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ELECTROCHEMISTRY

Overcoming the limitations of Kolbe coupling with waveform-controlled electrosynthesis

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The Kolbe reaction forms carbon-carbon bonds through electrochemical decarboxylative coupling. Despite more than a century of study, the reaction has seen limited applications owing to extremely poor chemoselectivity and reliance on precious metal electrodes. In this work, we present a simple solution to this long-standing challenge: Switching the potential waveform from classical direct current to rapid alternating polarity renders various functional groups compatible and enables the reaction on sustainable carbon-based electrodes (amorphous carbon). This breakthrough enabled access to valuable molecules that range from useful unnatural amino acids to promising polymer building blocks from readily available carboxylic acids, including biomass-derived acids. Preliminary mechanistic studies implicate the role of waveform in modulating the local pH around the electrodes and the crucial role of acetone as an unconventional reaction solvent for Kolbe reaction.

The Kolbe reaction, described by Faraday in 1834 and established by Kolbe in 1849, is one of the oldest electrochemical reactions and possibly the first carbon-carbon (C–C) bond-forming reaction in organic synthesis (Fig. 1) (*1*). Despite the appeal of making Csp^3–Csp^3 bonds from simple carboxylic acids through direct oxidation at an electrode, its use in mainstream organic synthesis is exceedingly rare. In its canonical form, a high current density is required to ensure high anodic potential for initiating oxidative radical generation over solvent oxidation, followed by immediate dimerization on a platinum (Pt) electrode surface. Such harsh oxidative conditions undermine its synthetic utility, with even dormant terminal unactivated olefins such as **1** (*2*) or benzylic systems such as **2** (*3*) and **3** (*4*) being incompatible (Fig. 1A). These limitations are seldom advertised, although numerous reviews on this classic reaction make it clear that minimally functionalized hydrocarbons are the best substrates (*5*–*9*), and barely any practical industrial applications exist (*10*). Interest in this potentially powerful transformation has reemerged with studies from the Lam group applying it to the synthesis of functionalized pyrrolidinones (*11*), and the Sevov group studying self-assembled monolayers to mitigate the harshly oxidative conditions (*3*). A reductive, electrocatalytic variant of the Kolbe reaction has also appeared by using in situ–generated redox active esters to enable controlled heterocoupling of different carboxylic acids (*12*).

One of the most industrially promising applications of the Kolbe reaction involves the upconversion of biomass-derived chemicals to reduce reliance on petroleum-based products. Thus far, reactions used in this space are mostly simple functional group manipulations such as hydrogenation, condensation, and elimination, with the exception of olefin cross metathesis for C–C bond formation (*13*, *14*). In this context, the Kolbe reaction has long been recognized as a potentially disruptive transformation because it forges saturated C–C bonds directly from carboxylic acids, which are ubiquitous in biomass-derived chemicals. No alternative reaction currently exists to form a saturated C–C bond with this level of simplicity and sustainability. This exciting prospect, which has generated intense study in the area of sustainable synthesis (*15*), still remains an unanswered challenge for the field, with the issues of limited substrate scope and reliance on precious metal–based electrodes presenting roadblocks for adoption.

We describe a promising solution to the chemoselectivity challenge posed by the strongly oxidative Kolbe reaction through the use of rapid alternating polarity (rAP), a waveform that is implemented on a commercial potentiostat. The rAP-Kolbe reaction features a wide substrate scope, inexpensive and sustainable C-based electrodes, operability in both dimerization and heterocoupling modes, and practicality for scale-up applications (Fig. 1B). As evidence of the practicality and dramatic cost-savings of this protocol, heretofore cost-prohibitive building blocks are now easily accessible, such as unnatural amino acids and highly coveted polymer building blocks derived from biomass-derived carboxylic acids. As a proof of concept, a distinctive acid-degradable polymer was constructed from these building blocks. Last, preliminary mechanistic studies explain why the rAP-Kolbe reaction conquers chemoselectivity constraints and the requirements of a Pt-based electrode encountered for more than 100 years.

Advantage of alternating electrode polarity

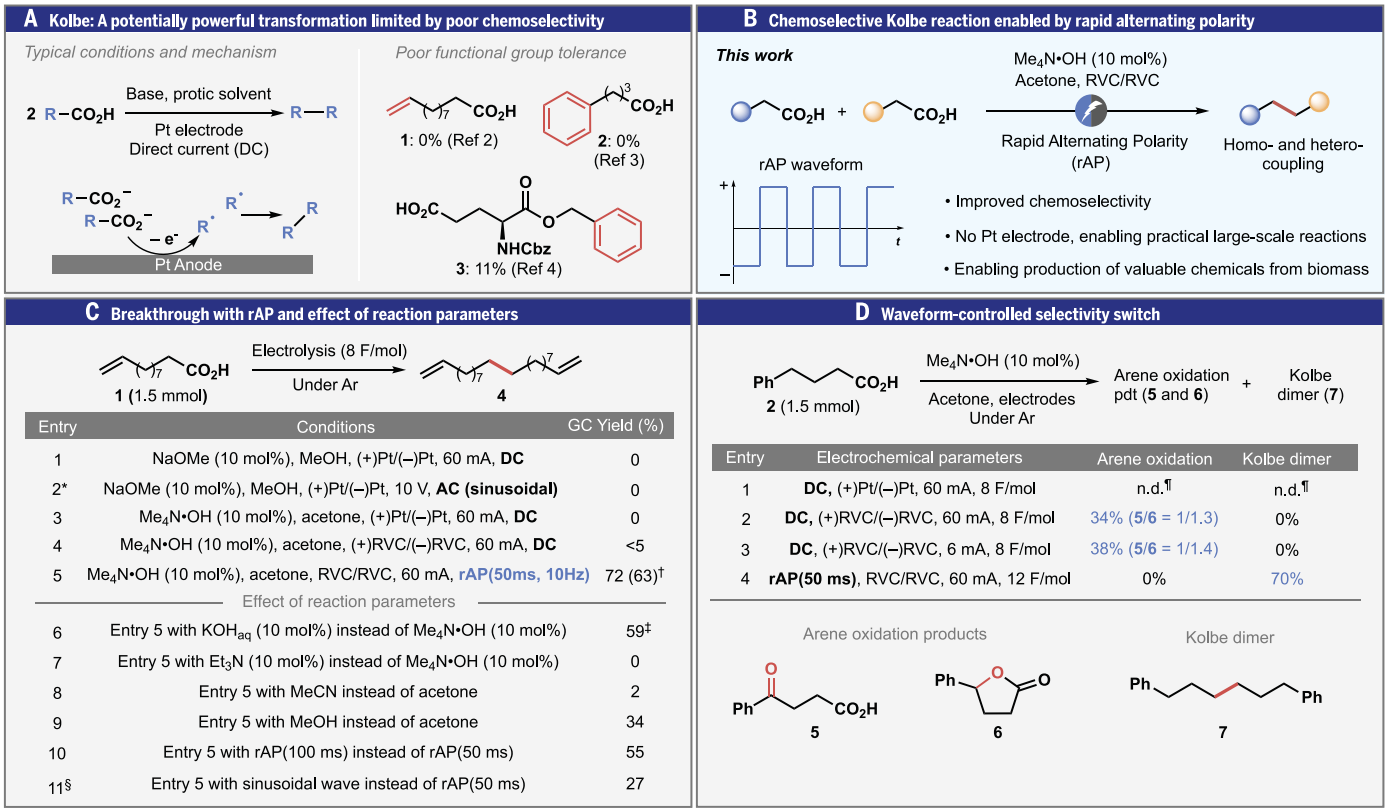
The use of different waveforms for electric current delivery as a means to improve reactivity and selectivity has only recently been recognized in the field of synthetic organic electrochemistry (*16*, *17*). Early studies were suggestive that such an approach might have potential, despite having minimal benefit in synthesis (*16*). Whereas certain reactions have been shown to benefit from alternating current in terms of achieving higher reaction efficiency (*17*, *18*), drastic changes in product distribution were unknown. In 2021, the rAP waveform was shown to enable chemoselectivity in carbonyl reduction that could not be replicated in other ways, including both electrochemical and chemical means (*19*). A completely different outcome was obtained by simply changing the waveform from direct current (dc) to rAP even when identical reaction conditions were used. The same phenomenon was also applied to chemoselective Birch-type reductions in which competing proton-reduction could be largely suppressed (*20*). Those prior studies both involved reductive processes, and thus our attention pivoted to the Kolbe reaction, one of the oxidative electrochemical processes most in need of a chemoselective variant.

Reaction development and chemoselectivity

Toward this end, we began our explorations with 10-undecenoic acid (**1**), a seemingly trivial biomass-derived acid that is not amenable to Kolbe electrolysis (Fig. 1C) (*2*). However, its dimerization product (1,19-eicosadiene; **4**) could have high utility as a polymer building block. Despite its simple structure, the price of **4** is prohibitive owing to the lack of practical access ($10,000/gram, Oakwood Chemical), whereas **1** is readily obtained from castor oil (~$20/kg). In good agreement with the prior report (*2*), conventional conditions that used Pt electrodes with direct current electrolysis led to no observable formation of **4** (entry 1), presumably because of electrode passivation (in which the surface becomes insulating, blocking current from passing) (*2*, *3*). The Kolbe reaction was previously studied with an ac waveform, and the detailed result was published in 1939 by Shipley and Rogers (*21*). The Shipley and Rogers report says they observed little difference between dc and ac, which is consistant with our observation that **4** was not formed in either case (entries 1 and 2). Altering the base, solvent, and electrodes under dc electrolysis gave no improvement on the product formation (entries 3 and 4). Notably, simply switching the waveform from dc to rAP under the identical conditions of entry 4 led to formation of **4** in 63% isolated yield (entry 5).

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Entry	Conditions	GC Yield (%)
1	NaOMe (10 mol%), MeOH, (+)Pt/(–)Pt, 60 mA, **DC**	0
2*	NaOMe (10 mol%), MeOH, (+)Pt/(–)Pt, 10 V, **AC (sinusoidal)**	0
3	Me_4N•OH (10 mol%), acetone, (+)Pt/(–)Pt, 60 mA, **DC**	0
4	Me_4N•OH (10 mol%), acetone, (+)RVC/(–)RVC, 60 mA, **DC**	<5
5	Me_4N•OH (10 mol%), acetone, RVC/RVC, 60 mA, **rAP(50ms, 10Hz)**	72 (63)†
	Effect of reaction parameters	
6	Entry 5 with KOH_{aq} (10 mol%) instead of Me_4N•OH (10 mol%)	59‡
7	Entry 5 with Et_3N (10 mol%) instead of Me_4N•OH (10 mol%)	0
8	Entry 5 with MeCN instead of acetone	2
9	Entry 5 with MeOH instead of acetone	34
10	Entry 5 with rAP(100 ms) instead of rAP(50 ms)	55
11§	Entry 5 with sinusoidal wave instead of rAP(50 ms)	27

Entry	Electrochemical parameters	Arene oxidation	Kolbe dimer
1	**DC**, (+)Pt/(–)Pt, 60 mA, 8 F/mol	n.d.¶	n.d.¶
2	**DC**, (+)RVC/(–)RVC, 60 mA, 8 F/mol	34% (**5**/**6** = 1/1.3)	0%
3	**DC**, (+)RVC/(–)RVC, 6 mA, 8 F/mol	38% (**5**/**6** = 1/1.4)	0%
4	**rAP(50 ms)**, RVC/RVC, 60 mA, 12 F/mol	0%	70%

Fig. 1. Challenges in classic Kolbe reaction and the breakthrough by using rapid alternating polarity (rAP). (**A**) Minimal functional group compatibility of the classic Kolbe reaction owing to its strongly oxidative nature. (**B**) Overcoming this limitation by applying the rAP waveform. (**C**) Trivial yet challenging substrates in Kolbe reaction. (**D**) Waveform-controlled chemoselectivity switch. *10 V–60 Hz ac was applied according to (*21*). †Isolated yield. ‡30 mA was applied instead of 60 mA because of high resistance of the solution. §10 V–10 Hz ac was applied to be consistent with the frequency and cell voltage to entry 5. Reaction time was 18 hours. ¶Electrode passivation occcurred in both MeOH and acetone as the solvent, causing termination of the reaction before achieving meaningful conversion.

The reaction proceeds by using technical-grade acetone as a solvent without any precaution to remove water and uses only a catalytic amount of inexpensive Me_4N•OH as a soluble base. On a small scale, we used an argon (Ar) or dinitrogen (N_2) balloon, but this precaution was not necessary on larger scales. It was unexpected that Pt electrodes were not required because Pt has for more than a century been considered as essential for radical-based Kolbe reactivity (*5*, *22*); C-based electrodes are known to promote carbocation reactivity instead, leading to Hofer-Moest products (*23*). However, the type of C-based electrode seems to be important; amorphous C electrodes such as reticulated vitreous carbon (RVC) was found to be optimal, and we observed no extensive degradation of electrodes. Glassy carbon, which is essentially the same material as RVC with less surface area, could also be used under similar conditions. By contrast, graphite and boron-doped diamond electrodes were found to be ineffective under several conditions examined (table S5). Me_4N•OH is available in bulk quantity and widely used in silicon-etching (*24*) but can also be replaced by the even less expensive base potassium hydroxide (KOH) (entry 6). An organic base [triethylamine (Et_3N)] and other solvents were found to deteriorate the reaction, probably because of competing oxidation (entries 7 to 9). The beneficial role of acetone is attributed to its ability to act as an electron and proton acceptor to balance oxidative decarboxylation, which is supported by the detection of isopropanol in the crude mixture (fig. S11). The optimal frequency of polarity switch for rAP-enabled reactivity is 50 ms (for example, entry 5), but a lower frequency is also effective (entry 10). Last, the use of a conventional sinusoidal ac waveform under otherwise identical conditions showed a similar effect to rAP, albeit with lower reaction efficiency that is consistent with previous reports (entry 11) (*19*, *20*, *25*).

Before exploring the scope of the rAP-Kolbe reaction, we also evaluated 4-phenylbutyric acid (**2**) (Fig. 1D) because of its documented tendency to undergo arene oxidation that leads to the benzylic functionalization in addition to productive dimerization to **7** (*3*). Under conventional Kolbe reaction conditions with Pt electrodes (entry 1), the reaction was discontinued because of electrode passivation, whereas arene oxidation products (**5** and **6**) were predominant with RVC electrodes regardless of the current density (entries 2 and 3). In stark contrast, the rAP-Kolbe reaction led to the desired dimer **7** in 70% isolated yield without detectable amount of arene oxidation (Entry 4).

Reaction generality and product utilities

With a general protocol established, we explored the scope of the chemoselective rAP-Kolbe reaction (Fig. 2A). In broad terms, this reaction is ideally suited toward the coupling of primary carboxylic acids because secondary and tertiary systems mainly lead to Hofer-Moest reactivity (supplementary materials). Performing the reaction with dc instead of rAP is detrimental (Fig. 1C). Unlike the classic Kolbe reaction, this reaction tolerates several synthetically useful functional groups such as esters (**8** to **10** and **16** to **18**), carbamates (**11** and **17** to **19**), free hydroxy (**12**), ketones (**13**), both electron-deficient (**15**) and electron-rich arenes (**16**), aryl halides (**15**), and terminal and internal olefins (**4** and **14**). Presumably because of the free-radical nature of the Kolbe reaction, the hindered neopentyl unit can also be readily coupled to afford diester **10** in 69% yield.

Many of the substrates shown in Fig. 2A are high-value building blocks that can now be accessed in much simpler or considerably

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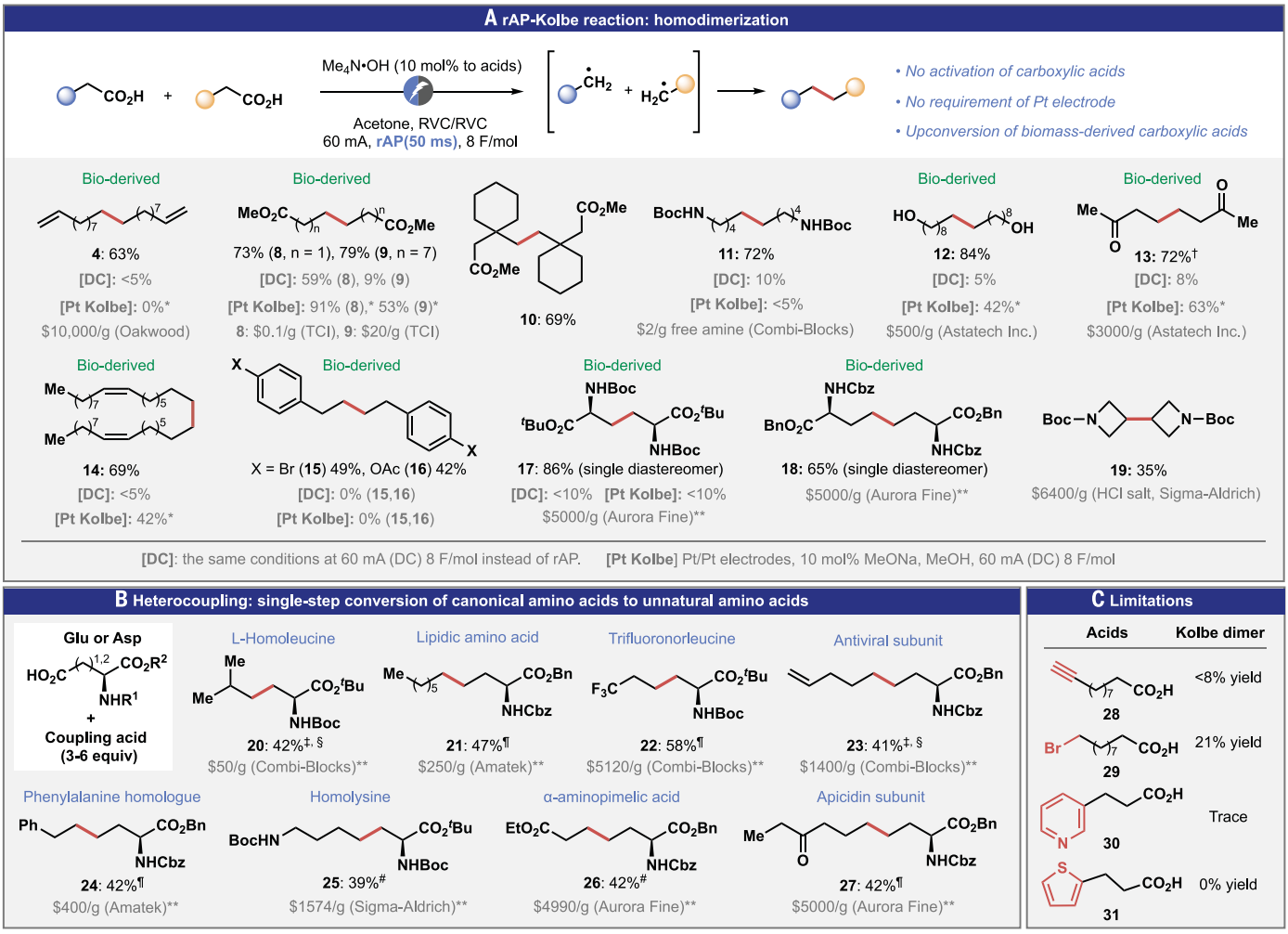


Fig. 2. Reaction generality of rAP-Kolbe reaction. (**A**) Scope of homodimerization. Reactions were performed on 1.5 mmol scale under the conditions described. (**B**) Scope of heterocoupling. Detailed reaction conditions for each substrate are provided in the supplementary materials. *Literature yield of Pt-based Kolbe reaction. Compound **4**, (*2*); compound **8**, (*28*); compound **9**, (*2*); compound **12**, (*2*); compound **13**, (*48*); compound **14**, (*2*). †NMR yield due to volatility of the product. ‡Acetone/toluene = 30/1 was used as solvent. §5 equiv of the coupling acid was used. ¶6 equiv of the coupling acid was used. #3 equiv of the coupling acid was used. **Price of free amino acid. (**C**) Redox-sensitive functionalities were not well tolerated.

different ways. These substrates serve as yet another demonstration of how labor-intensive $2e^-$-based approaches can be replaced with routes arising from radical retrosynthesis logic (*26*). For example, dimethyl adipate **8**, an important precursor for adipic acid, can be prepared from biomass-derived material by means of four-step functional group manipulations involving hydroformylation with precious metal catalysis (*27*). By contrast, the rAP-Kolbe reaction afforded **8** in a single step from monomethyl succinate (*28*), which could also be derived from bio-based succinic acid. The diamine parent of **11** is a valuable building block for polyamide 1010 and is currently prepared from sebacic acid after three functional group manipulation steps. By contrast, the rAP-Kolbe reaction opens a new avenue to access this compound from ε-caprolactam, a commodity chemical (~$3/kg), through efficient C–C bond formation. Diol **12** is an essential building block for a promising degradable surrogate of polyethylene, yet it is currently synthesized through hazardous lithium aluminum hydride (LAH) reduction of the corresponding diacid (*29*). By contrast, 10-hydroxydecanoic acid (derived from castor oil) can be converted to **12** in 84% isolated yield under rAP without any protection of the terminal alcohol. Diketone **13**, a potentially useful building block ($3000/g), can be easily derived from levulinic acid, one of the top-12 platform chemicals that can be mass produced from biorefineries, according to the US Department of Energy (*30*). Compounds **15** and **16**, now easily available by using rAP, represent a new derivatization method of hydrocinnamic acid derivatives, bio-based aromatic acids available from lignin (*31*). Amino acid dimer **17** (currently sold for ~$5000/g) is known to be an important intermediate for a potent allosteric inhibitor (*32*) and has been previously synthesized in seven steps as a racemate, whereas rAP dimerization of protected aspartate delivers it as a single diastereomer in 86% isolated yield. Similarly, dimeric amino acid **18**, a known carbon-isostere of disulfide linkages in peptides, can be easily accessed through glutamate dimerization. Past approaches to structures such as these are through a low-yielding Kolbe reaction (*4*) or olefin metathesis from unnatural amino acids (*33*, *34*). Last, bisazetidine **19** [$1600 for 250 mg; as hydrogen chloride (HCl) salt], a useful piperazine isostere in medicinal chemistry, is an example of a workable secondary coupling.

The reaction is also amenable to heterocoupling (Fig. 2B) to facilitate the rapid conversion of inexpensive natural amino acids (glutamic acid and aspartic acid) into valuable unnatural amino acids (of either absolute stereochemistry) without racemization (confirmation of no racemization is provided in figs. S7 and S8). Although 3 to 6 equiv of coupling acid is

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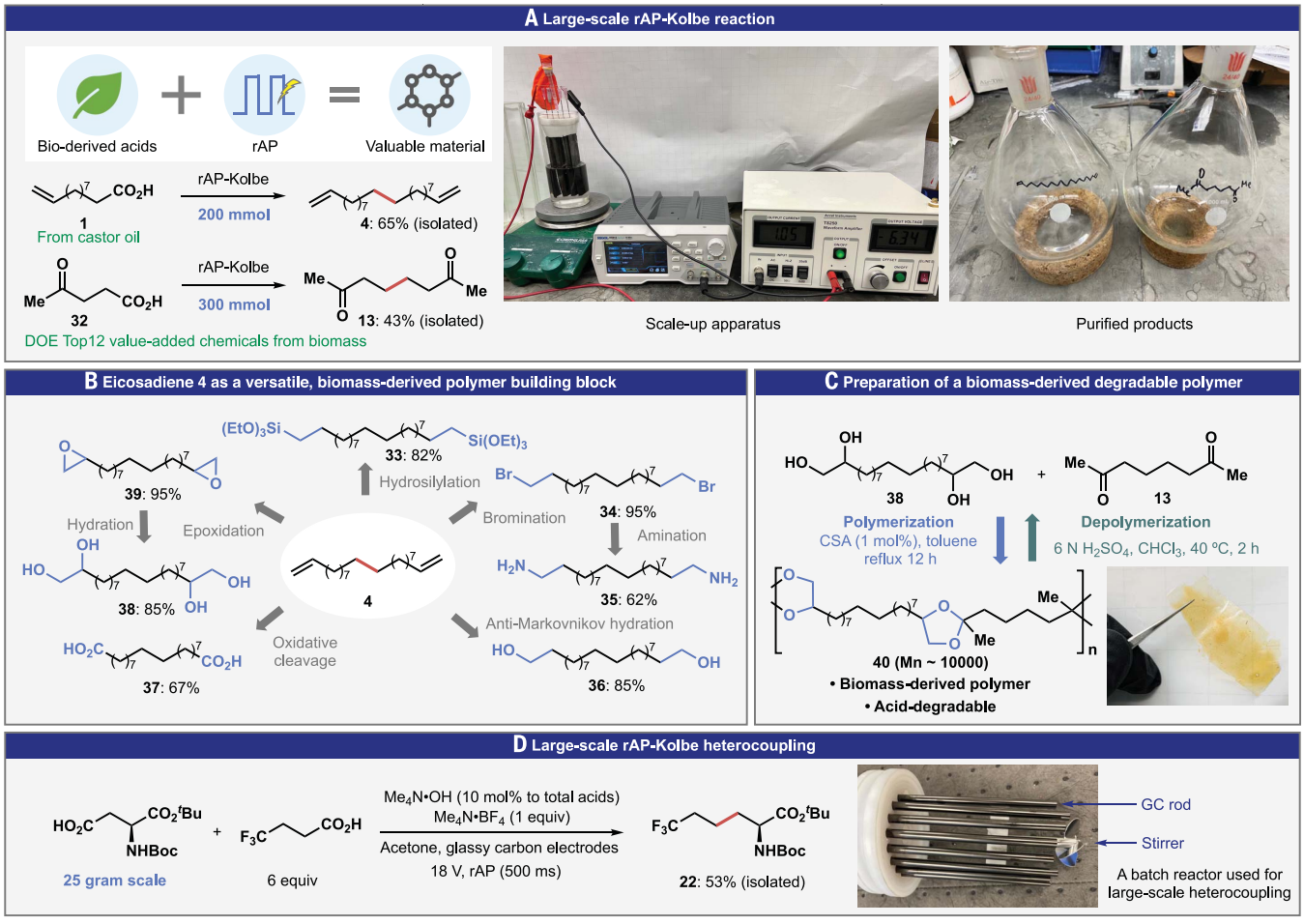


Fig. 3. Large-scale rAP-Kolbe reaction to produce biomass-derived polymers and fine chemicals. (**A**) Transforming biomass-derived carboxylic acids into useful polymer building blocks. Individual reaction conditions are provided in the supplementary materials. (**B**) Diene **4** as a biomass-derived versatile building block for various polymers. (**C**) Synthesis of an acid-degradable polymer from rAP-Kolbe reaction products. (**D**) Single-step access to a high-value unnatural amino acid on scale.

needed to achieve a synthetically useful yield (excess acid forms the homocoupling product), all the reagents as well as starting materials are inexpensive. Despite its simplicity and obvious utility, Kolbe heterocoupling of amino acids has been a formidable challenge for a conventional Kolbe reaction (*35*, *36*), and the rAP-based method exhibits the broadest reaction generality thus far. For example, lipophilic noncanonical side chains for **20** (~$50/g) and **21** (~$520/g) are readily accessible. Yet, a direct one-step access from a readily available starting material did not exist, and the most common ways of accessing such structures involve resolution, biocatalysis, asymmetric hydrogenation, and chiral auxiliary or chiral pool chemistry (a graphical compilation of prior approaches is available in the supplementary materials). Trifluoronorleucine (**22**; ~$5000/g) is a fluorinated analog of norleucine, and its only published enantioselective synthesis requires a stoichiometric amount of a chiral nickel complex (*37*). Olefin-containing amino acid **23** is a key building block to construct antiviral agents. Despite its importance, it is prohibitively expensive (~$1000/g) for practical use, and the previous syntheses require laborious preparation of a key intermediate before asymmetric hydrogenation (*38*) or a bespoke ligand for asymmetric coupling (*37*). **24** is an example of a phenyl alanine homolog that is useful for structure-activity relationship study (*39*, *40*). Homolysine **25** (~$1600/g) is a useful analog of lysine for fine-tuning peptide side chains (*41*), and α-aminopimelic acid **26** (~$5000/g) has documented bioactivity (*42*). Ketone-containing unnatural amino acid **27** (~$5000/g) is found in bioactive cyclic tetrapeptides (histone deacetylase inhibitors) (*43*). Direct access to **25** to **27** has been elusive thus far, leading to application of numerous indirect $2e^-$ strategies such as cross metathesis from an unnatural amino acid (*44*, *45*), chiral auxiliary-based α-amination of a carboxylic acid (*41*), or repurposing of chiral pool materials such as Garner's aldehyde (*46*) or glutamic acid (*47*). Although functional group compatibility was markedly improved by using rAP, redox-sensitive functionalities such as terminal alkynes (**28**), alkyl halides (**29**), as well as heterocycles (**30** and **31**) were not well tolerated (Fig. 2C).

Applications into biomass-derived polymer synthesis

As we described, one of the most sought-after applications of the Kolbe reaction involves upgrading biomass-derived carboxylic acids to high-value products, an aspiration yet to be realized (*15*). The practical conditions and broad reaction generality achieved with a rAP-Kolbe reaction can finally address this long-standing challenge, even on scale. As shown in Fig. 3A, we used biomass-derived acids **1** and **32** to produce 1,19-eicosadiene **4** and 2,7-octadione **13** (*48*, *49*) on a 200 and 300 mmol scale, respectively. No protection from air and moisture was necessary when performing large-scale reactions. Thus, **4** can now be considered a biomass-derived material that can potentially be accessible in bulk quantities. The terminal olefins can be readily converted into a variety of functional groups by using well-established

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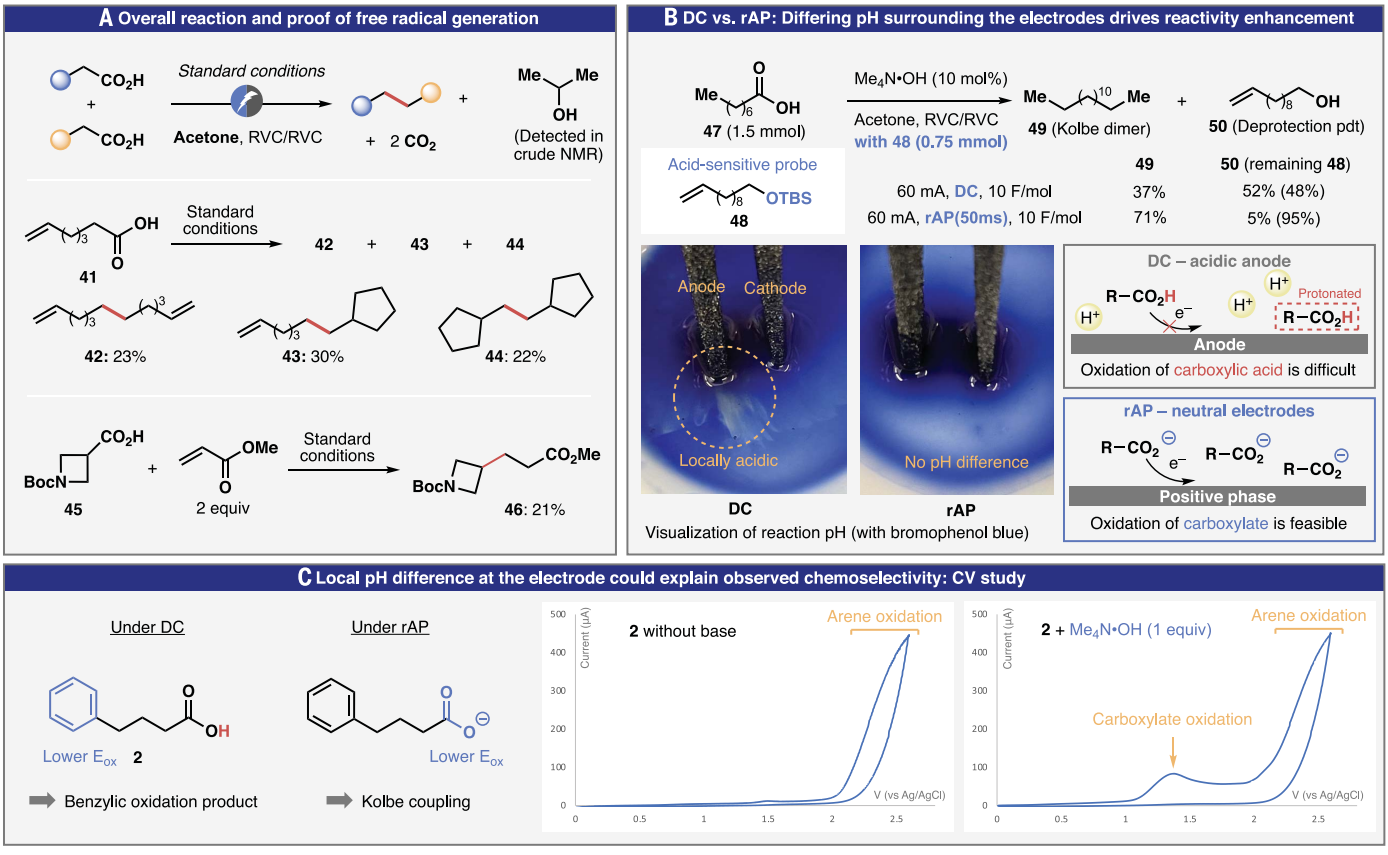


Fig. 4. Mechanistic studies on rAP-Kolbe reaction. (**A**) Overall reaction scheme and proof for free-radical generation. (**B**) Probing reaction acidity under dc and rAP as well as visualization of reaction pH. (**C**) Cyclic voltammograms of **2** with or without addition of a base.

reactions, providing additional building blocks **33** to **39**, with potential use for polymer additives or constructing degradable alternative of commodity polymers (Fig. 3B) (*50*). Degradable polymers are becoming increasingly more important to realize closed-loop recycling. Accessing such polymers from biomass-derived building blocks is attracting strong interest, as evidenced in the recent disclosure of biomass-derived polyesters and polycarbonates (*29*). As a proof of concept for this possibility, we synthesized a new polymer **40** from monomers **13** and **38** derived from a rAP-Kolbe reaction by connecting them through a ketal linkage under anhydrous conditions (catalytic camphorsulfonic acid, toluene)—an underused motif in degradable polymers (Fig. 3C) (*50*, *51*). Polymer **40** can be subsequently degraded under aqueous acidic conditions, an orthogonal degradation to polyesters or polycarbonates that require basic conditions. Furthermore, the highly practical conditions can be easily adapted to access to unnatural amino acid **22** on scale, demonstrating potential adoption of this reaction to the fine-chemical industry (Fig. 3D).

Mechanistic investigations

In Fig. 4, we outline a series of experiments that provide a qualitative mechanistic rationale for the rAP-Kolbe reaction. The net transformations are oxidative decarboxylation balanced by acetone reduction (Fig. 4A). As expected, oxidative decarboxylation invariably generated free radicals, as evidenced by cyclization of the 5-hexenyl radical derived from acid **41** as well as the Giese-type adduct **46** produced from the decarboxylation of **45** in the presence of methyl acrylate. Acetone reduction was confirmed with the detection of 0.5 equiv of isopropanol in crude proton nuclear magnetic resonance (^{1}H NMR) spectra, indicating that acetone is used as sacrificial electron- and proton-acceptor (fig. S11). How does the rAP-Kolbe reaction achieve substantially different levels of chemoselectivity relative to the classic Kolbe reaction? Unexpectedly, this fundamental reactivity difference may stem in large part from the local acidity at the electrode surface. In general, dc electrolysis creates local areas of enhanced acidity surrounding the anode at the microscopic level (regardless of stirring rate) through oxidation of solvent, water, or the substrate itself, known as electrogenerated acid (*52*). Counterintuitive to the reaction solution being partially neutralized, this phenomenon leads to protonation of carboxylate at the anode. Because the direct oxidation of a carboxylic acid is not favored, electrode passivation or oxidation of other functional groups outcompetes decarboxylative processes (that require a carboxylate). By contrast, rAP skirts this issue through fast polarity switching so that an anodic phase does not last long enough to create a persistent acidic electrode surface (because of rapid oscillation). As a result, oxidation of the deprotonated form (carboxylate) readily takes place in preference to other functional groups. To support this hypothesis, we added a compound sensitive to acidic deprotection (**48**) in both dc- and rAP-Kolbe reactions (Fig. 4B). With dc electrolysis, we generated the parent alcohol **50** in 52% yield with the formation of Kolbe dimer **49** in 37% yield, whereas the probe **48** was almost intact under rAP conditions, with a much higher yield of **49**. In addition to these experiments, we added a pH indicator (bromophenol blue) to the reaction solution to visualize the pH. As expected, a low pH was detected around the anode during dc electrolysis, whereas no visible pH difference was observed under rAP. Last, a cyclic voltammogram of **2** was recorded with or without base to understand the correlation between pH and the functional groups to be oxidized (Fig. 4C). An oxidation peak appeared above 2 V without addition of a base (Fig. 4C, left graph), which is in good agreement with the

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arene oxidation potential reported in the literature (*53*). Upon addition of 1 equiv of Me_4N•OH, a new peak appeared around 1.3 V (Fig. 4C, right graph), which is the typical oxidation potential of alkyl carboxylates (*53*). Taken together, these observations explain the reactivity switch illustrated in Fig. 1D: **2** is oxidized in its neutral form under dc electrolysis because of the locally acidic anode environment, resulting in arene oxidation. By contrast, **2** is oxidized as its deprotonated form under rAP, leading to selective decarboxylation without oxidizing the arene. The modulation of electrode pH is an overlooked phenomenon in synthetic organic electrochemistry that further illustrates the profound effect that altered waveforms can have on the course of a reaction.

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SUPPLEMENTARY MATERIALS

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Overcoming the limitations of Kolbe coupling with waveform-controlled electrosynthesis

Yuta Hioki, Matteo Costantini, Jeremy Griffin, Kaid C. Harper, Melania Prado Merini, Benedikt Nissl, Yu Kawamata, and Phil S. Baran

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Alternate approach to Kolbe coupling

Kolbe coupling is one of the very oldest reported reactions in organic chemistry. Essentially, an electrode oxidizes two carboxylic acids to release carbon dioxide and then couples the residual carbon fragments. Although direct and simple, the conventional reaction is incompatible with many common functionalities that can undergo competing oxidation. Hioki *et al*. now report that rapidly alternating the polarity of the electrochemical cell greatly expands the range of substituents compatible with the coupling (see the Perspective by Guo and Ye). This approach avoids pH lowering near the electrode that would otherwise slow down the decarboxylative oxidation at the expense of the side reactions. —JSY

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