Electrochemical Synthesis of Fluorinated Orthoesters from 1,3-Benzodioxoles

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A scalable, dehydrogenative, and electrochemical synthesis of novel highly fluorinated orthoesters is reported. This protocol provides easy and direct access to a wide variety of derivatives, using a very simple electrolysis setup. These compounds are surprisingly robust towards base and acid with an unusual high lipophilicity, making them interesting motifs for potentially active compounds in medicinal chemistry or agro applications. The use of electricity enables a safe and environmentally benign chemical transformation as only electrons serve as oxidants.
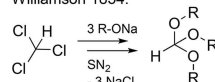
The orthoester is an extremely versatile structural feature, used as a protective group for esters[1] in peptide synthesis[2] and for alcohols in nucleoside synthesis.[3] This functional group is vital for transformations such as the Claisen-Johnson rearrangement,[4] the synthesis of a variety of nitrogen-based heterocycles[5] and various condensation reactions.[6] Orthoesters were first prepared via conversion of chloroform with alcoholates by Williamson and Kay in 1854.[7] This route generates a large amount of salt waste and results in low yields.[8] A common alternative is the Pinner route to orthoesters involving conversion of nitriles with alcohols in the presence of strong acids.[9] Hydrogen cyanide is often used in these reactions, which should be avoided. Additionally, a large amount of waste is generated. This can be avoided using an electrochemical approach, which was developed in 2000 by Fischer et al. at BASF.[10] This process is particularly suitable for the preparation of methyl orthoformate, from 1,1,2,2-tetramethoxy-ethane via anodic oxidation. Additionally, orthoesters can be synthesized using the Hofer-Moest reaction, a Kolbe-type electrolysis. This reaction leads to high yields ($\geq 95\%$) and can

also be applied to a broader variety of substrates compared to the Pinner approach. However, this reaction only proceeds with aliphatic moieties in the position β to the carboxylic acid (R^2, Scheme 1).[11] First reports on the direct anodic conversion of 1,3-benzodioxoles was given by Thomas et al.[12] The installation of the methoxy moiety at the heterocyclic skeleton could be achieved. However, the reaction is limited to a narrow scope. Only a few substrates with substituents on the aromatic system are tolerated. Furthermore, the setup for the electrolytic conversion is not straightforward, since carbon dioxide has to be applied and the reaction is carried out with cooling to $10\,°C$. The use of expensive platinum electrodes incorporates an additional disadvantage (Scheme 1).

Here, a scalable electrosynthetic method towards novel highly fluorinated orthoesters is presented. These molecules are a new class for potentially biologically active compounds with a high lipophilicity (Scheme 1).[13] LogP values were found to increase dramatically compared to those of the corresponding substrates, while the volatility remains almost the same like the
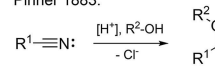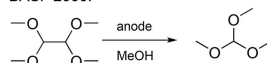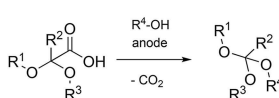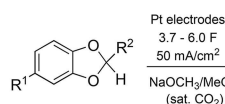
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Scheme 1. Synthetic strategies to orthoesters.

starting materials (see SI). Furthermore, this reaction allows the lipophilicity to be modulated via the installation of various highly fluorinated side-chains in the difficult-to-address position 2 of 1,3-benzodioxoles. These products proved to be surprisingly inert towards acids and bases, suggesting they are amenable to further functionalization or applicable in active ingredients. A broad substrate scope is tolerated (Scheme 2–4), providing access to a wide variety of derivatives in moderate yields. Graphite, glassy carbon, or boron-doped diamond (BDD) can be used as electrode material and no additional supporting electrolyte is needed. The constant current electrolysis is carried out in a simple undivided electrolytic cell at room temperature with the corresponding alcohols as solvent. This simple reaction
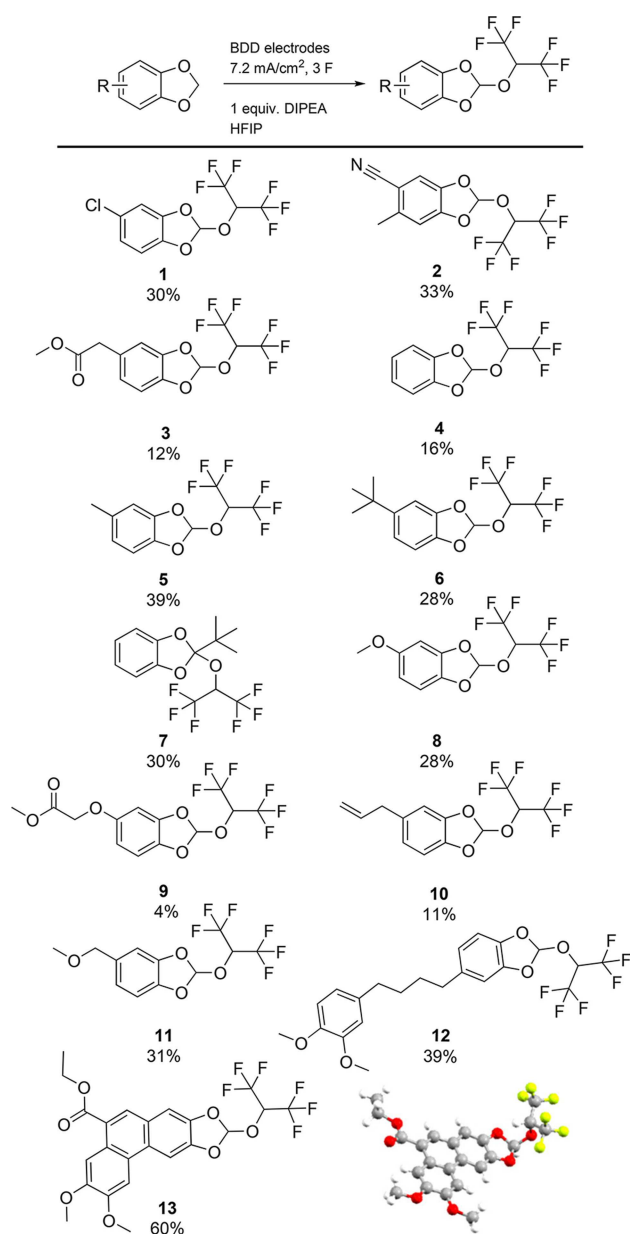
Table 1. Constant current electrolysis of 5-chloro-1,3-benzodioxole **1** (0.5 mmol) was performed in HFIP/TFE (5 mL) and 1.0 equiv. of a base (DIPEA/DBU) in an undivided Teflon cell. Isolated yields. BDD: Boron-doped diamond.

Entry	Current density [mA/cm^2]	Anode	Charge [F]	Yield **1** [%]
1	1.0	BDD	3.0	0
2	15	BDD	3.0	24
3	90	BDD	3.0	23
4	7.2	BDD	2.2	19
5	7.2	BDD	2.8	26
6	7.2	BDD	4.0	13
7	**7.2**	**BDD**	**3.0**	**30**
8	7.2	Graphite	3.0	23
9	7.2	Glassy carbon	3.0	27
10	7.2	Mo	3.0	0

setup makes this reaction easily scalable and therefore particularly attractive for technical applications.

Electrochemistry is an attractive concept in performing organic synthesis, because it can potentially diminish the amount of reagent waste, plus renewable energy can be used to contribute to more sustainable conversions.[14] The use of fluoroalcohols (in particular 1,1,1,3,3,3-hexafluoropropan-2-ol, HFIP) in electrosynthesis has major advantages, as it modulates the reactivity of intermediates,[15] and has an exceptional solvent microhetero-geneity.[16] This has been recently demonstrated by conversion of electrogenerated HFIP ethers with nucleophiles towards diarylmethanes[17] and 2-phenylacetonitriles.[18] We have also developed efficient electrochemical C–N, S–S, C–C, and N–N coupling reactions involving phenols,[19] anilides,[20] and dianilides as substrates.[21]

By electrosynthetic screening, the ideal reaction conditions such as concentration, electrode material, applied charge and current density were identified (Table 1).[22] The screening experiments were performed with 5-chloro-1,3-benzodioxole (**1**) as test system. Optimal reaction conditions were achieved when working with BDD electrodes at a concentration of 0.1 mol/L and an applied charge of 3.0 F. When more charge was applied, the respective orthocarbonates were observed as by-products, resulting in lower yields (Table 1, Entry 6). The optimal current density identified was 7.2 mA/cm^2. (Table 1, Entry 7). It should be noted that the protocol is very robust, since the yield remains almost unchanged up to a current density of 90 mA/cm^2 (Table 1, Entry 3). Inexpensive electrode materials can also be used, such as glassy carbon or graphite (Table 1, Entries 8 and 9). However, BDD is slightly superior. Sufficient conductivity was achieved, when using 0.02 vol% of *N,N*-diisopropylethylamine (DIPEA) consequently no additional supporting electrolyte is needed.[17] In addition, the concentration played an important role, as increased oligomerization was observed on the electrodes at higher concentrations (see SI).

Electrochemical functionalization with HFIP was achieved in yields up to 60%. Various functional groups are tolerated. Substrates carrying an electron-withdrawing substituent such as halogen or nitrile (**1**, **2**) can be converted in yields up to 33%. The yields were significantly lower for substrates involving

Scheme 2. Scope of the reaction with HFIP. Electrolysis was carried out in HFIP (5 mL) with 0.5 mmol substrate, 0.02 vol% of DIPEA, using BDD electrodes and 3.0 F at 7.2 mA/cm^2 in an undivided cell. Molecular structure (based on X-ray crystallography) of **13** is displayed. Isolated yields are given.

phenyl-acetates (**3**), allylic groups (**10**), or methoxyacetates (**9**). The unsubstituted 1,3-benzodioxole undergoes the reaction in 16% yield (**4**). Electron-releasing groups such as alkyl- (**5–7**) and methoxy groups (**8**) were also tolerated. Interestingly, benzylic positions (**5**) were not oxidized to the corresponding HFIP ethers.[17] Sterically demanding groups such as *tert*-butyl groups in 2- and 4-positions had no significant influence onto the yields (**6**, **7**). Substrates carrying a second aromatic system also formed the desired products (**12**). Substrates involving larger π systems form the corresponding 2-alkoxy-1,3-benzodioxoles in enhanced yields (**13**, **21**) (Scheme 2).

This can be rationalized upon analysis of the mechanism: First, a radical cation is generated, which undergoes the loss of a proton and a further oxidation step to a 1,3-benzodioxolium species. This cation will be trapped by a HFIP anion. Larger π systems can stabilize these cations and avoid unwanted side reactions (Scheme 3).

The proposed mechanism is supported by cyclic voltammetry (Figure S4 and Figure S5 in SI) and the anticipated 6π aromatic intermediates were isolated as BF_4^--salts and spectroscopically investigated by NMR.[23] We also found that the addition of base plays a crucial role.

Subsequently, we investigated the starting material in HFIP without any base and MTBS as supporting electrolyte. We found that this electron transfer process to the radical cation is reversible (Figure 1).

Afterwards, we added base to this solution and found that the process is now irreversible, due to the subsequent deprotonation reaction and we can again observe the two

irreversible oxidation steps ($E_{ox1} = 1.17$ V *vs* Fc/FcH$^+$, $E_{ox2} = 1.52$ V *vs* Fc/FcH$^+$) (Figure 2). This confirms our assumption that initially an oxidation step to a radical cation and then a deprotonation step occurs.

The reaction could be applied to other fluorinated alcohols, such as 2,2,2-trifluoroethanol (TFE) or, 2,2,3,3,4,4,5,5-octafluoro-pentan-1-ol. Therefore, stronger bases like 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and 1,8-bis(dimethylamino)naphtha-lene, are required in order to achieve sufficient conductivity. It was possible to convert the 1,3-benzodioxoles to TFE orthoesters in slightly lower yields, compared to the HFIP orthoesters. However, the trends are similar. Larger π systems also resulted in enhanced yields (**21**, 37%) (Scheme 4). Recently, an electro-
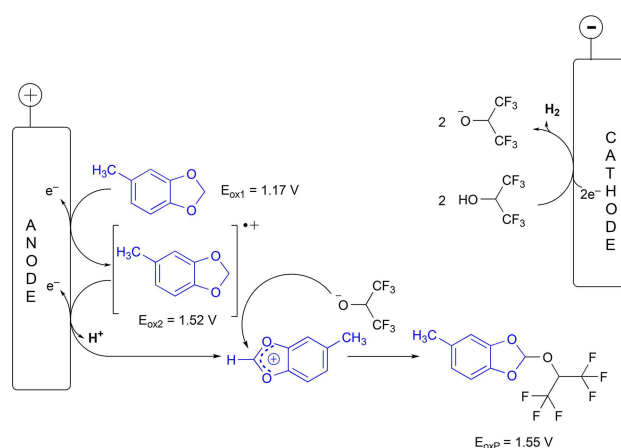
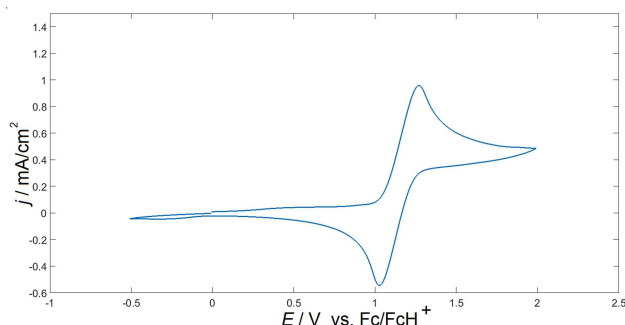**Scheme 3.** Proposed mechanism for the formation of orthoesters.

Figure 1. Cyclic voltammogram of a 5 mM solution of 5-methyl-1,3-benzo-dioxol in HFIP/MTBS at 50 mV/s.
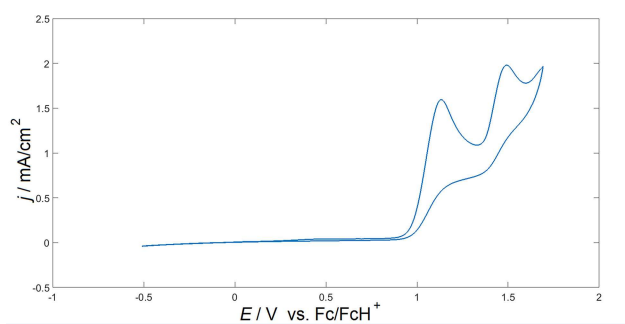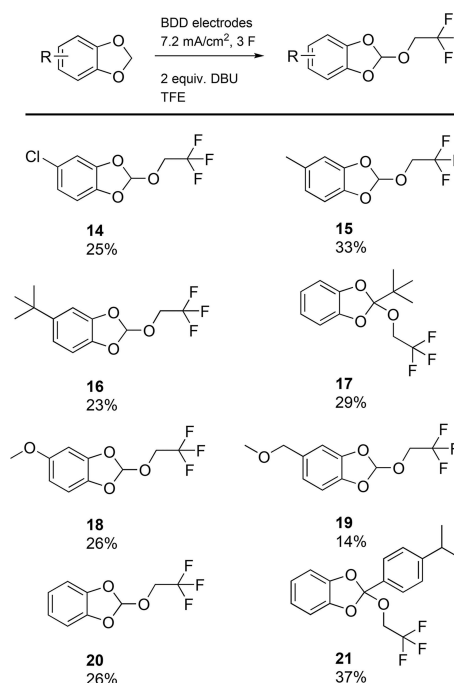
Figure 2. cyclic voltammogram of a 5 mM solution of 5-methyl-1,3-benzo-dioxol in HFIP/MTBS + DIPEA at 50 mV/s

Scheme 4. Scope of the reaction with TFE. Electrolysis was carried out in TFE (5 mL) with 0.5 mmol substrate, 0.03 vol% of DBU and BDD electrodes using BDD electrodes and 3.0 F at 7.2 mA/cm^2 in an undivided cell. Isolated yields are displayed.

chemical installation of TFE has been reported by an iodine(III)-mediated cyclisation reaction for the synthesis of 4-(2,2,2-trifluoroethoxy)isochroman-1-ones.[24]

For longer fluorinated alkyl chains the yields decreased to 15–17% (**22**, **23**). This can be explained by the higher viscosity of the solvent and therefore high local concentrations, and less conductivity (Scheme 5).
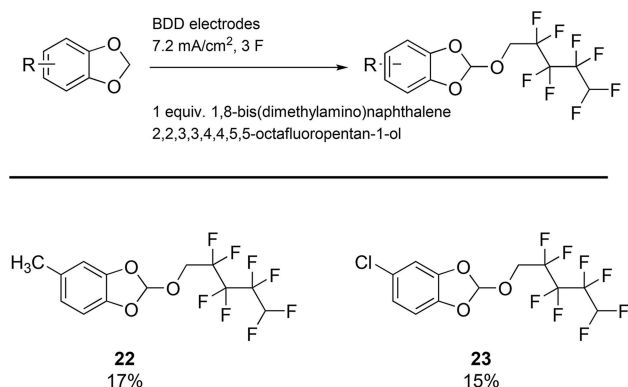
Scheme 5. Scope of the reaction with 2,2,3,3,4,4,5,5-octafluoropentan-1-ol. Electrolysis was carried out in the corresponding alcohol (5 mL) with 0.5 mmol substrate, 1 equiv. of 1,8-bis(dimethylamino)naphthalene using BDD electrodes and 3.0 F at 7.2 mA/cm² in an undivided cell. Isolated yields are given.
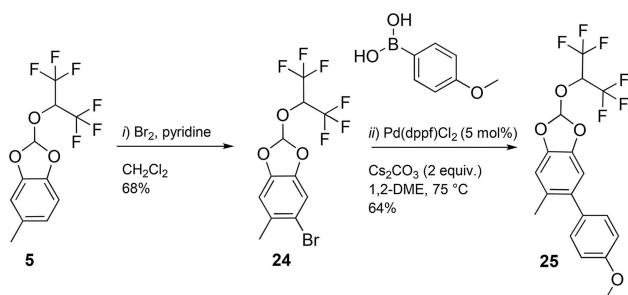
Scheme 6. Further conversions of fluorinated orthoesters. *i*) Bromine (1.5 equiv.) was added to pyridine (2 equiv.) and **5** (1 equiv.) in dichloromethane (2 mL) at 0 °C. *ii*) Pd(dppf)Cl₂ (0.05 equiv.), 4-methoxyphenylboronic acid (1.2 equiv.), caesium carbonate (2 equiv.) and **24** (1 equiv.) was added to 1,2-dimethoxyethane and heated to 75 °C for 8 h.

In addition, to demonstrate the scalability of our method, the electrolysis was scaled-up by a factor of 50. For this, we used 25 mmol of 5-methyl-1,3-benzodioxole in a 500 mL round-bottomed flask cell (Figure S2 in SI). No erosion of selectivity was observed. HFIP was then recovered and the residue was directly purified to give 2.75 g of the desired product **5** in a single batch (37% yield). The yield is not significantly lower compared to that obtained on 5 mL scale (39%), which supports the robustness and scalability of the developed reaction.

Further conversion of products **1** and **5** were investigated. When treated with 4-methylbenzene-1-sulfonic acid in THF (tetrahydrofuran), BF₃-etherate in ether, ethylmagnesium bromide in THF, or even *n*-butyllithium in THF absolutely no

conversion could be observed, leading to complete recovery of the orthoesters. Methoxy orthoesters usually undergo rapid reactions with Grignard reagents,[25] Lewis acids[26] and even water.[12,27] It was therefore possible to convert these molecules in presence of the orthoester moiety: **5** was selectively brominated in 68% yield, using bromine in CH₂Cl₂ with pyridine as additive. The resulting product **24** was then subjected to a Suzuki-Miyaura coupling in 64% yield (**25**) without affecting the orthoester functionality (Scheme 6). This proves the usefulness and robustness of these functionalities. The logP values of 1,3-benzodioxoles and the corresponding orthoesters have been calculated and compared (see SI). It was remarkable that these values increase by a factor of 1.5 to 2 when fluorinated side chains were installed. This transformation could boost the potency and impact target selectivity tremendously by influencing pK_a, modulating conformation, and hydrophobic interactions.[28] The unprecedented robustness and the high lipophilicity further enhance the potential of bioactive compounds involving 1,3-benzodioxoles.

In conclusion, we have established a scalable and simple protocol towards novel highly fluorinated orthoesters. This transformation allows the functionalization of 1,3-benzodioxoles in position 2 with different fluorinated alcohols. This makes it possible to adjust the physicochemical properties of a broad variety of potentially bioactive substrates. The high robustness towards acids and bases gives rise to subsequent conversions without affecting the moiety. This makes these structural motives particularly interesting for applications in medicinal and agrochemistry.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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