Regioselective Direct C–H Alkylation of NH Indoles and Pyrroles by a Palladium/Norbornene-Cocatalyzed Process

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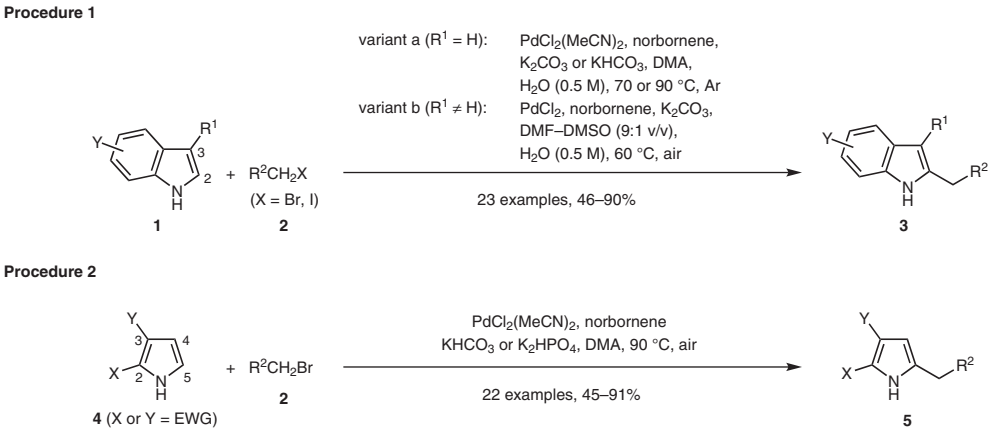
Abstract: Nitrogen-containing heterocycles, including 1*H*-indoles and electron-deficient 1*H*-pyrroles, undergo a palladium/norbornene-cocatalyzed regioselective alkylation at the C–H bond adjacent to the NH group. A primary alkyl halide is used as the electrophile and the reaction proceeds smoothly under mild conditions to give 2-alkyl-1*H*-indoles and 2-substituted or 2,3-disubstituted 5-alkyl-1*H*-pyrroles in good yields.

Key words: catalysis, alkylations, regioselectivity, heterocycles, palladium, indoles, pyrroles



Scheme 1

1 Introduction

Indoles and pyrroles are two important classes of N-heterocycles that occur widely in natural products, drugs, and biologically active molecules.[1] Alkyl-substituted indoles and pyrroles are of particular interest, because they form key structural elements of many structurally unique and biologically active natural products (Figure 1).[2] However, few methods are available for constructing such structures by direct C–H substitution. Although considerable advances have been made in the direct C–H functionalization of indoles and pyrroles,[3] the regioselective installation of an alkyl group onto these heterocyclic nuclei remains a challenge. Indoles undergo Friedel–Crafts alkylation selectively at the more electron-rich C3 position,[4] but it is difficult to achieve direct C2 alkylation.[5,6] In the case of pyrroles, Friedel–Crafts-type direct alkylation with alkyl electrophiles usually results in a mixture of regioisomers;[7] other methods for regioselective alkylation of pyrroles are either circuitous or limited in substrate scope.[8] Therefore, there remains a considerable need for efficient and regioselective methods for alkylation of indoles and pyrroles.

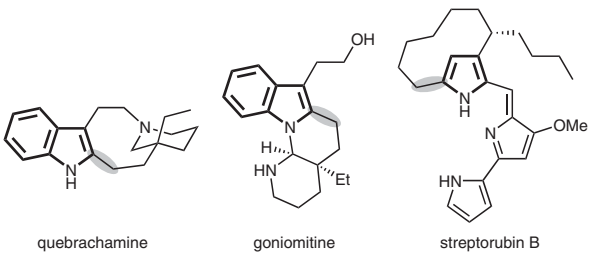


Figure 1 Natural products containing an alkylindole or alkylpyrrole structure

Inspired by the Catellani reaction,[9] we developed a palladium(II)/norbornene-cocatalyzed process that provides straightforward access to α-alkyl-substituted indole and

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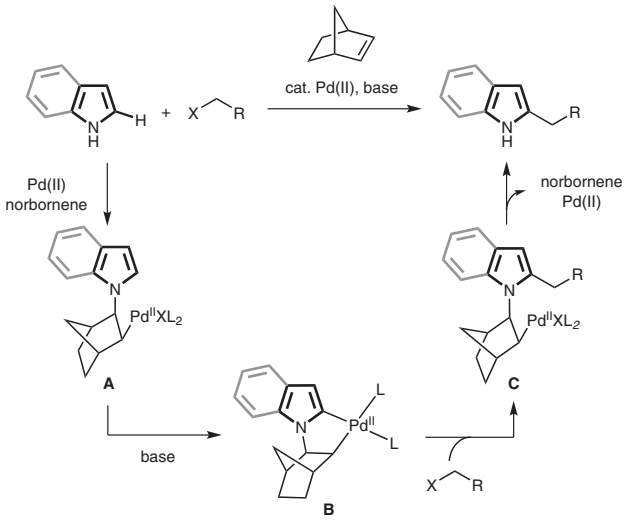
pyrrole derivatives from NH indoles[10] and pyrroles[11] (Scheme 1). In this reaction, the N-heterocycle interacts with palladium(II) and norbornene to give intermediate **A**, which then undergoes an intramolecular *ortho*-palladation to give palladaheterocycle **B** in the presence of a base (Scheme 2).[10b,11] Subsequently, intermediate **B** reacts with the alkyl halide by oxidative addition, reductive elimination, norbornene expulsion, and protodepalladation to give the alkyl-substituted heterocycle. The role of norbornene in this process is to act as a transpositional cocatalyst that assists palladium in activating the α-C–H bond of NH indoles and pyrroles, providing excellent regioselectivities for the alkylation reactions (C2-alkylation on indole and C5-alkylation on 2-substituted and 2,3-disubstituted pyrroles). This reaction adds to the toolbox of synthetic methods for direct C–H functionalization of N-heterocycles.



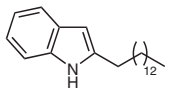
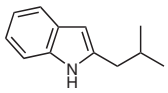
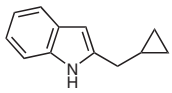
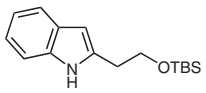
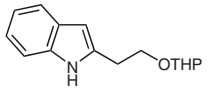
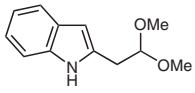
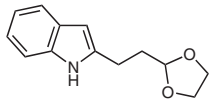
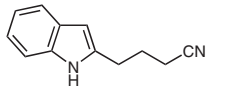
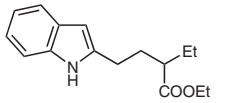
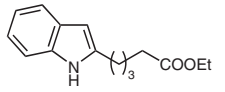
Scheme 2 The mechanism of the newly developed catalytic alkylation procedure

2 Scope and Limitations

The alkylation of 1*H*-indole (**1a**) with alkyl bromides **2a–j** proceeded smoothly with the palladium(II)/norbornene cocatalytic system to give 2-alkyl-1*H*-indoles regioselectively (Procedure 1, variant a).[10a] As shown in Table 1, a broad range of functionalized primary alkyl bromides are suitable as reaction partners. The reactions were conducted with bis(acetonitrile)dichloropalladium(II) as catalyst, norbornene as cocatalyst, and potassium carbonate as base in *N*,*N*-dimethylacetamide as solvent containing 0.5 M water as an additive. In general, the 2-alkylation products were obtained in moderate to good yields and, in certain cases, minor amounts of the 2,3-dialkyl-1*H*-indole (4–19%) were obtained as overalkylation byproducts. The steric effect of the alkyl bromide plays an important role in the alkylation reaction; primary alkyl bromides bearing a tertiary carbon center in the β-position reacted slowly (entries 2 and 6), whereas a secondary alkyl halide (2-iodopropane) failed to react. The reaction of 1*H*-indole with ethyl 3-bromopropanoate failed to give the desired alkylation product as a result of elimination of hydrobromic acid under basic conditions to form ethyl acrylate. The use of an alkyl iodide instead of the corresponding alkyl bromide accelerated the reaction, but resulted in a considerable amount of the 2,3-dialkylation byproduct. Alkyl tosylates failed to react. Therefore, both reactivity and stability should be taken into account when choosing the alkyl coupling partners in this reaction.

1*H*-Indoles bearing electron-donating or electron-withdrawing substituents were superior substrates in this 2-alkylation reaction (Procedure 1, variant a).[10a] Table 2 lists

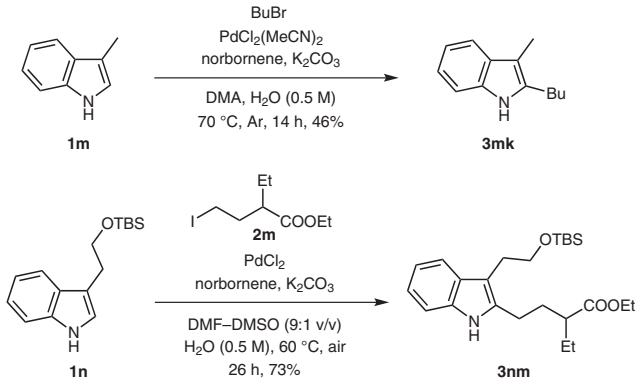
Table 1 Regioselective Direct Alkylation of 1*H*-Indole (**1a**) with Primary Alkyl Bromides **2a–j** (Scheme 1, Procedure 1a)

Entry[a]	Temp (°C)	Time (h)	Product		Yield[b] (%)
1	70	14	**3aa**		67[c]
2	90	61	**3ab**		59[c]
3	70	14	**3ac**		58[c]
4	70	14	**3ad**		82
5	70	14	**3ae**		73
6	90	20	**3af**		65
7	70	14	**3ag**		72
8	70	14	**3ah**		56[c]
9	70	19.5	**3ai**		65
10	70	14	**3aj**		66[c]

[a] Reaction conditions: indole **1** (1 mmol), primary alkyl bromide **2** (2 mmol), $PdCl_2(MeCN)_2$ (0.1 mmol), norbornene (2 mmol), K_2CO_3 (2 mmol), DMA + 0.5 M H_2O (5 mL), under argon.
[b] Yield of isolated product.
[c] A minor amount of the 2,3-dialkyl-1*H*-indole was isolated as a by-product.

some results obtained with 5-, 6-, and 7-substituted 1*H*-indoles **1b**–**k** and various primary alkyl bromides. Interestingly, electron-deficient 1*H*-indoles usually afforded better yields of the 2-alkylindole products than did electron-rich 1*H*-indoles (compare entries 1–4 with entries 5–11), but a weaker base, such as potassium bicarbonate or dipotassium hydrogen phosphate had to be used to prevent generation of undesired *N*-alkylindole byproducts. Halogen-substituted 1*H*-indoles were suitable substrates and successfully gave the corresponding halogen-substituted 2-alkyl-1*H*-indoles (for example, entries 4–8), allowing access to more-complex heterocyclic compounds through cross-coupling reactions.

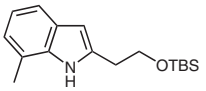
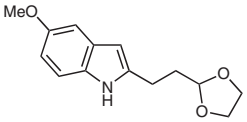
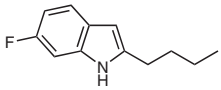
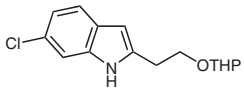
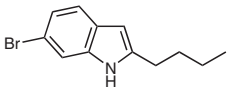
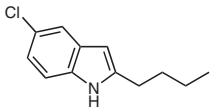
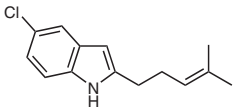
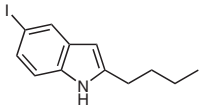
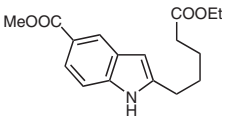
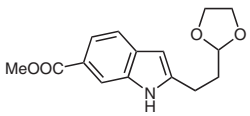
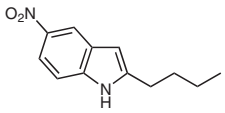
The same procedure also permits the 2-alkylation of 3-substituted 1*H*-indole derivatives (Scheme 3).[10b] The alkylation of 3-methyl-1*H*-indole (**1m**) with butyl bromide proceeded more slowly than the alkylation of 1*H*-indole and gave a moderate yield of the 2,3-dialkylated indole **3mk**. Therefore, an optimization study was conducted to improve this type of reaction, especially for more complex substrates. A modified procedure (Procedure 1, variant b) using alkyl iodide **2n** as the electrophile, palladium(II) chloride as the catalyst, and *N*,*N*-dimethylformamide–dimethyl sulfoxide as a solvent mixture in an atmosphere of air resulted in good conversion and a high yield in the 2-alkylation of tryptophol derivative **1n** (Scheme 3).



Scheme 3 Regioselective direct alkylation of 3-substituted 1*H*-indoles (Scheme 1, Procedure 1b)

Because of the structural similarity between indole and pyrrole, our palladium(II)/norbornene-cocatalyzed alkylation process can also be applied to pyrrole derivatives.[11] Interestingly, we found that the reaction worked properly only with electron-deficient pyrrole derivatives, and that it failed in the case of 1*H*-pyrrole itself and other electron-rich pyrroles. Given that the pyrrole nucleus is more electron rich and less acidic ($pK_a = 23$) than indole ($pK_a = 20.95$),[12] it is possible that electron-deficient pyrroles meet the electronic requirement of this reaction more closely. Alkyl 1*H*-pyrrole-2-carboxylates were found to be ideal substrates, and they underwent smooth 5-alkylation reactions with various primary alkyl bromides. In a slight departure from Procedure 1, these reactions were conducted by using potassium bicarbonate as a mild base in dry *N*,*N*-dimethylacetamide at 90 ºC under air (Procedure 2). Table 3 shows some typical examples of 5-alkyl-

Table 2 Regioselective Direct Alkylation of Substituted 1*H*-Indoles **1b**–**k** with Primary Alkyl Bromides **2** (Scheme 1, Procedure 1a)

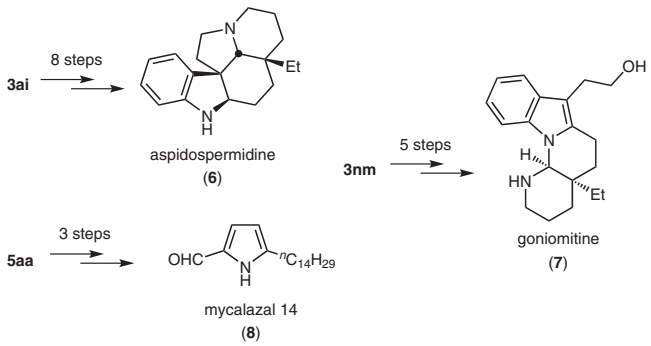
Entry[a]	Base (equiv)	Time (h)	Product		Yield[b] (%)
1	K_2CO_3 (2)	18	**3bd**		68
2	K_2CO_3 (2)	14	**3cg**		62[c]
3	K_2CO_3 (2)	20	**3dk**		59[d]
4	K_2CO_3 (2)	14	**3ee**		76
5	$KHCO_3$ (3)	15	**3fk**		74
6	$KHCO_3$ (3)	14	**3gk**		85
7	$KHCO_3$ (3)	38	**3gl**		56[e]
8[f]	$KHCO_3$ (4)	14	**3hk**		65
9	$KHCO_3$ (3)	14	**3ij**		87
10	$KHCO_3$ (3)	14	**3jg**		86
11	K_2HPO_4 (3)	17	**3kk**		90

[a] Reaction conditions: indole **1** (1 mmol), primary alkyl bromide **2** (2 mmol), $PdCl_2(MeCN)_2$ (0.1 mmol), norbornene (2 mmol), base, DMA + 0.5 M H_2O (5 mL), 70 °C, under argon.
[b] Yield of isolated product.
[c] 23% of the indole substrate was recovered.
[d] A minor amount of 2,3-dialkyl-1*H*-indole was isolated as a byproduct.
[e] 24% of the indole substrate was recovered.
[f] 4 equiv of BuBr were used.

ation reactions of pyrrole-2-carboxylates **4a**–**c**. The yields were generally good to excellent, and in all cases a single regioisomer was obtained. Although higher temperatures and longer reaction times were required for satisfactory conversion, this reaction, like the indole alkylation reaction, showed good tolerance to a range of functional groups. A limitation of this reaction is that is appears to be restricted to 1*H*-pyrrole-2-carboxylates as substrates; 2-cyano-, 2-(dimethylaminocarbonyl)-, 2-formyl-, and 2-acetyl-substituted 1*H*-pyrroles failed to give the desired products. Methyl 1*H*-pyrrole-3-carboxylate gave a mixture of 5-alkylation and 2,5-dialkylation products in low yield. Therefore, this procedure is best suited for the alkylation of alkyl 1*H*-pyrrole-2-carboxylates.

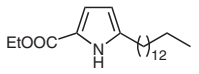
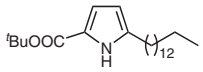
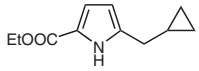
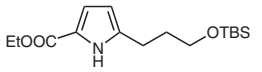
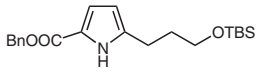
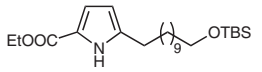
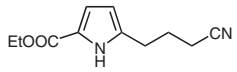
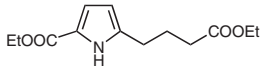
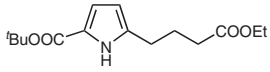
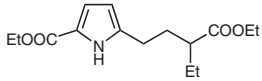
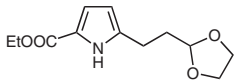
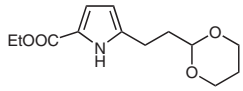
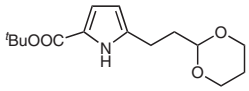
Procedure 2 can also be applied to a series of 2,3-disubstituted electron-deficient 1*H*-pyrroles **4d**–**i** (Table 4).[11] These substrates gave 5-alkylation products regioselectively, albeit in lower yields than pyrrole-2-carboxylates. Both alkoxycarbonyl and acyl groups can be used as electron-withdrawing substituents on either the C2- or the C3-position of pyrrole, although pyrrole carboxylates were found to be superior. A chlorinated pyrrole substrate **4i** underwent smooth alkylation to give the chloro-substituted alkylpyrrole **5iq** in high yield (entry 9). Because many methods have been reported for synthesizing 2,3-disubstituted electron-deficient pyrroles,[13] a combination of these methods and the present 5-alkylation procedure provides regioselective access to a range of advanced functionalized pyrrole derivatives.

The utility of the alkylation method for constructing α-alkylated N-heterocycles was showcased by its successful application in total syntheses of the *Aspidosperma* alkaloids aspidospermidine (**6**) and goniomitine (**7**)[10b] and the lipophilic pyrrole natural product mycalazal 14 (**8**).[11] In the syntheses of aspidospermidine and goniomitine, the indole alkylation protocol permitted an unprecedented synthetic strategy in which the creation of the indole C2–alkyl bonds served as key steps in building the core structures of the two natural products. The syntheses were completed via the key intermediates **3ai** and **3nm**, respectively. In the synthesis of mycalazal 14, reduction of the pyrrole 5-tetradecylation product **5aa** was carried out to afford the target molecule (Scheme 4).



Scheme 4 Natural products aspidospermidine (**6**), goniomitine (**7**), and mycalazal 14 (**8**) synthesized through regioselective direct α-alkylation of N-heterocycles

Table 3 Regioselective Direct Alkylation of Electron-Deficient 1*H*-Pyrroles **4a**–**c** with Primary Alkyl Bromides **2** (Scheme 1, Procedure 2)

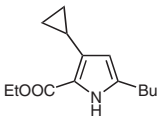
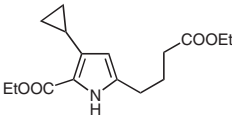
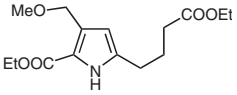
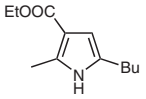
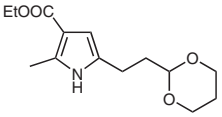
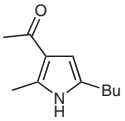
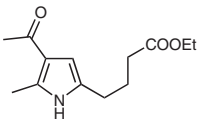
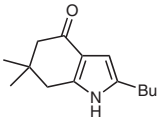
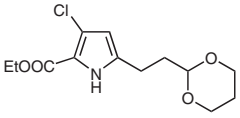
Entry[a]	Time (h)	Product		Yield[b] (%)
1	22	**5aa**		86
2	22	**5ba**		84
3	22	**5ac**		71
4[c]	22	**5an**		77
5	22	**5cn**		52
6	22	**5ao**		89
7[d]	21	**5ah**		87
8	23	**5ap**		90
9	22	**5bp**		79
10	22	**5ai**		84
11	22	**5ag**		68
12	22	**5aq**		82
13	22	**5bq**		83

[a] Reaction conditions: pyrrole **4** (1 mmol), primary alkyl bromide **2** (2 mmol), $PdCl_2(MeCN)_2$ (0.1 mmol), norbornene (2 mmol), $KHCO_3$ (3 mmol), DMA (1 mL), 90 ºC, under air.
[b] Yield of isolated product.
[c] DMA (3 mL) was used as the solvent.
[d] The reaction was conducted under 1 atm O_2 in a 9:1 v/v mixture of DMA and DMSO.

3 Summary

A straightforward and synthetically useful method for the regioselective α-alkylation of NH-indoles and pyrroles has been developed that uses a palladium(II)/norbornene cocatalytic system. The method provides a one-step transformation of easily available N-heterocycles and alkyl halides into structurally diverse alkylation products not

Table 4 Regioselective Direct Alkylation of 2,3-Disubstituted Electron-Deficient 1*H*-Pyrroles **4d–i** with Primary Alkyl Bromides **2** (Scheme 1, Procedure 2)

Entry[a]	Time (h)	Product	Yield[b] (%)
1[c]	28	**5dk** 	62
2	23	**5dp** 	70
3	22	**5ep** 	69
4[d]	23	**5fk** 	52
5	23	**5fq** 	71
6	23	**5gk** 	45
7	23	**5gp** 	47
8[d,e]	22	**5hk** 	59
9[e]	22	**5iq** 	91

[a] Reaction conditions: pyrrole **4** (1 equiv), primary alkyl bromide **2** (2 equiv), $PdCl_2(MeCN)_2$ (0.1 equiv), norbornene (2 equiv), $KHCO_3$ (3 equiv), DMA (1 mL per mmol of pyrrole substrate **4**, *c* = 1 M), 90 ºC, under air.
[b] Yield based on recovered starting material.
[c] BuBr (4 equiv) and $KHCO_3$ (5 equiv) were used.
[d] *c* = 0.2 M.
[e] K_2HPO_4 (3 equiv) as base.

readily available by conventional synthetic methods. The utility of this method was demonstrated by total syntheses of several indole- and pyrrole-based natural products.

Particulars of the reagents, substrates, and other chemicals that were used, together with analytical details, can be found in the appropriate references.[10a,b,11]

Procedures

Typical procedures for the various substrate classes shown in the schemes and in the tables are described below. Procedure 1 is subdivided into two variants (1a and 1b) that require modification of the catalyst and the solvent.

Procedure 1a (Tables 1 and 2)[10a]

A 50-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum was charged with 1*H*-indole substrate **1** (1.00 mmol), norbornene (188 mg, 2.00 mmol), the base [K_2CO_3 (276 mg, 2.00 mmol), $KHCO_3$ (300 mg, 3.00 mmol), or K_2HPO_4 (522 mg, 3.00 mmol) as indicated], and $PdCl_2(MeCN)_2$ (25.9 mg, 0.100 mmol). A 0.5 M solution of H_2O in DMA (5 mL) was added. The alkyl bromide **2** (2.00 mmol) was then added from a syringe, and the resulting mixture was degassed by three freeze–pump–thaw cycles with liquid nitrogen under high vacuum. The flask was then placed in an oil bath preheated to 70 °C or 90 °C, as indicated, and the mixture was stirred vigorously under balloon pressure of argon. Upon completion of the reaction (TLC), the mixture was cooled to r.t., diluted with Et_2O (30 mL), and filtered. The filtrate was concentrated in a rotary evaporator (60 °C water bath, 8–10 mbar) to remove the Et_2O and most of the DMA. The residue was purified directly by flash column chromatography [silica gel (dry loading)] to give the alkylation product **3**.

Analytical data for representative 2-alkyl-1*H*-indole products **3aa**, **3bd**, **3ee**, and **3ij** are provided below. Data for other products can be found in the appropriate reference.[10a]

2-Tetradecyl-1*H*-indole (3aa)

White solid; yield: 213 mg (0.679 mmol, 67%); R_f = 0.64 (pentane–Et_2O, 9:1, UV); mp 58–60 °C.

IR (ATR): 3413, 2916, 2847, 1616, 1584, 1551, 1457, 1408, 1290, 1231 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.23–1.34 (m, 20 H), 1.35–1.42 (m, 2 H), 1.71 (app quin, *J* ≈ 7.5 Hz, 2 H), 2.74 (t, *J* = 7.6 Hz, 2 H), 6.21 (br s, 1 H), 7.06 (app dt, *J* = 0.9, *J* ≈ 7.5 Hz, 1 H), 7.10 (app dt, *J* = 0.9, *J* ≈ 7.5 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.83 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.3, 22.8, 28.5, 29.3, 29.49, 29.52, 29.6, 29.7, 29.81, 29.85, 32.1, 99.6, 110.4, 119.7, 119.9, 121.1, 129.0, 136.0, 140.2.

MS (EI, 70 eV): *m/z* (%) = 313 (45) $[M^+]$, 144 (45) $[M - C_{12}H_{25}]^+$, 130 (100) $[M - C_{13}H_{27}]^+$.

HRMS (EI, 70 eV): *m/z* $[M^+]$ calcd for $C_{22}H_{35}N$: 313.2764; found: 313.2759.

7-Methyl-2-{2-[*tert*-butyl(dimethyl)siloxy]ethyl}-1*H*-indole (3bd)

Pale-yellow oil; yield: 196 mg (0.677 mmol, 68%); R_f = 0.65 (pentane–Et_2O, 9:1, UV).

IR (ATR): 3437, 2954, 2927, 2856, 1614, 1559, 1496, 1461, 1329, 1254 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.97 (s, 9 H), 2.45 (s, 3 H), 2.98 (t, *J* = 5.6 Hz, 2 H), 3.94 (t, *J* = 5.6 Hz, 2 H), 6.22 (s, 1 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 6.98 (app t, *J* ≈ 7.5 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 8.70 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –5.3, 16.9, 18.3, 26.1, 31.2, 63.3, 100.3, 117.7, 119.68, 119.70, 121.7, 127.9, 135.7, 138.3.

MS (EI, 70 eV): *m/z* (%) = 289 (21) $[M^+]$, 232 (100) $[M - C_4H_9]^+$, 158 (26) $[M - TBSO]^+$, 109 (36).

HRMS (EI, 70 eV): *m/z* $[M^+]$ calcd for $C_{17}H_{27}NOSi$: 289.1856; found: 289.1856.

6-Chloro-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-1*H*-indole (3ee)
Pale-yellow oil; yield: 212 mg (0.758 mmol, 76%); R_f = 0.29 (pentane–Et_2O, 2:1, UV).

IR (ATR): 3256, 2950, 2878, 1616, 1580, 1541, 1457, 1293, 1201 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.53–1.68 (m, 4 H), 1.75–1.81 (m, 1 H), 1.83–1.89 (m, 1 H), 3.02 (app t, *J* ≈ 5.9 Hz, 2 H), 3.48–3.53 (m, 1 H), 3.71 (app dt, *J* = 9.6, *J* ≈ 5.9 Hz, 1 H), 3.81–3.85 (m, 1 H), 4.05 (dt, *J* = 9.6, *J* ≈ 5.9 Hz, 1 H), 4.63 (dd, *J* = 4.8, 2.8 Hz, 1 H), 6.21–6.22 (m, 1 H), 7.02 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.26–7.29 (m, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 8.64 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.1, 25.4, 28.7, 31.0, 63.0, 67.3, 99.7, 100.1, 110.6, 120.2, 120.7, 126.9, 127.1, 136.5, 138.8.

MS (EI, 70 eV): *m/z* (%) = 281 (11) [M^+, ^{37}Cl], 279 (25) [M^+, ^{35}Cl], 232 (6), 195 (73), 177 (31), 164 (100), 85 (61).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{15}H_{18}{}^{35}ClNO_2$: 279.1021; found: 279.1017.

Methyl 2-(5-Ethoxy-5-oxopentyl)-1*H*-indole-5-carboxylate (3ij)
White solid; yield: 266 mg (0.877 mmol, 87%); R_f = 0.30 (pentane–Et_2O, 9:1, UV); mp 91–92 °C.

IR (ATR): 3336, 2932, 2861, 1712, 1695, 1614, 1556, 1439, 1325, 1292, 1238 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.69–1.80 (m, 4 H), 2.35 (t, *J* = 7.0 Hz, 2 H), 2.77 (t, *J* = 7.0 Hz, 2 H), 3.92 (s, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 6.31 (m, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 7.83 (dd, *J* = 8.5, 1.7 Hz, 1 H), 8.28 (m, 1 H), 8.52 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.3, 24.5, 27.9, 28.5, 34.0, 51.9, 60.5, 100.9, 110.2, 121.7, 122.7, 122.8, 128.5, 138.8, 141.0, 168.6, 173.8.

MS (EI, 70 eV): *m/z* (%) = 303 (56) [M^+], 257 (34), 201 (100), 188 (68), 170 (26), 129 (21).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{17}H_{21}NO_4$: 303.1465; found: 303.1456.

Ethyl (±)-4-[3-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-1*H*-indol-2-yl]-2-ethylbutanoate (3nm); Procedure 1b (Scheme 3)[10b]
A 250-mL round-bottom flask equipped with a magnetic stirring bar and a rubber septum was charged with indole **1n** (1.55 g, 5.63 mmol), norbornene (1.06 g, 11.3 mmol), K_2CO_3 (3.12 g, 22.6 mmol), alkyl iodide **2m** (6.11 g, 22.6 mmol), and $PdCl_2$ (100 mg, 0.564 mmol). Anhydrous DMF (25.3 mL), anhydrous DMSO (2.8 mL), and H_2O (269 mg, 14.9 mmol) were then added sequentially. The flask was placed in a preheated oil bath at 60 °C and the mixture was stirred under a balloon pressure of air for 26 h. The mixture was then cooled to r.t. and diluted with Et_2O (50 mL). H_2O was added to dissolve inorganic salts, and the resulting mixture was extracted with Et_2O (3 × 50 mL). The extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography [silica gel, pentane–Et_2O (15:1 to 5:1)] to give a pale-brown oil [yield: 1.71 g (73%); R_f = 0.49 (pentane–Et_2O, 2:1, UV)], together with recovered starting material **1n** (243 mg, 16% recovery).

IR (ATR): 3391, 2930, 2856, 1732, 1715, 1462, 1385, 1254, 1192 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.89 (t, *J* = 7.4 Hz, 3 H), 0.892 (s, 9 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.46–1.54 (m, 1 H), 1.63–1.70 (m, 1 H), 1.75 (app ddt, *J* = 12.9, 4.6 Hz, *J* ≈ 8.2 Hz, 1 H), 1.94–2.01 (m, 1 H), 2.33–2.38 (m, 1 H), 2.66 (app dt, *J* = 14.9 Hz, *J* ≈ 8.1 Hz, 1 H), 2.79 (ddd, *J* = 14.9, 8.6, 5.4 Hz, 1 H), 2.88–2.97 (m, 2 H), 3.77 (t, *J* = 7.8 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 7.06 (app dt, *J* = 1.1 Hz, *J* ≈ 7.4 Hz, 1 H), 7.11 (app dt, *J* = 1.1 Hz, *J* ≈ 7.5 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 8.16 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –5.1, 11.9, 14.5, 18.6, 24.1, 25.8, 26.2, 28.4, 32.8, 46.9, 60.6, 64.0, 108.4, 110.6, 118.3, 119.2, 121.2, 128.8, 135.4, 135.5, 176.3.

MS (EI, 70 eV): *m/z* (%) = 417 (29) [M^+], 360 (27) [$M - C_4H_9]^+$, 314 (12), 272 (100) [$M - CH_2OTBS]^+$, 240 (30), 198 (30).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{24}H_{39}NO_3Si$: 417.2694; found: 417.2691.

Procedure 2 (Tables 3 and 4)[11]
A reaction tube (30 × 190 mm) equipped with a magnetic stirring bar and a rubber septum was charged with 1*H*-pyrrole substrate **4** (1.00 mmol), norbornene (188 mg, 2.00 mmol), $KHCO_3$ (300 mg, 3.00 mmol), $PdCl_2(MeCN)_2$ (25.9 mg, 0.100 mmol), and alkyl bromide **2** (2.00 mmol). Anhydrous DMA (1 mL) was added, and the tube was heated in an aluminum block at 90 °C under a balloon pressure of air. When the reaction was complete (TLC), the mixture was cooled to r.t., diluted with Et_2O (30 mL), and filtered. The filtrate was washed with H_2O (20 mL), and the organic phase was separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layers were combined, washed with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel) to afford the alkylation product **5**.

Analytical data for representative pyrrole alkylation products **5ap**, **5fq**, and **5iq** are provided below. Data for other products can be found in the corresponding reference.[11]

Ethyl 5-(4-Ethoxy-4-oxobutyl)-1*H*-pyrrole-2-carboxylate (5ap)
Pale-yellow solid; yield: 228 mg (0.900 mmol, 90%); R_f = 0.15 (pentane–Et_2O, 3:1, UV); mp 54–56 °C.

IR (ATR): 3224, 2978, 1719, 1683, 1201 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.97 (app quin, *J* ≈ 7.4 Hz, 2 H), 2.33 (t, *J* = 7.3 Hz, 2 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 5.98 (app t, *J* ≈ 3.2 Hz, 1 H), 6.83 (dd, *J* = 3.7, 2.5 Hz, 1 H), 9.44 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.3, 14.6, 24.8, 27.1, 33.5, 60.2, 60.5, 108.5, 116.0, 121.7, 137.5, 161.5, 173.3.

MS (EI, 70 eV): *m/z* (%) = 253 (60) [M^+], 207 (35), 165 (70), 152 (100), 106 (75).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{13}H_{19}NO_4$: 253.1309; found: 253.1305.

Ethyl 5-[2-(1,3-Dioxan-2-yl)ethyl]-2-methyl-1*H*-pyrrole-3-carboxylate (5fq)
Pale-purple oil; yield: 165 mg (0.617 mmol, 61%; 71% based on recovered pyrrole substrate **4f**); R_f = 0.20 (pentane–Et_2O, 1:2, UV).

IR (ATR): 3278, 2926, 1655, 1458, 1232 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3 H), 1.34–1.38 (m, 1 H), 1.88 (dt, *J* = 5.0, 7.4 Hz, 2 H), 2.09 (app tq, *J* = 5.0 Hz, *J* ≈ 12.8 Hz, 1 H), 2.47 (s, 3 H), 2.64 (*J* = 7.4 Hz, 2 H), 3.74–3.80 (m, 2 H), 4.12 (dd, *J* = 11.7, 5.0 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.57 (t, *J* = 5.0 Hz, 1 H), 6.21 (d, *J* = 2.9 Hz, 1 H), 8.69 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.3, 14.6, 21.5, 25.8, 34.5, 59.3, 66.9, 101.5, 106.8, 111.4, 130.0, 134.4, 166.0.

MS (EI, 70 eV): *m/z* (%) = 267 (60) [M^+], 222 (33), 205 (100), 166 (49), 131 (76).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{14}H_{21}NO_4$: 267.1465; found: 267.1463.

Ethyl 3-Chloro-5-[2-(1,3-dioxan-2-yl)ethyl]-1*H*-pyrrole-2-carboxylate (5iq)

White solid; yield: 257 mg (0.893 mmol, 91%); R_f = 0.13 (pentane–EtOAc 4:1, UV); mp 93–94 °C.

IR (ATR): 3276, 2969, 1673, 1491 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.2 Hz, 3 H), 1.37–1.40 (m, 1 H), 1.92 (app q, *J* ≈ 6.3 Hz, 2 H), 2.06–2.16 (m, 1 H), 2.72 (t, *J* = 7.0 Hz, 2 H), 3.79 (app t, *J* ≈ 11.8 Hz, 2 H), 4.16 (dd, *J* = 11.6, 4.9 Hz, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 4.59 (t, *J* = 4.7 Hz, 1 H), 5.96 (d, *J* = 2.9 Hz, 1 H), 9.62 (br s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.6, 21.9, 25.8, 33.8, 60.5, 67.1, 101.0, 109.8, 117.0, 119.2, 136.6, 160.4.

MS (EI, 70 eV): *m/z* (%) = 289 (30) [M^+, ^{37}Cl], 287 (90) [M^+, ^{35}Cl], 212 (85), 140 (100), 114 (70), 101 (89).

HRMS (EI, 70 eV): *m/z* [M^+] calcd for $C_{13}H_{18}{}^{35}ClNO_4$: 287.0919; found: 287.0918.

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