Stereoselective aminoalcohol synthesis via chemoselective electrocatalytic radical cross couplings

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Abstract:

Aminoalcohols are vital in natural products, pharmaceuticals, agrochemicals, and as key building blocks for various applications. Traditional synthesis methods often rely on polar-bond retrosynthetic analysis, requiring extensive protecting group manipulations that complicate direct access. Here we show a streamlined approach using a serine-derived chiral carboxylic acid in stereoselective electrocatalytic decarboxylative transformations, enabling efficient access to enantiopure aminoalcohols. Unlike conventional strategies, this radical method is both modular and general, offering stereoselective and chemoselective synthesis of diverse substituted aminoalcohols. For example, aryl, alkenyl, alkyl and acyl fragments can be coupled efficiently with the serine-derived chiral acid under electrocatalytic decarboxylative conditions. We demonstrate its utility through the rapid synthesis of medicinally important compounds as well as useful building blocks, highlighting its ability to simplify complex synthetic pathways through entirely different bond disconnections. This electrocatalytic method is robust and scalable, as demonstrated in 72-gram-scale flow reaction.

Introduction:

Vicinal aminoalcohols are ubiquitous structural motifs present in many biologically active molecules as well as building blocks for organic synthesis (Fig. 1a). In fact, more than one million compounds that are unsubstituted at C-1 and bear C-2 substitution can be found in Reaxys, including 88 approved drugs and >3600 natural products (for example compounds **1**-**7**). As building blocks for organic synthesis, 2-substituted aminoethanols are a versatile input for chiral auxiliaries and catalysts.[1] In medicinal chemistry they also serve as vital precursors for constructing chiral morpholines and piperazines.[2,3] Numerous strategies to enantioselectively construct this unit have been reported over the years such as addition of nucleophilic carbon fragments into Garner's aldehyde, reduction of amino acids, asymmetric reductive amination and Sharpless asymmetric aminohydroxylation, all of which are accessed by polar bond analysis ($2e^-$ disconnections, Fig. 1b).[4,5] Although these approaches are valuable, a heavy reliance on harsh reactants such as organolithium/magnesium and $LiAlH_4$ or toxic metals (Os) limits their widespread use. By far, the most widely adopted approach employs nucleophilic addition of organometallic reagents to chiral imines (Davis, Ellman, etc.).[6–8] This strategy is modular and practical to conduct with the only caveat being a lack of chemoselectivity requiring additional protecting group manipulations with exposed acidic functional groups. Emblematic of this predicament is the reported enantiocontrolled synthesis of the natural product DAHD (**3**) through an 8-step route commencing from Garner's aldehyde wherein only 3 steps forge a C–C bond or install a key stereocenter (Fig. 1c).[9] Attempts to add radicals to such imines have been met with limited success and require an additional electron withdrawing group or extended conjugation to enhance reactivity.[10–15] Application of radical retrosynthetic logic to this problem could dramatically simplify access to such structures as has been demonstrated in a variety of different contexts.[16–23] As transformations that proceed by way of radical intermediates are often compatible with common functional groups such as carbonyls and unprotected acidic/basic functionalities, the chemoselectivity issues present in polar bond disconnections might therefore disappear. However, the realization of this plan was elusive due to the lack of a suitable radical acceptor and reliable stereocontrol, though enantioselective Ni-catalysis could be employed in some cases.[24–28] Recently, we disclosed a Ni-electrocatlaytic decarboxylative coupling to access 1,2-amino alcohols bearing substitution at the oxygen-bearing carbon leading to unbranched primary amino alcohols.[29] Applying the same strategy using Seebach-type chiral redox active

ester (RAE) **8** failed to provide useful levels of d.r.,[29] while a Ley-type auxiliary **9** was obtained as inseparable mixture of diastereomers (Fig. 1b).[22] Herein we disclose a simple and inexpensive solution to access this wide swath of chemical space utilizing an inexpensive, serine derived aminoalcohol cassette **10-RAE** that serves to shield the polar aminoalcohol and uniformly control the stereochemistry of ensuing radical cross coupling reactions (Fig. 1d). The scope of accessible stereopure 1,2-aminoalcohols is vast due to the high chemoselectivity, thereby enabling dramatic synthetic simplification such as access to DAHD **3** in a single operation from **10-RAE**.

Discovery and development of the reaction platform

As shown in Fig. 1b, several chiral amino alcohol radical "donors" were evaluated before arriving on **10-RAE** (Fig. 2a), a structure that is reminiscent of auxiliaries used extensively for stereoselective enolate alkylations by Meyers.[30,31] In fact, the parent methyl ester of **10-RAE** was reported by Zurbano and Avenoza for the purposes of enolate alkylation to produce serine derivatives.[32] This rigid bicyclic scaffold exhibits strong *exo*-preference for a new substituent, thereby ensuring high diastereocontrol. **10-RAE** could be easily procured on gram scale in 99% e.e. from *N*-Boc serine methyl ester (**11**) in three trivial steps. This structure is a stable solid insensitive to water, light, and even weak acid, although prolonged storage (several weeks) on the benchtop at ambient temperature generated a small amount of the parent carboxylic acid. With copious quantities of **10-RAE** in hand, its utility in a variety of radical cross couplings was evaluated. To our delight, after a series of optimizations (See Supplementary Table S1-S3), **10-RAE** cleanly engaged in five different types of electrocatalytic radical cross couplings: (1) arylation with aryl iodides (**condition A**), (2) arylation and vinylation with the corresponding bromides (**condition B**), (3) acylation with acyl chlorides (**condition C**), (4) doubly decarboxylative (dDCC) alkylation (**condition D**), and (5) benzylation (**condition D**). All of the optimization studies commenced with a set of initial conditions (Fig. 2b) that closely mirrored that of our previous studies on Ni/Ag-electrocatalytic arylation and alkenylation.[21] In the case of arylation with aryl iodides, an increased yield was observed when the aryl halide was used in slight excess (1.5 equiv.), resulting in the identification of **condition A**. When alkenyl and aryl bromides were employed, several modifications (**condition B**) were found to be beneficial including the addition of $MgCl_2$ (2.0 equiv.) and water (2.0 equiv.) in place of Ag salts, the use of

$LiBF_4$ as an electrolyte, and a slow addition of **10-RAE** to the reaction mixture (over 2 hours). In the case of electrochemical decarboxylative acylation, a new set of conditions (**condition C**) had to be developed as this reaction was unknown prior to these studies. The closest precedent for such a transformation was published by this lab in 2019 using chemical reductants.[33] Employing those conditions using benzoyl chloride resulted in only 19% yield of the ketone product with the mass balance mostly being composed of decarboxylated oxazolidine. Based on this finding, we reasoned that the more mildly reductive conditions of an electrocatalytic process might reduce this unproductive decarboxylation pathway. Fortuitously, the final set of optimized conditions (**C**) for this new electrocatalytic coupling mirrored that of **condition B** with a slight change in solvent composition (DMA/THF 1:1 vs. DMA only). When alkyl-containing acid anhydrides were employed, the original conditions published before using chemical reductants worked well.[33] For doubly decarboxylative coupling (dDCC), the additives which proved beneficial for **condition A** could again be employed to improve the yields resulting in **condition D**. It was also found that when more hindered 2º-RAE donors were employed, ligand-less conditions were optimal. To the best of our knowledge, there are no general conditions for electrocatalytic coupling of benzyl halides with RAEs.[34] We were pleased to find that by simply employing **condition D**, benzylation worked well using the corresponding bromides.

Reaction Scope

Upon completing the series of optimizations outlined above the scope of these radical cross couplings was examined as outlined in Table 1. Electrocatalytic decarboxylative arylation using aryl iodides (**condition A**, Table 1a) exhibited a broad functional group tolerance. Thus, cyanide (**12**), aldehyde (**13**), halide (**14**, **15**, **16**, **32**), free alcohol (**17**), thioethers (**18**), acetamide (**19**), amine (**20**), and other carbonyl functionalities such as ester (**25**) and ketone (**34**), which are sensitive to Grignard reagents, can be used. Even boronic ester and free carboxylic acids could be employed (*vide infra*). Due to the oxidative addition rate of low-valent nickel, aryl iodides are favored over the corresponding bromides thereby allowing for an orthogonal handle for downstream cross couplings (**15**, **32**). Ortho-substituted arenes and heteroarenes do not decrease yield or stereoselectivity (**18**, **24**, **29**, **32**, **33**). Lewis-basic pyridines, which can bind to Ni, can be easily coupled (**21**, **22**). Similarly, isoquinoline (**26**), quinoline (**27**), pyrimidine (**28**), and unprotected (aza)indoles (**30**, **33**), which can be problematic in conventional cross-couplings, are

tolerated. Under these conditions, certain pyrazole, indazole, and imidazole substrates were not viable coupling partners (N-H protection and different conditions could solve this issue as described below for indazole **37**).

With regards to the coupling of aryl bromides and electron rich aryl iodides, the low coupling efficiency often observed could be overcome by controlling the RAE consumption rate through its slow addition (**condition B**, Table 1a). Under these mildly reductive conditions, oxidatively sensitive motifs like thiophene (**41**), 9H-carbazole (**42**), benzo[d]thiazole (**43**), aniline (**44**), and even free phenol functionalities (**47**) are tolerated. This slow addition protocol could be used to engage previously problematic substrates. Whereas Boc-protected indazole **37** had poor coupling efficiency under **condition A** (<5% yield), using **condition B** the yield became synthetically useful (58% yield). These same conditions could be applied to decarboxylative alkenylation using alkenyl bromides (Table 1b).

Decarboxylative acylation of **10-RAE** represents a mild alternative to Grignard addition to the corresponding Weinreb amide. Under the newly developed electrocatalytic conditions (**condition C**, Table 1c) a variety of benzoyl chlorides could be employed including furanyl, trifluoromethyl, and halide containing substrates (**50**-**54**). Mixed anhydrides with alkyl groups could also be employed using chemical conditions previously developed (*vide infra*).[33]

With regards to dDCC alkylation of **10-RAE** (**condition D**, Table 1d), RAE coupling partners containing silyl (**55**), ester (**56**), olefin (**57**), fluorine (**58**, **60**), carbamates (**62**, **63**) and ketone functionality (**64**) can be employed regardless of the alkyl chain length (from six carbon to one carbon does not diminish reactivity). Secondary RAEs (**63**-**68**) also participated in the dDCC process with ring sizes ranging from four to six. The challenging coupling of a secondary acyclic substrate (**68**) proceeded in 25% isolated yield. It is noted that when an unsymmetrical 2º-RAE is used, a mixture of diastereomers could be obtained (See Supplementary Page S33).

Finally, with regards to decarboxylative benzylation (Table 1d), multiple substituted benzyl bromides with either electron-donating groups (EDG) or electron-withdrawing groups (EWG) can be easily coupled. It is worth noting that the coupling of benzyl bromide **74** gave a cleaner reaction profile than the corresponding RAE **75**. From a strategic perspective, access to benzyl halides (commercial or via radical halogenation of the corresponding methyl group) is easier than the corresponding aryl acetates in many cases (for example triazole **70**).

Synthetic applications

The power of these radical cross couplings to simplify access to 1,2-amino alcohols is vividly illustrated through multiple case studies. The enhanced chemoselectivity and modularity of this approach led to truncated syntheses of 15 different known building blocks and natural products (Fig. 3 and 4), in some cases rather dramatically so. With regards to the most trivial substrates (Fig. 3a), enantiopure functionalized amino alcohols **76**-**80** were accessed in a single step following acidic workup from **RAE-10** (or it enantiomer ***ent*-10-RAE**). They can be found in various pharmaceuticals such as VTP-23 (**81**, treatment for cancer and autoimmune disease),[35] SDZ MKS 492 (**82**, a potent PDE inhibitor),[36] ASTX029 (**83**, Phase I-II clinical trials for advanced solid malignancies),[37] and enantiopure aminoalcohol **79** and **80**, useful building blocks for the synthesis of highly selective asymmetric catalysts **84**[38] and **85**,[39] could also be easily synthesized.

The high chemoselectivity inherent to many single electron processes could be leveraged to delete functional group (FG) manipulations and protecting group (PG) chemistry as demonstrated in Fig. 3b and 3c. For instance, aryl bromide **86** bearing a free carboxylic acid could be easily coupled to **10-RAE** followed by acidic workup to deliver **5** directly. In contrast, the previous route to this molecule involved a tedious 7-step construction with only one of those steps being strategic (C–C bond formation).[40] Similarly, Bpin-containing aryl bromide **88** could be easily coupled to **10-RAE** followed by Suzuki coupling and acidic workup to deliver aminoalcohol **1**. The previous synthesis of **1** required Suzuki coupling with an elaborated aryl bromide (4 steps to synthesize) and an expensive boronate ester.[41] As the Bpin group can be preserved in Ni-electrocatalytic coupling, this strategy readily affords the functionalized boronate ester **89**, offering a more convenient intermediate that enables the use of inexpensive bromothiazole as a coupling partner thereby lowering both the cost and labor required for synthesis.

Historically, chiral aminoalcohols are essential building blocks to access chiral morpholines and piperazines, both of which are privileged structures in active pharmaceutical ingredients.[2,3] Yet, their syntheses are often time-consuming and laborious. For example, morpholine **92**[42] and piperazine **94**[43] were previously synthesized through 6 and 10-step routes, respectively (Fig. 3d). Of the sixteen combined steps in those routes, only four assembled key C–C bonds with the

remainder being redox fluctuations and PG/FG manipulations. The chemoselective nature of the decarboxylative coupling allows the pivotal ester-containing chiral aminoalcohol **90** to be accessed quickly on gram scale. Then, both morpholine **92** and piperazine **94** can be accessed divergently in 2-3 additional steps.

Having demonstrated the utility of diastereoselective decarboxylative arylation, attention shifted to analogous alkylations and acylations to build functionality-rich saturated carbon frameworks (Fig. 4). A simple hydroxylactam **4**, a known precursor for a number of bioactive compounds, was previously prepared via a 6-step synthesis from suitably protected aspartic acid wherein only one step is strategic (HWE, C–C bond forming).[44] In sharp contrast, **4** can be made in 3 steps by stitching together aminoalcohol cassette and inexpensive glutaric acid derived RAE **95** followed by deprotection and cyclization (Fig. 4a). The power of diastereoselective decarboxylative acylation can be brought to bear on the divergent synthesis of sphingoid bases **2**, **99**-**102** (Fig. 4b). This approach is well-suited to a hypothetical medicinal chemistry program, as all of these compounds can be divergently derived from common intermediate **97**, readily prepared by decarboxylative acylation between **10-RAE** and palmitic acid. Stereoselective reduction of the ketone by $NaBH_4$ or amine-directed reduction with $LiAlH(O^tBu)_3$ leads to the formation of **2** and **99**, respectively. Alternatively, reductive amination allows installation of the second amine, furnishing both diastereomers of diamine **101** and **102**, which are rather difficult to synthesize (previously requiring 23 steps). Although concise syntheses specific to **99** (4 steps) and **2** (2 steps) are known, those conventional approaches may be difficult to employ in more complex settings. For instance, in a molecule such as DAHD (**3**), the advantage of chemoselective decarboxylative acylation becomes apparent. The previous route[9] to access this natural product begins from Garner's aldehyde (with questionable long-term stability), which is a rather expensive starting material that can be synthesized in 3 steps from serine.[45] Since the terminal amino acid cannot be tolerated during the first Grignard addition, it was necessary to construct this motif separately in the synthesis. This chemoselectivity issue required many concession steps including expensive asymmetric hydrogenation, resulting in an 8-step synthesis (29% overall yield). In contrast, since the amino acid is compatible in decarboxylative acylation, **3** was synthesized in a single flask operation through sequential reagent addition (no intermediate solvent swap, workup, or removal of solvent, see Supplementary Page S121 for graphical

procedure): simple attachment of aminoalcohol cassette to *L*-Boc-Glu-O^{t}Bu followed by diastereoselective reduction and deprotection in 43% overall yield (Fig. 4c).

Scale-up

The utility and generality of this methodology prompted us to further evaluate it on a multigram scale (Fig. 5). The key issue to be addressed was the feasibility of using a sacrificial electrode in a flow electrolysis setup. Conventionally, such a system is not preferred due to the constant alteration of electrode distance and surface area caused by electrode consumption, raising some risk to operate the reaction reliably on scale. However, employing a sacrificial anode could be valuable to avoid extensive, time-consuming re-optimization campaigns to determine alternative paired electrolysis conditions.[20,21,46–50] Such additional labor is a roadblock to keep up with the fast pace at which new pharmaceutical targets are identified nowadays.

With regard to the preparation of a large quantity of RAE for our scale-up study, it was discovered that isoindolinone-type RAE **104** synthesized from *L*-Ser-OMe·HCl after a sequence of condensation with 2-acetylbenzoic acid and activation with *N*-hydroxyphthalimide, is preferable due to its high crystallinity, which removes the necessity of chromatographic purification on large scale. The change of the backbone does not compromise the stereoselectivity of the coupling, and the enantiopure aminoalcohol (99% e.e.) can be readily liberated by the treatment of the coupling product with hydrazine/acetic acid in EtOH.

With this modification in place, a 72-gram scale reaction was conducted using a rod-based flow reactor (Fig. 5a, 5b).[51–54] This type of reactor is advantageous as the electrodes do not provide any mechanical integrity to the entire reactor, while maintaining a high degree of mass transport enabling the flexibility to be used in flow or as a continuous stirred tank reactor (CSTR). Based on a limited number of batch experiments, it was determined that running the reaction under constant current conditions at 0.74 A, necessitated a residence time of 45 minutes to achieve >95% conversion of **104**. Accordingly, the flow reaction was initiated by first achieving high conversion in batch (45 minutes), followed by the initiation of reagent flow in and out of the CSTR (as depicted in Fig. 5b). The flow reaction proceeded continuously for 14 hours, achieving 84% conversion of **104** and yielding a 65% assay yield of the coupling product **105**. Initiation of the reaction proceeded smoothly, with the applied current resulting in an observed cell potential of 1.0-1.4 V over the initial 45 minutes. However, as the flow reaction commenced, the cell

potential rose to an excess of 20 V where it quickly stabilized again for the duration of the flow run as shown in Fig. 5c. The cell voltage increase as well as slightly lower conversion than batch may indicate that some irreversible processes can take place at the electrodes during the flow electrolysis, presumably because steady state concentration of the RAE is lower than batch. Regarding the impact of cell potential change upon the electrode consumption, the last 500 minutes of the reaction at steady state indicated that the cell potential only increased at a rate of 3 mV/min which is attributed to electrode gap increases as the electrode eroded. Concurrently, an increase in the Ohmic heating in the cell of 0.01 ºC/min was observed, which also supports the increase in cell potential being caused by slow erosion of the electrode. After the ~14 hours of constant operation, the magnesium electrodes were cleaned, dried and weighed and an average of 8% mass loss was observed across the seven electrodes as shown in Fig. 5d. Collectively, these findings indicate that impact of electrode corrosion during flow reaction is small; therefore it can be safely concluded that using a sacrificial anode is a viable option for flow scale-up, particularly valuable when developing an appropriate paired electrolysis system is challenging.

CONCLUSION

It is anticipated that the platform described in this study for accessing substituted aminoalcohols will be useful in many different contexts, both academic and industrial. A simple, serine-derived cassette (**10-RAE**) was developed and tested across an array of useful C–C bond forming radical cross coupling reactions (both electrochemical and chemical) with broad scope (60 examples) as a consequence of the enhanced chemoselectivity of such transforms. Its unassailable utility was demonstrated through the simplified synthesis of 15 different building blocks and natural products that have been made before using conventional polar bond analysis. Finally, the scalability of electrocatalytic decarboxylative arylation of such systems was field-tested thereby verifying that such chemistry is suitable for both small and large scale applications. This work is yet another chapter in the evolving story of how radical retrosynthesis can contribute to streamlining the way organic molecules can be made.

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Author contributions

J.S., Y.K. and P.S. conceived the concept. All the authors were involved in the process of designing, performing and analysing experiments. The manuscript was written by the contribution from all the authors. Y.K. and P.S. directed the project.

Competing interest

The authors declare no competing interests.

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Table 1. Scope, trend and limitations of Ni-electrocatalytic decarboxylative coupling. a, Coupling with aryl iodides, electron-deficient aryl iodides under condition A have higher reactivity in general. Certain pyrazole, indazole, and imidazole substrates as coupling partners cannot give products. Slow addition of RAE under condition B overcomes inefficient coupling with less reactive aryl halides such as aryl bromides and electron-rich aryl iodides. **b**, An alkenyl bromide can also be coupled under the condition B. **c**, Aryloyl chlorides afford the corresponding ketone products. Alkyl acids can also be employed under the conditions of ref 33 via in-situ acid activation. **d**, Both primary and secondary alkyl fragments can be coupled. No ligand is necessary for coupling with secondary redox-active ester and benzyl bromide. Ac, acetyl. Boc, *tert*-Butyloxycarbonyl. TBS, *tert*-Butyldimethylsilyl. The grey spheres represent the highlight of the halogen atom.

Fig. 1 Importance of vicinal aminoalcohols and synthetic approaches. **a**, Importance of chiral vicinal aminoalcohols, 2-substituted chiral aminoethanols are a prevalent motif in pharmaceuticals, natural products and organic building blocks. **b**, Prior art of polar ($2e^-$) and radical ($1e^-$) approach, conventional approaches to prepare 2-substituted aminoethanols. Utility of conventional polar bond formations is limited by chemoselectivity and reactivity issues. In contrast, radical approach might

obviate these problems, yet reliable stereocontrol has yet to be established. **c**, A case study, the natural product DAHD (**3**) was previously synthesized through an 8-step route, and functionalized Grignard does not exist. Radical retrosynthetic logic could access this structure in one step from glutamic acid. **d**, Our report on general access to vicinal aminoalcohols via radical Ni-electrocatalytic coupling. This work realizes robust stereoselective radical coupling with a broad range of coupling partners and functional group tolerance. PG, protecting group. Nu, nucleophile. NHPI, N-hydroxyphthalimide. Cbz, benzyloxycarbonyl. The blue spheres represent hydrogen atoms as well as alkyl, acyl or aryl groups.

Fig. 2 10-RAE as versatile aminoalcohol donor for radical coupling. a, Practical synthesis of **10-RAE** with 99% e.e. from inexpensive serine ester on 100 gram scale. **b**, Five reaction modes (arylation, alkenylation, acylation, alkylation, benzyaltion) and key parameters (RAE/ArI ratio, additive, electrolyte. slow addition, and solvent change) modified for identifying suitable reaction conditions, enabling radical access to broad chemical space. For acylation to make dialkyl ketone, conditions could be found in ref 33. For alkylation, no ligand was used for 2º-RAE partner. See Supplementary Table S1-S4 for full optimization summary. TCFH, *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate. NMI, *N*-methylimidazole. Bpy, 2,2'-bipyridyl. $TBABF_4$, tetrabutylammonium tetrafluoroborate. NMP, *N*-methylpyrrolidone. DMA, *N*,*N*-dimethylacetamide. RVC, reticulated vitreouscarbon. FG, functional group. RAE, redox-active ester.

Fig. 3 Simplifying syntheses using diastereoselective Csp^2–Csp^3 coupling. a, A facile access to useful aminoalcohols with variety of functionalities. See Supplementary Summary and Comparison with Previous Routes. **b**, Free carboxylic acid could be tolerated in Ni-electrocatalytic coupling to simplify the synthesis of **5** from 7 steps to 2 steps.[40] **c**, Bpin-containing aryl bromide **88** could be easily coupled.[41] High chemoselectivity of the radical coupling removes necessity of PG/FG manipulations, providing straightforward access to target structures. **d**, An ester-containing chiral morpholine and piperazine can be synthesized from the intermediate **90**, which is readily obtained from a commercial benzoate ester via radical coupling. Conventional methods accompany many concession steps due to the necessity of installing this functionality.[42,43] [a] *ent*-**10-RAE** was used as starting material. DPPA, diphenylphosphoryl azide. LAH, lithium aluminum hydride. NS, nitrobenzenesulfonyl. DIAD, diisopropyl azodicarboxylate. TBAF, tetrabutylammonium fluoride.

Fig. 4 Simplifying syntheses using diastereoselective decarboxylative alkylation and acylation. a, Rapid generation of useful building blocks **4** to lower both the cost and labor for drug discoveries.[44] **b**, Divergent syntheses of sphingoid bases, various downstream transformations further expand chemical space accessible by this strategy. See supplementary Summary and Comparison with Previous Routes. **c**, A rare natural amino acid DAHD (**3**) was accessed in singe operation with no solvent removal or work-up. Diastereoselective decarboxylative acylation bypasses chemoselectivity issue associated with organometallic reagents,[9] enabling exceedingly simple access to functionality-rich ketones.

Fig. 5 Reaction scale-up employing a flow reactor equipped with a sacrificial electrode. a, Scale-up was performed on 75 gram scale electrocatalytic coupling between **12** and RAE **104**. **b**, Overview of the reaction setup. **c**, Cell potential/conversion profile, the flow reaction was initiated in batch at 45 minutes, cell potential increased at a rate of 3 mV/min. **d**, 8% weight loss of the sacrificial anode did not significantly affect reaction outcome, successfully validating the use of a sacrificial electrode in electrochemical flow reaction.

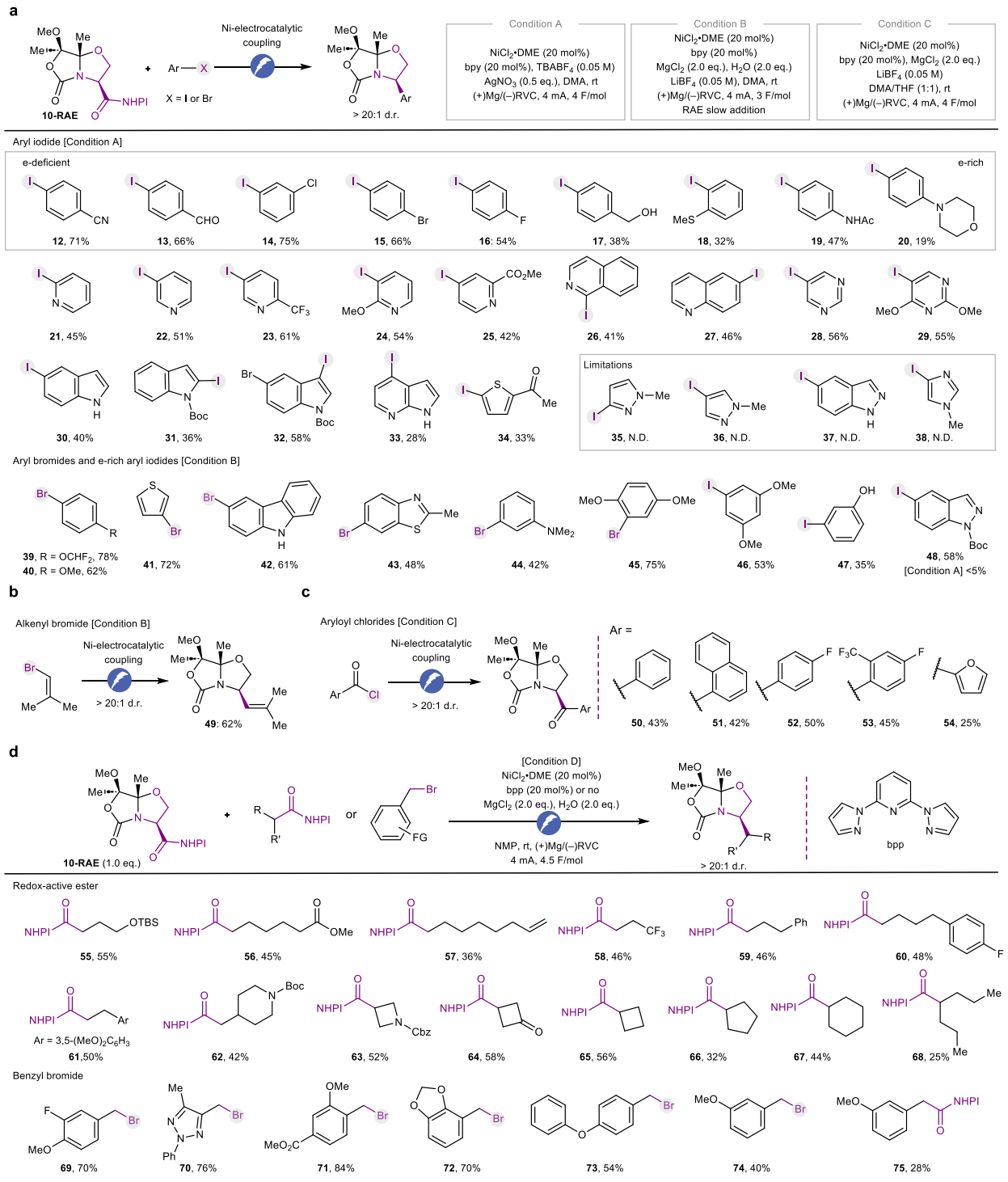
a
10-RAE
Ni-electrocatalytic coupling
X = I or Br
> 20:1 d.r.
Condition A
NiCl2•DME (20 mol%)
bpy (20 mol%), TBABF4 (0.05 M)
AgNO3 (0.5 eq.), DMA, rt
(+)Mg/(–)RVC, 4 mA, 4 F/mol
Condition B
NiCl2•DME (20 mol%)
bpy (20 mol%)
MgCl2 (2.0 eq.), H2O (2.0 eq.)
LiBF4 (0.05 M), DMA, rt
(+)Mg/(–)RVC, 4 mA, 3 F/mol
RAE slow addition
Condition C
NiCl2•DME (20 mol%)
bpy (20 mol%), MgCl2 (2.0 eq.)
LiBF4 (0.05 M)
DMA/THF (1:1), rt
(+)Mg/(–)RVC, 4 mA, 4 F/mol
Aryl iodide [Condition A]
e-deficient
e-rich
12, 71%
13, 66%
14, 75%
15, 66%
16: 54%
17, 38%
18, 32%
19, 47%
20, 19%
21, 45%
22, 51%
23, 61%
24, 54%
25, 42%
26, 41%
27, 46%
28, 56%
29, 55%
30, 40%
31, 36%
32, 58%
33, 28%
34, 33%
Limitations
35, N.D.
36, N.D.
37, N.D.
38, N.D.
Aryl bromides and e-rich aryl iodides [Condition B]
39, R = OCHF2, 78%
40, R = OMe, 62%
41, 72%
42, 61%
43, 48%
44, 42%
45, 75%
46, 53%
47, 35%
48, 58%
[Condition A] <5%
b
Alkenyl bromide [Condition B]
Ni-electrocatalytic coupling
> 20:1 d.r.
49: 62%
c
Aryloyl chlorides [Condition C]
Ni-electrocatalytic coupling
> 20:1 d.r.
Ar =
50, 43%
51, 42%
52, 50%
53, 45%
54, 25%
d
10-RAE (1.0 eq.)
or
[Condition D]
NiCl2•DME (20 mol%)
bpp (20 mol%) or no
MgCl2 (2.0 eq.), H2O (2.0 eq.)
NMP, rt, (+)Mg/(–)RVC
4 mA, 4.5 F/mol
> 20:1 d.r.
bpp
Redox-active ester
55, 55%
56, 45%
57, 36%
58, 46%
59, 46%
60, 48%
Ar = 3,5-(MeO)2C6H3
61,50%
62, 42%
63, 52%
64, 58%
65, 56%
66, 32%
67, 44%
68, 25%
Benzyl bromide
69, 70%
70, 76%
71, 84%
72, 70%
73, 54%
74, 40%
75, 28%

Table 1.

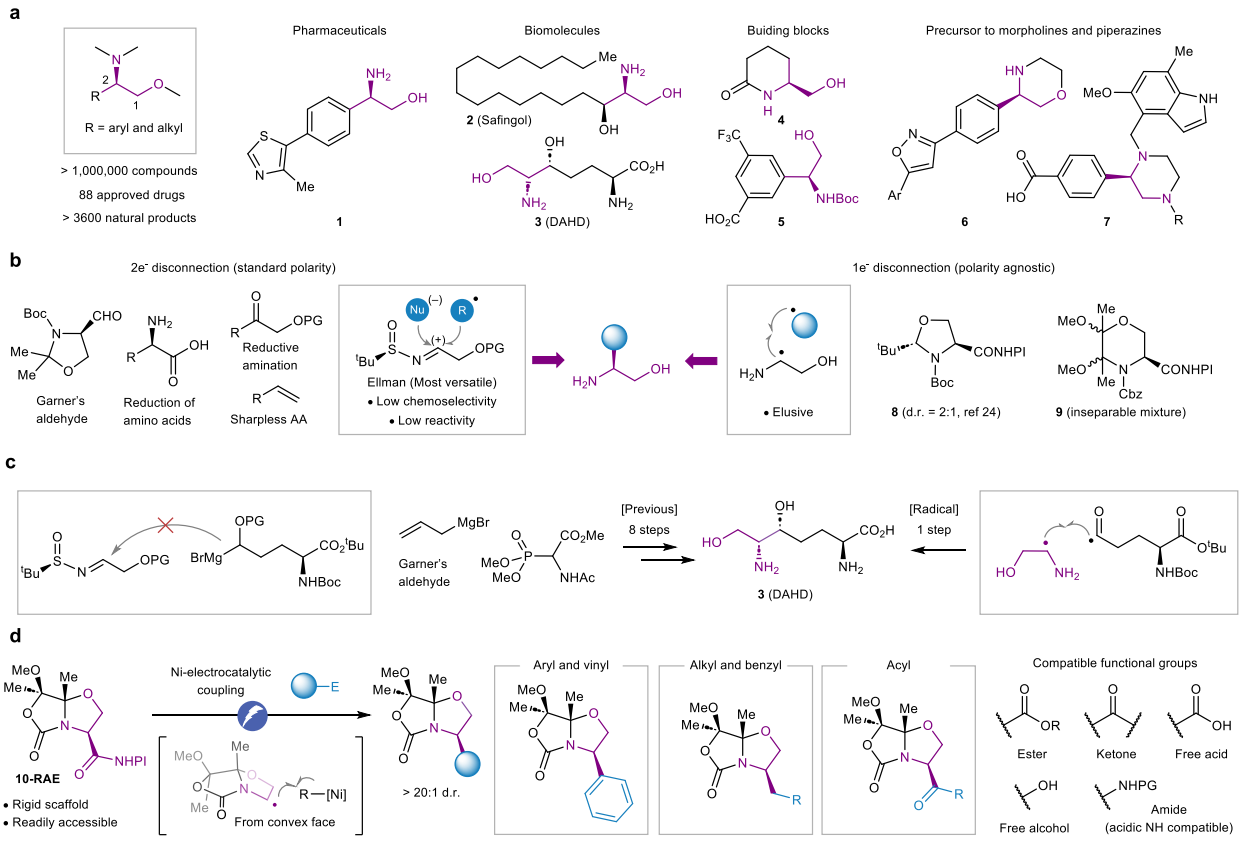
a
R = aryl and alkyl
> 1,000,000 compounds
88 approved drugs
> 3600 natural products
Pharmaceuticals
Biomolecules
Buiding blocks
Precursor to morpholines and piperazines
1
2 (Safingol)
3 (DAHD)
4
5
6
7
b
2e- disconnection (standard polarity)
1e- disconnection (polarity agnostic)
Garner's aldehyde
Reduction of amino acids
Reductive amination
Sharpless AA
Ellman (Most versatile)
• Low chemoselectivity
• Low reactivity
• Elusive
8 (d.r. = 2:1, ref 24)
9 (inseparable mixture)
c
Garner's aldehyde
[Previous] 8 steps
[Radical] 1 step
3 (DAHD)
d
10-RAE
• Rigid scaffold
• Readily accessible
Ni-electrocatalytic coupling
From convex face
> 20:1 d.r.
Aryl and vinyl
Alkyl and benzyl
Acyl
Compatible functional groups
Ester
Ketone
Free acid
Free alcohol
Amide
(acidic NH compatible)

Fig. 3

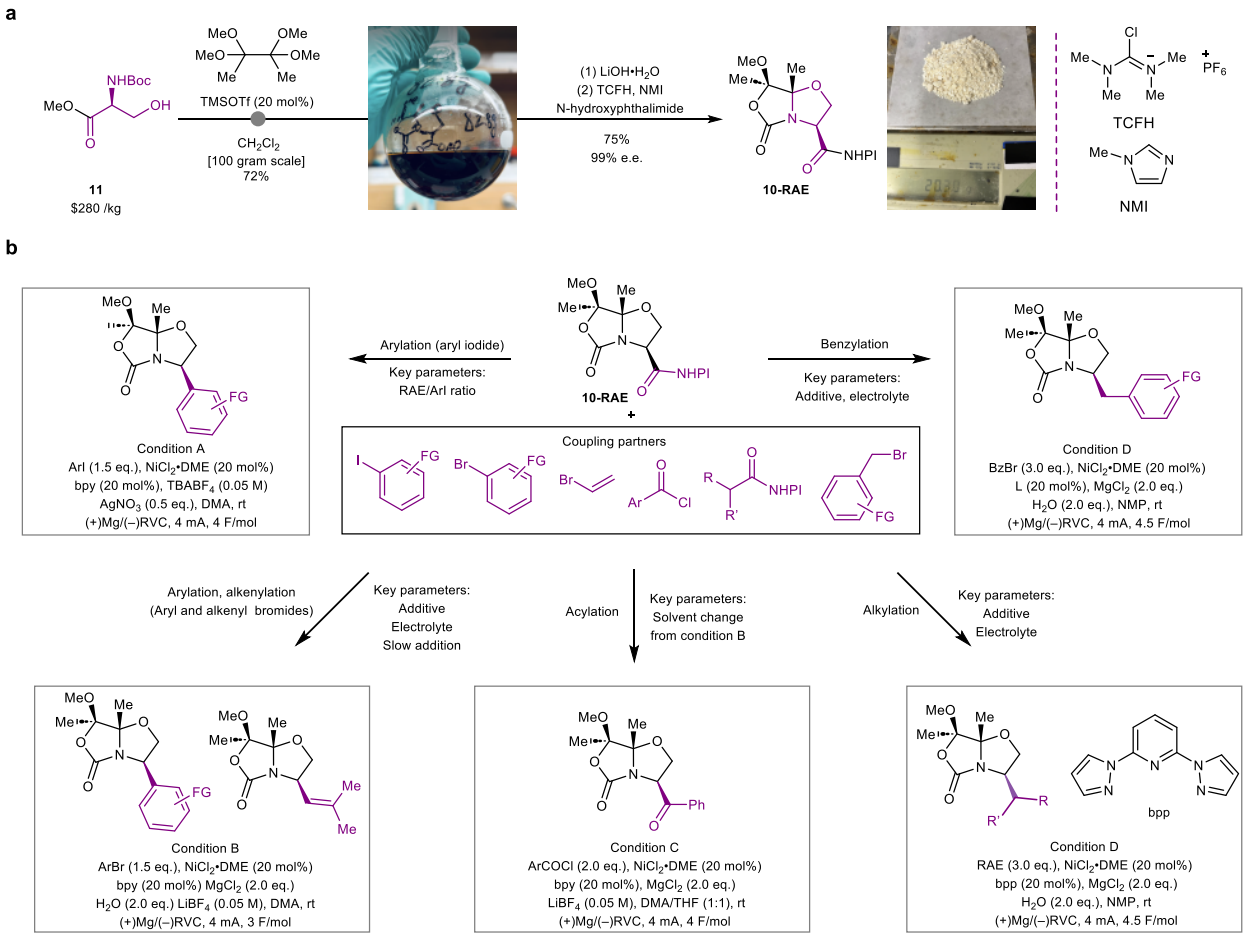
a
NHBoc
MeO
OH
O
11
$280 /kg
MeO
OMe
MeO
OMe
Me
Me
TMSOTf (20 mol%)
CH2Cl2
[100 gram scale]
72%
(1) LiOH•H2O
(2) TCFH, NMI
N-hydroxyphthalimide
75%
99% e.e.
MeO
Me
Me
O
N
O
NHPI
10-RAE
Cl
Me
N
N
Me
Me
Me
PF6
TCFH
Me
N
N
NMI
b
MeO
Me
Me
O
N
O
O
FG
Condition A
ArI (1.5 eq.), NiCl2•DME (20 mol%)
bpy (20 mol%), TBABF4 (0.05 M)
AgNO3 (0.5 eq.), DMA, rt
(+)Mg/(–)RVC, 4 mA, 4 F/mol
Arylation (aryl iodide)
Key parameters:
RAE/ArI ratio
10-RAE
NHPI
Benzylation
Key parameters:
Additive, electrolyte
Coupling partners
I
FG
Br
FG
Br
O
Ar
Cl
R
O
NHPI
R'
Br
FG
Condition D
BzBr (3.0 eq.), NiCl2•DME (20 mol%)
L (20 mol%), MgCl2 (2.0 eq.)
H2O (2.0 eq.), NMP, rt
(+)Mg/(–)RVC, 4 mA, 4.5 F/mol
Arylation, alkenylation
(Aryl and alkenyl bromides)
Key parameters:
Additive
Electrolyte
Slow addition
Acylation
Key parameters:
Solvent change
from condition B
Alkylation
Key parameters:
Additive
Electrolyte
Me
Me
Condition B
ArBr (1.5 eq.), NiCl2•DME (20 mol%)
bpy (20 mol%) MgCl2 (2.0 eq.)
H2O (2.0 eq.) LiBF4 (0.05 M), DMA, rt
(+)Mg/(–)RVC, 4 mA, 3 F/mol
Ph
Condition C
ArCOCl (2.0 eq.), NiCl2•DME (20 mol%)
bpy (20 mol%), MgCl2 (2.0 eq.)
LiBF4 (0.05 M), DMA/THF (1:1), rt
(+)Mg/(–)RVC, 4 mA, 4 F/mol
R
R'
bpp
Condition D
RAE (3.0 eq.), NiCl2•DME (20 mol%)
bpp (20 mol%), MgCl2 (2.0 eq.)
H2O (2.0 eq.), NMP, rt
(+)Mg/(–)RVC, 4 mA, 4.5 F/mol

Fig. 4

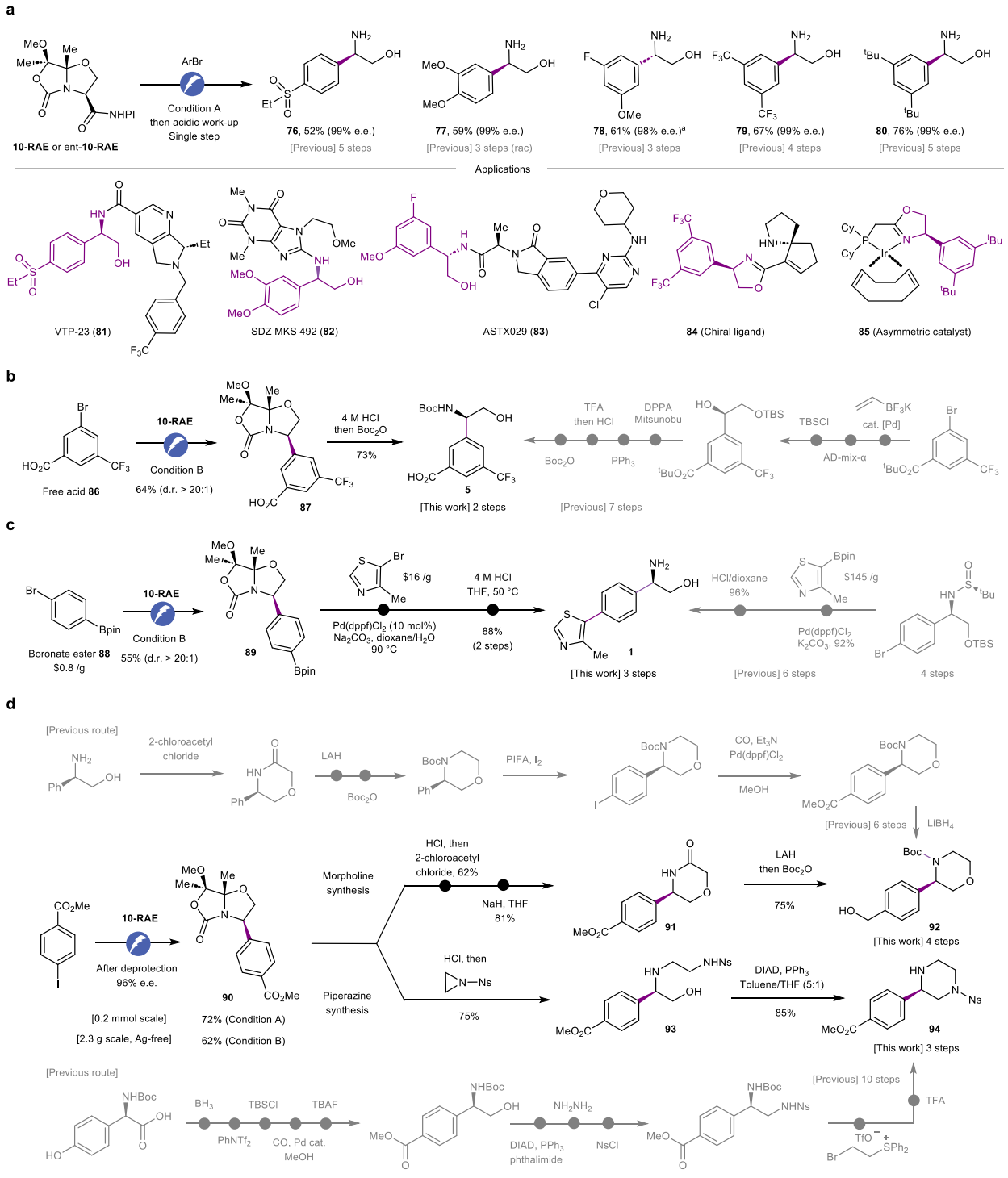
a
10-RAE or ent-10-RAE
ArBr
Condition A
then acidic work-up
Single step
76, 52% (99% e.e.)
[Previous] 5 steps
77, 59% (99% e.e.)
[Previous] 3 steps (rac)
78, 61% (98% e.e.)[a]
[Previous] 3 steps
79, 67% (99% e.e.)
[Previous] 4 steps
80, 76% (99% e.e.)
[Previous] 5 steps
Applications
VTP-23 (81)
SDZ MKS 492 (82)
ASTX029 (83)
84 (Chiral ligand)
85 (Asymmetric catalyst)
b
Free acid 86
10-RAE
Condition B
64% (d.r. > 20:1)
87
4 M HCl
then Boc2O
73%
5
[This work] 2 steps
TFA
then HCl
DPPA
Mitsunobu
Boc2O
PPh3
[Previous] 7 steps
TBSCl
BF3K
cat. [Pd]
AD-mix-α
c
Boronate ester 88
$0.8 /g
10-RAE
Condition B
55% (d.r. > 20:1)
89
$16 /g
Pd(dppf)Cl2 (10 mol%)
Na2CO3, dioxane/H2O
90 °C
4 M HCl
THF, 50 °C
88%
(2 steps)
1
[This work] 3 steps
HCl/dioxane
96%
$145 /g
Pd(dppf)Cl2
K2CO3, 92%
[Previous] 6 steps
4 steps
d
[Previous route]
2-chloroacetyl
chloride
LAH
Boc2O
PIFA, I2
CO, Et3N
Pd(dppf)Cl2
MeOH
[Previous] 6 steps
LiBH4
10-RAE
After deprotection
96% e.e.
[0.2 mmol scale]
[2.3 g scale, Ag-free]
90
72% (Condition A)
62% (Condition B)
Morpholine
synthesis
HCl, then
2-chloroacetyl
chloride, 62%
NaH, THF
81%
91
LAH
then Boc2O
75%
92
[This work] 4 steps
Piperazine
synthesis
HCl, then
N–Ns
75%
93
DIAD, PPh3
Toluene/THF (5:1)
85%
94
[This work] 3 steps
[Previous route]
BH3
TBSCl
TBAF
PhNTf2
CO, Pd cat.
MeOH
DIAD, PPh3
phthalimide
NsCl
[Previous] 10 steps
TFA

Fig. 3

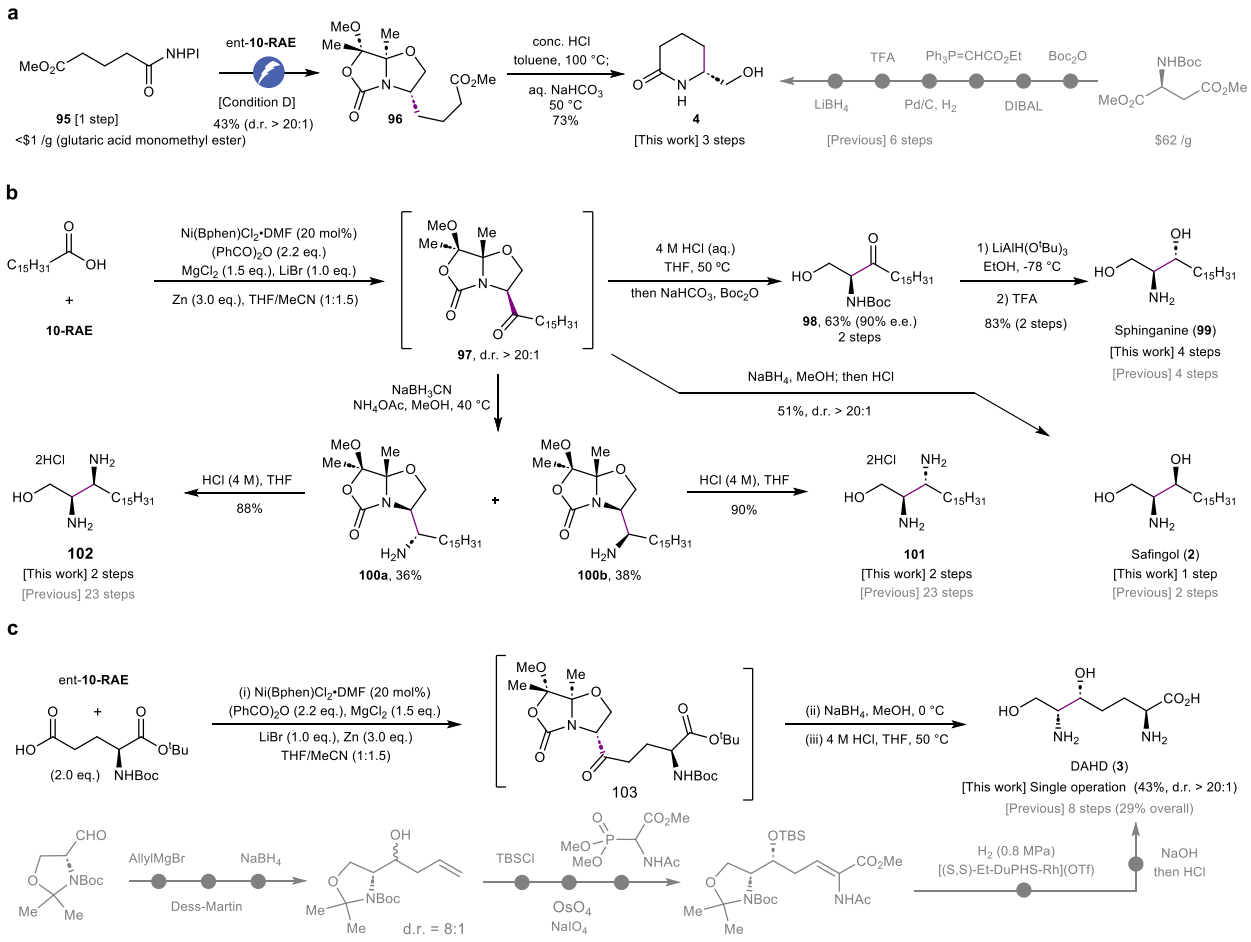
a
ent-10-RAE
[Condition D]
43% (d.r. > 20:1)
95 [1 step]
<$1 /g (glutaric acid monomethyl ester)
96
conc. HCl
toluene, 100 °C;
aq. NaHCO3
50 °C
73%
4
[This work] 3 steps
LiBH4
TFA
Ph3P=CHCO2Et
Pd/C, H2
Boc2O
DIBAL
[Previous] 6 steps
$62 /g
b
10-RAE
Ni(Bphen)Cl2•DMF (20 mol%)
(PhCO)2O (2.2 eq.)
MgCl2 (1.5 eq.), LiBr (1.0 eq.)
Zn (3.0 eq.), THF/MeCN (1:1.5)
97, d.r. > 20:1
4 M HCl (aq.)
THF, 50 °C
then NaHCO3, Boc2O
98, 63% (90% e.e.)
2 steps
1) LiAlH(OtBu)3
EtOH, -78 °C
2) TFA
83% (2 steps)
Sphinganine (99)
[This work] 4 steps
[Previous] 4 steps
NaBH3CN
NH4OAc, MeOH, 40 °C
NaBH4, MeOH; then HCl
51%, d.r. > 20:1
HCl (4 M), THF
88%
102
[This work] 2 steps
[Previous] 23 steps
100a, 36%
100b, 38%
HCl (4 M), THF
90%
101
[This work] 2 steps
[Previous] 23 steps
Safingol (2)
[This work] 1 step
[Previous] 2 steps
c
ent-10-RAE
(2.0 eq.)
(i) Ni(Bphen)Cl2•DMF (20 mol%)
(PhCO)2O (2.2 eq.), MgCl2 (1.5 eq.)
LiBr (1.0 eq.), Zn (3.0 eq.)
THF/MeCN (1:1.5)
103
(ii) NaBH4, MeOH, 0 °C
(iii) 4 M HCl, THF, 50 °C
DAHD (3)
[This work] Single operation (43%, d.r. > 20:1)
[Previous] 8 steps (29% overall)
AllylMgBr
NaBH4
Dess-Martin
d.r. = 8:1
TBSCl
OsO4
NaIO4
H2 (0.8 MPa)
[(S,S)-Et-DuPHS-Rh](OTf)
NaOH
then HCl

Fig. 4

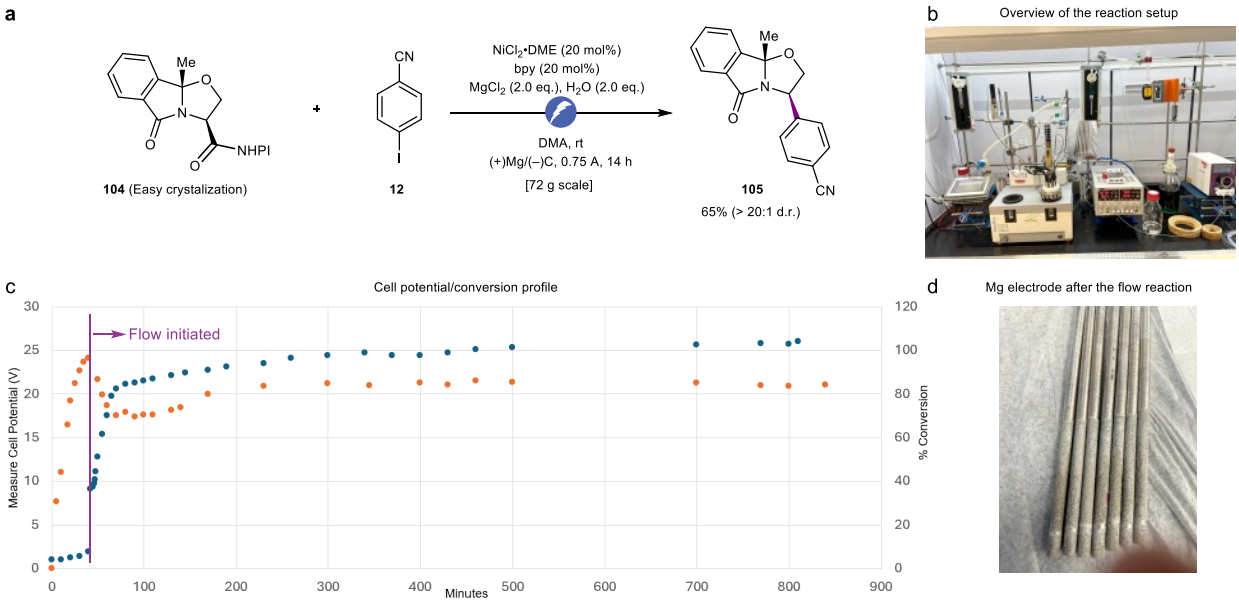
a
Me
O
N
O
NHPI
O
104 (Easy crystalization)
+
CN
I
12
NiCl2•DME (20 mol%)
bpy (20 mol%)
MgCl2 (2.0 eq.), H2O (2.0 eq.)
DMA, rt
(+)Mg/(–)C, 0.75 A, 14 h
[72 g scale]
Me
O
N
O
105
CN
65% (> 20:1 d.r.)
b
Overview of the reaction setup
c
Cell potential/conversion profile
Flow initiated
Measure Cell Potential (V)
% Conversion
Minutes
0
5
10
15
20
25
30
0
20
40
60
80
100
120
0
100
200
300
400
500
600
700
800
900
d
Mg electrode after the flow reaction

Fig. 5

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Methods

General procedure for arylation (condition A):

An ElectraSyn vial (5.0 mL) with a magnetic stir bar was charged with aryl iodide (0.3 mmol, 1.5 equiv.), redox-active ester (RAE) (0.2 mmol, 1.0 equiv.), $NiCl_2$·DME (20 mol%), 2,2'-bipyridine (bpy) (20 mol%), $AgNO_3$ (0.5 equiv.) and $TBABF_4$ (0.05 M). The ElectraSyn vial cap equipped with anode (magnesium) and cathode (RVC) (5.2 cm×0.7 cm×0.2 cm) was inserted into the mixture. The vial was then evacuated and backfilled with an argon balloon for three cycles, and DMA (3.5 mL) was added to the vial *via* a syringe and the resulting solution was stirred for another 1 min. The vial was connected to the ElectraSyn, and the ElectraSyn was set up as follows: New exp. > Constant current > 4 mA > No ref. electrode > Total charge > 0.2 mmol, 4.0 F/mol > No alternating polarity > Start. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 M) was then added [for products containing basic motifs, washing with 0.1 M HCl was omitted]. The organic layers were further washed with aqueous NaOH (0.5 M) [for products containing phenol, washing with 0.5 M NaOH was omitted] and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the desired product.

General procedure for alkenylation and arylation (condition B):

An ElectraSyn vial (17.0 mL) with a magnetic stir bar was charged with vinyl bromide or aryl bromide (1.5 mmol, 1.5 equiv.), $NiCl_2$·DME (20 mol%), 2,2'-bipyridine (bpy) (20 mol%), $MgCl_2$ (2.0 mmol, 2.0 equiv.), H_2O (2.0 mmol, 2.0 equiv.) and $LiBF_4$ (0.05 M). The ElectraSyn vial cap equipped with anode (magnesium) and cathode (RVC) (5.2 cm×0.7 cm×0.5 cm) was inserted into the mixture. The vial was then evacuated and backfilled with an argon balloon for three cycles, and DMA (7.0 mL) was added to the vial *via* a syringe and the resulting solution was stirred for another 1 min. The vial was connected to the ElectraSyn, and the ElectraSyn was set up as follows: New exp. > Constant current > 12 mA > No ref. electrode > Total charge > 1.0 mmol, 3.0 F/mol > No alternating polarity > Start. During electrolysis, redox-active ester (RAE) (1.0 mmol, 1.0 equiv.) in DMA (2.0 mL) was added at a rate of 450 μL/h *via* syringe pump. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and

aqueous HCl (0.1 M) was then added [for products containing basic motifs, washing with 0.1 M HCl was omitted]. The organic layers were further washed with aqueous NaOH (0.5 M) [for products containing phenol, washing with 0.5 M NaOH was omitted] and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the desired product.

General procedure for acylation (condition C):

An ElectraSyn vial (5.0 mL) with a magnetic stir bar was charged with bicyclic RAE (0.2 mmol, 1.0 equiv.), benzoyl chloride (0.3 mmol, 2.0 equiv.), $NiCl_2$·DME (20 mol%), 2,2'-bipyridine (bpy) (20 mol%), $MgCl_2$ (2.0 equiv.) and $LiBH_4$ (0.05 M). The ElectraSyn vial cap equipped with anode (magnesium) and cathode (RVC) (5.2 cm×0.7 cm×0.2 cm) was inserted into the mixture. The vial was then evacuated and backfilled with an argon balloon for three cycles, and 3.5 mL DMF/THF (1:1) was added to the vial *via* a syringe and the resulting solution was stirred for another 1 min. The vial was connected to the ElectraSyn, and the ElectraSyn was set up as follows: New exp. > Constant current > 4 mA > No ref. electrode > Total charge > 0.2 mmol, 4.0 F/mol > No alternating polarity > Start. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 M) was then added [for products containing basic motifs, washing with 0.1 M HCl was omitted]. The organic layers were further washed with aqueous NaOH (0.5 M) and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the desired product.

General procedure for alkylation and benzylation (condition D):

An ElectraSyn vial (5.0 mL) with a magnetic stir bar was charged with bicyclic RAE (0.2 mmol, 1.0 equiv.), RAE or benzyl bromide (0.6 mmol, 3.0 equiv.), $NiCl_2$·DME (20 mol%), 2,6-bis(pyrazole)pyridine (bpp) as indicated [bpp (20 mol%) or no ligand], $MgCl_2$ (2.0 equiv.) and H_2O (2.0 equiv.). The ElectraSyn vial cap equipped with anode (magnesium) and cathode (RVC) (5.2 cm×0.7 cm×0.2 cm) was inserted into the mixture. The vial was then evacuated and backfilled with an argon balloon for three cycles, and NMP (3.5 mL) was added to the vial *via* a syringe and the resulting solution was stirred for another 1 min. The vial was connected to the

ElectraSyn, and the ElectraSyn was set up as follows: New exp. > Constant current > 4 mA > No ref. electrode > Total charge > 0.2 mmol, 4.5 F/mol > No alternating polarity > Start. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 M) was then added [for products containing basic motifs, washing with 0.1 M HCl was omitted]. The organic layers were further washed with aqueous NaOH (0.5 M) and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the desired product.

Date Availability

All the data are available within the main text or Supplementary Information. Experimental and characterization data for all new compounds prepared during this study are provided in Supplementary Information. The X-ray crystallographic coordinate for compound **S9** has been deposited at the Cambridge Crystallographic Data Centre (CCDC) with accession codes 2334078. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.