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Bis(triphenylphosphine)palladium(II)phthalimide – an easily prepared precatalyst for efficient Suzuki–Miyaura coupling of aryl bromides

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Abstract

In this paper we report the synthesis and application of a novel palladium(II) complex, bis(triphenylphosphine)palladium(II)phthalimide **1**. Its utility in the Suzuki-Miyaura coupling of aryl bromides with a variety of aryl- and heteroarylboronic acids, under relatively mild conditions, is described. Complex **1** is easily prepared from tetrakis(triphenylphosphine)palladium(0) and phthalimide in 78% yield and is air, light and moisture stable. On following the kinetics of the cross-coupling reaction of 4-nitro-1-bromobenzene with phenylboronic acid, mediated by **1** (1 mol%) in THF/aqueous 1 M Na_2CO_3 (1/1, v/v) at 60 °C, an initial induction period is observed, indicating that **1** is a precatalyst. The described work extends on our recent finding that 'imidate' type ligands have an influence in palladium-catalysed cross-coupling processes.

Keywords: Palladium; Cross-coupling; Biaryls; Heteroaryls; Catalysis

1. Introduction

Palladium-catalysed carbon-carbon and carbon-heteroatom bond-forming technologies represent some of the most applied and important transformations in organic synthesis [1,2]. Examples include Hartwig–Buchwald amination [3], Heck [4], Negishi [5], Sonogashira [6,7], Stille [8,9] and Suzuki–Miyaura [10–13] coupling processes. The last two reactions are arguably the most important in natural product and materials synthesis, and although Stille coupling at the present time is the most powerful, Suzuki–Miyaura coupling is of increasing importance in industry. This is particularly in the pharmaceutical sector where tin toxicity, as well as the problems associated with the removal of tin byproducts, limits the use of the Stille methodology. Suzuki–Miyaura coupling, in which organohalides react with organoboronic acids in the presence of base and a Pd(0) catalyst, or a Pd(II) precatalyst, is particularly useful, as it occurs generally under mild conditions and does not produce toxic waste or side-products, which might contaminate final products (Eq. (1)).

$$R - X + R' - B(OH)_2 \xrightarrow[\text{Base}]{[Pd]} R - R' \quad (1)$$

This process has recently become a benchmark reaction by which new catalysts/precatalysts are screened and tested. Indeed, highly active Pd-catalysts have been developed by a number of research groups over the last 5 or so years [14–32]. The catalyst activity is usually tuned or attenuated through changes in the coordinating ligand for palladium. Here, use of electron-rich alkyl phosphines, such as $(t\text{-Bu})_3P$ or biphenyl$(t\text{-Bu})_2P$ as well as others, *N*-heterocyclic carbenes or phosphinites represent the most important, recently developed ligand systems [14]. Various electronic (σ-donor and/or π-acceptor) and steric (changes in bite and cone angles) properties of these ligands are important in tuning the reactivity of the nucleophilic low-coordinated d^{10} Pd(0) centre—the species that is often considered the active catalyst species, whether anionic or neutral (vide infra). The number of available Pd(0) catalysts has been expanded upon recently, most notably by Beller and co-workers [33,34], although the air and moisture sensitivity of these catalysts, which require some special handling and storage, could

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limit their utility. Pd(II) complexes, usually d^8/16-electron species, are more stable and may be stored for prolonged periods without any deleterious loss of activity observed.

Classically, it has been assumed that Pd(II) precatalysts are reduced to give an active Pd(0) species, although recent studies by Amatore and Jutand have demonstrated that halide ligands from Pd(II) precatalysts, or the halide substrate, could play a decisive role in the catalytic cycle – anionic Pd(0) species containing one halide ligand, of the type $[L_2Pd(0)X]^-$ (L = R_3P), have been implicated [35,36]. Somewhat surprisingly, the role of the halide ligand [37] in palladium(II) precatalysts has received little attention, particularly with respect to activity and substrate selectivity. Recent observations by our group suggest that alteration of this ligand could influence the catalytic properties of the active palladium species, whether that be an anionic or neutral Pd(II) or Pd(0) species. The availability of only four halides (F, Cl, Br and I) is quite restrictive in tuning the catalytic properties of the palladium centre, albeit still quite revealing. However, access to a plethora of pseudohalide ligands, such as alkoxides, acetate and imides, allows us to probe their effect, if any, in classical Pd-catalysed cross-coupling processes. Imidate ligands, such as deprotonated succinimide, maleimide and derivatives, and phthalimide have been described as pseudohalides, exerting potentially exploitable effects for metal centres [38]. Imidates may also act as hemilabile ligands, deriving from their ability to act as either monodentate or bidentate ligands (*N*–bonded, C=O→Pd coordination) [39,40]. In this paper, we detail the synthesis of a novel palladium complex, namely bis(triphenylphosphine)palladium(II)phthalimide **1**, and its application as an efficient precatalyst for Suzuki–Miyaura coupling of aryl bromides with aryl and heteroarylboronic acids.

2. Results and discussion

The oxidative addition of succinimide to $(Ph_3P)_4Pt$ and $(Ph_3P)_4Pd$, to give $(Ph_3P)_2Pt(N\text{-Succ})H$ and $(Ph_3P)_2Pd(N\text{-Succ})_2$, respectively, has been investigated by Roundhill [41] and ourselves [42]. In analogous fashion, we have found that the readily available complex, $(Ph_3P)_4Pd$, reacted with two equivalents of phthalimide in benzene at 25 °C for 15 h to give the novel *trans*-complex **1** in 78% yield (Fig. 1).

The mechanism by which complex **1** is formed appears unusual. It was proposed by Roundhill that a Pd(IV) species could be a transient intermediate to **1**– rapid reductive elimination of H_2 is expected [43]. Such a species was also proposed by Colquhoun and co-workers for the oxidative addition of succinimide to low-valent metal centres [38]. It is also possible that **1** is formed by σ-bond metathesis, which would also result in H_2 production. The ^{31}P NMR spectrum of **1** in $CDCl_3$ exhibits one singlet at δ 20.13, although the geometry around the palladium centre cannot be confirmed by this, as the phosphorus signal for both the *cis*- and *trans*-isomers would be expected to appear as a singlet, due to symmetry. Single crystals of **1** suitable for

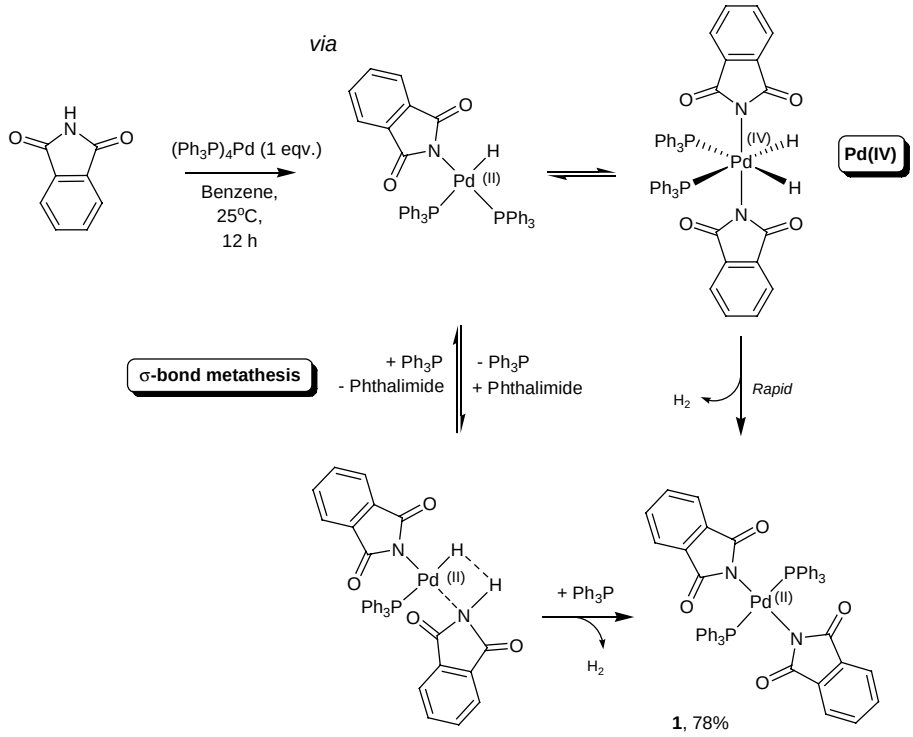


Fig. 1. Synthesis of **1** from $(Ph_3P)_4Pd$ and two equivalents of phthalimide in benzene at 25 °C.

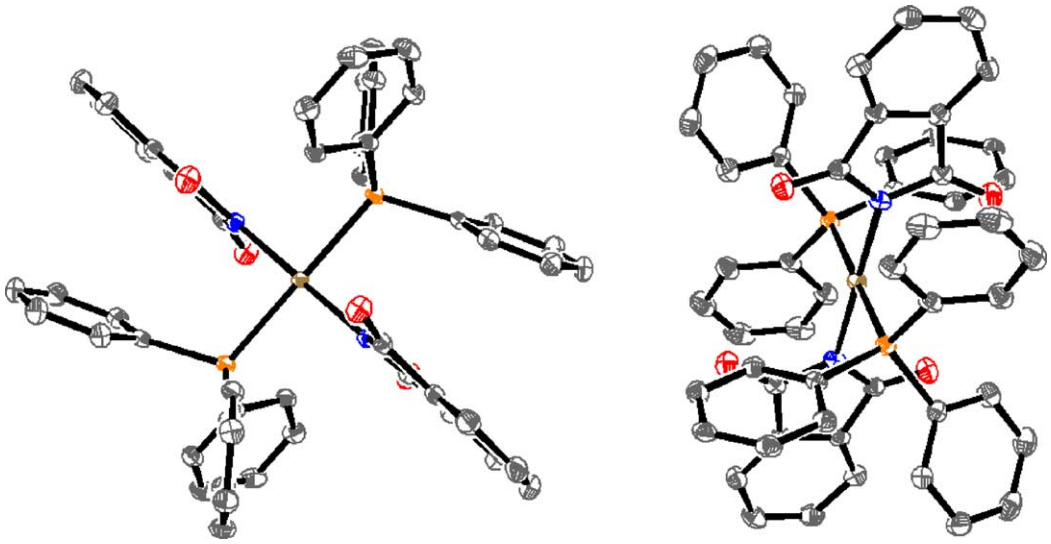


Fig. 2. ORTEP representation of complex **1**. Thermal ellipsoids are drawn at 50% probability.

X-ray analysis were grown from dichloromethane (0.83 M solution) by slow evaporation over 72 h at 20 °C [44].

The X-ray crystallographic data confirms the *trans*-geometry around the Pd-centre. The unit cell contains two molecules (Fig. 2)[1].

It is interesting to note that the carbonyl groups exhibit moderate π–π-stacking interactions with alternatively positioned aromatic groups (from Ph_3P) and that the phthalimide ligands deviate slightly from the plane, minimizing interactions with the nitrogen lone pair electrons (dihedral angle: C5−N2−N1−C1, $\theta = 6°$). This deviation is less than that seen in bis(triphenylphosphine)palladium(II)succinimide (dihedral angle: C5−N2−N1−C1, $\theta = 13°$). It is also noted that there is negligible π–π-stacking between molecules – moderate face-to-edge and edge-to-edge stacking interactions are observed.

2.1. Suzuki–Miyaura coupling mediated by *1*

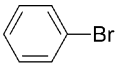
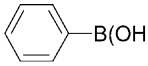
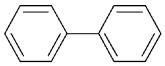
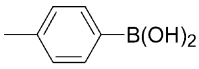
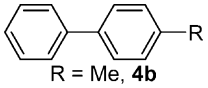
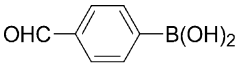
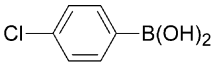
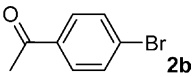
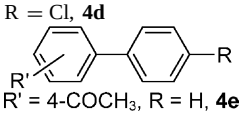
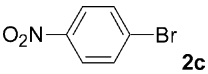
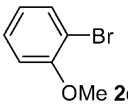
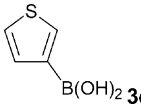
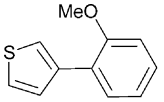
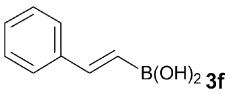
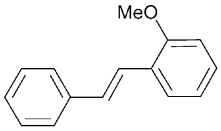
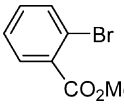
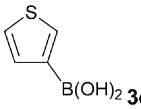
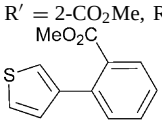
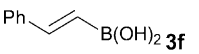
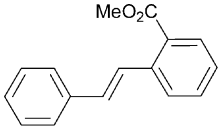
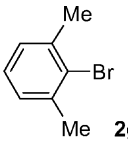
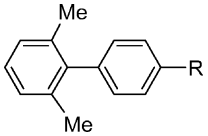
The reactions of selected benchmark activated and deactivated aryl bromides (**2a-g**) with four arylboronic acids (**3a-d**), an alkenylboronic acid (**3e**) and a heteroarylboronic acid (**3f**) were carried out, in the presence of 1 mol% of **1** (lowering the catalyst loading to 0.1 mol% generally results in lower product conversions) at 60 °C in a THF/1 M aqueous Na_2CO_3 solvent mixture, to give the cross-coupled products (**4a-v**, Table 1). In the first example, bromobenzene **2a** reacted with phenylboronic acid **3a** in 3 h to give biphenyl **4a** in 85% yield (entry 1). The more activated arylboronic acid **3b** coupled to **2a** to give **4b** in 89% yield, again after 3 h (entry 2). Similarly, the less reactive arylboronic acids **3c** and **3d** reacted with **2a** to give **4c** and **4d** in 79% and 91%, respectively (entries 3 and 4). The activated aryl bromide substrates **2b** and **2c** reacted with **3a-d** to give **4e-f** and **4h-l** in yields >81%, with the exception of the cross-coupling of **2b** with **3c** to give **4g** which proceeded in 69% yield – all these reactions were complete in essentially 4 h or less (entries 5–12). The deactivated substrate **2e** reacted with **3a** to give 2-methoxybiphenyl **4m** in 76% yield in 6 h (entry 13). Indeed, substrate **2e** further reacted with **3e** and **3f** to give the cross-coupled products **4n** and **4o** in 77% and 68% yields, respectively, again after 6 h (entries 14 and 15), demonstrating that vinylboronic acids and heteroarylboronic acids can be employed successfully. The activated substrate **2f** reacted with **3a** to give **4p** in 81% yield after 5 h (entry 16). In a similar manner to **2e**, substrate **2f** reacted with **3e** and **3f** to give **4q** and **4r** in 71% and 80% yields, respectively (entries 17 and 18). These results demonstrate that activated and deactivated substrates with *ortho*-substituents are tolerated, which are often problematic in coupling reactions mediated by more bulky ligand systems [44]. In the last set of examples, the sterically hindered and deactivated substrate **2g** was shown to cross-couple with **3a-d** to give the coupled products **4s-v** in yields >68% in reaction times (12–15 h) that were slightly longer than that seen above (entries 19–22).

2.2. Suzuki–Miyaura coupling of a brominated 2-pyrones

Interest in coupling heteroaromatic ring systems, clearly, stems from the use of heteroaromatic moieties in medicinal and biologically relevant targets. However, it is often the case that classic coupling reactions fail to produce yields of products comparable to reactions giving simple biaryls.

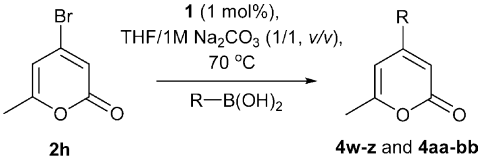
[1] The X-ray structure of **1** has been deposited to the Cambridge crystallographic database (UK): CCDC 237081. Crystal data for $PdP_2O_4N_2C_{52}H_{38}$: M = 923.18, triclinic, space group *P-1*, $a = 10.6513(14)$ Å; $b = 11.7510(15)$ Å; $c = 18.594(2)$ Å, $\beta = 103.620(3)°$, $V = 2058.6(4)$ Å^3, $Z = 2$, $T = 115(2)$ K, $D_c = 1.489$ Mg/m^3, μ(Mo-Kα) 0.580 mm^{-1}, $R1 = 0.0387$, $wR2 = 0.0727$, GOF = 1.033 for 553 parameters and 11774 reflections. Data collection on a Bruker Smart CCD. Structure solution and refinement was performed using the program SHELXL-97.

Table 1
Suzuki cross-coupling of aryl halides and organoboronic acids mediated by $(Ph_3P)_2Pd(N\text{-Phthal})_2$ **1**

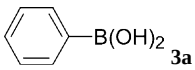
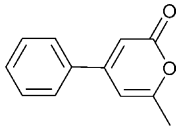
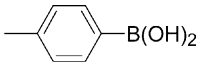
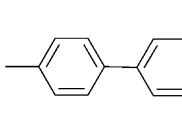
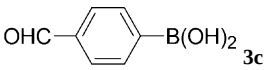
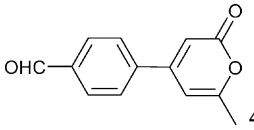
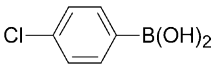
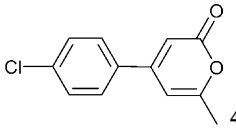
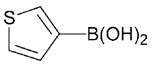
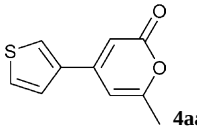
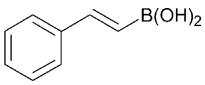
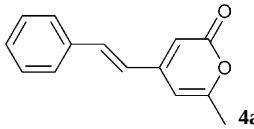
Entry	Aryl bromide	Aryl boronic acid	Product	Time (h)	Yield (%)
1	 **2a**	 **3a**	 **4a**	3	85
2	**2a**	 **3b**	 R = Me, **4b**	3	89
3	**2a**	 **3c**	R = CHO, **4c**	3	79
4	**2a**	 **3d**	R = Cl, **4d**	3	91
5	 **2b**	**3a**	 R' = 4-$COCH_3$, R = H, **4e**	3	88
6	**2b**	**3b**	R′ = 4-$COCH_3$, R = Me, **4f**	3	81
7	**2b**	**3c**	R′ = 4-$COCH_3$, R = CHO, **4g**	3	69
8	**2b**	**3d**	R′ = 4-$COCH_3$, R = Cl, **4h**	4	86
9	 **2c**	**3a**	R′ = 4-NO_2, R = H, **4I**	4	91
10	**2c**	**3b**	R′ = 4-NO_2, R = Me, **4j**	4	90
11	**2c**	**3c**	R′ = 4-NO_2, R = CHO, **4k**	4	82
12	**2c**	**3d**	R′ = 4-NO_2, R = Cl, **4l**	4	85
13	 **2e**	**3a**	R′ = 2-OMe, R = H, **4m**	6	76
14	**2e**	 **3e**	 **4n**	6	77
15	**2e**	 **3f**	 **4o**	6	68
16	 **2f**	**3a**	R′ = 2-CO_2Me, R = H, **4p**	5	81
17	**2f**	 **3e**	 **4q**	5	71
18	**2f**	 **3f**	 **4r**	5	80
19	 **2g**	**3a**	 R = H, **4s**	12	77
20	**2g**	**3b**	R = Me, **4t**	12	80
21	**2g**	**3c**	R = CHO, **4u**	15	68
22	**2g**	**3d**	R = Cl, **4v**	15	83

Reaction conditions: aryl bromide (1.05 eqv.), organoboronic acid (1.0 eqv.), **1** (1 mol%), 1 M Na_2CO_3, THF, 60 °C (unless otherwise stated). Isolated yields after chromatography.

Table 2
Suzuki cross-coupling of **2h** and organoboronic acids mediated by $(Ph_3P)_2Pd(N\text{-Phthal})_2$**1**



2h **4w-z** and **4aa-bb**

Entry	Aryl boronic acid	Product	Time (h)	Yield (%)
1	 **3a**	 **4w**	6	86 (56)
2	 **3b**	 **4x**	6	85 (52)
3	 **3c**	 **4y**	8	74 (20)
4	 **3d**	 **4z**	10	88 (53)
5	 **3e**	 **4aa**	6	90 (–)
6	 **3f**	 **4ab**	2	88 (27)

Reaction conditions: **2h** (1.05 eqv.), organoboronic acid (1.0 eqv.), **1** (1 mol%), 1 M Na_2CO_3, THF, 60 °C (unless otherwise stated).
Isolated yields after chromatography. Numbers in brackets are yields from reactions employing $Pd(OAc)_2$ (6 mol%), Ph_3P (18 mol%), Na_2CO_3 (2 M), EtOH/benzene (1/1, v/v) at reflux (~90 °C) taken from reference [45].

Alternative processes, such as hydrodehalogenation and homocoupling, may become involved to the extent that they can be major competing reaction pathways. Thus, in the search for more active and selective catalysts/precatalysts, it is important to screen more unusual, but challenging, substrates that contain heteroaromatic ring-systems. For medicinal targets it is desirable to employ reactions that avoid toxic side-products, which is one of the distinct advantages of Suzuki–Miyaura coupling (vide supra). Lowering catalyst loadings also reduces the amount of trace quantities of palladium present in the final products. In recent work, we have applied Suzuki–Miyaura methodology to the synthesis of novel chemotherapeutic agents based on the 2-pyrone-ring system [45–48]. The electrophilic partner is 4-bromo-6-methyl-2-pyrone **2h**, which we have established is a relatively activated substrate. Optimised conditions were developed, so as to avoid 2-pyrone ring-opening and/or rearrangement, that are essential for high yields (standard conditions: $Pd(OAc)_2$ (6 mol%), Ph_3P (18 mol%), 2 M Na_2CO_3, EtOH/benzene (1/1, v/v), reflux (~90 °C). In an effort to obtain higher yields, under less forcing conditions, Suzuki–Miyaura coupling of **2h** with **3a-f**, mediated by **1** were investigated (Table 2).

On initial inspection of Table 2, it is clear that **1** is able to efficiently mediate the cross-coupling of **2h** with organoboronic acids **3a-f**. In all cases, with the exception of **3e**, higher yields and more purer products (>90%; in selected examples >95%, pure by inspection of the ^1H NMR spectra of the crude products) are obtained compared to those previously reported, using $Pd(OAc)_2$ as the catalyst [45]. For example, **3a** reacted with **2h** to give **4w** in 86% yield after 6 h, which compares to 56% under our previous best conditions (entry 1, Table 2). 4-Methylphenylboronic acid **3b** reacts equally well with **2h** to give **4x** in 85% after 6 h, again comparing favourably to our previous best (entry 2). The yield from the less activated 4-formylphenylboronic acid **3c** improves tremendously on our previous best (entry 3). A further improvement is also seen for 4-chlorophenylboronic

acid **3d** (entry 4). 3-Thiopheneboronic acid **3e** reacts equally well with **2h** to give compound **4aa** in 90% yield (entry 5). In the last example, *E*-phenylethenylboronic acid **3f** reacts in less than 2 h to give **4ab** in 88% yield, which improves significantly on the 27% yield previously reported (entry 6).

The synthetic results clearly demonstrate the versatility of **1** under relatively low catalyst loading conditions, not only for simple aryl systems but also for the more demanding heterocyclic 2-pyrones.

In an effort to determine whether **1** is a precatalyst or the actual catalyst, the evolution of product **4i** from the cross-coupling of 4-nitro-bromobenzene **2c** with **3a** was followed by the withdrawal of small aliquots of the reaction mixture by gas-tight syringe under an atmosphere of N_2 at appropriate time intervals – samples were quenched by passage through a short silica-plug eluted with CH_2Cl_2 and then a solution of dppe added to ensure that the sample had been completely quenched for accurate gas chromatographic analysis of the reaction kinetics (at room temperature) [49]. The formation of **4i** and disappearance of **2c** are shown in Fig. 3.

The kinetic profile indicates an induction period in the initial stages of the reaction (∼0.25 h). The formation of a trace quantity of biphenyl (∼0.01 eqv.) is noted at this point – the amount of which does not increase throughout the course of the reaction, indicating it was formed during the induction period. After 0.5 h, the reaction enters into a linear regime until it reaches ∼80% conversion at 3 h. A retardation in rate is seen at this point, and after 5 h a 97% conversion to **4i** is observed. The induction period and the formation of biphenyl, presumably formed through reaction of Pd(II) with two equivalents of **3a** (per Pd) to generate "$(Ph_3P)_2Pd(0)$", imply that **1** is a precatalyst. At this point, the question as to whether phthalimidate is involved throughout the remaining course of the reaction needed to be addressed. Clearly, it is possible that its effect is to activate the organoboronic acid to undergo transmetallation (Scheme 1).

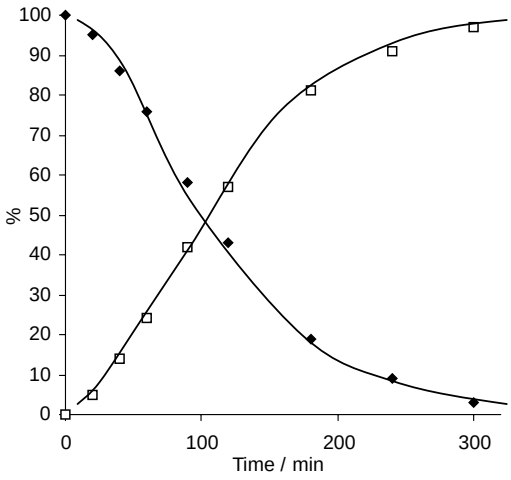
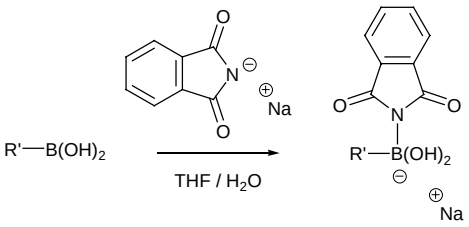


Fig. 3. Kinetic profile for the reaction of **2c** and **3a** mediated by **1** to give **4i** (1 mol%).



Scheme 1. Possible activation of the organoboronic acid by sodium phthalimide.

To address this issue, a profile of the reaction of **2c** with **3a** (illustrating the disappearance of **2c**) mediated by $(Ph_3P)_4Pd$ (1 mol%) with one equivalent of sodium phthalimide (NaPhthal) was generated (by GC analysis). The stoichiometric reaction was carried out in the presence and absence of aqueous 1 M Na_2CO_3. A reaction profile is shown for $(Ph_3P)_4Pd$ with 2 mol% NaPhthal, under the standard reaction conditions. For comparison, the profile from the reaction mediated by **1** is included (Fig. 4).

The profiles under the different reaction conditions are quite revealing. Firstly, the reaction mediated by $(Ph_3P)_4Pd$ in the presence of NaPhthal (1 eqv.) in THF/1 M Na_2CO_3 at 60 °C showed a lengthy induction period. After 3 h the reaction began to turn over at a relatively modest rate (∼40% conversion to **4i** after 6 h). In the absence of 1 M Na_2CO_3, the same reaction results in negligible conversion after 6 h (<3%). Both reaction profiles indicate that NaPhthal does not activate **3a**. The reaction in the presence of only 0.02 equivalents of NaPhthal exhibited a profile similar to the profile observed for the reaction mediated by **1** under the same conditions, albeit with a slightly longer induction pe-

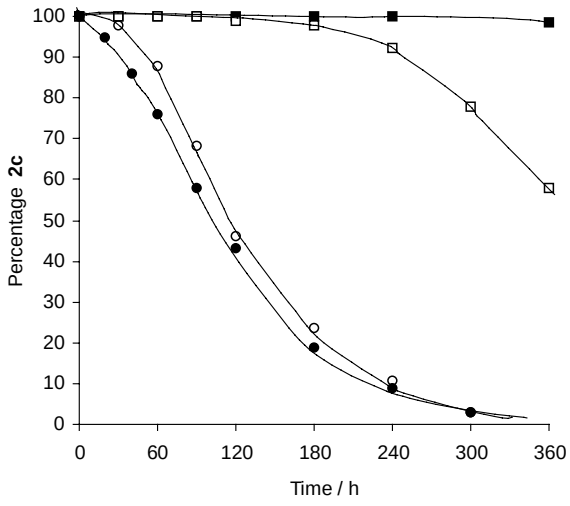


Fig. 4. Kinetic profiles for the reaction of **2c** and **3a** to give **4i**: open square, mediated by $(Ph_3P)_4Pd$ (1 mol%) in THF/1 M Na_2CO_3 (1/1, v/v) in the presence of sodium phthalimide (1 eqv.) at 60 °C; closed square, mediated by $(Ph_3P)_4Pd$ (1 mol%) in THF/H_2O (1/1, v/v) in the presence of sodium phthalimide (1 eqv.) at 60 °C; open circle $(Ph_3P)_4Pd$ (1 mol%) in THF/1 M Na_2CO_3 (1/1, v/v) in the presence of sodium phthalimide (0.02 eqv.) at 60 °C; closed circle, mediated by **1** (1 mol%) in THF/1 M Na_2CO_3 (1/1, v/v).

riod. After 1 h, the reaction profile enters a linear regime, reaching 97% conversion after 5 h.

3. Conclusions

In conclusion, we have synthesised the novel palladium(II) complex **1** and applied it to the successful Suzuki–Miyaura coupling of a range of aryl and heteroaryl bromides with aryl, vinyl and heteroarylboronic acids under relatively low catalyst loadings. Complex **1** is easy to synthesise, may be stored for prolonged periods and is air, light and moisture stable. Furthermore, a marked improvement in the yields of the cross-coupling products from the brominated 2-pyrone **2h** was seen over our previous best conditions. We have determined that sodium phthalimide does not activate the organoboronic acid. The true involvement of this imidate ligand, amongst others, as well as its effect in promoting Pd-catalysed cross-coupling processes, is part of on-going studies in our group.

4. Experimental

THF was dried over sodium–benzophenone ketyl (distilled prior to use). Benzene was distill over calcium hydride (distilled prior to use). All reactions were conducted under an inert atmosphere of Ar or N_2 on a Schlenk line. $Pd(PPh_3)_4$ was prepared by reduction of $(Ph_3P)_2PdCl_2$ with hydrazine [50]. $(PPh_3)_2PdCl_2$ was prepared from $PdCl_2$ in refluxing DMSO and PPh_3 (2 eqv.) using a known procedure [51]. Melting points were recorded on an electrothermal IA9000 Digital Melting Point Apparatus and are uncorrected. TLC analysis was performed on Merck 5554 aluminum-backed silica gel plates and compounds visualised by ultraviolet light (254 nm), phosphomolybdic acid solution (5% in EtOH), or 1% ninhydrin in EtOH. ^{1}H NMR spectra were recorded at 270 MHz using a JEOL EX270 spectrometer or at 400 MHz using a JEOL ECX400 spectrometer; ^{13}C NMR spectra at 67.9 or 100.5 MHz. Chemical shifts are reported ins parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz).

GC conditions: Analysis was performed using a Varian CP-3800 GC equipped with a CP-8400 Autosampler. Separation was achieved using a DB-1 column (30 m × 0.32 mm, 0.25 μm film thickness) with carrier gas flow rate of 3 mL min^{-1} and a temperature ramp from 50 to 250 °C at 20 °C min^{-1}. The injection volume was 1 μL with a split ratio of 50.

4.1. Typical Suzuki reaction

All reactions were performed in a Radleys carousel adapted for rigorous inert atmosphere reactions. Phenylboronic acid (50 mg, 0.41 mmol), bromobenzene (70.7 mg, 0.45 mmol), Na_2CO_3 (1 M (aqueous), 1 mL), THF (1.5 mL) and catalyst **1** (3.3 mg, 4.1 μmol, 0.01 eqv.) were degassed via three 'freeze-pump-thaw' cycles. The resulting mixture was heated at 60 °C for the specified time. The reaction mixture was allowed to cool to room temperature and water (10 mL) added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography gave biphenyl as a white solid.

The following compounds characterized by ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry are known within the literature: biphenyl **4a** [52], 4-methylbiphenyl **4b** [45], 4′-formylbiphenyl **4c** [53], 4-chlorobiphenyl **4d** [46] 4-acetylbiphenyl **4e** [54], 4-acetyl-4′-methylbiphenyl **4f** [55], 4-acetyl-4′-formylbiphenyl **4g** [56], 4-acetyl-4′-chlorobiphenyl **4h** [57], 4-nitrobiphenyl **4i** [58], 4-nitro-4′-methylbiphenyl **4j** [59], 4′-nitro-biphenyl-4-carbaldehyde **4k** [60], 4-nitro-4′-chlorobiphenyl **4l** [61], 2-methoxybiphenyl **4m** [62], 3-(2-methoxyphenyl)thiophene **4n** [63], 2-methoxy-*trans*-stilbene **4o** [64], 2-methoxycarbonylbiphenyl **4p** [65], 3-(2-methoxycarbonylphenyl)thiophene **4q** [66], 2-methoxycarbonyl-*trans*-stilbene **4r** [67], 2,6-dimethylbiphenyl **4s** [68], 2,6-dimethyl-4′-methylbiphenyl **4t** [42], 2,6-dimethyl-4′-formylbiphenyl **4u** [42], 2,6-dimethyl-4′-chlorobiphenyl **4v** [69], 4-bromo-6-methyl-2-pyrone **2h** [48], 4-phenyl-6-methyl-2-pyrone **4w**, 4-(4′-methylphenyl)-6-methyl-2-pyrone **4x** [48], 4-(4′-formylphenyl)-6-methyl-2-pyrone **4y** [48], 4-(4′-chlorophenyl)-6-methyl-2-pyrone **4z** [48], 4-(2′-phenyl-*trans*-ethenyl)-6-methyl-2-pyrone **4ab** [48].

4.2. 3-(2-Methoxycarbonylphenyl)thiophene (*4q*)

Mp 151–152 °C; ν_{max} (CH_2Cl_2, cm^{-1}) 1643, 1558, 1459, 1430, 1317, 1249, 1054, 948, 875; ^{1}H NMR (400 MHz, $CDCl_3$) 2.24 (s, 3H), 6.22 (s, 1H), 6.27 (s, 1H), 7.29 (m, 1H), 7.37 (m, 1H), 7.61 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.14, 102.91, 106.61, 125.38, 125.77, 127.54, 137.33, 149.10, 162.076, 163.68. MS (EI) m/z 192 (M^+, 45), 177 (10), 164 (100), 135 (34), 121 (56), 91 (6), 77 (8), 69 (12), 43 (25).

4.3. [Bis(triphenylphosphine)(bis(N-phthalimide)) palladium(II)] (*1*)

Freshly prepared $(Ph_3P)_4Pd$ (170 mg, 0.147 mmol) was dissolved in dry benzene (10 mL) and *N*-phthalimide (43.3 mg, 0.294 mmol) was added. The solution goes from an intense yellow colour to a pale yellow after only a few minutes, and a white crystalline salt begins to slowly appear. After ∼12 h the solid was filtered (no special precautions), washed with benzene and dried in vacuo to give the complex as a white powder. A small quantity (∼30 mg) of the complex was crystallised from CH_2Cl_2/ether (1/5, v/v) to give colourless crystals. Yield: 106.4 mg, 78.5%; Mp = 247–248 °C; ν_{max} (CH_2Cl_2, cm^{-1}) 2986, 3054, 1664,

1266; MS(FAB) (m/z): 923 [(M + 1), [5]], 776 [(M-Phthal), [24]], 629 [((Ph$_3$P)$_2$Pd-1), [12]], 514 [(M-Phthal-Ph$_3$P, 23); IR (CH_2Cl_2, cm^{-1}) 1663; ^{1}H NMR (400 MHz, $CDCl_3$) 7.01–7.25 (30H, m), 7.75 (8H, m); ^{31}P NMR (162 MHz, $CDCl_3$) 20.04. Anal. Found: C, 67.72; H, 4.21; N 3.40. Calc. C, 67.65; H, 4.15; N, 3.03.

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