# Synthesis of Highly Fluorinated 2,2′-Biphenols and 2,2′-Bisanisoles

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ABSTRACT
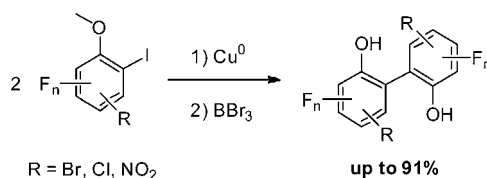
Multiply fluorine-substituted iodo anisoles are efficiently coupled in an Ullmann-type reaction to provide the corresponding bisanisoles. The coupling is selective and even tolerates bromo moieties. Subsequent deprotection of hydroxy groups gives access to highly fluorinated biphenols.

Biphenols and related biaryls are very useful molecular architectures in catalysis and asymmetric transformations. These particular scaffolds provide chelating ligand systems with an appropriate flexibility.[1] Partial fluorination of these biphenols and binaphthyls results in more acidic systems, which imparts enhanced Lewis acidity to the metal complexes.[2] Consequently, several strategies have been realized to obtain partially[3,4] and perfluorinated binaphthyl deriva-

tives.[5] The fluorination causes a considerable electronic perturbation of the aromatic systems. This results in inverted electrostatic potential surfaces compared to the nonfluorinated species.[6] Not surprisingly, such highly fluorinated compounds are of interest for energy storage applications.[7] Moreover, the specific lipophilicity and metabolic stability of fluorinated structures lead to significant application in drug development and pharmaceutical applications.[8] The strong polarization of C,F-bonds also attracted research in liquid crystal development.[9] While the fluorinated naphthyl derivatives are well investigated,[2−5] the biphenyl congeners are only scarcely treated.

A direct oxidative coupling of fluoro phenols to the corresponding 2,2′-biphenols by standard methods[10] or electrochemical protocols fails as a result of the deactivating

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properties of fluoro moieties.[11] Only when boron-doped diamond anodes are employed, less fluorinated 2,2′-biphenols can be obtained in moderate yields.[12] However, substrates containing more than one fluorine atom show no conversion in this particular method.[13] The common synthetic access to some derivatives involves the oxidation of lithiated intermediates.[14,15] In several cases the fluorinated biphenols appear only as byproducts.[15,16] The higher fluorinated biphenols are not reported as prepared compounds but rather investigated in silico.[17]

We report a reliable procedure to prepare the highly fluorinated biphenols by an Ullmann-type coupling reaction.[18] As starting material the fluorinated iodo anisoles **2** are used, which are readily accessible by a telescoped iodination/methylation sequence from commercially available fluorinated phenols **1**.[19] The iodination of **1** is carried out with an I_2/I^- mixture under alkaline conditions (Scheme 1).[20]

Scheme 1. Synthesis of the Substrates: Iodination and O-Methylation of Fluorinated Phenols
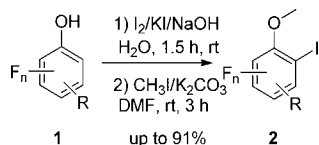
Most remarkably, our protocol tolerates bromo substituents in the Ullmann-type coupling. In previous synthetic studies bromo derivatives were exploited in the coupling process itself.[3] These brominated biaryls are of specific interest since they allow further manipulations based on transition metal cross-coupling reactions.[21]

For a successful reaction of the iodinated substrates **2**, solvent-free conditions are advantageous, since with the tested substrates the use of high-boiling solvents as quinoline or DMPU results in significantly lower yields. Addition of DMPU tremendously slows down the reaction rate and is therefore not recommended. However, a well-mixed and compressed reaction mixture of freshly activated copper and iodoarenes leads to good and reliable results (Scheme 2).

Scheme 2. Ullmann Coupling of Fluorinated Anisoles
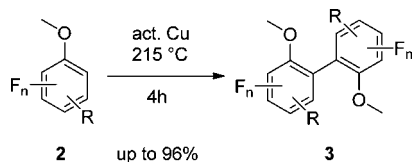
Conversion of monofluoro iodoanisole **2a** provides the corresponding bisanisole **3a** in a clean reaction with good isolated yields (Table 1, entry 1). The compatibility of other halogen substituents was studied in this particular transfor-

Table 1. Synthesis of Fluorinated Bisanisoles by Ullmann-Type Coupling

entry	substrate	conditions	bisanisole	yield (%)
1	**2a**	215 °C 4 h		80 (**3a**)
2	**2b**	215 °C 4 h		63 (**3b**)
3	**2c**	215 °C 4 h		82 (**3c**)
4	**2d**	215 °C 4 h		84 (**3d**)
5	**2e**	215 °C 4 h		87 (**3e**)
6	**2f**	215 °C 4 h		95 (**3f**)
7	**2g**	215 °C 4 h		95 (**3g**)
8	**2h**	215 °C 4 h		96 (**3h**)
9	**2i**	210 °C 0.5 h		57 (**3i**)

mation. Anisole **2b** involves beside the envisioned iodo leaving group also a bromo moiety, which can act as functionality for the coupling process. With the elaborated

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Scheme 3. Byproduct of the Conversion of **2b** to **3b** in the Ullmann-Type Coupling

Scheme 4. Deprotection of the Fluorinated Bisanisoles
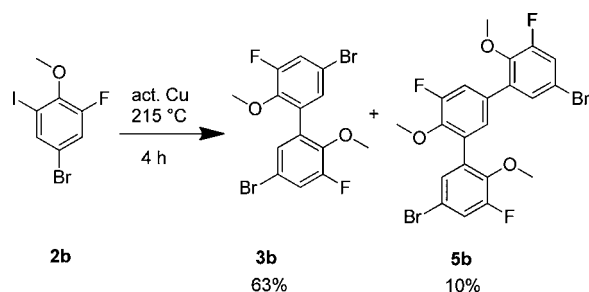
conditions the desired bisanisole **3b** was obtained in 63% isolated yield (entry 2).

As a byproduct the 2,2′;4,4′-teranisole **5b** was identified and isolated in 10% yield; **5b** is formed by a 2-fold Ullmann coupling wherein a single bromo function enters the reaction scene (Scheme 3). However, our conditions tolerate bromo substituents and still give preparative useful results, despite the prior use of fluorinated bromoarenes as substrates in the Ullmann coupling.[3] The chloro analogue substrates are less prone to side reaction and yield the desired biaryls **3c** and **3d** in good yields (entries 3 and 4). Employment of multiply fluorinated anisoles as substrates is rendered in significantly improved yields. Difluoroiodoanisoles **2e** and **2f** are homo-coupled in 87% and 95% isolated yield, respectively (entries 5 and 6). An additional fluorine in the substrate leads in the Ullmann coupling to almost quantitative yields for the bisanisoles **3g** and **3h** (entries 7 and 8).
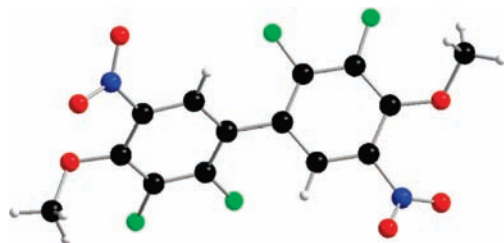

Figure 1. Molecular structure of **3i** by X-ray analysis of a single crystal.

The protocol is not limited to fluorinated 2-iodoanisoles, since anisole **2i** exhibiting the iodo function in position 4 is successfully converted to the highly functionalized biaryl **3i** (entry 9), although in this case the presence of nitro groups lowers the yield due to thermal decomposition. For this reason a slightly lower reaction temperature and a shorter reaction time is necessary. In order to confirm the aryl−aryl connectivity, an X-ray analysis of a suitable single crystal was carried out (Figure 1).

The demethylation reaction is best performed by boron tribromide (Scheme 4), since strong nucleophiles for the dealkylation, e.g., sulfide or cyanide, are not compatible with
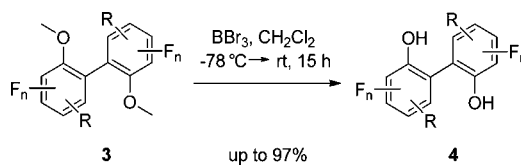
Table 2. Synthesis of Fluorinated Biphenols by Deprotection of the Corresponding Bisanisoles with BBr$_3$

entry	substrate	conditions	bisanisole	yield (%)
1	**3a**	0.5 h at 0 °C 3 equiv BBr$_3$		93 (**4a**)
2	**3b**	15 h at rt 4 equiv BBr$_3$		91 (**4b**)
3	**3c**	15 h at rt 4 equiv BBr$_3$		95 (**4c**)
4	**3d**	15 h at rt 4 equiv BBr$_3$		97 (**4d**)
5	**3e**	15 h at rt 4 equiv BBr$_3$		95 (**4e**)
6	**3f**	1 h at 0 °C 3 equiv BBr$_3$		96 (**4f**)
7	**3g**	15 h at rt 4 equiv BBr$_3$		92 (**4g**)
8	**3h**	10 d at rt 10 equiv BBr$_3$		80 (**4h**)
9	**3i**	15 h at rt 6 equiv BBr$_3$		94 (**4i**)

the fluorine moieties on the biaryls. Using excess of the demethylation agent guarantees quantitative conversions, and the desired 2,2′-biphenol derivatives **4** are isolated in excellent yields (Table 2).

While the substrate **3a** is demethylated in a short time, the other bisanisoles require prolonged reaction times. This might be due to substituents with hetero atoms in the vicinity of the methoxy functionality. This is also demonstrated in the conversion of **3f**, which is performed much faster since these heteroatoms are not in the proximity.

Heteroatoms in the positions 6 and 6′ also create a strong coordinating environment for boron tribromide. Therefore, reaction of **3h** requires larger amounts of reagent and prolongued reaction time for acceptable yields (Table 2, entry 8). In this case the incomplete conversion after 10 days to **4h** was observed and the single deprotected bisanisole could be isolated in 7% yield. The molecular structure of **4i** and **4h** was determined by X-ray analysis of suitable single crystals (Figure 2). A hydrogen bonding pattern was found only between substituents at the positions 2 and 2′ and not to the fluorine moieties. A closer look at the packing reveals a formation of ribbons that are dominated by hydrogen bonding (Supporting Information).

In conclusion, the Ullmann-type coupling represents the best synthetic way for the preparation of multiply fluorinated
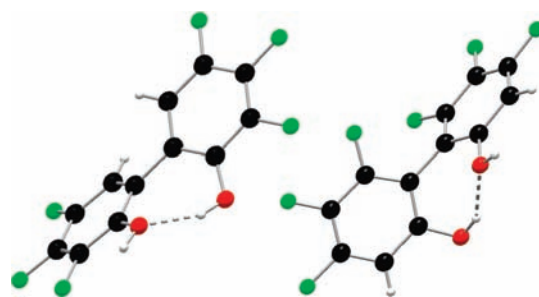

Figure 2. Molecular structure of **4i** (left) and **4h** (right) by X-ray analysis of a single crystals.

biphenols. The required substrates are readily available in excellent yields by a telescoped iodination/methylation sequence. The coupling is best performed under solvent-free reaction conditions. Since iodo groups are the preferred leaving functionalities, even bromo substituents are tolerated in this transformation. With an increasing number of fluoro substituents the coupling process is performed almost quantitatively. Demethylation to the desired biphenol requires prolonged reaction times and excess of boron tribromide since heteroatoms in the vicinity also coordinate to the reagent and slow down the process. By our approach the fluorinated 2,2′-biphenols are quickly and reliably prepared. The application in energy storage devices, e.g., biphenoxy borates,[22] and employment as ligands for catalysis will be reported in due course.

Supporting Information Available: Detailed synthetic procedures and characterization of all products including crystallograhic data for **3i**, **4g**, and **4h** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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