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1 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
2 **2-(trimethylsilyl)ethoxymethyl (SEM)**

1
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3 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
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8
9

10 **Dedication**

11 *Dedicated to Professor Neil Burford with thanks for teaching us so much.*

12 **Abstract**

13 Palladium-catalyzed decarboxylative arylation is reported using pyrroles *N*-protected with the 2-
14 (trimethylsilyl)ethoxymethyl (SEM) group and featuring 2-, 3- and 4-substituents about the pyrrolic
15 framework. In contrast to *N*-protected pyrroles previously used in decarboxylative arylation, the use of
16 SEM allows deprotection under mild conditions.

17

18 **Keywords**

19 Pyrroles, decarboxylative arylation, pyrrole *N*-protection, SEM, substituted pyrrolic core
20
21

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22

23**Introduction**

24 Considerable effort has addressed the development of efficient synthetic strategies to form (hetero)aryl-
25 (hetero)aryl¹⁻³ C-C bonds that proceed under mild reaction conditions and with high selectivity and
26 broad tolerance. In this vein, transition metal-catalyzed direct C-H arylation has earned significant
27 attention due to the large variety of tolerated functional groups and high yielding selectivity at low
28 catalyst loadings.⁴⁻⁶ More recently, transition metal-catalyzed decarboxylative arylation, using
29 carboxylic acids as synthetic equivalents of aryl halides, triflates and organometallic species, has been
30 investigated.⁷

31 Pyrroles are a recurrent feature in supramolecular, medicinal and agricultural chemistry.^{2,8-10}
32 There are numerous examples of transition metal-catalyzed direct C-H and decarboxylative arylation
33 using pyrroles and various transition metals. In this way, aryl groups have been efficiently adjoined to
34 the 2-position of pyrroles. However, most methodologies focus on using the unsubstituted pyrrole unit,
35 and do not embrace the necessity to work with pyrroles already bearing substituents on the 3-, 4- and 5-
36 positions. Furthermore, these methodologies typically involve *N*-alkyl and *N*-aryl pyrroles,^{3-7,11-16}
37 thereby incorporating protecting groups that, courtesy of inherent challenges encountered in
38 deprotection, are largely impractical for use in a synthetic sequence.¹⁷ An exception to these generalities
39 resulted in the first total synthesis of lamellarin L, and involved decarboxylative arylation of a pyrrole
40 that is *N*-protected by an ethyl benzene derivative and that is highly substituted about the carbon atoms
41 of the pyrrole.¹⁸ The complex natural product bears *N*-substitution with features based on ethyl
42 benzene, and thus deprotection was not required in this case.

43 Bilodeau, Forgione and co-workers reported a comprehensive investigation of the reactivity of
44 *N*-protected 2-pyrrole carboxylic acid in palladium-catalyzed decarboxylative arylation with Ar-X (X =
45 iodides, chlorides, bromides and triflates) affording the targeted biaryls (Scheme 1, top).¹⁹ The role of
46 both solvent and base was studied, as was the use of palladium-based catalysts either pre-made or

7 **Decarboxylative arylation of substituted pyrroles *N*-protected with** 8 **2-(trimethylsilyl)ethoxymethyl (SEM)**

47 formed *in situ*. The cross-coupling reaction was evaluated using conventional and microwave-promoted
48 heating. The pyrrolic nitrogen atom was protected with methyl or aryl groups to demonstrate that *N*-
49 methyl 2-pyrrole carboxylic acid undergoes decarboxylative arylation with higher efficiency than the
50 corresponding *N*-aryl analogue.¹⁹ However, despite significant success, this work was applied only to
51 the unsubstituted and commercially available 2-pyrrole carboxylic acid (no further substituents about
52 the pyrrolic core), and removal of these *N*-protecting groups is known to be challenging with pyrroles.¹⁷

53 **Scheme 1 Decarboxylative arylation and the work reported herein.**

54 We herein report palladium-catalyzed decarboxylative arylation involving stoichiometric
55 amounts of *N*-2-(trimethylsilyl)ethoxymethyl 2-pyrrole carboxylic acids and phenyl bromide. The 2-
56 (trimethylsilyl)ethoxymethyl (SEM) group is conducive to deprotection subsequent to coupling
57 (Scheme 1, bottom). Pyrroles substituted in the 3-, 4- and 5-positions, in addition to the requisite 2-
58 carboxylic acid, were used. These pyrroles stem from Knorr-type reactions,²⁰ are widely used in the
59 generation of di- and tri- species²⁰⁻²⁴ and bear benzyl esters in the 2-position functionality to provide
60 ready access to the required carboxylic acid.²⁵⁻²⁷ The efficiency of other aryl halides was also evaluated.

61 **Results and discussion**

62 We began by evaluating the effectiveness of decarboxylative arylation with pyrroles bearing 3-, 4- and
63 5-substituents. As *N*-methyl pyrroles feature prominently in the work involving the core (unsubstituted)
64 pyrrole unit,¹⁹ we *N*-methylated the substituted pyrroles **1a-c** (Scheme 2).¹⁷ Adapting a literature
65 procedure,²¹ pyrroles **1a-c** were reacted with MeI in the presence of NaOH and TBAB. Although the
66 protection of electron-deficient pyrroles (**1a** and **1c**) occurred smoothly and in quantitative yields,
67 methylation of electron-rich **1b** resulted in a lower yield.

68 **Scheme 2 *N*-Methylation of pyrroles **1a-c**.**

69 Given the benzyl ester functionality at the α -position, *N*-methyl pyrroles **2a-c** were submitted to
70 hydrogenolysis to form the targeted carboxylic acids **3a-c**.²⁸ The crude acids were carried directly into

9 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
10 **2-(trimethylsilyl)ethoxymethyl (SEM)**

71 the reported palladium-catalyzed decarboxylative arylation (Scheme 3, method a).¹⁹ Decarboxylative
72 cross-coupling using electron-rich **3b** was unsuccessful as polymerization dominated. However, 2-
73 phenyl pyrroles **4a** (50% yield, based on stoichiometry of pyrrole starting material) and **4c** (43%) were
74 isolated alongside the corresponding α -free derivatives **5a** and **5c** in 3:1 and 10:1 ratios, respectively
75 (the 2-Ph and 2-H analogs were inseparable in each case). As the literature conditions use 2 eq. of 2-
76 pyrrole carboxylic acids and 1 eq. of PhBr,¹⁹ the isolation of the α -free pyrrole is not unexpected and
77 presumably arises due to non-catalyzed decarboxylation of pyrroles at temperatures below 170 °C.⁷
78 Furthermore, the literature yields are based on the limiting reagent, which is the aryl halide, and so
79 necessarily result in conversion of <50% of the desired pyrrole.

80 **Scheme 3 Decarboxylative arylation of substituted *N*-Me pyrroles.**

81 Focusing on the electron-poor pyrrole, the reaction was repeated using 1 eq. of **3a** and 1.1 eq. of
82 PhBr to produce pure **4a** in 96% yield. These results demonstrate the electronic effect of substituents on
83 the reactivity of *N*-methyl pyrroles: electron-rich pyrroles undergo polymerization under these
84 conditions (**2b**), yet pyrroles bearing carbonyl functional group at either the distal \square - or \square -positions
85 (**2a**, **2c**) can be coupled in moderate to excellent yield.

86 The success of this decarboxylative coupling with pyrroles substituted in the 3-, 4- and 5-
87 positions is significant, as such pyrroles are routinely used in the preparation of di- and tri-pyrrolic
88 compounds such as BODIPYs and prodigiosenes. Furthermore, placement of a benzyl ester at the 2-
89 position is facile courtesy of Knorr-type reactions.²⁰ However, given that the deprotection of *N*-methyl
90 pyrroles is challenging,¹⁷ we sought a route towards pyrroles amenable to decarboxylative arylation at
91 the 2-position yet acquiescent to deprotection at the nitrogen atom. As palladium-catalyzed direct C-H
92 arylation with *N*-unprotected pyrroles is known,²⁹ we submitted the *N*-unprotected pyrrole **1a** to the
93 decarboxylative arylation conditions (method b, Scheme 3). However, ¹H NMR spectroscopic analysis
94 of the crude mixture showed only the two starting materials (PhBr and **1a**), as well as a significant

11 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
12 **2-(trimethylsilyl)ethoxymethyl (SEM)**

95 amount of the corresponding α -free pyrrole. This result suggested that protection of the pyrrolic
96 nitrogen atom is indeed required for decarboxylative arylation to proceed.

97 Cognizant that *N*-Boc pyrroles are facile to deprotect under mild conditions¹⁷ and that direct C-
98 H arylation involving *N*-Boc pyrroles has been reported,^{30,31} Boc-protected **6a** was submitted to
99 hydrogenolysis followed by the conditions for palladium-catalyzed decarboxylative arylation (Scheme
100 4). Unfortunately, the desired phenyl pyrrole **7a** was not isolated and the majority of the material was
101 recollected as the corresponding *N*-deprotected α -free derivative.³² *N*-Tosylation of pyrrole **1a** proved
102 wholly unsatisfactory,^{33,34} again demonstrating the fickle nature of *N*-protection of pyrroles.¹⁷

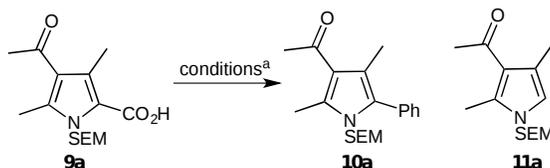
103 **Scheme 4 Attempted decarboxylative arylation using *N*-Boc pyrrole **6a**.**

104 We turned our attention to protecting groups that would mimic the methyl group of *N*-methyl
105 pyrrole yet enable removal after the cross-coupling step. The 2-(trimethylsilyl)ethoxy methyl (SEM)
106 protecting group has been used to protect functionalities such as alcohols, imines, imidazoles and
107 pyrroles. It is easily introduced, more selective than other protecting groups (*e.g.* methyl group), and,
108 most importantly is removed under reaction conditions compatible with other functional groups.^{35,36}
109 Furthermore, the SEM group has been shown to be effective as a protecting group for pyrazoles
110 undergoing C-H arylation.³⁷ Pleasingly, reaction of the pyrrolide of **1a** with SEM-Cl gave the *N*-SEM
111 pyrrole **8a**. Hydrogenolysis of the benzyl ester gave the acid **9a**, which was used in the subsequent
112 palladium-catalyzed decarboxylative arylation step without isolation (Scheme 5). The desired 2-phenyl
113 pyrrole **10a** was obtained in an inseparable mixture with the corresponding α -free pyrrole **11a**. Based
114 on ¹H NMR spectroscopic analysis of the isolated mixture, the conversion to **10a** and **11a** proceeded in
115 3:2 ratio (Scheme 5). With this encouraging result in hand, the conditions for the decarboxylative
116 arylation between 2-pyrrole carboxylic acid **9a** and PhBr were optimized (Table 1).

117 **Scheme 5 Decarboxylative arylation using SEM-protected pyrrole **8a**.**

118

13 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
 14 **2-(trimethylsilyl)ethoxymethyl (SEM)**
 119 **Table 1 Optimization using 2-pyrrole carboxylic acid **9****



120

Entry	Base	PhBr (eq.)	T (° C)	t (min)	Conversion ^{b,c} (10a:11a:9a)
1	Cs ₂ CO ₃ (1.5 eq.)	1.1	150	10	55:45:0
2	Cs ₂ CO ₃ (1.5 eq.)	1.1	190	10	77:23:0
3	KOAc (1.5 eq.)	1.1	170	10	83:17:0
4	KOAc (1.5 eq.)	1.1	150	10	78:22 :0
5	KOAc (1.5 eq.)	1.1	170	20	81:19:0
6	KOAc (1.5 eq.)	1.1	190	10	82:18:0
7	KOAc (1.5 eq.)	1.1	190	20	82:18:0
8	KOtBu (1.5 eq.)	1.1	170	10	85:0:15
9	KOtBu (1.5 eq.)	1.1	150	10	89:0:11
10	KOtBu (1.5 eq.)	1.1	190	10	85:0:15
11	KOtBu (3 eq.)	1.1	150	10	67:0:33
12	KOtBu (1.5 eq.)	1.3	150	10	92:traces:traces
13	KOtBu (1.5 eq.)	1.5	150	10	96:traces:traces
14	KOtBu (1.5 eq.)	2	150	10	93:traces:traces

121Note: ^aReactions were performed in 2-5 mL microwave vials, using 0.05 equivalents of Pd(PtBu₃)₂, as catalyst, and DMF, as solvent.
 122^bAccording to ¹H NMR spectroscopic analysis of the crude mixture; ^cPercentages are based on the integrals relative to the proton peaks of
 123the SEM-protecting group.

124
 125 The temperature was both decreased to 150 °C (entry 1) and increased to 190 °C (entry 2).
 126Formation of the α -free pyrrole **11a** decreased when the reaction was carried out at 190 °C. Cs₂CO₃ was
 127replaced by KOAc, and variation of temperature and time explored (entries 3-7). However, no
 128improvements were obtained. Surprisingly, the use of KtOBU (entries 8-14) afforded **10a** in 85%
 129conversion (entry 8), without formation of **11a**, yet with 15% of unreacted starting material. Cognizant
 130that KtOBU has a pka of 17, higher than that of Cs₂CO₃ (10) and KOAc (4.8), deprotonation of **9a**
 131might occur more readily than the palladium-catalyzed decarboxylation. Increasing the temperature to
 132190 °C (compare entries 9 and 10) did not increase the conversion to product. The presence of the
 133unreacted **9a** might be due to insufficient KtOBU or PhBr in the reaction mixture. However, when the
 134equivalents of the base were doubled (entry 11), the conversion of **9a** to **10a** decreased. Increasing the
 135equivalents of PhBr to 1.3 (entry 12), 1.5 (entry 13) and 2 (entry 14) gave almost full conversion to 2-

15 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
16 **2-(trimethylsilyl)ethoxymethyl (SEM)**

136phenyl pyrrole **10a**, with only traces of starting materials and α -free pyrrole observed in the product
137mixture. The optimized reaction conditions (entry 13) were repeated and **10a** was isolated in 54% yield,
138after purification using column chromatography on silica. The use of other phenyl halides met
139with little success. Indeed, when the optimized conditions (entry 13, using Ph-X)
140were applied with phenyl chloride and phenyl triflate, instead of phenyl bromide,
141only the α -free derivative **11a** was isolated. The use of phenyl iodide gave the
142desired pyrrole **10a** in a yield of only 25%. Thus, aryl bromides were established
143as the aryl halide coupling partner of choice.

144 With a successful route to **10a** in hand, the removal of the SEM-protecting group was
145investigated (Scheme 6). Adapting a literature procedure,³⁶ a solution of the *N*-SEM 2-phenyl pyrrole
146**10a** in THF was treated with 5 eq. of 1 M TBAF and heated at reflux temperature for 19 hours. The
147desired deprotected 2-phenyl pyrrole **12a** was thus obtained.

148 **Scheme 6 SEM-deprotection of pyrrole 10a.**

149 In order to evaluate the feasibility of palladium-catalyzed decarboxylative arylation and *N*-
150deprotection involving substituted *N*-SEM pyrroles, the substrate scope was explored using pyrroles
151**1b-h**, featuring various functionalities about the pyrrolic core (Scheme 7). Despite the different
152electronic nature of pyrroles **1b-h**, SEM-protection was consistent and high-yielding across all the
153substrates reported herein, although we note, from other examples in our lab, that this is not always the
154case for SEM-protection of pyrroles. The SEM-protected pyrroles **8b-h** were submitted to
155hydrogenolysis and the resulting carboxylic acids reacted with PhBr under the optimized
156decarboxylative arylation reaction conditions (Table 1, entry 13). Electron-rich pyrroles **10b** and **10e**
157were obtained successfully and in comparable isolated yields to that of **10a**. However, attempts to
158achieve *N*-deprotection resulted only in decomposition of the starting materials. SEM-deprotection was
159also attempted on pyrrole **8b** and again decomposition of the starting material was observed. This

17 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
18 **2-(trimethylsilyl)ethoxymethyl (SEM)**

160 suggests that removal of the SEM protecting group is challenging when working with electron-rich
161 pyrroles. Hydrogenolysis of the benzyl ester of pyrrole **8c** was unsuccessful and a mixture of
162 deformylated products was instead obtained. 2-Phenyl pyrroles **10d** and **10h** were successfully
163 produced as the major components of inseparable mixtures containing the corresponding α -free
164 derivatives (see Supporting Information). The yields are calculated based on the conversion of **9d** and
165 **9h** into **10d** and **10h**, respectively, and the mass of the product mixture. Upon deprotection, the targeted
166 compounds **12d** and **12h** were separated from the unwanted α -free derivatives, and isolated in 52% and
167 65% yields, respectively. Hydrogenolysis of unsubstituted SEM-protected pyrrole **8f**, followed by
168 decarboxylative arylation provided **10f** in 60% yield. In contrast, submitting the carboxylic acid **9f** to
169 Bilodeau and Forgiione's reaction conditions¹⁹ afforded **10f** in only 28% yield. Removal of the SEM-
170 protecting group proceeded smoothly to provide the *N*-unprotected 2-phenyl pyrrole **12f** in good yield.
171 The electron-poor pyrrole **9g** underwent successful decarboxylative arylation, but could not be purified
172 from the multiple other SEM-products that were unexpectedly generated.

173 **Scheme 7 Palladium-catalyzed decarboxylative arylation and SEM-deprotection of pyrroles 8b-h.**

174 The feasibility of the decarboxylative arylation and SEM-deprotection
175 involving pyrrole **8a** and various coupling partners was explored (Scheme 8). 2-
176 Aryl pyrroles **10i-10k** were successfully produced, giving **10i** and **10j** as the
177 major components of inseparable mixtures containing the corresponding α -free
178 derivative. Upon deprotection in each case, the unwanted α -free derivative was
179 separated from the targeted **12i** and **12j** and the desired 2-aryl pyrroles thus
180 isolated. The 2-thienyl pyrrole **10k** was produced in 37% and separated from the
181 α -free derivative prior to the successful deprotection step. However, 2-pyridyl
182 bromide was an unsuccessful coupling partner, with the reaction producing only
183 the unwanted α -free derivative.

19 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
20 **2-(trimethylsilyl)ethoxymethyl (SEM)**
184 **Scheme 8 Palladium-catalyzed decarboxylative arylation and SEM-deprotection with aryl bromides.**

185 In summary, we report palladium-catalyzed decarboxylative arylation for heteroaryl-aryl C-C
186bond formation using substituted *N*-SEM pyrroles in stoichiometric amounts. Aryl bromide was found
187to be a superior coupling partner compared to the corresponding chloride, triflate and iodide. Several
188aryl bromides were successfully coupled to the 2-position of pyrroles. The influence of substituents
189about the pyrrole core, both electron-donating and electron-withdrawing, was investigated. Compared
190to *N*-methyl pyrroles, the use of SEM as an *N*-protecting group enables both decarboxylative arylation
191and *N*-deprotection with select systems. Furthermore, the yields reported herein are based on the
192amount of pyrrole used (rather than following literature precedent that bases yields on the amount of
193aryl halide used).¹⁹ Although SEM-deprotection of some electron-rich pyrroles was unsuccessful, the
194deprotection of pyrroles bearing a mixture of alkyl- and H-substitution, as well as acyl or pendant
195carbonyl functionality, proceeded well. Certainly, the fickle nature of pyrroles as regards to
196(de)protection means that protection strategies must be chosen with care. Nevertheless, for certain
197systems, the use of *N*-SEM pyrroles provides a useful alternative when deprotection is required
198following decarboxylative arylation.

199Experimental section

200General

201All chemicals were purchased and used as received unless otherwise indicated. Moisture sensitive
202reactions were performed in oven-dried glassware and under a positive pressure of nitrogen via use of a
203Schlenk line or glove box, both producing comparable yields. Air- and moisture-sensitive compounds
204were introduced via syringe or cannula through a rubber septum. Flash chromatography was performed
205using ultra-pure silica (230-400 mm), unless indicated otherwise. The NMR spectra were recorded
206using a 500 MHz spectrometer instrument using CDCl₃, which was referenced at 7.26 ppm for ¹H and
207at 77.16 ppm for ¹³C. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained using

21 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
22 **2-(trimethylsilyl)ethoxymethyl (SEM)**

208 TOF and LCQ Duo ion trap instruments operating in ESI^{+/−} mode or APCI, as indicated. Compounds
209 **1a-h**^{25,27,38-42} were prepared according to literature procedures.

210 **Benzyl 4-acetyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2a)**

211 Adapting a literature procedure²¹ pyrrole **1a** (0.50 g, 1.84 mmol) was dissolved in CH₂Cl₂ (20 mL) and
212 NBu₄Br (59 mg, 0.184 mmol) and MeI (126 μL, 2.02 mmol) were added. The mixture was stirred
213 vigorously at 0 °C as 5 M NaOH (10 mL) was added drop-wise. The mixture darkened, and was
214 allowed to warm to room temperature and then stirred for 18 h. The organic fraction was separated and
215 washed with brine (100 mL), dried over Na₂SO₄, and filtered over a pad of neutral silica using
216 methanol:CH₂Cl₂ (5:95). After removal of the solvent *in vacuo*, pyrrole **2a** was isolated as an off-white
217 solid (0.61 g, 99%). ¹H NMR (500 MHz; CDCl₃) 2.45 (s, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 3.77 (s, 3H),
218 5.32 (s, 2H), 7.43-7.33 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) 12.4, 13.7, 32.0, 66.1, 123.5, 128.3,
219 128.8, 129.5, 136.2, 140.5, 162.1, 196.6 (1 carbon unaccounted for) ppm. HRMS-ESI (*m/z*): [M+Na]⁺
220 calcd for C₁₇H₁₉NO₃, 308.1263; found, 308.1257.

221 **Benzyl 4-ethyl-1,3,5-trimethyl-pyrrole-2-carboxylate (2b)**

222 Adapting a literature procedure,²⁸ pyrrole **1b** (2.12 g, 8.2 mmol) was dissolved in CH₂Cl₂ (20 mL), and
223 NBu₄Br (0.26 g, 0.82 mmol) and MeI (0.56 mL, 9.06 mmol) were added. The mixture was stirred
224 vigorously at 0 °C as 5 M NaOH (20 mL) was added drop-wise. The reaction vessel and condenser
225 tube were sealed, and the mixture was heated at 50 °C for 3 days. Although a considerable amount of
226 starting material was still present, the organic fraction was separated and washed with brine (100 mL),
227 and dried over Na₂SO₄. Purification using chromatography (SiO₂, hexane/EtOAc 90/10 then 80/20)
228 gave pyrrole **2b** as a colourless oil (0.48 g, 22%). ¹H NMR (500 MHz; CDCl₃) 1.02 (t, *J* = 7.5 Hz, 3H),
229 2.16 (s, 3H), 2.26 (s, 3H), 2.39 (q, *J* = 7.5 Hz, 2H), 3.77 (s, 3H), 5.29 (s, 2H), 7.30 (t, *J* = 7.2 Hz, 1H),
230 7.36 (t, *J* = 7.4 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H) ppm. ¹³C NMR (125 MHz; CDCl₃) 10.4, 11.8, 15.8,

23 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
24 **2-(trimethylsilyl)ethoxymethyl (SEM)**

231 17.6, 33.0, 65.26, 122.8, 127.6, 128.0, 128.1, 128.6, 137.1, 162.1 (1 carbon unaccounted for) ppm.

232 HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₁NO, 294.1470; found, 294.1465.

233 **Benzyl 4-ethyl-5-formyl-1,3-dimethyl-pyrrole-2-carboxylate (2c)**

234 Adapting a literature procedure,¹⁹ pyrrole **1c** (1.70 g, 6.27 mmol) was dissolved in CH₂Cl₂ (20 mL) and

235 NBu₄Br (0.20 g, 0.627 mmol) and MeI (0.43 mL, 6.89 mmol) were added. The mixture was stirred

236 vigorously at 0 °C as 5 M NaOH (15 mL) was added drop-wise. The mixture darkened, and was

237 allowed to warm to room temperature as the reaction stirred for 18 h. The organic fraction was

238 separated and washed with brine (100 mL), dried over Na₂SO₄, and filtered over a pad of neutral silica

239 using methanol:CH₂Cl₂ (5:95). After removal of the solvent *in vacuo*, pyrrole **2c** was isolated as a

240 brown solid (1.78g, 99%). ¹H NMR (500 MHz; CDCl₃) 1.13 (t, *J* = 7.6 Hz, 3H), 2.20 (s, 3H), 2.71 (q, *J*

241 = 7.6 Hz, 2H), 4.16 (s, 3H), 5.34 (s, 2H), 7.44-7.34 (m, 5H), 9.90 (s, 1H) ppm. ¹³C NMR (125 MHz;

242 CDCl₃) 10.8, 16.6, 16.8, 34.8, 66.7, 126.0, 127.0, 128.5, 128.8, 130.0, 135.8, 138.0, 161.7, 180.3 (1

243 carbon unaccounted for) ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₇H₁₉NO₃, 308.1263; found,

244 308.1257.

245 **General procedure for the decarboxylative Pd-coupling of pyrrole 2 (GP1):**

246 Adapting literature procedures,^{19,35} a solution of pyrrole **2** (1 equiv), 10 mol% Pd/C (10% of the mass of

247 **2**) and NEt₃ (few drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times

248 with N₂ before the introduction of H₂ atmosphere. After stirring the reaction mixture for 19 h, nitrogen

249 atmosphere was introduced and the reaction was filtered through a plug of Celite[®] and rinsed with

250 MeOH. Removal of the solvent under reduced pressure gave pyrrole **3**, which was used in the next step

251 without further purification. Pyrrole **3** (1 equiv), PhBr (1.1 equiv), NBu₄Cl (1 equiv), Cs₂CO₃ (1.5

252 equiv), and Pd(P(*t*Bu)₃)₂ (0.05 equiv) were combined in an open microwave vial. The vessel was

253 crimped through the use of a septum cap, a nitrogen atmosphere introduced and anhydrous DMF was

254 added (0.1 M). The mixture was stirred for 30 s, and then submitted to microwave-promoted heating

25 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
26 **2-(trimethylsilyl)ethoxymethyl (SEM)**

255 conditions (150 °C, 10 min, high absorption). The mixture was diluted with ethyl acetate (50 mL) and
256 washed with a saturated solution of NaHCO₃ (× 3) and water (× 2). The organic layer was dried over
257 Na₂SO₄ and concentrated under reduced pressure. The crude mixtures were purified using column
258 chromatography on SiO₂ (EtOAc/hexane, 10% □ 30%) to give the desired products.

259 **4-Acetyl 3,5-dimethyl-2-phenyl-1-methyl-pyrrole (4a)**

260 Pyrrole **4a** was obtained according to GP1 as a colorless solid (28 mg, 96%). ¹H NMR (500 MHz;
261 CDCl₃) 2.17 (s, 3H), 2.48 (s, 3H), 2.56 (s, 3H), 3.34 (s, 3H), 7.25 (d, *J* = 6.9 Hz, 2H), 7.38 (t, *J* = 7.4
262 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H) ppm. ¹³C NMR (125 MHz; CDCl₃) 12.7, 13.0, 31.6, 31.7, 116.4,
263 121.6, 127.8, 128.5 (2C), 131.2 (2C), 131.6, 132.1, 135.7, 196.1 ppm. HRMS-ESI (*m/z*): [M+Na]⁺
264 calcd for C₁₅H₁₇NO, 250.1208; found, 250.1202.

265 **3-Ethyl-1,4-dimethyl-5-phenyl-pyrrole-2-carbaldehyde (4c)**

266 Pyrrole **4c** was obtained according to GP1 as a beige solid containing both the product **4c** (43%, based
267 on the amount of **4c** in the isolated mixture) and the decarboxylated derivative **5c** in a 10:1 ratio, which
268 was not easily separated using chromatography. ¹H NMR (500 MHz; CDCl₃) 1.16 (t, *J* = 7.6 Hz, 0.1 ×
269 3H, CH₂CH₃ of **5c**), 1.22 (t, *J* = 7.6 Hz, 0.9 × 3H, CH₂CH₃ of **4c**), 1.93 (s, 0.9 × 3H, CH₃ of **4c**), 2.03 (s,
270 0.1 × 3H, CH₃ of **5c**), 2.69 (q, *J* = 7.6 Hz, 0.1 × 2H, CH₂CH₃ of **5c**), 2.76 (q, *J* = 7.6 Hz, 0.9 × 2H,
271 CH₂CH₃ of **4c**), 3.75 (s, 0.9 × 3H, CH₃ of **4c**), 3.85 (s, 0.1 × 3H, CH₃ of **5c**), 6.59 (s, 0.1 × 1H, Ar-*H* of
272 **5c**), 7.29 (d, *J* = 6.9 Hz, 0.9 × 2H, Ar-*H* of **4c**), 7.41 (t, *J* = 7.4 Hz, 0.9 × 1H, Ar-*H* of **4c**), 7.47 (t, *J* =
273 7.3 Hz, 0.9 × 2H, Ar-*H* of **4c**), 9.66 (s, 0.1 × 1H, CHO of **5c**), (9.75 (s, 0.9 × 1H, CHO of **4c**) ppm. ¹³C
274 NMR (125 MHz; CDCl₃) 9.2, 16.7, 17.3, 34.2, 117.3, 127.2, 128.5, 128.6, 130.3, 130.8, 139.7, 141.3,
275 177.7 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₅H₁₇NO, 250.1208; found, 250.1202.

27 **Decarboxylative arylation of substituted pyrroles N-protected with**
28 **2-(trimethylsilyl)ethoxymethyl (SEM)**

276 **Benzyl 4-acetyl-3,5-dimethyl-1-tert-butylcarboxylate-pyrrole-2-carboxylate (6a)**

277 Pyrrole **1a** (0.50 g, 1.84 mmol) and DMAP (25 mg, 0.22 mmol) were dissolved in anhydrous MeCN
278 (20 mL) and the solution was degassed with nitrogen for 10 minutes with stirring. (Boc)₂O (1.08 g,
279 4.97 mmol) was added dropwise as a solution in anhydrous MeCN (5 mL). The mixture was stirred for
280 20 minutes, after which no starting material was detectable using TLC analysis. Removal of the solvent
281 and excess (Boc)₂O *in vacuo* yielded the crude product, which was subjected to column
282 chromatography on Brockman III basic alumina using EtOAc:hexanes (5:95) as eluent. The product
283 was obtained as a light yellow oil (0.66 g, 97%). ¹H NMR (500 MHz; CDCl₃) 1.51 (s, 9H), 2.43 (s, 3H),
284 2.44 (s, 3H), 2.53 (s, 3H), 5.32 (s, 2H), 7.31-7.41 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) 12.7,
285 13.2, 27.6 (3C), 31.9, 66.7, 86.1, 120.9, 124.6, 128.4, 128.4, 128.7, 128.7, 129.1, 135.9, 139.3, 149.3,
286 161.1, 196.3 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₁H₂₅NO₅, 394.1630; found, 394.1608.

287 **General procedure for SEM-protection of pyrrole 1 (GP2)**

288 Adapting a literature procedure,³⁶ pyrrole **1** (1.0 equiv) was added in one portion to a stirred solution of
289 NaH (60% dispersion in mineral oil, 1.1 equiv) in DMF (0.4 M) at room temperature and under
290 nitrogen atmosphere. When the evolution of H₂ ceased, 2-(trimethylsilyl)ethoxymethyl chloride (1.1
291 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm up to room temperature,
292 stirred until complete consumption of the starting material (according to TLC analysis) and poured into
293 a saturated solution of NaHCO₃ at 0 °C. The crude mixture was extracted with EtOAc (× 3) and the
294 combined organic fractions washed with water (× 2) and brine, dried over Na₂SO₄ and concentrated
295 under reduced pressure.

296 **Benzyl 4-acetyl-3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8a)**

297 Pyrrole **8a** was obtained according to GP2. The crude mixture was purified using column
298 chromatography on SiO₂ (hexanes/EtOAc, 80/20) to give **8a** as a colorless oil (73%). ¹H NMR (500
299 MHz; CDCl₃) -0.04 (s, 9H), 0.83-0.87 (m, 2H), 2.45 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.47-3.50 (m,

29 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
30 **2-(trimethylsilyl)ethoxymethyl (SEM)**

3002H), 5.32 (s, 2H), 5.70 (s, 2H), 7.32-7.43 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 12.3, 13.7, 30118.1, 32.0, 65.8, 66.3, 73.2, 120.2, 124.5, 128.4, 128.8, 130.0, 136.1, 141.3, 161.9, 196.8 (1 carbon 302unaccounted for) ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₂H₃₁NNaO₄Si, 424.1915; found, 303424.1930.

304 **Benzyl 4-ethyl-3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8b)**

305 Pyrrole **8b** was obtained according to GP2. The crude mixture was purified using column 306 chromatography on SiO₂ (hexanes/EtOAc, 100/0, 98/2, 96/4) to give **8b** as a colorless oil (73%). ¹H 307 NMR (500 MHz; CDCl₃) -0.05 (s, 9H), 0.84-0.87 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H), 2.24 (s, 3H), 2.26 308 (s, 3H), 2.39 (q, *J* = 7.5 Hz, 2H), 3.48-3.51 (m, 2H), 5.30 (s, 2H), 5.69 (s, 2H), 7.29-7.43 (m, 5H) ppm. 309 ¹³C NMR (125 MHz; CDCl₃) -1.3, 10.1, 11.9, 15.5, 17.4, 18.1, 65.2, 65.5, 73.1, 118.3, 124.0, 128.0, 310 128.2, 128.6, 129.4, 134.1, 136.9, 162.0 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₂H₃₃NNaO₃Si, 311 410.2122; found, 410.2124.

312 **Benzyl 4-ethyl-5-formyl-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8c)**

313 Pyrrole **8c** was obtained according to GP2. The crude mixture was purified using column 314 chromatography on SiO₂ (hexanes/EtOAc, 90/10 to 80/20) to give **8c** as a colorless oil (81%). ¹H NMR 315 (500 MHz; CDCl₃) -0.07 (s, 9H), 0.81-0.86 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 3H), 2.21 (s, 3H), 2.73 (q, *J* = 316 7.5 Hz, 2H), 3.42-3.48 (m, 2H), 5.35 (s, 2H), 6.08 (s, 2H), 7.36-7.45 (m, 5H), 9.95 (s, 1H) ppm. ¹³C 317 NMR (125 MHz; CDCl₃) -1.3, 10.7, 16.2, 17.1, 18.0, 65.8, 66.9, 73.8, 126.6, 127.6, 128.5, 128.6, 318 128.8, 130.2, 135.7, 139.2, 161.6, 180.5 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₂H₃₁NNaO₄Si, 319 424.1915; found, 424.1912.

320 **Benzyl 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8d)**

321 Pyrrole **8d** was obtained according to GP2. The crude mixture was purified using column 322 chromatography on SiO₂ (hexanes/EtOAc, 100/0 to 95/5) to give **8d** as a colorless oil (78%). ¹H NMR

31 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
32 **2-(trimethylsilyl)ethoxymethyl (SEM)**

323(500 MHz; CDCl₃) -0.04 (s, 9H), 0.85-0.88 (m, 2H), 2.29 (s, 6H), 3.50-3.53 (m, 2H), 5.30 (s, 2H), 5.69
324(s, 2H), 5.82 (s, 1H), 7.31-7.43 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 12.4, 14.7, 18.1, 65.3,
32565.5, 73.2, 112.3, 119.0, 128.0, 128.2, 128.6, 131.3, 136.8, 137.2, 161.9 ppm. HRMS-ESI (*m/z*):
326[M+Na]⁺ calcd for C₂₀H₂₉NNaO₃Si, 382.1809; found, 382.1821.

327Benzyl **4-(2-methoxy-2-oxoethyl)-3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-**
328**carboxylate (8e)**

329Pyrrole **8e** was obtained according to GP2. The crude mixture was purified using column
330chromatography on SiO₂ (hexanes/EtOAc, 100/0, 90/10, 85/15) to give **8e** as a colorless oil (91%). ¹H
331NMR (500 MHz; CDCl₃) -0.04 (s, 9H), 0.84-0.88 (m, 2H), 2.26 (s, 3H), 2.27 (s, 3H), 3.40 (s, 2H),
3323.49-3.52 (m, 2H), 3.65 (s, 3H), 5.29 (s, 2H), 5.70 (s, 2H), 7.30-7.42 (m, 5H) ppm. ¹³C NMR (125
333MHz; CDCl₃) -1.3, 10.5, 12.1, 18.1, 30.3, 52.0, 65.3, 65.6, 73.2, 114.7, 118.7, 128.1, 128.2, 128.6,
334129.9, 135.7, 136.7, 161.9, 172.2 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₃H₃₃NNaO₅Si,
335454.2020; found, 454.2028.

336Benzyl **1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8f)**

337Pyrrole **8f** was obtained according to GP2. The crude mixture was purified using column
338chromatography on SiO₂ (hexanes/EtOAc, 95/5) to give **8f** as a colorless oil (85%). ¹H NMR (500
339MHz; CDCl₃) -0.04 (s, 9H), 0.87-0.92 (m, 2H), 3.50-3.55 (m, 2H), 5.29 (s, 2H), 5.71 (s, 2H), 6.19 (dd,
340J = 3.7, 2.8 Hz, 1H), 7.03-7.04 (m, 1H), 7.06 (dd, J = 3.8, 1.7 Hz, 1H), 7.31-7.36 (m, 1H), 7.37-7.39
341(m, 2H), 7.42-7.43 (m, 2H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 18.0, 65.7, 66.1, 77.0, 109.0,
342119.5, 123.3, 128.1, 128.2, 128.7, 129.0, 136.6, 160.9 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for
343C₁₈H₂₅NNaO₃Si, 354.1496; found, 354.1487.

344Benzyl **3,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1-((2-**
345**(trimethylsilyl)ethoxy)methyl)-pyrrole-2-carboxylate (8g)**

33 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
34 **2-(trimethylsilyl)ethoxymethyl (SEM)**

346 Pyrrole **8g** was obtained according to GP2. The crude mixture was purified using
347 column chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **8g** as a pale
348 yellow oil (53%). ¹H NMR (500 MHz; CDCl₃): -0.04 (s, 9H), 0.86 (t, *J* = 8.1 Hz, 2H),
349 2.44 (s, 3H), 2.51 (s, 3H), 3.51 (t, *J* = 8.1 Hz, 2H), 5.33 (s, 2H), 5.72 (s, 2H), 7.43-
350 7.34 (m, 5H) ppm. ¹⁹F NMR (471 MHz; CDCl₃) -74 ppm. ¹³C NMR (126 MHz; CDCl₃):
351 -1.3, 12.2, 12.7, 18.1, 66.2, 66.6, 73.6, 116.4 (q, *J* = 290 Hz), 117.7, 121.5, 128.5,
352 128.6, 128.8, 131.3, 135.8, 144.2, 161.6, 179.3 (q, *J* = 37 Hz) ppm. HRMS-ESI (*m/z*):
353 [M+Na]⁺ calcd for C₂₂H₂₈F₃NNaO₄Si, 478.1632; found, 478.1631.

354 **Benzyl 4-ethyl 3,5-dimethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-**
355 **2,4-dicarboxylate (8h)**

356 Pyrrole **8h** was obtained according to GP2. The crude mixture was purified using
357 column chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **8h** as a pale
358 yellow oil (79%). ¹H NMR (500 MHz; CDCl₃): -0.04 (s, 9H), 0.85 (t, *J* = 8.1 Hz, 2H),
359 1.36 (t, *J* = 7.1 Hz, 3H), 2.53 (s, 3H), 2.58 (s, 3H), 3.49 (t, *J* = 8.1 Hz, 2H), 4.29 (q, *J*
360 = 7.1 Hz, 2H), 5.32 (s, 2H), 5.72 (s, 2H), 7.39-7.31 (m, 3H), 7.42 (d, *J* = 7.1 Hz)
361 ppm. ¹³C NMR (126 MHz; CDCl₃): -1.3, 12.0, 13.1, 14.5, 18.1, 59.8, 65.7, 66.1,
362 73.2, 76.9, 77.2, 77.4, 114.1, 120.1, 128.29, 128.33, 128.7, 132.2, 136.3, 142.8,
363 161.9, 165.6 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₃H₃₃NNaO₅Si, 454.2020;
364 found, 454.2001.

365 **General procedure for the decarboxylative Pd-coupling of pyrrole 8 (GP3):**

366 Adapting GP1, a solution of pyrrole **8** (1 equiv), 10 mol% Pd/C (10% of the mass of **8**) and NEt₃ (few
367 drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times with nitrogen
368 before the introduction of a H₂ atmosphere. After stirring the reaction for 19 h, N₂ atmosphere was
369 introduced and the reaction was filtered through a plug of Celite® and rinsed with MeOH. Removal of

35 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
36 **2-(trimethylsilyl)ethoxymethyl (SEM)**

370 the solvent under reduced pressure gave pyrrole **9**, which was used in the next step without further
371 purification. Pyrrole **9** (1 equiv), PhBr (1.5 equiv), NBU₄Cl (1 equiv), KO^tBu (1.5 equiv), and
372 Pd(P(*t*Bu)₃)₂ (0.05 equiv) were combined in an open microwave vial. The vessel was crimped through
373 the use of a septum cap, a nitrogen atmosphere introduced and anhydrous DMF was added (0.1 M).
374 Alternatively, pyrrole **9** was added to a microwave vial which was subsequently sealed with a rubber
375 septum and a nitrogen atmosphere introduced. The vial was then brought into a glovebox, where the
376 remaining reagents and solvent were added and the vessel sealed. The mixture was stirred for 30 s, and
377 then submitted to microwave-promoted heating conditions (150 °C, 10 min, high absorption). The
378 mixture was diluted with ethyl acetate (50 mL) and washed with a saturated solution of NaHCO₃ (× 3)
379 and water (× 2). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure.

380 **4-Acetyl 3,5-dimethyl-2-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl) pyrrole (10a)**

381 Pyrrole **10a** was obtained according to GP3. The crude mixture was purified using column
382 chromatography on SiO₂ (hexanes/EtOAc, 80/20) to give **10a** as a colorless oil (54%). ¹H NMR (500
383 MHz; CDCl₃) -0.05 (s, 9H), 0.76-0.80 (m, 2H), 2.16 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.26-3.29 (m,
384 2H), 5.04 (s, 2H), 7.28-7.30 (m, 2H), 7.36-7.45 (m, 3H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 12.4,
385 12.8, 18.0, 31.7, 65.6, 72.8, 116.7, 122.8, 128.0, 128.5, 131.5, 131.9, 136.0, 196.5 (1 carbon
386 unaccounted for) ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₉NNaO₂Si, 366.1860; found,
387 366.1859.

388 **3-Ethyl-2,4-dimethyl-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole (10b)**

389 Pyrrole **10b** was obtained according to GP3. The crude mixture was purified using column
390 chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **10b** (43%) as a colorless oil. ¹H NMR (500
391 MHz; CDCl₃) -0.01 (s, 9H), 0.82-0.86 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 2.03 (s, 3H), 2.31 (s, 3H), 2.49
392 (q, *J* = 7.5 Hz, 2H), 3.31-3.34 (m, 2H), 5.06 (s, 2H), 7.30-7.44 (m, 5H) ppm. ¹³C NMR (125 MHz;

37 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
38 **2-(trimethylsilyl)ethoxymethyl (SEM)**

393CDCl₃) -1.3, 9.8, 10.0, 15.8, 18.0 (2C), 64.9, 73.1, 115.7, 122.3, 125.0, 126.6, 128.2, 130.1, 130.8,
394133.3 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₃₁NNaOSi, 352.2067; found, 352.2064.

395**3,5-Dimethyl-2-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole (10d)**

396Pyrrole **10d** was obtained according to GP3. The crude mixture was purified using column
397chromatography on SiO₂ (hexanes/EtOAc, 98/2) to give a colorless oil containing both the product **10d**
398(35%, based on the amount of **10d** in the isolated mixture) and the decarboxylated derivative **11d** in a
3994:1 ratio. ¹H NMR (500 MHz; CDCl₃) -0.04 (s, 0.8 × 9H, TMS of **10d**), 0.00 (s, 0.2 × 9H, TMS of
400**11d**), 0.78-0.82 (m, 0.8 × 2H, CH₂-TMS of **10d**), 0.87-0.93 (m, 0.2 × 2H, CH₂-TMS of **11d**), 2.03 (s,
4010.8 × 3H, CH₃ of **10d**), 2.05 (s, 0.2 × 3H, CH₃ of **11d**), 2.24 (s, 0.2 × 3H, CH₃ of **11d**), 2.34 (s, 0.8 ×
4023H, CH₃ of **10d**), 3.27-3.32 (m, 0.8 × 2H, CH₂CH₂-TMS of **10d**), 3.45-3.50 (m, 0.2 × 2H, CH₂CH₂-
403TMS of **11d**), 5.05 (s, 0.8 × 2H, CH₂O of **10d**), 5.07 (s, 0.2 × 2H, CH₂O of **11d**), 5.76 (s, 0.2 × 1H, Ar-
404H of **11d**) 5.88 (s, 0.8 × 1H, Ar-H of **10d**), 6.42 (s, 0.2 × 1H, Ar-H of **11d**), 7.30-7.43 (m, 5H) ppm. ¹³C
405NMR (125 MHz; CDCl₃) -1.3, -1.2, 11.8, 11.9, 12.2, 14.4, 17.9, 18.0, 65.0, 65.3, 73.0, 75.7, 109.8,
406116.4, 118.0, 118.9, 126.8, 128.3, 129.4, 130.8, 130.9, 133.2 (significant overlap between ¹³C-NMR
407signals of **10d** and **11d** in spectrum) ppm. HRMS-ESI (*m/z*) for **10d**: [M+Na]⁺ calcd for C₁₈H₂₇NNaOSi,
408324.1754; found, 324.1745. HRMS-ESI (*m/z*) for **11d**: [M+Na]⁺ calcd for C₁₂H₂₃NNaOSi, 248.1441;
409found, 248.1435.

410**3,5-Dimethyl-4-(2-methoxy-2-oxoethyl)-2-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole**
411**(10e)**

412Pyrrole **10e** was obtained according to GP3. The crude mixture was purified using column
413chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **10e** (52%) as a colorless oil. ¹H NMR (500
414MHz; CDCl₃) -0.04 (s, 9H), 0.78-0.83 (m, 2H), 1.98 (s, 3H), 2.30 (s, 3H), 3.27-3.32 (m, 2H), 3.46 (s,
4152H), 3.69 (s, 3H), 5.02 (s, 2H), 7.28-7.42 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 10.0, 10.1,

39 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
40 **2-(trimethylsilyl)ethoxymethyl (SEM)**

41 18.0, 30.9, 51.9, 65.0, 73.1, 112.9, 116.2, 126.9, 127.1, 128.3, 130.4, 130.9, 132.9, 172.9 ppm. HRMS-
42 ESI (*m/z*): [M+Na]⁺ calcd for C₂₁H₃₁NNaO₃Si, 396.1965; found, 396.1963.

418 **2-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole (10f)**

419 Pyrrole **10f** was obtained according to GP3. The crude mixture was purified using column
420 chromatography on SiO₂ (hexanes/EtOAc, 95/5) to give **10f** as a colorless oil (60%). ¹H NMR (500
421 MHz; CDCl₃) 0.00 (s, 9H), 0.90-0.93 (m, 2H), 3.51-3.54 (m, 2H), 5.23 (s, 2H), 6.25-6.26 (m, 1H), 6.31
422 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.90 (dd, *J* = 2.7, 1.7 Hz, 1H), 7.30-7.33 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 2H),
423 7.55 (d, *J* = 7.8 Hz, 2H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 18.0, 65.8, 76.2, 108.8, 109.7, 123.5,
424 127.1, 128.5, 129.0, 133.1, 135.3 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₆H₂₃NNaOSi, 296.1441;
425 found, 296.1436.

426 **Ethyl 2,4-dimethyl-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrole-3-carboxylate (10h)**

427 Pyrrole **10h** was obtained according to GP3. The crude mixture was purified using column
428 chromatography on SiO₂ (hexanes/EtOAc, 80/20) to give a colorless oil containing both the product
429 **10h** (35%) and the decarboxylated derivative **11h** in a 3:1 ratio. ¹H NMR (300 MHz; CDCl₃) -0.06 (s,
430 9H, TMS of **10h**), -0.02 (s, 9H, TMS of **11h**), 0.77 (t, *J* = 8.4 Hz, 2H, CH₂-TMS of
431 **10h**), 0.88 (t, *J* = 8.2 Hz, 2H, CH₂-TMS of **11h**), 1.34-1.39 (m, 6H, CH₃CH₂O(CO) of
432 **10h** and **11h**), 2.15 (s, 3H, CH₃ of **10h**), 2.21 (s, 3H, CH₃ of **11h**), 2.53 (s, 3H, CH₃
433 of **11h**), 2.63 (s, 3H, CH₃ of **10h**), 3.25 (t, *J* = 8.4 Hz, 2H, CH₂CH₂-TMS of **10h**),
434 3.46 (t, *J* = 8.4 Hz, 2H, CH₂CH₂-TMS of **11h**), 4.24-4.34 (m, 4H, CH₃CH₂O(CO) of
435 **10h** and **11h**), 5.04 (s, 2H, CH₂O of **10h**), 5.010 (s, 2H, CH₂O of **11h**), 6.38 (s, 1H,
436 Ar-*H* of **11h**), 7.27-7.28 (m, 2H, Ar-*H* of **10h**), 7.38-7.45 (m, 3H, Ar-*H* of **10h**) ppm
437 (significant overlap between ¹H-NMR signals of **10h** and **11h** in spectrum). ¹³C
438 NMR (125 MHz; CDCl₃) -1.3, -1.2, 11.8, 11.9, 12.2, 14.4, 17.9, 18.0, 65.0, 65.3,
439 73.0, 75.7, 109.8, 116.4, 118.0, 118.9, 126.8, 128.3, 129.4, 130.8, 130.9, 133.2

41 **Decarboxylative arylation of substituted pyrroles N-protected with**
42 **2-(trimethylsilyl)ethoxymethyl (SEM)**
440ppm (significant overlap between ¹³C-NMR signals of **10h** and **11h** in spectrum).
441HRMS-ESI (*m/z*) for **10h**: [M+Na]⁺ calcd for C₂₁H₃₁NNaO₃Si, 396.1965; found, 396.1982.
442HRMS-ESI (*m/z*) for **11h**: [M+Na]⁺ calcd for C₁₅H₂₇NNaOSi, 320.1652; found,
443320.1640.

444**1-(5-(4-methoxyphenyl)-2,4-dimethyl-1-((2-**
445**(trimethylsilyl)ethoxy)methyl)-pyrrol-3-yl)ethanone (10i)**

446Pyrrole **10i** was obtained according to GP3. The crude mixture was purified using column
447chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give a white solid containing both the product **10i**
448(20%) and the decarboxylated derivative **11a** in a 6:1 ratio. ¹H NMR (500 MHz; CDCl₃) -0.04 (s,
4499H, TMS of **10i**), -0.01 (s, 9H, TMS of **11a**), 0.79 (t, *J* = 8.3 Hz, 2H, CH₂-TMS of
450**10i**), 0.89 (t, *J* = 8.1 Hz, 2H, CH₂-TMS of **11a**), 2.14 (s, 3H, CH₃ of **10i**), 2.25 (s, 3H,
451CH₃ of **11a**), 2.43 (s, 3H, CH₃ of **11a**), 2.48 (s, 3H, CH₃ of **10i**), 2.52 (s, 3H, CH₃ of
452**11a**), 2.60 (s, CH₃ of **10i**), 3.29 (t, *J* = 8.3 Hz, 2H, CH₂CH₂-TMS of **10i**), 3.47 (t, *J* =
4538.1 Hz, 2H, CH₂CH₂-TMS of **11a**), 3.86 (s, 3H, Ar-OCH₃ of **10i**), 5.01 (s, 2H, CH₂O of
454**10i**), 5.11 (s, 2H, CH₂O of **11a**), 6.39 (s, 1H, Pyrrole-*H* of **11a**), 6.96 (d, *J* = 8.7 Hz,
4552H, Ar-*H* of **10i**), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-*H* of **10i**) ppm. ¹³C NMR (125 MHz;
456CDCl₃) -1.3, 12.2, 12.4, 12.9, 13.7, 17.9, 18.0, 31.4, 31.6, 55.4, 65.6, 65.9, 72.8,
45775.7, 113.9, 116.6, 119.2, 120.3, 122.7, 122.9, 124.0, 131.6, 132.7, 135.7, 136.3,
458159.4, 196.1, 196.5 ppm. HRMS-ESI (*m/z*) for **10i**: [M+Na]⁺ calcd for C₂₁H₃₁NNaO₃Si,
459396.1965; found, 396.1971. HRMS-ESI (*m/z*) for **11a**: [M+Na]⁺ calcd for C₁₄H₂₅NNaO₂Si, 290.1547;
460found, 290.1545.

461**1-(2,4-dimethyl-5-(4-(trifluoromethyl)phenyl)-1-((2-**
462**(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-3-yl)ethanone (10j)**

463Pyrrole **10j** was obtained according to GP3. The crude mixture was purified using column
464chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give a white solid containing both the product **10j**

43 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
44 **2-(trimethylsilyl)ethoxymethyl (SEM)**

465(36%) and the decarboxylated derivative **11a** in a 6:1 ratio. ¹H NMR (300 MHz; CDCl₃) -0.04 (s, 9H,
466TMS of **10j**), -0.02 (s, 9H, TMS of **11a**), 0.1 (t, *J* = 8.3 Hz, 2H, CH₂-TMS of **10j**), 0.89 (t, *J* = 8.2 Hz,
4672H, CH₂-TMS of **11a**), 2.17 (s, 3H, CH₃ of **10j**), 2.25 (s, 3H, CH₃ of **11a**), 2.43 (s, 3H, CH₃ of **11a**),
4682.49 (s, 3H, CH₃ of **10j**), 2.52 (s, 3H, CH₃ of **11a**), 2.61 (s, CH₃ of **10j**), 3.33 (t, *J* = 8.3 Hz, 2H,
469CH₂CH₂-TMS of **10j**), 3.46 (t, *J* = 8.2 Hz, 2H, CH₂CH₂-TMS of **11a**), 5.01 (s, 2H, CH₂O of
470**10j**), 5.11 (s, 2H, CH₂O of **11a**), 6.39 (s, 1H, Pyrrole-*H* of **11a**), 7.44 (d, *J* = 7.9 Hz,
4712H, Ar-*H* of **10j**), 7.69 (d, *J* = 8.0 Hz, 2H, Ar-*H* of **10j**) ppm. ¹⁹F NMR (471 MHz;
472CDCl₃) -63 ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 12.2, 12.4, 12.8, 13.7, 17.9, 18.0,
47331.4, 31.7, 65.8, 65.9, 72.9, 75.7, 110.1, 117.8, 119.2, 120.3, 123.1, 125.4, 129.8,
474130.1, 130.4, 131.6, 135.7, 136.7, 196.1, 196.3 ppm. HRMS-ESI (*m/z*) for **10j**:
475[M+Na]⁺ calcd for C₂₁H₂₈F₃NNaO₂Si, 434.1734; found, 434.1731. HRMS-ESI (*m/z*) for **11a**: [M+Na]⁺
476calcd for C₁₄H₂₅NNaO₂Si, 290.1547; found, 290.1551.

477**1-(2,4-dimethyl-5-(thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-**
478**1H-pyrrol-3-yl)ethanone (10k)**

479Pyrrole **10k** was obtained according to GP3. The crude mixture was purified using column
480chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **10k** (37%) as a colorless oil. ¹H NMR (500
481MHz; CDCl₃) -0.03 (s, 9H), 0.81-0.84 (m, 2H), 2.20 (s, 3H), 2.47 (s, 3H), 2.60 (s, 3H), 3.34-3.37 (m,
4822H), 5.10 (s, 2H), 7.00 (dd, *J* = 3.5 and 1.1 Hz, 1H) 7.12 (dd, *J* = 5.2 and 3.5 Hz, 1H), 7.44 (dd, *J* = 5.2
483and 1.1 Hz, 1H) ppm. ¹³C NMR (125 MHz; CDCl₃) -1.3, 12.5, 13.1, 18.0, 31.6, 65.8, 72.8,
484120.0, 122.9, 123.6, 127.2, 127.7, 130.4, 132.2, 136.9, 196.2 ppm. HRMS-ESI (*m/z*):
485[M+Na]⁺ calcd for C₁₈H₂₇NNaO₂SSi, 372.1424; found, 372.1414.

486**General procedure for the deprotection of pyrrole 10 (GP4):**

487Adapting literature procedures,³⁶ TBAF (1 M solution in THF, 5 equiv.) was added dropwise to a
488solution of pyrrole **10** (1 equiv.) in THF (0.1 M) at room temperature and under nitrogen atmosphere.

45 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
46 **2-(trimethylsilyl)ethoxymethyl (SEM)**

489 The reaction mixture was heated to reflux temperature for 19 h. If TLC analysis still showed starting
490 material, TBAF (1 M solution in THF, 5 equiv.) was added and the reaction mixture was heated at
491 reflux temperature for an additional 10 h. Water was added to the reaction mixture and the two layers
492 were separated. The aqueous layers was extracted with EtOAc ($\times 3$). The combined organic layers were
493 washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

494 **4-Acetyl 3,5-dimethyl-5-phenyl-1*H*-pyrrole (12a)**

495 Pyrrole **12a** was obtained according to GP4. The crude mixture was purified using column
496 chromatography on SiO_2 (hexanes/EtOAc, 50/50) to give **12a** as a white solid (54%). Mp: 160-162 °C.
497 ^1H NMR (500 MHz; CDCl_3) 2.38 (s, 3H), 2.47 (s, 3H), 2.56 (s, 3H), 7.27-7.45 (m, 5H), 8.17 (br s, 1H)
498 ppm. ^{13}C NMR (125 MHz; CDCl_3) 12.8, 15.3, 31.2, 117.0, 122.9, 127.0, 127.8, 127.9, 128.9, 132.7,
499 134.9, 195.8 ppm. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{NNaO}$, 236.1046; found, 236.1044.

500 **3,5-Dimethyl-2-phenyl-1*H*-pyrrole (12d)**

501 Pyrrole **12d** was obtained according to GP4. The crude mixture was purified using column
502 chromatography on SiO_2 (hexanes/EtOAc, 98/2) to give **12d** as a colorless oil (52%). ^1H NMR (500
503 MHz; CDCl_3) 2.11 (s, 3H), 2.16 (s, 3H), 5.70 (s, 1H), 7.05-7.12 (m, 1H), 7.23-7.27 (m, 4H), 7.66 (br s,
504 1H) ppm. ^{13}C NMR (125 MHz; CDCl_3) 12.6, 13.1, 110.4, 116.6, 125.6, 126.0, 126.9, 127.6, 128.8,
505 134.0 ppm. HRMS-ESI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}$, 172.1121; found, 172.1117.

506 **2-Phenyl-1*H*-pyrrole (12f)**

507 Pyrrole **12f** was obtained according to GP3. The crude mixture was purified using column
508 chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **12f** as a white solid (71%). ^1H NMR (500
509 MHz; CDCl_3) 6.29-6.32 (m, 1H), 6.52-6.54 (m, 1H), 6.86-6.88 (m, 1H), 7.18-7.24 (m, 1H), 7.34-7.39
510 (m, 2H), 7.46-7.50 (m, 2H), 8.43 (br s, 1H) ppm. ^{13}C NMR (125 MHz; CDCl_3) 106.1, 110.3, 118.9,

47 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
48 **2-(trimethylsilyl)ethoxymethyl (SEM)**

511124.0, 126.4, 129.0, 132.3, 132.9 ppm. HRMS-APCI (*m/z*): [M+H]⁺ calcd for C₁₀H₁₀N, 144.0808;
512found, 144.0814. The reported data are in agreement with those in the literature.⁴³

513**Ethyl 2,4-dimethyl-5-phenyl-1H-pyrrole-3-carboxylate (12h)**

514Pyrrole **12h** was obtained according to GP4. The crude mixture was purified using column
515chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give **12a** as a pale yellow solid (65%). ¹H NMR
516(500 MHz; CDCl₃) 1.37 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 2.55 (s, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 7.28-
5177.29 (m, 1H), 7.36-7.42 (m, 4H), 8.06 (br s, 1H) ppm. ¹³C NMR (125 MHz; CDCl₃) 12.0, 14.3,
51814.7, 59.3, 112.6, 118.1, 126.8, 127.4, 127.4, 128.9, 133.0 ppm. HRMS-ESI (*m/z*):
519[M+Na]⁺ calcd for C₁₅H₁₇NNaO₂, 266.1151; found, 266.1148.

520**1-(5-(4-methoxyphenyl)-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (12i)**

521Pyrrole **12i** was obtained according to GP4. The crude mixture was purified using
522column chromatography on SiO₂ (hexanes/EtOAc, 80/20) to give **12i** as a brown
523solid (24%). ¹H NMR (500 MHz; CDCl₃) 2.34 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 3.84
524(s, 3H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 8.04 (br s, 1H) ppm. ¹³C
525NMR (126 MHz; CDCl₃) 12.78, 15.28, 31.20, 55.50, 110.14, 114.36, 116.16,
526125.28, 127.72, 129.19, 134.41, 158.86, 195.80 ppm. HRMS-APCI (*m/z*): [M+H]⁺
527calcd for C₁₅H₁₈NO₂, 244.1332; found, 244.1324.

528**1-(2,4-dimethyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)ethanone**
529**(12j)**

530Pyrrole **12j** was obtained according to GP4. The crude mixture was purified using column
531chromatography on SiO₂ (hexanes/EtOAc, 80/20) to give **12j** as a pale beige solid (48%). ¹H NMR
532(500 MHz; CDCl₃) 2.38 (s, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2
533Hz, 2H), 8.33 (br s, 1H) ppm. ¹⁹F NMR (471 MHz; CDCl₃) -63 ppm. ¹³C NMR (125 MHz;
534CDCl₃) 12.8, 15.3, 31.3, 118.6, 123.2, 125.4, 125.9, 126.5, 127.6, 128.6, 135.8,

49 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
50 **2-(trimethylsilyl)ethoxymethyl (SEM)**

535136.2, 195.8 ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₅H₁₄FNNaO, 304.0920; found, 536304.0926.

5371-(2,4-dimethyl-5-(thiophen-2-yl)-1H-pyrrol-3-yl)ethanone (12k)

538Pyrrole **12k** was obtained according to GP4. The crude mixture was purified using column
539chromatography on SiO₂ (hexanes/EtOAc, 85/15) to give **12k** as a pale beige solid (58%). ¹H NMR
540(500 MHz; CDCl₃) 2.41 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 7.02 (dd, *J* = 3.5 and 0.9 Hz, 2H), 7.08 (dd,
541*J* = 5.1 and 3.6 Hz, 2H), 7.28 (dd, *J* = 5.1 and 1.0 Hz), 8.08 (br s, 1H) ppm. ¹³C NMR (125 MHz;
542CDCl₃) 12.7, 15.1, 31.1, 118.1, 122.8, 124.2, 124.3, 127.5, 133.3, 134.2, 134.9,
543195.5ppm. HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₂H₁₃NNaOS, 242.0610; found, 242.0615.

544Supplementary material

545Supplementary material is available with the article through the journal Web site at XXX.

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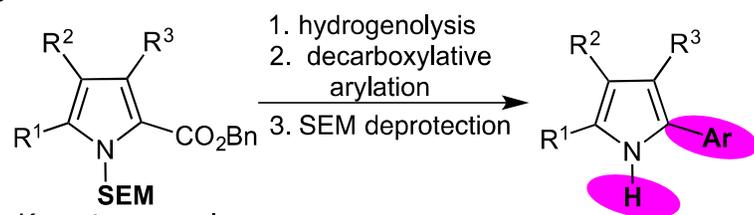
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57 **Decarboxylative arylation of substituted pyrroles *N*-protected with**
58 **2-(trimethylsilyl)ethoxymethyl (SEM)**

609TOC artwork

610



611 Knorr-type pyrrole