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ELECTROSYNTHESIS IN MODERN ORGANIC CHEMISTRY: FROM CO₂
FIXATION TO THE DIVERSIFICATION OF BIO-RELEVANT SCAFFOLDS

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Abstract

Electroorganic synthesis offers a sustainable alternative to traditional redox methodologies by replacing stoichiometric oxidants and reductants with electrons as traceless redox mediators, thereby improving atom economy and reducing waste. Despite its historical roots, its broader adoption has been limited by practical considerations. This thesis demonstrates the strategic value of electrosynthesis by developing of innovative methodologies for the construction and selective functionalization of synthetically relevant molecular scaffolds.

An initial study describes a catalyst- and additive-free electrochemical cross-electrophile coupling between allenates and carbon dioxide (CO₂), enabling the chemodivergent synthesis of mono- and dicarboxylated non-natural itaconic acid derivatives (up to 87% yield, 30 examples). Mechanistic insights were obtained through cyclic voltammetry.

Expanding electroreductive radical approaches, the first site-selective electrochemical alkylation of tropones was achieved via coupling of 2-acetoxytropones with redox-active esters, affording mono- and disubstituted products under mild conditions with broad functional group tolerance (27 examples). Voltammetric studies clarified the mechanistic profile. Complementarily, a nickel-mediated electroreductive C(sp²)-H functionalization of tropones with aldehydes enabled selective α -alkylation across a wide substrate scope (44 examples, up to 90% yield). Combined electrochemical, spectroelectrochemical, and computational analyses elucidated the catalytic pathway and the key role of reduced nickel species.

Finally, a general electrosynthetic strategy for the preparation and direct functionalization of 2-oxabicyclo[2.1.1]hexanes from bicyclo[1.1.0]butane precursors was developed. The anodic generation of electrophilic heteroatom-centered species enabled selective C(4) functionalization under mild, oxidant-free conditions. Mechanistic studies support a pathway involving anodic trigger formation followed by intramolecular cyclization, while late-stage functionalization and bioconjugation highlight the relevance of these scaffolds as benzene bioisosteres in drug discovery.

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Chapter 1: Electrosynthesis and its versatility

1.1 General aspects of Electrosynthesis

Electrolysis has been recognized as a technique in organic synthesis since the 19th century; nevertheless, modern chemists remain defensive towards its application. One reason for this hesitation starts from the fact that many redox processes can be simply accomplished using chemical redox agents, which allow to perform the transformation without the needed of the specific equipment that electrochemical techniques usually call for. However, this inevitably comes at the cost of stoichiometric amount of oxidants or reductants, impacting on the atom economy of the process. On the other hand, electrochemical strategies provide several distinct advantages over traditional methodologies in organic synthesis, by replacing chemical reagents with electrons as traceless redox mediators. These features include high functional group tolerance, mild reaction conditions, inherent sustainability, and excellent atom economy. This introductory chapter aims to highlight the practical and conceptual advantages of electrosynthesis over the conventional methods in organic chemistry, emphasizing its advantages in a brief exploration of the reasons behind the renewed interest in electrochemical methods. Specific examples on the applications of electrochemistry to organic methodologies can be found in the dedicated chapters, with a specific focus on the transformations that are more relevant with respect to the investigated processes.^{1,2} Over the past decade, significant progress has been made in the field of organic chemistry toward the development of sustainable and efficient synthetic strategies. A key factor in this evolution has been driven by the diversification of enabling technologies, which have played a crucial role in the way chemical reactions are conceived and, consequently, carried out. By harnessing the power of these diverse techniques, synthetic organic electrochemistry has emerged as a highly valuable approach. By employing electricity, this technique replaces stoichiometric oxidizing or reducing agents with electrons as greener equivalents and enables novel reaction pathways that would be often inaccessible to the other methods, achieving complementary selectivity.

¹ E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent.Sci.* **2016**, 2, 302.

² P. S. Baran, Y. Kawamata, B. Peters, J. Vantourout, Y. Takahira, D. M. Kingston, *Acc. Chem. Res.* **2020**, 53, 1.

1.1.1 Fundamental electrochemical parameters

The development of synthetic organic electrochemical reactions requires close attention to parameters that are not traditionally encountered by organic chemists. These are discussed in some detail below.

- Current

The flow of electrical current can be described as the flow of electrons through a medium, representing a substantial quantity of electrons passing through, per unit of time (Eq. 1). A high current intensity indicates a swift and abundant flow of electrons within the circuit.

$$I(t) = \frac{dQ}{dt}$$

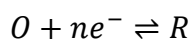
Eq. 1

In the process of electrolysis, oxidation occurs at the positively polarized electrode (anode), while reduction takes place at the negatively polarized electrode (cathode). According to the International Union of Pure and Applied Chemistry (IUPAC) convention, anodic processes are associated with positive currents, while cathodic processes are associated with negative currents.

From a synthetic point of view, the applied current defines the rate at which the electrons are delivered in or withdrawn from solution through the electrodes surface. As such, the value of the current dictates the reaction rate: electrolytic reactions conducted at high current values reach completion in less time, while reaction conducted at lower current values take longer to complete, but often lead to a more controlled transformation.

- Potential

The equilibrium between an oxidized species (O) and a reduced species (R) defines a redox couple and it is balanced by the required number of electrons as shown in Eq. 2.



Eq. 2

The Nernst equation is used to quantify the potential (E) of a redox couple (O/R), being a thermodynamic value that reflects the energy required for oxidizing or reducing a given species. This describes the electrochemical potential of the couple at equilibrium (Eq. 3), where R is the ideal gas constant, T the temperature, F the Faraday constant, a_{red} the activity in reductant and a_{ox} is the activity in oxidant.

$$E = E^0 - \frac{RT}{nF} \ln \frac{a_{red}}{a_{ox}}$$

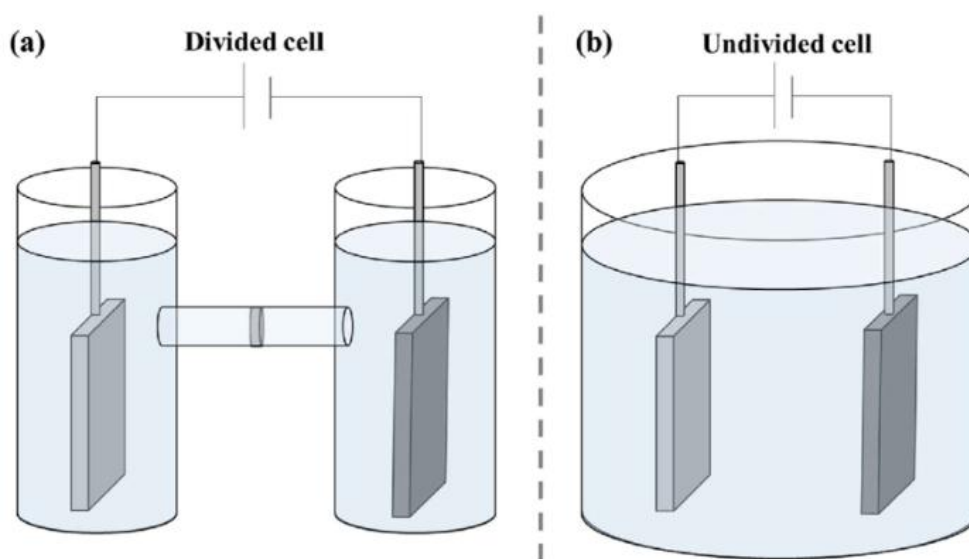
Eq. 3

From a synthetic perspective, it is crucial to understand the general outcome dictated by this parameter. If the applied reaction potential is insufficient, the process may not have enough energy to occur efficiently or not occur at all. On the other hand, excessively high voltages can activate competing redox events, leading to many undesired pathways and, therefore, by-products might become viable. To set up an electrosynthetic process, one key point is choosing between two operating modalities: constant current (galvanostatic) or constant voltage (potentiostatic) electrolysis. As this choice is the first to be taken, it is crucial to visualize the comparison between the two possible regimes. Running a reaction at a constant current ensures a consistent flow of electrons over time, guaranteeing complete consumption of the desired reactants. However, as the concentration of electroactive species decreases, the potential must increase to maintain the imposed current. The higher potential, therefore, can trigger parallel undesired processes leading to side reactions. In contrast, potentiostatic electrolysis provides higher selectivity by limiting higher-energy redox pathways but introduces kinetic unpredictability. Indeed, as the reaction proceeds and the concentration of the reactive species decreases, the current gradually diminishes, resulting in a slower reaction rate and, within a practical timeframe, incomplete conversion of the limiting reagent. Balancing the advantages and limitations of both galvanostatic and potentiostatic conditions is essential in electrochemical reactions, and the optimal choice must be done considering factors such as desired selectivity, reaction completion, and overall efficiency.

- Cell

Depending on reaction's specific requirements, electrolysis can be performed in either a divided or an undivided cell (Scheme 1.1). In the simplest configuration, an undivided cell (where both electrodes are placed into the same reaction mixture) allows all species to freely diffuse towards either the cathode or the anode. This setup is suitable if the reactants can undergo exclusively reduction or oxidation and the resulting product is not further electroactive.

However, in many cases, such a configuration may be inadequate if the product is prone to further reduction or oxidation, or if it may react with the counter electrode itself or with one of the co-products generated at the counter electrode. To overcome these scenarios, a divided cell with a permeable membrane becomes the best choice. Indeed, the membrane can separate the species generated in the cathodic compartment from the ones generated in the anodic compartment. This electrochemical setup prevents undesired reactions and guarantees isolation between the species generated at the opposite electrode, ensuring control over the outcome of the transformation.



Scheme 1.1: [a] Divided cell configuration versus [b] Undivided cell configuration.

- Electrodes

The correct choice of electrodes plays a decisive role for the success and selectivity of an electrochemical transformation. In many cases, the intrinsic properties of the electrode material and other characteristics, such as surface and morphology, can influence the outcome of the reaction. Based on these

properties, the specific material of the electrode can modulate interfacial reactivity and overpotential, thereby directing the reaction pathway to different products. Consequently, it is important to select the right couple of electrodes in order to enhance the selectivity or the efficiency when optimizing an electrosynthetic process.

A) Kolbe electrolysis



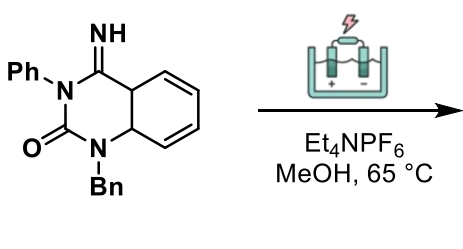
Anode	Major processes
Pt	$\cdot\text{Me} \longrightarrow \text{Me}-\text{Me}$
Graphite	$\oplus\text{Me} \longrightarrow \text{CH}_3\text{COOMe}$
PbO_2	$\text{CH}_3\text{OH}, \text{CO}, \text{CO}_2$

B) Acrylonitrile Reduction



Cathode	Major processes
Pt, Ni	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$
Sn	$\text{Sn}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CN})_4$
Pb	$\text{CH}_2=\text{CHNH}_2$
Hg, Pb, Cd, C	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CN}$ and $\text{NC}(\text{CH}_2)_2\text{CN}$

C) Cyclization of amidynil radicals



Anode	product yield (%)
RVC	94
Graphite	50
Pt	0

Scheme 1.2: Examples of the effect of electrode materials on different process.

As exemplified in Scheme 1.2, changing the electrode material profoundly alters the properties of the chosen processes, highlighting its central role in modifying the reaction pathway. In an anodic process (Scheme 1.2 A), the oxidation of acetic acid in aqueous solution can enter three different reaction mechanisms, by simply changing the nature of the anode material; different electrodes are related to the different radical that may be formed during the oxidation.

Conversely, in acrylonitrile reduction (Scheme 1.2B), the cathode plays the leading role in the process. Indeed, electrode materials dictate totally different outcomes. Finally, a similar dramatic dependence on electrode material is also reported in Scheme 1.2 C. Here, variations in the anode nature led to a markedly different efficiency of the protocol.

The main selection parameters for a specific electrode material should include not only reaction performance, yields, and selectivity, but also current efficiencies, corrosion events, cost, availability, and mechanical strength. In large-scale or energy-related processes, the right choice of electrode couple can have significant implications, including costs and waste generation. However, in methodological organic synthesis, where the scales are comparatively smaller, complete switches in selectivity or higher yields become more important parameters.

Any conductive material can be employed as an electrode, to make the appropriate choice based on mechanical and electrochemical properties.³

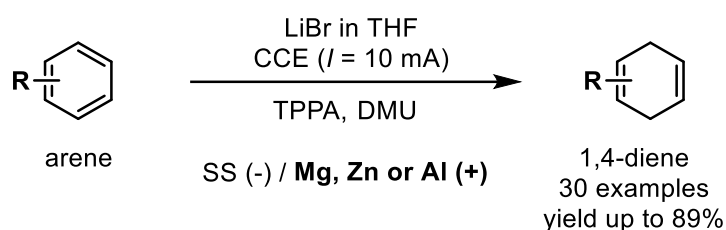
Most electrodes are composed of a single material; however, a support material combined with an electroactive coating, such as Pt and Ag coated on Cu rods, can be alternatively used.

The main requisites of any electrode are stability and corrosion resistance. But, in certain electrochemical transformations, an electrode can be used as sacrificial, undergoing controlled oxidation and dissolving to release metal ions into solution. This strategy offers the opportunity to avoid sacrificial chemical reductants and serves multiple purposes. In the first place, the oxidation of the anode counterbalances the cathodic process, avoiding the competition with solvent oxidation. In addition, the released metal ions can be useful for promoting the desired reaction or for stabilising the given product. A further aspect to consider is that anode oxidation lowers the energetic barrier of the process and serves as the driving force of the reaction, thereby increasing the thermodynamics of the overall transformation.⁴ Easily oxidizable non-noble metals such as magnesium, zinc and aluminium are often used as sacrificial anodes. In this context, in 2019, Baran et al. developed an electrochemical Birch

³ D.M. Heard, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, 59, 18866.

⁴ Y. Li, L. Wen, W. Guo, *Chem. Soc. Rev.*, **2023**, 52, 1168.

reduction.⁵ The original process is a strongly reductive organic transformation to obtain 1,4-dienes starting from aromatic rings (Scheme 1.3). The authors showed that, with electrochemistry, such potent reducing conditions (*i.e.* exploiting solvated electrons as reductants) can be achieved by using the sacrificial anode technique, avoiding harmful reagents.



Scheme 1.3: Electrochemical Birch reduction exploiting sacrificial anode technique. (TPPA = tris(pyrrolidino)phosphoramidate, DMU = 1,3-dimethylurea)

The main types of electrodes can be divided into three main families:

1. Carbon-based electrodes: Graphite and Glassy Carbon (RVC), RVC Foam.
2. Noble metal electrodes: Platinum (Pt), Gold (Au), Silver (Ag).
3. Non-Noble metal electrodes: Zinc (Zn), Magnesium (Mg), Iron (Fe), Nickel (Ni), Nickel Foam (Ni-Foam), Stainless-Steel (SS), Niobium (Nb), Titanium (Ti), Copper (Cu), Cobalt (Co).

- Solvent

Electrolysis is an interfacial process: it can only occur at the interface between the electrode and a conducting solution. Consequently, the choice of solvent is crucial in designing any electrochemical process. Therefore, several factors must be evaluated in order to obtain efficient charge transfer and compatibility with the reaction components:

1. Electrochemical Window:

This defines the range of potentials accessible to an electrochemical system in which the solvent remains stable. It depends on various factors

⁵ B. K. Peters, K. X. Rodriguez, S. H. Reisberg, S.B. Beil, D. P. Hickey, Y. Kawumata, M. Collins, J. Starr, L. Chen, P. S. Baran, *Science* **2019**, 363, 838.

such as temperature, supporting electrolyte, and electrode material. For a given solvent, the window is limited by the potentials at which solvent oxidation or reduction occurs, overriding the desired reactivity in solution. As such, when solvent degradation becomes competitive, it can exceed the reactivity of the substrates, leading to a less efficient process.

2. Dielectric Constant:

This factor influences the solution conductivity by controlling electrolyte dissociation. Solvents with a strong dielectric constant are preferred for efficient ion separation, reducing ohmic drop (resistance) by improving charge transport in the electrochemical system. For this reason, usually, polar solvents are preferred over the less polar ones.

3. Proton Activity:

The intrinsic acidity of a solvent plays an important role in determining its proton activity. An elevated proton activity facilitates the efficient reduction of a species to the relative radical anion, generated at the cathode, through protonation. At the same time, it may suppress the elimination reaction of radical cations formed during anodic oxidation. In a net-oxidative process, the protons may also provide an easy counter-electrode reaction where their reduction to molecular hydrogen acts as a sacrificial cathodic event. Due to its high conductivity, the capacity of stabilizing both radical and cationic species, and strong hydrogen-bond donating ability, hexafluoroisopropanol (HFIP) has recently emerged as a particularly effective solvent for many electrosynthetic oxidative transformations.⁶

Water can serve as a solvent in electrolysis when it is compatible with the intended reaction mechanism. Its high conductivity and environmental compatibility make it attractive; however, it provides limited solubility for numerous organic species, restricting its use in synthetic applications. Moreover, aqueous media become unsuitable when it is important to avoid trace of protons that could interfere with the desired reaction during electrolysis.

⁶ I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 88.

In such cases, the preferred choice would be polar aprotic solvents. Indeed, these media suppress side reactions while offering stability to the electrochemical working system.

Among these solvents, acetonitrile (ACN) stands out as a popular aprotic solvent thanks to its large electrochemical window, making it suitable for both reduction and oxidation processes. It also provides good conductivity in electrolytic solutions and is easily removed during workup. *N,N*-dimethylformamide (DMF) is another excellent solvent for organic electrolysis, given the high solvability of salts, stabilization of transient species and high conductivity; however, at high reaction potentials, it slowly breaks down into dimethylamine or formic acid.

Dimethyl sulfoxide (DMSO) is also a versatile solvent, capable of dissolving a wide range of inorganic and organic compounds. While relatively resistant to oxidation, it can be easily decomposed in cathodic events, limiting its application as a solvent for reductive processes.

Less polar and therefore less conductive solvents, such as nitromethane, ethers or dichloromethane may also be used. However, in these cases, a significant amount of supporting electrolyte is required in order to provide conductivity of the solution.⁷

- Electrolyte

The relationship between current (*I*) and potential (*E*), expressed in voltage (*V*), is governed by resistance (*R*), according to the fundamental principles of electrical circuits. All three parameters are intrinsically connected according to Ohm's Law (Eq. 4).

$$V = R * I$$

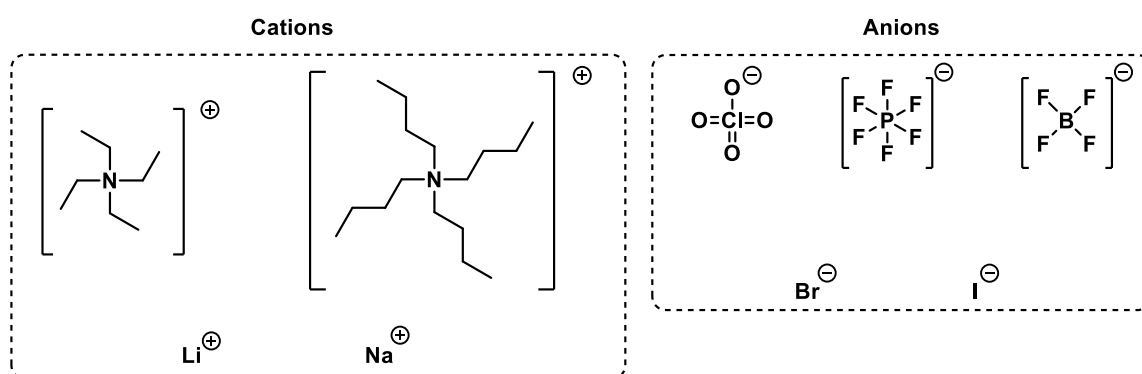
Eq. 4

This relationship demonstrates that the potential across a conductor is directly proportional to the current and inversely proportional to the resistance of the system. In electrochemical reactions, the role of the electrolyte is to decrease resistance and reduce the potential of the system. When selecting an

⁷ M. C. Leech, K. Lam, *Nat Rev Chem.* **2022**, 6, 275.

electrolyte, the most important factor to consider is its solubility. The electrolyte must be soluble in the reaction mixture and remain chemically inert under working conditions, unless a specific reactivity is desired (*vide infra*). If the electrolyte undergoes redox processes under the applied potential, it will limit the availability of electrons for the desired transformation and generate reactive species that can degrade reagents and products. Beyond its role in conductivity, the electrolyte may also serve as a chemical promoter. This effect can be relevant in reactions promoted by Brønsted bases or Lewis acids, which can be introduced as salts and thus act as electrolytes.

The most employed electrolytes are tetra-alkylammonium salts, such as tetra-*N*-butylammonium (TBA), or tetra-*N*-ethylammonium (TEA); alternatively, alkali metal salts can also be used. Halide counterions, such as bromides and chlorides, provide sometimes an inexpensive choice but may also undergo oxidation reactions if the reaction potential is too high. By contrast, non-coordinating counterions like PF_6^- , BF_4^- , and ClO_4^- (Scheme 1.4) are generally considered inert under most electrochemical conditions and are more commonly used. Generally, stoichiometric amounts of electrolyte are required to effectively lower resistance, but this can pose challenges for process purification and negatively affect atomic efficiency. Overall, the selection of electrolytes is crucial in determining the success of an electrochemical reaction, as it influences the solubility, stability, and overall reaction environment.⁸



Scheme 1.4: Most found cations and anions composing an electrolyte.

⁸ C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, 53, 1, 72.

1.1.2 General electrosynthetic processes

As briefly introduced in the previous sections, electrochemical organic reactions rely on the direct use of electrons, as traceless reagents, to promote chemical transformations. Reduction processes occur at the cathode, where electrons are given, while oxidation reactions take place at the anode, where electrons are withdrawn from the substrate. Therefore, the chemical transformation is governed by two half-reactions that are spatially separated, at the respective electrode, but coupled by the external circuit. A general electrosynthetic process (Scheme 1.5) can be described in four steps:

1. Electrochemical cell:

An energy source connects the two electrodes immersed in an electrolytic solution containing both substrates.

2. Potential/Voltage:

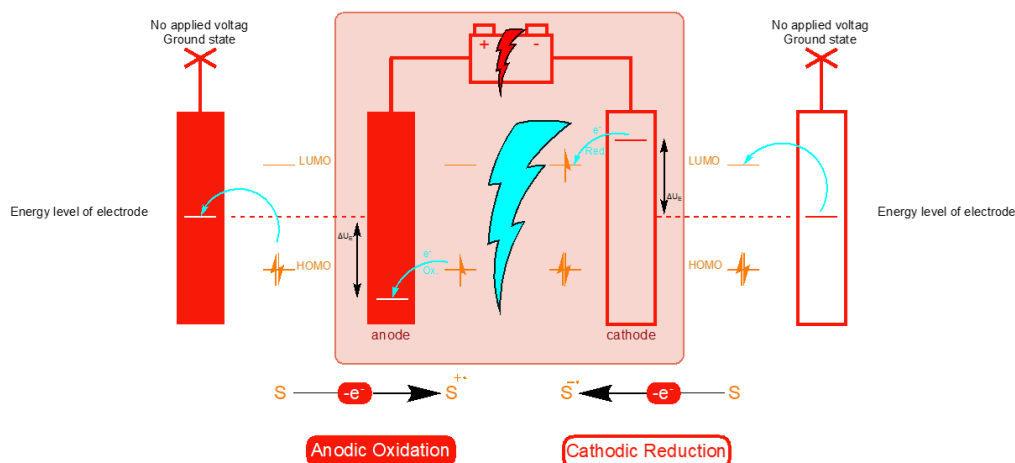
Electrons are transported from the anode (+) to the cathode (-) through a potential difference, enabling their movement between the two electrodes.

3. Current:

The potential difference drives the movement of species, resulting in a specific current intensity.

4. Substrate Ox/Red:

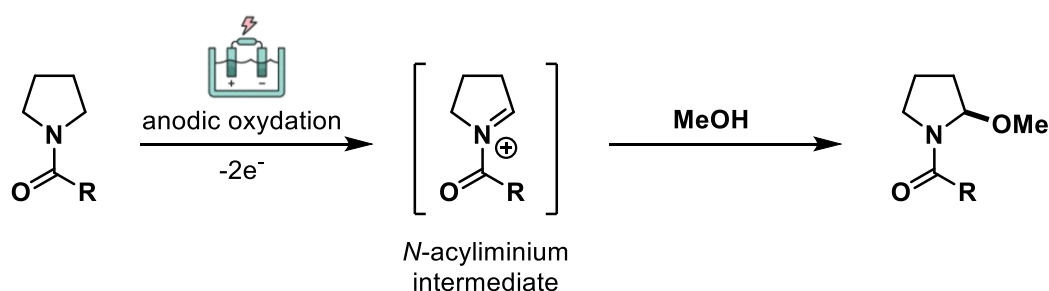
Electrons don't traverse the solution; rather, they oxidize or reduce the reactants present on the surface of the electrodes, completing the electrical circuit.



Scheme 1.5: General electrochemical mechanism for an undivided cell.

1.2 Impact of Electrosynthesis

Electro-organic synthesis can be traced back to the 19th century with Faraday's hydrolysis of acetic acid to hydrocarbons⁹ and Kolbe's electrochemical decarboxylative dimerization.¹⁰ One of the fundamental contributions to electrosynthesis is the work reported by Shono et al. in 1975.¹¹ In this report, the authors studied the anodic oxidation of protected amines-containing substrates, laying the foundation for what later became the Shono oxidation. In this transformation, Shono and co-workers controlled the electrochemical oxidation of amides and carbamates to generate an N-acyliminium intermediate in situ, able to undergo nucleophilic trapping (Scheme 1.6). This process could selectively functionalize the α -position of amides and carbamates under relatively mild conditions, and represents a breakthrough for electrochemistry, as it proves the viability of a method for the C-H activation adjacent to a nitrogen.



Scheme 1.6: Example of Shono oxydation.

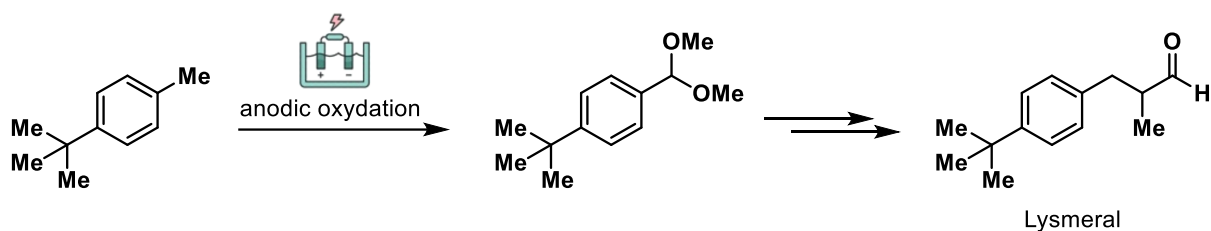
The company BASF is using electro-organic synthesis on an industrial scale. One of their most important electrichemical conversions is to afford protected benzaldehydes.¹² The electrochemical synthesis of this benzaldehyde equivalent is conducted in several 10,000 tons/year. For the production of the further production of Lysmeral, 4-*tert*-butyltoluene is dimethoxylated at a graphite anode (Scheme 1.7). By exploiting electricity, the process avoids classical dissolving-metal methodologies and minimizes waste generation. The potentiostatic electrochemical setup allows precise control over oxidation potential, thereby suppressing the formation of by-products and improving selectivity toward the target.

⁹ M. Faraday, *Ann. Phys.* **1834**, 109, 481.

¹⁰ H. J. Schäfer, *Top. Curr. Chem.* **1990**, 152, 91.

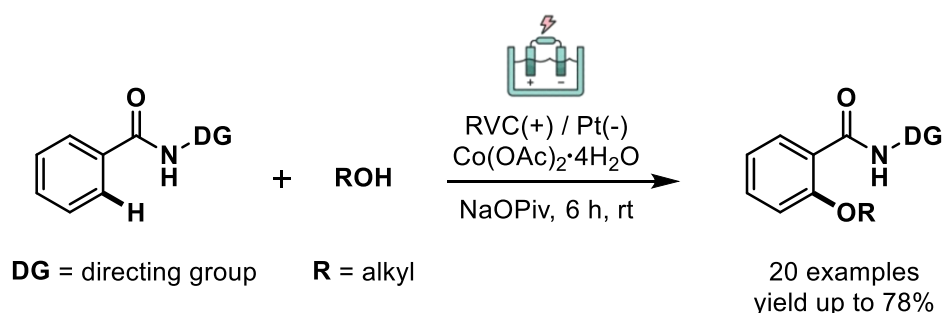
¹¹ A. Ikeda, J. Hayashi, S. Hakoziaki, T. Shono, *J. Am. Chem. Soc.* **1975**, 97, 4261.

¹² D. S. P. Cardoso, B. Šljukić, D. M. F. Santos, C. A. C. Sequeira, *Org. Process Res. Dev.* **2017**, 21, 1213.



Scheme 1.7: Industrial BASF process for the synthesis of Lysmeral.

In the context of academia, electrochemistry and organic research, Ackermann et al., in 2017, reported a major contribution to the field of metalla-electrosynthesis.¹³ In this work, the authors developed a cobalt-catalyzed protocol for the C-H oxygenation of aromatic substrates, without the need for external chemical oxidants (Scheme 1.8). Instead, anodic oxidation is enough to drive the catalytic process. The relative mechanistic investigations support the hypothesis of a catalytic cycle in which cobalt allows C-H activation step, and it is regenerated to the active high-valent cobalt species at the anode, thanks to the oxidation process. This work represents a pivotal contribution in the field of electrosynthesis by demonstrating the possibility of merging transition-metal catalysis and electrochemistry.



Scheme 1.8: Electrochemical Cobalt-Catalyzed C-H Oxygenation.

In the following chapters, four different applications of electrochemistry to organic transformations will be presented and discussed in detail. Both direct electrolysis and catalytic processes will be covered, operating under cathodic or anodic conditions. This work will therefore highlight the versatility and efficiency of electrosynthesis in promoting challenging processes in a selective, high-yielding manner. Moreover, through the implementation of novel methodologies, accessing a previously uncovered reactivity of the molecular scaffolds involved will both contribute to expanding the boundaries of electrosynthesis and of organic transformations.

¹³ N. Sauerman, T. H. Meyer, C. Tiang, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452.

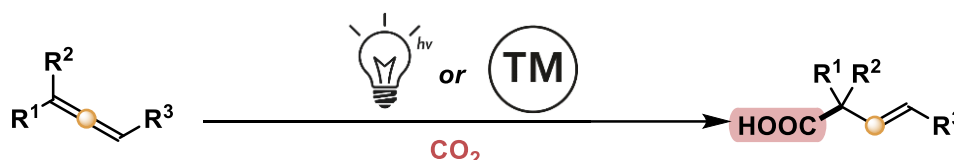
Chapter 2: Electrochemical Synthesis of Itaconic Acid Derivatives via Chemodivergent Single and Double Carboxylation of Allenes with CO₂

All the procedures and results here described are part of- and can be found in-:

- A. Brunetti, M. Garbini, G. Autuori, C. Zanardi, G. Bertuzzi, M. Bandini, "Electrochemical Synthesis of Itaconic Acid Derivatives via Chemodivergent Single and Double Carboxylation of Allenes with CO₂" *Chem. Eur. J.* **2024**, 30, e202401754.

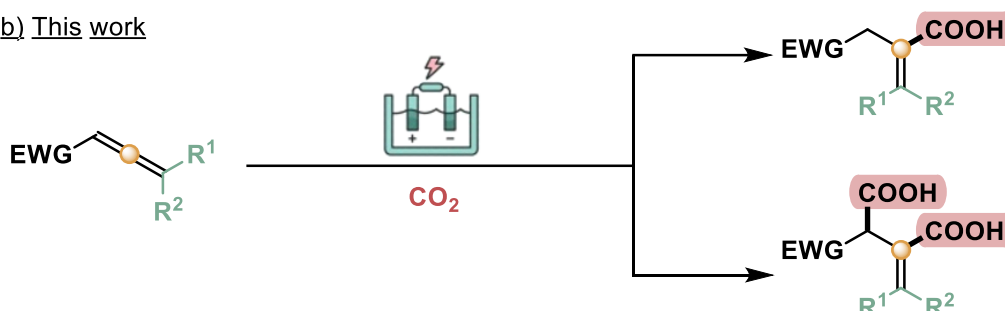
Abstract

a) carboxylation of allyl substrates: previous works



Electron rich allenenes: Carboxylation at C(sp²) carbon

b) This work



A novel electrochemical synthetic approach to non-natural derivatives of itaconic acid derivatives is presented, employing carbon dioxide (CO₂) as a valuable C1 synthon. An electrochemical cross-electrophile coupling between allenates and CO₂ was targeted, enabling the chemodivergent selective synthesis of both mono- and di-carboxylation products in a catalyst- and additive-free environment (yields up to 87%, 30 examples). Further functionalization of the model mono-carboxylation product, together with detailed cyclovoltammetric studies and mechanistic analyses, complete the present investigation.

2.1 Introduction

2.1.1 Carbon Dioxide as a C1 Building Block

Carbon dioxide is an abundant, inexpensive, and non-toxic C1 source, and its utilization as a chemical feedstock represents a central challenge and opportunity in modern chemistry. The continuous combustion of fossil fuels is driving to a relative increment of CO₂ levels in the atmosphere (Figure 2.1), and this has motivated intense research efforts toward the capture and valorization of Carbon Dioxide.¹⁴

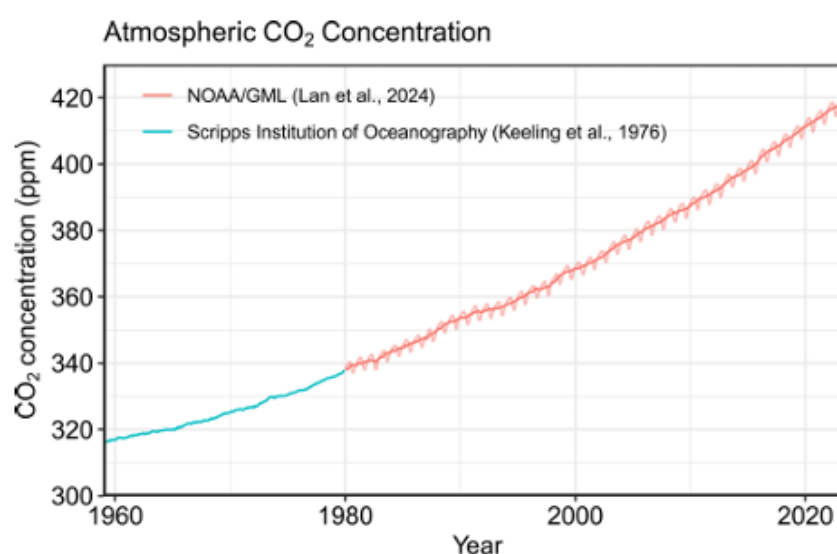


Figure 2.1: Increasing CO₂ levels in the atmosphere over the years.

Transforming CO₂ into value-added chemicals provides access to sustainable synthetic pathways that help close the so-called “fast carbon cycle” (i.e. a rapid exchange of carbon in the atmosphere, oceans, biosphere and surface soils in relatively short time). Despite its appealing features, CO₂ is a thermodynamically stable and kinetically inert molecule, which limits its direct participation in organic transformations. Conventional strategies for CO₂ functionalization often require high pressures, elevated temperatures, or the use of highly reactive organometallic reagents.¹⁵ These constraints inspired the development of new mild strategies for the valorization of CO₂ on long-vector organic scaffolds.¹⁶

¹⁴ J. Zeng et al., *Earth Syst. Sci. Data* **2025**, *17*, 965.

¹⁵ Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933.

¹⁶ I. T. Horváth, P. T. Anastas, *Chemical Reviews* **2007**, *107*, 2167.

2.1.2 Carbon Dioxide Utilization in Industry and Academia

2.1.2.2 Industrial Carbon Dioxide Uses

Nowadays the main industrial applications of CO₂ concern the EOR process (Enhanced Oil Recovery) or its direct mineralization into inorganic carbonates. These two strategies can be generally identified as CCS (Carbon Capture Storage) processes. Otherwise, the synthesis of four main chemicals: urea, polycarbonates, salicylates/cyclic carbonates and methanol are the only industrialized processes using CO₂ on a relevant scale (Tab. 2.1). In the last 15 years few companies have also implemented plants for the synthesis of methanol from by means of CO₂ capturing units. This latter strategy is generally labelled as CCU (Carbon Capture Utilization).

Chemical good	Annual scale production	CO ₂ captured
Urea	150 Mt	112 Mt
Methanol	107 Mt	2 Mt
Cyclic carbonates	80 kt	40 kt
Salicylates	70 kt	30 kt
Total Amount	250 Mt	114 Mt

Table 2.1. Global chemical goods production in which CO₂ is used as a process feedstock.¹⁷

The processes involved in this cycle are mostly photosynthesis, respiration and decomposition, and air-sea gas exchange. In this context (Fig. 2.2), CCS and CCU are included in the CRS (Carbon Removal Strategies) and should be the main drivers of CO₂ abatement in the atmosphere, representing a key step in the transition to an environmentally sustainable circular economy. Data reported in the figure below can give an idea of the magnitude of emissions in the atmosphere.

¹⁷ C. Breyer, M. Fasihi, *Energy Environ. Sci.* **2024**, 17, 3503.

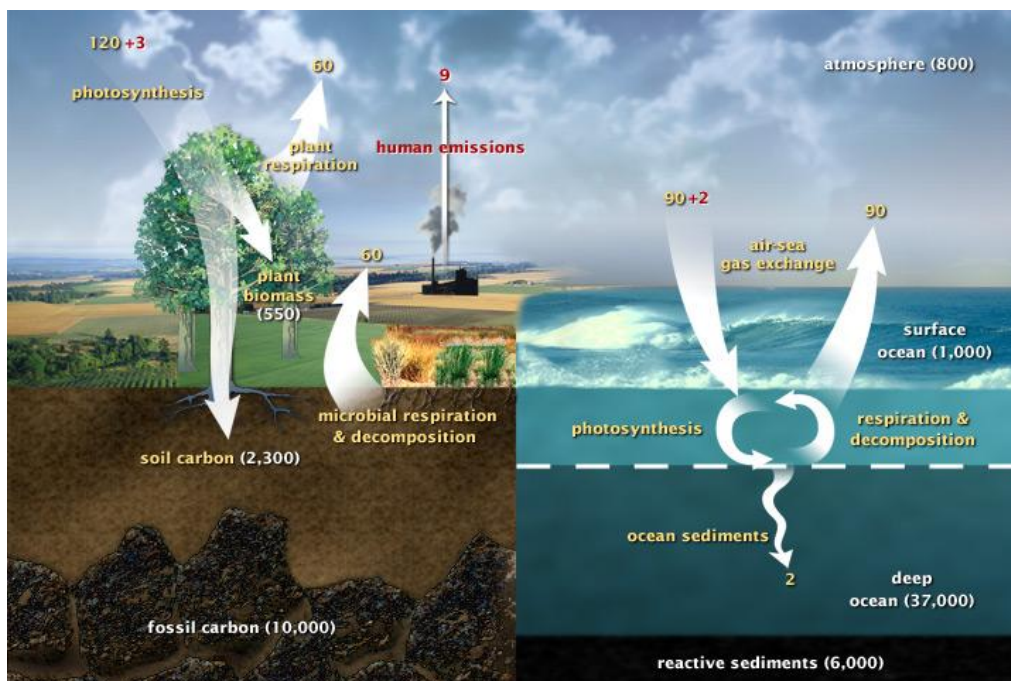


Figure 2.2: Numbers in yellow shows fluxes of carbon in Gt/y between the atmosphere and the land or the oceans. Numbers in red highlight the imbalance created by humankind's activity per year. White numbers show instead the stored amounts of carbon ascribed to the slow carbon cycle.

Urea, as mentioned above, is one of the four main chemicals produced from CO₂ and its synthesis is the only one relying on a carbonylation reaction. The first preparation of urea from carbon dioxide was developed by A. I. Bessarov in 1870 (Scheme 2.1).

Bessarov synthesis



Scheme 2.1: CO₂ based synthesis process from Bessarov still at the base of modern industrial preparation.

Nowadays urea production is estimated to be around 150 million of tonnes yearly, and it is still based on this chemical transformation. Later on, industrial application was appointed firstly in 1922 by Carl Bosch and Wilhelm Meiser. However, efficient plants have only been developed between the '40s and the '60s of the last century.^{18,19}

In stark contrast to urea, methanol production remains largely dependent on fossil fuels, although access to green methanol is seen as one of the next steps in the energy transition. Up to now, only one company worldwide is running a plant for CO₂ to

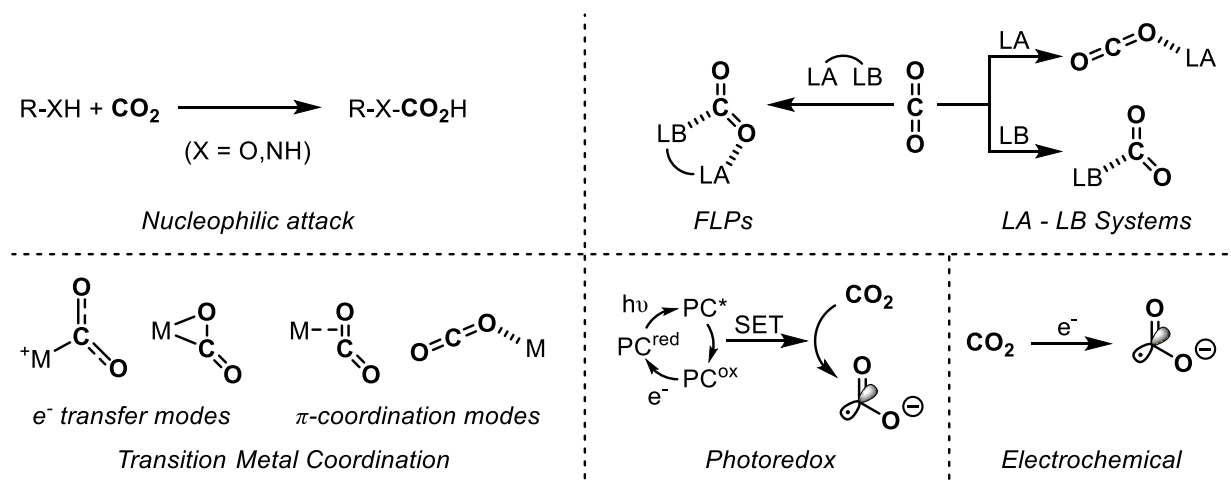
¹⁸ E. A. Werner, *J. Chem. Soc. Trans.* **1920**, 117, 1046.

¹⁹ J. F. T. Berliner, *Industrial & Engineering Chemistry* **1936**, 28, 517.

methanol conversion; nevertheless, the strategic location of such a plant over a geothermal site providing energy for the process is the key for its successful run also in terms of costs. Overall, utilization of CO₂ as a chemical feedstock in the industrial context represents a promising, yet complex feature of the ongoing energy and chemical transition. While successful examples, such as urea and methanol productions, demonstrate the practicability of large-scale CO₂ valorization, other processes remain heavily dependent on fossil-derived resources. The continued advances in catalysis and process efficiency will be fundamental to expand the CO₂ utilization in industrial processes, positioning carbon dioxide as a flexible carbon source for the future.

2.1.2.2 Academic Synthetic Applications of CO₂

Academic research on CO₂ chemistry is a widespread field nowadays. Synthetic utilization of CO₂ has risen a long time ago when chemists envisioned carbon dioxide as versatile C1 synthon, suitable for peripheral functionalization (i.e. carboxylation, carbonylation) or even structural core elaborations (i.e. lactonization) of organic molecules. The early steps undertaken by organic chemists were toward the activation of this inert gas. This was accomplished with the use of stoichiometric strong nucleophiles (i.e. organometallic reagents) in first instance. Then, many other activation strategies emerged and, currently, CO₂ activation methods are largely dominated by catalytic machinery. Carbon dioxide can be activated via several methods: through classical polar chemistry, often associated with capture by nucleophilic heteroatoms (i.e. amines or alcohols), by coordination to Lewis acid or bases (if LA and LB sites are within the same molecule, then the activation method is identified as Frustrated Lewis Pair: FLP), by coordination to a transition-metal center, via photoredox catalysis²⁰ or via electrochemical means (Scheme 2.2). Less common activation methods can indeed involve ionic liquids or carrying CO₂ to supercritical conditions.²¹

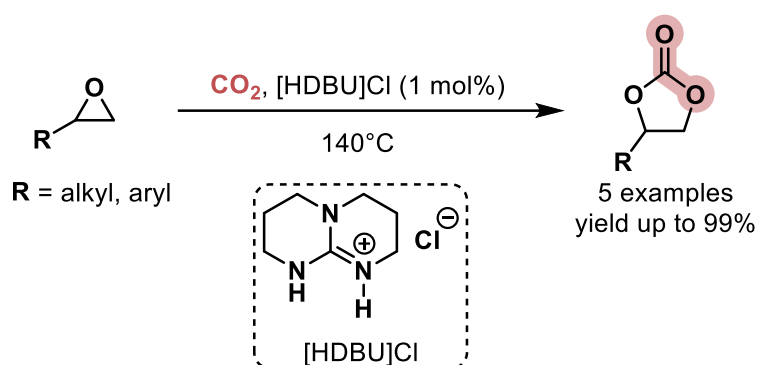


Scheme 2.2: CO₂ activation methods.

²⁰ W. Zhang, Z. Chen, Y. X. Jiang, L. L. Liao, W. Wang, J. H. Ye, Y. Da-Gang, *Nat. Commun.* **2023**, *14*, 3529.

²¹ A. Behr *Angew. Chem. Int. Ed. Engl.* **1988**, *271*, 661.

Regarding polar activation methods of carbon dioxide, an insightful example is provided by the work of Chanfreau et al.²² who developed a process to efficiently catalyze the cycloaddition of CO₂ to epoxides to produce five-membered cyclic carbonates, at low pressure and avoiding the use of solvents or additional additives (Scheme 2.3). The catalytic system consists of Lewis basic ionic liquids, such as 1,8-diazabicyclo[5.4.0]undec-7-enium chloride ([HDBU]⁺Cl⁻) and 1-butyl-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide ([C₄DABCO]⁺OH⁻), able to activate both CO₂ and the epoxide.

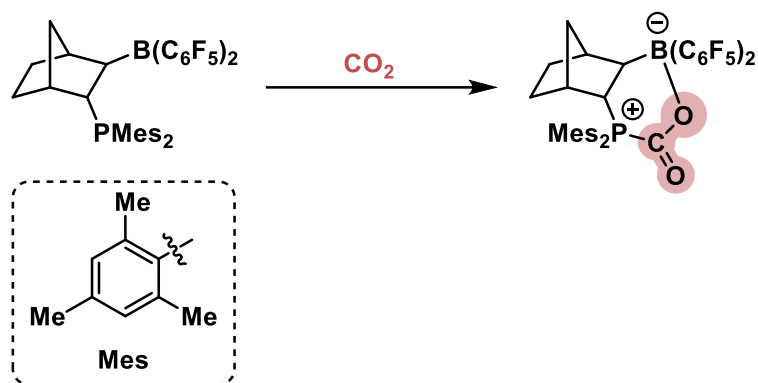


Scheme 2.3: Cycloaddition of CO₂ to epoxides

Species presenting a FLP behaviour present unquenched acidity and basicity on the same molecule, in combination with a sterically hindered Lewis acid and base. This peculiar reactivity is applied to the activation of small molecules such as CO₂. In 2013, Erker et al. worked on the preparation of an FLP in which a phosphine Lewis base (-PMe₂), and a borane Lewis acid (-B(C₆F₅)₂), are positioned at 2-*endo* a 3-*exo* position of the norbornane framework, respectively.²³ This moiety readily reacts with CO₂: the phosphorous LB is added to the carbonyl atom of the CO₂ molecule, and the boron LA is coordinated to an oxygen atom of the same CO₂ framework (Scheme 2.4).

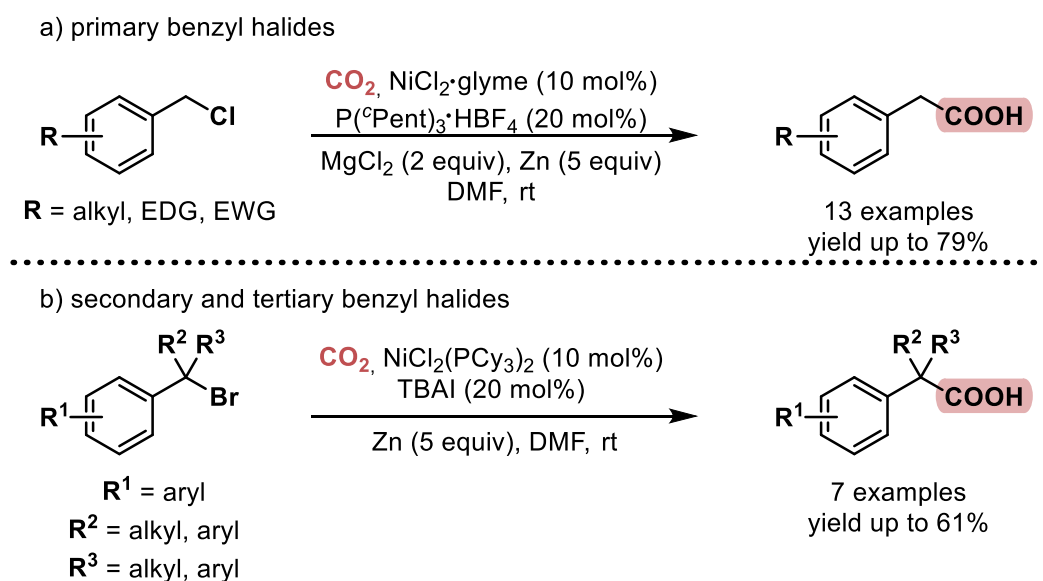
²² Z. Z. Yang, L. N. He, C. X. Miao, S. Chanfreau, *Adv. Synth. Catal.* **2010**, 352, 2233.

²³ M. Sajid, G. Kehr, T. Wiegand, H. Eckert, C. Schwickert, R. Pöttgen, A. P. J. Cardenas, T. H. Warren, R. Frölich, C. G. Daniliuc, G. Erker, *J. Am. Chem. Soc.* **2013**, 135, 8882.



Scheme 2.4: Noninteracting, Vicinal Frustrated P/B-Lewis Pair at the Norbornane Framework

In the field of CO₂ activation by transition-metal catalysis, Martin et al.²⁴ developed a novel nickel-catalyzed direct carboxylation of benzyl halides using CO₂ as the carbon source, to give the corresponding phenylacetic acids (Scheme 2.5). The nickel(0) catalyst can activate the benzyl halide via oxidative addition to form a benzyl-Nickel intermediate. This species can insert CO₂, generating a nickel carboxylate, which after protonation yields the desired product.

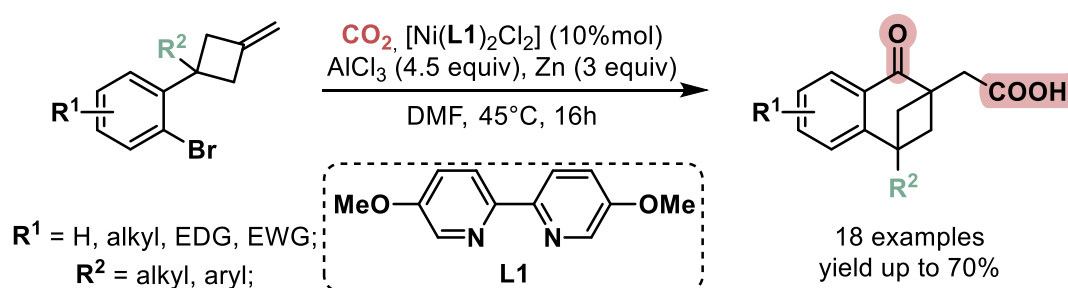


Scheme 2.5: Carboxylation of Benzyl Halides with CO₂.

Besides the preparation of simple carboxylic acids from activated compounds, transition-metal catalyzed reactions with CO₂ can be accompanied by skeletal manipulation of the starting material, prior or in concomitance with the carboxylation

²⁴ T. León, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2013**, 135, 1221.

step. In this regard, Bandini et al.²⁵ developed a new synthetic strategy to build ketones, that combines carbonylation and carboxylation in a single cascade sequence, via double CO₂ fixation (Scheme 2.6). A nickel (Ni) catalyzed cross-electrophile coupling system is used in combination with AlCl₃. The Lewis acid plays a dual role: activating CO₂ and promoting its incorporation at two different stages of the reaction. The cascade is triggered by oxidative addition of the Ni(I) intermediate to generate aryl-Ni(III) species, which after two SET steps (back to Ni(I)) is able to trap the first molecule of CO₂, activated by AlCl₃. At this point, another AlCl₃ coordinates the trapped CO₂ and olefin insertion occurs. After Al-promoted oxygen scavenging, the resulting organo Ni(I) intermediate can now trap a second molecule of CO₂.

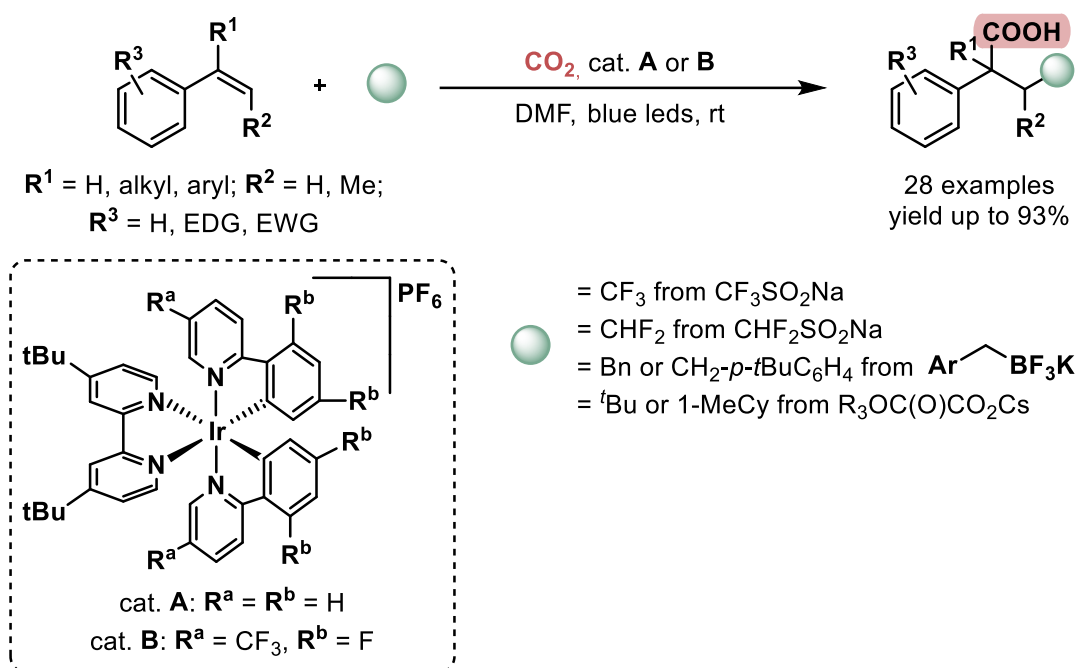


Scheme 2.6: Carbonylation/Carboxylation Sequence via Double CO₂ Incorporation.

The first report of a light-mediated functionalization-carboxylation reaction of olefins was disclosed in 2017 by the Martin group.²⁶ This consists of a catalytic dicarbofunctionalization of styrenes with radical precursors and CO₂, in the presence of an Ir-photocatalyst and blue-light irradiation. This redox-neutral reaction was developed under stoichiometric donor-less conditions or using organic (pseudo) halides, making it complementary to other carboxylation strategies (Scheme 2.7). The process was mainly optimized for a trifluoromethylation-carboxylation reaction towards phenylacetic acids, employing the Langlois reagent (CF₃SO₂Na) as a precursor for the trifluoromethyl radical. The radical intermediate, generated after the reaction of the olefin with the CF₃ radical, can now be reduced to its relative anion. This species is able to trap the molecule of CO₂, leading to the formation of the final product.

²⁵ R. Giovannelli, L. Lombardi, R. Pedrazzani, M. Monari, M. C. Reis, C. S. López, G. Bertuzzi, M. Bandini, *Org. Lett.* **2023**, 25, 6969.

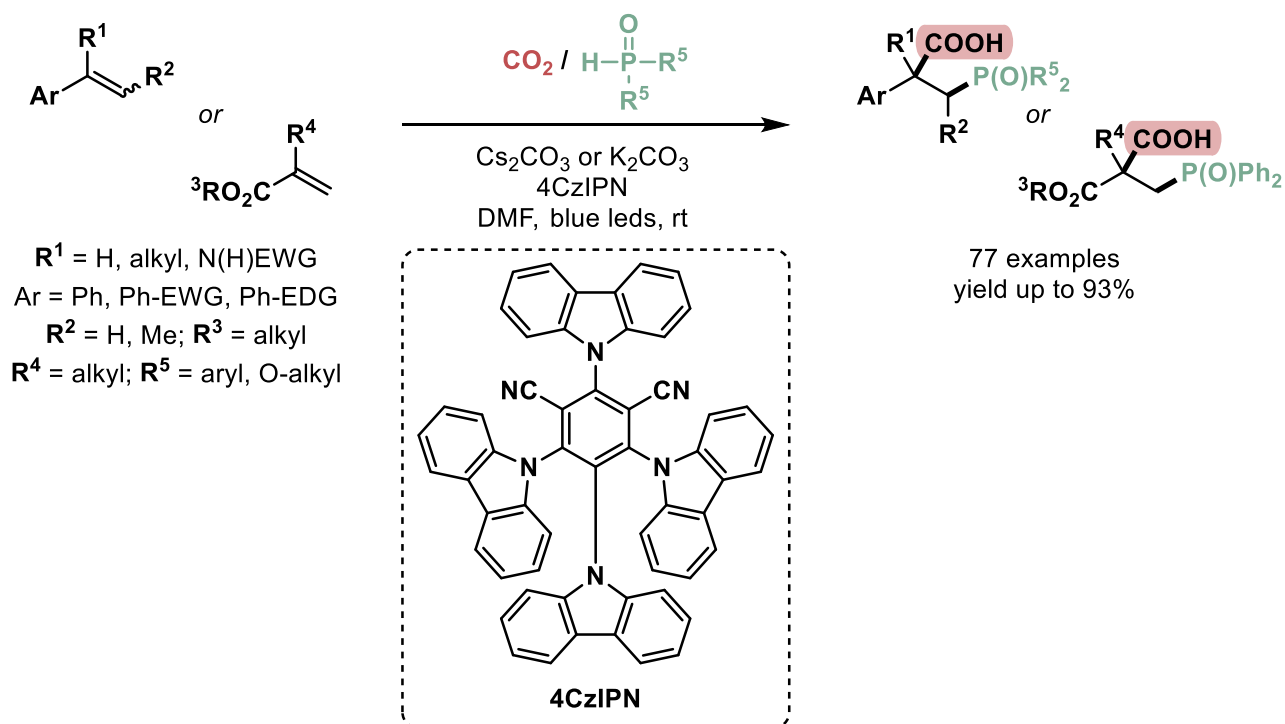
²⁶ V. R. Yatham, Y. Shen, R. Martini, *Angew. Chem. Int. Ed.* **2017**, 56, 10915.



Scheme 2.7: Dicarbofunctionalization of alkenes with CO_2 via visible-light photoredox catalysis.

Yu's interest in light-driven functionalization-carboxylation reactions led to the disclosure of additional protocols. In 2019, they reported a metal-free phosphonocarboxylation of a variety of alkenes with H-P(O) compounds in the presence of an organic photocatalyst (4-CzIPN), blue light irradiation and a base (Scheme 2.8).²⁷ The process ensures high yields over a very large volume of compounds, showing a broad and diversified protocol. In particular, dialkyl and diaryl phosphine oxides as well as phosphites could serve as phosphonylating agents. Moreover, an impressive variety of olefins could productively undergo the desired process: after radical trapping, their respective intermediates are reduced to obtain anions capable of capturing a molecule of CO_2 .

²⁷ Q. Fu, Z. Y. Bo, J. H. Ye, T. Ju, H. Hang, L. L. Liao, Y. Da-Gang, *Nat. Commun.* **2019**, *10*, 3592.



Scheme 2.8: Phosphonocarboxylation of alkenes with CO_2 under metal-free visible light photoredox regime.

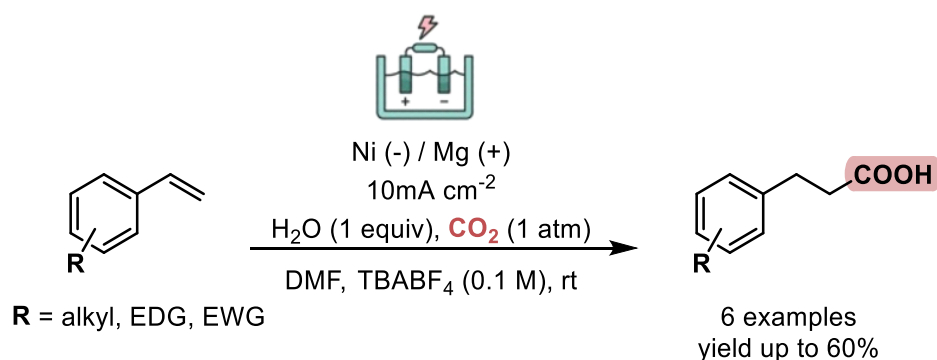
In the context of CO_2 activation and incorporation, electrochemical methods have emerged as a complementary and advantageous platform. These strategies usually allow direct access to the desired reactive intermediates under mild conditions by leveraging single-electron transfer as the driving force of the processes. Carboxylation via electrochemical means typically proceeds through the cathodic reduction of the selected organic substrate, generating radical or anionic species capable of reacting with CO_2 . On the other hand, this strategy can also proceed through the initial CO_2 activation, leading to the CO_2 radical-anion formation which can be trapped by the desired substrate.

From a sustainability perspective, the electrochemical activation of CO_2 offers several advantages. Indeed, the use of electrons as reducing agents prevents the use of other reactants in stoichiometric amounts or metal catalysts, thereby reducing waste generation and lowering process costs.

Moreover, in electrochemical systems, by adjusting the applied current or potential, it is possible to provide different reaction outcomes by tuning the reagents reactivity or to control the lifetime of the reaction intermediates, leading to enhanced selectivity toward the desired product.

Unsaturated substrates, such as alkenes and alkynes, offer attractive platforms for CO₂ incorporation due to their ability to undergo cathodic reduction and form stabilized radical or anionic intermediates. In the case of these substrates, regioselectivity remains a central challenge, as multiple carboxylation sites may be accessible.²⁸ Strategies to control selectivity include substrate design, use of directing groups, and fine-tuning of electrochemical conditions. Recent studies have highlighted the potential of chemodivergent electrocarboxylation, where mono- or dicarboxylated products can be selectively obtained by adjusting the applied charge or potential. These advances underscore the unique capabilities of electrochemical approaches for controlling complex reaction pathways.

In 2020, Nam et al. reported an electrochemical β -selective hydrocarboxylation of styrenes to obtain hydrocinnamic acid derivatives.²⁹ This process exploits the sacrificial anode strategy, employing a magnesium (Mg) electrode as terminal reductant, in order to trap CO₂ in the styrene moiety (Scheme 2.9).



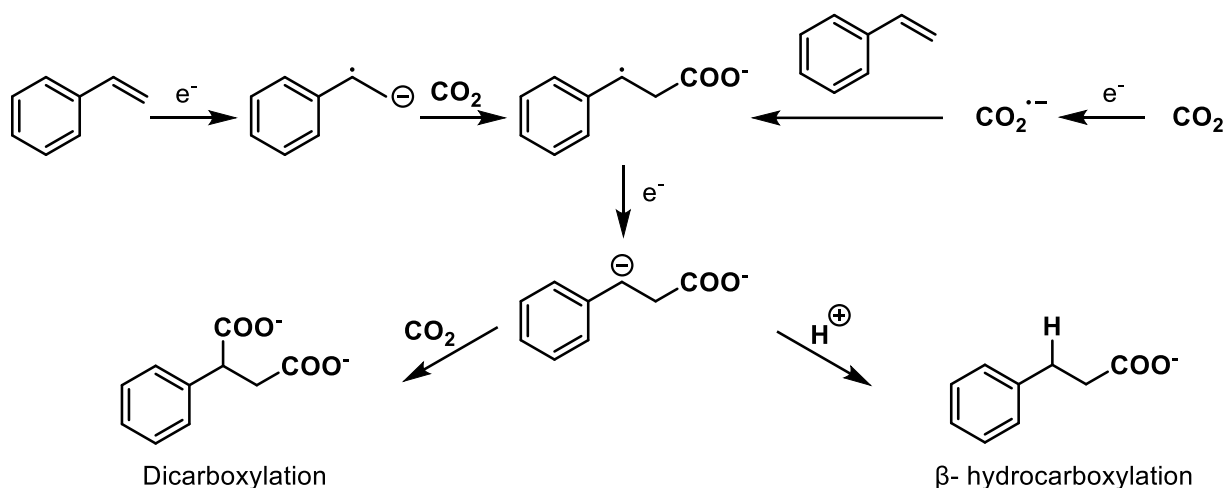
Scheme 2.9: Electrochemical β -Selective Hydrocarboxylation of Styrene Using CO₂ and Water.

The presence of water as a proton source is fundamental to suppress the competing di-carboxylative side reaction.

The proposed mechanistic pathway provides the reduction of styrene or CO₂ to form a β -carboxylate radical anion. This intermediate can be reduced to the respective β -carboxylate anion allowing the protonation step to occur, towards the desired product (Scheme 2.10).

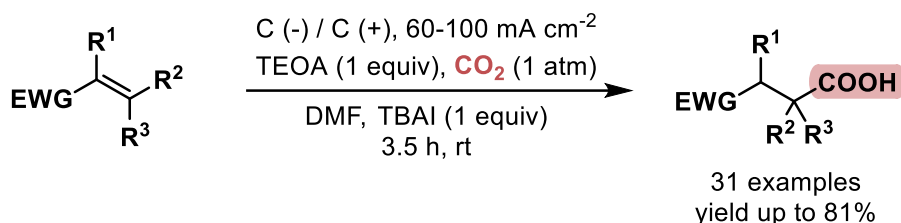
²⁸ Y. You, H. Takano, H. Hayashi, S. Maeda, T. Mita, *J. Am. Chem. Soc.* **2022**, *144*, 3685.

²⁹ Y. Kim, G. D. Park, M. Balamurugan, J. Seo, B. K. Min, K. T. Nam, *Adv. Sci.* **2020**, *7*, 1900137.



Scheme 2.10: Proposed mechanism of the electrochemical carboxylation of styrene.

In 2021, Buckley et al. reported an electrochemical selective hydrocarboxylation of α,β -unsaturated esters, offering a way to synthesize valuable carboxylic acids from simple alkene precursors.³⁰ The strategy of the process is developed around achieving excellent regioselectivity without using a sacrificial anode. In this work, a couple of graphite (C) electrodes is employed and triethanolamine (TEOA) is used as sacrificial reductant (Scheme 2.11).



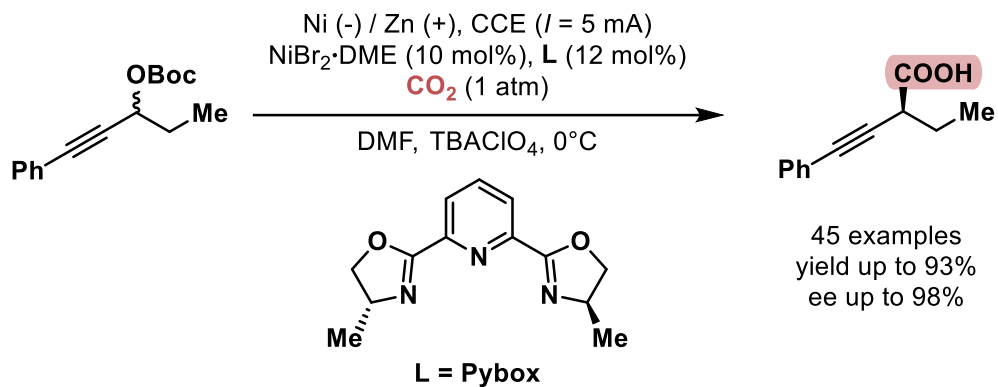
Scheme 2.11: Selective Electrosynthetic Hydrocarboxylation of α,β -Unsaturated Esters.

In 2024, Guo et al. reported a novel nickel-catalyzed electrochemical method to obtain propargylic carboxylic acids in an enantioselective fashion, starting from racemic propargylic carbonates and CO_2 (Scheme 2.12).³¹ The combination of the cathodic reduction and nickel catalysis promotes the transformation of electrophilic allenyl-nickel(II) intermediates into nucleophilic allenyl-nickel(I) species, with the capability of trapping the molecule of CO_2 . Notably, this process can be applied to the asymmetric

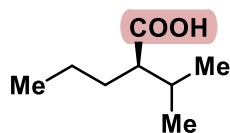
³⁰ A. M. Sheta, A. Alkayal, M. A. Mashaly, S. B. Said, S. S. Elmersy, A. V. Malkov, B. R. Buckley, *Angew. Chem. Int. Ed.* **2021**, 133, 22003.

³¹ Q. Hu, B. Wei, M. Wang, M. Liu, X. W. Chen, C. K. Ran, G. Wang, Z. Chen, H. Li, J. Song, Y. Da-Gang, C. Guo, *J. Am. Chem. Soc.* **2024**, 146, 14864.

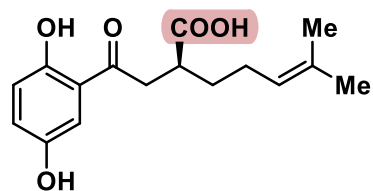
total synthesis of bioactive molecules such as (*S*)-arundic acid, (*R*)-PIA, (*S*)-chizhine D, (*S*)-cochlearin G and (*S,S*)-alexidine.



total syntheses



(*R*)-propylisopropylacetic acid
(*R*)-PIA

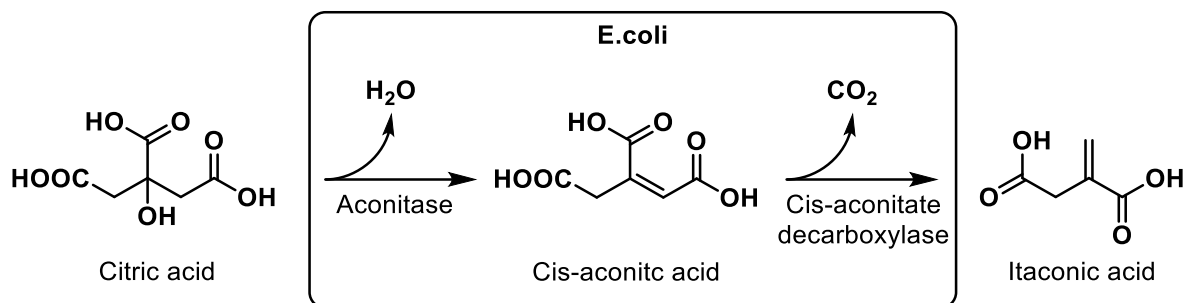


R = H, (*S*)-chizhine D
R = Me, (*S*)-cochlearin G

Scheme 2.12: Enantioselective Nickel-Electrocatalyzed Reductive Propargylic Carboxylation with CO₂.

2.1.3 Itaconic Acid Derivatives

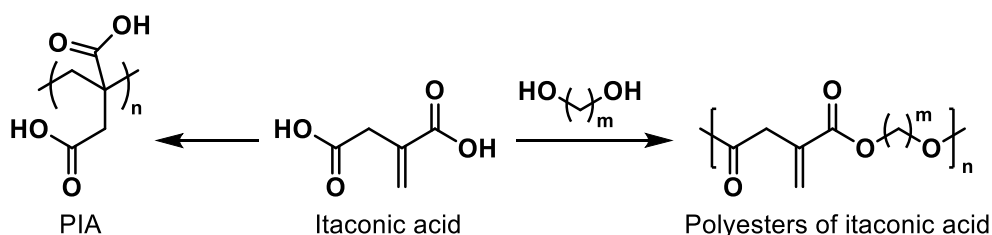
Itaconic acid (2-methylidenebutanedioic acid) is an unsaturated dicarboxylic acid characterized by the presence of a methylene unit conjugated with one of the acid functionalities, and it was first identified by Baup during pyrolytic distillation of citric acid in 1837. It is nowadays produced industrially through either the thermal decomposition of citric acid (Scheme 2.13) or the bio-fermentation of carbohydrates.³²



Scheme 2.13: Example of Itaconic Acid preparation, *Escherichia coli* whole-cell bioconversion strategy.

The chemical structure of Itaconic acid combines two carboxylic acid functionalities and the methylene moiety and it therefore can facilitate the synthesis of advanced polymers (Scheme 2.14) or the generation of essential building blocks such as 3-methyl substituted tetrahydrofuran, γ -butyrolactone, pyrrolidine and pyrrolidone, or even more intricate heterocycles.

As an example, poly(Itaconic acid) (PIA) is a polymer synthesized by radical polymerization of itaconic acid; given its structure, either radical polymerization or formation of a polyester is possible (Scheme 2.14)



Scheme 2.14: Polymerizations of Itaconic acid.

Surprisingly, non-natural derivatives of itaconic acid, bearing substituents on the double bond or the methylene unit remain underexplored in literature, primarily due to the limited availability of general and accessible synthetic methodologies for their

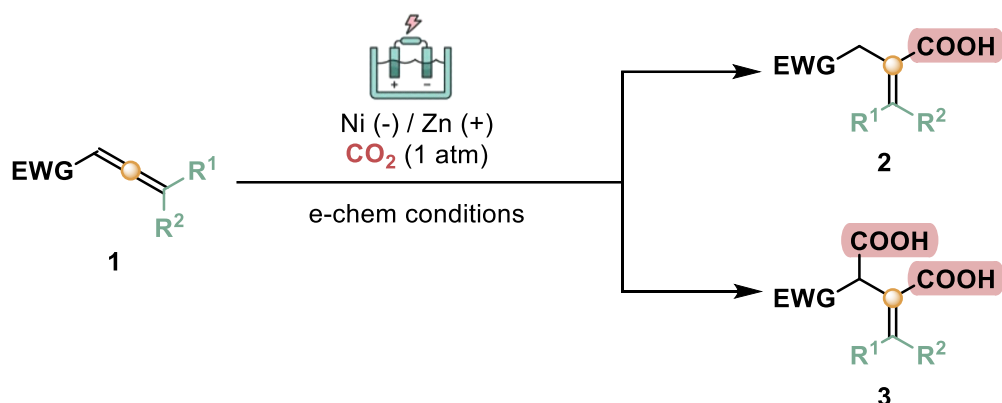
³² J. Becker, C. Wittmann, *Angew. Chem. Int. Ed.* **2015**, 54, 3328.

preparation.³³ Given the structural significance of the -COOH groups in itaconic acid, utilizing CO₂ for the development of a carboxylation protocol to synthesize its derivatives represents an exceptionally appealing strategy.

³³ P. Wang, L. Ling, S. H. Liao, J. B. Zhu, S. R. Wang, Y. X. Li, Y. Tang, **Chem. Eur. J.** 2013, 19, 6766.

2.2 Aim of the work

In continuation with our ongoing exploration into selective radical-based transformations for the electrochemical manipulation of electron-deficient olefins, as well as the synthetic valorization of CO₂,³⁴ we envisioned the possibility of integrating these approaches toward the preparation of structurally valuable itaconic acid derivatives. In this context, allenates³⁵ were identified as suitable and readily accessible starting materials, given their peculiar electronic properties and inherent reactivity under reductive conditions. Importantly, the strategy was studied to focus on a chemodivergent process, allowing selective access to two distinct carboxylated products from a common allenate scaffold (**1**). By exploiting the controlled electrochemical parameters, such as applied charge and current density, we aimed at selectively access the mono (**2**) or the double (**3**) carboxylation pathways (Scheme 2.15).



Scheme 2.15: Proposed strategy for electrochemical allene carboxylation.

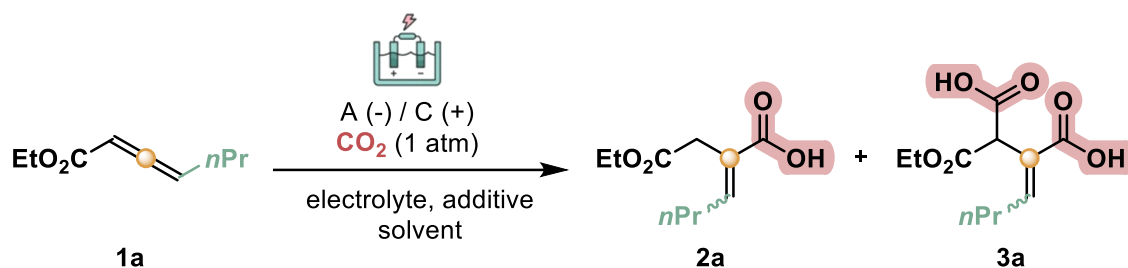
It is important to mention that the products were obtained in a mixture of the *E* and *Z* isomers, whose were not separated. The results are reported with the *E/Z* ratio. Notably, this strategy marks the first attempt to exploit the reactivity of electron-poor allenates in electrochemically mediated carboxylation protocols and can be carried out catalyst- and additive-free.

³⁴ A. Brunetti, G. Bertuzzi, M. Bandini, *Synthesis* **2023**, 55, 3047.

³⁵ W. Zhou, H. Wang, M. Tao, C. Z. Zhu, T. Y. Lin, J. Zhang, *Chem. Sci* **2017**, 8, 4660.

2.3 Results and discussion

2.3.1 Chemodivergent optimization



Scheme 2.16: Optimized reaction.

At the outset of our investigation, we subjected allenolate **1a** (easily prepared in one step from valeroyl chloride) to galvanostatic electrolysis (2.0 mA, 5.0 F/mol_{1a}) under a CO₂ atmosphere (1 atm), in the presence of TEABF₄ as supporting electrolyte (DMF, 0.05 M in **1a**) and using Ni and Zn rods as cathode and anode, respectively. We successfully isolated the mono carboxylation product **2a** in moderate yield (46 %), along with minor amounts of the di-carboxylation product **3a** detected in the crude mixture (Table 2.2, entry 1). We conducted three different reactions increasing applied currents to demonstrate that the desired chemodivergency can be achieved by tuning the electrolytic parameters, (6, 30, and 60 mA, Table 2.2, entries 2-4 respectively) under otherwise identical conditions. We observed a trend in which the increasing preferential formation of product **3a** correlated with increasing current intensity, with a near complete switch in the **2a/3a** product distribution between 2.0 and 60 mA (Table 2.2, entries 1 and 17).

We also tested the possibility to influence the **2a/3a** ratio by using additives. With respect to the reaction run in their absence (Table 2.2, entry 1), the use of Lewis acids (Table 2.2, entry 5), Brønsted acids (Table 2.2, entry 6), inorganic or organic bases (Table 2.2, entries 7 and 8) or water (Table 2.2, entry 9) did not influence the ratio significantly and proved detrimental to the reaction efficiency.

Entry	I (mA) F/mol	Solvent	Electrolyte	C(-) A(+)	Additive	2a/3a ^[b]	Yield (%); <i>E/Z</i> ^[c]
1	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	4.5:1	2a (46; 1.6:1)
2	6.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	1:1.4	3a (36; 1.9:1)
3	30 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	1:2.1	3a (37; 2.1:1)
4	60 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	1:3.4	3a (36; 2.0:1)
5	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	Sc(OTf) ₃ ^[d]	1.3:1	2a (38; 1.4:1)
6	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	AcOH ^[d]	1.1:1	2a (28; 1.6:1)
7	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	Cs ₂ CO ₃ ^[d]	2.5:1	2a (15; 2.5:1)
8	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	TBAOAc ^[d]	2.1:1	2a (41; 1.4:1)
9	2.0 (5.0)	DMF	TEABF ₄	Ni(-) Zn(+)	H ₂ O ^[e]	nd	<5

Table 2.2: Initial screening. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis (CCE, A: anode, C: cathode). ^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography. *E/Z* ratio determined on the isolated product. ^[d] 2.0 equiv. ^[e] 100 equiv.

We then proceeded with dedicated optimizations for each protocol, once we established that mono- or di-carboxylation events can be obtained selectively. We appreciated a remarkable solvent effect during the optimization of the mono-carboxylation methodology: while a switch from DMF to ACN completely suppressed the reactivity (Table 2.3, entry 1), the use of DMSO proved beneficial, increasing both the **2a/3a** ratio and isolated **2a** yield (Table 2.3, entry 2, 64%). This was further improved by running the reaction at 4.0 mA (Table 2.3, entry 3, 87% isolated yield) while maintaining an excellent **2a/3a** ratio (8.8:1).

At an advanced stage of optimization (entry 8 for comparison), we also tested different electrolytes (Table 2.3, entries 4 and 5) and electrodic couples (Table 2.3, entries 6, 7 and 8), leading selectively to mono-acid **2a**, confirming TEABF₄ and Zn(+) || Ni(-) couple as optimal.

Entry	I (mA) F/mol	Solvent	Electrolyte	C(-) A(+)	Additive	2a/3a ^[b]	2a Yield (%); <i>E/Z</i> ^[c]
1	2.0 (5.0)	ACN	TEABF ₄	Ni(-) Zn(+)	none	nd	nd
2	2.0 (5.0)	DMSO	TEABF ₄	Ni(-) Zn(+)	none	8.9:1	64; 1.8:1
3	4.0 (5.0)	DMSO	TEABF ₄	Ni(-) Zn(+)	none	8.8:1	87; 1.7:1
4	4.0 (5.0)	DMSO	TEAI	Ni(-) Zn(+)	none	8.7:1	79; 1.7:1
5	4.0 (5.0)	DMSO	TBAClO ₄	Ni(-) Zn(+)	none	nd	<5%
6	4.0 (5.0)	DMSO	TEABF ₄	C(-) Zn(+)	none	7.0:1	66; 1.7:1
7	4.0 (5.0)	DMSO	TEABF ₄	SS(-) Zn(+)	none	7.2:1	33; 1.6:1
8	4.0 (5.0)	DMSO	TEABF ₄	Ni(-) Mg(+)	none	nd	decomposition

Table 2.3: Mono acid optimization. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis (CCE, A: anode, C: cathode). ^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography. *E/Z* ratio determined on the isolated product.

Concurrently, in the optimization aimed at the selective formation of di-acid **3a**, electrolysis at a current intensity of 60 mA resulted in a drop in the faradic efficiency, with incomplete conversion of starting material and diminished yield in isolated **3a** (Table 2.4, entry 4). Thus, increasing the applied charge (15 F/mol) proved advantageous (Table 2.4, entry 1, 51% yield). Moreover, we proceeded by performing the reaction at lower temperature, with a completely chemoselective outcome being achieved at 0°C (Table 2.4, entry 2, **3a/2a** > 20:1), with a concomitant increase in isolated yield (64%), attributable to the suppression of parasitic pathways. While investigating different solvents, we found DMSO to be incompatible with the high current intensity required for this process (excessive reduction to DMSO, Table 2.4, entry 3), while the use of ACN led to the optimized reaction conditions, resulting in isolated yield of 75% and exclusive formation of the di-acid **3a** (Table 2.4, entry 4).

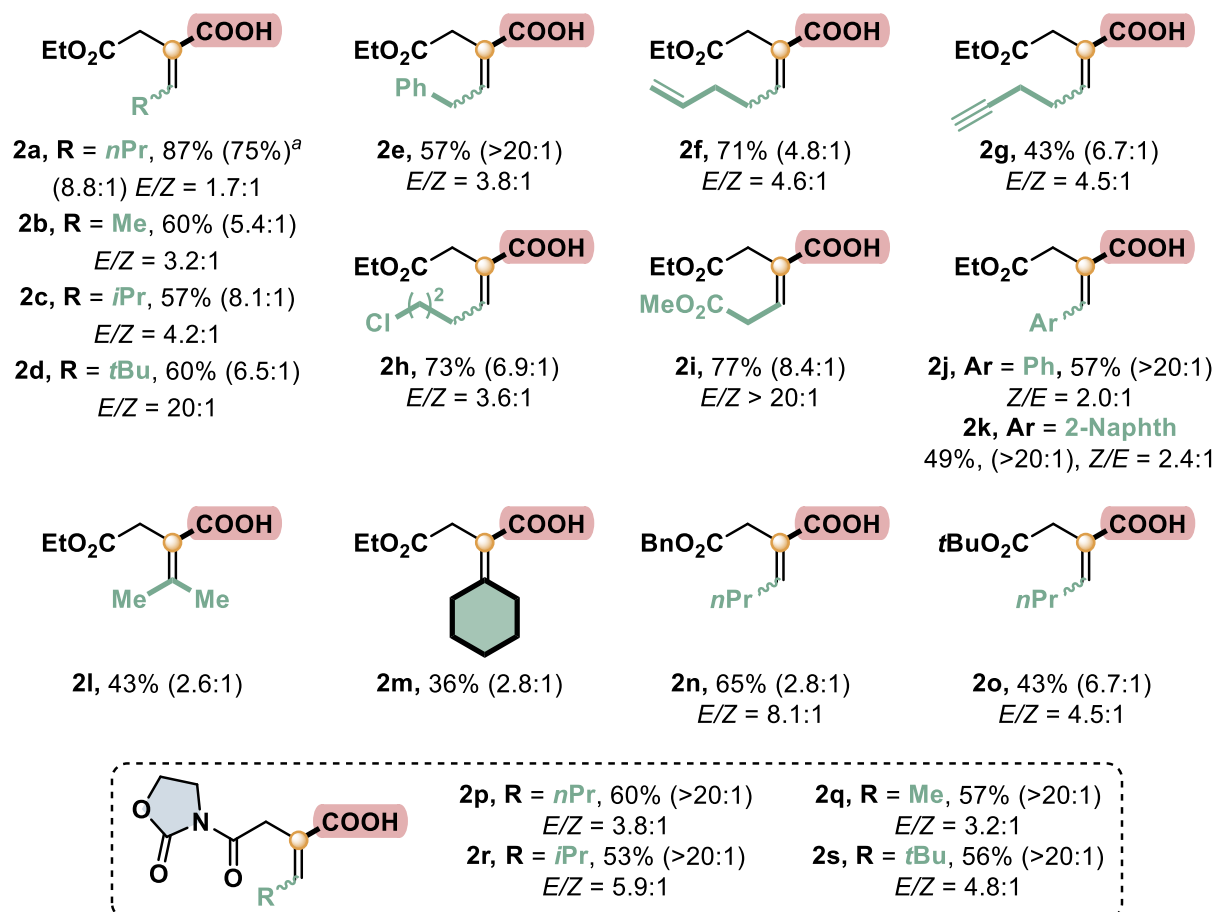
Further screening of electrolytes (Table 2.4, entries 5 and 6) and electrodic materials (Table 2.4, entries 7, 8 and 9) proved not beneficial to the reaction outcomes.

Entry	I (mA) F/mol	Solvent	Electrolyte	C(-) A(+)	Additive	2a/3a ^[b]	3a Yield (%); <i>E/Z</i> ^[c]
1	60 (15.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	1:3.5	51; 2.1:1
2 ^[e]	60 (15.0)	DMF	TEABF ₄	Ni(-) Zn(+)	none	1:20	64; 1.9:1
3	60 (15.0)	DMSO	TEABF ₄	Ni(-) Zn(+)	none	nd	nd
4 ^[e]	60 (15.0)	ACN	TEABF ₄	Ni(-) Zn(+)	none	1:20	75; 2.0:1
5 ^[e]	60 (15.0)	ACN	TEAI	Ni(-) Zn(+)	none	1:20	47; 2.1:1
6 ^[e]	60 (15.0)	ACN	TBAClO ₄	Ni(-) Zn(+)	none	1:20	67; 2.1:1
7 ^[e]	60 (15.0)	ACN	TEABF ₄	C(-) Zn(+)	none	1:20	31; 1.8:1
8 ^[e]	60 (15.0)	ACN	TEABF ₄	SS(-) Zn(+)	none	1:20	18, 2.0:1
9 ^[e]	60 (15.0)	ACN	TEABF ₄	Ni(-) Mg(+)	none	nd	decomposition

Table 2.4: Di-acid optimization. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis (CCE, A: anode, C: cathode). ^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography. *E/Z* ratio determined on the isolated product. ^[d] 2.0 equiv. ^[e] Reaction run at 0 °C.

2.3.2 Generality of the chemodivergent process

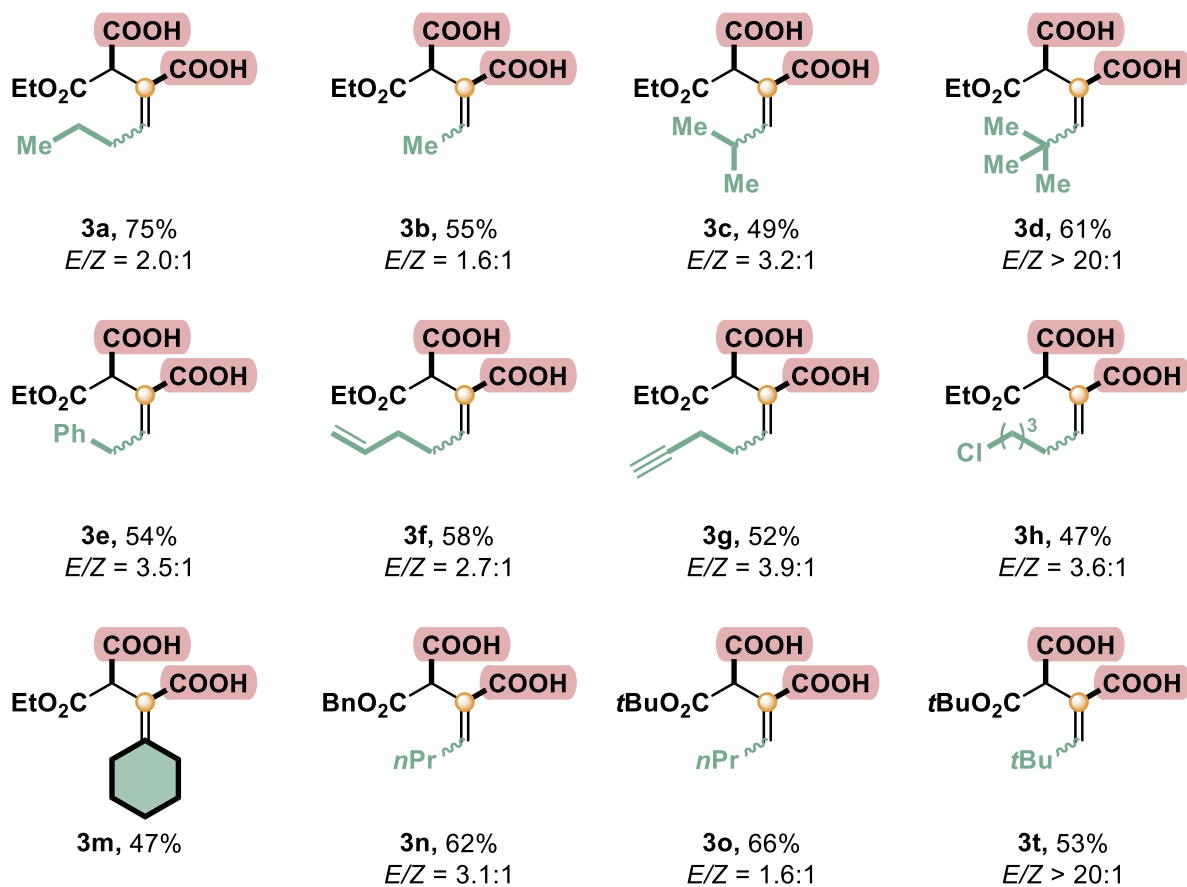
Once the optimized conditions for the chemodivergent carboxylation of allenes **1** were established, we proceeded to evaluate the generality of the reaction (Scheme 2.17). Importantly, efficient chromatographic separation facilitated the isolation of pure products **2** or **3** in all cases, even in the presence of mixtures in the reaction crudes, without separating the *E* and the *Z* isomers. First, employing the mono-carboxylation reaction protocol (Table 2.3, entry 3), we confirmed that steric encumbrance does not hinder the desired reactivity on substrates **1** bearing increasingly bulky substituents (-Me **1b**, -*n*Pr **1a**, -*i*Pr **1c**, and -*t*Bu **1d**), showing good yields and chemoselectivities in all four cases (57–87% yield, 2/3 ratios as low as 5.4:1). Importantly, to ascertain the scalability of the process, the protocol run on a 1.0 mmol scale of **1a** rendered the desired product **2a** in 75% yield. Moreover, the presence of a bulky group such as *t*Bu (**2d**) enhanced the stereoselectivity, favoring the formation of the *E* isomer predominantly. Tolerance towards a benzyl substituent (**2e**) was observed without isomerization of the resulting double bond to a presumably more stable styrenic isomer, demonstrating exquisite chemoselectivity (**2e/3e** > 20:1). Compatibility with various functional groups, including double bonds, triple bonds, alkyl halides, and esters (**2f**, **2g**, **2h**, and **2i**, respectively), was ascertained (43–77% yield, 2/3 ratios as low as 3.6:1). Reactivity of conjugated aromatic allenes (**1j** and **1k**) was confirmed, yielding the respective products **2j** and **2k** in moderate yields (49–57%). Notably, a prevalence of the *Z* isomer formation was observed for these products, alongside exclusive presence of the mono-carboxylation products **2**. Additionally, allenes with double substitution on the terminal carbon (**1l** and **1m**) underwent the desired process, yielding the respective products **2l** and **2m** in moderate yields (36–43 %), likely due to diminished chemoselectivity of the process (2.6:1 and 2.8:1 2/3 ratios, respectively). Finally, variation of the electron-withdrawing group showed tolerance towards different ester substituents (benzyl **2n**, 65% yield, and *t*Bu **2o**, 46% yield), and the introduction of an oxazolidinone unit (**1p–1s**). In particular, for this moiety, exclusive formation of the monocarboxylation products **2** was observed in all cases, alongside tolerance towards various sterically bulky groups on the terminal carbon of the allene moiety (53–60% yield), revealing results comparable to analogous esters (**1a–1d**).



Scheme 2.17: Scope of the reaction: mono carboxylation procedure. ^[a] Reaction run on 1.0 mmol scale.

We then proceeded to assess the generality of the dicarboxylation protocol (Table 2.4, entry 4) on a selection of allenes **1**, previously utilized in the mono-carboxylation process (Scheme 2.18). The exclusive formation of product **3** was consistently observed in all reactions under these conditions. We also confirmed the same level of tolerance exhibited by the previous protocol towards steric hindrance (**3a–3d**, yielding 49–75%) and various functional groups such as benzyls (**3e**, 54% yield), alkenes (**3f**, 58% yield), alkynes (**3g**, 52% yield), and halogens (**3h**, 47% yield). Notably, all these products were isolated with low to moderate *E/Z* ratios (up to 3.9:1), except for bulky allenes **1d** and **1t**, having a *t*Bu-substituted olefin, that delivered the respective products as the *E* isomer exclusively.

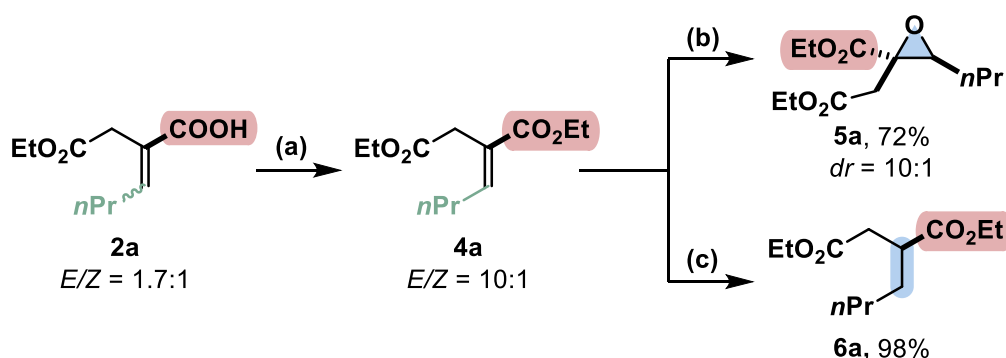
Additionally, triple substitution at the formed double bond (**3m**) and different ester groups (**3n**, **3o** and **3t**) was also tolerated, yielding the respective products in good yields (47-72 %).



Scheme 2.18: Scope of the reaction: dicarboxylation procedure.

2.3.3 Product Transformations

We then subjected the model product **2a** to selected relevant transformations, to demonstrate the synthetic utility of the newly described class of itaconic acid derivatives **2** (Scheme 2.19). Notably, the esterification of the carboxylic acid allowed diastereomeric enrichment of the obtained product **4a** by chromatographic purification (65% yield, *E/Z* = 10:1). The reactivity of the olefinic system of **4a** was then tested by successfully realizing an epoxidation reaction with *m*-CPBA (**5a**, 72% yield, *dr* = 10:1) and a Pd/C catalyzed hydrogenation towards substituted succinate **6a** (98% yield).



Scheme 2.19: Synthetic elaboration of mono-acid. (a) DIC (1.5 equiv), EtOH (5.0 equiv), DMAP (30 mol%), DCM, 0 °C to rt, 18 h. (b) *m*-CPBA (2 equiv), CHCl₃, 65 °C, 18 h. (c) H₂ (balloon), Pd/C (5 mol%), MeOH, rt, 2 h. DIC = *N,N*-5'-diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; *m*-CPBA = metachloroperbenzoic acid.

2.3.4 Mechanistic studies

We then moved to propose a mechanistic rationale for the observed reaction outcomes and the current-dependent chemodivergence. First, a cyclic voltammetric analysis revealed that compound **1a** exhibits two closely spaced reduction processes. The first occurs with a peak at -2.75 V vs Fc/Fc⁺, and a second one occurs at -2.82 V (Figure 2.3). Even if the peak associated with the reduction of CO₂ is centred at more negative potential values (-2.84 V), this electrochemical process seems to require less negative potentials to occur, since the onset potential can be estimated at ca. -2.4 V.

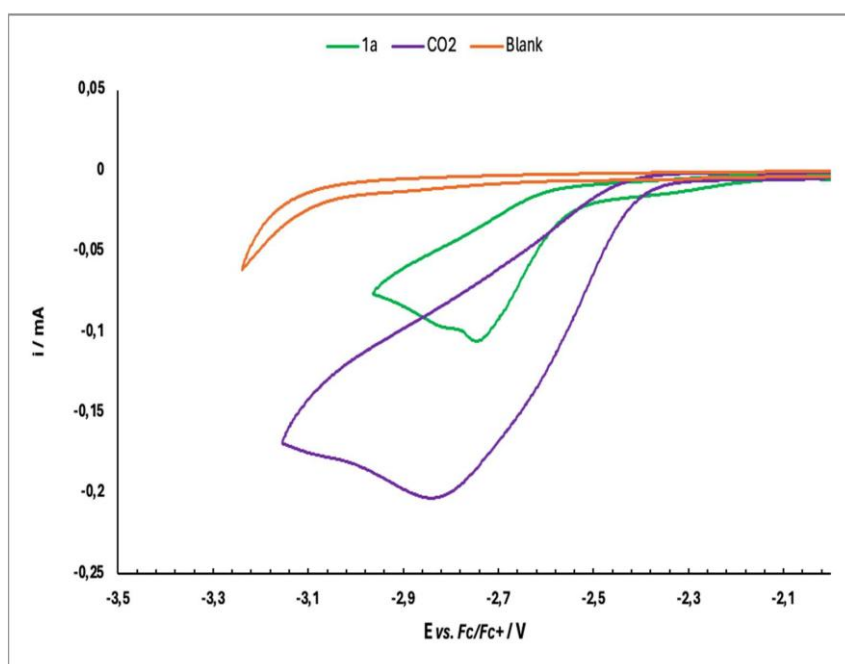


Figure 2.3: CV responses of 5 mM **1a** (grey line) and dissolved CO₂ (purple line) in 0.1 M TEABF₄, anhydrous DMF solution in comparison with the response obtained in the same solution before the addition of electroactive species (orange line). 0.050 Vs⁻¹ potential scan rate. Potentials are reported versus the Fc/Fc⁺ redox couple.

However, as testified by voltammetric traces recorded in an analogous solution of **1a**, the difference in the reduction capability of the two species is not significant, in absence and in presence of CO₂ (Figure 2.4). The addition of small amounts of CO₂ in solution does not affect the onset potential at which the reduction processes start to occur.

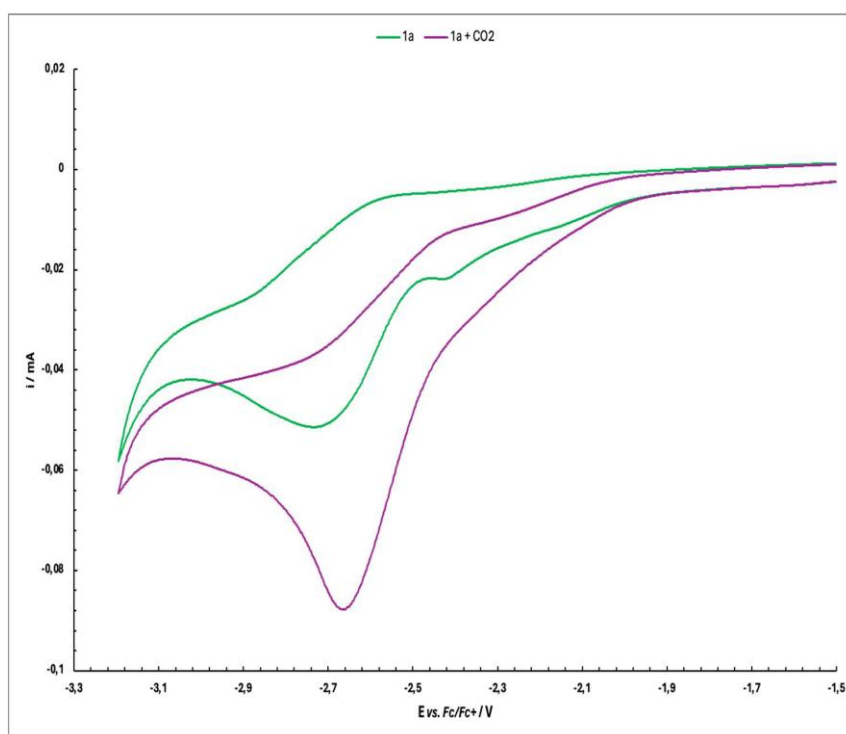
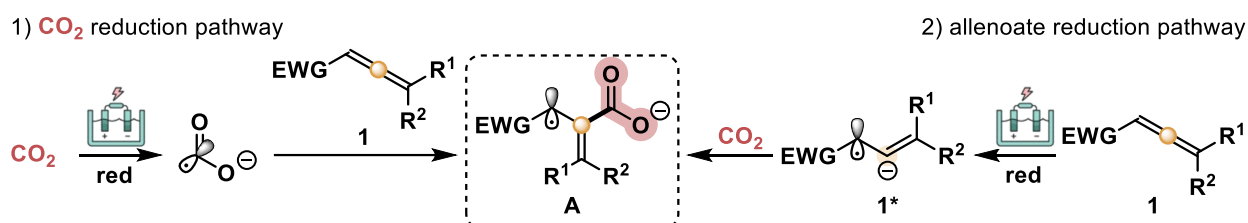


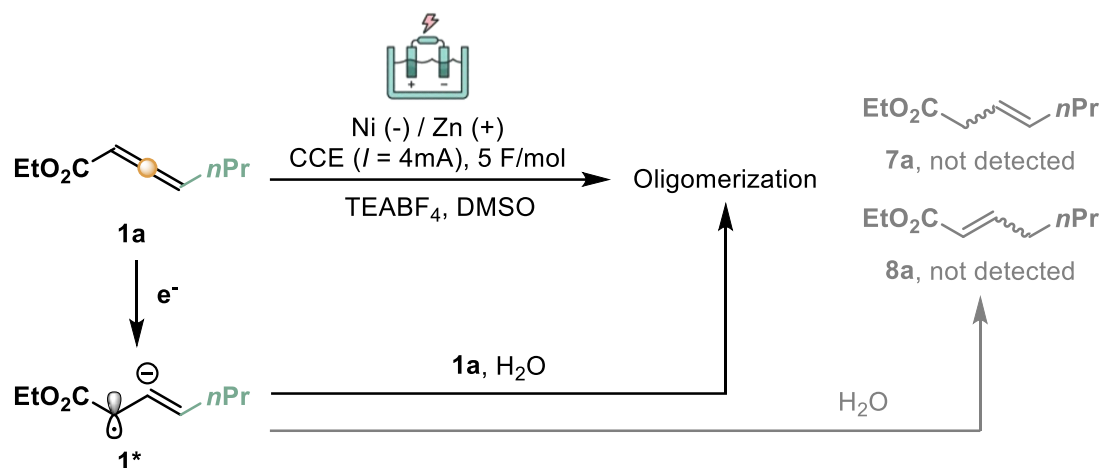
Figure 2.4: CV responses collected in a 5 mM **1a**, 0.1 M TEABF₄, anhydrous DMF solution before (green line) and after (purple line) bubbling CO₂ in solution for 4s. 0.05 Vs-1 potential scan rate. Potentials are reported versus the Fc/Fc⁺ redox couple.

Because of these voltammetric experiments, we can assume that the reduction of the two species can occur simultaneously. Thus, both carboxylation at the C(sp²) site of intermediate **A** and nucleophilic addition of CO₂ radical anion at the electrophilic central C(sp) carbon of **1a** are presumed likely (Scheme 2.20).



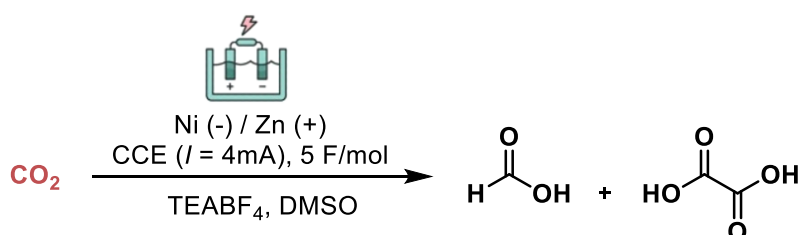
Scheme 2.20: Plausible pathways for the first cathodic event.

In order to discern between the two competing pathways, we further investigated the reactivity profile of **1a** and CO₂ under electrolytic conditions. The method applied to **1a** at the standard conditions (Table 2.2.2, entry 3) in the absence of CO₂, led to the formation of a complex mixture of oligomers (dimers and trimers detected by GC-MS analysis, Scheme 2.21).



Scheme 2.21: Electrolysis of **1a** in absence of CO₂.

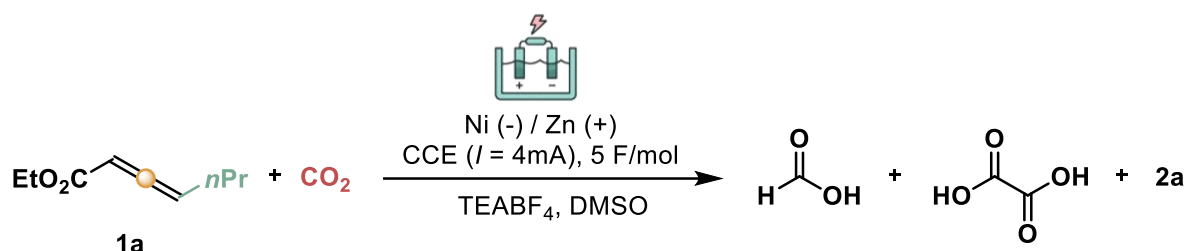
The reactivity of CO₂ under electrolytic conditions was also tested in the absence of **1a** (Scheme 2.22). In the reaction crude, oxalic and formic acid were detected, as reductive dimerization and hydrogenation products respectively, thanks to the analysis conducted by ¹³C NMR spectroscopy.



Scheme 2.22: Electrolysis of CO₂ in absence of **1a**.

We thus analyzed the crude reaction mixture of the standard electrolytic reaction (¹H and ¹³C NMR, Scheme 2.23). Here, the dimerization (and reduction-protonation) products of **1a** and/or CO₂ were detected. This analysis can help in identifying which species is actually the one being predominantly reduced under the applied operational conditions.

This interpretation assumes that if **1a** is the one undergoing first cathodic reduction, this will undergo parasitic oligomerization (and/or reduction-protonation) even in the presence of the reactive coupling partner. The same being said for CO₂.

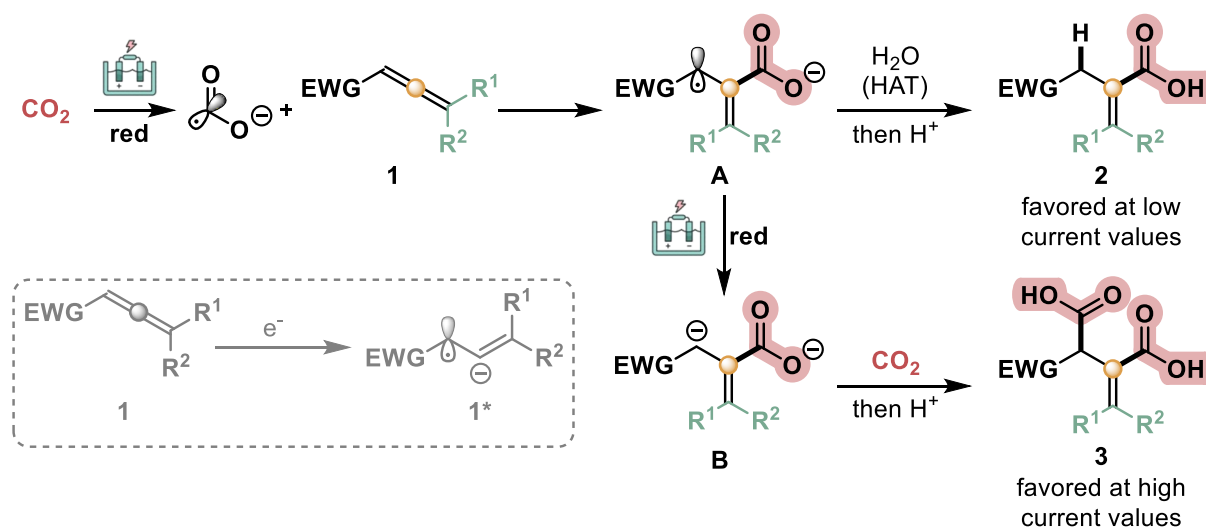


Scheme 2.23: Electrolysis of **1a** and CO₂.

Given the presence of oxalic and formic acid (Scheme 2.23) and the absence of oligomerization products deriving from **1a** (Scheme 2.21) in the crude mixture, it is assumed that CO₂ is the species undergoing predominantly cathodic reduction.

2.3.5 Mechanistic proposal

These experimental results led us to propose that, under the applied reaction conditions, CO₂ is preferentially reduced and subsequently reacted with the electrophilic allenoate **1a**, resulting in the formation of radical anion carboxylate intermediate **A**. This last species is then responsible for the observed chemodivergence, with the reaction outcome being controlled by the electrochemical parameters. We indeed propose that, the successive reduction of **A** to anion **B** and subsequent carboxylation, leads to the formation of dicarboxylic acid **3**. This pathway is therefore supposed to be facilitated at higher current values (and thus, higher voltages, selectivity towards **3** at 60 mA). In contrast, the formation of mono-carboxylated acid **2** is observed when the radical in **A** is quenched prior to further reduction, for instance through Hydrogen-Atom-Transfer (HAT) processes (Scheme 2.24). This pathway is accordingly favored under milder electrochemical conditions (selectivity towards **2** at 4 mA).

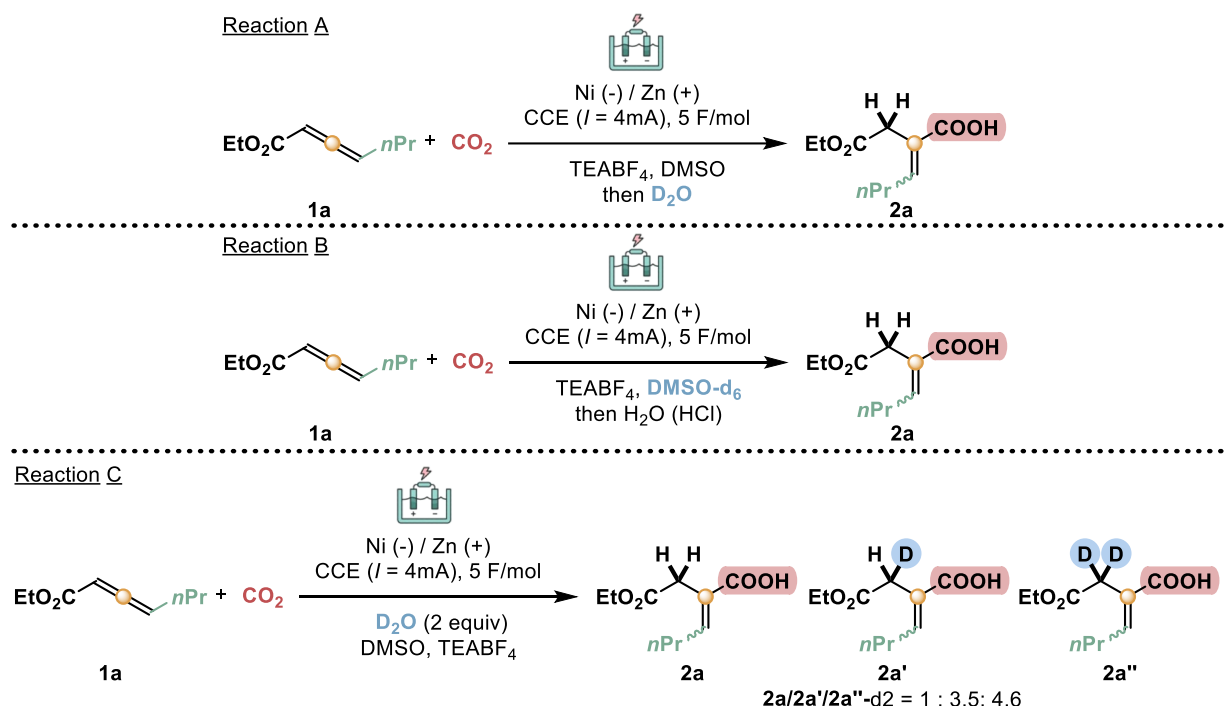


Scheme 2.24: Proposed mechanism for single and double carboxylation of allenes

At this stage, we performed dedicated deuteration experiments to verify the last hypothesis (Scheme 2.25) and in to ascertain the source of the H-atom in mono-acid **2**.

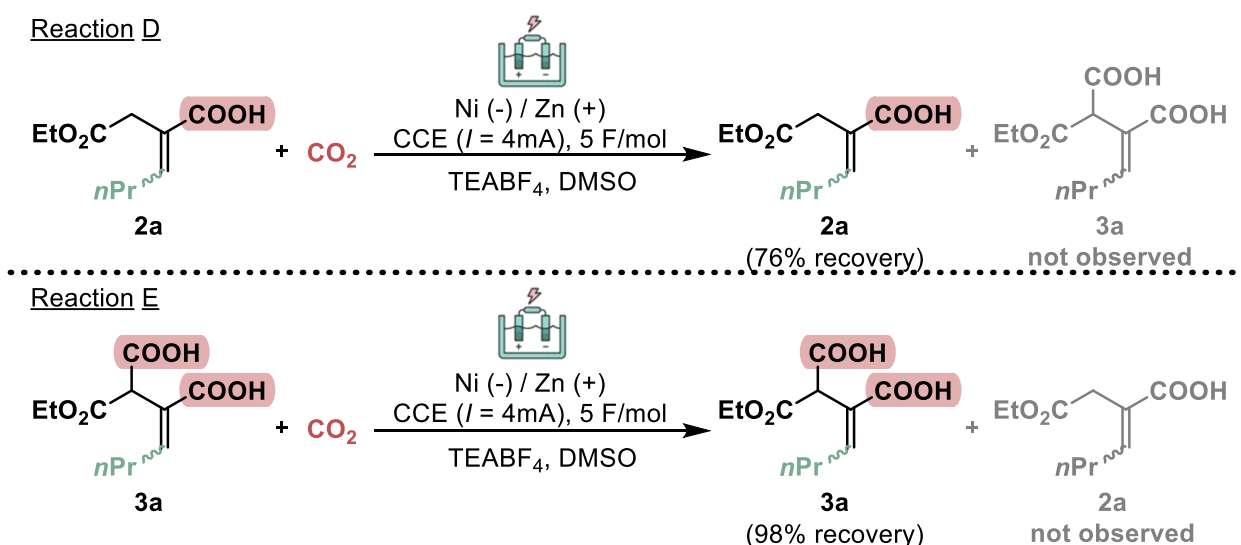
First of all, observing no deuterium incorporation by quenching of the reaction mixture after electrolysis (Reaction A) using D₂O, we excluded the possibility of the formation and survival of dianion **C** in the reaction mixture until the final acidic work-up. Thus, we suggest that traces of H₂O in the reaction solution are indeed responsible for the HAT

step generating **2a** (carboxylate) from **A**, as the reaction run in DMSO-d⁶ showed no deuteration of **2a** (reaction B), while the addition of 2 equivalents of D₂O in the reaction mixture led to 90% deuterium incorporation in **2a** (reaction C).



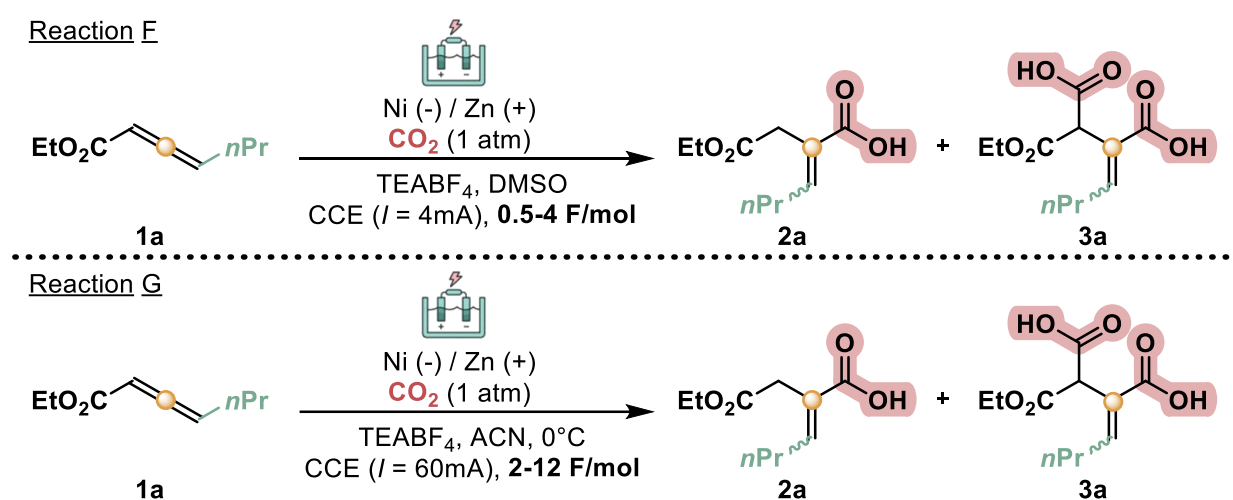
Scheme 2.25: Deuteration experiments.

At last, we envisioned the possibility to have intermediacy of **2a** and **3a** in the double or mono-carboxylation processes. In order to evaluate this hypothesis, we resubjected **2a** and **3a** to the optimal reaction conditions to obtain **3a** and **2a**, respectively (Scheme 2.26).



Scheme 2.26: Re-subjection of **2a** and **3a** to the reaction conditions.

By the results obtained in Reaction D (Scheme 2.26, no formation of product **3a** starting from mono-carboxylate **2a**) it is excluded that product **2a** is an intermediate in the double carboxylation of **1a** towards **3a**, by enolization-carboxylation process. It is also excluded that product **3a** is an intermediate in the mono-carboxylation of **1a** towards **2a**, by decarboxylation reaction, by the results obtained in Reaction E. We also envisioned the possibility of monitoring the two reaction protocols over time, by modulating the quantity of equivalents of electrons (F/mol) given in the reaction, to further confirm or exclude the intermediacy of products **2a** or **3a** in the di- or mono-carboxylation events (Scheme 2.27).



Scheme 2.27: Monitoring the reaction protocols over time.

For the purpose of experimental reproducibility and homogeneity, we chose to perform a different reaction each time and terminate it once the required charge was reached, rather than taking aliquots from a single reaction mixture over time.

This is due to an alteration of the wet surface of the electrodes or, in case of refilling of the solvent, concentration of the reactants, which can lead to poorly reproducible results.

Reaction	F/mol	3a/2a ratio
<u>E</u>	0.5	1:7.9
<u>E</u>	1	1:8.7
<u>E</u>	2	1:8.6
<u>E</u>	3	1:8.8
<u>E</u>	4	1:8.5
<u>G</u>	2	>20:1
<u>G</u>	5	>20:1
<u>G</u>	7	>20:1
<u>G</u>	9	>20:1
<u>G</u>	12	>20:1

Table 2.5: Monitoring the reaction protocols over time.

The possible intermediacy of product **2a** in the double carboxylation pathway, as well as that of product **3a** the mono-carboxylation protocol, was also excluded by observing that the **2a/3a** ratio is not a time (F/mol)-dependent factor in the two selective protocols (Table S2). These observations further support the hypothesis that the chemodivergent process is determined at an earlier stage, prior to the formation of product **2a**, and it emerges from competition between radical quenching pathways, such as HAT, and successive reduction.

2.4 Conclusions

In conclusion, a previously unexplored synthetic strategy to valorize CO₂ as C1 synthon, has been developed, enabling the preparation of itaconic acid derivatives, in a chemodivergent manner, from readily available allenolates as convenient chemical platform. This electrochemical process led to the production of both mono-carboxylated (18 examples) and di-carboxylated products (12 examples) in high yields (up to 87%). This synthetic protocol offers new opportunities for targeting densely functionalized carboxylic acids under catalyst- and additive-free conditions. Overall, the synthesis of non-natural itaconic acid derivatives described herein represents a significant advance in sustainable organic synthesis, offering access to valuable chemical space for applications in chemistry and materials science.

2.5 Experimental details

2.5.1 General methods and materials

¹H-NMR spectra were recorded on a Bruker 600 spectrometer (600 MHz). Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, td = triple doublet, dt = double triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz). ¹³C-NMR spectra were recorded on a Bruker 600 spectrometer (150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard. HRMS spectra were obtained with a G2XS QToF mass spectrometer using ESI ionization techniques, as specified case by case. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous solvents, including DMSO, DMF and ACN for the electrochemical processes, were supplied by Merck in Sureseal® bottles and used without any further purification. Compounds **1**^{36,37,38} are known compounds and were synthesized according to the reported literature procedures. Electrochemical characterization of **1a** and CO₂ were performed by cyclic voltammetry (CV). These experiments were carried out with a PGSTAT128N potentiostat driven by a Nova 2.0 software. The voltammetric responses were collected at room temperature in a three-electrode cell under N₂ flux. The working electrode consisted of a 3 mm diameter glassy carbon electrode (Metrohm), the counter electrode was a Pt wire (Metrohm) and an Ag wire was used as the pseudo-reference electrode. The potentials of the working electrode were finally referred to the ferrocene/ferrocenium redox couple ($E_{\text{Fc}^+/\text{Fc}} = +0.40$ V vs. SCE) by adding a few crystals of ferrocene in the solution. The working electrode surface was polished with 1 and 0.3 μm alumina and sonicated in deionized water for 5 min before the use. The electrochemical experiments were recorded by dissolving the compound under investigation in a 0.1 M tetraethylammonium tetrafluoroborate (TEABF₄) anhydrous DMF solution. Below the general procedures the characterization of the model compound only is reported. For the complete

³⁶ J. Sun, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 4568.

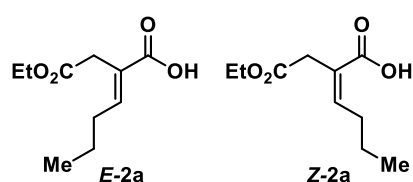
³⁷ A. Parodi, S. Battaglioli, Y. Liu, M. Monari, M. Marín-Luna, C. Silva-López, M. Bandini, *Chem. Commun.* **2019**, *55*, 9669.

³⁸ L. Rout, A. M. Harned, *Chem. Eur. J.* **2009**, *15*, 12926.

description of all the products reported see the Supporting Information of *Chem. Eur. J.* **2024**, *30*, e202401754.

2.5.2 General procedure for the electrochemical monocarboxylation of allenes **1**

The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with allene **1** (0.15 mmol), and TEABF₄ (0.30 mmol, 65.1 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ni), was inserted into the mixture, and closed with a rubber septum. The vessel was evacuated and backfilled with CO₂ (balloon) three times, then dry DMSO (3.0 mL) was added, and the mixture was stirred until complete dissolution of the solids occurred. Then, the solution was bubbled with CO₂ (balloon) under stirring for 1 min. The reaction mixture was electrolyzed at room temperature (under CO₂, balloon) at a constant current of 4.0 mA, until a total charge of 0.75 mF (5.0 F/mol₁) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and HCl(aq) (2M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with HCl(aq) (0.1 M, 3 x 10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was finally purified by FC to afford pure products **2**. The *E* configuration of the double bond of the major isomer was attributed by monodimensional NOE-NMR spectra performed on product **2p**.



2a. White solid. FC eluent: *n*-hexane/EtOAc: 7:3 + 1% HCOOH. Yield = 87%, (0.131 mmol, 26.2 mg); *E/Z* = 1.7:1; **2a/3a** = 8.8:1 in the crude mixture, > 20:1 after chromatography. ¹H NMR (600 MHz, CDCl₃) δ = 7.04 (t, *J* = 7.6 Hz, 1H *E*-**2a**), 6.13 (t, *J* = 7.4 Hz, 1H *Z*-**2a**), 4.08 (q, *J* = 7.2 Hz, 2H *Z*-**2a**) partially overlapped with 4.07 (q, *J* = 7.1 Hz, 2H *E*-**2a**), 3.27 (s, 2H *E*-**2a**), 3.19 (s, 2H *Z*-**2a**), 2.52 (q, *J* = 7.4 Hz, 2H *Z*-**2a**), 2.13 (q, *J* = 7.5 Hz, 2H *E*-**2a**), 1.50 – 1.37 (m, 2H *E*-**2a** + 2H *Z*-**2a**), 1.18 (t, *J* = 7.1 Hz, 3H *E*-**2a** + 3H *Z*-**2a**), 0.88 (t, *J* = 7.1 Hz, 3H *E*-**2a**) partially overlapped with 0.87 (t, *J* = 7.2 Hz, 3H *Z*-**2a**); ¹³C NMR (150 MHz, CDCl₃) δ = 172.5 (*E*-**2a**), 172.3 (*Z*-**2a**), 171.5 (*Z*-**2a**), 170.7 (*E*-**2a**), 150.6 (*Z*-**2a**), 148.4 (*E*-**2a**), 125.2 (*E*-**2a**), 124.5 (*Z*-**2a**), 60.9 (*E*-**2a**), 60.9 (*Z*-**2a**), 40.0 (*Z*-**2a**), 32.1 (*E*-**2a**), 31.8 (*Z*-

2a), 31.1 (*E*-**2a**), 22.4 (*Z*-**2a**), 21.6 (*E*-**2a**), 14.1 (*E*-**2a**), 14.1 (*Z*-**2a**), 13.8 (*E*-**2a**), 13.8 (*Z*-**2a**); **HRMS (ESI)** *m/z*: [M-H]⁻ calcd. for C₁₀H₁₅O₄ 199.0976; found 199.0985.

Preparation of **2a** on 1.0 mmol scale. The ElectraSyn vial (10 mL), equipped with a stir bar, was charged with allene **1** (1.0 mmol, 154 mg), and TEABF₄ (0.90 mmol, 195 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ni), was inserted into the mixture, and closed with a rubber septum. The vessel was evacuated and backfilled with CO₂ (balloon) three times, then dry DMSO (9.0 mL) was added, and the mixture was stirred until complete dissolution of the solids occurred. Then, the solution was bubbled with CO₂ (balloon) under stirring for 3 minutes. The reaction mixture was electrolyzed (under CO₂, balloon) at a constant current of 4.0 mA, until a total charge of 5.0 mF (5.0 F/mol_{1a}) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (30 mL) and HCl_(aq) (2M, 30 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with HCl_(aq) (0.1 M, 3 x 30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was finally purified by FC (*n*-hexane/EtOAc: 7:3 + 1% HCOOH) to afford **2a** as a white solid (75% yield, 0.75 mmol, 151 mg; *E/Z* = 1.7:1; **2a/3a** = 8.6:1 in the crude mixture, > 20:1 after chromatography).

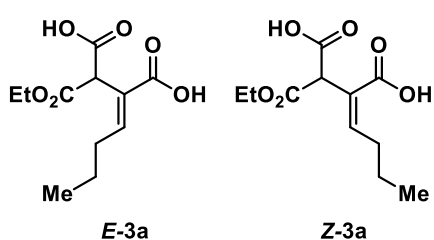
2.5.3 General procedure for the electrochemical double carboxylation of allenes **1**.

The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with allene **1** (0.15 mmol), and TEABF₄ (0.30 mmol, 65.1 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ni), was inserted into the mixture, and closed with a rubber septum. The vessel was evacuated and backfilled with CO₂ (balloon) three times, then dry ACN (3.0 mL) was added, and the mixture was stirred until complete dissolution of the solids occurred. Then, the solution was bubbled with CO₂ (balloon) under stirring for 1 min. The reaction mixture was cooled to 0 °C and electrolyzed at the same temperature (under CO₂, balloon) at a constant current of 60.0 mA, until a total charge of 2.25 mF (15.0 F/mol₁) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and HCl_(aq) (2M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The

combined organic layers were washed with $\text{HCl}_{(\text{aq})}$ (0.1 M, 3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was finally purified by FC to afford pure products **3**.

Additional notes:

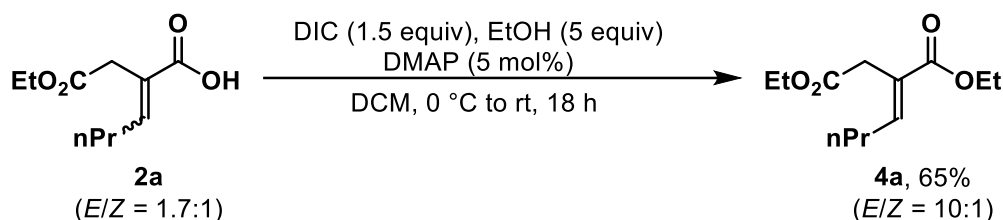
In some cases, cyanoacetic acid, formed from the carboxylation of ACN, may co-elute with the desired product from the FC. In this case, the impure mixture can be easily purified by dissolving it in a small amount of EtOAc (2-3 mL) and performing repeated washings with de-ionized water (4x10 mL).



3a. Colourless sticky oil. FC eluent: *n*-hexane/EtOAc: 7:3 + 1% HCOOH . Yield = 75%, (0.093 mmol, 22.7 mg); *E/Z* = 2.0:1; **3a/2a** > 20:1 in the crude mixture, > 20:1 after chromatography. ^1H NMR (600 MHz, CDCl_3) δ = 10.57 (bs, 2H **E-3a** + 2H **Z-3a**), 7.16 (t, J = 7.7 Hz, 1H **E-3a**), 6.32 (t, J = 7.4 Hz, 1H **Z-3a**), 4.41 (s, 1H **E-3a**), 4.26 (s, 1H **Z-3a**), 4.23 – 4.14 (m, 2H **E-3a** + 2H **Z-3a**), 2.58 (qd, J = 7.4, 1.8 Hz, 2H **Z-3a**), 2.19 (ddt, J = 16.7, 15.1, 7.5 Hz, 2H **E-3a**), 1.54 – 1.41 (m, 2H **E-3a** + 2H **Z-3a**), 1.20 (t, J = 7.1 Hz, 3H **E-3a**) partially overlapped with 1.19 (t, J = 7.0 Hz, 3H **Z-3a**), 0.89 (t, J = 7.4 Hz, 3H **E-3a**) partially overlapped with 0.88 (t, J = 7.7 Hz, 3H **Z-3a**); ^{13}C NMR (150 MHz, CDCl_3) δ = 172.1 (**Z-3a**), 171.3 (**E-3a**), 171.3 (**Z-3a**), 170.3 (**E-3a**), 169.9 (**E-3a**), 169.1 (**Z-3a**), 153.2 (**Z-3a**), 150.8 (**E-3a**), 125.3 (**E-3a**), 124.2 (**Z-3a**), 62.8 (**E-3a**), 62.5 (**Z-3a**), 55.5 (**Z-3a**), 48.4 (**E-3a**), 31.9 (**Z-3a**), 31.4 (**E-3a**), 22.2 (**Z-3a**), 21.5 (**E-3a**), 13.9 (**Z-3a**), 13.8 (**E-3a**), 13.8 (**E-3a**), 13.7 (**Z-3a**); HRMS (ESI) m/z : $[\text{M-H}]^-$ calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_6$ 243.0874; found 243.0881.

2.5.4 Elaborations of compound 2a

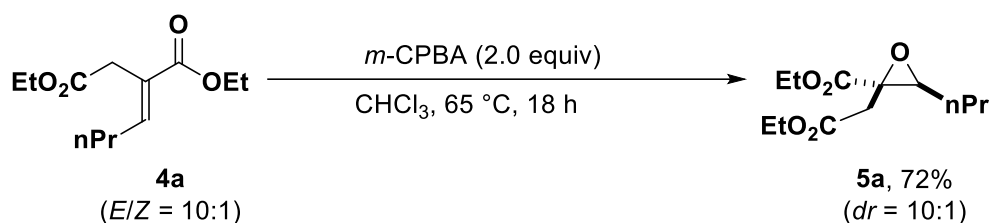
2.5.4.1 Preparation and characterization of diester 4a.



In heat-gun dried Schlenk flask equipped with a stir bar and under N₂ atmosphere, compound **2a** (0.5 mmol, 100 mg), DMAP (0.17 mmol, 20.1 mg) and EtOH (2.5 mmol, 115 mg, 148 μ L) were dissolved in dry DCM (3 mL). The resulting mixture was cooled to 0 °C and subsequently DIC (0.75 mmol, 94.5 mg, 117 μ L) was added dropwise. The mixture was stirred at 0 °C for 30 min and at room temperature for 18 h, then it was directly purified by FC on silica gel (*n*-hexane/EtOAc: 15:1) to afford **4a** as a colorless oil (0.33 mmol, 74.1 mg, 65% yield, *E/Z* = 10:1, partial separation of the *E* and *Z* isomers was achieved by chromatography).

¹H NMR (600 MHz, CDCl₃) δ = 6.95 (t, *J* = 7.6 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 2H), 2.16 (q, *J* = 7.5 Hz, 2H), 1.49 (h, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H) only the peaks relative to the *E* isomer are given; **¹³C NMR** (150 MHz, CDCl₃) δ = 171.0, 167.0, 145.4, 125.8, 60.8, 60.7, 32.4, 30.9, 21.8, 14.2, 14.2, 13.9; **HRMS (ESI)** *m/z*: [M+Na]⁺ calcd. for C₁₂H₂₀O₄Na 251.1254; found 251.1261.

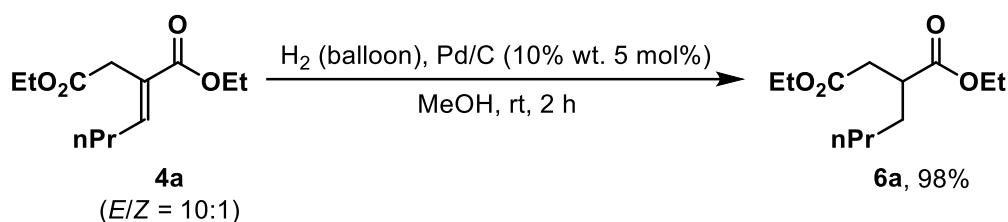
2.5.4.2 Preparation and characterization of epoxide 5a.



In a 4-mL screw-capped vial equipped with a stir bar, compound **4a** (0.1 mmol, 22.8 mg) and *m*-CPBA (0.2 mmol, 47.9 mg, 72% wt.) were dissolved in CHCl₃ (1.5 mL). The resulting mixture was stirred at 65 °C for 18 h, then it was cooled at room temperature and directly purified by FC on silica gel (*n*-hexane/EtOAc: 7:1) to afford **5a** as a colorless oil (0.072 mmol, 17.6 mg, 72% yield, *dr* = 10:1).

¹H NMR (600 MHz, CDCl₃) δ = 4.26 – 4.14 (m, 4H), 3.26 (dd, *J* = 7.2, 4.7 Hz, 1H), 2.98 (d, *J* = 17.2 Hz, 1H), 2.76 (d, *J* = 17.1 Hz, 1H), 1.71 – 1.63 (m, 1H), 1.59 – 1.43 (m, 3H), 1.28 (t, *J* = 7.3 Hz, 3H) partially overlapped with (1.27 t, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H) only the peaks relative to the major isomer are given; **¹³C NMR** (150 MHz, CDCl₃) δ = 170.3, 169.6, 62.0, 61.9, 61.0, 57.6, 34.4, 30.4, 19.7, 14.1, 14.1, 13.9; **HRMS (ESI)** *m/z*: [M+Na]⁺ calcd. for C₁₂H₂₀O₅Na 267.1203; found 267.1195.

2.5.4.3 Preparation and characterization of diethyl 2-butylsuccinate **6a**.



In a 10-mL round-bottom flask equipped with a stir bar, compound **4a** (0.1 mmol, 22.8 mg) and Pd/C (0.005 mmol, 5.3 mg, 10% wt.) were suspended in MeOH (1.5 mL). The resulting mixture was de-gassed with N₂ (balloon) for 1 min, bubbled with H₂ (balloon) for 1 min and finally stirred at room temperature for 2 h. Then, the suspension was filtered over a Celite pad, washing with DCM (2 x 3 mL) and concentrated *in vacuo* to directly afford pure product **6a** as a colorless oil (0.098 mmol, 22.5 mg, 98% yield).

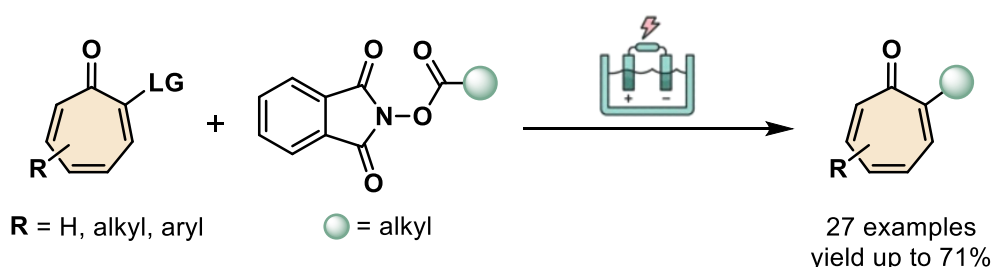
¹H NMR (600 MHz, CDCl₃) δ = 4.21 – 4.07 (m, 4H), 2.86 – 2.78 (m, 1H), 2.69 (dd, *J* = 16.4, 9.3 Hz, 1H), 2.41 (dd, *J* = 16.4, 5.2 Hz, 1H), 1.64 (dq, *J* = 13.4, 7.5 Hz, 1H), 1.50 (ddt, *J* = 13.4, 7.7, 6.5 Hz, 1H), 1.35 – 1.27 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H) partially overlapped with 1.25 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ = 174.1, 171.0, 59.5, 59.5, 40.2, 35.1, 30.6, 28.0, 21.5, 13.2, 13.1, 12.8; **HRMS (ESI)** *m/z*: [M+Na]⁺ calcd. for C₁₂H₂₂O₄Na 253.1410; found 253.1399.

Chapter 3: Electrochemical Site-Selective Alkylation of Tropones via Formal C(sp³)-C(sp²) Coupling Reaction

All the procedures and results here described are part of- and can be found in:-

A. Brunetti, M. Garbini, N. G. Kub, M. Monari, R. Pedrazzani, C. Zanardi, G. Bertuzzi and M. Bandini "Electrochemical Site-Selective Alkylation of Tropones via Formal C(sp³)-C(sp²) Coupling Reaction" *Adv. Synth. Catal.* **2024**, 366, 1965.

Abstract



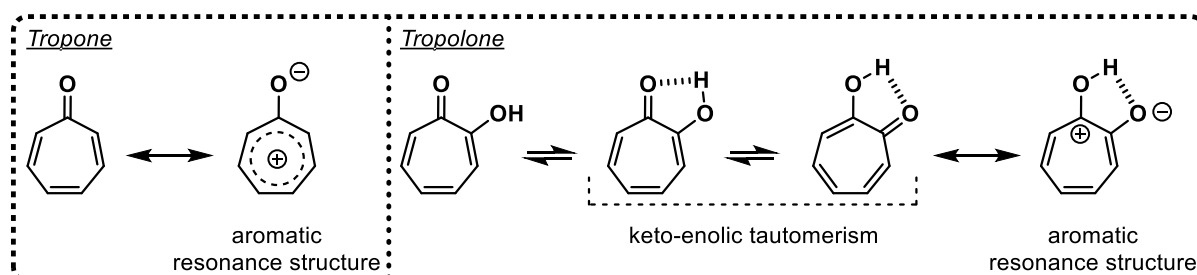
The first site-selective electrochemical alkylation of tropones is realized by reacting 2-acetoxytropones and redox-active-esters (RAEs). The electroreductive protocol enables the preparation of mono- and disubstituted tropones in high yields (up to 71%) under very mild conditions. Dedicated voltammetric measurements were used to identify 2-acetoxytropones as a class of valuable trapping agents of nucleophilic radical species and shed light on the overall mechanistic profile. Wide tolerance towards functional groups (27 examples) and application to late-stage functionalization of a bioactive compound (i. e. Colchicine analogue), emphasize the synthetic impact of the present methodology.

3.1 Introduction

3.1.1 Tropones and Tropolones

3.1.1.1 Structure

Tropones and tropolones constitute a class of seven-membered unsaturated aromatic carbocyclic compounds characterized by the presence of a conjugated carbonyl functionality; in the case of tropolones, this structure presents an additional hydroxyl group located α to the carbonyl moiety. These compounds represent examples of non-benzenoid aromatic systems, as they exhibit aromatic properties even if they don't present a six-membered benzene ring (Scheme 3.1). The aromatic character of tropones and tropolones, indeed, can be accounted for the resonance structures, characterized by a 6π -electron conjugated system, in agreement with Hückel's ($4n + 2$) rule.³⁹ In tropolones, a strong hydrogen bond between the oxygen of the carbonyl and the hydroxyl group enhance the aromatic stabilization (keto-enol tautomerism), improving the π -electron delocalization.



Scheme 3.1: Tropones and Tropolones structural characteristics.

The early study of tropones and tropolones served for the seminal demonstration that aromatic properties are not limited to benzenoid or six-membered ring systems, playing a pivotal role in broadening the conceptual definition of aromaticity.⁴⁰ Aside from their theoretical significance, tropones and tropolones are also considered both for their versatile chemical reactivity as well as studied for their biological interest. The tropolone scaffold is found, indeed, in a wide range of naturally occurring compounds, often associated with elevated biological activity.⁴¹

³⁹ P. L. Pauson, *Chem. Rev.* **1955**, 55, 1.

⁴⁰ W. V. E. Doering, L. H. Knox, *J. Am. Chem. Soc.*, **1954**, 72, 3203.

⁴¹ N. Liu, W. Song, C. M. Schienebeck, M. Zhang, W. Tang, *Tetrahedron* **2014**, 70, 9281.

3.1.1.2 Biological interest

Tropolones and natural products containing a tropolonoid motif are characterized by a unique cyclohepta-2,4,6-trienone moiety. Those scaffolds often display diverse bioactivities, including antimicrobial,⁴² antiviral,⁴³ and antitumor activities.⁴⁴ One of the most studied tropolone-containing metabolite is Colchicine and its related alkaloids, as they are used for the treatment of various diseases, including gouty arthritis. In more recent decades, extensive medical studies have revealed that Colchicine exhibits a wide spectrum of biological activities, such as antimitotic, antifibrotic and anti-inflammatory effects. Nowadays, Colchicine is an approved drug and it is used for the treatment of diseases like gout and scleroderma.⁴⁵ Given its biological relevance and its complex molecular architecture, the total synthesis of Colchicine was targeted by the interests of synthetic organic chemists.

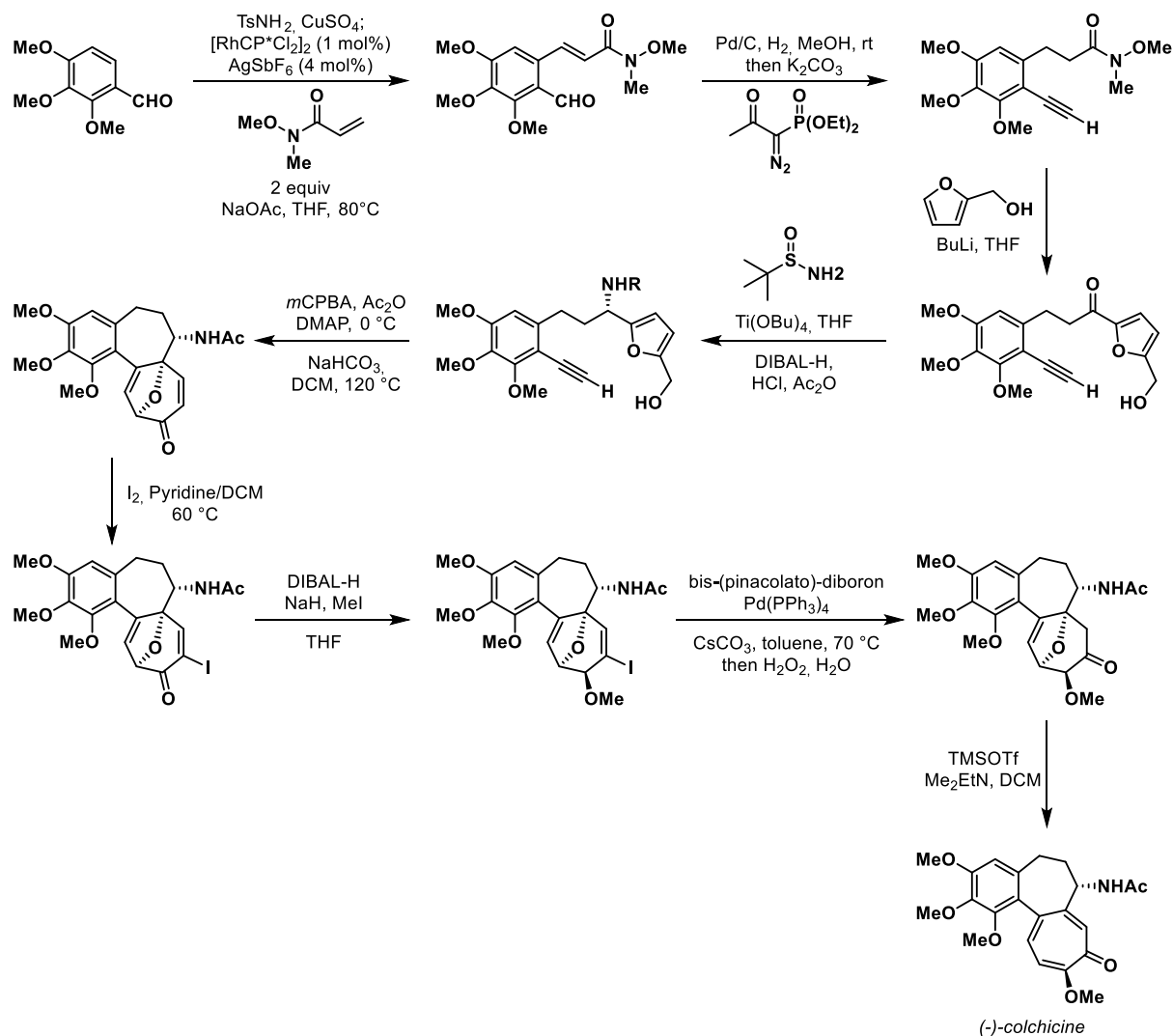
⁴² G. Pulverer, A. Zwiefak, M. Mordarski, N. A. Saleh, *Zbl. Bakt. Hyg. A* **1988**, 270, 160.

⁴³ E. Lomonosova, J. E. Tavis, *Antiviral Res.* **2015**, 118, 132.

⁴⁴ S. N. Ononye, M. D. VanHeyst, E. Z. Oblak, W. Zhou, M. Ammar, A. C. Anderson, D. L. Wrigth, *ACS Med. Chem. Lett.* **2013**, 4, 757.

⁴⁵ A. Slobodnick, B. Shah, M. H. Pillinger, S. Krasnokutsky, *Am. J. Med.* **2015**, 128, 461.

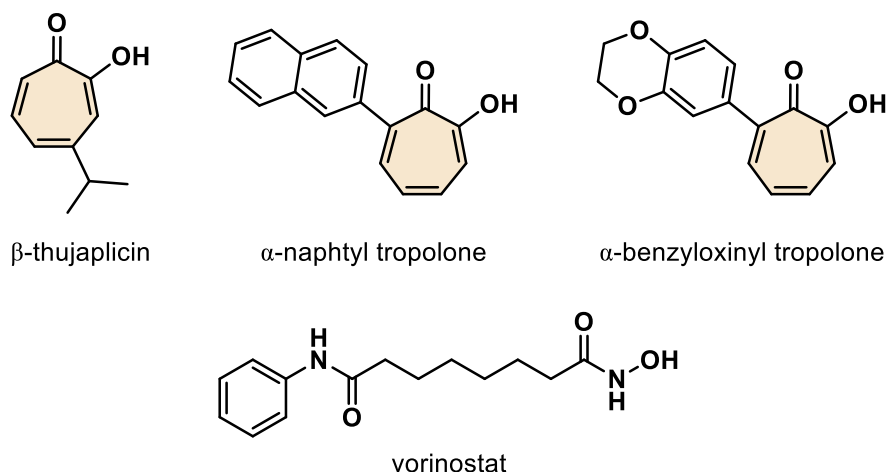
A recent asymmetric synthetic approach has been reported by Chen et al.⁴⁶ employing a (5+3) cycloaddition reaction to form the tropolone ring (Scheme 3.2).



Scheme 3.2: Total asymmetric synthesis of Colchicine.

⁴⁶ B. Chen, X. Liu, Y. J. Hu, D. M. Zhang, L. Deng, J. Lu, L. Min, W. C. Ye, C. C. Li, *Chem. Sci.* **2017**, 8, 4961.

In contrast with the complex structure of Colchicine, other relatively simple natural products containing the tropolone scaffold have emerged to exhibit relevant biological activities. As an example, β -thujaplicin and its analogues are potent inhibitors of human cancer cell proliferation (Scheme 3.3). In this context, α -substituted tropolones such as α -naphthyl tropolone and α -benzodioxinyl tropolone, have gained the interests of the scientific medical community due to their exceptional potency and selectivity, which in some cases have proven to surpass those of clinically approved Vorinostat.⁴⁷



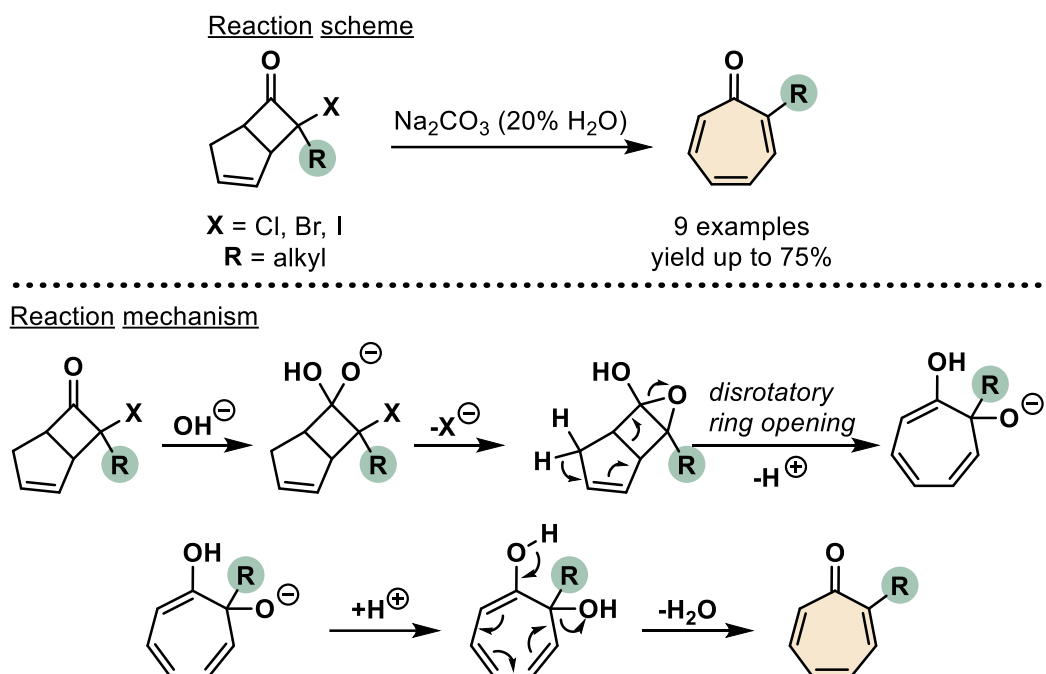
Scheme 3.3: biologically active substituted tropolones.

These studies highlight the scientific and therapeutic interest associated with α and β -substituted tropolones and tropolones, supporting their relevance as biologically active scaffolds. In this context, the work presented in this chapter aims to study a new electrochemical methodology for the synthesis of α -substituted tropolones, starting from tropolone derivative. These compounds can indeed broaden the spectrum of synthetically available tropone derivatives to build more complex biologically relevant architectures.

⁴⁷ J. Lin, E. R. Falcone, S. A. Holstein, A. C. Anderson, D. L. Wright, A. J. Wiemer, *Pharmacol. Res.* **2016**, 113, 438.

3.1.1.3 α -substituted tropones

Despite the undoubted medical and biological interest towards α -substituted tropones scaffold, direct and site-selective protocols (i. e. alkylations) for the troponone skeleton decoration are still rare and scattered in scope.⁴⁸ As a matter of fact, only few methodologies for the synthesis of 2-alkyltropones have been documented. In 1972, Brady et al.⁴⁹ reported a strategy for the conversion of alkyl-haloketene-cyclopentadiene adducts into 2-alkyltropones by solvolysis (Scheme 3.4), representing the first general synthesis of α -substituted tropones from readily available starting materials. The key step in the troponone formation is a disrotatory ring opening of the endo epoxide, effecting the desired trans displacement.



Scheme 3.4: Reaction scheme and mechanism of 2-substituted tropones, Brady et al.

One of the other existing methods to access α -substituted tropones was reported first by Borg et al. in 1962,⁵⁰ and in 1984, by Pietra et al..⁵¹ These two methodologies consist in a Grignard addition to 2-halo-substituted tropones (Scheme 3.5) to obtain α -alkyl tropones. The former involved 2-chloro-tropones while the latter relies on 2-fluoro-tropones as electrophiles.

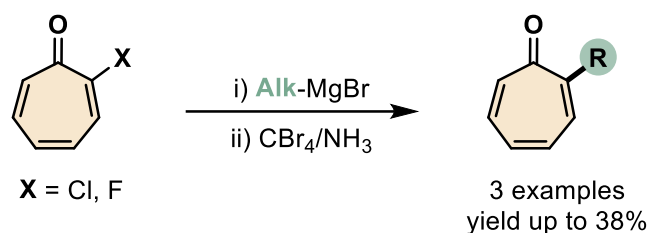
⁴⁸ R. P. Murelli, A. J. Berkowitz, D. W. Zuschlag, *Tetrahedron* **2023**, 130, 133175.

⁴⁹ J. P. Hieble, W. T. Brady, *J. Am. Chem. Soc.* **1971**, 94, 4278.

⁵⁰ A. P. ter Borg, R. van Helden, A. F. Bickel, *Recl. Trav. Chim.* **1962**, 81, 591.

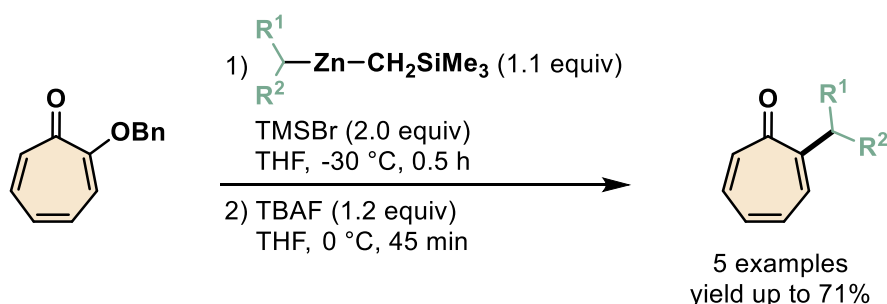
⁵¹ M. Cavazza, G. Morganti, F. Pietra, *J. Chem. Soc.* **1984**, 1, 727.

The mechanism proceeds by a conjugated Michael addition.



Scheme 3.5: Grignard addition to 2-halo-substituted tropones.

More recently, in 2016, Knochel et al. developed a new methodology for the selective α -functionalization of the tropolone scaffold via directed alkylation, representing a robust and general method for the regioselective modification of tropone derivatives.⁵² In this process, benzyl-protected tropolones are selectively alkylated in the α position via conjugate addition-elimination reactions of various secondary alkylzinc reagents. The OBn group undergoes a formal substitution reaction, in order to restore the aromaticity of the tropone scaffold after the addition step (Scheme 3.6).



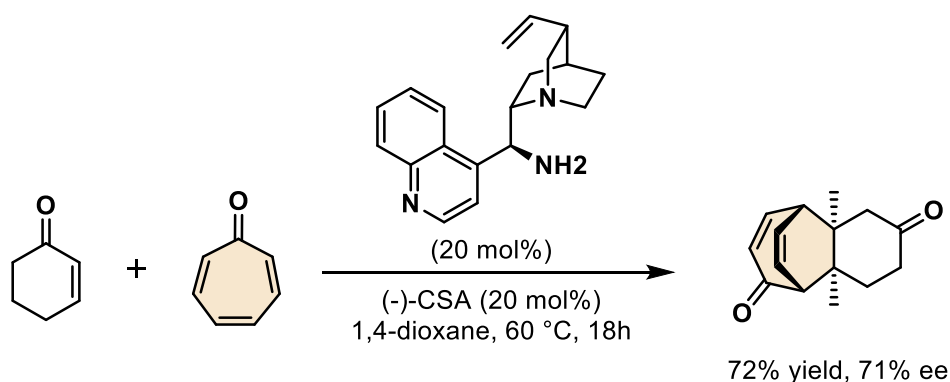
Scheme 3.6: Selective alkylation of tropolones.

The scarce presence of efficient methodologies aimed at the α -functionalization of tropones brought our research group to focus in developing a new electrochemical process to synthesize 2-substituted tropones selectively and efficiently, giving the fact that the request for robust, direct and selective C-alkylations of this non-benzenoid aromatic scaffold is still urgent.

⁵² D. Haas, D. Sustac-Roman, S. Schwarz, P. Knochel, *Org. Lett.* **2016**, *18*, 6380.

3.1.1.4 Reactivity and synthetic utility

Despite this undoubted wide interest, the available chemical portfolio for the manipulation of tropone is largely dominated by cycloaddition reactions. Tropone generally exhibits electrophilic reactivity, a feature that originates from the resonance structures in which the molecule adopts a tropylium-like aromatic character. This extensive π -electron delocalization, renders tropone electrophilic in the α -position, differentiating it from the standard carbonyl group reactivity. Furthermore, due to its ability to react as a 2π ,⁵³ 4π , 6π , or 8π component,⁵⁴ tropone arguably represents one of the most challenging and fascinating cyclic polyenes participating in higher-order cycloadditions, and these processes generally lead to non-aromatic structural rearrangements, disrupting the tropylium-like system. Regarding the 4π reactivity, in 2017, Jørgensen et al. envisioned the stereoselective $[4+2]$ cycloaddition of tropone with 2-cyclohexenones, via aminocatalysis, representing the first organocatalytic stereoselective tropone cycloaddition.⁵⁵ The authors postulated the possibility that 2-cycloalkenones can generate different catalytic dienamine intermediates by reaction with different aminocatalysts, and they opted for cinchona alkaloid derivative to determine the periselectivity of these reactions (Scheme 3.7).



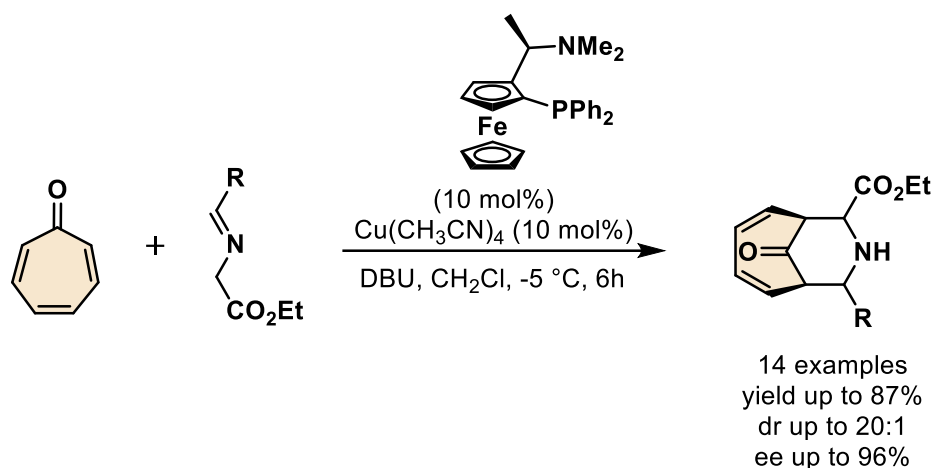
Scheme 3.7: Organocatalytic $[4+2]$ cycloaddition of tropone.

⁵³ H. Takeshita, Y. Wada, A. Mori, T. Hatsui, *Chem. Lett.* **1973**, 2, 335.

⁵⁴ F. Doraghi, M. H. Edareh, B. Larijani, M. Mahdavi, *RSC Adv.* **2025**, 15, 34282.

⁵⁵ R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen, K. A. Jørgensen, *Nature Chem.* **2017**, 9, 487.

In 2014, Guo et al. reported the first metal-catalyzed (6+3) cycloaddition of tropone⁵⁶ with azomethine ylides and its asymmetric variant, affording piperidine fused bicyclic heterocycles, where tropone acts as a 6 π component (Scheme 3.8). This work demonstrated that tropone can be engaged in metal-catalyzed higher-order cycloadditions.



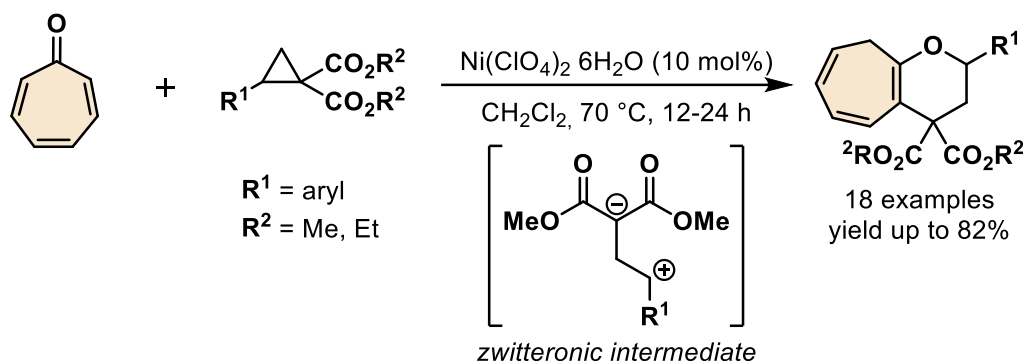
Scheme 3.8: Cycloaddition of Tropone with Azomethine Ylides.

Attracted by the chemical properties of Tropone and its derivatives, Carretero et al. developed a new methodology to prepare diverse cyclohepta-pyrane scaffolds via Ni-catalysed formal [8+3] cycloaddition of tropones with substituted 1,1-cyclopropane diesters.⁵⁷ In this work, tropone participates as an 8 π component, starting the machinery with the nucleophilic attack from the oxygen to the Ni-activated cyclopropane, in the substituted position. This process leads to the formation of a tropylium ion zwitteronic intermediate, followed by the ring closure (Scheme 3.9). The nickel catalyst, namely Ni(ClO₄)₂, acts as Lewis acid and enhances the electrophilicity of the cyclopropane derivatives, coordinating the two ester moieties.

⁵⁶ H. Liu, Y. Wu, Y. Zhao, Z. Li, L. Zhang, W. Yang, H. Jiang, C. Jing, H. Yu, B. Wang, Y. Xiao, H. Guo, *J. Am. Chem. Soc.* **2014**, *136*, 2625.

⁵⁷ R. Tejero, A. Ponce, J. Adrio, J. C. Carretero, *Chem. Commun.* **2013**, *49*, 10406.

Using enantioenriched ligands, the authors were also able to develop an asymmetric variant of the process.



Scheme 3.9: Ni-Catalyzed [8+3] cycloaddition of tropones with 1,1-cyclopropanediester.

Despite the reactivity and the biological activities associated with tropone and its derivatives, it remains evident that direct functionalization of the tropone scaffold without disruption of the aromaticity is still limited. In this context, the work presented in this chapter is directed toward the study and development of a new electrochemical cross electrophile coupling strategy to functionalize tropones.

3.2.1 Electrochemical cross electrophile couplings

3.2.1.1 Generality of cross electrophile couplings (XEC)

Cross-electrophile couplings have emerged as a powerful and versatile strategy for the formation of new carbon–carbon bonds, enabling the union of two electrophilic partners. This approach relies on reductive activation pathways, typically mediated by transition-metal catalysis, and usually offers improved functional-group tolerance with respect to standard cross-coupling reactions.⁵⁸

More recently, electrochemical cross-electrophile couplings (eXEC) are attracting increasing attention as an alternative to the use of stoichiometric chemical reductants, allowing the generation of reactive intermediates through the application of an external potential to drive paired reduction (cathodic) and oxidation (anodic) reactions. The eXEC reaction is a reductive cathodic process and must be paired with an oxidation at the anode and, usually, a sacrificial anode is employed. The use of electricity also provides enhanced modulability and tunability of reaction conditions, improving chemoselectivity, and reducing waste generation.⁵⁹ In this chapter, the focus will be exclusively on eXEC reactions that proceed via direct electrochemical reduction of the reactive species, while processes mediated by a transition metal catalyst will be described in the following chapter.

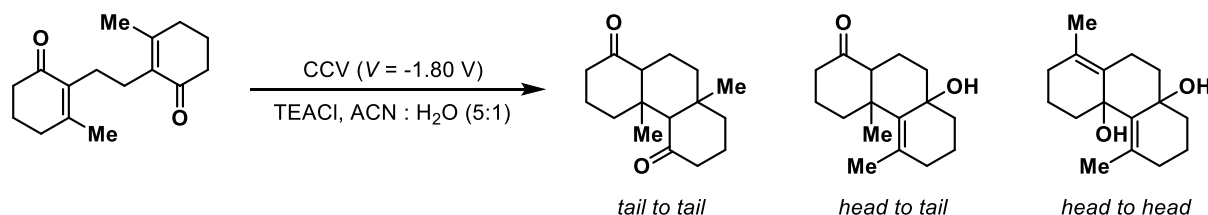
In 1976, Mendell et al. reported one of the early examples of application of electrochemical mediated cathodic reduction in synthetic organic chemistry.⁶⁰ The work focuses on electrochemical reduction of unsaturated carbonyl compounds, activating the π system and generating a reactive nucleophilic radical anion intermediate that undergoes cyclization or dimerization. The aim of this early report was to help establishing the idea that electrochemical cathodic activation can generate reactive intermediates without the need for stoichiometric reducing agents.

⁵⁸ L. E. Ehehalt, O. M. Beleh, I. C. Priest, J. M. Mouat, A. K. Olszewski, B. N. Ahern, A. R. Cruz, B. K. Chi, A. J. Castro, K. Kang, J. Wang, D. J. Weix, *Chem. Rev.* **2024**, *124*, 13397.

⁵⁹ M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230.

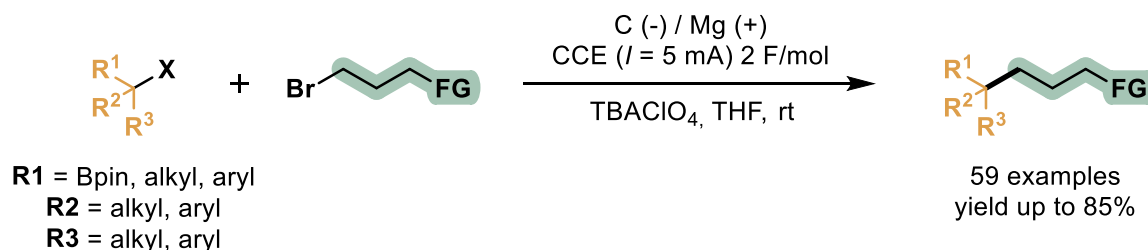
⁶⁰ R. F. Daley, R. A. Day Jr., L. Mandell, *J. Org. Chem.* **1976**, *41*, 4087.

In the example reported in Scheme 3.10, three cyclization products are possible, depending on the modality of the coupling.



Scheme 3.10: Application to Perhydrophenanthrene Syntheses.

More recently, in 2022, Lin et al.⁶¹ developed an electrochemical reductive strategy for the cross coupling between alkyl halides under metal-free conditions, allowing the challenging selective formation of new $\text{C(sp}^3\text{)} - \text{C(sp}^3\text{)}$ carbon-carbon bonds (Scheme 3.11). The innovation of this process lies in the selectivity of the differential activation of the two electrophiles, based on their diverse electronic and steric properties. The cathodic reduction is, indeed, more selective toward the more substituted halides and the reactivity of the relative intermediate is directed to the less substituted ones. It is worth to mention the broad substrate scope of both functionalized and unactivated alkyl halides.



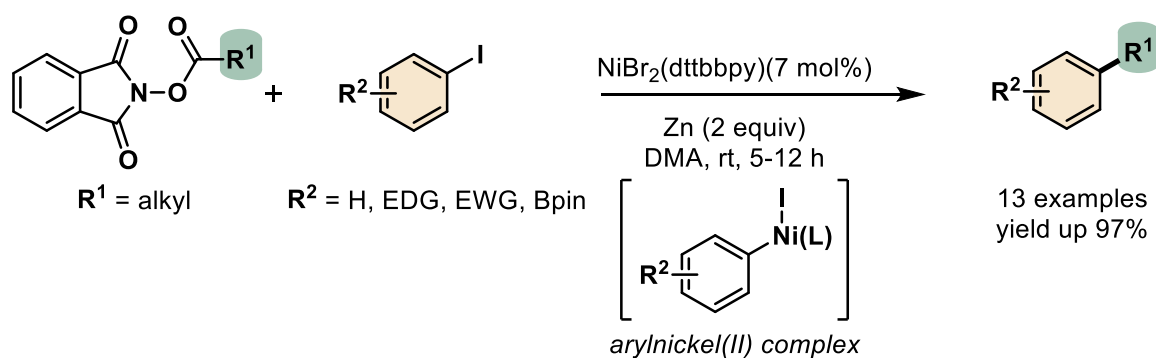
Scheme 3.11: Electrochemically driven cross-electrophile coupling of alkyl halides.

The discussed metal-free electrochemical cross-electrophile couplings demonstrate how direct electrochemical reduction can be used to generate reactive intermediates without the need of transition-metal catalysts. However, the scope of such approaches is often constrained by the redox properties of the electrophiles, which limits their general applicability. In this context, redox-active esters (RAEs) have emerged as powerful and versatile precursors for the controlled and selective generation of alkyl radicals under reductive conditions.

⁶¹ W. Zhang, L. Lu, W. Zhang, Y. Wang, S. D. Ware, J. Mondragon, J. Rein, N. Strotman, D. Lehnher, K. A. See, S. Lin, *Nature* **2022**, 604, 292.

3.2.1.2 Redox-active Esters (RAEs)

Redox-active esters (RAEs) are a class of activated carboxylic acid derivatives that have emerged as versatile precursors for the generation of alkyl radicals under mild reductive conditions. They typically derive from N-hydroxyphthalimide (NHPI) and they can easily undergo single-electron reduction followed by decarboxylation, providing carbon centered radicals.⁶² This activation strategy effectively transforms carboxylic acids moieties into synthetically useful radical precursors, offering an elegant alternative to the direct reduction of alkyl halides or other classical electrophiles. The versatility of RAEs lies in their tunable redox properties, which is a key advantage for radical generation at relatively mild potentials and with high chemoselectivity.⁶³ As a result, RAEs are employed and easily activated both in uncatalyzed as well as in transition-metal-mediated, photochemical and electrochemical protocols. Given these features, RAEs have been established as central building blocks in modern radical and cross-coupling chemistry, exploiting the synthetic utility of carboxylic acids as feedstock molecules.⁶⁴ In the context of transition-metal-catalyzed strategies, Weix et al., in 2016, reported a nickel-catalyzed decarboxylative cross-electrophile coupling between aryl iodides and RAEs, selecting zinc as a terminal reducing agent.⁶⁵ This methodology exploits arylnickel(II) complexes for the activation of NHP esters in order to promote the formation of a new C(sp³)-C(sp²) bond (Scheme 3.12).



Scheme 3.12: Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides.

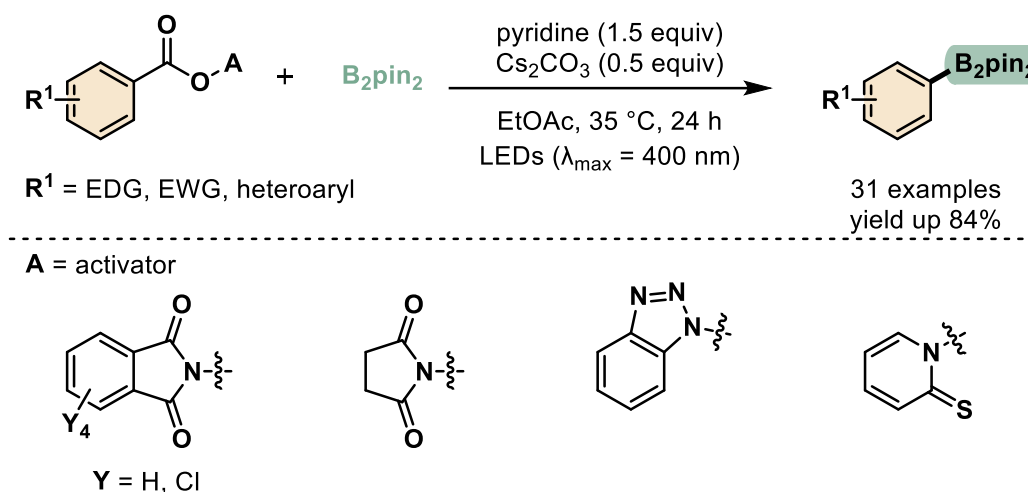
⁶² K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401.

⁶³ T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801.

⁶⁴ B. Jat, D. K. Yadav, S. S. Badsara, S. Sharma, *Org. Biomol. Chem.* **2025**, *23*, 4846.

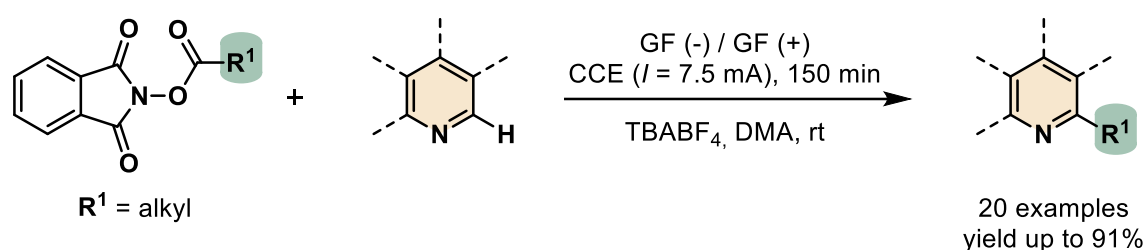
⁶⁵ K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackermann, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016.

In the field of photochemical activation of RAEs derivatives, Glorius et al., reported a metal-free method for the synthesis of aryl boronic esters.⁶⁶ The process uses photoinduced single electron transfer (SET) to activate RAEs, promoting decarboxylation to generate aryl radicals which can react with diboron reagents to afford the respective aryl boronic esters (Scheme 3.13). This method represents one of the first examples of harnessing RAEs as precursors of carbon-centred radicals exploiting mild photochemical conditions.



Scheme 3.13: Visible-Light-Enabled Decarboxylative Borylation of Aryl *N*-Hydroxyphthalimide Esters.

The activation of RAEs has been widely explored under electrochemical conditions as well. As an example, Lei et al., in 2019, developed an electrochemical catalyst-free decarboxylative cross coupling between *N*-hydroxyphthalimide esters and *N*-heteroarenes, in order to obtain a Minisci-type alkylation process.⁶⁷ Mechanistically, the method involves cathodic reduction of the RAEs to generate alkyl radicals, capable to react with the heteroarene to furnish the desired product (Scheme 3.14).



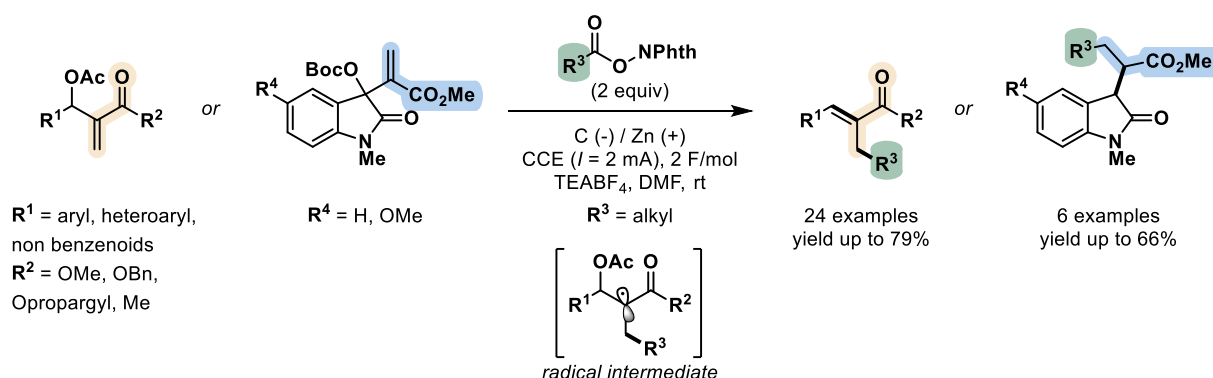
Scheme 3.14: Electrochemical decarboxylative cross-coupling of *N*-hydroxyphthalimide esters and *N*-heteroarenes.

⁶⁶ L. Candish, M. Teders, F. Glorius, *J. Am. Chem. Soc.* **2017**, 139, 7440.

⁶⁷ Y. Liu, L. Xue, B. Shi, F. Bu, D. Wang, L. Lu, R. Shi, A. Lei, *Chem. Commun.* **2019**, 55, 14922.

Giving the capability of Redox-active esters to generate nucleophilic alkyl radicals through single-electron reduction at relatively low potentials, our research group selected RAEs as an attractive choice for a coupling partner of the tropone framework, that can be activated under controlled reductive conditions, forming the foundation of the project described in the following sections.

Following the interest for electro-mediated cross electrophile couplings, Bandini et al., in 2022, developed a novel electrochemical regioselective alkylation of Morita-Bailys-Hillmann (MBH) adducts or oxindole scaffolds with N-acyloxypthalimides (redox-active esters, RAEs) as alkyl radical precursors, offering access to densely functionalized cinnamate and diverse oxindole derivatives.⁶⁸ The electrochemical setup exploited the sacrificial anode technique, selecting zinc in order to avoid the need of external chemical reductants. In this methodology the redox-active ester undergoes selectively the first cathodic reduction, generating the alkyl radical after a decarboxylation process, being trapped by the electrophilic partner. Subsequent cathodic reduction of the relative intermediate and elimination of the leaving group, lead to the formation of the desired product (Scheme 3.16).

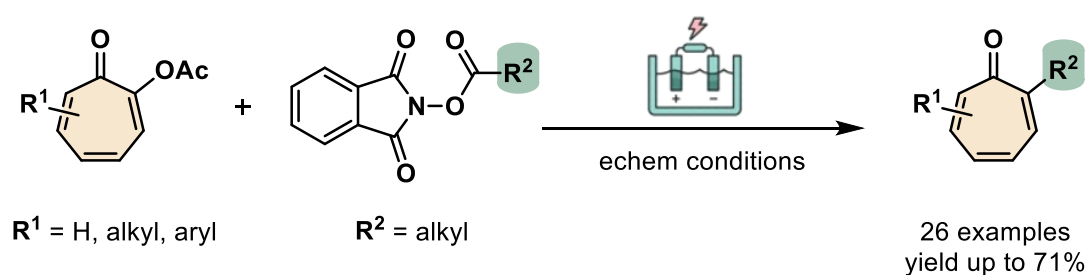


Scheme 3.16: Electrochemical Alkylation of Morita– Baylis–Hillman Adducts.

⁶⁸ G. Ombrosi, G. Bertuzzi, M. Bandini, *Org. Lett.* **2022**, *24*, 4354.

3.3 Aim of the work

Pursuing the interest toward developing a new electrochemical methodology for the α -alkylation of the tropone scaffold, we envisioned the possibility to exploit an eEXEC strategy, involving RAEs as alkyl radical precursors. By mediating the electrochemical parameters, we controlled the radical generation and reactivity of these scaffolds, avoiding undesired over-reduction or dearomatization of the tropone core (Scheme 3.17).



Scheme 3.17: General scheme for the Electrochemical Site-Selective Alkylation of Tropones.

3.4 Results and discussion

3.4.1 Protocol optimization

The main challenge in designing the titled electrochemical cross-electrophile coupling relies on the accomplishment of chemoselective cathodic events. In order to impose a selectivity in the reaction, that is, achieving preferential reduction of the RAE over the tropone derivative, the identification of an activated tropone **1-LG** turned out to be pivotal. Our first approach towards the optimization of the protocol was to find an adequate starting material that would be electrophilic enough to undergo radical trapping but, at the same time, less prone to cathodic reduction with respect to RAEs **2**. To this aim, we select readily available 2-chlorotropone **1a-Cl** and 2-acetoxytropone **1a-OAc** as potential radical acceptors, and subjected them to voltametric analysis, in combination with RAE **2a** as radical generator (Figure 3.1).

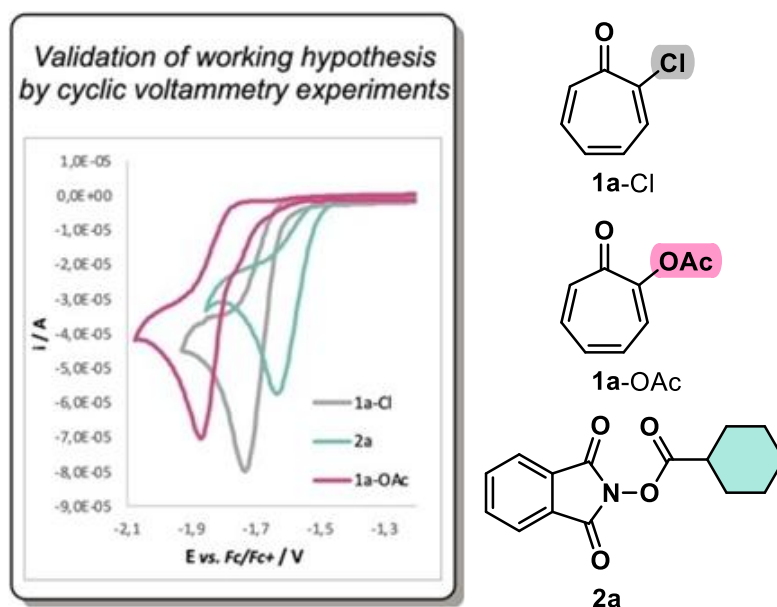
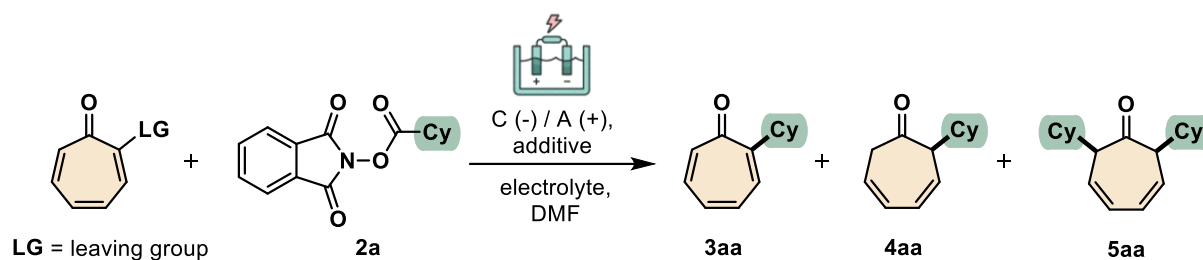


Figure 3.1: Cyclovoltammetric analysis for **1a-Cl**, **1a-OAc** and RAE **2a**.

Based on the voltametric analysis results, we anticipated the desired selectivity. Indeed, **2a** showed a cathodic reduction at a less negative potential (-1.63 V vs Fc/Fc⁺) with respect to **1a-Cl** (-1.73 V vs. Fc/Fc⁺) and **1a-OAc** (-1.87 V vs. Fc/Fc⁺).



Scheme 3.18: General scheme of the optimized reaction.

Based on these promising findings, **1a-Cl** and **2a** (1.5 equiv.) were subjected to a constant current electrolysis (2 mA, 3 F/mol_{1a-Cl}) using a graphite (C) cathode and a Zn sacrificial anode and TEABF₄ as the supporting electrolyte in DMF (Table 3.1, entry 1). Under these conditions, the desired product **3aa** was isolated in 15% yield. In the same reaction we also identified side-products **4aa** and **5aa**, deriving from an over reduction/alkylation sequence of **3aa**, occurring under these conditions. In order to suppress the over-reduction event, we lowered the total charge furnished to the reaction to 2 F/mol_{1a-Cl}, holding the same reaction stoichiometry (30% yield, Table 3.1, entry 2). Under the same conditions, we screened various combinations of electrodes (Table 3.1, entries 3–5) and we elected Zn(+) || Ag(-) as the best performing couple, enabling the isolation of **3aa** in yields up to 38%.

Entry	2a (equiv)	C(-) A(+)	Current (mA)	F/mol	4aa / 5aa ^[b] (%)	3aa yield ^[c] (%)
1	1.5	C / Zn	2	3	10 / 7	15
2	1.5	C / Zn	2	2	nd	30
3	1.5	SS / Zn	2	2	8 / 5	17
4	1.5	Ag / Zn	2	2	nd	38
5	1.5	Ag / Mg	2	2	nd	nd

Table 3.1: **1a-Cl** as starting material: optimization screening. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis, inert atmosphere, TEABF₄ as electrolyte.

^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography.

Although these conditions prevented the formation of over-reduction products **4aa** and **5aa**, a major degradation of **1a-Cl** was detected in the crude reaction mixture. This evidence indicates that, as the reaction progresses and the concentration of **2a** decreases, the electroreductive process may gradually lose chemoselectivity, by triggering uncontrolled single-electron-transfer processes of **1a-Cl**. This statement is

supported by the proximity of the reduction peaks observed in the voltametric responses of **2a** and **1a-Cl**. On this basis, we hypothesized that the employment of more electron-rich leaving groups could face this shortcoming. We thus proceed by testing diverse leaving groups (Table 3.2, entries 1-5) under the best conditions (Table 3.2, entry 4) achieved so far for **1a-Cl**, in order to overcome the loss of chemoselectivity of the process. At the outset of this screening, we selected the acetoxy group as the best candidate, given the highest observed yield and selectivity.

Entry	Leaving group	2a (equiv)	C(-) A(+)	Current (mA)	4aa / 5aa ^[b] (%)	3aa yield ^[c] (%)
1	OTs	1.5	Ag / Zn	2	nd	nd
2	OTf	1.5	Ag / Zn	2	nd	nd
3	OH*HCl	1.5	Ag / Zn	2	nd	nd
4	OPiv	1.5	Ag / Zn	2	nd	50
5	OAc	1.5	Ag / Zn	2	7 / 4	53

Table 3.2: Leaving groups screening. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis, 2 F/mol, inert atmosphere, TEABF₄ as electrolyte. ^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography.

We then moved into the investigation of the electrochemical setup, such as changing electrolytes and electrodes couple, keeping **1a**-OAc as starting material. Variations of the electrolyte (Table 3.3, entries 1-4) led to elect TEABF₄ as the best choice. Several electrode couples were also evaluated (Table 3.3, entries 5-9), but none gave an improved outcome with the respect of the already selected Ag/Zn couple.

Entry	C(-) A(+)	Electrolyte	Current (mA)	4aa / 5aa ^[b] (%)	3aa yield ^[c] (%)
1	Ag / Zn	TBAPF ₆	2	nd	52
2	Ag / Zn	TEAl	2	3 / 4	38
3	Ag / Zn	TEABr	2	6 / 7	36
4	Ag / Zn	TBAClO ₄	2	nd / 3	38
5	GC / Zn	TEABF ₄	2	2 / nd	36
6	Al / Zn	TEABF ₄	2	nd	nd
7	Pt / Zn	TEABF ₄	2	nd	12
8	Ni / Zn	TEABF ₄	2	2 / 7	31
9	Ni _{foam} / Zn	TEABF ₄	2	nd	nd

Table 3.3: Electrochemical setup screening. ^[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis, 2 F/mol, inert atmosphere. ^[b] Determined by ¹H NMR analysis on the crude mixture. ^[c] Isolated yields after flash chromatography.

Optimization studies were then continued by varying the relative equivalents of the starting material **1a**-OAc, increasing its concentration, while decreasing the one of RAE **2a**, with the aim of improving chemoselectivity. In particular, based on data studied from cyclic voltammetry (Figure 3.1), we expected to favor radical trapping, while maintaining the selectivity of the cathodic reduction (Table 3.4, entries 1-2). Indeed, these variations led to enhanced selectivity and improved yield (Table 3.4, entry 2).

Subsequently, the optimization was completed by changing the number of applied electron equivalents (F/mol) and screening different current values (Table 3.4, entries 3-7).

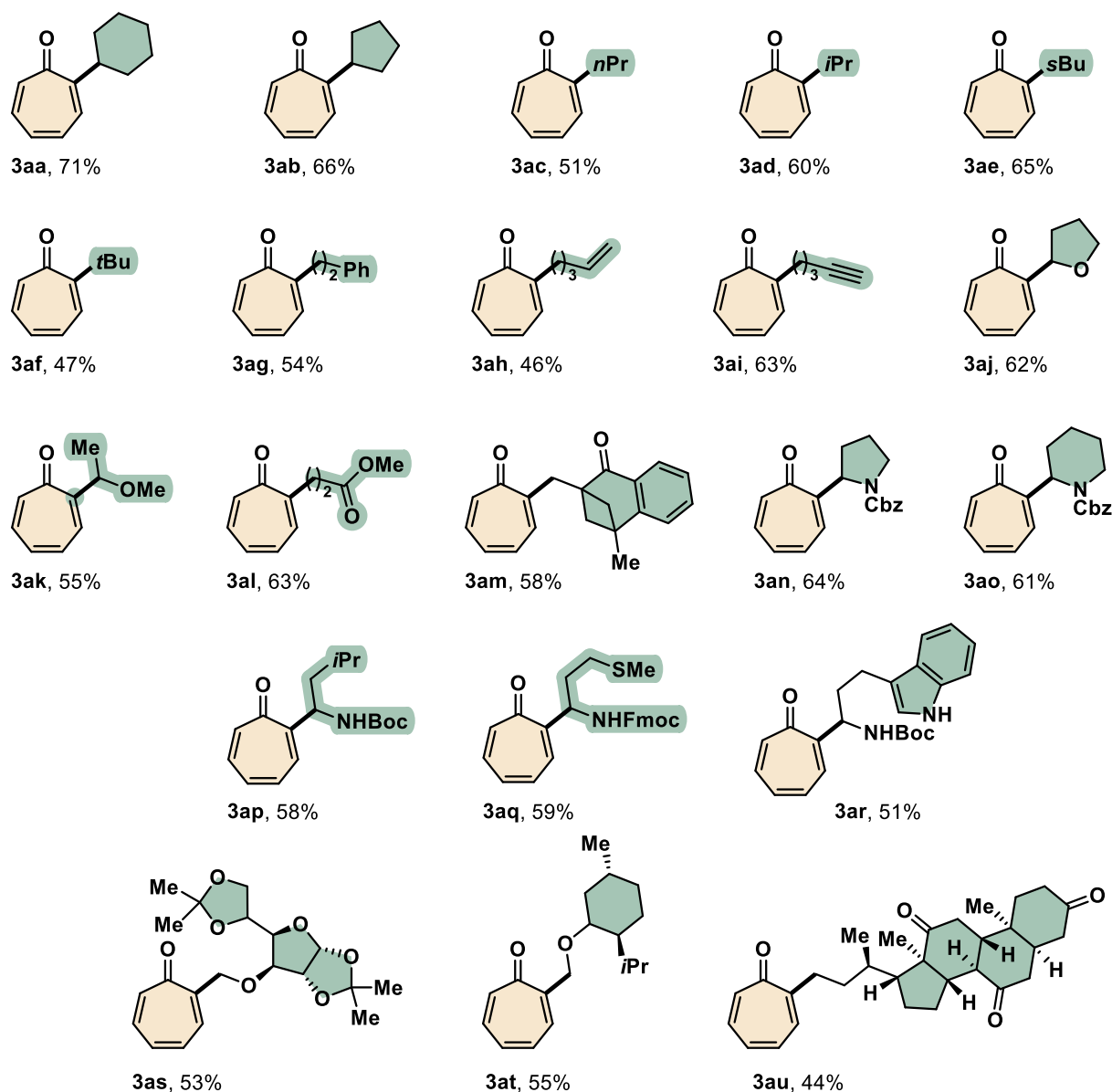
Entry	1a : 2a	F/mol _{1a}	Current (mA)	3aa yield ^[b] (%)
1	1.5 : 1	1.5	2	59
2	2.0 : 1	1	2	64
3	2.0 : 1	1	4	33
4	2.0 : 1	1	1.5	41
5	2.0 : 1	1	1	18
6	2.0 : 1	1	3	71
7	2.0 : 1	0.75	3	48

Table 3.4: Reagents stoichiometry and electrochemical parameters screening. [a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis, Ag(-)/Zn(+) as electrode couple, inert atmosphere, TEABF₄. [b] Isolated yields after flash chromatography.

We finally elected conditions reported in Table 3.4, entry 6 as optimal for the reaction outcome and we then proceed studying the generality of the process.

3.4.2 Generality of the process

The generality of the present electrochemical alkylation was then tested by engaging several different radical precursors **2** to optimal conditions (Scheme 3.19). Primary (**2c**), secondary (**2a**, **2b**, **2d**, **2e**) and tertiary (**2f**) radicals reacted promptly and regioselectively (exclusive α -alkylation was recorded) with **1a**-OAc to render products **3aa-3af** in up to 71% yield. Additionally, a range of functional groups such as arenes (**3ag**), alkenes (**3ah**), alkynes (**3ai**), esters (**3al**) and ketones (**3am**) was efficiently accommodated on the radical framework, unravelling a highly tolerant protocol. Subsequently, the compatibility of the proposed reaction towards α -oxy radicals, as well as α -amino radicals was ascertained. As a matter of fact, cyclic (**2j**) and acyclic (**2k**, from lactic acid) nucleophilic α -oxy radicals were found to be competent nucleophilic alkylating agents (55–62% yield). Analogously, proteogenic amino-acid-derived RAEs **2n-2r** were productively engaged under optimal conditions, providing a simultaneous validation towards amino protecting groups tolerance (i. e. Boc, Fmoc and Cbz) and functional groups (i. e. sulfides and unprotected indole) compatibility (51–64% yield). Finally, RAEs **2s-2u**, containing a protected form of D-glucofuranose, dehydrocholic acid and (-)-menthol, respectively, were subjected to optimal conditions as representative late-stage electrochemical bioconjugation examples. Remarkably, the corresponding products **3as-3au** were isolated in 44–55% yield.

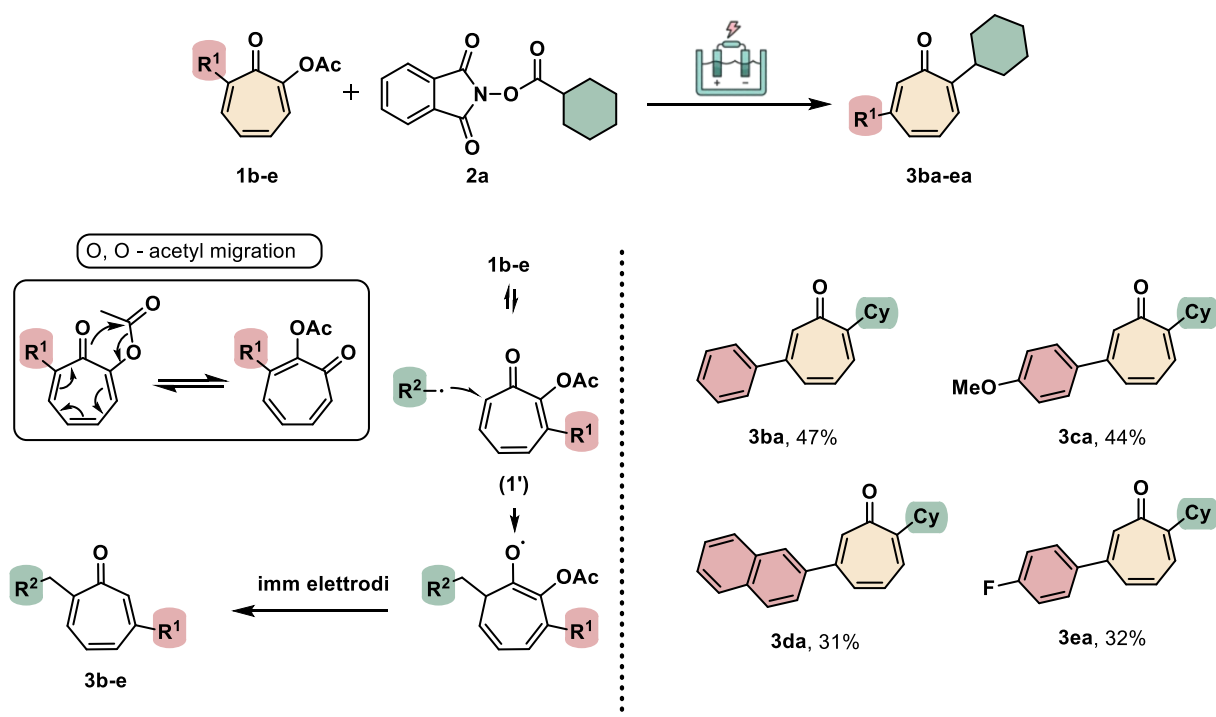


Scheme 3.19: Generality of the protocol. RAEs 2 screening.

Interestingly, the utilization of 2-acetoxytropones **1**-OAc as starting materials offers the unique opportunity to exploit the fluxionality of the acetyl group in testing the reactivity of substituted tropones. It is worth to mention that, in 2-acetoxytropone, a fast acetyl migration occurs via an intramolecular acyl shift involving transient deacetylation of the C2-oxygen followed by migration of the acetyl group to the C1 oxygen of the tropone system.⁶⁹ The process is facilitated by the high degree of π -conjugation of the tropone ring, which stabilizes the intermediates and lowers the barrier for acetyl transfer. As an example, this effect can be effectively employed for opening new perspectives in the

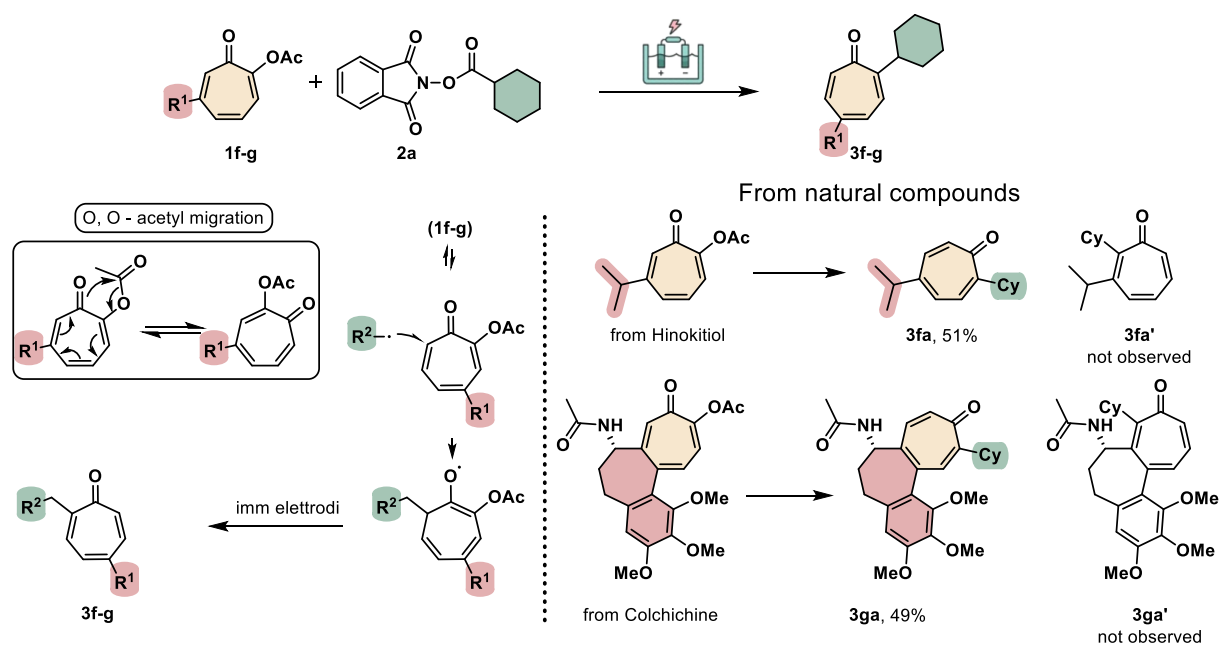
⁶⁹ Y. Sugihara, A. Yamato, I. Murata, *Tetrahedron Letters* **1981**, 22, 3251.

utilization of 2,7-disubstituted tropones by generating in situ a reactive form (Scheme 3.20). To prove this hypothesis, a range of 7-aryl-2-acetoxytropones **1b**-OAc–**1e**-OAc were readily accessed and subjected to optimal alkylating conditions with **2a**. Satisfyingly, four different 6-aryl-2-alkyl-tropones **3ba**–**3ea** were obtained in moderate yields (up to 47%). In these cases, only the form exhibiting a free α -position is able to undergo the desired alkylation, resulting in a completely selective process.



Scheme 3.20: Generality for 2,7-disubstituted tropones.

Analogously, acetylated β -thujalpicin **1f**-OAc underwent an electrochemical alkylation process with **2a**, delivering 2,5-disubstituted tropone **3fa** in 51% yield via site-selective C(sp²)-C(sp³) bond forming reaction at the less hindered position (Scheme 3.21). Importantly, the present procedure was also applicable to Colchicine acetate **1g**. A site selective alkylation with **2a** occurred at the less hindered position, resulting in alkylated Colchicine analogue **3ga** as a single isomer in 49% yield. The latter applications underlined the suitability of the present electrochemical methodology for late-stage functionalizations of tropone-based bioactive scaffolds.

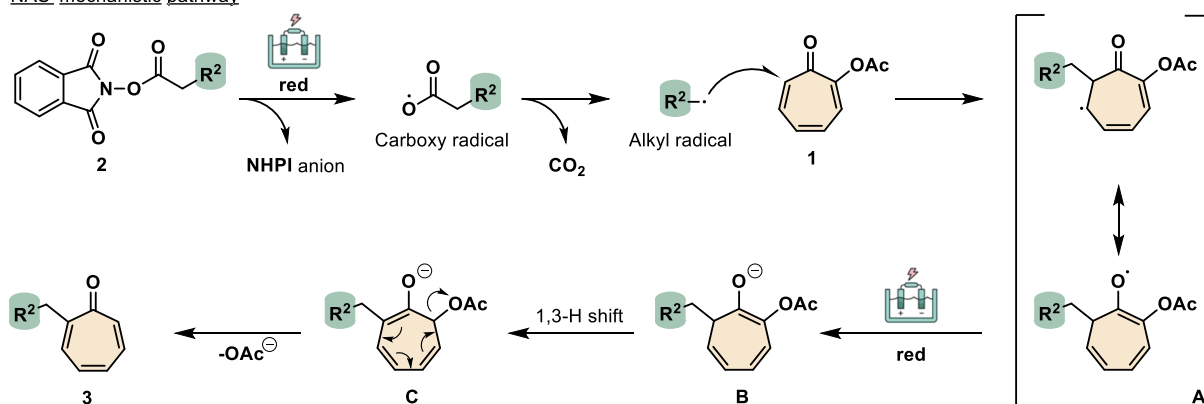


Scheme 3.21: Generality of tropone-based bioactive scaffolds.

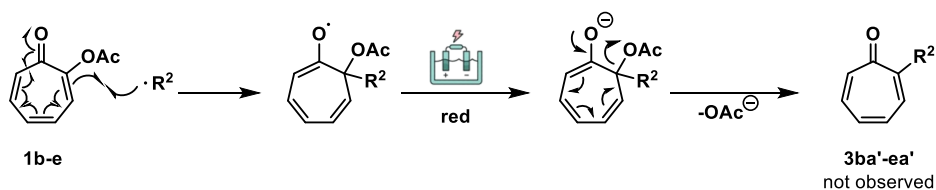
3.4.3 Mechanistic proposal

The electrochemical analyses described above (Figure 3.1) together with the site-specificity recorded on the alkylation of substituted tropones, prompted us to propose the reaction mechanism for the present electrochemical functionalization of tropones as depicted in Scheme 3.22. The experimental evidence suggests that the electroreductive process is initiated by a single-electron cathodic reduction of RAE **2** with consequent fragmentation to deliver a nucleophilic alkyl radical species ($R^\bullet$). Thereafter, this radical is trapped chemoselectively at the most electrophilic α -position of the troponone ring, affording open-shell intermediate **A**, which is stabilized by an extensive delocalized π -system. A second cathodic reduction leads to enolic form **B** that can undergo 1,3-hydrogen shift to form isomer **C**. This species is capable of completing the re-aromatization step via elimination of the acetoxyl group. Overall, the transformation can be described as a formal nucleophilic aromatic substitution prime (NAS'), with the postulated NAS vs NAS' regiochemistry being supported by the selectivity observed starting from functionalized tropones (i. e. **1b–g**).

NAS' mechanistic pathway



NAS mechanistic pathway (not observed)



Scheme 3.22: Mechanistic proposal for electrochemical alkylation of tropones.

3.5 Conclusions

In conclusion, we have documented the first general approach to α -alkyl tropones through a direct and site-selective electrochemical C(sp³)-C(sp²) coupling concept. Paving the ways of new troponone chemistry, this protocol provides the first insight into radical synthetic transformations of this class of compounds. A wide range of simple primary, secondary, and tertiary motifs as well as decorated alkyl radicals, proved to be suitable for the preparation of the target compounds, while the use of readily available 2-acetoxytropones enabled the realization of a highly regioselective protocol. Mechanistic elucidation supported by voltametric analysis, together with the efficient late-stage functionalization of bioactive scaffolds, further underscore the potential of the presented methodology.

3.6 Experimental details

3.6.1 General methods and materials

¹H-NMR spectra were recorded on a Bruker 600 spectrometer (600 MHz). Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (CHCl₃: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, td = triple doublet, dt = double triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz). ¹³C-NMR spectra were recorded on a Bruker 600 spectrometer (150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (CDCl₃: 77.0 ppm). HRMS spectra were obtained with a G2XS QToF mass spectrometer using either ESI or APCI ionization techniques, as specified case by case. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous solvents, including DMF for the electrochemical processes, were supplied by Merck in Sureseal® bottles and used without any further purification. Electrochemical characterization of **1a-OAc**, **1a-Cl** and **2a** were performed by cyclic voltammetry (CV). These experiments were carried out with a PGSTAT128N potentiostat driven by a Nova 2.0 software. The voltammetric responses were collected at room temperature in a three-electrode cell under N₂ flux. The working electrode consisted of a 3 mm diameter glassy carbon electrode (Metrohm), the counter electrode was a Pt wire (Metrohm) and an Ag wire was used as the pseudo-reference electrode. The potentials of the working electrode were finally referred to the ferrocene/ferrocenium redox couple ($E_{Fc^+/Fc} = +0.40$ V vs. SCE) by adding a few crystals of ferrocene in the solution. The working electrode surface was polished with 1 and 0.3 μm alumina and sonicated in deionized water for 5 minute before the use. The electrochemical experiments were recorded by dissolving the compound under investigation in a 0.1 M tetraethylammonium tetrafluoroborate (TEABF₄) in anhydrous DMF, both acquired from Sigma-Aldrich. Below the general procedures the characterization of the model compound only is reported. For the complete description of all the products reported as well as starting materials **1-OAc**, RAEs **2** see the Supporting Information of *Adv. Synth. Catal.* **2024**, 366, 1965.

3.6.2. Electrochemical Alkylation of Tropones 1

3.6.2.1 General procedures for the electrochemical alkylation of tropones 1.

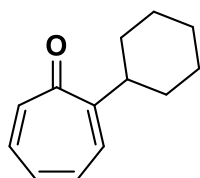
General Procedure A. The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with 2-acetoxytropone **1a** (0.30 mmol, 2.0 equiv, 49.2 mg), *RAE 2* (0.15 mmol, 1 equiv) and TEABF₄ (0.30 mmol, 65.0 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ag), was inserted into the mixture and closed with a rubber septum. The vessel was evacuated and backfilled with Ar three times, then dry DMF (3.0 mL) was added, and the mixture stirred until complete dissolution of the solids occurred while the mixture was bubbled with Ar (balloon). The reaction mixture was electrolyzed (under Ar, balloon) at a constant current of 3.0 mA, until a total charge of 0.30 mF (2.0 F/mol₂) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and NH₄Cl_(aq) (1 M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with NH₄Cl_(aq) (0.1 M, 3 x 20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was finally purified by FC to afford pure products **3**.

General Procedure B. The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with tropone derivative **1** (0.15 mmol, 1.0 equiv), *RAE 2a* (0.23 mmol, 1.5 equiv, 63.0 mg) and TEABF₄ (0.30 mmol, 65.0 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ag), was inserted into the mixture and closed with a rubber septum. The vessel was evacuated and backfilled with Ar three times, then dry DMF (3.0 mL) was added, and the mixture stirred until complete dissolution of the solids occurred while the mixture was bubbled with Ar (balloon). The reaction mixture was electrolyzed (under Ar, balloon) at a constant current of 2.0 mA, until a total charge of 0.30 mF (2.0 F/mol₁) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and NH₄Cl_(aq) (1 M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with NH₄Cl_(aq) (0.1 M, 3 x 20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was finally purified by FC to afford pure products **3**.

Additional notes:

For products **3ag**, **3ai**, **3aj**, **3ak**, and **3at** chromatographic separation from phthalimide coproduct was troublesome. Therefore, after FC a basic wash (aqueous 1M NaOH / Et₂O) was carried out to obtain the pure compounds.

3.6.2.2 Characterization data of compound **3a**.



3aa. Obtained following *General Procedure A*. Yellow sticky oil. FC eluent: *n*-hexane/EtOAc: 8:1. Yield = 71%, (0.107 mmol, 20.0 mg). **¹H NMR** (600 MHz, CDCl₃) δ = 7.15 (d, *J* = 9.0 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.99 (ddd, *J* = 10.2, 9.0, 1.1 Hz, 1H), 6.90 – 6.85 (m, 1H), 3.14 (tt, *J* = 11.9, 2.9 Hz, 1H), 1.86 – 1.73 (m, 5H), 1.52 – 1.42 (m, 2H), 1.29 – 1.17 (m, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ = 187.1, 160.2, 140.4, 134.9, 134.0, 132.4, 132.2, 40.2, 33.2 (2C), 26.8 (2C), 26.3; **HRMS (ESI)** *m/z*: [M + H]⁺ calcd. for C₁₃H₁₇O 189.1274; found 189.1285. Product **3aa** is a known compound, spectroscopic data match with the ones reported in literature.

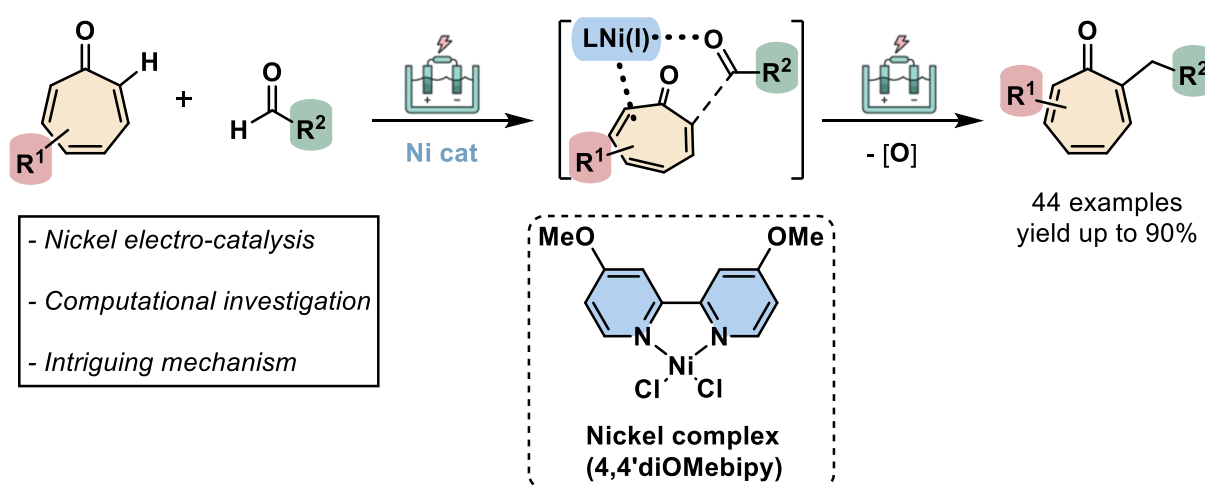
Preparation of **3aa** on 1.0 mmol scale. The ElectraSyn vial (10 mL), equipped with a stir bar, was charged with 2-acetoxytropone **1a** (2.0 mmol, 2.0 equiv, 328 mg), *RAE* **2a** (1.0 mmol, 1 equiv, 272 mg) and TEABF₄ (0.90 mmol, 195 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ag), was inserted into the mixture and closed with a rubber septum. The vessel was evacuated and backfilled with Ar three times, then dry DMF (9.0 mL) was added and the mixture stirred until complete dissolution of the solids occurred while the mixture was bubbled with Ar (balloon). The reaction mixture was electrolyzed (under Ar, balloon) at a constant current of 2 mA, until a total charge of 2.0 mF (2.0 F/mol_{2a}) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (20 mL) and NH₄Cl_(aq) (1 M, 20 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with NH₄Cl_(aq) (0.1 M, 5 x 40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was finally purified by FC (*n*-hexane/EtOAc: 8:1) to afford pure product **3aa** as a yellow sticky oil (122 mg, 0.65 mmol, 65%yield).

Chapter 4: Electrochemical Nickel-Catalyzed C(sp²)-H Functionalization of Tropones with Aldehydes

All the procedures and results here described are part of- and can be found in:-

A. Brunetti, S. Kiriakidi, M. Garbini, G. Monda, C. Zanardi, C. S. López, G. Bertuzzi and M. Bandini "Electrochemical Nickel-Catalyzed C(sp²)-H Functionalization of Tropones with Aldehydes" *ACS Catal.* **2025**, *15*, 3184.

Abstract



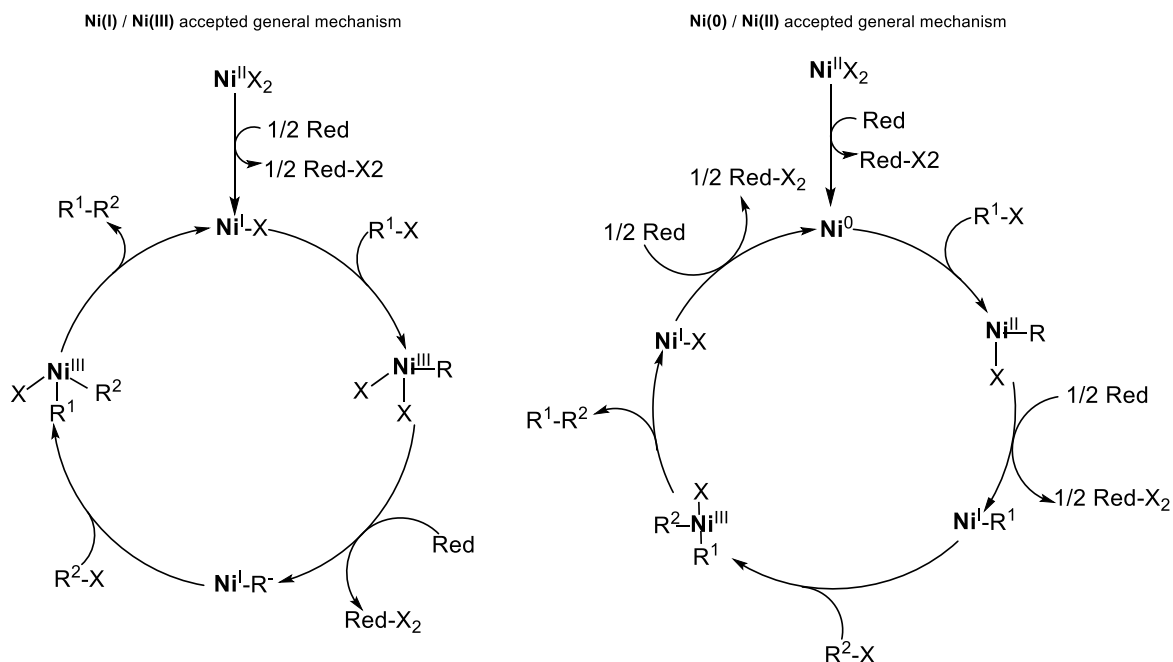
A direct electroreductive functionalization of tropones employing aldehydes as alkylating agents is reported. This C(sp²)-H functionalization process leverages the mediation of electroactive nickel complexes, enabling the selective, high yielding (up to 90%) α-alkylation of a wide range of both native and substituted tropones (44 examples). Combined electrochemical, spectroelectrochemical, and computational analyses reveals the complete mechanistic pathway and highlighted the key role of reduced Ni complexes in activating the troponone core for condensation with aldehydes.

4.1 Introduction

4.1.1 Nickel-mediated Cross Electrophile Couplings (XEC)

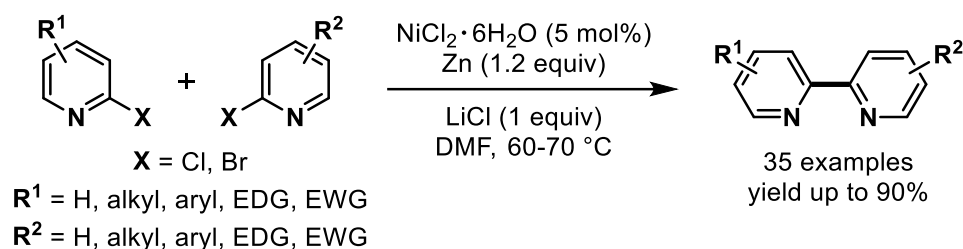
The electrochemical strategy described in the previous chapter demonstrated that direct reductive activation of RAEs to achieve α -functionalization of tropones can be obtained without the need of transition-metal catalysis. This metal-free approach emphasized a novel insight into the radical reactivity of the troponone moieties, and it also underlined the potential of cross-electrophile coupling (XEC) as an elegant strategy for C–C bond formation under reductive conditions.⁵⁵ However, in many cases, direct electrochemical activation is not sufficient to achieve the desired synthetic transformation. Indeed, either the generation itself, or the further evolution of reactive intermediates requires the presence of a catalyst. In a more general sense, Nickel catalysis has emerged as one of the most versatile and widely adopted strategies among the various XEC methodologies, disregarding the reductive system employed. The strategy to implement nickel-catalyzed approach in XEC reactions have been successfully achieved using stoichiometric metallic or organic reductants, through photochemical activation pathways, and more recently via electrochemical reduction. These complementary activation modalities highlight the adaptability of nickel in mediating reductive processes for the formation new C–C bonds, thanks to its versatility to access multiple oxidation states and to efficiently mediate reductive processes between electrophilic partners.⁷⁰ In most cases, after a first reduction of the Ni(II) pre-catalyst, these transformations start with a low-valent nickel species, typically Ni(0) or Ni(I), capable to undergo oxidative addition to one electrophile, followed by radical capture or trans-metalation, and finally reductive elimination to forge the new C–C bond. The regeneration of the catalytic Nickel-cycle can be achieved through chemical, photochemical, or electrochemical reduction, based on the activation modality employed. A simplified representation of the generally accepted nickel catalytic cycles in reductive cross-electrophile couplings is shown in Scheme 4.1.

⁷⁰ K. X. Du, Y. F. Chen, Z. H. He, P. Fang, C. Ma, N. Fu, Y. Qiu, T. S. Mei, *CCS Chem.* **2025**.



Scheme 4.1: Accepted Nickel general mechanism.

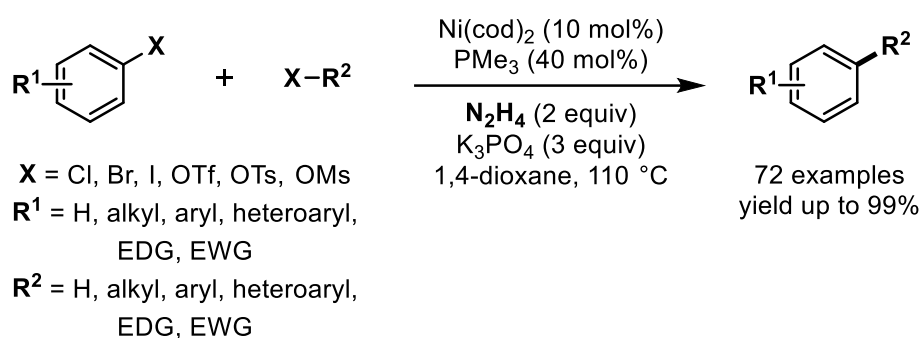
In the context of XEC using metal powders as stoichiometric reductants, Duan et al., in 2014 developed an unexpectedly efficient Ni-catalyzed reductive coupling of 2-halopyridines to obtain both symmetrical and unsymmetrical 2,2'-bipyridines.⁷¹ These substrates have previously been considered to be highly difficult to be achieved by such strategy, due to a product-inhibition effect. The authors took advantage of the in situ formed Ni-bipyridine complex to catalyze the coupling in the absence of external ligands (Scheme 4.2). Contrary to the common methods that need to use a large amount of metal catalyst and ligands, this strategy overcomes the adverse effect of 2,2'-bipyridine on the catalytic cycle.



Scheme 4.2: Reductive Couplings of 2-Halopyridines without External Ligand.

⁷¹ L. Y. Liao, X. R. Kong, X. F. Duan, *J. Org. Chem.* **2014**, 79, 777.

In 2018, Li et al. reported an efficient strategy for the synthesis of biaryl compounds exploiting reductive homo- and cross-coupling of aryl electrophiles.⁷² The authors considered using hydrazine (N₂H₄) as a “traceless mediator” in the presence of a nickel catalyst. It is worth to mention that N₂H₄ can act as a ligand, so, in order to outcompete the hydrazine binding the authors found electron-rich monodentate PMe₃, a phosphine ligand, to be effective. The hydrazine-mediated protocol generates N₂ and H₂ as byproducts, thereby eliminating the need for stoichiometric amounts of metal powders (Scheme 4.3).

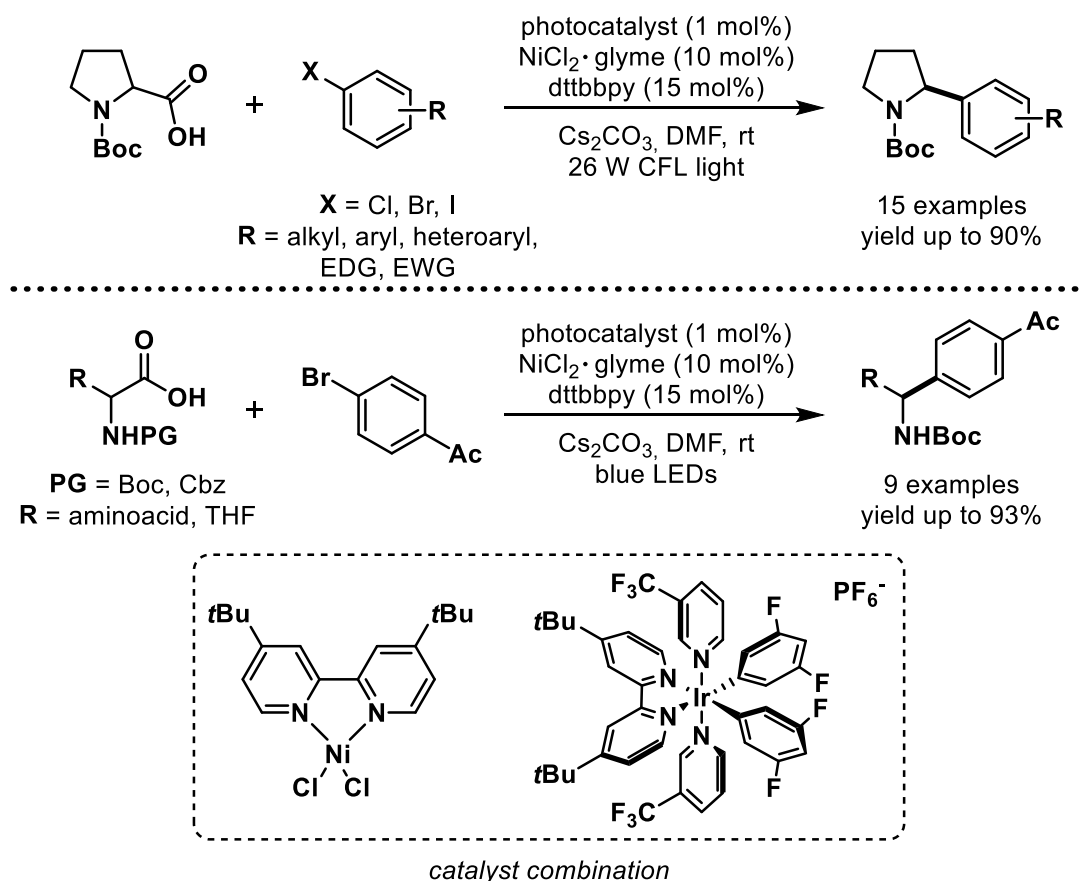


Scheme 4.3: N₂H₄ as traceless mediator for homo- and cross-aryl coupling.

Regarding the activation of nickel catalysts via photochemical pathway, MacMillan et al., in 2014, reported a novel dual catalytic protocol in which Nickel catalysis is merged with photoredox catalysis to enable single-electron transmetalation, in contrast with the classical metal-mediated cross couplings.⁷³ The strategy consists in using visible light and an iridium catalyst to oxidize α -aminoacids partners, via decarboxylation pathway, to give carbon-centered radicals. These radical intermediates are trapped by a low-valent nickel species, forming Ni-C(sp³) complex intermediates that can proceed to oxidative addition with the aryl bromide partner, followed by a reductive elimination step, that leads to the formation of the cross-coupled products (Scheme 4.4). This work is considered one of the fundamental reports regarding metalla-photoredox catalysis, a concept that has moved the scientific interest in developing new dual catalytic methods.

⁷² L. Lv, Z. Qiu, J. Li, M. Liu, C. J. Li, *Nat. Commun.* **2018**, 9, 4739.

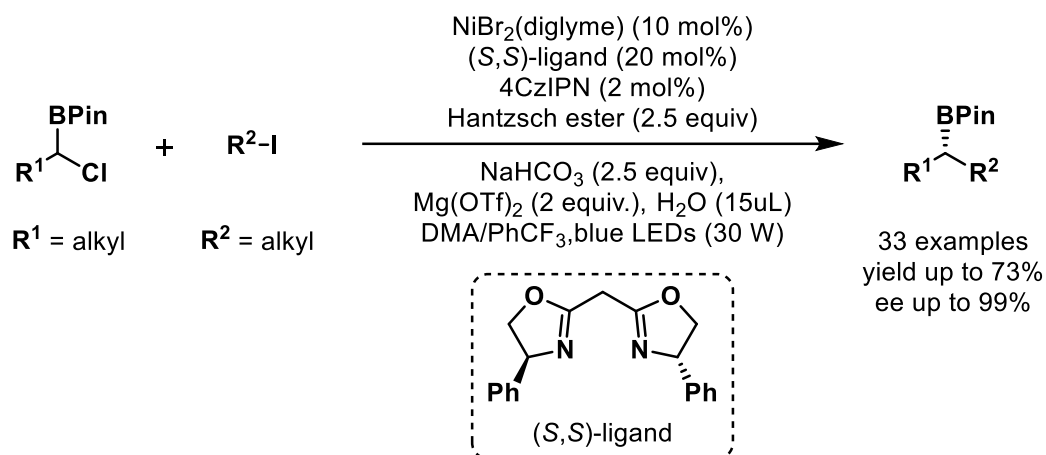
⁷³ Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, 345, 437.



Scheme 4.4: Merging photoredox and nickel catalysis: Coupling of α -carboxyl sp^3 -carbons with aryl halides.

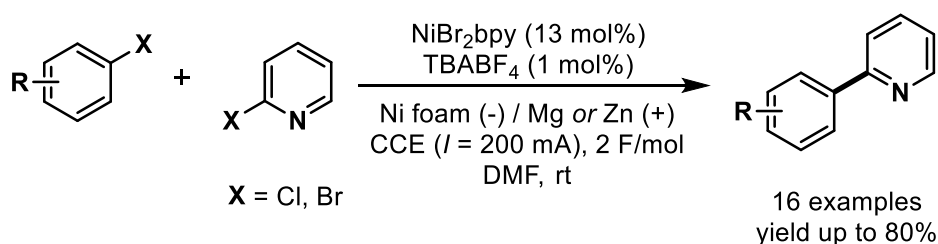
Following the interest regarding dual catalytic methods, Xu et al., in 2023, reported an unprecedented enantioselective $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ reductive cross-coupling by the direct utilization of two different alkyl halides by taking advantage of a dual nickel/photoredox catalytic system (Scheme 4.5).⁷⁴ Among other products that can be prepared following this methodology, this strategy allows the formation of enantioenriched secondary alkyl boronic esters, driven by the stereo-induction exerted by the selected BOX ligand. In this study, the Hantzsch ester is used as the reducing agent.

⁷⁴ J. Zhou, D. Wang, W. Xu, Z. Hu, T. XU, *J. Am. Chem. Soc.* **2023**, 145, 2081.



Scheme 4.5: Enantioselective C(sp³)-C(sp³) Reductive Cross-Electrophile Coupling of Unactivated Alkyl Halides with α-Chloroboronates via Dual Nickel/Photoredox Catalysis.

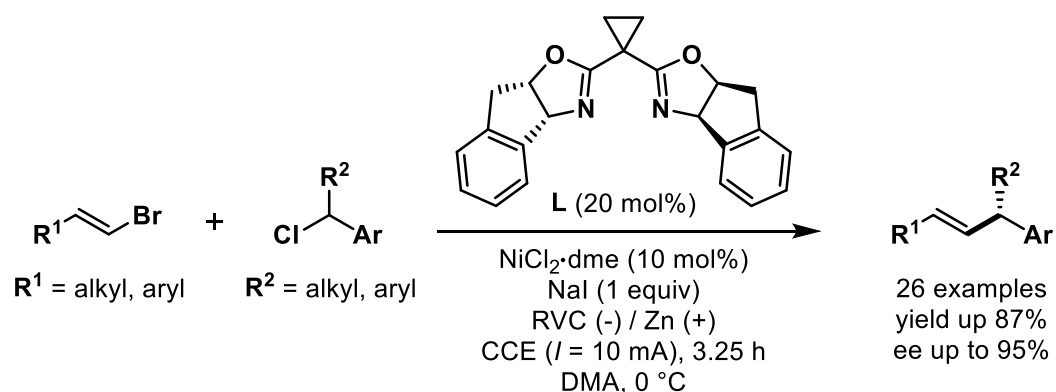
In the context of electrochemically promoted XECs, Nickel has emerged as one of the most widely used catalyst. The use of electric current to turn over the nickel catalyst eliminates the need for super-stoichiometric metal powder reductants. Electrosynthesis thus acts as a valuable platform for the development of new Nickel-catalyzed cross-coupling methodologies. As one of the first report, Perishon et al.,⁷⁵ in 1998 developed an electrochemical nickel-catalysed method to couple aryl halides with 2-halopyridines (Scheme 4.6). The reaction proceeds via cathodic reduction of the nickel catalyst, generating low-valent nickel species that can activate both partners of the reaction, thereby enhancing the selectivity toward the cross-coupling rather than the homocoupling.



Scheme 4.6: Ni-catalysed eXEC between 2-Halopyridines and Aryl halides.

⁷⁵ C. Gosmini, S. Lasry, J. Y. Nedelec, J. Perichon, *Tetrahedron* **1998**, 54, 1289.

Following the interest toward electrochemically driven cross-electrophile couplings, Reisman et al. reported an enantioselective reductive process between alkenyl bromides and benzyl chlorides, catalyzed by a chiral nickel BOX complex, demonstrating that asymmetric nickel-catalyzed cross-electrophile couplings can be achieved.⁷⁶ The reaction forms products bearing allylic stereogenic centers with good enantioselectivity under mild conditions. Also in this case, the transformation involves the generation of low-valent nickel species capable to activate the two electrophiles and, therefore promote the new C-C bond formation (Scheme 4.7).



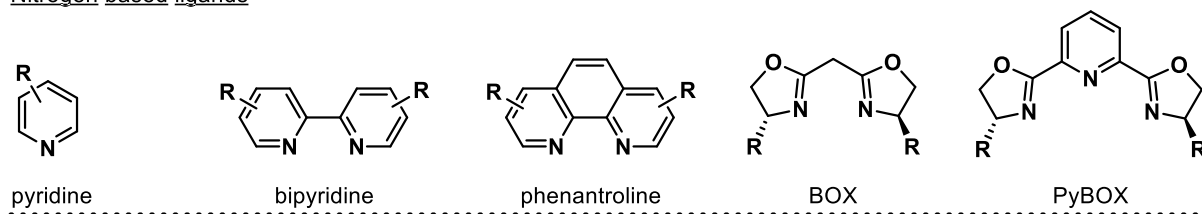
Scheme 4.7: Enantioselective Electroreductive Coupling of Alkenyl and Benzyl Halides.

⁷⁶ T. J. DeLano, S. E. Reisman, *ACS Catal.* **2019**, 9, 6751.

4.1.2 Ligands

In the field of transition-metal catalysis, a ligand is a molecule capable to coordinate a metal centre, modulating important characteristics such as solubility, steric hindrance and electronic properties. As highlighted in the previous section, the choice of the proper ligand can strongly influence the outcome of the reaction.⁵⁵ Beyond the stabilization of the metal, the electronic properties of the ligand and the geometry of the coordination sphere can tune the electron density at the metal centre, guiding the elementary steps of the reaction such as not only oxidative addition and reductive elimination, but also radical capture and migratory insertion. For these important factors, ligands represent a critical parameter in the optimization of nickel-catalyzed cross-electrophile couplings (Figure 4.1).

Nitrogen based ligands



Phosphine based ligands

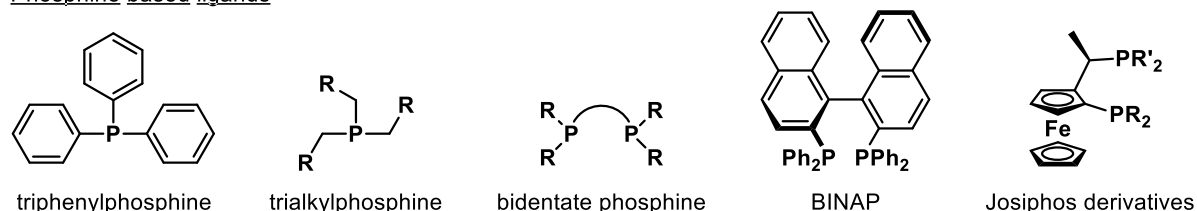


Figure 4.1: Most commonly used ligands in Ni-catalyzed XEC.

Various ligand classes have been explored in the field of XEC, with bipyridine derivatives remaining the most commonly employed, being roughly one-third of reported systems, and nitrogen-donor ligands overall represent approximately 85% of all examples (Figure 4.2). Bidentate ligands dominate the field ($\approx 79\%$), yet substrate-dependent trends are evident: monodentate ligands such as pyridine and tridentate systems such as terpyridine or bpp are often more prone than bidentate ligands in tertiary alkyl–aryl couplings, and tridentate ligands appear particularly effective in $C(sp^3)–C(sp^3)$ bond formations. Emerging ligand classes such as carboxamidine derivatives (e.g., PyCam and PyBCam) are gaining attention, but further expansion of

ligand design remains highly desirable. In enantioselective XEC, the landscape is similarly concentrated, being largely dominated by BiOx, PyOx, and BOX frameworks.

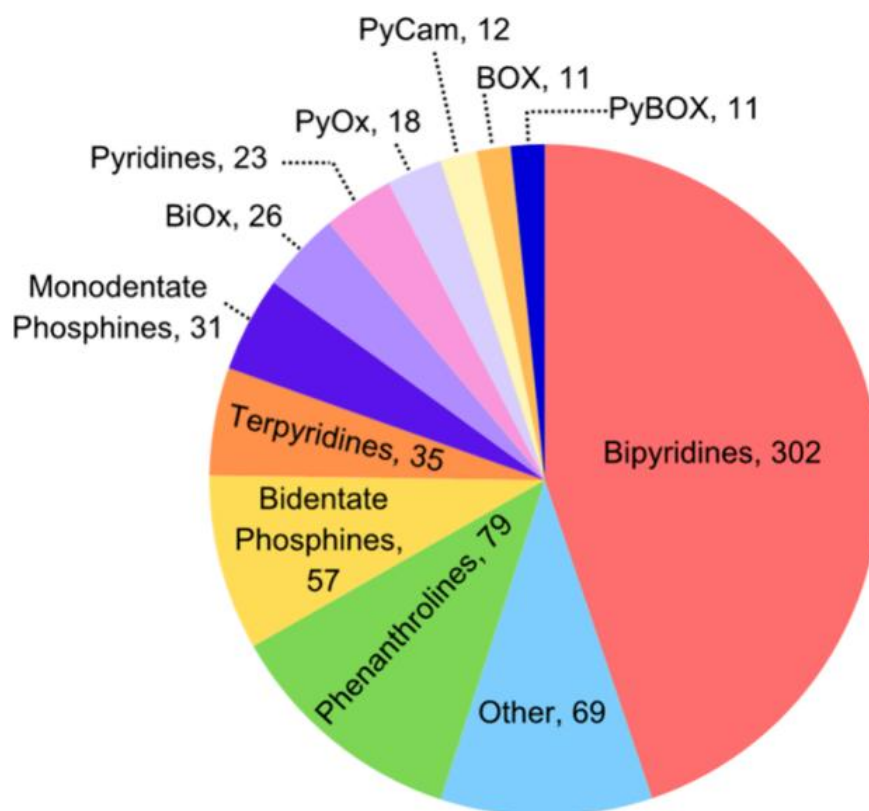
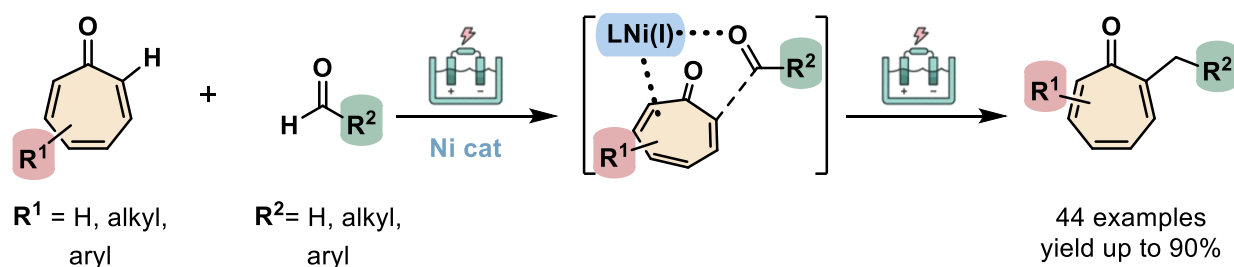


Figure 4.2: Ligand distribution.

4.2 Aim of the work

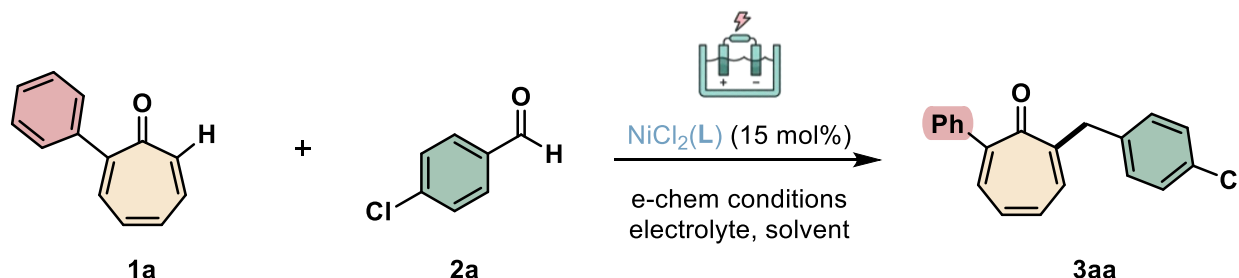
The selective C–H functionalization of Tropones remains an underexplored challenge. While electrochemical and ligand-controlled nickel-mediated C(sp²)–H and C(sp³)–C(sp²) bond formations have significantly been explored in recent years, methodologies that can selectively couple tropones with electrophilic carbonyl partners are scarce. Our idea was to develop a strategy for a nickel-catalyzed cross-electrophile coupling directed to the functionalization of the troponone scaffold with aldehydes partners, achieving the formation of new C–C bonds under reductive catalytic conditions (Scheme 4.8). The atypical reactivity of the formal C=O unit, together with its high propensity toward dearomatization processes, represents a major limitation that still narrow this scenario. To address these issues, we propose a new functionalization strategy based on a chemical conceptual analogy between tropones and α,β -unsaturated compounds (i.e., cyclohexanone or methyl acrylate). In particular, our approach is inspired from the well-established deoxygenative Baylis–Hillman reaction, where the (redox-neutral) Baylis–Hillman reaction is followed by a distinct reductive deoxygenation step.



Scheme 4.8: General scheme for Electrochemical Nickel-Catalyzed C(sp²)-H Functionalization of Tropones with Aldehydes.

4.3 Results and discussion

4.3.1 Protocol optimization



Scheme 4.9: General scheme of the optimized reaction.

We started our investigation by selecting Phenyl-tropone **1a** and p-chlorobenzaldehyde **2a** as optimal substrates and we targeted diverse readily available air stable bispyridil-Ni(II) complexes $[\text{Ni}(\text{L})\text{Cl}_2]$ as catalyst (Table 4.1, entries 2-7) (Figure 4.3). The reaction outcome without Nickel-catalyst (Table 4.1, entry 1) was inefficient (15% yield), rendering the catalyst essential for the synthetic utility of the process. Notably, a monodentate phosphine ligand (PtBu_3 (2 equiv.)) was inefficient for the reaction outcome as well (Table 4.1, entry 8), unraveling bipyridyl ligands as the most suitable ones to promote the desired transformation with 4,4'-(OMe)₂-bpy proving to be the best among those tested (Table 4.1, entry 2),

Entry	Current (mA)	F/mol _{2a}	C (+) II A (-)	Ligand (L) ^[b]	Yield (%) ^[c]
1	2	4	Ni II Zn	No catalyst	15
2	2	4	Ni II Zn	L1	83
3	2	4	Ni II Zn	L2	39
4	2	4	Ni II Zn	L3	65
5	2	4	Ni II Zn	L4	60
6	2	4	Ni II Zn	L12 ^[c]	56
7	2	4	Ni II Zn	L13 ^[c]	nd
8	2	4	Ni II Zn	L52 ^[c]	nd

Table 4.1: Ligand screening. ^[a] All reactions were carried out in an ElectraSyn 2.0 apparatus by means of undivided cell strategy at room temperature. Anhydrous conditions and inert atmosphere (i.e. Ar), were applied. **1a/2a/** TEABF₄ as electrolyte = 2:1:1.5, **[2a]**: 0.05 M in DMF. ^[b] isolated yield after flash chromatography. ^[c] equivalents of ligand.

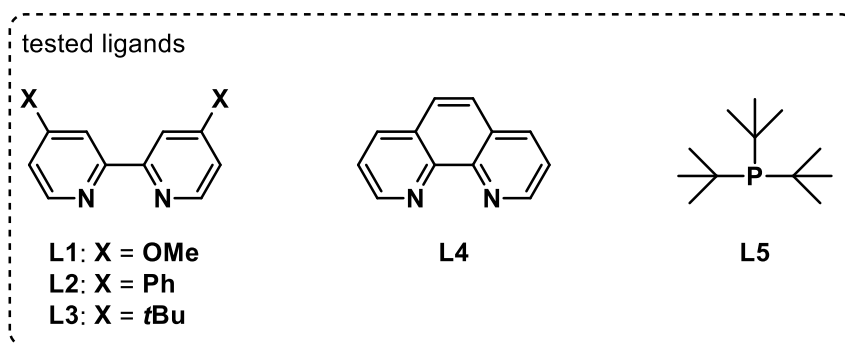


Figure 4.3: tested ligands during optimization studies.

After the ligand investigation, we proceeded with our optimization by changing various electrochemical setups, such as varying the electrode couples (Table 4.2, entries 1-6) and electrolytes (Table 4.2, entries 7-9). We decided to keep the nickel / zinc couple, given the fact that other metal electrodes resulted in less efficient reactions. Reducing the concentration of TEABF₄ resulted in a less efficient process and also using electrolytes bearing different anions or cations gave a non-synthetically useful yield.

Entry	Current (mA)	F/mol _{2a}	C (+) A (-)	Electrolyte	Yield (%) ^[b]
1	2	4	W Zn	TEABF ₄	75
2	2	4	C Zn	TEABF ₄	nd
3	2	4	SS Zn	TEABF ₄	54
4	2	4	Ag Zn	TEABF ₄	nr
5	2	4	Au Zn	TEABF ₄	72
6	2	4	Ni Mg	TEABF ₄	nd
7	2	4	Ni Zn	TEABF ₄ ^[c]	52
8	2	4	Ni Zn	LiBF ₄	24
9	2	4	Ni Zn	TEACl	> 10

Table 4.2: Electrochemical setup screening. ^[a] All reactions were carried out in an ElectraSyn 2.0 apparatus by means of undivided cell strategy at room temperature. Anhydrous conditions and inert atmosphere (i.e. Ar), were applied. **1a/2a**/ TEABF₄ as electrolyte = 2:1:1.5, **[2a]**: 0.05 M in DMF. ^[b] isolated yield after flash chromatography. ^[c] TEABF₄ (10 mol%).

Finally, the investigation was directed toward the electrochemical parameters such as current and F/mol, while also changing the relative stoichiometry of tropone **1a** and aldehyde **2a**. We noticed that 2 equivalents of **1a**, with respect of **2a**, are needed for the best reaction outcome, indeed lowering the tropone concentration leads to a

scarcely efficient process (Table 4.3, entries 1-2). 4 F/mol_{2a} are also necessary to consume all starting material **2a** (Table 4.3, entry 3). Finally, after screening different values of current intensity (Table 4.3, entries 4-5) we decided to keep 2 mA as the best choice. It is worth to notice that, modulating voltage at a constant value (potentiostatic conditions), set at 0.65 V, as the average value usually displayed by electrolyses run under galvanostatic conditions, the reaction outcome was not satisfying (Table 4.3, entry 6).

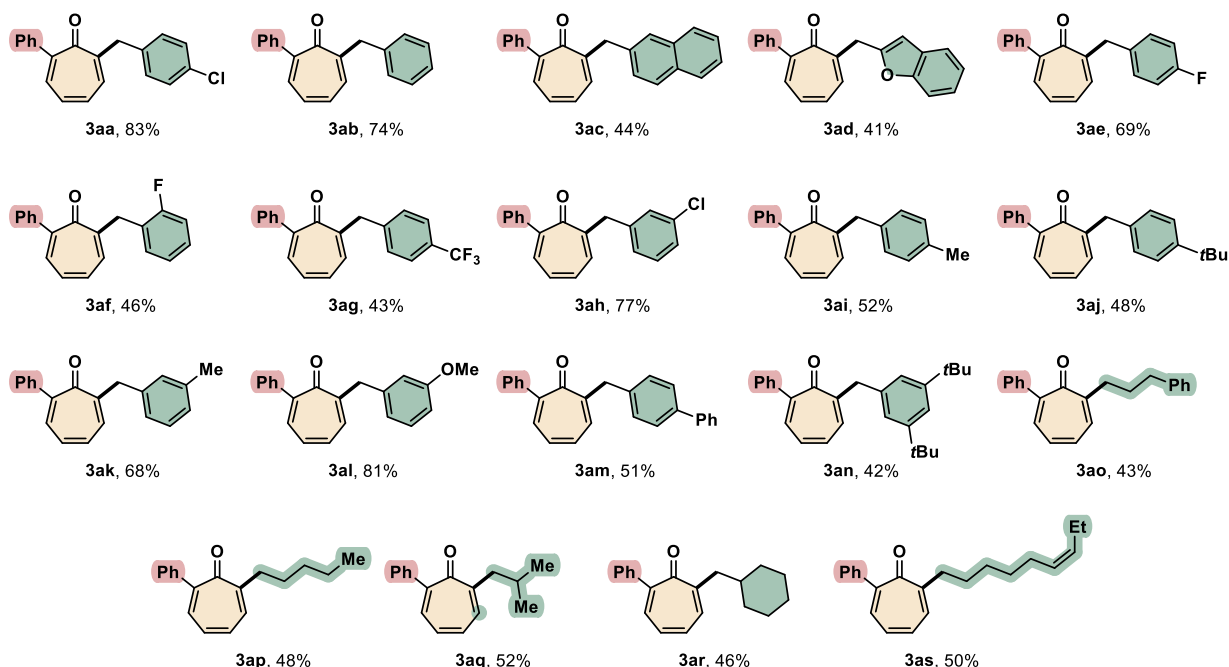
Entry	1a : 2a	Current (mA)	F/mol _{2a}	Yield (%) ^[b]
1	1 : 1	2	2	29
2	1.5 : 1	2	3	55
3	2 : 1	2	2	61
4	2 : 1	1.5	4	41
5	2 : 1	3	4	26
6	2 : 1	CVE (V = 0.65 V)	4	22

Table 4.3: Electrochemical parameters and SM concentration screening. ^[a] All reactions were carried out in an ElectraSyn 2.0 apparatus by means of undivided cell strategy at room temperature. Anhydrous conditions and inert atmosphere (i.e. Ar), TEABF₄ as electrolyte in DMF. ^[b] isolated yield after flash chromatography.

After the investigation we elected Table 4.1, entry 2 as the optimal conditions for the reaction outcome, and we then proceeded to study the generality of the process.

4.3.2 Generality of the process

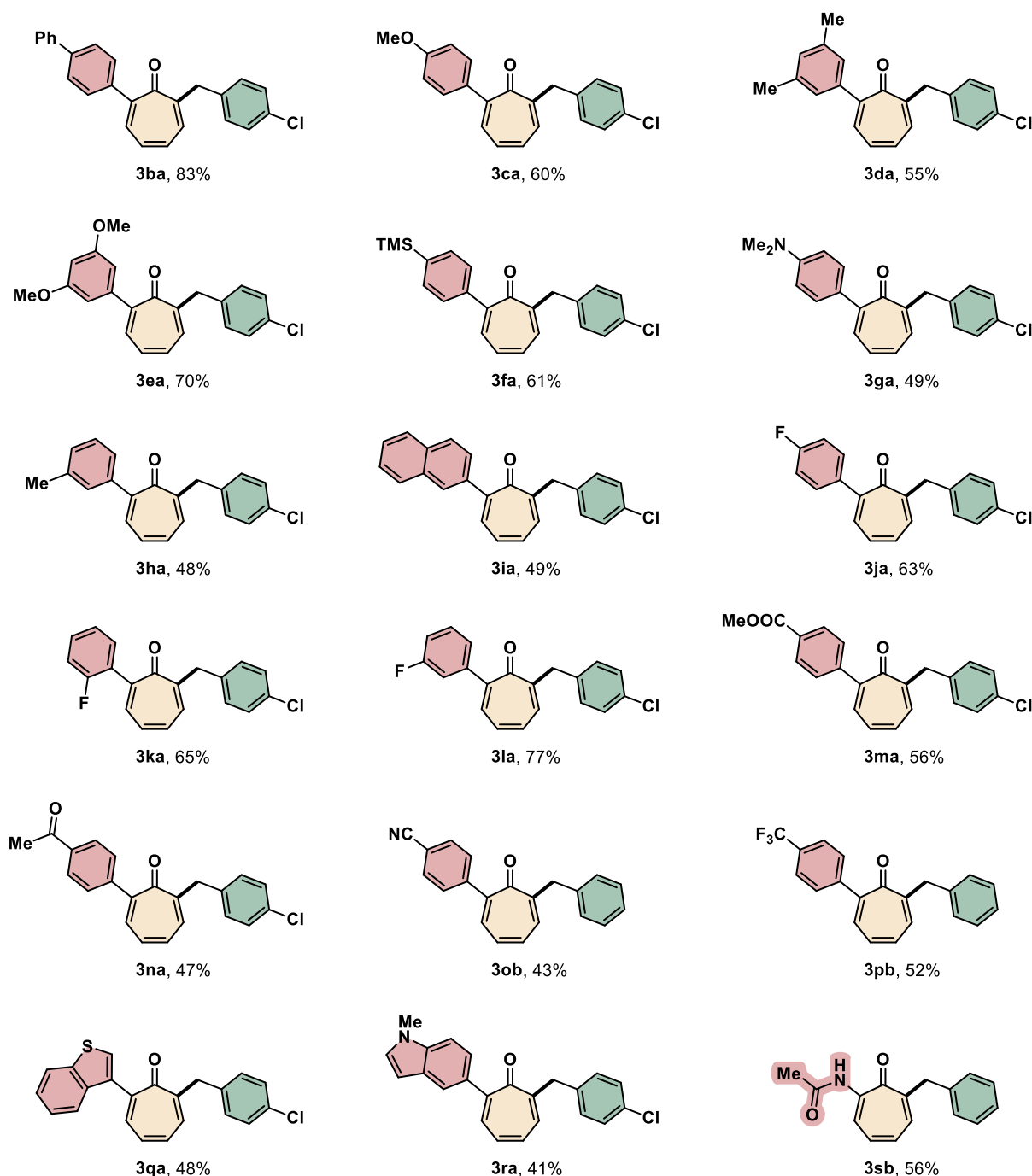
The generality of the present electrochemical procedure was then assessed by subjecting a range of α -substituted tropones (**1b–s**) as well as native tropone **1t** to reductive alkylating conditions with a family of aldehydes **2b–s** (aromatic as well as aliphatic). The obtained results regarding the aldehydes screening are summarized in Scheme 4.10. Aromatic aldehydes (**2b–n**) proved competent as benzylating agents regardless of the nature of the substituents and their positions. In particular, strong as well as mild electron-withdrawing groups (EWGs: F, CF₃, and Cl) could be accommodated at ortho-, meta-, and para-positions, ensuring satisfying levels of chemical outcomes (yield up to 77%). Analogously, aldehydes carrying electron-donating units (EDGs: alkyl, phenyl, and OMe) on the aromatic ring and benzo-fused systems (**2c,d**) underwent α -benzylation of 2-phenyltropone **1a** in synthetically useful yields (44–81%). Interestingly, the alkylation methodology could also be extended to aliphatic aldehydes (**2o,s**). In this regard, linear and branched alkyl chains could be conveniently introduced in the seven-membered ring unit via direct activation of the C(sp²)-H bond (yield up to 52%).



Scheme 4.10: Aromatic and aliphatic Aldehydes screening.

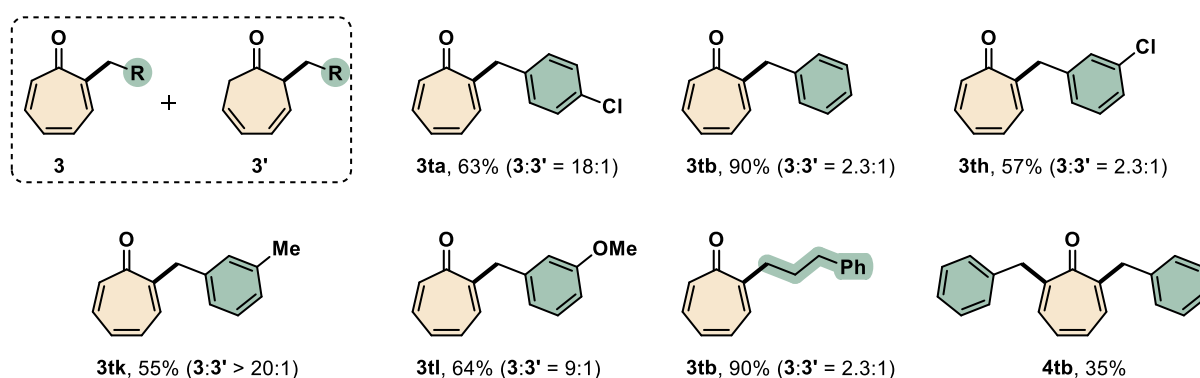
A range of α -aryltropones was also investigated with this protocol (**1b–r**), allowing combinations of substituted α -aryl and α -benzyl units without affecting the

corresponding C–H functionalization/alkylation process (Scheme 4.11). Notably, a wide range of functional groups (e.g., TMS, Ac, and CN) and heteroaromatic arenes were tolerated under these conditions, yielding the desired compounds **3** in moderate to very high yields (up to 83%). An excursion away from the starting aromatics also showed that α -acetamide groups are compatible with this approach (**3sb**).



Scheme 4.11: Aryl Tropone Screening.

Although α -substituted tropones were initially targeted aiming to exploit the higher stability of the corresponding alkylated compounds, we then turned our attention toward the alkylation strategy of native tropone **1t** (Scheme 4.12). Satisfyingly, the electrochemical α -alkylation of the unsubstituted tropone was found to be highly efficient with a range of both aromatic and aliphatic aldehydes. In particular, combined chemical yields up to 90% (including partially reduced cycloheptadienones **3'**) were recorded. The use of tropone **1t** also inspired us to challenge our protocol with a one-pot double alkylation strategy. Interestingly, by using an excess of benzaldehyde (**2b**), the 2,7-dibenzylated tropone **4tb** was isolated in 35% yield.



Scheme 4.12: Non substituted Tropone Screening.

4.3.3 Mechanistic studies

4.3.3.1 Voltametric analysis

In order to initiate the investigation of the reaction mechanism, voltametric analyses were performed on the individual reaction components (Figure 4.4). As revealed from the profiles, collected in a 3-electrode cell, the $[\text{Ni}(\text{L1})\text{Cl}_2]$ complex ($[\text{Ni}]$) shows two successive reduction processes, the first occurring at -1.75 V and the second one at -1.90 V vs the Fc^+/Fc redox couple. Notably, the first reduction event of this complex occurs at less negative potentials than those of substrates **1a** (-1.87 V) and **2a** (-2.18 V). This result suggests that the catalytic cycle is initiated by a single-electron reduction of the Ni(II) complex pre-catalyst to furnish a Ni(I) intermediate.

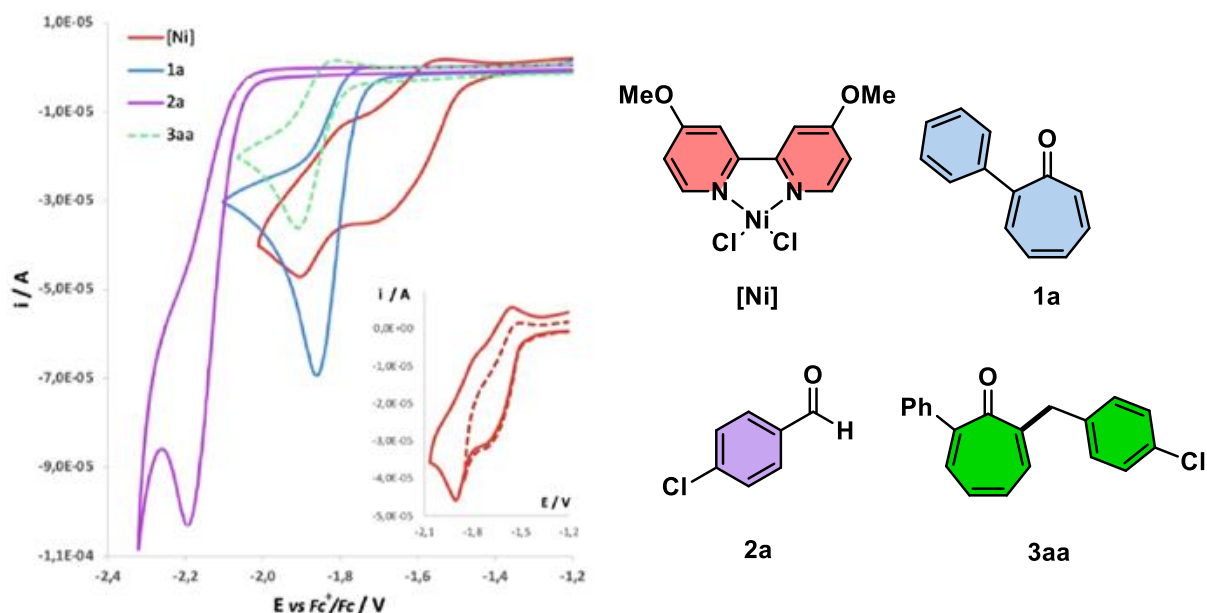


Figure 4.4: CV responses of the individual species participating in the electrochemical reaction.

Then, to gain further details about the initial stages of the catalytic process, additional voltametric studies were conducted on $[\text{Ni}]$ -**1a** mixtures, systematically increasing the concentration of the nickel complex at a constant concentration of **1a** (Figure 4.5). The voltammograms of these analyses revealed a new reduction peak, suggesting the formation of a new species. This behavior can be ascribed to the formation of a $[\text{Ni}]$ -**1a** intermediate during the electrochemical reaction, whose signal increases in intensity along with the concentration of $[\text{Ni}]$. Importantly, this new species undergoes reduction at a more negative potential than the parent $[\text{Ni}]$ complex and also at a

different potential than that expected for the free **L1** (-2.72 V). The distinction of these redox events renders CV analyses reliable for the distinction and characterization of these new species.

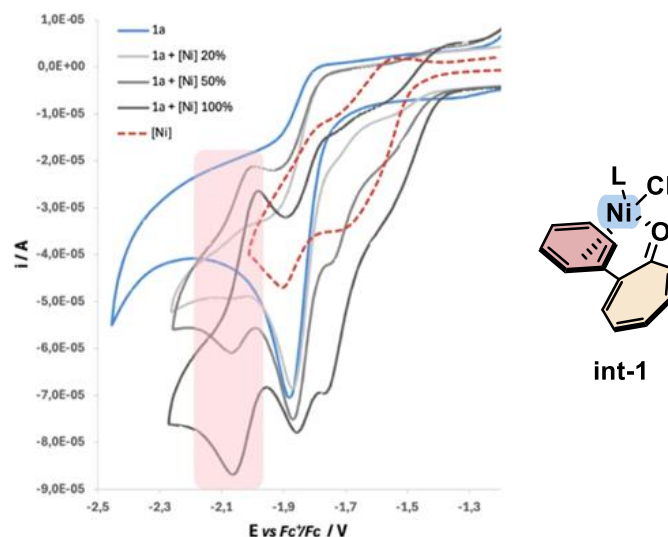


Figure 4.5: CV responses for subsequent addition of [Ni] in a solution containing a fixed amount of **1a** (pink bar highlights the new reversible reduction process ascribable to the intermediate of the reaction).

A similar electrochemical process was also observed by adding progressive amounts of **1a** to a solution maintaining a constant concentration of [Ni] (Figure 4.6).

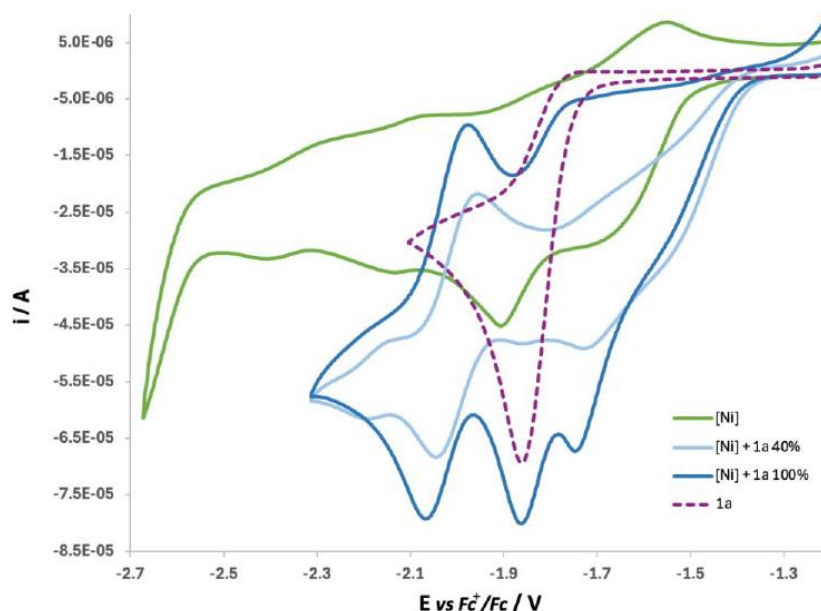


Figure 4.6: CV responses for subsequent addition of **1a** in a solution containing a fixed amount of [Ni].

This new electroactive organo-nickel intermediate was therefore postulated as a key for the formation of **3aa** upon reaction with **2a**.

4.3.3.2 Electro-photoluminescence analysis and DFT calculations

To corroborate this hypothesis, we recorded UV-vis spectra of solutions containing either **1a**, [Ni] or mixtures of the two species while polarizing a Pt grid working electrode. Interestingly, spectra recorded right before (-1.90 V, Figure 4.7 top) and after (-2.20 V, Figure 4.7 bottom) the reversible reduction peak associated with the [Ni]-**1a** intermediate, evidenced that this new species exhibits a main absorption at 560 nm in the neutral form (-1.90 V), or one at 520 nm after being reduced (-2.20 V).

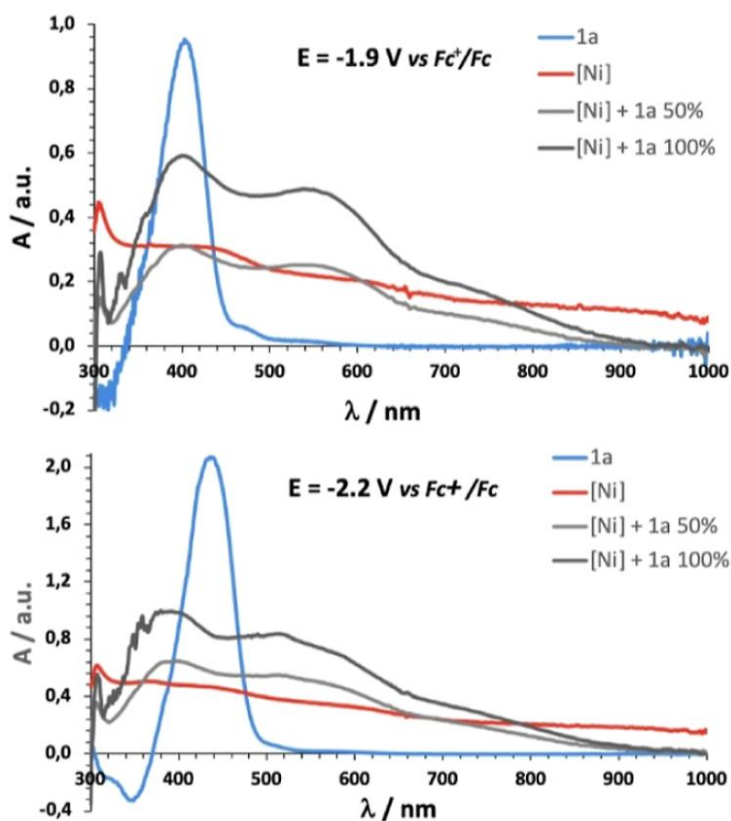


Figure 4.7: UV-vis spectra recorded in the various solutions during the polarization of the electrode at -1.9 V (top) and -2.2 V (bottom) vs Fc^+/Fc .

Furthermore, the lower intensity of the adsorption recorded at 400 nm (i.e., corresponding to reduced **1a**) when analyzing the mixture, suggests that the starting tropone is involved in the reaction with [Ni] for the formation of this intermediate. Indeed, in the presence of [Ni], the species associated with the reduction of free **1a** is progressively depleted (Figure 4.8).

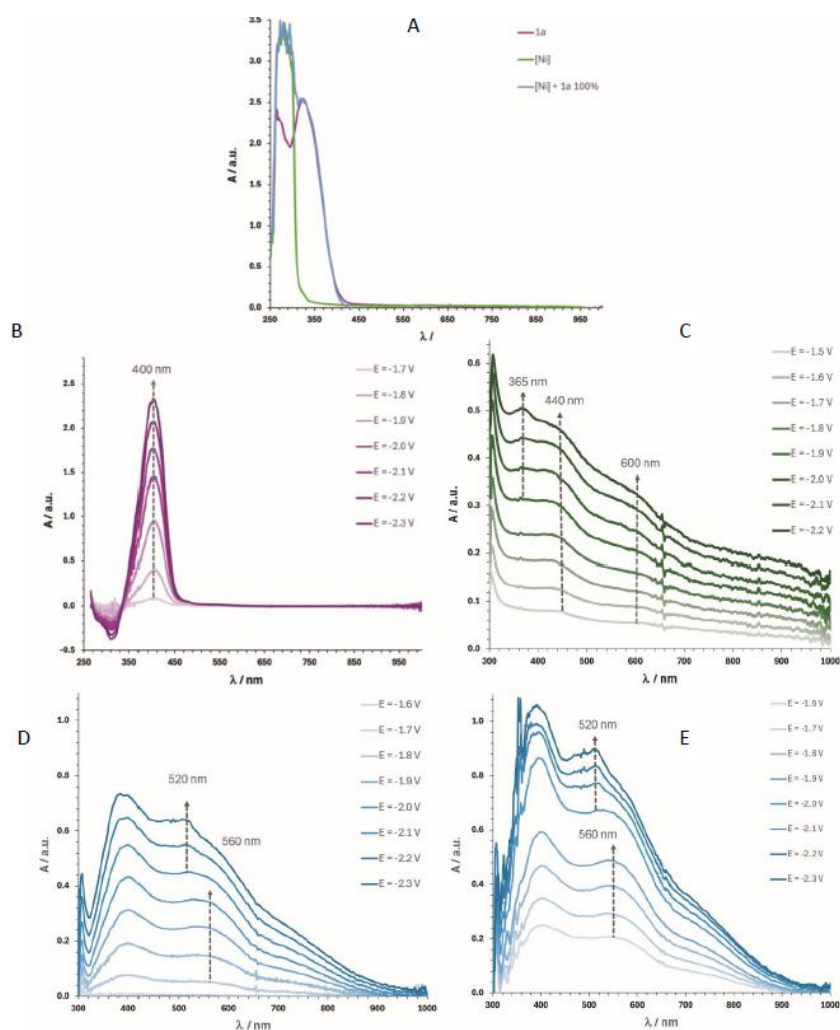


Figure 4.8: The following figures report spectra recorded at different applied potentials in solutions of B) 2.5 mM **1a**, C) 2.5 mM [Ni], D) 2.5 mM [Ni] + 1.25 mM **1a**, E) 2.5 mM [Ni] + 2.5 mM **1a**. In all cases 0.1 TEABF₄ and anhydrous DMF was the solvent medium. Arrows indicate the evolution of the main adsorption peak at the various applied potentials.

We then compared those results with computational simulations on the putative adsorption spectra of the postulated intermediate. We calculated UV-vis spectra for the [Ni(I)(L1)Cl] catalyst and compared them with the experimental spectra shown in Figure 4.9. The calculated absorption peaks for [Ni(I)] at 376 and 442 nm (Figure 4.9, top) are compatible with the experimental values of 365 and 440 nm. As a result, we have collected experimental and computational indications that in the initial stages of the reaction, Ni(II) is reduced to Ni(I), which subsequently reacts to form a complex with **1a**, resulting in an organo-nickel intermediate.

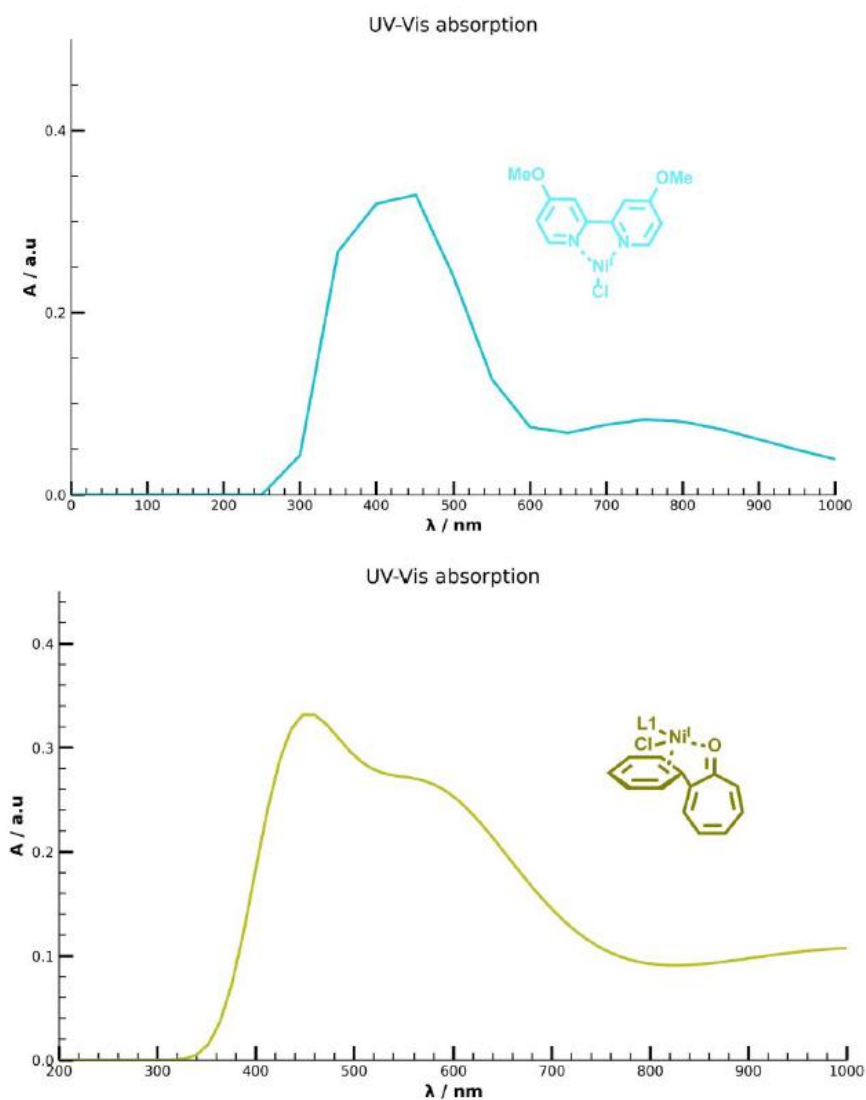
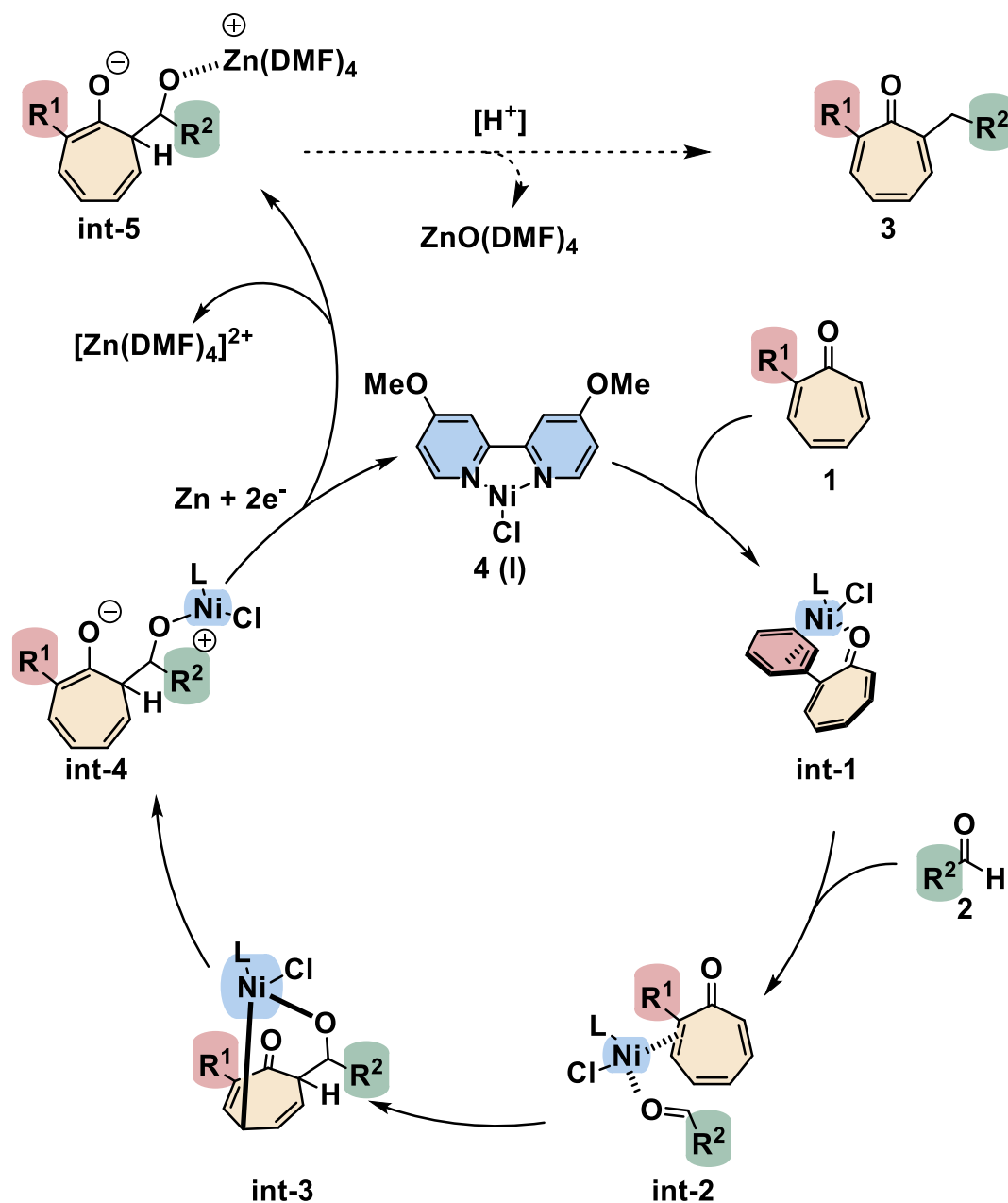


Figure 4.9: (top) DFT computed UV-Vis spectra of the Ni(I)(**L1**)Cl catalyst. The peaks are at 376 and 442 nm, in very good agreement with the experimental values (365 and 440 nm), thus confirming that the reacting catalyst is a Ni(I) species. (bottom) DFT computed UV-Vis spectra of the speculated intermediate organonickel compound. The peaks are at 430, 572, 604 and 607 nm, in very good agreement with the experimental values (400 and 560nm).

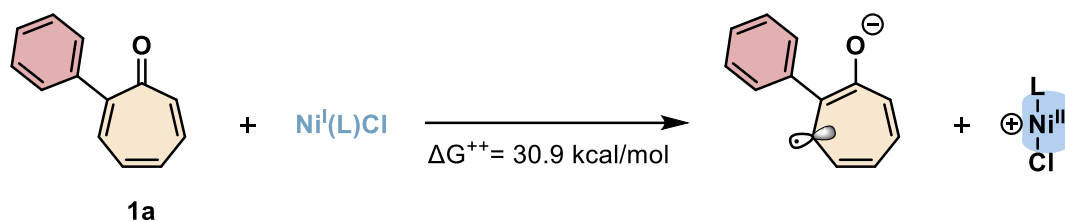
4.3.3.3 Mechanistic proposal (supported by DFT calculations)

The above mentioned results obtained by merging DFT calculations and experimental data, prompted us to perform further computational investigation to gain insights into the mechanism and the nature of the involved organo-nickel species. We employed density functional theory (DFT) calculations conducted at the SMD14 (DMF) M0615/def2svp(p) level of theory, using the Gaussian 09 software. Then, we next investigated the formation of a [Ni]-**1a** species, as suggested by the spectro-electrochemical investigation. Here, our calculations showed that a π -O-chelated organonickel complex intermediate **int-1** is formed in a barrierless exothermic process, stabilized by 4.5 kcal/mol. **int-1** has a chelating-like coordination mode of the Ni(I) metal center with **1a** through contacts involving the π -electron cloud of the phenyl ring (η^2 -like hapticity) and the lone pair of the oxygen atom of the tropone core. The proposed mechanism was thus postulated around the aforementioned **int-1**, whose Ni-center is proposed to act as a tethering unit to bring in proximity benzaldehyde **2b** (weak Ni–O coordination) and tropone **1a** (interacting with the ϵ - ζ double bond) for the formation of **int-2**. This coordination results in a net transfer of electron-density from the metal center to the tropone ring, as supported by the electrostatic potential and the NBO charges computed on **int-2** and **int-3**. In particular, upon nickel coordination (**int-2**), the tropone unit carries a negative charge of -0.43 au, while the aldehyde is unperturbed (+0.06 a.u). This interaction leads to an overall umpolung of reactivity of the tropone and triggers the consequent nucleophilic condensation to the aldehyde. The consequent C–C bond formation event occurs exclusively at the α -carbon of tropone, leading to the organo-Ni(III) **int-3** eventually featuring a C(δ)-Ni bond. Next, the weak Ni–C bond is broken with an activation energy of only 1.4 kcal/mol and a new Ni(III)–O alkoxide **int-4** is obtained. At this point, the final electrochemical reduction of Ni(III) to Ni(I) restores the catalytically active species and a Zn–Ni ion exchange, between **int-3** and the Zn(II) ions liberated from the sacrificial anode, affords the zinc-alkoxide **int-5** in a strongly exothermic step. This last intermediate is ready to furnish the final product either directly or assisted by the mild acidic media used during the work-up process. The mechanism is depicted in Scheme 4.13.



Scheme 4.13: Proposed Reaction Mechanism Computed at the DFT (M06/def2svp(p)) Level of Theory.

Finally, given the well-known propensity of organonickel species to react via single-electron-transfer (SET) processes, we investigated the possibility of a SET event in our case. Interestingly, the single-electron transfer alternative that would turn **1a** into a nucleophilic species, able to trap the electrophilic aldehyde (Scheme 4.14). Due to the high activation energy of 30.9 kcal/mol, this path is not competitive, and the SET mechanism was ruled out.



Scheme 4.14: Excluded SET pathway: **1a** + [Ni(I)] → [1a]^{-•} + [Ni(II)]⁺.

4.4 Conclusions

In conclusion, the combined use of nickel catalysis and electrosynthesis has proven to be a general and efficient strategy for the α -alkylation of tropones via C–H functionalization. The presented electrochemical cross-electrophile coupling involves common aldehydes as alkylating agents, expanding the synthetic versatility of tropone scaffold. A dedicated spectro-electrochemical investigation highlighted the active role of the nickel complex in the redox process, revealing the tropone core to be an effective π -acceptor ligand for the Ni-center, inducing an umpolung of reactivity of the seven-member ring. Furthermore, the catalytic mechanism was computed by DFT calculations, showing strong agreement with both experimental and spectroscopic analyses. In particular, computational studies shed light on the distinct behaviour of the two electrophiles (tropone and aldehyde) in the present cross-coupling and provided insight into the nature of the catalytically active Ni-species.

4.5 Experimental details

4.5.1 General methods and materials

General Methods: ^1H -NMR spectra were recorded on a Bruker 600 spectrometer (600 MHz). Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, td = triple doublet, dt = double triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz). ^{13}C -NMR spectra were recorded on a Bruker 600 spectrometer (150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard. HRMS spectra were obtained with a G2XS QToF mass spectrometer using ESI ionization techniques, as specified case by case. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous solvents, including DCM for the catalytic processes, were supplied by Merck in Sureseal® bottles and used without any further purification. Below the general procedures the characterization of the model compound only is reported. For the complete description of all the products reported as well as starting materials **1** see the Supporting Information of *ACS Catal.* **2025**, *15*, 3184. Liquid aldehydes were distilled under vacuum immediately prior to use. The solid ones were used without purification.

Computational methods: We used Density Functional Theory (DFT) at the M06⁷⁷/def2svp⁷⁸ level for all the calculations presented in this manuscript. All geometry optimizations have been optimized using tight convergence criteria in the SCF and an ultrafine grid to guarantee the accuracy of the reported results. Solvent effects were modelled using the universal solvation model based on solute's electron density (SMD)⁷⁹ with the default parameters for the main mechanism and using the non-equilibrium solvent cage for the SET calculations, as implemented in the Gaussian 09 package.⁸⁰ The *N,N*-dimethylformamide, abbreviated as DMF, was used as the

⁷⁷ Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

⁷⁸ F. Weogend, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057.

⁷⁹ A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.

⁸⁰ Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, F.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.;

solvent, while the calculations were performed considering 1.0 atm and 298 K to simulate the reaction conditions. The nature of all optimized structures was determined using frequency analysis to correctly identify them as minima or transition states. For all stationary points, the stability of the wave function was also examined.⁸¹

Electrochemical and Spectroelectrochemical Methods: Electrochemical characterization of the compounds was performed by cyclic voltammetry (CV). These experiments were carried out with a PGSTAT128N potentiostat driven by a Nova 2.0 software. The voltammetric responses were collected at room temperature in a three-electrode cell under N₂ flux, at 0.05 Vs⁻¹ potential scan rate. The working electrode consisted of a 3 mm diameter glassy carbon electrode (Metrohm), the counter electrode was a Pt wire (Metrohm) and an Ag wire was used as the pseudo-reference electrode. The potentials of the working electrode were finally referred to the ferrocenium/ferrocene redox couple ($E_{\text{Fc}^+/\text{Fc}} = +0.40$ V vs. SCE) by adding a few crystals of ferrocene in the solution. The working electrode surface was polished with 1 and 0.3 μm alumina and sonicated in deionized water for 5 min before the use. The electrochemical experiments were recorded by dissolving the compound under investigation in a 0.1 M tetraethylammonium tetrafluoroborate (TEABF₄) in anhydrous DMF. Where not differently specified, the concentration of the solution was 5 mM. The spectroelectrochemical experiments were carried out coupling the potentiostat with an HP diode array 8453 UV/Vis spectrophotometer, working in the wavelength range 190 $\pm$ 1100 nm. The electrochemical cell consisted in this case in quartz cuvette with an optical path of 100 μm filled with a Pt grid as the working electrode. The 3-electrode cell was completed by a Pt wire and Ag wire as the counter and the pseudo-reference electrodes. The composition of the solutions was similar to that previously reported for CV experiments, but with a concentration of the electroactive species of 2.5 mM, in order to avoid complete saturation of the signal. UV-Vis adsorption spectra were collected while polarizing the working electrode at different potentials in a CV experiment performed at 0.005 Vs⁻¹ and the spectra reported are the variation with respect to the reference one recorded at open circuit potential (Figure S2a). Also in

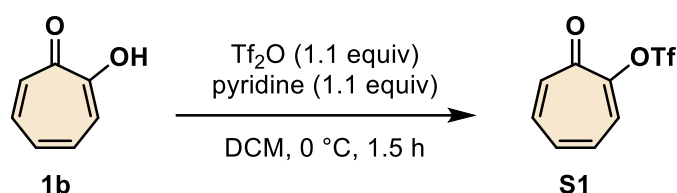
Throssell, K.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, **2009**.

⁸¹ R. Bauernschmitt, R. J. Ahlrichs, *Chem. Phys.* **1996**, *104*, 9047.

this case, the potentials finally reported are referred to the ferrocenium/ferrocene redox couple, by adding a few crystals of this species in the solution. It is possible to estimate that in such a system all the electroactive molecules present in the optical path are reduced on the time scale of the electrochemical tests.

4.5.2 Preparation and characterization data of starting materials

4.5.2.1 Preparation of Tropolone triflate **S1**



Tropolone triflate **S1** was prepared by a slight modification of the procedure reported by Jørgensen *et al.* In a Schlenk tube, under an Ar atmosphere and magnetic stirring, tropolone **1b** (8.0 mmol, 976 mg) was dissolved in dry DCM (25 mL) and the resulting solution was cooled to 0 °C. Then, pyridine (8.8 mmol, 708 μL , 1.1 equiv) and triflic anhydride (8.8 mmol, 1.48 mL, 1.1 equiv) were added dropwise in this order and the resulting suspension was stirred at 0 °C for 1.5 h. Then, while keeping the reaction mixture at 0 °C, a saturated solution of NH_4Cl (10 mL) was added dropwise and the resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, and the aqueous layer was extracted again with DCM (2 x 10 mL). The combined organic phases were then dried with Na_2SO_4 , evaporated *in vacuo* and finally purified by FC on silica gel (*n*-hexane/EtOAc 2:1) to obtain desired product **S1** as a light-yellow oil that solidifies in off-white crystals upon standing at -20 °C overnight (7.6 mmol, 1.93 g, 95% yield). Spectroscopic data match with the one reported in literature.

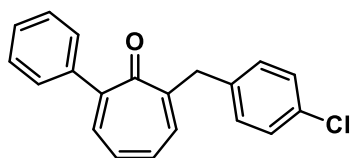
4.5.2.2 Preparation of 2-aryl tropones **1**

In a Schlenk tube, under an Ar atmosphere and magnetic stirring, tropolone triflate **S1** (2.0 mmol, 528 mg), Cs_2CO_3 (5.0 mmol, 1.63 g, 2.5 equiv) and the desired boronic acid (4.0 mmol, 2.0 equiv) were suspended in a THF/ H_2O mixture (10:1, 5.5 mL). The resulting suspension was de-gassed by bubbling Ar for 1 min, then $\text{PdCl}_2(\text{PPh}_3)_2$ (0.10 mmol, 70.0 mg, 5 mol%) was added and the resulting mixture was stirred at 70 °C for 3 h. The reaction mixture was cooled to room temperature and a saturated aqueous solution of K_2CO_3 (5 mL), H_2O (10 mL) and EtOAc (10 mL) were added, and the

resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, the aqueous layer was extracted again with EtOAc (10 mL), the combined organic phases were washed with a saturated aqueous solution of K₂CO₃ (2 x 10 mL), dried with Na₂SO₄, evaporated *in vacuo* and finally purified by FC on silica gel (c-hexane/EtOAc mixtures) to obtain desired products **1**.

4.5.2.3 Preparation and characterization of compound **3**

The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with the appropriate tropone derivative **1** (0.30 mmol, 2.0 equiv.), NiL₁Cl₂ (0.023 mmol, 15 mol%, 7.8 mg), TEABF₄ (0.30 mmol, 65 mg) and the appropriate aldehyde **2** (0.15 mmol, 1 equiv). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ni), was inserted into the mixture and closed with a rubber septum. The vessel was evacuated and backfilled with Ar three times, then dry DMF (3.0 mL) was added, and the mixture stirred until complete dissolution of the solids occurred, while bubbling with Ar (balloon, 1 min). The reaction mixture was electrolyzed (under Ar, balloon) at a constant current of 2.0 mA, until a total charge of 0.60 mF (4.0 F/mol₂) was reached. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and NH₄Cl_(aq) (saturated, 5 mL) and water (5 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with NH₄Cl_(aq) (0.1 M, 3 x 10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was finally purified by FC to afford pure products **3**.



3aa. Pale brown sticky oil. FC eluent: *n*-hexane/EtOAc: 18:1. Yield = 83% (0.125 mmol, 38.1 mg). ¹H NMR (600 MHz, CDCl₃) δ = 7.38 (d, *J* = 4.5 Hz, 4H), 7.36 – 7.32 (m, 2H), 7.28 – 7.25 (m, 2H), 7.24 – 7.22 (m, 2H), 7.15 (dq, *J* = 8.5, 1.0 Hz, 1H), 6.98 (ddd, *J* = 10.8, 8.6, 1.2 Hz, 1H), 6.91 (ddd, *J* = 10.8, 8.5, 1.1 Hz, 1H), 4.01 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ = 184.8, 152.7, 149.7, 139.9, 137.1, 134.7, 133.7, 131.2, 131.2, 131.1, 129.8 (2C), 128.1 (2C), 127.6 (2C), 127.1, 127.1 (2C), 40.0; HRMS (ESI) *m/z*: [M + H]⁺ calcd. for C₂₀H₁₆ClO 307.0884; found 307.0891.

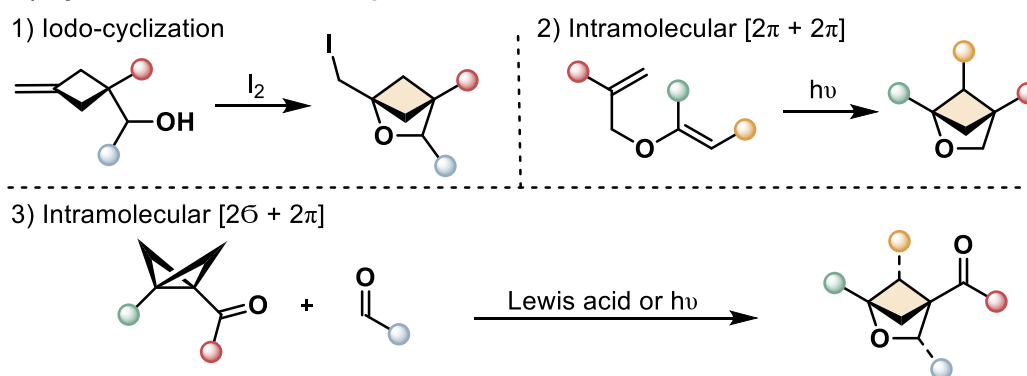
Chapter 5: Electrochemical Synthesis /Functionalization of 2-Oxabicyclo[2.1.1]hexanes by Anodic Oxidation-Cyclization Relay Strategy

All the procedures and results here described are part of- and can be found in:-

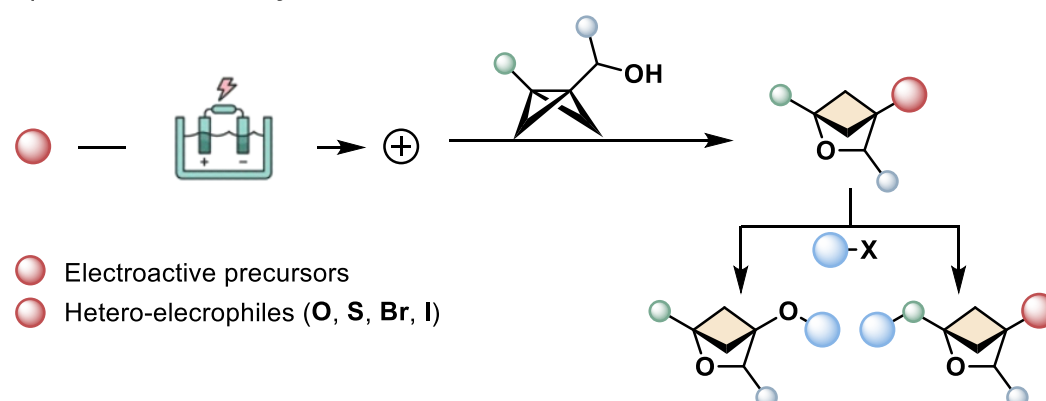
A. Brunetti, G. Monda, A. Mazza, M. Monari, G. Bertuzzi and M. Bandini
 “Electrochemical Synthesis/Functionalization of 2-Oxabicyclo[2.1.1]hexanes by Anodic Oxidation-Cyclization Relay Strategy” *manuscript under revision*.

Abstract

A) Synthesis of 2-oxaBCHs: previuos works



B) Electrochemical Synthesis of 2-oxaBCHs: this work



A general electrosynthetic strategy for the preparation and direct functionalization of 2-oxabicyclo[2.1.1]hexanes (i.e. 2-oxaBCHs) from hydroxymethyl-substituted bicyclo[1.1.0]butanes is reported. The method relies on the anodic generation of electrophilic heteroatom-centred species, including TEMPO-derived oxy-cations, halogen radicals, and thiyl radicals, rendering C(4) functionalized 2-oxaBCHs selectively in good to excellent yields. The protocol operates under mild conditions,

avoids stoichiometric oxidants, and displays broad substrate scope. The synthetic utility of the resulting scaffolds is further demonstrated through late-stage functionalization, bio-conjugation, and telescoped synthesis from commercially available precursors. Mechanistic studies support a pathway involving anodic oxidation for the formation of the electrophilic trigger followed by C–C bond capture and transannular intramolecular cyclization. Overall, this work establishes electrosynthesis as a powerful platform for the modular construction and diversification of 2-oxaBCHs with potential relevance in drug discovery and for expanding the chemical space of benzene bioisosteres.

5.1 Introduction

5.1.1 Bicyclo[1.1.0]butanes: structure and properties

Bicyclo[1.1.0]butanes (BCBs) are highly strained carbocyclic systems characterized by two fused cyclopropane rings sharing a common bond, resulting in a compact and rigid bicyclic framework. BCBs adopt a so called “butterfly” conformation, with the two cyclopropane rings bending from a planar conformation by 120-125° (Figure 5.1).⁸² Interestingly, the length of all C-C bonds is nearly identical and it is approximately 1.50 Å. The values of both the degree of distortion and the bond lengths depend on the substitution at the BCB moiety.⁸³ In particular, axial bridge substituents force an opening of the butterfly structure, increasing both the length of the central C-C bond and the angle between the cyclopropane rings. The internal cyclopropane angles are around 58-62°, representing a substantial deviation from the typical angle of 109.5° present in saturated hydrocarbons. This peculiar angular distortion is the major contributor to the high strain energy of BCBs ($\approx 64 \text{ kcal}\cdot\text{mol}^{-1}$), which is more than twice as high as the strain energy of the cyclopropane ring ($\approx 28 \text{ kcal}\cdot\text{mol}^{-1}$).⁸⁴ The frontier molecular orbitals of BCBs, particularly those associated with the central C-C bond, deserve particular consideration. Computational studies by Schulman and Fisanick showed that the molecular orbital has limited π character, estimated as 5:1 ratio of p - σ to p - π , although the atomic orbitals involved in the formation of the central bond are almost exclusively p , with an sp^2 hybridization of the involved carbons.⁸⁵

⁸² L.C. Snyder, S. Meiboom, *Acc. Chem. Res.* **1971**, 4, 81.

⁸³ P. G. Gassman, M. L. Greenlee, D. A. Dixon, S. Richtsmeier, J. Z. Gougoutas, *J. Am. Chem. Soc.* **1983**, 105, 5865.

⁸⁴ B. Wiberg, *Angew. Chem. Int. Ed.* **1986**, 25, 312.

⁸⁵ G. J. Fisanick, J. M. Schulman, *J. Am. Chem. Soc.* **1970**, 92, 6653.

Properties of bicyclobutanes

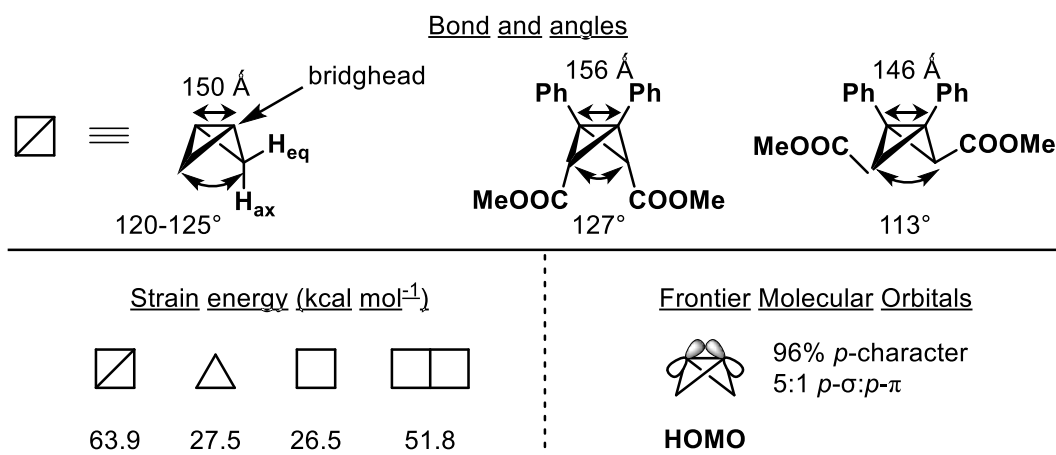


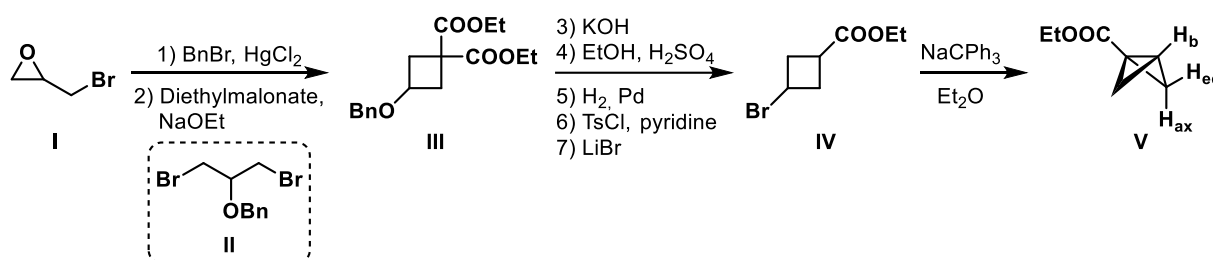
Figure 5.1: Properties of bicyclobutanes.

The peculiar combination of unique electronic structure and high strain energy renders bicyclobutanes powerful and versatile tools for the development of new methodologies and the study of new reactivity paradigms in organic synthesis.⁸⁶

⁸⁶ M. Golfmann, J. C. L. Walker, *Commun Chem* **2023**, 6, 9.

5.1.2 Bicyclobutanes synthesis

In recent years, a wide range of new synthetic methodologies, leveraging the enhanced reactivity of the BCB framework, has been reported, and these discoveries have often gone in parallel with the development of more efficient methods for their preparation. In 1959, Wiberg and Ciula were able to develop the first synthetic route to prepare and characterise the first example of a substituted bicyclo[1.1.0]butane:⁸⁷ starting from epibromohydrin **I** to obtain the corresponding benzyloxy- α -dibromide **II** after a benzyl bromide promoted ring opening. This compound was employed in the (intramolecular) double alkylation of diethyl malonate to afford cyclobutane **III**. Subsequent decarboxylation and conversion of the benzyl ether functionality in a bromide led to the desired intermediate **IV**, which was optimal for the intramolecular ring-closure to furnish the projected BCB **V** by transannular elimination (Scheme 5.1).

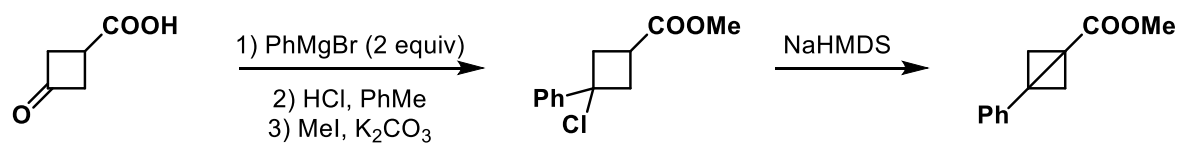


Scheme 5.1: First synthesis of BCB, Wiberg and Ciula.

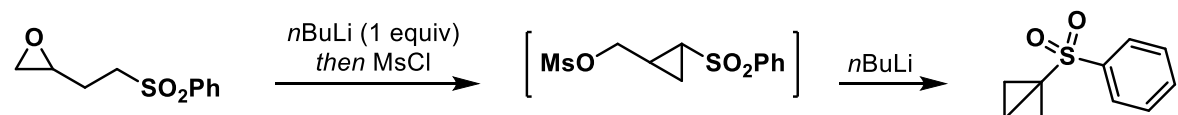
Today, many routes have been developed and the most commonly used can be categorised by the cyclization manifold; either through formation of the internal C–C bond, a strategy named *transannular cyclization*, or through formation of one of the peripheral C–C bonds, a strategy named *chain cyclization*. Another less used method involves cyclopropanation to form one or both cyclopropane rings (Scheme 5.2).

⁸⁷ K. B. Wiberg, R. P. Ciula, *J. Am. Chem. Soc.* **1959**, *81*, 5261.

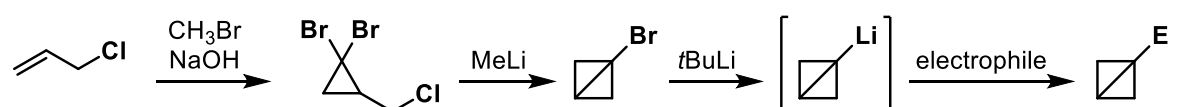
A) Transannular Cyclisation: from 3-oxocyclobutanecarboxylic acid, Mykhaliuk et al.



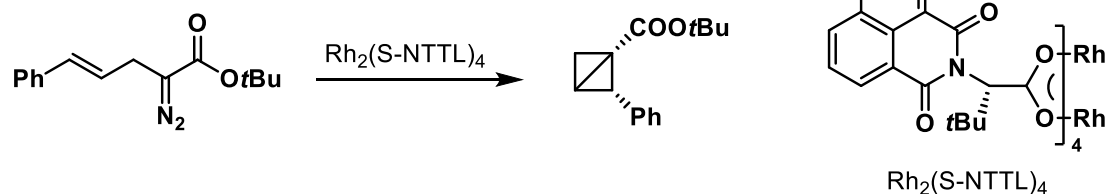
B) Side-chain Cyclisation: via epoxysulphone, Gaoni et al.



C) Side-chain Cyclisation: via dibromocyclopropane, Düker and Szeimies



D) Cyclopropanation: Fox et al.



Scheme 5.2: Synthesis methods for BCBs. A) Transannular Cyclization,⁸⁸ B) Side-chain Cyclisation,⁸⁹ C) Side-chain Cyclization,⁹⁰ D) Cyclopropanation.⁹¹

⁸⁸ R.M. Bychek, V. Hutskalova, Y. P. Bas, O. A. Zaporozhets, S. Zozulya, V. V. Levterov, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, 84,15106.

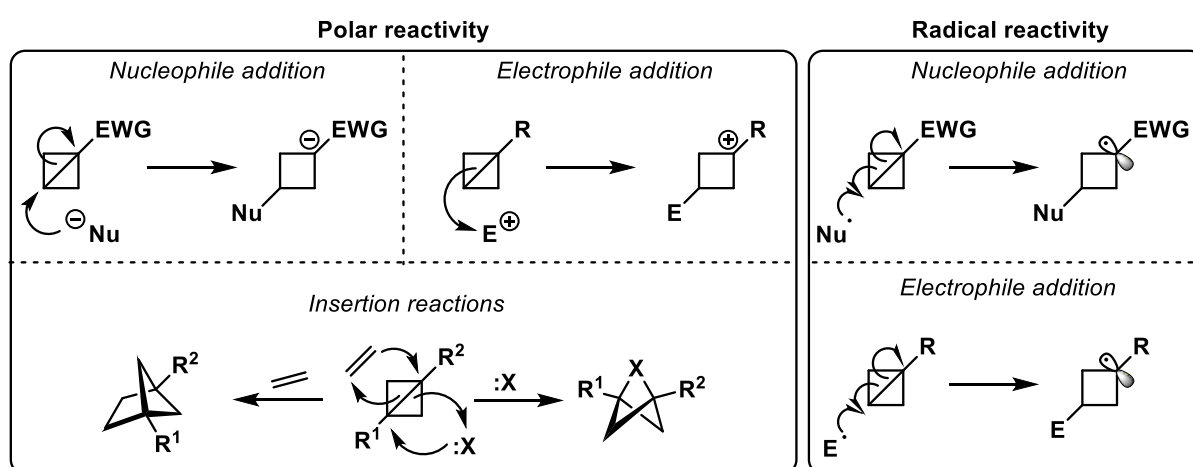
⁸⁹ Y. Gaoni, *Tetrahedron Lett.* **1981**, 22, 4339.

⁹⁰ A. Düker, G. Szeimies, *Tetrahedron Lett.* **1985**, 26, 3555.

⁹¹ R. Panish, S. R. Chintala, D. T. Boruta, Y. Fang, M. T. Taylor, J. M. Fox, *J. Am. Chem. Soc.* **2013**, 135, 9283.

5.1.3 Bicyclobutanes reactivity

The strained central C–C bond dominates the reactivity of the BCB moiety, and reactions that lead to its cleavage are highly favoured thanks to the release of strain energy. This distinctive reactivity has been exploited in a wide range of transformations (Scheme 5.3). In particular, BCBs participate in polar reactions: both electrophilic and nucleophilic addition (usually a Lewis acid is employed to enhance the reactivity of the strained C–C bond), as well as insertion processes have been thoroughly investigated. Their employment in radical chemistry with successful examples involving both electrophilic and electrophilic radical species is also reported.

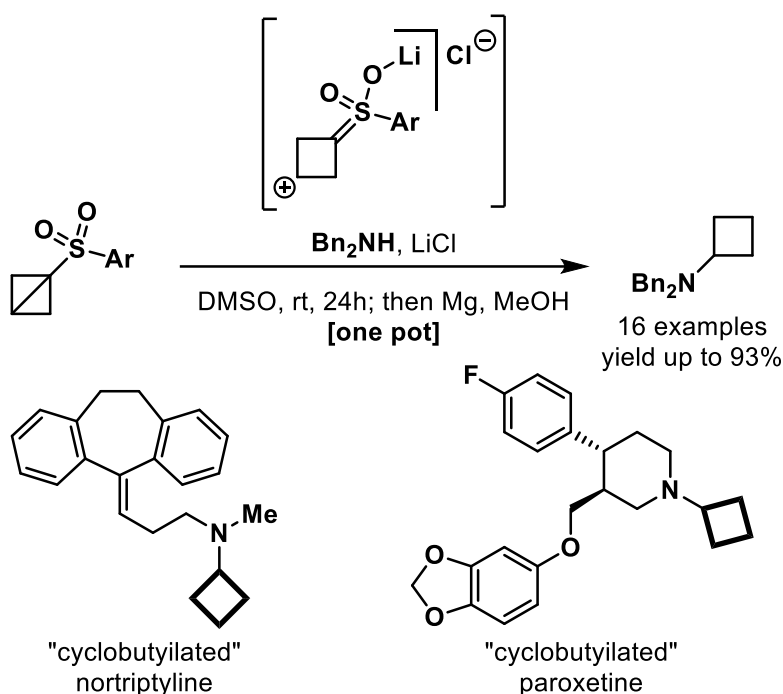


Scheme 5.3: General reactivities of BCBs scaffold, both polar and radical reactivity.

The broad reactivity profile of BCBs allows them to be flexible building blocks for the synthesis of a wide range of structural targets, from relatively simple cyclobutanes to more complex bridged, fused and spirocyclic motifs. Regarding the aforementioned polar reactivity of BCBs, in 2016, Ginatassio, Baran et al. reported a strain-release amination strategy exploiting an electron-poor bicyclobutane moiety, which acts as electrophilic platform for the nitrogen-containing functional groups of the coupling partners.⁹²

⁹² R. Ginatassio, J. M. Lopchuk, J. Wang, C. M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, 351, 241.

In this methodology, a Lewis Acid such as LiCl, is fundamental for the polar activation of the central strained C-C bond, leading to a highly reactive intermediate that undergoes the nucleophilic attack responsible for the ring opening (Scheme 5.4). Notably, this protocol was also used to synthesize four commercial drugs.

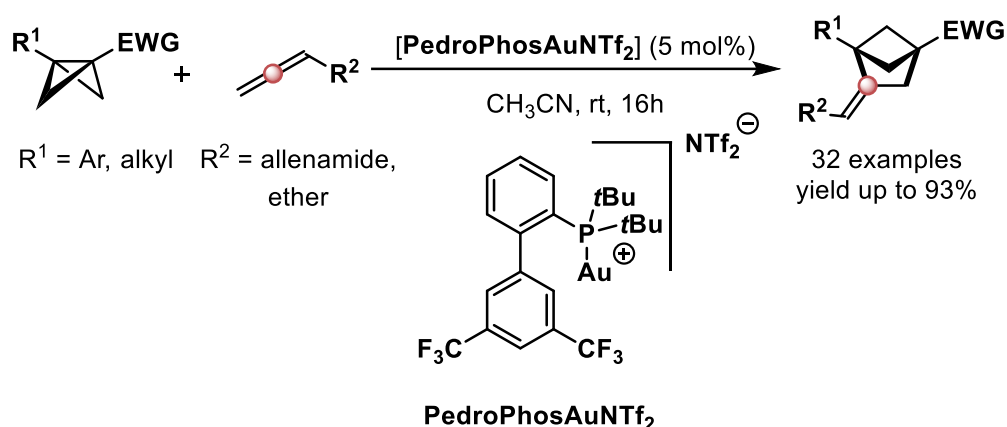


Scheme 5.4: General scheme for strain-release amination.

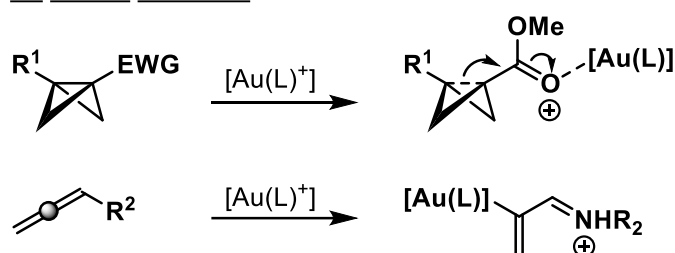
In order to further explore the polar reactivity of BCBs, in 2025, Bandini et al. reported a novel Au(I)-catalyzed regioselective cycloaddition between BCBs and electron-rich allenes,⁹³ leading to the synthesis of a broad array of densely functionalized bicyclohexanes (Scheme 5.5). The authors developed a dual Au(I) catalytic system, where the gold catalyst is employed to activate both the strain C-C bond, acting as Lewis acid, and the electron-rich allene, rendering it electrophilic and, therefore, a suitable target toward the nucleophilic attack of the BCB. Thus, the Au(I) catalyst can generate the reactive 2π component from allenes and the 2σ partner simultaneously, activating the strained C-C bond of the BCB, leading to a formal $[2\pi + 2\sigma]$ cycloaddition.

⁹³ R. Giovanelli, G. Gallorini, Y. Huang, A. Brunetti, K. D. Nikopoulos, M. Monari, C. S. Lopez, S. Kiriakidi, G. Bertuzzi, M. Bandini, *ACS Catal.* **2025**, *15*, 15698.

Reaction scheme



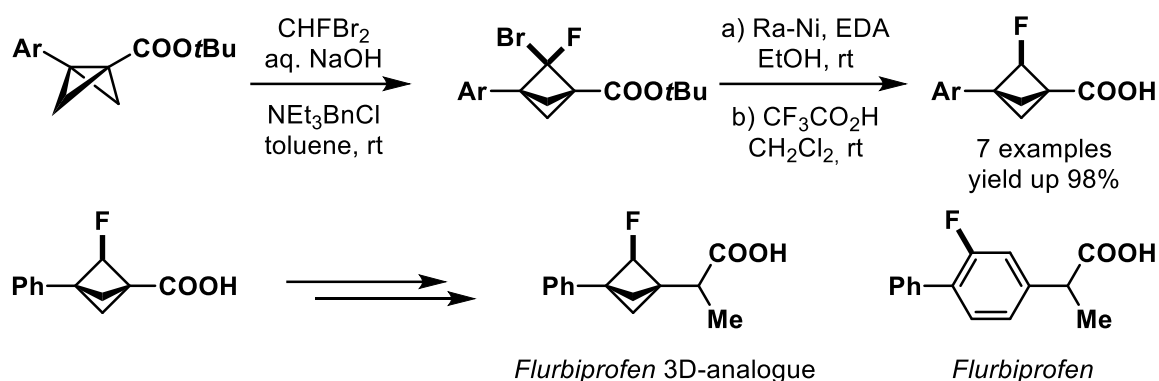
Au double activation



Scheme 5.5: General scheme for Dual Au(I) catalysis in regioselective cycloaddition of BCBs with allenes.

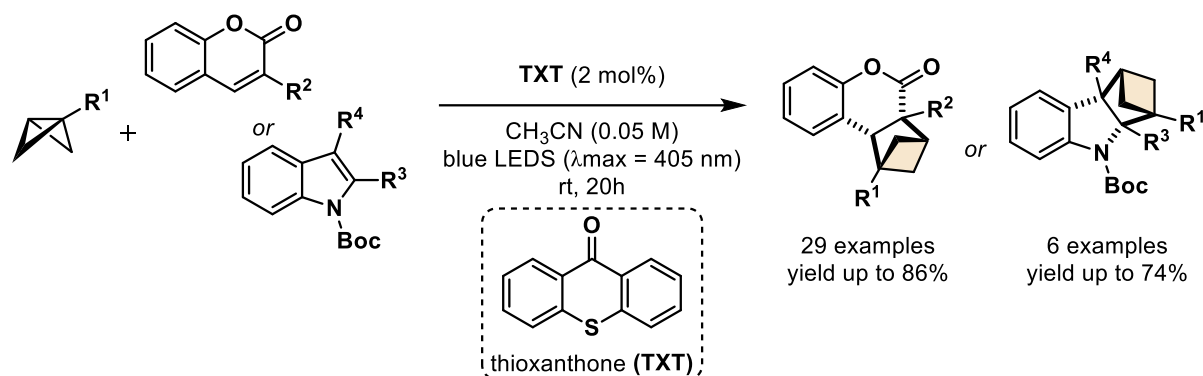
In the context of insertion-type reaction, in 2022, Mykhailiuk et al. reported a synthetic route to fluoro-substituted bicyclo[1.1.1]pentanes (F-BCPs), starting from BCB moieties and CH₂FBr₂ as bromo,fluoro-carbene (:CFBr) precursor.⁹⁴ Notably, the targeted product, a fluorinated bicyclo[1.1.1]pentane scaffold, is part of a class of saturated carbocycles of growing interest in medicinal chemistry, being classified as bioisosteres of aromatic rings (Scheme 5.6). This method is also scalable on multi-gram scale and can be exploited to synthesize molecules with enhanced physicochemical properties with respect to similar drug candidates.

⁹⁴ R. Bychek, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2022**, 61, e202205103.



Scheme 5.6: Practical and Scalable Approach to Fluoro-Substituted Bicyclo[1.1.1]pentanes.

As it concerns the reactivity of BCBs towards radical species, Glorius et al. reported the first demonstration of a visible light mediated $[2\pi + 2\sigma]$ photocycloaddition exploiting the versatility of the strained central C-C bond, enabled by triplet energy transfer.⁹⁵ This diastereoselective methodology enables the synthesis of bicyclo[2.1.1]hexanes from bicyclobutanes and olefin coupling partners, such as coumarin, flavones and indoles (Scheme 5.7). The use of simple thioxanthone as a triplet sensitizer (TXT) allowed the authors to carry out a metal-free process, by exciting this species via visible light irradiation. In the proposed mechanism the authors state that the olefin partner is sensitized by the excited TXT by energy transfer, resulting in its triplet state. The BCB is approached by this excited intermediate to form an exciplex that is responsible for the formation of the first C-C bond. Notably, also in this work, the fundamental role of bicyclo[2.1.1]hexanes as bioisosters in pharmaceutical research is strongly emphasized.

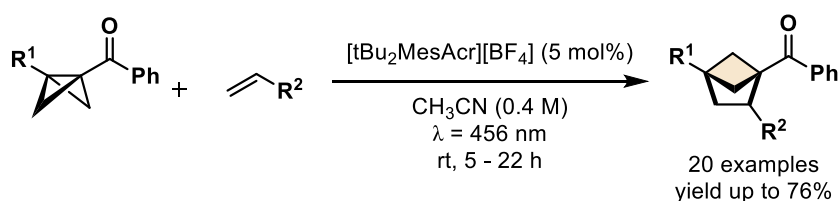


Scheme 5.7: Intermolecular $[2\pi+2\sigma]$ -photocycloaddition enabled by triplet energy transfer.

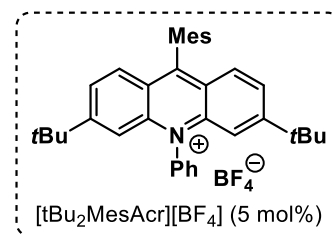
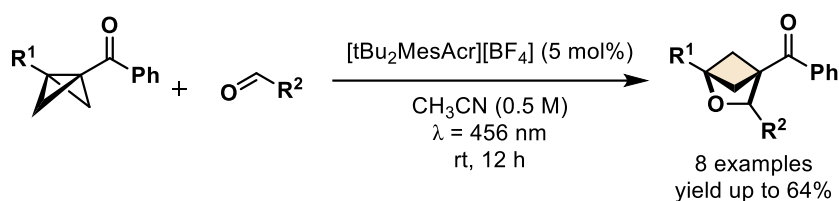
⁹⁵ R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc, F. Glorius, *Nature* **2022**, 605, 477.

Later on, following the interest in the activation of BCBs via photochemical pathways, Walker et al. proposed a further example of activation. This reactivity diverges from the well-established C-C bond activation strategies involving nucleophilic addition and reductive activation, enabling new possibilities for the synthetic application of BCBs.⁹⁶ The method represents a formal $[2\pi + 2\sigma]$ cycloaddition between bicyclo[1.1.1]butanes and alkenes or aldehydes to lead to bicyclo[2.1.1]hexanes or 2-oxabicyclo[2.1.1]hexanes respectively (Scheme 5.8). The authors discovered a rare example of a photocatalytic oxidative activation of BCBs, using a visible light-activated acridinium organo-photocatalyst.

a) alkene partners



a) aldehyde partners



Scheme 5.8: Photocatalytic Oxidative Activation of bicyclo[1.1.0]butanes.

Despite the extensive use of bicyclo[1.1.0]butanes as reactants in $[2\pi + 2\sigma]$ cycloaddition processes, no examples of electrochemically driven cycloaddition reactions of BCBs have been reported to date. The absence of established methodologies in this area has attracted the attention of our research group, motivating us to investigate bicyclo[1.1.0]butanes from an electrochemical point of view, exploiting the versatility and the adaptability of electrosynthetic techniques. The aim of the work presented in this chapter will indeed be to develop of a new methodology for accessing scaffolds of high structural relevance in medicinal and pharmaceutical chemistry.

⁹⁶ M. Golfmann, M. Reinhold, J. D. Steen, M. S. Deike, B. Rodemann, C. Golz, S. Crespi, J. C. L. Walker, *ACS Catal.* **2024**, *14*, 13987.

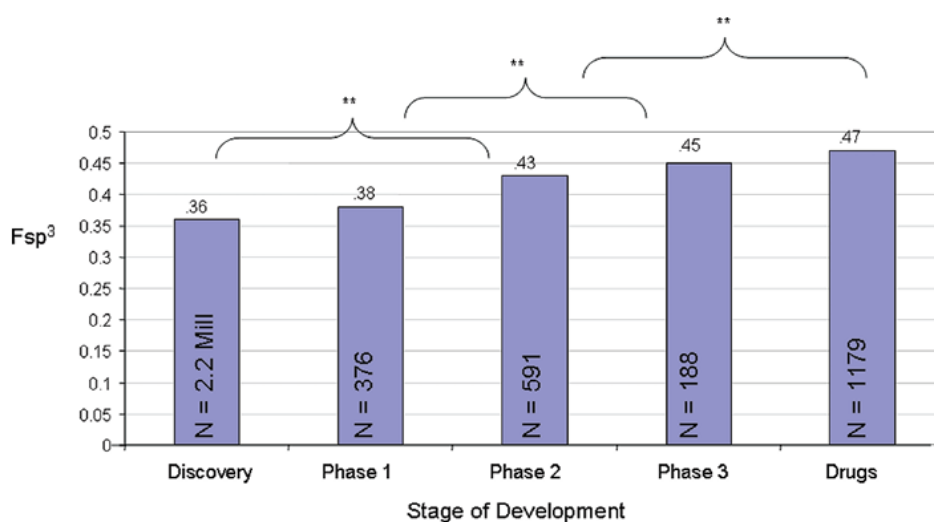
5.1.4 Escape from flatland: utility of BCB cycloaddition products in Medicinal Chemistry

5.1.4.1 Fsp³ descriptor

In medicinal chemistry, especially in the field of drug discovery, there is a long-standing predominance of aromatic-rich, planar molecules. It became evident that this two-dimensional chemical space often limits research to molecules with more complex architectures and, therefore, to the diverse (possibly improved) biological performances. As a result, increasing molecular three-dimensionality has been proposed as a strategy to access underexplored chemical spaces and to modulate physicochemical properties relevant to drug discovery. In this context, the concept of “Escape from flatland” was introduced by Lovering et al., in 2009.^{97,98} Their idea was to propose a descriptor of molecular saturation and three-dimensional character, namely Fsp³, and analyse this factor in compounds which hit an advanced stage in the clinical development.

$$Fsp3 = \frac{\text{number of } sp^3 \text{ hybridized carbons}}{\text{(total carbon count)}}$$

Using a database,⁹⁹ the authors demonstrated a trend that emerged when they applied their method of measurement to clinical progression (Figure 5.2)



⁹⁷ J. Bikker, C. Humblet, F. Lovering, *J. Med. Chem.* **2009**, 52, 6752.

⁹⁸ W. Wei, S. Cherakupalli, L. Jing, X. Liu, P. Zhan, *Drug Disc. Today* **2020**, 25, 1839.

⁹⁹ GVK Bio web site [online], <http://www.gvkbio.com/Informatics.html/>

Figure 5.2: Fsp³ value for compounds in different stages of development.

From their analysis, the average Fsp³ factor was shown to be 0.36 for discovery compounds and increased to 0.47 for drugs. This represents a 31% increase in the saturated fraction. Notably, the trend is maintained across all stages, from discovery to drug delivery, and each phase exhibits a higher Fsp³ factor. Those data illustrated how compounds with greater saturation are more likely to succeed at each stage of drug discovery and clinical development.

5.1.4.2 Bioisosterism

The benzene ring is a prevalent motif in many pharmaceuticals, being a fundamental building block in the drug discovery field.¹⁰⁰ This wide usage derives from the numerous and efficient methodologies developed around the formation of new C-C or C-heteroatom bonds involving C(sp²) atoms, with the respect of the fewer number of strategies to incorporate saturated analogues.¹⁰¹ In some cases, the benzene ring itself carries out the establishment of the aryl-protein interactions within biological targets, but usually its primary function is to connect other functionalized fragments, acting as a structural linker.¹⁰² In this context, the spatial orientation of the substituents on the benzene rings plays a fundamental role: the overall architecture of the molecule drives the interaction with the receptors of the target biological system. That is the reason why, in the last decades, the interest in the field of drug discovery has grown toward the development of new strategies for the synthesis of sp³-hybridized bioisosters of the traditional sp²-hybridized aromatic planar cores. A bioisoster is an atom, functional group, or molecular scaffold used to replace another within a biologically active compound while retaining similar biological activity. Bioisosterism is a fundamental strategy for the optimization of drug candidates in medicinal chemistry. The diverse structure offered by the bioisoster can modulate the properties of a molecule, including potency, solubility and metabolic stability.⁹⁷ Within these frameworks, bicyclo[2.1.1]hexanes (BCHs) and 2-oxabicyclo[2.1.1]hexanes (2-oxa-BCHs) have recently been identified as highly promising scaffolds to realize such strategy. In this context, the scientific interest was pivoted toward the development of new strategies for the synthesis of BCHs and 2-oxa-BCHs moieties.

¹⁰⁰ R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, 57, 5845.

¹⁰¹ M. J. Buskes, M. J. Blanco, *Molecules* **2020**, 25, 3493.

¹⁰² G. M. Locke, S. S. R. Bernhard, M. O. Senge *Chem. Eur. J.* **2019**, 25, 4590.

For example, in 2025, Tortosa et al. showed that BCH-centered Boscalide and Telmisartan analogues, retained or enhanced the activity of the respective parent aryl-containing molecules (Figure 5.3).¹⁰³ In particular, the former showed a minimal inhibitory concentration (MIC) of 450 $\mu\text{g mL}^{-1}$ for the inhibition of the growth of the fungal pathogen *Fusarium oxysporum*. The latter maintained the high affinity of Telmisartan, with K_i values in the low nanomolar range. Interestingly, there is a three-fold difference in the K_i values between the two enantiomers (K_i value = 3.4 nM versus 0.9 nM for its enantiomer), highlighting the influence of the three-dimensional structure of the compound in the interactions with the binding pocket of the receptor.

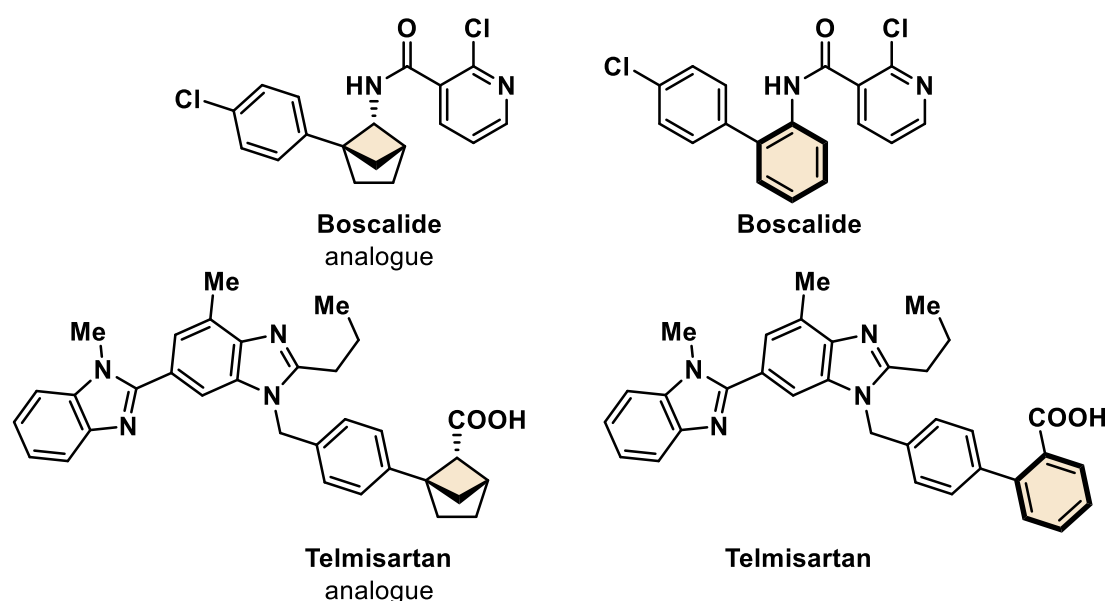


Figure 5.3: Boscalide and Telmisartan with the respective bioisoster analogues.

In 2024, Mykhailiuk et al. incorporated 2-oxa-BCHs in pharmaceutical analogues and validated their biological activity as bioisosters of benzene-based drugs (Figure 5.4).¹⁰⁴ Regarding the water solubility, replacement of the meta-substituted benzene ring in Sonidegib by a 2-oxabicyclo[2.1.1]hexane moiety had a negligible impact on the water solubility: 6 μM (Sonidegib) vs 8 μM . On the other hand, in the case of Phthalysulfathiazole, such replacement led to a two-threefold increase in solubility: 170 μM (Phthalysulfathiazole) vs 397 μM . The lipophilicity in the analogue bioactive compounds, decreased by ca. one or two units of clogP .

¹⁰³ P. Garrido-García, I. Quirós, P. Milán-Rois, S. Ortega-Gutiérrez, M. Martín-Fontecha, L. A. Campos, Á. Somoza, I. Fernández, T. Rigotti, M. Tortosa, *Nature Chemistry* **2025**, 17, 734.

¹⁰⁴ V. V. Levterov, Y. Panasyuk, V. O. Pivnytska, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2020**, 59, 7161.

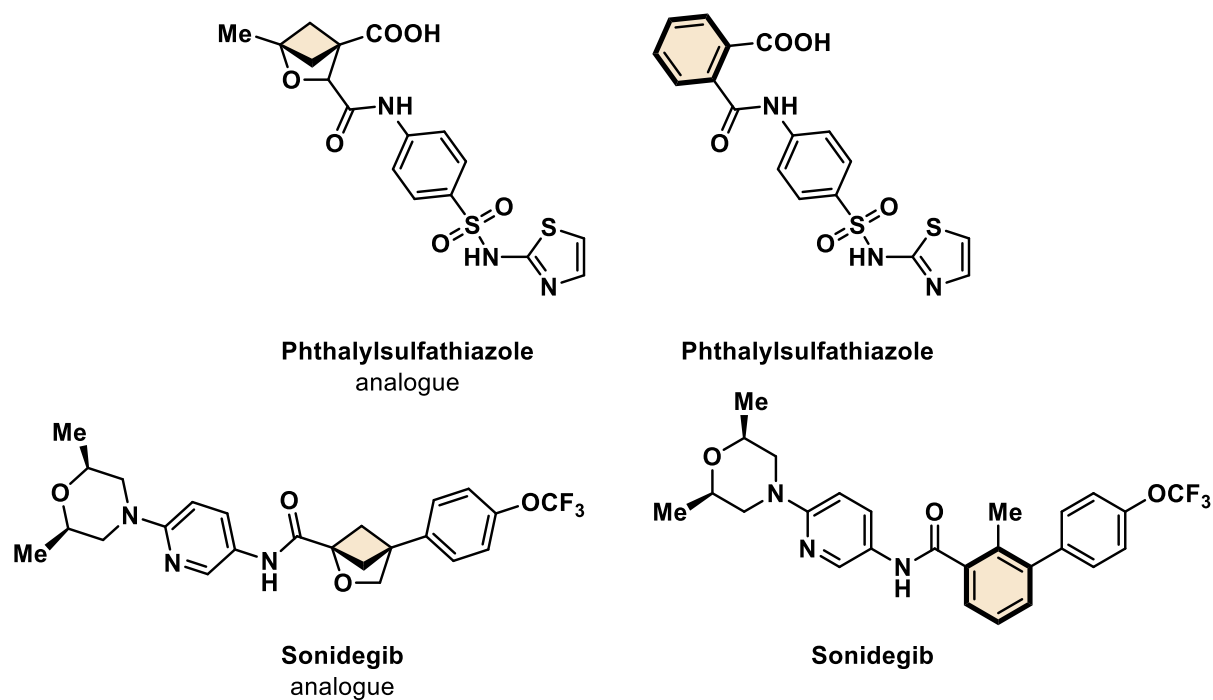


Figure 5.4: Phthalylsulfathiazole and Sonidegib with the respective bioisoster analogues.

Merging the concepts of bioisosterism in drug discovery and the fascinating reactivity of BCBs, the interest of our research group moved to the development of a new strategy for the synthesis of 2-oxabicyclo[2.1.1]hexanes, exploiting the versatility and modularity of electrocyclic synthesis, in an electrochemical cross-nucleophile coupling manifold.

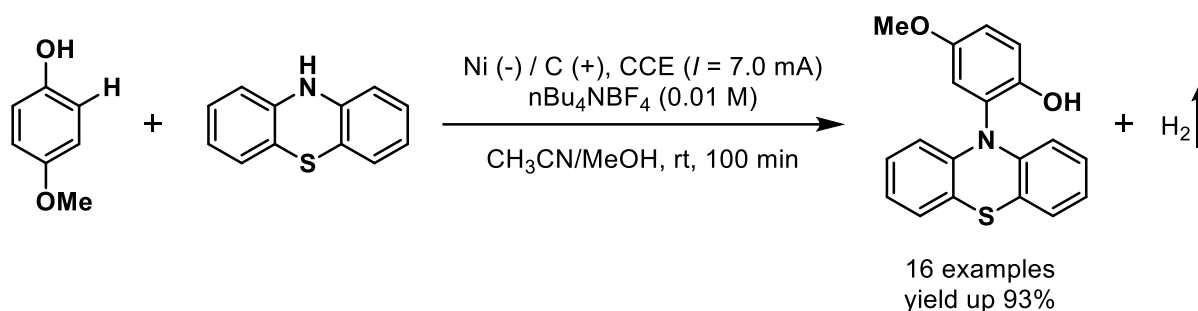
5.1.5 Electrochemical Cross-nucleophile couplings (XNC)

Cross nucleophile coupling refers to a class of reactions in which two nucleophiles are involved to form a new covalent bond. Typically, in cross coupling reactions, an electrophile and a nucleophile partner are reacted together to generate a new carbon-carbon or carbon-heteroatom bond, often under the influence of a metal catalyst, as exemplified by the Suzuki or Heck reaction. Therefore, finding a new reactivity between two nucleophiles presents additional challenges, as both partners are electron-rich and do not engage in the typical reactivity. To explore this, various strategies, in which nucleophiles are first converted into activated intermediates, or in which a catalytic system can discern between the two partners, have been developed.¹⁰⁵ In both cases, the transformation of one of the two nucleophilic partners into an electrophile entity by oxidation is typically carried out. In this context, electrochemical methodologies have recently emerged as a powerful tool for enabling XNC avoiding the usage of stoichiometric amounts of oxidants. Indeed, it is possible to selectively activate one or both partners by using electric current, generating the desired reactive intermediates under mild and sustainable conditions.¹⁰⁶ In particular, oxidative cross couplings, accompanied by cathodic hydrogen evolution reactions (HER), have proved to be one of the most straightforward strategies to form new covalent bonds between two nucleophilic molecules. As an example, in 2018, Lei et al.,¹⁰⁷ reported an electrochemical reaction protocol for the oxidative C-H amination of unprotected phenols (Scheme 5.9). Neither a metal catalyst nor external chemical oxidants are needed for the dehydrogenation process. The controlled electrolysis allows the selective oxidation of the amine moiety giving the reactive radical cation intermediate. This species undergoes nucleophilic addition by the phenol derivative, followed by a second oxidative event and deprotonation, leading to the formation of the target product.

¹⁰⁵ C. Liu, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780.

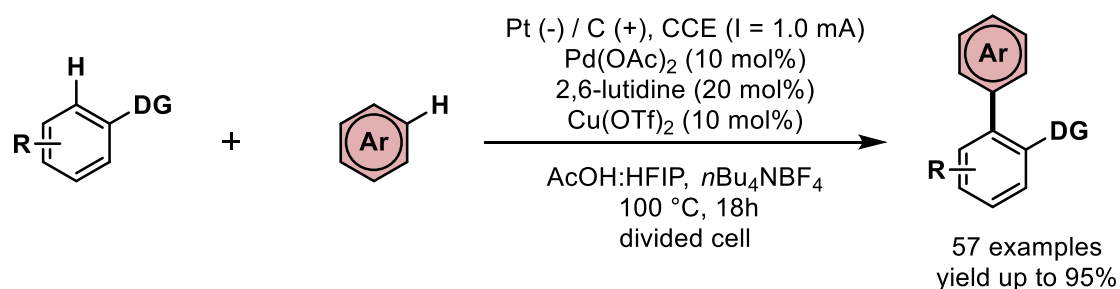
¹⁰⁶ Y. Yuan, A. Lei, *Acc. Chem. Res.* **2019**, *52*, 3309.

¹⁰⁷ S. Thang, S Wang, Y. Liu, H. Cong, A. Lei, *Angew. Chem. Int. Ed.* **2018**, *57*, 4737.



Scheme 5.9: Electrochemical Oxidative CH Amination of Phenols.

Ackermann et al., in 2024,¹⁰⁸ presented an electrochemical palladium/copper-catalysed oxidative coupling strategy to access biaryls in the absence of a stoichiometric chemical oxidant, in a divided cell system (Scheme 5.10). The authors envisioned a dual electrochemical C-H activation using *N*-acetyl-tetrahydroquinoline and *o*-xylene as optimal substrates to generate biaryl scaffolds. The key of the catalytic cycle proceeds via a bimetallic mechanism involving two palladium centers. The presence of $\text{Cu}(\text{OTf})_2$ serves to stabilize $\text{Pd}(0)$ intermediates, prior to be oxidized at the anode.



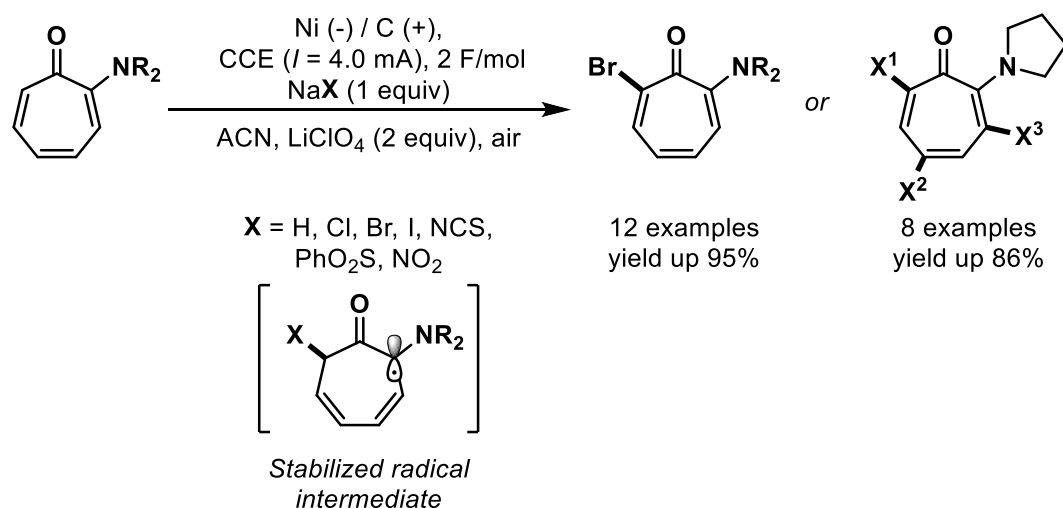
Scheme 5.10: Palladium-Catalyzed Electrooxidative Double C-H Arylation.

Following the interest in electro-oxidative cross couplings, Bandini et al. developed a general electrochemical synthetic procedure for the site-selective heterofunctionalization of activated tropones.¹⁰⁹ Mono- and poly-halogenation, nitration, sulfonation, and thiocyanation protocols are successfully executed starting from inexpensive sodium salts under oxidative electrolytic conditions. From the mechanistic point of view, the selective electrochemical oxidation of the target anion gives an electrophilic radical that is intercepted by the tropone scaffolds to form a highly stabilized radical intermediate, which undergoes a second anodic oxidation event

¹⁰⁸ Z. Lin, J. C. A. Oliveira, A. Scheremetjew, L. Ackermann, *J. Am. Chem. Soc.* **2024**, *146*, 228.

¹⁰⁹ M. Garbini, S. Moncullo, S. Kirikiadi, M. Melucci, S. Bellini, C. Zanardi, C. S. López, G. Bertuzzi, M. Bandini, *Adv. Synth. Catal.* **2025**, *367*, e9592

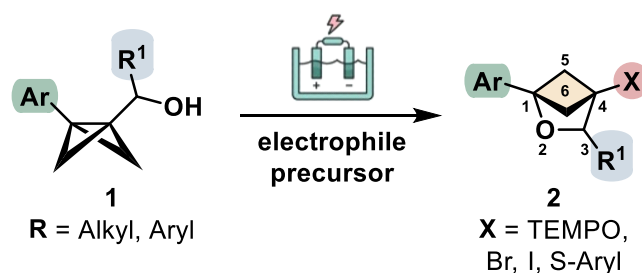
followed by deprotonation to give the desired product (Scheme 5.11). This method gives access to mono- and poly-functionalization of tropone moieties with high yields and faradic efficiencies, demonstrating broad tolerance toward multiple types of functional group.



Scheme 5.11: Heterofunctionalization of Tropones via C(sp₂)-H Derivatization.

5.2 Aim of the work

In continuation with our ongoing exploration into electrochemical oxidative cross couplings and following the scientific interest toward 2-oxabicyclo[2.1.1]hexanes, we targeted a new class of BCB-derivatives bearing a pendant hydroxymethyl group (**1**),¹¹⁰ easily obtainable from ester or ketone derivatives. Compounds **1** are expected to feature a greater nucleophilic transannular C-C bond profile than the parent EWG-substituted analogues. We then envisioned the possibility to merge these BCB-methanol derivatives and the anodic generation of electrophilic heteroatom-centred species into an electro-mediated cross nucleophile coupling. The process would enable a functionalization at C(4), followed by the ring closure operated by the hydroxyl group, to give 2-oxabicyclo[2.1.1]hexane moieties. This method relies on TEMPO-derived oxy-cations, halogen and thiyl radicals to access selectively 2-oxa-BCHs in good to excellent yields. (Scheme 5.12).



Scheme 5.12: Proposed strategy for the synthesis of 2-oxaBCHs.

¹¹⁰ M. Golfmann, J. C. L. Walker, *Commun. Chem.* **2023**, 6, 9

5.3 Results and discussion

5.3.1 Protocol optimization

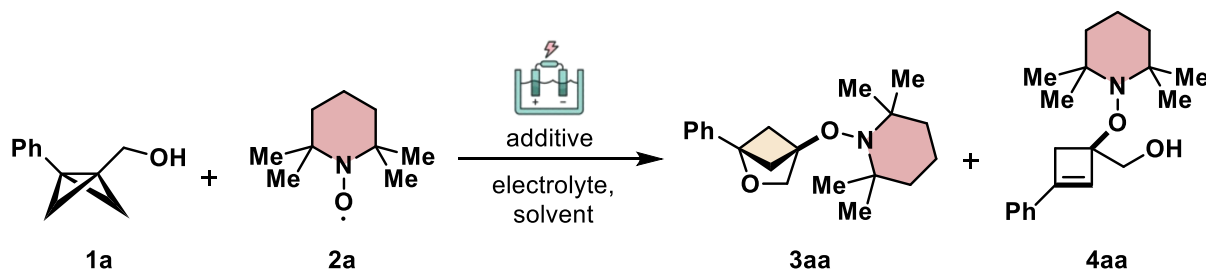


Figure 5.5: Optimized reaction

At the outset of our investigation, we subjected **1a** and TEMPO **2a** (2 equiv) to constant current electrolysis (CCE, $I = 2$ mA) in the presence of LiClO_4 as an electrolyte, a Ni cathode and a graphite (C) anode, in CH_3CN at room temperature in an undivided cell system (Table 5.1, entry 1). It is worth mentioning that a stoichiometric amount of electrons (1 F/mol) was sufficient to achieve complete conversion of **1a**. The feasibility of the proposed strategy was demonstrated by the successful isolation of the desired product **3aa** in 50% yield. We also obtained cyclobutene **4aa** in 25% yield as major side-product. Therefore, our optimization studies were conducted towards the selectivity of the process, promoting the formation of the 2-oxa-bicyclo[2.1.1]hexane (**3aa**) and suppressing the generation of **4aa**. We started our investigation by exploring different current from 6 mA (Table 5.1, entry 2) to 10 mA (Table 5.1, entry 3).

Entry	Current (mA)	Solvent	Electrolyte	C(-) A(+)	3aa:4aa ^[b]	Yield 3aa (%) ^[c]
1	2	ACN	LiClO_4	Ni C	2.0:1	50
2	6	ACN	LiClO_4	Ni C	2.2:1	55
3	10	ACN	LiClO_4	Ni C	2.4:1	57

Table 5.1: ^[a] All reactions were carried under air in the Electrasyn 2.0 apparatus at room temperature, **[1a]** = 0.33 M. ^[b] Determined on the ^1H NMR spectrum of the crude mixture. ^[c] Isolated yield after FC purification.

These results showed a progressive improvement in both isolated yield and **3aa:4aa** ratio (up to 57% and 2.4:1, respectively) with increasing applied current, thereby reducing reaction time and improving the process practicality.

We then proceed testing different electrochemical parameters, such as electrolytes different from LiClO₄ and various electrode couples. The use of LiBF₄ (Table 5.2, entry 1), TBAClO₄ (Table 5.2, entry 2), and TEABF₄ (Table 5.2, entry 3) as different electrolytes did not improve the reaction outcome. Similarly, anodes other than graphite (C), such as stainless steel (SS, Table 5.2, entry 4) and glassy carbon (GC, Table 5.2, entry 5) showed diminished yields and lower selectivity.

Entry	Current (mA)	Solvent	Electrolyte	C(-) A(+)	3aa:4aa ^[b]	Yield 3aa (%) ^[c]
1	10	ACN	LiBF ₄	Ni C	2.3:1	52
2	10	ACN	TBAClO ₄	Ni C	2.0:1	48
3	10	ACN	TEABF ₄	Ni C	1.6:1	39
4	10	ACN	LiClO ₄	Ni SS	-	traces
5	10	ACN	LiClO ₄	Ni GC	2.3:1	47

Table 5.2: ^[a] All reactions were carried under air in the Electrasyn 2.0 apparatus at room temperature, **[1a]** = 0.33 M. ^[b] Determined on the ¹H NMR spectrum of the crude mixture. ^[c] Isolated yield after FC purification.

We then pivoted the investigation of the optimal conditions to the solvent screening. We noticed that by changing solvent from ACN to DMF (Table 5.3, entry 1) or DMSO (Table 5.3, entry 2) increased the **3aa:4aa** ratio up to 8.8:1 and 13:1 respectively, indicating the polarity of the medium as a key factor to control the selectivity of the process. However, the use of these solvents resulted in lower isolated yields, and we decided to keep ACN as the optimal solvent, at this stage. We finally focused on lowering the temperature to 0 °C (Table 5.3, entry 3) and -30 °C (Table 5.3, entry 4). A trend of improvement in both yield and selectivity (up to 70% and 5:1) was observed as the temperature decreased.

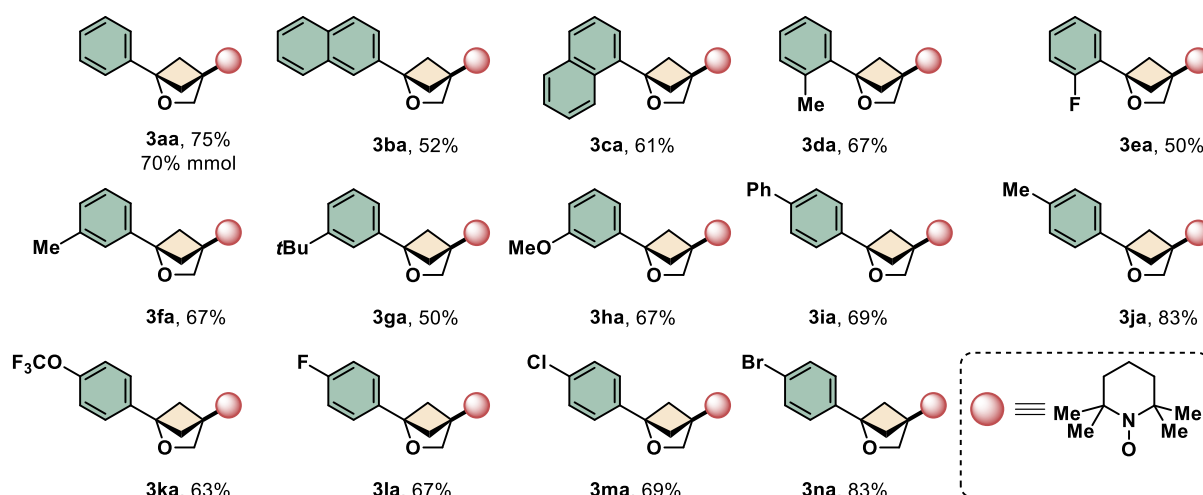
At last, by switching the solvent to a binary mixture of ACN and THF (1:2), we were able to completely suppress the formation of cyclobutene **4aa** and to recover the desired product in optimal 75% yield (Table 5.3, entry 5).

Entry	T (°C)	Solvent	Electrolyte	C(-) A(+)	3aa:4aa ^[b]	Yield 3aa (%) ^[c]
1	25	DMF	LiClO ₄	Ni C	8.8:1	44
2	25	DMSO	LiClO ₄	Ni C	13:1	50
3	0	ACN	LiClO ₄	Ni C	4.1:1	65
4	-30	ACN	LiClO ₄	Ni C	5:1	70
5 ^[d]	-30	ACN:THF	LiClO ₄	Ni C	18:1	75

Table 5.3: ^[a] All reactions were carried under air in the Electrasyn 2.0 apparatus at room temperature, CCE (*I* = 10mA), [**1a**] = 0.33 M. ^[b] Determined on the ¹H NMR spectrum of the crude mixture. ^[c] Isolated yield after FC purification. ^[d] ACN/THF 1:2.

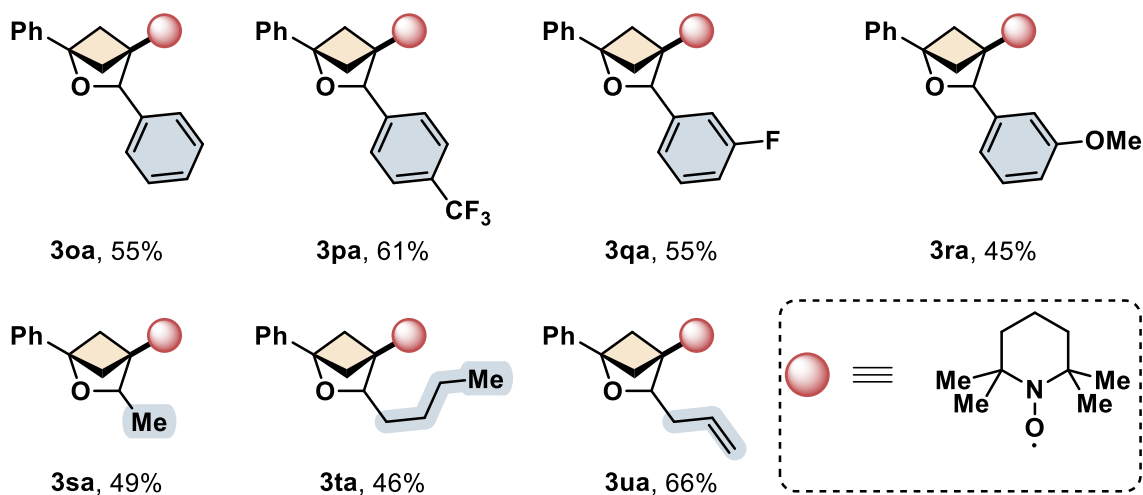
5.3.2 Generality of the process

The robustness of the process was first assessed by conducting the model reaction on 1 mmol-scale, leading to product **3aa** in a 70% yield. We then explored a range of BCB-alcohols **1** being subjected to the optimized conditions (Scheme 5.13). The presence of extended arenes (**3ba-ca**), alkyl (**3da, 3fa, 3ga, 3ja**), aryl (**3ia**) and alkoxy groups (**3ha, 3ka**), as well as of halogens (**3ea, 3la-na**) at the *ortho*, *meta* or *para* positions of the phenyl ring at the α -carbon, was very well tolerated, rendering the desired products **3** in high yields (up to 83%). In all cases, the reactions proved highly selective with no formation of cyclobutenes **4**, indicating a high and systematic selectivity of the disclosed methodology.



Scheme 5.13: Generality of the process starting from **1a**. [a] All reactions were carried under air in the Electrasyn 2.0 apparatus, under the conditions reported in Table 5.3, entry 5, unless otherwise noted. All reported yields refer to isolated products after FC purification.

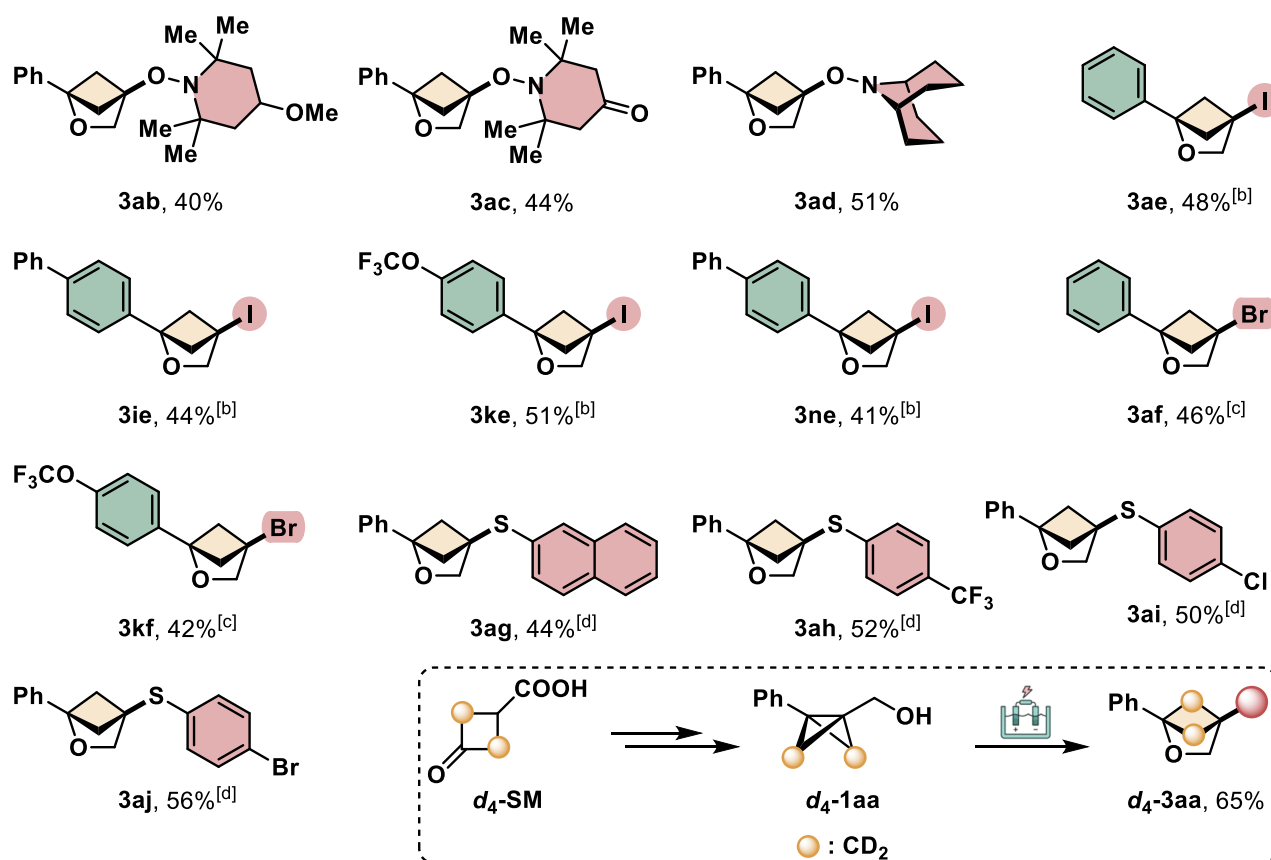
We then envisioned the possibility of introducing substituents at position C(3) of the 2-oxabicyclo[2.1.1]hexane core, by employing secondary alcohols **1o-u**, deriving from a chemoselective reduction of the corresponding ketones. In this context, alkyl (**3sa-ta**), allyl (**3ua**) and aryl (**3oa-ra**) groups could be efficiently introduced, providing a wide and faceted range of decorations and highlighting the versatility of this strategy in providing, following the same reaction concept, both C(3)-substituted and unsubstituted 2-oxa-BCHs **3**, otherwise difficult to achieve by a unified methodology (Scheme 5.14).



Scheme 5.14: Generality of the process starting from secondary **1**. [a] All reactions were carried under air in the Electrasyn 2.0 apparatus, under the conditions reported in Table 5.3, entry 5, unless otherwise noted. All reported yields refer to isolated products after FC purification.

Finally, we postulated that our strategy was not limited to oxy-cations for the trigger of the intra-molecular formation of 2-oxa-BCHs, but could be extended to electrophilic radicals generated by the electrochemical oxidation of other heteroatom-centred moieties (Scheme 5.15). To our delight, by subjecting a set of alcohols **1** to the optimized conditions, in the presence of tetrabutylammonium iodide (**2e**) or bromide (**2f**) the corresponding C(4)-halogenated compounds were isolated in moderate to good yields (up to 51%). Moreover, aromatic thiols (**2g-j**) were also shown to produce electrophilic radicals amenable to trigger the desired transformation upon treatment with a base (*i.e.* 2,6-lutidine, 2 equiv). The corresponding sulphides **3ag-j** were isolated in synthetically useful outcomes (44 - 56% yield). In all cases, the formation of cyclobutenes **4** was not observed, confirming a completely selective protocol, irrespective of the electrophile of choice. Importantly, the incorporation of halogens and sulphur at this position of 2-oxa-BCHs would contribute in opening new opportunities for accessing derivatives of significant synthetic and applicative relevance. Finally, we targeted the preparation of deuterated BCB **d₄-1a** and subjected it to the optimized conditions for the preparation of **d₄-3aa**, that was isolated in high yield (65%).

This represents the first entry to a 2-oxa-BCH motif featuring complete deuteration of the 4-membered ring that would meet the current “deuterium switch” strategy in medicinal chemistry.¹¹¹

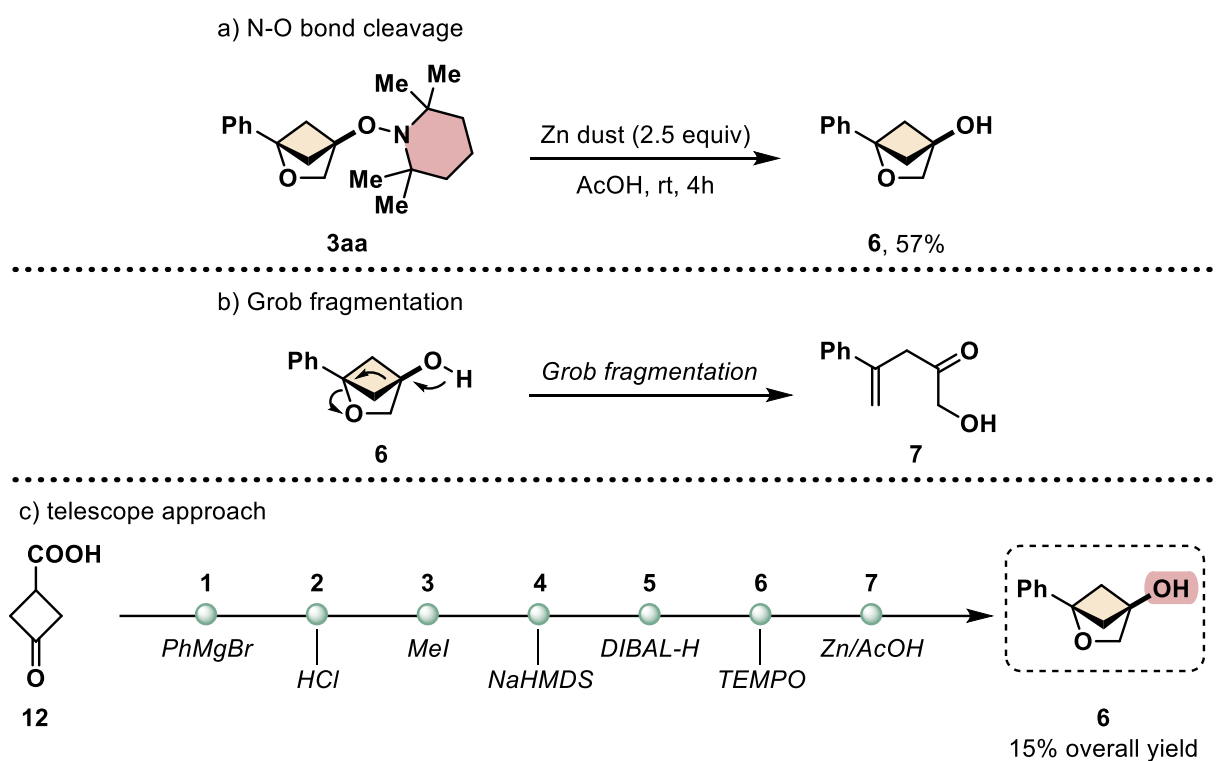


Scheme 5.15: Generality of the process starting from different electrophile precursors. ^[a] All reactions were carried under air in the Electrasyn 2.0 apparatus, under the conditions reported in Table 5.3, entry 5, unless otherwise noted. All reported yields refer to isolated products after FC purification. ^[b] Reaction run with TBAI (**2e**), 2.0 F/mol_{1a}. ^[c] Reaction run with TBABr (**2f**), 3.5 F/mol_{1a}. ^[d] Reaction run with thiophenols **2g-j**, in the presence of 2,6-lutidine (2 equiv), 2 F/mol_{1a}.

¹¹¹ Y. Chen, Y. Du, *ChemMedChem* **2024**, 20, e202400836.

5.3.3 Product Transformations

To demonstrate the utility of the previously synthesized 2-oxabicyclohexanes **3aa** we envisioned the high functional relevance of the oxygenation of C(4) and the flexibility of hydroxyl group as a further synthetic handle. Consequently, we submitted **3aa** to a reductive cleavage mediated by Zn/AcOH to achieve the N-O bond scission and afford the desired alcohol **6** (Scheme 5.16, a). Notably, it was necessary to suppress the formation of by-product **7** (Scheme 5.16, b), derived from a Grob-like fragmentation pathway.¹¹² To further emphasize the utility of the present methodology we decided to access directly alcohol **6** from commercially available ketone **12** through a telescopic sequence. Notably, the 7 step-process afforded the target compound with an average per-step yield of 76% (15% overall) and required only a single chromatographic purification at the final stage (Scheme 5.16, c).



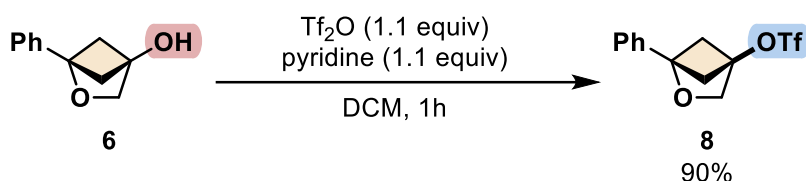
Scheme 5.16: a) N-O bond cleavage, b) Grob fragmentation, and c) telescopic approach for the synthesis of **6**.

We then proceed to further demonstrate the synthetic utility of alcohol **6**, by preparing the respective triflate **8**, (90% yield, Scheme 5.17, a), propargyl ether **9** (74% yield,

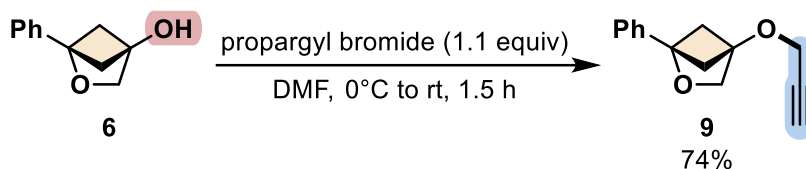
¹¹² W. Baumann, C. A. Grob, *Helvetica Chimica Acta* **1955**, 38, 594.

Scheme 5.17, b) and phenylaniline ester **10** (92% yield, Scheme 5.17, c), with the latter highlighting the potential of 4-hydroxy-2-oxaBCH **6** for bioconjugation applications. In addition, we also decided to functionalize the aromatic ring in the C(1) position, to establish that this substituent is also available for further modifications. We thus subjected derivative **3na** to Suzuki coupling conditions to obtain biaryl product **11**, which was isolated in 87% yield (Scheme 5.17, d).

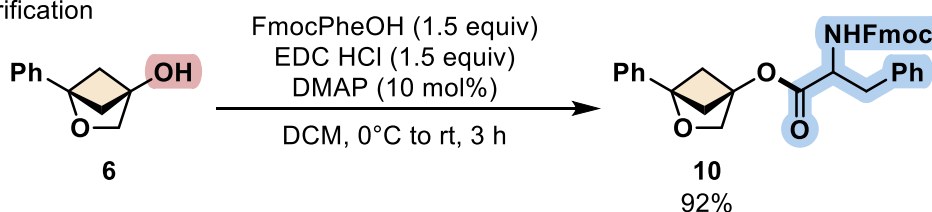
a) Triflation



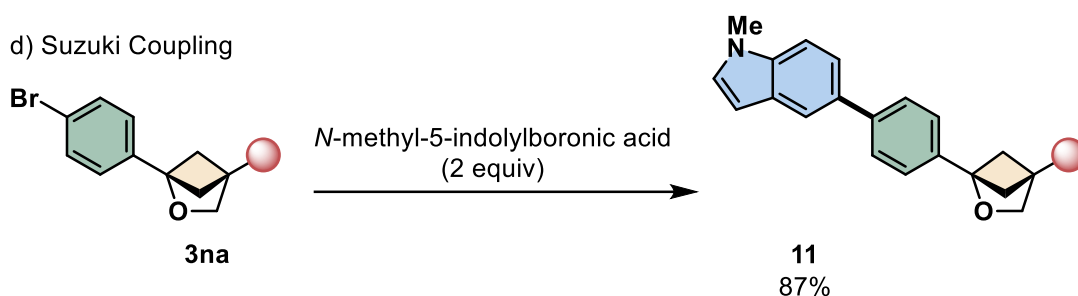
b) Propargylation



c) Esterification



d) Suzuki Coupling



Scheme 5.17: Post functionalizations. a) Triflation, b) Propargylation, c) Esterification and d) Suzuki coupling

5.3.4 Mechanistic studies

We then proposed a mechanistic rationale for the observed reaction. First, we subjected BCB **1a** and TEMPO **2a** to voltametric analysis (Figure 5.5). The results suggested that oxidation of **2a** occurs preferentially with respect to **1a** ($E_{1/2} = 0.20$ V and $E_p = 0.81$ V vs Fc/Fc⁺ redox couple, respectively), and, therefore, indicated that **2** are the electroactive species in this protocol.

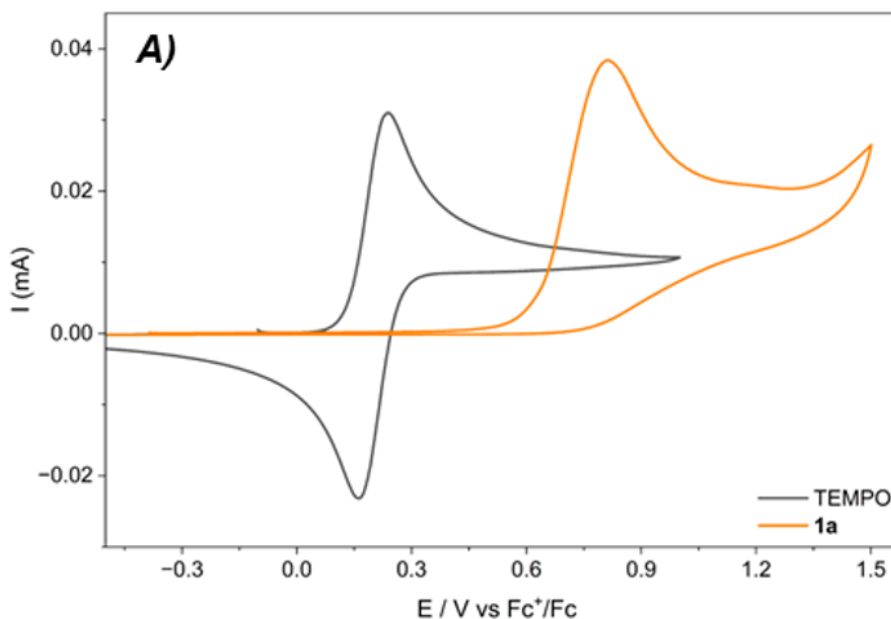


Figure 5.5: CV responses collected in a 3-electrode cell, ACN solvent, [**2a**, **1a**] = 2.1 mM, TEABF₄ electrolyte (0.10 M).

Then, we subjected TEMPO **2a** to a “titration” experiment with the aim of ascertaining the reactivity of the corresponding cation with the substrate **1a**. This set of measurements consists of a series cyclic voltammetry experiments performed on solutions containing a fixed concentration of **2a**, while the concentration of **1a** is systematically increased (Figure 5.6). By observing the progressive disappearance of the return curve, we were able to postulate a concentration-dependent depletion of TEMPO⁺ from the solution, due to irreversible reaction with **1a**.

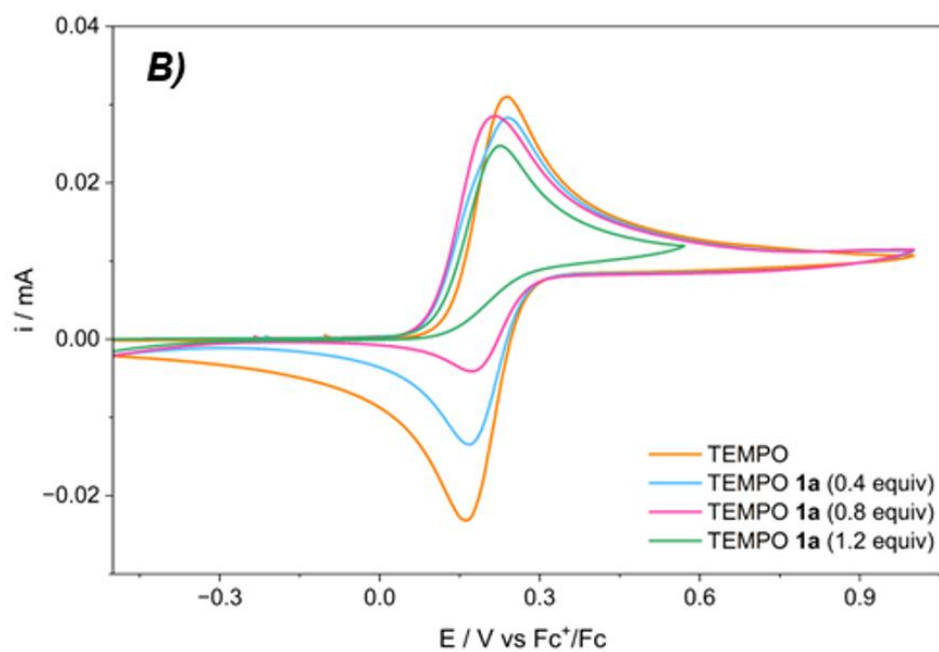
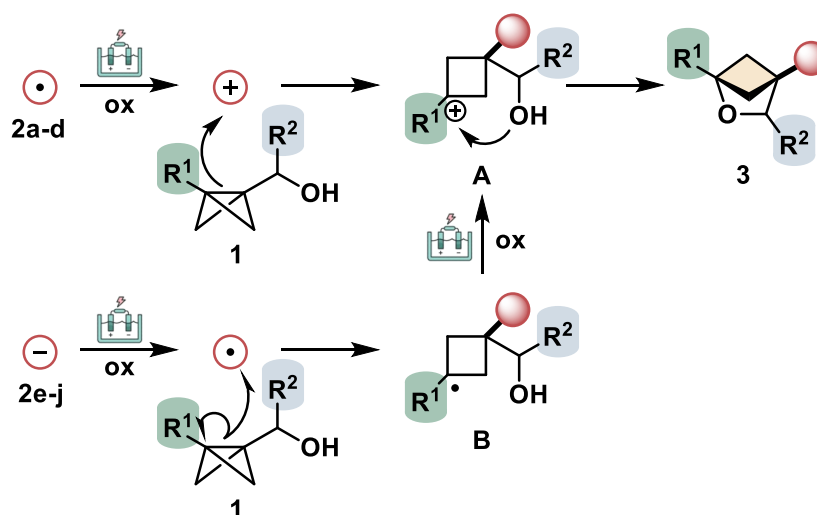


Figure 5.6: CV responses collected in a 3-electrode cell, ACN solvent, **[2a]** = 2.10 mM (all lines), TEABF₄ electrolyte (0.10 M), **[1a]** = 0.84 mM (light blue line), **[1a]** = 1.68 mM (pink line), **[1a]** = 3.76 mM.

5.3.5 Mechanistic proposal

These experimental results led us to propose that the first partners to undergo anodic oxidation are electroactive radicals such as **2a-d**, thereby generating electrophilic oxy-cation species. These, captured by the nucleophilic C α -C γ bond of BCB **1**, lead to the formation of carbocations **A**, finally trapped by the pendant hydroxyl group. On the other hand, when electroactive anions such as iodide (**2e**), bromide (**2f**) or thiolates (**2g-j**) are employed, their anodic oxidation forms electrophilic radicals that, after reaction with **1**, lead to the formation of stable benzyl radicals **B**, successively undergoing a second anodic oxidation to cations **A**. In this context, we postulated that the formation of cyclobutenes **4** is due to an undesired quench of the intermediate carbocation **A** by proton elimination, competing with the intramolecular nucleophilic trapping of the hydroxyl group (Scheme 5.18).



Scheme 5.18: Mechanistic proposal.

5.4 Conclusions

In summary, we developed a general and highly selective electrochemical methodology for the synthesis of 2-oxabicyclo[2.1.1]hexanes (2-oxaBCHs) as valuable benzene bioisosters, thereby overcoming the limitations of existing synthetic methods. By exploiting the versatility and the modularity of electrosynthesis, we combined an electrochemically generated electrophilic species with the peculiar reactivity of hydroxymethyl-substituted bicyclo[1.1.0]butanes to obtain 2-oxaBCHs under mild and oxidant free conditions. The methodology exhibits broad substrate scope, being compatible with both C(3)-substituted and unsubstituted systems, and permitting the installation of a wide range of heteroatom-based functionalities at the C(4) position, including oxygen, halogens, and sulfur, which provide handles for further functionalization. The mechanistic analysis is in accordance with the anodic formation of electrophilic intermediates, followed by selective trapping from the BCB scaffold. Overall, this work highlights electrosynthesis as a powerful and enabling platform for the preparation of 2-oxaBCHs, expanding the accessible chemical space of benzene bioisosteres, with implications in synthetic methodology, medicinal chemistry, and industrial applications.

5.5 Experimental Details

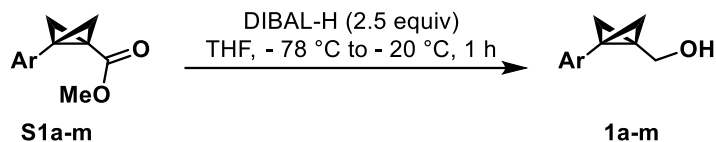
5.5.1 General methods and procedures

General Methods: ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker NeoAvance 600 (600 MHz) or INOVA 600 MR (600 MHz). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, td = triple doublet, dt = double triplet, q = quartet, sext = sextet, sept = septet, p = pseudo, b = broad, m = multiplet), coupling constants (Hz). Chemical shifts are reported in ppm from TMS with the solvent resonance peak as the internal standard. HRMS spectra were obtained with a G2XS QToF mass spectrometer using ESI ionization technique, as specified case by case. Melting points were determined with a Büchi Melting Point B-540 apparatus and are not corrected. Chromatographic purification was done with 240-400 mesh silica gel. Anhydrous solvents were supplied by Sigma Aldrich in Sureseal® bottles and used without any further purification. Commercially available chemicals and (non-anhydrous) solvents were purchased from Sigma Aldrich, Fluorochem and TCI Chemicals and used without any further purification. Starting materials **S1** were prepared by our reported modification of literature procedures.⁹³ Below the general procedures the characterization of the model compound only is reported.

Cyclic voltammetry methods: Cyclic voltammetry (CV) experiments reported in the main text were performed in a 15 mL vial using an Autolab PGSTAT302N potentiostat (Metrohm), with data acquisition controlled by the Nova 2.1.8 software. A total of 2.1 mg of **2a** or 3.4 mg of **1a** (Scheme 4A) were dissolved in 7 mL ACN. For the titration experiment to a total of 2.1 mg of **2a**, dissolved in 7 mL of ACN, 50 μL of a 0.1 M solution of **1a** in ACN were progressively added in three portions, until a total of 150 μL were reached. Tetraethylammonium tetrafluoroborate (TEABF_4) at a concentration of 0.1 mol L^{-1} was employed as the supporting electrolyte. The measurements were conducted at a scan rate of 50 mV s^{-1} using a glassy carbon working electrode and a platinum counter electrode (GC||Pt). A silver wire was used as the reference electrode, and all potentials were internally referenced to the ferrocene/ferrocenium (Fc/Fc^+) redox couple.

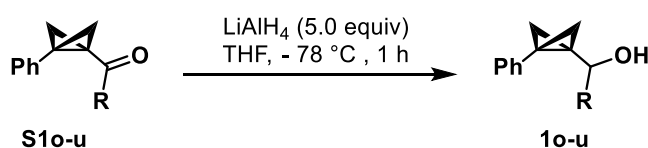
5.5.2 Preparation of starting materials

5.5.2.1 General Procedure A for the preparation of primary alcohols 1a-n



In a heat-gun dried 3-necked round bottom flask, equipped with a magnetic stirring bar and under Ar atmosphere, ester **S1a-m** (0.3 mmol) was dissolved in anhydrous THF (3 mL), cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of DIBAL-H (2.5 equiv, 0.83 mmol, 0.83 mL, 1.0 M in toluene) was added dropwise. After the addition was completed, the resulting solution was stirred for 1 h, during which time the temperature was allowed to rise to $-20\text{ }^{\circ}\text{C}$. Then, EtOAc (5 mL) was carefully added, followed by a saturated solution of Rochelle's salt (5 mL). The biphasic mixture was then vigorously stirred at room temperature for 1 h, until two clear phases were obtained and the transferred to a separatory funnel. The phases were separated, the aqueous phase was extracted again with EtOAc (2 x 5 mL), the combined organic phases were washed with a saturated solution of Rochelle's salt (2 x 5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to obtain primary alcohols **1a-m**, that were directly used in the electrochemical protocol without further purification.

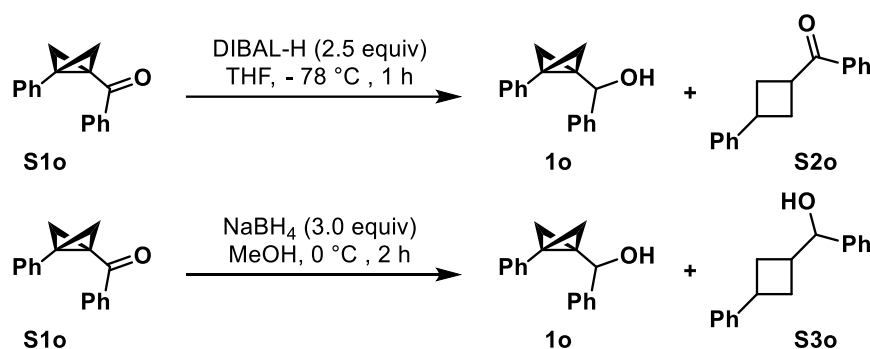
5.5.2.2 General Procedure B for the preparation of secondary alcohols 1o-u



In a heat-gun dried 3-necked round bottom flask, equipped with a magnetic stirring bar and under Ar atmosphere, ketone **S1o-u** (0.3 mmol) was dissolved in anhydrous THF (5 mL), cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of LiAlH_4 (5.0 equiv, 1.5 mmol, 0.73 mL, 2.3 M in 2-MeTHF) was added dropwise. After the addition was completed, the resulting solution was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$. Then, EtOAc (5 mL) was carefully added, followed by a saturated solution of Rochelle's salt (5 mL). The biphasic mixture was then vigorously stirred at room temperature for 1 h, until two clear phases were obtained, and transferred to a separatory funnel. The phases were separated, the aqueous

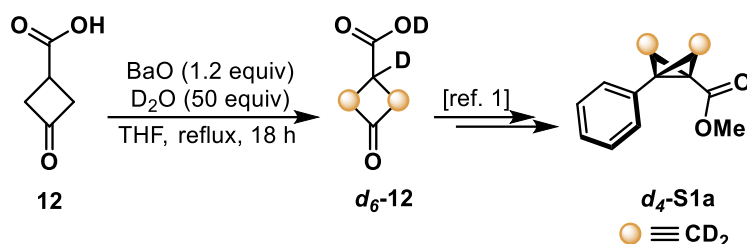
phase was extracted again with EtOAc (2 x 5 mL), the combined organic phases were washed with a saturated solution of Rochelle's salt (2 x 5 mL), dried over Na₂SO₄ and concentrated *in vacuo* to obtain secondary alcohols **1o-u**, that were directly used in the electrochemical protocol without further purification.

Note: In an attempted preparation of secondary alcohol **1o** from ketone **S1o**, the use of DIBAL-H led to a mixture of the desired product **1o** and byproduct **S2o**, deriving from the “conjugated” addition of the hydride to the C_α-C_γ bond. The use of NaBH₄ led to a mixture of the desired product **1o** and byproduct **S3o**, deriving from the reduction of **S2o**. On the contrary, LiAlH₄ afforded a completely selective reduction of the carbonyl unit. Therefore, the use of LiAlH₄ was extended to other ketones **S1p-u** for the preparation of the respective alcohols **1p-u**.



Note: Alcohols **1** were found to be particularly sensitive to column chromatography on silica gel, with very low recovery, even after fast purifications or passivation of SiO₂ with TEA. Furthermore, they showed to undergo a slow decomposition, probably through polymerization, in the solid state at room temperature. To ensure samples of high purity and long life-time, they were dissolved, straight after preparation, in anhydrous ACN (0.1 M solution) and stored at -20 °C under Ar.

5.5.2.3 Preparation and Characterization of *d*₄-S1a



Product ***d*₄-1a** (*vide infra*) was obtained by reduction of ***d*₄-S1a** following the general procedure. Product ***d*₄-S1a** was obtained following the same procedure reported for all other **S1** materials, starting from ***d*₆-12**. This was obtained by deuteration of **12** following an unmodified reported procedure.¹¹³

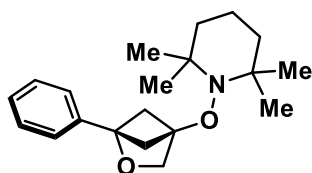
1a. White wax. **Yield** = 97% (0.29 mmol, 46.4 mg). ¹H NMR (600 MHz, CDCl₃) δ 7.29 – 7.24 (m, 2H, partially overlapped with residual solvent signal), 7.24 – 7.21 (m, 2H), 7.17 – 7.13 (m, 1H), 3.90 (s, 2H), 2.26 (s, 2H), 1.22 (s, 2H), the –OH signal was not detected in the spectrum. ¹³C NMR (151 MHz, CDCl₃) δ 135.8, 127.5 (2C), 124.2 (2C), 124.2, 61.2, 32.2 (2C), 22.8, 16.5. **HRMS (ESI)** m/z [M+Na]⁺ calcd. for C₁₁H₁₂NaO⁺: 183.0780; found 183.0781.

***d*₄-S1a** White solid. **m.p.** 68 – 80 °C. ¹H NMR (600 MHz, CDCl₃) δ 7.29 – 7.24 (m, 4H), 7.22 – 7.19 (m, 1H), 3.45 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 170.1, 133.6, 128.5 (2C), 127.0, 125.9 (2C), 51.8, 32.7, 23.0, the CD₂ peak was not detected. **HRMS (ESI)** m/z [M+Na]⁺ calcd. for C₁₂H₈D₄NaO₂⁺: 211.0730; found 211.0737.

¹¹³ H.-k. Fan, S. Yang, J.-h. Li, Q.-q. Teng, M. Chen, "Eur. J. Org. Chem. **2022**, e202201218.

5.5.2.4 Preparation and Characterization of Products 3

The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with the appropriate electroactive precursor **2** (0.20 mmol, 2.0 equiv.) and LiClO₄ (0.30 mmol, 31.9 mg). The ElectraSyn vial cap, equipped with anode (C) and cathode (Ni), was inserted into the mixture and closed with a rubber septum. Then THF (2.0 mL) and a solution of alcohol **1** in ACN (0.1 mmol, 1.0 mL, 0.1 M) were added, the mixture stirred until complete dissolution of the solids occurred and then cooled to -30 °C. The reaction mixture was electrolysed at a constant current of 10.0 mA at -30 °C, until the prescribed number of electrons (F/mol₁) was reached (see single cases below). Then, the ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (5 mL) and NH₄Cl_(aq) (saturated, 5 mL) and water (5 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with NH₄Cl_(aq) (0.1 M, 3 x 5 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was finally purified by FC on silica gel to afford pure products **3**.



3aa. Obtained from alcohol **1a** and TEMPO **2a** (1.0 F/mol_{1a}).

White solid. **m.p.** 101 - 103 °C. **FC eluent:** *n*Hex/EtOAc 50:1.

Yield = 75% (0.075 mmol, 23.6 mg). **¹H NMR** (600 MHz, CDCl₃) δ 7.42 – 7.38 (m, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.26

(m, 1H), 3.95 (s, 2H), 2.34 – 2.18 (m, 4H), 1.66 – 1.39 (m, 5H), 1.38 – 1.30 (m, 1H), 1.17 (s, 6H), 1.13 (s, 6H). **¹³C NMR** (151 MHz, CDCl₃) δ 138.1, 128.2 (2C), 127.7, 126.0 (2C), 83.4, 81.9, 69.1 (2C), 59.3, 49.9 (2C), 39.8 (2C), 33.8 (2C), 20.4 (2C), 17.1.

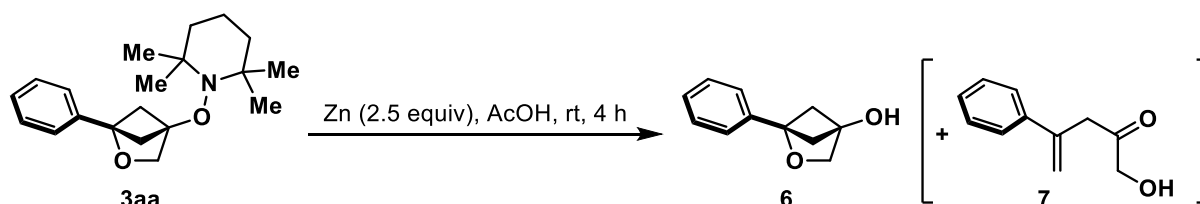
HRMS (ESI) *m/z* [M+Na]⁺ calcd. for C₂₀H₂₉NNaO₂⁺: 338.2090; found 338.2095.

5.5.2.5 Preparation of 3aa on 1mmol scale

The ElectraSyn vial (10 mL), equipped with a stir bar, was charged with TEMPO **2a** (2.0 mmol, 302 mg, 2.0 equiv) and LiClO₄ (3.0 mmol, 319 mg). The ElectraSyn vial cap, equipped with anode (C) and cathode (Ni), was inserted into the mixture and closed with a rubber septum. Then THF (6.0 mL) and a solution of alcohol **1** in ACN (1.0 mmol, 3.0 mL, 0.33 M) were added, the mixture stirred until complete dissolution of the solids occurred and then cooled to -30 °C. The reaction mixture was electrolysed at a constant current of 10.0 mA at -30 °C, until a total charge of 1.0 mF (F/mol_{1a}) was

reached. Then, the ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (5 mL) and $\text{NH}_4\text{Cl}_{(\text{aq})}$ (saturated, 15 mL) and water (15 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with $\text{NH}_4\text{Cl}_{(\text{aq})}$ (0.1 M, 3 x 15 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 50:1) to afford pure products **3aa** in 70% yield (0.70 mmol, 217 mg).

5.5.2.5 Preparation of Alcohol



In a Schlenk flask, equipped with a magnetic stirring bar and under Ar atmosphere, compound **3aa** (0.50 mmol, 158 mg) was dissolved in glacial AcOH (5.0 mL) and Zn dust (1.25 mmol, 2.5 equiv, 83 mg) was added and the resulting suspension was vigorously stirred at room temperature for 4 h. Then, a saturated solution of NaHCO_3 (25 mL) was carefully added, followed by EtOAc (10 mL). Then, the biphasic mixture was moved to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with NaHCO_3 (saturated, 3 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 5:1) to afford pure product **6** as a white waxy solid (50.2 mg, 0.29 mmol, 57% yield) as the third eluting fraction. By-product **7** (12.8 mg, 0.07 mmol, 14% yield, colourless oil) was isolated as the second eluting fraction and recovered starting material **3aa** (31.6 mg, 0.10 mmol, 20% yield, white solid) as the first one.

***Note:** The use of higher equivalents of Zn dust (5 equiv) or prolonged reaction times (10 h) ensured full conversion of **3aa** but worsened the **6/7** ratio. Running the reaction at temperatures higher than 45 °C led to a substantial decomposition of **3aa**. Running*

checked by ^1H NMR spectroscopy, which confirmed complete consumption of the starting material. Then, H_2O (5 mL) was carefully added, followed by HCl (aqueous, 2 M, 20 mL or until a strongly acidic pH was reached) and EtOAc (30 mL). The resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, the aqueous layer was extracted again with EtOAc (2 x 30 mL), the combined organic phases were dried with Na_2SO_4 , evaporated in vacuo and the resulting crude alcohol **S4a** (pale-yellow solid) was used in the next step without any purification.⁹³

Step 2. In a round-bottom flask equipped with a magnetic stirring bar, **S4a** (10 mmol, from the previous step) was suspended in toluene (20 mL) and HCl (aqueous, 37% w/w, 20 mL) was added. The resulting suspension was vigorously stirred for 1 h and the conversion was checked by ^1H NMR spectroscopy, which confirmed complete consumption of the starting material. The biphasic mixture was transferred to a separatory funnel, and the phases were separated. The aqueous layer was diluted with H_2O (60 mL) and extracted again with EtOAc (2 x 30 mL), the combined organic phases were dried with Na_2SO_4 , evaporated in vacuo and the resulting crude chloride **S5a** (pale-yellow solid) was used in the next step without purification.⁹³

Step 3. In a round-bottom flask equipped with a magnetic stirring bar, **S5a** (10 mmol, from the previous step) was dissolved in DMF (15 mL), K_2CO_3 (22 mmol, 2.2 equiv) was added under vigorous stirring, followed by MeI (24 mmol, 2.4 equiv, dropwise addition). The resulting suspension was stirred for 1 h and the conversion was checked by TLC (n -hexane/ EtOAc 7:3 + 1% HCOOH) that usually confirmed complete consumption of the starting material. A saturated aqueous solution of NH_4Cl (10 mL), H_2O (10 mL) and EtOAc (20 mL) were added, and the resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, the aqueous layer was extracted again with EtOAc (2 x 10 mL), the combined organic phases were washed with a 0.1 M aqueous solution of NH_4Cl (3 x 20 mL), dried with Na_2SO_4 , evaporated in vacuo and the resulting crude **S6a** (pale-yellow oil) was used in the next step without purification.⁹³

Step 4. In a heat-gun dried 3-necked round bottom flask equipped with a magnetic stirring bar and under Ar atmosphere crude **S6a** (10 mmol, from previous step) was dissolved in anhydrous THF (15 mL) and cooled to 0 °C. A solution of NaHMDS (11 mmol, 1.1 equiv, 1M in THF) was added dropwise and the resulting red-colored

solution was stirred at 0 °C until ^1H NMR spectroscopy confirmed complete consumption of the starting material (30 min). A saturated aqueous solution of NH_4Cl (20 mL), H_2O (20 mL) and EtOAc (20 mL) were added, and the resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, the aqueous layer was extracted again with EtOAc (2 x 15 mL), the combined organic phases were dried with Na_2SO_4 . Trituration with cold $n\text{Hex}/\text{Et}_2\text{O}$ (3:1, 3 x 30 mL) afforded product **S1a** in 47% yield over 4 steps (4.7 mmol, 884 mg, 83% average yield per step).⁹³

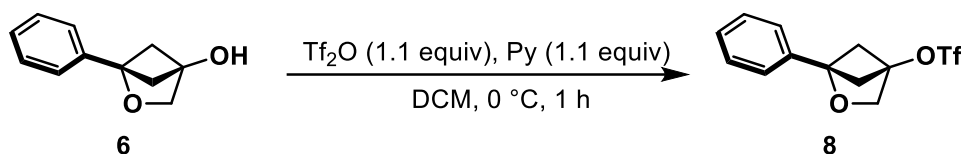
Step 5. In a heat-gun dried 3-necked round bottom flask, equipped with a magnetic stirring bar and under Ar atmosphere, ester **S1a** (1.0 mmol, from previous step) was dissolved in anhydrous THF (3 mL), cooled to – 78 °C and a solution of DIBAL-H (2.5 equiv, 2.5 mmol, 2.5 mL, 1.0 M in toluene) was added dropwise. After the addition was completed, the resulting solution was stirred for 1 h, during which time the temperature was allowed to rise to – 20 °C. Then, EtOAc (10 mL) was carefully added, followed by a saturated solution of Rochelle's salt (10 mL). The biphasic mixture was then vigorously stirred at room temperature for 1 h, until two clear phases were obtained and the transferred to a separatory funnel. The phases were separated, the aqueous phase was extracted again with EtOAc (2 x 10 mL), the combined organic phases were washed with a saturated solution of Rochelle's salt (2 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to obtain alcohol **1a** (152 mg, 0.95 mmol, 95% yield) that was directly used in the further step without purification.

Step 6. The ElectraSyn vial (10 mL), equipped with a stir bar, was charged with TEMPO **2a** (1.9 mmol, 287 mg, 2.0 equiv) and LiClO_4 (3.0 mmol, 319 mg). The ElectraSyn vial cap, equipped with anode (C) and cathode (Ni), was inserted into the mixture and closed with a rubber septum. Then THF (6.0 mL) and a solution of alcohol **1a** in CAN (from previous step, 0.95 mmol, 3.0 mL, 0.32 M) were added, the mixture stirred until complete dissolution of the solids occurred and then cooled to –30 °C. The reaction mixture was electrolysed at a constant current of 10.0 mA at –30 °C, until a total charge of 1.0 mF ($\text{F}/\text{mol}_{1\text{a}}$) was reached. Then, the ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (5 mL) and $\text{NH}_4\text{Cl}_{(\text{aq})}$ (saturated, 15 mL) and water (15 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with $\text{NH}_4\text{Cl}_{(\text{aq})}$ (0.1 M,

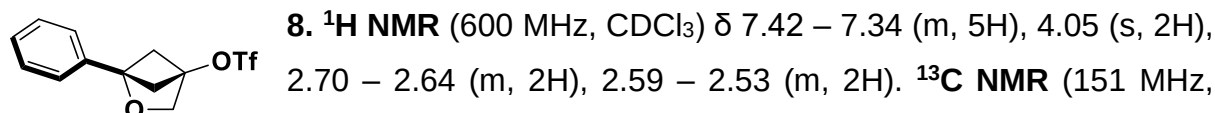
3 x 15 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 50:1) to afford crude product **3aa** that was used directly in the next step without further purification.

Step 7. In a Schlenk flask, equipped with a magnetic stirring bar and under Ar atmosphere, compound **3aa** (0.95 mmol, from the previous step) was dissolved in glacial AcOH (10.0 mL) and Zn dust (2.5 mmol, 2.5 equiv, 166 mg) was added and the resulting suspension was vigorously stirred at room temperature for 7 h. Then, a saturated solution of NaHCO₃ (50 mL) was carefully added, followed by EtOAc (20 mL). Then, the biphasic mixture was moved to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with NaHCO₃ (saturated, 3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 5:1) to afford pure product **6** as a white waxy solid in 34% yield over 2 steps (56.8 mg, 0.32 mmol).

5.5.2.6 Preparation of Triflate **8**

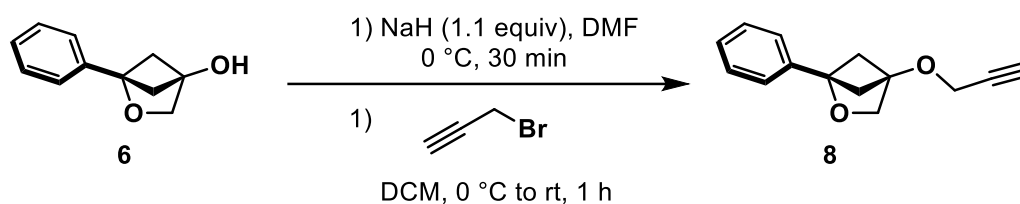


In a Schlenk flask, equipped with a magnetic stirring bar and under Ar atmosphere, compound **6** (0.10 mmol, 17.6 mg) was dissolved in dry DCM (0.5 mL), pyridine (0.11 mmol, 1.1 equiv, 8.9 μ L) was added and the solution was cooled to 0 °C. Then, triflic anhydride (0.11 mmol, 1.1 equiv, 18.5 μ L) was added and the resulting mixture was stirred at 0 °C for 1 h. A saturated solution of NaHCO₃ (3 mL) was carefully added, followed by DCM (3 mL). The biphasic mixture was moved to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organic layers were washed with NaHCO₃ (saturated, 3 x 2 mL), dried over Na₂SO₄ and concentrated in vacuo. Pure product **8** was directly obtained as a colourless oil (27.7 mg, 0.090 mmol, 90% yield) without further purification.

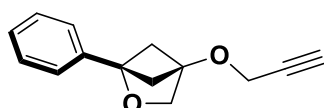


CDCl₃) δ 134.2, 127.8 (2C), 127.5, 125.0 (2C), 117.2 (d, J = 319.6 Hz), 82.1, 81.7, 67.1, 47.9 (2C). **¹⁹F NMR** (565 MHz, CDCl₃) δ -75.0 (s, 3F). **HRMS (ESI)** m/z [M+Na]⁺ calcd. for C₁₂H₁₁F₃NaO₄S⁺: 331.0222; found 331.0219.

5.5.2.7 Preparation of Propargyl ether **9**



In a Schlenk flask, equipped with a magnetic stirring bar and under Ar atmosphere, compound **6** (0.10 mmol, 17.6 mg) was dissolved in dry DMF (0.5 mL) and the solution was cooled to 0 °C. Then, NaH (0.11 mmol, 1.1 equiv, 3.9 mg, 65% wt. in mineral oil) was added and the resulting mixture was stirred at 0 °C for 30 min. Then, propargyl bromide (0.11 mmol, 1.1 equiv, 8.3 μL) was added and the reaction mixture was stirred at room temperature for 1 h. A saturated solution of NH_4Cl (3 mL) was carefully added, followed by EtOAc (3 mL). The biphasic mixture was moved to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were washed with NaH_4Cl (0.1 M, 3 x 2 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 20:1) to afford pure product **9** as a colourless oil (15.8 mg, 0.074 mmol, 74% yield).

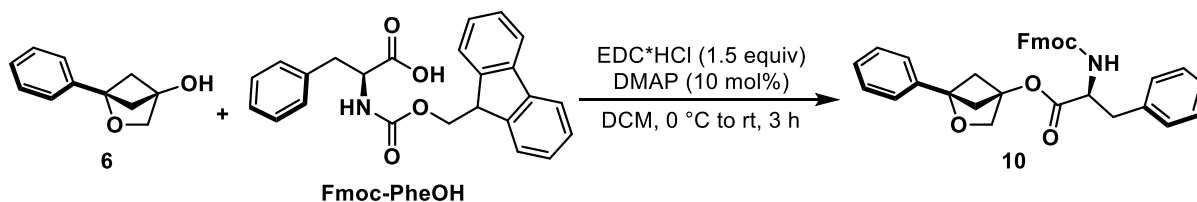


9. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.45 – 7.28 (m, 5H), 4.33 (d, J = 2.4 Hz, 2H), 3.88 (s, 2H), 2.49 (t, J = 2.4 Hz, 1H), 2.36 – 2.29 (m, 2H), 2.26 – 2.21 (m, 2H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3)

δ 136.4, 127.3 (2C), 127.1, 125.0 (2C), 82.2, 79.2, 79.1, 73.7, 67.8, 54.0, 45.6 (2C).

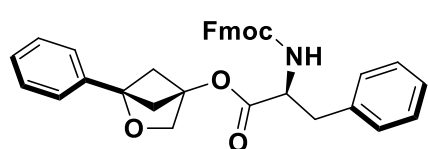
HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{NaO}_2^+$: 237.0886; found 237.0881.

5.5.2.8 Preparation of FmocPhe ester (**S**)-**10**



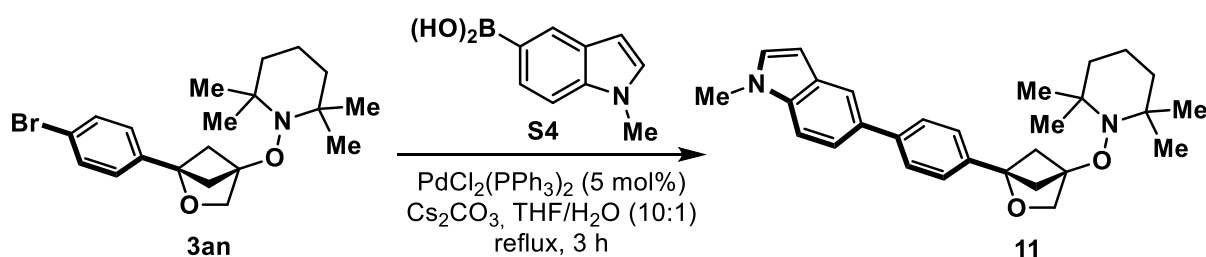
In a Schlenk flask, equipped with a magnetic stirring bar and under Ar atmosphere, compound **6** (0.10 mmol, 17.6 mg) was dissolved in dry DCM (0.5 mL) and the solution was cooled to 0 °C. Then, Fmoc-PheOH (0.15 mmol, 1.5 equiv, 58.1 mg), DMAP (0.01 mmol, 5 mol%, 1.2 mg) and EDC hydrochloride (28.7 mg) were sequentially added.

The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. A saturated solution of NH₄Cl (3 mL) was then added, followed by DCM (3 mL). The biphasic mixture was moved to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organic layers were washed with NaH₄Cl (0.1 M, 3 x 2 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude product was finally purified by FC on silica gel (*n*Hex/EtOAc 3:1) to afford pure product **(S)-10** as a white waxy solid (50.1 mg, 0.092 mmol, 92% yield).



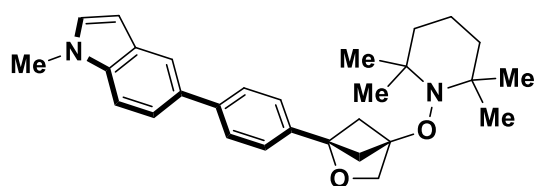
(S)-10. $[\alpha]_D = -44.6$ ($c = 0.33$, CHCl₃). **¹H NMR** (600 MHz, CDCl₃) δ 7.71 (dt, $J = 7.6, 0.9$ Hz, 2H), 7.53 – 7.47 (m, 2H), 7.37 – 7.28 (m, 6H), 7.28 – 7.20 (m, 6H), 7.06 (d, $J = 6.7$ Hz, 2H), 5.20 (d, $J = 8.3$ Hz, 1H), 4.64 (dt, $J = 8.2, 6.0$ Hz, 1H), 4.41 (dd, $J = 10.7, 7.1$ Hz, 1H), 4.31 (dd, $J = 10.7, 6.9$ Hz, 1H), 4.15 (t, $J = 7.0$ Hz, 1H), 3.83 (d, $J = 4.9$ Hz, 1H), 3.81 (d, $J = 5.0$ Hz, 1H), 3.10 (dd, $J = 13.8, 5.9$ Hz, 1H), 3.05 (dd, $J = 13.9, 6.2$ Hz, 1H), 2.39 – 2.29 (m, 4H). **¹³C NMR** (151 MHz, CDCl₃) δ 170.5, 155.5, 143.8 (2C, rotamer), 143.7 (2C, rotamer), 141.4 (2C), 136.6, 135.5, 129.4 (2C), 128.7 (2C), 128.4 (2C), 128.4, 127.8 (2C), 127.4, 127.1 (2C), 126.1 (2C), 125.1 (2C, rotamer), 125.0 (2C, rotamer), 120.1 (2C, rotamer), 120.0 (2C, rotamer), 83.7, 77.0 (overlapped with the CDCl₃ peak), 67.4, 67.0, 54.8, 47.9, 47.8, 47.2, 38.4. **HRMS (ESI)** m/z $[M+Na]^+$ calcd. for C₃₅H₃₁NNaO₅⁺: 568.2094; found 568.2093.

5.5.2.9 Suzuki coupling towards product 11



In a Schlenk tube, under an Ar atmosphere and magnetic stirring, bromo-derivative **3an** (39.3 mg, 0.10 mmol), Cs₂CO₃ (0.3 mmol, 81.0 mg) and boronic acid **S4** (35.0 mg, 0.20 mmol) were suspended in a THF/H₂O mixture (10:1, 0.55 mL). The resulting suspension was de-gassed by bubbling Ar for 1 min, then [PdCl₂(PPh₃)₂] (0.005 mmol, 3.5 mg, 5 mol%) was added and the resulting mixture was stirred at 70 °C for 3 h. The

reaction mixture was cooled to room temperature and a saturated aqueous solution of K_2CO_3 (2 mL), H_2O (5 mL) and EtOAc (5 mL) were added, and the resulting biphasic mixture was transferred to a separatory funnel. The phases were separated, the aqueous layer was extracted again with EtOAc (5 mL), the combined organic phases were washed with a saturated aqueous solution of K_2CO_3 (2 x 5 mL), dried with Na_2SO_4 , evaporated *in vacuo* and finally purified by FC on silica gel (*n*Hex/EtOAc 8:1) to afford pure product **11** as a white solid (38.6 mg, 0.087 mmol, 87% yield).



11. m.p. 115 - 117 °C. ^1H NMR (600 MHz, CDCl_3) δ 7.84 (dd, J = 1.7, 0.7 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.50 – 7.43 (m, 3H), 7.38 (dt, J = 8.5, 0.8 Hz, 1H), 7.08 (d, J = 3.0 Hz, 1H), 6.53 (dd, J = 3.1, 0.9 Hz, 1H), 3.97 (s, 2H), 3.82 (s, 3H), 2.35 – 2.31 (m, 2H), 2.29 – 2.25 (m, 2H), 1.65 – 1.58 (m, 1H), 1.54 – 1.43 (m, 4H), 1.35 (dp, J = 13.4, 3.4 Hz, 1H), 1.19 (s, 6H), 1.14 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ 141.1, 135.2, 135.0, 131.4, 128.5, 127.9, 126.1 (2C), 125.3 (2C), 120.3, 118.3, 108.4, 100.3, 82.4, 80.8, 68.1, 58.3 (2C), 49.0 (2C), 38.8 (2C), 32.8 (2C), 31.9, 19.4 (2C), 16.1. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{NaO}_2^+$: 467.2669; found 467.2676.