Electroreductive Olefin-Ketone Coupling

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ABSTRACT: A user-friendly approach to sidestep the venerable Grignard addition to unactivated ketones to access tertiary alcohols by reversing the polarity of the disconnection. In this work a ketone instead acts as a nucleophile when adding to simple unactivated olefins to accomplish the same overall transformation. The scope of this coupling is broad as enabled using an electrochemical approach and the reaction is scalable, chemoselective, and requires no precaution to exclude air or water. Multiple applications demonstrate the simplifying nature of the reaction on multi-step synthesis and mechanistic studies point to an intuitive mechanism reminiscent of other chemical reductants such as SmI_2 (which cannot accomplish the same reaction).

Tertiary alcohols are an abundant functional group with versatile reactivity that are found in natural products,[1] pharmaceuticals,[2] and a multitude of useful materials.[3] Traditionally, perhaps overwhelmingly, the ketone has served as a loyal progenitor of this species (Figure 1A) for good reasons. Every undergraduate organic textbook prescribes a direct nucleophilic addition of a strong nucleophile, such as RMgX or RLi, to these electrophilic species.[4] Although these incredibly robust reactions have been employed countless times, they can indirectly contribute to synthetic inefficiencies as their low chemoselectivity often necessitates the use of protecting groups.[5] This dilemma is nicely illustrated (Figure 1B) by examining the patented route to steroid derivative **2**.[6] Although a Grignard reaction with commercially available ketone **1** is an obvious disconnection, its use introduces several protecting group additions, removals and functional group manipulations throughout the course of a seven-step sequence (only one of which forges a C–C bond).

Within the specific realm of intermolecular alkyl nucleophile additions to unactivated ketones, Grignard and related organometallic additions are fundamentally limited by their 2-electron mechanisms, which render these nucleophiles both strongly nucleophilic and often highly basic.[4,5,7] Efforts to tone down their reactivity have been explored, with the most successful stemming from nucleophiles bearing activated positions (i.e. allylic, benzylic, propargylic, α-carbonyl, Figure 1C).[8,9] Studies employing Zr-,[10] Ti-,[11] Ru-,[12] and Os-[13] based systems, as well as HAT chemistry,[14] have also pointed to the use of olefins as precursors to species capable of adding to carbonyl groups although intermolecular additions into unactivated ketones are without

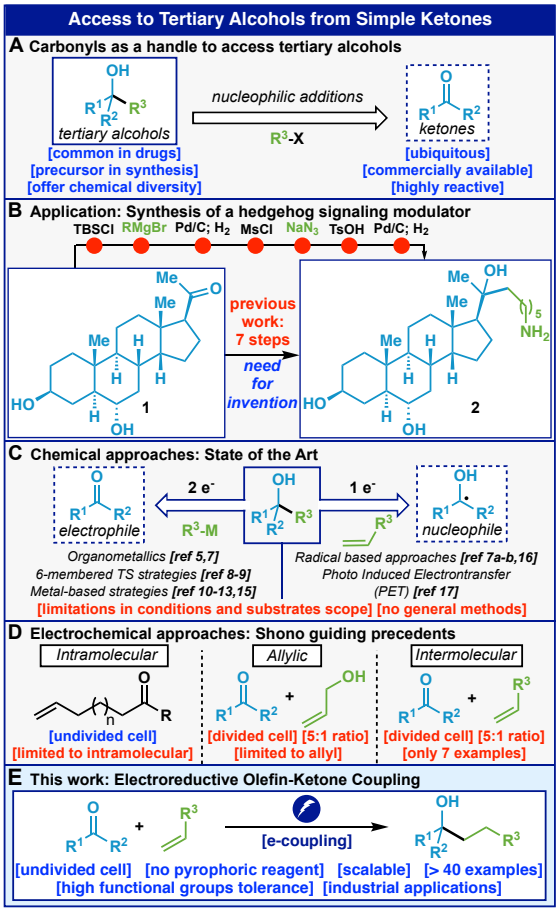


FIGURE 1. Tertiary alcohols from simple ketones remain a challenge for modern synthesis (A). Synthesis of **2** is em-

blematic of the problems with Grignard (B). Recent approaches so far do not address the problem (C). Electrochemical precedent on activated olefins (D) and a summary of this work (E).

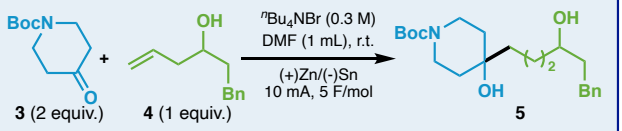
precedent.[15] A less intuitive approach involves an umpolung disconnection, which renders the ketone the nucleophilic group through a reductive 1-electron approach. Thus far, such approaches have relied primarily on Sm(II),[7a-b] Ti(III),[16] or photoinduced electron transfer[17] to couple activated olefins and styrenes to ketones. A general intermolecular reductive coupling of unactivated ketones and olefins is so far absent from the literature. The closest precedent for the desired transformation was disclosed by Shono and co-workers (Figure 1D).[18] These reports focus predominantly on *intra*molecular couplings,[18a-b] with only a few *inter*molecular examples[18c-d] presented. To the best of our knowledge, this chemistry has not been applied in the literature, despite being available for decades, presumably due to the challenges of using a divided cell setup under an argon atmosphere and the need for *at least* a five-fold excess of the ketone. In this Communication, a new protocol for electrochemically driven reductive couplings of unactivated ketones and olefins is presented. This method uses a simple undivided cell tolerating exogenous air and moisture, exhibits a broad scope, and can be easily scaled (Figure 1E).

Explorations began by studying Shono's original conditions[18c] on a medicinally-relevant model substrate pair: homoallylic alcohol **4** and piperidone **3** (Table 1A). In principle, the use of Grignard chemistry to carry out this assembly would necessitate the use of a protecting group on **4** and perhaps other precautions due to the enolizability of **3**, hence, more gentle methodologies were sought. Revisiting the electrochemical method developed by Shono for less *ornate* substrates,[18c] only resulted in low yields (Table 1A, entry 1). This method was pursued with some rigor (see SI for a full listing); however, the yield could not be improved beyond 17%. Chemical reductants such as SmI_2 and LiDBB were examined next, and while these methods have been shown to have success in similar *intramolecular* scenarios, they were found to be unsatisfactory for this purpose (entries 2-5, Table 1a). Developing this chemistry following the guiding principles from our own forays[19,20] into electrochemistry, specifically deeply reductive electrochemistry,[20] allowed us to hone in on the sacrificial anode, electrolyte, current density and concentration needed to facilitate a high yielding olefin-ketone coupling (Table 1A, see the SI for a full listing). As graphically illustrated in Table 1B, these three variables were crucial to the success of this transformation which, after optimization, let to 95% isolated yield of adduct **5** (Table 1A, entry 6). The use of an inexpensive sacrificial anode (Zn) was ideal and, in contrast to prior work, a lower current ensured broad functional group tolerance (10 mA vs. 200 mA). Notably, unlike prior precedent, only 2 equivalents of the ketone are required, inexpensive electrodes are employed, and an operationally simple undivided cell is used. No precautions are taken to exclude air or moisture and in fact the reaction can be run open to the air (cap removed). Finally, the linear *versus* branched selectivity is remarkable (>15:1 in most of the cases).

TABLE 1. Optimization of the reductive ketone olefin coupling. Comparison to known chemical methods (A) and a graphical optimization overview of the newly developed electrochemical protocol (B).

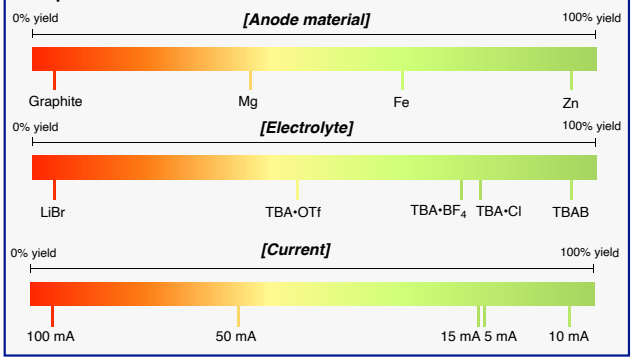
Optimization of the Electroreductive Olefin-Ketone Coupling

A Comparison with existing procedures



entry	deviation from above conditions	yield (%)[a]
1	**3**/**4** (5/1), (+)C/(-)Pt, divided cell, 0.2 A, 2.5 F/mol (Shono)	<10
2	SmI_2	<10
3	SmI_2 + HMPA	<10
4	SmI_2 + MeOH	<10
5	LiDBB	<5
6	None	95%

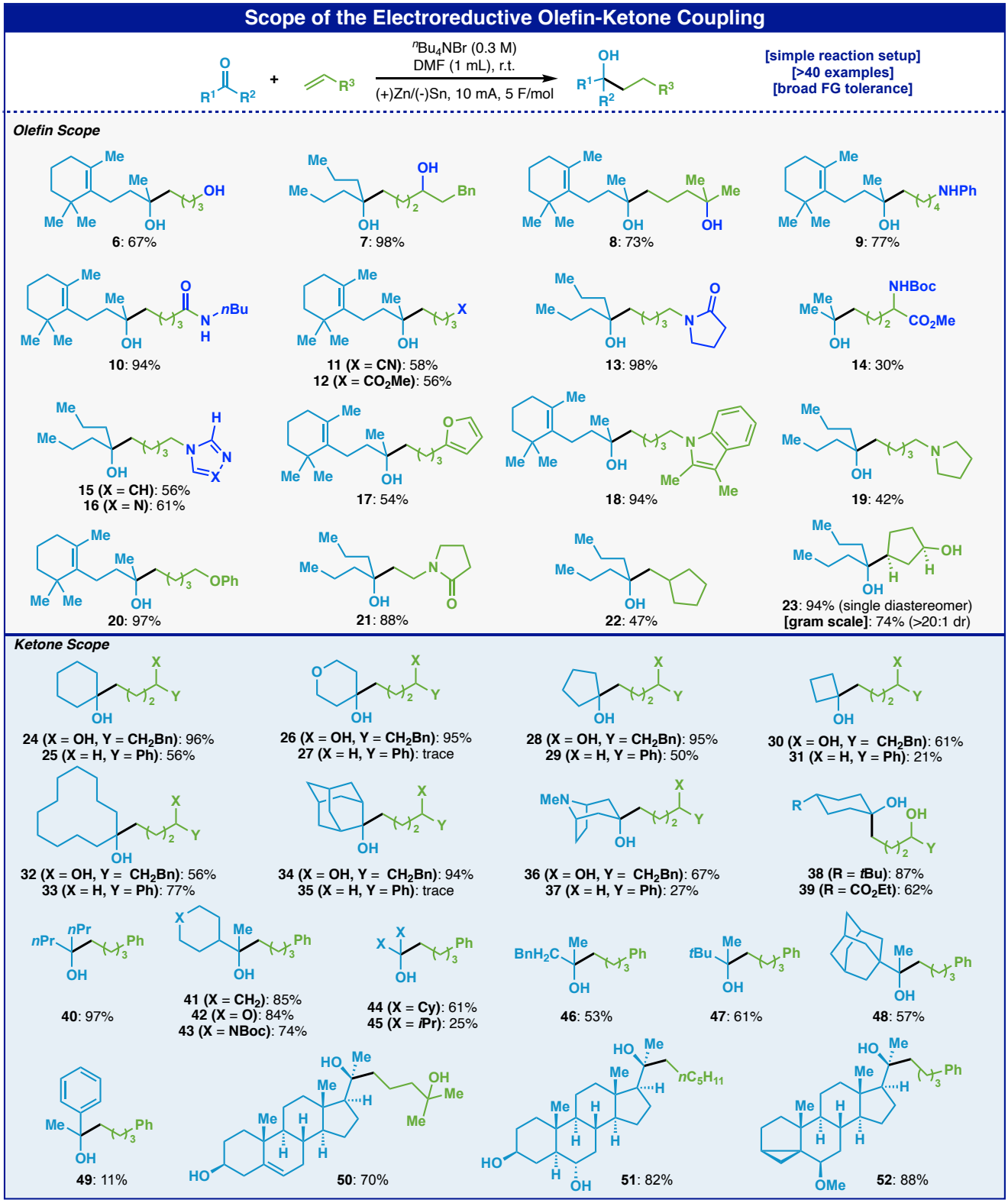
B Importance of Electrochemical Parameters



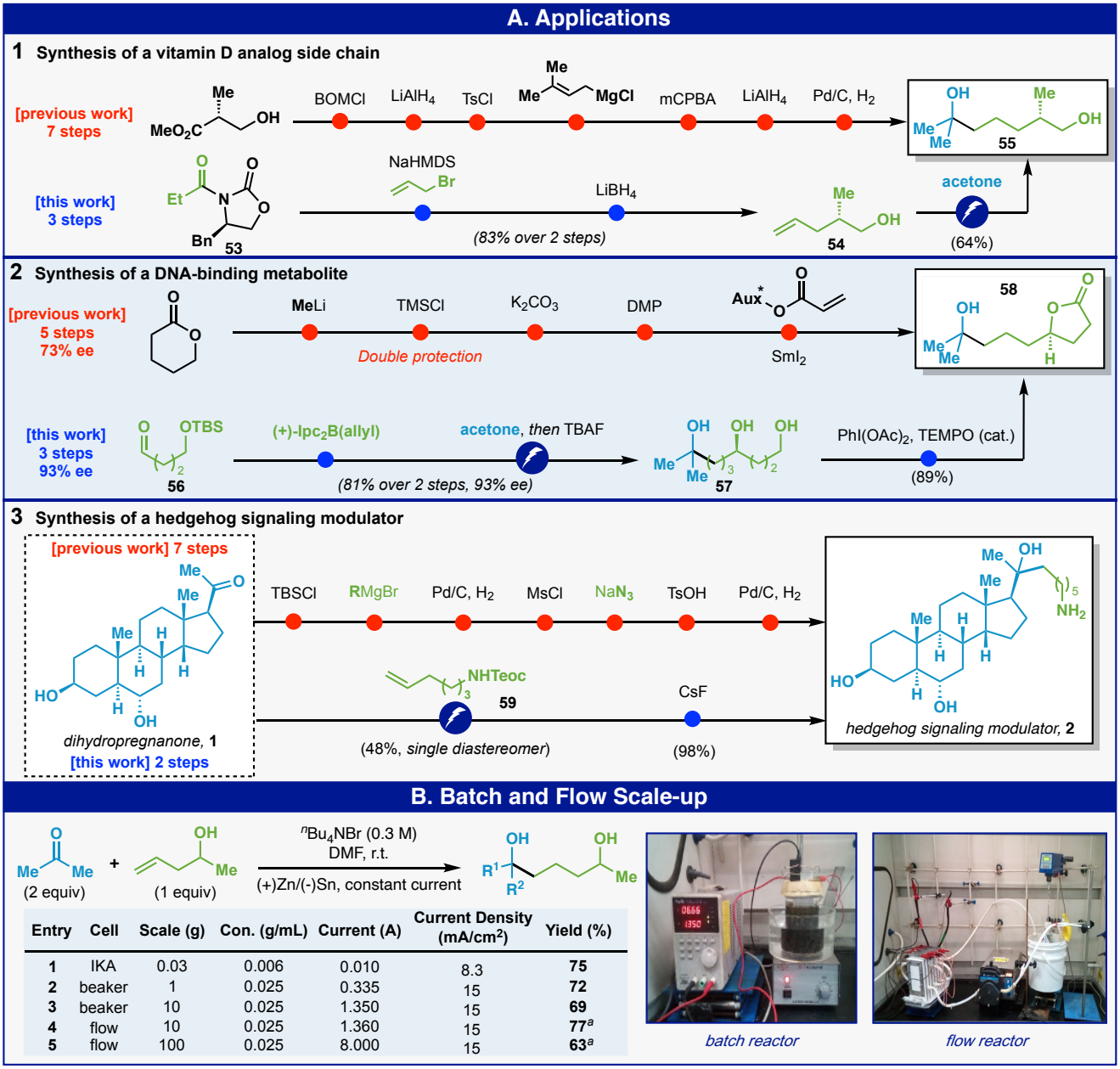
With these results in hand, the scope of the ketone-olefin coupling was investigated (Table 2). Several functionalities on the olefin were tolerated; free alcohols (1°, 2°, and 3°; **6** to **8**), aniline (**9**), amides (**10, 13, 21**), nitrile (**11**), ester (**12**), protected amino acid (**14**), and heterocycles (**15**-**19**) (moderate to high yields). Most of these functional groups would be challenging to employ using canonical 2e$^-$ tactics such as Grignard. The reaction tolerated mono-substituted olefins but performed less successfully with poly-substituted olefins with compound **22** and **23** being the only ones affording good yields. A plausible reason for this lack of reactivity with more substituted olefins could be due to a slower rate of addition (for steric reasons) compared to the lifetime of the ketyl radical.[21] In the case of cyclopentene-3-ol, an interesting finding was that the reaction took place in high yield with perfect *syn* diastereoselectivity. The analogous TBS-protected olefin did not react, nor did cyclopentene itself. The directing effect of homo-allylic alcohols in this chemistry is notable and perhaps relevant to the mechanism of the reaction (*vide infra*).

In a similar fashion, ketones bearing several different substituents were tolerated (moderate to high yields); ethers (**26**), protected amines (**36**-**37**), esters (**39**), carbamates (**43**), alcohols (**50**-**51**), cyclopropanes (**52**). When 4-substituted cyclohexanones were used, single diastereomers were isolated with the selectivity reminiscent of SmI_2 promoted reactions (*anti*, **38**-**39**).[22] Even cyclic ketones of varying ring sizes (**24**-**39**) worked well, which are often challenging for other methods; reduction products

TABLE 2. Scope of the electroreductive olefin-ketone coupling.



are often observed when sterically hindered ketones react with Grignards. For acyclic ketones, the sterics of the substituents showed a minor impact on the reaction yields (**40**-**48**), although only 25% yield of the desired product was isolated when very hindered diisopropylketone (**45**) was used. Notably, unprotected steroidal substrates **50**-**52** delivered a single diastereomeric product in high yield (see SI for structure confirmation).



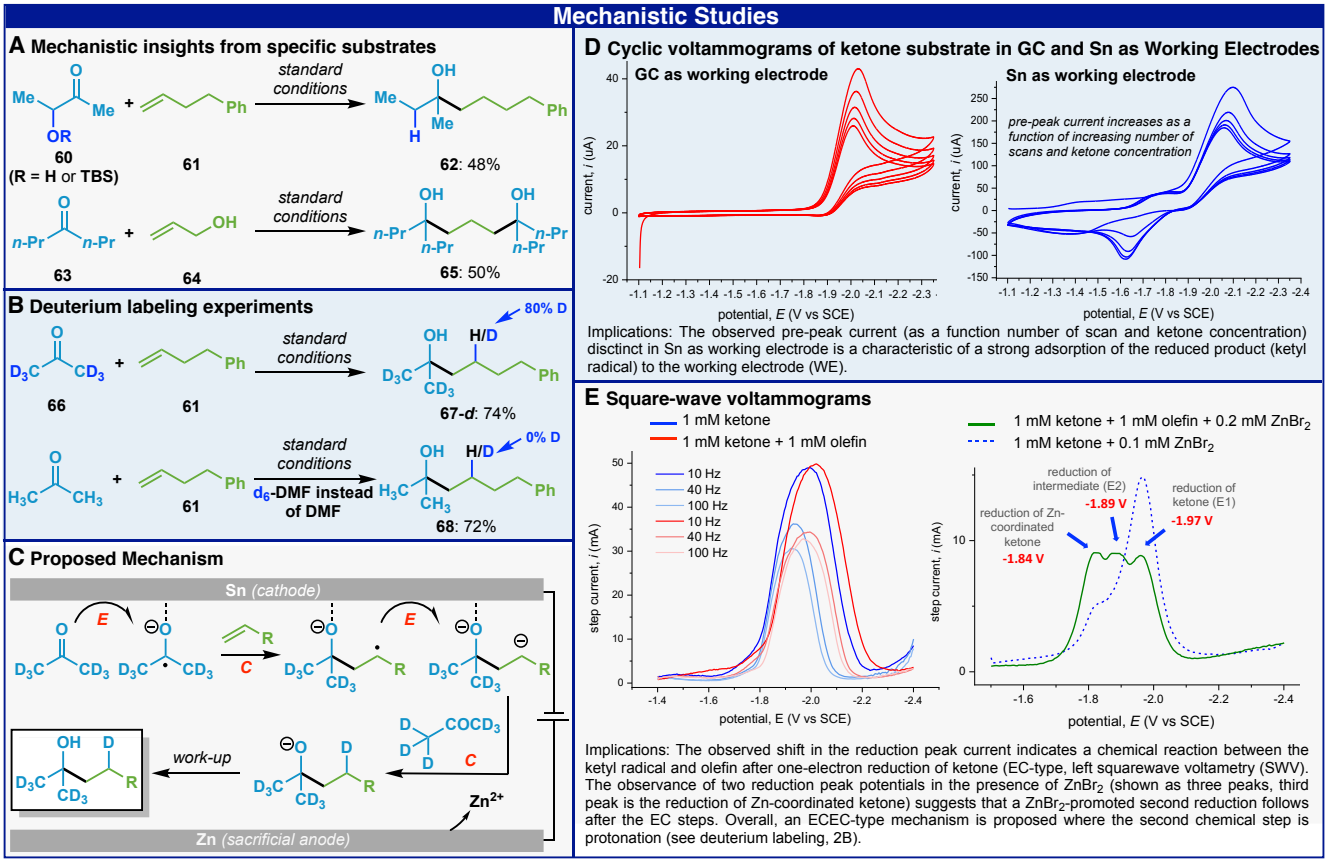
Entry	Cell	Scale (g)	Con. (g/mL)	Current (A)	Current Density (mA/cm^2)	Yield (%)
1	IKA	0.03	0.006	0.010	8.3	75
2	beaker	1	0.025	0.335	15	72
3	beaker	10	0.025	1.350	15	69
4	flow	10	0.025	1.360	15	77[a]
5	flow	100	0.025	8.000	15	63[a]

SCHEME 1. (A) Electrochemical ketone-olefin coupling facilitates rapid access to medicinally relevant structures such as a vitamin D sidechain (1), a DNA-binding metabolite (2), and a hedgehog signaling modulator (3). (B) Batch and flow scale-up. [a]Isolated yield

This reductive coupling could also be applied to simplify real-world challenges in medicinal chemistry (Scheme 1A). Thus, the synthesis of a simple vitamin D analog sidechain **55** was reported through a seven-step route wherein only one of those steps formed a C–C bond (Scheme 1A-1).[23] In contrast, commercially available oxazolidinone **53** could be allylated and reduced to yield (*S*)-2 methyl-4-penten-1-ol **54**. Coupling of **54** with acetone under the developed electrochemical conditions then smoothly furnished sidechain **55**. Of the three steps required to access **55**, two forged key C–C bonds. Next, the synthesis of DNA-binding metabolite **58** required a five-step sequence with two protecting groups and air-sensitive SmI_2 to forge a key C–C bond (73% ee, Scheme 1A-2).[24] Using the electrochemical strategy outlined above,

commercially available aldehyde **56** could be converted to the same product in only 3 steps via simple Brown allylation, followed by electrochemical addition of acetone/TBAF work-up and a final oxidative lactonization (72% yield, 93% ee). Finally, the steroidal example[6] mentioned in Figure 1 could be addressed in a similar way from the same starting material (Scheme 1A-3). Thus, electrochemical addition of **1** to Teoc-protected amine **59** delivered a single diastereomeric tertiary alcohol that, after CsF-induced deprotection delivered **2** in only 2 steps. Clearly, the success of the above applications benefits from the chemoselective (FG tolerant) nature of the electrochemical ketone-olefin coupling. The

reaction can be conducted on 100 gram-scale (>1 mol) using a flow system



SCHEME 2. Mechanistic insights from byproducts (A), deuterium labeling (B), proposed reaction mechanism (C), and voltammetry studies (D & E). See SI for details.

affording a comparable yield to the batch reaction(Scheme 1B, see SI for details).

The mechanism of this useful reaction (Scheme 2) was next interrogated through the observation of certain side-products (Scheme 2A), deuterium labeling (Scheme 2B), kinetics, and voltammetric studies (Scheme 2D & 2E). A notable limitation of this chemistry was that ketones bearing alpha-substituents (such as **60**) were not tolerated and elimination of the alpha-substituent was observed (**62**), suggestive of a ketyl radical intermediate. Using allyl alcohol (**64**), the bis addition adduct **65** was observed, perhaps pointing to a carbanion intermediate wherein $ZnBr_2$ generated from anodic oxidation could assist in the departure of the primary alcohol and regeneration of another olefin. Deuterium labeling using acetone-d_6 led to 80% incorporation at the highlighted position (Scheme 2B) further supporting a carbanion intermediate. When regular acetone was used in the same experiment but with deuterated DMF, no deuterated product was observed. Kinetic studies revealed zero-order dependence on all components except current indicating that reduction is purely electrochemical.

Finally, a series of voltammetric studies were performed (Scheme 2D & 2E) to understand how traditionally nucleophilic ketyl radical can serve as competent coupling partners with unactivated olefins, as well as to provide evidence for the overall electrochemical mechanistic sequence as proposed in Scheme 2C. We hypothesized that

the change in its electronic property and reactivity can be facilitated by a strong adsorption of the ketyl radical to the Sn electrode. Cyclic voltammetry studies were performed using Sn and glassy carbon (GC) as working electrodes with acetophenone[25] as the source of ketyl radical. Pre-peaks on the CV were observed using Sn as the working electrode but not observed using GC as the working electrode. These pre-peaks are distinct characteristics of an electron transfer where the product (ketyl radical) is strongly adsorbed into the working electrode.[26] Furthermore, the current response observed in the pre-peak in Sn was found to be dependent on the concentration of ketone (see SI).[27] This result also rationalizes the effectiveness of using Sn-cathode over other electrode materials (see SI). Square-wave voltammetry (SWV) studies were performed and the results are summarized in Scheme 2E. The addition of alkene **61** to acetophenone showed an anodic shift in the cathodic peak potential denoting a chemical reaction with the ketyl radical after one-electron reduction. However, even at high frequencies (100 Hz), the expected second reduction peak was not observed. We hypothesized that one crucial role of the sacrificial Zn-anode is to provide Zn^{2+} as a thermodynamic sink for

the second electron reduction. SWV analysis in the presence of catalytic amounts of $ZnBr_2$ showed three distinct reduction peaks where the third peak can be the reduction of the $ZnBr_2$-coordinated ketone (see SI). Taken together, these results suggest an ECEC-type electrochemical mechanism where the ketyl radical formation (E) takes place at the Sn-cathode with strong adsorption characteristic followed by radical addition (C) into the olefin. A second one-electron reduction (second E) of the radical anion to the dianion followed by protonation (second C) and then workup delivers the final product. The enhanced reactivity of homoallylic alcohols may be due to improved binding of the olefin substrate to the cathode surface.

In summary, a chemoselective, scalable method to combine unactivated olefins and ketones has been developed that subverts the issues encountered using Grignard reagents in conventional retrosynthetic analysis. The scope of this reaction is broad and it is operationally simple to perform. A number of applications demonstrate that the utility extends beyond that of a simple tactical change as when strategically employed, it can dramatically reduce overall step count. Mechanistic studies point to an intuitive electrochemically driven reductive pathway that initiates upon the formation of a ketyl radical, addition to the olefin, and further reduction to a stabilized carbanion prior to workup. This work is thus another example of how strongly reducing chemistry can be uniquely facilitated and enabled in complex settings under electrochemical control when classical chemical reagents fail.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information contains all experimental procedures, analysis, and compound characterization data.

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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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