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Through the Maze: Cross-Coupling Pathways to a Helical Hexaphenyl "Geländer" Molecule

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This paper highlights a new concept on how to induce chirality in a hexaphenyl Geländer-type system. Bridging a terphenyl backbone with a considerably longer benzyl ether oligomer enforces a continuous twist of the molecule, while preventing an achiral *meso* form. By highlighting cross-coupling strategies and explored synthetic pathways, this report aims to serve as an Ariadne's thread for the synthesis of precisely functionalized, complex polyaromatic systems. The synthetic challenges and considerations required to access the designed target are outlined and solutions to each step of the assembly are presented. Encountered isomerizations are discussed as much as synthetic tools to access highly functionalized intermediates with multiorthogonal moieties. A strong focus is made on the employment of Suzuki–Miyaura protocols for the targeted connection of polyaromatic fragments and ultimately the desired oligomeric structure.

Introduction

Polycyclic aromatic compounds (PAC) have caught the attention of material scientists and fundamental researchers since the very beginning of molecular chemistry.[1] Their unique electronic properties arise from the reduced spacing between their frontier orbitals, and their pronounced chemical stability makes them interesting building blocks for the development of components in electronics, optics, and functional materials.[2] Furthermore, such compounds offer the opportunity to study fundamental processes such as angular conductivity dependence, molecular motion, or even shed light on the origin of life.[3] Making PACs chiral allowed increasingly delicate aspects such as circular polarized luminescence (CPL), dynamic processes like racemization and controlled molecular motion to be explored.[4,5]

Several concepts have been developed to introduce chirality into PACs. Helically twisted acenes[6] (Figure 1, a) were obtained by the introduction of bulky substituents along the rim of the molecule; helicenes[7] (Figure 1, b) release the steric strain induced by the hydrogen atoms pointing into the cavity by adopting a spring-like conformation. By inducing defects in a graphene sheet, twisted nanosheets were obtained (Figure 1, c).[8] Chiral naphthalene oligomers (Figure 1, d) show extreme *cisoid* conformations and demonstrate impressive state-of-the-art chiroptical properties.[9] Geländer oligomers (Figure 1, e)[10] become chiral due to a second elongated bridging structure forcing the phenyl units of the backbone into an out-of-plane twist. In the Geländer oligomers reported so far, the two bridging motifs were attached in the *ortho*-position of the central phenyl ring. As a consequence of this spatial remoteness, their strain-releasing twist directions are independent and, in most cases, the *meso*-form with twists of opposed chirality is favored. Expanding on the concepts found in the literature, we developed a new approach[11] (Figure 1, f) to introduce helicity to a polymeric system: Similar to the reported Geländer-oligomers, the structure is based on a terphenyl backbone, but instead of solely bridging neighboring phenyl rings (i.e., two bridges), the backbone is wrapped by a benzyl ether oligomer (only one, continuous bridge). The appealing design feature of this new approach is the absence of an achiral *meso*-form. The central phenyl subunit of the wrapping oligo benzyl ether acts as a rigid joint that relays the helicity from one subunit to the other; as a consequence, the helicity of the system must become continuous. The geometrical molecular design considerations are sketched in Figure 2. A ladder structure consisting of two parallel rails and a finite numbers of cross linkages serves as a model. The model system is, by definition, an achiral, highly symmetrical oligomer or, depending on the length and number of linkages, a monodimensional polymer. Cutting one of the rails into segments (Figure 2, Panel 1) and elongating the sections (blue) by a significant amount (Figure 2, Panel 2b) induces strain after reclosing the system. The system may respond by wrapping the longer rail heli-

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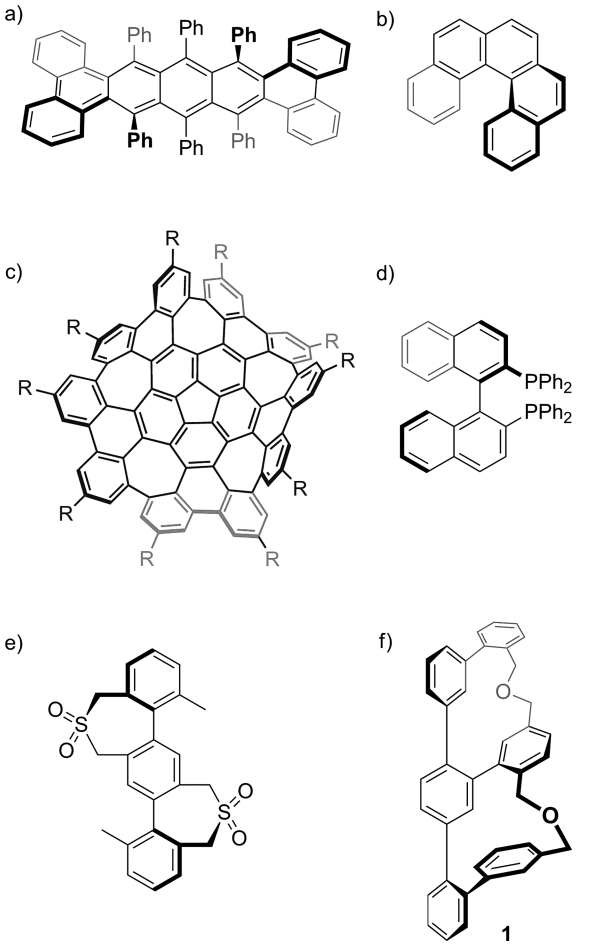


Figure 1. Various realizations of chiral polycyclic aromatic compounds (PACs). (a) Twisted pentacene; (b) [5]-helicene; (c) Scott's nanographene; (d) chiral naphthalene; (e) Vögtle's Geländer oligomer; (f) twisted terphenyl **1** as a new type of Geländer oligomer.

cally around the shorter rail, but if the bridge segments are spaced far apart it also has the option to adopt a *meso*-form, which is the case for most reported Geländer structures. To avoid the *meso*-form preference, a rotatable rigid joint (Figure 2, Panel 2a) is introduced, which guarantees that the helical information is propagated across the junction. Reclosing the system with the rigid joint (Figure 2, Panel 3) induces strain, which the system will try to minimize. The most efficient way to achieve this is to lengthen the spacing between two crosslinks by wrapping them around the principal axis. As a consequence of the length mismatch between both rails, the oligomer (or polymer) becomes helical (Figure 2, Panel 4).

We have recently discussed the conceptual ideas and the physical properties emerging from the Geländer helicity in detail elsewhere;[11] this full paper focuses mainly on an exploration of the synthetic pathway towards **1**. In particular, the use of Suzuki–Miyaura cross coupling as a synthetic tool with which to assemble complex polycyclic aromatic structures is addressed.[12] Although a vast number of publications deal with the development and application of undoubtedly very complex aryl-aryl couplings, only a minority of these go beyond the synthesis of (hetero-)biaryls. The target structure presented here provided an excellent opportunity to contribute to the exploration of cross couplings for the construction of complex polyaromatic systems. The target structure requires the precise connection of aryl subunits and, in particular the late stage of the synthesis, of very demanding (both electronically and sterically) systems.

Consequently, we discuss here synthetic strategies that were explored and ultimately allowed the assembly of **1**, the synthesis of the subunits, their convergent assembly to a suitable precursor, and its final cyclization to the target structure **1**, as well as the spectroscopic characterization of key intermediates and their purification by chiral HPLC.

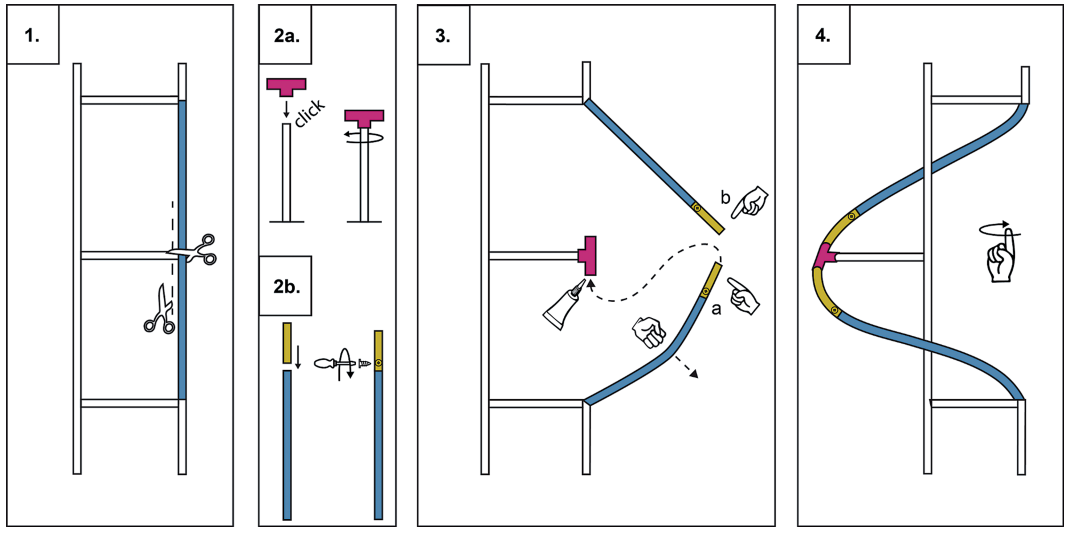


Figure 2. Generalized concept for the introduction of helicity: (1) A ladder-like structure with one of the rails divided. (2a) Introduction of a rotatable joint that relays the twist from one section to the other, and (2b) elongation of the liberated ends. (3) Stepwise reattachment of the significantly elongated sections, which induce strain in the system. (4) The system releases strain by twisting around the original rail and, as a consequence, becomes helical.

Retrosynthetic Analysis

The retrosynthetic analysis of the "Geländer" oligomer **1** is displayed in Figure 3. The lack of symmetry is an important structural feature that avoids the generation of *meso*-forms. As a consequence, the target helical hexaphenyl **1** bears six unique benzyl units: three of the rings feature a single aryl–aryl bond, two benzyls feature two aryl–aryl bonds and the central ring is directly linked to three neighboring aryl subunits. The end capping rings can be grouped into two structurally similar fragments that show reversed substitution patterns (**C** and **D**).

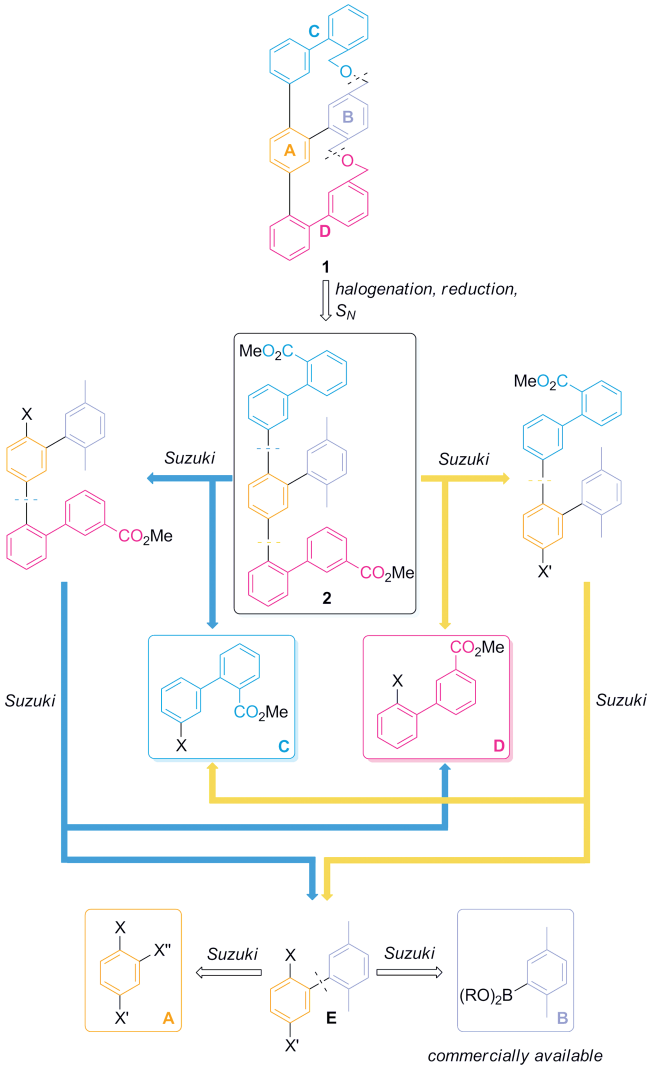


Figure 3. Retrosynthetic analysis for the stepwise assembly of **1**.

The most promising disconnection was the opening of the ether bridges in **1** such that ring **B** (purple ring in Figure 3) supplies the required leaving groups whereas the esters, upon reduction, can provide the necessary oxygen moieties. Esters were particularly interesting because they are generally very susceptible to reductive conditions, even in the presence of benzylic halides. The tolerance of ester groups to a vast range of reaction conditions further favored their choice as masking group for the benzylic hydroxyl function. A late-stage bromination of the two available benzylic positions of the *para*-xylene subunit would reduce the number of functional groups present over a broad range of the synthesis. Thus, the open precursor **2** becomes the actual key fragment with the entire carbon skeleton correctly connected.

For a convergent synthetic strategy, the use of ring **A** (orange ring in Figure 3) as the central unit interlinking three aryl subunits became the focus of interest. Our plan was to profit from Suzuki–Miyaura-type cross-coupling reactions to form the required aryl–aryl connections, mainly because of the high diversity, versatility, low toxicity, and well-established protocols.[13] Grouping the four end-capping phenyls into two biphenyl subunits (**C** and **D**) that differ only in their substitution patterns, enabled the transfer of obtained knowledge from one fragment to the other. Both fragments can subsequently be attached by Suzuki–Miyaura coupling to the core fragment **E**, which itself is also accessible by coupling a suitable core **A** with the commercially available boronic acid **B**. The remaining retrosynthetic challenge was to identify the most promising sequence for the stepwise assembly of the aryl subunits. By following a convergent strategy, it was reasonable to interconnect as many rings as possible prior to the attachment to the central core structure (i.e., assembly of the biphenyl groups **C** and **D** prior to attachment rather than attaching one ring at a time). However the exact order of attachment was not straightforward and the optimal synthetic route remained to be deduced experimentally.

The synthetic route that we identified as most likely to succeed was to attach the commercially available boronic acid to the highly substituted core **A**, which already bears all three required halogens, either masked or unmasked. Having accessed the biphenyl **E**, the fragments **C** and **D** (blue and pink, respectively) could be attached subsequently over two complementary pathways: Either by attaching first fragment **C** to **E** and then fragment **D** (olive arrow) or vice versa (dark-blue arrow). Given that there have been few or no preceding reports in this area, the choice of pathway had to be explored empirically. Fortunately, both pathways required the same fragments **C** and **D**. Our strategy was to develop the central building block towards the target structure by attaching boronic derivatives whenever possible.

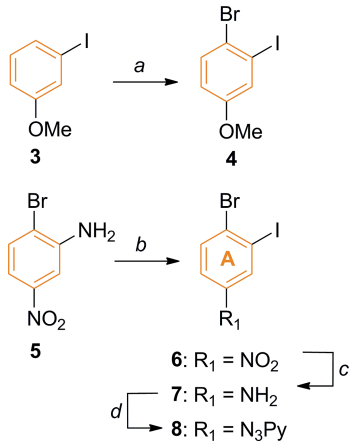
The structure of the central core **A** had to be designed such that it allowed the selective attachment of the three fragments **B**–**D**. A cornerstone of our synthetic strategy was to make use of the different reactivities of halides in Suzuki–Miyaura cross couplings. Central building blocks with suitable substitution patterns bearing an iodine and a bromine substituent were expected to allow two of the three fragments to be introduced chemoselectively. As third substituent, we planned to profit from a masked leaving group such as a methoxy group, which could later be converted into a triflate that was suitable for cross coupling, or a nitrogen moiety (nitro or triazene) as a precursor of an iodine substituent.

Results and Discussion

Synthesis of Fragments A–D

Fragments A and B

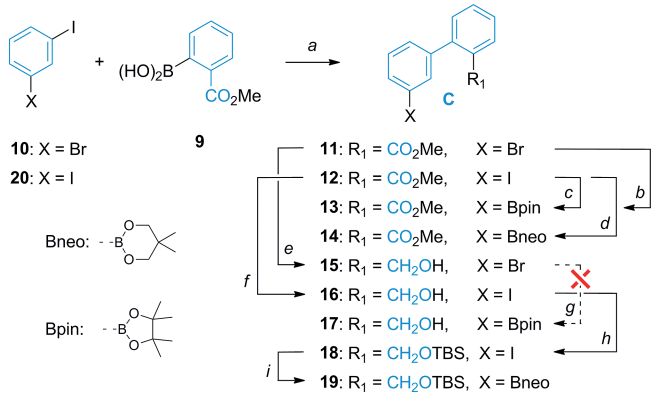
Several potential derivatives as fragment **A** were considered (Scheme 1). Bromination of commercially available 1-iodo-3-methoxybenzene (**3**) by using a reported protocol[14] with *N*-bromosuccinimide (NBS) yielded **4** in almost quantitative yield. We have recently described the synthesis of **6**–**8** elsewhere.[11] In summary, nitro compound **6** was obtained in excellent 97% yield from **5**. In two steps, **6** could be readily converted into the corresponding triazene **8**, giving access to three possible fragments **A** (**4**, **6**, and **8**) that were suitable for subsequent cross coupling with fragment **B**. 2,5-Dimethylphenylboronic acid as potential fragment **B** is commercially available and was not accessed synthetically.



Scheme 1. Reagents and conditions: (a) NBS, MeCN, r.t., 15 h, 96%; (b) BF_3·OEt_2, ONO*t*Bu, THF, –30 °C to r.t., 3 h, then I_2, KI, MeCN, r.t., 30 min, 97%; (c) Fe, HCl, EtOH, 0 °C, 2 h, 94%; (d) BF_3·OEt_2, ONO*t*Bu, CH_2Cl_2, –30 °C to r.t., 15 min, then pyrrolidine, K_2CO_3, r.t., 15 min, 95%; N_3Py = diazenylpyrrolidine.

Fragment C

The two remaining fragments **C** and **D** are both biphenyls, albeit with different substitution patterns. It turned out that the type of substitution pattern had a surprising impact on the chemistry we were able to perform on the fragments. The biphenyl fragment **C** features a borane in the 3-position and either an ester or a benzylic alcohol in the 2′-position. For fragment **D**, the pattern is reversed; the borane is in the 2′-position whereas the ester or benzylic alcohol is located at the 3-position. In particular, the position of the preceding halogen was crucial for the success of the borylation. Starting from 2-methoxycarbonyl phenyl boronic acid (**9** in Scheme 2), Suzuki–Miyaura cross coupling with 1-bromo-3-iodophenyl (**10**) was possible, rendering **11** in 53% after several optimizations (see Table 1 in the Supporting Information).



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, K_2CO_3, THF/MeOH (4:1), 60 °C, 15 h, **11**: 53%, **12**: 54%; (b) $Pd(dppf)Cl_2$, B_2pin_2, KOAc, DMF, 100 °C, 6.5 h, **13**: 5%; (c) $Pd(dppf)Cl_2$, B_2pin_2, KOAc, DMF, 100 °C, 2 h, >99% (75% for large scale); (d) *i*PrMgCl·LiCl, B(O*i*Pr)$_3$, neopentyl glycol (NPG), THF, –40 °C to r.t., 19 h, 72%; (e) DIBAL-H, CH_2Cl_2, 0 °C to r.t., 1–2 h, 90%; (f) DIBAL-H, CH_2Cl_2, 0 °C to r.t., 1–2 h, 94%; (g) $Pd(dppf)Cl_2$, B_2pin_2, KOAc, DMF, 100 °C, 6.5 h, <5%; (h) TBSCl, imidazole, CH_2Cl_2, r.t., 22 h, 86%; (i) *i*PrMgCl·LiCl, B(O*i*Pr)$_3$, NPG, THF, –40 °C to r.t., 20 h, 45%.

As a starting point, the widely used $Pd(PPh_3)_4$ was employed as catalyst under an oxygen-free atmosphere in a 1:2 ratio of wet tetrahydrofuran (THF) and methanol, using K_2CO_3 as base and 1.5 equiv. of 1-bromo-3-iodophenyl. Samples were taken after 3 and 24 h, respectively, and analyzed by GC–MS. Generally, it can be stated that $Pd(PPh_3)_2Cl_2$ showed superior conversions compared with other catalysts employed. Selective cross coupling on the iodine was observed exclusively even at 60 °C, allowing for subsequent attachment of the next fragment (or a boronic moiety) after the cross-coupling step. Both precatalyst XPhos- and SPhos-palladacycle systems described by Buchwald and co-workers,[15] showed a tendency to also initiate cross coupling on the bromines, which was undesired in this case. This observation, however, pointed to the possibility of employing these highly active systems at a later stage in the synthesis. The choice of solvents played a crucial role in the success of the reaction. A significant decrease in reactivity was observed without the addition of methanol. Interestingly the presence of methanol seems to be important but not the exact ratio, because similar conversions were observed for THF to methanol ratios of both 2:1 and 4:1.

To increase the reactivity of the fragment in a subsequent coupling or *trans*-functionalization reaction, the iodine analogue **12**, together with the benzylic alcohol **16** and the silyl-masked benzylic alcohol **18**, also became a focus of interest. Subjecting 1,3-diiodobenzene (**20**) and the corresponding boronic acid to Suzuki–Miyaura conditions provided **12** in up to 54% yield after optimization. Considering the statistical nature of the reaction, we were pleased with the isolated yield. The only observed side-products were the dicoupled analogue as well as starting material. It is important to note, however, that by adding more than 1 equiv. of boronic acid under suitable conditions [i.e., $Pd(PPh_3)_2Cl_2$, NaOH, dioxane/water (4:1), 60 °C, 21 h, 88%] it was also possible

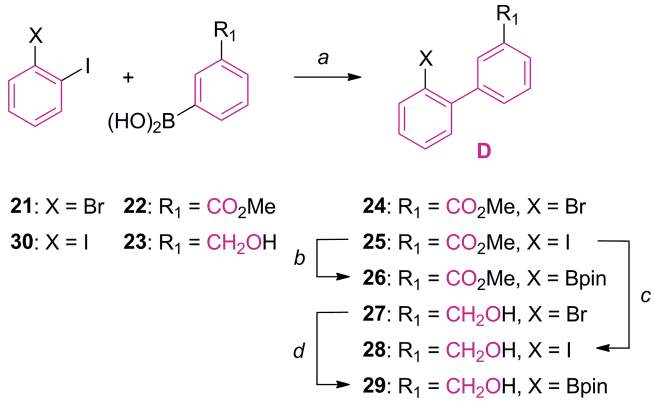
to initiate cross coupling on the bromine. The cross coupling was found to be very reliable and robust, even on large scale (>20 g, 54%).

The synthetic strategy relies on a reduction of the methyl esters at a late stage of the synthesis. Compounds **11** and **12** were considered as model compounds with which to investigate the required reaction conditions. Subjecting either **11** or **12** to reductive conditions using diisobutylaluminum hydride (DIBAL-H), the desired benzylic alcohols **15** and **16** were obtained in promising yields of 90 and 94%, respectively, corroborating the potential of these esters as masked benzylic alcohols. In case the reduction should fail on the further advanced (more crowded) precursor, a masked benzylic alcohol might be an alternative building block. Treating the obtained benzylic alcohol **16** with TBSCl under basic conditions provided the TBS-protected alcohol **18** in a pleasing 86% yield.

According to our convergent strategy, borylation of the biphenyl building block was investigated next (Table 2 in the Supporting Information). Reaction conditions were developed starting from reported protocols[16] with the ester-bearing biphenyls **11** and **12**, the free alcohols **15** and **16**, as well as the TBS-protected alcohol **18** as potential starting materials. Similar to the trends observed for Suzuki–Miyaura couplings, iodines were found to show significantly increased reaction rates towards Hosomi–Miyaura borylation (quantitative conversions for iodines vs. 5% for bromines). The conversion of the iodine worked most reliably on large scale (>14 g) when heating to approximately 112 °C in dioxane overnight (sealed flask). Lithiation of ester **11** by using *s*BuLi, *t*BuLi or lithium diisopropylamide (LDA) as lithium source[17] resulted in decomposition of the starting material. Another explored possibility to introduce the boronic moiety by metalation was the use of conditions developed by Knochel and co-workers in which the corresponding halide is subjected to Grignard conditions and the formed magnesium intermediate is quenched with a boron source. In our hands the Knochel conditions[18] turned out to be generally lower yielding compared to the classical Hosomi–Miyaura borylation. Furthermore, upscaling to multigram batches resulted in a substantial drop in yield and the reaction required extended reaction times (72% for small scale, 31% for large scale). For the free alcohol **15**, only low yields were obtained (<5%) with the Knochel system,[18] because decomposition of the free alcohol **17** was observed under basic conditions even without the presence of a metal source. The TBS-protected alcohol **18** could, however, be successfully borylated (45%).

Synthesis of Fragment D

Building on the knowledge obtained for fragment **C**, we turned our attention to the structurally related fragment **D** (Scheme 3). Starting from 1-bromo-2-iodobenzene (**21**) and [3-(methoxycarbonyl)phenyl]boronic acid (**22**) or [3-(hydroxymethyl)phenyl]boronic acid (**23**), access to **24** and **27** was achieved in good yields. The difference in reactivity of iodine and bromine towards Suzuki–Miyaura coupling again allowed the iodine to be selectively addressed over the bromine, giving yields of 73% for the ester **24**.



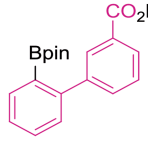
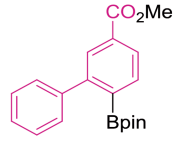
Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, K_2CO_3, THF/MeOH (4:1), 60 °C, 15 h; **21** + **22**→**24**: 73%; $Pd(PPh_3)_2Cl_2$; **30** + **22**→**25**: 41%; $Pd(PPh_3)_4$, Cs_2CO_3, THF/EtOH (4:1), 60 °C, 4 h; **21** + **23**→**27**, 71%; (b) $Pd(dppf)Cl_2$, B_2pin_2, KOAc, dioxane, 100 °C, 1 h, 57% as regioisomers; (c) DIBAL-H, CH_2Cl_2, 0 °C to r.t., 2 h, >99%; (d) $Pd(dppf)Cl_2$, B_2pin_2, KOAc, DMF, 100 °C, 1 h, 59% as regioisomers.

In contrast to the observations made for fragment **C**, it was also possible to directly cross couple the free alcohol without prior protection, giving **27** in comparable yield (71%). To benefit from the increased reactivity of iodines over bromines in Hosomi–Miyaura borylations, we also prepared the iodinated analogues **25** and **28**. Statistically subjecting 1,2-diiodobenzene (**30**) and the corresponding boronic acid to Suzuki–Miyaura conditions allowed **25** to be accessed in 41% yield, which is a reasonable yield for a statistical reaction. The only observed side-products were, as in the case for fragment **C**, the dicoupled analogue as well as the starting material. Subjecting **25** to reductive conditions using DIBAL-H again allowed access to the desired benzylic alcohol **28** quantitatively in 2 h.

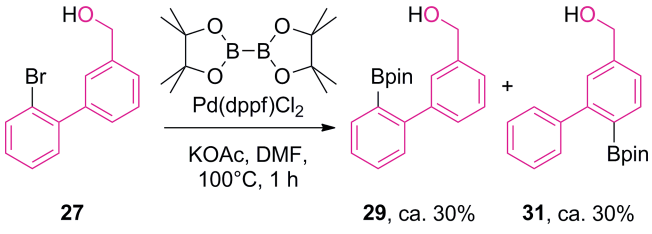
From the four precursors for the subunit **C** (**24**, **25**, **27**, and **28**), precursors **25** and **27** were initially selected and subjected to Hosomi–Miyaura conditions. Borylation of **27** provided a crude boronic ester derivative in reasonable 59% isolated yield. Interestingly, we were now able to obtain the borylated free hydroxy in good yields, whereas with reversed substitution patterns, the obtained boronic ester **17** was not stable. We found a strong dependence of the isolated yield on the concentration, and significantly lower yields tended to be obtained upon dilution. To our surprise, the isolated boronic ester derivative was not a pure compound, but an inseparable mixture of two regioisomers (Scheme 4). GC–MS, ^1H and ^{13}C NMR analyses confirmed the presence of exactly two regioisomers in a 1:1 ratio. 2-D NMR spectroscopy allowed the identification of both compounds as the expected biphenyl **29**, and **31** as the second isomer. Intriguingly, the boronic moiety in **31** is located *para* to the hydroxyl group on the opposite phenyl ring. Whether the formation of that second isomer occurs by deborylation and reborylation of the C–H bond at the 2-posi-

tion or whether the boronic moiety escapes the steric constraint it undoubtedly suffers from and directly isomerizes, is still under investigation. Similar observations have been reported for corannulene and biphenyl using an iridium-catalyzed system.[19] We wondered whether the observed isomerization was a unique feature of alcohol **27**. Subjecting ester **25** to the same conditions, however, rendered a similar picture (Table 1): The yield was as high as for **27** (isolated yield: 57%) again with a 1:1 ratio of similar regioisomers (entry 1, **26** and **32**). Both regioisomers could be separated by normal-phase HPLC (column: semipreparative Reprosil 100 Si, 5 µm, 250 × 16 mm, eluent: CH_2Cl_2, 8 mL/min) and both were fully assigned based on ^1H NMR and 2D NMR spectroscopy. GC–MS showed the same mass and fragmentation pattern for both compounds as expected for regioisomers (see Figure 4). It appears that an ester is equally capable to direct this unexpected rearrangement. However, we never observed the rearrangement when exchanging the positions of the halogen and the ester or alcohol (i.e., for the fragment **C** homologues), further indicating that steric strain plays an essential role in promoting this unexpected rearrangement. The use of dioxane instead of *N*,*N*-dimethylformamide (DMF) under otherwise unaltered conditions promoted the formation of the rearranged side-product **32** over the expected product **26** (entry 2; 84 and 16%, respectively). It thus appears that the choice of solvent can influence the formation of the regioisomer significantly. Lowering the temperature to 80 °C resulted in formation of the undesired isomer **32** in 71% yield (entry 3), demonstrating that temperature can also influence the extent of the rearrangement.

Table 1. Formation of regioisomers during the Hosomi–Miyaura borylation of **25**.[a]

Entry	Solvent[a]	Δ	 **26** [b]	 **32** [b]
1	DMF	100 °C	51	49
2[c]	dioxane	100 °C	16	84
3	dioxane	80 °C	29	71

[a] Reaction conditions: $Pd(dppf)Cl_2$, B_2pin_2, KOAc, 15 h. [b] By GC–MS analysis. [c] Significant amount of side-products observed.



Scheme 4. Formation of the two regioisomers **29** and **31** upon borylation of bromobiphenyl **27**, yields were determined by GC–MS analysis.

This unexpected and intriguing rearrangement prevented the synthetic availability of borylated building block **D** and challenged the envisaged synthetic strategy. In addition, borylation of the bromine analogue **24** showed significantly reduced reaction rates compared with those of **25**. We therefore decided to alter our synthetic strategy by exchanging the positions of the boronic acid derivative and of the halogen leaving group for the bond formation between the fragments **D** and **A**. The iodinated precursors **25** and **28** were thus considered as potential fragments **C**.

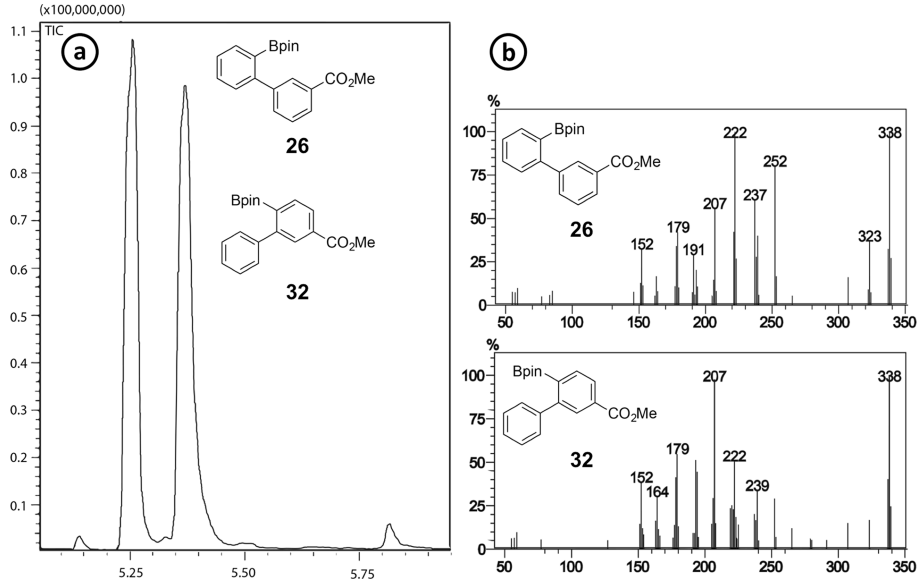
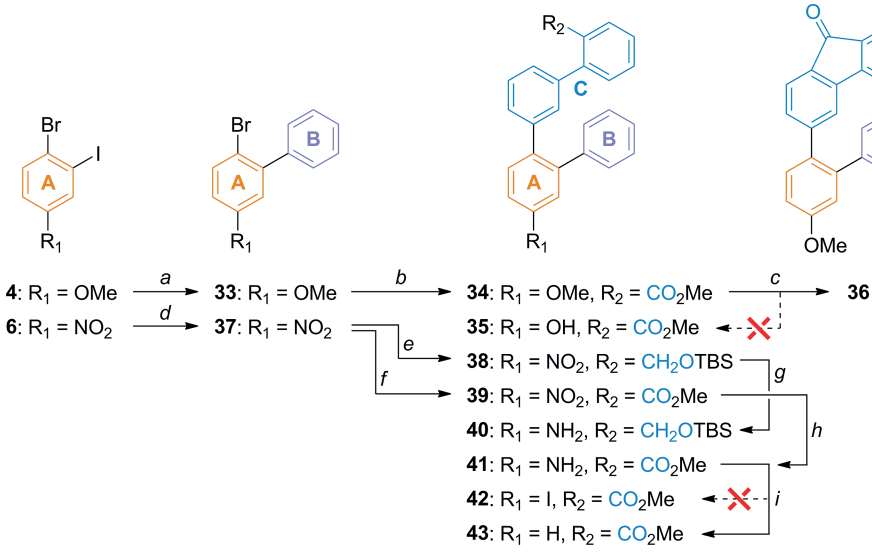


Figure 4. (a) GC–MS trace from the reaction mixture of the borylation of **25** displaying both regioisomers (**26** and **32**), which were formed in a 1:1 ratio. (b) Mass-spectrometric analysis of both GC signals. Both regioisomers give closely related patterns because of their structural similarity.

With all building blocks for a convergent synthesis in hand, our attention moved towards the assembly of the target structure **1**.

Stepwise Connection of the Fragments I: Preliminary Studies with Model Compounds

With all fragments in hand, we aimed to establish a viable sequence for their combination to give the target structure. Fragment **A**, that is **4**, **5** and ultimately **8**, allowed for the envisaged stepwise attachment of the other fragments. At this point we were mainly interested in exploring the synthetic strategy as far as possible. It was therefore of interest to attach a fragment **B** with diminished steric bulk. Coupling of **4** with commercially available phenyl boronic acid gave **33** in excellent 93% yield over 21 h using partially optimized conditions (Scheme 5). A solvent system consisting of dioxane/water (4:1) was found to promote cross coupling on both halides to a significant amount (up to 26% according to GC–MS analysis). Cross coupling **33** with crude **14** under similar conditions to those described before gave tetraphenyl **34** in reasonable 51% yield. To enable the introduction of the last fragment **D**, the hydroxy group needed to be liberated. Typically a strong Lewis acid such as BBr_3 is capable of demethylating the methoxy group.[20] When subjecting **34** to Lewis-acidic conditions at –78 °C, we observed the formation of a single isolable product in 56% yield. 1D ^{1}H NMR and 2D NMR spectroscopy (namely selective TOCSY), as well as GC–MS analysis allowed the isolated compound to be identified as cyclic ketone **36**, instead of the desired complex quarterphenyl **35** with a liberated phenolic OH group. Apparently, BBr_3 is capable of activating the ester such that cyclization is preferred to the desired methylation. Although Lewis-acid initiated bond formations are widely used in polyaromatic synthesis (e.g., Scholl-type reactions),[21] the inability to deprotect the methoxy group forced us to search for alternative routes. The nitro derivative **6** is ideally suited for cross-coupling reactions because of its electronic nature. Indeed, when subjected to the same cross-coupling conditions as applied above for **4**, compound **6** and phenyl boronic acid were converted into **37** in 68% yield. The electron-withdrawing effect of the nitro group has an even larger activating effect on the engagement of the bromine in the *para*-position in cross-coupling reactions. Subsequent coupling of the remaining bromine of the formed biphenyl **37** as a major side-reaction clearly reflected this effect. The increased activity of the bromine leaving group was also promising for the subsequent attachment of fragment **C**. We decided to directly subject the only marginally purified **37** together with **19** to cross-coupling conditions, giving the tetraphenyl building block **38** in excellent 84% yield. Purification of the test system **38** was very challenging and we decided to focus instead on the similar reaction between **37** and **14**, which provided the methyl ester functionalized tetraphenyl building block **39**. To enable the attachment of the remaining fragment **D**, the nitro groups of **38** and **39** had to be transformed into a leaving group. Reductive conditions using $SnCl_2$ are known to promote the reduction of nitro groups selectively, while leaving ester groups untouched.[22] Indeed, we were able to reduce the nitro group of both **38** and **39** to the corresponding amines **40** and **41**, albeit in low yields of <27% for the TBS-protected alcohol **40** and <50% for the methyl ester **41**. Reduction using Pd/C and H_2 as an alternative protocol resulted in decomposition of the starting material. Nevertheless, because **41** was accessible in sufficient purity, we attempted to substitute the amine group with an iodine, which would allow the remain-



Scheme 5. Reagents and conditions: (a) phenyl-B(OH)$_2$, Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, toluene/EtOH (4:1), 80 °C, 21 h, 93%; (b) **14**, Pd(PPh$_3$)$_2$Cl$_2$, K$_3$PO$_4$, dioxane/water (4:1), 80 °C, 4 h, 51%; (c) BBr_3, CH_2Cl_2, –78 °C to 0 °C, 4 h, 56% of **36**; (d) phenyl-B(OH)$_2$, Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, toluene/EtOH (4:1), 80 °C, 18 h, 68%; (e) **19**, Pd(PPh$_3$)$_2$Cl$_2$, K$_3$PO$_4$, dioxane/water (4:1), 80 °C, 5.5 h, 84%; (f) **14**, Pd(PPh$_3$)$_2$Cl$_2$, K$_3$PO$_4$, dioxane/water (4:1), 80 °C, 3 h, 81%; (g) $SnCl_2$, EtOAc, reflux, 8 h, <27; (h) $SnCl_2$, EtOAc, reflux, 6 h, <50%; (i) 1. BF_3·OEt_2, ONO*t*Bu, THF, –30 °C to r.t., 3 h; 2. I_2, KI, MeCN, r.t.

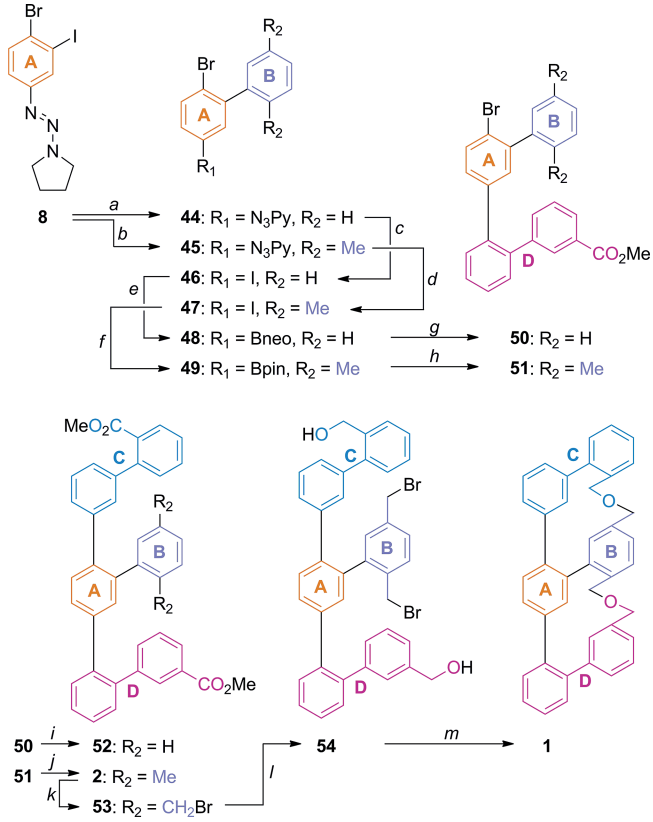
ing fragment **D** to be attached. By using the established conditions to convert anilines into iodines by forming the corresponding diazonium salt, the ester **41** was subjected to the iodination protocol. Unfortunately, the only observed product was the dehalogenated tetraphenyl **43** and in none of the attempts was the desired iodinated derivative **42** detected.

Stepwise Connection of the Fragments II: The End Game

The synthetic routes exploited so far mainly focused on the stepwise attachment of fragments **C** and **D** to **E** following the olive path of the retrosynthetic analysis (Figure 3). Thereby, we faced severe challenges with the attachment of fragment **D**, in particular its troublesome isomerization during borylation. Furthermore, the challenging introduction of a suitable leaving group at the quaterphenyl structure required for the attachment of the fragment **D** raised questions concerning the viability of this route. At this stage we reconsidered our synthetic strategy, building on the insights gained over the course of the various attempts.

The new plan was to profit from the fact that fragment **A** can already feature a masked iodine. Particularly interesting were triazenes, which can be converted into iodines without the need for a reduction/iodination sequence. The iodine was appealing because it would allow for selective borylation in the presence of less reactive bromines. By introducing the boronic ester to the assembled biphenyl system, the troublesome fragment **D** could then be introduced as a halide (iodine), thus potentially preventing the isomerization as well as moving the challenging attachment of the fragment to an earlier point in the synthesis. Thus, the blue path of the retrosynthetic analysis (Figure 3) became more appealing. As fragment **B**, a *para*-xylene derivative was envisaged, which should allow benzylic bromination in a late stage of the synthesis. The conceptual idea was to minimize the number of functional groups present over a large extent of the synthesis. Having all rings in place would allow the investigation and the full characterization of the structure before introducing the required bromines and reducing the ester moieties to benzylic alcohols. As a last step, basic cyclization should then provide the target structure **1**.

Starting from triazene **8**, two different fragments **B** were attached (Scheme 6): Either an unsubstituted phenyl ring, giving **44** as a test system, or 2,5-dimethyl phenyl, which results in **45**. The only difference in reactivity between both fragments might be some steric constrains from the two methyl groups. Both biphenyl fragments **44** and **45** were obtained: 62% for **44**, and excellent yields of up to >99% for **45** under optimized conditions. In both cases, selective substitution of the iodine was observed. Both triazenes **44** and **45** were converted into the corresponding iodines **46** and **47** in very good yields of 83 and 77–96%, respectively, by treatment with MeI at 120 °C overnight.[23] Subsequent borylation of iodines **46** and **47** was more challenging. The application of Knochels protocol gave access to neopentyl borane **48** in low yields of 32% for the unsubstituted biphenyl model compound. As this served merely as a test system, the conditions were not improved. As a consequence, however, the palladium-catalyzed Hosomi–Miyaura borylation protocol that we have already established was used for the dimethylated iodobiphenyl **47**, providing pinacol borane **49** in an improved yield of 53%. Given the metastable nature of the intermediate, the obtained borane was typically used directly in the next step.



Scheme 6. Reagents and conditions: (a) phenyl-$B(OH)_2$, $Pd(PPh_3)_2Cl_2$, K_2CO_3, toluene/EtOH (1:1), 80 °C, 23 h, 62%; (b) 2,5-dimethylphenyl-$B(OH)_2$, $Pd(PPh)_2Cl_2$, K_2CO_3, THF/H_2O (4:1), 60 °C, 15 h, 88% to >99%; (c) MeI, 120 °C, 15 h, 83%; (d) MeI, 120 °C, 15 h, 77–96%; (e) *i*PrMgCl·LiCl, $B(OiPr)_3$, NPG, THF, –40 °C to r.t., 19 h, 32%; (f) $Pd(dppf)Cl_2$, KOAc, B_2pin_2, dioxane, 100 °C, 15 h, 53%; (g) **25**, $Pd(PPh_3)_2Cl_2$, K_2CO_3, toluene/EtOH (4:1), 80 °C, 5.5 d, 33%; (h) **25**, XPhos Pd G2, K_2CO_3, toluene, 110 °C, 1–2 d, 58–94%; (i) **14**, $Pd(PPh_3)_2Cl_2$, K_3PO_4, dioxane/H_2O (4:1), 80 °C, 4 h, 90%; (j) **13**, SPhos Pd G2, K_2CO_3, toluene/H_2O (20:1), 110 °C, 1–3 d, 50%; (k) NBS, DBP, CCl_4, 75 °C, 1 h, 87% to >99%; (l) DIBAL-H, CH_2Cl_2, r.t., 30 min, >99%; (m) 1. NaH, THF, reflux, 12 h, 30% for the monocyclized intermediate; 2. NaH, [D_8]THF, 60 °C, 2–3 d, 28%.

With **48** and **49** in hand, the attachment of fragment **D** became the focus of interest. Suzuki–Miyaura cross coupling of the phenyl-bearing model system **48** with **25** under the conditions optimized for the assembly of the tetraphenyls **38** and **39** gave the desired tetraphenyl **50** in modest 33% yield. Relying on the observations made while screening for optimal Suzuki conditions for the assembly of fragment **C**, we decided to employ a catalyst system that showed a high tendency for cross coupling of sterically challenging

systems.[24] XPhos Pd G2 was found to be ideal for the successful promotion of the desired cross coupling of **49** with **25**, giving the desired quaterphenyl system **51** in up to 94% yield based on GC–MS analysis. At this stage of the synthesis, the obtained crude material was very challenging to purify and it was best used as obtained in the next step. The cross-coupling reaction was monitored by GC–MS analysis and full conversion was observed within 1–2 days. By placing the borane on the assembled structure rather than on the biphenyl fragment **D**, its troublesome isomerization was prevented entirely. Both quarterphenyls **50** and **51** were suitably functionalized for the attachment of the last fragment **C**.

Whereas slightly modified standard Suzuki–Miyaura conditions were used for the coupling between the sterically less demanding **50** and **14**, the sterically encumbered **51** together with the pinacol borane **C** fragment **13** were subjected to a previously reported, highly active catalyst system [$Pd(OAc)_2$/SPhos or SPhos Pd G2].[25] The less hindered model compound **52** was isolated in excellent 90% yield, while the sterically more challenging coupling product **2** was still obtained in a reasonable yield of 50%. Both hexaphenyl systems **52** and **2** were fully characterized by ^1H, ^{13}C, as well as 2D NMR spectroscopy, confirming not only the presence of all required rings, but also the desired substitution patterns. DART-MS as well as HRMS (ESI) provided further evidence for the molecular identity of **2**.

With compound **2** in hand, our attention turned to the bromination of its methyl groups. A bromination procedure adapted from a reported protocol was applied.[26] Treatment of **2** with NBS and dibenzoylperoxide in CCl_4 provided the dibrominated hexaphenyl **53** in up to quantitative yield. The reaction times varied with the batch size, and the course of the reaction had to be closely monitored to avoid over-bromination. All brominated species were structurally and electronically very similar, resulting in comparable retention values in all investigated chromatographic systems; thus, monitoring was best performed by DART-MS. The mono- and tri-brominated species were subsequently removed efficiently by semipreparative HPLC (column: semipreparative Reprosil 100 Si, 5 µm, 250 × 16 mm, eluent: 60:40 hexane/CH_2Cl_2, 8 mL/min). Conventional flash column chromatography (CC) could be used to enrich the dibrominated species **53**, but only after several repeated columns. Interestingly, the ^1H NMR spectrum revealed diastereotopic hydrogen signals for all benzylic positions, indicating that, on the NMR timescale, the structure was already subject to hindered rotation. For the reduction of diester **53**, the protocol established for fragment **C** was applied. Treatment of **53** with DIBAL-H in dichloromethane at room temperature for 30 min provided hexaphenyl diol **54** in almost quantitative yield. The latter diol displayed limited stability and thus subsequent cyclization was best carried out immediately after purification.

During the development of the synthetic strategy, we judged the assembly of the suitably functionalized hexaphenyl system to be the major challenge and assumed that once **54** became available, its double cyclization would be a straightforward and comparably facile final step. This assumption was based on the observation that, in **54**, the two benzylic alcohols as nucleophiles and the two benzylic bromides as substrates are ideally preorganized for two subsequent intramolecular substitution reactions. Potential polymerization reactions can be avoided by performing both ring-closing reactions under high-dilution conditions. Much to our surprise, the double ring-closing reaction of **54** to **1** turned out to be very challenging. Initial attempts to cyclize **54** to **1** under basic conditions resulted in traces of **1** at best, regardless of full consumption of the starting material. The only promising signs were obtained by DART-MS of the reaction mixture, which revealed at least partial formation of the desired structure. Attempts to isolate **1** failed; instead, substantial loss of mass was observed when exposing the reaction mixture to either silica (acidic or pH-neutral) or aluminum oxide. Closer inspection of the course of the double ring-closing reaction by TLC revealed the rapid formation of a new spot, which was subsequently consumed with the addition of more base. The working hypothesis was that this rapidly formed new spot might be a monocyclized intermediate; indeed, DART-MS analysis of the TLC spot revealed a molecular mass supporting the hypothesis. Given that we failed to cyclize **54** directly to **1**, our desperate final strategy was to isolate the monocyclized derivative of **54** and to investigate its ability to close the second ring. The hope was that cleaner reaction conditions might prevent the formation of side products and thereby favor the second intramolecular ring closure of the intermediate to **1**. By reducing the amount of sodium hydride and carefully monitoring the course of the reaction, selective monocyclization was possible. According to ^1H NMR analysis, a pure monocyclized derivative was isolated and, although we could not identify which, it seemed that exclusively one of the four possible regioisomers was formed. Considering the proximity of the functional subunits, we were confident that we obtained one of the two correctly closed systems, because we reasoned that the designed target structure is the energetically most favored spatial arrangement. Even though the isolation of the monocyclized compound was yield diminishing (30% isolated yield), we hoped that in the monocyclized derivative the remaining functional groups might be even better preorganized, further favoring the second ring closing over competing reaction pathways such as intermolecular substitution reactions. To monitor the course of the second ring closure, the reaction was directly performed in an NMR tube. The tube was charged with the monocyclized regioisomer in deuterated THF, and sodium hydride was added as base. The reaction mixture was heated to 60 °C and the formation of **1** was monitored by ^1H NMR spectroscopy.

Much to our delight, we observed an almost clean transformation of the monocyclized intermediated into a new compound with NMR signals matching the expectations for the desired target structure **1** over a period of 2–3 days (Figure 5). In particular, for each of the eight diastereotopic benzylic hydrogen atoms, an individual signal was observed

(each as a doublet) due to geminal coupling to the second hydrogen at the corresponding benzylic carbon atom. In spite of the clean transformation observed in the NMR spectra, all attempts to isolate the formed species by conventional column chromatography or by normal-phase HPLC failed; in other words, the results further documented the delicate stability properties of the compound at least on these solid phases. Given that the target structure **1** is formed as a racemate, we considered purification by chiral HPLC with the hope of isolating pure enantiomers. Interestingly, both Chiralpak IA and AD-H analytical columns were suitable (eluent: *n*-hexane/2-propanol, 99:1; flow rate 1 mL/min; T = 25 °C) to successfully separate **1** into its *M* and *P* enantiomers. The injected sample contained the reaction mixture as obtained directly after filtration and change of solvents. The obtained UV trace of one representative run is displayed in Figure 6, which clearly displays the enantiomeric peaks as major components in the mixture. No significant plateau between the peaks was observed, pointing to a relatively slow racemization process at room temperature on the timescale of a single run (ca. 20 min). The obtained fractions of numerous runs were combined to yield the target compound **1** in a combined yield of 28% (14% of each enantiomer). Although the yield was somewhat sobering considering the clean transformation monitored by ^{1}H NMR analysis, we were at this point more than pleased to finally have been able to isolate **1** as pure enantiomers. Interestingly, the purified samples of **1** were reasonably stable; the compounds tolerated air and moisture as well as evaporation of the solvents at elevated temperatures under reduced pressure.

The target structure **1** is a colorless solid that is soluble in common organic solvents (ethers, chlorinated hydrocarbons, aromatics, etc.). It was fully characterized by ^{1}H and ^{13}C NMR spectroscopy and by high-resolution mass spectrometry. 2D NMR experiments enabled the full assignment of all the peaks, confirming the identity of the structure. ^{1}H NMR spectra were identical for both enantiomers, which clearly demonstrated the diastereotopic benzylic protons (see Figure 5, c). The identity of **1** was finally corroborated without a doubt by X-ray diffraction, which was presented in detail in the preceding communication.[11] All compounds synthesized over the course of this work were characterized by ^{1}H and ^{13}C NMR spectroscopy and

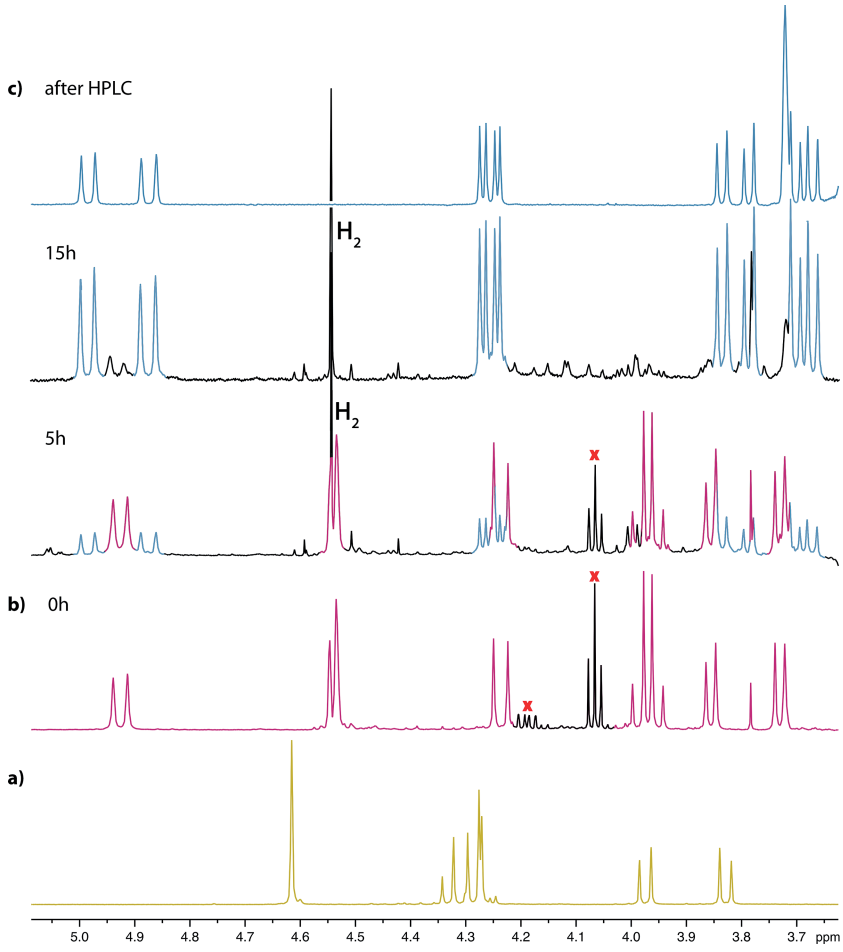


Figure 5. Conversion of the monocyclized intermediate into **1** with NaH in [D_8]THF at 60 °C, monitored by ^{1}H NMR spectroscopic analysis. (a) Selected ^{1}H NMR region of the open-chain precursor **54**. The observed benzylic hydrogen atoms are diastereotopic. (b) Monocyclized intermediate at the beginning of the second cyclization. (c) Spectra of the reaction with almost complete conversion into target structure **1**. The topmost spectrum shows the isolated Geländer oligomer **1** after chiral HPLC.

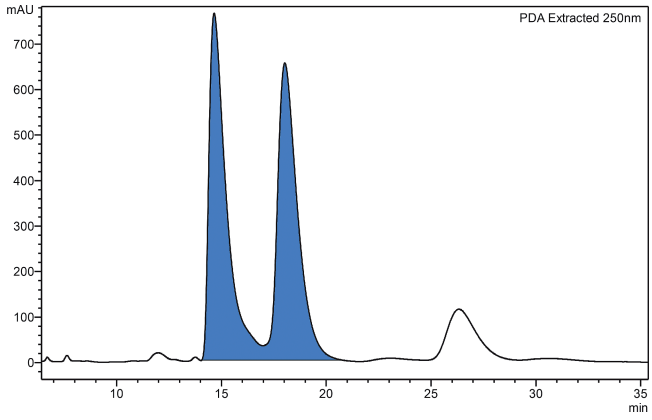


Figure 6. UV trace of a representative chiral HPLC run of the crude reaction mixture after filtration (Chiralpak IA; *n*-hexane/2-propanol (99:1), flow rate 1 mL/min, T = 25 °C). The chart reveals the two enantiomeric peaks (blue) as major compounds. The enantiomeric fractions were collected and combined to give 28% combined yield of the desired target structure **1**.

by mass spectrometry. The intermediates obtained on the synthetic route resulting in the successful assembly of **1** were also characterized by high-resolution ESI mass spectrometry.

Conclusions

We have discussed the synthesis of the new "Geländer" structure **1** as a model compound to demonstrate a new concept to induce helicity in polyaromatic systems. The synthesis of **1** is based on a broad range of Miyuara–Hosomi borylation/Suzuki–Miyaura cross-coupling protocols. In a convergent assembly strategy, suitable precursors were assembled and interlinked to increasingly complex oligophenyl systems to finally yield the suitably functionalized hexaphenyl precursor. The "Geländer" motif was installed by two subsequent intramolecular substitution reactions to build up the elongated benzyl ether oligomer. Whereas careful choice of masking substrates and placement of the boronic moieties allowed the stepwise assembly of the hexaphenyl precursor, persistence was required to close the benzyl ether banister and to isolate the obtained target structure. In spite of numerous obstacles, the "Geländer" oligomer **1** was assembled in an overall yield of 8%, considering only the convergent ten steps interlinking the fragments and installing the "Geländer" motif. Pure enantiomers of **1** were obtained by chiral HPLC.

We now intend to investigate various types of bridges and their influence on the chiroptical properties and racemization behavior.

Experimental Section

General Procedures: All commercially available compounds were purchased and used as received unless explicitly stated otherwise. [D_8]THF was purchased from Acros. ^{1}H NMR spectra were recorded with a Bruker UltraShield 500 MHz Avance III equipped with a 5 mm BBI probe head with Z-gradients. ^{13}C NMR and all 2D spectra were recorded with a Bruker Ascend 600 MHz Avance III HD equipped with a 1.7 mm TCI cryo probe head. The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane or a residual solvent peak, and the J values are given in Hz. DART-MS was measured with an IonSense DART-SVP100 (He, 450 °C) connected to a Shimadzu LC-2020. GC–MS analysis was performed with a Shimadzu GC–MS-2010 SE equipped with a Zebron 5 MS Inferon column, which allowed temperatures up to 350 °C to be achieved. High-resolution mass spectra (HRMS) were measured as HR-ESI-ToF-MS with a Maxis 4G instrument from Bruker with the addition of NaOAc. For column chromatography, usually silica gel Siliaflash p60 (40–63 μm) from Silicycle was used, and TLC was performed on silica gel 60 F254 glass plates with a thickness of 0.25 mm purchased from Merck. Buffered silica was prepared by using buffer solution pH 7 by Fluka and diluting 1:25 with water. 10 mL of the prepared solution was added to 100 g of silica and allowed to adsorb under mixing overnight. For HPLC, a Shimadzu LC-20AT HPLC was used equipped with a diodearray UV/Vis detector (SPD-M10A VP from Shimadzu, λ = 200–600 nm) equipped with the corresponding column (regular: Reprosil 100, 5 μm, 250 × 16 mm; chiral: Chiralpak IA 0.46 × 25 cm; Daicel Chemical Industries Ltd.). All solutions were prepared and measured under air-saturated conditions.

1-Bromo-2-iodo-4-methoxybenzene (**4**) was synthesized from 1-iodo-3-methoxybenzene according to a reported procedure.[27] The experimental data for the successful route including each intermediate step to access **1** (i.e., **6**–**8**, **12**, **13**, **25**, **45**, **47**, **49**, **51**, **53**, **54** and **1**) were described previously.[11]

Methyl 3′-Bromo-[1,1′-biphenyl]-2-carboxylate (11): To an oven-dried and argon-flushed Schlenk tube were consecutively added potassium carbonate (2.32 g, 16.6 mmol, 3.00 equiv.), 2-methoxycarbonylphenylboronic acid (**9**; 1.00 g, 5.56 mmol, 1.00 equiv.), $Pd(PPh_3)_2Cl_2$ (82.8 mg, 2 mol-%), and 1-bromo-3-iodobenzene (**63**; 1.42 mL, 11.1 mmol, 2.00 equiv.). Anhydrous THF (20 mL) and anhydrous MeOH (5 mL) were added and the solution was degassed for 15 min before heating to 60 °C and stirring overnight. EtOAc and water were added, the aqueous phase was extracted with EtOAc (2 ×), and the combined organic phases were washed with brine (1 ×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:15) gave **11** (859 mg, 2.95 mmol, 53%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.86 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.54 (td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.50–7.41 (m, 3 H), 7.34 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 0.7 Hz, 1 H), 7.29–7.20 (m, 2 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 143.4, 141.1, 131.5, 131.3, 130.7, 130.6, 130.2, 130.1, 129.5, 127.7, 127.1, 122.1, 52.1 ppm. MS (EI, +): m/z (%) = 292 (48), 291 (12), 290 (49), 261 (52), 259 (53), 181 (20), 180 (100), 152 (48), 151 (18), 76 (22).

Methyl 3′-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-[1,1′-biphenyl]-2-carboxylate (14): In an oven-dried and argon-flushed Schlenk tube, isopropylmagnesium chloride lithium chloride complex solution (1.13 mL, 1.47 mmol, 1.10 equiv.) was added to a degassed solution of **12** (451 mg, 1.33 mmol, 1.00 equiv.) in THF (8.5 mL) at –40 °C, followed by stirring for 40 min. After GC–MS analysis revealed full conversion, a solution of triisopropyl borate (380 μL, 1.6 mmol, 1.20 equiv.) in THF (1 mL) was added and the mixture was stirred at –40 °C for 2 h before warming to room temperature and stirring for an additional 2 h. After adding 2,2-dimethyl-1,3-propanediol (175 mg, 1.67 mmol, 1.25 equiv.), the mixture was stirred for 14 h at room temperature. CH_2Cl_2 and satd. aq. NH_4Cl were added, the

organic phase was washed with water and brine, the organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:20) gave **14** (312 mg, 962 μmol, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.84–7.80 (m, 1 H), 7.78 (dd, $^3J_{H,H}$ = 5.9, $^3J_{H,H}$ = 2.1 Hz, 2 H), 7.57–7.45 (m, 1 H), 7.44–7.34 (m, 4 H), 3.77 (s, 4 H), 3.61 (s, 3 H), 1.03 (s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.5, 143.0, 140.6, 134.0, 132.9, 131.4, 131.4, 131.1, 131.0, 130.8, 129.9, 127.4, 127.2, 72.6, 52.1, 32.1, 22.2 ppm. MS (EI, +): *m/z* (%) = 325.1 (21), 324.1 (99), 323.1 (44), 294.1 (20), 293.1 (99), 292.1 (26), 208.0 (15), 207.0 (100), 206.1 (27), 181.0 (17), 179.0 (22), 178.0 (25), 177.0 (10), 152.1 (27), 151.1 (12), 69.1 (13), 56.1 (12).

(3′-Bromo-[1,1′-biphenyl]-2-yl)methanol (15): An oven-dried and argon-flushed round-bottomed flask was charged with **11** (408 mg, 1.40 mmol, 1.00 equiv.) and anhydrous CH_2Cl_2 (20 mL) before cooling to 0 °C. DIBAL-H (1 M in hexanes, 4.90 mL, 3.50 equiv.) was slowly added while maintaining the temperature. After stirring for 30 min at 0 °C, the mixture was warmed to room temperature and stirring was continued for an additional 1 h. MeOH (10 mL) was slowly added to the yellow solution (which became dark), followed by *t*BME and aq. HCl (1 M). The organic layer was washed with water and the aqueous layer was extracted three times with *t*BME. The combined organic layers were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure, and the residual oil was passed through a plug of silica (eluent: EtOAc) to give **15** (332 mg, 1.26 mmol, 90%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.58–7.53 (m, 2 H), 7.53–7.49 (m, 1 H), 7.41 (td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.36 (td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.34–7.24 (m, 3 H), 4.61 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H), 1.57 (t, $^3J_{H,H}$ = 5.7 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.1, 140.2, 138.3, 132.5, 130.7, 130.5, 130.2, 129.0, 128.6, 128.3, 128.2, 122.8, 63.4 ppm. MS (EI, +): *m/z* (%) = 264 (45), 262 (46), 183 (56), 182 (11), 181 (17), 166 (19), 165 (100), 155 (18), 154 (32), 153 (17), 152 (26), 76 (13).

(3′-Iodo-[1,1′-biphenyl]-2-yl)methanol (16): An oven-dried, argon-flushed Schlenk tube was charged with **12** (369 mg, 1.09 mmol, 1.00 equiv.) and anhydrous CH_2Cl_2 (3 mL) and cooled to 0 °C before adding DIBAL-H (1 M in hexanes, 2.30 mL, 5.91 mmol, 4.20 equiv.) dropwise over 15 min. The mixture was stirred for 30 min at room temperature and cooled to 0 °C before adding more CH_2Cl_2. The reaction was carefully quenched with brine and the mixture was stirred for an additional 30 min. The solution was neutralized with satd. aq. NH_4Cl, the precipitate was filtered off and discarded, and the filtrate was extracted with CH_2Cl_2 (3×). The combined organics were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave **16** (317.3 mg, 1.02 mmol, 94%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (t, $^4J_{H,H}$ = 1.8 Hz, 1 H), 7.71 (ddd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.8, 1.1 Hz, 1 H), 7.58–7.53 (m, 1 H), 7.45–7.31 (m, 3 H), 7.27–7.22 (m, 1 H), 7.16 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H), 4.60 (s, 2 H) ppm; the hydroxy peak is most likely located underneath the broadened water peak at δ = 1.55 ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 143.0, 140.0, 138.2, 138.1, 136.5, 130.1, 130.1, 128.8, 128.7, 128.4, 128.0, 94.4, 63.2 ppm. MS (EI, +): *m/z* (%) = 311.1 (11), 310.1 (61), 183.1 (63), 182.1 (11), 181.1 (25), 166.0 (28), 165.1 (100), 164.1 (13), 163.1 (10), 155.2 (46), 154.1 (39), 153.1 (40), 152.1 (49), 151.1 (19), 139.1 (11), 128.1 (12), 127.0 (14), 115.1 (18), 91.2 (11), 82.5 (15), 77.0 (27), 76.1 (23), 75.1 (10), 63.0 (15), 51.0 (14).

***tert*-Butyl{[3′-iodo-(1,1′-biphenyl)-2-yl]methoxy}dimethylsilane (18):** An argon-flushed round-bottomed flask was charged with **16** (305 mg, 983 μmol, 1.00 equiv.), imidazole (203.5 mg, 2.96 mmol, 3.01 equiv.), and TBSCl (181 mg, 1.18 mmol, 1.20 equiv.) in anhydrous CH_2Cl_2 (3 mL) and the mixture was stirred at room temperature for 7 h, before adding more TBSCl (154.1 mg, 0.983 mmol, 1.0 equiv.) and stirring overnight. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (2 × 20 mL), aq. HCl (1 M, 3 × 20 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and adsorbed on Celite before subjecting to column chromatography (SiO_2; EtOAc/cyclohexane, 1:20) to give **18** (358 mg, 844 μmol, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (t, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.69 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.55 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.38 (td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.36–7.29 (m, 2 H), 7.20 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.14 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H), 4.56 (s, 2 H), 0.90 (s, 9 H), 0.04 (s, 6 H) ppm. MS (EI, +): *m/z* (%) = 367.9 (22), 366.9 (100), 336.9 (11), 292.9 (14), 167.1 (13), 166.0 (73), 165.0 (72), 75.0 (62).

***tert*-Butyl{[3′-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-(1,1′-biphenyl)-2-yl]methoxy}dimethylsilane (19):** In an oven-dried and argon-flushed Schlenk tube, isopropylmagnesium chloride lithium chloride complex solution (700 μL, 911 μmol, 1.10 equiv.) was added to a degassed solution of **18** (351 mg, 828 μmol, 1.00 equiv.) in THF (6.5 mL) at –40 °C before stirring for 40 min. After GC–MS analysis revealed full conversion, a solution of triisopropyl borate (230 μL, 994 μmol, 1.20 equiv.) in THF (1 mL) was added. Stirring was continued at –40 °C for 2 h before warming to room temperature and stirring for another 2.5 h. After adding 2,2-dimethyl-1,3-propanediol (109 mg, 1.03 mmol, 1.25 equiv.), the reaction was stirred for 14 h. CH_2Cl_2 and satd. aq. NH_4Cl were added and the organic phase was washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:20) gave **19** (243 mg, 604 μmol, 45%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.77 (tt, $^4J_{H,H}$ = 3.2, 1.2 Hz, 2 H), 7.59–7.54 (m, 1 H), 7.42–7.36 (m, 2 H), 7.36–7.32 (m, 1 H), 7.28 (td, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.22 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H), 4.59 (s, 2 H), 3.75 (s, 4 H), 1.02 (s, 6 H), 0.88 (s, 9 H), –0.01 (d, $^4J_{H,H}$ = 1.9 Hz, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.0, 140.2, 138.6, 134.8, 132.7, 131.6, 130.0, 127.8, 127.5, 127.4, 127.0, 72.5, 63.3, 32.1, 26.2, 22.1, 18.6, –5.1 ppm. MS (EI, +): *m/z* (%) = 354.1 (16), 353.1 (60), 352.2 (15), 225.9 (14), 225.0 (70), 193.0 (51), 192.1 (11), 191.0 (11), 180.0 (16), 179.0 (100), 167.0 (48), 166.1 (18), 165.0 (65), 119.0 (21), 75.0 (36), 73.1 (11), 69.1 (63), 57.1 (13).

Methyl 2′-Bromo-[1,1′-biphenyl]-3-carboxylate (24): To an argon-flushed Schlenk tube was consecutively added potassium carbonate (464 mg, 3.32 mmol, 2.98 equiv.), 3-methoxycarbonylphenylboronic acid (**22**; 201 mg, 1.12 mmol, 1.00 equiv.), $Pd(PPh_3)_2Cl_2$ (16.0 mg, 2 mol-%), and 1-bromo-2-iodobenzene (**21**; 284 μL, 2.19 mmol, 1.96 equiv.). Wet THF (4 mL) and MeOH (1 mL) were added and the solution was degassed for 10 min before heating to 60 °C and stirring overnight. EtOAc and water were added, the aqueous phase was extracted with EtOAc (2×) and the combined organic phases were washed with brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:15) gave **24** (238 mg, 817 μmol, 73%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.10–8.05 (m, 2 H), 7.68 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.2 Hz, 1 H), 7.62 (dt, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.54–7.48 (m, 1 H), 7.38 (td, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.2 Hz, 1 H), 7.33 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 2.0 Hz, 1 H), 7.26–7.21 (m, 1 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.9, 141.6, 141.3, 134.0, 133.2, 131.2, 130.5, 130.1, 129.2, 128.8, 128.1, 127.5, 122.5, 52.2 ppm. MS (EI, +): *m/z* (%) = 293 (14), 292 (95), 291 (15), 290

(96), 262 (13), 261 (97), 260 (13), 259 (98), 153 (13), 152 (100), 151 (18), 76 (28).

Regioisomers 26 and 32: A solution of **25** (202 mg, 597 μmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (38.7 mg, 47.3 μmol, 8 mol-%), bis-(pinacolato)diboron (166 mg, 653 μmol, 1.10 equiv.), and potassium acetate (175 mg, 1.79 mmol, 3.00 equiv.) in degassed dioxane (4 mL) was prepared in a dry round-bottomed flask under an argon atmosphere and heated to 100 °C. After stirring for 1 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2; EtOAc/cyclohexane, 1:20). The isolated mixture of regioisomers (**26** and **32**, 57%) was purified by HPLC (column: semipreparative Reprosil 100 Si, 5 μm, 250 × 16 mm, eluent: CH_2Cl_2).

Methyl 2′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1′-biphenyl]-3-carboxylate (26): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.00 (td, $^4J_{H,H}$ = 1.8, 0.5 Hz, 1 H), 7.95 (ddd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.8, 1.2 Hz, 1 H), 7.71 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.2 Hz, 1 H), 7.53 (ddd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.8, 1.2 Hz, 1 H), 7.43–7.38 (m, 1 H), 7.37 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 0.5 Hz, 1 H), 7.33–7.27 (m, 2 H), 3.85 (s, 3 H), 1.12 (s, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 146.7, 143.4, 135, 133.7, 130.6, 130.4, 129.5, 129.2, 128.1, 128, 126.9, 83.7, 24.5 ppm. MS (EI, +): *m*/*z* (%) = 339.3 (17), 338.3 (81), 337.3 (29), 323.2 (12), 307.2 (11), 252.2 (22), 239.2 (28), 238.2 (14), 237.2 (18), 225.1 (13), 223.2 (18), 222.1 (46), 221.1 (20), 220.2 (24), 219.2 (22), 208.1 (15), 207.1 (100), 206.1 (26), 205.1 (14), 194.1 (41), 193.2 (49), 180.1 (13), 179.1 (55), 178.1 (43), 177.1 (14), 165.2 (13), 164.2 (33), 163.2 (18), 153.2 (14), 152.2 (43), 151.1 (16), 59.1 (12).

Methyl 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1′-biphenyl]-3-carboxylate (32): ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.04 (d, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.98 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.76 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H), 7.43–7.35 (m, 5 H), 3.92 (s, 3 H), 1.21 (s, 12 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167, 147.5, 142.2, 134.4, 131.3, 129.7, 129.1, 128, 127.3, 127, 84.1, 52.2, 24.6 ppm. MS (EI, +): *m*/*z* (%) = 339.3 (13), 338.3 (59), 337.3 (15), 323.3 (18), 253.2 (10), 252.2 (46), 239.2 (24), 238.2 (18), 237.2 (39), 223.2 (18), 222.2 (100), 221.1 (27), 207.1 (46), 206.1 (10), 193.2 (16), 191.1 (21), 179.1 (30), 178.1 (25), 163.2 (14), 152.2 (27), 151.2 (11), 59.1 (11).

(2′-Bromo-[1,1′-biphenyl]-3-yl)methanol (27): In an oven-dried and argon-flushed Schlenk tube, 3-(hydroxymethyl)phenylboronic acid (**23**; 400 mg, 2.63 mmol, 1.00 equiv.), 1-bromo-2-iodobenzene (**21**; 410 μL, 3.16 mmol, 1.20 equiv.), Cs_2CO_3 (2.65 g, 8.04 mmol, 3.05 equiv.), and $Pd(PPh_3)_4$ (60.1 mg, 2 mol-%) were added consecutively and suspended in THF (8 mL) and EtOH (2 mL) before degassing for 15 min. The suspension was then heated to 60 °C for 4 h. The reaction mixture was cooled to room temperature, *t*BME was added, and the suspension was filtered through Celite. The orange solution was washed twice with aq. HCl (1 M), water and brine, dried with Na_2SO_4, before removing the solvent under reduced pressure. The residual oil was passed through a plug of silica (eluent: EtOAc/cyclohexane, 1:2), the solvent was removed under reduced pressure, and the orange oil was purified by column chromatography (SiO_2; EtOAc/cyclohexane, 1:4) to give **27** (492 mg, 1.97 mmol, 71%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.69–7.65 (m, 1 H), 7.47–7.30 (m, 6 H), 7.21 (ddd, $^3J_{H,H}$ = 8.0, 6.9, $^4J_{H,H}$ = 2.2 Hz, 1 H), 4.76 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H), 1.72 (t, $^3J_{H,H}$ = 5.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.8, 141.8, 141.1, 133.5, 131.7, 129.2, 129.2, 128.6, 128.4, 127.8, 126.6, 123.0, 65.7 ppm. MS (EI, +): *m*/*z* (%) = 264 (97), 262 (100), 183 (42), 165 (100), 154 (84), 152 (79), 107 (9), 76 (9).

(2′-Iodo-[1,1′-biphenyl]-3-yl)methanol (28): An oven-dried, argon-flushed Schlenk tube was charged with **25** (477 mg, 1.41 mmol, 1.00 equiv.) and anhydrous CH_2Cl_2 (4 mL) and cooled to 0 °C before adding DIBAL-H (1M in hexanes, 5.91 mL, 5.91 mmol, 4.20 equiv.) dropwise over 15 min. The mixture was stirred for 30 min at room temperature before adding more CH_2Cl_2, then the reaction was carefully quenched with brine and the mixture was stirred for an additional 30 min. The solution was neutralized with satd. aq. NH_4Cl, the precipitate was filtered off and discarded, and the filtrate was extracted with CH_2Cl_2 (3×). The combined organics were washed with brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure gave **28** (437 mg, 1.41 mmol, >99%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.96 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.2 Hz, 1 H), 7.45–7.36 (m, 3 H), 7.34 (t, $^4J_{H,H}$ = 1.8 Hz, 1 H), 7.30 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.8 Hz, 1 H), 7.28 (d, $^3J_{H,H}$ = 5.2 Hz, 1 H), 7.04 (ddd, $^3J_{H,H}$ = 7.9, 7.3, $^4J_{H,H}$ = 1.8 Hz, 1 H), 4.77 (d, $^3J_{H,H}$ = 5.8 Hz, 2 H) ppm; 1.71 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 146.6, 144.6, 140.8, 139.7, 130.3, 129.1, 128.8, 128.4, 128.4, 128.1, 126.4, 98.7, 65.5 ppm. MS (EI, +): *m*/*z* (%) = 310.8 (44), 309.9 (97), 183.1 (20), 182.1 (12), 181.1 (24), 166.1 (21), 165.2 (100), 155.1 (40), 154.1 (84), 153.1 (76), 152.2 (97), 151.1 (37), 150.1 (14), 139.1 (10), 128.1 (12), 127.1 (17), 126.1 (14), 115.1 (14), 77.1 (26), 76.0 (17), 75.0 (12), 63.0 (14), 51.0 (14).

Regioisomers 29 and 31: To an oven-dried and argon-flushed Schlenk tube was consecutively added **27** (236 mg, 897 μmol, 1.00 equiv.), potassium acetate (265 mg, 2.70 mmol, 3.01 equiv.), bis(pinacolato)diboron (251 mg, 987 μmol, 1.10 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (59.6, 8 mol-%), and anhydrous DMF (5 mL). The mixture was degassed for 5 min and then heated to 100 °C for 1 h (the solution became dark). After cooling to room temperature, *t*BME was added and the mixture was filtered through Celite, then thoroughly washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; CH_2Cl_2/EtOAc, 20:1) gave a mixture of **29** and **31** (163 mg, 525 μmol, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.76–7.70 (m, 2 H), 7.48–7.42 (m, 2 H), 7.41–7.30 (m, 12 H), 4.77–4.73 (m, 4 H), 1.68–1.59 (m, 2 H), 1.20 (s, 24 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.4, 147.7, 143.9, 143.4, 143.3, 140.7, 135.3, 135.0, 130.6, 129.5, 129.4, 129.0, 128.5, 128.2, 128.1, 127.8, 127.3, 126.8, 125.9, 125.0, 84.2, 65.8, 65.6, 25.0 (2 C) ppm. MS (EI, +): *m*/*z* (%) = 311 (15), 310 (75), 309 (18), 224 (16), 211 (14), 210 (18), 209 (16), 195 (14), 195 (100), 193 (64), 192 (15), 165 (23).

2-Iodo-5-methoxy-1,1′-biphenyl (33): To an oven-dried and argon-flushed Schlenk tube was consecutively added potassium carbonate (1.19 g, 8.55 mmol, 3.0 equiv.) and phenylboronic acid (348.7 mg, 2.86 mmol, 1.00 equiv.) and vacuum applied for 5 min. Compound **4** (1.00 g, 3.20 mmol, 1.12 equiv. as a solution in 5 mL anhydrous toluene) was added along with anhydrous toluene (23 mL) and anhydrous EtOH (7 mL), and the solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (61.6 mg, 3 mol-%) and heating to 80 °C for 21 h. After cooling to room temperature, EtOAc was added and the brown suspension was filtered. The solution was then adsorbed on Celite and subjected to column chromatography (SiO_2; EtOAc/pentane, 1:100 to 1:20) giving **33** (700 mg, 814 μmol, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.52 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.46–7.31 (m, 5 H), 6.87 (d, $^4J_{H,H}$ = 3.1 Hz, 1 H), 6.76 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 3.1 Hz, 1 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 158.9, 143.5, 141.24, 133.8, 129.4, 128.1, 127.8, 116.8, 114.8, 113.2, 55.6 ppm. MS (EI, +): *m*/*z* (%) = 264.9 (14), 263.9 (99), 262.9 (16), 261.9

(100), 220.9 (29), 218.9 (30), 168.0 (27), 153.1 (14), 152.0 (25), 140.1 (43), 139.0 (80), 63.0 (14).

Methyl 5′-Methoxy-[1,1′:2′,1′′:3′′,1′′′-quaterphenyl]-2′′′-carboxylate (34): To an oven-dried and argon-flushed Schlenk tube was added potassium phosphate (66.8 mg, 315 μmol, 3.00 equiv.) and vacuum applied for 5 min. Compound **33** (28.1 mg, 107 μmol, 1.00 equiv. as a solution in 0.5 mL dioxane) and **14** (34.0 mg, 105 μmol, 1.00 equiv. as a solution in 0.5 mL dioxane) were added along with dioxane (600 μL) and water (400 μL). The solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (2.50 mg, 3 mol-%) and heating to 80 °C for 4 h. After cooling to room temperature, EtOAc and water were added, the organic phase was washed with water (2×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:4) gave **34** (41.8 mg, 109 μmol, 51%) as a highly viscous, colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79–7.75 (m, 1 H), 7.46–7.33 (m, 3 H), 7.25–7.23 (m, 3 H), 7.21–7.17 (m, 3 H), 7.11–7.05 (m, 3 H), 7.02–6.95 (m, 3 H), 3.88 (s, 3 H), 3.63 (s, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.2, 158.9, 142.3, 141.8, 141.7, 141.6, 141.1, 140.9, 140.8, 131.6, 131.1, 130.8, 130.1, 129.9, 129.7, 128.7, 128.0, 127.5, 127.1, 126.6, 126.3, 115.9, 113.1, 55.4, 51.9 ppm. MS (EI, +): *m*/*z* (%) = 395.0 (31), 394.1 (100), 362.1 (16), 361.1 (13), 335.1 (15), 334.1 (11), 333.1 (13), 331.1 (11), 319.1 (12), 303.0 (11), 302.0 (17), 291.1 (18), 290.0 (13), 289.0 (27), 151.0 (13), 144.7 (22), 138.1 (14).

2-Bromo-5-nitro-1,1′-biphenyl (37): To an oven-dried and argon-flushed Schlenk tube was consecutively added potassium carbonate (513 mg, 3.67 mmol, 3.00 equiv.), **6** (449 mg, 1.37 mmol, 1.12 equiv.), and phenylboronic acid (149 mg, 1.22 mmol, 1.00 equiv.) before vacuum was applied for 5 min. Anhydrous toluene (10 mL) and anhydrous EtOH (2.5 mL) were added and the solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (26.0 mg, 3 mol-%) and heating to 80 °C for 18 h. After cooling to room temperature, EtOAc was added and the brown suspension was filtered. The residual oil was adsorbed on Celite and subjected to column chromatography (SiO_2; EtOAc/pentane, 1:20) to give **37** (232 mg, 833 μmol, 68%). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.20 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H), 8.06 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.7 Hz, 1 H), 7.86 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.52–7.44 (m, 3 H), 7.44–7.39 (m, 2 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 144.3, 139.2, 134.4, 130.4, 129.4, 128.9, 128.6, 126.0, 123.4 ppm. MS (EI, +): *m*/*z* (%) = 278.9 (41), 276.9 (41), 153.1 (13), 152.1 (100), 151.1 (28), 150.1 (14), 76.0 (14).

***tert*-Butyldimethyl{[5′-nitro-(1,1′:2′,1′′:3′′,1′′′-quaterphenyl)-2′′′-yl]-methoxy}silane (38):** To an oven-dried and argon-flushed Schlenk tube was added potassium phosphate (178 mg, 841 μmol, 3.00 equiv.) and vacuum applied for 5 min. Compound **37** (79.5 mg, 286 μmol, 1.02 equiv. as a solution in 1.8 mL dioxane) and **19** (115 mg, 280 μmol, 1.00 equiv. as a solution in 1 mL dioxane) were added along with dioxane (0.4 mL) and water (0.8 mL). The solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (5.9 mg, 3 mol-%) and heating to 80 °C for 5.5 h. After cooling to room temperature, EtOAc and water were added and the organic phase was washed with water (2×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:50) gave **38** (117 mg, 235 μmol, 84%) as a highly viscous, colorless oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.34–8.29 (m, 1 H), 8.28–8.23 (m, 1 H), 7.67–7.59 (m, 1 H), 7.55–7.51 (m, 1 H), 7.48–7.40 (m, 1 H), 7.38–7.33 (m, 1 H), 7.30–7.28 (m, 1 H), 7.28–7.25 (m, 4 H), 7.25–7.22 (m, 1 H), 7.20–7.16 (m, 1 H), 7.16–7.13 (m, 1 H), 7.13–7.11 (m, 1 H), 6.91 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.4 Hz, 1 H), 4.49 (s, 2 H), 0.87 (s, 9 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.1, 141.9, 140.8, 139.8, 139.2, 138.2, 131.5, 130.4, 129.7 (2 C), 129.6 (2 C), 129.4, 128.5, 128.4, 128.3 (2 C), 127.9, 127.8, 127.6, 127.5, 127.0, 126.8, 126.1, 125.5, 122.2, 30.0, 18.4, 0.1 ppm. MS (EI, +): *m*/*z* (%) = 439.1 (35), 438.0 (100), 408.0 (12), 364.0 (27), 318.0 (29), 317.1 (19), 315.1 (14), 302.0 (15), 75.0 (59).

Methyl 5′-Nitro-[1,1′:2′,1′′:3′′,1′′′-quaterphenyl]-2′′′-carboxylate (39): To an oven-dried and argon-flushed Schlenk tube was added potassium phosphate (313 mg, 1.47 mmol, 3.20 equiv.) and vacuum applied for 5 min. Compound **37** (131 mg, 470 μmol, 1.02 equiv. as a solution in 3.2 mL dioxane) and **14** (150 mg, 461 μmol, 1.00 equiv. as a solution in 1.0 mL dioxane) were added along with dioxane (2.3 mL) and water (1.6 mL) and the solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (10.4 mg, 3 mol-%) and heating to 80 °C for 3 h. After cooling to room temperature, EtOAc and water were added and the organic phase was washed with water (2×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:8) gave **39** (153 mg, 372 μmol, 81%) as a highly viscous, colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.32 (d, $^4J_{H,H}$ = 2.2 Hz, 1 H), 8.31–8.21 (m, 1 H), 7.94–7.74 (m, 2 H), 7.71–7.51 (m, 2 H), 7.44 (dddd, $^3J_{H,H}$ = 11.0, 7.4, 5.7, $^4J_{H,H}$ = 1.6 Hz, 2 H), 7.37–7.27 (m, 3 H), 7.25–7.10 (m, 4 H), 7.06–6.92 (m, 1 H), 3.67 (s, 3 H) ppm. MS (EI, +): *m*/*z* (%) = 410.1 (25), 409.1 (89), 378.0 (25), 377.0 (61), 376.1 (23), 360.1 (15), 350.1 (32), 349.1 (26), 348.1 (19), 332.1 (18), 331.1 (43), 330.1 (26), 329.1 (14), 313.1 (11), 304.1 (20), 303.1 (52), 302.1 (100), 301.1 (29), 300.1 (39), 289.1 (16), 276.1 (16), 226.0 (10), 165.6 (11), 152.1 (20), 151.1 (47), 150.1 (37), 144.6 (21), 143.7 (10), 138.1 (25).

Methyl 5′-Amino-[1,1′:2′,1′′:3′′,1′′′-quaterphenyl]-2′′′-carboxylate (41): A solution of **39** (41.5 mg, 101 μmol, 1.00 equiv.) and $SnCl_2$ (98.0 mg, 507 μmol, 5.00 equiv.) in EtOAc (4 mL) was heated to reflux for 6 h. After cooling to room temperature, EtOAc and satd. aq. $NaHCO_3$ were added, the organic phase was washed with water (1×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; EtOAc/cyclohexane, 1:2) gave **41** (19.4 mg, 51.1 μmol, <50%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.78–7.74 (m, 1 H), 7.43 (td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.35 (td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.30–7.21 (m, 4 H), 7.19–7.15 (m, 3 H), 7.08 (td, $^4J_{H,H}$ = 1.8, 0.6 Hz, 1 H), 7.07–7.02 (m, 2 H), 7.02–6.97 (m, 1 H), 6.78–6.73 (m, 2 H), 3.79 (s, 2 H), 3.63 (s, 3 H) ppm. MS (EI, +): *m*/*z* (%) = 380.0 (30), 379.0 (100), 330.0 (10), 319.0 (17), 318.1 (15), 302.0 (11), 158.7 (14), 152.1 (11).

1-{[6-Bromo-(1,1′-biphenyl)-3-yl]diazenyl}pyrrolidine (44): To an oven-dried and argon-flushed Schlenk tube was consecutively added potassium carbonate (733 mg, 5.25 mmol, 3.00 equiv.), **8** (745 mg, 1.96 mmol, 1.12 equiv.), and phenylboronic acid (213 mg, 1.75 mmol, 1.00 equiv.) then vacuum was applied for 5 min. Anhydrous toluene (14 mL) and anhydrous EtOH (14 mL) were added and the solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (37.2 mg, 3 mol-%) and heating to 80 °C for 23 h. After cooling to room temperature, EtOAc was added and the brown suspension was filtered and adsorbed on Celite. Column chromatography (SiO_2; CH_2Cl_2/toluene, 1:100) gave **44** (356 mg, 1.08 mmol, 62%) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.58 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 7.46–7.34 (m, 5 H), 7.28–7.24 (m, 2 H), 3.77 (s, 4 H), 2.10 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H), 2.00 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H) ppm. MS (EI, +): *m*/*z* (%) = 331.0 (4), 329.0 (4), 232.9 (18), 230.9 (18), 153.1 (16), 152.1 (100), 151.1 (16).

2-Bromo-5-iodo-1,1′-biphenyl (46):[23] In a pressure tube, **44** (345 mg, 1.04 mmol, 1.00 equiv.) was heated to reflux at 120 °C in

MeI (1 mL) overnight. The solvent was removed under reduced pressure and the remaining residue was dissolved in EtOAc. Water was added and the organic phase was washed with $NaHCO_3$ (2×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure, adsorbed on Celite and subjected to column chromatography (SiO_2; CH_2Cl_2/toluene, 1:100) to give **46** (309 mg, 861 μmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, $^4J_{H,H}$ = 2.2 Hz, 1 H), 7.50 (dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 2.2 Hz, 1 H), 7.46–7.42 (m, 1 H), 7.42–7.35 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 144.9, 140.1, 139.9, 137.8, 134.9, 129.4, 128.3, 128.3, 122.8, 92.5 ppm. MS (EI, +): *m/z* (%) = 359.9 (57), 357.8 (59), 153.1 (13), 152.1 (100), 151.1 (28), 150.1 (16), 126.1 (11), 76.1 (26), 75.1 (13), 74.0 (11), 63.0 (11).

2-(6-Bromo-[1,1′-biphenyl]-3-yl)-5,5-dimethyl-1,3,2-dioxaborinane (48): In an oven-dried and argon-flushed Schlenk tube, isopropylmagnesium chloride lithium chloride complex solution (700 μL, 909 μmol, 1.10 equiv.) was added to a degassed solution of **46** (297 mg, 826 μmol, 1.00 equiv.) in THF (6 mL) at –40 °C before stirring for 3 h. After GC–MS analysis revealed full conversion, a solution of triisopropyl borate (230 μL, 992 μmol, 1.20 equiv.) in THF (1 mL) was added and the mixture was stirred at –40 °C for 1 h and subsequently warmed to room temperature before stirring for another 2 h. After adding 2,2-dimethyl-1,3-propanediol (109 mg, 1.03 mmol, 1.25 equiv.), the reaction was stirred for 13 h. CH_2Cl_2 and saturated aq. NH_4Cl were added and the organic layer was washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; CH_2Cl_2/toluene, 1:100) gave **48** (90.5 mg, 262 μmol, 32%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.59 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.43–7.40 (m, 4 H), 7.40–7.33 (m, 1 H), 3.75 (s, 4 H), 1.02 (s, 6 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.0, 141.5, 137.0, 134.2, 132.6, 129.7, 128.1, 127.6, 125.8, 72.6, 32.1, 22.1 ppm. MS (EI, +): *m/z* (%) = 346.9 (19), 346.0 (99), 345.0 (43), 344.0 (100), 343.0 (26), 260.9 (13), 259.9 (62), 258.9 (28), 257.9 (62), 256.9 (16), 179.0 (22), 178.0 (34), 177.1 (13), 152.1 (34), 151.1 (14), 56.1 (26), 55.1 (13).

Methyl 4′′-Bromo-[1,1′:2′,1′′:3′′,1′′′-quaterphenyl]-3-carboxylate (50): To an oven-dried and argon-flushed Schlenk tube was consecutively added potassium carbonate (547 mg, 547 μmol, 3.04 equiv.), **25** (69.5 mg, 201 μmol, 1.12 equiv.), and **48** (61.0 mg, 180 μmol, 1.00 equiv.) before vacuum was applied for 5 min. Anhydrous toluene (2 mL) and anhydrous EtOH (0.5 mL) were added and the solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (3.7 mg, 3 mol-%) and heating to 80 °C for 5.5 d. After cooling to room temperature, EtOAc was added, the brown suspension was filtered and adsorbed on Celite. Twofold column chromatography (SiO_2; CH_2Cl_2/toluene, 1:100) gave **50** (26.1 mg, 59.5 μmol, 33%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.95 (tt, $^4J_{H,H}$ = 3.3, 1.5 Hz, 2 H), 7.51 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 7.45 (d, $^4J_{H,H}$ = 1.7 Hz, 4 H), 7.39–7.29 (m, 4 H), 7.29–7.22 (m, 1 H), 7.19–7.13 (m, 2 H), 7.07 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H), 6.98 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 2.3 Hz, 1 H), 3.90 (s, 3 H) ppm. MS (EI, +): *m/z* (%) = 444.9 (26), 444.0 (87), 443.0 (28), 441.9 (87), 332.1 (11), 331.1 (36), 305.0 (26), 304.1 (100), 303.1 (73), 302.0 (88), 301.1 (17), 300.1 (26), 289.0 (20), 276.0 (12), 226.0 (12), 152.0 (10), 151.0 (34), 150.1 (27), 144.6 (13), 138.1 (19).

Dimethyl 3′′-Phenyl-[1,1′:2′,1′′:4′′,1′′′:3′′′,1′′′′-quinquephenyl]-2′′′′,3-dicarboxylate (52): To an oven-dried and argon-flushed Schlenk tube was added potassium phosphate (37.9 mg, 179 μmol, 3.00 equiv.) and vacuum applied for 5 min. Compound **50** (26.4 mg, 107 μmol, 1.00 equiv. as a solution in 0.5 mL dioxane) and **14** (19.7 mg, 60.7 μmol, 1.02 equiv. as a solution in 0.5 mL dioxane) were added along with dioxane (0.6 mL) and water (0.4 mL). The solution was degassed for 15 min before adding $Pd(PPh_3)_2Cl_2$ (1.30 mg, 3 mol-%) and heating to 80 °C for 4 h. After cooling to room temperature, EtOAc and water were added, and the organic phase was washed with water (2×) and brine (1×). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (SiO_2; CH_2Cl_2/toluene, 1:100) gave **52** (30.7 mg, 53.4 μmol, 90%) as a highly viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.02 (dd, $^4J_{H,H}$ = 1.9, 0.9 Hz, 1 H), 7.98–7.93 (m, 1 H), 7.77 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.58–7.53 (m, 1 H), 7.50–7.39 (m, 4 H), 7.38–7.31 (m, 4 H), 7.19 (tdd, $^3J_{H,H}$ = 8.9, $^4J_{H,H}$ = 3.8, 1.6 Hz, 6 H), 7.10–7.06 (m, 3 H), 6.94 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1 H), 6.92–6.88 (m, 2 H), 3.88 (s, 3 H), 3.62 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1, 167.0, 142.2, 142.0, 141.4, 140.9, 140.8, 140.1, 139.9, 139.6, 138.5, 134.7, 132.4, 131.1, 130.9, 130.8, 130.7, 130.5, 130.5, 130.3, 130.2, 129.9, 129.9, 129.7, 129.0, 128.8, 128.6, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.4, 127.1, 126.6, 126.4, 52.1, 51.9, 29.7 ppm. MS (EI, +): *m/z* (%) = 576.1 (10), 575.1 (44), 574.1 (100), 511.1 (11), 482.1 (14), 481.1 (12), 454.0 (12), 450.0 (11), 219.3 (12).

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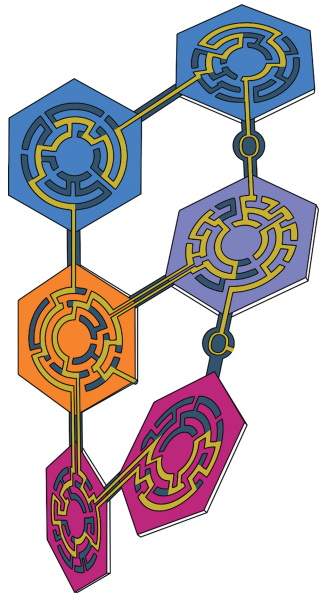
The synthesis of a helical, interlinked Geländer (banister) type hexaphenyl oligomer is symbolized in the figure as a maze; this is a representation of both the often convoluted synthetic possibilities as well as the successful resolution of the maze to reach the target structure.



Keywords: Helical structures / Cross-coupling / Conformation analysis / Chirality / Regioselectivity

