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1 **Complex molecule synthesis by electrocatalytic decarboxylative cross-coupling**

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28 **Abstract**

29 **Modern retrosynthetic analysis in organic chemistry is based on the principle of polar**
30 **relationships between functional groups to guide the design of synthetic routes.¹** This
31 **method, termed polar retrosynthetic analysis, assigns partial positive (electrophilic) or**
32 **negative (nucleophilic) charges to constituent functional groups in a complex molecules**
33 **followed by disconnecting bonds between opposing charges.²⁻⁴** While this approach forms
34 **the basis of undergraduate curriculum in organic chemistry⁵** and strategic applications of
35 **most synthetic methods,⁶** their implementation often requires a long list of ancillary
36 **considerations to mitigate chemoselectivity and oxidation state issues involving protecting**
37 **groups and precise reaction choreography.^{3,4,7}** Here we report a radical-based Ni/Ag-
38 **electrocatalytic cross coupling of a-substituted carboxylic acids thereby enabling an intuitive**
39 **and modular approach to accessing complex molecular architectures. This new method relies**
40 **on a key silver additive that forms an active Ag-nanoparticle coated electrode surface^{8,9} *in***
41 ***situ*** along with carefully chosen ligands that modulate the reactivity of Ni. Through judicious
42 **choice of conditions and ligands, the cross-couplings can be rendered highly**
43 **diastereoselective. To demonstrate the simplifying power of these reactions, concise**
44 **syntheses of 14 natural products and two medicinally relevant molecules were completed.**

45

46 **Main Text**

47 Polyfunctionalized carbon frameworks containing 1,2-, 1,3-heteroatom-substituted fragments
48 are ubiquitous in organic molecules. Construction of such motifs has been the central theme of
49 organic synthesis throughout its history. Numerous methods have been developed to access such
50 motifs, and the strategic usage of such reactions has historically been guided by polar
51 retrosynthetic analysis (2e⁻ disconnections).¹⁻⁴ These classic methods can be broadly categorized
52 into the functionalization of olefins and carbonyl compounds (Figure 1A). In the case of olefins,
53 for example, Sharpless epoxidation/dihydroxylation/aminohydroxylation and related reactions can
54 allow straightforward access to precursors that can then be converted to the desired target after
55 further functionalization. The rich chemistry of carbonyl compounds encompasses a myriad of
56 transformations ranging from the installation of heteroatoms in the adjacent position (e.g.
57 Rubottom oxidation or asymmetric enamine chemistry) or classic C–C bond forming events such
58 as aldol, Claisen condensation, pinacol coupling and Mannich reaction.⁶ The electrophilicity of

59 carbonyl compounds allows for a combination with orthogonal olefin chemistry such as in the case
60 of carbonyl allylation followed by oxidative cleavage.

61 Thousands of variants of these two-electron, polar reaction types have been reported thereby
62 forming the bedrock of the logic of retrosynthetic analysis. Designing a route to complex structures
63 using these methods can often involve a complex interplay of stereo-, regio-, and chemoselectivity
64 considerations along with balancing proper redox states. As such, vast realms of protecting groups,
65 reagents, and stereochemical rubrics have been developed to aid the practitioner in executing
66 synthetic plans.^{1,3,4} Years of experience is necessary to appropriately deploy various reactions with
67 successful synthetic strategies often being considered a form of “art”.^{10,11} Numerous computer-
68 based algorithms and software packages have been launched to simplify synthesis design which is
69 often equated with providing solutions to a complex puzzle.¹²

70 In contrast, a different approach to retrosynthesis that uses radical-based logic (1e⁻
71 disconnection) to create new C–C bonds is emerging that can directly access previously
72 challenging motifs, and in the process avoid downstream functional/protecting group
73 manipulations and extraneous redox fluctuations.¹³ Since disconnections based on radical
74 retrosynthesis are polarity agnostic, any C–C bond can, in principle, be constructed by the coupling
75 of carbon radicals *regardless of the surrounding functional groups*. This, in turn, opens up
76 completely different ways of making molecules since polarity assignments do not need to be the
77 sole criteria to guide a logical disconnection. Instead, maximization of convergency and starting
78 material availability/simplicity can serve as a primary guiding principle. Towards this end, doubly
79 decarboxylative cross coupling (dDCC) is a powerful tool to realize this vision as it directly forges
80 Csp³-Csp³ bonds between two carboxylic acids.¹⁴ Whereas the initial manifestation of this
81 chemistry did not tolerate adjacent functional groups, herein we disclose a method to extend the
82 scope of this reaction enabling the modular coupling of α -functionalized acids to access structures
83 classically associated with 2e⁻ synthetic strategies (Figure 1A).

84 The power of such a strategy for synthesis can be exemplified when considering the synthesis
85 of polyrhacitide A (Figure 1B). This polyketide has the typical stereochemical array of 1,3-diol
86 motifs; such structures have been made on countless occasions using classic 2e⁻ synthetic
87 strategies.¹⁵ As such, an iterative sequence of olefin/carbonyl chemistry involving
88 allylation/ozonolysis/HWE/oxa-Michael is employed to construct the carbon framework with the
89 requisite oxygen functionalities (key intermediate **4**). This conventional approach is the result of

90 decades of groundbreaking studies in polyketide synthesis to exquisitely control the
91 stereochemical outcomes of C–C and C–O bond formation. However, one lingering drawback of
92 this strategy is the many concession steps required to manipulate functional groups and adjust
93 appropriate oxidation states.^{16,17} In stark contrast, a radical retrosynthetic approach to **4** could
94 employ dDCC to sidestep many of these issues. Simply cutting bonds that lead to most accessible
95 carboxylic acids results in a logical disconnection, thereby permitting only two simple acids to be
96 stitched together, intuitively arriving at **4**. In principle, only three C–C bond formation steps would
97 be required without additional C–O bond formations or redox manipulations from octanoic acid
98 and the key building block **6**, which is readily accessible via one step from an inexpensive aldehyde
99 containing 1,3-diol used to make statin-based medicines (See Supplementary Information for the
100 preparation).

101

102 Two obstacles needed to be overcome to realize the vision set forth above (Figure 2A). First,
103 an expansion of the initial dDCC scope to encompass substrates containing an α -heteroatom
104 functionality was necessary. As a model system for this challenge, the coupling of proline
105 derivative **8** and glycine derivative **9** was studied. First generation dDCC conditions afforded only
106 8% of the desired coupling product **10** along with a variety of decarboxylated products such as the
107 corresponding pyrrolidine, dihydropyrrole, and proline dimer (see SI for details). These
108 byproducts were indicative of substantial redox-active ester (RAE) reduction without productive
109 coupling, a situation encountered previously in electrochemical decarboxylative vinylation and
110 arylation studies.^{8,9} In that work, the key breakthrough involved the use of an *in-situ* generated Ag-
111 nanoparticle deposited cathode, which primarily modulates multiple reduction events (e.g.
112 concomitant reduction of Ni as well as RAE) on the cathode to improve the chance of successful
113 coupling.⁹ Accordingly, this approach was tested for the dDCC coupling of **8** and **9**. Indeed, by
114 simply adding sub-stoichiometric amounts of Ag salt in addition to changing solvent (from DMF
115 to NMP) and sacrificial anode material (from Zn to Mg), the yield of **10** was dramatically improved
116 from 8% to 67% (see Supplementary Information for more details on reaction optimization as well
117 as additional experiments to investigate the role of the Ag salt). The optimal ligand for this coupling
118 was found to be tridentate ligands **L1** and **L2**, the same type of ligands used in the previous dDCC
119 study.

With the basic reactivity problem being solved, attention turned to the second obstacle: achieving diastereoselective coupling. In principle, **6** could serve as a versatile “cassette” that could be easily employed to make a vast array of polyketide natural products. Based on the assumption that the ligand could affect stereochemical outcome, those that were previously found to be effective for dDCC were re-screened. This extensive screen led to the discovery that terpyridine together with MgCl₂ as Lewis acidic additive rendered the coupling highly diastereoselective, favoring the *cis*-diol product (**6R**)-**12** (>20:1 dr). In striking contrast, the omission of ligand under these modified conditions still led to successful coupling, yet the diastereoselectivity was completely reversed to deliver *trans*-diol product (**6S**)-**12** (>20:1 dr). This intriguing stereodivergence could be explained by delicate interplay of stereoelectronic effect of the carbon radical and steric effect of the Ni-catalyst. Namely, in the case of ligand-free system, anomeric effect of the radical¹⁸ favors axial substitution since Ni-catalyst is not sterically encumbered (leading to *trans*-isomer), whereas this effect is overridden by unfavorable 1,3-diaxial interactions in the case of ligated Ni-complex (see Supplementary Information for details). Additional experiments were conducted to determine if such a unique outcome could be translated into other analogous reaction manifolds. However, attempts to replicate this coupling under photochemical¹⁹ and metal-powder conditions²⁰ were unsuccessful. The unique electrochemically enabled reactivity observed may stem from the fact that dDCC requires multiple concurrent reduction events: simultaneous reduction of two different RAEs along with reduction of Ni catalyst.¹⁴ Maintaining the subtle balance of these multiple reduction events may be a demanding task for alternative reductants. Regarding the generality of stereocontrol, high diastereoselectivity was observed on a variety of α -hydroxyacid derivatives (*vide infra*). α -aminoacids tend to give lower level of stereocontrol, yet observation of high diastereoselectivity in a certain case suggests that the stereochemical outcome is mostly substrate-controlled (see Supplementary Information for details).

With both the reactivity and stereoselectivity issue being solved for these key substrates, the basic reaction generality of these second-generation conditions to access densely functionalized carbon frameworks was evaluated (Figure 2B). dDCC between two α -heteroatom substituted acids directly affords 1,2-diol (**13-16**), aminohydroxy (**17-20**), diamino motifs (**21-24**) and higher order derivatives (**25-30**) from readily available carboxylic acids such as tartaric acid, amino acids and sugar derivatives. Accessing these classes of molecules often requires lengthy syntheses as

151 indicated in the step-count of previous syntheses (**16**, **20**, **23**, **24**, **26**, **27**, see Supplementary
152 Information for complete route comparisons). Regarding the choice of ligand, **L1** can be used
153 universally (except for diastereoselective cases); **L2** is useful when an amino acid-based RAE was
154 employed as a substrate since it gives slightly improved yields in such cases. Although 3
155 equivalents of the RAE coupling partner are used throughout this study, reducing the amount to
156 1.5 equivalents could still afford the coupling product in synthetically useful yield (see
157 Supplementary Information). Substrates **16** and **20** are the direct precursor for important medicines
158 that are now accessible via modular routes relative to $2e^-$ synthetic strategies. Molecules such as
159 **25**, **28-30** were prepared for ongoing drug discovery campaigns. As with other decarboxylative
160 couplings, the current reaction could be easily scaled (**13**, conducted on gram-scale). Regarding
161 the limitations of this method, forging fully substituted carbon centers results in lower yields (**31**,
162 **32**) and intramolecular couplings (**33**) are currently not tractable. Additionally, RAEs tend to have
163 lower stability when highly nucleophilic functionalities are in proximity. Such RAEs are not
164 applicable to the coupling (**34-36**). Finally, adoption of this reaction in high-throughput fashion is
165 in progress (See Supplementary Information for preliminary results).

166

167 With an understanding of the scope of this transformation, a series of total syntheses were designed
168 and executed to exemplify the powerfully simplifying nature of this new transformation. The
169 vision set forth in Figure 1B was realized for the total synthesis of polyrhacitides A (**5**) as
170 illustrated in Figure 3A. Thus, **6-RAE** could be subjected to *cis*-selective dDCC with octanoic acid
171 RAE, affording **37** in 52% isolated yield (>20:1 dr). Subsequent union of this fragment with
172 another equivalent of **6-RAE** after hydrolysis/RAE formation under *cis*-selective dDCC conditions
173 furnished protected polyol ester **38** in 30% isolated yield (>20:1 dr). The third and final C–C bond
174 forming event was accomplished again using another decarboxylative coupling method:
175 decarboxylative alkenylation with vinyl iodide **39** to deliver **40** in 62% yield, which upon exposure
176 to AcOH afforded the natural product **5** (67% yield). This intuitive approach to the construction of
177 **5** is a striking departure from prior art (Figure 1B) and to polyketide synthesis in general. The
178 overall strategy outlined for **5** could be employed seven more times for the divergent total
179 syntheses of solistatine (**41**), verbalactone (**42**), avocadene (**43**), gingerdiol (**44**), streptenol B (**45**),
180 exserolide (**46**), and PF1163A (**47**) resulting in reduced step-counts and improved ideality (Figure

181 3B). Notably, all previous routes to these natural products rely exclusively on polar-bond
182 disconnections (see SI for the full detail and references).

183

184 Solistatin (**41**), isolated from *Penicillium solitum* and known to inhibit cholesterol synthesis,²¹ was
185 previously prepared three times in 7-17 steps (57% ideality for the shortest route. Building blocks
186 in the shortest route are also illustrated in Figure 3B), featuring stereoselective aldol reactions²² or
187 iterative Overman esterification strategies.²³ However, the aldol approach suffers from low
188 diastereoselectivity (2:1), whereas the Overman approach requires multiple concession steps to set
189 the stage for this rearrangement along with expensive chiral ligands and multiple uses of
190 palladium. In contrast a *cis*-selective dDCC using the common diol unit **6-RAE** completed the
191 total synthesis in merely 4 steps (50% ideality) by quickly assembling the carbon skeleton followed
192 by lactonization. Verbalactone (**42**), possessing unique activity against various Gram-positive and
193 Gram-negative bacteria,²⁴ is an interesting case for analysis as it has been prepared at least 14
194 different ways ranging from 7-22 step-count (57% ideality for the shortest route). Although a
195 macrolactonization approach to unite the two symmetrical fragment is common, accessing the key
196 fragment requires multiple concession steps regardless of the strategy employed such as a
197 combination of dithiane chemistry and chiral epoxide opening^{24,25} or asymmetric allylation.²⁶
198 Again, the radical approach described herein employs a *cis*-selective dDCC on **6-RAE** with
199 hexanoic acid RAE followed by deprotection of the acetonide and *tert*-butyl ester, delivering the
200 key symmetrical unit in a concise manner. Avocadene (**43**), isolated from the avocado tree (*Persea*
201 *americana*), exhibits anticancer activity against the human prostate adenocarcinoma as well as
202 activity in the yellow fever mosquito larvae insecticidal assay.²⁷ The previous synthesis of **43**
203 proceeded in 9 steps (44% ideality) featuring a Noyori asymmetric reduction as well as a
204 diastereoselective reduction of a β -hydroxyketone to establish the key 1,3-diol stereochemistry.²⁷
205 In a significant departure from this conventional logic, *cis*-selective dDCC on **6-RAE** with 13-
206 tetradecenoic acid RAE set the stage for a 7-step synthesis of **43**. To install the third hydroxyl
207 group of **43**, another radical reaction on the remaining carboxylate, decarboxylative borylation,²⁸
208 was enlisted followed by oxidative workup. Gingerdiol (**44**), isolated from ginger rhizome,²⁹ was
209 previously prepared four times in 9-15 steps (33% ideality for the shortest route), featuring polar
210 transformations such as Keck allylation,³⁰ epoxide opening³¹ and iterative proline catalysed α -
211 aminoxylation of an aldehyde.²⁹ A more intuitive approach can be realized using *cis*-selective

212 dDCC of **6-RAE** with a functionalized phenylpropionic acid RAE, followed by another dDCC to
213 complete the total synthesis of **44** (7 steps, 29% ideality).

214

215 The completely programmable diastereoselectivity of dDCC reactions on **6** (delivering *cis*- or
216 *trans*-products at-will) could be also harnessed to access natural products bearing a *trans*-
217 arrangement between diol motifs as illustrated in the next three total syntheses. For instance,
218 streptenol B (**45**), a cholesterol synthesis inhibitor isolated from streptomyces species,³² was
219 previously prepared in 6 steps as a racemate (17% ideality) with a poor diastereoselectivity in the
220 Grignard reaction step.³² *Trans*-selective dDCC between **6-RAE** and (*E*)-4-hexenoic acid RAE
221 followed by acetonide deprotection and reduction of the remaining ester afforded **45** concisely (3
222 steps, 33% ideality). Exserolide F (**46**), isolated from plant endophytic fungus of *Exserohilum*
223 species, demonstrates significant antimicrobial activity³³ and was previously prepared twice in 10
224 steps (40 and 50% ideality).^{33,34} In both cases, substituted coumarin core was constructed *via*
225 Sonogashira coupling followed by cationic cyclization to furnish the lactone. In a complete
226 departure from this strategy, the coumarin fragment could be incorporated via decarboxylative
227 arylation^{8,9} after the *trans*-selective dDCC between butyric acid RAE and **6-RAE**, halving the step-
228 count (6 steps, 33% ideality). Finally, PF1163A (**47**), isolated from the fermentation broth of
229 *Penicillium* sp. and possessing antifungal activity by inhibiting ergosterol synthesis,³⁵ was
230 previously prepared on four different occasions in 13-27 steps (31% ideality in the shortest route).
231 Conventional tactics such as asymmetric allylation,^{36,37} HWE,^{35,36} RCM,^{35,37} asymmetric
232 epoxidation³⁷ for establishing C–C and C–O bonds with the requisite stereochemistry. A more
233 intuitive LEGO-like approach was enabled through three distinct uses of dDCC. Thus, a *trans*-
234 selective dDCC between **6-RAE** and butyric acid RAE followed by two additional dDCC reactions
235 stitched together the carbon skeleton. The macrolactamization after coupling with a tyrosine
236 derivative to complete the molecule has been described in the previous route³⁵; thus 10-step formal
237 synthesis has been accomplished (40% ideality). Aside from route simplification and step-count
238 reduction observed in all of the above syntheses, Grignard reagents, expensive transition metals,
239 diazo compounds, Wittig reactions, complex chiral ligands, and toxic tin reagents were entirely
240 avoided.

241

242 The case studies depicted above only scratch the surface of what is possible using dDCC as applied
243 to complex natural product synthesis. Figure 4 illustrates further the power of dDCC for another 6
244 natural product syntheses using unique carboxylic acid building blocks. *cis*-Solamin was isolated
245 from the roots of *Annona muricata* and is a potent cytotoxic compound that inhibits the
246 mitochondrial respiratory enzyme complex I (NADH ubiquinone oxidoreductase).³⁸ Intermediate
247 **52** is a well-established precursor for *cis*-Solamin and has been prepared three times in 7-15 steps
248 (33-57% ideality) based on conventional 2e⁻ synthetic strategies with extensive use of olefin
249 functionalization and phosphonium ylide chemistry.³⁸ The radical approach described herein uses
250 one of the most abundant chiral building blocks available, tartaric acid. Thus, sequential dDCC
251 couplings (proceeding in 60% and 43% yield with perfect diastereoccontrol) between readily
252 available **48** with simple acids **49** and **50** enabled the rapid assembly of the main chain, followed
253 by a simple stereocontrolled dihydroxylation/cyclization and deprotection to afford **52** in 8 steps
254 (38% ideality). Aphanorphine (**57**), isolated from the freshwater blue-green algae named
255 *aphanizomenon flos-aquae*,³⁹ has attracted considerable attention from the synthetic community
256 with more than 20 syntheses reported (shortest 7 steps, 43% ideality). By utilizing readily available
257 proline-derived olefin **53**, a dDCC with RAE **54** rapidly provided intermediate **55** which
258 underwent Shigehisa's Co-catalyzed HAT cyclization^{40,41} followed by reduction to complete the
259 synthesis of **57** in only 4 steps (50% ideality). Notably, both key C–C bond forming events relied
260 on recently developed 1e⁻ transformations. (-)-Indolizidine 195B (**61**) and (+)-Monomorine I (**62**)
261 are poisonous alkaloids secreted from ants and amphibians that have attracted extensive synthetic
262 studies, being prepared 10 and 20 times, respectively.⁴² Despite their structural similarity, most of
263 the reported routes have targeted each molecule independently rather than through a divergent path
264 delivering both diastereomers. A non-stereocontrolled dDCC between pyroglutamate-derived **58**
265 and ketoacid RAE **59** to afford **60** as a 2:3 mixture of diastereomers was intentionally deployed to
266 access both **61** and **62** at the same time. Following reductive C–N bond formation, the divergent
267 synthesis of these two alkaloids was accomplished in 6 steps with 67% ideality

268
269 Drawing inspiration from Ley's pioneering studies on dioxane-based chiral auxiliaries,⁴³ the
270 morpholino-acid RAE **63** was designed as a precursor to the 1,2-aminoalcohol motif (synthesized
271 in 4 steps, see Supplementary Information) and employed in the formal synthesis of two unrelated
272 amine-containing natural products. The first of these was SF2768 (**67**), a unique alkaloid

273 containing an isonitrile functionality, with biological relevance in the area of bacterial copper
274 homeostasis.⁴⁴ The key hydroxylysine unit **65** was previously constructed by lengthy functional
275 group manipulations of a chiral building block with poor stereocontrol (1:1).⁴⁴ By using a
276 stereocontrolled dDCC approach commencing from **63** and glutamate **64**, this key fragment **65** can
277 be accessed in a single step (42% yield, >20:1 dr) followed by exchange of the Cbz to Boc group
278 to complete the synthesis of the key intermediate in 7 steps. The second natural product prepared
279 from **63**, complanine (**71**), is an amphipathic substance isolated from the marine fireworm,
280 *Eurythoe complanata*.⁴⁵ The prior synthesis was accomplished via homologation of an alkyne
281 followed by the construction of amino alcohol motif by using enantioselective nitrosoaldol
282 reaction.⁴⁵ Stereoselective dDCC between **63** and RAE **68** (40% yield, >20:1 dr) followed by Cbz
283 deprotection afforded chiral amino alcohol **70** in 6 steps. More importantly, the modular approach
284 outlined here is attractive from a medicinal chemistry standpoint wherein numerous chiral 1,2-
285 aminoalcohols could be conceivably evaluated in a library-format using readily available
286 carboxylic acids.

287
288 To summarize, newly identified Ag-nanoparticle enabled conditions to expand the scope of dDCC
289 to encompass α -heteroatom substituted carboxylic acids can lead to a dramatic simplification of
290 the synthesis of molecules that have historically been prepared through conventional polar
291 retrosynthetic analysis. For the 14 natural products prepared herein, application of radical
292 retrosynthesis realized by the dDCC tactic required 88 steps overall compared to prior routes
293 ranging from 117-174 steps. The remarkable ability of this Ag-Ni-facilitated dDCC to be
294 diastereocontrolled in the presence or absence of ligands on substrate **6** offers an intriguing LEGO-
295 like approach for the synthesis of polypropionates. On average, dDCC-based syntheses required 6
296 steps to complete and deleted an array of protecting groups, redox manipulations, functional group
297 interconversions, Wittig/Grignard reagents, pyrophoric reagents, toxic/non-sustainable metals,
298 expensive chiral ligands, and diazo compounds that still beleaguer modern synthesis. The approach
299 outlined herein points to a fundamentally different approach to retrosynthetic analysis that is far
300 more intuitive and easier to execute.

301
302

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396 **Figure Legends**

397 **Figure 1. Accessing polyfunctionalized carbon framework via polar (2e⁻) and radical (1e⁻)**
398 **disconnection.** **a**, A complex interplay of chemo-, regio- and stereochemical considerations is
399 inevitable in classical 2e⁻ disconnection, whereas 1e⁻ logic provides a straightforward
400 disconnection as carbon radicals can be generated at any position. **b**, A striking departure from
401 conventional synthesis by employing radical disconnection. Three intuitive radical couplings
402 could assemble polyrhacitide A, which was previously synthesized via common 2e⁻ synthetic
403 strategies (Ref 15). To achieve such an aspirational goal, dDCC needs to be successful on α -
404 functionalized carboxylic acid with high diastereoselectivity.

405 **Figure 2. Development and scope of the 2nd-generation dDCC.** **a**, Ag-NP solved reactivity
406 problem, whereas diastereoselectivity was found to be fine-tuned by Ni–ligand interaction.
407 ^aDetailed reaction conditions are included in Supplementary Information. **b**, Reaction generality
408 and limitation. Reactions were performed on 0.1 mmol scale with 3 equiv. of coupling partner
409 RAE, 20 mol% NiCl₂•dme, 20 mol% **L1**, 50 mol% AgNO₃ and NBu₄•BF₄ (0.2 M) in NMP.
410 ^bReaction was performed without a ligand, ^c**L2** was used as a ligand instead of **L1**.

412
413 **Figure 3. Demonstration for radical simplification of natural product synthesis via 2nd-**
414 **generation dDCC.** **a**, Concise synthesis of polyrhacitide A via iterative electrochemical
415 decarboxylative coupling. **b**, Syntheses of 7 other natural products by utilizing the
416 diastereoselective dDCC on **6**.

417
418 **Figure 4. Natural product syntheses based on various chiral carboxylic acids enabled by**
419 **2nd-generation dDCC.** Various classes of natural products including alkaloids and peptides were
420 also accessible by dDCC from suitable carboxylic acid building blocks.

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438 **Author Contributions**

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441 Data analysis: BZ, JH, YG, LV, MSO, MDP, TGMD, MDM, MRC, DCS, PNB, TC, SC,
442 NNP, GL, YK, PSB

443 Manuscript writing: BZ, JH, YK, PSB

444 Funding acquisition: PSB, YK

445 Project administration: PSB, YK

446 **Competing Interests**

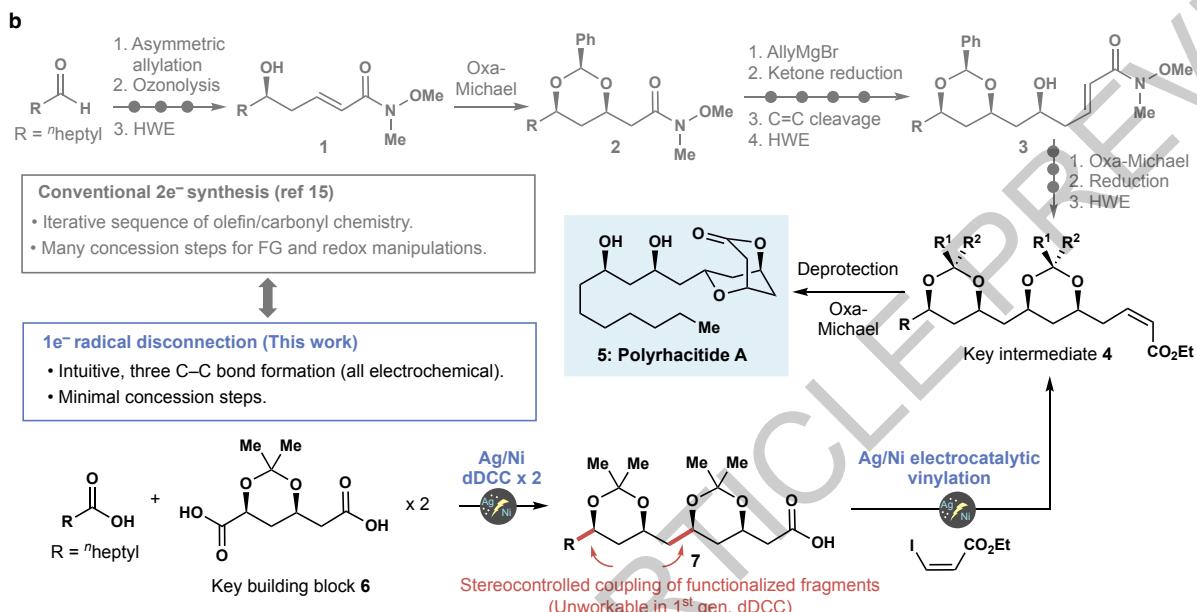
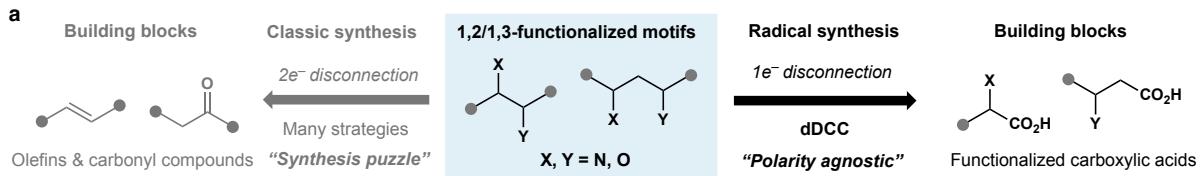
447 The authors declare no competing interest.

448

449 **Data Availability.** The data that support the findings in this work are available within the paper
450 and Supplementary Information.

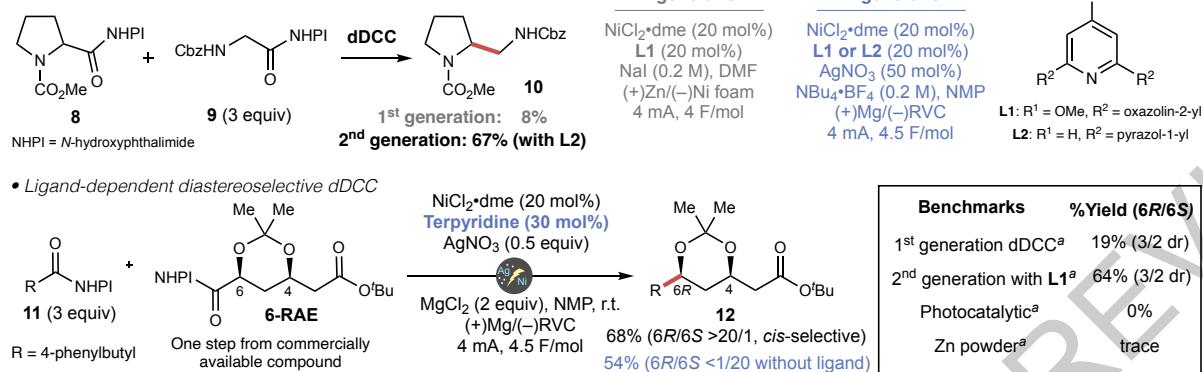
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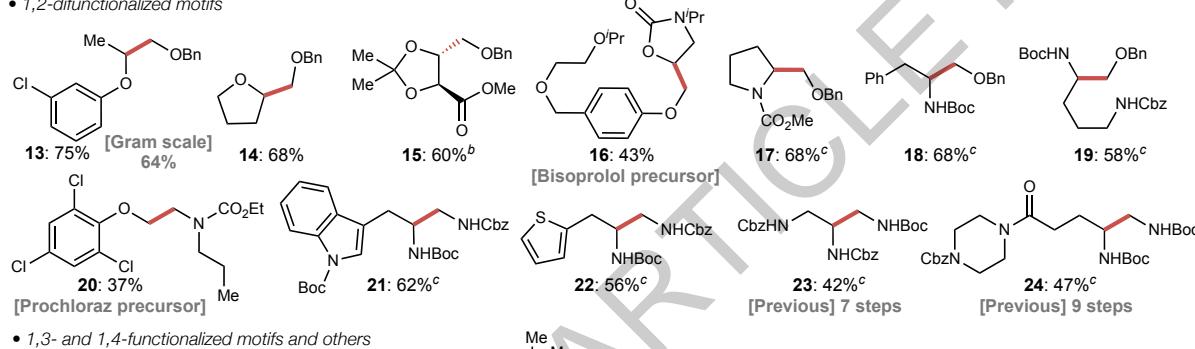


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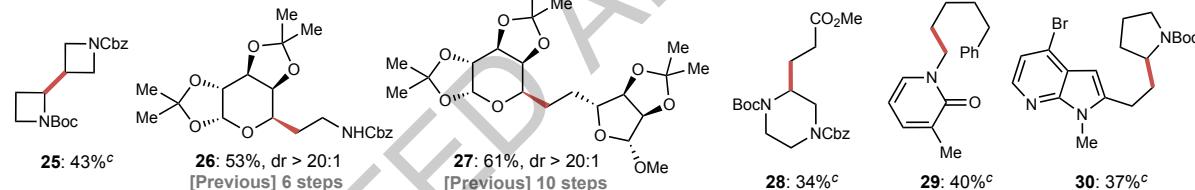
• Reactivity Breakthrough

**b**

• 1,2-difunctionalized motifs

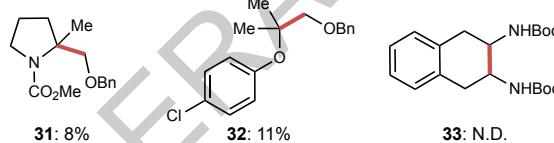


• 1,3- and 1,4-functionalized motifs and others

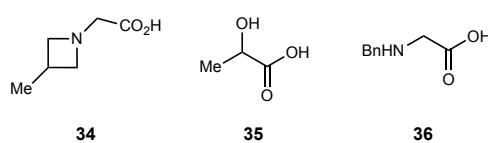


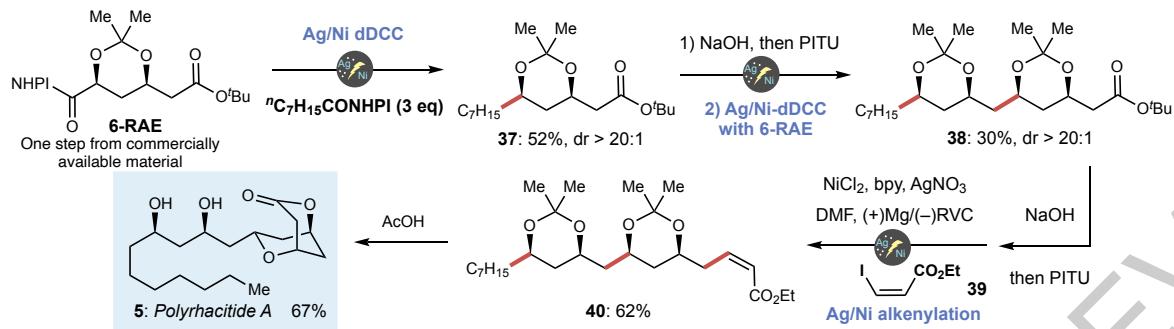
• Limitations

Tertiary and intramolecular coupling remain challenging.



RAEs with poor stability



a**b**