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Domino Reaction for the Synthesis of Polysubstituted Pyrroles and Lamellarin R

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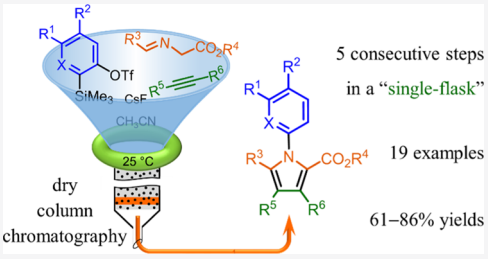
ABSTRACT: A three-component annulation reaction was developed for the synthesis of pyrroles, a class of compounds with various properties valuable to biomedical and polymer industries. Treatment of α-silylaryl triflates, Schiff bases, and alkynes generated polysubstituted pyrroles in good yields (61−86%) with regioselectivity. This domino reaction involved completion of five sequential steps in a single flask, which comprised aryne formation through 1,2-elimination, their alkylation by Schiff bases through 1,2-addition, 1,4-intramolecular proton transfer, Hüisgen 1,3-dipolar cycloaddition, and dehydrogenative aromatization. It was then successfully applied as the key step in the synthesis of the natural product lamellarin R. This new reaction represents an efficient, sustainable process for the production of chemical materials.



INTRODUCTION

Pyrrole is a five-membered heterocyclic aromatic compound, which darkens readily upon exposure to air. Although pyrrole is not naturally occurring, many of its derivatives are found in natural products.[1] Examples include chlorophylls, porphyrins, vitamin B_{12}, and so forth. Pyrrole-containing secondary metabolites include lamellarin, prodigiosin, rhazinilam, ryanodine, sceptrin, and so forth. It is of interest to note that pyrrole is also a constituent of tobacco smoke.[2]

As a flat and electron-rich ring, pyrrole is susceptible to electrophilic attack and can react with numerous biomolecules. Thus, it becomes an important constituent of well-established drugs, such as atorvastatin, chlorfenapyr, premazepam, pyrvinium, roseophilin, tolmetin, and zomepirac.[3] The pyrrole scaffold is used to construct therapeutic agents with antibacterial, anticancer, antifungal, anti-inflammatory, antimalarial, antimicrobial, antiprotozoal, antipsychotic, antiviral, antitubercular, and anxiolytic properties among others.[4,5] This molecule also plays an active role as a component of polymers and indigoid dyes.[5] In catalytic reactions, pyrroles are widely used for corrosion inhibition, metallurgy, polymerization, and preservation.[5]

Many methods have been developed for the synthesis of pyrroles,[6−11] such as the aza-Wittig reaction, the Hantzsch reaction, the Paal−Knorr condensation reaction, carbenoid insertions, the Friedel−Crafts acylation, the Heck coupling, hydroarylations, and the Michael addition. Quiclet-Sire and Zard[12] provided elegant convergent routes to pyrroles by exploiting unusual radical chemistry.

Schiff bases have been used in pyrrole synthesis. Examples include Ag-catalyzed tandem 1,3-dipolar cycloaddition/aromatization by Hu and Wang,[13] Cu-catalyzed three-component cyclization by Kostakis and Lykakis,[14] the Cu-catalyzed cascade process involving (3 + 2) cycloaddition of azomethine ylide by Lu and Wang,[15] Li-mediated annulation,[16] and phosphonite-mediated 1,3-dipolar cycloaddition by Cyr and Arndtsen.[17] Many other established methods for pyrrole generation require the use of expensive or toxic metal catalysts, some of which produce harmful waste streams.[18−20] These concerns inspired us to develop a novel and efficient approach for the synthesis of pyrroles with various substituents through a domino reaction.

Implementation of our newly developed method as the key step in the synthesis of natural products (e.g., lamellarins) would affirm its efficiency and applicability. Lamellarins are pyrrole-derived marine alkaloids with diverse biological properties.[21] This versatility makes lamellarins important subjects for research. They are often used as a starting point for the design of anticancer and antiviral compounds.[22] In addition, efforts have been devoted to the invention of new and improved methods for lamellarin synthesis.[23,24]

Herein, we report on a newly developed method for the direct synthesis of polysubstituted pyrroles from α-silylaryl triflates **1**, Schiff bases **2**, and alkynes **3**. It involves a "single-flask" reaction. It possesses advantages of a few synthetic steps,

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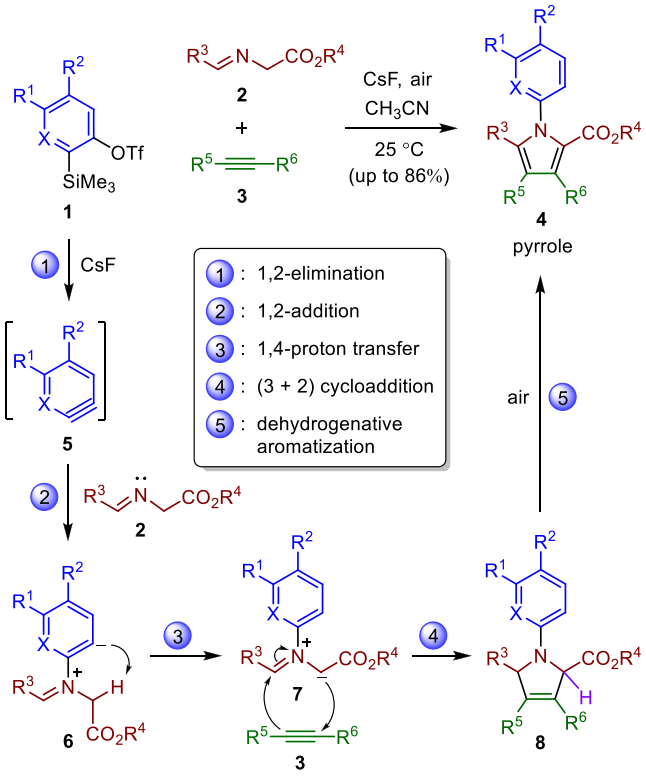
a moderate reaction temperature, and metal-free conditions and provides good regioselectivity and yields. This domino reaction was applied as the key step in the synthesis of lamellarin R, a tetrasubstituted natural pyrrole.

■ RESULTS AND DISCUSSION

The feasibility of the new method for the synthesis of the polysubstituted pyrroles shown in Scheme 1 was investigated.

Scheme 1. "Single-Flask" Synthesis of Pyrroles 4 from α-Silylaryl Triflates 1, Schiff Bases 2, and Alkynes 3



1				2		3	
	R^1 =	R^2 =	X=	R^3 =	R^4 =	R^5 =	R^6 =
a.	H	H	CH	a. Ph–	Me	a. CO_2Me	H
b.	MeO	H	CH	b. *p*-MePh–	Me	b. CO_2Et	H
c.	MeO	MeO	CH	c. *p*-MeOPh–	Me	c. C(=O)Me	H
d.	H	H	N	d. *p*-ClPh–	Me	d. CO_2Me	Me
				e. *p*-BrPh–	Me	e. CO_2Me	CO_2Me
				f. 1-$C_{10}H_7$–	Me	f. CO_2Et	CO_2Et
				g. 2-furyl–	Me	g. *n*-C_3H_7	*n*-C_3H_7
				h. 2-thienyl–	Me	h. *p*-MeOPh–	*p*-MeOPh–
				i. H	Me		
				j. Ph–	Et		
				k. *p*-MeOPh–	Et		

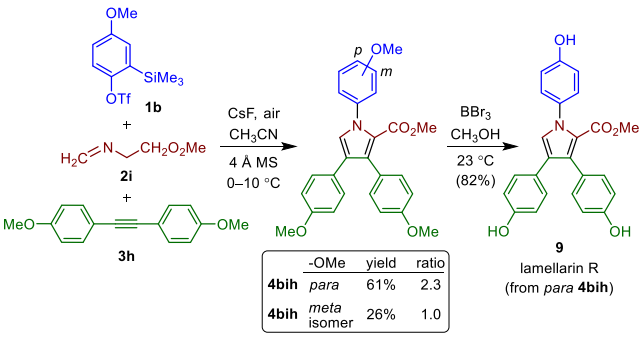
A mixture of (trimethylsilyl)aryl triflates **1** (1.0 equiv), Schiff bases **2** (1.0 equiv), and alkynes **3** (1.2 equiv) was treated with fluoride (2.0 equiv) in acetonitrile at 25 °C. During the optimization of the new reaction conditions, different combinations of solvents, fluorides, additive of 18-crown-6, temperatures, and reaction times were studied for the synthesis of pyrrole **4acb**. The data in Table 1 reveal that the reaction could be conducted in THF (entries 1−5), acetonitrile (entries 6−8), and toluene (entries 9 and 10). Acetonitrile was the best solvent (entry 8). Among the three fluorides *n*-Bu_4NF, CsF, and KF, the use of CsF without 18-crown-6 produced the highest yields of pyrroles (86% in entry 8). This annulation process proceeded well at 25 °C; elevation of the reaction temperature was unnecessary.

After 2.0 h of stirring under a nitrogen atmosphere followed by 6.0 h of stirring in open air, pyrroles **4aab**−**dbb** were often isolated in 61−86% yields with purity >99.2%. Regarding green chemistry characteristics, the atom economy[25] was calculated to be 62.8%, whereas the atom efficiency[26] was 54.0% for compound **4acb**.

Various starting materials were used to evaluate the scope of this new reaction. The methoxy group was allowed to attach to the benzene nucleus of α-silylaryl triflates **1**. The benzene nucleus could be replaced by a pyridine ring (i.e., **1d**). Methyl, methoxy, chloro, and bromo groups could be attached to the phenyl terminal (R^3) in Schiff bases **2**. This phenyl group could also be replaced by a naphthyl, furyl, and thienyl group (i.e., **2f**, **2g**, and **2h**, respectively). The alkyl terminal group of the Schiff bases **2** must have a methylene unit that was attached to an electron-withdrawing alkoxycarbonyl group. The two substituents in alkynes **3** could be hydrogen atoms, alkyl, acetyl, alkoxycarbonyl, or methoxyphenyl groups. The use of these starting materials often led to the desired pyrroles in 61−86% yields (Table 2). The exception involved the use of inactivated alkyne **3g**, which had alkyl groups on both sides of the carbon to carbon triple bond. As a result, product **4acg** was obtained only up to 15% yield.

To appraise the new reaction processes, we applied the new annulation reaction as the key step in the synthesis of lamellarin R (**9**, Scheme 2). Cesium fluoride (3.0 equiv) in

Scheme 2. Synthesis of Lamellarin R by Use of an Aryne-Induced Domino Reaction as the Key Step



	-OMe	yield	ratio
4bih	*para*	61%	2.3
4bih	*meta* isomer	26%	1.0

acetonitrile was added to a solution containing (methoxy)-silylphenyl triflate **1b** (1.2 equiv), Schiff base **2i** (1.0 equiv), and bis(methoxyphenyl)acetylene (**3h**, 1.2 equiv). Reagents **1b** and **3h** are commercially available; Schiff base **2i** is readily available through the simple condensation of glycine methyl ester hydrochloride with paraformaldehyde.[27] After the annulation reaction proceeded at 0−10 °C for 6.0 h, the desired pyrroles *para*-**4bih** and it's regioisomer *meta*-**4bih** were generated in a ratio of 2.3:1. Finally, the isolated pyrrole *para*-**4bih** (61%) underwent demethylation with BBr_3 in methanol at room temperature to produce lamellarin R (**9**) in a high yield by use of Jia's method.[23]

For verification of its configuration conclusively, the molecular framework of compound **4acb** was obtained through single-crystal X-ray diffraction analysis. The data and ORTEP

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Table 1. Optimization of Yield for the Reaction 1a + 2c + 3b → 4acb by Use of Various Solvents, Fluorides, Temperatures, and Reaction Times

entry	solvent	F^- source (2.0 equiv)	additive (2.0 equiv)	temperature (°C)	time (h)	yield (%)
1	THF	CsF		25	10	12
2	THF	KF	18-crown-6	25	10	20
3	THF	KF	18-crown-6	60	10	45
4	THF	n-Bu_4NF		60	4.0	18
5	THF	n-Bu_4NF		25	8.0	7.0
6	CH_3CN	KF	18-crown-6	25	10	
7	CH_3CN	KF	18-crown-6	60	8.0	
8	CH_3CN	CsF		25	6.0	86
9	toluene	CsF		25	6.0	23
10	toluene	KF	18-crown-6	80	8.0	38

diagram in the Supporting Information reveal the relative positions of the four substituents and the vinylic proton of the pyrrole nucleus.

Our design and concerns in the development of a single-flask method for the synthesis of pyrroles **4** from triflates, Schiff bases, and alkynes are described in Scheme 1. The α-silylaryl triflates **1** first react with cesium fluoride to generate aryne intermediates **5** through 1,2-elimination (step 1).[28] Then, Schiff bases **2** are added to arynes **5** in situ to produce iminium carbanions **6** through 1,2-addition (step 2). The carbanion center in betaines **6** may trap an acidic proton nearby to generate azomethine ylides **7** through 1,4-intramolecular proton transfer (step 3).[28] Subsequently, the Hüisgen 1,3-dipolar cycloaddition takes place between ylides **7** and alkynes **3** to give the (3 + 2) cycloadducts **8** (step 4). Noteworthily, the activated acetylenes **3** as the starting material are expected to be more competitive than the solvent acetonitrile for reacting with azomethine ylides **7**. Autoxidation in open air[29,30] would then lead the 3-pyrrolines **8** to pyrroles **4** as the final products (step 5). In a control experiment, a compound with a similar framework to intermediates **8** but with a CH_2 unit between the CO_2R^3 group and the pyrroline ring was produced. It was found inert to the dehydrogenative aromatization.

Results from our trials indicate that the dehydrogenative aromatization of pyrrolines **8** indeed proceeded gradually at 25 °C.[31] The smooth conversion of **8** → **4** was facilitated by the presence of a CO_2R^3 group attached directly to the C2 position of 3-pyrrolines **8**. Activity of the allylic hydrogen at the α position to the CO_2R^3 group increases significantly. Thus, pyrrolines **8** with such a framework are well-suited for dehydrogenative aromatization.

This approach to pyrrole synthesis accomplishes five steps sequentially in a single flask. This new domino reaction offers the following benefits: 1. The reaction generates the desired products in good-to-high yields at room temperature without any involvement of harsh conditions or reagents. 2. The entire "single-flask" reaction can be conducted with ease without isolation of the intermediates.

Application of this new reaction as the key step in the synthesis of the natural product lamellarin R (**9**) allowed the establishment of one pyrrole nucleus, three anisole moieties, and one ester functionality in its scaffold in a single flask. In the reaction shown in Scheme 2, a byproduct *meta*-**4bih** was isolated in a 26% yield. Its generation was due to two possible 1,2-additions of Schiff bases **2i** to an unsymmetrical benzyne intermediate. Thus, the addition may occur at both the meta and the para positions.

■ CONCLUSIONS

Polysubstituted pyrroles can be synthesized from silylaryl triflates, Schiff bases, and alkynes through an aryne-induced domino reaction. The overall pathway comprises 1,2-elimination, 1,2-nucleophilic addition, 1,4-proton transfer, (3 + 2) cycloaddition, and dehydrogenative aromatization. This reaction was applied successfully as the key step in the synthesis of lamellarin R.

Utilization of this new method in chemical synthesis minimizes waste production and reduces the need for extra reagents, solvents, and labor. Hence, this three-component synthetic protocol is ecologically and environmentally benign for the production of fine chemicals.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. Acetonitrile, dichloromethane, ethyl acetate, hexanes, and toluene from Mallinckrodt Chemical Co. were dried and distilled from CaH_2. Tetrahydrofuran (THF) from Mallinckrodt Chemicals Co. was dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. The reagents purchased from Alfa Aesar included 4-bromobenzaldehyde, 3-butyn-2-one, 4-chlorobenzaldehyde, diethyl acetylenedicarboxylate, dimethyl acetylenedicarboxylate (DMAD), ethyl acetylenecarboxylate, glycine ethyl ester hydrochloride, glycine methyl ester hydrochloride, 4-methoxybenzaldehyde, methyl acetylenecarboxylate, and 4-methylbenzaldehyde. The reagents purchased from Sigma-Aldrich included benzaldehyde, bis(4-methoxyphenyl)acetylene, furan-2-carboxaldehyde, α-naphthaldehyde, 4-octyne, paraformaldehyde, thiophene-2-carboxaldehyde, and 3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate. Cesium fluoride (CsF), 18-crown-6, methyl 2-butynoate, potassium fluoride (KF), tetra-n-butylammonium fluoride (TBAF), and trimethylamine (Et_3N) were purchased from Acros. The compounds purchased from Tokyo Chemical Industry Co. included 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate, 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate, and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate.

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254). Purification by gravity column chromatography was carried out by use of Silicycle ultrapure silica gel (particle size 40−63 μM, 230−400 mesh).

Infrared (IR) spectra were measured on a Fourier transform infrared (FT-IR) spectrometer. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; and w, weak. Proton NMR spectra were obtained on a 400 MHz spectrometer by use of chloroform-d ($CDCl_3$) as the solvent. Proton NMR chemical shifts were referenced to the residual protonated solvent (δ 7.24 ppm for chloroform). Carbon-13 NMR spectra were obtained on a 100 MHz spectrometer by use of chloroform-d ($CDCl_3$) as the solvent. Carbon-13 chemical shifts were referenced to the center of the $CDCl_3$

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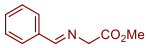
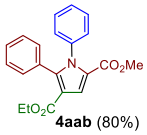
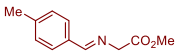
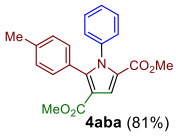
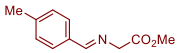
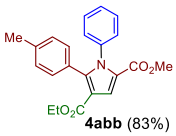
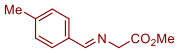
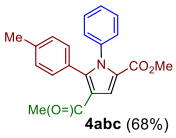
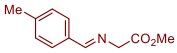
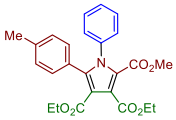
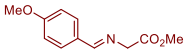
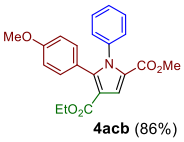
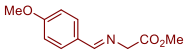
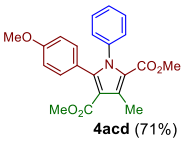
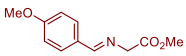
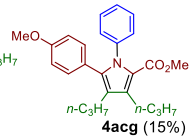
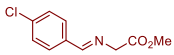
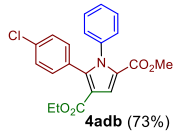
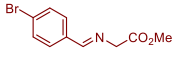
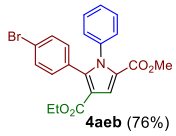
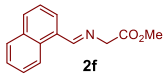
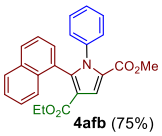
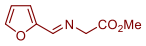
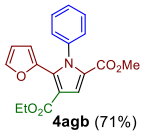
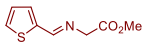
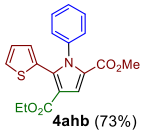
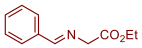
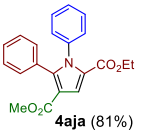
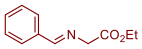
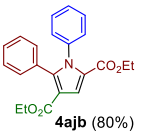
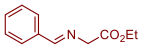
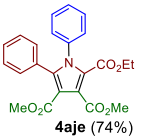
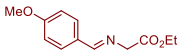
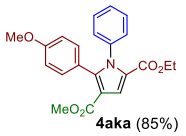
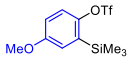
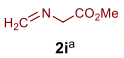
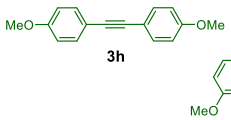
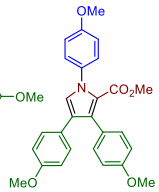
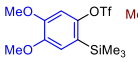
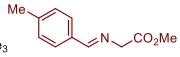
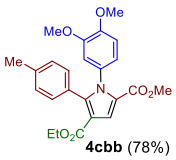
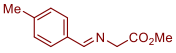
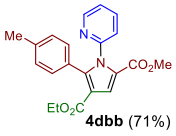
Table 2. Reactants 1−3 and Products 4 of the Newly Developed Annulation Reaction along with Their Isolated Yields

silylaryl triflate	Schiff base	acetylene	pyrrole
 1a	 2a	3b	 4aab (80%)
1a	 2b	3a	 4aba (81%)
1a	 2b	3b	 4abb (83%)
1a	 2b	3c	 4abc (68%)
1a	 2b	3f	 4abf (72%)
1a	 2c	3b	 4acb (86%)
1a	 2c	3d	 4acd (71%)
1a	 2c	3g	 4acg (15%)
1a	 2d	3b	 4adb (73%)
1a	 2e	3b	 4aeb (76%)
1a	 2f	3b	 4afb (75%)
1a	 2g	3b	 4agb (71%)
1a	 2h	3b	 4ahb (73%)
1a	 2j	3a	 4aja (81%)
1a	 2j	3b	 4ajb (80%)
1a	 2j	3e	 4aje (74%)
1a	 2k	3a	 4aka (85%)
 1b	 2i[a]	 3h	 4bih (61%)
 1c	 2b	3b	 4cbb (78%)
 1d	 2b	3b	 4dbb (71%)

[a]This Schiff base was generated in situ.

triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; and *J*, coupling constant (hertz). High-resolution mass spectra (HRMS) were measured on an instrument by use of a time-of-flight (TOF) mass analyzer with electrospray ionization (ESI).

Standard Procedure for the Single-Flask Synthesis of Pyrroles 4. To a stirred solution of 2-silylphenyl triflate 1 (1.0 equiv) in dry CH_3CN (2.0−2.5 mL) were added a Schiff base 2 (1.0 equiv), an alkyne 3 (1.2 equiv), and CsF (2.0−2.1 equiv) at room temperature under a nitrogen atmosphere. After the reaction mixture was stirred at 25 °C for 6.0−8.0 h, the reaction mixture was quenched with water (10 mL) and then extracted with EtOAc (3 × 10 mL). The

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combined organic layers were dried over $CaSO_4$ (s), filtered, and concentrated under reduced pressure to afford the products. It was then purified by use of dry column chromatography on silica gel with a limited amount[32] of EtOAc in hexanes as the eluent to give the desired pyrrole 4.

*4-Ethoxycarbonyl-2-methoxycarbonyl-5-phenyl-N-phenylpyrrole (**4aab**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.2 mg, 0.168 mmol, 1.0 equiv), Schiff base **2a**[33] (29.8 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.8 mg, 0.202 mmol, 1.2 equiv), and CsF (51.2 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.0 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aab** (46.4 mg, 0.134 mmol) in 80% yield as a yellow liquid: TLC R_f 0.45 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.25−7.23 (m, 3H), 7.22−7.18 (m, 3H), 7.12−7.10 (m, 2H), 7.06−7.04 (m, 2H), 4.13 (q, 2H, J = 7.3 Hz), 3.69 (s, 3H), 1.13 (t, 3H, J = 7.3 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.8, 160.5, 144.5, 137.9, 130.5, 128.8, 128.3, 128.2, 128.1, 127.9, 127.1, 123.4, 119.5, 114.4, 59.9, 51.4, 14.2; IR (neat): 2924 (s), 1714 (s, C═O), 1598 (m), 1470 (m), 1235 (s, C−O), 1122 (m), 1039 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_4$ + H, 350.1392; found, 350.1385.

*2,4-Dimethoxycarbonyl-5-(4-methylphenyl)-N-phenylpyrrole (**4aba**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.4 mg, 0.168 mmol, 1.0 equiv), Schiff base **2b**[34] (32.1 mg, 0.168 mmol, 1.0 equiv), methyl acetylenecarboxylate (**3a**, 16.9 mg, 0.202 mmol, 1.2 equiv), and CsF (51.6 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.0 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aba** (47.3 mg, 0.136 mmol) in 81% yield as a yellow liquid: TLC R_f 0.45 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.28−7.26 (m, 3H), 7.07−7.06 (m, 2H), 7.02−6.97 (m, 4H), 3.76 (s, 3H), 3.71 (s, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 159.9, 144.3, 137.9, 137.7, 130.3, 128.3, 128.2, 128.1, 127.9, 127.1, 123.5, 119.4, 114.2, 51.3, 51.1, 21.3; IR (neat): 2923 (s), 1713 (s, C═O), 1598 (m), 1470 (s), 1235 (s, C−O), 1116 (s), 1039 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_4$ + H, 350.1392; found, 350.1388.

*4-Ethoxycarbonyl-2-methoxycarbonyl-5-(4-methylphenyl)-N-phenylpyrrole (**4abb**).* (a) The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.3 mg, 0.168 mmol, 1.0 equiv), Schiff base **2b**[34] (32.3 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.9 mg, 0.201 mmol, 1.2 equiv), and CsF (51.4 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4abb** (50.2 mg, 0.139 mmol) in 83% yield as a yellow liquid: TLC R_f 0.45 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H), 7.26−7.24 (m, 3H), 7.07−7.05 (m, 2H), 7.01−6.95 (m, 4H), 4.15 (q, 2H, J = 6.9 Hz), 3.69 (s, 3H), 2.24 (s, 3H), 1.18 (t, 3H, J = 6.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.6, 160.3, 144.4, 138.0, 137.8, 130.5, 128.2, 128.1, 128.1, 127.9, 127.0, 123.3, 119.4, 114.3, 59.9, 51.4, 21.4, 14.2; IR (neat): 2924 (m), 1715 (s, C═O), 1598 (w), 1470 (m), 1201 (s, C−O), 1116 (m), 1039 (m), 758 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}NO_4$ + H, 364.1548; found, 364.1551.

(b) The same procedure was followed by use of 2-silylphenyl triflate **1a** (2.60 g, 8.71 mmol, 1.0 equiv), Schiff base **2b**[34] (1.67 g, 8.71 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 1.02 g, 10.5 mmol, 1.2 equiv), and CsF (2.65 g, 17.4 mmol, 2.0 equiv) in CH_3CN (100 mL). The desired pyrrole **4abb** (2.59 g, 7.14 mmol) was obtained in 82% yield as a yellow liquid.

*2-Methoxycarbonyl-4-methylcarbonyl-5-(4-methylphenyl)-N-phenylpyrrole (**4abc**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.1 mg, 0.168 mmol, 1.0 equiv), Schiff base **2b**[34] (32.2 mg, 0.168 mmol, 1.0 equiv), 3-butyn-2-one (**3c**, 13.7 mg, 0.201 mmol, 1.2 equiv), and CsF (51.1 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.2 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4abc** (38.1 mg, 0.114 mmol) in 68% yield as a yellow liquid: TLC R_f 0.40 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (s, 1H), 7.26−7.23 (m, 3H), 7.07−7.05 (m, 2H), 7.01−6.95 (m, 4H), 3.69 (s, 3H), 2.39 (s, 3H) 2.24 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 193.7, 160.3, 144.2, 138.4, 138.1, 130.3, 128.2, 128.1, 128.0, 127.8, 127.3, 123.3, 117.7, 114.2, 51.2, 28.7, 21.3; IR (neat): 2925 (m), 1717 (s, C═O), 1609 (m), 1438 (m), 1247 (s, C−O), 1122 (m), 1032 (s), 749 (w) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$ + H, 334.1443; found, 334.1447.

*3,4-Diethoxycarbonyl-2-methoxycarbonyl-5-(4-methylphenyl)-N-phenylpyrrole (**4abf**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.5 mg, 0.168 mmol, 1.0 equiv), Schiff base **2b**[34] (32.2 mg, 0.168 mmol, 1.0 equiv), diethyl acetylenedicarboxylate (**3f**, 34.5 mg, 0.202 mmol, 1.2 equiv), and CsF (51.3 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.2 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4abf** (52.6 mg, 0.121 mmol) in 72% yield as yellow solids: TLC R_f 0.40 (20% EtOAc in hexanes as the eluent); mp (recrystallized from EtOH) 144.7−146.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26−7.24 (m, 3H), 7.09−7.06 (m, 2H), 7.02−6.07 (m, 4H), 4.35 (q, 2H, J = 7.0 Hz), 4.19 (q, 2H, J = 7.2 Hz), 3.75 (s, 3H), 2.24 (s, 3H), 1.34 (t, 3H, J = 7.0 Hz), 1.21 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 165.2, 164.1, 160.5, 144.6, 138.1, 137.8, 130.6, 129.1, 128.4, 128.2, 128.1, 127.1, 125.5, 119.6, 112.4, 61.3, 60.2, 52.3, 21.3, 14.2, 13.8; IR (neat): 2924 (s), 1714 (s, C═O), 1599 (w), 1470 (s), 1235 (s, C−O), 1116 (s), 1039 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{25}NO_6$ + H, 436.1760; found, 436.1770.

*4-Ethoxycarbonyl-2-methoxycarbonyl-5-(4-methoxyphenyl)-N-phenylpyrrole (**4acb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (301 mg, 1.01 mmol, 1.0 equiv), Schiff base **2c**[33] (209 mg, 1.01 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 119 mg, 1.21 mmol, 1.2 equiv), and CsF (307 mg, 2.02 mmol, 2.0 equiv) in CH_3CN (15.0 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4acb** (328 mg, 0.867 mmol) in 86% yield as yellow solids: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); mp (recrystallized from EtOH) 137.6−139.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 1H), 7.26−7.23 (m, 3H), 7.06−7.03 (m, 4H), 6.69 (d, 2H, J = 8.8 Hz), 4.15 (q, 2H, J = 7.0 Hz), 3.71 (s, 3H), 3.69 (s, 3H), 1.19 (t, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.6, 160.2, 159.2, 144.1, 137.8, 132.0, 128.2, 128.1, 128.0, 123.3, 122.1, 119.5, 114.2, 112.7, 59.9, 55.1, 51.4, 14.3; IR (neat): 2925 (s), 1714 (s, C═O), 1612 (m), 1471 (s), 1250 (s, C−O), 1118 (m), 1041 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}NO_5$ + H, 380.1498; found, 380.1487.

*2,4-Dimethoxycarbonyl-5-(4-methoxyphenyl)-3-methyl-N-phenylpyrrole (**4acd**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.2 mg, 0.168 mmol, 1.0 equiv), Schiff base **2c**[33] (34.6 mg, 0.168 mmol, 1.0 equiv), methyl 2-butynoate (**3d**, 19.9 mg, 0.201 mmol, 1.2 equiv), and CsF (51.3 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4acd** (45.4 mg, 0.119 mmol) in 71% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27−7.24 (m, 3H), 7.06−7.02 (m, 4H), 6.69 (d, 2H, J = 8.4 Hz), 3.72 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 2.62 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.4, 158.9, 158.6, 143.5, 138.7, 131.8, 128.1, 128.0, 127.8, 123.1, 122.2, 117.1, 114.1, 112.6, 55.1, 51.1, 50.9, 12.5; IR (neat): 2925 (m), 1717 (s, C═O), 1598 (w), 1472 (m), 1240 (s, C−O), 1122 (m), 1032 (m), 836 (m)

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cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}NO_5$ + H, 380.1498; found, 380.1484.

*3,4-Di-n-propyl-2-methoxycarbonyl-5-(4-methoxyphenyl)-N-phenylpyrrole (**4acg**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (101 mg, 0.336 mmol, 1.0 equiv), Schiff base **2c**[33] (69.5 mg, 0.336 mmol, 1.0 equiv), 4-octyne (**3g**, 44.6 mg, 0.403 mmol, 1.2 equiv), and CsF (103 mg, 0.672 mmol, 2.0 equiv) in CH_3CN (4.1 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4acg** (19.6 mg, 0.051 mmol) in 15% yield as a yellow liquid: TLC R_f 0.40 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.18 (m, 3H), 6.99−6.95 (m, 4H), 6.67 (d, 2H, J = 8.4 Hz), 3.71 (s, 3H), 3.66 (s, 3H), 2.54 (t, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.0 Hz), 1.65−1.53 (m, 4H), 0.97−0.89 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.4, 159.2, 144.3, 137.7, 131.8, 128.2, 128.1, 128.0, 124.3, 122.2, 116.2, 114.1, 112.6, 55.1, 51.3, 29.9, 28.8, 25.6, 25.4, 13.8; IR (neat): 2953 (m), 1716 (s, C═O), 1599 (m), 1446 (m), 1235 (s, C−O), 1095 (m), 1029 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{29}NO_3$ + H, 392.2225; found, 392.2236.

*5-(4-Chlorophenyl)-4-ethoxycarbonyl-2-methoxycarbonyl-N-phenylpyrrole (**4adb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.1 mg, 0.168 mmol, 1.0 equiv), Schiff base **2d**[34] (35.7 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.8 mg, 0.201 mmol, 1.2 equiv), and CsF (51.6 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4adb** (46.7 mg, 0.123 mmol) in 73% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.44−7.40 (m, 2H), 7.28−7.25 (m, 2H), 7.23−7.19 (m, 3H), 7.05−7.01 (m, 2H), 4.21 (q, 2H, J = 6.9 Hz), 3.73 (s, 3H), 1.17 (t, 3H, J = 6.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.9, 161.0, 144.5, 140.2, 134.7, 130.2, 129.8, 128.5, 128.4, 128.3, 128.2, 124.7, 119.8, 114.6, 59.8, 51.2, 14.1; IR (neat): 2926 (m), 1716 (s, C═O), 1599 (w), 1490 (m), 1236 (s, C−O), 1092 (m), 1015 (m), 757 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{18}ClNO_4$ + H, 384.1002; found, 384.1007.

*5-(4-Bromophenyl)-4-ethoxycarbonyl-2-methoxycarbonyl-N-phenylpyrrole (**4aeb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.3 mg, 0.168 mmol, 1.0 equiv), Schiff base **2e**[35] (43.1 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.6 mg, 0.201 mmol, 1.2 equiv), and CsF (51.4 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.3 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aeb** (53.1 mg, 0.126 mmol) in 76% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.38−7.32 (m, 4H), 7.30 (t, 1H, J = 7.2 Hz), 7.15 (d, 2H, J = 8.0 Hz), 7.03 (d, 2H, J = 8.0 Hz), 4.17 (q, 2H, J = 7.2 Hz), 3.73 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 160.3, 143.9, 138.2, 132.2, 131.1, 130.3, 128.4, 128.2, 128.1, 123.5, 120.3, 119.7, 114.2, 59.8, 51.4, 14.4; IR (neat): 2925 (m), 1715 (s, C═O), 1599 (m), 1487 (m), 1236 (s, C−O), 1090 (m), 1011 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{18}BrNO_4$ + H, 428.0497; found, 428.0490.

*4-Ethoxycarbonyl-2-methoxycarbonyl-5-(naphthalen-1-yl)-N-phenylpyrrole (**4afb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.2 mg, 0.168 mmol, 1.0 equiv), Schiff base **2f**[34] (38.3 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.7 mg, 0.201 mmol, 1.2 equiv), and CsF (51.1 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.0 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4afb** (50.2 mg, 0.126 mmol) in 75% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 7.2 Hz), 7.63 (s, 1H), 7.54 (d, 2H, J = 7.6 Hz), 7.50−7.43 (m, 3H), 7.27 (t, 2H, J = 7.2 Hz), 7.13 (t, 2H, J = 7.4 Hz), 4.20 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.1, 160.2, 147.3, 142.9, 139.0, 133.9, 131.4, 128.6, 127.9, 127.7, 127.6, 125.8, 125.5, 125.3, 124.8, 123.9, 123.4, 121.9, 121.3, 113.6, 60.6, 53.3, 14.4; IR (neat): 2953 (m), 1731 (s, C═O), 1599 (m), 1505 (m), 1446 (w), 1235 (s, C−O), 1029 (m), 778 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{21}NO_4$ + H, 400.1548; found, 400.1550.

*4-Ethoxycarbonyl-5-(furan-2-yl)-2-methoxycarbonyl-N-phenylpyrrole (**4agb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.4 mg, 0.168 mmol, 1.0 equiv), Schiff base **2g**[33] (28.4 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.9 mg, 0.202 mmol, 1.2 equiv), and CsF (51.8 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.2 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4agb** (40.4 mg, 0.119 mmol) in 71% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H), 7.48 (d, 1H, J = 4.8 Hz), 7.41 (d, 2H, J = 6.8 Hz), 7.32 (t, 1H, J = 6.2 Hz), 7.08 (d, 2H, J = 6.8 Hz), 6.80 (d, 1H, J = 6.4 Hz), 6.46 (dd, 1H, J = 4.8, 1.6 Hz), 4.14 (q, 2H, J = 7.1 Hz), 3.71 (s, 3H), 1.15 (t, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.8, 160.1, 149.9, 148.4, 143.5, 139.6, 131.8, 129.4, 128.6, 124.0, 121.9, 116.5, 114.1, 111.6, 59.7, 51.1, 14.7; IR (neat): 2926 (s), 1716 (s, C═O), 1613 (m), 1472 (m), 1251 (s, C−O), 1117 (m), 1040 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{17}NO_5$ + H, 340.1185; found, 340.1181.

*3-Ethoxycarbonyl-5-methoxycarbonyl-2-(thien-2-yl)-N-phenylpyrrole (**4ahb**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.2 mg, 0.168 mmol, 1.0 equiv), Schiff base **2h**[35] (30.6 mg, 0.168 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 20.1 mg, 0.202 mmol, 1.2 equiv), and CsF (51.6 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.0 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4ahb** (43.6 mg, 0.123 mmol) in 73% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.41 (d, 2H, J = 6.4 Hz), 7.30−7.26 (m, 2H), 7.20 (d, 1H, J = 4.0 Hz), 7.12 (d, 2H, J = 6.4 Hz), 6.99 (dd, 1H, J = 7.2, 2.4 Hz), 4.20 (q, 2H, J = 6.6 Hz), 3.71 (s, 3H), 1.17 (t, 3H, J = 6.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.8, 160.1, 143.9, 139.9, 139.2, 132.1, 131.6, 129.1, 128.2, 127.9, 125.2, 123.4, 122.0, 114.1, 59.8, 51.3, 14.1; IR (neat): 2924 (m), 1715 (s, C═O), 1598 (w), 1470 (m), 1367 (m), 1234 (s, C−O), 1039 (m), 758 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{17}NO_4S$ + H, 356.0956; found, 356.0947.

*2-Ethoxycarbonyl-4-methoxycarbonyl-5-phenyl-N-phenylpyrrole (**4aja**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.3 mg, 0.168 mmol, 1.0 equiv), Schiff base **2j**[33] (32.1 mg, 0.168 mmol, 1.0 equiv), methyl acetylenecarboxylate (**3a**, 17.1 mg, 0.202 mmol, 1.2 equiv), and CsF (51.7 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.2 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aja** (47.6 mg, 0.136 mmol) in 81% yield as a yellow liquid: TLC R_f 0.45 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H), 7.24−7.23 (m, 3H), 7.20−7.16 (m, 3H), 7.14−7.12 (m, 2H), 7.07−7.03 (m, 2H), 4.06 (q, 2H, J = 7.2 Hz), 3.76 (s, 3H), 1.08 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.0, 160.2, 144.4, 138.0, 130.6, 128.9, 128.4, 128.2, 128.2, 127.8, 127.0, 123.5, 119.5, 114.3, 60.2, 51.1, 14.4; IR (neat): 2926 (m), 1714 (s, C═O), 1611 (m), 1470 (s), 1249 (s, C−O), 1118 (s), 1040 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_4$ + H, 350.1392; found, 350.1383.

*2,4-Diethoxycarbonyl-5-phenyl-N-phenylpyrrole (**4ajb**).* (a) The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.5 mg, 0.168 mmol, 1.0 equiv), Schiff base **2j**[33] (32.3 mg, 0.168

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mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.4 mg, 0.202 mmol, 1.2 equiv), and CsF (51.3 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.0 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4ajb** (48.5 mg, 0.134 mmol) in 80% yield as a yellow liquid: TLC R_f 0.45 (15% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 7.25−7.23 (m, 3H), 7.20−7.17 (m, 3H), 7.14−7.12 (m, 2H), 7.07−7.03 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz), 4.06 (q, 2H, J = 7.1 Hz), 1.14 (t, 3H, J = 7.1 Hz), 1.09 (t, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.1, 163.8, 144.6, 137.8, 130.8, 128.9, 128.4, 128.2, 128.2, 127.9, 126.9, 123.4, 119.4, 114.3, 60.2, 59.8, 14.4, 14.2; IR (neat): 2924 (s), 1714 (s, C═O), 1598 (w), 1470 (m), 1235 (s, C−O), 1116 (s), 1039 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}NO_4$ + H, 364.1548; found, 364.1552.

(b) The same procedure was followed by use of 2-silylphenyl triflate **1a** (2.70 g, 9.05 mmol, 1.0 equiv), Schiff base **2j**[33] (1.73 g, 9.05 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 1.07 g, 10.9 mmol, 1.2 equiv), and CsF (2.74 g, 18.1 mmol, 2.0 equiv) in CH_3CN (100 mL). The desired pyrrole **4ajb** (2.57 g, 7.06 mmol) was obtained in 78% yield as a yellow liquid.

*3,4-Dimethoxycarbonyl-2-ethoxycarbonyl-5-phenyl-N-phenylpyrrole (**4aje**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.7 mg, 0.168 mmol, 1.0 equiv), Schiff base **2j**[33] (31.9 mg, 0.168 mmol, 1.0 equiv), DMAD (**3e**, 28.9 mg, 0.202 mmol, 1.2 equiv), and CsF (51.4 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.5 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aje** (50.4 mg, 0.124 mmol) in 74% yield as yellow solids: TLC R_f 0.40 (20% EtOAc in hexanes as the eluent); mp (recrystallized from EtOH) 141.2−143.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.24 (m, 3H), 7.20−7.17 (m, 3H), 7.13−7.11 (m, 2H), 7.06−7.03 (m, 2H), 4.18 (q, 2H, J = 7.0 Hz), 3.87 (s, 3H), 3.73 (s, 3H), 1.17 (t, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.8, 162.2, 160.3, 144.5, 138.0, 130.5, 129.2, 128.5, 128.3, 128.2, 127.6, 127.2, 125.4, 121.2, 112.6, 60.1, 52.6, 51.5, 14.1; IR (neat): 2928 (m), 1738 (s, C═O), 1732 (s, C═O), 1599 (m), 1459 (m), 1235 (s, C−O), 1027 (m), 778 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{21}NO_6$ + H, 408.1447; found, 408.1442.

*2-Ethoxycarbonyl-4-methoxycarbonyl-5-(4-methoxyphenyl)-N-phenylpyrrole (**4aka**).* The standard procedure was followed by use of 2-silylphenyl triflate **1a** (50.3 mg, 0.168 mmol, 1.0 equiv), Schiff base **2k**[36] (37.1 mg, 0.168 mmol, 1.0 equiv), methyl acetylenecarboxylate (**3a**, 17.1 mg, 0.202 mmol, 1.2 equiv), and CsF (51.2 mg, 0.336 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4aka** (54.4 mg, 0.142 mmol) in 85% yield as yellow solids: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); mp (recrystallized from EtOH) 138.6−140.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H), 7.26−7.23 (m, 3H), 7.07−7.03 (m, 4H), 6.70 (d, 2H, J = 7.2 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.72 (s, 3H), 3.68 (s, 3H), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.9, 160.1, 159.1, 144.2, 137.6, 131.9, 128.4, 128.3, 128.2, 124.0, 122.3, 119.6, 114.4, 112.8, 60.1, 55.2, 51.2, 14.1; IR (neat): 2925 (m), 1714 (s, C═O), 1611 (m), 1470 (m), 1249 (s, C−O), 1117 (m), 1040 (m), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}NO_5$ + H, 380.1498; found, 380.1491.

*2-Methoxycarbonyl-3,4-di(4-methoxyphenyl)-N-4-methoxyphenylpyrrole (**4bih**).* To a stirred solution of glycine methyl ester hydrochloride (37.6 mg, 0.302 mmol, 1.0 equiv) in dry CH_3CN (2.5 mL) were added molecular sieves (4 Å, activated, 2.5 μm, powdered, 30.5 mg), Et_3N (30.7 mg, 0.302 mmol, 1.0 equiv), and paraformaldehyde (9.41 mg, 0.302 mmol, 1.0 equiv) to generate Schiff base **2i**[28] at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred at 0−10 °C for 1.0 h, 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[37] (**1b**, 101 mg, 0.302 mmol, 1.0 equiv), bis(4-methoxyphenyl)acetylene (**3h**, 86.5 mg, 0.362 mmol, 1.2 equiv), and CsF (134 mg, 0.906 mmol, 3.1 equiv) were added into the reaction mixture. The mixture was stirred at 0−10 °C for 8.0 h and then quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $CaSO_4$ (s), filtered, and concentrated under reduced pressure. It was then purified by use of silica gel column chromatography (20% EtOAc in hexanes as the eluent) to give the desired pyrrole **4bih** (81.5 mg, 0.184 mmol) in 61% yield as a yellow liquid: TLC R_f 0.45 (25% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.06 (s, 1H), 6.95 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.4 Hz), 6.77 (d, 2H, J = 8.8 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.6, 158.9, 158.9, 158.0, 136.2, 132.4, 131.8, 129.1, 129.0, 128.5, 126.9, 125.7, 124.8, 124.5, 113.8, 113.6, 113.5, 55.4, 55.2, 55.1, 51.3; IR (neat): 2925 (m), 1715 (s, C═O), 1598 (w), 1464 (m), 1235 (s, C−O), 1120 (w), 1011 (w), 759 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{25}NO_5$ + H, 444.1811; found, 444.1823.

*4-Ethoxycarbonyl-2-methoxycarbonyl-N-3,4-dimethoxyphenyl-5-(4-methylphenyl) pyrrole (**4cbb**).* The standard procedure was followed by use of 2-silylayl triflate **1c** (50.4 mg, 0.141 mmol, 1.0 equiv), Schiff base **2b**[34] (26.9 mg, 0.141 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 16.6 mg, 0.169 mmol, 1.2 equiv), and CsF (42.9 mg, 0.282 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 6.0 h and then worked up, the residue was purified by use of silica gel column chromatography (15% EtOAc in hexanes as the eluent) to give the desired pyrrole **4cbb** (46.5 mg, 0.110 mmol) in 78% yield as yellow solids: TLC R_f 0.40 (20% EtOAc in hexanes as the eluent); mp (recrystallized from EtOH) 143.1−145.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1H), 7.02−6.96 (m, 3H), 6.71 (s, 1H), 6.68 (d, 2H, J = 6.4 Hz), 6.48 (d, 1H, J = 6.4 Hz), 4.14 (q, 2H, J = 6.9 Hz), 3.83 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 2.25 (s, 3H), 1.17 (t, 3H, J = 6.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.6, 160.2, 148.4, 148.0, 144.6, 138.0, 130.5, 130.4, 128.0, 127.2, 123.3, 120.6, 119.3, 114.2, 111.7, 109.7, 59.8, 55.9, 55.8, 51.4, 21.4, 14.3; IR (neat): 2930 (m), 1714 (s, C═O), 1515 (s), 1471 (m), 1237 (s, C−O), 1112 (s), 1029 (m), 760 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{25}NO_6$ + H, 424.1760; found, 424.1758.

*4-Ethoxycarbonyl-2-methoxycarbonyl-5-(4-methylphenyl)-N-2-pyridylpyrrole (**4dbb**).* The standard procedure was followed by use of 2-silylaryl triflate **1d** (50.1 mg, 0.167 mmol, 1.0 equiv), Schiff base **2b**[34] (31.8 mg, 0.167 mmol, 1.0 equiv), ethyl acetylenecarboxylate (**3b**, 19.6 mg, 0.201 mmol, 1.2 equiv), and CsF (50.8 mg, 0.334 mmol, 2.0 equiv) in CH_3CN (2.1 mL). After the reaction mixture was stirred for 8.0 h and then worked up, the residue was purified by use of silica gel column chromatography (10% EtOAc in hexanes as the eluent) to give the desired pyrrole **4dbb** (43.1 mg, 0.119 mmol) in 71% yield as a yellow liquid: TLC R_f 0.45 (20% EtOAc in hexanes as the eluent); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, 1H, J = 7.2 Hz), 7.58 (s, 1H), 7.55 (t, 1H, J = 7.0 Hz), 7.29−7.25 (m, 3H), 7.18 (t, 1H, J = 7.2 Hz), 7.03 (d, 2H, J = 7.6 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.72 (s, 3H), 2.26 (s, 3H), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.1, 160.8, 151.7, 148.8, 144.2, 140.1, 139.2, 137.8, 130.5, 128.2, 127.9, 127.0, 123.3, 119.4, 114.3, 59.9, 51.4, 21.4, 14.2; IR (neat): 2924 (m), 1715 (s, C═O), 1598 (w), 1470 (m), 1201 (s, C−O), 1120 (w), 1011 (w), 758 (m) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{20}N_2O_4$ + H, 365.1501; found, 365.1512.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01134.

Crystallographic data for **4acb** (CIF)

NMR spectra, IR spectra, and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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