総 合 論 文

HYPERVALENT IODINE IN ELECTROCHEMICAL REACTIONS: ADVANTAGES AND PROSPECTS

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1．Introduction

The use of hypervalent iodine reagents in organic synthesis has regained much interest in the past decades. These reagents are non-metallic, environmentally friendly and offer a broad range of reactivities while being, at the same time, typically mild and highly efficient reagents.[1] Despite the popularity of hypervalent iodine reagents in organic synthesis, their preparation typically requires the use of an excess of expensive or hazardous oxidant. Willgerodt used elemental chlorine for the synthesis of the first reported iodine(III) compound,[2] but other oxidants such as bromates, perborates, peracids or persulfates are frequently employed in their synthesis. Ochiai and Miyamoto[3] and also Powers[4] have established that also molecular oxygen can be used to generate peracids *in situ* which can, in turn, then be used to generate iodine(III) reagents. Such a use of oxygen for iodine(III) synthesis can be very attractive, but the electrochemical generation of hypervalent iodine reagents through the anodic oxidation of iodine(I) precursors is also a highly promising alternative. Already in 1925, the first electrochemical synthesis of iodine(III) compounds has been reported,[5] but only in the last decades this methodology was further developed and is now a part of the hypervalent iodine chemists' toolbox.[6,7] In combination with other sustainable technologies, it can even further advance the area as reactions are now possible which otherwise were impossible to be performed.

2. Mechanistic Aspects

All electrochemical reactions will either proceed or will have to be initiated at the electrode surface. Early investigations on the direct oxidation of iodoarenes indicate that iodoarenes **1** must be pre-adsorbed on the electrode surface before the one electron oxidation to the radical cation **2** can proceed. This is typically the rate-limiting step. The next reaction, the addition of a nucleophilic ligand to intermediate **3** or the reaction with another arene to diaryliodonium compounds, is a fast process, which is followed by the second one-electron oxidation to the cation **4** as shown in Figure 1. Addition of another ligand completes the electrochemical generation of the iodine(III) species **5**. The cathodic half reaction is the reduction of protons rendering hydrogen as the sole by-product of the process.
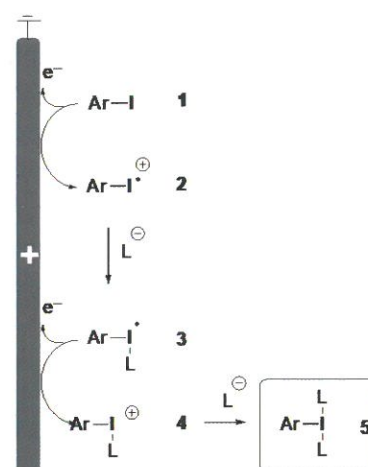

Figure 1. Electrochemical oxidation of iodoarenes on the electrode surface.

An electrochemically generated iodine(III) compound can be used in various ways. If compound **5** is stable, it can be isolated and then used. Should the compound **5** be unstable, a substrate for a next reaction could be added directly for a reaction to occur. And if **5** is generated in the presence of an electrochemically inactive substrate, the substrate can react to the product under reduction of the iodine(III) reagent, which could then be re-oxidized allowing a catalytic use of the iodoarene.

3. Electrochemical Generation of Hypervalent Iodine Reagents

3.1. Diaryliodonium Compounds

The electrochemical anodic oxidation of iodoarenes in the presence of arenes is a sustainable, single-step approach for

the synthesis of diaryliodonium compounds, which was first described by Miller and Hoffmann in 1966.[8] Using an electrochemical microreactor,[9] we have developed a flow protocol for the synthesis of diaryliodonium salts.[10] The microreactor consists of two platinum electrodes separated by a thin (250 μm) spacer. The reagent solution is being electrolyzed while passing through the channel between the two electrodes. As these reactions were performed in a first generation microreactor, the yields of symmetrical and unsymmetrical diaryliodonium compounds are not very high (Figure 2).
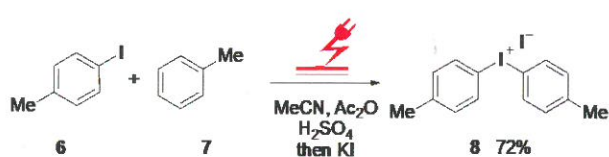

Figure 2. Flow electrochemical synthesis of diaryliodonium salts.

More recently, in a collaboration with Nachtsheim, an advanced synthetic method for the generation of cyclic iodonium compounds has been developed (Figure 3).[11]
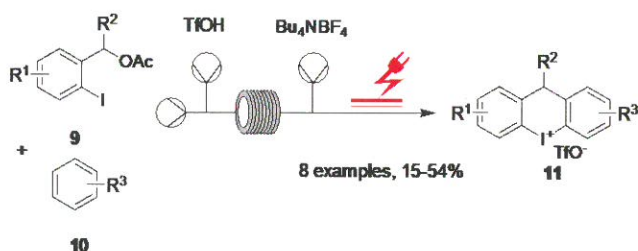

Figure 3. Flow electrochemical synthesis of cyclic iodonium compounds **11**.

In a multi-step continuous-flow procedure benzyl acetates **9** are submitted to this two-step procedure as readily available and cheap starting materials. An acid-catalyzed Friedel–Crafts alkylation with arenes **10** in the first reactor is followed by an anodic oxidative cyclization in the second electrochemical reactor, yielding cyclic iodonium compounds **11** in a highly substrate-dependent yield. Also other researchers have employed electrochemical methods for the batch synthesis of diaryliodonium salts as one class of hypervalent iodine compounds.[12,13,14]

3.2. Unstable iodine(III) reagents as intermediates

The electrochemically generated hypervalent iodine reagent [bis(trifluoroethoxy)iodo]benzene **13** (Figure 4) was introduced by the Nishiyama group as an unconventional substitute to the commercially available iodine(III) reagents such as (diacetoxyiodo)benzene.[15] Compound **13** cannot be isolated, but it's reactivity *in situ* is comparable and sometimes superior to (diacetoxyiodo)benzene, which is illustrated by its successful applications in the construction of a variety of oxygen and nitrogen-containing scaffolds such as **15**,[16] natural products and the oxidation of naturally occurring xanthone derivatives.[17]
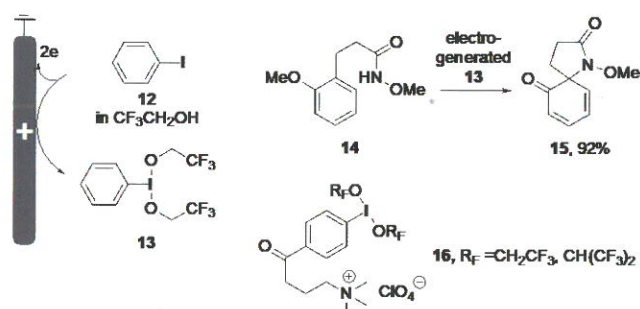

Figure 4. Electrochemical generation of the hypervalent iodine reagent **13** and its application in spirocyclization.

Francke *et al.* published a recyclable iodine(I)/iodine (III) redox mediator for electrosynthesis.[18] An ionically tagged aryl iodide (Figure 4) is electrochemically oxidized either in the presence of trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to the corresponding hypervalent iodine reagents **16**. The ionic substituent in **16** facilitates the recovery and recycling in addition to eliminating the need of supporting electrolytes. Also different iodoarenes with ionic substituents have been feveloped by the Francke group recently and applied in synthesis.[19]

Based on these discoveries, we have developed an efficient and reliable electrochemical generator of hypervalent iodine reagents.[20] In an electrochemical flow reactor, the anodic oxidation of iodoarenes under flow conditions proceeds to hypervalent iodine reagents. Unstable hypervalent iodine reagents can be prepared easily and coupled with different substrates to achieve oxidative transformations in high yields. Shown in Figure 5 are sulfide oxidations and α-functionalizations of ketones. The unstable electrochemically generated reagents can also easily be transformed into classic bench stable hypervalent iodine reagents such as [bis(trifluoroacetoxy)]iodobenzene *via* ligand exchange.
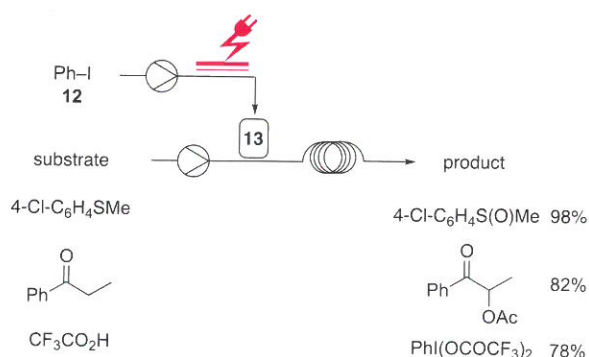
Figure 5. Continuous flow electrochemical generator of hypervalent iodine reagents: Synthetic applications.

The combination of electrochemical and flow chemistry advantages largely improves the ecological footprint of the overall process compared to conventional approaches. A similar approach was later also reported by He where the synthesis of hypervalent iodine(III) compounds has been performed in batch mode.[12]

3.3. Hazardous iodine(III) difluoride reagents as intermediates

The principle of generating unstable hypervalent iodine compounds in flow systems has been extended by us to iodine(III) difluorides. Iodine(III) difluorides are toxic and suffer from chemical instability, so the uninterrupted generation and immediate use in flow is highly advantageous. The electrochemical oxidation of iodoarenes to the corresponding difluorides has been already reported by Fuchigami in 1994.[21] This concept has been applied by the Waldvogel[22] and Lennox[23] groups for batch electrosynthesis, where the generation of iodine(III) difluorides is performed in the presence of the substrate (Figure 6).
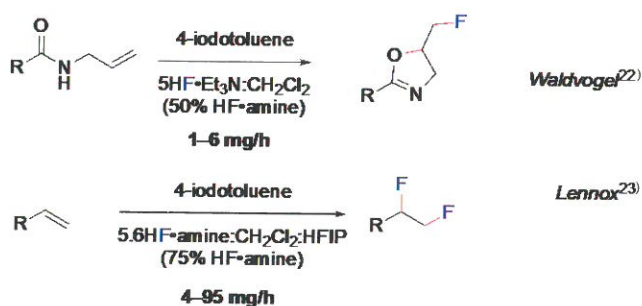

Figure 6. Batch electrochemical synthesis and use of iodine(III) difluorides.

Based on our previous research, we have developed a flow chemical synthesis of iodine(III) difluorides and their

direct use in fluorination reactions.[24] The flow synthetic approach allowed to increase yields in shorter reaction times as shown exemplary with products **17**–**19** (Figure 7). The spatial separation of electrochemical generation of iodine(III) difluorides and the fluorination reaction of substrates in the flow system allowed also the synthesis of products which could not be accessed in the batch process, some of these examples are also shown in Figure 7. High flow rates facilitated productivities of up to 834 mg h^{-1} with vastly reduced reaction times. Fluorocyclization to **20** and fluorination to **21** are only possible in flow as the products decompose under electrolysis reaction conditions. The addition of iodine directly after the reaction with the iodine(III) difluoride is also only possible in flow, therefore new products such as the fluoroiodoalkene **22** is obtainable from the corresponding alkyne. In addition, the productivity of the flow process is much higher than the productivity of the batch process and much more material can be obtained in the same amount of time. Even the isolation of iodine(III) difluorides was facile (not shown here) since electrolysis was performed in the absence of other reagents. Furthermore, integration into a fully automated machine and in-line quenching was key in reducing the hazards surrounding the use of hydrofluoric acid.
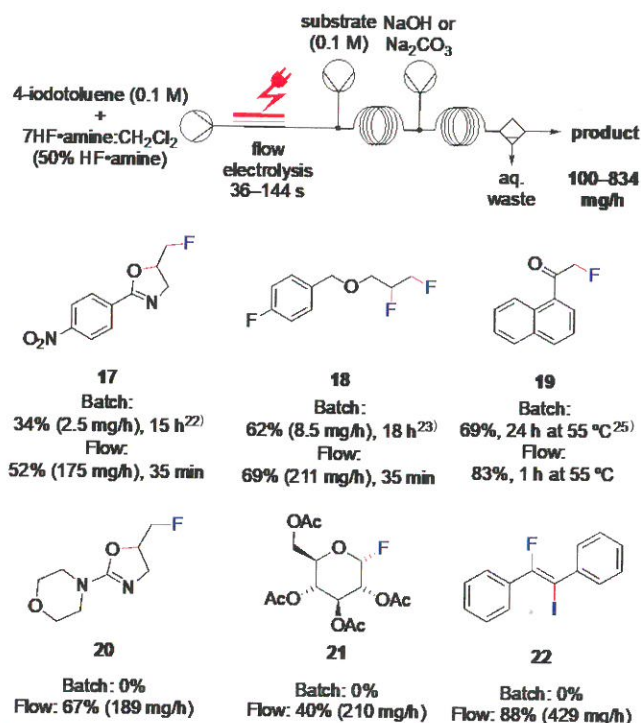

Figure 7. Flow electrochemical synthesis and use of iodine(III) difluorides.

3.4. Stereoselective synthesis with electrogene rated chiral iodine(III) reagents

We have reported the first use of chiral iodine(I) precursors for the electrochemical generation of chiral iodine(III) reagents. The enantioselective electrochemical α-lactonization of diketo acids using chiral iodoarenes as redox mediators led to the formation of products **23** in up to 71% *ee* (Figure 8). Adapting this enantioselective process in an electrochemical flow microreactor has also been demonstrated with the use of catalytic amount of supporting electrolyte.[26]
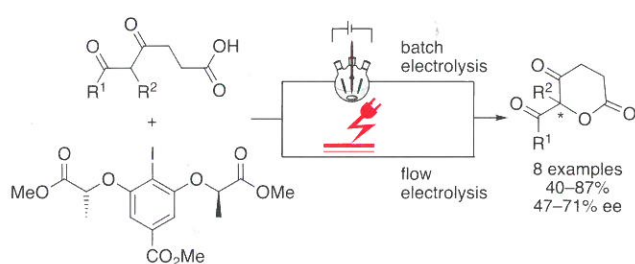

Figure 8. Electrochemical synthesis of chiral iodine(III) reagents for stereoselective synthesis.

3.5. Electrocatalysis with iodine(III) reagents

The electrocatalytic hydroxylation of arenes with a rhodium catalyst and the use of iodine(III) reagents was reported by Ackermann.[27] The reaction is taking place in an undivided cell and provides high yields of the reaction products. The rhodium catalytic cycle (not shown) has been investigated in detail in which the rhodium catalyst is re-oxidized with electrogenerated [(bistrifluoroacetoxy)iodo]-benzene (Figure 9).
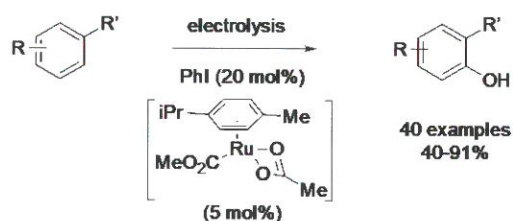

Figure 9. Rhoda-electrocatalyzed phenol synthesis.

Moran and Elsherbini have very recently disclosed some further developments towards iodine(I) / iodine(III) catalytic processes in which cyclizations and α-oxytosylations (not shown) have been investigated (Figure 10).[28]
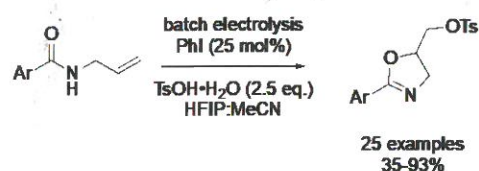

Figure 10. Batch electrochemical synthesis with iodine(III) catalysis.

4. Conclusions and Outlook

The main part of research efforts for a long time have been concerned with the electrochemical generation of iodine(III) reagents, only recently more detailed studies on the electrogeneration of iodine(V) compounds have been published.[29] A divided cell setup was employed to oxidize IBA to IBX in a safe and very efficient manner on an analytic scale, the development of a preparative scale electrolysis is still missing. Further developments on stereoselective reactions using electrogenerated iodine(III) reagents are currently ongoing. The approach of electrochemically generating hypervalent compounds can also be extended to the corresponding hypervalent bromine derivatives as several recent publications have impressively demonstrated.[30,31]

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