Efficient Multigram Syntheses of Air-Stable, Fluorescent Primary Phosphines via Palladium-Catalyzed Phosphonylation of Aryl Bromides

Laura H. Davies, Jennifer F. Wallis, Michael R. Probert, Lee J. Higham*

School of Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK
Fax +44(191)2226929; E-mail: lee.higham@ncl.ac.uk

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Abstract: Air-stable, fluorescent primary phosphines have been prepared on a multigram scale. The two key synthetic steps are an optimized palladium-catalyzed phosphonylation of aryl bromides and a boron–carbon bond formation reaction. The method provides a valuable synthetic route to novel fluorescent derivatives via a key phosphonate intermediate.

Key words: phosphorus, palladium, fluorescence, air stability, Bodipy

Primary phosphines are largely regarded as troublesome compounds from the perspective of synthetic methodology, due to their reputation as highly air-sensitive, volatile, toxic, and pyrophoric compounds.[1] The low air stability of many primary phosphines has made them an under-utilized class of ligand; however, they are versatile starting materials due to functionalization of the phosphorus–hydrogen bonds. In recent years, a very limited number of 'user-friendly' primary phosphines have been reported,[2] some of which take advantage of steric encumbrance in order to afford kinetic stability towards air oxidation.[3] A handful of other primary phosphines whose unexplained and surprising air stability cannot be accounted for on steric grounds have also appeared in the literature.[4] Very recently, we discovered the first air-stable fluorescent primary phosphines **1a** and **1b** based on Bodipy (Figure 1).[5] According to our density functional theory-based model, their air stability is attributable to the high level of π-conjugation in the Bodipy backbone.[5,6] We have also shown that despite this resistance to air oxidation (in air, no oxidation in the solid state or in chloroform solution after seven days was observed[5,6]), the phosphino group remains readily transformable to yield fluorescent derivatives of, for example, Triphos (Figure 1).[5] Tridentate phosphine **2** has been shown by us to form stable chelates with rhenium,[5] a metal used as a nonradioactive substitute for the gamma emitter ^{99m}Tc. Such complexes have potential as dual imaging agents by combining the desirable photophysical properties of the Bodipy fluorophore[7] for in vitro fluorescence microscopy, together with the in vivo radioimaging afforded by virtue of the ^{99m}Tc center.[5]

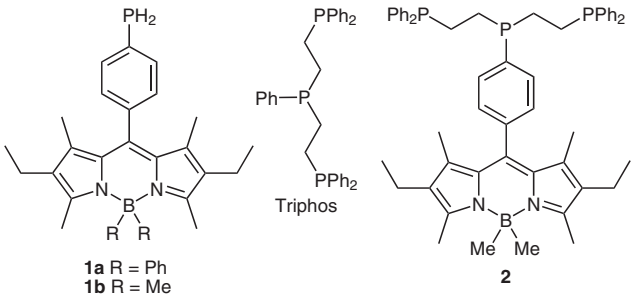

Figure 1 Bodipy primary phosphines **1a** and **1b** and the tridentate phosphine **2**, which is a fluorescent analogue of Triphos

The potential of **1a** and **1b** as ligand precursors is thus clear and we therefore sought an efficient large-scale synthesis of them. The aforementioned synthetic approach was reevaluated and two problematic steps were identified as (i) the substitution of the Bodipy fluorides for alkyl or aryl groups, as the dyes are formed in low yields (Scheme 1, step ii 44%: **4a**, 40%: **4b**) and (ii) the carbon–phosphorus coupling reaction, affording the diethyl phosphonates, is hindered by a reaction time of three days and a yield of 53% for **5b** (Scheme 1, step iii). These factors limited the previous syntheses to a scale of less than one gram.[5]

Herein we report a significantly improved synthetic method for preparing the primary phosphines **1a** and **1b** in multigram quantities via a simplified and improved approach, with the focus on the phosphonylation and the boron–carbon bond formation steps. We also include a number of new solid-state structures, together with a previously unreported, highly fluorescent Bodipy phosphonate.

The syntheses of the fluorescent primary phosphines **1a** and **1b** start from the preparation of the Bodipy aryl bromide derivative **3** in a one-pot condensation reaction between the commercially available reagents 4-bromobenzaldehyde and 3-ethyl-2,4-dimethyl-1-pyrrole, in a moderate yield of 47%, following the literature procedure (Scheme 1, step i).[8] Bodipy formation reactions are notoriously low yielding.[7] However, the situation could be improved to 55% by (i) ensuring the dichloromethane and reagents *N*-diisopropylethylamine and boron trifluoride were anhydrous, and (ii) by reducing the amount of trifluoroacetic acid (TFA) added to 0.025 mL, and using significantly less *N*-diisopropylethylamine (6 equiv instead of 11.4 equiv), boron trifluoride (8 equiv instead of 16 equiv),[9] and dichloromethane (100 mL per 5.4 mmol of 4-bromobenzaldehyde instead of 400 mL per 5.4 mmol).

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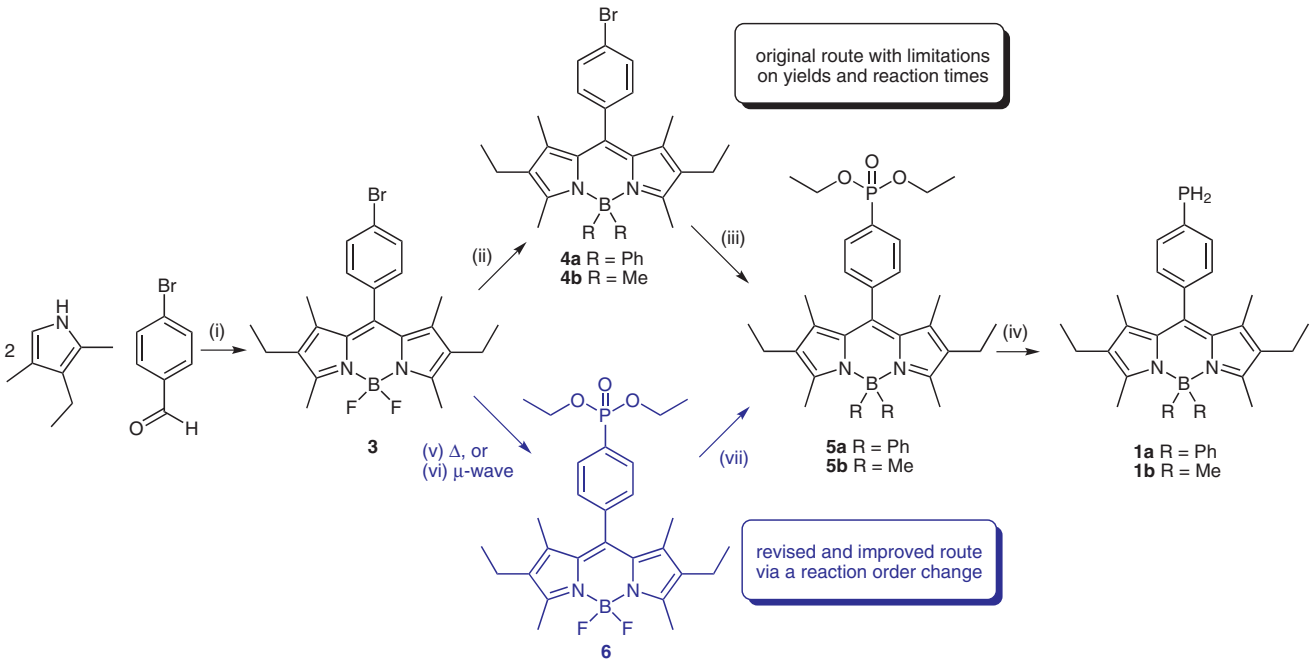


Scheme 1 Synthesis of **1a** and **1b**. *Reagents and conditions*: (i) TFA, DDQ, *i*-Pr_2NEt, $Et_2O{\cdot}BF_3$, CH_2Cl_2, r.t.; (ii) PhLi or MeLi, THF, r.t.; (iii) *i*-Pr_2NEt, $HP(O)(OEt)_2$, DPPB, and $[Pd(OAc)_2]$/DMSO (**4a**) or $[Pd(dba)_2]$/toluene (**4b**), 90 °C; (iv) $LiAlH_4$, Me_3SiCl, THF, –78 °C to r.t.; (v) *i*-Pr_2NEt, $HP(O)(OEt)_2$, $[Pd(PPh_3)_4]$, DMSO, 90 °C; (vi) μ-wave, DMSO, 120 °C; (vii) PhMgBr or MeMgBr, THF, r.t.

These changes resulted in a simplified work-up, higher yields, and a lower reaction expense.

The difluoro-substituted aryl bromide **3** was characterized by X-ray crystallography and its solid-state structure is depicted in Figure 2.

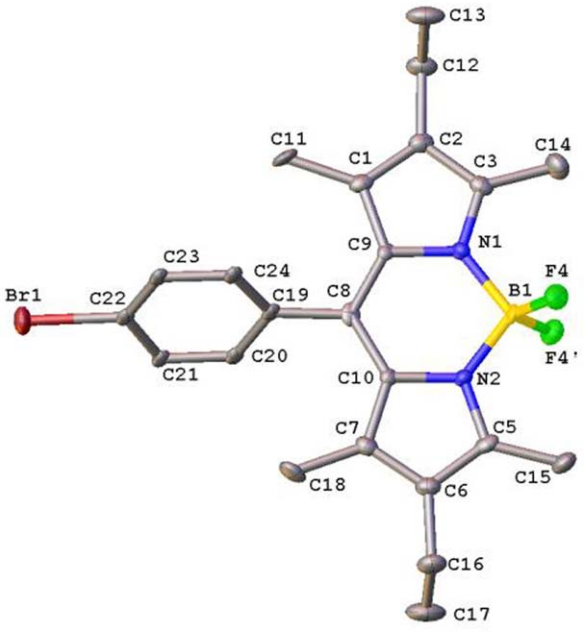


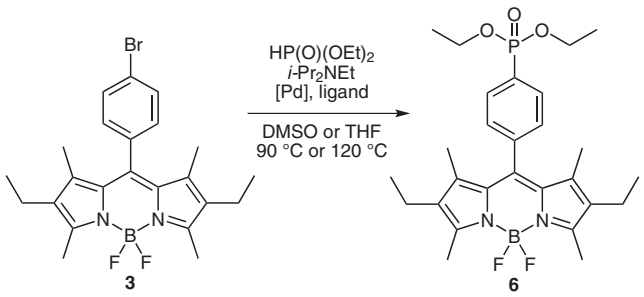
Figure 2 View of **3** with 50% probability displacement ellipsoids. Hydrogen atoms have been omitted for clarity (see Supporting Information for crystallographic details).

Originally, access to the phosphonate derivatives **5a** and **5b** came via the aryl bromides **4a** and **4b**; however, the boron–carbon and phosphorus–carbon bond formation steps (ii and iii, Scheme 1) were low yielding, for **4b** and **5b** in particular (40% and 53%, respectively).[5] Out of the two primary phosphines, **1b** has the superior quantum yield (Φ_F = **1a** 0.042; **1b** 0.33).[5] Therefore, the methylation reaction of step ii was carried out by using methylmagnesium bromide instead of methyllithium, but no improvements were observed. Compound **4b** also suffered from low solubility in DMSO, which therefore required a different catalyst/solvent combination to be found (iii, Scheme 1). A revised strategy was then considered in order to overcome this limiting factor. A phosphonylation reaction of **3** ought to give the novel phosphonate **6**, which could then in principle be arylated and alkylated to give the target compounds **5a** and **5b**, respectively (Scheme 1, lower route). We succeeded in effecting the transformation of aryl bromide **3** into the *F*-Bodipy phosphonate **6** via a palladium-catalyzed phosphonylation (Scheme 1, step v). Initially the same protocol was followed as for the synthesis of **5a** (step iii), using the catalyst palladium(II) acetate with the ligand 1,4-bis(diphenylphosphinobutane) (DPPB); however, only a yield of 58% was achieved. A number of protocols describing the transition metal-catalyzed phosphonylation reaction and mechanistic studies of phosphorus–carbon bond formation have been published, which show that the palladium source and phosphine ligand can both affect the reaction yields.[10,11] Following on from our earlier preliminary investigations, optimization of the reaction conditions was carried out by screening the phosphonylation of

3 to obtain **6** (Table 1). The amount of starting material (0.54 mmol), the relative ratio of substrates, the reaction time (42 h), and solvent (10 mL of anhydrous DMSO) were kept constant throughout. Only a small excess of diethyl phosphite (1.2 equiv) was used, because it has been reported that a significant excess of this compound can deactivate the palladium catalyst.[11]

First, the phosphine ligand that was added to the palladium(II) acetate was varied and quickly it was found that this had a significant impact on the reaction yield (Table 1, entries 1–5). 1,3-Bis(diphenylphosphinopropane) (DPPP, entry 3) and triphenylphosphine (entry 5) were found to be the best ligands (78% and 80%, respectively). Next the palladium source was changed, which showed that yields of 80% could also be achieved by employing bis(dibenzylideneacetone)palladium(0) and the ligand bis(diphenylphosphino)ferrocene (DPPF, entry 7). However, the best yield achieved was 85%, using tetrakis(triphenylphosphine)palladium(0) as catalyst (entry 9). This reaction was also attempted using lower catalytic loadings (5 mol%, entry 10); however, this reduced the yield to 50% and thus 10 mol% was required for this transformation to obtain an optimum yield.

Table 1 Thermal and Microwave Reaction Conditions for the Palladium-Catalyzed Phosphonylation of Aryl Bromide **3**[a]



Entry	Palladium catalyst	Ligand	Yield (%)[b]
1	$Pd(OAc)_2$ (10 mol%)	DPPB	58
2	$Pd(OAc)_2$ (10 mol%)	DPPE	10
3	$Pd(OAc)_2$ (10 mol%)	DPPP	78
4	$Pd(OAc)_2$ (10 mol%)	DPPF	71
5	$Pd(OAc)_2$ (10 mol%)	PPh_3	80
6	$Pd(dba)_2$ (10 mol%)	DPPP	28
7	$Pd(dba)_2$ (10 mol%)	DPPF	80
8	$Pd(dba)_2$ (10 mol%)	PPh_3	76
9	$Pd(PPh_3)_4$ (10 mol%)	–	85 (82[c], 64[d])
10	$Pd(PPh_3)_4$ (5 mol%)	–	50

[a] Conditions: **3** (250 mg, 0.54 mmol), *i*-Pr_2NEt (0.29 mL), diethyl phosphite (0.08 mL), bidentate ligand (0.054 mmol) or PPh_3 (0.108 mmol), anhydrous DMSO (10 mL), 90 °C, 42 h.
[b] Isolated yields after workup and column chromatography.
[c] Microwave, closed vessel: DMSO (10 mL), 120 °C, 10 min.
[d] Microwave, closed vessel: THF (10 mL), 120 °C, 10 min.

The effect of using microwave (MW) irradiation for our phosphonylation reactions was tested. The conversion of phenyl bromide to diethyl phenylphosphonate has been shown to be accelerated considerably by using a microwave power source.[12] The same reaction parameters from our initial thermal screening were chosen (vide supra), but using closed microwave vessels, at 120 °C for 10 minutes (Table 1, entry 9). The yield was very slightly decreased to 82% but the reaction time was dramatically reduced from 42 hours to 10 minutes. Following reports of decomposition of DMSO and starting materials at high concentration in microwave irradiation,[12,13] THF was also tried as an alternative solvent, but this only gave a yield of 64%.

An X-ray crystal structure of **6** was obtained from the single crystal obtained by slow evaporation of a dichloromethane solution (Figure 3). The P–C bond length of 1.7868(18) Å correlates well with other reported arylphosphonate structures[13b] and the bond lengths in the diazaindacene core are similar to that found for other *F*-Bodipy derivatives.[14] The novel *F*-Bodipy phosphonate **6** shows excellent photophysical properties.

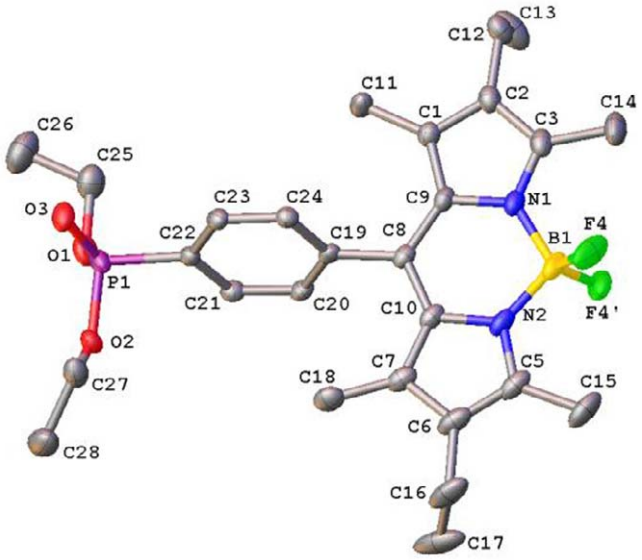


Figure 3 View of **6** with 50% probability displacement ellipsoids. Hydrogen atoms have been omitted for clarity (see the Supporting Information for crystallographic details).

The absorption maximum is at 526 nm (in THF), which is assigned to the S_0-S_1 (π-π*) electronic transition associated with the Bodipy core. The high molar absorption coefficient (ε = 56 000 $M^{-1}cm^{-1}$) is in keeping with previous findings for Bodipy compounds.[7] Room temperature fluorescence is readily detected with an emission maximum of 540 nm (in THF). The fluorescence quantum yield (Φ_F) of 0.56 is high and only somewhat reduced from the aryl bromide **3** (Φ_F = 0.65).[15] The photophysical data and spectra can be found in the Supporting Information. Phosphonates have received increasing attention for imaging bone diseases, due to their high calcium(II) affinity, which results in accumulation in areas of increased bone metabolism.[16] Thus this highly fluorescent phosphonate may

have applications in the study of bone cells by fluorescence microscopy.

Gratifyingly, we then discovered that the subsequent arylation/alkylation of *F*-Bodipy phosphonate **6** to the *C*-Bodipy phosphonates **5a** and **5b** respectively, via the addition of two equivalents of a 3.0 M solution of phenyl or methylmagnesium bromide, was successful. High yields of up to 86% were achieved (Scheme 1, step vii) and this is therefore the superior route.

The final step in the synthesis is the reduction of the phosphonates **5a** and **5b** to the primary phosphines **1a** and **1b** using trimethylsilyl chloride and lithium aluminum hydride as co-reductants. The combination of reducing agents allows for high yields (≥84%).[17] The reduction was found to be concentration dependent, in which the reaction was only successful using very dilute solutions of the phosphonates (0.20 mmol per 10 mL of THF). In too concentrated solutions other primary phosphines were formed and often none of the desired product (δ = **1a** −121.5; **1b** −121.7. $^1J_{P,H}$ = **1a** 202.5 Hz; **1b** 202.5 Hz), which therefore suggests decomposition of the Bodipy backbone in the basic conditions.[18] The remarkable air-stability of these primary phosphines allowed for their straightforward purification on silica gel media, a procedure seldom considered or indeed applicable for this family of compound. Indeed, recrystallization of **1a** in air from dichloroethane–methanol allowed us to determine its solid-state structure by X-ray crystallography (Figure 4), which is quite rare for uncoordinated primary phosphines. The P–C bond length of 1.844(3) Å compares well to the few other primary phosphines which have been characterized crystallographically.[2,4,19]

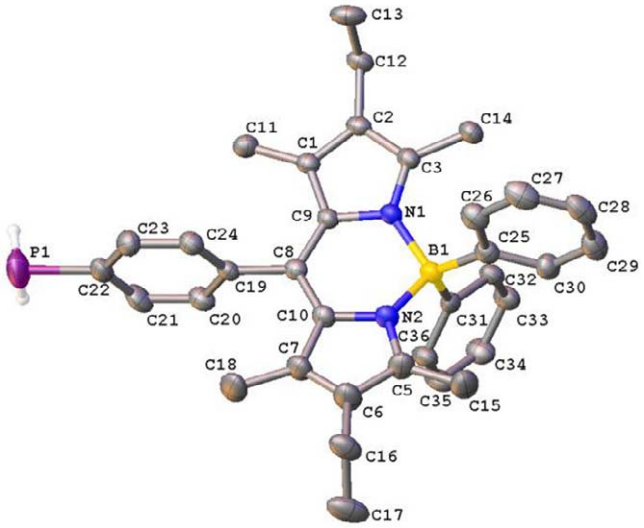


Figure 4 View of **1a** with 50% probability displacement ellipsoids. Hydrogen atoms have been omitted for clarity (see the Supporting Information for crystallographic details).

In summary, we have optimized a far more economical and versatile synthetic route to valuable fluorescent primary phosphines. In particular, the switch of the synthetic steps ii and iii in Scheme 1 is important. Novel phosphonate **6** can now by synthesized in high yield by an optimized palladium-catalyzed phosphonylation of Bodipy aryl bromide **3** by conventional thermal heating or by MW irradiation, whilst phosphonates **5a** and **5b** can now be synthesized from an arylation or alkylation of **6** using Grignard reagents, also in high yields (>79%). For the highly fluorescent primary phosphine **1b**, over the last three steps there is now an overall yield of 61%, which is greatly improved compared to the original 20%. All reactions have been carried out on a multigram scale without reductions in yields.

All air- and/or water-sensitive reactions were performed under a N_2 atmosphere using standard Schlenk line techniques. Toluene (sodium), THF (sodium/benzophenone ketyl), and CH_2Cl_2 (CaH_2) were dried and distilled prior to use. DMSO (Aldrich) was purchased in an anhydrous state and stored over molecular sieves. All other chemicals were used as received without further purification. Petroleum ether (PE) used refers to the fraction boiling in the 40–60 °C range. Microwave-assisted reactions were performed in 35 mL closed vessels on a CEM Discover model under automated power control based on temperature feedback. Flash chromatography was performed on silica gel from Fluorochem (silica gel, 40–63 μm, 60 Å, LC301). TLC was performed on Merck aluminum-based plates with silica gel and fluorescent indicator 254 nm. ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H}, ^{19}F{^{1}H}, and ^{11}B{^{1}H} NMR spectra were recorded on a JEOL Lambda 500 (^{1}H 500.16 MHz) or JEOL ECS-400 (^{1}H 399.78 MHz) spectrometer at r.t. (21 °C); ^{1}H and ^{13}C shifts were relative to TMS, ^{31}P relative to 80% H_3PO_4, ^{11}B relative to $Et_2O{\cdot}BF_3$, and ^{19}F relative to $CFCl_3$ (all shifts given in ppm). Infrared spectra were recorded on a Varian 800 FT-IR Scimitar spectrophotometer equipped with an ATR sampling accessory. Mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service Centre at Swansea. Absorption spectra were recorded with a Hitachi Model U-3310 spectrophotometer while fluorescence studies were recorded with a Hitachi F-4500 fluorescence spectrophotometer. Compounds **4a** and **4b** were prepared according to literature procedures.[5] Analytical data for compounds **1a**, **1b**, **3**, **5a**, and **5b** were consistent with the previously published values.[5]

X-ray Crystallography

All data were collected on an Oxford Diffraction (now Agilent Technologies) Gemini A Ultra diffractometer at 150.0(1) K, using MoKα radiation with λ = 0.71073 Å. Analytical absorption corrections were applied to all datasets. Data were collected and reduced using the CrysAlisPro software.[20] Structures were solved using direct methods and refined on all unique F^2 values, using the Olex2[21] interface to the SHELX[22] suite of programs. All non-H atoms were refined anisotropically. H atoms were placed using geometric riding constraints and isotropic parameters related to their parent atom (except for the H atoms of the PH_2 group of **1a**, which were refined with restrained bond lengths and free rotation). Minor disorder was present in all structures, with final occupancies fixed at their freely refined values. Key crystallographic data are given in Table 2.[23]

8-(4-Bromophenyl)-4,4-difluoro-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (3)

TFA (0.025 mL) was added dropwise to a stirred solution of 3-ethyl-2,4-dimethyl-1*H*-pyrrole (21.9 mL, 162 mmol) and 4-bromobenzaldehyde (15.0 g, 81 mmol) in anhydrous CH_2Cl_2 (1500 mL). The reaction mixture was stirred at r.t. under N_2 in a darkened flask overnight. DDQ (20.2 g, 81 mmol) was added in a single portion, and the mixture was stirred at r.t. for 2 h. Anhydrous *i*-Pr_2NEt (84.7 mL, 486 mmol) and $Et_2O{\cdot}BF_3$ (80.0 mL, 648 mmol) were added, and the mixture was stirred at r.t. overnight. The reaction mixture was washed with H_2O (2 × 150 mL) and brine (2 × 100 mL). The

Table 2 Selected Crystallographic Data for **1a**, **3**, and **6**

Compound	**1a**	**3**	**6**
Formula	$C_{35}H_{38}BN_2P$	$C_{23}H_{26}BBrF_2N_2$	$C_{27}H_{36}BF_2N_2O_3P$
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P2$	$P2_1/n$
a (Å)	12.1121(7)	7.623(2)	7.4182(3)
b (Å)	23.5024(14)	7.700(2)	12.1548(6)
c (Å)	11.3376(6)	9.2409(19)	29.7551(13)
α (°)	90	84.47(2)	90
β (°)	113.684(7)	81.04(2)	93.611(4)
γ (°)	90	83.39(2)	90
V (Å^3)	2955.6(3)	530.6(3)	2677.6(2)
Z	4	1	4
R (F, $F^2>2\sigma$)	0.069	0.045	0.037
R_w (F^2, all data)	0.174	0.1071	0.119
CCDC depos. no.	967539	967537	967538

separated organic layer was dried ($MgSO_4$), filtered, and the solvent removed in vacuo to yield a dark-violet solid with a green tint. Purification using column chromatography on silica gel (toluene) afforded the intended product. A sample suitable for X-ray crystallographic analysis was obtained from CH_2Cl_2; yield: 20.50 g (55%); dark red/purple solid; mp 239–242 °C; R_f = 0.6 (toluene).

IR (neat): 2971 (w), 2901 (w), 1532 (s), 1473 (m), 1405 (s), 1316 (w), 1259 (m), 1182 (s), 1065 (m), 973 (s), 754 (s), 623 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.16 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 2.52 (s, 6 H), 2.29 (q, $^3J_{H,H}$ = 7.8 Hz, 4 H), 1.30 (s, 6 H), 0.96 (t, $^3J_{H,H}$ = 7.8 Hz, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 154.2, 138.6, 138.2, 134.9, 133.1, 132.4, 130.6, 130.2, 123.1, 17.2, 14.7, 12.6, 12.0.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –145.6 [q (equal intensity), $^1J_{F,B}$ = 31.8 Hz, 2 F].

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$): δ = –0.2 (t, $^1J_{F,B}$ = 31.8 Hz, 1 B).

HRMS (ESI$^+$): m/z [M]$^+$ calcd for $C_{26}H_{26}BBrF_2N_2$: 457.1368; found: 457.1368.

UV (THF): λ_{max} (ε) = 526 nm (78 000).

8-[(4-Diethylphosphonato)phenyl]-4,4-difluoro-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (6)

Method A: [$Pd(PPh_3)_4$] (3.0 g, 2.6 mmol), and aryl bromide **3** (12.0 g, 25.9 mmol) were dissolved in anhydrous DMSO (480 mL) under N_2. *i*-Pr_2NEt (13.9 mL, 78.2 mmol) and diethyl phosphite (4.0 mL, 31.2 mmol) were added subsequently and the solution was heated to 90 °C for 42 h. H_2O (350 mL) was added to the reaction mixture and the suspension was extracted with CH_2Cl_2 (400 mL). The organic layer was washed with H_2O (1 × 150 mL) and brine (1 × 150 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to yield a red/purple solid. Purification was performed by column chromatography on silica gel (EtOAc–PE, 3:2) to give the intended product. A sample suitable for X-ray crystallographic analysis was obtained from a CH_2Cl_2–EtOAc solution; yield: 11.52 g (85%); red solid.

Method B: [$Pd(PPh_3)_4$] (0.063 g, 0.054 mmol), and aryl bromide **3** (0.250 g, 0.54 mmol) were placed in a microwave vessel and dissolved in anhydrous DMSO (10 mL). *i*-Pr_2NEt (0.29 mL, 1.63 mmol) and diethyl phosphite (0.084 mL, 0.65 mmol) were added and the solution was purged with N_2 for 10 min. The closed vessel was irradiated with microwaves at 120 °C for 10 min. H_2O (10 mL) was added to the reaction mixture and the suspension was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (1 × 20 mL) and brine (1 × 20 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to yield a red/purple solid. Purification was performed by column chromatography on silica gel (EtOAc–PE, 3:2) to give the intended product; yield: 0.230 g (82%); red solid; mp 152–154 °C; R_f = 0.3 (EtOAc–PE, 3:2).

IR (neat): 2971 (w), 2901 (w), 1534 (m), 1406 (m), 1315 (m), 1250 (m), 1183 (s), 1056 (m), 975 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, $^3J_{H,H}$ = 8.3 Hz, $^3J_{H,P}$ = 12.9 Hz, 2 H), 7.42 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,P}$ = 3.9 Hz, 2 H), 4.17 (m, 4 H), 2.52 (s, 6 H), 2.29 (q, $^3J_{H,H}$ = 7.6 Hz, 4 H), 1.34 (t, $^3J_{H,H}$ = 6.9 Hz, 6 H), 1.26 (s, 6 H), 0.97 (t, $^3J_{H,H}$ = 7.6 Hz, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 154.1, 139.9, 138.3, 137.9, 132.9, 132.23 (d, $J_{C,P}$ = 10.0 Hz), 130.1, 129.1 (d, $^1J_{C,P}$ = 187.4 Hz), 128.5 (d, $J_{C,P}$ = 15.3 Hz), 62.2 (d, $^2J_{C,P}$ = 5.8 Hz), 16.9, 16.2 (d, $^3J_{CP}$ = 5.8 Hz), 14.4, 12.3, 11.6.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –145.6 [q (equal intensity), $^1J_{F,B}$ = 32.0 Hz, 2 F].

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 18.3.

^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$): δ = –0.2 (t, $^1J_{F,B}$ = 32.0 Hz, 1 B).

HRMS (ESI$^+$): m/z [M + H]$^+$ calcd for $C_{27}H_{37}BF_2N_2PO_3$: 516.2634; found: 516.2626.

UV (THF): λ_{max} (ε) = 526 nm (56 000).

8-[(4-Diethylphosphonato)phenyl]-4,4-diphenyl-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (5a)

Phosphonate **6** (7.0 g, 13.6 mmol) was dissolved in anhydrous THF (200 mL). To this solution was added PhMgBr (10.2 mL, 30.6 mmol, 3 M solution in Et_2O) dropwise at r.t. The solution was

stirred at r.t. until complete consumption of starting material was observed by TLC (3 h). The reaction was quenched with MeOH (30 mL) and the solvent was evaporated to leave a deep red solid. Purification was performed by column chromatography on silica gel (EtOAc–PE, 2:1) to afford the product; yield: 6.78 g (79%); orange solid; mp 158–160 °C, R_f = 0.4 (EtOAc–PE, 2:1).

IR (neat): 2960 (w), 1547 (s), 1474 (m), 1386 (s), 1303 (m), 1254 (w), 1168 (m), 1141 (m), 1032 (m), 970 (s), 773 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (dd, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,P}$ = 13.2 Hz, 2 H), 7.53 (dd, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,P}$ = 4.0 Hz, 2 H), 7.42–7.40 (m, 4 H), 7.26–7.15 (m, 6 H), 4.18 (m, 4 H), 2.21 (q, $^3J_{H,H}$ = 7.4 Hz, 4 H), 1.79 (s, 6 H), 1.35 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H), 1.30 (s, 6 H), 0.86 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.1 (br), 141.3, 139.0, 134.8, 133.8, 133.1, 132.1 (d, $J_{C,P}$ = 10.4 Hz), 130.2, 129.1 (d, $J_{C,P}$ = 15.2 Hz), 128.8 (d, $^1J_{C,P}$ = 187.9 Hz), 127.2, 125.5, 62.2 (d, $^2J_{C,P}$ = 5.7 Hz), 17.3, 16.3 (d, $^3J_{C,P}$ = 5.8 Hz), 14.6, 14.7, 12.1.

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 18.7.

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$): δ = –1.1.

HRMS (NSI^+): *m/z* $[M + H]^+$ calcd for $C_{39}H_{47}BN_2O_3P$: 632.3448; found: 632.3447.

UV (THF): λ_{max} (ε) = 518 nm (83 000).

8-[(4-Diethylphosphonato)phenyl]-4,4-dimethyl-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (5b)

Phosphonate **6** (7.3 g, 14.1 mmol) was dissolved in anhydrous THF (200 mL). To this solution was added MeMgBr (9.9 mL, 29.7 mmol, 3 M solution in Et_2O) dropwise at r.t. The solution was stirred at r.t. until complete consumption of starting material was observed by TLC (3 h). The reaction was quenched with MeOH (30 mL) and the solvent was evaporated to leave a red solid. Purification was performed by column chromatography on silica gel (EtOAc–PE, 3:1) to give the intended product; yield: 6.18 g (86%); orange solid; mp 91–95 °C, R_f = 0.4 (EtOAc–PE, 3:1).

IR (neat): 2960 (w), 2931 (w), 1556 (s), 1453 (m), 1360 (m), 1322 (m), 1244 (m), 1172 (m), 1047 (m), 1014 (w), 945 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,P}$ = 13.1 Hz, 2 H), 7.42 (dd, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,P}$ = 3.8 Hz, 2 H), 4.19–4.05 (m, 4 H), 2.40 (s, 6 H), 2.25 (q, $^3J_{H,H}$ = 7.3 Hz, 4 H), 1.29 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 1.19 (s, 6 H), 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H), 0.24 (s, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.9, 141.5 (d, $J_{C,P}$ = 2.7 Hz), 138.7, 133.3, 132.6, 132.0 (d, $J_{C,P}$ = 10.0 Hz), 129.0 (d, $J_{C,P}$ = 15.3 Hz), 128.5 (d, $^1J_{C,P}$ = 188.6 Hz), 128.4, 62.0 (d, $^2J_{C,P}$ = 5.7 Hz), 17.3, 16.2 (d, $^3J_{C,P}$ = 5.8 Hz), 14.6, 14.2, 11.8, 10.3 (br).

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 18.7.

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$): δ = –1.7.

HRMS (NSI^+): *m/z* $[M + H]^+$ calcd for $C_{29}H_{43}BN_2O_3P$: 508.3135; found: 508.3129.

UV (THF): λ_{max} (ε) = 513 nm (91 000).

Reduction of Phosphonates: General Procedure

A THF solution of $LiAlH_4$ (49.2 mL, 49.2 mmol, 1 M solution in THF) was cooled to –78 °C. Me_3SiCl (6.2 mL, 49.2 mmol) was added and the reaction mixture was warmed up to r.t. over 30 min. The solution was cooled to –78 °C and the appropriate phosphonate **5** (19.7 mmol) in THF (1000 mL) was added slowly to the reaction mixture. The solution was allowed to warm up to r.t. and stirred for 3 h. The mixture was then concentrated in vacuo and degassed H_2O (50 mL) was added dropwise to quench the reaction after first cooling it in an ice bath. The product was extracted with Et_2O (4 × 75 mL), dried ($MgSO_4$), and the solvents were evaporated.

8-[(4-Phosphino)phenyl]-4,4-diphenyl-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (1a)

Purification was performed by column chromatography on silica gel (CH_2Cl_2–PE, 1:2) to afford the intended product. A sample suitable for X-ray crystallographic analysis was obtained from CH_2Cl_2–MeOH; yield: 9.06 g (87%); orange solid; mp 207–210 °C; R_f = 0.3 (CH_2Cl_2–PE, 1:5).

IR (neat): 2963 (w), 2928 (w), 2869 (w), 2285 (w, P–H), 1545 (s), 1469 (m), 1393 (m), 1303 (s), 1169 (s), 1142 (m), 962 (s), 774 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 2 H), 7.40–7.37 (m, 4 H), 7.29–7.16 (m, 8 H), 4.11 (d, $^1J_{H,P}$ = 202.5 Hz, 2 H), 2.21 (q, $^3J_{H,H}$ = 7.3 Hz, 4 H), 1.76 (s, 6 H), 1.31 (s, 6 H), 0.90 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 153.0, 150.3 (br), 139.9, 136.8, 135.1, 134.9 (d, $J_{C,P}$ = 15.3 Hz), 133.8, 132.8, 130.6, 129.0, 128.8 (d, $J_{C,P}$ = 5.6 Hz), 127.1, 125.4, 17.3, 14.7, 14.5, 12.1.

$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = –121.5 (tt, $^1J_{P,H}$ = 202.5 Hz, $^3J_{P,H}$ = 7.6 Hz).

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$): δ = –1.0.

HRMS ($APCI^+$): *m/z* $[M + H]^+$ calcd for $C_{35}H_{39}BN_2P$: 528.2975; found: 528.2970.

UV (THF): λ_{max} (ε) = 518 nm (79 000).

8-[(4-Phosphino)phenyl]-4,4-dimethyl-1,3,5,7-tetramethyl-2,6-diethyl-4-bora-3a,4a-diaza-*s*-indacene (1b)

Purification was performed by column chromatography on silica gel ($CHCl_3$–hexanes, 1:4) to afford the intended product, yield: 6.69 g (84%); orange solid; mp 196–198 °C; R_f = 0.4 ($CHCl_3$–hexanes, 1:4).

IR (neat): 2958 (w), 2925 (w), 2361 (w, P–H), 2341 (w, P–H), 1551 (s), 1470 (s), 1531 (m), 1167(s), 1143 (m), 1110 (m), 1060 (m), 942 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.60 (m, 2 H), 7.26 (m, 2 H), 4.11 (d, $^1J_{H,P}$ = 202.5 Hz, 2 H), 2.46 (s, 6 H), 2.32 (q, $^3J_{H,H}$ = 7.6 Hz, 4 H), 1.28 (s, 6 H), 0.99 (t, $^3J_{H,H}$ = 7.6 Hz, 6 H), 0.29 (s, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.8, 139.9, 137.3, 134.9 (d, $J_{C,P}$ = 15.4 Hz), 133.8, 132.6, 129.0, 128.9 (d, $J_{C,P}$ = 5.9 Hz), 128.8, 17.6, 14.8, 14.4, 12.1, 10.5 (br).

$^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = –121.7 (tt, $^1J_{P,H}$ = 202.5 Hz, $^3J_{P,H}$ = 7.4 Hz).

$^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$): δ = –2.1.

HRMS (NSI^+): *m/z* $[M + H]^+$ calcd for $C_{25}H_{35}BN_2P$: 404.2662; found: 404.2665.

UV (THF): λ_{max} (ε) = 512 nm (79 000).

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