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DI- AND TRIARYLSUBSTITUTED PYRROLES BY SEQUENTIAL REGIOSELECTIVE CROSS-COUPLING REACTIONS

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Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

Abstract — The di- and tribrominated pyrroles, such as methyl 3,4,5-tribromopyrrole-2-carboxylate (**1**), ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**), methyl 4,5-dibromopyrrole-2-carboxylate (**3**), and 4,5-dibromo-2-nitropyrrole (**4**), were prepared and evaluated for their use in successive Suzuki cross-coupling reactions. It was shown that monosubstitution at the 5-position is feasible with a variety of boronic acids **5** using $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and tri(2-furyl)-phosphane as the catalyst in a solvent system of an arene (mesitylene or toluene), ethanol and water (5/1/1). Starting from **2** and **4** the corresponding 5-substituted products **8** (8 examples, 33-65% yield) and **17** (9 examples, 34-86% yield) were obtained. Further Suzuki cross-coupling reactions at the remaining di- or monobromo-substituted positions were feasible as exemplified by the synthesis of the corresponding triarylpyrroles **9**, **16** and diarylpyrroles **18**-**20**.

INTRODUCTION

There are two systematically different routes to multiply substituted heterocycles. One route is based on ring construction reactions, in the course of which the ring is assembled with the required substituents already in the correct position. The other approach is based on substitution reactions at a preformed ring. If more than one chemically identical substituent is to be replaced, regioselectivity parameters have to be considered. In the synthesis of multiply substituted pyrroles most work has been directed towards an electrophilic displacement of hydrogen atoms by aromatic substitution reactions.[1] The preference for substitution either at C-2 or C-3 are well understood depending on the nitrogen substituent and on the nature of the attacking electrophile. Due to the electron-rich nature of the pyrrole core, nucleophilic displacement reactions are not as frequent as electrophilic substitutions. Nonetheless, there is an emerging number of reactions of this type, most notably, cross-coupling reactions, which are conducted on

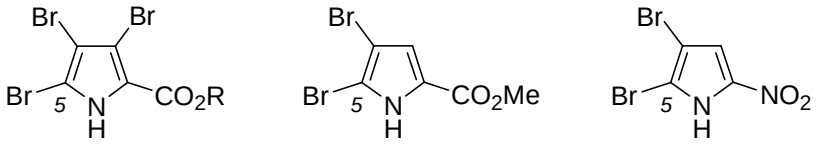
appropriately substituted halogen- or pseudohalogen-substituted pyrroles (X = halogen or pseudohalogen).[2,3] If a single halogen or pseudohalogen is being replaced, selectivity is not an issue because the cross-coupling can only take place at this single position. If, however, chemically similar or even identical C-X bonds are being attacked the regioselectivity issue needs to be addressed. The general reactivity order for C-X bonds follows the leaving group properties of the halogen (I > Br > Cl).[4] If there are more C-X bonds present with X being the same halogen and pseudohalogen, steric and electronic factors at the respective carbon atom determine the course of the reaction.[5] Studies in this area with pyrrole as the heterocyclic core are rare. Work by Iwao *et al.*[6] showed that a symmetric 2,5-disubstituted 3,4-pyrrole bistriflate can undergo monosubstitution with a boronic acid if the conditions are appropriately chosen (Suzuki cross-coupling). Steric reasons are most likely to account for this selectivity. In other reactions of symmetric 3,4-dibromopyrroles there was no selectivity observed.[7]

Our interest in the regioselectivity of pyrrole cross-coupling reactions arose from related work we had done with multiply brominated furans,[8] benzofurans,[9] and thiazoles[10] and which had revealed a preference for cross-coupling to occur at the most electrondeficient position, i.e. at carbon atom C-2 (in furans this position may correspond depending on the numbering of the product to C-5). With regard to pyrroles, we were particularly interested whether 2,3-dibromo- and 2,3,4-tribromopyrroles would show any regioselectivity in cross-coupling reactions. Preliminary work indeed established that Suzuki cross-coupling reactions on these pyrroles occur preferentially at carbon atom C-2 (C-5).[11] Our results were later confirmed by another group.[7g] In this report, we would like to disclose full details of our work, which establishes a rapid access to 2,3,4-triarylpyrroles and to 2,3-diarylpyrroles having different aryl substituents at C-2 and at C-3/C-4.

RESULTS AND DISCUSSION

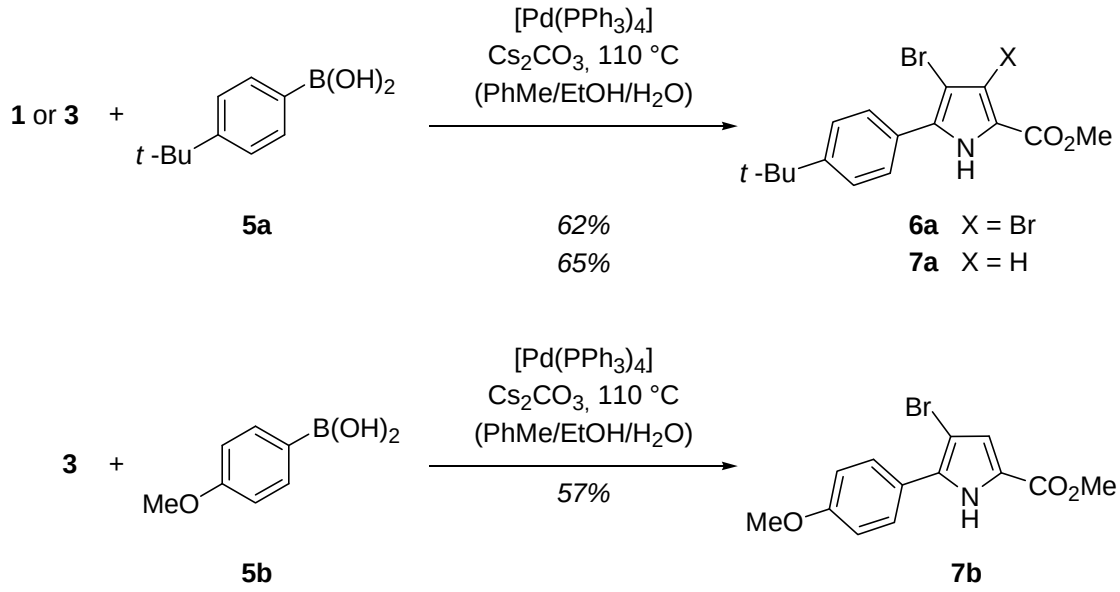
Brominated starting materials used in this study are depicted in Figure 1. Methyl 3,4,5-tribromo-pyrrole-2-carboxylate (**1**)[12] was prepared by comprehensive bromination of methyl pyrrole-2-carboxylate[13] in acetic acid at 60 °C (91% yield). The ethyl ester **2**[14] was obtained by transesterification with NaOEt in refluxing EtOH (72% yield). Dibromoester **3**[12, 15] was synthesized from methyl pyrrole-2-carboxylate by bromination with 2.05 equivalents of bromine in acetic acid at 60 °C (95% yield). The yet unknown 4,5-dibromo-2-nitropyrrole (**4**) was also accessible by bromination of 2-nitro-pyrrole in acetic acid (96% yield).[16] A comprehensive bromination to 3,4,5-tribromo-2-nitropyrrole was not feasible neither from 2-nitropyrrole nor from dibromopyrrole **4.**

Initial studies concerning a Suzuki cross-coupling were conducted with boronic acid **5a** (Scheme 1) and methyl esters **1** and **3**.[11] It turned out that the two substrates behave almost identical both preferring a cross-coupling at position C-5(C-2) under standard conditions with $Pd(PPh_3)_4$ as the catalyst. Elevated



1 R = Me **3** **4**
2 R = Et

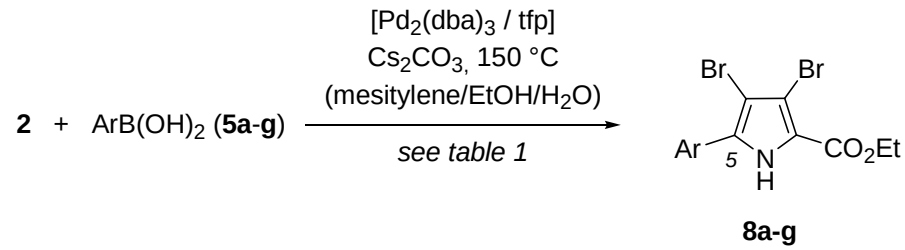
Figure 1. Structures of multiply substituted pyrroles **1**-**4** used in this study.



Scheme 1. Preparation of 5-substituted methyl pyrrole-2-carboxylates **6a**, **7a**,**b**.

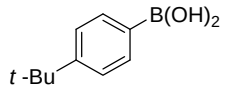
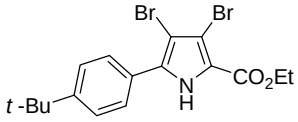
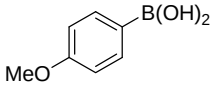
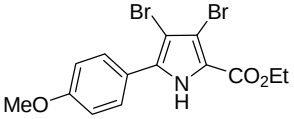
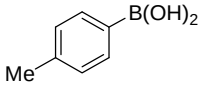
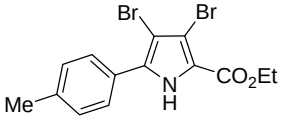
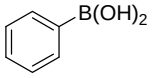
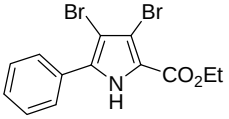
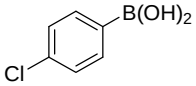
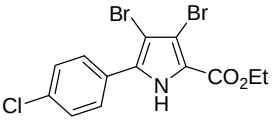
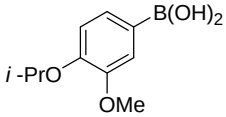
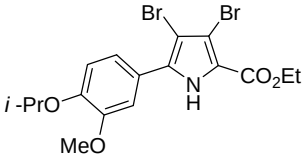
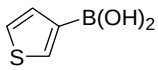
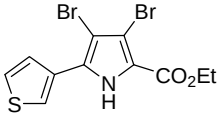
temperatures were required to achieve full conversion. The tendency for multiple substitution is higher in the dibromide **3** as compared to **1**. Short reaction times are required not only to avoid disubstitution but also because the reaction products turned out to be unstable. Whereas triaryl- and diarylpyrroles bearing no bromine atom could be stored without any decomposition over an extended period of time, the mono- or dibrominated products, e.g. **6a** and **7a**, were prone to severe degradation upon standing at room temperature. The initially white solids obtained after column chromatography transformed into black oils within hours. Even in the freezer their lifetime was limited and it is recommended to use them immediately after purification. Yields remained in the medium range as further exemplified by the cross-coupling of boronic acid **5b** to dibromopyrrole **3** yielding pyrrole **7b**. Due to the apparent similar reactivity of dibromide and tribromide towards a monosubstitution at C-5 (C-2) further studies were conducted with 3,4,5-tribromopyrrole-2-carboxylates.

A reason of concern when using methyl esters was a possible saponification under the basic reaction conditions of the Suzuki cross-coupling. We therefore conducted further optimization experiments with ethyl ester **2** employing boronic acid **5a** as the nucleophile.[11]



8a-g

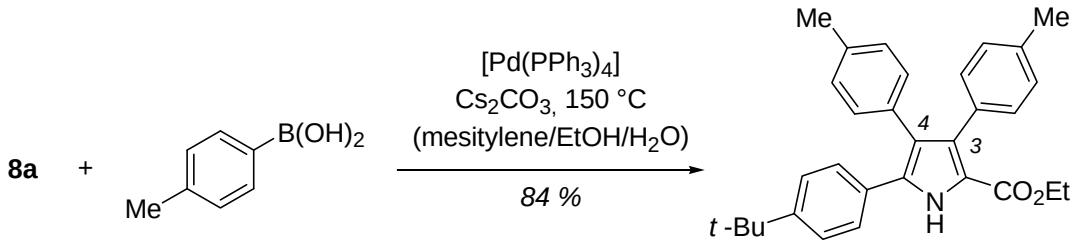
Table 1. Regioselective Suzuki cross-coupling reaction at C-5 of tribromopyrrole **2**

entry	$ArB(OH)_2$		time	product		yield
1		**5a**	8 h		**8a**	65%
2		**5b**	16 h		**8b**	46%
3		**5c**	24 h		**8c**	52%
4		**5d**	23 h		**8d**	51%
5		**5e**	7 h		**8e**	33%
6		**5f**	17 h		**8f**	57%
7		**5g**	16 h		**8g**	42%

Despite extensive experimentation a significant improvement was not achieved. We eventually settled for a catalyst system comprising of $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and tfp (tfp = tri(2-furyl)phosphane) in a three-component solvent mixture of mesitylene/EtOH/H_2O (5/1/1). The advantage of these conditions as compared to others was the dramatically shortened reaction time, after which the conversion of starting material was complete. As listed in Table 1 several boronic acids **5** could be coupled with tribromide **2** resulting in coupling products **8**.

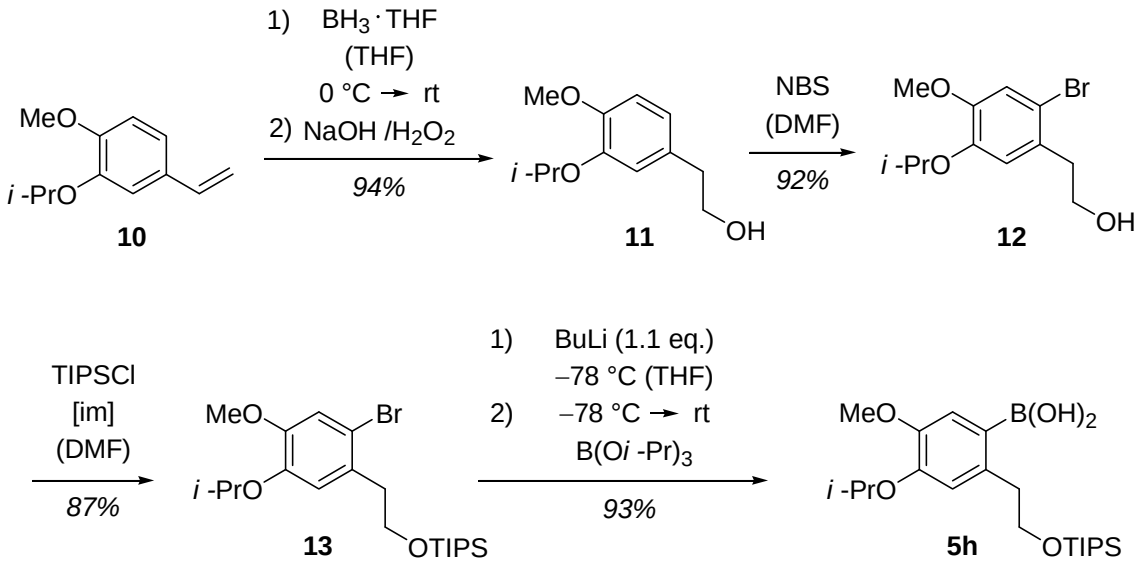
In our hands, it was not possible to selectively address one of the remaining positions C-3 and C-4 in the dibromopyrroles **8** by a subsequent cross-coupling reaction. The finding is in line with previous

observations reported by Banwell *et al.*[7d] Attempted reactions always resulted in a mixture of the three possible products (monosubstitution at C-3 or C-4, disubstitution at C-3 and C-4) and the starting materials in variable amounts. It was however possible to replace both bromo atoms by the same aryl substituents. Scheme 2 represents a typical reaction of this type, which upon using four equivalents of boronic acid **5c** proceeded to the triarylpyrrole **9** in excellent yield.

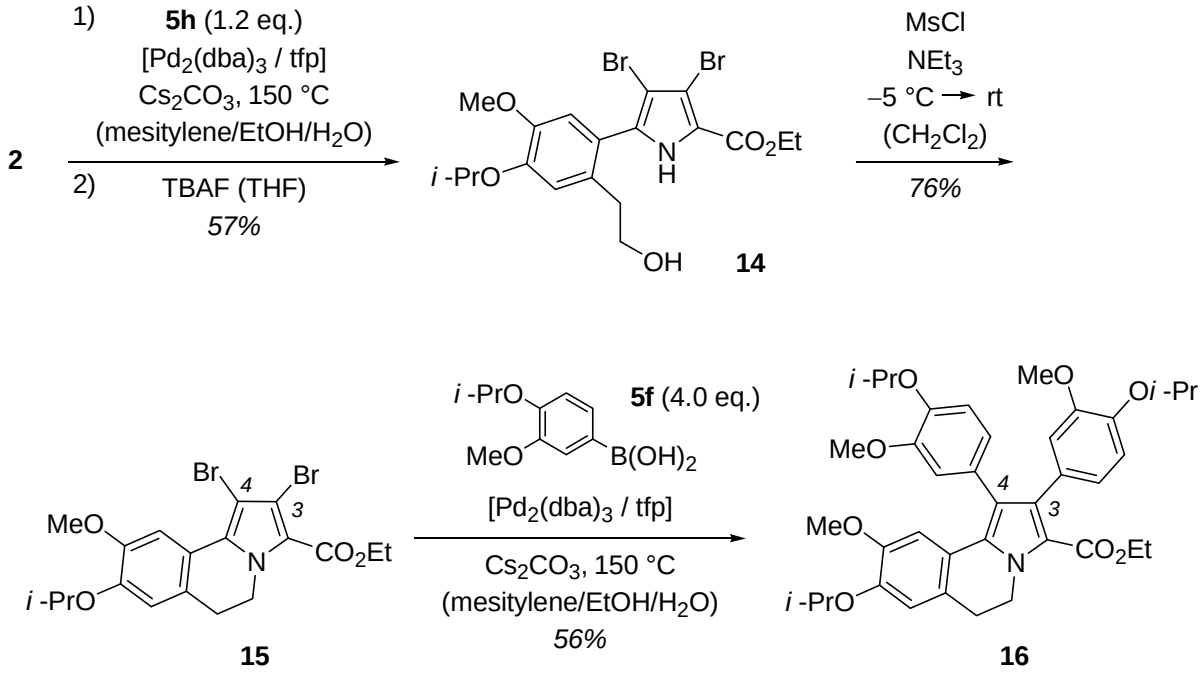


Scheme 2. Preparation of **9** by a two-fold Suzuki cross-coupling at C-3 and C-4 of dibromopyrrole **8a**.

Given the possibility to selectively introduce an aryl substituent at C-5 (C-2) and different aryl substituents at C-3 and C-4, it was attempted to demonstrate the usefulness of this method by generating an aryl substitution pattern relevant to the cytotoxic lamellarins.[17] With regard to lamellarin D,[18] boronic acid **5hl** was prepared in four synthetic steps starting from styrene **10**, which in turn was prepared in two steps from isovanilline (Scheme 3).[19] Hydroboration and oxidative work-up delivered primary alcohol **11** in 94% yield. While initial experiments had been conducted with 9-borabicyclononane (9-BBN) as the hydroboration reagent it was later found that borane itself is sufficiently regioselective (r.r. = 96/4). Bromination with *N*-bromosuccinimide (NBS) occurred exclusively *para* to the isopropoxy group delivering bromide **12**. The free hydroxyl group was silyl protected with triisopropylsilyl chloride (TIPSCl) and imidazole (im) in DMF to give silyl ether **13**. Finally the reaction sequence, which proceeded in an overall yield of 70%, was concluded by a bromine-lithium exchange reaction followed by transmetalation employing triisopropylborate as the source of boron. We were delighted to note that boronic acid **5h** – despite its sterically demanding *ortho*-substituent – underwent a clean cross-coupling to tribromopyrrole **2** under our optimized conditions (Scheme 4). Since partial deprotection of the silyl ether occurred in this step it proved advantageous to completely convert the silyl ether into the primary alcohol **14** by treatment with tetrabutylammonium fluoride (TBAF). A second cross-coupling in the presence of the free alcohol did not appear to be sensible. The 5,6-dihydropyrrolo[2,1-*a*]isoquinoline skeleton of the lamellarins was therefore generated by *O*-mesylation and subsequent nucleophilic displacement. The second cross-coupling reaction was conducted at C-3 and C-4 of dibromide **15** and yielded the desired triarylpyrrole **16**.



Scheme 3. Preparation of boronic acid **5h** from styrene **10**.



Scheme 4. Preparation of a potential lamellarin precursor **16** by successive cross-coupling reactions.

The single drawback of the sequence was an unusually high degree of debromination at C-4 in this last step. A significant amount (30%) of C-3 arylated, C-4 debrominated material was isolated besides the desired product **16**. Its formation can be explained by a ready cross-coupling at C-3 followed by a successful insertion of Pd(0) into the carbon-bromine bond at C-4. The reaction gets at rest presumably because transmetalation is retarded for steric reasons. Indeed, the environment at C-4 is more congested than for example in substrate **8a** (Scheme 2) with the aryl substituent at C-5 being locked in a planar array and being unable to rotate away. We looked briefly in the possibility to change the order of events. To

this end, the primary coupling product of silyl ether **5h** and tribromopyrrole **2** was not deprotected but isolated. A successive double cross-coupling reaction was possible but did not turn out to be more effective (49% yield) than the cross-coupling conducted with dibromide **15**.

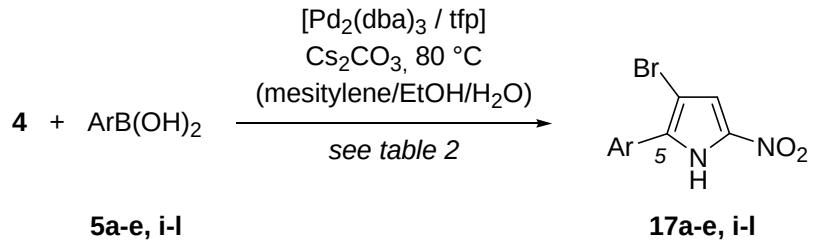
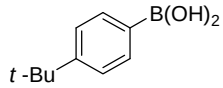
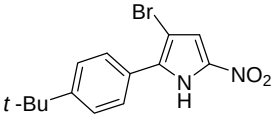
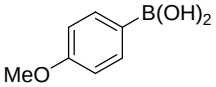
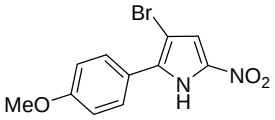
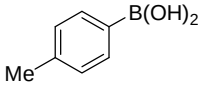
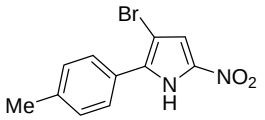
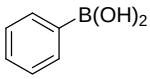
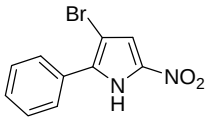
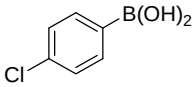
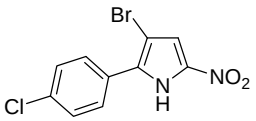
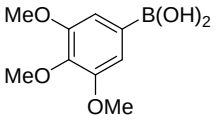
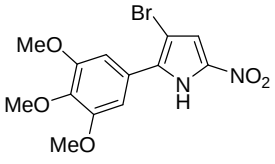
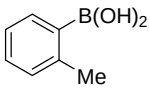
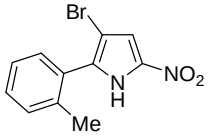
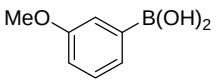
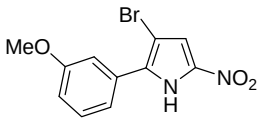
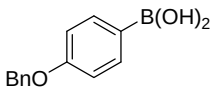
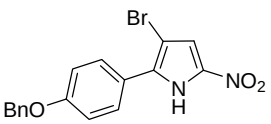
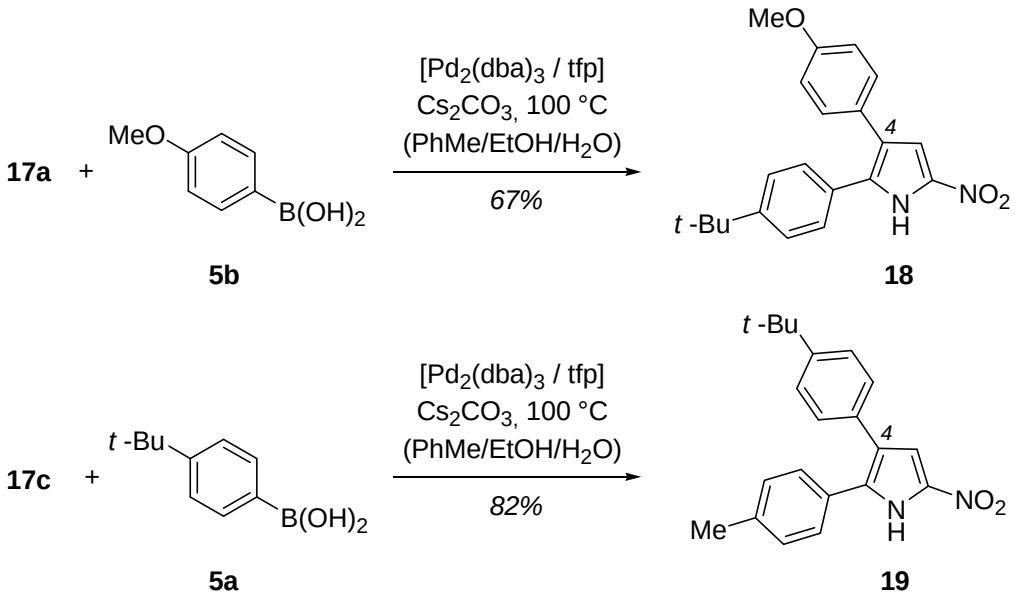


Table 2. Regioselective Suzuki cross-coupling reaction at C-5 of dibromopyrrole **4**

entry	$ArB(OH)_2$		time	product		yield
1		**5a**	6 h		**17a**	86%
2		**5b**	17 h		**17b**	61%
3		**5c**	19 h		**17c**	60%
4		**5d**	14 h		**17d**	56%
5		**5e**	10 h		**17e**	44%
6		**5i**	17 h		**17i**	69%
7		**5j**	13 h		**17j**	59%
8		**5k**	15 h		**17k**	54%
9		**5l**	24 h		**17l**	34%

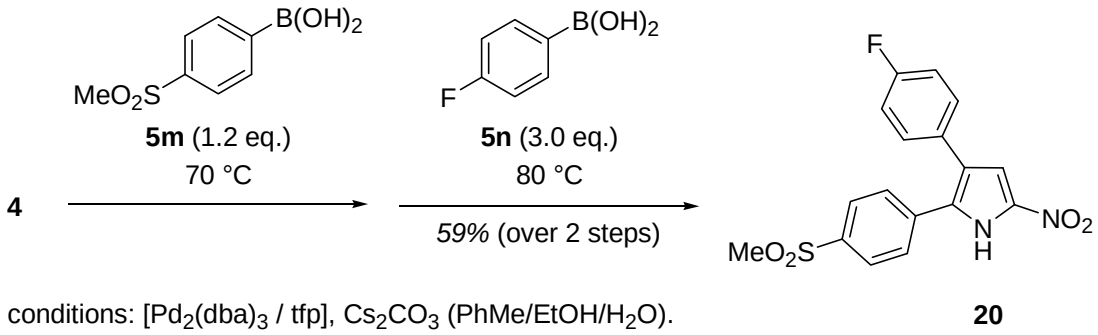
Turning to nitropyrroles we expected the strongly electron withdrawing nitro substituent to enhance the reaction velocity of possible Suzuki cross-coupling reactions on dibromopyrrole **4**. In agreement with this assumption the ^{13}C-NMR shifts for the bromine bearing carbon atoms C-4 and C-5 in compound **4** appear by ca. 2 ppm downfield relative to methyl 4,5-dibromopyrrole-2-carboxylate (**3**).[20] Furthermore, the nitro group should stabilize the electronrich monosubstituted pyrroles after an initial cross-coupling. Indeed, it was observed that regioselective cross-coupling reactions are possible with the previously established catalyst and solvent system at a significantly lower reaction temperature of 80 °C (Table 2). Yields generally exceeded the yields achieved in the cross-coupling of tribromopyrrole **2**. A substituent in *ortho*-position does not influence the reaction velocity or yield (cf. entries 3 and 7).

Given the ease with which disubstitution at C-4 and C-5 occurred, it was not surprising to note that a consecutive cross-coupling reaction at C-4 was feasible using 5-monosubstituted 2-nitropyrroles **17** as starting material. At slightly elevated temperature (100 °C vs. 80 °C), pyrrole **17a** was converted into diarylpyrrole **18** and pyrrole **17c** into product **19** (Scheme 5). The consecutive Suzuki cross-coupling reactions open an easy an general access to the yet less explored class of 4,5-diaryl-2-nitropyrroles.[21]



Scheme 5. Synthesis of 4,5-diarylpyrroles **18** and **19** by successive Suzuki cross-coupling reactions.

One of the few 4,5-diaryl-2-nitropyrroles mentioned in the literature is compound **20** (Scheme 6),[21a-c] which has been reported as an anti-inflammatory agent. It was tested whether a one-pot access to this compound is feasible with our methodology. We were delighted to see that the isolation of intermediates was not necessary, indeed, and that by simple consecutive addition of boronic acids **5m** and **5n**, the desired target compound could be synthesized in 59% yield (77% per step).



Scheme 6. Synthesis of the anti-inflammatory 2-nitropyrrole **20** in a one-pot reaction from 4,5-dibromo-2-nitropyrrole (**4**).

CONCLUSION

In summary, we have explored a general access to 2-nitro- and 2-alkoxycarbonylpyrroles, which carry different aryl substituents in the 5-position and in positions C-4 (for 2-nitro and 2-alkoxycarbonyl) or C-4 and C-5 (for 2-alkoxycarbonyl). The method exploits the reactivity pattern of the respective 2-substituted 4,5-dibromo- and 3,4,5-tribromopyrroles, which invite a selective monosubstitution by Suzuki cross-coupling of an aryl boronic acid at position C-5. In a further cross-coupling step the introduction of a second or third aryl substituent can be pursued using a different aryl boronic acid. Further works aims at an extension of the consecutive cross-coupling strategy by the use of other but aryl boronic acids and at an application to the synthesis of naturally occurring pyrroles.

EXPERIMENTAL

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glass ware with dried solvents under argon atmosphere. Common solvents [pentane (P), methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), tetrahydrofuran (THF), diethylether (Et_2O), dichloromethane (CH_2Cl_2)] were distilled prior to use. Boronic acids were synthesized from the corresponding aryl halides according to known procedures.[22] Aryl halides, all other reagents and solvents were used as received. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ unless otherwise noted. Chemical shifts are reported relative to the signals for residual solvent. TLC was performed on glass slices (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm, 366 nm) and by coloration with ceric ammonium molybdate (CAM). Flash chromatography was performed on silica gel 60 (40-63 μm) (ca 50 g for 1 g of material to be separated), with the indicated eluent. The given yields refer to yields of isolated compounds. Compounds **1**,[12] **2**,[14] **3**,[15] **5f**,[18e] **10**,[19] and 2-nitropyrrole[16] were prepared according to known procedures.

General Procedure A: $Pd(PPh_3)_4$-catalyzed Suzuki coupling reaction of bromopyrrole carboxylates

with aryl boronic acids. An oven-dried Schlenk flask, equipped with a reflux condenser and a stirring bar, was charged with the bromopyrrole (0.5 mmol), the boronic acid (0.6 mmol, 1.2 eq.), 195 mg Cs_2CO_3 (0.6 mmol, 1.2 eq.) and 35 mg $Pd(PPh_3)_4$ (0.05 mmol, 10 mol%). The Schlenk flask was evacuated and filled with argon (this sequence was repeated three times). Toluene (5 mL), EtOH (1 mL) and water (1 mL) were added and the flask was again carefully evacuated and filled with argon (this sequence was repeated three times). The reaction mixture was heated to 110 °C and vigorously stirred until TLC indicated complete conversion of the pyrrole. The reaction mixture was then allowed to cool to rt, diluted with EtOAc (5 mL) and water (5 mL). The layers were separated, and the aqueous layer was twice extracted with EtOAc (5 mL). The collected organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

General Procedure B: $Pd_2(dba)_3$-catalyzed Suzuki coupling reaction of bromopyrrole carboxylates with aryl boronic acids. Procedure A was used with the following changes: 23 mg $Pd_2(dba)_3$ (0.025 mmol, 5 mol%) and 23 mg P(2-furyl)$_3$ (0.10 mmol, 20 mol%) were used instead of $Pd(PPh_3)_4$. Toluene was replaced by mesitylene (5 mL) and the reaction mixture was heated to 150 °C. Concentration of the collected organic layers was performed by *Kugelrohr* distillation.

General Procedure C: $Pd_2(dba)_3$-catalyzed Suzuki coupling reaction of dibromonitropyrrole **4** with aryl boronic acids. Procedure A was used with the following changes: 23 mg $Pd_2(dba)_3$ (0.025 mmol, 5 mol%) and 23 mg P(2-furyl)$_3$ (0.20 mmol, 20 mol%) were used instead of $Pd(PPh_3)_4$. The reaction mixture was heated to 80 °C.

4,5-Dibromo-2-nitropyrrole (4) A solution of bromine (2.40 mL, 7.63 g, 47.8 mmol, 2.5 eq.) in 10 mL of AcOH was added to a solution of 2-nitropyrrole[16] (2.14 g, 19.1 mmol) in 50 mL of AcOH. The reaction mixture was then heated to 60 °C, stirred for 30 min and the solvent evaporated. The residue was dissolved in EtOAc (50 mL) and neutralized with saturated aqueous $NaHCO_3$ (200 mL). The layers were separated, and the aqueous layer was extracted five times with EtOAc (50 mL). The collected organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give 4.95 g of compound **4** (18.3 mmol, 96%) as a yellow oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3128 cm^{-1} (br m, NH), 1494 (m, NO_2), 1448 (m), 1375 (s, NO_2), 1347 (s), 1249 (m), 1083 (w), 975 (w), 832 (w), 740 (w); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 7.13 (d, ^4J = 2.7 Hz, 1 H, H-3), 9.78 (br s, 1 H, NH), ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 102.4 (s, C-4), 108.5 (s, C-5), 113.5 (d, C-3), 137.7 (s, C-2); MS

(EI, 70 eV), *m/z* (%): 272/270/268 (46/89/44) [M^+], 242/240/238 (48/100/46), 214/212/210 (27/63/28), 199/197/195 (39/80/36), 160/158 (100/98), 118/116 (78/78), 81/79 (64/63) [($^{81}Br/^{79}Br)^+$], 63 (60),52 (66). Anal. Calcd for $C_4H_2Br_2N_2O_2$: C 17.80, H 0.75, N 10.38. Found: C 18.08, H 0.84, N 10.30.

Methyl 5-(4-*tert*-butylphenyl)-3,4-dibromo-1*H*-pyrrole-2-carboxylate (6a) Following general procedure A, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**1**) (181 mg, 0.5 mmol) and 4-*tert*-butylphenylboronic acid (**5a**) (107 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 16 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **6a** (129 mg, 0.31 mmol, 62%) as a white solid. Mp 158-163 °C; IR (KBr): $\tilde{\nu}$ = 3238 cm^{-1} (s, NH), 2960 (m), 1672 (s, C=O), 1475 (m), 1414 (m, CH), 1310 (w), 1287 (w), 1261 (s, C-O), 1210 (w), 835 (w); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, C(CH_3)$_3$], 3.91 (s, 3 H, CO_2CH_3), 7.49 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.61 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 9.35 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 31.2 [q, C(CH_3)$_3$], 34.8 [s, C(CH_3)$_3$], 52.0 (q, CO_2CH_3), 101.0 (s, C-Br), 107.9 (s, C-Br), 119.9 (s, C-2), 125.9 (d, $C_{ar}H$), 127.0 (d, $C_{ar}H$), 127.2 (s, C_{ar}), 133.9 (s, C-5), 152.4 (s, C_{ar}), 160.1 (s, C=O); MS (EI, 70 eV), *m/z* (%): 417/415/413 (34/65/34) [M^+], 402/400/398 (11/25/11) [$(M - CH_3)^+$], 385/383/381 (3/9/2), 370/368/366 (50/100/50), 315/313/311 (5/6/5), 180 (12), 153 (12), 139 (15), 115 (8); HRMS calcd for $C_{15}H_{14}{}^{79}Br_2NO_2$: 397.9391. Found: 397.9387; Anal. Calcd for $C_{16}H_{17}Br_2NO_2$: C 46.29, H 4.13, N 3.37. Found: C 46.91, H 4.42, N 3.52.

Methyl 4-bromo-5-(4-*tert*-butylphenyl)-1*H*-pyrrole-2-carboxylate (7a) Following general procedure A, a mixture of methyl 4,5-dibromopyrrole-2-carboxylate (**3**) (141 mg, 0.5 mmol) and 4-*tert*-butylphenylboronic acid (**5a**) (107 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 16 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **7a** (109 mg, 0.33 mmol, 65%) as a white solid. Mp 161-163 °C; IR (KBr): $\tilde{\nu}$ = 3238 cm^{-1} (s, NH), 2960 (m), 1672 (s, C=O), 1475 (m), 1414 (m, CH), 1310 (w), 1287 (w), 1261 (s, C-O), 1210 (w), 835 (w); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, C(CH_3)$_3$], 3.85 (s, 3 H, OCH_3), 6.97 (d, ^4J = 2.7 Hz, 1 H, H-3), 7.48 (d, ^3J = 8.5 Hz, 2 H, H_{ar}), 7.63 (d, ^3J = 8.5 Hz, 2 H, H_{ar}), 9.33 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 31.5 [q, C(CH_3)$_3$], 34.7 [s, C(CH_3)$_3$], 51.8 (q, OCH_3), 96.0 (s, C-4), 119.1 (d, C-3), 121.9 (s, C-2), 125.7 (d, $C_{ar}H$), 127.4 (d, $C_{ar}H$), 127.4 (s, C_{ar}), 133.9 (s, C-5), 151.6 (s, C_{ar}), 161.0 (s, C=O); MS (EI, 70 eV), *m/z* (%): 337/335 (75/75) [M^+], 322/320 (55/55), 290/288 (100/100), 262/260 (6/6), 235/233 (11/11), 180 (14), 166 (10), 153 (20), 139 (10), 115 (8), 77 (5) ($C_6H_5^+$); HRMS calcd for $C_{16}H_{18}{}^{79}BrNO_2$: 335.0521. Found: 335.0518.

Methyl 4-bromo-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (7b) Following general procedure

A, a mixture of methyl 4,5-dibromopyrrole-2-carboxylate (**3**) (141 mg, 0.5 mmol) and 4-methoxyphenylboronic acid (**5b**) (91 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 21 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **7b** (88 mg, 0.28 mmol, 57%) as a white solid. Mp 160-163 °C; IR (KBr): $\tilde{\nu}$ = 3305 cm^{-1} (s, NH), 1692 (s, C=O), 1612 (m), 1468 (m), 1438 (m, CH), 1297 (m), 1249 (s, C-O), 1207 (m), 1148 (m), 1031 (m), 762 (m); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CO_2CH_3), 3.85 (s, 3 H, OCH_3), 6.96 (d, ^4J = 2.7 Hz, 1 H, H-3), 6.98 (d, ^3J = 8.5 Hz, 2 H, H_{ar}), 7.62 (d, ^3J = 8.5 Hz, 2 H, H_{ar}), 9.31 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 51.8 (q, OCH_3), 55.4 (q, CO_2CH_3), 95.7 (s, C-4), 114.2 (d, $C_{ar}H$), 119.0 (d, C-3), 121.6 (s, C-2), 122.8 (s, C_{ar}), 128.7 (d, $C_{ar}H$), 133.9 (s, C-5), 159.8 (s, C_{ar}), 161.0 (s, C=O); MS (EI, 70 eV), *m/z* (%): 311/309 (85/86) [M^+], 279/277 (80/80), 264/262 (8/8), 225/223 (10/11), 170 (100), 156 (9), 144 (9), 127 (18), 115 (5), 101 (11), 75 (9); Anal. Calcd for $C_{13}H_{12}BrNO_3$: C 50.34, H 3.90, N 4.52. Found: C 50.33, H 3.51, N 4.34.

Ethyl 3,4-dibromo-5-(4-*tert*-butylphenyl)-1*H*-pyrrole-2-carboxylate (8a) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and 4-*tert*-butylphenylboronic acid (**5a**) (107 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 8 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **8a** (139 mg, 0.33 mmol, 65%) as a white solid. Mp 162-164 °C; IR (KBr): $\tilde{\nu}$ = 3238 cm^{-1} (s, NH), 2960 (m), 1672 (s, C=O), 1475 (m), 1414 (m, CH), 1310 (w), 1287 (w), 1261 (s, C-O), 1210 (w), 835 (w); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.36 [s, 9 H, $C(CH_3)_3$], 1.38 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 7.49 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.62 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 9.55 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.5 (q, OCH_2CH_3), 31.4 [q, $C(CH_3)_3$], 35.0 [s, $C(CH_3)_3$], 61.4 (t, OCH_2CH_3), 101.1 (s, C-Br), 108.0 (s, C-Br), 120.3 (s, C-2), 126.0 (s, $C_{ar}H$), 127.3 (d, C_{ar}), 127.3 (d, $C_{ar}H$), 134.0 (s, C-5), 152.5 (s, C_{ar}), 160.0 (s, C=O); MS (EI, 70 eV), *m/z* (%): 431/429/427 (26/55/29) [M^+], 416/414/412 (5/17/5), 370/368/366 (49/100/55), 313 (8), 260 (8), 180 (9), 153 (12); Anal. Calcd for $C_{17}H_{19}Br_2NO_2$: C 47.58, H 4.46, N 3.26. Found: C 47.37, H 4.42, N 3.09.

Ethyl 3,4-dibromo-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (8b) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and 4-methoxyphenylboronic acid (**5b**) (91 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 16 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **8b** (105 mg, 0.26 mmol, 52%) as a white solid. Mp 130-134 °C; IR (KBr): $\tilde{\nu}$ = 3299 cm^{-1} (br s, NH), 2958 (s), 1728 (s), 1681 (s, C=O), 1606 (m), 1513 (m), 1462 (s, CH), 1290 (s), 1250 (s, C-O), 1179 (m); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 3.86 (s, 3 H, OCH_3), 4.36 (q, ^3J = 7.1 Hz,

2 H, OC*H*$_2$CH$_3$), 6.99 (d, ^3J = 8.7 Hz, 2 H, H$_{ar}$), 7.60 (d, ^3J = 8.7 Hz, 2 H, H$_{ar}$), 9.35 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.3 (q, OCH$_2$*C*H$_3$), 55.4 [q, OCH$_3$), 61.2 (t, O*C*H$_2$CH$_3$), 100.7 (s, C-Br), 107.8 (s, C-Br), 114.3 (d, C$_{ar}$H), 119.9 (s, C-2), 122.6 (s, C$_{ar}$), 128.9 (d, C$_{ar}$H), 133.7 (s, C-5), 159.7 (s, C$_{ar}$), 160.2 (s, C=O); MS (EI, 70 eV), *m/z* (%): 405/403/401 (35/69/35) [M$^+$], 359/357/355 (51/100/51), 305/303/301 (8/18/8), 250/248 (58/58), 207/205 (8/9), 170 (18), 155 (9), 143 (15), 100 (9); HRMS calcd for $C_{12}H_7{}^{79}Br_2NO_2$: 354.8843. Found: 354.8853; Anal. Calcd for $C_{14}H_{13}Br_2NO_3$: C 41.71, H 3.25, N 3.48. Found: C 41.67, H 3.36, N 3.52.

Ethyl 3,4-dibromo-5-*p*-tolyl-1*H*-pyrrole-2-carboxylate (8c) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and *p*-tolylboronic acid (**5c**) (82 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 24 h. The crude product was purified by flash chromatography on silica gel (P:Et$_2$O = 3:1) to give **8c** (101 mg, 0.26 mmol, 52%) as a white solid. Mp 122-124 °C; IR (KBr): $\tilde{\nu}$ = 3242 cm^{-1} (s, NH), 2958 (m), 1672 (s, C=O), 1475 (m), 1412 (m, CH), 1307 (w), 1290 (w), 1262 (s, C-O), 1215 (w), 837 (w). ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.39 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 2.41 (s, 3 H, C$_6$H$_4$C*H*$_3$), 4.35 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 7.27 (d, ^3J = 8.2 Hz, 2 H, H$_{ar}$), 7.56 (d, ^3J = 8.2 Hz, 2 H, H$_{ar}$), 9.55 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.3 (q, OCH$_2$*C*H$_3$), 21.3 (q, C$_6$H$_4$*C*H$_3$), 61.2 (t, O*C*H$_2$CH$_3$), 100.9 (s, C-Br), 107.8 (s, C-Br), 120.1 (s, C-2), 127.5 (d, C$_{ar}$H), 127.1 (s, C$_{ar}$), 129.7 (d, C$_{ar}$H), 133.9 (s, C-5), 139.1 (s, C$_{ar}$), 159.8 (s, C=O); MS (EI, 70 eV), *m/z* (%): 398/387/385 (42/89/46) [M$^+$], 343/341/339 (54/100/53), 289/287/285 (11/23/11), 234/232 (57/68), 209/207 (9/9), 153 (34), 127 (51), 116 (6), 101 (9), 91 (11), 77 (15), 65 (10), 51 (10).

Ethyl 3,4-dibromo-5-phenyl-1*H*-pyrrole-2-carboxylate (8d) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and phenylboronic acid (**5d**) (73 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 23 h. The crude product was purified by flash chromatography on silica gel (P:Et$_2$O = 3:1) to give **8d** (95 mg, 0.26 mmol, 51%) as a colorless oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3264 cm^{-1} (br s, NH), 2981 (w), 1668 (s, C=O), 1463 (m), 1418 (s), 1309 (m), 1288 (s, C-O), 1263 (s, C-O), 1210 (m), 769 (m), 694 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 4.36 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 7.41-7.50 (m, 5 H, H$_{ar}$), 9.46 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.5 (q, OCH$_2$*C*H$_3$), 61.4 (t, O*C*H$_2$CH$_3$), 101.4 (s, C-Br), 108.0 (s, C-Br), 120.6 (s, C-2), 127.6 (d, C$_{ar}$H), 128.9 (d, C$_{ar}$H), 129.2 (s, C$_{ar}$), 130.8 (s, C-5), 133.8 (s, C$_{ar}$), 159.9 (s, C=O); MS (EI, 70 eV), *m/z* (%): 375/373/371 (43/83/43) [M$^+$], 329/327/325 (49/100/52), 275/273/271 (11/22/11), 220/218 (60/60), 139 (32), 113 (53), 77 (10), 63 (13), 51 (9); HRMS calcd for $C_{11}H_5{}^{79}Br_2NO$: 324.8738. Found: 324.8735.

Ethyl 3,4-dibromo-5-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate (8e) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and 4-chlorophenylboronic acid (**5e**) (94 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 7 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **8e** (67 mg, 0.17 mmol, 33%) as a white solid. Mp 129-132 °C; IR (KBr): $\tilde{\nu}$ = 3253 cm^{-1} (s, NH), 1672 (s, C=O), 1461 (m), 1420 (m), 1284 (m), 1261 (w, C-O), 1094 (w, C-Cl); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.39 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 4.35 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 7.44 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 7.62 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 9.54 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.5 (q, OCH_2CH_3), 61.6 (t, OCH_2CH_3), 101.8 (s, C-Br), 108.1 (s, C-Br), 120.9 (s, C-2), 128.6 (s, C_{ar}), 128.9 (d, $C_{ar}H$), 129.3 (d, $C_{ar}H$), 132.7 (s, C-5), 135.3 (s, C_{ar}), 159.9 (s, C=O); MS (EI, 70 eV), *m/z* (%): 409/407/405 (62/89/37), [M^+], 363/361/359 (74/100/47), 309/307/305 (6/8/4), 279 (18), 256/254/252 (16/49/38), 174 (11), 167 (28), 149 (58), 113 (14), 87 (8), 71 (13), 57 (17), 43 (12); HRMS calcd for $C_{13}H_{10}{}^{79}Br_2ClNO_2$: 404.8767. Found: 404.8763.

Ethyl 3,4-dibromo-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (8f) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and 4-isopropoxy-3-methoxyphenylboronic acid (**5f**) (126 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 17 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **8f** (131 mg, 0.29 mmol, 57%) as a white solid. Mp 129-132 °C; IR (KBr): $\tilde{\nu}$ = 3264 cm^{-1} (s, NH), 2976 (s), 2932 (m), 1671 (s, C=O), 1514 (m), 1478 (s), 1446 (m), 1414 (s, CH), 1383 (m), 1289 (m), 1247 (s, C-O); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.40 [d, ^3J = 6.1 Hz, 6 H, $OCH(CH_3)_2$], 1.40 (t, ^3J = 7.3 Hz, 3 H, OCH_2CH_3), 3.91 (s, 3 H, OCH_3), 4.38 (q, ^3J = 7.3 Hz, 2 H, OCH_2CH_3), 4.60 [sept, ^3J = 6.1 Hz, 1 H, $OCH(CH_3)_2$], 6.96 (d, ^3J = 8.4 Hz, 1 H, H_{ar}), 7.15 (dd, ^3J = 8.4 Hz, ^4J = 2.3 Hz, 1 H, H_{ar}) 7.22 (d, ^4J = 2.3 Hz, 1 H, H_{ar}), 9.26 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.5 (q, OCH_2CH_3), 22.2 [q, $OCH(CH_3)_2$], 56.3 (q, OCH_3), 61.3 (t, OCH_2CH_3), 71.6 [d, $OCH(CH_3)_2$], 100.8 (s, C-Br), 108.0 (s, C-Br), 111.6 (d, $C_{ar}H$), 115.3 (d, $C_{ar}H$), 120.0 (s, C-2), 120.2 (d, $C_{ar}H$), 122.9 (s, C_{ar}), 133.9 (s, C-5), 148.4 (s, C_{ar}), 150.5 (s, C_{ar}), 159.9 (s, C=O); MS (EI, 70 eV), *m/z* (%): 463/461/459 (2/4/2) [M^+], 421/419/417 (3/6/3), 375/373/371 (4/10/4), 279 (36), 167 (63), 149 (100), 113 (16), 104 (4), 71 (23), 57 (30), 43 (14); HRMS calcd for $C_{17}H_{19}{}^{79}Br_2NO_4$: 458.9681. Found: 458.9686.

Ethyl 3,4-dibromo-5-(3-thienyl)-1*H*-pyrrole-2-carboxylate (8g) Following general procedure B, a mixture of ethyl 3,4,5-tribromopyrrole-2-carboxylate (**2**) (188 mg, 0.5 mmol) and 3-thienylboronic acid (**5g**) (154 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 16 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give **8g** (63 mg, 0.21 mmol, 42%) as a pale yellow solid. Mp 122-124 °C; IR (KBr): $\tilde{\nu}$ = 3266 cm^{-1} (s, NH), 1674 (s, C=O), 1476 (m), 1422 (m,

CH), 1372 (m), 1268 (s, C-O), 1206 (m), 1042 (m); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 4.38 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 7.44 (dd, ^3J = 5.0 Hz, ^4J = 2.8 Hz, 1 H, H-5'), 7.47 (dd, ^3J = 5.0 Hz, ^4J = 1.3 Hz, 1 H, H-4'), 7.80 (dd, ^4J = 2.8 Hz, ^4J = 1.3 Hz, 1 H, H-2'), 9.47 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.3 (q, OCH_2CH_3), 61.3 (t, OCH_2CH_3), 100.9 (s, C-Br), 107.8 (s, C-Br), 119.6 (s, C-2), 123.6 (d, C-2'), 125.6 (d, C-5'), 126.6 (d, C-4'), 129.7 (s, C-3'), 130.3 (s, C-5), 159.7 (s, C=O); MS (EI, 70 eV), *m/z* (%): 381/379/377 (42/80/43), [M^+], 335/333/331 (51/100/49), 281/279/277 (14/25/14), 226/224 (57/53), 146 (28), 119 (30), 110 (9), 100 (8), 93 (10), 76 (8), 69 (8); HRMS calcd for $C_{11}H_9{}^{79}Br_2NO_2S$: 376.8721. Found: 376.8719; Anal. Calcd for $C_{11}H_9Br_2NO_2S$: C 35.85, H 2.39, N 3.70. Found: C 36.11, H 2.46, N 3.59.

Ethyl 5-(4-*tert*-butylphenyl)-3,4-di-*p*-tolyl-1*H*-pyrrole-2-carboxylate (9) Following general procedure B, a mixture of dibromopyrrole **8a** (150 mg, 0.35 mmol) and *p*-tolylboronic acid (**5c**) (190 mg, 1.40 mmol, 4.0 eq.) was heated under vigorous stirring for 10 h. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 3:1) to give triarylpyrrole **9** (133 mg, 0.29 mmol, 84%) as a colorless oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (s, NH), 2964 (m, CH), 1667 (s, C=O), 1440 (m, CH), 1250 (w, C-O); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.30 [s, 9 H, $C(CH_3)_3$], 2.28 (s, $C_6H_4CH_3$), 2.31 (s, $C_6H_4CH_3$), 4.21 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 6.90 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 6.95 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.02 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.10 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.21 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.30 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 9.12 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 14.4 (q, OCH_2CH_3), 21.4 (2 × q, $C_6H_4CH_3$), 31.4 [q, $C(CH_3)_3$], 34.8 [s, $C(CH_3)_3$], 60.2 (t, OCH_2CH_3), 118.7 (s, C-2), 124.0 (s, C-5), 125.7 (d, $C_{ar}H$), 127.3 (d, $C_{ar}H$), 128.0 (d, $C_{ar}H$), 128.8 (d, $C_{ar}H$), 129.1 (s, C-4), 130.9 (d, $C_{ar}H$), 130.9 (d, $C_{ar}H$), 131.3 (s, C_{ar}), 131.6 (s, C-3), 132.1 (s, C_{ar}), 132.6 (s, C_{ar}), 135.7 (s, C_{ar}), 136.1 (s, C_{ar}), 150.9 (s, C_{ar}), 161.3 (s, C=O); MS (EI, 70 eV), *m/z* (%): 451 (100) [M^+], 432 (4), 405 (25), 376 (4), 362 (6), 244 (7), 209 (4), 195 (10), 181 (4), 152 (3), 57 (8), 40 (12); HRMS calcd for $C_{31}H_{33}NO_2$: 451.2511. Found: 451.2509; Anal. Calcd for $C_{31}H_{33}NO_2$: C 82.45, H 7.37, N 3.10. Found: C 82.28, H 7.20, N 3.07.

2-(3-Isopropoxy-4-methoxyphenyl)ethanol (11) A mixture of 2-isopropoxy-1-methoxy-4-vinyl-benzene (**10**) (12.9 g, 67.2 mmol) and dry THF 100 mL was cooled to 0 °C. Using a syringe, 73.9 mL of BH_3·THF (1.0 M, 73.9 mmol, 1.1 eq.) were slowly injected to the reaction mixture. The solution was then allowed to warm to rt and stirred for 2 h. Water (30 mL) was added slowly, followed by the addition of NaOH solution (6 M, 20 mL) and hydrogen peroxide (30% in water, 30 mL). After stirring the reaction mixture for 1 h, Et_2O (50 mL) was added and the aqueous layer was twice extracted with Et_2O (50 mL). The collected organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and the

solvent was removed. The crude product was purified by flash chromatography on silica gel (P:EtOAc = 1:1) to give **11** (13.9 g, 65.9 mmol, 98%) as a colorless oil. ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.36 [d, ^3J = 6.1 Hz, 6 H, OCH(CH_3)$_2$], 2.79 (t, ^3J = 6.4 Hz, 2 H, CH_2CH$_2$OH), 3.82 (t, ^3J = 6.4 Hz, 2 H, CH$_2$CH_2OH), 3.83 (s, 3 H, OCH_3), 4.52 [sept, ^3J = 6.1 Hz, 1 H, OCH(CH$_3$)$_2$], 6.75-6.84 (m, 3 H, H_{ar}); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 22.3 [q, OCH(CH$_3$)$_2$], 38.8 (t, CH$_2$CH$_2$OH), 56.2 (q, OCH_3), 63.9 (t, CH$_2$$CH_2$OH), 71.7 [d, O$C$H(CH$_3$)$_2$], 112.5 (d, C_{ar}H), 117.2 (d, C_{ar}H), 121.7 (d, C_{ar}H), 131.0 (s, C_{ar}), 147.6 (s, C_{ar}), 149.4 (s, C_{ar}); MS (EI, 70 eV): *m/z* (%) = 210 (23) [M^+], 168 (27), 137 (100).

2-(2-Bromo-3-isopropoxy-4-methoxyphenyl)ethanol (12)[18d] A solution of compound **11** (13.9 g, 65.9 mmol) in DMF 60 mL was cooled to 0 °C. After addition of *N*-bromosuccinimide (11.7 g, 65.9 mmol) the reaction mixture was stirred for 15 min at this temperature, the ice bath was removed and the solution stirred for 2 h at rt. Water (500 mL) and Et_2O (300 mL) were added. The aqueous layer was extracted with Et_2O (2 × 300 mL) and the collected organic layers washed with brine (500 mL), filtered and evaporated. The crude product was purified by flash chromatography on silica gel (P:EtOAc = 2:1) to give **12** (18.2 g, 62.8 mmol, 95%) as a colorless oil. ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.35 [d, ^3J = 6.2 Hz, 6 H, OCH(CH_3)$_2$], 2.93 (t, ^3J = 6.6 Hz, 2 H, CH_2CH$_2$OH), 3.82 (s, 3 H, OCH_3), 3.84 (t, ^3J = 6.6 Hz, 2 H, CH$_2$CH_2OH), 4.49 [sept, ^3J = 6.2 Hz, 1 H, OCH(CH$_3$)$_2$], 6.82 (s, 1 H, H_{ar}), 7.03 (s, 1 H, H_{ar}). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.0 [q, OCH(CH$_3$)$_2$], 38.9 (t, CH$_2$CH$_2$OH), 56.2 (q, OCH_3), 62.4 (t, CH$_2$$CH_2$OH), 71.8 [d, O$C$H(CH$_3$)$_2$], 114.8 (s, C_{ar}), 116.6 (d, C_{ar}H), 118.7 (d, C_{ar}H), 129.6 (s, C_{ar}), 146.6 (s, C_{ar}), 149.8 (s, C_{ar}).

(2-Bromo-5-isopropoxy-4-methoxyphenethoxy)triisopropylsilane (13) To a solution of **12** (18.2 g, 62.8 mmol) in dry DMF 70 mL was added imidazole (8.55 g, 126 mmol, 2.0 eq.) and triisopropylsilyl chloride (18.2 g, 94.2 mmol, 1.5 eq.). The reaction mixture was stirred at rt for 2 h. Water (600 mL) and Et_2O (300 mL) were then added, and after separation the aqueous layer was extracted with Et_2O (250 mL). The collected organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (P:Et_2O = 15:1) to give of **13** (18.8 g, 42.2 mmol, 67%) as a colorless oil. ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.06 {m, 21 H, Si[CH(CH$_3$)$_2$]$_3$/Si[CH(CH_3)$_2$]$_3$}, 1.34 [d, ^3J = 6.1 Hz, 6 H, OCH(CH_3)$_2$], 2.90 (t, ^3J = 6.9 Hz, CH_2CH$_2$O), 3.81 (s, 3 H, OCH_3), 3.86 (t, ^3J = 6.9 Hz, 2 H, CH$_2$CH_2O), 4.47 [sept, ^3J = 6.1 Hz, 1 H, OCH(CH$_3$)$_2$], 6.85 (s, 1 H, H_{ar}), 7.00 (s, 1 H, H_{ar}); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 12.1 {d, Si[CH(CH$_3$)$_2$]$_3$}, 18.1 {q, Si[CH(CH$_3$)$_2$]$_3$}, 22.2 [q, OCH(CH$_3$)$_2$], 39.5 (t, CH$_2$CH$_2$O), 56.3 (q, OCH_3), 63.2 (t, CH$_2$$CH_2$O), 72.0 [d, O$C$H(CH$_3$)$_2$], 114.9 (s, C_{ar}), 116.3 (d, C_{ar}H), 119.1 (d, C_{ar}H), 130.6 (s, C_{ar}), 146.6 (s, C_{ar}), 149.8 (s, C_{ar}); MS (EI, 70 eV): *m/z* (%) = 446/444 (7/6) [M^+], 403/401 (100/99), 361/359 (37/33), 315/313 (17/16), 279

(23), 264 (22), 151 (20).

4-Isopropoxy-5-methoxy-2-(2-(triisopropylsilyloxy)ethyl)phenylboronic acid (5h) *n*-Butyl lithium (1.94 mL, 4.64 mmol, 1.1 eq., 2.4 M in hexane) was added dropwise to a stirred suspension of the bromide **12** (1.88 g, 4.22 mmol) in dry THF 16 mL at −78 °C under argon atmosphere. The mixture was stirred for 45 min and then triisopropylborate (1.17 mL, 953 mg, 5.07 mmol, 1.2 eq.) were added. The solution was allowed to warm up to rt and the boronic ester was hydrolysed by the addition of water (20 mL) and 2 N HCl (5 mL), followed by 1 h of stirring. The reaction mixture was extracted with Et_2O (3 × 30 mL), the combined organic layers dried over Na_2SO_4 and evaporated. The crude product was recrystallized from Et_2O/cyclohexane (2 mL/10 mL) and afforded **5h** (1.09 g, 2.64 mmol, 63%) as a white solid, which eliminates water upon heating (boroxine formation). IR (KBr): $\tilde{\nu}$ = 3383 cm^{-1} (br m), 2944 (s), 2867 (s), 1402 (s), 1381 (s), 1346 (s), 1324 (s), 1250 (s), 1210 (m), 1190 (s), 1109 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.94 {d, ^3J = 6.0 Hz, 18 H, Si[CH(CH_3)$_2$]$_3$}, 1.06 {m, 3 H, Si[CH(CH_3)$_2$]$_3$}, 1.35 [d, ^3J = 6.1 Hz, 6 H, CH(CH_3)$_2$], 2.93 (t, ^3J = 5.2 Hz, 2 H, CH_2CH$_2$O), 3.86 (s, 3 H, OCH_3), 4.01 (t, ^3J = 5.2 Hz, 2 H, CH$_2$CH_2O), 4.54 [sept, ^3J = 6.1 Hz, 1 H, CH(CH_3)$_2$], 6.44 (s, 2 H, OH), 6.71 (s, 1 H, H_{ar}), 7.17 (s, 1 H, H_{ar}); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 12.0 {d, Si[*C*H(CH_3)$_2$]$_3$}, 17.7 {q, Si[CH-(*C*H$_3$)$_2$]$_3$}, 22.2 [q, OCH(*C*H$_3$)$_2$], 38.1 (t, *C*H$_2$CH$_2$O), 56.2 (q, OCH_3), 66.5 (t, CH$_2$*C*H$_2$O), 71.5 [d, O*C*H(CH$_3$)$_2$], 117.2 (d, C_{ar}H), 117.2 (d, C_{ar}H), 137.3 (s, C_{ar}), 148.7 (s, C_{ar}), 149.1 (s, C_{ar}). C-B(OH)$_2$ not detected; MS (EI, 70 eV), *m/z* (%): 410 (6) [M^+], 382 (12), 366 (26), 323 (94), 281 (100), 253 (11), 193 (29), 151 (69), 112 (23), 103 (16), 75 (24), 45 (27), 40 (25); HRMS calcd for $C_{21}H_{38}O_3Si$: 366.2590. Found: 366.2586; Anal. Calcd for $C_{21}H_{39}BO_5Si$: C 61.45, H 9.58. Found: C 61.50, H 9.73.

Ethyl 3,4-dibromo-5-(2-(2-hydroxyethyl)-4-isopropoxy-5-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (14) Following general procedure B, a mixture of ethyl-3,4,5-tribromopyrrole-2-carboxylate (**2**) (1.88 g, 5.00 mmol) and boronic acid **5h** (2.46 g,6.00 mmol, 1.2 eq.) was heated under vigorous stirring for 16 h. The reaction mixture was filtered through a pad of celite and the solvents were evaporated. The residue was dissolved in dry THF 30 mL and stirred over night after addition of a 1.0 M solution of TBAF in THF (10 mL, 10.0 mmol, 2.0 eq.). Water (40 mL) and Et_2O (50 mL) were added, the aqueous layer extracted with Et_2O (3 × 40 mL) and the collected organic layers dried over Na_2SO_4. After filtration and evaporation the crude product was purified by flash chromatography on silica gel (P:EtOAc = 2:1) to give the alcohol **14** (1.44 g, 2.85 mmol, 57%) as a white solid. Mp 146-148 °C; IR (KBr): $\tilde{\nu}$ = 3490 (br m, OH) cm^{-1}, 3158 (w, NH), 2976 (m, CH), 1694 (s, C=O), 1514 (m, C=N; C=C), 1483 (s, C=N), 1242 (s, C-O), 1098 (s, C-O), 1039 (s, C-Br); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.37 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.39 [d, ^3J = 6.1 Hz, 6 H, OCH(CH_3)$_2$], 2.21 (br s, 1 H, OH), 2.76 (t, ^3J = 5.3 Hz, 2 H,

C*H*$_2$CH$_2$OH), 3.87 (s, 3 H, OCH$_3$), 4.05 (t, ^3J = 5.3 Hz, 2 H, CH$_2$C*H*$_2$OH), 4.35 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.58 (sept, ^3J = 6.1 Hz, 1 H, OC*H*(CH$_3$)$_2$], 6.80 (s, 1 H, H$_{ar}$), 7.06 (s, 1 H, H$_{ar}$), 11.69 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, CDCl$_3$): δ = 14.5 (q, OCH$_2$*C*H$_3$), 22.3 [q, CH(*C*H$_3$)$_2$], 34.7 (t, *C*H$_2$CH$_2$OH), 56.3 (q, OCH$_3$), 60.9 (t, O*C*H$_2$CH$_3$), 64.5 (t, CH$_2$*C*H$_2$OH), 71.7 [d, *C*H(CH$_3$)$_2$], 101.9 (s, C-4), 106.6 (s, C-3), 114.6 (d, C$_{ar}$H), 116.6 (d, C$_{ar}$H), 119.8 (s, C-2), 123.3 (s, C$_{ar}$), 130.3 (s, C$_{ar}$), 133.4 (s, C-5), 148.4 (s, C$_{ar}$), 148.6 (s, C$_{ar}$), 160.1 (s, C=O). MS (EI, 70 eV), *m/z* (%): 507/505/503 (51/100/50) [M$^+$], 465/463/461 (43/77/46), 427/425 (30/30), 401/399/397 (23/42/23), 387/385/383 (28/40/28), 353/351 (28/26), 307/305 (39/28), 285 (22), 239 (16), 226 (32), 184 (21), 166 (17), 153 (48), 91 (7), 57 (6), 43 (43); HRMS calcd for C$_{16}$H$_{17}$^{79}Br$_2$NO$_5$: 460.9474. Found: 460.9479; Anal Calcd for C$_{19}$H$_{23}$Br$_2$NO$_5$: C 45.17, H 4.59, N 2.77. Found: C 44.98, H 4.83, N 2.48.

Ethyl 1,2-dibromo-8-isopropoxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (15)[19f] To a cooled (0 °C) solution of **14** (2.55 g, 5.00 mmol) in dry CH$_2$Cl$_2$ 30 mL triethylamine (4.2 mL, 3.03 g, 30.0 mmol, 6.0 eq.) were added. After 5 min addition of methylsulfonylchloride (1.20 mL, 1.72 g, 15.0 mmol, 3.0 eq.) was followed by the removal of the ice bath and the reaction mixture was stirred at rt over night. A saturated aqueous solution of NaHCO$_3$ (20 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 20 mL). The collected organic layers were washed with brine (50 mL), dried over Na$_2$SO$_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (P:EtOAc = 3:1) to provide **15** (2.00 g, 4.11 mmol, 81%) as a pale yellow solid. Mp 85 °C; ^{1}H-NMR (360 MHz, CDCl$_3$): δ = 1.39-1.44 [m, 9 H, OCH(C*H*$_3$)$_2$, OCH$_2$C*H*$_3$], 2.93 (t, ^3J = 6.4 Hz, 2 H, NCH$_2$*C*H$_2$), 3.92 (s, 3 H, OCH$_3$), 4.37 (q, ^3J = 7.3 Hz, 2 H, OC*H*$_2$CH$_3$), 4.54-4.61 [m, 3 H, OC*H*(CH$_3$)$_2$, NC*H*$_2$CH$_2$], 6.76 (s, 1 H, H$_{ar}$), 7.99 (s, 1 H, H$_{ar}$); ^{13}C-NMR (90.6 MHz, CDCl$_3$): δ = 14.4 (q, OCH$_2$*C*H$_3$), 22.3 [q, OCH(*C*H$_3$)$_2$], 29.1 (t, NCH$_2$*C*H$_2$), 43.9 (t, N*C*H$_2$CH$_2$), 56.4 (q, OCH$_3$), 60.9 (t, O*C*H$_2$CH$_3$), 71.7 [d, O*C*H(CH$_3$)$_2$], 97.9 (s, C-4), 109.4 (d, C$_{ar}$H), 109.3 (s, C-3), 114.9 (d, C$_{ar}$H), 119.5 (s, C-2), 119.7 (s, C$_{ar}$), 126.2 (s, C$_{ar}$), 131.7 (s, C-5), 147.6 (s, C$_{ar}$), 149.1 (s, C$_{ar}$), 160.3 (s, C=O).

Ethyl 8-isopropoxy-9-methoxy-1,2-bis(4-isopropoxy-3-methoxyphenyl)-5,6-dihydropyrrolo[2,1*a*]-isoquinoline-3-carboxylate (16) An oven-dried Schlenk flask, equipped with a reflux condenser and a stirring bar, was charged with 1.97 g of the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **15** (4.05 mmol), 5.10 g of boronic acid **5f** (24.3 mmol, 6.0 eq.), Cs$_2$CO$_3$ (5.28 g, 16.2 mmol, 4.0 eq.), Pd$_2$(dba)$_3$ (190 mg, 0.20 mmol, 5 mol%) and P(2-furyl)$_3$ (190 mg, 0.40 mmol, 20 mol%). The Schlenk flask was evacuated and filled with argon (this sequence was repeated three times). Mesitylene (15 mL), EtOH (5 mL) and water (5 mL) were added and the flask was again carefully evacuated and filled with argon (this sequence was repeated three times). The reaction mixture was heated to 150 °C and vigorously stirred for 15 h. The

reaction mixture was then allowed to cool to rt, diluted with EtOAc (30 mL) and water (30 mL). The layers were separated, and the aqueous layer was twice extracted with EtOAc (30 mL). The collected organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated by *Kugelrohr* distillation. The crude material obtained was purified by flash chromatography on silica gel (P:Et_2O = 1:1) to provide 1.49 g of compound **16** (2.27 mmol, 56%) as a pale yellow solid. Mp 233-237 °C; IR (KBr): $\tilde{\nu}$ = 3453 cm^{-1} (w), 2976 (s), 2934 (s), 1693 (s, C=O), 1681 (s), 1537 (s), 1504 (s), 1402 (s, CH), 1333 (s), 1257 (br s, C-O), 1133 (br s, C-O), 1063 (s, C-O), 923 (br s), 860 (s), 733 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 1.32 [d, ^3J = 6.1 Hz, 6 H, $OCH(CH_3)_2$], 1.32 [d, ^3J = 6.1 Hz, 6 H, $OCH(CH_3)_2$], 1.36 [d, ^3J = 6.0 Hz, 6 H, $OCH(CH_3)_2$], 3.02 (br t, 2 H, NCH_2CH_2), 3.32 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 4.09 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 4.39-4.50 [m, 2 H, 2 × $OCH(CH_3)_2$], 4.52 [sept, ^3J = 6.0 Hz, 1 H, $OCH(CH_3)_2$], 4.61 (t, ^3J = 6.6 Hz, 2 H, NCH_2CH_2), 6.62-6.80 (m, 6 H, H_{ar}), 6.72 (s, 1 H, H_{ar}), 6.73 (s, 1 H, H_{ar}); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 13.9 (q, OCH_2CH_3), 22.2 [q, $OCH(CH_3)_2$], 22.2 [q, $OCH(CH_3)_2$], 22.3 [q, $OCH(CH_3)_2$], 29.2 (t, NCH_2CH_2), 43.0 (t, NCH_2CH_2), 55.3 (q, OCH_3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 59.9 (t, OCH_2CH_3), 71.6 [d, $OCH(CH_3)_2$], 71.6 (d, $OCH(CH_3)_2$], 71.6 [d, $OCH(CH_3)_2$], 109.4 (d, $C_{ar}H$), 114.9 (d, $C_{ar}H$), 115.1 (d, $C_{ar}H$), 115.3 (d, $C_{ar}H$), 115.4 (d, $C_{ar}H$), 116.3 (d, $C_{ar}H$), 118.4 (s, C-2), 121.3 (s, C_{ar}), 121.6 (s, C-5), 123.4 (d, $C_{ar}H$), 123.6 (d, $C_{ar}H$), 125.9 (s, C_{ar}), 128.9 (s, C_{ar}), 129.0 (s, C_{ar}), 131.2 (s, C-4), 132.9 (s, C-3), 145.7(s, C_{ar}), 145.9 (s, C_{ar}), 146.5 (s, C_{ar}), 148.7 (s, C_{ar}), 149.4 (s, C_{ar}), 150.4 (s, C_{ar}), 162.2 (s, C=O); Anal. Calcd for $C_{39}H_{47}NO_8$: C 71.21, H 7.20, N 2.13. Found: C 70.84, H 7.07, N 2.14.

4-Bromo-5-(4-*tert*-butylphenyl)-2-nitro-1*H*-pyrrole (17a) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 4-*tert*-butylphenylboronic acid (**5a**) (107 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 6 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17a** (139 mg, 0.43 mmol, 86%) as a yellow solid. Mp 60-63 °C; IR (KBr): $\tilde{\nu}$ = 3262 cm^{-1} (br m, NH), 2963 (s), 1519 (s, NO_2), 1469 (s), 1434 (s), 1410 (s), 1367 (s, NO_2), 1278 (s), 1246 (s), 836 (s), 739 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, $C(CH_3)_3$], 7.24 (d, ^4J = 3.0 Hz, 1 H, H-3), 7.52 (d, ^3J = 8.4 Hz, 2 H, H_{ar}) 7.66 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 9.54 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 31.3 [q, $C(CH_3)_3$], 35.1 [q, $C(CH_3)_3$], 97.3 (s, C-4), 115.1 (d, C-3), 126.3 (d, $C_{ar}H$), 127.4 (d, $C_{ar}H$), 130.9 (s, C_{ar}), 134.5 (s, C-5), 153.5 (s, C_{ar}). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 324/322 (58/46) [M^+], 309/307 (81/100), 282 (16), 267 (23), 236 (14), 213 (17), 182 (18), 153 (9), 131 (12), 120 (10); HRMS calcd for $C_{14}H_{15}{}^{79}BrN_2O_2$: 322.0317. Found: 322.0320.

4-Bromo-5-(4-methoxyphenyl)-2-nitro-1*H*-pyrrole (17b) Following general procedure C, a mixture of

4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 4-methoxyphenylboronic acid (**5b**) (91 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 17 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17b** (91 mg, 0.31 mmol, 61%) as a yellow solid. Mp 85-90 °C; IR (KBr): $\tilde{\nu}$ = 3262 cm^{-1} (br m, NH), 1610 (s), 1514 (s, NO_2), 1463 (s), 1413 (s, CH), 1371 (s, NO_2), 1297 (s), 1244 (s, C-O), 1180 (s), 1029 (s, C-O), 831 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 7.01 (d, ^3J = 8.9 Hz, 2 H, H_{ar}), 7.24 (d, ^4J = 2.7 Hz, 1 H, H-3), 7.65 (d, ^3J = 8.9 Hz, 2 H, H_{ar}), 9.54 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 55.6 (q, OCH_3), 97.0 (s, C-4), 114.7 (d, $C_{ar}H$), 115.2 (d, C-3), 121.2 (s, C_{ar}), 129.2 (d, $C_{ar}H$), 134.6 (s, C-5), 161.0 (s, C_{ar}). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 298/296 (100/100) [M^+], 268/266 (28/28), 240/238 (5/5), 225/223 (35/35), 170 (88), 156 (20), 144 (31), 127 (31), 115 (20), 101 (31), 76 (21), 63 (15), 51 (8); HRMS calcd for $C_{11}H_9{}^{79}BrN_2O_3$: 295.9796. Found: 295.9791.

4-Bromo-2-nitro-5-*p*-tolyl-1*H*-pyrrole (17c) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and *p*-tolylboronic acid (**5c**) (82 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 19 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17c** (83 mg, 0.30 mmol, 60%) as a yellow oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3285 cm^{-1} (br m, NH), 1514 (s, NO_2), 1463 (s), 1410 (s, CH), 1371 (s, NO_2), 1285 (s), 1245 (s), 818 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, $C_6H_4CH_3$), 7.24 (d, ^4J = 2.8 Hz, 1 H, H-3), 7.31 (d, ^3J = 8.0 Hz, 2 H, H_{ar}) 7.60 (d, ^3J = 8.0 Hz, 2 H, H_{ar}), 9.51 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 21.6 (q, $C_6H_4CH_3$), 97.3 (s, C-4), 115.0 (d, C-3), 126.0 (s, C_{ar}), 127.6 (d, $C_{ar}H$), 130.0 (d, $C_{ar}H$), 134.6 (s, C-5), 140.4 (s, C_{ar}). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 282/280 (100/100) [M^+], 252/250 (50/50), 224/222 (12/12), 209/207 (42/42), 171 (12), 154 (51), 143 (28), 128 (51), 118 (14), 102 (25), 89 (12), 77 (18) [$(C_6H_5)^+$], 63 (18), 51 (18); HRMS calcd for $C_{11}H_9{}^{79}BrN_2O_2$: 279.9847. Found: 279.9850.

4-Bromo-2-nitro-5-phenyl-1*H*-pyrrole (17d) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and phenylboronic acid (**5d**) (73 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 14 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17d** (75 mg, 0.28 mmol, 56%) as a yellow oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3258 cm^{-1} (br m, NH), 1514 (s, NO_2), 1463 (s), 1422 (s), 1371 (s, NO_2), 1286 (s), 1246 (s), 765 (s), 695 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 7.24 (d, ^4J = 2.8 Hz, 1 H, H-3), 7.31 (d, ^3J = 8.0 Hz, 2 H, H_{ar}) 7.60 (d, ^3J = 8.0 Hz, 2 H, H_{ar}), 9.51 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 97.5 (s, C-4), 115.0 (d, C-3), 127.8 (d, $C_{ar}H$), 128.9 (s, C_{ar}), 129.3 (d, C_{ar}), 130.0 (d, $C_{ar}H$), 134.3 (s, C-5). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 268/266 (100/98) [M^+], 238/236

(58/63), 210/208 (18/20), 195/193 (45/49), 157 (17), 140 (72), 129 (46), 114 (100), 104 (23), 88 (48), 77 (34) [$(C_6H_5)^+$], 65 (31) [$(C_5H_5)^+$], 51 (42) [$(C_4H_3)^+$]; HRMS calcd for $C_{10}H_7{}^{79}BrN_2O_2$: 265.9691. Found: 265.9692.

4-Bromo-5-(4-chlorophenyl)-2-nitro-1*H*-pyrrole (17e) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 4-chlorophenylboronic acid (**5e**) (86 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 10 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17a** (66 mg, 0.22 mmol, 44%) as a yellow solid. Mp 138 °C; IR (KBr): $\tilde{\nu}$ = 3263 cm^{-1} (br s, NH), 1461 (s, NO_2), 1406 (s), 1370 (s, NO_2), 1277 (s), 1242 (s), 1093 (m, C-Cl); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 7.25 (d, ^4J = 2.5 Hz, 1 H, H-3), 7.49 (d, ^3J = 8.5 Hz, 2 H, H_{ar}) 7.66 (d, ^3J = 8.5 Hz, 2 H, H_{ar}), 9.58 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 97.8 (s, C-4), 114.9 (d, C-3), 127.3 (s, C_{ar}), 129.0 (d, $C_{ar}H$), 129.6 (d, $C_{ar}H$), 133.0 (s, C-5), 136.2 (s, C_{ar}). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 304/302/300 (25/100/77) [M^+], 274/272/270 (12/54/42), 231/229/227 (11/43/34), 209/207 (6/6), 174 (45), 163 (14), 148 (40), 138 (23), 113 (63), 87 (18), 75 (18), 63 (18), 51 (10); HRMS calcd for $C_{10}H_6{}^{81}Br{}^{35}ClN_2O_2$: 301.9280. Found: 301.9280.

4-Bromo-2-nitro-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (17i) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 3,4,5-trimethoxyphenylboronic acid (**5i**) (138 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 17 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc = 2/1) to give **17a** (124 mg, 0.35 mmol, 69%) as a pale yellow oil, which slowly solidified to a wax upon standing. ^{1}H-NMR [360 MHz, $(CD_3)_2CO$]: δ = 3.83 (s, 3 H, OCH_3), 3.94 (s, 6 H, OCH_3), 7.21 (s, 2 H, H_{ar}), 7.35 (s, 1 H, H-3); ^{13}C-NMR [90.6 MHz, $(CD_3)_2CO$]: δ = 56.4 (q, OCH_3), 60.4 (q, OCH_3), 96.7 (s, C-4), 106.8 (d, $C_{ar}H$), 114.8 (d, C-3), 124.7 (s, C_{ar}), 129.0 (s, C-5), 129.6 (s, C-2), 140.1 (s, C_{ar}), 154.2 (s, C_{ar}); MS (ESI, negative), *m/z* (%): 357/355 (95/100) [$(M - H)^-$], 342/340 (30/34), 327/325 (7); HRMS calcd for $C_{12}H_{10}{}^{79}BrN_2O_5$: 340.9772. Found: 340.9778.

4-Bromo-2-nitro-5-*o*-tolyl-1*H*-pyrrole (17j) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and *o*-tolylboronic acid (**5j**) (92 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 13 h. The crude product was purified by flash chromatography on silica gel (PE/CH_2Cl_2 = 1/1) to give **17j** (83 mg, 0.29 mmol, 59%) as a yellow solid. Mp 170 °C; IR (KBr): $\tilde{\nu}$ = 3260 cm^{-1} (br m, NH), (s, NO_2 st as), 1469 (s), 1423 (s, CH), 1384 (s), 1371 (s, NO_2), 1344 (s), 1278 (s), 1249 (s) 765 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, $C_6H_4CH_3$), 7.24 (d, ^4J = 2.7 Hz, 1 H, H-3), 7.30-7.35 (m, 3 H, H_{ar}), 7.41 (dt, ^3J = 7.3 Hz, ^4J = 1.9 Hz, 1 H, H_{ar}), 9.38 (br s, 1 H, NH);

^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 20.1 (q, $C_6H_4CH_3$), 99.6 (s, C-4), 113.5 (d, C-3), 126.2 (d, $C_{ar}H$), 128.4 (s, C_{ar}), 130.5 (d, $C_{ar}H$), 130.6 (d, $C_{ar}H$), 131.0 (d, $C_{ar}H$), 135.3 (s, C-5), 137.9 (s, C_{ar}). C-NO_2 not detected; MS (EI, 70 eV), *m/z* (%): 282/280 (86/88) [M^+], 265/263 (11/11), 209/207 (7/7), 183 (100), 167 (26), 153 (65), 140 (10), 127 (52), 115 (12), 102 (12), 77 (12) [$(C_6H_5)^+$], 65 (10) [$(C_5H_5)^+$], 51 (8) [$(C_4H_3)^+$]; HRMS calcd for $C_{11}H_9{}^{79}BrN_2O_2$: 279.9847. Found: 279.9846; Anal. Calcd for $C_{11}H_9BrN_2O_2$: C 47.00, H 3.23. Found: C 46.88, H 3.20.

4-Bromo-5-(3-methoxyphenyl)-2-nitro-1*H*-pyrrole (17k) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 3-methoxyphenylboronic acid (**5k**) (99 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 15 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17k** (79 mg, 0.27 mmol, 54%) as a yellow oil, which slowly solidified to a wax upon standing. ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 7.00 (d, ^4J = 2.8 Hz, 1 H, H-3), 7.40-7.42 (m, 3 H, H_{ar}) 7.62 (br s, 1 H, H_{ar}), 9.65 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 55.6 (q, OCH_3), 97.5 (s, C-4), 113.4 (d, $C_{ar}H$), 114.9 (d, $C_{ar}H$), 120.0 (d, $C_{ar}H$), 130.0 (s, C_{ar}), 130.4 (d, $C_{ar}H$), 134.2 (s, C-5), 134.9 (s, C-2), 160.1 (s, C_{ar}); HRMS calcd for $C_{11}H_9{}^{79}BrN_2O_3$: 295.9796. Found: 295.9791.

5-(4-Benzyloxyphenyl)-4-bromo-2-nitro-1*H*-pyrrole (17l) Following general procedure C, a mixture of 4,5-dibromo-2-nitropyrrole (**4**) (135 mg, 0.5 mmol) and 4-(benzyloxy)phenylboronic acid (**5l**) (125 mg, 0.6 mmol, 1.2 eq.) was heated under vigorous stirring for 24 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **17l** (64 mg, 0.17 mmol, 34%) as a yellow oil, which slowly solidified to a wax upon standing. IR (KBr): $\tilde{\nu}$ = 3250 cm^{-1} (br m, NH), 1514 (s, NO_2), 1462 (s), 1415 (s, C-O), 1371 (s, NO_2), 1293 (s), 1242 (s), 1179 (s), 1024 (s, C-O), 831 (s), 739 (s), 697 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 5.13 (s, 2 H, CH_2), 7.09 (d, ^3J = 8.9 Hz, 2 H, H_{ar}), 7.23 (d, ^4J = 2.7 Hz, 1 H, H-3), 7.35-7.45 (m, 5 H, $OCH_2C_6H_5$), 7.65 (d, ^3J = 8.9 Hz, 2 H, H_{ar}), 9.54 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 70.4 (t, CH_2), 97.0 (s, C-4), 115.2 (d, C-3), 115.6 (d, $C_{ar}H$), 121.4 (s, C_{ar}), 127.6 (d, $C_{ar}H$), 128.4 (d, $C_{ar}H$), 128.9 (d, $C_{ar}H$), 129.2 (d, $C_{ar}H$), 134.5 (s, C-5), 136.4 (s, C_{ar}), 160.1 (s, C_{ar}). C-NO_2 not detected.

5-(4-*tert*-Butylphenyl)-4-(4-methoxyphenyl)-2-nitro-1*H*-pyrrole (18) Following general procedure C, a mixture of **17a** (91 mg, 0.28 mmol) and 4-methoxyphenylboronic acid (**5b**) (86 mg, 0.56 mmol, 2.0 eq.) was heated to 100 °C and vigorously stirring for 16 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **18** (66 mg, 0.19 mmol, 67%) as a yellow solid. Mp 55-58 °C; IR (KBr): $\tilde{\nu}$ = 3263 cm^{-1} (br. m, NH), 2961 (s), 1470 (s), 1450 (s, CH), 1409 (s, CH), 1364 (s,

NO_2), 1290 (m), 1241 (s, C-O), 1176 (m); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.32 (s, 9 H, C(CH_3)$_3$], 3.82 (s, 3 H, OCH_3), 6.86 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 7.21 (d, ^4J = 2.7 Hz, 1 H, H-3), 7.22 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 7.32 (d, ^3J = 8.6 Hz, 2 H, H_{ar}) 7.37 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 9.66 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 31.3 [q, C(CH_3)$_3$], 34.9 [q, $C(CH_3)_3$], 55.4 (q, OCH_3), 112.7 (d, C-3), 114.2 (d, $C_{ar}H$), 124.8 (s, C-5), 126.1 (d, $C_{ar}H$), 126.3 (s, C-4), 127.7 (d, $C_{ar}H$), 129.9 (d, $C_{ar}H$), 133.9 (s, C_{ar}), 134.9 (s, C_{ar}), 137.1 (s, C-2), 152.6 (s, C_{ar}), 159.1 (s, C_{ar}); MS (EI, 70 eV), *m/z* (%): 350 (100) [M^+], 335 (75), 320 (9), 307 (6), 289 (5), 277 (5), 261 (10), 247 (10), 202 (7), 189 (4), 170 (4), 153 (11), 132 (12), 117 (9), 89 (4), 77 (3) [$(C_6H_5)^+$], 57 (4); HRMS calcd for $C_{21}H_{22}N_2O_2$: 350.1631. Found: 350.1630.

4-(4-*tert*-Butylphenyl)-2-nitro-5-*p*-tolyl-1*H*-pyrrole (19) Following general procedure C, a mixture of **17b** (140 mg, 0.50 mmol) and 4-*tert*-butylphenylboronic acid (**5a**) (276 mg, 1.50 mmol, 3.0 eq.) was heated to 100 °C and vigorously stirring for 16 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give **19** (137 mg, 0.41 mmol, 82%) as a yellow solid. Mp 55-58 °C; IR (KBr): $\tilde{\nu}$ = 3264 cm^{-1} (br. m, NH), 2963 (s), 1494 (s), 1450 (s, CH), 1410 (s, CH), 1371 (s, NO_2), 1284 (s), 1238 (s); ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.34 [s, 9 H, C(CH_3)$_3$], 2.38 (s, 3 H, CH_3), 7.17 (m, 5 H, H_{ar}), 7.30 (m, 4 H, H_{ar}); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 21.5 (q, CH_3), 31.4 [q, C(CH_3)$_3$], 34.7 [s, $C(CH_3)_3$], 112.7 (d, C-3), 124.9 (s, C-5), 125.6 (d, $C_{ar}H$), 127.5 (s, C-4), 128.1 (d, $C_{ar}H$), 128.2 (d, $C_{ar}H$), 129.8 (d, $C_{ar}H$), 130.8 (s, C_{ar}), 134.3 (s, C_{ar}), 139.5 (s, C_{ar}), 150.4 (s, C_{ar}); MS (EI, 70 eV), *m/z* (%): 334 (57) [M^+], 319 (100) [$(M - CH_3)^+$], 291 (7), 273 (5), 258 (7), 245 (9), 231 (8); HRMS calcd for $C_{21}H_{22}N_2O_2$: 334.1681. Found: 334.1673; Anal. Calcd for $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63. Found: C 75.56, H 6.58.

4-(4-Fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-nitro-1*H*-pyrrole (20)[21a] An oven-dried Schlenk flask, equipped with a reflux condenser and a stirring bar, was charged with 4,5-dibromo-2-nitropyrrole (**4**) (270 mg, 1.0 mmol), 4-(methylsulfonyl)phenylboronic acid (**5m**) (240 mg, 1.2 mmol, 1.2 eq.), Cs_2CO_3 (652 mg, 2.00 mmol, 2.0 eq.), $Pd_2(dba)_3$ (46.0 mg, 5 mol%) and P(2-furyl)$_3$ (46.0 mg, 20 mol%). The Schlenk flask was evacuated and filled with argon (this sequence was repeated three times). Toluene (10 mL), EtOH (2 mL) and water (2 mL) were added and the flask was again carefully evacuated and filled with argon (this sequence was repeated three times). The reaction mixture was heated to 70 °C and vigorously stirred until TLC indicated complete conversion of the pyrrole (16 h). 4-fluorophenylboronic acid (**5n**) (420 mg, 3.0 mmol, 3.0 eq.) were then added and the reaction temperature was increased to 80 °C and stirred for 21 h. The reaction mixture was then allowed to cool to rt, diluted with EtOAc (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The collected organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered

and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2) to give compound **20** (213 mg, 0.59 mmol, 59%) as a yellow oil, which slowly solidified to a wax upon standing. ^{1}H-NMR (360 MHz, $CDCl_3$): δ = 3.08 (s, 3 H, SO_2CH_3), 7.11 (dd, ^3J = 8.6 Hz, $^3J_{H\text{-}F}$ = 8.6 Hz, 2 H, H_{ar}), 7.31 (s, 1 H, H-3), 7.37 (dd, ^3J = 8.6 Hz, $^4J_{H\text{-}F}$ = 5.2 Hz, 2 H, H_{ar}), 7.45 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 7.88 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 9.90 (br s, 1 H, NH); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 44.6 (q, SO_2CH_3), 112.0 (dd, $^6J_{CF}$ = 4.0 Hz, C-3), 116.8 (dd, $^2J_{CF}$ = 22.5 Hz, $C_{ar}H$), 122.8 (s, C-5), 125.7 (dd, $^5J_{CF}$ = 4.0 Hz, C-4), 128.2 (dd, $^3J_{CF}$ = 16.5 Hz, $C_{ar}H$), 129.2 (d, $C_{ar}H$), 130.5 (ds, $^4J_{CF}$ = 7.9 Hz, C_{ar}), 133.5 (s, C_{ar}), 137.7 (s, C_{ar}), 139.4 (s, C_{ar}), 163.6 (ds, $^1J_{CF}$ = 251.7 Hz, C_{ar}). C-NO_2 not detected; ^{19}F-NMR (235 MHz, $CDCl_3$): δ = –109.5.

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REFERENCES (AND NOTES)

1. (a) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Science, Oxford, 2000. (b) T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, 2nd ed., Wiley-VCH, Weinheim, 2003. (c) T. L. Gilchrist, *Heterocyclic Chemistry*, 3rd ed., Prentice-Hall, 1997. (d) A. R. Katritzky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd ed., Elsevier Science, Oxford, 2000. (e) L. I. Belen'kii, T. G. Kim, I. A. Suslov, and N. D. Chuvylkin, *Russ. Chem. Bull., Int. Ed.,* 2005, **54**, 853. (f) L. I. Belen'kii, *Heterocycles,* 1994, **37**, 2029.
2. Recent examples: (a) J. T. Tomlinson, G. Park, J. A. Misenheimer, G. L. Kucera, K. Hesp, and R. A. Manderville, *Org. Lett.*, 2006, **8**, 4951. (b) J. K. Laha, C. Muthiah, M. Taniguchi, B. E. McDowell, M. Ptaszek, and J. S. Lindsey, *J. Org. Chem.*, 2006, **71**, 4092. (c) H. Zarrinmayeh, E. Tromiczak, D. M. Zimmerman, N. Rankl, K. H. Ho, E. Dominguez, A. Castano, A. Escribano, C. Fernandez, A. Jimenez, W. J. Hornback, and E. S. Nisenbaum, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5203. (d) M. G. Banwell, E. Hamel, D. C. R. Hockless, P. Verdier-Pinard, A. Willis, and D. J. Wong, *Bioorg. Med. Chem.*, 2006, **14**, 4627. (e) J. W. Huffman, L. W. Padgett, M. L. Isherwood, J. L. Wiley, and B. R. Martin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5432. (f) P. Vachal, L. M. Toth, J. J. Hale, L. Yan, S. G. Mills, G. L. Chrebet, C. A. Koehane, R. Hajdu, J. A. Milligan, M. J. Rosenbach, and S. Mandala, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3684.
3. Reviews: (a) M. G. Banwell, T. E. Goodwin, S. Ng, J. A. Smith, and D. J. Wong, *Eur. J. Org. Chem.*, 2006, 3043. (b) J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Oxford, 2000. (c) V. N. Kalinin, *Synthesis*, 1992, 413.

4. (a) V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047-1062. (b) A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4176. (c) A. Jutand, S. Negri, and J. G. deVries, *Eur. J. Inorg. Chem.*, 2002, 1711.
5. S. Schröter, C. Stock, and T. Bach, *Tetrahedron*, 2005, **61**, 2245.
6. (a) M. Iwao, T. Takeuchi, N. Fujikawa, T. Fukuda, and F. Ishibashi, *Tetrahedron Lett.*, 2003, **44**, 4443. (b) T. Yamaguchi, T. Fukuda, F. Ishibashi, and M. Iwao, *Tetrahedron Lett.*, 2006, **47**, 3755.
7. (a) A. Alvarez, A. Guzmán, A. Ruiz, E. Velarde, and J. M. Muchowski, *J. Org. Chem.*, 1992, **57**, 1653. (b) N. A. Bumagin, A. F. Nikitina, and I. P. Beletskaya, *Russ. J. Org. Chem.*, 1994, **30**, 1619. (c) Y. Sugihara, R. Miyatake, I. Murata, and A. Imamura, *J. Chem. Soc., Chem. Commun.*, 1995, 1249. (d) M. G. Banwell, B. L. Flynn, E. Hamel, and D. C. R. Hockless, *Chem. Commun.*, 1997, 207. (e) A. Fürstner, H. Krause, and O. R. Thiel, *Tetrahedron*, 2002, **58**, 6373. (f) P. N. Collier, I. Patel, and R. J. K. Taylor, *Tetrahedron Lett*., 2002, **43**, 3401. (g) S. T. Handy and Y. Zhang, *Synthesis* 2006, 3883.
8. (a) T. Bach and L. Krüger, *Tetrahedron Lett.*, 1998, **39**, 1729. (b) T. Bach and L. Krüger, *Synlett*, 1998, 1185. (c) T. Bach and L. Krüger, *Eur. J. Org. Chem.*, 1999, 2045. (d) C. Stock, F. Höfer, and T. Bach, *Synlett*, 2005, 511.
9. (a) T. Bach and M. Bartels, *Synlett*, 2001, 1284. (b) T. Bach and M. Bartels, *Tetrahedron Lett.*, 2002**,** **43**, 9125. (c) T. Bach and M. Bartels, *Synthesis*, 2003**,** 925.
10. (a) T. Bach and S. Heuser, *Tetrahedron Lett.,* 2000, **41**, 1707. (b) T. Bach and S. Heuser, *Angew. Chem. Int. Ed.*, 2001, **40**, 3184. (c) T. Bach and S. Heuser, *J. Org. Chem.*, 2002, **67**, 5789. (d) T. Bach and S. Heuser, *Chem. Eur. J.*, 2002, **8**, 5585. (e) T. Bach and S. Heuser, *Synlett*, 2002, 2089. (f) A. Spieß, G. Heckmann, and T. Bach, *Synlett*, 2004, 131. (g) G. Heckmann and T. Bach, *Angew. Chem. Int. Ed.*, 2005, **44**, 1199. (h) O. Delgado, G. Heckmann, M. Müller, and T. Bach, *J. Org. Chem.*, 2006, **71**, 4599. (i) M. Müller, O. Delgado, and T. Bach, *Angew. Chem. Int. Ed.*, 2007, **46**, 4771.
11. Preliminary communication: S. Schröter and T. Bach, *Synlett*, 2005, 1957.
12. P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 1965, 459.
13. J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 3618.
14. F. F. Blicke and E. S. Blake, *J. Am. Chem. Soc.*, 1930, **52**, 235.
15. I. J. Rinkes, *Rec. Trav. Chim. Pays-Bas*, 1941, **60**, 303.
16. K. J. Morgan and D. P. Morrey, *Tetrahedron*, 1966, **22**, 57.
17. (a) C. Bailly, *Curr. Med. Chem.-Anti-Cancer Agents,* 2004, **4**, 363. (b) P. Cironi, F. Albericio, M. Álvarez, *Prog. Heterocycl. Chem*., 2004, 1. (c) D. Fernandez, A. Ahaidar, G. Danelon, P. Cironi, M. Marfil, O. Perez, C. Cuevas, F. Albericio, J. A. Joule, and M. Álvarez, *Monatsh. Chem.*, 2004, **135**, 615. (d) S. T. Handy and Y. Zhang, *Org. Prep. Proced. Int.*, 2005, **25**, 641. (d) G. Yang, A.-L. Wang,

H.-L. Chen, and Y.-C. You, *Youji Huaxue*, 2005, **25**, 641. (e) N. Dias, H. Vezin, H. Lansiaux, A. Lansiaux, and C. Bailly, *Top. Curr. Chem.*, 2005, **253**, 89. (f) P. Ploypradith, T. Petchmanee, P. Sahakitpichan, N. D. Litvinas, and S. Ruchirawat, *J. Org. Chem.*, 2006, **71**, 9440. (g) Y.-R. He, D.-P. Li, G. Yang, A.-L. Wang, Y.-C. You, D.-H. Hu, and X.-S. Yu, *Zhongguo Tianran Yaowu*, 2007, **5**, 150.

18. For synthetic studies towards lamellarin D, see: (a) F. Ishibashi, Y. Miyazaki, and M. Iwao, *Tetrahedron*, 1997, **53**, 5951. (b) F. Ishibashi, S. Tanabe, T. Oda, and M. Iwao, *J. Nat. Prod.,* 2002, **65**, 500. (c) C. Tardy, M. Facompré, W. Laine, B. Baldeyrou, D. García-Gravalos, A. Francesch, C. Mateo, A. Pastor, J. A. Jiménez, I. Manzanares, C. Cuevas, and C. Bailly, *Bioorg. Med. Chem*., 2004, **12**, 1697. (d) D. Pla, A. Marchal, C. A. Olsen, F. Albericio, and M. Álvarez, *J. Org. Chem.*, 2005, **70**, 8231. (e) N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi, and M. Iwao, *Tetrahedron*, 2006, **62**, 594. (f) D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio, and M. Álvarez, *J. Med. Chem.*, 2006, **49**, 3257.
19. M. C. Pampín, J. C. Estévez, R. J. Estévez, R. Suau, and L. Castedo, *Tetrahedron*, 2003, **59**, 8057.
20. (a) S. T. Handy and Y. N. Zhang, *Chem. Commun.*, 2006, 299. (b) I. J. S. Fairlamb, *Chem. Soc. Rev.,* 2007, **36**, 1036.
21. (a) W. W. Wilkerson, W. Galbraith, K. Gansbrangs, M. Grubb, W. E. Hewes, B. Jaffee, J. P. Kenney, J. Kerr, and N. Wong, *J. Med. Chem.*, 1994, **37**, 988. (b) W. W. Wilkerson, R. A. Copeland, M. Covington, and J. M Traskos, *J. Med. Chem.*, 1995, **38**, 3895. (c) V. Zoete, F. Maglia, M. Rougee, and R. V. Bensasson, *Free Radical Biol. Med.*, 2000, **28**, 1638. (d) K. Hagiwara, H. Saso, K. Ichinose, C. Yokota, and S. Sano, *Patent Application*, WO 9617841, 1996.
22. D. G. Lloyd, R. B. Hughes, D. M. Zisterer, D. C. Williams, C. Fattorusso, B. Catalanotti, G. Campiani, and M. J. Meegan, *J. Med. Chem*., 2004, **47**, 5612.