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# New development in electrochemistry - Toward new methods for the functionalization of electron-rich olefins

Shinan Luan

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Normandie Université

# THÈSE

Pour obtenir le diplôme de doctorat

Spécialité **CHIMIE**

Préparée au sein de l'**INSA Rouen Normandie**

**New development in Electrochemistry - Toward new methods  
for the functionalization of electron-rich olefins**

Présentée et soutenue par  
**SHINAN LUAN**

**Thèse soutenue le 15/12/2023**  
devant le jury composé de :

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Thèse dirigée par **THOMAS POISSON** (CHIMIE ORGANIQUE, BIOORGANIQUE, REACTIVITE, ANALYSE)



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Finally, I would like to thank the China Scholarship Council (CSC) for the financial support.





# List of abbreviations

## A

**Ac:** Acetyl

**Ar:** Aromatic

**ATRA:** atom transfer radical addition

## B

**Bn:** Benzyl

**Bu:** Butyl

**Boc:** tert-butoxycarbonyl

**BHT:** 3,5-Di-tert-4-butylhydroxytoluene

**BDFAP:** bis(difluoroacetyl) peroxide

## C

**CFL:** compact fluorescent lamp

**CV:** Cyclic Voltammetry

**CPA:** chiral phosphoric acid

## D

**DAST:** diethylaminosulfur trifluoride

**DBU:** 1,8-diazabicyclo[5.4.0]undec-7-ene

**Deoxo-Fluor:**

bis(methoxyethyl)aminosulfur trifluoride

**DFMS:** Zinc difluoromethanesulfinate  
[Zn(SO<sub>2</sub>CF<sub>2</sub>H)<sub>2</sub>]

**DFAA:** difluoroacetic anhydride

**DFT:** Density Functional Theory

**DLP:** dilauroyl peroxide

**DMA:** *N,N*-Dimethylacetamide

**DMF:** *N,N*-Dimethylformamide

**DMSO:** Dimethyl sulfoxide

**DMAP:** 4-Dimethylaminopyridine

**d.r.:** diastereomeric ratio

## E

**Et:** ethyl

**Equiv:** equivalent

**Et<sub>3</sub>N:** Triethylamine

**EWG:** electron-withdrawing group

## F

**Fluolead:** 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride

**FG:** Functional group

## H

**HRMS** High Resolution Mass Spectroscopy

## L

**LED:** Light Emitting Diode

## M

**Me:** methyl

**MeCN:** Acetonitrile

## N

**NMP:** *N*-methyl-2-pyrrolidone

**NMR:** Nuclear Magnetic Resonance

**Nu:** Nucleophile

## P

**Ph:** phenyl

**PDFA:** Difluoromethylene

phosphobetaine ( $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ )

**PIDA:** phenyliodine(III) diacetate

**PET:** positron emission tomography

## Q

**QRE:** quasi-reference electrode

## R

**RVC:** reticulated vitreous carbon

**r.t.** Room Temperature

## S

**SET:** Single-electron transfer

**SCE:** Saturated calomel electrode

**SPECT:** single photon emission

computed tomography

**SHE:** standard hydrogen electrode

## T

**TBAF:** Tetrabutylammonium fluoride

**TMS:** Trimethylsilane

**TTMS:** Tris(trimethylsilyl)silane

**THF:** Tetrahydrofuran

**TEMPO:** 2,2,6,6-Tetramethylpiperidine

1-oxyl

**tBu:** tert-Butyl substituent

## X

**XAT:** halogen atom transfer

**XtalFluor-M:** Difluoro-4-

morpholinylsulfonium tetrafluoroborate

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# **Chapter 1**

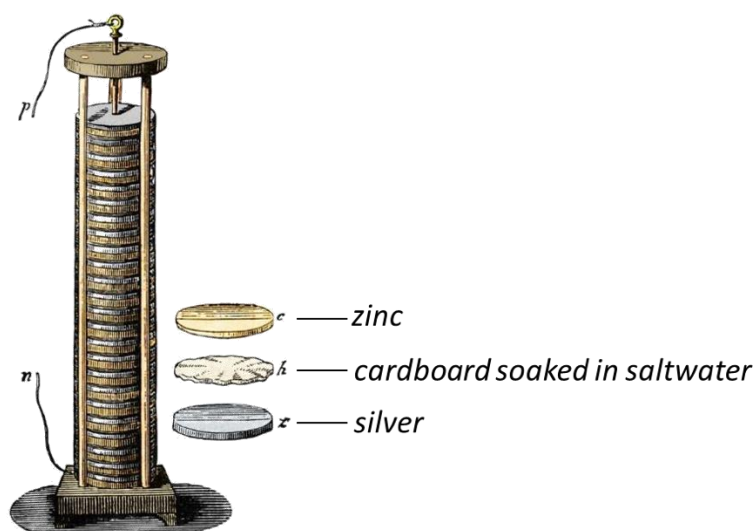
## General introduction



# 1. General introduction

## 1.1 Historical development

The beginnings of electrochemistry can be dated back to 1800 when the physicist Alessandro Volta invented the first electric battery allowing a continuous movement of electrons in a circuit.<sup>1,2</sup> This arrangement is depicted in **Figure 1**, where a vertical stack comprises a sequence of a zinc disc, a silver disc and a piece of cardboard soaked in saltwater. When a person touches the extremities of the zinc and the silver plates of this column, they effectively become conductors and will experience a shock. The intensity of this shock increases as more discs are added. Volta referred to this apparatus as a "pile" (he never used the term "battery"), and this invention marked the birth of electrochemistry.



**Figure 1.** Voltaic Pile.<sup>3</sup>

However, it took nearly a century before the correct chemical interpretation of the pile and of electrolysis was achieved. The operating mechanism of Volta's pile was not fully explained until the work of Walther Nernst in 1889,<sup>4</sup> in which he established a fundamental connection between thermodynamics and electrochemical solution

<sup>1</sup> Volta, A. *Phil. Trans. R. Soc. Lond.* **1800**, *90*, 403-431.

<sup>2</sup> Fabbrizzi, L. *Angew. Chem. Int. Ed.* **2019**, *58*, 5810-5822.

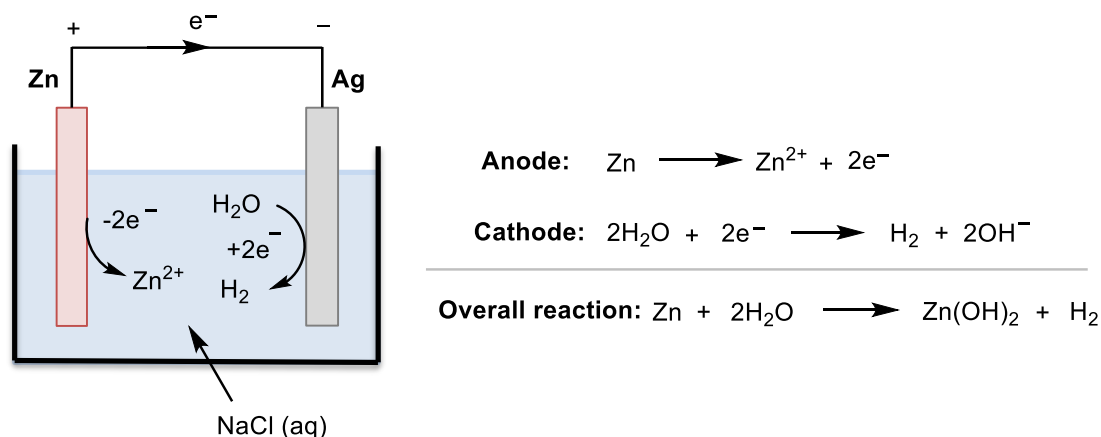
<sup>3</sup> Voltaic Pile. <https://www.sciencephoto.com/media/363826/view/early-electric-battery-1850> (accessed Oct 15, 2023).

<sup>4</sup> Nernst, W. *Zeitschrift für Physikalische Chemie* **1889**, *4U*, 129-181.



theory (the Nernst equation).

We now have a clear understanding of how this battery works: Electrons flow from the zinc electrode to the silver electrode, driven by the occurrence of the two half-reactions illustrated in the **Figure 2**. The zinc electrode acts as the sacrificial anode, releasing  $\text{Zn}^{2+}$  ions, while  $\text{H}_2$  is generated at the silver cathode.



**Figure 2.** Schematic representation of the unit cell of Voltaic pile.

Volta did not realize the crucial significance of the chemical reactions occurring at the electrodes for the function of the battery. It was not until the 1830s, with Faraday's pioneering work on the electrolysis of an acetate solution to form hydrocarbons, that the use of current to drive non-spontaneous organic transformation showcased some interest (**Scheme 1**, eq. a).<sup>5</sup> His systematic studies helped him to establish the fundamental principles of electrochemistry. Faraday discovered that it was actually the electrochemical potential that drives the movement of ions in the solution, leading to the contemporary use of ionic salts as electrolytes in a cell to enhance the conductivity of organic systems. Nowadays, it is well-understood that the organic product generated from Faraday's electrolysis is ethane. However, at that time, Faraday was unable to identify it. The electrolysis of acetate solution represents the first electro-organic reaction.

Later in 1847, inspired by Faraday's work, Kolbe developed the electrochemical oxidative decarboxylation of carboxylic acid, leading to the release of carbon dioxide and the generation of alkyl radicals, which could then dimerize into alkanes (**Scheme 1**, eq. b).<sup>6</sup> This pioneer work is nowadays recognized as the birth of the organic electrosynthesis.

In 1845, Schoenbein discovered the electrochemical dehalogenation reaction of trichloromethyl sulfonic acid, which appears to be the first cathodic reduction of an

<sup>5</sup> Faraday, M. *Ann. Phys. Leipzig* **1834**, 47, 438.

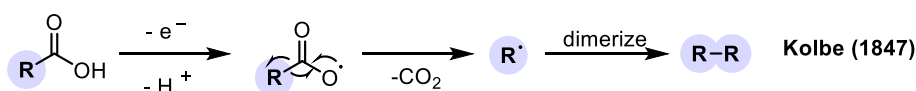
<sup>6</sup> Kolbe, H. J. *Prakt. Chem.* **1847**, 41, 138.

organic chemical in the field of electrochemistry (**Scheme 1**, eq. c),<sup>7,8,9</sup> while the Tafel rearrangement, a well-known cathodic reduction, was developed in 1907 to enable the preparation of hydrocarbons (**Scheme 1**, eq. d).<sup>10</sup>

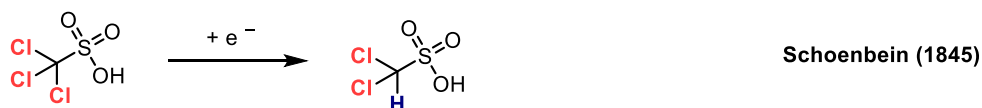
a) Electrolysis of acetate solution



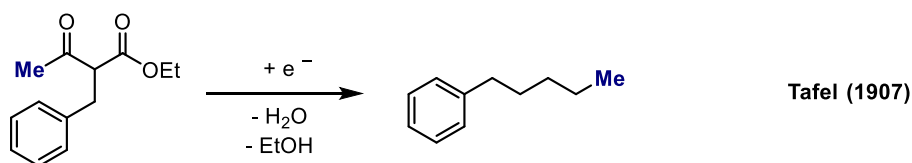
b) Anodic decarboxylation of carboxylic acid



c) Cathodic dehalogenation of trichloromethyl sulfonic acid



d) Tafel rearrangement



**Scheme 1.** The Early Development of Electro-organic Chemistry.

These initial reports sparked considerable interest in electrochemistry throughout the 20th century, leading to the emergence of industrial applications of organic electrochemistry.<sup>8</sup> For instance, we can cite the Simons fluorination reaction<sup>11</sup> and the Monsanto adiponitrile process.<sup>12</sup> These examples demonstrated the inherent ability of scalability of electrosynthesis.

Since then, organic synthetic chemists started to realize the significant potential of this innovative synthetic tool and the future trend in the development of organic synthesis, led to the establishment of the field of electroorganic synthesis.

<sup>7</sup> Schoenbein, C. F. *Liebigs Ann. Chem.* **1845**, 54, 164.

<sup>8</sup> Lund, H. J. *Electrochem. Soc.* **2002**, 149.

<sup>9</sup> Qian, L.; Shi, M.; Qian, L. *Chem. Commun. (Cambridge, U. K.)* **2023**, 59, 3487-3506.

<sup>10</sup> Tafel, J.; Hahl, H. *Berichte der deutschen chemischen Gesellschaft* **1907**, 40, 3312-3318.

<sup>11</sup> Simons, J. J. *Electrochem. Soc.* **1949**, 95, 47.

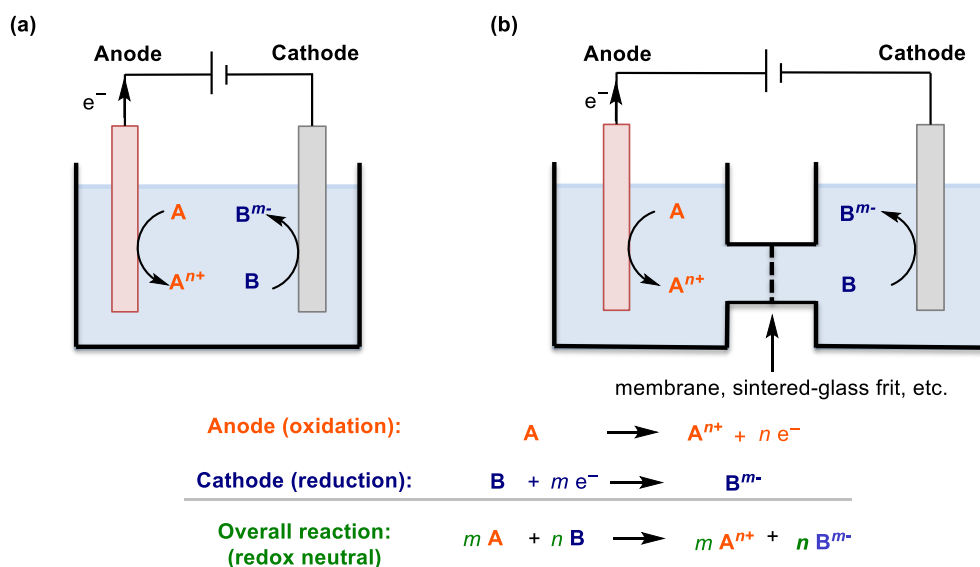
<sup>12</sup> Baizer, M. M. *J. Electrochem. Soc.* **1964**, 111, 215.

## 1.2 Fundamentals of electrosynthesis

### 1.2.1 Cell Design – Undivided cell & Divided cell

A basic electrochemical reaction device requires a power supply connected to an anode electrode and a cathode electrode, which are immersed in an electrolyte solution to form a closed-loop pathway. Mechanistically, electrochemical reactions occur by applying a potential across the electrodes, leading molecules to gain or lose electrons at the electrode, resulting in the corresponding oxidation reaction at the anode or the reduction reaction at the cathode. In general, only one of the two electrodes, known as the working electrode, generates a valuable product, while the counter electrode is involved in an unproductive reaction (with paired electrolysis being an exception). Charge conservation in a solution suggests that the rates of electron transfer at the interfaces of the anode and cathode must be equal, resulting in a balanced and redox neutral reaction (**Figure 3**).

In the simplest setup, working and counter electrodes are contained within the same chamber, which is referred to as an undivided cell (**Figure 3a**). The advantages of undivided cells include their simplicity and ease of use. However, the lack of separation between the electrodes can limit control over the specific reactions occurring at each electrode. In certain reactions, where the starting material, an intermediate, or the product is susceptible to undergo undesired reactions at the opposite electrode, leading to unwanted byproducts. Such side reactions reduce the selectivity in some cases, thus hampering the overall efficiency of the synthesis process.



**Figure 3.** Schematic Representation of an Electrolysis in Undivided cell & Divided cell.

In this case, the separation of the two half-reactions (oxidation at the anode and reduction at the cathode) may be needed, which can be accomplished by using a divided cell (**Figure 3b**). In order to maintain conservation of charge in solution, a salt bridge can be used to interface the two chambers. Or more commonly, a separator, such as a sintered-glass frit, porous ceramic, porous polymer sheet, or semipermeable ion-selective membrane, are used to directly interface the solutions.<sup>13</sup> The work of Maigrot and Sabates in 1889 represents an early example of divided cell.<sup>14,15</sup>

This design offers the advantage of a precise control over the reactions occurring at each electrode, minimizing cross-contamination and allowing for higher selectivity. Divided cells are especially useful when dealing with sensitive or highly reactive species, as they prevent undesirable side reactions. However, due to the presence of separative membranes and inherently higher resistance, such setups are often more complex. Therefore, undivided cells are the preferred choice for most applications.

## 1.2.2 Modes of Operation – Galvanostatic Electrolysis & Potentiostatic Electrolysis

In an electrosynthesis reaction, the external power source can take various forms, typically in the form of constant current (galvanostatic conditions) or constant potential (potentiostatic conditions) conducted with galvanostats or potentiostats, respectively. In the modern time, commercial power sources used for electrosynthesis can operate in both electrolysis modes and are commonly named as potentiostats.

In the 19th century, electrosynthesis exclusively relied on galvanostatic conditions (constant current).<sup>16</sup> This type of electrolysis is the easiest to setup and only two electrodes (anode and cathode) are needed. In a galvanostatic electrolysis, the potential is not controlled so that the substance with the lowest redox potential will be transformed first. As the reaction progresses, the cell potential ( $U_{cell}$ ) increases due to the gradual decrease in the concentration of the starting materials (species able to undergo the more facile redox events). Then, the galvanostat will increase the applied voltage to maintain a constant current. This allows for the transformation of the material with the second lowest redox potential. If this is the desired product, over-electrolysis may inevitably lead to the formation of side products. If the redox potential of the solvent or other components (such as additives) is lower than that of the product, further electrolysis can occur, leading to undesired side reactions as well as the generation of additional products that need to be separated during work-up

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<sup>13</sup> Tay, N. E. S.; Lehnerr, D.; Rovis, T. *Chem. Rev.* **2021**, *122*, 2487-2649.

<sup>14</sup> Maigrot, E.; Sabates, J. *German Patent* **1890**, 50443.

<sup>15</sup> Paidar, M.; Fateev, V.; Bouzek, K. *Electrochim. Acta* **2016**, *209*, 737-756.

<sup>16</sup> Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230-13319.

process.<sup>17</sup> To circumvent these problems, potentiostatic conditions can be employed (*vide infra*).

When a galvanostatic electrolysis is performed, the exact stoichiometry of electrons is known. The total charge (Q) transferred into the reaction is calculated from the current (I) over time (t). The total charge required for the reaction can be calculated from the number of electrons per substrate (z), the number of moles (N) and the Faraday constant.

$$Q = I \cdot t$$

$$Q = z \cdot N \cdot F$$

For a specific current the time for the required charge to pass into the reaction can be calculated:

$$t = \frac{z \cdot N \cdot F}{I}$$

where F = Faraday constant = 96,485 coulombs/mol, I = applied current (A) and T = time duration of the reaction (s). The time calculated is the time required for one electron equivalent, (equiv., often referred to as 1 F or 1 F·mol<sup>-1</sup>), and can be extended to achieve higher electron equivalents if needed.<sup>18</sup>

In 1942, the invention of the potentiostat by Hickling opened a new dimension in electrosynthesis, allowing reactions to be conducted under constant potential, with the current decreases over time.<sup>19,20</sup>

The development of electrochemical analysis techniques, such as cyclic voltammetry, enabled the accurate measurement of the redox potential of the starting material and products. In the presence of a reference electrode (commonly Ag/Ag<sup>+</sup> or saturated calomel electrode) the potential required for the desired transformation can be directly set on the potentiostat. This precise control over the potential in the reaction mixture enables a highly selective process, preventing the formation of undesired side products in the presence of multiple possible redox events.<sup>16</sup> Despite the many advantages of constant potential electrolysis, the use of galvanostatic setups still holds strategic significance due to their operational simplicity.

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<sup>17</sup> Hilt, G. *ChemElectroChem* **2019**, *7*, 395-405.

<sup>18</sup> Schotten, C.; Nicholls, T. P.; Bourne, R. A.; Kapur, N.; Nguyen, B. N.; Willans, C. E. *Green Chem.* **2020**, *22*, 3358-3375.

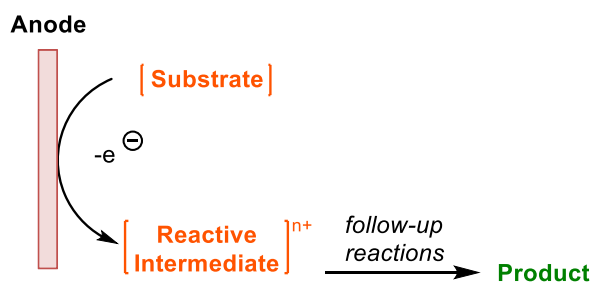
<sup>19</sup> Hickling, A.; Hickling, A. *Trans. Faraday Soc.* **1942**, *38*, 27-33.

<sup>20</sup> Lingane, J. J.; Swain, C. G.; Fields, M. J. *Am. Chem. Soc.* **1943**, *65*, 1348-1353.

### 1.2.3 Electron Transfer – Direct electrolysis & Mediated electrolysis

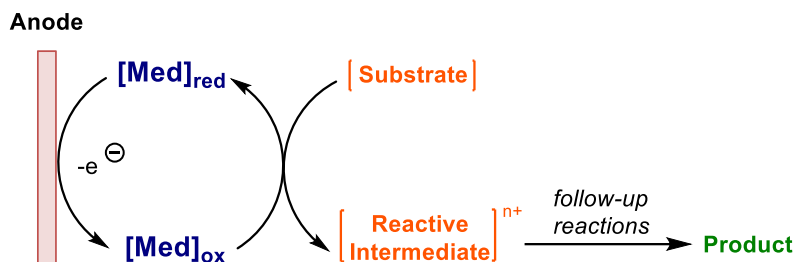
Electrosynthesis involves electron transfer between electrode and molecules (substrate or mediator), followed by the subsequent reaction to achieve the desired product. The reaction can be categorized into direct electrolysis or mediated (indirect) electrolysis based on whether electron transfer takes place directly between the substrate and the electrode.

In direct electrolysis, the substrate is either oxidized by losing electrons at the anode or reduced by gaining electrons at the cathode, which is a heterogeneous process, generating highly reactive intermediates. These intermediates then proceed to subsequent reaction to obtain the desired products (**Scheme 2**). Sometimes, direct electrolysis of a substrate can be challenging due to the high kinetic barrier caused by the heterogeneous electron transfer process. Another issue could be that organic species accumulate near the electrode surface and reduce the conductivity. And in some cases, the decomposition of these species can trigger electrode passivation, hindering the further reactions.<sup>16,17</sup>



**Scheme 2.** Direct electrolysis.

In these cases, the mediated (indirect) electrolysis can be helpful, where a redox mediator (stoichiometric or catalytic) with a lower redox potential than the substrates is employed to indirectly transfer electrons between the substrate and the electrode. The redox mediator undergoes an electron transfer through anodic oxidation or cathodic reduction, resulting in the formation of an active redox mediator. This active mediator subsequently undergoes electron transfer with the substrate, triggering the reaction of interest. (**Scheme 3**).



**Scheme 3.** Mediated (indirect) electrolysis.

Compared to direct electrosynthesis, mediated electrosynthesis employs mediators to lower the overpotentials for substrate activation, enhance functional group compatibility and selectivity by avoiding potential side reactions, and increase reaction efficiency by shifting the heterogeneous electron transfer process to a homogeneous one.<sup>21,22,23,24</sup> The development of novel mediators and electrocatalysts that reduce the overpotential for electrosynthetic reactions is one of the most promising opportunities in organic electrochemistry.

## 1.3 Advances in Electrochemical Synthesis

### 1.3.1 Development of Standardized reactor

One of the biggest challenges for the field of synthetic organic electrochemistry was the lack of standardized equipment. Chemists often had to design and assemble their own setups before starting any electrochemical experiments. Numerous homemade electrochemical cells have appeared in literature (**Figure 4**).<sup>17,25,26,27</sup>

<sup>21</sup> Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492-2521.

<sup>22</sup> Wang, F.; Stahl, S. S. *Acc. Chem. Res.* **2020**, *53*, 561-574.

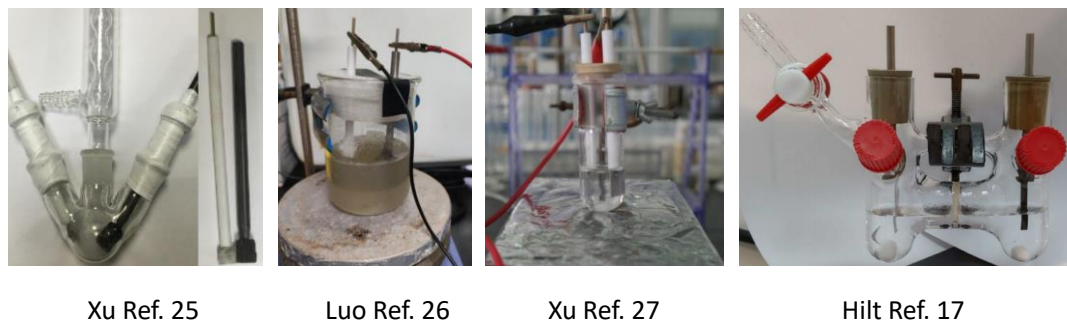
<sup>23</sup> Malapit, C. A.; Prater, M. B.; Cabrera-Pardo, J. R.; Li, M.; Pham, T. D.; McFadden, T. P.; Blank, S.; Minter, S. D. *Chem Rev* **2022**, *122*, 3180-3218.

<sup>24</sup> Nutting, J. E.; Gerken, J. B.; Stamoulis, A. G.; Bruns, D. L.; Stahl, S. S. *J. Org. Chem.* **2021**, *86*, 15875-15885.

<sup>25</sup> Xu, H. H.; Song, J.; Xu, H. C. *ChemSusChem* **2019**, *12*, 3060-3063.

<sup>26</sup> Zhang, F.; Zhao, X.; Zhang, J.; Zhao, L.; Li, L.; Yang, J.; Li, H.; Luo, H. *Adv. Synth. Catal.* **2022**, *364*, 4036-4042.

<sup>27</sup> Zhang, S.; Li, L.; Zhang, J.; Zhang, J.; Xue, M.; Xu, K. *Chem. Sci.* **2019**, *10*, 3181-3185.



**Figure 4.** Homemade electrochemical cells.

Apart from the inconveniences, the use of non-standardized setups introduced a multitude of variables, such as the electrode material, size and shape, position, and current density, significantly compromising the reproducibility of the experiments, which is one of the biggest challenges in electroorganic chemistry, hampering its widespread adoption.

Therefore, efforts have been made over the last few years to develop standardized reactors for laboratory-scale reaction screening and chemical synthesis. For instance, IKA collaborated with Baran's laboratory to develop the ElectraSyn 2.0 (**Figure 5**),<sup>28</sup> a commercially available device for synthetic electrochemistry.<sup>18,29</sup>



**Figure 5.** IKA ElectraSyn 2.0.

With the standardization of electrochemical synthesis equipment, electrochemistry has become widely adopted by synthetic chemists worldwide, enabling them to conduct electrochemical reactions in a more reliable manner.

### 1.3.2 Flow cells, continuous electrochemical synthesis

Electrochemical continuous-flow synthesis, often referred to as flow cells, represents

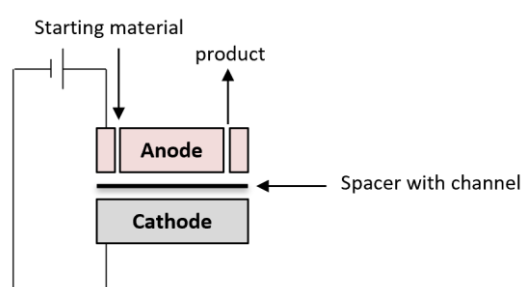
<sup>28</sup> IKA ElectraSyn 2.0. <https://www.ika.com/en/Products-LabEq/Electrochemistry-Kit-pg516/ElectraSyn-20-Package-20008980/> (accessed Oct 15, 2023).

<sup>29</sup> Yan, M.; Kawamata, Y.; Baran, P. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 4149-4155.



a specific application of continuous-flow synthesis where electrochemical reactions are continuous. This technology enables the continuous flow of the reactants and products within the reactor, offering a range of advantages over traditional batch methods:<sup>18,30,31,32</sup>

**Low resistance:** Typically, the two electrodes are separated by a thin spacer with flow channels. The interelectrode gap is equivalent to the thickness of the thin spacer (typically below 2 mm). This reduced gap size results in a low overall resistance, allowing reactions to be performed without or with lower concentration of electrolyte, thereby reducing waste production and simplifying the purification process. A schematic representation of flow cell is shown in **Figure 6**.



**Figure 6.** Schematic Representation of flow cell.

**High heat and mass transfer efficiency:** Given that electrochemical reactions are heterogeneous, the larger surface area-to-volume ratio will enhance energy transfer from the electrode to the solution as well as mass transfer at the solid/liquid interface. This effect leads to an increase in the reaction rate.

**High reproducibility:** The advantage of a continuous flow electrochemical reactor and its high reproducibility lies in its ability to provide consistent and controlled reaction conditions throughout the entire solution. In electrochemical batch reactors, the electric field is mostly homogeneous between the two electrodes. However, this uniformity does not extend to the majority of the reaction solution that is not located between the electrodes. This non-homogeneous electric field can lead to variations in local reaction conditions, potentially leading to underutilization of reactants and reduced efficiency. In contrast, continuous flow electrochemical reactors generate a homogeneous electric field throughout the entire solution as it is entirely situated between the electrodes. This results in more consistent and predictable reaction conditions throughout the solution.

**Scalability:** Continuous flow systems are more easily scalable, making them suitable

<sup>30</sup> Noel, T.; Cao, Y.; Laudadio, G. *Acc. Chem. Res.* **2019**, *52*, 2858-2869.

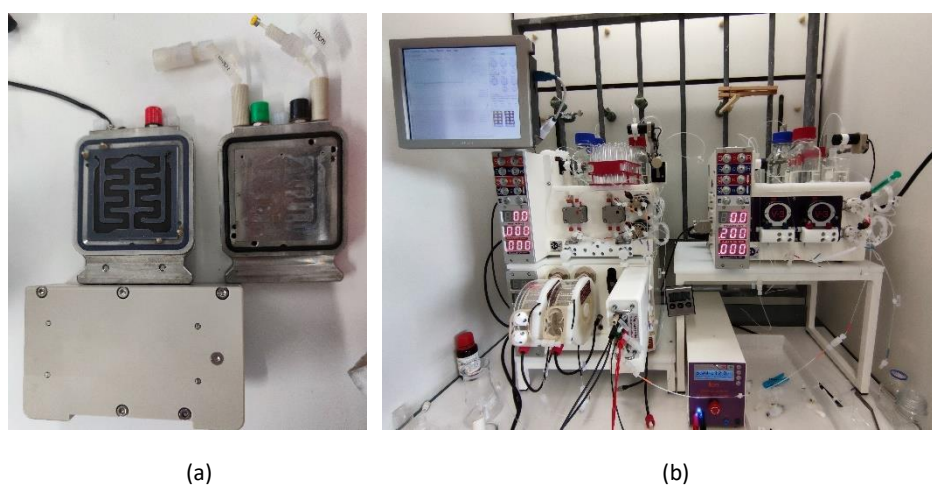
<sup>31</sup> Nicholls, T. P.; Schotten, C.; Willans, C. E. *Curr. Opin. Green Sustain. Chem.* **2020**, *26*, 100355.

<sup>32</sup> Elsherbini, M.; Wirth, T. *Acc. Chem. Res.* **2019**, *52*, 3287-3296.

for both research and large-scale production. The homogeneity of the electric field is maintained as the system is scaled up, ensuring consistent and reliable results.

In addition, continuous-flow electrochemistry offers advantages such as space efficiency and inherent safety. This rapidly advancing field holds substantial potential for industrial applications.

Several groups have developed their own electrochemical flow cells and employed them in a variety of chemical transformations.<sup>33, 34, 35</sup> Additionally, certain electrochemical flow cells have been commercialized. For instance, flow technology company Vapourtec Ltd.<sup>36</sup> developed the Ion reactor (**Figure 7**).<sup>37</sup>



**Figure 7.** Vapourtec Ion electrochemical reactor. (a) Stand-alone reactor. (b) Integrated with R-Series flow chemistry systems.

The commercialization of flow electrochemical cells has encouraged more research groups to investigate flow electrochemistry as a practical alternative in synthesis.

<sup>33</sup> Amemiya, F.; Fuse, K.; Fuchigami, T.; Atobe, M.; Amemiya, F. *Chem. Commun. (Cambridge, U. K.)* **2010**, 46, 2730-2732.

<sup>34</sup> Wang, D.; Wang, P.; Wang, S.; Chen, Y.-H.; Zhang, H.; Lei, A. *Nat. Commun.* **2019**, 10, 2796.

<sup>35</sup> Cao, Y.; Noël, T. *Organic Process Research & Development* **2019**, 23, 403-408.

<sup>36</sup> Vapourtec Ltd Home Page. <https://www.vapourtec.com/> (accessed Oct 15, 2023).

<sup>37</sup> Ion Electrochemical Reactor - Features. <https://www.vapourtec.com/products/flow-reactors/ion-electrochemical-reactor-features/> (accessed Oct 15, 2023).



# **Chapter 2**

## Electrochemical Difluoromethylation of Electron-Rich Olefins



## 2. Electrochemical Difluoromethylation of Electron-Rich Olefins

### 2.1 Introduction

#### 2.1.1 Fluorine

It is well-known that fluorine atom has great advantages and valuable features for the design of pharmaceutical and agrochemical compounds. The introduction of fluorine or fluorinated moieties into molecule can have a significant impact on their physicochemical and biological properties, including metabolic stability, lipophilicity, and bioavailability,<sup>38</sup> for the following reasons:

**The size of fluorine atom:** The size of a fluorine atom and length of C–F bond are between those of hydrogen and oxygen, but closer to the oxygen one. ( $r_{\text{H}} = 1.20 \text{ \AA}$ ,  $r_{\text{F}} = 1.47 \text{ \AA}$ ,  $r_{\text{O}} = 1.52 \text{ \AA}$ ; C–H = 1.09 Å, C–F = 1.35 Å, C–O = 1.43 Å) (**Table 1**). This unique property allows it to replace hydrogen or oxygen atoms without any impact on the steric environment of a molecule.<sup>39</sup>

Property	X				
	H	N	O	F	Cl
Van der Waals radius (Å)	1.20	1.55	1.52	1.47	1.75
Bond length C–X (Å)	1.09	1.47	1.43	1.35	1.77
Electronegativity (Pauling scale)	2.20	3.04	3.44	3.98	3.16
Bond dissociation energy C–X (kcal·mol <sup>-1</sup> )	98.8	69.7	84.0	105.4	78.5
Atom polarizability, $\alpha$ (10 <sup>-24</sup> cm <sup>3</sup> )	0.667	1.100	0.802	0.557	2.180

**Table 1.** A comparison of several different atomic properties.

**Electronegativity:** Due to its strong electronegativity (**Table 1**), fluorine can modulate the pKa of proximal functional groups and the electron density of aromatic and heteroaromatic rings. The modification of the pKa of ionizable centers in drug molecules alters the lipophilic character, which affects solubility, permeability, and protein binding. Changes in pKa can manifest as modification of potency, selectivity,

<sup>38</sup> Thayer, A. M. *Chemical & Engineering News Archive* **2010**, 84, 15-24.

<sup>39</sup> O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308-319.

toxicity and pharmacokinetic properties.<sup>40</sup>

**C–F bond strength:** The carbon-fluorine (C–F) bond stands out as the strongest bond in organic chemistry (105.4 kcal·mol<sup>-1</sup>) (**Table 1**). Moreover, fluorine is the most electronegative atom of the periodic table, giving it the greatest propensity for attracting electron density. As a result, the C–F bond is highly polarized and presents a strong dipole moment ( $\mu$  C–F = 1.41 D). The exceptional strength of C–F bond can thus be attributed to significant electrostatic attraction between F<sup>δ-</sup> and C<sup>δ+</sup> rather than the classical covalent bond.<sup>39,40,41</sup> This increased bond strength imparts enhanced stability to fluorinated molecules, making them less prompt to degradation or breakdown in metabolic processes.

**Polarizability:** The small atomic size and strong electronegativity of fluorine atoms result in low polarizability (**Table 1**). Being the most electronegative element on the periodic table, fluorine has a strong tendency to attract electrons towards itself, resulting in a tightly bound electron cloud. Additionally, its small atomic size means that the outer electrons are closer to the nucleus, leading to stronger electron-nuclear attractions. These combined factors reduce the susceptibility of the electron cloud to deformation in the presence of an external electric field, making fluorine less polarizable compared to atoms with larger atomic sizes or lower electronegativities. This directly affects the intermolecular force, which in turn affects the macroscopic physical properties of organic fluorine compounds, such as boiling point, lipophilicity, surface tension, etc. In general, organofluorine compounds have lower boiling points and weaker surface tensions than their non-fluorinated analogue.<sup>42</sup>

Today, the incorporation of one or more fluorine atoms into biologically active compounds has become a prevalent strategy in the design of pharmaceutical drugs and agrochemicals. Approximately 20% of marketed pharmaceuticals and 30 to 40% of marketed agrochemical products include at least one fluorine atom, to date.<sup>38</sup>

During the past decade, organofluorine chemistry has hence focused on how to efficiently build a carbon-fluorine (C–F) bond,<sup>43,44</sup> with extensive research on the incorporation of trifluoromethyl (CF<sub>3</sub>) group and perfluoroalkyl (C<sub>n</sub>F<sub>2n+1</sub>) groups (with

<sup>40</sup> Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315-8359.

<sup>41</sup> Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem Rev* **2004**, *104*, 1-16.

<sup>42</sup> Huheey, J. E.; Keiter, E. A.; Keiter, R. L.; Medhi, O. K., *Inorganic chemistry: principles of structure and reactivity*, Pearson Education India, **2006**.

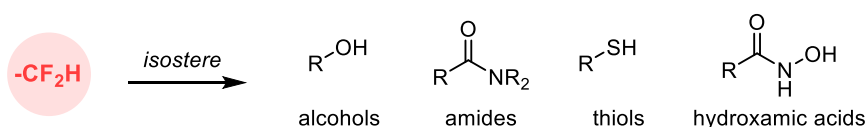
<sup>43</sup> Brown, J. M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8610-8614.

<sup>44</sup> Campbell, M. G.; Ritter, T. *Chem. Rec.* **2014**, *14*, 482-491.

a greater emphasis focus on trifluoromethylation).<sup>45, 46, 47, 48, 49, 50, 51, 52</sup> However, innovative fluorinated motifs are emerging and becoming of prime importance in order to modify the physico-chemical and biological properties of organic molecules for potent superior biological activities.

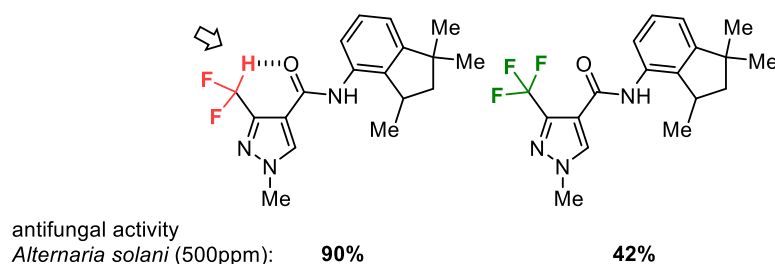
## 2.1.2 CF<sub>2</sub>H group

The difluoromethyl group (-CF<sub>2</sub>H) is one of them and is of significant importance due to its ability to function as a more lipophilic isostere for the alcohol, thiol, hydroxamic acid, or amide group (as shown in **Figure 8**).<sup>53</sup>



**Figure 8.** CF<sub>2</sub>H acts as isostere.

Moreover, the CF<sub>2</sub>H group is weakly acidic with a labile hydrogen atom that could be involved in hydrogen bonding, enabling for superior bioactivities compared with a chemical bearing a CF<sub>3</sub> motif (**Figure 9**).<sup>54</sup>



**Figure 9.** Hydrogen bonding property of CF<sub>2</sub>H.

Consequently, this motif is becoming a predominant residue in drug discovery programs and finds widespread application in the design of pharmaceuticals and agrochemicals (**Figure 10**).<sup>55</sup> Compared to the extensively developed methods for

<sup>45</sup> Prakash, G. K.; Yudin, A. K. *Chem Rev* **1997**, *97*, 757-786.

<sup>46</sup> Lundgren, R. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9322-9324.

<sup>47</sup> Tomashenko, O. A.; Grushin, V. V. *Chem Rev* **2011**, *111*, 4475-4521.

<sup>48</sup> Wu, X. F.; Neumann, H.; Beller, M. *Chem Asian J* **2012**, *7*, 1744-1754.

<sup>49</sup> Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950-8958.

<sup>50</sup> Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617-626.

<sup>51</sup> Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 2895-2906.

<sup>52</sup> Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. *RSC Adv.* **2015**, *5*, 62498-62518.

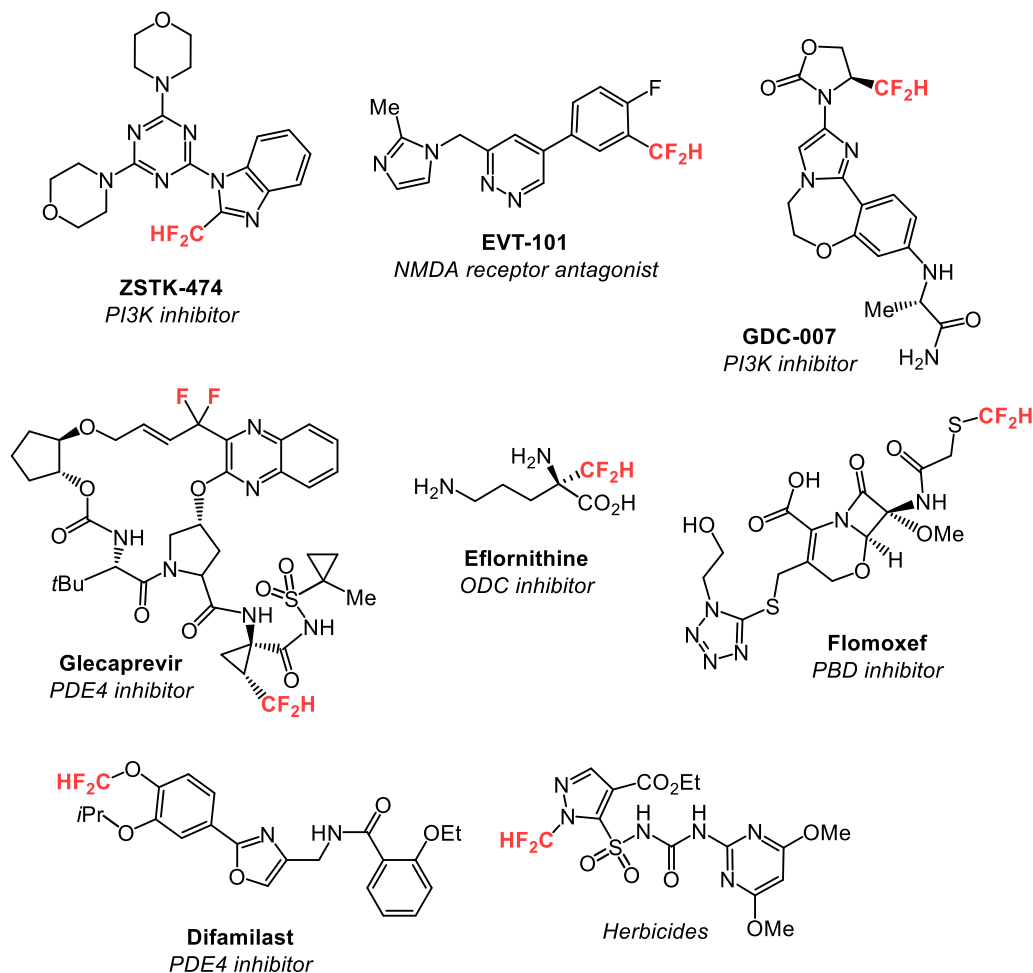
<sup>53</sup> Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529-2591.

<sup>54</sup> Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **2002**, *60*, 1626-1631.

<sup>55</sup> Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; am Ende, C. W.; Trabanco, A. A.;



trifluoromethylation ( $\text{CF}_3$ ) and perfluoroalkylation ( $\text{C}_n\text{F}_{2n+1}$ ) reactions, methods for the introduction of difluoromethyl group ( $\text{CF}_2\text{H}$ ) into organic molecules are still underdeveloped. In this chapter, we will disclose our investigation toward the direct electromediated introduction of difluoromethyl group onto electron-rich olefins.



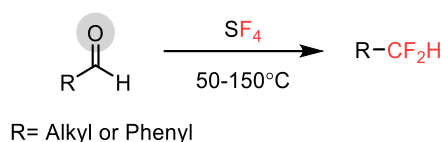
**Figure 10.** Representative pharmaceuticals and agrochemicals containing difluoromethyl group.

### 2.1.3 The introduction of $\text{CF}_2\text{H}$

Conventionally, the most widely adopted method to synthesize difluoromethylated compounds was the deoxyfluorination of aldehydes. Initially, in 1960, sulfur tetrafluoride ( $\text{SF}_4$ ) was used successfully for the deoxyfluorination of aldehydes, giving  $\text{CF}_2\text{H}$ -containing compounds (**Scheme 4**).<sup>56</sup> However, its strongly toxic and gaseous nature has prevented its large use as a reagent among synthetic organic chemists.

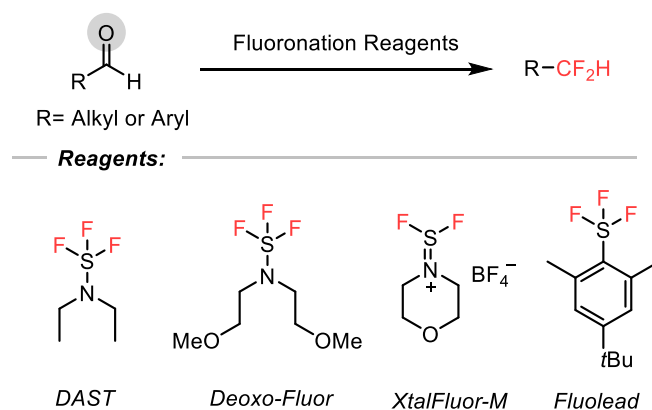
Gouverneur, V. *Chem. Soc. Rev.* **2021**, 50, 8214-8247.

<sup>56</sup> Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, 82, 543-551.



**Scheme 4.** Deoxyfluorination of aldehydes with SF<sub>4</sub>.

Later, the reactive and liquid reagent diethylaminosulfur trifluoride (DAST),<sup>57</sup> and its analogue, bis(methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),<sup>58</sup> were developed as alternatives to the gaseous SF<sub>4</sub> (**Scheme 5**). Although these reagents can provide a variety of CF<sub>2</sub>H-containing molecules, a notable drawback is their thermal instability, and their explosive nature, which restrict both their transportation and their application in high-temperature and large-scale reactions. The development of bench-stable crystalline solid reagents such as difluoro-4-morpholinylsulfonium tetrafluoroborate (XtalFluor-M)<sup>59</sup> and 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride (Fluolead),<sup>60</sup> is an important advance (**Scheme 5**). However, these methods exhibit significant limitations, including harsh reaction conditions and low functional groups tolerance, along with the necessity to pre-install the aldehyde functionality, which limited the application of these reagents.



**Scheme 5.** Deoxyfluorination of the aldehyde with alternative reagents.

Due to these limitations, chemists have been actively exploring alternative approaches. The discovery of novel CF<sub>2</sub>H-substituted bioactive organic molecules heavily relies on the availability of efficient and practical methods to introduce CF<sub>2</sub>H moieties into substrates with a large panel of chemical skeletons.

Among these strategies, nucleophilic and electrophilic difluoromethylation reactions with various newly developed difluoromethylating reagents have emerged as

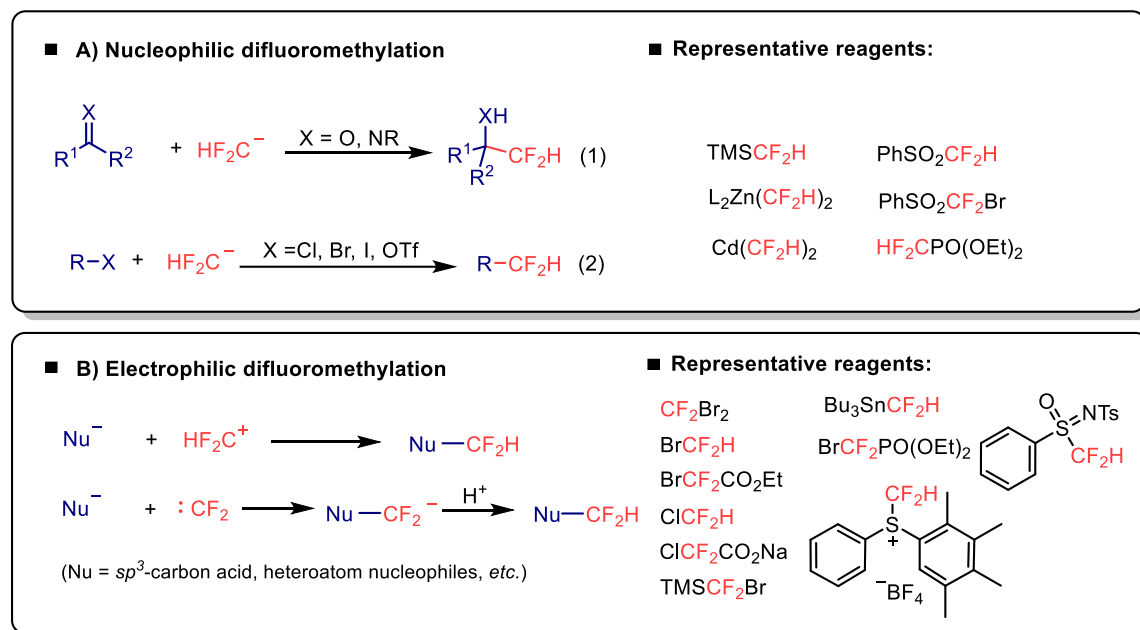
<sup>57</sup> Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 1973, 787-789.

<sup>58</sup> Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. J. *Org. Chem.* **1999**, 64, 7048-7054.

<sup>59</sup> Beaulieu, F.; Beauregard, L. P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, 11, 5050-5053.

<sup>60</sup> Umamoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, 132, 18199-18205.

promising alternatives. Traditionally, these approaches involve exploiting inherent reactivity of difluoromethylation reagents and substrates themselves to proceed nucleophilic and electrophilic reactions (**Scheme 6**). Consequently, such reactions often exhibit a limited scope.<sup>61,62</sup>



**Scheme 6.** Nucleophilic/electrophilic difluoromethylation reactions and related reagents.

In recent years, transition metal-catalyzed cross-coupling difluoromethylation reaction has gained increasing attention due to its milder reaction conditions, broad applicability, functional group compatibility, and enhanced selectivity, making them particularly suitable for late-stage difluoromethylation. This has provided chemists with more options for synthesizing difluoromethyl containing compounds. Currently, the difluoromethylation of (hetero)arenes, alkenes, alkynes, heteroatoms, and ketones has been achieved through transition metal-catalyzed cross-coupling strategy. Pd, Ni, Cu, Ag, Au, Fe have been employed as catalysts (**Scheme 7**).<sup>55,63,64,65</sup>

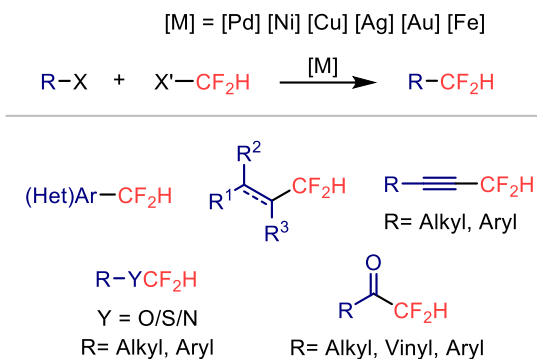
<sup>61</sup> Hu, J.; Zhang, W.; Wang, F. *Chem. Commun. (Camb.)* **2009**, 7465-7478.

<sup>62</sup> Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921-930.

<sup>63</sup> Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017**, *6*, 139-152.

<sup>64</sup> Ni, C.; Zhu, L.; Hu, J. *Acta Chimica Sinica* **2015**, *73*, 90-115.

<sup>65</sup> Ma, J. A.; Cahard, D., *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*, Wiley, **2020**.



**Scheme 7.** Transition metal-catalyzed difluoromethylation reactions.

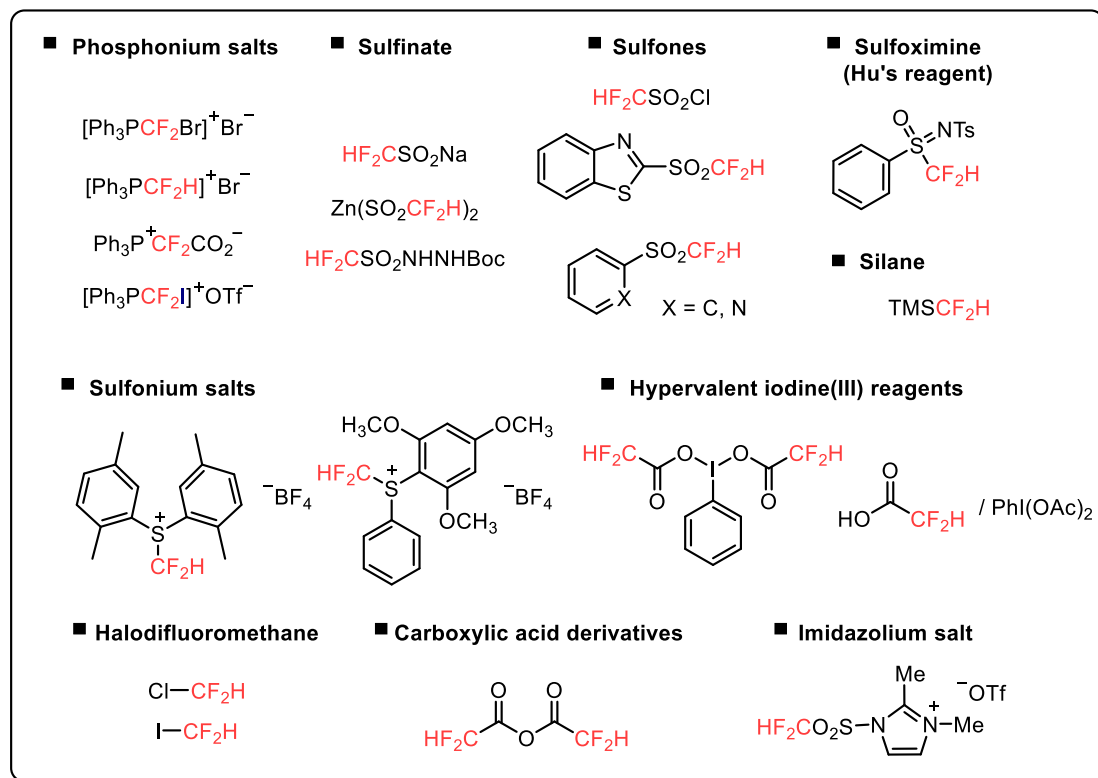
Another significant approach is the formation of difluoromethylated compounds involving radical processes. In the recent years, radical-based difluoromethylation has gained increasing attention due to their distinctive reactivity, presenting unique opportunities for introducing CF<sub>2</sub>H moiety into various substrates. The domain of C–H difluoromethylation mostly relies on the generation and reactivity of the difluoromethyl radical, although cross-coupling methodologies have emerged. One of the most actively studied reactions involve the CF<sub>2</sub>H radical-based difluoromethylation of alkenes, as it allows the construction of important and complex CF<sub>2</sub>H-substituted building blocks from relatively simple and easily accessible starting materials.

Unlike electrophilic/nucleophilic approaches, radical process involves the generation of difluoromethyl radical from various CF<sub>2</sub>H radical precursors, under conditions such as photoredox catalysis or electrochemistry. Subsequently, the difluoromethyl radical add onto polarity matching unsaturated bonds (such as alkenes, alkynes, isocyanides, and arenes), leading to the formation of corresponding difluoromethylated products, which can then undergo further transformations. Additionally, if any tandem intramolecular cyclization reactions are involved, a difluoromethylated cyclic skeleton can be obtained.

In this chapter, we provide a detailed overview of the radical difluoromethylation of alkenes. For the sake of clarity, the indirect multi-step strategies involving the incorporation of difluoromethyl units (CF<sub>2</sub>-FG, FG=Functional group) into the carbon skeletons, followed by a subsequent transformation to prepare CF<sub>2</sub>H-containing compounds, are not documented in the subsequent sections.

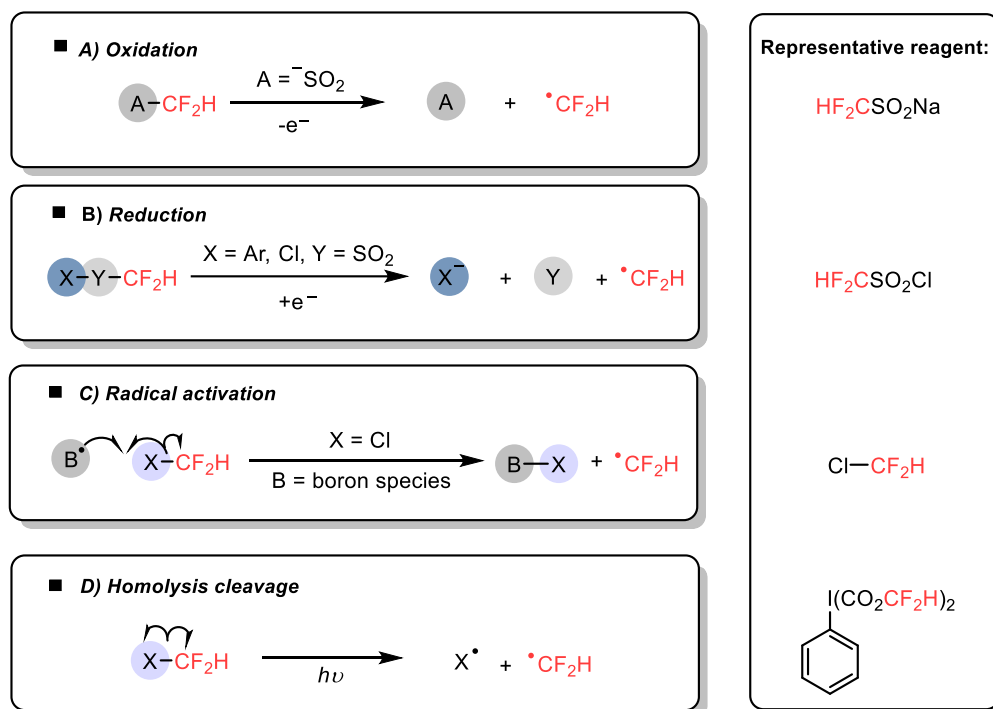
### 2.1.4 Difluoromethylation of alkenes via a radical process

The difluoromethyl radical is typically generated from appropriate difluoromethyl radical precursors via single-electron transfer (SET). In recent years, as radical difluoromethylation methods have rapidly expanded, a variety of difluoromethyl radical precursors have been developed, as illustrated in **Figure 11**.



**Figure 11.** Sources of difluoromethyl radicals.

The  $\text{CF}_2\text{H}$  radical can be obtained through activating processes such as single-electron oxidation (e.g.,  $\text{HF}_2\text{CSO}_2\text{Na}$ ,  $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ ), single-electron reduction (e.g.,  $\text{HF}_2\text{CSO}_2\text{Cl}$ ), halogen atom abstraction (e.g.,  $\text{ClCF}_2\text{H}$ ), or photo-induced homolytic bond cleavage (e.g.,  $\text{PhI}(\text{CO}_2\text{CF}_2\text{H})_2$ ) (**Scheme 8**).

Scheme 8. Generation of CF<sub>2</sub>H Radical.

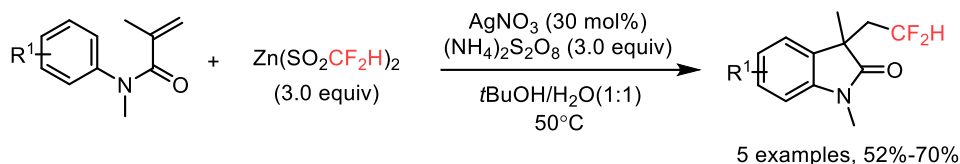
### a. Transition Metal-Catalyzed/Mediated Radical process

Although the CF<sub>2</sub>H radical-based photocatalytic difluoromethylation is well documented, catalytic difluoromethylation under thermal conditions is rather rare.

In 2012, Baran and co-workers synthesized a novel difluoromethylation reagent, zinc difluoromethanesulfinate [Zn(SO<sub>2</sub>CF<sub>2</sub>H)<sub>2</sub>] (DFMS), enabling the difluoromethylation of organic substrates through a radical process for the first time (*vide infra*, [section 2.1.4.b](#), **Scheme 39**).<sup>66</sup> In 2014, Tan *et al.* applied this reagent for the difluoromethylation of alkenes, through a silver-catalyzed difluoromethylation/cyclization reaction of *N*-arylacrylamides with Zn(SO<sub>2</sub>CF<sub>2</sub>H)<sub>2</sub> (**Scheme 9**).<sup>67</sup> This approach offered an efficient way to synthesize CF<sub>2</sub>H-substituted oxindoles via a radical addition/cyclization process, with a catalytic amount of AgNO<sub>3</sub> as catalyst and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as oxidant. The study of the mechanism suggested that the *N*-arylacrylamides underwent an addition with the *in situ* generated difluoromethyl radical, followed by a subsequent cyclization to yield a range of difluoromethyl-substituted oxindoles in 52%–50% yields.

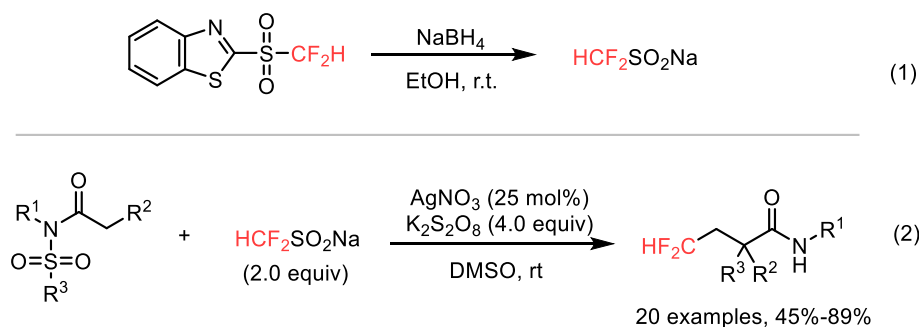
<sup>66</sup> Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494-1497.

<sup>67</sup> Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z. *Eur. J. Org. Chem.* **2014**, *2014*, 3196-3202.



**Scheme 9.** Silver-Catalyzed Difluoromethylation/Cyclization Reaction of *N*-Arylacrylamides.

In 2015, Hu's group developed a new method to synthesize  $\text{HCF}_2\text{SO}_2\text{Na}$  by reducing the corresponding benzo[d]thiazol-2-yl sulfone with  $\text{NaBH}_4$  (**Scheme 10**, eq. 1).<sup>68</sup> They further applied  $\text{HCF}_2\text{SO}_2\text{Na}$  as a difluoromethyl radical precursor, enabling the silver-catalyzed cascade difluoromethylation/aryl migration/ $\text{SO}_2$  extrusion of conjugated *N*-arylsulfonylated amides in the presence of  $\text{K}_2\text{S}_2\text{O}_8$  as oxidant. This transformation led to  $\alpha$ -aryl- $\beta$ -difluoromethyl amides (**Scheme 10**, eq. 2), highlighting the  $\text{HF}_2\text{CSO}_2\text{Na}$  reagent as an efficient radical difluoromethylation reagent.



**Scheme 10.** Silver-catalyzed cascade difluoromethylation/aryl migration/ $\text{SO}_2$  extrusion of conjugated *N*-arylsulfonylated amide with  $\text{HCF}_2\text{SO}_2\text{Na}$ .

Difluoromethyltrimethylsilane ( $\text{TMSCF}_2\text{H}$ ) is a nucleophilic difluoromethylating reagent commonly used in classical nucleophilic additions to carbonyl compounds.<sup>69,70</sup> In 2021, Chu, Qing and coworkers successfully investigated the utilization of  $\text{TMSCF}_2\text{H}$  as a novel source of  $\text{CF}_2\text{H}$  radical, leading to a silver-mediated oxidative difluoromethylation of styrenes (**Scheme 11**).<sup>71</sup> With the combination of  $\text{AgOPiv}$ , 1,10-phenanthroline-5,6-dione (phendio) as an oxidant,  $\text{CsF}$  as a base and  $n\text{Bu}_4\text{NH}_2\text{PO}_4$  as an additive, this method allowed for a direct and facile synthesis of  $\text{CF}_2\text{H}$ -alkenes from abundant alkenes with excellent functional-group compatibility. Furthermore, in the absence of phendio, non-activated alkenes underwent silver-mediated hydrodifluoromethylation reactions, yielding  $\text{CF}_2\text{H}$ -alkanes with exclusive regioselectivity. Thanks to radical trapping and radical clock experiments, it has been confirmed that this reaction proceeds via a radical pathway. The in situ generated

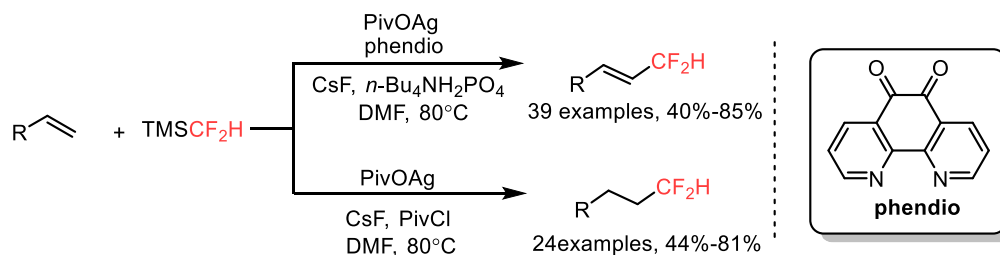
<sup>68</sup> He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 1838-1841.

<sup>69</sup> Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342-5345.

<sup>70</sup> Chen, D.; Ni, C.; Zhao, Y.; Cai, X.; Li, X.; Xiao, P.; Hu, J. *Angew. Chem.* **2016**, *128*, 12822-12826.

<sup>71</sup> Yang, J.; Zhu, S.; Wang, F.; Qing, F.-L.; Chu, L. *Angew. Chem. Int. Ed.* **2021**, *60*, 4300-4306.

“ligandless”  $\text{AgCF}_2\text{H}$  species might be involved in undergoing homolytic cleavage to release  $\text{CF}_2\text{H}$  radical.

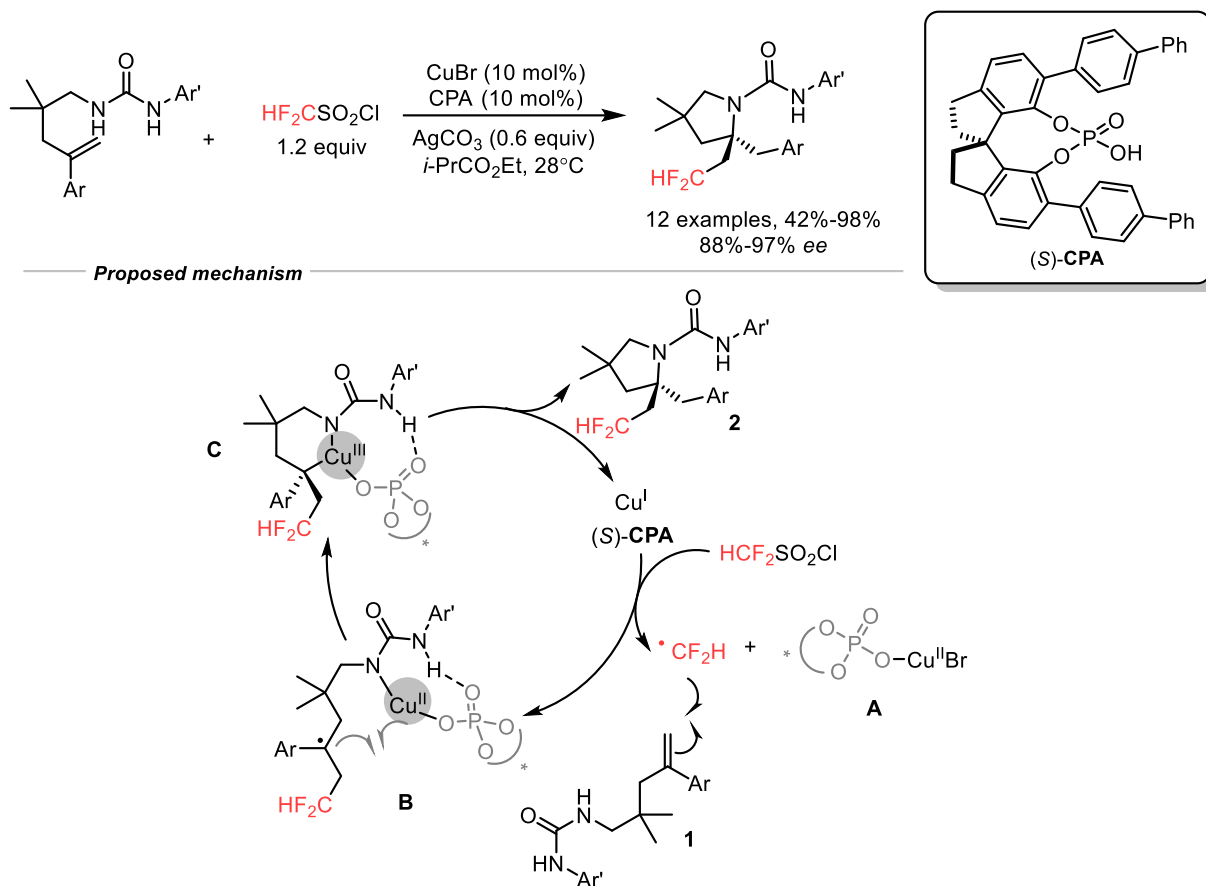


**Scheme 11.** Silver-mediated oxidative difluoromethylation of alkenes.

While nucleophilic and electrophilic fluoroalkylation reactions have gained significant advancements, the corresponding asymmetric radical fluoroalkylation remains notably underexplored. In 2017 Lin, Wang, Dong *et al.* reported a catalytic asymmetric radical aminodifluoromethylation of alkenes (**Scheme 12**).<sup>72</sup> The  $\text{CF}_2\text{H}$  radical was generated from the single-electron transfer of  $\text{HF}_2\text{CSO}_2\text{Cl}$  with  $\text{CuBr}$  and the chiral phosphoric acid (CPA), accompanied by the production of a stoichiometric amount of sulfur dioxide ( $\text{SO}_2$ ) and chloride anion. Subsequently, the  $\text{CF}_2\text{H}$  radical adds onto **1**, which allowed the formation of an alkyl radical intermediate, then captured by  $\text{Cu(II)}$  phosphate **A**. A chelation between the nitrogen of starting material and  $\text{Cu(II)}$  allowed for the formation of  $\text{Cu(II)}$  species **B**, in which the alkyl radical can be captured by  $\text{Cu(II)}$  to generate  $\text{Cu(III)}$  species **C**. During this process, chiral phosphate could control the facial selectivity of such reaction through hydrogen bonding interactions with N-H bond adjacent to the aryl group and ion-pairing interactions in a concerted transition state. A reductive elimination of the resulting  $\text{Cu(III)}$  species **C** led to the final product **2**, concomitantly regenerating copper  $\text{Cu(I)}$  and phosphoric acid. The key for success of this reaction is not only achieved by the introduction of the  $\text{CuBr}$ /chiral phosphoric acid dual-catalytic system but also by the use of silver carbonate ( $\text{Ag}_2\text{CO}_3$ ) as a chloride scavenger to suppress strong background and undesired hydroamination reactions caused by the *in situ* generated  $\text{HCl}$ . This approach enabled the synthesis of enantioenriched difluoromethyl-substituted pyrrolidines in high yields and excellent enantioselectivities.

<sup>72</sup> Lin, J. S.; Wang, F. L.; Dong, X. Y.; He, W. W.; Yuan, Y.; Chen, S.; Liu, X. Y. *Nat. Commun.* **2017**, *8*, 14841.

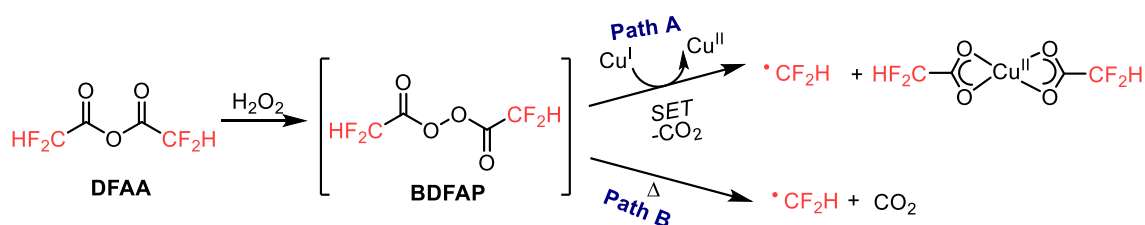
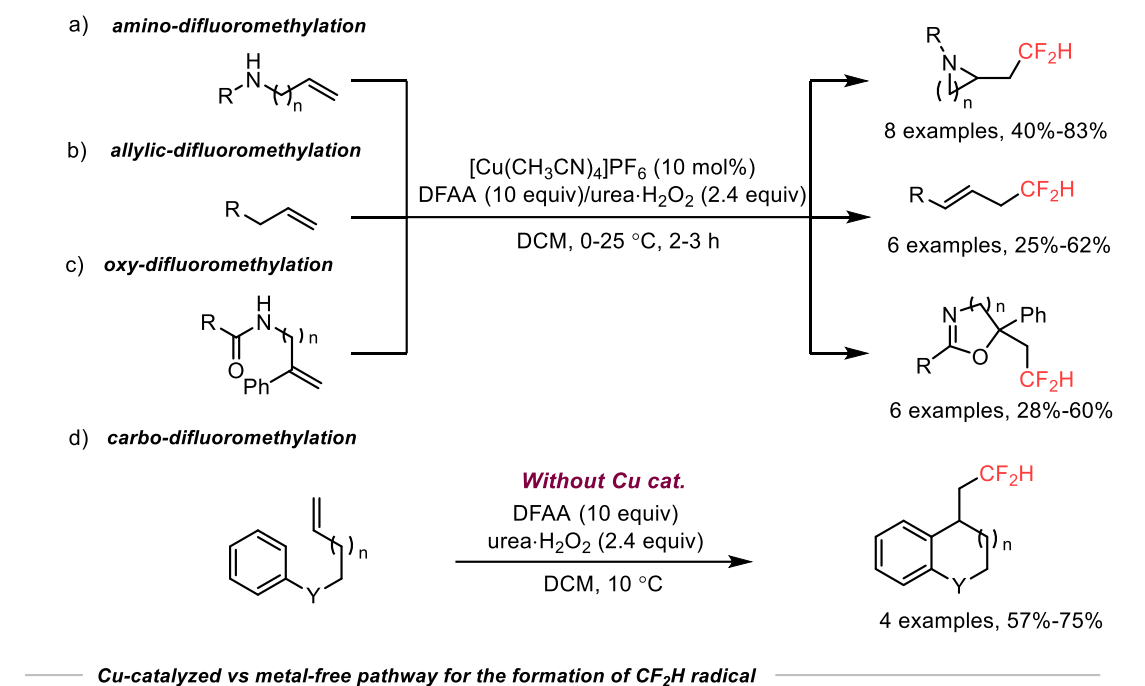




**Scheme 12.** Catalytic asymmetric radical aminodifluoromethylation of alkenes.

In 2023, Sodeoka, Kawamura and co-workers introduced a copper-catalyzed difluoromethylation of alkenes using difluoroacetic anhydride (DFAA) as the  $\text{CF}_2\text{H}$  source. This approach involved the *in situ* generation of bis(difluoroacetyl) peroxide (BDFAP) from DFAA and  $\text{H}_2\text{O}_2$ , enabling amino-, allylic-, and oxy-difluoromethylation of alkenes (**Scheme 13**).<sup>73</sup> Additionally, the exploration of catalyst-free conditions unveiled the occurrence of carbo-difluoromethylation. Mechanistic investigations revealed that the catalytic difluoromethylation with BDFAP permits the generation of a  $\text{CF}_2\text{H}$  radical from BDFAP in the presence of a  $\text{Cu}(\text{I})$  catalyst through a single-electron transfer (SET) (**Scheme 13**, path A). Whereas the metal-free carbo-difluoromethylation proceeds through a radical chain propagation mechanism. The reaction was initiated by the thermal cleavage of BDFAP, generating  $\text{CF}_2\text{H}$  radical (**Scheme 13**, path B).

<sup>73</sup> Tagami, T.; Mitani, Y.; Kawamura, S.; Sodeoka, M. *Adv. Synth. Catal.* **2023**, doi: 10.1002/adsc.202300337.



**Scheme 13.** Cu-Catalyzed & metal-free Difluoromethylation of Alkenes with Difluoroacetic Anhydride.

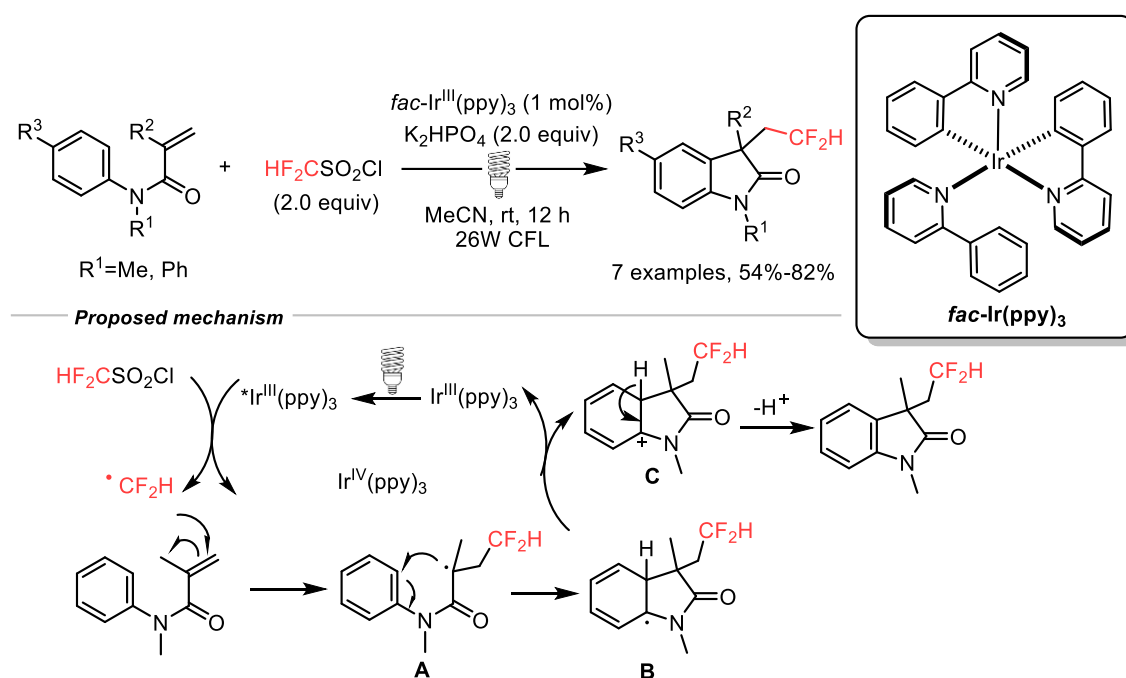
## b. Photochemical difluoromethylation (Transition-metal based catalysts & organic catalysts & catalyst-free)

The photoredox difluoromethylation is a powerful strategy for constructing CF<sub>2</sub>H-containing organic compounds. Generally, this involves the activation of the light-absorbing catalyst. Subsequently, the light-activated catalyst either donates or abstracts electrons from difluoromethylation reagents through single-electron transfer (SET) events, leading to the formation of highly reactive difluoromethyl radical species which subsequently adds to an alkene, for instance.

In 2014, Dolbier and his team reported a visible-light-catalyzed difluoromethylation of *N*-arylacrylamides, leading to CF<sub>2</sub>H-containing 3,3-disubstituted 2-oxindoles in good yields (**Scheme 14**).<sup>74</sup> HF<sub>2</sub>CSO<sub>2</sub>Cl reacted as an efficient source of the difluoromethyl radical in the presence of the *fac*-[Ir(ppy)<sub>3</sub>] photocatalyst under light irradiation with a

<sup>74</sup> Tang, X. J.; Thomason, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2014**, *16*, 4594-4597.

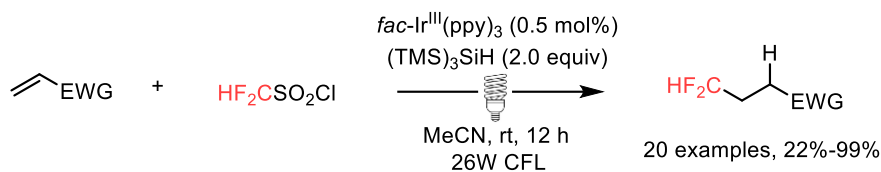
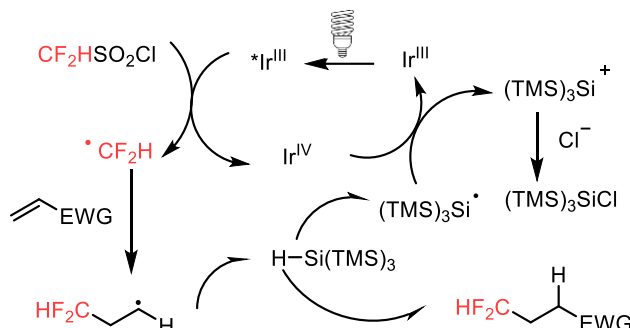
26 W compact fluorescent lamp (CFL). The reaction proceeded through a radical addition/cyclization mechanism, wherein the photocatalytically generated  $\text{CF}_2\text{H}$  radical reacted with the  $\text{C}=\text{C}$  bond to form radical intermediate **A**. The latter spontaneously cyclized into **B**, followed by oxidation to form carbocation **C**, ultimately leading to the formation of the oxindole (**Scheme 14**). Notably, the same methodology was used to introduce a  $\text{CF}_3$  moiety in the presence of  $\text{CF}_3\text{SO}_2\text{Cl}$ , using  $\text{Ru}(\text{phen})_3\text{Cl}_2$  ( $E_{1/2}^{\text{III}/*\text{II}} = -0.87$  V vs. SCE in MeCN) as a replacement for  $\text{fac}[\text{Ir}(\text{ppy})_3]$  ( $E_{1/2}^{\text{IV}/*\text{III}} = -1.73$  V vs. SCE in MeCN). This modification is attributed to the lower reduction potential of  $\text{HF}_2\text{CSO}_2\text{Cl}$  compared to  $\text{CF}_3\text{SO}_2\text{Cl}$ .



**Scheme 14.** Photoredox-catalysed radical difluoromethylation/cyclization of *N*-arylacrylamides.

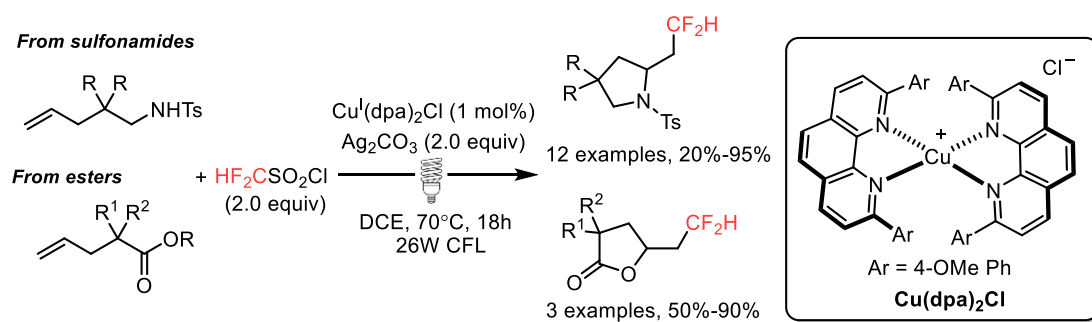
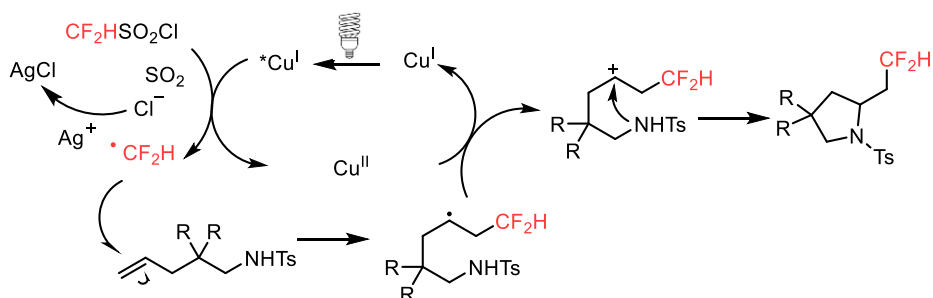
In 2015, photoredox-catalyzed hydrodifluoromethylation of electron-deficient alkenes was achieved by the same group,<sup>75</sup> using the same photocatalyst and  $\text{CF}_2\text{H}$  radical precursor (**Scheme 15**). TTMS (tris(trimethylsilyl)silane) acted as both the hydrogen atom donor and the electron donor in the catalytic cycle. This reaction provides an efficient approach for direct introduction of the difluoromethyl group at the  $\beta$ -position of various electron-withdrawing groups including acrylamides, esters, ketones, sulfones, or phosphonates with good to excellent yields. Experimental and DFT results provided evidence that  $\text{CF}_2\text{H}$  radical is nucleophilic in nature.

<sup>75</sup> Tang, X. J.; Zhang, Z.; Dolbier, W. R., Jr. *Chemistry* **2015**, *21*, 18961-18965.

**Proposed mechanism****Scheme 15.** Photoredox-Catalyzed Reductive Difluoromethylation of Electron-Deficient Alkenes.

Shortly afterwards, the same group described a photoredox-catalyzed intramolecular amino- and oxy-difluoromethylation reactions of unactivated alkenes, with sulfonamides and esters, respectively.  $\text{Cu}^{\text{I}}(\text{dap})_2\text{Cl}$  was selected as the catalyst and  $\text{HF}_2\text{CSO}_2\text{Cl}$  as radical precursor. The overall process involved a cascade addition/oxidation/cyclization resulting in  $\text{CF}_2\text{H}$ -containing pyrrolidines or lactones in moderate to good yields (**Scheme 16**).<sup>76</sup> It is worth noting that when both sulfonamide and ester moieties were present in the substrate, only lactone products were obtained, highlighting that ester carbonyls acted as better nucleophiles in the reaction than sulfonamide nitrogen. Mechanistic investigations revealed that the combination of a copper catalyst ( $\text{Cu}(\text{dap})_2\text{Cl}$ ) and silver carbonate played a crucial role in the cyclisation reaction, since it can suppress the competing chloro, difluoroalkylation process.

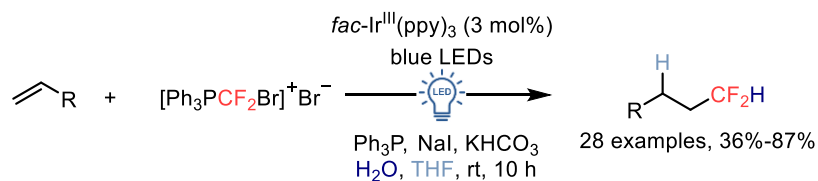
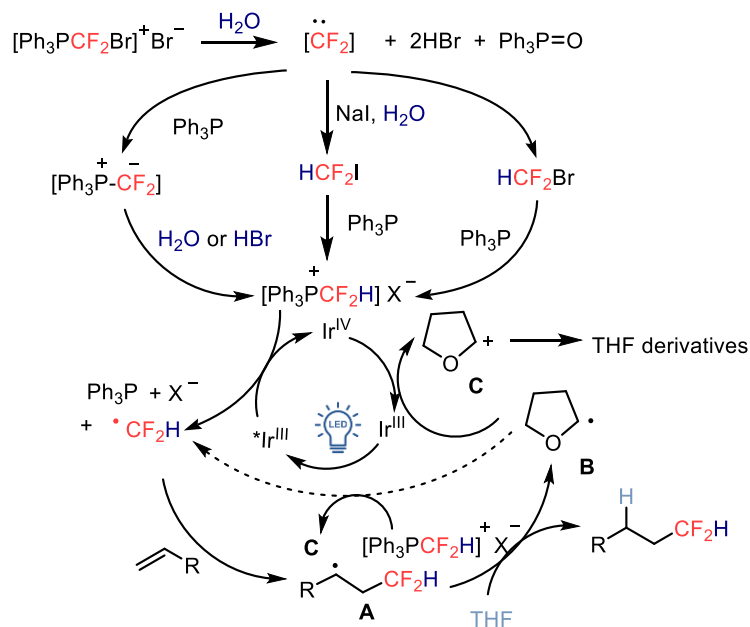
<sup>76</sup> Zhang, Z.; Tang, X.; Thomason, C. S.; Dolbier, W. R. *Org. Lett.* **2015**, *17*, 3528-3531.

**Proposed mechanism**

**Scheme 16.** Photoredox-catalysed intramolecular difluoromethylation/cyclization of sulfonamides and esters.

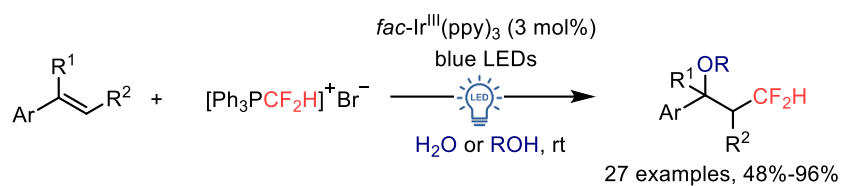
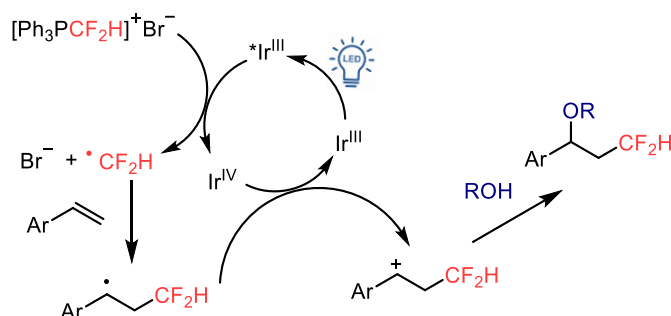
In 2015, Qing and co-workers described a new application of bromodifluoromethylphosphonium bromide ( $[\text{Ph}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$ ), which is commonly used as a precursor of difluoromethylcarbene, as an easily handled solid for difluoromethylation.<sup>77</sup> Under visible-light irradiation, the difluoromethylation reaction of alkenes was performed by using  $\text{H}_2\text{O}$  and THF as hydrogen sources, provided an efficient access to the hydrodifluoromethylated alkanes with excellent functional-group tolerance under mild conditions (**Scheme 17**). Mechanistic investigation revealed that difluoromethylcarbene was produced from the reaction of  $[\text{Ph}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$  and water. Subsequently, difluoromethylcarbene underwent three possible transformations to form difluoromethylphosphonium salt ( $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{X}^-$ ). Under visible light and with the presence of a catalyst, the difluoromethylphosphonium salt underwent a single-electron transfer (SET) process, generating difluoromethyl radical that participated in the reaction.

<sup>77</sup> Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1479-1483.

**Proposed mechanism****Scheme 17.** Visible-light-induced hydrodifluoromethylation of alkenes.

Inspired by this achievement, Qing's group further investigated the process where the reagent [Ph<sub>3</sub>PCF<sub>2</sub>H]<sup>+</sup>Br<sup>-</sup> can be reduced to generate CF<sub>2</sub>H radical through visible-light-induced single-electron transfer (SET) (**Scheme 18**). By using this reagent, they depicted an oxydifluoromethylation reaction of styrene, enabling the synthesis of CF<sub>2</sub>H-containing alcohols and ethers in moderate to good yields under mild conditions (**Scheme 18**).<sup>78</sup> Among the commonly used photocatalysts like ruthenium or iridium polypyridyl complexes and organic dyes (e.g. Eosin Y), only *fac*-[Ir(ppy)<sub>3</sub>] was effective in promoting this reaction. This is likely due to its stronger reducing excited state ( $E_{1/2}^{\text{IV}/\text{III}^*} = -1.73$  V vs SCE) compared to the other photocatalysts, which is capable of reducing [Ph<sub>3</sub>PCF<sub>2</sub>H]<sup>+</sup>Br<sup>-</sup> into a CF<sub>2</sub>H radical. The key aspects of the proposed mechanism involve the reduction of [Ph<sub>3</sub>PCF<sub>2</sub>H]<sup>+</sup>Br<sup>-</sup> to form the CF<sub>2</sub>H radical, which then adds to the styrene, followed by the oxidation of the intermediate to generate a benzylic carbocation and simultaneous regeneration of the photocatalyst. Finally, the benzylic carbocation undergoes nucleophilic attack by alcohols or water to yield the desired products.

<sup>78</sup> Ran, Y.; Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2016**, *81*, 7001-7007.

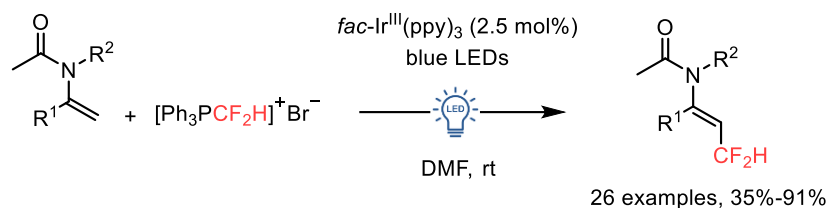
**Proposed mechanism****Scheme 18.** Visible-light-promoted oxydifluoromethylation of styrenes.

Qing and colleagues observed that the addition of Cu(II) salt: CuBr<sub>2</sub>, promoted bromide incorporation (**Scheme 19**).<sup>79</sup> By employing difluoromethyltriphenylphosphonium bromide as the CF<sub>2</sub>H radical precursor, they successfully carried out photoredox bromodifluoromethylation on a wide range of alkenes, yielding to the products in good to high yields. Furthermore, bromodifluoromethyl alkenes readily underwent dehydrobromination by quenching the reaction with DBU. Despite the success, the exact role of the copper salt as co-catalyst remained unclear.

**Scheme 19.** Visible-light-promoted bromodifluoromethylation of alkenes.

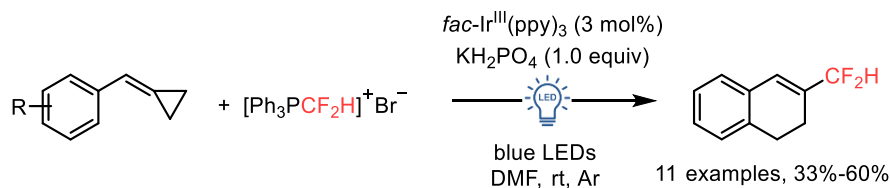
The photoredox-catalyzed difluoromethylation of enamides was also investigated. Loh, Zhao, and their co-workers demonstrated the regio- and stereoselective difluoromethylation of enamides using difluoromethyltriphenylphosphonium bromide (**Scheme 20**).<sup>80</sup> This method allowed for the synthesis of a diverse array of *E*-β-difluoromethylated enamides under mild conditions, utilizing blue LEDs and a catalytic amount of *fac*-[Ir(ppy)<sub>3</sub>].

<sup>79</sup> Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. *Org. Lett.* **2016**, *18*, 2419-2422.<sup>80</sup> Zhu, T. H.; Zhang, Z. Y.; Tao, J. Y.; Zhao, K.; Loh, T. P. *Org. Lett.* **2019**, *21*, 6155-6159.

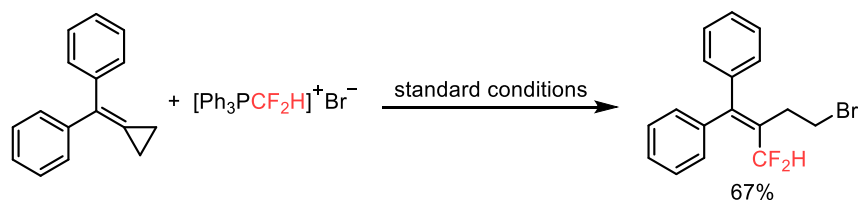


**Scheme 20.** Photoredox catalytic stereoselective difluoromethylation of enamides.

A ring expansion reaction based on a visible-light-induced radical difluoromethylation of methylenecyclopropanes was reported by Wu, Wang, Li and co-workers.  $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$  was employed as difluoromethyl reagent, while the blue LED-excited  $\text{fac-}[\text{Ir}(\text{ppy})_3]$  catalyzed the generation of the  $\text{CF}_2\text{H}$  radical, leading to the synthesis of difluoromethylated 1,2-dihydronaphthalenes (**Scheme 21**).<sup>81</sup> The reaction exhibited good tolerance towards several aryl substituents, except for the nitro group, which was not compatible under the given conditions. Interestingly, when diphenyl methylenecyclopropane was used as the substrate, dihydronaphthalene formation was not observed. Instead, the linear product, resulting from the capture of the bromide anion, was obtained in a 67% yield (**Scheme 21**).



— *Diphenyl methylenecyclopropane as substrate* —



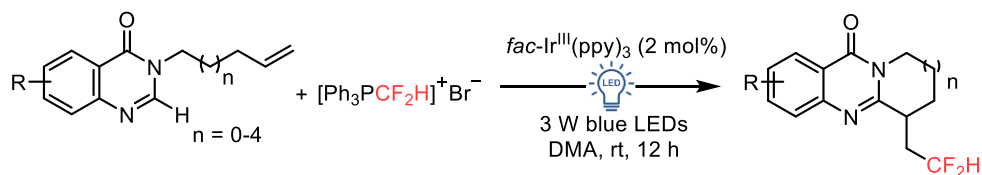
**Scheme 21.** Visible-light-promoted functionalizations of methylenecyclopropanes.

In 2021, Wu's group developed a cascade visible-light-induced difluoromethylation/cyclization of non-activated alkenes with the easily accessible  $[\text{Ph}_3\text{PCF}_2\text{H}]^+\text{Br}^-$  (**Scheme 22**).<sup>82</sup> This strategy provided an efficient approach to access valuable  $\text{CF}_2\text{H}$ -containing polycyclic quinazolinones.

<sup>81</sup> Zhu, B.; Wang, Z.; Xi, H.; Feng, Z.; Wang, B.; Jiao, W.; Li, Z.; Wang, Z.; Wu, J. *Org. Chem. Front.* **2021**, *8*, 6300-6308.

<sup>82</sup> Chen, X.; Liu, B.; Pei, C.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Org. Lett.* **2021**, *23*, 7787-7791.



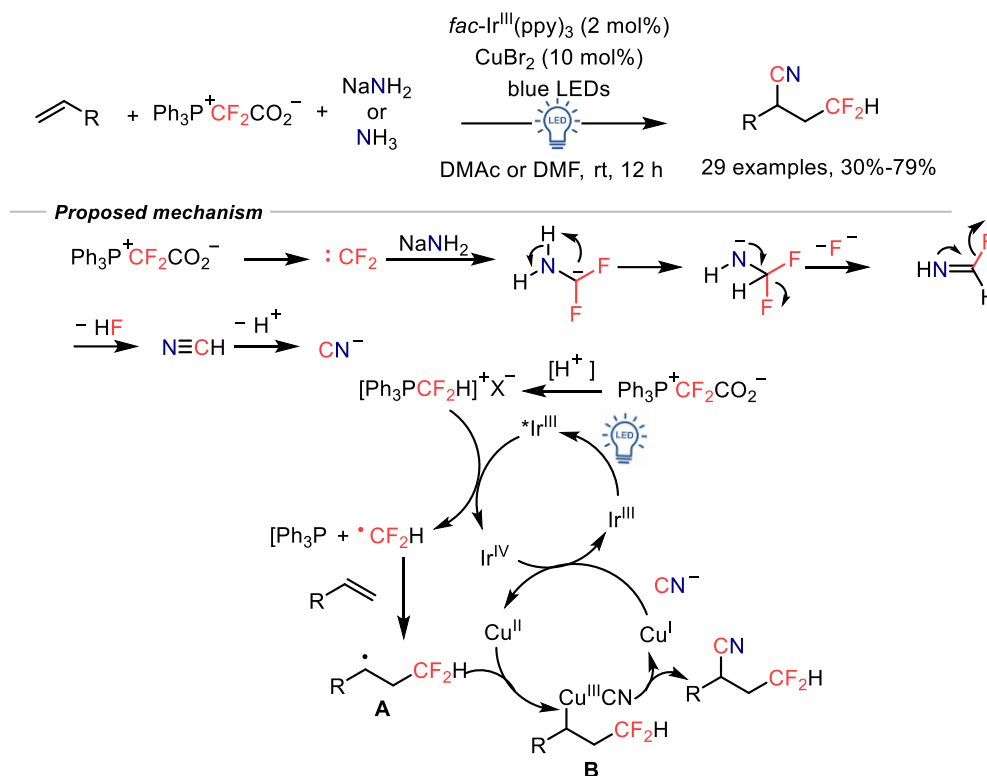


**Scheme 22.** Photoredox radical difluoromethylation/cyclization of unactivated alkenes.

Difluoromethylene phosphobetaine ( $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ , PDFA), previously developed for Wittig difluoroolefination of carbonyl derivatives,<sup>83</sup> was disclosed as precursor of the  $\text{CF}_2\text{H}$  radical. In 2019, Xiao and his team reported the photocatalyzed cyanodifluoromethylation of alkenes using PDFA in the presence of  $\text{NaNH}_2$  or  $\text{NH}_3$  (**Scheme 23**).<sup>84</sup> In this method, PDFA served not only as the  $\text{CF}_2\text{H}$  radical source but also as the CN carbon source, allowing *in situ* generation of the cyanide anion under mild conditions, providing a non-toxic cyanation reagent. The presence of a copper salt was crucial for the reaction. It was suggested that a  $\text{Cu(II)}$  cyanide was formed through oxidation ( $E_{1/2}^{\text{ox}}[\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}] = +0.71$  V vs. SCE) with  $\text{fac-}[\text{Ir}^{\text{IV}}(\text{ppy})_3]$  ( $E_{1/2}^{\text{ox}}[\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}] = +0.77$  V vs. SCE), and this  $\text{Cu(II)}$  cyanide further reacted with the radical intermediate **A**, resulting in the formation of the  $\text{Cu(III)}$  complex **B**. Reductive elimination then yielded the desired final product, while regenerating the  $\text{Cu(I)}$  catalyst (**Scheme 23**).

<sup>83</sup> Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C.; Zheng, J. *Chem. Commun. (Cambridge, U. K.)* **2013**, 49, 7513-7515.

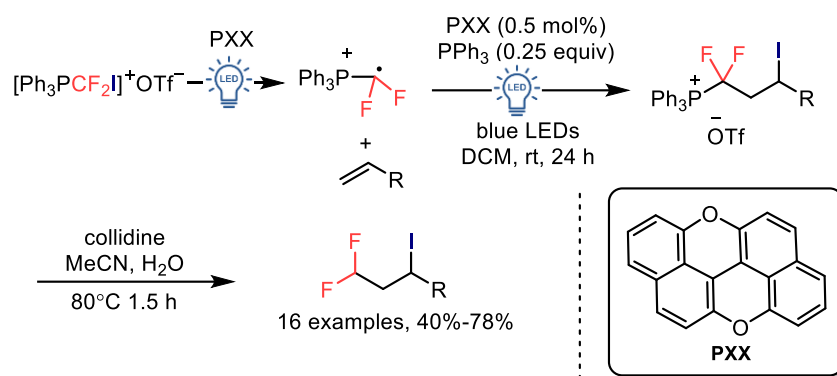
<sup>84</sup> Zhang, M.; Lin, J. H.; Xiao, J. C. *Angew. Chem. Int. Ed.* **2019**, 58, 6079-6083.



**Scheme 23.** Photoredox radical cyanodifluoromethylation of alkenes.

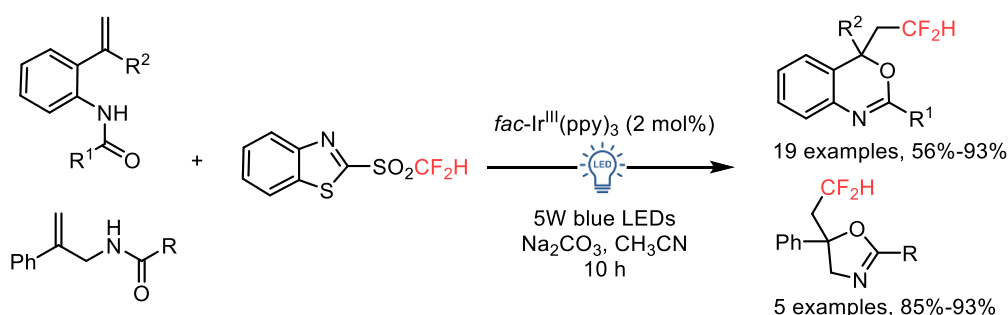
In 2020, Dilman's group described a visible-light induced iododifluoromethylation reaction of non-activated alkenes using iododifluoromethylphosphonium salt as difluoromethylating reagent, with an organic photocatalyst: *peri*-xanthenoxanthene (PXX) (**Scheme 24**).<sup>85</sup> The reaction proceeds *via* the activation of the C–I bond, leading to the (phosphonio)difluoromethyl radical cation, which reacts on the C=C bond and the resulting radical is subsequently quenched by the iodine. The intermediate phosphonium salts are easily hydrolyzed, furnishing products of the iododifluoromethylation of alkenes. The reaction worked well with terminal alkenes, providing moderate to good yields of the desired products. However, alkenes bearing nitrogen heterocycles, internal alkenes, and cyclohexene were found to be ineffective in this reaction.

<sup>85</sup> Trifonov, A. L.; Panferova, L. I.; Levin, V. V.; Kokorekin, V. A.; Dilman, A. D. *Org. Lett.* **2020**, *22*, 2409-2413.



**Scheme 24.** Visible-light-promoted iododifluoromethylation of alkenes.

Fluorinated sulfones have emerged as valuable fluoroalkylating reagents in various novel strategies for the synthesis of important fluorine-containing compounds, particularly through visible-light photoredox catalysis.<sup>86,87,88,89,90,91,92</sup> In 2016, Fu and co-workers developed a photocatalytic radical oxydifluoromethylation of substrates that featured both an olefin and an amide functional group.<sup>87</sup> This approach yielded various benzoxazines and oxazolines containing the  $\text{CF}_2\text{H}$  group (**Scheme 25**). The inclusion of sodium carbonate aimed at aiding final deprotonation step towards the formation of difluoromethylated heterocycles.



**Scheme 25.** Visible-light-promoted radical cascade difluoromethylation/cyclization.

In 2019, Liu and co-workers used difluoromethyl 2-pyridyl sulfones as radical precursors and disclosed a visible-light-induced difluoromethylation of *N*-arylacrylamides (**Scheme 26**).<sup>89</sup> This method provides a variety of difluoromethylated 2-oxindoles and quinoline-2,4-diones under mild conditions via a proposed tandem

<sup>86</sup> Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2743–2747.

<sup>87</sup> Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X. Q.; Song, M. P. *Chem. Commun. (Camb.)* **2016**, *52*, 13413–13416.

<sup>88</sup> Zou, G.; Wang, X.; Zou, G. *Org. Biomol. Chem.* **2017**, *15*, 8748–8754.

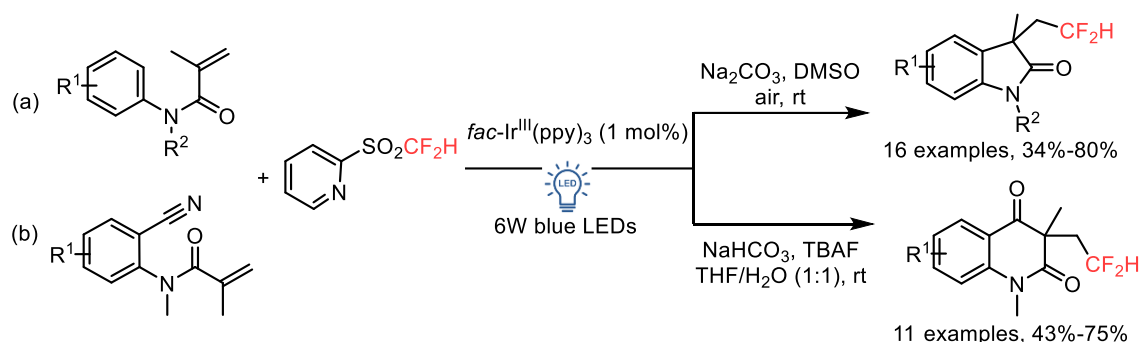
<sup>89</sup> Sun, H.; Jiang, Y.; Yang, Y. S.; Li, Y. Y.; Li, L.; Wang, W. X.; Feng, T.; Li, Z. H.; Liu, J. K. *Org. Biomol. Chem.* **2019**, *17*, 6629–6638.

<sup>90</sup> Zhu, M.; Fun, W.; Guo, W.; Tian, Y.; Wang, Z.; Xu, C.; Ji, B. *Eur. J. Org. Chem.* **2019**, *2019*, 1614–1619.

<sup>91</sup> Zhu, M.; You, Q.; Li, R. *J. Fluorine Chem.* **2019**, *228*, 109391.

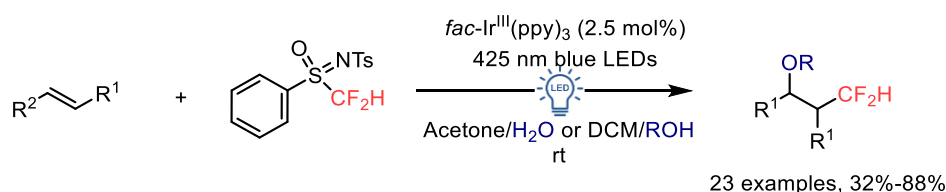
<sup>92</sup> Bao, K.; Wei, J.; Yan, H.; Sheng, R.; Bao, K. *RSC Adv.* **2020**, *10*, 25947–25951.

radical addition/cyclization process along with a good functional groups tolerance. Notably, the presence of TBAF significantly influenced the reaction, suggesting its possible role as a phase transfer catalyst.



**Scheme 26.** Visible-light-promoted tandem radical cyclization of  $N$ -arylacrylamides.

$N$ -Tosyl- $S$ -difluoromethyl- $S$ -phenylsulfoximine, also known as Hu's reagent, has been recognized as a useful source of difluorocarbene.<sup>93</sup> In 2015, Akita, Koike and co-workers reported the use of Hu's reagent as the  $\text{CF}_2\text{H}$  radical precursor in the photocatalytic oxydifluoromethylation of alkenes, giving various  $\beta$ - $\text{CF}_2\text{H}$  substituted alcohols, ethers, and esters, regioselectively (**Scheme 27**).<sup>94</sup> An Ir photocatalyst was effective in initiating the generation of a  $\text{CF}_2\text{H}$  radical through one-electron reduction of Hu's reagent.



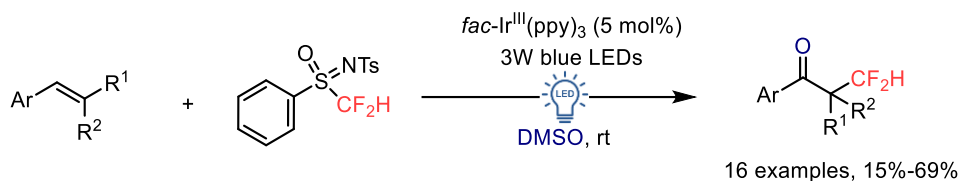
**Scheme 27.** Photoredox Catalyzed Oxydifluoromethylation of Alkenes.

In 2019, the same group extended their work to the photoredox-catalyzed synthesis of  $\alpha$ - $\text{CF}_2\text{H}$ -substituted ketones from alkenes, employing the Hu's reagent as the source of  $\text{CF}_2\text{H}$  radicals as well. Dimethyl sulfoxide (DMSO) was utilized as an oxygen source in this process (**Scheme 28**).<sup>95</sup>

<sup>93</sup> Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109-2112.

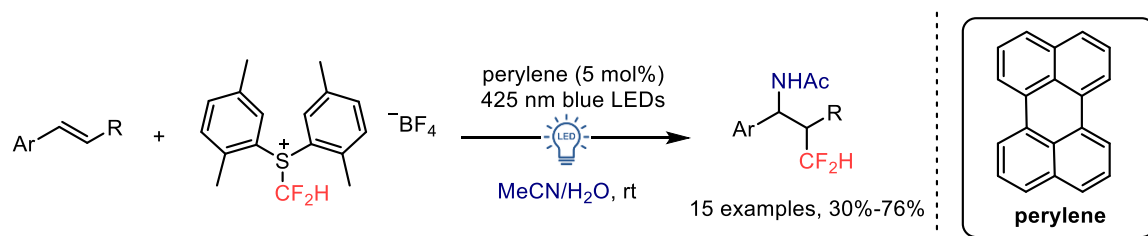
<sup>94</sup> Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. *Chem. Eur. J.* **2016**, *22*, 1262-1265.

<sup>95</sup> Nakayama, Y.; Ando, G.; Abe, M.; Koike, T.; Akita, M. *ACS Catalysis* **2019**, *9*, 6555-6563.



**Scheme 28.** Photoredox Catalyzed Keto-Difluoromethylation of Aromatic Alkenes.

In 2017, Akita, Koike and co-workers also designed and synthesized a novel reagent, *S*-difluoromethyl-*S*-di(*para*-xylyl)sulfonium tetrafluoroborate, as  $\text{CF}_2\text{H}$  source. The combination of this reagent with the organic photocatalyst perylene enabled the facile aminodifluoromethylation of aromatic alkenes through visible-light-induced radical processes, leading to valuable  $\beta\text{-CF}_2\text{H}$  substituted amines (**Scheme 29**).<sup>96</sup> It is worth noting that the Ir photocatalyst, *fac*-[Ir(ppy)<sub>3</sub>], exhibited significantly lower efficiency, giving only 29% yield.



**Scheme 29.** Visible-light-induced Perylene-catalysed amino-difluoromethylation of alkenes.

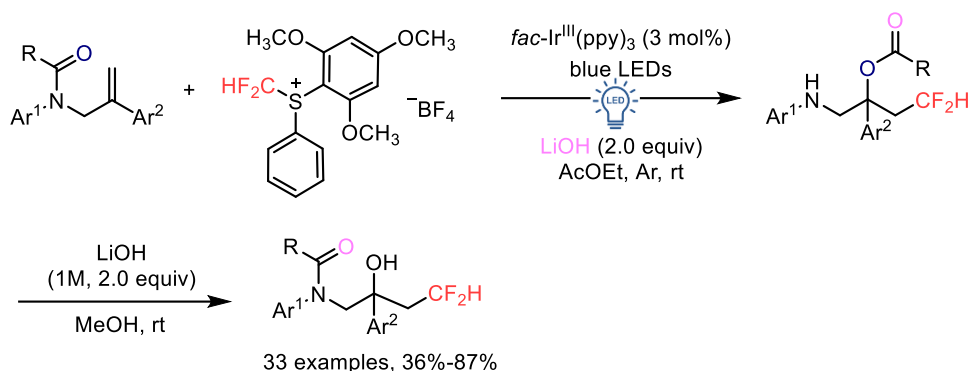
Liu and co-workers used a related sulfonium salt, *S*-(difluoromethyl)-*S*-phenyl-*S*-(2,4,6-trialkoxyphenyl) sulfonium salt, to accomplish the conversion of *N*-allyl amide into  $\text{CF}_2\text{H}$ - $\beta$ -amino alcohol by photoredox catalysis (**Scheme 30**). This approach proceeded smoothly under visible light irradiation with *fac*-[Ir(ppy)<sub>3</sub>] as photocatalyst. Mechanistic investigations revealed that a sequential difluoromethyl radical addition/carbocation trap/rearrangement is involved. In addition to serve as a good difluoromethyl radical precursor under photoredox catalysis, this sulfonium salt has also been depicted to function as an electrophilic difluoromethylating reagent<sup>97</sup> and a difluorocarbene precursor,<sup>98,99</sup> as outlined in the relevant literature.

<sup>96</sup> Noto, N.; Koike, T.; Akita, M. *Chem. Sci.* **2017**, *8*, 6375-6379.

<sup>97</sup> Lu, S. L.; Li, X.; Qin, W. B.; Liu, J. J.; Huang, Y. Y.; Wong, H. N. C.; Liu, G. K. *Org. Lett.* **2018**, *20*, 6925-6929.

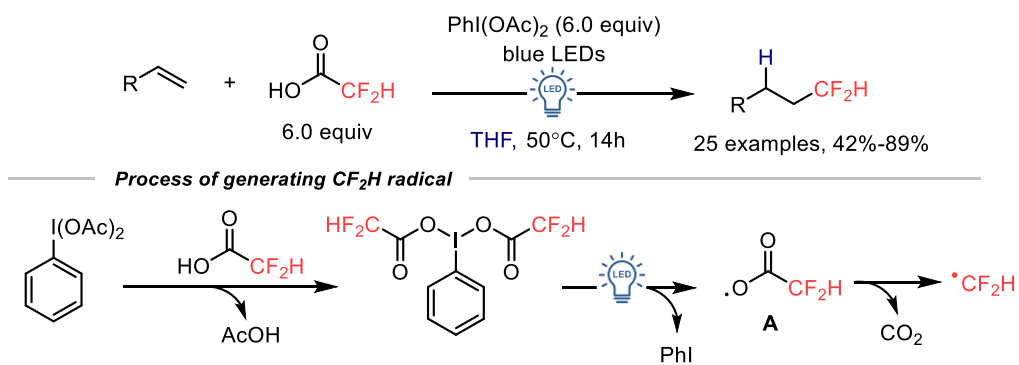
<sup>98</sup> Liu, G. K.; Li, X.; Qin, W. B.; Peng, X. S.; Wong, H. N. C.; Zhang, L.; Zhang, X. *Chem. Commun. (Camb.)* **2019**, *55*, 7446-7449.

<sup>99</sup> Liu, G. K.; Qin, W. B.; Li, X.; Lin, L. T.; Wong, H. N. C. *J. Org. Chem.* **2019**, *84*, 15948-15957.



**Scheme 30.** Photoredox Catalyzed Oxydifluoromethylation of *N*-allylamides.

In 2017, difluoroacetic acid was first used as a reagent for a silver(I)-catalyzed C–H difluoromethylation of heteroaromatic compounds.<sup>100</sup> Encouraged by the pioneer work from Maruoka on photolytically induced difluoromethylation of heteroarenes using hypervalent iodine(III) reagents,<sup>101</sup> in 2019, Gouverneur and co-workers developed a visible-light-induced hydrodifluoromethylation of alkenes using difluoroacetic acid and phenyliodine(III) diacetate (PIDA) in THF (**Scheme 31**).<sup>102</sup> This reaction proceeds without the requirement for a photocatalyst. Mechanistic investigations suggested a radical-based pathway (**Scheme 31**). The reaction starts with an acetate group exchange on PIDA with difluoroacetic acid. Under the visible-light irradiation of blue LEDs, PhI was released along with radical **A**, which subsequently generates the CF<sub>2</sub>H radical through decarboxylation event. This CF<sub>2</sub>H radical then adds to the alkene in a regioselective manner, along with an incorporation of a hydrogen atom from the solvent (THF).



**Scheme 31.** Visible-light-induced hydrodifluoromethylation of alkenes.

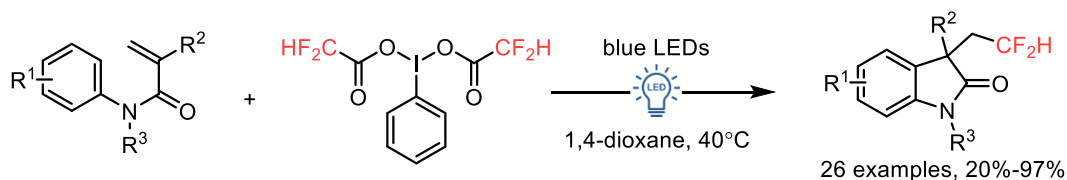
The Lu's group disclosed a visible-light-induced radical difluoromethylation of *N*-

<sup>100</sup> Tung, T. T.; Christensen, S. B.; Nielsen, J. *Chem. Eur. J.* **2017**, *23*, 18125-18128.

<sup>101</sup> Sakamoto, R.; Kashiwagi, H.; Maruoka, K. *Org. Lett.* **2017**, *19*, 5126-5129.

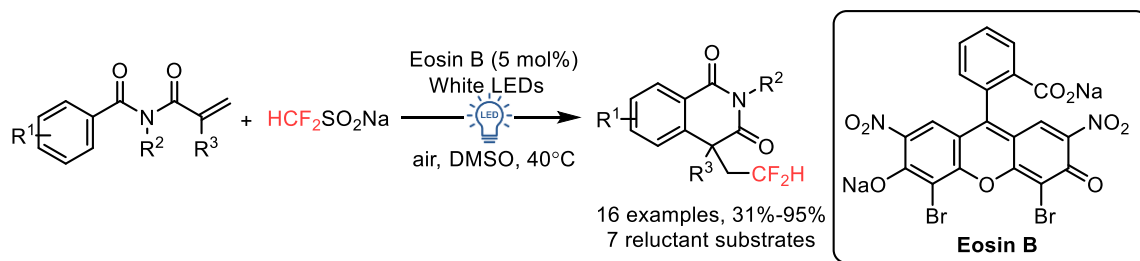
<sup>102</sup> Meyer, C. F.; Hell, S. M.; Misale, A.; Trabanco, A. A.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2019**, *58*, 8829-8833.

arylacrylamides using a hypervalent iodine(III) reagent, [bis(difluoroacetoxy)iodo]benzene as a difluoromethylation reagent (**Scheme 32**).<sup>103</sup> The inexpensive and readily accessible reagents, combined with the mild reaction conditions showcased this process as an alternative and practical strategy for the synthesis of difluoromethyl-substituted oxindoles.



**Scheme 32.** Visible-light-induced difluoromethylation of *N*-arylacrylamides using hypervalent iodine(III) reagent.

In 2020, Deng and co-workers reported a visible-light-induced radical difluoromethylation/cyclization reaction of *N*-benzamides by using  $\text{HF}_2\text{CSO}_2\text{Na}$  as reagent (**Scheme 33**).<sup>104</sup> This method offered an efficient pathway for synthesizing a variety of  $\text{CF}_2\text{H}$ -containing isoquinoline-1,3-diones. For this process, Eosin B was employed as the photocatalyst, demonstrating a higher efficiency compared to Eosin Y or *fac*-[Ir(ppy)<sub>3</sub>]. Notably, the  $\text{HF}_2\text{CSO}_2\text{Na}$  serves as the  $\text{CF}_2\text{H}$  radical source, enabling an oxidative quenching cycle of Eosin B in this reaction.



**Scheme 33.** Visible-light-induced difluoromethylation/cyclization of *N*-benzamides.

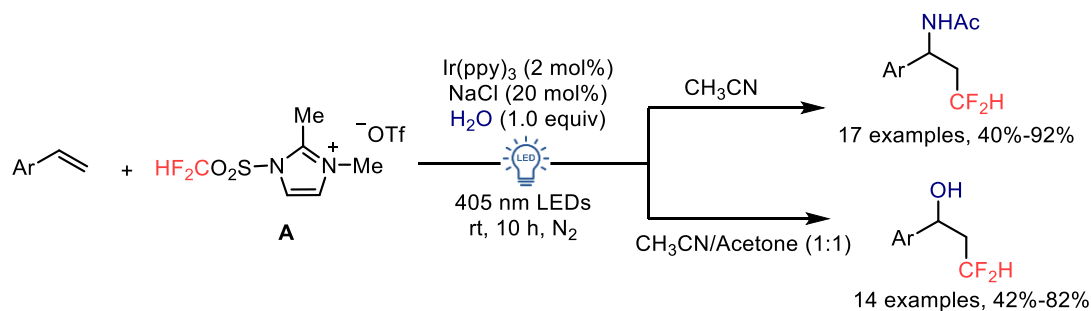
In 2022, Xiao and Lin's group described the design and synthesis of a new radical difluoromethylation reagent, difluoromethylsulfonyl imidazolium salt (**A**), enabling amino- and oxy-difluoromethylation of alkenes under the irradiation with visible-light using an Ir photocatalyst (**Scheme 34**).<sup>105</sup> The catalytic amount of NaCl was found to be crucial for this reaction, as it probably serve as a chloride source to *in situ* transform reagent **A** into difluoromethylsulfonyl chloride ( $\text{HCF}_2\text{SO}_2\text{Cl}$ ), which is more reactive and thus could be easily reduced. The amino- and oxy-difluoromethylation paths are

<sup>103</sup> Lu, K.; Lei, L.; Wei, Q.; Zhou, T.; Jia, X.; Li, Q.; Zhao, X. *Tetrahedron Lett.* **2021**, *67*, 152864.

<sup>104</sup> Shao, J.; Wang, Y.; Chen, S.; Wang, S.; Wu, Y.; Li, X.; Zhang, W.; Deng, C. *Tetrahedron* **2021**, *79*, 131822.

<sup>105</sup> Zhang, F.-X.; Lin, J.-H.; Xiao, J.-C. *Org. Lett.* **2022**, *24*, 7611-7616.

simply determined by the appropriate selection of the solvent. The use of CH<sub>3</sub>CN as the solvent resulted in aminodifluoromethylation, while the use of a CH<sub>3</sub>CN/Acetone mixture led to the oxy-difluoromethylation products. The mechanism behind the influence of acetone on the promotion of the oxy-difluoromethylation process remains unclear.

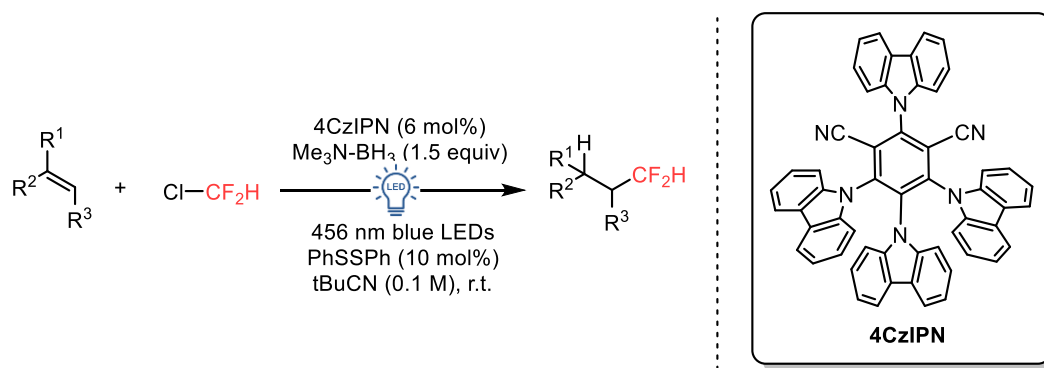


**Scheme 34.** Visible-light-induced Difluoromethylation of Alkenes by using Difluoromethylsulfonamide Salt.

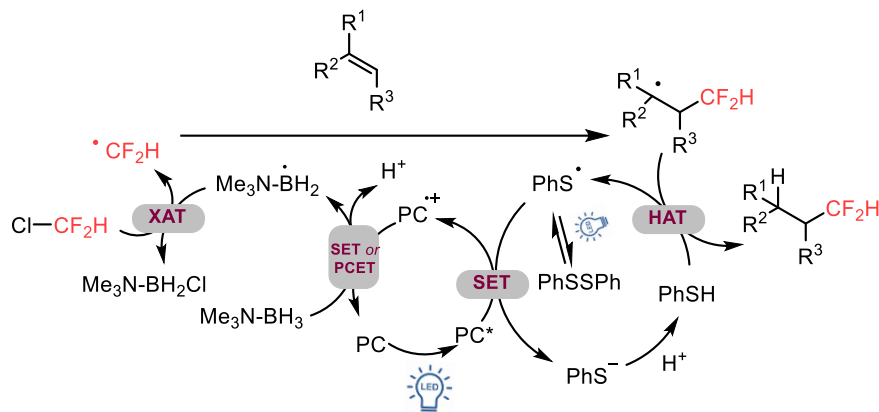
In 2022, Wu, Zhang, Ma *et al.* reported a photocatalytic radical hydrodifluoromethylation of non-activated alkenes using the chlorodifluoromethane (ClCF<sub>2</sub>H), which is widely used in the chemical industry (**Scheme 35**).<sup>106</sup> This approach merged tertiary amine-borane-triggered halogen atom transfer (XAT) with organophotoredox catalysis for the selective XAT with ClCF<sub>2</sub>H. Various alkenes, including different functional groups and pharmacologically relevant motifs, were efficiently difluoromethylated without metal catalysts.

<sup>106</sup> Zhang, Z.-Q.; Sang, Y.-Q.; Wang, C.-Q.; Dai, P.; Xue, X.-S.; Piper, J. L.; Peng, Z.-H.; Ma, J.-A.; Zhang, F.-G.; Wu, J. *J. Am. Chem. Soc.* **2022**, *144*, 14288-14296.





— *Proposed mechanism* —

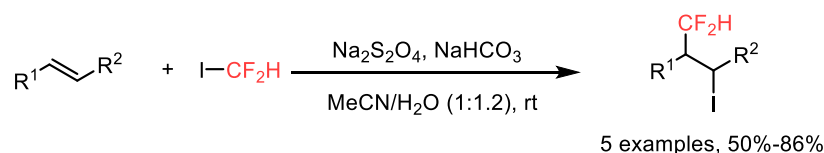


**Scheme 35.** Difluoromethylation of Unactivated Alkenes Using  $\text{ClCF}_2\text{H}$  through Tertiary Amine-Borane-Triggered Halogen Atom Transfer.

### c. Free radical strategy

The free radical strategy, which involves the formation of  $\text{CF}_2\text{H}$  radical using a chemical oxidant or reductant without transition-metal based catalysts or photochemical conditions, has only very limited examples.

In 1994, Chen and co-workers reported the radical iododifluoromethylation of alkenes in the presence of sodium dithionite and sodium bicarbonate by using  $\text{ICF}_2\text{H}$  as reagent, leading to the formation of difluoromethylated products in good yields at room temperature (**Scheme 36**).<sup>107</sup>

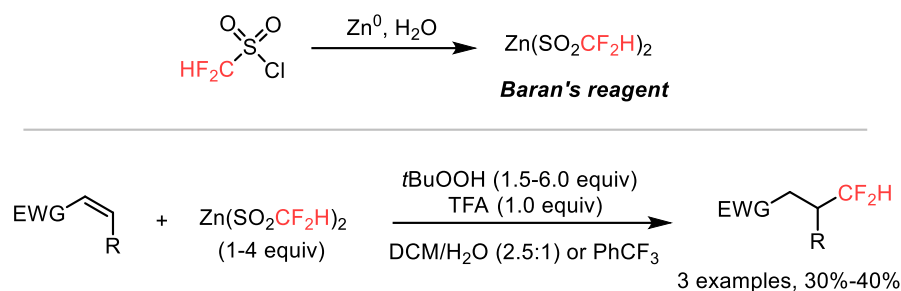


**Scheme 36.** Radical iododifluoromethylation of alkenes with  $\text{ICF}_2\text{H}$

In 2012, Baran's group reported the invention of a novel difluoromethylation reagent,

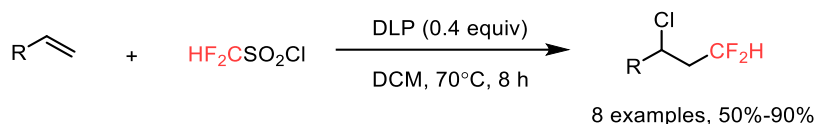
<sup>107</sup> Cao, P.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 737-738.

zinc difluoromethanesulfinate [ $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ ] (DFMS), for achieving difluoromethylation of organic substrates *via* a radical process.<sup>66</sup> DFMS is conveniently synthesized by the reduction of difluoromethanesulfonyl chloride ( $\text{HF}_2\text{CSO}_2\text{Cl}$ ) with Zn. The hydrodifluoromethylation of enones with DFMS in the presence of *t*BuOOH as oxidant was then disclosed (**Scheme 37**). In addition, heteroaromatics could be selectively difluoromethylated by DFMS under these conditions.



**Scheme 37.** Difluoromethylation of Enones with DFMS.

In 2015, Dolbier and co-workers introduced a metal-free approach for the regioselective chloro-difluoromethylation of non-activated alkenes. This method, conducted under thermal conditions, employed dilauroyl peroxide (DLP) as an initiator and possible oxidant. Difluoromethyl radical was generated from sulfonyl chloride, which then undergo atom transfer radical additions (ATRA) to alkenes, resulting in the formation of chloro-difluoromethylated products (**Scheme 38**).<sup>108</sup>



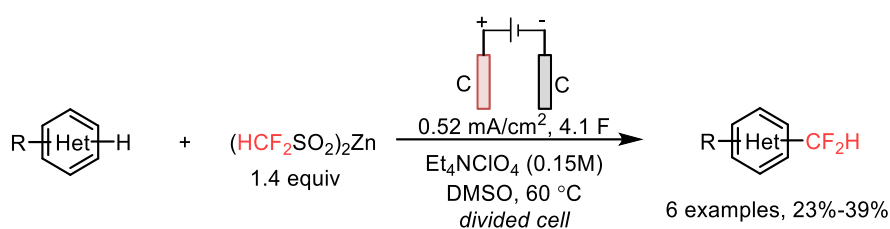
**Scheme 38.** Radical Chloro-Difluoromethylation of Unactivated Alkenes with  $\text{HF}_2\text{CSO}_2\text{Cl}$ .

#### d. Electrochemical transformation (via anodic oxidation or cathodic reduction)

As electrochemistry has known a resurgence as a sustainable strategy for organic synthesis, electrochemical approaches for the difluoromethylation of alkenes is gathering increasing attention from synthetic chemists. The electrochemical oxidative alkene difluoromethylation reactions offer a distinct advantage over conventional methods by generally avoiding the use of transition metal catalysts and/or harmful chemical oxidants. Besides, electrochemical reactions are often conducted at ambient

<sup>108</sup> Thomason, C. S.; Tang, X.-J.; Dolbier, W. R. *J. Org. Chem.* **2014**, *80*, 1264-1268.

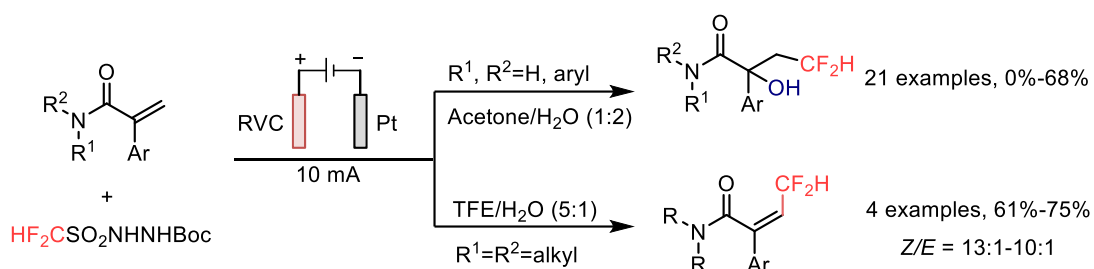
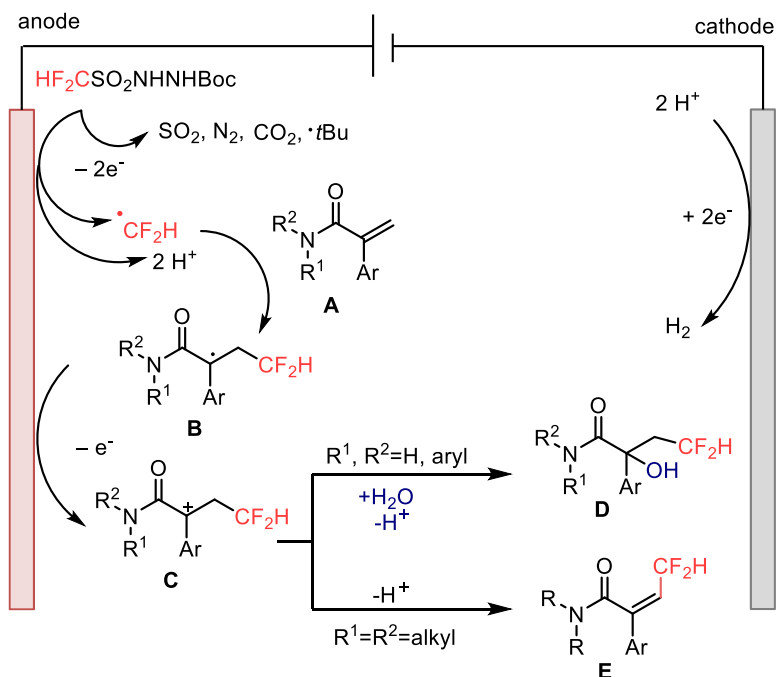
temperature and atmospheric pressure, which helps to preserve the delicate nature of certain functional groups on the starting materials. This mildness of the reaction conditions allows for better functional group compatibility, making electrochemical oxidative alkene functionalization an attractive and powerful tool for efficient transformations in organic synthesis. However, compared with the extensively investigated photocatalytic methods, the electrochemical radical approach for alkene difluoromethylation is still underdeveloped. The first electrochemical generation of the  $\text{CF}_2\text{H}$  radical was pioneered by Blackmond and Baran in the course of an electrochemical Minisci type reaction in 2014.<sup>109</sup> With  $(\text{HCF}_2\text{SO}_2)_2\text{Zn}$  as  $\text{CF}_2\text{H}$  radical source, they successfully accomplished the difluoromethylation of *N*-heterocycles. 6 examples were synthesized with yields of up to 39% (**Scheme 39**).



**Scheme 39.** Pioneering work on the electrochemical generation of  $\text{CF}_2\text{H}$  radical.

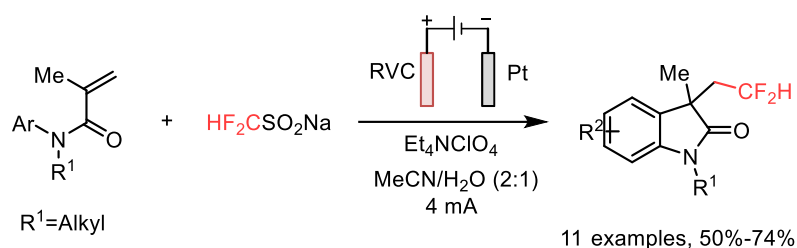
In 2018, Xu and co-workers reported the electrochemical difluoromethylation of acrylamides using  $\text{HF}_2\text{CSO}_2\text{NHNHBoc}$  as the  $\text{CF}_2\text{H}$  radical precursor (**Scheme 40**).<sup>25</sup> The use of a reticulated vitreous carbon (RVC)/Pt electrodes with an applied constant current of 10 mA at 70 °C in an undivided cell, resulted in the formation of 1,2-hydroxydifluoromethylated or  $\beta$ -difluoromethylated acrylamides, respectively, in moderate to good yields. The occurrence of 1,2-difunctionalization or C–H functionalization in acrylamides is determined by the substituents on the nitrogen atom, rather than reaction conditions. Isotope labeling experiments suggested that the hydroxyl group in product **1** was coming from  $\text{H}_2\text{O}$ . The proposed reaction mechanism involved the anodic oxidation of the difluoromethyl reagent to generate the difluoromethyl radical. This radical then adds to the substrate **A**, forming a radical intermediate **B**, which subsequently underwent a second anodic oxidation, leading to the formation of a carbon cationic intermediate **C**. Then, **C** reacted with  $\text{H}_2\text{O}$  or through a proton elimination, resulting in the formation of two different products **D** or **E**, respectively.

<sup>109</sup> O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11868-11871.

**Proposed mechanism****Scheme 40.** Electrochemical Difluoromethylation of acrylamides.

In 2019, Ackermann and co-workers introduced an electrochemical difluoromethylation/cyclization method with *N*-substituted acrylamides (**Scheme 41**).<sup>110</sup> The reaction was conducted under catalyst-free and external oxidant-free conditions in an undivided cell, by using inexpensive and bench-stable sodium difluoromethylsulfinate ( $\text{HF}_2\text{CSO}_2\text{Na}$ ) as  $\text{CF}_2\text{H}$  radical precursor, resulting in an efficient synthesis of difluoromethylated oxindoles. Mechanistic studies provided robust evidence to support a single-electron transfer (SET) based reaction pathway.

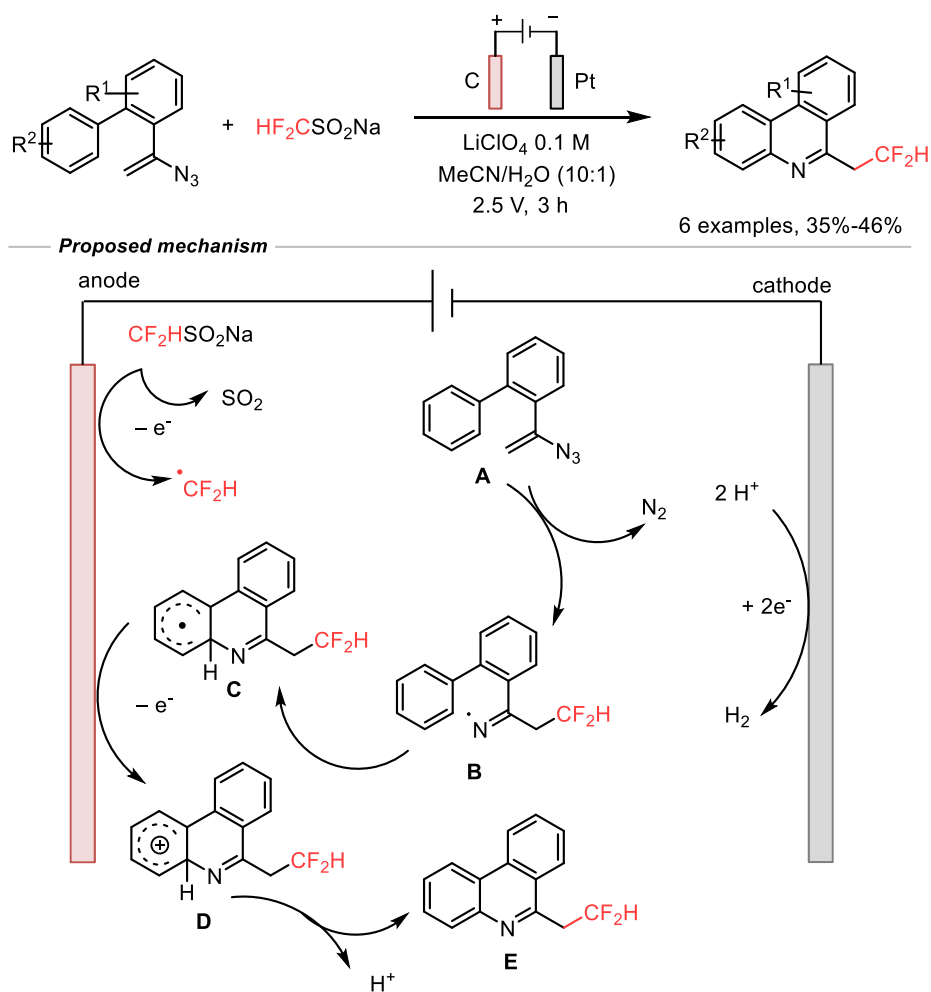
<sup>110</sup> Ruan, Z.; Huang, Z.; Xu, Z.; Mo, G.; Tian, X.; Yu, X.-Y.; Ackermann, L. *Org. Lett.* **2019**, *21*, 1237-1240.



**Scheme 41.** Electrochemical Difluoromethylation/cyclization of acrylamides.

In 2020, Xu and Kong developed an electrochemical strategy for radical difluoromethylation of vinyl azides (**Scheme 42**).<sup>111</sup> The reaction was carried out under mild conditions, using sodium difluoromethylsulfinate ( $\text{HF}_2\text{CSO}_2\text{Na}$ ) as the  $\text{CF}_2\text{H}$  radical precursor, Pt as anode, carbon as cathode, at a constant voltage of 2.5 V. Cyclic voltammetry studies revealed that the difluoromethyl radical was generated through the anodic oxidation of  $\text{HF}_2\text{CSO}_2\text{Na}$ . This radical then adds to biaryl vinyl azide (**A**) to produce the iminyl radical intermediate (**B**) by nitrogen extrusion. Subsequently, intermediate (**B**) undergoes homolytic aromatic substitution, forming radical **C**. Radical **C** is further oxidized to cation intermediate **D**, which then undergoes deprotonation to yield 6-fluoroalkylphenanthridine (**E**). This method provides a green approach to synthesize difluoromethylated nitrogen heterocycles.

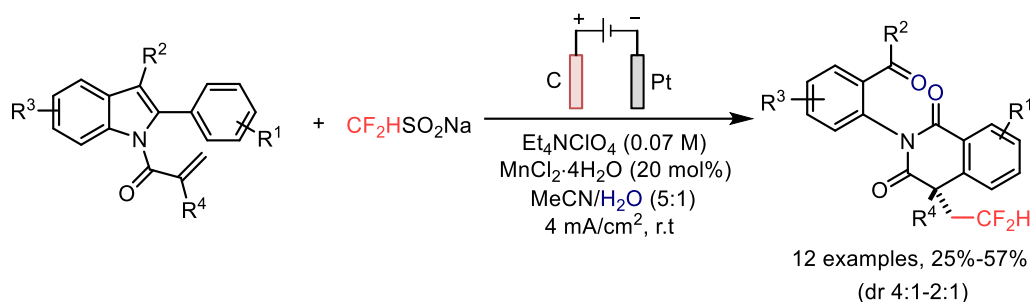
<sup>111</sup> Lin, L.; Liang, Q.; Kong, X.; Chen, Q.; Xu, B. *J. Org. Chem.* **2020**, *85*, 15708-15716.



**Scheme 42.** Electrochemical Difluoromethylation of vinyl azides.

The same  $\text{CF}_2\text{H}$  radical precursor was used for an electrochemical difluoromethylation/cyclization/indole oxidative cleavage reaction by Guo and co-workers in 2020 (**Scheme 43**),<sup>112</sup> affording a series of difluoromethylated 2-(2-acetylphenyl)isoquinoline-1,3-diones in moderate to good yields with good stereoselectivity. Detailed mechanistic studies provided strong support for the radical fluoroalkylation, cyclization, and indole oxidative cleavage sequence.

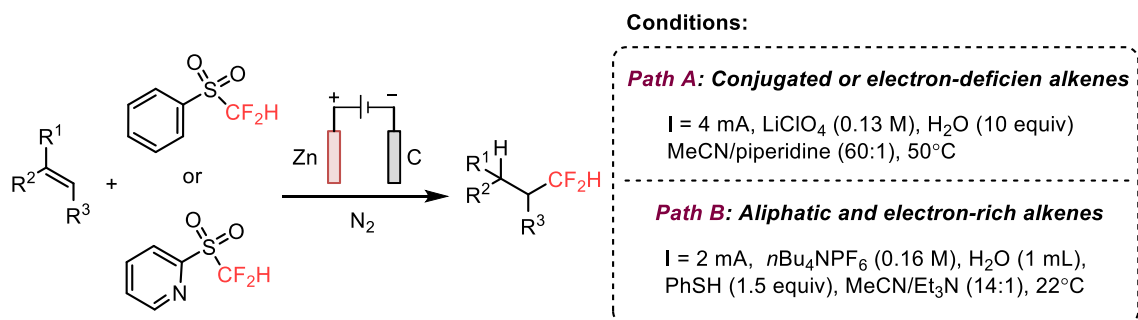
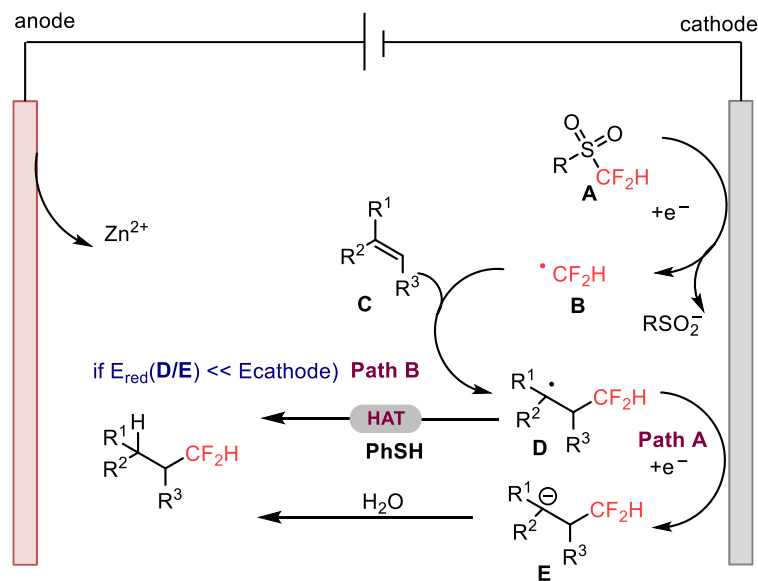
<sup>112</sup> Xin, Y.; Yu - Sheng, C.; Xin - Peng, Z.; Long - Zhou, Q.; Qi, S.; Xiu, D.; Lin, C.; Guigen, L.; Jiang - Kai, Q.; Kai, G. *Chem. Eur. J.* **2021**, *27*, 6522-6528.



**Scheme 43.** Electrochemical Difluoromethylation/cyclization of Indole Derivatives.

In 2022, Kim, Lee, Kwak *et al.* successfully achieved the radical hydrodifluoromethylation of unsaturated C – C bonds via an electroreductively triggered approach (**Scheme 44**).<sup>113</sup> The reaction conditions were selected based on the electronic properties of the alkenes. The cathodic reduction of **A** would generate  $\text{CF}_2\text{H}$  radical **B**, which, upon addition to the alkene substrate, forms the alkyl radical intermediate **D**. Based on the electronic properties of the introduced alkenes, two mechanistic pathways were proposed. When  $E_{\text{red}}(\text{D}/\text{E}) \approx E_{\text{red}}(\text{A}/\text{A}^{\cdot-})$ , radical **D** can either be reduced to carbanion **E**, leading to the final product after protonation with water (path A, for  $\text{R}_1 = \text{EWG}$  or Aryl). Alternatively, when  $E_{\text{red}}(\text{D}/\text{E})$  is too negative for the cathodic reduction, radical **D** would undergo a hydrogen-atom transfer (HAT) to yield the final product in the presence of a hydrogen atom donor such as a thiol (path B, for  $\text{R}^1 = \text{EDG}$  or Alkyl) (**Scheme 44**).

<sup>113</sup> Kim, S.; Hwang, K. H.; Park, H. G.; Kwak, J.; Lee, H.; Kim, H. *Commun. Chem.* **2022**, *5*, 96.

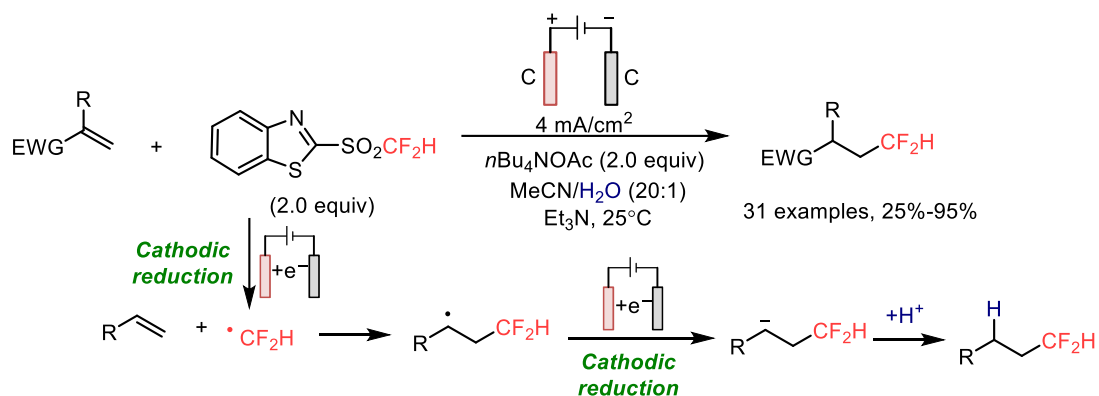
**Proposed mechanism**

**Scheme 44.** Electroreductively triggered Radical hydrodifluoromethylation of unsaturated C–C bonds.

The difluoromethyl radical can be generated not only through an anodic oxidation but also through a cathodic reduction. In 2021, Hu, Ni *et al.* depicted a radical difluoromethylation of electron-deficient alkenes through an electrochemical reduction of difluoromethyl heteroaryl sulfone (**Scheme 45**).<sup>114</sup> The reaction could be performed using inexpensive graphite electrodes under transition-metal-free conditions in an aqueous medium and undivided cell. A series of electron-deficient alkenes readily undergo hydrofluoroalkylation in good to excellent yields. A control experiment conducted in the absence of Et<sub>3</sub>N led to a decreased in yield from 90% to 49%, highlighting the essential role of this basic additive. This protocol represents the pioneering instance of electrochemically generating difluoromethyl radicals from sulfones.

<sup>114</sup> Zhou, X.; Ni, C.; Deng, L.; Hu, J. *Chem. Commun. (Camb.)* **2021**, 57, 8750-8753.



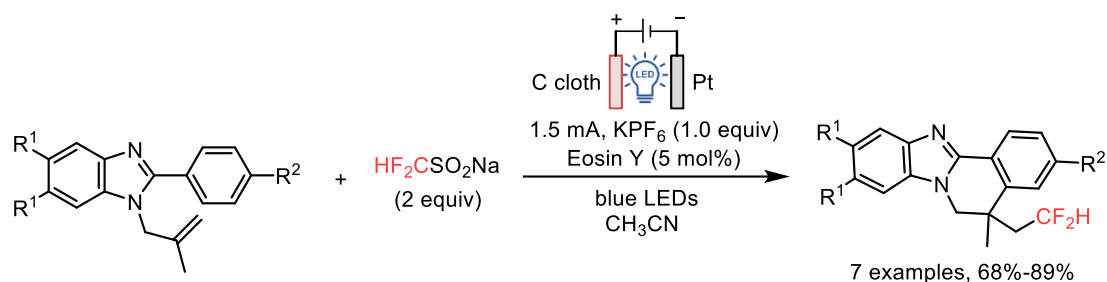


**Scheme 45.** Electrochemical reduction of difluoromethyl sulfone for radical difluoromethylation of alkenes.

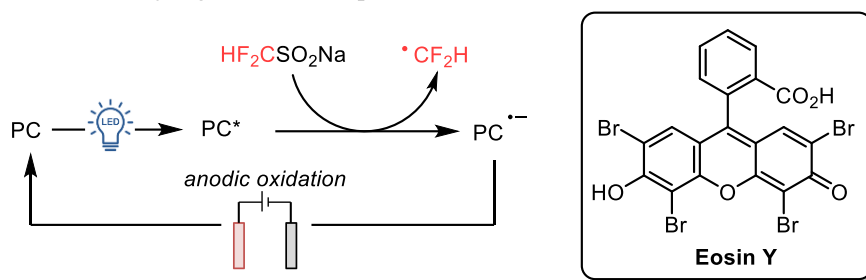
### e. Miscellaneous radical difluoromethylation reaction

Very recently, an electrophotocatalytic difluoromethylation/cyclization cascade of alkenes using difluoromethanesulfinate salts ( $\text{HF}_2\text{CSO}_2\text{Na}$ ) as the radical source and eosin Y as photocatalyst has been developed by Liang, Shi and co-workers (**Scheme 46**).<sup>115</sup> This reaction proceeds under mild electrode potentials, using  $\text{KPF}_6$  as the electrolyte, a C cloth anode and Pt plate cathode, under 1.5 mA constant current and blue light irradiation. With these reaction conditions a variety of difluoromethylated heterocycles were obtained with a high functional-group tolerance. The method allowed late-stage diversification of complex molecular and was performed on gram scale, even utilizing sunlight. This strategy harnesses both light and electricity and mechanistic insights suggested a combination of electrolysis and reductive quenching photocatalytic cycles of eosin Y.

<sup>115</sup> Chen, D.; Yang, X.; Wang, D.; Li, Y.; Shi, L.; Liang, D. *Org. Chem. Front.* **2023**, *10*, 2482-2490.



*Electrophotocatalytic generation of CF<sub>2</sub>H radical*



**Scheme 46.** Electrophotocatalytic difluoromethylative cyclization of alkenes.

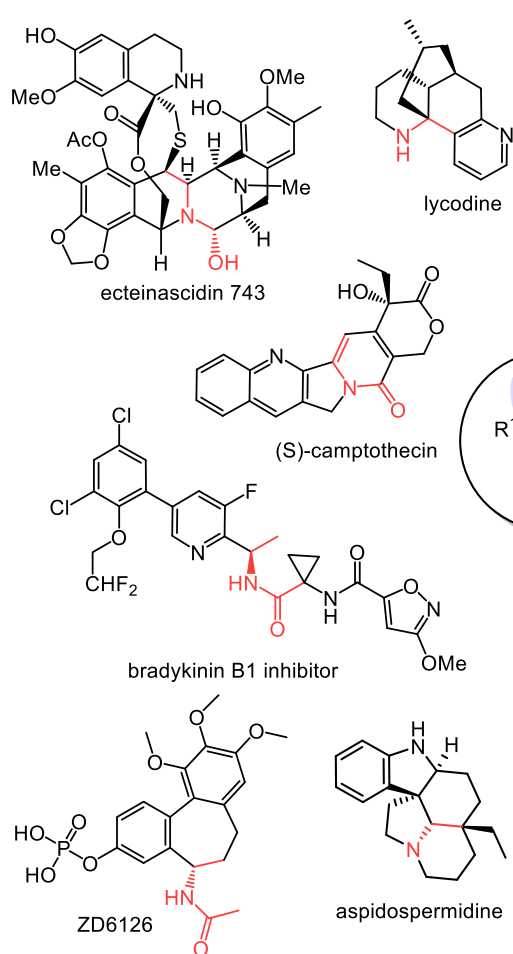
## 2.2 Electrochemical Difluoromethylation of enamides

With that depicted knowledges and based on our ongoing research program dedicated to electrocatalysis and organofluorine chemistry, we decided to develop a versatile methodology for accessing desired difluoromethylated molecules of interest. Currently, the electrochemical difluoromethylation of alkenes is restricted to electron-deficient olefins. For instance, most of the CF<sub>2</sub>H radical addition reactions were performed on acrylamides, α,β-unsaturated ketones, or vinyl azide, as discussed in the overview in [section 2.1.4.d](#). Therefore, taking advantage of the versatile reactivity of alkenes, we propose extending the addition of electrochemically generated CF<sub>2</sub>H radicals onto electron-rich alkenes. In this regard, enamides emerged as particularly attractive scaffolds, striking a delicate balance between reactivity and stability, allowing them to serve as valuable synthetic building blocks for the construction of numerous natural products and biological molecules (**Figure 12a**).<sup>116</sup> In addition, enamides are commonly present in natural products and active drugs (**Figure**

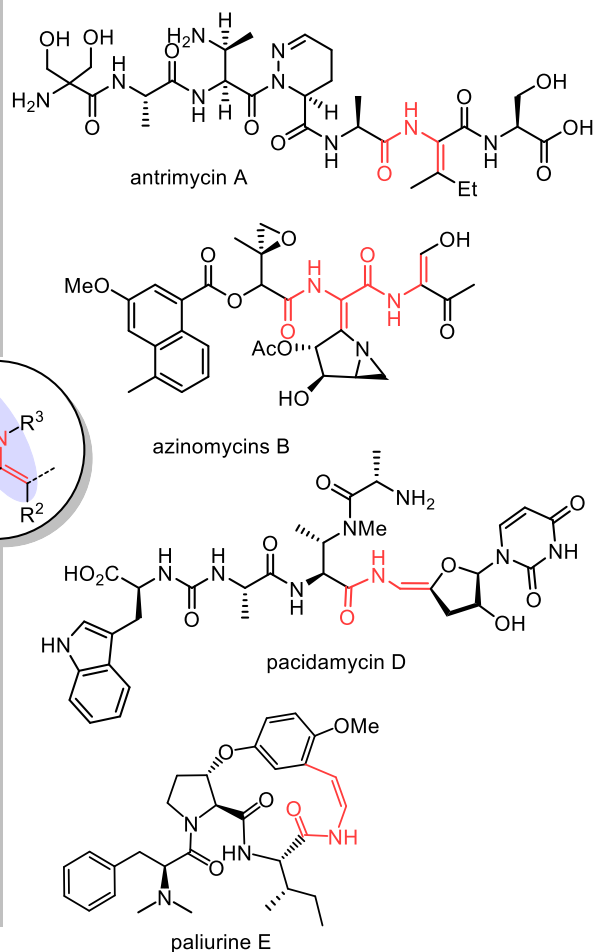
<sup>116</sup> Masson, G.; Courant, T.; Dagousset, G. *Synthesis* **2015**, *47*, 1799-1856.

12b).<sup>117,118,119,120,121,122,123</sup>

## a) Natural products and biological molecules synthesized from enamides



## b) Natural products and biomolecules containing enamides



**Figure 12.** Natural products and biological molecules synthesized from or containing enamides.

Consequently, the functionalization of enamides has recently flourished, particularly at their C(sp<sup>2</sup>)-H bonds, yielding diverse  $\beta$ -functionalized enamides containing

<sup>117</sup> Kuranaga, T.; Sesoko, Y.; Inoue, M. *Nat Prod Rep* **2014**, *31*, 514-532.

<sup>118</sup> Villa, M. V.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. *Org. Lett.* **2007**, *9*, 1631-1633.

<sup>119</sup> Mathieson, J. E.; Crawford, J. J.; Schmidtman, M.; Marquez, R. *Org. Biomol. Chem.* **2009**, *7*, 2170-2175.

<sup>120</sup> Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040-6041.

<sup>121</sup> Okamoto, K.; Sakagami, M.; Feng, F.; Togame, H.; Takemoto, H.; Ichikawa, S.; Matsuda, A. *Org. Lett.* **2011**, *13*, 5240-5243.

<sup>122</sup> Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013**, *135*, 5467-5474.

<sup>123</sup> Jiang, J.; Ma, Z.; Castle, S. L. *Tetrahedron* **2015**, *71*, 5431-5451.

aryl,<sup>124,125,126</sup> alkene,<sup>127,128,129</sup> alkyne,<sup>130,131,132</sup> alkyl,<sup>133,134</sup> carbonyl,<sup>135,136,137,138</sup> and arylsulfonyl functionalities.<sup>139,140,141,142,143</sup>

Although the catalyzed addition of fluorinated residues on enamides has already been developed,<sup>80,144,145,146,147</sup> the addition of electrogenerated fluorinated radicals on this scaffold remains scarce and restricted to the trifluoromethyl residue (**Scheme 47**).<sup>26</sup> Herein, we propose the addition of electrochemically generated difluoromethyl radicals onto electron-rich enamides under electrochemical conditions, aiming to access synthetically and pharmaceutically important  $\beta$ -difluoromethylated enamides (**Scheme 47**).

<sup>124</sup> Pankajakshan, S.; Xu, Y.-H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5701-5705.

<sup>125</sup> Bartoccini, F.; Cannas, D. M.; Fini, F.; Piersanti, G. *Org. Lett.* **2016**, *18*, 2762-2765.

<sup>126</sup> Gigant, N.; Chausset-Boissarie, L.; Belhomme, M.-C.; Poisson, T.; Pannecoucke, X.; Gillaizeau, I. *Org. Lett.* **2012**, *15*, 278-281.

<sup>127</sup> Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 7167-7171.

<sup>128</sup> Gigant, N.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 3304-3307.

<sup>129</sup> Xu, Y.-H.; Chok, Y. K.; Loh, T.-P.; Xu, Y.-H. *Chem. Sci.* **2011**, *2*, 1822-1825.

<sup>130</sup> Feng, C.; Feng, D.; Loh, T.-P.; Feng, C. *Chem. Commun. (Cambridge, U. K.)* **2014**, *50*, 9865-9868.

<sup>131</sup> Xu, Y.-H.; Zhang, Q.-C.; He, T.; Meng, F.-F.; Loh, T.-P. *Adv. Synth. Catal.* **2014**, *356*, 1539-1543.

<sup>132</sup> Shaikh, A. C.; Shinde, D. R.; Patil, N. T. *Org. Lett.* **2016**, *18*, 1056-1059.

<sup>133</sup> Jiang, H.; Huang, C.; Guo, J.; Zeng, C.; Zhang, Y.; Yu, S. *Chem. Eur. J.* **2012**, *18*, 15158-15166.

<sup>134</sup> Ding, R.; Huang, Z.-D.; Liu, Z.-L.; Wang, T.-X.; Xu, Y.-H.; Loh, T.-P.; Ding, R. *Chem. Commun. (Cambridge, U. K.)* **2016**, *52*, 5617-5620.

<sup>135</sup> Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430-11433.

<sup>136</sup> Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358-4361.

<sup>137</sup> Ding, R.; Zhang, Q.-C.; Xu, Y.-H.; Loh, T.-P.; Ding, R. *Chem. Commun. (Cambridge, U. K.)* **2014**, *50*, 11661-11664.

<sup>138</sup> Xiong, Z.; Liang, D.; Luo, S.; Xiong, Z. *Org. Chem. Front.* **2017**, *4*, 1103-1106.

<sup>139</sup> Jiang, H.; Chen, X.; Zhang, Y.; Yu, S. *Adv. Synth. Catal.* **2013**, *355*, 809-813.

<sup>140</sup> Sun, D.; Zhang, R.; Sun, D. *Org. Chem. Front.* **2018**, *5*, 92-97.

<sup>141</sup> Li, Y.; Cheng, K.; Lu, X.; Sun, J. *Adv. Synth. Catal.* **2010**, *352*, 1876-1880.

<sup>142</sup> Zhu, T.-H.; Zhang, X.-C.; Zhao, K.; Loh, T.-P.; Zhu, T.-H. *Org. Chem. Front.* **2019**, *6*, 94-98.

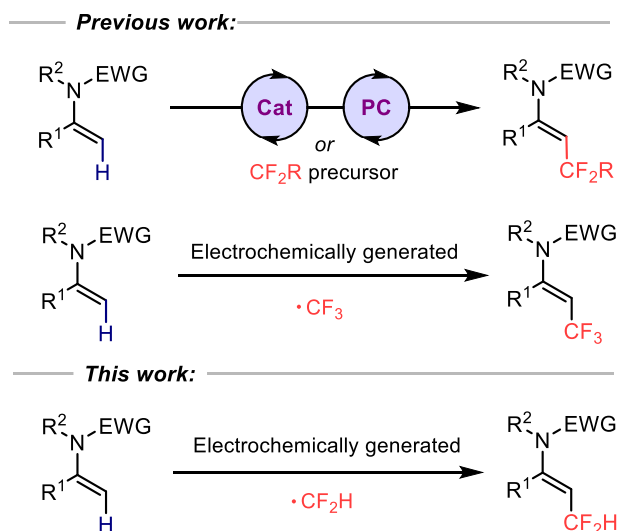
<sup>143</sup> Zhu, T.-H.; Zhang, X.-C.; Cui, X.-L.; Zhang, Z.-Y.; Jiang, H.; Sun, S.-S.; Zhao, L.-L.; Zhao, K.; Loh, T.-P. *Adv. Synth. Catal.* **2019**, *361*, 3593-3598.

<sup>144</sup> Liu, Q.; Lu, Y.; Sheng, H.; Zhang, C. S.; Su, X. D.; Wang, Z. X.; Chen, X. Y. *Angew. Chem. Int. Ed.* **2021**, *60*, 25477-25484.

<sup>145</sup> Zhao, Y.; Zhang, Y.; Liu, Y.; Zhu, T.; Wu, J. *Org. Chem. Front.* **2021**, *8*, 5948-5954.

<sup>146</sup> Li, P.; Liu, Q.; Sun, D.-Q.; Chen, X.-Y. *Org. Biomol. Chem.* **2022**, *20*, 7599-7603.

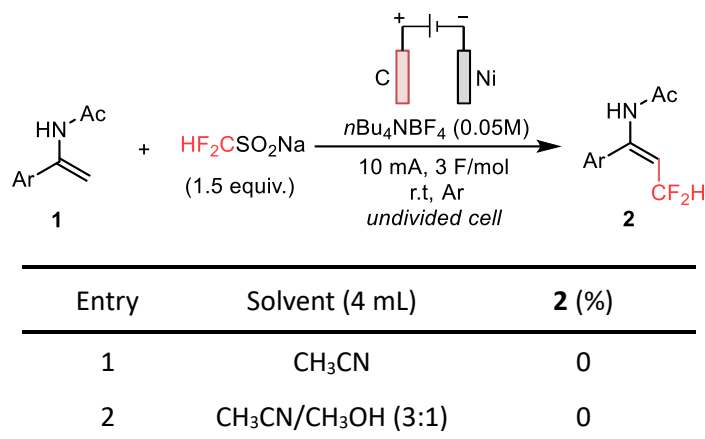
<sup>147</sup> Zhao, K.; Guo, J.-Y.; Guan, T.; Wang, Y.-X.; Tao, J.-Y.; Zhang, Y.; Zhang, Q.-H.; Ni, K.; Loh, T.-P. *Org. Chem. Front.* **2021**, *8*, 4086-4094.



**Scheme 47.** State of the art and this work.

## 2.2.1 Optimization

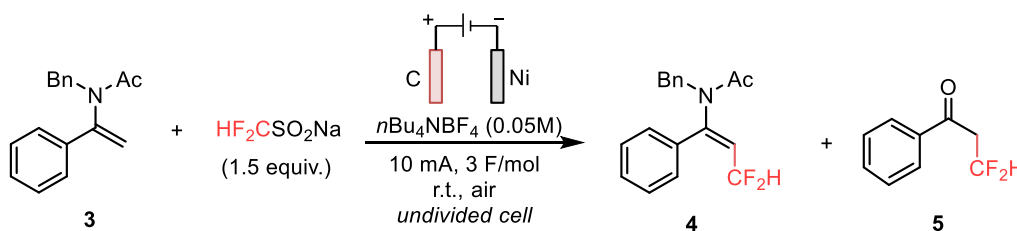
As a starting point, we employed 0.2 mmol of compound **1** as model substrate, along with 1.5 equivalents of  $\text{HF}_2\text{CSO}_2\text{Na}$  as the difluoromethyl source and 0.2 mmol of *n*-tetrabutylammonium tetrafluoroborate ( $n\text{Bu}_4\text{NBF}_4$ ) as the electrolyte. Using graphite as the anode and nickel as the cathode, with a constant current of 10 mA and 3 F/mol of electrons, at room temperature and under an argon atmosphere, the reaction was conducted using either sole acetonitrile 4 mL or a mixed solvent system including acetonitrile and methanol in a 3:1 ratio. Unfortunately, the desired product **2** could not be obtained under both conditions (**Table 2**).



**Table 2.** First Attempt of Enamide Difluoromethylation Reaction.

Then, we introduced a benzyl protecting group at the nitrogen atom to synthesize substrate **3**. On a scale of 0.2 mmol, the reaction employed 1.5 equivalents of  $\text{HF}_2\text{CSO}_2\text{Na}$  as the difluoromethyl source, using graphite as the anode and nickel as the

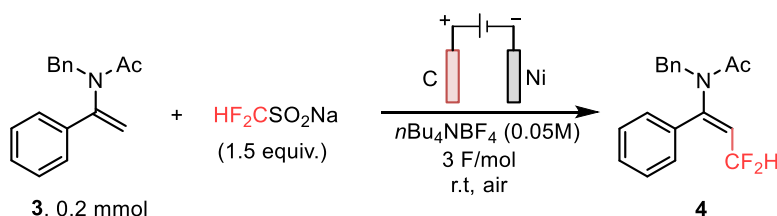
cathode under a constant current of 10 mA with 3 F/mol of charge, 0.2 mmol of *n*-tetrabutylammonium tetrafluoroborate (*n*Bu<sub>4</sub>NBF<sub>4</sub>) as the electrolyte in a mixture of acetonitrile and water with a 7:1 ratio. Pleasingly, under these reaction conditions, we obtained the desired product, difluoromethylated enamide **4**, in a 39% isolated yield. However, we also observed a concurrent side product **5** resulting from the hydrolysis of the targeted product in 50% isolated yield (**Table 3**, entry 1). Subsequently, under the same conditions but using only acetonitrile as the solvent, product **4** was obtained as a unique product in 35% yield (**Table 3**, entry 2).



Entry	Solvent	<b>4</b> (%)	<b>5</b> (%)
1	CH <sub>3</sub> CN/H <sub>2</sub> O (7:1)	39	50
2	CH <sub>3</sub> CN	35	0

**Table 3.** Difluoromethylation of Enamide **3**.

Thus, we employed acetonitrile as the solvent and began the optimization of the reaction conditions. Firstly, we investigated different applied constant current (**Table 4**, entries 1-3). Increasing up to 15 mA was deleterious for the reaction outcome, resulting in a decreased yield (**Table 4**, entry 1). Reducing the current to 5 mA led to an improved yield of 56% (**Table 4**, entry 3). Subsequently, under the conditions of 5 mA constant current, we screened several solvents (**Table 4**, entries 4-8). Solvents including DMF, mixture of CH<sub>3</sub>CN and methanol, THF, DMA, and NMP were tested, and the results indicated that DMF was the optimal solvent for our transformation. A 64% NMR yield and 69% isolated yield was obtained using DMF as solvent (**Table 4**, entry 4).

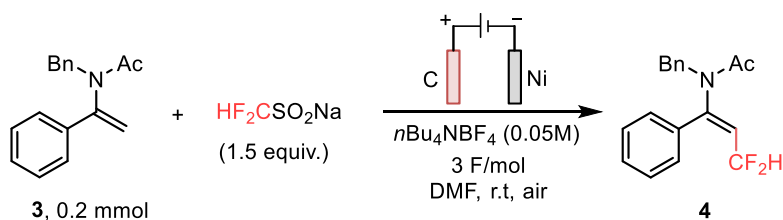


Entry	Solvent	Current (mA)	Yield of <b>4</b> (%) <sup>a</sup>	Starting material <b>3</b> (%) <sup>a</sup>	Conv. (%) <sup>a</sup>
1	CH <sub>3</sub> CN	15	35	15	85

Entry	Solvent	Current (mA)	Yield of <b>4</b> (%) <sup>a</sup>	Starting material <b>3</b> (%) <sup>a</sup>	Conv. (%) <sup>a</sup>
2	CH <sub>3</sub> CN	10	42	11	89
3	CH <sub>3</sub> CN	5	56	6	94
4	DMF	5	64 (69) <sup>b</sup>	9 (9) <sup>b</sup>	91
5	CH <sub>3</sub> CN:CH <sub>3</sub> OH (7:1)	5	48	5	95
6	THF	5	26	20	80
7	DMA	5	41	11	89
8	NMP	5	43	18	82

**Table 4.** Screening of current and solvents. <sup>a</sup><sup>1</sup>H-NMR yield with 0.2 mmol mesitylene as an internal standard. <sup>b</sup> Isolated yield.

Using DMF as the solvent, we observed that a continuous decrease in current down to 2 mA could enhance the reaction efficiency, yielding the product in 80% (**Table 5**, entries 1-5). However, further decrease of the current down to 1 mA led to a reduced yield. (**Table 5**, entry 5). As some unreacted starting material remained, we attempted to increase the charge from 3.0 F/mol to 3.5 F/mol under an applied 2 mA constant current. The reaction time increased from 8.04 hours to 9.38 hours. Nevertheless, the yield did not improve, with 4% of the starting material remaining (**Table 5**, entry 6). Therefore, we continued using 3.0 F/mol of charge.

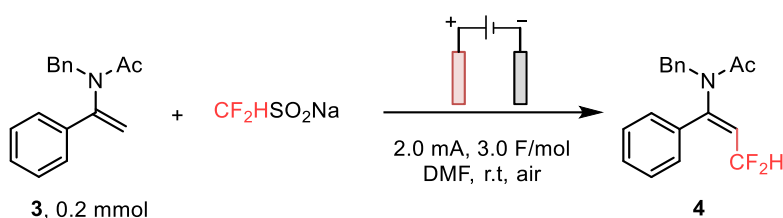


Entry	Current (mA)	T (h)	Yield of <b>4</b> (%) <sup>a</sup>	Starting material <b>3</b> (%) <sup>a</sup>	Conv. (%) <sup>a</sup>
1	5.0	3.21	64 (69) <sup>b</sup>	9 (9) <sup>b</sup>	91
2	3.0	5.36	68	7	93
3	2.5	6.43	71 (80) <sup>b</sup>	4 (4) <sup>b</sup>	96
4	2.0	8.04	74 (80) <sup>b</sup>	4	96
5	1.0	16.08	65	6	94

Entry	Current (mA)	T (h)	Yield of <b>4</b> (%) <sup>a</sup>	Starting material <b>3</b> (%) <sup>a</sup>	Conv. (%) <sup>a</sup>
6	2.0 mA, 3.5 F/mol	9.38	74 (77) <sup>b</sup>	4 (4) <sup>b</sup>	96

**Table 5.** Screening of current and charge. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol mesitylene as an internal standard. <sup>b</sup> Isolated yield.

Replacing the cathode with stainless steel did not improve the yield (**Table 6**, entry 1). Removing the electrolyte from the reaction showed almost no impact on the yield (**Table 6**, entry 2). Therefore, we decided to pursue without the addition of the electrolyte. Finally, we screened the stoichiometry of HF<sub>2</sub>CSO<sub>2</sub>Na and found that both reducing and increasing its amount were unfavorable to enhance the reaction efficiency (**Table 6**, entries 3-4). Hence, the optimal amount of HF<sub>2</sub>CSO<sub>2</sub>Na remained at 1.5 equivalents.

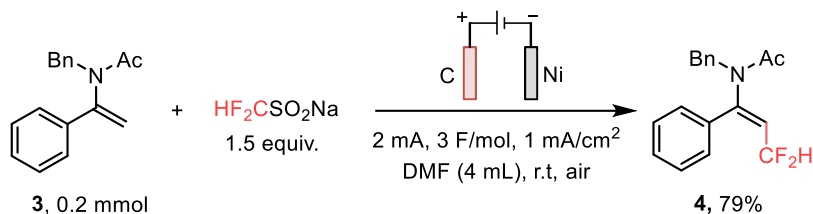


Entry	Electrode	Current (mA)	HF <sub>2</sub> CSO <sub>2</sub> Na (eq.)	Electrolyte	Yield (%) <sup>a</sup>	Conv. (%) <sup>a</sup>
1	C(+)-SS(-)	2.0	1.5	0.05 M	71	96
2	C(+)-Ni(-)	2.0	1.5	–	73 (79) <sup>b</sup>	94
3	C(+)-Ni(-)	2.0	1.2	–	68 (70) <sup>b</sup>	94
4	C(+)-Ni(-)	2.0	1.8	–	69	94

**Table 6.** Screening of electrode, electrolyte, and amount of HF<sub>2</sub>CSO<sub>2</sub>Na. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol mesitylene as an internal standard. <sup>b</sup> Isolated yield.

After this series of optimizations, we obtained the optimal reaction conditions (**Scheme 48**).



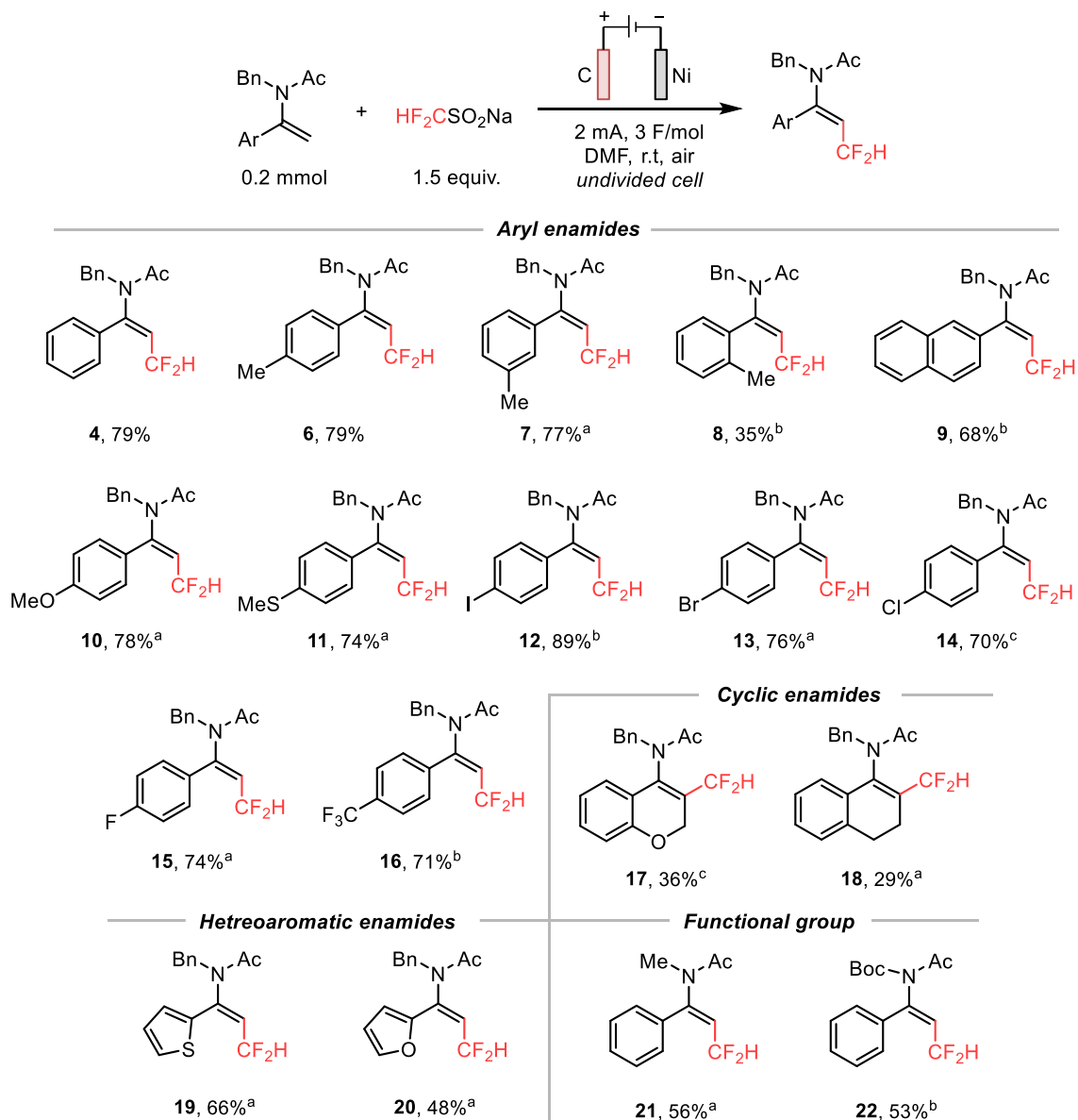


**Scheme 48.** Optimal conditions.

The reaction was performed using 0.2 mmol of **3** as model substrate, with 1.5 equivalents of sodium difluoromethanesulfinate ( $\text{HF}_2\text{CSO}_2\text{Na}$ ) as the difluoromethyl radical source. A carbon graphite electrode was employed as the anode, while a nickel plate electrode served as the cathode. The reaction was carried out under a constant current of 2 mA with a total charge of 3 F/mol in DMF, within an air atmosphere and an undivided cell setup (**Table 6**, entry 2). As a result, product **4** was isolated with a satisfactory yield of 79%.

## 2.2.2 Substrates scope and limitations of the methodologies - reluctant substrates

With the optimized reaction conditions in hand (**Scheme 48**), the scope of this electrochemical difluoromethylation of enamides was investigated.

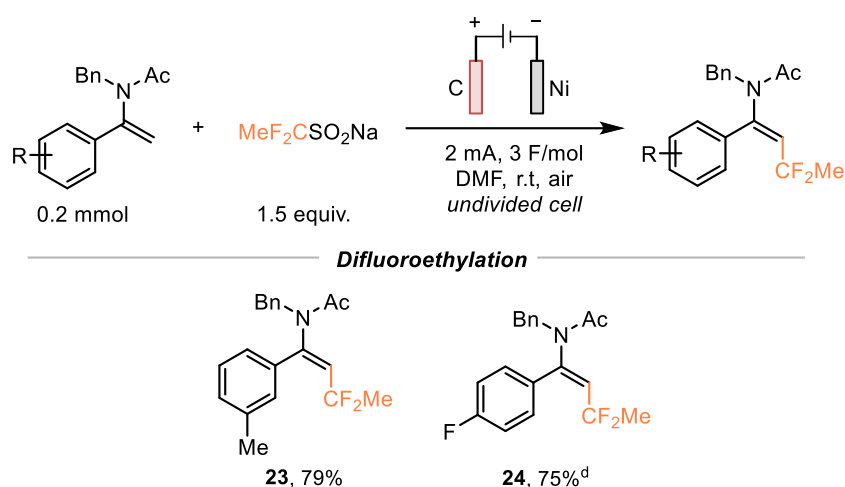


**Scheme 49.** Substrate Scope of Enamide Derivatives. <sup>a</sup> 4 F/mol for 10 h 43 min. <sup>b</sup> 6 F/mol for 16 h 5 min. <sup>c</sup> 5 F/mol for 13 h 24 min.

The substitution on the aromatic ring was first studied (**Scheme 49**). The reaction efficiency was not affected by the presence of a methyl group at the *para* or *meta* position (**6** and **7**). However, an *ortho* methyl functional group afforded the desired product **8** in a modest yield, even with an increased total charge. The reaction with enamides containing an electron-donating group such as naphthyl or methoxy proceeded well with good efficiencies (**9** and **10**). Interestingly, our electrochemical conditions were fully tolerant of various functional groups. High yields were obtained by reacting  $\alpha$ -aryl enamides containing either thioether, iodine, bromine, chlorine or fluorine residues at the *para* position (**11–15**), giving products that could be used in further valuable synthetic transformations. Moreover, a trifluoromethyl-substituted

derivative **16** was synthesized in a good 71% yield, showing a tolerance for electron-withdrawing groups. Under the optimal reaction conditions, 2H-chromene and 1,2-dihydronaphthalene derivatives were tested, affording the desired products **17** and **18**, respectively, albeit in moderate yields (36% and 29%, respectively). Complementary, heteroaryl derivatives were efficient substrates in our hands, yielding valuable heteroaromatic molecules (**19** and **20**). To showcase the versatility of the transformation, the benzyl residue on the nitrogen center was replaced with an alkyl or carbamate group. The *N*-methyl and *N*-Boc derivatives reacted smoothly, yielding the desired products **21** and **22** in decent 56% and 53% yields, respectively.

Finally, sodium difluoromethanesulfinate was replaced by sodium 1,1-difluoroethanesulfinate. The synthesis of the CF<sub>2</sub>Me-containing molecules is quite appealing and in high demand. Indeed, this motif is recognized as an excellent bioisostere of the methoxy group, enhancing the metabolic stability of molecules. Moreover, the methodology for efficiently introducing this fluorinated motif is so far restricted to a handful of protocols.<sup>148</sup> Pleasingly, our reaction conditions proved to be efficient for the electrochemical  $\alpha,\alpha$ -difluoroethylation of enamides as shown by the good yields obtained for products **23** and **24** (Scheme 50). Importantly, the reaction was highly stereoselective, furnishing exclusively the *E*-isomers.

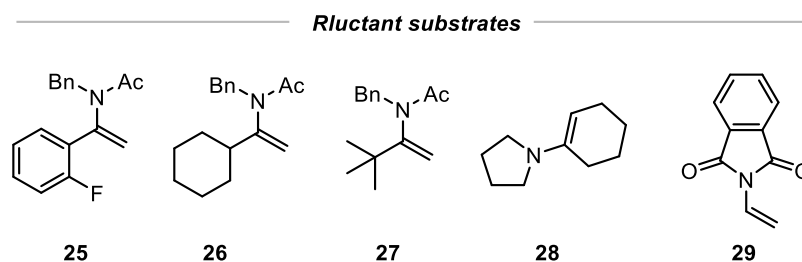


**Scheme 50.** Examples of difluoroethylation. <sup>d</sup>3.5 F/mol for 9 h 23 min

Unfortunately, some substrates remained reluctant or poorly reactive in our hands (**Scheme 51**). No desired product was obtained from the substrate with fluorine at the *ortho* position (**25**), and the starting material was recovered in a yield of 76%. Aliphatic enamides were not reactive (**26** & **27**), highlighting the importance of the formation of a transient stabilized alkyl radical resulting from the addition of the CF<sub>2</sub>H radical (*vide infra*). Likewise, enamine derived from cyclohexanone (**28**) and *N*-vinyl-phthalimide

<sup>148</sup> Carbonnel, E.; Poisson, T.; Jubault, P.; Pannecoucke, X.; Besset, T. *Front Chem* **2019**, 7, 111.

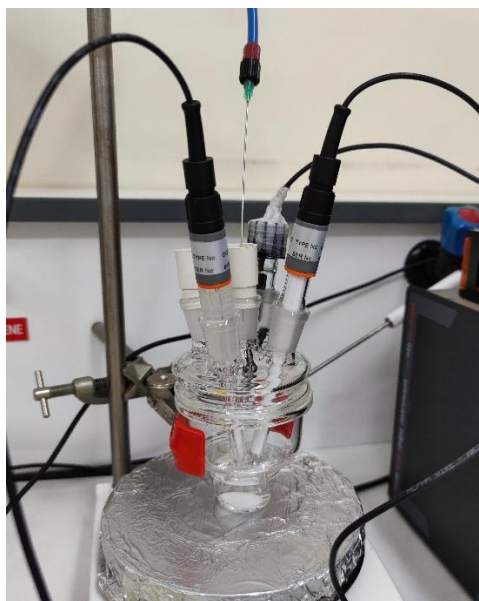
(29) were reluctant.



**Scheme 51.** Reluctant substrates.

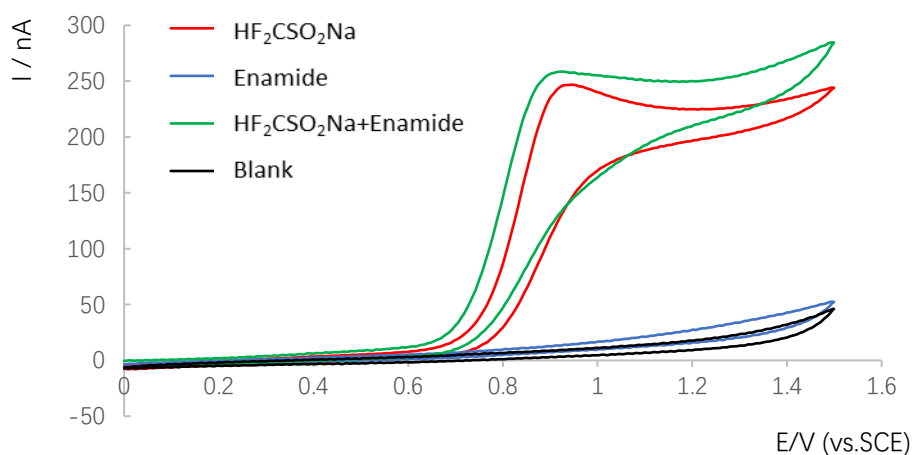
### 2.2.3 Mechanistic study

For the integration of the theoretical foundations of electrochemistry with practical experimental data, cyclic voltammetry (CV) proved to be a powerful tool. It can be used to obtain information about redox processes and the kinetics of electron transfer reactions, helping to determine electron transfer mechanisms and to study reactive intermediates. To gain insights into the reaction mechanism, we conducted CV measurements using OrigaLys<sup>®</sup> Potentiostat Galvanostat OrigaFlex OGF01A. These experiments were carried out within a 150 mL five-necked conic electrochemical cell, utilizing a three-electrode setup under a scan rate of 0.1 V/s. A platinum electrode (diameter = 0.1 mm, polish before each recording) served as the working electrode, while a platinum wire (diameter = 1 mm) acted as the auxiliary electrode. A SCE (Saturated Calomel Electrode) was used as the reference electrode (**Figure 13**). The solutions were degassed by nitrogen bubbling and CV experiments were performed under a nitrogen atmosphere at room temperature. In a typical case, a 15 mL solution volume was utilized.



**Figure 13.** Cyclic voltammetry cell.

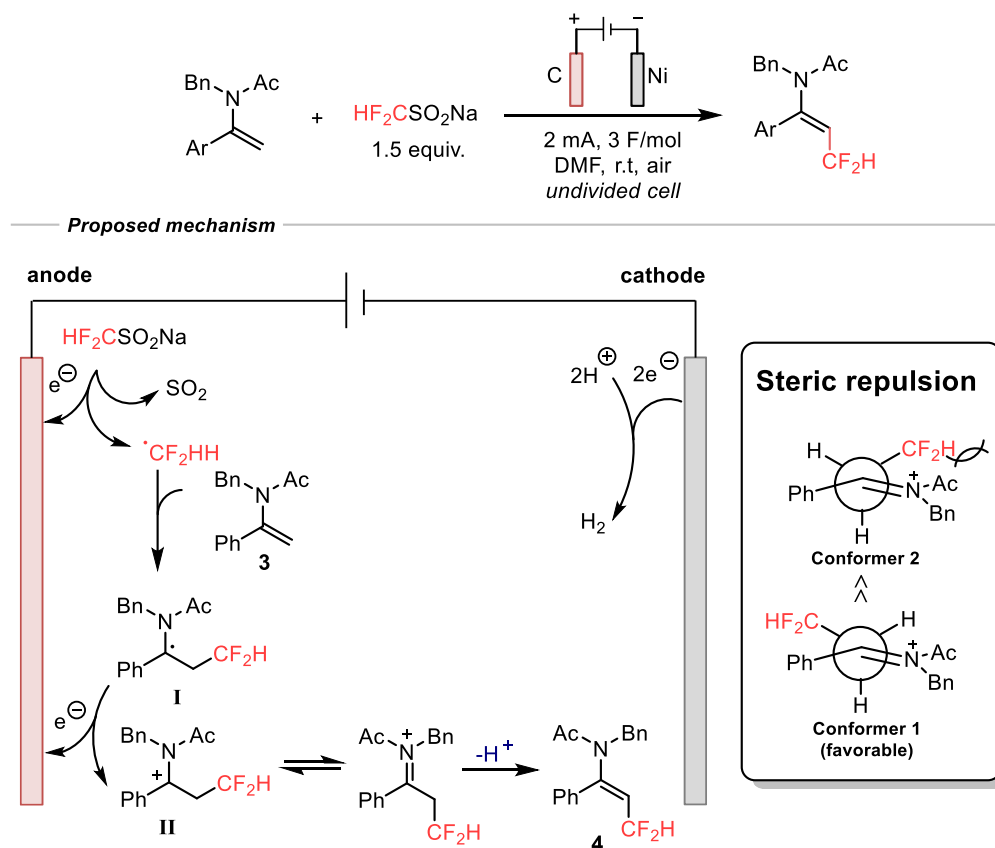
Using DMF as the solvent, we performed cyclic voltammetry scans on blank electrolyte solution, enamide,  $\text{HF}_2\text{CSO}_2\text{Na}$ , as well as a mixed solution of enamide and  $\text{HF}_2\text{CSO}_2\text{Na}$ , obtaining their respective cyclic voltammograms (**Figure 14**).  $\text{HF}_2\text{CSO}_2\text{Na}$  (**Figure 14**, red) showed an irreversible oxidative wave, while no oxidation nor reduction of enamide (*N*-benzyl-*N*-(1-(*p*-tolyl)vinyl)acetamide) (**Figure 14**, blue) was observed in the studied potential range (up to + 1.5 V). Moreover, CV measurements of a mixture of  $\text{HF}_2\text{CSO}_2\text{Na}$  and enamide (**Figure 14**, green) demonstrated similar profiles, meaning that there is no mediation of a plausible oxidation of enamide.



**Figure 14.** CV curve for a solution of 0.01 M  $\text{HF}_2\text{CSO}_2\text{Na}$  /0.01M Enamide and 0.05 M *n*Bu<sub>4</sub>NBF<sub>4</sub> in DMF on a Pt working electrode (*d* = 0.1 mm), Pt wire (*d* = 1 mm) auxiliary electrode, SCE reference electrode under a scan rate of 0.1 V/s ranging from 0 V to 1.5 V in oxidation. Following IUPAC CV

plotting convention.

Based on the CV measurements and previous literatures, we have suggested a plausible reaction mechanism initiated by the anodic oxidation of  $\text{HF}_2\text{CSO}_2\text{Na}$  (**Scheme 52**). Subsequently, the resulting  $\text{CF}_2\text{H}$  radical adds to the C=C bond of enamide, generating a stabilized nucleophilic  $\alpha$ -aminated radical I. The formation of this radical appeared to be crucial, as evidenced by the lack of reaction with alkyl residues. A subsequent anodic oxidation of this open-shell intermediate leads to carbocation II, prompting it undergo an E1 elimination yielding the desired products. Concomitantly, a cathodic reduction of  $\text{H}^+$  from the elimination event results in the production of  $\text{H}_2$ .



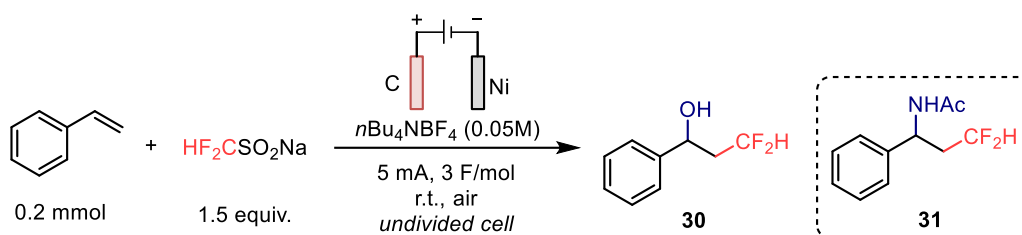
**Scheme 52.** Proposed Mechanism.

## 2.3 Electrochemical Oxydifluoromethylation of styrenes

### 2.3.1 Optimization

To further expand the applicability of this electrochemical difluoromethylation transformation, the reaction conditions were then tested on styrene, because to the best of our knowledge no electrochemical difluoromethylation of styrene derivatives

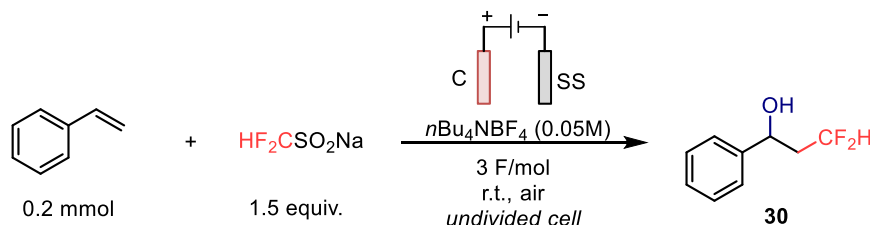
has been reported.<sup>149,150</sup> Pleasingly, a hydroxydifluoromethylation product, identified as product **30**, was produced with a modest 24% NMR yield (**Table 7**, entry 1). Based on this interesting result, we started investigations to determine the optimal reaction conditions for the formation of product **30**. Addition of 10% H<sub>2</sub>O in DMF led to an increase in the reaction yield to 43% NMR yield (**Table 7**, entry 2). When acetonitrile was used as the solvent, product **30** was obtained with a 28% NMR yield. Simultaneously, amino-difluoromethylated product **31** was generated in 48% NMR yield (**Table 7**, entry 3). Interestingly, the acetone/H<sub>2</sub>O mixture (9:1) emerged as the optimal solvent system, providing product **30** in a substantial 71% NMR yield (**Table 7**, entry 4).



Entry	Solvent (4 mL)	Yield of <b>30</b> (%) <sup>a</sup>
1	DMF	24
2	DMF/H <sub>2</sub> O (9:1)	43
3	MeCN/H <sub>2</sub> O (9:1)	27
4	Acetone/H <sub>2</sub> O (9:1)	71

**Table 7.** Screening of solvent. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol trifluoromethylbenzene as an internal standard.

The use of a cheaper stainless-steel cathode was beneficial, and **30** was isolated in 77% yield (**Table 8**, entry 1). Increasing or decreasing the current did not lead to an improvement in yield (**Table 8**, entries 2-4). Control experiments showed that no reaction was observed without current (**Table 8**, entry 5).



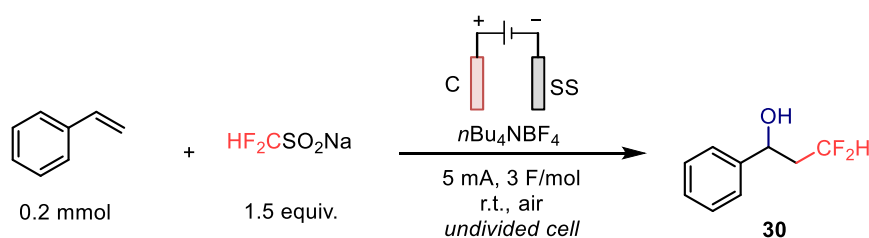
<sup>149</sup> Kisukuri, C. M.; Fernandes, V. A.; Delgado, J. A. C.; Haring, A. P.; Paixao, M. W.; Waldvogel, S. R. *Chem. Rec.* **2021**, *21*, 2502-2525.

<sup>150</sup> Zou, Z.; Zhang, W.; Wang, Y.; Pan, Y. *Org. Chem. Front.* **2021**, *8*, 2786-2798.

Entry	Electrode	Current (mA)	T (h)	Yield (%) <sup>a</sup>
1	C(+)-SS(-)	5	3.22	81 (71) <sup>b</sup>
2	C(+)-SS(-)	10	1.61	74
3	C(+)-SS(-)	8	2.10	73
4	C(+)-SS(-)	2	8.04	57
5	C(+)-SS(-)	–	3.22	0

**Table 8.** Screening of electrode and current. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol trifluoromethylbenzene as an internal standard. <sup>b</sup> isolated yield.

Then, we attempted to perform the reaction without using electrolyte, but the yield slightly decreased. (**Table 9**, entry 1). When the concentration of the electrolyte was reduced from 0.05 M to 0.025 M, the NMR yield remained unchanged. (**Table 9**, entry 2). Increasing the electrolyte concentration from 0.05 M to 0.075 M resulted in a slight improvement in isolated yield, from 71% to 73% (**Table 9**, entry 3). However, overall, the electrolyte had minimal impact on the reaction efficiency. Based on these results, we selected 0.025 M as the optimal electrolyte concentration. Conducting the reaction under an argon atmosphere led to an increase in the yield (**Table 9**, entry 4).

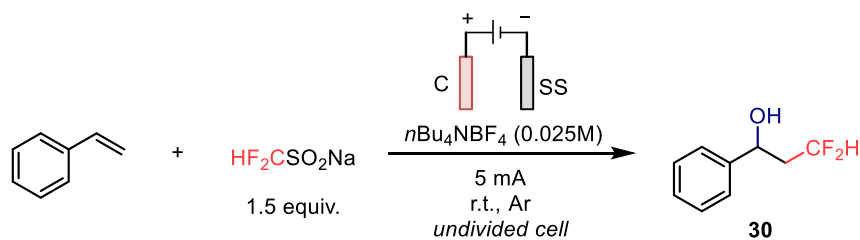


Entry	Electrolyte (M)	Atmosphere	Yield (%) <sup>a</sup>
1	–	Air	75 (67) <sup>b</sup>
2	0.025	Air	81
3	0.075	Air	90 (73) <sup>b</sup>
4	0.025	Ar	100 (77) <sup>b</sup>

**Table 9.** Screening of amount of electrolyte and atmosphere. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol trifluoromethylbenzene as an internal standard. <sup>b</sup> isolated yield.

Next, we attempted to decrease the amount of total charge to 2.5 F/mol, resulting in the same isolated yield of 77% (**Table 10**, entry 1).

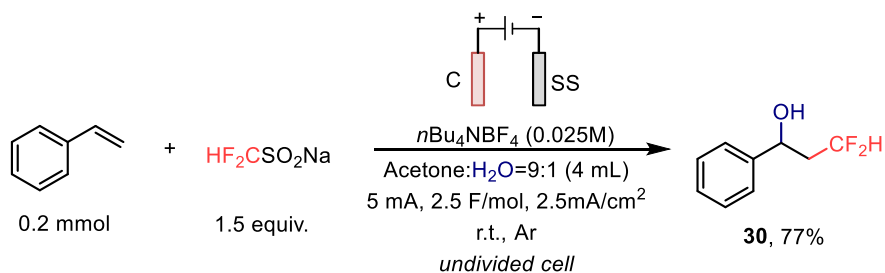




Entry	Styrene (mmol)	Charge (F/mol)	Yield (%) <sup>a</sup>
1	0.2	2.5	89 (77) <sup>b</sup>
2	0.2	2.0	75
3	0.4	2.5	82 (73) <sup>b</sup>

**Table 10.** Screening of amount of charge and reaction scale. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol trifluoromethylbenzene as an internal standard. <sup>b</sup> isolated yield.

Further reduction to 2.0 F/mol led to a decreased yield, and unreacted styrene was detected by GC-MS analysis (**Table 10**, entry 2). This suggested that the reaction required a charge of 2.5 F/mol to achieve the highest conversion. Finally, we scaled up the reaction to 0.4 mmol in the same reaction vessel, using the same amount of solvent and maintaining the same electrolyte concentration. Surprisingly, we still obtained a satisfactory yield of 73% (**Table 10**, entry 3), indicating that the reaction can be successfully scaled to 0.4 mmol, while maintaining good yields.

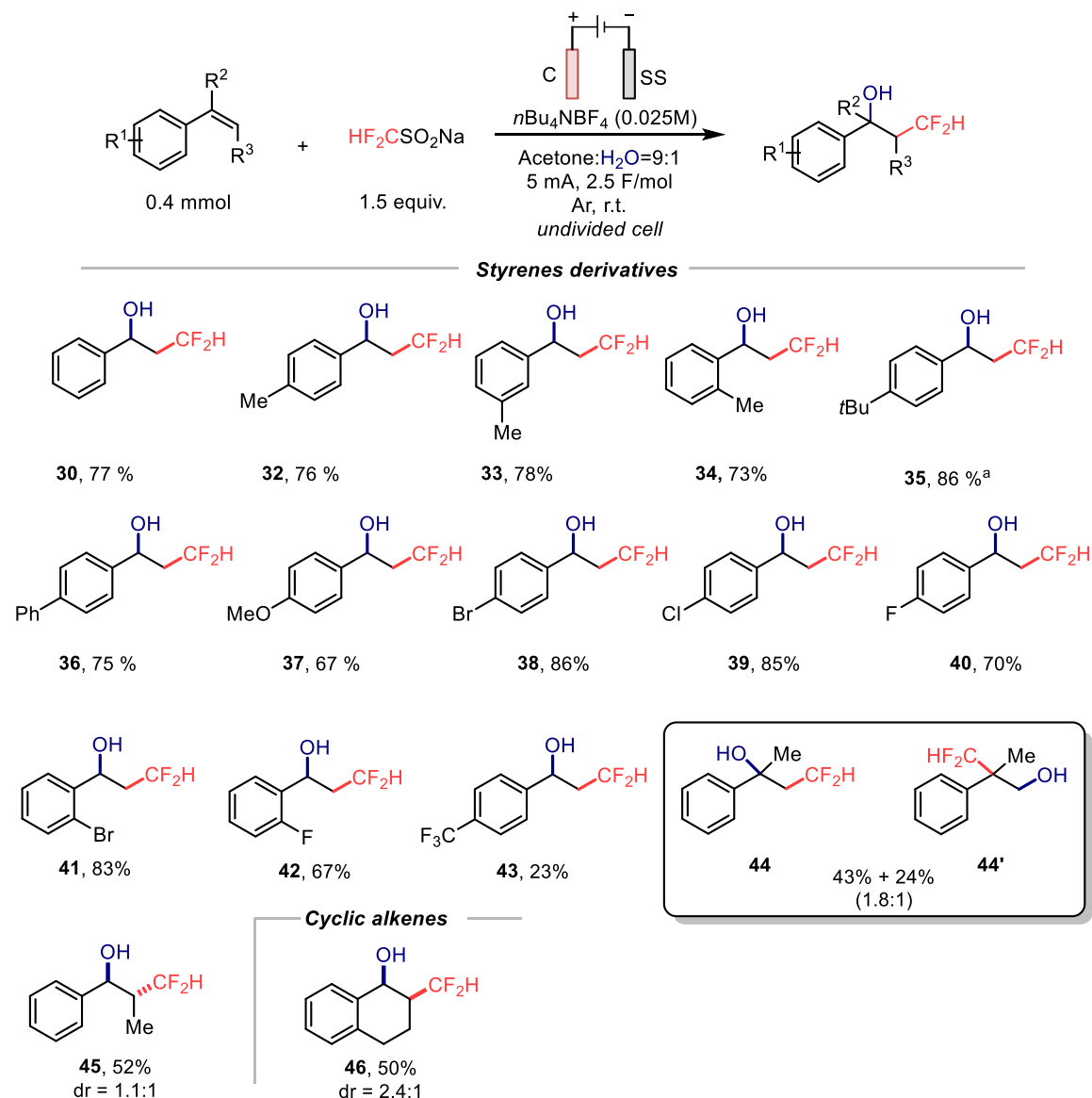


**Scheme 53.** Optimal conditions.

Thus, we have established the optimal conditions (**Scheme 53**): employing 1.5 equivalents of sodium difluoromethanesulfinate ( $\text{HF}_2\text{CSO}_2\text{Na}$ ) as the difluoromethyl source, conducting the reaction in an undivided cell with graphite as anode and stainless steel plate as cathode, under constant current of 5 mA and a charge of 2.5 F/mol, 0.025 M *n*-tetrabutylammonium tetrafluoroborate ( $n\text{Bu}_4\text{NBF}_4$ ) as the electrolyte in an acetone/ $\text{H}_2\text{O}$  solvent mixture (9:1), under an argon atmosphere at room temperature. Under these conditions, we obtained the product **30** with an isolated yield of 77%.

## 2.3.2 Substrates scope and limitations of the methodologies - reluctant substrates

With the optimized conditions in hand, we examined the reaction scope (**Scheme 54**).

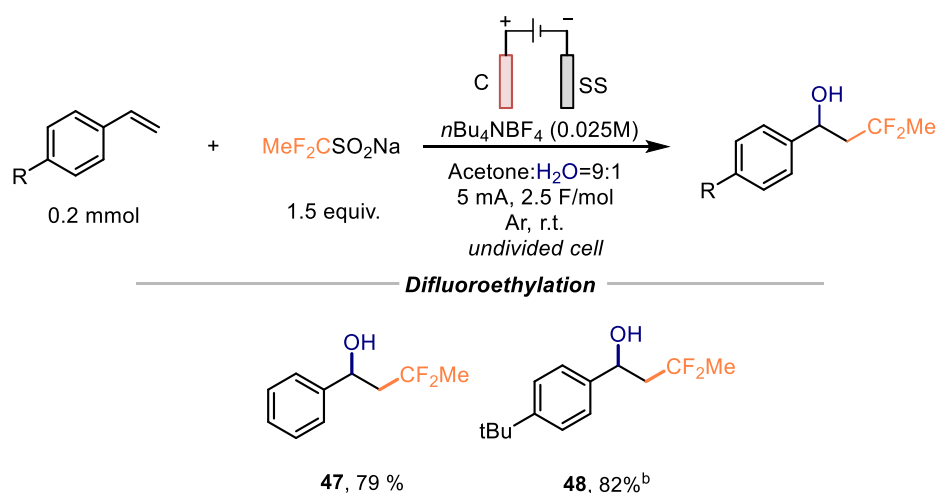


**Scheme 54.** Substrate Scope. On a scale of 0.4 mmol. <sup>a</sup>4.5 F/mol for 9 h 38 min.

A set of styrene derivatives was first reacted. Regardless of the position of a methyl group on the aromatic ring (*ortho*, *meta*, or *para*), yields remained good, showing a tolerance to steric hindrance (**32-24**). The presence of electron-donating groups such as a tert-butyl, phenyl, or methoxy led to the corresponding products (**35-37**), and the presence of an electron-withdrawing substituent was also tolerated, albeit giving a lower yield (**43**, 23%). Independent of the substitution pattern (*ortho* or *para* position),

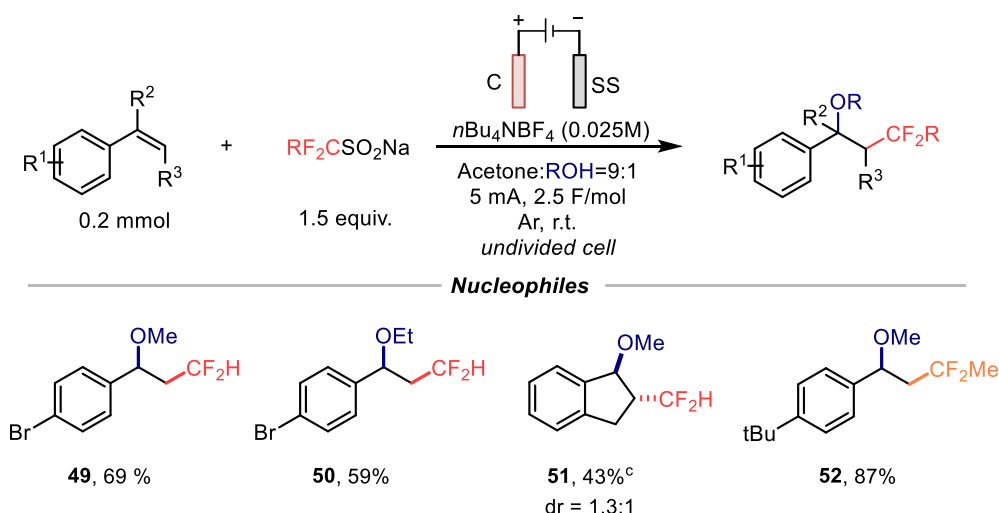
halogens were well tolerated in our transformation, allowing access to the corresponding derivatives (**38-42**) in an efficient manner. 1,1- and 1,2- disubstituted alkenes reacted smoothly, furnishing products **44** and **45**, respectively, in moderate to good yields. It has to be noted that both regioisomers of **44** were isolated separately (**44** and **44'**). However, **45** was obtained with poor diastereoselectivity, albeit with a full regioselectivity in favor of the Markovnikov product. 1,2-Dihydronaphthalene also proved to be a suitable substrate producing **46** with good diastereoselectivity.

Sodium 1,1-difluoroethanesulfinate was here also used in place of sodium difluoromethylsulfinate in our electrochemical transformation, showing the high efficiency of the electrochemical  $\alpha,\alpha$ -difluoroethylation of nonactivated alkenes without any modification of the reaction conditions (**Scheme 55**, **47** and **48**).



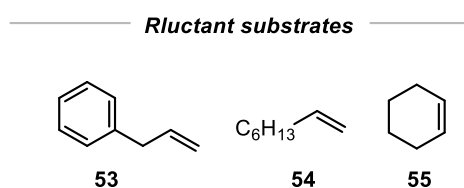
**Scheme 55.** Examples of difluoroethylation. On a scale of 0.2 mmol. <sup>b</sup> 3.5 F/mol for 3 h 45 min.

Finally, the reaction was extended to the introduction of the MeO and EtO groups by a simple replacement of water with the corresponding alcohol. As a result, difluoromethylated products **49** and **50** were isolated in 69% and 59% yields, respectively. Indene in the presence of MeOH led to a separable cis/trans mixture (**51**) in a 42% yield. The extension to the  $\alpha,\alpha$ -difluoroethylation reaction was performed, giving product **52** in 87% yield (**Scheme 56**).



**Scheme 56.** Other nucleophiles. On a scale of 0.2 mmol. <sup>c</sup> On a 0.25 mmol scale at 3.5 F/mol for 4 h 40 min.

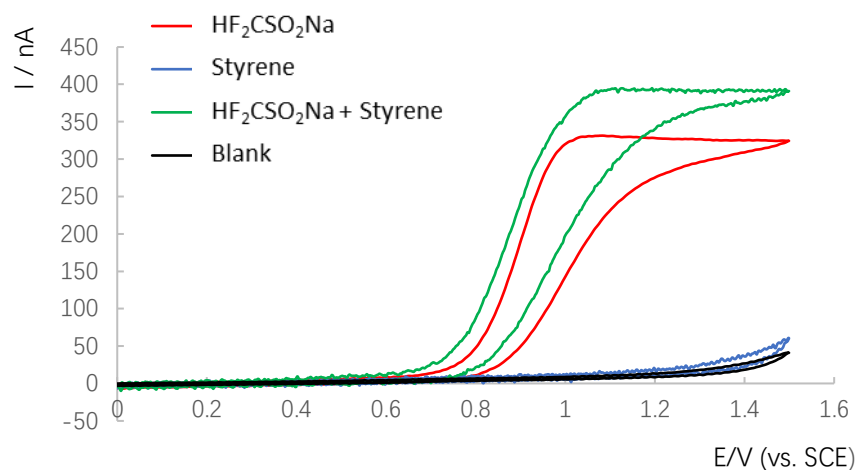
Some substrates remained reluctant (**Scheme 57**). Aliphatic terminal alkenes were poorly reactive (**53** and **54**, <20% yields), while cyclohexene (**55**) led to no reaction.



**Scheme 57.** Reluctant substrates.

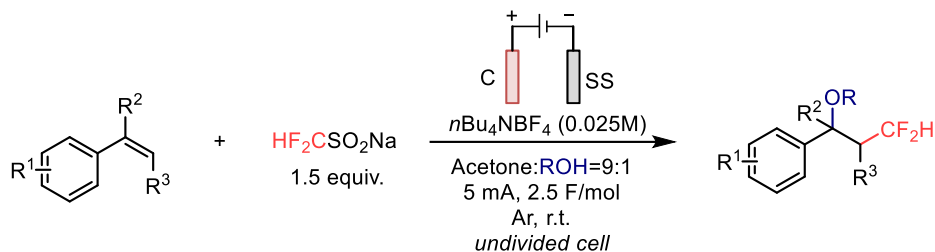
### 2.3.3 Mechanistic study

In line with our previous study regarding the difluoromethylation of enamides, we performed cyclic voltammetry experiments to gain insights into the reaction mechanism (**Figure 15**). Likewise in our previous study,  $\text{HF}_2\text{CSO}_2\text{Na}$  (**Figure 15**, red) exhibited an irreversible oxidative wave, while styrene showed neither oxidation nor reduction within the investigated potential range (up to +1.5 V) (**Figure 15**, blue). Furthermore, cyclic voltammetry measurements of a mixture of  $\text{HF}_2\text{CSO}_2\text{Na}$  and styrene (**Figure 15**, green) demonstrated similar profiles, suggesting the absence of any plausible mediated oxidation of styrene.

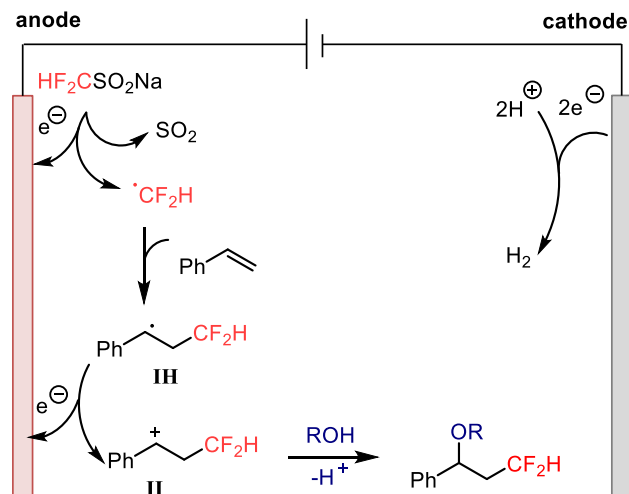


**Figure 15.** CV curve for a solution of 0.01 M HF<sub>2</sub>CSO<sub>2</sub>Na /0.02 M Styrene and 0.05 M *n*Bu<sub>4</sub>NBF<sub>4</sub> in Acetone on a Pt working electrode (*d* = 0.1 mm), Pt wire (*d* = 1 mm) auxiliary electrode, SCE reference electrode under a scan rate of 0.1 V/s ranging from 0 V to 1.5 V in oxidation. Following IUPAC CV plotting convention.

Based on the CV measurements and previous literature, we suggested a plausible reaction mechanism initiated by the anodic oxidation of HF<sub>2</sub>CSO<sub>2</sub>Na (**Scheme 58**). The resulting CF<sub>2</sub>H radical then adds to the C=C bond of styrene, forming benzylic radical **I**, which subsequently undergoes further anodic oxidation to generate carbocation **II**, facilitating a nucleophilic addition of the solvent to yield the desired products. A cathodic reduction of H<sup>+</sup> resulting from the nucleophilic addition leads to the generation of H<sub>2</sub>.



Proposed mechanism

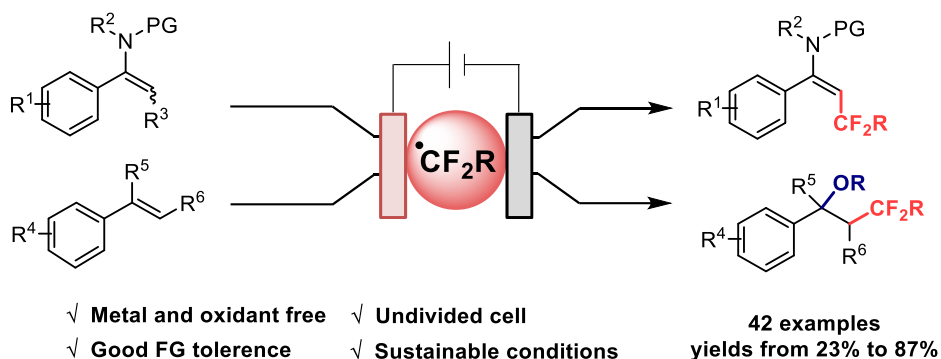


Scheme 58. Proposed Mechanism.

## 2.4 Conclusion

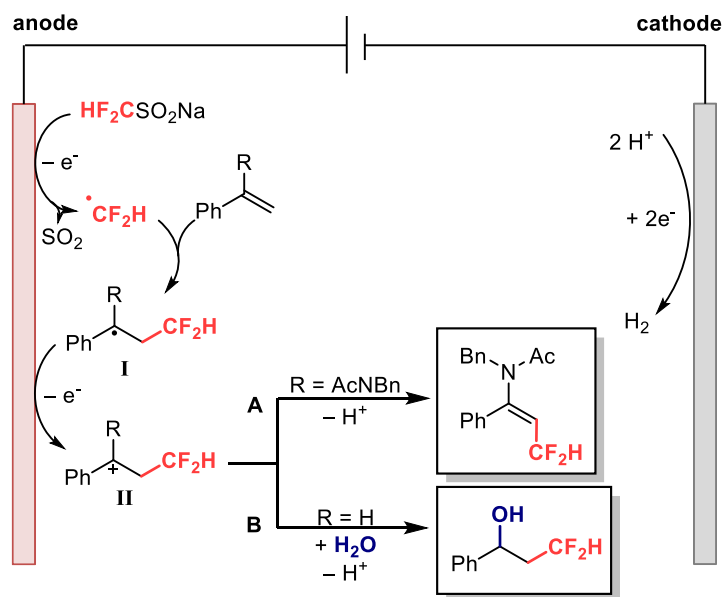
In conclusion, we developed an innovative difluoromethylation and  $\alpha,\alpha$ -difluoroethylation of enamide and styrene derivatives. With regard to enamides, the reaction conditions provided the corresponding difluoromethylated derivatives as a single (*E*)-isomer in good to excellent yields (20 examples, 29 – 80% yields). The hydroxydifluoromethylation of styrenes was also developed under slightly modified conditions, giving the difunctionalized products in good to excellent yields (22 examples, 23 – 86% yields) (Scheme 59).<sup>151</sup>

<sup>151</sup> Luan, S.; Castanheiro, T.; Poisson, T. *Org. Lett.* **2023**, *25*, 1678-1682.



**Scheme 59.** Electrochemical Difluoromethylation of Electron-Rich Olefins.

A plausible mechanism involving anodic oxidation and the addition of the  $\text{CF}_2\text{H}$  radical to electron-rich alkenes is proposed for both functionalizations (**Scheme 60**). The formation of intermediate radical **I** is followed by a subsequent anodic oxidation, yielding carbocation **II**, which leads to either an E1 elimination (route **A**) or a nucleophilic addition of the solvent (route **B**), resulting in the formation of the desired products. Cathodic reduction of  $\text{H}^+$  generated from either the elimination or nucleophilic addition would generate  $\text{H}_2$  within the medium, closing the redox cycle.



**Scheme 60.** General Mechanism.

# **Chapter 3**

## Electrochemical halogenation of alkenes



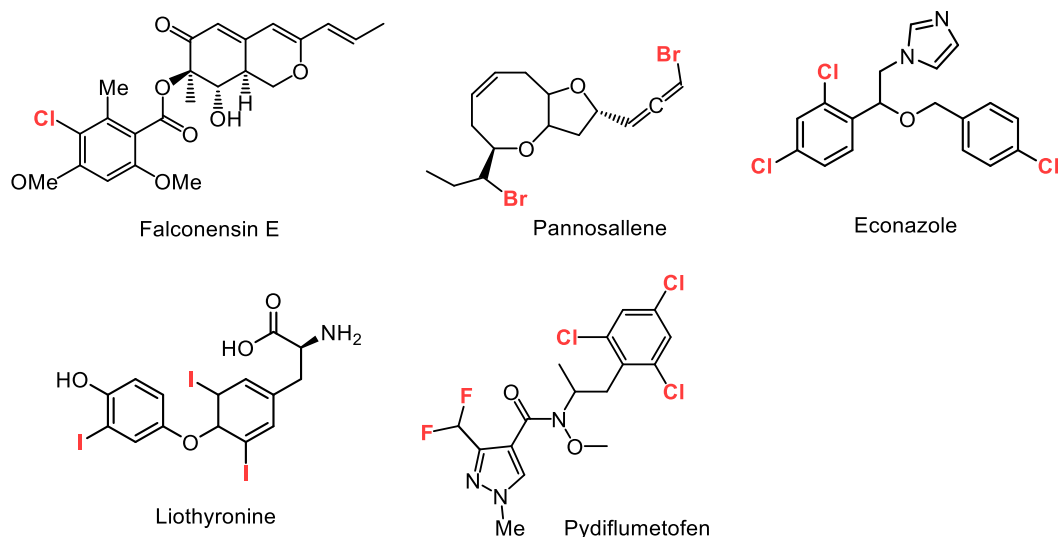


## 3. Electrochemical halogenation of alkenes

### 3.1 Introduction

#### 3.1.1 Applications and synthesis of organic halides (R-X)

Halogen-containing compounds are present in numerous natural substances<sup>152,153</sup> and are found in many pharmaceuticals<sup>154,155,156</sup> and agrochemicals (**Figure 16**).<sup>157</sup> Since 2010, around 81% of the marketed agrochemicals had at least one halogen atom in their structure.<sup>158</sup> Therefore, the introduction of halogens into organic molecules has played an important role in the development of drugs, herbicides, and insecticides.



**Figure 16.** Representative halogen-containing natural products, pharmaceutical and agrochemical molecules.

Organohalogenated chemicals also play a key role as highly versatile synthetic intermediates and building blocks for the synthesis of fine chemicals *via* transition-metal-catalyzed cross-coupling reactions, which have gained widespread use both in

<sup>152</sup> Gribble, G. W. *J. Chem. Educ.* **2004**, *81*, 1441.

<sup>153</sup> Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141-152.

<sup>154</sup> Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.

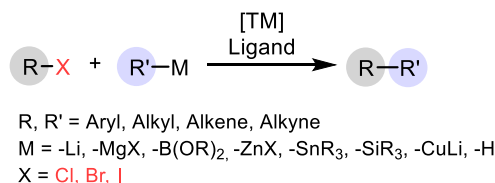
<sup>155</sup> Thomas, G., *Medicinal Chemistry: An Introduction*, Wiley, **2008**.

<sup>156</sup> Hernandes, M.; Cavalcanti, S. M.; Moreira, D. R.; de Azevedo Junior, W.; Leite, A. C. *Curr. Drug Targets* **2010**, *11*, 303-314.

<sup>157</sup> Jeschke, P. *Pest Management Science* **2010**, *66*, 10-27.

<sup>158</sup> Jeschke, P. *Eur. J. Org. Chem.* **2022**, *2022*, e202101513.

academic and industrial laboratories, as a powerful methodology for the formation of C–C and C–heteroatom bonds (**Scheme 61**). Their ability to efficiently and selectively generate complex organic molecules highlights their significant value in modern organic synthesis.<sup>159,160,161,162,163</sup>



**Scheme 61.** Transition-metal-catalyzed cross-coupling reaction.

In addition to their crucial role in organic synthesis, organohalides have a multitude of industrial applications, including their use as flame retardants,<sup>164</sup> plastics and polymers,<sup>165</sup> dyes and pigments,<sup>166</sup> and as solvents.

Additionally, halogenated organic compounds are utilized in the field of medical imaging (**Figure 17**).<sup>167, 168, 169, 170, 171, 172, 173</sup> Fluorine-containing compounds have exhibited potential in clinical applications for magnetic resonance imaging (MRI).<sup>171,172</sup> Furthermore, the radioactive isotopes of fluorine (<sup>18</sup>F), bromine (<sup>76</sup>Br) and iodine (<sup>121</sup>I, <sup>123</sup>I, <sup>125</sup>I and <sup>131</sup>I) are commonly employed as radiotracers in molecular imaging to visualize metabolic processes within the human body, using positron emission tomography (PET) or single photon emission computed tomography (SPECT), which are two imaging protocols based on radiotracers.<sup>167,168,169,170,173</sup> These non-invasive imaging modalities are essential in the fields of diagnostic medicine and clinical pharmaceutical researches, where gathering *in vivo* pharmacological information is crucial for advancing drug development.

<sup>159</sup> Guérinot, A.; Cossy, J. *Acc. Chem. Res.* **2020**, *53*, 1351-1363.

<sup>160</sup> De Meijere, A.; Diederich, F.; de Meijere, A., *Metal-catalyzed cross-coupling reactions, Vol. 1*, Wiley-VCH Weinheim, **2004**.

<sup>161</sup> Fairlamb, I. J. S.; Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036-1045.

<sup>162</sup> Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710.

<sup>163</sup> Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

<sup>164</sup> Weil, E. D.; Levchik, S. *J. Fire Sci.* **2004**, *22*, 251-264.

<sup>165</sup> Lee, Y.; Boyer, C.; Kwon, M. S. *Nature Reviews Materials* **2021**, *7*, 74-75.

<sup>166</sup> Venkataraman, K., *The Chemistry of Synthetic Dyes*, Academic Press, **1952**.

<sup>167</sup> Schlyer, D. *Ann. Acad. Med. Singapore* **2004**, *33*, 146-154.

<sup>168</sup> Wester, H. J. *Clin. Cancer Res.* **2007**, *13*, 3470-3481.

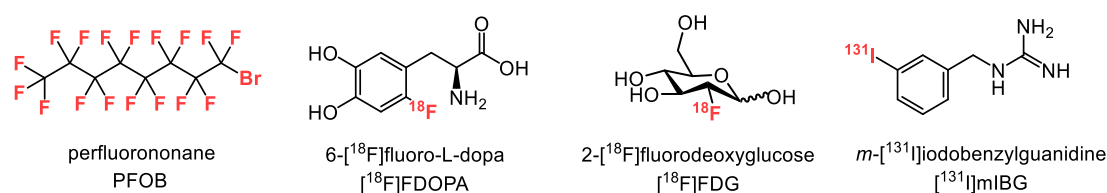
<sup>169</sup> Yamashina, S.; Yamazaki, J. *Eur. J. Nucl. Med. Mol. Imaging* **2007**, *34*, 939-950.

<sup>170</sup> Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501-1516.

<sup>171</sup> Janjic, J. M.; Ahrens, E. T. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* **2009**, *1*, 492-501.

<sup>172</sup> Srinivas, M.; Heerschap, A.; Ahrens, E. T.; Figdor, C. G.; Vries, I. J. M. d. *Trends in Biotechnology* **2010**, *28*, 363-370.

<sup>173</sup> Pimlott, S. L.; Sutherland, A.; Pimlott, S. L. *Chem. Soc. Rev.* **2011**, *40*, 149-162.



**Figure 17.** Representative halogen-containing chemicals used as imaging tracking agents.

Given the versatile applications of organohalogen compounds, the development of practical and efficient approaches to synthesize these compounds is of considerable importance. Extensive efforts have been made, and great achievement has been reached.<sup>174, 175, 176, 177, 178, 179, 180, 181, 182, 183</sup> Among them, electrophilic halogenating agents such as *N*-halosuccinimides (NXS: X = Cl, Br, I), and molecular halogen (Cl<sub>2</sub>, Br<sub>2</sub>, I<sub>2</sub>) have conventionally been the most commonly used approaches. Additionally, the combination of halogen anions and stoichiometric external oxidants has emerged as an attractive alternative. Since halides are less hazardous than molecular halogens, *in situ* oxidation of halides is a good alternative to the use of molecular halogen. Another advantage of this strategy relies in the halogen atom economy. At last but not least, we can mention the venerable Sandmeyer reaction as a powerful manifold to build up halogenated aryls from anilines, as well as the straightforward balz-Schiemann reaction for the access to fluoroarenes.<sup>184</sup>

However, both of these strategies exhibit limitations regarding cost-effectiveness and environmental sustainability. Therefore, the development of novel and efficient synthetic methods consistent with the principles of green chemistry is of high demand to adhere to the contemporary concern of sustainability.

### 3.1.2 Electrochemical Halogenation reactions

Electrochemistry has demonstrated a distinctive ability in the halogenation of organic compounds, offering a green and advantageous alternative to traditional synthetic methods. In general, the anodic oxidation of inexpensive and bench-stable halide anions or organic halide enables the generation of highly reactive halogenating

<sup>174</sup> Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003-8104.

<sup>175</sup> Luo, T.; Tian, S.; Wan, J.-P.; Liu, Y. *Curr. Org. Chem.* **2021**, *25*, 1180-1193.

<sup>176</sup> Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766-5776.

<sup>177</sup> Chung, W.-j.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 4396-4434.

<sup>178</sup> Saikia, I.; Borah, A. J.; Phukan, P. *Chem. Rev.* **2016**, *116*, 6837-7042.

<sup>179</sup> Lorpaiboon, W.; Bovonsombat, P. *Org. Biomol. Chem.* **2021**, *19*, 7518-7534.

<sup>180</sup> Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y.; Cheng, Y. A. *Org. Biomol. Chem.* **2014**, *12*, 2333-2343.

<sup>181</sup> Cresswell, A. J.; Eey, S. T. C.; Denmark, S. E. *Angew. Chem. Int. Ed.* **2015**, *54*, 15642-15682.

<sup>182</sup> Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938-10953.

<sup>183</sup> Tan, C. K.; Yeung, Y.-Y.; Tan, C. K. *Chem. Commun. (Cambridge, U. K.)* **2013**, *49*, 7985-7996.

<sup>184</sup> Bruice, P. Y., *Organic Chemistry*, Pearson, **2016**, p.900-901.

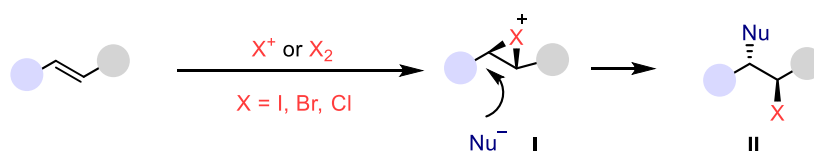
intermediates such as halogen cations, halogen radicals or molecular halogen, by using only electrons as redox reagents. Therefore, this approach eliminates the need for toxic reagents and external chemical oxidants or reductants. These relatively mild conditions typically exhibit good tolerance toward various functional groups, presenting a unique opportunity to reduce hazards, minimize chemical wastes and lower synthesis costs. In addition, the development of electrochemical flow setups enables large-scale transformations.

In recent years, significant progresses have been made in this field, showcasing that electrolysis can be used as a powerful tool for environmentally friendly halogenation of  $sp$ ,  $sp^2$  and  $sp^3$  carbon atoms. In this section, we provide an overview of the advances in electrochemical halogenation of alkenes. For the sake of the reader these process were categorized by their mechanisms.

### 3.1.3 Electrochemical Halogenation of alkenes

#### a. Through cyclic halonium ion intermediate

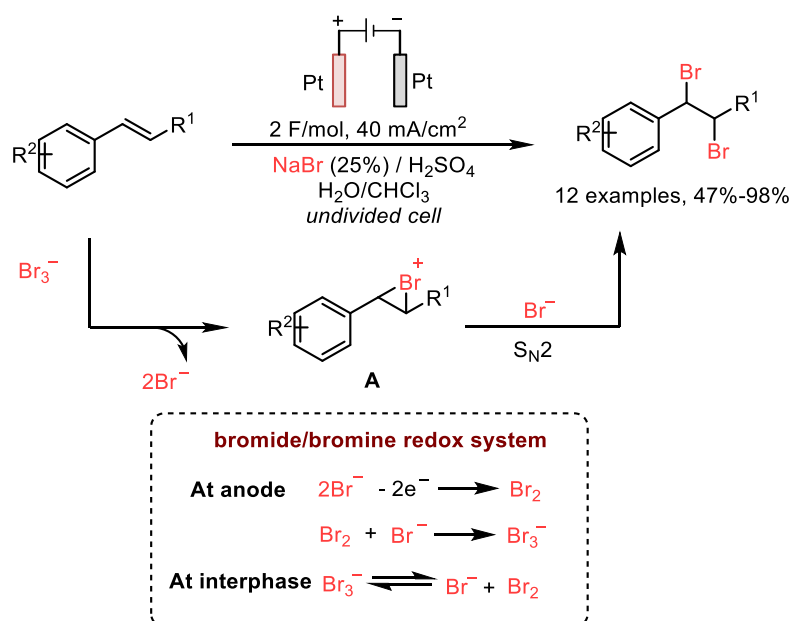
The halogenation reaction of alkenes *via* halonium ion intermediates is a common process in organic chemistry and developed in most of the organic chemistry textbook as a classical reaction (**Scheme 62**). The extension of this process under electrochemical conditions relies on the anodic oxidation of halide salts, organic halides or hydrohalic acids. This oxidative process generates electrophilic halogen intermediates, which subsequently react with a nucleophilic alkene to form cyclic halonium ion intermediates. These intermediates are then converted into the corresponding products. This process has been used for the synthesis of organic iodides, bromides, and chlorides. Note that the extension to the fluorination reaction is not yet achieved, due to the high oxidation potential of fluoride anion ( $F_{2(g)} + 2e^- \rightarrow 2F^-_{(aq)}$ ,  $E^\circ = 2.87$  V vs. SHE), and no reagents are currently available for oxidizing fluorine to a positive oxidation state.



**Scheme 62.** General reaction manifold for the halogenation of alkenes via a halonium intermediate.

In 2016, Raju and co-workers developed a straightforward approach for the electrochemical bromination of olefins through a two-phase electrolysis mediated by

bromide/bromine redox system (**Scheme 63**).<sup>185</sup> The optimal conditions were determined using a two-phase solvent system (H<sub>2</sub>O/CHCl<sub>3</sub>) in an undivided cell, equipped with two platinum electrodes, operated at a current density of 40 mA cm<sup>-2</sup>. The aqueous layer is a mixture of aqueous solution of NaBr and H<sub>2</sub>SO<sub>4</sub>. The resulting dibrominated products were obtained stereoselectivity, enabling their formation with moderate to excellent yields ranging from 47% to 98%. The proposed mechanism was suggested based on reports of the literature.<sup>186</sup> The process begins with the oxidation of bromide ion at the anode, resulting in the production of bromine, which then combines with bromide ion to form Br<sub>3</sub><sup>-</sup>. At the interface of aqueous and organic phases, Br<sub>3</sub><sup>-</sup> existed in equilibrium with Br<sub>2</sub> and Br<sup>-</sup>. Cyclic bromonium ion **A** was formed as intermediate through the reaction of alkene and Br<sub>3</sub><sup>-</sup>, which then undergoes nucleophilic attack by Br<sup>-</sup> via a S<sub>N</sub>2 type pathway, leading to the formation of the desired product, with the *anti*-product being the major one.



**Scheme 63.** Electrochemical dibromination of olefins.

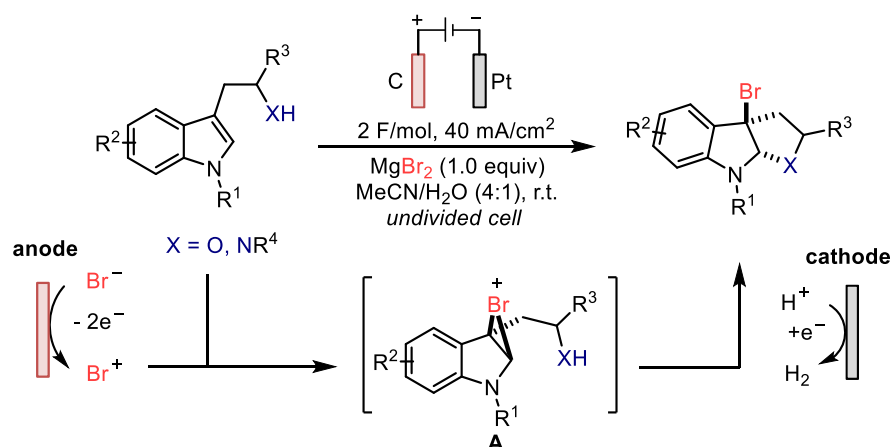
In 2020, Vincent's group reported an electrochemical dearomative procedure for the bromocyclization of indoles (**Scheme 64**).<sup>187</sup> The reaction could be performed either in galvanostatic mode (4.5 mA cm<sup>-2</sup>) or potentiostatic mode (5.0 V) in an undivided cell that was equipped with a graphite anode and a platinum cathode. Bromide salt served both as electrophilic reagent source and electrolyte. This transformation was initiated with the generation of an electrophilic bromine species through the anodic

<sup>185</sup> Kulangiappar, K.; Ramaprakash, M.; Vasudevan, D.; Raju, T. *Synth. Commun.* **2016**, *46*, 145-153.

<sup>186</sup> Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R. S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **2002**, *113*, 8012-8016.

<sup>187</sup> Wu, J.; Abou-Hamdan, H.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun. (Camb.)* **2020**, *56*, 1713-1716.

oxidation of  $\text{MgBr}_2$ . Subsequently, this electrophilic bromine intermediate was trapped by the nucleophilic indole, generating the cyclic bromonium ion intermediate **A**, which would then be converted into the corresponding product, while protons would be reduced into  $\text{H}_2$  at the cathode. The reaction scope was evaluated by the bromocyclization of tryptophol, tryptamine and tryptophan derivatives, yielding bromopyrroloindolines and bromofuranoindoline derivatives with moderate to excellent efficiencies.



**Scheme 64.** Electrochemical bromocyclization of indoles.

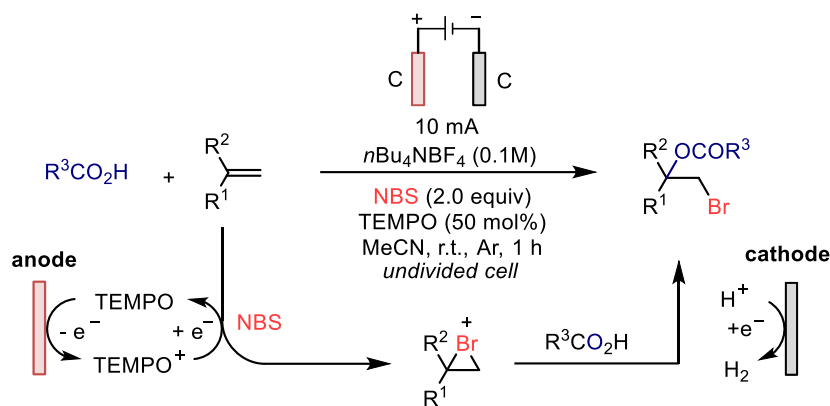
In the same year, Lei's group reported a similar electrochemical dearomative halocyclization of tryptamine and tryptophol derivatives.<sup>188</sup> By using lithium salts as halogen source, a catalytic quantity of  $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  as an additive, and  $\text{Et}_4\text{NBF}_4$  as the electrolyte, the reaction was conducted in an undivided cell with a constant current of 10 mA and a total charge of 5.6 F/mol. Both chloro- and bromo-cyclization could be achieved through this approach.

In 2019, Li, Song and Wan reported a 1,2-bromoesterification of alkenes with carboxylic acids and *N*-bromosuccinimide (NBS) under electrochemical oxidative conditions (**Scheme 65**).<sup>189</sup> This reaction involved the use of a carbon rod anode and a carbon plate cathode in an undivided cell under constant current of 10 mA at room temperature. With 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) serving as the initiator, the reaction enabled the synthesis of  $\beta$ -bromoalkyl esters through oxidative C–Br/C–O difunctionalization. Several organic and inorganic bromine sources were evaluated, and the results indicated that NBS provided notable results whereas inorganic bromine sources such as LiBr,  $\text{NH}_4\text{Br}$ , and KBr were not suitable for the reaction. They also demonstrated a broad substrate scope compatibility. Various alkenes, including styrenes and cycloalkenes, reacted efficiently with a wide range of

<sup>188</sup> Liu, K.; Deng, Y.; Song, W.; Song, C.; Lei, A. *Chin. J. Chem.* **2020**, *38*, 1070-1074.

<sup>189</sup> Wan, C.; Song, R. J.; Li, J. H. *Org. Lett.* **2019**, *21*, 2800-2803.

acids, such as aromatic acids, aliphatic acids, and amino acids. A possible pathway was proposed: the reaction was initiated with the anodic oxidation of TEMPO to TEMPO<sup>+</sup>, which facilitates the addition of NBS to the C=C bond to form cyclic bromonium ion intermediate. Subsequently, the nucleophilic attack of this intermediate along with deprotonation yielded the desired product.

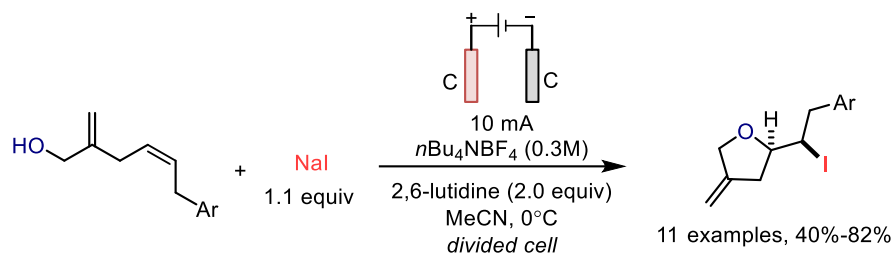


**Scheme 65.** Electro-oxidative 1,2-Bromoesterification of Alkenes with Acids and *N*-Bromosuccinimide.

In 2015, Hilt and co-workers introduced an electrochemical iodonium-initiated cyclization procedure that converts 1,4-dienols into tetrahydrofuran derivatives under indirect electrochemical conditions (**Scheme 66**).<sup>190</sup> This reaction proceeds *via* formation of an iodonium cation intermediate, resulting in good yields with a full regio- and diastereoselectivity and exhibiting good tolerance towards various functional groups. The experimental setup involved an H-type divided cell equipped with carbon fiber electrodes. Both chambers were charged with *n*Bu<sub>4</sub>NBF<sub>4</sub> and 2,6-lutidine in MeCN. 1,4-dienol and sodium iodide (NaI) were placed only in the anode chamber. The reaction was performed under a constant current of 10 mA at 0 °C. In absence of lutidine only traces of the product were observed, with oxidation of the alcohol moiety. Alternative iodide sources such as KI, I<sub>2</sub> or *n*Bu<sub>4</sub>NI, proved to be effective, whereas other halides such as NaBr, Et<sub>4</sub>NBr or *n*Bu<sub>4</sub>NCl resulted in a complex mixture of products.

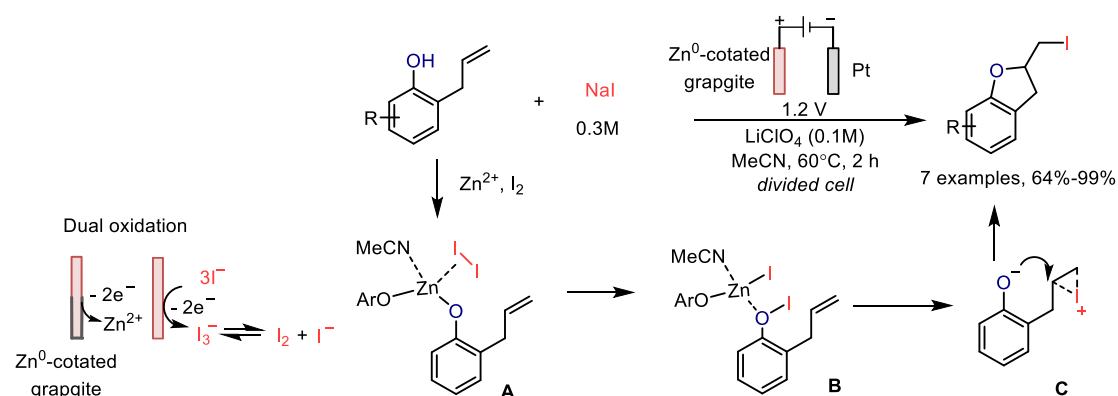
<sup>190</sup> Rose, P.; Emge, S.; Yoshida, J.; Hilt, G. *Beilstein J. Org. Chem.* **2015**, *11*, 174-183.





**Scheme 66.** Iodonium-initiated cyclization of 1,4-dienols for the synthesis of tetrahydrofuran derivatives.

In 2019, Wilden and co-workers reported an iodoetherification transformation of 2-allylphenols for the synthesis of iodinated dihydrobenzofurans, employing zinc as a sacrificial electrode (**Scheme 67**).<sup>191</sup> The authors had previously demonstrated that under electrochemical conditions, Glaser-Hay coupling could be promoted by Cu(I) released from a Cu(0)-coated electrode.<sup>192</sup> In this paper, the reaction was performed in a H-type divided cell, equipped with Zn(0)-coated graphite anode and Pt wire cathode. Given that the reduction potential for Zn(II) is lower than that for I<sub>2</sub> (−0.76 V vs. +0.54 V vs. SHE), the authors proposed that, at the potential for NaI oxidation, zinc coating would undergo oxidation first, yielding both Zn<sup>2+</sup> and I<sub>2</sub>. After cyclic voltammetry experiments, the optimal potential for these reaction conditions was determined to be 1.2 V vs. Ag QRE. The proposed mechanism started with the formation of a bis(aryloxy)zinc complex, followed by coordination of anodically generated I<sub>2</sub>. Subsequent metathesis of the I–I and Zn–O bonds led to the formation of reactive iodophenoxy intermediate **B**. The latter then underwent a rearrangement to produce iodonium **C**, followed by an intramolecular nucleophilic attack, yielding to the desired product.

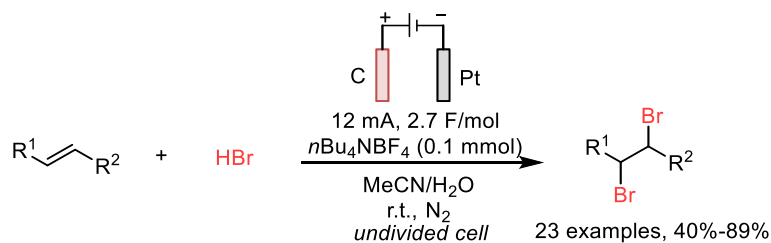


**Scheme 67.** Iodoetherification of 2-allylphenols for the synthesis of iodinated dihydrobenzofurans.

<sup>191</sup> Li, D.; Seavill, P. W.; Wilden, J. D. *ChemElectroChem* **2019**, *6*, 5829-5835.

<sup>192</sup> Seavill, P. W.; Holt, K. B.; Wilden, J. D.; Seavill, P. W. *Green Chem.* **2018**, *20*, 5474-5478.

Lei and co-workers reported an electrochemical oxidative bromination of alkenes using an aqueous solution of HBr as bromine source (**Scheme 68**).<sup>193</sup> Several styrene derivatives and aliphatic alkenes were found to be compatible with the reaction conditions, giving products with yields of up to 89%. In addition to terminal alkenes, internal alkenes were also well-tolerated and *trans*-1,2-dibromide products were isolated as the sole diastereomer. This observation suggested that molecular Br<sub>2</sub> may be the key intermediate in this transformation. To further validate the involvement of a molecular Br<sub>2</sub> intermediate in alkene dibromination, the reaction of molecular Br<sub>2</sub> with styrene in absence of electricity was investigated. The product was isolated with a 53% yield, which is lower than the 80% yield obtained under standard conditions using HBr as the reagent. These results provided evidence supporting involvement of molecular Br<sub>2</sub> as key intermediate

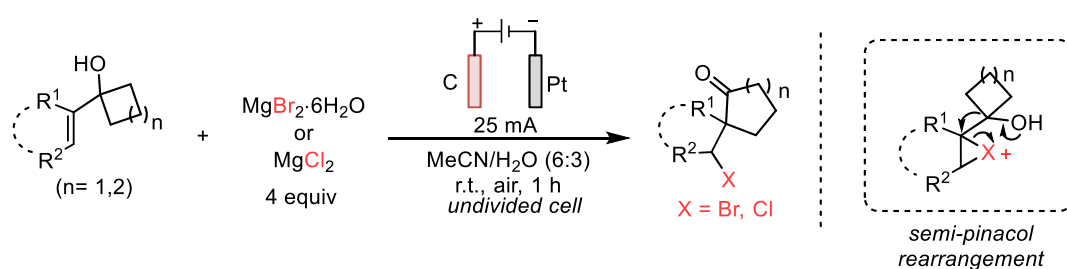


**Scheme 68.** Electrochemical Oxidative Dibromination of Alkenes.

Zhang and co-workers have developed an electrochemical synthetic method for the synthesis of  $\beta$ -halocarbonyl compounds (**Scheme 69**).<sup>194</sup> This approach involved the halogenation/semi-pinacol rearrangement of allylic alcohols using MgBr<sub>2</sub>·6H<sub>2</sub>O and MgCl<sub>2</sub> as halogen sources. Excellent diastereoselectivities were obtained when tri-substituted alkenes were employed as substrates, suggesting the involvement of a cation migration process in the reaction. When secondary alcohols were used as substrates, the reaction yields a range of  $\beta$ -bromo-aldehydes. Mechanistic studies revealed that the process was initiated with the anodic oxidation of bromide ions to generate molecular bromine, followed by the formation of a bromonium ion, which allowed a classic electrophilic semi-pinacol rearrangement to yield  $\beta$ -halocarbonyls.

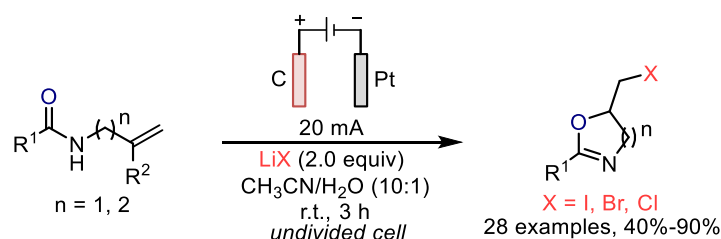
<sup>193</sup> Yuan, Y.; Yao, A.; Zheng, Y.; Gao, M.; Zhou, Z.; Qiao, J.; Hu, J.; Ye, B.; Zhao, J.; Wen, H.; Lei, A. *iScience* **2019**, *12*, 293-303.

<sup>194</sup> Chen, C.; Kang, J.-C.; Mao, C.; Dong, J.-W.; Xie, Y.-Y.; Ding, T.-M.; Tu, Y.-Q.; Chen, Z.-M.; Zhang, S.-Y. *Green Chem.* **2019**, *21*, 4014-4019.



**Scheme 69.** Synthesis of  $\beta$ -halocarbonyl derivatives by halogenation/ semi-pinacol rearrangement of allylic alcohols.

In 2022, Yin and Wu's group reported an electrochemical oxidative cyclization of *N*-allylcarboxamides to synthesize various halogenated oxazolines (**Scheme 70**).<sup>195</sup> This approach was carried out in a simple undivided cell equipped with a graphite rod anode and a platinum cathode at room temperature. By employing lithium halogen salts ( $\text{LiX}$ ,  $\text{X} = \text{I}, \text{Br}, \text{Cl}$ ) as redox mediators and halogen sources, a wide range of oxazolines, as well as the corresponding six-membered heterocycles, bearing an iodo-, bromo-, or chloromethyl substituent were efficiently generated in moderate to good yields.



**Scheme 70.** Electrochemical cyclization of *N*-allylcarboxamides to synthesize halogenated oxazolines.

Interestingly, in 2019, Waldvogel's group have reported the synthesis of fluoromethyl oxazolines from *N*-allylcarboxamides. Due to the significant differences in the redox properties of fluoride ions compared to chloride, bromide, and iodide ions, the proposed reaction mechanism involved a distinct pathway. A detailed explanation is provided in the following sections ([section 3.1.1.c](#), **Scheme 76**).

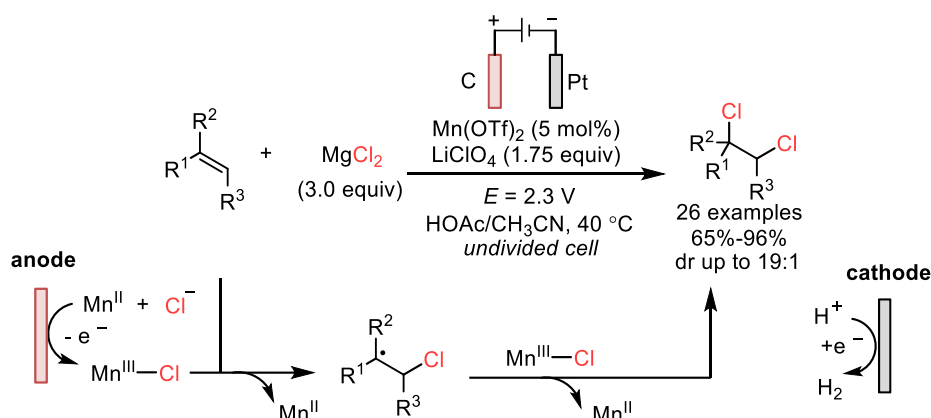
## b. Radical pathway

Halide ions can be oxidized to halogen radicals through anodic oxidation, and

<sup>195</sup> He, Y.; Yin, Y.; Liu, C.; Wu, X.-F.; Yin, Z. *New J. Chem.* **2022**, *46*, 663-667.

participate in the reaction as active open-shell intermediates.

In 2017, Lin and co-workers reported an electrochemical vicinal dichlorination of alkenes employing  $\text{MgCl}_2$  as a chlorine source and  $\text{Mn}(\text{OTf})_2$  as the catalyst (**Scheme 71**).<sup>196</sup> This approach offered an efficient alternative for the radical-based vicinal dichlorination of alkenes. The reaction conditions demonstrated an excellent tolerance toward oxidatively sensitive functional groups such as alcohols, aldehydes, sulfides, and amines, yielding products in excellent yields. Notably, cyclic alkenes and  $\beta$ -alkylstyrenes underwent high diastereoselective conversion into their respective *anti*-dichlorides, with a diastereomeric ratio (dr) of up to 19:1. The high diastereoselectivity can be attributed to a combination of the steric and electronic properties of the potential chlorine transfer agent ( $[\text{Mn}^{\text{III}}-\text{Cl}]$ ). A mechanistic investigation revealed that in this electrochemical system, the chlorine radical existed in the form of anodically generated  $\text{Mn}^{\text{III}}\text{ClX}_2$  ( $\text{X} = \text{Cl}$  or  $\text{OAc}$ ), which acts as an atom-transfer agent to deliver both equivalents of chlorine to the alkene and thus facilitating the vicinal dichlorination.



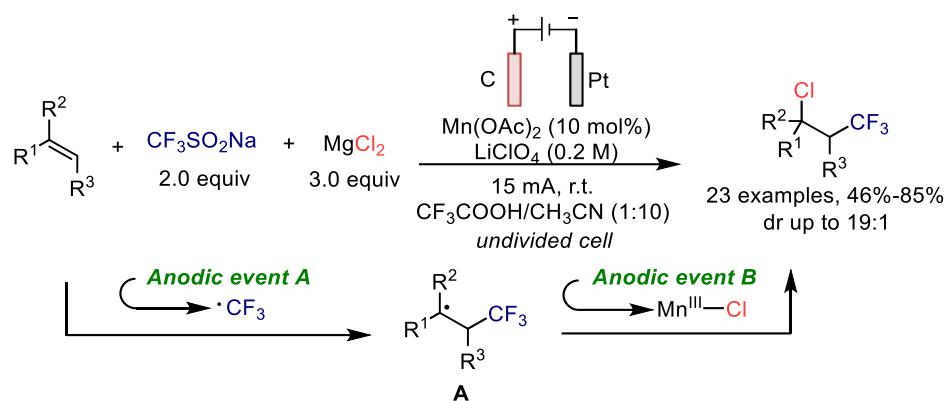
**Scheme 71.** Electrocatalytic Radical Dichlorination of Alkenes with Nucleophilic Chlorine Sources.

One year later, Lin and co-workers described a chlorotrifluoromethylation reaction of alkenes by developing a new strategy that combine two distinct and parallel oxidative events (**Scheme 72**).<sup>197</sup>  $\text{CF}_3\text{SO}_2\text{Na}$  was chosen as the  $\text{CF}_3$  radical source, combined with anodically generated  $[\text{Mn}^{\text{III}}]-\text{Cl}$  from  $\text{Mn}(\text{OAc})_2$  and  $\text{MgCl}_2$  as a chlorinating agent. The challenge of such a process was to combine two distinct anodic functionalization events while achieving both high selectivity and decent yields. Initially, the addition of  $\text{CF}_3$  radical, generated from the first anodic event, formed a stabilized alkyl radical intermediate **A**. Then the latter, add onto the  $\text{Mn}(\text{III})-\text{Cl}$  intermediate, which is a masked  $\text{Cl}\cdot$  radical, generated through the second anodic event allowing the formation

<sup>196</sup> Fu, N.; Sauer, G. S.; Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 15548-15553.

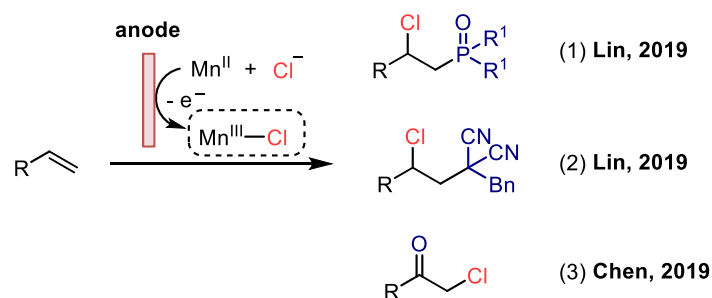
<sup>197</sup> Ye, K.-Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. *J. Am. Chem. Soc.* **2018**, *140*, 2438-2441.

of the C–Cl bond. The chlorine atom was in all the cases added to the most substituted carbon atom enabling the formation of diverse range of chlorotrifluoromethylated compounds with good yields and full regioselectivity. In the case of cyclic alkenes, a highly diastereoselective process favoring the *trans* isomers was reported, with a diastereomeric ratio (dr) of up to 19:1. It has to be noted that when using potassium bromide in place of magnesium chloride, the brominated product can be formed in moderate yield.



**Scheme 72.** Anodically Coupled Electrolysis for the chlorotrifluoromethylation of Alkenes.

In 2019, Lin's group reported the chlorophosphinoylation and chloroalkylation of alkenes (**Scheme 73**, eq 1&2),<sup>198,199</sup> while Chen's group reported the oxychlorination of alkenes (**Scheme 73**, eq 3).<sup>200</sup> These reactions both involve the formation of  $[\text{Mn}^{\text{III}}]\text{--Cl}$  intermediates, which are generated through anodic oxidation of Mn(II) catalyst and chlorine salt, as a source of chlorine radicals for chlorination reactions.



**Scheme 73.** Heterodifunctionalization of Alkenes using  $[\text{Mn}^{\text{III}}]\text{--Cl}$  as a mediator.

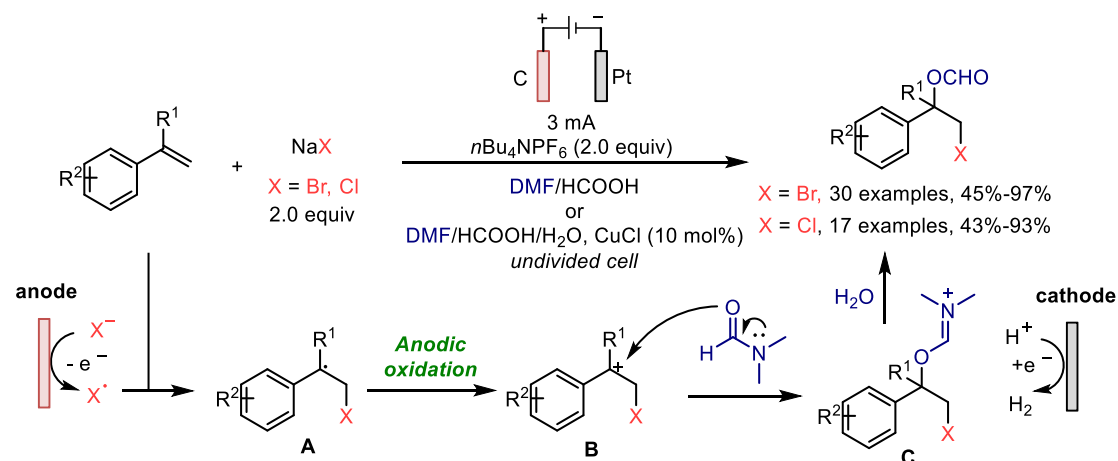
Sun and co-workers developed an electrochemical bromination, chlorination and trifluoromethylation-formyloxylation of various alkenes with readily available NaCl,

<sup>198</sup> Lu, L.; Fu, N.; Lin, S. *Synlett* **2019**, 30, 1199–1203.

<sup>199</sup> Fu, N.; Shen, Y.; Allen, A. R.; Song, L.; Ozaki, A.; Lin, S. *ACS Catal* **2019**, 9, 746–754.

<sup>200</sup> Tian, S.; Jia, X.; Wang, L.; Li, B.; Liu, S.; Ma, L.; Gao, W.; Wei, Y.; Chen, J.; Tian, S. *Chem. Commun. (Cambridge, U. K.)* **2019**, 55, 12104–12107.

NaBr and CF<sub>3</sub>SO<sub>2</sub>Na, and DMF as formyloxylating reagent (**Scheme 74**).<sup>201</sup> The reaction was conducted in an undivided cell, equipped with a carbon rod anode and a platinum plate cathode. A constant current of 3.0 mA was applied, while HCOOH (0.5 mL) was present along with *n*Bu<sub>4</sub>NPF<sub>6</sub> as the electrolyte. For the chloroformyloxylating reaction, the addition of CuCl (10 mol%) was required, as it could potentially serve as a catalyst. This methodology was also successfully applied to produce the desired trifluoromethylformyloxylating products when halogen salts were replaced by CF<sub>3</sub>SO<sub>2</sub>Na. Mechanistic studies revealed that radical intermediates are potentially involved in this transformation. The reaction initiated with the oxidation of Cl<sup>-</sup>, Br<sup>-</sup>, or <sup>-</sup>CF<sub>3</sub> at the anode to generate the respective radicals, which added to alkene to form radical intermediate **A**. This intermediate can be further oxidized to benzyl carbocation **B**, which underwent nucleophilic attack by DMF to yield imine intermediate **C**. Hydrolysis of intermediate **C** afforded the desired product along with a hydrogen ion, which was reduced at the cathode to release H<sub>2</sub>.



**Scheme 74.** Electrochemical oxidation halogenation-formyloxylating of alkenes.

### c. Nucleophilic addition of halide ions

The halogenation reaction of alkenes *via* nucleophilic addition of a halide ions is commonly employed for the synthesis of fluorinated molecules. Due to the relatively high oxidation potential of fluoride ion, it is less likely to be oxidized under electrochemical conditions, allowing for the possibility of nucleophilic addition. The electrophilic center is typically formed by the addition of hypervalent iodides that are generated *in situ* at the anode to the C=C bond of the alkenes or by the anodic oxidation of the C=C bond of alkenes to a radical cation intermediate.

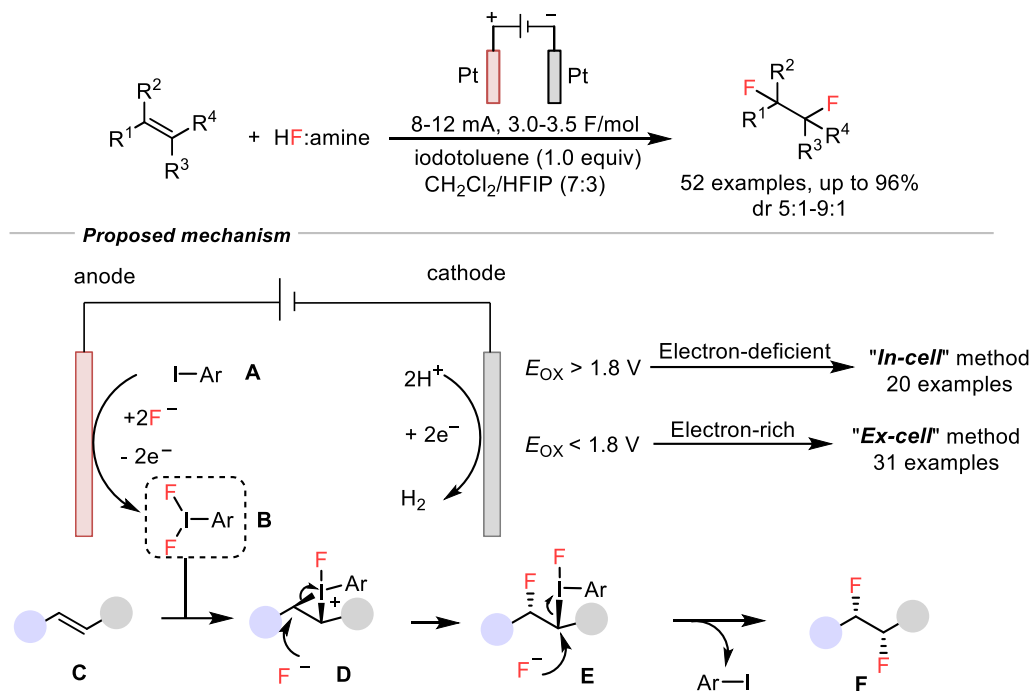
In 2020, Lennox and co-workers disclosed an electrochemical vicinal 1,2-difluorination

<sup>201</sup> Sun, X.; Ma, H. X.; Mei, T. S.; Fang, P.; Hu, Y. *Org. Lett.* **2019**, *21*, 3167-3171.

of non-activated alkenes, using nucleophilic fluoride and iodotoluene **A** as a mediator (**Scheme 75**).<sup>202</sup> The key to success was the anodic generation of a hypervalent iodine **B** from iodoarene **A**. The activated hypervalent iodine atom in **B** was attacked by the nucleophilic double bond of olefin **C**, forming the iodonium species **D**. Subsequently, nucleophilic ring opening of this three-membered ring by a fluoride ion resulted in the formation of **E**, which was further converted into product **F** through an S<sub>N</sub>2-type substitution reaction, with the F<sup>-</sup> acting as the nucleophile. The “in-cell” method enabled the difluorination of electro-deficient alkenes in good to excellent yields. However, the efficiency of the “in-cell” conditions within an undivided cell was reduced when applied to more electron-rich substrates. Cyclic voltammetry analysis of various electron-rich substrates indicated they were oxidized preferentially to iodotoluene **A**, which crucially hampered the formation of the essential hypervalent iodine mediator **B** and therefore decrease the efficiency of the whole process. To avoid this issue, the “ex-cell” method in a divided cell was employed to facilitate the difluorination of electron-rich olefins, which was previously challenging. The “ex-cell” approach effectively prevented the oxidative decomposition of these electron-rich substrates. Terminal and internal alkenes were transformed into the corresponding products in good yields. Both *cis* and *trans* internal alkenes proved to be suitable substrates, and their stereochemical information was translated into products, with diastereomeric ratios ranging from 5:1 to 9:1.

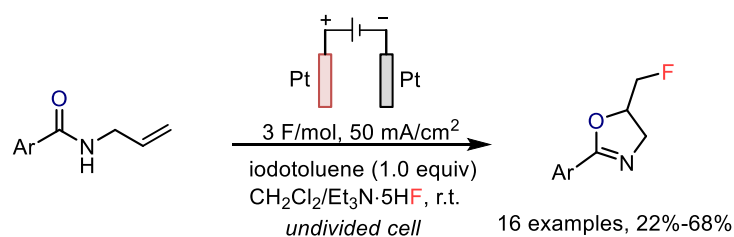
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<sup>202</sup> Doobary, S.; Sedikides, A. T.; Caldora, H. P.; Poole, D. L.; Lennox, A. J. J. *Angew. Chem. Int. Ed.* **2020**, *59*, 1155-1160.



**Scheme 75.** Electrochemical vicinal 1,2-difluorination of non-activated alkenes.

Similarly, Waldvogel's group reported the synthesis of 5-fluoromethyl-2-oxazolines from *N*-allylcarboxamides *via* hypervalent iodoarene-mediated fluorocyclization in 2019 (**Scheme 76**).<sup>203</sup> In this transformation, the key step involved the anodic generation of the hypervalent iodine species, which is attached to the allyl moiety to facilitate the cyclization process. Notably, the reaction is conducted in an undivided cell without the need of external oxidants, offering an attractive approach to the synthesis of 2-oxazolines containing a fluoromethyl group as a potential building block for medicinal chemistry.



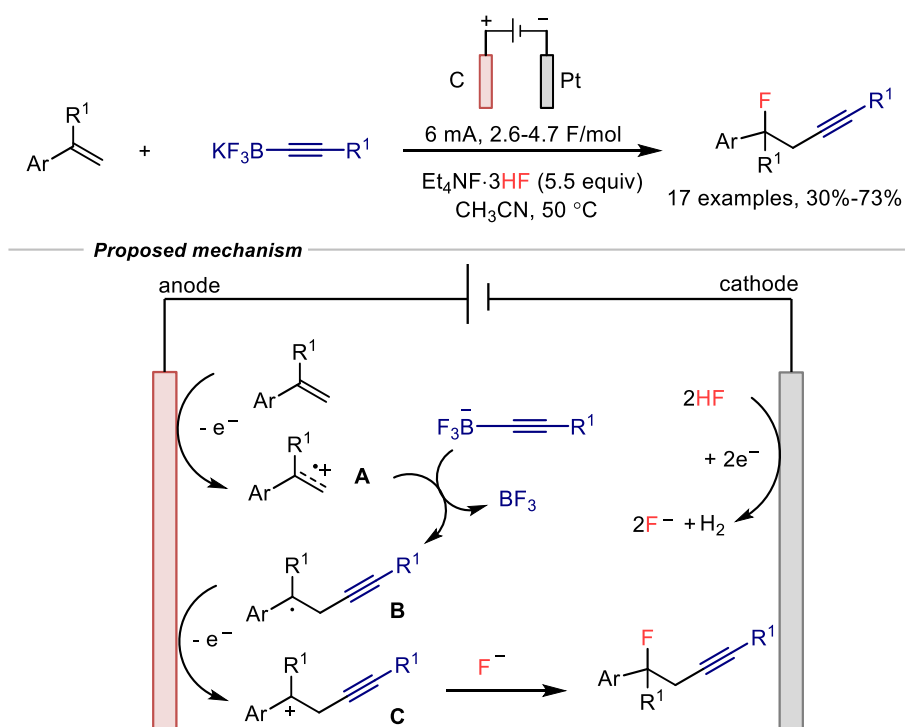
**Scheme 76.** Electrochemical Fluorocyclization of *N*-Allylcarboxamides to 2-Oxazolines.

Xu and coworkers developed an electrochemical fluoroalkynylation reaction of aryl alkenes, using fluoride ions and alkynyltrifluoroborate salts as the functional group

<sup>203</sup> Haupt, J. D.; Berger, M.; Waldvogel, S. R. *Org. Lett.* **2019**, *21*, 242-245.



sources (**Scheme 77**).<sup>204</sup> The use of a graphite anode proved to be crucial in the success of this transformation. By applying a current of 6.0 mA and employing Et<sub>4</sub>NF·3HF as the source of fluoride ions, the difunctionalized products were formed with a complete regioselectivity in moderate to good yields. The proposed mechanism involved the anodic oxidation of the alkene, generating radical cation **A**, which was subsequently captured by the alkynyltrifluoroborate to form carbon-centered radical **B**. Further oxidation of **B** led to the formation of the carbocation **C**, which selectively reacts with the nucleophilic fluoride anion to yield the desired product.



**Scheme 77.** Electrochemical Fluoroalkynylation of Aryl Alkenes.

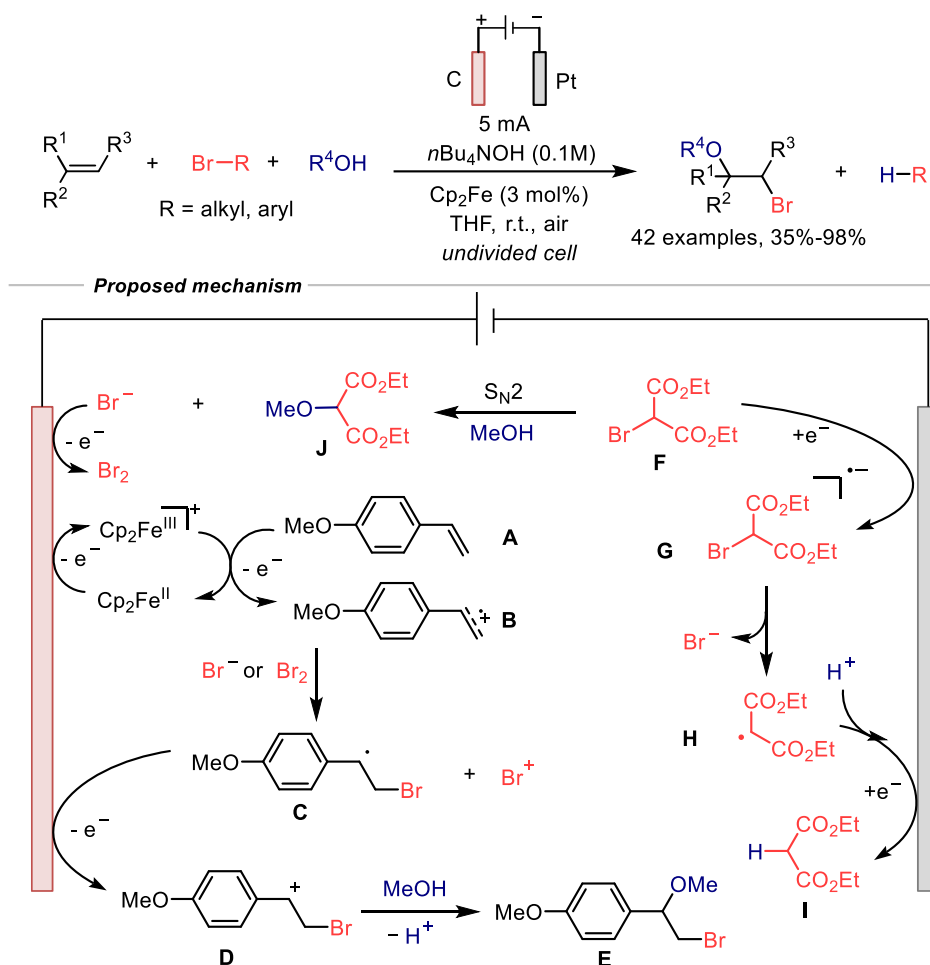
In the above examples, the halogenation reactions proceeds *via* the nucleophilic addition of halide ions (ie the fluoride) under electrochemical conditions due to its resistance to anodic oxidation. In contrast, iodide, bromide, and chloride ions are more susceptible to be oxidized at the anode, which offers wider synthetic opportunities. Screening for new halogen sources with higher oxidation potentials than the alkenes might permit to the halide anions to become the primary nucleophiles in the course of the reaction.

In this regard, Li, Luo and co-workers reported a novel approach for alkene alkoxyhalogenation and organohalide dehalogenation in one-pot reaction conditions (**Scheme 78**).<sup>205</sup> This method, for the first time, employed organohalides, including

<sup>204</sup> Xiong, P.; Long, H.; Xu, H. C. *Asian J. Org. Chem.* **2019**, *8*, 658-660.

<sup>205</sup> Zhang, T. T.; Luo, M. J.; Li, Y.; Song, R. J.; Li, J. H. *Org. Lett.* **2020**, *22*, 7250-7254.

alkyl and aryl halides, as nucleophilic halogen sources. In an undivided cell equipped with a graphite rod anode and platinum plate cathode, with a constant current of 5 mA, in the presence of  $n\text{Bu}_4\text{NOH}$  as the electrolyte and  $\text{Cp}_2\text{Fe}$  (3 mol%) as the catalyst, the  $\beta$ -haloether were obtained in good to excellent yields. This method exhibits excellent tolerance towards various aryl and alkyl substituted olefins as well as various alcohols, including primary, secondary, and tertiary alkyl alcohols. Internal olefins yielded the *trans* diastereomers as the sole products. When using deuterated alcohols, the reaction could also offer access to deuterated compounds by deuteration of the organohalides. It has to be noted that alkyl chloride and iodide could enable the corresponding alkoxychlorination and iodination of alkenes. Cyclic voltammetry investigations have revealed that the use of  $\text{Cp}_2\text{Fe}$  leads to a decreased alkene oxidation potential, providing support for the notion that  $\text{Cp}_2\text{Fe}$  promoted this reaction. The proposed mechanism involves the anodic oxidation of alkene **A**, catalyzed by  $\text{Cp}_2\text{Fe}$ , leading to the formation of radical cation intermediate **B**. Simultaneously, bromide **F** may follow two pathways: one involving an  $\text{S}_{\text{N}}2$  process, yielding  $\text{Br}^-$  and **J**, and the other is the generation of radical anion **G** through cathodic reduction of **F**, followed by its decomposition into  $\text{Br}^-$  anion and alkyl radical **H**. The  $\text{Br}^-$  anion reacted directly with intermediate **B** to form alkyl radical intermediate **C**, which was then oxidized to alkyl cation **D**. The nucleophilic reaction of cation **D** with methanol produced product **E** and  $\text{H}^+$ . Furthermore, there is a possibility that the  $\text{Br}^-$  anion may undergo oxidative conversion to  $\text{Br}_2$ , which would react directly with intermediate **B**. In addition, process involving bromonium cation formation cannot be ruled out.



**Scheme 78.** Electrochemical Alkoxyhalogenation of Alkenes with Organohalides as the nucleophilic halogen sources.

## 3.2 Electrochemical Synthesis of Iodohydrins

Halohydrin derivatives have extensive applications in modern organic synthesis and are found in some bioactive molecules such as marine natural products.<sup>206</sup> They have been used as versatile key intermediates in synthesis of diverse chemicals of interest such as epoxides<sup>207</sup> or ketones<sup>208</sup> and in pharmaceuticals, agrochemicals and materials syntheses.<sup>209,210,211</sup> Production of halohydrins from alkenes is a well-known

<sup>206</sup> Christophersen, C. *Acta Chemica Scandinavica B* **1985**, *39*, 517-529.

<sup>207</sup> Smith Michael, B., *March's advanced organic chemistry : reactions, mechanisms, and structure*, 5th edition ed., John Wiley and Sons, New York, **2001**.

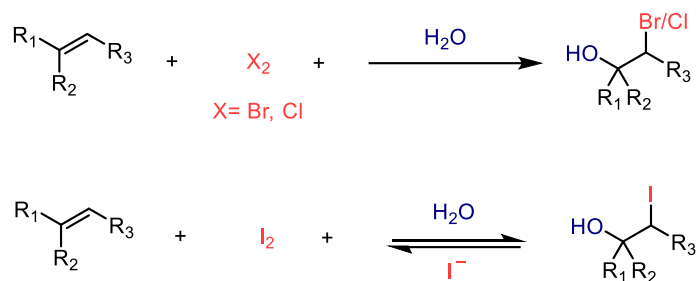
<sup>208</sup> Dolenc, D.; Harej, M. *J. Org. Chem.* **2002**, *67*, 312-313.

<sup>209</sup> Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1988**, *29*, 5197-5200.

<sup>210</sup> Cabanal-Duvillard, I.; Berrien, J.-F.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1998**, *39*, 5181-5184.

<sup>211</sup> Shakya, N.; Srivastav, N. C.; Desroches, N.; Agrawal, B.; Kunimoto, D. Y.; Kumar, R. *J. Med. Chem.* **2010**, *53*, 4130-4140.

procedure.<sup>212</sup> However, in contrast to their homologous chloro- and bromohydrins, iodohydrins are hardly accessible through the direct reaction of olefins with water and iodine, mainly due to the high reversibility of the addition of hypoiodous acid onto the double bond (**Scheme 79**).



**Scheme 79.** Synthesis of halohydrins from the reaction of olefins with water.

Consequently, in most cases, iodide ion scavengers<sup>213, 214</sup> is needed to obtain satisfactory yields. The lower electrophilicity of iodine compared to chlorine or bromine, explains the lower yields and longer reaction time. Alternatively, iodohydrins can be prepared from epoxides, at the cost of a two-step process and the use of peracid or peroxides. Moreover, the ring opening reaction usually involves expensive and/or toxic reagents, such as heavy metal salts, transition metals or acidic conditions.<sup>215, 216, 217, 218, 219</sup> The “cohalogenation” is a powerful tool to synthesize halohydrins. Therefore, a number of research groups have focused on the direct synthesis of iodohydrins from feedstock alkenes. Two main synthetic pathways have been developed, including: (1) redox systems including use of a chemical oxidants or reductants with an iodine source such as  $\text{I}_2$ ,  $\text{NaIO}_4$  or  $\text{H}_5\text{IO}_6$ , for instance (**Scheme 80**,

<sup>212</sup> Rodriguez, J.; Dulcère, J.-P. *Synthesis* **1993**, 1993, 1177-1205.

<sup>213</sup> Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* **1983**, 39, 1765-1768.

<sup>214</sup> Barluenga, J.; Rodríguez, M. A.; Campos, P. J.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1987**, 0, 1491-1492.

<sup>215</sup> Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 28, 4435-4436.

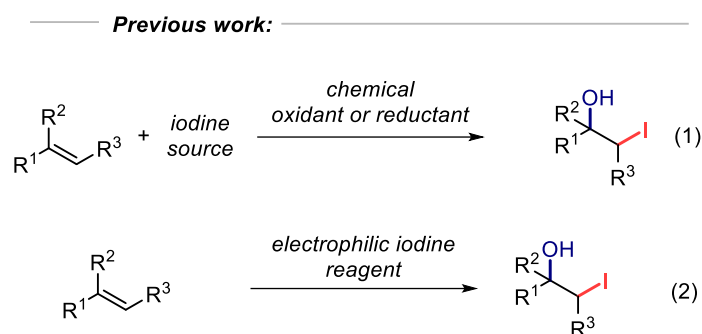
<sup>216</sup> Sharghi, H.; Massah, A. R.; Eshghi, H.; Niknam, K. *J. Org. Chem.* **1998**, 63, 1455-1461.

<sup>217</sup> Ranu, B. C.; Banerjee, S. *J. Org. Chem.* **2005**, 70, 4517-4519.

<sup>218</sup> Alvarez, E.; Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, 55, 3429-3431.

<sup>219</sup> S., Y. J.; S., R. B. V.; Srinivas, R. C.; K., R. *Chem. Lett.* **2004**, 33, 476-477.

eq. 1),<sup>220,221,222,223,224,225,226,227,228,229</sup> (2) the use of a stoichiometric quantity of a strong electrophilic iodinating agent such as *N*-iodosuccinimide, *N*-iodosaccharine or triiodoisocyanuric acid, to name a few (**Scheme 80**, eq. 2).<sup>230,231,232,233,234,235,236</sup>



**Scheme 80.** State of art.

Considering the contemporary concerns to discover sustainable, safer, and cost-effective chemical transformations, the development of protocols that avoid the use of hazardous additives such as chemical oxidants or reductants, expensive catalysts, and stoichiometric reagents, as well as process which minimize waste, is of high demand. Electrochemical oxidative reactions have highly participated in the development of original vicinal difunctionalization of alkenes feedstocks.<sup>237,238,239</sup> In

<sup>220</sup> Moorthy, J. N.; Senapati, K.; Kumar, S. *J. Org. Chem.* **2009**, *74*, 6287-6290.

<sup>221</sup> Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550-5555.

<sup>222</sup> De Corso, A. R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2001**, *42*, 7245-7247.

<sup>223</sup> Barluenga, J.; Marco-Arias, M.; González-Bobes, F.; Ballesteros, A.; González, J. M. *Chem. Eur. J.* **2004**, *10*, 1677-1682.

<sup>224</sup> Sels, B.; Levecque, P.; Brosius, R.; De Vos, D.; Jacobs, P.; Gammon, D. W.; Kinfe, H. H. *Adv. Synth. Catal.* **2005**, *347*, 93-104.

<sup>225</sup> Adimurthy, S.; Ramachandraiah, G.; Ghosh, P. K. *Synth. Commun.* **2007**, *37*, 1579-1585.

<sup>226</sup> Gottam, H.; Vinod, T. K. *J. Org. Chem.* **2010**, *76*, 974-977.

<sup>227</sup> Chakraborty, N.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Majee, A.; Chakraborty, N. *RSC Adv.* **2015**, *5*, 56780-56788.

<sup>228</sup> Rao, D. S.; Reddy, T. R.; Babachary, K.; Kashyap, S.; Rao, D. S. *Org. Biomol. Chem.* **2016**, *14*, 7529-7543.

<sup>229</sup> Zeng, Y.-F.; Liu, X.-G.; Tan, D.-H.; Fan, W.-X.; Li, Y.-N.; Guo, Y.; Wang, H.; Zeng, Y.-F. *Chem. Commun. (Cambridge, U. K.)* **2020**, *56*, 4332-4335.

<sup>230</sup> Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 193-195.

<sup>231</sup> Barluenga, J.; Alvarez-Perez, M.; Rodriguez, F.; Fananas, F. J.; Cuesta, J. A.; Garcia-Granda, S. *J. Org. Chem.* **2003**, *68*, 6583-6586.

<sup>232</sup> Urankar, D.; Rutar, I.; Modec, B.; Dolenc, D. *Eur. J. Org. Chem.* **2005**, *2005*, 2349-2353.

<sup>233</sup> Narender, M.; Reddy, M. S.; Nageswar, Y. V. D.; Rao, K. R. *J. Mol. Catal. A: Chem.* **2006**, *258*, 10-14.

<sup>234</sup> Ribeiro, R. d. S.; Esteves, P. M.; de Mattos, M. C. S. *Tetrahedron Lett.* **2007**, *48*, 8747-8751.

<sup>235</sup> Das, B.; Venkateswarlu, K.; Damodar, K.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *269*, 17-21.

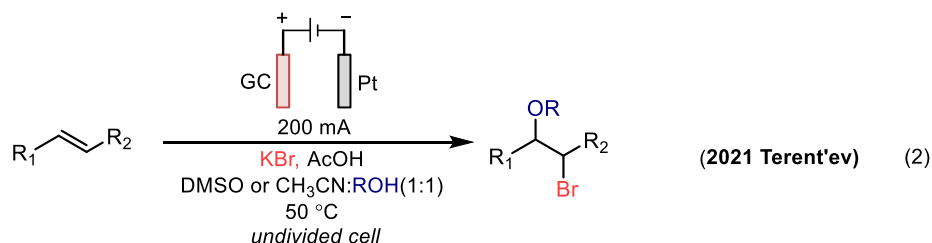
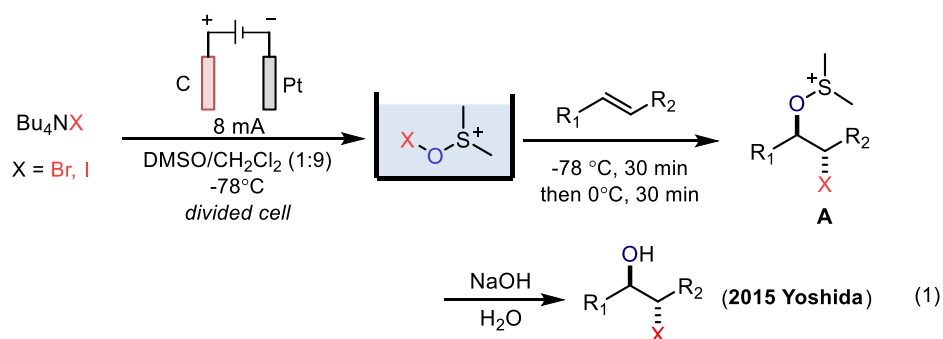
<sup>236</sup> Reddy, A. R.; Sangwan, P. L.; Chinthakindi, P. K.; Farooq, S.; Siddaiah, V.; Koul, S. *Helv. Chim. Acta* **2013**, *96*, 1313-1324.

<sup>237</sup> Thadathil, D. A.; Varghese, A.; Radhakrishnan, K. V. *Asian J. Org. Chem.* **2021**, *10*, 2820-2847.

<sup>238</sup> Mei, H.; Yin, Z.; Liu, J.; Sun, H.; Han, J. *Chin. J. Chem.* **2019**, *37*, 292-301.

<sup>239</sup> Martins, G. M.; Shirinfar, B.; Hardwick, T.; Ahmed, N. *ChemElectroChem* **2019**, *6*, 1300-1315.

2015, Yoshida *et al.* depicted an electrochemical process for the synthesis of halohydrins using the “cation pool” method in a divided cell (**Scheme 81**, eq 1).  $\beta$ -haloalkoxysulfonium ions **A** were generated by the reaction of electrogenerated  $\text{Br}^+$  and  $\text{I}^+$ , which were stabilized by dimethyl sulfoxide (DMSO) at  $-78^\circ\text{C}$ . The  $\beta$ -haloalkoxysulfonium ions then underwent a reaction with sodium hydroxide, leading to the formation of either bromo- or iodohydrins with good yields. This synthesis occurred through a three-step process. However, this reaction is carried out in a relatively complex divided cell, and it requires three steps to complete under harsh conditions.<sup>240</sup> Recently, the group of Terent’ev reported an efficient and selective electrochemical formation of bromohydrins and their ethers in DMSO (**Scheme 81**, eq 2).<sup>241</sup> Acetic acid was needed as an additive, and the reaction needed to be carried out at  $50^\circ\text{C}$  and is limited to bromine.

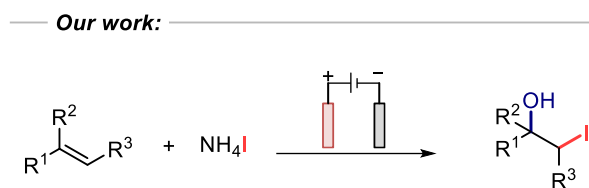


**Scheme 81.** Previews work in electrochemical synthesis of halohydrins.

However, there is still a conspicuous lack of a straightforward and selective synthesis of difficult-to-access iodohydrins using mild and simple reaction conditions. Thus, we conjectured that the anodic oxidation of a non-toxic and readily available iodide reagent would allow the formation of a highly electrophilic iodonium intermediate. This highly reactive species would then react with alkenes and water to access iodohydrins (**Scheme 82**).

<sup>240</sup> Shimizu, A.; Hayashi, R.; Ashikari, Y.; Nokami, T.; Yoshida, J. *Beilstein J. Org. Chem.* **2015**, *11*, 242-248.

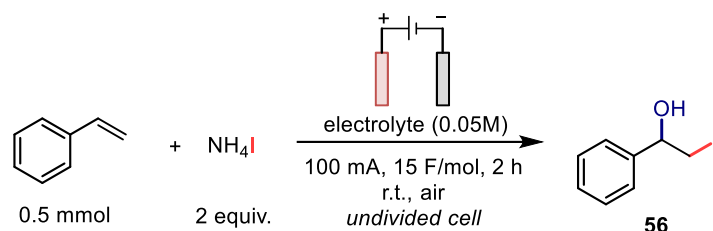
<sup>241</sup> Bityukov, O. V.; Vil, V. A.; Nikishin, G. I.; Terent'ev, A. O. *Adv. Synth. Catal.* **2021**, *363*, 3070-3078.



Scheme 82. Our work.

### 3.2.1 Optimization

At the outset of our investigations, we chose styrene as the model substrate to react with ammonium iodide ( $\text{NH}_4\text{I}$ ). By using carbon graphite electrode as the anode, nickel electrode as the cathode along with  $n\text{Bu}_4\text{NBF}_4$  as the electrolyte (0.05 M), a constant current of 100 mA under an air atmosphere for 2 h in a 10:1 mixture of THF:H<sub>2</sub>O (**Table 11**, entry 1) the desired iodohydrin **56** was obtained with a promising 42% yield based on <sup>1</sup>H-NMR analysis. When THF was used as the sole solvent no product was detected (**Table 11**, entry 2). Using graphite as anode the yield decreased. When the cathode material was replaced with stainless steel, there was a slight increase of the yield to 44%. When using stainless steel as the cathode, better performance was observed in a yield of 44% (**Table 11**, entry 4). When using stainless steel as the anode, the reaction was completely inhibited (**Table 11**, entry 5).  $\text{Et}_4\text{NBF}_4$  exhibited superior performance as an electrolyte, and the absence of electrolyte is unfavorable for our transformation. (**Table 11**, entries 6&7).

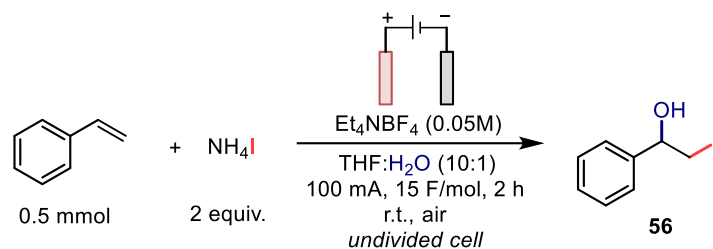


Entry	Electrode	Electrolyte	Solvent (5 mL)	Yield (%) <sup>a</sup>
1	C(+)-Ni(-)	$n\text{Bu}_4\text{NBF}_4$	THF:H <sub>2</sub> O (10:1)	42 (40) <sup>b</sup>
2	C(+)-Ni(-)	$n\text{Bu}_4\text{NBF}_4$	THF	0
3	C(+)-C(-)	$n\text{Bu}_4\text{NBF}_4$	THF:H <sub>2</sub> O (10:1)	24
4	C(+)-SS(-)	$n\text{Bu}_4\text{NBF}_4$	THF:H <sub>2</sub> O (10:1)	44
5	SS(+)-SS(-)	$n\text{Bu}_4\text{NBF}_4$	THF:H <sub>2</sub> O (10:1)	0
6	C(+)-SS(-)	$\text{Et}_4\text{NBF}_4$	THF:H <sub>2</sub> O (10:1)	46
7	C(+)-SS(-)	—	THF:H <sub>2</sub> O (10:1)	26

**Table 11.** Screening of solvent, electrode, and electrolyte. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.5 mmol 1,1,2,2-

Tetrachloroethane as an internal standard. <sup>b</sup> Isolated yield.

Several other solvents were tested, and we found that a mixture of CH<sub>3</sub>CN and H<sub>2</sub>O significantly improved the reaction efficiency (**Table 12**, entries 1-3). Employing platinum as the cathode, or using either glassy carbon or platinum as the anode did not lead to an enhancement of the reaction efficiency (**Table 12**, entries 4-6). We tried to increase the reaction outcome by modifying the solvent ratio and we found that a 4:1 ratio of CH<sub>3</sub>CN and H<sub>2</sub>O resulted in an improved yield (**Table 12**, entries 7-10).

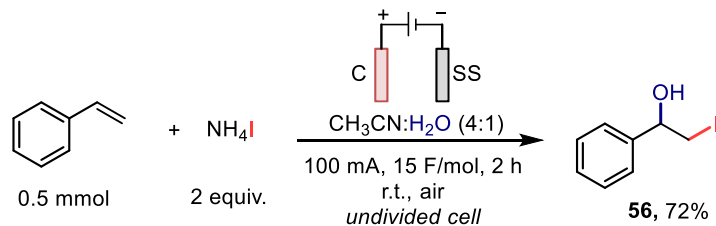


Entry	Electrode	Solvent	Yield (%) <sup>a</sup>
1	C(+)-SS(-)	1,4-Dioxane:H <sub>2</sub> O (10:1)	18
2	C(+)-SS(-)	Acetone:H <sub>2</sub> O (10:1)	6
3	C(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O, 10:1	78
4	C(+)-Pt (-)	CH <sub>3</sub> CN:H <sub>2</sub> O (10:1)	74
5	GC(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (10:1)	54
6	Pt(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (10:1)	66
7	C(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (4:1)	84 (72) <sup>b</sup>
8	C(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (2:1)	68
9	C(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (1.5:1)	42
10	C(+)-SS(-)	CH <sub>3</sub> CN:H <sub>2</sub> O (24:1)	44

**Table 12.** Screening of solvent, electrode, and ratio of solvent. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.5 mmol 1,1,2,2-Tetrachloroethane as an internal standard. <sup>b</sup> Isolated yield.

Other electrolytes such as Et<sub>4</sub>NPF<sub>6</sub>, *n*Bu<sub>4</sub>NHSO<sub>4</sub>, *n*Bu<sub>4</sub>NCl, resulted in lower yields (**Table 13**, entries 1-4), and *n*Bu<sub>4</sub>NI totally inhibits the reaction (**Table 13**, entry 5). A decreased concentration of electrolyte is detrimental to the reaction (**Table 13**, entry 6).

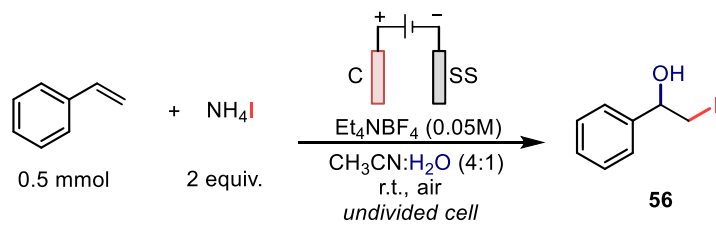




Entry	Electrolyte	Concentration of electrolyte	Yield (%) <sup>a</sup>
1	<i>n</i> Bu <sub>4</sub> NPF <sub>6</sub>	0.05 M	58
2	Et <sub>4</sub> NPF <sub>6</sub>	0.05 M	6
3	<i>n</i> Bu <sub>4</sub> NHSO <sub>4</sub>	0.05 M	26
4	<i>n</i> Bu <sub>4</sub> NCl	0.05 M	14
5	<i>n</i> Bu <sub>4</sub> NI	0.05 M	0
6	Et <sub>4</sub> NBF <sub>4</sub>	0.025 M	46

**Table 13.** Screening of electrolyte and its concentration. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.5 mmol 1,1,2,2-Tetrachloroethane as an internal standard. <sup>b</sup> Isolated yield.

Lowering the current to 80 mA resulted in a decrease in yield, while a further reduction of the current to 50 mA suppressed the reaction (**Table 14**, entry 1 & 2). A reduction of the charge from 15 F·mol<sup>-1</sup> to 10 or 7.46 F·mol<sup>-1</sup> led to lower yields, while the increase to 20 F·mol<sup>-1</sup> did not afford a better yield (entries 3-6). When the reaction was performed under argon, a similar yield than the one obtained under an air atmosphere was obtained (entry 7). Finally, a control experiment showed that no reaction occurred in absence of electricity (entry 8).

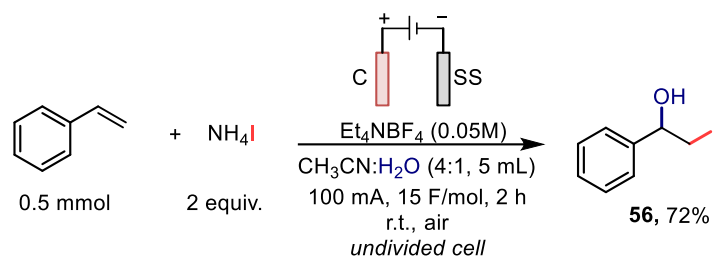


Entry	Current	Charge (time)	Yield (%) <sup>a</sup>
1	80 mA	15 F·mol <sup>-1</sup> (2.51 h)	71
2	50 mA	15 F·mol <sup>-1</sup> (4 h)	n.r. <sup>c</sup>
3	100 mA	7.46 F·mol <sup>-1</sup> (1.0 h)	54
4	100 mA	10 F·mol <sup>-1</sup> (1.34 h)	60
5	100 mA	15 F·mol <sup>-1</sup> (2.01 h)	84 (72) <sup>b</sup>
6	100 mA	20 F·mol <sup>-1</sup> (2.68 h)	78

Entry	Current	Charge (time)	Yield (%) <sup>a</sup>
7 <sup>d</sup>	100 mA	15 F·mol <sup>-1</sup> (2.01 h)	85
8	No current	2 h	n.r. <sup>c</sup>

**Table 14.** Screening of current and charge. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.5 mmol 1,1,2,2-tetrachloroethane as an internal standard. <sup>b</sup> Isolated yield. <sup>c</sup> n.r.: no reaction. <sup>d</sup> under argon.

Thus, we have established the optimal conditions (**Scheme 83**): employing 2 equivalents of ammonium iodide (NH<sub>4</sub>I) as the iodine source, conducting the reaction in an undivided cell with graphite as the anode and stainless steel plate as cathode, under constant current of 100 mA for 2 h (a total charge of 15 F/mol), a 0.05 M solution of tetraethylammonium tetrafluoroborate (Et<sub>4</sub>NBF<sub>4</sub>) as the electrolyte in CH<sub>3</sub>CN/H<sub>2</sub>O solvent mixture (4:1), under air at room temperature. Under these conditions, we obtained the product **56** with an isolated yield of 72%.

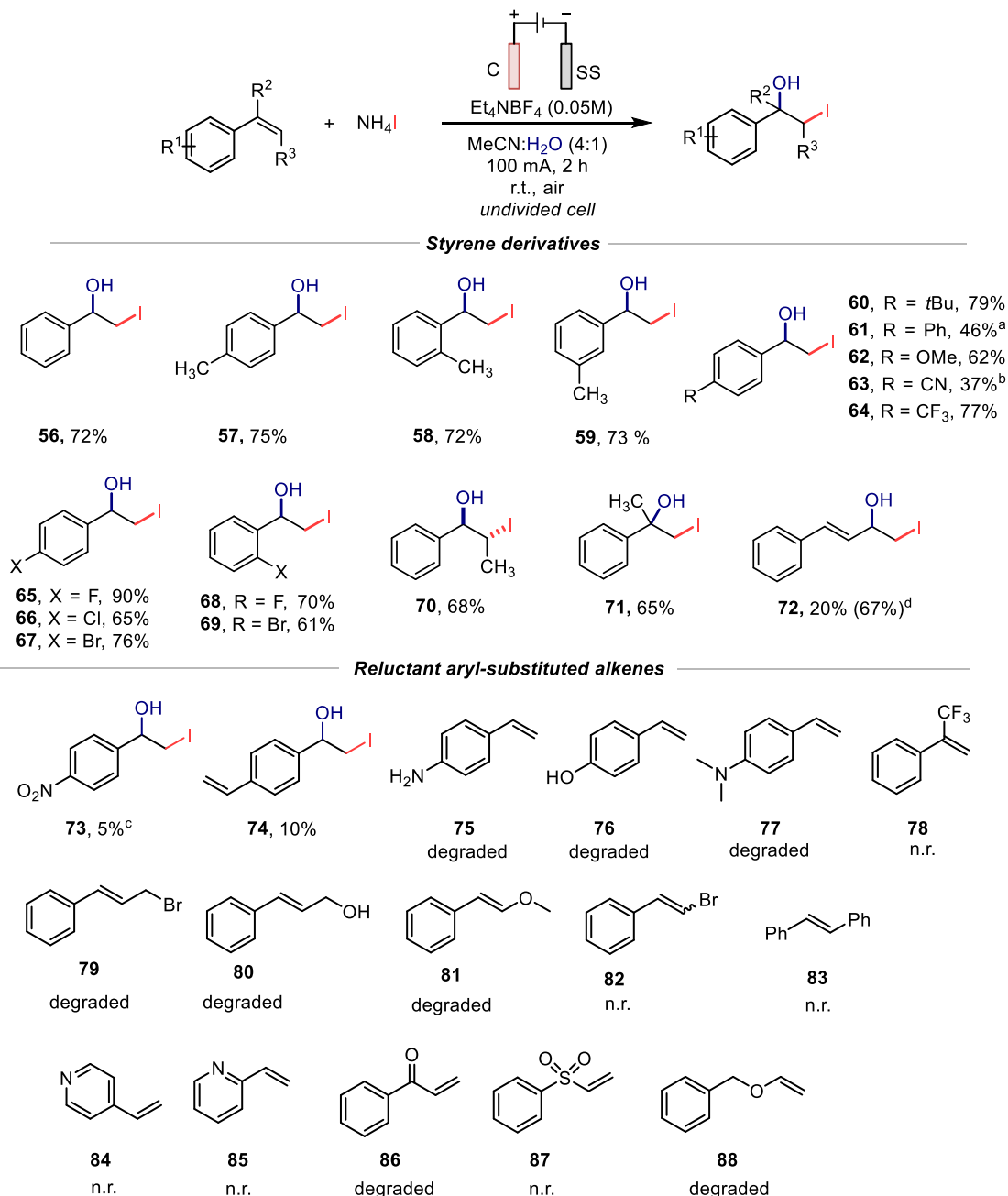


**Scheme 83.** Optimal conditions.

### 3.2.2 Substrates scope and limitations of the method - reluctant substrates

With the optimal conditions in hand, the scope of this electrochemical synthesis of iodohydrins was investigated. A wide range of styrene derivatives was firstly investigated (**Scheme 84**). The presence of a methyl substituent at the *ortho*-, *meta*- or *para*-position on the aromatic ring (**57-59**) did not affect the reaction efficiency. Electron-donating groups such as *t*-butyl, phenyl or methoxy were well tolerated and the reaction afforded the corresponding products (**60-62**) in good efficiencies. Although the cyano derivative **63** was obtained in a 37% yield, a trifluoromethyl substituted derivative **64** was synthesized in a good 77% yield, showcasing the tolerance toward electron-withdrawing groups. Regardless of the substitution pattern, styrenes containing halogens on the aromatic ring provided the corresponding iodohydrins with good yields (**65-69**). The  $\alpha$ - and  $\beta$ -substituted styrene derivatives were also reacted, furnishing the corresponding products **70** & **71** in moderate to good yields. It has to be noted that **70** was isolated with an exclusive *trans*-

diastereoselectivity. Interestingly, a 1,3-diene, which is a versatile substrate in organic synthesis, was efficient in this transformation, and the reaction was selective to the terminal position, giving **72** in a modest 20% isolated yield due to a tedious purification over silica gel, albeit a decent 67% NMR yield.

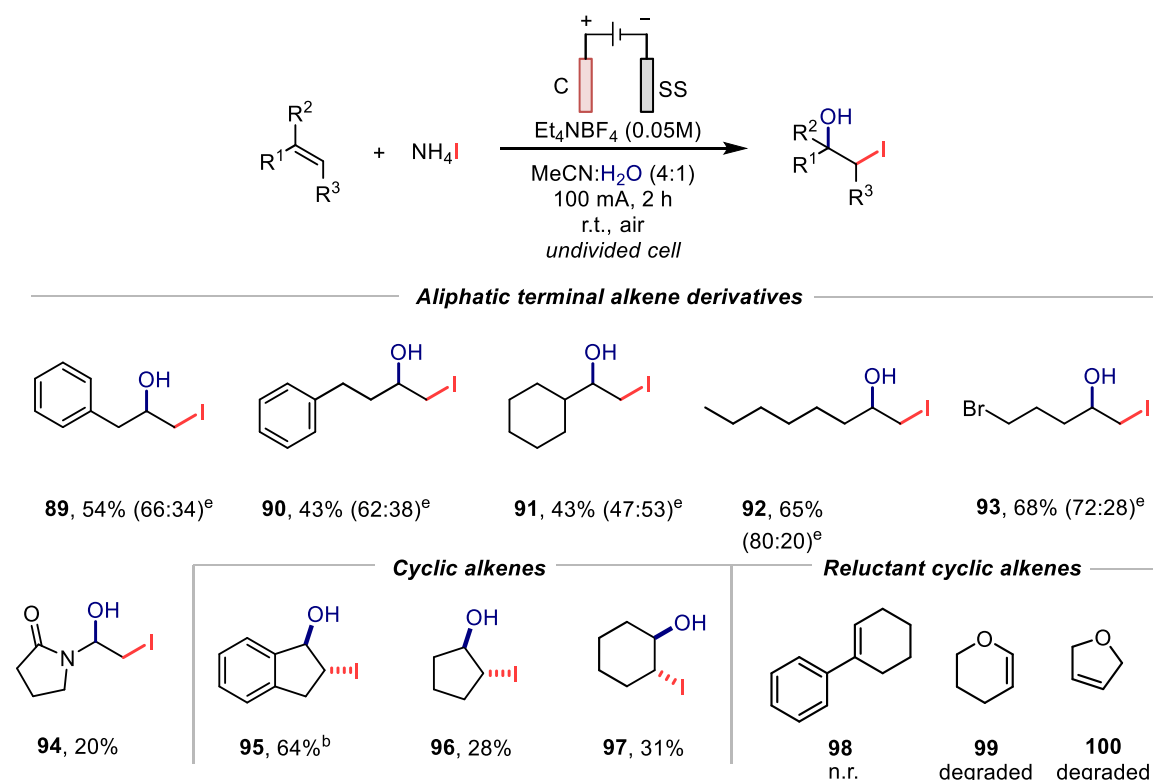


**Scheme 84.** Substrate scope of styrene derivatives. <sup>a</sup> 5 h reaction time. <sup>b</sup> 4 h of reaction time. <sup>c</sup> 3 h of reaction time. <sup>d</sup> NMR yield by using 1,1,2,2-tetrachloroethane as an internal standard.

However, some aryl alkenes were not compatible or poorly reactive (**Scheme 84**). For instance, 4-nitrostyrene provided only 5 % of the desired product (**73**) and 12% of the epoxide at the same time. In the case of 1,4-divinylbenzene, reaction occurred on only one side of the double bond, yielding only 10 % of product **74**. Substrates like 4-

vinylaniline, 4-vinylphenol, and *N,N*-dimethyl-4-vinylaniline (**75-77**) led to complete decomposition of the starting material.  $\alpha$ -(trifluoromethyl)styrene was unreactive, and the starting material was recovered (**78**). We also attempted several  $\beta$ -substituted styrene derivatives, but they either degraded or did not react (**79-83**). Vinyl pyridine (**84 & 85**) showed no reactivity. Other alkenes, such as 1-Phenyl-2-propen-1-one (**86**), phenyl vinyl sulfone (**87**), benzylvinylether (**88**) either degraded or did not react.

In addition to aryl-substituted alkenes, aliphatic terminal alkenes proved to be efficient substrates (**Scheme 85**). However, compared to aryl-substituted alkenes, aliphatic alkenes yield two regioisomers, with the Markovnikov product obtained as the major one. Halohydrin derivatives (**89-93**) were obtained in decent yields. Moreover, an alkyl-substituted olefin bearing a substituent able to undergo an intramolecular nucleophilic displacement reacted efficiently, yielding the desired product without the formation of side products and exhibiting good regioselectivity (**93**). Interestingly, an exceptional case is *N*-vinyl-2-pyrrolidinone, which proved to be a suitable substrate for this transformation. Indeed, the iodohydrin derivative **94** was synthesized with a complete regioselectivity, offering a valuable approach to a versatile building block.

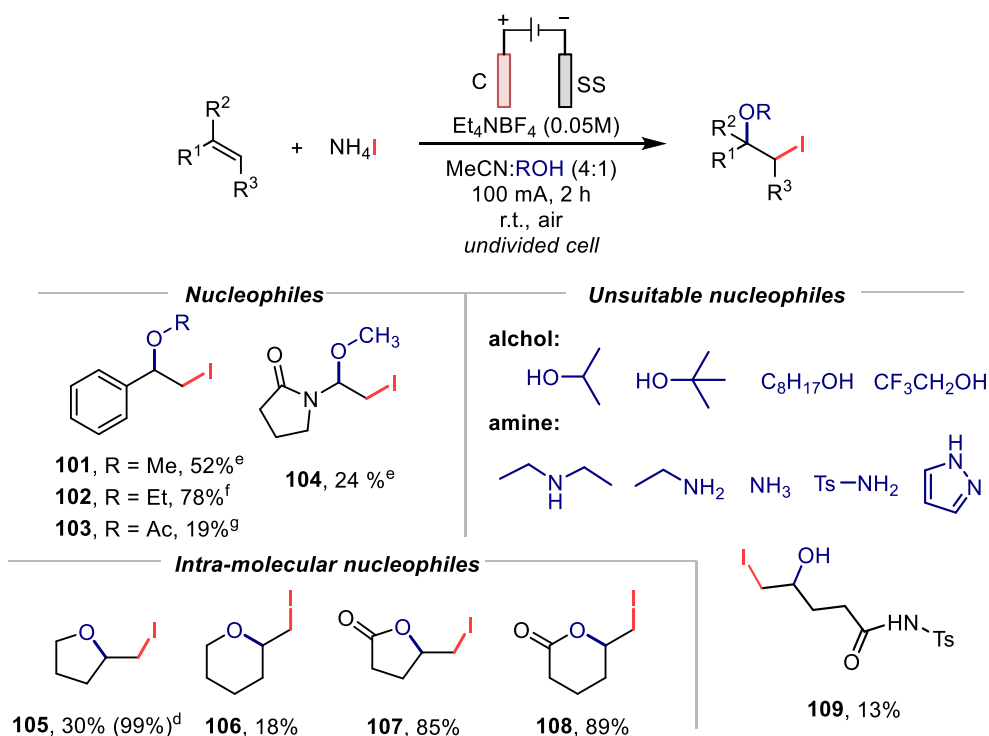


**Scheme 85.** Substrate scope of aliphatic terminal alkenes and cyclic alkenes. <sup>b</sup> 4 h of reaction time. <sup>e</sup> Regioisomeric ratio calculated on crude <sup>1</sup>H NMR, for clarity the major Markovnikov product is depicted.

A representative set of internal cyclic olefins was also examined (**Scheme 85**). Under the optimal reaction conditions, indene efficiently yields the iodohydrin **95**, while

cyclopentene or cyclohexene afforded the desired product (**96 & 97**) in a moderate 28% and 31% yield, respectively, with a full *trans*-diastereoselectivity. However, cyclic alkenes such as 1-Phenyl-1-cyclohexene, 3,4-Dihydro-2H-pyran and 2,5-dihydrofuran (**98-100**) did not show any reactivity.

The reaction with other nucleophiles, in place of water was explored (**Scheme 86**). Indeed, similarly to halohydrins,  $\beta$ -iodo ethers are recognized as strategic compounds in medicinal chemistry, material sciences, and are common building blocks in the portfolio of synthetic chemists. The reactions were carried out using a mixture of MeCN:ROH (4:1, 5.0 mL) as the solvent. It was observed that methanol and ethanol were compatible with our electrochemical reactions as nucleophiles, ethanol allowing a better efficiency than methanol (**101**, **102 & 104**). Acetic acid was also a suitable nucleophile, albeit furnishing **103** in a lower 19% yield. It is worth mentioning that when using MeCN:H<sub>2</sub>O:AcOH (8:1:1, 5.0 mL) as the solvent, compound **103** was not obtained, and instead, the hydroxyiodinated product **56** was obtained with 82% <sup>1</sup>H-NMR yield. This result is attributed to the stronger nucleophilicity of water compared to acetic acid.

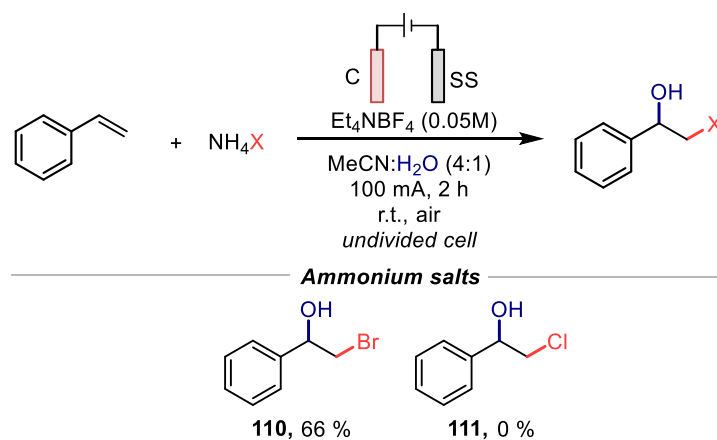


**Scheme 86.** Scope of nucleophiles. <sup>d</sup> NMR yield by using 1,1,2,2-tetrachloroethane as an internal standard. <sup>e</sup> MeCN:MeOH (4:1, 5.0 mL). <sup>f</sup> MeCN:EtOH (4:1, 5.0 mL). <sup>g</sup> MeCN:AcOH (4:1, 5.0 mL).

We also attempted *t*-butanol, isopropanol, trifluoroethanol, and 1-octanol as nucleophilic reagents, but corresponding ether products were not obtained (**Scheme 86**). In addition to alcohol-based nucleophilic reagents, we tested amine-based nucleophilic reagents such as diethylamine, ethylamine, aniline, *p*-

Toluenesulfonamide, and 1H-pyrazole. However, neither using stoichiometric amount (2 equiv.) of amine reagents nor employing 1.0 mL of amine reagents mixed with acetonitrile as solvents yielded the desired products (**Scheme 86**). Under standard conditions, the intramolecular iodocyclization of 4-penten-1-ol has been accomplished, giving exclusively iodinated tetrahydrofuran **105** in a modest isolated yield. Considering the nucleophilic nature of the intramolecular hydroxyl group, we carried out the reaction using acetonitrile as the sole solvent, rather than a mixed solvent of CH<sub>3</sub>CN and H<sub>2</sub>O. However, no product was formed. Similarly, intramolecular iodocyclization of 5-Hexen-1-ol gave an iodinated tetrahydropyran **106** in a lower yield. Pentenoic acid or hexenoic acid derivatives were also efficient precursors for the synthesis of valuable iodinated lactones **107** and **108**, obtained through an electrochemical iodolactonization. Intramolecular nucleophilic addition of an amine moiety was also tried under our reaction conditions. However, the use of *N*-tosylpent-4-enamide did not yield the cyclized product. Instead, hydroxyiodination reaction occurred, affording **109** with a yield of 13% (**Scheme 86**).

We sought to extend our methodology to the synthesis of bromo- and chlorohydrins by using ammonium bromide or chloride (**Scheme 87**). Although, NH<sub>4</sub>Br reacted smoothly, yielding to the bromohydrins **110** in a good 66% yield, NH<sub>4</sub>Cl was not reactive at all.



**Scheme 87.** Scope of ammonium salts.

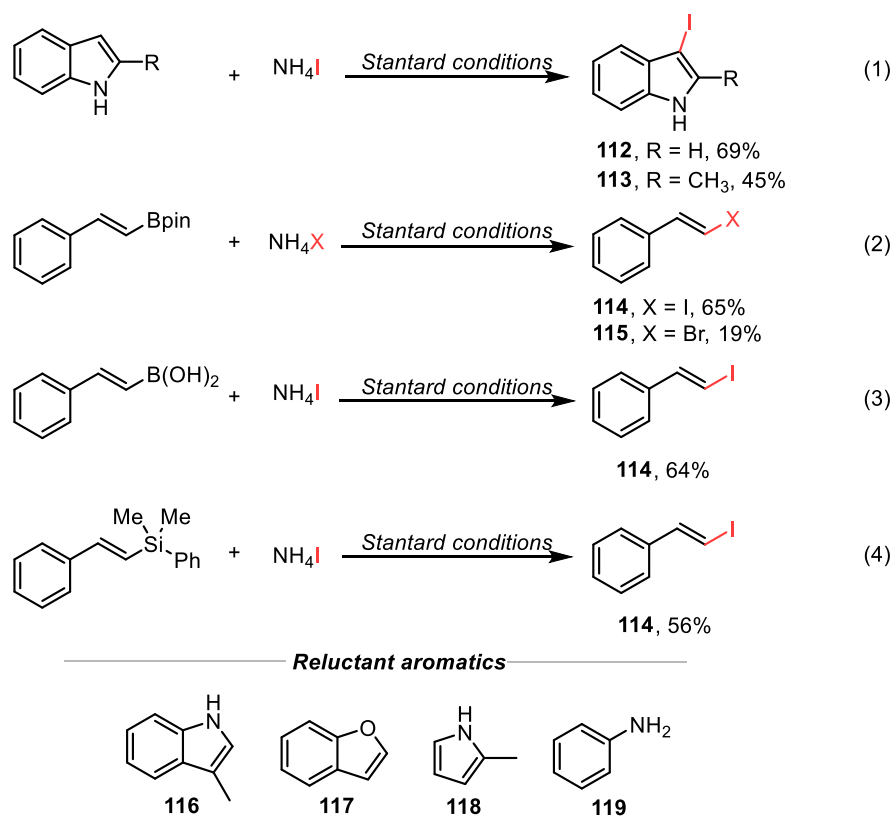
Finally, we showcased the utility of our methodology through the synthesis of other valuable iodinated chemicals under the same reaction conditions. Indeed, iodinated molecules have been recognized over the years as important and versatile building blocks in organic synthesis, and their utility largely grew up following the discovery of cross-coupling reactions, for instance.<sup>242,243,244</sup> Their synthesis has been investigated

<sup>242</sup> Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508-524.

<sup>243</sup> Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457-2483.

<sup>244</sup> de Meijere, A.; Diederich, F., *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, **2004**.

by using elemental iodine as source of the iodonium donating agent. Thus, we sought to provide a complementary approach using our electrochemical method to the synthesis of valuable iodinated chemicals (**Scheme 88**). First, we were able to synthesize 3-iodo substituted indoles (**112** & **113**) in decent to good yields by reacting non-protected indole and 2-methylindole (**Scheme 88**, eq. 1). Interestingly, vinyl halides, designated as one of the most important building blocks for transition-metal-catalyzed syntheses,<sup>245,246</sup> were easily synthesized either from the corresponding styryl boronic acid, styryl pinacolborane (**Scheme 88**, eq. 2&3, **114**) or  $\beta$ -dimethylphenylsilyl styrene (**Scheme 88**, eq. 4, **114**) derivatives using our developed electrochemical conditions in good yields. The reaction was also extended to the synthesis of 2-bromovinylbenzene **115**, from the corresponding alkenyl boronate derivative, albeit with a lower efficiency (19%, **Scheme 88**, eq. 2). However, other (hetero)aromatics such as, 3-methylindole **116**, benzofuran **117**, 2-methylpyrrole **118** and aniline **119** were not reactive at all.



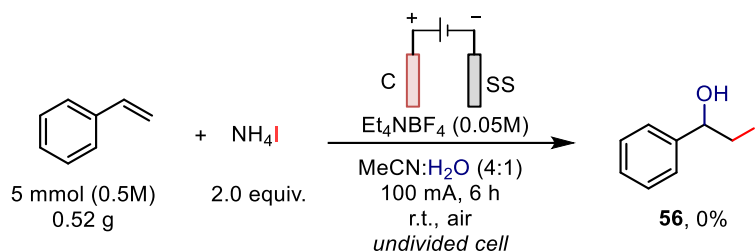
**Scheme 88.** Electrochemical iodination/bromination.

<sup>245</sup> Tsuji, J., *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, **2002**, p. 27-108.

<sup>246</sup> Chao, W.; Mahajan, Y. R.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3815-3818.

### 3.2.3 Scale-up reaction

Having proved the potential of our transformation regarding the wide tolerance to various functional groups and application to iodination of valuable chemicals, we evaluated the potential application of this electrochemical oxidative hydroxyiodination of alkenes by conducting reactions on a 5 mmol scale (**Scheme 89**).



**Scheme 89.** 5 mmol scale reaction.

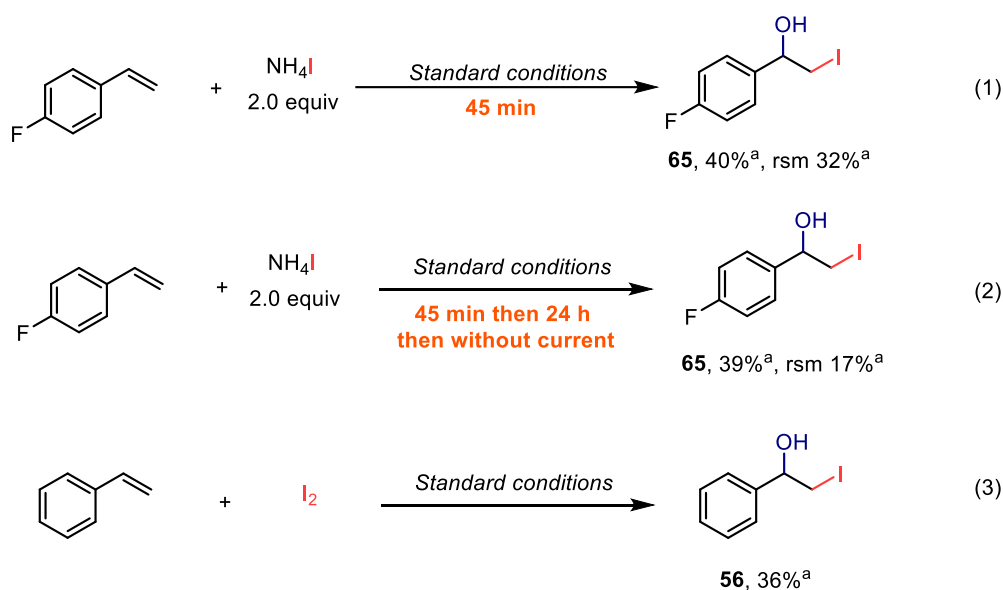
In a 10 mL reaction vessel from IKA, we employed a mixture of 10 mL CH<sub>3</sub>CN/H<sub>2</sub>O (4:1) as the solvent, maintaining the electrolyte concentration at the same value than standard conditions (0.05 M). At 5 mmol scale, the substrate concentration is five times that of standard conditions (0.5 M vs 0.1 M). The reaction was conducted at room temperature under air atmosphere and a constant current of 100 mA for 6 hours (**Scheme 89**). Although as usually observed, the reaction mixture color turned from colorless to deep reddish-brown, the formation of the desired product was not detected. Only the starting material, ie styrene, was observed on <sup>1</sup>H-NMR spectra and thin-layer chromatography (TLC) analysis. There could be multiple reasons to explain this result, such as a significant change in reactant concentration, variations in current density (due to change in electrode immersion length), temperature fluctuations, or the potential need for a larger current in the scaled-up reaction, which exceeds the capability of the IKA equipment (maximum 100 mA). Additionally, while the volume of the reaction solution and the amount of substrate increased, the electrode surface area remained unchanged, potentially leading to limitations in mass and charge transfer. To address these issues, it might be necessary to optimize the electrolysis cell design, increase the electrode surface area, adjust the current density, or consider modifying reaction conditions to achieve a better balance between charge and mass transfer, thereby facilitating scaled-up reactions and higher reaction rates.

### 3.2.4 Mechanistic study

To gain insights into the reaction mechanism, control experiments were carried out (**Scheme 90**). First, to preclude any side reaction resulting from the presence of



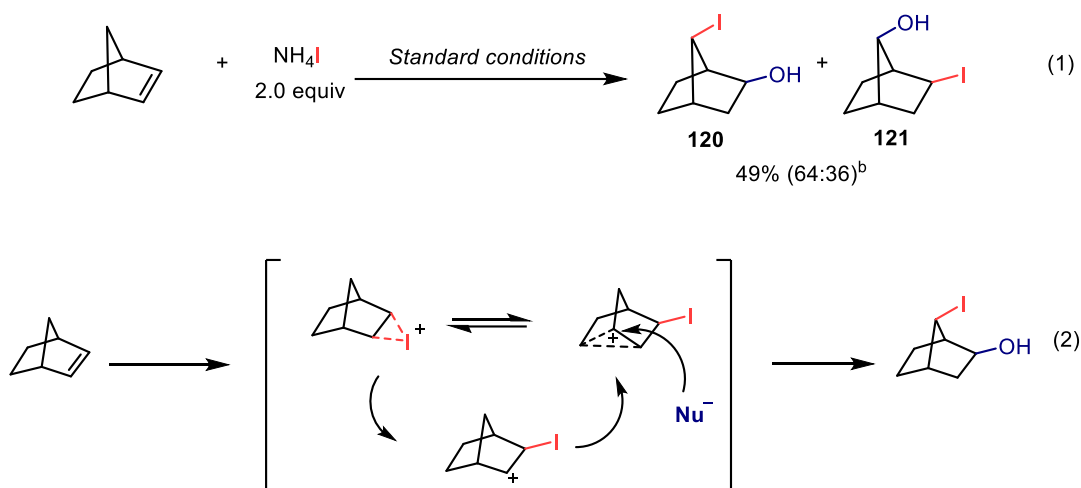
metallic salts released by the cathode, the electrochemical reaction was stopped after 45 min and stirred for an additional 24 h in the absence of current within the electrochemical cell (**Scheme 90**, eq. 1 & 2). As expected, no increase of reaction yield after additional 24 h was observed, showcasing that no reaction resulted from potential metallic salts released from the cathode. Since molecular iodine can be generated from the anodic oxidation of iodide,<sup>247</sup> we performed the reaction using molecular iodine, instead of  $\text{NH}_4\text{I}$  (**Scheme 90**, eq. 3). The desired product was obtained, albeit with a decreased NMR yield of 36 % compared to 84 %, suggesting that involvement of in situ generated  $\text{I}_2$  in the reaction mechanism cannot be ruled out.



**Scheme 90.** Control experiments. rsm=remaining starting materials. <sup>a</sup> <sup>1</sup>H-NMR yield.

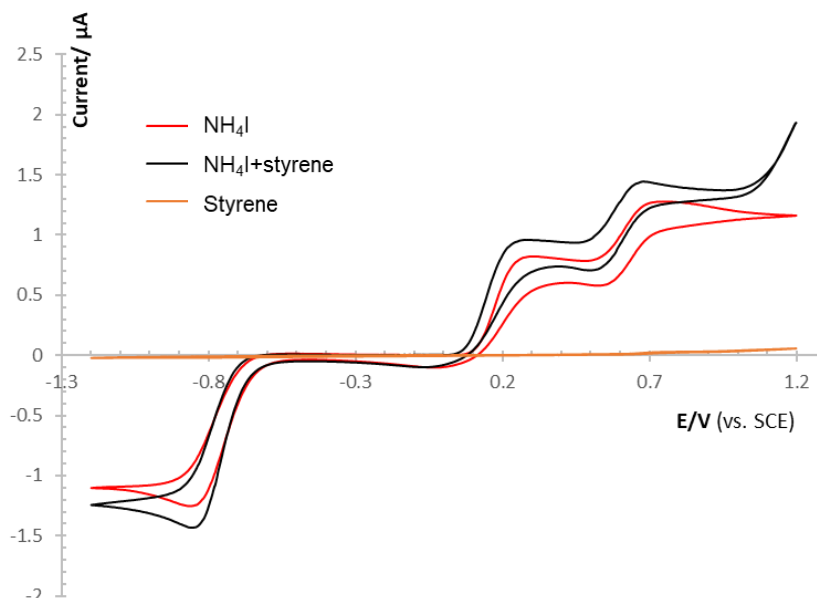
It is pertinent to mention that norborn-2-ene was found to be compatible with our conditions and produced two separable isomeric products, **120** and **121**, in a 64:36 ratio (**Scheme 91**, eq. 1). These two isomers result from the rearrangement of a cationic intermediate (**Scheme 91**, eq. 2). Thus, we can presume that the mechanism of this reaction goes through the formation of an iodonium intermediate and then a carbocation.

<sup>247</sup> Liu, K.; Song, C.; Lei, A.; Liu, K. *Org. Biomol. Chem.* **2018**, *16*, 2375-2387.



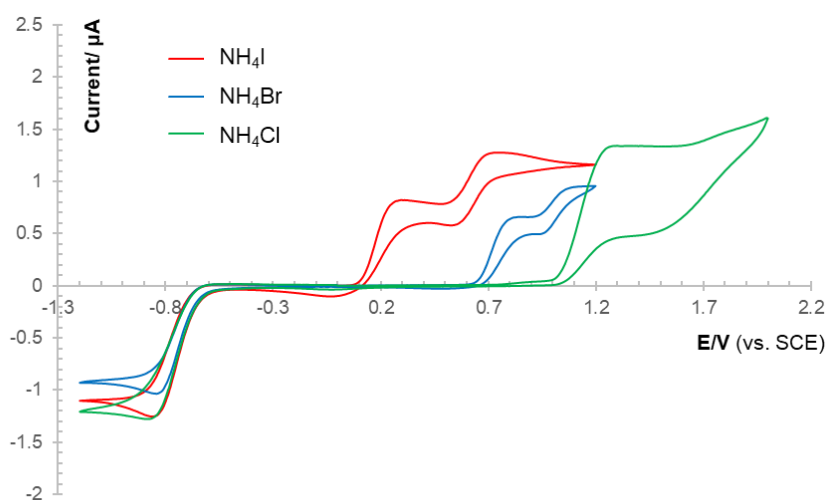
**Scheme 91.** Probable rearrangement for norbornene iodofunctionalization. <sup>b</sup> The ratio of **120:121**.

Subsequently, we performed cyclic voltammetry (CV) measurements using the same apparatus under identical conditions as described herein. First, in a 15 mL acetonitrile solution with 0.05 M  $\text{Et}_4\text{NBF}_4$  as the electrolyte, we conducted cyclic voltammetry scans on 0.05 M  $\text{NH}_4\text{I}$ , 0.1 M styrene, and a mixed solution of  $\text{NH}_4\text{I}$  and styrene, respectively (**Figure 18**). The CV curve of  $\text{NH}_4\text{I}$  (red) showed two successive oxidation waves, while no oxidation or reduction of the styrene (orange) was observed in the potential range studied (up to +1.2 V). Moreover, CV measurements of a mixture of  $\text{NH}_4\text{I}$  and styrene (black) demonstrated a similar profile, meaning that there is no iodine mediation of a plausible styrene oxidation.



**Figure 18.** CV curve for a solution of 0.05 M  $\text{NH}_4\text{I}$ /0.1 M Styrene and 0.05 M  $\text{Et}_4\text{NBF}_4$  in  $\text{CH}_3\text{CN}$  on a Pt working electrode ( $d = 0.1$  mm), Pt wire ( $d = 1$  mm) auxiliary electrode, SCE reference electrode under a scan rate of 0.1 V/s ranging from -1.2 V to 1.2 V.

Since  $\text{NH}_4\text{Br}$  allowed the formation of the corresponding bromohydrin, while no reaction was observed using  $\text{NH}_4\text{Cl}$ , CV experiments of these ammonium salts were carried out (**Figure 19**). Unlike  $\text{NH}_4\text{I}$ , due to poor solubility of  $\text{NH}_4\text{Br}$  and  $\text{NH}_4\text{Cl}$  in acetonitrile, no oxidation wave was observed when using acetonitrile as the sole solvent. Therefore, a small amount of water was added to facilitate the dissolution of starting materials. In a 15 mL  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (15:1, v/v) solution with 0.05 M  $\text{Et}_4\text{NBF}_4$  as the electrolyte, cyclic voltammetry scans on 0.05 M  $\text{NH}_4\text{Br}$  and  $\text{NH}_4\text{Cl}$  were conducted, respectively (**Figure 19**). Two successive oxidative waves of  $\text{NH}_4\text{Br}$  (blue) were observed within the same range as  $\text{NH}_4\text{I}$  (red), while the CV measurement of  $\text{NH}_4\text{Cl}$  (green) showcased an oxidative wave at a higher potential, which could explain its non-reactivity in our reaction conditions. The values of their two anodic oxidation peak potentials are listed in **Table 15**.



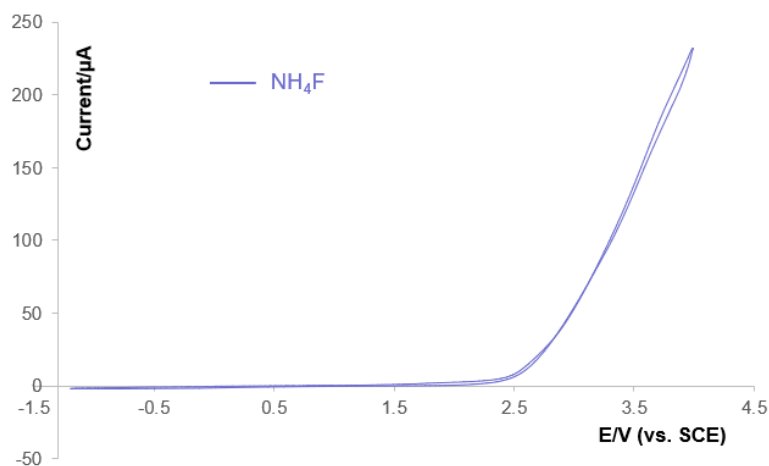
**Figure 19.** CV curve for a solution of 0.05 M  $\text{NH}_4\text{I}$ /  $\text{NH}_4\text{Br}$ /  $\text{NH}_4\text{Cl}$  and 0.05 M  $\text{Et}_4\text{NBF}_4$  in  $\text{CH}_3\text{CN}$  or  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (15/1, v/v) on a Pt working electrode ( $d = 0.1$  mm), Pt wire ( $d = 1$  mm) auxiliary electrode, SCE reference electrode under a scan rate of 0.1 V/s.

Ammonium salts	$E_{p,a1}$ (vs. SCE)	$E_{p,a2}$ (vs. SCE)
$\text{NH}_4\text{I}$	0.21 V	0.66 V
$\text{NH}_4\text{Br}$	0.78 V	1.06 V
$\text{NH}_4\text{Cl}$	1.27 V	—

**Table 15.** Anodic Peak Potential of  $\text{NH}_4\text{I}$ ,  $\text{NH}_4\text{Br}$  and  $\text{NH}_4\text{Cl}$ .

In addition to  $\text{NH}_4\text{I}$ ,  $\text{NH}_4\text{Br}$  and  $\text{NH}_4\text{Cl}$ , we conducted cyclic voltammetry measurement on  $\text{NH}_4\text{F}$  as well (**Figure 20**). As shown in the resulting CV curve,  $\text{NH}_4\text{F}$  did not undergo oxidation within the potential range investigated (up to 4 V). From this result it can be predicted that the hydroxyfluorination of alkenes is unlikely to be accomplished using

NH<sub>4</sub>F as a reagent under our conditions.

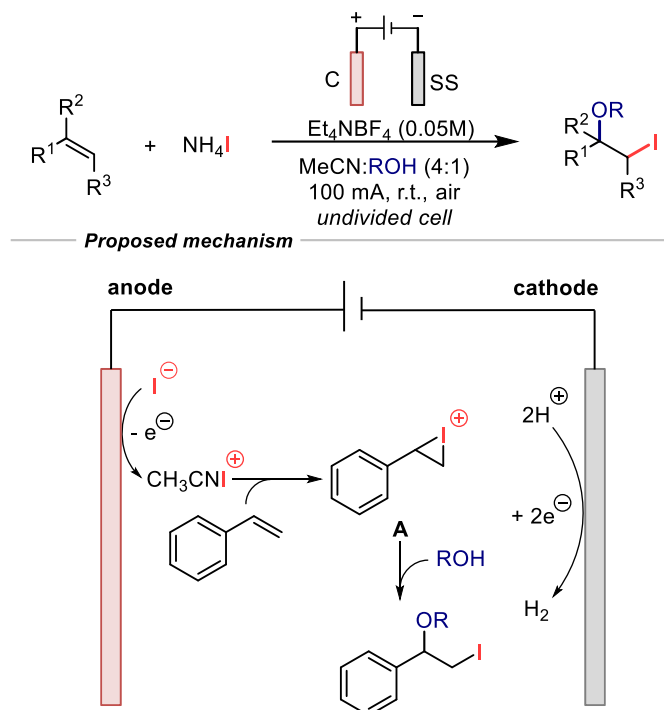


**Figure 20.** CV curve for a solution of 0.1 M NH<sub>4</sub>F and 0.1 M Et<sub>4</sub>NBF<sub>4</sub> in CH<sub>3</sub>CN/H<sub>2</sub>O (15:1, v/v) on a Pt working electrode (d = 0.2 mm), Pt wire (d = 1 mm) auxiliary electrode, SCE reference electrode under a scan rate of 0.2 V/s.

Hence, with all these data in hand, we suggested a plausible reaction mechanism, initiated by the anodic oxidation of I<sup>-</sup> (**Scheme 92**). As reported in the literature, a second anodic oxidation of iodine radical could lead to a high electrophilic acetonitrile stabilized iodonium species.<sup>248,249</sup> As seen in the control experiments, the direct reaction of molecular iodine with the styrene cannot be excluded (**Scheme 90**, eq 3). However, considering the low electrophilicity of I<sub>2</sub> and the lower yield obtained by a direct reaction of I<sub>2</sub>, the formation of I<sup>+</sup> stabilized by acetonitrile, would be more productive. The reaction between the styrene derivative and CH<sub>3</sub>CNI<sup>+</sup> as an equivalent of I<sup>+</sup> would give an iodonium complex **A**, which is supported by the stereochemistry observed in the product **62** (**Scheme 84**). Then, **A** is prompt to perform a Markovnikov nucleophilic addition of the solvent (water or alcohol) to yield corresponding product. A cathodic reduction of H<sup>+</sup>, resulting from the nucleophilic addition would generate H<sub>2</sub> within the media, thus closing the redox cycle.

<sup>248</sup> Miller, L. L.; Watkins, B. F. *J. Am. Chem. Soc.* **1976**, *98*, 1515-1519.

<sup>249</sup> Midorikawa, K.; Suga, S.; Yoshida, J.-i.; Midorikawa, K. *Chem. Commun. (Cambridge, U. K.)* **2006**, 3794-3796.



Scheme 92. Proposed reaction mechanism.

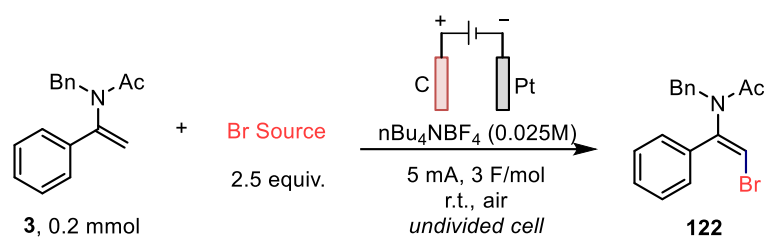
## 3.3 Electrochemical halogenation of enamides

### 3.3.1 Optimization

In order to further expand the scope of this electrochemical halogenation transformation, we proceeded to test the reaction conditions on enamide derivatives. Given the versatile applications of enamides as building blocks for the synthesis of variety of synthetically and biologically relevant chemical in organic synthesis, as demonstrated in section 2.2, we speculated that by using a suitable halide agent, we would develop a direct C–H electrochemical halogenation affording synthetically useful enamide derivatives. To the best of our knowledge, neither enamide derivatives nor vinyl electrochemical halogenation have been previously reported.

At the beginning of our investigations, we selected the enamide **3** as a model substrate to react with the inexpensive and non-toxic ammonium bromide. Using a carbon graphite electrode as the anode and a platinum electrode as the cathode, along with  $n\text{Bu}_4\text{NBF}_4$  as the electrolyte (0.025 M) applying a constant current of 5 mA with a total charge of 3 F/mol under ambient air conditions in  $\text{CH}_3\text{CN}$  (Table 16, entry 1), the bromination of **3** was performed with a 37% yield based on  $^1\text{H-NMR}$  analysis. The reaction performed with various solvents demonstrated that dimethylacetamide (DMA) exhibited an improved performance (Table 16, entries 2-5). Regarding the

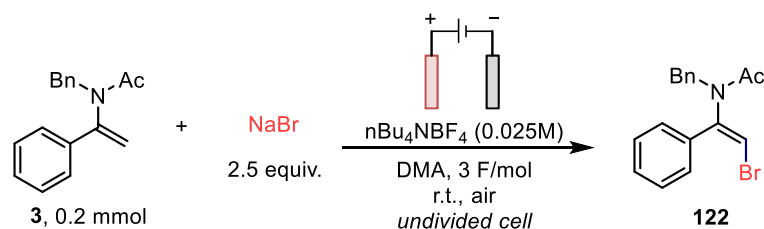
bromine source, it was found that sodium bromide (NaBr) proved to be more efficient, resulting in a higher yield (**Table 16**, entry 6), while, *n*Bu<sub>4</sub>NBr did not allowed formation of the desired product (**Table 16**, entry 7).



Entry	Solvent (4 mL)	Br source	Yield (%) <sup>a</sup>	Conver. (%) <sup>a</sup>
1	CH <sub>3</sub> CN	NH <sub>4</sub> Br	37	100
2	DMA	NH <sub>4</sub> Br	43 (40) <sup>b</sup>	96
3	DMF	NH <sub>4</sub> Br	39	99
4	CH <sub>3</sub> CN:H <sub>2</sub> O (9:1)	NH <sub>4</sub> Br	0	100
5	Acetone	NH <sub>4</sub> Br	37	80
6	DMA	NaBr	55	81
7	DMA	<i>n</i> Bu <sub>4</sub> NBr	0	57

**Table 16.** Screening of solvent and Br source. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol dibromomethane as an internal standard. <sup>b</sup> Isolated yield.

Several different cathode materials were tested (**Table 17**, entries 1-4), and it was found that graphite and stainless steel were more efficient, yielding comparable results with isolated yields of 83% and 81%, respectively (**Table 17**, entries 1&3). When modifying the anode material, the reaction was either hampered or completely inhibited (**Table 17**, entries 5-7). Increasing or decreasing the current was unfavorable for the reaction outcome, leading to a decreased yield (**Table 17**, entries 8&9).

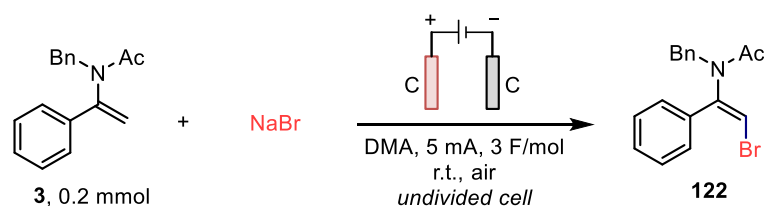


Entry	Electrode	Current	Yield (%) <sup>a</sup>	Conver. (%) <sup>a</sup>
1	C(+)-SS(-)	5 mA	76 (83) <sup>b</sup>	100
2	C(+)-GC(-)	5 mA	70	100
3	C(+)-C(-)	5 mA	76 (81) <sup>b</sup>	100

Entry	Electrode	Current	Yield (%) <sup>a</sup>	Conver. (%) <sup>a</sup>
4	C(+)-Zn(-)	5 mA	63	89
5	Pt(+)-C(-)	5 mA	73	100
6	SS(+)-C(-)	5 mA	0	7
7	GC(+)-C(-)	5 mA	68	100
8	C(+)-C(-)	3 mA	77 (78) <sup>b</sup>	100
9	C(+)-C(-)	10 mA	56	82

**Table 17.** Screening of electrodes and current. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol dibromomethane as an internal standard. <sup>b</sup> Isolated yield.

We then conducted the reaction without using the electrolyte, the yield decreased to 50% (**Table 18**, entry 1). Even after increasing the amount of sodium bromide from 2.5 to 8 equivalents, the absence of the electrolyte could not be offset, demonstrating that the electrolyte is needed for this reaction (**Table 18**, entries 1-3). Both decreasing and increasing the amount of sodium bromide are deleterious regarding the reaction outcome, highlighting that the use of 2.5 equivalents is optimal (**Table 18**, entries 8&9).

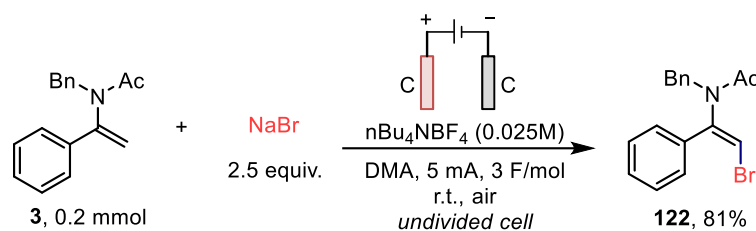


Entry	Electrolyte	NaBr (equiv)	Yield (%) <sup>a</sup>	Conver. (%) <sup>a</sup>
1	–	2.5	50	77
2	–	4.0	56	78
3	–	8.0	53	66
4	0.025 M	1.5	63	99
5	0.025 M	2.0	74 (76) <sup>b</sup>	100
6	0.025 M	3.0	72	95

**Table 18.** Screening of equivalent of electrolyte and NaBr. <sup>a</sup> <sup>1</sup>H-NMR yield with 0.2 mmol dibromomethane as an internal standard. <sup>b</sup> Isolated yield.

The optimal reaction conditions were thus obtained by using 0.2 mmol of **3** as model substrate with 2.5 equivalents of sodium bromide (NaBr) as the bromine source. Carbon graphite served both as anode and cathode. The reaction was carried out under a constant current of 5 mA with a total charge of 3 F/mol in DMA, 0.025 M *n*-

tetrabutylammonium tetrafluoroborate ( $n\text{Bu}_4\text{NBF}_4$ ) as the electrolyte, under an air atmosphere in an undivided cell (**Table 17**, entry 3). As a result, product **122** was isolated with a satisfactory yield of 81%. (**Scheme 93**).



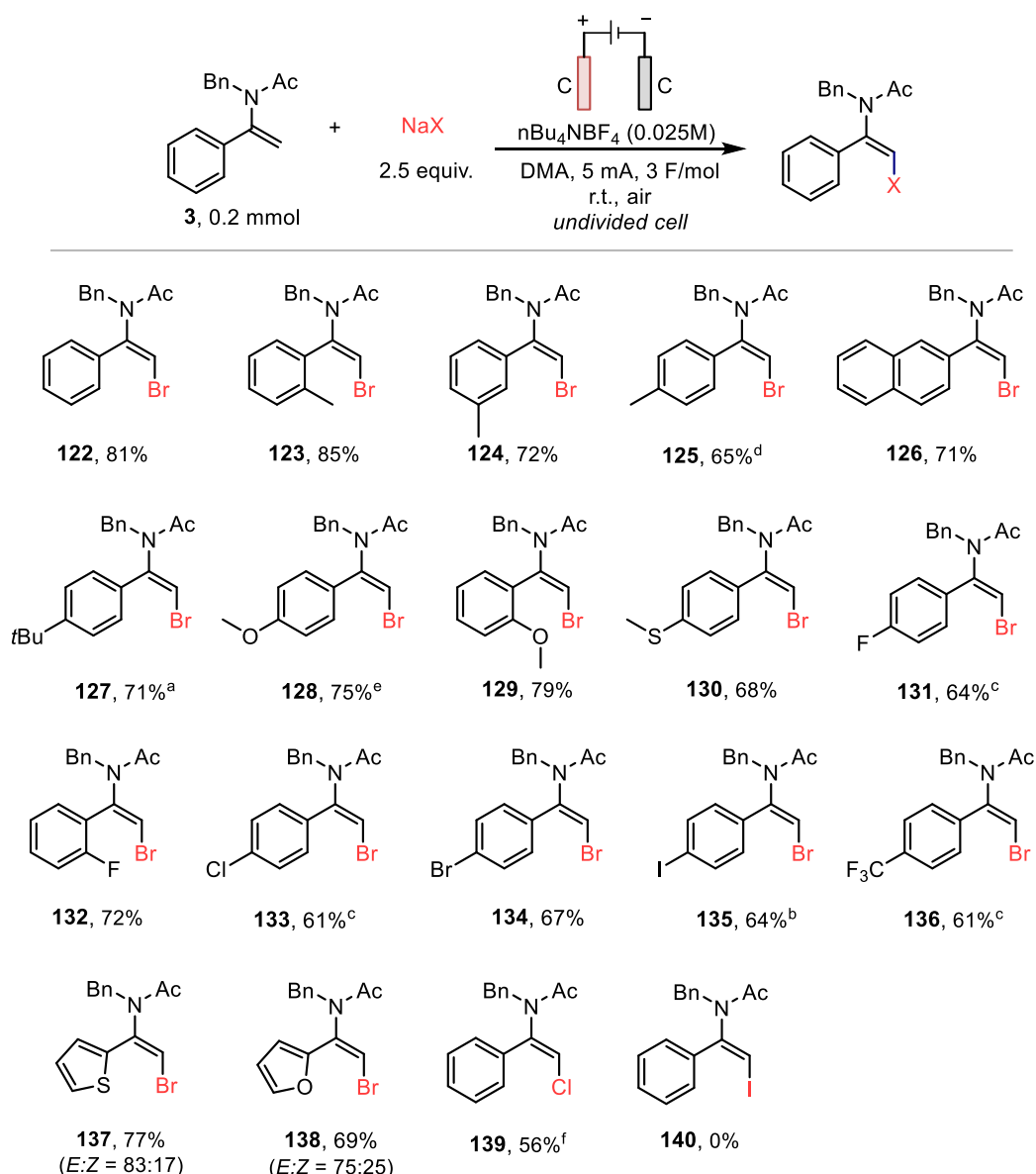
**Scheme 93.** Optimal conditions.

### 3.3.2 Substrates scope and limitations of the methodologies - reluctant substrates

With the optimized reaction conditions in hand, the scope of this electrochemical halogenation of enamides was investigated (**Scheme 94**). We initiated our study by examining the substitutions on the aromatic ring. The reaction efficiency was not affected by the substitution pattern. An aryl enamide substituted with a methyl group at the *para*-, *meta*- or *ortho*-position afforded the desired products in good to excellent yields, showcasing no impact of the steric hindrance (**123-125**). Moreover, reactions of enamides substituted by electron-donating functional group such as naphthyl, *tert*-butyl, methoxy, and thiomethoxy proceeded well with good efficiencies (**126-130**). Once again, the steric hindrance had no influence on the reaction outcome, as a larger methoxy group installed at the *ortho*-position did not alter the electrochemical bromination and the product **129** was obtained with 79% yield. Additionally, no further oxidation of sulfur atom was observed under our electrochemical conditions (**130**). Under our electrochemical conditions, the presence of halogen atoms was well tolerated, as the aryl motif could be substituted with fluorine (**131**, **132**), chlorine (**133**), bromine (**134**) and iodine (**135**), giving the products with good yields, enabling good opportunities for further transformations, such as metal-catalyzed cross-coupling, for instance. Electron-withdrawing group trifluoromethyl proved to be compatible with our reaction conditions as the desired product was synthesized in a 61% yield (**136**). Furthermore, heteroaryl derivatives proved to be efficient substrates in this transformation, yielding valuable heteroaromatic molecules (**137** and **138**) as two separable isomers, with the *E* isomer being the major product. To demonstrate the versatility of the transformation, we conducted a chlorination reaction using 4 equivalents of NaCl as the chlorine source, pleasingly the isolation 56% yield of chlorinated product (**139**) was performed. We also attempted the reaction with NaI as the iodine source under standard reaction conditions; unfortunately, the

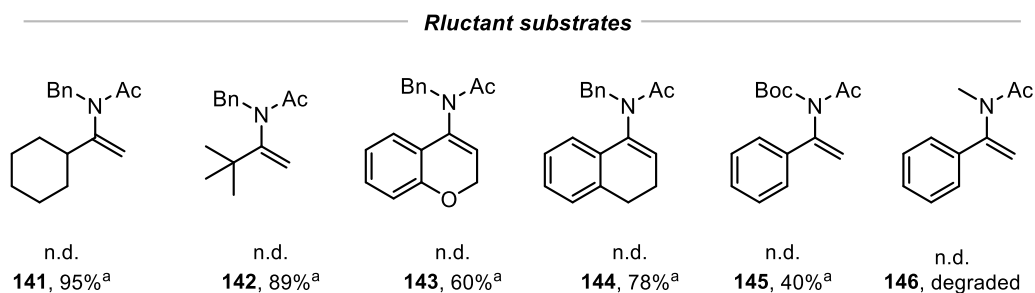


corresponding iodinated product was not obtained (**140**).



**Scheme 94.** Substrate Scope of Enamide Derivatives. <sup>a</sup> 3.5 F/mol. <sup>b</sup> 4.5 F/mol. <sup>c</sup> 5 F/mol. <sup>d</sup> Substrate 0.17 mmol. <sup>e</sup> Substrate 0.1 mmol. <sup>f</sup> 4 eq NaCl was used.

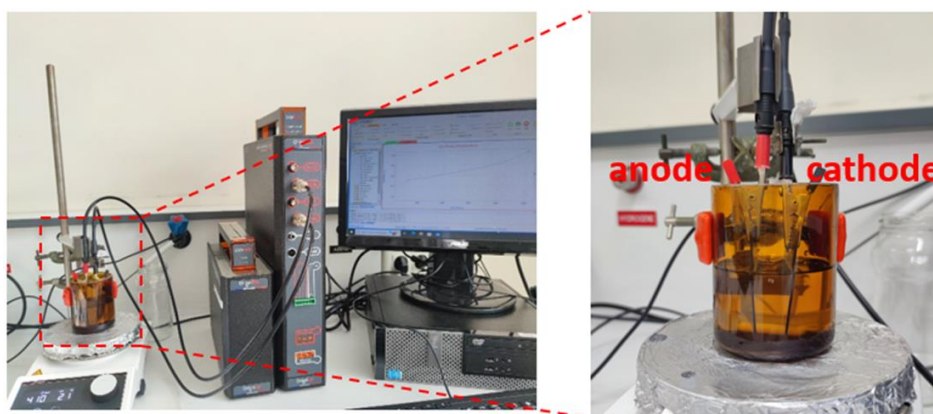
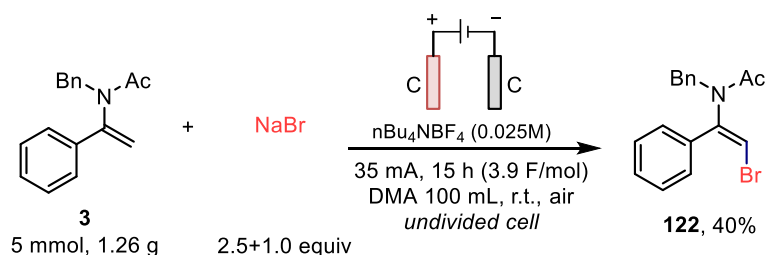
Unfortunately, some substrates remained reluctant in our hand (**Scheme 95**). Aliphatic enamides (**141** and **142**), 2H-chromene and 1,2-dihydronaphthalene derivatives (**143** and **144**) as well as the *N*-Boc derivative (**145**) were not reactive, and the starting materials were recovered, while the *N*-methyl derivative (**146**) decomposed under the standard conditions.



**Scheme 95.** Reluctant substrates. <sup>a</sup> yield of starting material recovery, <sup>1</sup>H-NMR yield with 0.2 mmol dibromomethane as an internal standard.

### 3.3.3 Scale-up reaction

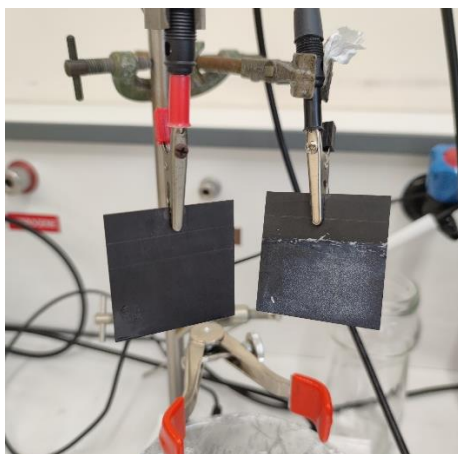
For further validation of the practical application of this halogenation method, we performed a scale-up experiment using **3** (5 mmol, 1.26 g) and NaBr (2.5 equiv.) with the OrigaLys® OrigaFlex OGF01A galvanostat. The reaction was conducted in an undivided cell equipped with graphite plate anode and cathode under a constant current of 35 mA ( $J = 2.33 \text{ mA/cm}^2$ ) under ambient air conditions, as shown in **Figure 21**.



**Figure 21.** Scale-up electrochemical halogenation reaction. Graphite plate electrodes as anode and cathode (5 cm x 5 cm, immersion length 3 cm,  $J = 2.33 \text{ mA/cm}^2$ ).

After 11.5 hours, the reaction was monitored using a TLC plate and it was observed that a significant amount of starting material had not yet reacted completely.

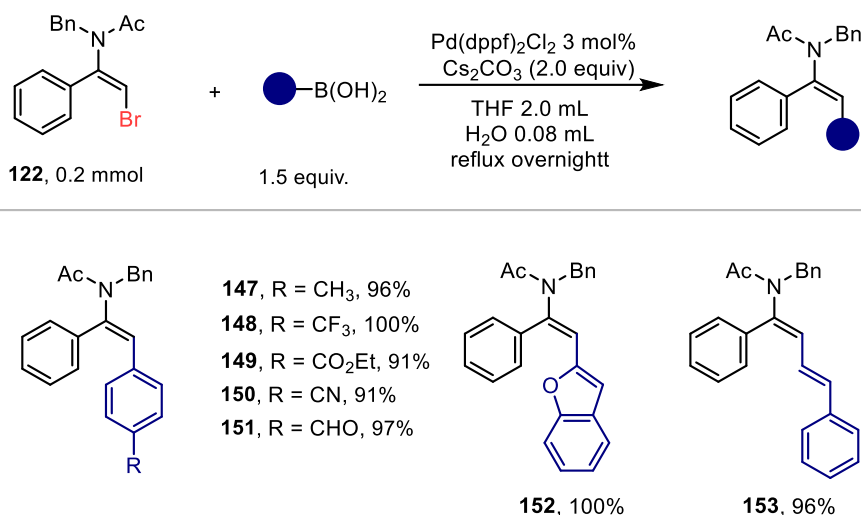
Consequently, one more equivalent of NaBr was added to the cell, and the reaction time was extended to 15 hours (with a total charge of 3.9 F/mol). When the reaction was completed, **122** was isolated in 40 % yield, which is lower than the yield in the small-scale reaction (81%). During the reaction, we observed the formation of a white precipitate on the cathode electrode as shown in **Figure 22**. This might be a factor, which affects the reaction efficiency. In our subsequent research, we will attempt to address this issue by periodically swapping the anode and cathode.



**Figure 22.** The white deposit on cathode.

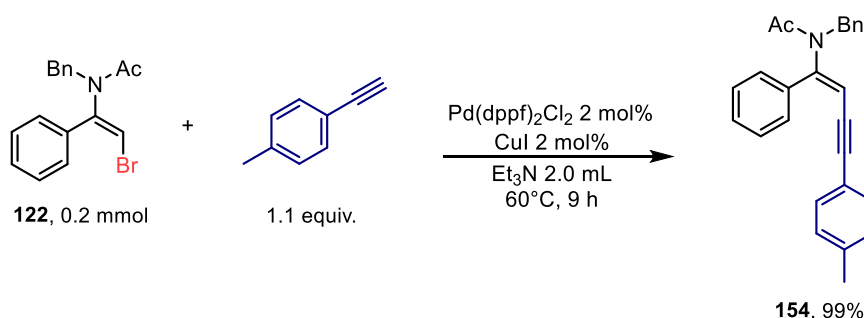
### 3.3.4 Post-functionalization

To further explore the synthetic utility of the established methodology, post-functionalization reactions were explored. Indeed, these halogenated enamides have never been reported before and the presence of the bromine atom is a powerful anchor to carry out versatile post-functionalization. Initially, **122** was subjected to Suzuki cross-coupling transformations with various boronic acids (**Scheme 96**). To our delight, all the boronic acids reacted smoothly, including aryl boronic acid containing electron-donating or electron-withdrawing groups and heteroaryl boronic acid, yielding the desired products in excellent yields ranging from 91 to 100% (**147-153**). In all cases, the reaction proceeds with a stereoretention of the enamide configuration, offering an interesting reaction manifold to control the two-dimensional space. It is worth mentioning that vinyl boronic acids readily participated in the reaction, providing an interesting polyfunctionalized diene derivative with excellent yield and a complete retention of the configuration of the enamides and the boronic acid derivatives (**153**).



**Scheme 96.** Suzuki Cross-Coupling reaction.

Then, we conducted a Sonogashira cross-coupling reaction using toluene-4-ethynyl as coupling partner (**Scheme 97**). The desired product **154** was isolated in an excellent 99% yield. The outstanding performance in cross-coupling reactions highlighted the huge potential of the established protocol in the fields of drug discovery, late-stage functionalization, as well as organic synthesis.

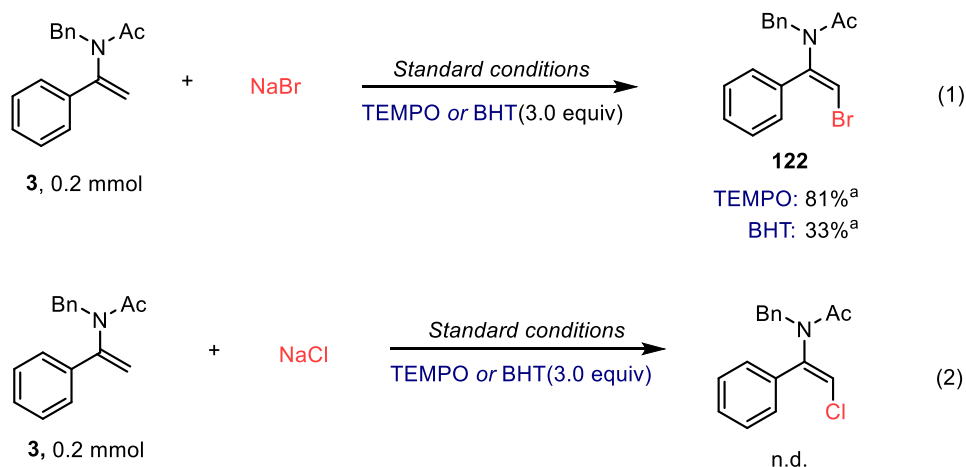


**Scheme 97.** Sonogashira Cross-coupling reaction.

### 3.3.5 Mechanistic study

In order to gain insight into the reaction mechanism, a couple of control experiments were carried out (**Scheme 98**). Electrochemical bromination reaction between enamide **3** and  $\text{NaBr}$  was performed with addition of 3 equivalent of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-tertbutyl-4-methylphenol (BHT) as radical scavenger under our standard reaction conditions. In the presence of TEMPO, no impact on the yield was observed compared to the optimal reaction condition without radical scavenger (**Scheme 98**, eq 1), while in the presence of BHT the yield of **122** decreased from 81% to 33% (**Scheme 98**, eq 2). These results indicated that the involvement of bromine radical in this bromination reaction cannot be ruled out.

Regarding the chlorination of enamide **3** with NaCl, the addition of TEMPO or BHT completely suppressed the reaction, highlighting the involvement of a radical pathway in the chlorination process (**Scheme 98**, eq 2).

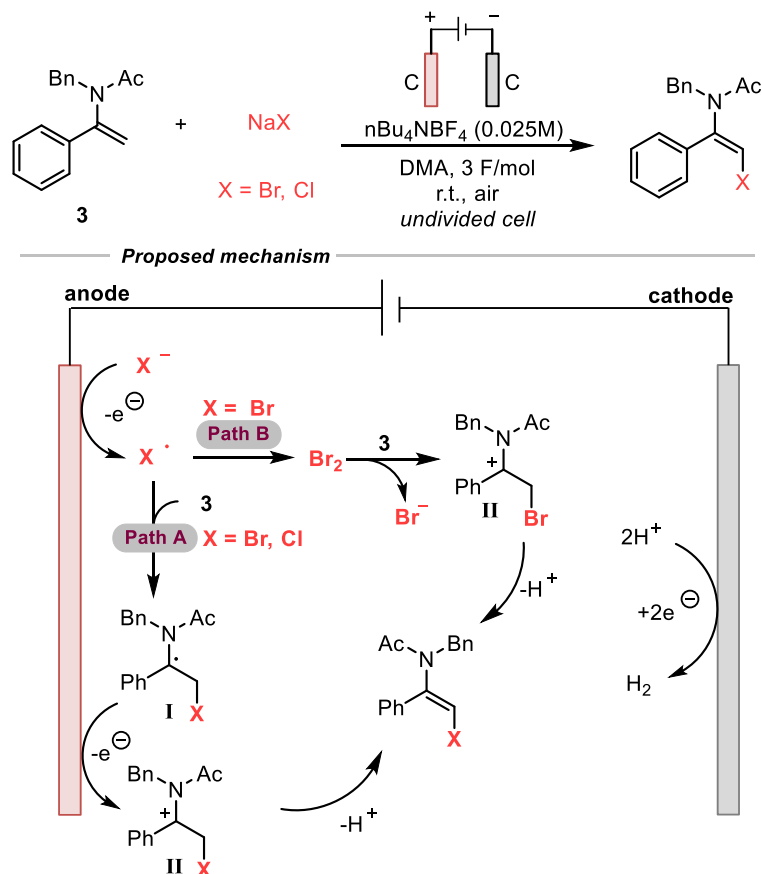


**Scheme 98.** Radical-Trapping Experiments.

On the basis of the above experiments and literature reports,<sup>193,250</sup> we suggested a plausible reaction mechanism for halogenation of enamides with NaX (X = Cl, Br) (**Scheme 99**). For the bromination reaction, under the electrochemical conditions, bromide ions underwent anodic oxidation to generate a bromine radical. The latter then reacted with enamide **3**, yielding a stabilized alkyl radical intermediate **I** (path **A**). A subsequent single-electron oxidation followed by the deprotonation led to the formation of the product. Additionally, bromide radical could dimerized to generate *in situ* the molecular Br<sub>2</sub>, which then reacted with **3** to form the carbocation intermediate **II** (path **B**). The subsequent hydrogen elimination of this intermediate **II** led to the formation of the final product.

For the chlorination reaction, we speculated that chloride ion was oxidized at the anode to generate a chlorine radical, which could add onto the enamide to form the stabilized alkyl radical intermediate **I**. This intermediate could then be further oxidized at the anode, resulting in cationic intermediate **II**. A hydrogen elimination ultimately led to the formation of the product. Meanwhile, a cathodic reduction of H<sup>+</sup>, resulting from the E<sub>1</sub> elimination would release H<sub>2</sub>, equilibrating the redox balance.

<sup>250</sup> Liu, X.; Wu, Z.; Feng, C.; Liu, W.; Li, M.; Shen, Z. *Eur. J. Org. Chem.* **2022**, 2022, e202200262.



Scheme 99. Proposed Mechanism.

### 3.4 Conclusion

In summary, we have developed practical electrochemical halogenation methods for styrene derivatives and enamides in an undivided cell under air atmosphere. These methods relied on the anodic oxidation of inexpensive and non-toxic ammonium iodide ( $\text{NH}_4\text{I}$ ) or sodium bromide ( $\text{NaBr}$ ) under metal-free and external oxidant-free conditions, offering a straightforward and environmentally friendly synthetic approach (Scheme 100).

Under the optimized conditions, the hydroxyiodination of styrene derivatives afforded various valuable iodohydrins and the corresponding ethers by using ammonium iodine. In addition to styrene derivatives, various aliphatic alkenes and cyclic alkenes were also compatible with these conditions. Furthermore, the reaction conditions proved to be versatile as hydroxybromination was successfully carried out on styrene under the same conditions by replacing  $\text{NH}_4\text{I}$  with  $\text{NH}_4\text{Br}$ . Moreover, this method was also applied to the synthesis of important building blocks such as vinyl halides and iodinated heterocycles, which are amenable substrates for further functionalization. The results of control experiments and cyclic voltammetry analysis indicated that an iodonium



# Conclusion

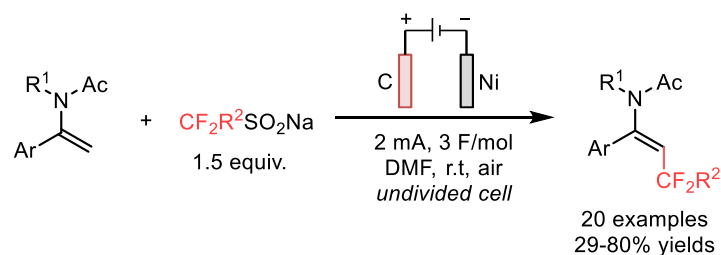




# Conclusion

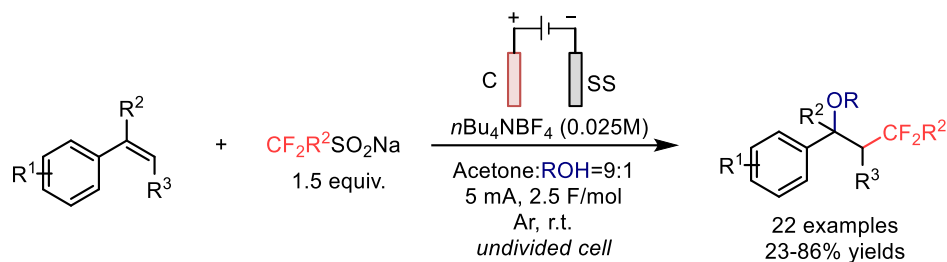
These works have led to the development of new electrochemical methods for the synthesis of organofluorine-containing compounds and organic halides through anodic oxidation.

Due to the unique properties of difluoromethyl, the introduction of difluoromethyl groups into organic molecules has sparked significant interest. Currently, electrochemical difluoromethylation of alkenes is limited to electron-deficient olefins. Therefore, we proposed extending the addition of electrochemically generated  $\text{CF}_2\text{H}$  radicals onto electron-rich alkenes. Initially, we aimed to incorporate difluoromethyl groups into enamides, which are important in both synthetic and pharmaceutical chemistry. After optimizing the conditions, we applied a series of enamide derivatives to the optimised conditions, obtaining the corresponding difluoromethylated and  $\alpha,\alpha$ -difluoroethylated enamides as a single (*E*)-isomer in good to excellent yields (20 examples, 29-80% yields) (**Scheme 101**), while aliphatic enamides were not reactive.



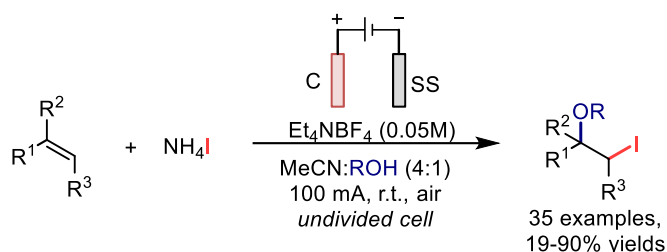
**Scheme 101.** Electrochemical difluoromethylation of enamides.

Next, we extended this electrochemical difluoromethylation transformation to another electron-rich olefin, styrene. Under the same conditions, a hydroxydifluoromethylated product was obtained instead of a viny difluoromethylated product. Subsequently, we developed the hydroxydifluoromethylation of styrenes under slightly modified conditions, obtaining the difunctionalized products in good to excellent yields (22 examples, 23–86% yields) (**Scheme 102**), whereas aliphatic terminal alkenes exhibited poorly reactive. Finally, a plausible mechanism involving an anodic oxidation and the addition of the  $\text{CF}_2\text{H}$  radical on electron-rich alkenes is suggested for both functionalizations, based on experiments.



**Scheme 102.** Electrochemical hydroxydifluoromethylation of styrenes derivatives.

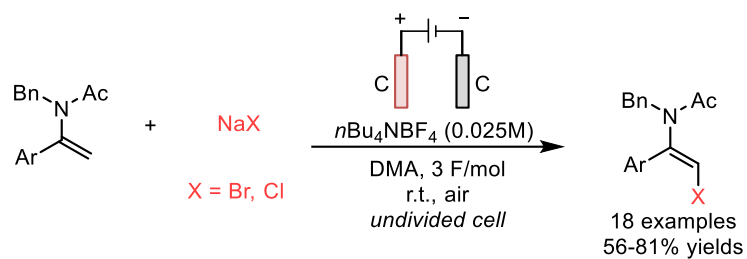
Halohydrins are versatile building blocks in the arsenal of organic chemists. We developed a practical and straightforward synthesis of valuable iodohydrins and the corresponding ethers by using  $\text{NH}_4\text{I}$ , as non-toxic and inexpensive iodine reagent, under chemical oxidants or reductants-free conditions, which provides a greener synthetic strategy. The practical reaction conditions were applied to a large panel of olefinic substrates and the products were obtained in moderate to excellent yields (**Scheme 103**). Furthermore, the reaction conditions proved to be versatile as hydroxybromination was successfully carried out on styrene under the same conditions by replacing  $\text{NH}_4\text{I}$  with  $\text{NH}_4\text{Br}$ . Finally, this method was also applied to the synthesis of important building blocks, such as vinyl halides and iodinated heterocycles, which are amenable substrates for further functionalization. The results of control experiments and cyclic voltammetry analysis indicated that an iodonium intermediate is a crucial intermediate in the reaction.



**Scheme 103.** Electrochemical Synthesis of Iodohydrins.

We also developed a halogenation reaction of enamides. Using  $\text{NaBr}$  as the bromine source, the C-H bromination reaction was accomplished, and the reaction conditions proved to be tolerant to various electron-donating or withdrawing substituents, providing the products with a full (*E*)-stereoselectivity in good to excellent yields. When  $\text{NaCl}$  was used to replace  $\text{NaBr}$ , a chlorinated enamide was obtained, demonstrating the versatility of the reaction conditions (**Scheme 104**). The synthetic utility of our product was proved through its application in Suzuki and Sonogashira cross-coupling reactions, resulting in excellent yields of coupling products were obtained from the brominated enamide. Based on Radical trapping experiments, it could be proposed that the mechanism of C-H bromination or chlorination reaction of enamides mainly

involved the generation of halogen radicals at the anode.



**Scheme 104.** Electrochemical halogenation of enamides.



# **Experimental section**



## Experimental section

### 1. General informations

Electrochemical reactions were performed with IKA® ElectraSyn 2.0 using a 5 mL cell. All reactions were carried out using oven-dried glassware and magnetic stirring under air unless otherwise stated. When needed, reactions were heated with an oil bath. Column chromatographies were carried out using silica gel (40-63  $\mu\text{m}$ ) supplied by VWR or Merck PTLC on silica gel 60 F<sub>254</sub>, 2 mm. Analytical thin layer chromatographies performed on pre-coated silica gel aluminum plates with F-254 indicator (from Merck) and visualized by UV light (254 nm) and/or chemical stained with a KMnO<sub>4</sub> solution.

<sup>1</sup>H (300 MHz), <sup>13</sup>C (75.5 MHz), and <sup>19</sup>F (282.4 MHz) NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer in CDCl<sub>3</sub> unless otherwise noted. Chemical shifts ( $\delta$ ) are quoted in ppm relative to the residual solvent peak of CDCl<sub>3</sub> (<sup>1</sup>H:  $\delta_{\text{H}} = 7.26$  ppm and <sup>13</sup>C:  $\delta_{\text{C}} = 77.16$  ppm) or to the peak of an internal standard Tetramethylsilane (<sup>1</sup>H:  $\delta_{\text{H}} = 0.00$  ppm) and relative to the internal standard CFCl<sub>3</sub> (<sup>19</sup>F:  $\delta_{\text{F}} = 0.0$  ppm). Coupling constants ( $J$ ) are quoted in Hz. The following abbreviations were used to show multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, p = pentuplet, dd = doublet of doublets, brs = broad singlet. High-resolution mass (HRMS) was carried out on a Waters LCP Premier XR spectrometer with a TOF analyzer. IR spectra were recorded on a PerkinElmer FT-IR Spectrum 100 (ATR), the wave numbers ( $\nu$ ) of recorded IR-signals (ATR) are quoted in cm<sup>-1</sup>. Melting points were reported for new compounds, measured on a Stuart SMP3 melting point apparatus in open capillaries.

Anhydrous acetonitrile (MeCN), methanol (MeOH), ethanol (EtOH), dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF) and *N,N*-Dimethylacetamide (DMA) were purchased from Acros Organics (Solvents Extra Dry Over Molecular Sieve, AcroSeal®). Dichloromethane (DCM) was purified by distillation over CaH<sub>2</sub>. Tetrahydrofuran (THF) and Toluene were distilled over sodium/benzophenone prior to use. Technical grade solvents for extraction and purification (cyclohexane, dichloromethane (DCM), pentane, ethyl acetate (EtOAc), diethyl ether (Et<sub>2</sub>O), petroleum ether (PE) and ethanol) were used without purification.

All reagents and catalysts that are not characterized were purchased from several suppliers including Sigma Aldrich, Fisher Scientific, Acros Organics, Alfa Aesar, TCI, VWR, Apollo Scientific and Fluorochem.



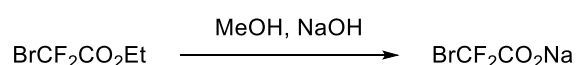
## 2. Chapter 2 - Electrochemical Difluoromethylation of Electron-Rich Olefins

### 2.1 Synthesis of substrates

#### a. Procedures for the Synthesis of HCF<sub>2</sub>SO<sub>2</sub>Na

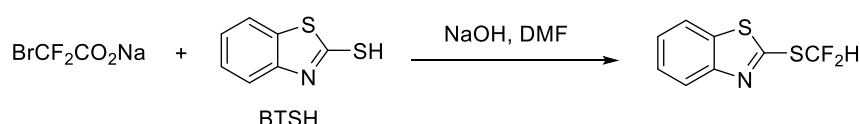
The following procedure is a modified procedure from the literature.

##### Step 1:<sup>251</sup>



Methanol (100 mL, 0.5 M) and Sodium Hydroxide (8 g, 200 mmol, 1.0 equiv.) were added to a reactor, and the solution was cooled to 0±5°C. Ethyl bromodifluoroacetate (40.6 g, 200 mmol, 1.0 equiv.) was added slowly to keep the reaction temperature below 10°C. Then the reaction was allowed to warm to 25±5°C and stirred for 3 h. The mixture was concentrated under vacuum to obtain a solution of the product in methanol. The solution of the product is used directly for the next step. The purity of product is 98.8%.

##### Step 2:<sup>251</sup>

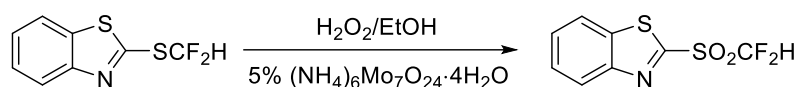


DMF (300 mL), BTSH (33.5 g, 200 mmol, 1.0 equiv.), and NaOH (8.08 g, 202 mmol, 1.01 equiv.) were added into a reactor and stirred for 20 h at 20-30°C. The solution of step 1 in methanol (assuming quantitative yield in first step) was added slowly to the reactor. The batch was heated to 40-45°C and stirred overnight. Then H<sub>2</sub>O (600 mL) was added to the reaction mixture followed by extraction with Et<sub>2</sub>O (3×200 mL). The combined organic phase was washed successively with water (3×150 mL) and saturated brine (150 mL), then dried over anhydrous MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, the residue was distilled under reduced pressure to give the difluoromethyl sulfide (37.2 g, 171.45 mmol, yield 86%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.04 – 7.98 (m, 1H), 7.88 – 7.80 (m, 1H), 7.64 (t, *J* = 56.0 Hz, 1H), 7.54 – 7.47 (m, 1H),

<sup>251</sup> Meng, D.; Li, L.; Brown, A.; Desrosiers, J.-N.; Duan, S.; Hayward, C. M.; He, Z.; Hu, J.; Makowski, T.; Maloney, M.; Monfette, S.; Perfect, H.; Piper, J. L.; Zhou, M.; Widlicka, D. W. *Cell Rep. Phys. Sci.* **2021**, *2*, 100394.

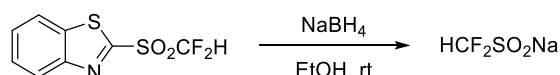
7.44 – 7.37 (m, 1H).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.7.

**Step 3:**<sup>252</sup>



To a mixture of the difluoromethyl sulfide (37.2 g, 172 mmol, 1.0 equiv.),  $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$  (10.6 g, 8.6 mmol, 0.05 equiv.) in EtOH (172 mL, 1.0 M) was added  $\text{H}_2\text{O}_2$  (30% W.t., 78 g, 70.27 mL, 688 mmol, 4.0 equiv.). After stirring at room temperature for 35 hours, another  $\text{H}_2\text{O}_2$  (30% W.t., 172 mmol, 17.56 mL) was added and stirred at the same temperature for 12 hours. Then the reaction mixture was diluted with water (1000 mL) and the product precipitated as white solid. The white solid was collected by filtration, washed with  $\text{H}_2\text{O}$  (1500 mL), and recrystallized from EtOAc/pentane to give the pure product (30 g, 120.35 mmol, yield 70%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 – 8.29 (m, 1H), 8.14 – 8.04 (m, 1H), 7.77 – 7.63 (m, 2H), 6.59 (t,  $J$  = 53.1 Hz, 1H).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.4.

**Step 4:**<sup>68</sup>

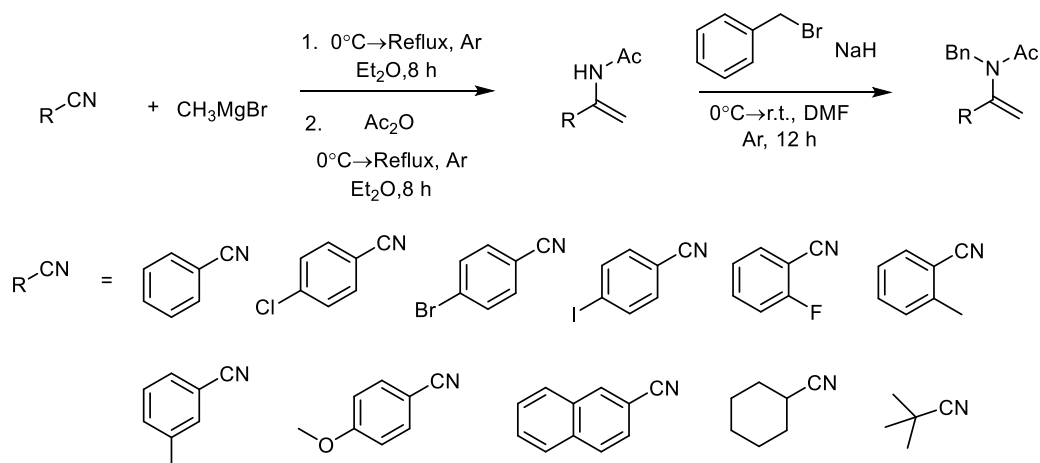


Under  $\text{N}_2$  atmosphere, into a reaction flask equipped with a magnetic stirring bar and a reflux condenser, were added 2-(difluoromethylsulfonyl)benzo[d]thiazole (30 g, 120.35 mmol, 1.0 equiv.) and absolute ethanol (170 mL, 0.7 M). The mixture was stirred at room temperature, then sodium tetrahydroborate (4.644 g, 122.76 mmol, 1.02 equiv.) was added slowly. (Caution: A large amount of gas was produced when sodium tetrahydroborate was added, so sodium tetrahydroborate must be added in small batches, about 1.50 g every ten minutes). After all of the sodium tetrahydroborate had been added, the reaction was still stirred at room temperature for 30 min. Evaporation of the solvent followed by the addition of hexane pentane (100 mL) caused white precipitates of sodium difluoromethylsulfinate. The crude product was obtained by filtration. Then 45 mL (0.15 mL/g) absolute ethanol and 130 mL pentane, were added to the crude product, the mixture was stirred at room temperature for 30 min, and the pure product was obtained after filtration and vacuum drying white solid (7.6 g, 55.09 mmol, yield 46%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  5.12 (t,  $J$  = 56.0 Hz, 1H).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  -128.8.  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ )  $\delta$  5.48 (t,  $J$  = 55.3 Hz, 1H).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{D}_2\text{O}$ )  $\delta$  -130.1.

<sup>252</sup> Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559-2563.

## b. Procedures for the Synthesis of Enamides

### General procedure A:<sup>124,253</sup>



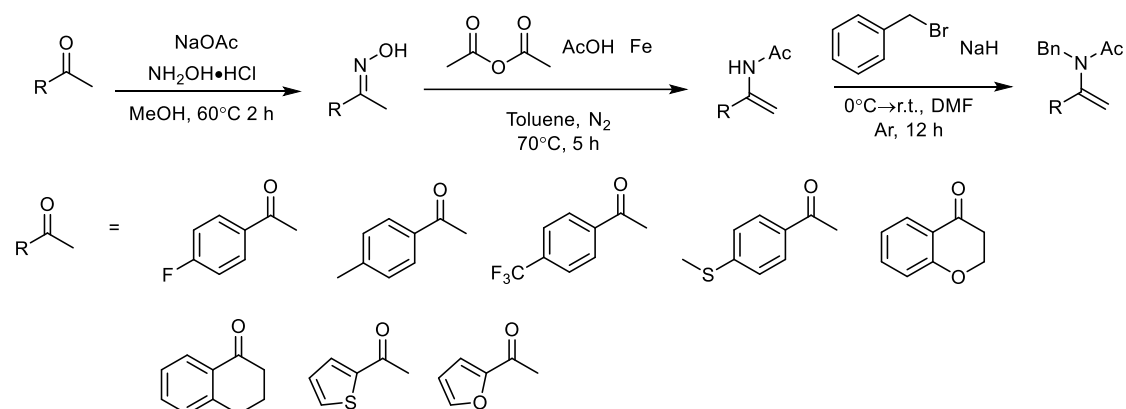
Synthetic procedure: (a) To a stirred solution of methylmagnesium bromide (17.0 mmol, 3.0 mol/L diethyl ether, 6.0 mL, 1.0 equiv.) in diethyl ether (50 mL, 0.34 M) at 0°C a solution of the corresponding benzonitrile (17.0 mmol, 1.0 equiv.) in diethyl ether (20 mL, 0.85 M) was added dropwise during a period of 30 minutes. After complete addition the solution was refluxed for eight hours. Within a few hours a yellow precipitate was formed. After refluxing the reaction mixture was cooled to 0°C, and a solution of acetic anhydride (17.0 mmol, 1.0 equiv.) in diethyl ether (20 mL, 0.85 M) was added carefully over 30 minutes. The reaction mixture was refluxed for eight hours. To the resulting suspension methanol was added at room temperature whilst stirring until all precipitates were dissolved (approximately 50 mL). The homogeneous solution was mixed with water/ethyl acetate (1:1, 100 mL). After phase separation the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give the pure product.

(b) 10 mmol (1.0 equiv.) of the N-acrylamides was dissolved in 30 mL (0.33 M) dry DMF in a dry two-necked round-bottom flask under nitrogen. The solution was cooled to 0°C, and 15 mmol sodium hydride (60% dispersion in mineral oil, 600 mg, 1.5 equiv.) was added in portions. The resulting suspension was stirred at the same temperature for 10 min. Then 20 mmol (3.42 g, 2.0 equiv.) Benzyl bromide was added dropwise and the final solution was continued to stir overnight at room temperature. The completion of the reaction was confirmed by checking TLC and the excess sodium hydride was quenched by adding 10 mL water at 0°C. The organic layer was extracted

<sup>253</sup> Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2006, 2912-2917.

with ethyl acetate. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give the pure product. (All manipulations were performed under argon using standard Schlenk techniques. Diethyl ether and toluene were distilled from sodium benzophenone ketyl under argon.)

### General procedure B:<sup>254</sup>



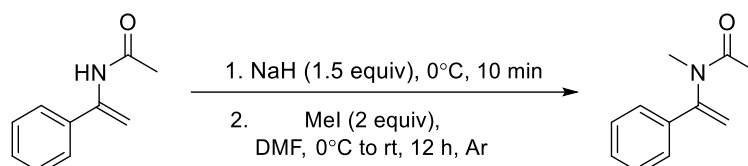
Synthetic procedure: (a) A mixture of ketone (10 mmol, 1.0 equiv.), NaOAc (984 mg, 12mmol, 1.2 equiv.) and hydroxylamine hydrochloride (834 mg, 12 mmol, 1.2 equiv.) in methanol (5 mL, 2.0 M) was stirred for 2 h at 60° C. Add water after cooling down to room temperature, then the mixture was extracted with ethyl acetate (2×50 mL). The organic layer was collected, dried over MgSO<sub>4</sub> and vacuo to afford the ketoxime which was used without further purification for the next step.

(b) To an oven-dried 50 mL two-neck round-bottom flask assembled with condenser was added the above ketoxime. The flask was vacuumed and back filled with N<sub>2</sub> for three times. Anhydrous toluene (20 mL, 0.5 M) was added followed by acetic anhydride (3.06 g, 30 mmol, 3.0 equiv.), acetic acid (1.80 g, 30 mmol, 3.0 equiv.) and iron powder (1.12 g, 20 mmol, 2.0 equiv.). The reaction flask was put into a 70° C preheated oil bath and allowed to stir under nitrogen atmosphere. After the reaction completed and cooled to room temperature, ethyl acetate was added and the mixture was filtered through a short pad of celite. The solution thus was evaporated to get the crude enamide, which was directly purified by column chromatography.

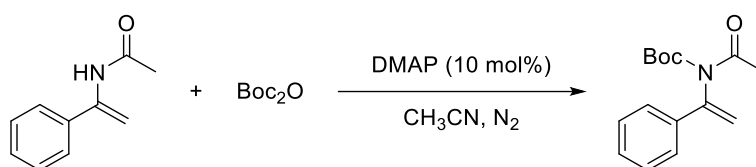
(c) N-acyl enamides (1.0 equiv.) was dissolved in dry DMF (0.33 M) in a dry two-necked round-bottom flask under nitrogen. The solution was cooled to 0° C. and sodium hydride (60% dispersion in mineral oil, 1.5 equiv.) was added in portions. The resulting suspension was stirred at the same temperature for 10 min. Then Benzyl bromide (2.0 equiv.) was added dropwise and the final solution was continued to stir overnight at room temperature. The completion of the reaction was confirmed by checking TLC and the excess sodium hydride was quenched by adding 10 mL water at 0° C. The organic

<sup>254</sup> Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458-3462.

layer was extracted with ethyl acetate through stages of extraction with water. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give the pure product.

**Procedure C:**<sup>124</sup>

For the synthesis of N-methyl-N-(1-phenylvinyl)acetamide: 2.5 mmol (402.7 mg, 1.0 equiv.) of the N-(1-phenylvinyl)acetamide was dissolved in 7.5 mL dry DMF (0.33 M) in a dry two-necked round-bottom flask under nitrogen. The solution was cooled to 0 ° C. and 3.75 mmol sodium hydride (60% dispersion in mineral oil, 150.0 mg, 1.5 equiv.) was added in portions. The resulting suspension was stirred at the same temperature for 10 min. Then 5.0 mmol (709.7 mg, 2.0 equiv.) Methyl iodide was added dropwise and the final solution was continued to stir overnight at room temperature. The completion of the reaction was confirmed by checking TLC and the excess sodium hydride was quenched by adding 5 mL water at 0 ° C. The organic layer was extracted with ethyl acetate through stages of extraction with water. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give the pure product.

**Procedure D:**<sup>255</sup>

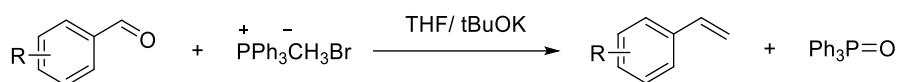
For the synthesis of tert-butyl acetyl(1-phenylvinyl)carbamate: 3.0 mmol (483.3 mg, 1.0 equiv.) N-acyl enamides and DMAP (10% mol, 36.7 mg) were dissolved in 9 mL CH<sub>3</sub>CN (0.33 M) in a dry two-necked round-bottom flask under nitrogen. Then 4.5 mmol (981.5 mg, 1.5 equiv.) Boc<sub>2</sub>O was added in dropwise at room temperature. The completion of the reaction was confirmed by checking TLC and the reaction was quenched by adding 5 mL water. The organic layer was extracted with ethyl acetate through stages of extraction with water. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel to give the pure product.

<sup>255</sup> Yu, W.; Chen, J.; Gao, K.; Liu, Z.; Zhang, Y. *Org. Lett.* **2014**, *16*, 4870-4873.

### c. Synthesis of Styrene derivatives

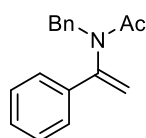
1-methyl-2-vinylbenzene, 1-methyl-3-vinylbenzene, 1-fluoro-2-vinylbenzene, 1-(trifluoromethyl)-4-vinylbenzene were prepared accordingly to literature procedures.<sup>256,257</sup> The spectroscopic data are in agreement with those reported in the literature:

#### General procedure E:



To a flame-dried round-bottom flask was added methyltriphenylphosphonium bromide (4.2 g, 11.7 mmol, 1.3 equiv.) and THF (20 mL per 1 g of aldehyde). *t*BuOK (1.4 g, 12.6 mmol, 1.4 equiv.) was added in one portion at 0°C under N<sub>2</sub> atmosphere, and the resulting yellow solution was stirred at room temperature for 1 h. Then the aromatic aldehyde (9.0 mmol, 1.0 equiv.) was added dropwise as a solution in THF (9.0 mL, 1.0 M). After consumption of the introduced aldehyde, the solution was filtered over a pad of celite and the residue was washed with Et<sub>2</sub>O. The filtrate was concentrated under vacuum and purified by silica gel flash column chromatography by dry loading and eluting with petroleum ether to give the desired styrene.

## 2.2 Characterization of substrates



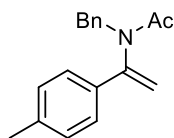
#### Compound 3: N-benzyl-N-(1-phenylvinyl)acetamide

Following the general procedure A (eluent: petroleum ether/ethyl acetate = 86:14), the desired product **3** was obtained as a pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 – 7.35 (m, 5H), 7.31 – 7.22 (m, 5H), 5.62 (s, 1H), 4.88 (s, 1H), 4.65 (s, 2H), 2.10 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>

<sup>256</sup> Mo, J.-N.; Yu, W.-L.; Chen, J.-Q.; Hu, X.-Q.; Xu, P.-F. *Org. Lett.* **2018**, *20*, 4471-4474.

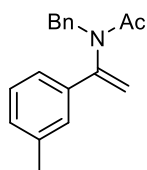
<sup>257</sup> Puleo, T. R.; Strong, A. J.; Bandar, J. S. *J. Am. Chem. Soc.* **2019**, *141*, 1467-1472.

<sup>258</sup> Chang, X.-H.; Wang, Z.-L.; Zhao, M.; Yang, C.; Li, J.-J.; Ma, W.-W.; Xu, Y.-H. *Org. Lett.* **2020**, *22*, 1326-1330.



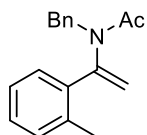
### **N-benzyl-N-(1-(p-tolyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.16 (m, 9H), 5.57 (s, 1H), 4.82 (s, 1H), 4.64 (s, 2H), 2.38 (s, 3H), 2.09 (s, 3H). The analytical data was consistent with the literature.<sup>124</sup>



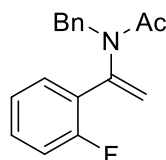
### **N-benzyl-N-(1-(m-tolyl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.15 (m, 9H), 5.60 (s, 1H), 4.86 (s, 1H), 4.65 (s, 2H), 2.37 (s, 3H), 2.10 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 146.7, 138.8, 137.8, 135.5, 130.1, 129.1, 129.0, 128.4, 127.4, 126.5, 123.1, 114.5, 50.0, 22.2, 21.6. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}$ : 265.1467, Found: 265.1466 ( $\Delta = -0.13$  ppm).



### **N-benzyl-N-(1-(o-tolyl)vinyl)acetamide**

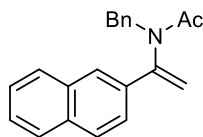
Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.12 (m, 9H), 5.17 (s, 1H), 5.12 (s, 1H), 4.53 (s, 2H), 2.28 (s, 3H), 2.26 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>



### **N-benzyl-N-(1-(2-fluorophenyl)vinyl)acetamide**

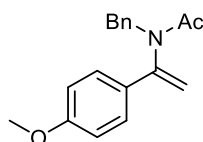
Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.08 (m, 9H), 5.70 (d,  $J = 1.1$  Hz, 1H), 5.13 (d,  $J = 1.8$  Hz, 1H), 4.62 (s, 2H), 2.18 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.85, 160.81 (d,  $J = 251.7$  Hz), 141.47 (d,  $J = 1.9$  Hz), 137.47, 130.69 (d,  $J = 8.5$  Hz), 129.18 (d,  $J = 2.5$  Hz), 129.06, 128.41, 127.44, 124.59 (d,

$J = 3.9$  Hz), 119.78 (d,  $J = 8.5$  Hz), 116.74 (d,  $J = 22.8$  Hz), 65.35, 49.64, 22.22. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>17</sub>H<sub>17</sub>NOF: 270.1294, Found: 270.1295 ( $\Delta = 0.4$  ppm).



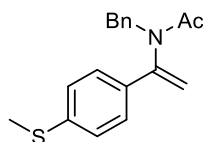
#### **N-benzyl-N-(1-(naphthalen-2-yl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow solid; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.92 – 7.79 (m, 3H), 7.76 (d,  $J = 1.9$  Hz, 1H), 7.62 – 7.48 (m, 3H), 7.35 – 7.21 (m, 5H), 5.77 (s, 1H), 4.99 (s, 1H), 4.75 (s, 2H), 2.14 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>



#### **N-benzyl-N-(1-(4-methoxyphenyl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 85:15), the desired product was obtained as a pale yellow oil; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 – 7.22 (m, 7H), 6.95 – 6.86 (m, 2H), 5.49 (s, 1H), 4.77 (s, 1H), 4.65 (s, 2H), 3.84 (s, 3H), 2.09 (s, 3H). The analytical data was consistent with the literature.<sup>124</sup>

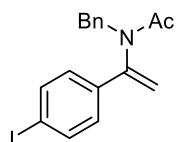


#### **N-benzyl-N-(1-(4-(methylthio)phenyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 85:15), the desired product was obtained as a pale yellow oil; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 – 7.20 (m, 9H), 5.57 (s, 1H), 4.84 (s, 1H), 4.65 (s, 2H), 2.51 (s, 3H), 2.08 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 146.1, 140.3, 137.7, 132.1, 129.1, 128.4, 127.5, 126.5, 126.3, 114.0, 49.9, 22.1, 15.5. **HRMS** (EI<sup>+</sup>)  $m/z$ : [M] Calcd for C<sub>18</sub>H<sub>19</sub>NOS: 297.1187, Found: 297.1183 ( $\Delta = -1.42$  ppm). The <sup>1</sup>H NMR was consistent with the literature,<sup>259</sup> <sup>13</sup>C NMR and HRMS are new data.

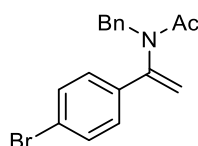
<sup>259</sup> Lu, X.-Y.; Wang, J.-C.; Sun, X.-M.; Gao, M.-T.; Ying, W.-J.; Ge, M.-Y.; Wei, Z.-H.; Liu, Z.; Chen, X.-K. *J. Org. Chem.* **2023**, *88*, 513-524.





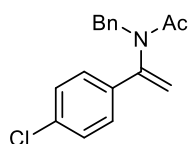
### **N-benzyl-N-(1-(4-iodophenyl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 85:15), the desired product was obtained as a yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 – 7.67 (m, 2H), 7.33 – 7.18 (m, 5H), 7.15 – 7.06 (m, 2H), 5.62 (s, 1H), 4.91 (s, 1H), 4.64 (s, 2H), 2.07 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 145.8, 138.2, 137.4, 135.2, 129.1, 128.5, 127.6, 127.6, 115.3, 95.2, 50.0, 22.1. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{17}\text{H}_{16}\text{INO}$ : 377.0277, Found: 377.0292 ( $\Delta = 4.11$  ppm). The  $^1\text{H NMR}$  was consistent with the literature,<sup>259</sup>  $^{13}\text{C NMR}$  and **HRMS** are new data.



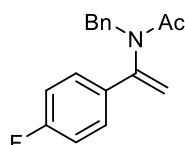
### **N-benzyl-N-(1-(4-bromophenyl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.46 (m, 2H), 7.34 – 7.18 (m, 7H), 5.61 (s, 1H), 4.91 (s, 1H), 4.64 (s, 2H), 2.08 (s, 3H). The analytical data was consistent with the literature.<sup>259</sup>



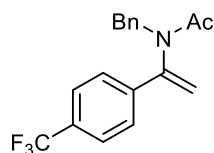
### **N-benzyl-N-(1-(4-chlorophenyl)vinyl)acetamide**

Following the general procedure **A** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.20 (m, 9H), 5.60 (d,  $J = 0.6$  Hz, 1H), 4.91 (s, 1H), 4.64 (s, 2H), 2.08 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>



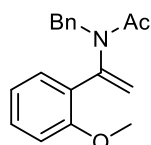
### **N-benzyl-N-(1-(4-fluorophenyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.20 (m, 7H), 7.12 – 7.01 (m, 2H), 5.55 (s, 1H), 4.87 (s, 1H), 4.64 (s, 2H), 2.09 (s, 3H).  $^{19}\text{F}\{^1\text{H}\}$  **NMR** (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -112.5. The analytical data was consistent with the literature.<sup>258</sup>



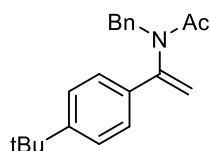
### **N-benzyl-N-(1-(4-(trifluoromethyl)phenyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69 – 7.59 (m, 2H), 7.54 – 7.43 (m, 2H), 7.34 – 7.15 (m, 5H), 5.72 (s, 1H), 5.02 (s, 1H), 4.66 (s, 2H), 2.08 (s, 3H).  $^{19}\text{F}\{^1\text{H}\}$   $\text{NMR}$  (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.3. The analytical data was consistent with the literature.<sup>260</sup>



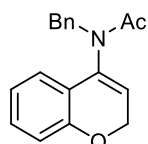
### **N-benzyl-N-(1-(2-methoxyphenyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 87:13), the desired product was obtained as yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.15 (m, 7H), 7.03 – 6.88 (m, 2H), 5.54 (s, 1H), 5.04 (s, 1H), 4.56 (s, 2H), 3.83 (s, 3H), 2.24 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 157.8, 145.1, 138.1, 130.5, 130.4, 128.9, 128.3, 127.1, 125.0, 120.8, 117.8, 111.2, 55.6, 49.3, 22.5. The analytical data was consistent with the literature.<sup>124</sup>



### **N-benzyl-N-(1-(4-(tert-butyl)phenyl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 90:10), the desired product was obtained as yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.23 (m, 5H), 5.58 (s, 1H), 4.82 (s, 1H), 4.65 (s, 2H), 2.10 (s, 3H), 1.34 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 152.6, 146.5, 137.9, 132.6, 129.1, 128.4, 127.4, 126.0, 125.7, 114.0, 49.8, 34.8, 31.4, 22.1. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{21}\text{H}_{26}\text{NO}$ : 308.2014, Found: 308.2023 ( $\Delta$  = 2.9 ppm).

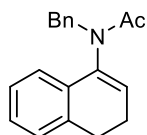


### **N-benzyl-N-(2H-chromen-4-yl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33

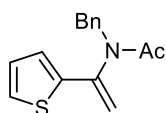
<sup>260</sup> Li, X.; Sun, K.; Shen, W.; Zhang, Y.; Lu, M.-Z.; Luo, X.; Luo, H. *Org. Lett.* **2021**, *23*, 31-36.

– 7.16 (m, 6H), 7.00 – 6.88 (m, 2H), 6.88 – 6.82 (m, 1H), 5.49 (d,  $J = 14.2$  Hz, 1H), 5.29 (t,  $J = 3.9$  Hz, 1H), 4.87 – 4.69 (m, 2H), 3.90 (d,  $J = 14.2$  Hz, 1H), 2.05 (s, 3H).  **$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 155.4, 137.6, 136.0, 130.6, 129.2, 128.5, 127.6, 122.6, 121.9, 121.4, 120.1, 116.6, 65.3, 50.2, 21.9. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}_2$ : 279.1259, Found: 279.1254 ( $\Delta = -1.88$  ppm).



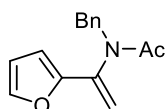
### **N-benzyl-N-(3,4-dihydronaphthalen-1-yl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.15 (m, 9H), 7.09 – 7.02 (m, 1H), 5.61 – 5.50 (m, 2H), 3.84 (d,  $J = 14.2$  Hz, 1H), 2.81 – 2.72 (m, 2H), 2.41 – 2.14 (m, 2H), 2.02 (s, 3H).  **$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 138.3, 138.0, 137.0, 131.4, 129.2, 128.8, 128.4, 128.3, 128.1, 127.4, 127.0, 122.0, 50.1, 27.3, 22.8, 21.8. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}$ : 277.1467, Found: 277.1468 ( $\Delta = 0.65$  ppm).



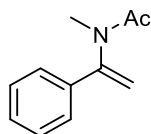
### **N-benzyl-N-(1-(thiophen-2-yl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 – 7.26 (m, 6H), 7.03 – 6.98 (m, 2H), 5.52 (s, 1H), 4.73 (s, 3H), 2.11 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>



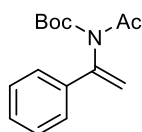
### **N-benzyl-N-(1-(furan-2-yl)vinyl)acetamide**

Following the general procedure **B** (eluent: petroleum ether/ethyl acetate = 86:14), the desired product was obtained as a pale yellow oil;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (d,  $J = 1.8$  Hz, 1H), 7.33 – 7.22 (m, 5H), 6.41 (dd,  $J = 3.3, 1.8$  Hz, 1H), 6.25 (d,  $J = 4.1$  Hz, 1H), 5.64 (s, 1H), 4.79 (s, 1H), 4.72 (s, 2H), 2.07 (s, 3H).  **$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 150.7, 143.8, 137.9, 137.8, 129.2, 128.4, 127.6, 113.0, 111.8, 108.5, 50.6, 21.8. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_2$ : 241.1103, Found: 241.1114 ( $\Delta = 4.50$  ppm).



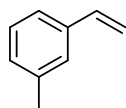
### **N-methyl-N-(1-phenylvinyl)acetamide**

Following the procedure **C** (eluent: petroleum ether/ethyl acetate = 85:15), the desired product was obtained as a pale yellow oil;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 – 7.33 (m, 5H), 5.69 (s, 1H), 5.23 (s, 1H), 3.09 (s, 3H), 2.03 (s, 3H). The analytical data was consistent with the literature.<sup>258</sup>



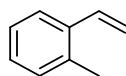
### **tert-butyl acetyl(1-phenylvinyl)carbamate**

Following the procedure **D** (eluent: petroleum ether/ethyl acetate = 90:10), the desired product was obtained as a white solid;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.27 (m, 5H), 5.78 (d,  $J = 0.8$  Hz, 1H), 5.18 (d,  $J = 0.8$  Hz, 1H), 2.58 (s, 3H), 1.29 (s, 9H). The analytical data was consistent with the literature.<sup>258</sup>



### **1-methyl-3-vinylbenzene**

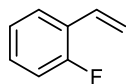
Following the general procedure **E** (eluent: petroleum ether), the desired product **1v** was obtained as a colorless liquid;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 – 7.19 (m, 3H), 7.13 – 7.03 (m, 1H), 6.70 (dd,  $J = 17.6, 10.9$  Hz, 1H), 5.74 (dd,  $J = 17.6, 1.0$  Hz, 1H), 5.23 (dd,  $J = 10.9, 1.1$  Hz, 1H), 2.36 (s, 3H). The analytical data was consistent with the literature.<sup>261</sup>



### **1-methyl-2-vinylbenzene**

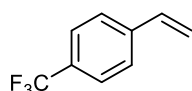
Following the general procedure **E** (eluent: petroleum ether), the desired product **1w** was obtained as a colorless liquid;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.42 (m, 1H), 7.23 – 7.09 (m, 3H), 6.96 (dd,  $J = 17.5, 11.0$  Hz, 1H), 5.65 (dd,  $J = 17.4, 1.5$  Hz, 1H), 5.30 (dd,  $J = 11.0, 1.4$  Hz, 1H), 2.37 (s, 3H). The analytical data was consistent with the literature.<sup>261</sup>

<sup>261</sup> Wang, C.; Gong, S.; Liang, Z.; Sun, Y.; Cheng, R.; Yang, B.; Liu, Y.; Yang, J.; Sun, F. *ACS Omega* **2019**, *4*, 16045-16051.



### 1-fluoro-2-vinylbenzene

Following the general procedure **E** (eluent: petroleum ether), the desired product **1x** was obtained as a colorless liquid;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.43 (m, 1H), 7.25 – 7.16 (m, 1H), 7.15 – 6.97 (m, 2H), 6.88 (dd,  $J = 17.8, 11.2$  Hz, 1H), 5.83 (dd,  $J = 17.8, 1.2$  Hz, 1H), 5.38 (dd,  $J = 11.2, 1.2$  Hz, 1H). The analytical data was consistent with the literature.<sup>261</sup>



### 1-(trifluoromethyl)-4-vinylbenzene

Following the general procedure **E** (eluent: petroleum ether), the desired product **1y** was obtained as a colorless liquid;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J = 8.5$  Hz, 2H), 7.50 (d,  $J = 8.3$  Hz, 2H), 6.75 (dd,  $J = 17.7, 10.9$  Hz, 1H), 5.85 (d,  $J = 17.6$  Hz, 1H), 5.39 (d,  $J = 10.9$  Hz, 1H).  $^{19}\text{F NMR}$  (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.5. The analytical data was consistent with the literature.<sup>261</sup>

## 2.3 Synthesis of products

### a. General procedure A: for the synthesis of 4, 6-24

$\text{HCF}_2\text{SO}_2\text{Na}$  (41.4 mg, 0.3 mmol, 1.5 equiv.) or  $\text{CF}_2\text{CH}_3\text{SO}_2\text{Na}$  (45.6 mg, 0.3 mmol, 1.5 equiv.), corresponding enamide (0.2 mmol, 1.0 equiv.), 4 mL DMF were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm  $\times$  52 mm  $\times$  2 mm, immersion length is 25 mm) and a Nickel cathode (8 mm  $\times$  52 mm  $\times$  2 mm, immersion length is 25 mm). The electrochemical reactor was operated under 2 mA, 3.0-6.0 F/mol (1 mA/cm<sup>2</sup>, 8.04 h-16.08 h) constant current mode at room temperature under magnetic stirring (800 rpm). When the desired amount of charge was passed, 10 mL water was added and the mixture was extracted with ethyl acetate (3  $\times$  10 mL). The combined organic layers were washed by brine and dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products **4** and **6** to **24**

### b. General procedure B: for the synthesis of 30, 32-46

$\text{HCF}_2\text{SO}_2\text{Na}$  (82.8 mg, 0.6 mmol, 1.5 equiv.) corresponding alkene (0.4 mmol, 1.0 equiv.),  $n\text{Bu}_4\text{NBF}_4$  (32.9 mg, 0.1 mmol, 0.025M) in a solvent system (Acetone/ $\text{H}_2\text{O}$  =

3.6 mL:0.4 mL) were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 25 mm) and a Stainless-Steel cathode (8 mm × 52 mm × 2 mm, immersion length is 25 mm). All reactions were purged with Ar for 5 min before applying electricity. The electrochemical reactor was operated under 5 mA, 2.5 - 4.5 F/mol (2.5 mA/cm<sup>2</sup>, 5.36-9.65 h) constant current mode at room temperature under magnetic stirring (800 rpm). After the desired amount of charge was passed, the reaction solution was concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products **30** and **32** to **37**.

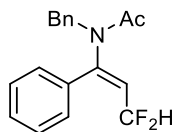
### c. General procedure C: for the synthesis of **47** and **48**

CF<sub>2</sub>CH<sub>3</sub>SO<sub>2</sub>Na (45.6 mg, 0.3 mmol, 1.5 equiv.) corresponding alkene (0.2 mmol, 1.0 equiv.), nBu<sub>4</sub>NBF<sub>4</sub> (32.9 mg, 0.1 mmol, 0.025M) in a solvent system (Acetone/H<sub>2</sub>O = 3.6 mL:0.4mL) were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 25 mm) and a Stainless-Steel cathode (8 mm × 52 mm × 2 mm, immersion length is 25 mm). All reactions were purged with Ar for 5 min before applying electricity. The electrochemical reactor was operated under 5 mA, 2.5 - 3.5 F/mol (2.5 mA/cm<sup>2</sup>, 2.68-3.75 h) constant current mode at room temperature under magnetic stirring (800 rpm). After the desired amount of charge was passed, the reaction solution was concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products **47** and **48**.

### d. General procedure D: for the synthesis of **49** to **52**

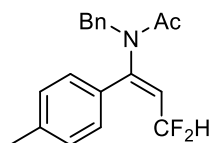
HCF<sub>2</sub>SO<sub>2</sub>Na (41.4 mg, 0.3 mmol, 1.5 equiv.) or CF<sub>2</sub>CH<sub>3</sub>SO<sub>2</sub>Na (45.6 mg, 0.3 mmol, 1.5 equiv.), corresponding alkene (0.2 mmol, 1.0 equiv.), nBu<sub>4</sub>NBF<sub>4</sub> (32.9 mg, 0.1 mmol, 0.025M) (for product **42**, reaction was performed on a 0.25 mmol scale with a total of 3.5 F/mol amount of charge, 4.69 h), 4 mL Methanol or Ethanol were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 25 mm) and a Stainless-Steel cathode (8 mm × 52 mm × 2 mm, immersion length is 25 mm). All reactions were purged with Ar for 5 min before applying electricity. The electrochemical reactor was operated under 5 mA, 3.5 F/mol (2.5 mA/cm<sup>2</sup>, 3.75 h) constant current mode at room temperature under magnetic stirring (800 rpm). After the desired amount of charge was passed, the reaction solution was concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products **49** to **52**.

## 2.4 Characterization of products



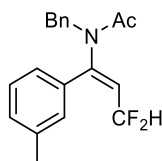
### Compound 4: (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-phenylprop-1-en-1-yl)acetamide

Synthesized from *N*-benzyl-*N*-(1-phenylvinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained a colorless crystal (47.3 mg, 80% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.48. mp: 79-80°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 – 7.40 (m, 3H), 7.35 – 7.23 (m, 5H), 7.22 – 7.12 (m, 2H), 6.07 (td,  $J$  = 54.8, 7.7 Hz, 1H), 5.61 – 5.49 (m, 1H), 4.58 (s, 2H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 148.38 (t,  $J$  = 14.0 Hz), 136.8, 133.33 (t,  $J$  = 1.9 Hz), 130.8, 129.3, 128.99 (t,  $J$  = 1.6 Hz), 128.8, 128.6, 127.7, 121.63 (t,  $J$  = 27.9 Hz), 113.07 (t,  $J$  = 230.3 Hz), 50.0, 22.7.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3002, 1647, 1387, 1261, 1009, 765, 701. Analytical data for compound **4** was consistent with the literature.<sup>80</sup>



### Compound 6: (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-(*p*-tolyl)prop-1-en-1-yl)acetamide

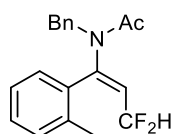
Synthesized from *N*-benzyl-*N*-(1-(*p*-tolyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a light yellow solid (49.8 mg, 79% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.49. mp: 78-79°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.22 (m, 5H), 7.21 – 7.10 (m, 4H), 6.07 (td,  $J$  = 54.8, 7.6 Hz, 1H), 5.55 – 5.44 (m, 1H), 4.57 (s, 2H), 2.41 (s, 3H), 2.17 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 148.5 (t,  $J$  = 14.0 Hz), 141.2, 137.0, 130.5 (t,  $J$  = 1.9 Hz), 130.0, 128.9 (t,  $J$  = 1.7 Hz), 128.8, 128.6, 127.7, 121.1 (t,  $J$  = 27.8 Hz), 113.2 (t,  $J$  = 230.2 Hz), 50.0, 22.7, 21.5.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.3. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3040, 1647, 1388, 1118, 1051, 1008, 833, 763, 702, 523. Analytical data for compound **6** was consistent with the literature.<sup>80</sup>



### Compound 7: (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-(*m*-tolyl)prop-1-en-1-yl)acetamide

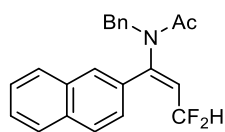
Synthesized from *N*-benzyl-*N*-(1-(*m*-tolyl)vinyl)acetamide following general procedure

**A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless crystal (48.8 mg, 77% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.43. mp: 59-60°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 – 7.24 (m, 5H), 7.22 – 7.13 (m, 2H), 7.09 – 7.00 (m, 2H), 6.07 (td,  $J = 54.8, 7.7$  Hz, 1H), 5.58 – 5.48 (m, 1H), 4.58 (s, 2H), 2.37 (s, 3H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 148.6 (t,  $J = 14.0$  Hz), 139.2, 136.9, 133.3 (t,  $J = 1.9$  Hz), 131.5, 129.3 (t,  $J = 1.6$  Hz), 129.1, 128.8, 128.6, 127.7, 126.3 (t,  $J = 1.7$  Hz), 121.4 (t,  $J = 27.9$  Hz), 113.1 (t,  $J = 230.2$  Hz), 50.0, 22.7, 21.5.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{19}\text{H}_{20}\text{NOF}_2$ : 316.1513, Found: 316.1512 ( $\Delta = -0.3$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2925, 1646, 1380, 1228, 1116, 1008, 794, 700.



**Compound 8: (E)-N-benzyl-N-(3,3-difluoro-1-(o-tolyl)prop-1-en-1-yl)acetamide**

Synthesized from N-benzyl-N-(1-(o-tolyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (8:1). Obtained as a yellow solid (24.6 mg, 35% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.41. mp: 59-61°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.32 (m, 1H), 7.32 – 7.19 (m, 5H), 7.11 – 7.02 (m, 3H), 6.04 – 5.59 (m, 2H), 4.51 (s, 2H), 2.35 (s, 3H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 148.3 (t,  $J = 13.9$  Hz), 137.2 (t,  $J = 1.7$  Hz), 137.1, 132.2, 131.4, 131.0 (t,  $J = 1.7$  Hz), 130.4, 128.6, 127.8, 127.5, 126.4, 119.9 (t,  $J = 27.6$  Hz), 113.5 (t,  $J = 230.2$  Hz), 49.3, 23.2, 19.7.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -109.1 (d,  $J = 351.7$  Hz). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3021, 1650, 1376, 1265, 1070, 1009, 976, 752, 700. Analytical data for compound **8** was consistent with the literature.<sup>80</sup>

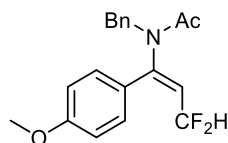


**Compound 9: (E)-N-benzyl-N-(3,3-difluoro-1-(naphthalen-2-yl)prop-1-en-1-yl)acetamide**

Synthesized from N-benzyl-N-(1-(naphthalen-2-yl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (95:5). Obtained as a light yellow oil (47.8 mg, 68% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.8.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 – 7.82 (m, 3H), 7.76 – 7.70 (m, 1H), 7.65 – 7.53 (m, 2H), 7.35 – 7.26 (m, 4H), 7.23 – 7.15 (m, 2H), 6.13 (td,  $J = 54.8, 7.7$  Hz, 1H), 5.69 – 5.59 (m, 1H), 4.63 (s, 2H), 2.24 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 148.5 (t,  $J = 14.0$  Hz), 136.8, 134.1, 133.0, 130.6 (t,  $J = 1.9$  Hz), 129.6 (t,  $J = 1.9$  Hz), 129.3, 128.8, 128.7, 127.9, 127.8, 127.4, 125.1, 121.84 (t,  $J = 27.9$  Hz), 113.20 (t,  $J = 230.4$  Hz), 50.1, 22.9.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,

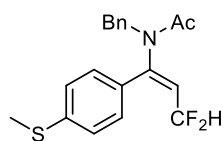


CDCl<sub>3</sub>)  $\delta$  -107.1. IR (neat, cm<sup>-1</sup>):  $\nu$  3030, 1666, 1645, 1379, 1072, 1010, 750, 699, 610. Analytical data for compound **9** was consistent with the literature.<sup>80</sup>



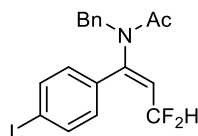
**Compound 10:** (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-(4-methoxyphenyl)prop-1-en-1-yl)acetamide

Synthesized from *N*-benzyl-*N*-(1-(4-methoxyphenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (91:9). Obtained as a colorless oil (51.8 mg, 78% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.40. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.34 – 7.24 (m, 3H), 7.23 – 7.12 (m, 4H), 7.00 – 6.91 (m, 2H), 6.08 (td,  $J$  = 54.9, 7.7 Hz, 1H), 5.52 – 5.41 (m, 1H), 4.59 (s, 2H), 3.86 (s, 3H), 2.17 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 161.5, 148.2 (t,  $J$  = 13.9 Hz), 136.9,  $\delta$  130.5 (t,  $J$  = 1.6 Hz), 128.8, 128.6, 127.7, 125.4 (t,  $J$  = 1.9 Hz), 120.4 (t,  $J$  = 27.8 Hz), 114.7, 113.3 (t,  $J$  = 230.0 Hz), 55.5, 50.0, 22.7. <sup>19</sup>F{<sup>1</sup>H} NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -106.9. IR (neat, cm<sup>-1</sup>):  $\nu$  2936, 1664, 1605, 1512, 1380, 1252, 1175, 1007, 840, 699, 528. Analytical data for compound **10** was consistent with the literature.<sup>145</sup>



**Compound 11:** (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-(4-(methylthio)phenyl)prop-1-en-1-yl)acetamide

Synthesized from *N*-benzyl-*N*-(1-(4-(methylthio)phenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (91:9). Obtained as a white solid (51.45 mg, 74% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.49. mp: 52-53°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 – 7.24 (m, 5H), 7.21 – 7.09 (m, 4H), 6.31 – 5.84 (m, 1H), 5.57 – 5.44 (m, 1H), 4.59 (s, 2H), 2.52 (s, 3H), 2.16 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.4, 148.0 (t,  $J$  = 14.0 Hz), 142.8, 136.8, 129.5, 129.2, 128.8, 128.6, 127.7, 126.2, 121.15 (t,  $J$  = 27.9 Hz), 113.06 (t,  $J$  = 230.3 Hz), 50.1, 22.7, 15.1. <sup>19</sup>F{<sup>1</sup>H} NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -107.1. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>19</sub>H<sub>20</sub>NOF<sub>2</sub>S: 348.1234, Found: 348.1243 ( $\Delta$  = 2.6 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  3030, 1665, 1647, 1380, 1124, 1089, 1072, 1011, 826, 702.

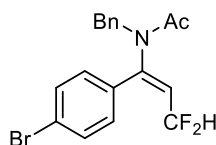



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**Compound 12: (E)-N-benzyl-N-(3,3-difluoro-1-(4-iodophenyl)prop-1-en-1-yl)acetamide**


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Synthesized from N-benzyl-N-(1-(4-iodophenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless oil (75.9 mg, 89% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.5.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 – 7.74 (m, 2H), 7.35 – 7.24 (m, 3H), 7.20 – 7.11 (m, 2H), 7.04 – 6.89 (m, 2H), 6.02 (td,  $J$  = 54.7, 7.6 Hz, 1H), 5.65 – 5.49 (m, 1H), 4.58 (s, 2H), 2.17 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 147.52 (t,  $J$  = 13.8 Hz), 138.6, 136.6, 132.9, 130.49 (t,  $J$  = 1.7 Hz), 128.8, 128.7, 127.9, 122.05 (t,  $J$  = 37.8 Hz), 112.76 (t,  $J$  = 230.8 Hz), 97.3, 50.2, 22.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2919, 2850, 1651, 1381, 1121, 1072, 1004, 825, 698. Analytical data for compound **12** was consistent with the literature.<sup>80</sup>

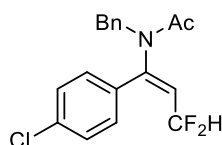



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**Compound 13: (E)-N-benzyl-N-(1-(4-bromophenyl)-3,3-difluoroprop-1-en-1-yl)acetamide**


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Synthesized from N-benzyl-N-(1-(4-bromophenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless crystal (57.9 mg, 76% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.65. mp: 88-89°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 – 7.54 (m, 2H), 7.36 – 7.23 (m, 3H), 7.22 – 7.04 (m, 4H), 6.01 (td,  $J$  = 54.6, 7.6 Hz, 1H), 5.65 – 5.49 (m, 1H), 4.58 (s, 2H), 2.17 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 147.37 (t,  $J$  = 13.9 Hz), 136.6, 132.6, 132.3, 130.45 (t,  $J$  = 1.6 Hz), 128.8, 128.7, 127.9, 125.3, 122.05 (t,  $J$  = 28.1 Hz), 112.75 (t,  $J$  = 230.8 Hz), 50.1, 22.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2945, 1649, 1386, 1072, 1007, 852, 774, 702. Analytical data for compound **13** was consistent with the literature.<sup>80</sup>



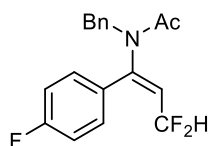

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**Compound 14: (E)-N-benzyl-N-(1-(4-chlorophenyl)-3,3-difluoroprop-1-en-1-yl)acetamide**


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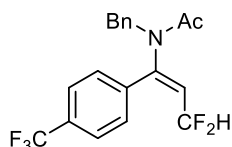
Synthesized from N-benzyl-N-(1-(4-chlorophenyl)vinyl)acetamide following general

procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless crystal (46.8 mg, 70% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.49. mp: 101-102°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 – 7.38 (m, 2H), 7.34 – 7.24 (m, 3H), 7.21 – 7.11 (m, 4H), 6.02 (td,  $J$  = 54.7, 7.6 Hz, 1H), 5.65 – 5.49 (m, 1H), 4.58 (s, 2H), 2.17 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 147.3 (t,  $J$  = 13.9 Hz), 137.0, 136.6, 131.8, 130.2 (d,  $J$  = 1.7 Hz), 129.6, 128.7, 128.7, 127.9, 122.0 (t,  $J$  = 28.2 Hz), 112.8 (t,  $J$  = 230.8 Hz), 50.1, 22.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3036, 1647, 1387, 1070, 1009, 854, 776, 702, 523. Analytical data for compound **14** was consistent with the literature.<sup>80</sup>



**Compound 15: (E)-N-benzyl-N-(3,3-difluoro-1-(4-fluorophenyl)prop-1-en-1-yl)acetamide**

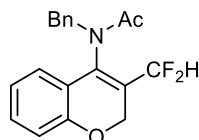
Synthesized from N-benzyl-N-(1-(4-fluorophenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless crystal (47 mg, 74% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.39. mp: 116-118°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.20 (m, 5H), 7.19 – 7.09 (m, 4H), 6.02 (td,  $J$  = 54.7, 7.6 Hz, 1H), 5.61 – 5.49 (m, 1H), 4.58 (s, 2H), 2.18 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 164.02 (d,  $J$  = 252.3 Hz), 147.38 (t,  $J$  = 14.0 Hz), 136.6, 131.01 (dt,  $J$  = 8.8, 1.9 Hz),  $\delta$  129.57 – 129.31 (m), 128.8, 128.7, 127.8, 121.64 (t,  $J$  = 27.9 Hz), 116.53 (d,  $J$  = 22.0 Hz), 112.91 (t,  $J$  = 230.5 Hz), 50.1, 22.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.3 (s, 2F), -109.2 (s, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3002, 1647, 1510, 1389, 1228, 1070, 1009, 857, 704, 525. Analytical data for compound **15** was consistent with the literature.<sup>80</sup>



**Compound 16: (E)-N-benzyl-N-(3,3-difluoro-1-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)acetamide**

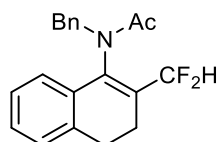
Synthesized from N-benzyl-N-(1-(4-(trifluoromethyl)phenyl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a colorless crystal (52.4 mg, 71% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.48. mp: 60-62°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 – 7.67 (m, 2H), 7.40 – 7.33 (m, 2H), 7.32 – 7.25 (m, 3H), 7.19 – 7.11 (m, 2H), 6.00 (td,  $J$  = 54.5, 7.6 Hz, 1H), 5.72 – 5.61 (m, 1H), 4.60 (s, 2H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 147.1 (t,  $J$  = 13.8 Hz), 137.1, 136.5, 132.7 (q,  $J$  = 33.1 Hz), 129.4 (t,  $J$  = 1.8 Hz), 128.8, 128.7, 128.0, 126.3 (q,  $J$  = 3.8 Hz),

123.6 (q,  $J = 272.6$  Hz), 123.0 (t,  $J = 28.4$  Hz), 112.5 (t,  $J = 231.1$  Hz), 50.3, 22.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.5 (s, 3F), -107.6 (s, 2F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2939, 1650, 1388, 1323, 1173, 1112, 1013, 863, 705, 650. Analytical data for compound **16** was consistent with the literature.<sup>80</sup>



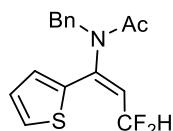
#### Compound 17: N-benzyl-N-(2H-chromen-4-yl)acetamide

Synthesized from N-benzyl-N-(3-(difluoromethyl)-2H-chromen-4-yl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (92:8). Obtained as a colorless crystal (23.7mg, 36% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.61. mp: 82–84°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.26 (m, 6H), 7.08 – 6.93 (m, 3H), 5.73 – 5.33 (m, 2H), 4.98 – 4.78 (m, 2H), 3.76 (d,  $J = 13.8$  Hz, 1H), 2.02 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 156.4, 136.52 (t,  $J = 10.0$  Hz), 135.9, 132.3, 129.9, 129.0, 128.5, 124.1, 123.90 (dd,  $J = 26.2, 23.1$  Hz), 122.5, 118.7, 117.2, 111.12 (dd,  $J = 235.4, 230.0$  Hz), 62.39 (dd,  $J = 3.9, 2.4$  Hz), 50.4, 21.7.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.98 (d,  $J = 324.3$  Hz, 1F), -120.76 (d,  $J = 324.4$  Hz, 1F). HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{F}_2$ : 330.1306, Found: 330.1320 ( $\Delta = 4.2$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2928, 1659, 1484, 1375, 1314, 1235, 1085, 1012, 755, 705, 535.



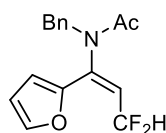
#### Compound 18: N-benzyl-N-(2-(difluoromethyl)-3,4-dihydronaphthalen-1-yl)acetamide

Synthesized from N-benzyl-N-(3,4-dihydronaphthalen-1-yl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (93:7). Obtained as a yellow oil (18.8 mg, 29% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.6.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.22 (m, 8H), 7.16 – 7.08 (m, 1H), 5.85 – 5.44 (m, 2H), 3.71 (d,  $J = 13.7$  Hz, 1H), 2.93 – 2.78 (m, 2H), 2.62 – 2.29 (m, 2H), 1.97 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 138.44 – 137.86 (m), 136.1, 131.07 (dd,  $J = 26.6, 23.1$  Hz), 130.0, 130.0, 129.8, 128.8, 128.5, 128.3, 127.4, 123.7, 112.24 (dd,  $J = 234.4, 229.7$  Hz), 50.3, 27.01 (d,  $J = 1.3$  Hz), 21.53 (d,  $J = 1.3$  Hz), 19.57 (t,  $J = 2.5$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.35 (d,  $J = 323.4$  Hz, 1F), -120.34 (d,  $J = 323.7$  Hz, 1F). HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{20}\text{H}_{20}\text{NOF}_2$ : 328.1513, Found: 328.1517 ( $\Delta = 1.2$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2932, 1666, 1647, 1376, 1290, 1251, 1081, 1010, 754, 703, 518.



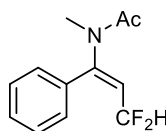
**Compound 19: (E)-N-benzyl-N-(3,3-difluoro-1-(thiophen-2-yl)prop-1-en-1-yl)acetamide**

Synthesized from N-benzyl-N-(1-(thiophen-2-yl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (90:10). Obtained as a yellow oil (40.6 mg, 66% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.49.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 (dd,  $J = 5.1, 1.2$  Hz, 1H), 7.34 – 7.26 (m, 3H), 7.25 – 7.19 (m, 3H), 7.11 (dd,  $J = 5.1, 3.7$  Hz, 1H), 6.29 (td,  $J = 54.8, 7.2$  Hz, 1H), 5.52 – 5.42 (m, 1H), 4.67 (s, 2H), 2.13 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 141.7 (t,  $J = 14.0$  Hz), 136.8 (t,  $J = 2.0$  Hz), 136.7, 130.7 (t,  $J = 2.0$  Hz), 129.8, 129.1, 128.6, 128.3, 127.9, 122.1 (t,  $J = 28.0$  Hz), 112.5 (t,  $J = 231.2$  Hz), 50.4, 22.3.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.4. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{16}\text{H}_{16}\text{NOF}_2\text{S}$ : 308.0921, Found: 308.0927 ( $\Delta = 1.9$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2929, 1666, 1638, 1430, 1379, 1065, 1008, 853, 699.



**Compound 20: (E)-N-benzyl-N-(3,3-difluoro-1-(furan-2-yl)prop-1-en-1-yl)acetamide**

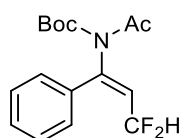
Synthesized from N-benzyl-N-(1-(furan-2-yl)vinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (93:7). Obtained as a yellow oil (28.2 mg, 48% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.55.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 – 7.54 (m, 1H), 7.34 – 7.23 (m, 5H), 6.83 (td,  $J = 55.2, 7.2$  Hz, 1H), 6.53 – 6.44 (m, 2H), 5.39 – 5.26 (m, 1H), 4.71 (s, 2H), 2.06 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 148.51 (t,  $J = 2.6$  Hz), 145.6, 136.9, 136.86 (t,  $J = 14.3$  Hz), 129.3, 128.6, 127.9, 121.88 (t,  $J = 28.0$  Hz), 114.01 (t,  $J = 1.7$  Hz), 112.2, 111.68 (t,  $J = 231.1$  Hz), 51.1, 22.0.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -110.3. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{16}\text{H}_{16}\text{NO}_2\text{F}_2$ : 292.1149, Found: 292.1159 ( $\Delta = 3.4$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3032, 1668, 1644, 1392, 1121, 1073, 1010, 750, 700, 593.



**Compound 21: (E)-N-(3,3-difluoro-1-phenylprop-1-en-1-yl)-N-methylacetamide**

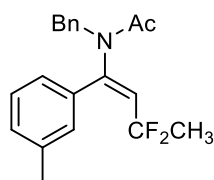
Synthesized from N-methyl-N-(1-phenylvinyl)acetamide following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (92:8). Obtained as a yellow oil (37.9 mg, 56% yield).  $R_f$

(in petroleum ether/ethyl acetate = 3:1): 0.45.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.40 (m, 3H), 7.36 – 7.28 (m, 2H), 6.11 (td,  $J = 54.8$ , 7.7 Hz, 1H), 5.80 – 5.69 (m, 1H), 2.99 (s, 3H), 2.10 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 150.22 (t,  $J = 13.9$  Hz), 133.48 (t,  $J = 2.1$  Hz), 130.7, 129.3, 128.74 (t,  $J = 1.8$  Hz), 119.43 (t,  $J = 28.1$  Hz), 113.29 (t,  $J = 230.1$  Hz) 35.5, 22.5.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -107.1. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2989, 1667, 1645, 1371, 1071, 1007, 784, 736, 701, 635, 547. Analytical data for compound **21** was consistent with the literature.<sup>145</sup>



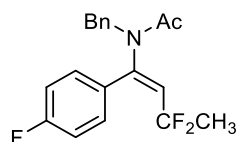
### Compound 22: tert-butyl (*E*)-acetyl(3,3-difluoro-1-phenylprop-1-en-1-yl)carbamate

Synthesized from tert-butyl acetyl(1-phenylvinyl)carbamate following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (96:4). Obtained as a yellow oil (33.0 mg, 53% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.56.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 – 7.30 (m, 5H), 6.15 (td,  $J = 54.8$ , 7.6 Hz, 1H), 5.83 – 5.73 (m, 1H), 2.55 (s, 3H), 1.33 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  172.7, 151.9, 145.10 (t,  $J = 14.9$  Hz), 134.73 (t,  $J = 2.0$  Hz), 129.8, 128.84 (t,  $J = 1.8$  Hz), 128.7, 123.26 (t,  $J = 27.8$  Hz), 113.08 (t,  $J = 230.7$  Hz) 84.2, 27.8, 26.3.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -108.6. IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2982, 1741, 1710, 1369, 1291, 1248, 1124, 1017, 719, 698. Analytical data for compound **22** was consistent with the literature.<sup>80</sup>



### Compound 23: (*E*)-*N*-benzyl-*N*-(3,3-difluoro-1-(*m*-tolyl)but-1-en-1-yl)acetamid

Synthesized from *N*-benzyl-*N*-(1-(*m*-tolyl)vinyl)acetamide following general procedure **A** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 80:20). Obtained as a colorless oil (50.0 mg, 79% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.32.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.13 (m, 8H), 7.10 (s, 1H), 5.46 (t,  $J = 12.2$  Hz, 1H), 4.48 (s, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 1.48 (t,  $J = 18.1$  Hz, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 145.38 (t,  $J = 8.4$  Hz), 138.4, 137.0, 133.9, 131.0, 129.57 (t,  $J = 2.3$  Hz), 128.9, 128.5, 128.4, 127.6, 126.76 (t,  $J = 2.9$  Hz), 126.15 (t,  $J = 30.3$  Hz), 119.64 (t,  $J = 235.6$  Hz), 49.2, 24.76 (t,  $J = 28.6$  Hz), 22.6, 21.5.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -78.6. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{20}\text{H}_{22}\text{NOF}_2$ : 330.1669, Found: 330.1681 ( $\Delta = 3.6$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2931, 1647, 1380, 1254, 1122, 977, 912, 782, 700.

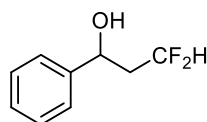



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**Compound 24: (E)-N-benzyl-N-(3,3-difluoro-1-(4-fluorophenyl)but-1-en-1-yl)acetamide**


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Synthesized from N-benzyl-N-(1-(4-fluorophenyl)vinyl)acetamide following general procedure **A** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 80:20). Obtained as a colorless oil (48.0 mg, 75% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.32.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.23 (m, 5H), 7.19 – 7.04 (m, 4H), 5.46 (t,  $J = 12.5$  Hz, 1H), 4.49 (s, 2H), 2.25 (s, 3H), 1.50 (t,  $J = 18.1$  Hz, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 163.70 (d,  $J = 250.9$  Hz),  $\delta$  144.20 (t,  $J = 7.4$  Hz), 136.8, 131.36 (dt,  $J = 8.5, 2.8$  Hz), 130.05 (d,  $J = 3.9$  Hz), 128.9, 128.6, 127.7, 126.25 (t,  $J = 29.3$  Hz), 119.43 (t,  $J = 236.2$  Hz), 115.74 (d,  $J = 21.7$  Hz), 49.3, 24.94 (t,  $J = 28.6$  Hz), 22.6.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -79.4 (s, 2F), -110.4 (s, 1F). HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{19}\text{H}_{19}\text{NOF}_3$ : 334.1419, Found: 334.1415 ( $\Delta = -1.2$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2936, 1647, 1603, 1509, 1381, 1220, 1123, 913, 844, 702, 577, 532.

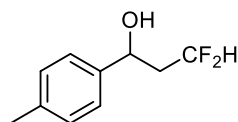



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**Compound 30: 3,3-difluoro-1-phenylpropan-1-ol**


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Synthesized from styrene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (26.5 mg, 77% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.29 (m, 5H), 5.99 (tdd,  $J = 56.7, 6.3, 3.4$  Hz, 1H), 4.92 (dt,  $J = 9.6, 3.6$  Hz, 1H), 2.45 – 2.05 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 128.9, 128.4, 125.7, 116.1 (t,  $J = 238.4$  Hz), 69.6 (dd,  $J = 7.8, 5.8$  Hz), 43.2 (t,  $J = 20.8$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J = 286.6$  Hz, 1F), -118.4 (d,  $J = 286.6$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3392, 2981, 1402, 1117, 1043, 759, 699, 540. Analytical data for compound **30** was consistent with the literature.<sup>94</sup>



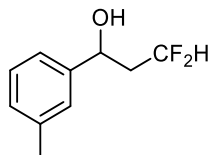

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**Compound 32: 3,3-difluoro-1-(p-tolyl)propan-1-ol**


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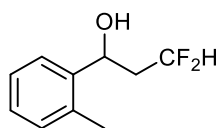
Synthesized from 1-methyl-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (56.6 mg, 76% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.15 (m, 4H), 5.98 (tdd,  $J = 56.7, 6.3, 3.5$  Hz, 1H), 4.95 – 4.82 (m, 1H), 2.38 (s, 3H), 2.35 – 2.08 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.2, 138.2, 129.6, 125.7, 116.2 (t,  $J = 238.4$

Hz) 69.5 (dd,  $J = 7.7, 5.8$  Hz), 43.2 (t,  $J = 20.7$  Hz), 21.2.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J = 286.4$  Hz, 1F), -118.4 (d,  $J = 286.4$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3390, 2980, 1514, 1427, 1400, 1117, 1042, 1021, 816, 574, 540. Analytical data for compound **32** was consistent with the literature.<sup>94</sup>



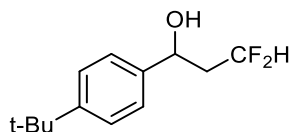
### Compound 33: 3,3-difluoro-1-(m-tolyl)propan-1-ol

Synthesized from 1-methyl-3-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (58.0 mg, 78% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.30.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 – 7.13 (m, 1H), 7.12 – 7.00 (m, 3H), 5.88 (tdd,  $J = 56.7, 6.4, 3.5$  Hz, 1H), 4.78 (dt,  $J = 9.5, 3.7$  Hz, 1H), 2.28 (s, 3H), 2.25 – 1.95 (m, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 138.7, 129.1, 128.8, 126.4, 122.8, 116.2 (t,  $J = 238.4$  Hz), 69.7 (dd,  $J = 7.7, 5.8$  Hz), 43.2 (t,  $J = 20.8$  Hz), 21.5.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J = 286.6$  Hz, 1F), -118.4 (d,  $J = 286.5$  Hz, 1F). HRMS (EI<sup>+</sup>)  $m/z$ : [M] Calcd for  $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}$ : 186.0856, Found: 186.0855 ( $\Delta = -0.56$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3377, 2923, 1401, 1118, 1044, 852, 787, 703, 532.



### Compound 34: 3,3-difluoro-1-(o-tolyl)propan-1-ol

Synthesized from 1-methyl-2-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (54.2 mg, 73% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.35.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.31 (m, 1H), 7.22 – 7.00 (m, 3H), 6.19 – 5.68 (m, 1H), 5.06 (dt,  $J = 9.6, 3.4$  Hz, 1H), 2.23 (s, 3H), 2.20 – 1.90 (m, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.2, 134.3, 130.8, 128.0, 126.7, 125.0, 116.3 (t,  $J = 238.5$  Hz), 65.9 (dd,  $J = 8.7, 4.7$  Hz), 42.3 (t,  $J = 20.7$  Hz), 18.8.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.1 (d,  $J = 286.0$  Hz, 1F), -118.6 (d,  $J = 286.0$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3400, 2975, 1401, 1115, 1042, 950, 757, 726, 580, 548. Analytical data for compound **34** was consistent with the literature.<sup>78</sup>

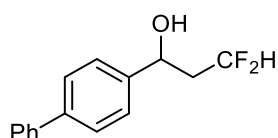


### Compound 35: 1-(4-(tert-butyl)phenyl)-3,3-difluoropropan-1-ol

Synthesized from 1-(tert-butyl)-4-vinylbenzene following general procedure **B** and

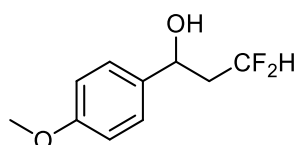


purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/diethyl ether (15:1). Obtained as a colorless oil (78.9 mg, 86% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.25.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.38 (m, 2H), 7.34 – 7.27 (m, 2H), 5.99 (tdd,  $J$  = 56.8, 6.4, 3.4 Hz, 1H), 4.91 (dd,  $J$  = 9.7, 4.0 Hz, 1H), 2.47 – 2.04 (m, 3H), 1.34 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  151.5, 140.1, 125.9, 125.6, 116.2 (t,  $J$  = 238.4 Hz), 69.5 (dd,  $J$  = 7.8, 5.8 Hz), 43.1 (t,  $J$  = 20.7 Hz), 34.7, 31.4.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J$  = 286.5 Hz, 1F), -118.5 (d,  $J$  = 286.2 Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3372, 2963, 2870, 1399, 1364, 1269, 1206, 1117, 1081, 1046, 835, 584. Analytical data for compound **35** was consistent with the literature.<sup>94</sup>



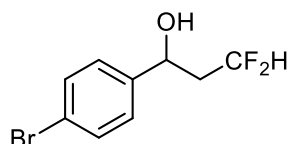
### Compound 36: 1-([1,1'-biphenyl]-4-yl)-3,3-difluoropropan-1-ol

Synthesized from 4-vinyl-1,1'-biphenyl following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (92:8). Obtained as a white solid (74.3 mg, 75% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.25.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66 – 7.56 (m, 4H), 7.51 – 7.42 (m, 4H), 7.41 – 7.33 (m, 1H), 6.04 (tdd,  $J$  = 56.7, 6.3, 3.4 Hz, 1H), 5.00 (dd,  $J$  = 9.7, 3.9 Hz, 1H), 2.51 – 1.99 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.1, 141.4, 140.7, 129.0, 127.7, 127.6, 127.2, 126.2, 116.15 (t,  $J$  = 238.5 Hz), 69.43 (dd,  $J$  = 7.7, 5.8 Hz), 43.25 (t,  $J$  = 20.8 Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J$  = 286.6 Hz, 1F), -118.4 (d,  $J$  = 286.8 Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3313, 2987, 1487, 1400, 1116, 1035, 761, 736, 694, 511. Analytical data for compound **36** was consistent with the literature.<sup>78</sup>



### Compound 37: 3,3-difluoro-1-(4-methoxyphenyl)propan-1-ol

Synthesized from 1-methoxy-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (95:5). Obtained as a colorless oil (54.5 mg, 67% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.26.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.22 (m, 2H), 6.94 – 6.84 (m, 2H), 6.19 – 5.70 (m, 1H), 4.93 – 4.81 (m, 1H), 3.80 (s, 3H), 2.45 – 1.99 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  159.6, 135.3, 127.1, 116.22 (t,  $J$  = 238.4 Hz), 114.3, 69.24 (dd,  $J$  = 7.7, 5.8 Hz), 55.4, 43.20 (t,  $J$  = 20.6 Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J$  = 286.6 Hz, 1F), -118.4 (d,  $J$  = 286.1 Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3419, 2938, 2840, 1612, 1512, 1244, 1175, 1116, 1031, 830, 575, 545. Analytical data for compound **37** was consistent with the literature.<sup>94</sup>

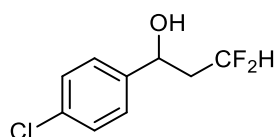



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**Compound 38: 1-(4-bromophenyl)-3,3-difluoropropan-1-ol**


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Synthesized from 1-bromo-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (86.2 mg, 86% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.29.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 – 7.49 (m, 2H), 7.32 – 7.24 (m, 2H), 6.03 (tdd,  $J$  = 56.6, 6.2, 3.4 Hz, 1H), 4.94 (dt,  $J$  = 9.7, 3.0 Hz, 1H), 2.47 (s, 1H), 2.42 – 2.02 (m, 2H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.2, 132.1, 127.5, 122.2, 115.9 (t,  $J$  = 238.7 Hz), 69.1 (dd,  $J$  = 7.6, 5.7 Hz), 43.3 (t,  $J$  = 20.9 Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3 (d,  $J$  = 287.1 Hz, 1F), -118.4 (d,  $J$  = 287.1 Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3553, 3406, 2933, 1485, 1400, 1115, 1047, 1009, 871, 827, 537. Analytical data for compound **38** was consistent with the literature.<sup>94</sup>

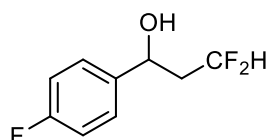



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**Compound 39: 1-(4-chlorophenyl)-3,3-difluoropropan-1-ol**


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Synthesized from 1-chloro-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry load and eluting with petroleum ether/ethyl acetate (95:5). Obtained as a colorless oil (70.3 mg, 85% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.27.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 6.03 (tdd,  $J$  = 56.6, 6.3, 3.4 Hz, 1H), 4.95 (dt,  $J$  = 9.6, 3.4 Hz, 1H), 2.56 (d,  $J$  = 3.1 Hz, 1H), 2.45 – 2.03 (m, 2H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.6, 134.0, 129.0, 127.1, 115.9 (t,  $J$  = 238.6 Hz), 68.9 (dd,  $J$  = 7.6, 5.9 Hz), 43.1 (t,  $J$  = 20.9 Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.2 (d,  $J$  = 287.0 Hz, 1F), -118.3 (d,  $J$  = 287.0 Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3407, 2983, 1708, 1492, 1399, 1117, 1084, 1043, 1014, 822, 539. Analytical data for compound **39** was consistent with the literature.<sup>94</sup>



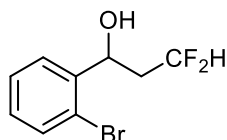

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**Compound 40: 3,3-difluoro-1-(4-fluorophenyl)propan-1-ol**


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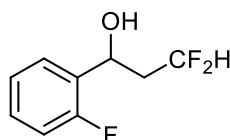
Synthesized from 1-fluoro-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (53.0 mg, 70% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.28 (m, 2H), 7.12 – 7.00 (m, 2H), 5.97 (tdd,  $J$  = 56.7, 6.2, 3.4 Hz, 1H), 4.91 (dd,  $J$  = 9.7, 4.0 Hz,

1H), 2.47 – 2.02 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (d,  $J = 246.4$  Hz), 138.9 (d,  $J = 3.1$  Hz), 127.5 (d,  $J = 8.2$  Hz), 116.0 (t,  $J = 238.5$  Hz), 115.8 (d,  $J = 21.5$  Hz), 69.0 (dd,  $J = 7.7, 5.9$  Hz), 43.3 (t,  $J = 20.8$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.4 (s, 1F), -117.3 (d,  $J = 286.8$  Hz, 1F), -118.4 (d,  $J = 287.1$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3392, 2990, 1605, 1509, 1401, 1223, 1118, 1044, 834, 570, 541. Analytical data for compound **40** was consistent with the literature.<sup>94</sup>



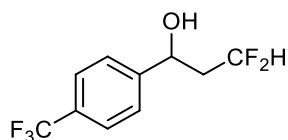
#### Compound 41: 1-(2-bromophenyl)-3,3-difluoropropan-1-ol

Synthesized from 1-bromo-2-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (93:7). Obtained as a colorless oil (83.7 mg, 83% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.28.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 – 7.49 (m, 2H), 7.42 – 7.32 (m, 1H), 7.23 – 7.12 (m, 1H), 6.10 (tdd,  $J = 56.7, 6.5, 3.1$  Hz, 1H), 5.32 (dd,  $J = 9.9, 3.0$  Hz, 1H), 2.54 – 2.01 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.0, 133.0, 129.6, 128.1, 127.2, 121.6, 116.1 (t,  $J = 238.9$  Hz), 68.41 (dd,  $J = 8.2, 5.3$  Hz), 41.5 (t,  $J = 21.1$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.1 (d,  $J = 286.6$  Hz, 1F), -118.3 (d,  $J = 286.4$  Hz, 1F). HRMS (EI<sup>+</sup>)  $m/z$ : [M] Calcd for  $\text{C}_9\text{H}_9\text{BrF}_2\text{O}$ : 249.9805, Found: 249.9807 ( $\Delta = 0.79$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3408, 2935, 1469, 1399, 1196, 1117, 1045, 753, 677, 545.

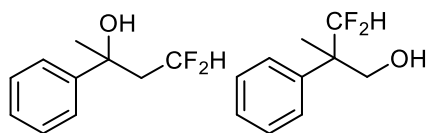


#### Compound 42: 3,3-difluoro-1-(2-fluorophenyl)propan-1-ol

Synthesized from 1-fluoro-2-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (94:6). Obtained as a colorless oil (51 mg, 67% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.31.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 – 7.42 (m, 1H), 7.35 – 7.24 (m, 1H), 7.23 – 7.14 (m, 1H), 7.10 – 7.00 (m, 1H), 6.04 (tdd,  $J = 56.6, 6.2, 3.4$  Hz, 1H), 5.25 (dd,  $J = 9.5, 3.8$  Hz, 1H), 2.48 – 2.10 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7 (d,  $J = 246.1$  Hz), 130.0 (d,  $J = 13.1$  Hz), 129.8 (d,  $J = 8.3$  Hz), 127.2 (d,  $J = 4.2$  Hz), 124.7 (d,  $J = 3.6$  Hz), 116.0 (t,  $J = 238.7$  Hz), 115.7 (d,  $J = 21.5$  Hz), 64.0 (ddd,  $J = 8.7, 6.0, 3.0$  Hz), 41.9 (t,  $J = 21.0$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.2 (d,  $J = 286.8$  Hz, 1F), -118.3 (d,  $J = 286.8$  Hz, 1F), -120.0 (s, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3406, 2989, 1588, 1489, 1403, 1224, 1119, 1048, 832, 756. Analytical data for compound **42** was consistent with the literature.<sup>105</sup>


**Compound 43: 3,3-difluoro-1-(4-(trifluoromethyl)phenyl)propan-1-ol**

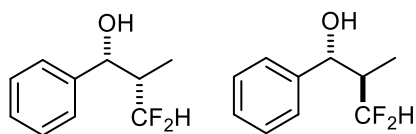
Synthesized from 1-(trifluoromethyl)-4-vinylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (95:5). Obtained as a colorless oil (22.4 mg, 23% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 – 7.58 (m, 2H), 7.56 – 7.45 (m, 2H), 6.04 (tdd,  $J = 56.6, 6.3, 3.2$  Hz, 1H), 5.05 (dt,  $J = 9.4, 3.3$  Hz, 1H), 2.44 – 2.06 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  147.1,  $\delta$  130.57 (q,  $J = 32.5$  Hz), 126.1, 125.94 (q,  $J = 3.8$  Hz), 122.3, 115.8 (t,  $J = 238.8$  Hz), 69.1 (dd,  $J = 7.6, 5.7$  Hz), 43.3 (t,  $J = 21.0$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.1 (s, 1F), -117.4 (d,  $J = 287.6$  Hz, 1F), -118.5 (d,  $J = 287.6$  Hz, 1F). HRMS (EI<sup>+</sup>)  $m/z$ : [M] Calcd for  $\text{C}_{10}\text{H}_9\text{F}_5\text{O}$ : 240.0574, Found: 240.0569 ( $\Delta = -1.86$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3411, 2982, 1621, 1403, 1324, 1165, 1114, 1065, 1016, 842, 607.


**Compound 44 & 44': 4,4-difluoro-2-phenylbutan-2-ol & 3,3-difluoro-2-methyl-2-phenylpropan-1-ol**

Synthesized from prop-1-en-2-ylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (96:4).

**44** was obtained as a colorless oil (32.0 mg, 43% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.40.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.25 (m, 5H), 6.02 – 5.56 (m, 1H), 2.47 – 2.29 (m, 2H), 2.08 (s, 1H), 1.64 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  146.6, 128.7, 127.4, 124.5, 116.4 (t,  $J = 238.2$  Hz), 72.4 (t,  $J = 5.9$  Hz), 47.6 (t,  $J = 19.9$  Hz), 30.6.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ ) -113.4 (s, 2F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3439, 2931, 1401, 1113, 1030, 766, 700, 551. Analytical data for compound **44** was consistent with the literature.<sup>94</sup>

**44'** was obtained as a colorless oil (19.1 mg, 24% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.10.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 – 7.29 (m, 5H), 5.81 (t,  $J = 53.5$  Hz, 1H), 3.79 – 3.45 (m, 2H), 3.42 (s, 1H), 1.85 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  144.6, 129.0, 128.3, 124.6, 114.5 (t,  $J = 286.9$  Hz), 73.0, 60.1, 29.9.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.74 (d,  $J = 272.7$  Hz, 1F), -128.22 (d,  $J = 272.8$  Hz, 1F). HRMS (EI<sup>+</sup>)  $m/z$ : [M] Calcd for  $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}$ : 186.0856, Found: 186.0857 ( $\Delta = 0.64$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3517, 2982, 1332, 1156, 1096, 762, 699, 555, 505.

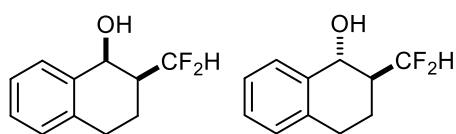


diastereomer mixture

**Compound 45: 3,3-difluoro-2-methyl-1-phenylpropan-1-ol**

Synthesized from (E)-prop-1-en-1-ylbenzene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (93:7). Obtained as a colorless oil (39.0 mg, 52% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.25. The diastereomer ratio was determined to be 1.1:1 from the mixture product using  $^1\text{H}$  NMR spectroscopy. The configuration of two diastereomers were determined by  $^3J_{\text{H-H}}$  of  $\text{CHOH}$ . Among them, **trans-3,3-difluoro-2-methyl-1-phenylpropan-1-ol** is the major diastereomer.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.27 (m, 10H, Ar, overlap of major and minor diastereomers), 6.20 (td,  $J = 57.1, 2.2$  Hz, 1H,  $\text{CF}_2\text{H}$ , major diastereomer), 5.70 (td,  $J = 56.8, 5.0$  Hz, 1H,  $\text{CF}_2\text{H}$ , minor diastereomer), 4.95 (d,  $J = 4.5$  Hz, 1H,  $\text{CHOH}$ , minor diastereomer), 4.56 (d,  $J = 9.5$  Hz, 1H,  $\text{CHOH}$ , major diastereomer), 2.41 – 2.00 (m, 2H,  $\text{OH}$  and  $\text{CHCF}_2\text{H}$ , overlap of major and minor diastereomers), 1.02 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ , minor diastereomer), 0.77 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ , major diastereomer).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.0, 128.8, 128.7, 128.5, 127.9, 126.9, 126.0, 118.4 (t,  $J = 241.6$  Hz), 117.3 (t,  $J = 241.6$  Hz), 75.10 (dd,  $J = 8.1, 2.1$  Hz), 72.45 (t,  $J = 5.7$  Hz), 44.9 (t,  $J = 18.7$  Hz), 44.2 (dd,  $J = 20.1, 18.8$  Hz), 7.8 (t,  $J = 4.8$  Hz), 6.7 (dd,  $J = 5.8, 3.9$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.3 (d,  $J = 282.0$  Hz, 1F, minor diastereomer), -126.1 (d,  $J = 282.0$  Hz, 1F, minor diastereomer);  $\delta$  -124.4 (d,  $J = 282.9$  Hz, major diastereomer), -132.1 (d,  $J = 283.0$  Hz, major diastereomer). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3417, 2986, 1456, 1149, 1059, 985, 762, 700, 622, 535. Analytical data for compound **45** is consistent with the literature.<sup>94</sup>

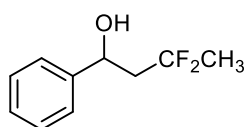


diastereomer mixture

**Compound 46: 2-(difluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol**

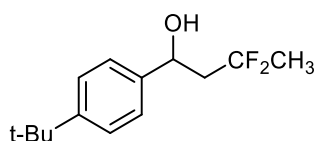
Synthesized from 1,2-dihydronaphthalene following general procedure **B** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (95:5). Obtained as a yellow oil (39.6 mg, 50% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.38. The diastereomers ratio was determined to be 2.4:1 from the mixture product using  $^1\text{H}$  NMR spectroscopy. The configuration of two diastereomers were determined by  $^3J_{\text{H-H}}$  of  $\text{CHOH}$ . Among them, **cis-2-(difluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol** is the major diastereomer.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.07 (m, 4H, Ar), 6.31 – 5.73 (m, 1H, CF<sub>2</sub>H), 4.89 (s, 0.79H, CHOH, major diastereomer), 4.80 (d, *J* = 9.0 Hz, 0.29H, CHOH, minor diastereomer), 3.05 – 2.72 (m, 2H), 2.28 – 1.85 (m, 3H), 1.83 – 1.53 (m, 1H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ 137.9, 136.9, 136.4, 130.0, 129.4, 128.8, 128.7, 118.5 (t, *J* = 241.6 Hz), 117.33 (t, *J* = 241.6 Hz), 68.4 – 68.3 (m), 47.0 (t, *J* = 19.5 Hz), 44.41 (t, *J* = 22.6 Hz), 28.2, 28.0, 19.2 (t, *J* = 4.7 Hz), 17.1 – 17.0 (m). **<sup>19</sup>F{<sup>1</sup>H} NMR** (282.4 MHz, CDCl<sub>3</sub>) δ -122.1 (d, *J* = 285.6 Hz, 1F, major diastereomer), -126.9 (d, *J* = 285.6 Hz, 1F, major diastereomer); -125.6 (d, *J* = 283.7 Hz, 1F, minor diastereomer), -128.0 (d, *J* = 284.0 Hz, 1F, minor diastereomer). **IR** (neat, cm<sup>-1</sup>): ν 3303, 2918, 1405, 1138, 1106, 1075, 1050, 1000, 831, 771, 739. Analytical data for compound **46** was consistent with the literature.<sup>78</sup>



#### Compound 47: 3,3-difluoro-1-phenylbutan-1-ol

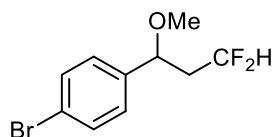
Synthesized from styrene following general procedure **C** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 90:5). Obtained as a colorless oil (29.5 mg, 79% yield). *R<sub>f</sub>* (in petroleum ether/ethyl acetate = 8:1): 0.32. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.42 – 7.27 (m, 5H), 5.06 (dt, *J* = 9.4, 2.9 Hz, 1H), 2.51 – 2.08 (m, 3H), 1.70 (t, *J* = 19.0 Hz, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ 143.7, 128.8, 128.1, 125.8, 123.98 (t, *J* = 238.4 Hz), 69.71 (dd, *J* = 6.3, 4.1 Hz), 47.02 (t, *J* = 24.2 Hz), 24.26 (t, *J* = 27.4 Hz). **<sup>19</sup>F{<sup>1</sup>H} NMR** (282.4 MHz, CDCl<sub>3</sub>) δ -87.7 (d, *J* = 242.7 Hz, 1F), -90.0 (d, *J* = 242.7 Hz, 1F). **HRMS** (EI<sup>+</sup>) *m/z*: [M] Calcd for C<sub>10</sub>H<sub>12</sub>F<sub>2</sub>O: 186.0856, Found: 186.0860 (Δ = 1.79 ppm). **IR** (neat, cm<sup>-1</sup>): ν 3404, 3034, 1392, 1229, 1121, 914, 753, 699, 559.



#### Compound 48: 1-(4-(tert-butyl)phenyl)-3,3-difluorobutan-1-ol

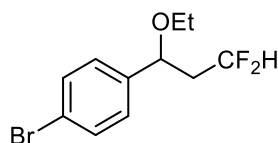
Synthesized from 1-(tert-butyl)-4-vinylbenzene following general procedure **C** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 90:5). Obtained as a colorless oil (39.6 mg, 82% yield). *R<sub>f</sub>* (in petroleum ether/ethyl acetate = 8:1): 0.43. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.45 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 5.04 (dt, *J* = 9.4, 2.6 Hz, 1H), 2.50 – 2.11 (m, 3H), 1.71 (t, *J* = 19.1 Hz, 3H), 1.34 (s, 9H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ 151.1, 140.8, 125.7, 125.6, 124.02 (t, *J* = 238.4 Hz), 69.49 (dd, *J* = 6.2, 4.3 Hz), 46.89 (t, *J* = 24.2 Hz), 34.7, 31.5, 24.24 (t, *J* = 27.2 Hz). **<sup>19</sup>F{<sup>1</sup>H} NMR** (282.4 MHz, CDCl<sub>3</sub>) δ -87.45 (d, *J* = 242.7 Hz, 1F), -90.03 (d, *J* = 242.7 Hz, 1F). **HRMS** (EI<sup>+</sup>) *m/z*: [M] Calcd for C<sub>14</sub>H<sub>20</sub>F<sub>2</sub>O: 242.1482, Found:

242.1488 ( $\Delta = 2.18$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3405, 2963, 1392, 1229, 1128, 1110, 916, 839, 582.



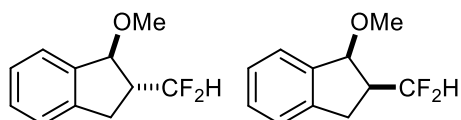
**Compound 49: 1-bromo-4-(3,3-difluoro-1-methoxypropyl)benzene**

Synthesized from 1-bromo-4-vinylbenzene following general procedure **D** and purified by Puriflash by dry loading (4 g, 6 mL/min, petroleum ether). Obtained as a colorless liquid (36.5 mg, 69% yield).  $R_f$  (in petroleum ether/ethyl acetate = 10:1): 0.56.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 – 7.46 (m, 2H), 7.25 – 7.14 (m, 2H), 6.18 – 5.71 (m, 1H), 4.30 (dd,  $J = 9.8, 3.5$  Hz, 1H), 3.19 (s, 3H), 2.41 – 2.14 (m, 1H), 2.16 – 1.92 (m, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  139.6, 132.1, 128.3, 122.2, 115.70 (t,  $J = 238.5$  Hz), 78.15 (dd,  $J = 8.5, 5.0$  Hz), 56.8, 42.83 (t,  $J = 21.5$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.16 (d,  $J = 286.6$  Hz, 1F), -118.51 (d,  $J = 286.6$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2936, 1486, 1397, 1104, 1069, 1027, 823, 798, 546. Analytical data for compound **49** was consistent with the literature.<sup>78</sup>



**Compound 50: 1-bromo-4-(1-ethoxy-3,3-difluoropropyl)benzene**

Synthesized from 1-bromo-4-vinylbenzene following general procedure **D** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether. Obtained as a colorless liquid (33.1 mg, 59% yield).  $R_f$  (in petroleum ether/ethyl acetate = 10:1): 0.68.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.45 (m, 2H), 7.24 – 7.15 (m, 2H), 6.19 – 5.73 (m, 1H), 4.45 – 4.36 (m, 1H), 3.46 – 3.21 (m, 2H), 2.39 – 2.14 (m, 1H), 2.13 – 1.90 (m, 1H), 1.16 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.4, 132.0, 128.2, 122.0, 115.81 (t,  $J = 238.5$  Hz), 76.22 (dd,  $J = 8.8, 5.0$  Hz), 64.5, 42.95 (t,  $J = 21.3$  Hz), 15.2.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.38 (d,  $J = 286.1$  Hz, 1F), -118.72 (d,  $J = 286.1$  Hz, 1F). HRMS ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{11}\text{H}_{13}\text{BrF}_2\text{O}$ : 278.0118, Found: 278.0127 ( $\Delta = 3.21$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2977, 1485, 1395, 1093, 1038, 1010, 822, 545.



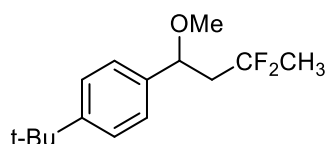
**Compound 51 & 51': *Trans*-2-(difluoromethyl)-1-methoxy-2,3-dihydro-1H-indene & *Cis*-2-(difluoromethyl)-1-methoxy-2,3-dihydro-1H-indene**

Synthesized from indene following general procedure **D** and purified by Puriflash by dry loading (4 g, 7 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 90:5).

**51** and **51'** were separated as single pure products with a 1.3:1 ratio. The configuration of two diastereomers were determined by  $^3J_{\text{H-H}}$  of *CHOMe*.

**Trans-2-(difluoromethyl)-1-methoxy-2,3-dihydro-1H-indene 51** was obtained as a colorless liquid (12.0 mg, 24% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.67.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.37 (m, 1H, Ar), 7.35 – 7.30 (m, 2H, Ar), 7.29 – 7.20 (m, 1H, Ar), 6.12 (ddd,  $J = 57.6, 55.8, 7.3$  Hz, 1H,  $\text{CF}_2\text{H}$ ), 4.69 (d,  $J = 5.7$  Hz, 1H, *CHOMe*), 3.35 (s, 3H,  $\text{CH}_3$ ), 3.22 – 3.07 (m, 1H,  $\text{CH}_2$ ), 3.02 – 2.90 (m, 1H,  $\text{CH}_2$ ), 2.90 – 2.73 (m, 1H,  $\text{CHCF}_2\text{H}$ ).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.89 (d,  $J = 1.4$  Hz), 141.09 (d,  $J = 1.4$  Hz), 129.3, 126.5, 125.59 (d,  $J = 1.7$  Hz), 125.51 (d,  $J = 1.7$  Hz), 117.88 (dd,  $J = 239.5, 236.5$  Hz), 83.23 (d,  $J = 9.6$  Hz), 56.5, 48.45 (t,  $J = 21.5$  Hz), 31.48 (d,  $J = 7.7$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -116.09 (d,  $J = 287.6$  Hz, 1F), -123.58 (d,  $J = 287.6$  Hz, 1F). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2928, 1404, 1116, 1069, 1033, 918, 757, 708, 620, 523. Analytical data for compound **51** was consistent with the literature.<sup>78</sup>

**Cis-2-(difluoromethyl)-1-methoxy-2,3-dihydro-1H-indene 51'** was obtained as a colorless liquid (9.6 mg, 19% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.45.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.38 (m, 1H, Ar), 7.34 – 7.21 (m, 3H, Ar), 5.86 (td,  $J = 56.6, 4.6$  Hz, 1H,  $\text{CF}_2\text{H}$ ), 4.92 (d,  $J = 3.9$  Hz, 1H, *CHOMe*), 3.49 (s, 3H,  $\text{CH}_3$ ), 3.33 – 3.17 (m, 1H,  $\text{CH}_2$ ), 3.00 – 2.77 (m, 2H,  $\text{CH}_2$  and  $\text{CHCF}_2\text{H}$ ).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.4, 141.0, 129.2, 127.2, 125.5, 125.1, 117.28 (t,  $J = 241.6$ ), 84.48 (t,  $J = 5.2$  Hz), 56.8, 48.98 (t,  $J = 19.7$  Hz), 30.45 (t,  $J = 5.0$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -120.09 (d,  $J = 281.0$  Hz, 1F), -121.46 (d,  $J = 281.0$  Hz, 1F). HRMS ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{11}\text{H}_{12}\text{F}_2\text{O}$ : 198.0853, Found: 198.0856 ( $\Delta = -1.89$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2933, 1386, 1091, 1063, 1033, 959, 748, 730, 529.



#### **Compound 52: 1-(tert-butyl)-4-(3,3-difluoro-1-methoxybutyl)benzene**

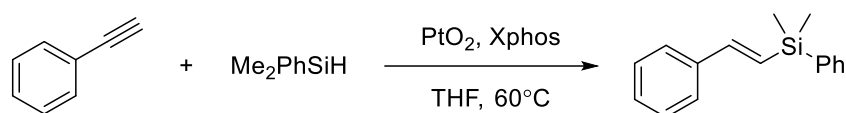
Synthesized from 1-(tert-butyl)-4-vinylbenzene following general procedure **D** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether. Obtained as a colorless liquid (44.5 mg, 87% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.63.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.34 (m, 2H), 7.27 – 7.19 (m, 2H), 4.41 – 4.32 (m, 1H), 3.20 (s, 3H), 2.47 – 2.25 (m, 1H), 2.22 – 2.04 (m, 1H), 1.66 (t,  $J = 18.8$  Hz, 3H), 1.32 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  151.0, 138.3, 126.3, 125.6, 123.61 (dd,  $J = 238.9, 237.6$  Hz), 78.75 (dd,  $J = 8.5, 3.9$  Hz), 56.6, 46.39 (t,  $J = 25.4$  Hz), 34.7, 31.5, 24.13 (t,  $J = 27.2$  Hz).  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -84.04 (d,  $J = 242.7$  Hz, 1F), -89.73 (d,  $J = 243.2$  Hz, 1F). HRMS ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_{15}\text{H}_{22}\text{F}_2\text{O}$ : 256.1639, Found: 256.1643 ( $\Delta = 1.71$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2964, 1392, 1236, 1129, 1103, 915, 834, 592.



### 3. Chapter 3 - Electrochemical halogenation of alkenes

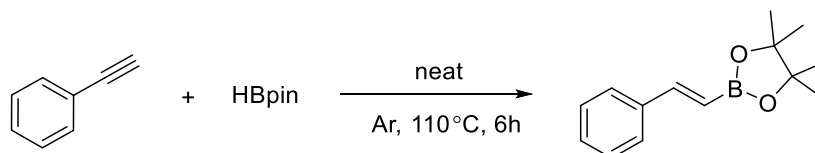
#### 3.1 Synthesis of substrates

(*E*)-dimethyl(phenyl)(styryl)silane was prepared accordingly to the literature procedure.<sup>262</sup> The NMR data are in agreement with those reported in the literature.



Under a nitrogen atmosphere, PtO<sub>2</sub> (55 mg, 0.25 mmol, 0.05 equiv.) and Xphos (240 mg, 0.5 mmol, 0.1 equiv.) in THF (2.5 mL) were heated at 60°C for 15 min. Then, terminal alkyne (5 mmol, 1.0 equiv.) and hydrosilane (1.02 g, 7.5 mmol, 1.5 equiv.) were successively added via syringe and the mixture was stirred at 60°C for 1 h. Then the reaction mixture was concentrated under vacuum and the residue was purified by silica gel flash column chromatography by dry loading eluting with petroleum ether to yield (*E*)-vinylsilane as a colorless liquid (1.29 g, 73 %). R<sub>f</sub> (in petroleum ether): 0.52.

(*E*)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane was prepared accordingly to literature procedures.<sup>263</sup> The NMR data are in agreement with those reported in the literature.

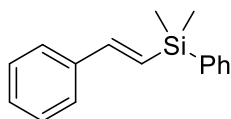


A 25 mL flask was charged with phenylacetylene (1.02 g, 10.0 mmol, 1.0 equiv.), pinacolborane (2.90 mL, 20 mmol, 2.0 equiv.) under argon atmosphere at room temperature. Reaction mixture was then brought to 110 °C and stirred for 6 h. Then, the reaction mixture was cooled to room temperature, unreacted substrates were quenched by the addition of 10 mL of water. The crude mixture was extracted with ethyl acetate and combined organic layers were dried over MgSO<sub>4</sub>. Then the reaction mixture was concentrated under vacuum and the residue was purified by silica gel flash column chromatography by dry loading eluting with petroleum ether/ethyl acetate (15/1) to yield (*E*)-dimethyl(phenyl)(styryl)silane as a colorless liquid (1.90 g, 80 %).

<sup>262</sup> Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Organomet. Chem.* **2008**, *693*, 2789-2797.

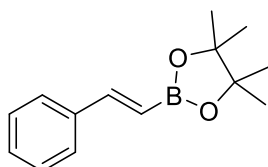
<sup>263</sup> Jaladi, A. K.; Choi, H. S.; An, D. K.; Jaladi, A. K. *New J. Chem.* **2020**, *44*, 13626-13632.

### 3.2 Characterization of substrates



#### **(E)-dimethyl(phenyl)(styryl)silane**

Purified by silica gel flash chromatography and eluting with pentane. Obtained as a colorless liquid.  $R_f$  (in petroleum ether): 0.6.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 – 7.54 (m, 2H), 7.51 – 7.42 (m, 2H), 7.42 – 7.26 (m, 6H), 6.95 (d,  $J$  = 19.1 Hz, 1H), 6.60 (d,  $J$  = 19.1 Hz, 1H), 0.44 (s, 6H).



#### **(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane**

Purified by silica gel flash chromatography and eluting with petroleum ether/ethyl acetate (15:1). Obtained as a yellow liquid.  $R_f$  (in petroleum ether): 0.6.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 – 7.38 (m, 2H), 7.37 – 7.17 (m, 4H), 6.10 (d,  $J$  = 18.4 Hz, 1H), 1.24 (s, 12H).

### 3.3 Synthesis of products

#### **General procedure A**

For synthesis of Iodo(Bromo)hydrins **56** to **74**, **89** to **97**, **105** to **111**, and **120** to **121**:

$\text{NH}_4\text{I}$  (144.0 mg, 1.0 mmol, 2.0 equiv.) or  $\text{NH}_4\text{Br}$  (97.94 mg, 1.0 mmol, 2.0 equiv.) or  $\text{NH}_4\text{Cl}$  (53.49 mg, 1.0 mmol, 2.0 equiv.), corresponding alkene (0.5 mmol, 1.0 equiv.), and supporting electrolyte  $\text{Et}_4\text{NBF}_4$  (54.3 mg, 0.25 mmol, 0.5 equiv.) in a solvent system ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  = 4 mL/1 mL) were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm  $\times$  52 mm  $\times$  2 mm, immersion length is 30mm) and a stainless-steel cathode (8 mm  $\times$  52 mm  $\times$  2 mm, immersion length is 30mm). The electrochemical reactor was operated under 100 mA constant current mode at room temperature under magnetic stirring (600 rpm) for 2 h. After completion of reaction (measured by TLC), 10 mL saturated solution of aq.  $\text{Na}_2\text{S}_2\text{O}_3$  was added and the mixture was extracted with ethyl acetate (3  $\times$  10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products.

#### **General procedure B**

For synthesis of iodohydrins ethers **101** to **104**:

NH<sub>4</sub>I (144.0 mg, 1.0 mmol, 2.0 equiv.), corresponding alkene (0.5 mmol, 1.0 equiv.) and supporting electrolyte Et<sub>4</sub>NBF<sub>4</sub> (54.3 mg, 0.25 mmol, 0.5 equiv.) in a solvent system (CH<sub>3</sub>CN/CH<sub>3</sub>OH or CH<sub>3</sub>CN/EtOH or CH<sub>3</sub>CN/AcOH = 4 mL/1 mL) were added to a 5 mL IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 30mm) and a stainless-steel cathode (8 mm × 52 mm × 2 mm, immersion length is 30mm). The electrochemical reactor was operated under 100 mA constant current mode at room temperature under magnetic stirring (600 rpm) for 2 h. After completion of reaction (measured by TLC), 10 mL saturated solution of aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluted with the appropriate solvent mixture to afford the products.

#### General procedure C:

For synthesis of 3-iodine indoles (**112** & **113**) and vinyl halides (**114** & **115**):

NH<sub>4</sub>I (144.0 mg, 1.0 mmol, 2.0 equiv.), corresponding substrate (0.5 mmol) and supporting electrolyte Et<sub>4</sub>NBF<sub>4</sub> (54.3 mg, 0.25 mmol, 0.5 equiv.) in a solvent system (CH<sub>3</sub>CN/H<sub>2</sub>O = 4 ml/1 ml) were added to a 5 ml IKA undivided cell equipped with a graphite anode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 30mm) and a stainless-steel cathode (8 mm × 52 mm × 2 mm, immersion length is 30mm). The electrochemical reactor was operated under 100 Ma constant current mode at room temperature under magnetic stirring (600 rpm) for 2 h. After completion of reaction (measured by TLC), 10 ml saturated solution of aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and the mixture was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was finally purified by silica gel column chromatography and eluting with the appropriate solvent mixture to afford corresponding products.

#### General procedure D:

For the synthesis of **122-140**:

NaBr (51.4 mg, 0.5 mmol, 2.5 equiv.) or NaCl (46.8 mg, 0.8 mmol, 4.0 equiv.), corresponding enamide (0.2 mmol, 1.0 equiv.), 4 mL DMA were added to a 5 mL IKA undivided cell equipped with a graphite anode and cathode (IKA Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 25 mm). The electrochemical reactor was operated under 5 mA, 3.0-5.0 F/mol (2.5 mA/cm<sup>2</sup>) constant current mode at room temperature under magnetic stirring (800 rpm). When the desired amount of charge was passed, 10 mL water was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed by brine and dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was finally purified by silica gel

column chromatography and eluted with the appropriate solvent mixture to afford the products **122** to **140**

### General procedure E

For Suzuki Cross-Coupling reaction for the synthesis of **147-153**:

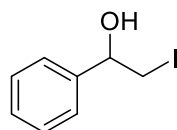
In a 5 mL tube equipped with a stir bar, product **2** (66.0 mg, 0.2 mmol, 1.0 equiv.), arylboronic acid (0.3 mmol, 1.5 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (131 mg, 0.4 mmol), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (4.4 mg, 3 mol%) were sequentially added. The mixture was pumped and refilled with argon three times before adding distilled THF/water (2.08 mL, 25/1, v/v). The resulting mixture was relaxed under argon overnight, then cooled to room temperature. The reaction solution was diluted with EtOAc (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered through cotton. Then, the organic phase was concentrated under reduced pressure and purified by silica gel column chromatography to provide products **147-153**.

### Procedure F:

For Sonogashira Cross-coupling reaction for the synthesis of **154**:

In a 5 mL tube equipped with a stir bar, product **122** (66.0 mg, 0.2 mmol, 1.0 equiv.), 4-Ethynyltoluene (35.6 mg, 0.3 mmol, 1.5 equiv.), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2.8 mg, 2 mol %), CuI (0.8 mg, 2 mol %), and 2 mL Et<sub>3</sub>N were added in order. The tube was sealed and purged with argon three times. The reaction mixture was stirred at 60°C for 9 hours. After completion, the reaction mixture was diluted with 10 mL H<sub>2</sub>O. The aqueous phase was extracted with EtOAc (10 ml x 3) and the combined organic phase was washed with brine (15 mL) and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent under reduced pressure followed by purification of the residue through silica gel column chromatography yielded the desired product **154**.

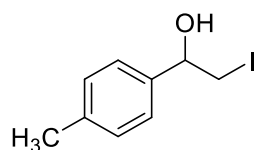
## 3.4 Characterization of products



### Compound 56: 2-iodo-1-phenylethan-1-ol

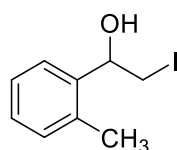
Synthesized from styrene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (10:1). Obtained as a pale-yellow oil (89.3 mg, 72 % yield). R<sub>f</sub> (in petroleum ether/ethyl acetate = 8/1): 0.31. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46-7.29 (m, 5H), 4.85 (dt, *J* = 8.7, 3.6 Hz, 1H), 3.50 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.41 (dd, *J* = 10.3, 8.8 Hz, 1H), 2.46 (d, *J* = 3.3 Hz, 1H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 141.2, 128.9,

128.6, 125.9, 74.2, 15.6. **HRMS** (AP<sup>+</sup>) m/z: [M+H-H<sub>2</sub>O] Calcd for C<sub>8</sub>H<sub>8</sub>I: 230.9671, Found: 230.9659 ( $\Delta$  = -5.2 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3421, 3029, 2981, 1709, 1452, 1373, 1242, 1173, 1044, 763, 698, 569, 497.



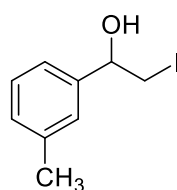
#### **Compound 57: 2-iodo-1-(p-tolyl)ethan-1-ol**

Synthesized from 1-methyl-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a yellow oil (97.4 mg, 75 % yield). R<sub>f</sub> (in petroleum ether/ethyl acetate = 8/1): 0.32. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.19-7.03 (m, 4H), 4.67 (dd, *J* = 8.4, 3.9 Hz, 1H), 3.34 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.27 (dd, *J* = 10.2, 8.5 Hz, 1H), 2.63 (s, 1H), 2.25 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  138.3, 138.2, 129.4, 125.7, 73.9, 21.3, 15.4. **HRMS** (AP<sup>+</sup>) m/z: [M+H-H<sub>2</sub>O] Calcd for C<sub>9</sub>H<sub>10</sub>I: 244.9827, Found: 244.9833 ( $\Delta$  = 2.4 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3454, 2974, 2921, 1711, 1672, 1605, 1274, 1171, 1087, 1007, 815, 607, 573, 497.



#### **Compound 58: 2-iodo-1-(o-tolyl)ethan-1-ol**

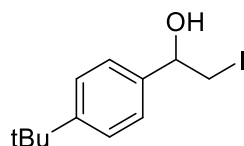
Synthesized from 1-methyl-2-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a colorless solid (93.9 mg, 72 % yield). R<sub>f</sub> (in petroleum ether/ethyl acetate = 8/1): 0.32. mp: 38-39 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.45-7.33 (m, 1H), 7.19-7.00 (m, 3H), 4.94 (dt, *J* = 9.0, 3.2 Hz, 1H), 3.32 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.20 (dd, *J* = 10.5, 9.3 Hz, 1H), 2.61 (d, *J* = 2.7 Hz, 1H), 2.22 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  139.3, 134.6, 130.7, 128.2, 126.5, 125.0, 71.1, 19.2, 13.8. **HRMS** (AP<sup>+</sup>) m/z: [M+H-H<sub>2</sub>O] Calcd for C<sub>9</sub>H<sub>10</sub>I: 244.9827, Found: 244.9839 ( $\Delta$  = 4.9 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3377, 3024, 2957, 1459, 1264, 1173, 1056, 907, 757, 726, 580, 452.



#### **Compound 59: 2-iodo-1-(m-tolyl)ethan-1-ol**

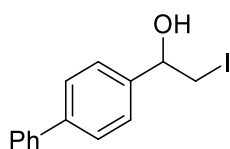
Synthesized from 1-methyl-3-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent)

and eluting with petroleum ether/ethyl acetate (15/1). Obtained as a colorless solid (95.5 mg, 73% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.30. mp: 43-44 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20-7.12 (m, 1H), 7.11-7.01 (m, 3H), 4.68 (dt,  $J = 8.7, 3.6$  Hz, 1H), 3.36 (dd,  $J = 10.2, 3.6$  Hz, 1H), 3.27 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.62 (d,  $J = 3.6$  Hz, 1H), 2.27 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.1, 138.5, 129.2, 128.7, 126.5, 122.9, 74.2, 21.6, 15.4. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}$ : 244.9827, Found: 244.9831 ( $\Delta = 1.6$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3241, 3140, 3028, 2909, 1412, 1337, 1157, 1060, 968, 778, 699, 584, 434.



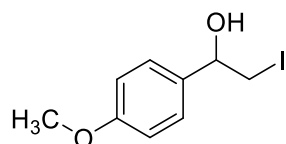
#### **Compound 60: 1-(4-(tert-butyl)phenyl)-2-iodoethan-1-ol**

Synthesized from 1-(tert-butyl)-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a yellow oil (120.0 mg, 79% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.35.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46-7.37 (m, 2H), 7.36-7.27 (m, 2H), 4.81 (dd,  $J = 8.7, 3.9$  Hz, 1H), 3.46 (dd,  $J = 10.2, 3.9$  Hz, 1H), 3.38 (dd,  $J = 10.3, 8.7$  Hz, 1H), 2.85 (s, 1H), 1.35 (s, 9H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  151.3, 138.2, 125.6, 125.6, 73.9, 34.6, 31.4, 15.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_{12}\text{H}_{16}\text{I}$ : 287.0297, Found: 287.0309 ( $\Delta = 4.2$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3453, 2962, 2869, 1712, 1674, 1605, 1407, 1363, 1269, 1239, 833, 601, 564.



#### **Compound 61: 1-([1,1'-biphenyl]-4-yl)-2-iodoethan-1-ol**

Synthesized from 4-vinyl-1,1'-biphenyl following general procedure **A** and purified by silica gel chromatography by dry loading and eluting with petroleum ether/ethyl acetate (12/1) after 5 h of electrolysis. Obtained as a white solid (74.3 mg, 46 % yield). mp: 84-85 °C.  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.29.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64-7.56 (m, 4H), 7.49-7.41 (m, 4H), 7.40-7.32 (m, 1H), 4.90 (dt,  $J = 8.7, 3.6$  Hz, 1H), 3.54 (dd,  $J = 10.2, 3.6$  Hz, 1H), 3.45 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.50 (d,  $J = 3.6$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.5, 140.7, 140.2, 129.0, 127.6, 127.6, 127.2, 126.3, 74.0, 15.4. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_{14}\text{H}_{12}$ : 306.9984, Found: 306.9995 ( $\Delta = 3.6$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3320, 3027, 2951, 1486, 1401, 1173, 1057, 841, 764, 733, 692, 632, 578, 486.

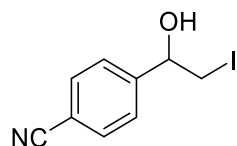



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**Compound 62: 2-iodo-1-(4-methoxyphenyl)ethan-1-ol**


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Synthesized from 1-methoxy-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a yellow solid (85.5 mg, 62 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.35. mp: 45-57 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.21 (m, 2H), 6.97-6.82 (m, 2H), 4.79 (dt,  $J = 8.4, 3.3$  Hz, 1H), 3.80 (s, 3H), 3.45 (dd,  $J = 10.2, 3.9$  Hz, 1H), 3.38 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.53 (d,  $J = 2.7$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  159.6, 133.4, 127.1, 114.1, 73.8, 55.4, 15.6. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}\text{OI}$ : 260.9776, Found: 260.9770 ( $\Delta = -2.3$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3551, 2961, 2876, 1602, 1505, 1303, 1240, 1168, 1051, 1028, 829, 757, 569, 520.

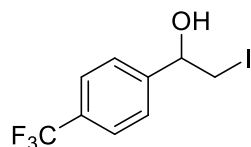



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**Compound 63: 4-(1-hydroxy-2-iodoethyl)benzonitrile**


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Synthesized from 4-vinylbenzonitrile following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (10/1) after 4 h of electrolysis. Obtained as a yellow solid (51.1 mg, 37% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.19. mp: 93-95 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69-7.59 (m, 2H), 7.54-7.44 (m, 2H), 4.85 (dd,  $J = 8.1, 3.9$  Hz, 1H), 3.49 (dd,  $J = 10.5, 3.9$  Hz, 1H), 3.35 (dd,  $J = 10.5, 8.1$  Hz, 1H), 2.90 (brs, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  146.5, 132.5, 126.7, 118.7, 112.0, 73.0, 14.3. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}+\text{ACN}]$  Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{OI}$ : 314.9994, Found: 314.9987 ( $\Delta = -2.2$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3505, 3040, 2891, 2225, 1680, 1604, 1499, 1410, 1268, 1187, 1056, 837, 596, 450.



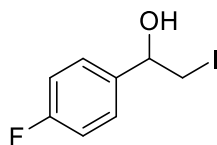

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**Compound 64: 2-iodo-1-(4-(trifluoromethyl)phenyl)ethan-1-ol**


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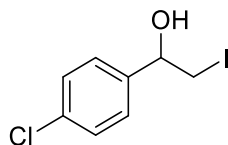
Synthesized from 1-(trifluoromethyl)-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a white solid (121.5 mg, 77 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.29. mp: 40-41 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d,  $J = 8.1$  Hz, 2H), 7.48 (d,  $J = 8.1$  Hz, 2H), 4.93-4.76 (m, 1H), 3.49 (dd,  $J = 10.5, 3.6$  Hz, 1H), 3.36 (dd,  $J = 10.5, 8.4$  Hz, 1H), 2.92 (brs,

1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  145.1 (q,  $J = 1.5$  Hz), 130.5 (q,  $J = 32.5$  Hz), 126.3, 125.7 (q,  $J = 3.8$  Hz), 124.1 (q,  $J = 272.5$  Hz), 73.3, 14.7.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.6. HRMS (AP<sup>+</sup>)  $m/z$ : [M+H-H<sub>2</sub>O] Calcd for  $\text{C}_9\text{H}_7\text{F}_3$ : 298.9545, Found: 298.9554 ( $\Delta = 3.0$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3253, 2954, 1620, 1419, 1320, 1165, 1105, 1062, 1015, 833, 607, 438.



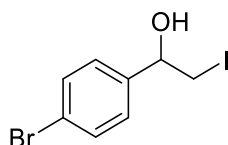
#### Compound 65: 1-(4-fluorophenyl)-2-iodoethan-1-ol

Synthesized from 1-fluoro-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a colorless oil (118.9 mg, 90% yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.33.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.27 (m, 2H), 7.11-6.99 (m, 2H), 4.88-4.71 (m, 1H), 3.44 (dd,  $J = 10.2, 3.9$  Hz, 1H), 3.35 (dd,  $J = 10.2, 8.4$  Hz, 1H), 2.71 (d,  $J = 3.3$  Hz, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (d,  $J = 246.9$  Hz), 137.0 (d,  $J = 3.0$  Hz), 127.6 (d,  $J = 8.3$  Hz), 115.7 (d,  $J = 21.9$  Hz), 73.4, 15.3.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.0. HRMS (AP<sup>+</sup>)  $m/z$ : [M+H-H<sub>2</sub>O] Calcd for  $\text{C}_8\text{H}_7\text{IF}$ : 248.9577, Found: 248.9580 ( $\Delta = 1.2$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3417, 2982, 1708, 1603, 1508, 1374, 1221, 1044, 835, 608, 553, 508.



#### Compound 66: 1-(4-chlorophenyl)-2-iodoethan-1-ol

Synthesized from 1-chloro-4-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (14/1). Obtained as yellowish solid (90.5 mg, 65 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.37. mp: 73-74 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.28 (m, 4H), 4.81 (dt,  $J = 8.7, 3.6$  Hz, 1H), 3.47 (dd,  $J = 10.5, 3.7$  Hz, 1H), 3.36 (dd,  $J = 10.5, 8.7$  Hz, 1H), 2.48 (d,  $J = 3.6$  Hz, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  139.7, 134.2, 129.0, 127.3, 73.4, 15.3. HRMS (AP<sup>+</sup>)  $m/z$ : [M+H-H<sub>2</sub>O] Calcd for  $\text{C}_8\text{H}_7\text{I}^{35}\text{Cl}$ : 264.9281, Found: 264.9283 ( $\Delta = 0.8$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3283, 2918, 1594, 1487, 1402, 1170, 1088, 1063, 968, 808, 721, 644, 586, 495, 440.

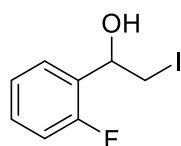


#### Compound 67: 1-(4-bromophenyl)-2-iodoethan-1-ol

Synthesized from 1-bromo-4-vinylbenzene following general procedure **A** and purified

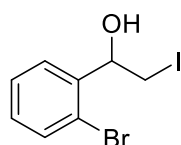


by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (10/1). Obtained as a yellow solid (123.3 mg, 76 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.28. mp: 87-89 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58-7.47 (m, 2H), 7.33-7.21 (m, 2H), 4.81 (dt,  $J = 8.7, 3.7$  Hz, 1H), 3.48 (dd,  $J = 10.2, 3.7$  Hz, 1H), 3.37 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.53 (d,  $J = 3.9$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.2, 131.9, 127.6, 122.4, 73.4, 15.1. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_8\text{H}_7^{79}\text{BrI}$ : 308.8776, Found: 308.8790 ( $\Delta = 4.5$  ppm); Calcd for  $\text{C}_8\text{H}_7^{81}\text{BrI}$ : 310.8755, Found: 310.8760 ( $\Delta = 1.6$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3331, 3262, 2921, 1682, 1587, 1483, 1409, 1173, 1063, 1008, 804, 640, 510, 424.



#### **Compound 68: 1-(2-fluorophenyl)-2-iodoethan-1-ol**

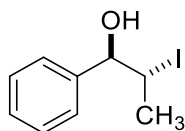
Synthesized from 1-fluoro-2-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (15/1). Obtained as a colorless oil (93.0 mg, 70 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (td,  $J = 7.5, 1.8$  Hz, 1H), 7.29-7.15 (m, 1H), 7.09 (td,  $J = 7.5, 1.2$  Hz, 1H), 7.01-6.88 (m, 1H), 5.06-4.94 (m, 1H), 3.48 (dd,  $J = 10.2, 3.6$  Hz, 1H), 3.31 (dd,  $J = 10.2, 8.1$  Hz, 1H), 2.68 (d,  $J = 4.5$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  159.6 (d,  $J = 246.1$  Hz), 129.8 (d,  $J = 8.3$  Hz), 128.3 (d,  $J = 12.8$  Hz), 127.3 (d,  $J = 4.5$  Hz), 124.5 (d,  $J = 3.8$  Hz), 115.5 (d,  $J = 21.9$  Hz), 68.1 (d,  $J = 3.0$  Hz), 14.0.  $^{19}\text{F}\{^1\text{H}\}$  **NMR** (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -119.0. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_8\text{H}_7\text{FI}$ : 248.9577, Found: 248.9585 ( $\Delta = 3.2$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3148, 2925, 1585, 1486, 1454, 1220, 1173, 1064, 967, 751, 514, 468.



#### **Compound 69: 1-(2-bromophenyl)-2-iodoethan-1-ol**

Synthesized from 1-bromo-2-vinylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a white solid (93.0 mg, 61 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.33. mp: 60-62 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (ddd,  $J = 21.9, 7.8, 1.5$  Hz, 2H), 7.35 (td,  $J = 7.8, 1.2$  Hz, 1H), 7.18 (td,  $J = 7.8, 1.8$  Hz, 1H), 5.12 (d,  $J = 8.4$  Hz, 1H), 3.63 (dd,  $J = 10.2, 2.7$  Hz, 1H), 3.27 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.78 (s, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.2, 132.9, 129.7, 127.9, 127.3, 121.9, 72.8, 13.6. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_8\text{H}_7^{79}\text{BrI}$ : 308.8776, Found: 308.8779 ( $\Delta = 1.0$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3290, 2981, 1733, 1567,

1464, 1241, 1175, 1045, 969, 750, 675, 563, 439.

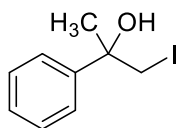


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**Compound 70: anti-2-iodo-1-phenylpropan-1-ol**

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Synthesized from (Z)-prop-1-en-1-ylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a colorless oil (88.6 mg, 68 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.30.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41-7.28 (m, 5H), 4.48-4.33 (m, 2H), 2.65 (brs, 1H), 1.86-1.74 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1, 128.7, 128.4, 126.4, 79.7, 39.0, 25.5. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}\text{I}$ : 244.9827, Found: 244.9828 ( $\Delta = 0.4$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3424, 3028, 2971, 1675, 1596, 1448, 1270, 1226, 1066, 761, 698, 571, 480.

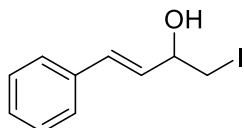


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**Compound 71: 1-iodo-2-phenylpropan-2-ol**

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Synthesized from prop-1-en-2-ylbenzene following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (16/1). Obtained as a colorless liquid (84.6 mg, 65 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.6.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41-7.16 (m, 5H), 3.61-3.50 (m, 2H), 2.33 (s, 1H), 1.65 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  144.4, 128.6, 127.6, 124.8, 72.8, 29.1, 24.4. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}\text{I}$ : 244.9827, Found: 244.9837 ( $\Delta = 4.1$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3444, 3059, 2977, 1723, 1445, 1373, 1177, 1059, 1025, 762, 697, 569.



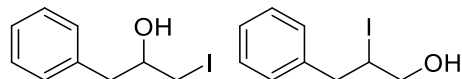
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**Compound 72: 1-iodo-4-phenylbut-3-en-2-ol**

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Synthesized from (E)-buta-1,3-dien-1-ylbenzene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a brown liquid (67 %  $^1\text{H NMR}$  yield, 20 % isolated yield, 26.2 mg).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.29. Product is very sensitive to light and partially decomposed in the column.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.12 (m, 5H), 6.62 (d,  $J = 16.5$  Hz, 1H), 6.11 (dd,  $J = 15.9, 6.3$  Hz, 1H), 4.39-4.17 (m, 1H), 3.36 (dd,  $J = 10.2, 3.9$  Hz, 1H), 3.25 (dd,  $J = 10.2, 3.9$  Hz, 1H).

= 10.2, 7.2 Hz, 1H), 2.17 (d,  $J = 4.5$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  136.2, 132.5, 129.0, 128.8, 128.3, 126.8, 72.0, 14.8. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_{10}\text{H}_{10}\text{I}$ : 256.9827, Found: 256.9837 ( $\Delta = 3.9$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3429, 3028, 2923, 1677, 1604, 1449, 1330, 1268, 1179, 1044, 965, 692, 748, 552, 454.

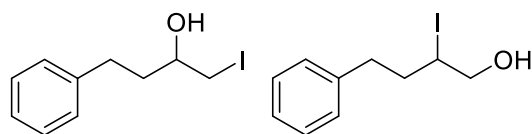


### Compound 89 & 89': 1-iodo-3-phenylpropan-2-ol & 2-iodo-3-phenylpropan-1-ol

Synthesized from allylbenzene following general procedure **A**. **89** and **89'** were obtained as a mixture of regioisomers with a 62:38 ratio observed with the crude NMR and a 66:34 ratio after purification by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Both regioisomers were separated as single pure products.

**1-iodo-3-phenylpropan-2-ol 89** was obtained as a colorless oil (46.7 mg, 36 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.34.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30-7.09 (m, 5H), 3.73-3.59 (m, 1H), 3.28 (dd,  $J = 10.2, 4.2$  Hz, 1H), 3.13 (dd,  $J = 10.2, 6.3$  Hz, 1H), 2.80 (d,  $J = 6.6$  Hz, 2H), 2.08 (d,  $J = 5.1$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  137.2, 129.4, 128.8, 127.0, 71.9, 42.9, 15.1. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}\text{I}$ : 244.9827, Found: 244.9837 ( $\Delta = 4.1$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3406, 3026, 2918, 1495, 1453, 1177, 1079, 1010, 739, 698, 496, 451.

**2-iodo-3-phenylpropan-1-ol 89'** was obtained as a colorless oil (24.1 mg, 18 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.25.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.08 (m, 5H), 4.41-4.27 (m, 1H), 3.73-3.56 (m, 2H), 3.32-3.09 (m, 2H), 1.96 (brs, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  139.1, 129.1, 128.7, 127.1, 67.4, 43.1, 40.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_{10}\text{I}$ : 244.9827, Found: 244.9821 ( $\Delta = -2.4$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3388, 3062, 2925, 1724, 1495, 1453, 1242, 1041, 908, 731, 697, 487.



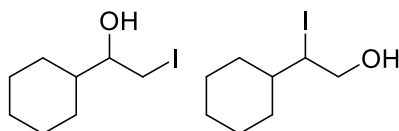
### Compound 90 & 90': 1-iodo-4-phenylbutan-2-ol & 2-iodo-4-phenylbutan-1-ol

Synthesized from but-3-en-1-ylbenzene following general procedure **A**. **90** and **90'** were obtained as a mixture of regioisomers with a 60:40 ratio observed with the crude NMR and a 62:38 ratio after purification by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Both regioisomers were separated as single pure products.

**1-iodo-4-phenylbutan-2-ol 90** was obtained as a colorless solid (36.7 mg, 27 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.31. mp: 48-50 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27-7.18 (m, 2H), 7.17-7.07 (m, 3H), 3.54-3.38 (m, 1H), 3.30 (dd,  $J = 10.2, 3.6$

Hz, 1H), 3.17 (dd,  $J = 10.2, 6.9$  Hz, 1H), 2.80-2.56 (m, 2H), 2.00 (brs, 1H), 1.86-1.73 (m, 2H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  141.4, 128.6, 128.6, 126.2, 70.3, 38.3, 32.0, 16.7. **HRMS** ( $\text{AP}^+$ )  $m/z$ : [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ] Calcd for  $\text{C}_{10}\text{H}_{12}\text{I}$ : 258.9984, Found: 258.9989 ( $\Delta = 1.9$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3325, 3028, 2924, 2858, 1602, 1493, 1451, 1251, 1181, 1074, 918, 748, 698, 613, 502.

**2-iodo-4-phenylbutan-1-ol 90'** was obtained as a colorless oil (22.5 mg, 16 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.22.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.17 (m, 2H), 7.17-7.09 (m, 3H), 4.14-3.99 (m, 1H), 3.78-3.54 (m, 2H), 2.92-2.77 (m, 1H), 2.72-2.56 (m, 1H), 2.20-1.91 (m, 2H), 1.91-1.82 (m, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.6, 128.7, 128.7, 126.4, 68.7, 40.9, 37.9, 35.4. **HRMS** ( $\text{AP}^+$ )  $m/z$ : [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ] Calcd for  $\text{C}_{10}\text{H}_{12}\text{I}$ : 258.9984, Found: 258.9980 ( $\Delta = -1.5$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3354, 3025, 2923, 2856, 1495, 1453, 1006, 746, 697, 464.

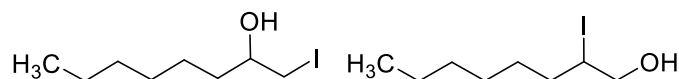


#### **Compound 91 & 91': 1-cyclohexyl-2-iodoethan-1-ol & 2-cyclohexyl-2-iodoethan-1-ol**

Synthesized from vinylcyclohexane following general procedure **A** and purified by silica gel chromatography by dry loading and eluting with petroleum ether/ethyl acetate (10/1). **91** and **91'** were obtained with a 47:53 ratio after purification. Both regioisomers were separated as single pure products.

**1-cyclohexyl-2-iodoethan-1-ol 91** was obtained as a colorless oil (24.6 mg, 20 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.29.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.45 (dd,  $J = 9.9, 2.7$  Hz, 1H), 3.30 (dd,  $J = 9.9, 7.2$  Hz, 1H), 3.26-3.17 (m, 1H), 2.02-1.86 (m, 2H), 1.82-1.70 (m, 2H), 1.70-1.58 (m, 2H), 1.55-1.37 (m, 1H), 1.36-0.94 (m, 5H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  75.3, 43.4, 29.2, 28.3, 26.4, 26.1, 26.0, 15.7. **HRMS** ( $\text{AP}^+$ )  $m/z$ : [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ] Calcd for  $\text{C}_8\text{H}_{14}\text{I}$ : 237.0140, Found: 237.0137 ( $\Delta = -1.3$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3393, 2921, 2850, 1448, 1177, 1093, 1029, 977, 892, 551, 469.

**2-cyclohexyl-2-iodoethan-1-ol 91'** was obtained as a colorless oil (28.5 mg, 23 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.20.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.30-4.15 (m, 1H), 3.94-3.81 (m, 1H), 3.80-3.64 (m, 1H), 2.02 (brs, 1H), 1.88-1.59 (m, 5H), 1.40-1.06 (m, 6H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  66.7, 52.1, 41.5, 32.6, 32.3, 26.3, 26.1, 26.1. **HRMS** ( $\text{AP}^+$ )  $m/z$ : [ $\text{M}+\text{H}-\text{H}_2\text{O}$ ] Calcd for  $\text{C}_8\text{H}_{14}\text{I}$ : 237.0140, Found: 237.0134 ( $\Delta = -2.5$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3335, 2922, 2851, 1447, 1235, 1123, 1057, 1007, 874, 628, 563, 527.

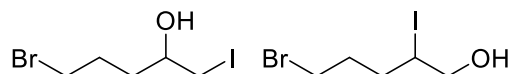


#### **Compound 92 & 92': 1-iodooctan-2-ol & 2-iodooctan-1-ol**

Synthesized from oct-1-ene following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (20/1). **92** and **92'** were obtained with a 80:20 ratio after purification. Both regioisomers were separated as single pure products.

**1-iodooctan-2-ol 92** was obtained as a colorless oil (65.6 mg, 52 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 15/1): 0.28.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.56-3.43 (m, 1H), 3.38 (dd,  $J = 10.2, 3.3$  Hz, 1H), 3.22 (dd,  $J = 10.2, 6.6$  Hz, 1H), 2.09 (brs, 1H), 1.60-1.47 (m, 2H), 1.46-1.21 (m, 8H), 0.93-0.81 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  71.1, 36.7, 31.8, 29.2, 25.7, 22.7, 16.9, 14.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_8\text{H}_{16}\text{I}$ : 239.0297, Found: 239.0300 ( $\Delta = 1.3$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3372, 2954, 2925, 2855, 1458, 1180, 1022, 621.

**2-iodooctan-1-ol 92'** was obtained as a colorless oil (16.6 mg, 13 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 15/1): 0.38.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.29-4.15 (m, 1H), 3.80-3.62 (m, 2H), 2.00 (t,  $J = 6.9$  Hz, 1H), 1.94-1.67 (m, 2H), 1.60-1.46 (m, 1H), 1.44-1.21 (m, 7H), 0.94-0.83 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  68.7, 42.3, 36.4, 31.7, 29.5, 28.6, 22.7, 14.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_8\text{H}_{16}\text{I}$ : 239.0297, Found: 239.0306 ( $\Delta = 3.8$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3336, 2954, 2924, 2855, 1457, 1010, 606.



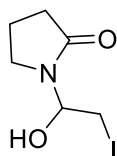
#### **Compound 93 & 93': 5-bromo-1-iodopentane-2-ol & 5-bromo-2-iodopentane-1-ol**

Synthesized from 5-bromopent-1-ene following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (10/1). **93** and **93'** were obtained with a 72:28 ratio after purification. Both regioisomers were separated as single pure products.

**5-bromo-1-iodopentane-2-ol 93** was obtained as a colorless oil (71.1 mg, 49 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.35.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.63-3.52 (m, 1H), 3.44 (t,  $J = 6.6$  Hz, 2H), 3.37 (dd,  $J = 10.2, 3.6$  Hz, 1H), 3.23 (dd,  $J = 10.2, 6.9$  Hz, 1H), 2.15 (s, 1H), 2.11-1.84 (m, 2H), 1.84-1.55 (m, 2H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  70.4, 35.0, 33.6, 29.0, 16.3. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_5\text{H}_9^{79}\text{Br I}$ : 274.8932, Found: 274.8941 ( $\Delta = 3.3$  ppm); Calcd for  $\text{C}_5\text{H}_9^{81}\text{Br I}$ : 276.8912, Found: 276.8909 ( $\Delta = -1.1$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3274, 2949, 2870, 1073, 1436, 1245, 1181, 1026, 921, 607, 557.

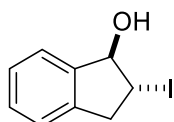
**5-bromo-2-iodopentane-1-ol 93'** was obtained as a colorless oil (27.5 mg, 19 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.27.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.26-4.12 (m, 1H), 3.86-3.66 (m, 2H), 3.54-3.34 (m, 2H), 2.24-1.85 (m, 5H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  68.6, 39.4, 34.6, 32.6, 32.5. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_5\text{H}_9^{79}\text{Br I}$ : 274.8932, Found: 274.8936 ( $\Delta = 1.5$  ppm); Calcd for  $\text{C}_5\text{H}_9^{81}\text{Br I}$ : 276.8912 ( $\Delta$

= 3.6 ppm), Found: 276.8922. **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3389, 2963, 2866, 1708, 1438, 1373, 1254, 1043, 1012, 605, 559.



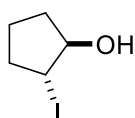
**Compound 94: 1-(1-hydroxy-2-iodoethyl)pyrrolidin-2-one**

Synthesized from 1-vinylpyrrolidin-2-one following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (1/1). Obtained as a colorless oil (24.9 mg, 20 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 1/1): 0.12.  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.72-5.47 (m, 1H), 5.10 (d,  $J$  = 4.8 Hz, 1H), 3.67-3.50 (m, 1H), 3.47-3.32 (m, 2H), 3.24 (dd,  $J$  = 10.2, 8.1 Hz, 1H), 2.54-2.30 (m, 2H), 2.14-1.99 (m, 2H).  **$^{13}\text{C NMR}$**  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  176.7, 75.5, 41.8, 31.8, 18.2, 5.0. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_6\text{H}_9\text{NOI}$ : 237.9729, Found: 237.9723 ( $\Delta$  = -2.5 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3292, 2957, 1660, 1460, 1419, 1287, 1219, 1035, 647, 470.



**Compound 95: anti-2-iodo-2,3-dihydro-1H-inden-1-ol**

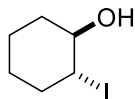
Synthesized from 1H-indene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (10/1) after 4 h of electrolysis. Obtained as a white solid (82.9 mg, 64 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.19. mp: 165-167 °C (degradation observed).  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46-7.39 (m, 1H), 7.33-7.27 (m, 2H), 7.26-7.20 (m, 1H), 5.40 (t,  $J$  = 6.3 Hz, 1H), 4.28-4.13 (m, 1H), 3.59 (dd,  $J$  = 16.2, 7.2 Hz, 1H), 3.31 (dd,  $J$  = 16.2, 8.1 Hz, 1H), 2.40 (d,  $J$  = 6.0 Hz, 1H).  **$^{13}\text{C NMR}$**  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  142.1, 141.0, 128.8, 127.5, 124.3, 123.9, 85.0, 42.3, 30.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_9\text{H}_8\text{I}$ : 242.9671, Found: 242.9661 ( $\Delta$  = -4.1 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3019, 2913, 2846, 1601, 1476, 1457, 1152, 1023, 742, 555, 419.



**Compound 96: anti-2-iodocyclopentan-1-ol**

Synthesized from cyclopentene following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a yellow liquid (28.8 mg, 28 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.31.  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.49-4.39 (m, 1H), 4.09-3.98 (m, 1H), 2.45-2.28 (m, 1H), 2.22-1.97 (m, 3H), 1.89-1.74

(m, 2H), 1.65-1.51 (m, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  82.3, 35.7, 34.3, 31.1, 22.2. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_5\text{H}_8\text{I}$ : 194.9671, Found: 194.9667 ( $\Delta = -2.1$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3326, 2964, 2872, 1663, 1436, 1332, 1168, 1108, 1065, 1031, 977, 838, 587, 418.

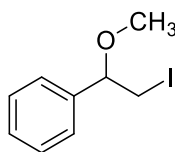



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**Compound 97: anti-2-iodocyclohexan-1-ol**

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Synthesized from cyclohexene following general procedure **A** and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Obtained as a colorless liquid (34.7 mg, 31 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.40.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.10-3.97 (m, 1H), 3.77-3.52 (m, 1H), 2.57-2.40 (m, 1H), 2.35 (d,  $J = 2.7$  Hz, 1H), 2.19-1.94 (m, 2H), 1.91-1.78 (m, 1H), 1.57-1.45 (m, 1H), 1.44-1.17 (m, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  76.1, 43.6, 38.7, 33.8, 28.1, 24.6. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{H}_2\text{O}]$  Calcd for  $\text{C}_6\text{H}_{10}\text{I}$ : 208.9827, Found: 208.9823 ( $\Delta = -1.9$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3380, 2932, 2856, 1723, 1446, 1353, 1248, 1160, 1063, 1032, 950, 858, 656, 552.

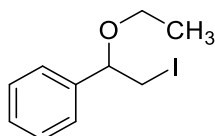



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**Compound 101: (2-iodo-1-methoxyethyl)benzene**

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Synthesized from styrene following general procedure **B** using solvent  $\text{CH}_3\text{CN}/\text{CH}_3\text{OH} = 4$  mL/1 mL and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (20/1). Obtained as a pale-yellow oil (71.2 mg, 52 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.66.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47-7.27 (m, 5H), 4.35-4.25 (m, 1H), 3.40-3.32 (m, 2H), 3.31 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  139.8, 128.8, 128.5, 126.6, 83.6, 57.4, 10.6. **HRMS** ( $\text{AP}^+$ )  $m/z$ :  $[\text{M}+\text{H}-\text{CH}_3\text{OH}]$  Calcd for  $\text{C}_8\text{H}_8\text{I}$ : 230.9671, Found: 230.9677 ( $\Delta = 2.6$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3028, 2931, 2823, 1492, 1452, 1173, 1106, 953, 762, 698, 579, 505.



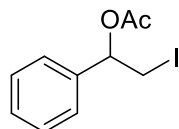

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**Compound 102: 1-ethoxy-2-iodoethylbenzene**

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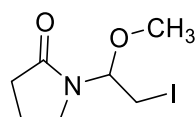
Synthesized from styrene following general procedure **B** using solvent  $\text{CH}_3\text{CN}/\text{C}_2\text{H}_5\text{OH} = 4$  mL/1 mL and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (20/1). Obtained as a light yellow oil (112.0 mg, 78 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.28 (m, 5H), 4.42 (dd,  $J = 7.8, 5.4$  Hz, 1H), 3.57-3.39 (m, 2H), 3.38-3.29 (m, 2H),

1.24 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.6, 128.7, 128.4, 126.6, 81.9, 65.1, 15.3, 11.0. HRMS (AP<sup>+</sup>)  $m/z$ : [M+H-C<sub>2</sub>H<sub>5</sub>OH] Calcd for C<sub>8</sub>H<sub>8</sub>I: 230.9671, Found: 230.9673 ( $\Delta = 0.9$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3028, 2974, 2870, 1452, 1171, 1114, 1090, 760, 698, 581, 498.



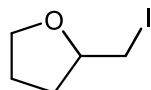
#### Compound 103: 2-iodo-1-phenylethyl acetate

Synthesized from styrene following general procedure **B** using solvent  $\text{CH}_3\text{CN}/\text{AcOH} = 4$  mL/1 mL and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (12/1). Obtained as a colorless oil (27.0 mg, 19 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.60.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.30 (m, 5H), 5.88 (dd,  $J = 7.5, 5.7$  Hz, 1H), 3.53-3.42 (m, 2H), 2.14 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 138.6, 128.9, 128.8, 126.5, 75.3, 21.2, 7.9. HRMS (EI<sup>+</sup>)  $m/z$ : [M] Calcd for C<sub>10</sub>H<sub>11</sub>IO<sub>2</sub>: 289.98037, Found: 289.98034 ( $\Delta = -0.11$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3033, 1739, 1370, 1226, 1206, 1046, 1016, 955, 752, 697, 600.



#### Compound 104: 1-(2-iodo-1-methoxyethyl)pyrrolidin-2-one

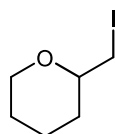
Synthesized from 1-vinylpyrrolidin-2-one following general procedure **B** using solvent  $\text{CH}_3\text{CN}/\text{CH}_3\text{OH} = 4$  mL/1 mL and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (1/1). Obtained as a colorless oil (31.0 mg, 24 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 1/1): 0.19.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.36-5.26 (m, 1H), 3.37-3.29 (m, 3H), 3.28 (s, 3H), 3.12 (dd,  $J = 10.5, 7.8$  Hz, 1H), 2.52-2.39 (m, 2H), 2.15-1.96 (m, 2H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  176.5, 82.2, 56.5, 40.5, 31.4, 18.3, 2.8. HRMS (ES<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>7</sub>H<sub>13</sub>NO<sub>2</sub>I: 269.9991, Found: 269.9991 ( $\Delta = 0.0$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  2934, 2828, 1687, 1459, 1411, 1267, 1069, 942, 625, 569, 514.



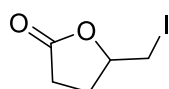
#### Compound 105: 2-(iodomethyl)tetrahydrofuran

Synthesized from pent-4-en-1-ol following general procedure **A** and purified by silica gel flash chromatography and eluting with petroleum ether/ethyl acetate (10:1). Obtained as a yellow oil (31.3 mg, 30 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.65.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.08 – 3.89 (m, 2H), 3.89 – 3.75 (m, 1H), 3.32 – 3.13 (m, 2H), 2.18 – 2.04 (m, 1H), 2.04 – 1.83 (m, 2H), 1.74 – 1.58 (m, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  78.6, 69.1, 32.0, 26.2, 10.5.

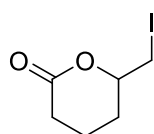



**Compound 106: 2-(iodomethyl)tetrahydro-2H-pyran**

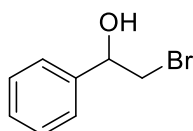
Synthesized from pent-4-en-1-ol following general procedure **A** and purified by silica gel flash chromatography and eluting with petroleum ether/ethyl acetate (15:1). Obtained as a yellow oil (20.8 mg, 18 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8:1): 0.85.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.07 – 3.98 (m, 1H), 3.53 – 3.41 (m, 1H), 3.35 – 3.24 (m, 1H), 3.22 – 3.10 (m, 2H), 1.94 – 1.73 (m, 2H), 1.62 – 1.41 (m, 3H), 1.38 – 1.22 (m, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  77.1, 68.9, 31.8, 25.7, 23.3, 10.2.


**Compound 107: 5-(iodomethyl)dihydrofuran-2(3H)-one**

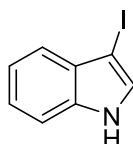
Synthesized from pent-4-enoic acid following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (1:1). Obtained as a yellow oil (95.7 mg, 85 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 1/1): 0.45.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.61-4.43 (m, 1H), 3.37 (dd,  $J = 10.5, 4.5$  Hz, 1H), 3.29 (dd,  $J = 10.5, 6.9$  Hz, 1H), 2.69-2.36 (m, 3H), 2.04-1.88 (m, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  176.2, 78.4, 28.9, 28.1, 7.7. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_5\text{H}_7\text{IO}_2$ : 225.94907, Found: 225.94826 ( $\Delta = -3.57$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  2954, 1763, 1334, 1152, 1011, 979, 907, 609, 496.


**Compound 108: 5-(iodomethyl)tetrahydro-2H-pyran-2-one**

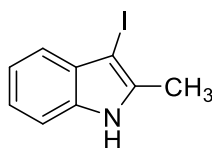
Synthesized from hex-5-enoic acid following general procedure **A** and purified by silica gel flash chromatography by wet loading (use dichloromethane as solvent) and eluting with petroleum ether/ethyl acetate (1/1). Obtained as a colorless oil (107 mg, 89 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 1/1): 0.46.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.30-4.16 (m, 1H), 3.35-3.21 (m, 2H), 2.59-2.47 (m, 1H), 2.45-2.31 (m, 1H), 2.16-2.03 (m, 1H), 1.98-1.74 (m, 2H), 1.67-1.49 (m, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 78.6, 29.2, 27.9, 18.0, 7.8. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_6\text{H}_9\text{IO}_2$ : 239.96472, Found: 239.96553 ( $\Delta = 3.37$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  2959, 1715, 1370, 1328, 1246, 1206, 1174, 1074, 1052, 1029, 930, 825, 602, 427.

**Compound 110: 2-bromo-1-phenylethan-1-ol**

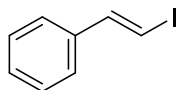
Synthesized from styrene following general procedure **A**, using  $\text{NH}_4\text{Br}$  as reagent and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Obtained as a yellow oil (65.8 mg, 66 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 8/1): 0.50.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47-7.28 (m, 5H), 4.91 (dd,  $J = 8.7, 3.6$  Hz, 1H), 3.63 (dd,  $J = 10.2, 3.6$  Hz, 1H), 3.53 (dd,  $J = 10.2, 8.7$  Hz, 1H), 2.89 (brs, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  140.4, 128.8, 128.6, 126.1, 73.9, 40.3. **HRMS** ( $\text{EI}^+$ )  $m/z$ : [M] Calcd for  $\text{C}_8\text{H}_9\text{BrO}$ : 199.9837, Found: 199.9836 ( $\Delta = -0.52$  ppm); Calcd for  $\text{C}_8\text{H}_9^{81}\text{BrO}$ : 201.9816, Found: 201.9815 ( $\Delta = -0.56$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3390, 3030, 1453, 1215, 1196, 1058, 987, 753, 698, 590, 511.

**Compound 112: 3-iodo-1H-indole**

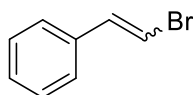
Synthesized from 1H-indole following general procedure **C** and purified by silica gel chromatography by dry loading and eluting with pentane/ethyl acetate (5/1). Obtained as a white solid (89.2 mg, 74 % yield,). mp: 78 – 79 °C (degradation observed).  $R_f$  (in pentane/ethyl acetate 5/1): 0.52.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (brs, 1H), 7.53-7.42 (m, 1H), 7.42-7.32 (m, 1H), 7.32-7.17 (m, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  135.7, 129.9, 128.5, 123.3, 121.1, 121.0, 111.4, 57.7. LC-MS ( $\text{ESI}^+$ )  $m/z$ : [M+H] 243.0. **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3384, 3053, 1451, 1236, 1083, 958, 811, 738, 598, 503, 422.

**Compound 113: 3-iodo-2-methyl-1H-indole**

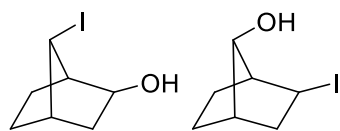
Synthesized from 2-methyl-1H-indole following general procedure **C** and purified by silica gel chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Obtained as pale-yellow solid (57.7 mg, 45 % yield,). mp: 75 – 76 °C (degradation observed).  $R_f$  (in petroleum ether/ethyl acetate 8/1): 0.50.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (s, 1H), 7.46-7.35 (m, 1H), 7.25-7.17 (m, 3H), 2.43 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  136.5, 136.0, 130.8, 122.4, 120.6, 120.3, 110.8, 59.0, 14.5. LC-MS ( $\text{ESI}^+$ )  $m/z$ : [M+H] 258.1. **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3387, 3053, 2907, 1614, 1451, 1290, 1215, 1042, 738, 619, 475, 431.


**Compound 114: (E)-(2-iodovinyl)benzene**

Synthesized either from (E)-styrylboronic acid, (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane or (E)-dimethyl(phenyl)(styryl)silane following general procedure C and purified by silica gel chromatography by dry loading and eluting with petroleum ether/ethyl acetate (15/1). Obtained as a yellow liquid (73.6 mg, 64 % yield from (E)-styrylboronic acid; 75.0 mg, 65% yield from (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane and 64.3 mg, 56% yield from (E)-dimethyl(phenyl)(styryl)silane).  $R_f$  (in petroleum ether/ethyl acetate 8/1): 0.80.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J = 14.7$  Hz, 1H), 7.28-7.12 (m, 5H), 6.72 (d,  $J = 14.7$  Hz, 1H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  145.0, 137.7, 128.8, 128.5, 126.1, 76.7. HRMS (EI+)  $m/z$ : [M] Calcd for  $\text{C}_8\text{H}_7\text{I}$ : 229.95924, Found: 229.95851 ( $\Delta = -3.18$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3058, 1734, 1595, 1568, 1444, 1210, 1169, 944, 724, 686, 549, 486.


**Compound 115: (E)-2-bromovinylbenzene**

Synthesized from (E)-styrylboronic acid, following general procedure C and purified by silica gel flash chromatography by dry loading and eluting with petroleum ether/ethyl acetate (30/1). Obtained as a yellow liquid as a mixture of Z and E stereoisomers, Z:E ratio = 15:85, (17.4 mg, 19 % yield).  $R_f$  (in petroleum ether/ethyl acetate 8/1): 0.90.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79-7.70 (m, 0.35H, Z isomer), 7.47-7.28 (m, E isomer 5H, Z isomer 0.72H), 7.18-7.07 (m, E isomer 1H, Z isomer 0.17 H), 6.47 (d,  $J = 8.2$  Hz, 1H, Z isomer).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  137.2 (E isomer), 136.0 (E isomer), 135.0 (Z isomer), 132.4 (Z isomer), 129.1 (Z isomer), 128.9 (E isomer), 128.4 (Z isomer), 128.4 (E isomer), 128.3 (Z isomer), 126.2 (E isomer), 106.6 (E isomer), 106.5 (Z isomer). HRMS (EI+)  $m/z$ : [M] Calcd for  $\text{C}_8\text{H}_7\text{Br}$ : 181.9731, Found: 181.9734 ( $\Delta = 1.6$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3075, 3024, 1606, 1495, 1444, 1221, 937, 728, 688, 564, 491, 391.

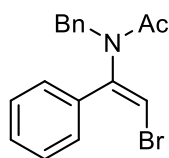

**Compound 120 & 121: 7-iodobicyclo[2.2.1]heptan-2-ol & 2-iodobicyclo[2.2.1]heptan-7-ol**

Synthesized from norbornene following general procedure A and purified by silica gel chromatography by dry loading and eluting with petroleum ether/ethyl acetate (12/1). **120** and **122** were obtained with a 64:36 ratio. Both regioisomers were separated as single pure products.

**7-iodobicyclo[2.2.1]heptan-2-ol 120** was obtained as a colorless solid (36.7 mg, 31 % yield). mp: 46-48 °C.  $R_f$  (in petroleum ether/ethyl acetate 8/1): 0.38.  $^1\text{H NMR}$  (300 MHz,

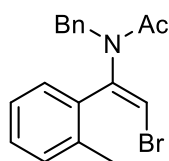
CDCl<sub>3</sub>)  $\delta$  3.94-3.76 (m, 1H), 3.71 (p,  $J$  = 1.5 Hz, 1H), 2.50 (d,  $J$  = 3.9 Hz, 1H), 2.46-2.39 (m, 1H), 2.30 (d,  $J$  = 10.5 Hz, 1H), 2.07-1.98 (m, 2H), 1.64-1.53 (m, 2H), 1.27-1.13 (m, 1H), 1.07-0.94 (m, 1H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  76.7, 50.0, 44.1, 42.8, 30.4, 25.8, 25.0. **HRMS** (AP<sup>+</sup>)  $m/z$ : [M+H-H<sub>2</sub>O] Calcd for C<sub>7</sub>H<sub>10</sub>: 220.9827, Found: 220.9824 ( $\Delta$  = -1.4 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3269, 2960, 2868, 1449, 1351, 1301, 1212, 1088, 1042, 1013, 777, 713, 597.

**2-iodobicyclo[2.2.1]heptan-7-ol 121** was obtained as a colorless solid (21.0 mg, 18 % yield).  $R_f$  (in petroleum ether/ethyl acetal 8/1): 0.28. mp: 72-73 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.18 (p,  $J$  = 1.6 Hz, 1H), 3.85-3.78 (m, 1H), 2.39-2.31 (m, 1H), 2.31-2.23 (m, 1H), 2.00-1.78 (m, 3H), 1.63 (brs, 1H), 1.58-1.43 (m, 1H), 1.23-1.06 (m, 2H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  72.2, 52.6, 43.4, 39.9, 32.5, 27.3, 23.8. **HRMS** (AP<sup>+</sup>)  $m/z$ : [M+H-H<sub>2</sub>O] Calcd for C<sub>7</sub>H<sub>10</sub>: 220.9827, Found: 220.9835 ( $\Delta$  = 3.6 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3332, 2962, 2873, 1447, 1338, 1217, 1157, 1080, 1004, 771, 703.



#### **Compound 122: (E)-N-benzyl-N-(2-bromo-1-phenylvinyl)acetamide**

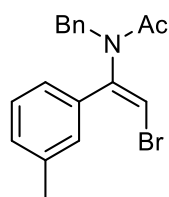
Synthesized from N-benzyl-N-(1-phenylvinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **122** was obtained as a colorless crystal (53.3 mg, 81% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.53. mp: 95.6 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.61 – 7.51 (m, 2H), 7.48 – 7.39 (m, 3H), 7.34 – 7.24 (m, 3H), 7.22 – 7.15 (m, 2H), 6.10 (s, 1H), 4.50 (s, 2H), 2.22 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 142.3, 137.0, 133.2, 129.8, 129.1, 128.7, 128.6, 127.7, 107.1, 49.4, 22.3. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>17</sub>H<sub>17</sub>NO<sup>79</sup>Br: 330.0494, Found: 330.0481 ( $\Delta$  = - 3.9 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3067, 1655, 1382, 1255, 768, 698, 511.



#### **Compound 123: (E)-N-benzyl-N-(2-bromo-1-(o-tolyl)vinyl)acetamide**

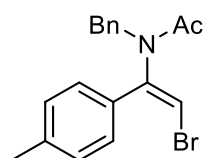
Synthesized from N-benzyl-N-(1-(o-tolyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 87:13). **123** was obtained as a colorless crystal (58.4 mg, 85% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.48. mp: 87.6°C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 – 7.19 (m, 7H), 7.18 – 7.10 (m, 2H), 6.31 (s, 1H), 4.44 (s, 2H), 2.39 (s, 3H), 2.21 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 142.9, 137.6, 137.2, 133.2, 130.9, 129.6, 129.3, 128.5, 128.1, 127.4, 126.0, 107.7, 48.8, 22.4, 19.9. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>18</sub>H<sub>19</sub>NO<sup>79</sup>Br: 344.0650, Found: 344.0655 ( $\Delta$  = 1.5 ppm). **IR** (neat,

cm<sup>-1</sup>):  $\nu$  3062, 2923, 1650, 985, 751, 724, 478.



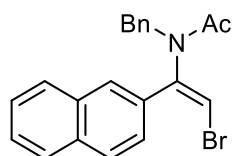
**Compound 124: (E)-N-benzyl-N-(2-bromo-1-(m-tolyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(m-tolyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 86:14). **124** was obtained as a colorless oil (49.9 mg, 72% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.44. mp: 79.2°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.42 – 7.24 (m, 7H), 7.23 – 7.17 (m, 2H), 6.08 (s, 1H), 4.50 (s, 2H), 2.39 (s, 3H), 2.22 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 142.5, 138.5, 137.1, 133.2, 130.6, 129.3, 129.1, 128.6, 127.7, 126.4, 106.9, 49.4, 22.3, 21.6. HRMS (ESI<sup>+</sup>) m/z: [M+H] Calcd for C<sub>18</sub>H<sub>19</sub>NO<sup>79</sup>Br: 344.0650, Found: 344.0652 ( $\Delta$  = 0.6 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  3065, 1654, 1382, 1254, 772, 702.



**Compound 125: (E)-N-benzyl-N-(2-bromo-1-(p-tolyl)vinyl)acetamide**

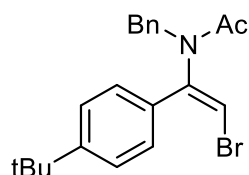
Synthesized from N-benzyl-N-(1-(p-tolyl)vinyl)acetamide following general procedure **A** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **125** was obtained as a colorless crystal (37.8 mg, 65% yield).  $R_f$  (in petroleum ether/ethyl acetate = 3:1): 0.63. mp: 95.7°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.49 – 7.42 (m, 2H), 7.32 – 7.24 (m, 4H), 7.24 – 7.17 (m, 3H), 6.05 (s, 1H), 4.50 (s, 2H), 2.40 (s, 3H), 2.20 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 142.3, 140.1, 137.1, 130.2, 129.4, 129.1, 129.0, 128.6, 127.6, 106.4, 49.3, 22.3, 21.5. HRMS (ESI<sup>+</sup>) m/z: [M+H] Calcd for C<sub>18</sub>H<sub>19</sub>NO<sup>79</sup>Br: 344.0650, Found: 344.0656 ( $\Delta$  = 1.7 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  3073, 1650, 822, 763, 703, 517.



**Compound 126: (E)-N-benzyl-N-(2-bromo-1-(naphthalen-2-yl)vinyl)acetamide**

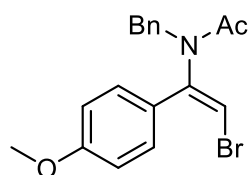
Synthesized from N-benzyl-N-(1-(naphthalen-2-yl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **126** was obtained as a yellow oil (53.9 mg, 71% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.65. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.00 (d,  $J$  = 1.9 Hz, 1H), 7.93 – 7.83 (m, 3H), 7.64 (dd,  $J$  = 8.6, 1.8 Hz, 1H), 7.61

– 7.50 (m, 2H), 7.36 – 7.27 (m, 3H), 7.26 – 7.18 (m, 2H), 6.19 (s, 1H), 4.56 (s, 2H), 2.28 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 142.5, 137.0, 133.7, 133.0, 130.7, 129.1, 129.1, 128.6, 128.6, 128.5, 127.9, 127.7, 127.5, 126.9, 125.8, 107.3, 49.6, 22.4. HRMS (ESI<sup>+</sup>) m/z: [M+H] Calcd for  $\text{C}_{21}\text{H}_{19}\text{NO}^{79}\text{Br}$ : 380.0650, Found: 380.0652 ( $\Delta$  = 0.5 ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3061, 1656, 1380, 819, 729, 698, 478.



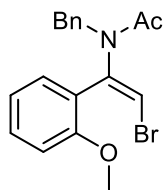
**Compound 127: (E)-N-benzyl-N-(2-bromo-1-(4-(tert-butyl)phenyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(4-(tert-butyl)phenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **127** was obtained as a white solide (54.6 mg, 71% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.73. mp: 87.2°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.48 (m, 2H), 7.47 – 7.41 (m, 2H), 7.33 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 6.04 (s, 1H), 4.50 (s, 2H), 2.20 (s, 3H), 1.35 (s, 9H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 153.2, 142.2, 137.2, 130.2, 129.2, 128.8, 128.6, 127.7, 125.7, 106.5, 49.5, 35.0, 31.3, 22.3. HRMS (ESI<sup>+</sup>) m/z: [M+H] Calcd for  $\text{C}_{21}\text{H}_{25}\text{NO}^{79}\text{Br}$ : 386.1120, Found: 386.1122 ( $\Delta$  = 0.5 ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3068, 2962, 1664, 1380, 839, 700, 545.

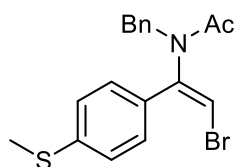


**Compound 128: (E)-N-benzyl-N-(2-bromo-1-(4-methoxyphenyl)vinyl)acetamid**

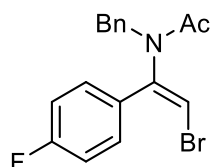
Synthesized from N-benzyl-N-(1-(4-methoxyphenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (4 g, 7 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 50:50). **128** was obtained as a colorless oil (26.9 mg, 75% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.27.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.47 (m, 2H), 7.33 – 7.24 (m, 3H), 7.22 – 7.15 (m, 2H), 6.99 – 6.91 (m, 2H), 6.00 (s, 1H), 4.50 (s, 2H), 3.86 (s, 3H), 2.20 (s, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 160.6, 142.0, 137.1, 130.6, 129.1, 128.6, 127.7, 125.3, 114.1, 105.6, 55.5, 49.4, 22.3. HRMS (ESI<sup>+</sup>) m/z: [M+H] Calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_2^{79}\text{Br}$ : 360.0599, Found: 360.0605 ( $\Delta$  = 1.7 ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3067, 2933, 1657, 1509, 1250, 1175, 1028, 836, 700, 521.


**Compound 129: (E)-N-benzyl-N-(2-bromo-1-(2-methoxyphenyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(2-methoxyphenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **129** was obtained as a white solid (56.7 mg, 79% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.53. mp: 108.4°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.26 (m, 1H), 7.23 – 7.13 (m, 4H), 7.12 – 7.05 (m, 2H), 6.91 (td,  $J = 7.5, 1.1$  Hz, 1H), 6.84 (dd,  $J = 8.4, 1.1$  Hz, 1H), 6.11 (s, 1H), 4.38 (s, 2H), 3.71 (s, 3H), 2.24 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 157.6, 142.0, 137.5, 132.5, 131.2, 128.7, 128.4, 127.3, 122.4, 120.4, 111.4, 108.3, 55.4, 48.7, 22.5. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_2^{79}\text{Br}$ : 360.0599, Found: 360.0594 ( $\Delta = -1.4$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3047, 1649, 1387, 1274, 1025, 759, 697.

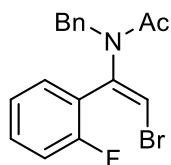

**Compound 130: (E)-N-benzyl-N-(2-bromo-1-(4-(methylthio)phenyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(4-(methylthio)phenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 87:13). **130** was obtained as a yellow solid (51.0 mg, 68% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.39. mp: 59.9°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.43 (m, 2H), 7.33 – 7.24 (m, 5H), 7.22 – 7.15 (m, 2H), 6.06 (s, 1H), 4.50 (s, 2H), 2.52 (s, 3H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 141.8, 141.3, 136.9, 129.4, 129.3, 129.0, 128.6, 127.7, 125.8, 106.5, 49.4, 22.3, 15.2. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{18}\text{H}_{19}\text{NOS}^{79}\text{Br}$ : 376.0371, Found: 376.0368 ( $\Delta = -0.8$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3065, 2918, 1652, 1380, 701, 514.


**Compound 131: (E)-N-benzyl-N-(2-bromo-1-(4-fluorophenyl)vinyl)acetamide**

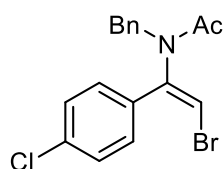
Synthesized from N-benzyl-N-(1-(4-fluorophenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **131** was obtained as a white solid (44.4 mg, 64% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.40. mp: 63.1°C.  $^1\text{H NMR}$

(300 MHz, CDCl<sub>3</sub>)  $\delta$  7.59 – 7.48 (m, 2H), 7.33 – 7.25 (m, 3H), 7.21 – 7.08 (m, 4H), 6.10 (s, 1H), 4.50 (s, 2H), 2.21 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 163.3 (d,  $J$  = 251.2 Hz), 141.5, 136.9, 131.1 (d,  $J$  = 8.5 Hz), 129.3 (d,  $J$  = 3.6 Hz), 129.1, 128.7, 127.8, 115.9 (d,  $J$  = 22.0 Hz), 107.1, 49.4, 22.3. <sup>19</sup>F{<sup>1</sup>H} NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -110.4. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>17</sub>H<sub>16</sub>NOF<sup>79</sup>Br: 348.0399, Found: 348.0405 ( $\Delta$  = 1.7 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  3063, 1657, 1598, 1505, 1225, 1160, 848, 525.



### **Compound 132: (E)-N-benzyl-N-(2-bromo-1-(2-fluorophenyl)vinyl)acetamide**

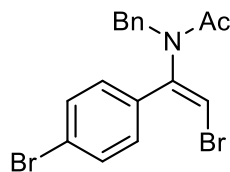
Synthesized from N-benzyl-N-(1-(2-fluorophenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 87:13). **132** was obtained as a white solid (50.0 mg, 72% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.45. mp: 89.9°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.47 – 7.35 (m, 1H), 7.35 – 7.24 (m, 4H), 7.23 – 7.09 (m, 4H), 6.27 (s, 1H), 4.49 (s, 2H), 2.28 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.44, 160.10 (d,  $J$  = 251.4 Hz), 138.76, 136.94, 131.77 (d,  $J$  = 8.5 Hz), 131.49 (d,  $J$  = 3.0 Hz), 128.81, 128.55, 127.59, 124.30 (d,  $J$  = 3.6 Hz), 121.79 (d,  $J$  = 13.5 Hz), 116.53 (d,  $J$  = 21.7 Hz), 110.37, 49.09, 22.31 (d,  $J$  = 2.8 Hz). <sup>19</sup>F{<sup>1</sup>H} NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -111.0. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>17</sub>H<sub>16</sub>NOF<sup>79</sup>Br: 348.0399, Found: 348.0394 ( $\Delta$  = - 1.4 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  3064, 1654, 1381, 766, 705, 502, 406.



### **Compound 133: (E)-N-benzyl-N-(2-bromo-1-(4-chlorophenyl)vinyl)acetamide**

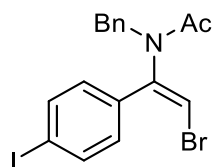
Synthesized from N-benzyl-N-(1-(4-chlorophenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **133** was obtained as a colorless crystal (44.6 mg, 61% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.53. mp: 82.3°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 – 7.45 (m, 2H), 7.44 – 7.37 (m, 2H), 7.32 – 7.25 (m, 3H), 7.21 – 7.14 (m, 2H), 6.13 (s, 1H), 4.50 (s, 2H), 2.20 (s, 3H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.4, 141.4, 136.8, 135.7, 131.7, 130.4, 129.1, 129.0, 128.7, 127.8, 107.7, 49.5, 22.3. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for C<sub>17</sub>H<sub>16</sub>NO<sup>35</sup>Cl<sup>79</sup>Br: 364.0104, Found: 364.0096 ( $\Delta$  = - 2.2 ppm). IR (neat, cm<sup>-1</sup>):  $\nu$  2326, 1652, 1090, 833, 743, 514, 454.





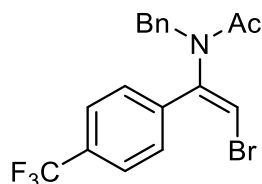
#### **Compound 134: (E)-N-benzyl-N-(2-bromo-1-(4-bromophenyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(4-bromophenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 87:13). **134** was obtained as a white solid (54.9 mg, 67% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.53. mp: 89.9°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 – 7.52 (m, 2H), 7.45 – 7.38 (m, 2H), 7.32 – 7.24 (m, 3H), 7.21 – 7.13 (m, 2H), 6.13 (s, 1H), 4.50 (s, 2H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 141.4, 136.7, 132.2, 132.0, 130.6, 129.0, 128.6, 127.8, 124.0, 107.7, 49.4, 22.3. **HRMS** (ESI<sup>+</sup>) m/z: [M+H] Calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}^{79}\text{Br}_2$ : 407.9599, Found: 407.9593 ( $\Delta$  = - 1.5 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3069, 2914, 1652, 1378, 830, 699, 511.



#### **Compound 135: (E)-N-benzyl-N-(2-bromo-1-(4-iodophenyl)vinyl)acetamide**

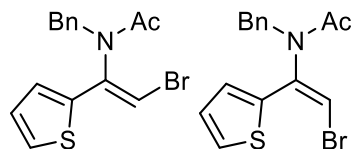
Synthesized from N-benzyl-N-(1-(4-iodophenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **135** was obtained as a yellow solid (58.0 mg, 64% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.42. mp: 100.1°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 – 7.72 (m, 2H), 7.34 – 7.24 (m, 5H), 7.22 – 7.12 (m, 2H), 6.13 (s, 1H), 4.49 (s, 2H), 2.19 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 141.6, 138.0, 136.7, 132.8, 130.6, 129.0, 128.6, 127.8, 107.8, 96.0, 49.4, 22.3. **HRMS** (ESI<sup>+</sup>) m/z: [M+H] Calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}^{79}\text{BrI}$ : 455.9460, Found: 455.9458 ( $\Delta$  = - 0.4 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3067, 1668, 1644, 1379, 1255, 828, 698, 510.



#### **Compound 136: (E)-N-benzyl-N-(2-bromo-1-(4-(trifluoromethyl)phenyl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(4-(trifluoromethyl)phenyl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (10 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 88:12). **136** was obtained as a white solid (48.5 mg, 61% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.44. mp: 81.8°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 – 7.58 (m, 4H), 7.39 – 7.24 (m, 3H), 7.22 – 7.12 (m,

2H), 6.23 (s, 1H), 4.51 (s, 2H), 2.22 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.37, 141.32, 137.04, 136.67, 131.61 (q,  $J = 32.9, 32.5$  Hz), 129.47, 129.04, 128.72, 127.90, 125.77 (q,  $J = 3.9$  Hz), 123.83 (q,  $J = 272.4$  Hz), 109.01, 49.58, 22.29.  $^{19}\text{F}\{^1\text{H}\}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.4. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{18}\text{H}_{16}\text{NOF}_3^{79}\text{Br}$ : 398.0367, Found: 398.0378 ( $\Delta = 2.8$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3068, 2919, 1655, 1317, 1173, 1115, 1066, 845, 699, 512.

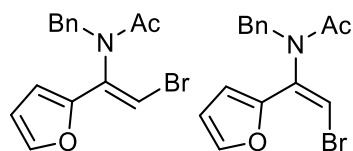


**Compound 137' & 137: (Z)-N-benzyl-N-(2-bromo-1-(thiophen-2-yl)vinyl)acetamide & (E)-N-benzyl-N-(2-bromo-1-(thiophen-2-yl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(thiophen-2-yl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (10 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 89:11). **137'** and **137** were separated as single pure products with a 17:83 ratio.

**137'** was obtained as a yellow oil (8.7 mg, 13% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.58.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 – 7.27 (m, 3H), 7.25 – 7.21 (m, 2H), 6.94 (dd,  $J = 5.1, 3.7$  Hz, 1H), 6.83 (dd,  $J = 3.7, 1.3$  Hz, 1H), 6.72 (s, 1H), 4.96 (d,  $J = 14.0$  Hz, 1H), 4.51 (d,  $J = 13.9$  Hz, 1H), 2.09 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 139.7, 139.6, 136.5, 130.4, 128.3, 128.0, 127.9, 127.0, 126.2, 106.6, 50.0, 21.9. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{15}\text{H}_{15}\text{NOS}^{79}\text{Br}$ : 336.0058, Found: 336.0068 ( $\Delta = 3.0$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3063, 2925, 1666, 1383, 1300, 701.

**137** was obtained as a yellow solid (43.1 mg, 64% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.57. mp: 64.2°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 – 7.46 (m, 1H), 7.43 (dt,  $J = 3.8, 1.0$  Hz, 1H), 7.37 – 7.21 (m, 5H), 7.14 – 7.07 (m, 1H), 5.93 (s, 1H), 4.87 – 4.51 (m, 2H), 2.07 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 137.3, 137.2, 137.0, 129.4, 129.3, 128.7, 128.6, 127.9, 127.3, 106.8, 50.4, 21.8. HRMS (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{15}\text{H}_{15}\text{NOS}^{79}\text{Br}$ : 336.0058, Found: 336.0043 ( $\Delta = -4.1$  ppm); [M+H+ $\text{CH}_3\text{CN}$ ] Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OS}^{79}\text{Br}$ : 377.0323, Found: 377.0306 ( $\Delta = -4.5$  ppm). IR (neat,  $\text{cm}^{-1}$ ):  $\nu$  3071, 1655, 1388, 725, 700, 507.



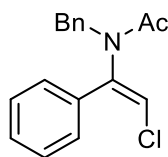
**Compound 138' & 138: (Z)-N-benzyl-N-(2-bromo-1-(furan-2-yl)vinyl)acetamide and (E)-N-benzyl-N-(2-bromo-1-(furan-2-yl)vinyl)acetamide**

Synthesized from N-benzyl-N-(1-(furan-2-yl)vinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum

ether/ethyl acetate, gradient: 100:0 to 90:10). **18'** and **18** were separated as single pure products with a 25:75 ratio.

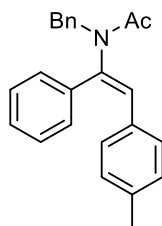
**138'** was obtained as a yellow oil (10.7 mg, 17 % yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.52.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 – 7.36 (m, 1H), 7.35 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 6.88 (s, 1H), 6.29 (dd,  $J = 3.5, 1.8$  Hz, 1H), 5.95 (dt,  $J = 3.4, 0.7$  Hz, 1H), 4.78 (d,  $J = 13.9$  Hz, 1H), 4.69 (d,  $J = 13.9$  Hz, 1H), 2.02 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 150.1, 143.9, 136.8, 136.3, 130.2, 128.3, 127.8, 111.8, 109.4, 107.1, 50.4, 21.7. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_2^{79}\text{Br}$ : 320.0286, Found: 320.0275 ( $\Delta = -3.4$  ppm); [M+H+ $\text{CH}_3\text{CN}$ ] Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2^{79}\text{Br}$ : 361.0552, Found: 361.0547 ( $\Delta = -1.4$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3031, 1729, 1388, 1229, 706.

**138** was obtained as a yellow oil (33.0 mg, 52% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.51. mp: 59-60°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (dd,  $J = 1.8, 0.8$  Hz, 1H), 7.28 – 7.13 (m, 5H), 6.94 (dd,  $J = 3.6, 0.8$  Hz, 1H), 6.45 (dd,  $J = 3.5, 1.8$  Hz, 1H), 5.88 (s, 1H), 4.58 (s, 2H), 1.97 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 147.9, 143.4, 137.3, 134.0, 129.3, 128.6, 127.7, 113.9, 112.0, 106.2, 50.7, 21.9. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_2^{79}\text{Br}$ : 320.0286, Found: 320.0294 ( $\Delta = 2.5$  ppm); [M+H+ $\text{CH}_3\text{CN}$ ] Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2^{79}\text{Br}$ : 361.0552, Found: 361.0563 ( $\Delta = 3.0$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3065, 3031, 1662, 1386, 1307, 703, 591.



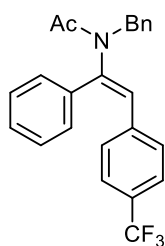
#### **Compound 139: (E)-N-benzyl-N-(2-chloro-1-phenylvinyl)acetamide**

Synthesized from N-benzyl-N-(1-phenylvinyl)acetamide following general procedure **D** and purified by Puriflash by dry loading (10 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 89:11). **139** was obtained as a white solid (32.0 mg, 56% yield).  $R_f$  (in petroleum ether/ethyl acetate = 4:1): 0.68. mp: 88.6°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 – 7.52 (m, 2H), 7.49 – 7.40 (m, 3H), 7.34 – 7.25 (m, 3H), 7.24 – 7.17 (m, 2H), 5.95 (s, 1H), 4.52 (s, 2H), 2.20 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 140.3, 137.0, 132.3, 129.8, 129.1, 128.8, 128.8, 128.6, 127.7, 119.0, 49.6, 22.2. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}^{35}\text{Cl}$ : 286.0999, Found: 286.0988 ( $\Delta = -3.8$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3065, 1657, 1387, 1263, 772, 699, 513.



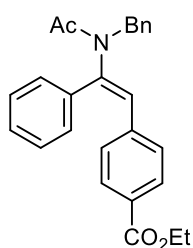
#### **Compound 147: (E)-N-benzyl-N-(1-phenyl-2-(p-tolyl)vinyl)acetamide**

Synthesized following general procedure **E** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 82:18). **147** was obtained as a yellow oil (65.9 mg, 96% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.43.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 – 7.22 (m, 10H), 7.00 – 6.92 (m, 2H), 6.92 – 6.84 (m, 2H), 6.17 (s, 1H), 4.54 (s, 2H), 2.32 (s, 3H), 2.27 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 138.5, 137.6, 137.5, 135.0, 132.3, 130.6, 129.5, 129.2, 129.1, 129.0, 128.8, 128.3, 127.3, 48.7, 22.5, 21.3. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{24}\text{H}_{24}\text{NO}$ : 342.1858, Found: 342.1865 ( $\Delta$  = 2.0 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3027, 2923, 1655, 1385, 699.



**Compound 148: (E)-N-benzyl-N-(1-phenyl-2-(4-(trifluoromethyl)phenyl)vinyl)acetamide**

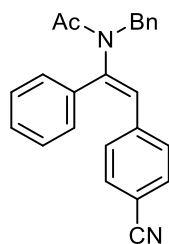
Synthesized following general procedure **E** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 87:13). **148** was obtained as a colorless oil (80.0 mg, 100% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.40.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.18 (m, 12H), 7.10 – 7.02 (m, 2H), 6.21 (s, 1H), 4.56 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.73, 141.54, 139.03 (q,  $J$  = 1.5 Hz), 137.32, 134.23, 129.65, 129.58, 129.39, 129.18, 129.14, 129.11, 128.77, 128.47, 127.55, 125.29 (q,  $J$  = 3.9 Hz), 124.05 (q,  $J$  = 272.1 Hz), 48.93, 22.58.  $^{19}\text{F}\{^1\text{H}\}$  **NMR** (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.2. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{24}\text{H}_{21}\text{NOF}_3$ : 396.1575, Found: 396.1584 ( $\Delta$  = 2.3 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  2938, 1648, 1322, 1107, 1065, 699.



**Compound 149: ethyl (E)-4-(2-(N-benzylacetamido)-2-phenylvinyl)benzoate**

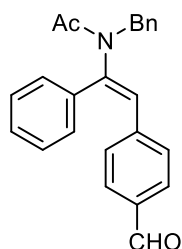
Synthesized following general procedure **E** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **149** was obtained as a yellow oil (72.7 mg, 91% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.19.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 – 7.67 (m, 2H), 7.31 – 7.07 (m, 10H), 6.98 – 6.89 (m, 2H), 6.14 (s, 1H), 4.47 (s, 2H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 2.23 (s, 3H), 1.26 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 166.2, 141.3, 139.9, 137.3, 134.3, 129.6, 129.5, 129.5, 129.3, 129.3, 129.1, 129.0, 129.0, 128.4, 127.5, 61.0, 48.9, 22.6,

14.4. **HRMS** (ESI<sup>+</sup>) m/z: [M+H] Calcd for C<sub>26</sub>H<sub>26</sub>NO<sub>3</sub>: 400.1913, Found: 400.1918 ( $\Delta$  = 1.2 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  2980, 2248, 1713, 1655, 1269, 1101, 725, 697.



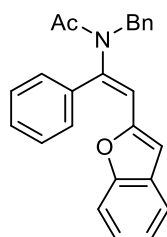
**Compound 150: (E)-N-benzyl-N-(2-(4-cyanophenyl)-1-phenylvinyl)acetamide**

Synthesized following general procedure E and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **150** was obtained as a white solid (64.4 mg, 91% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.23. mp: 145.9°C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 – 7.26 (m, 8H), 7.26 – 7.15 (m, 4H), 7.07 – 7.00 (m, 2H), 6.19 (s, 1H), 4.55 (s, 2H), 2.30 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 142.5, 140.1, 137.2, 133.9, 132.1, 129.9, 129.7, 129.5, 129.2, 129.0, 128.5, 128.1, 127.6, 118.7, 110.8, 49.0, 22.6. **HRMS** (ESI<sup>+</sup>) m/z: [M+H] Calcd for C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O: 353.1654, Found: 353.1652 ( $\Delta$  = - 0.6 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  2223, 1648, 1384, 699, 564, 512.

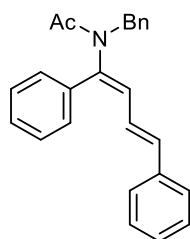


**Compound 151: (E)-N-benzyl-N-(2-(4-formylphenyl)-1-phenylvinyl)acetamide**

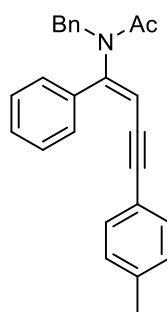
Synthesized following general procedure E and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 85:15). **151** was obtained as a colorless oil (68.6 mg, 97% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.39. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  9.90 (s, 1H), 7.70 – 7.60 (m, 2H), 7.42 – 7.17 (m, 10H), 7.14 – 7.07 (m, 2H), 6.24 (s, 1H), 4.56 (s, 2H), 2.32 (s, 3H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  191.5, 170.7, 142.2, 141.7, 137.2, 135.1, 134.2, 129.7, 129.7, 129.6, 129.1, 128.9, 128.4, 127.5, 49.0, 22.6. **HRMS** (ESI<sup>+</sup>) m/z: [M+H] Calcd for C<sub>24</sub>H<sub>22</sub>NO<sub>2</sub>: 356.1651, Found: 356.1662 ( $\Delta$  = 3.1 ppm). **IR** (neat, cm<sup>-1</sup>):  $\nu$  3029, 2824, 1697, 1653, 1598, 1382, 697, 505.


**Compound 152: (E)-N-(2-(benzofuran-2-yl)-1-phenylvinyl)-N-benzylacetamide**

Synthesized following general procedure **E** and purified by Puriflash by dry loading (12 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 75:25). **152** was obtained as a yellow oil (74.0 mg, 100% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.53.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.24 (m, 6H), 7.23 – 6.99 (m, 8H), 6.26 (s, 1H), 6.06 (s, 1H), 4.46 (s, 2H), 2.21 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 154.4, 151.9, 140.7, 137.3, 134.8, 129.7, 129.4, 128.9, 128.7, 128.5, 128.4, 127.5, 125.0, 123.1, 120.9, 118.2, 111.0, 106.9, 49.2, 22.6. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{25}\text{H}_{22}\text{NO}_2$ : 368.1651, Found: 368.1654 ( $\Delta$  = 0.8 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3030, 2931, 2245, 1655, 1381, 749, 696, 510.


**Compound 153: N-benzyl-N-((1E,3E)-1,4-diphenylbuta-1,3-dien-1-yl)acetamide**

Synthesized following general procedure **E** and purified by Puriflash by dry loading (10 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 86:14). **153** was obtained as a yellow sticky oil (67.8 mg, 96% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.40.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 – 7.16 (m, 15H), 6.99 (dd,  $J$  = 15.6, 11.3 Hz, 1H), 6.57 (d,  $J$  = 15.6 Hz, 1H), 6.07 (d,  $J$  = 11.2 Hz, 1H), 4.57 (s, 2H), 2.22 (s, 3H).  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 139.9, 137.6, 136.8, 135.7, 135.3, 130.4, 129.3, 129.1, 129.0, 128.9, 128.7, 128.4, 128.1, 127.4, 126.6, 124.4, 49.7, 22.6. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{25}\text{H}_{24}\text{NO}$ : 354.1858, Found: 354.1859 ( $\Delta$  = 0.3 ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3028, 2244, 1651, 1383, 697, 517.


**Compound 154: (E)-N-benzyl-N-(1-phenyl-4-(p-tolyl)but-1-en-3-yn-1-yl)acetamide**

Synthesized following general procedure **F** and purified by Puriflash by dry loading (10 g, 15 mL/min, petroleum ether/ethyl acetate, gradient: 100:0 to 80:20). **154** was obtained as a colorless oil (73.0 mg, 99% yield).  $R_f$  (in petroleum ether/ethyl acetate = 5:1): 0.43.  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 – 7.76 (m, 2H), 7.51 – 7.39 (m, 3H), 7.33 – 7.22 (m, 7H), 7.15 – 7.07 (m, 2H), 5.60 (s, 1H), 4.65 (s, 2H), 2.34 (s, 3H), 2.19 (s, 3H).  **$^{13}\text{C NMR}$**  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 147.7, 139.0, 137.3, 134.4, 131.4, 129.7, 129.3, 129.1, 128.6, 128.5, 128.3, 127.5, 119.8, 109.7, 96.4, 85.9, 50.3, 22.5, 21.6. **HRMS** (ESI<sup>+</sup>)  $m/z$ : [M+H] Calcd for  $\text{C}_{26}\text{H}_{24}\text{NO}$ : 366.1858, Found: 366.1863 ( $\Delta = 1.4$  ppm). **IR** (neat,  $\text{cm}^{-1}$ ):  $\nu$  3028, 2923, 2191, 1658, 1383, 815, 695, 513.

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## New development in Electrochemistry - Toward new methods for the functionalization of electron-rich olefins

**Abstract:** Electrochemistry have been considered as a powerful and sustainable methodology for the synthesis of organic molecules, as it is the most cost-effective method to add or remove electrons in terms of redox chemistry. Due to the unique properties of difluoromethyl ( $\text{CF}_2\text{H}$ ) group, this moiety has found widespread application in the design of pharmaceuticals and agrochemicals. Thus the introduction of  $\text{CF}_2\text{H}$  group into organic molecules has sparked considerable interest. This thesis described our investigations aimed at developing novel electrochemical methods for the synthesis of  $\text{CF}_2\text{H}$ -containing compounds through anodic generation of  $\text{CF}_2\text{H}$  radical. Moreover, considering the versatile utility of organohalogen compounds, the development of practical and efficient strategies for their synthesis is of significant importance. This manuscript also described our work on the new electrochemical methods for the halogenation of alkenes, through anodic generation of halogen radical or halonium species. These unprecedented methods have been effectively applied to a variety of styrene derivatives and enamides, giving the  $\text{CF}_2\text{H}$ - or halogen-containing products in good to excellent yields, without the use of metals, catalyst or chemical oxidants.

**Keywords:** electrosynthesis, difluoromethylation, halogenation, enamides, alkenes

## Nouveau développement en électrochimie - Vers de nouvelles méthodes de fonctionnalisation des oléfines riches en électrons.

**Résumé:** L'électrochimie est considérée comme un outil synthétique puissant et respectueux de l'environnement pour la synthèse de molécules organiques, car elle est la méthode la plus efficace pour générer des intermédiaires hautement réactifs via une oxydation ou une réduction en utilisant simplement des électrons comme réactifs principaux. En raison des propriétés uniques du groupe difluorométhyl ( $\text{CF}_2\text{H}$ ), ce motif a trouvé de nombreuses applications dans les domaines de l'industrie pharmaceutique et agrochimique. Ainsi, l'introduction du groupe  $\text{CF}_2\text{H}$  dans les molécules organiques suscite un intérêt considérable. Cette thèse décrit nos recherches visant à développer de nouvelles méthodes électrochimiques pour la synthèse de composés contenant le groupe  $\text{CF}_2\text{H}$  par génération anodique du radical  $\text{CF}_2\text{H}$ . De plus, compte tenu de l'utilité grandissante des composés organohalogénés en synthèse organique mais aussi dans l'industrie pharmaceutique, le développement de stratégies efficaces et peu coûteuses pour leur synthèse revêt une importance significative. Ce manuscrit décrit également notre travail sur le développement de nouvelles méthodes électrochimiques d'halogénéation d'alcènes *via* la génération de radicaux d'halogène ou d'espèces d'halonium par une oxydation anodique. Ces méthodes sans précédent ont été appliquées avec succès à divers dérivés du styrène et d'énamides, produisant des produits contenant le motif  $\text{CF}_2\text{H}$  ou des halogènes avec de bons à d'excellents rendements, sans nécessiter l'utilisation de métaux, de catalyseurs ou d'oxydants chimiques.

**Mots-clés:** électrosynthèse, difluorométhylation, halogénéation, énammides, alcènes