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Reactions of substituted arynes and diphenylphosphine oxide or diphenylphosphine-borane complex towards dibenzophospholes – Impact of aryne substituents

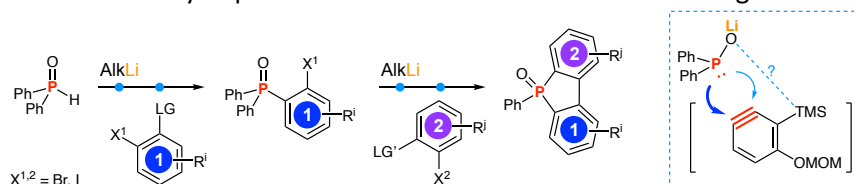
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Abstract

The reaction of diphenylphosphine oxide successively with two aryne precursors was investigated in order to access valuable functionalizable non-symmetrical dibenzophospholes. The reactions proved sensitive to substituents of aryne precursors able to coordinate the incoming lithiated nucleophile.

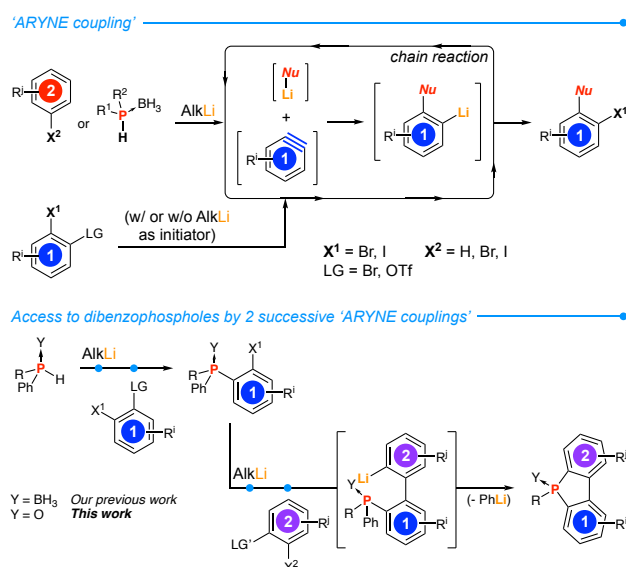


Keywords

arynes, organolithiums, secondary phosphine oxides, secondary phosphine-borane complexes, dibenzophospholes, halogen/metal exchange

Introduction

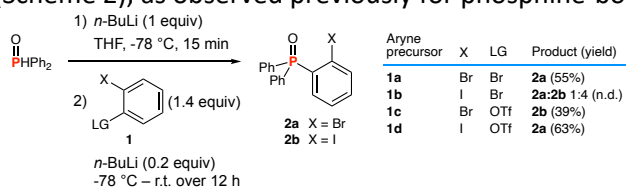
Dibenzophospholes are very valuable compounds with applications in organic electronics, optoelectronics or catalysis, and whose synthesis has been achieved following diverse strategies.¹ Among them, the access to dibenzophospholes by reactions with arynes are scarce,² which contrasts with the otherwise numerous reactions of arynes with phosphorous species.³ We had reported the preparation of non-symmetrical dibenzophosphole-borane complexes by the reaction of arynes with *ortho*-lithiated arylphosphine-boranes,^{2c} themselves being accessed by reaction of arynes with secondary phosphine-boranes.⁴ These two steps rely on the so-called 'ARYNE coupling' strategy, which involves a chain reaction based on halogen/lithium exchanges and attack of (formal)⁵ arynes by lithiated nucleophiles (for selected work, see refs.^{2e, 4a, 5-6}). Interestingly, phosphine oxides, which are more stable than phosphine-borane complexes, have not been used in processes with arynes to access dibenzophospholes. We disclose in this paper our efforts in this direction (Scheme 1).



Scheme 1 Application of the ‘ARYNE coupling’ to the synthesis of benzophospholes

Results and Discussion

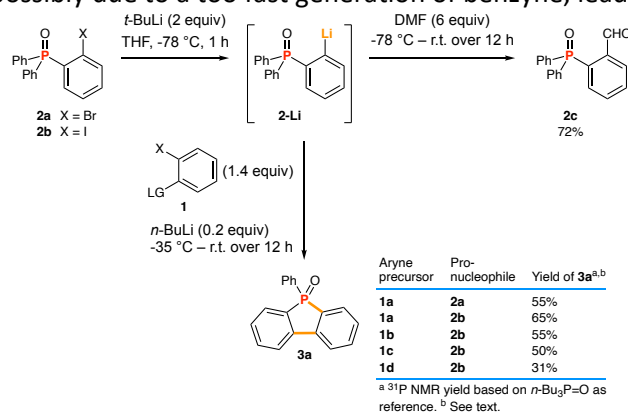
We started our work by examining the coupling of diphenylphosphine oxide and *ortho*-benzyne generated from 1,2-dibromobenzene **1a**, using a procedure similar to the one used in the case of the diphenylphosphine-borane complex as pronucleophile, or (*o*-anisyl)phenylphosphine oxide in a preliminary result.^{4a} After a quick optimization, lithiation of diphenylphosphine oxide was carried out with 1 equiv *n*-BuLi in THF at -78 °C for 15 min, then followed by addition of excess 1,2-dibromobenzene and a small amount of additional *n*-BuLi as initiator, and the mixture was allowed to warm gently from -78 °C to r.t. overnight, affording the expected (2-bromophenyl)diphenylphosphine oxide **2a** in 55% yield. The compound could be separated from triphenylphosphine oxide as side-product upon silica gel chromatography. Other benzyne sources were then assessed, such as 2-bromo (**1c**) and 2-iodophenyl (**1d**) triflates, which gave the corresponding *ortho*-halogenated phosphine oxides in 39% (**2a**) and 63% (**2b**) yields respectively. On the other hand, when 2-bromiodobenzene **1b** was used as benzyne source, a mixture of *ortho*-brominated and *ortho*-iodinated products **2a,b** was obtained in a 5.25:1 ratio and was contaminated with some unidentified impurity. This result indicates an imperfect selectivity in the propagation step of the ARYNE coupling chain reaction, namely in the halogen/lithium exchange between the *ortho*-lithiotriphenylphosphine oxide intermediate and 2-bromiodobenzene **1b** (Scheme 2), as observed previously for phosphine-boranes.^{4a}



Scheme 2 Arylation of diphenylphosphine oxide with benzyne

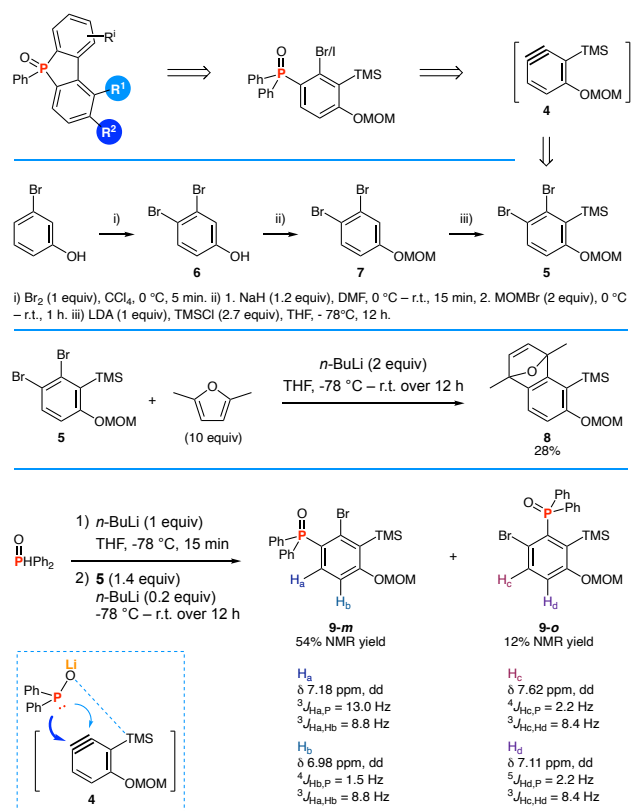
We then turned our attention to the following step, i.e. the ARYNE coupling between the obtained (2-halophenyl)diphenylphosphine oxides and aryne precursors, in order to access non-symmetrical dibenzophosphole oxides (Scheme 3). The key phosphorylated aryllithium intermediate **2-Li** could be formed upon bromine/lithium exchange on **2a,b** using *tert*-butyllithium, as demonstrated by its subsequent trapping with DMF to afford the corresponding aldehyde **2c** after workup in 72% yield. Other products were identified as triphenylphosphine oxide (10%) and *tert*-butyldiphenylphosphine oxide (10%). When 1,2-dibromobenzene **1a** was then engaged in the reaction as benzyne precursor, *n*-butyllithium (0.2 equiv) had to be added to trigger the generation of benzyne and start the chain reaction. We had already used this trick in the case of aryllithium species which were too well-stabilized by an *ortho*-coordinating group, disfavoring the halogen/lithium exchange with the aryne precursor.⁷ Under these conditions, the desired dibenzophosphole oxide **3a** was formed with 55% NMR yield

(using tributylphosphine oxide as reference), accompanied here again by triphenylphosphine oxide (7%) and *tert*-butyldiphenylphosphine oxide (3%) as well as regenerated substrate **2a** (14%). When (2-iodophenyl)diphenylphosphine oxide **2b** was used as substrate in the same reaction, a better yield of **3a** was obtained (65% NMR yield). Other benzyne sources led to somewhat lower yields, especially 2-iodophenyl triflate **1d**, possibly due to a too fast generation of benzyne, leading to side-reactions.



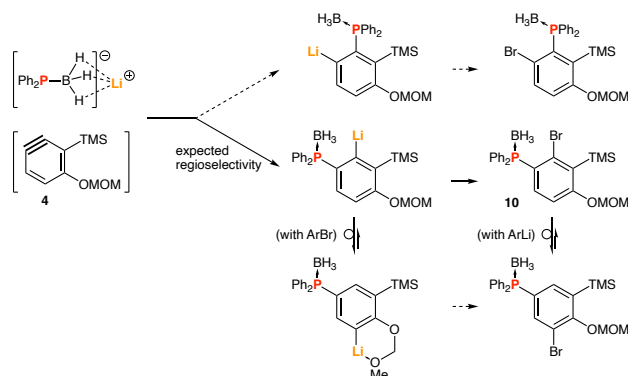
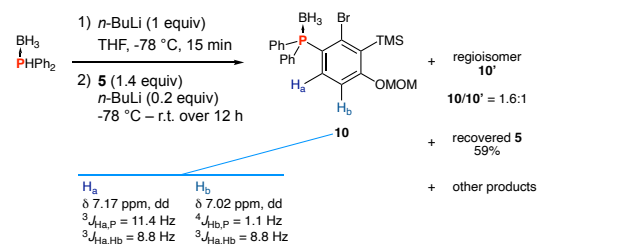
Scheme 3 Formylation and 'ARYNE coupling' of (2-halophenyl)diphenylphosphine oxides

Towards more valuable structures of dibenzophospholes, we targeted reactions with aryne precursors bearing transformable handles for orthogonal functionalization. We imagined that arynes such as **4**, bearing TMS and MOM-protected hydroxy groups, would be suitable for this purpose (Scheme 4). The positions of these 2 groups with respect to the aryne triple bond were determined to minimize regioselectivity issues. Indeed, we had already shown that a TMS group adjacent to the triple bond fully orients the attack of a lithiated nucleophile, namely an aryllithium, in *meta* position with regard to TMS;^{6c, 7b} moreover, the O-MOM substituent being a good directing group for lithiation, it should not be adjacent to the triple bond of the aryne, to avoid competition between the thermodynamically favored *meta*-attack and the kinetically favored *ortho*-attack, as observed in the case of oxazolinyli substituents by Meyers.⁸ Accordingly, compound **5** was prepared from 3-bromophenol in an overall yield of 28%, by *para*-bromination, protection of the phenol with a MOM group and a lithiation/*in situ* quench sequence introducing the silyl group. The ability of **5** to serve as aryne precursor was assessed in a control experiment, by bromine/lithium exchange with *n*-butyllithium and trapping with excess 2,5-dimethylfuran under the conditions that would be used for 'ARYNE coupling', leading to the Diels-Alder reaction product **8**. When 1 equiv of *n*-butyllithium was used, only 10% NMR yield of **8** was obtained, along with 56% of unreacted **5**; with 2 equiv of *n*-butyllithium, **8** was formed with 34% NMR yield (along with 21% unreacted **5**) and 28% isolated yield. Despite these modest results, **5** was thus shown to be able to generate an aryne and was therefore engaged in the reaction with diphenylphosphine oxide. The desired product was obtained as a mixture of 2 regioisomers in a 4.3:1 ratio, respectively the expected product **9-m** of attack in *meta* position regarding TMS and the unexpected product **9-o** of attack *ortho* to TMS. The assignment of regioisomers was possible thanks to ¹H NMR signals of aromatic protons showing distinct H–P scalar couplings in the 2 regioisomers (Scheme 4). This lack of regioselectivity is, as mentioned above, quite unexpected for a reaction directed by the otherwise very good *meta*-directing trimethylsilyl group in the case of aryllithium^{6c, 7b} or lithium amide⁹ nucleophiles. It could then be attributed to a coordination of the oxygen atom of the incoming lithiated diphenylphosphine oxide to the TMS group of the aryne (Scheme 4), a scenario that we were trying to avoid in the case of the OMOM substituent as explained earlier.



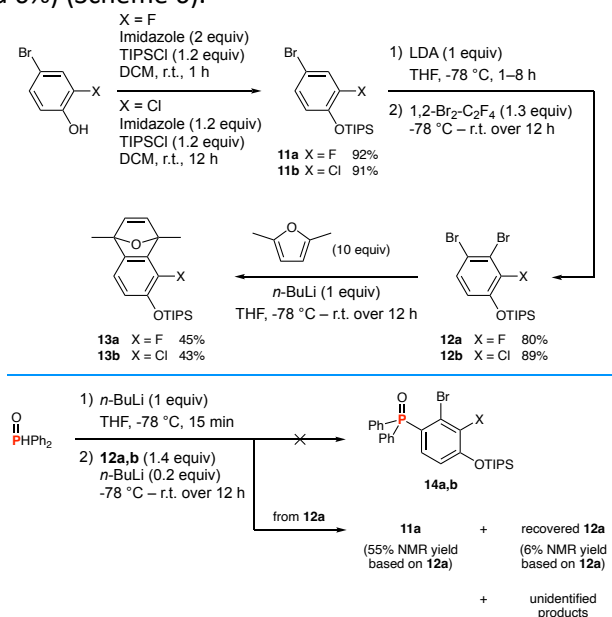
Scheme 4 Design and synthesis of functionalized aryne precursor **5** and reactions with 2,5-dimethylfuran and diphenylphosphine oxide

To probe this hypothesis, the same aryne precursor **5** was submitted to a coupling with the lithiated diphenylphosphine-borane complex, which is not expected to be able to coordinate to the TMS group, or at least not as efficiently. Indeed, phosphido-boranes are known to coordinate, by means of the hydrides, alkali metals such as lithium, alkaline earth metals and some transition metals,¹⁰ however we are unaware of any report concerning their coordination with silicon. Under the reported conditions for the coupling of the diphenylphosphine-borane complex with arynes, i.e. by maintaining the reaction mixture at -78°C for 1–2 h during the coupling, **5** only underwent trace conversion. The coupling step was then performed under a slow increase of the temperature from -78°C to r.t. overnight. In this case, 59% of the initial 1.4 equiv of **5** are recovered after purification. The remaining material was a mixture of compounds from which the desired product **10** and one regioisomer could be observed in a 1.6:1 ratio, based on combined NMR and GCMS analysis. The obtention of a regioisomer could be caused by the undocumented phosphido-borane/TMS complexation mentioned above, or, more probably, by a hydrogen and/or bromine/lithium interconversion favoring a more stabilized aryllithium base,¹¹ considering the good directing ability of the OMOM group (Scheme 5).



Scheme 5 Reaction of aryne precursor **5** with lithium diphenylphosphido-borane and possible regioisomers of the expected product **10**

To overcome this issue, we then designed other aryne precursors, where the group adjacent to the triple bond could not be coordinated by the phosphine oxide and where the OMOM directing group would be replaced by a much less directing group for lithiation. Precursors **12a,b** bearing 3 contiguous halogens and an OTIPS group were thus synthesized in 2 steps from commercial 2-halo-4-bromophenols. Again, their ability to generate arynes under the 'ARYNE coupling' conditions was confirmed by Diels-Alder reaction leading to **13a,b** in 45 and 43% yield respectively. However, when **12a,b** were engaged in the coupling with diphenylphosphine oxide, the desired coupling products **14a,b** could not be observed. Instead, and puzzlingly, when starting from **12a** (X = F), analysis of the reaction mixture after workup showed mainly the presence of debrominated compound **11a** (77% with regard to starting diphenylphosphine oxide, i.e. 55% with regard to starting **12a**) and some recovered **12a** (respectively 8% and 6%) (Scheme 6).



Scheme 6 Synthesis and reactivity of aryne precursors **12a,b**

Conclusion

In summary, the reaction of decorated aryne precursors with lithiated diphenylphosphine oxide or borane complexes as nucleophiles appears more impacted by the nature of substituents on the aryne than in the case of aryllithium nucleophiles. Another design of the reaction partners is required to access the targeted, non-symmetrical and decorated dibenzophospholes.

Acknowledgements

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Disclosure Statement

The authors declare no conflict of interest.

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Experimental Section

All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of argon. Flash chromatography was performed with silica gel (0.040-0.063 μm). Analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm). ^1H NMR spectra were recorded on a Bruker Avance spectrometer at 400 MHz, ^{13}C NMR spectra at 100 MHz, ^{19}F NMR spectra at 282 MHz and proton-decoupled ^{31}P NMR spectra at 161 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to residual solvent (CHCl_3 : $\delta = 7.27$ ppm for ^1H , $\delta = 77.0$ ppm for ^{13}C or relative to external CFCl_3 : $\delta = 0$ ppm). The following abbreviations have been used: δ (chemical shift), J (coupling constant), s (singlet), brs (broad signal), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), dq (doublet of quartets), m (multiplet). Elemental analyses and high resolution mass spectrometry (HRMS) analyses were carried out by the analytical facility of the Université de Strasbourg.

THF was distilled prior to use over Na/benzophenone. DMF, dichloromethane and acetonitrile were dried on molecular sieves. *n*-BuLi in hexanes (concentration around 1.6 M) and *t*-BuLi in pentane (concentration around 1.7 M) were purchased from Sigma-Aldrich and were titrated before use by means of the Wittig-Harborth double titration method.¹² Diisopropylamine and chlorotrimethylsilane were distilled over CaH_2 and stored over molecular sieves under an argon atmosphere. *N*-Chlorosuccinimide was recrystallised from benzene. 1,2-Dibromobenzene, 2-bromiodobenzene, 3-bromophenol, bromomethyl methyl ether, 2,5-dimethylfuran, 4-bromo-2-chlorophenol, imidazole, chlorotriisopropylsilane, 4-bromo-2-fluorophenol and 1,2-dibromo-1,1,2,2-tetrafluoroethane were purchased from Acros, Fluorochem or Sigma-Aldrich and were used without purification. 2-Bromophenyl trifluoromethanesulfonate **1c**¹³ and 2-iodophenyl trifluoromethanesulfonate **1d**¹⁴ were prepared according to the known procedures.

Procedures

General procedure A for the synthesis of (2-halophenyl)diphenylphosphine oxides or the corresponding phosphine-borane complexes

n-BuLi (2-2.1 mmol) was added dropwise at -78 °C to a solution of diphenylphosphine oxide or diphenylphosphine-borane complex (2 mmol) in THF (5 mL) under argon. After 15 minutes at that temperature, the aryne precursor (2.8 mmol) was added dropwise followed by *n*-BuLi (0.4 mmol). After stirring at the indicated temperature and reaction time, the resulting reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (2x10 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel, with cyclohexane/EtOAc as eluent system.

(2-Bromophenyl)diphenylphosphine oxide 2a. Prepared following general procedure A from freshly prepared diphenylphosphine oxide¹⁵ and 1,2-dibromobenzene **1a**, using 1 equivalent of *n*-BuLi. The reaction mixture was stirred for 12 h from -78 °C to room temperature. Compound **2a** was obtained as a white solid in 55% yield (394 mg) after flash chromatography (SiO₂, cyclohexane/EtOAc 3:7). Spectral data are in accordance with literature.¹⁶

¹H NMR (CDCl₃, 400 MHz) δ = 7.75-7.68 (m, 5H), 7.60-7.56 (m, 2H), 7.52-7.47 (m, 4H), 7.42-7.32 (m, 3H).

¹³C NMR (CDCl₃, 100 MHz) δ = 135.7 (d, *J*_{CP} = 10.3 Hz), 134.7 (d, *J*_{CP} = 7.3 Hz), 133.2 (d, *J*_{CP} = 2.2 Hz), 132.9 (d, *J*_{CP} = 104.9 Hz), 131.9 (d, *J*_{CP} = 10.3 Hz), 131.8 (d, *J*_{CP} = 2.9 Hz), 131.5 (d, *J*_{CP} = 107.8 Hz), 128.45 (d, *J*_{CP} = 12.5 Hz), 128.37 (d, *J*_{CP} = 12.5 Hz), 126.82 (d, *J*_{CP} = 11.0 Hz), 126.80.

³¹P NMR (CDCl₃, 161 MHz) δ = 30.4.

(2-Iodophenyl)diphenylphosphine oxide 2b. Prepared following general procedure A from freshly prepared diphenylphosphine oxide¹⁵ and 2-iodophenyl trifluoromethanesulfonate **1d**, using 1 equivalent of *n*-BuLi. The reaction was performed on a 10 mmol scale. The reaction mixture was stirred for 12 h from -78 °C to room temperature. Compound **2b** was obtained as a white solid in 63% yield (2.6 g) after flash chromatography (SiO₂, cyclohexane/EtOAc 3:7). Spectral data are in accordance with literature.¹⁷

¹H NMR (CDCl₃, 400 MHz) δ = 8.06-8.04 (m, 1H), 7.73-7.68 (m, 4H), 7.61-7.57 (m, 2H), 7.52-7.48 (m, 4H), 7.36-7.31 (m, 1H), 7.21-7.16 (m, 2H).

¹³C NMR (CDCl₃, 100 MHz) δ = 142.2 (d, *J*_{CP} = 8.8 Hz), 136.0 (d, *J*_{CP} = 106.4 Hz), 135.6 (d, *J*_{CP} = 11.7 Hz), 133.0 (d, *J*_{CP} = 2.9 Hz), 132.3 (d, *J*_{CP} = 9.5 Hz), 131.9 (d, *J*_{CP} = 2.9 Hz), 131.5 (d, *J*_{CP} = 107.1 Hz), 128.5 (d, *J*_{CP} = 12.5 Hz), 127.3 (d, *J*_{CP} = 11.7 Hz), 99.5.

³¹P NMR (CDCl₃, 161 MHz) δ = 33.1.

(2-Formylphenyl)diphenyl phosphine 2c. To a solution of (2-bromophenyl)diphenylphosphine oxide **2a** (357 mg, 1.0 mmol) in THF (7.5 mL) was added dropwise *t*-BuLi (1.1 mL, 2.0 mmol, C=1.77 M in pentane) at -78 °C. After 1 h at that temperature, dimethylformamide (0.5 mL, 6.0 mmol) was added and the reaction mixture was stirred overnight from -78 °C to room temperature. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (2x10 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc 2:3) to afford compound **2c** as a white solid in 72% yield (219 mg). Spectral data were in accordance with literature.¹⁸

¹H NMR (CDCl₃, 400 MHz) δ = 10.8 (brs, 1H), 8.19-8.16 (m, 1H), 7.72-7.49 (m, 12H), 7.25-7.21 (m, 1H).

¹³C NMR (CDCl₃, 100 MHz) δ = 191.2 (d, *J*_{CP} = 5.9 Hz), 139.6 (d, *J*_{CP} = 6.6 Hz), 135.2 (d, *J*_{CP} = 96.1 Hz), 133.6 (d, *J*_{CP} = 11.0 Hz), 132.7 (d, *J*_{CP} = 11.7 Hz), 132.4 (d, *J*_{CP} = 2.9 Hz), 132.3 (d, *J*_{CP} = 104.9 Hz), 132.0 (d, *J*_{CP} = 10.3 Hz), 131.9 (d, *J*_{CP} = 10.3 Hz), 129.1 (d, *J*_{CP} = 8.8 Hz), 128.8 (d, *J*_{CP} = 17.7 Hz), 128.4 (d, *J*_{CP} = 12.5 Hz).

³¹P NMR (CDCl₃, 161 MHz) δ = 30.9.

General procedure B for the 'ARYNE coupling' of (2-halophenyl)diphenylphosphine oxides with aryne precursors

t-BuLi (3 mmol) was added dropwise at -78 °C to a solution of the (2-halophenyl)diphenyl phosphine oxide (1.5 mmol) in THF (15 mL) under argon. After 1 hour at that temperature, the reaction mixture was warmed to -35 °C and the aryne precursor (2.1 mmol) was added dropwise followed by *n*-BuLi (0.3 mmol). After stirring at -35 °C for 2 h, the resulting reaction mixture was stirred for 12 h from -35 °C to room temperature. The mixture was then quenched with water (15 mL) and tributylphosphine oxide (0.75 mmol, 164 mg) was added as an internal standard. The mixture was extracted with dichloromethane (20 mL), the aqueous phase was extracted with dichloromethane (2x20 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the NMR yield was determined by quantitative ³¹P NMR analysis.

***P*-Phenyldibenzophosphole oxide 3a.** Prepared following general procedure B from (2-bromophenyl)diphenylphosphine oxide **2a** and 1,2-dibromobenzene **1a**. Yield was determined by quantitative ³¹P NMR analysis : 55%. We were able to isolate one fraction of compound **3a** (contaminated by 8% of triphenylphosphine oxide) by flash chromatography (spherical silica, cyclohexane/EtOAc 1:4). Spectral data were in accordance with literature.¹⁹

¹H NMR (CDCl₃, 400 MHz) δ = 7.86-7.83 (m, 2H), 7.75-7.45 (m, 7H), 7.42-7.38 (m, 4H).

¹³C NMR (CDCl₃, 100 MHz) δ = 141.7 (d, *J*_{CP} = 22.0 Hz), 133.3 (d, *J*_{CP} = 2.2 Hz), 132.5 (d, *J*_{CP} = 104.2 Hz), 132.1 (d, *J*_{CP} = 2.9 Hz), 130.9 (d, *J*_{CP} = 11.0 Hz), 130.8 (d, *J*_{CP} = 103.4 Hz), 129.8 (d, *J*_{CP} = 9.5 Hz), 129.3 (d, *J*_{CP} = 11.0 Hz), 128.6 (d, *J*_{CP} = 12.5 Hz), 121.1 (d, *J*_{CP} = 9.5 Hz).

³¹P NMR (CDCl₃, 161 MHz) δ = 33.6.

Synthesis and Diels-Alder reactions of aryne precursors 5

3,4-Dibromophenol 6. To a solution of 3-bromophenol (15 g, 86.7 mmol) in CCl₄ (260 mL) was added bromine (4.4 mL, 86.7 mmol) dropwise at 0 °C (addition over 15 min). After stirring for 5 min at 0 °C and filtration, the precipitate was washed with cold heptane (2x50 mL) and taken up in dichloromethane (200 mL) and water (200 mL). A saturated aqueous solution of Na₂S₂O₃ (30 mL) was added and the two phases were separated. The aqueous phase was extracted with dichloromethane (2x100 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum to give compound **6** as a white solid in 44% yield (9.7 g). Spectral data were in accordance with literature.²⁰

mp = 75.5 – 79.5 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 7.46 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.91 (brs, 1H).

¹³C NMR (CDCl₃, 100 MHz) δ = 155.0, 134.0, 125.0, 120.7, 116.2, 115.5.

1,2-Dibromo-4-(methoxymethoxy)benzene 7. To a suspension of NaH (1.0 g, 26.2 mmol, 60% in mineral oil) in dry DMF (40 mL) was added dropwise, at 0 °C, a solution of 3,4- dibromophenol **6** (5.5 g, 21.8 mmol) in DMF (15 mL). Stir the reaction mixture at room temperature for 15 min and then bromomethyl methyl ether (3.5 mL, 43.7 mmol) was added dropwise at 0 °C. After stirring for 5 min at 0 °C and then 1 h at room temperature, the reaction mixture was quenched with water (50 mL) at 0 °C and extracted with diethylether (50 mL). The aqueous phase was extracted with diethylether (2x50 mL). The combined organic layers were washed with water (2x50 mL), brine (5x50 mL) and dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc 49:1) to afford compound **7** as a colourless oil in 79% yield (5.1 g).

¹H NMR (CDCl₃, 400 MHz) δ = 7.50 (d, *J* = 8.9 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.15 (s, 2H), 3.47 (s, 3H).

¹³C NMR (CDCl₃, 100 MHz) δ = 156.8, 133.8, 124.9, 121.5, 117.0, 116.6, 94.6, 56.1.

HRMS (ESI+, APCI+, *m/z*): calcd. for C₈H₈Br₂O₂: 293.8886; found, 293.8884.

(2,3-Dibromo-6-(methoxymethoxy)phenyl)trimethylsilane 5. To a solution of diisopropylamine (0.7 mL, 5.07 mmol) in THF (9 mL) was added dropwise *n*-BuLi (3.3 mL, 5.07 mmol, C = 1.55 M in hexanes) at -78 °C. This solution was stirred for 15 min before chlorotrimethylsilane (1.7 mL, 13.68 mmol) was

added followed by a solution of 1,2-dibromo-4-(methoxymethoxy)benzene **7** (1.5 g, 5.07 mmol) in THF (4 mL) cooled at -78 °C. The mixture was stirred at -78 °C overnight and quenched with methanol (20 mL). At room temperature, water (20 mL) and EtOAc (50 mL) were added and the two phases separated. The aqueous phase was extracted with EtOAc (2x50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under vacuum and the residue was filtered on a pad of Celite® to afford compound **5** as a colourless oil in 80% yield (1.5 g). In the case when the conversion was not complete, the desired compound was separated from the unreacted starting material by flash chromatography (SiO₂, cyclohexane as eluent). ¹H NMR (CDCl₃, 400 MHz) δ = 7.55 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 5.13 (s, 2H), 3.48 (s, 3H), 0.46 (s, 9H).

¹³C NMR (CDCl₃, 100 MHz) δ = 161.7, 134.8, 132.4, 131.6, 118.9, 114.0, 94.4, 56.2, 2.7.

HRMS (ESI+, APCI+, *m/z*): calcd. for C₁₁H₁₆Br₂O₂Si: 365.9281; found, 365.9299.

(6-(Methoxymethoxy)-1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)trimethylsilane 8. To a solution of (2,3-dibromo-6-(methoxymethoxy)phenyl)trimethylsilane **5** (184 mg, 0.5 mmol) and 2,5-dimethylfuran (0.5 mL, 5 mmol) in THF (1.5 mL) was added *n*-BuLi (0.6 mL, 1 mmol, C = 1.59 M in hexanes) dropwise at -78 °C. The reaction mixture was stirred from -78 °C to room temperature over 12 h. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (2x5 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc 19:1) to afford compound **8** as a colourless oil in 28% yield (43 mg).

¹H NMR (CDCl₃, 400 MHz) δ = 7.02 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 5.3 Hz, 1H), 6.78 (d, *J* = 5.3 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 2H), 3.46 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 0.40 (s, 9H).

¹³C NMR (CDCl₃, 100 MHz) δ = 162.1, 159.7, 147.4, 145.3, 144.8, 123.2, 119.3, 107.5, 94.7, 90.9, 86.5, 55.9, 19.4, 15.3, 2.9.

Anal. Calcd for C₁₇H₂₄O₃Si (304.46): C 67.06, H 7.95; found: C 67.03, H 7.92 (%).

(4-Bromo-2-fluorophenoxy)(triisopropyl)silane 11a. To a solution of 4-bromo-2-fluorophenol (10 g, 52.4 mmol) in dichloromethane (100 mL) was added imidazole (7.1 g, 104.7 mmol). Chlorotriisopropylsilane (13.4 mL, 62.83 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (150 mL) and the two phases were separated. The aqueous phase was extracted with dichloromethane (2x150 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane) to afford compound **11a** as a colourless oil in 92% yield (16.8 g). Spectral data were in accordance with literature.²¹

¹H NMR (CDCl₃, 400 MHz) δ = 7.23 (dd, *J*_{HF} = 10.2, *J*_{HH} = 2.4 Hz, 1H), 7.11 (ddd, *J*_{HH} = 8.7, *J*_{HH} = 2.4, *J*_{HF} = 1.5 Hz, 1H), 6.84 (dd, *J*_{HH} = *J*_{HF} = 8.7 Hz, 1H), 1.29 (septet, *J*_{HH} = 7.2 Hz, 3H), 1.12 (d, *J*_{HH} = 7.2 Hz, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 154.0 (d, *J*_{CF} = 249.4 Hz), 143.3 (d, *J*_{CF} = 11.7 Hz), 127.2 (d, *J*_{CF} = 3.7 Hz), 122.8 (d, *J*_{CF} = 2.2 Hz), 119.8 (d, *J*_{CF} = 22.7 Hz), 112.2 (d, *J*_{CF} = 8.1 Hz), 17.7, 12.7.

¹⁹F NMR (CDCl₃, 282 MHz) δ = -128.7 (t, *J*_{FH} = 9.5 Hz, 1F).

(4-Bromo-2-chlorophenoxy)(triisopropyl)silane 11b. To a solution of 4-bromo-2-chlorophenol (10 g, 48.2 mmol) in dichloromethane (100 mL) was added imidazole (3.9 g, 57.8 mmol). Chlorotriisopropylsilane (12.4 mL, 57.8 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water (150 mL) and the two phases were separated. The aqueous phase was extracted with dichloromethane (2x150 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane) to afford compound **11b** as a colourless oil in 91% yield (16.0 g). Spectral data were in accordance with literature.²²

¹H NMR (CDCl₃, 400 MHz) δ = 7.49 (d, *J* = 2.5 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 1.33 (septet, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 7.3 Hz, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 151.4, 132.7, 130.4, 126.5, 121.1, 112.7, 17.9, 12.8.

(3,4-Dibromo-2-fluorophenoxy)(triisopropyl)silane 12a. To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (5 mL) was added dropwise *n*-BuLi (1.6 mL, 2.5 mmol, C = 1.60 M in hexanes) at -78 °C. This solution was stirred for 15 min and a solution of (4-bromo-2-fluorophenoxy)(triisopropyl)silane **11a** (868 mg, 2.5 mmol) in THF (1 mL) was added. After 1 h at -78 °C, 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.39 mL, 3.25 mmol) was added dropwise and the reaction was stirred for 12 h from -78 °C to room temperature. The reaction mixture was quenched with water (10 mL) and extracted with diethylether (15 mL). The aqueous phase was extracted with diethylether. (2x15 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane) to afford compound **12a** as a colourless oil in 80% yield (852 mg).

¹H NMR (CDCl₃, 400 MHz) δ = 7.26 (dd, *J*_{HH} = 8.8, *J*_{HF} = 2.1 Hz, 1H), 6.81 (dd, *J*_{HH} = 8.8, *J*_{HF} = 8.2 Hz, 1H), 1.29 (septet, *J*_{HH} = 7.2 Hz, 3H), 1.11 (d, *J*_{HH} = 7.2 Hz, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 152.0 (d, *J*_{CF} = 248.0 Hz), 143.9 (d, *J*_{CF} = 13.2 Hz), 127.6 (d, *J*_{CF} = 4.4 Hz), 121.2 (d, *J*_{CF} = 2.2 Hz), 115.9, 113.5 (d, *J*_{CF} = 21.3 Hz), 17.7, 12.7.

¹⁹F NMR (CDCl₃, 282 MHz) δ = -115.6 (d, *J*_{FF} = 8.2 Hz, 1F).

Anal. Calcd for C₁₅H₂₃Br₂FOSi (426.2): C 42.27, H 5.44; found: C 42.26, H 5.47 (%).

(3,4-Dibromo-2-chlorophenoxy)(triisopropyl)silane 12b. To a solution of diisopropylamine (0.37 mL, 2.6 mmol) in THF (5 mL) was added dropwise *n*-BuLi (1.6 mL, 2.62 mmol, C = 1.60 M in hexanes) at -78 °C. This solution was stirred for 15 min and a solution of (4-bromo-2-chlorophenoxy)(triisopropyl)silane **11b** (909 mg, 2.5 mmol) in THF (1 mL) was added. After 8 h at -78 °C, 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.39 mL, 3.25 mmol) was added dropwise and the reaction was stirred for 12 h from -78 °C to room temperature. The reaction mixture was quenched with water (10 mL) and extracted with diethylether (15 mL). The aqueous phase was extracted with diethylether. (2x15 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane) to afford compound **12b** as a colourless oil in 89% yield (990 mg).

¹H NMR (CDCl₃, 400 MHz) δ = 7.39 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 1.32 (septet, *J* = 7.3 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 152.2, 131.0, 128.0, 126.3, 119.2, 116.5, 17.9, 12.9.

Anal. Calcd for C₁₅H₂₃Br₂ClOSi (442.7): C 40.70, H 5.24; found: C 40.77, H 5.19 (%).

((5-Fluoro-1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalen-6-yl)oxy)triisopropylsilane 13a. To a solution of (3,4-dibromo-2-fluorophenoxy)(triisopropyl)silane **12a** (213 mg, 0.5 mmol) and 2,5-dimethylfuran (0.5 mL, 5 mmol) in THF (1.5 mL) were added a few chunks of CaH₂. After stirring for 10 min at room temperature, *n*-BuLi (0.3 mL, 0.5 mmol, C = 1.59 M in hexanes) was added dropwise at -78 °C. The reaction mixture was stirred from -78 °C to room temperature over 12 h. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (2x5 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc 19:1) to afford compound **13a** as a colourless oil in 45% yield (82 mg).

¹H NMR (CDCl₃, 400 MHz) δ = 6.81 (d, *J*_{HH} = 5.4 Hz, 1H), 6.78 (d, *J*_{HH} = 5.4 Hz, 1H), 6.68 (d, *J*_{HH} = 7.4 Hz, 1H), 6.48 (dd, *J*_{HH} = 7.4, *J*_{HF} = 8.2 Hz, 1H), 2.01 (s, 3H), 1.86 (s, 3H), 1.30-1.21 (m, 3H), 1.11-1.09 (m, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 148.4 (d, *J*_{CF} = 247.2 Hz), 147.4 (d, *J*_{CF} = 2.9 Hz), 147.3, 146.1, 142.4 (d, *J*_{CF} = 13.2 Hz), 137.7 (d, *J*_{CF} = 16.1 Hz), 116.5, 113.6 (d, *J*_{CF} = 2.9 Hz), 88.8, 88.7 (d, *J*_{CF} = 2.2 Hz), 17.8, 16.7, 15.2, 12.6.

¹⁹F NMR (CDCl₃, 282 MHz) δ = -142.4 (d, *J*_{FF} = 8.2 Hz, 1F).

Anal. Calcd for C₂₁H₃₁FO₂Si (362.6): C 69.57, H 8.62; found: C 68.64, H 8.61 (%).

((5-Chloro-1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalen-6-yl)oxy)triisopropylsilane 13b. To a solution of (3,4-dibromo-2-chlorophenoxy)(triisopropyl)silane **12b** (221 mg, 0.5 mmol) and 2,5-dimethylfuran (0.5 mL, 5 mmol) in THF (1.5 mL) were added a few chunks of CaH₂. After stirring for 10 min at room temperature, *n*-BuLi (0.3 mL, 0.5 mmol, C = 1.59 M in hexanes) was added dropwise at -

78 °C. The reaction mixture was stirred from -78 °C to room temperature over 12 h. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (2x5 mL). The combined organic layers were dried over Na₂SO₄. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc 19:1) to afford compound **13b** as a white solid in 43% yield (82 mg).

mp = 57.3–58.2 °C.

¹H NMR (CDCl₃, 400 MHz) δ = 6.81 (d, *J* = 5.2 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 5.2 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 2.07 (s, 3H), 1.85 (s, 3H), 1.34–1.26 (m, 3H), 1.13–1.10 (m, 18H).

¹³C NMR (CDCl₃, 100 MHz) δ = 150.5, 149.7, 147.4, 146.6, 146.1, 119.8, 116.2, 114.4, 90.6, 88.2, 17.9, 17.4, 15.2, 12.9.

Anal. Calcd for C₂₁H₃₁ClO₂Si (379.0): C 65.55, H 8.24; found: C 66.49, H 8.19 (%).

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