
Yong-Tang Zheng
Kunming Institute of Zoology https://orcid.org/0000-0001-5469-0324

Article

Keywords:

Posted Date: September 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-64642/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published at Nature Communications on April 15th, 2021. See the published version at https://doi.org/10.1038/s41467-021-22654-7.

Modification of N-Terminal α-Amine of Proteins via Biomimetic *ortho*-quinone-mediated Oxidation

Siyao Wang#,[a] Qingqing Zhou#,[a] Xiaoping Chen#,[b] Rong-Hua Luo#,[c] Yunxue Li,[a] Liu-Meng Yang,[c] Yong-tang Zheng,*[c] Ping Wang*[a]

[a] Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China

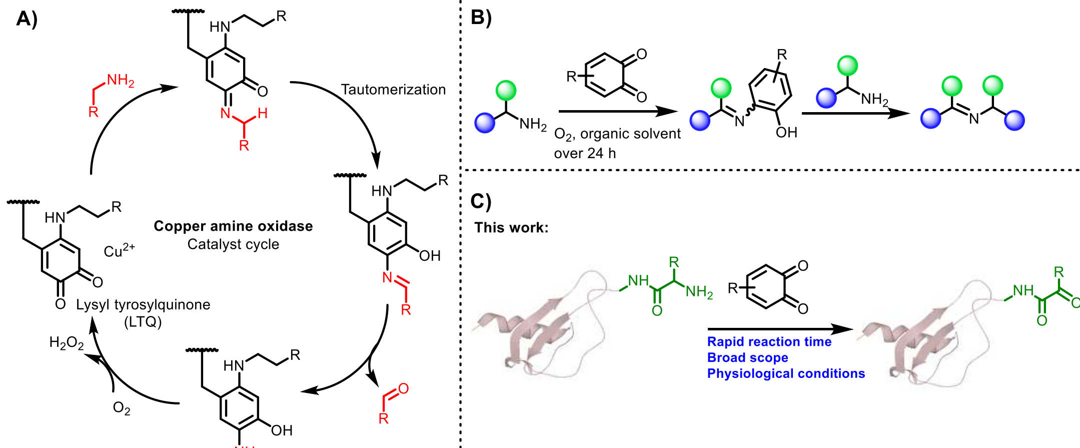
[b] Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province College of Physics and Optoelectronic Engineering, Shenzhen University, Shenzhen 518060, China

[c] Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences, Key Laboratory of Bioactive Peptides of Yunnan Province, KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research in Common Diseases, Center for Biosafety Mega-Science, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan 650223, China.

ABSTRACT

Naturally abundant quinones are important molecules, which play essential roles in various biological processes due to their reduction potential. In contrast to their universality, the reactions between quinones and proteins remain sparse. Herein, we report the development of unprecedented strategy to protein modification via a biomimetic quinone-mediated oxidation at the N-terminus. By exploiting unique reactivity of an ortho-quinone reagent, the α-amine of protein N-terminus was oxidized to generate aldo or keto handle for orthogonal conjugation. Its applications have been demonstrated using a range of proteins, including myoglobin and ubiquitin. The effect of this method was further highlighted via the preparation of a series of 17 MIP-1β analogs, followed by preliminary anti-HIV activity and cell viability assays, respectively. This method offers a fast, efficient and complementary approach to existing strategies for protein N-terminus modification.

29



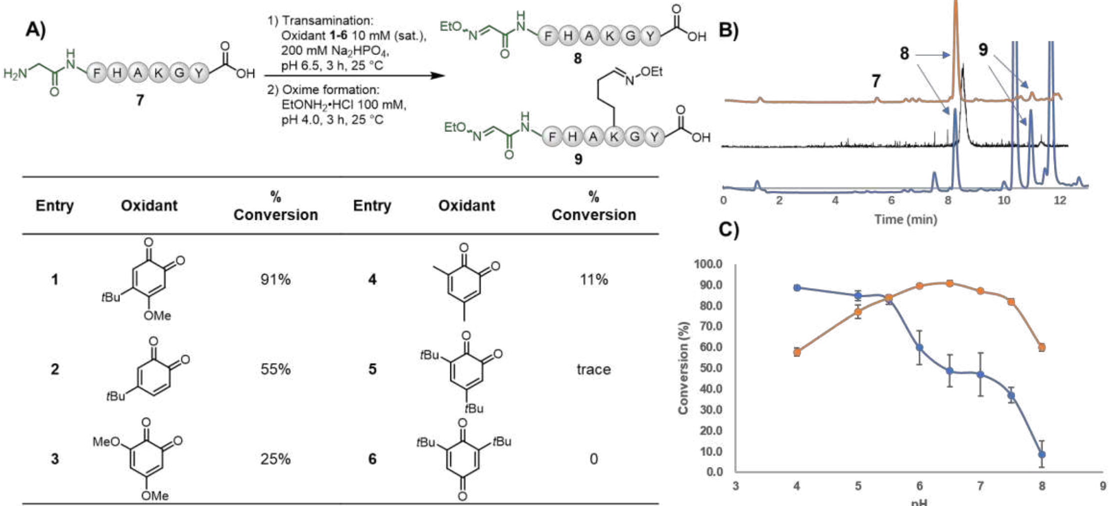
30 **Figure 1: Development of protein N-terminus modification via quinone-mediated**
31 **transamination:** A) Natural catalytic cycle of CuAOs, B) Oxidation of primary amines
32 with ortho-quinone to form imines, C) Biomimetic quinone-mediated transamination
33 inspired by CuAOs.

34 Oxidation reactions play an important role in organic chemistry and are widely
35 involved in crucial biological transformations.[1-2] In line with the broad interest in the
36 development of more selective and mild oxidation reactions, *ortho*-quinone cofactors
37 of copper amine oxidases (CuAOs) have been extensively studied due to their high
38 catalytic efficiency. In the catalytic cycle, the Tyr side chain is converted into lysyl
39 tyrosylquinone, which can readily oxidize primary amines into aldehydes *via* a
40 quinone-mediated transamination pathway using O_2 as a co-oxidant to complete the
41 catalytic cycle (Fig. 1A).[3-4] Recently, significant progress has been achieved toward the
42 design of quinone-based catalysts with major contributions from Corey,[5] Fleury,[6]
43 Kobayashi,[7] Stahl[8-10] and Luo (Fig. 1B).[11-13] These biomimetic quinone-based catalysts
44 show specific chemoselectivity toward the dehydrogenation of primary, secondary,
45 tertiary amines or other reactions.[14-16] The applications of quinone oxidation have been
46 largely limited to small molecule transformations despite the significant progress in this
47 area of research.[17-18] On the other side, in nature, the interactions between quinones and
48 proteins are important but complex in fundamental process of life. Early work was
49 provided by Mason in 1955, who reported that *o*-quinones can react with proteins to
50 form a colored complex *via* the N-terminal residue.[19] In addition, many research studies
51 have been carried out on the role of quinone in protein cross-linking.[20-22] However, the

52 relationships between quinones and proteins have not been fully elucidated on a
53 molecular level. Nevertheless, the intrinsic design of quinones may provide an effective
54 opportunity to modify proteins under physiological conditions.

55 Existing methods used to modify proteins are mainly confined to nucleophilic
56 amino acids, such as Cys and Lys, and hence result in heterogeneous conjugates because
57 of the high frequency of these amino acids.[23-25] In this context, the emergency of
58 selective modification of the N-terminus of proteins has led to the single site
59 functionalization of proteins.[26-30] Although significant progress has been made, many
60 current methods relied on assistance of a side-chain functional group, such as β-
61 nucleophilically-functionalized Cys[31-35] or Ser/Thr.[36-38] Transamination reactions
62 performed under physiological conditions have been elegantly developed by Francis
63 and co-workers utilizing pyridoxal-5-phosphate (PLP)[39-46] or N-methylpyridinium-4-
64 carboxaldehyde benzenesulfonate salt (Rapoport's salt)[47] as oxidants, which can
65 convert the N-terminus of proteins into aldo or keto functionalities for oxime ligation
66 or other bio-conjugation reactions.[48-50] However, the efficiency of these methods relies
67 on the specific N-terminal sequence[51] and prolonged reaction times in the presence of
68 PLP can potentially result in denaturation.[52] Thus, given the generality of quinone and
69 its derivates in the effective oxidation of amines, we hope to investigate whether or not
70 the quinones may be suitable for the selective oxidation of the N-terminal α-amine of
71 protein to aldehyde or ketone with fast kinetics as well as a wide scope of amino acids.
72 Herein, we report a selective, efficient and rapid method for modifying the N-terminus
73 of proteins *via* a quinone-mediated oxidation of N-terminal α-amine of complex
74 peptides and proteins under physiological conditions (Fig. 1C). Several examples have
75 been demonstrated using a range of peptides and proteins, including ubiquitin and
76 myoglobin. Moreover, we prepared a library of macrophage inflammatory protein-1β
77 (MIP-1β)[53-54] analogues using a combination of native chemical ligation and quinone-
78 mediated transamination, where the late-stage modification of the N-terminus of MIP-
79 1β can lead to a 20-fold increase in its anti-HIV-1 activity.

80 To begin our journey, a range of quinone derivates **1–6** were prepared with
81 different functionalities with an aim toward fine-tuning their reactivity to be selective
82 for the α-amine selective rather than the ε-amine of Lys, as well as other functionalities.[7,
83 11-12] We tested the transamination reaction of model peptide **7** (1 mM) with the sequence
84 of GFHAKGY in an aqueous solution buffered at pH 6.5 using 10 mM (saturated) of
85 each of the quinone (**1–6**) as the oxidant (Fig. 2A). The oxidized product was
86 subsequently reacted with $EtONH_2$ to form its corresponding oxime **8**. 4-*tert*-Butyl-5-
87 methoxy-4-*tert*-butyl-*o*-benzylquinone 1 achieved near quantitative conversion (>90%)
88 to generate product **8** at pH 6.5 in 3 h with <2% Lys oxidation observed *via* LCMS due
89 to the extraordinary low pKa of the N-terminal amine compared to that of the Lys side
90 chain amine .[26] 4-*tert*-Butyl-*o*-benzylquinone 2 could also achieve 55% conversion at
91 pH 6.5; the major by-product **9** was attributed to the undesired Lys side chain oxidation
92 (>40%) (Fig. 2B). Further optimization of the pH of the transamination reaction with
93 either quinone **1** or **2** showed that methoxyquinone **1** has an optimal pH range of 6.0–
94 6.5, while the side reaction during using quinone **2** can be minimized by lowering
95 reaction pH to 4.0 (90% conversion to give target product **8**) (Fig. 2C). Thus,
96 methoxyquinone **1** serves as the most effective oxidant (see Section 8 in the SI for the
97 discussion of the mechanism). A time-course monitoring study was performed to verify
98 that the reaction reached to completion in 3 h at room temperature (see section 3.1.3. in
99 the SI). Although an early work demonstrated that using Cu^{2+} salts is necessary for N-
100 termini oxidation with glyoxylate as reagent,[55] addition of Cu^{2+} in this reaction did not
101 increase the yield of the oxidative product formed. Interestingly, when compared with
102 such reactions with small molecules, quinone-mediated transamination can readily push
103 towards completion (90% conversion) without formation of the imine derivative of the
104 starting material, which may potentially quench the reaction.

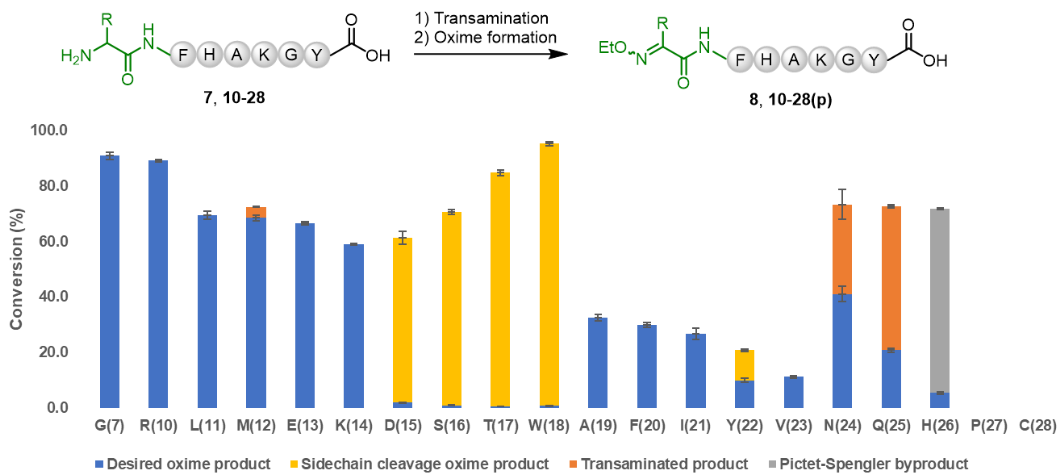


Entry	Oxidant	% Conversion	Entry	Oxidant	% Conversion
1	tBu, OMe	91%	4		11%
2	tBu	55%	5	tBu, tBu	trace
3	MeO, OMe	25%	6	tBu, tBu	0

Figure 2. Optimization of the reaction conditions used in the biomimetic transamination reaction. A) Screening of oxidants **1-6** used for the transamination reaction with model peptide **7**; B) LC trace obtained for the transamination reaction using quinone **1** (in yellow) or **2** (in blue); C) Optimization of the pH of the transamination reaction using quinone 1 (in yellow) or **2** (the rate of conversion was calculated by integrating the related peaks of the LC trace measured at 280 nm, although TIC showed a >99% conversion rate of product **8**).

Next, to investigate the scope of the N-terminal residue, we expanded the N-terminal residue of peptide **7** to the remaining 19 amino acid residues **10-28**. As it shows in Fig. 3, Arg peptide **10**, Leu peptide **11**, Met peptide **12,** Glu peptide **13** and Lys peptide **14** reacted cleanly and gave satisfactory conversion (>60%) in 3 h to afford their desired products without any significant observation of the expected side-products. Asp peptide **15** underwent decarboxylation during the oxidation and thereafter formed the methylated product (R = Me, see SI). Ser peptide **16**, Thr peptide **17** and Trp peptide **18** were oxidized, but all formed the side-chain cleaved oxime product **8.** Peptides **19-23** (containing Ala, Phe, Ile, Tyr and Val as N-termini, respectively) can also be converted into their desired oxime products, but with lower conversions. Asn peptide **24** and Gln peptide **25** were oxidized in the first step, but the resulting side-chain cyclized ketal product could not be effectively reopened using ethoxyamine, which caused a decrease in conversion to the desired oxime product. His peptide **26** failed to be oxidized due to the quinone oxidant **1** remaining bonded to the peptide, which was

127 in line with that previously reported and attributed to a Pictet-Spengler-type side
128 reaction.[40] Unfortunately, Pro peptide **27** was not oxidized as a secondary amine. For
129 comparison, Cys peptide **28** decomposed (see section 3.2. in the SI for predicted
130 structures of all by-products).

131 

132 **Figure 3. Landscape for the transamination of 20 canonical amino acids attached**
133 **on the N-terminal residue of the model peptides.** Reaction conditions: 1)
134 Transamination: oxidant **1** (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2)
135 Oxime formation: $EtONH_2$·HCl (100 mM), pH 4.0, 3 h, 25 °C.

136 After screening the scope of N-terminal residue in the reaction, we next applied
137 this method to more complex therapeutic peptides and proteins. The first target chosen
138 was COVID-19 spike protein 319-347 fragment, which was located in its receptor
139 binding domain. The peptide has an Arg residue at its N-terminus and a free cysteine
140 residue, which originally forms a disulfide bond with another Cys in the spike protein.
141 However, the free Cys residue was not tolerated under our oxidative conditions. An
142 Acm group was introduced to the peptide during this stage. Due to the low solubility of
143 this peptide, the transamination step was carried out in 2 M Gn·HCl buffer with all the
144 other reaction conditions unchanged with the exception of the reaction time, which was
145 also extended to 6 h. The reaction proceeded smoothly to afford the oxime product **29**
146 with 85% conversion (Fig. 4A). Tetracosactide, a therapeutic peptide bearing an N-
147 terminal Ser, one Met and four Lys residues in its sequence, was successfully oxidized

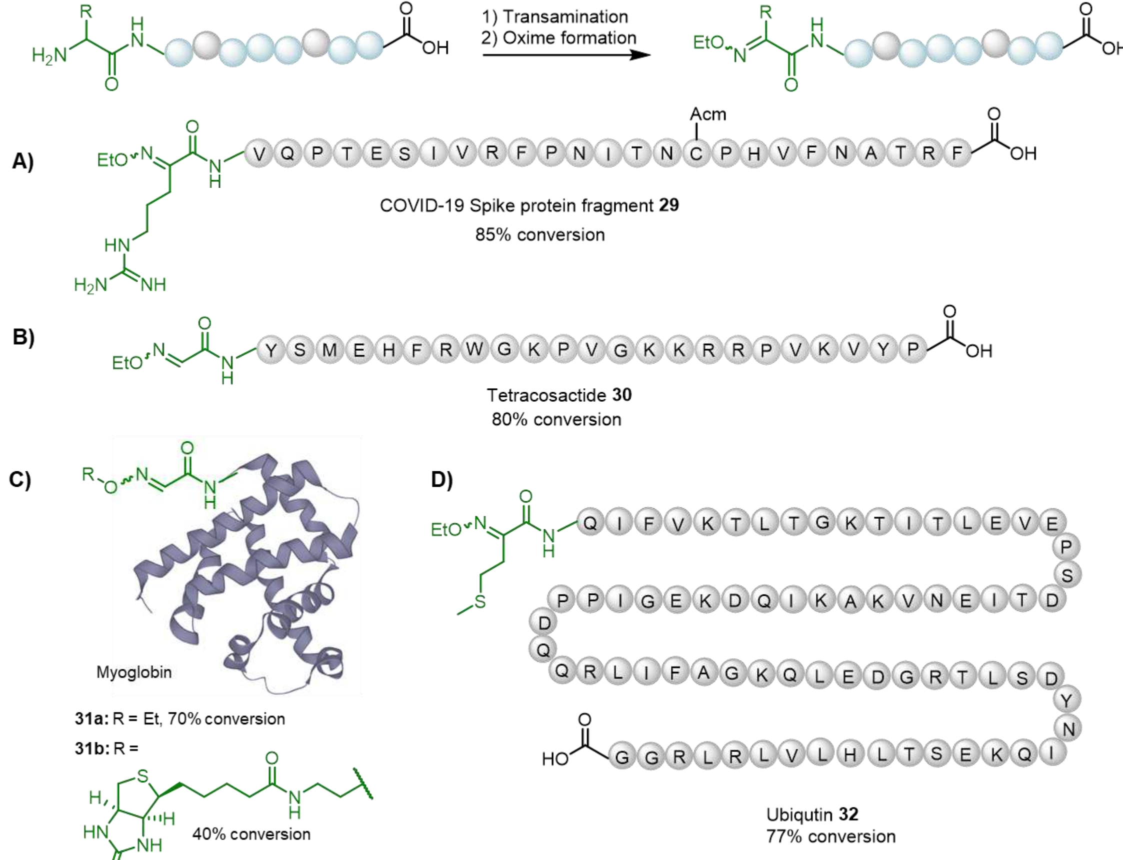
148 under the standard reaction conditions in 3 h. The desired oxime product **30** was formed
149 with 80% conversion monitored by LCMS (Fig. 4B).

150 The scope of this transformation was next examined using myoglobin, which
151 contains 18 Lys residues in the sequence (Fig. 4C). This reaction was conducted in
152 aqueous buffer at pH 6.0 to minimize over-oxidation of the Lys side chain and thus the
153 reaction time was extended to 5 h. Due to the limitation of the chromatographic
154 techniques used, total ion counts (TICs) were used to determine the conversion rate
155 after a simple workup procedure (see section 3.5 in the SI). The desired ethyl oxime
156 product **31a** was observed with 70% conversion, 15% unreacted starting material and
157 15% of the over-oxidized by-product. Furthermore, a biotinylated tagcwas synthesized
158 and incorporated to myoglobin. However, due to the low reactivity of this tag, an excess
159 of oxidant 1 could not be quenched immediately, which then led to further oxidation
160 during the oxime formation step. To address this issue, once the first transamination
161 reaction was complete, an ethyl acetate extraction step was carried out to remove the
162 excess oxidant. The resulting solution underwent the oxime formation step overnight
163 to afford a 40% conversion of biotinylated protein **31b**.

164 In nature, many proteins are expressed with Met as their N-terminus. Therefore,
165 we examined this transformation with ubiquitin, which contained an N-terminal Met.
166 In 2 M Gn·HCl buffer, ubiquitin was easily converted into its oxime product **32** with
167 77% conversion (Fig. 4D).

168 With all the examples above, we confirmed that ortho-quinone 1 was able to
169 oxidize peptides or proteins with various N-termini. Therefore, it can serve as an
170 alternative strategy to existing methods and used to expand the application of
171 transamination in biological research.

172 Considering the fast kinetics and wide N-termini tolerance of our transamination
173 reaction, we applied this methodology to a medicinal target, macrophage inflammatory



174

175 **Figure 4. Site selective peptide modification via quinone-mediatated**
176 **transamination reaction.** A) Reaction conditions for COVID-19 spike protein
177 fragment **29**: 1) Transamination: 2 M Gn·HCl, oxidant **1** (10 mM, sat.), 200 mM
178 Na_2HPO_4, pH 6.5, 6 h, 25 °C; 2) Oxime formation: $EtONH_2$·HCl (100 mM), pH 4.0, 3
179 h, 25 °C. B) Reaction conditions for tetracosactide **30**: 1) Transamination: oxidant 1
180 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2) Oxime formation:
181 $EtONH_2$·HCl (100 mM), pH 4.0, 3 h, 25 °C; C) Reaction conditions for myoglobin
182 **31a-b**: 1) Transamination: oxidant **1** (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.0, 5 h,
183 25 °C; 2) Oxime formation for **31a**: $EtONH_2$·HCl (100 mM), pH 4.0, 3 h, 25 °C; oxime
184 formation for **31b**: extraction with EtOAc (2 x 1.0 mL), then biotinylated tag **S4** (100
185 mM), pH 4.0, 16 h, 25 °C. D) Reaction conditions for ubiquitin **32**: 1) Transamination:
186 2 M Gn·HCl, oxidant **1** (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2) Oxime
187 formation: $EtONH_2$·HCl (100 mM), pH 4.0, 3 h, 25 °C.

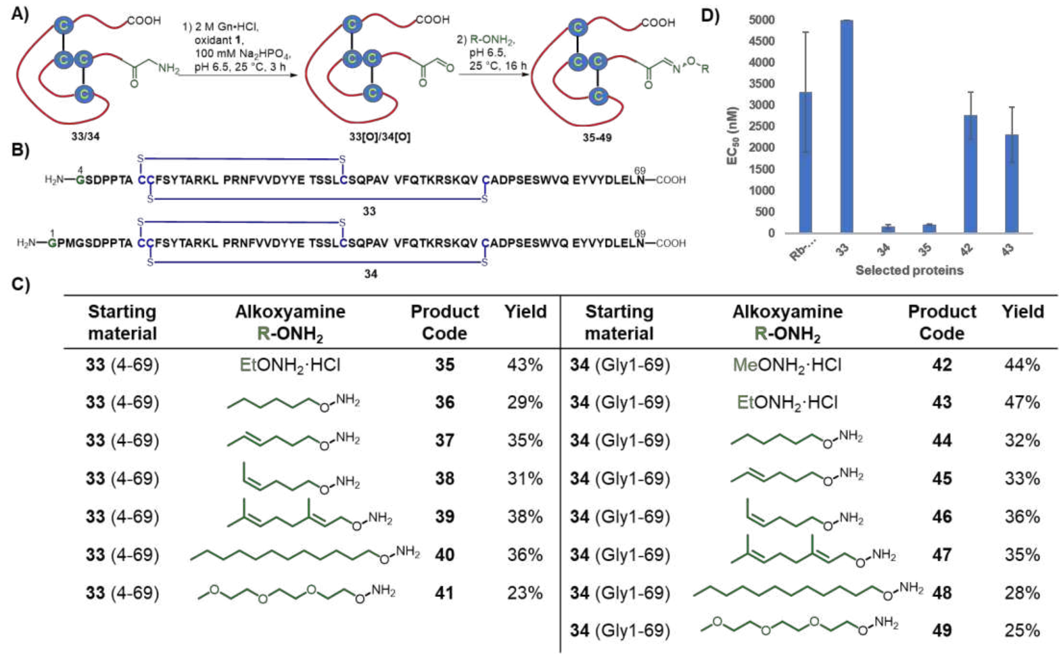
188 protein-1β (MIP-1β). MIP-1β (CCL4)[56] exhibits potent anti-HIV-1 activity[57] by binding
189 to the hydrophobic transmembrane helix bundle of CCR5 *via* its N-terminal domain.[58-
190 61] Due to the increasing viral resistance and inefficient therapies, the discovery of new
191 HIV-1 inhibitors is still highly coveted.[62-63] Therefore, diversification of the N-terminal
192 region of CCLs can be greatly beneficial toward the development of new peptide HIV-

193 1 inhibitors.[64-67] However, current methods rarely facilitate such direct modifications
194 of its N-termini. Thus, the late-stage modification of CCL N-termini will afford an ideal
195 strategy for this area of research.

196 Thus, a merging of late-stage oxidation and state-of-the-art peptide ligation
197 method will allow the fast generation of a protein library for the rapid screening of
198 potential drugs. We synthesized a truncated MIP-1β 4-96 protein **33**, which contained
199 Gly4 and the full-length form of MIP-1β **34** with the mutation of Ala1 to Gly for
200 oxidation (Fig. 5B). Both proteins were chemically synthesized *via* native chemical
201 ligation[68-69] and re-folded using Cys/Cys_2 redox[70] buffer (see SI) on a >30 mg scale (see
202 section 4 for the synthesis of MIP-1β variants **33** and **34**).

203 Having established a facile protocol to prepare MIP-1β proteins on a large-scale,
204 we next performed the protein N-terminal transamination-oxime ligation reaction to
205 modify the protein. Various alkyl alkoxyamines were chosen to optimize the anti-HIV-
206 1 activity of MIP-1β due to their hydrophobicity (Fig. 5A). Hexyl, (*E*)-hexyl, (*Z*)-hexyl,
207 geranyl and decyl hydroxylamine were used to investigate the influence of the
208 hydrocarbon chains with different conformation or chain lengths toward fine-tuning the
209 bioactivity (Fig. 5C). In addition, we also synthesized PEGylated hydroxylamine as a
210 hydrophilic tag for comparison. The oxidation reactions were performed in 2 M
211 guanidine buffer, because this concentration of guanidine can solubilize target proteins
212 without denaturing them. Oxidant **1** was added into the target protein **33** or **34** in buffer
213 solution at pH 6.5 and the solution was incubated at 25°C for 3 h. Subsequently, after
214 the addition of the alkoxyamine, the mixture was readjusted to pH 6.5 and reacted for
215 a further 16 h to afford modified proteins **35**-**49** (Fig. 5C). Because MIP-1β proteins
216 and $MeONH_2 \cdot HCl$ or $EtONH_2 \cdot HCl$ were dissolved well in this buffer solution, the
217 ligations proceeded smoothly and gave high isolated yields (43% for **35**, 44% for **42**
218 and 47% for **43** respectively). Reactions with fatty alkoxyamines became biphasic due
219 to their poor solubility. Therefore, vigorous stirring was necessary during these
220 reactions. After 24 h of reaction, a small amount of starting material was still present

221 (~20% by HPLC analysis), which suggested that these lipo-hydroxylamines did not mix
222 well even in an aqueous buffer and hence resulted in a decreased yield (28–38%).
223 PEGylated variants (**41** and **49**) were extremely low yielding (23 and 25%, respectively)
224 due to unknown side reactions. Transamination with quinone **1** is fully compatible with
225 the disulfide bonds in these proteins without disrupting their biological activity, as
226 shown by HPLC-MS and the anti-HIV-1 assay.



Starting material	Alkoxyamine R-ONH2	Product Code	Yield	Starting material	Alkoxyamine R-ONH2	Product Code	Yield
33 (4-69)	EtONH2·HCl	**35**	43%	**34** (Gly1-69)	MeONH2·HCl	**42**	44%
33 (4-69)	NH2	**36**	29%	**34** (Gly1-69)	EtONH2·HCl	**43**	47%
33 (4-69)	NH2	**37**	35%	**34** (Gly1-69)	NH2	**44**	32%
33 (4-69)	NH2	**38**	31%	**34** (Gly1-69)	NH2	**45**	33%
33 (4-69)	NH2	**39**	38%	**34** (Gly1-69)	NH2	**46**	36%
33 (4-69)	NH2	**40**	36%	**34** (Gly1-69)	NH2	**47**	35%
33 (4-69)	NH2	**41**	23%	**34** (Gly1-69)	NH2	**48**	28%
				34 (Gly1-69)	NH2	**49**	25%

227

228 **Figure 5. Late-stage modification of MIP-1β proteins *via* quinone-mediated**
229 **selective oxidation of N-terminal amine.** A) Reaction scheme for the transamination
230 of MIP-1β protein **33** and **34**; B) The sequences of protein **33** and **34**; C) A summary
231 of the transamination/oxime ligation of protein 33 and 34 and the isolated yields for all
232 reactions; D) Anti-HIV-1 activity of selected MIP-1β analogs with EC50 <5000 nM.

233 With all the modified MIP-1β variants in hand, we performed an anti-HIV-1
234 activity assay to evaluate their inhibitory activity. Recombinant MIP-1β (**Rh-CCL4**)
235 was used as the primary standard with a measured half maximal effective concentration
236 (EC_{50}) value of 3.3 µM (Fig. 5D). Protein **33** (4-69) resulted in a complete loss of anti-
237 HIV-1 activity within the concentration range studied (up to 5 µM). Interestingly,
238 ethylated variant **35** regained its activity with an EC_{50} value of 200 nM. Full-length
239 Gly1-69 protein **34** also displayed increased inhibitory activity with an EC_{50} value of

240 157 nM upon substitution of Ala1 with Gly, which suggested that a branched methyl
241 group decreases the binding affinity between MIP-1β and CCR5. Further extension of
242 full-length protein **34** with methoxyamine and ethoxyamine showed comparable
243 activities against HIV-1 by an order of magnitude (**42**: EC_{50} = 2.7 μM and **43**: EC_{50} =
244 2.3 μM), whereas all the lipo-variants and PEGylated variants exhibited no activity
245 within the concentration range studied (all EC_{50} >5 μM, see SI). Besides, a cell viability
246 assay with MTT was also performed to explore the cytotoxicity of the synthetic proteins
247 toward Tzm-bl cells. In our investigations, all the synthetic proteins exhibited
248 cytotoxicity with 50% cytotoxic concentration (CC_{50}) values of >50 μM (see SI), which
249 indicated that the proteins showed no cytotoxic behavior. In our future studies, we will
250 further optimize the N-terminal domain with hydroxyamines bearing other
251 functionalities and thereafter explain the exact mechanism of how these modified
252 proteins exhibit their inhibitory activity against HIV-1 both *in vitro* and *in vivo*.

253 **CONCLUSION**

254 In summary, we have demonstrated a highly selective and mild method for
255 modifying the N-terminus of protein *via* a biomimetic quinone-based transamination
256 reaction. The key features of this reaction include rapid reaction time, high selectivity
257 and a broad scope of amino acids. Covid-19 spike protein fragment (Arg),
258 tetracosactide (Ser), myoglobin (Gly) and ubiquitin (Met) along with a range of model
259 peptides were given as examples. Furthermore, the preparation of several MIP-1β
260 analogs *via* native chemical ligation and late-stage N-terminal modification has
261 demonstrated its potential utility in medicinal chemistry. We believe this method will
262 be a useful tool for protein modification and medicinal chemistry studies.

263 **References**

264 1. Wall, S. B.; Oh, J.-Y.; Diers, A. R.; Landar, A., Oxidative modification of proteins:
265 an emerging mechanism of cell signaling. *Front. Physiol.* **2012,** *3*, 369-369.
266 2. Cai, Z.; Yan, L.-J., Protein Oxidative Modifications: Beneficial Roles in Disease
267 and Health. *J. Biochem. Pharmacol. Res.* **2013,** *1* (1), 15-26.

268 3. Klinman, J. P.; Bonnot, F., Intrigues and intricacies of the biosynthetic pathways
269 for the enzymatic quinocofactors: PQQ, TTQ, CTQ, TPQ, and LTQ. *Chem. Rev.* **2014,**
270 *114* (8), 4343-65.
271 4. Ling, K.-Q.; Kim, J.; Sayre, L. M., Catalytic Turnover of Benzylamine by a Model
272 for the Lysine Tyrosylquinone (LTQ) Cofactor of Lysyl Oxidase. *J. Am. Chem. Soc.*
273 **2001,** *123* (39), 9606-9611.
274 5. Corey, E. J.; Achiwa, K., Oxidation of primary amines to ketones. *J. Am. Chem.*
275 *Soc.* **1969,** *91* (6), 1429-1432.
276 6. Largeron, M.; Fleury, M.-B., Bioinspired Oxidation Catalysts. *Science* **2013,** *339*
277 (6115), 43-44.
278 7. Yuan, H.; Yoo, W.-J.; Miyamura, H.; Kobayashi, S., Discovery of a
279 Metalloenzyme-like Cooperative Catalytic System of Metal Nanoclusters and Catechol
280 Derivatives for the Aerobic Oxidation of Amines. *J. Am. Chem. Soc.* **2012,** *134* (34),
281 13970-13973.
282 8. Wendlandt, A. E.; Stahl, S. S., Quinone-Catalyzed Selective Oxidation of Organic
283 Molecules. *Angew. Chem. Int. Ed.* **2015,** *54* (49), 14638-14658.
284 9. Wendlandt, A. E.; Stahl, S. S., Bioinspired Aerobic Oxidation of Secondary
285 Amines and Nitrogen Heterocycles with a Bifunctional Quinone Catalyst. *J. Am. Chem.*
286 *Soc.* **2014,** *136* (1), 506-512.
287 10. Wendlandt, A. E.; Stahl, S. S., Modular o-Quinone Catalyst System for
288 Dehydrogenation of Tetrahydroquinolines under Ambient Conditions. *J. Am. Chem.*
289 *Soc.* **2014,** *136* (34), 11910-11913.
290 11. Zhang, R.; Qin, Y.; Zhang, L.; Luo, S., Mechanistic Studies on Bioinspired Aerobic
291 C–H Oxidation of Amines with an ortho-Quinone Catalyst. *J. Org. Chem.* **2019,** *84* (5),
292 2542-2555.
293 12. Qin, Y.; Zhang, L.; Lv, J.; Luo, S.; Cheng, J.-P., Bioinspired Organocatalytic
294 Aerobic C–H Oxidation of Amines with an ortho-Quinone Catalyst. *Org. Lett.* **2015,**
295 *17* (6), 1469-1472.
296 13. Zhang, R.; Luo, S., Bio-inspired quinone catalysis. *Chin. Chem. Lett.* **2018,** *29* (8),
297 1193-1200.
298 14. Huang, Z.; Lumb, J. P., A Catalyst-Controlled Aerobic Coupling of ortho-
299 Quinones and Phenols Applied to the Synthesis of Aryl Ethers. *Angew. Chem. Int. Ed.*
300 **2016,** *55* (38), 11543-7.
301 15. Chen, Y. H.; Li, H. H.; Zhang, X.; Xiang, S. H.; Li, S.; Tan, B., Organocatalytic
302 Enantioselective Synthesis of Atropisomeric Aryl-p-Quinones: Platform Molecules for
303 Diversity-Oriented Synthesis of Biaryldiols. *Angew. Chem. Int. Ed.* **2020,** *59* (28),
304 11374-11378.
305 16. Zhu, S.; Chen, Y. H.; Wang, Y. B.; Yu, P.; Li, S. Y.; Xiang, S. H.; Wang, J. Q.;
306 Xiao, J.; Tan, B., Organocatalytic atroposelective construction of axially chiral
307 arylquinones. *Nat Commun* **2019,** *10* (1), 4268.
308 17. Kim, B.; Storch, G.; Banerjee, G.; Mercado, B. Q.; Castillo-Lora, J.; Brudvig, G.
309 W.; Mayer, J. M.; Miller, S. J., Stereodynamic Quinone–Hydroquinone Molecules That

310 Enantiomerize at sp3-Carbon via Redox-Interconversion. *J. Am. Chem. Soc.* **2017,** *139*
311 (42), 15239-15244.
312 18. Storch, G.; Kim, B.; Mercado, B. Q.; Miller, S. J., A Stereodynamic Redox-
313 Interconversion Network of Vicinal Tertiary and Quaternary Carbon Stereocenters in
314 Hydroquinone–Quinone Hybrid Dihydrobenzofurans. *Angew. Chem. Int. Ed.* **2018,** *57*
315 (46), 15107-15111.
316 19. Mason, H. S., Reactions between Quinones and Proteins. *Nature* **1955,** *175* (4461),
317 771-772.
318 20. Waite, J. H.; Tanzeer, M. L., Polyphenolic Substance of Mytilus
319 edulis: Novel Adhesive Containing L-Dopa and Hydroxyproline. *Science* **1981,**
320 *212* (4498), 1038-1040.
321 21. Peter, M. G., Chemical Modifications of Biopolymers by Quinones and Quinone
322 Methides. *Angew. Chem. Int. Ed.* **1989,** *28* (5), 555-570.
323 22. Bruins, J. J.; Westphal, A. H.; Albada, B.; Wagner, K.; Bartels, L.; Spits, H.; van
324 Berkel, W. J. H.; van Delft, F. L., Inducible, Site-Specific Protein Labeling by Tyrosine
325 Oxidation-Strain-Promoted (4 + 2) Cycloaddition. *Bioconjug. Chem.* **2017,** *28* (4),
326 1189-1193.
327 23. Chow, H. Y.; Zhang, Y.; Matheson, E.; Li, X., Ligation Technologies for the
328 Synthesis of Cyclic Peptides. *Chem. Rev.* **2019,** *119* (17), 9971-10001.
329 24. Zhang, Y.; Zhang, Q.; Wong, C. T. T.; Li, X., Chemoselective Peptide Cyclization
330 and Bicyclization Directly on Unprotected Peptides. *J. Am. Chem. Soc.* **2019,** *141* (31),
331 12274-12279.
332 25. Wright, T. H.; Bower, B. J.; Chalker, J. M.; Bernardes, G. J. L.; Wiewiora, R.; Ng,
333 W.-L.; Raj, R.; Faulkner, S.; Vallée, M. R. J.; Phanumartwiwath, A.; Coleman, O. D.;
334 Thézénas, M.-L.; Khan, M.; Galan, S. R. G.; Lercher, L.; Schombs, M. W.; Gerstberger,
335 S.; Palm-Espling, M. E.; Baldwin, A. J.; Kessler, B. M.; Claridge, T. D. W.;
336 Mohammed, S.; Davis, B. G., Posttranslational mutagenesis: A chemical strategy for
337 exploring protein side-chain diversity. *Science* **2016,** *354* (6312), aag1465.
338 26. Baker, D. P.; Lin, E. Y.; Lin, K.; Pellegrini, M.; Petter, R. C.; Chen, L. L.; Arduini,
339 R. M.; Brickelmaier, M.; Wen, D.; Hess, D. M.; Chen, L.; Grant, D.; Whitty, A.; Gill,
340 A.; Lindner, D. J.; Pepinsky, R. B., N-Terminally PEGylated Human Interferon-β-1a
341 with Improved Pharmacokinetic Properties and in Vivo Efficacy in a Melanoma
342 Angiogenesis Model. *Bioconjug. Chem.* **2006,** *17* (1), 179-188.
343 27. Chan, A. O.-Y.; Ho, C.-M.; Chong, H.-C.; Leung, Y.-C.; Huang, J.-S.; Wong, M.-
344 K.; Che, C.-M., Modification of N-Terminal α-Amino Groups of Peptides and Proteins
345 Using Ketenes. *J. Am. Chem. Soc.* **2012,** *134* (5), 2589-2598.
346 28. Chan, W.-K.; Ho, C.-M.; Wong, M.-K.; Che, C.-M., Oxidative Amide Synthesis
347 and N-Terminal α-Amino Group Ligation of Peptides in Aqueous Medium. *J. Am.*
348 *Chem. Soc.* **2006,** *128* (46), 14796-14797.
349 29. Chen, D.; Disotuar, M. M.; Xiong, X.; Wang, Y.; Chou, D. H.-C., Selective N-
350 terminal functionalization of native peptides and proteins. *Chem. Sci.* **2017,** *8* (4), 2717-
351 2722.

352 30. MacDonald, J. I.; Munch, H. K.; Moore, T.; Francis, M. B., One-step site-specific
353 modification of native proteins with 2-pyridinecarboxyaldehydes. *Nat. Chem. Biol.*
354 **2015,** *11* (5), 326-331.
355 31. Dawson, P.; Muir, T.; Clark-Lewis, I.; Kent, S., Synthesis of proteins by native
356 chemical ligation. *Science* **1994,** *266* (5186), 776-779.
357 32. Becker, C. F. W.; Liu, X.; Olschewski, D.; Castelli, R.; Seidel, R.; Seeberger, P.
358 H., Semisynthesis of a Glycosylphosphatidylinositol-Anchored Prion Protein. *Angew.*
359 *Chem. Int. Ed.* **2008,** *47* (43), 8215-8219.
360 33. Roller, R. F.; Malik, A.; Carillo, M. A.; Garg, M.; Rella, A.; Raulf, M.-K.; Lepenies,
361 B.; Seeberger, P. H.; Varón Silva, D., Semisynthesis of Functional
362 Glycosylphosphatidylinositol-Anchored Proteins. *Angew. Chem. Int. Ed.* **2020,** *59* (29),
363 12035-12040.
364 34. Li, K.; Wang, W.; Gao, J., Fast and Stable N-Terminal Cysteine Modification
365 through Thiazolidino Boronate Mediated Acyl Transfer. *Angew. Chem. Int. Ed.*, DOI:
366 10.1002/anie.202000837.
367 35. Bandyopadhyay, A.; Cambray, S.; Gao, J., Fast and selective labeling of N-
368 terminal cysteines at neutral pH via thiazolidino boronate formation. *Chem. Sci.* **2016,**
369 *7* (7), 4589-4593.
370 36. Geoghegan, K. F.; Stroh, J. G., Site-directed conjugation of nonpeptide groups to
371 peptides and proteins via periodate oxidation of a 2-amino alcohol. Application to
372 modification at N-terminal serine. *Bioconjug. Chem.* **1992,** *3* (2), 138-146.
373 37. Huang, J.; Qin, H.; Sun, Z.; Huang, G.; Mao, J.; Cheng, K.; Zhang, Z.; Wan, H.;
374 Yao, Y.; Dong, J.; Zhu, J.; Wang, F.; Ye, M.; Zou, H., A peptide N-terminal protection
375 strategy for comprehensive glycoproteome analysis using hydrazide chemistry based
376 method. *Sci. Rep.* **2015,** *5* (1), 10164.
377 38. Zhang, Y.; Xu, C.; Lam, H. Y.; Lee, C. L.; Li, X., Protein chemical synthesis by
378 serine and threonine ligation. *Proc. Natl. Acad. Sci. U.S.A.* **2013,** *110* (17), 6657-6662.
379 39. Gilmore, J. M.; Scheck, R. A.; Esser-Kahn, A. P.; Joshi, N. S.; Francis, M. B., N-
380 Terminal Protein Modification through a Biomimetic Transamination Reaction. *Angew.*
381 *Chem. Int. Ed.* **2006,** *45* (32), 5307-5311.
382 40. Scheck, R. A.; Dedeo, M. T.; Iavarone, A. T.; Francis, M. B., Optimization of a
383 Biomimetic Transamination Reaction. *J. Am. Chem. Soc.* **2008,** *130* (35), 11762-11770.
384 41. Chen, J.; Gong, X.; Li, J.; Li, Y.; Ma, J.; Hou, C.; Zhao, G.; Yuan, W.; Zhao, B.,
385 Carbonyl catalysis enables a biomimetic asymmetric Mannich reaction. *Science* **2018,**
386 *360* (6396), 1438-1442.
387 42. Zhang, M.; Zhang, X.; Li, J.; Guo, Q.; Xiao, Q., A New Pyridoxal Derivative for
388 Transamination of N-Terminus of Proteins. *Chin. J. Chem.* **2011,** *29* (8), 1715-1720.
389 43. Karukurichi, K. R.; de la Salud-Bea, R.; Jahng, W. J.; Berkowitz, D. B.,
390 Examination of the New α-(2‘Z-Fluoro)vinyl Trigger with Lysine Decarboxylase: The
391 Absolute Stereochemistry Dictates the Reaction Course. *J. Am. Chem. Soc.* **2007,** *129*
392 (2), 258-259.

393 44. McCune, C. D.; Beio, M. L.; Sturdivant, J. M.; de la Salud-Bea, R.; Darnell, B. M.;
394 Berkowitz, D. B., Synthesis and Deployment of an Elusive Fluorovinyl Cation
395 Equivalent: Access to Quaternary α-(1′-Fluoro)vinyl Amino Acids as Potential PLP
396 Enzyme Inactivators. *J. Am. Chem. Soc.* **2017,** *139* (40), 14077-14089.
397 45. Nelson, D. L.; Applegate, G. A.; Beio, M. L.; Graham, D. L.; Berkowitz, D. B.,
398 Human serine racemase structure/activity relationship studies provide mechanistic
399 insight and point to position 84 as a hot spot for β-elimination function. *J. Biol. Chem.*
400 **2017,** *292* (34), 13986-14002.
401 46. Liu, Y. E.; Lu, Z.; Li, B.; Tian, J.; Liu, F.; Zhao, J.; Hou, C.; Li, Y.; Niu, L.; Zhao,
402 B., Enzyme-Inspired Axially Chiral Pyridoxamines Armed with a Cooperative Lateral
403 Amine Chain for Enantioselective Biomimetic Transamination. *J. Am. Chem. Soc.* **2016,**
404 *138* (34), 10730-10733.
405 47. Witus, L. S.; Netirojjanakul, C.; Palla, K. S.; Muehl, E. M.; Weng, C.-H.; Iavarone,
406 A. T.; Francis, M. B., Site-Specific Protein Transamination Using N-
407 Methylpyridinium-4-carboxaldehyde. *J. Am. Chem. Soc.* **2013,** *135* (45), 17223-17229.
408 48. Agarwal, P.; van der Weijden, J.; Sletten, E. M.; Rabuka, D.; Bertozzi, C. R., A
409 Pictet-Spengler ligation for protein chemical modification. *Proc. Natl. Acad. Sci. U.S.A.*
410 **2013,** *110* (1), 46-51.
411 49. Alam, J.; Keller, T. H.; Loh, T.-P., Functionalization of Peptides and Proteins by
412 Mukaiyama Aldol Reaction. *J. Am. Chem. Soc.* **2010,** *132* (28), 9546-9548.
413 50. Kitov, P. I.; Vinals, D. F.; Ng, S.; Tjhung, K. F.; Derda, R., Rapid, Hydrolytically
414 Stable Modification of Aldehyde-Terminated Proteins and Phage Libraries. *J. Am.*
415 *Chem. Soc.* **2014,** *136* (23), 8149-8152.
416 51. Purushottam, L.; Adusumalli, S. R.; Singh, U.; Unnikrishnan, V. B.; Rawale, D.
417 G.; Gujrati, M.; Mishra, R. K.; Rai, V., Single-site glycine-specific labeling of proteins.
418 *Nat. Commun.* **2019,** *10* (1), 2539.
419 52. Palla, K. S.; Witus, L. S.; Mackenzie, K. J.; Netirojjanakul, C.; Francis, M. B.,
420 Optimization and Expansion of a Site-Selective N-Methylpyridinium-4-
421 carboxaldehyde-Mediated Transamination for Bacterially Expressed Proteins. *J. Am.*
422 *Chem. Soc.* **2015,** *137* (3), 1123-1129.
423 53. Bystry, R. S.; Aluvihare, V.; Welch, K. A.; Kallikourdis, M.; Betz, A. G., B cells
424 and professional APCs recruit regulatory T cells via CCL4. *Nat. Immunol.* **2001,** *2* (12),
425 1126-32.
426 54. Irving, S. G.; Zipfel, P. F.; Balke, J.; McBride, O. W.; Morton, C. C.; Burd, P. R.;
427 Siebenlist, U.; Kelly, K., Two inflammatory mediator cytokine genes are closely linked
428 and variably amplified on chromosome 17q. *Nucleic Acids Res.* **1990,** *18* (11), 3261-
429 70.
430 55. Dixon, H. B. F., N-terminal modification of proteins—a review. *J. Protein Chem.*
431 **1984,** *3* (1), 99-108.
432 56. Menten, P.; Wuyts, A.; Van Damme, J., Macrophage inflammatory protein-1.
433 *Cytokine Growth Factor Rev.* **2002,** *13* (6), 455-81.

434 57. Cocchi, F.; DeVico, A. L.; Garzino-Demo, A.; Arya, S. K.; Gallo, R. C.; Lusso, P.,
435 Identification of RANTES, MIP-1α, and MIP-1β as the Major HIV-Suppressive Factors
436 Produced by CD8+ T Cells. *Science* **1995,** *270* (5243), 1811.
437 58. Blanpain, C.; Doranz, B. J.; Bondue, A.; Govaerts, C.; De Leener, A.; Vassart, G.;
438 Doms, R. W.; Proudfoot, A.; Parmentier, M., The Core Domain of Chemokines Binds
439 CCR5 Extracellular Domains while Their Amino Terminus Interacts with the
440 Transmembrane Helix Bundle. *J. Biol. Chem.* **2003,** *278* (7), 5179-5187.
441 59. Park, S. H.; Das, B. B.; Casagrande, F.; Tian, Y.; Nothnagel, H. J.; Chu, M.; Kiefer,
442 H.; Maier, K.; De Angelis, A. A.; Marassi, F. M.; Opella, S. J., Structure of the
443 chemokine receptor CXCR1 in phospholipid bilayers. *Nature* **2012,** *491*, 779.
444 60. Rajagopalan, L.; Rajarathnam, K., Ligand Selectivity and Affinity of Chemokine
445 Receptor CXCR1: ROLE OF N-TERMINAL DOMAIN. *J. Biol. Chem.* **2004,** *279* (29),
446 30000-30008.
447 61. Wang, X.; Watson, C.; Sharp, J. S.; Handel, T. M.; Prestegard, J. H., Oligomeric
448 Structure of the Chemokine CCL5/RANTES from NMR, MS, and SAXS Data.
449 *Structure* **2011,** *19* (8), 1138-1148.
450 62. Pennings, P. S., HIV Drug Resistance: Problems and Perspectives. *Infect. Dis. Rep.*
451 **2013,** *5* (Suppl 1), e5-e5.
452 63. Correia, C. A.; Gilmore, K.; McQuade, D. T.; Seeberger, P. H., A Concise Flow
453 Synthesis of Efavirenz. *Angew. Chem. Int. Ed.* **2015,** *54* (16), 4945-4948.
454 64. Vangelista, L.; Secchi, M.; Liu, X.; Bachi, A.; Jia, L.; Xu, Q.; Lusso, P.,
455 Engineering of Lactobacillus jensenii To Secrete RANTES and a CCR5 Antagonist
456 Analogue as Live HIV-1 Blockers. *Antimicrob. Agents Chemother.* **2010,** *54* (7), 2994-
457 3001.
458 65. Simmons, G.; Clapham, P. R.; Picard, L.; Offord, R. E.; Rosenkilde, M. M.;
459 Schwartz, T. W.; Buser, R.; Wells, T. N. C.; Proudfoot, A. E. I., Potent Inhibition of
460 HIV-1 Infectivity in Macrophages and Lymphocytes by a Novel CCR5 Antagonist.
461 *Science* **1997,** *276* (5310), 276.
462 66. Proudfoot, A. E.; Power, C. A.; Hoogewerf, A. J.; Montjovent, M. O.; Borlat, F.;
463 Offord, R. E.; Wells, T. N., Extension of recombinant human RANTES by the retention
464 of the initiating methionine produces a potent antagonist. *J. Biol. Chem.* **1996,** *271* (5),
465 2599-603.
466 67. Vakili, J.; Ständker, L.; Detheux, M.; Vassart, G.; Forssmann, W.-G.; Parmentier,
467 M., Urokinase Plasminogen Activator and Plasmin Efficiently Convert Hemofiltrate
468 CC Chemokine 1 into Its Active [9–74] Processed Variant. *J. Immunol.* **2001,** *167* (6),
469 3406.
470 68. Wang, S.; Thopate, Y. A.; Zhou, Q.; Wang, P., Chemical Protein Synthesis by
471 Native Chemical Ligation and Variations Thereof. *Chin. J. Chem.* **2019,** *37* (11), 1181-
472 1193.
473 69. Yin, H.; Zheng, M.; Chen, H.; Wang, S.; Zhou, Q.; Zhang, Q.; Wang, P.,
474 Stereoselective and divergent construction of β-thiolated/selenolated amino acids via

475 photoredox-catalyzed asymmetric Giese reaction. *J. Am. Chem. Soc.* **2020**, doi:
476 10.1021/jacs.0c04994.
477 70. Chen, X.; Tang, S.; Zheng, J.-S.; Zhao, R.; Wang, Z.-P.; Shao, W.; Chang, H.-N.;
478 Cheng, J.-Y.; Zhao, H.; Liu, L.; Qi, H., Chemical synthesis of a two-photon-activatable
479 chemokine and photon-guided lymphocyte migration in vivo. *Nat. Commun.* **2015,** *6*,
480 7220.
481

482 **Supplementary Information:** Detailed synthetic procedures, compound
483 characterization and NMR spectra are provided.

484 **Acknowledgements:** Financial support for this work was gratefully received from the
485 National Natural Science Foundation of China (91753102, 21672146 and 21907064),
486 the Shanghai Committee of Science and Technology (17JC1405300) and the Strategic
487 Priori-ty Research Program of the Chinese Academy of Sciences (Grant No.
488 XDA12020227).

489 **Author Contributions:** P. W. supervised the project and wrote the manuscript. Y. T.
490 supervised the project. S. W., Q. Z. and X. P. made contributions to the project design
491 and prepared the supporting information. # these three authors contributed equally to
492 this project. Y. L. synthesized some of the peptides used in this project. R. L. and L. M.
493 conducted anti-HIV assays for all CCL4 variants.

494 **Competing interests:** There are no competing financial interests in this work.
495 Correspondence and requests for materials should be addressed to Yong-Tang Zheng,
496 zhengyt@mail.kiz.ac.cn; Ping Wang, wangp1@sjtu.edu.cn.

Figures

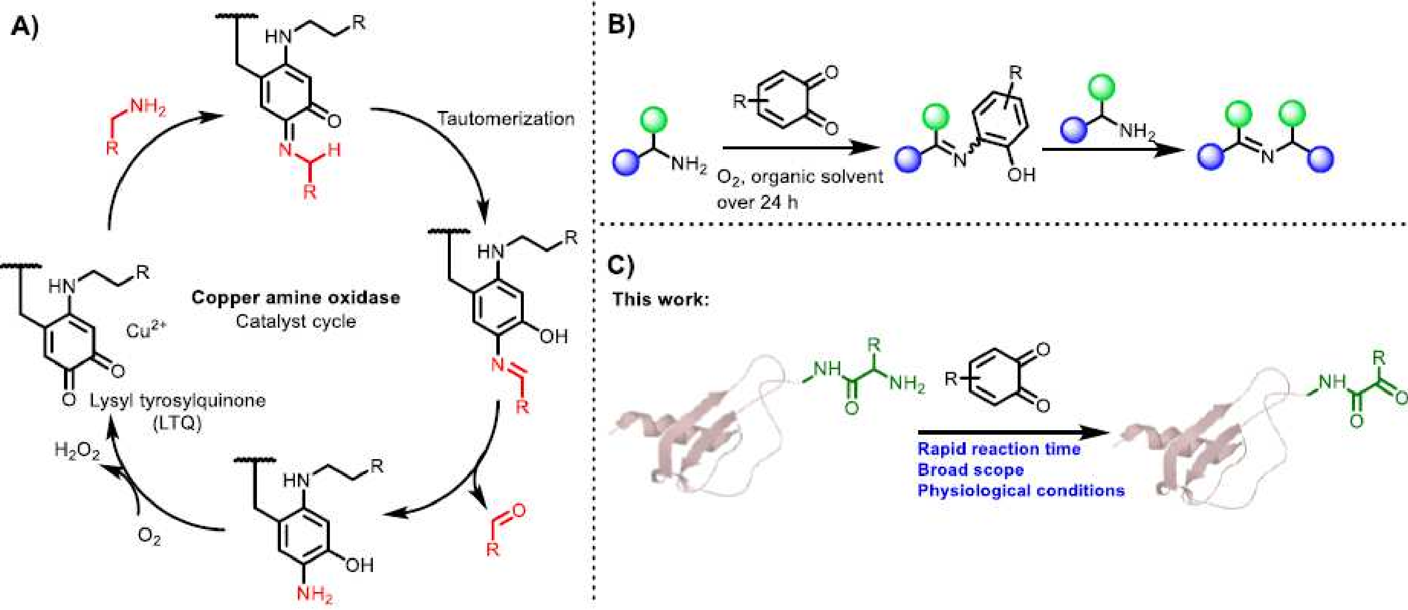
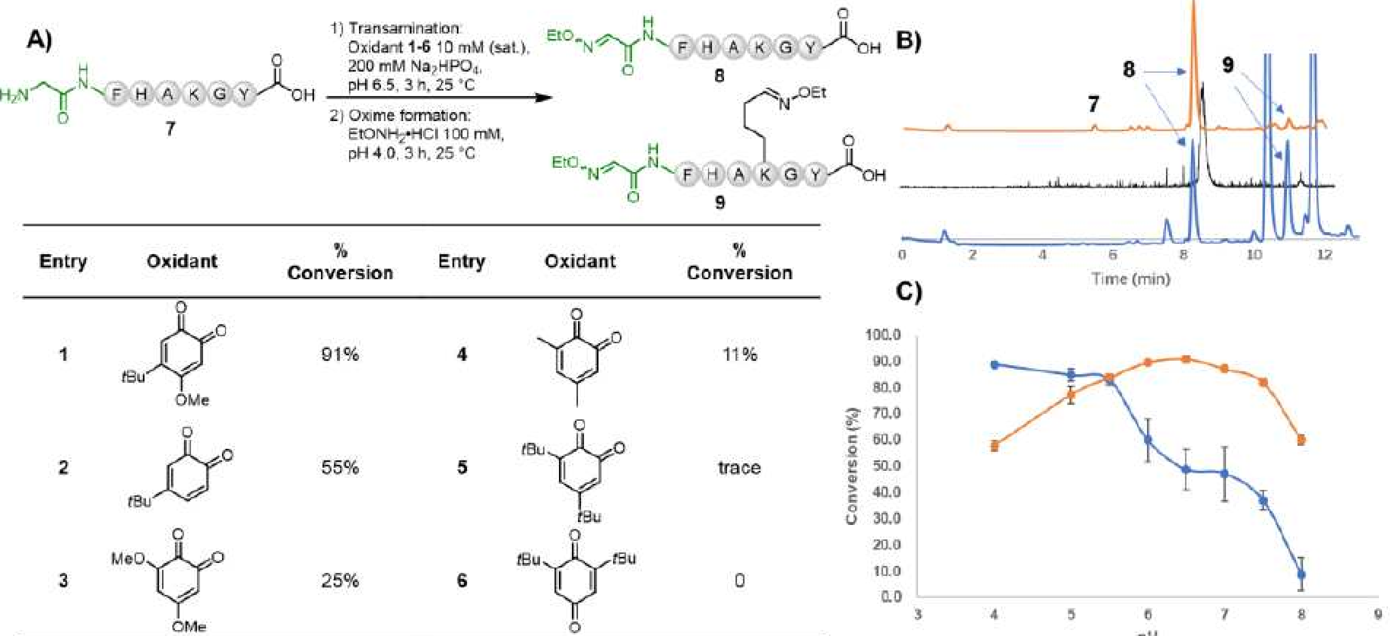


Figure 1

Development of protein N-terminus modification via quinone-mediated transamination: A) Natural catalytic cycle of CuAOs, B) Oxidation of primary amines with ortho-quinone to form imines, C) Biomimetic quinone-mediated transamination inspired by CuAOs.



Entry	Oxidant	% Conversion	Entry	Oxidant	% Conversion
1		91%	4		11%
2		55%	5		trace
3		25%	6		0

Figure 2

Optimization of the reaction conditions used in the biomimetic transamination reaction. A) Screening of oxidants 1-6 used for the transamination reaction with model peptide 7; B) LC trace obtained for the

transamination reaction using quinone 1 (in yellow) or 2 (in blue); C) Optimization of the pH of the transamination reaction using quinone 1 (in yellow) or 2 (the rate of conversion was calculated by integrating the related peaks of the LC trace measured at 280 nm, although TIC showed a >99% conversion rate of product 8).

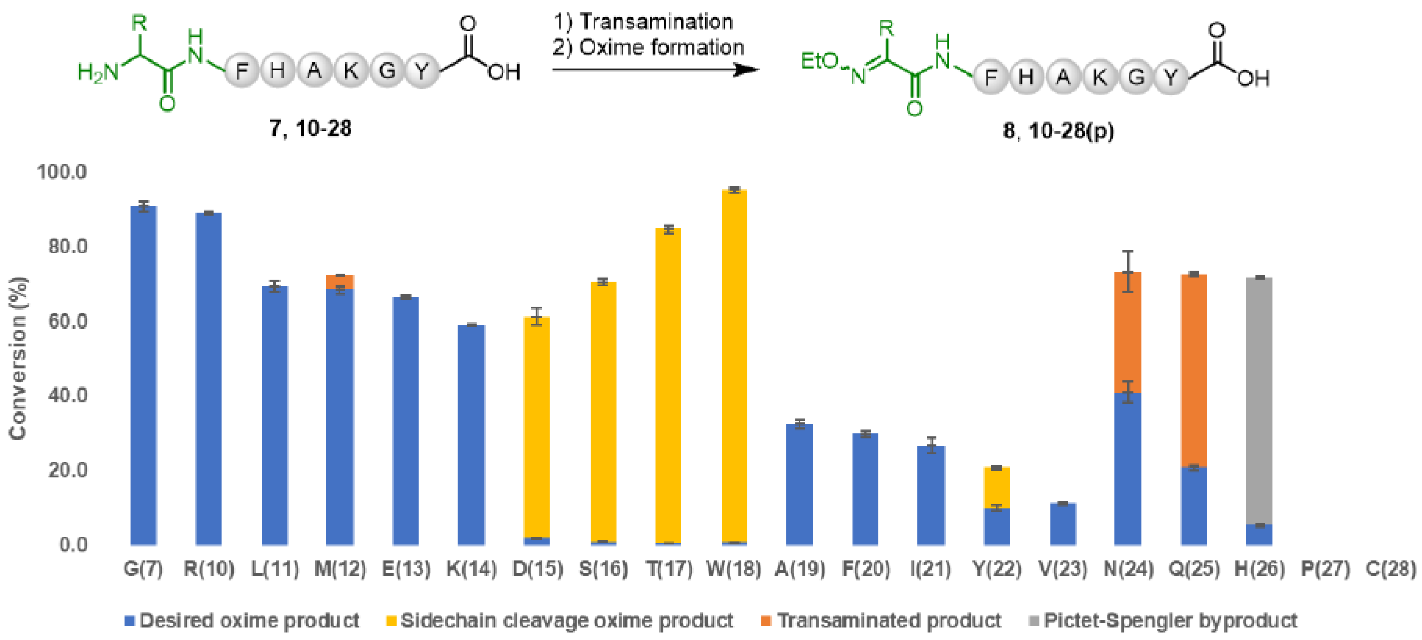


Figure 3

Landscape for the transamination of 20 canonical amino acids attached on the N-terminal residue of the model peptides. Reaction conditions: 1) Transamination: oxidant 1 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2) Oxime formation: $EtONH_2 \cdot HCl$ (100 mM), pH 4.0, 3 h, 25 °C.

Figure 4

Site selective peptide modification via quinone-mediatated transamination reaction. A) Reaction conditions for COVID-19 spike protein fragment 29: 1) Transamination: 2 M Gn·HCl, oxidant 1 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 6 h, 25 °C; 2) Oxime formation: $EtONH_2\cdot HCl$ (100 mM), pH 4.0, 3 h, 25 °C. B) Reaction conditions for tetracosactide 30: 1) Transamination: oxidant 1 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2) Oxime formation: $EtONH_2\cdot HCl$ (100 mM), pH 4.0, 3 h, 25 °C; C) Reaction conditions for myoglobin 31a-b: 1) Transamination: oxidant 1 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.0, 5 h, 25 °C; 2) Oxime formation for 31a: $EtONH_2\cdot HCl$ (100 mM), pH 4.0, 3 h, 25 °C; oxime formation for 31b: extraction with EtOAc (2 x 1.0 mL), then biotinylated tag S4 (100 mM), pH 4.0, 16 h, 25 °C. D) Reaction conditions for ubiquitin 32: 1) Transamination: 2 M Gn·HCl, oxidant 1 (10 mM, sat.), 200 mM Na_2HPO_4, pH 6.5, 3 h, 25 °C; 2) Oxime formation: $EtONH_2\cdot HCl$ (100 mM), pH 4.0, 3 h, 25 °C.

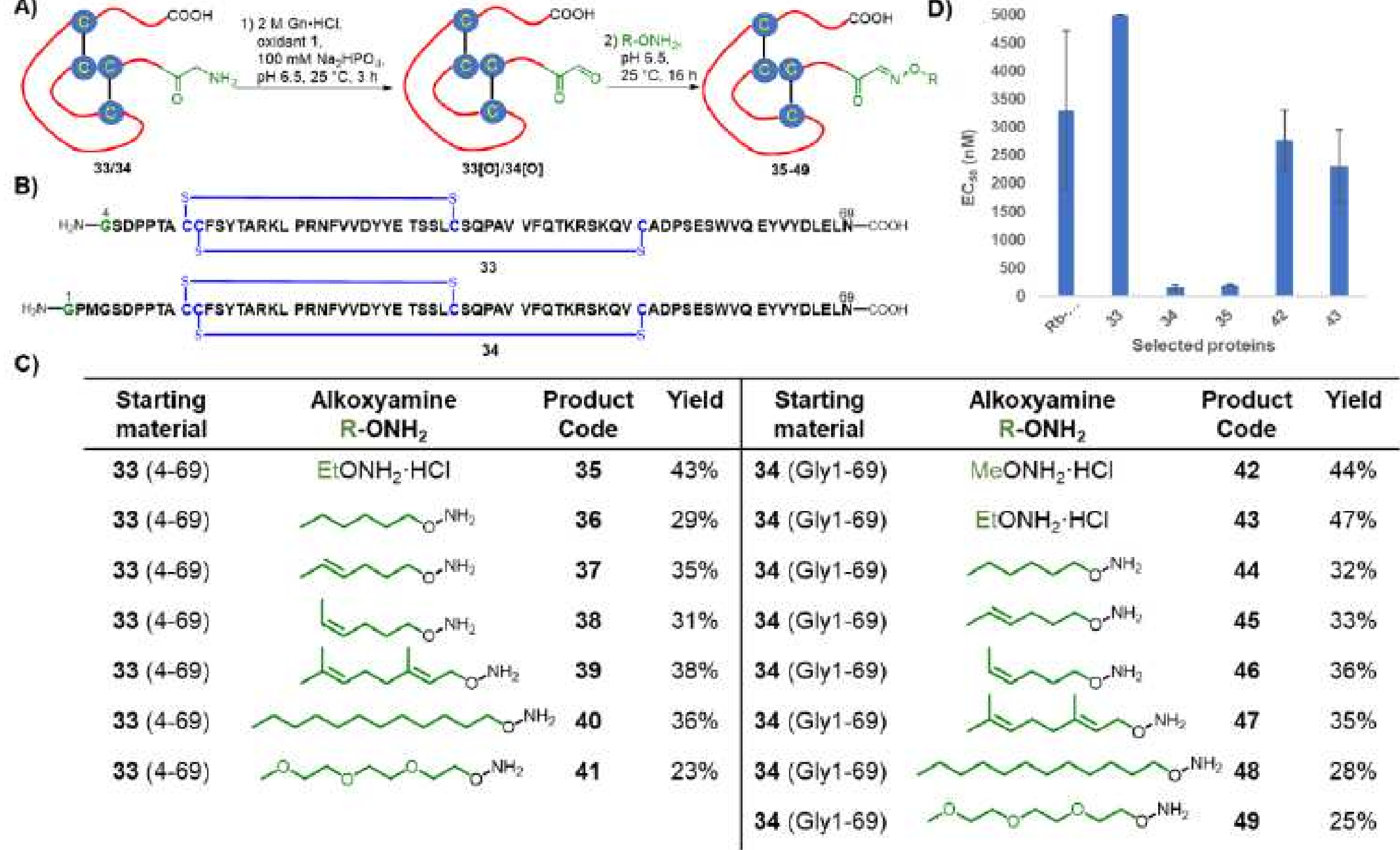


Figure 5

Late-stage modification of MIP-1β proteins via quinone-mediated selective oxidation of N-terminal amine. A) Reaction scheme for the transamination of MIP-1β protein 33 and 34; B) The sequences of protein 33 and 34; C) A summary of the transamination/oxime ligation of protein 33 and 34 and the isolated yields for all reactions; D) Anti-HIV-1 activity of selected MIP-1β analogs with EC50 <5000 nM.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SIquinoneoxidation0824.pdf