Reinvestigation of the Noncatalyzed Coupling of Aryllithium with Haloarene: A Novel Aromatic Nucleophilic Substitution Pathway

Jean-Michel Becht, Arnaud Gissot, Alain Wagner,* and Charles Mioskowski*[a]

Abstract: Noncatalyzed coupling reactions of aryllithiums and haloarenes proceed not only through the well-known aryne route but also, in some cases, through a novel addition–elimination pathway. Indeed, *ortho*-chloro- and *ortho*-bromomethoxyarenes lead selectively to the corresponding *ortho*-biaryls through a chelation-driven aromatic nucleophilic substitution pathway. Contrary to common belief, such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield. These results underline the potency of such simple reactions and open up a straightforward access to a wide range of biaryl structures; this also appears particularly useful for large-scale and biaryl building-block syntheses, as only cheap and readily available substrates are involved.

Keywords: aromatic substitution · arynes · biaryls · metalation · nucleophilic substitution

Introduction

Biaryls are found in important biologically active molecules[1] such as the naturally occurring terprenin[1f] or in synthetic anti-HIV derivatives[1g–i] and are used as core structures for molecular recognition devices,[2] organic semiconductors, material for nonlinear optics, and metal ligands for catalysts.[3] Several powerful synthetic methods are available for their preparation,[4] including long-known reactions such as Ullmann[4] or Gomberg–Bachmann–Hey couplings,[6] or more modern reactions such as Stille,[7] Suzuki Pd-catalyzed, and Ni-catalyzed cross-coupling reactions.[8] Although these reactions make it possible to prepare complex, polyfunctionalized biaryl structures under mild conditions, more efficient and simpler approaches are still suitable.

Based on this analysis, we reinvestigated the noncatalyzed reaction of aryllithiums with haloarenes. Surprisingly, this reaction has only been little studied and very sparsely used in organic synthesis. The mechanism generally proposed in the literature proceeds via the in-situ formation of a highly reactive aryne intermediate[9] that reacts with the aryllithium, leading to the biaryl structure. The mixture of regioisomers formed in the process is due to the two electrophilic positions present on the aryne intermediate.[10, 11] In addition to the classical mechanism involving arynes, another mechanism operates through competing halogen displacement and halogen–metal exchange processes. The reaction of phenyllithium, for example, with a 4-halotoluene leads to the formation of a complex mixture of the two possible *meta* and *para* isomers along with homocoupling reaction products arising from metal–halogen exchange side reactions.[11]

These complex results proved discouraging for further synthetic developments, and stimulated no additional investigations or research in the field despite publication of three interesting reports. In 1983 Meyers succeeded in controlling the regioselectivity of the reaction by using an aryne precursor bearing a phenyloxazolidine substituent, which acts as a strong *ortho*-directing and chelating group.[12] More recently, Schulte and Laschat found that 3,3′,4,4′-tetraalkoxybiphenyl was obtained regioselectively by treatment of 4-bromo-1,2-dimethoxybenzene with 0.5 equiv of *n*-butyllithium in THF at −78 °C.[13]

These results prompted us to reinvestigate the potential of this interesting transformation. We found that, in many cases, the reaction proceeds with high and predictable regioselectivity, making the transformation of interest for synthetic purposes. The substitution pattern of the haloarenes directs the formation of the biaryl structures, which are always obtained in good to moderate yields.
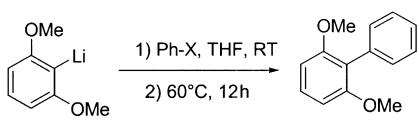
[a] Dr. A. Wagner, Dr. C. Mioskowski, J.-M. Becht, A. Gissot
Laboratoire de Synthèse Bioorganique, UMR 7514 associée au CNRS, Faculté de Pharmacie
74 Route du Rhin, 67400 Illkirch (France)
Fax: (+33) 3-90-24-43-06
E-mail: wagner@bioorga.u-strasbg.fr
           mioskowski@bioorga.u-strasbg.fr

Results and Discussion

To evaluate the scope and limitations of this cross-coupling reaction we investigated the reactivity of several haloarenes

with different aryllithiums. In a first set of experiments we used 1,3-dimethoxybenzene as the anion precursor and chlorobenzene as the aryne source. Addition of *n*-butyllithium to a mixture of 1,3-dimethoxybenzene and chlorobenzene in various solvents (hexane, diethyl ether, THF, THF/HMPA) at various temperatures did not afford the desired biaryl structure. In contrast, good results were obtained when chlorobenzene was added to a solution of 2-lithio-1,3-dimethoxybenzene in THF or DME and the resulting mixture was heated overnight at 60 °C. Under these conditions, the desired biaryl was obtained in 95% yield (Table 1, entry 2). At room temperature only poor yields are obtained. Notably, when the reaction was carried out on a 1.0 mol scale under the optimized conditions, the biaryl structure was obtained in a quantitative yield.

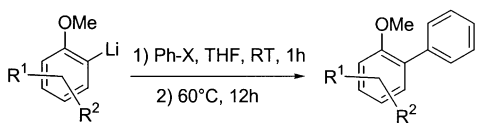Table 1. Reaction of 2-lithio-1,3-dimethoxybenzene with halobenzene.

X	Yield [%]
F	> 95
Cl	95
Br	82
I	no reaction

Next, we varied the nature of the halogen. The order of reactivity, F > Cl > Br ≫ I, is in accordance with a mechanism involving a transient aryne, the hydrogen abstraction being the rate-determining step.[11–14] Interestingly, with iodobenzene no biaryl structure could be detected in the crude mixture by ^{1}H NMR analysis. The reaction was then extended to other aryllithiums generated under classical *ortho*-metalation conditions (Table 2).

Compared with 1,3-dimethoxybenzene (entry 2), the lower yields observed in the case of mono-stabilized anions (entries 1, 3) might be due to the lower thermal stability of the 2-lithio anion. In accordance 1,2-dimethoxybenzene, which readily decomposes upon metallation, gave only traces of product (< 10%). With phenyloxazoline, *N,N*-dimethylbenzamide and *N-tert*-butylbenzamide *ortho* anions, we observed a comparable lack of reactivity.
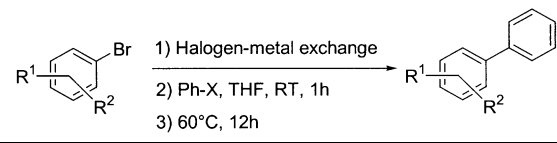
Table 2. Reaction of various aryllithiums and chloro- or fluorobenzene

Entry	R^1	R^2	X	Yield [%]
1	H	H	F	48
2	3-OMe	H	Cl	95
3	4-OMe	H	F	52
4	2-OMe	H	Cl or F	–
5	3-OMe	5-OMe	F	55
6	5-Me	H	F	41

To access a larger panel of biaryl structures, other aryllithiums were then generated by metal–halogen exchange (Table 3).[15]

Table 3. Reaction of aryllithiums generated by metal/halogen exchange.

Entry	R^1	R^2	X	Yield [%]
1	2-OMe	H	Cl	57
2	4-OMe	H	F	70
3	3,4-O–CH$_2$–O		F	42

2-Lithioanisole was generated by bromine–lithium exchange from 2-bromoanisole by using metallic lithium (entry 1).[16] Reaction with chlorobenzene led to the desired biaryl in 57% yield. 4-Bromoanisole treated with *tert*-butyllithium gave the biaryl in 70% yield. 4-Lithio-1,2-benzodioxole generated from 4-bromo-1,2-benzodioxole reacted with fluorobenzene to afford the coupling product in 42% yield (entry 3).

To extend the scope of this reaction, anions generated from *α*-metalated heterocycles were tested (Scheme 1).
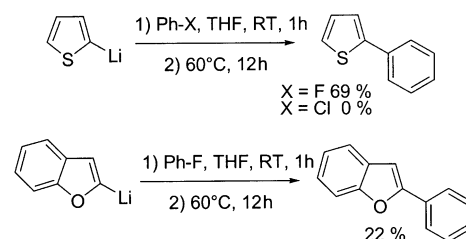

Scheme 1. Reaction of *α*-metalated heterocycles and chloro- or fluorobenzene.

In both cases, only fluorobenzene allowed the reaction to proceed; coupling products were isolated in moderate 69% and low 22% yield.
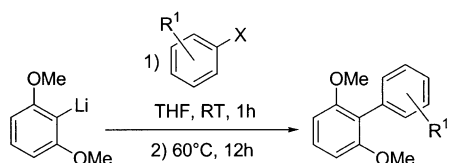
In this preliminary study, since only chloro- or fluorobenzene was used as the aryne precursor, the regioselectivity issue was avoided. To address this issue, we employed functionalized haloarenes for which random aryne formation and/or subsequent random nucleophilic attack are expected to lead to a mixture of isomers (Scheme 2).

Reaction of 2-, 3-, and 4-haloanisoles with 2-lithio-1,3-dimethoxybenzene (Table 4) was studied first. The *ortho/meta/para*-biaryl ratios were determined by GC analysis of the crude mixtures. The *ortho* and *para* isomers were identified unambiguously by comparison with reference samples synthesized by classical Pd coupling reactions.[8] The structures of the *meta* isomers were assessed by X-ray analysis. Reaction of 2-lithio-1,3-dimethoxybenzene with 2-chloroanisole gave the *ortho*-biaryl in 80% yield and 82% selectivity (entry 1), whereas 3-chloroanisole led predominantly to the *meta* isomer with 97% selectivity and 82% overall yield (entry 4).

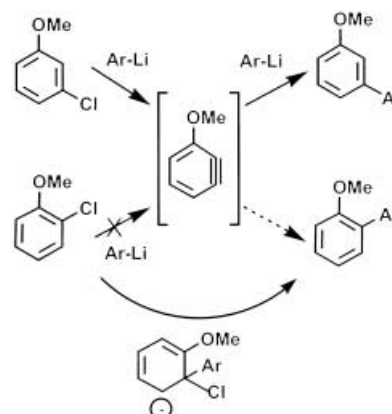3210

www.chemeurj.org *Chem. Eur. J.* **2003**, *9*, 3209 – 3215
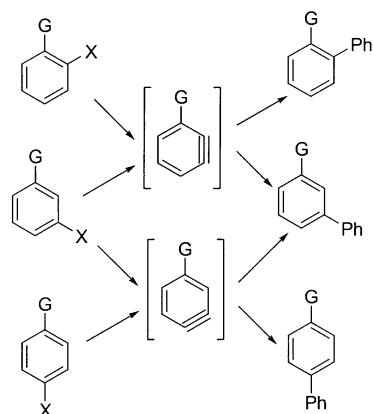
Scheme 2. Possible products formed through random aryne formation and subsequent random nucleophilic attack.

Scheme 3. Possible mechanism for the reaction of 2- and 3-chloroanisole.

Table 4. Reaction of 2-lithio-1,3-dimethoxybenzene with substituted chloro- and fluorobenzene.

Entry	R^1	X	ortho [%]	meta [%]	para [%]	Yield [%]
1	2-OMe	Cl	82	18	–	80
2	2-OMe	F	–	>95	–	80
3	2-OMe	Br	90	10	–	75
4	3-OMe	Cl	–	97	3	82
5	4-OMe	Cl	–	50	50	53
6	2-NMe$_2$	Cl		>90	–	40
7	3-NMe$_2$	Cl	–	>85	–	47
8	2-NMe$_2$	Br	–	>90	–	10
9	2-Me	F	36	64	–	72
10	2-Me	Cl	37	63	–	30
11	2-Me	I	40	60	–	<20
12	3-Me	Cl	9	54	37	40
13	3-Me	F	11	55	34	84
14	4-Me	Cl	–	51	49	96
15	3-CF$_3$	Cl	–	70	30	30
16	4-CF$_3$	Cl	–	45	55	60

Exclusive formation of a transient 2,3-aryne, followed by addition of the aryllithium specifically at the 3-position, leads to the most stabilized anionic intermediate. This set of steps accounts for the formation of the *meta*-biaryl obtained from 3-chloroanisole. According to this mechanism, 2-chloroanisole is expected to give the same 2,3-aryne intermediate and thus the same reaction product. Instead, the observed formation of the *ortho*-biaryl isomer, in total contradiction of the classical aryne-based mechanism, suggests a novel aromatic nucleophilic substitution pathway (Scheme 3). To support this hypothesis, substitution of 2-chloroanisole by 2-fluoroanisole reversed the reaction selectivity (entry 2). The strong *ortho*-acidifying effect of the fluorine atom favors hydrogen abstraction and thus the aryne pathway. In accordance with this, 2-fluoroanisole yielded the *meta* isomer cleanly. In contrast, since the bromine atom has little or no acidifying effect, with 2-bromoanisole nucleophilic substitu-

tion took over and the *ortho* isomer was obtained in 75% yield (entry 3).

4-Chloroanisole afforded a 1:1 mixture of the two possible *meta* and *para* isomers, as a result of formation of the 3,4-aryne and subsequent random nucleophilic attack at positions 3 and 4 (entry 5).

To check whether this regioselectivity was specific for the anion of 1,3-dimethoxybenzene, we carried out experiments under similar conditions using phenyllithium. 2-Chloroanisole afforded the *ortho*-biaryl in 78% isolated yield and 3-chloroanisole the *meta* isomer in 80% isolated yield. These results indicate clearly that the selectivity is mainly governed by the substitution pattern and the nature of the haloarenes.

Other substrates, such as 2-chloro- and 3-chloro-*N,N*-dimethylanilines (entries 6, 7), afforded exclusively *meta*-biphenyl in 40% and 47% yield respectively. Replacement of the chlorine atom by a less acidifying bromine atom (entry 8) did not change the selectivity, but resulted in a dramatic drop in the yield. Similar results were obtained with phenyllithium.

Results observed with the halotoluenes (entries 9 – 14) are in total accordance with the aryne pathway and with an early report by Chlebowski.[11] Here again, the increase in yield by switching from chloro- to fluorotoluene indicates that α-hydrogen abstraction is a determining step in the mechanism (Table 1). The slight deviation from the statistical ratio of the possible regioisomers might be explained by the steric hindrance of the methyl group, which disfavors the nucleophilic addition at the 2-position.

3-Chlorotrifluoromethylbenzene gave a mixture of *meta* and *para* isomers in a 7:3 ratio (entry 15), which differs from the ratio obtained with 3-chlorotoluene (entry 12). The better *ortho*-stabilizing effect of the trifluoromethyl group accounts for this result. 4-Chlorotrifluoromethylbenzene gave a statistical mixture of *meta*- and *para*-biaryls (entry 16).

To prove the ipso nucleophilic substitution pathway, we synthesized 2-chloro-3-deuteroanisole. *meta*-Anisidine was first converted into 2-chloro-3-aminoanisole,[17a] which was diazotized[17b] and reduced with sodium borodeuteride[17d] to afford the desired deuterated substrate. The latter was employed in an anionic cross-coupling reaction (Scheme 4). As expected, 2-chloro-3-deuteroanisole leads to the coupling product with less than 5% of deuterium loss, showing
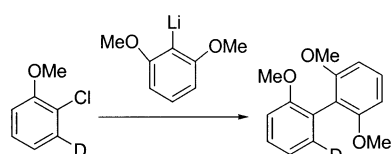
Scheme 4. Ipso substitution reaction on deuterated substrate.

that no hydrogen abstraction occurs. This result clearly demonstrates that, for this isomer, the biaryl structure is formed through an ipso nucleophilic substitution mechanism. Next, we tested the hypothesis that the selectivity could result from the chelation of the lithium cation by the oxygen atom of the methoxy group. Addition of HMPA, which is known to disrupt the lithium chelation, resulted in the reversal of selectivity with formation of the *meta* isomer in 68 % yield. Similarly, when the reaction was carried out in the presence of LiClO$_4$ both the *ortho* and the *meta* isomers were obtained in a 55:45 ratio. It thus appears that lithium chelation has a predominant role in directing the ipso substitution. Such chelation-driven selectivity also accounts for the experimental results obtained with 2-haloaniline (Table 4, entries 6–8), for which the biaryl formation proceeds through the aryne pathway since the nitrogen atom has weak lithium chelation ability.

Even though a chelation-driven addition of phenylmagnesium bromide to *ortho*-methoxyphenyloxazoline was described recently,[18] to the best of our knowledge this unusual mechanistic pathway has been neither studied nor exploited in organic synthesis. To extend its scope further, we considered haloarenes bearing two directing groups (Table 5).

Table 5. Reaction of 2-lithio-1,3-dimethoxybenzene with di-substituted chloro- and fluorobenzene derivatives.
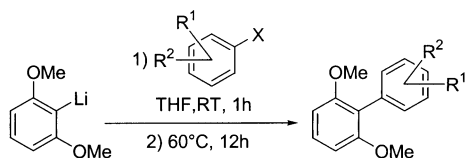
Entry	R^1	R^2	X	*ortho* [%]	*meta* [%]	Yield [%]
1	3-OMe	5-OMe	Cl	–	> 95	40
2	3-OMe	4-OMe	F	–	> 95	66
3	3,4-O–CH$_2$O–		Cl	–	> 95	38
4	2-OMe	5-Me	Cl	> 95	–	60
5	2-Me	5-OMe	Cl	–	> 95	62

These results indicate that the rules governing the reaction pathways are perfectly understood and predictable. The nucleophilic substitution is preferred when possible; if it is not possible, the major isomer arises from the most stable anion adduct (Scheme 5).

In conclusion, we have shown that noncatalyzed coupling of aryllithiums with haloarene often proceeds with high selectivity. *ortho*-Chloro- and *ortho*-bromomethoxyarenes give the corresponding *ortho*-biaryls through chelation-driven aromatic nucleophilic substitution. For other substrates the biaryl comes from the addition of the aryllithium to an aryne intermediate at the position leading to the most stable anionic
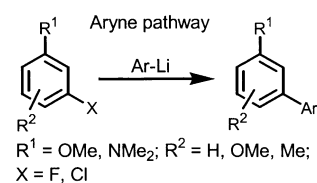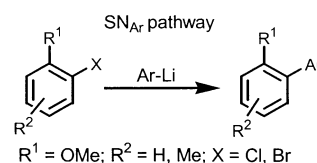
Scheme 5. Summary of the substrate substitution reaction pathways.

adduct. For haloarenes bearing substituents which do not stabilize the anionic adduct, a statistical mixture of the possible isomers is obtained. For substrates bearing two stabilizing groups, the regioselectivity is governed by the strongest directing group.

These noncatalyzed reactions give a straightforward access to a wide range of useful biaryl structures. As only cheap and readily available substrates are involved, our process appears to be of special interest for large-scale synthesis of basic biaryl building blocks.

To pioneer a novel type of aromatic chemistry, such chelation-driven substitution might be extendable to other carbanionic nucleophiles. Studies are currently being undertaken in that direction.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra in CDCl$_3$ were recorded using either a 200 MHz or a 300 MHz instrument. Chemical (δ) shifts are reported in parts per million downfield from TMS. Gas chromatography was performed on a Carlo Erba 6000 Vega equipped with a flame ionization detector using a 25 m BPX5 fused silica column. The GC conditions for isomer analysis were: pressure of carrier 20 kPa; injection of the sample at 170 °C kept constant for 3 min then increased to 240 °C at 40 °C min^{-1} for 17 min. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dimethoxyethane (DME) was dried with molecular sieves. All biaryl syntheses by our methodology were performed in flame-dry glassware under an argon atmosphere. Since the descriptions of the various biaryl structures are dispersed and incomplete in the literature, we give full characterizations of all the synthesized compounds.

General procedure for synthesis of the biaryls in Tables 1, 4, and 5: *n*-Butyllithium (1.6 M solution in hexane, 3.9 mL, 6.3 mmol) was added dropwise at RT to a solution of 1,3-dimethoxybenzene (6.3 mmol) in THF (5 mL). After 1 h a solution of aryl halide (2.9 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for another hour at RT and then heated at 60 °C for 12 h. The reaction mixture was cooled to RT and quenched by addition of H$_2$O (40 mL). The aqueous layer was extracted twice with Et$_2$O (total 60 mL), and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography with Et$_2$O/hexane. If they were still colored after chromatographic purification, the products were filtered on charcoal.

2,6-Dimethoxybiphenyl (Table 1 and Table 2, entry 2): White solid, m.p. 89 °C; R_f = 0.5 (10 % Et$_2$O/hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20 °C): δ = 3.83 (s, 6 H; 2 OCH$_3$), 6.76 (d, ^3J(H,H) = 8.8 Hz, 2 H; 3,5-H), 7.39 (t, ^3J(H,H) = 8.8 Hz, 1 H; 4-H), 7.49 – 7.59 ppm (m, 5 H; 5-H'); ^{13}C NMR (50 MHz, [D$_1$]CHCl$_3$, 20 °C): δ = 55.8, 104.1, 119.4, 126.7, 127.6, 128.5, 130.8, 134.1, 157.6 ppm; IR (CHCl$_3$): $\tilde{v}$ = 3054, 2946, 1584, 1470, 1427, 1242, 1103 cm^{-1}; MS (NH$_4$+): *m/z*: 232 [*M*+NH$_4$]+; elemental analysis calcd (%)

for $C_{14}H_{14}O_2$ (214.26): C 78.48, H 6.58, O 14.94; found: C 78.32, H 6.56, O 14.89.

2-Methoxybiphenyl (Table 2, entry 1): After a solution of 2-bromoanisole (15 mmol) in Et₂O (16.8 mL) had been added dropwise at RT to a suspension of lithium wires (400 mg, 58 mmol) in Et₂O (16.8 mL), the medium was stirred for 2 h at RT, then a portion (16.8 mL) of this solution was diluted with THF (8 mL). A solution of fluorobenzene (2.4 mmol) in THF (2 mL) was added dropwise at RT. The reaction mixture was stirred for 1 h at RT and refluxed to 60 °C for 12 h. The reaction mixture was allowed to cool to RT and quenched by addition of water (40 mL). The aqueous layer was extracted twice with Et₂O (total 100 mL), then the combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel with hexane as eluent. Yield 250 mg (57 %).

2-Methoxybiphenyl (Table 2, entry 1): Colorless oil; $R_f = 0.5$ (10 % AcOEt/hexane); ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.98$ (s, 3H; OCH₃), 7.15–7.26 (m, 2H; 3,5-H), 7.52–7.79 ppm (m, 7H; 4,6-H, 5H′); ¹³C NMR (50 MHz, [D₁]CHCl₃, 20 °C): $\delta = 56.2$, 112.0, 121.6, 127.7, 128.8, 129.4, 130.3, 131.4, 131.6, 139.4, 157.2 ppm; IR (CHCl₃): $\tilde{\nu} = 3060$, 2926, 1599, 1499, 1482, 1258, 1025 cm⁻¹; MS (NH₄⁺): m/z: 202 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{13}H_{12}O$ (184.24): C 84.75, H 6.56, O 8.68; found: C 84.56, H 6.54, O 8.71.

General procedure for the synthesis of biaryls (Table 3): The bromoaryl (5.4 mmol) was added at −78 °C to a solution of *t*BuLi (1.7 M in pentane, 6.4 mL, 10.8 mmol). The reaction mixture was warmed to RT for 30 min. After it had been cooled to 0 °C, DME (3 mL) and THF (3 mL) were added successively. Halobenzene (1.5 mmol) was diluted in DME (2.5 mL), and the resulting solution was heated at 70 °C; a solution of aryllithium (10.4 mL) was added quickly at 70 °C. The reaction mixture was stirred at this temperature for 12 h. After cooling to RT, the reaction was quenched by addition of water (40 mL). The aqueous layer was extracted twice with Et₂O (total 100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel.

2,5-Dimethoxybiphenyl (Table 2, entry 3): Colorless oil; $R_f = 0.4$ (10 % Et₂O/hexane); ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.77$ (s, 3H; OCH₃), 3.83 (s, 3H; OCH₃), 6.84–6.96 (m, 3H; 3,4,6-H), 7.34–7.61 ppm (m, 5H; 5H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.8$, 56.3, 112.7, 113.1, 116.7, 127.1, 128.0, 129.4, 131.7, 138.4, 150.8, 153.8 ppm; IR (CHCl₃): $\tilde{\nu} = 3069$, 2944, 1601, 1505, 1488, 1216, 1040 cm⁻¹; MS (NH₄⁺): m/z: 232 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{14}H_{14}O_2$ (214.26): C 78.48, H 6.58, O 14.93; found: C 78.39, H 6.60, O 14.89.

2,4,6-Trimethoxybiphenyl (Table 2, entry 5): White solid, m.p. 152 °C; $R_f = 0.4$ (20 % Et₂O/hexane); ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.74$ (s, 6H; 2OCH₃), 3.89 (s, 3H; OCH₃), 6.26 (s, 2H; 3,5-H), 7.28–7.44 ppm (m, 5H; 5H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.3$, 55.9, 90.9, 126.4, 127.6, 130.9, 131.2, 134.1, 158.3, 160.5 ppm; IR (CHCl₃): $\tilde{\nu} = 3020$, 2930, 1607, 1484, 1461, 1211, 1127 cm⁻¹; MS (NH₄⁺): m/z: 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_3$ (244.29): C 73.75, H 6.60, O 19.65; found: C 73.98, H 6.57, O 19.70.

2-Methoxy-5-methylbiphenyl (Table 2, entry 6): Colorless oil; $R_f = 0.5$ (4 % Et₂O/hexane); ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 2.43$ (s, 3H; CH₃), 3.85 (s, 3H; OCH₃), 6.96 (d, $^3J(H,H) = 8.4$ Hz, 1H; 3-H), 7.19–7.27 (m, 2H; 4,6-H), 7.39–7.64 ppm (m, 5H; 5H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 20.4$, 55.7, 111.3, 126.8, 127.9, 128.8, 129.5, 129.9, 130.5, 131.6, 138.6, 154.4 ppm; IR (CHCl₃): $\tilde{\nu} = 3025$, 2936, 1603, 1508, 1490, 1236, 1029 cm⁻¹; MS (NH₄⁺): m/z: 216 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{14}H_{14}O$ (198.26): C 84.81, H 7.11, O 8.08; found: C 84.67, H 7.10, O 8.05.

4-Methoxybiphenyl (Table 3, entry 2): White solid, m.p. 89 °C; $R_f = 0.3$ (hexane); ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.90$ (s, 3H; OCH₃), 7.03 (d, $^3J(H,H) = 8.8$ Hz, 2H; 3,5-H), 7.31–7.66 (m, 7H; 2,6-H, 5H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.2$, 114.1, 126.6, 126.7, 128.1, 128.7, 133.7, 140.8, 159.1 ppm; IR (CHCl₃) $\tilde{\nu} = 3050$, 2958, 1606, 1516, 1485, 1272, 1037 cm⁻¹; MS (NH₄⁺): m/z: 185 $[M+H]^+$; elemental analysis calcd (%) for $C_{13}H_{12}O$ (184.24): C 84.75, H 6.56, O 8.68; found: C 84.99, H 6.54, O 8.65.

2,6,2′-Trimethoxybiphenyl (Table 4, entries 1, 3): White solid, m.p. 141 °C; $R_f = 0.2$ (10 % AcOEt/hexane); GC retention time = 9.29 min; ¹H NMR (200 MHz, [D₃]CH₃CN, 20 °C): $\delta = 3.67$ (s, 6H; 2OCH₃), 3.70 (s, 3H;

OCH₃), 6.70 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 6.90–7.10 (m, 3H; 3′,5′,6′-H), 7.25–7.35 ppm (m, 2H; 4,4-H); ¹³C NMR (75 MHz, [D₃]CH₃CN, 20 °C): $\delta = 56.1$, 56.4, 105.2, 112.1, 121.1, 124.9, 129.4, 129.9, 133.0, 158.6, 159.0 ppm; IR (CHCl₃): $\tilde{\nu} = 3008$, 2938, 1591, 1504, 1471, 1250, 1111 cm⁻¹; MS (NH₄⁺): m/z: 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_3$ (244.29): C 73.75, H 6.60, O 19.65; found: C 73.71, H 6.61, O 19.61.

2,6,3′-Trimethoxybiphenyl (Table 4, entries 2, 4): White solid, m.p. 70 °C; $R_f = 0.2$ (5 % Et₂O/hexane); GC retention time = 11.16 min; ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.75$ (s, 6H; 2OCH₃), 3.83 (s, 3H; OCH₃′), 6.66 (d, $^3J(H,H) = 7.8$ Hz, 2H; 3,5-H), 6.85–6.97 (m, 3H; 2′,4′,6′-H), 7.25–7.38 ppm (m, 2H; 4,5′-H); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.1$, 55.9, 104.2, 112.4, 113.2, 116.6, 123.3, 128.5, 131.9, 135.5, 157.7, 159.0 ppm; IR (CHCl₃): $\tilde{\nu} = 3050$, 2953, 1587, 1468, 1243, 1106 cm⁻¹; MS (NH₄⁺): m/z: 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_3$ (244.29): C 73.75, H 6.60, O 19.65; found: C 73.66, H 6.62, O 19.59.

2,6,4′-Trimethoxybiphenyl (Table 4, entry 5): White solid, m.p. 122 °C; $R_f = 0.2$ (5 % AcOEt/hexane); GC retention time = 11.83 min; ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.79$ (s, 6H; 2OCH₃), 3.88 (s, 3H; OCH₃′), 6.69 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 6.99 (d, $^3J(H,H) = 9.0$ Hz, 2H; 3′,5′-H), 7.26–7.35 (m, 3H; 4,2′,6′-H); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.0$, 55.8, 104.2, 113.2, 119.1, 126.1, 128.3, 131.9, 157.7, 158.2 ppm; IR (CHCl₃): $\tilde{\nu} = 3015$, 2954, 1588, 1519, 1471, 1247, 1112 cm⁻¹; MS (NH₄⁺): m/z: 245 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_3$ (244.29): C 73.75, H 6.60, O 19.65; found: C 73.47, H 6.59, O 19.68.

(2′,6′-Dimethoxybiphenyl-3-yl)dimethylamine (Table 4, entries 6–8): White solid, m.p. 118 °C; $R_f = 0.3$ (30 % Et₂O/hexane); GC retention time = 12.30 min; ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 2.97$ (s, 6H; NMe₂), 3.76 (s, 6H; 2OCH₃), 6.68 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3′,5′-H), 6.70–6.77 (m, 3H; 2,4,6-H), 7.26–7.33 ppm (m, 2H; 5,4′-H); ¹³C NMR (50 MHz, [D₁]CHCl₃, 20 °C): $\delta = 40.6$, 55.8, 104.1, 111.3, 115.4, 119.3, 120.4, 128.2, 128.3, 134.7, 150.0, 157.7 ppm; IR (CHCl₃): $\tilde{\nu} = 3054$, 2989, 1604, 1471, 1266, 1112 cm⁻¹; MS (NH₄⁺): m/z: 258 $[M+H]^+$; elemental analysis calcd (%) for $C_{16}H_{19}NO_2$ (257.33): C 74.68, H 7.44, O 12.43; found: C 74.48, H 7.45, O 12.46.

2,6-Dimethoxy-3′-methylbiphenyl (Table 4, entries 9–14): Colorless oil; $R_f = 0.5$ (10 % AcOEt/hexane); GC retention time = 8.75 min; ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 2.41$ (s, 3H; CH₃), 3.76 (s, 6H; 2OCH₃), 6.67 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 7.13–7.37 ppm (m, 5H; 4-H, 4H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 21.6$, 56.1, 104.6, 120.3, 127.6, 127.7, 128.0, 128.6, 131.7, 134.2, 137.1, 158.0 ppm; IR (CHCl₃): $\tilde{\nu} = 3048$, 2930, 1606, 1589, 1466, 1242, 1110 cm⁻¹; MS (NH₄⁺): m/z: 229 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_2$ (228.29): C 78.92, H 7.06, O 14.02; found: C 78.71, H 7.05, O 14.06.

2,6-Dimethoxy-4′-methylbiphenyl (Table 4, entries 12–14): White solid, m.p. 86 °C; $R_f = 0.5$ (10 % AcOEt/hexane); GC retention time = 9.15 min; ¹H NMR (300 MHz, [D₁]CHCl₃, 20 °C): $\delta = 2.41$ (s, 3H; CH₃), 3.75 (s, 6H; 2OCH₃), 6.67 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 7.21–7.32 (m, 5H; 4-H, 4H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 21.4$, 56.1, 104.7, 120.1, 128.6, 128.7, 130.9, 131.3, 136.3, 158.1 ppm; IR (CHCl₃): $\tilde{\nu} = 3053$, 2986, 1653, 1589, 1469, 1264, 1110 cm⁻¹; MS (NH₄⁺): m/z: 229 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{16}O_2$ (228.29): C 78.92, H 7.06, O 14.02; found: C 78.71, H 7.04, O 13.98.

2,6-Dimethoxy-4′-trifluoromethylbiphenyl (Table 4, entries 15, 16): White solid, m.p. 82 °C; $R_f = 0.5$ (10 % AcOEt/hexane); GC retention time = 7.71 min; ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.76$ (s, 6H; 2OCH₃), 6.68 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 7.38 (t, $^3J(H,H) = 8.3$ Hz, 1H; 4-H), 7.48 (d, $^3J(H,H) = 8.0$ Hz, 2H; 2′,6′-H), 7.66 ppm (d, $^3J(H,H) = 8.3$ Hz, 2H; 3′,5′-H); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 55.8$, 104.2, 118.0, 124.5, 124.5 (q, $^1J(C,F) = 270$ Hz), 127.9, 129.4, 131.4, 138.1, 157.5 ppm; IR (CHCl₃): $\tilde{\nu} = 3059$, 2924, 1664, 1592, 1469, 1248, 1113 cm⁻¹; MS (NH₄⁺): m/z: 300 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{15}H_{13}F_3O_2$ (282.26): C 63.83, H 4.64, O 11.34; found: C 64.01, H 4.63, O 11.30.

2,6-Dimethoxy-3′-trifluoromethylbiphenyl (Table 4, entries 15, 16): Colorless oil; $R_f = 0.5$ (10 % AcOEt/hexane); GC retention time = 7.37 min; ¹H NMR (200 MHz, [D₁]CHCl₃, 20 °C): $\delta = 3.81$ (s, 6H; 2OCH₃), 6.73 (d, $^3J(H,H) = 8.3$ Hz, 2H; 3,5-H), 7.34 (t, $^3J(H,H) = 8.4$ Hz, 1H; 4-H), 7.51–7.78 ppm (m, 4H; 4H′); ¹³C NMR (75 MHz, [D₁]CHCl₃, 20 °C): $\delta = 56.3$, 104.6, 118.3, 124.0, 125.0 (q, $^1J(C,F) = 270$ Hz), 128.5, 129.8, 130.0, 130.7, 134.9, 135.3, 157.9 ppm; IR (CH₂Cl₂): $\tilde{\nu} = 3011$, 2955, 1589, 1467, 1239,

1111 cm^{-1}; MS (NH$_4^+$): m/z: 300 $[M+$NH$_4]^+$; elemental analysis calcd (%) for C$_{15}$H$_{13}$F$_3$O$_2$ (282.26): C 63.83, H 4.64, O 11.34; found: C 63.75, H 4.63, O 11.31.

Biphenyl-3-yldimethylamine: Colorless oil; $R_f = 0.6$ (10% Et$_2$O/hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.08$ (s, 6H; NMe$_2$), 6.75–7.08 (m, 3H; 2,4,6-H), 7.32–7.69 ppm (m, 6H; 5′-H, 5H′); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 40.6$, 111.5, 111.6, 115.8, 127.0, 127.3, 128.5, 129.4, 142.2, 150.9 ppm; IR (CHCl$_3$): $\tilde{v} = 3008$, 2884, 1601, 1568, 1487, 1214 cm^{-1}; MS (NH$_4^+$): m/z: 198 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{14}$H$_{15}$N (197.28): C 85.24, H 7.66; found: C 85.51, H 7.65.

3-Methoxybiphenyl: Colorless oil; $R_f = 0.3$ (10% AcOEt/hexane); GC retention time = 7.15 min; ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.90$ (s, 3H; OCH$_3$), 6.93 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 5.5 Hz, 2H; 2-H), 7.17–7.26 (m, 2H; 4,6-H), 7.38–7.66 ppm (m, 6H, 5-H; 5H′); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.2$, 112.6, 112.9, 119.7, 127.2, 127.4, 128.7, 129.7, 141.1, 142.7, 159.9 ppm; IR (CHCl$_3$): $\tilde{v} = 3054$, 2959, 1599, 1479, 1266, 1220 cm^{-1}; MS (NH$_4^+$): m/z: 185 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{13}$H$_{12}$O (184.24): C 84.75, H 6.56, O 8.68; found: C 84.52, H 6.58, O 8.65.

2,6,3′,5′-Tetramethoxybiphenyl (Table 5, entry 1): White solid, m.p. 122°C; $R_f = 0.3$ (10% AcOEt/hexane); GC retention time = 17.23 min; ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.79$ (s, 6H; 2OCH$_3$), 3.84 (s, 6H; 2OCH$_3$), 6.50 (t, ^4J(H,H) = 2.2 Hz, 1H; 4′-H), 6.55 (d, ^4J(H,H) = 2.2 Hz, 2H; 2′,6′-H), 6.69 (d, ^3J(H,H) = 8.3 Hz, 2H; 3,5-H), 7.32 ppm (t, ^3J(H,H) = 8.3 Hz, 1H; 4-H); ^{13}C NMR (50 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.7$, 56.4, 99.7, 104.6, 109.4, 119.9, 129.2, 136.5, 158.1, 160.5 ppm; IR (CHCl$_3$): $\tilde{v} = 3094$, 2944, 1598, 1450, 1253, 1194, 1149 cm^{-1}; MS (NH$_4^+$): m/z: 275 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{16}$H$_{18}$O$_4$ (274.31): C 70.06, H 6.61, O 23.33; found: C 69.81, H 6.63, O 23.41.

2,6,3′,4′-Tetramethoxybiphenyl (Table 5, entry 2): White needles, m.p. 148°C; $R_f = 0.5$ (30% Et$_2$O/hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.79$ (s, 6H; 2OCH$_3$), 3.90 (s, 3H; OCH$_3^-$), 3.96 (s, 3H; OCH$_3$′), 6.70 (d, ^3J(H,H) = 8.3 Hz, 2H; 3,5-H), 6.93–6.99 (m, 3H; 2′,5′,6′-H), 7.29 ppm (t, ^3J(H,H) = 8.3 Hz, 1H; 4-H); ^{13}C NMR (50 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.7$, 55.8, 55.9, 104.2, 110.5, 114.3, 119.2, 123.1, 126.4, 128.4, 147.7, 148.1, 157.8 ppm; IR (CHCl$_3$): $\tilde{v} = 3012$, 2935, 1587, 1523, 1470, 1292, 1247, 1106, 1024 cm^{-1}; MS (NH$_4^+$): m/z: 275 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{16}$H$_{18}$O$_4$ (274.31): C 70.06, H 6.61, O 23.33; found: C 70.31, H 6.62, O 23.39.

5-(2,6-Dimethoxyphenyl)benzo[1,3]dioxole (Table 5, entry 3): White solid, m.p. 90°C; $R_f = 0.2$ (5% Et$_2$O/hexane); ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.76$ (s, 6H; 2OCH$_3$), 5.99 (s, 2H; OCH$_2$O), 6.65 (d, ^3J(H,H) = 8.1 Hz, 2H; 3,5-H), 6.80–6.90 (m, 3H; 3,4,6-H), 7.27 ppm (t, ^3J(H,H) = 8.1 Hz, 1H; 4-H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.9$, 100.8, 104.2, 107.9, 111.5, 119.1, 124.2, 127.5, 128.5, 146.3, 147.0, 157.8 ppm; IR (CHCl$_3$): $\tilde{v} = 3025$, 2997, 1590, 1500, 1467, 1214 cm^{-1}; MS (NH$_4^+$): m/z: 276 $[M+$NH$_4]^+$; elemental analysis calcd (%) for C$_{15}$H$_{14}$O$_4$ (258.27): C 69.76, H 5.46, O 24.78; found: C 70.01, H 5.48, O 24.84.

2,2′,6′-Trimethoxy-5-methylbiphenyl (Table 5, entry 4): White solid, m.p. 114°C; $R_f = 0.3$ (20% Et$_2$O/hexane); ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 2.37$ (s, 3H; CH$_3$), 3.77 (s, 3H; OCH$_3$), 3.78 (s, 6H; 2OCH$_3$′), 6.69 (d, ^3J(H,H) = 8.3 Hz, 2H; 3′,5′-H), 6.93 (d, ^3J(H,H) = 8.3 Hz, 1H; 3-H), 7.04 (d, ^4J(H,H) = 1.9 Hz, 1H; 6-H), 7.16 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.9 Hz, 1H; 4-H), 7.32 ppm (t, ^3J(H,H) = 8.3 Hz, 1H; 4′-H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 18.7$, 55.2, 55.9, 104.0, 112.8, 116.2, 118.9, 128.7, 129.4, 130.2, 157.1, 157.7 ppm; IR (CHCl$_3$): $\tilde{v} = 2991$, 2931, 1607, 1586, 1507, 1250, 1109, 1040 cm^{-1}; MS (NH$_4^+$): m/z: 259 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{16}$H$_{18}$O$_3$ (258.32): C 74.39, H 7.02, O 18.58; found: C 74.67, H 7.04, O 18.52.

5,2′,6′-Trimethoxy-2-methylbiphenyl (Table 5, entry 5): White solid, m.p. 99°C; $R_f = 0.2$ (20% Et$_2$O/hexane); ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 2.04$ (s, 3H; CH$_3$), 3.77 (s, 6H; 2OCH$_3$′), 3.83 (s, 3H; OCH$_3$), 6.69 (d, ^3J(H,H) = 8.3 Hz, 2H; 3′,5′-H), 6.76 (d, ^4J(H,H) = 2.9 Hz, 1H; 6-H), 6.86 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 2.9 Hz, 1H; 4-H), 7.22 (d, ^3J(H,H) = 8.3 Hz, 1H; 3-H), 7.35 ppm (t, ^3J(H,H) = 8.3 Hz, 1H; 4′-H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 20.5$, 55.9, 104.1, 111.2, 116.3, 123.2, 128.5, 128.9, 132.6, 155.4, 158.0 ppm; IR (CHCl$_3$): $\tilde{v} = 3005$, 2935, 1607, 1590, 1500, 1468, 1246, 1111 cm^{-1}; MS (NH$_4^+$): m/z: 259 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{16}$H$_{18}$O$_3$ (258.32): C 74.39, H 7.02, O 18.58; found: C 74.21, H 7.01, O 18.61.

1-(2,6-Dimethoxyphenyl)naphthalene: White solid, m.p. 108°C; $R_f = 0.3$ (4% AcOEt/hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.69$ (s, 6H; 2OCH$_3$), 6.76 (d, ^3J(H,H) = 8.3 Hz, 2H; 3,5-H), 7.34–7.54 (m, 6H; naphthalene H), 7.59 (t, ^3J(H,H) = 8.3 Hz, 1H; 4-H), 7.88–7.98 ppm (m, 2H; naphthalene H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.9$, 104.2, 125.3, 125.4, 126.0, 127.4, 128.0, 128.1, 129.1, 132.6, 133.5, 158.4 ppm; IR (CHCl$_3$): $\tilde{v} = 3025$, 2952, 1596, 1529, 1472, 1214, 1113 cm^{-1}; MS (NH$_4^+$): m/z: 265 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{18}$H$_{16}$O$_2$ (264.32): C 81.79, H 6.10, O 12.11; found: C 82.01, H 6.08, O 12.15.

2-(2,6-Dimethoxyphenyl)naphthalene: White solid, m.p. 83°C; $R_f = 0.3$ (4% AcOEt/hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.80$ (s, 6H; 2OCH$_3$), 6.75 (d, ^3J(H,H) = 8.3 Hz, 2H; 3,5-H), 7.38 (t, ^3J(H,H) = 8.3 Hz, 1H; 4-H), 7.46–7.57 (m, 3H; naphthalene H), 7.84–8.00 ppm (m, 4H; naphthalene H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 55.9$, 104.3, 119.5, 125.5, 126.9, 127.7, 128.1, 128.8, 129.3, 129.7, 131.7, 132.5, 133.3, 157.9 ppm; IR (CHCl$_3$): $\tilde{v} = 3003$, 2941, 1585, 1496, 1274, 1105 cm^{-1}; MS (NH$_4^+$): m/z: 265 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{18}$H$_{16}$O$_2$ (264.32): C 81.79, H 6.10, O 12.11; found: C 81.97, H 6.11, O 12.09.

2-Phenylthiophene (Scheme 1): A solution of n-butyllithium (1.6 M solution in hexane, 6.9 mL, 11 mmol) was added dropwise at –40°C to a solution of thiophene (11 mmol) in THF (8.2 mL). The mixture was stirred for 1 h at –30°C, then cooled at –40°C, and a solution of fluorobenzene (5 mmol) in THF (3.2 mL) was added dropwise. The resulting mixture was warmed to RT for 1 h and heated to 60°C for 12 h. The reaction mixture was allowed to cool to RT and quenched by addition of water (40 mL). The aqueous layer was extracted with Et$_2$O (60 mL). The organic phase was dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane as eluent. Yield 552 mg (69%) of white solid, m.p. 35°C; $R_f = 0.5$ (hexane); ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 7.11–7.16$ (m, 1H; 5-H), 7.31–7.70 ppm (m, 7H; 3,4-H, 5H′); ^{13}C NMR (50 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 123.0$, 124.8, 125.9, 127.4, 128.0, 128.9, 134.3, 144.4 ppm; IR (CHCl$_3$): $\tilde{v} = 3065$, 3014, 1596, 1523, 1486 cm^{-1}; MS (NH$_4^+$): m/z: 161 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{10}$H$_8$S (160.24): C 74.96, H 5.03; found: C 74.68, H 5.04.

2-Phenylbenzofuran (Scheme 1): A solution of n-butyllithium (1.6 M solution in hexane, 3.3 mL, 5.3 mmol) was added dropwise at –10°C to a solution of benzofuran (5.3 mmol) in THF (10 mL). The reaction mixture was stirred at –10°C for 1 h and warmed to 0°C; then a solution of fluorobenzene (2.4 mmol) in THF (1.6 mL) was added dropwise. After the reaction mixture had been stirred for 1 h at RT, it was heated to 60°C for 12 h, then allowed to cool to RT, and quenched by addition of water (40 mL). The aqueous layer was extracted with Et$_2$O (50 mL), dried over MgSO$_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane as eluent. Yield 102 mg (22%) of a white solid, m.p. 123°C; $R_f = 0.3$ (hexane); ^{1}H NMR (200 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 7.08$ (s, 1H; 3-H), 7.20–7.70 (m, 8H; 2H′), 7.88–7.97 ppm (m, 2H; 2H′); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 101.3$, 111.2, 120.9, 122.9, 124.2, 124.9, 128.5, 128.8, 129.2, 130.5, 154.9, 155.9 ppm; IR (CHCl$_3$): $\tilde{v} = 3020$, 1615, 1510, 1492 cm^{-1}; MS (NH$_4^+$): m/z: 195 $[M+$H$]^+$; elemental analysis calcd (%) for C$_{14}$H$_{10}$O (194.23): C 86.57, H 5.19, O 8.24; found: C 86.81, H 5.17, O 8.26.

2-Chloro-1-methoxy-3-deuterobenzene: Colorless liquid; $R_f = 0.5$ (hexane); ^{1}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 3.92$ (s, 3H; OCH$_3$), 6.92 (m, 2H; 4,6-H), 7.24 ppm (t, ^3J(H,H) = 7.8 Hz, 1H; 5-H); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 56.0$, 112.0, 121.1, 122.3, 127.7, 129.9 (t, ^1J(C,H) = 24.5 Hz, C,D), 155.0 ppm; IR (CHCl$_3$): $\tilde{v} = 3069$, 2922, 1583, 1474, 1434, 1272, 1047 cm^{-1}; MS (NH$_4^+$): m/z: 145 $[M+$H$]^+$; elemental analysis calcd (%) for C$_7$H$_6$ClOD (143.58): C 58.56, H 4.21, O 11.14; found: C 58.37, H 4.22, O 11.10.

2,6,2′-Trimethoxy-6′-deuterobiphenyl (Scheme 4): White solid, m.p. 140°C; $R_f = 0.2$ (10% AcOEt/hexane); ^{1}H NMR (300 MHz, [D$_3$]CH$_3$CN, 20°C): $\delta = 3.68$ (s, 6H; 2OCH$_3$), 3.70 (s, 3H; OCH$_3$′), 6.70 (d, ^3J(H,H) = 8.1 Hz, 2H; 3,5-H), 6.93–7.09 (m, 2H; 3′,5′-H), 7.25–7.36 ppm (m, 2H; 4,4′-H); ^{2}H NMR (300 MHz, [D$_1$]CHCl$_3$, 20°C): $\delta = 7.40$ ppm (6′-D); ^{13}C NMR (125 MHz, [D$_3$]CH$_3$CN, 20°C) $\delta = 56.2$, 56.4, 105.2, 112.1, 112.2, 121.0, 124.0 (d, ^1J(C,D) = 10.3 Hz), 129.5, 129.9, 133.0, 158.6, 159.1 ppm; IR (CHCl$_3$): $\tilde{v} = 3053$, 2930, 1656, 1589, 1499, 1264, 1110 cm^{-1}; MS (NH$_4^+$): m/z: 263 $[M+$NH$_4]^+$; elemental analysis calcd (%) for C$_{15}$H$_{15}$O$_3$D (245.29): C 73.46, H 6.57, O 19.57 found C 73.71, H 6.58, O 19.51.

Acknowledgements

[1] a) G. R. Brown, D. S. Clarke, A. J. Foubister, S. Freeman, P. J. Harrison, M. C. Johnson, K. B. Mallion, J. McCormick, F. McTaggart, A. C. Reid, G. J. Smith, M. J. Taylor, *J. Med. Chem.* **1996**, *39*, 2971 – 2979; b) Y. Tamura, F. Watanabe, T. Nakatani, K. Yasui, M. Fuji, T. Komurasaki, H. Tsuzuki, R. Maekawa, T. Yoshioka, K. Kawada, K. Sugita, M. Ohtani, *J. Med. Chem.* **1998**, *41*, 640 – 649; c) M. L. Quan, A. Y. Liauw, C. D. Ellis, J. R. Pruitt, D. J. Carini, L. L. Bostrom, P. P. Huang, K. Harrison, R. M. Knabb, M. J. Thoolen, P. C. Wong, R. R. Wexler, *J. Med. Chem.* **1999**, *42*, 2752 – 2759; d) W. V. Ruyle, H. Jones, A. R. Matzuk, K. W. Kelly, B. E. Witzel, W. J. Holtz, R. A. Houser, T. Y. Shen, L. H. Sarett, *J. Med. Chem.* **1978**, *21*, 1093 – 1099; e) M. C. Chrysselis, E. A. Rekka, P. N. Kourounakis, *J. Med. Chem.* **2000**, *43*, 609 – 612; f) K. Kawada, A. Arimura, T. Tsuri, M. Fuji, T. Komurasaki, S. Yonezawa, A. Kugimiya, N. Haga, S. Mitsumori, M. Inagaki, T. Nakatani, Y. Tamura, S. Takechi, T. Taishi, J. Kishino, M. Ohtani, *Angew. Chem.* **1998**, *110*, 1015 – 1017; *Angew. Chem. Int. Ed.* **1998**, *37*, 973 – 975; g) Y. F. Hallock, J. H. Cardellina II, M. Schäffer, G. Bringmann, G. François, M. R. Boyd, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1729 – 1734; h) J. Milton, M. J. Slater, A. J. Bird, D. Spinks, G. Scott, C. E. Price, S. Downing, D. V. S. Green, S. Madar, R. Bethell, D. K. Stammers, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2623 – 2628; i) G. Bringmann, J. Holenz, R. Weirich, M. Rübenacker, C. Funke, *Tetrahedron* **1998**, *54*, 497 – 512.

[2] J. L. Schulte, S. Laschat, V. Vill, E. Nishikawa, H. Finkelmann, M. Nimtz, *Eur. J. Org. Chem.* **1998**, 2499 – 2506.

[3] A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154 – 3159.

[4] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359 – 1469.

[5] P. E. Fanta, *Synthesis* **1974**, 9 – 21.

[6] M. Gomberg, W. E. Bachmann, *J. Am. Chem. Soc.* **1924**, *46*, 2339 – 2343.

[7] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504 – 519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508 – 524.

[8] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483; b) K. Tamao, K. Sumitani, M. Kumada *J. Am. Chem. Soc.* **1972**, *94*, 4374 – 4376; c) K. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144 – 146.

[9] a) R. A. Benkeser, R. G. Severson, *J. Am. Chem. Soc.* **1949**, *71*, 3838 – 3839; b) R. A. Benkeser, W. E. Buting, *J. Am. Chem. Soc* **1952**, *74*, 3011 – 3014; c) J. D. Roberts, H. E. Simmons, L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc* **1953**, *71*, 3290 – 3291; d) R. A. Benkeser, G. Schroll, *J. Am. Chem. Soc.* **1953**, *75*, 3196 – 3197; e) E. R. Biehl, A. Razzuk, M. V. Jovanovic, S. P. Khanapure, *J. Org. Chem.* **1986**, *51*, 5157 – 5160; f) A. T. Bottini, J. D. Roberts, *J. Am. Chem. Soc.* **1957**, *79*, 1458 – 1462; g) R. W. Hoffmann, *Chem. Rev.* **1965**, *65*, 98, 222 – 234; h) G. Wittig, R. W. Hoffmann, *Chem. Ber.* **1962**, 2729 – 2734; i) H. Hart, K. Harada, C.-J. F. Du, *J. Org. Chem.* **1985**, *50*, 3104 – 3110; j) A. Saednya, H. Hart, *Synthesis* **1996**, 1455 – 1458; k) R. Huisgen, J. Sauer, *Angew. Chem.* **1960**, *3*, 91 – 126.

[10] A. Adejare, D. D. Miller, *Tetrahedron. Lett.* **1984**, *25*, 5597 – 5598.

[11] L. Friedman, J. F. Chlebowski, *J. Am. Chem. Soc.* **1969**, *91*, 4864 – 4871.

[12] A. I. Meyers, P. D. Pansegrau, *Tetrahedron. Lett.* **1983**, *24*, 4935 – 4938.

[13] J. L. Schulte, S. Laschat, *Synthesis* **1999**, *3*, 475 – 478.

[14] F. W. Bergstrom, R. E. Wright, C. Chandler, W. A. Gilkey, *J. Org. Chem.* **1936**, *1*, 170 – 178.

[15] a) H. Gilman, E. A. Zoellner, W. M. Selby, *J. Am. Chem. Soc.* **1933**, *55*, 1252 – 1257; b) T. Oshiki, T. Imamoto, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3719 – 3721.

[16] W. E. Truce, E. Wellisch, *J. Am. Chem. Soc.* **1952**, *74*, 5177 – 5179.

[17] a) G. M. Shutske, R. C. Allen, M. F. Försch, L. L. Setescak, J. C. Wilker, *J. Med. Chem.* **1983**, *26*, 20, 1307 – 1311; b) M. P. Doyle, W. J. Bryker, *J. Org. Chem.* **1979**, *44*, 1572 – 1574; c) J. B. Hendrickson, *J. Am. Chem. Soc.* **1961**, *83*, 1251.

[18] A. I. Meyers, J. R. Flisak, R. A. Aitken, *J. Am. Chem. Soc.* **1987**, *109*, 5446 – 5452.