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Electrochemical Synthesis of Biaryls via Oxidative Intramolecular Coupling of Tetra(hetero)arylborates

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Supporting Information Placeholder

ABSTRACT: We report herein versatile, transition metal-free and additive-free (hetero)aryl-aryl coupling reactions promoted by the oxidative electrocoupling of unsymmetrical tetra(hetero)arylborates (TABs) prepared from ligand-exchange reactions on potassium trifluoroarylborates. Exploiting the power of electrochemical oxidations, this method complements the existing organoboron toolbox. We demonstrate the broad scope, scalability and robustness of this unconventional catalyst-free transformation, leading to functionalized biaryls and ultimately furnishing drug-like small molecules as well as late stage derivatization of natural compounds. In addition, the observed selectivity of the oxidative coupling reaction is related to the electronic structure of the TABs through quantum-chemical calculations and experimental investigations.

Scientific progress is not linear: Even the most trusted and acknowledged chemical transformations deserve to be examined and leave room for new ideas. As cross-coupling reactions have undoubtedly changed the way organic chemists think about C-C bond formation, they represent an essential tool for synthesis and are one of the most used transformations in organic chemistry.^{1,2} Since their discovery in the late 1970s,³ countless modifications, extensions and improvements of the pioneering Suzuki-Miyaura-coupling have been reported, which have led to a library of available metal catalysts, ligands and organoboron species as well as detailed mechanistic insights into this remarkable coupling process.^{1,4}

As electrochemistry has recently been welcomed by the community of synthetic chemists as an innately sustainable route to forge new C-C bonds, this work introduces a complementary approach to original transition-metal catalysis by merging the potential of organoboron- and electrochemistry.^{8,9} Remarkable advances in the field by Baran,⁹ Yoshida¹⁰, and many more¹¹⁻¹³ have led to a revival of vintage electrochemistry from the early 19th century. In an early report from the 1950s Geske (Scheme 1A) discovered that the tetraphenylborate anion undergoes formation of biphenyl under electrochemical conditions using a rotating platinum disc electrode.¹⁴ More recently, the Waldvogel group was able to demonstrate the electrochemical instability of highly fluorinated commercial tetraphenylborates, resulting interestingly in the formation of homocoupling products (Scheme 1B).¹⁵ They revealed that the oxidative process had to be intramolecular, as only traces of free radical species were detected in solution. In addition, the same group was able to observe one heterocoupling product by GC-MS analysis.^{16,17} The exact mechanism of the reaction remained however unclear, as both cationic and radical pathways are conceivable.^{15,18-19}

These findings motivate the present work. We envision that "unsymmetrical TAB salts" consisting of three identical aryl moieties and a fourth more electron-rich aryl moiety (Scheme 1C) would be prone to selectively achieve electrochemical heterocoupling reactions. While this work does not attempt to compete with the wellestablished Suzuki-Miyaura coupling, it represents an alternative way to think about coupling reactions in general, in which the C-C forming step is enabled by assembling the components onto boron instead of a transition-metal as a templating scaffold. We hypothesize that the most electron-rich aromatic ring gets oxidized first, which then triggers an intramolecular, yet unusual 1,2-rearrangement of one of the remaining aromatics and therefore prevents undesired homocoupling side-reactions.^{18,20}

Scheme 1. Precedence in Electrocoupling

A: Geske, 1959: Synthesis of biphenyl from the tetraphenyl borate anion



B: Waldvogel, **2018**: Electrochemical homocoupling of highly fluorinated tetraphenyl borates



C: This work: Coupling of tetra(hetero)aryl borates via electrochemical oxidation



The synthesis of symmetrical TABs was established by Wittig and coworkers²¹ and is performed using organometallic reagents and alkali tetrafluoroborates or boron trifluoride diethyl etherate, performing up to four B-F exchange reactions.^{22,23} We were surprised that - to the best of our knowledge - such methods were not reported for unsymmetrical TABs. Most of the literature relies on the use of highly unstable and oxygen-sensitive triarylboranes via addition of an organometallic reagent, which usually result in low yields and are synthetically unpractical.^{17,24}

We were pleased to find that bench-stable potassium trifluoroarylborates, mainstreamed by the group of Molander,²⁵ undergo rapid ligand-exchange reactions with Grignard reagents under mild conditions, an approach already utilized in the synthesis of sterically demanding triarylboranes and the design of borate ligand/catalyst systems.26,27 Following 11B NMR, complete formation of the desired unsymmetrical TAB salt 1a was observed within an hour at room temperature with stochiometric amounts of Grignard reagents.²⁸ After an aqueous workup, the air-stable salt was dissolved in MeCN and subjected to non-destructive electrochemical oxidation. Carbon-based electrodes proved to be the most reliable and the best results were obtained with RVC electrodes, probably due to their greater working surface. To gain more insight into the reaction pathway, the oxidation process was followed by ¹H NMR spectroscopy in deuterated MeCN (Scheme 2). We found that - in agreement with the results on homocoupled products of Waldvogel¹⁵ - TAB salt 1a was consumed after 2.5 F. In addition, the reaction proceeded very selectively, as only traces of the undesired homocoupled product were obtained, yielding 2a as the sole product.

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Scheme 2. NMR Study on Oxidative Coupling



The formation of bis(4-fluorophenyl)borinic acid **2ab** as the major side product was also observed in the ¹H NMR spectra, but its instability under electrochemical conditions did not allow for its quantitative isolation. Interestingly, water did not disturb the reaction process, but was consumed during the electrochemical oxidation, indicating its importance in the reaction mechanism.

As neither inert conditions nor the presence of an electrolyte influenced the conversion into 2a, we decided to routinely perform the electrochemical oxidations in an open-flask setup without electrolyte in wet acetonitrile. The reactions were conducted in an undivided cell under galvanostatic conditions applying a constant current of 7 mA/cm².

As depicted in Scheme 3, various substituted biaryls were synthesized with this procedure, for which no isolation of the intermediate TAB salt was required. 4-Fluoro-4'-methyl-1,1'-biphenyl (2b) and three other electron-rich compounds (2a, 2c-d) were isolated in 52–62% yield over two steps. Interestingly, the oxidation process was found to be generally preferred in *p*-position compared to *o*-position, furnishing products 2e–f in 55–66% yield. Using *p*-(4-(trifluoromethyl)phenyl)- (2g–i), 3,5-bis(trifluoromethyl)- (2j–m), (3,5-difluorophenyl)- (2n) and (4-(trifluoromethoxy)phenyl)-magnesium bromide (2o), diversely substituted biaryls were isolated in up to 87% yield. As seen for products 2l and 2m, the position of the methoxy moiety was crucial to navigate the oxidation towards the right aromatic ring within the naphthyl group. A more sterically demanding substrate leading to product 2p gave a diminished yield of 14%. Interestingly, the process proved to tolerate free alcohol moieties, as shown by example 2q, isolated in 40% yield. Lastly, sensitive functional groups were introduced using organozinc chemistry in the first step. To ensure full conversion into the TAB salts, the reaction mixtures employing arylzinc reagents were heated to 50 °C for 16 hours. After successful electrochemical oxidations, ester-substituted product 2r was isolated in 54% yield.

Scheme 3. Oxidative Heterocoupling of TAB Salts^a



^{*a*}Yields are stated as isolated yields over two-steps. ^{*b*}Reactions performed using 3.15 equiv. of arylzinc reagents. ^{*c*}4.20 equiv. of aryl-Grignard reagent was used.

With these results in hands, we decided to question the reactivity of heterocyclic derivatives. The smooth formation of the heterocyclic TAB salts was completed within one hour employing aryl-Grignard reagents. A broad range of electron-rich heterocycles was tolerated (Scheme 4), resulting in 4-1*H*-pyrazolyl (**3a–b**), 3-benzothiophenyl (**3c**), 5-benzofuranyl (**3d–e**) and 5benzo[*c*][1,2,5]oxadiazolyl (**3f**) substituted biaryl products in 38% to 75% yield. Moreover, dibenzo[*b*,*d*]thiophenyl (**3g**) derivatives afforded the corresponding (hetero)aryl-aryl coupling products in up to 56% yield, including a diisopropylamide group (**3h**).

Next, we examined electron-poor heterocyclic trifluoroborate salts. Implementation of substituted 3-pyridyl, 5- and 6-quinolinyl and 5-pyrimidinyl building blocks allowed us to synthesize compounds 3i-m in moderate to good yields of up to 59% over two steps. Unsubstituted five-membered heterocycles such as furanes (3n) resulted in reduced yields of 25% due to polymerization and

employing dibenzo[b,d]furan-2-ylmagnesium bromide as the corresponding Grignard reagent enabled the synthesis of product **30** in 66%.

Scheme 4. Oxidative Coupling of Heterocyclic TAB Salts^a



^{*a*}Yields are stated as isolated yields over two-steps. ^{*b*}Reactions performed using 3.15 equiv. of arylzinc reagents.

Scheme 5. Electrocoupling Reactions of Halogen- and Pseudo-halogen Containing Substrates^a



^aYields are stated as isolated yields over two-steps. ^bReactions performed using 3.15 equiv. of arylzinc reagents. ^cUsing Suzuki-Miyaura conditions: boronic acid (1 equiv., in blue) and iodoaryl (1.1 equiv., in green), Pd(PPh₃)₄ (5 mol%), K₂CO₃ (2.7 equiv.), dioxane/H₂O (2:1, 0.05 M), 70 °C, 24 h, GC-yield.

In order to evaluate the feasibility of the electrocoupling in the presence of potentially sensitive halogens and pseudo-halogen groups, a library of new borate salts was in situ created from the corresponding organotrifluoroborates and organometallic reagents. Following the precedent procedure, these salts were submitted to electrochemical oxidation without purification. The nitrile group was tested first, giving biaryls 4a-b in 38-46% yield. We attribute such moderate yield to the lower reactivity of the cyano-substituted organozinc reagent in the ligand-exchange reaction to form the intermediate borate salt. The reaction is therefore improved when the cyano group is attached to the organotrifluoroborate (4c, 53%). Starting from a bromo-substituted carbazole-BF3K derivative, the electrocoupling furnished compounds 4d-e in 46-64% yield. With a chloride substituent in the para-position, the biaryl product 4f was isolated in 80% yield. Remarkably, bromide and iodide were also tolerated in this reaction as compounds 4g and 4h were obtained in moderate to good yield (49-78%). As compounds 4f-h were generated from the halogenated organotrifluoroborates, we set out to employ a procedure in which the halogens would be introduced from the organometallic reagents. Therefore, meta-substituted chlorinated and iodinated Grignard reagents were engaged in the electrocoupling reaction, giving 4i and 4j in good yields (60-77%). Suzuki-Miyaura cross-coupling conditions only yielded 7% of the desired compound 4h.

Scheme 6. Extension to Drug-like Compounds, Decagramscale Reactions and Olefinations^a



^{*a*}Yields are stated as isolated yields over two-steps. ^{*b*}Reactions performed using 3.15 equiv. of arylzinc reagents.

Having proven the robustness and versatility of this novel approach, we set out to tackle some more interesting molecular architectures. Simple functionalization of estrone derivative 5 was carried out by employing the established two-pot procedure to furnish biaryl compounds in good yields of up to 65%, utilizing organozinc reagents (6a-c, Scheme 6A).²⁹ In addition, the trifluoroborate salt 7 derived from celecoxib was engaged in the oxidative coupling process,³⁰ delivering two drug-like analogs **8a-b** in 54% and 55%, respectively. The reaction was successfully scaled up to 6 mmol, vielding product 8b on a gram-scale (1.57 g, 48%, Scheme 6B) and an additional decagram-scale process was designed.²⁸ The initial test substrate 1a was considered for this experiment, and acetonitrile was replaced by ethanol as a more environmentally benign solvent.31 The crude material was simply plugged through a short pad of silica to remove residual salts and product 2a was isolated in 60% yield (9.0 g, Scheme 6C). To further showcase the potential of boron as a templating scaffold, we engaged E- and Z-styryltrifluoroborate salts as coupling partners in our sequential approach (Scheme 6D). The existence of those novel tetraorganoborate salts was confirmed by X-ray of intermediate 1h. Performing the subsequent electrochemical olefination, only the thermodynamically favored product 9a was isolated with high selectivity in up to 68% yield, resulting in a stereoconvergent method. We propose that the intermediate radical species is allowed to freely rotate around the oxidized C-C double bond.

Scheme 7. Electrocoupling of Pure Salts^a

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"IAB salts were isolated by precipitation.²⁰ "GC-ratios determined from crude mixtures using n-undecane as an internal standard.

In order to support our postulate that electronic effects play a determinant role in the selectivity of the electrochemical process, we set out to isolate selected organoborate salts and run the electrocoupling on pure compounds (Scheme 7). TAB salt **1a** bearing a *p*-anisyl group was prepared, as well as its *m*- (**1b**) and *o*-anisyl (**1c**) isomers. As seen in Scheme 7, the yields decreased from 79% to 18% going from *para*- over *meta*- to *ortho*-substituted compounds (**2a**, **10a-b**), while increasing amounts of homocoupling products were observed. While the lower yield in the case of *ortho*-substituted substrates was attributed to sterical hindrance, the destabilizing effects of a *meta*-methoxy group provoked a slight decrease in selectivity. However, this negative effect was compensated when replacing the *p*-fluoride of the electron-deficient aryl

groups on the borate by electron-poorer moieties such as *p*-(trifluoromethyl)phenyl. In this case, product **10c** was isolated in 70% yield. Increasing the electron-richness of the partner gave similar results (**10d-e**). Careful choice of the aromatic residues and accompanied balance of the electronic properties can clearly overcome most limitations even though some challenges still need to be tackled.²⁸ We lastly submitted the *C*₂-symmetrical potassium bis(4methoxyphenyl)diphenylborate **1g** to the electrocoupling conditions in order to evaluate the propensity of the remaining unoxidized aryl groups to undergo C-C bond formation. As expected, the experiment resulted in trace amounts of biphenyl **13**. However, an almost statistical distribution of homocoupled 4,4'-dimethoxy-1,1'-biphenyl **12** and the desired heterocoupled product **11** was observed, which indicates that the migratory step is extremely fast and therefore leads to a lack of selectivity (Scheme 7).

Consequently, we became interested in a greater understanding of our electrocoupling reaction. Thus, next paragraphs will be devoted to creating a mechanistical picture of the oxidative transformation. In order to assess the influence of substituents borne by the aryl groups in the first oxidation step, we conducted quantumchemical calculations based on coupled-cluster and density functional theory (DFT). These theoretical results correlate with experimental values for oxidation potential studies of salts **1a**–**g**, measured by cyclic voltammetry (Figure 1, **B**).²⁸ These results also adhere to the correlation between electron-richness of the different aromatic patterns of the TAB salts and a decrease in their oxidation potentials. It is important to note that cyclic voltammetry performed on all salts only revealed one significant oxidation value within the measured range (Figure 1, **D**).²⁸



Figure 1. TAB salts 1b-g (A), experimental oxidation potentials of TAB salts 1a-g (B) with spin density after oxidation of 1a (C)

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and cyclic voltammetry of TAB salt 1a (D) calibrated to the reversible ferrocene oxidation (Fc/Fc⁺).

To characterize the change in the electronic structure upon oxidation of the TAB salts (1a-g), spin and charge densities were computed based on Mulliken population analysis of the DFT results. Charge densities were additionally computed using the ChElPG approach.²⁸ These analyses indicate that only the most electron-rich aromatic ring is selectively oxidized in all cases while the charge and spin densities of the other aromatic substituents only change insignificantly and thereby confirm our assumptions. This is illustrated for TAB salt **1a** in Figure 1 (**C**), where blue and red areas represent positive and negative spin densities after oxidation.

As a next step, crossover experiments were performed in order to confirm or exclude the possibility of intermolecular couplings (Scheme 8). For this purpose, two non-symmetrical borate salts 1a and 1h bearing different aryl groups were generated from the corresponding organotrifluoroborates and submitted to the electrocoupling reaction together. If one assumes that the reaction is exclusively intramolecular, the only products of the reaction are heterocoupling products 2j and 2a, and homocoupling 14e and 14f. As previously discussed, homocoupling products result from an unselective oxidation and are only observed as the minor biaryl in the reaction. However, if the intramolecular reaction were to be in competition with an intermolecular process, one can expect products 14a, 14b, 14c, 14d and 14g. Submitting 1a and 1h to electrochemical conditions revealed the exclusive formation of 2j and 2a in major amounts and 14e and 14f as minor products. The absence of other products in the reaction mixture brings additional proof that the transformation goes through an intramolecular rearrangement, excluding any possibility of intermolecular coupling.

Scheme 8. Crossover Experiments^a



^aTAB salts were generated in situ.

To reveal the one or two-electron character of the electrocoupling reaction several tests were conducted building on the cyclic voltammetry data, as it has shown that only one oxidation potential can be observed in the measurement window (Figure 1, **D**). To advocate this hypothesis, we performed potentiostatic experiments on **1a** in which the voltage was set up to the constant value of 1.6 V (vs. SCE). The same conversion as for galvanostatic conditions into the biaryl **2a** was detected, indicating a one electron process. To support this first assumption, a detailed look at the conversion rates during the electrocoupling reaction of TAB salt **1a** was carried out. Therefore, a sample with an internal standard was gradually taken during the electrochemical oxidation process (Figure 2). As highlighted in Figure 2, the transformation at 1 F already results in a GC-Yield of 57% for 2a, which assists the hypothesis of a oneelectron process. Even in the unlikely scenario in which every electron performs the oxidation on one borate molecule, the conversion in a two-electron pathway after 1 F cannot exceed 50%.



Figure 2. Measured GC-yields during the electrochemical oxidation of 1a towards 2a with *n*-undecane as an internal standard.

The oxidative coupling of **1a** towards the formation of **2a** can also be promoted under non-electrochemical conditions with chemical oxidants such as CAN, PIDA and ferrocenium. However, while ferrocenium furnished comparable results, CAN and PIDA gave significantly lower selectivity and yields.²⁸ Although those one-electron oxidants showcased similar reactivity to our electrochemical procedure, the use of two-electrons oxidants such as I₂ or NBS resulted in the decomposition of our salts.

Scheme 9. Proposed Mechanism for the Electrocoupling of TAB Salts 1a



Even though a two-electron process is still conceivable, all indications (theoretical calculations, crossover experiments, cyclic voltammetry, potentiostatic/chemical experiments and conversion rates) contribute and support the mechanistic pathway proposed in

Scheme 9. The reaction starts with the selective oxidation of the most electron-rich aromatic ring of 1a (supported by quantumchemical calculations, as shown in Figure 1, giving intermediate [A]) and is followed by a pseudo-1,2-metallate rearrangement. This can be done via σ -bond cleavage or through π -addition, given that the reaction proceeds exclusively in an intramolecular way (as demonstrated with crossover experiments, Scheme 8). Although no calculations could be performed on this step, we assume - for geometrical reasons - that the rearrangement takes place through π -orbitals and gives the radical cationic boracyclopropane species [C]. Such intermediate was already proposed in previous literature reports.^{18,19} It is important to note however that a σ -bond cleavage would result in the same intermediate [B]. Two different pathways can follow in the elimination / rearomatization process. Either an additional electron abstraction can occur (second oxidation, [D]) or a direct elimination of a boron-radical species. As supported by galvanostatic experiments (Figure 2) and tests under chemical oxidation, we assume that the rearomatization likely occurs through a one-electron process, furnishing the biaryl compound 2a.

In summary, we have demonstrated that a broad range of heterosubstituted TAB salts are accessible using simple and rapid ligand-exchange reactions on potassium trifluoroborates. We have furthermore shown, that these salts are smoothly oxidized exploiting the power of electrochemistry to furnish substituted heterocyclic biaryl systems without the necessity of any additives or transition-metals. This conceptual two-pot approach has shown to be robust towards moisture and air and therefore allowed us to routinely synthesize small drug-like molecules on gram scale. A great variety of functional groups were tolerated, including several heterocyclic systems. Lastly, theoretical calculations analyzing the electronic structure of these systems combined with measured oxidation potentials, crossover- and potentiostatic experiments allowed us to rationalize the outcome of the oxidative electrocoupling presented.

ASSOCIATED CONTENT

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The Supporting Information is available free of charge on the ACSPublicationswebsiteatDOI:.

Experimental procedures, compound characterization, theoretical calculation, cyclic voltammetry, X-ray diffraction data (PDF)

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Notes

The authors declare no competing financial interests.

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