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Aryne-mediated fluorination: Synthesis of fluorinated biaryls *via* a sequential desilylation–halide elimination–fluoride addition process

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ABSTRACT

An unusual aryne-mediated fluorination of aromatic ring systems during the desilylation of *ortho*-bromo-biphenyl-trimethylsilanes with tetrabutylammonium fluoride (TBAF) is described. *In* situ formation of an aryne and addition of fluoride affords fluorinated biphenyls. The structures have been undoubtfully confirmed by synthesis of authentic samples *via* Suzuki–Miyaura cross-coupling and X-ray analysis. *In situ* trapping experiments with furan proved the transient formation of aryne by fluoride-induced displacement of the TMS group and subsequent bromide elimination.

The "Laboratoire de stéréochimie" belongs to a mixed CNRS-University of Strasbourg research group (UMR CNRS 7509) implemented at the European School of Chemistry, Polymers and Material Sciences (ECPM) in Strasbourg. Our research focuses on the development of new organic and organometallic methodologies and find their application in the synthesis of biologically active compounds, new ligands for asymmetric catalysis and pharmacophores as well as agrochemical targets. One of the principal research activities of the group lies in the total synthesis of natural products. The second research topic focuses on the control of axial chirality in biaryls employing atropo-diastereo- and enantioselective Suzuki–Miyaura cross-coupling reactions, C–H activation or transition-metal free aryl–aryl ARYNE coupling reactions. This expertise has been successfully applied in the synthesis of biaryl-based ligands for C–C, C–N, C–O and, more recently, C–F coupling protocols. The use of fluorinated ligands being intensively studied in this field. The third research area concerns the development of new fluorination methodologies with application in the synthesis of uncommon heterocycles bearing fluorinated substituents like α-fluoroethers with application in Life Science oriented research. The group succeeded recently in the first modular synthesis of trifluoromethoxy pyridine building-blocks.

1. Introduction

Arynes (1,2-dehydrobenzenes) and their heterocyclic analogues (heteroarynes) are highly reactive intermediates in organic chemistry and have attracted in recent years increasing interest due to their wide synthetic applications [1,2]. They react with a variety of *N*-, *S*-, *O*-, *Se*- [3–11], and *P*-nucleophiles [12] as well as with carbanions [13–19]. With alkenes they undergo Diels–Alder-type cycloaddition reactions [20–22], [2 + 2] cycloaddition [23,24], 1,3-dipolar cycloaddition [25,26] and transition-metal catalyzed reactions making them powerful tools in organic synthesis [27–31]. Note that aryl–aryl couplings using arynes as key intermediates have been described in the literature in some cases [14,32–35]. In this research area, our group made intensive researches and reported very recently on the efficient synthesis of *ortho*,*ortho*′-tri- and tetrasubstituted bromobiphenyls *via* a transition metal free cross-coupling procedure. This so-called "ARYNE coupling" methodology is based on the reaction of thermodynam-

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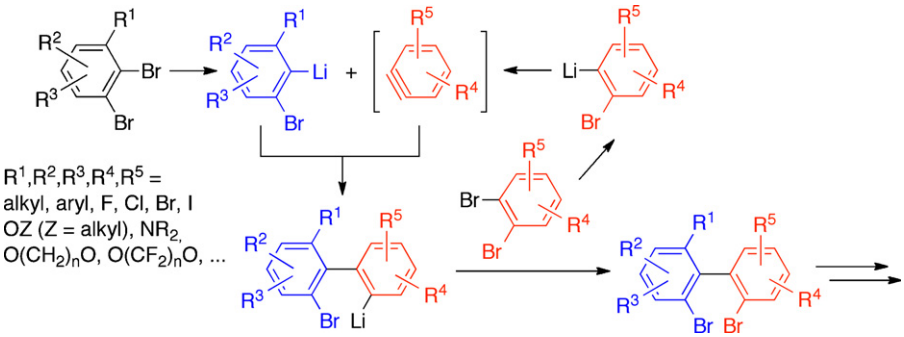


Fig. 1. ARYNE coupling methodology.

ically stable organolithium intermediates with arynes [13,14] generated *in situ* by reaction with symmetrical [13], and more recently, unsymmetrical 1,2-dibromobenzenes (Fig. 1) [36]. The latter became accessible due to highly complementary transition-metal catalyzed and polar organometallic protocols [37]. We could show that unsymmetrical arynes undergo with perfect regioselectivity the ARYNE coupling by using sterically demanding silyl-groups in the *ortho*-position of the aryne functionality [36]. The advantage of trialkylsilyl groups is, beside their sterical crowding, that they can be easily displaced by protodesilylation [38,39], bromodesilylation [38,40], or iododesilylation [38,41–43].

In the ARYNE cross coupling, 1,2-dibromobenzenes are used as aryne precursors, but various other methods for the *in situ* generation of an aryne are known. They imply most oftenly the elimination of a leaving group such as halide, tosylate, triflate, diazonium, trialkyl-ammonium, etc. from the *ortho*-position of a metalated aromatic ring [44–50].

For example, *ortho*-metalations on aromatic triflates [51] as well as halogen/metal permutations on *ortho*-halotriflates [52] or 1,2-dibromobenzenes (as shown in Fig. 1 in the mechanism of the ARYNE cross-coupling) have been successfully applied to produce arynes. Beside these well-established organometallic methods, an alternative strategy has emerged starting from trimethylsilyl triflate precursors (Kobayashi reagent). In that case, the elimination of the leaving group is induced under mild conditions by displacement of the trimethylsilyl group with fluoride anions [53]. This approach requires, however, the synthesis of aryl trimethylsilyl triflates [54].

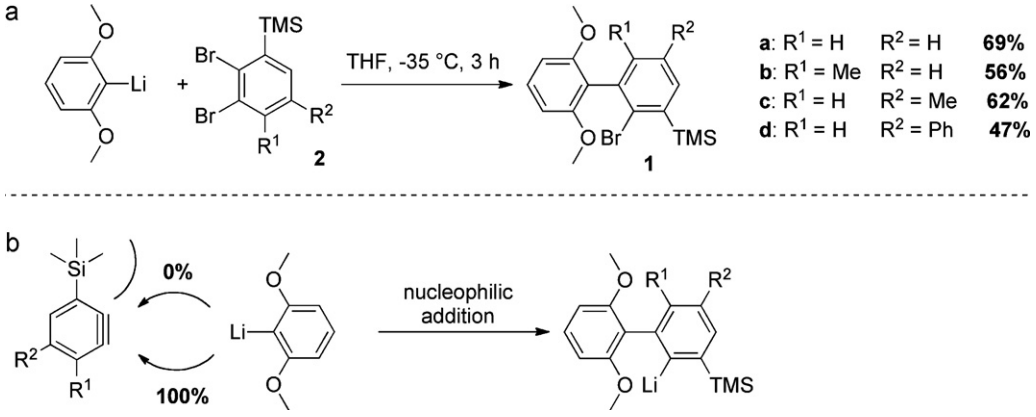
In the context of our researches dedicated to the removal of the directing silyl-group in the ARYNE coupling methodology, we describe now the generation of aryne by fluoride induced elimination of bromide on *ortho*-trimethylsilyl-bromoarenes. It will be shown that the combination of this new desilylation–halide elimination process with subsequent fluoride addition allows the access to fluorinated aromatic scaffolds.

2. Results and discussion

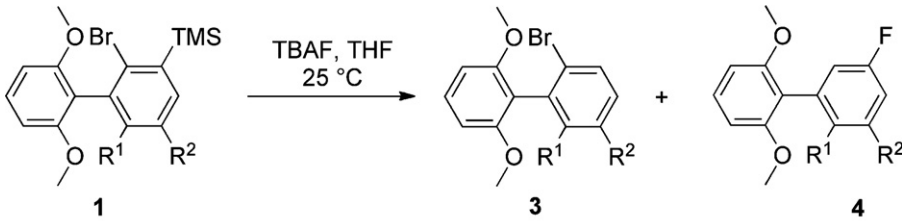
2.1. Desilylation of biaryls 1a–d with TBAF

The *ortho*-bromobiaryls **1a–d** were prepared by applying the ARYNE cross-coupling methodology [13,36] starting from 2,6-dimethoxy aryllithium and functionalized 1,2-dibromobenzenes **2a–d** (Scheme 1a). As outlined previously, the trimethylsilyl group (TMS) has been chosen in order to guarantee a perfect control of the regioselectivity during the addition of the aryllithium nucleophile onto the aryne by virtue of its steric hindrance (Scheme 1b). Moreover, the TMS group can be easily introduced on the starting material by means of selective *ortho*-metalation reactions [37].

Classically, the TMS group can be removed with tetrabutylammonium fluoride (TBAF) in THF at 25 °C. However, in case of the *ortho*-bromobiaryls **1a–d**, the expected desilylated biaryls **3a–d** were obtained in mixture with the fluorinated derivatives **4a–d** (Scheme 2). The isolated yields as well as the ratio of desilylated and fluorinated products depended on the substitution pattern of the aryl silane moiety. Starting from the non-substituted compound **1a**, a mixture that mainly contained the fluorinated derivative **4a** (70%) was isolated in 49% yield. When a phenyl group was present in *meta*-position of the silane, the yield of the reaction was increased to 72% and the ratio between fluoro and bromobiaryls increased in favor of the latter one (**3d**/**4d** = 74:26). Crystallization from MeOH provided the analytically pure terphenyl **3d** in 40% yield. An intermediate situation was observed with biaryls **1b–c** substituted with a methyl group either at the 5′- or 6′-position of the biaryl ring system.



Scheme 1. Synthesis of biaryls **1a–d** by ARYNE cross-coupling. (a) Experimental results. (b) Regioselectivity of the addition.



a: R^1 = H	R^2 = H	49% yield	30 : 70
b: R^1 = Me	R^2 = H	49% yield	46 : 54
c: R^1 = H	R^2 = Me	55% yield	47 : 53
d: R^1 = H	R^2 = Ph	72% yield	74 : 26

Scheme 2. Main products obtained by desilylation of biaryls **1a–d**.

In order to elucidate the chemical structure of all fluorinated side products, authentic samples of **4a–d** were synthesized *via* Suzuki–Miyaura cross-coupling reactions (Scheme 3). The biaryls **4a** and **4b** were prepared in one step starting from 1-fluoro-3-iodobenzene and 2-bromo-4-fluoro-1-methyl-benzene, respectively. Heating at reflux these halogenated compounds with the 2,6-dimethoxyphenyl boronic acid in a mixture of toluene, ethanol and aqueous Na_2CO_3 in the presence of catalytic amount of $Pd(PPh_3)_4$ cleanly gave the expected products **4a** and **4b** in 55% and 76% yield, respectively. In the case of compound **4c** we prepared also the regioisomer **5** with fluorine at the 2′-position in order to confirm the relative position of the fluorine atom on the aromatic ring. The 2′-fluoro regioisomer **5** was synthesized analogously as compound **4a** with 49% yield, starting from 2-bromo-1-fluoro-4-methylbenzene. On the other hand, a two-step procedure was needed to access compound **4c**. 1,3-Dibromo-5-fluorobenzene was converted by Suzuki–Miyaura coupling into biaryl **6** in a yield of 59%. Subsequent bromine/lithium permutation with BuLi in THF at −78 °C followed by electrophilic trapping with methyl iodide led to the 3′-fluoro regioisomer **4c**. The comparison of the NMR data unambiguously proved that the fluorine atom was introduced in the 3′-position relative to the biaryl bond. The regioselectivity of the fluorination was also confirmed in the case of **1d** by the synthesis of the terphenyl **4d**. A three-step procedure converted 1,3-dibromo-5-fluoro benzene into terphenyl **4d** with 40% overall yield. First, magnesiation of the starting material at −40 °C in THF using *i*PrMgCl followed by trapping with 2-isopropoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane afforded the boronic ester **7** in 53%. A first Suzuki–Miyaura cross-coupling with an excess of iodobenzene in a mixture of EtOH, toluene and aqueous Na_2CO_3 in presence of $Pd(PPh_3)_4$ provided the biaryl **8** with 90% yield. Due to the perfect chemoselectivity of iodide *vs.* bromide, no homocoupling of **7** was observed. Finally, a second Suzuki–Miyaura cross-coupling under similar conditions afforded terphenyl **4d** in 79% yield.

In addition, we succeeded to obtain from biaryl **4a** single crystals for X-ray analysis (Fig. 2). Although the fluorine atom is disordered on two positions (60% on C11 and 40% on C13 (F1b)) the X-ray determination confirmed the structure of biaryl **4a**.

Next, we studied more in detail the outcome of the desilylation/fluorination reaction on compound **1c** as model (Table 1, Entry 1). Combined NMR and GC–MS analysis confirmed the main presence of biaryls **3c** (41%) and **4c** (41%) and revealed the formation of other side products in smaller quantities. The 3′-bromo regioisomer **9** of biaryl **3c** and the benzofuran **10** were present in 12% and 6%, respectively. At the same time, the 2′-fluoro regioisomer **5** (Scheme 3) was not at all detected in the reaction mixture. Small amounts of benzofuran **10** were isolated and NMR (^1H, ^{13}C) and GC–MS analysis were in agreement with the heterocyclic structure. To confirm the structure of compound **9**, a pure sample was prepared in two steps starting from 1,3,5-tribromobenzene (Scheme 3) *via* Suzuki–Miyaura cross-coupling with 2,6-dimethoxyphenylboronic acid affording biaryl **11** (47% yield). Lithiation followed by trapping with methyl iodide gave biaryl **9** in 74% yield.

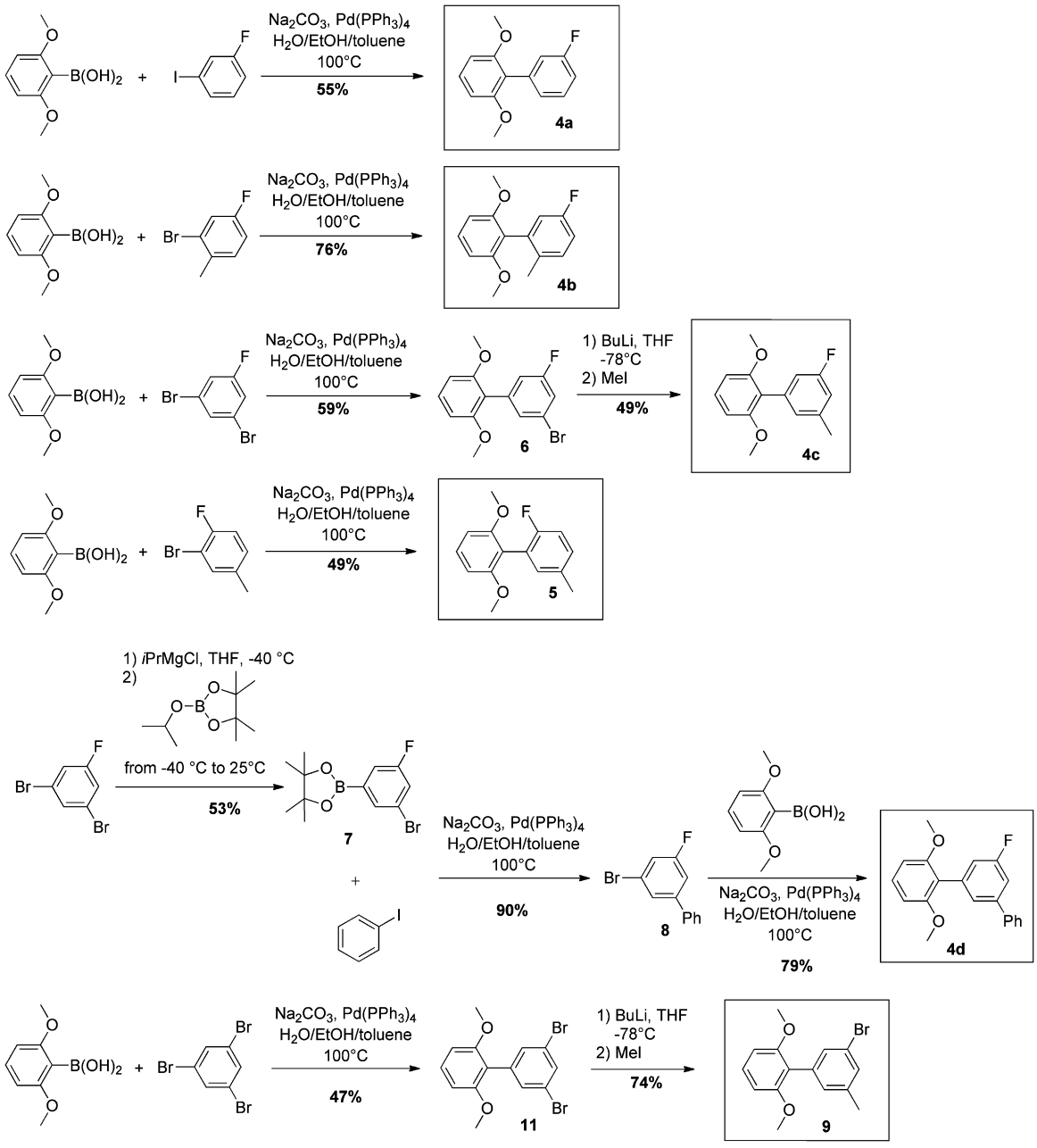
2.2. Trapping with furan

In order to elucidate further the regioselective fluorination during the desilylation reaction of *ortho*-bromobiaryls **1a–d**, we performed the reaction in presence of an excess of furan (10 equiv.). Under these conditions, possible aryne intermediates can be trapped *via* their [4 + 2] Diels–Alder cycloaddition. As described previously in the absence of furan, mixtures of biaryls **3a–c** and **4a–c** were isolated by column chromatography in 22%, 23% and 33% yield, respectively. Crystallization from MeOH provided pure samples of methylated 2-bromobiaryls **3b** and **3c.**

However, a new product, the polycyclic compound **12** was now detected as major product beside compounds **3** and **4** (Table 2). The sterically more hindered cycloadduct **12b** was obtained in a lower yield (34%) compared to **12a** and **12c** (51% and 45%, respectively). The structure of the cycloaddition product could be undoubtfully confirmed by single-crystal X-ray analysis in the case of **12c** (Fig. 3).

The formation of compound **12** revealed that after fluoride-induced desilylation, the intermediate carbanion eliminates bromide affording the corresponding aryne. At the same time, the presence of furan dramatically decreased the ratio of 3′-fluorinated derivative **4** (Table 2). The ratio of **4** did not exceed 11% in the mixture whatever the substitution pattern of the starting 2-bromosilane **1**. These results imply that the formation of biaryl **4** is due to the nucleophilic addition of the fluoride anion on the transient aryne species (Fig. 4). When furan is present in excess, the cycloaddition becomes faster than the nucleophilic fluoride addition onto the aryne intermediate leading to a decreased formation of the 3′-fluorinated derivative **4**.

The formation of 3′-bromobiaryl **9** (Table 1) starting from bromosilane **1c** can be explained in a similar manner by regioselective addition of the bromide anion onto the aryne (Fig. 4). Bromide anions are formed during the aryne formation. However, their concentration remains low until the end of the reaction. As a consequence, fluoride addition leading to 3′-fluorobiaryl **4c** largely dominates even in presence of furan. This selectivity was amplified when the initial concentration of TBAF with respect to $[TBAF]_0$ was increased in the reaction mixture by the addition of 5 and 10 equiv. of TBAF. In this case, the amount of 3-bromobiaryl **9** decreased from 12% to 7% in favor of the 3′-fluorinated derivative **4c** (Table 1, Entries 1, 3 and 4). On the other hand, addition of tetrabutylammonium bromide (TBABr)



Scheme 3. Synthesis of reference compounds **4a**–**d**, **5** and **9** *via* Suzuki–Miyaura-cross coupling reactions.

completely reversed the composition of the reaction mixture (Table 1, Entry 7). Starting material was mainly converted into 3-bromobiaryl **9** (40%) and the 3′-fluorinated derivative **4c** was only detected as minor products (26%) at the end of the reaction. These experimental data confirm that compounds **4c** and **9** result from a competitive addition of bromide and fluoride anions on the aryne *via* an intermolecular processes. The kinetics of these two reactions are mainly controlled by the relative concentration of the halogenated anions. In parallel, an intramolecular pathway involving a demethylation–cyclisation sequence provided, as depicted in Fig. 4 the benzofuran **10** from bromosilane **1c**.

The attack of fluoride at the TMS group first promotes the cleavage of the Ar–Si bond. Due to the leaving group ability of the neighboring bromide anion, the removal of the TMS group induces the partial elimination of bromide and leads, besides the classical desilylation pathway, to the formation of the aryne intermediate. Efficient precursors like 2-(trimethylsilyl)phenyl triflates [53,56] and (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflates [57,58] have already been described in the literature to generate aryne by fluoride displacement of a TMS group. Due to the high leaving group ability of triflate and iodonium, the intermediate carbanion forms quantitatively the transient aryne species. Triflate and iodonium groups being better leaving groups than iodide anions [58], we can assume similar properties for the bromide anion. However, its weaker nucleofugacity is responsible for the partial conversion of the *ortho*-bromobiaryls **1** into aryne. Note, as shown in the case of compound **1c**, that neither increasing the temperature of the reaction (Table 1, Entries 5 and 6) nor changing the concentration of TBAF (Table 1, Entries 2–4) or the nature of the nucleophile (Table 1, Entry 7) modified the product ratios resulting from the classical desilylation (**3c,** 30–40%) and aryne-mediated reactions (**4c**, **9**, and **10,** 60–70%). These results confirmed that the proportion of aryne in the reaction mixture is mainly controlled by the nature of leaving group.

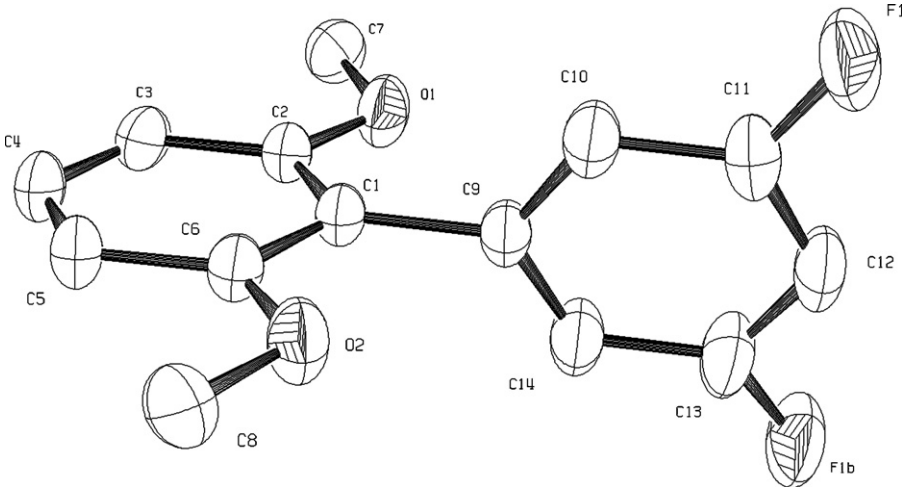


Fig. 2. Thermal ellipsoid drawing of **4a** with ellipsoids drawn to the 50% probability level (ORTEP plot) [55].

Table 1
Desilylation of biaryl **1c** under different experimental conditions.

Entry	TBABr	TBAF	$[TBAF]_0$ (in M)	Reaction conditions	Composition of the reaction mixture (in %)[a,c]	
					10	**3c**/**9**/**4c**[b]
1	–	3 equiv.	0.23	25 °C, 18 h	6	41/12/41 (81)
2	–	3 equiv.	0.23	25 °C, 18 h reverse addition	5	42/13/40 (77)
3	–	5 equiv.	0.50	25 °C, 3 h	4	40/7/49 (75)
4	–	10 equiv.	0.77	25 °C, 18 h	5	39/7/49
5	–	3 equiv.	0.23	At reflux 3 h	5	33/18/44 (72)
6	–	10 equiv.	0.77	At reflux 3 h	5	38/15/42 (70)
7	10 equiv.	3 equiv.	0.23	25 °C, 18 h	2	32/40/26 (71)

[a] Ratio of **3c**, **4c**, **9** and **10** determined by ^{1}H NMR analysis of the reaction mixture.
[b] Isolated yields of **3c** + **4c** + **9** in brackets.
[c] No starting material was detected in the reaction mixture.

Although arynes are widely used for aryl-carbon and aryl-heteroatom bond formation as outlined in the introduction, information on aryne-mediated fluorination is scarce and lacking in detail. Carbon–fluorine bond formation *via* arynes has been observed by Schwesinger's group, although this type of fluorination is only mentioned in one brief sentence in the conclusion [59]. Otherwise, the fluoride induced aryne formation from a trimethylsilyl aryl triflate and successive fluoride addition has been reported by Pérez [60,61]. Grushin nicely showed during their studies on *N,N*- and *S,S*-chelate-stabilized aryl palladium fluorides that aryne-mediated fluorination of nonactivated haloarenes with Me_4NF in DMSO is possible [61].

Although there are few precedents in the literature, trapping experiments with furan clearly demonstrate that the mechanism leading to the fluorinated product **4** is based on the addition of the fluoride anion onto the transient aryne. Steric hindrance generated by the 2,6-dimethoxyphenyl group in *ortho* position of the aryne favors this addition in 3′-position of the biaryl ring. This steric

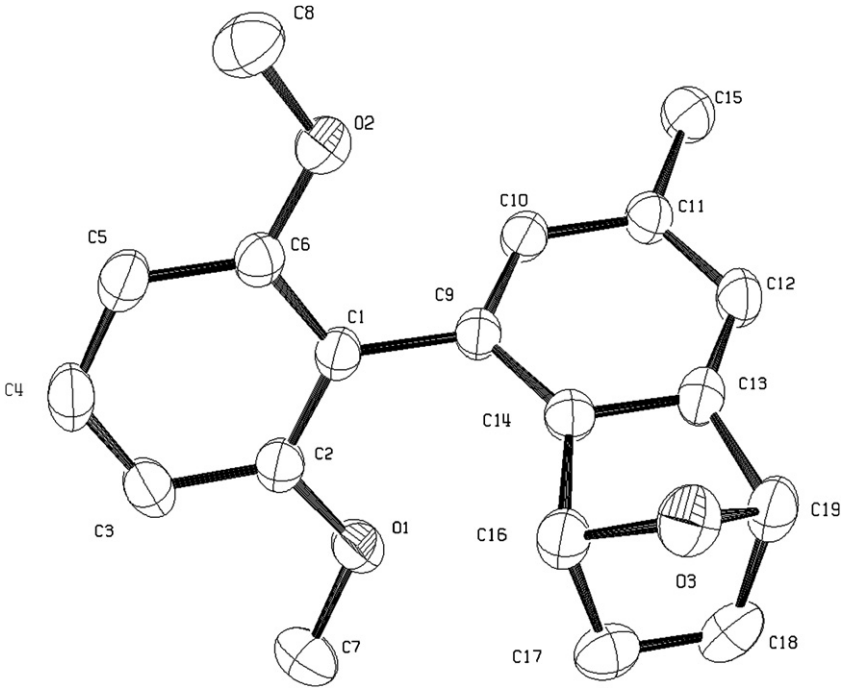


Fig. 3. Thermal ellipsoid drawing of **12c** with ellipsoids drawn to the 50% probability level (ORTEP plot) [55].

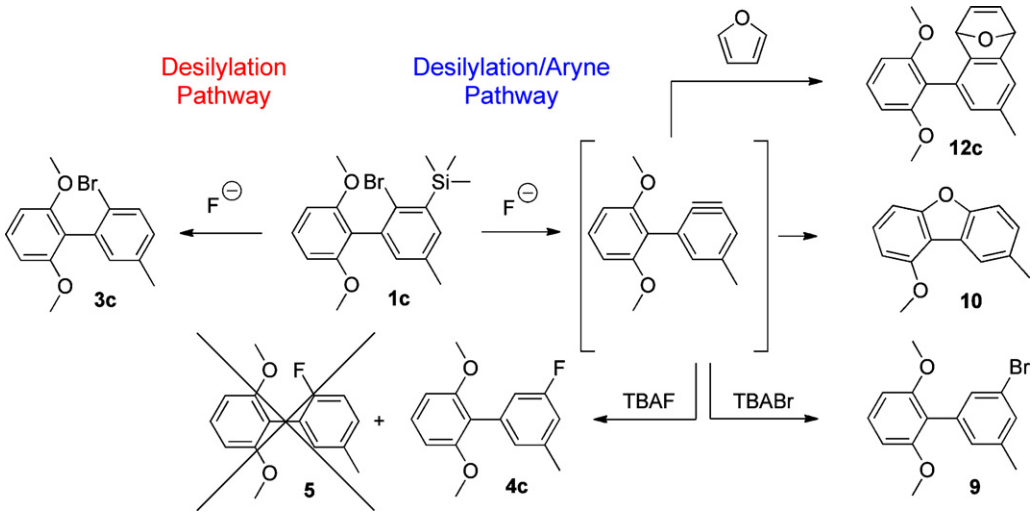


Fig. 4. Aryne-mediated mechanism leading to side products **4c**, **9**, **10** and **12c**.

Table 2
Desilylation of biaryls **11a–c** in presence of furan.

Entry	R^1	R^2	Ratio[a] **4/3/12**	Yield of **3**+**4** (in %)[e]	Yield of **12** (in %)
1	H	H	11/30/59[b]	22 (72/28)	51
2	Me	H	4/36/60[c]	23 (85/15)	34
3	H	Me	9/32/59[d]	33 (77/23)	45

[a] Ratios of **3**, **4** and **12** determined by NMR analysis of the reaction mixture.
[b] 13% of starting material (**1a**) was recovered at the end of the reaction.
[c] 35% of starting material (**1b**) was recovered at the end of the reaction.
[d] 13% of starting material (**1c**) was recovered at the end of the reaction.
[e] Values in brackets ratios of **3** and **4** determined by NMR analysis of the isolated mixture.

repulsion, amplified by the bulky tetrabutylammonium counterion of the nucleophile, prevented, as unambiguously proven in the case of bromosilane **1c**, the formation of 2′-fluorobiaryls **5**. Such a regioselectivity observed with *ortho*-substituted arynes [62,63,51,64] constitutes an additional proof for the aryne-mediated mechanism of the fluorination reaction.

3. Conclusion

Fluoride displacement of the TMS group on (2-bromobiphenyl-3-yl)trimethylsilanes led to the partial conversion of the starting material into arynes. Regioselective and nucleophilic addition on this highly reactive intermediate provided, besides the expected desilylated product, uncommon fluorinated derivatives. So far, in contrast to aryl-carbon and aryl-heteroatom bond formations involving arynes, only scarce information on aryne-mediated fluorination is described in the literature. Starting from more efficient aryne precursor this process might be used as fluorination method of aromatic rings. In light of the importance of fluorinated arenes and the practical limitations of current methods for their preparation, the conversion of easy accessible aryl halide (Br, I) or sulfonate (e.g., triflate ≡•OTf) with a nucleophilic fluorine source (such as an alkali metal fluoride) to yield the corresponding aryl fluoride is a highly desirable transformation [65–67].

4. Experimental

Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Tetrahydrofuran was dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone-sodium "radical-anion") had been found to persist. Melting ranges (mp) given were determined on a Kofler heated stage and found to be reproducible after recrystallization, unless stated otherwise ("decomp."), and are uncorrected. If melting points are missing, it means all attempts to crystallize the liquid at temperatures down to −75 °C failed. Column chromatography was carried out on a column packed with silica-gel 60 N spherical neutral size 63–210 μm. ^{1}H and (^{1}H decoupled) ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded at 400 or 300 and 101 or 75 MHz and 282 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sp (septuplet), td (triplet of doublets), m (multiplet), app. s (apparent singlet) and br (broad). Tetrabutylammonium fluoride (TBAF) was used as commercially available 1 M solution in THF.

Compounds **1a–d** and **2a–d** were prepared as previously described in the literature [36,37].

4.1. Synthesis of fluoro and bromo derivatives 4a-d, 5 and 9

4.1.1. 3′-Fluoro-2,6-dimethoxy-biphenyl (4a)

To 2,6-dimethoxyphenylboronic acid (4.50 mmol, 819 mg) in a mixture of toluene (45.0 mL), 2 M aqueous Na_2CO_3 (18.0 mL) and EtOH (9 mL) were successively added under Argon 1-fluoro-3-iodo-benzene (3.00 mmol, 666 mg) and $Pd(PPh_3)_4$ (0.15 mmol, 173 mg). This well-stirred mixture was heated at reflux for 18 h and then diluted at 25 °C with water (100 mL) and toluene (50 mL). The aqueous layer was separated and washed with CH_2Cl_2 (2 × 100 mL). All the organics layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 75:25) followed by crystallization from MeOH afforded biaryl **4a** as a colorless solid (380 mg, 55%). mp 81–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H, 2 × OCH_3), 6.66 (d, *J* = 8.4 Hz, 2H, Ar–H), 6.98–7.14 (m, 3H, Ar–H), 7.27–7.39 (m, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.0 (2 × CH_3), 104.3 (2 × CH), 113.7 (d, J_{CF} = 21 Hz, CH),

118.1 (d, J_{CF} = 22 Hz, CH), 118.4 (C), 126.8 (d, J_{CF} = 3 Hz CH), 129.0 (d, J_{CF} = 8 Hz, CH), 129.2 (CH), 136.5 (d, J_{CF} = 8 Hz, C), 157.7 (2 × C), 162.5 (d, J_{CF} = 241 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.6 (m). Anal. Calcd for $C_{14}H_{13}FO_2$: C, 72.40; H, 5.64. Found: C, 72.53; H, 5.67.

4.1.2. 5-Fluoro-2′,6′-dimethoxy-2-methyl-biphenyl (4b)

Prepared analogously as biaryl **4a**, starting from 2-bromo-4-fluoro-toluene (5.00 mmol, 0.95 g) and 2,6-dimethoxyphenylboronic acid (7.50 mmol, 1.37 g). Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 75:25) followed by crystallization from hexane at −78 °C afforded biaryl **4b** as a colorless solid (0.94 g, 76%). mp 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H, Ar–CH_3), 3.72 (s, 6H, 2 × OCH_3), 6.64 (d, J = 8.4 Hz, 1H, Ar–H), 6.86 (dd, J = 9.6, 2.7 Hz, 1H, Ar–H), 6.93 (dt, J = 8.4, 2.8 Hz, 1H, Ar–H), 7.20 (dd, J = 8.2, 6.1 Hz, 1H, Ar–H), 7.31 (t, J = 8.3 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (CH_3), 55.9 (2 × CH_3), 104.1 (2 × CH), 113.9 (d, J_{CF} = 21 Hz, CH), 117.6 (d, J_{CF} = 21 Hz, CH), 118.1 (C), 129.2 (CH), 130.6 (d, J_{CF} = 8 Hz, CH), 133.1 (d, J_{CF} = 3 Hz, C), 136.1 (d, J_{CF} = 8 Hz, C), 157.7 (2 × C), 160.9 (d, J_{CF} = 241 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −119.1 (m). Anal. Calcd for $C_{15}H_{15}FO_2$: C, 73.15; H, 6.14. Found: C, 73.19; H, 6.18.

4.1.3. 3′-Fluoro-2,6-dimethoxy-5′-methyl-biphenyl (4c)

To a solution of biaryl **6** (2.00 mmol, 622 mg) in THF (8.00 mL) was added dropwise, under Argon and at −78 °C, a solution of BuLi (2.20 mmol) in hexane (1.37 mL). The mixture was stirred at −78 °C for 2 h and methyl iodide (2.40 mmol, 0.15 mL) was added dropwise. The mixture was warmed to 25 °C overnight, hydrolyzed with water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Crystallization from MeOH at −20 °C gave biaryl **4c** (242 mg, 49%) as a colorless solid. mp 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, Ar–CH_3), 3.75 (s, 6H, 2 × OCH_3), 6.65 (d, J = 8.3 Hz, 2H, Ar–H), 6.82–6.85 (m, 2H, Ar–H), 6.94 (br s, 1H, Ar–H), 7.29 (t, J = 8.4 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (CH_3), 56.1 (2 × CH_3), 104.3 (2 × CH), 114.6 (d, J_{CF} = 21 Hz, CH), 115.0 (d, J_{CF} = 21 Hz, CH), 118.6 (d, J_{CF} = 2 Hz, C), 127.4 (d, J_{CF} = 3 Hz, CH), 129.1 (CH), 136.0 (d, J_{CF} = 9 Hz, C), 139.3 (d, J_{CF} = 8 Hz, C), 157.7 (2 × C), 162.5 (d, J_{CF} = 242 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −118.9 (br s). Anal. Calcd for $C_{15}H_{15}FO_2$: C, 73.15; H, 6.14. Found: C, 73.24; H, 6.07.

4.1.4. 5′-Fluoro-2,6-dimethoxy-[1,1′;3′,1″]terphenyl (4d)

Prepared analogously as biaryl **4a**, starting from 5-bromo-3-fluoro-biphenyl **8** (5.00 mmol, 1.26 g) and 2,6-dimethoxyphenylboronic acid (7.50 mmol, 1.37 g). Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 7:3) followed by crystallization from cyclohexane afforded terphenyl **4d** as a colorless solid (1.22 g, 79%). mp 112–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 6H, 2 × OCH_3), 6.69 (d, J = 8.4 Hz, 2 H, Ar–H), 7.08 (dm, J = 9.9 Hz, 1H, Ar–H), 7.26 (td, J = 9.9, 1.8 Hz, 1H, Ar–H), 7.33 (t, J = 8.4 Hz, 1H, Ar–H), 7.34–7.47 (m, 4H, Ar–H), 7.61–7.64 (m, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1 (2 × CH_3), 104.3 (2 × CH), 112.5 (d, J_{CF} = 22 Hz, CH), 116.9 (d, J_{CF} = 21 Hz, CH), 118.3 (d, J_{CF} = 2 Hz, C), 125.8 (d, J_{CF} = 2 Hz, CH), 127.4 (2 × CH), 127.7 (CH), 128.9 (2 × CH), 129.3 (CH), 136.6 (d, J_{CF} = 9 Hz, C), 140.5 (d, J_{CF} = 2 Hz, C), 142.3 (d, J_{CF} = 8 Hz, C), 157.7 (2 × C), 162.9 (d, J_{CF} = 242 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.8 (t, J = 9.9 Hz). Anal. Calcd for $C_{20}H_{17}FO_2$: C, 77.90; H, 5.56. Found: C, 77.46; H, 5.54.

4.1.5. 2-Fluoro-2′,6′-dimethoxy-5-methyl-biphenyl (5)

Prepared analogously as biaryl **4a**, starting from 2-bromo-1-fluoro-4-methyl-benzene (5.00 mmol, 0.95 g) and 2,6-dimethoxyphenylboronic acid (6.00 mmol, 1.09 g). Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 75:25) followed by crystallization from MeOH afforded biaryl **5** as a colorless solid (0.61 g, 49%). mp 85–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, Ar–CH_3), 3.76 (s, 6H, 2 × OCH_3), 6.65 (d, J = 8.4 Hz, 2H, Ar–H), 7.00 (t, J = 8.4 Hz, 1H, Ar–H), 7.06–7.12 (m, 2H, Ar–H), 7.31 (t, J = 8.3 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9 (CH_3), 56.2 (2 × CH_3), 104.2 (2 × CH), 113.6 (C), 115.0 (d, J_{CF} = 22 Hz, CH), 121.5 (d, J_{CF} = 17 Hz, C), 129.5 (CH), 129.5 (d, J_{CF} = 8 Hz, CH), 132.7 (d, J_{CF} = 3 Hz, C), 133.3 (d, J_{CF} = 4 Hz, CH), 158.2 (2 × C), 158.7 (d, J_{CF} = 242 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −118.9 (m). Anal. Calcd for $C_{15}H_{15}FO_2$: C, 73.15; H, 6.14. Found: C, 73.15; H, 6.19.

4.1.6. 5′-Bromo-3′-fluoro-2,6-dimethoxy-biphenyl (6)

Prepared analogously as biaryl **4a**, starting from 1,3-dibromo-5-fluoro-benzene (5.00 mmol, 1.27 g) and 2,6-dimethoxyphenylboronic acid (5.50 mmol, 1.00 g). Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 8:2) afforded biaryl **6** as a colorless solid (0.92 g, 59%) mp 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H, 2 × OCH_3), 6.64 (d, J = 8.4 Hz, 2H, Ar–H), 7.01 (dm, J = 9.5 Hz, 1H, Ar–H), 7.18 (td, J = 8.3, 2.0 Hz, 1H, Ar–H), 7.27 (m, 1H, Ar–H), 7.29 (t, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0 (2 × CH_3), 104.2 (2 × CH), 117.0 (d, J_{CF} = 1 Hz, C), 117.3 (d, J_{CF} = 21 Hz, CH), 117.4 (d, J_{CF} = 24 Hz, CH), 121.6 (d, J_{CF} = 10 Hz, C), 129.8 (CH), 130.0 (d, J_{CF} = 3 Hz, CH), 137.9 (d, J_{CF} = 9 Hz, C), 157.6 (2 × C), 162.3 (d, J_{CF} = 247 Hz, C); ^{19}F (282 MHz, $CDCl_3$): δ −112.6 (t, J = 8.8 Hz). Anal. Calcd for $C_{14}H_{12}BrFO_2$: C, 54.04; H, 3.89. Found: C, 54.01; H, 4.09.

4.1.7. 2-(3-Bromo-5-fluoro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (7)

To 1,3-dibromo-5-fluoro-benzene (40.0 mmol, 10.2 g) in THF (100 mL) was added dropwise, under inert atmosphere and at −40 °C, a solution of *iso*propyl magnesium chloride (44.0 mmol) in THF (22.0 mL). After 3 h at −40 °C, 2-isopropoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (48.0 mmol, 8.93 g) was added dropwise. The reaction mixture was warmed to 25 °C overnight, hydrolyzed with saturated ammonium chloride solution (300 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 and solvents were removed by evaporation under reduced pressure. Purification by distillation (1 mbar, 102 °C) afforded boronic ester **7** as a colorless oil (6.34 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 12H, 4 × CH_3), 7.31 (td, J = 8.3, 2.1 Hz, 1H, Ar–H), 7.40 (dd, J = 8.5, 2.3 Hz, 1H, Ar–H), 7.71 (s, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0 (4 × CH_3), 84.6 (2 × C), 119.9 (d, J_{CF} = 19 Hz, CH), 121.8 (d, J_{CF} = 24 Hz, CH), 122.5 (d, J_{CF} = 8 Hz, C), 133.4 (d, J_{CF} = 3 Hz, CH), 162.5 (d, J_{CF} = 250 Hz, C) (C–B not observed); ^{19}F NMR (282 MHz, $CDCl_3$): δ −111.5 (t, J = 8.3 Hz).

4.1.8. 5-Bromo-3-fluoro-biphenyl (8)

Prepared analogously as biaryl **4a**, starting from iodobenzene (20.0 mmol, 4.08 g) and boronic ester **7** (10.0 mmol, 3.01 g). Purification of the residue by column chromatography (cyclohexane) afforded biaryl **8** as a colorless oil (2.26 g, 90%). ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H, Ar–H), 7.37–7.48 (m, 3H, Ar–H), 7.52–7.56 (m, 3H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.2 (d, J_{CF} = 22 Hz, CH), 117.8 (d, J_{CF} = 24 Hz, CH), 123.0 (d, J_{CF} = 10 Hz, C), 126.3 (d, J_{CF} = 3 Hz, CH), 127.2 (2 × CH), 128.6 (CH), 129.2 (2 × CH), 138.7 (d, J_{CF} = 2 Hz, C), 145.0 (d, J_{CF} = 8 Hz, C), 163.1 (d, J_{CF} = 248 Hz, C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −110.6 (m). HRMS (EI) calcd for: $C_{12}H_8{}^{79}BrF$ (M^+) 249.9793, found: 249.9814; calcd for: $C_{12}H_8{}^{81}BrF$ (M^+) 251.9773, found: 251.9795.

4.1.9. 5′-Bromo-2,6-dimethoxy-3′-methyl-biphenyl (9)

Prepared analogously as biaryl **4c**, starting from compound **11** (3.76 mmol, 1.40 g). Purification of the residue by column

chromatography (cyclohexane/CH_2Cl_2 85:15) afforded biaryl **9** (0.85 g, 74%) as a colorless solid. mp 141–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, Ar–CH_3), 3.74 (s, 6H, 2 × OCH_3), 6.63 (d, J = 8.4 Hz, 2H, Ar–H), 7.07 (br s, 1H, Ar–H), 7.25–7.30 (m, 3H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4 (CH_3), 56.1 (2 × CH_3), 104.2 (2 × CH), 118.3 (C), 121.6 (C), 129.2 (CH), 130.5 (CH), 130.6 (CH), 131.0 (CH), 136.1 (C), 139.3 (C), 157.7 (2 × C). Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.29; H, 4.73.

*4.1.10. 3′,5′-Dibromo-2,6-dimethoxy-biphenyl (**11**)*

Prepared analogously as biaryl **4a**, starting from 1,3,5-tribromobenzene (10.0 mmol, 3.15 g) and 2,6-dimethoxyphenylboronic acid (11.0 mmol, 2.00 g). Purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 75:25) followed by crystallization from acetonitrile afforded biaryl **11** as a colorless solid (1.73 g, 47%). mp 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H, 2 × OCH_3), 6.63 (d, J = 8.4 Hz, 2H, Ar–H), 7.30 (t, J = 8.4 Hz, 1H, Ar–H), 7.42 (d, J = 1.8 Hz, 2H, Ar–H), 7.59 (t, J = 1.8 Hz, 1H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0 (2 × CH_3), 104.2 (2 × CH), 116.8 (C), 122.1, 129.8, 132.3, 132.9 (2 × CH), 137.9 (C), 157.6 (2 × C) ppm. Anal. Calcd for $C_{14}H_{12}Br_2O_2$: C, 45.20; H, 3.25. Found: C, 44.87; H, 3.43.

4.2. Desilylation of ortho-bromobiarylsilanes 1a–d

*4.2.1. Desilylation of **1a***

To (2-bromo-2′,6′-dimethoxy-biphenyl-3-yl)trimethylsilane **1a** (1.50 mmol, 548 mg) in THF (15.0 mL) was added under Argon and at 25 °C a solution of TBAF (4.50 mmol) in THF (4.50 mL). The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (2 × 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, a mixture of **3a** and **4a** (**3a**/**4a** 30:70, 183 mg, 49%) was isolated by column chromatography (cyclohexane/CH_2Cl_2 8:2). Spectroscopic data of **3a** were in agreement with literature [36,68].

*4.2.2. Desilylation of **1b***

To (2-bromo-2′,6′-dimethoxy-6-methyl-biphenyl-3-yl)trimethylsilane **1b** (1.50 mmol, 568 mg) in THF (15.0 mL) was added under Argon and at 25 °C a solution of TBAF (4.50 mmol) in THF (4.50 mL). The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (2 × 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, a mixture of **3b** and **4b** (**3b**/**4b** 46:54, 200 mg, 49%) was isolated by column chromatography (cyclohexane/CH_2Cl_2 8:2).

*4.2.3. Desilylation of **1c***

To (2-bromo-2′,6′-dimethoxy-5-methyl-biphenyl-3-yl)trimethylsilane **1c** (1.00 mmol, 379 mg) in THF (10.0 mL) was added under Argon and at 25 °C a solution of TBAF (3.00 mmol) in THF (3.00 mL). The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (2 × 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, purification of the residue by column chromatography (cyclohexane/CH_2Cl_2 8:2) afforded a small amount of dibenzofuran **10** (15 mg, 7%) and a mixture of **3c** and **4c** (**3c**/**4c** 47:53, 150 mg, 55%).

*4.2.3.1. 1-Methoxy-8-methyl-dibenzofuran (**10**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, Ar–CH_3), 4.06 (s, 3H, OCH_3), 6.78 (d, J = 8.1 Hz, 1H, Ar–H), 7.16 (d, J = 8.2 Hz, 1H, Ar–H), 7.21 (dd, J = 8.3, 1.5 Hz, 1H, Ar–H), 7.36 (t, J = 8.2 Hz, 1H, Ar–H), 7.41 (d, J = 8.4 Hz, 1H, Ar–H), 7.93 (br s, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 55.8 (CH_3), 103.8 (CH), 104.6 (CH), 110.6 (CH), 113.7 (C), 123.0 (CH), 123.7 (C), 127.3 (CH), 127.7 (CH), 132.4 (C), 153.9 (C), 156.0 (C), 157.7 (C). GC–MS (EI) Calcd for: $C_{14}H_{12}O_2$ (M^+) 212.1, Found: 212.2.

*4.2.4. Desilylation of **1d***

To (4′-bromo-2″,6″-dimethoxy-[1,1′;3′,1″]terphenyl-5′-yl)trimethylsilane **1d** (1.50 mmol, 663 mg) in THF (15.0 mL) was added under Argon and at 25 °C a solution of TBAF (4.50 mmol) in THF (4.50 mL). The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (2 × 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, a mixture of **3d** and **4d** (**3d**/**4d** 74:26, 382 mg, 72%) was isolated by column chromatography (cyclohexane/CH_2Cl_2 8:2).

*4.2.4.1. 4′-Bromo-2″,6″-dimethoxy-[1,1′;3′,1″]terphenyl (**3d**).* Crystallization from MeOH at −20 °C afforded **3d** as a colorless solid (220 mg, 40%). mp 102–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 6H, 2 × OCH_3), 6.67 (d, J = 8.4 Hz, 2H, Ar–H), 7.26–7.48 (m, 6H, Ar–H), 7.59–7.61 (m, 2H, Ar–H), 7.71 (d, J = 8.2 Hz, 1H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.2 (2 × CH_3), 104.2 (2 × CH), 118.9 (C), 124.5 (C), 127.2 (2 × CH), 127.3 (CH), 127.5 (CH), 128.9 (2 × CH), 129.7 (CH), 131.2 (CH), 132.8 (CH), 136.5 (C), 140.0 (C), 140.4 (C), 157.9 (2 × C). Anal. Calcd for $C_{20}H_{17}BrO_2$: C, 65.05; H, 4.64. Found: C, 65.45; H, 4.55.

4.3. Desilylation of ortho-bromobiarylsilanes 1a-c in presence of furan

*4.3.1. Desilylation of **1a** in presence of furan*

To a mixture of (2-bromo-2′,6′-dimethoxy-biphenyl-3-yl)trimethylsilane **1a** (0.87 mmol, 318 mg) and furan (8.70 mmol, 0.63 mL) in THF (9.00 mL) was added under Argon and at 25 °C a solution of TBAF (2.61 mmol) in THF (2.61 mL). The mixture was stirred at 25 °C for 3 h, hydrolyzed with water (75 mL) and extracted with Et_2O (75 mL). The organic layer was washed with water (2 × 50 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, compounds **3a**, **4a**, and **12a** contained in the residue (**3a**/**4a**/**12a** 30:11:59 according to NMR analysis) were separated by column chromatography (cyclohexane/CH_2Cl_2 80:20 for **3a** and **4a** then cyclohexane/EtOAc 75:25 for **12a**). **12a** was isolated as colorless solid (124 mg, 51%) whereas **3a** was recovered in mixture with **4a** (**3a**/**4a** 72:28 according to NMR analysis, 53 mg, 22%). Spectroscopic data of **3a** were in agreement with literature [36,68].

*4.3.1.1. 3-(2,6-Dimethoxyphenyl)-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (**12a**).* Analytic pure sample was obtained by crystallization from cyclohexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.39 (s, 1H, bridgehead), 5.74 (s, 1H, bridgehead), 6.67 (t-like, J = 7.6 Hz, 2H, Ar–H), 6.96–7.08 (m, 4H, Ar–H + vinyl), 7.20 (d, J = 6.5 Hz, 1H, Ar–H), 7.31 (t, J = 8.3 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8 (CH_3), 56.0 (CH_3), 82.3 (CH), 82.7 (CH), 103.9 (CH), 104.6 (CH), 116.7 (C), 118.8 (CH), 124.3 (CH), 126.9 (C), 128.2 (CH), 129.2 (CH), 142.6 (CH), 143.3 (CH), 148.4 (C), 149.2 (C), 157.6 (C), 157.9 (C). HRMS (EI) calcd for: $C_{18}H_{16}O_3$ (M^+) 280.1099, found: 280.1149.

*4.3.2. Desilylation of **1b** in presence of furan*

To a mixture of (2-bromo-2′,6′-dimethoxy-6-methyl-biphenyl-3-yl)trimethylsilane **1b** (2.43 mmol, 921 mg) and furan (24.3 mmol, 1.77 mL) in THF (25.0 mL) was added under Argon and at 25 °C a solution of TBAF (7.29 mmol) in THF (7.29 mL). The mixture was stirred at 25 °C for 3 h, hydrolyzed with water (100 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (2 × 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, compounds **3b**,

4b, and **12b** contained in the residue (**3b**/**4b**/**12b** 36:4:60 according to NMR analysis) were separated by column chromatography (cyclohexane/CH_2Cl_2 80:20 for **3b** and **4b** then cyclohexane/EtOAc 75:25 for **12b**). **12b** was isolated as colorless solid (245 mg, 34%) whereas **3b** was recovered in mixture with **4b** (**3b**/**4b** 85:15 according to NMR analysis, 170 mg, 23%).

*4.3.2.1. 6′-Bromo-2,6-dimethoxy-2′-methyl-biphenyl (**3b**).* Analytically pure sample of **3b** was obtained by crystallization from MeOH at −20 °C. Colorless solid; mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, Ar–CH_3), 3.74 (s, 6H, OCH_3), 6.66 (d, J = 8.4 Hz, 2H, Ar–H), 7.09 (t, J = 7.7 Hz, 1H, Ar–H), 7.21 (br d, J = 7.5 Hz, 1H, Ar–H), 7.35 (t, J = 8.4 Hz, 1H, Ar–H), 7.49 (d, J = 7.8 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (CH_3), 56.0 (2 × CH_3), 104.1 (2 × CH), 118.1 (C), 125.5 (C), 128.4 (2 × CH), 129.4 (CH), 129.6 (CH), 135.7 (C), 139.7 (C), 157.4 (2 × C) ppm. HRMS (EI) calcd for: $C_{15}H_{15}{}^{79}BrO_2$ (M^+): 306.0255, found: 306.0296; calcd for: $C_{15}H_{15}{}^{81}BrO_2$ (M^+) 308.0235, found: 308.0277.

*4.3.2.2. 3-(2,6-Dimethoxy-phenyl)-4-methyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (**12b**).* mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H, Ar-CH_3), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.24 (s, 1H, bridgehead), 5.71 (s, 1H, bridgehead), 6.65 (d, J = 8.4 Hz, 1H, Ar–H), 6.66 (d, J = 8.4 Hz, 1H, Ar–H), 6.88 (d, J = 7.2 Hz, 1H, Ar–H), 6.93 (dd, J = 5.5, 1.7 Hz, 1H, vinyl), 7.03 (dd, J = 5.5, 1.7 Hz, 1H, vinyl), 7.12 (d, J = 7.2 Hz, 1H, Ar–H), 7.33 (t, J = 8.3 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4 (CH_3), 55.7 (CH_3), 55.9 (CH_3), 82.2 (CH), 82.8 (CH), 103.8 (CH), 104.2 (CH), 115.5 (C), 119.0 (CH), 125.6 (CH), 127.5 (C), 129.3 (CH), 134.8 (C), 142.9 (CH), 143.2 (CH), 145.7 (C), 149.7 (C), 157.8 (2 × C). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.14; H, 6.32.

*4.3.3. Desilylation of **1c** in presence of furan*

To a mixture of (2-bromo-2′,6′-dimethoxy-5-methyl-biphenyl-3-yl)trimethylsilane **10c** (7.00 mmol, 2.65 g) and furan (70.0 mmol, 5.09 mL) in THF (70.0 mL) was added under Argon and at 25 °C a solution of TBAF (21.0 mmol) in THF (21.0 mL). The mixture was stirred at 25 °C for 3 h, hydrolyzed with water (200 mL) and extracted with Et_2O (200 mL). The organic layer was washed with water (2 × 150 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, compounds **3c**, **4c** and **12c** contained in the residue (**3c**/**4c**/**12c** 32:9:59 according to NMR analysis) were separated by column chromatography (cyclohexane/CH_2Cl_2 75:25 for **3c** and **4c** then cyclohexane/EtOAc 75:25 for **12c**). **12c** was isolated as colorless solid (925 mg, 45%) whereas **3c** was recovered in mixture with **4c** (680 mg, **3c**/**4c** 77:23 according to NMR analysis, 33%).

*4.3.3.1. 2-Bromo-2′,6′-dimethoxy-5-methyl-biphenyl (**3c**).* Analytically pure sample of **3c** was obtained by crystallization from hexane. Colorless solid; mp 99–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, Ar–CH_3), 3.74 (s, 6H, 2 × OCH_3), 6.65 (d, J = 8.3 Hz, 2H, Ar–H), 6.99–7.04 (m, 2H, Ar–H), 7.33 (t, J = 8.3 Hz, 1H, Ar–H), 7.52 (d, J = 8.1 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 (CH_3), 56.2 (2 × CH_3), 104.3 (2 × CH), 119.2 (C), 122.0 (C), 129.5 (CH), 129.7 (CH), 132.1 (CH), 133.1 (CH), 135.8 (C), 136.8 (C), 157.9 (2 × C). Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.67; H, 4.91.

*4.3.3.2. 3-(2,6-Dimethoxy-phenyl)-5-methyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene (**12c**).* mp 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, Ar–CH_3), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.37 (s, 1H, bridgehead), 5.70 (s, 1H, bridgehead), 6.67 (t-like, J = 8.1 Hz, 2H, Ar–H), 6.78 (s, 1H, Ar–H), 7.01–7.05 (m, 3H, Ar–H + vinyl), 7.31 (t, J = 8.3 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_3), 55.8 (CH_3), 56.0 (CH_3), 82.1 (CH), 82.7 (CH), 103.9 (CH), 104.6 (CH), 116.8 (C), 120.4 (CH), 126.4 (C), 128.1 (CH), 129.1 (CH), 133.9 (C), 142.4 (CH), 143.6 (CH), 146.4 (C), 148.7 (C), 157.7 (C), 157.9 (C). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.42; H, 6.12.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.02.017.

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