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Synthesis of a Bcl9 Alpha-Helix Mimetic for Inhibition of PPIs by a Combination of Electrooxidative Phenol Coupling and Pd-Catalyzed Cross Coupling †

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† Dedicated to Prof. Marko Mihovilovic on the occasion of his 50th birthday.

Received: 12 February 2020; Accepted: 16 March 2020; Published: 19 March 2020

Abstract: Teraryl-based alpha-helix mimetics have resulted in efficient inhibitors of protein-protein interactions (PPIs). Extending the concept to even longer oligoarene systems would allow for the mimicking of even larger interaction sites. We present a highly efficient synthetic modular access to quateraryl alpha-helix mimetics, in which, at first, two phenols undergo electrooxidative dehydrogenative cross-coupling. The resulting 4,4'-biphenol is then activated by conversion to nonaflates, which serve as leaving groups for iterative Pd-catalyzed Suzuki-cross-coupling reactions with suitably substituted pyridine boronic acids. This work, for the first time, demonstrates the synthetic efficiency of using both electroorganic as well as transition-metal catalyzed cross-coupling in the assembly of oligoarene structures.

Keywords: alpha-helix; anode; CH-activation; cross-coupling; electrosynthesis; oligoarene; peptidomimetics; phenol; protein-protein interactions; triflate

1. Introduction

Over the last two decades, the inhibition of protein-protein-interactions (PPI) with small molecules has emerged as a challenging but rewarding new paradigm in Chemical Biology and Drug Discovery [1–4]. The challenge is associated with the fact that—in contrast to established drug targets such as enzymes, G protein-coupled receptors (GPCRs), ion channels, etc.—protein-protein-interaction interfaces are characterized by a large, rather flat surface, in which several amino acids distributed over a wide surface area contribute synergistically to the binding of the protein partner. This requires new types of compounds being able to mimic such interaction partners. Among them foldamers [5], stapled peptides [6], and α-helix mimetics [7–13] have turned out to be of particular value. Hamilton and co-workers have demonstrated that trisubstituted linear teraryls can function as α-helix mimetics, displaying the i, i+4 and i+7 amino acid residues in angle and distance characteristic for the α-helix motif within proteins [14]. These teraryl structures have resulted in efficient inhibitors of protein-protein

interactions, with the advantages of lower molecular weight, better bioavailability, and hydrolytic stability, when compared with peptide drugs. We could show that such teraryl peptide mimetics can be assembled in a modular way using aryltriflates via Pd-catalyzed cross-coupling reactions [15–18]. In order to address an even larger part of the protein-protein interaction site, we are aiming to synthesize α-helix mimetics in the form of quateraryls featuring four amino acid residues. Ideally, these structures should be accessible from simple starting materials by an iterative cross-coupling process [19]. We envisioned that electrooxidative dehydrogenative coupling of suitably substituted phenols would produce 4,4′-biphenols as building blocks for core fragments [20]. Electroorganic synthesis activates molecules by the simple addition or removal of electrons. Consequently, this method requires no stoichiometric reagents. Currently, this methodology exhibits the lowest environmental impact and is considered as inherently safe [21–24]. Upon conversion of the biphenols into sulfonate esters, these structure motifs could be connected with pyridine boronic acids via Pd-catalyzed cross-coupling reactions.

In this manuscript, we report about the implementation of such a strategy, which enabled us to synthesize a quateraryl fragment, which could function as a mimic of the β-catenin/B-cell CLL/lymphoma 9 protein (Bcl9) interaction site.

2. Results and Discussion

As a test case for our synthetic methodology (see Supplementary Materials), we choose the PPI between β-catenin and Bcl9, which is an important regulatory factor in the development of cancer via the Wnt signaling pathway [25]. The β-catenin/Bcl9 PPI has been well characterized, and the group of Verdine has developed stapled peptides addressing this PPI [26]. By analyzing available structural information from the β-catenin/Bcl9 interface [27], we identified Arg-359, Leu-363, Leu-366, Ile-369, and Leu-373 as relevant amino acids of an α-helix structural element. This led us to propose the following quateraryl structures as target molecules (Figure 1).

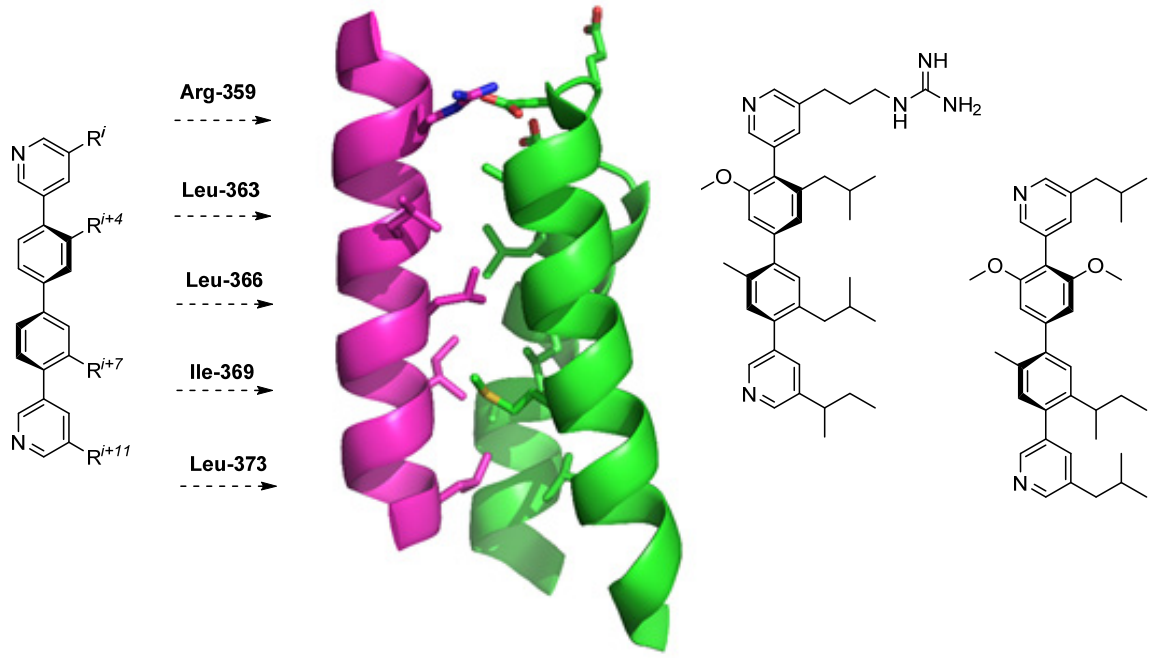
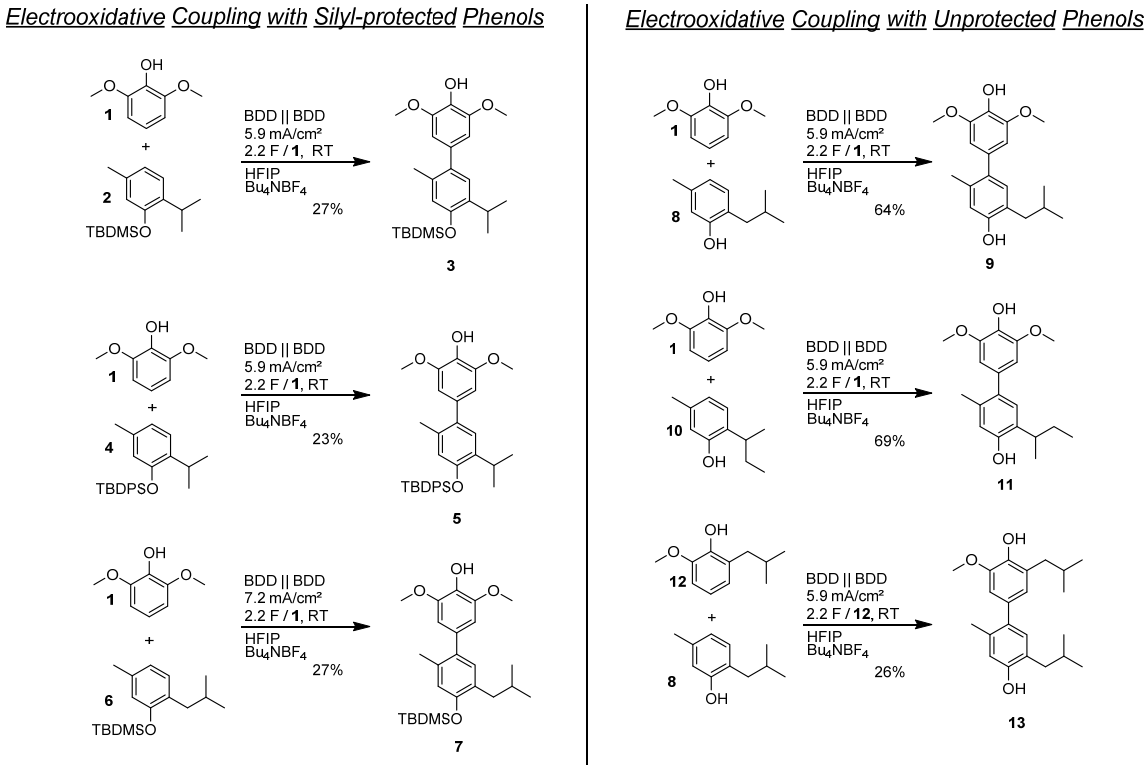


Figure 1. Proposed design for quateraryl mimetics of Bcl9 based on available crystal structure information [27]. The protein structure has been generated using Pymol [28].

2.1. Electrooxidative Cross-Coupling of Phenols

According to our retrosynthetic reasoning, the quateraryls will be assembled from 4,4′-biphenols. In order to have maximum flexibility in the selection of side-chain substituents, the core fragments should be synthesized from differently substituted phenols. In earlier work we could show that symmetric or non-symmetric 4,4′-biphenols can be prepared from suitable ortho-blocked phenols by direct anodic dehydrogenative coupling, using boron-doped diamond (BDD) electrodes and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as suitable solvent in yields up to 77% [20]. We reasoned that we could improve the selectivity in the electrochemical cross-coupling if we would offer one reaction partner as a free phenol and the second one as a protected phenol [29–31]. For synthetic efficiency, we considered a silyl-protecting group as a good choice. In the event, we tried *tert*-butyldimethylsilyl (TBDMS)-protected phenols **2** and **6** and *tert*-butyldiphenylsilyl (TBDPS)-protected phenol **4** in the coupling with 2,6-dimethoxyphenol (**1**). The yields for the cross-coupling reactions were with 23–27% rather low (Scheme 1, left column). As a comparison, the yields for the unprotected building blocks are displayed (Scheme 1, right column), which, except for **13**, provided the 4,4′-biphenols in yields >60%.



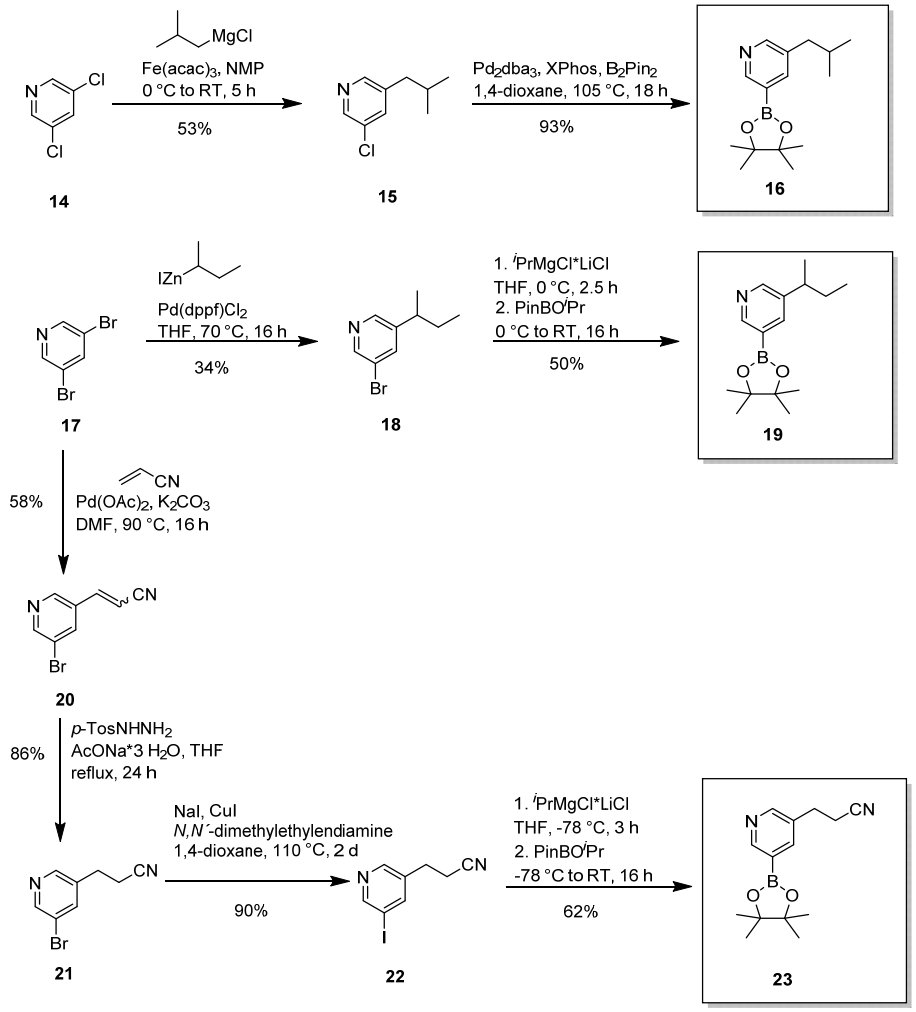
Scheme 1. Electrooxidative cross-coupling of phenols and phenolethers forming 4,4′-biphenol building blocks.

In addition to its poor coupling yields, the silyl-monoprotected building blocks could also not be successfully used in the subsequent nonaflation/Pd-cross coupling steps. Therefore, we preferred to use the unprotected 4,4′-biphenols as core fragments for the assembly of our target quateraryls, which would make the synthetic route even more efficient and shorter.

2.2. Synthesis of Pyridine Boronic Acids

For the final assembly of our target structures we would need pyridine boronic acids featuring the side chain of leucine (**16**), isoleucine (**19**), and arginine (Scheme 2). The leucine pyridine boronic acid was produced in an efficient two-step synthesis starting from 3,5-dichloropyridine (**14**). Fe-catalyzed Kochi-Fürstner cross-coupling [32] of **14** with isobutyl-Grignard delivered **15** in a 53% yield, which could

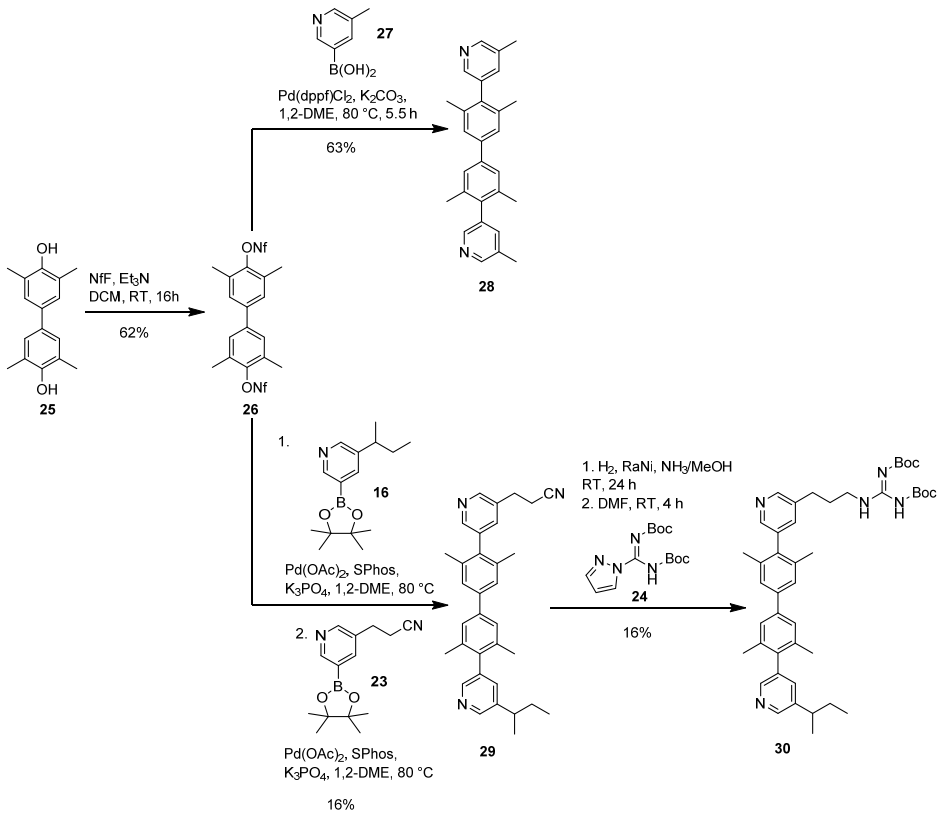
be converted to leucine pyridine boronic acid **16** via Miyaura-borylation with Pd/XPhos in an excellent yield of 93%. For the synthesis of the isoleucine pyridine boronic acid ester **19** a Negishi-coupling strategy was chosen. Starting from 3,5-dibromopyridine (**17**) Negishi-coupling with the in-situ prepared 2-butyl zinc reagent furnished pyridine **18** in a 34% yield. Activation of **18** with a Knochel-Grignard [33] and an electrophilic quench with (pin)BO^{i}Pr resulted in an isoleucine boronic acid ester **19** in a 50% yield. In previous work, we have realized that an arginine building block would be very difficult to handle, not only in the synthesis of building blocks, but also in the assembly of the oligoarenes. Therefore, we preferred to incorporate this building block in a latent alkylnitrile form **23**, which, after oligoarene assembly, can be efficiently converted to the arginine side chain by nitrile reduction, and converting the resulting primary amine with $(Boc)_2$N-guanylation reagent **24**. The Heck reaction of 3,5-dibromopyridine (**17**) with acrylonitrile furnished **20** in a 58% yield. Chemoselective alkene reduction with diimide in situ generated from tosylhydrazide produced **21** in an 86% yield. Building on earlier experience, we chose to convert the bromopyridine **21** to the iodopyridine **22** using the Buchwald–Finkelstein reaction [34] in order to facilitate the planned metalation, with the Knochel–Grignard forming a pyridinyl-Grignard intermediate. Indeed, this transformation and subsequent electrophilic quench with (pin)BO^{i}Pr allowed the isolation of latent Arg-building block (Arg*) **23** in a good yield of 62%.



Scheme 2. Synthesis of the pyridine boronic acid ester building blocks.

2.3. Quateraryl Assembly

In order to establish the conditions for the assembly of the quateraryls, we used commercial 3,3′,5,5′-tetramethyl-4,4′-biphenol (**25**) as a model core fragment (Scheme 3). With its two ortho-substituents, it represents a sterically and electronically challenging pattern for subsequent cross-coupling reactions. The methyl substituents are representative of Ala-side chains, giving rise to test compounds, which could serve as control compounds in biological assays following the strategy of an alanine scan widely used in the biochemistry of proteins [35]. Despite considerable effort in optimization, we never succeeded in using the bistriflate of **25** in Pd-catalyzed cross-coupling reactions. We faced considerable side reactions in the form of hydrolysis of the triflate by any type of inorganic base used in the Suzuki-coupling reactions. Therefore, we chose nonaflates as leaving groups, which have been described as a more stable and convenient substrate in Pd-catalyzed cross-coupling reactions [36]. Nonaflation of **25** with nonafluorobutanesulfonylfluoride (NfF) in DCM delivered bisnonaflate **26** in a 62% yield. Suzuki-coupling with 5-methyl-3-pyridine boronic acid ester (**27**) with $Pd(dppf)Cl_2$ as catalyst and K_2CO_3 as base produced the Ala-Ala-Ala-Ala-quateraryl **28** in a 63% yield. For the synthesis of the asymmetrically substituted Arg-Ala-Ala-Ile quateraryl **30**, $Pd(OAc)_2$/SPhos was chosen as the catalyst. Bisnonaflate **26** was coupled first with Ile-building block **16** and then—after isolation of the teraryl—with the cyanoethyl-building block **23**, using the same catalyst system. As the selectivity of the reaction for the heterocoupling product was only moderate, desired product **29** could only be isolated in a 16% yield. The cyanoethyl group could be converted into the arginine-side chain by first reducing the nitrile to a primary amine with Raney-Ni, followed by reaction with guanylating reagent **24**, producing Arg-Ala-Ala-Ile-quateraryl **30** in a 16% yield over two steps.

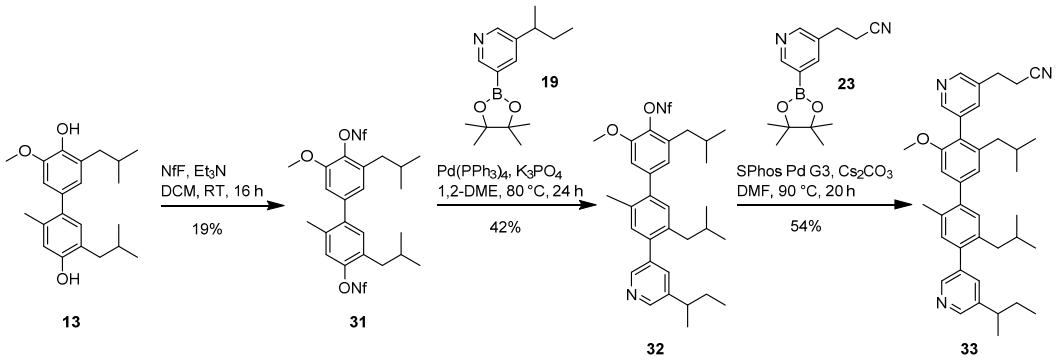


Scheme 3. Synthesis of the quateraryls in the form of Ala-controls.

2.4. Synthesis of Quateraryls as Bcl9-Mimetics

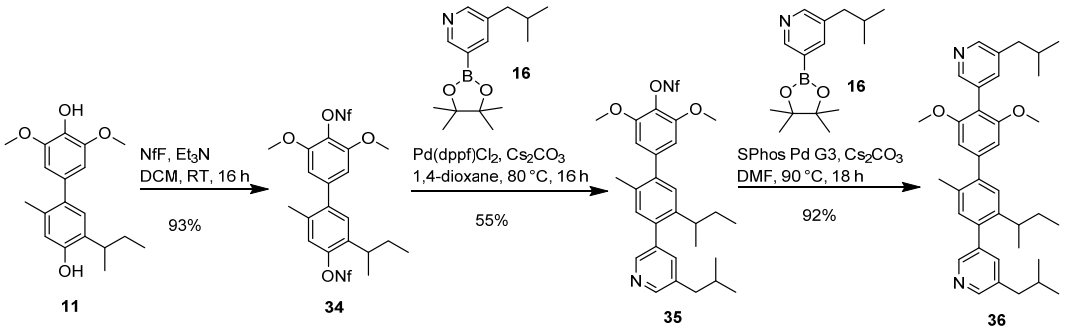
With the productive nonaflate strategy for quateraryl assembly at hand, we could take on the challenge of preparing quateraryls with four different aryl building blocks. As a first target, we selected

the Ile-Leu-Leu-Arg*-quateraryl **33** (Scheme 4). Starting from heterocoupling product **13** nonaflation produced **31** in a 19% yield. From the two nonaflate groups in **31**, we expected the nonaflate at the bottom ring for steric and electronic reasons to be more reactive than the one at the top ring, which is flanked by two ortho-substituents, among which one is a strongly electron-donating methoxy group. As expected, the bottom ring nonaflate reacted first in a Suzuki-coupling with Ile-pyridine boronic acid ester **19**, leaving the top ring nonaflate intact for a second Suzuki-coupling with cyanoethyl building block **23**, furnishing target Ile-Leu-Leu-Arg*-quateraryl **33** in decent yields.



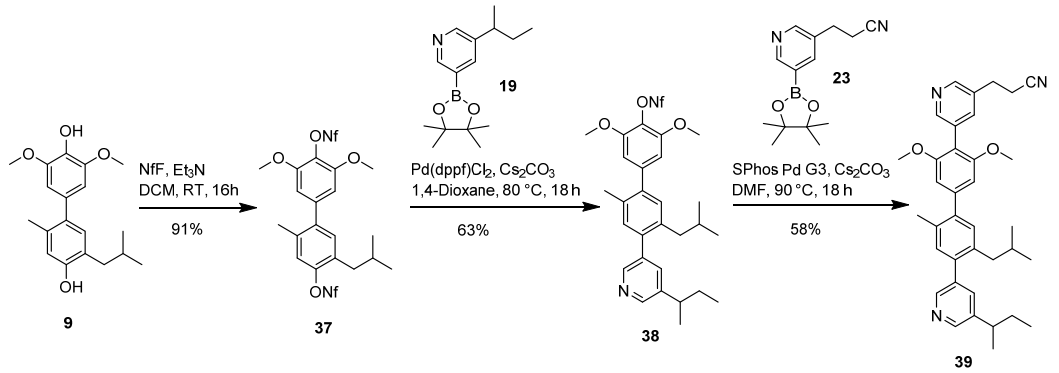
Scheme 4. Synthesis of the Ile-Leu-Leu-Arg*-quateraryl **33**.

Similarly, the Leu-Ile-"MeO"-Leu-quateraryl **36** could be assembled in an impressive 47% overall yield from the bisphenol **11** (Scheme 5). For the coupling of the second nonaflate, again the SPhos Pd G3 catalyst [37] turned out to be very efficient.



Scheme 5. Synthesis of the Leu-Ile-"MeO"-Leu-quateraryl **36**.

The same precursor also served as the starting material for the synthesis of Ile-Leu-"MeO"-Arg*-quateraryl **39**, which could be synthesized in a 33% overall yield (Scheme 6).



Scheme 6. Synthesis of the Ile-Leu-"MeO"-Arg*-quateraryl **39**.

3. Materials and Methods

Electrochemical Anodic Dehydrogenative Cross-Coupling Reactions

Reaction parameter optimization of anodic cross-coupling reactions was carried out in undivided 5 mL Teflon cells (self-made by the mechanical workshop at JGU Mainz, Germany; or commercially available from IKA, Staufen, Germany as the IKA Screening System), equipped with a Teflon cap for precise alignment (electrode distance: 4.8 mm) of the electrodes. As the electrode material BDD was used (0.3 × 1.0 × 7.0 cm, 15 µm boron-doped diamond layer on silica, commercially available from CONDIAS GmbH, Itzehoe, Germany, DIACHEM^{TM}). Preparative scale electrolysis reactions were carried out in 25 mL undivided beaker-type glass cells with or without cooling jacket (self-made by the mechanical workshop at JGU Mainz), capped with a Teflon plug for precise alignment (electrode distance: 0.8 cm) of the BDD electrodes (0.3 × 2.0 × 6.0 cm, 15 µm boron-doped diamond layer on silica, commercially available from CONDIAS GmbH, Itzehoe, Germany, DIACHEM^{TM}).

4. Conclusions

With the examples shown above, we could for the first time demonstrate the synthetic potential which can be harvested when combining the synthetic efficiency of electrooxidative dehydrogenative cross-coupling of ortho-substituted phenols with the power of Pd-catalyzed cross-coupling reactions. In our research it appeared necessary that the phenols are activated as nonaflates instead of triflates, as the latter showed considerable liabilities in the subsequent Pd-catalyzed reactions due to their hydrolytic lability against bases. In contrast, the nonaflates could be conveniently subjected to Pd-catalyzed cross-coupling reactions. The selectivity could be controlled by electronic and steric effects differentiating the reactivity of the two nonaflate groups. With the synthesis of a Bcl9 quateraryl mimetic, we could highlight this synthetic strategy on a particularly challenging substrate. The overall efficiency was shown in the highly convergent assembly of this quateraryl α-helix mimetic featuring the side chains of Bcl9. We expect that the synthetic methodology reported here will find applications in the synthesis of oligoarene structures, as required in Chemical Biology and Material Sciences.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/3/340/s1, Experimental procedures and full spectroscopic characterization of all synthesized compounds.

Author Contributions: Conceptualization, M.V., S.R.W. and R.B.; development of the electrochemical coupling, B.D., M.V. and S.R.W.; synthesis of building blocks and oligoarene assembly, M.V., M.L., M.T. and M.H.H.; writing—original draft preparation, R.B.; structural assignment via NMR, H.W.; writing—review and editing, M.V., M.M.H. and S.R.W.; funding acquisition, S.R.W. and R.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Austrian Science Fund (FWF) (Project I-2712) to R.B. and by the DFG (Wa1276/14-1) to S.R.W. as a joint D-A-CH project. Support for M.H.H. by the OeAD (Österreichischer Austauschdienst) via an Ernst-Mach-fellowship is gratefully acknowledged.

Acknowledgments: We thank Amber Ford and Sarah Berger for skillful assistance in the lab and for Open Access Funding by the Austrian Science Fund (FWF).

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results".

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