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Phosphine-Free Palladium-Catalyzed Direct Bisarylation of Pyrroles with Aryl Iodides on Water

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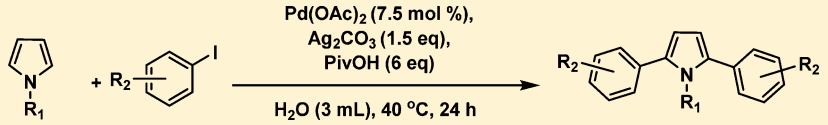
Supporting Information



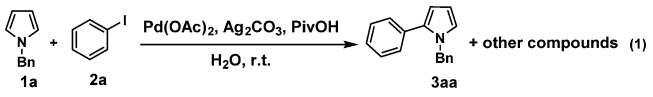
ABSTRACT: The Pd-catalyzed bisarylation of pyrroles with aryl iodides on water is described. The reaction proceeds under mild reaction conditions, i.e., relatively low temperature (40 °C) and phosphine-free.

Inspired by nature's ability to utilize C−H bonds as latent functional groups, transition metal-catalyzed selective cleavage of C−H bond, followed by its functionalization into a C-X bond, has long been studied and developed.[1] This type of direct C−H bond functionalization has become a potentially applicable and powerful class of organic transformations in organic synthesis. The application of this strategy helps in overcoming the drawbacks of stoichiometrically employed organometallic reagents, which have a relatively high price, toxicity, and sensitivity to air and moisture. Among the transition metal-catalyzed C−H arylation, Pd(0)-catalyzed C−H arylation reactions has been comprehensibly studied by several groups, especially by the groups of Doucet,[2] Fagnou,[3] and Daugulis.[4] However, most of these reactions proceed under rather harsh reaction conditions, which significantly lowers their appeal.

Since Ohta and his co-workers reported[5] the Pd-catalyzed arylation of several heteroarenes through C−H bond activation with moderate to good yields, the Pd-catalyzed direct C−H arylation of heteroarenes has been proven to be a very powerful method for the synthesis of a variety of arylated heteroarenes. Owing to the widespread applications of arylated pyrroles,[6−9] the development of new and more convenient synthetic methods is a topic of ongoing interest.[10] Recently, Gryko et al. reported[10c] the arylation of pyrroles without Pd catalyst. They found that lithium *tert*-butoxide alone could promote the arylation of pyrroles with aryl iodides and bromide. However, they used a large excess (15 equiv) of pyrroles and carried out the reaction at 145 °C. The Pd-catalyzed direct C-2 arylation of pyrroles by a C−H bond activation using aryl halides has met with great success in recent years, allowing the one-step synthesis of a wide variety of arylated pyrroles.[11] However, most of the reported studies directed on direct arylation reactions of heterocyclic compounds to deal with monoarylations.[2−4] In contrast, multiple C−H activation is rare,[12] and hence, we examined the possibility of double C−H activation reactions of different N-substituted pyrroles.

Several years ago, Greaney et al. reported[13] the first Pd-catalyzed direct arylation of thioles on water at 60 °C. To the best of our knowledge, reports on the use of water as a reaction medium in the arylation of pyrroles has not been reported. While we were attempting to establish greener reaction conditions for the Pd-catalyzed arylation of pyrroles, we discovered that a bisarylation of pyrroles can be carried out on water at 40 °C. The low temperature required implied that the reaction was highly activated on water, though the reason for this behavior is not yet clear. We report herein our preliminary results on the environmentally friendly direct bisarylation of pyrroles on water.

We expected that the reactivity of pyrroles seemed to be similar to that of its benzo analogue, indole. Therefore, we selected the reaction conditions developed for indole as the starting point of our study.[14] Initially, the reaction of N-benzylpyrrole (**1a**) with iodobenzene (**2a**) affording the C-2 arylated product, 1-benzyl-2-phenylpyrroles, (**3aa**), "on water" was chosen as the model reaction in the presence of $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1 equiv), and pivalic acid (PivOH) (1 equiv) in water (3 mL) at room temperature for 24 h (eq 1).



In the Pd-catalyzed direct arylation of pyrroles, the most reactive positions are generally the carbons C2 and C5, whereas the positions C3 and C4 exhibit a poor reactivity.[15] Thus, we expected the formation of 1-benzyl-2-phenylpyrrole (**3aa**) and/or 1-benzyl-2,5-diphenylpyrrole (**5aa**) as (a) major product(s). However, surprisingly, a mixture of regioisomers was formed, presumably due to an activation on water.[16,17] The formation of two monoarylated and four bisarylated products was confirmed by GC-MS and NMR studies. Even when 1.2 equiv iodobenzene was used, a considerable amount of bisarylated products was formed. Thus, we decided to optimize the reaction conditions for the regioselective bisarylation of pyrroles.

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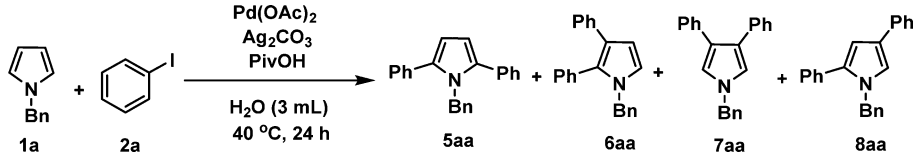
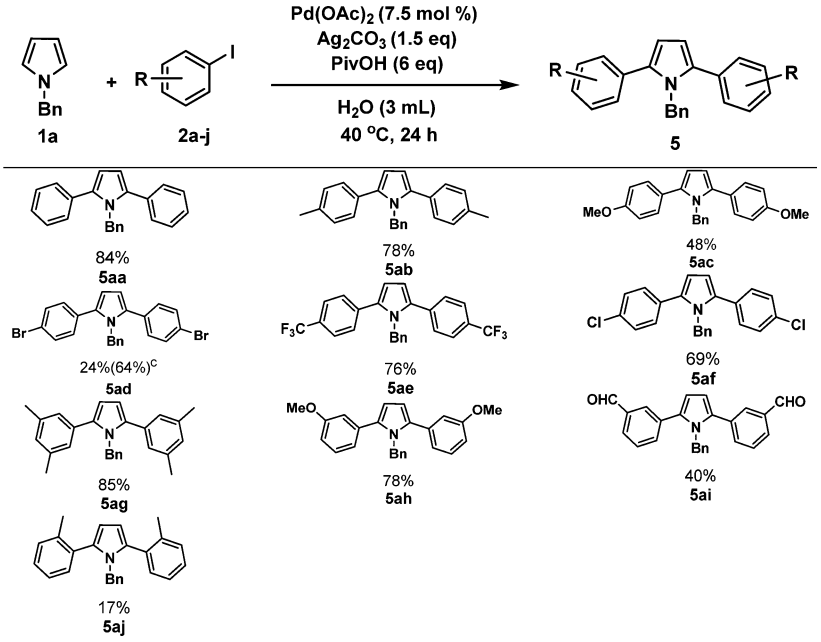
Table 1. Reaction Condition Optimization



	$Pd(OAc)_2$ (mol %)	**2a** (eq)	[Ag] (eq)	[Acid] (eq)	yield (%)[a]	selectivity[b]
1	7.5	4.5	1.5	0	1	100:0:0:0
2	7.5	4.5	1.5	1	75	53:0:28:19
3	7.5	4.5	1.5	2	60	86:0:7:7
4	7.5	4.5	1.5	4	67	91:0:4:4
5	7.5	4.5	1.5	6	87	95:0:3:2
6	5	4.5	1.5	6	42	94:2:2:2
7	3	4.5	1.5	6	24	94:0:3:3
8	0	4.5	1.5	6	N.R.	
9	7.5	4.5	1	6	72	87:0:4:9
10	7.5	4.5	0	6	0	
11	7.5	3.5	1.5	6	73	94:0:3:3
12	7.5	2.5	1.5	6	63	94:0:4:2
13[c]	7.5	4.5	1.5	6	68	88:2:4:6

[a]The total isolated yield of bisarylated pyrroles. For the yields of all compounds, see the Supporting Information. [b]The selectivies for bisarylated pyrroles based on GC analysis. For the selectivities of all compounds, see the Supporting Information. [c]The reaction was carried out at room temperature. [Ag] = Ag_2CO_3, [Acid] = PivOH.

Scheme 1. Bisarylation of 1a with Iodobenzenes



[a]General conditions: **1a** (0.5 mmol), **2a−j** (4.5 equiv), $Pd(OAc)_2$ (7.5 mol %), Ag_2CO_3 (1.5 equiv), PivOH (6 equiv) in H_2O (3 mL) at 40 °C for 24 h. [b]Isolated yield. [c]Run at 60 °C.

The amounts of PivOH, Ag_2CO_3, $Pd(OAc)_2$, and iodobenzene were screened in order to maximize the yield of **5aa** (Table 1).

We first investigated the effect of PivOH on the reaction (entries 1−5). Without PivOH, a negligible amount of a monoarylated pyrrole was formed (entry 1). As the amount of PivOH was increased, the regioselectivity and the total yield of bisarylated pyrroles (**5aa−8aa**) were increased. When 6 equiv of PivOH was used, the ratio of the bisarylated pyrroles **5aa**:**6aa**:**7aa**:**8aa** was 95:0:3:2 and their total yield was to 87% (entry 5). Thus, the optimal amount of pivalic acid used was determined to be 6 equiv. The regioselectivity and the total yield of bisarylated pyrroles were decreased with a decrease in the amount of $Pd(OAc)_2$ (entries 5−8). In the absence of $Pd(OAc)_2$, no reaction was observed (entry 8). Similarly, the regioselectivity and the total yield of the bisarylated pyrroles deteriorated with a decrease in the amount of Ag_2CO_3 (entries 5, 9, and 10). Without the silver salt, a monoarylated pyrrole was formed in only 6% yield (entry 10).These results showed that the presence of $Pd(OAc)_2$, a silver salt (Ag_2CO_3), and an acid (PivOH) was essential for the reaction. Decreasing the amount of iodobenzene used did not influence the

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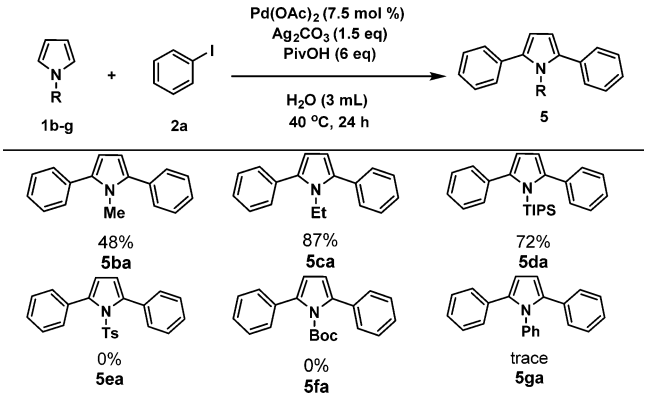
regioselectivity of the reaction, but decreased the yield of the reaction (entries 5, 11, and 12). Moreover, the regioselectivity and the yields of bisarylated pyrroles were highly temperature dependent (entries 4, 13). Therefore, the optimized reaction conditions were as follows: 1 mmol of pyrrole, 4.5 mmol of iodobenzene, 7.5 mol % $Pd(OAc)_2$, 6 mmol of PivOH, and 1.5 mol of Ag_2CO_3 in 3 mL H_2O at 40 °C. With the optimum reaction conditions in hands, we studied the effect of different Pd catalysts, such as $Pd(MeCN)_2Cl_2$ (71%; **5aa:6aa:7aa:8aa** = 96:0:2:2) and $PdCl_2$ (12%; **5aa:6aa:7aa:8aa** = 88:6:0:6), on the efficiency of the catalyst system. Then, $Pd(OAc)_2$ was chosen as the catalyst. Silver salts, such as silver acetate (AgOAc), and carboxylic acids, such as *o*-nitrobenzoic acid, have been proven to be efficient additives for the direct C-2 arylation of indoles that increase the rate of the palladation step, thus enhancing the electrophilicity of the cationic Pd species.[18] Thus, silver salts and carboxylic acids were screened (see the Supporting Information). When AgOAc or Ag_2O was used in the presence of PivOH and $Pd(OAc)_2$, both the regioselectivity and yield were diminished. When acetic acid was used in the presence of Ag_2CO_3 and $Pd(OAc)_2$, the yield of the bisarylated pyrroles was abruptly dropped to 3%. Interestingly, the use of trifluoroacetic acid (TFA) in the presence of Ag_2CO_3 and $Pd(OAc)_2$ led to the exclusive formation of **5aa** in 79% yield. However, in the case of TFA, the yield of the **5** was highly substrate dependent. $Pd(OAc)_2$ was used as a homogeneous catalyst under the optimized conditions in different organic solvents, such as DMF (no reaction), dichloromethane (52% yield), toluene (65% yield), and ethanol (15% yield). Thus, the activation of the C−H bond by the Pd catalyst system was less efficient in organic solvents than water. Interestingly, when the reaction was carried out without a solvent, the corresponding product **5aa** was formed in 72% yield.

Using the optimized reaction conditions, the substrate scope of the reaction was examined (Scheme 1). Broad functional group compatibility was observed among the substituted aryl iodides: both electron-donating (compounds **5ab**, **5ac**, **5ag**, **5ah**, and **5aj**) and electron-withdrawing substituents (compounds **5ad**, **5ae**, **5af**, and **5ai**) were tolerated. On the contrary, the reaction yields were significantly influenced by the steric effects of the iodobenzene derivatives. Thus, when 1-iodo-2-methylbenzene was used, the corresponding product was **5aj** isolated in a poor yield (17%). Interestingly, with 1-bromo-4-iodobenzene, the yield of **5ad** was highly temperature dependent. In fact, operating at 40 °C, **5ad** was isolated in 24% yield, whereas, when the reaction was carried out 60 °C, the yield dramatically increased to 64%. Iodoarenes having an acidic proton, such as 4-iodophenol and 4-iodoaniline, were not good substrates under our reaction conditions. Moreover, 1-benzyl-2,5-dimethylpyrole did not give any arylation product. This result may provide indirect evidence for the direct arylation to the 2,5-position. This method is particularly advantageous because of the large pool of commercially available aryl iodides. We also attempted to extend our arylation protocol to aryl bromides and chlorides, but the corresponding products were not formed.

Subsequently, we investigated the bisarylation of different N-substituted pyrroles with iodobenzene (Scheme 2). Pyrroles bearing an electron-donating substituent (TIPS, Et) were efficiently bisarylated. In contrast, a relatively lower yield (48%) was observed for *N*-methylpyrrole. Pyrroles containing N-electron-withdrawing groups (Ts, Boc, Ph) were not good

Scheme 2. Bisarylation of N-Substituted Pyrroles with 2a

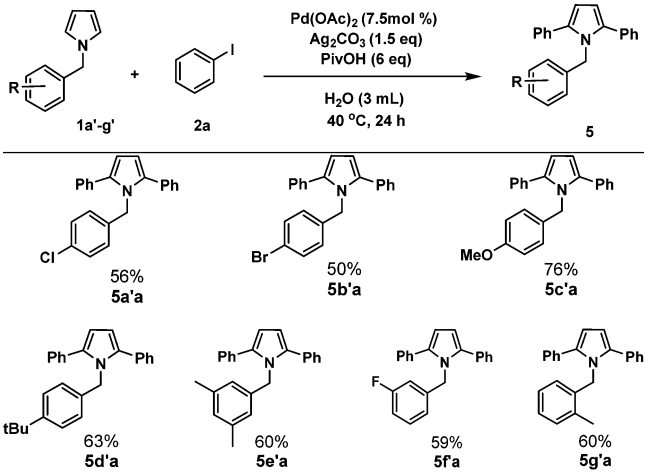


[a]General conditions: **1b−g** (0.5 mmol), **2a** (4.5 equiv), $Pd(OAc)_2$ (7.5 mol %), Ag_2CO_3 (1.5 equiv), PivOH (6 equiv) in H_2O (3 mL) at 40 °C for 24 h. [b]Isolated yield.

substrate for the bisarylation[19] and only monoarylated products were formed in poor yields (12−19%).[20] In the case of free pyrrole or indole, only decomposition products were detected under the reaction conditions.[14] These results suggest that a sufficient electron density on the pyrrole ring is necessary to facilitate substitution.[21]

Subsequently, the influence of the substituent at the benzyl group on the direct arylation was also was examined (Scheme 3). N-Benzylpyrroles were found to react smoothly

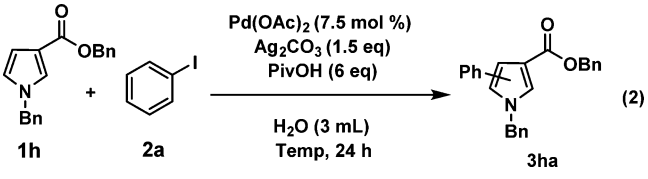
Scheme 3. Bisarylation of Substituted Benzylpyrroles with 2a



[a]General conditions: **1a′-g′** (0.5 mmol), **2a** (4.5 equiv), $Pd(OAc)_2$ (7.5 mol %), Ag_2CO_3 (1.5 equiv), PivOH (6 equiv) in H_2O (3 mL) at 40 °C for 24 h. [b]Isolated yield.

with iodobenzene to afford the corresponding bisarylated products in good yields, irrespective of the electronic or steric effect of the (a) substituent(s) on the benzene ring.

We also investigated the arylation of the pyrrole **1h** having an electron-withdrawing group at the 3-position (eq 2). Under



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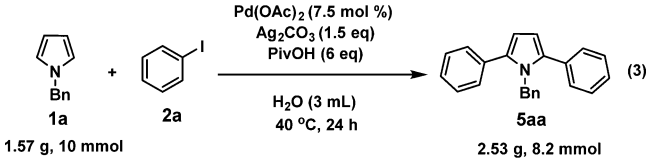
the standard reaction conditions (at 40 °C for 24 h), only monoarylated products (C-2 and C-5 adducts) were isolated in low yield (7%) with a recovery of most of the reactant. When the reaction was carried out at 60 °C, monoarylated products were isolated in 40% yield[22] (see Supporting Information).

Finally, it is worth noting that the reaction may be scaled up: the reaction of 1.57 g of N-benzylpyrrole (10 mmol) gave 2.53 g (82% yield) of **5aa** (eq 3).



Although the exact reaction pathway is not clear at this stage, our experimental observation suggests the electrophilic activation of the pyrrole C−H bonds by the Pd^{II} species as described previously by other research groups.[11c,22]

In conclusion, we have developed the first direct bis-arylation of pyrroles on water in the absence of phosphine ligand at 40 °C. The direct C−H arylation of pyrroles with aryl iodides gives 2,5-diarylpyrroles in good yields. The pyrrole arylation reaction is carried out under conditions much milder than those commonly described in the literature for pyrrole arylation. The application of this methodology to the arylation of other heteroarene molecules is currently being investigated in our laboratory.

EXPERIMENTAL SECTION

All reactions for preparation of novel compounds were conducted under nitrogen using standard Schlenk-type flasks. NMR spectra were recorded at 25 °C on 400 or 300 MHz spectrometers: ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz). ^{1}H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (0 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.16 ppm). High-resolution mass spectra were obtained using the electronic impact (EI) mode using a magnetic sector−electric sector focusing mass analyzer. GC-MS analyses were performed with a HP-5 capillary column (30 m × 0.25 mm; coating thickness 0.25 μm): analytical conditions: initial temperature, 50 °C; raising temperature, 10 °C/min; final temperature, 300 °C; He gas, pressure 7.56 psi; total flow, 53.7 mL/min. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates. The TLC plates were visualized by UV-light (254 nm). Workup procedures were done in air. Flash column chromatography was carried out on silica gel (230−400 mesh). Substrates, **1a**, **1f**, **1h**, **1a′-g′**, were prepared according to the literature procedure.[23]

1-Benzylpyrrole (1a). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.24 (m, 3 H), 7.13−7.09 (m, 2 H), 6.70−6.66 (m, 2 H), 6.20−6.16 (m, 2 H), 5.07 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.8, 127.76, 127.12, 121.3, 108.6, 53.5. HRMS (EI^+) *m*/*z*: Calcd for $C_{11}H_{11}N$: 157.0891, found: 157.0889.

1-(*tert*-Butoxycarbonyl)pyrrole (1f). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 2 H), 6.12 (s, 2 H), 1.51 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 120.0, 111.9, 83.61, 28.1. HRMS (EI^+) *m*/*z*: Calcd for $C_9H_{13}NO_2$: 167.0946, found: 167.0948.

Benzyl 1-Benzyl-1*H*-pyrrole-3-carboxylate (1h). White solid. Mp: 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 6.9 Hz, 2H), 7.37−7.27 (m, 7H), 7.10 (d, *J* = 6.6 Hz, 2H), 6.66−6.62 (m, 1H), 6.60−6.57 (m, 1H), 5.24 (s, 2H), 4.99 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 136.8, 136.7, 128.9, 128.5, 128.2, 128.1, 128.0, 127.3, 126.6, 122.2, 116.1, 110.7, 65.5, 53.9. HRMS (EI^+) *m*/*z*: Calcd for $C_{19}H_{17}NO_2$: 291.1259, found: 291.1257.

1-(4-Chlorobenzyl)pyrrole (1a′). Dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 5.0, 3.4 Hz, 2 H), 6.99−6.94 (m, 2 H), 6.61 (dd, *J* = 3.7, 1.8 Hz, 2 H), 6.18 (dt, *J* = 4.2, 2.1 Hz, 2 H), 4.93 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 133.4, 128.8, 128.3, 121.1, 108.8, 52.5. HRMS (EI^+) *m*/*z*: Calcd for $C_{11}H_{10}NCl$: 191.0502, found: 191.0501.

1-(4-Bromobenzyl)pyrrole (1b′). Dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 10.6, 4.6 Hz, 2 H), 6.81 (t, *J* = 7.3 Hz, 2 H), 6.55−6.49 (m, 2 H), 6.12−6.05 (m, 2 H), 4.83 (d, *J* = 6.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 131.8, 128.6, 121.5, 121.1, 108.8, 52.6. HRMS (EI^+) *m*/*z*: Calcd for $C_{11}H_{10}NBr$: 234.9997, found: 234.9998.

1-(4-Methoxybenzyl)pyrrole (1c′). Dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11−7.05 (m, 2 H). 6.86 (dd, *J* = 8.8, 2.3 Hz, 2 H), 6.70−6.66 (m, 2 H), 6.20−6.15 (m, 2 H), 5.00 (s, 2 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 130.3, 128.6, 121.1, 114.2, 108.5, 55.4, 52.9. HRMS (EI^+) *m*/*z*: Calcd for $C_{12}H_{13}NO$: 187.0997, found: 187.0996.

1-(4-(*tert*-Butyl)benzyl)pyrrole (1d′). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.3 Hz, 2 H), 7.07−7.03 (m, 2 H), 6.69 (d, *J* = 1.1 Hz, 2 H), 6.18 (dd, *J* = 2.1, 1.2 Hz, 2 H), 5.04 (s, 2 H), 1.31−1.29 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 135.3, 126.9, 125.8, 121.3, 108.5, 53.2, 34.7, 31.5. HRMS (EI^+) *m*/*z*: Calcd for $C_{15}H_{19}N$: 213.1517, found: 213.1516.

1-(3,5-Dimethylbenzyl)pyrrole (1e′). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1 H), 6.72 (d, *J* = 0.5 Hz, 2 H), 6.64 (t, *J* = 2.1 Hz, 2 H), 6.16 (t, *J* = 2.1 Hz, 2 H), 4.92 (s, 2 H), 2.25 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.1, 129.3, 125.0, 121.1, 108.4, 53.3, 21.3. HRMS (EI^+) *m*/*z*: Calcd for $C_{13}H_{15}N$: 185.1204, found: 185.1203.

1-(2-Fluorobenzyl)pyrrole (1f′). Dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.20 (m, 1 H), 6.92 (t, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.75 (d, *J* = 9.6 Hz, 1 H), 6.65 (d, *J* = 2.0 Hz, 2 H), 6.19 (d, *J* = 2.0 Hz, 2 H), 5.00 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, *J* = 246.6 Hz), 141.0 (d, *J* = 7.1 Hz), 130.3 (d, *J* = 8.2 Hz), 122.5 (d, *J* = 2.9 Hz), 121.2, 114.6 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.0 Hz), 108.9, 52.8, 52.8. HRMS (EI^+) *m*/*z*: Calcd for $C_{11}H_{10}NF$: 175.0797, found: 175.0797.

1-(2-methylbenzyl)pyrrole (1g′). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (m, 3 H), 6.68 (t, *J* = 7.8 Hz, 1 H), 6.48−6.43 (m, 2 H), 6.06−6.00 (m, 2 H), 4.82 (d, *J* = 4.8 Hz, 2 H), 2.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 135.8, 130.3, 127.8, 126.3, 121.1, 108.4, 51.3, 18.9. HRMS (EI^+) *m*/*z*: Calcd for $C_{12}H_{13}N$: 171.1048, found: 171.1050.

General Procedure for Palladium-Catalyzed Bisarylation of N-Substituted Pyrroles. Reactions were performed in a Schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube flask in order: 0.0375 mmol of catalyst, 2.25 mmol of iodobenzenes, 0.75 mmol of silver salt, 3 mmol of carboxylic acid, 0.5 mmol of N-benzylpyrrole, and 3 mL of water. The mixture was stirred at 40 °C for 24 h. The mixture was extracted with ethyl acetate, filtered to remove catalyst residue, and finally evaporated under reduced pressures. The mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product. Ratios of bisarylated isomers were determined by GC-MS. Compounds **3aa**,[24] **4aa**,[25] **6aa**,[26] **7aa**,[27] and **8aa**[28] were known.

1-Benzyl-2,5-diphenylpyrrole (5aa). White solid. Mp: 144 °C (0.26 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 10 H), 7.13−7.06 (m, 3 H), 6.65 (d, *J* = 7.0 Hz, 2 H), 6.36 (d, *J* = 2.5 Hz, 2 H), 5.22 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 136.9, 133.8, 129.2, 128.44, 128.40, 127.1, 126.9, 126.0, 109.8, 48.8. HRMS (EI^+) *m*/*z*: Calcd for $C_{23}H_{19}N$: 309.1517, found: 309.1514.

1-Benzyl-2,5-di-*p*-tolylpyrrole (5ab). White solid. Mp: 160 °C (0.26 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 4 H), 7.10 (t, *J* = 9.0 Hz, 7 H), 6.68 (d, *J* = 6.6 Hz, 2 H), 6.31 (s, 2 H), 5.20 (s, 2 H), 2.31 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 136.8, 136.6, 131.0, 129.12, 129.05, 128.3, 126.8, 126.0, 109.4, 48.7, 21.3. HRMS (EI^+) *m*/*z*: Calcd for $C_{25}H_{23}N$: 337.1830, found: 337.1828.

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1-Benzyl-2,5-bis(4-methoxyphenyl)pyrrole (5ac). White solid. Mp: 126 °C (0.18 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.22 (m, 4 H), 7.16−7.10 (m, 3 H), 6.84−6.81 (m, 4 H), 6.71−6.67 (m, 2 H), 6.27 (t, J = 1.9 Hz, 2 H), 5.15 (s, 2 H), 3.77−3.76 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 139.7, 135.9, 130.5, 128.4, 126.84, 126.48, 126.0, 113.8, 109.0, 55.4, 48.6. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{23}NO_2$: 369.1729, found: 369.1727.

1-Benzyl-2,5-bis(4-bromophenyl)pyrrole (5ad). White solid. Mp: 159 °C (0.11 g, 24%, 299 mg, 64% at 60 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.37 (m, 4 H), 7.21−7.10 (m, 7 H), 6.65 (d, J = 7.0 Hz, 2 H), 6.34 (d, J = 2.3 Hz, 2 H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 136.0, 132.4, 131.7, 130.5, 128.7, 127.2, 125.8, 110.4, 48.7. HRMS (EI$^+$) m/z: Calcd for $C_{23}H_{17}NBr_2$: 464.9728, found: 464.9727.

1-Benzyl-2,5-bis(4-(trifluoromethyl)phenyl)pyrrole (5ae). White solid. Mp: 136 °C (0.34 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 4 H), 7.45 (d, J = 8.3 Hz, 4 H), 7.14 (dd, J = 6.0, 4.6 Hz, 3 H), 6.67 (dd, J = 7.2, 1.8 Hz, 2 H), 6.45 (s, 2 H), 5.22 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 136.9, 136.5, 129.4, 129.0, 128.8, 127.4, 125.8, 125.4 (q, J = 3.7 Hz), 124.4, 123.0, 111.4, 49.2. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{17}F_6N$: 445.1265, found: 445.1263.

1-Benzyl-2,5-bis(4-chlorophenyl)pyrrole (5af). White solid. Mp: 137 °C (0.26 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.22 (m, 8 H), 7.14 (d, J = 6.9 Hz, 3 H), 6.65 (d, J = 6.0 Hz, 2 H), 6.33 (s, 2 H), 5.15 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 136.0, 133.2, 132.0, 130.3, 128.7, 128.6, 137.2, 125.8, 110.3, 48.8. HRMS (EI$^+$) m/z: Calcd for $C_{23}H_{17}NCl_2$: 377.0738, found: 377.0741.

1-Benzyl-2,5-bis(3,5-dimethylphenyl)pyrrole (5ag). Colorless oil (0.31 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.07 (m, 3 H), 6.95 (s, 4 H), 6.87 (s, 2 H), 6.68 (d, J = 7.6 Hz, 2 H), 6.30 (s, 2 H), 5.20 (s, 2 H), 2.24 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 137.8, 137.0, 133.7, 128.7, 128.3, 127.1, 126.7, 126.2, 109.5, 49.0, 21.4. HRMS (EI$^+$) m/z: Calcd for $C_{27}H_{27}N$: 365.2143, found: 365.2141.

1-Benzyl-2,5-bis(3-methoxyphenyl)pyrrole (5ah). Pale red oil (0.29 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.15 (m, 4 H), 7.13−7.09 (m, 1 H), 6.97−6.94 (m, 2 H), 6.87−6.85 (m, 2 H), 6.82−6.76 (m, 4 H), 6.39−6.36 (m, 2 H), 5.23 (s, 2 H), 3.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 139.9, 136.8, 134.9, 129.4, 128.5, 126.9, 126.0, 121.6, 113.9, 113.4, 109.8, 55.0, 49.0. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{23}NO_2$: 369.1729, found: 369.1727.

1-Benzyl-2,5-bis(3-benzaldehyde)pyrrole (5ai). White solid. Mp: 86 °C (0.15 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 2H), 7.85 (s, 2 H), 7.78 (d, J = 7.5 Hz, 2 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.17−7.08 (m, 3 H), 6.64 (d, J = 5.2 Hz, 2 H), 6.45 (s, 2 H), 5.24 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 138.7, 136.7, 136.2, 134.7, 134.5, 130.3, 129.3, 128.7, 128.3, 127.4, 125.8, 111.0, 49.2. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{19}NO_2$: 365.1416, found: 365.1414.

1-Benzyl-2,5-di-*o*-tolylpyrrole (5aj). Colorless oil (0.06 g, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.19 (m, 7 H), 7.16−7.13 (m, 2 H), 7.03−7.01 (m, 2 H), 6.43 (dd, J = 6.6, 1.4 Hz, 2 H), 6.20 (s, 2 H), 4.70 (s, 2 H), 2.18 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.2, 134.0, 133.6, 131.7, 130.1, 128.01, 127.98, 126.8, 126.7, 125.6, 109.0, 48.4, 20.2. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{23}N$: 337.1830, found: 337.1828.

1-Methyl-2,5-diphenylpyrrole (5ba). White solid. Mp: 200 °C (0.11 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.46 (m, 4 H), 7.42 (td, J = 7.5, 3.4 Hz, 4 H), 7.32 (d, J = 7.3 Hz, 2 H), 6.32 (s, 2 H), 3.61 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 133.7, 128.9, 128.6, 127.0, 108.8, 34.5. HRMS (EI$^+$) m/z: Calcd for $C_{17}H_{15}N$: 233.1204, found: 233.1203.

1-Ethyl-2,5-diphenypyrrole (5ca). Pale red solid. Mp: 68 °C (0.21 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.44 (m, 4 H), 7.42−7.37 (m, 4 H), 7.33−7.27 (m, 2 H), 6.29−6.24 (m, 2 H), 4.12−4.07 (m, 2 H), 0.86−0.81 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 134.2, 129.2, 129.1, 128.53, 128.51, 127.1, 109.64, 109.62, 40.0, 16.2. HRMS (EI$^+$) m/z: Calcd for $C_{18}H_{17}N$: 247.1361, found: 247.1358.

2,5-Diphenyl-1-(triisopropylsilyl)pyrrole (5da). Pale purple solid. Mp: 131 °C (0.27 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.49 (m, 4 H), 7.32 (dd, J = 7.0, 0.9 Hz, 4 H), 7.29 (s, 2 H), 6.29 (s, 2 H), 1.08−1.01 (m, 3 H), 0.92 (d, J = 7.9 Hz, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 137.5, 129.4, 129.2, 128.0, 127.8, 127.0, 115.3, 19.3, 14.9. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{33}NSi$: 375.2382, found: 375.2381.

1-(4-Chlorobenzyl)-2,5-diphenylpyrrole (5a′a). White solid. Mp: 120 °C (0.19 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.28 (m, 8 H), 7.25 (d, J = 6.8 Hz, 2 H), 7.05 (d, J = 8.4 Hz, 2 H), 6.52 (d, J = 8.3 Hz, 2 H), 6.35 (s, 2 H), 5.17 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 136.9, 133.6, 132.6, 129.1, 128.5, 127.4, 127.3, 110.1, 48.2. HRMS (EI$^+$) m/z: Calcd for $C_{23}H_{18}NCl$: 343.1128, found: 343.1125.

1-(4-Bromobenzyl)-2,5-diphenylpyrrole (5b′a). White solid. Mp: 113 °C (0.19 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.19 (m, 12 H), 6.49−6.44 (m, 2 H), 6.35−6.32 (m, 2 H), 5.15 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 136.9, 133.6, 131.5, 129.1, 128.5, 127.8, 127.3, 120.8, 110.1, 48.3. HRMS (EI$^+$) m/z: Calcd for $C_{23}H_{18}NBr$: 387.0623, found: 387.0623.

1-(4-Methoxybenzyl)-2,5-diphenyl-pyrrole (5c′a). White solid. Mp: 113 °C (0.26 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.33 (m, 4 H), 7.31−7.26 (m, 4 H), 7.25−7.19 (m, 2 H), 6.62 (d, J = 8.8 Hz, 2 H), 6.54 (d, J = 8.4 Hz, 2 H), 6.34 (d, J = 1.1 Hz, 2 H), 5.16 (s, 2 H), 3.65 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 136.8, 133.9, 131.4, 129.1, 128.4, 127.2, 127.0, 113.8, 109.8, 55.2, 48.2. HRMS (EI$^+$) m/z: Calcd for $C_{24}H_{21}NO$: 339.1623, found: 339.1624.

1-(4-(*tert*-Butyl)benzyl)-2,5-diphenylpyrrole (5d′a). White solid. Mp: 110 °C (0.23 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.33 (m, 4 H), 7.28 (t, J = 7.6 Hz, 4 H), 7.23 (d, J = 7.3 Hz, 2 H), 7.10 (d, J = 8.2 Hz, 2 H), 6.56 (d, J = 8.2 Hz, 2 H), 6.34 (s, 2 H), 5.19 (s, 2 H), 1.21 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 136.9, 136.3, 133.9, 129.2, 128.4, 127.0, 125.9, 125.2, 109.8, 48.6, 34.5, 31.4. HRMS (EI$^+$) m/z: Calcd for $C_{27}H_{27}N$: 365.2143, found: 365.2141.

1-(3,5-Dimethylbenzyl)-2,5-diphenylpyrrole (5e′a). Colorless oil (0.20 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 7.1 Hz, 4 H), 7.28 (dd, J = 11.1, 4.1 Hz, 4 H), 7.22 (d, J = 6.6 Hz, 2 H), 6.72 (s, 1 H), 6.35 (d, J = 1.8 Hz, 2 H), 6.30 (s, 2 H), 5.14 (s, 2 H), 2.13 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 137.9, 136.7, 133.9, 129.2, 128.6, 128.4, 127.0, 124.0, 109.7, 48.7, 21.4. HRMS (EI$^+$) m/z: Calcd for $C_{25}H_{23}N$: 337.1830, found: 337.1832.

1-(3-Fluorobenzyl)-2,5-diphenylpyrrole (5f′a). White solid. Mp: 110 °C (0.19 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 10 H), 7.03 (td, J = 8.0, 6.0 Hz, 1 H), 6.75 (td, J = 8.5, 2.4 Hz, 1 H), 6.40 (d, J = 7.7 Hz, 1 H), 6.36 (s, 2 H), 6.31 (d, J = 9.8 Hz, 1 H), 5.19 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (d, J = 246.0 Hz), 141.9 (d, J = 7.0 Hz), 136.9, 133.6, 129.8 (d, J = 8.3 Hz), 129.1, 128.5, 127.3, 121.6 (d, J = 2.8 Hz), 113.8 (d, J = 21.2 Hz), 113.0 (d, J = 22.2 Hz), 110.1, 48.39, 48.37. HRMS (EI$^+$) m/z: Calcd for $C_{23}H_{18}NF$: 327.1423, found: 327.1423.

1-(2-Methylbenzyl)-2,5-diphenylpyrrole (5g′a). White solid. Mp: 132 °C (0.19 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 7.1 Hz, 4 H), 7.24 (d, J = 7.8 Hz, 6 H), 7.05 (dd, J = 5.6, 3.4 Hz, 2 H), 7.00−6.97 (m, 1 H), 6.57−6.53 (m, 1 H), 6.40 (s, 2 H), 5.13 (s, 2 H), 1.99 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.5, 133.7, 133.6, 129.7, 128.9, 128.3, 127.0, 126.7, 126.3, 125.9, 109.6, 46.7, 18.8. HRMS (EI$^+$) m/z: Calcd for $C_{24}H_{21}N$: 323.1674, found: 323.1672.

Benzyl 1-Benzyl-5-phenyl-1*H*-pyrrole-3-carboxylate (3ha-1). Colorless oil (0.02 g, 6%, 0.11 g, 30% at 60 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48−7.42 (m, 3H), 7.34−7.23 (m, 11H), 7.18 (d, J = 7.4 Hz, 2H), 6.66−6.63 (m, 1H), 5.19 (s, 2H), 5.03 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.42, 137.18, 136.73, 136.47, 134.74, 129.41, 129.09, 128.48, 128.36, 128.17, 127.91, 127.86, 127.66, 127.52, 126.62, 121.69, 113.27, 65.43, 54.03. HRMS m/z: Calcd for $C_{25}H_{21}NO_2$: 367.1572, found: 367.1571.

Benzyl 1-Benzyl-2-phenyl-1*H*-pyrrole-3-carboxylate (3ha-2). Colorless oil (0.06 g, 2%, 0.04 g, 10% at 60 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42−7.27 (m, 14H), 7.01−6.96 (m, 2H), 6.70 (d, J = 1.8 Hz, 1H), 5.28 (s, 2H), 5.11 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ

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164.73, 137.47, 136.87, 132.15, 129.28, 128.97, 128.65, 128.61, 128.21, 128.07, 127.96, 127.90, 126.79, 115.86, 110.23, 65.65, 51.32. HRMS *m/z*: Calcd for $C_{25}H_{21}NO_2$: 367.1572, found: 367.1573.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00451.

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Notes

The authors declare no competing financial interest.

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