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One-Pot Synthesis of Pyrrole-2-carboxylates and -carboxamides via an Electrocyclization/Oxidation Sequence

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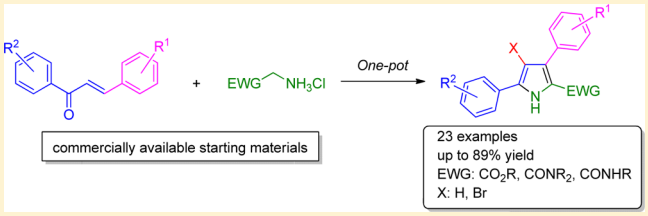
Supporting Information

ABSTRACT: An electrocyclic ring closure is the key step of an efficient one-pot method for the synthesis of pyrrole-2-carboxylates and -carboxamides from chalcones and glycine esters or amides. The 3,4-dihydro-2*H*-pyrrole intermediates generated in situ are oxidized to the corresponding pyrroles by stoichiometric oxidants or by catalytic copper(II) and air in moderate to high yields. A wide range of functional groups are tolerated, and further combination with an in situ bromination gives access to polyfunctional pyrrole scaffolds.



Pyrroles are nitrogen-containing heterocycles of high importance due to their occurrence as common structural motifs of natural products in alkaloids,[1,2] porphyrins, chlorins, and corrins. Since pyrrole-containing molecules often exhibit pronounced bioactivities, such as antibacterial,[3] antifungal,[4] anti-inflammatory,[5] or antitumor[6] effects, there are also several drugs possessing pyrrole units.[7] Furthermore, pyrrole-2-carboxylates and -carboxamides are frequently used intermediates in the total synthesis of natural products like the lamellarins,[8,9] or bromopyrrole alkaloids like hanishin or longamide B.[10] Moreover, they are building blocks for the assembly of polycyclic heterocycles such as indolones and pyrroloindolones.[11] For various substituted pyrrole-2-carboxylates, antimitotic and cytostatic effects have been reported.[12] Moreover, pyrrole-2-carboxyl units formed via a four-electron oxidation from *L*-proline play a vital role in the biosynthesis of monopyrrolic natural products such as the antibiotics prodigiosin, undecylprodigiosin, clorobiocin, coumermycin A_1, and pyoluteorin.[13]

Since the pioneering work of Knorr and Fischer, numerous methods for the synthesis of the pyrrole-2-carboxylate motif have been developed,[14−23] including transition-metal-catalyzed cycloaddition reactions of isocyanides and alkynes,[24,25] and cycloisomerization of functionalized intermediates, such as dienyl azides,[26] homopropargyl azides,[27−29] alkynyl aziridines,[30−32] homopropargyl amines,[33] 2-amino-3-iodoacrylates,[34,35] or vinyl diazomethanes.[36] A particularly efficient method for their synthesis is the Barton−Zard reaction[37] of ethyl isocyanoacetate with nitroolefins or the related Montforts synthesis using α,β-unsaturated sulfones as the electrophilic component.[38] The Barton−Zard reaction even works on 9-nitrophenanthrenes,[39] but it only yields products devoid of a 5-substituent. Other methods build up the five-membered ring and adjust the oxidation stage by a dehydrogenation of a 4,5-, 3,4-, and 2,5-dihydropyrrole intermediate. The most common oxidants that have been used in this context are chloranil,[40] Pd/C,[41,42] MnO_2,[43] CrO_3,[44] $FeCl_3$,[45] and DDQ.[46,47] Generally, these methods were applied to isolated dihydropyrroles. Here, we report a one-pot synthesis of pyrrole-2-carboxylates[48−55] and -carboxamides from enones and glycine esters or amides that is based on the oxidation of 3,4-dihydropyrrole intermediates formed in a spontaneous 6π-electrocyclization.

As reported previously,[56,57] 3,4-dihydropyrrole-2-carbonitriles can be obtained by cyclocondensation[22,23,40] of aminoacetonitrile with chalcones. While the nitrile function can be used as a removable acceptor group, an ester function would remain in the products instead but should allow the preparation of the useful pyrrole-2-carboxylates. Ideally, air should be used as the stoichiometric oxidant and condensation, cyclization, and oxidation should be combined to a one-pot sequence. In this case, a pyrrole-2-carboxylate would be obtained from an enone and a glycine ester by loss of two molecules of water. A similar cyclocondensation approach has recently been used by Zu et al. to generate 3,4-disubstituted pyrrole-2-carboxylates in a cascade reaction, but the scope of this process is limited to products with an allylic 4-substituent (Scheme 1).[58]

In our first attempt to react (*E*)-chalcone (**1a**) with glycine ethyl ester hydrochloride (**2a**) in boiling pyridine, dihydropyrrole **5a** was isolated in 73% yield as a mixture of its diastereomers (trans/cis = 4:1). Subsequent oxidation with DDQ in toluene afforded pyrrole-2-carboxylate **6a** in 65% yield (48% overall yield, Scheme 2).

Substitution of refluxing pyridine by combinations of various solvents (1,4-dioxane, THF, toluene, AcOH, and *N*,*N*-diethylaniline) with bases (triethylamine, DIPEA, DBU, KO^{t}Bu, *N*,*N*-diethylaniline) gave inferior results in terms of

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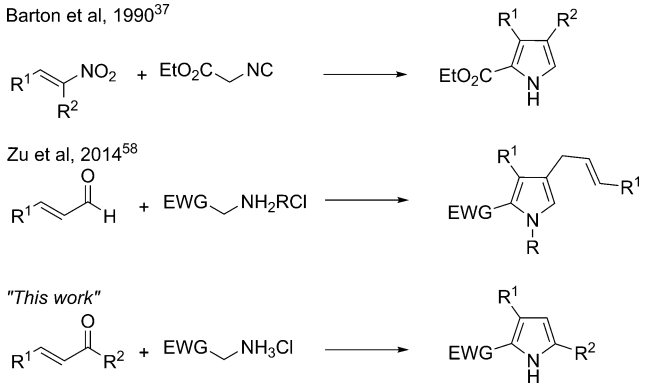
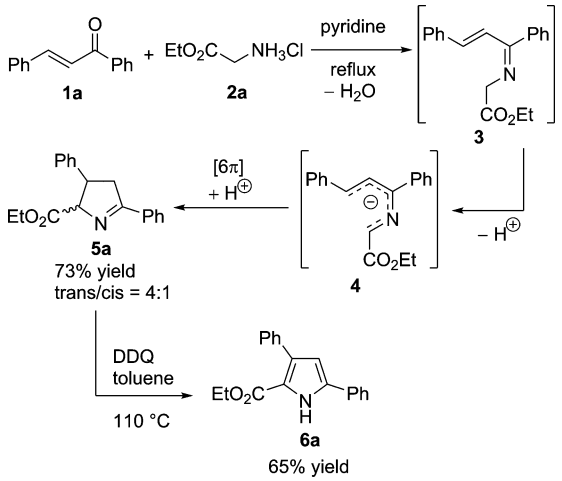
Scheme 1. Cyclocondensation Routes to Pyrrole-2-carboxylates



Scheme 2. Two-Step Synthesis of Pyrrole-2-carboxylate 6a



conversion and purity of the product, as judged by HPLC/MS and TLC. In contrast to the analogous reaction with glycine nitrile hydrochloride, microwave irradiation proved to be feasible and reduced the reaction time from days to hours. The high stability of glycine esters allows the use of a stoichiometric amount instead of an excess of the amine component. To test the compatibility of the cyclization conditions with the oxidation reaction, various oxidants were employed.

Initially, the one-pot procedure was investigated by adding DDQ to the crude reaction mixture of the cyclocondensation to dihydropyrrole **5a** in pyridine to furnish pyrrole **6a**. Using 2.0 equiv of DDQ gave a modest yield of **6a** (32% yield), whereas lowering the amount to 1.1 equiv afforded a higher yield (56% yield). The addition of a stoichiometric amount of acetic acid proved beneficial and not only led to the hitherto highest yield (58%) but also reduced the formation of black, tarry oxidation products. Unlike the cyclocondensation step, DDQ oxidation under microwave irradiation was unsuccessful. With the established method, a series of enones **1a–k** and **1o** were transformed into the corresponding pyrrole-2-carboxylates **6a–k** and **6o** in moderate to high yields. Glycine *tert*-butyl ester (**2b**) could successfully be used, although dealkoxycarbonylation was observed under harsh microwave conditions. Performing the reaction under conventional heating in pyridine gave the best results. An oxidation-sensitive 2-furyl moiety, as present in substrate **1o**, resulted in a low yield, and reactions with alkyl substituted enones failed. Several products were synthesized in a two-step procedure with isolation of the 3,4-dihydro-2*H*-pyrrole intermediates that gave inferior results compared to the one-pot procedure.

As an alternative to DDQ, Cu^{2+} salts were investigated as potential oxidants, which not only are cheaper and have a lower toxicity but also may provide an easier workup. Finally, copper could be used in catalytic amounts in combination with oxygen or air as a stoichiometric oxidant.

First attempts with stoichiometric amounts of copper(II) acetate (1.2 equiv), added to the solution of crude dihydropyrrole **5a** in pyridine, were carried out under microwave irradiation to obtain pyrrole **6a** (82% yield). The addition of 1.2 equiv of copper(II)acetate to various crude dihydropyrroles **5a–n** prepared by either conventional or microwave heating yielded pyrrole-2-carboxylates **6a–n** in 47–82% yield within an 8 h reaction time. A larger amount (2.0 equiv) of copper(II) acetate yielded pyrrole-2-carboxylates in 44–84% yield in less than 2 h.

To investigate the copper-catalyzed aerobic oxidation, copper was first added from the beginning of the reaction sequence. The addition of 1 mol % copper(II) acetate to the solution of chalcone (**1a**) and **2a** in pyridine led to incomplete conversion after 32 h of stirring at reflux under air flow. Dihydropyrrole **5a** was consumed entirely, but chalcone was still present (TLC and HPLC-MS), and the reproducibility of the procedure was low. Therefore, the addition of catalytic amounts of copper to the solution of crude dihydropyrrole **5a** was investigated as an alternative. CuCl and $Cu(MeCN)_4PF_6$ were similarly efficient Cu sources so that the former salt was chosen due to its low cost. Lowering the reaction temperature to 60–100 °C led to significantly longer reaction times or complete stagnation of the cyclization compared to boiling pyridine. While the addition of K_3PO_4 or CsOPiv led to lower yields of pyrrole (36% and 25%), the addition of diethyl azodicarboxylate (DEAD) or iron(III) chloride as cooxidants had no positive effect on the yield (55% and 43%).[59] After screening different copper sources and ligands (*N*,*N*′-di-*tert*-butylethylenediamine, 2,2′-bipyridine, 1,10-phenanthroline, *N*,*N*-dimethylglycine), the highest yield (56%) was obtained with 10 mol % CuCl, air flow, and without any added ligand. Thus, the ecologically attractive copper-catalyzed one-pot procedure is feasible but provides the desired compounds in moderate yields of 23–56%. The results obtained with all three methods are summarized in Table 1.

Adding *N*-bromosuccinimide (NBS) to the reaction mixture after complete oxidation of dihydropyrrole **5a** with DDQ smoothly led to the brominated pyrrole **7** in 49% yield over three consecutive steps (Scheme 3). Similarly, the crude reaction mixture of the dihydropyrrole **5a** was oxidized by air in the presence of $Cu(MeCN)_4PF_6$ (10 mol %) and bipyridine (10 mol %) prior to bromination with NBS. In the latter case, bromopyrrole **7** was obtained in 56% yield.

The copper-mediated two-step, one-pot procedure also proved to be effective for the synthesis of the pyrrole-2-carboxamides. Cyclization of enones **1** with glycine amides **8** and subsequent oxidation with copper(II) acetate (1.2 or 2.0 equiv) gave pyrrole-2-carboxamides **9a–c** in moderate yields (Table 2).

While tertiary amides could be reacted smoothly, glycine amide did not even cyclize with enones under identical conditions, presumably due to its insolubility. Secondary amides could be transformed into the desired products

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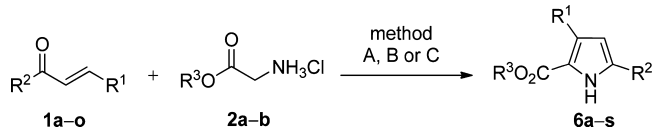
Table 1. Synthesis of Pyrrole-2-carboxylates 6a–s[a]

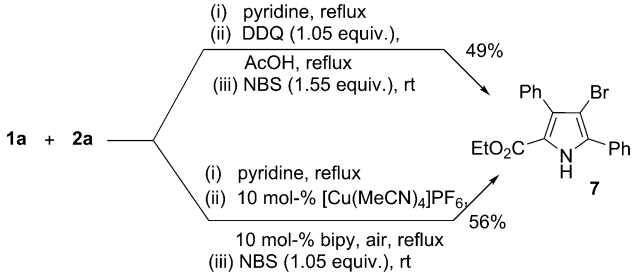


1a–o 2a–b 6a–s

entry	R^1	R^2	R^3	(A) %	(B) %	(C) %	product
1	Ph	Ph	Et	58	82*[b,c], 84**	56	**6a**
2	Ph	2-Naph	Et	55	57*	37	**6b**
3	3-NO_2-C_6H_4	4-Cl-C_6H_4	Et	56	65*, 56**[d]	45	**6c**
4	2,3-Cl_2-C_6H_3	Ph	Et	60	67*	23	**6d**
5	2-Br-C_6H_4	2-Naph	Et	89	56*	23	**6e**
6	4-CN-C_6H_4	Ph	Et	61	61*	38	**6f**
7	4-MeO-C_6H_4	4-F-C_6H_4	Et	74	65*[d], 55**		**6g**
8	2-Cl-C_6H_4	4-F-C_6H_4	Et	54	61*	28	**6h**
9	4-MeO-C_6H_4	Ph	Et	56	61*	40	**6i**
10	3,4-$(MeO)_2$-C_6H_3	3,4-$(MeO)_2$-C_6H_3	Et	28	55*	37[e]	**6j**
11	Biphenyl-4-yl	Ph	Et	61	55**	29[e]	**6k**
12	4-NMe_2-C_6H_4	Ph	Et		46**		**6l**
13	4-OH-C_6H_4	Ph	Et		44**		**6m**
14	2-Br-4,5-$(MeO)_2$-C_6H_2	3,4-$(MeO)_2$-C_6H_3	Et		47*		**6n**
15	3,4-$(MeO)_2$-C_6H_3	2-Furyl	Et	21[b]			**6o**
16	Ph	Ph	^{t}Bu	30[f]			**6p**
17	4-MeO-C_6H_4	4-F-C_6H_4	^{t}Bu	40[f]			**6q**
18	2-Cl-C_6H_4	4-F-C_6H_4	^{t}Bu	57[f]			**6r**
19	3,4-$(MeO)_2$-C_6H_3	2-Furyl	^{t}Bu	19			**6s**

[a]Reaction conditions: enone (1.00 mmol), glycine ester (1.05 mmol), AcOH (1.00 mmol), pyridine (5–10 mL) at reflux, method A: DDQ (1.10 mmol); B*: $Cu(OAc)_2$ (1.20 mmol); B**: $Cu(OAc)_2$ (2.00 mmol); C: CuCl (10–20 mol %), air flow. [b]Both cyclization and oxidation were performed under microwave irradiation. [c]After 1 h oxidation, an additional 0.3 equiv of $Cu(OAc)_2$ was used. [d]Cyclization was performed under microwave irradiation. [e]DEAD (20 mol %) and 1,10-phenanthroline (20 mol %) were added in the oxidation step. [f]1.5 equiv of **2b** and 2.0 equiv of DDQ were used.

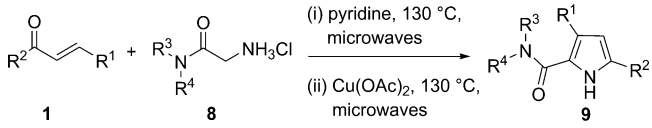
Scheme 3. One-Pot Cyclization–Oxidation–Bromination Sequence



depending on the length of the alkyl chain, which also governs their solubility in hot pyridine (Table 2, entries 3 and 4 compared to entry 6).

In conclusion, our method permits a simple one-pot synthesis of 3,5-disubstituted pyrrole-2-carboxylates or -carboxamides from enones and glycine esters or amides by cyclocondensation, followed by oxidation of the dihydropyrrole intermediates by DDQ or copper(II). Copper can also be used in catalytic amounts in combination with air as a stoichiometric oxidant, but lower yields and reaction rates are observed. A wide range of substituents, such as chloro, bromo, fluoro, nitro, cyano, dialkylamino, and hydroxyl groups, are tolerated. The combination of the two-step sequence with an in situ bromination allows the preparation of 3,5-disubstituted 4-bromopyrrole-2-carboxylates.

Table 2. Pyrrole-2-carboxamides[a]



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entry	R^1	R^2	R^3	R^4	yield (%)	product
1	Ph	Ph	Me	Me	46[b]	**9a**
2	Ph	Ph	Me	Me	55[c]	**9a**
3	Ph	Ph	*i*-Bu	H	59[b]	**9b**
4	4-MeO-C_6H_4	4-F-C_6H_4	*i*-Bu	H	43[c]	**9c**
5	Ph	Ph	H	H	n.r.	
6	Ph	Ph	Me	H	n.r.	

[a]Reaction conditions: (i) enone (1.00 mmol), glycine amide (1.20 mmol), MS 3 Å, pyridine (4 mL) at 130 °C, microwave irradiation; (ii) $Cu(OAc)_2$ (1.20 or 2.00 mmol) at 130 °C, microwave irradiation. [b]Oxidation was performed with 1.20 equiv of $Cu(OAc)_2$. [c]Oxidation was performed with 2.00 equiv of $Cu(OAc)_2$.

EXPERIMENTAL SECTION

General Procedure for DDQ Oxidation (A). Unless otherwise noted, the respective enone (1.00 mmol, 1.00 equiv) and ethyl or *tert*-butyl glycine ester hydrochloride (1.05 mmol, 1.05 equiv) were dissolved in pyridine (10 mL). Acetic acid (1.00 mmol, 60 μL, 1.00 equiv) was added, and the reaction mixture was stirred at 125 °C oil bath temperature until complete conversion of the enone was determined, as indicated by TLC or HPLC-MS (reaction time indicated for each compound). After complete consumption of the enone, DDQ (1.10 mmol, 250 mg, 1.10 equiv) was added in one portion and the mixture was refluxed until complete conversion of the dihydropyrrole was determined, as indicated by TLC or HPLC-MS.

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Upon completion, the solvent was removed by azeotropic distillation with toluene. The residue was purified by column chromatography on silica gel to afford the particular pyrroles, with yields ranging from 19% to 89%.

General Procedure for Copper-Mediated Oxidation, 1.2 equiv* or 2.0 equiv (B).** Unless otherwise noted, the respective enone (1.00 mmol, 1.00 equiv) and ethyl glycine ester hydrochloride (1.05 mmol, 147 mg, 1.05 equiv) were dissolved in pyridine (5 mL). Grained molecular sieve 3 Å (100 mg) was added, and the mixture was stirred at 125 °C oil bath temperature until complete conversion of the enone was determined, as indicated by TLC or HPLC-MS. Then, $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.2 equiv or 2.00 mmol, 363 mg, 2.00 equiv) was added in one portion and the mixture was refluxed until complete conversion of the dihydropyrrole was determined, as indicated by TLC or HPLC-MS. Upon completion of the oxidation, the solvent was removed by azeotropic distillation with toluene. The residue was dissolved in dichloromethane (60 mL) and subsequently washed with a 0.1 M Na_2-EDTA solution (3 × 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to afford the particular pyrroles, with yields ranging from 44% to 84%.

General Procedure for Copper-Catalyzed Oxidation (C). Unless otherwise noted, the respective enone (1.00 mmol, 1.00 equiv) and ethyl glycine ester hydrochloride (1.05 mmol, 147 mg, 1.05 equiv) were dissolved in pyridine (5 mL). Molecular sieve 3 Å (100 mg) was added, and the mixture was stirred at 125 °C oil bath temperature until complete conversion of the enone was determined, as indicated by TLC or HPLC-MS. Following, CuCl (10−20 mol %, 10−20 mg) was added in one portion and the mixture was refluxed with air continuously passing through the reaction mixture until complete conversion of the dihydropyrrole was determined, as indicated by TLC or HPLC-MS. Purification and isolation as described before. Pyrroles were isolated with yields ranging from 23% to 56%.

Optional Method for 3,4-Dihydro-2*H*-pyrrole Formation via Microwave Irradiation. Unless otherwise noted, the respective enone (1.00 mmol, 1.00 equiv) and ethyl glycine ester hydrochloride (1.05 mmol, 147 mg, 1.05 equiv) were placed in a microwave vessel, and pyridine (3 mL) was added. Molecular sieve 3 Å (100 mg) was added, followed by sealing the vessel and heating to 130 °C for 60 min (200 W, air cooling) in a microwave reactor. The reaction temperature increased from 25 to 130 °C in 180 s and was maintained at 130 °C for the rest of the period. An additional portion of ethyl glycine ester hydrochloride (0.20 mmol, 27.9 mg, 0.20 equiv) was added, followed by sealing the vessel and repeating the aforementioned procedure for another 60 min. The aromatization reaction was performed in an oil bath by adding the oxidant and proceeding as described before.

Alternatively, the oxidation can also be performed under microwave irradiation. In this case, $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv) was added to the reaction mixture, followed by sealing the vessel and heating to 140 °C for 60 min (250 W, air cooling). The reaction temperature increased from 25 to 140 °C in 180 s and was maintained at 140 °C for the rest of the period. An additional portion of $Cu(OAc)_2$ (0.30 mmol, 55 mg, 0.30 equiv) was added, followed by sealing the vessel and repeating the aforementioned method for another 60 min. Purification and isolation were performed as described before.

Ethyl 3,5-Diphenyl-1*H*-pyrrole-2-carboxylate (6a).[50] According to the general procedure A, **1a** and **2a** were cyclized by conventional heating (29 h), followed by oxidation (66 h). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6a** (168 mg, 58%) as a colorless solid: mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.43 (br s, 1H, N*H*), 7.65−7.58 (m, 4H), 7.50−7.29 (m, 6H), 6.64 (d, J = 3.1 Hz, 1H, *H*-4), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 1.26 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.5 (*C*=O), 135.6, 135.3, 133.6, 131.2, 129.7, 129.1, 128.0, 127.8, 127.2, 125.0, 118.8 (*C*-2), 110.1 (*C*-4), 60.6 (CH_2), 14.3 (CH_3). According to the general procedure B*, **1a** and **2a** were cyclized by microwave-assisted reaction (2 h), followed by microwave-assisted oxidation (2 h) (additional 0.3 equiv of $Cu(OAc)_2$ added after 1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6a** (238 mg, 82%) as a colorless solid. According to general procedure B**, **1a** and **2a** were cyclized by microwave-assisted reaction (2 h), followed by oxidation (30 min). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6a** (245 mg, 84%) as a colorless solid. According to general procedure C, **1a** and **2a** were cyclized by conventional heating (21 h), followed by oxidation (19 h) with anhydrous copper(I) chloride (10 mg, 10 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6a** (162 mg, 56%) as a colorless solid. The data are in accordance with the literature.[50]

Ethyl 5-(Naphth-2-yl)-3-phenyl-1*H*-pyrrole-2-carboxylate (6b). According to the general procedure A, **1b** and **2a** were cyclized by conventional heating (25 h), followed by oxidation (45 h). Purification by flash column chromatography (cyclohexane/EtOAc, 15:1) yielded **6b** (187 mg, 55%) as a yellow solid: mp 156−160 °C; R_f = 0.42 (silica gel, cyclohexane/EtOAc, 3:1); IR (ATR) ν (cm^{-1}) = 3300, 3056, 2980, 1709, 1663, 1630, 1604, 1507, 1435, 1281; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.58 (br s, 1H, N*H*), 8.07−8.03 (m, 1H, *H*-1″), 7.93−7.83 (m, 3H, Ar), 7.73 (dd, J = 8.5, 1.8 Hz, 1H, *H*-3′), 7.66−7.62 (m, 2H, *H*-2′/6′), 7.56−7.46 (m, 2H, Ar), 7.44−7.39 (m, 2H, *H*-3′/5′), 7.37−7.31 (m, 1H, *H*-4′), 6.76 (d, J = 3.1 Hz, 1H, *H*-4), 4.30 (q, J = 7.1 Hz, 2H, CH_2), 1.27 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.4 (C=O), 135.5 (C_q), 135.2 (C_q), 133.7 (C_q), 133.6 (C_q), 133.0 (C_q), 129.7 (2C, *C*-2′/6′), 129.0, 128.5 (C_q), 128.2, 127.9, 127.8 (2C, *C*-3′/5′), 127.3 (*C*-4′), 126.9, 126.4, 123.2, 123.2, 119.0 (*C*-2), 110.6 (*C*-4), 60.6 (CH_2), 14.4 (CH_3); ESI-HRMS calcd for $[C_{23}H_{19}NO_2 + Na]^+$ 364.1313, found 364.1323. According to the general procedure B*, **1b** and **2a** were cyclized by conventional heating (16 h), followed by oxidation (4 h). Purification by flash column chromatography (cyclohexane/EtOAc, 15:1) yielded **6b** (193 mg, 57%) as a yellow solid. According to general procedure C, **1b** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (26 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6b** (125 mg, 37%) as a yellow solid.

Ethyl 5-(4-Chlorophenyl)-3-(3-nitrophenyl)-1*H*-pyrrole-2-carboxylate (6c). According to the general procedure A, **1c** and **2a** were cyclized by conventional heating (53 h), followed by oxidation (41 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6c** (207 mg, 56%) as an orange solid: mp 179−182 °C; R_f = 0.49 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3309, 1667, 1608, 1588, 1572, 1529, 1514, 1483, 1427, 1283; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.48 (br s, 1H, N*H*), 8.48 (pseudo-t, $J \approx 2$ Hz, 1H, *H*-2′), 8.19 (ddd, J = 8.3, 2.3, 1.1 Hz, 1H, *H*-4′), 7.92 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H, *H*-6′), 7.58−7.52 (m, 3H, *H*-2″/6″/5′), 7.46−7.39 (m, 2H, *H*-3″/5″), 6.65 (d, J = 3.1 Hz, 1H, *H*-4), 4.29 (q, J = 7.1 Hz, 2H, CH_2), 1.25 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 160.9 (C=O), 148.0 (*C*-3′), 136.7 (*C*-5), 135.7 (*C*-6′), 134.8 (*C*-1′), 134.3 (*C*-4″), 130.7 (*C*-1″), 129.5 (2C, *C*-3″/5″), 129.2 (*C*-3), 128.7 (*C*-5′), 126.2 (2C, *C*-2″/6″), 124.7 (*C*-2′), 122.1 (*C*-4′), 119.5 (*C*-2), 110.1 (*C*-4), 61.1 (CH_2), 14.3 (CH_3); ESI-HRMS calcd for $[C_{19}H_{15}ClN_2O_4 + Na]^+$ 393.0618, found 393.0606. According to the general procedure B*, **1c** and **2a** were cyclized by conventional heating (10 h), followed by oxidation (4 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6c** (240 mg, 65%) as an orange solid. According to general procedure B**, **1c** and **2a** were cyclized by microwave-assisted reaction (2 h), followed by oxidation (1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6c** (207 mg, 56%) as an orange solid. According to general procedure C, **1c** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (21 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6c** (166 mg, 45%) as an orange solid.

Ethyl 3-(2,3-Dichlorophenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (6d). According to the general procedure A, **1d** and **2a** were cyclized by conventional heating (23.5 h), followed by oxidation (69.5

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h) with DDQ (277 mg, 1.30 mmol, 1.3 equiv). Purification by flash column chromatography (cyclohexane/EtOAc, 12:1) yielded **6d** (214 mg, 60%) as a light yellow solid: mp 150−152 °C; R_f = 0.57 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3309, 1667, 1572, 1477, 1438, 1427, 1413, 1283, 1260, 1211; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.00 (br s, 1H, N*H*), 7.65 (d, *J* = 7.4 Hz, 2H, *H*-2″/6″), 7.45 (dd, *J* = 8.0, 1.7 Hz, 1H, *H*-4′), 7.44−7.38 (m, 2H, *H*-3″/5″), 7.35−7.31 (m, 1H, *H*-4″), 7.29 (dd, *J* = 7.8, 1.7 Hz, 1H, *H*-6′), 7.21 (pseudo-t, *J* ≈ 8 Hz, 1H, *H*-5′), 6.56 (d, *J* = 2.9 Hz, 1H, *H*-4), 4.16 (q, *J* = 7.1 Hz, 2H, CH_2), 1.08 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.4 (*C*═O), 137.5 (*C*-1′), 135.9 (*C*-5), 132.9 (*C*-3′), 132.6 (*C*-2′), 131.1 (*C*-1″), 130.0 (*C*-6′), 129.6 (*C*-3), 129.3 (*C*-4′), 129.1 (2C, *C*-3″/5″), 128.1 (*C*-4″), 126.6 (*C*-5′), 125.0 (2C, *C*-2″/6″), 120.4 (*C*-2), 110.0 (*C*-4), 60.7 (CH_2), 13.9 (CH_3); ESI-HRMS calcd for $[C_{19}H_{15}Cl_2NO_2 + Na]^+$ 382.0378, found 382.0383. According to the general procedure B*, **1d** and **2a** were cyclized by conventional heating (36 h), followed by oxidation (5 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6d** in (239 mg, 67%) as a light yellow solid. According to general procedure C, **1d** and **2a** were cyclized by conventional heating (48 h), followed by oxidation (24 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6d** (81 mg, 23%) as a light yellow solid.

Ethyl 3-(2-Bromophenyl)-5-(naphth-2-yl)-1*H*-pyrrole-2-carboxylate (6e). According to the general procedure A, **1e** and **2a** were cyclized by conventional heating (28.5 h), followed by oxidation (29 h). Purification by flash column chromatography (cyclohexane/EtOAc, 10:1) yielded **6e** (375 mg, 89%) as a colorless solid: mp 144−145 °C; R_f = 0.21 (silica gel, cyclohexane/EtOAc, 12:1); IR (ATR) ν (cm^{-1}) = 3294, 1668, 1479, 1443, 1277; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.69 (br s, 1H, N*H*), 8.06−8.04 (m, 1H, *H*-1″), 7.92 (d, *J* = 8.5 Hz, 1H, *H*-4″), 7.88−7.85 (m, 1H, *H*-8″), 7.85−7.82 (m, 1H, *H*-5″), 7.74 (dd, *J* = 8.5, 1.8 Hz, 1H, *H*-3″), 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H, *H*-3′), 7.54−7.50 (m, 1H, *H*-6″), 7.50−7.45 (m, 1H, *H*-7″), 7.41 (dd, *J* = 7.6, 1.8 Hz, 1H, *H*-6′), 7.34 (ddd, *J* = 8.0, 7.5, 1.2 Hz, 1H, *H*-5′), 7.21 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H, *H*-4′), 6.69 (d, *J* = 3.0 Hz, 1H, *H*-4), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2), 1.09 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.3 (*C*═O), 137.2 (*C*-1′), 135.3 (*C*-5), 133.6 (*C*-2″), 133.0 (*C*-4a″), 132.4 (*C*-3′), 131.9 (*C*-6′), 131.8 (*C*-3), 129.0 (*C*-4″), 128.8 (*C*-4′), 128.5 (*C*-8a″), 128.2 (*C*-8″), 127.9 (*C*-5″), 126.9 (*C*-6″), 126.7 (*C*-5′), 126.4 (*C*-7″), 124.4 (*C*-2′), 123.3 (*C*-1″), 123.2 (*C*-3″), 120.6 (*C*-2), 110.8 (*C*-4), 60.6 (CH_2), 14.1 (CH_3); ESI-HRMS calcd for $[C_{23}H_{18}(^{79}Br)NO_2 + Na]^+$ 442.0419, found 442.0424. According to the general procedure B*, **1e** and **2a** were cyclized by conventional heating (36 h), followed by oxidation (5 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6e** (234 mg, 56%) as a colorless solid. According to general procedure C, **1e** and **2a** were cyclized by conventional heating (30 h), followed by oxidation (24 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6e** (95 mg, 23%) as a colorless solid.

Ethyl 3-(4-Cyanophenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (6f). According to the general procedure A, **1f** and **2a** were cyclized by conventional heating (23 h), followed by oxidation (22 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6f** (192 mg, 61%) as a colorless solid: mp 200−204 °C; R_f = 0.37 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3319, 3285, 2222, 1658, 1607, 1471, 1460, 1443, 1290, 1260; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.56 (br s, 1H, N*H*), 7.73−7.69 (m, 2H, *H*-3′/5′), 7.69−7.64 (m, 2H, *H*-2′/6′), 7.65−7.58 (m, 2H, *H*-2″/6″), 7.53−7.47 (m, 2H, *H*-3″/5″), 7.39−7.32 (m, 1H, *H*-4″), 6.62 (d, *J* = 3.0 Hz, 1H, *H*-4), 4.29 (q, *J* = 7.1 Hz, 2H, CH_2), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 160.9 (*C*═O), 140.1 (*C*-1′), 136.0 (*C*-5), 131.6 (2C, *C*-3′/5′), 131.4 (*C*-1″), 130.7 (*C*-3), 130.3 (2C, *C*-2′/6′), 129.3 (2C, *C*-3″/5″), 128.4 (*C*-4″), 125.0 (2C, *C*-2″/6″), 119.3 (*C*N), 119.1 (*C*-2), 110.7 (*C*-4′), 109.8 (*C*-4), 60.9 (CH_2), 14.4 (CH_3); ESI-HRMS calcd for $[C_{20}H_{16}N_2O_2 + Na]^+$ 339.1109, found 339.1111. According to the general procedure B*, **1f** and **2a** were cyclized by conventional heating (10 h), followed by oxidation (9 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6f** (191 mg, 61%) as a colorless solid. According to general procedure C, **1** and **2a** were cyclized by conventional heating (21 h), followed by oxidation (8 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6** (120 mg, 38%) as a colorless solid.

Ethyl 5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (6g). According to the general procedure A, **1g** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (63 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6g** (252 mg, 74%) as a colorless solid: mp 177−179 °C; R_f = 0.43 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3329, 1664, 1611, 1600, 1577, 1570, 1532, 1506, 1477, 1292; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.24 (br s, 1H, N*H*), 7.63−7.48 (m, 4H, *H*-2′/6′/2″/6″), 7.20−7.06 (m, 2H, *H*-3″/5″), 6.97−6.89 (m, 2H, *H*-3′/5′), 6.53 (d, *J* = 3.1 Hz, 1H, *H*-4), 4.29 (q, *J* = 7.1 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 162.6 (d, $^1J_{C,F}$ = 248.2 Hz, *C*-4″), 161.3 (*C*═O), 159.1 (*C*-4′), 134.5 (*C*-5), 133.5 (*C*-3), 130.8 (2C, *C*-2′/6′), 127.6 (d, $^4J_{C,F}$ = 3.4 Hz, *C*-1″), 127.4 (*C*-1′), 126.7 (d, $^3J_{C,F}$ = 8.2 Hz, 2C, *C*-2″/6″), 118.5 (*C*-2), 116.3 (d, $^2J_{C,F}$ = 22.0 Hz, 2C, *C*-3″/5″), 113.3 (2C, *C*-3′/5′), 109.8 (C-4), 60.6 (CH_2), 55.4 (OCH_3), 14.5 (CH_3); ESI-HRMS calcd for $[C_{20}H_{18}FNO_3 + H]^+$ 340.1349, found 340.1338. According to the general procedure B*, **1g** and **2a** were cyclized by microwave-assisted cyclization (2.5 h), followed by oxidation (8 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6g** (220 mg, 65%) as a colorless solid. According to general procedure B**, **1g** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6g** (185 mg, 55%) as a colorless solid.

Ethyl 3-(2-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate (6h). According to the general procedure A, **1h** and **2a** were cyclized by conventional heating (28 h), followed by oxidation (28.5 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6h** (185 mg, 54%) as a yellow solid: mp 129−131 °C; R_f = 0.57 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3302, 1670, 1479, 1450, 1292, 1266, 1233, 1213, 1162, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.81 (br s, 1H, N*H*), 7.68−7.55 (m, 2H, *H*-2″/6″), 7.47−7.42 (m, 1H, *H*-6′), 7.40−7.35 (m, 1H, *H*-3′), 7.30−7.25 (m, 2H, *H*-4′/5′), 7.14−7.07 (m, 2H, *H*-3″/5″), 6.51 (d, *J* = 3.0 Hz, 1H, *H*-4), 4.15 (q, *J* = 7.1 Hz, 2H, CH_2), 1.08 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 162.5 (d, $^1J_{C,F}$ = 248.0 Hz, *C*-4″), 161.5 (*C*═O), 135.0 (*C*-1′), 134.8 (*C*-5), 134.0 (*C*-2′), 131.9 (*C*-3′), 129.9 (*C*-3), 129.2 (*C*-6′), 128.6 (*C*-5′), 127.6 (d, $^4J_{C,F}$ = 3.4 Hz, *C*-1″), 126.8 (d, $^3J_{C,F}$ = 8.1 Hz, 2C, *C*-2″/6″), 126.1 (*C*-4′), 120.5 (*C*-2), 116.1 (d, $^2J_{C,F}$ = 21.9 Hz, 2C, *C*-3″/5″), 110.2 (*C*-4), 60.6 (CH_2), 14.0 (CH_3); ESI-HRMS calcd for $[C_{19}H_{15}ClFNO_2 + Na]^+$ 366.0673, found 366.0673. According to the general procedure B*, **1h** and **2a** were cyclized by conventional heating (46 h), followed by oxidation (17 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6h** (208 mg, 61%) as a yellow solid. According to general procedure C, **1h** and **2a** were cyclized by conventional heating (29 h), followed by oxidation (29 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6h** (97 mg, 28%) as a yellow solid.

Ethyl 3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (6i).[50] According to the general procedure A, **1i** and **2a** were cyclized by conventional heating (25.5 h), followed by oxidation (30 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6i** (179 mg, 56%) as a yellow solid: mp 134−137 °C (Lit.[43]: 132−133 °C); R_f = 0.44 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3308, 1707, 1661, 1608, 1601, 1573, 1528, 1460, 1290, 1266; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.37 (br s, 1H, N*H*), 7.64−7.58 (m, 2H, Ar), 7.58−7.54 (m, 2H, Ar), 7.47−7.40 (m, 2H, *H*-3″/5″), 7.36−7.30 (m, 1H, *H*-4″), 6.97−6.89 (m, 2H, *H*-3′/5′), 6.60 (d, *J* = 3.1 Hz, 1H, *H*-4), 4.29 (q, *J* = 7.1 Hz, 2H, CH_2), 3.86 (s,

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3H, OCH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.3 (C_q), 159.0 (C_q), 135.4 (C_q), 133.4 (C_q), 131.2 (C_q), 130.8 (2C), 129.2 (2C), 128.0 (C_q), 127.6, 124.9 (2C), 118.4 (*C*-2), 113.3 (2C), 109.9 (*C*-4), 60.5 (CH_2), 55.4 (OCH_3), 14.5(CH_3).[43] ESI-HRMS calcd for $[C_{20}H_{19}NO_3 + Na]^+$ 344.1263, found 344.1264. The data are in accordance with the literature. According to the general procedure B*, **1i** and **2a** were cyclized by conventional heating (30 h), followed by oxidation (4 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6i** (193 mg, 61%) as a yellow solid. According to general procedure C, **1i** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (8 h) with anhydrous copper(I) chloride (20 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6i** (127 mg, 40%) as a yellow solid.

Ethyl 3,5-Bis(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylate (6j). According to the general procedure A, **1j** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (24 h). Purification by flash column chromatography (cyclohexane/EtOAc, 3:1) yielded **6j** (113 mg, 28%) as a yellow foam: R_f = 0.18 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3322, 2835, 1680, 1509, 1436, 1244, 1107, 1023, 802, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.26 (br s, 1H, N*H*), 7.19 (d, J = 1.9 Hz, 1H, *H*-2′), 7.17 (dd, J = 8.1, 1.9 Hz, 1H, *H*-6′), 7.16 (dd, J = 8.2, 2.0 Hz, 1H, *H*-6″), 7.08 (d, J = 2.0 Hz, 1H, *H*-2″), 6.92 (d, J = 8.2, 1H, *H*-5″), 6.90 (d, J = 8.1 Hz, 1H, *H*-5′), 6.51 (d, J = 3.1, 1H, *H*-4), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3-4″), 3.92 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 1.27 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.4 (*C*═O), 149.5 (*C*-3″), 149.2 (*C*-4″), 148.4 (*C*-3′), 148.2 (*C*-4′), 135.7 (*C*-5), 133.5 (*C*-3), 127.9 (*C*-1′), 124.3 (*C*-1″), 122.0 (*C*-6′), 118.0 (*C*-2), 117.5 (*C*-6″), 113.2 (*C*-2′), 111.7 (*C*-5″), 110.6 (*C*-5′), 109.3 (*C*-4), 108.5 (*C*-2″), 60.4 (CH_2), 56.2 (OCH_3), 56.1 (2C, OCH_3), 56.0 (OCH_3), 14.6 (CH_3); ESI-HRMS calcd for $[C_{23}H_{25}NO_6 + Na]^+$ 434.1580, found 434.1560. According to the general procedure B*, **1j** and **2a** were cyclized by conventional heating (36 h), followed by oxidation (2 h). Purification by flash column chromatography (cyclohexane/EtOAc, 2:1) yielded **6j** (226 mg, 57%) as a yellow foam. According to general procedure C, **1j** and **2a** were cyclized by conventional heating (36 h), followed by oxidation (9 h) with anhydrous copper(I) chloride (20 mg, 20 mol %) with addition of diethyl azodicarboxylate (92 μL, 20 mol %, 40% in toluene) and 1,10-phenanthroline (36 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 2:1) yielded **6j** (152 mg, 37%) as a yellow foam.

Ethyl 3-(Biphenyl-4-yl)-5-phenyl-1*H*-pyrrole-2-carboxylate (6k). According to the general procedure A, **1k** and **2a** were cyclized by conventional heating (24 h), followed by oxidation (48 h) (additional 0.27 equiv of DDQ added after 24 h). Purification by flash column chromatography (cyclohexane/EtOAc, 10:1) yielded **6k** (225 mg, 61%) as a light brown solid: mp: 197−200 °C; R_f = 0.52 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3310, 1654, 1443, 1291, 1265, 1134, 1033, 816, 761, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.39 (br s, 1H, N*H*), 7.75−7.58 (m, 8H, *H*-2′/3′/5′/6′/2″/6″/2‴/6‴), 7.51−7.40 (m, 4H, *H*-3″/5″/3‴/5‴), 7.40−7.30 (m, 2H, *H*-4″/4‴), 6.69 (d, J = 3.0 Hz, 1H, *H*-4), 4.32 (q, J = 7.1 Hz, 2H, CH_2), 1.30 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.3 (*C*═O), 141.2 (*C*-1″), 140.0 (*C*-4′), 135.6 (*C*-5), 134.2 (*C*-1′), 133.2 (*C*-3), 131.2 (*C*-1‴), 130.1 (2C, *C*-2′/6′), 129.2 (2C, *C*-3‴/5‴), 128.9 (2C, *C*-3″/5″), 128.1 (*C*-4‴), 127.3 (*C*-4″), 127.2 (2C, *C*-3′/5′), 126.6 (2C, *C*-2″/6″), 124.9 (2C, *C*-2‴/6‴), 118.7 (*C*-2), 110.0 (*C*-4), 60.6 (CH_2), 14.5 (CH_3); ESI-HRMS calcd for $[C_{25}H_{21}NO_2 + H]^+$ 368.1651, found 368.1654. According to the general procedure B**, **1k** and **2a** were cyclized by conventional heating (8 h), followed by oxidation (1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6k** (200 mg, 55%) as a light brown solid. According to general procedure C, **1k** and **2a** were cyclized by conventional heating (36 h), followed by oxidation (22 h) with anhydrous copper(I) chloride (20 mg, 20 mol %) with addition of diethyl azodicarboxylate (92 μL, 20 mol %, 40% in toluene) and 1,10-phenanthroline (36 mg, 20 mol %). Purification by flash column chromatography (cyclohexane/EtOAc, 8:1) yielded **6k** (106 mg, 29%) as a light brown solid.

Ethyl 3-[4-(Dimethylamino)phenyl]-5-phenyl-1*H*-pyrrole-2-carboxylate (6l).[23] According to the general procedure B**, **1l** and **2a** were cyclized by conventional heating (12 h), followed by oxidation (1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6l** (151 mg, 46%) as a yellow solid: mp 130−133 °C; R_f = 0.39 (silica gel, cyclohexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.30 (br s, 1H, N*H*), 7.64−7.58 (m, 2H, *H*-2′/6′), 7.58−7.52 (m, 2H, *H*-3″/5″), 7.46−7.39 (m, 2H, *H*-2″/6″), 7.36−7.29 (m, 1H, *H*-4″), 6.82−6.75 (m, 2H, *H*-3′/5′), 6.61 (d, J = 3.1 Hz, 1H, *H*-4), 4.31 (q, J = 7.1 Hz, 2H, CH_2), 3.00 [s, 6H, $N(CH_3)_2$], 1.32 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.3 (*C*═O), 149.8, 135.2, 134.0, 131.3, 130.3 (2C), 129.0 (2C), 127.8, 124.7 (2C), 123.0, 118.0 (*C*-2), 111.9 (2C), 109.6 (*C*-4), 60.3 (CH_2), 40.7 (2C, N-CH_3), 14.4 (CH_3). The data are in accordance with the literature.[23]

Ethyl 3-(4-Hydroxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (6m).[43] According to the general procedure B**, **1m** and **2a** were cyclized by conventional heating (18 h), followed by oxidation (1 h). Purification by flash column chromatography (cyclohexane/EtOAc, 3:1) yielded **6m** (135 mg, 44%) as a light yellow solid: mp 204−206 °C; R_f = 0.27 (silica gel, cyclohexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.25 (br s, 1H, N*H*), 7.62−7.56 (m, 2H, *H*-2″/6″), 7.53−7.48 (m, 2H, *H*-2′/6′), 7.47−7.40 (m, 2H, *H*-3″/5″), 7.36−7.29 (m, 1H, *H*-4″), 6.89−6.82 (m, 2H, *H*-3′/5′), 6.59 (d, J = 3.0 Hz, 1H, *H*-4), 4.92 (br s, 1H, O*H*), 4.30 (q, J = 7.1 Hz, 2H, CH_2), 1.29 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.2 (*C*═O), 154.8, 135.3, 133.3, 131.1, 130.8 (2C), 129.1 (2C), 127.9, 127.6, 124.7 (2C), 118.2 (*C*-2), 114.6 (2C), 109.7 (*C*-4), 60.4 (CH_2), 14.3 (CH_3). The data are in accordance with the literature.[43]

Ethyl 3-(2-Bromo-4,5-dimethoxyphenyl)-5-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylate (6n). According to the general procedure B*, **1n** (203 mg, 0.50 mmol) and **2a** (74 mg, 0.53 mmol, 1.05 equiv) were cyclized by conventional heating (6 h), followed by oxidation (2 h). Purification by flash column chromatography (cyclohexane/EtOAc, 2:1) yielded **6n** (114 mg, 47%) as a light brown foam: R_f = 0.20 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3313, 2837, 1669, 1504, 1435, 1249, 1208, 1022, 782, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.29 (br s, 1H, N*H*), 7.16 (dd, J = 8.3, 2.1 Hz, 1H, *H*-6″), 7.10 (s, 1H, *H*-3′), 7.08 (d, J = 2.1 Hz, 1H, *H*-2″), 6.92 (d, J = 8.3, 1H, *H*-5″), 6.89 (s, 1H, *H*-6′), 6.46 (d, J = 3.0, 1H, *H*-4), 4.19 (q, J = 7.1 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3-4″), 3.92 (s, 3H, OCH_3-4′), 3.91 (s, 3H, OCH_3-3″), 3.86 (s, 3H, OCH_3-5′), 1.14 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.3 (*C*═O), 149.5 (*C*-3″), 149.2 (*C*-4″), 148.7 (*C*-4′), 147.7 (*C*-5′), 135.4 (*C*-5), 131.6 (*C*-3), 129.1 (*C*-1′), 124.3 (*C*-1″), 119.8 (*C*-2), 117.5 (*C*-6″), 115.2 (*C*-3′), 114.5 (*C*-6′), 114.4 (*C*-2′), 111.7 (*C*-5″), 109.8 (*C*-4), 108.4 (*C*-2″), 60.4 (CH_2), 56.3 (OCH_3), 56.2 (2C, OCH_3), 56.1 (OCH_3), 14.3 (CH_3); ESI-HRMS calcd for $[C_{23}H_{24}(^{79}Br)NO_6 + Na]^+$ 512.0685, found 512.0695.

Ethyl 3-(3,4-Dimethoxyphenyl)-5-(furan-2-yl)-1*H*-pyrrole-2-carboxylate (6o). According to the general procedure A, **1o** and **2a** were cyclized by microwave-assisted reaction (2 h, 150 °C, 120 W), followed by microwave-assisted oxidation (2 h, 150 °C, 120 W). Purification by flash column chromatography (cyclohexane/EtOAc, 7:1) yielded **6** (71 mg, 21%) as a yellow oil: R_f = 0.32 (silica gel, cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3301, 2931, 1665, 1523, 1438, 1241, 1113, 1024, 802, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.38 (br s, 1H, N*H*), 7.44 (dd, J = 1.8, 0.7 Hz, 1H, *H*-5″), 7.19 (d, J = 2.0 Hz, 1H, *H*-2′), 7.18 (dd, J = 8.2, 2.0 Hz, 1H, *H*-6′), 6.89 (d, J = 8.2 Hz, 1H, *H*-5′), 6.57 (dd, J = 3.4, 0.7 Hz, 1H, *H*-3″), 6.52 (d, J = 3.0 Hz, 1H, *H*-4), 6.48 (dd, J = 3.4, 1.8, 1H, *H*-4″), 4.29 (q, J = 7.1 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.0 (*C*═O), 148.5 (*C*-4′), 148.2 (*C*-3′), 146.6 (*C*-2″), 142.0 (*C*-5″), 133.3 (*C*-3), 127.5 (*C*-1′), 126.9 (*C*-5), 122.0 (*C*-6′), 117.7 (*C*-2), 113.2 (*C*-2′), 111.9 (*C*-4″), 110.6 (*C*-5′), 108.8 (*C*-4),

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105.7 (*C*-3″), 60.5 (CH_2), 56.0 (2C, OCH_3), 14.5 (CH_3); ESI-HRMS calcd for $[C_{19}H_{19}NO_5 + Na]^+$ 364.1161, found 364.1174.

***tert*-Butyl 3,5-Diphenyl-1*H*-pyrrole-2-carboxylate (6p).** According to the general procedure A, **1a** and **2b** (251 mg, 1.50 mmol, 1.5 equiv) were cyclized by conventional heating (17 h), followed by oxidation (96 h) with DDQ (454 mg, 2.00 mmol, 2.0 equiv). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6p** (94 mg, 30%) as a purple oil: R_f = 0.40 (silica gel, cyclohexane/EtOAc, 4:1); IR (ATR) ν (cm^{-1}) = 3306, 2977, 1657, 1432, 1270, 1253, 1164, 1129, 757, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.50 (br s, 1H, N*H*), 7.66−7.57 (m, 4H, *H*-2′/6′/2″/6″), 7.49−7.38 (m, 4H, *H*-3′/5′/3″/5″), 7.38−7.30 (m, 2H, *H*-4′/4″), 6.63 (d, J = 3.0 Hz, 1H, *H*-4), 1.48 (s, 9H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 161.1 (*C*═O), 135.7 (*C*-1″), 134.9 (*C*-5), 132.7 (*C*-3), 131.3 (*C*-1′), 129.8 (2C, *C*-2′/6′), 129.1 (2C, *C*-3′/5′), 127.8 (*C*-4″), 127.7 (2C, *C*-3″/5″), 127.0 (*C*-4′), 124.8 (2C, *C*-2″/6″), 120.3 (*C*-2), 109.9 (*C*-4), 81.4 ($C(CH_3)_3$), 28.4 (3C, CH_3); ESI-HRMS calcd for $[C_{21}H_{21}NO_2 + Na]^+$ 342.1470, found 342.1473.

***tert*-Butyl 5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (6q).** According to the general procedure A, **1g** and **2b** (251 mg, 1.50 mmol, 1.5 equiv) were cyclized by conventional heating (21.5 h), followed by oxidation (72 h) with DDQ (454 mg, 2.00 mmol, 2.0 equiv). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6q** (145 mg, 40%) as a light yellow solid: mp 121−123 °C; R_f = 0.22 (silica gel, cyclohexane/EtOAc, 6:1); IR (ATR) ν (cm^{-1}) = 3352, 2931, 1660, 1504, 1444, 1244, 1161, 1129, 1040, 805; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.18 (br s, 1H, N*H*), 7.56−7.48 (m, 4H, *H*-2″/6″/H-3′/H-6″), 7.15−7.08 (m, 2H, *H*-4′/5′), 6.95−6.90 (m, 2H, *H*-3″/5″) 6.49 (d, J = 3.0 Hz, 1H, *H*-4), 3.85 (s, 3H, OCH_3), 1.48 (s, 9H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 162.5 (d, $^1J_{C,F}$ = 248 Hz, *C*-4″), 160.1 (*C*═O), 158.9 (*C*-4′), 133.9 (*C*-5), 132.5 (*C*-3), 130.8 (2C, *C*-2′/6′), 127.9 (*C*-1′), 127.8 (d, $^4J_{C,F}$ = 3.3 Hz, *C*-1″), 126.6 (d, 2C, $^3J_{C,F}$ = 8.1 Hz, *C*-2″/6″), 120.0 (*C*-2), 116.2 (d, 2C, $^2J_{C,F}$ = 22 Hz, *C*-3″/5″), 113.2 (2C, *C*-3′/5′), 109.7 (*C*-4), 81.4 ($C(CH_3)_3$), 55.4 (OCH_3), 28.0 (3C, CH_3); ESI-HRMS calcd for $[C_{22}H_{22}FNO_3 + Na]^+$ 390.1481, found 390.1488.

***tert*-Butyl 3-(2-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate (6r).** According to the general procedure A, **1h** (108 mg, 0.40 mmol) and **2b** (104 mg, 0.6 mmol, 1.5 equiv) were cyclized by conventional heating (17.5 h), followed by oxidation (72 h) with DDQ (182 mg, 0.80 mmol, 2.0 equiv). Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **6r** (84 mg, 57%) as a light purple solid: mp 127−129 °C; R_f = 0.37 (silica gel, cyclohexane/EtOAc, 6:1); IR (ATR) ν (cm^{-1}) = 3273, 2978, 1660, 1444, 1303, 1158, 1136, 838, 817, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.58 (br s, 1H, N*H*), 7.59−7.51 (m, 2H, *H*-2″/6″), 7.46−7.40 (m, 1H, *H*-3′), 7.37−7.31 (m, 1H, *H*-6″), 7.29−7.22 (m, 2H, *H*-4′/5′), 7.13−7.06 (m, 2H, *H*-3″/5″) 6.46 (d, J = 3.0 Hz, 1H, *H*-4), 1.29 (s, 9H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 162.4 (d, $^1J_{C,F}$ = 248 Hz, *C*-4″), 161.0 (*C*═O), 135.6 (*C*-2′), 134.1 (*C*-5), 134.1 (*C*-1′), 131.8 (*C*-6′), 129.1 (*C*-3′), 129.0 (*C*-3), 128.4 (*C*-4′), 127.8 (d, $^4J_{C,F}$ = 3.0 Hz, *C*-1″), 126.6 (d, 2C, $^3J_{C,F}$ = 8.1 Hz, *C*-2″/6″), 126.1 (*C*-5′), 122.0 (*C*-2), 116.2 (d, 2C, $^2J_{C,F}$ = 22 Hz, *C*-3″/5″), 109.9 (*C*-4), 81.1 ($C(CH_3)_3$), 28.0 (3C, CH_3); ESI-HRMS calcd for $[C_{21}H_{19}FClNO_2 + Na]^+$ 394.0986, found 394.0990.

***tert*-Butyl 3-(3,4-Dimethoxyphenyl)-5-(furan-2-yl)-1*H*-pyrrole-2-carboxylate (6s).** According to the general procedure A, **1o** and **2b** were cyclized by conventional heating (48 h), followed by oxidation (30 h). Purification by flash column chromatography (cyclohexane/EtOAc, 4:1) yielded **6s** (69 mg, 19%) as a yellow oil: R_f = 0.35 (silica gel, cyclohexane/EtOAc, 4:1); IR (ATR) ν (cm^{-1}) = 3307, 2933, 1672, 1438, 1241, 1164, 1153, 1026, 803, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.34 (br s, 1H, N*H*), 7.41 (dd, J = 1.8, 0.7 Hz, 1H, *H*-5″), 7.12 (dd, J = 8.2, 2.0 Hz, 1H, *H*-6′), 7.10 (d, J = 2.0 Hz, 1H, *H*-2′), 6.88 (d, J = 8.2 Hz, 1H, *H*-5′), 6.53 (dd, J = 3.4, 0.7 Hz, 1H, *H*-3″), 6.47 (d, J = 3.0 Hz, 1H, *H*-4), 6.45 (dd, J = 3.4, 1.8, 1H, *H*-4″), 3.91 (s, 3H, OCH_3-3′), 3.89 (s, 3H, OCH_3-4′), 1.47 (s, 9H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 160.5 (C═O), 148.2 (*C*-4′), 148.1 (*C*-3′), 146.7 (*C*-2″), 141.8 (*C*-5″), 132.5 (*C*-3), 128.0 (*C*-1′), 126.3 (*C*-5), 122.1 (*C*-6′), 119.2 (*C*-2), 113.2 (*C*-2′), 111.8 (*C*-4″), 110.5 (*C*-5′), 108.7 (*C*-4), 105.3 (*C*-3″), 81.2 ($C(CH_3)_3$), 55.9 (2C, OCH_3), 28.4 (3C, CH_3); ESI-HRMS calcd for $[C_{21}H_{23}NO_5 + Na]^+$ 392.1474, found 392.1479.

Ethyl 4-Bromo-3,5-diphenyl-1*H*-pyrrole-2-carboxylate 7. Method I: According to general procedure A, **1a** and **2a** were placed in a microwave vessel, dissolved in pyridine (3 mL), and cyclized via microwave-assisted cyclization (2 h). After dilution with pyridine (7 mL) and adding DDQ (250 mg, 1.10 mmol, 1.1 equiv) in acetic acid (4 mL), the reaction mixture was refluxed for 20 h. The crude reaction mixture was subjected to bromination at ambient temperature by the addition of NBS (187 mg, 1.05 mmol, 1.05 equiv), and additional NBS (100 mg, 0.5 equiv) was added after 24 h, followed by stirring for another 5 h. Purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **7** (181 mg, 49%) as a colorless solid: mp 145−148 °C; R_f = 0.28 (silica gel, cyclohexane/EtOAc, 6:1); IR (ATR) ν (cm^{-1}) = 3282, 2979, 1670, 1434, 1289, 1264, 1165, 1024, 762, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.30 (br s, 1H, N*H*), 7.78−7.72 (m, 2H, *H*-2″/6″), 7.54−7.46 (m, 2H, *H*-3″/5″), 7.46−7.33 (m, 6H, *H*-4″/Ph′), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 1.13 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 160.8 (*C*═O), 133.4 (C_q), 133.1 (*C*-5), 132.3 (C_q), 130.8 (2C, *C*-2′/6′), 130.7 (*C*-1″), 129.0 (2C, *C*-3″/5″), 128.8 (*C*-4″), 127.73 (*C*-4′), 127.72 (2C, *C*-2″/6″), 127.6 (2C, *C*-3′/5′), 119.3 (*C*-2), 99.0 (*C*-4), 60.8 (CH_2), 14.1 (CH_3); ESI-HRMS calcd for $[C_{19}H_{16}(^{79}Br)NO_2 + Na]^+$ 392.0262, found 392.0267. **Method II**: **1a** and **2a** were subjected to microwave-assisted cyclization (1 h), followed by oxidation via anhydrous $[Cu(MeCN)_4]PF_6$ (38 mg, 10 mol %) with addition of 2,2′-bipyridine (16 mg, 10 mol %) (with air continuously passing through the reaction mixture for copper) for 13 h. To the crude reaction mixture was added NBS (187 mg, 1.05 mmol, 1.05 equiv). After stirring for 5 h at ambient temperature, purification by flash column chromatography (cyclohexane/EtOAc, 6:1) yielded **7** (208 mg, 56%) as a colorless solid.

General Procedure for the Synthesis of Pyrrole-2-carboxamides 9. Unless otherwise noted, the respective enone (1.00 mmol, 1.00 equiv) and amide (1.20 mmol, 1.20 equiv) were placed in a microwave vessel and dissolved in pyridine (4 mL). Molecular sieve 3 Å (100 mg) was added, followed by sealing the vessel and heating to 130 °C for 60 min at 200 W in a microwave reactor. The reaction temperature increased from 25 to 130 °C in 180 s and was maintained at 130 °C for the rest of the period (until complete conversion of the enone was determined, as indicated by TLC or HPLC-MS, 1−2 h). Then, $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv or 2.00 mmol, 363 mg, 2.00 equiv) was introduced in one portion and the mixture was heated under the same microwave conditions until complete conversion of the dihydropyrrole was determined (1−2 h), as indicated by TLC or HPLC-MS. Upon completion, the solvent was removed by azeotropic distillation with toluene. The residue was dissolved in dichloromethane (60 mL) and subsequently washed with a 0.1 M Na_2-EDTA solution (3 × 30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed in vacuo, and the resiude was purified by column chromatography on silica gel.

***N*,*N*-Dimethyl-3,5-diphenyl-1*H*-pyrrole-2-carboxamide (9a).** The general procedure was applied using **2a**, 2-amino-*N*,*N*-dimethylacetamide hydrochloride (**8a**), and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (2 h) and oxidation (2 h), purification of the crude reaction mixture by flash column chromatography (cyclohexane/EtOAc, 3:1) yielded **9a** (133 mg, 46%) as a colorless solid: mp 155−156 °C; R_f = 0.16 (silica gel, cyclohexane/EtOAc, 3:1); IR (ATR) ν (cm^{-1}) = 3145, 3062, 3025, 2929, 1650, 1595, 1491, 1274, 760, 696; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.78 (d, J = 2.8 Hz, 1H, N*H*), 7.80−7.73 (m, 2H, *H*-2″/6″), 7.43−7.32 (m, 6H, *H*-2′/6′/3′/5′/3″/5″), 7.27−7.17 (m, 2H, *H*-4′/4″), 6.84 (d, J = 2.8 Hz, 1H, *H*-4), 2.95 (s, 3H, CH_3), 2.64 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm) = 164.4 (*C*═O), 135.4 (*C*-1′), 132.3 (*C*-5), 131.9 (*C*-1″), 128.7 (2C, C_{Ph}), 128.6 (2C, C_{Ph}), 126.43 (2C, C_{Ph}), 126.36 (*C*-4″), 126.0 (*C*-4′), 124.2 (*C*-3), 124.0 (2C, *C*-2″/6″), 123.3 (*C*-2), 105.3 (*C*-4), 37.7 (CH_3), 34.4 (CH_3); ESI-HRMS calcd for $[C_{19}H_{18}N_2O + H]^+$ 291.1497, found

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291.1503. The general procedure was applied using **2a**, **8a**, and $Cu(OAc)_2$ (2.00 mmol, 363 mg, 2.00 equiv). After cyclization (2 h) and oxidation (2 h), purification of the crude reaction mixture by flash column chromatography (cyclohexane/EtOAc, 3:1) yielded **9a** (160 mg, 55%) as a colorless solid.

***N*-Isobutyl-3,5-diphenyl-1*H*-pyrrole-2-carboxamide (9b).** The general procedure was applied using **1a**, 2-amino-*N*-isobutylacetamide hydrochloride (**8b**), and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (1 h) and oxidation (2 h), purification of the crude reaction mixture by flash column chromatography (cyclohexane/EtOAc, 4:1) yielded **9b** (189 mg, 59%) as a colorless solid: mp 143−144 °C; R_f = 0.18 (silica gel, cyclohexane/EtOAc, 4:1); IR (ATR) ν (cm^{-1}) = 3420, 3240, 3062, 2958, 1630, 1533, 1491, 1267, 817, 760, 701; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.60 (d, J = 2.8 Hz, 1H, N*H*), 7.84−7.77 (m, 2H, *H*-2″/6″), 7.54−7.47 (m, 2H, *H*-2′/6′), 7.45−7.32 (m, 4H, *H*-3′/5′, *H*-3″/5″), 7.35−7.20 (m, 3H, C(=O)N*H*/*H*-4′/*H*-4″), 6.69 (d, J = 2.8 Hz, 1H, *H*-4), 3.02 (dd, J = 6.7, 5.8 Hz, 2H, CH_2), 1.69 (n, J = 6.7 Hz, 1H, C*H*), 0.82 (d, J = 6.7 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm) = 161.1 (C=O), 135.7 (*C*-1′), 132.7 (*C*-5), 131.6 (*C*-1″), 128.8 (2C, *C*-2′/6′), 128.7 (2C, *C*-3″/5″), 128.1 (2C, *C*-3′/5′), 127.3 (*C*-3), 126.7 (*C*-4″), 126.4 (*C*-4′), 124.6 (2C, *C*-2″/6″), 123.6 (*C*-2), 108.3 (*C*-4), 46.3 (CH_2), 28.1 (CH), 20.2 (2C, CH_3); ESI-HRMS calcd for $[C_{21}H_{22}N_2O + H]^+$ 319.1810, found 319.1800.

5-(4-Fluorophenyl)-*N*-isobutyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxamide (9c). The general procedure was applied using **1g**, **8b**, and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (2 h) and oxidation (1 h), purification of the crude reaction mixture by flash column chromatography (cyclohexane/EtOAc, 4:1) yielded **9c** (156 mg, 43%) as a colorless solid: mp 175−176 °C (dec.); R_f = 0.10 (silica gel, cyclohexane/EtOAc, 5:1); IR (ATR) ν (cm^{-1}) = 3414, 3245, 2959, 2872, 1627, 1529, 1502, 1248, 837, 812; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.53 (d, J = 2.8 Hz, 1H, N*H*), 7.88−7.79 (m, 2H, *H*-2″/6″), 7.47−7.38 (m, 2H, *H*-2′/6′), 7.28−7.18 (m, 2H, *H*-3″/5″), 7.11 (t, J = 5.8 Hz, C(=O)N*H*), 6.98−6.21 (m, 2H, *H*-3′/5′), 6.61 (d, J = 2.8 Hz, 1H, *H*-4), 3.77 (s, 3H, OCH_3), 3.01 (dd, J = 6.7, 5.8 Hz, 2H, CH_2), 1.68 (n, J = 6.7 Hz, 1H, C*H*), 0.81 (d, J = 6.7 Hz, 6H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm) = 161.13 (d, $^1J_{C,F}$ = 243.6 Hz, *C*-4″), 161.08 (C=O), 158.1 (*C*-4′), 131.8 (*C*-5), 130.0 (2C, *C*-2′/6′), 128.4 (d, $^4J_{C,F}$ = 3.4 Hz, *C*-1″), 127.9 (*C*-1′), 127.2 (*C*-3), 126.6 (d, $^3J_{C,F}$ = 8.0 Hz, 2C, *C*-2″/6″), 123.2 (*C*-2), 115.5 (d, $^2J_{C,F}$ = 21.7 Hz, 2C, *C*-3″/5″), 113.6 (2C, *C*-3′/5′), 108.4 (*C*-4), 55.1 (OCH_3), 46.2 (CH_2), 28.1 (CH), 20.2 (2C, CH_3); ESI-HRMS calcd for $[C_{22}H_{23}N_2O_2F + H]^+$ 367.1822, found 367.1830.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all synthesized compounds, COSY, HSQC and HMBC spectra of all new compounds, as well as the crystallographic data (.cif) for compounds **6c** and **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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