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Microwave-mediated synthesis of *N*-methyliminodiacetic acid (MIDA) boronates

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ABSTRACT

A library of over 20, mainly aryl or heteroaryl, *N*-methyliminodiacetic acid (MIDA) boronates have been synthesised. A rapid microwave-mediated (MW) method (5–10 min) has been developed using polyethylene glycol 300 (PEG 300) as solvent. However, acetonitrile (MeCN) and dimethylformamide (DMF) were found to be alternative solvents, the latter especially for 2-substituted aryl boronic acids.

1. Introduction

The twelve *Principles Of Green Chemistry*, encompassing inter alia, atom economy, less hazardous chemical syntheses, safer solvent use, improved energy efficiency and the use of renewable feedstocks, are invaluable guidelines for evaluating the greenness in the design and implementation of any new process or technology.[1–3]

Burke's group has pioneered MIDA boronate chemistry, showing these compounds to be orthogonal to boronic acids in Suzuki–Miyaura (SM) reactions. By virtue of an sp^3 hybridised boron, MIDA boronates, Fig. 1,[4] are less prone to transmetallation, exemplified by the selective cross-coupling of bromophenyl MIDA boronates with *p*-tolylboronic acid, affording biaryl-MIDA boronates, under anhydrous conditions.[5]

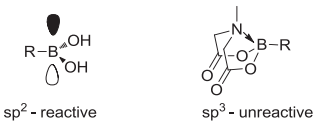

Fig. 1. sp^2 versus sp^3 boronic acids and derivatives in cross-couplings.

The scope of MIDA boronates as protecting groups has been underlined in other related coupling reactions, e.g., Negishi, Heck, Sonogashira, Stille and Buchwald–Hartwig amination,[6–10] as well as in various functional group interconversions on arenes. Examples of the latter include oxidations under Jones or Swern conditions or the cycloisomerisation of arylethynyl MIDA boronates.[11,12] These allow for greener, multistep *telescopic reactions* with an in situ cleavage of the MIDA boronate, enabling a second coupling, minimising work–up and solvent usage in these one-pot processes. This is desirable in medicinal chemistry as the deployment of faster reaction times, fewer reaction steps and lower solvent volumes is desirable.[13] MIDA boronates are crystalline solids that are air stable and silica-gel column-compatible[14] and may also be used as 'handles' to enhance the stability of otherwise unstable boronic acids.[15–18]

Due to their advantageous attributes, many MIDA boronates are, not surprisingly, commercially available.[19] Current methods of MIDA boronate synthesis include (Fig. 2); (i) metallation to form an organolithium or Grignard reagent, followed by borylation with trimethyl or triisopropyl-borate to form the corresponding boronate followed by in situ esterification with MIDA in dimethylsufoxide (DMSO). (ii) Electrophilic arene borylation followed by an overnight MIDA esterification with the bis-trimethylsilyl ester of MIDA, the disodium salt of MIDA or MIDA alone. (iii) MIDA esterification of a boronic acid with 4-methylmorpholine-2,6-dione (MIDA anhydride). (iv) Esterification of a boronic acid with MIDA in DMSO/benzene or toluene via an 8 h azeotropic removal of water with a Dean Stark trap. (v) Esterification of a boronic acid with MIDA in DMF at 85 °C for 18 h, hitherto deemed to be the method of choice.[20–23]

Many current synthetic methods towards MIDA boronates require a multistep process, large solvent volume or an extensive

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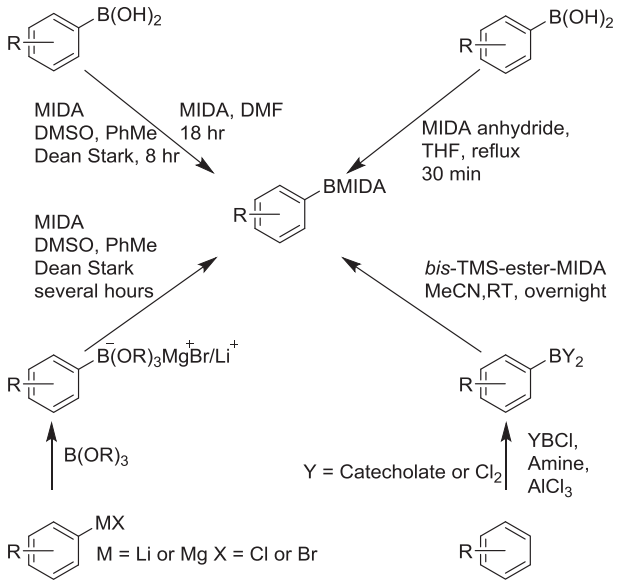


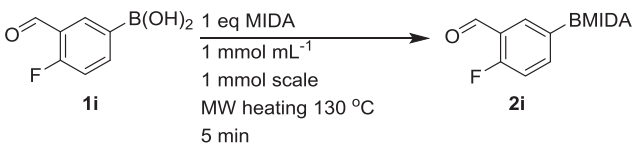
Fig. 2. MIDA arylboronate synthesis.

period of heating. Given the above, the increasing numbers of green processes employing MIDA boronates would be far more attractive were a general, scalable, efficient process for preparing the starting material available. Herein, we describe our efforts aimed at reducing reaction times and solvent usage. Moreover, the use of microwave chemistry[24–26] for enabling quick, more efficient reactions was anticipated to be advantageous in the synthesis MIDA boronates **2** from their boronic acid precursors.

2. Results and discussion

We wished to form the MIDA ester of 4-fluoro-3-formyl boronic acid **1i** using the standard literature method of choice. However, we were frustrated with the reaction times involved and, hence, examined the use of microwave-mediated methods. Hence, a rapid screen of (minimal volume) solvent and potential additives was performed to ascertain the best conditions. This method was particularly propitious for screens employing small volumes of deuterated NMR solvents such that, upon cooling, the reaction mixture was transferred directly to an NMR tube then spectrometer for inspection. Employing 1 equiv of MIDA, a microwave-mediated route using a short hold time of 5 min was attempted and results are summarised in Table 1.

Table 1
Rapid solvent screen for test reaction



Entry	Solvent/additive	% Conversion[a]
1	Acetonitrile-d_3	95
2	Acetonitrile-d_3+3 Å molecular sieves	93
3	Water	5[b]
4	DMSO-d_6	60
5	DMSO-d_6+4 Å molecular sieves	0
6	DMF dry	97
7	DMF reagent grade	72
8	PEG 300	69[b]

[a] Calculated from ^{1}H NMR integration of crude mixture.
[b] Isolated yield.

Table 1 shows that, apart from water (entry 3), DMSO gave the poorest results out of the solvents trialled, and reactions mixtures tended to blacken, with dimethylsulphide odour detected (entries 4, 5). This was more noticeable when molecular sieves were used as they are known to be Lewis acidic and could increase decomposition (entry 5) and large amounts of impurities in the crude NMR were observed.[27] It is notable that dry DMF was the best solvent (entry 6). We concluded that small amounts of water in reagent grade DMF (entry 7) may lead to in situ MIDA ester cleavage due to possible (basic) dimethylamine generation.[28] The result employing acetonitrile (entry 1), although comparable to that of entry 6, was deemed to be the most promising, due to the reduced toxicity and lower boiling point of this solvent.[29,30] Interestingly, the use of molecular sieves (entry 2) did not push the reaction to completion.

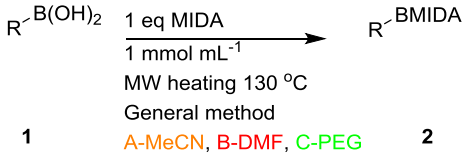
To test the reaction scope, we next synthesised a small library of MIDA boronates using the initial solvent of choice, *acetonitrile*, and employing a short, 5 min, reaction hold time, see Table 2 (general method A, orange highlight). Yields, in general, were good to excellent, e.g., **2a**, **2c**, **2o** and the reaction showed good functional group tolerance. A simple alkyl MIDA boronate **2m** was formed in near quantitative yield. However, **2b** was formed in a low yield, for unknown reasons, and one other notable exception is compound **2p**, which we were unable to synthesise. We hypothesised the lack of reaction may at least be partly due to the presence of two *ortho* substituents flanking the boronic acid functionality and that a higher boiling point solvent and/or extended reaction times might enable this reaction.

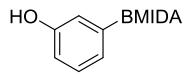
For **2d**, **2h** and **2o** similar yields were achieved when the reactions were run on a small (1 mmol) or large (gram) scale. However, for the high scale reactions, some technical adjustments were required; for example, a 5 mmol scale reaction in a 35 mL CEM microwave vial often gave rise to increased pressurisation, due to a reduction in relative head space in the closed system. In order to resolve this, a like-for-like mmol mL^{-1} ratio (to the original 1 mmol conditions) was implemented, enabling the same relative head space. Hence, a 1 mmol scale reaction was conducted in a 10 mL vial whereas a 3.5 mmol scale reaction was performed in a 35 mL vial. Given that we had no access to 50 mL microwave vials, we ran 5 mmol scale reactions under open vessel microwave conditions.

Next, we turned our attention to *DMF* as solvent and increased the reaction time to 10 min, as a rapid screen showed 5 min to lead to incomplete reactions (Table 2 general method B, red highlight). Gratifyingly, **2p** was now formed in 62% yield and a series of 2-substituted aryl and heteroaryl MIDA boronates were synthesised, mostly in moderate to good yields. Relatively poor yields were recorded for the 2-phenol derivative **2v** and the chloropyridine **2t** whereas **2y** was not formed at all. Reaction optimisation studies, beyond the scope of the current work, may lead to improved yields. On increasing the scale of these conditions we found, comparable or slightly lower yields for **2p**, **2s** and **2w**. Due to the higher boiling point of DMF, compared with acetonitrile, it allowed us to work on a larger 5 mmol scale in a closed vessel, and even an open vessel on a 10 mmol scale in the case of **2s**. We also note an acceptable 44% yield for the somewhat elusive benzaldehyde derivative **2q**.[23]

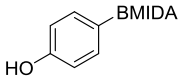
Having considerably improved upon conventional reaction times for MIDA boronate synthesis using microwave chemistry, our next iteration needed to address the issues of solvent suitability. *PEG 300* was considered as a worthy candidate solvent as it has similar properties to DMSO, in terms of polarity and hydrogen bond acceptor properties, as highlighted by Jessop, in two Kamlet–Taft plots of common solvents.[31] It also has the desired green solvent properties, viz. negligible vapour pressure, low flammability, reduced environmental damage adding to the advantage of a complete toxicity report and it is approved by the FDA for human

Table 2
Isolated yields (%) for MIDA boronates

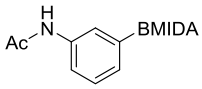




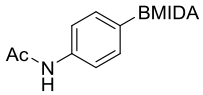
2a)
80[a]



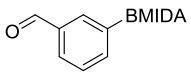
2b)
35[a]



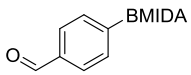
2c)
79[a], 85[b]
77[a]



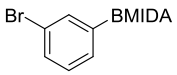
2d)
80[a], 76[b]
87[a]



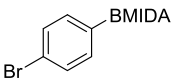
2e)
76[a]
51[a]



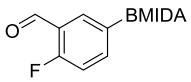
2f)
99[a]
87[a]



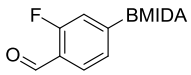
2g)
88[a]
70[a]



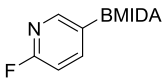
2h)
89[a], 79[b]
83[a], 72[c], 82[d]



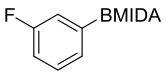
2i)
81[a]
69[a]



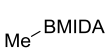
2j)
84[a]
73[a]



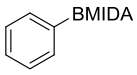
2k)
60[a]
48[a]



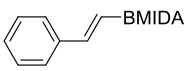
2l)
92[a]
68[a]



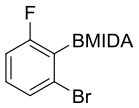
2m)
99[a]
51[a]



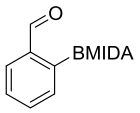
2n)
53[a]
55[a]



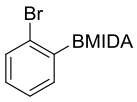
2o)
52%[a]. 53[b]
29%[a]



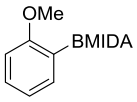
2p)
0[a]
62[a], 56[c]
14[a]



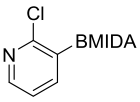
2q)
44[a]
9[a]



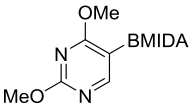
2r)
72[a]
52[a]



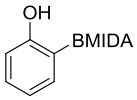
2s)
97[a], 87[c], 92[d]
51[a]



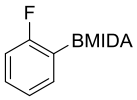
2t)
25[a]
82[a]



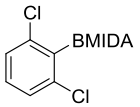
2u)
83[a]
60[a]



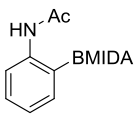
2v)
42[a]



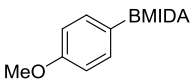
2w)
80[a], 79[c]



2x)
69[a]



2y)
0[a]



2z)
70[a]

consumption.[32] Finally, we already found it to be suitable for microwave-mediated MIDA boronate synthesis (entry 8, Table 1).

Hence, yields in PEG 300 were generally good but, again, some technical adjustments were necessary at the start. The higher viscosity of the medium led to difficulty in stirring the reaction during microwave irradiation, sometimes leading to overheating by up to 40 °C. This was averted by limiting the maximum power on the microwave's dynamic setting to 40 W. A few trends need to be outlined (Table 2 general method C, green highlight); yields for 2-substituted MIDA boronates tend to be lower than those obtained in DMF, e.g., the poorer yields for **2s** (51% vs 97%), **2u** (60% vs 83%) or the significantly lower yields for **2p** (14% vs 62%), **2q** (9% vs 44%) in PEG 300 signify that DMF would be a solvent of choice in their synthesis. In PEG 300 comparable yields for the synthesis of **2h** were obtained when performed on a low to multigram scale and an isolated yield of 82% for **2t** was observed. The low vapour pressure

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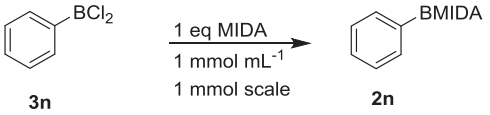
of PEG 300 made scale up easy and we no longer experienced a limitation in vial size, as noted for acetonitrile (vide supra). Product **2h** was easily made in an open vessel MW reaction on a 10 mmol scale and the work up procedure using PEG 300 proved easy; precipitation of the pure MIDA boronate product, after cooling, was achieved using water. After collection by filtration the product was washed with minimal water to remove any residual solvent.

Compatibility issues with the attempted MIDA protection of 2-heterocyclic boronic acids, which are of particular interest for slow release couplings, were encountered.[18] Test reactions were carried out on *N*-Boc-pyrrole-2-boronic acid, 2-furanylboronic acid and 2-thienylboronic acid, but ^{1}H NMR inspection of the crude material in these three cases showed a large amount of impurities, and these were not pursued any further.

Finally, we have checked the applicability of this MIDA forming reaction with other boron-containing precursors and selected dichlorophenylborane **3n** as a precursor (Table 3). The latter, being highly reactive, was not suitable for use in the aprotic solvent, PEG 300, (entry 1) and best yields were obtained in DMF (entry 3), which are comparable to those obtained using phenylboronic acid (entry 5).

Table 3
Dichlorophenylborane as a precursor to the MIDA analogue **2n**



3n **2n**

Entry	Solvent	Method	Isolated yield (%)
1	PEG 300	5 min MW heating 130 °C	0
2	MeCN dry	5 min MW heating 130 °C	39
3	DMF dry	5 min MW heating 130 °C	63
4	DMF dry	24 h rt	12
5[a]	PEG 300	5 min MW heating 130 °C	55

[a] Entry **2n**, Table 2, (from $PhB(OH)_2$), for comparison.

3. Conclusion

A rapid microwave-mediated synthesis of a library of MIDA boronates has been developed. In many cases this reaction is high yielding, uses minimal solvent and reaction times, can be performed on a multigram scale and is tolerant of a range of functional groups. At best, performed in PEG 300 as solvent, this protocol should now represent the method of choice for the synthesis of synthetically important MIDA boronates and used in the synthesis of bioactive compounds. Results in this respect will be reported in due course. We have also found that this reaction can be used with a dichlorophenylborane precursor. Moreover, full characterisation data for these products, many of which are commercially available, are provided.

3.1. General experimental methods

Solvents and reagents were purchased from commercial suppliers and used without further purification. Boronic acids were typically purchased, and used as such, from Sigma Aldrich or Boron Molecular. Reactions were heated using a CEM discovery microwave fitted with an explorer unit ensure a ventilated fumehood with the sash lowered is used as these reactions are under high pressure and temperature. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent peak or to TMS used as an internal standard; note that in some cases the C–B bond is not detectable in the ^{13}C NMR.[25] LCMS were ran with a 5 μm C18 110 Å column. Percentage purities were performed using a 30 min method in water/acetonitrile with 0.1% formic acid (5 min at 5%, 5–95% over 20 min, 5 min at 95%) with the UV set to 254 nm. High-resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, University of Swansea on an LTQ Orbitrap XL. A number of the products described below are commercially available or known, e.g., in patents. In these cases, ^{1}H, ^{13}C, HRMS and % purity data are presented since in many cases these data are not published. For compounds that appear to be novel, more analytical data are presented including ^{11}B NMR.

3.2. General procedure for MIDA boronate formation with acetonitrile (general method A)

The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, and then acetonitrile (1 mL) was added, followed by methyliminodiacetic acid (MIDA) (147 mg, 1 mmol). The Teflon cap was added and the reaction mixture was heated using the dynamic heating method, with the maximum power set to 300 W, max pressure 250 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 5 min. After cooling, the magnetic stirrer was retrieved and the acetonitrile was removed under reduced pressure giving a crude white powder. This crude material was first triturated via sonication with deionised water (5 mL), cooled in an ice bath and collected by filtration and washed with cold water (5 mL). This solid was then further triturated with diethyl ether (5 mL), cooled in an ice bath, collected by filtration and washed with diethyl ether (5 mL) giving pure product as a white precipitate (if not otherwise quoted), which was air dried.

Notes: The 3.5 mmol scale reaction was done using a 35 mL microwave vial, with the same heating profile.

3.3. General procedure for MIDA boronate formation with DMF (general method B)

The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, followed by methyliminodiacetic acid (MIDA) (1 mmol) and dry DMF (1 mL) was added to the vial. The Teflon cap was added and the reaction mixture was heated using the dynamic heating method, with max power set to 300 W, max pressure 300 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 10 min.

After cooling, the DMF was removed under reduced pressure giving crude yellow oil. The latter was triturated via sonication with deionised water (5 mL), cooled in an ice bath and collected by filtration and washed with cold water (5 mL). This solid was then further triturated with diethyl ether (5 mL), cooled in an ice bath, collected by filtration and washed with diethyl ether (5 mL) then air dried giving pure product as a white precipitate.

3.4. General procedure for MIDA boronate formation with PEG 300 (general method C)

The boronic acid (1 mmol) was added to a 10 mL microwave vial equipped with a magnetic stirrer, and then PEG 300 (1 mL) was added followed by methyliminodiacetic acid (MIDA) (147 mg, 1 mmol). The Teflon cap was added and the reaction was heated using the dynamic heating method, with max power set to 40 W, max pressure 250 psi, max temperature 130 °C, high stirring throughout and power max turned off. This method was used to hold the reaction mixture at 130 °C for 5 min.

After cooling, the mixture was added to water (9 mL). This mixture was stirred forming a white precipitate, then cooled in an ice bath allowing flocculation, then collected by filtration and

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washed with cold water (5 mL). The precipitate was allowed to dried in an oven set to 100 °C, giving pure product as a white precipitate (if not otherwise quoted).

Notes: The 5 mmol scale reaction was performed using a 35 mL microwave vial and the 10 mmol scale was carried out using a 100 mL round bottomed flask with a small air condenser attached with the open vessel attenuator installed. The heating parameters were kept the same but the hold time was changed to 7.5 min for the 5 mmol scale and 10 min for the 10 mmol scale reactions.

3.4.1. 3-Hydroxyphenyl MIDA boronate ***2a***. Made following general method A. *Yield*: 199 mg (80%). CAS number 1257724-90-5. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.25 (d, J=8.0 Hz, 1H), 6.96–6.90 (m, 2H), 6.84 (d, J=8.0 Hz, 1H), 4.40 (d, J=17.1 Hz, 2H), 4.18 (d, J=17.1 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 156.7, 128.8, 122.9, 119.0, 115.8, 61.7, 47.5. ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.68. LCMS purity >99% (UV), ret. time=11.61 min. HRMS-ESI (m/z) found 250.0878, calcd for $[C_{11}H^{10}_{12}BNO_5H]^+$ 250.0881.

3.4.2. 4-Hydroxyphenyl MIDA boronate ***2b***. Made following general method A. *Yield*: 87 mg (35%). CAS number 1312788-59-2. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.33 (d, J=8.0 Hz, 2H), 6.93 (s, 1H), 6.82 (d, J=8.0 Hz, 2H), 4.02 (d, J=17.1 Hz, 2H), 3.84 (d, J=17.1 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 169.6, 159.0, 135.0, 115.9, 62.7, 48.4. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 11.60. LCMS purity >99% (UV), ret. time=11.14 min. HRMS-ESI (m/z) found 272.0700, calcd for $[C_{11}H^{10}_{12}BNO_5Na]^+$ 272.0701.

3.4.3. 3-Acetamidophenyl MIDA boronate ***2c***. Made following general method A. *Yield*: 230 mg (1 mmol scale, 79%), 861 mg (3.5 mmol scale, 85%) as a pink precipitate. Made following general method C. *Yield*: 223 mg (77%) as a pink precipitate. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.79–7.74 (m, 1H), 7.46 (s, 1H), 7.31–7.24 (m, 1H), 7.12–7.06 (m, 1H), 4.33 (d, J=17.2 Hz, 2H), 4.09 (d, J=17.2 Hz, 2H), 2.49 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 168.1, 138.7, 128.0, 127.0, 122.9, 119.7, 61.6, 47.5, 23.9. ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.34. LCMS purity >99% (UV), ret. time=11.76 min. HRMS-FTMS (m/z) found 290.1180, calcd for $[C_{13}H^{10}_{15}BN_2O_5H]^+$ 290.1183.

3.4.4. 4-Acetamidophenyl MIDA boronate ***2d***. Made following general method A. *Yield*: 232 mg (1 mmol scale, 80%), 768 mg (3.5 mmol scale, 76%) as a brown crystalline solid. Made following general method C. *Yield*: 252 mg (1 mmol scale, 87%) as a brown crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.55 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 4.30 (d, J=17.2 Hz, 2H), 4.08 (d, J=17.2 Hz, 2H), 2.48 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 168.2, 139.9, 132.8, 118.2, 61.7, 47.5, 24.0. ^{11}B NMR (128 MHz, DMSO-d_6) δ 10.36. LCMS purity >99% (UV), ret. time=11.37 min HRMS-FTMS (m/z) found 290.1181, calcd for $[C_{13}H^{10}_{15}BN_2O_5H]^+$ 290.1183.

3.4.5. 3-Formylphenyl MIDA boronate ***2e***. Made following general method A. *Yield*: 200 mg (76%). Made following general method C. *Yield*: 264 mg (51%). CAS number 1257642-72-0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.0 (s, 1H), 7.91 (d, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H), 7.60 ($_{app}$t, J=7.5 Hz, 1H), 4.37 (d, J=17.2 Hz, 2H), 4.17 (d, J=17.2 Hz, 2H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 193.5, 169.2, 138.6, 135.5, 133.9, 129.8, 128.4, 62.0, 47.7. ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.31. LCMS purity UV=98%, ret. time=13.45 min. HRMS-ESI (m/z) found 284.0701, calcd for $[C_{12}H^{10}_{12}BNO_5Na]^+$ 284.0701.

3.4.6. 4-Formylphenyl MIDA boronate ***2f***. Made following general method A. *Yield*: 264 mg (99%). Made following general method C. *Yield*: 227 mg (87%). CAS number 1257650-77-3. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 10.04 (s, 1H), 7.89 (d, J=8.0 Hz, 2H), 7.72 (d, J=8.0 Hz, 2H), 4.10 (d, J=17.1 Hz, 2H), 3.93 (d, J=17.1 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 193.4, 169.2, 136.5, 133.1, 128.5, 62.0, 47.7. ^{11}B NMR (128 MHz, DMSO-d_6) δ 10.82. LCMS purity >99% (UV), ret. time=11.76 min. HRMS-ESI (m/z) found 284.0699, calcd for $[C_{12}H^{10}_{12}BNO_5Na]^+$ 284.0701.

3.4.7. 3-Bromophenyl MIDA boronate ***2g***. Made following general method A. *Yield*: 274 mg (88%). Made following general method C. *Yield*: 218 mg (70%). CAS number 943552-25-8. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.65 (s, 1H), 7.63–7.59 (m, 1H), 7.53–7.48 (m, 1H), 7.37–7.33 (m, 1H), 4.07 (d, J=17.1 Hz, 2H), 3.91 (d, J=17.1 Hz, 2H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 169.3, 136.2, 133.2, 132.3, 131.0, 123.4, 63.0, 48.7. ^{11}B NMR (128 MHz, Acetonitrile-d_3) δ 11.31. LCMS purity >99% (UV), ret. time=16.73 min. HRMS-ESI (m/z) found 333.9851, calcd for $[C_{11}H^{10}_{11}BBrNO_4Na]^+$ 333.9857.

3.4.8. 4-Bromophenyl MIDA boronate ***2h***. Made following general method A. *Yield*: 278 mg (1 mmol scale, 89%), 861 mg (3.5 mmol scale, 79%). Made following general method C. CAS number 943552-04-3.

Yield: 259 mg (1 mmol scale, 83%), 1.127 g (5 mmol scale, 72%), 2.551 g (10 mmol scale, 82%). ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.55 (d, J=8.0 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 4.07 (d, J=17 Hz, 2H), 3.89 (d, J=17 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 169.4, 135.6, 132.0, 124.4, 62.9, 48.6. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 11.24. LCMS purity >99% (UV), ret. time=16.87 min. HRMS-ESI (m/z) found 333.9857, calcd for $[C_{11}H^{10}_{11}BBrNO_4Na]^+$ 333.9857.

3.4.9. 4-Fluoro-3-formylphenyl MIDA boronate ***2i***. Made following general method A. *Yield*: 226 mg (81%).

Made following general method C. *Yield*: 193 mg (69%). ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 10.30 (s, 1H), 7.96 (dd, $^4J_{FH}$=7.4, $^4J_{HH}$=2.0 Hz, 1H), 7.82 (ddd, $^3J_{HH}$=8.3, $^4J_{FH}$=5.6, $^4J_{HH}$=2.0 Hz, 1H), 7.27 (dd, $^3J_{FH}$=11.0, $^3J_{HH}$=8.3 Hz, 1H), 4.10 (d, J=17.2 Hz, 2H), 3.93 (d, J=17.2 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 187.9 (d, $^3J_{FC}$=6.0 Hz), 168.3, 165.0 (d, $^1J_{FC}$=260 Hz), 140.9 (d, $^3J_{FC}$=9 Hz), 134.0 (d, $^3J_{FC}$=2 Hz), 123.7 (d, $^2J_{FC}$=8.0 Hz), 116.1 (d, $^2J_{FC}$=20 Hz), 62.1, 47.7. ^{19}F NMR (376 MHz, acetonitrile-d_3) δ −110.85 (ddd, J=12.2, 7.7, 5.1 Hz). ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 10.6. LCMS purity 96% (UV), ret. time=14.10 min. HRMS-ESI (m/z) found 302.0607, calcd for $[C_{12}H^{10}_{11}BFNO_5Na]^+$ 302.0607.

3.4.10. 3-Fluoro-4-formylphenyl MIDA boronate ***2j***. Made following general method A. *Yield*: 235 mg (84%).

Made following general method C. *Yield*: 204 mg (73%). ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 10.34 (s, 1H), 7.87 ($_{app}$t, $^3J_{HH}$,$^4J_{FH}$ J=7.5 Hz, 1H), 7.49 (d, $^3J_{HH}$=7.5 Hz, 1H), 7.43 (d, $^3J_{FH}$=11.4 Hz, 1H), 4.15 (d, J=17.2 Hz, 2H), 3.98 (d, J=17.2 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 188.7 (d, $^3J_{FC}$=6.0 Hz), 169.2, 164.9 (d, $^1J_{FC}$=258.0 Hz), 129.8, (d, $^3J_{FC}$=4.0 Hz), 129.4, 125.7 (d, $^2J_{FC}$=9.0 Hz), 121.3 (d, $^2J_{FC}$=19.0 Hz), 63.2, 48.7. ^{19}F NMR (376 MHz, acetonitrile-d_3) δ −112.46 (dd, J=11.7, 7.3 Hz). LCMS purity 94% (UV), ret. time=14.24 min. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 10.6. HRMS-ESI (m/z) found 302.0605, calcd for $[C_{12}H^{10}_{11}BFNO_5Na]^+$ 302.0607.

3.4.11. 2-Fluoropyridin-5-yl MIDA boronate ***2k***. Made following general method A. *Yield*: 152 mg (60%). Made following general method C. *Yield*: 121 mg (48%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26–8.23 (m, 1H), 8.03–7.97 (m, 1H), 7.17–7.13 (m, 1H), 4.36 (d, J=17.2 Hz, 2H), 4.16 (d, J=17.2 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 164.0 (d, $^1J_{FC}$=236.2 Hz), 151.6 (d, $^3J_{FC}$=14.1 Hz), 146.4 (d, $^3J_{FC}$=7.6 Hz), 108.7 (d, $^2J_{FC}$=35.8 Hz), 62.0,

47.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −68.77 (d, J=9.0 Hz). ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.16. LCMS purity >99% (UV), ret. time=12.13 min. HRMS-ESI (m/z) found 253.0789, calcd for $[C_{10}H^{10}_{10}BN_2O_4H]^+$ 253.0790.

3.4.12. 3-Fluorophenyl MIDA boronate ***2l***. Made following general method A. *Yield*: 231 mg (92%). Made following general method C. *Yield*: 171 mg (68%). CAS number 1313614-50-4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44–7.38 (m, 1H), 7.26 (d, J=7.3 Hz, 1H), 7.23–7.12 (m, 2H), 4.34 (d, J=17.2 Hz, 2H), 4.14 (d, J=17.2 Hz, 2H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 162.0 (d, $^1J_{FC}$=244.0 Hz), 129.8 (d, $^3J_{FC}$=7.3 Hz), 128.3 (d, $^4J_{FC}$=2.6 Hz), 118.6 (d, $^2J_{FC}$=18.7 Hz), 115.6 (d, $^2J_{FC}$=20.8 Hz), 61.9, 47.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ −114.11 (td, J=9.6, 5.8 Hz). ^{11}B NMR (128 MHz, DMSO-d_6) δ 10.69. LCMS purity >99% (UV), ret. time=15.22 min. HRMS-FTMS (m/z) found 274.0664, calcd for $[C_{11}H_{11}O_4NBFNa]^+$ 274.0664.

3.4.13. Methyl MIDA boronate ***2m***. Made following general method A. *Yield*: 171 mg (99%). Made following general method C. *Yield*: 87 mg (51%). CAS number 1104637-40-2. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 3.92 (d, J=17.0 Hz, 2H), 3.78 (d, J=17.0 Hz, 2H), 2.84 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 169.1, 62.6, 46.9. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 13.37. HRMS-ESI (m/z) found 194.0594, calcd for $[C_6H^{10}_{10}BNO_4Na]^+$ 194.0595.

3.4.14. Phenyl MIDA boronate ***2n***. Made following general method A. *Yield*: 123 mg (53%). Made following general method C. *Yield*: 128 mg (55%). Made following modified general method B ($PhBCl_2$ (Sigma Aldrich)) was first added dropwise to stirred MIDA in DMF in microwave vial (CAUTION, HCl evolution!) *Yield*: 147 mg (63%). CAS number 109737-57-7. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.53–7.47 (m, 2H), 7.44–7.36 (m, 3H), 4.06 (d, J=17.1 Hz, 2H), 3.88 (d, J=17.1 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 169.6, 133.4, 130.3, 128.9, 62.8, 48.5. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 10.64. LCMS purity >99% (UV), ret. time=14.38 min. HRMS-ESI (m/z) found 256.0750, calcd for $[C_{11}H^{10}_{12}BNO_4Na]^+$ 256.0752.

3.4.15. (E)-Styryl MIDA boronate ***2o***. Made following general method A. *Yield*: 135 mg (52%), 480 mg (3.5 mmol scale, 53%). Made following general method C. *Yield*: 75 mg (29%). CAS number 1152427-93-4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52–7.47 (m, 2H), 7.39–7.32 (m, 2H), 7.29–7.24 (m, 1H), 6.83 (d, J=18.2 Hz, 1H), 6.28 (d, J=18.2 Hz, 1H), 4.25 (d, J=17.0 Hz, 2H), 4.04 (d, J=17.0 Hz, 2H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.0, 141.0, 137.8, 128.5, 127.8, 126.4, 61.3, 46.7, 39.5. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 10.54. LCMS purity ≥99% (UV), ret. time=1.75 min. HRMS-FTMS (m/z) found 328.9971, calcd for $[C_{11}H^{10}_{10}BBrFNO_4H]^+$ 328.9979.

3.4.16. 2-Bromo-6-fluorophenyl MIDA boronate ***2p***. Made following general method B. *Yield*: 205 mg (62%), 924 mg (5 mmol scale, 56%). Made following general method C. *Yield*: 46 mg (14%). CAS number 1257650-76-2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (d, $^3J_{HH}$=8.0 Hz, 1H), 7.36 (dd, $^3J_{HH}$=8.0, 8.2 Hz, 1H), 7.19 (dd, $^3J_{FH}$=10.9, $^3J_{HH}$=8.2 Hz, 1H), 4.42 (d, J=17.3 Hz, 2H), 4.16 (d, J=17.3 Hz, 2H), 2.72 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.6, 166.5 (d, $^1J_{CF}$=248.0 Hz), 132.6 (d, $^3J_{FC}$=11 Hz), 130.5 (d, $^4J_{FC}$=3.0 Hz), 127.8 (d, $^3J_{FC}$=9.0 Hz), 115.2 (d, $^2J_{FC}$=27.0 Hz), 63.0, 47.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ −97.67 (dd, J=10.9, 6.3 Hz). ^{11}B NMR (128 MHz, DMSO-d_6) δ 10.6. LCMS purity ≥99% (UV), ret. time=15.42 min. HRMS-FTMS (m/z) found 328.9971, calcd for $[C_{11}H^{10}_{10}BBrFNO_4H]^+$ 328.9979.

3.4.17. 2-Formylphenyl MIDA boronate ***2q***. Following general method B. *Yield*: 116 mg (44%), CAS number 1257651-51–6. Following general method C. *Yield*: 23 mg (9%). ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 10.11 (s, 1H), 7.93 (m, 1H), 7.80 (m, 1H), 7.66 (m, 2H), 4.14 (d, J=17.8, 2H), 4.14 (d, J=17.8, 2H), 2.68 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3): 196.8, 169.9, 142.1, 136.8, 135.2, 134.0, 130.7, 65.7, 50.0. ^{11}B NMR (128 MHz, acetonitrile-d_3): 11.83. LCMS purity ≥99% (UV), ret. time=12.94 min. HRMS-FTMS (m/z) found 262.0880, calcd for $[C_{12}H^{10}_{12}BNO_5H]^+$ 262.0881.

3.4.18. 2-Bromophenyl MIDA boronate ***2r***. Made following general method B. *Yield*: 224 mg (72%). Made following general method C. *Yield*: 218 mg (70%). CAS number 1257649-57-2. ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 7.67 (d, J=7.4 Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.39 (dd, J=7.4 Hz, 7.5 Hz, 1H), 7.30 (dd, J=7.8, 7.5 Hz, 1H), 4.13 (d, J=17.3 Hz, 2H), 4.03 (d, J=17.3 Hz, 2H), 2.71 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3): 169.5, 137.4, 134.6, 132.4, 128.7, 128.0, 65.3, 49.6. ^{11}B NMR (128 MHz, acetonitrile-d_3): 11.60. LCMS purity ≥99% (UV), ret. time=15.44 min. HRMS-FTMS (m/z) found 333.9862, calcd for $[C_{11}H^{10}_{11}BBrNO_4Na]^+$ 333.9857.

3.4.19. 2-Methoxyphenyl MIDA boronate ***2s***. Made following general method B. *Yield*: 254 mg (97%), 1144 mg (5 mmol scale, 87%), 2420 mg (10 mmol scale, 92%). Made following general method C. *Yield*: 134 mg (51%). CAS number 1257737-05-5. ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 7.56 (dd, J=7.2, 1.9 Hz, 1H), 7.39 (ddd, J=8.2, 7.2, 1.9 Hz, 1H), 6.97 (m, 2H), 4.06 (d, J=17.0 Hz, 2H), 3.95 (d, J=17.0 Hz, 2H), 3.77 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): 169.2, 162.0, 133.9, 130.7, 120.2, 110.3, 63.2, 54.8, 47.2. ^{11}B NMR (128 MHz, acetonitrile-d_3): 7.66. LCMS purity ≥99% (UV), ret. time=14.76 min. HRMS-FTMS (m/z) found 286.0860, calcd for $[C_{12}H^{10}_{14}BNO_5Na]^+$ 286.0857.

3.4.20. 2-Chloro-3-pyridyl MIDA boronate ***2t***. Made following general method B. *Yield*: 67 mg (25%). Made following general method C. *Yield*: 220 mg (82%). CAS number 1309676-59-2. ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 8.39 (dd, J=4.7, 1.8 Hz, 1H), 8.11 (dd, J=1.8, 7.4 Hz, 1H), 7.35 (dd, J=7.4, 4.7 Hz, 1H), 4.16 (d, J=17.3 Hz, 2H), 4.05 (d, J=17.3 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3): 169.3, 151.6, 146.6, 123.5, 111.0, 65.2, 49.3. ^{11}B NMR (128 MHz, acetonitrile-d_3): 11.01. LCMS purity ≥99% (UV), ret. time=11.43 min. HRMS-FTMS (m/z) found 291.0309, calcd for $[C_{10}H^{10}_{10}BClN_2O_4Na]^+$ 291.0314.

3.4.21. 2,4-Dimethoxypyrimidine-5-MIDA boronate ***2u***. Made following general method B. *Yield*: 245 mg (83%). Made following general method C. *Yield*: 177 mg (60%). ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 8.38 (s, 1H), 4.08 (d, J=17.0 Hz, 2H), 3.95 (s, 3H), 3.94 (d, J=17.0 Hz, 2H), 3.91 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3): δ 174.8, 169.3, 167.9, 164.9, 111.0, 64.0, 55.2, 54.3, 48.2. ^{11}B NMR (128 MHz, acetonitrile-d_3): δ 11.24. LCMS purity 97% (UV), ret. time=10.34 min. HRMS-FTMS (m/z) found 296.1046, calcd for $[C_{11}H^{10}_{14}BN_3O_6H]^+$ 296.1048.

3.4.22. 2-Hydroxyphenyl MIDA boronate ***2v***. Made following general method B. *Yield*: 105 mg (1 mmol scale, 42%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H), 7.38 (dd, J=7.3, 1.6 Hz, 1H), 7.17 (ddd, J=7.9, 7.3, 1.6 Hz, 1H), 6.80–6.73 (m, 2H), 4.32 (d, J=17.0 Hz, 2H), 4.03 (d, J=17.0 Hz, 2H), 2.63 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): 169.3, 160.0, 134.0, 130.2, 118.7, 114.6, 63.1, 47.1. ^{11}B NMR (128 MHz, DMSO-d_6): 11.80. LCMS purity ≥99% (UV), Ret. time=12.76 min. HRMS-FTMS (m/z) found 272.0702, calcd for $[C_{11}H^{10}_{12}BNO_5Na]^+$ 272.0701.

3.4.23. 2-Fluorophenyl MIDA boronate ***2w***. Following general method B. *Yield*: 208 mg (83%), 991 mg (5 mmol scale, 79%). ^{1}H NMR (500 MHz, acetonitrile-d_3): 7.59 (dd, J=7.4 Hz, 1H), 7.49–7.41 (m, 1H), 7.22 (dd, J=7.4 Hz, 1H), 7.08 (dd, J=10.4, 8.4 Hz, 1H), 4.12 (d, J=17.1 Hz, 2H), 3.95 (d, J=17.1 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): 168.9, 165.5 (d, J=241.1 Hz), 134.7 (d,

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J=9.2 Hz), 131.6 (d, J=8.7 Hz), 124.1 (d, J=2.7 Hz), 114.9 (d, J=24.8 Hz), 62.4 (d, J=2.2 Hz), 47.5. ^{19}F NMR (376 MHz, DMSO-d_6): −107.45 (m). ^{11}B NMR (128 MHz, acetonitrile-d_3): 10.48. LCMS purity ≥99% (UV), ret. time=14.72 min. HRMS-FTMS (m/z) found 274.0661, calcd for $[C_{11}H^{10}_{11}BFNO_4Na]^+$ 274.0657.

3.4.24. 2,6-Dichlorophenyl MIDA boronate ***2x***. Following general method B. *Yield*: 104 mg (35%). ^{1}H NMR (500 MHz, acetonitrile-d_3): δ 7.40 (m, 1H), 7.34–7.29 (m, 2H), 4.15 (d, J=17.4 Hz, 2H), 4.01 (d, J=17.4 Hz, 2H), 2.83 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3): δ 169.2, 142.0, 132.4, 130.9, 65.4, 49.7. ^{11}B NMR (128 MHz, acetonitrile-d_3); δ 11.36. LCMS purity ≥99% (UV), ret. Time=15.56 min. HRMS-FTMS (m/z) found 323.9967, calcd for $[C_{11}H^{10}_{10}BCl_2NO_4Na]^+$ 323.9972.

3.4.25. 4-Methoxyphenyl MIDA boronate ***2z***. Made following general method C. *Yield*: 184 mg (70%). CAS number 1257739-11-9. ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.42 (d, J=8.6 Hz, 2H), 6.94 (d, J=8.5 Hz, 2H), 4.03 (d, J=17.1 Hz, 2H), 3.86 (d, J=17.1 Hz, 2H), 3.80 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 169.6, 161.8, 134.9, 114.5, 62.7, 55.8, 48.4. ^{11}B NMR (128 MHz, acetonitrile-d_3) δ 11.56. LCMS purity >99% (UV), ret. time=14.36 min. HRMS-ESI (m/z) found 286.0869, calcd for $[C_{12}H^{10}_{14}BNO_5Na]^+$ 286.0857.

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Supplementary data

Scanned ^{1}H, ^{13}C, ^{11}B, ^{19}F NMR spectra, where applicable, for all compounds are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.044.

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