

Regioselective Routes to Orthogonally-Substituted Aromatic MIDA Boronates.

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Adam J. Close^a, Paul Kemmitt^b, S. Mark Roe^c, John Spencer^{a,*}

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A series of tetrasubstituted aromatics has been synthesized, many of which are based on elaborated *N*-methyliminodiacetic acid (MIDA)-boronates. A sequence employing nitration, bromination, stepwise Suzuki-Miyaura (SM) coupling with a boronic acid, then base-mediated unmasking of the boronic acid from the MIDA-boronate and a second SM-coupling has led to our desired, mainly 1,2,4,5-substituted tetrasubstituted aromatic targets.

Introduction.

Tetrasubstituted aromatics are present in a number of bioactive molecules including kinase inhibitors such as Iressa, Tagrisso and Vemurafenib.^{1–3} Carey *et al.* outlined that these seemingly simple, desired scaffolds are not readily available or are highly expensive; thus new methodology towards these molecules is required.⁴ In order to enable the generation of libraries of related 1,2,4,5- and 1,2,3,4- substituted systems, we sought novel, selective, efficient synthetic routes to the crucial generic building blocks I and II (Figure 1).

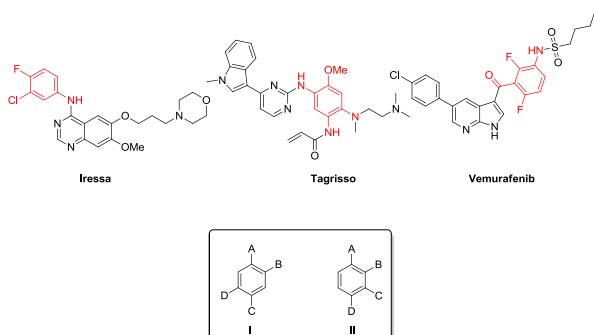


Figure 1. Examples of 1,2,4,5- and 1,2,3,4- substituted aromatic scaffolds.

MIDA-boronates (Figure 2) are versatile intermediates in a host of coupling reactions. Of note is their orthogonality with boronic acids in metal-catalyzed coupling chemistry, whereupon a subsequent aqueous base-mediated reaction can unmask the boronic acid functionality to enable a second coupling reaction.^{5,6} This iterative methodology has been used in a variety of palladium cross-coupling reactions e.g. Buchwald-Hartwig, Negishi, Sonogashira, Heck and Stille couplings.^{7–11} Indeed, these steps can be combined in environmentally-friendly telescopic couplings.¹²

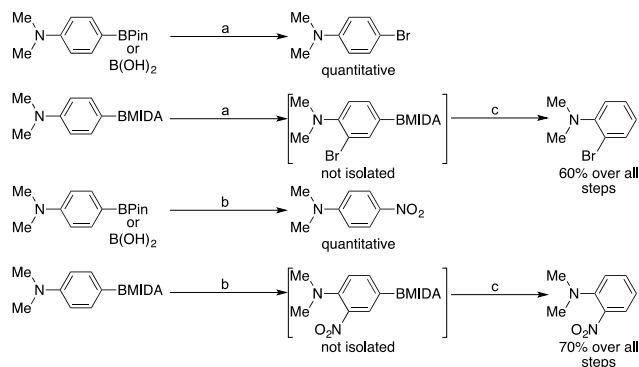
Burke *et al.* published a paper in 2015, that outlines a machine that

enabled the synthesis 14 distinct classes of small molecules in a fully automated process.¹³ This uses a catch and release method of purification and shows the potential for MIDA boronates to enable quick library generation. However, they stated that the current drawbacks included the low availability of interesting MIDA boronate starting materials *outlining the importance of new methodologies towards polysubstituted aromatic MIDA boronate cores.*



Figure 2. Bicyclic form of MIDA boronate.

Cheon *et al.* showed that under mild conditions, MIDA boronates can be used to block the *para* position in an aromatic group in order to enable selective *ortho* electrophilic substitution *i.e.* bromination or nitration. These intermediates were never isolated, as the MIDA boronate moiety was removed *in situ* (Scheme 1).¹⁴ Conversely, they showed that the corresponding boronic acids or pinacol esters underwent *ipso* substitution under these conditions. This was also observed as early as 1959 by Soloway¹⁵ who showed that if the directing effect of the substituents in a given phenylboronic acid



Scheme 1. Reaction conditions: ^aNBS 1eq, DCM, rt, 10 min. ^bNBS 1eq, AgNO₃ 1 eq, EtCN, reflux, 3 h. ^ci) NaOH, THF, 10 min, ii) wet DMSO 100 °C, 24 h.

^aDept of Chemistry, School of Life Sciences, University of Sussex, Falmer, BN1 9QJ, UK.

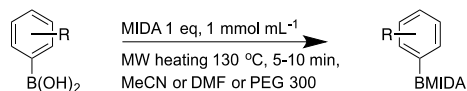
^bAstraZeneca, Mereside Alderley Park, Macclesfield, SK10 4TG, UK.

^cDept of Biochemistry, School of Life Sciences, University of Sussex, Falmer, BN1 9QJ, UK.

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would present nitration at the carbon *ipso* to the boronic acid, *ipso* nitration would be observed, displacing the boron.

Our recently reported microwave-mediated synthesis of MIDA-boronates enabled us to quickly access a number of templates on which to attempt electrophilic nitration and bromination chemistry (Scheme 2).^{16,17}



Scheme 2. Formation of MIDA boronates.

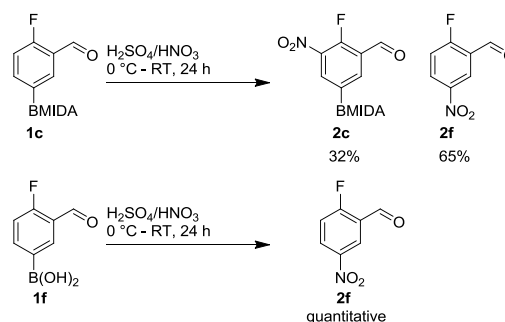
It has also been reported that MIDA boronates are highly stable under acidic Jones oxidations conditions.¹⁸ We found that nitration could be easily achieved using classical conditions *e.g.* nitric acid in sulfuric acid (Table 1).¹⁹

Table 1. Nitration of aryl-boronic acid and aryl-MIDA-boronates

Entry	Starting material	Product	Yield (%)
1			88 ^{a,d}
2			85 ^{a,c}
3			32 ^{a,c}
4			92 ^{b,c}
5			39 ^{b,c}

^a H₂SO₄/HNO₃ 0 °C – rt, 16 h, ^bH₂SO₄/ 1.02 eq HNO₃ 0 °C – rt, 16 h, ^c1 mmol scale, ^d12 mmol scale

The nitration of poly-substituted phenylboronic acids has previously been achieved; hence we were not overly surprised when the nitration of **1a** was high yielding, scalable and conveniently regioselective, directed by the halogen and formyl substituents (12 mmol scale, Table 1).²⁰ Gratifyingly, comparable yields were observed when its corresponding MIDA boronate **1b** was nitrated under these harsh conditions yielding **2b**. It was also found that the MIDA “handle” aided the solubility of **1b** in the reaction mixture. *ipso* nitration at the boron was observed in the nitration of **1f** (Scheme 3), due to the directing effect discussed above. Nevertheless we were pleased to see that its corresponding MIDA boronate **1c** was somewhat resistant to *ipso* nitration at the boron center (Table 1, entry 3). The nitration of **1d** and **1e** required the nitric acid to be added in approximately stoichiometric amounts, affording **2d** and **1e** respectively (Table 1, entries 4 and 5).



Scheme 3. Nitration of **1c** and its corresponding parent boronic acid **1f**.

After the success of the initial nitration studies our efforts moved on to the bromination of phenyl MIDA boronates. We did not attempt the bromination of **1a** since we preferred to adhere to the orthogonality afforded by the MIDA protecting group. We note that Hall *et al.* described the orthogonality of iodides with BPin.²¹ This first foray in to bromination again used harsh conditions described by Saiganesh *et al.* *e.g.* H₂SO₄ with *N*-bromosuccinimide (NBS).²² Adopting this methodology, **3b** and **3d** were synthesized (Table 2)

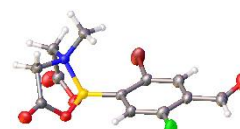
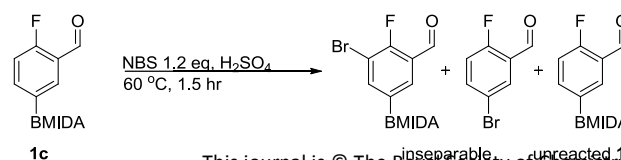
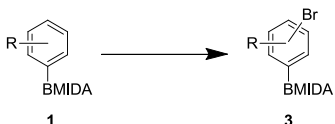


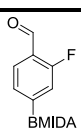
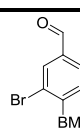
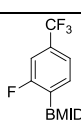
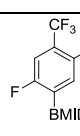
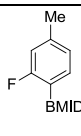
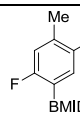
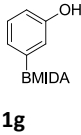
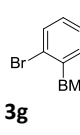
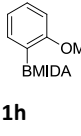
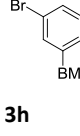
Figure 3. Solid state structure of **3b**.

and we were able to acquire a single crystal x-ray diffraction structure of **3b** (Figure 3). Higher yields were observed in the case of **3d** when the reaction temperature was reduced to 30 °C.

We found that activated compounds *e.g.* Table 2, entries 3-5, required milder conditions. Bovonsombat *et al.* demonstrated that NBS could be used to brominate phenols in the presence of stoichiometric PTSA.²³ Adopting a similar methodology, utilizing H₂SO₄ instead of PTSA, led to the synthesis of **3e**, **3g**, and **3h**, all in good yields. The bromination of **1c** unfortunately gave an inseparable mixture of products, including the product of *ipso* bromination. (Scheme 4).



Scheme 4. Bromination of compound **1c**.**Table 2.** Bromination of aryl-MIDA-boronates


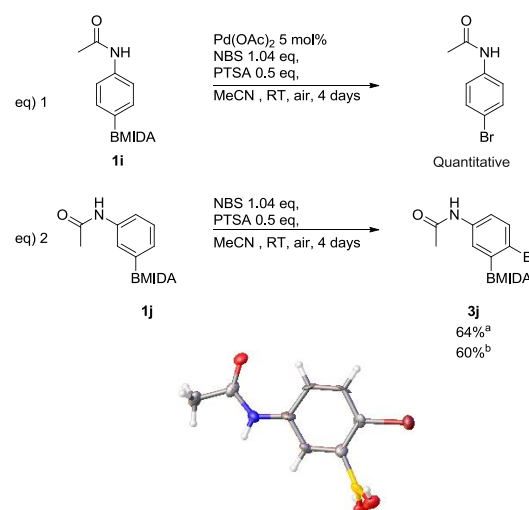
Entry	Starting material	Product	Yield (%)
1			54 ^a
2			99 ^b
3			72 ^c
4			76 ^c
5			87 ^c

^aNBS 1.2 eq, H₂SO₄, 60 °C, 2 h. ^b NBS 1.2 eq, H₂SO₄, 30 °C, 2 h. ^cNBS 1 eq, H₂SO₄ 0.5 eq, MeCN, rt, 12 h.

Bromination via *ortho*-selective C-H activation using aryl acetamide MIDA boronates with respect to the acetamide. This was done adopting a similar protocol to Bedford *et al.*, (Scheme 5).²⁴

The only modification from Bedford's original protocol was changing the solvent from toluene to MeCN due to the poor solubility of the MIDA boronate. The reaction of 4-acetamidophenyl MIDA boronate, (**1i**) led to complete *ipso*-bromination of the MIDA boronate, forming *N*-4-bromophenylacetamide in a quantitative yield (Scheme 5, eq 1). This shows that the acetamide was unable to *ortho* direct the reaction. 3-Acetamidophenyl MIDA boronate was also subjected to these conditions yet in this case only substitution *para* to the acetamide occurred leading to **3j** (Scheme 5, eq 2). These same conditions were also trialled using DMF as the

solvent giving **3j** in a comparable yield, hence MeCN was kept as the solvent of choice due to its relative ease of handling *i.e.* low boiling point. The reaction was also attempted without palladium (II) acetate in MeCN (Scheme 5, eq 2); **3j** was again obtained in a comparable yield. This was expected due to the lack of C-H activation observed in the earlier reactions. This regiochemistry was confirmed via single crystal x-ray diffraction (Scheme 5). During the crystallization process the MIDA group was cleaved and the structure of the resulting free boronic acid **3j'** is shown. NOESY NMR also confirmed this regiochemistry of the parent MIDA boronate **3j**.



Scheme 5. Attempted bromination via *ortho*-selective C-H activation, including x-ray structure of **3j'** (MIDA protection was cleaved in crystallisation process). ^a with 5 mol% Pd(OAc)₂, ^bwithout Pd(OAc)₂.

It is pertinent to reflect upon failed bromination attempts on aryl MIDA derivatives (Table 3). These results show one of the drawbacks of this technique; if more than one major regioisomer can be produced then these reactions produce inseparable mixtures of compounds; evidenced by LCMS and ¹H NMR analysis of crude reaction mixtures.²⁵

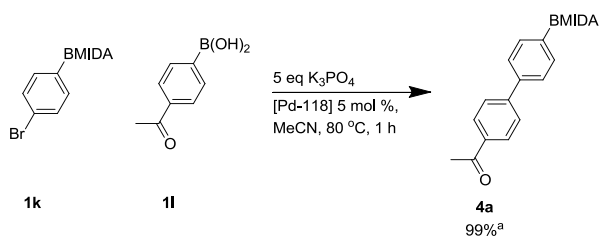
Notwithstanding the latter unsuccessful examples this methodology is still a very simple, cheap and powerful tool for producing new interesting scaffolds when directing groups are propitiously placed to enable the formation of a major or single regioisomer.

Table 3. Study of bromination aryl-MIDA-boronates.

R	Conditions	Results
<i>m</i> -formyl	a	Multiple products
	b	Multiple products
<i>p</i> -formyl	a	Multiple products
	b	Multiple products
	e	No reaction
	f	No reaction
<i>m</i> -methyl	c	Multiple products
	d	Multiple products
Ph	c	Multiple products
<i>m</i> -fluoro	c	No reaction
	d	Multiple products
<i>o</i> -fluoro	d	Multiple products
<i>m</i> -fluoro- <i>p</i> -methyl	d	Multiple products

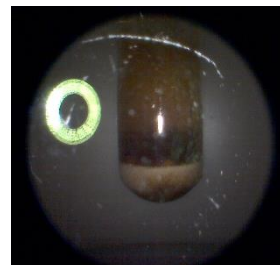
^aNBS 1.2 eq, H₂SO₄, 60 °C, 2 h. ^b NBS 1.2 eq, H₂SO₄, 30 °C, 2 h. ^cNBS 1 eq, H₂SO₄ 0.5 eq, MeCN, 50 °C, 36 hr. ^dNBS 1 eq, H₂SO₄ 1 eq, MeCN, 50 °C, 36 hr. ^eNBS 1.2 eq, FeCl₃, MeCN, 1 eq, 80 °C, 2 hr. ^fNBS 1.2 eq, NH₄NO₃, MeCN 1 eq, 80 °C, 2 hr

To show the synthetic value of these intermediates we attempted some rapid Suzuki cross coupling reactions. A rapid screen of catalysts and bases was undertaken under anhydrous conditions (to maintain the MIDA boronate) in the absence of a glovebox, since we desired a method that was more widely applicable for medicinal chemists and industrialists. To do this an electronically challenging model reaction system was selected as (Scheme 6) where we took the relatively electron poor 4-acetylphenylboronic acid **11**.

**Scheme 6.** Suzuki reaction using Pd-118. ^aConversion calculated by LCMS.

Initially this was attempted using microwave heating as in previous studies it has shown to reduce reaction times.^{26–29} Under the anhydrous conditions this cross-coupling gave low yields, using a

variety of catalysts and bases. Camera monitoring of these microwave-mediated processes revealed that stirring never initiated due to flocculation of the base under these anhydrous conditions (Figure 4).^{30–32}

**Figure 4.** Flocculation of the potassium phosphate, demonstrating that no stirring occurs in the microwave vessel while the solvent is boiling.

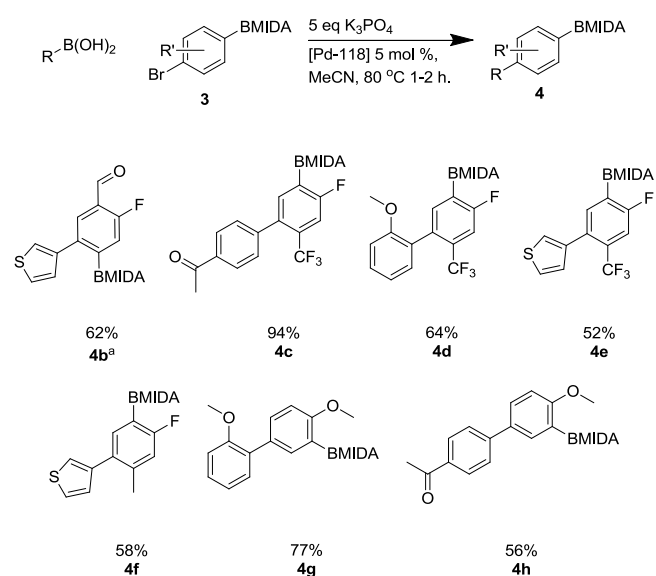
Stirring is key to uniform heating in microwave reactions; studies have shown that reaction temperatures can differ up to 30 °C between the middle and outside of the reaction vessel in the absence of efficient stirring.³³ We observed boiling of the MeCN (boiling point 82 °C) in these reactions before the microwave heated to its maximum temperature setting of 80 °C, as measured by an external IR thermometer. Also the microwave continued to heat to almost 90 °C after the irradiation was removed due to it overshooting the maximum temperature. As the heating in these reactions was monitored via an IR thermometer on the outside of the vessel, we could conclude that the internal temperature of these unstirred reactions was much higher internally, than the set parameters. This was hypothesized to be the cause of the low yields, in these microwave reactions.

During microwave studies the most successful catalyst trialed was Pd 118 ([1,1'-bis(di-tert-butylphosphino)ferrocene]dichloro palladium (II) or PdCl₂(dtbpf)) with potassium phosphate. (see ESI). Consequently, Pd-118 was used as catalyst with K₃PO₄, with standard thermal heating, giving a fast full conversion by LCMS to product **4a** within 1 h.³⁴

This methodology facilitated the generation of a small library of compounds, as shown in Scheme 7. As can be seen, this was tolerant of a number of substituents including heterocycles (**4b**, **4e**, **4f**) and fluoro substituents, which are important in a number of bioactive molecules.³⁵

3	Dioxane/H ₂ O	5	56
4	THF/H ₂ O	2.5	73

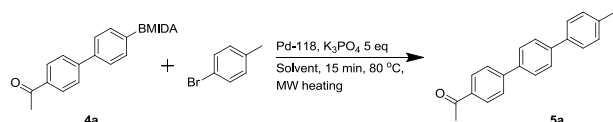
^a calculated via ¹H-NMR.



Scheme 7. Suzuki reaction using Pd-118 including x-ray structure of 4f.^aReaction required a 12 hour reaction time.

Next, aqueous Suzuki couplings were attempted, with the aim of deprotecting the MIDA group *in situ* in order to perform a second C-C bond formation. This was optimized on the coupling of 4a with *p*-bromotoluene to form the known *para*-terphenyl 5a (Table 4).^{6,36} This enabled quick microwave-mediated optimization via crude ¹H-NMR analysis on a small scale using a phase separator to facilitate efficient work-up.

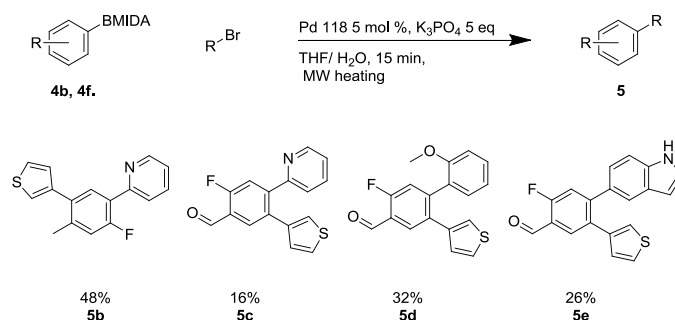
Table 4. Optimization of aqueous Suzuki coupling.



Entry	Solvent	Catalyst loading (mol%)	Conversion (%) ^a
1	THF/H ₂ O	5	>99
2	MeCN/H ₂ O	5	70

Initial optimization reactions with 5 mol% of Pd-118 catalyst, established that a THF/water mixture was superior to acetonitrile or dioxane/water mixtures although lowering the catalyst loading to 2.5 mol% led to a respectable 73% conversion to product.

This methodology was applied to the unoptimized synthesis of a small library of four representative final tetrasubstituted aromatic compounds with the required regiochemistry (Scheme 8).



Scheme 8. Aqueous deprotection Suzuki cross-couplings.

Conclusions

In conclusion, examples of iterative Suzuki cross-couplings have been achieved, illustrating the potential of polysubstituted aromatic compounds derived from the electrophilic aromatic substitution of synthons containing orthogonal groups. This demonstrates how complex polyaromatics with tetrasubstituted cores can be synthesized in a simple four-step procedure i.e. MIDA protection, bromination, anhydrous cross-coupling and aqueous cross-coupling. This was performed using inexpensive reagents starting from commercially available trisubstituted boronic acid. The Suzuki cross-coupling reactions, both anhydrous and aqueous, suffered from low yields, particular the latter. Eleven polysubstituted MIDA-aromatics have been synthesized, ten of which are novel, via traditional bromination and nitration methodologies. These methods have shown to be scalable and give the desired products containing orthogonal groups, with specific regiochemistry.

Acknowledgements

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