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Metal- and Reagent-Free Dehydrogenative Formal Benzyl-Aryl Cross-Coupling by Anodic Activation in 1,1,1,3,3,3-Hexafluoropropan-2-ol

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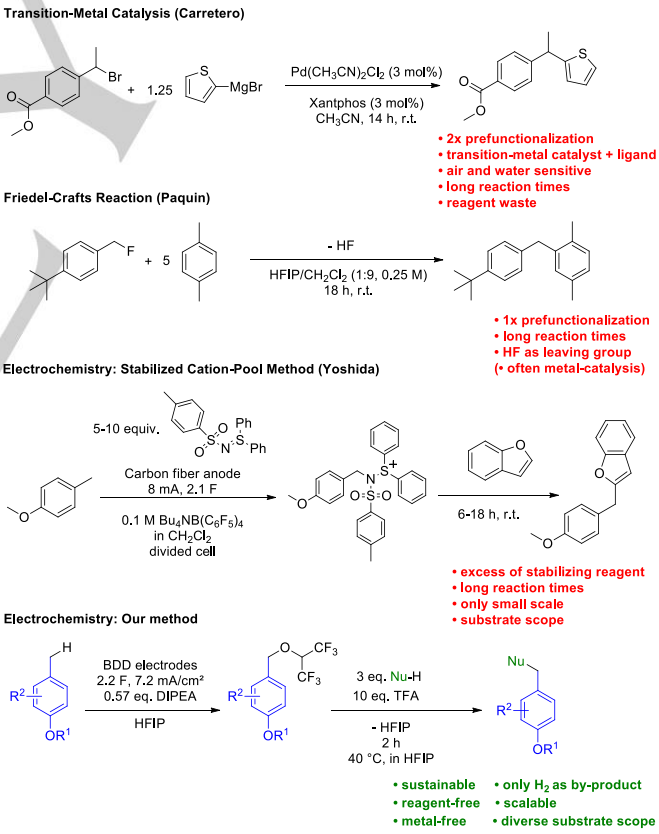
Abstract: The selective dehydrogenative electrochemical functionalization of benzylic positions by 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) is presented for the first time. The electro-generated products are versatile intermediates for subsequent functionalizations, as they act as masked benzylic cations, which can be easily activated. Herein, we report a sustainable, scalable, reagent- and metal-free dehydrogenative formal benzyl-aryl cross-coupling. Liberation of the benzylic cation is accomplished by acid. Valuable diarylmethanes are accessible in the presence of aromatic nucleophiles. The direct application of electricity enables a safe and environmentally benign chemical transformation, since oxidizers are replaced by electrons. A broad variety of different substrates and nucleophiles is suitable.

Diarylmethanes are an important motif in biologically active compounds,[1] medicinal chemistry,[2] and material science.[3] In general, two different synthetic approaches to symmetric and non-symmetric diarylmethanes are available. Common protocols exploit transition metal-catalyzed coupling reactions of benzyl halides with pre-functionalized aromatic nucleophiles, or aryl halides with benzylic nucleophiles.[4] However, conventional cross-coupling reactions (e.g. Suzuki-Miyaura or Kumada-Corriu coupling reactions) share several major disadvantages: the synthesis of the desired diarylmethanes involves a multi-step sequence, being cost- and time-consuming, and lacking atom efficiency. Pre-functionalized starting materials have to be prepared under difficult reaction conditions. Catalysts, mostly Pd-based, are also required for the final coupling reaction. Furthermore, reagent waste is generated in each individual step. The activation of C-H bonds in such reactions has only been achieved in a few examples, with a limited substrate scope.[5] A considered as a Friedel-Crafts-type conversion. Hydroxyl-, halogens or acetoxy substituents are cleaved in benzylic positions by metal catalysts to generate cationic intermediates. These can undergo coupling reactions with nucleophilic arenes. The activation by metal catalysts is indispensable in most cases and a variety of catalysts has been employed ($RhCl_3$,[6] $IrCl_3$,[6] H_2PdCl_4,[6] H_2PtCl_6,[6] $HAuCl_4$,[7] $FeCl_3$[8], and $Bi(OTf)_3$).[9]



Scheme 1. Strategies to benzyl-aryl coupling in comparison to our new method.

In addition to the complex reaction conditions required (elevated temperature, dry solvents, and/or inert atmosphere), low regioselectivity and large amounts of salts as reagent waste are further disadvantages.[6]

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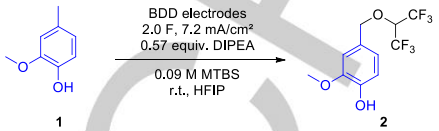
The avoidance of the use of stoichiometric reagents and reagent waste is an important factor in developing an environmentally benign, "greener" route to diarylmethanes.[10] For this purpose, methods for dehydrogenative coupling reactions are of great interest. Electrochemistry, in particular anodic conversion, is a valuable tool for the development of such metal- and reagent-free sustainable transformations.[11] This has been recently demonstrated with an electrochemical benzylic-arylic coupling for the synthesis of diarylmethanes developed by Yoshida.[12] For accumulation of the electrochemically oxidized species in this procedure, the intermediates require trapping of the benzylic cations formed with an additional reagent, due to their highly reactive nature. Subsequent elimination of the stabilizing reagent and coupling with aromatic nucleophiles was then carried out. Due to separation of oxidative and coupling events, bond formation occurs in a selective manner. However, this method exhibits some drawbacks. The stabilizing reagent is not commercially available and has to be used in large excess. The coupling reaction can require up to 35 hours to completion, and all conversions were only demonstrated at small scale (0.1 mmol). The application of free phenols for the anodic step has not been reported. In addition, due to the complex electrolysis set-up (a divided cell equipped with a very specific carbon fiber anode) the procedure is not easily scalable. Consequently, a simple, sustainable, and scalable approach for the synthesis of diarylmethanes is still highly desired. In a recent contribution by Stahl and co-workers, an electrochemical mediated iodination delivers substates for benzylic-arylic coupling.[13]

Following our interest in electrochemical conversions, our group has developed efficient electrochemical C-C and N-N coupling reactions involving phenols,[14] anilides,[15] and dianilides as substrates.[16] Key to these conversions was the application of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as solvent. HFIP has unique properties. It stabilizes reactive intermediates,[17] has a unique solvent microstructure,[18] as well as interesting solvation properties, and as such, it can enable selective transformations.[14e,19] HFIP has also been used as a solvent by Paquin *et al.* in a non-electrochemical approach for the activation of benzyl fluorides in benzyl-aryl coupling reactions.[20] Due to its low nucleophilicity, reactions involving nucleophilic attack of HFIP are rarely reported.[21] Recently, our group demonstrated the anodic functionalization of anilides with HFIP at the benzylic and aromatic position.[16b]

Herein, we report the selective electrochemical functionalization of benzylic positions by HFIP. Those direct electrochemical C-H functionalizations often require catalyst systems.[22] The ether acts as a molecular mask for the benzylic cation, and stabilizes this reactive intermediate by solvent-trapping in a less reactive state. The activation of such masked cations to facilitate an efficient and selective benzyl-aryl coupling reaction is reported for the first time. We present a simple, sustainable, easily scalable, reagent- and metal-free electrochemical benzyl-aryl cross-coupling reaction in a two-step, one-pot sequence (Scheme 1).

Initially, the electrochemical HFIP ether formation was optimized (Table 1). Phenol **1** was selected as a test substrate. The electrochemical parameters for anodic phenol-thiophene cross-coupling were used as initial conditions.[14c] Screening of additives resulted in efficient HFIP ether formation with 0.57 equiv. *N*-ethyl-*N,N*-di(methylethyl)amine (DIPEA) (Table 1, Entry 1). We attributed this to the base character of the additive. A similar effect, but in lower yield and selectivity, was observed using triethylamine (TEA), K_2CO_3, or Cs_2CO_3 as bases (Table 1, Entry 2 and SI). k 2.2 F and 7.2 mA/cm^2 were found to be the optimal electrolytic conditions (Table 1, entries 3–7).

Table 1. Optimization of the anodic functionalization of 4-methylguaiacol by HFIP.[a]



Entry	Deviation from standard conditions	Yield[b] (%)
1	-	72
2	TEA instead of DIPEA	42
3	1.9 F	64
4	2.2 F	78
5	2.4 F	56
6	2.2 F, 5 mA/cm^2	67
7	2.2 F, 10 mA/cm^2	63
8	Graphite electrodes, 2.2 F	76
9	Graphite electrodes, without supporting electrolyte, 2.2 F	72
10	Without supporting electrolyte, 2.2 F	78
11	Without supporting electrolyte, 2.2 F, 1.14 equiv. DIPEA	69
12	Without DIPEA	0

[a] All reactions were carried out on a 1.0 mmol scale of phenol **1** in 5 mL of HFIP in an undivided cell. [b] Yields were determined by ^{1}H NMR spectroscopy with benzaldehyde as standard.

Notably, oxidation at graphite anodes, which are less expensive than boron-doped diamond (BDD) anodes, provides the desired HFIP ether in similar yields (Table 1, entry 8). This is particularly interesting for technical large scale applications. However, it should be noted that we proceeded here with BDD anodes in the subsequent electrolysis because of a slightly better yield according to optimization studies. A significant step towards a greener protocol was made with the observation that DIPEA forms in-situ a supporting electrolyte and additional salt is not necessary in this transformation (entries 9 and 10). This can be rationalized by salt formation between the solvent HFIP (pK_a =9.3)[21] and DIPEAH$^+$ (pK_a = 11.4)[23] which enables sufficient electrical conductivity. Doubling the amount of DIPEA did not improve the yield (entry 11). In a control experiment (entry 12) the significance of DIPEA as an additive was determined. Without additive, phenol homo-coupling and oligomerization dominated.

While the selective formation of benzylic HFIP ethers using HFIP as a nucleophile is an unprecedented transformation, we were particularly interested in exploring applications of this motif in further synthesis. The ether can be seen as a molecular mask for the benzylic cation in this case. However, compared to a

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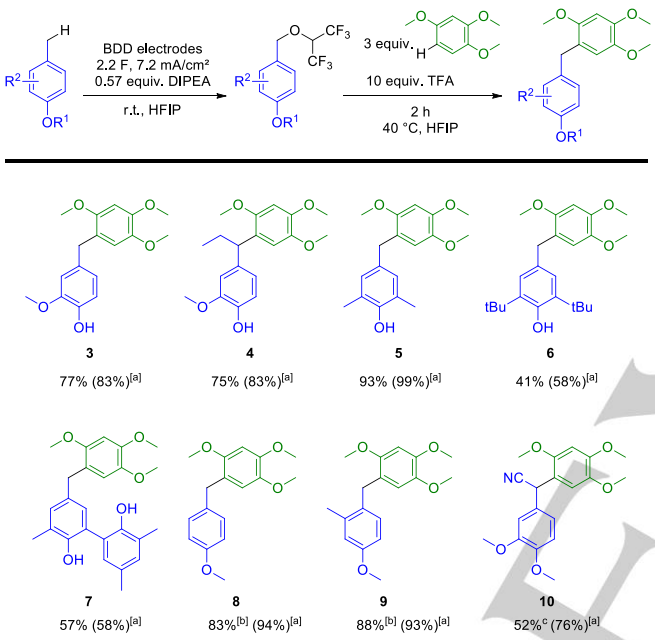
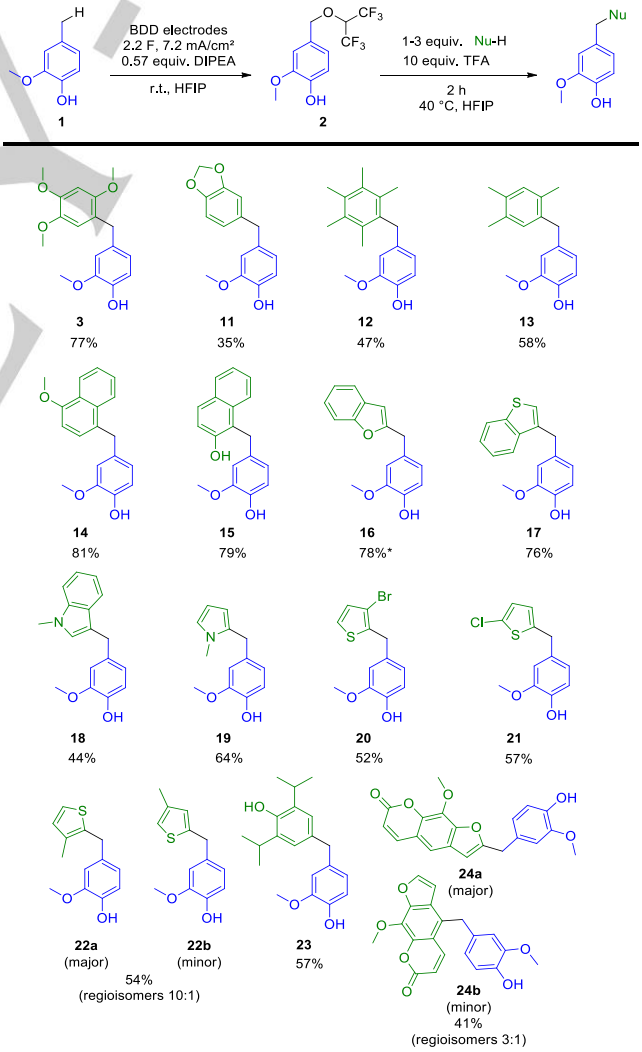
recently presented approach demonstrating the trapping of cations in the α-position of amides in Shono-oxidation products of lactams,[24] the stabilization and subsequent activation of benzylic cations is a challenging task. We found that treatment with 2,2,2-trifluoroacetic acid led to subsequent formation of an active benzylic cation. If this activation is carried out in the presence of an equimolar to three-fold excess of an aromatic nucleophile, selective benzyl-aryl cross-coupling can be achieved. We optimized this coupling reaction with 1,2,4-trimethoxybenzene as a test substrate. With optimized conditions for the first and second step in hand, we explored the scope of potential substrates for HFIP ether formation. For the subsequent benzylic cross-coupling reaction, 1,2,4-trimethoxybenzene served as test nucleophile (Scheme 2).



Scheme 2. Scope for anodic functionalization by HFIP and subsequent coupling to 1,2,4-trimethoxybenzene. Electrolyses were carried out in 5 mL HFIP on 1 mmol of substrate in an undivided cell. a) Yield of the benzylic HFIP ether after electrolysis, determined by ^{19}F NMR, b) 0.5 mmol of substrate have been used instead and 3.0 F were applied for optimum electrochemical conversion, c) electrolysis with 1.8 F, activation for second reaction carried out with *p*-TsOH instead of TFA, reaction time 3 h.

Electrochemical functionalization with HFIP at the benzylic position and subsequent benzyl-aryl cross-coupling was achieved with a variety of substrates in yields up to 93% (**5**). Unprotected phenols can be coupled at primary (**3**, **5**, **6**) and secondary benzylic positions (**4**). Additionally, functionalization of biphenols was demonstrated (**7**). Our method proved to be complementary to the "stabilized cation-pool" since anisole and anisole derivatives could be coupled in high yields (**8**–**10**). Product **10** is particularly interesting, since the nitrile moiety allows further facile functionalization. When dehydrodimerization or oligomerization became noticeable during electrolysis (**8** and **9**), the concentration of the starting material was reduced, leading to high yields (83% and 88%) of the desired coupling products. As a logical step we carried on investigations for the coupling with different nucleophiles. For this approach, the electrolysis was carried out under optimized reaction conditions with 4-methylguaiacol as a test system, and the subsequent coupling step was investigated (Scheme 3). The reaction was found to succeed with a broad variety of different nucleophiles. Arenes with strongly electron-releasing groups (**3** and **11**), as well as methylated arenes (**12** and **13**) were successfully cross-coupled with 4-methylguaiacol. The reaction with a free phenol proceeded in good yield (**23**). Naphthalene derivatives including 1-methoxynaphthalene and unprotected 2-naphthol were coupled in high yields of up to 81% (**14** and **15**). Coupling of 4-methylguaiacol with heterocycles such as benzofuran, benzothiophene, *N*-methyl indole, *N*-methyl pyrrole, and thiophene derivatives is possible moderate to high yields (**16**–**22b**). The transformation tolerates a variety of substituents (methoxy, methyl, hydroxyl, chloro, and bromo). In most cases, the coupling reaction occurs smoothly and selectively. Only in the case of 3-methylthiophene was the formation of regioisomers (**22a** and **22b**) observed. Importantly, the benzyl-aryl cross-coupling reaction can be conducted in much shorter time compared to Yoshida's approach.[12] It should be noted that HFIP was used as both the solvent and nucleophile in this procedure, and can be fully recovered and reused.[21] This leads to a total reaction balance with only hydrogen as a by-product for the C-C cross-coupling reaction.



Scheme 3. Variation of the nucleophile in the coupling reaction with 4-methylguaiacol. Electrolyses were carried out in 5 mL HFIP on 1 mmol of phenol **1** in an undivided cell.

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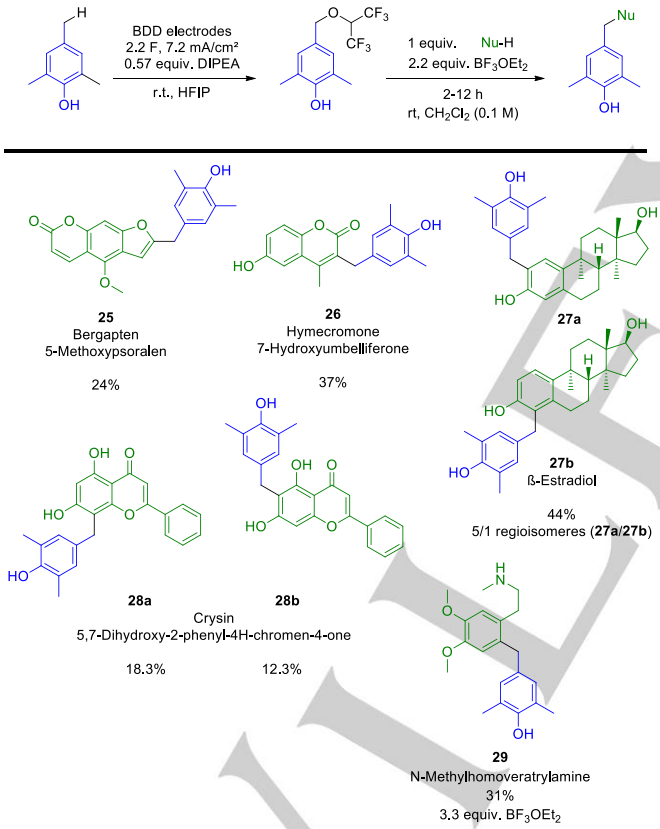
In order to explore the full potential of this method, its application to natural product derivatization was of high interest. Our initial approaches to this end using 2,2,2-trifluoroacetic acid led to complex mixtures. Further attempts using Lewis acids in dichloromethane proved promising. Using beta-estradiol as a nucleophile and aluminium chloride led to a 32% yield of the coupled product. Further optimization of this system using BF_3OEt_2 (2.2 equiv.) increased the yield of the coupled product to 44%. Based on these initial results, we were able to carry out late-stage functionalization of a range of natural products and biologically active compounds in moderate yields (Scheme 4). Five different classes of natural product (steroids **27**, umbelliferones **26**, psolarenes **25**, phenylethylamines **29** and flavones **28**) were successfully derivitized. The coupling was achieved at a range of positions, illustrating the generality of this method for exclusive C-functionalization even in the presence of nucleophilic oxygen (**26**, **27** and **28)** or nitrogen moieties (**29**). Additionally, crystal structures of the psolarene and umbelliferone derivatives were obtained (see Supporting Information). These novel derivatives may be of interest as potentially biologically active compounds. Testing of biological activity is ongoing.



Scheme 4. Benzylated natural products and bioactive compounds using BF_3OEt_2 (2.2 equiv.), 0.1M in CH_2Cl_2, rt, 2-12 h;

To demonstrate the scalability of our method we chose the synthesis of compound **17** as model reaction. The structural moiety of **17** is of significant interest in pharmaceutically active compounds.[25] Therefore, a simple and scalable method for the synthesis of these diarylmethanes will provide a new versatile strategy. We scaled-up the electrolysis by a factor of 40. So electrolysis was conducted with 40 mmol of phenol **1** in a 200 mL beaker-type cell (Figure 1). No erosion of selectivity has been observed for the anodic functionalization with HFIP. This mixture was directly subjected to the coupling reaction with benzothiophene to give 6.91 g of the desired **17** in a single batch (64% yield). The yield is slightly lower compared to the 5 mL scale (76%). This can be rationalized by a not yet optimized addition of TFA on larger scale. Nevertheless, the reaction time could be even decreased from 2 h to 1 h within this upscaling approach.

Figure 1. 5 mL and 200 mL beaker-type cells employed for scale-up studies. For size comparison, a 2 € coin (diameter 25.75 mm ≈ 1.01 inches) was placed between both cells. More details are given in the Supporting Information.

In conclusion, we established a very efficient protocol for the electrochemical functionalization of benzylic groups by HFIP. Small amounts of DIPEA can be used as an additive to selectively lead to this reaction pathway and fully replace any additional supporting electrolyte. The scope was demonstrated with phenols anisoles and the late-stage functionalization of natural products. The benzylic HFIP functionalization can be activated with acid to undergo a dehydrogenative benzyl-aryl cross-coupling reaction with a variety of different nucleophiles in high yields. This protocol provides a scalable, metal-free, and reagent-saving route to diarylmethanes, which has the potential to short-cut a variety of synthetic routes. Activation of electro-generated HFIP ethers for applications in various reactions with nucleophiles can be imagined. Additionally, this method could be extended and optimized for anilides, as already shown from our group for the first step. Therefore, this route provides a general pathway for numerous chemical transformations.

Acknowledgements

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Keywords: benzylic coupling • electrochemistry • HFIP • green chemistry • natural products

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Layout 2:

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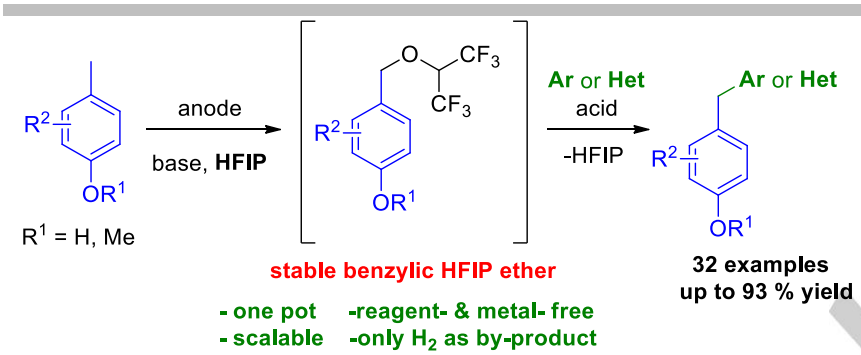

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Metal- and Reagent-Free Dehydrogenative Formal Benzyl-Aryl Cross-Coupling by Anodic Activation in 1,1,1,3,3,3-Hexafluoropropan-2-ol

Simply the base makes the difference for the electrified benzylic cross-coupling via intermediate ethers of 1,1,1,3,3,3-hexafluoroisopropanol. These ethers can serve for the selective arene functionalization of various substrates and late-stage functionalization.