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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-
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positions. Furthermore, these methodologies typically involve N-alkyl and N-aryl pyrroles, thereby incorporating protecting groups that, courtesy of inherent challenges encountered in deprotection, are largely impractical for use in a synthetic sequence. 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. 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). 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. 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.
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\[
\begin{align*}
\text{Previous work:} & \quad \text{Pd(P}^{\text{Bu}}\text{)}_2\text{, } \text{Cs}_2\text{CO}_3, \\
& \quad \text{N}^\text{Bu}_4\text{Cl, } \text{DMF} \\
\text{170 }^\circ\text{C, 8 min microwave} \\
\text{This work:} & \quad \text {1. hydrogenolysis} \\
& \quad \text{2. decarboxylative arylation} \\
& \quad \text{deprotect} \\
\end{align*}
\]

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.
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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.\textsuperscript{28} The crude acids were carried directly into the reported palladium-catalyzed decarboxylative arylation (Scheme 3, method a).\textsuperscript{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,\textsuperscript{10} the isolation of the α-free pyrrole is not unexpected and presumably arises due to non-catalyzed decarboxylation of pyrroles at temperatures below 170 °C.\textsuperscript{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
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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. However, given that the deprotection of N-methyl pyrroles is challenging, 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, we submitted the N-unprotected pyrrole 1a to the decarboxylative arylation conditions (method b, Scheme 3). However, 1H 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 and that direct C-H arylation involving N-Boc pyrroles has been reported, 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. N-Tosylation of pyrrole 1a proved wholly unsatisfactory, again demonstrating the fickle nature of N-protection of pyrroles.
We turned our attention to protecting groups that would mimic the methyl group of \textit{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 pyroles. It is easily introduced, more selective than other protecting groups (\textit{e.g.} methyl group), and, most importantly is removed under reaction conditions compatible with other functional groups.\textsuperscript{35,36} Furthermore, the SEM group has been shown to be effective as a protecting group for pyrazoles undergoing C–H arylation.\textsuperscript{37} Pleasingly, reaction of the pyrrolide of 1a with SEM-Cl gave the \textit{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 \textalpha-free pyrrole 11a. Based on \textsuperscript{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).
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![Scheme 5 Decarboxylative arylation using SEM-protected pyrrole 8a.](image)

### Table 1 Optimization using 2-pyrrole carboxylic acid 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>PhBr (eq.)</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Conversion (10a:11a:9a)</th>
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<td>1</td>
<td>Cs$_2$CO$_3$ (1.5 eq.)</td>
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<td>150</td>
<td>10</td>
<td>55:45:0</td>
</tr>
<tr>
<td>2</td>
<td>Cs$_2$CO$_3$ (1.5 eq.)</td>
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<td>190</td>
<td>10</td>
<td>77:23:0</td>
</tr>
<tr>
<td>3</td>
<td>KOAc (1.5 eq.)</td>
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<td>10</td>
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<td>20</td>
<td>81:19:0</td>
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<tr>
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<td>1.1</td>
<td>150</td>
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<td>190</td>
<td>20</td>
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<tr>
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<td>10</td>
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<td>1.3</td>
<td>150</td>
<td>10</td>
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<td>KOtBu (1.5 eq.)</td>
<td>2.0</td>
<td>150</td>
<td>10</td>
<td>93:traces:traces</td>
</tr>
</tbody>
</table>

Note: aReactions were performed in 2-5 mL microwave vials, using 0.05 equivalents of Pd(PtBu$_3$)$_2$, as catalyst, and DMF, as solvent. bAccording to $^1$H NMR spectroscopic analysis of the crude mixture; cPercentages are based on the integrals relative to the proton peaks of the SEM-protecting group.

The temperature was both decreased to 150 °C (entry 1) and increased to 190 °C (entry 2). Formation of the α-free pyrrole 11a decreased when the reaction was carried out at 190 °C. Cs$_2$CO$_3$ was replaced by KOAc, and variation of temperature and time explored (entries 3-7). However, no improvements were obtained. Surprisingly, the use of KtOBu (entries 8-14) afforded 10a in 85% conversion (entry 8), without formation of 11a, yet with 15% of unreacted starting material. Cognizant that KtOBu has a pka of 17, higher than that of Cs$_2$CO$_3$ (10) and KOAc (4.8), deprotonation of 9a might...
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Occur more readily than the palladium-catalyzed decarboxylation. Increasing the temperature to 190 °C (compare entries 9 and 10) did not increase the conversion to product. The presence of the unreacted 9a might be due to insufficient KO\(\text{OBu} \) 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 \( \alpha \)-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 \( \alpha \)-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.

![Scheme 6 SEM-deprotection of pyrrole 10a.](image)

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
Decarboxylative arylation of substituted pyrroles N-protected with 2-(trimethylsilyl)ethoxymethyl (SEM) 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 conditions19 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.
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![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.

![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
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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). 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 $^1$H 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 were prepared according to literature procedures.

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

Adapting a literature procedure pyrrole 1a (0.50 g, 1.84 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and NBu$_4$Br (59 mg, 0.184 mmol) and MeI (126 µL, 2.02 mmol) were added. The mixture was stirred...
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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 Na₂SO₄, and filtered over a pad of neutral silica using methanol:CH₂Cl₂
(5:95). After removal of the solvent in vacuo, pyrrole 2a was isolated as an off-white 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), 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, 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 C₁₇H₁₉NO₃,
308.1263; found, 308.1257.

Benzy1 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 CH₂Cl₂ (20 mL), and
NBu₄Br (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 Na₂SO₄. Purification using chromatography (SiO₂, hexane/EtOAc 90/10 then 80/20) gave pyrrole
2b as a colourless oil (0.48 g, 22%). ¹H NMR (500 MHz; CDCl₃) 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. ¹³C NMR (125 MHz; CDCl₃) 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 C₁₇H₂₁NO, 294.1470; found, 294.1465.

Benzy1 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 CH₂Cl₂ (20 mL) and
NBu₄Br (0.20 g, 0.627 mmol) and MeI (0.43 mL, 6.89 mmol) were added. The mixture was stirred
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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 Na₂SO₄, and filtered over a pad of neutral silica using methanol:CH₂Cl₂ (5:95). After removal of the solvent in vacuo, pyrrole 2c was isolated as a 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 = 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; 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 carbon unaccounted for) ppm. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₇H₁₉NO₃, 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 NEt₃ (few drops) were dissolved in EtOH (0.08 M). The reaction mixture was purged three times with N₂ before the introduction of H₂ 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), NBu₄Cl (1 equiv), Cs₂CO₃ (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 NaHCO₃ (× 3) and water (× 2). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixtures were purified using column chromatography on SiO₂ (EtOAc/hexane, 10% → 30%) to give the desired products.
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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$_2$CH$_3$ of 5c), 1.22 (t, $J = 7.6$ Hz, 0.9 × 3H, CH$_2$CH$_3$ 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$_2$CH$_3$ of 5c), 2.76 (q, $J = 7.6$ Hz, 0.9 × 2H, CH$_2$CH$_3$ 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, CHO of 5c), (9.75 (s, 0.9 × 1H, CHO 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.

Benzy 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)$_2$O (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)$_2$O in vacuo yielded the crude product, which was subjected to column chromatography on
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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, 128.7, 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 ($\times$ 3) and the combined organic fractions washed with water ($\times$ 2) and brine, dried over Na$_2$SO$_4$ 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), 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$_{33}$NNaO$_4$Si, 424.1915; found, 424.1930.
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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$_3$Si, 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$_4$Si, 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$_{26}$H$_{29}$NNaO$_3$Si, 382.1809; found, 382.1821.
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Benzy1 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$_5$Si, 454.2020; found, 454.2028.

Benzy1 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$_3$Si, 354.1496; found, 354.1487.

Benzy1 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,
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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.

**Benzy1 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%). ^1H 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. ^13C 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), KOtBu (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).
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mixture was diluted with ethyl acetate (50 mL) and washed with a saturated solution of NaHCO₃ (× 3) and water (× 2). The organic layer was dried over Na₂SO₄ 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 SiO₂ (hexanes/EtOAc, 80/20) to give 10a as a colorless oil (54%). ¹H NMR (500 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, 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, 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 C₂₀H₂₉NNaO₂Si, 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 SiO₂ (hexanes/EtOAc, 90/10) to give 10b (43%) as a colorless oil. ¹H NMR (500 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), 2.24 (q, J = 7.5 Hz, 2H), 7.30-7.44 (m, 5H) ppm. ¹³C NMR (125 MHz; CDCl₃) -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 C₂₀H₃₁NNaO₂Si, 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 SiO₂ (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. ¹H NMR (500 MHz; CDCl₃) -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, CH₂-TMS of 10d), 0.87-0.93 (m, 0.2 × 2H, CH₂-TMS of 11d), 2.03 (s, 0.8 × 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 × 3H, CH₃ of
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10d), 3.27-3.32 (m, 0.8 × 2H, CH$_2$CH$_2$-TMS of 10d), 3.45-3.50 (m, 0.2 × 2H, CH$_2$CH$_2$-TMS of 11d),
5.05 (s, 0.8 × 2H, CH$_2$O of 10d), 5.07 (s, 0.2 × 2H, CH$_2$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. ¹³C 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 ¹³C-NMR signals of 10d and 11d in spectrum) ppm. HRMS-ESI (m/z) for 10d: [M+Na]$^+$ calcd for C$_{18}$H$_{27}$NaOSi, 324.1754; found, 324.1745. HRMS-ESI (m/z) for 11d: [M+Na]$^+$ calcd for C$_{12}$H$_{23}$NaOSi, 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. ¹H 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. ¹³C 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$_{31}$NaOSi, 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%). ¹H 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. ¹³C NMR (125 MHz; CDCl$_3$) -1.3, 18.0, 65.8, 76.2, 108.8, 109.7, 123.5, 127.1, 128.5,
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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$_3$ 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$_2$CH$_2$-TMS of 10h), 3.46 (t, $J$ = 8.4 Hz, 2H, CH$_2$CH$_2$-TMS of 11h), 4.24-4.34 (m, 4H, CH$_3$C of 10h and 11h), 5.04 (s, 2H, CH$_2$O of 10h), 5.010 (s, 2H, CH$_2$O 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$_2$Si, 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$_2$CH$_2$-
Decarboxylative arylation of substituted pyrroles N-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)

TMS of 10i, 3.47 (t, J = 8.1 Hz, 2H, CH₂CH₂-TMS of 11a), 3.86 (s, 3H, Ar-CH₃ of 10i), 5.01 (s, 2H, CH₂O of 10i), 5.11 (s, 2H, CH₂O 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. ¹³C NMR (125 MHz; CDCl₃) -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, 159.4, 196.1, 196.5 ppm. HRMS-ESI (m/z) for 10i: [M+Na]⁺ calcd for C₂₁H₃₁NNaO₂Si, 396.1965; found, 396.1971. HRMS-ESI (m/z) for 11a: [M+Na]⁺ calcd for C₁₄H₁₄NNaO₂Si, 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 SiO₂ (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. ¹H NMR (300 MHz; CDCl₃) -0.04 (s, 9H, TMS 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, 2H, 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), 2.49 (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, CH₂CH₂-TMS of 10j), 3.46 (t, J = 8.2 Hz, 2H, CH₂CH₂-TMS of 11a), 5.01 (s, 2H, CH₂O of 10j), 5.11 (s, 2H, CH₂O 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. ¹⁹F NMR (471 MHz; CDCl₃) -63 ppm. ¹³C NMR (125 MHz; CDCl₃) -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 C₂₁H₂₃F₃NNaO₂Si, 434.1734; found, 434.1731. HRMS-ESI (m/z) for 11a: [M+Na]⁺ calcd for C₁₄H₁₄NNaO₂Si, 290.1547; found, 290.1551.

1-(2,4-dimethyl-5-(thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-3-yl)ethanone (10k)
Decarboxylative arylation of substituted pyrroles N-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)

Pyrrole 10k was obtained according to GP3. The crude mixture was purified using column chromatography on SiO₂ (hexanes/EtOAc, 90/10) to give 10k (37%) as a colorless oil. ¹H NMR (500 MHz; 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, 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. ¹³C NMR (125 MHz; CDCl₃) -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 C₁₈H₂₇NNaO₂Si, 372.1424; found, 372.1414.

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

Adapting literature procedures, 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 Na₂SO₄ and concentrated under reduced pressure.

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

Pyrrole 12a was obtained according to GP4. The crude mixture was purified using column chromatography on SiO₂ (hexanes/EtOAc, 50/50) to give 12a as a white solid (54%). Mp: 160-162 °C. ¹H NMR (500 MHz; CDCl₃) 2.38 (s, 3H), 2.47 (s, 3H), 2.56 (s, 3H), 7.27-7.45 (m, 5H), 8.17 (br s, 1H) ppm. ¹³C NMR (125 MHz; CDCl₃) 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 C₁₄H₁₅NNaO, 236.1046; found, 236.1044.
Decarboxylative arylation of substituted pyrroles $N$-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)

3,5-Dimethyl-2-phenyl-1H-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-1H-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, 144.0814; 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, 3H).
Decarboxylative arylation of substituted pyrroles \(N\)-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)

\[ = 8.7 \text{ Hz, 2H}, 8.04 \text{ (br s, 1H) ppm.}\]

\[ \text{\(^{13}C\) NMR (126 MHz; CDCl}\text{\(_3\)) 12.78, 15.28, 31.20, 55.50, 110.14,}\]

\[ 114.36, 116.16, 125.28, 127.72, 129.19, 134.41, 158.86, 195.80 \text{ ppm.}\]

\[ \text{HRMS-APCI (m/z): } [\text{M+H}]^+ \text{ calcd for C}_{15}\text{H}_{18}\text{NO}_2, 244.1332; \text{ found, 244.1324.}\]

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

Pyrrole 12j was obtained according to GP4. The crude mixture was purified using column chromatography on SiO\textsubscript{2} (hexanes/EtOAc, 80/20) to give 12j as a pale beige solid (48%). \(^{1}H\) NMR (500 MHz; CDCl\textsubscript{3}) 2.38 (s, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 7.46 (d, \(J = 8.2 \text{ Hz, 2H})\), 7.64 (d, \(J = 8.2 \text{ Hz, 2H})\), 8.33 (br s, 1H) ppm. \(^{19}F\) NMR (471 MHz; CDCl\textsubscript{3}) -63 ppm. \(^{13}C\) NMR (125 MHz; CDCl\textsubscript{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): \([\text{M+Na}]^+ \text{ calcd for C}_{15}\text{H}_{14}\text{FNNaO}, 304.0920; \text{ found, 304.0926.}\]

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

Pyrrole 12k was obtained according to GP4. The crude mixture was purified using column chromatography on SiO\textsubscript{2} (hexanes/EtOAc, 85/15) to give 12k as a pale beige solid (58%). \(^{1}H\) NMR (500 MHz; CDCl\textsubscript{3}) 2.41 (s, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 7.02 (dd, \(J = 3.5 \text{ and 0.9 Hz, 2H})\), 7.08 (dd, \(J = 5.1 \text{ and 3.6 Hz, 2H})\), 7.28 (dd, \(J = 5.1 \text{ and 1.0 Hz})\), 8.08 (br s, 1H) ppm. \(^{13}C\) NMR (125 MHz; CDCl\textsubscript{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): \([\text{M+Na}]^+ \text{ calcd for C}_{12}\text{H}_{13}\text{NNaOS}, 242.0610; \text{ 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 pyroles N-protected with 2-(trimethylsilyl)ethoxymethyl (SEM)

References and Notes


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Knorr-type pyrrole

1. hydrogenolysis
2. decarboxylative arylation
3. SEM deprotection