Ni-Electrocatalytic C(sp^3)–C(sp^3) Doubly Decarboxylative Coupling

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ABSTRACT:

This work presents a modern spin on one of the oldest known Csp^3–Csp^3 bond forming reactions in synthetic chemistry: the Kolbe electrolysis. This reaction holds incredible promise for synthesis, yet its use has been near non-existent in mainstream organic synthesis. In contrast to the strongly oxidative electrolytic protocol employed traditionally since the 19th century, the present method utilizes in situ generated redox-active esters (RAEs) which are combined with a mildly reductive Ni-electrocatalytic cycle. It can be used to heterocouple 1º, 2º, and even certain 3º RAEs with a protocol reminiscent of amide bond formation in terms of simplicity. Due to its mild nature the reaction tolerates a range of functional groups, is scalable, and was strategically enlisted for the synthesis of 25 known compounds to reduce overall step-counts by 74%.

MAIN TEXT:

As perhaps the oldest preparative C–C bond formation reaction known, the Kolbe electrolysis has been extensively studied since its first appearance in literature in the mid 19th century.[1–10] In its classical manifestation, oxidative decarboxylation of an aliphatic carboxylic acid generates a

transient alkyl radical, which combines to form a Csp^3–Csp^3 bond. In complex molecule synthesis it is rarely employed but can be particularly useful for the homocoupling of alkyl acids such as in Corey's classic syntheses of pentacyclosqualene and onoceradienes[11]. Industrially, Kolbe electrolysis is employed in the lubricant sector and it has recently attracted attention as a promising approach for upgrading biomass-derived material.[12,13] Despite the long history of Kolbe electrolysis and the intuitive disconnection it enables, the reaction has yet to be established as a reliable Csp^3–Csp^3 bond formation method in mainstream organic synthesis.[14] This may be due to the harsh electrolysis conditions dictated by an incredibly high current density on an expensive Pt electrode (>250 mA/cm^2!).[3] Such a high overpotential limits its chemoselectivity, and thus it is mostly applicable to hydrocarbon synthesis wherein minimal functional groups are present.

Kolbe heterocoupling (Figure 1A) between two carboxylic acids – a potentially powerful Csp^3–Csp^3 coupling method – has also been studied, albeit to a lesser extent. Such heterocouplings were historically used as a key step to synthesize prostaglandin[15,16] and jasomonic acid analogs[17] as well as a modular route to access sugar derivatives.[18] More recently, the Lam group has expanded the oxidative heterocouplings of Schaefer to accomplish vicinal olefin functionalizations.[19] In general, Kolbe heterocoupling has been limited to structurally simple primary acids and certain secondary carboxylic acids that generate stabilized radicals. For more complex substrates with nitrogen-containing functionalities such as amides or amines, successful Kolbe heterocoupling is scarcely reported (See more detailed survey in SI for these limitations).

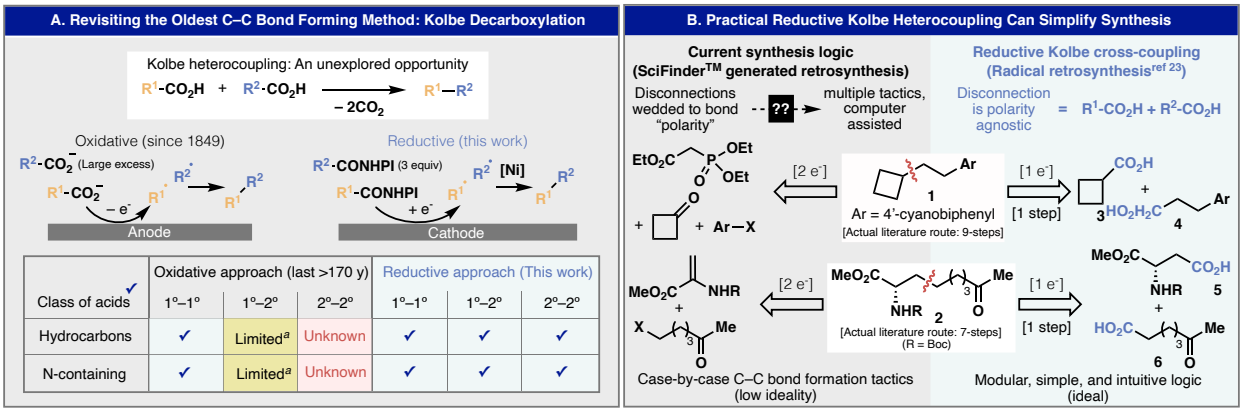

Figure 1. Kolbe heterocoupling simplifies synthesis. (A) Reductive approach is the key to improving generality of Kolbe heterocoupling. [a]Limited to acids that generate stabilized radicals. (B) 1 e$^-$ logic simplifies retrosynthetic analysis and increases ideality.

Whereas the oxidative approach to Kolbe couplings suffers from limited scope, we hypothesized that a reductive approach employing in-situ generated redox active esters (RAEs) in concert with a suitable transition metal catalyst might represent a milder and more practical alternative. The use of RAEs in Ni-catalyzed Negishi, Suzuki, and Kumada couplings is well documented[20–22] and served as the inspiration for this approach due to its robust and chemoselective nature. Most importantly, from the standpoint of synthetic design, such a reaction could dramatically simplify the routes to seemingly trivial molecules by democratizing access to intuitive $1e^-$ disconnections (radical retrosynthesis, Figure 1B).[23] For instance, cyclobutane **1** has been prepared through a laborious 9-step route wedded to polar bond disconnections.[24] Computation is often touted as a magic-bullet to identify promising routes yet SciFinder™-generated retrosynthesis provided similarly laborious or highly speculative options (See SI). In contrast, a reductive Kolbe cross-coupling could conceivably access **1** in a single step from commercial/readily available acid **3** and **4**. Similarly, unnatural amino acid **2** has been prepared through a 7-step route[25] with SciFinder™-generated retrosynthesis offering no discernable improvement whereas a reductive Kolbe might offer one-step access from acid **5** and **6**. The direct C–C bond formation between ubiquitous alkyl carboxylic acids has the potential to increase the ideality with which broad sections of chemical space are accessed.

In this Communication we report the invention of a reductive Kolbe variant that enables a massive step count reduction (74% step reduction relative to literature routes across 25 compounds) to access both simple and complex building blocks. Scalable heterocouplings of a wide range of 1° and 2° RAEs are now possible using an inexpensive Ni-catalyst, a commercial potentiostat, and a remarkably simple experimental setup on-par with the simplicity of classic amide-bond formation.

In its fully optimized form, the reductive Kolbe heterocoupling of carboxylic acids takes place through a convenient one pot procedure, which does not require rigorous degassing and anhydrous conditions (Table 1A). The general procedure proceeds as follows: to a mixture of acid components (the less expensive of which is used in 3 equiv.) in CH_2Cl_2 are added DIC and NHPI (1.1 equiv each relative to total acid quantity, 4.4 equiv total) along with catalytic amount of DMAP (10 mol% to total acid quantity, 0.4 equiv total). After stirring for 1 h, without any solvent removal, the solution is diluted with DMF and $NiCl_2$•dme along with **L4** are added (*ca*. 5 mol% each relative

to total acid quantity, 20 mol% total), followed by the addition of NaI (0.2 M). Electrolysis using a standard ElectraSyn2.0 potentiostat (Zn anode and Ni foam cathode) for about 2.5 h (0.1 mmol scale) followed by standard workup and purification delivers the coupled product.

To arrive at these optimized conditions, extensive experimentation was conducted as summarized graphically in Table 1B. Regarding the activating agent, PITU and CITU are less effective than DIC. Presumably, the protonated tertiary amine generated via acid activation by these reagents negatively affects the following reductive coupling step. In general, tridentate ligands often provides superior outcome to bidentate analogs in Ni-catalyzed C–C couplings (*vide infra*).[26–35] Empirical screening of electrolytes, electrodes, and solvents were also conducted. Finally, control experiments demonstrated that the Ni-catalyst was essential for the reaction and it could not be recapitulated using simple metal powder additives.

Ni-electrocatalytic Kolbe heterocoupling exhibits a broad scope and functional group tolerance across a range of substrate classes (Table 1C), including 1°-1°, 1°-2°, and even selected 1°-3° coupling. Thus, an aryl halide (**7**), esters (**8**, **10**, **13**, **21**- **23**), carbamates (**8**, **9**, **11**, **15**-**17**, **19**, **21**-**23**, **25**, **26**), amides (**20**, **27**), tertiary amines (**18**, **19**), ethers (**7**, **9**, **10**, **12**, **11**, **14**, **21**, **23**, **24**, **26**, **27**), a ketal (**13**), an alkyl halide (**18**), an alkyne (**16**), olefins (**15**, **17**, **20**, **28**), a free alcohol (**12**),

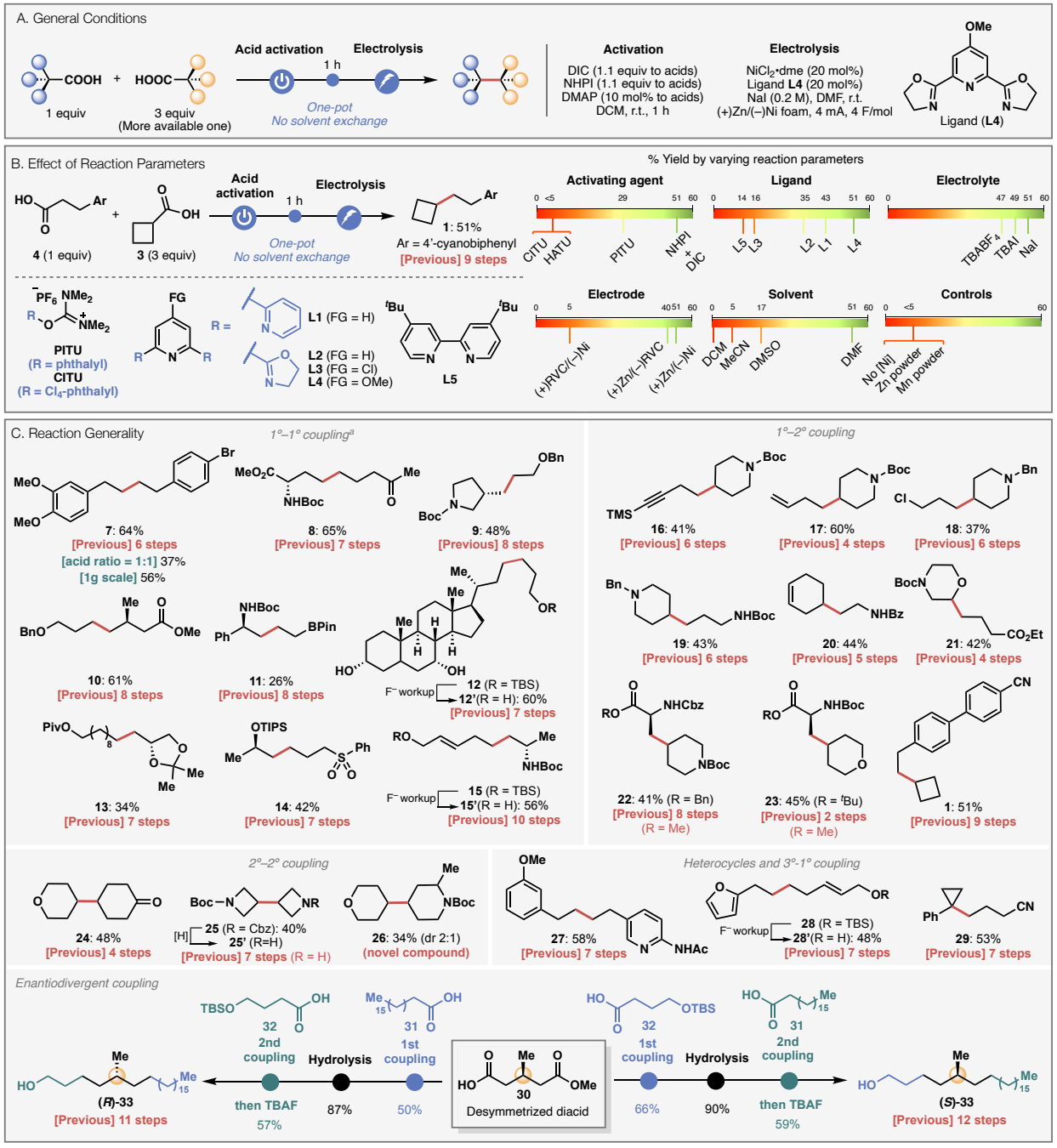

Table 1. Reaction Detail. (A) General reaction conditions. (B) Effect of reaction parameters. (C) Reaction generality. All reactions were performed under the general conditions. See SI for further reaction detail. [a] **L1** was used as a ligand instead of **L4**.

a sulfone (**14**), ketones (**8**, **24**), an alkyl boronic ester (**11**), and an azetidines (**25**) are all tolerated. It is unlikely that many of these functionalities would survive under strongly oxidizing conditions of conventional Kolbe electrolysis. As mentioned above, the direct nature of this new C–C bond forming method allows for a dramatic reduction in step-count to access chemical space. 25 of the 26 compounds shown in Table 1C have been prepared before. In every single case, the retrosynthesis of these known compounds was wedded to a polar bond analysis. As such, they all exhibit low ideality and are plagued with multiple functional group manipulations, protecting groups, and redox fluctuations.[36] It is instructive to discuss some of these examples in greater detail. The pathways to these 25 known compounds make extensive use of conventional 2e⁻ tactics, and can be classified into three categories based on how a carbon skeleton is assembled: (i) Olefination chemistry [i.e., Wittig-type, Knoevenagel reaction, and vinylation] followed by hydrogenation into a new C–C single bond (**7**, **9**, **12**, **13**, **15**, **16**, **18**, **21**, **23**, **28, 33**), (ii) C–C single bond forged directly through standard polar disconnections, [i.e. alkylation, Grignard, Friedel-Crafts, Suzuki or Glaser coupling] (**1**, **8**, **10**, **11**, **14**, **16**, **20**, **24**, **25**, **27, 28, 29, 33**), or (iii) repurposing existing structures with mostly functional group manipulations, where no C–C bond was formed (**19**, **22**). For instance, cyclobutane **1** was previously prepared using 2e⁻ logic commencing from cyclobutane carboxylic acid requiring lengthy one-carbon homologation, followed by a Friedel-Crafts acylation/Wolff-Kishner sequence (9 steps total, 11% overall yield). In contrast, the 1e⁻ disconnection is identified by simply selecting the most readily available building blocks and coupling them using reductive Kolbe heterocoupling, thereby deleting nearly all extraneous concession steps. Such a tactic is particularly valuable for the formation of seemingly distal stereocenters, as a myriad of chiral carboxylic acid building blocks can be easily purchased. In this way, expensive catalytic asymmetric methods (**23**) and chiral auxiliaries which generally require at least three more steps (installation, diastereoselective reaction and removal) can be avoided (**8**, **10**, **14**, **22**). A particularly striking example of this concept involves the enantiodivergent synthesis of insect pheromones (*R*)-and (*S*)-**33**, previously prepared in 11-12 steps (7-8% overall yield) using a category (i) and (ii) approaches for assembling the main carbon chain (*vide supra*). In contrast, commercially available desymmetrized acid **30** can be subjected to tandem reductive Kolbe heterocouplings to access the same materials in 3 steps (*ca*. 30% overall yield). Either enantiomer is accessed at will simply by choosing the order of coupling. A complete

comparison of conventional routes to the 25 known molecules in Table 1 versus simple pathways employing reductive Kolbe heterocoupling is graphically illustrated in the SI.

It is equally important to mention current limitations of this method (see SI) which include difficulty in coupling alkyl carboxylic acids adjacent to aromatic rings, phosphonates, and esters. The scalability of this powerful C–C bond forming reaction was demonstrated using compound **7**, which proceeded in 56% yield on a gram scale. In certain cases, if both carboxylic acid components are valuable, a 1:1 ratio can be employed to deliver a coupling product with lower yet synthetically useful yield as demonstrated with compound **7**.

To confirm the radical nature of this reaction, a radical clock experiment was conducted (Figure 2A). Submission of RAEs **34** and **35** to standard conditions led to a mixture of heterocoupled products **36** and **37** resulting from immediate cyclopropane opening and coupling with 5-hexenyl radical either in cyclized or open form, respectively. This is consistent with the common reactivity that RAEs generate alkyl radicals via single electron transfer (SET) followed by rapid fragmentation. Since the coupling reaction barely proceeded when Ni catalyst was omitted (Table 1B, control experiments), the role of the Ni catalyst is presumably either mediating the SET[20,37] or effectively capturing free radicals generated by direct cathodic reduction to facilitate productive reaction pathway. Furthermore, the ratio of **36** and **37** is dependent on Ni catalyst concentration, indicating that cage-escaped radical might be involved for Ni–C bond formation. In addition, such observation is diagnostic for involvement of multiple Ni species in the mechanism, and could exclude possibility of double oxidative addition on a single Ni species (or cage-rebound mechanism).[38–40] Although detailed mechanistic understanding is outside the scope of this initial report, future in-depth kinetic studies may provide further support for this hypothesis.

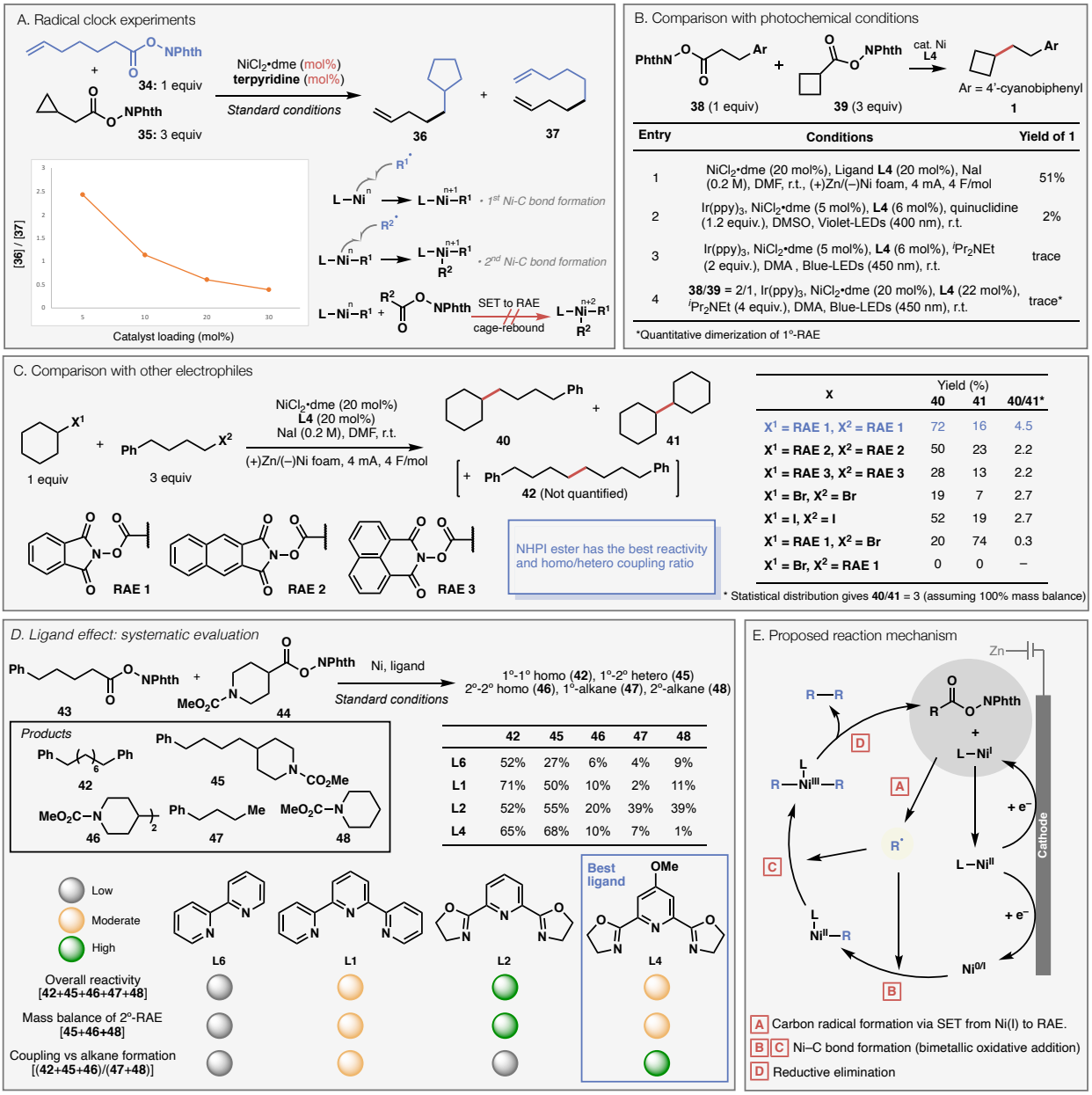

Figure 2. Control studies and ligand analysis. (A) Radical clock experiments to probe the intermediacy of radical species. (B) Comparison with photochemical reactions. (C) Effect of redox active motifs on reactivity and product distribution. (D) Impact of ligand structure on reactivity and coupling efficiency. (E) Overview of proposed reaction mechanism.

In principle, this reductive Kolbe heterocoupling should be amenable by other means of single-electron reduction. Thus, photoinduced electron transfer was interrogated for the same reactivity (Figure 2B, entries 2-4). Based on the results of three different experiments, this process appears to be exclusively workable under electrochemical conditions, as no observable product or only traces were observed. In one case, exclusive homodimerization of the 1° RAE **38** was observed

when $^{i}Pr_2NEt$ was employed as sacrificial reductant. These results could indicate that the successful coupling requires fine balance between radical generation from two RAEs and C–C bond formation processes catalyzed by Ni species.

The simultaneous radical generation from two RAEs under electrochemical conditions was further studied by changing a redox-active motif in a starting material. **RAE 2** and **RAE 3** were synthesized based on the expectation that extended π-system could have an influence on SET and following radical generation. As illustrated in Figure 2C, amongst several RAE/halide combinations explored, NHPI-based RAE's delivered the best yields of heterocoupled products (closely matching the statistically predicted outcome which would be 3:1, assuming 100% mass balance). Alkyl halide precursors are not as versatile as NHPI-based RAEs due to lower reactivity for bromides and slightly higher homocoupling tendency for iodides.

Finally, the role of ligand was further explored (Figure 2D, see SI for the complete survey). The product distribution in the coupling of **43** and **44** was analyzed in detail. It was found that ligand structure has an impact on i) conversion of RAEs, ii) radical capture efficiency and iii) side-product formation. By switching from bidentate ligand **L6** to tridentate ligand **L1**, the reactivity of the Ni complex notably increased to realize efficient radical generation from RAEs. A change of ligand skeleton to pybox **L2** further increased the reactivity; more notably, the efficiency of capturing 2º-carbon radical was enhanced based on the analysis of the mass balance of **44**. Yet, **L2** furnished considerable amount of alkane side-product **48**, which did not contribute to the productive coupling reaction. Subtle electronic modulation of **L2** to **L4** led to the suppression of the alkane formation, delivering the heterocoupling product **45** efficiently. These qualitative trends found in this work warrants further rigorous and systematic studies to elucidate the role of a ligand, possibly contributing deeper mechanistic understanding.

With these results taken collectively, the overall reaction mechanism is depicted in Figure 2E. Electrochemical reduction of Ni(II) generates low valent Ni species active for reducing RAEs, efficiently supplying alkyl radicals (step A). Direct cathodic reduction of RAEs is also a possible source of alkyl radicals. Then, the alkyl radicals combine with Ni species consecutively (step B

and C). During these two Ni–C bond formation, adjustment of Ni oxidation state via chemical (disproportionation or comproportionation) or electrochemical pathway might be involved. Finally, reductive elimination forges a new C–C bond, closing the catalytic cycle.

New methods for the construction of C–C linkages in a modular way from ubiquitous building blocks can immediately simplify the logic of chemical synthesis. Polar bond analysis is routinely taught at the undergraduate level to help guide chemists to make strategic disconnections. Radical retrosynthesis[23] effectively divorces polarity from the analysis and prioritizes simplicity and building block availability. The reductive Kolbe heterodimerization reported herein has been applied to 25 arbitrarily chosen, previously synthesized substrates containing a myriad of functional groups. The simple one-step procedure and wide LEGO-like availability of starting materials makes this protocol promising despite the near-statistical homo/heterocoupling ratio. Finally, the dramatic reduction in documented step-count and labor relative to the prior art bodes well for its immediate adoption for a range of organic molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, and the detail of DFT calculation.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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