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Regioselectivity in the Aryne Cross-Coupling of Aryllithiums with Functionalized 1,2-Dibromobenzenes

Vincent Diemer,[a] Manon Begaud,[a] Frédéric R. Leroux,*[a] and Françoise Colobert[a]

Keywords: Arynes / Cross-coupling / Bromine / Biaryls / Regioselectivity / Lithiation

Tri- and tetrasubstituted *ortho*-bromobiaryls have been synthesized in good-to-excellent yields by aryne cross-coupling reactions starting from 1,3-dimethoxybenzene and functionalized 1,2-dibromobenzenes. This study outlines the influence of the 1,2-dibromobenzene precursor as well as the reaction temperature on the outcome of the aryl–aryl bond formation and indicates, in the case of dissymmetrical benzyne precursors, how structural parameters (electronic effects, steric hindrance, temperature, etc.) control the regioselectivity of the aryne cross-coupling reactions.

Introduction

Substituted biphenyls are important moieties with various applications. In particular, biaryl substructures are of general interest in pharmaceuticals and agrochemicals.[1] In addition, they have widespread applications as ligands in catalysis and materials science.[2] Biaryls are most frequently prepared by transition-metal-catalyzed reactions, for example, the palladium-catalyzed coupling of aryl halides or pseudo halides with arylboronic acids (Suzuki–Miyaura reaction).[3] Although this method is well established, alternatives are being investigated to avoid the use of expensive transition metals or ligands especially required for the coupling of deactivated or sterically hindered substrates.

Arynes have attracted widespread interest in organic synthesis in recent years. Their chemistry was reviewed in 2003 by Pellissier[4] and in 2008 by Sanz.[5] They react with a variety of N-, S-, O-, and Se-nucleophiles[6] and, as recently shown, with P-nucleophiles[7] as well as with carbanions in addition reactions.[8] With alkenes they undergo Diels–Alder-type cycloaddition reactions,[9] [2+2] cycloadditions,[10] and 1,3-dipolar cycloadditions.[11] Transition-metal-catalyzed reactions using benzynes as the substrate have recently become a powerful tool in organic synthesis.[12]

Some cases of aryl–aryl coupling based on arynes have been reported in the literature.[13] Our group reported recently on the efficient coupling of organolithium intermediates with arynes, the so-called "aryne coupling" reaction.[8a,8b] This methodology involves the formation of a thermodynamically stable aryllithium intermediate and its subsequent reaction with 1,2-dibromobenzene. The transient benzyne adds the aryllithium derivative, which is followed by in situ transfer of bromine between the resulting 2-biaryllithium intermediate and another molecule of 1,2-dibromobenzene. Mono-, di-, or even tetrasubstituted *ortho*-bromobiaryls can be obtained on gram scale (Figure 1). The most impressive application of this methodology has been the preparation by Milne and Buchwald of one of the most versatile ligands (*S*-Phos) for the Suzuki–Miyaura coupling reaction.[14] The advantage of these *ortho*-bromobiphenyls lies in the possibility of functionalizing common precursors by regioselective bromine/lithium permutations[15] to give a large family of target ligands.[16]

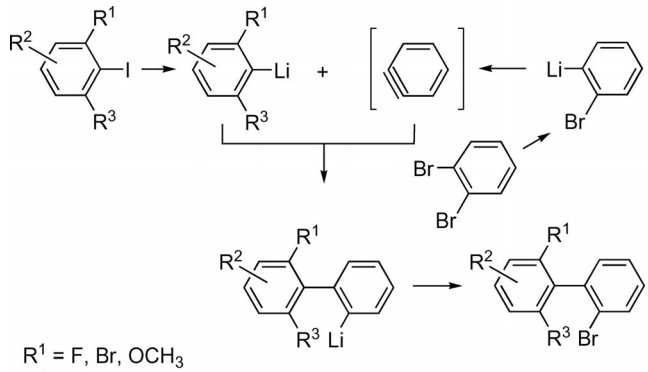

Figure 1. "Aryne coupling" yielding *ortho*-bromobiaryls.

Unfortunately, the use of this protocol had been restricted to accessing suitable "aryne precursors". Only a few functionalized 1,2-dibromobenzenes have been described in the literature or were accessible. Very recently our group overcame these restrictions and developed a straightforward access to 1,2-dibromobenzenes that could be functionalized at will at any vacant position.[17]

[a] CNRS et Université de Strasbourg (ECPM),
UMR CNRS 7509,
25 rue Becquerel, 67087 Strasbourg, France
Fax: +33-3-68852742
E-mail: frederic.leroux@unistra.fr

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However, in contrast to the addition of an aryllithium precursor to a symmetrical benzyne, we have now studied the regioselectivity of the addition to dissymmetrical benzynes (Figure 2) and found reaction conditions that allow "aryne" coupling with complete control of regioselectivity. These results will be reported in this paper.

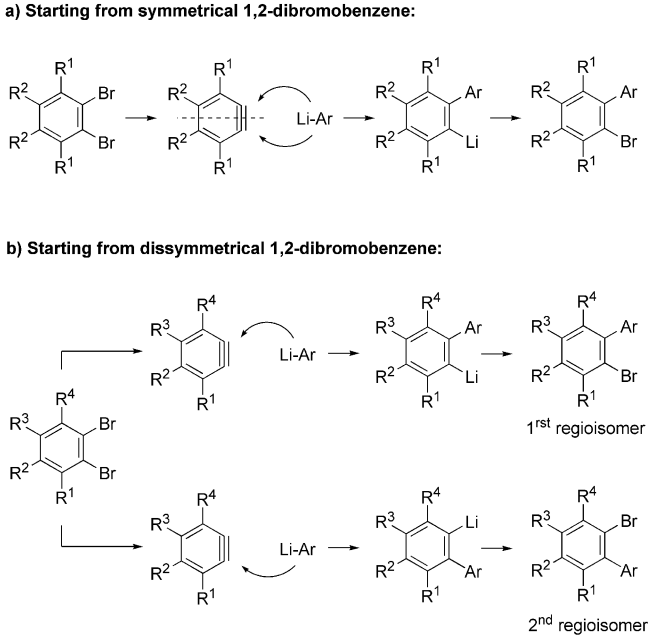


Figure 2. Regioselectivity of the addition of aryllithium to arynes.

1,3-Dimethoxybenzene was chosen as a model compound due to its facile metalation with butyllithium in THF at room temperature thus avoiding the use of nucleophiles, which might obstruct a clean aryne coupling. We systematically studied the influence of different reaction conditions on the outcome of the aryne coupling (electronic effects, steric hindrance of the substituents, temperature, etc.) that both control the formation of the aryl–aryl bond and orient, in the case of dissymmetrical benzyne precursors, the regioselectivity. In most cases the coupling products, 2-bromobiaryls **2**, were easily purified by column chromatography or crystallization (Figure 3).

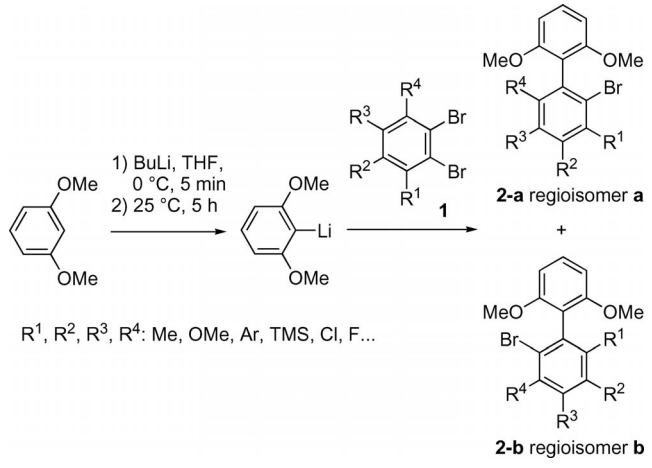


Figure 3. 1,3-Dimethoxybenzene as the model substrate for elucidating the regioselectivity of the addition of aryllithium to arynes.

Results and Discussion

Aryne Cross-Coupling Reaction with Symmetrically Substituted 1,2-Dibromobenzenes

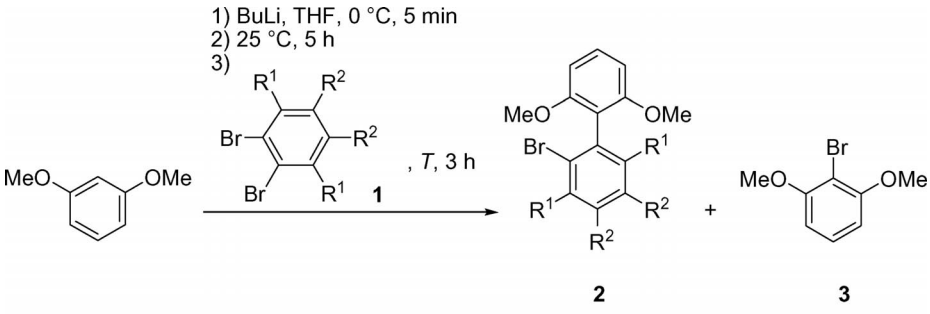
As described by Buchwald and co-workers,[18] 2,6-dimethoxyphenyllithium and 1-bromo-2-chlorobenzene afforded after aryne coupling in THF at 0 °C 2-bromobiaryl **2a** in 81% yield. Analogously, **2a** was obtained in 59% yield after simple crystallization from MeOH, starting from 1,2-dibromobenzene (Table 1, entry 1). When the cross-coupling reaction was performed at lower temperatures (Table 1, entries 2 and 3), the conversion into **2a** decreased in favor of 2-bromo-1,3-dimethoxybenzene (**3**), a result of a simple bromine/lithium permutation between 2,6-dimethoxyphenyllithium and 1,2-dibromobenzene (**1a**; Scheme 1). This competitive reaction, which was observed in all cases, can be avoided by adjusting the reaction temperature depending on the substitution pattern of the 1,2-dibromobenzene. For example, the cross-coupling of 1,2-dibromo-4,5-dimethoxybenzene (**1b**) had to be performed at –35 °C to obtain biaryl **2b** in a satisfactory yield (67%; Table 1, entries 4 and 5). In contrast, 1,2-dibromo-4,5-dimethylbenzene (**1c**) cleanly gave biphenyl **2c** in 57% yield at –78 °C (Table 1, entry 6).

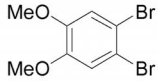
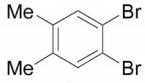
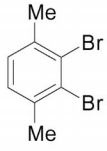
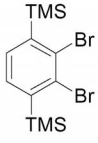
With 1,2-dibromobenzenes symmetrically functionalized at the *ortho* positions, *o*,*o*′-tetrasubstituted biaryls were readily obtained (Table 1, entries 8 and 10). Compared with its *meta* isomer **1c**, which cleanly reacted at –78 °C, the 1,2-dibromobenzene **1d**, which bears methyl groups *ortho* to the benzyne functionality, was converted into biaryl **2d** in 49% yield when the aryne cross-coupling was performed at 0 °C. At a lower temperature, the proportion of the brominated side-product **3** in the reaction mixture increased (Table 1, entry 7). This lack of reactivity was certainly due to the steric repulsion of the neighboring methyl groups that limited, in favor of the halogen/metal permutation, the attack of the nucleophilic aryllithium intermediate on the transient benzyne species. In the case of the 1,2-dibromobenzene **1e** substituted with TMS groups, the highly sterically hindered biaryl structure **2e** was obtained at 25 °C in 77% yield. The structure was confirmed by single-crystal X-ray analysis (Figure 4).

Aryne Cross-Coupling with 3-Functionalized 1,2-Dibromobenzenes

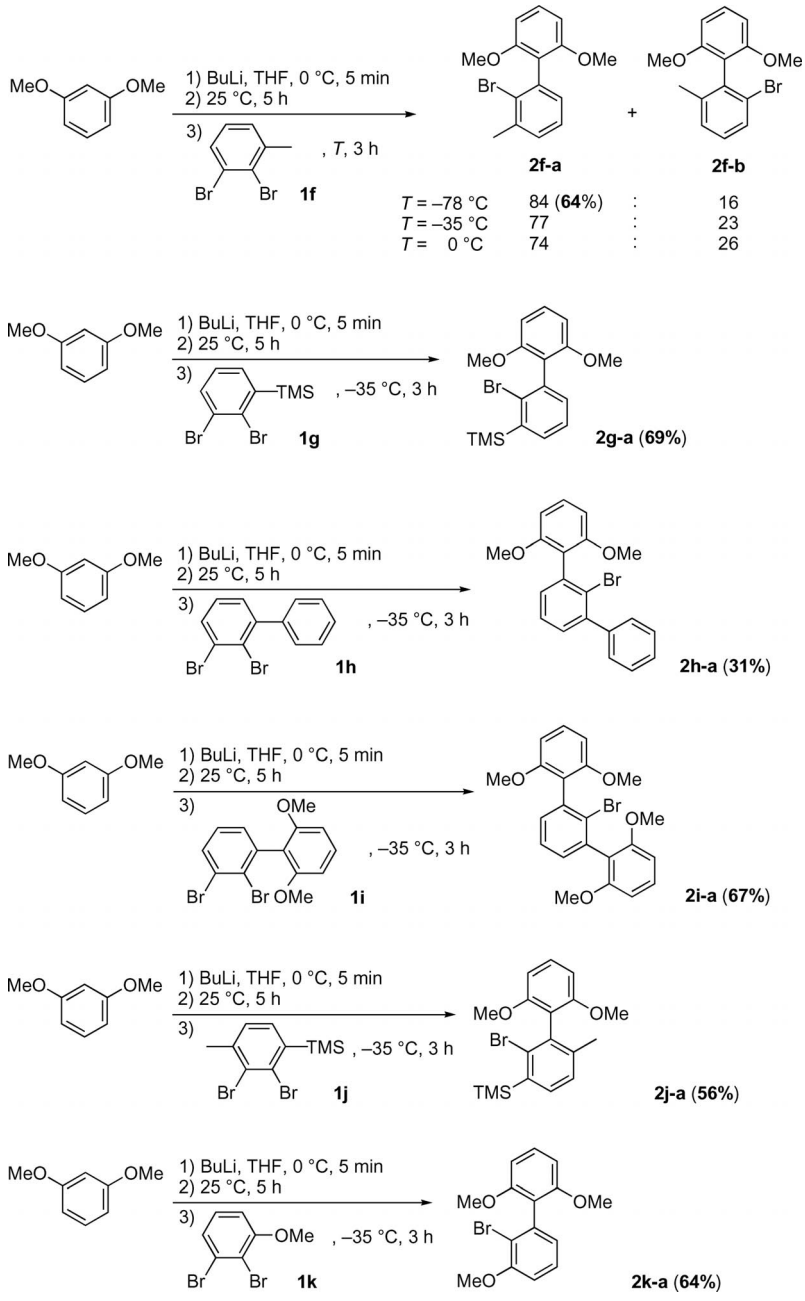
Next we studied 3-functionalized 1,2-dibromobenzenes as the benzyne source. The results are depicted in Scheme 1. When a methyl group is present *ortho* to the benzyne functionality, a mixture of *o*,*o*′-tri- and tetrasubstituted *ortho*-bromobiaryls (**2f-a** and **2f-b**, respectively) was obtained, each regioisomer resulting from the attack of 2,6-dimethoxyphenyllithium on each side of the dissymmetrical benzyne. The less sterically hindered substituted product (**2f-a**) was present as the major component according to ^{1}H NMR analysis of the reaction mixture (**2f-a**/**2f-b** = 84:16) and was isolated in a yield of 64% by crystallization from

Table 1. Aryne cross-coupling reactions with symmetrically substituted 1,2-dibromobenzenes.



Entry	1,2-Dibromobenzene	T [°C]	Composition of the reaction mixture[a]		
			2	**3**	1,3-Dimethoxybenzene recovered
1	 **1a**	0	82 % (**2a**: 59 %, MeOH)[b]	9 %	9 %
2		–35	76 % (**2a**: 50 %, MeOH)[b]	16 %	8 %
3		–78	61 % (**2a**: 48 %, MeOH)[b]	29 %	10 %
4	 **1b**	–78	48 % (**2b**)	21 %	31 %
5		–35	79 % (**2b**: 67 %, MeOH)[b]	7 %	14 %
6	 **1c**	–78	81 % (**2c**: 57%, MeOH)[b]	11 %	8 %
7	 **1d**	–35	47 % (**2d**: 19 %)[b]	22 %	31 %
8		0	73 % (**2d**: 49%, MeOH)[b]	11 %	16 %
9	 **1e**	–35	66 %	10 %	24 %
10		25	80 % (**2e**: 77%)[b]	5 %	15 %

[a] The proportions of **2**, **3**, and 1,3-dimethoxybenzene were determined by ^{1}H NMR analysis of the reaction mixture. [b] Isolated yield of **2** after crystallization and the solvent given in parentheses.



Scheme 1.

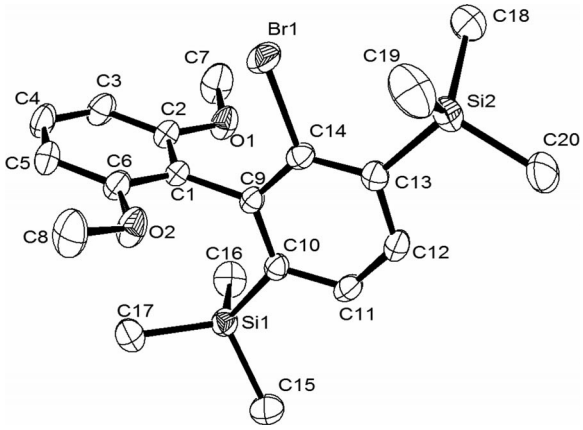


Figure 4. X-ray structure of **2e**.[19]

MeOH. The structure of this major regioisomer **2f-a** was confirmed by single-crystal X-ray analysis (Figure 5). The regioselectivity of the addition slightly decreased with temperature and is in accord with the literature on the addition of N-nucleophiles[20] and heteroaryllithiums.[21] The aryllithium addition to 3-methylbenzyne occurs mainly at the remote *meta* position relative to the methyl group to minimize steric repulsions between the incoming nucleophile and the methyl group (Figure 6, a).

With bulkier substituents than a methyl group, perfect regioselectivity of the aryne cross-coupling was observed. Starting from the 1,2-dibromobenzenes **1g**–**i** functionalized at the *ortho* position with a TMS group or aryl moieties, the *o*,*o*′-trisubstituted biaryl **2g-a** as well as the terphenyls **2h-a** and **2i-a** were the only detected products isolated in

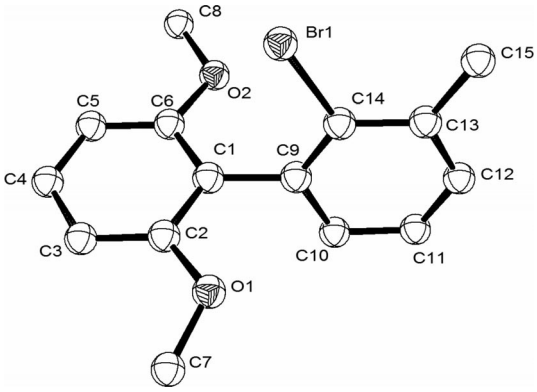
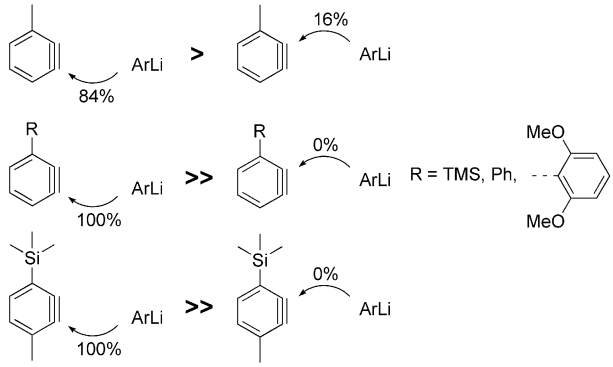
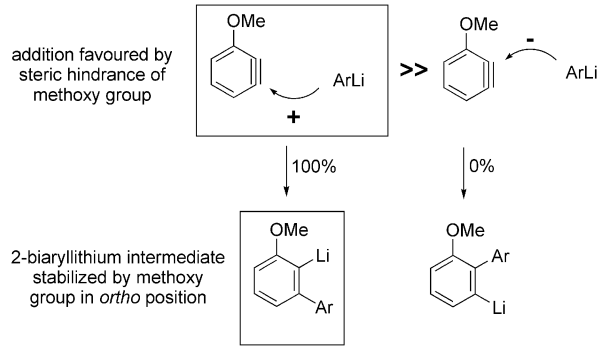


Figure 5. X-ray structure of **2f-a**.[19]

a) Sterically favoured addition of aryllithium on benzyne:



b) Sterically and electronically favoured addition of aryllithium on benzyne:



c) Electronically favoured addition of aryllithium on benzyne:

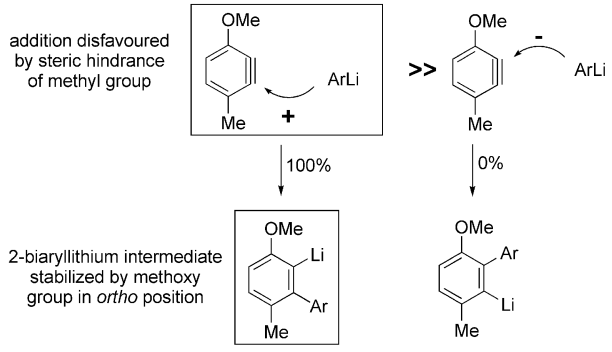


Figure 6. Regioselectivity of the aryne coupling reaction.

69, 31, and 67% yields, respectively. The structures of **2g-a** and **2i-a** were determined by single-crystal X-ray analysis (see Figures 7 and 8) and indicated that the addition of the nucleophile occurred exclusively on the sterically less hindered side of the benzyne (Figure 6, a).

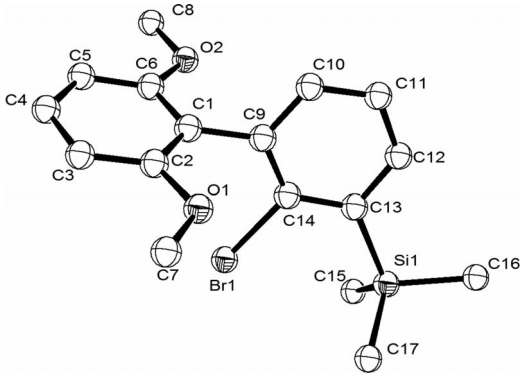


Figure 7. X-ray structure of **2g-a**.[19]

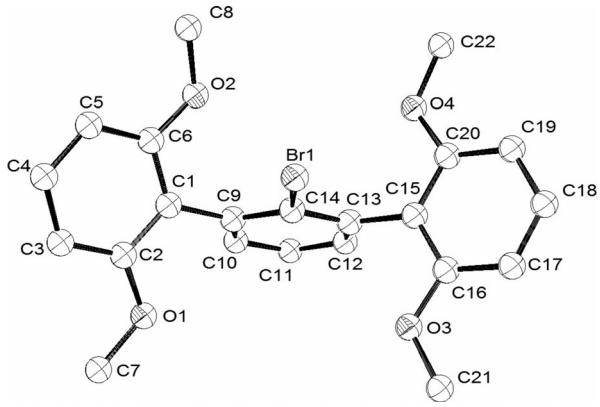


Figure 8. X-ray structure of **2i-a**.[19]

This perfect regioselectivity has already been observed by Hiyama and co-workers in benzodiazepine synthesis.[22] Similarly, the only isolated regioisomer resulting from aryllithium addition to 3-phenylbenzyne, obtained as a transient species from 2,3-dibromobiphenyl (**1h**), corroborated the selectivity of the aryne cross-coupling reaction.

In the case of dissymmetrical coupling partners, the regioselectivity of the reaction is highly dependent upon the relative steric hindrance of the *ortho* substituents. Owing to the poor regioselectivity of the aryllithium addition to the benzyne resulting from 1,2-dibromo-3-methylbenzene (**1f**) we decided to introduce a sterically demanding TMS group at the 6-position. The TMS group has the advantage of being easily removed at the end of the reaction or to be converted by halo-desilylation into a bromine or iodine atom. We were therefore satisfied that the reaction with the 1,2-dibromobenzene **1j** furnished with perfect regiocontrol the coupling product **2j-a** in 56% yield. We wish to emphasize that this *o*,*o*′-tetrasubstituted biphenyl is obtained in excellent yield without any ligands or transition metals. The single-crystal X-ray structure of **2j-a** unambiguously shows

that the C–C bond was created, as expected, *ortho* to the methyl group (i.e., on the sterically less hindered side of the intermediate benzyne) (Figure 6a and Figure 9).

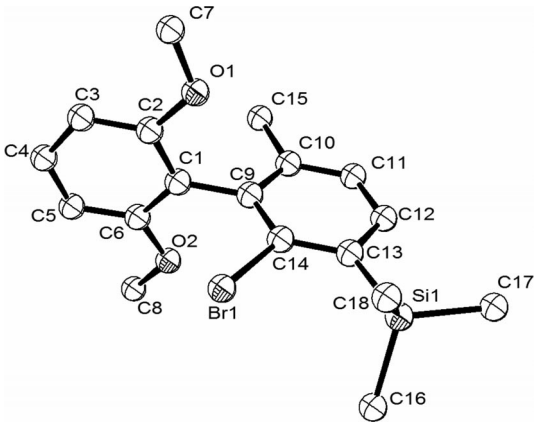
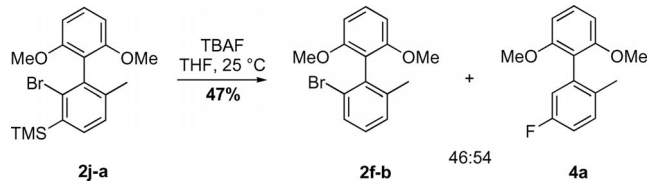


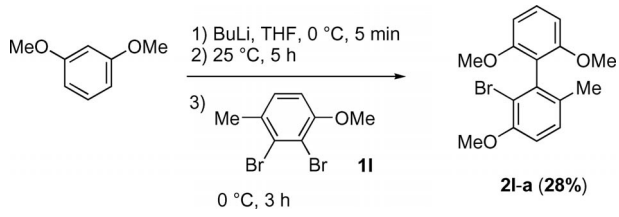
Figure 9. X-ray structure of **2j-a**.[19]

Desilylation of compound **2j-a** in THF with TBAF led to the minor regioisomer **2f-b** in a mixture with the fluoro derivative **4a** (47%, **2f-b**/**4a** = 46:54; Scheme 2).

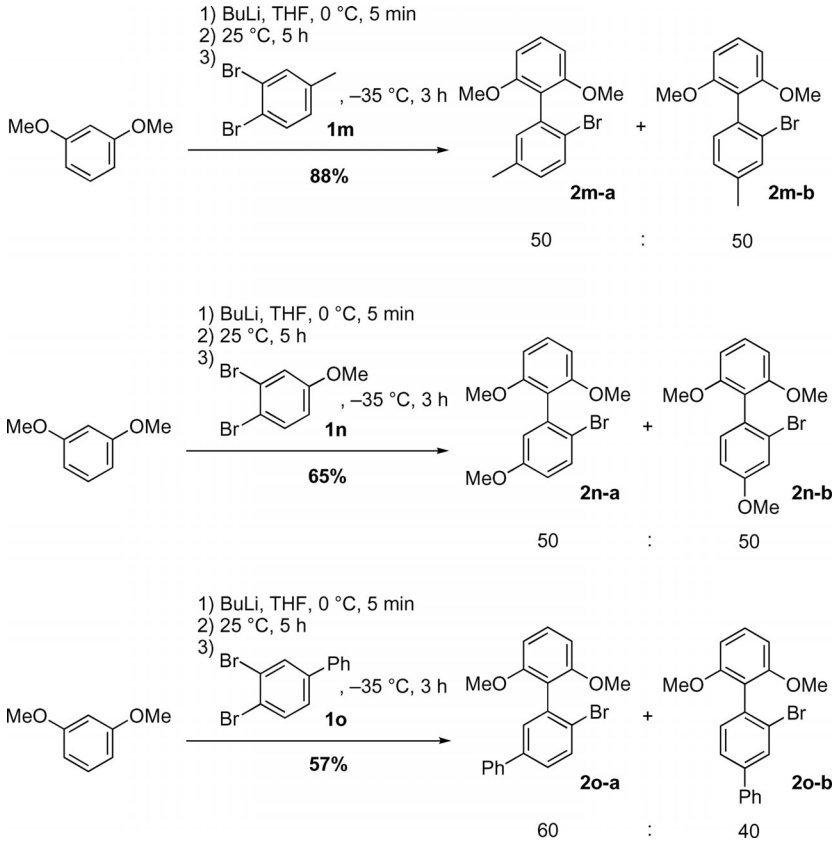


Scheme 2.

Benzyne precursors like **1k** bearing a hetero-element such as a methoxy group in the *ortho* position afford exclusively a single regioisomer (**2k-a**) isolated in 64% yield. Regiocontrolled additions to arynes have been reported in some cases.[6e,20b,21,23] The regioselectivity can be attributed to a combination of steric and electronic effects. As previously seen, steric hindrance by the methoxy group favors the ad-



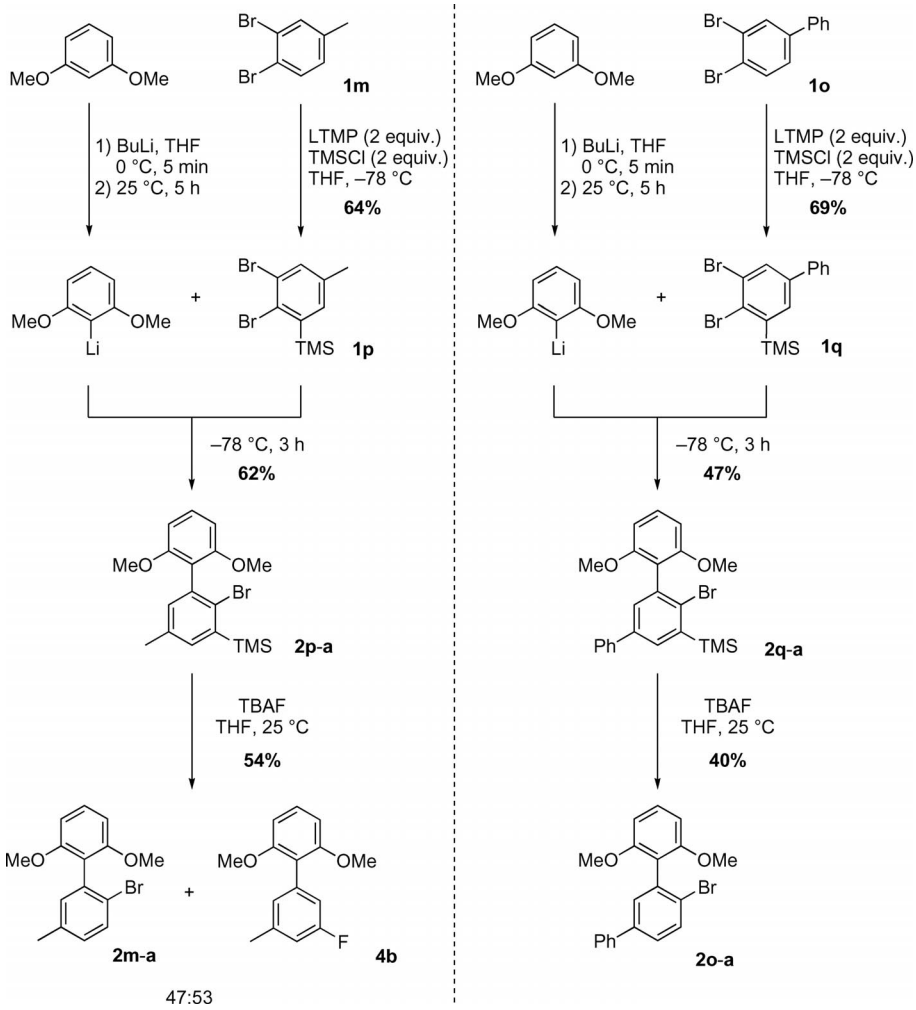
Scheme 3.



Scheme 4.

dition of the aryllithium at the *meta* position relative to the substituent. This selectivity is amplified by the stabilization of the resulting 2-biaryllithium intermediate (Figure 6b). Gorecka-Kobylinska and Schlosser recently reported on the stabilization of various substituents at the *ortho*, *meta*, or *para* positions relative to lithium. According to their studies the methoxy group stabilizes an adjacent aryllithium by 2.7 kcal/mol.[24]

So far the regioselectivity of the aryne coupling has been dictated either by steric effects (Figure 6, a) or by a combination of steric and electronic effects (Figure 6, b). In the following model reaction we were intrigued to see which effect, steric or electronic, would dominate in the addition of 2,6-dimethoxyphenyllithium to 2-methoxy-6-methylbenzyne. The reaction had to be conducted at 0 °C. Only one regioisomer (**2l-a**) was formed (according to GC–MS analysis). To determine the structure of **2l-a** and to elucidate the regioselectivity of the aryne coupling, ^{1}H NMR spectroscopic data of the methylated compounds **2d**, **2f-a**, **2j-a**, and **2l-a** were compared. Owing to their spatial orientation in the direction of the 2,6-dimethoxyphenyl moiety, methyl groups at the *ortho* position of the aryl–aryl bond are more shielded than those at *meta* positions. For example, the signal of the methyl group was shifted upfield from 2.48 to 2.04 ppm for biaryls **2j-a** and **2f-a** substituted at the 2- and 3-positions, respectively. Similar results were obtained with the 3,6-dimethylated biaryl **2d** [δ(3-CH_3) = 2.43 ppm; δ(6-CH_3) = 2.01 ppm]. At the same time the ^{1}H NMR signal of the methyl group was detected at δ = 1.99 ppm in the case of biaryl **2l-a**. On the basis of our previous observations, this result clearly indicates that the coupling occurred only under electronic control at the *ortho* position of the methyl group (Scheme 3). In spite of the fact that the attack of the nucleophile is disfavored by the steric hindrance of the methyl group, the electronic stabilization of the intermediate 2-biaryllithium induced by the adjacent methoxy group largely directs the coupling process and explains the exclusive formation of the biaryl **2l-a** (Figure 6, c). Nevertheless, despite having no effect on the regioselectivity of the aryne coupling, the steric hindrance induced by the methyl group seems to be responsible for the low yield of the reaction (28%).



Scheme 5.

Aryne Cross-Coupling with 4-Functionalized 1,2-Dibromobenzenes

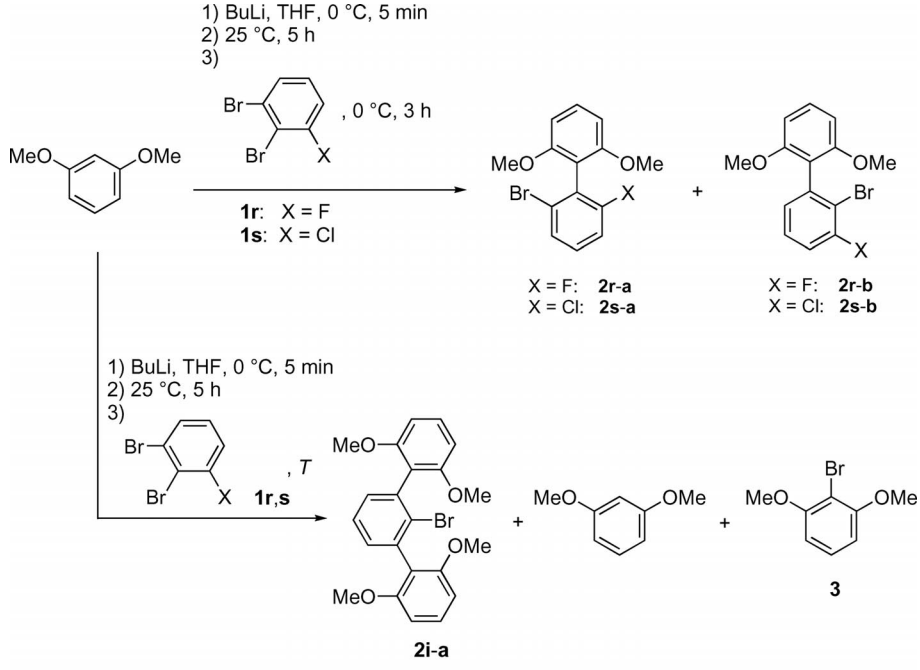
When the aryne cross-coupling was performed on 1,2-dibromobenzenes **1m** and **1n** functionalized at the 4-position with a methyl or methoxy group, mixtures of equal amounts of the corresponding two regioisomers were obtained. In the case of the 1,2-dibromobenzene **1o** substituted with a phenyl group, NMR analysis indicated a slight preference for the regioisomer **2o-a** (**2o-a**/**2o-b** = 60:40). The addition of aryllithium to the *meta* or *para* positions relative to the benzyne substituent implies neither steric preference nor extra electronic stabilization and therefore gives both regioisomers (Scheme 4).

Once again, to perform the aryne coupling reaction regioselectively we introduced a bulky TMS group on to the benzyne precursor (Scheme 5). The silylated 1,2-dibromobenzenes **1p** and **1q** afforded readily and in perfect regioselectivity the desired biaryls **2p-a** and **2q-a** in 62 and 47% yields, respectively. The aryllithium intermediate adds to the remote position to avoid steric repulsion with the TMS group. As a consequence, the methyl and phenyl substituents in the cross-coupling products **2p-a** and **2q-a** are now at the *meta* position of the newly created C–C bond. Desilylation of compound **2q-a** was performed in THF with TBAF and afforded after crystallization from methanol regioisomer **2o-a** in 40% yield. Removal of the TMS group under similar conditions starting from silane **2p-a** afforded the expected biaryl **2m-a** together with the fluoro derivative **4b** (54%, **2m-a**/**4b** = 47:53).

Aryne Cross-Coupling with 3-Halogenated 1,2-Dibromobenzenes

The aryne cross-coupling reaction performed with 3-fluoro-1,2-dibromobenzene (**1r**) at 0 °C did not lead, as expected, to one of the biaryls **2r-a** or **2r-b** but to the terphenyl **2i-a** obtained previously (Scheme 6). This compound, isolated in 24% yield after crystallization from EtOAc, resulted from a double addition of 2,6-dimethoxyphenyllithium to the polyhalogenated aromatic ring. Increasing the proportion of the aryllithium in the reaction mixture did not improve the yield. When the reaction was conducted at a lower temperature, –35 °C instead of 0 °C, the starting material was recovered together with 2-bromo-1,3-dimethoxybenzene (**3**) as a result of direct halogen/metal exchange.

The formation of terphenyl **2i-a** can be explained by two consecutive aryne cross-coupling reactions (Figure 10). First, 2,6-dimethoxyphenyllithium is involved in a bromine/lithium permutation with the 1-fluoro- or 1-chloro-2,3-dibromobenzene, the bromine atom adjacent to the fluorine or chlorine atom being replaced. Elimination of lithium



Scheme 6.

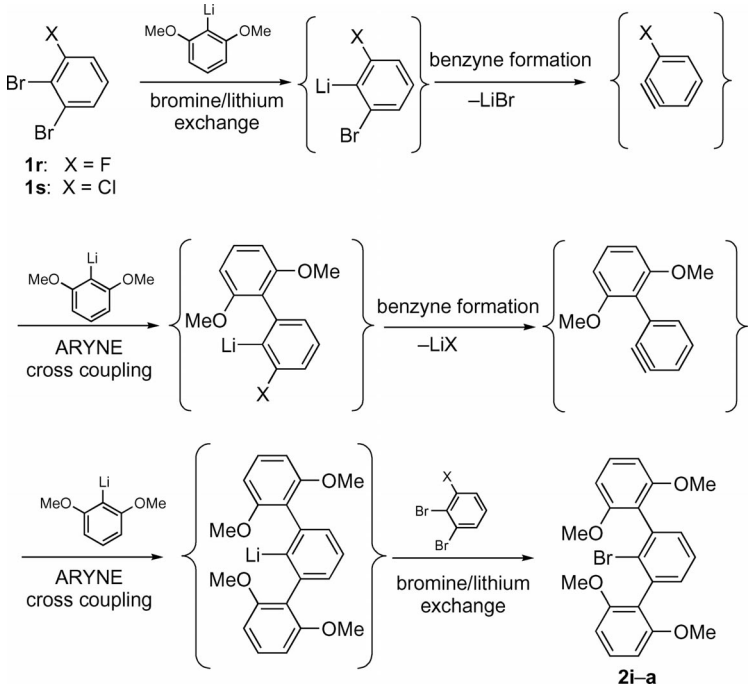


Figure 10. Terphenyl formation by aryne coupling.

bromide affords the transient aryne species. Nucleophilic addition of 2,6-dimethoxyphenyllithium affords an aryllithium intermediate, which undergoes a further lithium halide elimination and generates another aryne. The latter adds another equivalent of 2,6-dimethoxyphenyllithium and is stabilized by a bromine/lithium permutation with the remaining starting material affording the terphenyl **2i-a**. A few cases of successive nucleophilic additions to arynes have been described in the literature.[13a–13c,25]

Conclusions

In this work we studied the regioselectivity of the aryne cross-coupling reaction by using various dissymmetric benzynes. These highly reactive intermediates were generated for the first time starting from functionalized 1,2-dibromobenzene precursors, recently accessible through short and efficient synthetic pathways. *o*,*o*′-Tri- and -tetrasubstituted bromobiphenyls were efficiently synthesized by this transition-metal-free cross-coupling procedure. We have shown how substituents present at the *ortho*, *meta*, or *para* positions relative to the benzyne functionality control by steric and/or electronic effects the addition of the aryllithium intermediate. As a consequence, the temperature of the reaction had to be optimized, especially when sensitive aryllithium species were used as the coupling partner. We showed that the introduction of bulky or chelating substituents at the *ortho* position of the benzyne directed the addition of the nucleophile during the coupling reaction. In this way, the coupling of dissymmetrical 1,2-dihalogenated benzyne precursors, otherwise lacking regioselectivity, occurred with complete regiocontrol. Considering the recent progress made in developing synthetic routes to functionalized 1,2-dibromobenzenes, the aryne cross-coupling reaction has become a powerful alternative to the classic transition-metal-catalyzed cross-coupling protocols.

Experimental Section

General Methods: 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 were 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 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 were determined with a Kofler hot-plate and found to be reproducible after recrystallization unless stated otherwise ("decomp."). 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 60N (spherical neutral size 63–210 μm). ^{1}H and ^{1}H-decoupled ^{13}C NMR spectra were recorded at 400 or 300 and 101 or 75 MHz, respectively. Chemical shifts are reported in δ units (ppm) and were measured relative to the signals for residual chloroform (δ = 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, for example, as s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), td (triplet of doublets), m (multiplet), app. s (apparent singlet), and br. (broad).

The 1,2-dibromobenzene derivatives **1a**–**c**,**m** are commercially available and the 1,2-dibromobenzenes **1d**–**i**,**k**–**l**,**o**–**s** were synthesized ac-

cording to methods developed in our laboratory or described in the literature.[17]

(2,3-Dibromo-4-methylphenyl)trimethylsilane (1j): Lithium tetramethylpiperidide (LTMP; 20.0 mmol) was added dropwise to TMSCl (2.54 mL, 20.0 mmol) and 1,2-dibromo-3-methylbenzene (2.50 g, 10.0 mmol) in anhydrous THF (10 mL) under Ar at –78 °C. LTMP was prepared in anhydrous THF (10 mL) at 0 °C by deprotonation of tetramethylpiperidine (3.37 mL, 20.0 mmol) with BuLi (20.0 mmol) in hexane (12.5 mL). The mixture was stirred at –78 °C for 2 h and then hydrolyzed with methanol (20 mL) at –78 °C and with water (20 mL) at 25 °C. The organic layer obtained after addition of Et_2O (200 mL) was successively washed with 1 M aqueous HCl (2 × 100 mL) and water (1 × 100 mL) and dried with Na_2SO_4. The solvents were evaporated under reduced pressure and the silane **1j** contained in the crude was purified by column chromatography (cyclohexane). The isolated product (2.76 g) was used in the next step in spite of the presence of impurities (10%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.38 [s, 9 H, Si(CH_3)$_3$], 2.47 (s, 3 H, Ar-CH_3), 7.14 (d, J = 7.5 Hz, 1 H, Ar-*H*), 7.25 (d, J = 7.5 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.2 (3 CH_3), 25.5 (CH_3), 128.9 (C), 129.0 (CH), 132.8 (C), 134.3 (CH), 141.7 (C), 141.8 (C) ppm.

1,2-Dibromo-4-methoxybenzene (1n): A solution of $NaNO_2$ (3.20 g, 46.4 mmol) in water (7.00 mL) was added dropwise to a suspension of 3,4-dibromoaniline (10.0 g, 40.0 mmol) in aqueous H_2SO_4 (prepared from 20.0 mL water and 8.00 mL concentrated H_2SO_4) at 0 °C. After 20 min at 0 °C, urea (0.32 g) was added and the reaction mixture was poured portionwise into a mixture of water (10.0 mL), Na_2SO_4 (15.0 g), and concentrated H_2SO_4 (20.0 mL) heated at 120 °C. The reaction mixture was heated at 120 °C for 2 h and diluted, at room temperature, with water (500 mL). The aqueous layer was then extracted with Et_2O (3 × 300 mL) and the combined organic layers were dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue that contained 3,4-dibromophenol (^{1}H NMR spectrum was in agreement with the literature)[26] was dissolved in acetone (100 mL). MeI (3.00 mL, 48.0 mmol) and K_2CO_3 (6.62 g, 48.0 mmol) were successively added and the mixture was heated at reflux for 5 h. After evaporation of acetone under reduced pressure, the residue was dissolved in Et_2O (400 mL) and the obtained organic layer was successively washed with 1 M aqueous NaOH (200 mL) and water (2 × 200 mL), dried with Na_2SO_4, and evaporated under reduced pressure. Distillation of the crude (99–105 °C, 1 mbar) furnished anisole **1n** (3.55 g) as an oil. Purification of the residue by column chromatography (cyclohexane) gave an additional fraction of **1n** (0.82 g). Yield: 41%. The spectroscopic data are in agreement with the literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 6.73 (dd, J = 2.9, 8.8 Hz, 1 H, Ar-*H*), 7.17 (d, J = 2.9 Hz, 1 H, Ar-*H*), 7.48 (d, J = 8.8 Hz, 1 H, Ar-*H*) ppm.

2′-Bromo-2,6-dimethoxybiphenyl (2a): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to 0 °C. 1,2-Dibromobenzene (**1a**; 6.00 mmol, 0.72 mL) was added dropwise. The mixture was stirred at 0 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Crystallization from MeOH afforded the biaryl **2a** (0.86 g, 59%) as a colorless solid. The spectroscopic data are in agreement with the literature.[14] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 6 H, 2 OCH_3), 6.65 (d, J = 8.4 Hz, 2 H, Ar-*H*), 7.17–7.25 (m, 2 H, Ar-*H*), 7.31–7.38 (m, 2 H, Ar-*H*), 7.66 (br. d, J = 8.1 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1 (2 CH_3), 104.2 (2 CH), 119.0 (C), 125.4 (C), 127.0 (CH), 128.7 (CH), 129.6 (CH), 132.4 (CH), 132.4 (CH), 136.2 (C), 157.8 (2 C) ppm.

2-Bromo-4,5,2′,6′-tetramethoxybiphenyl (2b): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **2b** (6.00 mmol, 1.77 g) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/EtOAc, 8:2) followed by crystallization from MeOH afforded the biaryl **2b** (1.20 g, 67%) as a colorless solid. The spectroscopic data are in agreement with the literature.[8a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 6 H, 2 OCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.65 (d, J = 8.4 Hz, 2 H, Ar-*H*), 6.74 (s, 1 H, Ar-*H*), 7.13 (s, 1 H, Ar-*H*), 7.33 (t, J = 8.4 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1 (CH_3), 56.1 (CH_3), 56.2 (2 CH_3), 104.3 (2 CH), 115.0 (CH), 115.3 (C), 115.3 (CH), 119.0 (C), 128.0 (C), 129.5 (CH), 148.2 (C), 148.7 (C), 158.0 (2 C) ppm.

2-Bromo-2′,6′-dimethoxy-4,5-dimethylbiphenyl (2c): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –78 °C. A solution of the 1,2-dibromobenzene **1c** (6.00 mmol, 1.58 g) in anhydrous THF was added dropwise. The mixture was stirred at –78 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Crystallization from MeOH afforded the biaryl **2c** (0.91 g, 57%) as a colorless solid; m.p. 138–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, Ar-CH_3), 2.28 (s, 3 H, Ar-CH_3), 3.76 (s, 6 H, 2 OCH_3), 6.66 (d, J = 8.3 Hz, 2 H, Ar-*H*), 7.02 (s, 1 H, Ar-*H*), 7.33 (t, J = 8.3 Hz, 1 H, Ar-*H*), 7.45 (s, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_3), 19.5 (CH_3), 56.2 (2 CH_3), 104.2 (2 CH), 119.0 (C), 121.9 (C), 129.3 (CH), 133.1 (C), 133.2 (CH), 133.3 (CH), 135.5 (C), 137.5 (C), 157.9 (2 C) ppm. $C_{16}H_{17}BrO_2$ (321.21): C 59.83, H 5.33; found C 59.87, H 5.24.

2-Bromo-2′,6′-dimethoxy-3,6-dimethylbiphenyl (2d): Butyllithium (1.65 mmol) in hexane (1.03 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.23 g, 1.65 mmol) in anhydrous THF (4.00 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to 0 °C. A solution of the 1,2-dibromobenzene **1d** (1.98 mmol, 0.52 g) in anhydrous THF was added dropwise. The mixture was stirred at 0 °C for 3 h and then warmed to 25 °C overnight. Water (60 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 75:25) followed by crystallization from MeOH afforded the biaryl **2d** (0.26 g, 49%) as a colorless solid; m.p. 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, Ar-CH_3), 2.43 (s, 3 H, Ar-CH_3), 3.73 (s, 6 H, 2 OCH_3), 6.66 (d, J = 8.3 Hz, 2 H, Ar-*H*), 7.12 (br. s, 2 H, Ar-*H*), 7.35 (t, J = 8.3 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (CH_3), 24.0 (CH_3), 56.2 (2 CH_3), 104.3 (2 CH), 119.1 (C), 127.9 (C), 128.2 (CH), 129.3

(CH), 129.5 (CH), 135.4 (C), 136.1 (C), 136.8 (C), 157.5 (2 C) ppm. $C_{16}H_{17}BrO_2$ (321.21): C 59.83, H 5.33; found C 59.51, H 5.60.

2-Bromo-2′,6′-dimethoxy-3,6-bis(trimethylsilyl)biphenyl (2e): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and a solution of the 1,2-dibromobenzene **1e** (6.00 mmol, 2.28 g) in anhydrous THF was added dropwise. The mixture was stirred at 25 °C for 18 h, hydrolyzed with water (150 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 85:15) afforded the biaryl **2e** (1.69 g, 77%) as a colorless solid; m.p. 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.06 [s, 9 H, Si(CH_3)$_3$], 0.41 [s, 9 H, Si(CH_3)$_3$], 3.70 (s, 6 H, 2 OCH_3), 6.60 (d, J = 8.3 Hz, 2 H, Ar-*H*), 7.35 (t, J = 8.3 Hz, 1 H, Ar-*H*), 7.43 (d, J = 7.3 Hz, 1 H, Ar-*H*), 7.56 (d, J = 7.3 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.5 (3 CH_3), –0.1 (3 CH_3), 55.6 (2 CH_3), 103.6 (2 CH), 120.6 (C), 129.6 (CH), 132.7 (CH), 134.6 (CH), 134.8 (C), 141.6 (C), 142.5 (C), 144.0 (C), 158.2 (2 C) ppm. $C_{20}H_{29}BrO_2Si_2$ (437.52): C 54.90, H 6.68; found C 54.53, H 7.08.

2-Bromo-2′,6′-dimethoxy-3-methylbiphenyl (2f-a): Butyllithium (1.00 mmol) in hexane (0.13 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.14 g, 1.00 mmol) in anhydrous THF (2.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –78 °C. A solution of the 1,2-dibromobenzene **1f** (1.20 mmol, 0.30 g) in anhydrous THF was added dropwise. The mixture was stirred at –78 °C for 3 h and was warmed to 25 °C overnight. Water (60 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Regioisomers **2f-a** and **2f-b** (**2f-a**/**2f-b**, 84:16 according to NMR analysis) contained in the crude product were isolated as a mixture by chromatography (cyclohexane/CH_2Cl_2, 8:2). Crystallization from MeOH afforded the biaryl **2f-a** (0.20 g, 64%) as a colorless solid; m.p. 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, Ar-CH_3), 3.74 (s, 6 H, 2 OCH_3), 6.66 (d, J = 8.4 Hz, 2 H, Ar-*H*), 7.05 (dd, J = 2.4, 6.9 Hz, 1 H, Ar-*H*), 7.19–7.28 (m, 2 H, Ar-*H*), 7.34 (t, J = 8.4 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.2 (2 CH_3), 104.2 (2 CH), 120.0 (C), 126.7 (CH), 127.8 (C), 129.3 (CH), 129.6 (CH), 129.7 (CH), 136.7 (C), 138.3 (C), 157.8 (2 C) ppm. $C_{15}H_{15}BrO_2$ (307.18): C 58.65, H 4.92; found C 58.42, H 4.91.

2′-Bromo-2,6-dimethoxy-6′-methylbiphenyl (2f-b): A solution of tetrabutylammonium fluoride (4.50 mmol) in THF (4.50 mL) was added to silane **2j-a** (1.50 mmol, 568 mg) in anhydrous THF (15.0 mL) under Ar at 25 °C. The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL), and diluted with Et_2O (100 mL). The organic layer was separated, washed with water (2 × 100 mL), dried with Na_2SO_4, and evaporated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/CH_2Cl_2, 8:2) afforded a mixture (200 mg, 47%) of biaryls **2f-b** and **4a** (**2f-b**/**4a**, 46:54). The ^{1}H NMR spectrum of biaryl **2f-b** was determined by comparison of the spectroscopic data of mixtures **2f-b**/**4a** and **2f-a**/**2f-b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, Ar-CH_3), 3.74 (s, 6 H, 2 OCH_3), 6.66 (d, J = 8.4 Hz, 2 H, Ar-*H*), 7.10 (t, J = 7.7 Hz, 1 H, Ar-*H*), 7.20–7.22 (m, 1 H, Ar-*H*), 7.35 (t, J = 8.4 Hz, 1 H, Ar-*H*), 7.49 (d, J = 7.9 Hz, 1 H, Ar-*H*) ppm.

(2-Bromo-2′,6′-dimethoxybiphenyl-3-yl)trimethylsilane (2g-a): Butyllithium (4.00 mmol) in hexane (2.50 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.55 g, 4.00 mmol) in anhydrous THF (10.0 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **1g** (4.80 mmol, 1.48 g) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (120 mL) was added and the mixture was extracted with Et_2O (3 × 80 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 80:20) afforded the biaryl **2g-a** (1.01 g, 69%) as a colorless solid; m.p. 124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.42 [s, 9 H, Si(CH_3)$_3$], 3.73 (s, 6 H, 2 OCH_3), 6.65 (d, J = 8.3 Hz, 2 H, Ar-*H*), 7.20 (dd, J = 1.9, 7.4 Hz, 1 H, Ar-*H*), 7.33 (t, J = 8.3 Hz, 1 H, Ar-*H*), 7.34 (t, J = 7.4 Hz, 1 H, Ar-*H*), 7.42 (dd, J = 1.9, 7.4 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 (3 CH_3), 56.2 (2 CH_3), 104.3 (2 CH), 120.1 (C), 126.3 (CH), 129.4 (CH), 133.2 (CH), 133.3 (C), 135.1 (CH), 136.5 (C), 141.7 (C), 157.8 (2 C) ppm. $C_{17}H_{21}BrO_2Si$ (365.34): C 55.89, H 5.79; found C 55.63, H 6.07.

2′-Bromo-2,6-dimethoxy-1,1′:3′,1′′-terphenyl (2h-a): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **1h** (6.00 mmol, 1.87 g) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 75:25) followed by crystallization from MeOH at –20 °C afforded the biaryl **2h-a** (0.58 g, 31%) as a colorless solid; m.p. 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 6 H, 2 OCH_3), 6.67 (d, J = 8.4 Hz, 2 H, Ar-*H*), 7.21 (dd, J = 1.8, 7.5 Hz, 1 H, Ar-*H*), 7.29 (dd, J = 1.8, 7.6 Hz, 1 H, Ar-*H*), 7.33–7.51 (m, 7 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.2 (2 CH_3), 104.3 (2 CH), 119.9 (C), 125.6 (C), 126.8 (CH), 127.4 (CH), 127.9 (2 CH), 129.5 (CH), 129.8 (2 CH), 130.0 (CH), 131.1 (CH), 137.3 (C), 142.4 (C), 143.2 (C), 157.8 (2 C) ppm. $C_{20}H_{17}BrO_2$ (369.25): C 65.05, H 4.64, found C 65.14, H 4.73.

2′-Bromo-2,6,2′′,6′′-tetramethoxy-[1,1′;3′,1′′]terphenyl (2i-a)

Synthesis of 2i-a by Direct Aryne Cross-Coupling: Butyllithium (2 mmol) in hexane (1.25 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.28 g, 2.00 mmol) in anhydrous THF (5.00 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene (**1i**) (2.40 mmol, 0.89 g) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (60 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 6:4) afforded the biaryl **2i-a** (0.57 g, 67%) as a colorless solid.

Synthesis of 2i-a by Consecutive Aryne Cross-Coupling: Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and then cooled to 0 °C. A solution of the 1,2-dibromobenzene (**1r**) (6.00 mmol, 1.52 g) in anhydrous THF was added dropwise. The mixture was stirred at 0 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was

extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Crystallization from EtOAc afforded the biaryl **2i-a** (0.25 g, 24%) as a colorless solid.

2i-a: M.p. 243–245 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 12 H, 4 OCH_3), 6.65 (d, J = 8.3 Hz, 4 H, Ar-H), 7.19 (d, J = 7.6 Hz, 2 H, Ar-H), 7.32 (t, J = 8.3 Hz, 2 H, Ar-H), 7.36–7.41 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3 (4 CH_3), 104.5 (4 CH), 120.4 (CH), 126.5 (2 C), 128.1 (C), 129.2 (2 CH), 130.8 (2 CH), 136.4 (2 C), 157.9 (4 C) ppm. $C_{22}H_{21}BrO_4$ (429.30): C 61.55, H 4.93; found C 61.23, H 4.89.

(2-Bromo-2′,6′-dimethoxy-6-methylbiphenyl-3-yl)trimethylsilane (2j-a): Butyllithium (8.00 mmol) in hexane (5.00 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (1.10 g, 8.00 mmol) in anhydrous THF (20.0 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **1j** (3.09 g, 9.60 mmol) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (300 mL) was added and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Crystallization from MeOH afforded the biaryl **2j-a** (1.50 g) as a colorless solid. Column chromatography (cyclohexane/CH_2Cl_2, 8:2) of the mother liquors followed by crystallization from MeOH furnished an additional portion of **2j-a** (0.20 g). Yield: 56%; m.p. 120–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.40 [s, 9 H, Si(CH_3)$_3$], 2.04 (s, 3 H, Ar-CH_3), 3.74 (s, 6 H, 2 OCH_3), 6.66 (d, J = 8.4 Hz, 2 H, Ar-H), 7.20 (d, J = 7.5 Hz, 1 H, Ar-H), 7.34 (d, J = 7.5 Hz, 1 H, Ar-H), 7.35 (t, J = 8.4 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.00 (3 CH_3), 21.0 (CH_3), 56.2 (2 CH_3), 104.4 (2 CH), 119.1 (C), 127.9 (CH), 129.4 (CH), 133.8 (C), 135.1 (CH), 136.3 (C), 138.4 (C), 140.9 (C), 157.6 (2 C) ppm. $C_{18}H_{23}BrO_2Si$ (379.36): C 56.99, H 6.11; found C 56.76, H 6.20.

2-Bromo-3,2′,6′-trimethoxybiphenyl (2k-a): Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **1k** (1.60 g, 6.00 mmol) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/CH_2Cl_2, 6:4) gave **2k-a** (1.03 g, 64%) as a colorless solid; m.p. 127–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 6 H, 2 OCH_3), 3.93 (s, 3 H, OCH_3), 6.65 (d, J = 8.4 Hz, 2 H, Ar-H), 6.85–6.90 (m, 2 H, Ar-H), 7.29–7.36 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.2 (2 CH_3), 56.4 (CH_3), 104.3 (2 CH), 110.5 (CH), 114.8 (C), 119.2 (C), 124.3 (CH), 127.6 (CH), 129.5 (CH), 138.1 (C), 156.2 (C), 157.8 (2 C) ppm. $C_{15}H_{15}BrO_3$ (323.18): C 55.75, H 4.68; found C 55.41, H 4.45.

2-Bromo-3,2′,6′-trimethoxy-6-methylbiphenyl (2l-a): Butyllithium (2.70 mmol) in hexane (1.69 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.37 g, 2.70 mmol) in anhydrous THF (10.0 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to 0 °C. A solution of the 1,2-dibromobenzene **1l** (0.91 g, 3.24 mmol) in anhydrous THF was added dropwise. The mixture was stirred at 0 °C for 3 h and then warmed to room temperature overnight. Water (100 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/CH_2Cl_2, 6:4) gave **2l-a** (0.25 g, 28%) as a viscous oil. Crystallization from MeOH afforded colorless needles. ^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 3 H, CH_3), 3.72 (s, 6 H, 2 OCH_3), 3.90 (s, 3 H, OCH_3), 6.67 (d, J = 8.4 Hz, 2 H, Ar-H), 6.83 (d, J = 8.4 Hz, 1 H, Ar-H), 7.18 (d, J = 8.4 Hz, 1 H, Ar-H), 7.36 (t, J = 8.4 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9 (CH_3), 56.0 (2 CH_3), 56.2 (CH_3), 104.2 (2 CH), 110.5 (CH), 114.7 (C), 118.3 (C), 128.6 (CH), 129.3 (CH), 131.1 (C), 137.3 (C), 154.0 (C), 157.3 (2 C) ppm. MS (EI): m/z (%) = 336.0 (9) [M]$^+$, 322.0 (23) [M – Me]$^+$, 258.1 (6) [M – Br]$^+$, 243.1 (43) [M – Me – Br]$^+$, 228 (100) [M – Br – OMe]$^+$, 213.1 (16) [M – Me – Br – OMe]$^+$. $C_{16}H_{17}BrO_3$ (337.21): C 56.99, H 5.08; found C 56.84, H 5.13.

2-Bromo-2′,6′-dimethoxy-5-methylbiphenyl (2m-a)

Synthesis of 2m-a by Aryne Cross-Coupling Reaction: Butyllithium (5.00 mmol) in hexane (3.12 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5.00 mmol) in anhydrous THF (12.5 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –35 °C. A solution of the 1,2-dibromobenzene **1m** (1.50 g, 6.00 mmol) in anhydrous THF was added dropwise. The mixture was stirred at –35 °C for 3 h and then warmed to 25 °C overnight. Water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 70:30) afforded a mixture (1.35 g, 88%) of biaryls **2m-a** and **2m-b** (**2m-a/2m-b**, 50:50).

Synthesis of 2m-a by Desilylation of Biaryl 2p-a: A solution of tetrabutylammonium fluoride (3.00 mmol) in anhydrous THF (3.00 mL) was added to silane **2p-a** (0.38 g, 1.00 mmol) in THF (10 mL) under Ar at 25 °C. The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL), and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/CH_2Cl_2, 80:20) afforded a mixture (150 mg, 54%) of biaryls **2m-a** and **4b** (**2m-a/4b**, 47:53).

2m-a: The ^{1}H NMR spectrum of biaryl **2m-a** was determined by comparison of the spectroscopic data of mixtures of **2m-a/4b** and **2m-a/2m-b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, Ar-CH_3), 3.74 (s, 6 H, 2 OCH_3), 6.65 (d, J = 8.3 Hz, 2 H, Ar-H), 6.99–7.04 (m, 2 H, Ar-H), 7.33 (t, J = 8.3 Hz, 1 H, Ar-H), 7.53 (d, J = 8.1 Hz, 1 H, Ar-H) ppm.

4′-Bromo-2′′,6′′-dimethoxy-1,1′:3′,1′′-terphenyl (2o-a): A solution of tetrabutylammonium fluoride (4.50 mmol) in THF (4.50 mL) was added to silane **2q-a** (1.50 mmol, 0.66 g) in anhydrous THF (15.0 mL) under Ar at 25 °C. The mixture was stirred at 25 °C for 16 h, hydrolyzed with water (100 mL), and diluted with Et_2O (100 mL). The organic layer was separated, washed with water (2 × 100 mL), dried with Na_2SO_4, and evaporated under reduced pressure. Purification of the crude by column chromatography (cyclohexane/CH_2Cl_2, 8:2) followed by crystallization from MeOH at –20 °C afforded the biaryl **2o-a** (0.22 g, 40%) as a colorless solid; m.p. 102–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 6 H, 2 OCH_3), 6.67 (d, J = 8.4 Hz, 2 H, Ar-H), 7.30–7.48 (m, 6 H, Ar-H), 7.58–7.61 (m, 2 H, Ar-H), 7.72 (d, J = 8.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1 (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) ppm. $C_{20}H_{17}BrO_2$ (369.25): C 65.05, H 4.64; found C 65.45, H 4.55.

(2-Bromo-2′,6′-dimethoxy-5-methylbiphenyl-3-yl)trimethylsilane (2p-a): Butyllithium (2.00 mmol) in hexane (1.25 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.28 g, 2.00 mmol) in anhydrous THF (5.00 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –78 °C. A solution of the 1,2-dibromobenzene **1p** (0.77 g, 2.40 mmol) in anhydrous THF was added dropwise. The mixture was stirred at –78 °C for 3 h and then warmed to 25 °C overnight. Water (60 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 75:25) afforded the biaryl **2p-a** (0.47 g, 62%) as a colorless solid; m.p. 117–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.42 [s, 9 H, Si(CH_3)$_3$], 2.33 (s, 3 H, Ar-CH_3), 3.74 (s, 6 H, 2 OCH_3), 6.65 (d, J = 8.3 Hz, 2 H, Ar-*H*), 7.04 (d, J = 1.9 Hz, 1 H, Ar-*H*), 7.23 (d, J = 1.9 Hz, 1 H, Ar-*H*), 7.32 (t, J = 8.3 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 (3 CH_3), 21.1 (CH_3), 56.2 (2 CH_3), 104.3 (2 CH), 120.2 (C), 129.3 (CH), 130.0 (C), 133.9 (CH), 135.7 (C), 136.2 (CH), 136.3 (C), 141.1 (C), 157.9 (2 C) ppm. $C_{18}H_{23}BrO_2Si$ (379.36): C 56.99, H 6.11; found C 56.81, H 6.27.

(4′-Bromo-2′′,6′′-dimethoxy-1,1′:3′,1′′-terphenyl-5′-yl)trimethylsilane (2q-a): Butyllithium (2.00 mmol) in hexane (1.25 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (0.28 g, 2.00 mmol) in anhydrous THF (5.00 mL) under Ar at 0 °C. The mixture was stirred at 25 °C for 5 h and was then cooled to –78 °C. A solution of the 1,2-dibromobenzene **1q** (0.92 g, 2.40 mmol) in anhydrous THF was added dropwise. The mixture was stirred at –78 °C for 3 h and then warmed to 25 °C overnight. Water (60 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/CH_2Cl_2, 75:25) followed by crystallization from EtOH afforded the biaryl **2q-a** (0.41 g, 47%) as a colorless solid; m.p. 138–140 °C. ^{1}H NMR ($CDCl_3$): δ = 0.47 [s, 9 H, Si(CH_3)$_3$], 3.75 (s, 6 H, 2 OCH_3), 6.67 (d, J = 8.4 Hz, 2 H, Ar-*H*), 7.30–7.44 (m, 5 H, Ar-*H*), 7.59–7.63 (m, 3 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 0.1 (3 CH_3), 56.2 (2 CH_3), 104.2 (2 CH), 119.9 (C), 127.3 (2 CH), 127.4 (CH), 128.8 (2 CH), 129.5 (CH), 132.0 (CH), 132.5 (C), 133.8 (CH), 136.9 (C), 139.1 (C), 140.8 (C), 141.9 (C), 157.9 (2 C) ppm. $C_{23}H_{25}BrO_2Si$ (441.43): C 62.58, H 5.71; found C 62.47, H 5.63.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

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