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Aryl *N*-methyliminodiacetic acid (MIDA) boronates from cyclotrimerization of ethynyl MIDA boronate with diynes

Silje Melnes [a], Annette Bayer [b], Odd R. Gautun [a,*]

[a] Department of Chemistry, Norwegian University of Science and Technology (NTNU), NO-7491 Trondheim, Norway
[b] Department of Chemistry, University of Tromsø (UiT), N-9037 Tromsø, Norway

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ABSTRACT

Cyclotrimerizations of ethynyl *N*-methyliminodiacetic acid (MIDA) boronate (**1**) with 1,6-diynes **2** have been studied, using three different catalysts (based on ruthenium, rhodium, and iridium) and variable reaction conditions. Successful cyclotrimerization reactions were obtained with both Cp*RuCl(cod) and $Rh(cod)_2BF_4$/BINAP as pre-catalysts in THF or acetone. Ruthenium-catalyzed cyclotrimerization of an unsymmetrically bromo-substituted diyne (**2f**) with **1** was successfully scaled up (2 g) and included in a total synthesis strategy toward potential selective inhibitors of tyrosine kinase 2.

1. Introduction

The high stability of *N*-methyliminodiacetic acid (MIDA) chelated boronic acids was first mentioned in the late 1980s.[1,2] Two decades later, the great value of the MIDA boronates was demonstrated. In 2007, Burke and Gillis reported MIDA as a highly versatile boronic acid protective group, and showed how the reactivity could be controlled between two different reaction sites in iterative Suzuki–Miyaura cross coupling reactions of MIDA-protected haloboronic acids.[3] Since then, MIDA boronates have gained increased popularity and shown to be remarkably useful in small molecule synthesis of important building blocks,[4–15] and in the synthesis of natural products[3,16–20] and peptides.[21] In general, MIDA boronates are stable to air, tolerant to a wide range of common reaction conditions, and compatible to silica chromatography.[4,17] Yet, they can easily be deprotected to the corresponding boronic acids by mild basic hydrolysis. Several MIDA boronates are now commercially available. Among them is the alkyne building block ethynyl MIDA boronate (**1**, Fig. 1), first described by Struble and co-workers in 2010.[22]

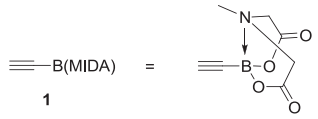

Fig. 1. Ethynyl MIDA boronate (**1**).

Alkynes are important components in several synthetic transformations. For instance, transition metal catalyzed cyclotrimerization of alkynes is a direct route to highly substituted aromatic compounds.[23–25] In our synthetic studies toward potential selective inhibitors of tyrosine kinase 2, we have prepared highly substituted aromatic key-compounds by ruthenium- and rhodium-catalyzed cyclotrimerization of unsymmetrically substituted diynes with ethynyltrimethylsilane.[26] Our main goal is to selectively prepare *meta*-substituted bicyclic products in high yield from simple alkyne precursors (Scheme 1). In this context, we found MIDA-protected arylboronic acids attractive [Y=B(MIDA), Scheme 1], as boronic acids can be precursors for hydroxyl-[27,28] and amino groups.[29] Normally, aryl MIDA boronates are prepared by condensation of MIDA and the arylboronic acid.[1,3,17] If the boronic acids are not easily accessible however, transition metal catalyzed cyclotrimerization of **1** should be a highly direct and powerful approach to more complex aryl MIDA boronates, as those depicted in Scheme 1. Interestingly, while our work was ongoing, Iannazzo and co-workers[30] reported failed attempts on cyclotrimerization of **1** under different reaction conditions. The reason of their failure was not clarified.

We will here report the first successful formation of highly substituted aryl MIDA boronates by transition metal catalyzed cyclotrimerization reactions of **1** with diynes **2**.

2. Results and discussion

A short screen for suitable reaction conditions was performed with the unsymmetrically methyl-substituted diyne **2a** (Table 1). Three different transition metal complexes were tested as pre-

* Corresponding author. Tel.: +47 73594101; fax: +47 73550877; e-mail address: odd.r.gautun@ntnu.no (O.R. Gautun).

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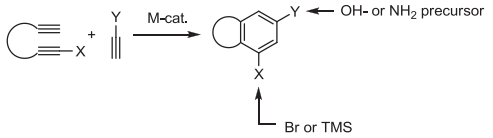
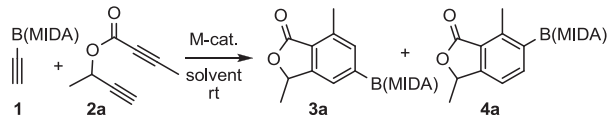


Scheme 1. Synthetic goal: the preparation of *meta*-substituted bicyclic aromatic compounds from simple alkyne precursors.

catalysts; Cp*RuCl(cod),[31,32] $Rh(cod)_2BF_4$/BINAP,[33,34] and Ir(cod)Cl/DPPE[35] [Cp*=pentamethylcyclopentadienyl, cod=1,5-cyclooctadiene, BINAP=2,2′bis(diphenylphosphino)-1,1′-binaphthyl, and DPPE=ethylenebis(diphenylphosphine)]. Room temperature and 5 mol % of catalyst were generally used. Initially, a ruthenium-catalyzed reaction of **1** and **2a** was performed in dichloroethane (DCE), a solvent earlier employed for this catalyst (Table 1, entry 1).[26] None of the desired products, **3a** and **4a**, were detected by ^{1}H NMR analysis of the crude reaction mixture. A mixture of autotrimerization products of **2a** was however seen. As the solubility of **1** in DCE was observed to be poor, THF and acetone were tested as alternative solvents. In both cases, the reaction worked smoothly, giving the *meta*-product **3a** selectively over **4a** (Table 1, entries 2 and 5). The observed regioselectivity in favor of the *meta*-product was in accordance with reports from Yamamoto and co-workers,[36] and with our own experience.[26] The isolated total yield of **3a** and **4a** was slightly higher when acetone was employed, compared to THF. The rhodium-based catalyst also worked well both in THF and acetone (Table 1, entries 3 and 7). However, the regioselectivity was only moderate in both cases, and in favor of the *ortho*-product **4a**. Unfortunately, the air-stable and easy-to-handle iridium-based catalyst did not afford any reaction products of **1** and **2a** (Table 1, entries 4, 9, and 10), even though successful cyclotrimerization of selected alkynes has been reported to work well with this catalyst in both THF and acetone.[35] Under no circumstances were autotrimerization or other by-reactions of **1** observed. In general, the total yield of **3a**/**4a** increased when a large excess of **1** was employed in the reactions (compare Table 1, entries 5 and 6, and 7 and 8). However, removal of excess **1** from the product mixtures turned out to be challenging, and hence, the amounts of **1** had to be kept as low as possible. For the ruthenium-based catalyst, 1.5 equiv of **1** gave satisfying results. Slightly more, 2 equiv of **1**, were needed for the rhodium-based catalyst to work effectively.

Based on our experience with **2a** (Table 1), cyclotrimerization of different diynes **2b**–**h** with **1** was examined. The results are given in Table 2. Diyne **2b** has been utilized as a model substrate in many studies of transition metal catalyzed alkyne cyclotrimerizations.[37] Being an electron poor 1,6-diyne with two CO_2Me-substituents contributing positively to the kinetic Thorpe–Ingold effect,[38] **2b** is especially suitable for such reactions. In this study, **2b** reacted with **1** both under ruthenium- and rhodium-catalyzed conditions to give the product **3b** in high isolated yields (87 and 70%, respectively, Table 2, entries 1 and 2). For the rhodium-catalyzed reaction, one extra purification step was necessary to obtain pure **3b**, which might explain the lower isolated yield. Again, the iridium-catalyzed cyclotrimerization did not proceed sufficiently, even though cyclotrimerizations of **2b** with this catalyst and selected monoynes have been described.[35] Only traces of **3b** were observed (Table 2, entry 3). The iridium-based catalyst was therefore concluded not suitable for reactions with **1**. As expected, the activated[38] tosyl amide tethered diyne **2c** reacted smoothly under the ruthenium-catalyzed conditions to afford aryl MIDA boronate **3c** in 80% yield (Table 2, entry 4).

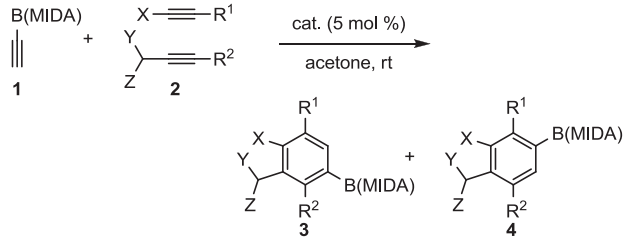
Table 1
Cyclotrimerization of **1** and **2a**



Entry	**1** (equiv)	Catalyst[a]	Solvent	Time (h)	% Yield[b] (**3a**/**4a**)[c]
1	1.5	Ru	DCE	20	No reaction[d]
2	1.5	Ru	THF	1	65 (88:12)
3	2	Rh	THF	2	67 (37:63)
4	1.5	Ir	THF[e]	20	No reaction
5	1.5	Ru	Acetone	1	84 (87:13)
6	1.1	Ru	Acetone	20	59[d] (87:13)
7	2	Rh	Acetone	20	66 (39:61)
8	1.1	Rh	Acetone	20	Traces[d]
9	1.5	Ir	Acetone[e]	20	No reaction
10	3	Ir[f]	Acetone[e]	20	No reaction

[a] Ru=5 mol % Cp*RuCl(cod); Rh=5 mol % $[Rh(cod)_2]BF_4$/BINAP; Ir=2 mol % $[Ir(cod)Cl]_2$/DPPE.
[b] Isolated yield after work-up.
[c] Determined by ^{1}H NMR analysis of crude.
[d] A mixture of autotrimerization products of **2a** was observed.
[e] Reflux.
[f] 5 mol %.

Table 2
Cyclotrimerization of **1** and **2**



b: X = CH_2, Y = $C(CO_2CH_3)_2$, Z = H, $R^1 = R^2$ = H
c: X = CH_2, Y = NTs, Z = H, $R^1 = R^2$ = H
d: X = CH_2, Y = O, Z = H, $R^1 = R^2$ = H
e: X = CH_2, Y = $C(CO_2CH_2CH_3)_2$, Z = H, $R^1 = R^2 = CH_3$
f: X = C=O, Y = O, Z = CH_3, R^1 = Br, R^2 = H
g: X = C=O, Y = O, Z = CH_3, R^1 = TMS, R^2 = H
h: X = C=O, Y = O, Z = CH_3, R^1 = H, R^2 = TMS

Entry	Diyne	**1** (equiv)	Catalyst[a]	Product (**3**/**4**)[b]	% Yield[c] (**3**+**4**)
1	**2b**	1.5	Ru	**3b**	87
2	**2b**	2	Rh	**3b**	70
3	**2b**	1.5	Ir	**3b**	Traces[b]
4	**2c**	1.5	Ru	**3c**	80
5	**2d**	1.5	Ru	**3d**	53
6	**2d**	2	Rh	**3d**	64
7	**2e**	1.5	Ru	**3e**	Traces[b]
8	**2e**	1.01	Rh	**3e**	46[d,e]
9	**2f**	1.5	Ru	**3f**+**4f** (87:13)	53[f]
10	**2g**	1.5	Ru	**3g**+**4g**+**5** (1:0:1)	nd[g]
11	**2g**	5	Ru	**3g**+**4g**+**5** (4:0:1)	nd[g]
12	**2h**	1.5	Ru	—	nr[h]

[a] Ru=Cp*RuCl(cod); Rh=$[Rh(cod)_2]BF_4$/BINAP; Ir=$[Ir(cod)Cl]_2$/DPPE.
[b] Determined by ^{1}H NMR of the crude.
[c] Isolated yield after work-up.
[d] Slow addition of **2**.
[e] Estimated yield from ^{1}H NMR. Traces of **1** were still present after purification.
[f] Pure **3f** was isolated in 19% after washing the mixture with acetone.
[g] nd=not determined. Pure **3g** was not isolated. Various amounts of **5** (Fig. 2) were obtained.
[h] nr=no reaction. A complex mixture of autotrimerization products of **2h** was observed after ^{1}H NMR analysis of the crude.

Cyclotrimerization of the less activated oxygen-tethered diyne **2d** with **1** resulted in the product **3d** in slight lower yields. Here, a higher yield was obtained from the rhodium-catalyzed procedure (64%, entry 6), compared to the ruthenium-catalyzed method (53%, entry 5). Slow addition of the diyne to a solution of **1** and the rhodium-catalyst using a syringe pump, did not improve the yield of **3d**. Ruthenium-catalyzed cyclotrimerization of the terminally

methyl-substituted diyne **2e** with **1** afforded only traces of the product **3e** (Table 2, entry 7). Fortunately, rhodium-catalysis was more successful. The rhodium-catalyst afforded **3e** in 46% yield (estimated from ^{1}H NMR, Table 2, entry 8) when **2e** was added by slow addition.

We then turned our attention to the more challenging diynes **2f**–**h** (Table 2, entries 9–12). Not unexpectedly, the yields dropped. The reduced yields can partly be explained by the less suitable electronic and/or steric properties of the diynes. In some cases, autotrimerization of the diyne gained increased importance. The formation of **3g** by ruthenium-catalyzed cyclotrimerization of **2g** with **1** competed with formation of the by-product **5** (Fig. 2) from autotrimerization of **2g** (Table 2, entries 10 and 11). The formation of **5** could, however, be suppressed by increasing the load of **1** in the reaction. Applying 5 equiv of **1** instead of 1.5, the ratio **3g**/**5** changed from 1:1 to 4:1. The unwanted regioisomer **4g** was not observed from the reactions of **2g**. For diyne **2h**, only autotrimerization products were observed after ruthenium catalysis (Table 2, entry 12). Increasing the equivalents of **1** from 1.5 to 5 did not help. The rhodium catalyst was neither efficient, and applying slow addition of **2h** did not help. These results probably originate from unfavorable steric- and electronic properties of the diyne.

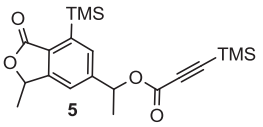
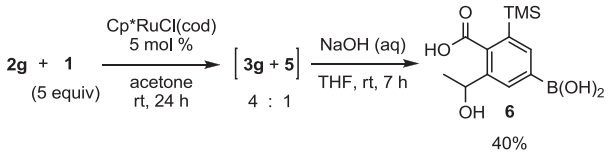


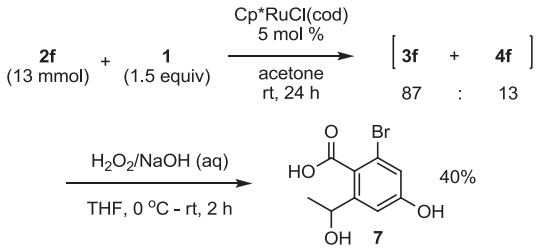
Fig. 2. Side-product **5** from autotrimerizaton of **2g**.

In addition to the diyne properties, another important factor for the reduced yields obtained, was the challenging separation of **1**, **3**, and **4**. The purification of MIDA boronates has in details been described by Burke and Gillis.[4,39] In many cases, MIDA boronates can be easy to purify. However, **1**, **3**, and **4** showed strikingly similar behavior regarding both R_f—values on silica with several mobile phases, such as Et_2O/CH_3CN, Et_2O/acetone, and hexane/EtOAc/MeOH, and solubility/crystallization properties. The only remarkable difference found between the alkyne and the aryl MIDA boronate products, was the behavior on C18-modified SiO_2 TLC-plates. However, purification was sensitive to amounts of **1** present, and several repeating purification steps were necessary in some cases. For **3g** (Table 2, entries 10 and 11), we were not able to remove the remaining **1**, even after extensive work-up. Removal of excess **1** from the product mixture by chemical modification, hydrogenation ($Rh-Al_2O_3/H_2$), terminal bromination ($NBS/AgNO_3$),[40] or complexation to cobalt $[Co_2(CO)_8]$[41] was unsuccessful. Fortunately, transforming the crude mixture containing **3g** to the corresponding boronic acid **6** by basic hydrolysis (Scheme 2), proved feasible, as **1** decomposes under the reaction conditions. The boronic acid **6** was hence isolated in 40% yield.



Scheme 2. Preparation of the boronic acid **6** after basic hydrolysis of the cyclotrimerization product mixture of **3g** and **5**.

Finally, we wanted to include cyclotrimerization of **1** with the unsymmetrically bromo-substituted diyne **2f** in our synthetic work toward potential selective inhibitors of tyrosine kinase 2. The ruthenium-catalyzed reaction of **1** and **2f** gave 53% total yield of the products **3f** and **4f** in an 87:13 ratio (Table 2, entry 9). Pure **3f** was isolated in 19% yield after washing the product mixture with acetone. The reaction was easily scaled up (2.7 g, 13 mmol **2f**, Scheme 3), and fortunately, ^{1}H NMR analysis of the crude showed no change in regioselectivity. The crude mixture of **3f** and **4f** was directly transformed to the wanted phenols by treatment with $NaOH/H_2O_2$ (aq). The pure regioisomer **7** was isolated in 40% yield after simply washing the product mixture with acetone.



Scheme 3. Preparation of **7** from **2f** and **1**.

3. Conclusion

In summary, we have described the first successful transition metal catalyzed cyclotrimerization reactions of **1** with different diynes **2**. Three different pre-catalysts have been tested, Cp*RuCl(cod), $[Rh(cod)_2]BF_4$/BINAP, and $[Ir(cod)Cl]_2$/DPPE, of which the former two worked well in acetone and THF at rt. The cyclotrimerization reactions of **1** with **2** provided rapid construction of highly substituted aryl MIDA boronates not easily accessible from other conventional methods. Several synthetic transformations of aryl MIDA boronates are available, and hence, cyclotrimerization of **1** is a promising new approach to molecules of high complexity.

4. Experimental section

4.1. General information

Chemicals were purchased from Sigma–Aldrich and used without further purification. The non-commercial diynes **2a**, **2f**, and **2h** were prepared as described earlier.[26] The diynes **2b**,[42] **2c**,[43] and **2e**[44] were prepared according to the literature. All reactions sensitive to air or moisture were performed under argon atmosphere with dried solvents and reagents. DCM, THF, and Et_2O were dried using MBRAUN solvent purification system (MB SPS-800). Acetone was dried over activated 4 Å molecular sieves. For the Ru-catalyzed procedure, acetone was degassed with helium for 10–20 min prior to use. Melting points were determined on a Buchi 535 apparatus and are uncorrected.

TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 312 nm and a 5% solution of molybdophosphoric acid in 96% EtOH or a $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 2.5 mL 5 M NaOH, 200 mL H_2O) for detection. Column chromatography was performed with Silica gel (pore size 60 Å, 230–400 mesh particle size) from Fluka. Crude products from cyclotrimerization reactions were concentrated on Florisil® and dry-loaded on top of the prepacked silica gel columns. Reverse phase preparative TLC was performed using Analtech TLC uniplates C18-silica gel matrix, 20 cm×20 cm, purchased from Sigma–Aldrich. ^{1}H and ^{13}C NMR spectra were recorded from Bruker Advance DPX instruments (300/75 MHz and 400/100 MHz). Chemical shifts (δ) are reported in parts per million. Where $CDCl_3$ has been used, shift values for proton are reported with reference to TMS (0.00) via the lock signal of the solvent. Reference values for other NMR-solvents are taken from Silverstein[45] (^{1}H NMR: CD_3CN: 1.93, acetone-d_6: 2.04, DMSO-d_6: 2.49; C NMR: CD_3CN: 1.30; acetone-d_6: 29.8, DMSO-d_6: 39.7, CD_3Cl:

77.0). Signal patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). ^{1}H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC). Carbons bearing boron substituents were often not observed due to quadrupolar relaxation. IR spectra were recorded from a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed (cm^{-1}). Accurate mass determination, EI and ESI, was performed on MAT95XL ThermoFinnigan and Agilent G1969 TOF MS instrument, respectively. For ESI analyses, samples were injected into the instrument using an Agilent 1100 series HPLC. A direct injection analysis without any chromatography was performed for the EI analyses.

4.2. Preparation of but-3-yn-2-yl 3-(trimethylsilyl)propiolate (2g)

A solution of 3-(trimethylsilyl)propynoic acid (1.06 g, 7.28 mmol, 1 equiv) and DEAD (40wt % in toluene, 3.32 mL, 7.28 mmol, 1 equiv) in THF (10 mL) was added dropwise over 20 min to a cooled (0 °C) solution of PPh_3 (1.91 g, 7.28 mmol, 1 equiv) and 3-butyn-2-ol (0.86 mL, 11 mmol, 1.5 equiv) in THF (12 mL). The resulting suspension was stirred and slowly warmed to rt. After 16 h, the mixture was filtered through a silica-pad, prepacked with Et_2O. The pad was washed with Et_2O. The filtrate was concentrated, and the crude product was purified by column chromatography (1.5% EtOAc in *n*-hexane) to give the title compound (0.944 g, 4.86 mmol, 67%) as a colorless oil. R_f (10% EtOAc/*n*-hexane) 0.46. IR (neat): 3297 (w), 2963 (w), 2190 (w), 2125 (w), 1712 (s), 1214 (s), 842 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (1H, dq, *J* 6.7, 2.2 Hz, CH), 2.50 (1H, d, *J* 2.2 Hz, alkyne–H), 1.56 (3H, d, *J* 6.7 Hz, CH_3), 0.25 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 95.1, 94.0, 81.0, 73.8, 61.7, 21.0, −0.9; HRMS (EI): *m*/*z* calcd for $C_9H_{11}O_2Si$ $[M-CH_3]^+$: 179.0523; found: 179.0524.

4.3. Representative procedures for transition metal catalyzed cyclotrimerization of 1 and 2

4.3.1. Representative procedure for ruthenium-catalyzed cyclotrimerization. Ruthenium-catalyzed cyclotrimerization reactions were performed as described by Yamamoto and co-workers.[31,32]

A solution of **2** (1.00 mmol, 1 equiv) in acetone (3 mL) was added dropwise over 10 min to a mixture of **1** (0.271 g, 1.50 mmol, 1.5 equiv) and Cp*RuCl(cod) (19 mg, 0.050 mmol, 5 mol %) in acetone or THF (2 mL). The resulting dark red mixture was stirred at rt until TLC (10% EtOAc/*n*-hexane) showed complete conversion of **2**. The crude mixture was concentrated under reduced pressure, and analyzed by ^{1}H NMR (acetone-d_6).

4.3.2. Representative procedure for rhodium-catalyzed cyclotrimerization. Rhodium-catalyzed cyclotrimerization reactions were performed as described by Tanaka and co-workers.[34]

A mixture of $[Rh(cod)_2]BF_4$ (20 mg, 0.050 mmol, 5 mol %) and BINAP (31 mg, 0.050 mmol, 5 mol %) was added DCM (7.5 mL), and the resulting yellow solution was stirred at rt for 5 min. The flask was evacuated, and 1 atm of H_2 was introduced (balloon). After stirring at rt for 1 h, the red solution was concentrated to dryness, and an atmosphere of argon was introduced. A solution of **1** (0.362 g, 2.00 mmol, 2 equiv) and **2** (1.00 mmol, 1 equiv) in acetone or THF (10 mL) was added dropwise over 20 min. The mixture was stirred at rt until TLC (10% EtOAc/*n*-hexane) showed complete conversion of **2**. The crude mixture was concentrated under vacuum and analyzed by ^{1}H NMR (acetone-d_6).

4.3.3. Representative procedure for rhodium-catalyzed cyclotrimerization using slow addition. A mixture of $[Rh(cod)_2]BF_4$ (20 mg, 0.050 mmol, 5 mol %) and BINAP (31 mg, 0.050 mmol, 5 mol %) was added DCM (7.5 mL), and the resulting yellow solution was stirred at rt for 5 min under argon atmosphere. The flask was evacuated, and 1 atm of H_2 was introduced (balloon). After stirring for 1 h at rt, the red solution was concentrated to dryness under vacuum, and an atmosphere of argon was introduced. A solution of **1** (0.271 g, 1.50 mmol) in acetone (4.5 mL) was added. To the stirred solution, a solution of **2** (1.00 mmol) in acetone (4 mL) was slowly added at rt over 10 h via a syringe pump. The resulting mixture was stirred at rt over night, then concentrated under vacuum and analyzed by ^{1}H NMR (acetone-d_6).

4.3.4. Representative procedure for iridium-catalyzed cyclotrimerization. Iridium-catalyzed cyclotrimerization reactions were performed as described by Kezuka and co-workers.[35]

A mixture of $[Ir(cod)Cl]_2$ (14 mg, 0.02 mmol, 2 mol %), DPPE (17 mg, 0.04 mmol, 4 mol %), and **2** (1.00 mmol, 1 equiv) was dissolved in acetone or THF (5 mL), and added **1** (0.271 g, 1.50 mmol, 1.5 equiv) against a positive argon-flow. The resulting suspension was warmed to reflux and stirred for 20 h. After cooling to rt, the crude solution was concentrated under vacuum, and analyzed by ^{1}H NMR (acetone-d_6).

4.3.5. General procedure for work-up after cyclotrimerization. The products **3** and **4** were purified in accordance with a procedure described by Gillis and Burke[17] with modifications.

The crude product was dissolved in MeCN and added Florisil®. The mixture was concentrated to dryness, and loaded on top of a silica column pre-packed with Et_2O. The column was flushed with copious amounts of Et_2O, before the product was eluated with a gradient of MeCN in Et_2O (5–30%). $KMnO_4$ was used for visualization on TLC. If **1** still remained in the product after the column, this product mixture was further purified by a second column, crystallization, washing, and/or C18-modified preparative TLC with 5% MeCN in H_2O as mobile phase.

4.4. Experimental details for aryl MIDA boronates 3 and 4

*4.4.1. 3,7-Dimethyl-1-oxo-1,3-dihydroisomenzofuran-5-yl MIDA boronate (**3a**) and 1,4-dimethyl-3-oxo-1,3-dihydroisomenzofuran-5-yl MIDA boronate (**4a**).* Conditions and results from the preparation of **3a** and **4a** are summarized in Table 1.

The representative procedure for ruthenium-catalysis, using **1** (0.201 g, 1.16 mmol) and **2a** (0.105 g, 0.771 mmol) in acetone (4 mL) for 1 h, gave an 87:13 mixture of the products **3a** and **4a** (0.205 g, 0.645 mmol, 84%, Table 1, entry 5) as a white solid after column chromatography (general procedure). Pure **3a** (white solid) was obtained after crystallization of the product mixture from acetone (1 mL).

The representative procedure for rhodium-catalysis, using **1** (0.362 g, 2.00 mmol) and **2a** (0.136 g, 1.00 mmol) in acetone (10 mL) for 20 h, gave a 39:61 mixture of **3a** and **4a** (0.209 g, 0.659 mmol, 66%, Table 1, entry 7) as a colorless oil after column chromatography (general procedure). The regioisomers were inseparable.

R_f (**3a**+**4a**, 40% MeCN/Et_2O) 0.57.

Data for **3a**: mp >250 °C. IR (neat): 2955 (w), 1739 (s), 1698 (m), 1279 (s), 1251 (m), 1022 (s, br), 956 (s), 859 (s) cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN): δ 7.47 (1H, s, ArH), 7.42 (1H, s, ArH), 5.50 (1H, q, *J* 6.7 Hz, CH), 4.10 (2H, d, *J* 17.1 Hz, MIDA–CH_2), 3.93 (2H, app. dd, *J* 17.1, 7.2 Hz, MIDA–CH_2), 2.62 (3H, s, $ArCH_3$), 2.50 (3H, s, NCH_3), 1.55 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN): δ 171.5 (CO), 169.41 (MIDA–CO), 169.35 (MIDA–CO), 167.6 (ArC–B(MIDA)), 152.7, 139.0, 135.5 (ArCH), 124.8, 124.3 (ArCH), 77.9 (CH), 63.0 (MIDA–CH_2), 48.7 (NCH_3), 20.7 (CH_3), 17.3 ($ArCH_3$); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}{}^{10}BNO_6$ $[M]^+$: 316.1102; found: 316.1100.

Data for **4a**: ^{1}H NMR (400 MHz, CD_3CN): δ 7.75 (1H, d, *J* 7.8 Hz, ArH), 7.35 (1H, d, *J* 7.8 Hz, ArH), 5.48 (1H, q, *J* 6.7 Hz, CH), 4.11 (2H, d,

J 17.2 Hz, MIDA–CH_2), 3.94 (2H, d, *J* 17.2 Hz, MIDA–CH_2), 2.74 (3H, s, $ArCH_3$), 2.55 (3H, s, NCH_3), 1.54 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, CD_3CN): δ 171.7 (CO), 169.4 (MIDA–CO), 169.3 (MIDA–CO), 154.5, 145.5, 140.8 (ArCH), 124.4, 119.7 (ArCH), 76.8 (CH), 63.8 (MIDA–CH_2), 48.6 (NCH_3), 20.6 (CH_3), 16.3 ($ArCH_3$).

*4.4.2. 2,2-Bis(methoxycarbonyl)-2,3-dihydro-1H-inden-5-yl MIDA boronate (**3b**).* Conditions and results from the preparation of **3b** are given in Table 2, entries 1–3.

The representative procedure for ruthenium-catalysis, using **1** (0.136 g, 0.752 mmol) and **2b** (0.104 g, 0.500 mmol) in acetone (2.5 mL) for 30 min, afforded **3b** (0.169 g, 0.434 mmol, 87%) as a white solid after column chromatography (general procedure).

The representative procedure for rhodium-catalysis, using **1** (0.362 g, 2.00 mmol) and **2b** (0.208 g, 1.00 mmol) in acetone (10 mL) for 1 h, afforded **3b** (0.272 g, 0.700 mmol, 70%) as a white solid after column chromatography (general procedure) and crystallization from acetone (1 mL).

R_f (20% MeCN/Et_2O) 0.37. Mp 206–207 °C. IR (neat): 2959 (w), 1772 (m), 1728 (s), 1250 (s), 1031 (s), 1008 (s) cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.33 (1H, s, ArH), 7.29 (1H, d, *J* 7.6 Hz, ArH), 7.21 (1H, d, *J* 7.6 Hz, ArH), 4.04 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 3.86 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 3.69 (6H, s, CO_2CH_3), 3.54 (4H, s, CH_2), 2.47 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, CD_3CN): δ 173.0 (CO), 169.5 (MIDA–CO), 142.4, 140.8, 132.2 (Ar–CH), 129.3 (ArCH), 124.8 (ArCH), 62.8 (MIDA–CH_2), 60.9 (CH_2), 53.5 (CH_2), 48.5 (NCH_3), 41.1 (OCH_3), 41.0 (OCH_3); HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}{}^{10}BNO_8$ $[M]^+$: 388.1313; found: 388.1314.

*4.4.3. 2-Tosylisoindolin-5-yl MIDA boronate (**3c**).* Conditions and result from the preparation of **3c** are given in Table 2, entry 4.

The representative procedure for ruthenium-catalysis, using **1** (0.273 g, 1.51 mmol) and **2c** (0.246 g, 0.994 mmol) in acetone (5 mL) for 30 min, afforded **3c** (0.339 g, 0.792 mmol, 80%) as white crystals after column chromatography (general procedure).

R_f (20% MeCN/Et_2O) 0.20. Mp 147–150 °C. IR (neat): 3013 (w), 2959 (w), 1768 (s), 1752 (s), 1159 (s), 1043 (s), 815 (s), 666 (s), 565 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 7.78 (2H, d, *J* 8.0 Hz, Ts–H), 7.42–7.38 (4H, m, ArH, Ts–H), 7.24 (1H, d, *J* 7.9 Hz, Ar–H), 4.59 (4H, s br, 2× CH_2), 4.32 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 4.10 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 2.67 (3H, s, NCH_3), 2.37 (3H, s, Ts–CH_3); ^{13}C NMR (100 MHz, CD_3CN): δ 169.2 (MIDA–CO), 144.5, 138.1, 136.8, 134.8, 132.7 (Ar–CH), 130.6 (Ar–CH), 128.5 (Ts–CH), 127.6 (Ar–CH), 122.9 (Ts–CH), 62.7 (MIDA–CH_2), 54.4 (CH_2), 54.3 (CH_2), 48.2 (NCH_3), 21.3 (Ts–CH_3); HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}{}^{11}BN_2O_6S$ $[M]^+$: 428.1208; found: 428.1208.

*4.4.4. 1,3-Dihydroisobenzofuran-5-yl MIDA boronate (**3d**).* Conditions and results from the preparation of **3d** are given in Table 2, entries 5 and 6.

The representative procedure for ruthenium-catalysis, using **1** (0.271 g, 1.50 mmol) and **2d** (0.103 mL, 1.00 mmol) in acetone (5 mL) for 30 min, afforded **3d** (0.147 g, 0.534 mmol, 53%) as white crystals after column chromatography (general procedure).

The representative procedure for rhodium-catalysis, using **1** (0.362 g, 2.00 mmol) and **2d** (0.10 mL, 1.0 mmol) in acetone (10 mL) for 1 h, afforded **3d** (0.178 g, 0.64 mmol, 64%) as white crystals after column chromatography (general procedure, two columns).

R_f (20% MeCN/Et_2O) 0.19. Mp 191–192 °C. IR (neat): 2856 (w), 1746 (s, br), 1275 (s), 1241 (s), 1031 (s), 993 (s), 813 (s) cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.41–7.36 (2H, m, ArH), 7.28 (1H, d, *J* 8.1 Hz, ArH), 5.02 (4H, s br, 2× CH_2), 4.06 (2H, d, *J* 17.1 Hz, MIDA–CH_2), 3.88 (2H, d, *J* 17.1 Hz, MIDA–CH_2), 2.48 (3H, s, NCH_3); ^{13}C NMR (100 MHz, CD_3CN): δ 169.6 (MIDA–CO), 167.8 (ArC–B(MIDA)), 141.7, 140.2, 132.4, 126.0, 121.6, 73.82 (OCH_2Ar), 73.79 (OCH_2Ar), 62.8 (MIDA–CH_2), 48.5 (NCH_3); HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}{}^{11}BNO_5$ $[M]^+$: 275.0960; found: 275.0962.

*4.4.5. 2,2-Bis(ethoxycarbonyl)-4,7-dimethyl-2,3-dihydro-1H-inden-5-yl MIDA boronate (**3e**).* Conditions and results from the preparation of **3e** are given in Table 2, entries 7 and 8.

The representative procedure for rhodium-catalysis with slow addition, using **1** (0.182 g, 1.01 mmol) and **2e** (0.264 g, 0.999 mmol) in acetone (8 mL), afforded **3e** (0.206 g, 0.463 mmol, 46%, estimated yield from ^1H NMR analysis) in mixture with **1** as a colorless oil after column chromatography (general procedure).

Data for **3e** (analytical sample): R_f (20% MeCN/Et_2O) 0.22. IR (neat): 2982 (m), 1768 (s, br), 1730 (s), 1286 (s), 1241 (s), 1023 (s), 1001 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 7.10 (1H, s, ArH), 4.30 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 4.18 (4H, q, *J* 7.1 Hz, $COCH_2CH_3$), 4.11 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 3.51 (4H, app d, *J* 7.9 Hz, 2× CH_2), 2.75 (3H, s, NCH_3), 2.29 (3H, s, $ArCH_3$), 2.18 (3H, s, $ArCH_3$), 1.23 (6H, t, *J* 7.1 Hz, $COCH_2CH_3$); ^{13}C NMR (100 MHz, acetone-d_6): δ 172.3 (CO_2Et), 169.3 (MIDA–CO), 140.6, 140.4, 136.1, 135.0, 130.6, 63.3 (OCH_2CH_3), 62.1 (MIDA–CH_2), 59.8 ($C(CH_2CH_3)_2$), 48.0 (NCH_3), 40.8 (CH_2), 40.2 (CH_2), 18.8 ($ArCH_3$), 18.5 ($ArCH_3$), 14.3 (OCH_2CH_3); HRMS (EI): *m*/*z* calcd for $C_{22}H_{28}{}^{11}BNO_8$ $[M]^+$: 445.1902; found: 445.1909.

*4.4.6. 7-Bromo-3-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl MIDA boronate (**3f**).* Conditions and results from the preparation of **3f** are given in Table 2, entry 9.

The representative procedure for ruthenium-catalysis, using **1** (0.267 g, 1.48 mmol) and **2f** (0.198 g, 0.985 mmol) in acetone (5 mL) for 1 h, gave an 87:13 mixture of the regioisomers **3f** and **4f** (0.201 g, 0.526 mmol, 53%) as a white solid after column chromatography (general procedure). Pure **3f** (70 mg, 0.18 mmol, 19%) was afforded after washing the product mixture with acetone (5×1 mL).

Mp >250 °C. R_f (20% MeCN/Et_2O) 0.22. IR (neat): 2998 (w), 1751 (s, br), 1199 (s), 1044 (s), 1008 (s), 862 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.77 (1H, s, ArH), 7.71 (1H, s, ArH), 5.63 (1H, q, *J* 6.6 Hz, CH), 4.39 (2H, app. dd, *J* 17.2, 2.6 Hz, MIDA–CH_2), 4.18 (2H, app. dd, *J* 17.2, 12.0 Hz, MIDA–CH_2), 2.58 (3H, s, NCH_3), 1.56 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.33 (MIDA–CO), 169.28 (MIDA–CO), 167.4 (CO), 166.4 (ArC–B(MIDA)), 153.8, 137.2 (ArCH), 126.0 (ArCH), 123.7, 118.9, 76.3 (CH), 62.54 (MIDA–CH_2), 62.50 (MIDA–CH_2), 48.2 (NCH_3), 20.1 (CH_3); HRMS (EI): *m*/*z* calcd for $C_{14}H_{13}{}^{10}B^{79}BrNO_6$ $[M]^+$: 381.0014; found: 381.0014.

*4.4.7. 3-Methyl-1-oxo-7-(trimethylsilyl)-1,3-dihydroisobenzofuran-5-yl MIDA boronate (**3g**) and 1-(3-methyl-1-oxo-7-(trimethylsilyl)-1,3-dihydroisobenzofuran-5-yl)ethyl 3-(trimethylsilyl)propiolate (**5**).* Cyclo trimerization reactions of **1** and **2g** afforded mixtures of **3g** and **5** (Fig. 2). Conditions and results are given in Table 2, entries 10 and 11.

The representative procedure for ruthenium-catalysis, using **1** (0.172 g, 0.951 mmol) and **2g** (0.123 g, 0.633 mmol) in acetone (6 mL) for 24 h, afforded a 1:1 mixture of **3g** and **5** (observed by ^1H NMR of the crude), in addition to excess **1**.

The MIDA boronate **3g** was isolated in mixture with **1** (1:0.65, 52 mg) as a white solid after column chromatography (standard procedure), followed by preparative C18-TLC (3% NaCl in H_2O) and a second column (standard procedure). R_f (20% MeCN/Et_2O) 0.37. ^1H NMR (400 MHz, acetone-d_6): δ 7.89 (1H, s, ArH), 7.82 (1H, s, ArH), 5.62 (1H, q, *J* 6.6 Hz, CH), 4.41 (2H, d, *J* 17.0 Hz, MIDA–CH_2), 4.19 (2H, app. dd, *J* 17.0, 6.2 Hz, MIDA–CH_2), 2.78 (3H, s, NCH_3), 1.60 (3H, d, *J* 6.6 Hz, CH_3), 0.36 (9H, s, TMS); ^{13}C NMR (100 MHz, acetone-d_6): δ 171.7 (CO), 169.11 (MIDA–CO), 169.06 (MIDA–CO), 152.0, 139.83 (ArC-TMS), 139.80 (ArCH), 131.5, 127.9 (ArCH), 78.2 (CH), 62.90 (MIDA–CH_2), 62.88 (MIDA–CH_2), 48.4 (NCH_3), 20.7 (CH_3), −0.9 (TMS).

The autotrimerization product **5** (colorless oil, 60 mg, 0.15 mmol, 47%) was isolated as a mixture of diastereomers (observed in the ^{13}C NMR spectrum) after column chromatography (10% EtOAc in *n*-

hexane) of the concentrated Et_2O-fractions from the first purification step of **3g** (see above). The diastereomers are symbolized a and b under assignation of ^{13}C NMR shift values. R_f (10% EtoAc/*n*-hexane) 0.34. IR (neat): 2958 (w), 1759 (m), 1709 (m), 1218 (s), 1050 (s), 839 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, app. br d, *J* 5.6 Hz, H6), 7.41–7.39 (1H, m, H4), 6.03 (1H, q, *J* 6.6 Hz, H2′), 5.52 (1H, q, *J* 6.6 Hz, H3), 1.66–1.61 (6H, m, H10 and H1′), 0.41 (9H, s, H11), 0.26 (9H, s, H7′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (C1), 152.2 (C4′b), 152.1 (C4′a), 151.9 (C9a), 151.8 (C9b), 145.6 (C5a), 145.5 (C5b), 142.45 (C7a), 142.43 (C7b), 133.11 (C6b), 133.07 (C6a), 130.0 (C8b), 129.9 (C8a), 119.7 (C4b), 119.4 (C4a), 94.9 (C6′a), 94.4 (C6′b), 77.2 (br, C5′), 77.17 (C3a), 77.15 (C3b), 73.84 (C2′a), 73.77 (C2′b), 22.4 (C10a), 22.1 (C10b), 20.4 (C1′), −0.9 (C7′), −1.2 (C11); HRMS (EI): *m*/*z* calcd for $C_{19}H_{25}O_4Si_2$ $[M-CH_3]^+$: 373.1286; found: 373.1293.

*4.4.8. 4-Borono-2-(1-hydroxyethyl)-6-(trimethylsilyl)benzoic acid (**6**).* Conditions and results from the preparation of **6** from **1** and **2g** are illustrated in Scheme 2.

The representative procedure for ruthenium-catalysis, using **1** (1.38 g, 7.63 mmol) and **2g** (0.298 g, 1.53 mmol) in acetone (15 mL) gave a 4:1 mixture of **3g** and **5** (observed by ^1H NMR of the crude), in addition to excess **1**, after 24 h at rt. The crude was suspended in THF (20 mL) and cooled to 0 °C. NaOH (1 M in H_2O, 25 mL) was added. The resulting solution was warmed to rt and stirred. After 7 h, the mixture was cooled to 0 °C. HCl (1 M in H_2O, 16 mL) was added (pH 3), and the mixture was warmed to rt and diluted with Et_2O (30 mL). The phases were separated. The water phase was extracted with THF/Et_2O (1:1, 3×40 mL). The collected organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude was recrystallized from THF/MeOH (9:1, 4 mL), to afford a light brown mass. Washing the mass with EtOAc (3×0.5 mL) afforded **6** (0.173 g, 0.613 mmol, 40%) as a white powder.

Mp 250–260 °C. R_f (80% EtOAc/*n*-hexane) 0.33. IR (neat): 3545 (m), 3334 (m, br), 2969 (w), 1735 (s), 842 (s), 705 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.39 (1.7H, s br), 8.25 (0.14H, s, ArH), 8.09 (0.14H, s, ArH), 8.06 (1H, s, ArH), 7.98 (1H, s, ArH), 5.72 (0.14H, q, *J* 6.7 Hz, CH), 5.67 (1H, q, *J* 6.7 Hz, CH), 1.59 (0.42H, d, *J* 6.7 Hz, CH_3), 1.54 (3H, d, *J* 6.7 Hz, CH_3), 0.38 (1.35H, s, TMS), 0.34 (9H, s, TMS); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.1 (COOH), 166.5 (app. d, *J* 1.5 Hz, $ArCB(OH)_2$), 150.8, 140.5 (ArCH), 138.1, 130.6, 128.6 (ArCH), 77.5 (CH), 20.4 (CH_3), −0.72 (TMS); HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}{}^{10}BO_6Si$ $[(M+CH_3COO)-H_2O]^-$: 323.1131; found 323.1135.

*4.4.9. 2-Bromo-4-hydroxy-6-(1-hydroxyethyl)benzoic acid (**7**).* Conditions and results from the preparation of **7** from **1** and **2f** are given in Scheme 3. The oxidative work-up was performed in accordance with a procedure described by Yamamoto and Hattori.[28]

The representative procedure for ruthenium-catalysis, using **1** (3.60 g, 19.9 mmol) and **2f** (2.67 g, 13.3 mmol) in acetone (65 mL) was followed. After 24 h at rt, the resulting suspension was concentrated to dryness. ^1H NMR analysis (acetone-d_6) conformed the formation of **3f** (87%) and **4f** (13%). The crude was suspended in THF (60 mL), and cooled to 0 °C. A mixture of NaOH (1 M in H_2O) and H_2O_2 (35 wt % in H_2O) (2:1, 120 mL) was slowly added. The resulting solution was warmed to rt and stirred. After 2 h, the mixture was cooled to 0 °C. HCl (1 M in H_2O, 40 mL) was added (pH ~3), the mixture was warmed to rt and diluted with Et_2O/THF (3:2, 250 mL). The phases were separated. The water phase was extracted with THF/Et_2O (1:1, 3×200 mL). The collected organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light brown mass was washed with acetone (5 mL) and EtOAc (2 mL) to afford **7** (1.37 g, 5.25 mmol, 40%) as a white powder.

R_f (50% acetone/*n*-hexane) 0.38. Mp 248–249 °C. IR (neat): 3175 (m, br), 1730 (s), 1610 (m), 1578 (m), 1056 (s), 865 (s) 741 (s), 708 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 11.08 (1H, s br), 7.11 (1H, d br, *J* 1.9 Hz, ArH), 6.95–6.92 (1H, m, ArH), 5.48 (1H, q, *J* 6.6 Hz, CH), 1.48 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2 (COOH), 163.8 (ArCOH), 156.6, 121.0 (ArCH), 120.3, 114.0, 108.1 (ArCH), 75.4 (CH), 20.3 (CH_3); HRMS (ESI): *m*/*z* calcd for $C_9H_6{}^{79}BrO_3$ $[(M-H)-H_2O]^-$: 240.9506; found 240.9504.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.027. These data include MOL files and InChiKeys of the most important compounds described in this article.

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