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COMMUNICATION

Iridium-catalysed 3,5-bis-borylation of phthalonitrile enables access to a family of C_{18} octaarylphthalocyanines

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Ir-catalysed borylation of phthalonitrile produces both 4-(Bpin)phthalonitrile (1) and 3,5-bis(Bpin)phthalonitrile (2), which are potential divergent intermediates for the synthesis of functionalized phthalocyanines. To exemplify the utility of 2, we have prepared a series of 3,5-bis-arylphthalonitriles that in turn undergo sterically controlled regioselective cyclotetramization to give previously unknown C_{18} 1,3,8,10,15,17,22,24-octaarylphthalocyanines.

Phthalocyanines (Pcs) have been extensively explored over recent decades for their use in dye-sensitized solar cells, single-molecule magnets, (photo)catalysis, and various cancer phototherapies, making them one of the most important classes of synthetic chromophores. PCs are commonly synthesized by thecyclization of four substituted phthalonitrile precursors around a metal-ion template. A recurring issue in Pcs chemistry is that the synthesis of substituted phthalonitrile precursors is often lengthy and hindered by the low reactivity of electron-poor phthalonitrile in S_{Ar} reactions. Here, we report our initial investigation into the use of sterically controlled Ir-catalysed C-H borylation to functionalize phthalonitrile that circumvents its unfavourable steric hindrance.

This study was further motivated by the ease with which aryl boronic acid pinacol ester (Bpin) groups introduced by this reaction might, in general, be converted to a wide range of other functional groups, including various amines, ethers, thioethers, (hetero)arenes, or to an azide, halide, nitro or alcohol group for further functionalization using known transformations. Such conversions can often be performed using one-pot borylation-functionalization methodologies, such as demonstrated by the cyanation of in situ generated arylboronic esters or their conversion to perfluoroalkyl groups, which would make this a versatile route for preparing substituted phthalonitriles.

Scheme 1. Synthesis of C_{18} octaarylphthalocyanines 6-10 starting from phthalonitrile. (a) Ir-catalysed borylation: 1.0 eq. B(pin), 1.5 mol% [Ir(COD)(OMe)]_2, 3.0 mol% dtbpy, MTBE, 1.0 M, r.t., 48 h. (b) Mizoroki-Heck coupling: 1.1 eq. 3,5-bis(R)bromobenzene (R = CF_3), 5 mol% Pd(dba)_2, 20 mol% Phos, 4.0 eq. CsF, 1,4-dioxane, 110 °C (19%), 50% (4), and 21% (5). (c) Yield of 3 increased to 68% using 4.0 eq. 3,5-bis(CF_3)iodobenzene, 4.0 eq. CsCO_3. (d) Demetallation: Acetic acid, 110 °C, 2 h. (e) One-pot macrocyclization-demetallation: (i) as (c) with Mg(OAc)_2, 4H_2O or Mg(OAc)_2·4H_2O (9), 1-pentanol, 1.0 eq. DBU, 132 °C [39% (6), 25% (7), 13% (8), 5% (9)]. (ii) Chloroform, 110 °C, 2 h. (iii) HCl (1 M, 5 mL), 60 °C, 16 h (9%). All yields are isolated. See ESI for further details.

Based on the steric, rather than electronic selectivity of Ir-catalysed borylation, it was expected that borylation of phthalonitrile using 1.0 eq. B(pin) (pin = pinacolato), 1.5 mol% [Ir(COD)(OMe)]_2, and 3.0 mol% dtbpy (dtbpy = 4,4’-bis(‘Bu)-2,2’-bipyridyl) in methyl tert-butyl ether (MTBE) at room temperature would afford 1,2-dicyano-4-(Bpin)benzene, 1.
selectively (Scheme 1). This reaction did indeed proceed with quantitative consumption of phthalonitrile to give 1 as the major product; however, traces of the bis-borylated 3,5-bis(Bpin)-1,2-dicyanobenzene (2) were also observed by $^1$H NMR spectroscopy. Borylation ortho to the relatively low steric-demand cyano group in the absence of more sterically accessible sites, as observed here in the bis-borylation reaction to give unpredicted compound 2, has been reported for para-substituted benzonitriles\textsuperscript{16} and was also observed during the borylation of 2-methylbenzonitrile, where 2,4-bis(8Pin)-6-methylbenzonitrile was obtained as a minor by-product.\textsuperscript{17} We also note that arylnitride groups are competent directing groups for a range of metal-catalysed reactions.\textsuperscript{18-21}

By increasing the reaction temperature to 55 °C and the amount of Bpin$_2$ to 1.1 eq., 70% bis-borylation, 30% monoborylation and quantitative consumption of phthalonitrile was achieved. Sublimation (150 °C/0.3 mbar) separated 1 from the crude mixture, while recrystallization of the residue from MTBE provided 2. The structures of 1-0.25H$_2$O and 2 were obtained by SC-XRD (Figure S22). Increasing the amount of Bpin$_2$ to 1.5 eq. and using a higher reaction concentration (1.3 M vs. 1.0 M) increased conversion to 2 (46% isolated yield) and removed the need for the sublimation step.

With the unexpected product 2 in hand, we decided to consider first its potential for the preparation of phthalocyanines for the following reasons. A common problem in the synthesis of functionalized PCs is that reaction of substituted phthalonitriles lower than C$_{2v}$ symmetry usually produces a 1:4:2:1 statistical, and often inseparable, mixture of C$_{4h}$, C$_i$, C$_{2v}$, and D$_{3h}$ regioisomers.\textsuperscript{22} Regardless of which function or application is sought, formation of a single Pc isomer is desirable due to their potentially differing physical, optical and biological properties. In the rare cases where separation of one or more of these four isomers has been possible, it has been necessary to use bespoke HPLC columns\textsuperscript{23, 24} or repeated column chromatography,\textsuperscript{25} limiting the generality of the procedure. Recrystallization has occasionally been successful as part of a multi-step purification of the C$_{4h}$ isomer.\textsuperscript{26, 27} If, however, bulky substituents, e.g. substituted phenyl rings,\textsuperscript{28, 29} branched alkoxides,\textsuperscript{24, 26, 30} amines,\textsuperscript{27, 31} or trialkylsilyl groups,\textsuperscript{32} are introduced at the 3-position of the phthalonitrile precursor, then exclusive formation of the C$_{4h}$ Pc isomer can sometimes be enforced through steric control or the number of isomers formed in the mixed A/B phthalonitrile synthesis of A$_2$B$_3$-33, 34 and AABAT-type\textsuperscript{35, 36} PCs can be reduced. The substituted phthalonitriles used in these previous studies were prepared by cross-coupling of 3-(OTf)phthalonitrile, nucleophilic aromatic substitution of 3-nitrophthalonitrile, or directed ortho-lithiation of 4-alkylphthalonitriles, respectively. While successful, these previous reports have been limited in allowing the introduction of further functionalization on to the phthalonitrile, either due to the difficulty of synthesizing the substituted phthalonitriles via traditional routes or the incompatibility of desired substituents with organolithium reagents. With this in mind, 2 was seen as a potential precursor to 3,5-bis-substituted phthalonitriles, which could include derivatives having a bulky substituent in the 3-position to direct the regioselective synthesis of C$_{4h}$ phthalocyanines through steric control, while also bearing a second substituent in the 5-position, and so we decided to focus on functionalization of 2.

As a first demonstration of the potential utility of 2 as a divergent intermediate in the synthesis of functionalized regioregular Pcs, a series of 3,5-bis(aryl)phthalonitriles 3-5 with varying steric demand and electronic character was prepared from 2 by Suzuki-Miyaura cross-coupling with 3,5-bis(R)bromobenzenes (R = CF$_3$, tBu, OMe, respectively).\textsuperscript{5} mol\% Pd$_2$(dba)$_3$ pre-catalyst, 20 mol% SPhos ligand and 4 eq. CsF base in 1,4-dioxane at 65 °C gave 3-5 in moderate yields (19-50%). Using 3,5-bis(CF$_3$)iodobenzene and CsCO$_3$ as the base improved the yield of 3 from 19 to 68%. The structures of 3-5 are shown in Figure S22. These products were expected to undergo regioselective cyclotetramization to the previously unexplored C$_{4h}$ 1,3,8,10,15,17,22,24-octaarylphthalocyanine family of compounds.

Reaction of 3 with Zn(OAc)$_2$, 2H$_2$O in 1-pentanol in the presence of DBU indeed afforded 1,3,8,10,15,17,22,24-octaarylphthalocyanine 6. TLC showed only a single dark-green compound, which could be separated by recrystallization in 39% yield, with the mass balance likely being oligomeric by-products. Figure 1 shows partial 1H and 19F(1H) NMR spectra of 6, which confirm the high symmetry of the Pc by the single set of sharp resonances for the six aryl proton environments and two inequivalent CF$_3$ environments, respectively. Only the C$_{4h}$ and D$_{3h}$ isomers would show this equivalence of the rings; these are the least and most sterically encumbered isomers.

Pcs 7 and 8, starting from precursors 4 and 5, were synthesized analogously in isolated yields of 25 and 14%, respectively. Sharp, well-defined 1H NMR spectra were obtained for 7 and 8 with six aromatic proton environments clearly observed (Figure 1).

![Figure 1](https://example.com/fig1.png)

Figure 1. Partial 1H NMR spectra of 6-8 and 19F(1H) NMR spectrum of 6. The spectra are consistent with the high symmetry of each Pc.

The SC-XRD structure of 6, obtained after recrystallization from acetone/pyridine, confirmed the nominal C$_{4h}$ symmetry of 6, although the Zn atom is additionally ligated by a 3:1 mixture of pyridine and water (pyridine adduct 6-NC$_6$H$_5$ shown in Figure 2). Distortion of the Pc ring away from planarity can be seen, with a maximum fold angle of 6.79(9)° for benzo group 1 relative to the meso-N$_2$ plane (N1, N2 and symmetry equivalents). The coordinated Zn atom is 0.49 Å out of the Pc meso-N$_2$ plane and is disordered 50:50 either side of the ring; thus, crystals of the axially chiral adduct are racemic. The α-
substituents, rings B/D, have mean-plane dihedral angles of 50.49(10) and 56.30(12)° with respect to adjoining benzo groups 1 and 2, respectively. These large twist angles prevent neighbouring α-substituents from overlapping (unlike when unsubstituted α-phenyl groups are used, which can overlap with distortion of the Pc ring(37)), enforcing the formation of the single C\textsubscript{4}h isomer. Peripheral β-position rings A/C have dihedral angles of 49.0(1) and 40.6(1)°, which presumably may limit solution aggregation, notwithstanding their greater rotational freedom.

![Figure 2](image_url) Structures of 6-N\textsubscript{2}C\textsubscript{5}H\textsubscript{4} and 9-H\textsubscript{2}O from SC-XRD. Disorder and hydrogen atoms are omitted for clarity. Analogous ring labelling to that of 6 is used for all structures.

The SC-XRD structure of 7 was obtained following recrystallization from acetone (Figure S23); however, the quality of this structure is low, due to a large amount of incorporated disordered solvent, the rotational disorder of the t\textsubscript{Bu} groups of the two crystallographically independent Pcs 7(A) and 7(B), and the weak diffraction of the crystal that was at the limit of our lab-based instrument. Nonetheless, the Pc rings and the eight aryl substituents of both 7(A) and 7(B) were unambiguously refined and the structure conclusively confirms the C\textsubscript{4}h symmetry of both molecules. Ligation of the Zn atoms can only be defined conclusively for 7(B) and has been resolved as a water molecule. The large size of the 3,5-bis(tBu)phenyl groups means that the β-positions are not free to rotate due to close proximity of neighbouring α-substituents, i.e. groups A/D and B/C orient concerted. In comparison, the smaller 3,5-bis(trifluoromethyl)phenyl groups of 6 show less correlation and thus have less restricted rotation.

C\textsubscript{4}h MgPc 9 was synthesized analogously to 6 in an unoptimized 5% yield by reaction of 3 with Mg(O\textsubscript{2}Ac\textsubscript{2})\textsubscript{2}-4\textsubscript{H}2O. The SC-XRD structure of 9 (recrystallized from acetone/hexane, Figure 2) has disordered solvent in the voids between the cuplike Pcs, but the Pc structure itself is well resolved and the symmetry confirmed. The Mg atom has a ligand that was resolved as water, and sits 0.74 Å out of the Pc plane. The α-substituents have large dihedral angles of 54.8(3) and 49.0(3)° for B and D respectively. The β-aryl rings A and C are twisted by 36.6(3) and 51.8(3)°. Similar to 6, there is no correlation between dihedral angles of close contacting rings: B/C rings twist in the opposite sense, while A/D differ in dihedral angle by about 12° and are therefore assumed to have some rotational freedom.

Successful de-metalation of 9 to free-base Pc 10 by heating in acetic acid was monitored by UV-visible absorption and \textsuperscript{1}H/\textsuperscript{19}F NMR spectroscopies. Alternatively, 10 can be synthesized in 5% yield with a one-pot procedure using HCl to demetallate the intermediate MgPc. The split Q band in the UV-visible absorption spectrum of 10 confirmed symmetry reduction from C\textsubscript{4}h to nominal C\textsubscript{2h} (Figure S22). As free-base Pcs can be metalated with a range of metals, it can reasonably be assumed that other metals could be introduced into these regioregular 1,3,8,10,15,17,22,24-octaarylphthalocyanines.\textsuperscript{38}

The presence of eight aryl ring substituents on 6-9 makes them highly soluble in organic solvents of different polarity and coordinating ability, e.g. toluene, CH\textsubscript{3}Cl\textsubscript{2}, CHCl\textsubscript{3}, THF, acetone, pyridine, and MeCN. The extinction coefficient of 6 at the Q-band maximum (694 nm) is large (3.8 × 10\textsuperscript{4} M\textsuperscript{-1} cm\textsuperscript{-1}, acetone solution). Normalized UV-visible absorption spectra of 6 in acetone solution in the measurable concentration range of 1.7 × 10\textsuperscript{-7} to 1.7 × 10\textsuperscript{-4} M were identical within experimental error (Figure S25), indicating that 6 does not aggregate at these concentrations, unlike many common Pc derivatives. The introduction of the eight aryl groups around the Pc core in a regioregular fashion is therefore an effective strategy to inhibit interactions through π-stacking, with the large dihedral angles of the α-substituents being especially beneficial. As aggregation of Pcs often leads to quenching of excited states, and thus lower fluorescence and singlet-oxygen quantum yields, minimizing aggregation is beneficial for most applications.\textsuperscript{39}

![Figure 3](image_url) Normalized absorption (solid lines) and emission (dotted lines) spectra of 6-8 in acetone solution.

The Q\textsubscript{00} bands in the absorption spectra of 6-8 are single peaks (Figure 3), rather than split into Q\textsubscript{00}/Q\textsubscript{y} components, consistent with their C\textsubscript{4}h symmetry and the two-fold degeneracy of the LUMO. Near-infrared emitting 6-9 (λ\textsubscript{max} = 701-717 nm) have small Stokes shifts (260-280 cm\textsuperscript{-1}) and fluorescence lifetimes of ca. 1.9-5.4 ns (Figures 3, S24, and S26-31; Table 1). The fluorescence and singlet-oxygen quantum yields of 6 are 0.17 and 0.67, respectively. Thus, encouragingly for potential applications, the eight aryl substituents of 6-9 only lead to a minor increase in non-radiative decay, despite the additional rotational freedom relative to the parent ZnPc, and the triplet state is still sufficiently energetic to sensitize singlet oxygen efficiently. Both the absorption and emission spectra of 7 are significantly broader than 6, 8 or 9; the hindered rotation of the aryl groups of 7 observed in its SC-XRD structure may be causing inhomogeneous broadening, i.e. there are different solution conformations of 7 that relatively slowly interconvert due to steric crowding. This suggests that having 3,5-bis(tBu)aryl groups in both the α and β-positions is close to the steric
crowding limit for successful synthesis of 1,3,8,10,15,17,22,24-octaaryltetraphthalocyanines.

Table 1. Room-temperature photophysical properties of 6-9 and unsubstituted ZnPc in acetone solution.

<table>
<thead>
<tr>
<th>λ_{αc} (nm)</th>
<th>λ_{αm} (nm)</th>
<th>τ (ns)</th>
<th>Φ</th>
<th>k (10^4 s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnPc</td>
<td>665</td>
<td>671</td>
<td>4.3 (1)</td>
<td>0.17 (1)</td>
</tr>
<tr>
<td>6</td>
<td>694</td>
<td>707</td>
<td>2.72</td>
<td>0.17</td>
</tr>
<tr>
<td>7</td>
<td>704</td>
<td>717</td>
<td>1.87</td>
<td>0.10</td>
</tr>
<tr>
<td>8</td>
<td>704</td>
<td>714</td>
<td>2.45</td>
<td>0.20</td>
</tr>
<tr>
<td>9</td>
<td>695</td>
<td>701</td>
<td>5.39</td>
<td>0.34</td>
</tr>
</tbody>
</table>

[a] in DMSO solution, ref. 40. [b] Ref. 41. In conclusion, we report 4-(Bpin)- and 3,5-bis(Bpin)phthalonitrile (1 and 2, respectively), synthesized by Ir-catalysed direct C–H mono- and unpredicted bis-borylation of phthalonitrile, as potential divergent intermediates for phthalocyanine chemistry. As a first demonstration of the utility of 2, we synthesized a series of 3,5-substituted phthalonitrile derivatives bearing bulky aryl groups that subsequently undergo regioselective cyclization to afford a series of 1,3,8,10,15,17,22,24-octaaryltetraphthalocyanines, 6-10, as confirmed by NMR spectroscopy and by XRD-for 6, 7 and 9. The high symmetry of these non-aggregating Pc derivatives was further confirmed by UV-visible absorption spectroscopy. We are currently investigating the use of 1 in preparing phthalonitrile derivatives, as well as exploring methods to differentiate the two Bpin groups of 2 to facilitate the synthesis of multifunctional phthalocyanines with controlled symmetry, and we will report this work in due course. The rapid functionalization of phthalonitrile reported herein may also find use in the preparation of near-infrared azaBODIPY dyes, potentially further extending its usefulness.42,43

Conflicts of interest
There are no conflicts to declare.

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Notes and references
† Single crystal structures have been deposited to the Cambridge Crystallographic Data Centre (deposition numbers 1989433-1989438 and 1989726-1989727) and can be downloaded from their webpage https://www.ccdc.cam.ac.uk/ free of charge.

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by R. M. Edkins et al.

3,5-Bis(Bpin)phthalonitrile is a divergent intermediate of regioregular $C_{4h}$ 1,3,8,10,15,17,22,24-octaarylphthalocyanines that can be synthesised by Ir-catalysed C–H bis-borylation of phthalonitrile.