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Synthesis of 1*H*-1,3-benzazaphospholes: substituent influence and mechanistical aspects

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Abstract—Various substituted carboxylic acid 2-chloro- and 2-bromoanilides **1a–j** react with triethylphosphite in the presence of anhydrous $NiCl_2$ or $NiBr_2$ to give *o*-acylamido-benzenephosphonic acid esters **2a–g** and **2j**. Yields depend strongly on the substituents. 2-Fluoro-4,6-dibromoacetanilide **1g** reacts only at 6-position, indicating an *o*-directed process. Based on substituent effects, we infer a mechanism via Ni(0) intermediates that insert into the carbon–halogen bond. The *N*-tertiary 2-bromoformanilide **4** does not undergo phosphonylation to **5** in the presence of the Ni-catalyst but reacts in the presence of Pd-catalysts. The subsequent reduction of the *N*-secondary *o*-acylamido-benzenephosphonic acid esters **2** with excess $LiAlH_4$ is coupled with an intramolecular cyclisation to the 1*H*-1,3-benzazaphospholes **6** whereas the *N*-tertiary derivative **5** does not undergo cyclisation upon reduction. NMR data and the crystal structure of **6d** are reported.

1. Introduction

Stressing the nitrogen–phosphorus analogy and the closer diagonal relationship of low-coordinated carbon and phosphorus,[1] 1*H*-1,3-benzazaphospholes[2–5] are close relatives of the well known benzimidazoles[6] and indoles.[7] Whereas the latter display a varied and well-established chemistry, comparably little is known of the chemical behaviour of the low-coordinated phosphorus analogues. Apart from the relatively recent discovery of P=C compounds and their absence in nature, the laborious synthesis of benzazaphospholes[2–4] may be a major reason. 1*H*-1,3-benzazaphospholes are thermally very stable and easy to handle. They have an interesting reactivity essentially intermediate between that of the two classical heterocycles and additionally display a coordination chemistry at the low-coordinated phosphorus atom that has scarcely been investigated. We have studied alternative synthetic routes[5] to these compounds and their reactivity towards organometallic reagents and electrophiles.[8–11] We report here in more detail on the new three-step synthesis of benzazaphospholes, together with its mechanisms and limitations.

Keywords: anilides; phosphorus heterocycles; catalytic phosphonylation; cyclisation.

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2. Results and discussion

2.1. P–C-coupling reaction

The key steps in the novel synthesis of 2-methyl-, 2-*t*-butyl- and 2-phenyl-1*H*-1,3-benzazaphosphole presented recently[5] are the P–C coupling and the ring closure reaction. The former is accomplished by a nickel catalysed arylation of phosphite (phosphonylation of aryl halide), often referred to as Tavs' reaction,[12–14] which usually is strongly disfavoured by *o*-substituents and prevented by OH or NH_2 groups in *p*-position.[12] This is in agreement with our observation that 2-bromoaniline gives only phosphorous acid derivatives $HP(O)(OEt)_2$, $HP(O)(OEt)(NHC_6H_4Br)$ and a diamide, identified by typical chemical shifts of $\delta^{31}P$ 7.6, 4.6, 2.7 and large $^1J(PH)$ coupling constants. However, *N*-secondary *o*-bromoanilides of acetic, pivalic, and benzoic acid were found to couple with triethylphosphite in the presence of anhydrous $NiBr_2$ in excellent yields,[5] comparable to the reaction of 2-bromoacetanilide with methylphosphonous acid ethyl ester.[13] Problems in utilising this coupling reaction for *N*-tertiary *o*-bromoanilides inspired us to explore its scope and mechanism. We synthesised various *o*-haloanilides **1a–j** and studied their coupling reactions with triethyl phosphite. Most of the anilides were easily accessible from carboxylic acids, or their acyl chlorides, and the respective anilines by standard procedures. The coupling attempts showed a more sophisticated chemical

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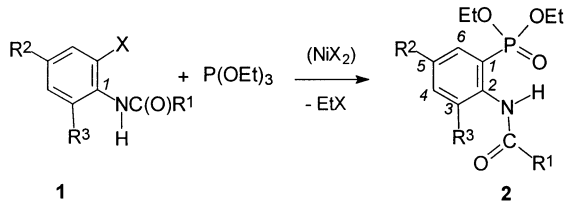
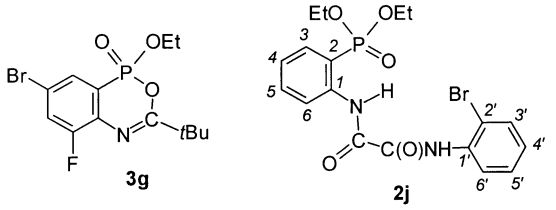


1,2	a	b	c	d	e	f	g	h	i
X	Cl	Cl	Br	Br	Br	Br	Br	Br	Br
R^1	Me	Ph	Me	*t*Bu	Ph	Me	*t*Bu	H	C_5H_4N
R^2	H	H	Me	Me	Me	F	Me	H	H
R^3	H	H	H	H	H	F	F	H	H

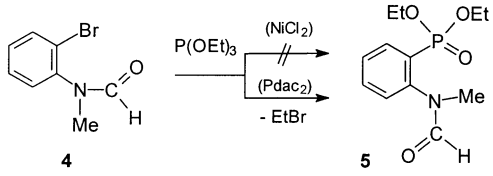
Scheme 1.

behaviour of **1a–g** (Scheme 1) than was expected from prior results.

o-Chloroacetanilide **1a** and *o*-chlorobenzanilide **1b** were found to couple in moderate yields (about 50%) with triethyl phosphite in presence of $NiCl_2$ to give **2a** and **2b**, respectively. Although this conversion is significantly lower than with *o*-bromoacetanilide (81%),[5] and about three times as much of the catalyst is needed to suppress the competing formation of phosphorus acid derivatives (δ^{31}P −0.7 to −1), it is remarkable considering the generally much lower reactivity of chlorobenzene derivatives. *o*-Bromoanilides display a varied reactivity. The $NiCl_2$-catalysed coupling reaction of the ring-alkylated 2-bromo-4-methylanilides **1c–e** with $P(OEt)_3$ gives **2c–e** in good yields, comparable with the non-methylated 2-bromoanilides.[5] Electron-withdrawing substituents, i.e. bromine or fluorine in 4-/6-position of the 2-bromoacetanilides, cause lower yields of the coupling products **2f** and **2g** and increase the amount of the Arbuzov product $EtPO(OEt)_2$ (δ^{31}P 34.1) formed with EtBr, of $PO(OEt)_3$ (δ^{31}P −0.8 to −0.5) and of by-products with phosphorus signals in the region of δ^{31}P 15. As seen from the P–F– and F–H coupling pattern, the latter are related to the substitution products, judging from the integral ratios in the ^{1}H NMR spectrum of **2f** probably the monoesters, formed by partial *O*-dealkylation. Crude **2g** contains a further weak signal in this region (δ^{31}P 15.4) and also a signal (δ^{31}P 2.7) for a small amount of another P–C coupling product **3g** that distils together with **2g** and gives rise to ^{1}H NMR signals consistent with a cyclic structure. The aryl protons of **2g** and of **3g** exhibit the same splitting, typical ^3J(PH) and ^3J(FH) coupling constants (14.0, 15.1; 9.3, 9.3 Hz), aryl/ethyl/*t*Bu integral ratios of 2:4:6:9 and 2:2:3:9, and no NH or OH signal for **3g**. However, no evidence was obtained for a product formed by replacement of the 4-bromo substituent by phosphorus, which should easily be recognised by large ^3J(PH) couplings to both aryl hydrogens. This means that the $NiCl_2$-catalysed phosphonylation of 2-fluoro-4,6-dibromoacetanilide **1g** proceeds regioselectively at the bromine in *o*-position of the amide group (6-position), although this is sterically hindered compared to the 4-position. To be sure that the phosphonylation of the above NH-species is possible in the 4-position, we checked the reaction of 4-bromoacetanilide with $P(OEt)_3$ in presence of $NiBr_2$ under equal conditions and found in the crude product according to the NMR spectra a high conversion to 4-acetamido-benzenephosphonic acid diethyl ester (δ^{31}P 19.1). The observed regioselectivity in the phosphonylation of **1g** indicates therefore a supporting *o*-directed process that will be discussed later. More serious problems arise with *o*-bromoanilides of formic, picolinic or oxalic acid, which seem not to benefit from the above-mentioned support. The nickel catalysed coupling reaction of 2-bromoformanilide **1h** with $P(OEt)_3$ failed completely. Heating to 190°C in the presence of $NiBr_2$ led to vigorous evolution of a gas and formation of an insoluble brown polymer along with a mixture of phosphorus compounds. Studies of the $NiCl_2$-catalysed reaction of picolinic acid *o*-bromoanilide **1i** with $P(OEt)_3$ in the temperature range 180–200°C displayed strong ^{31}P signals at δ −0.5, 0.4, 7.8 and 34.0 but only small ^{31}P signals at δ 18, the typical region for the P–C_{aryl} coupling products. Oxalic acid bis(*o*-bromoanilide) **1j** reacts with excess $P(OEt)_3$ in the presence of $NiCl_2$ to give the monosubstitution product **2j** in rather low yield. The disubstitution product constitutes only a minor component in the crude product and was not isolated in pure form.

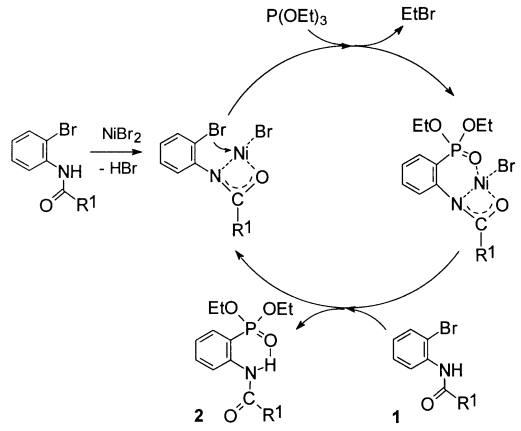


The *N*-tertiary *o*-bromoformanilide **4** behaves differently from the NH–CHO derivative **1h**. Heating **4** with $P(OEt)_3$ in the presence of $NiBr_2$ did not lead to a polymer, nor was any P–C coupling observed. Attempts with other transition metal compounds showed that palladium acetate may be used as catalyst for the coupling of **4** with $P(OEt)_3$ (Scheme 2), but the yield of the *N*-tertiary 2-formamidobenzenephosphonic acid ester **5** was much lower than in the above-mentioned reactions, 35–40% when excess triethyl phosphite and a stream of argon or nitrogen was used to remove EtBr, thus reducing the amount of the Arbuzov-product $EtPO(OEt)_2$. It should be mentioned that the competing Arbuzov reaction is not observed in the Ni-catalysed coupling reactions with reactive *N*-secondary *o*-bromoanilides such as **1c–e**.

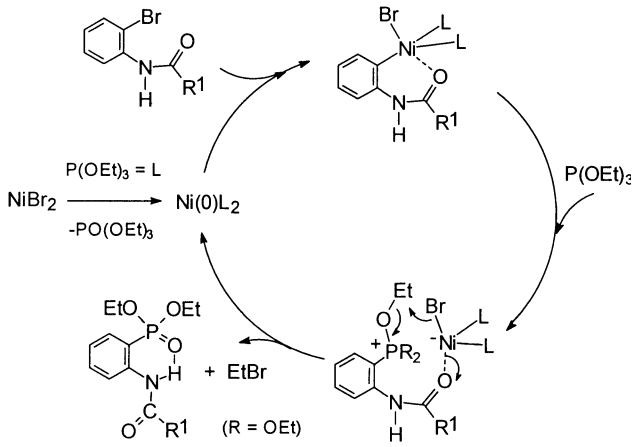


Scheme 2.

Since in the above experiments the NH-amide function is essential for the nickel-catalysed, but not for the Pd-catalysed coupling reaction, different mechanisms might be possible and could involve a Ni(II) catalyst. It is known that *o*-chloroanilines or -phenols react with triphenylphosphine in presence of anhydrous nickel chloride at comparable elevated temperature by polarisation of the C–Br bond and nucleophilic attack of the phosphine to give phosphonium tetrachloroniccolate.[15] The above observed substitution by triethylphosphite, the necessity



Scheme 3.



Scheme 4.

for the NH function and the *o*-direction can be accounted for by deprotonation and formation of a catalytic amount of an amidate nickel complex supporting the activation of the C–Br bond, as illustrated in Scheme 3. This should allow the attack of triethyl phosphite as in the above mentioned coupling with Ph_3P or in the usual Arbuzov reactions and lead to formation of an intermediate phosphonium niccolate complex $[arP(OEt)_3]^+$ $[Br_2NiL]^-$ that eliminates EtBr. The transfer of the nickel(II) to unreacted *o*-bromoanilide might be accomplished by a combined proton-transfer and complex formation equilibrium in which uncomplexed **2** seems to be favoured. As the NH and C=O stretching vibrations in **2f** ($\bar{\nu}$=3682 w, 3619 w, 3431 m, sharp, 3346 m br, 1694 s cm^{-1}, c=0.06–0.015 m in $CHCl_3$; $\bar{\nu}$=3423 s, 3346 s NH in KBr) are independent of the concentration, stabilisation by an intramolecular hydrogen bond can be proposed.

Since it is known that NiX_2 and triethylphosphite form $Ni[P(OEt)_3]_4$ along with some $PO(OEt)_3$[14] and that Ni(0) inserts into C–I or C–Br bonds[16] a mechanism via nickel(0) has also to be considered. In contrast to the above path, formation of an intermediate arylnickel(II)bromide complex should promote a nucleophilic attack of the carbanion at the polar P–O bond of triethylphosphite and thus be influenced by electronic substituent effects in the opposite fashion to the situation described above. Electron withdrawal by fluorine or bromine in *m,m′*-position should reduce the negative charge and lower the activity of the anion, whereas the polarisation of the C–Br bond should be enhanced and attack by nucleophiles favoured. This should allow a distinction between the two conceivable mechanisms.

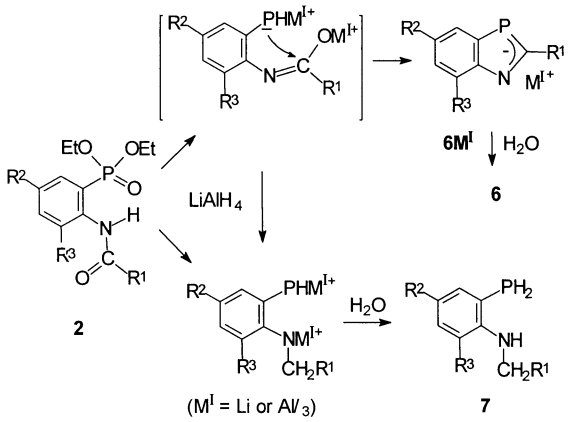
A control experiment showed that 2-bromobenzanilide couples with triethylphosphite if heated to 200°C in presence of catalytic amounts of $Ni(1,5\text{-}COD)_2$. The selectivity is high, as indicated by the ^{31}P NMR spectrum of the crude mixture, and $PO(OEt)_3$ could not be detected, but the yield of the coupling product is considerably lower than upon catalysis with NiX_2. This may be attributed to thermal decomposition of the Ni(0) species and permanent generation of small amounts of the Ni(0) catalyst when $P(OEt)_3$ is added to the mixture of *o*-haloanilide and NiX_2 at high temperature. The substituent effects are also consistent with the second mechanistic proposal. The much lower yields of the coupling products in reactions with 4,6-difluoro- or 4-bromo-6-fluoro-substituted 2-bromoacet- or -pivalanilides may be due to a lower rate of the P–C coupling in relation to the competing Arbuzov and other side reactions. Since the intermediate arylnickel(II)bromide complex can be stabilised by intramolecular coordination of the amide–oxygen, forming a six-membered chelate ring, the lack of the usual steric hindrance and preference of *o*-substitution can also be explained. The low reactivity of the *N*-methyl-*o*-bromoformamide may be attributed to steric hindrance of a coplanar orientation of the benzene ring and the amido group necessary to support the *o*-substitution as proposed above. The catalytic cycle would be closed by the liberation of EtBr and a phosphite-stabilised Ni(0) species (Scheme 4). The mechanism assuming Ni(0) is preferred by us since it explains better the influence of the substituents.

The lack of coupling in the case of the 2-picolinic acid derivative **1i** could be understood within both models by formation of an alternative five-membered chelate complex, which is more stable than an amidate intermediate. Disubstitution of the oxalic acid bis(*o*-bromoanilide) **1j** may similarly be prevented by interactions of nickel at the catalytic centre with the phosphonodiester group in the monosubstitution product **2j**.

2.2. Reductive cyclisation of 2-acylamidobenzene-phosphonic acid ester

The reduction of the 2-acylamidophosphonates with 2 equiv. of $LiAlH_4$, sufficient to reduce both the phosphonodiester and the amido group, led to a mixture of products containing small amounts of benzazaphospholes. Whereas utilisation of a smaller amount of $LiAlH_4$ did not result in a selective reduction of either of the two groups, excess $LiAlH_4$ gave rise to formation of 1*H*-1,3-benzazaphospholes **6a–f** in reasonable yields (Scheme 5). The *N*-secondary 2-phosphinoanilines **7**, of interest as starting materials for *N*-substituted 1,3-benzazaphospholes,[4,10] are observed as by-products but have not been isolated in pure form.

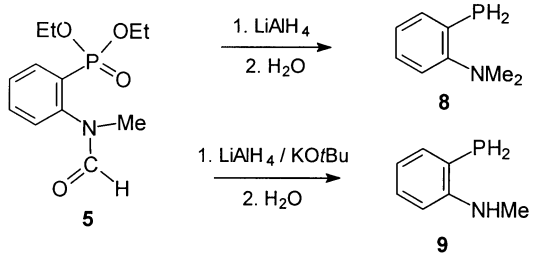
The formation of 1*H*-1,3-benzazaphospholes can be understood in terms of a reduction of the phosphonodiester group in the first step and subsequent preferred cyclisation,



Scheme 5.

initiated by intramolecular attack of the nucleophilic phosphido group on the electrophilic amidate carbon. Metalation at phosphorus and of the amido group increases the reactivity by formation of phosphide and amidate structures, the latter with increased weight of C–N double bond character as compared to amides. As observed in earlier investigations on the reactivity of arsino-substituted amines and anilines towards carbonic acid derivatives, cyclisation under mild conditions could be achieved only with iminoacyl compounds whilst amides formed with acyl chlorides did not undergo ring closure.[17] The resulting metalated 1,3-benzazaphospholides **6M^{I}** are stable under the reaction conditions in presence of excess $LiAlH_4$. The formation of a delocalised, π-excess aromatic system with increased electron density at the phosphorus atom prevents the attack of the reducing agent at the P═C bond. Hydrolysis liberates the NH-compounds. In view of the stability of **6M^{I}** the formation of **7** is attributable to competing reduction of the amido group, either of **2** or of the intermediate primary phosphine or phosphide.

The reduction of the *N*-methyl-2-formamido benzenephosphonic acid ester **5** with $LiAlH_4$ did not result in the corresponding *N*-methyl-1,3-benzazaphosphole but gave a small amount of 2-phosphino-*N*,*N*-dimethylaniline **8**. When the reduction was carried out in presence of potassium *t*-butoxide to activate the amide group by intermolecularly mediated polarisation of the C═O bond, the formyl group was cleaved instead of undergoing cyclisation affording 2-phosphino-*N*-methylaniline **9** (Scheme 6).



Scheme 6.

2.3. Properties of 1*H*-1,3-benzazaphospholes and structural aspects

As reported earlier, 1*H*-1,3-benzazaphospholes are thermally stable and in most cases not very sensitive towards hydrolysis. They are relatively stable towards air oxidation in the solid state, but are oxidised in solution. Purification of 2-methyl- and 2-aryl-1,3-benzazaphospholes can be accomplished by extracting the basic or acidic impurities from ethereal solutions with dilute (10%) sulphuric acid or dilute aqueous sodium hydroxide solutions. Only 2-*t*-butyl-1,3-benzazaphospholes add water during such a procedure forming *P*-secondary phosphine oxides. This shows that the *t*-butyl group does not provide steric protection but rather activates the P═C bond. An X-ray structure investigation of **6d** (Fig. 1,

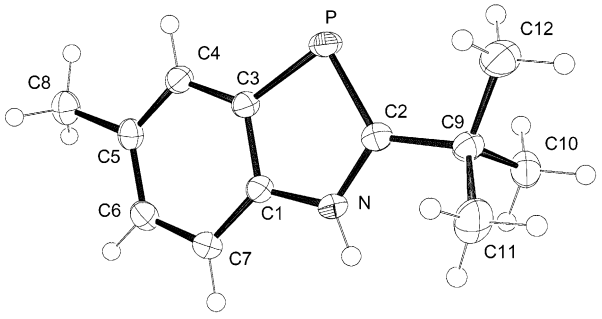


Figure 1. Crystal structure of **6d**. Ellipsoids represent 50% probability levels. Selected bond lengths (Å) and angles (°): P–C2 1.7278(12), P–C3 1.7820(12), N–C2 1.3562(15), N–C1 1.3836(15), C1–C3 1.4007(16); C2–P–C3 89.47(6), P–C2–N 112.95(9), P–C3–C1 111.09(8), C2–N–C1 114.86(10), N–C1–C3 111.61(10), P–C2–C9 126.99(9), N–C2–C9 119.88(11).

Table 1. Crystal data and structure refinement of **6d**

Empirical formula	$C_{12}H_{16}NP$
Formula weight	205.23
Temperature	133(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a=5.9957(6) Å b=8.8699(8) Å c=21.3567(18) Å
Volume	1135.78(18) Å^3
Z	4
Density (calculated)	1.200 mg m^{-3}
Absorption coefficient	0.203 mm^{-1}
F(000)	440
Crystal size	0.37×0.23×0.16 mm^3
Theta range for data collection	1.91–30.03°
Index ranges	$-8\le h\le 8$, $-12\le k\le 12$, $-30\le l\le 30$
Reflections collected	16446
Independent reflections	3321 [R(int)=0.0328]
Completeness to theta=30.00°	99.8%
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.962 and 0.810
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3321/0/135
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	$R1$=0.0323, $wR2$=0.0853
R indices (all data)	$R1$=0.0351, $wR2$=0.0869
Largest diff. peak and hole	0.386 and −0.171 e Å^{-3}

Table 1), crystallised after high-vacuum distillation from toluene, shows the planar benzazaphosphole ring system with the *t*-butyl group hindering access to the nitrogen rather than the phosphorus atom, which is of importance in substitution reactions.[9] The angle N–C2–C9 corresponds closely to ideal sp^2 geometry, whereas the angle P–C2–C9 is significantly larger at 126.99(9)°. This is certainly attributable in part to the size of phosphorus and the constraints of the five-membered ring, but also to an additional effect of the *t*-butyl group. In comparison with the values determined for the unsubstituted 1*H*-1,3-benzazaphosphole [1.807(7), 1.695(9), 115.7(7)][18] the distances P–C3 [1.7820(12) Å] and P–C2 [1.7278(12) Å] are slightly shorter and longer, respectively, and the P–C–N angle [112.95(9)°] is reduced, suggesting that the phosphorus atom is repelled slightly towards C3 by the methyl groups of the 2-*t*-butyl substituent [cf. torsion angle C12–C9–C2–P 17.9(2)°]. The resulting better bond equalisation in **6d** should enhance the aromatic stabilisation and does not explain the increased sensitivity towards hydrolysis. Thus, the electronic effect of the *t*-butyl group has to be considered.

The +I effect of the *t*-butyl group results in an increased σ-electron density at C-2, which in turn repels π-electron density, in part towards phosphorus. The resulting increased polarity of the P=C bond facilitates the acid-catalysed addition of water. The effect on the NMR spectra resembles that of lithiation at C2,[10] though to a much smaller extent. The C2 signal is strongly deshielded and the P–C coupling is significantly increased ($^1J_{PC}$=57.5 Hz versus 51.5 and 51.3 Hz in **6c** and **6e**), whereas the phosphorus resonance is shifted to higher field (δ^{31}P=63.5 versus 71.8 in **6c** and 74.4 in **6e**). The influence of the 5-methyl group in **6c–e** on the δ^{31}P values is low. Substituents at the benzene ring may have some influence, however, as seen by the significant downfield shift of the phosphorus resonance in 5,7-difluoro-2-methyl-1,3-benzazaphosphole **6f** (δ^{31}P 80.5) and four-bond couplings with the fluorine nuclei ($^4J_{PF}$=15.9, 8.3 Hz). The carbon atoms C2 and C3 are influenced similarly but to a smaller degree. The strongest changes are restricted to the residual carbon nuclei of the benzene ring. As the polarity of the P–C bonds is not much changed, the influence of the substituents at the benzene ring on the reactivity, such as the stability towards hydrolysis or alcoholysis, is low. Reactivity studies concerning the lithiation of the NH function and substitution or complex formation of the resulting ambident benzazaphospholides,[8,9] formation of transition metal carbonyl benzazaphosphole[10] or cyclopentadienylnickel–benzazaphospholide complexes,[11] or cycloaddition reactions with *o*-choranil will all be reported separately.

3. Conclusions

The influence of substituents on the NiX_2-catalysed (X=Cl, Br) coupling of 2-haloanilides of carboxylic acids with triethyl phosphite and on the reduction of the coupling products with $LiAlH_4$ was studied. Apart from effects on the yields it was found that the P–C coupling reaction takes place selectively in *o*-position of the amide group, that the NH function is essential for the NiX_2-catalysed P–C coupling, and that donor functions at the acyl group, possibly enabling the formation of chelate complexes with Ni(II), suppress this reaction. Based upon these observations two models for a possible mechanism were discussed. The substituent effects on the yields account rather for catalysis by Ni(0) and intermediate carbanionic aryl–NiBr complexes reacting with the polar P–O bond than an intramolecular, Ni-amidate-supported polarisation of the C–Br bond and nucleophilic attack of phosphite. The reduction of the resulting *o*-amidobenzenephosphonic acid diesters with excess $LiAlH_4$ again depends on the nature of the amide group. Whereas the *N*-tertiary *N*-methyl-formamidobenzenephosphonic diethyl ester furnishes either 2-phosphino-*N*,*N*-dimethylaniline or, in presence of KO*t*Bu, 2-phosphino-*N*-methylaniline, NH-derivatives form benzazaphospholes. This is explained by primary reduction of the phosphonodiester group and rapid ring closure by intramolecular attack of the *o*-phosphido group at the amidate carbon. Thus, only a minor part of the amidate group can be reduced giving rise to small amounts of by-products, the respective *N*-secondary 2-phosphinoanilines. The influence of substituents on some properties of 1*H*-1,3-benzazaphospholes is discussed.

4. Experimental

4.1. General considerations

All reactions were conducted under an atmosphere of dry argon using Schlenk techniques. Ether, THF and hydrocarbons were dried and deoxygenated by refluxing and distilling from sodium/benzophenone ketyl before use. The bromoanilines and the acetanilides **1a** and **1c** were commercially available (Lancaster) and used as purchased. The other anilides were prepared by a standard procedure, if known (**1b**,[19] **1e**,[20] **1f**,[21]), mps agree. **4**[22] was obtained as reported earlier. NMR spectra were measured on a multinuclear FT-NMR spectrometer Bruker Model ARX300 at 300.1 (^{1}H), 75.5 (^{13}C), and 121.5 (^{31}P) MHz. The ^{1}H, ^{13}C and ^{31}P chemical shifts are δ values relative to Me_4Si and H_3PO_4 (85%), respectively. Assignment numbers are identical with the position number according to the nomenclature unless indicated otherwise; for phenyl substituents the indices *i*, *o*, *m*, *p* are used. Coupling constants refer to H–H (^{1}H NMR) or P–C couplings (^{13}C NMR) unless stated otherwise. IR spectra were recorded on a Perkin–Elmer Model system 2000 and mass spectra on a single-focussing mass spectrometer AMD40 (Intectra). Elemental analyses were carried out with an elemental analyzer LECO Model CHNS-932 with standard combustion conditions and handling of the samples at air. Melting points were determined in sealed capillaries under argon and are uncorrected.

4.2. 2-Bromoanilides; general procedure

The acid chloride was added dropwise at 0–5°C with stirring to a solution of the respective 2-haloaniline and a slight excess of triethylamine in ether. After 2 d at room temperature, unless indicated otherwise, the precipitate was separated, thoroughly washed with ether and treated with water to remove $Et_3N{\cdot}HCl$. The remaining anilide (if less soluble in ether) was dried in vacuum. The filtrate was washed with

cold 10% aqueous sulphuric acid, cold 10% aqueous sodium hydroxide solution, and water and was dried with sodium sulphate. The solvent was removed in vacuo and the residue was recrystallised from ethanol.

4.2.1. 2-Bromo-4-methyl-(2′,2′-dimethyl)propionanilide (1d). The reaction of pivaloyl chloride (12.5 mL, 102 mmol), 2-bromo-4-methylaniline (18.94 g, 101 mmol) and Et_3N (14.5 mL, 104 mmol) in ether (250 mL) furnished 26 g (94%) of **1d**, isolated from the filtrate, mp 69°C (EtOH). IR (KBr): $\bar{\nu}$ 3423, 3309, 1657 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, 9H, Me), 2.29 (s, 1H, Me), 7.11 (dd, ^3J=8.4 Hz, ^4J=1.8 Hz, 1H, H-5), 7.35 (d, ^4J=1.8 Hz, 1H, H-3), 7.91 (br, 1H, NH), 8.23 (d, ^3J=8.4 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 20.5 (s, 4-Me), 27.6 (s, Me), 40.1 (*C*Me_3), 113.5 (C-2), 121.5 (C-6), 129.0 (C-5), 132.3 (C-3), 133.3 (C-4), 134.9 (C-1), 176.5 (CO). Anal. calcd for $C_{12}H_{16}NOBr$ (270.17): C, 53.35; H, 5.97; N, 5.18. Found: C, 53.29; H, 6.21; N, 5.35.

4.2.2. 2-Bromo-4-methyl-benzanilide (1e).[20] The reaction of benzoic acid chloride (13.62 mL, 117 mmol), 2-bromo-4-methylaniline (21.81 g, 117 mmol) and Et_3N (16.34 mL) in ether (300 mL) gave a total of 23.8 g (79%) of **1e**, thereof 16.7 g (mp 148°C) isolated from the precipitate. IR (KBr): $\bar{\nu}$ 3415, 3254, 1649 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, Me), 7.18 (dd, ^3J=8.4 Hz, ^4J=1.8 Hz, 1H, H-5), 7.40 (dd, ^4J=1.8 Hz, ^5J=0.6 Hz, 1H, H-3), 7.48–7.61 (m, 3H, 2H-*m*, H-*p*), 7.93 (dm, 2H, H-*o*), 8.38 (s br, NH), 8.40 (d, ^3J=8.4 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 20.56 (4-Me), 113.6 (C-2), 121.6 (C-6), 127.1 and 128.9 (2 C-*o*,*m*), 129.1 (C-5), 132.1, 132.5 (C-3, C-*p*), 133.2 (C-4), 134.7 (C-*i*), 135.4 (C-1), 165.1 (CO).

4.2.3. 2-Bromo-4,6-difluoro-acetanilide (1f).[21] The reaction of acetyl chloride (22.4 mL, 316 mmol), 2-bromo-4,6-difluoroaniline (32.85 g, 158 mmol) and Et_3N (44.2 mL, 316 mmol) in Et_2O (250 mL), work up after 3 d, gave a total of 23.7 g (60%) of **1f**, mp 157°C, isolated from the precipitate and from the filtrate. IR (KBr): $\bar{\nu}$ 3432, 3240, 3194, 1670, 850, 833 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, Me), 6.87 (m br, $^3J_{FH}$=8 Hz, 2H, H-5, NH), 7.16 (d br, $^3J_{FH}$=7 Hz, 1H, H-3).

4.2.4. 2,4-Dibromo-6-fluoro-(2′,2′-dimethyl)propionanilide (1g). Excess pivaloyl chloride (8.2 mL, 66.9 mmol) was added to 2,4-dibromo-6-fluoroaniline (12.0 g, 44.6 mmol) and Et_3N (9.86 mL, 71.2 mmol) in ether (90 mL). Control by NMR indicated a very slow conversion at ambient temperature (4 d 25%, 7 d 50%, 13 d 66%, 20 d 75%; reflux for further 4 d 78%). Work-up gave 11.6 g (74%) of **1g**, mp 144°C (EtOH). IR (KBr): $\bar{\nu}$ 3433, 3291, 1658, 909, 852 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 9H, CMe_3), 6.95 (s br, 1H, NH), 7.29 (dd, $^3J_{FH}\approx$8.9 Hz, $^4J\approx$2.1 Hz, 1H, H-5), 7.56 (dd, $^5J_{FH}\approx$1.7 Hz, 1H, H-3). Anal. calcd for $C_{11}H_{12}Br_2$ FNO (353.03): C 37.42, H 3.43, N 3.97. Found: C 37.38, H 3.71, N 4.25.

4.2.5. 2-Picolinic acid 2-bromoanilide (1i). A mixture of 2-bromoaniline (5.13 g, 29.8 mmol) and picolinic acid (3.67 g, 29.8 mmol) was heated for 2 d to 200°C. The resulting solid was crystallised from ethanol to give 3.5 g (42%) of needle-shaped crystals, mp 128–129°C. ^1H NMR ($CDCl_3$): δ 7.01 (td, $^3J\approx$7.9, 7.5 Hz, ^4J=1.6 Hz, 1H, H-4), 7.38 (td, $^3J\approx$8.6, 8.4 Hz, ^4J=1.5 Hz, 1H, H-5), 7.50 (ddd, $^3J_{5'4'}$=7.6 Hz, $^3J_{5'6'}$=4.8 Hz, ^4J=1.2 Hz, 1H, H-5′), 7.60 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, H-3), 7.92 (td, ^3J=7.8, 7.6 Hz, ^4J=1.7 Hz, 1H, H-4′), 8.30 (ddd, ^3J=7.8 Hz, $^{4/5}J\approx$2.0, 1.0 Hz, 1H, H-3′), 8.64 (dd, ^3J=8.3 Hz, ^4J=1.6 Hz, 1H, H-6), 8.68 (ddd, $^3J_{6'5'}$=4.8 Hz, $^{4/5}J\approx$1.5, 0.8 Hz, 1H, H-6′), 10.71 (s br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 113.9 (C-2), 121.4 (C-6), 122.5, 125.1 (C-4), 126.6, 128.4 (C-5), 132.5 (C-3), 135.9 (C-1), 137.6 (C-5′), 148.3 (C-6′), 149.7 (C-2′), 162.3 (C=O). Anal. calcd for $C_{12}H_9BrN_2O$ (277.12): C, 52.01; H, 3.27; N, 10.11. Found: C, 51.97; H, 3.41; N, 10.11.

4.2.6. Oxalic acid bis(2-bromoanilide) (1j). The reaction of oxalyl chloride (0.87 mL, 10.0 mmol), 2-bromoaniline (3.45 g, 20.0 mmol) and triethylamine (2.8 mL, 20.0 mL) gave 2.5 g (63%) of the dianilide **1j**, mp 210°C. It is insoluble in $CHCl_3$, C_6H_6 and CH_3OH. IR (KBr): $\bar{\nu}$ 3434, 3328, 3307, 1703, 1678, 1521 cm^{-1}. Anal. calcd for $C_{14}H_{10}Br_2N_2O_2$ (398.05): C, 42.24; H, 2.53; N, 7.04. Found: C, 42.42; H, 2.73; N, 7.10.

4.3. Phosphonylation of 2-bromoanilides; general procedure

The corresponding 2-haloanilide and 0.2 g of anhydrous $NiCl_2$ or $NiBr_2$ were placed in a distillation device and heated to 180–190°C while excess triethyl phosphite was added dropwise (10–20 min). Heating was continued for a while to complete the reaction. EtCl or EtBr and a small amount of triethyl phosphite distilled off. The residue was fractionally distilled in vacuum.

4.3.1. 2-Acetamido-benzenephosphonic acid diethylester (2a). Triethyl phosphite (16.14 mL, 94 mmol) was added within 5 min to a mixture of 2-chloro-acetanilide (13.3 g, 78.4 mmol) and anhydrous $NiCl_2$ (0.2 g) at 180°C and heating continued at 205°C for 15 min. Only little conversion (but main product $\delta^{31}P$ 20) took place. To complete the reaction more $NiCl_2$ (1 g) was added and the mixture heated to 215°C for 30 min). Distillation furnished 11 g (46%) of a colourless oil, bp 120–125°C/4×10^{-2} Torr, identified as **2a**; analytical data as described earlier.[5]

4.3.2. 2-Benzamido-benzenephosphonic acid diethylester (2b). Triethyl phosphite (13.7 mL, 79.8 mmol) was added to a mixture of 2-chloro-benzanilide (15.4 g, 66.5 mmol) and anhydrous $NiBr_2$ (0.2 g) at 180°C and heated to 205°C for 15 min. Since there was no conversion, $NiCl_2$ (1 g) and $NiCl_2$dioxane (0.3 g) was added and heating repeated (30 min 215°C) until no more $P(OEt)_3$ distilled off. Vacuum distillation was accompanied by partial decomposition and gave 11 g (45%) of an yellow oil, bp 140–145°C/1.5×10^{-3} Torr, analytical data as described earlier.[5]

4.3.3. 2-Acetamido-5-methylbenzenephosphonic acid diethylester (2c). Triethyl phosphite (29.54 mL, 172.3 mmol) was added to a mixture of **1c** (Lancaster) (32.75 g, 143.6 mmol) and $NiCl_2$ (0.2 g) at 180–190°C. Heating to 190°C was continued for 15 min and the residue was distilled in vacuum to give 34.7 g (85%) of colourless oily **2c**, bp 123–128°C/5×10^{-4} Torr. ^1H NMR ($CDCl_3$): δ

2.19 (s, 3H, 5-Me), 1.34 (t, ^3J=7.1 Hz, 6H, Me), 4.10 (m, 4H, OCH_2), 7.34 (dd, superimposed with H-6, $^3J\approx$8 Hz, $^4J_{HH}$=2 Hz, 1H, H-4), 7.35 (d br, $^3J_{PH}\approx$14.4 Hz, 1H, H-6), 8.47 (t, $^3J\approx$8 Hz, $^4J_{PH}\approx$7 Hz, 1H, H-3), 10.48 (br, 1H, NH). ^{31}P NMR ($CDCl_3$): δ 20.3. Anal. calcd for $C_{13}H_{20}NO_4NP$ (285.50): C, 54.69; H, 7.06; N, 4.91. Found: C, 54.27; H, 7.30; N, 4.85.

4.3.4. 2-(2′,2′-Dimethylpropionamido)-5-methyl-benzenephosphonic acid diethyl ester (2d). Triethyl phosphite (21.1 mL, 0.123 mol) was added to **1d** (27.7 g, 0.10 mol) and $NiCl_2$ (0.1 g) at 180–195°C. Heating was continued for 20 min, then the residue was distilled in vacuum yielding 26.23 g (80%) of viscous oily **2d**, bp 139–141°C/3.8×10^{-4} Torr. IR (KBr): $\bar{\nu}$ 3430, 3293, 3259, 1688 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H, CMe_3), 1.33 (t, ^3J=7.2 Hz, 6H, Me), 2.33 (s, 5-Me), 4.11 (m, 4 H, OCH_2), 7.34 (d, ^3J=8.5 Hz, 1H, H-4), 7.39 (dd, $^3J_{PH}$=14.9 Hz, ^4J=1.6 Hz, 1H, H-6), 8.50 (dd, ^3J=8.4 Hz, $^4J_{PH}$=7.0 Hz, 1H, H-3), 10.41 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 16.0 (d, ^3J=6.6 Hz, Me), 20.4 (s, 5-Me), 27.3 (CMe_3), 39.8 (CMe_3), 62.2 (d, ^2J=4.8 Hz, OCH_2), 113.6 (d, ^1J=179.5 Hz, C-1), 120.9 (d, ^3J=12.0 Hz, C-3), 131.9 (d, ^3J=14.4 Hz, C-5), 132.2 (d, ^2J=6.2 Hz, C-6), 134.4 (d, ^4J=2.1 Hz, C-4), 140.3 (d, ^2J=7.0 Hz, C-2), 177.2 (s, CO). ^{31}P NMR ($CDCl_3$): δ 20.1. MS (EI, 70 eV): *m/z* (%)=328 (35), 327 (50) [M^+], 271 (25), 270 (100), 242 (54), 214 (92), 170 (42). Anal. calcd for $C_{16}H_{26}PO_2N$ (327.36): C, 58.70; H, 8.01; N, 4.28. Found: C, 58.48; H, 8.10; N, 4.54.

4.3.5. 2-Benzamido-5-methyl-benzenephosphonic acid diethyl ester (2e). Triethyl phosphite (11.74 mL, 68.5 mmol) was added to **1e** (16.685 g, 57.5 mmol) and $NiCl_2$ (0.1 g) at 165–190°C and heating continued for 15 min at 190°C. Distillation of the residue in a short-path high-vacuum device furnished 10.96 g (55%) of syrupy **2e**, boiling range 180–205°C/3.5×10^{-4} Torr (partially overheated). ^{1}H NMR ($CDCl_3$): δ 1.33 (td, ^3J=7.1 Hz, $^4J_{PH}$=0.5 Hz, 6H, Me), 2.36 (s, 3H, 5-Me), 4.00–4.30 (m, 4H, 2 OCH_2), 7.38–7.55 (m, 5H, H-*m*/*p*, H-4, H-6), 8.08-8.14 (m, 2H, H-*o*), 8.73 (dd, ^3J=8.1 Hz, $^4J_{PH}$=7.3 Hz, 1H, H-3), 11.38 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.9 (d, ^3J=6.7 Hz, Me), 20.4 (s, 5-Me), 62.4 (d, ^2J=4.9 Hz, OCH_2), 113.5 (d, ^1J=179.4 Hz, C-1), 120.7 (d, ^3J=12.4 Hz, C-3), 126.8 and 128.0 (2C-*o*/*m*), 130.8 (C-*p*, uncertain), 132.5 (d, ^2J=6.0 Hz, C-6), 132.6 (d, ^3J= 14.0 Hz, C-5), 134.5 (C-*i*, uncertain), 134.6 (d, ^4J=2.0 Hz, C-4), 140.2 (d, ^2J=7.1 Hz, C-2), 167.3 (s, CO). ^{31}P NMR ($CDCl_3$): δ 20.5. Anal. calcd for $C_{18}H_{22}NO_4P$ (347.35): C, 62.24; H, 6.38; N, 4.03. Found: C, 61.72; H, 6.17; N, 3.95.

4.3.6. 2-Acetamido-3,5-difluorobenzenephosphonic acid diethylester (2f). Triethyl phosphite (10.95 mL, 63.9 mmol) was added to **1f** (13.74 g, 54.9 mmol) and $NiCl_2$ (0.2 g) at 170°C and heating continued for 30 min at 190°C. ^{31}P NMR control of the residue displays compounds with δ^{31}P -0.8, 7.7, 13.8 (main product), 15.2 and 33.9 [$EtPO(OEt)_2$]. Distillation gave 7.3 g (44%) of a viscous liquid fraction, bp 129–131°C/2.6×10^{-3} Torr, identified by NMR as **2f** contaminated by a second P–C coupling product: ^{31}P NMR ($CDCl_3$) δ=13.7 (t, $J_{PF}\approx$10, 9 Hz, **2f**), 15.2 (dd, J_{PF}=12.1, 9.2 Hz, impurity; estimated intensity ratio 80:20%). The increased content of the impurity after distillation and the integral ratio of $CH_3C(O)$ to OCH_2 protons indicate partial loss of O-ethyl groups by thermal elimination and formation of the monoethyl ester. The mixture was used for the synthesis of **6f** without further purification.

4.3.7. 5-Bromo-2-(2′,2′-dimethylpropionamido)-3-fluorobenzenephosphonic acid diethyl ester (2g). Triethyl phosphite (3.8 mL, 22.0 mmol) was added to **1g** (5.04 g, 14.3 mmol) and $NiBr_2$ (0.2 g) at 180°C, heating at 200°C continued for 20 min. The residue exhibits ^{31}P NMR signals at δ^{31}P −0.5, 2.8 (d, J_{PF}=13.1 Hz,), 14.2 (d, J_{PF}=10.4 Hz, strong), 15.1 and 15.4 (small) and 33.9. Repeated distillation gave 4.23 g of a viscous oil with bp 121°C/10^{-2} Torr which became solid at room temperature. It is **2g**, contaminated by monoester **3g** (16 mol% based upon the ^{1}H integral ratio); corrected yield: **2g** 62%, **3g** 12%. (The mixture can be used to prepare **6g**.) IR: in KBr $\bar{\nu}$ 3423, 3346, 1694, 1666, 1257, 1117; in $CHCl_3$ (0.06, 0.03, 0.015 mol L^{-1}) $\bar{\nu}$ 3682, 3619, 3431, 3346, 1694 cm^{-1}. **2g**: ^{1}H NMR ($CDCl_3$): δ 1.33 (td, ^3J=7.0 Hz, $^4J_{PH}$=0.5 Hz, 6H, Me), 1.34 (s, 9H, CMe_3), 4.04–4.20 (m, 4H, OCH_2), 7.48 (dd, $^3J_{FH}$=9.3 Hz, ^4J= 2.2 Hz, 1H, H-4), 7.62 (ddd, $^3J_{PH}$=14.0 Hz, ^4J=2.2 Hz, $^5J_{FH}$=1.1 Hz, 1H, H-6), 8.58 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 16.2 (d, ^3J=6.5 Hz, Me), 27.4 (CMe_3), 39.3 (CMe_3), 63.1 (d, ^2J=5.6 Hz, OCH_2), 118.7 (dd, ^4J= 8.5 Hz, $^2J_{FC}$=22.4 Hz, C-4), 124.3 (dd, ^3J=24.0 Hz, $^3J_{FC}$=2.5 Hz, C-5), 125.2 (dd, ^1J=182.0 Hz, $^3J_{FC}$=1.7 Hz, C-1), 128.1 (dd, ^2J=6.5 Hz, $^2J_{FC}$=13.7 Hz, C-2), 130.6 (dd, ^2J=7.2 Hz, $^4J_{FC}$=3.7 Hz, C-6), 157.0 (dd, ^3J=20.0 Hz, $^1J_{FC}$=260.3 Hz, C-3), 177.2 (s, CO). ^{31}P NMR ($CDCl_3$): δ 14.2 (d, J_{PF}=10.6 Hz). **3g**: ^{1}H NMR: δ 1.35 (s, 9H, CMe_3), 1.38 (td, ^3J=7.0 Hz, $^4J_{PH}$=0.5 Hz, 3H, Me), 4.15–4.30 (m, 2H, OCH_2), 7.54 (dd, $^3J_{FH}$=9.3 Hz, ^4J=2.1 Hz, 1H, H-4), 7.74 (ddd, $^3J_{PH}$=15.1 Hz, ^4J=2.1 Hz, $^5J_{FH}$=1.3 Hz, 1H, H-6). ^{31}P NMR: δ 2.8 (d, J_{PF}=13.1 Hz). **2g**+**3g**: MS (EI, 70 eV, 205°C): *m/z* (%)=411 (38)/409 (35) [M^+], 365 (25)/363 (26) [M'^+], 364 (84)/362 (84) [$M'-1^+$], 340 (58)/338 (56), 339 (52), 337 (37), 314 (37)/311 (35), 312 (67) 310 (62). Anal. calcd for $C_{15}H_{22}BrFNO_4P$ (410.21)/ $C_{13}H_{16}BrFNO_3P$ (364.15) (84/16 mol%): C, 43.75; H, 5.25; N, 3.48. Found C, 43.51; H, 5.31; N, 3.71.

4.3.8. Oxalic acid 2-(diethoxyphosphono)anilide 2-bromoanilide (2j). Excess triethyl phosphite (15.65 mL, 91.1 mmol) was added to **1j** (15.2 g, 38.2 mmol) and 0.2 g $NiCl_2$ at 190–200°C. Heating was continued for 15 min at 200–215°C. After cooling to room temperature, the crude solid (δ^{31}P 18.5 and 18.2 st, 7.8 w) was extracted several times with ether. On concentration and cooling of the ether fraction 5.2 g (30%) of pale yellow **2j** were collected, mp 117–119°C. (Extraction of the residue with ethanol and removal of the solvent gave further 2 g of a pale green solid, mp 78–83°C, consisting mainly of **2j**.) ^{1}H NMR ($CDCl_3$): δ 1.34 (t, ^3J=7.0 Hz, 6H, Me), 4.12, 4.25 (m, $^2J_{HH}$=10.0 Hz, $^3J_{PHB}$=7.9 Hz, $^3J_{PHA}\approx$8.6 Hz, $^3J_{HH}$= 7.1 Hz, 4H, $POCH_AH_B$), 7.05 (td, ^3J=8, 7.6 Hz, $^4J\approx$1.5 Hz, 1H, 4-H′), 7.26 (tdd superimposed, $^3J\approx$7.5 Hz, $J_{PH}\approx$3.1 Hz, $^4J\approx$1 Hz, 4-H), 7.36 (td, ^3J=8.1, 7.5 Hz, $^4J\approx$1 Hz, 1H, 5-H′), 7.62 (t br, $^3J\approx$7.8 Hz, 1H, 5-H), 7.60 (dd, ^3J=8.1 Hz, $^4J\approx$1.5 Hz, 1H, 3-H′), 7.74 (ddd, $^3J_{PH}$=14.3 Hz, ^3J=7.6 Hz, ^4J=1.4 Hz, 1H, 3-H), 8.60 (dd,

^3J=8.2 Hz, ^4J=1.2 Hz, 1H, 6-H′), 8.70 (dd, ^3J≈7.6 Hz, $^4J_{PH}$≈6.8 Hz, 1H, 6-H), 9.98 (s, 1H, NH′), 12.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.2 (d, ^3J=6.2 Hz, Me), 61.8 (d, ^2J=5.2 Hz, OCH_2), 112.8 (C-2′), 115.2 (d, ^1J=180.9 Hz, C-2), 119.8 (d, ^3J=10.9 Hz, C-6), 120.2 (C-6′), 123.6 (d, ^3J=13.1 Hz, C-4), 125.1 (C-4′), 127.5 (C-5′), 131.5 (C-3′), 132.2 (d, ^2J=6.3 Hz, C-3), 133.0 (C-1′), 133.6 (C-5), 139.3 (C-1), 156.4 and 157.1 (C=O). ^{31}P NMR ($CDCl_3$): δ 18.3. Anal. calcd for $C_{18}H_{20}BrN_2O_5P$ (455.24): C, 47.49; H, 4.43; N, 6.15. Found: C, 47.25; H, 4.55; N, 6.03.

4.3.9. 2-(*N*-Methyl)formamido-benzenephosphonic acid diethyl ester (5). Triethyl phosphite (14.9 mL, 86.7 mmol) was added to **4**[22] (16.15 g, 75.4 mmol) and 0.1 g $PdCl_2$ heated at 170°C. Heating up to 190°C was continued for 1 h. The resulting yellow-brown solution was distilled in vacuum to give 8.84 g (43%) colourless oily **5**, bp 125–128°C/0.01 Torr. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, ^3J=7.1 Hz, 6H, Me), 3.27 (s, 3H, NMe), 4.19 (m, 4H, OCH_2), 7.31 (ddd, ^3J=7.8 Hz, $^3J_{PH}$=5.9 Hz, ^4J=1.1 Hz, 1H, H-3), 7.51 (tdd, ^3J=7.6 Hz, $^4J_{PH}$=3.4 Hz, ^4J=1 Hz, 1H, H-5), 7.66 (tdd, ^3J=7.7 Hz, $^4J_{PH}$=1.6 Hz, $^5J_{PH}$=1.3 Hz, 1H, H-4), 8.04 (ddd, ^3J=7.7 Hz, $^3J_{PH}$=14.7 Hz, ^4J=1.6 Hz, 1H, H-6), 8.13 (s, CHO). ^{13}C NMR ($CDCl_3$): δ 16.0 (d, ^3J=6.4 Hz, Me), 33.7 (s, NMe), 62.3 (d, ^2J=6.1 Hz, OCH_2), 127.9 (d, ^1J=187.9 Hz, C-1), 128.1 (d, ^3J=15.1 Hz, C-3), 129.6 (d, ^3J=10.6 Hz, C-5), 133.7 (d, ^4J=2.3 Hz, C-4), 134.5 (d, ^2J=8.3 Hz, C-6), 143.8 (d, ^2J=4.5 Hz, C-2), 162.6 (s, CO). ^{31}P NMR ($CDCl_3$): δ 15.9. (Low intensity set of signals for less populated rotamer not indicated.) MS (EI, 70 eV): *m/z* (%)=271 (6) [M^+], 258 (17), 248 (100), 223 (58), 205 (49), 194 (62), 173 (76), 153 (31), 134 (37), 106 (47), 77 (43), 65 (19), 47 (19), 29 (31). Anal. calcd for $C_{12}H_{18}NO_4P$ (271.25): C, 53.14; H, 6.69; N, 5.15. Found: C, 52.87; H, 6.66; N, 5.50.

4.4. Reduction of 2-amidobenzenephosphonic acid esters with $LiAlH_4$

Reduction of **2a** and **2b** was described earlier.[5]

4.4.1. 2,5-Dimethyl-1*H*-1,3-benzazaphosphole (6c). $LiAlH_4$ tablets (4.0 g, 105.4 mmol) were stirred in ether (ca. 300 mL) for 20 min, and **2c** (13.79 g, 48.0 mmol) was added dropwise at 15–20°C. The mixture was allowed to stir for 1 d. Then, degassed water was added dropwise until the evolution of hydrogen ceased. Solids were filtered off and washed with ether. The slightly yellow filtrate was extracted with air-free cold 10% aqueous H_2SO_4 to remove contamination by 2-phosphinoanilines. The ether layer was then washed with water, dried over Na_2SO_4, and filtered. White crystals were obtained from the concentrated solution and were recrystallised from toluene, yield 4.01 g (51%), mp 125–127°C. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, 5-Me), 2.70 (d, $^3J_{PH}$=12.1 Hz, 3H, Me), 7.08 (dm, ^3J=8.3 Hz, ^4J≈1.6 Hz, $^5J_{PH}$≈0.5 Hz, 1H, H-6), 7.36 (d, ^3J=8.3 Hz, 1H, H-7), 7.72 (dm, $^3J_{PH}$=3.6 Hz, ^4J≈1.6 Hz, 1H, H-4), 9.00 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.6 (d, ^2J=22.4 Hz, 2-Me), 21.2 (s, 5-Me), 112.6 (s, C-7), 125.9 (d, ^3J=2.2 Hz C-6), 127.8 (d, ^3J=20.1 Hz, C-4), 129.5 (d, ^2J=10.6 Hz, C-5), 140.6 (d, ^2J=5.7 Hz, C-7a), 141.4 (d, ^1J=41.7 Hz, C-3a), 173.3 (d, ^1J=51.5 Hz, C-2). ^{31}P NMR ($CDCl_3$): δ 71.8. MS (EI, 70 eV): *m/z* (%)=164 (11), 163 (100) [M^+], 162 (79), 161 (10), 148 (19), 131 (7), 121 (6), 77 (7). Anal. calcd for $C_9H_{10}NP$ (163.16): C, 66.25; H, 6.17; N, 8.58. Found: C, 65.90; H, 6.10; N, 8.50.

4.4.2. 2-*t*-Butyl-5-methyl-1*H*-1,3-benzazaphosphole (6d). A solution of **2d** (25.50 g, 0.077 mol) in ether (20 mL) was added dropwise at 0–5°C to $LiAlH_4$ tablets (7.36 g, 0.193 mol) stirred in ether (250 mL). Stirring was continued for 2 d at 20°C, then the mixture was cooled to 0–5°C, and hydrolysed with degassed water until the hydrogen evolution ceased. Na_2SO_4 was added, the mixture was filtered and the solid thoroughly washed with ether. Removal of the solvent gave a viscous oil which was distilled at 90–95°C/0.5×10^{-4} Torr. Crystallisation from dry pentane furnished 7.2 g (46%) **6d** as colourless solid, mp 97–99°C. IR (Nujol): $\bar{\nu}$ 3375 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.49 (d, $^4J_{PH}$=1.2 Hz, 9H, CMe_3), 2.17 (s, 5-Me), 7.10 (dm, ^3J=8.3 Hz, ^4J=0.9 Hz, $^5J_{PH}$=0.5 Hz, 1H, H-6), 7.43 (d br, ^3J=8.3 Hz, 1H, H-7), 7.76 (m, $^3J_{PH}$=3.5 Hz, *J*=1.8, 0.9 Hz, 1H, H-4), 9.24 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.2 (5-Me), 31.4 (d, ^3J=9.1 Hz, CMe_3), 35.8 (d, ^2J=13.3 Hz, *C*Me_3), 112.8 (s, C-7), 126.0 (d, ^4J=2.1 Hz, C-6), 128.0 (d, ^2J=21.1 Hz, C-4), 129.3 (d, ^3J=11.6 Hz, C-5), 140.5 (d, ^1J=40.9 Hz, C-3a), 140.6 (d, ^2J=5.8 Hz, C-7a), 189.8 (d, ^1J=57.5 Hz, C-2). ^{31}P NMR ($CDCl_3$): δ 63.5. MS (EI, 70 eV): *m/z* (%)=206 (42), 205 (100) [M^+], 191 (56), 190 (45), 177 (23), 162 (36), 158 (63), 150 (50), 149 (57), 148 (35). Anal. calcd for $C_{12}H_{16}PN$ (205.24): C, 70.23; H, 7.86; N, 6.82. Found: C, 69.87; H, 8.00; N, 6.70.

4.4.3. 2-Phenyl-5-methyl-1*H*-1,3-benzazaphosphole (6e). **2e** (10.43 g, 30 mmol) was added in small portions at 0–5°C to $LiAlH_4$ tablets (3 g, 79 mmol) stirred in ether (250 mL). After stirring for 2 d at 20°C the mixture was hydrolysed. **7e** (δ^{31}P −152.3) and smaller amounts of other side products were removed as described for **6c**. 4.61 g (68%) of yellow **6e** was crystallised from toluene, mp 175–177°C. ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 5-Me), 7.15 (dm, ^3J=8.4 Hz, *J*≈1.1, 0.5 Hz, 1H, H-6), 7.30-7.44 (m, 3H, H-*m*/*p*), 7.48 (d br, ^3J=8.4 Hz, 1H, H-7), 7.74–7.78 (m, 2H, H-*o*), 7.81 (m, $^3J_{PH}$=3.9 Hz, *J*≈1.5, 0.7 Hz, 1H, H-4), 9.45 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.2 (5-Me), 113.2 (s, C-7), 125.2 (d, ^3J=12.6 Hz, C-*o*), 127.0 (d, ^4J=3.1 Hz, C-6), 128.2 (d, ^2J=21.1 Hz, C-4), 128.8 (d, ^5J=3.0 Hz, C-*p*), 129.1 (s, C-*m*), 129.8 (d, ^3J=12.9 Hz, C-5), 135.1 (d, ^2J=15.3 Hz, C-*i*), 141.2 (d, ^2J=7.0 Hz, C-7a), 141.9 (d, ^1J=41.0 Hz, C-3a), 174.1 (d, ^1J=51.3 Hz, C-2); CH-COSY supported assignment. ^{31}P NMR ($CDCl_3$): δ 74.4. MS (EI, 70 eV): *m/z* (%)=226 (99), 225 (100) [M^+], 224 (80), 211 (10), 197 (74), 183 (19), 148 (31), 121 (41), 107 (28), 91 (99), 77 (57). Anal. calcd for $C_{14}H_{12}NP$ (225.23): C, 74.66; H, 5.37; N, 6.22: Found: C, 74.57; H, 5.57; N, 6.16.

4.4.4. 5,7-Difluoro-2-methyl-1*H*-1,3-benzazaphosphole (6f). A solution of crude **2f** (7.34 g, 23.9 mmol) in ether (20 mL) was added dropwise to four tablets of $LiAlH_4$ (ca. 4 g, 105 mmol) stirred in ether (100 mL) at ca. 5°C. The mixture was stirred for a further 2 d at 20°C and hydrolysed. Minor amounts of **7f** (δ^{31}P −136) and traces of two other PH compounds were removed as described for **6c** yielding 1.22 g (28%) of **6f** as colourless crystals, mp 105°C. ^{1}H NMR ($CDCl_3$): δ 2.79 (d, $^3J_{PH}$=12.3 Hz, 3H, Me), 6.82 (ddd, J_{FH}=11.0, 8.9 Hz, ^4J=2.3 Hz, 1H, H-6),

7.40 (ddd, J_{FH}=8.4 Hz, J_{PH}=3.0 Hz, ^4J=2.3 Hz, 1H, H-4), 9.13 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.6 (d, ^2J=22.6 Hz, 2-Me), 149.5 (dd, J_{FC}=250.7, 12.9 Hz, C-7), 108.2 (dt, ^3J=4.1 Hz, J_{FC}=22.1 Hz, C-6), 99.4 (ddd, ^3J=20.1 Hz, J_{FC}=30.0, 1.5 Hz, C-4), 156.9 (ddd, ^2J=8.9 Hz, J_{FC}=241.7, 12.4 Hz, C-5), 127.6 (dd, ^2J=4.3 Hz, J_{FC}=9.9 Hz, C-7a), 144.5 (ddd, ^1J=46.6 Hz, J_{FC}=8.5, 1.6 Hz, C-3a), 175.5 (dd, ^1J=54.5 Hz, J_{FC}=1.4 Hz, C-2). ^{31}P NMR ($CDCl_3$): δ 80.5 (dd, J_{PF}=15.9, 8.3 Hz). MS (EI, 70 eV): *m/z* (%)=186 (23), 185 (100) [M^+], 184 (94), 183 (15), 157 (11), 153 (19), 143 (18), 142 (27), 139 (12), 134 (24), 75 (18), 69 (24). Anal. calcd for $C_8H_6F_2NP$ (185.11): C, 51.91; H, 3.27; N, 7.57. Found: C, 52.4; H, 3.88; N, 7.52.

4.4.5. 5-Bromo-2-*t*-butyl-7-fluoro-1*H*-1,3-benzazaphosphole (6g). A solution of **2g** and **3g** (6.48 g, ca. 15.8 mmol) in ether (30 mL) was added dropwise at 0–5°C to $LiAlH_4$ tablets (1.44 g, 37.9 mmol) stirred in ether (70 mL). Stirring was continued for 4 d at 20°C. Then the mixture was hydrolysed with degassed water at 0–5°C, filtered and the filtrate was dried with Na_2SO_4. Removal of the solvent gave viscous oily **6g**, slightly contaminated by primary (mainly δ^{31}P −141.7) and secondary phosphines and a small amount of another 1*H*-1,3-benzazaphosphole with δ(^{31}P) 72.6, $^4J_{PF}$=7.9 Hz. Distillation furnished 1.8 g (40%) of a colourless oil, bp 85–90°C/2×10^{-2} Torr which was crystallised from pentane (−5°C), mp 63–65°C. It is easily soluble in common organic solvents. IR (KBr): $\bar{\nu}$ 3403, 3349 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.51 (d, $^4J_{PH}$=1.2 Hz, 9H, CMe_3), 7.15 (dd, $^3J_{FH}$=10.3 Hz, ^4J=1.6 Hz, 1H, H-6), 7.86 (t, $^3J_{PH}$=2.5 Hz, J=1.6 Hz, 1H, H-4), 9.18 (br, 1H, NH). ^{13}C NMR (C_6D_6): δ 31.6 (d, ^3J=9.2 Hz, CMe_3), 36.4 (d, ^2J=13.0 Hz, CMe_3), 113.5 (dd, ^4J=1.5 Hz, $^2J_{FC}$=20 Hz, C-6), 113.6 (dd, ^3J=10.6 Hz, $^3J_{FC}$=6.9 Hz, C-5), 127.5 (dd, ^2J=22.2 Hz, $^4J_{FC}$=3.8 Hz, C-4), 130.8 (dd, ^2J=4.5 Hz, $^2J_{PF}$=10.7 Hz, C-7a), 146.5 (d, ^1J=47.9 Hz, $^3J_{PF}$=1.3 Hz, C-3a), 150.9 (dd, $^1J_{FC}$=251.7 Hz, ^3J=1.5 Hz, C-7), 192.5 (dd, ^1J=61.4 Hz, $^4J_{FC}$=1.5 Hz, C-2). ^{31}P NMR ($CDCl_3$): δ 72.6 (d, $^4J_{PF}$=8.5 Hz). MS (EI, 70 eV, 60°C,): *m/z* (%)=290 (20), 289 (99) [M^+(^{81}Br)], 288 (23), 287 (100) [M^+(^{79}Br)], 275 (21), 274 (100), 273 (24), 272 (100), 233 (21), 231 (21), 193 (95) [M^+−Me−Br], 153 (98). Anal. calcd for $C_{11}H_{12}BrFPN$ (288.10): C, 45.86; H, 4.20; N, 4.86. Found: C, 46.23; H, 4.52; 4.90.

4.4.6. *N*-Methyl-2-phosphinoaniline (9). 5 (9.47 g, 34.9 mmol), dissolved in ether (10 mL), was added to potassium *t*-butylate (4.0 g, 35.6 mmol) in ether (50 mL) yielding an orange solution from which a white solid precipitated. The mixture was added in small portions to $LiAlH_4$ (2 g, 52 mmol) in ether (50 mL) at −20°C. Stirring was continued overnight at room temperature. After cooling to ca. 10°C water was added dropwise until the hydrogen evolution ceased. The mixture was filtered, the remaining solid was washed with ether, and the ethereal solution was dried with Na_2SO_4. Then the solvent was removed and the residue distilled to give 1.95 g (40%) of colourless liquid **9**, bp 72–73°C/0.1 Torr, identical with **9** obtained from reduction of 2-methylamino-benzenephosphonous acid diethyl ester.[5] ^{1}H NMR (C_6D_6): δ 2.33 (s, 3H, Me), 3.33 (d, $^1J_{PH}$=197.7 Hz, 2H, PH_2), ca. 3.5 (br, 1H, NH), 6.39 (d br, ^3J=8.2 Hz, 1H, H-6), 6.63 (tt, ^3J=7.3, 7.4 Hz, $^4J\approx{}^4J_{PH}\approx$1.1 Hz, 1H, H-4), 7.21 (tm, ^3J=8.2, 7.3 Hz, 1H, H-5), 7.51 (ddd, ^3J=7.4 Hz, $^3J_{PH}$=12.6 Hz, ^4J=1.5 Hz, 1H, H-3). ^{13}C NMR (C_6D_6): δ 31.0 (Me), 110.1 (br, C-6), 111.3 (d, ^1J=10.8 Hz, C_q-2), 117.4 (d, ^3J=12.1 Hz, C-4), 132.4 (s, C-5), 139.2 (d, ^2J=34.2 Hz, C-3), 152.5 (s, C_q-1). ^{31}P NMR (C_6D_6): δ −155.1.

4.5. Crystal-structure analysis of 6d

A yellow tablet was mounted in inert oil on a glass fiber and transferred to the cold gas stream of a Bruker SMART 1000 CCD diffractometer. The structure was solved by direct methods and refined using the program SHELXL-97 (G.M. Sheldrick, University of Göttingen). Hydrogen atoms were refined either freely (NH), as rigid methyl groups, or using a riding model. The compound crystallises in a chiral space group; the absolute structure for the crystal investigated was determined by the Flack parameter of −0.02(7).

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC 164270, and may be obtained free of charge from the Director (deposit@ccdc.cam.ac.uk).

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