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Sustainable Drug and Organic Target Synthesis via Innovative Electrochemical and Flow Technologies

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Abstract

The presented thesis explores sustainable methods for synthesizing pharmaceutical compounds using electrochemical and flow-based technologies. Traditional chemical processes often involve hazardous reagents and waste, while these green alternatives offer cleaner, safer, and more efficient reactions. Electrochemistry uses electric current to drive reactions without stoichiometric reagents, improving atom economy and reducing waste. Flow chemistry enhances safety, control, and scalability. The work focuses on three projects: (1) electrochemical decarboxylative hydroxylation for making bempedoic acid under mild, safe conditions; (2) NHPI-mediated lactonization of benzylic alcohols to synthesize phthalides using oxygen as oxidant; (3) a modular flow system for synthesizing α,α-difluoromethylene amines, key medicinal compounds. Together, these strategies aim to enable greener, scalable routes to drug-like molecules, addressing key challenges in sustainable organic synthesis.

Riassunto

Il progetto di tesi esplora metodi sostenibili per la sintesi di composti farmaceutici utilizzando tecnologie elettrochimiche e flow chemistry. I processi chimici tradizionali implicano spesso reagenti pericolosi e produzione di scarti, mentre queste alternative verdi offrono reazioni più pulite, sicure ed efficienti. L'elettrochimica sfrutta la corrente elettrica per attivare le reazioni senza l'uso di reagenti stechiometrici, migliorando l'economia atomica e riducendo i rifiuti. La flow chemistry aumenta sicurezza, controllo e scalabilità. Il lavoro si concentra su tre progetti: (1) idrossilazione decarbossilativa elettrochimica per la sintesi dell'acido bempedoico in condizioni mild e sicure; (2) lattonizzazione elettrocatalitica mediata da NHPI per ottenere ftalidi da alcoli benzilici usando ossigeno molecolare; (3) un sistema modulare a flusso continuo per la sintesi di ammine α,α-difluorometileniche, importanti in ambito farmaceutico. Queste strategie mirano a sviluppare sintesi green e scalabili per molecole a rilevanza terapeutica.

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Introduction

The development of sustainable chemical processes represents an important scientific goal, particularly in light of the growing global demand for pharmaceutical agents and fine chemicals. Traditional synthetic methodologies often rely on stoichiometric reagents, hazardous oxidants or reductants, and energy-intensive conditions, leading to significant environmental and economic costs. As the chemical industry confronts the challenge of minimizing its ecological footprint, the exploration of greener synthetic routes has become a major priority. Within this framework, electrochemical and flow-based methodologies have emerged as powerful tools for enabling efficient and environmentally benign transformations in organic synthesis.

Electrochemical synthesis, which exploits the direct transfer of electrons to induce chemical change, is inherently aligned with the principles of green chemistry. It eliminates the need for stoichiometric reagents by using electric current as a clean redox agent, offering improved atom economy, reduced waste, and precise control over reaction conditions. In parallel, continuous flow chemistry, defined by the controlled movement of reactants through tubular reactors, provides enhanced heat and mass transfer, increased safety, and facile scalability. Together, these technologies represent a paradigm shift in how complex organic molecules, including pharmaceutical intermediates and active ingredients, can be synthesized more sustainably.

Over the past decade, numerous studies have demonstrated the utility of electrochemical methods for constructing carbon-carbon and carbon-heteroatom bonds, activating inert substrates, and generating reactive intermediates under mild conditions. Key advances include direct and mediated electrolysis protocols, the development of selective redox mediators such as N-hydroxyphthalimide (NHPI), and electroauxiliary-based strategies for controlling site-selectivity. Likewise, continuous flow platforms have been leveraged to intensify reaction efficiency, minimize reagent exposure, and improve reaction reproducibility. Despite these advances, significant challenges remain. Many electrochemical processes suffer from narrow substrate scope, limited functional group tolerance, and poor compatibility with complex molecular architectures.

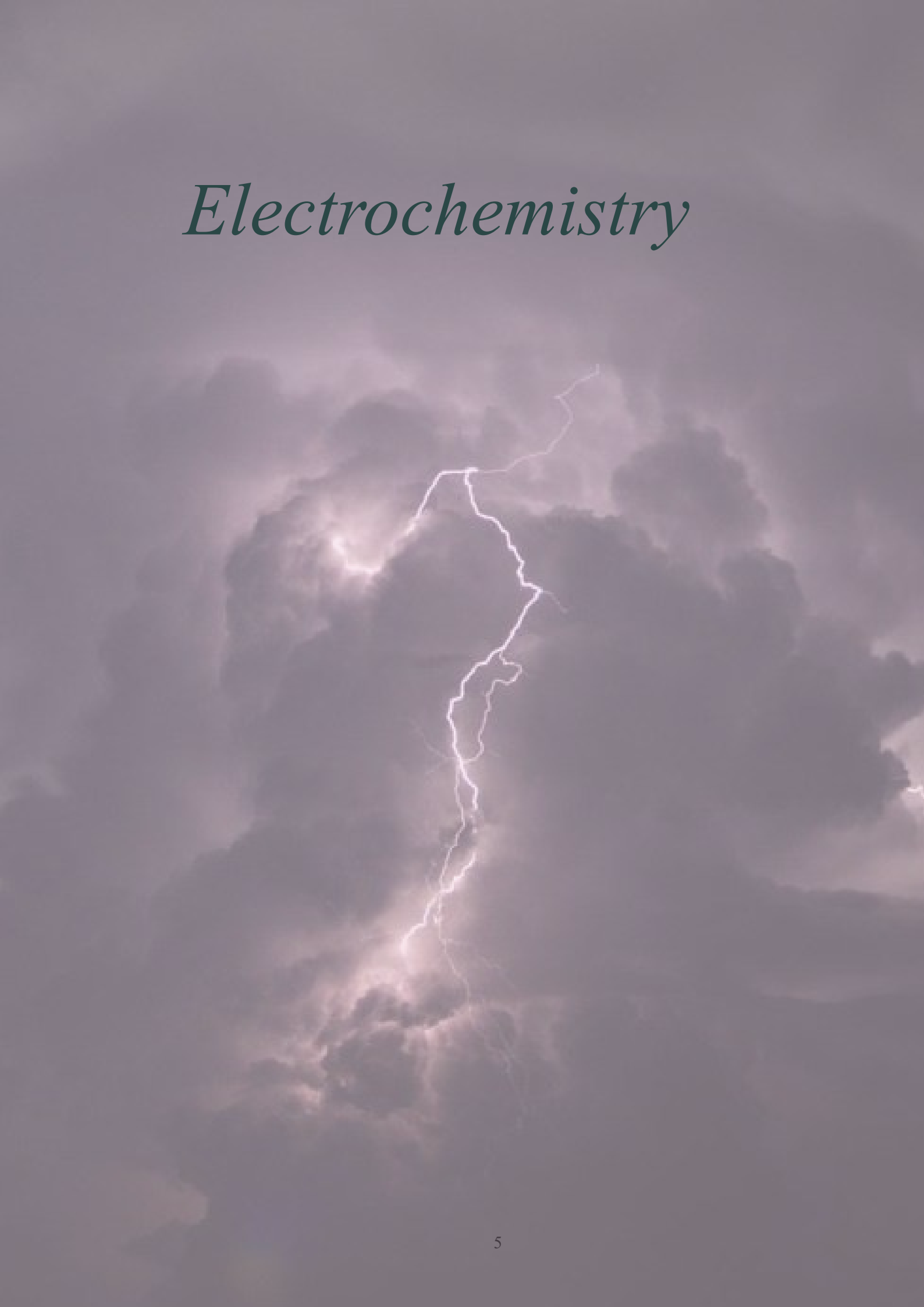
This thesis addresses a specific gap in the field: the limited availability of sustainable, scalable methods for the synthesis of pharmaceutically relevant targets and advanced intermediates using electrochemical and flow technologies. The central research question guiding this work is: How can innovative electrochemical and flow-based methodologies be

strategically developed and applied to enable efficient and sustainable synthesis of drug-like molecules and functional organic targets? To address this question, the thesis aims to design and implement novel electrochemical transformations, including decarboxylative hydroxylation and dehydrogenative lactonization, with a particular focus on enhancing selectivity, scalability, and sustainability.

The methodological approach combines experimental electroorganic chemistry, synthetic organic design, and flow reactor engineering. Specific emphasis is placed on mediator-driven electrocatalysis, anodic activation strategies, and the development of modular flow platforms. These approaches are selected for their ability to operate under mild conditions, reduce the use of hazardous reagents, and facilitate precise control over reaction parameters. Importantly, the work also incorporates process optimization techniques and mechanistic investigations to ensure robustness and reproducibility.

The present scientific investigation explores three integrated projects aimed at developing sustainable synthetic methodologies using electrochemical and flow technologies. The first project focuses on the electrochemical decarboxylative hydroxylation of Meldrum's acid derivatives to access bempedoic acid, a cholesterol-lowering agent, through a safer and more efficient route that avoids hazardous reagents and enables selective alcohol formation under mild conditions. The second project presents a sustainable electrocatalytic strategy for the synthesis of phthalides via NHPI-mediated dehydrogenative lactonization of benzylic alcohols. Utilizing molecular oxygen as the terminal oxidant, this method achieves efficient $C(sp^3)$–H oxidation with broad substrate compatibility and excellent yields, demonstrating its applicability to bioactive scaffolds. The third project introduces a flow-enabled, modular approach for synthesizing α,α-difluoromethylene amines, key motifs in medicinal chemistry, using a continuous flow system that enhances control, safety, and scalability. Colletively, these studies contribute to advancing green and modular synthetic strategies for the efficient preparation of pharmaceutically relevant targets.

Electrochemistry

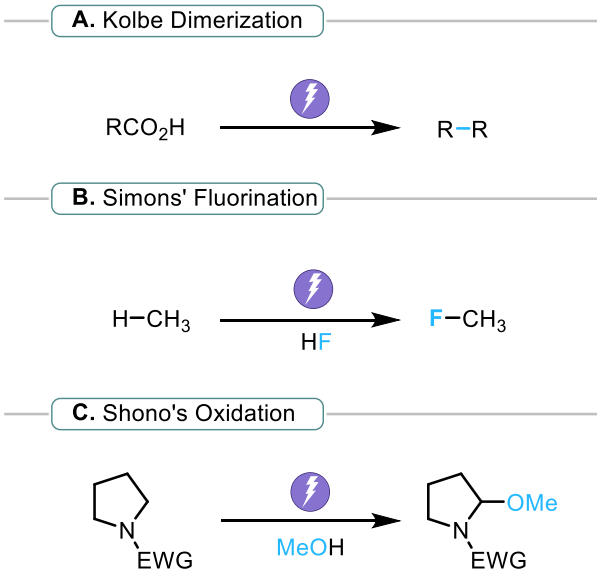


1) Electrochemistry

1.1.1 General Aspects

Organic electrochemistry can be traced back to the mid-19th century with Faraday's electrolysis of acetic acid to produce hydrocarbons, and the well-known Kolbe electrochemical decarboxylative dimerization (Scheme 1.1A).[1,2] During this period, other important synthetic strategies were also discovered, including Simons' electrochemical fluorination process (Scheme 1.1B)[3] and Shono's oxidation of amines (Scheme 1.1C).[4]

Although research in electrocatalytic organic transformations continued throughout the 20th century, recent years have witnessed a resurgence of interest in electrochemical synthesis, both in academia and industry.[5–7] This renewed attention is largely driven by the growing demand for sustainable and environmentally friendly synthetic methodologies.



Scheme 1.1 A. Kolbe Decarboxylative Dimerization**. B.** Simons' Fluorination**. C.** Shono's Oxidation**.**

At the core of electrocatalysis lies the concept of electron transfer, in which an electron is either added or removed from an organic molecule.[8] Electron transfer is reversible only when the resulting species is sufficiently stable under the reaction conditions. In most cases, however, an initial electron transfer triggers a cascade of subsequent chemical events, such as bond cleavage (dissociation) or new bond formation.

Electrochemical methods offer a powerful and versatile approach for generating reactive intermediates under mild and controlled conditions.[9] Radical cations and radical anions can

be readily formed from neutral organic molecules via anodic or cathodic electron transfer, respectively. Accordingly, carbocations, radicals, and carbanions can be accessed through associative or dissociative processes that follow the initial redox event. These highly reactive carbon-centered intermediates serve as valuable tools in organic synthesis, particularly for the formation of carbon-carbon bonds.

Two main strategic approaches exist for generating such reactive intermediates in electrochemical transformations:

1. Direct electrochemical activation, in which the substrate undergoes electron transfer at the electrode surface.
2. Indirect (or mediated) electrochemical activation, where a redox mediator facilitates electron transfer to or from the substrate, often enhancing selectivity or reducing the required overpotential.

These fundamental principles provide the conceptual and practical foundation for the development of modern electrochemical synthetic methodologies.

In electrochemical processes, the propensity of a substrate to undergo electron transfer (ET) is fundamentally governed by its oxidation and reduction potentials.[10] An electron transfer event is thermodynamically favored when the oxidation potential of the molecule is less positive (i.e., lower energy required for oxidation) or when the reduction potential is less negative (i.e., easier to reduce). Thus, the feasibility of an electrochemical transformation depends directly on the electrochemical window within which these redox events can take place.

To effectively drive a selective electron transfer process, it is essential to activate a specific site within the molecule toward oxidation or reduction. This requires precise intramolecular control of reactivity, which can be achieved through the strategic incorporation of suitable functional groups that direct the electron flow and influence the redox behavior of the substrate.

One particularly efficient and widely adopted strategy for achieving regio- and chemoselectivity in electrochemical reactions involves the use of electroauxiliaries (EAs), functional groups specifically designed to modulate the redox properties of a molecule. Introduced by Yoshida and co-workers,[11] electroauxiliaries fulfill two key roles in the context of electrochemical synthesis:

a. They facilitate electron transfer by lowering the oxidation potential of the substrate, thereby making the molecule more prone to undergo oxidation under milder conditions;

b. They direct the electron transfer to a specific molecular site, activating it selectively toward subsequent chemical transformations following the initial ET event.

From the perspective of Frontier Molecular Orbital (FMO) Theory,[12] oxidative electron transfer involves the removal of an electron from the highest occupied molecular orbital (HOMO) of the substrate (Figure 1.1). Accordingly, the most straightforward way to render a substrate more susceptible to oxidation is by increasing the energy level of its HOMO.[13] When multiple substrates are present in a reaction mixture, each capable of oxidation, selectivity is determined by the relative HOMO energies of the different species. If these energy levels are too close, achieving selective oxidation becomes highly challenging, as the electrode cannot discriminate effectively between substrates. However, by introducing a suitably designed electroauxiliary, it becomes possible to selectively raise the HOMO energy of one substrate relative to the others, thus enabling site- or substrate-selective oxidation (Figure 1.2).

A similar principle applies when multiple potentially oxidizable sites exist within a single molecule. In such cases, the introduction of an electroauxiliary can localize the electron transfer event by activating only one functional group toward oxidation, thereby enhancing regio- and chemoselectivity.

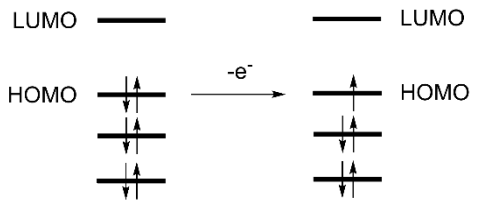


Figure 1.1 Molecular Orbital Diagram for the Electron Transfer Process.

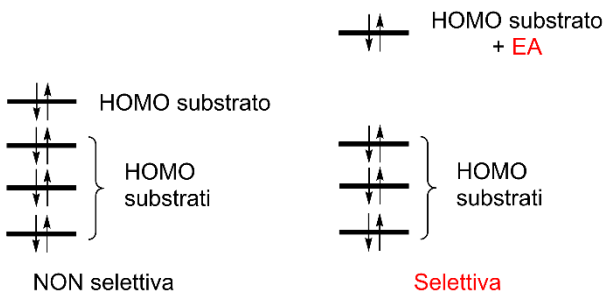


Figure 1.2 Increase in the HOMO energy of the substrate due to the electroauxiliary (EA).

Several types of electroauxiliaries have been developed, and their selection depends on the structure, electronic properties, and intended reactivity of the substrate. Among the various options available, carboxylic acids can be chosen as electroauxiliaries, due to their ease of introduction, redox-activity, and compatibility with different synthetic pathways. Their use enables selective generation of carbon-centered intermediates via oxidative decarboxylation, a well-established and synthetically valuable strategy in organic electrochemistry.

1.1.2 Direct electrolysis

Direct electrolysis (Figure 1.3) represents one of the most fundamental and efficient strategies in modern organic synthesis.[14] By leveraging the direct transfer of electrons between a molecule and an electrode, this method enables the precise and sustainable activation of chemical bonds. In contrast to mediated electrolysis, which relies on redox-active intermediates, direct electrolysis operates without additives, offering a clean and elegant approach to redox transformations.

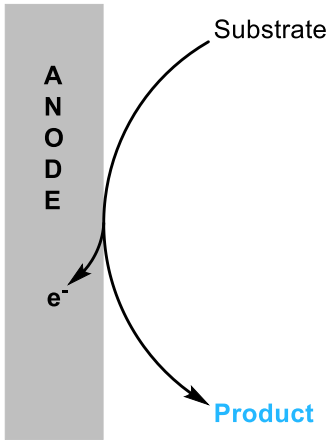


Figure 1.3 Schematic direct electrolysis.

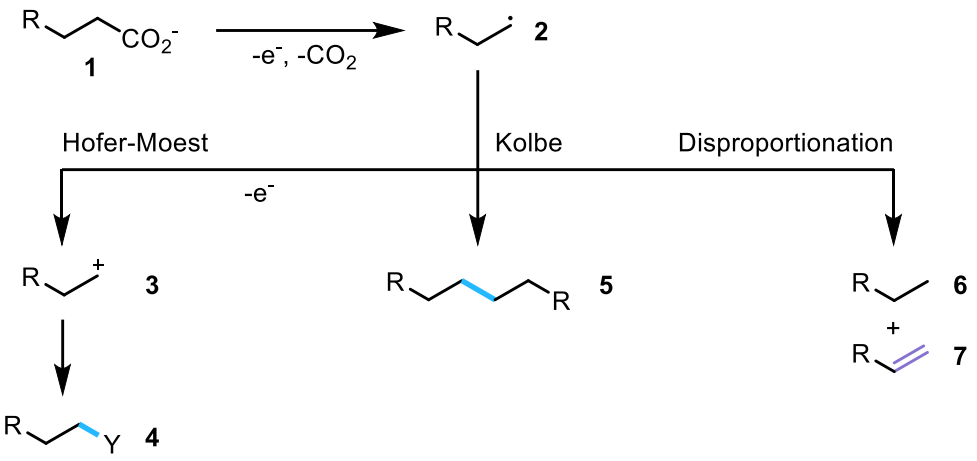
The foundation of direct electrolysis lies in electrochemical redox reactions, where electrons are either removed from (oxidation) or added to (reduction) organic substrates. These reactions take place at the interface between the electrode and the substrate, typically in an undivided or divided electrochemical cell. In undivided cells, both oxidation and reduction occur in the same compartment, while in divided cells, the electrodes are separated to prevent undesired side reactions.[15]

One of the key advantages of direct electrolysis is its high selectivity. By precisely controlling the applied potential or current, chemists can target specific functional groups, eliminating the need for stoichiometric chemical oxidants or reductants. This not only enhances sustainability but also reduces waste, making direct electrolysis highly attractive for green chemistry applications.[16,17]

1. Kolbe Electrolysis and Related Decarboxylations

Among the earliest electroorganic reactions, the Kolbe electrolysis involves the anodic decarboxylation of carboxylate salts to generate carbon-centered radicals. These radicals

typically dimerize to form new C-C bonds. Despite its long history, the Kolbe reaction remains relevant today, with applications in natural product synthesis, ligand construction, and flow electrolysis.[18] Modern adaptations allow for selective cross-coupling of different acids and incorporation into complex synthetic sequences.[19]



Scheme 1.2 Electrochemical decarboxylation pathway.

The electrochemical oxidation of carboxylates has been extensively studied, and if the reaction conditions are not carefully controlled, a wide variety of products may be obtained (Scheme 1.2).[20,21] Following the anodic oxidation of carboxylate ion **1** and subsequent loss of CO_2, radical **2** is generated. This radical can undergo a second oxidation event to form carbocation **3**, which may be trapped in situ by a nucleophile **Y** (Hofer-Moest process). Alternatively, instead of proceeding through further redox chemistry, radical **2** can react with a second radical via two distinct pathways. The first involves dimerization of the reactive intermediates to form the homocoupling product **5** (Kolbe reaction). In the second pathway, two radicals **2** may undergo disproportionation to yield one saturated product **6** and one unsaturated product **7**. By appropriately tuning the reaction conditions, it is possible to favor one of these pathways over the others.

2. Amines and Amides: Access to N-Centered Radicals and Iminium Ions

Direct anodic oxidation of amines and amides offers a powerful route to nitrogen-centered radicals and reactive iminium species. Baran and co-workers demonstrated the efficient dimerization of xiamycin into dixiamycin using controlled potential electrolysis; transformation that would be challenging with traditional chemical methods.[22] Similarly, Moeller and Waldvogel showed that amidyl radicals generated anodically could participate in heterocyclizations to form valuable motifs such as pyrazolidinones.[23,24]

A particularly important transformation in this area is the Shono oxidation, which converts α-C-H bonds in amides or carbamates into reactive iminium ions. These intermediates can then be trapped by nucleophiles such as alcohols, enol ethers, or cyanides. The Shono oxidation has been widely applied in asymmetric synthesis, complex molecule construction, and pharmaceutical development.[25,26]

The use of electroauxiliaries, that lower oxidation potential, greatly enhances the regio- and chemoselectivity of anodic oxidations. For instance, TMS and arylsulfide groups help guide oxidation to specific positions, facilitating transformations even in complex peptides.[27,28]

3. Direct Oxidation of Alcohols

While nitroxyl-mediated oxidation is more common, direct anodic oxidation of alcohols remains viable under carefully tuned conditions. Using electrodes like PbO_2 or graphite, primary alcohols, can be selectively oxidized to ketones or aldehydes.[29] Electrode material choice can influence site-selectivity, for example in the oxidation of cholic acid where PbO_2 enabled selective C7 oxidation.[30]

Despite its advantages, direct electrolysis poses several technical challenges:

- Electrode passivation, where reactive species degrade or coat the electrode surface, limiting further reaction.
- Overoxidation or overreduction, especially when multiple reactive sites are present.
- Competitive oxidation/reduction of nucleophiles, particularly in undivided cells.

These issues can often be mitigated through thoughtful cell design (e.g., divided cells), current density control, use of flow systems, and electrode material optimization.

Direct electrolysis has found widespread use in total synthesis, late-stage functionalization, and drug development. Notable examples include the synthesis of natural products via Shono oxidation, late-stage oxidation of complex molecules, and anodic generation of reactive intermediates like acyliminium or oxocarbenium ions for further transformations.[31,32]

1.1.3 Mediated electrolysis

Mediated electrolysis (Figure 1.4), also known as indirect electrolysis, represents a transformative evolution in synthetic organic electrochemistry. Unlike direct electrolysis, where the substrate directly undergoes electron transfer at the electrode surface, mediated electrolysis uses a redox mediator, a species that shuttles electrons between the electrode and the substrate in solution. This method effectively decouples the electrochemical activation step from the chemical transformation, allowing for greater control, improved efficiency, and expanded substrate compatibility. The general principle involves the oxidation or reduction of a mediator at the electrode to generate a highly reactive species (radical or ionic), which then undergoes homogeneous reaction with the substrate in solution. This approach mitigates common limitations of direct electrolysis, such as electrode passivation, overoxidation, or poor selectivity. It also enables transformations that are otherwise unfeasible due to the high kinetic barriers or instability of reactive intermediates at the electrode interface.[33]

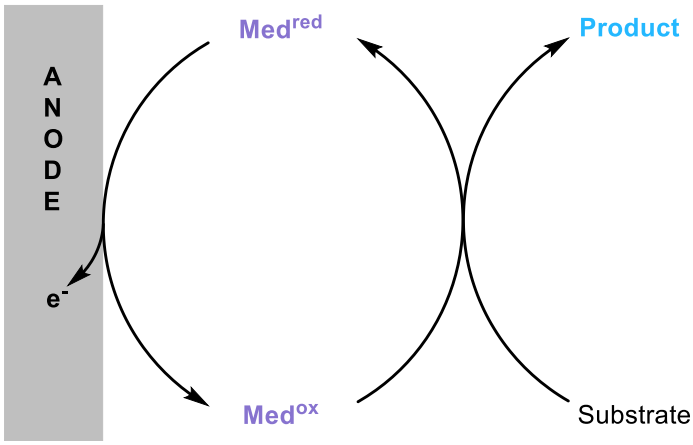


Figure 1.4 Schematic mediated electrolysis.

Historically, the earliest applications of mediated electrolysis date back to 1900, where inorganic salts such as chromium were employed to facilitate the anodic synthesis of quinones. Steckhan's contributions in the 1980s laid the foundations of mediated electrolysis and promoted the application of organic mediators, including nitroxyl radicals and triarylamines.[34] This opened new avenues in both anodic and cathodic processes and set the foundation for many redox catalysis methods that followed.

Among the most celebrated mediators is TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), a nitroxyl radical used extensively in the oxidation of alcohols.[35] TEMPO is anodically converted into an oxoammonium ion, which can oxidize primary and secondary alcohols in a highly selective and mild fashion. TEMPO has been widely adopted for its ability to deliver

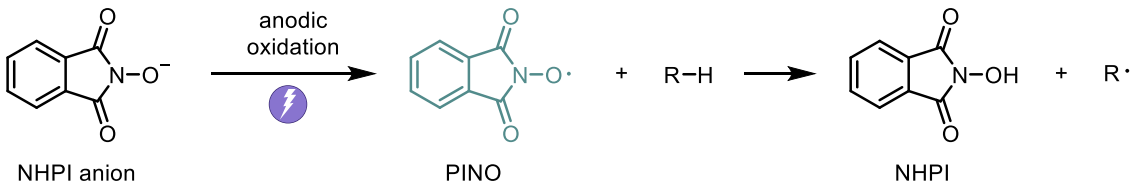
oxidation reactions in a sustainable and green manner, often with water as the only byproduct.[36] Its broad applicability has led to innovations such as biphasic mediator systems,[37] immobilized redox catalysts,[38] and the design of chiral nitroxyl derivatives for asymmetric electrocatalysis.[39]

Another significant class of mediators includes transition metal complexes, such as ferrocene derivatives, which are frequently used in the anodic generation of nitrogen-centered radicals (amidyl, nitrenyl, nitrenium species). These reactive intermediates can engage in intramolecular cyclizations or intermolecular bond-forming events, including hydroamination, cyclization to benzimidazoles, and azaindole synthesis.[40]

Mediated systems are not limited to oxidation. Cathodic processes also benefit from redox mediators, for instance in the generation of low-valent metal species or radical anions from stable precursors. Such approaches allow for novel reductive coupling reactions that bypass the need for stoichiometric metallic reductants.[41]

The Role of NHPI in Mediated Electrolysis

A particularly noteworthy organic mediator in electrochemical oxidation is N-hydroxyphthalimide (NHPI). Under anodic conditions, NHPI is converted into the phthalimide-N-oxyl radical (PINO), which serves as an efficient hydrogen atom abstractor. The PINO radical can activate C-H bonds, particularly those at benzylic, allylic, or otherwise weak positions, enabling oxidative functionalizations that are otherwise challenging. The oxidative power and selectivity of NHPI-based systems make them attractive for late-stage functionalization of complex molecules. Additionally, they represent a milder and more environmentally benign alternative to traditional oxidants such as permanganate or chromium(VI) reagents. NHPI-mediated electrochemical systems have been applied to oxidize alkylarenes, amines, and even saturated hydrocarbons, often in the presence of oxygen as the terminal oxidant. Co-mediation with transition metals such as Co(II) or Mn(III) salts has also been reported to enhance the reactivity and improve catalyst turnover.[42]



Scheme 1.3 NHPI radical mechanism.

Furthermore, NHPI is compatible with continuous-flow electrochemical systems, enabling scalable and efficient oxidation processes. Its relatively low oxidation potential and ability to selectively engage in hydrogen atom transfer reactions make it ideal for the development of site-selective C-H functionalization strategies, a current frontier in green chemistry. Mechanistically, the NHPI system operates via a radical chain process (Scheme 1.3): anodic oxidation of NHPI anion yields PINO, which abstracts a hydrogen atom from the substrate to generate a carbon-centered radical. This radical can then react with molecular oxygen or be intercepted by another oxidant or trap, depending on the desired transformation. Importantly, the mediator is regenerated at the electrode, completing the catalytic cycle with high atom economy.[43] NHPI has thus emerged as a highly effective and sustainable mediator in electrochemical oxidations. It exemplifies the potential of mediated electrolysis to replace stoichiometric oxidants and minimize environmental impact, while maintaining or enhancing synthetic utility.

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1st Project

Electrochemical Decarboxylative Hydroxylation for the Sustainable Synthesis of Bempedoic Acid

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Ronco Pietro performed and analyzed the experiments

In collaboration with Flamma S.p.A

Dr. Beatrice Trucchi and Dr. Federico Della Negra directed the project

Supervisors: Massimo Verzini and Prof. Giuseppe Zanoni

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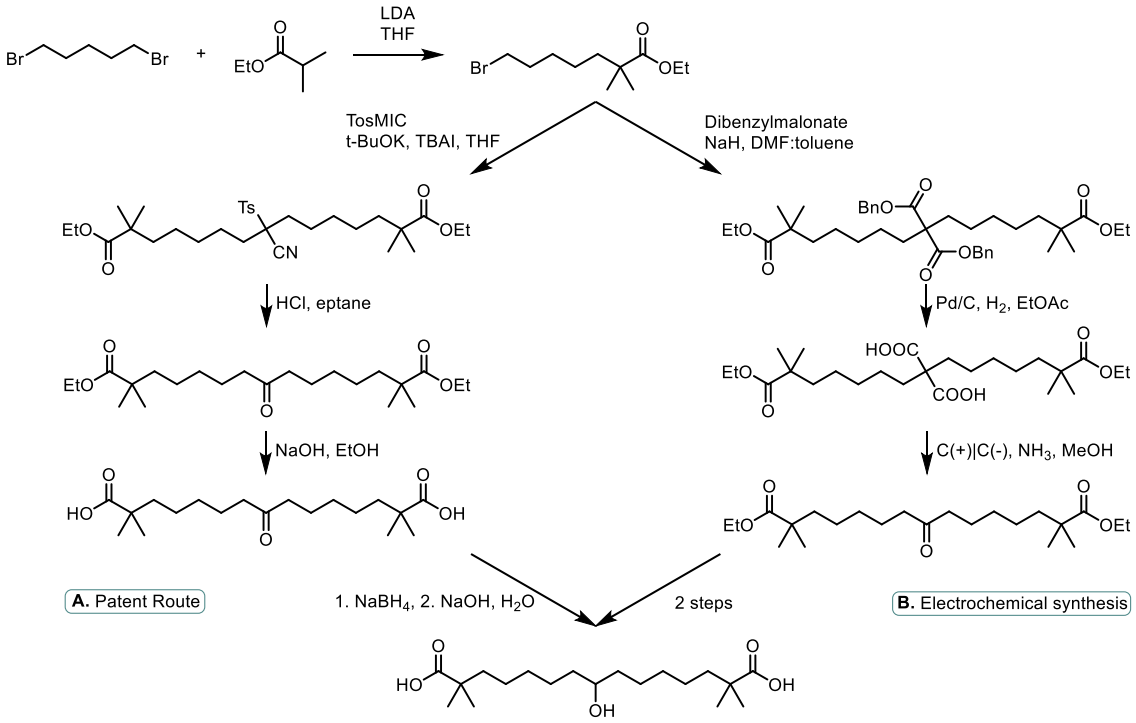
1.2 Electrochemical Decarboxylative Hydroxylation for the Sustainable Synthesis of Bempedoic Acid

Cardiovascular disease (CVD) remains one of the leading causes of death globally, necessitating the continued development of safe and effective lipid-lowering therapies. Statins, which act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), are currently the first-line treatment for reducing low-density lipoprotein cholesterol (LDL-C) and lowering cardiovascular risk. However, a considerable subset of patients either fail to achieve target LDL-C levels or cannot tolerate statins due to adverse muscular effects, particularly myopathy and muscle pain.[1] Bempedoic acid has emerged as a promising alternative. It is a prodrug that, once converted to its active form (bempedoic acid-coenzyme A), inhibits adenosine triphosphate-citrate lyase (ACL), a key enzyme involved in the biosynthesis of cholesterol upstream of HMG-CoA reductase.[2] This mechanism leads to upregulation of LDL receptors and enhanced clearance of circulating LDL-C. Unlike statins, bempedoic acid is activated primarily in the liver and not in skeletal muscle, due to the tissue-specific expression of activating enzyme. Consequently, it does not interfere with cholesterol synthesis in muscle and is associated with a significantly lower risk of muscle-related side effects.[3]

Bempedoic acid has shown efficacy as both monotherapy and in combination with statins or ezetimibe. Its favorable tolerability profile makes it particularly suitable for patients with statin intolerance or those requiring adjunctive LDL-C lowering. Despite its clinical promise, efficient and scalable synthetic methods for bempedoic acid remain a topic of active research. Early synthetic approaches, such as the five-step route described by Dasseux et al. (Scheme 1.4A),[4] suffered from serious drawbacks including the use of highly toxic reagents (e.g., tosylmethyl isocyanide), generation of potentially genotoxic impurities, and reliance on large quantities of sodium borohydride. In 2021, Xu et al. (Scheme 1.4B)[5] reported an electrochemical synthesis of bempedoic acid designed to minimize the use of toxic reagents. The key transformation involved the decarboxylation of a disubstituted malonic acid to generate the corresponding ketone. This reaction, originally developed by Markó et al.,[6] enables the formation of acetals under mild conditions, which can subsequently be converted into the target ketones via acidic workup. However, the proposed synthetic route still involves the use of transition metals, such as palladium, for the deprotection of the benzyl malonate, as well as hazardous steps such as alkylation in the presence of sodium hydride (NaH).



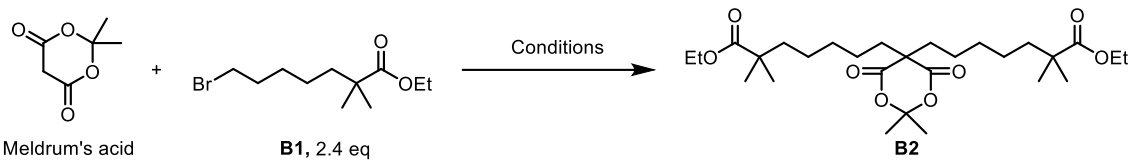
Scheme 1.4 A. Patent Route for bempedoic acid synthesis. **B.** Electrochemical synthesis of bempedoic acid.

Our research focused on developing an optimized electrochemical synthesis of bempedoic acid. The first stage involved refining the alkylation step by employing Meldrum's acid instead of the traditional malonate derivative, thereby eliminating the need for hazardous reagents. This was followed by a hydrolysis and thermal decarboxylation sequence, yielding the corresponding carboxylic acid intermediate. Drawing inspiration from the work of Cantillo and colleagues,[7] who demonstrated the electrochemical conversion of carboxylic acids into acetates, we investigated this transformation as a key step in our synthetic pathway. The resulting acetate intermediate, upon subsequent acidic hydrolysis, efficiently furnished an advanced precursor to bempedoic acid.

1.2.1 Results and discussion

We began our research by exploring various conditions for the bis-alkylation of Meldrum's acid, employing B1 derivative as the electrophilic partner. A range of bases, solvents, additives, temperatures, and reaction times were evaluated to optimize the isolated yield of the desired product (Table 1.1).

Table 1.1 Meldrum's acid alkylation optimization.



Meldrum's acid **B1,** 2.4 eq **B2**

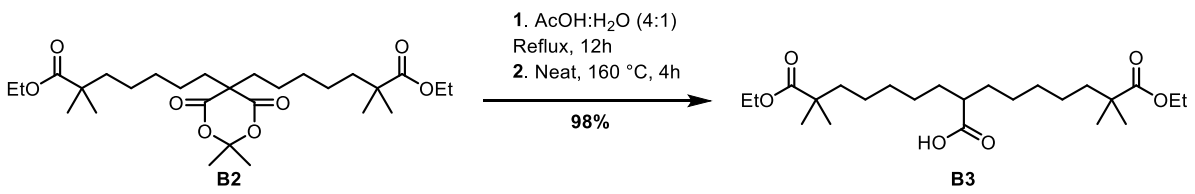
Entry	Solvent	Base	T	Additive	Time	Yield
1	DMF	K_2CO_3 (3 eq)	70 °C	-	2 h	**27%**
2	DMF	K_2CO_3 (3 eq)	70 °C	-	16 h	**ND**
3	DMF	K_2CO_3 (3 eq)	70 °C	TBAI (cat)	16 h	**31%**
4	DMF	K_2CO_3 (3 eq)	50 °C	-	16 h	**21%**
5	DMF	K_2CO_3 (3 eq)	50 °C	TBAI (cat)	16 h	**37%**
6	DMF	K_2CO_3 (3 eq)	25 °C	TBAI (cat)	16 h	**42%**
7	DMF	Et_3N (2 eq)	50 °C	TBAI (cat)	16 h	**30%**
8	DMSO	Et_3N (2 eq)	50 °C	-	16 h	**18%**
9	DMSO	DIPEA (2 eq)	50 °C	-	16 h	**14%**
10	DMSO	DIPEA (2 eq)	50 °C	NMP (0.1 mL)	16 h	**19%**
11	DMSO	DIPEA (2 eq)	50 °C	TMSCl (2 eq)	16 h	**ND**
12	DMF	K_2CO_3 (2.2 eq)	25 °C	TBAI (0.5 eq)	120 h	**55%**
13	DMF	K_2CO_3 (2.2 eq)	25 °C	TBAI (1.5 eq)	120 h	**58%**
14	DMF	K_2CO_3 (2.2 eq)	25 °C	KI (0.5 eq)	120 h	**59%**
15	DMF	K_2CO_3 (2.2 eq)	25 °C	KI (1.5 eq)	120 h	**61%**
16	**DMF**	**K_2CO_3 (2.2 eq)**	**25 °C**	**KI (1.5 eq)**	**168 h**	**70%**

Conditions: 10 mL reaction mixture, 6.94 mmol Meldrum's acid, yields are isolated.

Initial experiments (Entries 1-6) employed potassium carbonate (K_2CO_3, 3 equivalents) in DMF at different temperatures (70 °C, 50 °C, and 25 °C). Without additives, only moderate yields were obtained (Entry 1). However, the use of catalytic TBAI (tetrabutylammonium iodide) significantly improved yields, reaching a maximum of 42% at 25 °C (Entry 6). Organic bases such as triethylamine (Et_3N) and DIPEA (*N,N*-diisopropylethylamine) were

evaluated in both DMF and DMSO (entries 7-11), but resulted in poor performance, with isolated yields ranging from 14% to 30%. Additives such as NMP and TMSCl failed to significantly enhance the efficiency, and one entry (11) did not yield an isolated product. Encouraged by the results with TBAI, further optimization was carried out using slightly reduced amounts of K_2CO_3 (2.2 eq) and longer reaction times (entries 12-16). Entries 12 and 13 involved different loadings of TBAI, showing yield improvements up to 58%. A switch to potassium iodide (KI) as an additive proved to be particularly effective: yields increased from 59% (entry 14) to 70% (Entry 16), demonstrating that KI is superior to TBAI under these reaction conditions. In summary, table 1.1 highlights that optimal bis-alkylation of Meldrum's acid was achieved using K_2CO_3 (2.2 eq) and KI (1.5 eq) in DMF at 25 °C with prolonged reaction time (168 h), affording a 70% isolated yield.

With a reproducible synthetic approach for intermediate B2 established, we focused our attention on its hydrolysis and subsequent decarboxylation. Hydrolysis of Meldrum's acid derivatives generally requires acidic conditions. Attempts using strong acids such as HCl in combination with organic solvents like DMF were unsuccessful in achieving complete conversion. However, a mixture of acetic acid and water in a 4:1 ratio proved highly effective, leading to full conversion of the intermediate. The thermal decarboxylation was then performed directly on the crude reaction mixture, without any prior purification, and this two-step sequence led to the quantitative isolation of derivative B3. The optimization work yielded several key improvements over previously reported routes. Most notably, the hazardous sodium hydride (NaH) was replaced with the safer and more manageable potassium carbonate (K_2CO_3). In addition, the process was made more cost-effective by employing Meldrum's acid as a cheaper starting material. Importantly, the method also avoids the use of transition metals in the deprotection step, enhancing the overall safety, sustainability, and economic viability of the synthesis. These advances make the developed approach not only efficient but also highly competitive.



Scheme 1.5 Hydrolysis and decarboxylation of intermediate B2.

Substrate B3 contained the ideal framework for the direct electrochemical transformation from carboxylic acid to alcohol. However, the decarboxylative reaction course can lead to the formation of several different products (Figure 1.5). A single electron oxidation of the

carboxylate followed by the loss of CO_2 results in the generation of a secondary radical that can combine with molecular oxygen and subsequently form, through the rearrangement of the hydroperoxide intermediate, the corresponding ketone. The radical can also undergo a second single electron oxidation, giving rise to a secondary carbocation. This intermediate is able to react with a nucleophile such as acetic acid or water, or alternatively eliminate a β-hydrogen to form an unsaturated byproduct. Our goal was to identify specific conditions that favored the generation of alcohol **B4** while minimizing the formation of undesired byproducts. The analysis of the reaction mixture was carried out using LC-MS, since it represented the most suitable method for the detection of all the structurally similar products that exhibited low UV absorption.

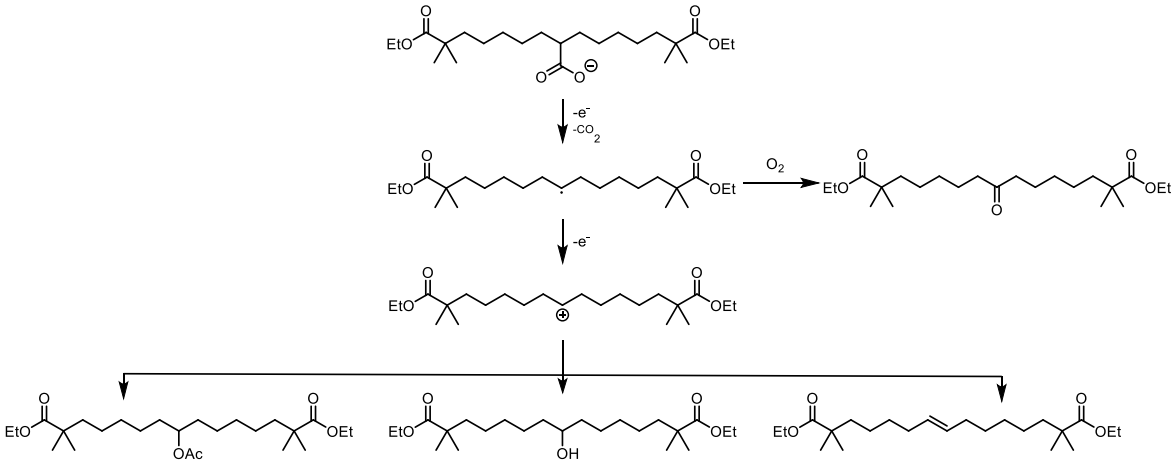
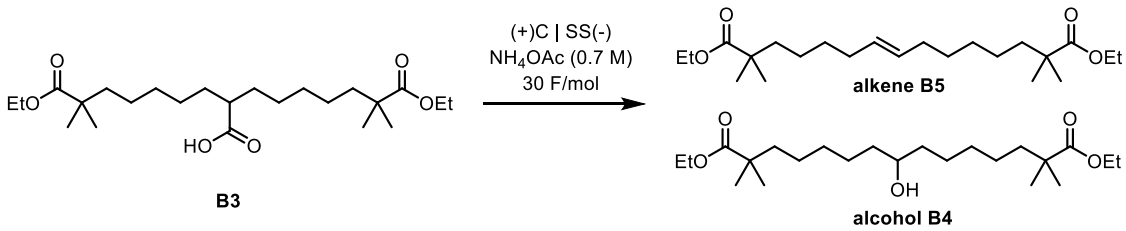


Figure 1.5 Possible products from electrochemical decarboxylation.

Our initial idea was to employ reaction conditions analogous to those reported by Cantillo for electrochemical acetoxylation (C anode, SS cathode, NaOAc in Acetic acid). In this context, the use of an acetate buffer was expected to facilitate decarboxylation while maintaining a stable pH throughout the electrolysis, thereby disfavoring the formation of olefinic byproducts. However, initial experiments employing acetic acid as the solvent resulted in no observable conversion. Consequently, a range of alternative polar solvents was subsequently evaluated. Table 1.2 summarizes the optimization of the electrochemical conversion of substrate B3 into the desired alcohol product under various conditions. Different solvents, additives, current intensities, and temperatures were tested in order to maximize the alcohol yield while minimizing the formation of the competing alkene byproduct. Among the solvents examined (DMF, DMSO, MeCN), only DMF consistently delivered satisfactory results. Both DMSO (Entry 2) and MeCN (Entry 3) provided significantly lower alcohol yields (23% and no detectable alcohol, respectively), confirming that DMF is the only suitable medium for this transformation. The presence of HFIP

(hexafluoroisopropanol) proved crucial, as conditions without it (entries 1-3) gave poorer results, while its inclusion at 20% v/v (entries 4-11) led to higher and more reproducible yields of alcohol. In terms of applied current, a clear trend emerged: higher current densities favored the formation of alcohol. For instance, under DMF/HFIP (20%) at 25 °C and low current (10 mA, Entry 4), the alcohol yield was 47%. Increasing the current to 50 mA (entry 5) improved the alcohol yield to 54%, while at 200 mA (entries 7-11) the alcohol reached up to 60% (Entry 11). Temperature effects were less decisive. At elevated temperature (50-75 °C), alcohol yields remained comparable or slightly improved compared to room temperature, although high current appeared to have a stronger impact than temperature alone. Finally, the addition of small amounts of water (entry 11, 2.0 eq) in combination with acetic acid at higher current (200 mA) provided the best conditions, affording 60% alcohol with only 39% alkene.

Table 1.2 Selected conditions for electrochemical decarboxylation.



Entry	Solvent	HFIP	T	Additive	Current	Alkene[b]	Alcohol[b]
1	DMF	10%	25 °C	AcOH 5%	20 mA	**50%**	**43%**
2	DMSO	-	25 °C	AcOH 15%	20 mA	**43%**	**23%**
3	MeCN	-	25 °C	AcOH 15%	20 mA	**31%**	**-**
4	DMF	20%	25 °C	AcOH 5%	10 mA	**52%**	**47%**
5	DMF	20%	25 °C	AcOH 5%	50 mA	**45%**	**54%**
6	DMF	20%	50 °C	AcOH 5%	50 mA	**41%**	**54%**
7	DMF	20%	50 °C	AcOH 5%	200 mA	**39%**	**51%**
8	DMF	20%	75 °C	AcOH 5%, H_2O 2.0 eq	200 mA	**45%**	**55%**
9	DMF	20%	50 °C	AcOH 5%, H_2O 10.0 eq	200 mA	**45%**	**33%**
10	DMF	20%	50 °C	H_2O 2.0 eq	200 mA	**55%**	**45%**
11	**DMF**	**20%**	**50 °C**	**AcOH 5%, H_2O 2.0 eq**	**200 mA**	39%	60%

[a]Conditions: 4 mL reaction mixture,5 mL ElectraSyn 2.0 vial, 0.3 mmol, 30 $Fmol^{-1}$. C= graphite; SS = stainless steel. [b]Calibrated LC-MS yield.

In summary, the proposed synthetic strategy for bempedoic acid represents a significant improvement over earlier methods, offering clear advantages in terms of safety, sustainability, and efficiency. By replacing hazardous reagents such as sodium hydride with safer bases like potassium carbonate, and avoiding toxic intermediates like tosylmethyl isocyanide, this approach substantially reduces the environmental and safety risks associated with the synthesis. The use of Meldrum's acid as a starting material not only lowers costs but it also allows the elimination of transition metals such as palladium. The electrochemical decarboxylation step was optimized to favor the formation of the desired alcohol intermediate with minimal byproduct formation, showcasing the method's selectivity and tunability. Key variables such as solvent system, current intensity, and additive presence were systematically optimized, with the best conditions yielding 60% alcohol.

Altogether, this synthetic route not only meets but also exceeds the criteria for a modern, scalable, and green approach to bempedoic acid production. It demonstrates a thoughtful integration of electrochemical innovation, cost-effectiveness, and safer chemistry.

1.2.2 Experimental details

General experimental details

NMR spectra were recorded on Bruker-400 MHz or Bruker-300 MHz spectrometer. The high resolution mass spectra were recorded on a Thermo LTQOrbitrap XL (ESI-). GC-MS analyses were performed on "Thermo scientific" Focus GC-DSQ II. Column chromatography was performed on silica gel Sigma-Aldrich High-purity grade (9385), pore size 60˚A (230-400 mesh). TLC was performed on GF-254 Merck (0.25 mm) per TLC Sigma-Aldrich. Electrolysis experiments have been performed on IKA Electrasyn 2.0. Flow electrochemical experiments have been performed using a peristaltic pump Vapourtech SF-10 and a self-assembled flow cell. All commercially available chemicals were used without purification unless otherwise noted.

Abbreviations

K2CO3: potassium carbonate

KI: potassium iodide

DMF: dimethylformamide

AcOH: acetic acid

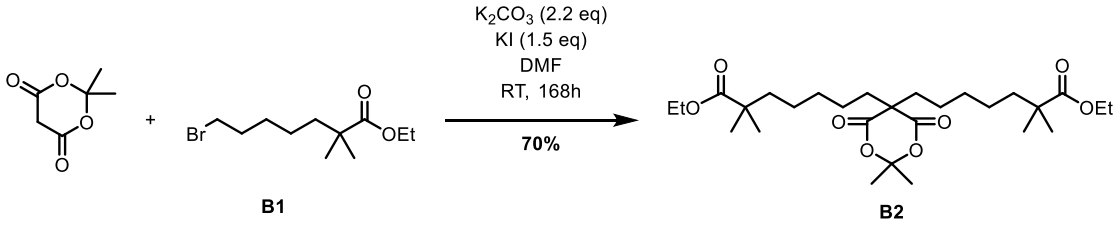
NH_4OAc: ammonium acetate

HFIP: 1,1,1,3,3,3-Hexafluoro-2-propanol

SS: stainless steel

C: graphite

diethyl 7,7'-(2,2-dimethyl-4,6-dioxo-1,3-dioxane-5,5-diyl)bis(2,2-dimethylheptanoate), B2

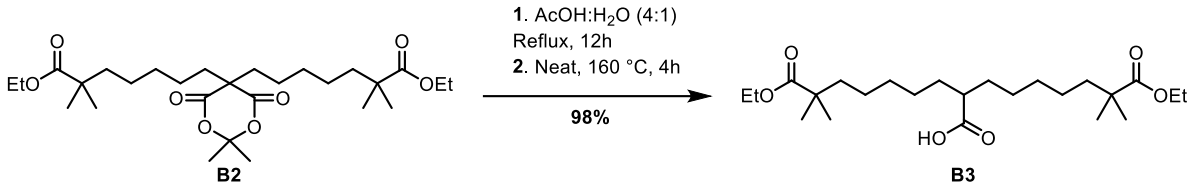


6.94 mmol of Meldrum's acid are dissolved in 10 mL of DMF, to which 15.26 mmol of potassium carbonate (2.11 g, 2.2 eq) and 10.41 mmol of KI (1.73 g, 1.5 eq) are added. After adding 13.88 mmol of B1 (3.68 g, 2.0 eq), the solution is stirred for 7 days. 70 mL of water are added to the reaction and the aqueous phase is extracted with 3x50 mL ethyl acetate. The organic phase is washed twice with water (50 mL) and once with brine (50 mL) and dried over Na2SO4. The crude product is purified by column chromatography using 80:20 hexane:ethyl acetate (1.5 L total) as the eluent. The isolated yield was 70%, corresponding to 2.5 g of B2 as clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J = 8.1 Hz, 4H), 2.02 (t, J = 7.1 Hz, 4H), 1.77 (s, 6H), 1.51 (m, 4H), 1.39 – 1.20 (m, 18H), 1.18 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 169.5, 105.5, 62.6, 56.0, 42.7, 36.4, 29.0, 28.6, 25.5, 23.8, 13.9.

9-ethoxy-2-(7-ethoxy-6,6-dimethyl-7-oxoheptyl)-8,8-dimethyl-9-oxononanoic acid, B3

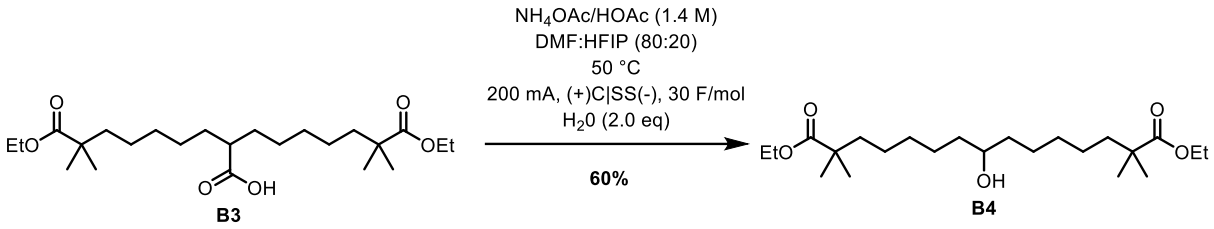


2.5 g of dialkylated Meldrum's acid B2 are added to 11 mL of acetic acid and 2.7 mL of water. The mixture is brought to reflux and stirred for 12 h. The solvent is removed by rotary evaporation and the crude product is heated to 160 °C for 4 h. 2.1 g of mono-acid B3, as a clear oil, are obtained without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 – 4.06 (q, J = 8.0 Hz, 4H), 2.51 (m, 1H), 1.74 (m, 2H), 1.67 – 1.50 (m, 6H), 1.34 – 1.10 (m, 30H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 178.8, 62.6, 45.5, 42.7, 39.6, 31.7, 29.0, 26.8, 25.5, 24.0, 13.9.

Diethyl 8-hydroxy-2,2,14,14-tetramethylpentadecanedioate, B4



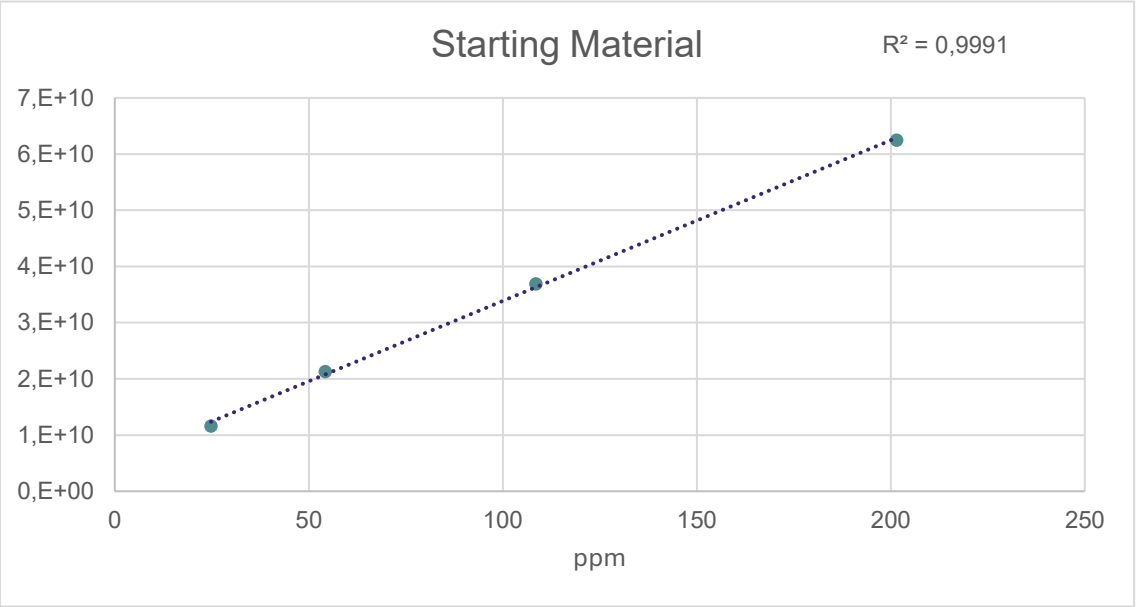
0.3 mmol of monoacid B3 (129 mg), 212 mg of NH_4OAc, 0.157 mL of acetic acid, and 0.011 mL of water (2.0 eq) are dissolved in 3.2 mL of DMF and 0.8 mL of HFIP. The solution is stirred for 15 minutes before connecting it to the potentiostat and applying 200 mA using graphite (anode) and steel (cathode) electrodes for 72 minutes (1000 rpm). After electrolysis, 10 mL of water are added, followed by extraction with ethyl acetate (3 × 20 mL), and the organic phase is dried over Na_2SO_4. The crude product is purified by column chromatography using a hexane (120 mL) and acetate (80 mL) eluent mixture. The final product B4 is obtained as a colorless oil in 60% yield.

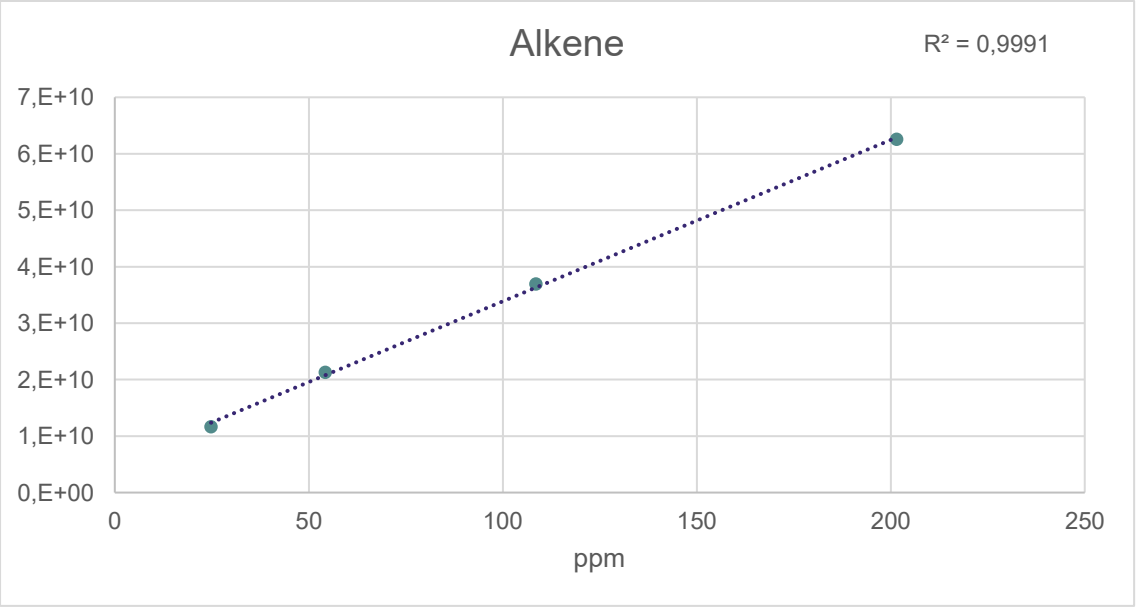
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (q, J = 7.1 Hz, 4H), 3.49 (t, J = 5.8 Hz, 1H), 3.41 (q, J = 7.0 Hz, 1H), 1.50 – 1.11 (m, 26H), 1.08 (s, 12H).

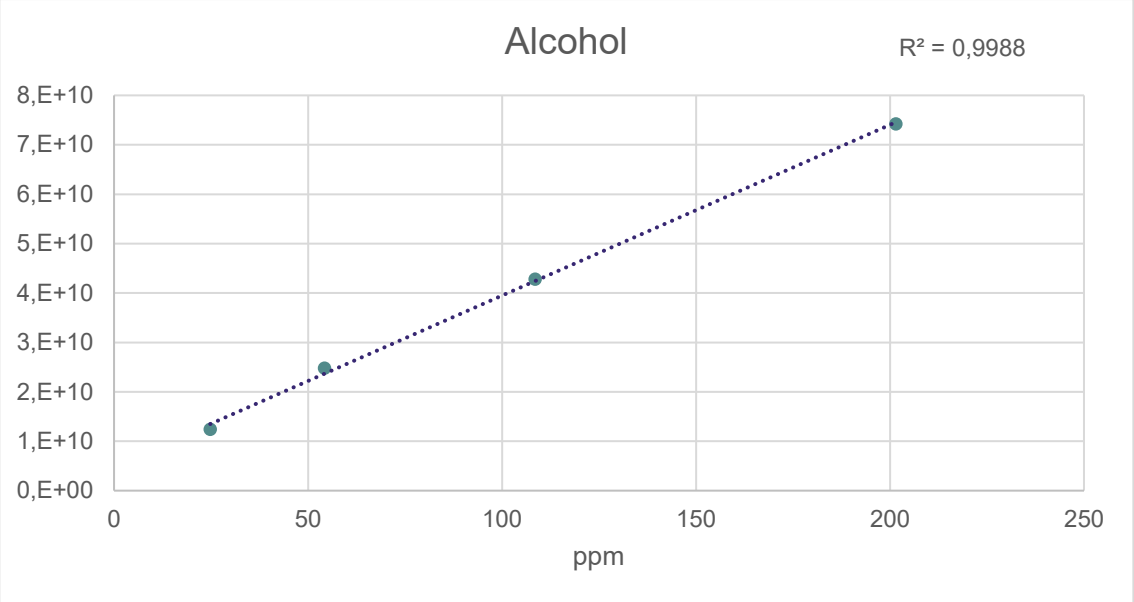
^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 71.3, 62.6, 42.7, 39.6, 37.9, 29.2, 25.5, 25.2, 24.0, 13.9.

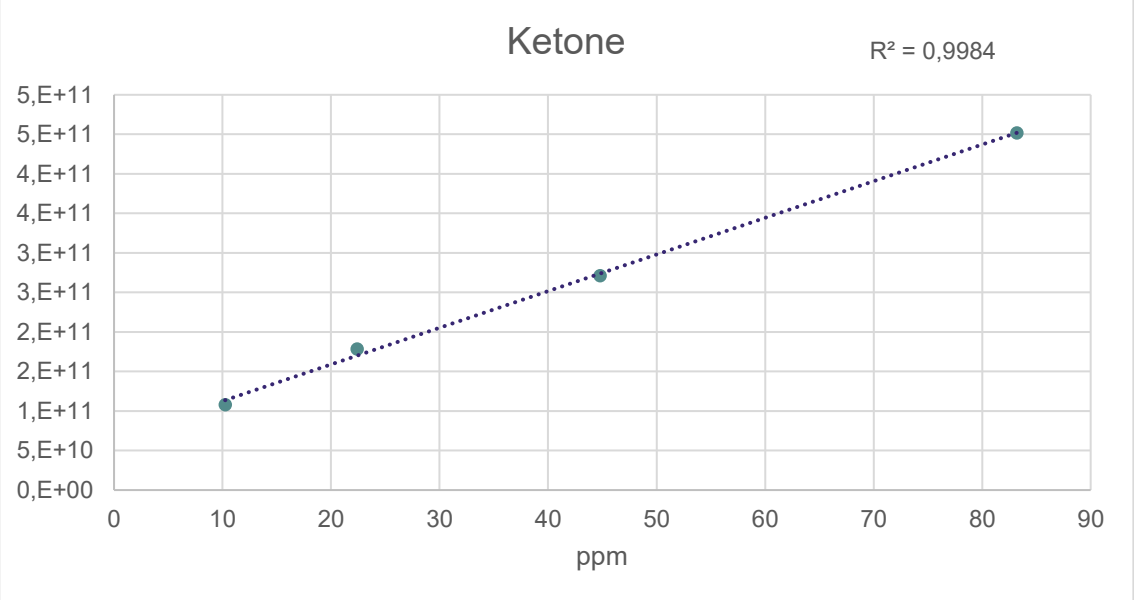
Calibration curve for LC-MS

The calibration curves were obtained by LC-MS analysis (LTQ XL Thermo) in SRM mode using isolated components.






Alcohol
R² = 0,9988
8,E+10
7,E+10
6,E+10
5,E+10
4,E+10
3,E+10
2,E+10
1,E+10
0,E+00
0
50
100
150
200
250
ppm


Ketone
R² = 0,9984
5,E+11
5,E+11
4,E+11
4,E+11
3,E+11
3,E+11
2,E+11
2,E+11
1,E+11
5,E+10
0,E+00
0
10
20
30
40
50
60
70
80
90
ppm

1.2.3 References

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Electrocatalytic Dehydrogenative Lactonization of Benzylic Alcohols: A Sustainable Access to Phthalides via NHPI Mediation

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Pietro Ronco and Antonia Simi performed and analyzed the experiments

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1.3 Electrocatalytic Dehydrogenative Lactonization of Benzylic Alcohols: A Sustainable Access to Phthalides via NHPI Mediation

Phthalides, consisting of a γ-lactone fused to a benzene ring, are common structural elements found in many biologically active and medicinally relevant compounds. Their unique scaffold is frequently encountered in pharmaceutical and natural products with therapeutic potential (Figure 1.6).[1-3]

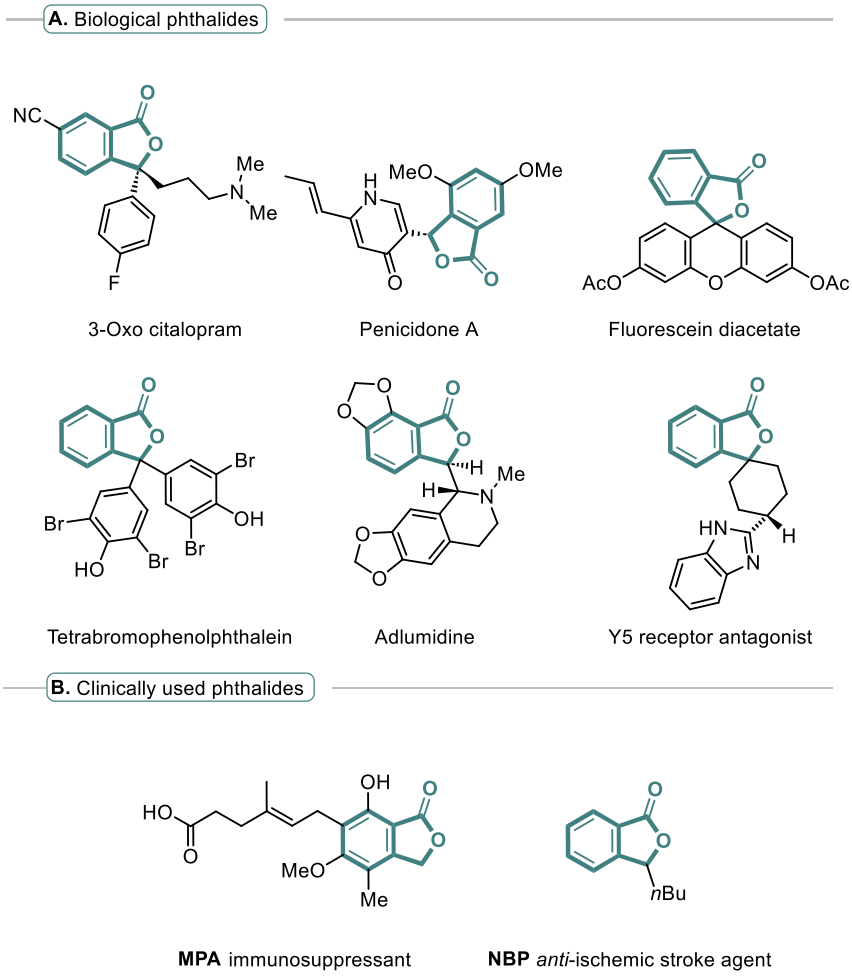
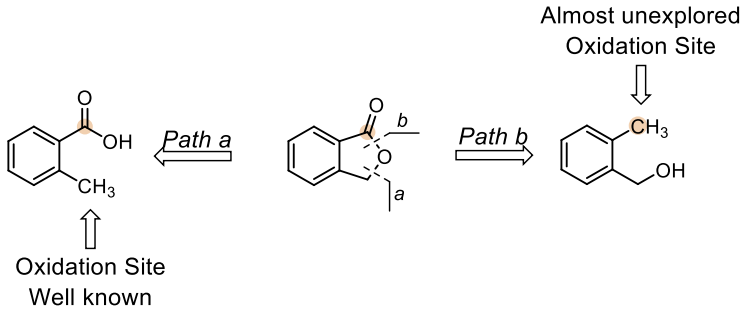


Figure 1.6 Representative biologically active and clinically used phthalide derivatives.

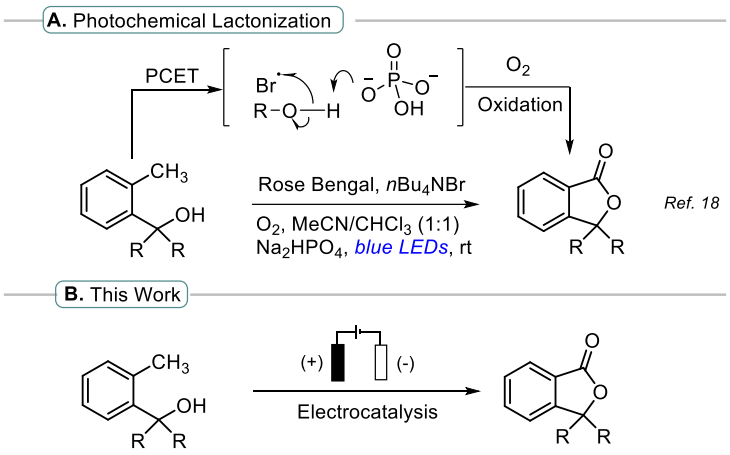
Given the significance of the phthalide framework, numerous synthetic strategies have been established for constructing the isobenzofuranone unit. Among these, methods that maximize atom-economy, such as direct oxidation processes and [4+1] annulations,[4] are particularly attractive. One of the most straightforward and atom-efficient disconnections involves direct dehydrogenative lactonization between a C(sp^3)-H bond and an oxygen-containing

functionality, such as COOH or OH (Scheme 1.6). In this context, the ortho-C(sp^3)-H oxidation of benzoic acids to generate the corresponding carbinol, followed by intramolecular lactonization, has been extensively developed through different catalytic systems. These include transition-metal catalysis,[5-8] photocatalysis,[9] electrochemical approaches,[10] and metal-free conditions,[11] as illustrated in Scheme 1.6, path a. Conversely, a complementary but less explored approach relies on the oxidation of the C(sp^3)-H group to a carboxylic acid, followed by simultaneous lactonization of a suitably positioned benzyl alcohol. This alternative pathway represents an emerging and underutilized paradigm for the synthesis of phthalides (Scheme 1.6, path b).



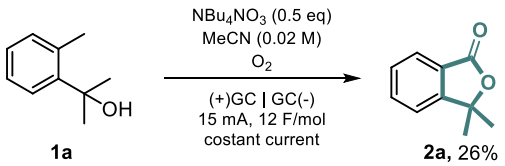
Scheme 1.6 Intuitive phthalide disconnection via *ortho*-C(sp^3)-H oxidation.

The earliest report of this strategy can be traced back to 1932, when $KMnO_4$ was employed as a stoichiometric oxidant,[12] and was later followed in 1976 by the use of the Jones reagent, a Cr(VI)-based oxidant now recognized for its genotoxic and carcinogenic properties.[13] In the context of modern sustainable chemistry, the pursuit of greener methodologies has highlighted photo- and electrocatalysis as transformative and environmentally friendly technologies.[14-17] Notably, in 2022, S. Cai and co-workers introduced an elegant photocatalytic protocol for this transformation (Scheme 1.7A).[18] Under photoexcited catalytic conditions, in situ generated open-shell hydrogen atom transfer (HAT) species, such as halogen radicals, have been proposed to cooperate with a Brønsted base to promote homolytic cleavage of the O-H bond of alcohol substrates, thereby generating alkoxy radicals. These intermediates can undergo a selective 1,5-hydrogen atom transfer from a benzylic -–H bond to form a benzylic radical, which subsequently engages in a sequence of oxygen trapping, acylation, and oxidation steps to afford the corresponding phthalide products. In contrast, the development of a related electrocatalytic variant remains largely unexplored, representing a promising opportunity for further methodological advancement (Scheme 1.7B).



Scheme 1.7 A. photocatalytic blue LED promoted dehydrogenative lactonization by proton-coupled electron transfer on *ortho*-methyl benzyl alcohol; **B.** electrocatalytic approach developed in this work.

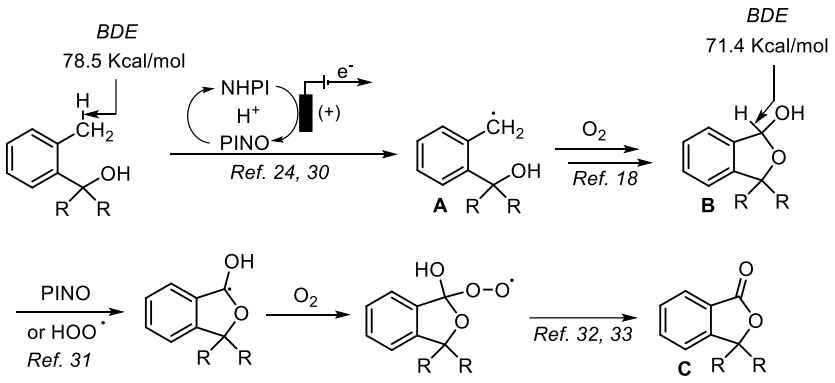
We anticipated that the key challenge in our strategy would be the oxidation of a C(sp^3) carbon to a carboxylic C(sp^2) carbon under electrocatalytic conditions. While electrochemical methods for the oxidation of methyl-arenes to their corresponding aldehydes are well established, direct C(sp^3) oxidation to carboxylic acids remains problematic. Reported approaches often suffer from significant limitations, including low yields,[19] the need for elevated temperatures, the use of catalysts,[20] strongly acidic media,[21] narrow substrate scope, or reliance on lanthanoid-based electrochemical mediators.[22] In 2023, S. Waldvogel and co-workers introduced a noteworthy advancement by developing an electrochemical protocol for the oxidation of C(sp^3) carbons to carboxylic acids using simple nitrate salts and oxygen, achieving broader substrate compatibility.[23] However, when these nitrate-mediated electro-oxidative conditions were applied to substrate 1, the desired lactone 2a was isolated in only 26% yield (Scheme 1.8).



Scheme 1.8 Electrochemical aerobic lactonization under Waldvogel conditions.

To overcome this limitation, we directed our efforts toward exploiting the unique oxidative capacity of N-hydroxyphthalimide (NHPI) as a mediator. Under electrochemical conditions, NHPI is transformed into the phthalimide-N-oxyl (PINO)

radical through abstraction of its O-H hydrogen.[24-30] We hypothesized that PINO could abstract the benzylic hydrogen of substrate 1 to generate radical intermediate A, which would subsequently undergo oxygen capture and elimination to afford hemiacetal B (Scheme 1.9). A second oxidation step, mediated by another PINO radical, could then convert hemiacetal B into the corresponding lactone C via hydrogen abstraction at the hemiacetal C-H bond.[31-34] This pathway appears particularly favorable, as supported by the low bond dissociation energy (BDE) estimated for the relevant C-H bond.[35]



Scheme 1.9 Working hypothesis for electrocatalytic direct dehydrogenative lactonization between the C(sp^3)-H and benzylic alcohol. BDE = Bond Dissociation Energy; NHPI = *N*-hydroxyphthalimide; PINO = phthalimide-*N*-oxyl radical.

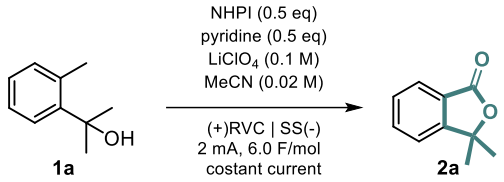
1.3.1 Results and discussion

The electrochemical lactonizations were carried out under various conditions, including alterations in current density, cathode and anode materials, base, and substrate concentration. Each condition was systematically investigated on the model substrate 1a (Table 1.3) to understand its influence on the overall catalytic process. The optimal conditions were identified with 0.5 equivalents of NHPI and pyridine, an RVC anode, a stainless steel cathode, an applied current of 2.0 mA, and a substrate concentration of 0.04 M in acetonitrile.

Entries 2 and 3 furnished lower yields when the current density was increased. The applied current has emerged as a crucial parameter in the catalytic process, with a value of 2.0 mA demonstrating enhanced yield. This observation underscored the critical role of current modulation in optimizing the catalytic efficiency. Graphite cathode led to an 88% yield, while platinum cathode slightly enhanced the yield to 95%. The stainless steel cathode demonstrated yields comparable to those achieved with the platinum cathode. Considering its cost-effectiveness, stainless steel was selected as the preferred cathode for subsequent reactions. Modifying the anode material to graphite resulted in an 85% yield, while a subsequent transition to a glassy carbon (GC) anode yielded a reduced 82% (Entry 7). The increased surface area of the reticulated vitreous carbon (RVC) electrode contributed to an improved yield in the reaction. The threshold for maintaining elevated reaction yields with NHPI is observed at a minimum of 0.5 equivalents. Below this value, a substantial reduction in the reaction yield was observed (Entry 8). Substituting pyridine with collidine preserved a high yield of 90%, highlighting its compatibility with the electrocatalytic system. However, the introduction of an inorganic base, such as Li_2CO_3, led to a significant reduction in yield to 40%. Increasing the concentration to 0.04 M did not produce observable variations in reaction yield.

Remarkably, under the optimized electrochemical conditions employing NHPI (0.5 eq.) as mediator, pyridine (0.5 eq.) as additive, $LiClO_4$ (0.1 M) as supporting electrolyte, and MeCN (0.02 M) as solvent, in combination with a reticulated vitreous carbon (RVC) cathode and a stainless-steel anode, at a constant current of 2 mA delivering 6.0 F/mol, the model substrate 1a was efficiently transformed into the desired lactone 2a. This transformation proceeded with an excellent 95% isolated yield, clearly demonstrating the effectiveness of the optimized electrocatalytic protocol.

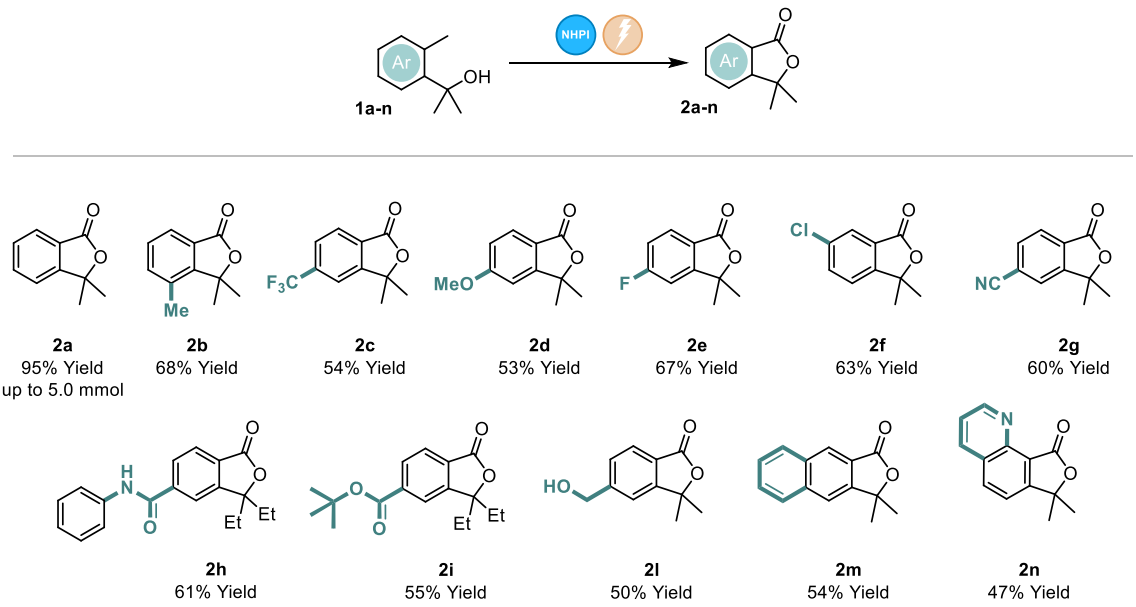
Table 1.3 Optimization of Reaction Conditions[a].



Entry	Variation from standard condition	Yield[b]
1	none	99% (95)[c]
2	4.0 mA	40%
3	3.0 mA	91%
4	Graphite cathode	88%
5	Platinum cathode	95%
6	Graphite anode	85%
7	GC anode	82%
8	NHPI (0.7 eq)	99%
9	NHPI (0.3 eq)	68%
10	Collidine instead pyridine	90%
11	Li_2CO_3 instead pyridine	40%
12	Pyridine (1.0 eq) instead pyridine	99%
13	Substrate concentration 0.04 M	95%

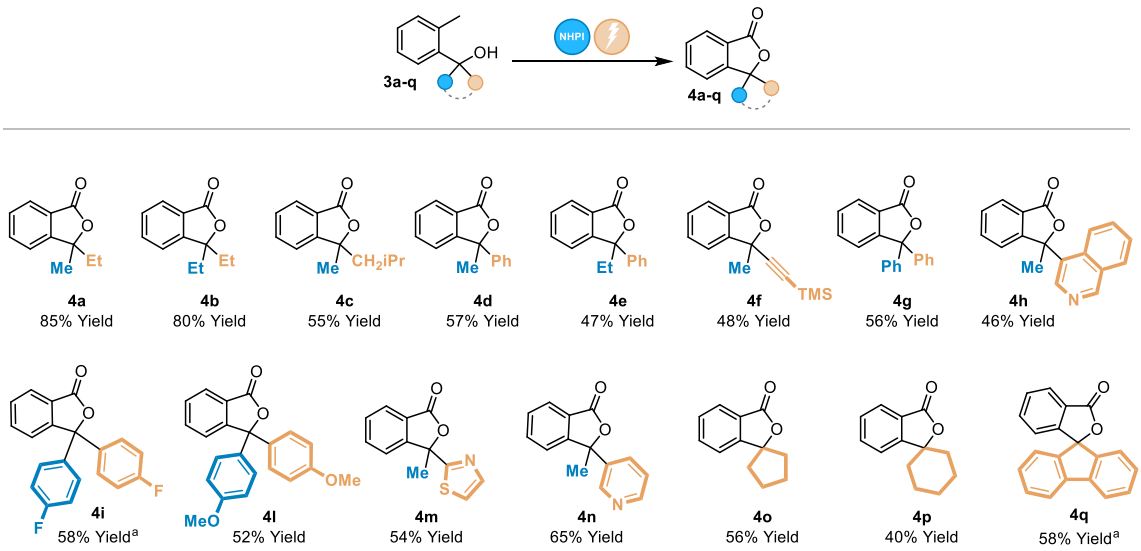
[a]Conditions: 10 mL reaction mixture,10 mL ElectraSyn 2.0 vial, constant current 16 h for 0.2 mmol. RVC= reticulated vitreous carbon; SS = stainless steel. [b]Calibrated HPLC yield. [c]Isolated yield.

Having established appropriate reaction conditions, we explored the scope of the electrochemical lactonization catalyzed by NHPI (Scheme 1.10). We started by testing the reaction with different substituted tertiary alcohols: first, we explored the reactivity of substituted aromatic rings under our reaction conditions. Both electron-donating and electron-withdrawing groups exhibited good reactivity, indicating broad functional group tolerance. Additionally, benzofused aromatic cores performed well, delivering high yields under these conditions, further highlighting the robustness of the transformation. Notably model substrate 2a was obtained in 85% yield from a scale-up experiment on 5.0 mmol.



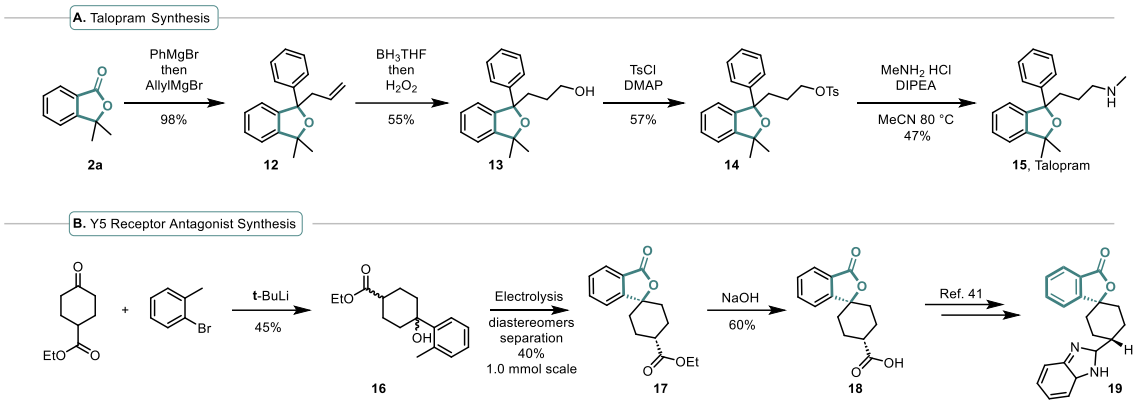
Scheme 1.10 Aromatic functionalized substrates scope. *Reaction conditions*: 10 mL MeCN,10 mL ElectraSyn 2.0 vial, constant current 2.0 mA 16 h, RVC, SS, NHPI (0.5 eq), Py (0.5 eq), $LiClO_4$ (0.1 M).

Then, we investigated the optimized transformation across various substitutions patterns at the benzylic position (Scheme 1.11). Various alkyl substituents allowed high reactivity, affording good yields under the optimized conditions. Sterically hindered diaryl-substituted substrates exhibited higher yields when employing 1.5 equivalents of NHPI. Additionally, the reaction demonstrated excellent tolerance toward heterocyclic substituents, further expanding its applicability. Remarkably, spirocyclic lactones were successfully synthesized with good yields, underlining the method's efficiency in constructing structurally complex frameworks.



Scheme 1.11 Benzylic substituted substrates scope. *Reaction conditions*: 10 mL MeCN,10 mL ElectraSyn 2.0 vial, constant current 2.0 mA 16 h, RVC, SS, NHPI (0.5 eq), Py (0.5 eq), $LiClO_4$ (0.1 M); a) 1.0 eq NHPI e 1.0 eq Py.

To further demonstrate the synthetic versatility of our electrocatalytic direct dehydrogenative lactonization, we extended its application to the preparation of biologically relevant molecules, including the norepinephrine transporter inhibitor talopram and an advanced intermediate (18) and to neuropeptide Y5 receptor antagonists (Scheme 1.12).[36] Beginning with lactone 2a, talopram was efficiently synthesized in four steps by following the established Newman protocol (Scheme 1.12A).[37] In addition, spiro-isobenzofuran-4-carboxylic acid 18 was obtained in three steps starting from 4-carboxyethylcyclohexanone. The key transformation involved the in situ generation of *o*-tolyllithium from 2-bromotoluene and *t*-BuLi, which successfully added to the ketone substrate. Notably, standard organolithium (n-BuLi) and Grignard reagents failed to deliver the desired tertiary alcohol. The resulting intermediate alcohol 16 was subsequently subjected to our optimized electrocatalytic oxidation, affording lactone 17 in 40% isolated yield on a 1.0 mmol scale, following diastereomer separation (2:1 trans:cis). Hydrolysis of 17 under basic conditions (NaOH) then furnished carboxylic acid 18, representing a key advanced intermediate toward the synthesis of Y5 receptor antagonists (Scheme 1.12B).



Scheme 1.12 A. Synthesis of Talopram; **B.** Synthesis of intermediate 18 for the Y5 receptor antagonist.

The proposed mechanism for the electrocatalytic direct dehydrogenative lactonization between the C(sp^3)-H and the benzylic alcohol follows a sequence of radical-driven transformations. As shown in Scheme 8, the process begins with the anodic oxidation of *N*-hydroxyphthalimide (NHPI), which generates the active phthalimide *N*-oxyl (PINO) radical[38-39] as confirmed by cyclic-voltammetry studies (Figure 1.7A). These studies also demonstrate that the presence of pyridine is essential in lowering the oxidation potential of the NHPI mediator, due to the stabilization of the PINO radical.[40] This species plays a crucial role in facilitating hydrogen atom transfer (HAT) from the benzylic alcohol, effectively converting it into a benzylic radical. Once formed, this benzylic radical captures an oxygen atom to form a peroxy intermediate. This intermediate undergoes a Russell-type rearrangement, introducing a carbonyl functional group at the benzylic position (Figure 1.7C). This key step sets the stage for the subsequent lactonization process. With the carbonyl in place, an intramolecular nucleophilic attack by the hydroxyl group occurs, driving the formation of the benzofused lactone ring. Meanwhile, pyridine acts as a proton shuttle, facilitating the release of protons at the cathode, thereby improving overall efficiency.

To validate our mechanistic hypothesis, we conducted a series of control experiments (Figure 1.7B). The presence of molecular oxygen proved to be crucial for the reaction outcome, as degassing the reaction mixture with argon for 15 minutes resulted in a significant decrease in yield. Additionally, the use of tert-butyl hydroperoxide (*t*-BuOOH) as an alternative oxidant led to comparable reactivity, suggesting a common radical-mediated pathway. The formation of the desired product from a lactol precursor further supports the involvement of this transient intermediate during the reaction.

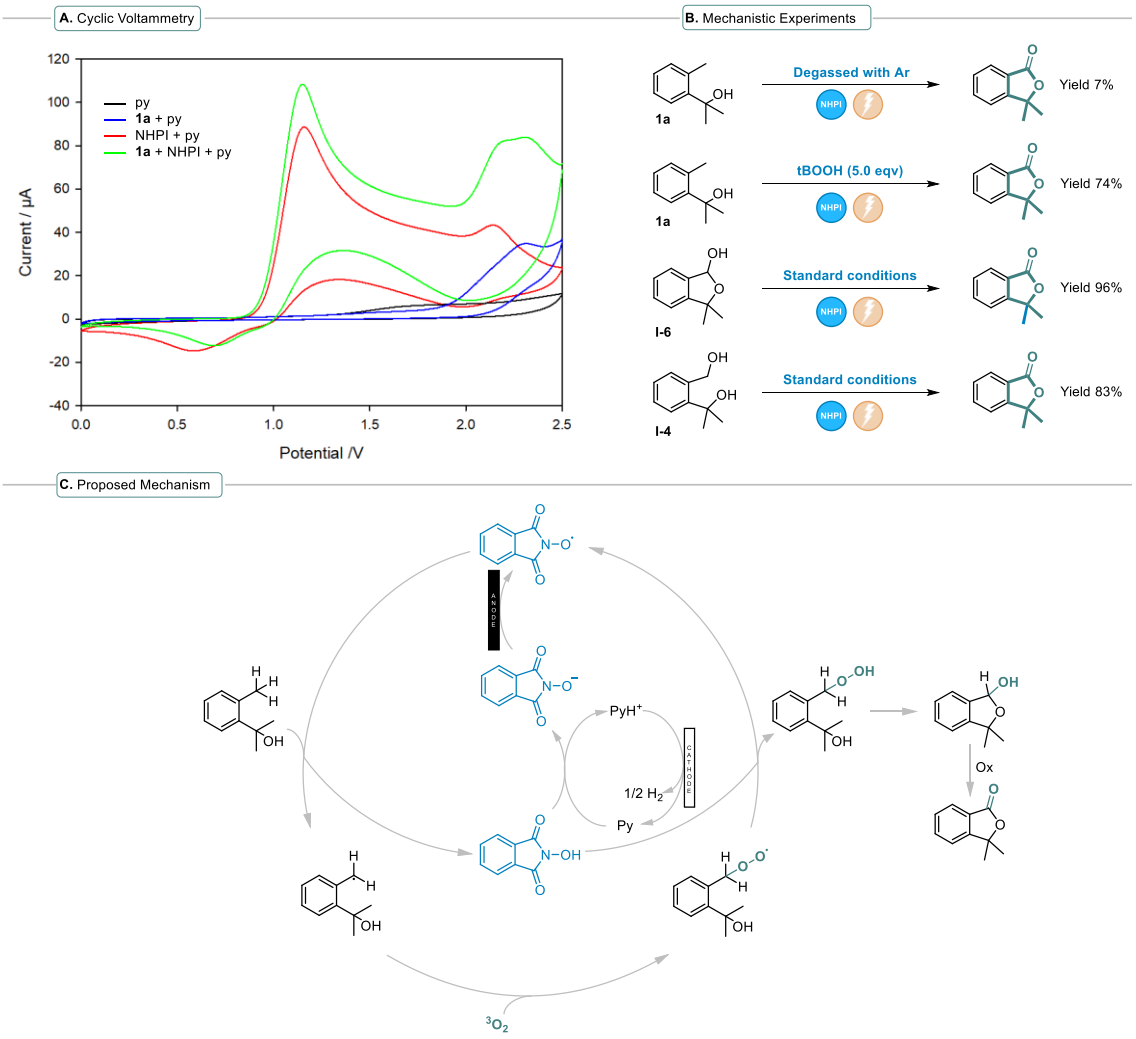


Figure 1.7 A. CVs of pyridine (5 mM) in acetonitrile (**black**); **1a** and pyridine (5 mM) in acetonitrile (**blue**); NHPI and pyridine (5 mM) in acetonitrile (**red**); NHPI, **1a** and pyridine in acetonitrile (**green**). Other conditions: glassy carbon working electrode, scan rate = 0.1 V/s, and 0.1 M $LiClO_4$ electrolyte; **B.** Mechanistic experiments; **C.** Proposed mechanism for NHPI promoted lactonization.

In this chapter, we developed a novel electrocatalytic method for direct dehydrogenative lactonization between benzylic C(sp^3)-H bonds and proximal hydroxyl groups using NHPI as a redox mediator. The approach effectively overcomes long-standing challenges in benzylic oxidation, achieving high yields under mild and sustainable conditions without relying on toxic or heavy-metal catalysts. Key parameters such as current intensity, electrode materials, and NHPI loading; were systematically optimized, leading to a robust and scalable protocol. The reaction showcased broad functional group tolerance and was applicable to structurally diverse substrates, including the synthesis of complex spirocyclic and biologically relevant lactones. Mechanistic studies confirmed the involvement of a PINO-radical-mediated pathway and highlighted the essential role of pyridine in stabilizing the mediator. This work not only expands the utility of NHPI in electro-organic synthesis but

also provides a practical and green alternative for constructing pharmaceutically valuable phthalide frameworks.

1.3.2 Experimental details

General experimental details

NMR spectra were recorded on Bruker-400 MHz or Bruker-300 MHz spectrometer. The high resolution mass spectra were recorded on a Thermo LTQOrbitrap XL (ESI-). GC-MS analyses were performed on "Thermo scientific" Focus GC-DSQ II. Column chromatography was performed on silica gel Sigma-Aldrich High-purity grade (9385), pore size 60˚A (230-400 mesh). TLC was performed on GF-254 Merck (0.25 mm) per TLC Sigma-Aldrich. Electrolysis experiments have been performed on IKA Electrasyn 2.0. Flow electrochemical experiments have been performed using a peristaltic pump Vapourtech SF-10 and a self-assembled flow cell. All commercially available chemicals were used without purification unless otherwise noted.

Abbreviations

BuLi: n-butyl lithium

$LiClO_4$: Lithium Perchlorate

NHPI: n-hydroxyphthalimide

Li_2CO_3 : lithium carbonate

TBSCl: tert-Butyldimethylsilyl chloride

MeMgBr: methylmagnesium bromide

EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

DMAP: 4-Dimethylaminopyridine

MnO_2 : Manganese dioxide

Et_2O: diethylether

EtOH: ethanol

EtOAc: ethyl acetate

MeCN: acetonitrile

THF: tetrahydrofuran

DCM: dichloromethane

TBSCl: tert-Butyldimethylsilyl chloride

C: graphite

GC: glassy carbon

RVC: reticulated vitreous carbon

CF: carbon felt

Pt: platinum

SS: stainless steel

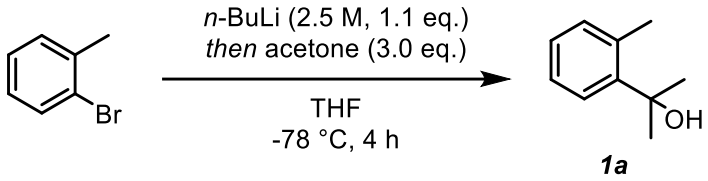
TLC: thin layer chromatography

t-BuLi: Tert-Butyllithium

$LiBH_4$: lithium borohydride

I. Synthesis of starting materials

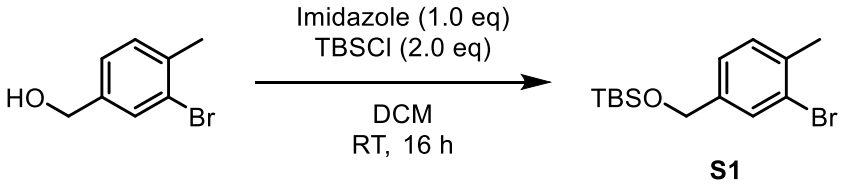
2-(o-tolyl)propan-2-ol (1a)



1a

A flame-dried round bottom flask was charged with 2-bromotoluene (1.0 eq., 16.6 mmol, 2.00 mL). Anhydrous THF (50 mL) was added under nitrogen, followed by *n*-BuLi (1.1 eq., 18.3 mmol, 7.30 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 30 min and then freshly distilled acetone (3.0 eq., 50 mmol, 3.66 mL) was added dropwise. The reaction was stirred at -78 °C for 4 hours and then quenched with saturated aqueous NH_4Cl (50 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x30 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, 9:1 Hexane/EtOAc) to afford the title compound (**1a**) as a colorless oil (1.43 g, 53%). Data in accordance with literature (41).

((3-bromo-4-methylbenzyl)oxy)(tert-butyl)dimethylsilane (S1)

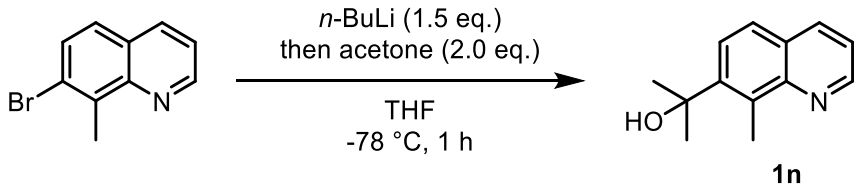


S1

To a solution of (3-bromo-4-methylphenyl)methanol (1.0 eq., 2.49 mmol, 2.00 mL) in anhydrous DCM (10 mL) under N_2 at room temperature was added TBSCl (2.0 eq., 4.97 mmol, 750 mg) portion-wise, followed by imidazole (1.0 eq., 2.5 mmol, 169 mg). The reaction was stirred for 16 hours and then quenched with water (10 mL). The organics were separated and the aqueous phase was extracted with DCM three times (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, 95:5 Hexane/EtOAc) to afford the title compound (**S1)** as a colorless oil (790 mg, 90%). Data in accordance with the literature (42).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.20 – 7.12 (m, 2H), 4.67 (s, 2H), 2.37 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H).

2-(8-methylquinolin-7-yl)propan-2-ol (1n)



1n

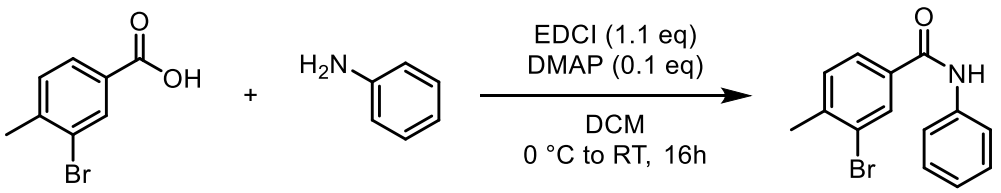
To a solution of 7-bromo-8-methylquinoline (1.0 eq., 1.35 mmol) in anhydrous THF (10 mL) under nitrogen was added *n*-BuLi (1.5 eq., 2.03 mmol, 810 µL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 30 min and then the freshly distilled acetone (2.0 eq., 2.70 mmol, 0.20 mL) was added dropwise. The reaction was stirred at -78 °C for 1 hour and then quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 8:2) to afford the title compound (**1n)** as a yellow oil (20%, 54 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, J = 4.2, 1.9 Hz, 1H), 8.07 (dd, J = 8.2, 1.9 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.2, 4.2 Hz, 1H), 3.07 (s, 3H), 2.15 (s, 1H), 1.77 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 148.2, 146.5, 136.0, 134.4, 126.9, 125.0, 124.5, 120.6, 73.9, 31.3, 15.8.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{13}H_{15}NO$, 201.1154; found: 201.1159.

3-bromo-4-methyl-N-phenylbenzamide (S2)



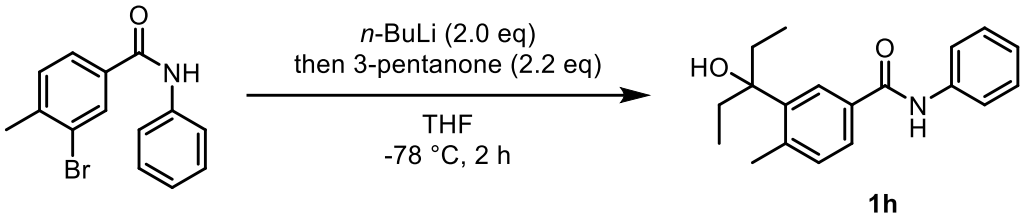
S2

Aniline (0.9 eq., 4.18 mmol, 380 µL) was added to a solution 4-bromo-3-methylbenzoic acid (1.0 eq, 4.65 mmol, 1.0 g), EDCI (1.1 eq., 5.11 mmol, 980 mg) DMAP (0.1 eq., 0.465 mmol, 47 mg) in anhydrous DCM (10 mL) at 0 °C. The reaction was stirred at RT for 16 hours and then quenched with 1.0 M aqueous HCl (10 mL). The organic phase was separated and the aqueous phase was extracted with DCM (3x10 mL). The reunited organics were washed with 1.0 M HCl and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting solid was washed on a fritted filter with Et_2O three times to obtain the title compound (**S2**) as a white solid (76%, 1.03 g). Data in accordance with literature (43).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.68 – 7.59 (m, 3H), 7.52 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.21 – 7.12 (m, 1H), 2.48 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): 163.8, 141.1,139.0, 134.4, 131.1, 131.1, 128.6 , 127.1, 124.1, 123.8, 120.5, 22.5.

3-(3-hydroxypentan-3-yl)-4-methyl-N-phenylbenzamide (1h)



1h

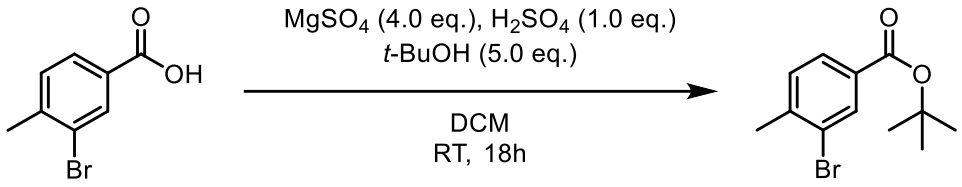
To a solution of **24a** (1.0 eq., 2.74 mmol) in anhydrous THF (25 mL) under N_2 was added *n*-BuLi (2.0 eq., 5.49 mmol, 2.19 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 1 hour and then freshly distilled 3-pentanone (2.2 eq., 6.04 mmol, 640 µL) was added dropwise. The reaction was stirred at -78 °C for 1 hour and then quenched with saturated aqueous NH_4Cl (25 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 9:1) to afford the title compound (**1h)** as a (40%, 325 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.68 – 7.55 (m, 5H), 7.40 – 7.31 (m, 2H), 7.18 – 7.09 (m, 1H), 2.54 (s, 3H), 2.15 – 1.99 (m, 2H), 1.94 – 1.79 (m, 2H), 1.74 (s, 1H), 0.77 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 147.1, 138.1, 135.8, 133.1, 131.3, 129.1, 128.0, 124.5, 123.8, 120.2, 78.9, 33.5, 22.6, 8.0.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{19}H_{23}NO$, 297.1729; found: 297.1722.

tert-butyl 3-bromo-4-methylbenzoate (S3)



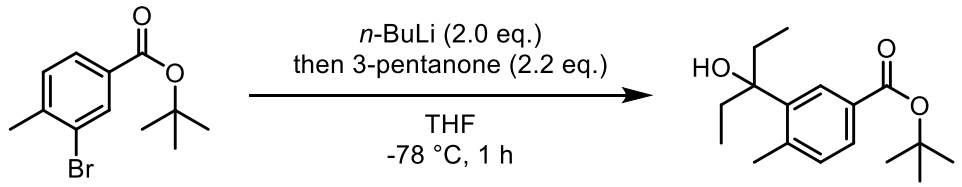
S3

To a vigorously stirred suspension of anhydrous magnesium sulfate (4.0 eq., 40 mmol, 4.81 g) in DCM (40 mL) was added concentrated sulfuric acid (1.0 eq., 10 mmol, 0.55 mL). The mixture was stirred for 15 minutes. Then 4-bromo-3-methylbenzoic acid (1.0 eq., 2.15 g, 10 mmol,) was added, followed by *t*-BuOH (5.0 eq., 50 mmol, 4.78 mL). The reaction was stirred at 25°C for 18 hours, then quenched with saturated aqueous $NaHCO_3$ (75 mL). The organic phase was separated and the aqueous phase was extracted with DCM (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 95:5) to afford the title compound (**S3)** as a yellow oil (42%, 1.11 g). Data in accordance with literature (44).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 2.42 (s, 3H), 1.58 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.20, 137.92, 132.27, 131.54, 131.12, 129.79, 128.17, 81.26, 28.17, 22.85.

tert-butyl 3-(3-hydroxypentan-3-yl)-4-methylbenzoate (1i)



1i

To a solution of **S3** (1.0 eq, 2.80 mmol) in anhydrous THF (25 mL) under N_2 was added *n*-BuLi (1.7 eq., 4.76 mmol, 1.90 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 15 minutes and then freshly distilled 3-pentanone (2.1 eq., 5.89

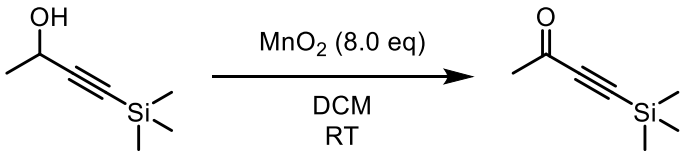
mmol, 620 µL) was added dropwise. The reaction was stirred at -78 °C for 45 minutes and then quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 9:1) to afford the title compound (**1i)** as a yellow oil (55%, 433 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.53 (d, *J* = 8.1 Hz, 1H), 2.51 (s, 3H), 2.13 – 2.00 (m, 2H), 1.88 – 1.78 (m, 2H), 1.71 (s, 1H), 1.59 (s, 9H), 0.75 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.91, 147.64, 135.04, 133.30, 130.20, 127.54, 126.54, 80.75, 78.94, 33.50, 28.22, 22.50, 7.98.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{17}H_{26}O_3$, 278.1882; found: 278.1888.

4-(trimethylsilyl)but-3-yn-2-one (S4)

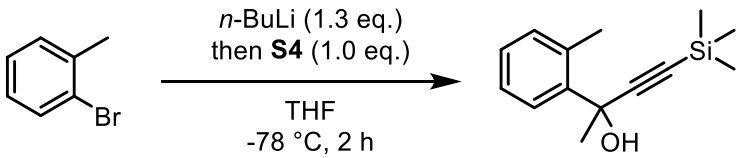


1.0 eq of 4-(Trimethylsilyl)-3-butyn-2-ol (6.13 mmol, 1.00 mL) was added To a mixture of manganese dioxide (8.0 eq, 49.0 mmol) in anhydrous DCM (10 mL) at room temperature. The reaction was stirred at room temperature until the total conversion of alcohol monitored by TLC.

The mixture was filtered over silica and the solid residue washed three times with DCM (3x10 mL). The organic phase was dried over sodium sulphate then the solvent was evaporated under vacuum.

The resulting colorless oil was used for synthesis of 29b. Y: 93% (798 mg) The ^{1}H NMR analysis was correspondent to the one reported by D. Lee et al. (45)

2-(o-tolyl)-4-(trimethylsilyl)but-3-yn-2-ol (3f)

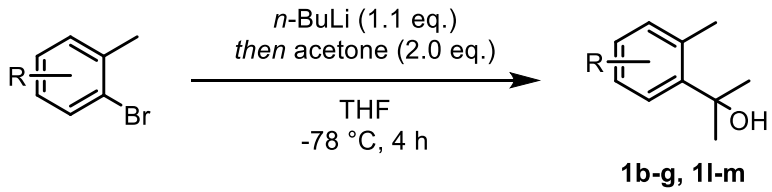


To a solution of 2-bromotoluene (1.2 eq., 6.83 mmol, 0.80 mL) in anhydrous THF (20 mL) under N_2 was added *n*-BuLi (1.3 eq., 7.40 mmol, 2.96 mL, 2.5 M in hexane) at -78 °C. The reaction was stirred at the same temperature for 30 min and then 4-(trimethylsilyl)but-3-yn-2-one (1.0 eq., 796 mg, 5.69 mmol,) dissolved in THF (5 mL) was added dropwise. The reaction was stirred at -78 °C for 2 hours and then quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 9:1) to afford the title compound (**1i)** as a colorless oil (58%, 770 mg). Data in accordance with literature (46).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 1H), 7.27 – 7.16 (m, 3H), 2.65 (s, 3H), 2.54 (s, 1H), 1.84 (s, 3H), 0.21 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.30, 135.82, 132.41, 127.82, 125.91, 125.09, 109.31, 89.10, 69.89, 31.11, 21.40, -0.07.

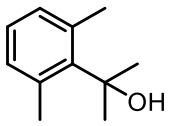
II. General Procedure (GP1)



1b-g, 1l-m

A flame-dried round bottom flask was charged with the appropriate aryl bromide (1.0 eq., 2.50 mmol). Anhydrous THF (15 mL) was added under N_2, followed by *n*-BuLi (1.1 eq., 2.80 mmol, 1.10 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 30 min and then freshly distilled acetone (2.0 eq., 5.0 mmol, 370 µL) was added dropwise. The reaction was stirred at -78 °C for 1-4 hours and then quenched with saturated aqueous NH_4Cl (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc).

2-(2,6-dimethylphenyl)propan-2-ol (1b)

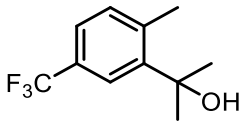


Following **GP1**, 2-bromo-1,3-dimethylbenzene gave the title compound (**1b**) as a clear oil after flash column chromatography (156 mg, 38%). Data in accordance with literature (47).

^{1}H NMR (400 MHz, CDCl3) δ 7.00 (s, 3H), 2.54 (s, 6H), 1.74 (s, 6H); 1.68 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 135.9, 131.1, 126.1, 76.0, 31.7, 25.2.

2-(2-methyl-5-(trifluoromethyl)phenyl)propan-2-ol (1c)

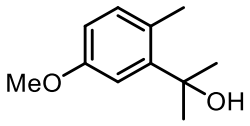


Following **GP1**, 2-bromo-1-methyl-4-(trifluoromethyl)benzene gave the title compound (**1c**) as a clear oil after flash column chromatography (350 mg, 64%). Data in accordance with literature (48).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 1H), 7.35 – 7.29 (m, 1H), 7.18 (m, 1H), 2.55 (s, 3H), 1.69 (s, 1H), 1.60 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 140.1, 132.9, 127.9 (q, J = 32.1 Hz), 124.4 (q, J = 271.9 Hz), 123.7 (q, J = 3.8 Hz), 122.2 (q, J = 3.8 Hz), 73.4, 30.7, 22.2.

2-(5-methoxy-2-methylphenyl)propan-2-ol (1d)

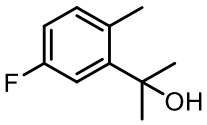


Following **GP1**, 2-bromo-4-methoxy-1-methylbenzene gave the title compound (**1d**) as a clear oil after flash column chromatography (333.5 mg, 74%). Data in accordance with literature (48).

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.13 – 6.98 (m, 2H), 6.70 (dd, J = 8.3, 2.8 Hz, 1H), 3.79 (s, 3H), 2.50 (s, 3H), 1.76 (s, 1H), 1.64 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 147.2, 133.4, 127.5, 112.2, 111.2, 73.6, 55.3, 30.6, 21.3.

2-(5-fluoro-2-methylphenyl)propan-2-ol (1e)

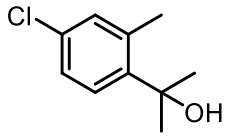


Following **GP1**, 2-bromo-4-fluoro-1-methylbenzene gave the title compound (**1e**) as a clear oil after flash column chromatography (260 mg, 62%). Data in accordance with literature (9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 11.3, 2.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.83 (td, J = 8.0, 2.8 Hz, 1H), 2.55 – 2.49 (m, 3H), 1.87 (s, 1H), 1.63 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0 (d, J = 242.6 Hz), 148.0 (d, J = 5.8 Hz), 133.7 (d, J = 7.6 Hz), 131.0 (d, J = 3.3 Hz), 113.3 (d, J = 20.6 Hz), 112.5 (d, J = 22.9 Hz), 73.3 (d, J = 1.7 Hz), 30.5, 21.4.

2-(4-chloro-2-methylphenyl)propan-2-ol (1f)

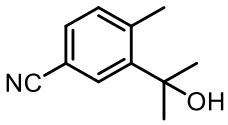


Following **GP1**, 1-bromo-4-chloro-2-methylbenzene gave the title compound (**1f**) as a clear oil after flash column chromatography (255 mg, 50%). Data in accordance with literature (48).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 1H), 7.15 – 7.09 (m, 2H), 2.56 (s, 3H), 1.64 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 138.0, 132.4, 132.2, 126.8, 125.5, 73.4, 30.9, 22.0.

3-(2-hydroxypropan-2-yl)-4-methylbenzonitrile (1g)



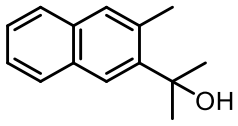
Following **GP1**, 3-bromo-4-methylbenzonitrile gave the title compound (**1g**) as a clear oil after flash column chromatography (118 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 1.8 Hz, 1H), 7.43 (dd, J = 7.8, 1.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 2.64 (s, 3H), 1.76 (s, 1H), 1.66 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 142.0, 133.4, 130.6, 129.4, 119.5, 109.6, 73.4, 30.8, 22.7.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{11}H_{13}NO$, 175.0997; found: 175.0993.

2-(3-methylnaphthalen-2-yl)propan-2-ol (1m)



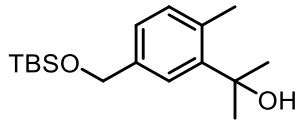
Following **GP1**, 2-bromo-3-methylnaphthalene gave the title compound (**1m**) as a clear oil after flash column chromatography (355 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.68 (m, 1H), 7.76 (dd, J = 7.9, 1.8 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.20 (d, J = 8.3 Hz, 1H), 2.69 (s, 3H), 1.95 (s, 6H), 1.90 (s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 134.1, 133.0, 132.3, 132.1, 129.0, 128.0, 127.9, 125.0, 124.6, 33.1, 26.0.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{16}O$, 200.1201; found: 200.1204.

2-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylphenyl)propan-2-ol (1l)



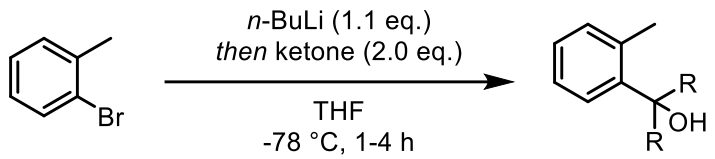
Following **GP1**, ((3-bromo-4-methylbenzyl)oxy)(tert-butyl)dimethylsilane (**S1**) gave the title compound (**1l**) as a clear oil after flash column chromatography (287 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.12 (s, 2H), 4.72 (s, 2H), 2.58 (s, 3H), 1.71 (s, 1H), 1.66 (s, 6H), 0.95 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 138.6, 134.4, 132.6, 124.7, 123.2, 73.8, 65.0, 30.9, 26.0, 21.9, 18.4, -5.2.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{17}H_{30}O_2Si$, 294.2015; found: 294.2018.

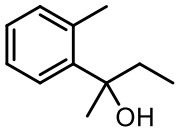
III. General Procedure 2 (GP2)



3a-e, 3o-p

To a solution of 2-bromotoluene (1.0 eq., 6.65 mmol, 0.80 mL) in anhydrous THF (20 mL) under nitrogen was added *n*-BuLi (1.1 eq., 7.32 mmol, 2.90 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 30 min and then the appropriate ketone (2.0 eq., 13.3 mmol) dissolved in THF (5 mL) was added dropwise. The reaction was stirred at -78 °C for 1-4 hours and then quenched with saturated aqueous NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc).

2-(o-tolyl)butan-2-ol (3a)

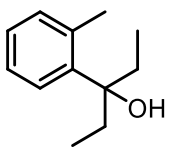


Following **GP2**, butan-2-one gave the title compound (**3a**) as a clear oil after flash column chromatography (382 mg, 35%). Data in accordance with literature (50).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 1H), 7.19 – 7.12 (m, 3H), 2.55 (s, 3H), 2.08 – 1.86 (m, 2H), 1.62 (s, 4H), 0.82 (t, J = 7.5 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 135.6, 132.7, 127.0, 126.4, 125.7, 76.4, 34.7, 29.1, 22.5, 8.8.

3-(o-tolyl)pentan-3-ol (3b)

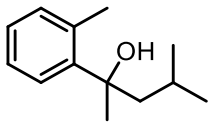


Following **GP2**, pentan-3-one gave the title compound (**3b**) as a clear oil after flash column chromatography (460 mg, 42%). Data in accordance with literature (51).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.8 Hz, 1H), 7.20 – 7.10 (m, 3H), 2.49 (s, 3H), 2.10 – 1.99 (m, 2H), 1.90 – 1.79 (m, 2H), 1.64 (s, 1H), 0.78 (t, J = 7.5 Hz, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 135.2, 132.6, 127.5, 126.7, 125.6, 79.0, 33.5, 22.7, 8.2.

4-methyl-2-(o-tolyl)pentan-2-ol (3c)



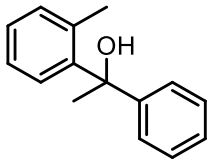
Following **GP2**, 4-methylpentan-2-one gave the title compound (**3c**) as a clear oil after flash column chromatography (345 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 1H), 7.32 – 7.22 (m, 3H), 2.64 (s, 3H), 2.12 – 2.03 (m, 1H), 1.93 – 1.85 (m, 1H), 1.82 (s, 1H), 1.76 (s, 3H), 1.73 – 1.64 (m, 1H), 0.94 (dd, J = 6.7, 1.9 Hz, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 135.3, 132.6, 126.9, 126.1, 125.8, 76.4, 50.6, 30.5, 24.9, 24.5, 24.3, 22.5.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{13}H_{20}O$, 192.1514; found: 192.1507.

1-phenyl-1-(o-tolyl)ethan-1-ol (3d)

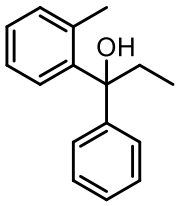


Following **GP2**, acetophenone gave the title compound (**3d**) as a clear oil after flash column chromatography (620 mg, 44%). Data in accordance with literature (52).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.2, 2.0 Hz, 1H), 7.37 – 7.22 (m, 7H), 7.17 – 7.12 (m, 1H), 2.16 (s, 1H), 2.02 (s, 3H), 1.97 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 144.7, 137.3, 132.6, 128.3, 127.8, 126.7, 126.1, 125.5, 125.4, 76.9, 32.3, 21.5.

1-phenyl-1-(o-tolyl)propan-1-ol (3e)

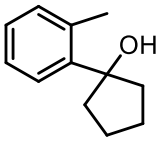


Following **GP2**, propiophenone gave the title compound (**3e**) as a clear oil after flash column chromatography (497 mg, 33%). Data in accordance with literature (53).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.6, 1.7 Hz, 1H), 7.29 – 7.15 (m, 7H), 7.09 – 7.05 (m, 1H), 2.40 – 2.20 (m, 2H), 1.98 (s, 3H), 1.93 (s, 1H), 0.85 (t, J = 7.3 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 144.1, 137.5, 132.7, 128.0, 127.5, 126.6, 126.6, 126.2, 125.3, 78.8, 35.0, 21.6, 8.4.

1-(o-tolyl)cyclopentan-1-ol (3o)

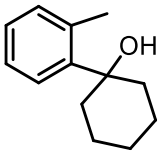


Following **GP2**, cyclopentanone gave the title compound (**3o**) as a clear oil after flash column chromatography (586 mg, 50%). Data in accordance with literature (54).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.1, 1.7 Hz, 1H), 7.21 – 7.11 (m, 3H), 2.59 (s, 3H), 2.21 – 2.07 (m, 4H), 2.01 – 1.89 (m, 2H), 1.83 – 1.72 (m, 2H),

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 137.5, 132.4, 127.3, 125.4, 125.4, 84.1, 39.9, 23.6, 21.9.

1-(o-tolyl)cyclohexan-1-ol (3p)

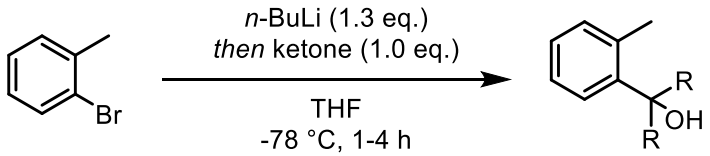


Following **GP2**, cyclohexanone gave the title compound (**3p**) as a clear oil after flash column chromatography (658 mg, 52%). Data in accordance with literature (55).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.33 (m, 1H), 7.30 – 7.01 (m, 3H), 2.64 (s, 3H), 2.08 – 1.54 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 136.6, 132.9, 126.9, 125.6, 125.3, 74.8, 37.4, 25.6, 22.4, 22.1.

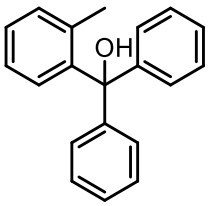
IV. General Procedure 3 (GP3)



3g-n, 3q

To a solution of 2-bromotoluene (1.0 eq., 6.65 mmol, 0.80 mL) in anhydrous THF (20 mL) under nitrogen was added *n*-BuLi (1.1 eq., 7.32 mmol, 2.90 mL, 2.5 M in hexanes) at -78 °C. The reaction was stirred at the same temperature for 30 min and then the appropriate ketone (1.0 eq, 1.66 mmol) dissolved in THF (5 mL) was added dropwise. The reaction was stirred at -78 °C for 1-4 hours and then quenched with saturated aqueous NH_4Cl in water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc).

diphenyl(o-tolyl)methanol (3g)



Following **GP3**, benzophenone gave the title compound (**3g)** as clear oil after column chromatography (53%, 241 mg). Data in accordance with literature (56).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 12H), 7.06 – 6.99 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 2.96 (s, 1H), 2.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 144.5, 138.1, 132.6, 129.6, 128.0, 127.8, 127.7, 127.16, 124.9, 83.1, 22.1.

1-(isoquinolin-4-yl)-1-(o-tolyl)ethan-1-ol (3h)

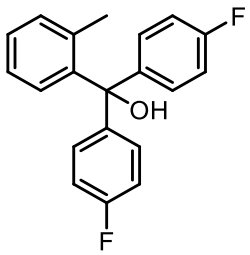
Following **GP3**, 1-(isoquinolin-4-yl)ethan-1-one gave the title compound (**3h)** as clear oil after column chromatography (43%, 437 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.4 Hz, 1H), 8.17 – 8.05 (m, 2H), 7.89 – 7.63 (m, 4H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.17 – 7.06 (m, 1H), 2.17 (s, 1H), 2.04 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 146.8, 143.1, 140.6, 137.4, 132.9, 131.7, 129.3, 129.0, 128.3, 128.0, 127.5, 126.8, 126.1, 125.7, 75.9, 32.8, 21.5.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{18}H_{17}NO$, 263.1310; found: 263.1306.

bis(4-fluorophenyl)(o-tolyl)methanol (3i)



Following **GP3**, bis(4-fluorophenyl)methanone gave the title compound (**3i)** as clear oil after column chromatography (85%, 437 mg).

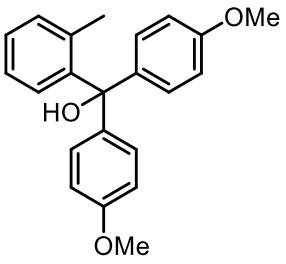
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.27 – 7.18 (m, 3H), 7.11 – 6.99 (m, 5H), 6.81 (d, *J* = 7.4 Hz, 1H), 2.23 (s, 1H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 140.3, 140.1, 135.2, 131.5, 129.2, 128.6, 127.6, 126.7, 125.8, 124.4, 120.3, 82.8, 19.5.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{20}H_{16}F_2O$, 310.1169; found: 310.1175.

^{19}F NMR (376 MHz, CDCl 3) δ -115.5.

bis(4-methoxyphenyl)(o-tolyl)methanol (3l)

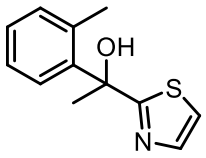


Following **GP3**, bis(4-methoxyphenyl)methanone gave the title compound (**3l)** as clear oil after column chromatography (80%, 443 mg). Data in accordance with literature (57).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 6H), 7.07 – 7.00 (m, 1H), 6.87 – 6.81 (m, 4H), 6.77 (d, *J* = 7.6 Hz, 1H), 3.81 (s, 6H), 2.86 (s, 1H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 144.9, 139.2, 137.9, 132.5, 132.2, 129.4, 128.9, 127.7, 127.3, 124.9, 113.2, 82.6, 55.3, 22.1.

1-(thiazol-2-yl)-1-(o-tolyl)ethan-1-ol (3m)



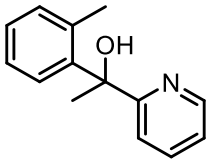
Following **GP3**, 1-(thiazol-2-yl)ethan-1-one gave the title compound (**3m)** as clear oil after column chromatography (87%, 316 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 3.3 Hz, 1H), 7.65 – 7.52 (m, 1H), 7.35 – 7.17 (m, 3H), 7.17 – 7.09 (m, 1H), 3.52 (s, 1H), 2.12 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 142.6, 141.7, 137.2, 132.5, 128.4, 126.0, 125.7, 119.7, 76.5, 31.1, 21.2.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{12}H_{13}NOS$, 219.0718; found: 219.0713.

1-(pyridin-2-yl)-1-(o-tolyl)ethan-1-ol (3n)

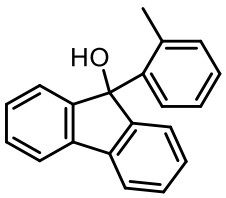


Following **GP3**, 1-(pyridin-2-yl)ethan-1-one gave the title compound (**3n)** as clear oil after column chromatography (59%, 210 mg). Data in accordance with literature (58).

^{1}H NMR (400 MHz, $CDCl_3$ δ 8.48 (d, *J* = 4.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.49 (td, *J* = 7.7, 1.8 Hz, 1H), 7.17 – 7.06 (m, 3H), 7.04 – 6.97 (m, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 2.01 (s, 1H), 1.82 (s, 3H), 1.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 147.1, 142.6, 138.2, 137.0, 132.4, 127.8, 126.9, 125.3, 121.8, 120.2, 76.0, 31.8, 21.1.

9-(o-tolyl)-9H-fluoren-9-ol (3q)

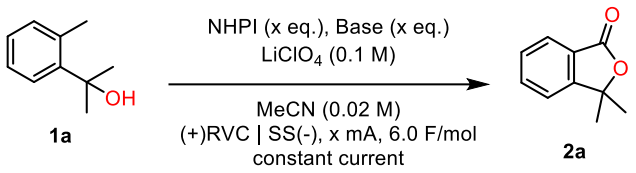


Following **GP3**, 9H-fluoren-9-one gave the title compound (**3q)** as clear oil after column chromatography (78%, 352 mg). Data in accordance with literature (59).

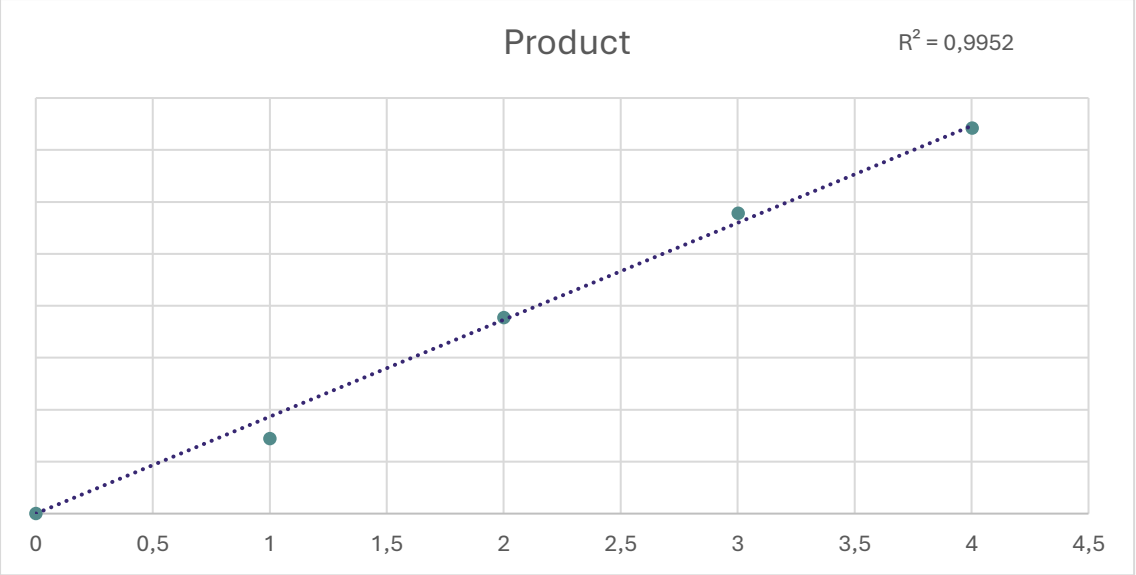
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.23 (td, *J* = 7.4, 1.4 Hz, 3H), 7.10 – 7.00 (m, 5H), 6.81 (d, *J* = 7.0 Hz, 1H), 2.23 (s, 1H), 1.19 (s, 3H).

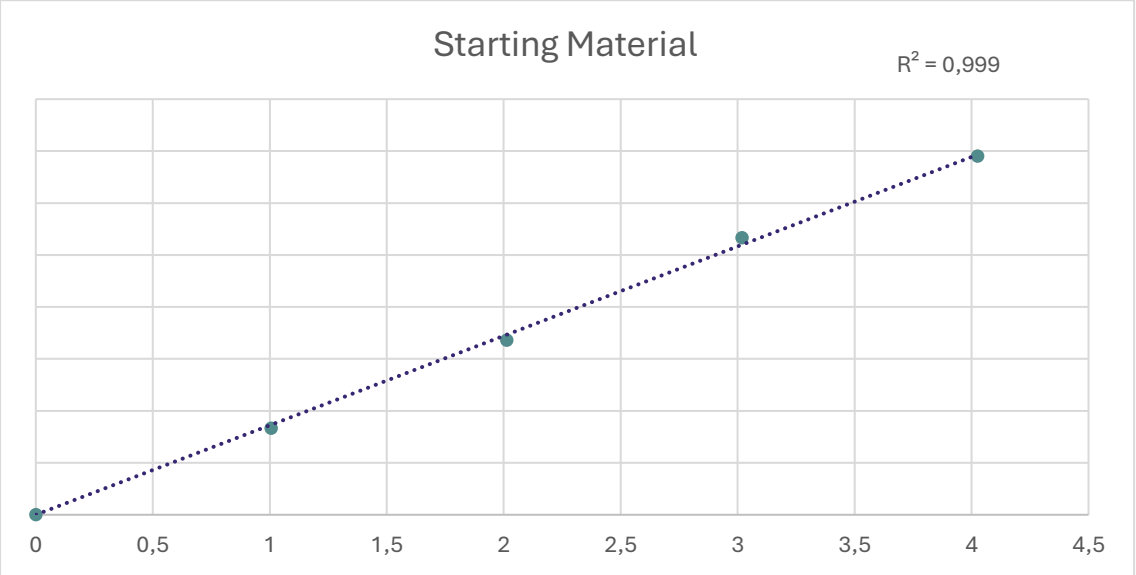
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 140.3, 140.2, 135.2, 131.5, 129.2, 128.6, 127.6, 126.7, 125.8, 124.4, 120.3, 82.7, 19.5.

V. Reaction Optimization



All reactions were performed in an IKA ElectraSyn 2.0 using electrodes purchased from IKA. In a 10 mL IKA ElectraSyn vial equipped with a magnetic stir bar, $LiClO_4$ (1 mmol, 106 mg), **1a** (1 eq., 0.2 mmol, 33 mg), pyridine and NHPI were dissolved in MeCN, then the electrochemical cell was assembled. The instrument was operated under constant current mode while stirring at 700 rpm. After 6 F/mol were passed through, 1,3,5-trimethoxybenzene (1 mL, 0.1 M in $CDCl_3$) was added and the solution stirred for 1 min. and then analyzed by HPLC to determine the yield.


Product
R² = 0,9952
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5


Starting Material
R² = 0,999
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5

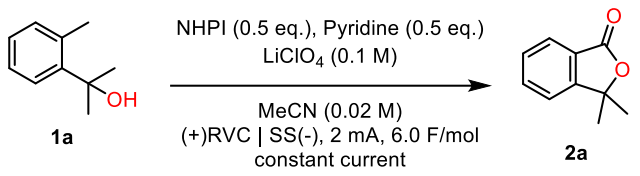
Entry	Solvent	NHPI loading	Base	Electrode	Current (mA)	Yield (%)
1	MeCN	0.5 eq.	Li_2CO_3		2 mA	40%
2			Collidine			90%
3			Picoline			39%
4			Pyridine (0.5 eq.)			99% (95%*)
5			Pyridine (1.0 eq.)			99%
6			Pyridine (0.5 eq.)	Pt cathode		95%
7				Graphite cathode		88%
8				Graphite anode		85%
9				GC anode		82%
10				CF anode		80%
11		1.0 eq.				91%
12		0.7 eq.				99%
13		0.3 eq.				68%
14		0.1 eq.				<5%
15		0.5 eq.			3 mA	91%
16					4 mA	40%
17					6 mA	n.p.d.

Table S1.1: Optimization of reaction conditions. *isolated yield.

For the isolated yield, the mixture was poured into water and extracted with Et_2O (3x10 mL). The reunited organics were washed with 1.0 M HCl and brine. The organic phase was collected and dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 9:1) to afford compound **2a** as a colorless oil (95%, 31 mg). Data in accordance with literature (60).

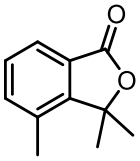
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.1 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz, 1H), 7.40 (dt, *J* = 7.6, 0.9 Hz, 1H), 1.65 (s, 6H).

VI. Substrate Scope, General procedure 4 (GP4)



All reactions were performed in an IKA ElectraSyn 2.0 using electrodes purchased from IKA. In a 10 mL IKA ElectraSyn vial, equipped with a magnetic stir bar, $LiClO_4$ (1 mmol, 106 mg), the appropriate alcohol (1 eq., 0.2 mmol, 33 mg), pyridine (0.5 eq., 0.1 mmol, 8.0 µL) and NHPI (0.5 eq., 0.1 mmol, 16 mg) were dissolved MeCN (10 mL), then the electrochemical cell was assembled. The instrument was operated under constant current mode with stirring at 700. After 6 F/mol were passed through, the mixture was poured into water and extracted with Et_2O or EtOAc three times. The reunited organics were washed with 1 M HCl and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane to Hexane/EtOAc 8:2) to afford the pure lactones.

3,3,4-trimethylisobenzofuran-1(3H)-one (2b)



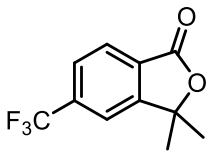
Following **GP4,** 2-(2,6-dimethylphenyl)propan-2-ol gave the title compound (**2b)** as clear oil after column chromatography (68%, 24 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.69 (m, 1H), 7.44 – 7.36 (m, 2H), 2.47 (s, 3H), 1.72 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 152.1, 135.9, 131.4, 129.0, 125.7, 123.3, 85.8, 77.2, 76.8, 76.5, 25.4, 17.9.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{11}H_{12}O_2$, 176.0837; found: 176.0837.

3,3-dimethyl-5-(trifluoromethyl)isobenzofuran-1(3H)-one (2c)



Following **GP4,** 2-(2-methyl-5-(trifluoromethyl)phenyl)propan-2-ol gave the title compound (**2c)** as clear oil after column chromatography (54%, 25 mg).

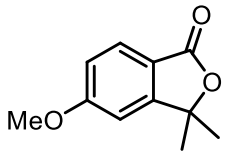
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.71 – 7.64 (m, 1H), 1.71 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 155.3, 135.9 (q, *J* = 32.7 Hz), 128.6, 126.6, 126.3 (q, *J* = 3.6 Hz), 123.4 (q, *J* = 273.3 Hz), 118.1 (q, *J* = 3.9 Hz), 85.7, 27.3.

^{19}F NMR (376 MHz, CDCl 3) δ -62.7.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{11}H_9F_3O_2$, 230.0555; found: 230.0549.

5-methoxy-3,3-dimethylisobenzofuran-1(3H)-one (2d)

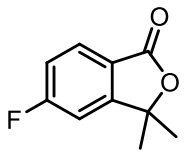


Following **GP4,** 2-(5-methoxy-2-methylphenyl)propan-2-ol gave the title compound (**2d)** as clear oil after column chromatography (53%, 20 mg). Data in accordance with literature (61).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.80 (d, *J* = 2.1 Hz, 1H), 3.90 (s, 3H), 1.63 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 164.8, 157.7, 127.4, 117.7, 115.9, 105.0, 84.5, 55.9, 27.3.

5-fluoro-3,3-dimethylisobenzofuran-1(3H)-one (2e)

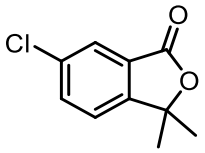


Following **GP4,** 2-(5-fluoro-2-methylphenyl)propan-2-ol gave the title compound (**2e)** as clear oil after column chromatography (67%, 24 mg). Data in accordance with literature (62).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 1H), 7.18 (td, *J* = 8.7, 2.2 Hz, 1H), 7.06 (dd, *J* = 7.8, 2.2 Hz, 1H), 1.64 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 166.4 (d, *J* = 256.1 Hz), 157.6 (d, *J* = 9.6 Hz), 128.0 (d, *J* = 10.3 Hz), 121.2 (d, *J* = 2.1 Hz), 116.9 (d, *J* = 24.1 Hz), 107.9 (d, *J* = 24.1 Hz), 84.5 (d, *J* = 2.8 Hz), 27.0.

6-chloro-3,3-dimethylisobenzofuran-1(3H)-one (2f)

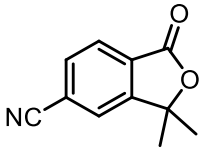


Following **GP4,** 2-(4-chloro-2-methylphenyl)propan-2-ol gave the title compound (**2f)** as clear oil after column chromatography (63%, 25 mg). Data in accordance with literature (63).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.9 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 1.65 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 153.1, 135.2, 134.4, 127.2, 125.7, 122.1, 85.5, 77.4, 77.0, 76.7, 27.3.

3,3-dimethyl-1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile (2g)

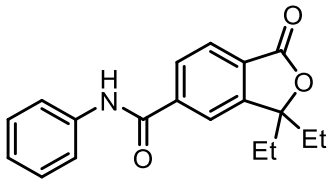


Following **GP4,** 3-(2-hydroxypropan-2-yl)-4-methylbenzonitrile gave the title compound (**2g)** as clear oil after column chromatography (60%, 22 mg). Data in accordance with literature (64).

^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR δ 7.99 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.73 – 7.71 (m, 1H), 1.70 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 132.7, 129.0, 126.7, 124.7, 117.5, 117.3, 85.4, 27.1.

3,3-diethyl-1-oxo-N-phenyl-1,3-dihydroisobenzofuran-5-carboxamide (2h)



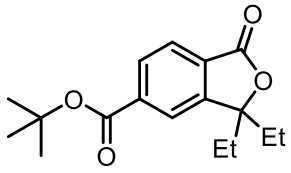
Following **GP4,** 3-(3-hydroxypentan-3-yl)-4-methyl-N-phenylbenzamide gave the title compound (**2h)** as clear oil after column chromatography (61%, 38 mg).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 – 8.29 (m, 2H), 7.96 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.45 – 7.36 (m, 1H), 7.22 – 7.17 (m, 1H), 2.15 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.97 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 164.0, 155.2, 137.6, 136.3, 134.1, 129.2, 127.8, 125.0, 123.2, 122.1, 120.3, 91.4, 31.3, 7.5.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{19}H_{19}NO_3$, 309.1365; found: 309.1368.

tert-butyl 3,3-diethyl-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (2i)



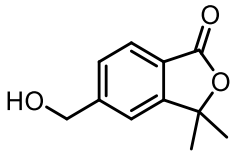
Following **GP4,** tert-butyl 3-(3-hydroxypentan-3-yl)-4-methylbenzoate gave the title compound (**2i)** as clear oil after column chromatography (55%, 32 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 1.5 Hz, 1H), 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (d, *J* = 8.0 1H), 2.17 – 2.05 (m, 2H), 1.98 – 1.88 (m, 2H), 1.60 (s, 9H), 0.70 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 164.3, 155.7, 135.0, 133.4, 127.6, 126.9, 121.2, 91.0, 82.1, 31.3, 28.2, 7.5.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{17}H_{22}O_4$, 290.1518; found: 290.1524.

5-(hydroxymethyl)-3,3-dimethylisobenzofuran-1(3H)-one (2l)



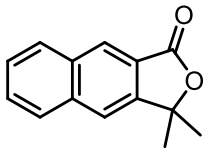
Following **GP4,** 2-(5-(hydroxymethyl)-2-methylphenyl)propan-2-ol gave the title compound (**2l)** as clear oil after column chromatography (50%, 19 mg).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.34 (m, 2H), 4.79 (s, 2H), 1.59 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 155.6, 148.0, 127.2, 125.8, 124.4, 118.4, 85.5, 64.5, 27.3.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{11}H_{12}O_3$, 192.0786; found: 192.0790.

3,3-dimethylnaphtho[2,3-c]furan-1(3H)-one (2m)

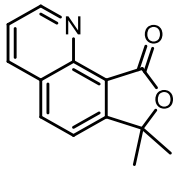


Following **GP4,** 2-(3-methylnaphthalen-2-yl)propan-2-ol gave the title compound (**2m)** as clear oil after column chromatography (54%, 23 mg). Data in accordance with literature (65).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.64 (m, 2H), 1.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.06, 153.50, 136.70, 130.49, 129.81, 128.57, 127.64, 126.26, 124.19, 123.33, 120.71, 85.89, 27.15.

7,7-dimethylfuro[3,4-h]quinolin-9(7H)-one (2n)



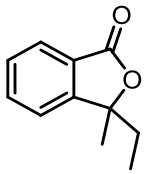
Following **GP4,** 2-(8-methylquinolin-7-yl)propan-2-ol gave the title compound (**2n)** as clear oil after column chromatography (47%, 20 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.29 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.51 (m, 2H), 1.72 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 160.3, 153.4, 144.6, 136.7, 135.9, 129.7, 128.4, 122.3, 120.1, 118.8, 83.7, 26.9.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{15}NO_2$, 241.1103; found: 241.1098.

3-ethyl-3-methylisobenzofuran-1(3H)-one (4a)



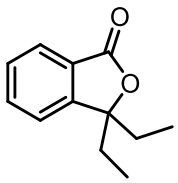
Following **GP4,** 2-(o-tolyl)butan-2-ol gave the title compound (**4a)** as clear oil after column chromatography (85%, 30 mg). Data in accordance with literature (66).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.51 – 7.42 (m, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.60 (s, 2H), 0.71 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 153.6, 134.1, 128.9, 126.2, 125.6, 120.9, 88.0, 32.9, 25.7, 7.8.

3,3-diethylisobenzofuran-1(3H)-one (4b)

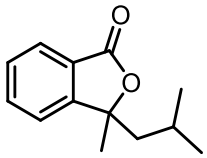


Following **GP4,** 2-(o-tolyl)pentan-3-ol gave the title compound (**4b)** as clear oil after column chromatography (80%, 30 mg). Data in accordance with literature (62).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.1 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz, 1H), 7.32 (dt, *J* = 7.6, 0.9 Hz, 1H), 2.16 – 2.04 (m, 2H), 1.98 – 1.86 (m, 2H), 0.71 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 152.0, 133.9, 128.8, 127.3, 125.6, 121.1, 90.8, 31.4, 7.5.

3-isobutyl-3-methylisobenzofuran-1(3H)-one (4c)

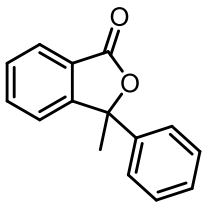


Following **GP4,** 4-methyl-2-(o-tolyl)pentan-2-ol gave the title compound (**4c)** as clear oil after column chromatography (55%, 22.5 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6, 1.0 Hz, 1H), 7.65 (td, *J* = 7.5, 1.1 Hz, 1H), 7.49 (td, *J* = 7.5, 1.0 Hz, 1H), 7.36 (dt, *J* = 7.6, 0.9 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.78 – 1.70 (m, 1H), 1.62 (s, 3H), 1.58 – 1.49 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 154.4, 134.0, 128.9, 126.0, 125.7, 121.1, 87.9, 48.2, 26.9, 24.3, 24.2, 23.8.

3-methyl-3-phenylisobenzofuran-1(3H)-one (4d)

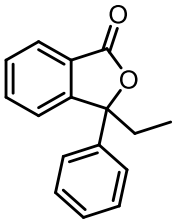


Following **GP4,** 1-phenyl-1-(o-tolyl)ethan-1-ol gave the title compound (**4d)** as clear oil after column chromatography (57%, 25.6 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.1 Hz, 1H), 7.52 (td, *J* = 7.5, 1.0 Hz, 1H), 7.48 – 7.43 (m, 3H), 7.39 – 7.28 (m, 3H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 154.2, 140.8, 134.3, 129.1, 128.7, 128.3, 125.9, 125.1, 125.1, 122.1, 87.6, 27.3.

3-ethyl-3-phenylisobenzofuran-1(3H)-one (4e)

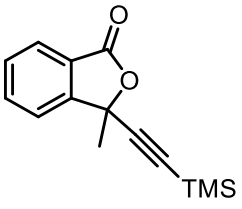


Following **GP4,** 1-phenyl-1-(o-tolyl)propan-1-ol gave the title compound (**4e)** as clear oil after column chromatography (47%, 22 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.87 (m, 1H), 7.69 – 7.63 (m, 1H), 7.54 – 7.48 (m, 4H), 7.39 – 7.27 (m, 3H), 2.57 – 2.44 (m, 1H), 2.33 – 2.21 (m, 1H), 0.81 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 152.8, 140.4, 134.2, 129.1, 128.7, 128.1, 125.9, 125.8, 125.1, 122.2, 90.5, 33.3, 8.1.

3-methyl-3-((trimethylsilyl)ethynyl)isobenzofuran-1(3H)-one (4f)



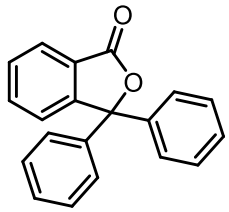
Following **GP4,** 2-(o-tolyl)-4-(trimethylsilyl)but-3-yn-2-ol gave the title compound (**4f)** as clear oil after column chromatography (48%, 23.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.6 Hz, 1H), 7.57 (td, *J* = 7.5, 1.1 Hz, 1H), 7.46 – 7.35 (m, 2H), 1.73 (s, 3H), 0.00 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 152.3, 135.1, 130.0, 126.1, 125.1, 122.0, 101.8, 92.4, 79.3, 29.3, 0.0.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{16}O_2Si$, 244.0902; found: 244.0909.

3,3-diphenylisobenzofuran-1(3H)-one (4g)

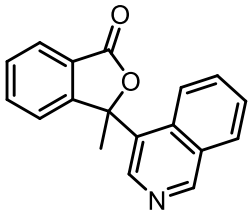


Following **GP4,** diphenyl(o-tolyl)methanol gave the title compound (**4g)** as clear oil after column chromatography (56%, 32 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.53 – 7.46 (m, 2H), 7.30 – 7.23 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 152.0, 140.9, 134.2, 129.4, 128.6, 128.5, 127.1, 126.1, 125.6, 124.2, 121.2, 91.7.

3-(isoquinolin-4-yl)-3-methylisobenzofuran-1(3H)-one (4h)



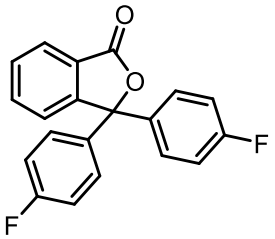
Following **GP4,** 1-(isoquinolin-4-yl)-1-(o-tolyl)ethan-1-ol gave the title compound (**4h)** as clear oil after column chromatography (46%, 25.3 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.5 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.54 – 7.44 (m, 3H), 2.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 153.2, 147.8, 147.6, 134.7, 133.6, 132.0, 130.2, 129.7, 129.2, 128.1, 127.4, 127.2, 126.3, 125.1, 122.0, 86.1, 27.4.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{18}H_{13}NO_2$, 275.0946; found: 275.0940.

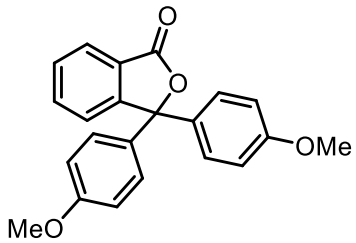
3,3-bis(4-fluorophenyl)isobenzofuran-1(3H)-one (4i)



Following **GP4,** bis(4-fluorophenyl)(o-tolyl)methanol gave the title compound (**4i)** as clear oil after column chromatography (58%, 37 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.62 – 7.49 (m, 2H), 7.34 – 7.26 (m, 4H), 7.07 – 6.96 (m, 4H).

3,3-bis(4-methoxyphenyl)isobenzofuran-1(3H)-one (4l)

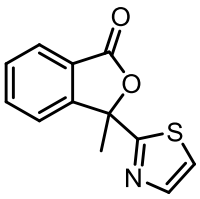


Following **GP4,** bis(4-methoxyphenyl)(o-tolyl)methanol gave the title compound (**4l)** as clear oil after column chromatography (52%, 36 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 7.6 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.60 – 7.50 (m, 2H), 7.30 – 7.23 (m, 4H), 6.90 – 6.80 (m, 4H), 3.81 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 159.7, 152.7, 134.3, 134.1, 133.1, 129.2, 128.6, 126.0, 125.6, 124.0, 123.6, 113.8, 91.7, 55.3.

3-methyl-3-(thiazol-2-yl)isobenzofuran-1(3H)-one (4m)



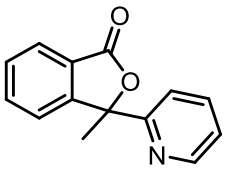
Following **GP4,** 1-(thiazol-2-yl)-1-(o-tolyl)ethan-1-ol gave the title compound (**4m)** as clear oil after column chromatography (54%, 25 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 3.3 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.70 (td, *J* = 7.5, 1.1 Hz, 1H), 7.56 (td, *J* = 7.4, 1.1 Hz, 1H), 7.28 (d, *J* = 3.3 Hz, 1H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.0, 152.1, 143.4, 134.8, 129.8, 125.9, 124.2, 122.8, 119.7, 86.6, 27.3.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{12}H_9NO_2S$, 231.0354 found: 231.0347.

3-methyl-3-(pyridin-2-yl)isobenzofuran-1(3H)-one (4n)

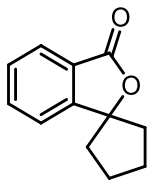


Following **GP4,** 1-(pyridin-2-yl)-1-(o-tolyl)ethan-1-ol gave the title compound (**4n)** as clear oil after column chromatography (65%, 29 mg). Data in accordance with literature (67).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.87 (t, *J* = 8.2 Hz, 2H), 7.68 – 7.61 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 (td, *J* = 7.5, 1.0 Hz, 1H), 7.23 – 7.17 (m, 1H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 159.9, 153.4, 149.1, 136.9, 134.2, 129.0, 125.3, 124.3, 123.2, 122.6, 118.5, 87.8, 27.2.

3'H-spiro[cyclopentane-1,1'-isobenzofuran]-3'-one (4o)

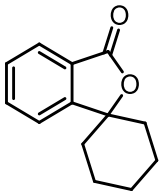


Following **GP4,** 1-(o-tolyl)cyclopentan-1-ol gave the title compound (**4o)** as clear oil after column chromatography (56%, 21 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.1 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 2.19 – 2.04 (m, 6H), 2.03 – 1.90 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 152.7, 134.1, 128.9, 126.2, 125.5, 120.9, 95.5, 39.7, 24.9.

3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one (4p)

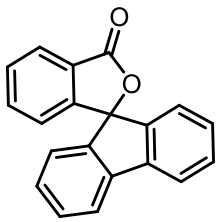


Following **GP4,** 1-(o-tolyl)cyclohexan-1-ol gave the title compound (**4p)** as clear oil after column chromatography (40%, 16 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.64 (td, *J* = 7.5, 1.1 Hz, 1H), 7.49 (td, *J* = 7.5, 1.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 1.90 – 1.72 (m, 9H), 1.47 – 1.35 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 155.0, 133.9, 129.0, 125.9, 125.6, 121.0, 87.0, 36.4, 24.8, 22.4.

3'H-spiro[fluorene-9,1'-isobenzofuran]-3'-one (4q)

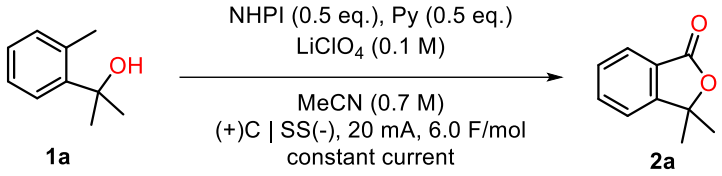


Following **GP4,** 9-(o-tolyl)-9H-fluoren-9-ol gave the title compound (**4q)** as clear oil after column chromatography (58%, 33 mg). Data in accordance with literature (18).

^{1}H NMR (400 MHz, , $CDCl_3$) δ 8.06 (d, *J* = 6.4 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.62 – 7.51 (m, 2H), 7.46 (td, *J* = 7.5, 1.1 Hz, 2H), 7.25 (td, *J* = 7.6, 1.1 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 6.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 150.6, 142.8, 140.8, 134.7, 130.4, 129.6, 128.5, 126.1, 125.6, 124.54, 122.3, 120.5, 91.9.

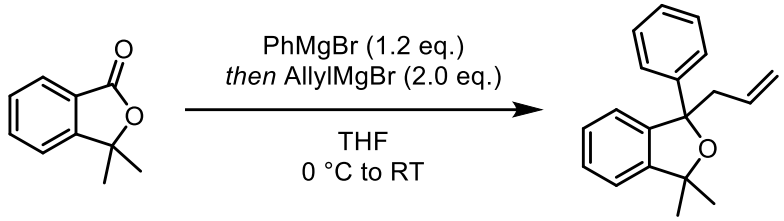
VII. Scale-up



Scale-up synthesis was performed using **1a** (5.0 mmol, 750 mg) in a 70 mL vial equipped with 13 cm^2 electrodes, cut from a plate of the reported material. After the reaction completion the crude mixture was concentrated under reduced pressure, diluted with water and extracted Et_2O (3x20 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc 9:1) to afford the product as a clear oil (82%, 665 mg).

VIII. Synthesis of Talopram

1-allyl-3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran (12)

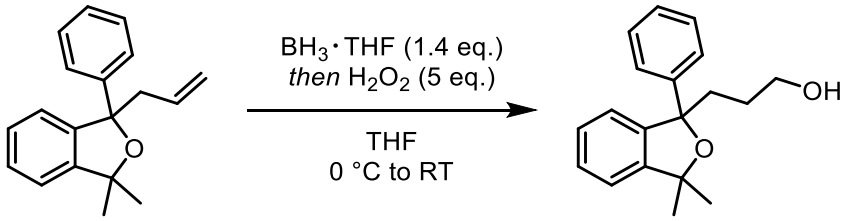


Following a reported procedure (37) 3,3-dimethylisobenzofuran-1(3H)-one gave the title compound **(12)** as a brown oil after column chromatography (98%, 523 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 2H), 7.44 – 7.19 (m, 6H), 7.17 – 7.06 (m, 1H), 5.84 – 5.66 (m, 1H), 5.69 – 5.56 (m, 1H), 5.07– 4.98 (m, 1H), 3.06 – 2.80 (m, 1H), 2.63 – 2.52 (m, 1H), 1.61 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.2, 142.6, 134.1, 128.1, 127.9, 127.3, 126.7, 125.4, 122.7, 120.7, 117.9, 89.3, 85.0, 48.0, 30.0, 29.9.

3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propan-1-ol (13)

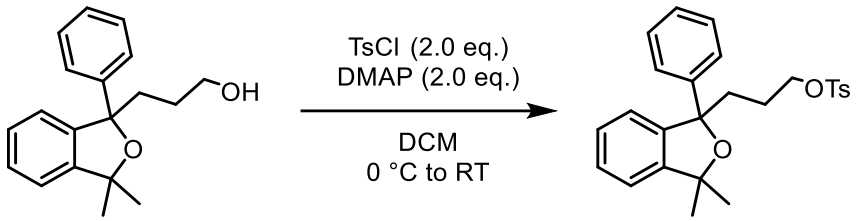


Following a reported procedure (37) 1-allyl-3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran gave the title compound **(13)** as a clear oil after column chromatography (55%, 307 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 2H), 7.43 – 7.35 (m, 1H), 7.39 – 7.27 (m, 4H), 7.27 – 7.18 (m, 1H), 7.17 – 7.07 (m, 1H), 3.70 – 3.55 (m, 2H), 2.38 (ddd, J = 14.4, 8.7, 5.5 Hz, 1H), 2.23 – 2.08 (m, 2H), 1.67 (s, 3H), 1.49 (s, 3H), 1.28 (t, J = 7.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 146.1, 143.1, 128.1, 127.9, 127.6, 126.7, 125.3, 122.3, 120.8, 89.7, 85.3, 63.0, 40.6, 30.0, 29.9, 28.0.

3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propyl 4-methylbenzenesulfonate (14)

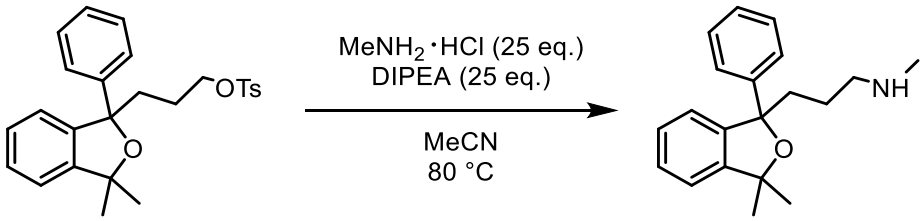


Following a reported procedure (37) 3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propan-1-ol gave the title compound **(14)** as a yellow oil after column chromatography (57%, 270 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.49 – 7.38 (m, 2H), 7.29 – 7.16 (m, 7H), 7.14 – 7.07 (m, 1H), 7.02 – 6.92 (m, 1H), 3.92 (td, *J* = 6.4, 1.4 Hz, 2H), 2.31 (s, 3H), 2.12 – 2.01 (m, 1H), 1.98 – 1.84 (m, 1H), 1.63 – 1.38 (m, 5H), 1.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.84, 146.11, 144.63, 142.42, 133.19, 129.81, 128.15, 128.05, 127.89, 127.58, 126.81, 125.21, 122.32, 120.83, 89.16, 84.98, 71.02, 39.41, 29.90, 29.87, 24.48, 21.64.

3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)-N-methylpropan-1-amine (15)



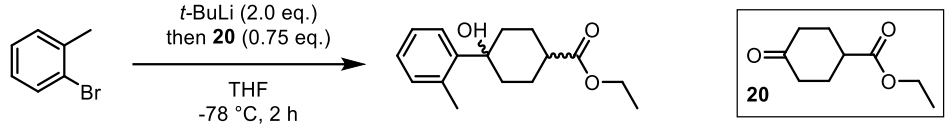
Following a reported procedure (37) 3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propyl 4-methylbenzenesulfonate gave the title compound **(15)** as a clear oil after column chromatography (47%, 86 mg).

^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.49 (m, 2H), 7.38 – 7.33 (m, 1H), 7.26 – 7.17 (m, 4H), 7.13 – 7.02 (m, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.20 (s, 3H), 2.18 – 2.05 (m, 1H), 1.99 – 1.88 (m, 1H), 1.51 (s, 3H), 1.48 – 1.25 (m, 5H), 1.20 (s, 1H).

^{13}C NMR (101 MHz, MeOD) δ 146.60, 146.49, 142.77, 127.69, 127.66, 127.21, 126.35, 125.04, 122.22, 120.50, 89.60, 84.75, 51.14, 40.78, 34.27, 28.92, 28.88, 23.94.

I. Synthesis of NPY Y5 receptor antagonists

Ethyl 4-hydroxy-4-(o-tolyl)cyclohexane-1-carboxylate (16)



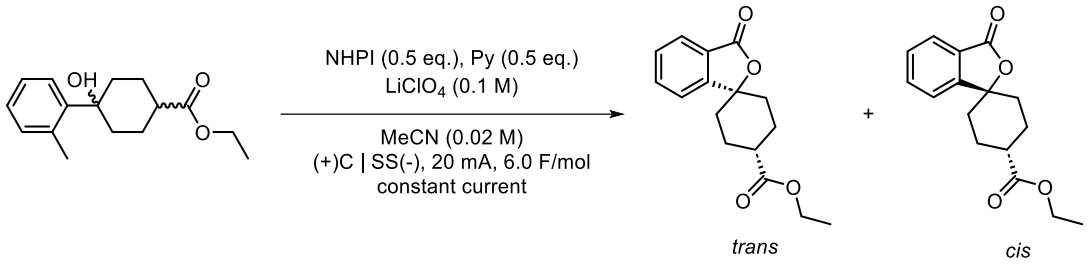
To a solution of 2-bromotoluene (1.0 eq., 5.92 mmol, 1.00 mL) in dry THF (60 mL) under N_2 was added *t*-BuLi (11.80 mmol, 6.97 ml, 1.7 M in pentane) at -78°C. The reaction was stirred at the same temperature for 30 min and then ethyl 4-oxocyclohexanecarboxylate in toluene (0.75 eq., 4.44 mmol) was added dropwise. The reaction was stirred at -78 °C for 2 hours and then quenched with saturated aqueous NH_4Cl. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x10 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The crude was purified by flash column chromatography (Silica gel, Hexane/EtOAc) to afford the title compound (16) as a mixture of diastereomers (42%, 650 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 1H), 7.18 – 7.16 (m, 3H), 4.21 – 4.12 (m, 2H), 2.65 – 2.56 (m, 3H), 2.43 – 1.78 (m, 9H), 1.36 – 1.21 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.68, 175.30, 145.48, 145.03, 136.56, 136.53, 133.03, 127.15, 127.12, 125.72, 125.68, 125.64, 125.09, 125.06, 73.98, 73.23, 60.28, 42.64, 39.06, 36.35, 34.50, 24.46, 23.72, 22.30, 22.19, 14.31, 14.28.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{16}H_{22}O_3$, 262.1569; found: 262.1575.

Ethyl 3'-oxo-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-carboxylate (mixture of diastereomers (17)



Following **GP5,** ethyl 4-hydroxy-4-(o-tolyl)cyclohexane-1-carboxylate gave the title compound (17) as a clear oil after separation of the two diastereomers with flash column chromatography (40%, 110 mg *trans* isomer; 20%, 55 mg *cis* isomer)

Trans-17

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 1H), 7.65 (t, J = 7.7, 7.3 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.52 – 2.36 (m, 1H), 2.14 – 1.73 (m, 8H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.78, 169.74, 154.11, 134.09, 129.25, 125.97, 125.53, 120.80, 85.52, 60.49, 42.00, 35.65, 24.89, 14.23.

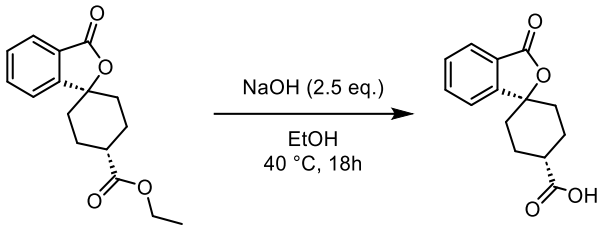
HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{16}H_{18}O_4$, 274.1205; found: 274.1201.

Cis-17b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.64 (td, J = 7.5, 1.1 Hz, 1H), 7.50 (td, J = 7.5, 1.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.95 – 2.67 (m, 1H), 2.25 – 2.00 (m, 6H), 1.80 – 1.66 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.91, 169.87, 154.28, 133.99, 129.14, 125.92, 125.54, 121.32, 86.27, 60.49, 38.04, 33.06, 23.70, 14.32.

(1α,4β)-3′-Oxospiro[cyclohexane-1,1′(3′H)-isobenzofuran]-4-carboxylic acid (18)



To a solution of ethyl 3'-oxo-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-carboxylate (*trans* isomer, 0.25 mmol, 70 mg) in EtOH (5 mL), was added NaOH (2.5 eq., 25.5 mg) and the reaction was stirred 40 °C. After 18h, the solvent was removed under vacuum and water was added. The mixture was washed with EtOAc (3x10 mL), acidified with 2.0 M HCl and then extracted with EtOAc (3x20 mL). The reunited organics were washed with water and brine, dried over Na_2SO_4, filtered and evaporated under vacuum to afford the title compound (18) a white solid without further purification (90%, 89 mg). Data in accordance with the literature (68).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 2.53 (tt, *J* = 10.3, 4.8 Hz, 1H), 2.20 – 2.03 (m, 4H), 2.03 – 1.91 (m, 2H), 1.91 – 1.80 (m, 2H).

Based on the spectroscopic data for the reported compound, we assigned the *trans* stereochemistry to both the product and the precursor.

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Flow Chemistry

2) Flow chemistry

2.1.1 General Aspects

Flow chemistry replaces flasks with reactions carried out inside tubing and microreactors, where controlled flow enables more extreme yet safer conditions than batch processes.[1] Reagents are delivered by pumps into small channels, tubes, or microreactors (Figure 2.1) where they mix and transform under tightly set flow rate, temperature, pressure, and residence time.[2] Common architectures include tubular systems and continuously stirred tanks, often with packed or immobilized catalysts. Because the volumes are small and the geometry is controlled, heat and mass transfer are fast and predictable. These same platforms readily host inline analytics and computer control, making them natural partners for automation and "self-driving" optimization loops.[3]

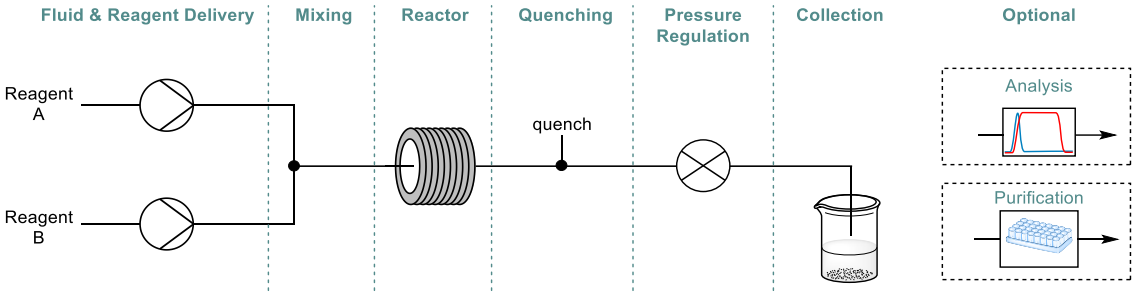

Figure 2.1 Different zones for a schematic flow-chemistry apparatus.

Compared with a flask on a stir plate, continuous operation offers practical wins. Parameters stay steady, so reactions are reproducible. Scaling is straightforward, extend the run time or the number of channels rather than rebuild the vessel. Exothermic or otherwise hazardous chemistry is easier to manage because only small amounts are reactive at any moment and heat is removed efficiently.[4] Precise dosing and residence-time control sharpen selectivity, lift yields, and cut side products. Waste is often lower, especially when using solid-supported reagents or catalysts in fixed beds that can be reused and separated from products without extra steps.[5] These strengths explain why flow has taken hold across pharmaceuticals, fine and specialty chemicals, materials, and increasingly in nanoparticle synthesis, as well as in photo- and electrochemical methods where uniform irradiation or current distribution is essential.[6-7]

Early on, many synthetic chemists viewed flow as complex, expensive, or "for engineers." The field is inherently interdisciplinary: success depends on understanding kinetics and transport, but also on plumbing, back-pressure regulation, and sensor placement. That skills

gap, together with the cost and perceived opacity of commercial skids, slowed uptake.[8] The picture is changing. Modular "do-it-yourself" assemblies, low-cost electronics, and 3D-printed parts have lowered barriers and made systems easier to build, customize, and repair.[9,10]

Flow's safety profile is a major driver.[11] Reactions that challenge batch equipment, strongly exothermic steps, unstable intermediates, toxic or energetic reagents, are more manageable when inventory is minimized and quenching can occur inline. Processes that once demanded elaborate containment or were avoided entirely can be reconsidered with continuous handling, better heat removal, and staged reagent addition. Historically, continuous processing grew from chemical engineering and large-scale manufacturing.[12] Lab-scale flow is newer and faces different constraints: smaller budgets, varied chemistry, and the need to reconfigure quickly. A rich body of reviews[13-14] and textbooks[15-16] now supports newcomers, but uneven access to equipment and cross-disciplinary training still limits routine use outside established hubs.

Heat Transfer

Microreactors excel at removing heat because their channels have a very high surface-area-to-volume ratio compared with round-bottom flasks. The large exchange surface prevents local hot spots, stabilizes temperature, and lowers the risk of thermal runaway. Practically, that means reactions can be run close to isothermal conditions or, with back-pressure, safely in the superheated regime. Even when mixing is not rate-limiting, continuous flow pays off at both ends of the spectrum: highly exothermic transformations are easier to cool, and very slow reactions can be intensified by running at elevated temperature and pressure to shorten residence times dramatically. Both heated and cooled processes benefit when selectivity hinges on small differences in transition-state energies, because tight temperature control nudges the system toward the desired pathway. Runaway behavior arises when heat released by the reaction raises the temperature and therefore the rate, creating a positive feedback loop that can cause side reactions. In tubular reactors, small dimensions and efficient heat transfer break that loop. Flow conditions offer a key advantage over batch processes when it comes to reaction scaling.[17] In flow systems, the resistance to heat transfer increases linearly with the size of the reactor channel, making the scaling process more predictable. In contrast, scaling batch reactors is less straightforward, as convective heat transfer depends not only on the size of the vessel but also on factors like impeller design and liquid level. As a result, for syntheses involving runaway reactions, flow systems provide a more reliable way to produce preparative-scale quantities without requiring advanced engineering knowledge. Increasing

the operation time, also known as scaling out, allows for the production of larger amounts of material.

Mass Transfer

Mass transfer in flow chemistry plays a pivotal role in enhancing reaction efficiency, particularly for synthetic organic chemists. In continuous flow systems, the small channel dimensions and high surface-area-to-volume ratios significantly improve mass transfer compared to traditional batch reactors. This improvement stems from the enhanced control over fluid dynamics, which promotes efficient mixing of reactants and ensures uniform concentration profiles throughout the reactor.[18] Mass transfer refers to the movement of a chemical species from one location to another within the system, primarily driven by diffusion and convection. In flow systems, reactants are constantly introduced and transported through narrow channels, which creates laminar flow conditions.[19] Although laminar flow might seem restrictive, the short diffusion distances and controlled flow profiles actually lead to rapid and predictable mixing. This efficient mass transfer is especially beneficial in fast or heterogeneous reactions, where the rate of reaction depends on how quickly reactants come into contact. It reduces concentration gradients and allows for better reaction control, leading to higher yields, reduced side-product formation, and safer operation, especially in exothermic or hazardous processes.

Packed Bed

Packed bed flow reactors (PBRs) (Figure 2.2) are a cornerstone of modern continuous-flow chemistry, particularly in organic synthesis. These reactors are typically tubular columns filled with a solid catalyst or inert support, through which reactants are flowed continuously. The packed bed structure enhances surface area for catalytic activity and facilitates efficient heat and mass transfer. PBRs are especially suitable for heterogeneous catalytic reactions, enabling prolonged operation, catalyst reuse, and ease of separation between phases.[20] One of the major advantages of packed-bed reactors is that the supported catalyst can be readily reused without the need for labor-intensive recovery procedures. In many cases, the catalyst-containing cartridge can simply be washed and directly employed in subsequent runs. This feature enables the use of highly valuable catalysts while ensuring exceptionally efficient recovery, making such systems particularly attractive for industrial applications. Another key advantage of PBRs is the ability to maintain high reaction selectivity and throughput under steady-state conditions. They also allow for fine control of residence time and temperature gradients, which are critical for sensitive transformations. In organic synthesis, PBRs have

been effectively used for hydrogenations, oxidations, C-C bond formations, and even multistep tandem reactions.[21]

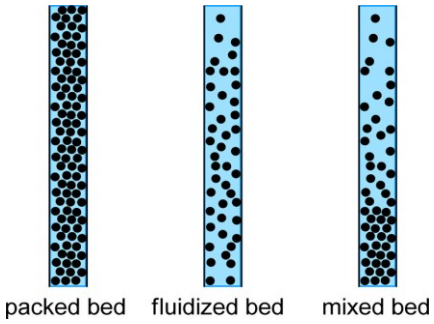

Figure 2.2 Schematic representation of a packed bed compared with other packed types.

2.1.2 Packed Bed Flow Reactors in Organic Synthesis

Packed bed flow reactors (PBRs) have emerged as one of the most prominent technologies in continuous flow chemistry, particularly in the context of heterogeneously catalyzed reactions.[22-23] In recent years, PBRs have become increasingly attractive for applications in organic synthesis, driven by the demand for scalable, efficient, and sustainable chemical processes. Traditionally, batch reactors have dominated laboratory-scale organic synthesis due to their simplicity, flexibility, and ease of operation. However, batch processes often encounter challenges in heat and mass transfer, especially during scale-up. In contrast, flow systems like packed bed reactors provide a more controllable and scalable solution. As a result, PBRs are transitioning from being industrial tools for petrochemicals to valuable assets in fine and pharmaceutical chemical synthesis.

Continuous-flow systems can be divided into four main categories, based on different possible scenarios under flow conditions (in Figure 2.3).[24] The simplest setup is Type I, where all reactants are continuously introduced into the flow reactor and the resulting product is collected non-stop. However, this method also allows unreacted starting materials and byproducts to pass through with the product, often resulting in complicated purification steps. To reduce these efforts, researchers have explored Type II systems, where one of the reagents is immobilized and packed into the reactor. If the immobilized reagent B is used in large excess compared to the flowing reagent A, unwanted contamination from A and B can be minimized. A drawback, however, is that once the supported reagent is exhausted, the reactor must be replaced, temporarily halting the process. Since catalysis plays a key role in modern organic synthesis by enhancing both efficiency and selectivity, Type III systems utilize homogeneous catalysts in continuous-flow reactions. While this allows the reaction to proceed continuously, separating the dissolved catalyst from the product stream can pose purification challenges. Type IV systems address this issue by using heterogeneous catalysts, which remain in the reactor and do not mix with the product. This eliminates the need for catalyst separation and also boosts reaction rates due to improved contact between the reactants in the flow and the solid catalyst surface. As a result, Type IV systems are considered the most efficient approach for continuous-flow organic synthesis. However, their effectiveness depends on various design factors, such as particle size, surface area, and how well the catalytic material is distributed on the support. Careful optimization of these parameters is essential for achieving high performance in Type IV reactions.

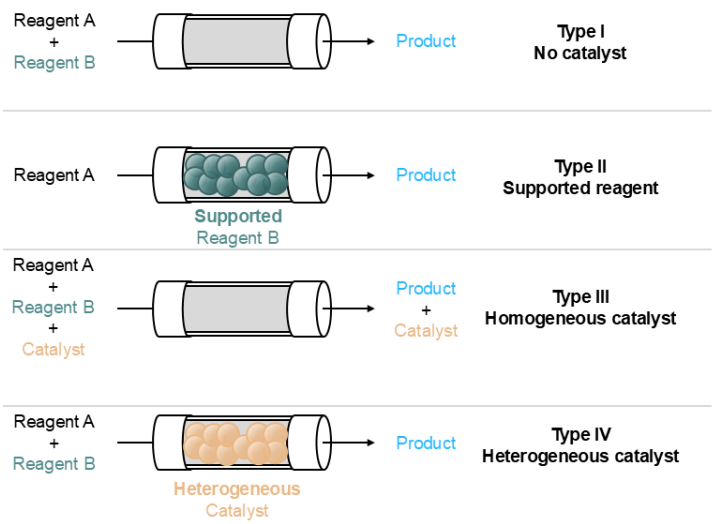

Figure 2.3 Classification of flow reactors.

Packed bed reactors offer numerous advantages that make them particularly well-suited for modern synthetic chemistry. One of their most notable benefits lies in catalyst utilization. Since the catalyst is immobilized within the reactor bed, it can be reused over extended periods without requiring removal or replacement after each cycle. This not only reduces material costs but also simplifies downstream purification. The design of packed beds, offers a high surface-to-volume ratio, which increases the effective contact area between reactants and catalytic surfaces.[25] As a result, reactions often proceed with higher conversion rates and improved selectivity. Moreover, packed bed systems provide enhanced heat transfer.[26] The narrow channels typical of microreactors allow for efficient heat dissipation and reduce the formation of localized hot spots, an issue that can compromise safety and product quality in exothermic processes. In terms of scalability, PBRs can be expanded through a strategy known as numbering-up, where multiple identical units operate in parallel. This approach avoids the inefficiencies often introduced when increasing the size of a single reactor.[27] Finally, their inherent safety advantages make them ideal for handling hazardous, toxic, or unstable intermediates.[28] Because only small quantities of reagents are present in the system at any given time, the risk of runaway reactions or thermal events is greatly minimized. This, combined with their compatibility with automation, positions packed bed reactors as a valuable tool for continuous and safe chemical manufacturing.

Despite their strengths, packed bed reactors also have limitations that must be addressed during design and operation: Pressure Drop: Small particle sizes increase the surface area but also result in high pressure drop, which may require more powerful pumps and energy input. This tradeoff must be optimized for each system.[29] Clogging and Channeling: Over time, accumulation of solids or gas bubbles may lead to non-uniform flow, affecting reaction

performance. This is particularly problematic in microstructured beds with narrow channels.[30] Limited Empirical Correlations: Most transport and kinetic models are derived from macro-scale systems and may not be directly applicable to micro- or meso-scale reactors. There is a need for new correlations and experimental data specifically tailored for micro-PBRs.[31]

In the field of flow methodologies for fluorination,[32] Lindhardt et al. (2018) developed reactors packed with a CsF-CaF_2 mixture, applying them to a range of nucleophilic fluorination reactions (Figure 2.4A).[33] Traditional support materials like silica gel and alumina are Lewis acidic and tend to react with fluoride ions from CsF, which limits their suitability. When Amberlyst 900 was used as a support loaded with fluoride ions to fluorinate 2-chloropyridine, the substrate remained bound to the support and failed to elute effectively. However, switching to CaF_2 as the support material allowed the reaction to proceed smoothly, enabling fluorination of various substrates such as benzyl bromide, 3-chloropyridine, carbonyl compounds, and silyl-protected species. Scale-up studies showed that efficient water removal by solvent washing of the packed bed was crucial. A notable example was the fluorination of 4-cyanoacetophenone, yielding 7.4 g of the target compound in 94% yield after just 42 minutes.

Further advancements were reported by Xu, Hammond, and colleagues,[34] who introduced an unbalanced ion-pair promoter system using a bulky, charge-delocalized cation with a localized anion. This system enhanced the nucleophilic fluorination with KF in a packed bed setup (Figure 2.4B), enabling efficient transformations of substrates bearing leaving groups like OMs, Br, and sulfonyl chlorides. They also utilized a polymer-supported ion pair (A26-SO_4^{2-}) in a packed bed reactor, maintaining high conversion rates even after 24 hours of continuous operation.

In a separate study, Xu et al.[35] developed a highly enantioselective flow fluorination process using a polystyrene-supported diphenylamine-bis(oxazoline)-$Cu(OTf)_2$ complex as the catalyst (Figure 2.4C). By optimizing ligand structure, solvent choice, and catalyst loading, they achieved excellent yields and high enantioselectivity. The system demonstrated impressive catalytic efficiency, with a turnover number exceeding 4000.

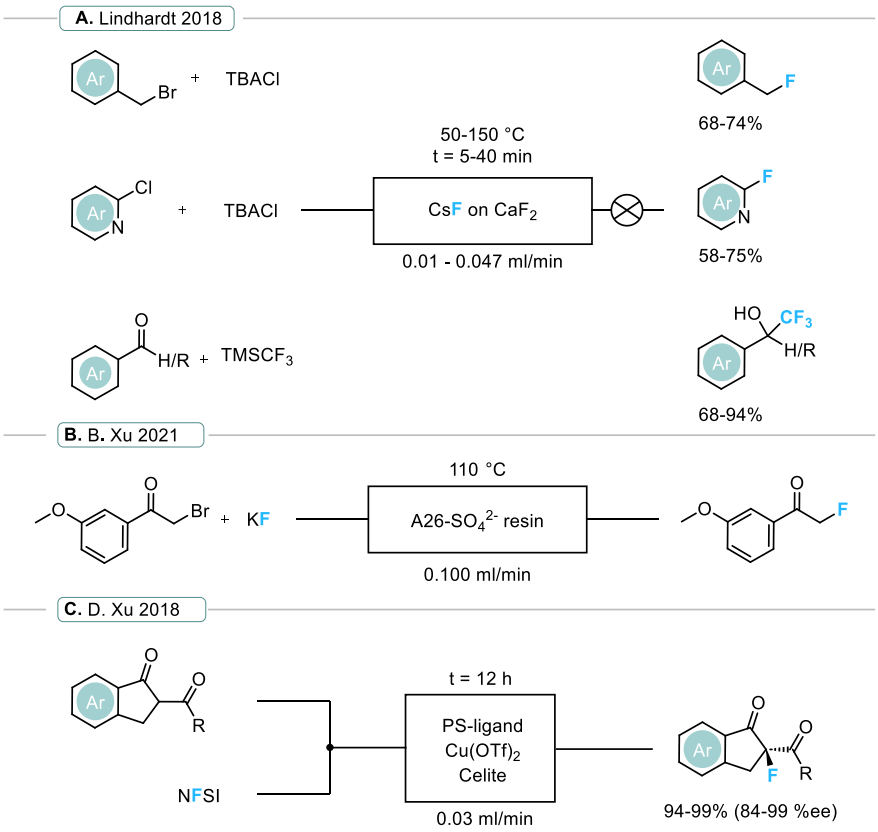

Figure 2.4 A. Nucleophilic fluorination reactions using packed bed reactors with $CsF\text{-}CaF_2$. **B.** Nucleophilic fluorination reactions using packed bed reactor with polymer-supported ion pair A26-SO_4^{2-}. **C.** Enantioselective fluorination catalyzed by a polystyrene-supported diphenylamine-bis(oxazoline)-$Cu(OTf)_2$ complex.

Packed bed flow reactors represent a versatile and efficient platform for continuous organic synthesis, offering advantages in scalability, reaction control, and safety. Their success hinges on a solid understanding of transport phenomena and reactor design. While challenges such as pressure drop and catalyst deactivation remain, ongoing research and modeling improvements continue to expand the capabilities of PBRs in both academic and industrial settings. As flow chemistry becomes more integrated with synthetic strategies, packed bed reactors will undoubtedly play a central role in shaping the future of green and scalable chemical manufacturing.

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3rd Project

Flow-Enabled, Modular Access to α,α-Difluoromethylene Amines

Pietro Ronco and Dmitrii Nagornîi performed and analyzed the experiments

Supervisors: Timothy Noël

Flow Chemistry Group, Van 't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Amsterdam, The Netherlands.

2.2 Flow-Enabled, Modular Access to α,α-Difluoromethylene Amines

Fluorinated groups are critically important in the design of pharmaceutical and agrochemical compounds, as they can profoundly influence the physicochemical and biological behavior of small molecules.[1,2] Introducing fluorine atoms into molecular structures can enhance metabolic stability, fine-tune lipophilicity, and improve bioavailability, making fluorination a key tactic in modern drug development (Figure 2.5A).[3,4] Among the diverse fluorinated functionalities, the difluoromethylene unit (CF_2) is particularly notable for its ability to serve as a bioisostere for both methylene (CH_2) and carbonyl (C=O) groups.[5] Recent breakthroughs in difluoromethylation and carbene chemistry have enabled efficient incorporation of CF_2 units into organic scaffolds, allowing for their direct attachment to carbon, oxygen, and sulfur atoms.[6-13] However, the synthesis of α,α-difluoromethylene amines (NCF_2R, where $R \neq H$) remains underexplored. This is largely due to the synthetic challenges associated with direct fluoroalkylation of amines and the poor stability of the resulting products (Figure 2.5B, C).[14-16] Currently, practical and scalable routes to access α,α-difluoromethylene amines bearing substituents other than hydrogen or fluorine ($R \neq H$ or F) are extremely limited.[17-19] To date, the only dependable method for generating such motifs involves using pre-functionalized thioamides in combination with silver fluoride, as demonstrated by Hu and colleagues, emphasizing the pressing need for more general and versatile synthetic approaches.[20] To fill this gap, we devised a safer and more efficient method using caesium fluoride (CsF) in a packed-bed microreactor to generate NCF_2R anions under mild conditions (Figure 2.5D).[21-23] In this process, imidoyl chlorides, easily available starting materials, are passed through a CsF-packed reactor, where a fast chloride-to-fluoride (Cl-F) exchange occurs, followed by fluoride addition, resulting in the formation of NCF_2R anions in situ and in excellent yields.[24,25] These anions can then be reacted with a range of electrophiles to produce stable α,α-difluoromethylene amines. This approach provides a robust, scalable, and modular synthetic platform for accessing a wide array of NCF_2R compounds. Structural diversity is readily achieved by modifying the benzoic acid or sulfonamide precursors of the imidoyl chlorides or by choosing different electrophilic coupling partners. Importantly, our strategy bypasses the use of pre-fluorinated starting materials, enabling late-stage CF_2 installation and significantly minimizing the generation of unnecessary fluorinated waste.

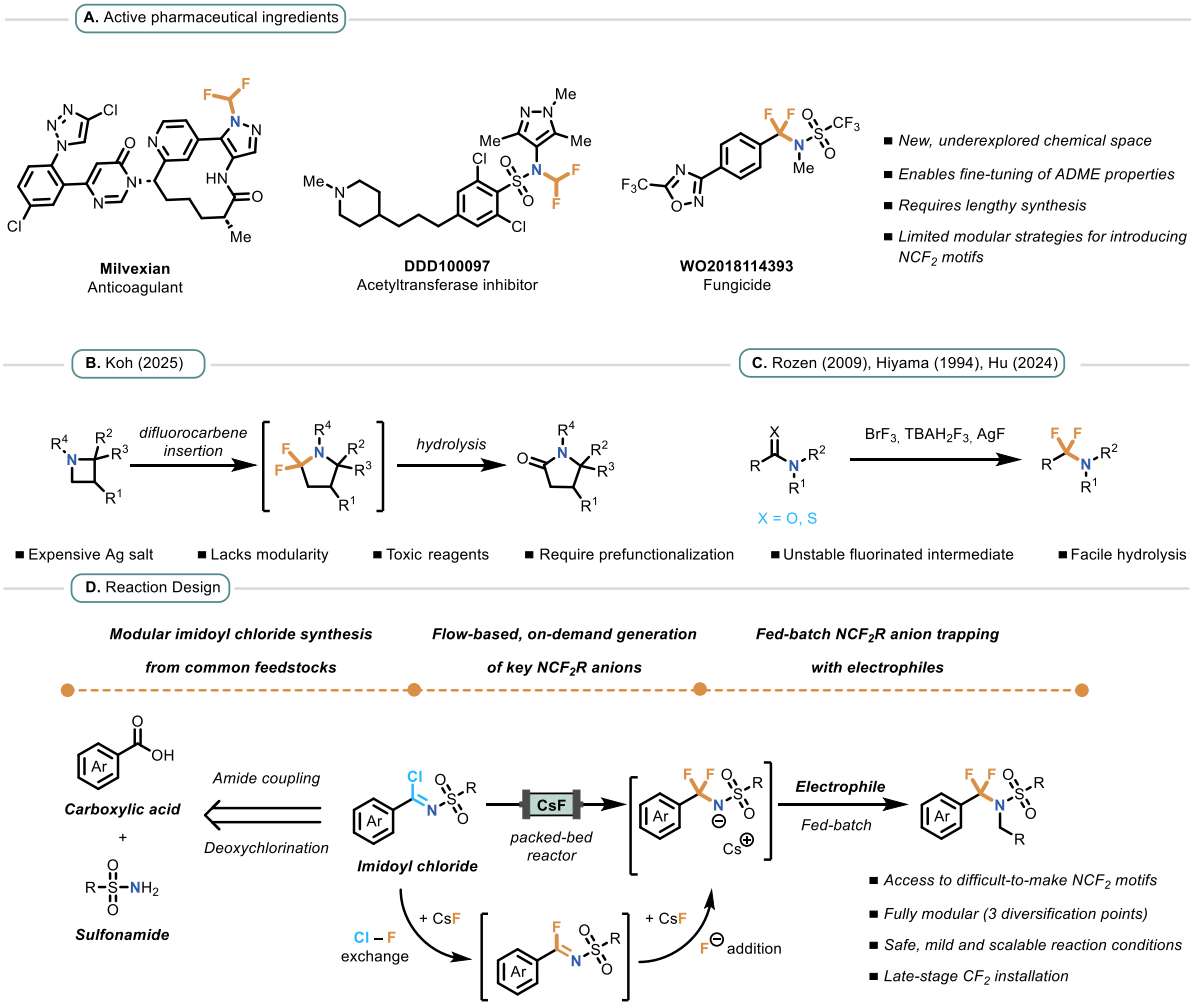


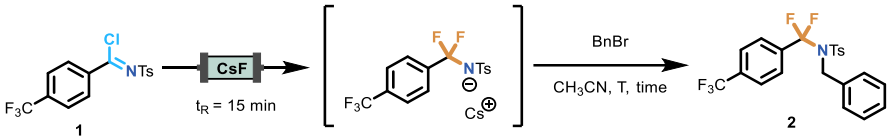
Figure 2.5 A. Examples of active pharmaceutical ingredients containing NCF_2 motifs. **B & C.** Prior art in the synthesis of NCF_2R motifs. **D.** Reaction design: modular and scalable access to NCF_2 motifs using flow-enabled anion generation and fed-batch trapping.

2.2.1 Results and discussion

Building on previous work by the Noël group,[26] we developed a new difluorination strategy that begins with substituted imidoyl chlorides. These starting materials were readily prepared via a simple and modular two-step synthesis: an amide coupling followed by deoxychlorination, using easily accessible benzoic acid derivatives and sulfonamides. Most of the aryl-substituted imidoyl chlorides synthesized in this study could be isolated as crystalline solids by straightforward precipitation, although a few required further purification via column chromatography. Notably, these compounds demonstrated excellent stability under ambient conditions, remaining bench-stable for several weeks without any detectable loss of reactivity. In preliminary batch reactions, aryl-substituted imidoyl chloride 1 was successfully transformed into the corresponding difluorinated anion, which underwent nucleophilic substitution with benzyl bromide to afford product 2 in 64% isolated yield. However, due to the comparable nucleophilicity of the fluoride ion and the in situ-generated anion, side reactions such as the formation of benzyl fluoride were observed. This undesired pathway consumed a significant portion of the electrophile, rendering the batch process inefficient. To resolve this issue, we developed a continuous flow protocol employing a packed-bed reactor filled with CsF and glass beads as packing material. This setup enhanced the efficiency of the Cl-F exchange and subsequent fluoride addition by maximizing CsF availability, improving reagent contact through better mixing, and increasing surface area. Moreover, the flow system safely confined reactive intermediates, offering both operational simplicity and safety. The optimized flow conditions effectively drove the equilibrium toward NCF_2R anion formation via sequential Cl-F exchange and fluoride addition. Residence time optimization showed that full conversion of the imidoyl chloride to the desired anion could be achieved within 15 minutes. After exiting the reactor, the anion was immediately combined with an electrophile in a fed-batch configuration. This integration of continuous-flow anion generation with batch nucleophilic substitution also minimized fluoride ion carryover, thereby suppressing the side formation of benzyl fluoride.

Subsequent optimization of the nucleophilic substitution step revealed that using an excess of the anion relative to the electrophile substantially improved product yield (Table 2.1, Entries 1-3, 9). At room temperature, applying 1.5 and 3.0 equivalents of the anion gave moderate yields of 41% and 67%, respectively, albeit with prolonged reaction times (Table 1, Entries 4 and 5). Additive screening (Table 2.1, Entries 6 and 7) showed that introducing 1.1 equivalents of tetrabutylammonium iodide (TBAI) increased the yield to 75% under mild heating at 40 °C. However, raising the amount of TBAI beyond this level did not lead to further improvements in yield (Table 2.1, Entry 8).

Table 2.1 Reaction optimization: Influence of reagent stoichiometry, temperature, and time optimization on the formation of compound **2**.



Entry[a]	Anion	BnBr	Temperature	Time	Additive	Product yield[a]
001	1.5 eq	1.0 eq	80 °C	3 h	–	39%
002	2.0 eq	1.0 eq	80 °C	3 h	–	53%
003	3.0 eq	1.0 eq	80 °C	3 h	–	46%
004	1.5 eq	1.0 eq	20 °C	60 h	–	41%
005	3.0 eq	1.0 eq	20 °C	60 h	–	67%
006	3.0 eq	1.0 eq	40 °C	18 h	KI (1.5 eq.)	25%
007[b]	**3.0 eq**	**1.0 eq**	**40 °C**	**18 h**	**TBAI (1.1 eq.)**	**75%**
008	3.0 eq	1.0 eq	40 °C	18 h	TBAI (3.0 eq.)	79%
009	1.0 eq	3.0 eq	40 °C	18 h	–	25%

[a]Yields were determined by ^{19}F NMR using 1,2-difluorobenzene as external standard (0.1 mmol scale).

[b] These conditions were selected as optimal and were used to explore the reaction scope.

With the optimized conditions established, we next turned our attention to evaluating the substrate scope. The modular nature of our synthetic design allows for diversification at three key points throughout the sequence. We began by exploring the first diversification element: varying the electrophilic coupling partners used with our model imidoyl chloride 1 (Figure 2.6). The reaction proved highly tolerant of structural and electronic diversity in the electrophiles. Benzyl and allyl bromides bearing a range of functional groups that participated smoothly in the transformation. Substituted benzyl bromides incorporating halogens (F, Cl, Br, and I; compounds 3-6), methoxy (7), aldehyde (8), nitrile (9), ketone (10), and ester (11) groups all reacted effectively with the NCF_2R anion, furnishing the desired α,α-difluoromethylene amines in moderate to good yields (49-77%). Importantly, the method was readily scalable without the need for further optimization, as demonstrated by the 1-gram scale synthesis of compound 5 in 70% isolated yield. Beyond simple aryl substrates, the methodology also tolerated heteroaryl electrophiles. Benzothiophene (12), quinoline (13), pyridine (14), and furan (15) derivatives were efficiently functionalized, affording products in yields ranging from 44% to 84%. The scope further extended to allylic (16-17, 67-85%) and propargylic bromides (18, 44%), illustrating the broad compatibility of the reaction with diverse electrophilic partners. Given the prevalence of N-methylation in

medicinal chemistry, we also examined the reaction of the NCF_2R anion with methyl triflate. This led to the successful formation of both the N-methylated product and its ^{13}C-labeled variant (compounds 19-20) in excellent yields (82-83%).[27] Finally, the synthetic utility of our strategy was demonstrated through late-stage functionalization of complex, drug-like molecules. A range of pharmaceutically relevant substrates, including derivatives of Rosuvastatin (21), Probenecid (22), Ataluren (23), Repaglinide (24), and Menthol (25), underwent smooth transformation to the corresponding NCF_2R products, with isolated yields ranging from 21% to 64%. These examples highlight the broad applicability of our flow-enabled, modular platform for the rapid construction of structurally diverse and pharmacologically relevant α,α-difluoromethylene amines.

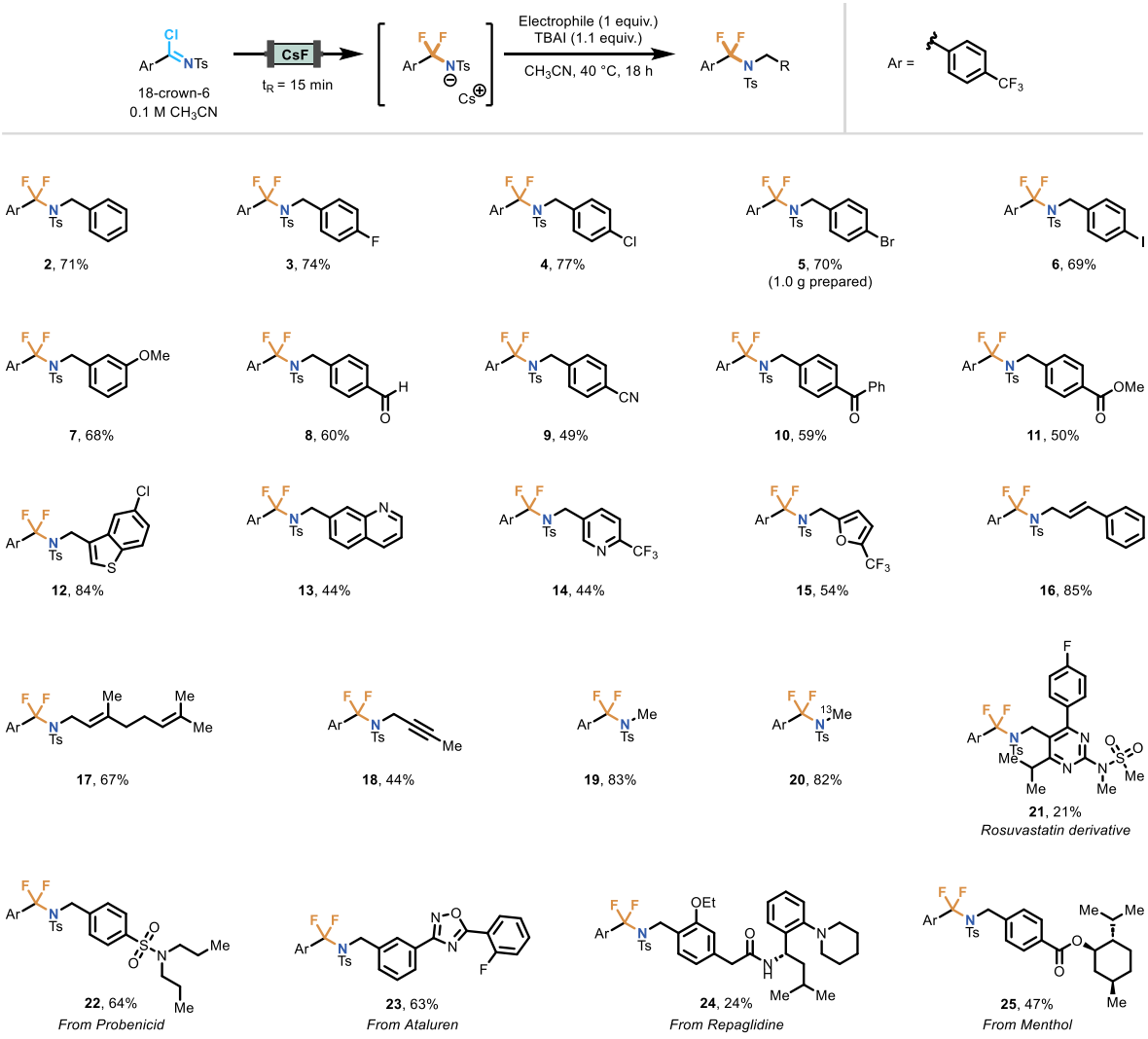


Figure 2.6 Electrophile scope of the difluorinative functionalization reaction. *Reaction conditions:* A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the CsF packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The outflow (6 mL, 3 equiv.) was collected in an oven-dried vial containing TBAI (1.1 equiv.) and the corresponding

electrophile (if solid) (1 equiv., 0.2 mmol). Upon collection of the desired amount of outflow, the electrophile (if liquid) (0.2 mmol, 1 equiv.) was added, and the reaction was stirred at 40 °C for 18 h.

In medicinal chemistry, the development of synthetic methods with wide functional group tolerance, adaptable modification of molecular frameworks, and straightforward operation is crucial for accelerating drug discovery. To showcase these attributes in our platform, we investigated variations in the imidoyl chloride fragment, focusing specifically on the carboxylic acid-derived component (Figure 2.7). Using our established protocol, a series of imidoyl chlorides, easily synthesized from substituted benzoic acids or acyl chlorides, were passed through the CsF-packed bed reactor and subsequently coupled with cinnamyl bromide in a fed-batch configuration. In general, substrates bearing electron-withdrawing groups delivered higher yields compared to those lacking substituents (compound 29, 53%) or containing electron-donating groups. This observation is likely due to the enhanced electrophilicity of the intermediate imidoyl fluoride, which facilitates nucleophilic attack by the fluoride ion and promotes more efficient generation of the NCF_2R anion. A wide array of electron-withdrawing substituents was well tolerated, including halogens (F, Cl, Br; compounds 26-28), trifluoromethyl (7), trifluoromethoxy (30), nitrile (31), methyl ester (32), and methyl sulfone (33), affording the corresponding α,α-difluoromethylene amines in good to excellent yields (57-85%). Additional substrates such as benzoyl chloride (29) and a thiophene-containing derivative (34) also underwent the transformation successfully, providing the target compounds in 43-60% yield. To further highlight the synthetic utility of this approach, we applied it to the imidoyl chloride derived from the marketed drug Probenecid (35), which was efficiently functionalized under the optimized conditions to give the desired product in 71% isolated yield.

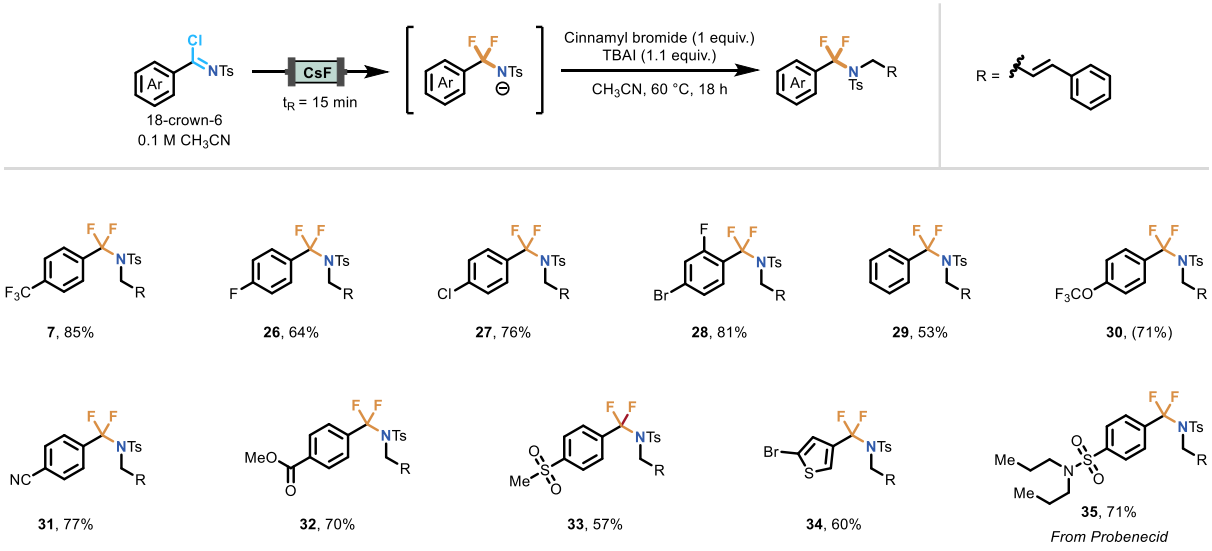


Figure 2.7 Scope of the difluorinative functionalization reaction starting from various benzoic acid or acyl chloride derivatives**.** *Reaction conditions:* A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the CsF packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The outflow (6 or 8 mL, 3 or 4 equiv.) was collected in an oven-dried vial containing TBAI (1.1 equiv.). Upon collection of the desired amount of outflow, cinnamyl bromide (0.2 mmol, 1 equiv.) was added, and the reaction was stirred at 60 °C for 18 h.

To complete the exploration of the diversification potential of our modular platform, we examined the third tunable component: the sulfonamide-derived fragment (Figure 2.8). A variety of commercially available sulfonamides were tested under the optimized conditions, demonstrating broad compatibility. Commonly used functional groups in synthetic chemistry, including tosyl (7), nosyl (39), mesyl (43), and triflyl (44),were successfully incorporated in the final products. Substitution on the aromatic ring of the sulfonamide was well tolerated. Electron-donating and electron-withdrawing groups such as chloride (36), fluoride (37), and methoxy (38) all participated efficiently in the transformation. Moreover, several heterocyclic sulfonamides, including pyrazole (40) and thiophene-based derivatives (41-42), proved to be competent coupling partners, further illustrating the method's versatility. To demonstrate the strategy's relevance to drug development, we applied it to sulfonamide derivatives of the nonsteroidal anti-inflammatory drugs Valdecoxib (45) and Deracoxib (46). Both were successfully functionalized using our protocol, underscoring the method's utility for late-stage diversification of complex and pharmacologically significant molecules.

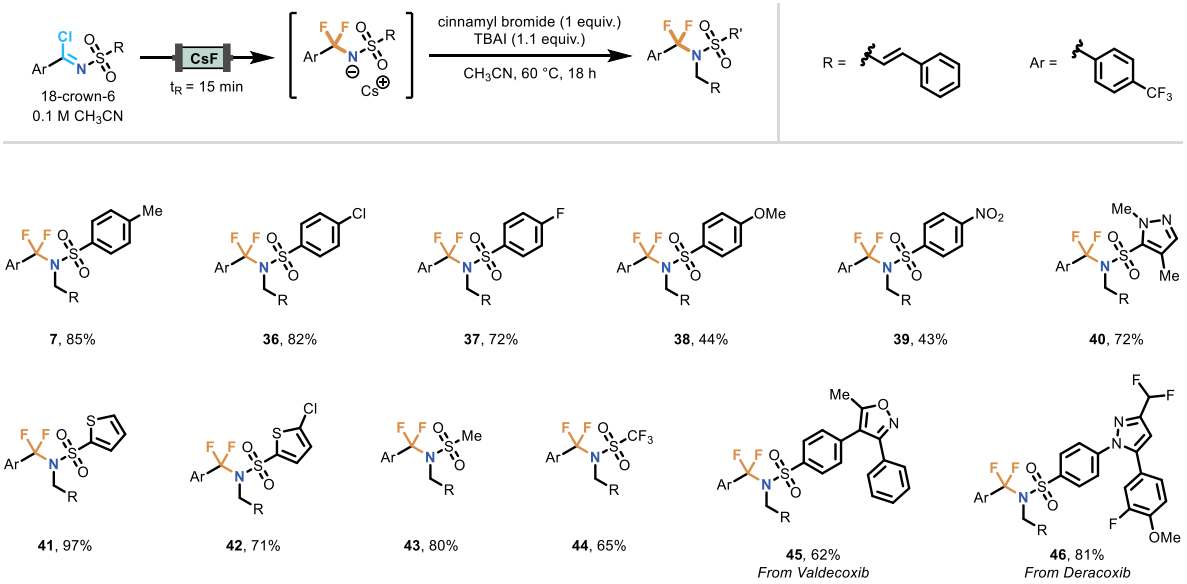


Figure 2.8. Scope of the difluorinative functionalization reaction starting from various sulfonamides**.** *Reaction Conditions:* A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the CsF packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The outflow (6 or 8 mL, 3 or 4 equiv.) was collected in an oven-dried vial containing TBAI (1.1 equiv.). Upon collection of the desired amount of outflow, cinnamyl bromide (0.2 mmol, 1 equiv.) was added, and the reaction was stirred at 60 °C for 18 h.

Geminal difluoro groups are well-established as bioisosteres for both carbonyl and methylene functionalities, making them valuable motifs in drug design.[28-33] To highlight the synthetic utility of our method, we applied our difluorinative strategy to the selective modification of biologically active molecules (Figure 2.9A,B).

For instance, imidoyl chloride 47 was converted into α,α-difluoromethylene amine 48, which served as a precursor for the synthesis of a difluoro analogue of compound 49, a sodium channel blocker used clinically for pain management and prevention.[34] In a similar fashion, imidoyl chloride 50 was coupled with a bromo-thiophene derivative to afford product 51. This intermediate was then further elaborated to access a difluorinated analogue of compound 52, a known modulator of liver X receptors α (LXR-α) and β (LXR-β).[35]

To further underscore the broad applicability of our platform, we developed a direct approach to transform biologically active amides into α,α-difluoromethylene amines. This sequence involves an initial deoxygenative chlorination followed by our flow-enabled difluorination protocol. As a representative example, the antitumor agent Tasisulam (60), which is known to inhibit mitotic progression and promote vascular normalization, was subjected to this two-step transformation, affording a series of fluorinated analogues (61-63). Notably, this

included the generation of a hybrid structure combining features of Tasisulam and Ataluren (63), illustrating the potential of this method for generating structurally novel, pharmacologically relevant compounds.[36]

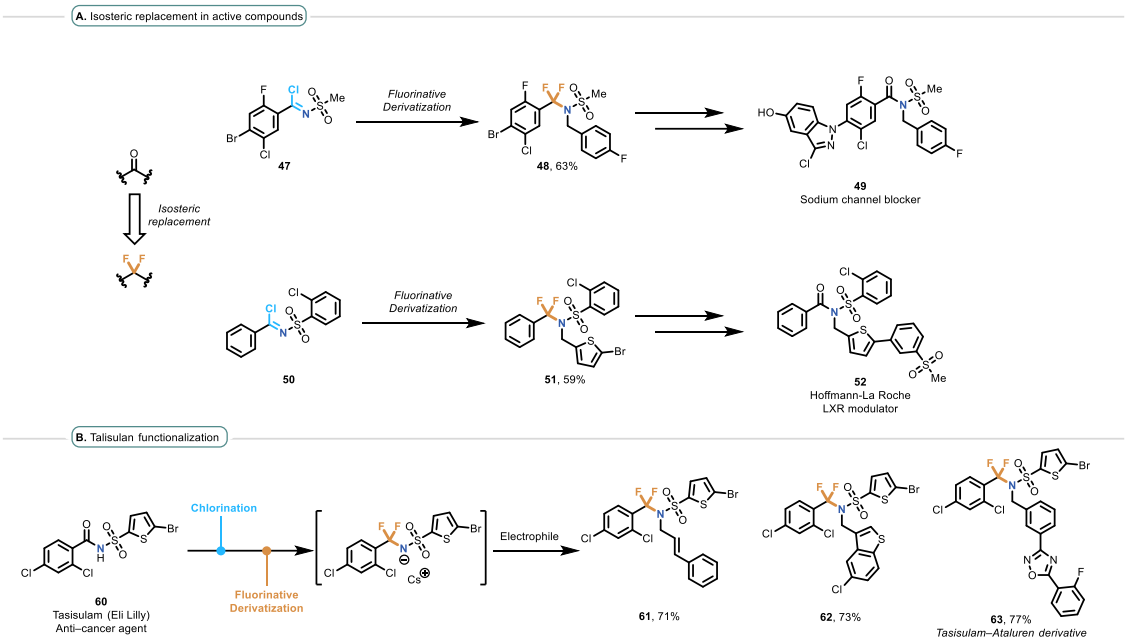


Figure 2.9. Late-stage diversification strategies**. A**. Strategic replacement of carbonyl motifs with the difluoromethylene unit and application to the formal synthesis of fluorinated analogues of drug molecules. **B**. Rapid fluorinative functionalization of Tasisulam using the developed methodology.

2.2.2 Experimental details

General experimental details

^{1}H (300 MHz), ^{13}C (75 MHz) and ^{19}F (282 MHz) spectra were recorded at ambient temperature using Bruker AV 300-I. ^{1}H NMR spectra are reported in parts per million (ppm) downfield relative to $CDCl_3$ (7.26 ppm) and all ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.16 ppm). The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), ddd (doublet of doublet of doublets), br s (broad singlet). Coupling constants (*J*) are reported in hertz (Hz). NMR data was processed using the MestReNova 14 software package. High resolution mass spectra (HRMS) were collected on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan) or on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan), or on a 7200 GC-qTOF (Agilent Technologies). Disposable syringes were purchased from Laboratory Glass Specialist. Syringe pumps were purchased from Chemix Inc. model Fusion 200 Touch. Product isolation was performed automatically, by a Biotage® Isolation Four, with Biotage® Ultra C18 10 g flash chromatography cartridges, or manually, using silica (P60, SILICYCLE). TLC analysis was performed using Silica on aluminum foils TLC plates (F254, SILICYCLE) with visualization under ultraviolet light (254 nm and 365 nm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator (in vacuo at 40 ºC, ~5 mbar).

Abbreviations

TBAI : Tetrabutylammonium iodide

BnBr : Benzyl bromide

Ts: Tosyl

CH_3CN : Acetonitrile

CsF : Caesium fluoride

18-crown-6 : 1,4,7,10,13,16-Hexaoxacyclooctadecane (crown ether)

Et_3N : Triethylamine

DMAP : 4-(Dimethylamino)pyridine

EtOAc : Ethyl acetate

PCl_5 : Phosphorus pentachloride

PhCl : Chlorobenzene

$NaBH_4$: Sodium borohydride

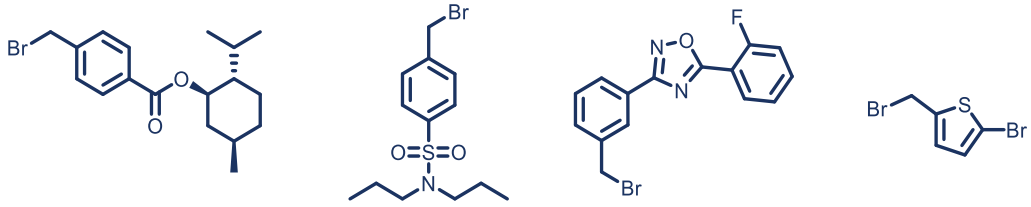
THF : Tetrahydrofuran

LiBr : Lithium bromide

Materials

All the solvents were used as received without further purification. Reagents and solvents were purchased from Sigma Aldrich, TCI, abcr, BLD Pharma and Fluorochem. Technical solvents were purchased from VWR International and used as received. Empty cartridges used for the packed-bed reactor were purchased at Screening Devices (catalogue number SD-0000-004). Dry CH_3CN was purchased from Fisher Scientific (Landsmeer, The Netherlands). Flow module was assembled using PFA tubing (ID = 0.8 mm, OD = 1.6 mm) and PEEK connectors.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-(bromomethyl)benzoate (SI-1)[37], 4-(bromomethyl)-N,N-dipropylbenzenesulfonamide (SI-2)[38], 3-(3-bromophenyl)-5-(2-fluorophenyl)-1,2,4-oxadiazole (SI-3)[39] and 2-bromo-5-(bromomethyl)thiophene[40] were prepared according to reported literature procedures.



SI-1 SI-2 SI-3 SI-4

Packed-Bed Reactor Preparation

An empty polypropylene (PP) cartridge for automated flash chromatography was used as a packed-bed reactor module. The cartridge was loaded with a dried mixture of caesium

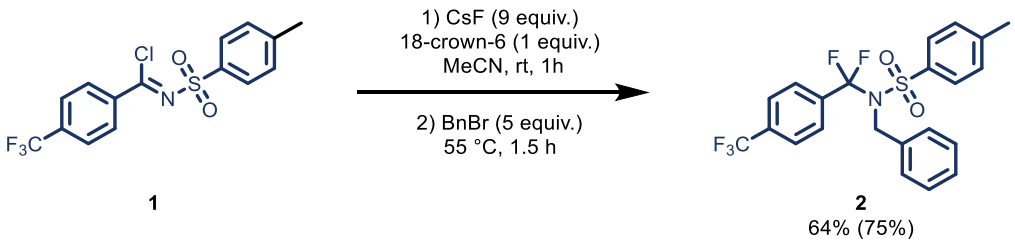
fluoride (CsF) and glass beads (425-600 µm) in a weight ratio of 7:3. This mixture was prepared by mixing previously ground CsF and glass beads in a Schlenk flask, followed by overnight drying at 300 ºC under vacuum (0.02 to 1 mbar). During the drying process, CsF is prone to forming aggregates that are challenging to break apart upon cooling. This can be mitigated by manually breaking the aggregates by using a spatula or a glass rod under a stream of nitrogen. The cartridge was then completely filled with this mixture (approximately 15.8 g) with gentle tapping against a flat surface to ensure optimal packing. A frit, included with the cartridge, was then used to seal the top and the Luer cap was attached. The CsF-packed cartridges were used immediately after preparation. The dead volume of the reactor was determined by weighting the filled cartridge before and after flushing it with dry CH_3CN and dividing the mass difference by the density of CH_3CN (0.786 g mL-1). For the sake of clarity, averaged dead volume (3.3 mL) will be used throughout the rest of the document. The CsF packed cartridges, filled with dry CH_3CN, were kept under nitrogen until they were used for the reaction. As the dead volume of the reactor would slightly vary each time, the flow rates used were calculated for each cartridge in order to satisfy targeted residence time.

Preparation of 18-crown-6 Solution

In a 250 mL round-bottom flask, 18-crown-6 (5.30 g, 20.0 mmol) and propan-2-ol were charged (ca. 10.0 mL). The solution was then concentrated under reduced pressure at 40 ˚C in a rotary evaporator system. Next, the resulting 18-crown-6 was dried under high vacuum for 15 minutes. This procedure was repeated 3 more times for azeotropic drying, and after the last cycle 18-crown-6 was left under the high vacuum overnight. Next, the flask was backfilled with nitrogen, and 18-crown-6 was dissolved in dry CH_3CN (200 mL). Then, the 0.1 M 18-crown-6 solution was transferred to another flask containing activated 3 Å molecular sieves. 18-Crown-6 solutions can be stored for extended periods of time, but freshly prepared solutions usually provided the best results and are recommended to ensure the highest reaction yields and reproducible results.

I. Optimizations

Preliminary Batch Experiments

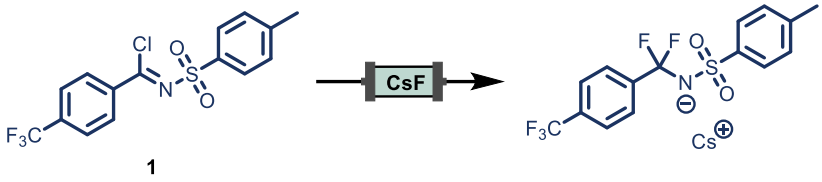


1

2
64% (75%)

A 7 mL vial containing a magnetic stirring bar was charged with CsF (273 mg, 1.8 mmol, 9 equiv.). The inorganic salt was then dried in the vial by heating it with a heat gun under vacuum (300 ºC, 5 minutes). Then, the flask was backfilled with nitrogen and left cooling down at room temperature. A solution of the corresponding imidoyl chloride (72 mg, 0.2 mmol, 1 equiv.) and 18-crown-6 ether (52.8 mg, 0.2 mmol, 1 equiv.) in anhydrous CH_3CN (2 mL, 0.1 M) was added to the vial and stirred for 1 hour at room temperature. Next, benzyl bromide (118 µL, 1 mmol, 5 equiv.) was added to the vial and the solution was stirred at 55 °C for 1.5 hours. Then, 1,2-difluorobenzene (19.7 µL, 0.2 mmol) was added and an aliquot was taken to measure the amount of product formed by quantitative ^{19}F NMR (75%). The crude was purified using column chromatography to confirm the formation of the desired product (64%).

Optimization of the $TsNCF_2R$ Anion Generation in Flow



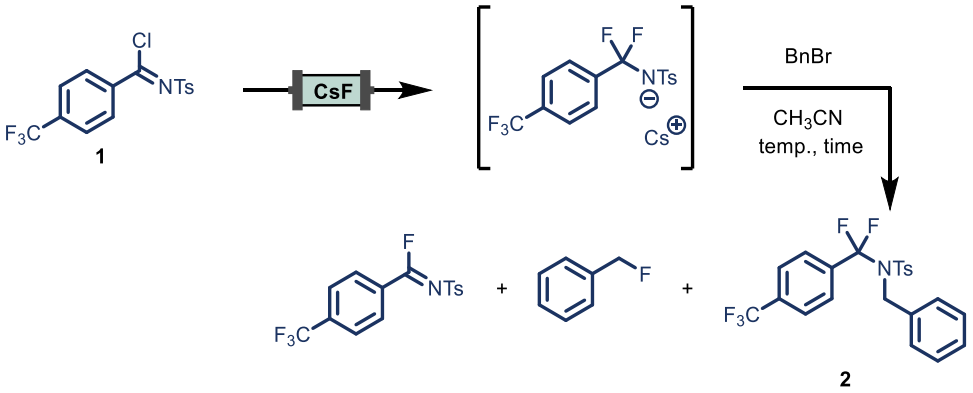
1

The optimization of the generation of the $TsNCF_2R$ anion was performed by feeding a 0.1 M solution of imidoyl chloride and 18-crown-6 ether in dry CH_3CN to the packed-bed reactor at different flow rates and determining the yield of the reaction by quantitative ^{19}F NMR (Table S1). Solutions were prepared by dissolving the appropriate amount of the imidoyl chloride in the 18-crown-6 solution, the preparation of which is described above, under nitrogen. Three empty volumes of the reactor (ca. 10 mL) were discarded prior to the collection to ensure equilibration of the system. Samples were prepared by feeding the reaction stream (0.500 mL) into a N_2 filled oven-dried NMR tube, containing 1,2-difluorobenzene as the external standard. Conversion was analysed by ^{19}F NMR. A residence time of 15 minutes was chosen as optimal and used for all further reactions.

Table S2.1. Flow rate optimization for the generation of the $TsNCF_2R$ anion.

Entry	Residence time (min)	Flow rate (mL/min)	Anion Yield (%)
1	5 min	0.63	68%
2	10 min	0.32	92%
3	15 min	0.21	99%

Optimization of Reaction Stoichiometry, Temperature, and Time



An extensive optimization of the reaction parameters of the fed batch step was performed (Table S2). Increasing the equivalents of anion added to the reaction resulted in an increased yield (Entry 3, 6 and 12). Increasing the temperature resulted in higher yields of the desired product, but also decomposition of the anion and the formation of benzyl fluoride byproduct. Lower temperatures din not yield satisfying results, unless extremely long reaction times were used (Entry 8). Using an excess amount of benzyl bromide (Entry 13 and 14) did not result in the desired product in a sufficient yield.

Table S2.2: Stoichiometry, temperature, and time optimization for the formation of compound **1**.

Entry[a]	Anion (equiv.)	BnBr (equiv.)	Temperature (°C)	Time (hours)	Product	BnF	F exchange	Anion left
1	1.5	1	20	3	**14%**	3%	11%	112%
2	1.5	1	20	60	**41%**	11%	72%	–
3	1.5	1	80	3	**39%**	39%	77%	–
4	2	1	40	3	**28%**	15%	44%	60%
5	2	1	60	3	**38%**	31%	73%	–
6	2	1	80	3	**53%**	52%	57%	–
7	3	1	20	3	**13%**	4%	–	250%
8	3	1	20	60	**67%**	12%	84%	60%
9	3	1	40	3	**24%**	10%	12%	106%
10	3	1	40	18	**48%**	16%	38%	–
11	3	1	60	3	**52%**	44%	109%	42%
12	3	1	80	3	**46%**	46%	43%	5%
13	1	3	40	18	**25%**	12%	20%	–
14	1	5	40	18	**28%**	14%	22%	–

[a]Reaction conditions: A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The appropriate amount of outflow (1-3 mL, 1-3 equiv.) was collected in an oven-dried vial. The corresponding amount of BnBr (1-5 equiv.) was added, and the reaction was stirred at the stated temperature for the corresponding time. Then, 1,2-difluorobenzene was added and an aliquot was taken to measure the amount of product formed by quantitative ^{19}F NMR.

Optimization of Additives

Various additives were screened to determine their effects on the reaction yield (Table S3). Only the addition of tetra-*n*-butylammonium iodide (TBAI) was observed to have a beneficial effect on the reaction yield, and further optimizations focused on optimizing the amount of TBAI added. The addition of AgOTf, NaI and KI were found to be detrimental to the reaction yield.

Table S2.3: Additive optimization for the formation of compound **1**

Entry[a]	Additive	Product	BnF	F exchange	Anion left
1[b]	AgOTf (1.1 equiv.)	**2%**	22%	183%	7%
2	NaI (1.5 equiv.)	**–**	–	160%	–
3	KI (1.5 equiv.)	**25%**	4%	132%	–
4	TBAI (1.5 equiv.)	**71%**	16%	92%	–

[a]Reaction conditions: A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The appropriate amount of outflow (3 mL, 3 equiv.) was collected in an oven-dried vial containing the corresponding additive (1.1 or 1.5 equiv.). BnBr (1 equiv.) was added, and the reaction was stirred at 40 °C for 18h. Then, 1,2-difluorobenzene was added and an aliquot was taken to measure the amount of product formed by quantitative ^{19}F NMR. [b]Reaction time: 3 hours.

Optimization with TBAI

The reaction temperature, the amount of anion and TBAI in the reaction mixture were screened to obtain the highest reaction yield (Table S4). Temperature screening revealed that increased temperature (40°C, Table S3, Entry 4 and 60°C, Table S4, Entry 2) resulted in similar yields (71% and 68% respectively). Increasing the equivalents of TBAI added (Entry 3,4 and 5) resulted in a slightly increased reaction yield, which was deemed insufficient to

justify the large excess of TBAI salt. Hence, 1.1 equivalents of TBAI were chosen as the best reaction condition and used for all the following reactions. Lowering or increasing the amount of NCF_2R anion added did not yield improved results.

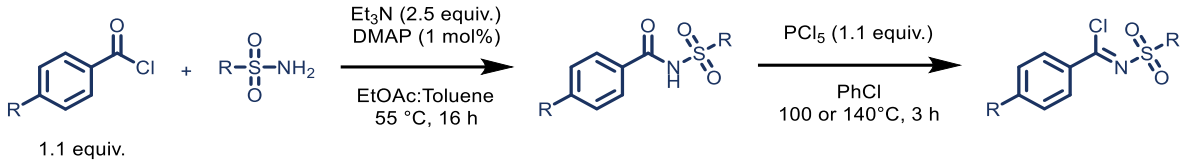
Table S2.4: Optimization of reaction temperature, the amount of anion and TBAI added

Entry[a]	Anion (equiv.)	TBAI (equiv.)	Temperature (°C)	Product	BnF	F exchange	Anion left
1	3	1.5	20	**56%**	4%	56%	54%
2	3	1.5	60	**68%**	26%	98%	–
3	3	1.1	40	**75%**	16%	86%	–
4	3	2	40	**77%**	10%	70%	17%
5	3	3	40	**79%**	14%	68%	24%
6	1.1	1.5	40	**44%**	10%	16%	–
7	2	1.5	40	**62%**	12%	44%	–
8	4	1.5	40	**72%**	18%	88%	113%

[a]Reaction conditions: A 0.1 M solution of imidoyl chloride and 18-crown-6 in dry CH_3CN was passed through the packed-bed reactor at a flow rate of 0.22 mL min^{-1} (residence time of 15 minutes). The appropriate amount of outflow (1.1–4 mL, 1.1–4 equiv.) was collected in an oven-dried vial containing TBAI (1.1–3 equiv.). BnBr (1 equiv.) was added, and the reaction was stirred at the corresponding temperature for 18h. Then, 1,2-difluorobenzene was added and an aliquot was taken to measure the amount of product formed by quantitative ^{19}F NMR.

II. Experimental Procedures

General Procedure (A): Synthesis of Imidoyl Chlorides from Acyl Chlorides



To a solution of sulfonamide (1.0 equiv.), 4-dimethylaminopyridine (1.0 mol%) and triethylamine (2.5 equiv.) in AcOEt (2.0 M) was dropwise added a solution of the respective benzoyl chloride (1.1 equiv.) in toluene (0.8 M). The mixture was stirred at 55 °C overnight, cooled to room temperature and quenched with a 2.0 M aqueous HCl solution. The resulting mixture was extracted with AcOEt, dried over $MgSO_4$, and concentrated in vacuo. The crude was washed with a minimal amount of diethyl ether and used in the next step without further purification.

The corresponding sulfonimide (1 equiv.) and PCl_5 (1.1 equiv.) were dissolved in chlorobenzene (0.6 M). The reaction mixture was heated to reflux for 3 h, after which the solvent was evaporated under reduced pressure at 60 °C. The crude was purified by the below-mentioned method.

General Procedure (B): Synthesis of Imidoyl Chlorides from Carboxylic Acids

To a stirring solution of carboxylic acid (20 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.2 M), oxalyl chloride (1.2 equiv.) and few drops of dry DMF were added dropwise at 0 °C under N_2 atmosphere. Then, the reaction mixture was stirred overnight at room temperature. Upon completion, the solvent was removed under reduced pressure to afford the crude carbonyl chloride, which was immediately used in the next step. The synthesis sequence then follows **General Procedure A**.

General procedure (C): Synthesis of NCF_2R Compounds from Different Electrophiles

The respective *N*-tosyl imidoyl chloride (3.5 mmol) was dissolved in an 18-crown-6 solution in dry CH_3CN (35 mL, 0.1 M) in an oven-dried, N_2 filled 100 mL round bottom flask with a rubber septum. The packed-bed reactor was flushed with dry CH_3CN (ca. 15 mL). The 0.1 M solution of *N*-tosyl imidoyl chloride was taken up with a 50 mL syringe and mounted on a syringe pump. Then, N-tosyl imidoyl chloride solution (10.0 mL) was passed through the reactor at a flowrate of 0.22 mL min-1 to equilibrate it. Once this procedure was done, the

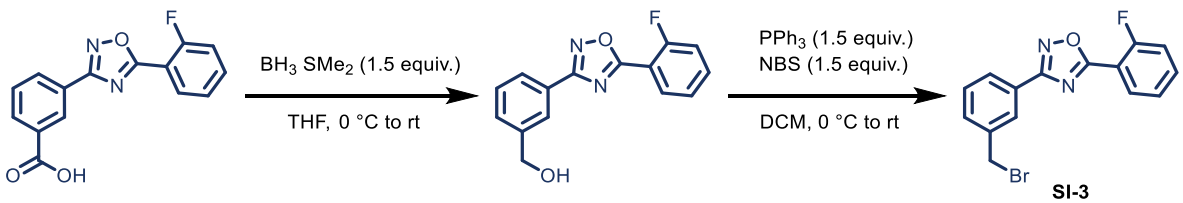
cartridge could be used continuously until its exhaustion. The solution of N-tosyl imidoyl chloride was constantly pushed through the equilibrated CsF/glass beads packed-bed at 0.22 mL min-1 (t_R = ca. 15 min). The resulting caesium $TsNCF_2R$ anion solution (6 mL, 0.6 mmol, 3 equiv.) was collected into an oven-dried, N_2 filled 20 mL reaction vial equipped with a Teflon stirring bar, containing tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and the respective electrophile (if solid) (0.2 mmol, 1 equiv.). Upon collection of the desired amount of caesium $TsNCF_2R$ anion solution, electrophile (if liquid) (0.2 mmol, 1 equiv.) was added, and the reaction mixture was heated for 18 hours at 40 °C. After reaction completion, the solvent was evaporated *in vacuo* and the crude was purified using flash column chromatography (pentane/AcOEt).

General procedure (D): Synthesis of NCF_2 Compounds from Different Acyl Chlorides/Sulfonamides

The respective imidoyl chloride (2.0 mmol) was dissolved in an 18-crown-6 solution in dry CH_3CN (20 mL, 0.1 M) in an oven-dried, N_2 filled 50 mL round bottom flask with a rubber septum. The packed-bed reactor was flushed with dry CH_3CN (ca. 15 mL). The 0.1 M solution of imidoyl chloride was taken up with a 20 mL syringe and mounted on a syringe pump. Then, imidoyl chloride solution (10.0 mL) was passed through the reactor at flowrate of 0.22 mL min-1 to equilibrate it. The solution of imidoyl chloride was constantly pushed through the equilibrated CsF/glass beads packed-bed at 0.22 mL min-1 (t_R = ca. 15 min). The resulting anion solution (8 mL, 0.8 mmol, 4 equiv.) was collected into an oven-dried, N_2 filled 20 mL reaction vial equipped with a Teflon stirring bar, containing tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.). Upon collection of the desired amount of anion solution, cinnamyl bromide (39.4 mg, 29.6 µL, 0.2 mmol, 1 equiv.) was added, and the reaction mixture was heated for 18 hours at 60 °C. After reaction completion, the solvent was evaporated *in vacuo* and the crude was purified using flash column chromatography (pentane/AcOEt).

Synthesis of Benzyl Bromide Derivatives

Synthesis of Compound SI-3



SI-3

According to a previously reported literature procedure[3], ataluren (568 mg, 2.0 mmol) was added to an oven-dried, nitrogen-purged flask with a stir bar, followed by THF (0.1 M), and the mixture was cooled in an ice bath. $BH_3 \cdot SMe_2$ (1.5 equiv., 0.284 mL, 3.0 mmol) was added dropwise, and the reaction progress was monitored using TLC. Once complete, the reaction was quenched by slowly adding water while maintaining cooling. THF was removed using a rotary evaporator, and the crude product was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The crude product was used in the next step without further purification.

The crude alcohol and PPh_3 (1.5 equiv., 787 mg, 3.0 mmol) were added to an oven-dried two-necked flask containing a stir bar under nitrogen. Dry DCM (0.1 M) was added, the flask was placed in an ice bath, and NBS (1.5 equiv., 534 mg, 3.0 mmol) was slowly added portion-wise. The ice bath was then removed, and the reaction completion was monitored using TLC. The reaction was concentrated under vacuum and the crude was purified using flash column chromatography (100% *n*-pentane to 5% AcOEt in *n*-pentane), affording compound **SI-3** (543 mg, 82%) as a white solid.

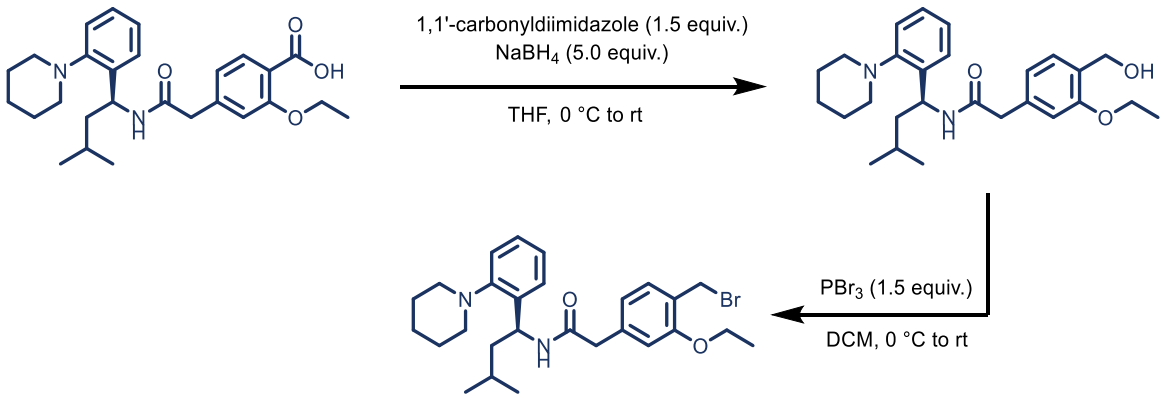
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 2H), 8.13 (dt, J = 7.5, 1.6 Hz, 1H), 7.69 – 7.45 (m, 3H), 7.43 – 7.25 (m, 2H), 4.56 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (d, J = 4.6 Hz), 168.2, 160.8 (d, J = 260.8 Hz), 138.7, 134.7 (d, J = 8.4 Hz), 131.9, 130.9, 129.5, 128.1, 127.5, 127.3, 124.7 (d, J = 3.8 Hz), 117.2 (d, J = 20.7 Hz), 112.7 (d, J = 11.2 Hz), 32.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -108.8 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{10}BrFN_2O$, 331.9961; found: 331.9968.

Synthesis of Compound SI-5



Repaglinide (453 mg, 1.0 mmol) was dissolved in THF (0.1 M), and 1,1'-carbonyldiimidazole (1.5 equiv., 243 mg, 1.5 mmol) was added in one portion. The solution was stirred at room temperature for 15 minutes, then cooled to 0°C for 10 minutes. $NaBH_4$ (5.0 equiv., 189 mg, 5.0 mmol) was added portion-wise and the mixture was stirred at 0°C for 25 minutes. The reaction was quenched with water, then extracted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product is used in the next step without further purification.

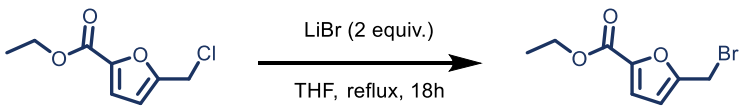
The crude alcohol was added to an oven-dried two-necked flask containing a stir bar under nitrogen. DCM (1 M) was added, the flask was placed in an ice bath, and PBr_3 (1.5 equiv., 0.140 mL, 1.5 mmol) was slowly added dropwise. The ice bath was removed, and the reaction progress was monitored using TLC. The reaction was quenched by the slow addition of water while maintaining the mixture in an ice bath, then the crude product was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The crude was purified using flash column chromatography (100% DCM to 1% MeOH in DCM), affording compound **SI-5** (358 mg, 72%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.10 – 7.01 (m, 2H), 6.81 – 6.68 (m, 3H), 5.47 – 5.24 (m, 1H), 4.55 (s, 2H), 4.16 – 3.84 (m, 2H), 3.51 (s, 2H), 2.92 (s, 2H), 2.59 (t, *J* = 8.4 Hz, 2H), 1.87 – 1.48 (m, 9H), 1.41 (t, *J* = 7.0 Hz, 4H), 0.91 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 157.1, 152.6, 138.9, 137.7, 131.1, 127.9, 127.7, 125.1, 125.0, 122.7, 121.3, 112.6, 63.9, 55.0, 49.8, 46.6, 44.2, 28.9, 26.8, 25.4, 24.2, 22.9, 22.6, 4.8.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{27}H_{37}BrN_2O_2$, 502.2022; found: 502.2047.

Synthesis of Compound SI-6



5-Chloromethyl-furan-2-carboxylic acid ethyl ester (943 mg, 5 mmol, 1 equiv.) was dissolved in THF (50 mL). LiBr (868 mg, 10 mmol, 2 equiv.) was added and the mixture was refluxed for 18 hours. The solvent was removed in vacuo and the crude was extracted with AcOEt and water, affording the product SI-6 (1.16 g, quantitative) as a slightly orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.5 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 4.47 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

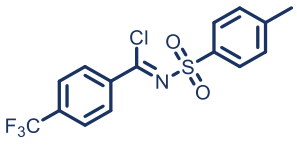
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 154.2, 145.1, 118.8, 111.6, 61.2, 22.1, 14.4.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_8H_9BrO_3$, 231.9735; found: 231.9743.

III. Characterization data

Starting materials

N-Tosyl-4-(trifluoromethyl)benzimidoyl chloride (1)



Prepared according to **General Procedure A**, from p-toluenesulfonamide (12.0 g, 70 mmol) and 4-(trifluoromethyl) benzoyl chloride (11.5 mL, 77 mmol). The crude mixture was purified either using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt) (or via precipitation in *n*-pentane, giving a similar purity and yield), to afford compound **SI-5** (18.6 g, 73% over 2 steps) as a white solid.

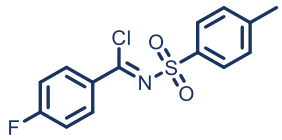
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.13 (m, 2H), 7.99 – 7.89 (m, 2H), 7.75 – 7.65 (m, 2H), 7.44 – 7.33 (m, 2H), 2.47 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 145.0, 137.3, 136.8, 135.8 (q, J = 33.1 Hz), 130.5, 129.9, 127.9, 125.8 (d, J = 3.7 Hz), 123.3 (d, J = 273.0 Hz), 21.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.32 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{11}ClF_3NO_2S$, 361.0151; found: 361.0142.

4-Fluoro-*N*-tosylbenzimidoyl chloride (SI-7)



Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.42 g, 20 mmol) and 4-fluorobenzoyl chloride (2.60 mL, 22 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt), to afford compound **SI-7** (3.90 g, 69% over 2 steps) as a white solid.

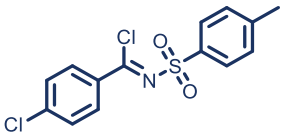
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.07 (m, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.18 – 7.06 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (d, J = 258.6 Hz), 155.1, 144.7, 137.0, 132.9 (d, J = 9.8 Hz), 130.2 (d, J = 9.8 Hz), 129.7, 127.7, 116.1 (d, J = 22.3 Hz), 21.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -101.81 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{11}C_{l1}FNO_2S$, 311.0183; found: 311.0173.

4-Chloro-*N*-tosylbenzimidoyl chloride (SI-8)



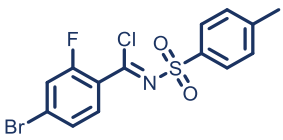
Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.42 g, 20 mmol) and 4-chlorobenzoyl chloride (2.80 mL, 22 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-8** (4.08 g, 65% over 2 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.47 – 7.33 (m, 4H), 2.47 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 144.8, 141.7, 137.1, 132.6, 131.6, 129.8, 129.3, 127.9, 21.8.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{11}Cl_2NO_2S$, 326.9888, found: 326.9888.

4-bromo-2-fluoro-*N*-tosylbenzimidoyl chloride (SI-9)



Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.42 g, 20 mmol) and 4-bromo-2-fluorobenzoyl chloride (3.00 mL, 22 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt), to afford compound **SI-9** (4.20 g, 59% over 2 steps) as a white solid.

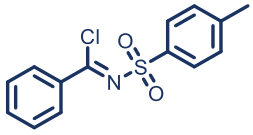
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.80 – 7.69 (m, 1H), 7.44 – 7.29 (m, 4H), 2.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (d, *J* = 268.1 Hz), 150.6, 144.8, 136.9, 133.1, 129.8, 129.3 (d, *J* = 9.8 Hz), 128.0 (d, *J* = 3.8 Hz), 127.6, 122.6 (d, *J* = 7.9 Hz), 120.9 (d, *J* = 25.1 Hz), 21.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -105.16 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{10}BrClFNO_2S$, 390.9266; found: 390.9293.

***N*-tosylbenzimidoyl chloride (SI-10)**



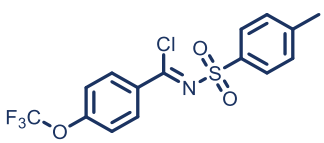
Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.42 g, 20 mmol) and benzoyl chloride (2.55 mL, 22 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-10** (3.24 g, 58% over 2 steps) as a white solid.

^{1}H NMR (300 MHz, , $CDCl_3$) δ 8.13 – 7.98 (m, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.46 – 7.32 (m, 4H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 144.6, 137.1, 134.8, 134.0, 130.2, 129.7, 128.8, 127.7, 21.7.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_{12}ClNO_2S$, 293.0277; found: 293.0274.

***N*-tosyl-4-(trifluoromethoxy)benzimidoyl chloride (SI-11)**



Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.43 g, 20 mmol) and 4-(trifluoromethoxy)benzoyl chloride (3.47 mL, 22 mmol). The crude mixture was

dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-11** (3.96 g, 52% over 2 steps) as a white solid.

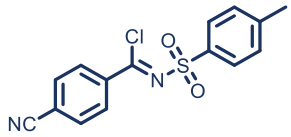
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 – 8.07 (m, 2H), 7.98 – 7.88 (m, 2H), 7.43 – 7.33 (m, 2H), 7.32 – 7.20 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.9 (q, J = 1.9 Hz), 144.8, 137.0, 132.3, 132.2, 129.8, 127.8, 120.3 (d, J = 1.1 Hz), 120.3 (q, J = 259.9 Hz), 21.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -57.61 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{11}ClF_3NO_3S$, 377.0100; found: 377.0089.

4-cyano-*N*-tosylbenzimidoyl chloride (SI-12)



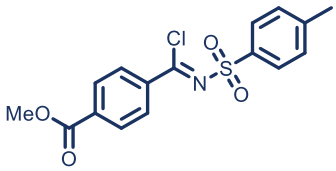
Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.43 g, 20 mmol) and 4-cyanobenzoyl chloride (3.63 g, 22 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-12** (2.94 g, 46% over 2 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 2.47 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 145.1, 137.7, 136.5, 132.5, 130.4, 129.9, 127.8, 117.6, 117.5, 21.7.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{11}ClN_2O_2S$, 318.0230; found: 318.0229.

Methyl -4-(chloro(tosylimino)methyl)benzoate (SI-13)



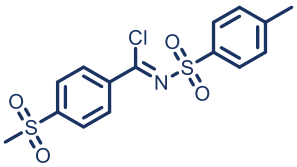
Prepared according to **General Procedure A**, from p-toluenesulfonamide (3.43 g, 20 mmol) and methyl 4-(chlorocarbonyl)benzoate (4.37 g, 22 mmol). The crude mixture was washed with Et_2O, obtaining compound **SI-13** (4.5 g, 64% over 2 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 8.03 (m, 4H), 7.95 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 3.95 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.3, 144.8, 137.6, 136.8, 135.2, 130.0, 129.8, 129.7, 127.8, 52.6, 21.7.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{16}H_{14}ClNO_4S$, 351.0332; found: 351.0323.

4-(methylsulfonyl)-*N*-tosylbenzimidoyl chloride (SI-14)



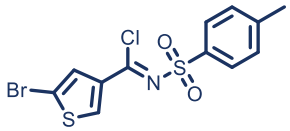
Prepared according to **General Procedure B**, from 4-methylsulfonylbenzoic acid (4.0 g, 20 mmol) and p-toluenesulfonamide (3.08 g, 18 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 80:20 AcOEt), to afford compound **SI-14** (4.68 g, 70% over 3 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 145.4, 145.2, 138.7, 136.5, 130.9, 129.9, 127.9, 127.8, 44.3, 21.8.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{14}ClNO_4S_2$, 371.0052; found: 371.0057.

5-bromo-*N*-tosylthiophene-3-carbimidoyl chloride (SI-15)



Prepared according to **General Procedure B**, from 5-bromothiophene-3-carboxylic acid (4.14 g, 20 mmol) and p-toluenesulfonamide (3.08 g, 18 mmol). The crude mixture was

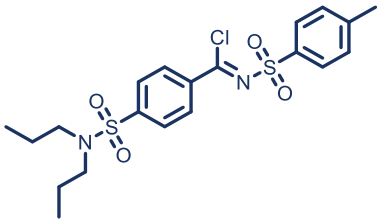
dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-15** (4.71 g, 69% over 3 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.6 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 144.8, 138.1, 137.4, 137.0, 129.8, 129.6, 127.8, 114.5, 21.8.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{12}H_9BrClNO_2S_2$, 376.8946; found: 376.8958.

4-(*N*,*N*-dipropylsulfamoyl)-*N*-tosylbenzimidoyl chloride (SI-16)



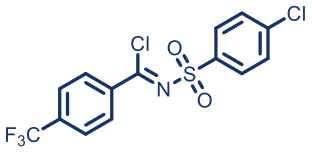
Prepared according to **General Procedure B**, from 4-(*N*,*N*-dipropylsulfamoyl)benzoic acid (6.28 g, 22 mmol) and p-toluenesulfonamide (3.22 g, 20 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 80:20 AcOEt), to afford compound **SI-16** (4.22 g, 46% over 3 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 3.14 – 3.04 (m, 4H), 2.45 (s, 3H), 1.62 – 1.44 (m, 4H), 0.93 – 0.80 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 145.6, 145.0, 137.1, 136.6, 130.7, 129.8, 127.8, 127.2, 49.9, 21.9, 21.6, 11.1.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{20}H_{25}ClN_2O_4S_2$, 456.0944; found: 456.0956.

***N*-((4-chlorophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-17)**



Prepared according to **General Procedure A**, from 4-chlorobenzenesulfonamide (3.83 g, 20 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-17** (4.74 g, 62% over 2 steps) as a white solid.

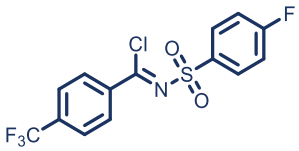
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 2H), 8.03 – 7.95 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.53 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 140.6, 138.2, 137.0 (q, *J* = 1.3 Hz), 136.0 (q, *J* = 33.1 Hz), 130.6, 129.6, 129.3, 125.9 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 273.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.33 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_8Cl_2F_3NO_2S$, 380.9605; found: 380.9610.

***N*-((4-fluorophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-18)**



Prepared according to **General Procedure A**, from 4-fluorobenzenesulfonamide (3.50 g, 20 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-18** (3.64 g, 58% over 2 steps) as a white solid.

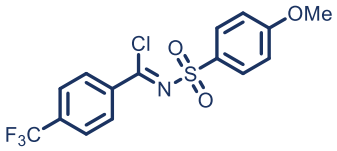
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 2H), 8.12 – 8.02 (m, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.21 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (d, *J* = 256.6 Hz), 155.6, 137.1 (q, *J* = 1.3 Hz), 135.9 (q, *J* = 33.1 Hz), 135.8 (d, *J* = 3.3 Hz), 130.7 (d, *J* = 9.6 Hz), 130.5, 125.9 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 273.0 Hz), 116.6 (d, *J* = 22.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.35 (s, 3F), -103.04 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_8ClF_4NO_2S$, 364.9900; found: 364.9886.

***N*-((4-methoxyphenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-19)**



Prepared according to **General Procedure A**, from 4-methoxybenzenesulfonamide (3.74 g, 20 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt), to afford compound **SI-19** (3.80 g, 50% over 2 steps) as a white solid.

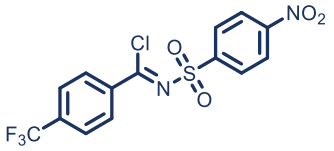
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 2H), 8.01 – 7.93 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.06 – 7.00 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 154.4, 137.3 (d, *J* = 1.3 Hz), 135.6 (q, *J* = 33.0 Hz), 131.0, 130.5, 130.2, 125.8 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 273.0 Hz), 114.5, 55.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.30 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{11}ClF_3NO_3S$, 377.0100; found 377.0089.

***N*-((4-nitrophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-20)**



Prepared according to **General Procedure A**, from 4-(hydroxyamino)benzenesulfonamide (4.04 g, 20 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt), to afford compound **SI-20** (6.4 g, 81% over 2 steps) as a white solid.

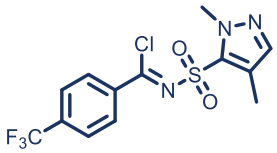
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 – 8.41 (m, 2H), 8.30 – 8.22 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.8, 145.3, 137.0, 136.7 (d, *J* = 1.37 Hz), 136.4 (q, *J* = 33.2 Hz), 130.7, 129.1, 126.1 (q, *J* = 3.7 Hz), 123.2 (q, *J* = 273.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.39 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{14}H_8ClF_3N_2O_4S$, 391.9845; found 391.9846.

***N*-((1,4-dimethyl-1H-pyrazol-5-yl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-21)**



Prepared according to **General Procedure A**, from 1,4-dimethyl-1H-pyrazole-5-sulfonamide (3.50 g, 20 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 90:10 AcOEt), to afford compound **SI-21** (3,01 g, 41% over 2 steps) as a white solid.

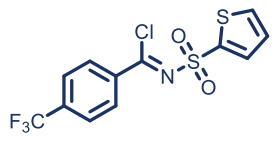
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 2H), 7.93 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 3.90 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 148.7, 137.2 (d, *J* = 1.4 Hz), 135.6 (q, *J* = 33.0 Hz), 134.4, 130.3, 125.8 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 273.0 Hz), 119.3, 39.3, 12.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.33 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{13}H_{11}ClF_3N_3O_2S$, 365.0213; found 365.0209.

***N*-(thiophen-2-ylsulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-22)**



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol) and 2-thiophenesulfonamide (3.26 g, 20 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 80:20 AcOEt), to afford compound **SI-22** (3.46 g, 49% over 2 steps) as a slightly orange solid.

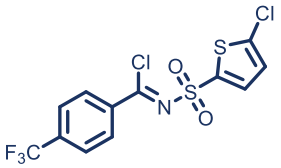
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.86 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.76 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.16 (dd, *J* = 5.0, 3.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 140.0, 137.0, 135.9 (q, J = 33.1 Hz), 134.2, 134.2, 130.6, 127.6, 125.9 (q, J = 3.7 Hz), 123.3 (q, J = 273.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.34 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{12}H_7ClF_3NO_2S_2$, 352.9558; found: 352.9573.

***N*-((5-chlorothiophen-2-yl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-23)**



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol) and 5-chloro-2-thiophenesulfonamide (3.95 g, 20 mmol). The crude mixture was purified using column chromatography (100% *n*-pentane to *n*-pentane 80:20 AcOEt), to afford compound **SI-23** (4.02 g, 55% over 2 steps) as a white solid.

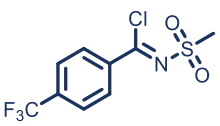
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 4.0 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 139.9, 137.8, 136.9, 136.2 (q, *J* = 33.3 Hz), 133.7, 130.7, 127.0, 126.0 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 273.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.34.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{12}H_6Cl_2F_3NO_2S_2$, 386.9169; found 386.9176.

***N*-(methylsulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-24)**



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol) and methanesulfonamide (1,90 g, 20 mmol). The crude mixture was

dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-24** (4,46 g, 78% over 2 steps) as a white solid.

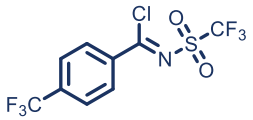
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 3.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 136.9, 135.8 (q, *J* = 33.2 Hz), 130.3, 125.9 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 273.0 Hz), 43.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.32.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_9H_7ClF_3NO_2S$, 284.9838; found 284.9830.

4-(trifluoromethyl)-*N*-((trifluoromethyl)sulfonyl)benzimidoyl chloride (SI-25)



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (3.27 mL, 22 mmol) and trifluoromethanesulfonamide (2,98 g, 20 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **SI-25** (5,13 g, 75.5% over 2 steps) as a white solid.

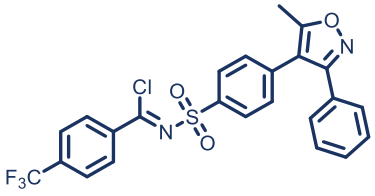
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 137.3 (q, *J* = 33.5 Hz), 135.5 (d, *J* = 1.4 Hz), 131.0, 126.2 (q, *J* = 3.7 Hz), 123.0 (q, *J* = 273.2 Hz), 118.5 (q, *J* = 319.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.66 (s, 3F), -78.52 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_9H_4ClF_6NO_2S$, 338.9555; found 338.9544.

***N*-((4-(5-methyl-3-phenylisoxazol-4-yl)phenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-26)**



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (1.65 mL, 11 mmol) and 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (3.14 g, 10 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, precipitating compound **SI-26** (2.01 g, 40% over 2 steps) as a white solid.

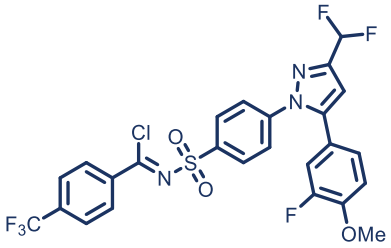
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.34 (m, 7H), 2.51 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 161.1, 155.8, 138.7, 137.1 (q, *J* = 1.4 Hz), 136.5, 135.9 (q, *J* = 32.9 Hz), 130.6, 130.4, 129.9, 128.8, 128.6, 128.4, 128.1, 125.9 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 273.0 Hz), 114.4, 11.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.28 (s, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{16}ClF_3N_2O_3S$, 504.0522; found 504.0524.

***N*-((4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)phenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (SI-27)**



Prepared according to **General Procedure A**, from 4-(trifluoromethyl)benzoyl chloride (1.65 mL, 11 mmol) and 4-[5-(4-methylphenyl)-3-trifluoromethyl)-1H-pyrazolyl]benzenesulfon-amide (3.97 g, 10 mmol). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **SI-27** (2.75 g, 43% over 2 steps) as an off-white solid.

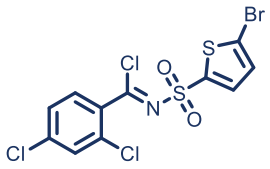
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 2H), 8.09 – 8.01 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.49 (m, 2H), 7.04 – 6.95 (m, 3H), 6.75 (t, *J* = 54.7 Hz, 1H), 6.71 (s, 1H), 3.91 (s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$) δ 156.0, 152.2 (d, *J* = 248.3 Hz), 148.8 (d, *J* = 10.5 Hz), 148.6 (t, *J* = 30.0 Hz), 143.9, 143.5, 138.9, 137.0 (q, *J* = 1.3 Hz), 136.1 (q, *J* = 33.1 Hz), 130.6, 128.9, 126.0 (q, *J* = 3.7 Hz), 125.4, 125.3, 123.3 (q, *J* = 273.0 Hz), 121.7 (d, *J* = 7.1 Hz), 116.7 (d, *J* = 19.8 Hz), 113.7 (d, *J* = 2.4 Hz), 111.0 (t, *J* = 234.7 Hz), 106.1, 56.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.34 (s, 3F), -112.41 (s, 2F), -133.23 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{25}H_{16}ClF_6N_3O_3S$, 587.0505; found 587.0509.

_N_-((5-bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzimidoyl chloride (SI-28)



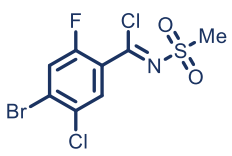
Prepared according to **General Procedure B**, from 2,4-dichlorobenzoic acid (4.04 g, 21.2 mmol) and 5-bromo-2-thiophenesulfonamide (4.5 g, 18 mmol). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **SI-28** (4.65 g, 60% over 2 steps) as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 1H), 7.54 (d, *J* = 4.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.07 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.0, 139.0, 134.2, 133.2, 132.4, 132.1, 130.7, 130.4, 127.3, 122.4.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{11}H_5BrC3NO_2S_2$, 430.8011; found 430.8001.

4-bromo-5-chloro-2-fluoro-_N_-(methylsulfonyl)benzimidoyl chloride (47)



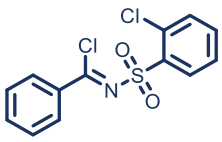
Prepared according to **General Procedure A**, from methanesulfonamide (1,90 g, 20 mmol) and 4-bromo-2-chloro-5-fluorobenzoyl chloride (5.71 g, 21 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **47** (3.70 g, 53% over 2 steps) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.9 Hz, 1H), 7.52 (d, *J* = 9.8 Hz, 1H), 3.27 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (d, *J* = 267.6 Hz), 150.0, 132.5, 131.0 (d, *J* = 4.0 Hz), 129.6 (d, *J* = 9.9 Hz), 123.4 (d, *J* = 9.1 Hz), 123.0 (d, *J* = 26.2 Hz), 43.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -108.67 (s, 1F).

***N*-((2-chlorophenyl)sulfonyl)benzimidoyl chloride (50)**



Prepared according to **General Procedure A**, from 2-chlorobenzenesulfonamide (5.0 g, 26 mmol) and benzoyl chloride (4.0 g, 29 mmol). The crude mixture was dissolved in a minimal amount of DCM and added to a large excess of pentane, after which the mixture was briefly cooled down in liquid nitrogen, precipitating compound **50** (5.37 g, 66% over 2 steps) as a white solid.

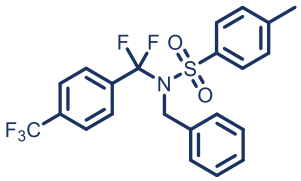
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (dt, *J* = 7.8, 1.0 Hz, 1H), 8.18 – 8.06 (m, 2H), 7.67 – 7.54 (m, 3H), 7.51 – 7.40 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 137.9, 135.1, 134.5, 133.9, 133.0, 132.0, 130.4, 130.4, 129.0, 127.1.

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{13}H_9Cl_2ClNO_2S$, 312.9731; found: 312.9730.

Scope of Electrophiles

N-benzyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (2)



Prepared according to **General Procedure C**, using benzyl bromide (34.2 mg, 23.8 µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl)benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **2** (65 mg, 71%) as a clear oil.

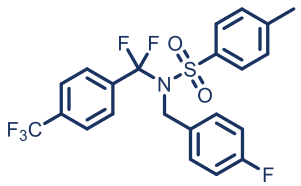
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 4H), 7.42 – 7.28 (m, 7H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.74 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 137.4 (t, *J* = 30.0 Hz), 137.0, 136.7, 132.7 (q, *J* = 32.8f Hz), 129.5, 128.5, 128.4, 127.9, 127.6 (t, *J* = 4.7 Hz), 124.9 (q, *J* = 3.8 Hz), 123.0 (t, *J* = 272.4 Hz), 122.7 (q, *J* = 256.9 Hz), 49.6 (t, *J* = 2.0 Hz), 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.08 (s, 3F), -69.80 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{18}F_5NO_2S$, 455.0978; found: 455.0969.

N-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*-(4-fluorobenzyl)-4-methylbenzenesulfonamide (3)



Prepared according to **General Procedure C**, using 4-fluorobenzyl bromide (37.8 mg, 24.9 µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl)benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.).

The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **3** (70 mg, 74%) as an off-white solid.

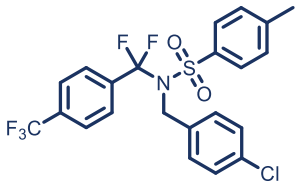
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.43 (m, 4H), 7.42 – 7.29 (m, 4H), 7.21 – 7.11 (m, 2H), 7.08 – 6.95 (m, 2H), 4.71 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J = 246.7 Hz), 144.5, 137.3 (t, J = 31.3 Hz), 137.0, 132.8 (q, J = 32.7 Hz), 132.6 (d, J = 3.3 Hz), 130.3 (d, J = 8.2 Hz), 129.6, 127.7 (t, J = 4.8 Hz), 127.6, 125.0 (q, J = 3.7 Hz), 123.6 (q, J = 272.8 Hz), 119.9 (t, J = 255.7 Hz), 115.5 (d, J = 21.5 Hz), 48.9, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.09 (s, 3F), -69.79 (s, 2F), -114.24 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{17}F_6NO_2S$, 473.0884; found: 473.0884.

***N*-(4-chlorobenzyl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (4)**



Prepared according to **General Procedure C**, using 4-chlorobenzyl bromide (41.1 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl)benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **4** (75.4 mg, 77%) as a white solid.

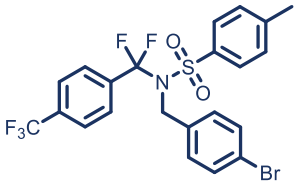
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.43 (m, 4H), 7.39 – 7.27 (m, 6H), 7.21 – 7.13 (m, 2H), 4.70 (t, J = 1.8 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.2 (t, J = 31.0 Hz) 136.9, 135.4, 133.9, 132.9 (q, J = 32.8 Hz), 129.9, 129.6, 128.8, 127.6 (t, J = 4.8 Hz), 127.6, 125.1 (q, J = 3.7 Hz), 123.6 (q, J = 272.6 Hz), 119.9 (t, J = 255.6 Hz), 48.9, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.08 (s, 3F), -69.83 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{17}ClF_5NO_2S$, 489.0589; found: 489.0589.

***N*-(4-bromobenzyl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (5)**



Prepared according to a modified version of **General Procedure C**, using 4-bromobenzyl bromide (666.4 mg, 2.66 mmol, 1 equiv.), tetrabutylammonium iodide (1.08 g, 2.93 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl)benzimidoyl chloride solution (80 mL, 0.1 M, 8 mmol, 3 equiv.). The solution was charged into 2 syringes that were mounted on the syringe pump and each solution was passed through a separate CsF cartridge, and the outflow was collected in the receiving flask containing TBAI. The electrophile was added to the mixture after all the outflow was collected. The reaction mixture was heated at 40°C for 18 hours. The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **5** (1.00 g, 70%) as a white solid.

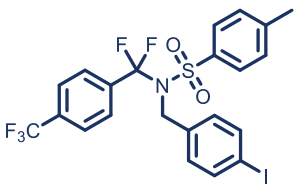
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.41 (m, 6H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.21 – 7.12 (m, 2H), 4.68 (s, 2H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.2 (t, *J* = 31.0 Hz), 136.9, 135.9, 132.9 (q, *J* = 32.8 Hz), 131.7, 130.2, 129.6, 127.6 (t, *J* = 4.8 Hz), 127.6, 125.1 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 273.5 Hz), 122.0, 119.9 (t, *J* = 255.8 Hz), 49.0, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.09 (s, 3F), -69.83 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{17}BrF_5NO_2S$, 535.0065; found: 535.0180.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*-(4-iodobenzyl)-4-methylbenzenesulfonamide (6)**



Prepared according to **General Procedure C**, using 4-iodobenzyl bromide (59.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-

4-(trifluoromethyl)benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **6** (79.6 mg, 69%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.43 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.24 – 7.10 (m, 4H), 4.67 (s, 2H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.7, 137.1 (t, *J* = 30.3 Hz), 136.8, 136.5, 132.8 (q, *J* = 33.1 Hz), 130.3, 129.6, 127.5, 127.5 (t, *J* = 5.3 Hz), 125.0 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.5 Hz), 119.8 (t, *J* = 255.6 Hz), 93.5, 49.0, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.05 (s, 3F), -69.83 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{17}F_5INO_2S$, 580.9945; found: 580.9941.

_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-_N_-(3-methoxybenzyl)-4-methylbenzenesulfonamide (7)

Prepared according to **General Procedure C**, using 3-(bromomethyl)anisole (40.2 mg, 28.0 µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **7** (66 mg, 68%) as a yellow oil.

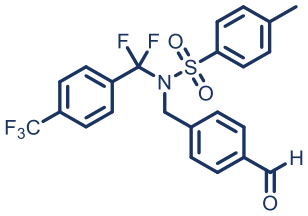
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 4H), 7.50 – 7.42 (m, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.04 – 6.83 (m, 3H), 4.75 (t, *J* = 2.1 Hz, 2H), 3.83 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 144.3, 138.2, 137.4 (t, *J* = 30.3 Hz), 137.0, 132.6 (q, *J* = 32.7 Hz), 129.5, 129.4, 127.6, 127.5 (t, *J* = 4.8 Hz), 124.9 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.5 Hz), 119.8 (t, *J* = 255.6 Hz), 120.5, 113.7, 113.3, 55.2, 49.6, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.07 (s, 3F), -69.90 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{20}F_5NO_3S$, 485.1084; found: 485.1101.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*-(4-formylbenzyl)-4-methylbenzenesulfonamide (8)**



Prepared according to **General Procedure C**, using 4-(bromomethyl)benzaldehyde (39.8 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **8** (58 mg, 60%) as a clear oil.

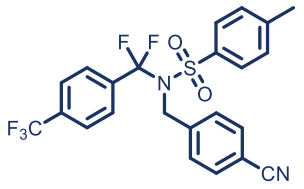
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.90 – 7.82 (m, 2H), 7.60 – 7.44 (m, 6H), 7.41 – 7.32 (m, 2H), 7.21 – 7.13 (m, 2H), 4.80 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 144.7, 143.7, 137.0 (t, J = 30.3 Hz), 136.6, 135.9, 132.9 (q, J = 32.8 Hz), 130.0, 129.7, 128.7, 127.7, 127.6 (t, J = 4.9 Hz), 125.14 (q, J = 3.8 Hz), 123.5 (q, J = 272.8 Hz), 119.9 (t, J = 256.0 Hz), 49.3, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -69.99 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{18}F_5NO_3S$, 483.0928; found: 483.1001.

***N*-(4-cyanobenzyl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (9)**



Prepared according to **General Procedure C**, using 4-(bromomethyl) benzonitrile (39.2 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **9** (47 mg, 49%) as a clear oil.

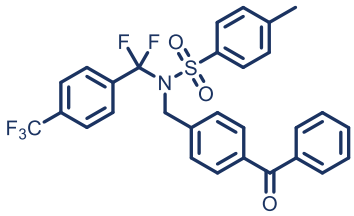
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 2H), 7.60 – 7.46 (m, 6H), 7.42 – 7.32 (m, 2H), 7.25 – 7.16 (m, 2H), 4.80 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 142.3, 136.8 (t, *J* = 30.7 Hz), 136.5, 133.0 (q, *J* = 32.9 Hz), 132.4, 129.7, 128.8, 127.6 (t, *J* = 4.8 Hz), 127.6, 125.2 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 272.8 Hz), 119.8 (t, *J* = 255.5 Hz), 118.6, 111.9, 49.1 (t, *J* = 2.1 Hz), 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -69.94 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{17}F_5N_2O_2S$, 480.0931; found: 480.0938.

***N*-(4-benzoylbenzyl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzene-sulfonamide (10)**



Prepared according to **General Procedure C**, using 4-(bromomethyl) benzophenone (55 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **10** (66 mg, 59%) as a clear oil.

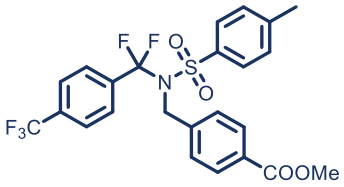
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.74 (m, 4H), 7.67 – 7.56 (m, 1H), 7.56 – 7.45 (m, 8H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.82 (s, 2H), 2.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 144.6, 141.5, 137.5, 137.2 (t, *J* = 30.6 Hz), 137.1, 136.8, 132.9 (q, *J* = 32.9 Hz), 132.6, 130.4, 130.1, 129.6, 128.4, 128.0, 127.7, 127.6 (t, *J* = 5.0 Hz), 125.1 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.5 Hz), 119.9 (t, *J* = 255.8 Hz), 49.3, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.05 (s, 3F), -69.88 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{29}H_{22}F_5NO_3S$, 559.1241; found: 559.1227.

Methyl-4-(((*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylphenyl)sulfonamido) methyl) benzoate (11)



Prepared according to **General Procedure C**, using 4-(bromomethyl) benzonitrile (45.8 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **11** (51 mg, 50%) as a clear oil.

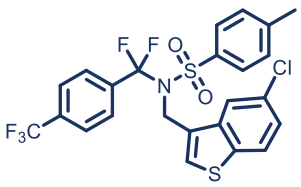
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.41 (m, 6H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 2H), 3.93 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 144.5, 141.9, 137.1 (t, *J* = 30.2 Hz), 136.7, 132.8 (q, *J* = 32.9 Hz), 129.8, 129.7, 129.6, 128.1, 127.7, 127.5 (t, *J* = 3.8 Hz), 125.0 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 272.6 Hz), 119.8 (t, *J* = 255.6 Hz), 52.2, 49.2, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -69.93 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_5NO_4S$, 513.1033; found: 513.1252.

***N*-((5-chlorobenzo[b]thiophen-3-yl)methyl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (12)**



Prepared according to **General Procedure C**, using 3-(bromomethyl)-5-chlorobenzo[b]thiophene (52.3 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **12** (92 mg, 84%) as a white solid.

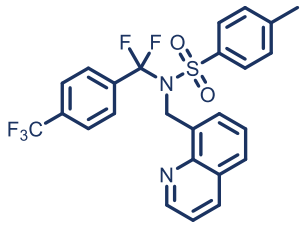
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.70 (m, 2H), 7.62 (s, 1H), 7.59 – 7.44 (m, 6H), 7.32 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.96 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 138.6, 138.3, 137.1 (t, *J* = 31.0 Hz), 136.9, 132.7 (q, *J* = 32.8 Hz), 130.7, 129.6, 128.3, 127.5, 127.4 (t, *J* = 4.8 Hz), 125.0, 124.9 (q, *J* = 4.5 Hz), 123.8, 123.4 (q, *J* = 272.3 Hz), 121.1, 119.9 (t, *J* = 256.4 Hz), 43.5, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -70.12 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{17}C_{l1}F_5NO_2S_2$, 545.0309; found: 545.0304.

_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methyl-_N_-(quinolin-8-ylmethyl)benzenesulfonamide (13)



Prepared according to **General Procedure C**, using 8-(bromomethyl)quinoline (44.2 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **13** (45 mg, 44%) as a clear oil.

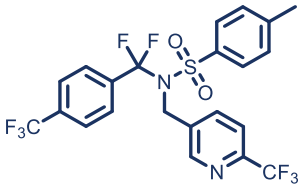
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 – 8.03 (m, 2H), 7.77 – 7.66 (m, 3H), 7.62 – 7.54 (m, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.32 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.46 (s, 2H), 2.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 145.3, 144.5, 137.3 (t, *J* = 30.5 Hz), 137.0, 136.3, 134.9, 132.4 (q, *J* = 32.8 Hz), 129.6, 128.0, 127.9, 127.8, 127.2, 127.2 (t, *J* = 5.0 Hz), 126.4, 124.7 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 274.2 Hz), 121.5 (t, *J* = 260.9 Hz), 121.1, 46.3, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -70.38 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{25}H_{19}F_5N_2O_2S$, 507.1166; found: 507.1156.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methyl-*N*-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzenesulfonamide (14)**



Prepared according to **General Procedure C**, using 5-(bromomethyl)-2-(trifluoromethyl)pyridine (48.0 mg, x µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **14** (66 mg, 68%) as a yellow oil.

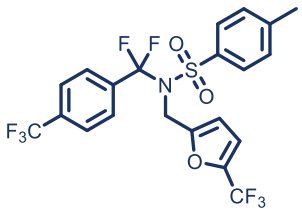
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.47 (m, 4H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.88 (d, *J* = 2.1 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 147.7 (q, *J* = 34.9 Hz), 145.0, 137.4, 136.4 (t, *J* = 30.1 Hz), 136.2, 135.0, 133.1 (q, *J* = 32.4 Hz), 129.7, 127.6 (t, *J* = 4.9 Hz), 127.5, 125.2 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 272.9 Hz) 121.4 (q, *J* = 274.0 Hz), 120.3 (q, *J* = 2.7 Hz), 119.8 (t, *J* = 255.7 Hz), 46.5 (t, *J* = 2.3 Hz), 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.17 (s, 3F), -67.90 (s, 3F), -70.07 (s, 2F).

HRMS (FD+) (m/z): $[M+H]^+$ calculated for $C_{22}H_{16}F_8N_2O_2S$, 525.0883; found: 525.0880.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methyl-*N*-((5-(trifluoromethyl)furan-2-yl)methyl)benzenesulfonamide (15)**



Prepared according to **General Procedure C**, using 2-(bromomethyl)-5-(trifluoromethyl)furan (45.8 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg,

0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **15** (55.2 mg, 54%) as an oil.

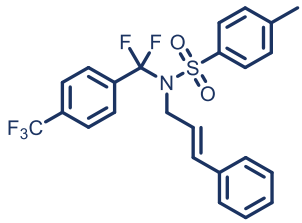
^{1}H NMR (300 MHz, $CDCl_{3z}$) δ 7.57 – 7.44 (m, 4H), 7.37 – 7.28 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.73 (dd, *J* = 3.5, 1.3 Hz, 1H), 6.39 (d, *J* = 3.5 Hz, 1H), 4.83 (s, 2H), 2.39 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 144.5, 141.5 (q, *J* = 42.8 Hz), 136.9, 136.6 (t, *J* = 30.1 Hz), 133.2 (q, *J* = 34.4 Hz), 129.4, 127.6 (t, *J* = 4.8 Hz), 127.4, 125.1 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 272.4 Hz), 119.4 (t, *J* = 256.2 Hz), 118.9 (q, *J* = 266.9 Hz), 112.5 (q, *J* = 2.9 Hz), 110.1, 41.5, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.20 (s, 3F), -64.18 (s, 3F), -71.00 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{21}H_{15}F_8NO_3S$, 513.0645; found: 513.0636.

_N_-cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (16)



Prepared according to **General Procedure C**, using cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **16** (82 mg, 85%) as a yellow oil.

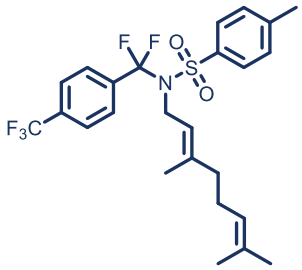
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.53 (m, 6H), 7.38 – 7.27 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.51 – 6.35 (m, 1H), 6.28 – 6.11 (m, 1H), 4.38 – 4.24 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 137.6 (t, *J* = 30.8 Hz), 137.4, 136.2, 134.2, 132.8 (q, *J* = 32.7 Hz), 129.5, 128.6, 128.1, 127.7, 127.5 (t, *J* = 4.8 Hz), 126.5, 125.1 (q, *J* = 3.7 Hz), 124.4, 123.5 (q, *J* = 272.6 Hz), 119.8 (t, *J* = 255.4 Hz), 48.5, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.02 (s, 3F), -70.20 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_5NO_2S$, 481.1135; found: 481.1140.

(E)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*-(3,7-dimethylocta-2,6-dien-1-yl)-4-methylbenzenesulfonamide (17)



Prepared according to **General Procedure C**, using geranyl bromide (43.4 mg, 39.7 µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **17** (67 mg, 67%) as a yellow oil.

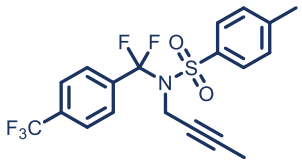
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.51 (m, 6H), 7.22 (d, J = 8.1 Hz, 2H), 5.25 (t, J = 6.9 Hz, 1H), 5.08 (t, J = 6.1 Hz, 1H), 4.16 (d, J = 6.7 Hz, 2H), 2.42 (s, 3H), 2.12 – 1.92 (m, 4H), 1.69 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 139.7, 138.0 (t, J = 31.4 Hz), 137.7, 132.7 (q, J = 32.7 Hz), 131.9, 129.5, 127.6, 127.5 (t, J = 4.7 Hz), 125.2 (q, J = 3.7 Hz), 123.8, 123.6 (q, J = 272.2 Hz), 120.1, 119.9 (t, J = 255.2 Hz), 44.8, 39.6, 26.3, 25.8, 21.6, 17.7, 16.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.04 (s, 3F), -70.12 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{25}H_{28}F_5NO_2S$, 501.1761; found: 501.1753.

***N*-(but-2-yn-1-yl)-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide (18)**



Prepared according to **General Procedure C**, using 1-bromo-2-butyne (26.6 mg, 17.7 µL, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **18** (36.7 mg, 44%) as a clear oil.

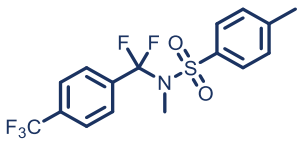
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.53 (m, 6H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.29 (q, *J* = 1.9 Hz, 2H), 2.43 (s, 3H), 1.75 (t, *J* = 2.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 137.3 (t, *J* = 31.0 Hz), 137.2, 132.9 (q, *J* = 32.9 Hz), 129.4, 127.9, 127.6 (t, *J* = 4.8 Hz), 125.2 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.4 Hz), 119.5 (t, *J* = 255.5 Hz), 80.8, 73.9, 36.2, 21.6, 3.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.07 (s, 3F), -71.08 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{19}H_{16}F_5NO_2S$, 417.0821; found: 417.0819.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*,4-dimethylbenzenesulfonamide (19)**



Prepared according to a modified version of **General Procedure C**, using methyl trifluoromethanesulfonate (32.8 mg, 22.6 µL, 0.2 mmol, 1.0 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **19** (63.2 mg, 83%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.56 (m, 6H), 7.33 – 7.23 (m, 2H), 3.06 (t, *J* = 1.9 Hz, 3H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.8 (t, *J* = 31.0 Hz), 136.2, 132.9 (qt, *J* = 32.8, 1.6 Hz), 129.7, 127.8, 127.2 (t, *J* = 4.8 Hz), 125.4 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.2 Hz), 119.7 (t, *J* = 255.0 Hz), 32.4 (t, *J* = 2.7 Hz), 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.02 (s, 3F), -74.12 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{16}H_{14}F_5NO_2S$, 379.0665; found: 379.0656.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*,4-dimethylbenzenesulfonamide-^{13}C (20)**

Prepared according to a modified version of **General Procedure C**, using methyl-^{13}C trifluoromethanesulfonate (32.8 mg, 22.6 µL, 0.2 mmol, 1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **20** (62.5 mg, 82%) as a clear oil.

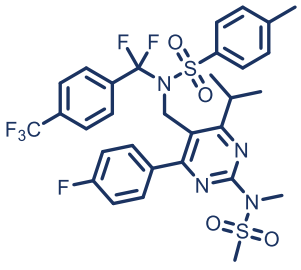
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.56 (m, 6H), 7.33 – 7.23 (m, 2H), 3.05 (dt, *J* = 142.2, 1.9 Hz), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.8 (t, *J* = 30.6 Hz), 136.2, 132.9 (qt, *J* = 32.8, 1.6 Hz), 129.7, 127.8, 127.2 (t, *J* = 4.8 Hz), 125.4 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.2 Hz), 119.7 (t, *J* = 255.0 Hz), 32.5 (t, *J* = 2.7 Hz), 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.02 (s, 3F), -74.13 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}\,^{13}CH_{14}F_5NO_2S$, 380.0698; found: 380.0697.

***N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-*N*-((4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)methyl)-4-methylbenzenesulfonamide (21)**



Prepared according to a modified **General Procedure C**, using bromide *N*-(5-(bromomethyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (185 mg, 0.44 mmol, 1 equiv.), tetrabutylammonium iodide (246 mg, 0.67 mmol, 1.5 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution

(13.2 mL, 0.1 M, 1.32 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 20% AcOEt in *n*-pentane), affording compound **21** (64.4 mg, 21%) as a clear oil.

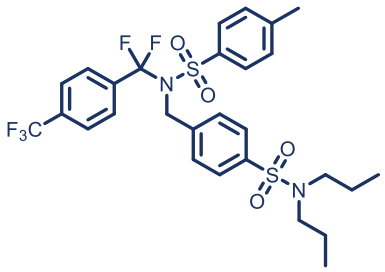
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.26 – 7.10 (m, 6H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.12 (s, 2H), 3.68 (h, *J* = 6.6 Hz, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 2.39 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 166.9, 163.6 (d, *J* = 250.2 Hz), 157.5, 144.8, 137.3 (t, *J* = 30.6 Hz), 136.5, 134.3 (d, *J* = 3.4 Hz), 132.8 (q, *J* = 32.9 Hz), 131.7 (d, *J* = 8.5 Hz), 129.6, 127.4, 127.2 (t, *J* = 5.0 Hz), 125.1 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.4 Hz), 120.0 (t, *J* = 258.4 Hz), 116.9, 115.5 (d, *J* = 21.7 Hz), 42.6 (t, *J* = 2.6 Hz), 42.5, 33.0, 31.5, 22.0, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.01 (s, 3F), -70.60 (s, 2F), -111.02 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{31}H_{30}F_6N_4O_4S_2$, 700.1613; found: 700.1599.

_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-_N_-(4-(N,N-dipropylsulfamoyl)benzyl)-4-methylbenzenesulfonamide (22)



Prepared according to **General Procedure C**, using 4-(bromomethyl)-N,N-dipropylbenzenesulfonamide **SI-2** (66.8 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **22** (67 mg, 64%) as a clear oil.

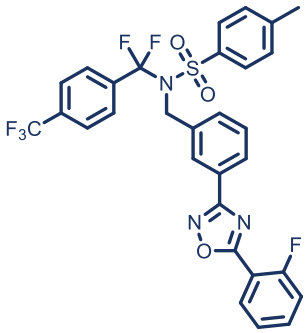
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.58 – 7.46 (m, 6H), 7.41 – 7.33 (m, 2H), 7.23 – 7.15 (m, 2H), 4.81 (t, *J* = 2.1 Hz, 2H), 3.19 – 3.03 (m, 4H), 2.43 (s, 3H), 1.70 – 1.49 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 141.4, 139.7, 136.9 (t, *J* = 29.0 Hz), 136.5, 132.9 (q, *J* = 33.2), 129.6, 128.7, 127.5, 127.5 (t, *J* = 4.7 Hz), 127.3, 125.1 (q, *J* = 3.7 Hz), 122.5 (q, *J* = 273.9 Hz), 121.5 (t, *J* = 256.4 Hz), 50.0, 48.9, 22.0, 21.5, 11.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.07 (s, 3F), -69.79 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{28}H_{31}F_5N_2O_4S_2$, 618.1645; found: 618.1634.

_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-_N_-(3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzyl)-4-methylbenzenesulfonamide (23)



Prepared according to a modified **General Procedure C**, using 3-(3-(bromomethyl)phenyl)-5-(2-fluorophenyl)-1,2,4-oxadiazole **SI-3** (112.7 mg, 0.34 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 0.65 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 1.76 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **23** (132 mg, 63%) as a clear oil.

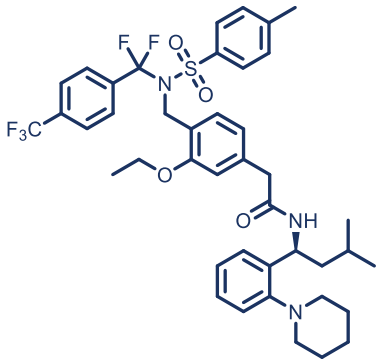
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.16 (m, 1H), 8.15 – 8.08 (m, 1H), 8.05 (s, 1H), 7.68 – 7.27 (m, 11H), 7.20 – 7.11 (m, 2H), 4.85 (s, 2H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (d, *J* = 4.5 Hz), 168.4, 160.8 (d, *J* = 260.6 Hz), 144.5, 137.8, 137.2 (t, *J* = 30.7 Hz), 136.8, 134.7 (d, *J* = 8.7 Hz), 132.8 (q, *J* = 32.7 Hz), 131.0 (2C), 129.6, 129.3, 127.7, 127.6 (t, *J* = 4.8 Hz), 127.2, 127.0, 126.9, 125.1 (q, *J* = 3.7 Hz), 124.8 (d, *J* = 3.8 Hz), 123.6 (q, *J* = 273.2 Hz), 120.0 (t, *J* = 256.0 Hz), 117.2 (d, *J* = 20.9 Hz), 112.8 (d, *J* = 11.4 Hz), 49.2, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.12 (s, 3F), -70.19 (s, 2F), -108.32 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{30}H_{21}F_6N_3O_3S$, 617.1208; found: 617.1182.

(S)-2-(4-(((*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylphenyl)sulfonamido)methyl)-3-ethoxyphenyl)-*N*-(3-methyl-1-(2-(piperidin-1-yl)phenyl)butyl)acetamide (24)



Prepared according to **General Procedure C**, using bromide **SI-5** (100.3 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **24** (37 mg, 24%) as a clear oil.

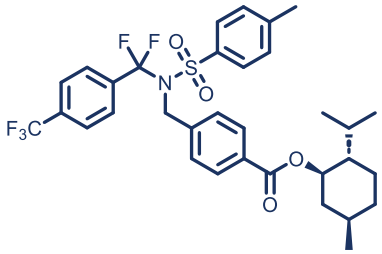
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.41 (m, 7H), 7.26 – 7.13 (m, 4H), 7.11 – 6.99 (m, 2H), 6.88 – 6.79 (m, 1H), 6.69 – 6.52 (m, 2H), 5.46 – 5.32 (m, 1H), 4.72 (s, 2H), 3.90 – 3.70 (m, 2H), 3.50 (s, 2H), 3.08 – 2.83 (m, 2H), 2.71 – 2.53 (m, 2H), 2.43 (s, 3H), 1.77 – 1.35 (m, 9H), 1.28 (t, J = 6.9 Hz, 3H), 1.01 – 0.80 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 156.0, 152.5, 144.3, 138.9, 137.5 (t, J = 30.1 Hz), 137.2, 135.9, 132.5 (q, J = 33.4 Hz), 129.5, 129.0, 127.8, 127.7, 127.5, 127.3 (t, J = 4.8 Hz), 125.0, 124.8 (q, J = 3.7 Hz), 123.9, 123.4 (q, J = 273.0 Hz), 122.7, 121.1, 119.9 (t, J = 255.1 Hz), 111.6, 63.5, 49.6, 46.7, 44.4, 44.1, 26.8, 25.4, 24.2, 22.8, 22.5, 21.6, 14.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.00 (s, 3F), -69.96 (s, 2F).

HRMS (FD+) (m/z): $[M+H]^+$ calculated for $C_{42}H_{48}F_5N_3O_4S$, 786.3364; found: 786.3365.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-(((*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methylphenyl)sulfonamido)methyl)benzoate (25)



Prepared according to **General Procedure C**, using bromide **SI-1** (70.6 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-(trifluoromethyl) benzimidoyl chloride solution (6 mL, 0.1 M, 0.6 mmol, 3 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **25** (60.5 mg, 47%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.95 (td, *J* = 10.9, 4.4 Hz, 1H), 4.78 (s, 2H), 2.41 (s, 3H), 2.19 – 2.09 (m, 1H), 1.97 (pd, *J* = 7.0, 2.8 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.66 – 1.51 (m, 2H), 1.19 – 1.08 (m, 2H), 0.97 – 0.90 (m, 7H), 0.81 (d, *J* = 7.0 Hz, 3H).

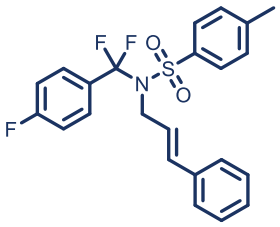
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 144.5, 141.7, 137.3 (t, *J* = 29.7 Hz), 136.7, 132.8 (q, *J* = 33.0 Hz), 130.4, 129.8, 129.6, 128.0, 127.6, 127.5 (t, *J* = 5.0 Hz), 125.0 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 272.1 Hz), 119.9 (t, *J* = 255.6 Hz), 75.0, 49.2, 41.0, 34.3, 31.5, 26.6, 23.7, 22.0, 21.5, 20.8, 16.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s, 3F), -69.99 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{33}H_{36}F_5NO_4S$, 637.2285; found: 637.2277.

Scope of Aryl Groups

N-cinnamyl-*N*-(difluoro(4-fluorophenyl)methyl)-4-methylbenzenesulfonamide (26)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-fluoro-*N*-tosylbenzimidoyl chloride solution (**S-7**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **26** (55 mg, 64%) as a clear oil.

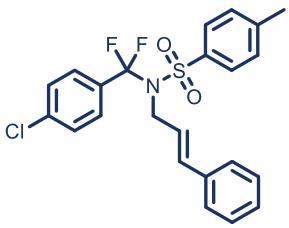
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.41 – 7.22 (m, 7H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.53 – 6.37 (m, 1H), 6.30 – 6.13 (m, 1H), 4.34 – 4.24 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, *J* = 251.4 Hz), 144.2, 137.8, 136.3, 133.9, 130.1 (td, *J* = 31.2, 3.3 Hz), 129.5, 129.2(dt, *J* = 9.3, 4.8 Hz), 128.6, 128.3, 127.7, 126.6, 124.7, 120.3 (t, *J* = 254.6 Hz), 115.3 (d, *J* = 22.3 Hz), 48.8, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.72 (s, 2F), -108.86 – -109.12 (m, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{20}F_3NO_2S$, 431.1167; found: 431.1160.

N-((4-chlorophenyl)difluoromethyl)-*N*-cinnamyl-4-methylbenzenesulfonamide (27)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-chloro-*N*-tosylbenzimidoyl chloride solution (**S-8**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was

purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **27** (68 mg, 76%) as a clear oil.

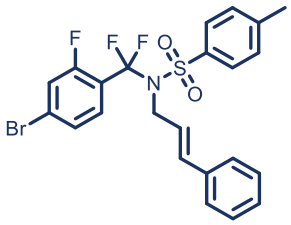
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.28 (m, 7H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.53 – 6.35 (m, 1H), 6.27 – 6.08 (m, 1H), 4.28 (d, *J* = 6.6 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 137.6, 137.2 (t, *J* = 2.2 Hz), 136.2, 134.0, 132.5 (t, *J* = 31.3 Hz), 129.5, 128.6, 128.4, 128.3 (t, *J* = 4.6 Hz), 128.0, 127.7, 126.6, 124.6, 120.2 (t, *J* = 254.9 Hz), 48.7, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -69.59 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{20}ClF_2NO_2S$, 447.0871; found: 447.0866.

_N_-((4-bromo-2-fluorophenyl)difluoromethyl)-_N_-cinnamyl-4-methylbenzenesulfonamide (28)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-bromo-2-fluoro-*N*-tosylbenzimidoyl chloride solution (**S-9**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **28** (83 mg, 81%) as a clear oil.

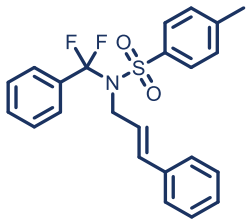
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 3H), 7.40 – 7.24 (m, 6H), 7.23 – 7.16 (m, 2H), 7.07 – 6.97 (m, 1H), 6.53 – 6.41 (m, 1H), 6.32 – 6.16 (m, 1H), 4.44 – 4.34 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (dt, *J* = 259.6, 3.7 Hz), 144.3, 137.0, 136.4, 133.7, 130.4 (td, *J* = 5.4, 1.8 Hz), 129.4, 128.6, 128.0, 127.6, 127.1 (d, *J* = 3.7 Hz), 126.6, 126.3 (dt, *J* = 9.3, 1.6 Hz), 124.8, 121.0 (td, *J* = 31.8, 10.7 Hz), 119.9 (d, *J* = 24.1 Hz), 118.1 (td, *J* = 254.8, 1.8 Hz), 48.4, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.57 (d, J = 11.8 Hz, 2F), -109.50 (t, J = 11.8 Hz, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{19}BrF_3NO_2S$, 509.0272; found: 509.0280.

***N*-cinnamyl-*N*-(difluoro(phenyl)methyl)-4-methylbenzenesulfonamide (29)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosylbenzimidoyl chloride solution (**S-10**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **29** (44 mg, 53%) as a clear oil.

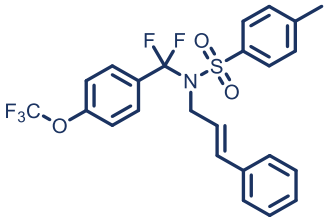
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.8 Hz, 2H), 7.56 – 7.21 (m, 12H), 6.43 – 6.26 (m, 1H), 6.26 – 6.11 (m, 1H), 4.24 (d J = 6.6 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 138.0, 136.4, 134.0 (t, J = 30.6 Hz), 133.8, 130.9 (t, J = 1.9 Hz), 129.5, 128.6, 128.7, 127.9, 127.7, 126.8 (t, J = 4.8 Hz), 126.6, 124.8, 120.7 (t, J = 254.8 Hz), 48.9, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -69.81 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{21}F_2NO_2S$, 413.1261; found: 413.1255.

***N*-cinnamyl-*N*-(difluoro(4-(trifluoromethoxy)phenyl)methyl)-4-methylbenzenesulfonamide (30)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-tosyl-4-

(trifluoromethoxy)benzimidoyl chloride (**SI-11**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **30** (71 mg, 71%) as a clear oil.

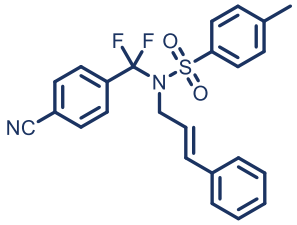
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 4H), 7.42 – 7.27 (m, 5H), 7.27 – 7.15 (m, 4H), 6.48 (m, 1H), 6.23 (m, 1H), 4.44 – 4.28 (d, *J* = 6.7 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9 (q, *J* = 1.9 Hz), 144.2, 137.6, 136.2, 134.11, 132.4 (t, *J* = 31.3 Hz), 129.5, 129.0 (t, *J* = 4.8 Hz), 128.6, 128.1, 127.60, 126.6, 124.6, 120.3, 120.3 (q, *J* = 258.4 Hz) 120.0 (t, *J* = 254.8 Hz), 48.6, 21.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -57.73(s, 3F), -69.18 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_5NO_3S$, 497.1084; found: 497.1068.

***N*-cinnamyl-*N*-((4-cyanophenyl)difluoromethyl)-4-methylbenzenesulfonamide (31)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-cyano-*N*-tosylbenzimidoyl chloride (**SI-12**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **31** (70 mg, 80%) as a clear oil.

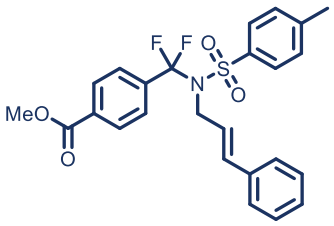
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.54 (m, 6H), 7.42 – 7.21 (m, 7H), 6.53 – 6.40 (m, 1H), 6.26 – 6.10 (m, 1H), 4.34 – 4.21 (m, 2H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 138.8 (t, *J* = 31.7 Hz), 137.1, 136.1, 134.3, 132.0, 129.7, 128.7, 128.2, 127.8, 127.7 (t, *J* = 4.9 Hz), 126.6, 124.2, 119.6 (t, *J* = 255.8 Hz), 117.8, 114.8 (t, *J* = 2.0 Hz), 48.6, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -70.25 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_2N_2O_2S$, 438.1214; found: 438.1229.

Methyl 4-(*N*-cinnamyl-*N*-tosylfluorocarbonyl)benzoate (32)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and methyl-4-(chloro(tosylimino)methyl)benzoate (**SI-13**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **32** (66 mg, 70%) as a clear oil.

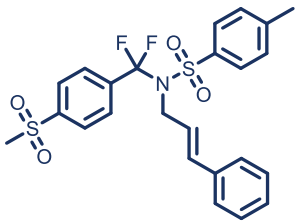
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.68 – 7.53 (m, 4H), 7.39 – 7.17 (m, 7H), 6.45 – 6.33 (m, 1H), 6.23 – 6.07 (m, 1H), 4.30 – 4.20 (m, 2H), 3.94 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 144.3, 138.3 (t, *J* = 30.9 Hz), 137.6, 136.2, 134.0, 132.4 (t, *J* = 1.5 Hz), 129.6, 129.5, 128.6, 128.0, 127.8, 127.0 (t, *J* = 4.7 Hz), 126.6, 124.5, 120.2 (t, *J* = 255.5 Hz), 52.5, 48.8, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -70.04 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{25}H_{23}F_2NO_4S$, 471.1316; found: 471.1321.

***N*-cinnamyl-*N*-(difluoro(4-(methylsulfonyl)phenyl)methyl)-4-methylbenzenesulfonamide (33)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-(methylsulfonyl)-*N*-tosylbenzimidoyl chloride (**SI-14**) solution (8 mL, 0.1 M, 0.8 mmol, 4

equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **33** (56 mg, 57%) as a clear oil.

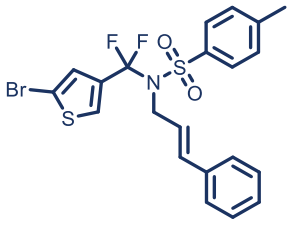
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.18 (m, 7H), 6.47 – 6.35 (m, 1H), 6.23 – 6.07 (m, 1H), 4.34 – 4.24 (m, 2H), 2.99 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 142.8, 139.7 (t, *J* = 31.6 Hz), 137.1, 136.1, 134.2, 129.7, 128.7, 128.2, 128.0 (t, *J* = 4.6 Hz), 127.7, 127.4, 126.6, 124.3, 119.6 (t, *J* = 256.0 Hz), 48.6, 44.3, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -70.37 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{23}F_2NO_4S_2$, 491.1037; found: 491.1049.

_N_-((5-bromothiophen-3-yl)difluoromethyl)-_N_-cinnamyl-4-methylbenzenesulfonamide (34)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 5-bromo-*N*-tosylthiophene-3-carbimidoyl chloride (**SI-15**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **34** (59.3 mg, 60%) as a white solid.

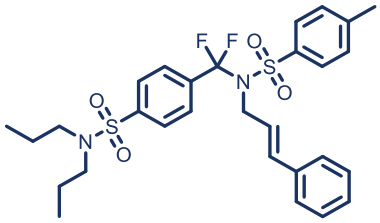
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 2H), 7.50 – 7.44 (m, 1H), 7.40 – 7.18 (m, 7H), 6.85 (d, J = 1.5 Hz, 1H), 6.56 – 6.44 (m, 1H), 6.29 – 6.13 (m, 1H), 4.41 – 4.22 (m, 2H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 137.7, 136.3, 135.3 (t, *J* = 34.7 Hz), 134.1, 129.6, 128.9 (t, *J* = 5.2 Hz), 128.7, 128.6 (t, *J* = 3.1 Hz), 128.1, 127.6, 126.7, 124.8, 117.5 (t, *J* = 252.9 Hz), 113.3, 48.5, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -66.61 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{21}H_{18}BrF_2NO_2S_2$, 496.9930; found: 496.9933.

_N_-cinnamyl-_N_-((4-(N,N-dipropylsulfamoyl)phenyl)difluoromethyl)-4-methylbenzenesulfonamide (35)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-(*N*,*N*-dipropylsulfamoyl)-N-tosylbenzimidoyl chloride (**SI-16**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **35** (82 mg, 71%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 2H), 7.69 – 7.54 (m, 4H), 7.37 – 7.18 (m, 7H), 6.48 – 6.36 (m, 1H), 6.24 – 6.08 (m, 1H), 4.32 – 4.22 (m, 2H), 3.10 – 2.97 (m, 4H), 2.41 (s, 3H), 1.54 (h, J = 7.4 Hz, 4H), 0.86 (t, J = 7.4 Hz, 6H).

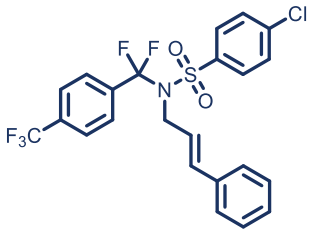
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 142.6, 137.8 (t, J = 31.3 Hz), 137.3, 136.1, 134.1, 129.6, 128.7, 128.1, 127.7, 127.7 (t, J = 4.6 Hz), 126.8, 126.6, 124.4, 119.8 (t, J = 255.6 Hz), 50.1, 48.6, 22.1, 21.6, 11.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -69.98 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_5NO_3S$, 576.1928; found: 576.1951.

Scope of Sulfonamides

4-Chloro-*N*-cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)benzenesulfonamide (36)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((4-chlorophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-17**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **36** (82 mg, 82%) as a clear oil.

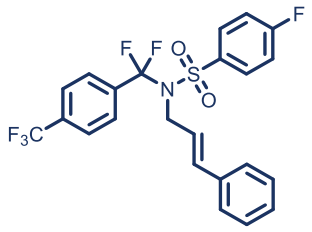
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.57 (m, 6H), 7.46 – 7.32 (m, 7H), 6.54 – 6.41 (m, 1H), 6.29 – 6.12 (m, 1H), 4.33 (d, *J* = 6.8, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 138.9, 137.4 (t, *J* = 31.3 Hz), 135.9, 134.7, 133.1 (q, *J* = 32.8 Hz), 129.3, 129.1, 128.7, 128.3, 127.5 (t, *J* = 4.8 Hz), 126.6, 125.4 (q, *J* = 3.7 Hz), 123.9, 123.4 (q, *J* = 272.8 Hz), 119.7 (t, *J* = 256.1 Hz), 53.5, 48.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.01 (s, 3F), -70.35 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{17}ClF_5NO_2S$, 501.0589; found: 501.0583.

N-Cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-fluorobenzenesulfonamide (37)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((4-

fluorophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-18**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **37** (69.7 mg, 72%) as a clear oil.

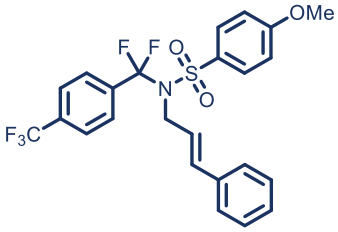
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.68 – 7.59 (m, 4H), 7.40 – 7.26 (m, 5H), 7.16 – 7.03 (m, 2H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.25 – 6.09 (m, 1H), 4.36 – 4.26 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (d, *J* = 256.7 Hz), 137.5 (t, *J* = 31.3 Hz), 136.5 (d, *J* = 3.3 Hz), 136.0, 134.7, 133.2 (q, *J* = 32.5 Hz), 130.6 (d, *J* = 9.5 Hz), 128.8, 128.3, 127.6 (t, *J* = 4.7 Hz), 126.6, 125.4 (q, *J* = 3.8 Hz), 124.1, 123.5 (q, *J* = 272.8 Hz), 119.9 (t, *J* = 255.5 Hz), 116.3 (d, *J* = 22.8 Hz), 48.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.03 (s, 3F), -70.37 (s, 2F), -103.71 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{17}F_6NO_2S$, 485.0884; found: 485.0878.

_N_-Cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-methoxybenzenesulfonamide (38)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((4-methoxyphenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-19**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **38** (44 mg, 44%) as a clear oil.

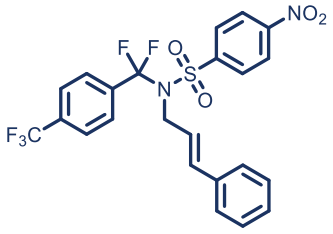
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.57 (m, 6H), 7.37 – 7.25 (m, 5H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.53 – 6.38 (m, 1H), 6.29 – 6.17 (m, 1H), 4.33 (d, *J* = 6.6 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 137.7 (t, *J* = 31.5 Hz), 136.2, 134.1, 132.8 (q, *J* = 32.7 Hz), 131.8, 129.9, 128.7, 128.1, 127.6 (t, *J* = 4.8 Hz), 126.6, 125.2 (q, *J* = 3.8 Hz), 124.5, 123.1 (q, *J* = 273.7 Hz), 119.9 (t, *J* = 255.2 Hz), 114.1, 55.6, 48.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.99 (s, 3F), -70.22 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{24}H_{20}F_5NO_3S$, 497.1084; found: 497.1078.

_N_-Cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-nitrobenzenesulfonamide (39)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and _N_-((4-nitrophenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-20**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% _n_-pentane to 10% AcOEt in _n_-pentane), affording compound **39** (39 mg, 38%) as a clear oil.

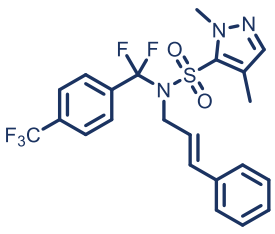
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 9.1 Hz, 2H), 7.97 (d, J = 9.1 Hz, 2H), 7.73 – 7.64 (m, 4H), 7.41 – 7.25 (m, 5H), 6.55 – 6.44 (m, 1H), 6.25 – 6.05 (m, 1H), 4.32 (d, J = 6.8, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 146.0, 137.0 (t, J = 32.7 Hz), 135.6, 135.3, 133.4 (q, J = 31.6 Hz), 129.0, 128.8, 128.5, 127.3 (t, J = 4.6 Hz), 126.5, 125.5 (q, J = 4.0 Hz), 124.1, 123.2, 123.3 (q, J = 272.3 Hz), 119.7 (t, J = 256.9 Hz), 49.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.08 (s, 3F), -70.46 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{23}H_{17}F_5N_2O_4S$, 512.0829; found: 512.0839.

_N_-Cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-1,4-dimethyl-1H-pyrazole-5-sulfonamide (40)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((1,4-dimethyl-1H-pyrazol-5-yl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-21**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **40** (70 mg, 72%) as a clear oil.

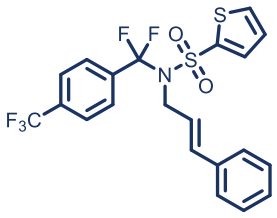
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 4H), 7.38 – 7.25 (m, 6H), 6.52 – 6.40 (m, 1H), 6.33 – 6.20 (m, 1H), 4.35 (d, *J* = 6.6 Hz, 2H), 3.70 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 137.6 (t, *J* = 31.1 Hz), 136.1, 134.5, 134.1, 132.9 (q, *J* = 32.8 Hz), 128.7, 128.1, 127.7 (t, *J* = 4.9 Hz), 126.5, 125.1 (q, *J* = 3.8 Hz), 124.7, 123.4 (q, *J* = 272.6 Hz), 120.0 (t, *J* = 255.0 Hz), 119.9, 48.6, 39.0, 12.5.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.81 (s, 3F), -70.76 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{22}H_{20}F_5N_3O_2S$, 485.1196; found: 485.1181.

_N_-Cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)thiophene-2-sulfonamide (41)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-(thiophen-2-ylsulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-22**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **41** (91 mg, 96%) as a clear oil.

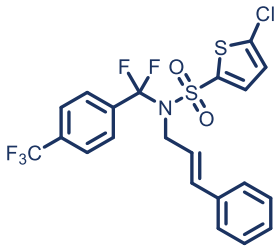
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.61 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.39 – 7.27 (m, 5H), 7.00 (dd, *J* = 5.0, 3.9 Hz, 1H), 6.54 – 6.41 (m, 1H), 6.31 – 6.15 (m, 1H), 4.33 (d, *J* = 6.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 137.7 (t, *J* = 31.9 Hz), 136.1, 134.5, 134.0, 133.3, 132.9 (q, *J* = 32.7 Hz), 128. 7, 128.2, 127.4 (t, *J* = 4.8 Hz), 127.2, 126.6, 125.3 (q, *J* = 3.7 Hz), 123.9, 123.6 (d, *J* = 272.6 Hz), 119.9 (t, *J* = 256.3 Hz), 49.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.95 (s, 3F), -70.32 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{21}H_{16}F_5NO_2S_2$, 473.0543; found: 473.0528.

5-Chloro-*N*-cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)thiophene-2-sulfonamide (42)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((5-chlorothiophen-2-yl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-23**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **42** (72 mg, 71%) as a clear oil.

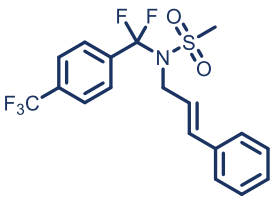
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.68 (m, 4H), 7.43 – 7.25 (m, 6H), 6.86 (d, *J* = 4.1 Hz, 1H), 6.53 – 6.45 (m, 1H), 6.21 (m, 1H), 4.31 (d, *J* = 5.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.6, 137.5 (t, *J* = 30.8 Hz), 135.9, 134.9, 133.3, 132.7 (q, *J* = 32.7 Hz), 128.7, 128.3, 127.3 (t, *J* = 4.8 Hz), 126.6, 126.5, 125.4 (q, *J* = 3.8 Hz), 123.5, 124.3 (q, *J* = 272.7 Hz), 119.8 (t, *J* = 256.8 Hz), 49.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.00 (s, 3F), -70.40 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{21}H_{15}ClF_5NO_2S_2$, 507.0153; found: 507.0180.

***N*-Cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)methanesulfonamide (43)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-(methylsulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-24**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **43** (65 mg, 80%) as a clear oil.

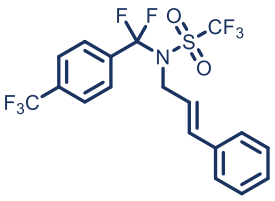
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.71 (m, 4H), 7.46 – 7.26 (m, 5H), 6.55 – 6.44 (m, 1H), 6.31 – 6.17 (m, 1H), 4.23 (d, *J* = 6.8, 2H), 3.15 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (t, *J* = 32.2 Hz), 135.9, 135.0, 133.2 (q, *J* = 32.8 Hz), 128.7, 128.4, 127.1 (t, *J* = 4.6 Hz), 126.6, 125.7 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 274.3 Hz), 123.5, 120.2 (t, *J* = 255.9 Hz), 48.9, 43.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.98 (s, 3F), -70.36 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{18}H_{16}F_5NO_2S$, 405.0822; found: 405.0618.

***N*-Cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-1,1,1-trifluoromethanesulfonamide (44)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and 4-(trifluoromethyl)-*N*-((trifluoromethyl)sulfonyl)benzimidoyl chloride (**SI-25**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **44** (60 mg, 65%) as a clear oil.

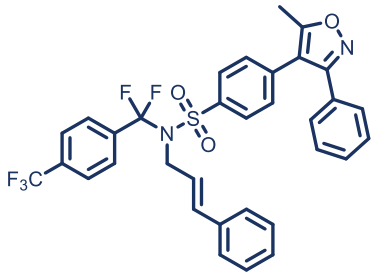
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.72 (m, 4H), 7.39 – 7.33 (m, 5H), 6.45 – 6.31 (m, 1H), 6.21 – 6.06 (m, 1H), 4.31 (d, *J* = 6.8, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5 (t, *J* = 30.4 Hz), 135.8, 135.4, 133.8 (q, *J* = 34.1 Hz), 128.8, 128.6, 127.1 (t, *J* = 5.0 Hz), 126.7, 125.8 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 273.5 Hz), 122.1, 119.9 (q, *J* = 323.5 Hz), 119.3 (t, *J* = 260.2 Hz), 51.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.16 (s, 3F), -69.17 (s, 2F), -75.15 (t, *J* = 6.9 Hz, 3F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{18}H_{13}F_8NO_2S$, 459.0539; found: 459.0521.

_N_-Cinnamyl-_N_-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (45)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((4-(5-methyl-3-phenylisoxazol-4-yl)phenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-26**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **45** (77 mg, 62%) as a clear oil.

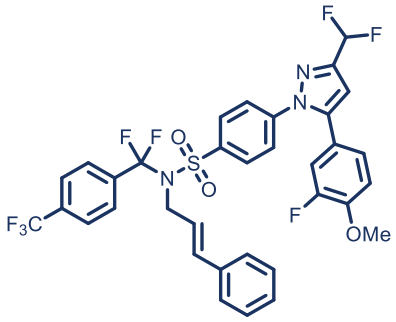
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.73 – 7.62 (m, 4H), 7.50 – 7.22 (m, 12H), 6.64 – 6.32 (m, 1H), 6.33 – 6.08 (m, 1H), 4.44 – 4.10 (m, 2H), 2.48 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 161.1, 139.5, 137.7 (t, *J* = 31.3 Hz), 136.0, 135.9, 134.5, 133.1 (q, *J* = 32.7 Hz), 130.1, 129.8, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.5 (t, *J* = 4.8 Hz), 126.5, 125.4 (q, *J* = 3.8 Hz), 124.0, 123.2 (q, *J* = 272.5 Hz), 119.8 (t, *J* = 256.1 Hz), 114.3, 48.9, 11.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.97 (s, 3F), -70.04 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{33}H_{25}F_5N_2O_3S$, 624.1506; found: 624.1507.

***N*-Cinnamyl-*N*-(difluoro(4-(trifluoromethyl)phenyl)methyl)-4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (46)**



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)phenyl)sulfonyl)-4-(trifluoromethyl)benzimidoyl chloride (**SI-27**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **46** (114 mg, 81%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.69 – 7.64 (m, 4H), 7.46 – 7.38 (m, 2H), 7.37 – 7.26 (m, 5H), 7.04 – 6.90 (m, 3H), 6.80 (t, *J* = 54.8 Hz, 1H), 6.74 (s, 1H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.18 (s, 1H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 3H).

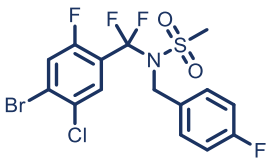
^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1 (d, *J* = 248.4 Hz), 148.6 (d, *J* = 10.5 Hz), 148.4 (t, *J* = 30.0 Hz), 143.7, 143.0, 139.5, 137.4 (t, *J* = 31.9 Hz), 135.8, 134.6, 133.1 (q, *J* = 32.7 Hz), 128.8, 128.7, 128.2, 127.4 (t, *J* = 4.7 Hz), 126.5, 125.4 (q, *J* = 3.7 Hz), 125.1 (q, *J* = 3.6 Hz), 125.0, 123.8, 123.4 (q, *J* = 272.8 Hz), 121.6 (d, *J* = 7.0 Hz), 119.7 (t, *J* = 255.5 Hz), 116.5 (d, *J* = 19.8 Hz), 113.5 (d, *J* = 2.3 Hz), 110.9 (t, *J* = 234.6 Hz), 105.9, 56.2, 48.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.02 (s, 3F), -70.35 (s, 2F), -112.38 (s, 2F), -133.25 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{34}H_{25}F_8N_3O_3S$, 707.1489; found: 707.1488.

Applications

N-((4-bromo-5-chloro-2-fluorophenyl)difluoromethyl)-*N*-(4-fluorobenzyl)methanesulfonamide (48)



Prepared according to a modified version of **General Procedure D**, using 4-fluorobenzyl bromide (37.8 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and 4-bromo-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzimidoyl chloride (**47**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The reaction was heated at 60 °C for 18 hours after which the solvent was evaporated and the crude was purified using column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **48** (58.1 mg, 63%) as a clear oil.

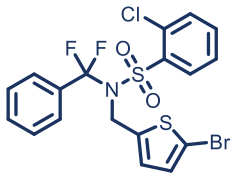
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 9.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.09 – 6.96 (m, 2H), 4.67 (s, 2H), 2.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, *J* = 247.2 Hz), 157.3 (dt, *J* = 257.7, 3.3 Hz), 131.6 (d, *J* = 3.2 Hz), 130.5 (d, *J* = 3.9 Hz), 130.2 (d, *J* = 8.2 Hz), 129.5 (td, *J* = 6.0, 2.2 Hz), 126.7 (dt, *J* = 9.7, 1.6 Hz), 122.8 (td, *J* = 32.6, 12.2 Hz), 122.1 (d, *J* = 25.4 Hz), 119.62 (td, *J* = 255.1, 2.2 Hz), 115.6 (d, *J* = 21.6 Hz), 49.1, 43.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.45 (d, *J* = 10.7 Hz, 2F), -113.71 (s, 1F), -114.21 (t, *J* = 10.8 Hz, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{15}H_{11}BrClF_4NO_2S$, 458.9318; found: 458.9298.

N-((4-*N*-((5-bromothiophen-2-yl)methyl)-2-chloro-*N*-(difluoro(phenyl)methyl)-benzenesulfonamide (51)



Prepared according to a modified version of **General Procedure D**, using 2-bromo-5-(bromomethyl)thiophene (51.2 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (81.3 mg, 0.22 mmol, 1.1 equiv.) and *N*-((2-chlorophenyl)sulfonyl)benzimidoyl chloride (**50**) (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The reaction was heated at 60 °C for 18 hours after which the solvent was evaporated and the crude was purified using column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **51** (58.1 mg, 59%) as a white solid.

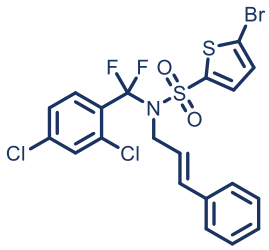
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.38 – 7.29 (m, 3H), 7.24 – 7.12 (m, 3H), 6.88 (d, *J* = 3.7 Hz, 1H), 6.76 (d, *J* = 3.7 Hz, 1H), 4.99 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 138.4, 134.0, 132.3 (t, *J* = 29.5 Hz), 131.8, 131.6, 131.6, 131.3, 129.5, 128.7, 128.2, 127.1, 127.1 (t, *J* = 5.0 Hz), 120.2 (t, *J* = 255.5 Hz), 113.1, 45.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -69.89 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{18}H_{13}BrClF_2NO_2S_2$, 490.9227; found: 490.9214.

5-Bromo-*N*-cinnamyl-N-((2,4-dichlorophenyl)difluoromethyl)thiophene-2-sulfonamide (61)



Prepared according to **General Procedure D**, cinnamyl bromide (39.4 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((5-bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzimidoyl chloride (**SI-28**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **61** (78 mg, 71%) as a clear oil.

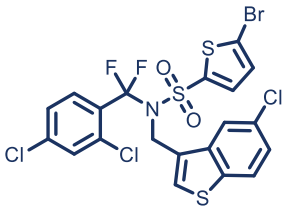
^{1}H NMR ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.29 (m, 7H), 7.14 (d, *J* = 4.0 Hz, 1H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.52 – 6.39 (m, 1H), 6.26 (m, 1H), 4.35 (d, *J* = 6.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 138.0, 136.1, 134.2, 133.9 (t, *J* = 3.4 Hz), 133.7, 130.9, 130.7 (t, *J* = 6.8 Hz), 130.1, 129.9 (t, *J* = 30.3 Hz), 128.7, 128.1, 126.9, 126.6, 123.8, 121.5, 118.7 (t, *J* = 256.6 Hz), 49.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.58 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{20}H_{14}BrCl_2F_2NO_2S_2$, 552.8971; found: 552.9022.

5-Bromo-*N*-((5-chlorobenzo[b]thiophen-3-yl)methyl)-*N*-((2,4-dichlorophenyl)difluoromethyl) thiophene-2-sulfonamide (62)



Prepared according to **General Procedure D**, 3-(bromomethyl)-5-chlorobenzo[b]thiophene (52.3 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((5-bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzimidoyl chloride (**SI-28**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **62** (90 mg, 73%) as a white solid.

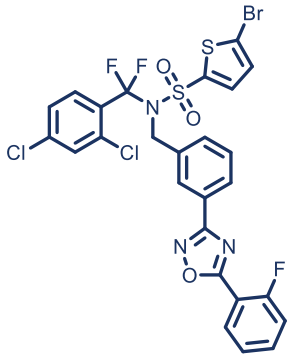
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.25 (dd, *J* = 8.5, 2.2 Hz, 2H), 7.03 (d, *J* = 4.0 Hz, 1H), 6.98 (d, *J* = 4.0 Hz, 1H), 4.95 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 138.4, 138.2, 138.2 (t, *J* = 1.8 Hz), 133.7, 133.7 (t, *J* = 3.3 Hz), 130.7, 130.7 (t, *J* = 6.7 Hz), 130.6, 130.0, 130.0, 129.2 (t, *J* = 30.2 Hz), 128.3, 126.9, 124.9, 123.8, 121.8, 120.9, 118.7 (t, *J* = 256.8 Hz), 44.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.08 (s, 2F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{20}H_{11}BrCl_3F_2NO_2S_3$, 616.8144; found: 616.8262.

5-Bromo-*N*-((2,4-dichlorophenyl)difluoromethyl)-*N*-(3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzyl)thiophene-2-sulfonamide (63)



Prepared according to **General Procedure D**, 3-(3-(bromomethyl)phenyl)-5-(2-fluorophenyl)-1,2,4-oxadiazole (66.6 mg, 0.2 mmol, 1 equiv.), tetrabutylammonium iodide (83.26 mg, 0.22 mmol, 1.1 equiv.) and *N*-((5-bromothiophen-2-yl)sulfonyl)-2,4-dichlorobenzimidoyl chloride (**SI-28**) solution (8 mL, 0.1 M, 0.8 mmol, 4 equiv.). The crude was purified using flash column chromatography (100% *n*-pentane to 10% AcOEt in *n*-pentane), affording compound **63** (105 mg, 77%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (td, *J* = 7.3, 1.9 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.70 – 7.60 (m, 3H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.41 – 7.26 (m, 4H), 7.06 (d, *J* = 4.1 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 4.86 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (d, *J* = 4.4 Hz), 168.3, 160.7 (d, *J* = 260.6 Hz), 140.4, 138.2, 136.6, 134.6 (d, *J* = 8.7 Hz), 134.0, 133.8, 131.2, 130.9, 130.8, 130.8, 130.1, 129.3 (t, *J* = 30.0 Hz), 129.1, 127.3, 127.0, 126.9, 126.8, 124.7 (d, *J* = 3.8 Hz), 121.7, 118.9 (t, *J* = 256.5 Hz), 117.1 (d, *J* = 20.9 Hz), 112.8 (d, *J* = 11.4 Hz), 50.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -68.71 (s, 2F), -108.18 (s, 1F).

HRMS (FD+) (m/z): $[M]^+$ calculated for $C_{26}H_{15}BrCl_2F_3N_3O_3S_2$, 688.9045; found: 688.9074.

2.2.3 References

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Conclusion

This thesis demonstrates the transformative potential of electrochemical and flow-based methodologies in modern organic synthesis, with a focus on sustainability, safety, and industrial relevance. By addressing key synthetic challenges through innovative design and optimization, this research not only contributes valuable methodologies to the field but also lays a foundation for future applications in drug development and fine chemical manufacturing.

The first part of the work centers on the electrochemical synthesis of bempedoic acid, a clinically relevant lipid-lowering agent. Traditional routes for its preparation rely on hazardous reagents and inefficient protocols. This thesis presents a significantly improved alternative based on electrochemical decarboxylative hydroxylation, eliminating the need for toxic substances such as sodium hydride and palladium catalysts. The approach uses Meldrum's acid as a cost-effective starting material and demonstrates precise control over selectivity and yield through systematic optimization of reaction conditions, solvent, current density, additives, and temperature. The final optimized conditions enabled the desired alcohol intermediate to be obtained in a 60% yield, highlighting the method's robustness and practical utility.

The second major contribution involves the development of a NHPI-mediated electrocatalytic protocol for the dehydrogenative lactonization of benzylic alcohols. This strategy provides an efficient, metal-free route to synthesize phthalides, valuable compounds with broad pharmacological applications. The work leverages the unique reactivity of the PINO radical generated from NHPI under anodic conditions. Through careful modulation of electrochemical parameters and reaction design, a wide variety of aromatic and benzylic substrates were successfully transformed, including sterically hindered and heterocyclic compounds. The approach proved highly scalable and was extended to the synthesis of pharmaceutically relevant targets such as talopram and advanced intermediates for Y5 receptor antagonists. The mechanistic investigation, supported by cyclic voltammetry and control experiments, confirms a radical-mediated oxidation sequence that underlines the versatility and selectivity of the NHPI system.

Both projects reflect a clear and consistent emphasis on green chemistry principles: reduction of waste, elimination of toxic reagents, and increased energy efficiency. Electrochemistry serves not just as a functional tool but as a strategic framework for addressing limitations in conventional synthesis. Likewise, the integration of flow technologies presents a scalable and

reproducible alternative to batch processes, opening avenues for safer and more controlled chemical manufacturing.

The third and final project expands the thesis's innovation into the realm of modular flow synthesis. It presents a telescoped, three-step flow process for the rapid assembly of α,α-difluoromethylene amines, motifs of high interest in medicinal chemistry due to their metabolic stability and ability to mimic amide bonds. The design allows for highly flexible and safe synthesis, drastically shortening reaction times while enabling quick access to structurally diverse analogs. This modular strategy exemplifies how flow chemistry can integrate multiple complex transformations into a streamlined, scalable process, ideal for drug discovery pipelines and lead optimization.

In conclusion, the thesis makes a strong case for electrochemical and flow chemistry as enabling technologies in the future of organic synthesis. The strategies developed here illustrate how careful method development can bridge the gap between lab-scale innovation and industrial relevance.