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Ruthenium-Catalyzed [3+2] Cycloaddition of 2*H*-azirines with alkynes: Access to Polysubstituted Pyrroles

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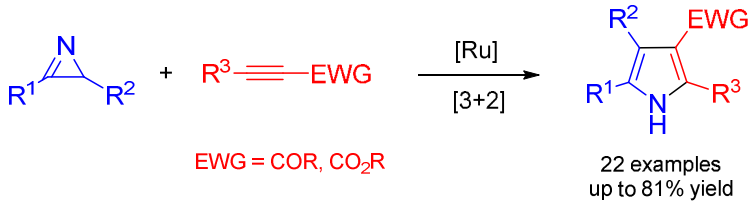
ABSTRACT



A ruthenium-catalyzed intermolecular [3+2] cycloaddition of 2*H*-azirines and activated alkynes is reported, which provides polysubstituted pyrroles in moderate to good yields. This approach features a C–N bond cleavage of 2*H*-azirines by a ruthenium catalyst. The results of this study would provide a complementary method to synthesize polysubstituted pyrroles from the known 2*H*-azirine approaches and advance the 2*H*-azirines chemistry.

Polysubstituted pyrrole derivatives are important skeletal units that are widely distributed in numerous natural products, pharmaceuticals and material science (Figure 1).[1] Owing to the significant bioactive and therapeutic properties of the pyrrole moiety, many efforts have been devoted to the preparation of

pyrrole-containing heterocycles in recent decades.[2] Generally, the construction of the pyrrole ring involves a multistep process from preformed intermediates, such as the classical Hantzsch and Paal−Knorr reactions.[3] Recently, some more efficient approaches, including using new building blocks[4] as well as oxidative cyclization of allylimines or enamides[5] and multicomponent reactions,[2b,6] have been developed to access functionalized pyrroles. Although much progress have been made in the synthesis of pyrrole derivatives, direct access to polysubstituted pyrroles in an atom- and step-economic manner still remains challenging and highly desirable.

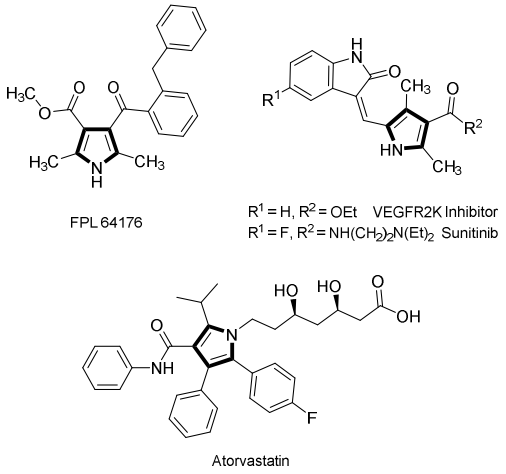
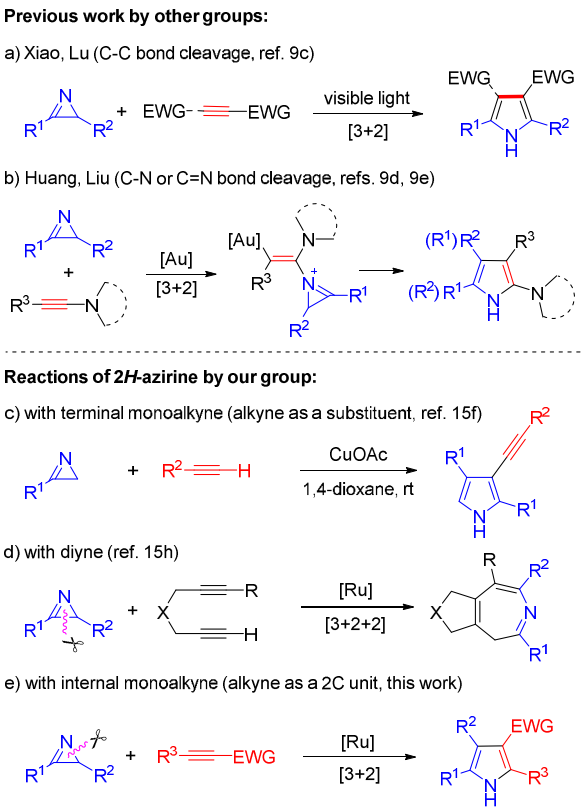


Figure 1. Examples of biologically and therapeutically active molecules containing pyrrole scaffold.

Recently, cycloadditions or cyclizations of strained rings have been recognized as one of the most powerful strategies for constructing carbocycles and heterocycles.[7] 2*H*-azirines are highly strained three-membered heterocyclic compounds and have been exploited as valuable three-atom building units such as vinyl nitrenes and nitrile ylides.[8] Therefore, 2*H*-azirines have been employed in the synthesis of various nitrogen containing heterocycles, such as pyrroles,[9] indoles,[10] pyridines,[11] oxazoles,[12]

pyrazines[13] and others[14]. Among these transformations, [3+2] cycloaddition of 2*H*-azirines with alkynes has proven to be a direct and powerful strategy to produce pyrroles with high atom efficiency. Xiao and Lu developed a practical pyrrole synthesis by means of a visible-light-induced photocatalytic formal [3+2] reaction of 2*H*-azirines with electron-deficient alkynes (Scheme 1a).[9c] This reaction is initiated by single-electron oxidation of the 2*H*-azirines in the presence of an excited photocatalyst, followed by homolytic cleavage of the C−C bond. Subsequently, an effective gold-catalyzed intermolecular nitrene transfer by the reaction of 2*H*-azirines and ynamides has been achieved by Huang[9d] and Liu[9e] respectively, which provides highly substituted pyrroles in good to excellent yields (Scheme 1b). It is noteworthy that the bond cleavage mode of 2*H*-azirine is quite crucial in determining the position of introduced substituents in the pyrrole ring. For example, electron-withdrawing (EWG) groups were introduced into 3- and 4-positions of pyrrole ring in Xiao and Lu's work by C−C bond cleavage of 2*H*-azirine,[9c] while amino groups were incorporated at 2-position by C–N or C=N bond cleavage.[9d,9e] In this regard, precise introduction of substituents into a certain position of the pyrrole ring by controlling the bond cleavage mode of 2*H*-azirine is of great interest and importance.

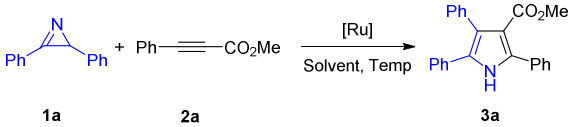
Scheme 1. Pyrroles Synthesis via Cycloaddition of 2*H*-azirines with Alkynes.



Recently, we are interested in the metal-catalyzed cycloaddition reactions.[15] As a part of our work, we have developed the Cu-catalyzed ring opening reaction of 2*H*-azirines with terminal alkynes to access 3-alkynylated pyrroles, in which the alkyne moiety was incorporated as a substituent (Scheme 1c).[15f] The *in situ* generated copper acetylide is proved to initialize the reaction, and thus internal alkynes failed to provide the desired products. Very recently, we also reported a ruthenium-catalyzed cycloaddition of 2*H*-azirines with diynes for constructing azepine architectures (Scheme 1d).[15h] [3+2+2] rather than [3+2] cycloadducts were preferentially generated in this reaction. As our continue interest in the 2*H*-azirine chemistry, we envisioned that 2*H*-azirines could be converted to pyrroles by [3+2] cycloaddition with internal alkynes (Scheme 1e). Unlike our previous work,[15h] however, C–N bond cleavage of 2*H*-azirine was observed in the presence of ruthenium catalyst. Consequently,

electron-withdrawing groups were introduced at 3-position of the resulting pyrrole products, which would provide a complementary method to synthesize polysubstituted pyrroles from the known 2*H*-azirine approaches (Scheme 1e *vs* Scheme 1a,b).[9c-9e] Herein, we report our results.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

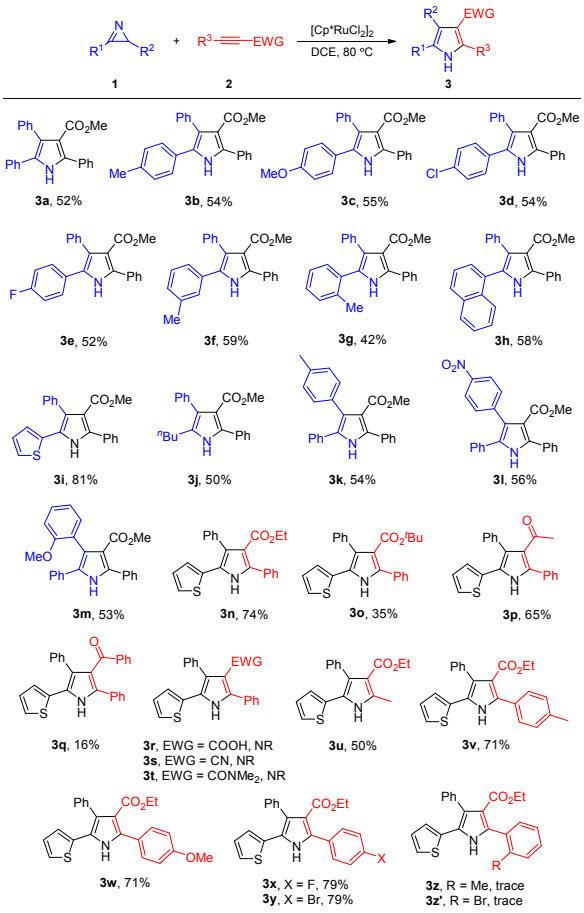
Entry	Solvent	Temp[b]	**1a** : **2a**	Yield[c]
1[d]	DCE	80 °C	1 : 1.5	29%
2	DCE	80 °C	1 : 1.5	35%
3	DMF	80 °C	1 : 1.5	11%
4	toluene	80 °C	1 : 1.5	16%
5	DCM	80 °C	1 : 1.5	35%
6	THF	80 °C	1 : 1.5	25%
7	MeOH	80 °C	1 : 1.5	0
8	DCE	25 °C	1 : 1.5	9%
9	DCE	50 °C	1 : 1.5	22%
10	DCE	100°C	1 : 1.5	34%
11	DCE	80 °C	1:3	38%
12	DCE	80 °C	1:5	55%
13[e]	DCE	80 °C	1:5	45%

[a]Reaction conditions: *2H*-azirine **1a** (0.20 mmol), alkyne **2a**, $[Cp^*RuCl_2]_2$ (5 mol%) in solvent (2 mL) for 12 h unless otherwise stated. [b]The temperature of oil bath. [c]Determined by HPLC using naphthalene as an internal standard. [d]Cp*Ru(COD)Cl (10 mol%). [e]2.5 mol% of $[Cp^*RuCl_2]_2$ was used as catalyst.

At the outset, 2,3-diphenyl-2*H*-azirine **1a** and methyl 3-phenylpropiolate **2a** were chosen as model substrates for the optimization of the reaction conditions. The results are summarized in Table 1. In agreement with our previous observations in the [3+2+2] cycloaddition,[15h] most ruthenium(II) catalysts such as $[Cp^*RuCl]_4$,

Cp*Ru(CH_3CN)PF_6, [Ru(COD)Cl_2]$_n$ and [Ru(p-cymene)Cl_2]$_2$ failed to provide any desired product. Pleasingly, by employing Cp*Ru(COD)Cl as catalyst which has shown the best performance in our previous study,[15h] the reaction of 2*H*-azirine **1a** and alkyne **2a** proceeded under relatively mild conditions (80 °C, in DCE), affording the desired product pyrrole **3a** in 29% yield (Table 1, entry 1). Replacing the ruthenium(II) catalyst by a ruthenium(III) catalyst [Cp*$RuCl_2$]$_2$, led to a slightly higher yield (35%, entry 2). Subsequently, examination of different solvents revealed that DCE or DCM showed the best performance (entries 3–7). Furthermore, a simple inspection on the reaction temperatures indicated that lowering or raising the temperature did not improve the yields (entries 8–10). A higher product yield can be achieved by increasing the ratio of **2a** to **1a** (55%, entry 12). However, attempts to lower the catalyst loading to 2.5 mol% resulted in a decreased yield (45%, entry 13). It is noteworthy that dimerization of 2*H*-azirine was commonly detected under ruthenium catalyst, which slightly lowered the yield of **3a**. Unfortunately, the reaction with slow addition of 2*H*-azirine **1a** into the mixture of catalyst and alkyne **2a** in 3 hours via syringe pump did not afford any desired product. Similar result was also observed when a mixture of **1a** and **2a** was slowly added into the catalyst solution. Importantly, the structure of **3a** was unambiguously confirmed by X-ray crystal diffraction of its analogous **3h** and **3w**,[16] revealing that the C–N bond of 2*H*-azirine was cleaved in the reaction. It is interesting that the alkyne carbons are incorporated into the 2- and 3-positions of the pyrrole product, rather than the 3- and 4-positions observed in the light-induced versions of this formal cycloaddition.[17]

Scheme 2. Substrate scope.



[a]Reaction conditions: 2*H*-azirine **1** (0.2 mmol) and alkynes **2** (1.0 mmol) with $[Cp^*RuCl_2]_2$ (5 mol %) in DCE (2 mL) at 80 °C for 12 h. Isolated yields are given. NR = No reaction.

With the optimized reaction conditions in hand, we set out to screen the scope of both 2*H*-azirines and alkynes for this [3+2] cycloaddition. Variations of R^1 group on the C=N double bond moiety of 2*H*-azirines were first examined. As highlighted in Scheme 2, both electron-donating and electron-withdrawing groups on the phenyl ring could be successfully introduced, thus providing the corresponding polysubstituted pyrroles (**3b**–**3g**) in moderate yields. A 2*H*-azirine with an *ortho*-methyl group on the phenyl ring afforded product **3g** in 42% yield due to the steric effect, while 2*H*-azirine bearing a sterically demanding naphthyl group gave pyrrole **3h** in 58% yield. The electronic effect may be the dominant reason for the moderate yield of **3h**. Moreover,

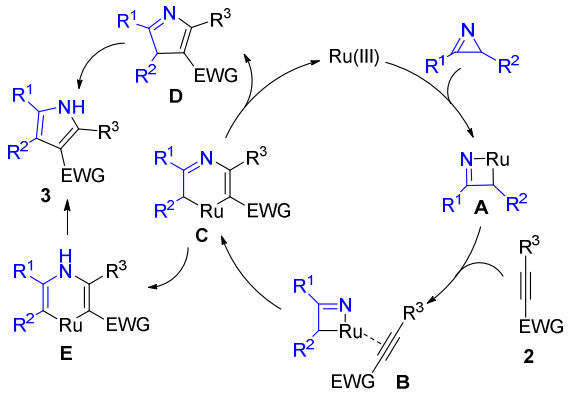
2-thienyl group was compatible to provide the desired product **3i** with good yield. Replacement of the aryl group with an alkyl substituent also led to the effective formation of the corresponding pyrrole in moderate yield (**3j**). Notably, the electronic and steric nature of the R^2 substituent had no great effect on this reaction. Different groups at *para* or *ortho* position of the phenyl ring were tolerated as well (**3k**–**3m**).

Subsequently, we turned our attention to investigate various alkynes with thienyl 2*H*-azirine **1i**. Both ester- (**2a**, **2n**, **2o**) and ketone-derived alkynes (**2p**, **2q**) reacted well with **1i** to afford the corresponding tetrasubstituted pyrroles. However, it seems that the reactivity is quite sensitive to the steric effect of the carbonyl substituents, as sterically demanding alkynes **2o** and **2q** provided the desired product with much lower yields (35% and 16%). Moreover, other electron-withdrawing groups such as carboxylic acid (COOH), nitrile (CN) and amide ($CONMe_2$) failed to provide any products (**3r**–**3t**). The variations of R^3 group on the alkynes were further evaluated. It was found that ethyl but-2-ynoate was suitable substrate, thus providing the desired product **3u** in moderate yield. When R^3 was a phenyl group, this reaction was sensitive to steric effect of the R^3 substituent on alkynes. Alkynes having electron-deficient groups on the *para* position of the phenyl ring showed similar reactivity as the ones bearing electron-rich groups (**3v**–**3y**). However, alkynes bearing an *ortho*-substituted phenyl ring (**2z**, **2z'**) were hardly reactive, even at higher temperature.

To account for the results of the present catalytic reaction, we propose the mechanism shown in Scheme 3. The catalytic cycle starts with the oxidative addition

of 2*H*-azirine **1** on the ruthenium center to form the azaruthenacyclobutene intermediate **A**.[8a,18] Subsequently, coordination of the activated alkyne **2** converts the ruthenacyclobutene **A** into the complex **B**, which readily undergoes the alkyne insertion into Ru–C single bond to deliver the six-membered ruthenacycle intermediate **C**. The site of alkyne insertion switches depends on the nature of alkynes, as Cheng et al.[19] explained for their *N*-cyclization reaction. Then, the reductive elimination of the intermediate **C** provides the intermediate **D** and regenerates the catalyst for the next catalytic cycle. Finally, isomerization of the intermediate **D** provides the thermodynamically stable product pyrrole **3**. However, the possibility that the imine double bond in intermediate **C** isomerizes to the enamine **E** before the reductive elimination cannot be completely excluded at present time. In the case of the alkynes **2z** and **2z'**, the steric repulsion between *ortho* groups and ligand on Ru catalyst may cause the diminished yields in products. It is noteworthy that our hypothesis is mechanistically similar to the previously reported procedures for 2,3-dihydropyrroles synthesis from aziridines and alkynes.[20]

Scheme 3. Plausible Catalytic Cycles for the Pyrrole Synthesis.



CONCLUSION

In summary, we have reported a ruthenium-catalyzed formal [3+2] cycloaddition of 2*H*-azirines with the activated alkynes, which provides a straightforward approach to fully substituted pyrroles in moderate to good yields. A possible mechanism involving the azaruthenacyclobutene intermediate is proposed for the generation of desired products and specific selectivity of pyrroles. The results of this study would provide a complementary method to synthesize polysubstituted pyrroles from the known 2*H*-azirine approaches and advance the 2*H*-azirines chemistry.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all manipulations and reactions were performed under inert atmosphere using standard Schlenk techniques or in an argon-filled glove-box. All chemicals were purchased from commercial sources and were used without further purification. Solvents were treated prior to use according to the standard methods. Column chromatography was carried out on silica gel (200–300 mesh) using a forced flow of eluent at 0.3–0.5 bar pressure. NMR Spectra were recorded at room temperature in $CDCl_3$ on 400 MHz spectrometers. The chemical shifts for ^1H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with $CDCl_3$ (7.26 ppm) as the internal standard. The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.16 ppm) as the internal standard. Coupling constants (J) are reported in hertz and refer to apparent peak multiplications. The abbreviations *s*, *d*, *t*, *q* and *m* stand for singlet, doublet, triplet, quartet and multiplet in that order. HRMS data were obtained with HPLC-Q-TOF mass spectrometer (ESI).

General procedure for the preparation of 2*H*-azirines:

The 2*H*-azirines are prepared by the following procedure according to literature report.[9d] Reaction scheme is shown in the supporting information.

A mixture of ketone **4** (1 equiv), $NH_2OH·HCl$ (1.5 equiv) and sodium acetate (1.5 equiv) was added to a mixture solvent of MeOH/H_2O (10:1) in a round bottom flask. The resulting solution was stirred at room temperature and monitored by TLC. After reaction completed, the solvent was removed in vacuo and DCM was added. Then, the mixture was sequentially washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Concentration led to the oxime **5**, which was used directly for the next step.

To a solution of the crude oxime (1 equiv) in dry THF was added triethylamine (1.5 equiv) and methanesulfonyl chloride (1.5 equiv) sequentially at room temperature. The solution got cloudy after the addition of methanesulfonyl chloride. The resulting mixture was stirring for 30 min, and DBU (1.5 equiv) was then added over 1 min. After stirred for additional 30 min, the reaction mixture was passed through a pad of silica gel, and washed with EtOAc. The mixture was concentrated in vacuo and purified by silica gel column chromatography to give the 2*H*-azirine **1**.

Representative procedure for the synthesis of pyrrole

Catalyst $[Cp^*RuCl_2]_2$ (6.1 mg, 0.01 mmol, 5 mol%) was weighed in the glove box and placed in a dried Schlenk tube. Subsequently, 2 mL of solvent (DCE) was added. The resulting mixture was stirred at room temperature. After 5 min, 2*H*-azirine **1a** (0.2 mmol, 1 equiv) was added followed by alkyne **2a** (1.0 mmol, 5.0 equiv). The

reaction mixture was stirred at 80 °C (oil bath) for 12 h. The solvent was evaporated and the crude product was directly purified by silica gel column chromatography to give the desired product (eluent: petroleum ether/ethyl acetate = 10:1~8:1).

Methyl 2,4,5-triphenyl-1*H*-pyrrole-3-carboxylate (3a). White solid; 36.7 mg (52% yield), m.p. 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.59–7.52 (m, 2H), 7.38 (m, 3H), 7.29 (d, *J* = 4.4 Hz, 5H), 7.23–7.12 (m, 5H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 136.4, 135.4, 132.3, 131.9, 130.7, 129.5, 128.7, 128.6, 128.4, 128.3, 127.9, 127.2, 127.1, 126.7, 124.2, 113.3, 51.0; HRMS Calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$ 354.1489, found 354.1488.

Methyl 2,4-diphenyl-5-(p-tolyl)-1*H*-pyrrole-3-carboxylate (3b). White solid; 39.4 mg (54% yield), m.p. 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.31 (dt, *J* = 15.1, 7.0 Hz, 3H), 7.26–7.15 (m, 5H), 6.95 (q, *J* = 8.1 Hz, 4H), 3.40 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 136.9, 136.1, 135.5, 132.4, 130.7, 129.7, 129.4, 129.1, 128.7, 128.4, 128.3, 127.9, 127.1, 126.6, 123.8, 113.2, 51.0, 21.3; HRMS Calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645, found 368.1658.

Methyl 5-(4-methoxyphenyl)-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (3c). White solid; 41.8 mg (55% yield), m.p. 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.44–7.34 (m, 3H), 7.32–7.22 (m, 5H), 7.11–7.04 (m, 2H), 6.79–6.69 (m, 2H), 3.73 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 158.8, 135.9, 135.5, 132.4, 130.7, 129.6, 128.7, 128.6, 128.5, 128.2, 127.9, 126.6, 124.6, 123.4, 114.1, 113.1, 55.3, 50.9; HRMS Calcd for $C_{25}H_{22}NO_3$ $[M+H]^+$

384.1594, found 384.1602.

Methyl 5-(4-chlorophenyl)-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (3d). White solid; 41.8 mg (54% yield), m.p. 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.49–7.44 (m, 2H), 7.34–7.26 (m, 3H), 7.22–7.15 (m, 5H), 7.09–7.05 (m, 2H), 7.00–6.95 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 136.8, 135.1, 132.8, 132.1, 130.6, 130.4, 128.80, 128.79, 128.5, 128.43, 128.41, 128.38, 128.0, 126.9, 124.7, 113.3, 51.0; HRMS Calcd for $C_{24}H_{19}ClNO_2$ $[M+H]^+$ 388.1099, found 388.1105.

Methyl 5-(4-fluorophenyl)-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (3e). White solid; 38.7 mg (52% yield), m.p. 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.60–7.54 (m, 2H), 7.44–7.36 (m, 3H), 7.32–7.25 (m, 5H), 7.15–7.10 (m, 2H), 6.94–6.88 (m, 2H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 161.9 (d, J = 247.4 Hz), 136.4, 135.2, 132.2, 130.7, 129.1 (d, J = 7.9 Hz), 128.8, 128.7, 128.44, 128.41, 128.1 (d, J = 3.4 Hz), 128.0, 126.8, 124.2, 115.7 (d, J = 21.7 Hz), 113.2, 51.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.5; HRMS Calcd for $C_{24}H_{19}FNO_2$ $[M+H]^+$ 372.1394, found 372.1392.

Methyl 2,4-diphenyl-5-(m-tolyl)-1*H*-pyrrole-3-carboxylate (3f). Yellow oil; 43.5 mg (59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.61–7.56 (m, 2H), 7.43 (dd, J = 8.3, 6.6 Hz, 2H), 7.40–7.36 (m, 1H), 7.27–7.10 (m, 9H), 3.58 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 137.7, 135.7, 135.2, 132.3, 131.8, 131.1, 130.5, 130.0, 129.7, 128.54, 128.47, 128.3, 127.7, 126.3, 125.9, 125.0, 112.0, 51.1, 20.2; HRMS Calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645, found 368.1656.

Methyl 2,4-diphenyl-5-(o-tolyl)-1*H*-pyrrole-3-carboxylate (3g). White solid; 30.7 mg (42% yield), m.p. 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.54–7.47 (m, 2H), 7.39–7.28 (m, 3H), 7.26–7.14 (m, 5H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.42 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 138.3, 136.2, 135.5, 132.4, 131.9, 130.7, 129.7, 128.8, 128.5, 128.4, 128.3, 127.90, 127.87, 127.7, 126.7, 124.5, 124.2, 113.3, 51.0, 21.5; HRMS Calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645, found 368.1660.

Methyl 5-(naphthalen-1-yl)-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (3h). White solid; 46.9 mg (58% yield), m.p. 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.91–7.72 (m, 3H), 7.60–7.51 (m, 2H), 7.47–7.25 (m, 7H), 7.20–7.12 (m, 2H), 7.13–6.98 (m, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 136.0, 134.9, 133.7, 132.5, 132.1, 130.1, 129.7, 129.4, 128.7, 128.55, 128.54, 128.45, 128.4, 128.2, 127.5, 126.6, 126.2, 126.1, 125.8, 125.7, 125.4, 112.3, 51.1; HRMS Calcd for $C_{28}H_{22}NO_2$ $[M+H]^+$ 404.1645, found 404.1658.

Methyl 2,4-diphenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3i). White solid ; 58.1 mg (81% yield), m.p. 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.62–7.55 (m, 2H), 7.48–7.31 (m, 8H), 7.09 (d, *J* = 5.1 Hz, 1H), 6.89 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.82 (d, *J* = 3.6 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 136.5, 135.1, 133.9, 132.1, 130.8, 128.9, 128.54, 128.45, 128.0, 127.2, 124.7, 124.6, 124.4, 123.9, 113.4, 51.0; HRMS Calcd for $C_{22}H_{18}NO_2S$ $[M+H]^+$ 360.1053, found 360.1057.

Methyl 5-butyl-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (3j). White oil; 33.4 mg

(50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.57–7.52 (m, 2H), 7.44–7.34 (m, 5H), 7.32–7.24 (m, 3H), 3.50 (s, 3H), 2.59–2.50 (m, 2H), 1.53 (t, *J* = 7.7 Hz, 2H), 1.29 (q, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 135.8, 135.0, 132.7, 130.8, 130.3, 128.7, 128.3, 128.0, 127.7, 126.3, 123.7, 111.5, 50.8, 32.2, 25.4, 22.5, 13.9; HRMS Calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$ 334.1802, found 334.1811.

Methyl 2,5-diphenyl-4-(p-tolyl)-1*H*-pyrrole-3-carboxylate (3k). White solid; 39.8 mg (54% yield), m.p. 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.60–7.54 (m, 2H), 7.45–7.35 (m, 3H), 7.27–7.15 (m, 7H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.51 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 136.21, 136.19, 132.4, 132.2, 132.1, 130.5, 129.5, 128.73, 128.66, 128.4, 128.3, 127.2, 127.1, 124.3, 113.4, 51.0, 21.4; HRMS Calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645, found 368.1670.

Methyl 4-(4-nitrophenyl)-2,5-diphenyl-1*H*-pyrrole-3-carboxylate (3l). Yellow solid ; 44.5 mg (56% yield), m.p. 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.18–8.10 (m, 2H), 7.62–7.55 (m, 2H), 7.44 (dtd, *J* = 12.5, 6.8, 5.8, 3.6 Hz, 5H), 7.26 (dd, *J* = 5.3, 1.9 Hz, 3H), 7.14 (dt, *J* = 6.9, 2.4 Hz, 2H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 146.6, 143.0, 137.5, 131.9, 131.6, 131.1, 130.6, 128.99, 128.96, 128.8, 128.5, 127.9, 127.6, 123.2, 122.0, 112.7, 51.1; HRMS Calcd for $C_{24}H_{19}N_2O_4$ $[M+H]^+$ 399.1339, found 399.1342.

Methyl 4-(2-methoxyphenyl)-2,5-diphenyl-1*H*-pyrrole-3-carboxylate (3m). Yellow oil; 40.8 mg (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.57–7.50 (m, 2H), 7.37–7.25 (m, 3H), 7.23–7.08 (m, 6H), 7.04 (dd, *J* = 7.5, 1.7 Hz,

1H), 6.87–6.76 (m, 2H), 3.61 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.7, 136.2, 132.5, 132.3, 132.0, 129.7, 128.9, 128.6, 128.4, 128.3, 128.2, 127.0, 126.9, 124.6, 120.5, 120.0, 113.9, 110.7, 55.5, 50.8; HRMS Calcd for $C_{25}H_{22}NO_3$ $[M+H]^+$ 384.1594, found 384.1600.

Ethyl 2,4-diphenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3n). Yellow oil ; 54.9 mg (74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.62–7.54 (m, 2H), 7.46–7.27 (m, 8H), 7.07 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.82 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 135.5, 134.3, 133.0, 131.0, 129.9, 128.0, 127.5, 127.3, 127.0, 126.2, 126.1, 123.8, 123.4, 123.2, 122.7, 112.8, 58.8, 12.7; HRMS Calcd for $C_{23}H_{20}NO_2S$ $[M+H]^+$ 374.1209, found 374.1222.

***tert*-Butyl 2,4-diphenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3o).** Yellow solid, yield: 28.1 mg (35%), m.p. 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.37 (m, 5H), 7.09 (d, *J* = 5.1 Hz, 1H), 6.89 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.82 (dd, *J* = 3.6, 0.9 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 135.8, 135.7, 134.1, 132.1, 130.9, 128.8, 128.5, 128.4, 128.0, 127.2, 127.1, 124.6, 124.3, 123.9, 123.6, 115.6, 80.1, 27.9; HRMS Calcd for $C_{25}H_{24}NO_2S$ $[M+H]^+$ 402.1522, found 402.1520.

1-(2,4-Diphenyl-5-(thiophen-2-yl)-1*H*-pyrrol-3-yl)ethanone (3p). White solid; 44.9 mg (65% yield), m.p. 190–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.60–7.53 (m, 2H), 7.39 (m, 8H), 7.09 (d, *J* = 5.0 Hz, 1H), 6.89 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.83 (d, *J* = 3.6 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3,

135.4, 135.3, 133.8, 132.2, 131.0, 129.1, 128.69, 128.66, 128.5, 127.7, 127.2, 124.5, 124.2, 124.0, 123.84, 123.81, 31.4; HRMS Calcd for $C_{22}H_{18}NOS$ $[M+H]^+$ 344.1104, found 344.1113.

(2,4-Diphenyl-5-(thiophen-2-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (3q). Yellow solid, yield: 13.0 mg (16%), m.p. 191–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.63 (d, 2H), 7.31 (d, 2H), 7.21–7.15 (m, 5H), 7.13–7.04 (m, 7H), 6.88–6.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 138.7, 134.2, 134.1, 133.9, 132.4, 131.4, 130.8, 130.0, 128.7, 128.1, 128.0, 127.9, 127.8, 127.4, 127.0, 125.0, 124.7, 124.5, 124.0, 122.5; HRMS Calcd for $C_{27}H_{20}NOS$ $[M+H]^+$ 406.1260, found 406.1263.

Ethyl 2-methyl-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3u). Yellow oil; 31.2 mg (50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.37–7.25 (m, 5H), 7.03 (d, *J* = 5.1 Hz, 1H), 6.89–6.80 (m, 1H), 6.75 (d, *J* = 3.7 Hz, 1H), 4.04 (d, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 135.9, 135.7, 134.4, 130.9, 127.8, 127.1, 126.9, 123.9, 123.8, 123.0, 122.3, 112.8, 59.4, 14.0, 13.9; HRMS Calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.1053, found 312.1064.

Ethyl 4-phenyl-5-(thiophen-2-yl)-2-(p-tolyl)-1*H*-pyrrole-3-carboxylate (3v). White solid; 55.2 mg (71% yield), m.p. 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.40–7.29 (m, 5H), 7.24–7.17 (m, 2H), 7.07 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.81 (dd, *J* = 3.7, 1.1 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 138.4, 136.7, 135.5, 134.0, 130.9, 129.1, 128.9, 127.9, 127.2, 127.1, 124.7,

124.3, 124.0, 123.6, 113.5, 59.7, 21.5, 13.7; HRMS Calcd for $C_{24}H_{22}NO_2S$ $[M+H]^+$ 388.1366, found 388.1375.

Ethyl 2-(4-methoxyphenyl)-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3w). Yellow solid; 57.2 mg (71% yield), m.p. 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.51–7.40 (m, 2H), 7.26 (d, *J* = 3.3 Hz, 5H), 6.97 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.78 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.74 (dd, *J* = 3.7, 1.2 Hz, 1H), 3.85 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 159.8, 136.7, 135.6, 134.1, 130.9, 130.4, 127.9, 127.1, 127.0, 124.7, 124.4, 124.2, 123.8, 123.5, 113.7, 113.2, 59.7, 55.4, 13.7; HRMS Calcd for $C_{24}H_{22}NO_3S$ $[M+H]^+$ 404.1315, found 404.1321.

Ethyl 2-(4-fluorophenyl)-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3x). Yellow oil; 62.0 mg (79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.54–7.39 (m, 2H), 7.25 (d, *J* = 2.7 Hz, 5H), 6.96 (t, *J* = 7.8 Hz, 3H), 6.76 (dd, *J* = 8.7, 3.6 Hz, 2H), 3.82 (qd, *J* = 7.1, 2.2 Hz, 2H), 0.75 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.8 ($J_{C\text{-}F}$ = 248.4 Hz), 134.7, 134.3, 132.8, 130.0 ($J_{C\text{-}F}$ = 8.1 Hz), 129.9, 127.0 ($J_{C\text{-}F}$ = 3.5 Hz), 126.9, 126.14, 126.05, 123.7, 123.5, 123.3, 122.8, 114.2 ($J_{C\text{-}F}$ = 21.7 Hz), 112.5, 58.8, 12.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.8; HRMS Calcd for $C_{23}H_{19}FNO_2S$ $[M+H]^+$ 392.1115, found 392.1125.

Ethyl 2-(4-bromophenyl)-4-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (3y). Yellow solid; 70.9 mg (79% yield), m.p. 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 5H), 6.99 (d, *J* = 5.0 Hz, 1H), 6.78 (t, *J* = 4.3 Hz, 1H), 6.75 (d, *J* = 3.6 Hz, 1H), 3.84 (q, *J* = 7.1 Hz,

2H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.20, 135.17, 133.7, 131.4, 130.9, 130.8, 130.6, 128.0, 127.2, 127.1, 124.9, 124.7, 124.6, 123.9, 122.6, 113.9, 59.9, 13.7; HRMS Calcd for $C_{23}H_{19}BrNO_2S$ $[M+H]^+$ 452.0314, found 452.0322.

■ ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website. Crystallographic data (CIF), X-ray structure of products, and copies of ^{1}H and ^{13}C NMR spectra data for all products (PDF).

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Notes

The authors declare no competing financial interest.

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