Exploring Electrochemical C(sp^3)–H Oxidation for the Late-Stage Methylation of Complex Molecules

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ABSTRACT: The "magic methyl" effect – a dramatic boost in the potency of biologically active compounds from the incorporation of a single methyl group – provides a simple yet powerful strategy employed by medicinal chemists in the drug discovery process. Despite significant advances, methodologies that enable the selective C(sp^3)–H methylation of structurally complex medicinal agents remain very limited. In this work, we disclose a modular, efficient, and selective strategy for the α-methylation of protected amines (i.e., amides, carbamates, and sulfonamides) by means of electrochemical oxidation. Mechanistic analysis guided our development of an improved electrochemical protocol on the basis of the classic Shono oxidation reaction, which features broad reaction scope, high functional group compatibility, and operational simplicity. Importantly, this reaction system is amenable to the late-stage functionalization of complex targets containing basic nitrogen groups that are prevalent in medicinally active agents. When combined with organozinc-mediated C–C bond formation, our protocol enabled the direct methylation of a myriad of amine derivatives including those that have previously been explored for the "magic methyl" effect. This synthetic strategy thus circumvents multistep *de novo* synthesis that are currently necessary to access such compounds and has the potential to accelerate drug discovery efforts.

INTRODUCTION

In medicinal chemistry, a dramatic boost in biological activity is commonly observed with the addition of a single innocuous methyl group to potential drug candidates.[1] This aptly named "magic methyl" effect has led to the incorporation of the methyl group in a variety of biologically active molecules and active pharmaceutical ingredients (APIs). Thus, the value of a synthetic method to incorporate these methyl groups is compounded further when applying it in the late stage of drug development, enabling rapid analogue evaluation during the drug discovery process.

Owing to the prevalence of protected amines (e.g., amides and sulfonamides) in medicinally active agents,[2] recent studies have highlighted specific instances in which the incorporation of a methyl group in the α-position of a nitrogen atom drives potency optimization in drug discovery campaigns. In 2018, a team at Genentech explored antagonists of the transient receptor potential ankyrin 1 (TRPA1),[3] a Ca^{2+} ion channel implicated in asthma, identifying the sulfonamide **1** as a promising compound (**Scheme 1A**).[4] During the optimization process, enhanced potency was observed with the incorporation of a methyl group at the 5-position of the proline ring (**2**). This boost in potency was attributed to enhanced binding affinity as a result of a key interaction between the new methyl group and a hydrophobic pocket within the TRPA1 binding site.[5] In 2012, Merck identified compound **3** as a dual orexin 1 and orexin 2 receptor antagonist (**Scheme 1A**).[6] During the structure-activity relationship investigation, analogue **4**, having a methyl group at the α position of the amide, exhibited an astounding 505-fold increase in potency for the orexin 1 receptor compared to its parent compound. In this case, the additional methyl group imparts steric interactions with the amide group and thus induces a subtle conformation change of the molecule that favors its binding to the orexin receptors. Notably, however, the preparation of many such methylated drug candidates required multi-step *de novo* syntheses, which hampers the discovery process. In contrast, the development of a late-stage functionalization (LSF)[7] approach for the methylation of these and analogous molecules would substantially increase medicinal chemists' ability to explore the "magic methyl" effect and thus accelerate drug discovery efforts.

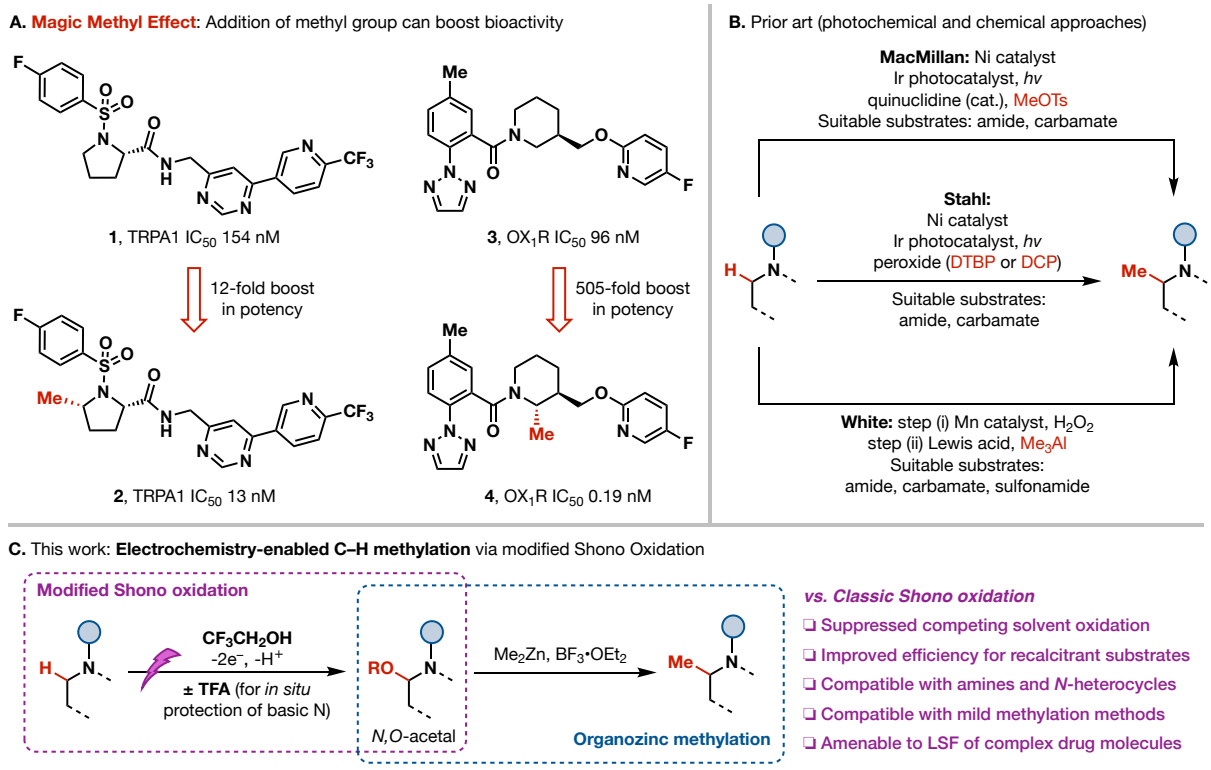
Despite this significance, only a limited number of methods have been reported for the selective α-C–H methylation of amine derivatives,[8] and this is particularly underexplored in the context of LSF of complex targets (**Scheme 1B**). In 2017, MacMillan and coworkers reported an elegant multi-catalytic system encompassing photochemistry, nickel catalysis, and organocatalysis to achieve C(sp^3)–H methylation of carbamates and amides.[9] Currently, this method employs an excess of the substrate and the LSF of polyfunctional medicinal agents was not reported. In 2021, Stahl and co-workers employed a combination of photochemistry and nickel catalysis to

achieve α-methylation of amides and carbamates.[10] The use of peroxides provided an innovative solution, having dual roles of supplying an alkoxy radical for the C–H abstraction as well as serving as the methyl radical source upon β-scission of RO•. Nevertheless, this protocol has yet to be demonstrated for the installation of substituents other than methyl. In addition, neither of the aforementioned methodologies explored the functionalization of sulfonamides, a common motif in medicinal chemistry (i.e., sulfa drugs).[11] In 2020, White and co-workers reported a general and powerful approach for the methylation of amides, carbamates, and sulfonamides[12] via tandem Mn-catalyzed C–H oxidation and Lewis acid-mediated methyl addition using Me_3Al. This two-step methodology was shown to be compatible with a variety of complex molecules using a commercial Mn catalyst.[13]

Each of the aforementioned examples represents a key milestone in the development of late-stage methylation. Nevertheless, in contrast to the methylation of C(sp^2)–H bonds, analogous methods for functionalizing C(sp^3)–H bonds remains very limited,[1c] and there exists a clear impetus for developing complementary and general strategies to further enable the exploration of the "magic methyl" effect in complex molecular settings. Against this backdrop, we sought to advance a new approach for the α-methylation of amine derivatives by means of electrochemistry.[14,15] An ideal protocol in this regard would present the following features: (1) compatibility with substrates with various *N*-substituents and diverse structures; (2) tolerance of functional groups prevalent in medicinal agents such as basic amines and *N*-heteroarenes; (3) modularity toward installation of groups other than methyl for systematic medicinal chemistry studies; and (4) operational simplicity with commercially available reaction setups and reagents.

To this end, we were inspired by the Shono oxidation reaction, a classic electroorganic transformation for the functionalization of protected amines. In the original report in 1975, the direct electrolysis of carbamates in methanol gave rise to the corresponding *N*,*O*-acetals via a formal C–H activation process.[16] Later, Shono and co-workers demonstrated the feasibility of such a reaction with sulfonamides.[17] Since then, the Shono oxidation has seen numerous applications in organic synthesis, but it has been generally used for the functionalization of structurally simple compounds or the preparation of building blocks at early stages of synthetic campaigns.[18] In a recent work by Aubé and Moeller,[19] electrochemistry was used to achieve the derivatization of polycyclic lactams. Further, Stahl reported an electrocatalytic approach to circumvent the high overpotentials required for traditional Shono oxidation, thus enabling expanded functional group compatibility in the conversion of carbamates to imides.[14a] Nevertheless, these two systems have yet to be explored for the functionalization of more recalcitrant sulfonamides or substrates with basic amines and pyridines. Thus, a major barrier to the adoption of the Shono oxidation in the LSF of complex targets is the current lack of knowledge about functional group compatibility, preventing its widespread use in drug discovery. We hypothesized that under the high potentials required to oxidize amides and sulfonamides, many side reactions could arise and complicate the desired reactivity in complex molecular systems.

Scheme 1. Background Information



Herein, we explored a combination of synthetic and electroanalytic tools to define the limitations of the canonical Shono oxidation in the context of complex target derivatization (**Scheme 1C**). Guided by this mechanistic

information, we report a modified variant of the Shono oxidation that shows improved generality for the functionalization of a diverse array of amine derivatives. Importantly, this method tolerates a variety of medicinally prevalent functional groups such as free amines and *N*-heteroarenes. The resultant *N*,*O*-acetal species readily underwent alkylation using organozinc reagents, which enables the facile installation of methyl as well as various other alkyl and aryl groups. This two-step synthetic strategy was demonstrated for a broad range of sulfonamides, amides, and carbamates including many derived from medicinal agents.

RESULTS AND DISCUSSION

Methylation Of Compounds Without Basic *N*-Containing Groups

Our initial investigations started with testing the standard Shono oxidation conditions with a panel of six arylsulfonamides derived from pyrrolidine with different electronic properties (**Scheme 2A**). Classic electrolysis conditions using methanol as the solvent and nucleophile, Et_4NBF_4 as the electrolyte, and graphite as the electrodes performed well with sulfonamides bearing electron-neutral and electron-rich substituents. However, we observed a dramatic loss in efficiency with substrates containing electron-withdrawing groups such as bromine and nitro. Both of these substrates failed to undergo full conversion even after passing a large excess of charge (10 and 12 F/mol, respectively). To understand this deficit, cyclic voltammetry analysis and *ab initio* density functional theory (DFT) calculations were carried out (**Figure 1** and Supporting Information), and not surprisingly, substrates **5**-Br and **5**-NO_2 displayed higher oxidation potentials of 1.43 V *vs.* Fc^+/Fc^0 (1.67 V from DFT) for **5-Br** and 1.51 V *vs.* Fc^+/Fc^0 (1.75 V from DFT) for **5-NO_2**. At these potentials, substantial background current was observed for the oxidation of methanol. Thus, we suspected the competitive solvent oxidation as the main culprit for the unproductive consumption of current, leading to poor Faradaic efficiencies and low yields. Indeed, NMR studies of the reaction mixture revealed degradation products that are likely the result of methanol oxidation.

This mechanistic insight led us to investigate a simple solution—to replace methanol with a solvent that is more resistant to anodic oxidation while remaining sufficiently nucleophilic to capture the key iminium ion intermediate (**Scheme 1C**). As such, we evaluated the oxidation potential of a variety of alcohols using CV and DFT computation, and found that fluorinated congeners such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP)[20] (with calculated redox potentials of 3.04 V *vs.* Fc^+/Fc^0 and 3.96 V *vs.* Fc^+/Fc^0, respectively) are substantially more tolerant to anodic conditions under which the Shono oxidation takes place. In addition to enabling the activation of more recalcitrant substrates, the incorporation of such fluorinated alcohols into the *N*,*O*-acetal intermediates should also facilitate the subsequent methylation process by presenting a better leaving group. Additionally, this simple solution could pave the way for addressing the compatibility issue of Shono oxidation with basic nitrogen groups via *in situ* protection (*vide infra*).

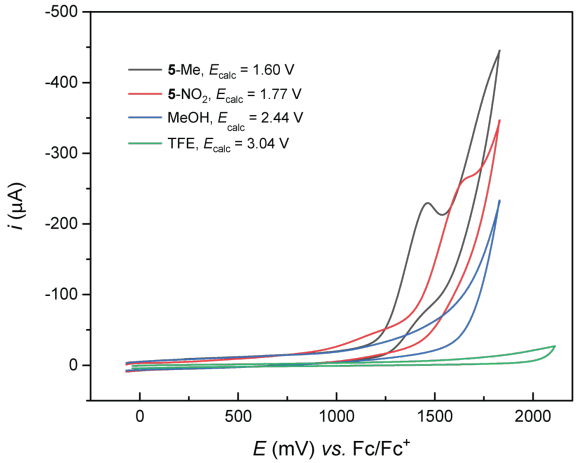
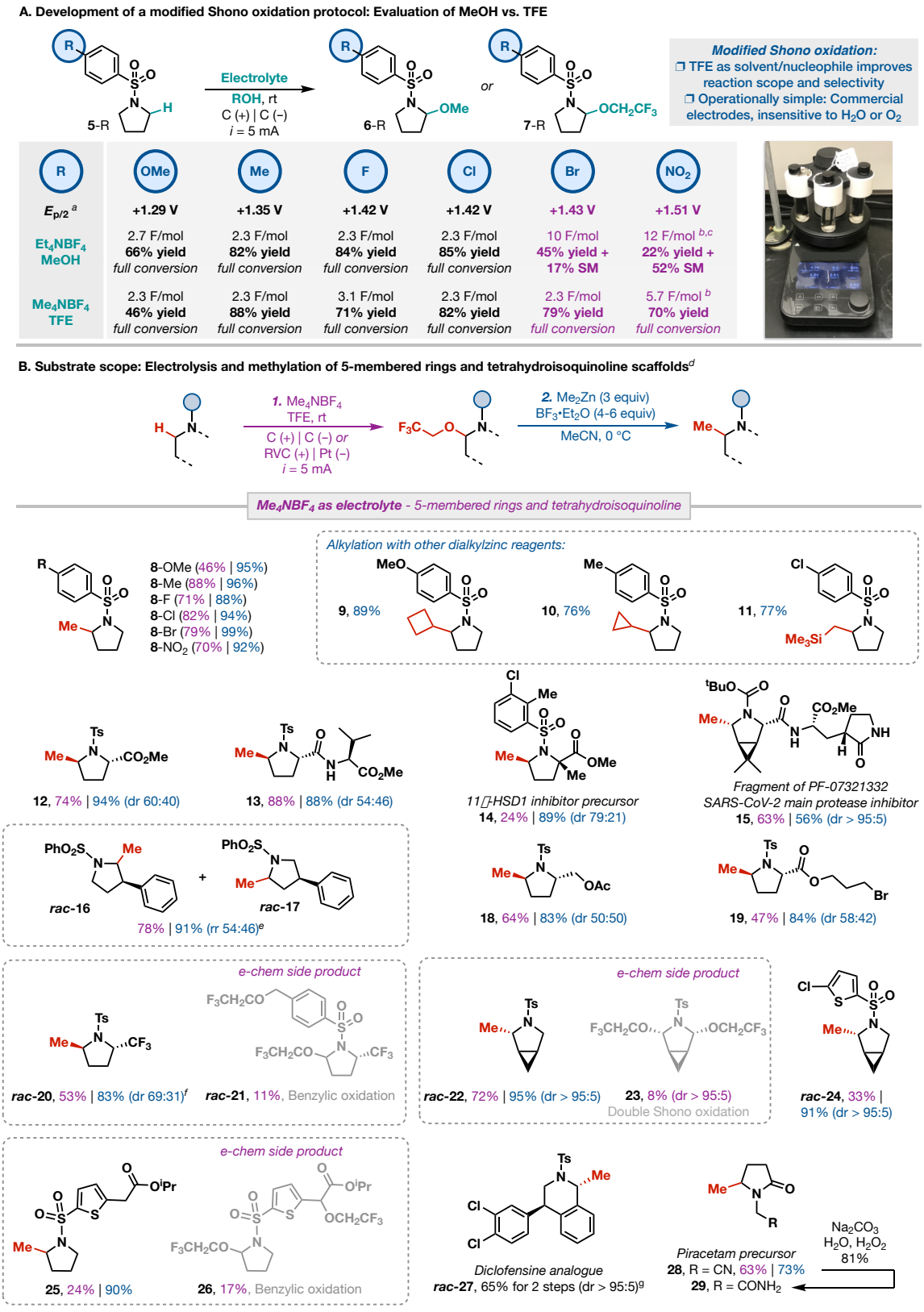


Figure 1. Cyclic voltammetry data for various substrates and solvents. Calculated thermodynamic potentials are listed in the figure legend.

Our initial exploration of the use of HFIP as the solvent resulted in low yields of the *N*,*O*-acetal product. Despite overcoming the challenge of solvent oxidation, the corresponding product suffered from low stability. TFE as the solvent, however, provides an ideal balance between resistance to oxidation and product stability. Thus, under constant current conditions using graphite as both cathode and anode, the generation of *N*,*O*-acetal **7**-Br from substrate **5**-Br was achieved in 79% yield after passing only 2.3 F/mol charge. Me_4NBF_4 was shown as the optimal electrolyte, which could also be readily removed via precipitation with a less polar solvent (e.g., DCM and EtOAc). In addition to improved yield, this modified protocol also showed drastically higher Faradaic efficiency (FE) of 69% (vs. 9% with MeOH). Likewise, the improved yield and current efficiency were evident with **5**-NO_2, giving 70% yield and 25% FE vs. 22% yield and 4% FE with MeOH. In this case, a platinum cathode was used in lieu of graphite to favor H_2 evolution over nitro reduction.[21] This improved protocol maintained the operational simplicity, which can be conducted open to air using commercially available reagents, electrodes, and electrolysis vessels (ElectraSyn 2.0).

N,*O*-acetals are highly versatile intermediates that can engage in reactions with a myriad of nucleophiles[22] including allyl silanes, cyanide, silyl enol ethers, and electron-rich aromatics. We are particularly interested in providing a robust protocol to incorporate $-CH_3$ into the *N*,*O*-acetal products from the modified Shono oxidation. Upon surveying a number of nucleophilic organometallic agents, organozinc stood out as an optimal selection. These compounds feature broad functional group compatibility[23] vis-à-vis Grignard[24] and organolithium reagents. In addition, a large variety of organozinc complexes are commercially available or can be conveniently prepared from Grignard reagents and zinc salts. Thus, organozinc can be readily employed for the LSF of complex bioactive molecules to explore the "magic methyl" effect. Further, this methodology could be expanded beyond methylation to other alkylation and arylation reactions to facilitate synthetic and medicinal studies. Notably, dialkylzinc reagents have rarely seen use for the alkylation of *N*-protected iminium ions.[25]

Scheme 2. Development of an Improved Version of Shono Oxidation and Its Application in the Methylation of Amine Derivatives



[a] $E_{p/2}$ *vs.* Fc^+/Fc^0, [b] Pt was used as cathode, [c] MeCN/MeOH (1:1) was used as solvent, [d] Electrochemical oxidation yields are shown in purple, the concentration for this step ranged from 0.05-0.25 M, while methylation yields and dr (or rr) are shown in blue, the concentration for this step ranged from 0.05-0.20 M; all products with relative stereochemistry shown and without the descriptor *rac* are enantioenriched, [e] The relative configuration of the new methyl group could not be assigned unambiguosly at this moment, [f] Methylation in CH_2Cl_2 in lieu of MeCN, [g] Crude *N*,*O*-acetal was used on 2nd step

The overall synthetic strategy for the formal C–H methylation of sulfonamides encompasses the modified Shono oxidation followed by treatment of the resultant *N*,*O*-acetal with dimethylzinc in the presence of BF_3•Et_2O in acetonitrile at 0 °C (for optimization of the methylation step, see SI). The scope of this strategy was initially investigated with aryl sulfonamides derived from pyrrolidines (**8**–**27**, **Scheme 2B**), wherein several functional groups such as esters (**12**–**15** and **18**), secondary amides (**13** and **15**), thiophenes (**24**–**25**), aryl halides (**8-F**, **8-Cl**, **8-Br** and **14**), alkyl halide (**19**), and nitroarene (**8-NO_2**) were well tolerated (**Scheme 2B**). The enantiomeric excess of **12** remained >99% (checked by HPLC, see SI for details), highlighting the stereofidelity of our protocol . Importantly, compounds **22** and **24** were readily prepared, whereas previous radical-based methods[9,10,12] would likely induce cyclopropane ring-opening.[26] Two main side reactions were identified from this set of substrates: (1) products **21** and **26** were isolated in 11% and 17% yield respectively, indicative of competitive aromatic ring oxidation,[27] and (2) substrates containing two identical methylene groups neighboring the nitrogen are susceptible to double Shono oxidation as observed in the isolation of minor side product **23**. In addition to methylation, we further showcased this strategy in the incorporation of cyclobutyl (**9**), cyclopropyl (**10**), and (trimethylsilyl)methyl (**11**) groups at the α-position of sulfonamides using organozinc reagents, which were readily synthesized from the corresponding Grignard reagents and $ZnCl_2$. Importantly, although we isolate most *N*,*O*-acetal intermediates to provide a full characterization of the desired and side reaction products, this purification is not necessary and the crude product can be directly carried forward in the methylation step.

We set out to further explore the selective methylation of biologically and medicinally relevant substrates. A diclofensine analogue underwent Shono oxidation and methylation, without purification of the intermediate, to give product **27** in high yield with an excellent diastereomeric ratio. A piracetam precursor underwent efficient C(sp^3)–H methylation to form **28**, which upon nitrile hydrolysis furnished methyl piracetam **29**. We note that piracetam itself can also be readily oxidized to the *N*,*O*-acetal but the subsequent methylation proved to be low yielding (~30%). Finally, a complex fragment of PF-07321332,[28] a potential anti-viral compound developed by Pfizer currently in Phase I clinical trials to treat COVID-19, underwent methylation to generate compound **15** with excellent regio- and chemoselectivity without rupture of the cyclopropane ring. Again, this substrate is likely incompatible with existing methylation strategies that rely on radical C–H activation. The latter two examples showed that our strategy is also applicable to the functionalization of amides and carbamates.

Direct adoption of these new conditions from *N*-sulfonylpyrrolidines to the piperidine and azepane congeners led to lower reaction yields accompanied by undesired desulfonylation giving byproduct **32** (**Scheme 3A**). To address this issue, we employed a recently developed HT*e*$^-$Chem reactor[29] to rapidly screen numerous electrolysis conditions and identified a new set of optimal reaction parameters. Using TBAF as the electrolyte afforded improved yield toward *N*,*O*-acetal formation and suppressed side reactions (**Scheme 3A**).

This model system was further applied to the functionalization of various piperidine and azepane derivatives (**Scheme 3B**). For 6-membered rings, the methylation step was carried out at lower temperature (–20 °C) to suppress undesired elimination generating enamine products. The elimination pathway is exemplified by the formation of the side-product **38**, in which enamine **39** is thought to be initially produced. The application of the C(sp^3)–H methylation on different molecular architectures gave rise to products with interesting selectivity. For example, while compounds **46** and **47** were generated in a nearly 1:1 mixture of regioisomers, compounds ***rac*-44** and ***rac*-45** were regioselectively methylated α to the cyclopropane. The methylation of Ts-coniine and a varenicline simplified analogue afforded compounds ***rac*-40** and ***rac*-43** respectively, effectively as single diastereomers. A 3-phenyl-piperidine derivative could be functionalized selectively on the least hindered side, furnishing product ***rac*-41** as the major regioisomer.[30] For nootropic drug sunifiram, electrolysis furnished a single regioisomeric product favoring oxidation of the more electron-rich amide (**48**). Results from examples ***rac*-44**, ***rac*-45** and **48** highlight the site selectivity of the modified Shono oxidation, effectively controlling the location of C–H methylation based on the inherent electronic and steric environment of the substrate. Finally, acyclic sulfonamides also proved suitable substrates as shown in the synthesis of methylated product **49**.

Methylation of compounds with basic *N*-containing groups

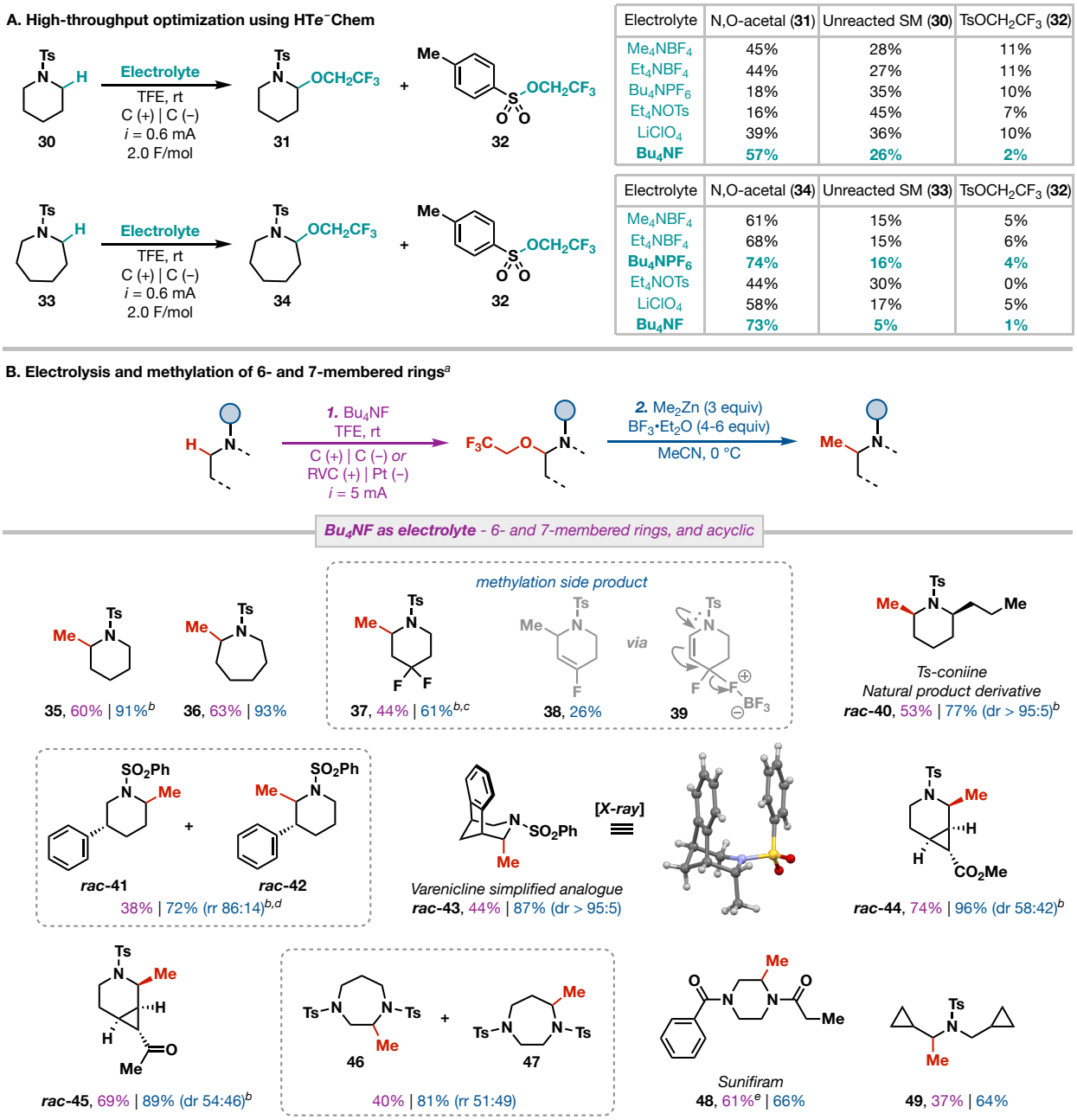
Basic *N*-containing groups are prevalent in biologically and medicinally active compounds. In particular, amines and *N*-heteroarenes are among the most common motifs present in top-selling pharmaceuticals.[31] Thus, a critical criterion for a C–H methylation reaction is its amenability to the LSF of structurally and functionally complex targets with such basic *N*-containing groups. However, the sensitivity of these functionalities to oxidation poses a key challenge for their compatibility with our electrolysis conditions.

Our investigation began with proline 3-picolyl ester **50** as the model substrate (**Scheme 4A**). Upon electrolysis of **50** under traditional Shono oxidation conditions with methanol as the solvent, no product was obtained. The unsuccessful generation of the *N*,*O*-acetal was attributed to the unproductive anodic oxidation of the pyridine, likely to a radical cation. Changing to TFE, however, provided **52** in 42% yield albeit requiring a large excess of charge (10 F/mol) with substantial side product formation. To address this challenge, we envisioned a simple solution in which the addition of a Brønsted acid could serve to transiently protect any basic nitrogens,[32] thereby allowing the Shono oxidation to occur selectively. We anticipate that upon protonation, **50** will become more resistant to anodic oxidation, but that the modified Shono conditions using TFE would conveniently circumvent the potential issue of suppressed reactivity due to competing solvent oxidation.

Electrolysis of **50** with five different Brønsted acids showed that the use of a weak acid (HOAc) led to no product formation, whereas *N*,*O*-acetal **52** was obtained in the

presence of a strong acid such as TFA, H_2SO_4, MsOH, and TfOH. The conditions employing TFA in TFE proved to be the most promising, giving desired product in 64% yield on 0.2 mmol scale and 76% yield on 1 mmol scale. With acids stronger than TFA, anode degradation was apparent likely due to competing graphite oxidation (see SI). As anticipated, reactions in MeOH provided substantially lower yield even in the presence of a Brønsted acid. Product **51** was only observed when TFA was employed. Nevertheless, shorter reaction time (5 F/mol) gave incomplete conversion whereas increased reaction time (12 F/mol) led to acid-promoted transesterification (**SP**). Importantly, the reaction under modified optimal conditions using TFA/TFE was readily scalable using ElectraSyn 2.0 with the desired *N,O*-acetal **52** isolated in 70% yield on gram scale.

Scheme 3. Optimization and Scope for the C(sp³)–H Methylation of 6- and 7-membered Nitrogenated Rings



Electrolyte	N,O-acetal (**31**)	Unreacted SM (**30**)	$TsOCH_2CF_3$ (**32**)
Me_4NBF_4	45%	28%	11%
Et_4NBF_4	44%	27%	11%
Bu_4NPF_6	18%	35%	10%
Et_4NOTs	16%	45%	7%
$LiClO_4$	39%	36%	10%
Bu_4NF	**57%**	**26%**	**2%**

Electrolyte	N,O-acetal (**34**)	Unreacted SM (**33**)	$TsOCH_2CF_3$ (**32**)
Me_4NBF_4	61%	15%	5%
Et_4NBF_4	68%	15%	6%
Bu_4NPF_6	**74%**	**16%**	**4%**
Et_4NOTs	44%	30%	0%
$LiClO_4$	58%	17%	5%
Bu_4NF	**73%**	**5%**	**1%**

[a]Electrochemical oxidation yields are shown in purple, the concentration for this step ranged from 0.1-0.25 M, while methylation yields and dr (or rr) are shown in blue, the concentration for this step ranged from 0.07-0.1 M; all products with relative stereochemistry shown and without the descriptor *rac* are enantioenriched, [b]Methylation at –20 °C, [c]Methylation in CH_2Cl_2 in lieu of MeCN, [d]The relative configuration of the new methyl group could not be assigned unambiguously at this moment, [e]Electrolysis was carried out in MeOH, Et_4NBF_4

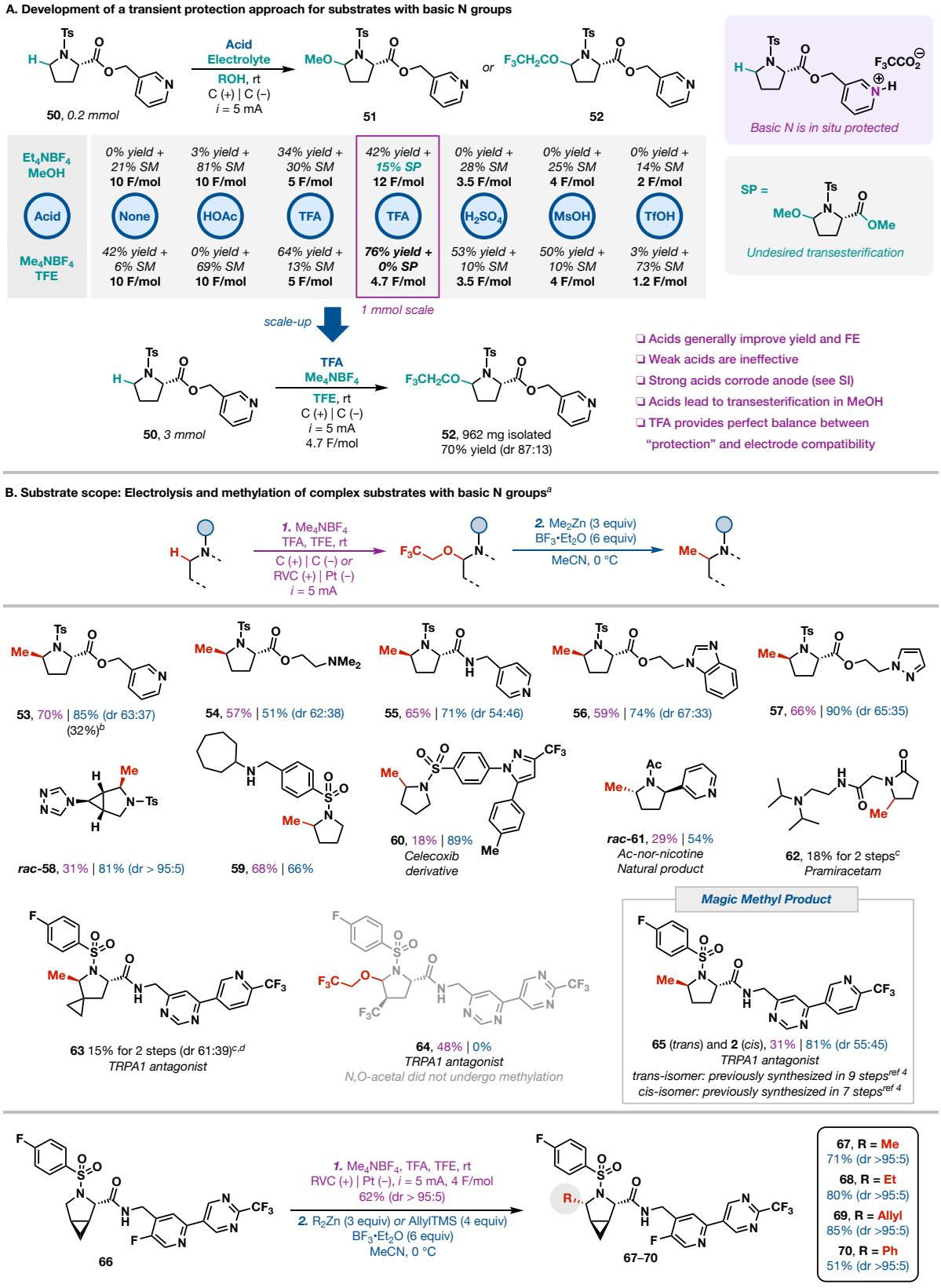
With this strategy, an additional scope of substrates containing basic nitrogens was explored (**Scheme 4B**). Efficient conversion to *N,O*-acetal intermediates was achieved in the presence of TFA. The basic nitrogen

moieties also proved challenging for the subsequent methylation step presumably due to inhibition of the Lewis acid BF_3. This issue was readily addressed by increasing the loading of BF_3•Et_2O and modifying workup procedure to cleave the N–BF_3 bond. This new set of conditions were successfully applied to a diverse suite of substrates containing pyridine (**53**, **55**), benzimidazole (**56**), pyrazole (**57**), 1,2,4-triazole (**58**), secondary and tertiary amine (**59**, **54**) groups. Importantly, medicinal compounds and natural products including celecoxib derivative **60**, acetyl-nor-nicotine **61**, and nootropic drug pramiracetam **62** proved suitable substrates for the C(sp^3)–H methylation protocol.

In an effort to apply this methylation strategy to complex drug-like molecules, a series of pre-clinical TRPA1 antagonist sulfonamides were evaluated. Thus, methylated compounds **63**, **65** and **2** were readily synthesized upon electrolysis and nucleophilic alkylation, the stereoretention of the center alpha to carbonyl was confirmed by HPLC for compounds **65** and **2** (see SI for details). When a CF_3 substituted analog was used as substrate, compound **64** was isolated in 48% yield but failed to undergo subsequent methylation under various conditions. We attribute this issue to the electron-withdrawing effect of CF_3 that disfavors the iminium ion generation (see DFT data support in the SI). Despite challenges in methylating *N*,*O*-acetal **64**, this result nonetheless highlights the power of the modified Shono oxidation conditions, which allowed the activation of a highly inert substrate, generating an iminium ion that is elusive even under strong Lewis acid activation.

Both diastereomers of compound **65** were previously evaluated by Genentech for TRPA1 antagonist activity.[4] While the *trans* isomer displayed reduced potency (IC_{50} 239 nM *vs.* 154 nM), the *cis* isomer presented a considerable >10-fold boost in potency (13 nM *vs.* 154 nM), compared to the non-methylated derivative. Formerly, both diastereomers were synthesized using *de novo* routes, requiring a total of 7 and 9 steps for the *cis*- and *trans*-isomers, respectively. In comparison, our method allows for direct late-stage functionalization of parent inhibitor **1** to yield both diastereomers in a single sequence of operation, thus providing a means to markedly accelerate the exploration of the "magic methyl" effect in drug discovery.

Scheme 4. C(sp^3)–H Methylation for Substrates with Basic Nitrogen



Electrochemical oxidation yields are shown in purple, the concentration for this step ranged from 0.015-0.25 M, while methylation yields and dr are shown in blue, the concentration for this step ranged from 0.007-0.1 M; all products with relative stereochemistry shown and without the descriptor *rac* are enantioenriched, [b]Yield from an unoptimized tandem procedure wherein the crude *N,O*-acetal was subjected to methylation without column purification, [c]Partially purified *N,O*-acetal was used in the second step, [d]See SI for details.

Finally, we expanded the methylation strategy further to other alkylation and arylation reactions to enable rapid analog synthesis that is typically desirable in a medicinal chemistry context. From parent compound **66**, the *N,O*-acetal obtained from electrolysis was subjected to different organozinc reagents (**67**–**70**). Commercially available

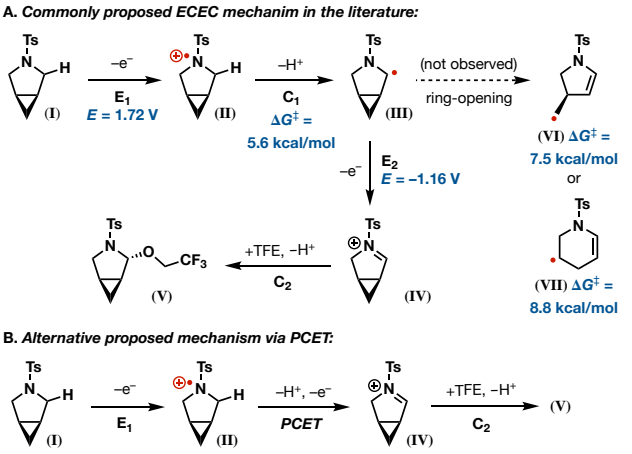
Me_2Zn and Et_2Zn furnished clean reactions, providing 71% and 80% yield, respectively. Installation of a phenyl group was carried out with Ph_2Zn prepared from the corresponding Grignard reagents with $Zn(OMe)_2$.[33] Additionally, allyl derivative **69** was obtained in 85% yield using allyltrimethylsilane. All derivatives **67-70** were obtained as a single diastereomer likely as a result of steric repulsion from the adjacent cyclopropane group. Thus, our LSF methodology circumvents the *de novo* multi-step syntheses that are currently necessary for the synthesis of such drug analogs.

MECHANISTIC INVESTIGATION

Despite being a classic electroorganic reaction, the mechanism for Shono oxidation remains a topic under debate. The most commonly acknowledged reaction path for Shono oxidation in the literature features a sequence of electrochemical-chemical-electrochemical-chemical (ECEC) events (**Scheme 5A**). Specifically, an initial $1e^-$ oxidation of the protected amine **I** generates the corresponding radical cation **II** (Step E_1), which then undergoes deprotonation at the α-position to form the C-centered radical **III** (Step C_1). A second $1e^-$ oxidation generates the iminium ion **IV** (Step E_2), which is subsequently trapped by reaction with the alcohol solvent to complete the *N*,*O*-acetal **V** formation (Step C_2). This mechanism, however, is inconsistent with our reaction results with cyclopropane-substituted substrates (e.g., **15**, ***rac*-22**, ***rac*-24**, ***rac*-44**, ***rac*-45**, **49**, ***rac*-58**, **67-70**). Specifically, radical-triggered ring-opening of cyclopropanes have been measured to be very facile due to the release of ring strain (activation energy of about 5–8 kcal/mol depending on the structure).[26] Nevertheless, no ring-opening alkene products were observed with these substrates. These findings led us to propose a revised reaction mechanism involving a hydrogen atom transfer (HAT) or concerted proton-coupled electron transfer (PCET) from radical cation **II** to directly generate the iminium ion **IV**, circumventing the intermediacy of radical **III**.

First-principles DFT calculations were carried out to evaluate this mechanistic proposal. The oxidation potentials, activation free energies, and reaction energies for specific elementary steps along with method details are reported in sections 13-16 of the SI. The reaction proceeds via the anodic oxidation of **I** to form the radical cation **II**, which is calculated to occur at $E°$ = 1.72 V *vs.* Fc^+/Fc^0. Hydrogen is subsequently removed either by PCET or via HAT. The radical cation can carry out proton transfer (PT) either to the TFE solvent or its conjugate anion. While PT to the anion is barrierless, the concentration of TFE anion is likely negligible. Instead, PT more likely proceeds via the TFE solvent. The free energy for TFE to deprotonate **II** is only 5.6 kcal/mol with an overall reaction energy of 3.7 kcal/mol. Notably, the second oxidation step to form **IV** is calculated to take place at $E°$ = −1.16 V *vs.* Fc^+/Fc^0, which is 2.88 V more negative than the potential required to oxidize **I** (i.e., the overpotential for the second oxidation is 2.88 V). Therefore, at an applied potential that is sufficient to oxidize **I**, Step E_2 should proceed spontaneously without barrier for electron transfer (ET), in accordance with Marcus theory (as reported in section 15 of SI). These results suggest that the C_1 and E_2 steps most likely take place in a concerted fashion (i.e., a PCET mechanism, **Scheme 5B**). This analysis further explains the lack of observation of cyclopropane ring-opening, which displays a calculated free energy barrier of $\Delta G^‡$ = 7.5 kcal/mol to generate **VI** and $\Delta G^‡$ = 8.8 kcal/mol to generate **VII**. This barrier is estimated to be even lower for gem-dimethyl substituted cyclopropane (e.g., **15**). These pathways are thus unlikely to compete with barrierless Step E_2. Current data do not allow us to exclude the possibility of a stepwise PT-ET mechanism, although the combination of a weak base (TFE) and a strong oxidizing agent (2.88 V overpotential on the anode) does not favor this scenario.[34] If the stepwise mechanism is operative, the lifetime of the intermediate radical (**III**) must be very short that it cannot even be captured by some of the fastest radical clocks ($k > 10^9\ s^{-1}$).[26b]

Scheme 5. The Shono Oxidation Mechanism along with DFT-Calculated Reduction Potentials and Free Energy Barriers.



We also examined the hydrogen atom transfer (HAT) mechanism from **II** to form **IV**. Given the simple reaction conditions, we considered TFE as the most probable H-abstracting species. This pathway is excluded on both thermodynamic and kinetic grounds, as it has an unreasonably high activation energy barrier (> 200 kcal/mol) and overall Gibbs free energy change ($\Delta G_{reaction} \sim$ 200 kcal/mol). A detailed charge analysis shows that structure **II** and TFE have positive charges of 0.99 and 0.01, respectively, before the reaction and charges of 0.12 and 0.88 after, which indicates that in this step hydrogen does not transfer as a radical but instead as a proton.

CONCLUSIONS

In summary, we report a new synthetic strategy for the site-selective α-methylation of sulfonamides, amides, and carbamates by using a combination of electrochemically driven formal C–H activation and organozinc-mediated methylation. To enable the late-stage functionalization of complex bioactive molecules, we developed an anodic electrolysis protocol by modifying the classic Shono oxidation. Replacing the commonly used alcohol solvents/nucleophiles with TFE allowed for recalcitrant

substrates to be readily activated. This new system in combination with a transient protection strategy using TFA rendered unprotected amines and *N*-heterocycles compatible functional groups. Subsequent treatment of the resultant *N*,*O*-acetals with organozinc provided a diverse array of methylated products including previously reported "magic methyl" compounds that would otherwise require multistep *de novo* synthesis. With mild reaction conditions, simple experimental operation, and readily available reagents, this transformation will likely find broad use in both academic and industrial settings. In particular, the capability of selective and modular LSF of bioactive targets will rapidly accelerate drug discovery campaigns.

ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra, computational data (PDF)

NMR data (ZIP)

Crystallographic information file for compounds ***rac*-43** and ***cis*-SI-33** (CIF)

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Notes

The authors declare no competing financial interest.

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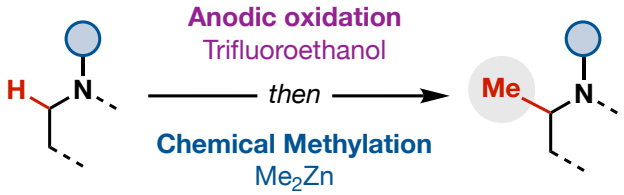
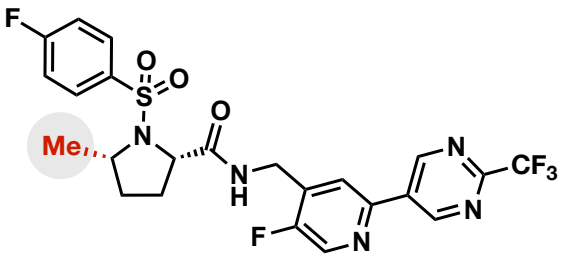


- *Simple operation: commercial vessels and reagents*
- *Broad scope: tolerates substrates with high E_{ox}*
- *Late-stage methylation: compatible with basic nitrogens*

Late Stage C(sp^3)–H methylation



TRPA1 antagonist (vs. 7 step de novo synthesis)

TOC graphic