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Review

Recent Advances in Enantioselective Catalytic Electrochemical Organic Transformations

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Abstract: Different approaches can be undertaken to realise a stereoselective electrochemical synthesis. Significant contributions to enantioselective electrochemical organic synthesis have been reported and largely reviewed in recent years. However, the development of general strategies for the electrochemical enantiocontrol of a transformation still presents considerable challenges; in particular, relatively few contributions of highly enantioselective catalytic electrochemical reactions have been reported to date. In this review article, the most recent examples of asymmetric electrochemical catalysis are discussed. The article is organised by the three types of enantioselective catalysis: metal-based catalysis, organocatalysis and biocatalysis; in each section, the most significant and recent advances are presented and discussed.

Keywords: electrochemistry; chiral catalysts; electroorganic synthesis; enzymes; stereoselective reactions

Citation: Medici, F.; Resta, S.; Andolina, S.; Benaglia, M. Recent Advances in Enantioselective Catalytic Electrochemical Organic Transformations. *Catalysts* **2023**, *13*, 944. https://doi.org/10.3390/catal13060944

Academic Editors: Giorgio Della Sala and Rosaria Schettini

Received: 26 April 2023
Revised: 17 May 2023
Accepted: 22 May 2023
Published: 28 May 2023

1. Introduction

The synthetic applications of electrochemistry and the development of electroorganic synthesis have come to the forefront of organic synthesis only in the last thirty years. The lack of standard equipment and some difficulties in establishing reproducible and reliable results may be some of the reasons for the delay [1,2]. However, recently, the topic has been revitalised and has recently become one of the main streams of synthetic organic chemistry, with an increasing number of publications and the development of remarkable and attractive electroorganic synthesis methodologies. At the same time, the development and commercialisation of standardised electrolysis cells and equipment for electrosynthesis both under batch and flow conditions have allowed several research groups to enter the field [3–5].

In this framework of hectic and feverish research activities, the development of general strategies for exerting electrochemical enantiocontrol presented considerable challenges, and relatively few contributions of highly enantioselective catalytic electrochemical reactions have been reported to date. The first reviews in the area of asymmetric electrochemical catalysis are very recent and were published in 2019 [6,7].

Different strategies can be followed to realise a stereoselective electrochemical synthesis; one well-established approach relies on the use of chiral substrates as starting materials, which direct and control the diastereoselectivity of the reaction. However, a more general strategy involves the introduction of external chiral sources into each of the basic elements of an electrochemical setting, including chiral media, chiral catalysts, chiral mediators and chiral electrodes. In the last two years, a few reviews have summarised the most significant contributions to the field of enantioselective electrochemical organic synthesis [8–10].

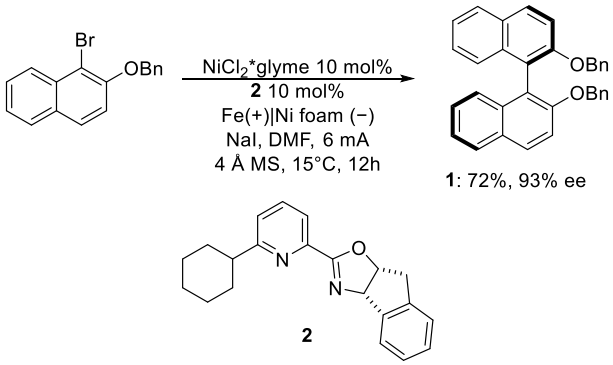
Considering these very recent publications on asymmetric electrosynthesis, we have decided to discuss only the most recent examples of asymmetric electrochemical catalysis in this review article. This article is organised by the three types of enantioselective catalytic

strategies: metal-based catalysis, organocatalysis and biocatalysis; in each section, the most significant and recent advances are presented and discussed.

2. Metal-Catalysed Enantioselective Electrosynthesis

With high tunability properties, metal catalysts have always played a central role in enantioselective reactions. The possibility to synthesise complexes, combining all sorts of ligands with different metallic elements, allowed the development of numerous enantioselective synthetic strategies in the last six decades [11–15]. Hence, it was only natural that also electrochemistry took advantage of chiral metal complexes.

Biaryl compounds are privileged scaffolds applied in different chemistry fields, from drugs to materials [16]. Their synthesis remains a hot topic for organic chemistry, always looking for new synthetic pathways, including electrochemical routes. Mei's group in 2020 published an electrochemical Ni-catalysed synthesis with high enantioselection [17]. Their approach involves Ni*glyme as a catalyst precursor and pyridine-oxazoline as chiral ligands **2**, using an undivided cell (Scheme 1).



Scheme 1. Reaction protocol for the enantioselective biaryl synthesis proposed by Mei and co-worker.

By the described protocol, the desired biaryl **1** is obtained in good yields and excellent enantiomeric excess, often higher than 90%. Optimisation studies evidenced how the presence of water was detrimental to the yield, dropping at 10%, while the ee% remained stable. The substrate's scope shows the tolerance of the methodology toward different functional groups, ketone, ester, borane and heteroarenes. Cyclovoltammetry indicates that after the oxidative addition of the aryl moiety on Ni(0), the cathodic reduction will form the Ni(I) species that is able to undergo another oxidative addition without the necessity of a transmetallation step or ligand exchange, which would have affected the final ee%. After reductive elimination and product formation, the catalyst is regenerated by another cathodic reduction (Figure 1).

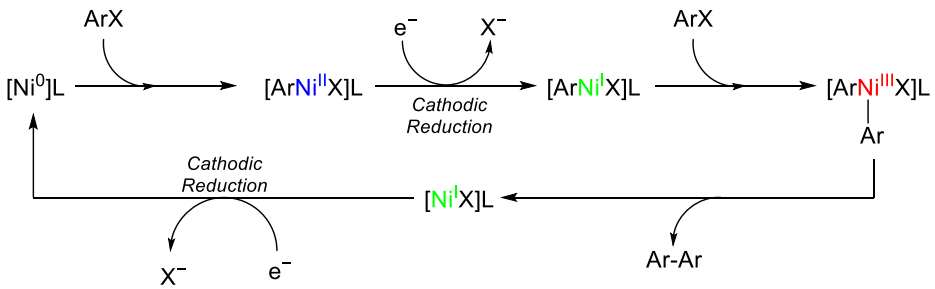
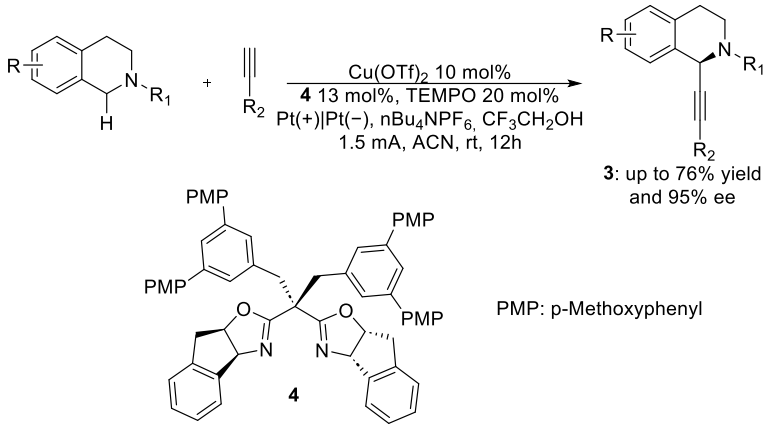


Figure 1. Ni-catalysed biaryl synthesis proposed mechanism.

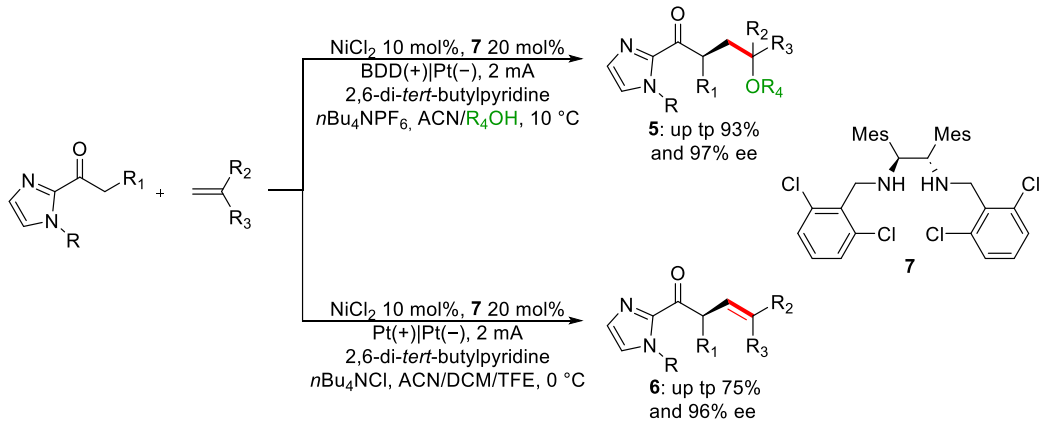
In the same year, Mei's group proposed an enantioselective copper-catalysed alkynylation of tertiary amines [18], another important class of molecules in various fields [19–21]. Inspired by the work of Shono [22], they used a combination of Cu(II), TEMPO and Box ligands, **4**, to achieve the desired product **3** (Scheme 2).



Scheme 2. Protocol for the enantioselective alkynylation of tertiary amines.

Further, in this case, the reaction scope was wide, and different substituents on the tetrahydroisoquinoline skeleton or on the nitrogen atom could be tolerated. Regarding the alkynyl moiety, both aromatic and aliphatic alkyne can be employed, including ethynylferrocene; yields range from 30% to 80%., while the enantiomeric excess never goes under 80%. As for the mechanism, the role of copper is to activate the alkynyl moiety. By hydride transfer from the tetrahydroisoquinoline, TEMPO will generate the iminium ion that the organocuprate can easily attack. Anodic oxidation will then regenerate the oxoammonium species TEMPO.

Olefins are a class of compounds of extraordinary value as building blocks [23,24]. For this reason, their synthesis and functionalisation among the hot topics in synthetic chemistry [25–28]. Guo and co-workers published an article where enantioselective alkene functionalisation was achieved through electrochemistry (Scheme 3) [29].



Scheme 3. Enantioselective olefins functionalisation.

Optimisation of the condition reveals that in the presence of a good nucleophile, e.g., alcohol, the olefinic product, **6**, is not observed. Instead, a polyfunctionalised product featuring an alkoxy group, **5**, was obtained. To avoid this phenomenon, a less nucleophilic protic solvent must be used. In particular, fluorinated alcohols, a class of solvents of choice in electrochemistry, such as HFIP (1,1,1,3,3,3-hexafluoroethanol) or TFE (1,1,1-trifluoroethanol) [30], are suitable candidates. The two methodologies differentiate for the last step of the mechanism. Anodic oxidation of the intermediate product **I**, derived from the previous steps of the mechanism, generates the transient common cation **II**, which, in the presence of an alcohol, will lead to the polyfunctionalised system **5**. At the same time, in the absence of nucleophiles, simple deprotonation will restore alkene **6** (Figure 2).

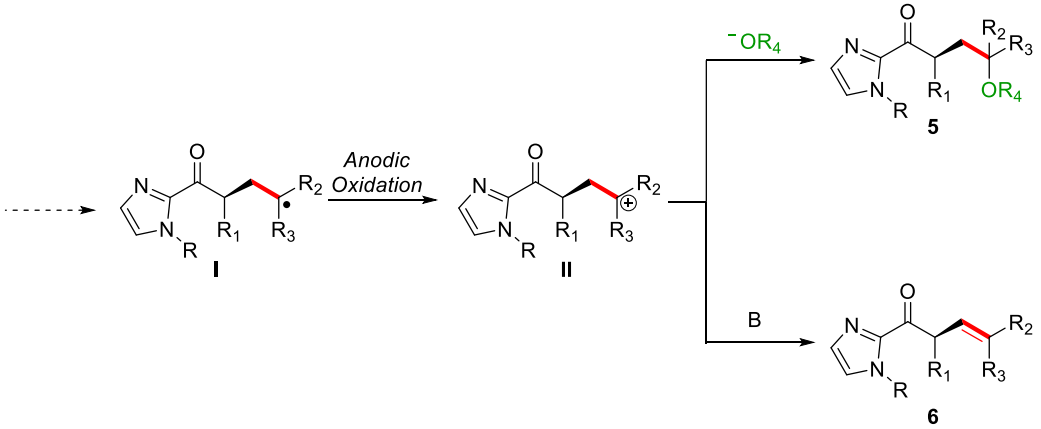
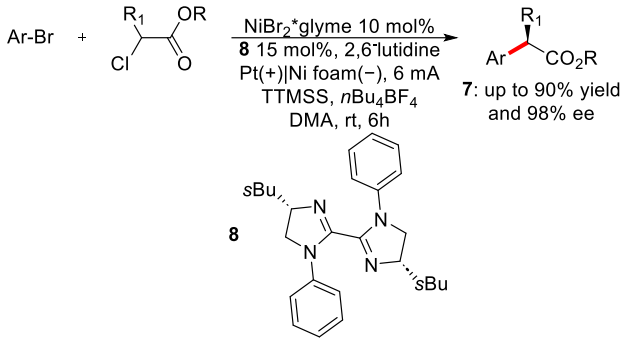


Figure 2. Last steps of the proposed mechanism.

Both aromatic and aliphatic olefins were tested; moreover, EDG and EWG groups seem not to affect the final yield. The enantiomeric excess of the reaction with different substrates was always >80%.

In the area of enantioselective metal-catalysed electrochemistry, Mei's group in 2022 published a paper on enantiospecific paired electrolysis for the α-arylation of carbonylic compounds [31]. Paired electrolysis refers to a condition in which the anodic oxidation and the cathodic reduction occur simultaneously [32,33]. Without the use of a sacrificial anode or the hydrogen formation to maintain the electroneutrality of the reaction, paired electrolysis is a more atom economical strategy; however, fine-tuning of the anodic and cathodic potential is necessary. The optimised protocol is depicted here (Scheme 4).



Scheme 4. Optimised conditions for the arylation of α−chlorocarbonyl.

EPR investigations and CV suggest the following mechanism. Anodic oxidation of the bromide generates the corresponding bromo-radical that will easily abstract hydrogen from the silyl derivative TTMSS (tris(trimethylsilyl)silane). The Si-radical will abstract the chlorine forming the carbonyl radical species. The Ni(I) catalyst goes under oxidative addition by the aryl bromide forming the corresponding Ni(II) complex. Ni(III) was not formed because, during the oxidative addition, another Ni(I) molecule will be oxidised at Ni(II). This latter will then be reduced at the cathode. At the same time, the Ar-Ni(II) complex will be trapped by the carbonyl radical, generating the Ni(III) species, which will regenerate the catalyst after reductive elimination. Different aryl bromide and chloroesters were tested, obtaining good results; the ee% in most cases was higher than 80%. The strategy was also applied to synthesise drug precursors (**9**, **10**, **11**) for Flurbiprofen, Ibuprofen and Canagliflozin (Figure 3).

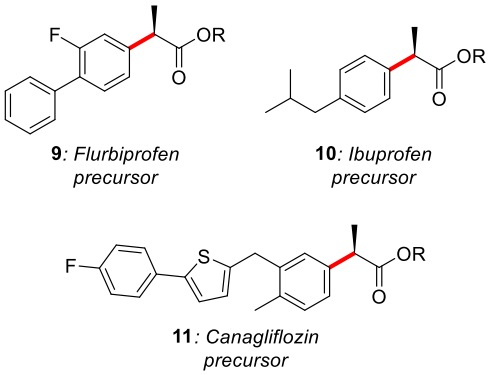
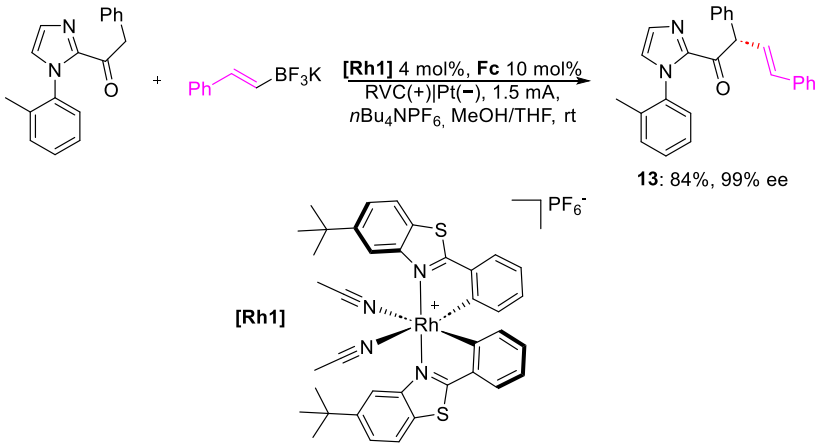


Figure 3. Drug precursors synthesised by Mei's group.

Meggers and co-workers, in 2022, published the enantioselective alkenylation of acyl-imidazole [34]. The work is an evolution of a previous paper, where a ruthenium chiral catalyst could perform the electrochemical reaction with a high level of enantioselection; however, different problems were observed, such as electrode passivation, overoxidation, side reactions, etc. To avoid those issues, in the more recent publication, the authors used a redox mediator to transform the heterogeneous SET step into a homogeneous one, becoming an indirect oxidation. Moreover, in this case, a chiral rhodium catalyst, [Rh1], was used as an alkenyl precursor, paired with a trifluoroborate salt, and ferrocene (Fc) was used in the role of redox mediator (Scheme 5).



Scheme 5. Reaction conditions for the alkenylation of 2-acylimidazole.

The new protocol proves to be effective in affording product **13** in high yields and with high ee%. To demonstrate the necessity of ferrocene, a test without it afforded the product with only a 12% yield, with degradation of the acyl-derivative. The scope shows how the R group in the α-position can be an aryl moiety, with EDG or EWG substituents, as well as aliphatic. Indeed, good-to-excellent yields were achieved, maintaining excellent enantiomeric excess. The methodologies resulted compatible with a variety of borates, without affecting the enantioselectivity. The reaction was also tested with a highly complex scaffold in α the carbonyl, e.g., abietic acid **14** (Figure 4).

As already mentioned, in the previously analysed papers, the following mechanism was proposed by EPR, CV and radical trapping experiments (Figure 5). While the rhodium catalyst is coordinated by the acyl moiety(**III**), at the anode, oxidation of ferrocene(II) to ferrocene(III) occurred. At the same time, methanol was reduced by the cathode to methanolate. MeO^- acts as a base deprotonating **III**, lending to the corresponding anion **IV**; this species can be oxidised by Fc(III) to the carbon-centred radical **V**. Radical trapping by the alkenyl-trifluoroborate will lead to the intermediate **VI**. Thus, after oxidation, de-borylation and de-coordination from the rhodium catalyst give the desired product **13**.

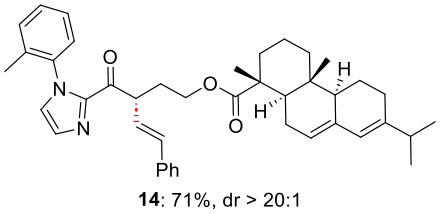


Figure 4. Late-stage functionalisation of abietic acid precursor.

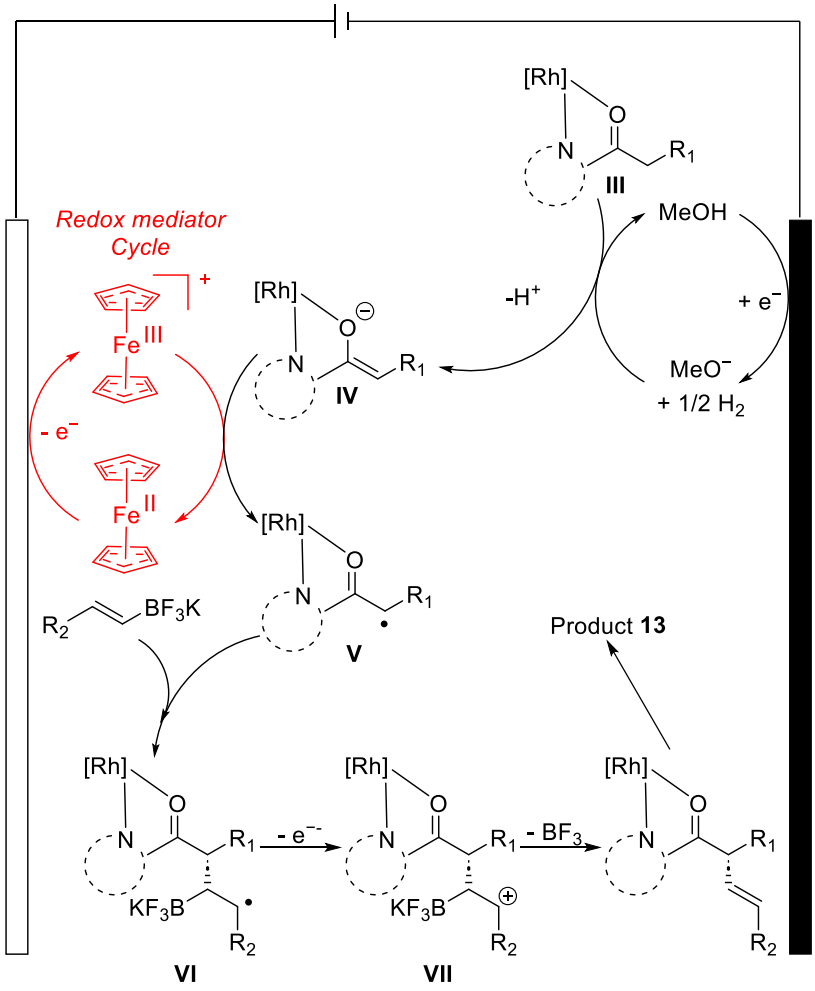


Figure 5. Proposed mechanism.

The stereocontrol and the E/Z configuration preference were decided by the geometry of the intermediate **V** and **VII,** as shown in Figure 6.

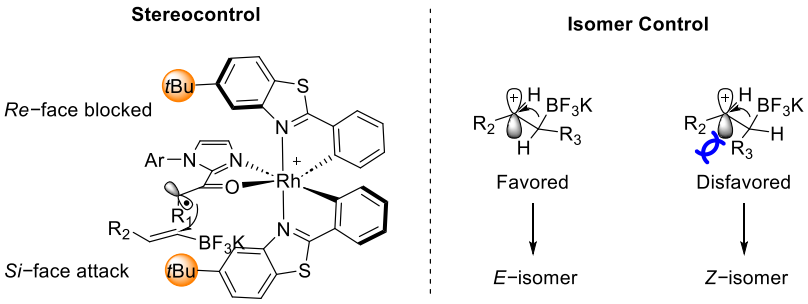
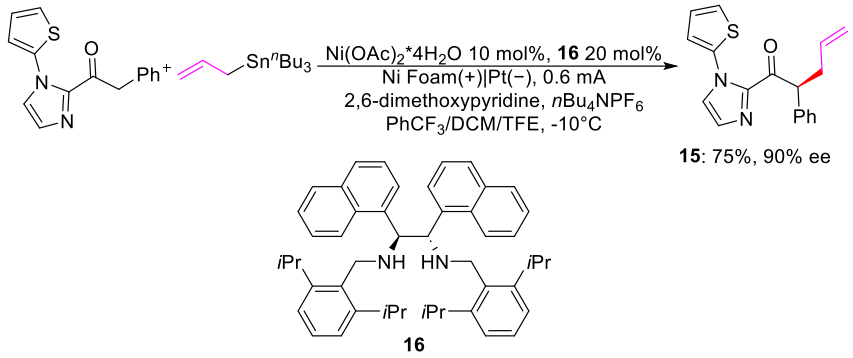


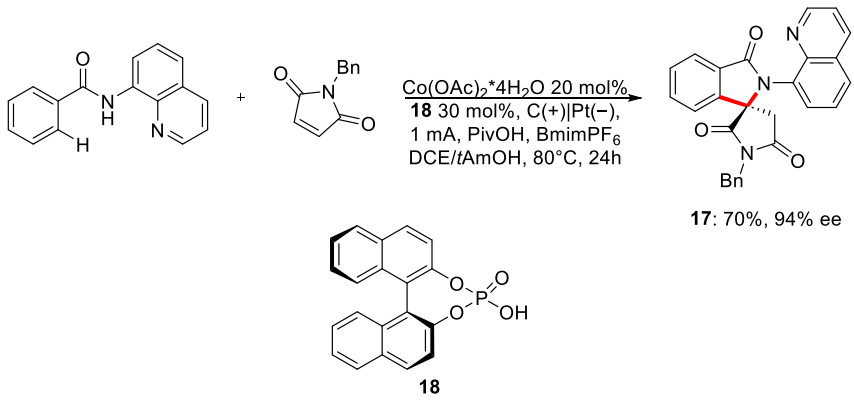
Figure 6. Configuration of intermediate **V** (**left**) and **VII** (**right**).

Similar work was performed by Guo and co-workers using allyl stannanes [11]. Compared to the study of Meggers, no redox mediator is necessary, and oxidation of the substrates takes place at the anode surface. Nevertheless, good yields and high enantioselectivity were obtained (Scheme 6).



Scheme 6. Enantioselective allylation.

Ackermann and co-workers recently published a contribution where the enantioselective C-H activation was achieved by cobalt electrocatalysis [35]. They obtained enantioenriched spiro compound **17**, *N*-annulation and phosphorous-containing molecules in galvanostatic conditions (Scheme 7).



Scheme 7. Reaction condition for the enantioselective electrosynthesis of spiro-compounds.

As chiral ligand, phosphoric acid **18** was chosen, achieving an ee% >90% in the reaction scope, in good yields. The protocol also worked if EWG or EDG groups were present on the amidic moiety. Besides the excellent enantioselectivity, there is another point in favour of the methodology: the formation of hydrogen as the only by-product. During the investigation needed for the mechanism validation, when electricity was substituted with silver carbonate, a moderate drop in the yield was noted, from 70% to 54%; however, more surprisingly, almost a racemic product mixture was obtained. The crucial role of the current in enantioselection was undoubtedly proved. To rationalise this surprising result, oxidation-induced reductive elimination was questioned [36,37]. Indeed, a reductive elimination would lead to a high enantiocontrol with the substrates coordinated to the chiral cobalt catalyst. However, the step from Co(III) to Co(I) is not energetically favourable under the present conditions. Instead, anodic oxidation of the Co(III) to Co(IV) gave access to the highly favourable reduction Co(IV)/Co(II) (Figure 7).

Meanwhile, Shi's group also published an article about a cobalt-catalysed C-H/N-H annulation with alkenes [38]. The principal differences from the work of Ackermann's group are the use of a Salox-type chiral ligand, **20**, and pyridine derivatives **21**, to further enhance the regioselectivity (Scheme 8).

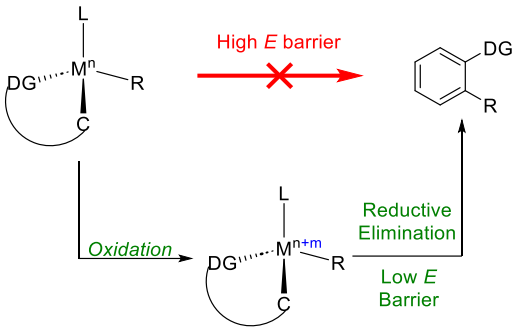
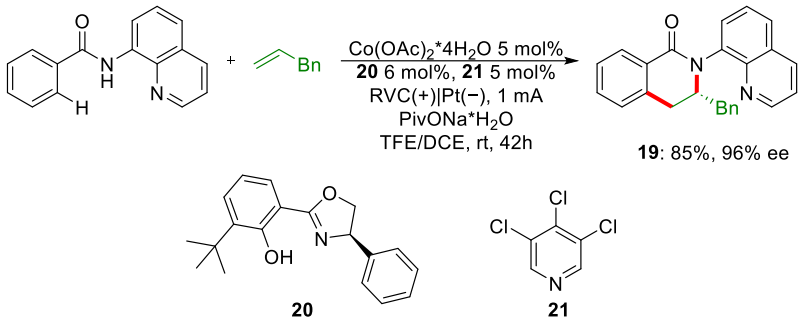


Figure 7. Oxidation-induced reductive elimination.



Scheme 8. Reaction conditions for the enantioselective benzamide annulation with alkene.

The reaction was compatible with a plethora of different substrates. Moreover, cyclic olefins were used with success. The designed Salox-type ligand coordinates to the cobalt metal centre and will ensure the formation of a chiral pocket that the substrates will accommodate. Strong π-π interaction between the benzamide ring and the phenyl moiety on the chiral ligand **20** will stiffen the conformation even more due to the π-π stacking generated by the coordinate pyridine additive. Regiocontrol can be increased by the steric hindrance of the *t*Bu group.

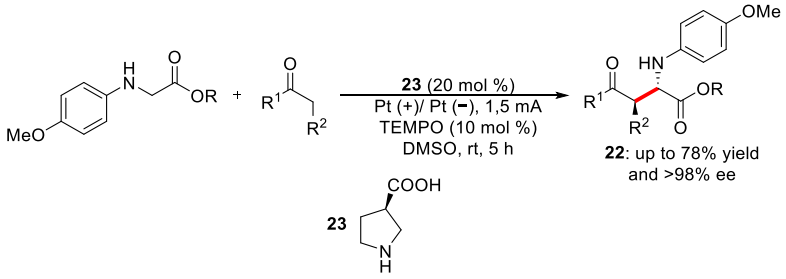
3. Enantioselective Organocatalytic Electrochemical Transformations

Several challenging electrochemical enantioselective new carbon-carbon and carbon-halogen bond formations are discussed in the present section. We focused our attention on three different topics, based on the interaction modes of the chiral catalyst within the substrate. The first examples are related to an organocatalytic cycle that involves the generation of an enamine species, where a covalent bond between the chiral catalyst and the substrate is present. Then, a de-trifluoroacetylative alkylation reaction promoted by squaramide catalysts is discussed, where the squaramide and the substrate are bounded through H-bonding. Finally, a bromocyclisation reaction took place thanks to a phase transfer catalyst, where an ion pair is generated between the chiral catalyst and the substrate. All these reactions successfully combine electrochemical organic synthesis and organocatalytic cycles to afford an enantiopure product exploiting the advantages of electrochemistry.

3.1. Organocatalytic Imine-Enamine Cycle

Electrochemical reactions that exploit an enamine intermediate to obtain enantiopure products have been established during the last years and are characterised by the presence of a covalently linked adduct between the catalyst and the substrate, which helps in controlling the stereochemical outcome of the reaction, even if other interactions could take place in such complex electrochemical environment [39,40]. Wang et al. reported an electrochemical asymmetric coupling of secondary acyclic amines with ketones via a Shono-type oxidation [41]. In this work, the authors synthesised 41 different compounds by changing the nature of R, R^1 and R^2 with good yields (40-80%), excellent diastereoselectivity (up to 99:1) and enantioselectivity (up to 99% ee). As reported in Scheme 9, the reaction

involves the use of a generally acyclic amine, ketones and β-aminoacid, **23**, as an organocatalyst. This innovative strategy consists of using TEMPO as a redox mediator that facilitates the reaction, oxidising the secondary amine at a lower potential and avoiding starting material decomposition.



Scheme 9. Electrochemical reaction conditions between secondary amines and ketones.

As shown in Figure 8, the presence of TEMPO (oxidation potential = 0.231 V vs. Fc/Fc^+) increased the anodic current and, at the same time, decreased the cathodic current, which means that its oxidated species $TEMPO^+$, generated during the oxidation process at the anode surface, is able to react with the amine leading to the formation to its oxidised form. Hence, TEMPO prevented the direct interaction between the amine at the anode surface that could promote the generation of by-products due to its low oxidation potential (0.295 V vs. Fc/Fc^+). Meanwhile, product **22,** which has an oxidation potential of 0.308 V vs. Fc/Fc^+, showed no decrease in the cathodic current in the solution with TEMPO, leading to the conclusion that it did not interact with $TEMPO^+$.

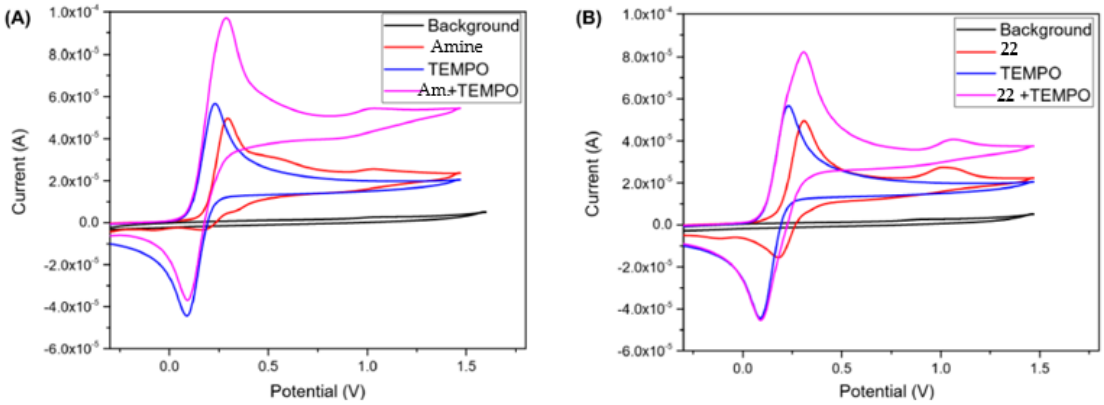


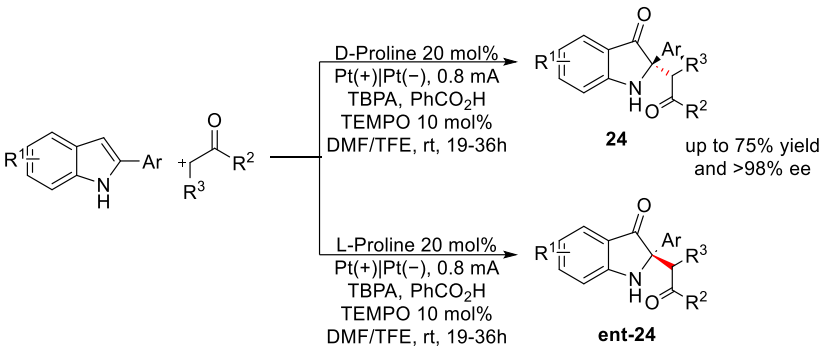
Figure 8. (**A**) Influence of TEMPO in the redox properties of the starting amine. (**B**) Influence of TEMPO in the redox properties of 22.

After the two e^- oxidation of the secondary amine, the enamine was able to attack the oxidated species releasing the iminium ion, which was hydrolysed, generating **22**.

Along with the use of TEMPO as a redox mediator, Lu et al, in 2020 [42], proposed a highly enantioselective (up to 99 % ee) and diastereoselective (up to 20:1) synthesis of C2-quaternary indolin-3-ones from 2-arylindoles, exploiting an organocatalytic cyclic through an enamine intermediate. The general reaction is reported in Scheme 10.

In dependence on the catalyst enantiomer used, it was possible to control the enantioselectivity of the reaction by exploiting benzoic acid as a co-catalyst for the in situ enamine generation. DMF was the best solvent, along with trifluoroethanol (TFE) as a co-solvent, which decreased the by-product formation amount, probably due to the lifetime radical enhancement. After several mechanistic studies, the authors proposed the mechanism reported in Figure 9. It starts with TEMPO oxidation at the anode surface generating $TEMPO^+$ that interacts with **VIII** by releasing its radical cation form (**IX**). This species loses a proton, forming radical **X**. Its resonance structure **XI** reacted with O_2, leading to

compound **XII**. When **XII** reacts with another molecule of **VIII,** it will generate **X**, fed back in the catalytic cycle, and **XIII**, which, after losing an H_2O molecule, leads to the formation of intermediate **XIV**. At this point, the enamine species **XV**, generated by the reaction between the ketone and the proline, can react with **XIV**, leading to the iminium ion compound **XVI**. When **XVI** was hydrolysed, the formation of product **ent-24** occurred together with the release of the organocatalyst.



Scheme 10. Electrochemical reaction conditions for the synthesis of C2-quaternary indolin-3-ones.

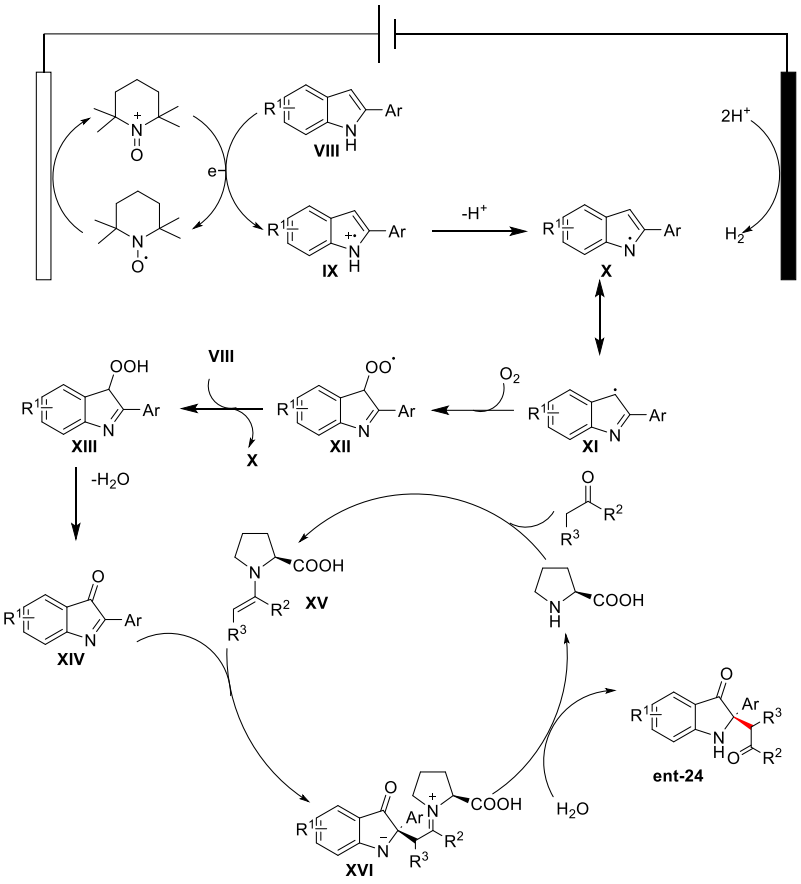
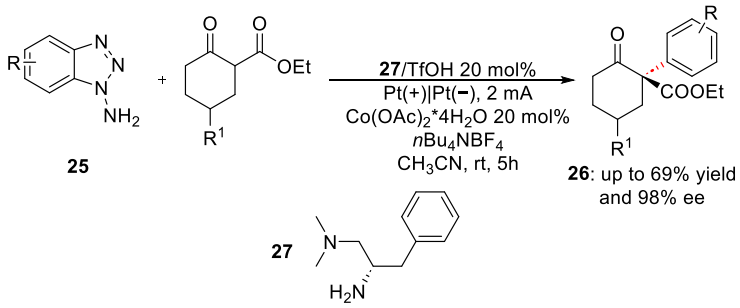


Figure 9. Mechanism representation.

These works remark that TEMPO could be crucial in reactions where direct anodic oxidation leads to the decomposition of substrates. The high instability of molecules in the electrochemical environment leads to the generation of several by-products that decrease the overall yield.

Recently, a catalytic enantioselective α-arylation of cyclic β-ketocarbonyls was reported, using the benzyne intermediate. This work was published in 2020 by Li et al. [43]. Several α-arylated β-ketocarbonyls were obtained in good yields (up to 70 %) and excellent

ee (up to 99 %). As reported in Scheme 11, triazole **25** is the benzyne precursor. Its oxidation potential (0. 84 V vs. Ag/AgCl) is lower than those of the amines and the enamine.



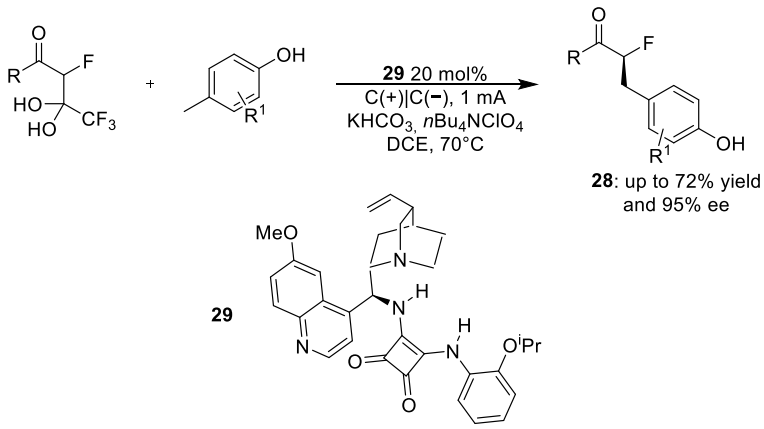
Scheme 11. Electrochemical synthetic pathway for the synthesis of α-arylated β-ketocarbonyls.

When the triazole interacts with the anode surface, it releases the benzyne and N_2. The presence of $Co(OAc)_2$ is crucial for the reaction, due to the ability of the copper species to coordinate the triple bond of the benzyne. In such a proper position, this intermediate is attacked by the enamine compound that controls the reaction's enantioselectivity.

3.2. Organocatalytic Cycle with Squaramide as Organocatalyst

While the substrate was covalently linked to the chiral enamine-catalyst, squaramides interacted by H-bonds. Typically, these catalysts have a very rigid structure, responsible for the reaction's stereocontrol; on the other hand, the complicated space disposition between the catalyst and the substrate shows up the real challenge of this chemistry.

Chang et al. [44] performed an enantioselective de-trifluoroacetylative alkylation reaction with excellent enantiocontrol (up to 95%). As shown in Scheme 12, the reaction involves the α-fluorinated β-keto gem-diol with a p-methylphenol derivative using squaramide **29** as an organocatalyst and $KHCO_3$ as the base. This latter plays two different roles: the first one in the organocatalytic cycle and the second one at the cathode surface.



Scheme 12. Electrochemical synthetic pathway for the de-trifluoroacetylative alkylation reaction.

The proposed mechanism is reported in Figure 10.

Squaramide **29** can coordinate the α-fluorinated β-keto gem-diol leading to the formation of the compound **XVII**. Meanwhile, the p-methylphenol is oxidised at the anode surface, forming the corresponding p-chinone **XVIII**. When the $KHCO_3$ deprotonated one of the two OH groups of the gem-diol, the de-trifluoacetylation occurred with the alkylation, **XIX**. At this point, the product was still coordinated to **29** in a blocked conformation. The enolate restored is ketonic using the Re-Re face by taking an H^+ from the squaramide, **XX**, leading to the enantioenriched product **28**.

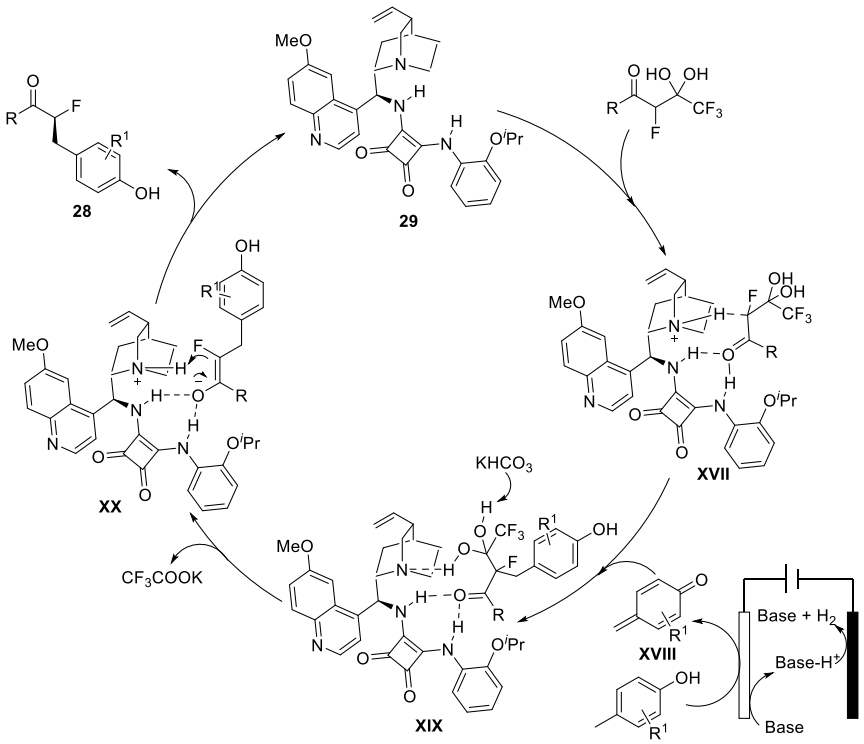


Figure 10. Mechanism of the de-trifluoroacetylative alkylation reaction.

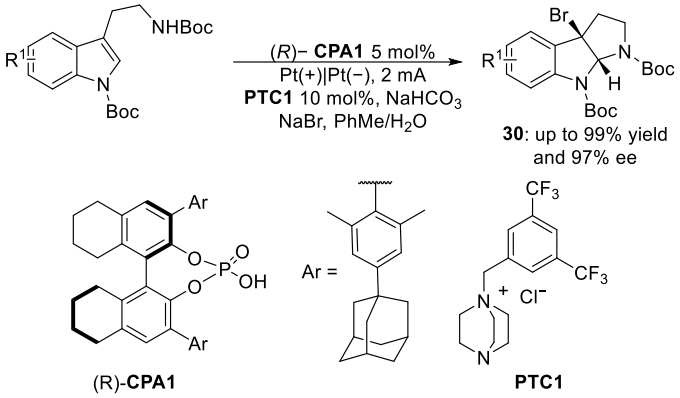
3.3. Enantioselective Electrochemical Reaction Promoted by a Phase Transfer Catalyst (PTC)

Another type of substate-catalyst interaction is represented by an ion-pair species in which the interaction mode is weaker than the enamine and the H-bonding ones. This chemistry has been studied only in recent years due to its challenging applicability in the electrochemical environment. Several issues can occur by combining electrochemistry with the formation of an ion pair that controls the enantioselectivity of the reaction. First, the choice of the solvent is a crucial point. Typically, all electrochemical reactions are run in polar solvents due to their dielectric constant ε. On the other hand, ion-pair reactions are promoted by using non-polar solvents since they avoid competition with the phase transfer catalyst for ion-pair formation. For the same reason, the electrolyte could be an important issue for the development of this type of reaction: it is well known that most electrochemical reactions need the presence of an electrolyte; however, at the same time, the system features charged species which, inside the solution, could prevent the generation of the ion-pair specie.

Tan et al. published a paper [45] in 2023 where they ran a bromocyclisation reaction promoted by a phase transfer catalyst in excellent yields (up to 99%) and excellent enantioselectivity (up to 97% ee). Reaction conditions are reported in Scheme 13, where a double-phase system has been used with toluene and water as solvents. NaBr is both the electrolyte and the reagent dissolved in the water phase along with $NaHCO_3$, which prevent the Br_2 decomposition. (R)-**CPA1** has been used as chiral phosphoric acid and **PTC1** as a phase transfer catalyst to promote the bromocyclisation reaction, leading to product **30**.

The mechanism of the reaction is shown in Figure 11, where water reduction took place at the cathode surface and bromine oxidation at the anode one, releasing OH^- and Br_2, respectively. If $NaHCO_3$ is in solution, the OH^- interacts with the base to restore water; but if it is not, the two species react with each other to form BrO^-, which prevents the formation of the product. So, $NaHCO_3$ has the role of reacting with OH^-, thus inhibiting the harmful reaction. Thanks to the presence of the $NaHCO_3$, Br_2 can react with the phase transfer catalyst generating PTC-Br2, which can move from the aqueous solvent to the organic one, in which the formation of the ion-pair species **PTC-Br$_2$-CPA** occurs due to the

presence of the chiral phosphoric acid **CPA**$^-$. Finally, when the ion-pair reacts with the tryptamine derivative, the formation of **30** takes place with the release of PTC-CPA, which goes into the aqueous solution to restore the PTC phase transfer catalyst.



Scheme 13. Bromocyclisation reaction conditions.

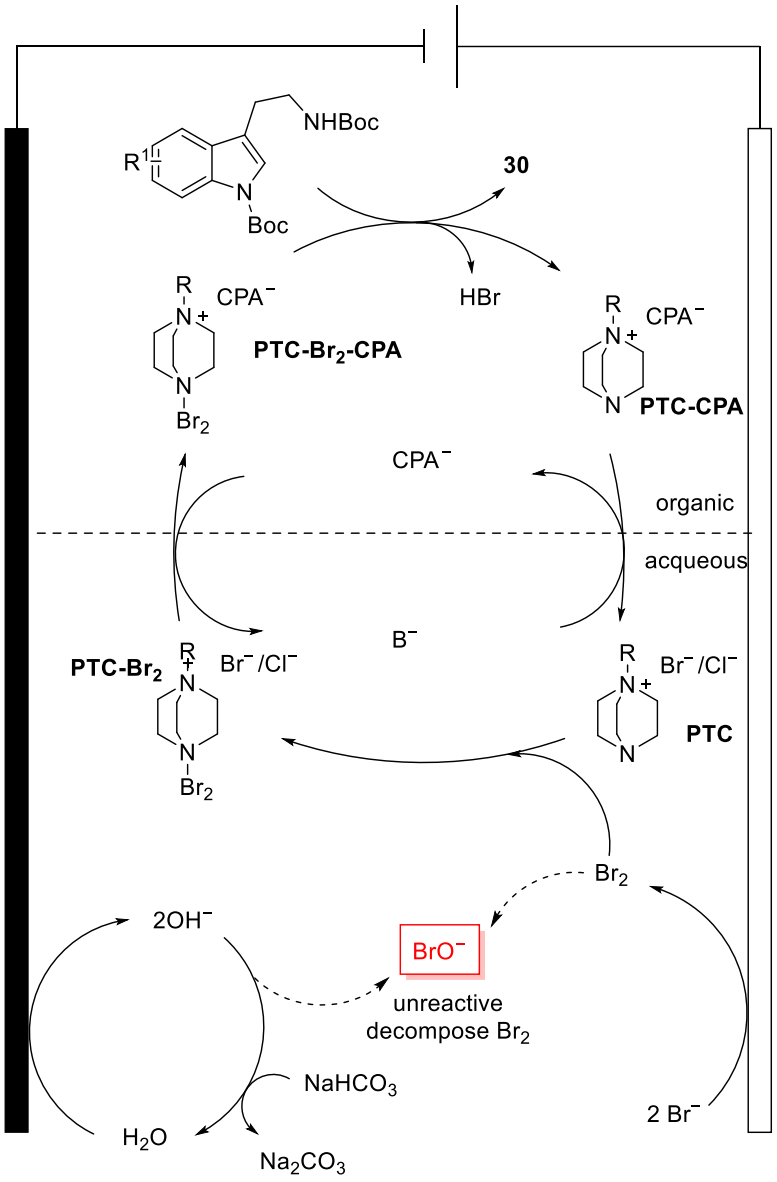


Figure 11. Bromocyclisation reaction mechanism.

4. Enantioselective Enzymatic Electrosynthesis

In the last two decades, the high catalytic activity and selectivity of enzymes have been exploited to develop new enantioselective catalytic reactions. For instance, the asymmetric formation of C-C and C-hetero bonds was accomplished by hydrolases in the presence of mild reaction conditions. Moreover, the increasing need to develop green and environmentally friendly processes has led to electroorganic synthesis playing an important role since it takes advantage of electrons as an energy source. In this context, enzymatic electrosynthesis merges enzymatic catalysis and the electrochemical technique to achieve the desired compounds. Two approaches have been used in the last years to develop asymmetric enzymatic electrosynthetic processes: the electrode surface functionalisation with enzymes through polymeric nanopores material; and the direct or indirect interaction between enzymes and electrodes. Wan and Co. [46] exploited the first approach, which investigated a two-stage electrochemical process to favour the interconversion, in a bidirectional way, between secondary alcohol enantiomers and ketone and how electrodes could be designed to afford the de-racemisation of enantiomers mixtures. To move on the problems, the electrode support was covered with indium tin oxide nanoparticles which form nanopores that can be deeply bound by ferredoxin NADP+ reductase (FNR), acting as a transducer, interconverting electricity and chemical flow and thus catalysing NADP+/NADPH interconversion. A second co-confining enzyme, an alcohol dehydrogenase (ADH), within the same nanopores, interacting with the cofactors, produces alcohol (reduction) or ketone(oxidation) depending on the potential applied (Figure 12A). In this way, changing the electrode potential makes it possible to control and measurement the rate at which a process occurs.

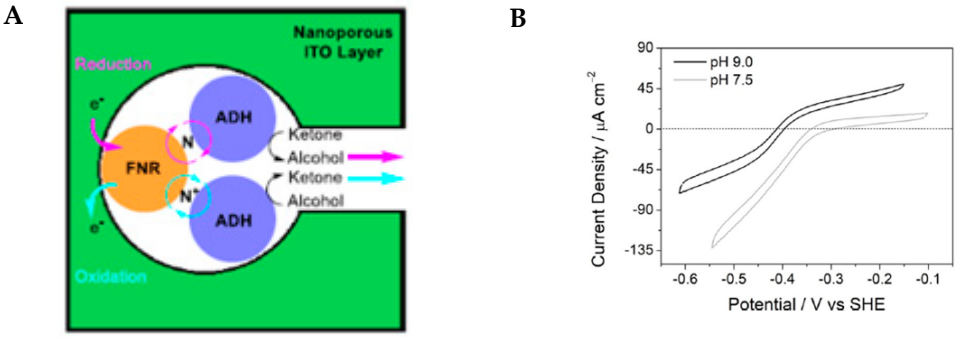
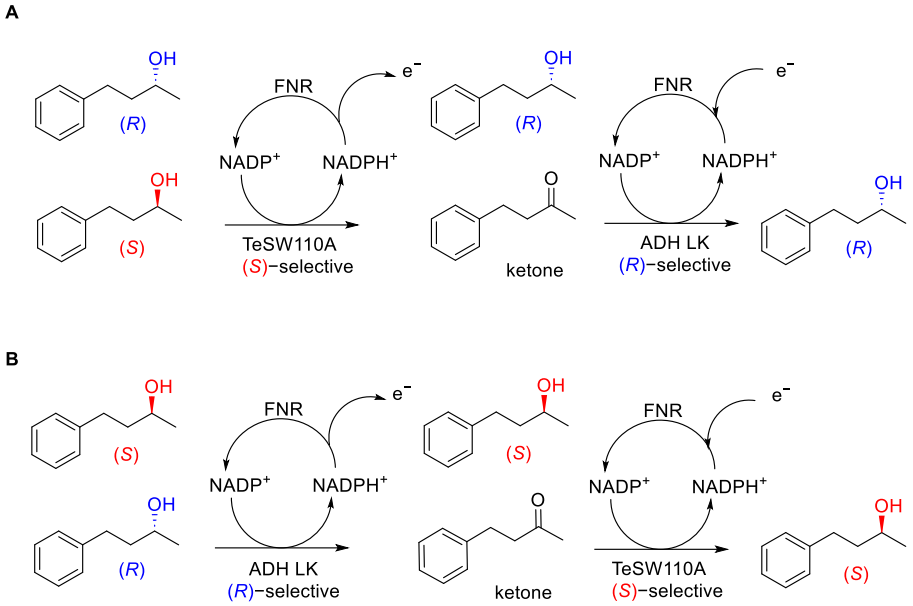


Figure 12. (**A**) Electrode nanopore in which FNR and ADH are confined. (**B**) cyclic voltammogram of ketone/alcohol interconversion.

Different tests have been conducted to individuate the optimal pH (Figure 12 right) and to select the ADH enzyme. The cyclic voltammogram (Figure 12B) displays that ketone/alcohol interconversion is bidirectional at pH = 9 (black trace), while at pH = 7.5 (light grey trail), the ketone reduction is strongly favoured. Moreover, two different alcohol dehydrogenases were chosen: an *(S)*-selective, TeSW110A variant (ADH *(S)*-selective) derived from *Thermoanaerobacter ethanolicus* 39E; and a sec-ADH *(R)*-selective from *Lactobacillus kefir* (here referred as ADH LK).

The objective was that each oxidative half cycles should convert a significant amount of *(R)*-4-phenyl-2-butanol [*(R)*-4P2B], as well as *(S)*-4-phenyl-2-butanol [*(S)*-4P2B], to the ketone. In contrast, each reductive half-cycle would almost entirely produce a single specific enantiomer. First, alcohol-ketone interconversion was tested at a single electrode using the *(S)*-selective TeSW110A variant. Unfortunately, this strategy demonstrated that although racemisation occurs, it is very slow and requires a moderate enzyme concentration, and de-racemisation was also challenging. So, they moved towards a two electrodes strategy where the two stages were separated and less reversible. In fact, the oxidation occurred at pH 9.0 using an electrode selective for the oxidation of the undesired enantiomer as the final product. At the same time, the re-reduction was performed at pH 7.5, using an electrode with very high enantioselectivity to yield the desired product (Scheme 14).



Scheme 14. (**A**) Electrochemical de-racemisation of (rac)-4P2B to produce (R)-4P2B. (**B**) Electrochemical de-racemisation of (rac)-4P2B to produce (S)-4P2B.

ADH *(R)*-selective and ADH *(S)*-selective were tested separately for the ketone-alcohol reduction half-cycle, affording the (R)-4-phenyl-2-butanol with 91.9% ee and the (S)-4-phenyl-2-butanol with 92.5% ee respectively. The reported alcohol dehydrogenases are included in the main enantioselective oxidoreductases (amino acid dehydrogenases, carbonyl reductases, etc.), commonly employed in asymmetric synthesis and resolution. However, the real applications are limited by two issues: the high consumption of reduced cofactor; and the low solubility of organic compounds in the aqueous phase. Electrochemistry provides a powerful and green tool to regenerate the cofactor without adding a second reductant since the electrode can easily furnish electrodes necessary for the regeneration of all cofactors (NAD/NADH, NADP/NADPH etc.). Dong and Co. [47], in the last year, developed a new and efficient biphasic bioelectrocatalytic system (Figure 13), which contains a diaphorase (DH) from *Geobacillus stearothermophilus*, an *(S)*-specific alcohol dehydrogenase from *Lactobacillus kefir* (Lk-AdhS) and a mutant halohydrin dehalogenase (HHDH) from *Agrobacterium radiobacter* to prepare chiral β-hydroxy nitriles.

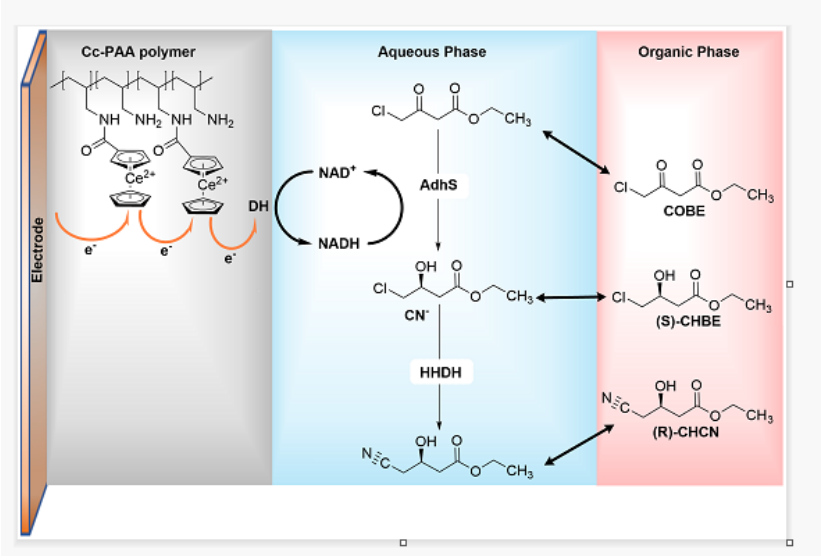


Figure 13. Preparation of (R)-CHCN through a biphasic bioelectrocatalytic approach.

The diaphorase (DH) regenerates the NADH to support the reduction of ethyl-4-chloroacetoacetate, catalysed by AdhS, which determines the enantioselectivity of the process. In the presented system, DH is immobilised by a low-potential redox polymer cobaltocene-modified poly(allylamine) on the electrode surface. Moreover, the organic solvent was added to the phosphate buffer, thus forming a biphasic bioelectrocatalytic system. The organic phase improves the solubility of organic compounds in the reaction mixture and acts as a "substrate reservoir and product sink" [47], which is able to furnish COBE to the aqueous phase and extract the product (CHCN) from the organic phase. Different solvents were tested; hexane, ethyl acetate and DCM, along with Tris HCl buffer, decreased the activity of AdhS and HHDH, while the MTBE improved the activity of AdhS and HHDH slightly. Moreover, since the specific activity of AdhS is lower than the HHDH one, the pH value was set at pH = 8 to (optimum pH of AdhS) to maximise Adhs activity. CHBE and chiral β-hydroxy nitrile production were evaluated in biphasic and single-phase systems. In the first case, as shown in Figure 14A, the single-phase system seriously affects the reaction outcome. At 30 mM COBE concentration, the conversion achieved in the biphasic system was 100%. Indeed, after 8 h, the concentration of the produced CHBE was 29 ± 3 mM compared with 8 mM after 6 h of the single-phase one. The low conversion of COBE in the single-phase system was due to the spontaneous hydrolysis of COBE in basic aqueous conditions and to the dissolution of Cc-PAA polymer in DMSO, used in the synthesis of Cc-PAA.

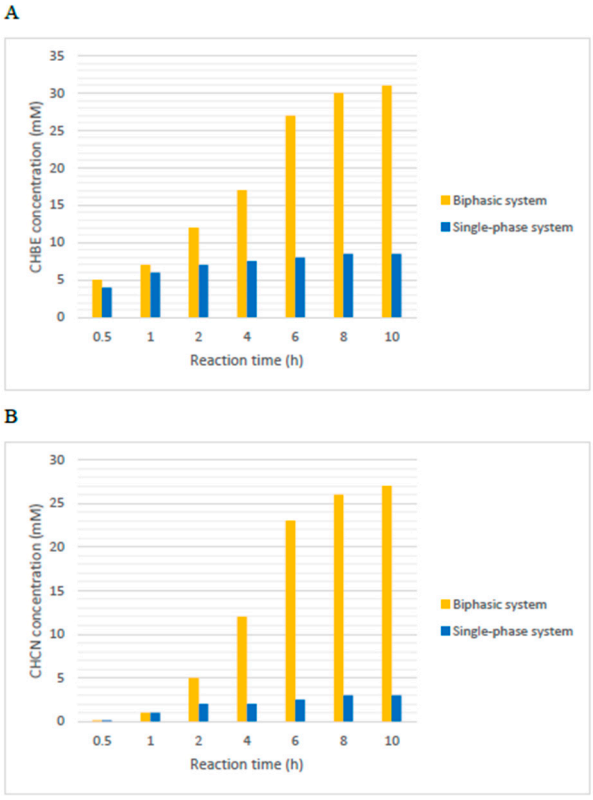


Figure 14. Concentration of CHBE (**A**) and CHCN (**B**), respectively, in biphasic and single-phase systems [47].

The bioelectrosynthetic production of β-hydroxy nitriles was also improved by using biphasic systems compared with single-phase ones (Figure 14B). In fact, for the biphasic systems, the highest concentration of CHCN achieved after 10 h (25 ± 2 mM) was 8.8 times higher than that in the single-phase systems (2.9 mM). The MTBE addition seriously disfavoured the COBE hydrolysis and increased the lifetime of the DH/CC-PA electrode. Moreover, the presence of biphasic systems, along with modified HHDH, re-

duces the inhibition effect of COBE on HHDH activity, which could also be afforded by separating the reaction catalysed by AdhS and HHDH. However, the desired *(R)*-3-hydroxy-3-phenylpropanenitrile was obtained with 96.8% ee, while the *(S)*-3-hydroxy-3-phenylpropanenitrile with 94.6%.

As previously reported, enzymatic electrosynthesis could also be run without direct functionalisation of the electrode surface with the enzyme through a polymeric chain. In fact, an enzymatic electrosynthetic process can be carried out by direct (Figure 15A) or indirect (Figure 15B) electron transfer between enzymes and electrodes [48].

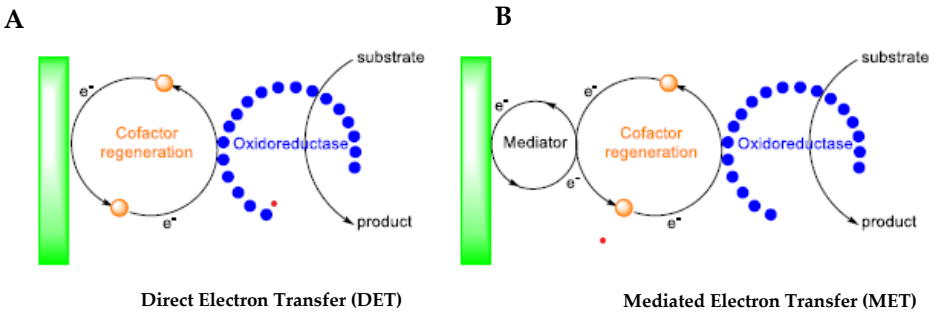
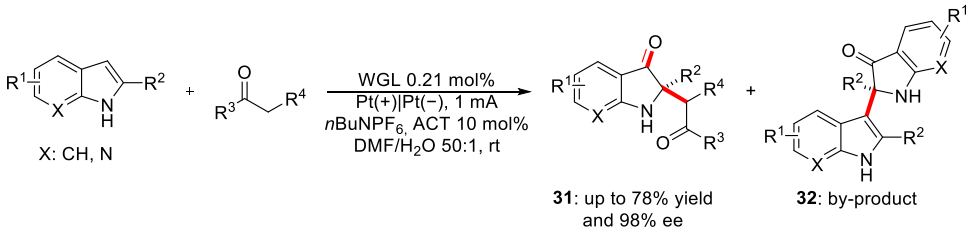


Figure 15. Direct (**A**) and mediated (**B**) interaction between oxidoreductase and electrode [29].

Generally, only oxidoreductases can catalyse the electron transfer between molecules and electrodes. In most cases, oxidoreductases are tightly connected with a cofactor, the regenerations of which could require the presence of a mediator.

Although enzymatic electrosynthesis with oxidoreductases displays different advantages, it is very limited to this type of enzymes and to reactions that can catalyse. Moreover, the cofactor regeneration often remains inefficient. To expand the scope of enzymatic electrosynthesis, in 2022, Long et al. [49] decided to investigate hydrolase-catalysed reactions in electrochemical systems; in particular, they focused their attention on the oxidative cross-coupling of 2-substituted indoles and ketones in the presence of wheat germ lipase (WGL), which is a readily available hydrolase (Scheme 15).



Scheme 15. Cross-coupling between 2-substituted indoles and ketones under enzymatic electrosynthetic conditions.

Optimisation studies of the reaction conditions led the authors to use the 4-acetamido 2,2,6,6-tetramethyl-1-piperidineoxy (ACT) as a redox mediator to facilitate the oxidation process under milder conditions. An appropriate amount of water was added to inhibit the generation of the inactive "locked" formation, which occurs when the polar and charged enzyme's functional groups interact with the organic phase. Thus, the enzymes hold the right flexibility to perform their activity. The importance of the enzyme in the electrochemical reaction was demonstrated when electricity was replaced by an oxidant (DDQ). This led to the predominant formation of the by-product **32**, reducing the enantiomeric excess of the product. Moreover, differently substituted indoles in the presence of various ketones were successfully tested, affording the desired compounds **31** in up to 78% yield and 92:8 ee%. To understand the effect of the electrochemical conditions on the catalytic activity of WGL, the reaction using 2-aryl-3H-indol-3-ones catalysed by WLG was investigated

under non-electrochemical conditions. In most cases, the yields and the enantioselectivities were nearly the same as under electrochemical conditions.

5. Conclusions

In conclusion, these recent works demonstrated the high selectivity and performance that can be achieved by matching enzyme activity with electrochemistry properties. It is possible to expand this approach to different types of enzymes (not only oxidoreductases), enabling the synthesis of complex chiral molecules without using transition metals, ligands or oxidant agents. The possibility of exploiting chiral organocatalysts and chiral organometallic systems in combination with electrochemistry to achieve enantioselective transformations has also been successfully demonstrated.

However, the use of asymmetric catalysts to realise enantioselective, efficient and organic reactions is still largely underdeveloped, and the application of more classes of chiral catalysts and enzymes is expected; catalytic electrochemical synthesis offers the possibility to develop green processes due to the use of electrons as reagents instead of traditional reagents that would generate chemical waste.

Regarding the future, it is easy to predict a major entanglement between flow chemistry and electrochemistry. Continuous flow systems will further increase the attractiveness of electrosynthesis [50,51] as a powerful tool for developing more sustainable chemical processes.

Author Contributions: Supervision: M.B. and F.M; Writing: M.B., F.M., S.R. and S.A. All authors have read and agreed to the published version of the manuscript.

Funding: M.B. and F.M. thank MUSA—Multilayered Urban Sustainability Action—project, funded by the European Union—NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) Mission 4 Component 2 Investment Line 1.5: Strenghtening of research structures and creation of R&D "innovation ecosystems", set up of "territorial leaders in R&D". S.A. thanks Chimica Bussi for cofinancing a PhD fellowship.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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