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

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Dedication

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

Abstract

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

Introduction

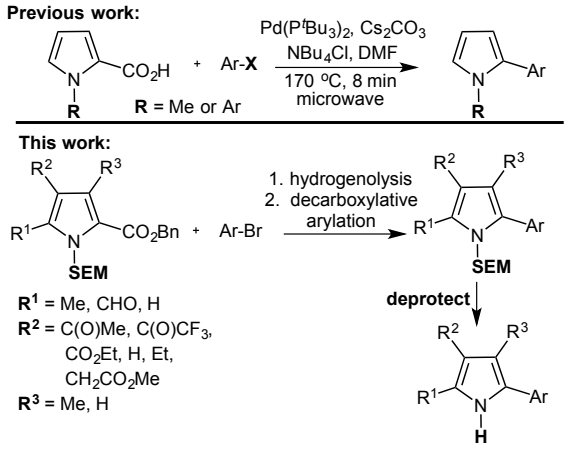
Considerable effort has addressed the development of efficient synthetic strategies to form (hetero)aryl-(hetero)aryl[1-3] C-C bonds that proceed under mild reaction conditions and with high selectivity and broad tolerance. In this vein, transition metal-catalyzed direct C-H arylation has earned significant attention due to the large variety of tolerated functional groups and high yielding selectivity at low catalyst loadings.[4-6] More recently, transition metal-catalyzed decarboxylative arylation, using carboxylic acids as synthetic equivalents of aryl halides, triflates and organometallic species, has been investigated.[7]

Pyrroles are a recurrent feature in supramolecular, medicinal and agricultural chemistry.[2,8-10] There are numerous examples of transition metal-catalyzed direct C-H and decarboxylative arylation using pyrroles and various transition metals. In this way, aryl groups have been efficiently adjoined to the 2-position of pyrroles. However, most methodologies focus on using the unsubstituted pyrrole unit, and do not embrace the necessity to work with pyrroles already bearing substituents on the 3-, 4- and 5-

positions. Furthermore, these methodologies typically involve *N*-alkyl and *N*-aryl pyrroles,[3-7,11-16] thereby incorporating protecting groups that, courtesy of inherent challenges encountered in deprotection, are largely impractical for use in a synthetic sequence.[17] An exception to these generalities resulted in the first total synthesis of lamellarin L, and involved decarboxylative arylation of a pyrrole that is *N*-protected by an ethyl benzene derivative and that is highly substituted about the carbon atoms of the pyrrole.[18] The complex natural product bears *N*-substitution with features based on ethyl benzene, and thus deprotection was not required in this case.

Bilodeau, Forgione and co-workers reported a comprehensive investigation of the reactivity of *N*-protected 2-pyrrole carboxylic acid in palladium-catalyzed decarboxylative arylation with Ar-X (X = iodides, chlorides, bromides and triflates) affording the targeted biaryls (Scheme 1, top).[19] The role of both solvent and base was studied, as was the use of palladium-based catalysts either pre-made or formed *in situ*. The cross-coupling reaction was evaluated using conventional and microwave-promoted heating. The pyrrolic nitrogen atom was protected with methyl or aryl groups to demonstrate that *N*-methyl 2-pyrrole carboxylic acid undergoes decarboxylative arylation with higher efficiency than the corresponding *N*-aryl analogue.[19] However, despite significant success, this work was applied only to the unsubstituted and commercially available 2-pyrrole carboxylic acid (no further substituents about the pyrrolic core), and removal of these *N*-protecting groups is known to be challenging with pyrroles.[17]

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



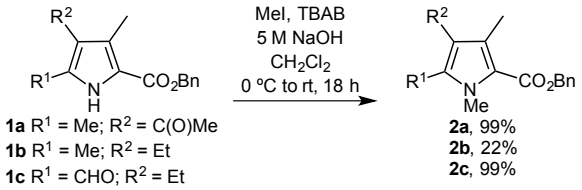
Scheme 1 Decarboxylative arylation and the work reported herein.

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

Results and discussion

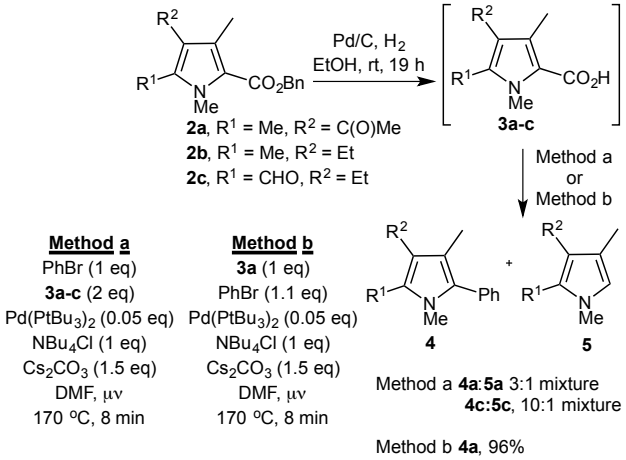
We began by evaluating the effectiveness of decarboxylative arylation with pyrroles bearing 3-, 4- and 5-substituents. As *N*-methyl pyrroles feature prominently in the work involving the core (unsubstituted) pyrrole unit,[19] we *N*-methylated the substituted pyrroles **1a-c** (Scheme 2).[17] Adapting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

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



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

Given the benzyl ester functionality at the α-position, *N*-methyl pyrroles **2a-c** were submitted to hydrogenolysis to form the targeted carboxylic acids **3a-c**.[28] The crude acids were carried directly into the reported palladium-catalyzed decarboxylative arylation (Scheme 3, method a).[19] Decarboxylative cross-coupling using electron-rich **3b** was unsuccessful as polymerization dominated. However, 2-phenyl pyrroles **4a** (50% yield, based on stoichiometry of pyrrole starting material) and **4c** (43%) were isolated alongside the corresponding α-free derivatives **5a** and **5c** in 3:1 and 10:1 ratios, respectively (the 2-Ph and 2-H analogs were inseparable in each case). As the literature conditions use 2 eq. of 2-pyrrole carboxylic acids and 1 eq. of PhBr,[19] the isolation of the α-free pyrrole is not unexpected and presumably arises due to non-catalyzed decarboxylation of pyrroles at temperatures below 170 ºC.[7] Furthermore, the literature yields are based on the limiting reagent, which is the aryl halide, and so necessarily result in conversion of <50% of the desired pyrrole.



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

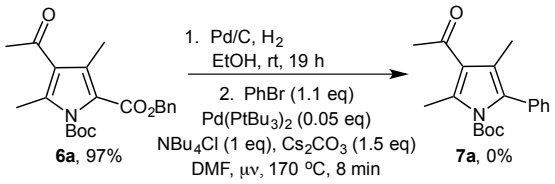
Focusing on the electron-poor pyrrole, the reaction was repeated using 1 eq. of **3a** and 1.1 eq. of PhBr to produce pure **4a** in 96% yield. These results demonstrate the electronic effect of substituents on

the reactivity of *N*-methyl pyrroles: electron-rich pyrroles undergo polymerization under these conditions (**2b**), yet pyrroles bearing carbonyl functional group at either the distal β- or α-positions (**2a**, **2c**) can be coupled in moderate to excellent yield.

The success of this decarboxylative coupling with pyrroles substituted in the 3-, 4- and 5-positions is significant, as such pyrroles are routinely used in the preparation of di- and tri-pyrrolic compounds such as BODIPYs and prodigiosenes. Furthermore, placement of a benzyl ester at the 2-position is facile courtesy of Knorr-type reactions.[20] However, given that the deprotection of *N*-methyl pyrroles is challenging,[17] we sought a route towards pyrroles amenable to decarboxylative arylation at the 2-position yet acquiescent to deprotection at the nitrogen atom. As palladium-catalyzed direct C-H arylation with *N*-unprotected pyrroles is known,[29] we submitted the *N*-unprotected pyrrole **1a** to the decarboxylative arylation conditions (method b, Scheme 3). However, ^{1}H NMR spectroscopic analysis of the crude mixture showed only the two starting materials (PhBr and **1a**), as well as a significant amount of the corresponding α-free pyrrole. This result suggested that protection of the pyrrolic nitrogen atom is indeed required for decarboxylative arylation to proceed.

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

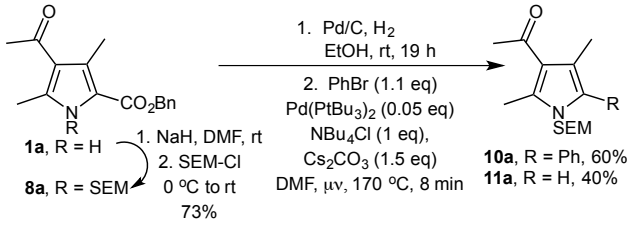
Decarboxylative arylation of substituted pyrroles *N*-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)



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

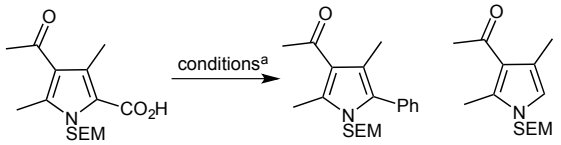
We turned our attention to protecting groups that would mimic the methyl group of *N*-methyl pyrrole yet enable removal after the cross-coupling step. The 2-(trimethylsilyl)ethoxy methyl (SEM) protecting group has been used to protect functionalities such as alcohols, imines, imidazoles and pyrroles.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

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



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

Table 1 Optimization using 2-pyrrole carboxylic acid 9



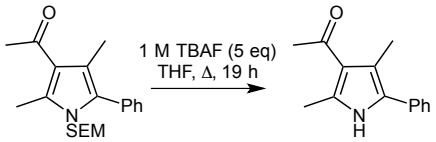
Entry	Base	PhBr (eq.)	T (º C)	t (min)	Conversion[b,c] (**10a**:**11a**:**9a**)
1	Cs_2CO_3 (1.5 eq.)	1.1	150	10	55:45:0
2	Cs_2CO_3 (1.5 eq.)	1.1	190	10	77:23:0
3	KOAc (1.5 eq.)	1.1	170	10	83:17:0
4	KOAc (1.5 eq.)	1.1	150	10	78:22 :0
5	KOAc (1.5 eq.)	1.1	170	20	81:19:0
6	KOAc (1.5 eq.)	1.1	190	10	82:18:0
7	KOAc (1.5 eq.)	1.1	190	20	82:18:0
8	KO*t*Bu (1.5 eq.)	1.1	170	10	85:0:15
9	KO*t*Bu (1.5 eq.)	1.1	150	10	89:0:11
10	KO*t*Bu (1.5 eq.)	1.1	190	10	85:0:15
11	KO*t*Bu (3 eq.)	1.1	150	10	67:0:33
12	KO*t*Bu (1.5 eq.)	1.3	150	10	92:traces:traces
13	KO*t*Bu (1.5 eq.)	1.5	150	10	96:traces:traces
14	KO*t*Bu (1.5 eq.)	2	150	10	93:traces:traces

Note: [a]Reactions were performed in 2-5 mL microwave vials, using 0.05 equivalents of $Pd(PtBu_3)_2$, as catalyst, and DMF, as solvent. [b]According to ^{1}H NMR spectroscopic analysis of the crude mixture; [c]Percentages are based on the integrals relative to the proton peaks of the SEM-protecting group.

The temperature was both decreased to 150 ºC (entry 1) and increased to 190 ºC (entry 2). Formation of the α-free pyrrole **11a** decreased when the reaction was carried out at 190 ºC. Cs_2CO_3 was replaced by KOAc, and variation of temperature and time explored (entries 3-7). However, no improvements were obtained. Surprisingly, the use of K*t*OBu (entries 8-14) afforded **10a** in 85% conversion (entry 8), without formation of **11a**, yet with 15% of unreacted starting material. Cognizant that K*t*OBu has a pka of 17, higher than that of Cs_2CO_3 (10) and KOAc (4.8), deprotonation of **9a** might

occur more readily than the palladium-catalyzed decarboxylation. Increasing the temperature to 190 ºC (compare entries 9 and 10) did not increase the conversion to product. The presence of the unreacted **9a** might be due to insufficient K*t*OBu or PhBr in the reaction mixture. However, when the equivalents of the base were doubled (entry 11), the conversion of **9a** to **10a** decreased. Increasing the equivalents of PhBr to 1.3 (entry 12), 1.5 (entry 13) and 2 (entry 14) gave almost full conversion to 2-phenyl pyrrole **10a**, with only traces of starting materials and α-free pyrrole observed in the product mixture. The optimized reaction conditions (entry 13) were repeated and **10a** was isolated in 54% yield, after purification using column chromatography on silica. The use of other phenyl halides met with little success. Indeed, when the optimized conditions (entry 13, using Ph-X) were applied with phenyl chloride and phenyl triflate, instead of phenyl bromide, only the α-free derivative **11a** was isolated. The use of phenyl iodide gave the desired pyrrole **10a** in a yield of only 25%. Thus, aryl bromides were established as the aryl halide coupling partner of choice.

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



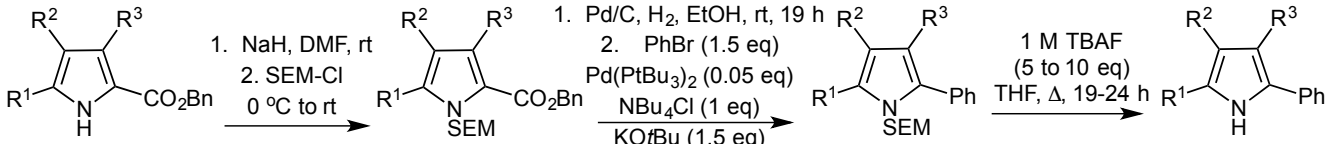
10a **12a**, (54%)

Scheme 6 SEM-deprotection of pyrrole 10a.

In order to evaluate the feasibility of palladium-catalyzed decarboxylative arylation and *N*-deprotection involving substituted *N*-SEM pyrroles, the substrate scope was explored using pyrroles **1b-h**, featuring various functionalities about the pyrrolic core (Scheme 7). Despite the different electronic nature of pyrroles **1b-h**, SEM-protection was consistent and high-yielding across all the substrates

reported herein, although we note, from other examples in our lab, that this is not always the case for SEM-protection of pyrroles. The SEM-protected pyrroles **8b-h** were submitted to hydrogenolysis and the resulting carboxylic acids reacted with PhBr under the optimized decarboxylative arylation reaction conditions (Table 1, entry 13). Electron-rich pyrroles **10b** and **10e** were obtained successfully and in comparable isolated yields to that of **10a**. However, attempts to achieve *N*-deprotection resulted only in decomposition of the starting materials. SEM-deprotection was also attempted on pyrrole **8b** and again decomposition of the starting material was observed. This suggests that removal of the SEM protecting group is challenging when working with electron-rich pyrroles. Hydrogenolysis of the benzyl ester of pyrrole **8c** was unsuccessful and a mixture of deformylated products was instead obtained. 2-Phenyl pyrroles **10d** and **10h** were successfully produced as the major components of inseparable mixtures containing the corresponding α-free derivatives (see Supporting Information). The yields are calculated based on the conversion of **9d** and **9h** into **10d** and **10h**, respectively, and the mass of the product mixture. Upon deprotection, the targeted compounds **12d** and **12h** were separated from the unwanted α-free derivatives, and isolated in 52% and 65% yields, respectively. Hydrogenolysis of unsubstituted SEM-protected pyrrole **8f**, followed by decarboxylative arylation provided **10f** in 60% yield. In contrast, submitting the carboxylic acid **9f** to Bilodeau and Forgione's reaction conditions[19] afforded **10f** in only 28% yield. Removal of the SEM-protecting group proceeded smoothly to provide the *N*-unprotected 2-phenyl pyrrole **12f** in good yield. The electron-poor pyrrole **9g** underwent successful decarboxylative arylation, but could not be purified from the multiple other SEM-products that were unexpectedly generated.

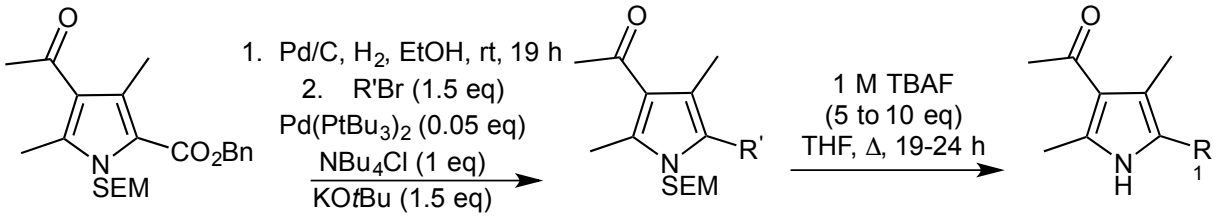
Decarboxylative arylation of substituted pyrroles *N*-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)



1b $R^1 = R^3 = Me$; $R^2 = Et$ — **8b** (73%); **10b** (43%); **12b** (0%)
1c $R^1 = CHO$; $R^2 = Et$, $R^3 = Me$ — **8c** (81%); **10c** (0%)
1d $R^1 = R^3 = Me$; $R^2 = H$ — **8d** (78%); **10d** (35%); **12d** (52%)
1e $R^1 = R^3 = Me$; $R^2 = CH_2CO_2Me$ — **8e** (91%); **10e** (52%); **12e** (0%)
1f $R^1 = R^2 = R^3 = H$ — **8f** (85%); **10f** (60%); **12f** (71%)
1g $R^1 = R^3 = Me$; $R^2 = C(O)CF_3$ — **8g** (53%)
1h $R^1 = R^3 = Me$; $R^2 = CO_2Et$ — **8h** (79%); **10h** (35%); **12h** (65%)

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

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



1a

10i R' = *p*-Ph-OCH_3 (20%); **12i** (24%)
10j R' = *p*-Ph-CF_3 (36%); **12j** (48%)
10k R' = 2-thienyl (37%); **12k** (58%)
10l R' = 2-pyridyl (0%)

Scheme 8 Palladium-catalyzed decarboxylative arylation and SEM-deprotection with aryl bromides.

In summary, we report palladium-catalyzed decarboxylative arylation for heteroaryl-aryl C-C bond formation using substituted *N*-SEM pyrroles in stoichiometric amounts. Aryl bromide was found to be a superior coupling partner compared to the corresponding chloride, triflate and iodide. Several aryl bromides were successfully coupled to the 2-position of pyrroles. The influence of substituents about the

pyrrole core, both electron-donating and electron-withdrawing, was investigated. Compared to *N*-methyl pyrroles, the use of SEM as an *N*-protecting group enables both decarboxylative arylation and *N*-deprotection with select systems. Furthermore, the yields reported herein are based on the amount of pyrrole used (rather than following literature precedent that bases yields on the amount of aryl halide used).[19] Although SEM-deprotection of some electron-rich pyrroles was unsuccessful, the deprotection of pyrroles bearing a mixture of alkyl- and H-substitution, as well as acyl or pendant carbonyl functionality, proceeded well. Certainly, the fickle nature of pyrroles as regards to (de)protection means that protection strategies must be chosen with care. Nevertheless, for certain systems, the use of *N*-SEM pyrroles provides a useful alternative when deprotection is required following decarboxylative arylation.

Experimental section

General

All chemicals were purchased and used as received unless otherwise indicated. Moisture sensitive reactions were performed in oven-dried glassware and under a positive pressure of nitrogen via use of a Schlenk line or glove box, both producing comparable yields. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Flash chromatography was performed using ultra-pure silica (230-400 mm), unless indicated otherwise. The NMR spectra were recorded using a 500 MHz spectrometer instrument using $CDCl_3$, which was referenced at 7.26 ppm for ^1H and at 77.16 ppm for ^{13}C. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in $ESI^{+/-}$ mode or APCI, as indicated. Compounds **1a-h**[25,27,38-42] were prepared according to literature procedures.

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

Adapting a literature procedure[21] pyrrole **1a** (0.50 g, 1.84 mmol) was dissolved in CH_2Cl_2 (20 mL) and NBu_4Br (59 mg, 0.184 mmol) and MeI (126 μL, 2.02 mmol) were added. The mixture was stirred

vigorously at 0 °C as 5 M NaOH (10 mL) was added drop-wise. The mixture darkened, and was allowed to warm to room temperature and then stirred for 18 h. The organic fraction was separated and washed with brine (100 mL), dried over Na_2SO_4, and filtered over a pad of neutral silica using methanol:CH_2Cl_2 (5:95). After removal of the solvent *in vacuo,* pyrrole **2a** was isolated as an off-white solid (0.61 g, 99%). ^{1}H NMR (500 MHz; $CDCl_3$) 2.45 (s, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 3.77 (s, 3H), 5.32 (s, 2H), 7.43-7.33 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.4, 13.7, 32.0, 66.1, 123.5, 128.3, 128.8, 129.5, 136.2, 140.5, 162.1, 196.6 (1 carbon unaccounted for) ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{19}NO_3$, 308.1263; found, 308.1257.

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

Adapting a literature procedure,[28] pyrrole **1b** (2.12 g, 8.2 mmol) was dissolved in CH_2Cl_2 (20 mL), and NBu_4Br (0.26 g, 0.82 mmol) and MeI (0.56 mL, 9.06 mmol) were added. The mixture was stirred vigorously at 0 °C as 5 M NaOH (20 mL) was added drop-wise. The reaction vessel and condenser tube were sealed, and the mixture was heated at 50 °C for 3 days. Although a considerable amount of starting material was still present, the organic fraction was separated and washed with brine (100 mL), and dried over Na_2SO_4. Purification using chromatography (SiO_2, hexane/EtOAc 90/10 then 80/20) gave pyrrole **2b** as a colourless oil (0.48 g, 22%). ^{1}H NMR (500 MHz; $CDCl_3$) 1.02 (t, J = 7.5 Hz, 3H), 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), 7.36 (t, J = 7.4 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 10.4, 11.8, 15.8, 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. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{21}NO$, 294.1470; found, 294.1465.

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

Adapting a literature procedure,[19] pyrrole **1c** (1.70 g, 6.27 mmol) was dissolved in CH_2Cl_2 (20 mL) and NBu_4Br (0.20 g, 0.627 mmol) and MeI (0.43 mL, 6.89 mmol) were added. The mixture was stirred

vigorously at 0 °C as 5 M NaOH (15 mL) was added drop-wise. The mixture darkened, and was allowed to warm to room temperature as the reaction stirred for 18 h. The organic fraction was separated and washed with brine (100 mL), dried over Na_2SO_4, and filtered over a pad of neutral silica using methanol:CH_2Cl_2 (5:95). After removal of the solvent *in vacuo,* pyrrole **2c** was isolated as a brown solid (1.78g, 99%). ^{1}H NMR (500 MHz; $CDCl_3$) 1.13 (t, J = 7.6 Hz, 3H), 2.20 (s, 3H), 2.71 (q, J = 7.6 Hz, 2H), 4.16 (s, 3H), 5.34 (s, 2H), 7.44-7.34 (m, 5H), 9.90 (s, 1H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 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 carbon unaccounted for) ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{19}NO_3$, 308.1263; found, 308.1257.

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

Adapting literature procedures,[19,35] a solution of pyrrole **2** (1 equiv), 10 mol% Pd/C (10% of the mass of **2**) and NEt_3 (few drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times with N_2 before the introduction of H_2 atmosphere. After stirring the reaction mixture for 19 h, nitrogen atmosphere was introduced and the reaction was filtered through a plug of Celite® and rinsed with MeOH. Removal of the solvent under reduced pressure gave pyrrole **3**, which was used in the next step without further purification. Pyrrole **3** (1 equiv), PhBr (1.1 equiv), NBu_4Cl (1 equiv), Cs_2CO_3 (1.5 equiv), and $Pd(P(tBu)_3)_2$ (0.05 equiv) were combined in an open microwave vial. The vessel was crimped through the use of a septum cap, a nitrogen atmosphere introduced and anhydrous DMF was added (0.1 M). The mixture was stirred for 30 s, and then submitted to microwave-promoted heating conditions (150 °C, 10 min, high absorption). The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated solution of $NaHCO_3$ (× 3) and water (× 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixtures were purified using column chromatography on SiO_2 (EtOAc/hexane, 10% → 30%) to give the desired products.

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

Pyrrole **4a** was obtained according to GP1 as a colorless solid (28 mg, 96%). ^{1}H NMR (500 MHz; $CDCl_3$) 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 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.7, 13.0, 31.6, 31.7, 116.4, 121.6, 127.8, 128.5 (2C), 131.2 (2C), 131.6, 132.1, 135.7, 196.1 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}NO$, 250.1208; found, 250.1202.

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

Pyrrole **4c** was obtained according to GP1 as a beige solid containing both the product **4c** (43%, based on the amount of **4c** in the isolated mixture) and the decarboxylated derivative **5c** in a 10:1 ratio, which was not easily separated using chromatography. ^{1}H NMR (500 MHz; $CDCl_3$) 1.16 (t, J = 7.6 Hz, 0.1 × 3H, CH_2CH_3 of **5c**), 1.22 (t, J = 7.6 Hz, 0.9 × 3H, CH_2CH_3 of **4c**), 1.93 (s, 0.9 × 3H, CH_3 of **4c**), 2.03 (s, 0.1 × 3H, CH_3 of **5c**), 2.69 (q, J = 7.6 Hz, 0.1 × 2H, CH_2CH_3 of **5c**), 2.76 (q, J = 7.6 Hz, 0.9 × 2H, CH_2CH_3 of **4c**), 3.75 (s, 0.9 × 3H, CH_3 of **4c**), 3.85 (s, 0.1 × 3H, CH_3 of **5c**), 6.59 (s, 0.1 × 1H, Ar-*H* of **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 = 7.3 Hz, 0.9 × 2H, Ar-*H* of **4c**), 9.66 (s, 0.1 × 1H, C*H*O of **5c**), (9.75 (s, 0.9 × 1H, C*H*O of **4c**) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 9.2, 16.7, 17.3, 34.2, 117.3, 127.2, 128.5, 128.6, 130.3, 130.8, 139.7, 141.3, 177.7 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}NO$, 250.1208; found, 250.1202.

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

Pyrrole **1a** (0.50 g, 1.84 mmol) and DMAP (25 mg, 0.22 mmol) were dissolved in anhydrous MeCN (20 mL) and the solution was degassed with nitrogen for 10 minutes with stirring. $(Boc)_2O$ (1.08 g, 4.97 mmol) was added dropwise as a solution in anhydrous MeCN (5 mL). The mixture was stirred for 20 minutes, after which no starting material was detectable using TLC analysis. Removal of the solvent and excess $(Boc)_2O$ *in vacuo* yielded the crude product, which was subjected to column chromatography on

Brockman III basic alumina using EtOAc:hexanes (5:95) as eluent. The product was obtained as a light yellow oil (0.66 g, 97%). ^{1}H NMR (500 MHz; $CDCl_3$) 1.51 (s, 9H), 2.43 (s, 3H), 2.44 (s, 3H), 2.53 (s, 3H), 5.32 (s, 2H), 7.31-7.41 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.7, 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, 161.1, 196.3 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{25}NO_5$, 394.1630; found, 394.1608.

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

Adapting a literature procedure,[36] pyrrole **1** (1.0 equiv) was added in one portion to a stirred solution of NaH (60% dispersion in mineral oil, 1.1 equiv) in DMF (0.4 M) at room temperature and under nitrogen atmosphere. When the evolution of H_2 ceased, 2-(trimethylsilyl)ethoxymethyl chloride (1.1 equiv) was added dropwise at 0 ºC. The reaction mixture was allowed to warm up to room temperature, stirred until complete consumption of the starting material (according to TLC analysis) and poured into a saturated solution of $NaHCO_3$ at 0 ºC. The crude mixture was extracted with EtOAc (× 3) and the combined organic fractions washed with water (× 2) and brine, dried over Na_2SO_4 and concentrated under reduced pressure.

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

Pyrrole **8a** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **8a** as a colorless oil (73%). ^{1}H NMR (500 MHz; $CDCl_3$) -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, 2H), 5.32 (s, 2H), 5.70 (s, 2H), 7.32-7.43 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 12.3, 13.7, 18.1, 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 unaccounted for) ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{31}NNaO_4Si$, 424.1915; found, 424.1930.

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

Pyrrole **8b** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 100/0, 98/2, 96/4) to give **8b** as a colorless oil (73%). ^{1}H NMR (500 MHz; $CDCl_3$) -0.05 (s, 9H), 0.84-0.87 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H), 2.24 (s, 3H), 2.26 (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. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 10.1, 11.9, 15.5, 17.4, 18.1, 65.2, 65.5, 73.1, 118.3, 124.0, 128.0, 128.2, 128.6, 129.4, 134.1, 136.9, 162.0 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{33}NNaO_3Si$, 410.2122; found, 410.2124.

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

Pyrrole **8c** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10 to 80/20) to give **8c** as a colorless oil (81%). ^{1}H NMR (500 MHz; $CDCl_3$) -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 = 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. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 10.7, 16.2, 17.1, 18.0, 65.8, 66.9, 73.8, 126.6, 127.6, 128.5, 128.6, 128.8, 130.2, 135.7, 139.2, 161.6, 180.5 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{31}NNaO_4Si$, 424.1915; found, 424.1912.

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

Pyrrole **8d** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 100/0 to 95/5) to give **8d** as a colorless oil (78%). ^{1}H NMR (500 MHz; $CDCl_3$) -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 (s, 2H), 5.82 (s, 1H), 7.31-7.43 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 12.4, 14.7, 18.1, 65.3, 65.5, 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*): $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_3Si$, 382.1809; found, 382.1821.

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

Pyrrole **8e** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 100/0, 90/10, 85/15) to give **8e** as a colorless oil (91%). ^{1}H NMR (500 MHz; $CDCl_3$) -0.04 (s, 9H), 0.84-0.88 (m, 2H), 2.26 (s, 3H), 2.27 (s, 3H), 3.40 (s, 2H), 3.49-3.52 (m, 2H), 3.65 (s, 3H), 5.29 (s, 2H), 5.70 (s, 2H), 7.30-7.42 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -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, 129.9, 135.7, 136.7, 161.9, 172.2 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{33}NNaO_5Si$, 454.2020; found, 454.2028.

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

Pyrrole **8f** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 95/5) to give **8f** as a colorless oil (85%). ^{1}H NMR (500 MHz; $CDCl_3$) -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, J = 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 (m, 2H), 7.42-7.43 (m, 2H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 18.0, 65.7, 66.1, 77.0, 109.0, 119.5, 123.3,128.1, 128.2, 128.7, 129.0, 136.6, 160.9 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_3Si$, 354.1496; found, 354.1487.

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

Pyrrole **8g** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **8g** as a pale yellow oil (53%). ^{1}H NMR (500 MHz; $CDCl_3$): -0.04 (s, 9H), 0.86 (t, J = 8.1 Hz, 2H), 2.44 (s, 3H), 2.51 (s, 3H), 3.51 (t, J = 8.1 Hz, 2H), 5.33 (s, 2H), 5.72 (s, 2H), 7.43-7.34 (m, 5H) ppm. ^{19}F NMR (471 MHz; $CDCl_3$) -74 ppm. ^{13}C NMR (126 MHz; $CDCl_3$): -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, 128.6,

128.8, 131.3, 135.8, 144.2, 161.6, 179.3 (q, J = 37 Hz) ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{28}F_3NNaO_4Si$, 478.1632; found, 478.1631.

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

Pyrrole **8h** was obtained according to GP2. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **8h** as a pale yellow oil (79%). ^{1}H NMR (500 MHz; $CDCl_3$): -0.04 (s, 9H), 0.85 (t, J = 8.1 Hz, 2H), 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 = 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) ppm. ^{13}C NMR (126 MHz; $CDCl_3$): -1.3, 12.0, 13.1, 14.5, 18.1, 59.8, 65.7, 66.1, 73.2, 76.9, 77.2, 77.4, 114.1, 120.1, 128.29, 128.33, 128.7, 132.2, 136.3, 142.8, 161.9, 165.6 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{33}NNaO_5Si$, 454.2020; found, 454.2001.

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

Adapting GP1, a solution of pyrrole **8** (1 equiv), 10 mol% Pd/C (10% of the mass of **8**) and NEt_3 (few drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times with nitrogen before the introduction of a H_2 atmosphere. After stirring the reaction for 19 h, N_2 atmosphere was introduced and the reaction was filtered through a plug of Celite® and rinsed with MeOH. Removal of the solvent under reduced pressure gave pyrrole **9**, which was used in the next step without further purification. Pyrrole **9** (1 equiv), PhBr (1.5 equiv), NBu_4Cl (1 equiv), KO*t*Bu (1.5 equiv), and $Pd(P(tBu)_3)_2$ (0.05 equiv) were combined in an open microwave vial. The vessel was crimped through the use of a septum cap, a nitrogen atmosphere introduced and anhydrous DMF was added (0.1 M). Alternatively, pyrrole **9** was added to a microwave vial which was subsequently sealed with a rubber septum and a nitrogen atmosphere introduced. The vial was then brought into a glovebox, where the remaining reagents and solvent were added and the vessel sealed. The mixture was stirred for 30 s, and then submitted to microwave-promoted heating conditions (150 °C, 10 min, high absorption). The

mixture was diluted with ethyl acetate (50 mL) and washed with a saturated solution of $NaHCO_3$ (× 3) and water (× 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

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

Pyrrole **10a** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **10a** as a colorless oil (54%). ^{1}H NMR (500 MHz; $CDCl_3$) -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, 2H), 5.04 (s, 2H), 7.28-7.30 (m, 2H), 7.36-7.45 (m, 3H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 12.4, 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 unaccounted for) ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_2Si$, 366.1860; found, 366.1859.

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

Pyrrole **10b** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **10b** (43%) as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$) -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 (q, J = 7.5 Hz, 2H), 3.31-3.34 (m, 2H), 5.06 (s, 2H), 7.30-7.44 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -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, 133.3 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{31}NNaOSi$, 352.2067; found, 352.2064.

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

Pyrrole **10d** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 98/2) to give a colorless oil containing both the product **10d** (35%, based on the amount of **10d** in the isolated mixture) and the decarboxylated derivative **11d** in a 4:1 ratio. ^{1}H NMR (500 MHz; $CDCl_3$) -0.04 (s, 0.8 × 9H, TMS of **10d**), 0.00 (s, 0.2 × 9H, TMS of **11d**), 0.78-0.82 (m, 0.8 × 2H, CH_2-TMS of **10d**), 0.87-0.93 (m, 0.2 × 2H, CH_2-TMS of **11d**), 2.03 (s, 0.8 × 3H, CH_3 of **10d**), 2.05 (s, 0.2 × 3H, CH_3 of **11d**), 2.24 (s, 0.2 × 3H, CH_3 of **11d**), 2.34 (s, 0.8 × 3H, CH_3 of

10d), 3.27-3.32 (m, 0.8 × 2H, C*H*$_2$CH$_2$-TMS of **10d**), 3.45-3.50 (m, 0.2 × 2H, C*H*$_2$CH$_2$-TMS of **11d**), 5.05 (s, 0.8 × 2H, C*H*$_2$O of **10d**), 5.07 (s, 0.2 × 2H, C*H*$_2$O of **11d**), 5.76 (s, 0.2 × 1H, Ar-*H* 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. ^{13}C NMR (125 MHz; $CDCl_3$) -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, 116.4, 118.0, 118.9, 126.8, 128.3, 129.4, 130.8, 130.9, 133.2 (significant overlap between ^{13}C-NMR signals of **10d** and **11d** in spectrum) ppm. HRMS-ESI (*m/z*) for **10d**: $[M+Na]^+$ calcd for $C_{18}H_{27}NNaOSi$, 324.1754; found, 324.1745. HRMS-ESI (*m/z*) for **11d**: $[M+Na]^+$ calcd for $C_{12}H_{23}NNaOSi$, 248.1441; found, 248.1435.

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

Pyrrole **10e** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **10e** (52%) as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$) -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, 2H), 3.69 (s, 3H), 5.02 (s, 2H), 7.28-7.42 (m, 5H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 10.0, 10.1, 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-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3Si$, 396.1965; found, 396.1963.

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

Pyrrole **10f** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 95/5) to give **10f** as a colorless oil (60%). ^{1}H NMR (500 MHz; $CDCl_3$) 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 (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), 7.55 (d, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 18.0, 65.8, 76.2, 108.8, 109.7, 123.5, 127.1, 128.5,

129.0, 133.1, 135.3 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{23}NNaOSi$, 296.1441; found, 296.1436.

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

Pyrrole **10h** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give a colorless oil containing both the product **10h** (35%) and the decarboxylated derivative **11h** in a 3:1 ratio. ^{1}H NMR (3 MHz; $CDCl_3$) -0.06 (s, 9H, TMS of **10h**), -0.02 (s, 9H, TMS of **11h**), 0.77 (t, J = 8.4 Hz, 2H, CH_2-TMS of **10h**), 0.88 (t, J = 8.2 Hz, 2H, CH_2-TMS of **11h**), 1.34-1.39 (m, 6H, CH_3CH$_2$O(CO) of **10h** and **11h**), 2.15 (s, 3H, CH_3 of **10h**), 2.21 (s, 3H, CH_3 of **11h**), 2.53 (s, 3H, CH_3 of **11h**), 2.63 (s, 3H, *CH$_3$* of **10h**), 3.25 (t, J = 8.4 Hz, 2H, CH_2CH$_2$-TMS of **10h**), 3.46 (t, J = 8.4 Hz, 2H, CH_2CH$_2$-TMS of **11h**), 4.24-4.34 (m, 4H, CH$_3$CH_2O(CO) of **10h** and **11h**), 5.04 (s, 2H, CH_2O of **10h**), 5.010 (s, 2H, CH_2O of **11h**), 6.38 (s, 1H, 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 (significant overlap between ^{1}H-NMR signals of **10h** and **11h** in spectrum). ^{13}C NMR (125 MHz; $CDCl_3$) -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, 116.4, 118.0, 118.9, 126.8, 128.3, 129.4, 130.8, 130.9, 133.2 ppm (significant overlap between ^{13}C-NMR signals of **10h** and **11h** in spectrum). HRMS-ESI (*m/z*) for **10h**: $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3Si$, 396.1965; found, 396.1982. HRMS-ESI (*m/z*) for **11h**: $[M+Na]^+$ calcd for $C_{15}H_{27}NNaOSi$, 320.1652; found, 320.1640.

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

Pyrrole **10i** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give a white solid containing both the product **10i** (20%) and the decarboxylated derivative **11a** in a 6:1 ratio. ^{1}H NMR (500 MHz; $CDCl_3$) -0.04 (s, 9H, TMS of **10i**), -0.01 (s, 9H, TMS of **11a**), 0.79 (t, J = 8.3 Hz, 2H, CH_2-TMS of **10i**), 0.89 (t, J = 8.1 Hz, 2H, CH_2-TMS of **11a**), 2.14 (s, 3H, CH_3 of **10i**), 2.25 (s, 3H, CH_3 of **11a**), 2.43 (s, 3H, CH_3 of **11a**), 2.48 (s, 3H, CH_3 of **10i**), 2.52 (s, 3H, *CH$_3$* of **11a**), 2.60 (s, *CH$_3$* of **10i**), 3.29 (t, J = 8.3 Hz, 2H, CH_2CH$_2$-

TMS of **10i**), 3.47 (t, J = 8.1 Hz, 2H, CH_2CH$_2$-TMS of **11a**), 3.86 (s, 3H, Ar-OCH_3 of **10i**), 5.01 (s, 2H, CH_2O of **10i**), 5.11 (s, 2H, CH_2O of **11a**), 6.39 (s, 1H, Pyrrole-*H* of **11a**), 6.96 (d, J = 8.7 Hz, 2H, Ar-*H* of **10i**), 7.21 (d, J = 8.6 Hz, 2H, Ar-*H* of **10i**) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -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, 75.7, 113.9, 116.6, 119.2, 120.3, 122.7, 122.9, 124.0, 131.6, 132.7, 135.7, 136.3, 159.4, 196.1, 196.5 ppm. HRMS-ESI (*m/z*) for **10i**: $[M+Na]^+$ calcd for $C_{21}H_{31}NNaO_3Si$, 396.1965; found, 396.1971. HRMS-ESI (*m/z*) for **11a**: $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2Si$, 290.1547; found, 290.1545.

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

Pyrrole **10j** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give a white solid containing both the product **10j** (36%) and the decarboxylated derivative **11a** in a 6:1 ratio. ^{1}H NMR (300 MHz; $CDCl_3$) -0.04 (s, 9H, TMS of **10j**), -0.02 (s, 9H, TMS of **11a**), 0.1 (t, J = 8.3 Hz, 2H, CH_2-TMS of **10j**), 0.89 (t, J = 8.2 Hz, 2H, CH_2-TMS of **11a**), 2.17 (s, 3H, CH_3 of **10j**), 2.25 (s, 3H, CH_3 of **11a**), 2.43 (s, 3H, CH_3 of **11a**), 2.49 (s, 3H, CH_3 of **10j**), 2.52 (s, 3H, *CH$_3$* of **11a**), 2.61 (s, *CH$_3$* of **10j**), 3.33 (t, J = 8.3 Hz, 2H, CH_2CH$_2$-TMS of **10j**), 3.46 (t, J = 8.2 Hz, 2H, CH_2CH$_2$-TMS of **11a**), 5.01 (s, 2H, CH_2O of **10j**), 5.11 (s, 2H, CH_2O of **11a**), 6.39 (s, 1H, Pyrrole-*H* of **11a**), 7.44 (d, J = 7.9 Hz, 2H, Ar-*H* of **10j**), 7.69 (d, J = 8.0 Hz, 2H, Ar-*H* of **10j**) ppm. ^{19}F NMR (471 MHz; $CDCl_3$) -63 ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 12.2, 12.4, 12.8, 13.7, 17.9, 18.0, 31.4, 31.7, 65.8, 65.9, 72.9, 75.7, 110.1, 117.8, 119.2, 120.3, 123.1, 125.4, 129.8, 130.1, 130.4, 131.6, 135.7, 136.7, 196.1, 196.3 ppm. HRMS-ESI (*m/z*) for **10j**: $[M+Na]^+$ calcd for $C_{21}H_{28}F_3NNaO_2Si$, 434.1734; found, 434.1731. HRMS-ESI (*m/z*) for **11a**: $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2Si$, 290.1547; found, 290.1551.

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

Pyrrole **10k** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **10k** (37%) as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$) -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, 2H), 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 and 1.1 Hz, 1H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) -1.3, 12.5, 13.1, 18.0, 31.6, 65.8, 72.8, 120.0, 122.9, 123.6, 127.2, 127.7, 130.4, 132.2, 136.9, 196.2 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{27}NNaO_2SSi$, 372.1424; found, 372.1414.

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

Adapting literature procedures,[36] TBAF (1 M solution in THF, 5 equiv.) was added dropwise to a solution of pyrrole **10** (1 equiv.) in THF (0.1 M) at room temperature and under nitrogen atmosphere. The reaction mixture was heated to reflux temperature for 19 h. If TLC analysis still showed starting material, TBAF (1 M solution in THF, 5 equiv.) was added and the reaction mixture was heated at reflux temperature for an additional 10 h. Water was added to the reaction mixture and the two layers were separated. The aqueous layers was extracted with EtOAc (× 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

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

Pyrrole **12a** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 50/50) to give **12a** as a white solid (54%). Mp: 160-162 ºC. ^{1}H 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) 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, 134.9, 195.8 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{15}NNaO$, 236.1046; found, 236.1044.

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

Pyrrole **12d** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 98/2) to give **12d** as a colorless oil (52%). ^{1}H NMR (500 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, 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, 134.0 ppm. HRMS-ESI (*m/z*): $[M]^+$ calcd for $C_{12}H_{14}N$, 172.1121; found, 172.1117.

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

Pyrrole **12f** was obtained according to GP3. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **12f** as a white solid (71%). ^{1}H NMR (500 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 (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, 124.0, 126.4, 129.0, 132.3, 132.9 ppm. HRMS-APCI (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{10}N$, 144.0808; found, 144.0814. The reported data are in agreement with those in the literature.[43]

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

Pyrrole **12h** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 90/10) to give **12a** as a pale yellow solid (65%). ^{1}H NMR (500 MHz; $CDCl_3$) 1.37 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 2.55 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 7.28-7.29 (m, 1H), 7.36-7.42 (m, 4H), 8.06 (br s, 1H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.0, 14.3, 14.7, 59.3, 112.6, 118.1, 126.8, 127.4, 127.4, 128.9, 133.0 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}NNaO_2$, 266.1151; found, 266.1148.

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

Pyrrole **12i** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **12i** as a brown solid (24%). ^{1}H NMR (500 MHz; $CDCl_3$) 2.34 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 3.84 (s, 3H), 6.96 (d, J = 8.7 Hz, 2H), 7.29 (d, J

= 8.7 Hz, 2H), 8.04 (br s, 1H) ppm. ^{13}C NMR (126 MHz; $CDCl_3$) 12.78, 15.28, 31.20, 55.50, 110.14, 114.36, 116.16, 125.28, 127.72, 129.19, 134.41, 158.86, 195.80 ppm. HRMS-APCI (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1332; found, 244.1324.

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

Pyrrole **12j** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 80/20) to give **12j** as a pale beige solid (48%). ^{1}H NMR (500 MHz; $CDCl_3$) 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 Hz, 2H), 8.33 (br s, 1H) ppm. ^{19}F NMR (471 MHz; $CDCl_3$) -63 ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.8, 15.3, 31.3, 118.6, 123.2, 125.4, 125.9, 126.5, 127.6, 128.6, 135.8, 136.2, 195.8 ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{14}FNNaO$, 304.0920; found, 304.0926.

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

Pyrrole **12k** was obtained according to GP4. The crude mixture was purified using column chromatography on SiO_2 (hexanes/EtOAc, 85/15) to give **12k** as a pale beige solid (58%). ^{1}H NMR (500 MHz; $CDCl_3$) 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, J = 5.1 and 3.6 Hz, 2H), 7.28 (dd, J = 5.1 and 1.0 Hz), 8.08 (br s, 1H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$) 12.7, 15.1, 31.1, 118.1, 122.8, 124.2, 124.3, 127.5, 133.3, 134.2, 134.9, 195.5ppm. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{13}NNaOS$, 242.0610; found, 242.0615.

Supplementary material

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

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

592 **TOC artwork**

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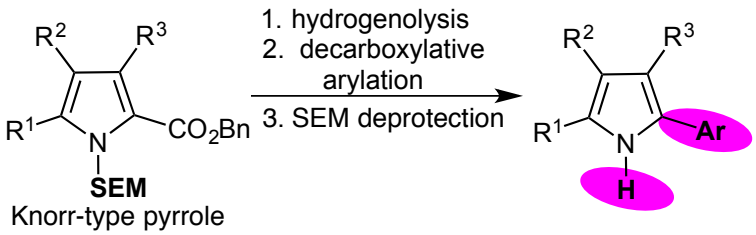

Knorr-type pyrrole

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