Review Article

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Organic electrochemistry: Synthesis and functionalization of β-lactams in the twenty-first century

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Abstract: Organic electrochemistry is a technique that allows for the heterogeneous redox reactions avoiding both the use of stoichiometric amounts of redox reagents and the resulting formation of stoichiometric by-products. In fact, the redox reagent in these reactions is the electron, which is naturally eco-friendly and produces no side compounds. It is therefore quite obvious that electrochemistry can be classified as a "green" technology. The use of this methodology in the synthesis of β-lactams is not a novelty, but the growing interest in this class of biologically active compounds, due to the discovery of new fields of application (after a moment of decrease in interest due to antibiotic resistance) has been a stimulus for the search for more efficient electrochemical ways to synthesize and transform β-lactams. Thus, this review deals with the twenty-first-century applications of electroorganic technique to the chemistry of β-lactams, by analyzing first the syntheses classified by the type of reactions (cyclization, cycloaddition, etc.) and then by manipulating the β-lactam structure, using it as a synthon. Lastly, the importance of this technique is demonstrated by a study of a pilot plant scale reduction of a cephalosporanic acid derivative to a commercially important antibiotic.

Keywords: cathodic reduction, anodic oxidation, azetidin-2-ones, electroorganic synthesis, electrogenerated base

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1 Introduction

β-Lactams (azetidin-2-ones; Figure 1) are four-membered heterocyclic compounds containing an amide moiety. This class of molecules is so famous in medicinal chemistry that there is no need to describe their importance in the antibiotic field. In fact, since the discovery of penicillin in 1928 by Fleming, β-lactam antibiotics have been extensively used as antibacterial agents, their use being less frequent in recent years due to the onset of antibiotic resistance [1,2].

Nonetheless, the importance of β-lactams has not decreased over time, as in recent years other important pharmacological activities (anticancer, anticholesterolemic, antidiabetic, etc.) have been evidenced [3]. Just think of the extensive use of ezetimibe (Figure 2) as anticholesterolemic in combination with statins. The use of ezetimibe is so widespread that this drug is in the Top 300 Drugs of 2020 in the United States [4].

Moreover, β-lactams are important and highly functionalized starting materials in organic synthesis so much that their use earned the name of "β-Lactam Synthon Method" from Ojima in 1995 [5]. In particular, enantiopure β-lactams were used as the starting materials in the synthesis of dipeptides, oligopeptides, taxoids, and similar molecules. It is thus evident that although β-lactam formation has been reported in a myriad of different synthetic routes [6], there is still room for new, efficient, and "green" methodologies.

In this regard, electrochemistry (after an initial period of distrust) is gaining increasing popularity as a "green" way to carry out heterogeneous redox reactions, the electron being a natural reagent without by-products [7–16].

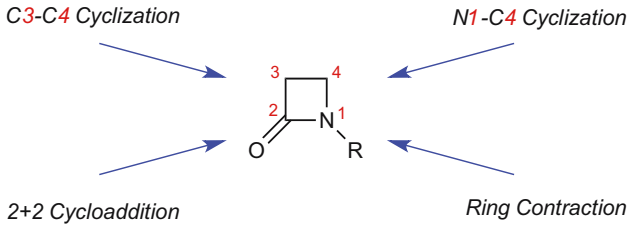


Figure 1: Electrochemically induced synthesis of β-lactams. Explored routes.

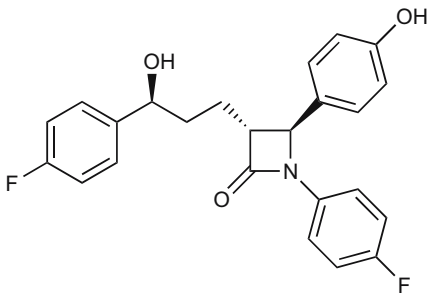


Figure 2: Ezetimibe structure.

As a matter of fact, electrochemistry has been used in the chemistry of β-lactams since 1974 [17], but only in recent times has its validity has been recognized by organic chemists. The advent of modern and cheap instrumentation, the use of "greener" conditions (non-volatile and recyclable ionic liquids [ILs] [18–20], flow cells [21–23], etc.), and the awareness of the advantages inherent in electrochemistry render this technique more useful for organic chemists. Moreover, one of the main reasons to oppose the use of electrochemistry by organic chemists is the use of massive amounts of supporting electrolytes which, besides their cost, hinder the purification of products. The advent of flow cells, which need very low supporting electrolyte amounts, and the possibility of using recyclable and non-volatile ILs as both solvents and supporting electrolytes (being constituted only by ions), have mitigated the mistrust of organic chemists. In addition, electrochemistry allows careful modulation of the electrons' reactivity by choosing the working potential.

It is thus evident that electrochemistry can still give a valid contribution to the chemistry of β-lactams, besides the obvious importance of the electroactivity of β-lactams in their electrochemical detection in biological fluids, food, waste waters, etc., [24,25].

Since the electrochemistry of β-lactams has been previously reviewed in 2002 [26], for this reason we will deal with electrochemically induced synthesis and functionalization of β-lactams during the twenty-first century.

2 Electrochemically induced synthesis of β-lactams

The four-membered ring of β-lactams can be obtained using electrochemistry following three different pathways (Figure 1), namely, intramolecular cyclization of a linear starting material, usually a bromoamide (N1–C4 and C3–C4 cyclizations, with the formation of 1-ring bond), reaction between a carbonyl derivative and an amine derivative (2+2 cycloaddition, with the formation of 2-ring bonds), and rearrangement of a five-membered ring (ring contraction, with ring opening and subsequent closure).

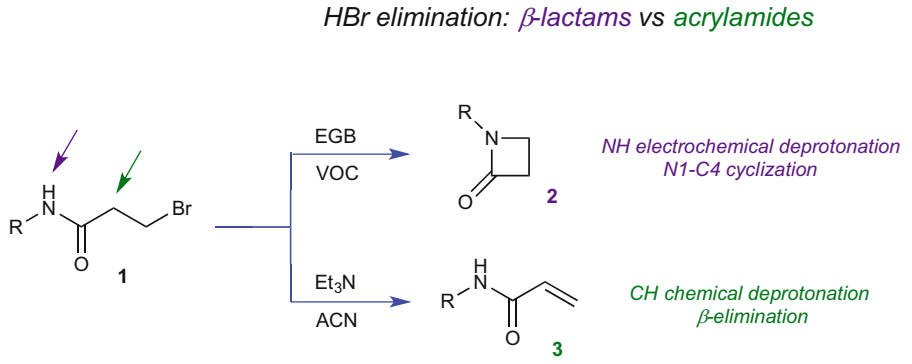
The different routes will be separately considered in the following sections.

2.1 N1–C4 cyclization

Linear amides having a leaving group in β-position (**1**, Scheme 1) can be deprotonated at the nitrogen atom, generating an anion which, under suitable conditions, can give internal nucleophilic displacement to the corresponding β-lactams (**2**, Scheme 1). Such linear amides possess a second acidic position, i.e., the CH_2 in alpha position relative to the carbonyl group. If the deprotonation occurs in this latter position, the β-elimination produces the corresponding acrylamides (**3**, Scheme 1).

Consequently, the product of the formal HBr elimination from bromoamide **1** depends on the deprotonation site. The interesting aspect is that it is possible to decide where to deprotonate simply by choosing the experimental conditions. In particular, when this deprotonation is carried out using triethylamine in acetonitrile, the acrylamide is selectively obtained (Scheme 1, [27]). While if electrochemical conditions are chosen, the outcome is the selective formation of the corresponding β-lactam [28]. These results demonstrate that the competition between the two sites of deprotonation is strongly influenced by the chemical environment of the reaction and the nature of the base.

In regards to the electrochemical reaction, deprotonation is carried out using an "electrogenerated base" (EGB, [29]) which is a species obtained by electrochemical means and which behaves mainly as a base. In this case, the EGB is obtained by cathodic reduction of a solution of a polar solvent (volatile organic solvent, VOC) containing a tetraalkylammonium salt as the supporting electrolyte. Although the mechanism of this electrochemical process is still debated [15], its outcome



	2	3
R = Ph	98%	95%
R = 2-Me-Ph	98%	91%
R = 3-Me-Ph	95%	95%
R = 4-Me-Ph	98%	95%
R = 2,4,6-Me_3-Ph	57%	83%
R = 2-Cl-Ph	54%	95%
R = 3-Cl-Ph	86%	95%
R = 4-Cl-Ph	59%	95%
R = 4-Br-Ph	95%	95%
R = 4-I-Ph	90%	95%
R = 4-OMe-Ph	98%	95%
R = Ph-CH_2	81%	*
R = *c*-C_5H_9	74%	*

*: not reported

EGB: electrogenerated base, *i.e.* conjugate base of solvent (VOC)
VOC: ACN, DMF, EtCN, DMSO

Scheme 1: Electrochemical and chemical deprotonation of linear β-bromoamides: competition between cyclization and β-elimination in acetonitrile (ACN).

is clear: the conjugate base of the solvent is obtained in a very polar environment. Moreover, the counterion of this quite strong base is a tetraalkylammonium cation, not coordinated and quite sterically hindered, which renders the anion a "naked", highly reactive one.

In this way, very high yields of β-lactams are obtained (Scheme 1).

When substituted amides are considered, the reaction is still more interesting, as in the case of the threonine derivative **4** (Scheme 2) for which, along with high yields (up to 86%), a complete diastereoselection is observed, meaning the *trans* β-lactam **5** is being the only form produced.

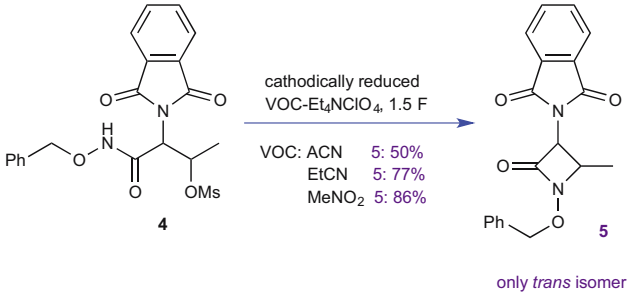
2.2 C3–C4 cyclization

The cyclization of a linear bromoamide can also be obtained by deprotonation of a carbon atom. Of course, in this case, suitable acidity must be obtained relying on an electron withdrawing group, such as the ethoxycarbonyl one (**6**, Scheme 3) [30,31]. Moreover, when the bromoamide is substituted in the alpha position, the formation of two isomers (*cis* and *trans*) is possible.

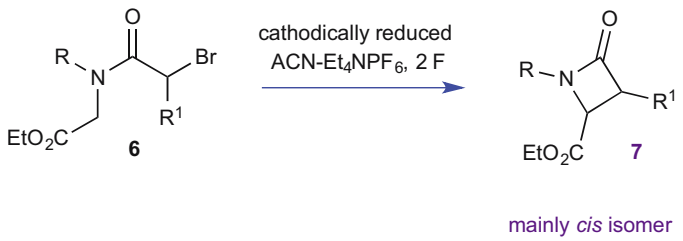
Also, in this case, the electrochemical reduction of a solution containing acetonitrile and a tetraalkylammonium salt (as supporting electrolyte) yields the formation of an anion of the solvent, the cyanomethyl anion (whose counterion is the tetraalkylammonium ion), a very strong base (pK_a for ACN: 33 in ACN). This EGB is able to deprotonate the carbon atom in the alpha position to the nitrogen and induce the four-membered ring formation (Scheme 3).

It should be noted that in this case, as in the case of N1–C4 cyclization, the electrogeneration of the base must be carried out in the absence of the bromoamide, as the latter is an electroactive species that is more easily reducible than the solvent-supporting electrolyte system.

As reported in Scheme 3, β-lactams **7** demonstrated good to high yield (in accordance with the acidity of the deprotonation site and with the steric hindrance), but the real peculiarity of this synthesis is the stereoselectivity. In



Scheme 2: Electrochemical deprotonation of threonine derivative **4**: diastereoselective synthesis of *trans* β-lactam **5**.



R	R^1	7	*cis/trans*
$PhCH_2$	*i*-Pr	75%	87/13
$PhCH_2$	Me	84%	91/9
$PhCH_2$	Et	90%	90/10
$PhCH_2$	*n*-Bu	85%	93/7
$PhCH_2$	*c*-C_5H_9	57%	90/10
$PhCH_2$	*c*-C_6H_{11}	63%	91/9
p-OMe-Ph	Me	33%	97/3
p-NO_2-Ph	Me	55%	74/26

Scheme 3: Electrochemical deprotonation of bromoamides **6** by cyanomethyl anion: diastereoselective synthesis of *cis* β-lactams **7**.

fact, it is opposite to the one obtained by N1–C4 cyclization (Scheme 2). In this case, the selective formation of the *cis* isomers is achieved, with very good diastereomeric ratio (only the *trans* isomer was obtained by N1–C4 cyclization; Scheme 2).

When a chiral substituent is present in the starting bromoamide, either on the nitrogen atom or in an outermost position, the new chiral center formed in the cyclization process can be influenced by the chiral substituent (Figure 3) [32]. In this case, the electrogenerated

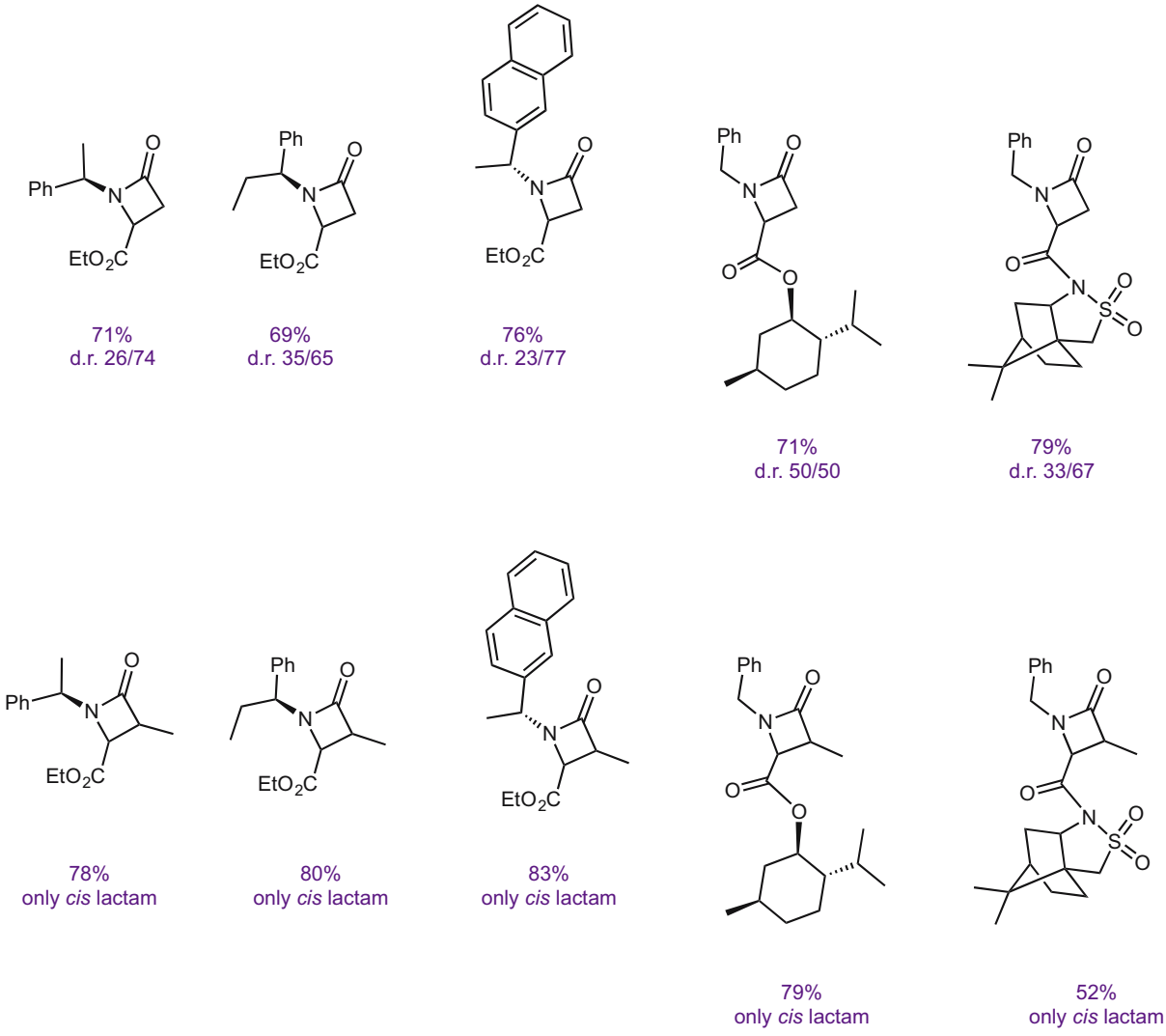
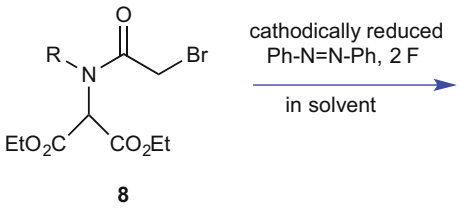


Figure 3: Electrochemical deprotonation of chiral bromoamides by cyanomethyl anion: diastereoselective synthesis of *cis* β-lactams.



Solvent	9
ACN	68%
EtCN	96%
DMF	99%
DMSO	78%
BMIm-BF_4	99%
BMIm-PF_6	99%

Scheme 4: Electrochemical deprotonation of bromoamide **8** by EGB: diastereoselective synthesis of β-lactams **9**. Effect of the solvent.

cyanomethyl anion was used as an efficient base and the stereochemical outcome of the reaction depended on the distance between the chiral auxiliary and the cyclization site. In almost all cases, a good diastereoselection was obtained and, as in the previous case, only *cis* isomers were isolated.

In order to enhance the yields of β-lactams by linear bromoamides cyclization, an EGB different from the conjugate base of the solvent can be used. In this case a probase (PB) must be added to the solution before the cathodic reduction. A PB is a species that can be converted into an EGB by cathodic reduction. When azobenzene is the PB, the outcome of the reaction is strongly influenced by the solvent (Scheme 4) [33]. Considering the classical solvents (VOCs), *N,N*-dimethylformamide (DMF) yielded the best results, but quantitative yields could also be obtained using imidazolium ILs. The advantage of using ILs resides in the possibility of reusing them in subsequent runs (their very low vapour pressure along with the immiscibility in diethyl ether allows for their easy recovery after product extraction). Both 1-butyl-3-methylimidazolium tetrafluoroborate (BMIm-BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate (BMIm-PF_6), in the absence of other supporting electrolytes, allowed the β-lactam **9** to be obtained in 99% yield.

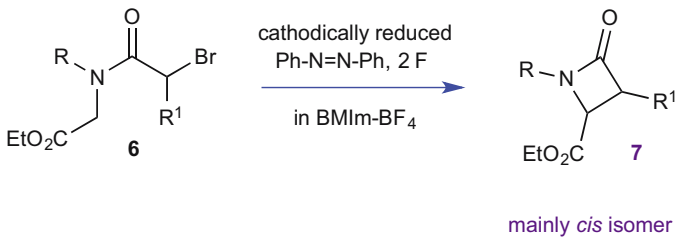
When the latter experimental conditions were used with substituted bromoamides **6**, *cis* β-lactams **7** were obtained with good diastereoselectivity and yields, which depended mainly on the nitrogen substituent (Scheme 5).

It should be noted that the $BMIm^+$ cation itself is electroactive and can be reduced at the cathode, yielding the corresponding *N*-heterocyclic carbene (NHC) after reductive scission of the C–H bond between two nitrogen atoms (Scheme 6). This NHC can behave as a base, deprotonating the bromoamide and inducing the ring formation [34], or as a nucleophile, acting as an organocatalyst. NHCs and, more in general, organocatalysts have proved to be valid and efficient tools to perform organic synthesis in an environmentally friendly way [35–38].

This electrochemical methodology allows for a simpler reaction, as no PB is necessary besides the IL solvent, and no by-products must be removed from the catholyte before reusing the IL. In fact, when the NHC acts as a base, it again forms the starting IL cation (Scheme 6). The yields of β-lactams are also good when the internal displacement occurs at a disubstituted C–Br site, irrespective of the nitrogen substituent.

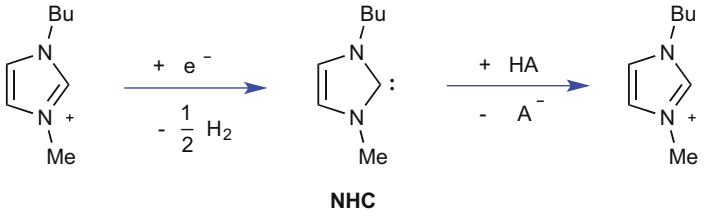
2.3 2+2 cycloaddition

The most famous way to synthesize β-lactams is the Staudinger reaction [39] which is formally a [2+2] cycloaddition between a ketene and an imine (Scheme 7). The ketene, usually not stable, is very often obtained by the *in situ* dehydrohalogenation of a suitable acyl halide. Despite being reported for the first time in 1907, this

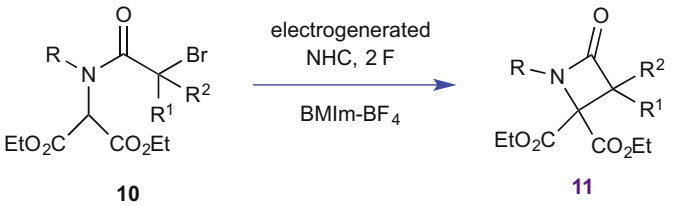


R	R^1	7	*cis/trans*
$PhCH_2$	Et	70%	90/10
$PhCH_2$	*n*-Bu	78%	*cis*
$PhCH_2$	*c*-C_6H_{11}	56%	73/27
p-OMe-Ph	Me	32%	*cis*
p-OMe-Ph	Et	43%	81/19

Scheme 5: Electrochemical deprotonation of bromoamides **6** by EGB in ionic liquid: diastereoselective synthesis of *cis* β-lactams **7**.



NHC



10 11

R	R^1	R^2	11
p-OMe-Ph	H	H	82%
p-OMe-Ph	H	Me	91%
p-OMe-Ph	H	Et	81%
p-OMe-Ph	Me	Me	59%
$PhCH_2$	H	H	87%
$PhCH_2$	H	Me	81%
$PhCH_2$	Me	Me	72%
Ph	H	H	92%
Ph	H	Me	89%
c-C_5H_9	H	H	87%
c-C_5H_9	H	Me	84%

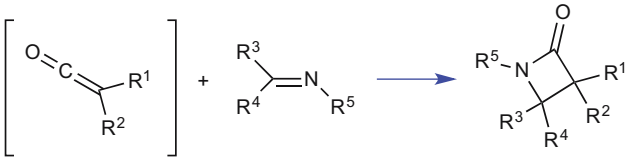
Scheme 6: Electrochemical deprotonation of bromoamides **10** by NHC in ionic liquid: synthesis of β-lactams **11**.

reaction's mechanism is still debated [40]. Moreover, the stereochemical outcome is not univocal.

Also, in this case, electrochemistry can give a contribution, both in generating the base necessary for the dehydrohalogenation to yield the ketene and in allowing the use of more friendly reaction conditions (solid electrodes, ILs as solvent-supporting electrolyte system, etc.).

In particular, when an imidazolium IL is used as a solvent, the generation of the corresponding NHC at the cathode (Scheme 6) yields a quite strong base in solution. This base can deprotonate an acyl chloride, starting the Staudinger reaction with an imine (Scheme 8) [41].

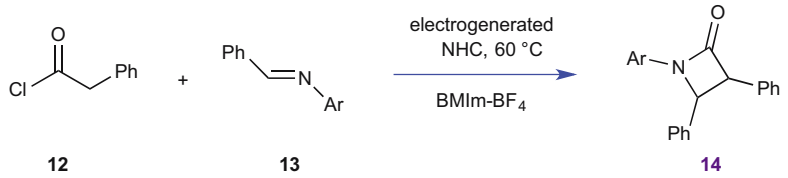
As previously stated, due to the uncertainty of the mechanism, the stereochemical outcome of the reaction is not taken for granted. In fact, either a concerted or a two-step mechanism is possible, with different relative configuration in the final β-lactam. In the case of electrosynthesis of IL BMIm-BF_4, *cis* β-lactams were selectively obtained (Scheme 8); and depending on the substituent of the nitrogen atom, the addition of an external base (triethylamine) to a variable amount of NHC (F/mol, Scheme 8) was necessary to obtain good yields in products. In this reaction, electrogenerated NHC behaved not only as a base but also as a nucleophile, activating the imine (Scheme 9), and excluding a concerted mechanism [42].



Scheme 7: The Staudinger reaction to β-lactams.

2.4 Ring contraction

The last electrochemical contribution to the synthesis of β-lactams is an anodically induced ring contraction. Onomura and coworkers [43] studied the iodine-induced ring opening, the subsequent closure of substituted pyrrolidin-2-ones, and five-membered cyclic forms of linear β-oxo-amides. The chemical reaction was carried out with a stoichiometric amount of iodine in the presence of a base. In the electrochemical technique, Onomura and coworkers envisaged the possibility of generating *in situ* the active "I^+" by anodic oxidation of iodide (from the supporting electrolyte) and simultaneously indirectly generating an EGB contemporarily at the cathode. When the reaction in the presence of chiral pyrrolidones **15** was carried out in acetonitrile at 85°C, the corresponding β-lactams showed good to high yields (Scheme 10).



12 13 14

Ar	Et_3N	F/mol	14	*cis/trans*
p-OMe-Ph	-	0.30	36%	10/90
p-OMe-Ph	-	0.50	66%	9/91
p-OMe-Ph	-	1.00	38%	16/84
p-OMe-Ph	-	1.70	35%	11/89
Ph	-	0.50	16%	*trans*
Ph	0.3 eq.	0.50	42%	14/86
Ph	1.0 eq.	0.50	22%	*trans*
Ph	-	0.15	-	
Ph	0.5 eq.	0.15	55%	11/89
Ph	1.0 eq.	0.15	64%	11/89

Scheme 8: Electrochemical synthesis of β-lactams **14** by NHC-induced cycloaddition of **12** and **13**.

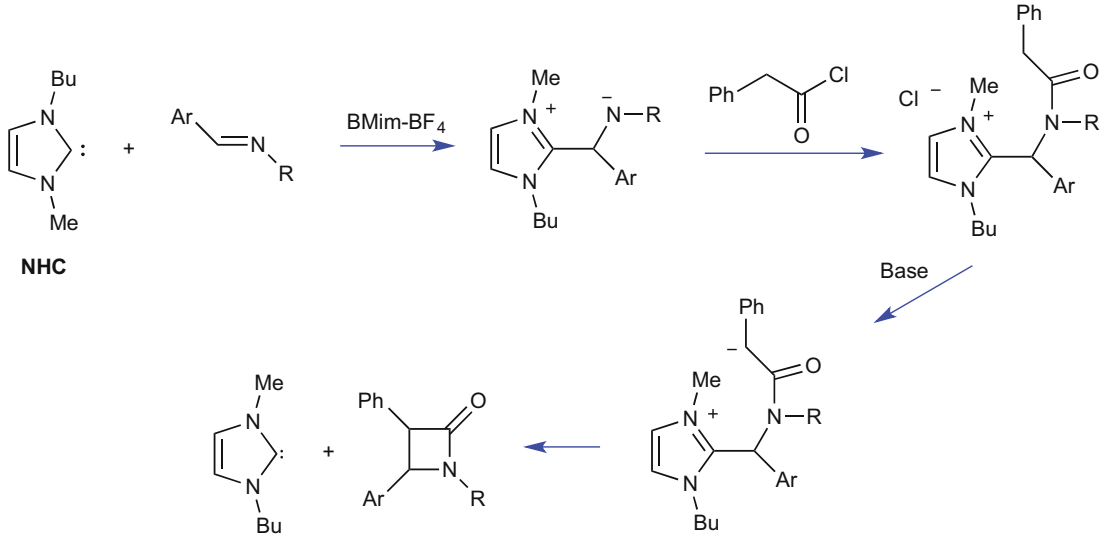
The most important feature of this electrochemical synthesis is the very good production of diastereoselection (Scheme 10). In fact, starting from a pyrrolidone with *R* chiral benzyl substituent on the nitrogen atom, an excess of the diastereoisomer **16** with an *S* configuration at the C3 ring position was obtained.

This particular stereoselectivity is probably due to a thermodynamically controlled equilibration of the produced β-lactam in the presence of EGB. The hypothesized mechanism is reported in Scheme 11. The electroactive species is the iodide anion, which is oxidized at the anode, yielding a "I^+" species that is able to react with the open form of **15**, yielding the corresponding α-iodide. The deprotonation by a base and intramolecular iodide displacement yields the corresponding β-lactam, most probably in a equimolar *R*- and *S*- forms at C3.

Being the most thermodynamically stable isomer, equilibration in the presence of the base yields an excess of the *S*-diastereoisomer, which could be isolated in pure form after crystallization. In this case, an evident advantage of the electrochemical methodology is the possibility of handling a catalytic amount of iodide anion instead of a stoichiometric amount of iodine.

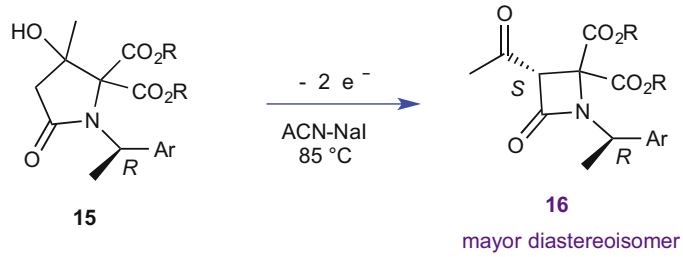
3 Electrochemically induced functionalization of β-lactams

Electrochemistry can also give a noteworthy contribution to the functionalization of the β-lactam ring. In particular, the introduction of a halogen atom either on a



NHC

Scheme 9: Possible mechanism for the NHC-induced electrochemical synthesis of β-lactams in ionic liquid.



Ar	R	16	dr (%)
Ph	Et	56%	68
Ph	*t*-Bu	94%	80
p-OMe-Ph	*t*-Bu	89%	74

Scheme 10: Electrochemical synthesis of β-lactams **16** by anodically induced ring contraction.

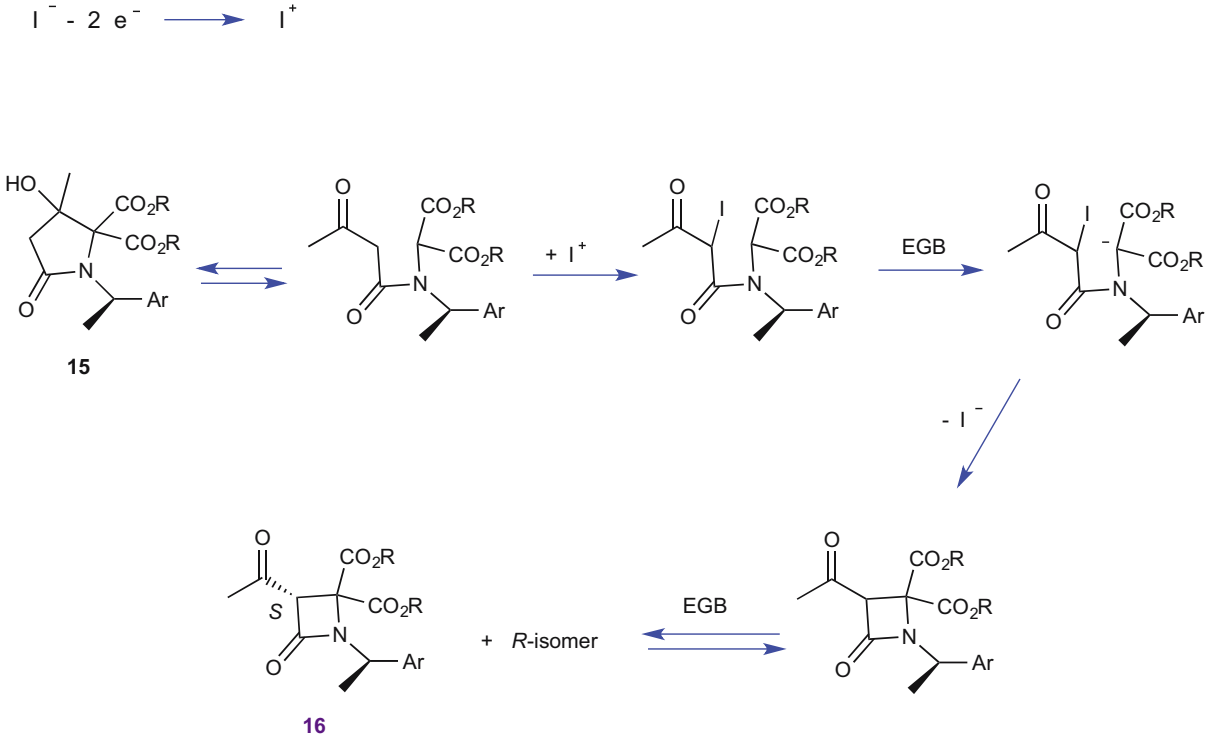
C-atom or on the N-atom, or the anodic-induced intramolecular cyclization to a cephalosporinic derivative is possible. Moreover, the possibility of electrochemically transforming a cephalosporanic acid into a valuable intermediate has been exploited from a pilot plant point of view (see below).

Here the electrochemically induced transformations of the β-lactam ring are divided based on the reaction type.

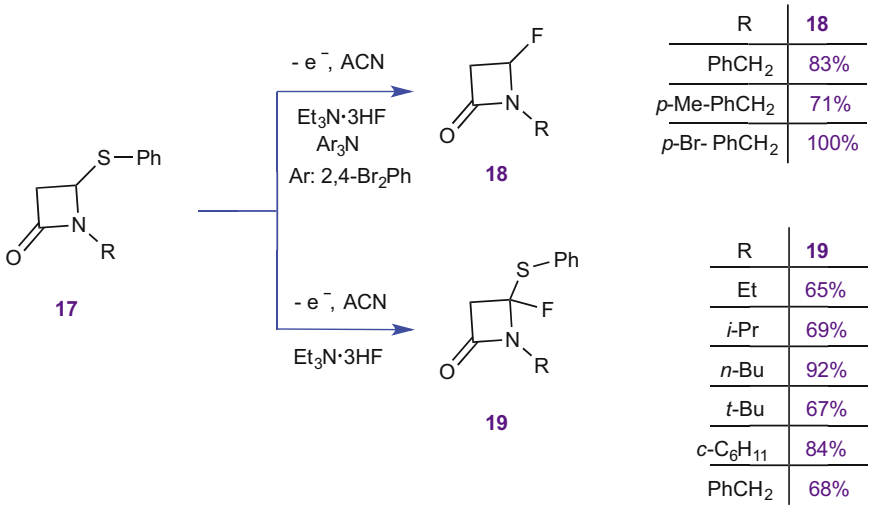
3.1 Anodic ring fluorination

The possibility of inserting a fluorine atom into the β-lactam ring by electrochemical means was exploited by Fuchigami and coworkers, starting from a ring containing a phenyl sulfide substituent which is the oxidable species (compound **17**; Scheme 12) [44,45]. This oxidation can directly be obtained at the electrode or using an electrochemical mediator (in this case a triarylamine) [46]. The presence of fluoride ions in the reaction mixture allowed for the insertion of this atom in the ring structure.

The really interesting feature of this electrochemical fluorination reaction is the different outcomes in the presence and absence of the triarylamine mediator, as reported in Scheme 12. In the presence of the electrochemical mediator, a substitution of the phenyl sulfide group with the fluorine atom was obtained (compound **18**). While in the absence of the mediator, the retention of



Scheme 11: Anodically induced synthesis of β-lactams **16**. Proposed possible mechanism.



R	18
$PhCH_2$	83%
p-Me-$PhCH_2$	71%
p-Br- $PhCH_2$	100%

R	19
Et	65%
i-Pr	69%
n-Bu	92%
t-Bu	67%
c-C_6H_{11}	84%
$PhCH_2$	68%

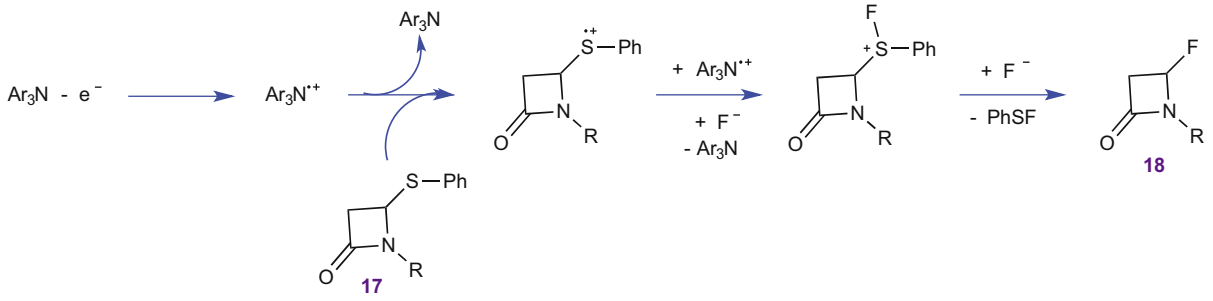
Scheme 12: Anodic fluorination of β-lactams **17**. Effect of additives.

the phenyl sulfide group was evidenced, with the insertion of the fluorine atom in the place of the hydrogen atom (compound **19**).

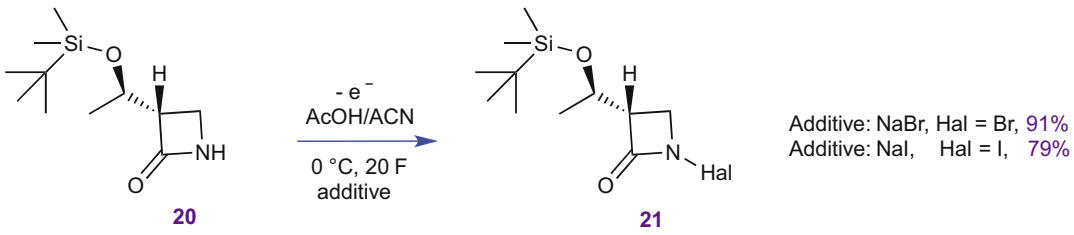
A hypothesized mechanism is reported by the authors in the case of indirect electrooxidation of compound **17** (Scheme 13). In this case, the electroactive species is the arylamine which, once oxidized, in turn oxidizes the sulfur atom. In the presence of an excess of fluoride ions, the elimination of phenyl hypofluorothioite (PhSF) and the insertion of a fluorine atom on the ring were achieved.

3.2 Anodic N-halogenation

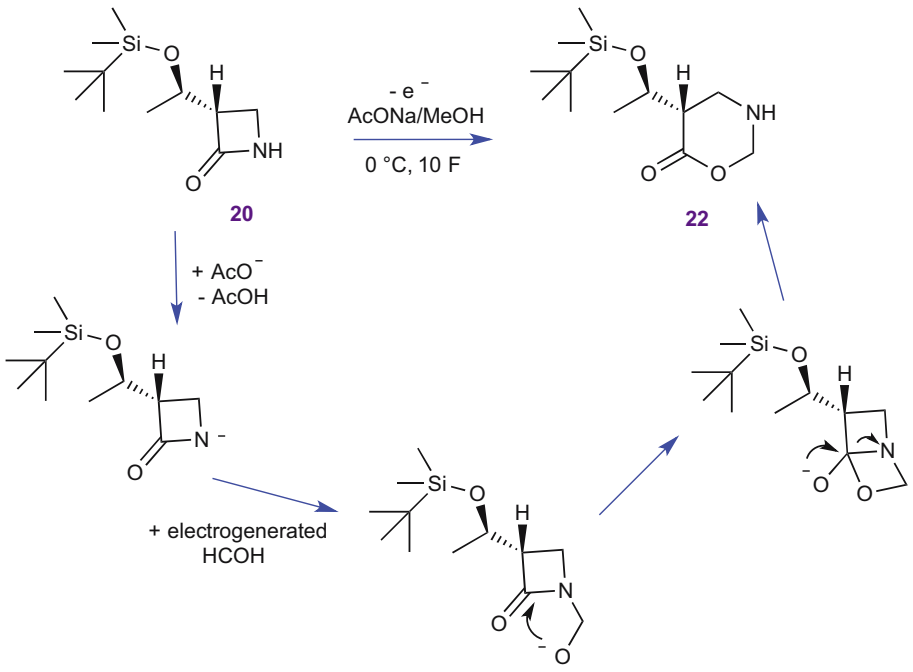
Besides the ring functionalization with a fluorine atom, the halogenation of the nitrogen atom is also possible, although in a less efficient way. In fact, β-lactam **20** (Scheme 14) needed 20 F of anodic charge to yield compound **21**. The anodic oxidation was carried out in the presence of acetic acid and an excess of a salt of the halide ion [47]. The electrooxidative iodination was less effective than bromination, as reported in Scheme 14.



Scheme 13: Anodic fluorination of β-lactams **17**. Proposed possible mechanism.



Scheme 14: Anodic N-halogenation of β-lactams.



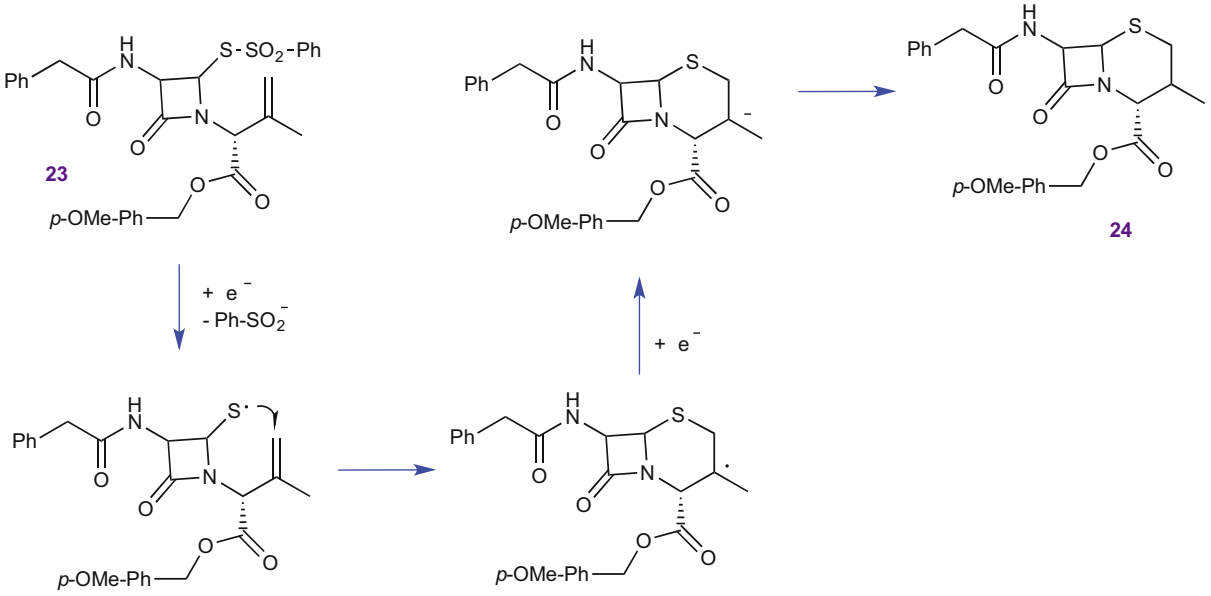
Scheme 15: Anodic ring expansion of β-lactam **20**.

3.3 Anodic ring expansion

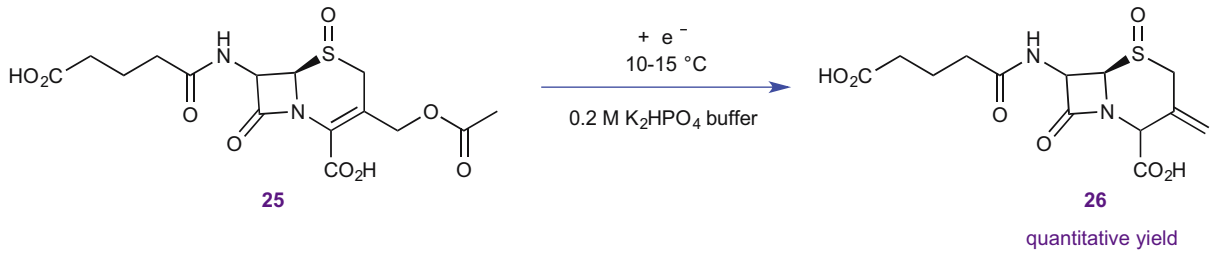
The same authors reported an electroinduced ring expansion of β-lactam **20** when electrolysis was carried out in methanol as the solvent and in the absence of the additive containing the halide ion (Scheme 15) [47]. In this case, the hypothesized mechanism depicts for the anodic oxidation of methanol to formaldehyde and the subsequent reaction of the latter with the nitrogen atom of β-lactam **20** to yield the ring opening product **22** with 84% yield. Also, in this case, the reaction was not very efficient as an excess of current (10 F) was necessary.

3.4 Cathodic ring formation

Electrochemistry can help in the construction of not only the β-lactam ring (as reported in the first part of this review) but also the fused ring of a cephalosporinic



Scheme 16: Cathodic ring formation from β-lactam **23**.



Scheme 17: Cathodic deacetylation from cephalosporanic acid **25**.

acid derivative starting from a monocyclic β-lactam. In one example, the cathodic reduction of a 4-sulfoxythio β-lactam (compound **23**, Scheme 16) containing an exocyclic double bond led to the formation of the radical anion at the sulfur atom, with subsequent mesolytic cleavage to yield a sulfur radical and sulfoxy anion. An intramolecular radical cyclization of the double bond then allowed for the formation of the second fused ring of the cephalosporinic acid derivative **24** (Scheme 16) in 68% yield [48].

3.5 Pilot plant scale reduction of a cephalosporanic acid derivative

The demonstration of the real utility of electroorganic chemistry is given by the use of such a technology for a proof-of-concept study at the pilot plant level. Ceftibuten is a third-generation cephalosporin antibiotic used to treat some acute bacterial infections such as pneumonia or chronic bronchitis. The established synthetic route starts from cephalosporin C, but has some problems of costs and chemical reactions [49]. The introduction of an electrochemical step (Scheme 17) could allow for a cheaper, fully aqueous commercial process. In this process, the cathodic deacetylation of compound **25** gave, in phosphate buffer, a quantitative yield of the intermediate **26** to ceftibuten, rendering this synthesis not only cheaper but also more eco-compatible.

The electrode material was inexpensive (tin), and minimized the effects of the competitive hydrogen evolution reaction. Each electrode had an area of 0.42 m^3. In this way, 113 L of the solution could be treated, obtaining nearly 3 kg of product [49].

4 Conclusions

Although electrochemistry applied to β-lactam chemistry dates back to 1974, the recent renaissance of interest in this class of compounds (due to the new possible chemical and pharmaceutical applications) has led to the publication of new syntheses and ring transformations carried out by electrochemical means in the current century. This is mainly due to the fact that this intrinsic "green" technique uses the electrons as a reagent, and they do not contribute to by-products.

As an example, by carefully choosing the kind of synthesis and the reaction conditions, it is possible not only to carry out eco-friendly and efficient ring construction processes but also to direct the synthesis toward a specific isomer (*cis* using a C3–C4 cyclization, *trans* if using an N1–C4 cyclization).

Moreover, the possibility of using the different kinds of solvents (classical organic solvents or ILs) has a noteworthy influence on the outcome of the reactions.

In almost all reported syntheses of β-lactams, very high yields were obtained. In some cases the outcomes of the reactions carried out by chemical or electrochemical means are different (see Section 2.1). In other cases, the possibility of handling safe reagents (to be electrochemically activated) instead of highly reactive ones allows for safer processes (see Section 2.4).

Besides synthesis, the ring functionalization can also be easily obtained electrochemically by the introduction of a halogen atom in different positions, the formation of the second fused ring of a cephalosporin derivative, and the ring expansion to a new class of compounds.

The interest of the pharmaceutical industry in this field is demonstrated by a proof-of-concept study for the application of an electrochemical step to the synthesis of the commercial antibiotic ceftibuten.

It is thus evident that the potential of this technique is still to be duly exploited. This includes the possibility of significantly lowering the amount of supporting electrolyte using flow conditions, and with the lowering of the electrochemical apparatus costs, could induce an increased number of "classical" organic chemists giving a chance to organic electrochemistry.

The high atom economy inherent in the use of the electron as redox reagent, the ease of dosing it, and the simplicity of separating the solid electrodes from the solution are only some of the bright sides of this technique. Nonetheless, still issues are to be solved in order to enable the large-scale industrial application of electrochemistry in organic synthesis. Examples include the construction of devices that support high current densities using low amounts of supporting electrolytes or the setup of efficient flow electrochemistry devices for a continuous production. Nevertheless, the use of renewable electrical energy to build value-added chemicals is and will be an important issue to be pursued by the chemical industry.

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