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► **To cite this version:**

Yi Liu, Sophie G Bender, Damien Sorigué, Daniel J Diaz, Andrew D Ellington, et al.. Asymmetric Synthesis of α -Chloroamides via Photoenzymatic Hydroalkylation of Olefins. *Journal of the American Chemical Society*, 2024, 146 (11), pp.7191 - 7197. <10.1021/jacs.4c00927>. <hal-05291403>

HAL Id: hal-05291403

<https://hal.science/hal-05291403v1>

Submitted on 1 Oct 2025

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Asymmetric Synthesis of α -Chloroamides via Photoenzymatic Hydroalkylation of Olefins

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KEYWORDS Photoenzyme, asymmetric catalysis, biocatalysts, chiral amides, alkene functionalization

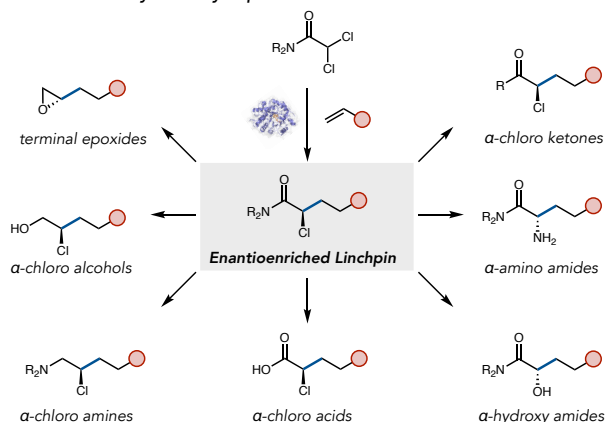
ABSTRACT: Photoenzymatic intermolecular hydroalkylations of olefins are highly enantioselective for chiral centers formed during radical termination but poorly selective for centers set in the C–C bond-forming event. Here, we report the evolution of a flavindependent “ene”-reductase to catalyze the coupling of α,α -dichloroamides with alkenes to afford α -chloroamides in good yield with excellent chemo- and stereoselectivity. These products can serve as linchpins in the synthesis of pharmaceutically valuable motifs. Mechanistic studies indicate that radical formation occurs by exciting a charge-transfer complex templated by the protein. Precise control over the orientation of molecules within the charge-transfer complex potentially accounts for the observed stereoselectivity. The work expands the types of motifs that can be prepared using photoenzymatic catalysis.

Enantioenriched α -haloamides are attractive linchpins for preparing many chiral motifs found in molecules used by the agrochemical and pharmaceutical industries (Figure 1).^{1–6} For instance, the chloride functionality can readily undergo S_N2 reactions to afford α -amino and α -oxyamides with the inversion of stereochemistry. Alternatively, the amide motif can be diversified to yield an array of diverse alkyl chlorides. Asymmetric synthesis of α -halocarbonyl compounds is most commonly achieved through selective redox reactions such as asymmetric halogenation of enolizable substrates or ketenes^{7–24} or hydrodehalogenation of dihalocarbonyl compounds.^{25,26} In the realm of molecular complexity building reactions, asymmetric alkylations of enolizable α -halocarbonyls can be achieved using chiral auxiliaries^{27–30} or small-molecule catalysts.^{31,32} We envisioned the reductive coupling of α,α -dihaloamides with alkenes using radical intermediates as an attractive alternative to these methods, as it would enable the preparation of α -haloamides on less activated substrates. However, small molecule catalysts struggle to achieve high levels of enantioselectivity for this type of reaction and are plagued by hydrodehalogenation of the α -haloamide product.^{32–38} We recognized that an enzyme would be ideally suited to overcome these selectivity challenges because their active sites can be tailored using protein engineering.^{39–41}

Our group and others previously demonstrated that flavindependent “ene”-reductases (EREDs) could catalyze the intermolecular hydroalkylations of olefins using α -halocarbonyl compounds as radical precursors.^{42–45} Building upon these foundational methods has enabled a variety of stereoselective reactions involving the formation of C–C,^{46–50} C–N,^{51,52} C–O,⁵³ and C–S bonds.⁵⁴ These reactions proceed via the single electron reduction of the alkyl halide by flavin

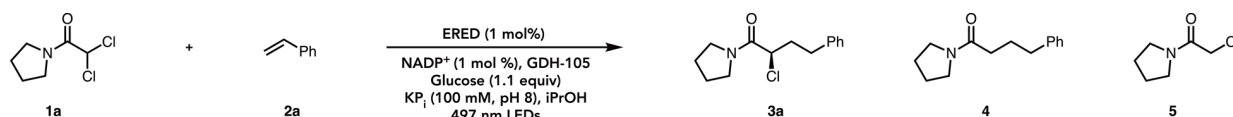
hydroquinone (FMN_{hq}) to afford a radical intermediate that reacts with the alkene to afford an alkyl radical. This prochiral radical is reductively terminated via hydrogen atom transfer (HAT) from the flavin semiquinone (FMN_{sq}) to afford the product. In these reports, radical termination occurs with high enantioselectivity.⁴¹ Control over stereocenters generated in the C–C bond-forming step has proved to be elusive, with radical additions into nitronates being the only known example.^{55,56} To achieve high selectivity, the alkyl halide and alkene need to be preorganized in the protein active site prior to radical formation. Under this hypothesis, engineering the active site to favor a particular binding orientation should enable C–C bond formation with high enantioselectivity. Beyond controlling the stereoselectivity, this method requires a protein that exhibits a preference for hydroalkylation over the competing hydrodehalogenation of the starting material or the product.

Chloroamides as Synthetic Linchpins



73

74 **Figure 1.** α -Chloroamides as a linchpin for synthesizing
75 various important motifs.



GluER-M6 Crystal Structure (8VCN)

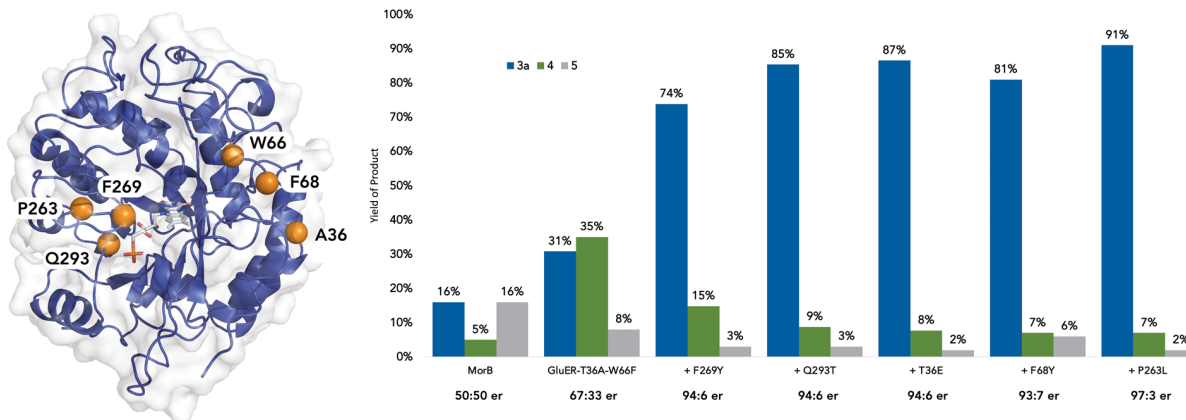


Figure 2. Protein engineering of GluER-T36A-W66F for synthesizing α -chiral chloroamides.

76 We began by exploring the coupling of α,α -dichloro-
77 pyrrolidine amide **1a** with styrene **2a** to prepare the
78 corresponding α -chloroamide **3a**. After evaluating a
79 collection of EREDs under cyan LED irradiation ($\lambda_{\text{max}} =$
80 497 nm), we identified two catalysts that exhibited
81 promising performance. The ERED from *Gluconobacter*
82 *oxydans* with previously identified mutations
83 (GluER-T36A-W66F) furnished the product with 31%
84 yield and moderate enantioselectivity (65:35 er), al-
85 beit with 26% and 8% of the hydrodehalogenated by-
86 products **4** and **5**, respectively. This catalyst was se-
87 lected from a library of diverse GluER-T36A active site
88 mutants for its improved activity for α -substituted amide
89 substrates (Figure S1).⁵⁷ The morphinone reduc-
90 tase from *Pseudomonas putida* (MorB) furnished a su-
91 perior ratio of the desired product to the undesired
92 coupled hydrodehalogenated product (3.2:1), how-
93 ever with the product formed as a racemate (Figure 2).
94 Control experiments revealed that the ERED, the cofac-
95 tor turnover system (GDH105, NADP⁺, and glucose),
96 and light are essential for the reaction (Table S1).

97 Given the orthogonal strengths and weaknesses of
98 the two most promising catalysts, we initiated protein
99 engineering campaigns on both enzymes, aimed at en-
100 hancing yield, enantioselectivity, and chemoselectivity
101 (Figure 2). In each protein, we targeted 10–15 resi-
102 dues lining the protein active site for iterative site-sat-
103 uration mutagenesis (ISM). For MorB, the first round
104 of evolution led to the identification of two mutants,
105 MorB-N189H and MorB-Y72S, with improved ability of
106 suppressing both dehalogenated byproducts. How-
107 ever, this enhancement was accompanied by a reduc-
108 tion in yield and no improvement in enantioselectivity
109 (Table S2). In contrast, mutations to GluER-T36A-
110 W66F had a more significant effect on the reaction out-
111 come. Introduction of a tyrosine residue at position
112 269 (F269Y) significantly boosted the yield of the

113 desired product **3a** to 74%, diminishing the formation
114 of the dehalogenated side product **4** to 15% and **5** to

115 3%, while enhancing the enantioselectivity to 94:6 er.
116 A second round of ISM identified a Q293T mutation,
117 which further improved the yield to 85%, decreased
118 the yield of **4** to 9%, and maintained the low yield of **5**
119 (3%).

120 With the goal of identifying mutations distal to the
121 protein active site, we used MutComputeX, a 3D self-
122 supervised machine learning (ML) framework trained
123 to identify residues where the wild-type amino acid is
124 chemically incongruent with its local environment, for
125 ML-guided rational design of surface mutations based
126 on the GluER-T36A crystal structure.^{58–62} We antici-
127 pated that these mutations could enhance the stability
128 or catalytic performance of the protein. Among the resi-
129 dues predicted, we found that mutating alanine (origi-
130 nally threonine) at position 36 to aspartic acid (T36E)
131 and phenylalanine at position 68 to tyrosine (F68Y)
132 led to variants that provided product in comparable
133 yields and enantioselectivities but with decreased for-
134 mation of the hydrodehalogenated product **4**. Con-
135 trary to our initial hypothesis for these ML mutations,
136 they did not thermally stabilize the protein, as has
137 been previously observed (Figure S13), but rather
138 served to decrease formation of the hydrodehalogenated
139 product.^{59–62} This observation is aligned with the
140 learning objective of self-supervised protein ML
141 frameworks: they are trained to predict the extant
142 wild-type amino acids of natural proteins, which have
143 been evolutionarily selected to optimize overall fitness
144 rather than a particular phenotype. Thus, residues
145 where the wild-type amino acid is poorly predicted are
146 primed for identifying gain-of-function mutations, and
147 it is up to the experimentalist to screen these ML pre-
148 dictions and select for the phenotype to optimize, such
149 as decreased shunt production formation. Finally, we
150 subjected the new gene to a final round of ISM, leading
151 to the identification of P263L. This variant increased

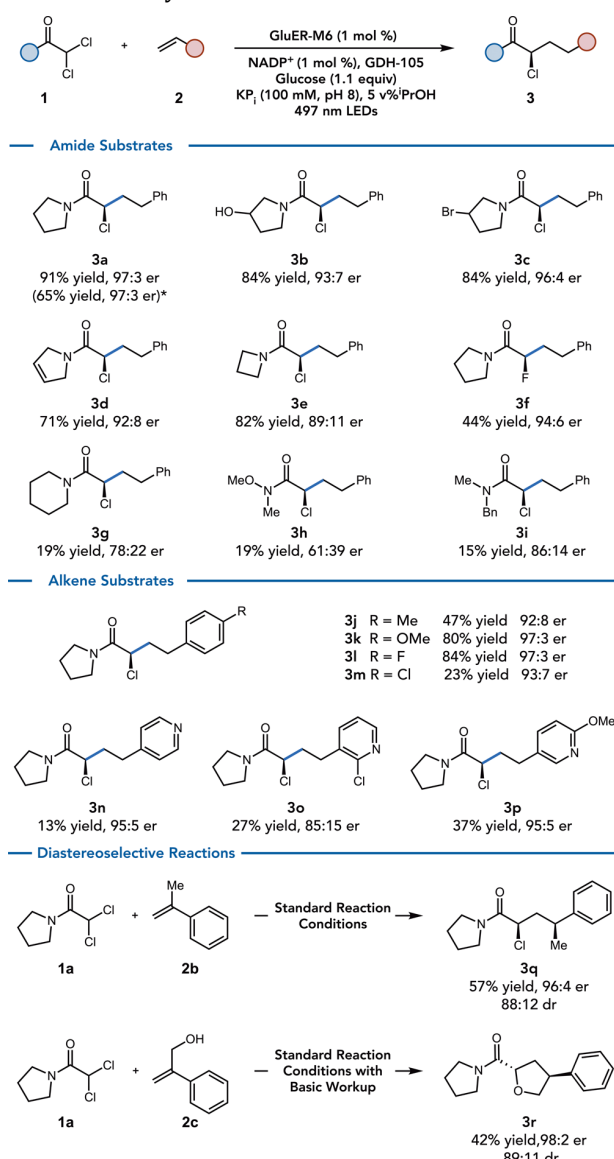
152 the yield of **3a** to 91% and er to 97:3, with a mere 7%
 153 yield of **4** and 2% of **5**. While these results were
 154 achieved using purified enzyme, reactions can be run
 155 using lyophilized enzyme lysate as the catalyst, giving
 156 a 60% yield and excellent enantioselectivity (99:1 er)
 157 (Figure S2). The enhanced enantioselectivity could be
 158 attributed to the more stabilized protein in lysate form
 159 than in its purified form. Finally, the reaction can be
 160 run on a 1.0 mmol scale in 65% yield with 97:3 er (Fig-
 161 ure S2).

162 To investigate the structural effects of introduced
 163 mutations, we grew crystals of GluER-M6 and obtained
 164 a high-resolution structure (PDB: 8VCN). The overall
 165 structure of GluER-M6 is similar to that of GluER-T36A
 166 (PDB: 6MYW) with an RMSD of 0.198 Å. Notable in this
 167 structure is the introduction of a weak hydrogen-
 168 bonding contact between F269Y and Y343 (3.6 Å) at
 169 the solvent-exposed face of the active site.

170 With the evolved catalyst in hand, we investigated
 171 the generality of this method. Substituted pyrrolidinyl
 172 amides, including 3-hydroxyl and 2-bromo pyrroli-
 173 dinyl amides, emerged as outstanding substrates for
 174 this transformation, affording α -stereogenic chloro
 175 products with remarkable yields and enantioselectivity
 176 (Figure 3, **3b,c**). Moreover, 2,5-dihydropyrrole (**3d**)
 177 and azetidiny (**3e**) substrates proved to be highly
 178 amenable to the process. When a chloro-fluoro sub-
 179 strate was employed, the reaction delivered a product
 180 (**3f**) featuring an α -fluoro chiral center. Although the
 181 yield was moderate (44%), the enantioselectivity re-
 182 mained high (94:6 er), showcasing the potential of this
 183 method to access the α -fluoro chiral center. Of note,
 184 there was no hydrodefluorinated product observed in
 185 the reaction. Although substrates featuring larger cy-
 186 clic amides exhibited reactivity, the yields were
 187 slightly diminished, and enantioselectivities reduced
 188 (**3g**). Notably, acyclic amides, such as Weinreb amides
 189 and N-methyl benzyl amides, were found to be active
 190 substrates within this catalytic system (**3h** and **3i**).
 191 These findings offer valuable starting points for future
 192 protein engineering endeavors aimed at enhancing the
 193 performance of selected target substrates.

194 We then explored the alkene substrates. Styrenes
 195 bearing para-methyl, -methoxy, -fluoro, and -chloro
 196 groups exhibited moderate to good reactivity, yielding
 197 products with exceptional enantioselectivities (Figure
 198 3, **3j-m**). Beyond substituted styrenes, the system is
 199 also compatible with heterocyclic vinyl substrates. Vin-
 200 ylpyridines, featuring diverse substituents, delivered
 201 products with moderate yields and moderate to good
 202 enantioselectivities (**3n-p**). Notably, when α -me-
 203 thylstyrene was subjected to the reaction, a product
 204 featuring both α - and γ -stereocenters was obtained
 205 with impressive enantioselectivity and diastereoselec-
 206 tivity (**3q**). Finally, employing 2-phenyl allylic alcohol
 207 as a coupling partner led to the corresponding 1,3-di-
 208 substituted tetrahydrofuran product (**3r**) in 42% yield
 209 with 89:11 dr and 98:2 er. For both substrates, the
 210 α -stereocenter formed in the C-C bond-forming event
 211 is set with high enantioselectivity, while the γ -stereo-
 212 center set in the HAT event is less precisely controlled.

213 To unravel the intricacies of this catalytic system, we
 214 conducted a series of mechanistic experiments. Notably,
 215 a small degree of catalytic activity was observed
 216 with dichloroamide substrate **1a** under ambient light
 217 conditions (Figure S3). This observation was associ-
 218 ated with the generation of flavin quinone (FMN_{ox}),
 219 which absorbs light in a spectral region akin to the an-
 220 ticipated charge-transfer complex we were investigat-
 221 ing.⁶³ Consequently, we employed the corresponding
 222 difluoro amide **1j** for UV-vis spectroscopic studies, as
 223 this substrate does not display any reactivity under
 224 ambient conditions but is reactive under the reaction
 225 conditions (Figure S3). Initially, we generated FMN_h
 226 through titration with sodium dithionite (Figure 4a,
 227 green trace). Upon the addition of either styrene **2a** or
 228 amide **1j**, no significant changes in absorbance were
 229 observed in the visible light region (Figure 4a, purple
 230 and orange traces, respectively). However, when both
 231 the amide and styrene



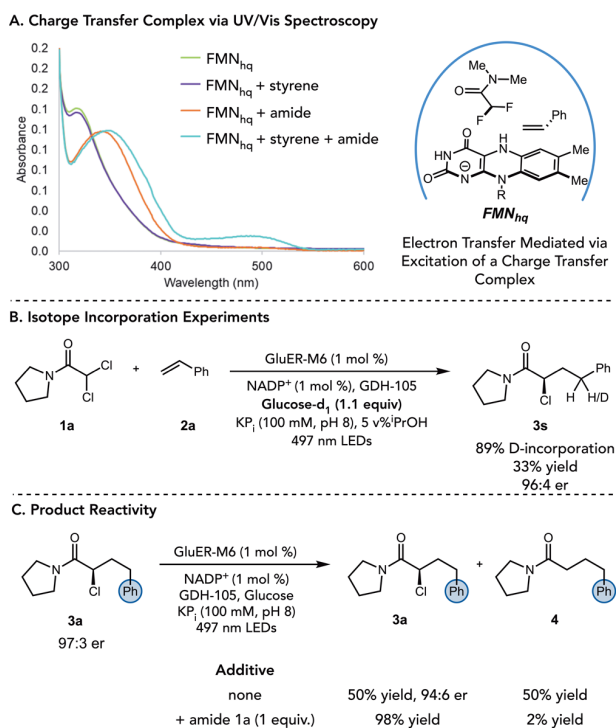
232

233 **Figure 3.** Substrate scope. Analytic reactions were per-
 234 formed on a 20 μ mol scale, and yields were determined
 235 by NMR analysis using benzyl benzoate as the internal

236 standard. The enantioselectivities were determined by
 237 isolating the products via preparative TLC or reverse
 238 phase preparative HPLC from a 0.2 mmol scale enzy-
 239 matic reaction. *1 mmol reaction scale.

240 substrates were concurrently present, a highly absorb-
 241 ing species emerged, predominantly in the cyan light
 242 region (Figure 4a, cyan trace). These findings support
 243 the hypothesis that the ERED templates a ternary
 244 charge-transfer complex responsible for light absorp-
 245 tion and subsequent radical initiation. As both the am-
 246 ide and alkene are necessary for complex formation,
 247 undesired hydrodehalogenation of the starting mater-
 248 ial is avoided.^{43,52,64} Of note, we conducted similar
 249 UV-vis spectroscopic studies on the starting variant,
 250 GluER-T36A-W66F, and no obvious charge-transfer
 251 complex was observed (Figure S14).

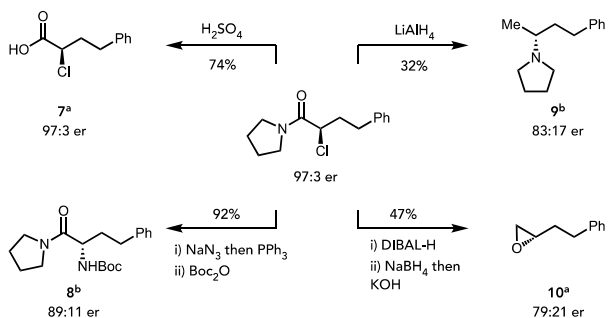
252 To investigate the radical termination step, we con-
 253 ducted deuterium incorporation experiments. Deuter-
 254 ated FMN_{hq} was generated in situ by using D-glucose-
 255 1-*d*₁. A high level



256
 257 **Figure 4.** Mechanistic studies. a. UV-Vis studies; b. deu-
 258 terium incorporation studies; c. competition experiments
 259 with the product.

260 of deuterium incorporation (89%) was observed at the
 261 benzylic position, consistent with HAT from the FMN_{sq}
 262 to the radical intermediate (Figure 4b). Next, we were
 263 interested in determining how hydrodehalogenation
 264 product **4** is formed (Figure 4c). We considered two
 265 hypotheses, the first is that the dichloroamide **1a** is
 266 dehalogenated to form a monochloroamide, which en-
 267 gages in the intermolecular coupling to generate prod-
 268 uct **4**. Alternatively, the chloroamide product **3a** could
 269 be hydrodehalogenated under the reaction conditions.

271 When chloroamide **3a** is subjected to the standard re-
 272 action conditions without additional substrates, 50%
 273 is hydrodehalogenated, indicating that the enzyme can
 274 react with the product (Figure 4c). However, addition
 275 of dichloroamide **1a** decreased the consumption of
 276 chloroamide **3a** to only 2%, indicating that the enzyme
 277 preferentially reacts with the more electronically acti-
 278 vated dichloroamide (Figure S4). Consequently, we hy-
 279 pothesize that coupling of styrene to the monochloro-
 280 amide is the primary mechanism by which the hydro-
 281 dehalogenated product is formed. Finally, we
 282 sought to demonstrate that these α -chloroamides can
 283 serve as linchpins for the synthesis of a diverse range
 284 of valuable motifs through a selection of representa-
 285 tive transformations (Figure 5). Treatment of the α -
 286 chloroamides with sulfuric acid cleanly afforded the
 287 corresponding α -chlorocarboxylic acid with no ero-
 288 sion in enantioselectivity. Alternatively, employing
 289 NaN₃ followed by PPh₃ enabled synthesis of the α -
 290 aminoamide. Utilizing LiAlH₄ under refluxing conditions
 291 on the α -chloroamide led to the preparation of the chi-
 292 ral α -methyl amine with minimal loss in enantioselecti-
 293 vity.⁶⁵ Finally, reduction of the amide with DIBAL-H
 294 affords the corresponding α -chloroaldehyde, which
 295 can be



296 **Figure 5.** Product derivatization. Enantiomeric ratios
 297 were determined by HPLC (*major:minor*). ^aReactions per-
 298 formed with a starting material er of 97:3; ^bReactions per-
 299 formed with a starting material er of 88:12.

300
 301
 302
 303 further reduced to the halohydrin and upon cyclization
 304 affords the chiral terminal epoxide.

305 In summary, an engineered photoenzyme has ena-
 306 bled the efficient synthesis of linchpin α -chiral amides
 307 from readily available dichloro amides and alkenes.
 308 The high enantioselectivity achieved stems from the
 309 enzyme-controlled radical addition to alkenes, com-
 310 plementing the previously reported enantioselective
 311 HAT mechanism. Leveraging protein engineering
 312 strategies and machine learning, we successfully en-
 313 hanced various facets of the reaction including yield,
 314 enantioselectivity, and chemoselectivity. Overall, this
 315 method demonstrates that intermolecular C-C bond
 316 formation can be rendered asymmetric within photo-
 317 enzymatic catalysis, expanding the synthetic utility of
 318 the field.
 319

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355 Author Contributions

356 The manuscript was written through contributions of all
357 authors. All authors have approved the final version of
358 the manuscript. # These authors contributed equally.

359 Funding Sources

360 T.K.H. thanks Novartis and the NIH (R01 GM127703)
361 for financial support. D.S. thanks the Marie-Curie Ac-
362 tions for an International Outgoing Fellowship. A.D.E.
363 thanks the NIH (R01 GM146093-01A1) and the Welch
364 Foundation (F-1654) for support. D.J.D. thanks the NSF
365 AI Institute for Foundations of Machine Learning
366 (IFML) for funding support and AMD for the donation
367 of critical hardware and support resources from its HPC
368 fund.

369 ACKNOWLEDGMENT

370 The authors thank Yingru Zhang from Lotus Separations
371 for assistance in developing analytical separation condi-
372 tions, Phil Jeffrey for assistance with protein crystallog-
373 raphy and structure determination, Venu Vandavasi for

374 assistance running DSC on protein samples, and Claire
375 Page for preliminary experiments.

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