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Mild One-Pot Horner-Wadsworth-Emmons Olefination and Intramolecular *N*-arylation for the Syntheses of Indoles, All Regio-isomeric Azaindoles, and Thienopyrroles

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Abstract

The syntheses of various *N*-protected aromatic-ring fused pyrrole-2-carboxylate derivatives have been accomplished using mild one-pot Horner-Wadsworth-Emmons olefination and Cu-catalyzed intramolecular *N*-arylation reactions. The optimized mild one-pot reaction conditions of various 2-bromo arylcarboxaldehyde with commercially available *N*-protected phosphonoglycine trimethylesters gave the desired aromatic-ring fused pyrrole-2-carboxylates, such as substituted indole-, all regio-isomeric azaindole-, and thienopyrrole-2-carboxylates, in good to excellent yields. These conditions showed broad substrate compatibility, without the loss of the protecting group.

Keywords

One-pot; Indole; Azaindole; Thienopyrrole; Copper; *N*-arylation; Horner-Wadsworth-Emmons

Introduction

Pyrrole is a prototypical 5-membered heterocycle, and methods for pyrrole syntheses and its' reactivity patterns are well established.[1,2] Representative pyrrole-ring syntheses are the Paal-Knorr synthesis,[2a] Hantzsch synthesis,[2b] and Kenner synthesis,[2c] as well as recent examples that utilize metal-catalyzed coupling reactions.[2d] Pyrrole fused-heterocycles such as indoles and azaindoles are also crucial targets requiring the development of efficient synthetic methods for various purposes.[1,3] Among these compounds, fused pyrrole-2-carboxylates are one of the most versatile precursors for the construction of more complex natural products and medicinally important molecules. The synthesis of porphobilinogen from 6-azaindole,[4a] the potent anti-cancer agent CC-1065 from pyrrolo-indole,[4b] duocarmycin A from indole,[4c] and other novel compounds with high potency are a few representative examples (Figure 1).[5] Moreover, in recent efforts to develop new materials for varying applications, such as semiconductors, glucose sensors, and fluorescence-emitting dyes, pyrrole has become an indispensable structural unit.[6]

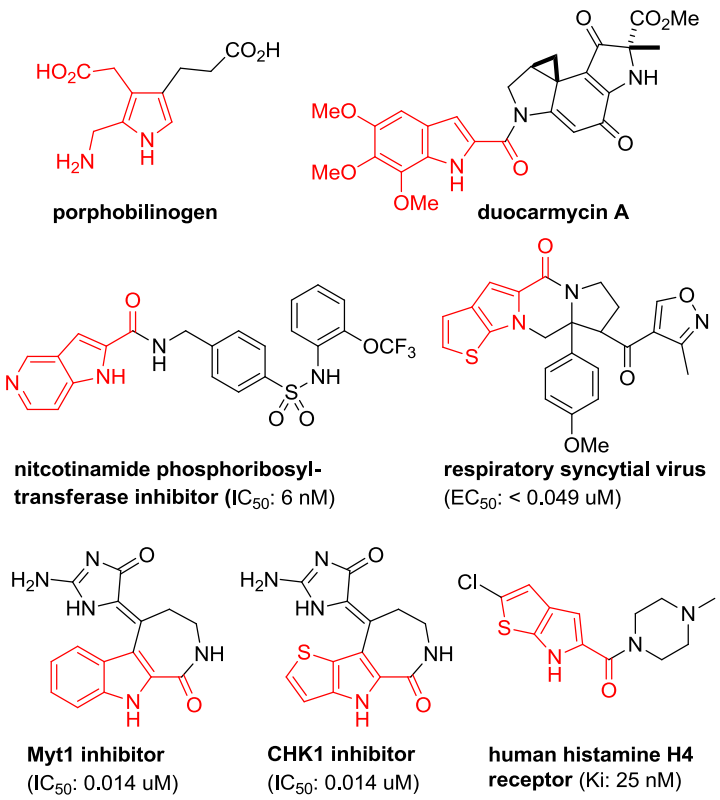


Figure 1: Pyrrole-2-carboxylate Containing Natural Products and Drugs.

For the synthesis of pyrrole-fused heterocycles, recent efforts have focused on developing methods for the preparation of diverse substituted pyrrole-fused heterocycles under mild conditions using straightforward procedures without any special equipment. Among them, a strategy based on the metal-catalyzed intramolecular *N*-arylation[7] of 1-alkyl substituted 2-haloarenes, initially reported by Buchwald and his coworkers,[8a] is one of the most promising tactics to achieve these goals.[4c,8] There are many studies related to the metal-catalyzed intramolecular N-arylation for the syntheses of various heterocycles, and some results for the formation of indoles are summarized in Figure 2.

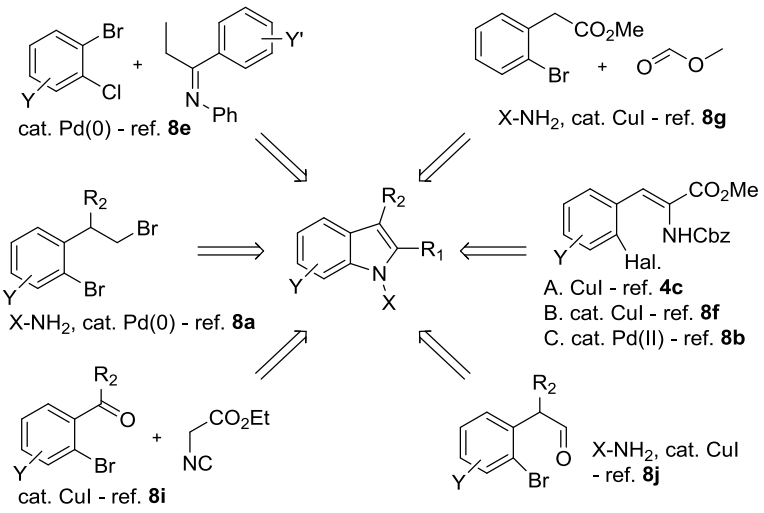


Figure 2: Reported Synthetic Approaches *via* a Metal-Catalyzed Intramolecular *N*-Arylation.

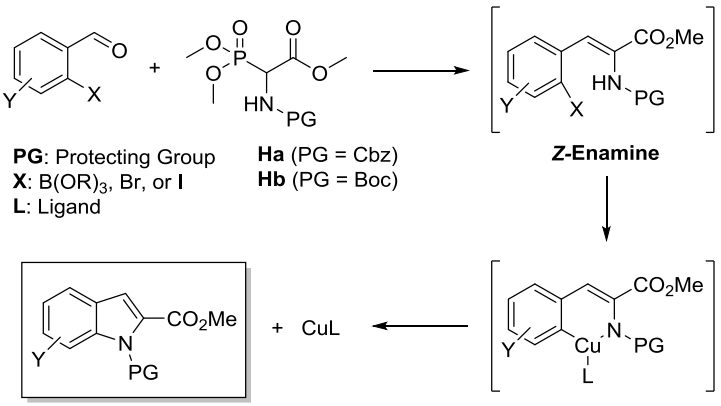
The reported methods clearly show the utility of this concept for the preparation of various indole derivatives, and they primarily involve stepwise formation of C-C or C-N bonds and then *N*-arylation sequences. In a few cases, tandem processes were successful for constructing the rings.[8i] Although the reported methods are valuable for each purpose, they generally rely on reaction conditions involving strong bases and/or elevated temperatures, which makes them less likely to be applicable for the synthesis of various substituted pyrrole-based heterocycles. Due to these reasons, there are quite few methods that can be applied for the syntheses of indoles and all regio-isomeric azaindoles. To the best of our knowledge, only two synthetic methods, using Larock's heteroannulation[9] and Hegedus-Mori-Heck reaction, [10] can successfully make all regio-isomeric azaindoles. Therefore, it is necessary to develop more efficient, mild, and user-friendly methods with broad substrate tolerance to access diverse pyrrole-fused heterocycles for substituted indoles and all regio-isomeric azaindoles.

In the course of our drug discovery program, we became interested in developing an efficient method to prepare substituted indole-2-carboxylate derivatives. Of the syntheses based on metal-catalyzed cyclizations, reports related to the stepwise syntheses of substituted

indole-2-carboxylates attracted our attention, because of the potential for the current sequential approaches to be modified into cascade processes.[4c,8b,8f] In previous reports, a C=C bond was formed through the Horner-Wadsworth-Emmons olefination[11] of 2-bromo benzaldehydes with *N*-Cbz phosphonoglycine trimethyl ester, and the resulting enamines were cyclized to indoles using Pd- or Cu-catalyzed reactions. Although these results partially solved the issues related to the harsh conditions previously employed, these sequential strategies not only are time-consuming but also suffered from uncontrollable deprotection of the *N*-Cbz group.[8f] Thus, they were only applicable to a narrow scope of substrates as a result of the necessity of a strong base and/or a high reaction temperature.[8] Therefore, a mild, straightforward, versatile single-step reaction for the synthesis of diverse pyrrole-fused heterocycles is necessary.

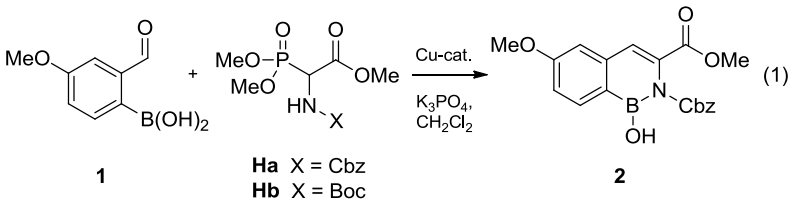
Results and Discussion

Among previously reported methods for a C=C double bond formation, we thought that the Horner-Wadsworth-Emmons olefination[11] using commercial reagents could be an optimal choice for the one-pot reaction for the synthesis of various aromatic ring-fused pyrroles including indoles and azaindoles, due to mild reaction conditions and exceptional selectivity to *Z*-alkenes, which is essential for the subsequent cyclization (Scheme 1).



Scheme 1: General Scheme of One-pot Horner-Wadsworth-Emmons Olefination and Intramolecular *N*-arylation Reactions.

We began our investigation with the coupling reaction of commercially available *N*-Cbz protected phosphonoglycine trimethylester with benzaldehydes possessing a boronic acid group at the 2-position for a subsequent metal-catalyzed intramolecular *N*-arylation. In general, Cu-catalyzed intermolecular *N*-arylations using arylboronic acids occurred under milder conditions than those using aryl-halides.[7a] However, an unusual cyclized compound was obtained when 2-formyl phenylboronic acid **1** was reacted with *N*-Cbz phosphonoglycine trimethyl ester (**Ha**) under Cu-catalyzed reaction conditions that were reported for the reaction of arylboronic acids with amines (Eq. 1).[12] With the 2-iodo substituted substrate, similar intramolecular *N*-arylations *via* known Cu- or Pd-catalyzed *N*-arylation conditions were not successful, according to a previous report by Taylor and Schriber.[8h]

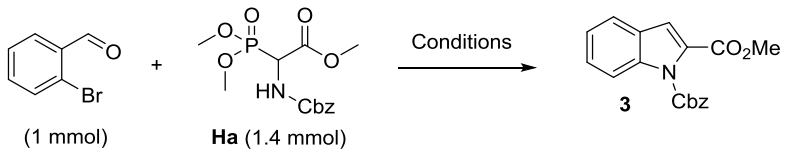


1 **Ha** X = Cbz **Hb** X = Boc **2**

Therefore, we began our research using 2-bromobenzaldehyde and Cbz-protected phosphonoglycine trimethyl ester (**Ha**). Pd(0)-catalyzed reaction gave a complex mixture of products (entry 1, Table 1). $Cu(OAc)_2$-mediated conditions gave only the enamine intermediate **A** in good yield (entry 2. Table 1).[13] Additionally, Fukuyama's stoichiometric CuI/CsOAc mediated conditions[4c] and catalytic CuI/*L*-proline conditions[8f] did not result in cyclization of the enamine (entries 3-4, Table 1). Buchwald's diamine ligand-based conditions[14] (entries 5-7, Table 1) showed better results, but the yields still needed to be further improved. When the metal (0.4 eq.), 2,2'-bipyridine (bipy, 0.4 eq.), and K_3PO_4 (6.0 eq.) were utilized in CH_2Cl_2, two substrates underwent smooth coupling to provide the

corresponding indole-2-carboxylates in decent yields at room temperature (entry 8, Table 1). The effects of a base and a solvent during the cyclization step were quite significant, and a large excess amount of K_3PO_4 (6.0 eq.) in CH_2Cl_2 afforded better results within shorter reaction time (entries 8, 9, and 11, Table 1). Unfortunately, lowering the amount of the catalyst below 0.4 eq. did not give full conversions, even after 24 h (entry 10, Table 1).

Table 1: Optimization of the One-pot Synthesis Using 2-Bromobenzaldehyde.



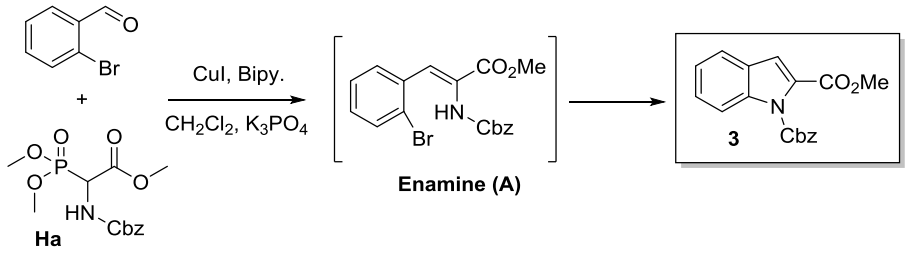
(1 mmol) **Ha** (1.4 mmol)

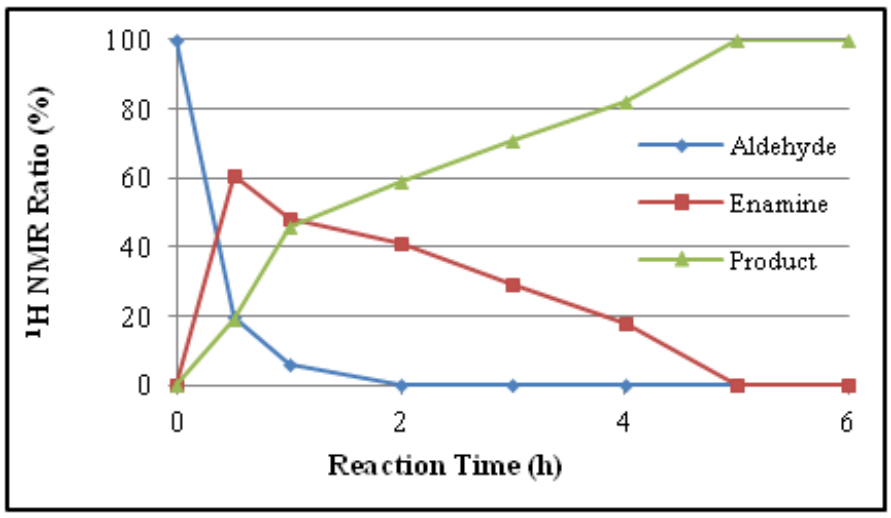
Entry	Conditions[a]	Ligand[b]	Indole **3** (**A**) (%)[c]
1	$Pd(PPh_3)_4$ (0.1 eq.), DMF, DIPEA(3.0 eq.)[f]	-	16 (-)[c]
2	$Cu(OAc)_2$ (2.0 eq.), Py. K_2CO_3 (2.0 eq.)	-	- (79)
3	CuI (0.2 eq.), DMSO, CsOAc (3.0 eq.)	-	11 (62)
4	CuI (0.4 eq.), Tol. K_3PO_4 (3.0 eq.)	*L*-Proline	9 (55)
5	CuI (0.4 eq.), Tol. K_3PO_4 (3.0 eq.)	*N*,*N*-Dimethyl ethylenediamine	43 (29)
6	CuI (0.4 eq.), Tol. K_3PO_4 (3.0 eq.)		34 (31)
7[f]	CuI (0.4 eq.), Tol. K_3PO_4 (3.0 eq.)[g]		52 (-)[d]
8	CuI (0.4 eq.), CH_2Cl_2 K_3PO_4 (3.0 eq.)	2,2′-Bipyridyl (Bipy.)	68 (-)
9	**CuI (0.4 eq.), CH_2Cl_2 K_3PO_4 (6.0 eq.)**		**71 (-)**
10	CuI (0.2 eq.), CH_2Cl_2 K_3PO_4 (6.0 eq.)		45 (-)[e]
11	CuI (0.4 eq.), Tol. K_3PO_4 (3.0 eq.)		29 (39)

[a]Performed at rt for 12 h.; [b]40 mol% of a ligand was used.; [c]Large amount of inseparable complex mixture was obtained.; [d]15 % of Cbz-deperotected indole-2-carboxylate was obtained.; [e]22 % of the enamine A was still remained after 24 h.; [f]Reacted at 100 °C for 12 h.; Reacted at 100 °C for 2 h.

To understand the order of the one-pot reaction, we checked the reaction over time by ^{1}H NMR spectroscopy using the condition of entry 9 in Table 1 (Graph 1). The initial

formation of the enamine **A** occurred within an hour, and cyclization then occurred. Overall the one-pot reaction completed within 6 h even at room temperature, and prolonged reaction did not lower the yield of the reaction through deprotection of *N*-Cbz group, which has been a major concern in previous Cu- and Pd-catalyzed stepwise syntheses.





Graph 1: Profile of the One-pot Reaction.

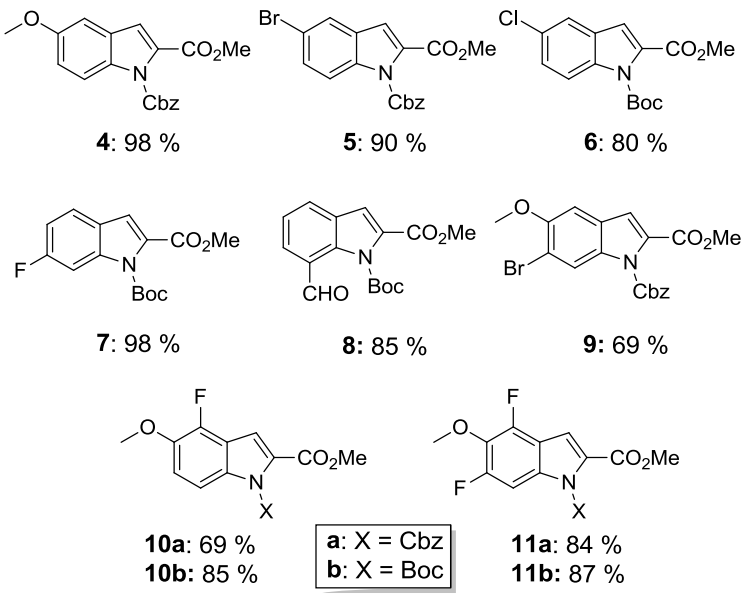


Figure 3: Mild One-pot Reaction Products of Substituted *Ortho*-Bromobenzaldehydes.

Using the optimal conditions (entry 9, Table 1), substituted 2-bromobenzaldehydes were tested. Regardless of the electronic properties of the substituents (halogens (**5**-**7**) vs methoxy (**4**)), the reactions gave the desired compounds in good to excellent yields (Figure 3). However, most of the reactions needed longer reaction times (12 h) than unsubstituted 2-bromobenzaldehyde for full conversions. Both commercially available Boc- and Cbz-protected phosphonoglycine trimethylesters (**Ha-b**) gave indole-2-carboxylates, and protection with the Boc group provided slightly better yields of the products in these substrates (**10a** *vs* **10b** & **11a** *vs* **11b**). When 2-bromo-4-fluorobenzaldehyde and 2-bromo-4,6-difluorobenzaldehyde were utilized as starting materials, the reaction was slower, and a longer reaction time was required (24 h, **10a-b** & **11a-b**). Notably, these reaction conditions were specific for the bromine next to the carboxaldehyde (**5** & **9**). Previously, 7-formyl indole-2-carboxylates were prepared through 4-step syntheses based on Hemtsberger-Knittel's approach[15] in 14 % overall yields using azidoacetate.[16a] Additionally, Friedel-Crafts acylation of indole-2-carboxylate gave the 7-formyl compound as a mixture of regio-isomers in a low yield.[16b] With our mild one-pot reaction using commercially available 2-

bromo-isophthaldehyde, the 7-formyl-substituted product **8** was efficiently prepared in excellent yields. Moreover, multiple substitutions at the 4 and 5 positions (**10a-b**), the 5 and 6 positions (**9**), and even 4, 5, and 6 positions (**11a-b**) were successfully synthesized. To further utilize the cyclized product **10a** for our medicinal project, 10 g-scale synthesis was performed. The desired product **10a** (9.2 g, 60 %) was obtained as an off-white solid, and most of the bipy ligand (2.4 g, 89 %) was recovered by acid-base work-up after the reaction.

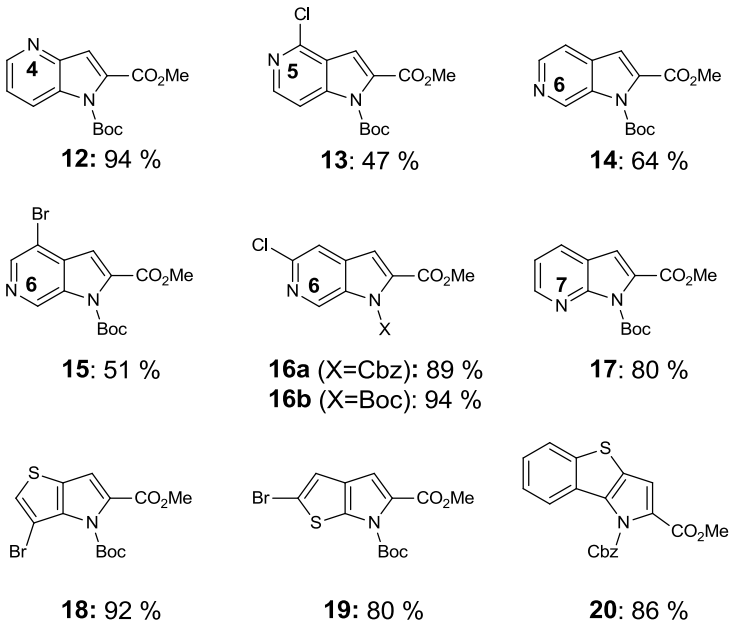


Figure 4: Mild One-pot Reaction Products of heterocyclic substrates.

Next, we applied our method to *ortho*-bromopyridine carboxaldehyde derivatives for the synthesis of various azaindoles, which is one of the most promising templates for the development of various enzyme inhibitors including kinase inhibitors for treatment of various human diseases.[1,17] Previously, azaindole-2-carboxylate derivatives were primarily prepared using the Hemtsberger-Knittel synthesis, which is a stepwise synthesis and not amenable for 6- and 7-azaindoles.[18] Our exceptionally mild Cu-bipy conditions gave four types of azaindole-2-carboxylates in good to excellent yields without the loss of the *N*-Boc group, and additional halogen groups in the substrates remained intact (Figure 4). According to a

previous report, Cu/*L*-proline conditions gave only deprotected pyrrolo[2,3-*c*]pyridines.[8f] Using the optimized Cu/bipy conditions, the 4-azaindole **12** was obtained from 3-bromopyridine-2-carboxaldehyde in an excellent yield. For the 5-azaindole, 2-chloro substituted 4-bromopyridine-3-carboxylate was applied, and 5-azaindole **13** was obtained in lower yield. Substituted 6-azaindoles **14-16** were also prepared from their corresponding pyridines. Preparation of the 7-isomer **17** using 2-bromo pyridine-3-carboxaldehyde completed the series, demonstrating that *practically all 4- to 7-azaindoles with substitutions can be prepared using this method.* In addition, 3,4-Dibromo thiophene-2-carboxaldehyde and 2,5-dibromo thiophene-3-carboxaldehyde were smoothly converted into 4-bromo thieno[3,2-*b*]pyrrole compound **18** and 2-bromothieno- [2,3-*b*]pyrrole **19**, respectively. Moreover, tricyclic 1*H*-benzo[4,5]-thieno[3,2-*b*]pyrrole-2-carboxylate **20** was easily prepared by the same condition. Two of the crystalline products **16a** (CCDC 1031291) and **20** (CCDC 1031292) were unequivocally confirmed by X-ray crystallographic analysis (Figure 5).

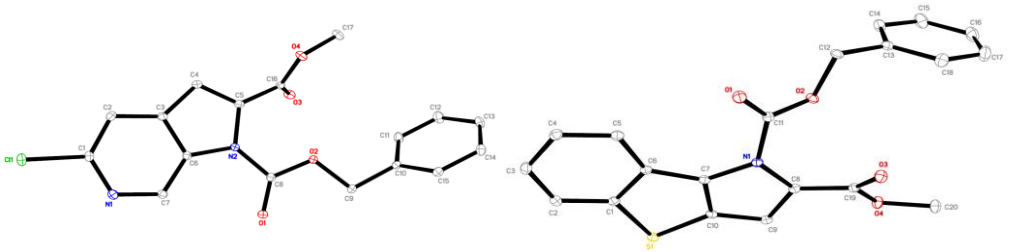


Figure 5: X-ray Structures of **16a** and **20**.

Conclusion

Overall, we have shown that various aromatic-ring fused pyrrole-2-carboxylates can be synthesized via one-pot Horner-Wadsworth-Emmons olefination and intramolecular *N*-arylation reactions under exceptionally mild conditions. Diverse *N*-protected indole-2-carboxylates containing mono to tri-substitutions at the 4- to 7- positions were easily prepared using commercially available reagents. Especially notable is that, these conditions were

applicable for the preparation of all regio-isomeric azaindole-2-carboxylate derivatives that could be useful templates for various medicinal projects. Additionally, thiophene- and benzothiophene-linked pyrroles were successfully obtained in good yields. Further applications of these compounds in our drug discovery programs will be reported in due course.

Experimental Section

In an oven-dried flask, starting aldehyde (1.0 mmol), *N*-Cbz or *N*-Boc-2-phosphonoglycine trimethyl ester (1.4 mmol, 1.4 eq.), CuI (0.4 mmol, 40 mol%), 2,2'-bipyridine (0.4 mmol, 40 mol%) and K_3PO_4 (6.0 mmol, 600 mol%) were dissolved in dry CH_2Cl_2 (5 ml). The resulting mixture was stirred at rt for 6~24 h. After the reaction was completed, the mixture was filtered through a celite pad and evaporated. The residue was diluted with EtOAc (10 mL) then washed with 0.1 N HCl (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by column chromatography and analyzed by LCMS and NMR.

Synthesis of borazaaromatic compound 2

N-Cbz-2-phosphonoglycine trimethyl ester (0.23 g, 0.70 mmol) and (2-formyl-4-methoxyphenyl)boronic acid (90 mg, 0.50 mmol) were reacted using the same condition in the general procedure. Unexpected borazaaromatic compound **2** was obtained as colorless oil (0.105 g, 57 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.08-8.05 (d, *J* = 9.0 Hz, 1H, Ar), 7.66 (s, 1H, Ar), 7.38 (s, 5H, Ar), 7.05-7.02 (d, *J* = 9.0 Hz, 1H, Ar), 6.92-6.90 (d, *J* = 6.0 Hz, 2H, Ar), 5.26 (s, 2H, -**CH$_2$**(C_6H_5)), 3.87 (s, 3H, -CO_2**CH$_3$**), 3.55 (s, 3H, -O**CH$_3$**); ^{13}C NMR δ ($CDCl_3$) : 165.28, 162.87, 156.93, 140.89, 134.88, 134.16, 130.08, 128.87, 128.80, 128.70, 118.74,

115.73, 111.40, 69.59, 55.28, 52.23; HRMS (EI) m/z: [M^+] Calcd' for $C_{19}H_{18}BNO_6$ 367.1227; found 367.1201.

Synthesis of 1-benzyl 2-methyl 1*H*-indole-1,2-dicarboxylate (3)

Colorless oil (0.109 g, 70 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.09-8.06 (d, *J* = 9.0 Hz, 1H, Ar), 7.59-7.56 (d, *J* = 9.0 Hz, 1H, Ar), 7.46-7.34 (m, 6H, Ar), 7.27-7.22 (t, *J* = 7.5 Hz, 1H, Ar), 7.11 (s, 1H, Ar), 5.40 (s, 2H, -$\mathbf{CH_2}$(C_6H_5)), 3.71 (s, 3H, -$CO_2\mathbf{CH_3}$); ^{13}C NMR δ ($CDCl_3$) : 162.21, 150.72, 137.66, 134.52, 130.37, 128.83, 128.78, 128.72, 127.67, 127.12, 123.69, 122.29, 115.69, 115.07, 69.69, 52.33; LCMS (ESI) 310.2 ($M+H^+$; calc' for $C_{18}H_{16}NO_4$ 310.1).

Synthesis of 1-benzyl 2-methyl 5-methoxy-1*H*-indole-1,2-dicarboxylate (4)

Colorless oil (0.167 g, 98 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.98-7.95 (d, *J* = 9.0 Hz, 1H, Ar), 7.47-7.36 (m, 5H, Ar), 7.04-7.01 (m, 3H, Ar), 5.40 (s, 2H, -$\mathbf{CH_2}$(C_6H_5)), 3.84 (s, 1H, -$CO_2\mathbf{CH_3}$), 3.72 (s, 1H, -O$\mathbf{CH_3}$); ^{13}C NMR δ ($CDCl_3$) : 162.21, 156.48, 150.66, 134.53, 132.37, 130.84, 128.80, 128.74, 128.70, 128.41, 116.52, 115.98, 115.42, 103.90, 69.58, 55.67, 52.30; HRMS (EI) m/z: [M^+] Calcd' for $C_{19}H_{17}NO_5$ 339.1107; found 339.1105.

Synthesis of 1-benzyl 2-methyl 5-bromo-1*H*-indole-1,2-dicarboxylate (5)

White solid (0.175 g, 90 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.98-7.95 (d, *J* = 9.0 Hz, 1H, Ar), 7.74 (s, 1H, Ar), 7.51-7.48 (d, *J* = 9.0 Hz, 1H, Ar), 7.45-7.39 (m, 5H, Ar), 7.04 (s, 1H, Ar), 5.41 (s, 2H, -$\mathbf{CH_2}$(C_6H_5)), 3.72 (s, 3H, -$CO_2\mathbf{CH_3}$); ^{13}C NMR δ ($CDCl_3$) : 159.23, 147.73, 133.58, 131.62, 128.80, 127.33, 126.72, 126.37, 126.24, 126.17, 122.14, 114.33, 114.00, 111.55, 67.37, 49.86; HRMS (EI) m/z: [M^+] Calcd' for $C_{18}H_{14}BrNO_4$ 387.0106; found 387.0106.

Synthesis of 1-benzyl 2-methyl 5-chloro-1*H*-indole-1,2-dicarboxylate (6)

White solid (0.124, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.04-8.01 (d, *J* = 9.0 Hz, 1H, Ar), 7.56 (s, 1H, Ar), 7.37-7.34 (d, *J* = 9.0 Hz, 1H, Ar), 7.00 (s, 1H, Ar), 3.92 (s, 3H, -CO_2**CH_3**), 1.62 (s, 9H, -C(**CH_3**)**$_3$**); ^{13}C NMR δ ($CDCl_3$) : 161.99, 148.85, 136.00, 131.55, 128.91, 128.56, 126.97, 121.47, 116.05, 113.49, 85.09, 52.44, 27.77.; HRMS (EI) m/z: [M^+] Calcd' for $C_{15}H_{16}ClNO_4$ 309.0768; found 309.0764.

Synthesis of 1-*tert*-butyl 2-methyl 6-fluoro-1*H*-indole-1,2-dicarboxylate (7)

White solid (0.145 g, 98 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.83-7.79 (d, *J* = 12.0 Hz, 1H, Ar), 7.55-7.50 (dd, *J* = 6.0 Hz, 1H, Ar), 7.07 (s, 1H, Ar), 7.05-6.98 (dt, *J* = 3.0 Hz, 1H, Ar), 3.91 (s, 3H, -CO_2**CH_3**), 1.62 (s, 9H, -C(**CH_3**)**$_3$**); ^{13}C NMR δ ($CDCl_3$) : 163.94, 161.94, 160.71, 148.97, 138.38, 138.21, 130.81, 123.74, 123.18, 123.04, 114.68, 112.25, 111.92, 102.30, 101.92, 85.03, 52.31, 27.77; HRMS (EI) m/z: [M^+] Calcd' for $C_{15}H_{16}FNO_4$ 293.1063; found 293.1057.

Synthesis of 1-*tert*-butyl 2-methyl 7-formyl-1*H*-indole-1,2-dicarboxylate (8)

Yellow oil (0.130 g, 85 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 10.42 (s, 1H, CHO), 7.88-7.83 (t, *J* = 7.5 Hz, 2H, Ar), 7.42-7.37 (t, *J* = 7.5 Hz, 1H, Ar), 7.25 (s, 1H, Ar), 3.94 (s, 3H, -CO_2**CH_3**), 1.62 (s, 9H, -C(**CH_3**)**$_3$**); ^{13}C NMR δ ($CDCl_3$) : 189.71, 161.56, 149.78, 135.29, 131.83, 129.38, 128.98, 127.84, 124.91, 123.12, 114.50, 86.23, 52.39, 27.62; HRMS (EI) m/z: [M^+] Calcd' for $C_{16}H_{17}NO_5$ 303.1107; found 303.1075.

Synthesis of 1-benzyl 2-methyl 6-bromo-5-methoxy-1*H*-indole-1,2-dicarboxylate (9)

White solid (0.145 g, 69 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.34 (s, 1H, Ar), 7.47-7.39 (m, 5H, Ar), 7.03 (s, 1H, Ar), 7.02 (s, 1H, Ar), 5.41 (s, 2H, -**CH_2**(C_6H_5)), 3.93 (s, 3H, -CO_2**CH_3**), 3.72 (s, 3H, -O**CH_3**); ^{13}C NMR δ ($CDCl_3$) : 161.93, 152.78, 150,32, 134.30, 132.25, 130.94,

128.93, 128.82, 128.76, 127.49, 119.91, 115.00, 112.48, 103.28, 69.87, 56.54, 52.41; HRMS (EI) m/z: [M^+] Calcd' for $C_{19}H_{16}NO_5$ 417.0212; found : 417.0223.

Synthesis of 1-benzyl 2-methyl 4-fluoro-5-methoxy-1*H*-indole-1,2-dicarboxylate (10a)

Off-white solid (0.124 g, 69 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.79-7.76 (d, *J* = 9.0 Hz, 1H, Ar), 7.46-4.39 (m, 5H, Ar), 7.16 (s, 1H, Ar), 7.13-7.08 (t, *J* = 7.5 Hz, 1H, Ar), 5.40 (s, 2H, -**CH$_2$**(C_6H_5)), 3.93 (s, 3H, -CO_2**CH$_3$**), 3.72 (s, 3H, -O**CH$_3$**); ^{13}C NMR δ ($CDCl_3$) : 161.77, 150.54, 146.35, 144.36, 142.87, 142.80, 134.30, 133.23, 133.18, 131.22, 128.91, 128.80, 128.74, 118.84, 118.18, 115.44, 110.61, 69.83, 57.87, 52.47; HRMS (EI) m/z: [M^+] Calcd' for $C_{19}H_{16}FNO_5$ 357.1013; found : 357.1022.

Synthesis of 1-*tert*-butyl 2-methyl 4-fluoro-5-methoxy-1*H*-indole-1,2-dicarboxylate (10b)

White solid (0.138 g, 85 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.80-7.77 (d, *J* = 9.0 Hz, 1H, Ar), 7.15-7.09 (m, 2H, Ar), 3.94 (s, 3H, -CO_2**CH$_3$**), 3.92 (s, 3H, -O**CH$_3$**), 1.61 (s, 9H, -C(**CH$_3$)$_3$**); ^{13}C NMR δ ($CDCl_3$) : 161.89, 149.07, 147.00, 143.69, 142.55, 142.44, 133.63, 133.53, 131.27, 118.20, 117.95, 115.37, 110.46, 110.40, 109.76, 84.90, 57.93, 52.44, 27.78; HRMS (EI) m/z: [M^+] Calcd' for $C_{16}H_{18}FNO_5$ 323.1169; found : 323.1161.

Synthesis of 1-benzyl 2-methyl 4,6-difluoro-5-methoxy-1*H*-indole-1,2-dicarboxylate (11a)

White solid (0.158 g, 84 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69-7.65 (d, *J* = 12.0 Hz, 1H, Ar), 7.47-7.37(m, 5H, Ar), 7.16 (s, 1H, Ar), 5.40 (s, 2H, -**CH$_2$**(C_6H_5)), 4.00 (s, 3H, -CO_2**CH$_3$**), 3.72 (s, 3H, -O**CH$_3$**); ^{13}C NMR δ ($CDCl_3$) : 161.34, 157.75, 150.24, 134.05, 130.67, 130.61, 129.03, 128.88, 128.77, 113.78, 110.84, 110.82, 99.46, 99.40, 99.10, 99.04, 70.12, 62.39, 52.47; HRMS (EI) m/z: [M^+] Calcd' for $C_{19}H_{15}F_2NO_5$ 375.0918; found : 375.0891.

Synthesis of 1-*tert*-butyl 2-methyl 4,6-difluoro-5-methoxy-1*H*-indole-1,2-dicarboxylate (11b)

Colorless oil (0.149 g, 87 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.70-7.66 (d, *J* = 12.0 Hz, 1H, Ar), 7.13 (s, 1H, Ar), 4.00 (s, 3H, -CO_2**CH_3**), 3.92 (s, 3H, -O**CH_3**), 1.62 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) : 161.48, 157.70, 157.63, 154.42, 154.36, 150.29, 150.19, 148.74, 146.95, 146.86, 132.74, 130.71, 130.66, 113.85, 113.83, 113.58, 113.56, 110.04, 110.01, 99.18, 99.12, 98.82, 98.76, 85.48, 62.39, 52.46, 27.72; HRMS (EI) m/z: [M^+] Calcd' for $C_{16}H_{17}F_2NO_5$ 341.1075; found : 341.1067.

Synthesis of 1-*tert*-butyl 2-methyl 1*H*-pyrrolo[3,2-*b*]pyridine-1,2-dicarboxylate (12)

Colorless oil (0.130 g, 94 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.61-8.59 (d, *J* = 6.0 Hz, 1H, Ar), 8.38-8.35 (d, *J* = 9.0 Hz, 1H, Ar), 7.34-7.30 (dd, *J* = 7.5 Hz, 1H, Ar), 7.22 (s, 1H, Ar), 3.96 (s, 3H, -CO_2**CH_3**), 1.63 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) : 162.04, 148.43, 146.63, 145.63, 133.21, 131.22, 122.63, 120.84, 114.26, 85.55, 52.64, 27.76; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{16}N_2O_4$ 276.1114; found : 276.1114.

Synthesis of 1-*tert*-butyl 2-methyl 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine-1,2-dicarboxylate (13)

Colorless oil (0.074 g, 47 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.31-8.29 (d, *J* = 6.0 Hz, 1H, Ar), 7.90-7.88 (d, *J* = 6.0 Hz, 1H, Ar), 7.20 (s, 1H, Ar), 3.96 (s, 3H, -CO_2**CH_3**), 1.64 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) : 161.26, 147.94, 145.41, 145.07, 142.83, 131.48, 122.82, 111.93, 109.26, 86.43, 52.73, 27.70; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{15}ClN_2O_4$ 310.0720; found 310.0711.

Synthesis of 1-*tert*-butyl 2-methyl 1*H*-pyrrolo[2,3-*c*]pyridine-1,2-dicarboxylate (14)

Colorless oil (0.089 g, 64 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.42 (s, 1H, Ar), 8.47 (s, 1H, Ar), 7.54-7.52 (d, *J* = 6.0 Hz, 1H, Ar), 7.00 (s, 1H, Ar), 3.96 (s, 3H, -CO_2**CH_3**), 1.66 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) : 162.10, 148.23, 142.43, 137.96, 135.88, 133.38, 133.06, 111.75, 85.94, 52.80, 27.87; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{16}N_2O_4$ 276.1110; found 276.1099.

Synthesis of 1-*tert*-butyl 2-methyl 4-bromo-1*H*-pyrrolo[2,3-*c*]pyridine-1,2-dicarboxylate (15)

White solid (0.091 g, 51 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.32 (s, 1H, Ar), 8.54 (s, 1H, Ar), 7.06 (s, 1H, Ar), 3.97 (s, 3H, -CO_2**CH_3**), 1.66 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) : 161.59, 147.85, 143.25, 136.42, 133.85, 133.73, 133.49, 113.05, 111.31, 86.55, 52.91, 27.80; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{15}BrN_2O_4$ 354.0215; found 354.0219.

Synthesis of 1-benzyl 2-methyl 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-1,2-dicarboxylate (16a)

White solid (0.154 g, 89 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.12 (s, 1H, Ar), 7.53 (s, 1H, Ar), 7.48-7.39 (m, 5H, Ar), 6.94 (s, 1H, Ar), 5.45 (s, 2H, -**CH_2**(C_6H_5)), 3.77 (s, 3H, -CO_2**CH_3**); ^{13}C NMR δ ($CDCl_3$) : 161.46, 149.35, 144.36, 137.31, 136.39, 135.00, 133.61, 132.43, 129.29, 129.05, 128.93, 128.91, 115.92, 111.24, 70.65, 52.93; HRMS (EI) m/z: [M^+] Calcd' for $C_{17}H_{13}ClN_2O_4$ 344.0564; found 344.0558.

Synthesis of 1-*tert*-butyl 2-methyl 5-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-1,2-dicarboxylate (16b)

Yellow oil (0.147 g, 94 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 9.17 (s, 1H, Ar), 7.54 (s, 1H, Ar), 6.92 (s, 1H, Ar), 3.97 (s, 3H, -CO_2**CH_3**), 1.65 (s, 9H, -C(**CH_3**)$_3$); ^{13}C NMR δ ($CDCl_3$) :

161.64, 147.83, 143.88, 137.21, 136.15, 135.05, 132.62, 115.76, 110.50, 86,41, 52.92, 27.80; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{15}ClN_2O_4$ 310.0720; found 310.0701.

Synthesis of 1-*tert*-butyl 2-methyl 1*H*-pyrrolo[2,3-*b*]pyridine-1,2-dicarboxylate (17)

White solid (0.111 g, 80 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.60-8.59 (d, *J* = 3.0 Hz, 1H, Ar), 7.98-7.95 (d, *J* = 9.0 Hz, 1H, Ar), 7.23-7.21(m, 1H, Ar), 7.09 (s, 1H, Ar), 3.94 (s, 3H, -$CO_2\mathbf{CH_3}$), 1.64 (s, 9H, -C($\mathbf{CH_3}$)$_3$); ^{13}C NMR δ ($CDCl_3$) : 161.59, 149.48, 147.93, 147.71, 130.79, 129.82, 119.77, 119.01, 111.21, 85.22, 52.44, 27.69; HRMS (EI) m/z: [M^+] Calcd' for $C_{14}H_{16}N_2O_4$ 276.1110; found 276.1089.

Synthesis of 4-*tert*-butyl 5-methyl 3-bromo-4*H*-thieno[3,2-*b*]pyrrole-4,5-dicarboxylate (18)

white solid (0.166 g, 92 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.30 (s, 1H, Ar), 7.11 (s, 1H, Ar), 3.88 (s, 3H, -$CO_2\mathbf{CH_3}$), 1.67 (s, 9H, -C($\mathbf{CH_3}$)$_3$); ^{13}C NMR δ ($CDCl_3$) : 160.62, 148.00, 137.72, 128.51, 127.61, 124.68, 110.59, 94.92, 86.23, 52.04, 27.51; HRMS (EI) m/z: [M^+] Calcd' for $C_{13}H_{14}BrNO_4S$ 358.9827; found 358.9799.

Synthesis of 6-*tert*-butyl 5-methyl 2-bromo-3a*H*-thieno[2,3-*b*]pyrrole-5,6(6a*H*)-dicarboxylate (19)

Colorless oil (0.45 g, 80 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 7.03 (s, 1H, Ar), 7.02 (s, 1H, Ar), 3.88 (s, 3H, -$CO_2\mathbf{CH_3}$), 1.64 (s, 9H, -C($\mathbf{CH_3}$)$_3$); ^{13}C NMR δ ($CDCl_3$) : 160.78, 147.41, 139.11, 128.85, 128.05, 120.49, 114.29, 110.00, 86.14, 52.17, 27.86.; HRMS (EI) m/z: [M^+] Calcd' for $C_{13}H_{14}BrNO_4S$ 358.9827; found 358.9844.

Synthesis of 1-benzyl 2-methyl 1H-benzo[4,5]thieno[3,2-b]pyrrole-1,2(3aH,8bH)-dicarboxylate (20)

Yellow crystal (0.158 g, 86 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.46-8.43 (t, *J* = 4.5 Hz, 1H, Ar), 7.80-7.77 (t, *J* = 4.5 Hz, 1H, Ar), 7.48-7.34 (m, 7H, Ar), 7.19 (s, 1H, Ar), 5.47 (s, 2H, -**CH_2**(C_6H_5)), 3.73 (s, 3H, -CO_2**CH_3**); ^{13}C NMR δ ($CDCl_3$) : 161.00, 150.89, 144.10, 136.25, 134.05, 129.53, 129.02, 128.98, 128.72, 126.52, 125.21, 124.66, 123.80, 123.03, 113.90, 70.68, 52.14.; HRMS (EI) m/z: [M^+] Calcd' for $C_{20}H_{15}NO_4S$ 365.0722; found 365.0676.

Supporting Information

Copies of ^{1}H and ^{13}C NMR Data are available on the web.

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References

[1] a) J. A. Joule, K. Mills, Heterocyclic Chemistry, 5th Ed. 2010, Wiley-Blackwell; b) T. Eicher, S. Hauptmann, A. Speicher, The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Application 3rd Ed. 2012, Wiley.

[2] a) L. Knorr, Ber. 1884, 17, 2863; Paal, C. *Ber.* **1884**, *17*, 2756; b) A. Hantzsch, *Ber.* **1881**, *14*, 1637; c) W. G. Terry, A. H. Jackson, G. W. Kenner, G. Kornis, *J. Chem. Soc.*, **1965**, 4389; d) For a recent review, see V. Estévez, M. Villacampa, C. Menéndez, *Chem. Soc. Rev.* **2010**, *39*, 4402 and references cited therein.

[3] For recent reviews of the synthesis of indole, see a) R. J. Sundberg, Indoles. Academic Press Ltd. San Diego: 1996; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron*, **2011**, *67*, 7195.

[4] a) B. Frydman, S. Reil, M. E. Despuy, H. Rapoport, *J. Am. Chem. Soc.* **1969**, *91*, 2338; b) P. Carter, S. Fitzjohn, S. Halazy, P. Magnus, *J. Am. Chem. Soc.* **1987**, *109*, 2711; c) K. Yamada, T. Kurokawa, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, *125*, 6630.

[5] a) Nicotinamide phosphoribosyltransferase inhibitor, see G. R. W. Pitt, P. A. Mayes, L. Andrau, WO 2013020164, 2013; b) Myt1 inhibitor, see M. A. Lago, WO 2000033842, 2000; *Chem. Abstr.* **2001**, *135*, 211033; c) CHK1 inhibitor, see J. -G. Parmentier, B. Portevin, R. M. Golsteyn, A. Pierré, J. Hickman, P. Gloanec, G. D. Nanteuil, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 841; d) Human histamine H4 receptor, see H. Cai, N. I. Carruthers, C. A. Dvorak, J. P. Edward, A. K. Kwok, US 20040048878, **2004**; e) Respiratory syncycial virus, see G. R. W. Pitt, P. A. Mayes, L. Andrau, WO 2013020164, **2013**.

[6] For an example of pyrrole containing materials for chemosensors, see a) M. Lazerges, K. I. Chane-Ching, S. Aeiyach, S. Chelli, B. Peppin-Donnat, M. Billon, C. Lombard, F. Maurel, M. Jouini, *J. Solid State Electrochem.*, **2009**, *13*, 231; b) For glucose sensors, see A. Kros, S. W. F. M. van Hövel, R. J. M. Nolte, N. A. J. M. Sommerdijk, *Sens. Actuators, B*, **2001**, *80*, 229; c) For detectors of volatile organic compounds, see S. Hamilton, M. J. Hepher, J. Sommerville, *Sens. Actuators, B*, **2005**, *107*, 424; d) For a review of pyrrole-containing dye, see: A. Loudet, K. Burgess, *Chem. Rev.*, **2007**, *107*, 4891.

[7] For reviews of metal-catalyzed N-arylations involving copper, see a) S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; b) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; c) T. Liu, H. Fu, *Synthesis* **2012**, *44*, 2805; for reviews involving palladium, see d) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; e) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; f) C. Fischer, B. Koenig, *Beilstein J. Org. Chem.* **2011**, *7*, 59; g) J. E. R. Sadig, M. C. Willis, *Synthesis* **2011**, *43*, 1.

[8] For indoles via Pd-catalyzed intramolecular N-arylations, see a) K. Aoki, A. J. Peat, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 3068; b) J. A. Brown, *Tetrahedron Lett.* **2000**, *41*, 1623; c) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Chem. Soc., Perkin Trans.* 1 **2002**, 2137;

d) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Org. Chem.* **2003**, *68*, 6011; e) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem., Int. Ed.* **2007**, *46*, 1529; using Cu-catalyzed conditions, see f) C. Barberis, T. D. Gordon, C. Thomas, X. Zhang, K. P. Cusack, *Tetrahedron Lett.* **2005**, *46*, 8877; g) F. S. Melkonyan, A. V. Karchava, M. A. Yurovskaya, *J. Org. Chem.* **2008**, *73*, 4275; h) A. M. Taylor, S. L. Schreiber, *Tetrahedron Lett.* **2009**, *50*, 3230; i) Q. Cai, Z. Li, J. Wei, C. Ha, D. Pei, K. Ding, *Chem. Commun.* **2009**, 7581; j) R. Besandre, M. Jaimes, J. A. May, *Org. Lett.* **2013**, *15*, 1666.

[9] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689; b) X. Li, W. Yin, P. V. V. Sarma, H. Zhou, J. Ma, J. M. Cook, *Tetrahedron Lett.* **2004**, *45*, 8569.

[10] a) N. Lachance, M. April, *Synthesis*, **2005**, 2571; b) M. Nazaré, C. Schneider, A. Lindenschmidth, D. W. Will, *Angew. Chem. Int. Ed.* **2004**, *43*, 4526.

[11] For reviews, see a) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863; b) M. Edmonds, A. Abell, In Modern Carbonyl Olefination Methods and Applications; T. Takeda, Ed.; Wiley-VCH: Weinheim, Germany, **2004**, pp. 1-17; c) B. J. Walker, In Organophosphorus Reagents in Organic Synthesis; J. I. G. Gadogan, Ed.; Academic Press: London, UK, **1979**, pp. 155-205; for an relevant example of heterocycle syntheses using HWE reaction, see d) C. W. Muir, A. R. Kennedy, J. A. Redmond, A. J. B. Watson, *Org. Biomol. Chem.* **2013**, *11*, 3337.

[12] Similar borazaaromatic compounds were reported previously, see P. R. Ashton, K. D. M. Harris, B. M. Kariuki, D. Philp, J. M. A. Robinson, N. Spencer, *J. Chem. Soc., Perkin Trans. 2*, **2001**, 2166.

[13] a) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941; b) A. P. Combs, S. Saubern, M. Rafalski, P. Y. S. Lam, *Tetrahedron Lett.* **1999**, *40*, 1623; c) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan, A. Combs, *Synlett* **2000**, 674.

[14] J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684.

[15] H. Hemtsberger,; D. Knittel, H. Wiedmann, *Monatsh. Chem.* **1970**, *101*, 161.

[16] Former syntheses of 7-formyl indole-2-carboxylate, see a) D. L. Boger, WO 2004101767, **2004**; b) M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Tashiro, Y. Yokoyama, Y. Murakami, *Chem. Pharm. Bull.* **1990**, *38*, 3261.

[17] For general reviews of azaindole synthesis, see a) F. Popowycz, S. Routier, B. Joseph, J. -Y. Mérour, *Tetrahedron* **2007**, *63*, 1031; b) F. Popowycz, J.-Y. Mérour, B. Joseph, *Tetrahedron* **2007**, *63*, 8689; c) J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, C. H. Senanayake, *Chem. Soc. Rev.* **2007**, *36*, 1120 and references cited therein.

[18] a) P. M. Fresneda, P. Molina, S. Delgado, J. A. Bleda, *Tetrahedron Lett.* **2000**, *41*, 4777; b) T. Lomberget, S. Radix, R. Barret, *Synlett* **2005**, 2080; c) P. Roy, M. Boisvert, Y. Leblanc, *Org. Synth.* **2007**, *84*, 262.