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An improved C-P cross-coupling route for the synthesis of novel V-shaped aryldiphosphonic acids

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Abstract

The synthesis of phosphonate esters is a topic of interest for various fields, including the preparation of phosphonic acids to be employed as organic linkers for the construction of metal phosphonate materials. Various methods have been reported to obtain phosphonate esters in the literature. Discussed here is the transition metal-catalysed cross-coupling reaction, often referred to as the Tavs reaction, which employs $NiCl_2$ as a pre-catalyst in the phosphonylation of aryl bromide substrates using triisopropyl phosphite. We report an improvement to the existing method which decreases the reaction time from 24+ hours to around 4 hours, with yields above 80%. Compared to conventional methods, our procedure requires no solvent and involves a different order of addition of reactants. This new method was employed in the synthesis of three novel aryl phosphonate esters which were subsequently transformed to phosphonic acids through silylation and hydrolysis.

Keywords

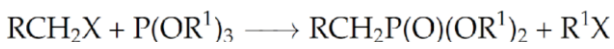
Cross-coupling reaction; transition metal catalysis; phosphonate esters; arylphosphonic acids

Introduction

Phosphonates and phosphonic acids are a very interesting class of compounds and examples of their use can be found in a number of different areas, including pharmaceuticals [1-6], metal chelation [7-9], anti-corrosion coatings [10-12], and fertilisers [13-14], amongst others. Phosphonates can also be employed as organic linkers in combination with metal ions to afford coordination polymers and metal-organic frameworks (MOFs), or more aptly, metal phosphonate frameworks. Conventionally, MOFs are most often synthesised using carboxylates as the primary coordinating group, though other functionalities have been employed, including sulfonates, amines, and N-heterocycles. The carboxylate ligand has proven to be one of the most versatile and ubiquitous groups in coordination chemistry, and the bonding modes it presents are relatively simple in comparison to phosphonates, which makes it more predictable and much easier to work with. In fact, as is shown in Figure S1, phosphonates have double the number of bonding modes at 18, versus 9 for carboxylates, clearly showing the increased complexity involved in working with phosphonates [15].

One of the main challenges in the synthesis of metal phosphonates is that the linkers are rarely commercially available and can often be difficult to prepare. Most often, the challenge is, in fact, not in the synthesis of the phosphonic acid itself, but in that of the phosphonic ester precursor. Various routes for obtaining these compounds have been explored, with a large majority involving a reaction between a primary alkyl halide and

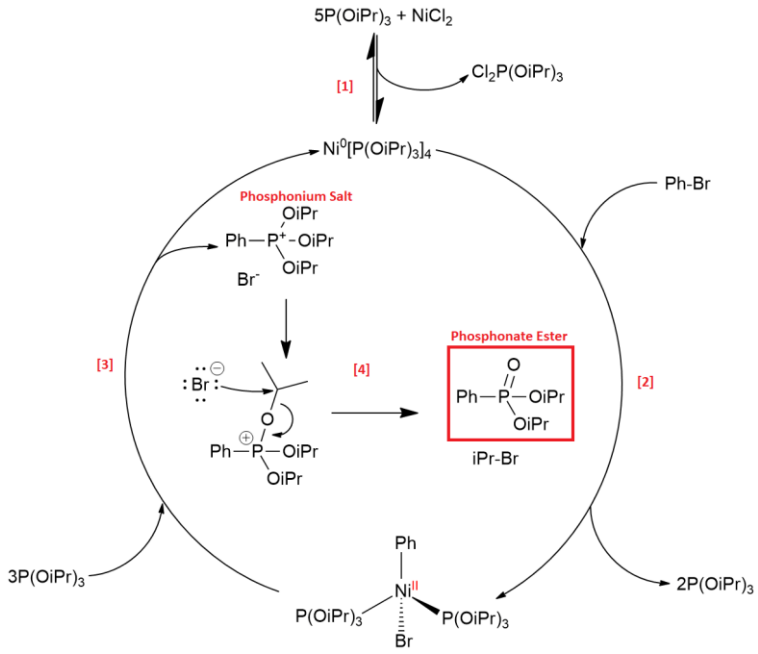
a trialkyl phosphite. Perhaps the most well-known C-P coupling procedure is the Michaelis-Arbuzov rearrangement, first reported in the late 1890s, the general scheme for which can be seen in Scheme 1 [16]. This reaction proceeds in two steps, initiating when the α-carbon of the primary alkyl halide undergoes a nucleophilic attack from the phosphorus lone pair of the trialkyl phosphite, leading to the formation of a quasi-phosphonium salt. In the second step, the α-carbon on one of the three alkoxy groups undergoes nucleophilic attack by the free halide ion generated in the first step, resulting in the formation of a new C-X bond and the cleavage of the C-O bond. Recent advances in the reaction have included a decrease in reaction time when microwave-assisted heating is applied, resulting in almost stoichiometric yields with no requirement for the use of solvents [17]. It should be noted that this reaction is not suitable for use with aryl halide substrates due to the poor reactivity between aryl halides and trialkyl phosphites [18].



Scheme 1: General scheme for the Michaelis-Arbuzov reaction.

Some of the most studied C-P coupling reactions involving aryl substrates are those employing catalysts, which are required in order to lower the energy barrier of the reaction and overcome the poor reactivity between aryl halides and trialkyl phosphites [19-21]. These catalytic cross-coupling reactions tend to follow similar pathways to the Michaelis-Arbuzov reaction, with the inclusion of a catalytic intermediate step. A number of suitable catalysts have been identified, ranging from nickel(II) bromide and nickel(II) chloride, to palladium(II) acetate and palladium(II) chloride. Reactions involving these catalysts are most often carried out at high temperatures, usually in excess of 160 °C, and involves slow dropwise addition of the trialkyl phosphite to the

substrate [18]. In the search for milder reaction conditions, a new catalyst, tetrakis(triphenylphosphine)palladium(0), was introduced, which allowed for the lowering of the reaction temperature to approximately 90 °C [22-24]. Although new to this kind of cross-coupling reaction, it has been commonly used in the Suzuki-Miyaura cross-coupling reaction, where new C-C bonds form between boronic acids and aryl halides [25]. In this work, the Tavs reaction, which employs a nickel(II) chloride pre-catalyst, was chosen due to its relatively low cost in comparison to the palladium catalysts. Despite the harsher conditions, the nickel catalysts are still widely used, but the mechanism for the reaction has proven difficult to pin down. However, a mechanism put forward shows the full catalytic cycle for the reaction, as shown in Scheme 2 [26].



Scheme 2: The catalytic cycle for the nickel-catalysed cross coupling reaction of aryl halides with triisopropyl phosphite. Scheme 2 was adapted with permission of The Royal Society of Chemistry from [18] (“Chapter 6: Synthesis of Phosphonic Acids and Their Esters as Possible Substrates for Reticular Chemistry. In Metal Phosphonate

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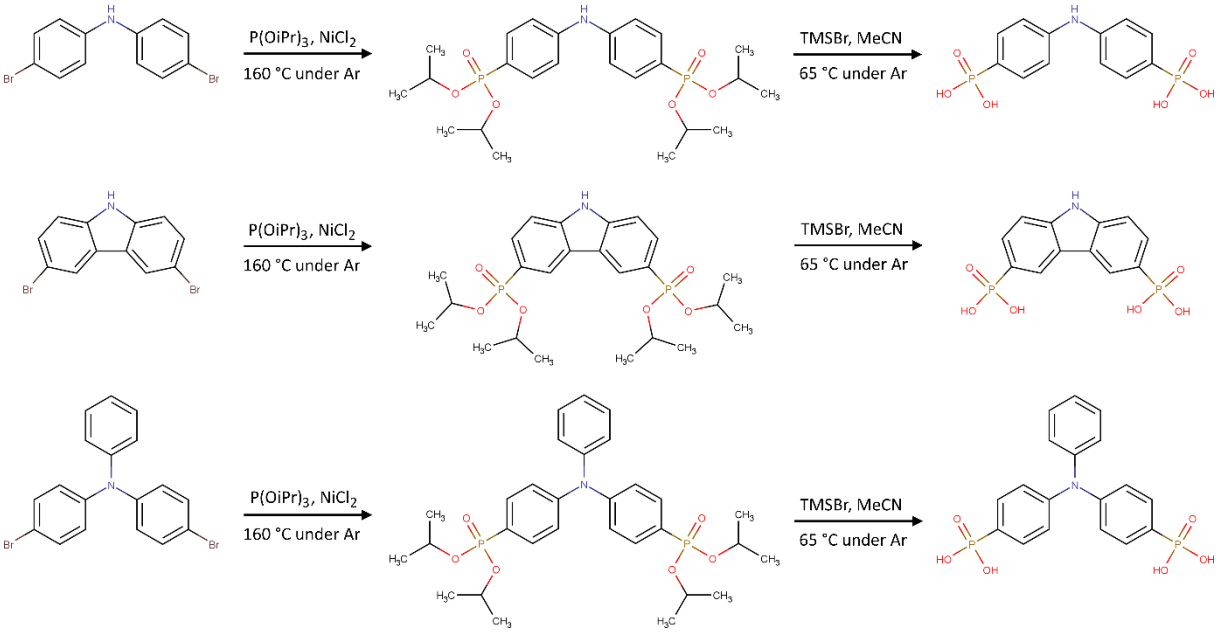
The cycle begins with the reduction of the nickel(II) chloride pre-catalyst by the trialkyl phosphite (shown here as triisopropyl phosphite) to form the catalyst, tetrakis(triisopropyl phosphite)nickel(0) [Step 1]. The aryl halide then undergoes oxidative addition to the nickel complex, forming a new nickel(II) complex [Step 2]. We then see the formation of the arylphosphonium salt and the regeneration of the nickel(0) catalyst *via* eliminative reduction [Step 3]. The final step in the cycle is identical to the Michaelis-Arbuzov reaction, whereby diisopropyl phosphonate and isopropyl bromide are formed through a nucleophilic substitution of the halide anion [Step 4].

In this work, we have developed an alternative experimental protocol to perform the Ni-catalysed P-C cross-coupling reaction, or Tavs reaction, starting from commercially available bromide precursors and targeting a series of novel aryldiphosphonic acids. These phosphonic acids share the feature of having non-linear – or V-shaped – geometry and are intended to be employed as organic linkers for the synthesis of open framework metal phosphonate materials. The proposed protocol does not require a solvent, features a greatly reduced reaction time, and affords yields comparable to those of other procedures commonly employed in the literature.

Results and Discussion

The main driver for this work was to produce a series of non-linear aryldiphosphonic acids to be used as linkers in open framework metal phosphonates, which have been

of great interest in various fields of research. We focus here on the nickel-catalysed cross-coupling reaction, for which the pre-catalyst, anhydrous nickel chloride, is a cheap and commercially available material. Specifically, we are looking at the phosphonylation of the bromo-substituted *N*-aryl precursors bis(4-bromophenyl)amine (Br_2BPA), 3,6-dibromocarbazole (Br_2DPC), 4-bromo-N-(4-bromophenyl)-N-phenylaniline (Br_2DPPA) (see Scheme 3). Two of the main considerations made when selecting these substrates were rigidity and geometry. In the compounds considered here, rigidity is ensured by the network of sp^2 hybridised carbon atoms, or aromatic rings, and is important to ensure stability in the potential MOF structures derived from the proposed linkers. The geometry of these linkers, termed as V-shaped, was selected to try and move away from the pillared-layered structures that are obtained when using linear diphosphonate linkers, which are often either non-porous or have low porosity and have little to no long-range order. The idea here was that the V-shaped linkers, as well as different substituents attached to nitrogen, could potentially force a non-layered porous structure, as seen in CAU-8, which is a carboxylate-based geometric analogue of some of the linkers considered in this work, though the presence of the carboxylate coordinating group prevents direct comparisons [27].



Scheme 3: Scheme showing the transformation of the Br-substrates to phosphonate esters and then to phosphonic acids.

Conventionally, the transition metal catalysed P-C cross coupling reaction described is carried out by placing the aryl halide and the pre-catalyst into a round-bottom flask in the presence of a suitable solvent, most often 1,3-diisopropylbenzene, and setting to reflux. The advantage of using such solvent lies in its high boiling point (203 °C), which allows for reactions to be run at much higher temperatures, thus increasing the rate of the reaction. While the reaction mixture is refluxing, the alkyl phosphite is added in several small portions.

Where the work we present differs from the conventional nickel-catalysed cross coupling reaction is in two aspects: we use no solvent and we employ a different order of addition of reactants. The absence of solvent presents a few advantages over the original method. First of all, the removal of said solvent after the completion of the reaction is no longer required and thus there is a simplification of the work-up procedure. Second, there is no dilution of the reaction mixture, which obviously lends itself to an increased reaction rate, something we have observed in our results. As

described previously, the conventional procedure involves the addition of the aryl halide and the pre-catalyst ($NiCl_2$ or $NiBr_2$) into a round-bottom flask in the presence of a suitable solvent. The alkyl phosphite is then added dropwise over a relatively long time. In this improved method, however, we have discovered that the reaction time can be greatly decreased when the aryl halide (in solid form) is added to an alkyl phosphite and pre-catalyst mixture. Contrary to the conventional method, this improved method starts with the nickel(II) pre-catalyst and the alkyl phosphite, triisopropyl phosphite in our case, being added to a round-bottom flask and heated to approximately 160 °C, leading to the formation of the nickel(0) catalyst, more accurately representing the catalytic cycle presented in Scheme 2. The solid aryl bromide is then added to the mixture via a powder addition funnel over a 2–4-hour period, depending on the substrate, and is then left to react for an additional 1 hour to reach complete conversion of the substrate into the respective phosphonic ester. In this way, the dibromide substrate is always the limiting reagent, promoting full conversion to the respective diphosphonic ester and limiting the accumulation of an undesired, partially converted product that would need to be separated during workup.

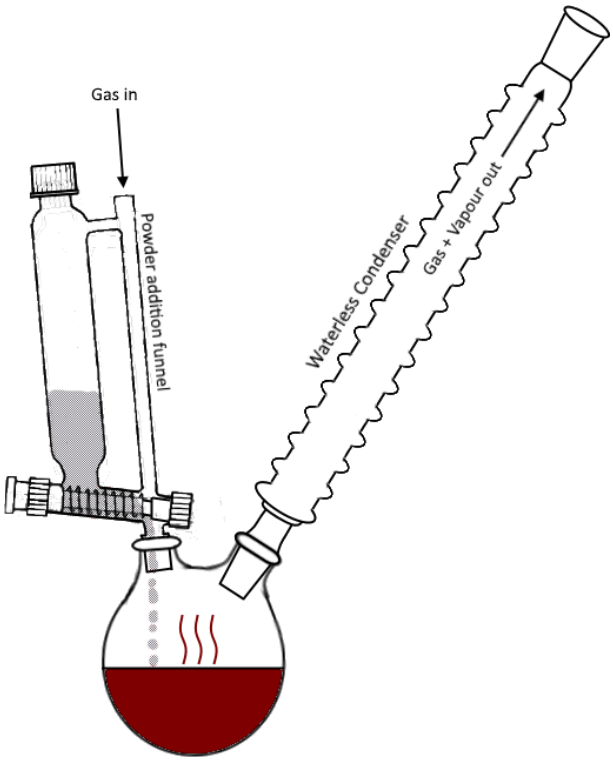


Figure 1: Experimental setup for the improved C-P cross coupling reaction.

Figure 1 shows the set-up for the reaction, with the solid aryl bromide in grey and the pre-catalyst/triisopropyl phosphite mixture in red. It is important to note here that the system is kept under a constant flow of either argon or nitrogen, mainly to avoid side reactions with components in the air (humidity, oxygen), but also to prevent the solid in the addition funnel from contacting any vapour and turning soggy before it is added to the round-bottom flask. As can be seen in Figure 1, this is achieved by flowing the gas through the powder addition funnel via a gas inlet. This also allowed for the quick removal of residual triisopropyl phosphite at the end of the reaction by simply increasing the gas flow, thus preventing the equilibrium between the gas and liquid phases and allowing to bypass the further step which would have involved removing these components by vacuum distillation. Although not shown in Figure 1, the addition of a second condenser and collection flask perpendicular, as in a distillation, to the first column also allows for the collection of unreacted phosphite, and by-products, such as

isopropyl bromide. Firstly, this prevents any release of vapours of toxic compounds and facilitates appropriate disposal procedures. Secondly, it is likely that the majority of what remains in the flask at the end is simply unreacted phosphite, which would ideally need to be investigated to assess its recyclability, and lead to a process with greener attributes. In this sense, the phosphite is likely to be the last product coming over via distillation, and should be relatively pure, but further investigation would be required in order to confirm this. The choice of phosphite is also important, partially due to the boiling point and the potential for running reactions at higher temperatures, and also the formation of an alkyl halide by-product. It is the reactivity of this by-product that determines which phosphite is chosen. In this case, triisopropyl phosphite has been chosen over others, such as the commonly employed triethyl phosphite, since the latter results in a more reactive alkyl halide (i.e. ethyl bromide), which would react with triethyl phosphite to produce diethyl ethylphosphonate, thus consuming the triethyl phosphite in a competing reaction and introducing undesired side-products that would make the workup procedure more laborious. Furthermore, the boiling point of triisopropyl phosphite is 181 °C, versus 156 °C for triethyl phosphite, which allows to run the reaction at higher temperature and reduce the time.

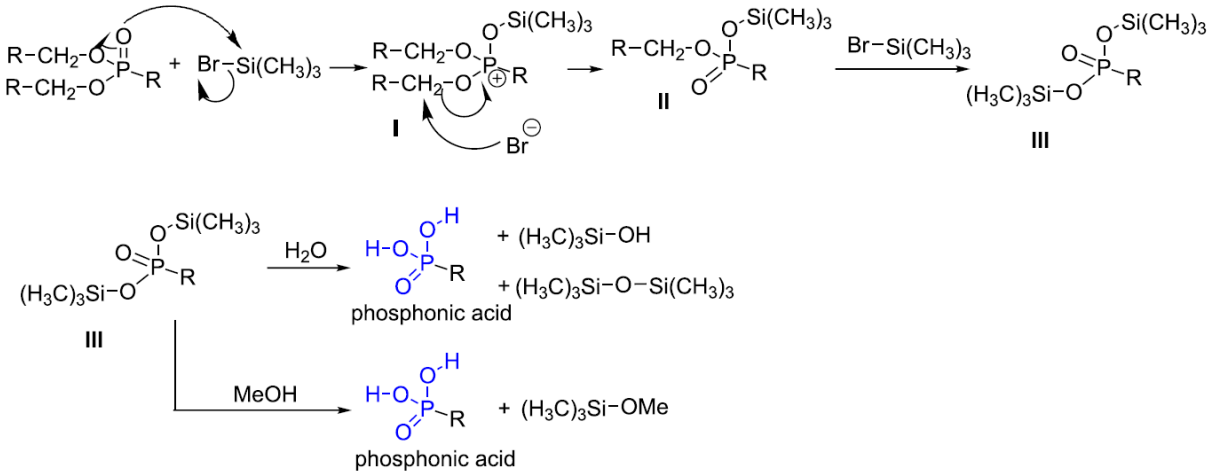
Table 1: A comparison of conventional phosphonate synthesis with the improved method proposed in this work. The microwave-assisted method made use of a pressure-resistant vessel due to considerable pressure buildup (~10 bar), while the other methods were run under reflux conditions.

	This work	Conventional A [28]	Conventional B [29]	Conventional C [30]	Conventional D [31]
Time	2-5 h	20 h	20 h	20 h	45 mins
Scale	2-5 g	30 g	8 g	10 g	0.5 g
Temperature	160 °C	180 °C	180 °C	170 °C	225 °C
Solvent	No solvent	1,3-diisopropyl benzene	1,3-diisopropyl benzene	*tert*-butylbenzene	No solvent
P/Br Ratio	7	1.5	3	2.1	5
Mol%/Br (NiX_2)	13% X=Cl	17% X=Cl	39% X=Br	16% X=Br	15% X=Cl
Isolated Yield	70-90%	60%	89%	61%	82%
Procedure	Addition of Br-substrate	Addition of phosphite	Addition of phosphite	Addition of phosphite	One-pot synthesis

In Table 1, we see a range of different methods based on cross-coupling reactions compared to the improved method proposed in this work. The first, and one of the most important comparisons, is time. The upper range for our method is around the 5-hour mark, whereas the conventional routes, excluding the microwave-assisted reaction, often run for 20 hours or more. This, in part, can be attributed to the absence of solvent, which we cited previously as an advantage in that we are not diluting the reaction mixture and thus not slowing down the reaction. This in turn explains the high phosphite:bromine ratio, which in our case is higher than all the other routes, since the phosphite itself acts as the solvent as well as being a reactant. If this ratio was lower, there would be a considerable drop in the reaction rate towards the end and would likely lead to generally lower yields. This issue could be further minimised upon exploration of recycling the phosphite distillate. We also manage to use less catalyst than some of the other methods, again, except for the microwave-assisted reaction. In keeping with the mild conditions, the temperature we use is 160 °C, which is lower than that of the other reactions. Notably, the yield we achieve, which varies between substrates, is generally comparable to those of conventional routes. With regards to

the microwave-assisted reaction, we note that the scale of the method used for comparison, originally reported by one of us, was limited to 0.543 g (1 mmol) of substrate. Scale up of this protocol was not attempted, but it might become problematic due to issues with microwave penetration in a medium that contains a strong absorber, such as the Ni catalytic complex. In this work, we have employed either 5.0 g (15.3 mmol) or 3.0 g (7.4 mmol) of substrate.

Once the phosphonate esters had been successfully obtained and characterized by ^{1}H, ^{31}P, ^{13}C-NMR and mass spectrometry (see experimental section and SI), they were then subject to silylation and subsequent hydrolysis using the method put forward by McKenna et al. (1977), which involves the use of trimethylbromosilane (TMSiBr) in a transesterification of the dialkyl phosphonate to bis(trimethylsilyl) phosphonate, followed by treatment in water or short-chain alcohols to obtain a phosphonic acid, as shown in Scheme 4 [32-33]. The initial step in this mechanism proceeds via an oxophilic substitution on the silicon of TMSiBr, whereby bromide acts as the leaving group, resulting in the formation of intermediate I. A nucleophilic attack by the bromide on the electrophilic carbon then leads to the formation of intermediate II, and then intermediate III through repetition of the same process. From here, there are two possible routes for obtaining a phosphonic acid. The first route is hydrolysis, leading to the formation of the phosphonic acid and two volatile side products, trimethylsilanol and hexamethyldisiloxane. The second route is methanolysis, leading to the formation of the phosphonic acid and methoxytrimethylsilane, a side product that is inherently more volatile than those formed during hydrolysis. Here we followed the water hydrolysis route.



Scheme 4: Proposed mechanism for the hydrolysis of dialkyl phosphonates using trimethylbromosilane. Scheme 4 was adapted from Ref. [34] (© 2017 C. M. Sevrain et al., published by Beilstein-Institut, distributed under the terms of the Creative Commons Attribution 4.0 International License, https://creativecommons.org/licenses/by/4.0).

Prior to using this method, the standard hydrolysis under prolonged reflux in 6 M HCl was attempted, though these conditions proved too harsh, and often led to cleavage of the C-P bond. Thus, this popular method was abandoned in favour of using the less harsh method employing TMSiBr, which most often led to achieve overall yields above 70% for the phosphonic acid based on the initial Br-substrate.

Conclusion

Presented in this article is the synthesis of three novel phosphonate esters and their corresponding phosphonic acids. While the phosphonic acids are indeed the target products, the progress made here is mainly focused on the improvement of the cross-coupling procedure used to obtain the phosphonate esters. Oftentimes, these reactions take up to 24 hours to reach completion, sometimes more, while here we

have presented a simple yet effective change that can be made to the order of addition of reactants, which affords a reaction time that is at least five times faster than most conventional methods with no considerable effect on the yield or the purity of the product. This has also completely removed the requirement of a solvent, since triisopropyl phosphite acts as the solvent. In making savings for both cost of reagents and in total reaction time, and with no detriment to the yield, it is clear that this method presents a considerable advantage over the conventional route, both in terms of cost and efficient use of time. Referring specifically to the phosphonic acids presented in this work, we have obtained three novel and structurally related linkers for the preparation of metal phosphonates. Each of the linkers were obtained in good yields and with no considerable impurities identified during characterisation. This series of linkers will allow to determine the effects of the geometry and of different substituents on the formation of metal phosphonate frameworks.

Experimental

Materials

All materials were used as received and not subject to further purifications.

- Acetonitrile, anhydrous (75-05-8, 99.8%, CH_3CN, Sigma-Merck)
- Bis-(4-bromophenyl)amine (16292-17-4, 97%, $C_{12}H_9Br_2N$, Sigma-Merck)
- 4-Bromo-N-(4-bromophenyl)-N-phenylaniline (81090-53-1, 98%, $C_{18}H_{13}Br_2N$, Fluorochem)
- 3,6-Dibromo-9H-carbazole (6825-20-3, 97%, $C_{12}H_7Br_2N$, Fluorochem)
- Ethyl acetate (141-78-6, 99.7%, $CH_3CO_2C_2H_5$, Sigma-Merck)
- Hexane (110-54-3, 97%, $CH_3(CH_2)_4CH_3$, Sigma-Merck)
- Nickel(II) chloride, anhydrous (7718-54-9, 98%, $NiCl_2$, Alfa Aesar)

- Triisopropyl phosphite (116-17-6, 95%, $[(CH_3)_2CHO]_3P$, Sigma-Merck)
- Trimethylbromosilane (2857-97-8, 97%, $(CH_3)_3SiBr$, Sigma-Merck)

Methods

^1H, ^{13}C, ^{31}P, and HSQC NMR spectra were recorded on a Bruker Avance III 500 MHz instrument. Phosphonate esters were dissolved in $CDCl_3$. Phosphonic acids were dissolved in a 0.1 M solution of NaOH in D_2O. ^1H-NMR parameters: 16 scans, 5 s relaxation delay (d1). ^{31}P-NMR parameters: 32 scans, 2 s relaxation delay (d1). ^{13}C-NMR parameters: 1024 scans, 2 s relaxation delay (d1). ^1H-^{13}C HSQC: 2 scans, 2 s relaxation delay (d1).

All mass spectral analyses were carried out at the National Mass Spectrometry Facility (NMSF), Swansea University Medical School, and processed using vendor XCalibur software. iPr_4BPA, iPr_4DPC, and iPr_4DPPA samples were prepared for analysis by solvation in 350 µL MeOH and further 1:1000 dilution in MeOH with 30 mM ammonium acetate (NH_4OAc). 20 µL was aliquoted into a 96 well plate and sprayed via an Advion NanoMate in positive ion mode at +1.5 kV into the API source of a Thermo LTQ Orbitrap XL. API source conditions were capillary temperature 200 °C, capillary voltage 41 V and tube lens voltage 150 V. H_4BPA, H_4DPC, and H_4DPPA samples were prepared for analysis by solvation in 350 µL MeOH and further 1:1000 dilution in MeOH with 1% diethylamine (DEA) to promote deprotonation. 20 µL was aliquoted into a 96 well plate and sprayed via an Advion NanoMate in negative ion mode at -1.5 kV into the API source of a Thermo LTQ Orbitrap XL. API source conditions were capillary temperature 200 °C, capillary voltage -32 V and tube lens voltage -100 V.

TM-Catalysed C-P Coupling Reactions

(1A) *N*,*N*-Bis(4-diisopropylphosphonophenyl)amine [iPr$_4$BPA]

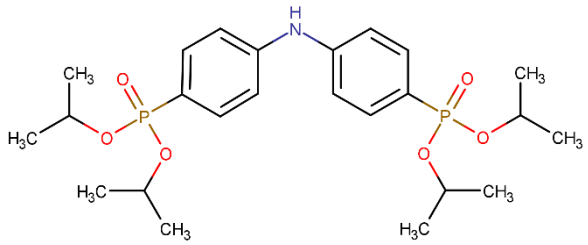


Figure 3: Chemical structure of iPr$_4$BPA (1A).

Bis(4-bromophenyl)amine (5.0 g, 15.3 mmol) was placed into a screw powder addition funnel and attached to a 100 mL round-bottom flask. Triisopropyl phosphite (52.5 mL, 214 mmol, 7 equivalents) and anhydrous nickel chloride (13 mol%) were then added to the round-bottom flask and set to reflux (160 °C) under argon. Once the mixture had reached temperature, the bis(4-bromophenyl)amine was added slowly over 2 hours and the reaction monitored via TLC using an acetone:ethyl acetate mixture in a 1:9 ratio. Once the addition was complete, the reaction mixture was left for a further 3.5 hours and again monitored by TLC to identify when the reaction had gone to completion. After 3.5 hours, the gas flow rate was increased in order to remove excess phosphite and remaining byproducts, resulting in a dark treacle-like substance. This was left to cool and subsequently washed overnight in hexane, resulting in the formation of a fine grey powder (5.57 g). This powder was then placed in an acetone:ethyl acetate mixture (1:9), whereby partial dissolution of the powder resulted in an off-yellow solution and a dark black solid. After filtering to remove the dark solid, the solvent mixture was removed by vacuum rotary evaporation, resulting in 5.36 g of the expected product, which is a fine white powder. (Yield = 85.3%)

^{31}P NMR (202 MHz, $CDCl_3$): δ 17.31 (m, J ≈ 4.4 Hz, 2P)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, J = 12.6, 8.4 Hz, 4H, aromatic), δ 7.19 (dd, J = 8.5, 3.1 Hz, 4H, aromatic), δ 4.68 (dp, J = 7.9, 6.1 Hz, 4H, O-C(H)-CH3), δ 1.31 (dd, 24H, O-C-CH3)

^{13}C NMR (500 MHz, $CDCl_3$): δ 145.13 (s, 2C), δ 133.50 (d, J = 10.95 Hz, 4C), δ 122.65 (s, 2C), δ 116.97 (s, 4C), δ 70.50 (d, J = 5.54 Hz, 4C), δ 24.00 (dd, J = 25.6, 4.4 Hz, 8C)

m/z: 498.22 ($[M+H]^+$), 995.43 ($[2M+H]^+$)

(2A) 3,6-bis(diisopropylphosphono)-9H-carbazole [iPr$_4$DPC]

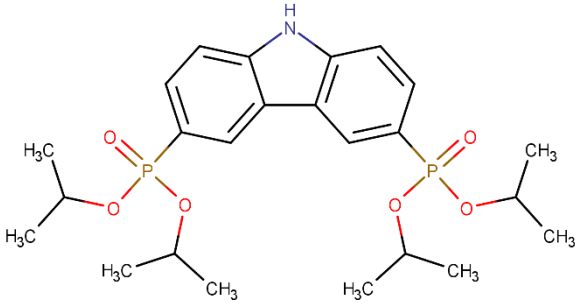


Figure 4: Chemical structure of iPr$_4$DPC (2A).

3,6-dibromo-9H-carbazole (5.0 g, 15.4 mmol) was placed into a screw powder addition funnel and attached to a 100 mL round-bottom flask. Triisopropyl phosphite (52.5 mL, 214 mmol, 7 equivalents) and anhydrous nickel chloride (13 mol%) were then added to the round-bottom flask and set to reflux (160 °C) under argon. Once the mixture in the round-bottom had reached temperature, the 3,6-dibromo-9H-carbazole was added slowly over 1.5 hours and monitored via TLC. Once the addition was complete, the reaction mixture was left for a further 2.5 hours and monitored by TLC to identify when the reaction had gone to completion. After 2.5 hours, the flow of argon had already removed the bulk of the excess phosphite, resulting in a pink-brown sticky mixture. This was washed overnight in hexane, resulting in the formation of a pale pink/off-white

powder. This was isolated by vacuum filtration and washed in acetone. This resulted in 6.26 g of the target product, an off-white powder. (Yield = 86.1%)

^{31}P NMR (202 MHz, $CDCl_3$): δ 18.63 (s, 2P)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H, N-H), δ 8.66 (d, J = 15.1 Hz, 2H, aromatic), δ 7.91 (ddd, J = 12.4, 8.3, 1.4 Hz, 2H, aromatic), δ 7.55 (dd, J = 8.4, 3.1 Hz, 2H, aromatic), δ 4.75 (dp, J = 8.0, 6.2 Hz, 4H, CH), δ 1.35 (dd, J = 83.4, 6.2 Hz, 24H, O-C-(CH3)2)

^{13}C NMR (500 MHz, $CDCl_3$): δ 141.98 (s, 2C), δ 129.68 (d, J = 11.76 Hz, 2C), δ 125.40 (s, J = 10.87 Hz, 2C), δ 122.84 (s, 2C), δ 121.40 (s, 2C), δ 110.96 (d, J = 16.55 Hz, 2C), δ 70.66 (d, J = 5.36 Hz, 4C), δ 24.04 (dd, J = 25.9, 4.1 Hz, 8C)

m/z: 496.2 ($[M+H]^+$), 991.39 ($[2M+H]^+$)

(3A) 4-diisopropylphosphono-*N*-(4-diisopropylphosphonophenyl)-*N*-phenylaniline [iPr$_4$DPPA]

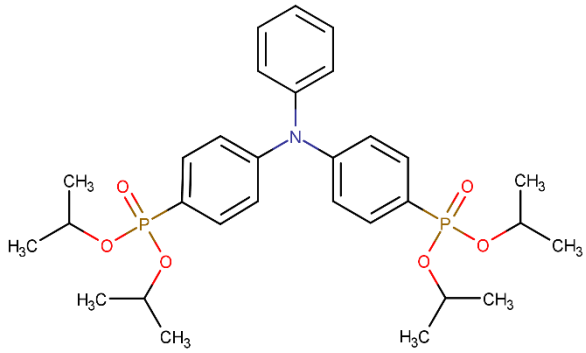


Figure 5: Chemical structure of iPr$_4$DPPA (3A).

4-bromo-N-(4-bromophenyl)-N-phenylaniline (3.0 g, 7.4 mmol) was placed into a screw powder addition funnel and attached to a 100 mL round-bottom flask. Triisopropyl phosphite (25.7 mL, 104.2 mmol, 7 equivalents) and anhydrous nickel chloride (13 mol%) were then added to the round-bottom flask and set to reflux (160 ◦C) under argon. Once the mixture in the round-bottom had reached temperature, the 4-bromo-N-(4-bromophenyl)-N-phenylaniline was added slowly over 2.5 hours and monitored

via TLC. Once the addition was complete, the reaction mixture was left for a further 3 hours and monitored by TLC to identify when the reaction had gone to completion. After 3 hours, the gas flow rate was increased in order to remove excess phosphite and remaining byproducts. The mixture was then left to cool and became a sticky, treacle-like substance, and was subsequently washed overnight in hexane, resulting in the formation of a fine white solid. The hexane was decanted, and the powder again washed in hexane. (Yield = 93.2%)

^{31}P NMR (202 MHz, $CDCl_3$): δ 17.02 (m, 2P)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (dd, J = 12.8, 8.2 Hz, 4H, Aromatic), δ 7.36 (t, J = 7.8 Hz, 2H, Aromatic), δ 7.20 (t, J = 7.5 Hz, 1H, Aromatic), δ 7.15 (d, J = 8.1 Hz, 2H, Aromatic), δ 7.12 (dd, 4H, Aromatic), δ 4.73 (h, J = 6.6 Hz, 4H), δ 1.34 (dd, J = 55.1, 6.2 Hz, 24H).

^{13}C NMR (500 MHz, $CDCl_3$): δ 150.25 (s, 2C), δ 146.08 (s, 1C), δ 133.03 (d, J = 10.80 Hz, 4C), δ 129.84 (s, 2C), δ 126.54 (s, 2C), δ 125.27 (s, 2C), δ 123.95 (s, 1C), δ 122.46 (d, J = 15.5 Hz, 4C), δ 70.63 (d, J = 5.7 Hz, 4C), δ 70.63 (dd, J = 21.3, 4.4 Hz, 8C)

m/z: 574.2 ($[M+H]^+$)

Phosphonic Acid Synthesis through Silylation and Hydrolysis

(1B) *N*,*N*-Bis(4-phosphonophenyl)amine [H_4BPA]

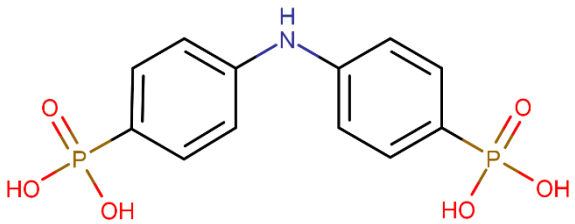


Figure 6: Chemical structure of H_4BPA (1B).

iPr_4BPA (2.0 g, 4.02 mmol) was dissolved in approximately 50 mL of acetonitrile inside a 100 mL round bottom flask and flushed with argon. The temperature of the vessel

was then set to 65 °C. Trimethylbromosilane (3.7 mL, 28.14 mmol) was then added to the flask, resulting in a colour change of the solution to a blue colour. After one and a half hours, TLC showed that the starting material had already been consumed, thus the heating was turned off and the solution allowed to cool. Once sufficiently cooled, rotary evaporation was used to remove the solvent, acetonitrile, resulting in a blue oil. On treatment of this oil with water, a white solid began forming. Water was then progressively added until no oil remained. The white solid was then washed with water and acetone. (Step yield = 82.6%)

^{31}P NMR (202 MHz, 0.1M NaOH in D_2O): δ 12.39 (s, 2P)

^{1}H NMR (500 MHz, 0.1M NaOH in D_2O): δ 7.50 (dd, J = 11.6, 8.1 Hz, 4H, aromatic), δ 7.05 (d, J = 8.6 Hz, 4H, aromatic)

^{13}C NMR (500 MHz, 0.1M NaOH in D_2O): δ 143.43 (s, 2C), δ 133.70 (s, 2C), δ 131.53 (d, J = 9.8 Hz, 4C), δ 116.81 (d, J = 13.3 Hz, 4C)

m/z: 163.5 ($[M-2H]^{2-}$), 163.5 ($[M-H]^{-}$)

(2B) 3,6-diphosphono-9H-carbazole [H_4DPC]

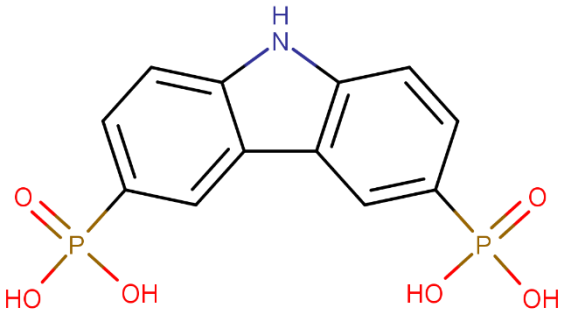


Figure 3: Chemical structure of H_4DPC (2B).

iPr_4DPC (3.0 g, 6.05 mmol) was partially dissolved in approximately 100 mL of acetonitrile inside a 250 mL round bottom flask and flushed with argon. Trimethylbromosilane (5.6 mL, 42.4 mmol) was then added to the flask, resulting in a

colour change of the solution to a blue colour. The temperature was then set to 65 °C and left to react for five and a half hours and monitored via TLC. Once the starting material was consumed, the heating was turned off and the solution allowed to cool. Once sufficiently cooled, rotary evaporation was used to remove the solvent, acetonitrile, resulting in a blue oil. On treatment of this oil with water, a white solid began forming. Water was then progressively added until no oil remained. The white solid was then washed with water and acetone. (Yield = 93.0%)

^{31}P NMR (202 MHz, 0.1M NaOH in D_2O): δ 12.91 (t, J = 11.7 Hz, 2P)

^{1}H NMR (500 MHz, 0.1M NaOH in D_2O): δ 8.41 (d, J = 12.2 Hz, 2H, aromatic), δ 7.72 (dd, J = 10.9, 8.3 Hz, 2H, aromatic), δ 7.46 (dd, J = 8.2, 2.3 Hz, 2H, aromatic)

^{13}C NMR (500 MHz, 0.1M NaOH in D_2O): δ 140.15 (s, 2C), δ 128.38 (s, 2C), δ 122.18 (s, 4C), δ 110.22 (s, 4C) - Intensity not great enough for full characterisation.

m/z: 162.5 ($[M-2H]^{2-}$), 325.99 ($[M-H]^{-}$)

(3B) 4-phosphono-*N*-(4-phosphonophenyl)-*N*-phenylaniline [H_4DPPA]

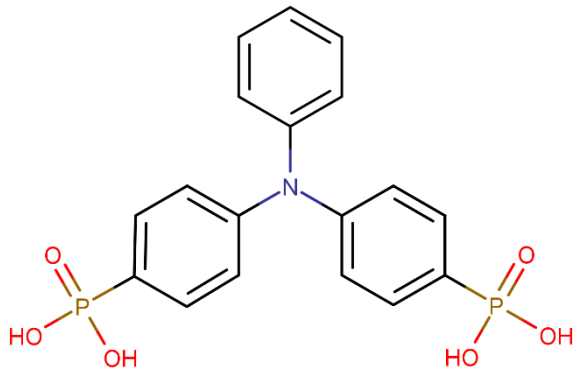


Figure 7: Chemical structure of H_4DPPA (3B).

iPr_4DPPA (2.5 g, 3.46 mmol) was dissolved in approximately 10 mL of acetonitrile inside a 100 mL round bottom flask, resulting in a clear light green solution, and was then flushed with argon. Trimethylbromosilane (2.8 mL, 30.5 mmol) was then added to the flask, resulting in a colour change of the solution to a blue colour. The temperature

was then set to 65 °C and left to react for four hours and monitored via TLC. Once the starting material was consumed, the heating was turned off and the solution allowed to cool. Once sufficiently cooled, rotary evaporation was used to remove the solvent, acetonitrile, resulting in a blue oil. On treatment of this oil with water, a white solid began forming. Water was then progressively added until no oil remained. The white solid was then washed with water and acetone. (Yield = 94.2%)

^{31}P NMR (202 MHz, 0.1M NaOH in D_2O): δ 11.32 (t, J = 11.2 Hz, 2P)

^{1}H NMR (500 MHz, 0.1M NaOH in D_2O): δ 7.52 (dd, J = 11.2, 8.0 Hz, 4H, Aromatic), δ 7.29 (t, J = 7.7 Hz, 2H, Aromatic), δ 7.13 (d, J = 7.9 Hz, 2H), δ 7.07 (t, J = 7.5 Hz, 1H, Aromatic), δ 7.03 (d, J = 6.1 Hz, 4H)

^{13}C NMR (500 MHz, 0.1M NaOH in D_2O): δ 133.97 (d, 4C), δ 132.11 (s, 2C), - Intensity not great enough for full characterisation.

m/z: 162.5 ($[M-2H]^{2-}$), 325.99 ($[M-H]^{-}$)

Supporting Information

Supporting Information File 1:

File Name: Shearan - BJOC - Supporting Info

File Format: MS Word document

Content: NMR Spectra, MS spectra, and respective discussions.

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