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Electrosynthesis Using a Recyclable Mediator–Electrolyte System Based on Ionically Tagged Phenyl Iodide and 1,1,1,3,3,3-Hexafluoroisopropanol

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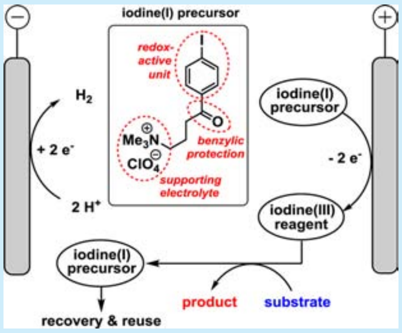
Supporting Information

ABSTRACT: A new type of redox mediator for electrosynthesis based on the iodine(I)/iodine(III) redox couple is reported. It is demonstrated that the use of 1,1,1,3,3,3-hexafluoroisopropanol as solvent plays a crucial role for both the selective anodic generation of the active iodine(III) species and the subsequent chemical transformation. Furthermore, the supporting electrolyte is merged with the mediator by tethering the redox-active iodophenyl moiety to an alkylammonium group, allowing for straightforward recovery and reuse of both components.

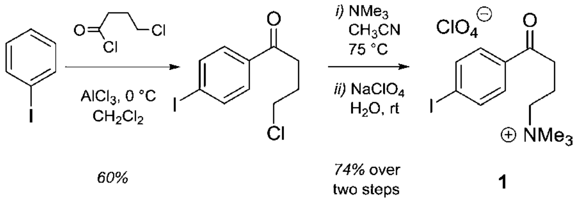


The electrochemical conversion of organic compounds (electroorganic synthesis) is considered to be a well-established and useful method in organic synthesis.[1−5] Among several other advantages, it is recognized as a safe and environmentally friendly methodology since dangerous and toxic redox reagents can be replaced by electric current or generated in situ in the course of electrolysis.[6−8] Despite the substantial progress that has been made, the potential of organic electrosynthesis has yet to be fully exploited and expressed. This is in part due to the fact that the necessity for excess amounts of supporting electrolyte constitutes a severe drawback.[9,10] Thus, following the completion of a reaction, the supporting electrolyte must be separated from the reaction mixture. Unless it is recovered and reused, it constitutes a source of waste. Due to their good solubility in organic solvents and high electrochemical stability, tetraalkylammonium salts are often employed.[11,12] However, the good solubility often leads to difficulties with separation of the salts from the products after the reaction has completed. A further separation issue is caused by the use of redox mediators. Such mediators are often employed to facilitate electron transfer between electrode and substrate and to influence the selectivity of the electrosynthetic process.[13] Since both the supporting electrolyte and the mediator represents a source of waste and a key-expense factor, their recovery and reuse for multiple cycles is highly desirable for industrial applications.[14,15]

In conventional organic synthesis, hypervalent iodine compounds represent a powerful and versatile class of reagents with applications in C−C, C−Het, and Het−Het bond forming reactions,[16−20] rearrangements[21,22] and as terminal oxidants in transition metal catalyzed transformations.[23,24] Instead of the stoichiometric use of iodine(III) reagents, their electrochemical in situ generation represents an intriguing alternative. In this context, Wirth et al. have accomplished the electrosynthesis of diaryliodonium salts using a flow microreactor.[25] However, only few cases of their use as mediators in electrosynthesis have been reported thus far, namely, in the anodic partial fluorination in $NR_3 \cdot nHF$-based ionic liquids (Fuchigami et al.)[26−28] and in the context of intramolecular C−N bond forming reactions in 2,2,2-trifluoroethanol (Nishiyama et al.).[29,30]

In the context of the aforementioned separation issues and the yet unlocked potential of the iodine(I)/iodine(III) redox couple with regard to electrosynthesis, we developed a mediator based on compound **1** (see Scheme 1) containing a 4-iodophenyl moiety as redox-active unit, which is tethered to a quaternary ammonium group. The latter one serves both to provide ionic conductivity (supporting electrolyte) and to facilitate separation and reuse of the redox-active salt after completed conversion with a substrate according to Scheme 2. Our elaborated synthesis provides convenient access to **1** in three scalable steps from inexpensive starting materials (phenyl iodide and 4-chloro

Scheme 1. Synthesis of the Redox-Active Supporting Electrolyte 1



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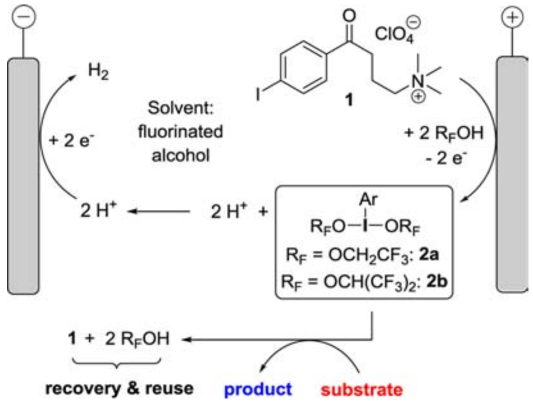
Scheme 2. Concept for the Electrochemical Generation of an Iodine(III) Species and the Subsequent Use for Chemical Transformations



butyryl chloride) without the use of column chromatography (Scheme 1, for details see Supporting Information (SI)).

For several reasons we targeted fluorinated alcohols as solvents for the mediated electrochemical process depicted in Scheme 2. First, fluorinated solvents such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or 2,2,2-trifluoroethanol (TFE) are known to have excellent electrochemical properties such as high conductivity and excellent anodic stability (provided that an appropriate supporting electrolyte is employed).[31] Second, the alcohol is expected to play an active role in the electrochemical generation of the active form of the mediator by stabilizing iodine(III) (structure **2** in Scheme 2). Furthermore, fluorinated alcohols exhibit a positive influence on the rate and selectivity of transformations containing radical and/or ionic intermediates[32,33] and are therefore frequently employed in iodine(III)-mediated reactions.[34−36] Finally, selective proton reduction is feasible as cathodic half-reaction due to the relatively low pK_a values of fluorinated alcohols, rendering H_2 as the only byproduct of the electrochemical process.

In order to study the feasibility of the process depicted in Scheme 2, we started with cyclic voltammetry of **1** (2 mM) in TFE (Figure 1, top, red line) and HFIP (Figure 1, bottom, red line), each solution containing 0.1 M NBu_4ClO_4 as supporting electrolyte. In both media, **1** is irreversibly oxidized at similar peak potentials E_P (2.12 V in TFE and 2.16 V in HFIP, all potentials referenced vs $Ag/AgNO_3$). Whereas in TFE this anodic wave is superimposed with a further process, a selective oxidation is observed in HFIP. The origin of this difference becomes obvious upon considerations of the CVs of the blank electrolytes (Figure 1, blue lines): Whereas the electrolyte based on TFE is already significantly degraded at E_{lim} = 2.04 V (with an arbitrary stability criterion defined as j_{lim} = 0.1 mA cm^{-1}), the HFIP-based electrolyte is about 0.6 V more stable toward anodic oxidation (E_{lim} = 2.65 V). Consequently, the Faradaic efficiency for the oxidation of **1** is generally lower in TFE than in HFIP, and therefore, we directed subsequent studies toward the use of the latter solvent.

The results depicted in Figure 1 allow for a further conclusion with regard to the use of **1** as mediator: Due to the relatively high redox potential of the **1**/**2b** couple, most of the substrates of interest have to be added to the electrolyte after completed anodic conversion of **1** to **2b** ("ex-cell process").[13] In contrast, a continuous regeneration of iodine(III) in a one-pot approach ("*in-cell* process") would lead to direct anodic oxidation of the substrate.

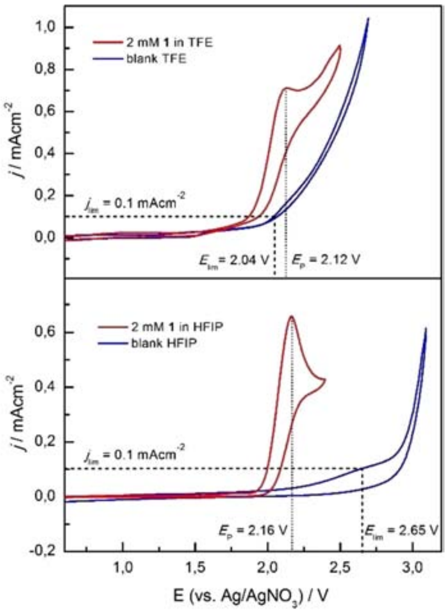


Figure 1. Cyclic voltammetry of mediator **1** (2 mM) in TFE (top) and HFIP (bottom). The voltammograms for the blank electrolytes are inserted for comparison (blue lines). Working electrode, glassy carbon; supporting electrolyte, 0.1 M NBu_4ClO_4; reference electrode, Ag/0.01 M $AgNO_3$ in 0.1 M NBu_4ClO_4; scan rate, 10 mV s^{-1}.

We continued our studies with solubility tests and conductivity measurements and found that **1** is soluble in HFIP at concentrations well above 1 M. In contrast, the salt is only sparsely soluble in polar aprotic organic solvents such as acetone or acetonitrile and almost insoluble in less polar solvents such as ethyl acetate and alkanes. This solubility behavior is beneficial for the recovery of **1** from product mixtures and allows for straightforward separation procedures (*vide infra*). With regard to ionic conductivity, **1** exhibits a behavior comparable to $LiClO_4$, a frequently used supporting electrolyte in electroorganic synthesis. For example, a 0.5 M solution of **1** in HFIP renders a conductivity σ of 1.9 mS cm^{-1} (compared to 2.3 mS cm^{-1} for a $LiClO_4$ solution of the same concentration; a plot of σ vs concentration is depicted in the SI). We note that this observation is of fundamental importance with regard to cell voltage and energy efficiency of the electrolysis since **1** is supposed to serve both as supporting electrolyte and mediator.

We then proceeded with the exploration of the reactivity and the identity of the species formed upon anodic oxidation of the phenyl iodide derivative. As a proof of the concept presented in Scheme 2, we added hydroquinone to a pre-electrolyzed solution of **1** in HFIP (undivided cell, no additional supporting electrolyte) and found quantitative conversion to 1,4-benzoquinone after approximately 15 min stirring at room temperature. Remarkably, no decomposition products were detected after completed reaction, and mediator salt **1** was almost fully recovered by a simple solid phase extraction. However, the characterization of the active iodine species turned out to be less straightforward. Whereas the oxidation product of **1** is stable in HFIP for several days (more details: see SI), the active species slowly decomposes as soon as HFIP is removed, and our attempts for isolation and the usual characterization were therefore unsuccessful. ^1H NMR spectroscopy of an electrolyzed solution of **1** in HFIP (20 vol % $CDCl_3$ added) reveals an additional set of aromatic signals with a downfield displacement, consistent with the selective formation of a more electron-

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deficient iodine(III) species (see Figure 2; for full ^{1}H and ^{13}C spectra see SI). On the basis of this observation, the ^{19}F NMR spectrum (single signal at −75.2 ppm, see SI) and the general preference of iodine(III) toward a T-shaped structure with a trans configuration of the electron withdrawing substituents[18,19] we propose structure **2b** (Scheme 2) for the anodically generated species.

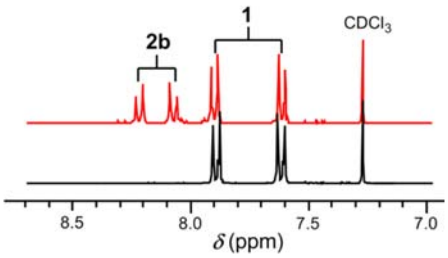
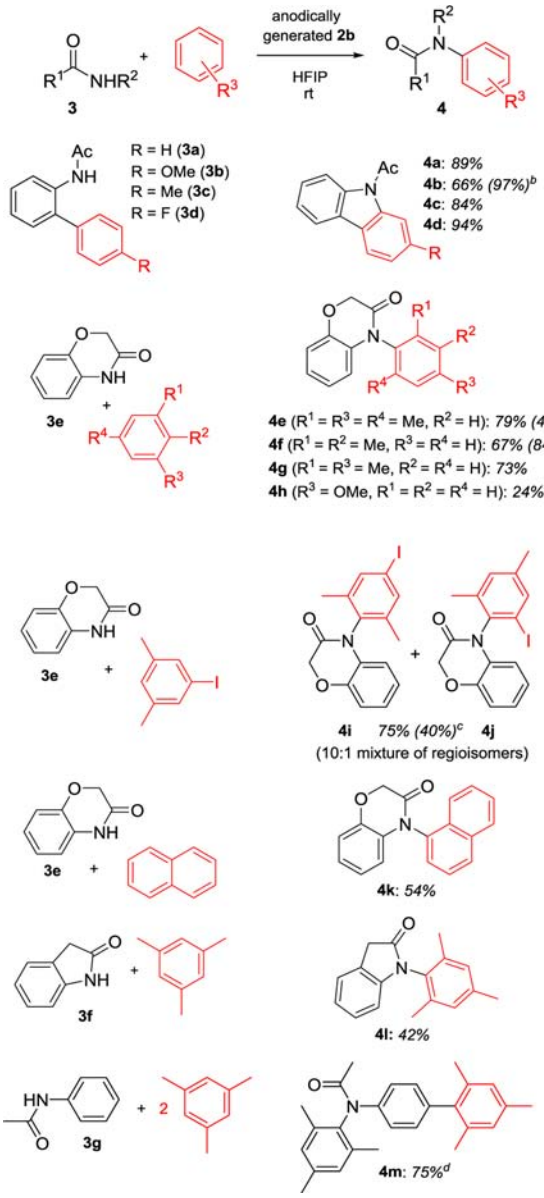


Figure 2. Aromatic range of the ^{1}H NMR spectrum of a solution of **1** in HFIP (20 vol % $CDCl_3$ added) after electrolysis (red line) and prior to electrolysis (black line).

Monitoring the conversion of **1** to **2b** in HFIP via ^{1}H NMR spectroscopy, we optimized the electrolysis conditions with regard to electrode material, concentration of **1**, and current density (see SI). We found that an optimum Faradaic efficiency of 70% is achieved when a glassy carbon working electrode in combination with a platinum counter electrode is used in an undivided cell applying a current density of 15 mA cm^{-2} (0.2 M solution of **1** in HFIP). With these optimized parameters in hand, we proceeded with investigating the scope of applications, starting with direct oxidative C–N bond forming reactions, which have been previously reported in the context of other hypervalent iodine reagents. With regard to our focus on the electrochemical construction of heterocycles,[37] we were particularly interested in the synthesis of *N*-acetyl carbazoles **4a–d** via intramolecular cyclization of 2-(*N*-acetylamino)-biphenyls **3a–d** (see Scheme 3). Similar transformations of biaryls to carbazoles have been previously reported using $PhI(OAc)_2/Pd(OAc)_2$,[38] $PhI(OAc)_2/Cu(OTf)_2$,[39] and under metal-free conditions with $PhI(OCH_2CF_3)_2$.[29] In our case, the carbazole formation proceeds cleanly upon addition of **3** to the electrolyzed solution of **1** in HFIP. During the electrolysis, 3 equiv of charge per mol **3** (3 F mol^{-1}) are passed, which corresponds to 1.05 equiv of active species **2b** (2e$^-$ oxidation, 70% Faradaic efficiency). After addition of **3** to the electrolyte and stirring for 21 h at room temperature, **4a–d** are obtained in 66–94% isolated yield. A limitation of the scope is represented by biphenyl substrates bearing electron withdrawing substituents. For R = CN, only 4% conversion could be observed after 24 h reaction time (determined via ^{1}H NMR spectroscopy). We also note that direct anodic cyclization is not possible. The electrolysis of **3a–d** in HFIP containing 0.1 M NBu_4ClO_4 in absence of mediator **1** (j = 15 mA cm^{-2}, 2 F mol^{-1}) leads to a complex reaction mixture with no detectable amounts of cyclization product **4a–d**. In all cases presented in Figure 3, both the solvent HFIP and **1** were almost entirely recovered. Whereas HFIP is removed from the reaction mixture by distillation, the mediator can be isolated in analytical purity by dissolving the remaining solid in acetone and precipitation upon cooling and addition of ether (recovery typically >95%).

Scheme 3. Intra- and Intermolecular C–N Bond Forming Reactions Using Electrolyzed Salt 1 in HFIP[a]



[a] Reaction conditions: Addition of **3** (and 10 equiv of arene in the case of intermolecular coupling) to 10 mL of pre-electrolyzed solution of **1** (0.2 M) in HFIP (charge passed: 3 F per mol **3**). Stirring of reaction mixture at room temperature. Isolated yields. [b] Yields based on recovered starting material. [c] Only 2 equiv of arene were employed. [d] Charge passed: 6 F per mol **3**.

Upon further exploration of the substrate scope, we found that the procedure is also applicable to intermolecular oxidative C–N coupling between 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**3e**) and methyl-substituted arene compounds (see Scheme 3), a reaction type that has been previously reported in the context of the $PhI(OAc)_2$ reagent.[40] Thus, addition of **3e** and 10 equiv of mesitylene, *o*-xylene, or *m*-xylene to electrolyzed **1** in HFIP render **4e**, **4f**, and **4g** in 67–79% yield. We note that decreasing the amount of arene to two equiv leads to significantly lower yields of the C–N coupling product (see footnote c in Scheme 3). A limitation of the scope is represented by methoxy-substituted arene components: Application of our protocol to **3e** in combination with anisole, 1,2-dimethoxybenzene, and 1,3,5-trimethoxybenzene renders complex reaction mixtures in each case, whereby the amide component remains mostly unaffected (reaction monitored using TLC and GCMS). Only in the case of anisole, a small amount of the desired C−N coupling product was detected and isolated (**4h**, 24% yield). Interestingly, iodo moieties are tolerated by our procedure: When 1-iodo-3,5-dimethylbenzene is used as arene component, coupling products **4i** and **4j** are obtained as a mixture of regioisomers (10:1) in 75% yield. Furthermore, we found that **3e** can also be coupled to naphthalene, rendering **4k** in 54% yield.

In contrast to **3e**, 2-indolinone (**3f**) appears to be a less suitable candidate for this type of transformation since reaction with mesitylene renders the corresponding coupling product **4l** in only 42% yield after 18 h at room temperature (compare to 79% for **4e**). Interestingly, the conversion of mesitylene with acetanilide (**3g**) leads to a different outcome: In this case, the application of our standard conditions leads regioselectively to both C−N and C−C bond formation, rendering diarylation product **4m** in 75% yield. A similar reactivity has been observed before by Antonchick et al. in an analogous nonelectrochemical transformation using stoichiometric amounts of the 4-MeC$_6$H$_4$I-(OAc)$_2$ reagent.[41]

In conclusion, we developed a new type of redox mediator for electrosynthesis based on the iodine(I)/iodine(III) redox couple in HFIP as solvent. By tethering the iodophenyl component to an alkylammonium moiety we integrated supporting electrolyte and mediator, which allows for straightforward recovery and reuse of both components in a single step. This mediator−salt concept was successfully applied to several direct oxidative C−N and C−C coupling reactions, whereby H$_2$ represents the only generated byproduct and reagent waste is avoided. We are currently exploring further applications for this new system, including mechanistic studies and attempts for the direct proof of structure **2b**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02979.

> Experimental details, characterization of compounds, optimization of reaction parameters, and conductivity measurements (PDF)

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Notes

The authors declare no competing financial interest.

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