THE CHEMICAL RECORD
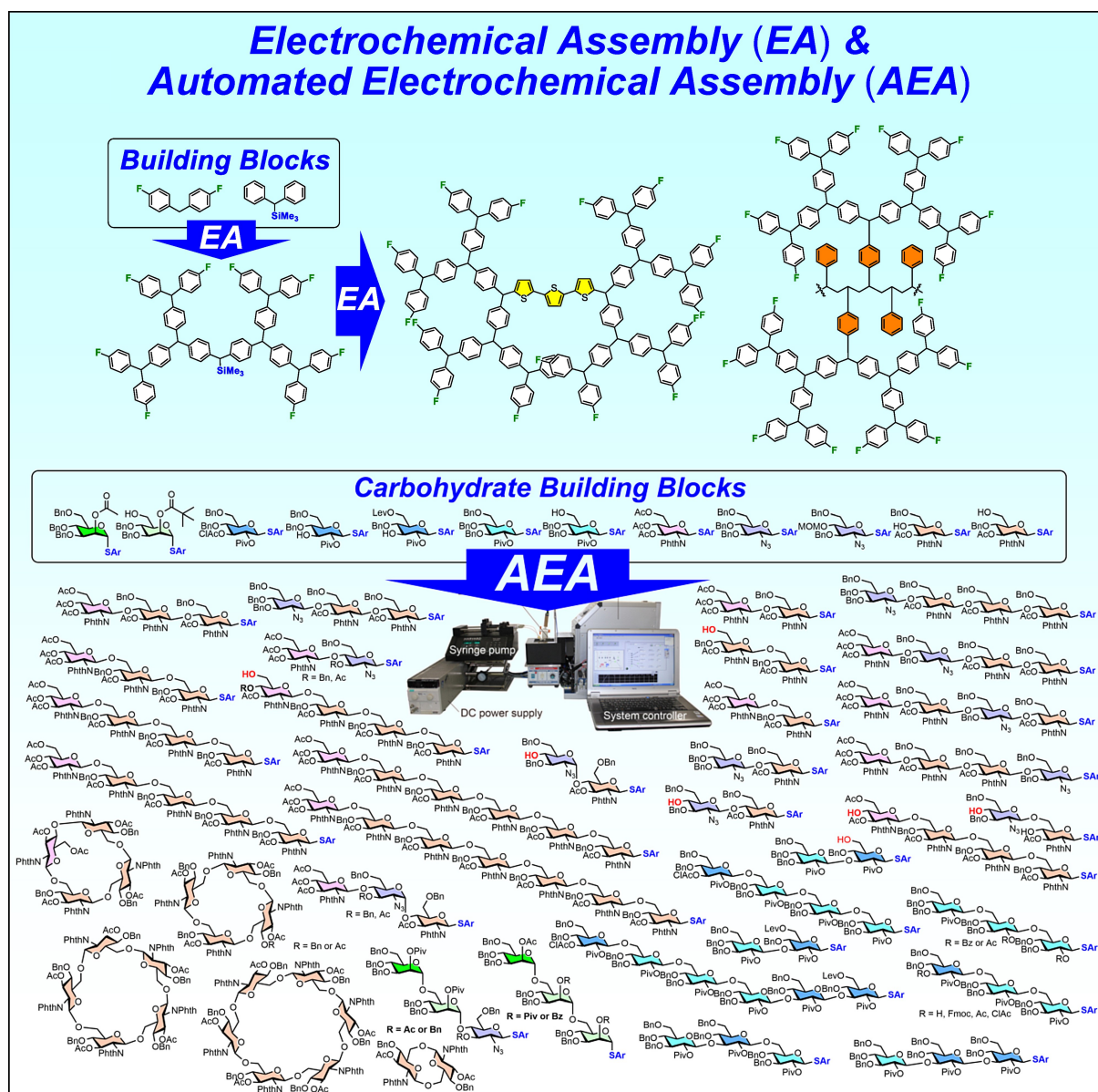
Electrochemical Assembly for Synthesis of Middle-Sized Organic Molecules

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Dedicated to the memory of late Professor Jun-ichi Yoshida.

Abstract: Electrochemical methods offer a powerful, reliable, and environmentally benign approach for the synthesis of small organic molecules, and such methods are useful not only for the transformation of small molecules, but also for the preparation of oligomers and polymers. Electrochemical assembly is a concept that allows structurally well-defined middle-sized organic molecules to be synthesized by applying electrochemical methods. The preparation of dendrimers, dendronized polymers, and oligosaccharides are introduced as examples of such an approach. Automated electrochemical assembly of oligosaccharides is also demonstrated using the electrochemical synthesizer developed by our group.

Keywords: Electrolysis, Oligosaccharide, Dendrimer, Reaction Integration, Automated Synthesis

1. Introduction

Organic electrochemistry, especially electrochemical synthesis of organic compounds, is an emerging research area.[1] Although the subject has a long history since the first report of the Kolbe reaction,[2] electrochemical conversion of organic molecules has been reevaluated as a truly environmentally benign method and unique transformations have been reported.[3] We have been interested in the use of reactive intermediates generated by electrochemical oxidative activation of small organic molecules for the assembly of middle-sized organic molecules. There are several reasons why we have been interested in developing methodology based on electrochemical methods, which are summarized in the following sections.

1.1. Electrochemical Activation as a Powerful Method to Generate Reactive Intermediates

Activation of organic molecules is a key issue in organic synthesis, for example, strong oxidants or reductants are commonly used to activate substrates with low reactivities. Constant-current electrolysis is sufficiently powerful that organic molecules including organic solvents are activated at a constant reaction rate. For example, the cation pool method is a revolutionary approach that enables the generation and accumulation of carbocations **1–4** by electrochemical oxidation in the absence of nucleophiles (Figure 1). By using this approach, electrochemical reactions of nucleophiles with lower oxidation potentials than that of the precursor of the carbocation can be carried out by using the cation pool method.

1.2. Electrochemical Reactions as Synthetic Methods Without Reagents, Except for Electrodes and Electrolytes

Electrochemical reactions are heterogeneous reactions between solid electrodes and organic molecules that are dissolved in solvent. Therefore, electrochemical processes are ideal for integration of reactions in one pot by the sequential process of addition and activation of substrate.[4] In this review article, one-pot synthesis of oligosaccharides is introduced as an example of automated synthesis based on electrochemical methods.

1.3. Easy Control of Reactions under the Electrochemical Conditions

Electrochemical reactions can be started and stopped by simply switching on and off the power supply. The rate of reaction can be controlled under the constant-current conditions, and constant-potential electrolysis enables selective activation of organic compounds. Therefore, electrochemical methods make organic reactions controllable, repeatable, and reproducible.

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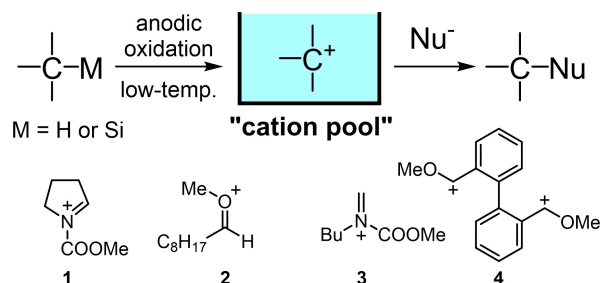4-101 Koyamacho-minami, Tottori city, 680-8552 Tottori, Japan

Figure 1. Examples of cations generated by the cation pool method.

2. Electrochemical Generation of Reactive Species

2.1. Electrochemical Generation of Diarylcarbenium Ions

Electrochemical oxidative activation of organic compounds in the presence of a nucleophile is a useful transformation, and carbocations have been proposed as reactive intermediates in this reaction. Diarylcarbenium ions **6** are examples of carbocations that can be generated and accumulated by using the "cation pool method" and reacted with carbon nucleophiles such as allyltrimethylsilane (**7**) (allylsilane) (Figure 2).[5–7] The simplest precursors of **6** are diarylmethanes **5**; however, diphenylmethane **5b**, which has no substituents on the phenyl rings, does not work as a precursor for the generation of the diphenylcarbenium ion **6**, even though the oxidation potential of diphenylmethane (**5b**) ($E_{ox} = 1.81$ V vs. SCE) is lower than that of di(p-fluorophenyl)methane (**5a**) ($E_{ox} = 1.96$ V vs. SCE). An explanation for the puzzling lack of the desired product from **5b** is presented in Section 3.

2.2. Electrochemical Generation of Glycosyl Triflates

We have been interested in the spectroscopic observation of glycosyl cations, which have been proposed as reactive intermediates for glycosylation; however, to date, no such glycosyl cations have been detected by spectroscopic methods.[8] Although electrochemical generation of glycosyl cations from thioglycoside was investigated using various electrolytes, including tetrabutylammonium tetrakis (pentafluorophenyl) borate ($Bu_4NB(C_6F_5)_4$), glycosyl cations could not be detected by NMR analysis even at low temperature. Later, a flow-microreactor was utilized to generate glycosyl cation equivalents and the thus-generated intermediates were trapped with methanol; however, the structure of the glycosyl cation equivalent could not be confirmed by spectroscopic methods.[9]
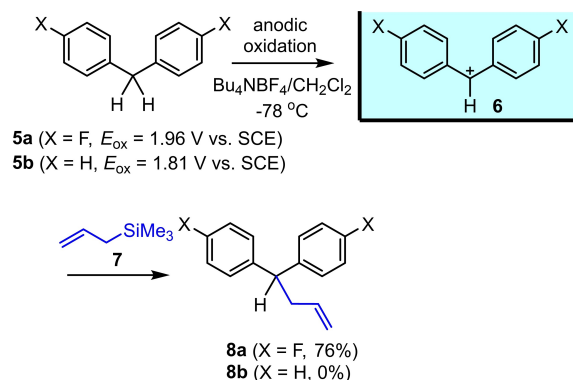

Figure 2. Generation and reaction of diarylcarbenium ions.

Glycosyl triflates **10** are known to be one of the most reactive intermediates for chemical glycosylation, and these intermediates can be observed by NMR spectroscopic analysis under low-temperature conditions.[10] Thus, we expected that electrochemical activation of thioglycoside **9** in the presence of tetrabutylammonium triflate (Bu_4NOTf) might be a useful method to generate and accumulate glycosyl triflates **10** (Figure 3).[11–14] Indeed, a variety of glycosyl triflates **10a–g** have been generated electrochemically and utilized for glycosylation of alcohols, including hydroxyl groups of carbohydrates. Based on these results, we developed an automated electrochemical assembly as a methodology for the synthesis of oligosaccharides, as shown in Section 4.

3. Electrochemical Assembly for Synthesis of Dendritic Molecules

### 3.1. Electrochemical Synthesis of Dendrimers

We envisioned that electrochemical assembly of diphenylmethane (**5b**) could be used to generate dendritic structures

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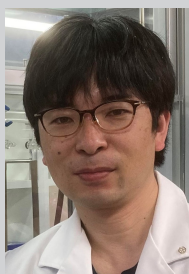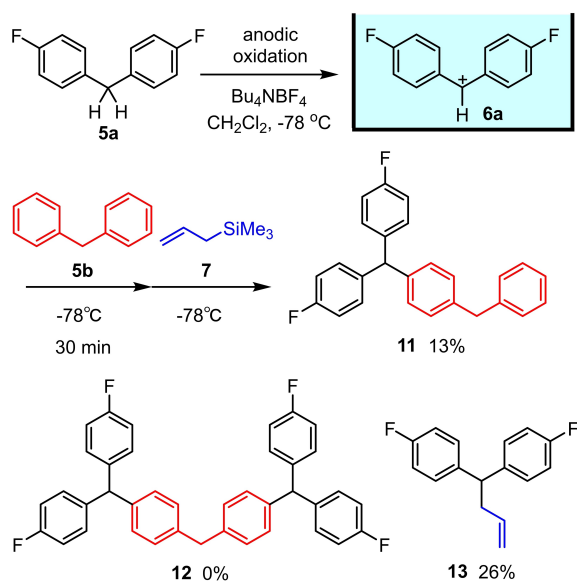
Professor Toshiki Nokami obtained his Ph.D. from Kyoto University in 2004 under the guidance of Professor Jun-ichi Yoshida. Then he spent 11 months in ETH Zurich as a post-doctoral fellow under the supervision of Professor Peter H. Seeberger. In 2005 he joined Kyoto University as Assistant Professor and was promoted to Lecturer in 2011. He moved to Tottori University as Associate Professor in 2012 and he has been Professor of the same department since 2019. His research interests include synthetic organic chemistry, organic electrochemistry, and carbohydrate chemistry.
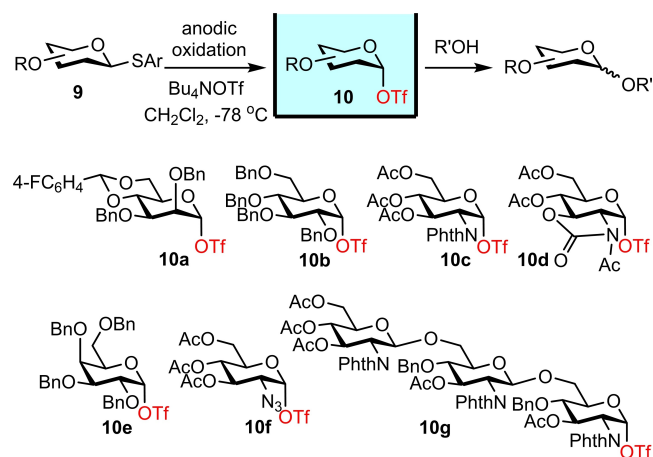
Figure 3. Structures of electrochemically generated glycosyl triflates.

with triphenylmethane repeating units.[15] Thus, diarylcarbenium ion **6a**, generated from di(*p*-fluorophenyl)methane (**5a**), was treated with **5b** and then allylsilane **7** at −78 °C (Figure 4). Although the yield was poor, **5b** acted as a nucleophile, which may explain why this compound did not work as a precursor for generating the diphenylcarbenium ion. Thus, we became interested in applying diphenylmethane (**5b**) as a nucleophile and how to raise its reactivity.

Benzhydryltrimethylsilane (**14**) ($E_{ox} = 0.98$ V vs. SCE), which has lower oxidation potential than that of diphenylmethane (**5b**), is a derivative of diphenylmethane bearing a trimethylsilyl group at the benzylic position. The low

oxidation potential of benzhydryltrimethylsilane (**14**) suggested an electron-donating effect of the trimethylsilyl group toward phenyl groups. Indeed, reaction of diarylcarbenium ion **6a** with benzhydryltrimethylsilane (**14**) afforded the first generation of dendritic diarylmethane **15** in 79% yield (Figure 5). The oxidation potential of **15** ($E_{ox} = 1.25$ V vs. SCE) is higher than that of benzhydryltrimethylsilane (**14**); however, the value is still lower than that of diphenylmethane (**5b**). Therefore, **15** also worked as a precursor of diarylcarbenium ion and reacted with **14** to afford the second generation of dendritic diarylmethane **16** in 77% yield. The oxidation potential of dendritic diarylmethane **16** ($E_{ox} = 1.21$ V vs. SCE) is even lower than that of **15**. Dendritic structures up to the fourth generation were prepared under the same electrochemical conditions.[16]

Further extension of dendritic structures by repeating the activation and coupling sequence enabled access to dendrimers **17** and **18** (Figure 6).[17] Reaction of more than two equivalents of dendritic diarylcarbenium ion with nucleophiles bearing several reaction sites, such as terthiophene, afforded dendrimer **17**. Electrochemical reduction of dendritic diarylcarbenium ions afforded the homo-coupling product **18** via an intermediate dendritic diarylmethyl radical. The peripheral functional groups are not limited to the *para*-fluorophenyl group, and dendritic structures with other halogen atoms such as chlorine and bromine have also been prepared according to the same reaction procedure.

Figure 4. Sequential reaction of diaryl carbenium ion with diphenylmethane and allylsilane as nucleophiles.
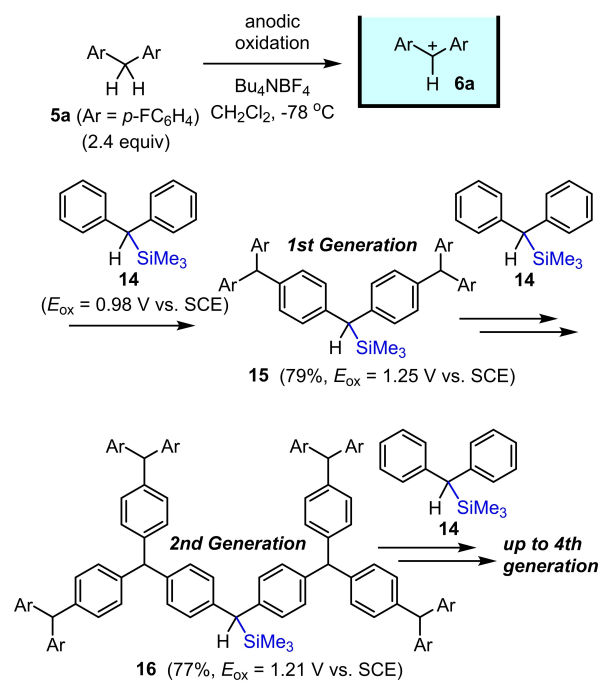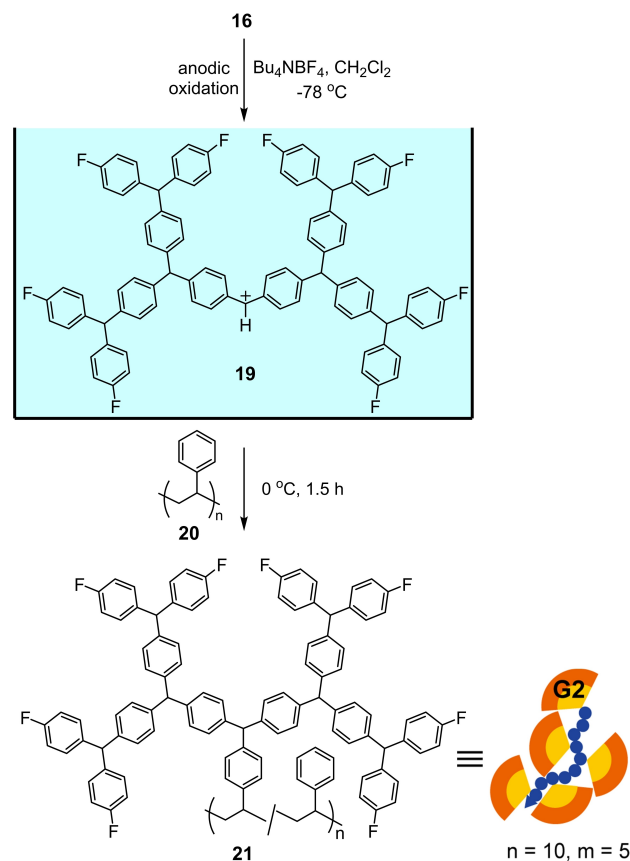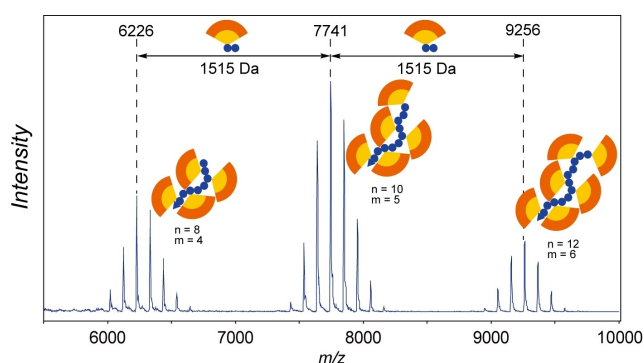

Figure 5. Iterative reaction of diarylcarbenium ion with benzhydryltrimethylsilane.
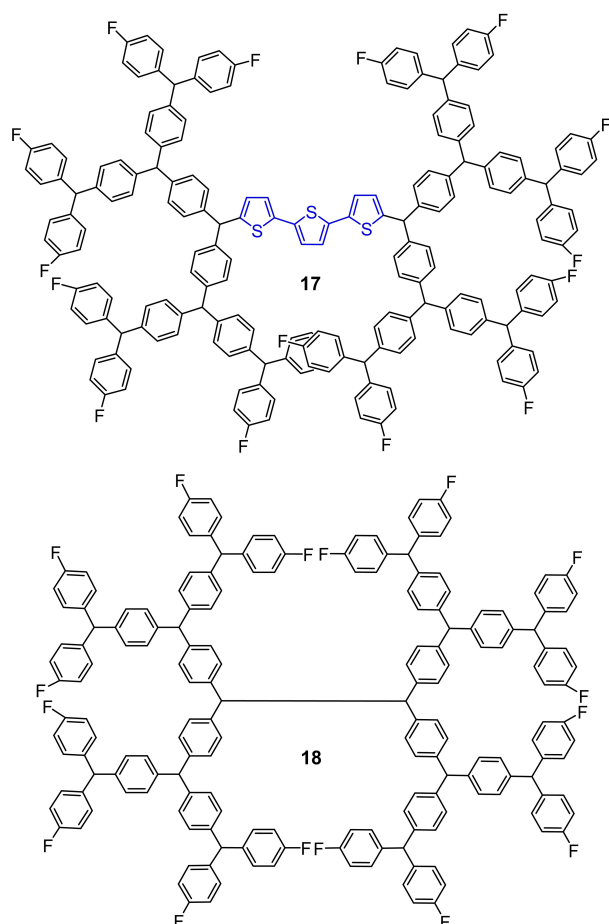
Figure 6. Dendritic structures prepared by electrochemical assembly of diarylmethanes.

Figure 7. Direct dendronization of polystyrene with dendritic diarylcarbenium ion (n: number of monomer units, m: number of dendritic substituents).

3.2. Electrochemical Synthesis of Dendronized Polymers

Dendronized polymers are polymers with dendritic substituents, and large dendritic substituents can be used to visualize a single chain of dendronized polymers.[18] Initially, we planned to prepare dendronized polymers by reacting dendritic diarylcarbenium ion with synthetic polymers bearing reactive functional groups; however, very limited numbers of dendritic substituents were introduced into the polymer. We have also been interested in direct dendronization of polystyrene (**20**) with dendritic diarylcarbenium ion **19**, because modifications of polystyrenes have been performed by applying Friedel-Crafts-type reactions (Figure 7).[19] After optimization of reaction conditions, we synthesized dendronized polymers **21** with dendritic diarylmethane structures that were detectable by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and/or atomic force microscope (AFM) (Figure 8). The mass spectra clearly showed that, on average, one dendritic substituent was introduced into every repeating unit of two styrene monomers. Peripheral


Figure 8. MALDI-TOF MS spectra of a very short dendronized polystyrene.

modification of dendronized polymer **22**, bearing *para*-bromophenyl groups at the terminal of the dendritic substituents, was performed by palladium-catalyzed reactions (Figure 9).[20] Hartwig-Buchwald amination with di(*p*-methoxyphenyl)amine (**23**) afforded dendronized polymer **24**, equipped with peripheral triarylamine moieties. Cyclic voltam-
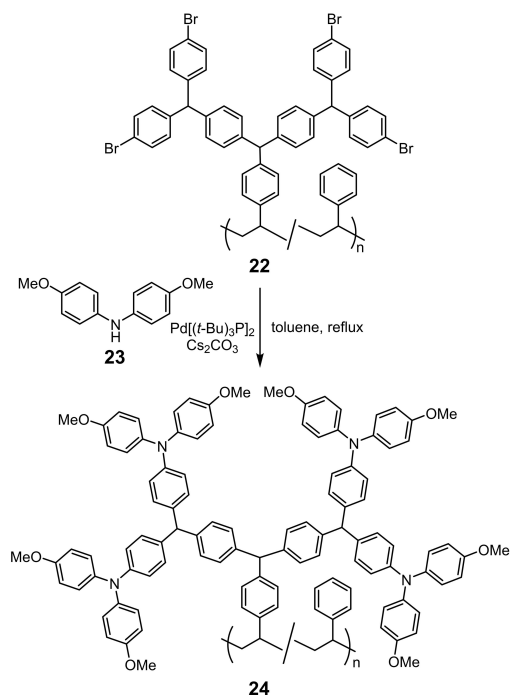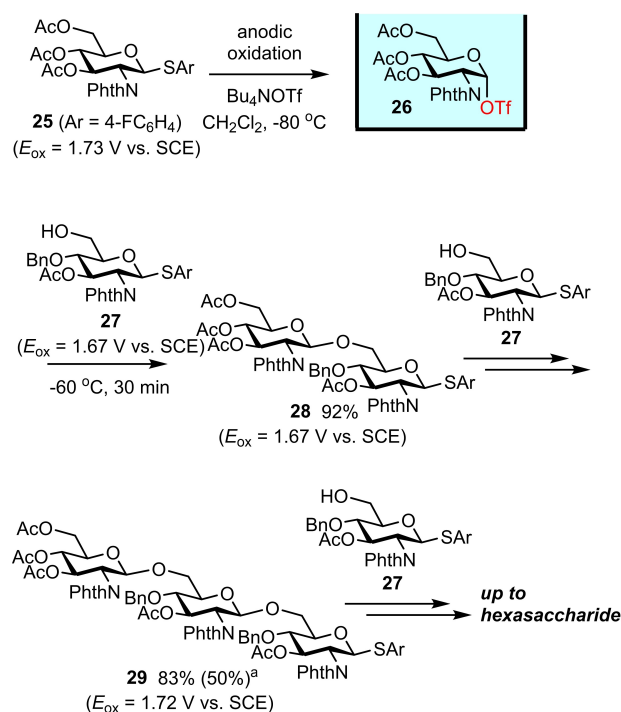
Figure 9. Peripheral modification of dendronized polymer by Hartwig-Buchwald amination.

Figure 10. Disaccharide synthesis by automated electrochemical assembly. [a]Yield of one-pot two-cycles reaction from monosaccharide **25**.

metry measurements of solutions of dendronized polymer **24** in dichloromethane showed two sets of reversible redox waves ($E_{1/2} = 0.80$ and 1.04 V vs. SCE), which might derive from redox reactions of two neighboring triarylamine groups.

4. Electrochemical Assembly for the Synthesis of Oligosaccharides

4.1. Automated Electrochemical Assembly of Oligosaccharides

The success of the electrochemical synthesis of dendronized polymers gave us the confidence to apply the electrochemical method to prepare middle-sized molecules. As a proof of principle reaction, disaccharide synthesis was performed by applying the electrochemical method in an automated manner using a synthesizer that was constructed in-house (Figure 10).[21] Electrochemical conversion of thioglycoside **25** ($E_{ox} = 1.73$ V vs. SCE) into the corresponding glycosyl triflate intermediate **26**, and subsequent reaction with thioglycoside **27** ($E_{ox} = 1.67$ V vs. SCE) afforded disaccharide **28** ($E_{ox} = 1.67$ V vs. SCE) in 92% yield. Oxidation potentials of thioglycosides **25**, **27** and **28** suggest that this synthetic transformation is possible only by applying this procedure. If thioglycoside **25** is activated in the presence of thioglycoside

27, the latter is oxidized selectively because of its low oxidation potential. Disaccharide **28** has lower oxidation potential than thioglycoside **25**. Therefore, disaccharide **28** was activated under the same electrochemical conditions and afforded trisaccharide **29** ($E_{ox} = 1.72$ V vs. SCE) by reaction with thioglycoside **27**. Further elongation of oligosaccharides via one-pot synthesis by automated electrochemical assembly enables synthesis of oligosaccharides of glucosamine up to hexasaccharide.

4.2. Synthesis of Biologically Active Oligosaccharides

To demonstrate the synthetic utility of the method, total synthesis of biologically active oligosaccharides TMG-chitotriomycin[22–24] and Myc-IV (C16:0, S) was carried out[25] (Figure 11). Although their tetrasaccharide precursors differ, automated electrochemical assembly for the synthesis of tetrasaccharide precursors **30 a** and **30 b** started from the same disaccharide **31** as a building block. The reaction conditions for disaccharide synthesis were optimized because stereo-selective synthesis of disaccharide **31** was a key step of their total syntheses (Figure 12).[26] The electrochemical glycosylation for the preparation of disaccharide **31** required a mixed-electrolyte of Bu$_4$NOTf and Bu$_4$NNTf$_2$, and increasing-selectivity for the disaccharide was observed for higher ratios of Bu$_4$NNTf$_2$ as the second electrolyte.
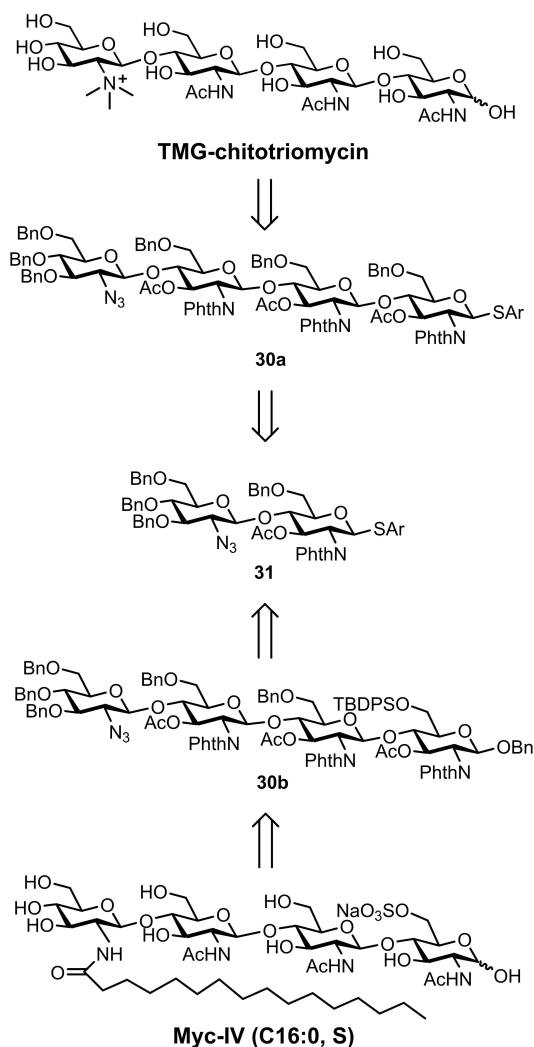
Figure 11. Structures of TMG-chitotriomycin and Myc-IV(16 C:0, S) and their retrosynthesis.
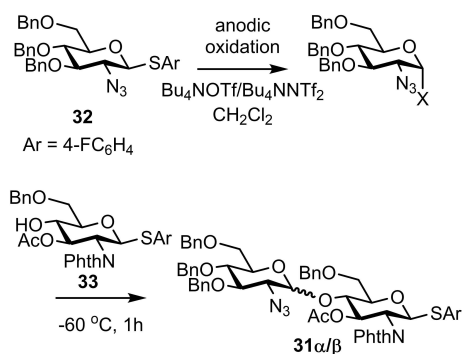
**Figure 12.** Stereoselective synthesis of disaccharide under the mixed-electrolyte conditions.

Ionic liquid tags (IL-tags), which are introduced as protecting groups of carbohydrate hydroxyl moieties, are also useful for electrochemical glycosylation.[27,28] They work not only as a separation tag, but also as electrolyte and stereo-directing group. A combination of automated electrochemical assembly and IL-tag strategy may enable rapid synthesis of complex oligosaccharides.

4.3. Synthesis of Cyclic Oligosaccharides

The successful preparation of linear oligosaccharides encouraged us to convert them into cyclic oligosaccharides by intramolecular electrochemical glycosylation (Figure 13).[29] Linear oligosaccharides **35**, with a protecting-group-free hydroxyl group, were prepared by automated electrochemical assembly and subsequent one-pot deprotection of the Fmoc group.[30] Intramolecular electrochemical glycosylation of linear oligosaccharide **35** afforded the corresponding cyclic oligosaccharide **36** in high yield with complete stereoselectivity.

5. Summary and Outlook

In this review article, we introduced two types of middle-sized molecules synthesized by electrochemical assembly. Automated electrochemical assembly of carbohydrate building blocks enables the efficient synthesis of variety of oligosaccharides;[31,32] however, the synthesis of dendritic triarylmethanes by automated electrochemical assembly has not yet been attempted. In addition to dendritic triaryl-methanes, dendritic oligosaccharides may also be synthesized
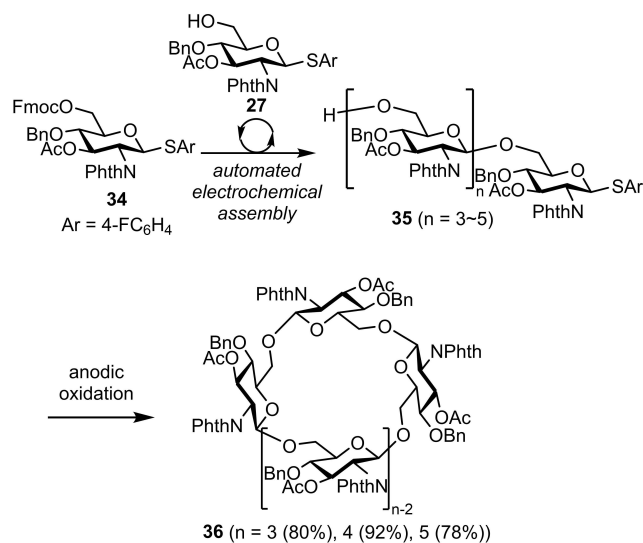
Figure 13. Synthesis of cyclic oligosaccharides via automated electrochemical assembly.

by using this method. Clearly, electrochemical assembly is not limited to the synthesis of these two types of molecules; indeed, we believe that automated electrochemical assembly could become a general method to prepare middle-sized molecules in an automated manner.

Acknowledgements

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