Electrochemically Driven Desaturation of Carbonyl Compounds

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ABSTRACT: Electrochemical techniques have long been heralded for their innate sustainability as efficient methods for achieving redox reactions. Carbonyl desaturation, as a fundamental organic oxidation, is an oft-employed transformation to unlock adjacent reactivity. To date, the most reliable methods for achieving it have relied on transition metals (Pd/Cu) or stoichiometric reagents based on I, Br, Se, or S. Herein we report an operationally simple pathway to such structures from enol silanes and phosphates using electrons as the primary reagent. This electrochemically driven desaturation exhibits a broad scope across an array of carbonyl derivatives, is easily scalable (1-100g), and can be predictably implemented into synthetic pathways using experimentally or computationally derived NMR shifts. Mechanistic interrogation suggests a radical-based reaction pathway.
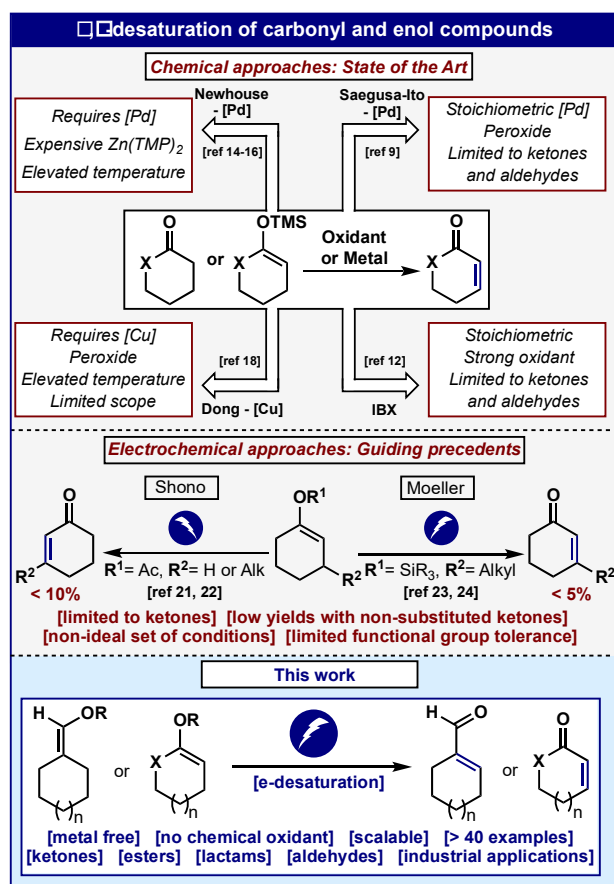
Figure 1. Desaturation of carbonyl and enol compounds: State-of-the-art, electrochemical precedents, and Electrochemically Driven Desaturation (EDD).

The removal of one molecule of hydrogen adjacent to a carbonyl compound is one of the simplest organic oxidation reactions known and is a widely employed tactic in synthesis.[1-3] Classic methods for accomplishing this transformation involve indirect α-functionalization approaches traversing through halide, sulfur, and selenium derivatives.[4-8] Chemoselective methods that directly afford enones from ketones are indeed more desirable and have been extensively explored (**Figure 1**). Amongst them, the Saegusa-Ito reaction, discovered in 1978, remains the most oft-applied method for such applications.[9] In its canonical implementation, formation of a silyl enol ether, followed by exposure to stoichiometric (from 0.5–1.0 equiv) quantities of Pd delivers the desired α,β-desaturated product.[9] Variants that employ a co-oxidant (e.g. O_2, quinone or [Cu]) to lower the [Pd]-levels have also been reported.[10,11] Another popular approach involves the use of stoichiometric IBX through an SET-based process.[12,13] Recently, two new methods have also appeared from the Newhouse and Dong groups that allow the use of catalytic amounts of palladium and copper, respectively.[14-20] These methods expand the scope of available desaturation methods to nitriles, esters, lactones, and lactams and do not require the preparation of enol ethers. Since the essence of this reaction involves a formal 2-electron oxidation, it stands to reason that even simpler redox approaches might be developed. Indeed, in 1973, the Shono group demonstrated that enol acetates can undergo anodic oxidation in AcOH as solvent to afford the corresponding enone. In order to deliver synthetically useful yields of product, α-substitution was required with simple cyclohexanone-substrates providing <10% enone.[21,22] Similar reactivity was also observed by Moeller and co-workers in their studies of silyl enol ether alkylation where

trace amounts of enone were isolated as a by-product (<5% yield).[23-25] Building on these encouraging studies, we report herein an electrochemically driven approach to elicit desaturation that requires no metals or chemical oxidants and features a broad substrate scope with inherent scalability. The utility of this method is placed in the context of the most popular and recently disclosed methods, and a simple method for predicting reactivity is also described.

The TMS-enol ether of cyclododecanone **1** was chosen for initial optimization of electrochemically driven desaturation (EDD); an abbreviated summary is depicted in **Table 1** (see SI for more extensive tabulation). Trial runs using the literature

EDD Reaction optimization

Conditions (Scheme): compound **1** (OTMS) → compound **2** (O); 2,6-lutidine (3.5% v/v), LiClO$_4$ (0.15 M), MeCN (0.1 M), 1.5 h, C+/C-, Undivided cell, 10mA under Ar

entry	deviation from above	yield (%)[a]
1	none	22 (17)
2	TEAOTs, AcOK in acetic acid (*Shono*, enol acetate, ref 21)	n.d.
3	LiClO$_4$, 3.5% lutidine in MeCN/^{i}PrOH (1:1) (*Moeller*, ref 23/25)	8
4	TBABF$_4$ instead of LiClO$_4$	n.d.
5	LiBF$_4$ instead of LiClO$_4$	12
6	NaOTs instead of LiClO$_4$	14
7	NaSbF$_6$ instead of LiClO$_4$	30
8	RVC anode, NaSbF$_6$ instead of LiClO$_4$	< 5%
9	Platinum anode, NaSbF$_6$ instead of LiClO$_4$	n.d.
10	Nickel foam anode, NaSbF$_6$ instead of LiClO$_4$	19
11	RVC cathode, NaSbF$_6$ instead of LiClO$_4$	12
12	Acetone instead of MeCN, NaSbF$_6$ instead of LiClO$_4$	14
13	DMF instead of MeCN, NaSbF$_6$ instead of LiClO$_4$	11
14	DMA instead of MeCN, NaSbF$_6$ instead of LiClO$_4$	18
15	TEA instead of lutidine, NaSbF$_6$ instead of LiClO$_4$	n.d.
16	Collidine instead of lutidine, NaSbF$_6$ instead of LiClO$_4$	45 (39)
17	20% collidine, , NaSbF$_6$ instead of LiClO$_4$	55
18	30% collidine, NaSbF$_6$ instead of LiClO$_4$	70 (62)
19	50% collidine, NaSbF$_6$ instead of LiClO$_4$	68
20	under air	65
21	non-anhydrous MeCN	64
22	no 2,4,6-collidine	n.d.
23	no NaSbF$_6$	n.d.
24	no electrolysis	n.d.

Table 1. Optimization of the EDD reaction. [a]Isolated yield. n.d.: not detected

conditions noted above provided only trace quantities of product. Our prior experiences for electrochemical reaction development served as a template for this study.[26-33] A myriad of electrolytes, electrodes, and solvents were evaluated. First, an electrolyte screen revealed that inorganic non-nucleophilic salts proved optimal (entries 4-7) with NaSbF$_6$ ($0.56/gram) delivering the highest conversion. The use of a graphite anode was found to be essential whereas several materials were suitable for the cathode (entries 8-11). Ultimately the low cost (ca. $0.1/cm^2) and efficiency of graphite motivated its selection for both electrode materials. Of all solvents screened, MeCN, acetone, DMA, and DMF could be employed but MeCN gave the highest yield across a broad range of substrates. A variety of bases were also tested with heteroaromatic amines proving most promising (entries 15-16). 2,4,6-Collidine (30% v/v – entry 18) emerged as optimum providing the desired product **2** in 62% isolated yield. The final set of EDD conditions tolerates exogenous air and moisture, lead to completion in 90 minutes or less, and can be setup in minutes, using a simple undivided cell and a commercial potentiostat.

EDD could be applied to a diverse set of carbonyl derivatives as illustrated in **Table 2**. As there are numerous desaturation methods available to the practitioner all of the results are placed into context with direct comparison to the powerful Pd, Cu, and hypervalent iodine-based systems. With regards to ketone substrates, both cyclic (from 5-15 membered rings) and acyclic derivatives could be employed (**2-17**). This stands in contrast to recently developed catalytic methods that operate smoothly on cyclic systems but fail on acyclic ones (**14 and 15**).[15,18] As EDD of ketones is reliant on formation of a silyl enol ether, regioselective desaturation is possible simply by tuning conditions (i.e. **7** vs. **8**). Substituents at the α-, β-, and γ-position are all tolerated as well as Lewis-basic heteroatoms (**16**), alkynes (**10**), proximal cyclopropanes (**15**), esters (**16 and 17**), TBS protected alcohols (**11**), and acid-labile ketals (**6**). A two-step *in situ* EDD protocol was also developed to afford enones

6, **12** and **17** in decent yields directly from the respective ketone starting material. Esters and lactones, substrate classes that have only recently succumbed to direct dehydrogenation,[14,17,18] can also be subjected to EDD using the corresponding diphenylphosphate ester derivatives (**18-31**). Such enol derivatives are easily prepared and hydrolytically stable unlike the corresponding silyl ketene acetals. Simple lactones and benzolactones, which are outside the substrate scope of IBX and Saegusa methodologies can be smoothly dehydrogenated. As with EDD of ketones, the functional group tolerance here is also broad including aryl halides (**22 and 24**), CF$_3$ (**30**), oxidizable anisoles (**23**), tosyl protected amines (**29**), and alkenes (**32**). In addition, α-aryl lactones also afforded the desired products in satisfactory yields (**21-23** and **25**). The difficulty of desaturating such substrates has been documented by Dong. They are often alternatively accessed through cross-coupling on the corresponding vinyl halide derivatives or through α-bromination/elimination sequences.[34,35] It worth noting that while comparing EDD with other precedented methods, the set of conditions reported by the Newhouse group was found to provide the desaturated α-aryl lactones in moderate yields. Next, the particularly difficult class of aldehydes were investigated (**32-34**, silyl enol ethers employed). Due to the instability of such desaturated products the yields observed were moderate (and accompanied by 5-11% of recovered parent aldehyde). Other direct catalytic methods for this dehydrogenation are not applicable, with the Saegusa protocol being the only other option. Lactams, a similarly challenging class of carbonyls, were surveyed as diphenylphosphate-ketenimine acetals, and in select cases (**35-37**) were viable.

The scalability of the method was evaluated using cyclopentadecanone-derived silyl enol ether **38** on a 4-gram scale (**Scheme 1A**) to afford enone **12**, a key intermediate in the synthesis of (*R*)-muscone **39**, a valuable ingredient in the fragrance industry.[36] A simple increase of current (from 10 mA to 300 mA) and the use of alternating polarity (to avoid any accumulation of material at the anode) enabled the standard EDD reaction to smoothly deliver compound **12** in 66% yield. To increase scale further, the design and assembly of a flow apparatus containing six reaction cells was undertaken (**Scheme 1A**). After optimization, 100 grams of **38** were successfully converted to compound **12** by increasing the current value to 3.6 A (compared to 300 mA in batch) to obtain 61% isolated yield and 27% recovered starting material **38**.

From a mechanistic standpoint, the EDD reaction accomplishes the formal removal of two electrons and one proton from the corresponding silyl enol ether. The electrochemical oxidation of silyl enol ethers has been previously disclosed by Moeller and studied mechanistically by Wright.[25] These studies demonstrated that initial anodic oxidation leads to the formation of an enol ether radical cation intermediate by using a cyclopropyl ring-opening clock. A similar conclusion was made by Moeller and co-workers when they oxidized various alkylenol ethers and thio-enol ethers.[37] It is therefore postulated that EDD proceeds through three elementary steps: (1) formation of the radical cation intermediate **40**; (2) deprotonation to afford **41**; (3) a second oxidation to form oxonium **42** which affords the desired enone product **5** (**Scheme 1B**, panel A). To provide empirical support for the proposed mechanism, three control experiments were designed and tested (**Scheme 1B**, panel B to D). First, the standard reaction conditions under air revealed the formation of the 1,2-diketone side product **44** in 9% yield. The amount of this by-product decreases to 4% when the reaction performed under inert atmosphere. In addition,

Table 2. Scope of the EDD reaction

Scope of the EDD reaction

Reaction conditions: NaSbF$_6$ (0.15 M), MeCN/2,4,6-collidine (7:3), 10 mA, rt, 1.5 to 4.0 h, [e-desaturation], R = TMS, P(O)(OPh)$_2$; X = CH$_2$, O, N

Comparison to State-of-the-Art:
[Pd1] = Saegusa-Ito (cat. [Pd] with oxidant)
[Pd2] = Newhouse (cat. [Pd] with Zn(TMP)$_2$ or LiTMP)
[Cu] = Dong (cat. [Cu] with (O^{t}Bu)$_2$)
[IBX] = Nicolaou (stoichiometric IBX in DMSO)

Ketones (via TMS-enol ethers)

2	3	4	5	6	7	8	9	10	11
[EDD]: 62%	[EDD]: 62%	[EDD]: 81%[a]	[EDD]: 67%	[EDD]: 64%, 35%[b]	[EDD]: 78%	[EDD]: 72%	[EDD]: 33%[a]	[EDD]: 50%	[EDD]: 67%
[Pd1]: 52%	[Pd1]: 85%	[Pd1]: 46%	[Pd1]: 87%	[Pd1]: 92%	[Pd1]: n.d.	[Pd1]: 45%	[Pd1]: 88%	[Pd1]: n.d.	[Pd1]: 72%
[Pd2]: 6%	[Pd2]: 71%	[Pd2]: 75%	[Pd2]: 63%	[Pd2]: 68%	[Pd2]: n/a	[Pd2]: 71%	[Pd2]: 74%	[Pd2]: 19%	[Pd2]: 75%
[Cu]: n.d.	[Cu]: n/a	[Cu]: traces	[Cu]: 7%	[Cu]: n.d.	[Cu]: n/a	[Cu]: 52%	[Cu]: 13%	[Cu]: 39%	[Cu]: 46%
[IBX]: 51%	[IBX]: 70%	[IBX]: n.d.	[IBX]: 60%	[IBX]: 53%	[IBX]: 9%	[IBX]: 19%	[IBX]: 85%	[IBX]: 30%	[IBX]: 31%

12	13	14	15	16	17
[EDD]: 44%, 54%[b]	[EDD]: 88%	[EDD]: 46%	[EDD]: 38%	[EDD]: 50%[c]	[EDD]: 27, 24%[b]
[Pd1]: 65%	[Pd1]: 81%	[Pd1]: 56%	[Pd1]: 56%	[Pd1]: 55%	[Pd1]: 51%
[Pd2]: traces	[Pd2]: 31%	[Pd2]: n/a	[Pd2]: n/a	[Pd2]: 67%	[Pd2]: 94%
[Cu]: n.d.	[Cu]: n/a	[Cu]: n.d.	[Cu]: n/a	[Cu]: n.d.	[Cu]: 45%
[IBX]: 83%	[IBX]: 58%	[IBX]: 34%	[IBX]: 31%	[IBX]: 38%	[IBX]: n.d.

Esters (via diphenylphosphate-ketene acetals)

18	19	20	21	22	23	24
[EDD]: 41%	[EDD]: 55%	[EDD]: 53%	[EDD]: 54%	[EDD]: 36%	[EDD]: 41%	[EDD]: 58%
[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a
[Pd2]: n/a	[Pd2]: n/a	[Pd2]: 47%	[Pd2]: 31%	[Pd2]: 39%	[Pd2]: 13%	[Pd2]: 15%
[Cu]: 73%	[Cu]: n/a	[Cu]: n/a	[Cu]: n/a	[Cu]: n/a	[Cu]: n/a	[Cu]: traces
[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a

25	26	27	28	29	30	31
[EDD]: 64%	[EDD]: 54%	[EDD]: 71%	[EDD]: 81%	[EDD]: 54%	[EDD]: 52%	[EDD]: 34%
[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a
[Pd2]: 44%	[Pd2]: 81%	[Pd2]: 72%	[Pd2]: 44%	[Pd2]: 62%	[Pd2]: n/a	[Pd2]: n/a
[Cu]: n/a	[Cu]: n.d.	[Cu]: n.d.	[Cu]: n.d.	[Cu]: n.d.	[Cu]: n/a	[Cu]: 41%
[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a	[IBX]: n/a

Lactams (via diphenylphosphate-keteniminyl acetals) and Aldehydes (via TMS-enol ethers)

32	33	34	35	36	37
[EDD]: 38%[b]	[EDD]: 37%[c]	[EDD]: 50%	[EDD]: 58%[d]	[EDD]: 69%	[EDD]: 24%
[Pd1]: 74%	[Pd1]: 61%	[Pd1]: 55%	[Pd1]: n/a	[Pd1]: n/a	[Pd1]: n/a
[Pd2]: n/a	[Pd2]: n/a	[Pd2]: n/a	[Pd2]: n/a	[Pd2]: n/a	[Pd2]: n/a
[Cu]: n/a	[Cu]: n/a	[Cu]: n/a	[Cu]: 48%	[Cu]: 32%	[Cu]: 30%
[IBX]: 11%	[IBX]: 7%	[IBX]: n.d.	[IBX]: n.a.	[IBX]: n/a	[IBX]: n/a

Table 2. Scope of the EDD reaction. [a]Yield based on GCMS conversion. [b]Using in-situ protocol. [c]Yield based on NMR conversion. [d]Prepared from phenyl acetate-keteniminyl acetals. n/a: not applicable. n.d.: not detected.

the parent ketone is the only product observed when water is added to the reaction. These results suggest that formation of compound **44** derived from molecular oxygen via a radical type mechanism. Next, to support the crucial role of the base in the deprotonation event, the EDD reaction conditions were applied to compound **1** with various amounts of 2,4,6-collidine (**Scheme 1B**, panel C). No desired product was obtained when base was excluded, reinforcing the importance of the base for the EDD reaction and its implication in the deprotonation step 2 (**Scheme 1**, panel A). Furthermore, a noticeable improvement was observed between the reaction efficiency and the base
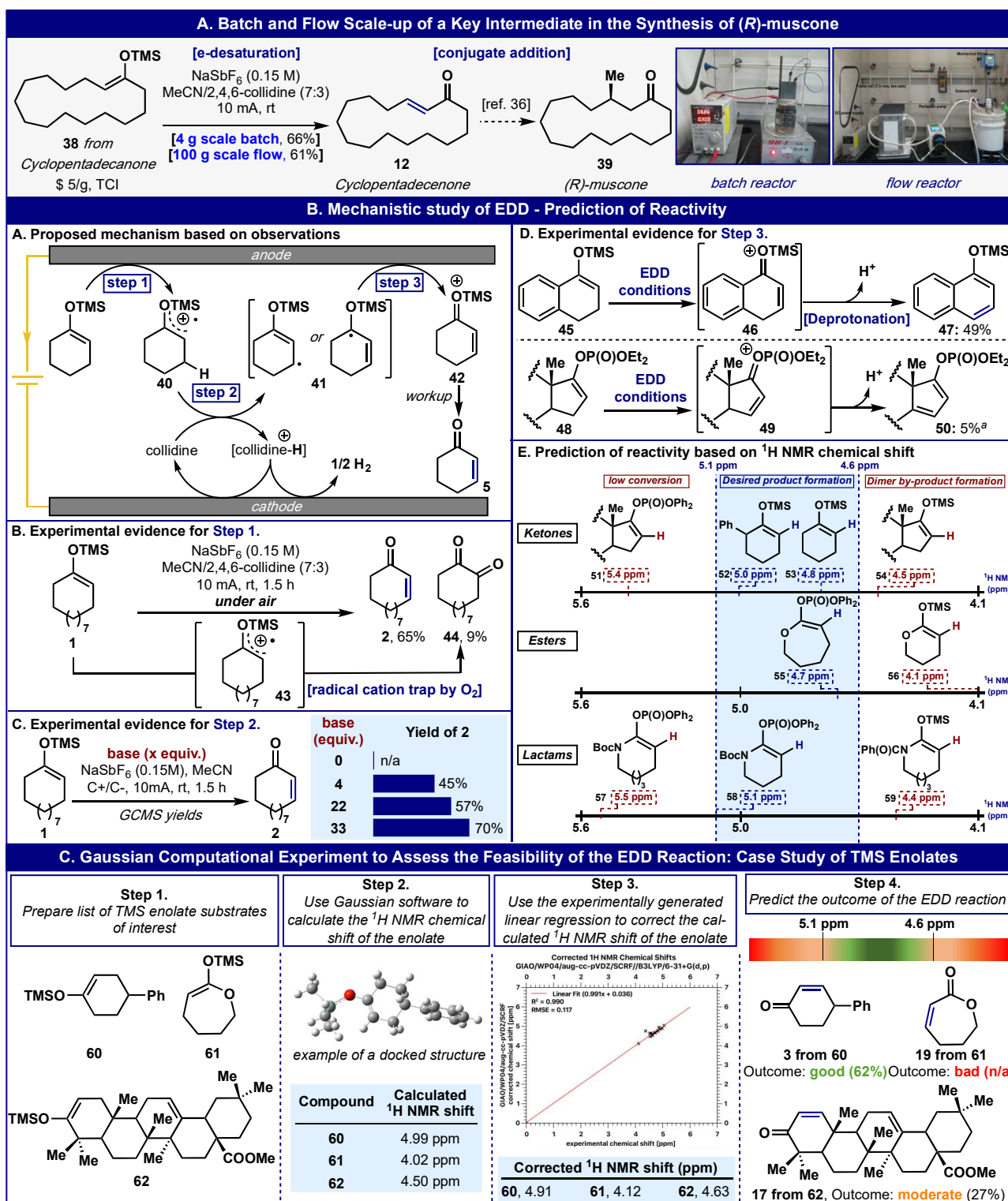
Scheme 1. (A) Batch and flow scale-up of a key intermediate in the synthesis of (*R*)-muscone. (B) Mechanistic study of the EDD reaction. (C) Gaussian computational experiment to assess the feasibility of the EDD reaction: Case study of TMS enolates. [a]Yield based on LCMS conversion.

concentration. Finally, a third experiment was conducted to explore the formation of an oxonium intermediate (**Scheme 1B**, panel D). Compound **45** was subjected to the reaction conditions affording naphthalene **47** in 49% yield. The formation of this product is in accordance with the formation of intermediate (**46**), which after elimination would deliver **47**. Similarly,

when the diethylphosphate **48** derived from dehydroepiandrosterone was subjected to EDD, diene **50** was also observed as a side-product.

During these studies it was empirically noted that ketone, lactam and lactone substrates whose vinylic proton shifts registered between 4.6 and 5.1 ppm showed good conversion to the

desaturated product. However, compounds with NMR shifts lower than 4.6 ppm led to the formation of dimer, hydrolysis, and other by-products. Compounds with NMR shifts higher than 5.1 ppm showed low reactivity toward oxidation. Based on these findings and Moeller's reports,[37] it is possible to identify a trend between the oxidation potential of the enol ether (to form a radical cation intermediate similar to **40**) and the electron density of the pi-system (see SI, figure S10 for details). Compounds such as dehydroepiandrosterone-phosphate **51** and the 8-membered lactam **57** cannot be oxidized under the EDD reaction conditions due to the deshielded vinylic proton correlating to a higher oxidation potential (CV = 2.06 to 2.47 V). When the vinylic proton is shielded, the oxidation potential becomes lower and reactivity toward EDD is observed (CV = 1.54 to 1.72 V). On the other hand, compounds such as dehydroepiandrosterone-TMS **54**, lactone-TMS **56**, and lactam-TMS **59** whose vinylic protons that are too shielded, afforded low amounts of the desaturated product (CV = 1.32 to 1.4 V). In this case, the enol derivatives react as nucleophilic radicals rather than electrophilic radical cations due to greater cationic stabilization, which renders the EDD pathway less favorable.[38,39] Accordingly, this explains why electron withdrawing enol-phosphates are required for esters and lactams in EDD rather than the corresponding silyl enol ethers.

Based on these observations, one could imagine predicting the outcome of the EDD reaction by calculating the NMR shift of the TMS enol ethers of interest (**Scheme 1C**, Step 1). With this idea in mind, a simple protocol using GAUSSIAN16, a quantum chemical calculation software, was developed. This protocol gives access to a calculated NMR shift based on the shielding constants using the gauge-including atomic orbital (GIAO) method in the WP04 database (functional) with an aug-cc-pVDZ basis set using tetramethylsilane as a reference (Scheme 1C, Step 2). Next, to obtain a more accurate value, the NMR shift value was corrected using an experimentally generated linear regression (**Scheme 1C**, Step 3 and see SI for detailed graphical step-by-step guide). Finally, the corrected NMR shift can be used to predict the efficiency of the EDD reaction (**Scheme 1C**, Step 4). To our knowledge, this is a rare example of using calculated NMR shift to predict the scope of an organic methodology.[40]

The desaturation of carbonyl derivatives is a basic reaction of utmost utility in organic chemistry as it unlocks a variety of useful downstream transformations. Studies in this area continue to the present day; the contribution reported herein affords a potentially simple solution to this problem. Drawing from early studies in electrosynthesis and more recent mechanistic studies of anodic enol-oxidation, a useful protocol for EDD has been uncovered. This oxidation protocol can be performed in an undivided cell, on multiple scales, without strict removal of air or water, and in the absence of expensive metals, ligands, or stoichiometric organic oxidants. As with the oxidation of alcohols, for which numerous methods are available, this desaturation study has been placed into context with the most powerful methods currently available to aid the practitioner. Finally, a simple ^{1}H NMR-based rubric was created to allow users to experimentally or computationally predict which substrates are suitable for EDD, which should facilitate its rapid adoption.

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REFERENCES

(1) Muzart, J. One-Pot Syntheses of α, β-Unsaturated Carbonyl Compounds through Palladium-Mediated Dehydrogenation of Ketones, Aldehydes, Esters, Lactones and Amides. *Eur. J. Org. Chem.* **2010**, *20*, 3779–3790.

(2) Otera, J. Modern Carbonyl Chemistry; Wiley-VCH: Weinheim, Germany, **2000**.

(3) Turlik, A.; Chen, Y.; Newhouse, T. R. Dehydrogenation Adjacent to Carbonyls Using Palladium–Allyl Intermediates. *Synlett* **2016**, *27*, 331–336.

(4) Reich, H. J.; Reich, I. L.; Renga, J. M. Organoselenium chemistry: alpha-Phenylseleno carbonyl compounds as precursors for alpha, beta-unsaturated ketones and esters. *J. Am. Chem. Soc.* **1973**, *95*, 5813–5815.

(5) Sharpless, K. B.; Gordon, K. M. Selenium dioxide oxidation of ketones and aldehydes. Evidence for the intermediacy of beta-ketoseleninic. *J. Am. Chem. Soc.* **1976**, *98*, 300–301.

(6) Trost, B. M.; Salzmann, T. N.; Hiroi, K. New synthetic reactions. Sulfenylations and dehydrosulfenylations of esters and ketones. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902.

(7) Trost, B. M.; Salzmann, T. N. New synthetic reactions. Sulfenylation-dehydrosulfenylation as a method for introduction of unsaturation. *J. Am. Chem. Soc.* **1973**, *95*, 6840–6842.

(8) Larock, R. C. Comprehensive Organic Transformations; VCH Publishers: New York, **1989**, 129–131.

(9) Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of α,β-unsaturated carbonyl compounds by palladium (II)-catalyzed dehydrosilylation of silyl enol ethers. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(10) Shimizu, I.; Tsuji, J. Palladium-Catalyzed Decarboxylation-Dehydrogenation of Allyl β-Keto Carboxylates and Allyl Enol Carbonates as a Novel Synthetic Method for α-Substituted α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **1982**, *104*, 5844–5846.

(11) Diao, T.; Stahl, S. S. Synthesis of cyclic enones via direct palladium-catalyzed aerobic dehydrogenation of ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.

(12) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. A new method for the one-step synthesis of α,β-unsaturated carbonyl systems from saturated alcohols and carbonyl compounds. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.

(13) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. Iodine (V) Reagents in Organic Synthesis. Part 4. o-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

(14) Chen, Y.; Romaire, J. P.; Newhouse, T. R. Palladium-catalyzed α,β-dehydrogenation of esters and nitriles. *J. Am. Chem. Soc.* **2015**, *137*, 5875–5878.

(15) Huang, D.; Zhao, Y.; Newhouse, T. R. Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β-Dehydrogenation. *Org. lett.* **2018**, *20*, 684–687.

(16) Chen, Y.; Turlik, A.; Newhouse, T. R. Amide α,β-dehydrogenation using allyl-palladium catalysis and a hindered monodentate anilide. *J. Am. Chem. Soc.* **2016**, *138*, 1166–1169.

(17) Huang, D.; Szewczyk, S. M.; Zhang, P.; Newhouse, T. R. Allyl-Nickel Catalysis Enables Carbonyl Dehydrogenation and Oxidative Cycloalkenylation of Ketones. *J. Am. Chem. Soc.* **2019**, *141*, 5669–5674.

(18) Chen, M.; Dong, G. Copper-catalyzed desaturation of lactones, lactams, and ketones under pH-neutral conditions. *J. Am. Chem. Soc.* **2019**, *141*, 14889–14897.

(19) Chen, M.; Dong, G. Direct catalytic desaturation of lactams enabled by soft enolization. *J. Am. Chem. Soc.* **2017**, *139*, 7757–7760.

(20) Chen, M.; Rago, A. J.; Dong, G. Platinum-Catalyzed Desaturation of Lactams, Ketones, and Lactones. *Angew. Chem. Int. Ed.* **2018**, *130*, 16437–16441.

(21) Shono, T.; Matsumura, Y.; Nakagawa, Y. Electroorganic chemistry. XII. Anodic oxidation of enol esters. *J. Am. Chem. Soc.* **1974**, *96*, 3532–3536.

(22) Shono, T.; Okawa, M.; Nishiguchi, I. Electroorganic chemistry. XXI. Selective formation of. alpha-acetoxy ketones and general synthesis of 2, 3-disubstituted 2-cyclopentenones through the anodic oxidation of enol acetates. *J. Am. Chem. Soc.* **1975**, *97*, 6144–6147.

(23) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. Anodic oxidations of electron-rich olefins: radical cation based approaches to the synthesis of bridged bicyclic ring skeletons. *Tetrahedron* **2001**, *57*, 5183–5197.

(24) Perkins, R. J.; Feng, R.; Lu, Q.; Moeller, K. D. Anodic Cyclizations, Seven-Membered Rings, and the Choice of Radical Cation vs. Radical Pathways. *Chin. J. Chem.* **2019**, *37*, 672–678.

(25) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. Electrooxidative coupling of furans and silyl enol ethers: application to the synthesis of annulated furans. *J. Org. Chem.* **2004**, *69*, 3726–3734.

(26) Kingston, C.; Palkowitz, M. D.; Takahira, Y.; Vantourout, J. C.; Peters, B. K.; Kawamata, Y.; Baran, P. S. A Survival Guide for the "Electro-curious" *Acc. Chem. Res.* **2020**, *53*, 72–83.

(27) Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M.; Davies, A.; Del Bel, M.; Gallego, G.; Spangler, J.; Starr, J. T.; Yang, S.; Blackmond, D.; Baran, P. S. Hindered Dialkyl Ether Synthesis via Electrogenerated Carbocations. *Nature* **2019**, *573*, 398–401.

(28) Takahira, Y.; Chen, M.; Kawamata, Y.; Mykhailiuk, P.; Nakamura, H.; Peters, B. K.; Reisberg, S. H.; Li, C.; Chen, L.; Hoshikawa, T.; Shibuguchi, T.; Baran, P. S. Electrochemical C(sp3)-H Fluorination. *Synlett* **2019**, *30*, 1178–1182.

(29) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402.

(30) Peters, B. K.; Rodriguez, K. X.; Reisberg, S. H.; Beil, S. B.; Hickey, D. P.; Kawamata, Y.; Collins, M.; Starr, J.; Chen, L.; Udyavara, S.; Klunder, K.; Gorey, T. J.; Anderson, S. L.; Neurock, M.; Minteer, S. D.; Baran, P. S. Scalable and Safe Synthetic Organic Electroreduction Inspired by Li-Ion Battery Chemistry. *Science* **2019**, *363*, 838–845.

(31) Yan, M.; Kawamata, Y; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230–13319.

(32) Li, C; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S. Electrochemically Enabled, Nickel-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2017**, *56*, 13088–13093.

(33) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D. H.; Chen, J.; Starr, J. T.; Baran, P.S. Scalable, electrochemical oxidation of unactivated C–H bonds. *J. Am. Chem. Soc.* **2017**, *139*, 7448–7451.

(34) Rosen, J. D.; Nelson, T. D.; Huffman, M. A.; McNamara, J. M. A convenient synthesis of 3-aryl-δ-lactones. *Tet. Lett.* **2003**, *44*, 365–368.

(35) Cai, X. C.; Snider, B. B. Synthesis of the Spiroiminal Moiety and Approaches to the Synthesis of Marineosins A and B. *J. Org. Chem.* **2013**, *78*, 12161–12175.

(36) Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. Asymmetric synthesis of (R)-(-)-and (S)-(+)-muscone by enantioselective conjugate addition of chiral dimethylcuprate to (E)-cyclopentadec-2-en-1-one. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 1445–1452.

(37) Feng, R.; Smith, J. A.; Moeller, K. D. Anodic cyclization reactions and the mechanistic strategies that enable optimization. *Acc. Chem. Res.* **2017**, *50*, 2346–2352.

(38) Murphy, J. A.; Khan, T. A.; Zhou, S.; Thomson, D. W.; Mahesh, M. *Angew.Chem. Int. Ed.* **2005**, *44*, 1356–1360.

(39) Tang, F.; Moeller, K. D. Anodic oxidations and polarity: exploring the chemistry of olefinic radical cations. *Tetrahedron* **2009**, *65*, 10863–10875.

(40) Handy, S. T.; Zhang, Y. A simple guide for predicting regioselectivity in the coupling of polyhaloheteroaromatics. *Chem. Comm.* **2006**, *3*, 299–301.