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Electrons as a Reagent in Solid-Phase Organic Synthesis

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Solid-Phase Organic Synthesis (SPOS) has become an important tool for the high-throughput synthesis of bioactive molecules or new catalysts. The main advantage of this approach is the covalent attachment of the substrate to an insoluble support, enabling reaction workup through simple filtration. However, the heterogeneous nature of SPOS imposes limitations on the organic reactions applicable on solid phase. Electron-transfer reactions and electroorganic synthesis are reaction types that have not yet received much attention in this context. In this review the current status of electron-transfer reactions carried out on solid phase is described and future developments are discussed.

Abbreviations

Bn = benzyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl, CSA = camphorsulfonic acid, DCM = dichloromethane, DEAD = diethyl azodicarboxylate, DIC = 1,3-diisopropylcarbodiimide, DMF = *N*,*N*-dimethylformamide, DMPU = 1,3-dimethylpropylurea, DMSO = dimethyl sulfoxide, DMTMM = (4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride, F = Faraday, *j* = current density, mCPBA = *meta*-chloroperbenzoic acid, NMM = *N*-methylmorpholine, NMP = *N*-methylpyrrolidinone, Np = 4-nitrophenyl, Phth = phthaloyl, r.t. = room temperature, SAM = self-assembled monolayer, SPOS = Solid-Phase Organic Synthesis, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = *para*-tolylsulfonyl

I. Introduction

The invention of solid-phase organic synthesis (SPOS) as a tool for the preparation of compound libraries with potentially interesting activity in life sciences, catalysis, or supramolecular chemistry has revolutionized this field. The past 15 years have seen the rapid embracing of this methodology and the success of this development is attested to by a series of elegant applications to the synthesis of compound libraries of challenging natural product structures,[1] such as epothilone,[2] galanthamine,[3] saframycin,[4] spiroketals,[5] or dysidiolide.[6] These spectacular triumphs have

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been based on the adaptation of successful synthetic strategies of solution-phase organic synthesis to the different reaction environment ordained by the solid phase. Since the pioneering work of Bruce Merrifield, organic chemists have implemented many of the organic reactions known in solution onto solid phase,[7] but the toolbox available for SPOS is still limited. Even these notable achievements in library synthesis described above still reflect the limitations imposed by the accessible reactions, as in most cases the diversity elements have been introduced only through a few powerful reactions already well established in SPOS.

II. Challenges in SPOS

In contrast with total synthesis efforts in solution, in which a single target molecule is accessed through specific, highly optimized reactions, synthetic efforts in SPOS are usually motivated by the aim to produce not just one, but many different compounds exhibiting huge diversity in their structural and functional features. Consequently, the corresponding transformations have to proceed with a high degree of reliability and robustness. This extra demand is further complicated by the stringencies imposed by the anchoring of the substrate to the polymeric support.

The following difficulties are faced when transferring organic reactions from the solution to the solid phase: a) cross-reactivity of intermediates and reagents with the polymeric support, b) difficulty in removing water from the resins, c) problems with adapting reactions that require careful reaction monitoring or temperature control under the, by definition, inhomogeneous kinetic situation of a polymeric bead, and d) any synthetic operation involving heterogeneous reagents. Here the problem is that, in most resins used in SPOS, more than 99.9% of the substrate molecules are buried within the interior of the resin bead,[7a] and direct contact between the heterogeneous reagent and the immobilized substrate is made impossible for steric reasons.

The current status of the tool box of organic reactions implemented in SPOS can be organized by distinguishing three types of maturity (Table 1).[1f]

Type 1 reactions are reactions that work for a broad range of substrates on solid phase, for which robust reaction protocols exist. These reactions typically have a long history in solid-phase synthesis and very reliable reaction protocols have been established through optimization (e.g. oligopeptide synthesis, oligonucleotide synthesis). Another characteristic of these reactions is that the reaction products represent thermodynamic sinks, which form easily and are less prone to further reactions leading to side products. The most useful C–C bond-forming reaction on solid phase is Pd-catalyzed cross-coupling.

Type 2 reactions are reactions that have already been implemented on solid phase but with unexplored scope. As a rule, the reaction protocols are limited to the few reported substrates in the few reported applications. Interestingly, the most important C–C bond-forming reactions in solution organic synthesis show limitations on solid phase: stereoselective aldol reactions have so far been reported only by a few groups.[8–11] Cycloadditions have been described more often, but still limitations are imposed by the resin, which makes both low and high reaction temperature conditions problematic. In general, the use of stereoselective – and especially enantioselective – methods has so far largely been neglected.[12]

Type 3 reactions are reactions that have not yet been applied on solid phase or if so, then only in proof-of-concept experiments. For more general application, several intrinsic problems still have to be solved.

As can be seen from this list, reactions involving electron-transfer reagents and electrochemical reactions fall into the last category. In solution-phase synthesis, redox reactions represent one of the most important class of reactions, as they allow the activation of reaction partners or the adjustment of oxidation states of functional groups. Among these reactions, electrochemical reactions, with their

Table 1. Classification of reactions in SPOS.

Type 1 reactions	Type 2 reactions	Type 3 reactions
Amide bond formation	Cycloaddition	Catalytic hydrogenation
Nucleotide oligomerization	Aldol reaction	Electroorganic synthesis
Esterification/saponification	Allylation	Organometallic reagents on solid phase (Grignard, Li-organyls, …)
Protection/deprotection	Reaction of solid phase bound electrophiles with organometallic reagents	Reactions involving carbocations (skeletal rearrangements, etc.)
Reductive amination	Many functional group transformations	Reactions involving radicals, radical cations, radical anions, and other high energy intermediates
Pd–catalyzed cross–coupling	Stereoselective (especially enantioselective) reactions	
Knoevenagel condensation	Photochemical reactions	
Heterocycle condensations		
Reactions with isocyanates/thioisocyanates		
Oxidation of alcohols		
Reductions of amides		
Ozonolysis		

advantages of complementary reactivity and mild reaction conditions, play a special role. In this article we review recent efforts in implementation of electrochemical methods for use in combinatorial chemistry and solid-phase library synthesis. In order to put those efforts in perspective, the use of single-electron-transfer reagents in SPOS is also discussed, although no comprehensive description of this field is possible within the limited space available.

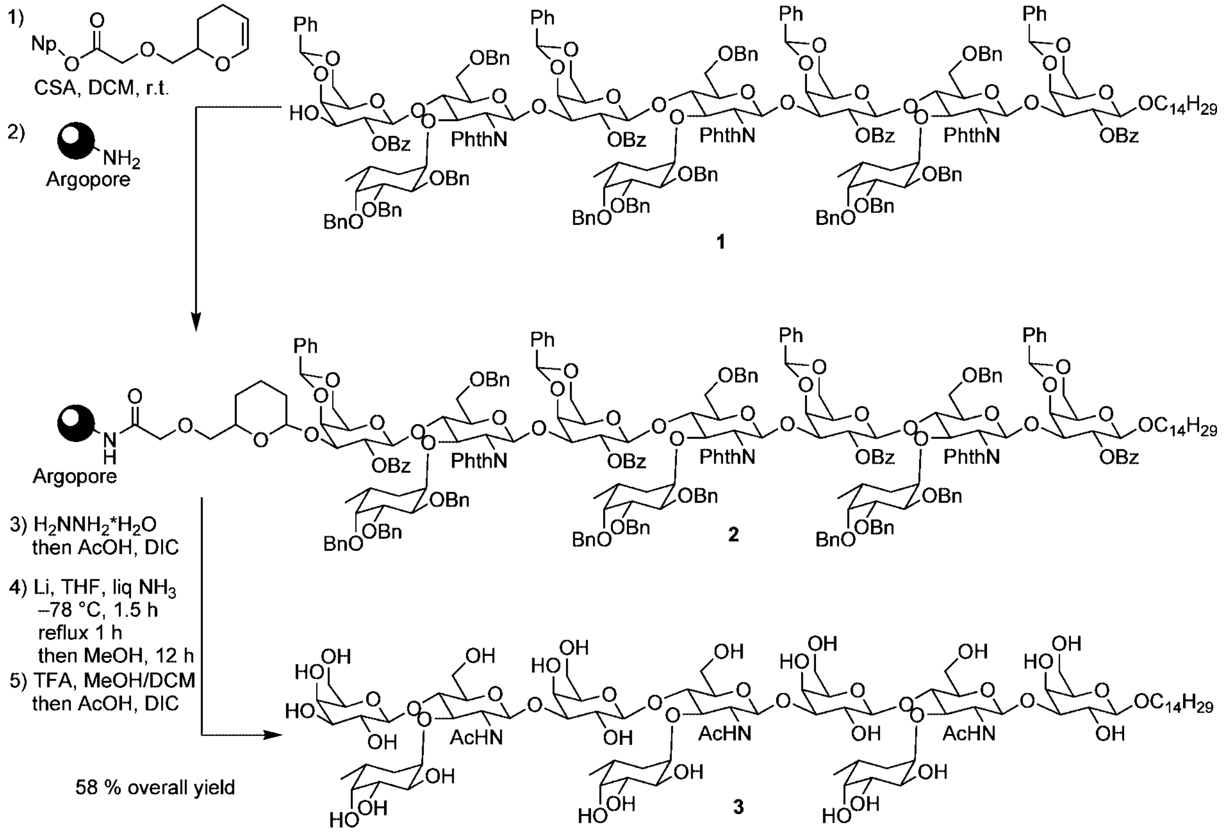
III. Single-Electron-Transfer Reagents in SPOS

Alkali metals in liquid ammonia produce solvated electrons, used in organic synthesis as very powerful reducing agents. Only recently has this reagent combination been applied in SPOS: Takahashi et al. have presented an ingenious method to facilitate the global deprotection of highly substituted oligosaccharides.[13] One problem associated with the synthesis of oligosaccharides is the careful selection of the reaction solvents to prevent the partially deprotected intermediates from precipitating during deprotection steps. They solved this problem by preparing the protected dimeric Lewis X derivative **1** in solution, and attaching this to a polymeric support through a known tetrahydropyran linkage. At this stage, the phthalimido protecting group was removed by hydrazinolysis and the resulting free amine was acylated to furnish the desired acetamido moiety. Cleavage of the *O*-benzyl protecting groups was then achieved by exposure of resin **2** to Birch reduction conditions. Previous studies had shown that conventional polystyrene resins are not suitable for this purpose, due to poor swelling, but ArgoPore resin exhibited the desired properties and allowed deprotection with Li/liq. NH_3. Treatment with TFA allowed the deprotection of the remaining acid-labile groups and cleavage from the linker, and product **3** could be isolated in an excellent 58% overall yield (Scheme 1).

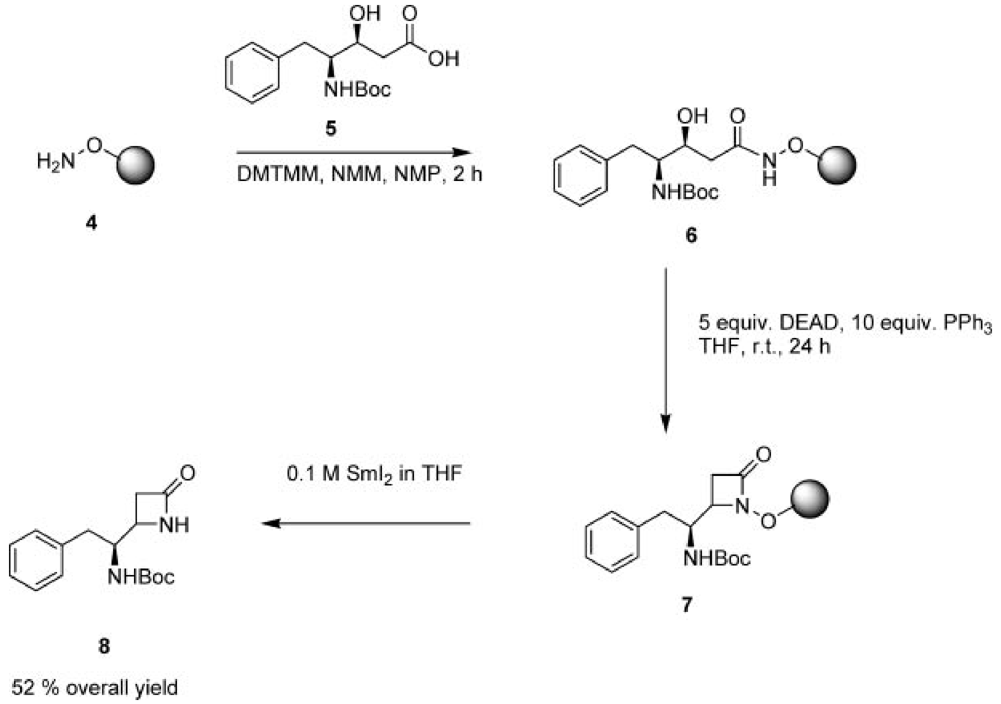
SmI_2 is an excellent electron-transfer reagent, which has attracted considerable attention as a reagent in SPOS. A comprehensive review on this subject has just recently been published by Sloan and Procter,[14] which allows us to restrict our discussion by acknowledging a few representative examples highlighting this approach.

Taddei has reported a very nice SPOS of β-lactams taking advantage of a traceless linker strategy previously developed by Abell for amides.[15] Hydroxylamine resin **4** was acylated with β-hydroxyamino acid **5** to produce intermediate **6**, which cyclized to lactam **7** under Mitsunobu conditions. Reductive cleavage of the N–O bond with SmI_2 furnished lactam **8** in excellent overall yield (Scheme 2).[16]

Among the carbon–carbon bond-forming reactions that play a prominent role in connecting fragments in total synthesis, the Julia–Lythgoe olefination has received special attention. A solid-phase variant of this reaction faces two challenges. Firstly, a solid-phase sulfonyl carbanion has to be generated, and this then reacts with an aldehyde, requiring the absence of moisture. Secondly, the reductive elimination of a β-acyloxysulfone has to be induced by a single-



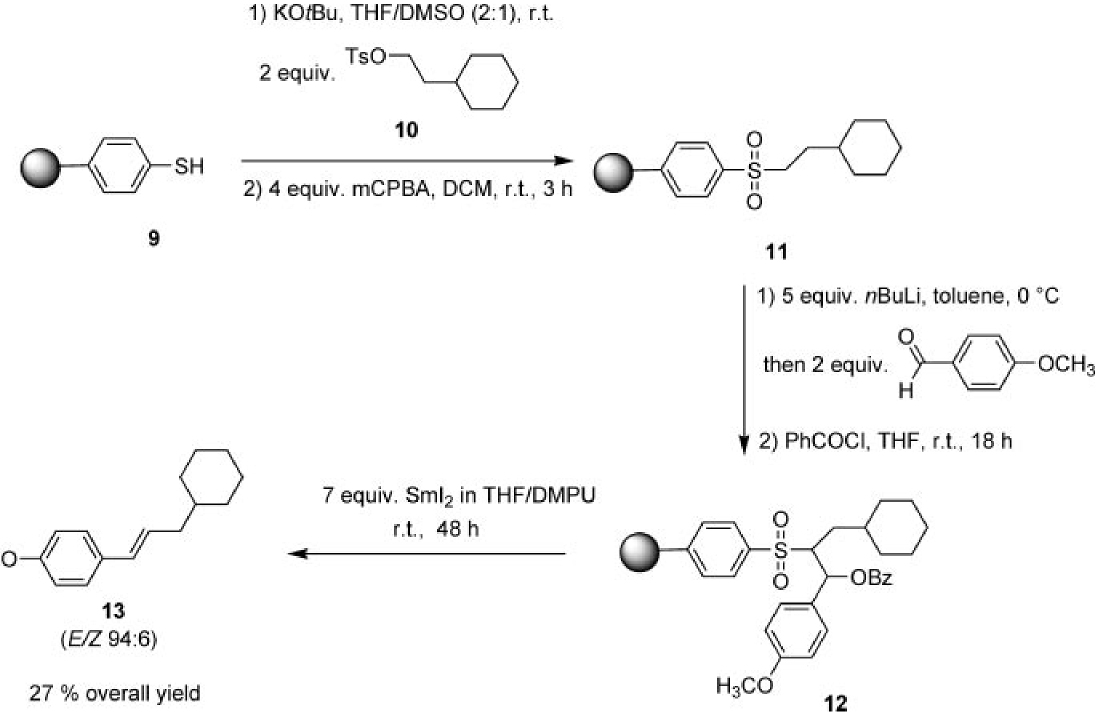
Scheme 1. Solid-phase assisted deprotection of oligosaccharides with Li/NH_3.



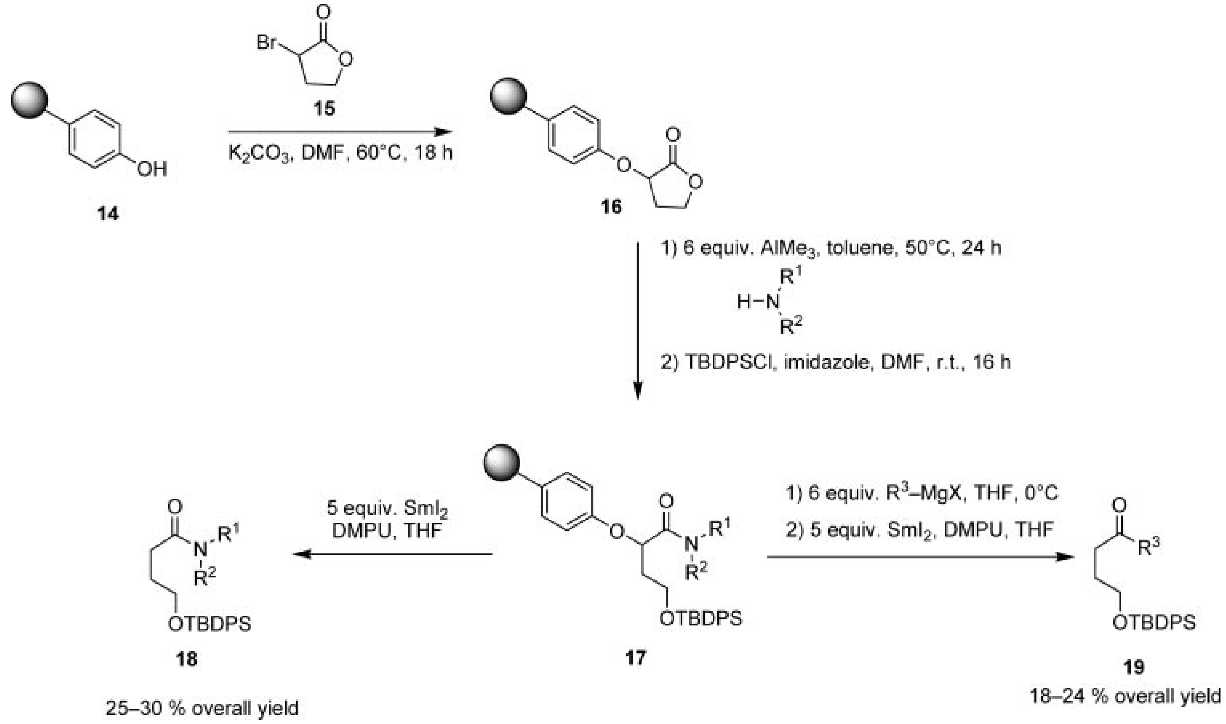
Scheme 2. Synthesis of β-lactams by the Miller cyclisation reaction.

electron donor. De Clerq has accomplished this goal by following the strategy depicted in Scheme 3, using SmI_2 as the electron source. The overall yield of olefin **13** – of 27% – is quite respectable, considering that it also involves the preparation of resin **9** starting from 4-bromopolystyrene.[17]

Procter et al. have attached α-bromo lactone **15** to phenol resin **14**. Me_3Al-mediated amidation delivered the acyclic α-hydroxy amide derivatives **17**, which could be reductively cleaved from the resin by treatment with SmI_2 with concomitant deoxygenation of the α-functionality. The diversity of this route could be increased when the resin-bound amides **17** were treated with Grignard reagents, affording ketones **19** after reductive cleavage (Scheme 4).[18]



Scheme 3. SmI_2-mediated Julia–Lythgoe olefination on solid phase.



Scheme 4. SmI_2-mediated reductive cleavage on solid support.

Very recently, Bräse et al. have reported the chemoselective reduction of solid-phase bound nitroarenes with dioctyl viologen as a single-electron-transfer catalyst and sodium sulfide as a stoichiometric reductant.[19]

IV. Electrochemical Methods in Combinatorial Chemistry

Electroorganic synthesis is a powerful method with tremendous as yet not fully exploited potential.[20] One aspect commonly regarded as a handicap for the widespread application of electroorganic synthesis is the experimental setup, which requires an electrochemical cell, a power source, and control elements. Although simple solutions exist for many examples, this aspect of instrumentation becomes even more significant if a parallel setup is considered.[21] Yudin's group in Toronto has pioneered the design of a spatially addressable electrolysis platform (SAEP), which consists of a rectangular array of electrochemical cells, controlled through a single power source and controlling unit. They have used the SAEP devices for parallel solution-phase galvanostatic electrolysis in the preparation of libraries of α-alkoxy-amides, α-alkoxy-carbamates, and α-alkoxy-sulfonamides, and also of libraries of vicinal diamines.[22] Just recently, Speiser et al. have elaborated this concept and have constructed a computer-controlled instrument, based on electrochemical microscope technology, for the miniaturized combinatorial electrosynthesis of iminoquinol ethers and triazolopyridinium ions in the wells of microtiter plates by potentiostatic electrolysis.[23]

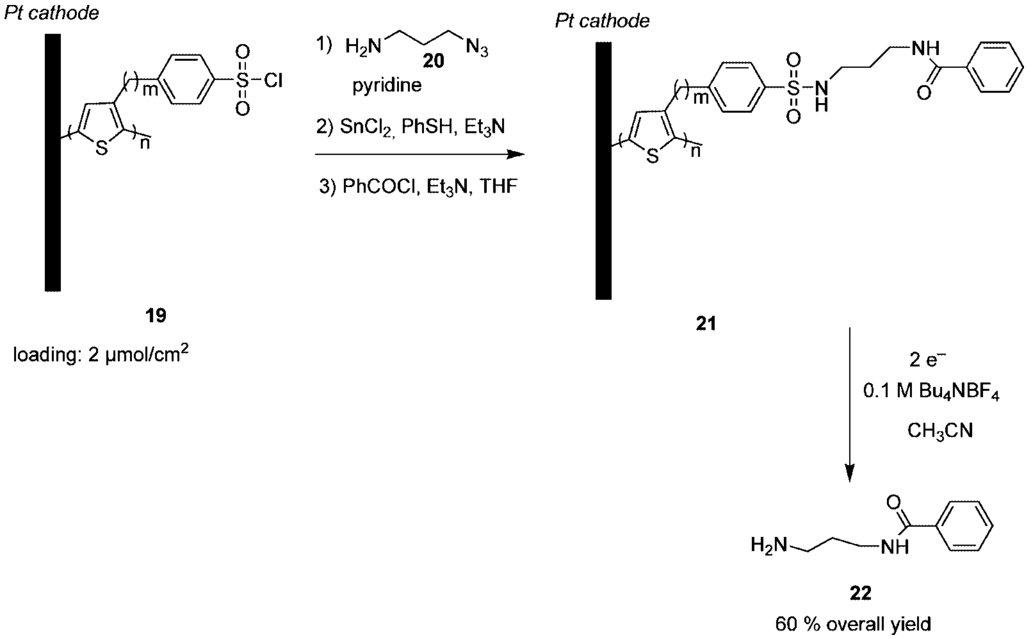
A different strategy has been designed and extensively used by Yoshida's group.[24] Iminium ions or oxocarbenium ions are electrogenerated at low temperatures; at the reaction temperature these are sufficiently stable to be pooled and can then react with sets of different electrophiles such as allylsilanes, enolethers, alcohols, or halogen ions. In a modification of this "cation-pool" strategy, the use of a microfluidic device ("cation-flow") enabled the combinatorial synthesis of substituted nitrogen heterocycles. All these approaches have advanced the concept of solution-phase parallel electrochemistry.

Solid-Phase Electroorganic Synthesis

As described above, SPOS offers a number of advantages over solution-phase synthesis. Immobilization of substrate molecules allows the use of an excess of reagent to drive reactions to completion. Consumed or excess reagent can be easily removed by filtration as a simple workup operation. Electroorganic synthesis could benefit a lot by such an isolation procedure, as the removal of the complex electrolyte from the product can be troublesome. Three strategies have been used towards this goal: 1) immobilization of substrates on an electrode, 2) use of polymeric bases as the supporting electrolyte, and 3) immobilization of substrates on established polymeric beads followed by an indirect electroorganic synthesis.

Immobilization of Substrates on an Electrode

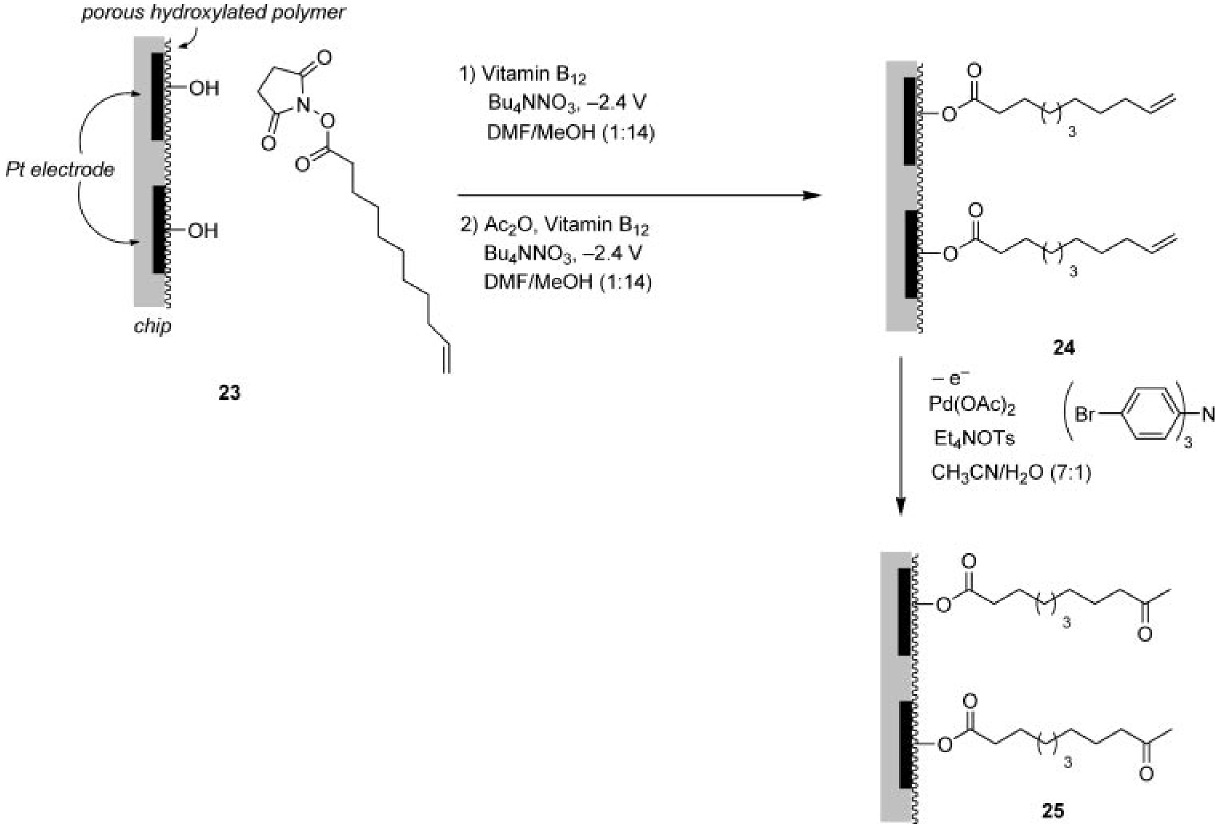
Pilard's group was the first to report solid-phase synthesis using an electrode as the solid support.[25] A Pt electrode was modified by electrochemical polymerization of a thio-



Scheme 5. SPOS on an electrode surface.

phene derivative bearing a sulfonylchloride linker substituent in the 3-position. Loading of electrode **19** with amine **20** allowed the subsequent conversion of the azide moiety to provide the benzamide **21**. Applying voltage at the coated electrode initiated the cathodic reduction of the sulfonamide, delivering amine **22** in good yield and excellent purity (Scheme 5).

Pickett et al. have reported the use of amino-functionalized pyrrole polymers generated on an electrode surface,[26] and Mrksich that of Diels–Alder reactions of elec-



Scheme 6. Spatially addressable electrode array used for Wacker oxidation.

trochemically oxidized quinones on a SAM-Au surface.[27] The disadvantage of low loading of planar Pt electrodes was overcome by Pinson and Pulicani, who demonstrated the use of carbon felt as both electrode and solid support.[28] Unfortunately, this material adsorbs reagents strongly: for example, for a Suzuki reaction, overstoichiometric amounts of reagents and palladium catalysts were required. More recently, Kashiwagi demonstrated Sonogashira coupling on iodo aromatics immobilized on graphite felt bearing a polypyrrole coating.[29]

A conceptual breakthrough in the use of modified electrodes as a support has been reported recently by Moeller et al., who created up to 12000 individually addressable platinum electrodes on a 1 cm^2 chip. The chip was coated with a porous hydroxylated polymer membrane, which could be site-selectively functionalized with ester moieties by electrogeneration of a base using vitamin B$_{12}$ as a mediator. Substrates could then be modified by Wacker oxidation (Scheme 6),[30] Heck reaction,[31] deprotection through electrogenerated acids,[32] reductive amination,[33] or coumarin synthesis.[34] The space resolution of this process is very high and, as each electrode can be addressed individually, any desired surface pattern can be achieved. In a recent publication the authors also introduced an electrochemical screening method for protein–ligand interactions in such compound libraries.[34]

Solid Supported Bases as Supporting Electrolytes

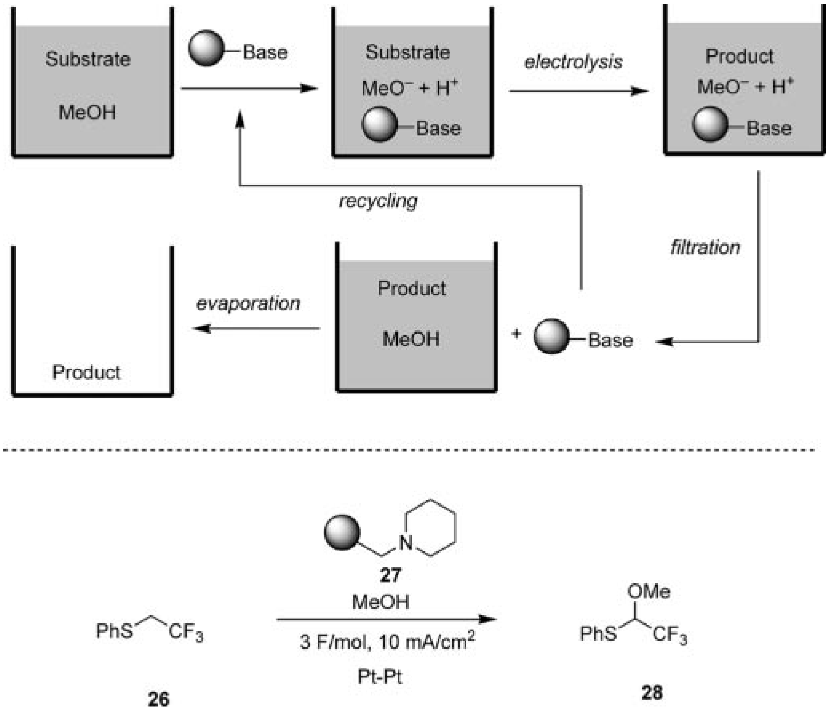
One problem often faced in electroorganic synthesis is the removal of the supporting electrolyte from the reaction product. With the workup advantage of solid-supported reagents in mind, Fuchigami introduced solid-supported bases for the in situ generation of a supporting electrolyte from methanol as a solvent (Scheme 7).[35–36] In this polar solvent, the use of silica-supported amine bases delivered better results than the use of polystyrene beads.

In the meantime, Fuchigami et al. have successfully applied this concept for the anodic acetoxylation of organic compounds[37] and the Kolbe electrolysis of carboxylic acids.[38]

Indirect Electroorganic Synthesis on a Solid Phase

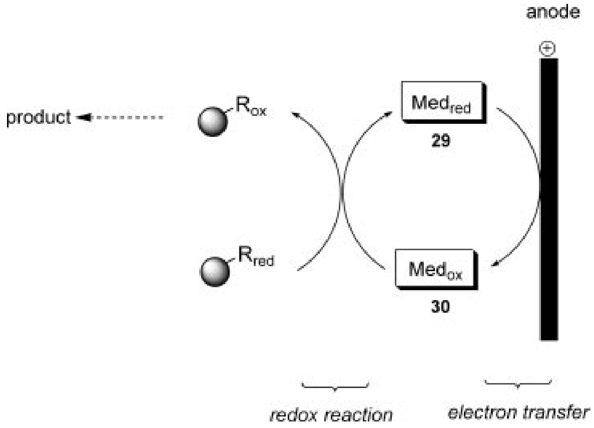
Although the above strategies represent ingenious solutions to important problems in electroorganic synthesis, a different approach has to be sought for the implementation of electrochemical methods on a solid phase. Ideally, such a strategy is guided by three imperatives. Firstly, any solid-phase strategy should be compatible with polystyrene beads as a commercially available solid support, because these materials are inexpensive and high loading, and have known properties. Secondly, the use of polystyrene beads allows the application of existing SPOS protocols for the preparation of starting materials and for the derivatization of reaction products. This would allow the integration of the electrochemical process in multi-step syntheses, as is required for the creation of diverse libraries of complex structures. Finally, a simple experimental setup in the form of a beaker-type cell should lower the barrier for other groups to use such a methodology.

Breinbauer and Nad have established such a strategy, which appears to be quite general, at least for anodic oxidation processes on a solid phase.[39] It is based on the prin-



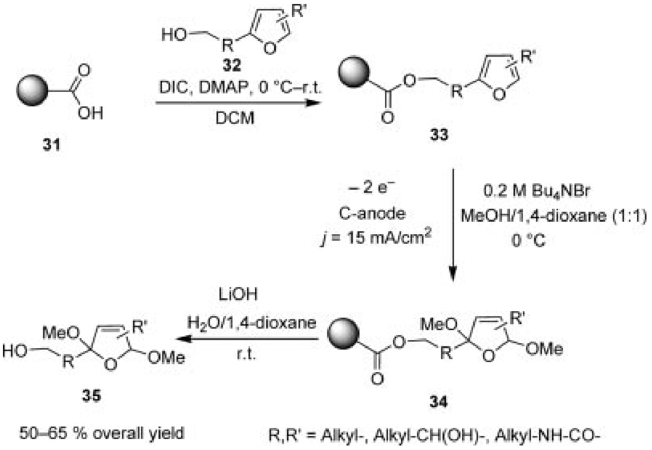
Scheme 7. Anodic methoxylation in an electrolyte system defined by a solid-supported base.

ciple of "indirect electrolysis",[40] which has already found widespread application in solution-phase electroorganic synthesis, where it offers significant experimental advantages over a direct electrode contact, such as reduced overpotential or higher selectivity. Here, the electron-transfer step at the electrode and the redox reaction with the substrate are separated and a redox catalyst (**29** and **30**) serves as a mediator (Scheme 8). In the context of SPOS, the redox mediator as a homogeneous reagent shuttles electrons from the electrode surface to the substrate molecules buried within the polymeric beads, therefore overcoming the limitations of the use of heterogeneous reagents. Halogen ions, transition metal complexes, triarylamines, and others can serve as mediators, and the literature contains many more examples, raising the hope that for any application an appropriate reagent with the desired redox potential and chemical properties can be found.



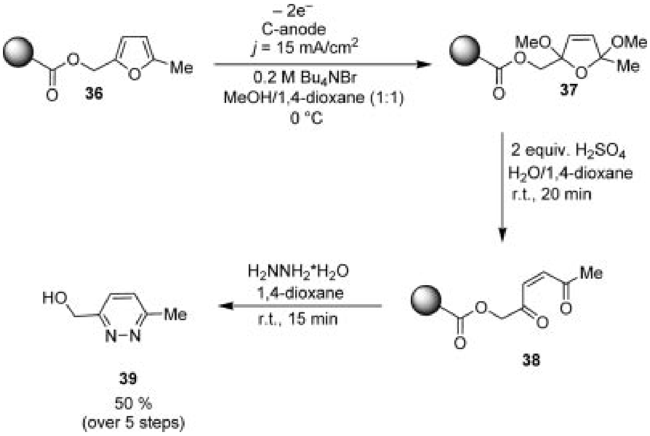
Scheme 8. Principle of redox catalyst-mediated electroorganic synthesis on a solid phase.

As a model reaction they chose the electrochemical oxidation of furans to afford 2,5-dialkoxydihydrofurans, using tetrabutylammonium bromide both as a supporting electrolyte and as a redox mediator. As the acetal moiety in the expected reaction products easily undergoes acidic hydrolysis, an ester linkage that could be cleaved by saponification with base was chosen. In a five-step synthesis, 2,5-dialkoxydihydrofurans **35** were isolated in 50–65% yields (Scheme 9).



Scheme 9. Electrochemical oxidation on solid phase using polystyrene beads.

As mentioned before, the use of polystyrene beads as a polymeric support allows the integration of electrochemical methods into synthetic sequences by the methods discussed in the Introduction. To give an example, the latent carbonyl-type reactivity of 2,5-dialkoxydihydrofurans can be used for the synthesis of pyridazine heterocycles. Following a strategy developed by Clauson–Kaas for pyridazine synthesis in solution, Breinbauer and Nad attached (5-methylfuran-2-yl)methanol to a solid support using an esterification protocol. Application of their electrochemical oxidation method produced the solid-phase-bound 2,5-dialkoxydihydrofuran **37** (Scheme 10). The formation of pyridazines required the controlled hydrolysis of the ketal moieties of **37** to furnish the unstable dicarbonyl compound **38**, which, upon treatment with hydrazine hydrate, underwent a double condensation reaction with the carbonyl groups, and with concomitant hydrazinolysis, pyridazine **39** was isolated in very good yield (50%) and excellent purity (>95%, determined by NMR and GC/MS) after extractive workup without requiring any chromatographic purification.[41]



Scheme 10. Electrochemical synthesis of pyridazines using polystyrene beads.

The attempted reduction of the olefin moiety within the electrochemically generated 2,5-dialkoxydihydrofurans could not be achieved on a solid phase, but by using hyberbranched polyglycerol as a soluble polymeric support, Haag's and Breinbauer's groups were able to perform both electrochemical oxidation and catalytic hydrogenation, allowing them to prepare a small library of *N*-substituted pyrroles.[42]

Summary and Outlook

The last few years have seen considerable progress in the use of electron-transfer reagents and electroorganic synthesis in the context of SPOS. For the practitioner it will be important that these methods are compatible with standard resins used in SPOS, such as polystyrene or tentagel resins. As high-throughput synthesis increasingly turns to parallel solution-phase methods, the parallel solution-phase electrochemistry platform highlighted in this article will see further development and application. The modification of electrodes has gained a new boost through the work of Moeller, which might in future see the integration of electrochemical synthesis of true compound libraries and the screening of biological activity using electroanalytical tools as well. Finally, the use of solid-supported bases and acids for the in situ generation of supporting electrolyte is a new concept of great potential for solution-phase electroorganic synthesis, which will inspire many future chemists.

Acknowledgments

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