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An Electrochemical Approach to Directed Fluorination

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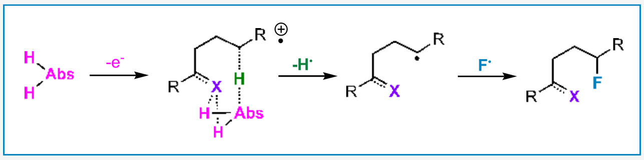
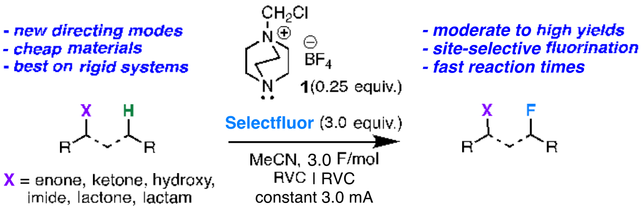
ABSTRACT: Electrosynthesis has made a revival in the field of organic chemistry and, in particular, radical-mediated reactions. Herein, we report a simple directed, electrochemical C−H fluorination method. Employing a dabconium mediator, commercially available Selectfluor, and RVC electrodes, we provide a range of steroid-based substrates with competent regioselective directing groups, including enones, ketones, and hydroxy groups, as well as never reported before lactams, imides, lactones, and esters.



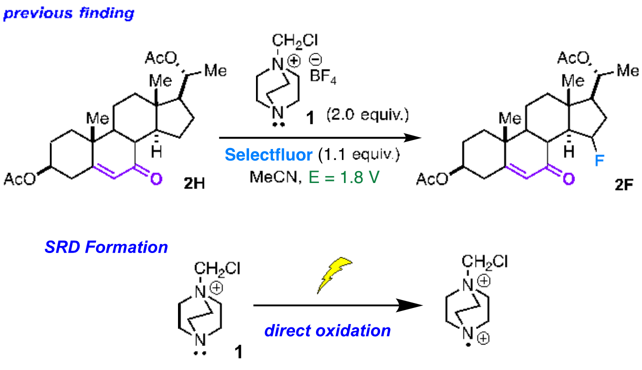
A resurgence of organic electrosynthesis has recently been observed after a long period of comparative stasis.[1] Recently, the drive for green, inexpensive methodology in conjunction with the emergence of novel radical/electron transfer-based reactions has permitted the field to blossom.[2] Nevertheless, relatively few methods have been developed to functionalize unactivated $C(sp^3)$-H bonds.[3] Notable advances in the development of electrochemical conditions[4] that serve as guiding precedents for C−H oxidation processes[5] have been made by Baran[6] and others.[7] Herein, we report electrochemical, directed fluorination[8] of unactivated sp^3 C−H bonds with ketones, enones, and show proof of concept that imides, lactams, lactones, hydroxy groups, and esters are exploitable as directing groups as well (Scheme 1).

Scheme 1. General Electrochemical Fluorination System



Our mechanistic investigation of carbonyl-directed fluorination led us to the discovery that a Selectfluor radical dication (SRD)[9] can act as a coordinated hydrogen atom abstraction agent (Scheme 2).[10] Consequently, we envisioned that electrolysis could directly access this reactive intermediate (SRD) by employing the amine salt compound 1, 1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate, as a promotor.[11] Ultimately, we found that using this amine, Selectfluor, and MeCN with RVC|RVC 1.8 V for 3 h successfully fluorinates at the predicted site.[12] This voltage was determined in previous work using cyclic voltammetry. Figure 1 demonstrates the observed peak oxidation values for

Scheme 2. Preliminary Mechanistic Probe



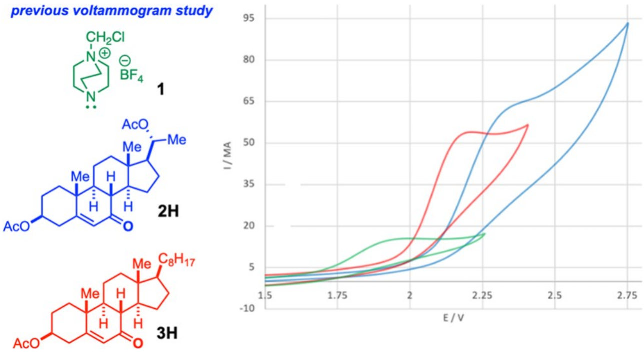


Figure 1. Cyclic voltammograms of starting materials of compounds 1, 2H, and 3H in dry and deoxygenated MeCN with 0.1 M $TBAPF_6$ and a potential sweep rate of 100 mV/s (vs Fc/Fc^+).

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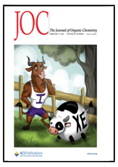

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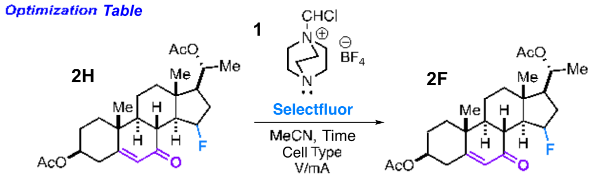
compounds 1, 2H, and 3H. As the scheme suggests, the ideal voltage to oxidize the amine while minimally affecting enones 2H and 3H directly is approximately 1.8 V. Another key observation is that increasing the voltage further saw little change in the yield. Additionally, direct oxidation of the enone in the absence of 1 (voltage at 2.3 V) results in roughly 10% yield of desired product, consistent with the importance of a significant initiating concentration of SRD. Finally, to demonstrate the importance of the amine, an experiment was run at 1.8 V with Selectfluor and compound 2H, which produced a yield of roughly 3%. This is significantly lower than the 48% observed when 1 is included, proving its key role in the electrochemical process.

Optimization (Table 1) of the electrochemical reaction resulted in our ultimate set of conditions: The reaction was electrolyzed at a constant current of 3 mA, total charge set at 3.0 F/mol, and an alternating polarity every 2 min for the full 3 h (S2). Our finalized reaction conditions addressed multiple matters of concern for eficiency and scalability: (1) we found no need for electrolytes; (2) only substoichiometric quantities of mediator amine were necessary; and (3) a shorter reaction time compared to previous photochemical conditions was warranted, all of which resulted in minimal change to the yield.

Table 1. Optimization Table for Compound 2F



Cell Type	Amine (1) EQ's	Selectfluor EQ's	nBu_4PF_6 Con.	V/mA	Time (min)	Yield
Divided	4.0	4.0	0.1M	1.8V	90	38%
Divided	4.0	4.0	0.1M	1.8V	180	50%
Divided	4.0	4.0	0.1M	2.2V	45	33%
Divided	4.0	4.0	0.1M	2.2V	90	50%
Divided	4.0	4.0	0.1M	2.2V	180	53%
Undivided	0.5	3.0	0	3mA	180	46%
Undivided	4.0	4.0	0	3mA	180	46%
Undivided	0.25	3.0	0	3mA	180	48%

Initially, our aim in substrate selection was to confirm that the carbonyl directing system was compatible with electrochemical initiation.[10] Thus, we employed several compounds that were previously synthesized photochemically. We report ^1H NMR data for these compounds to prove matching spectral data as well as a purity confirmation for the electrochemical conditions. Additionally, it should be noted that no other major fluorine regioisomers were observed. Accordingly, glycyrrhetinic and oleanolic acid derivatives 4H and 7H were chosen, whose biological relevance ranges from potential anti-inflammatory[13] to anti-HIV[14] and even anticancer[15] properties. Both provide a comparable yield to the photochemical system in 1/3 the reaction time; longer reaction times did not push conversion forward. Additionally, enones 2H, 3H, 5H, and 6H gave product yields of 48%, 60%, 49%, and 87%, while also demonstrating a degree of functional group tolerance on the A and D rings of the steroids, given the presence of chloro groups, ketones, and ethers.

We turned toward ketones to expand the breadth of electrolysis beyond the enone-directed work. Compound 9 was chosen as a prototypical candidate for electrochemical fluorination conditions. The C6 steroidal carbonyl selectively targets the C4 position in 60% yield, comparable to the previously reported photochemical conditions. Moreover, ketones 8H and 10H successfully provide the predicted fluorinated congeners in 40% and 89% yields. These steroids give a good insight into the abilities of ketone-directed fluorination as each compound directs fluorination to distinct areas on the steroid, thus demonstrating a novel way to fluorinate[16] these potential bioactive sites in relatively good yields.[17]

Furthermore, we offer preliminary data for heretofore unexplored imides[18] and lactams[19] operating as competent directing groups in at least a few cases. In the past, we have had little success exploring these carbonyl derivatives for various reasons, including their recalcitrance in our hands to undergo a smooth reaction under photochemical conditions. The precursor to imide product 12H, a D-homosteroid, was synthesized by a Beckmann rearrangement with a C16 oxime moiety. We predicted fluorination directedto the C12 position, as observed (41%).[20] This imide-based synthetic intermediate has been employed in structure–activity relationships studies of D-ring azasteroid modulators of $GABA_A$ receptors.[21]

X-ray crystallography aided the regiochemical assignment (Figure 2), revealing the alpha C12 fluoride 12F as the major product. The importance of this result is notable given the inherent bioactivity of imide-based natural products.[22] The ability to direct fluorination on an already bioactive molecule can have considerable potential in the field of medicinal chemistry.[23]

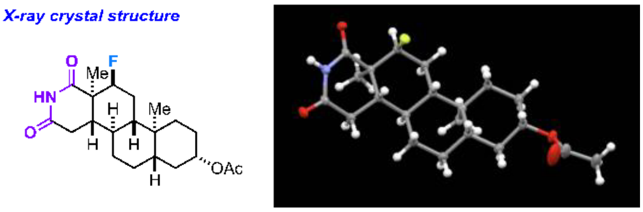


Figure 2. Crystal structure of compound 12F.

Next, we chose to examine a lactam-based candidate. Molecule 13H was synthesized by treating *trans*-androsterone with azidopropanol and boron trifluoride etherate, followed by acetylation of the resultant intermediate to afford the product. On the other hand, this D-ring expanded lactam provides the predicted fluorinated product 13F in only a modest 26%, although this provides a significant improvement over attempted photochemical conditions. Lactams, just like imides, are commonly found in natural products that possess biological capabilities.[24]

Our next objective was to demonstrate that lactones[28] and esters are also compatible. We began our endeavor by acetylating testosterone[29] (compound 16H), an important sex hormone and anabolic steroid, to provide the exocyclic C17 acetate targeting the C12 and C16 positions (combined 31%). We were able to successfully collect the primary regioisomer (C16) in this case, which had a yield of 23%. The successful functionalization of a well-known drug like testosterone could affect hormone therapy treatments.[30] Lactone 15H was found to be an excellent parallel to lactam

13H, affording product in 62%. Additionally, as we finished exploring photochemical hydroxy-directed fluorination, we tested alcohol 14H in our electrochemistry setup.[31] The 51% yield obtained is comparable with that of the photochemical fluorination conditions and affords another potential route for further exploration of electrochemical fluorination (Figure 3).

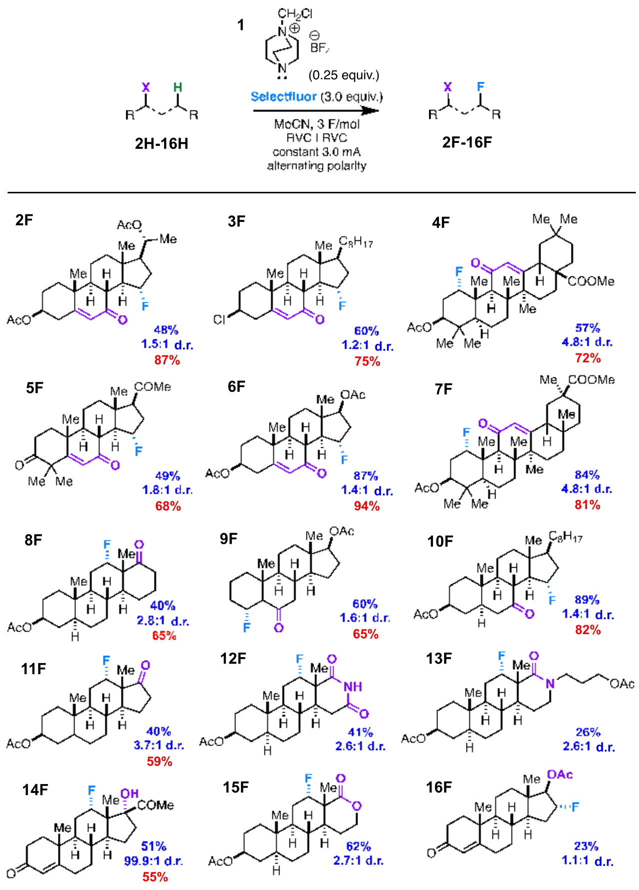


Figure 3. Fluorinated compounds (2F−16F); major diastereomer collected. Photochemical yields given in red where applicable.[25−27]

All in all, this note demonstrates the next advancement in electrochemically directed fluorination. Unlocking novel and scalable ways to perform these fluorinations have the potential to push the boundaries in several fields, particularly that of medicinal chemistry, given the number of bioactive molecules chosen for this study. Future studies will expand the capabilities of lactones, lactams, imides, alcohols, and esters through directed fluorination and explore novel functional groups.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01886.

General experimental information and procedures, starting material syntheses and characterization data, fluorinated product syntheses and characterization data, NMR spectral data, and mass spectral data (PDF)

Accession Codes

CCDC 2195614 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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