

# Radical Simplification of Complex Molecule Retrosynthesis Enabled by Electrocatalytic Cross-Coupling of $\alpha$ -Substituted Carboxylic Acids

**Authors:** Benxiang Zhang<sup>†1</sup>, Jiayan He<sup>1†</sup>, Yang Gao<sup>1</sup>, Laura Levy<sup>1</sup>, Martins S. Oderinde<sup>2</sup>, Maximilian D. Palkowitz<sup>3</sup>, T. G. Murali Dhar<sup>4</sup>, Michael D. Mandler<sup>4</sup>, Michael R. Collins<sup>5</sup>, Daniel C. Schmitt<sup>6,7</sup>, Philippe N. Bolduc<sup>8</sup>, TeYu Chen<sup>8</sup>, Sebastian Clementson<sup>9</sup>, Nadia Nasser Petersen<sup>9</sup>, Gabriele Laudadio<sup>1</sup>, Yu Kawamata<sup>\*1</sup>, Phil S. Baran<sup>\*1</sup>

## Affiliations:

<sup>1</sup> Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA, 92037, United States.

<sup>2</sup> Department of Discovery Synthesis, Bristol Myers Squibb, Research & Early Development, Princeton, NJ, 08540, United States.

<sup>3</sup> Small Molecule Drug Discovery, Bristol Myers Squibb, Research & Early Development, 100 Binney Street, Cambridge, MA, 02142, United States.

<sup>4</sup> Bristol Myers Squibb, Research & Early Development, Princeton, New Jersey 08543-4000, United States.

<sup>5</sup> Oncology Medicinal Chemistry Department, Pfizer Pharmaceuticals, San Diego, CA, 92121, United States.

<sup>6</sup> Medicine Design, Pfizer Worldwide Research and Development, Groton, CT, 06340, United States.

<sup>7</sup> Discovery Chemistry Research and Technologies, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, United States

<sup>8</sup> Biogen Inc., Cambridge, MA, 02142, United States.

<sup>9</sup> Research and Early Development, LEO Pharma A/S, 2750 Ballerup, Denmark.

\*Correspondence to: yukawama@scripps.edu, pbaran@scripps.edu

†These authors contributed equally.

## ABSTRACT:

The polar retrosynthetic analysis has been widely employed in the field of organic synthesis and forms the basis of undergraduate curriculum. Although most reactions in organic synthesis rely on this rubric to guide their strategic application, their implementation often requires a long list of ancillary considerations to mitigate chemoselectivity and oxidation state issues involving protecting groups and precise reaction choreography. Here we demonstrate a complete departure from this norm by the use of a radical based Ni/Ag-electrocatalytic cross coupling of  $\alpha$ -substituted carboxylic acids, thereby enabling an intuitive and modular approach to accessing complex molecular architectures. This new method relies on a key silver additive that forms an active Ag-nanoparticle coated electrode surface *in situ* along with carefully chosen ligands that modulate the reactivity of Ni. Through judicious choice of conditions and ligands, the cross-couplings can be rendered highly diastereoselective. To demonstrate the simplifying power of these reactions, exceedingly concise syntheses of 14 natural products and two medicinally relevant molecules were completed.

## MAIN TEXT:

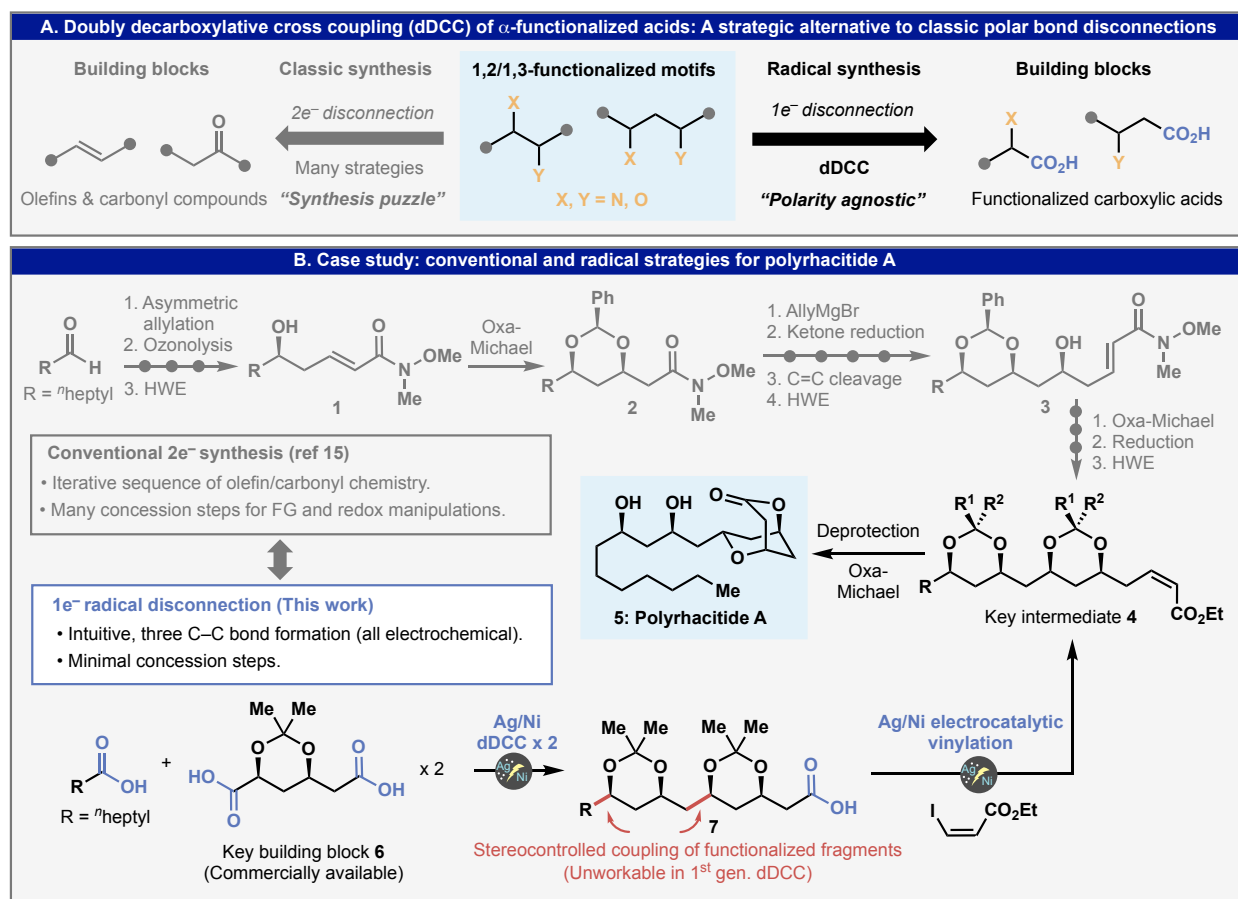
Polyfunctionalized carbon frameworks containing 1,2-, 1,3-heteroatom-substituted fragments are ubiquitous in organic molecules. Construction of such motifs has been the central theme of organic synthesis throughout its history. Numerous methods have been developed to access such motifs, and the strategic usage of such reactions has historically been guided by polar retrosynthetic analysis ( $2e^-$  disconnections).<sup>1-5</sup> These classic methods can be broadly categorized into the functionalization of olefins and carbonyl compounds (Figure 1A). In the case of olefins, for example, Sharpless epoxidation/dihydroxylation/aminohydroxylation and related reactions can allow straightforward access to precursors that can then be converted to the desired target after further functionalization. The rich chemistry of carbonyl compounds encompasses a myriad of transformations ranging from the installation of heteroatoms in the adjacent position (e.g. Rubottom oxidation or asymmetric enamine chemistry) or classic C–C bond forming events such as aldol, Claisen condensation, pinacol coupling and Mannich reaction.<sup>6</sup> The electrophilicity of carbonyl compounds allows for a combination with orthogonal olefin chemistry such as in the case of carbonyl allylation followed by oxidative cleavage.

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

In contrast, a different approach to retrosynthesis that uses radical-based logic ( $1e^-$  disconnection) to create new C–C bonds is emerging that can directly access previously challenging motifs, and in the process avoid downstream functional/protecting group manipulations and extraneous redox fluctuations.<sup>13</sup> Since disconnections based on radical retrosynthesis are polarity agnostic, any C–C bond can, in principle, be constructed by the coupling of carbon radicals *regardless of the surrounding functional groups*. This, in turn, opens up completely different ways of making molecules since polarity assignments do not need to be the sole criteria to guide a logical disconnection. Instead, maximization of convergency and starting material availability/simplicity can serve as a primary guiding principle. Towards this end, doubly decarboxylative cross coupling (dDCC) is a powerful tool to realize this vision as it directly forges  $Csp^3-Csp^3$  bonds between two carboxylic acids.<sup>14</sup> Whereas the initial manifestation of this chemistry did not tolerate adjacent functional groups, herein we disclose a method to extend the scope of this reaction enabling the modular coupling of  $\alpha$ -functionalized acids to access structures classically associated with  $2e^-$  synthetic strategies (Figure 1A).

The power of such a strategy for synthesis can be exemplified when considering the synthesis of polyrhacitide A (Figure 1B). This polyketide has the typical stereochemical array of 1,3-diol motifs; such structures have been made on countless occasions using classic  $2e^-$  synthetic strategies.<sup>15</sup> As such, an iterative sequence of olefin/carbonyl chemistry involving allylation/ozonolysis/HWE/oxa-Michael is employed to construct the carbon framework with the requisite oxygen functionalities (key intermediate **4**). This conventional approach is the result of decades of groundbreaking studies in polyketide synthesis to exquisitely control the stereochemical outcomes of C–C and C–O bond formation. However, one lingering drawback of

this strategy is the many concession steps required to manipulate functional groups and adjust appropriate oxidation states.<sup>16,17</sup> In stark contrast, a radical retrosynthetic approach to **4** could employ dDCC to sidestep many of these issues. Simply cutting bonds that lead to most accessible carboxylic acids results in a logical disconnection, thereby permitting only two simple commercially available acids to be stitched together, intuitively arriving at **4**. In principle, only three C–C bond formation steps would be required without additional C–O bond formations or redox manipulations from octanoic acid and the key building block **6**, an inexpensive 1,3-diol used to make statin-based medicines.



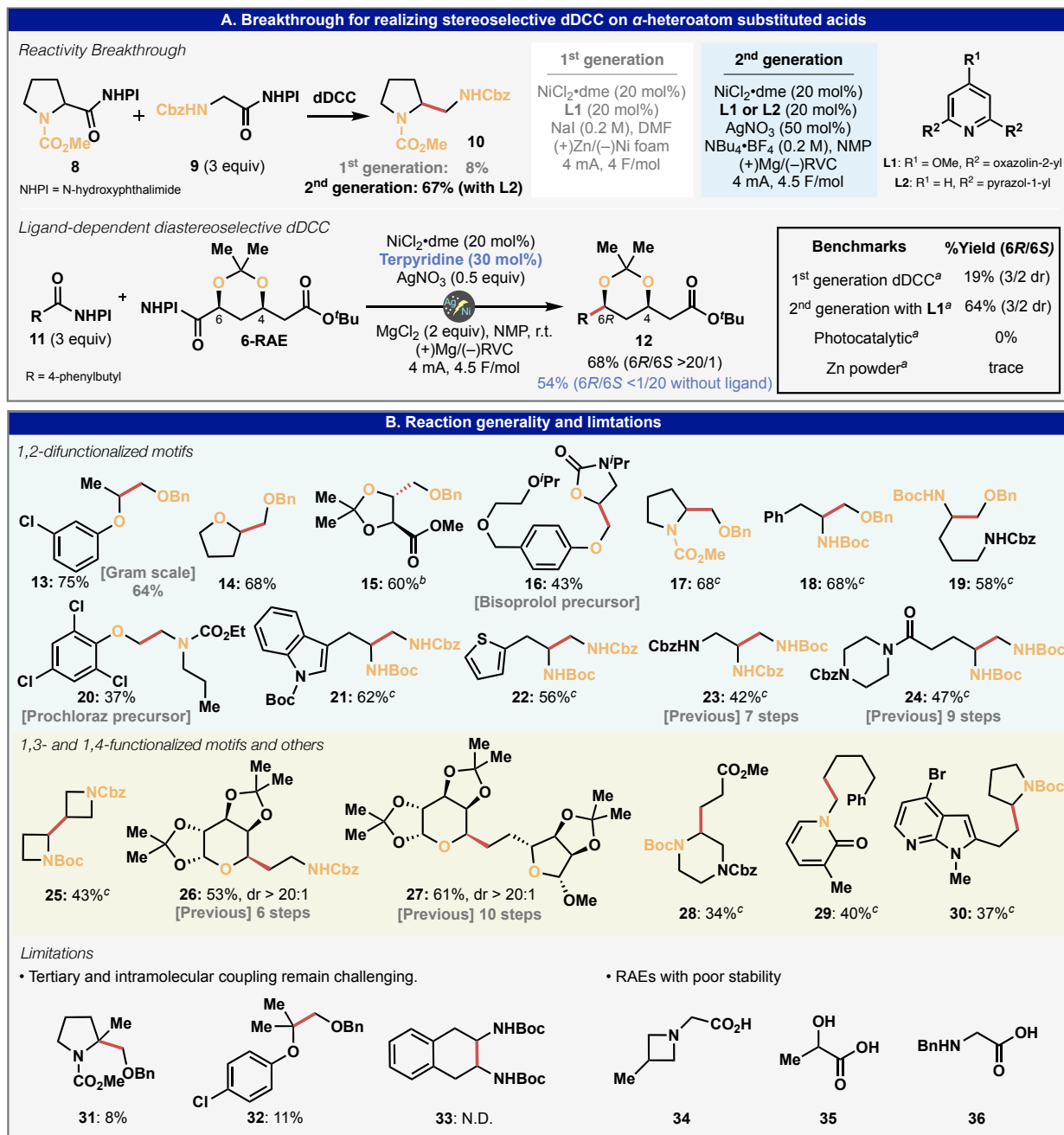
**Figure 1. Accessing polyfunctionalized carbon framework via polar ( $2e^-$ ) and radical ( $1e^-$ ) disconnection.** (A) A complex interplay of chemo-, regio- and stereochemical considerations is inevitable in classical  $2e^-$  disconnection, whereas  $1e^-$  logic provides a straightforward disconnection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

Two obstacles needed to be overcome to realize the vision set forth above (Figure 2A). First, an expansion of the initial dDCC scope to encompass substrates containing an  $\alpha$ -heteroatom functionality was necessary. As a model system for this challenge, the coupling of proline derivative **8** and glycine derivative **9** was studied. First generation dDCC conditions afforded only 8% of the desired coupling product **10** along with a variety of decarboxylated products such as the corresponding pyrrolidine, dihydropyrrole, and proline dimer (see SI for details). These byproducts were indicative of substantial redox-active ester (RAE) reduction without productive coupling, a situation encountered previously in electrochemical decarboxylative vinylation and arylation studies.<sup>8,9</sup> In that work, the key breakthrough involved the use of an *in-situ* generated Ag-nanoparticle deposited cathode, which primarily modulates multiple reduction events (e.g. concomitant reduction of Ni as well as RAE) on the cathode to improve the chance of successful coupling.<sup>9</sup> Accordingly, this approach was tested for the dDCC coupling of **8** and **9**. Indeed, by simply adding sub-stoichiometric amounts of Ag salt in addition to changing solvent (from DMF to NMP) and sacrificial anode material (from Zn to Mg), the yield of **10** was dramatically improved from 8% to 67% (see SI for more details on reaction optimization). The optimal ligand for this coupling was found to be tridentate ligands **L1** and **L2**, the same type of ligands used in the previous dDCC 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 MgCl<sub>2</sub> 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, see SI for working hypothesis). Additional experiments were conducted to determine if such a unique stereochemical outcome could be translated into other analogous reaction manifolds. However, attempts to replicate this coupling under photochemical<sup>18</sup> and metal-powder conditions<sup>19</sup> 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.<sup>14</sup> Maintaining the subtle balance of these multiple reduction events may be a demanding task for alternative reductants.

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  $\alpha$ -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 indicated in the step-count of previous syntheses (**16, 20, 23, 24, 26, 27**, see SI for complete route comparisons). Regarding the choice of ligand, **L1** can be used universally (except for diastereoselective cases); **L2** is useful when an amino acid-based RAE was employed as a substrate since it gives slightly improved yields in such cases. Substrates **16** and **20** are the direct precursor for important medicines that are now accessible via truncated, modular routes relative to  $2e^-$  synthetic strategies. Molecules such as **25, 28-30** were prepared for ongoing drug discovery campaigns. As with other decarboxylative couplings, the current reaction could be easily scaled (**13**, conducted on gram-scale). Regarding the limitations of this method, forging fully substituted carbon centers results in lower yields (**31, 32**) and intramolecular couplings (**33**) are currently not tractable. Additionally, RAEs tend to have lower stability when highly nucleophilic functionalities are in close proximity. Such RAEs are not applicable to the coupling (**34-36**). Finally, adoption of this reaction in high-throughput fashion is in progress (See SI for preliminary results).



**Figure 2. Development and scope of the 2<sup>nd</sup>-generation dDCC.** (A) Ag-NP solved reactivity problem, whereas diastereoselectivity was found to be fine-tuned by Ni–ligand interaction. <sup>a</sup>Detailed reaction conditions are included in SI. (B) Reaction generality and limitation. Reactions were performed on 0.1 mmol scale with 3 equiv. of coupling partner RAE, 20 mol% NiCl<sub>2</sub>·dme, 20 mol% L1, 50 mol% AgNO<sub>3</sub> and NBu<sub>4</sub>·BF<sub>4</sub> (0.2 M) in NMP. <sup>b</sup>Reaction was performed without a ligand, <sup>c</sup>L2 was used as a ligand instead of L1.

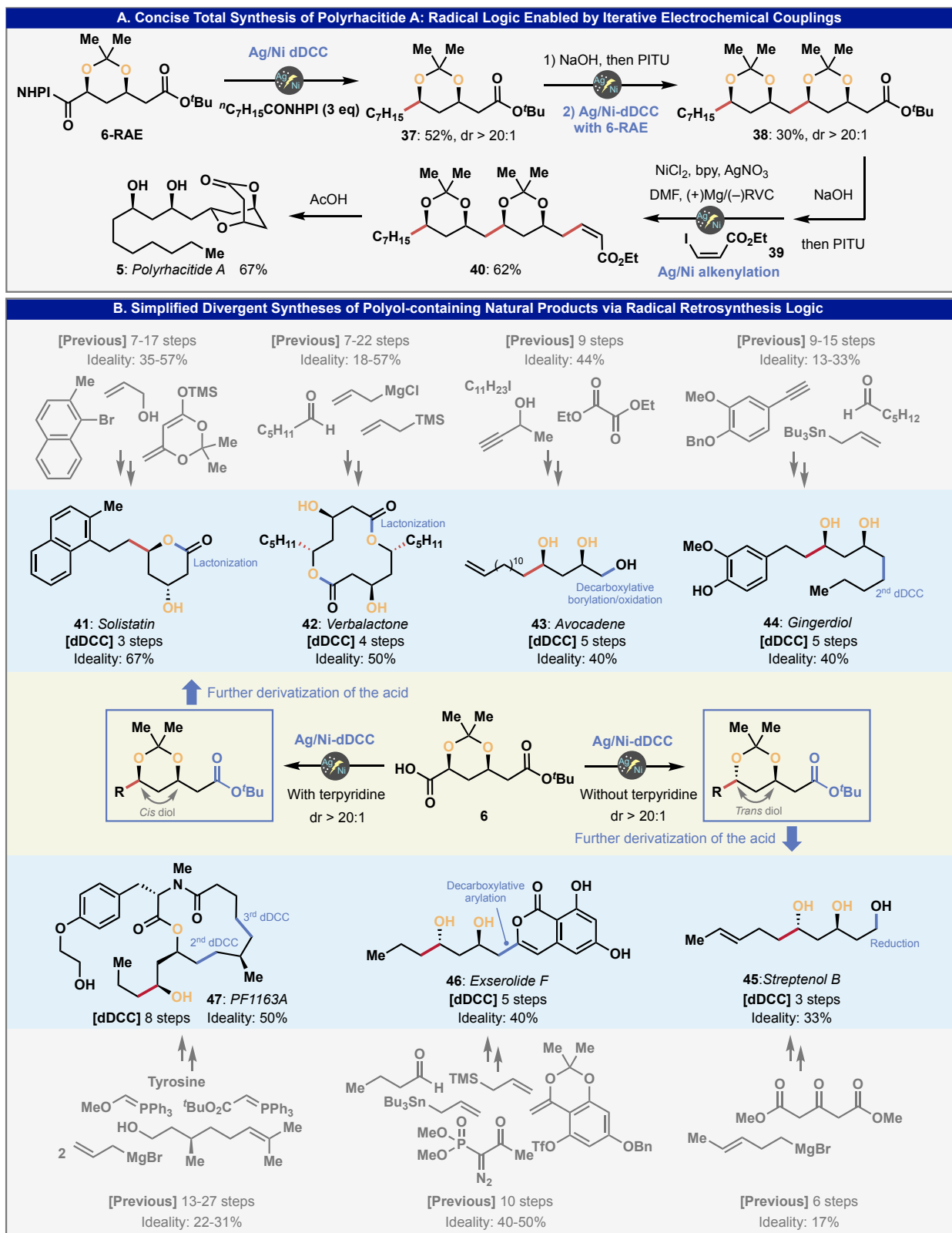
With an understanding of the scope of this transformation, a series of total syntheses were designed and executed to exemplify the powerfully simplifying nature of this new transformation. The vision set forth in Figure 1B was realized for the total synthesis of polyrhacitides A (5) as illustrated in Figure 3A. Thus, 6-RAE could be subjected to *cis*-selective dDCC with octanoic acid

RAE, affording **37** in 52% isolated yield (>20:1 dr). Subsequent union of this fragment with another equivalent of **6-RAE** after hydrolysis/RAE formation under *cis*-selective dDCC conditions furnished protected polyol ester **38** in 30% isolated yield (>20:1 dr). The third and final C–C bond forming event was accomplished again using another decarboxylative coupling method: decarboxylative alkenylation with vinyl iodide **39** to deliver **40** in 62% yield, which upon exposure to AcOH afforded the natural product **5** (67% yield). This intuitive approach to the construction of **5** is a striking departure from prior art (Figure 1B) and to polyketide synthesis in general. The overall strategy outlined for **5** could be employed seven more times for the divergent total syntheses of solistatine (**41**), verbalactone (**42**), avocadene (**43**), gingerdiol (**44**), streptenol B (**45**), exserolide (**46**), and PF1163A (**47**) resulting in reduced step-counts and improved ideality (Figure 3B). Notably, all previous routes to these natural products rely exclusively on polar-bond disconnections (see SI for the full detail and references).

Solistatin (**41**), isolated from *Penicillium solitum* and known to inhibit cholesterol synthesis,<sup>20</sup> was previously prepared three times in 7-17 steps (57% ideality for the shortest route. Building blocks in the shortest route are also illustrated in Figure 3B), featuring stereoselective aldol reactions<sup>21</sup> or iterative Overman esterification strategies.<sup>22</sup> However, the aldol approach suffers from low diastereoselectivity (2:1), whereas the Overman approach requires multiple concession steps to set the stage for this rearrangement along with expensive chiral ligands and multiple uses of palladium. In contrast a *cis*-selective dDCC using the common diol unit **6-RAE** completed the total synthesis in merely 3 steps (67% ideality) by quickly assembling the carbon skeleton followed by lactonization. Verbalactone (**42**), possessing unique activity against various Gram-positive and Gram-negative bacteria,<sup>23</sup> is an interesting case for analysis as it has been prepared at least 14 different ways ranging from 7-22 step-count (57% ideality for the shortest route). Although a macrolactonization approach to unite the two symmetrical fragment is common, accessing the key fragment requires multiple concession steps regardless of the strategy employed such as a combination of dithiane chemistry and chiral epoxide opening<sup>23,24</sup> or asymmetric allylation.<sup>25</sup> Again, the radical approach described herein employs a *cis*-selective dDCC on **6-RAE** with hexanoic acid RAE followed by deprotection of the acetonide and *tert*-butyl ester, delivering the key symmetrical unit in 2 steps. Avocadene (**43**), isolated from the avocado tree (*Persea americana*), exhibits anticancer activity against the human prostate adenocarcinoma as well as activity in the



yellow fever mosquito larvae insecticidal assay.<sup>26</sup> The previous synthesis of **43** proceeded in 9 steps (44% ideality) featuring a Noyori asymmetric reduction as well as a diastereoselective reduction of a  $\beta$ -hydroxyketone to establish the key 1,3-diol stereochemistry.<sup>26</sup> In a significant departure from this conventional logic, *cis*-selective dDCC on **6-RAE** with 13-tetradecenoic acid RAE set the stage for a 5-step synthesis of **43**. To install the third hydroxyl group of **43**, another radical reaction on the remaining carboxylate, decarboxylative borylation,<sup>27</sup> was enlisted followed by oxidative workup. Gingerdiol (**44**), isolated from ginger rhizome,<sup>28</sup> was previously prepared four times in 9-15 steps (33% ideality for the shortest route), featuring polar transformations such as Keck allylation,<sup>29</sup> epoxide opening<sup>30</sup> and iterative proline catalysed  $\alpha$ -aminoxylation of an aldehyde.<sup>28</sup> A far more intuitive approach can be realized using *cis*-selective dDCC of **6-RAE** with a functionalized phenylpropionic acid RAE, followed by another dDCC to complete the total synthesis of **44** (5 steps, 40% ideality).



The completely programmable diastereoselectivity of dDCC reactions on **6** (delivering *cis*- or *trans*-products at-will) could be also harnessed to access natural products bearing a *trans*-arrangement between diol motifs as illustrated in the next three total syntheses. For instance, streptenol B (**45**), a cholesterol synthesis inhibitor isolated from streptomyces species,<sup>31</sup> was previously prepared in 6 steps as a racemate (17% ideality) with a poor diastereoselectivity in the Grignard reaction step.<sup>31</sup> *Trans*-selective dDCC between **6-RAE** and (*E*)-4-hexenoic acid RAE followed by acetonide deprotection and reduction of the remaining ester afforded **45** concisely (3 steps, 33% ideality). Exserolide F (**46**), isolated from plant endophytic fungus of *Exserohilum* species, demonstrates significant antimicrobial activity<sup>32</sup> and was previously prepared twice in 10 steps (40 and 50% ideality).<sup>32,33</sup> In both cases, substituted coumarin core was constructed *via* Sonogashira coupling followed by cationic cyclization to furnish the lactone. In a complete departure from this strategy, the coumarin fragment could be incorporated via decarboxylative arylation<sup>8,9</sup> after the *trans*-selective dDCC between butyric acid RAE and **6**, halving the step-count (5 steps, 40% ideality). Finally, PF1163A (**47**), isolated from the fermentation broth of *Penicillium* sp. and possessing antifungal activity by inhibiting ergosterol synthesis,<sup>34</sup> was previously prepared on four different occasions in 13-27 steps (31% ideality in the shortest route). Conventional tactics such as asymmetric allylation,<sup>35,36</sup> HWE,<sup>34,35</sup> RCM,<sup>34,36</sup> asymmetric epoxidation<sup>36</sup> for establishing C–C and C–O bonds with the requisite stereochemistry. A more intuitive LEGO-like approach was enabled through three distinct uses of dDCC. Thus, a *trans*-selective dDCC between **6-RAE** and butyric acid RAE followed by two additional dDCC reactions stitched together the carbon skeleton. The macrolactamization after coupling with a tyrosine derivative to complete the molecule has been described in the previous route<sup>35</sup>; thus 8-step formal synthesis has been accomplished (50% ideality). Aside from the dramatic route simplification and step-count reduction observed in all of the above syntheses, Grignard reagents, expensive transition metals, diazo compounds, Wittig reactions, complex chiral ligands, and toxic tin reagents were entirely avoided.

The case studies depicted above only scratch the surface of what is possible using dDCC as applied to complex natural product synthesis. Figure 4 illustrates further the power of dDCC for another 6 natural product syntheses using unique carboxylic acid building blocks. *cis*-Solamin was isolated from the roots of *Annona muricata* and is a potent cytotoxic compound that inhibits the

mitochondrial respiratory enzyme complex I (NADH ubiquinone oxidoreductase).<sup>37</sup> Intermediate **52** is a well-established precursor for *cis*-Solamin and has been prepared three times in 7-15 steps (33-57% ideality) based on conventional 2e<sup>-</sup> synthetic strategies with extensive use of olefin functionalization and phosphonium ylide chemistry.<sup>37</sup> The radical approach described herein uses one of the most abundant chiral building blocks available, tartaric acid. Thus, sequential dDCC couplings (proceeding in 60% and 43% yield with perfect diastereocontrol) between readily available **48** with simple acids **49** and **50** enabled the rapid assembly of the main chain, followed by a simple stereocontrolled dihydroxylation/cyclization and deprotection to afford **52** in 6 steps (50% ideality). Aphanorphine (**57**), isolated from the freshwater blue-green algae named *aphanizomenon flos-aquae*,<sup>38</sup> has attracted considerable attention from the synthetic community with more than 20 syntheses reported (shortest 7 steps, 43% ideality). By utilizing readily available proline-derived olefin **53**, a dDCC with RAE **54** rapidly provided intermediate **55** which underwent Shigehisa's Co-catalyzed HAT cyclization<sup>39,40</sup> followed by reduction to complete the synthesis of **57** in only 3 steps (67% ideality). Notably, both key C–C bond forming events relied on recently developed 1e<sup>-</sup> transformations. (-)-Indolizidine 195B (**61**) and (+)-Monomorphine I (**62**) are poisonous alkaloids secreted from ants and amphibians that have attracted extensive synthetic studies, being prepared 10 and 20 times, respectively.<sup>41</sup> Despite their structural similarity, most of the reported routes have targeted each molecule independently rather than through a divergent path delivering both diastereomers. A non-stereocontrolled dDCC between pyroglutamate-derived **58** and ketoacid RAE **59** to afford **60** as a 2:3 mixture of diastereomers was intentionally deployed to access both **61** and **62** at the same time. Following reductive C–N bond formation, the divergent synthesis of these two alkaloids was accomplished in 4 steps with no concession step involved (100% ideality).

Drawing inspiration from Ley's pioneering studies on dioxane-based chiral auxiliaries,<sup>42</sup> the morpholino-acid RAE **63** was designed as a precursor to the 1,2-aminoalcohol motif (synthesized in 3 steps, see SI) and employed in the synthesis of two unrelated amine-containing natural products. The first of these was SF2768 (**67**), a unique alkaloid containing an isonitrile functionality, with biological relevance in the area of bacterial copper homeostasis.<sup>43</sup> The key hydroxylysine unit **65** was previously constructed by lengthy functional group manipulations of a chiral building block with poor stereocontrol (1:1).<sup>43</sup> By using a stereocontrolled dDCC approach

commencing from **63** and glutamate **64**, this key fragment **65** can be accessed in a single step (42% yield, >20:1 dr) followed by exchange of the Cbz to Boc group to complete the formal synthesis in 5 steps. The second natural product prepared from **63**, complanine (**71**), is an amphipathic substance isolated from the marine fireworm, *Eurythoe complanata*.<sup>44</sup> The prior synthesis was accomplished via homologation of an alkyne followed by the construction of amino alcohol motif by using enantioselective nitrosoaldol reaction.<sup>44</sup> Stereoselective dDCC between **63** and RAE **68** (40% yield, >20:1 dr) followed by Cbz deprotection afforded chiral amino alcohol **70** in 5 steps. More importantly, the modular approach outlined here is attractive from a medicinal chemistry standpoint wherein numerous chiral 1,2-aminoalcohols could be conceivably evaluated in a library-format using readily available carboxylic acids.

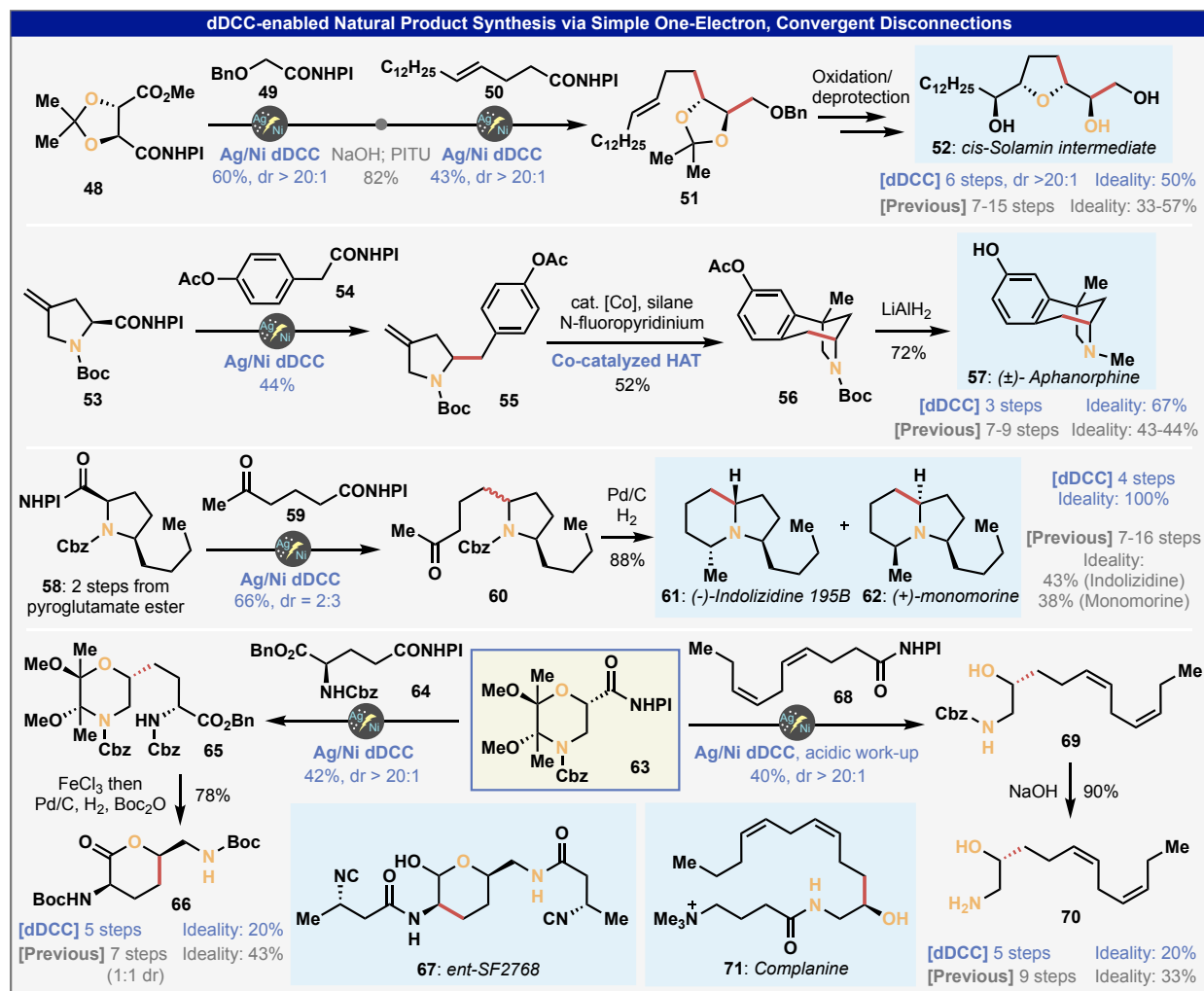


Figure 4. Natural product syntheses based on various chiral carboxylic acids enabled by 2<sup>nd</sup>-generation dDCC.

## **CONCLUSION:**

To summarize, newly identified Ag-nanoparticle enabled conditions to expand the scope of dDCC to encompass  $\alpha$ -heteroatom substituted carboxylic acids can lead to a dramatic simplification of the synthesis of molecules that have historically been prepared through conventional polar retrosynthetic analysis. For the 14 natural products prepared herein, application of radical retrosynthesis realized by the dDCC tactic required 60 steps overall compared to prior routes ranging from 117-174 steps. The remarkable ability of this Ag-Ni-facilitated dDCC to be diastereocontrolled in the presence or absence of ligands on substrate **6** offers an intriguing LEGO-like approach for the synthesis of polypropionates. On average, dDCC-based syntheses required 4 steps to complete and deleted an array of protecting groups, redox manipulations, functional group interconversions, Wittig/Grignard reagents, pyrophoric reagents, toxic/non-sustainable metals, expensive chiral ligands, and diazo compounds that still beleaguer modern synthesis. The approach outlined herein points to a fundamentally different approach to retrosynthetic analysis that is far more intuitive and easier to execute.

## **ASSOCIATED CONTENT**

### **Supporting Information**

Experimental procedures and characterizations of compounds.

## **AUTHOR INFORMATION**

### **Corresponding Author**

\*yukawama@scripps.edu

\*pbaran@scripps.edu

## **ACKNOWLEDGMENT**

Financial support for this work was provided by National Science Foundation Center for Synthetic Organic Electrochemistry (CHE-2002158, for optimization of reactivity and initial scope), and the National Institutes of Health (grant number GM-118176, for the application of the method to

natural product synthesis). We also thank Pfizer, Bristol Myers Squibb, Biogen Inc., and LEO Pharma for industrial collaborations.

## REFERENCES

1. Corey, E. J.; Cheng, X. M. *Logic of chemical synthesis*. (Wiley, 1995).
2. Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258.
3. Warren, S.; Wyatt, P. *Organic synthesis: the disconnection approach*. (Wiley, 2008).
4. Hoffmann, R. W. *Elements of synthesis planning*. (Springer, 2009).
5. Clayden, J.; Greeves, N.; Warren, S. *Organic chemistry*. (OUP Oxford, 2012).
6. Kurti, L.; Czako, B. *Strategic applications of named reactions in organic synthesis* (Elsevier Science, 2005).
7. Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. (Wiley, 2013).
8. Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blaszczak, V. D.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.; Vokits, B.; Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S. Overcoming Limitations in Decarboxylative Arylation via Ag–Ni Electrocatalysis. *J. Am. Chem. Soc.* **2022**, *144*, 17709–17720.
9. Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. L.; Baran, P. S. Modular terpene synthesis enabled by mild electrochemical couplings. *Science* **2022**, *375*, 745–752.
10. Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. The Art and Science of Organic and Natural Products Synthesis. *J. Chem. Educ.* **1998**, *75*, 1225–1258.
11. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.
12. Shen, Y.; Borowski, J. E.; Hardy, M. A.; Sarpong, R.; Doyle, A. G.; Cernak, T. Automation and Computer-Assisted Planning for Chemical Synthesis. *Nat. Rev. Methods Primers* **1**, **2021**, 23.

13. Smith, J. M.; Harwood, S. J.; Baran, P. S. Radical Retrosynthesis. *Acc. Chem. Res.* **2018**, *51*, 1807–1817.
14. Zhang, B.; Gao, Y.; Hioki, Y.; Oderinde, M. S.; Qiao, J. X.; Rodriguez, K. X.; Zhang, H.-J.; Kawamata, Y.; Baran, P. S. Ni-electrocatalytic Csp<sup>3</sup>–Csp<sup>3</sup> doubly decarboxylative coupling. *Nature* **2022**, *606*, 313–318.
15. Yadav, J. S.; Rajendar, G. Stereoselective Total Synthesis of Polyrhacitides A and B. *Eur. J. Org. Chem.* **2011**, 6781–6788.
16. Gaich, T.; Baran, P. S. Aiming for the Ideal Synthesis. *J. Org. Chem.* **2010**, *75*, 4657–4673.
17. Peters, D. S.; Pitts, C. R.; McClymont, K. S.; Stratton, T. P.; Bi, C.; Baran, P. S. Ideality in Context: Motivations for Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 605–617.
18. Zhang, Y.; Ma, D.; Zhang, Z. Utilization of Photocatalysts in Decarboxylative Coupling of Carboxylic N-Hydroxyphthalimide (NHPI) Esters. *Arab. J. Chem.* **2022**, *15*, 103922.
19. Goldfogel, M. J.; Huang, L.; Weix, D. J. *Nickel Catalysis in Organic Synthesis* 183–222 (Wiley, 2019).
20. Halperin, S. D.; Britton, R. Chlorine, an atom economical auxiliary for asymmetric aldol reactions. *Org. Biomol. Chem.* **2013**, *11*, 1702–1705.
21. Borg, T.; Danielsson, J.; Somfai, P. Mukaiyama aldol addition to  $\alpha$ -chloro-substituted aldehydes. Origin of the unexpected syn selectivity. *Chem. Commun.* **2010**, *46*, 1281–1283.
22. Binder, J. T.; Kirsch, S. F. Iterative approach to polyketide -type structures: stereoselective synthesis of 1,3-polyols utilizing the catalytic asymmetric Overman esterification. *Chem. Commun.* **2007**, 4164–4166.
23. Vanjivaka, S.; Ramanakumar, K.; Rajeswari, M.; Vantikommu, J.; Sridhar, G.; Palle, S. An alternative stereoselective total synthesis of Verbalactone. *Arkivoc* **2018**, 50–57.
24. Wu, J.-Z.; Gao, J.; Ren, G.-B.; Zhen, Z.-B.; Zhang, Y.; Wu, Y. Facile access to some chiral building blocks. Synthesis of verbalactone and exophilin A. *Tetrahedron* **2009**, *65*, 289–299.
25. Allais, F.; Louvel, M.-C.; Cossy, J. A Short and Highly Diastereoselective Synthesis of Verbalactone. *Synlett*, **2007**, 0451–0452.
26. Cunha, V. L. S.; Liu, X.; Lowary, T. L.; O'Doherty, G. A. De Novo Asymmetric Synthesis of Avocadyne, Avocadene, and Avocadane Stereoisomers. *J. Org. Chem.* **2019**, *84*, 15718–15725.
27. Wang, J.; Shang, M.; Lundberg, H.; Feu, K. S.; Hecker, S. J.; Qin, T.; Blackmond, D. G.; Baran, P. S. Cu-Catalyzed Decarboxylative Borylation. *ACS Catal.* **2018**, *8*, 9537–9542.



28. Markad, S. B.; Bhosale, V. A.; Bokale, S. R.; Waghmode, S. B. Stereoselective Approach towards the Synthesis of 3R, 5 S Gingerdiol and 3 S, 5 S Gingerdiol. *ChemistrySelect* **2019**, *4*, 502–505.
29. Sabitha, G.; Srinivas, C.; Reddy, T. R.; Yadagiri, K.; Yadav, J. S. Synthesis of gingerol and diarylheptanoids. *Tetrahedron Asymmetry* **2011**, *22*, 2124–2133.
30. Wan, Z.; Zhang, G.; Chen, H.; Wu, Y.; Li, Y. A Chiral Pool and Cross Metathesis Based Synthesis of Gingerdiols. *Eur. J. Org. Chem.* **2014**, 2128–2139.
31. Blechert, S.; Dollt, H. Synthesis of (–)-Streptenol A, (±)-Streptenol B, C and D. *Liebigs Ann.* **1996**, 2135–2140.
32. Mallampudi, N. A.; Reddy, G. S.; Maity, S.; Mohapatra, D. K. Gold(I)-Catalyzed Cyclization for the Synthesis of 8-Hydroxy-3- substituted Isocoumarins: Total Synthesis of Exserolide F. *Org. Lett.* **2017**, *19*, 2074–2077.
33. Dumpala, M.; Kadari, L.; Krishna, P. R. Brønsted acid promoted intramolecular cyclization of O-alkynyl benzoic acids: Concise total synthesis of exserolide F. *Synthetic Commun.* **2018**, *48*, 2403–2408.
34. Kumar, H.; Reddy, A. S.; Reddy, B. V. S. The stereoselective total synthesis of PF1163A. *Tetrahedron Lett.* **2014**, *55*, 1519–1522.
35. Tatsuya, K.; Takano, S.; Ikeda, Y.; Nakano, S.; Miyazaki, S. The Total Synthesis and Absolute Structure of Antifungal Antibiotics (–)-PF1163A and B. *J. Antibiotics* **1999**, *52*, 1146–1151.
36. Krishna, P. R.; Srinivas, P. Total synthesis of the antifungal antibiotic PF1163A. *Tetrahedron Asymmetry* **2012**, *23*, 769–774.
37. Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. Recent progress on the total synthesis of acetogenins from Annonaceae. *Beilstein J. Org. Chem.* **2008**, *4*, 48.
38. Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. Aphanorphine, a novel tricyclic alkaloid from the blue-green alga Aphanizomenon flos-aquae. *Tetrahedron Lett.* **1988**, *29*, 4381–4384.
39. Shigehisa, H.; Ano, T.; Honma, H.; Ebisawa, K.; Hiroya, K. Co-Catalyzed Hydroarylation of Unactivated Olefins. *Org. Lett.* **2016**, *18*, 3622–3625.
40. Wang, C.; Guan, Y. Concise Total Synthesis of (+)-Aphanorphine. *Synlett* **2021**, *32*, 913–916.
41. Ziarani, G. M.; Mohajer, F.; Kheilkordi, Z. Recent Progress Towards Synthesis of the Indolizidine Alkaloid 195B. *Curr. Org. Synth.* **2020**, *17*, 82–90.

42. Harding, C. I.; Dixon, D. J.; Ley, S. V. The preparation and alkylation of a butanedione-derived chiral glycine equivalent and its use for the synthesis of  $\alpha$ -amino acids and  $\alpha,\alpha$ -disubstituted amino acids. *Tetrahedron* **2004**, *60*, 7679–7692.
43. Xu, Y.; Tan, D. S. Total Synthesis of the Bacterial Diisonitrile Chalkophore SF2768. *Org. Lett.* **2019**, *21*, 8731–8735.
44. Kamanos, K. A. D.; Withey, J. M. Enantioselective total synthesis of (R)-(-)-complanine. *Beilstein J. Org. Chem.* **2012**, *8*, 1695–1699.