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# Tandem Copper-Catalyzed Propargylation/Alkyne Azacyclization/Isomerization Reaction under Microwave Irradiation: Synthesis of Fully Substituted Pyrroles

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Supporting Information

**ABSTRACT:** A copper-catalyzed and microwave-assisted synthesis of fully substituted pyrroles has been developed. A series of pentasubstituted pyrroles, especially α-arylpyrroles, could be obtained in moderate to good yields (up to 93%) through a tandem propargylation/alkyne azacyclization/isomerization sequence from readily available β-enamino compounds and propargyl acetates.


## INTRODUCTION

Fully substituted pyrroles are important bioactive motifs, widely presented in many biologically active compounds and natural products (Figure 1),[1] including Permethyl Storniamide A[1c] acting as inhibitors of multidrug resistance (MDR) phenomenon, Atorvastatin[1e,f] for the treatment of dyslipidemia, Bcl-2/Bcl-xL inhibitor,[1d] and $CB_1$ antagonist.[1h] The great importance and potent bioactivity suggest the need for simple and efficient methods to construct these molecules, especially the convenient one-step synthesis of fully substituted pyrroles.[2,3]

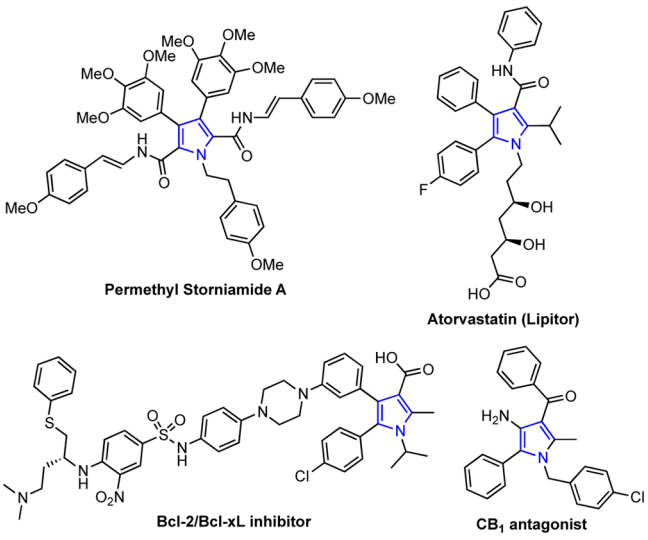


**Figure 1.** Natural product and pharmaceuticals bearing fully substituted pyrrole.

Recently, the activation of propargyl alcohols and their derivatives by transition-metal catalysts or organocatalysts has emerged as a powerful tool for the easy assembly of multisubstituted pyrroles and other heterocycles with potent activity.[4−9] The multicomponent reaction of propargyl alcohols, amines, and 1,3-dicarbonyl compounds is an elegant and general route for the synthesis of fully substituted pyrroles.[5] Cadierno and Gimeno developed a one-pot three-component synthesis of fully substituted pyrroles from propargylic alcohols, 1,3-dicarbonyl compounds, and primary amines under the catalysis of a combination of ruthenium and trifluoroacetic acid.[6] Zhan and co-workers disclosed an indium chloride promoted propargylation/amination/isomerization tandem reaction affording highly substituted pyrroles in good yields.[7] Roy and co-workers used Ir−Sn bimetallic catalyst to synthesize fully decorated furan and pyrroles through alkylation of 1,3-dicarbonyl compounds with benzylic and propargylic alcohols.[8] Zheng and co-workers demonstrated a silver-catalyzed synthesis of fully substituted pyrroles.[9] The use of simple materials with high efficiency shows the unique advantages of these methodologies on the synthesis of fully substituted pyrroles. However, these methods suffered from the employment of an expensive metal catalyst or a special substrate scope. As far as we know, acetoacetates and 1,3-diketones were employed to afford pyrroles in most cases, whereas the application of aromatic β-ketoesters has never been reported in the synthesis of substituted pyrroles via activation of propargyl alcohols and their derivatives until now, probably due to their relatively poor reactivities.[10] Given the importance of the corresponding α-

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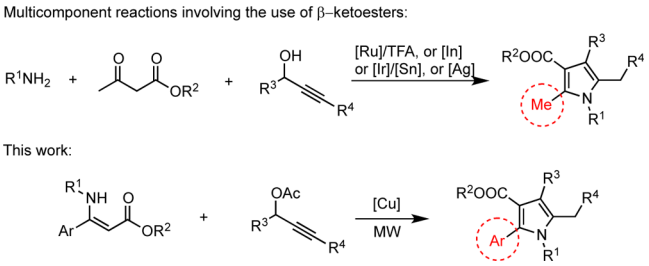
aryl-substituted pyrroles that form a set of molecules exhibiting a broad range of bioactivities and pharmacological activities,[1] the development of a rapid and easy construction of pentasubstituted $\alpha$-arylpyrroles derived from simple aromatic $\beta$-ketoesters derivatives is extremely desirable.[11] We felt that preformed $\beta$-enamino compounds from aromatic $\beta$-ketoesters may be used instead of $\beta$-ketoesters and amines in the multicomponent reactions to improve the reaction activities and avoid the formation of byproducts.[12,13] Thus, as hypothesized, the desired $\alpha$-aryl-pentasubstituted pyrroles could be obtained through a domino copper-catalyzed propargylation/alkyne azacyclization/isomerization sequence of propargyl acetates with preformed $\beta$-enamino compounds from aromatic $\beta$-ketoesters (Scheme 1).[14,15] Herein, we report

**Scheme 1. Design for the Synthesis of $\alpha$-Arylsubstituted Pyrroles**



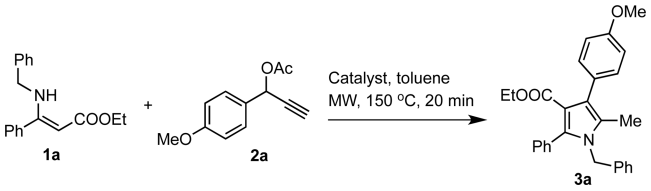

our development of an efficient copper-catalyzed synthesis of fully substituted $\alpha$-arylpyrroles from $\beta$-enamino compounds and propargyl acetates under microwave irradiation.[16]

## RESULTS AND DISCUSSION

We chose $\beta$-enamino ester **1a** and secondary propargyl acetate **2a** as model substrates to react with each other in toluene in the presence of 10 mol % of CuBr as catalyst at 150 °C under microwave irradiation. The reaction proceeded smoothly to give the desired pentasubstituted pyrrole **3a** with a pleasing of 91% yield (by $^1$H NMR), while only 8% yield was observed without the employment of catalyst (Table 1, entry 1 versus entry 2). To improve the yield, other copper salts were screened (entries 3−7). Among these copper salts, $Cu(OTf)_2$ showed the best catalytic ability, giving 95% NMR yield. Other salts such as AgOTf, $Yb(OTf)_3$, $Ni(OTf)_3$, and $Sc(OTf)_3$ were less effective compared with $Cu(OTf)_2$ (entries 8−11). Without microwave irradiation, 74% yield was attained by heating at 150 °C for 100 mintues (entry 12). Excellent NMR yield (99%) and isolated yield (91%) were achieved by reducing the catalyst loading to 5 mol % (entry 13). However, the yield was slightly decreased when the reaction was performed at a higher concentration (entries 14 and 15). It should be noted that all the reactions were carried out without exclusion of moisture or air from the reaction system.

The substrate scope was then examined with the optimized reaction condition in hand. As shown in Table 2, variation at the N1 position including benzyl, furylmethyl, phenethyl, isopropyl, methoxyethyl, morpholinylethyl, cyclopropyl, cyclohexyl, and phenyl groups was successful, giving moderate to excellent yields ranging from 43% to 91%. Electron-donating and electron-withdrawing groups on the ring of the aromatic $\beta$-enamino ester could be tolerated, delivering the corresponding products in 70−80% yields. $\beta$-Enamino ester derived from methyl acetoacetate also worked well in this system, yielding

**Table 1. Reaction Development**[a]




| entry | catalyst | yield [%][b] |
|---|---|---|
| 1 | CuBr | 91 |
| 2 | | 8 |
| 3 | CuI | 73 |
| 4 | CuCl | 78 |
| 5 | $Cu(OTf)_2$ | 95 |
| 6 | $Cu(OAc)_2$ | 5 |
| 7 | $CuBr_2$ | 66 |
| 8 | AgOTf | 61 |
| 9 | $Yb(OTf)_3$ | 58 |
| 10 | $Ni(OTf)_3$ | 16 |
| 11 | $Sc(OTf)_3$ | 35 |
| 12[c] | $Cu(OTf)_2$ | 74 |
| 13[d] | $Cu(OTf)_2$ | 99 (91)[e] |
| 14[d,f] | $Cu(OTf)_2$ | 98 |
| 15[f] | $Cu(OTf)_2$ | 64 |

[a]Unless otherwise noted, reaction was performed with 0.2 mmol of **1a**, 0.24 mmol of **2a**, and 10 mol % of catalyst in 1.0 mL of toluene irradiated by microwave for 20 min. [b]Yield determined by $^1$H NMR with $CH_2Br_2$ as internal standard. [c]Heated at 150 °C for 100 min without microwave irradiation. [d]With 5 mol % of catalyst. [e]Isolated yield. [f]At 0.4 M.

the pyrroles **3p** and **3q** in 93% and 54% yields, respectively. Pleasingly, the cyclic $\beta$-enamino compound could be employed successfully in this system, giving **3r** in 59% yield.

Next, various secondary propargyl acetates were submitted to this process. Aryl or heteroaryl groups substituted propargyl acetates with terminal alkyne proceed smoothly to give pyrroles in moderate to good yields (54−75%), regardless of electron-donating and electron-withdrawing groups on the ring. Surprisingly, in the case of alkylated propargyl acetate, the corresponding pyrrole failed to be obtained and a complicated mixture was observed in this reaction probably due to the instable intermediate. The desired product could be obtained in 57% yield when propargyl acetate with internal alkyne was employed.

This process could be easily scaled up for further biomedical research. As shown in Scheme 2, when 1.13 g of compound **1a** was treated in this system, 1.53 g of the corresponding product **3a** was obtained in 90% yield.

In order to investigate the mechanism of this reaction, control reactions and D−H exchange experiments were conducted (Scheme 3). Three-component reactions were performed under the current catalytic system. When methyl acetoacetate was used, the corresponding product **3p** can be detected in 40% yield. However, no desired $\alpha$-aryl-pentasubstituted pyrrole **3a** was observed. The results demonstrate that the use of preformed $\beta$-enamino compounds from aromatic $\beta$-ketoesters is essential for the synthesis of $\alpha$-aryl-pentasubstituted pyrroles.[10] The reactions with enamino esters were then performed in the presence of $D_2O$ to gain evidence for the mechanism proposal. As shown in Scheme 3, 90% deuterium incorporation in compound **3a** was observed. It indicates that


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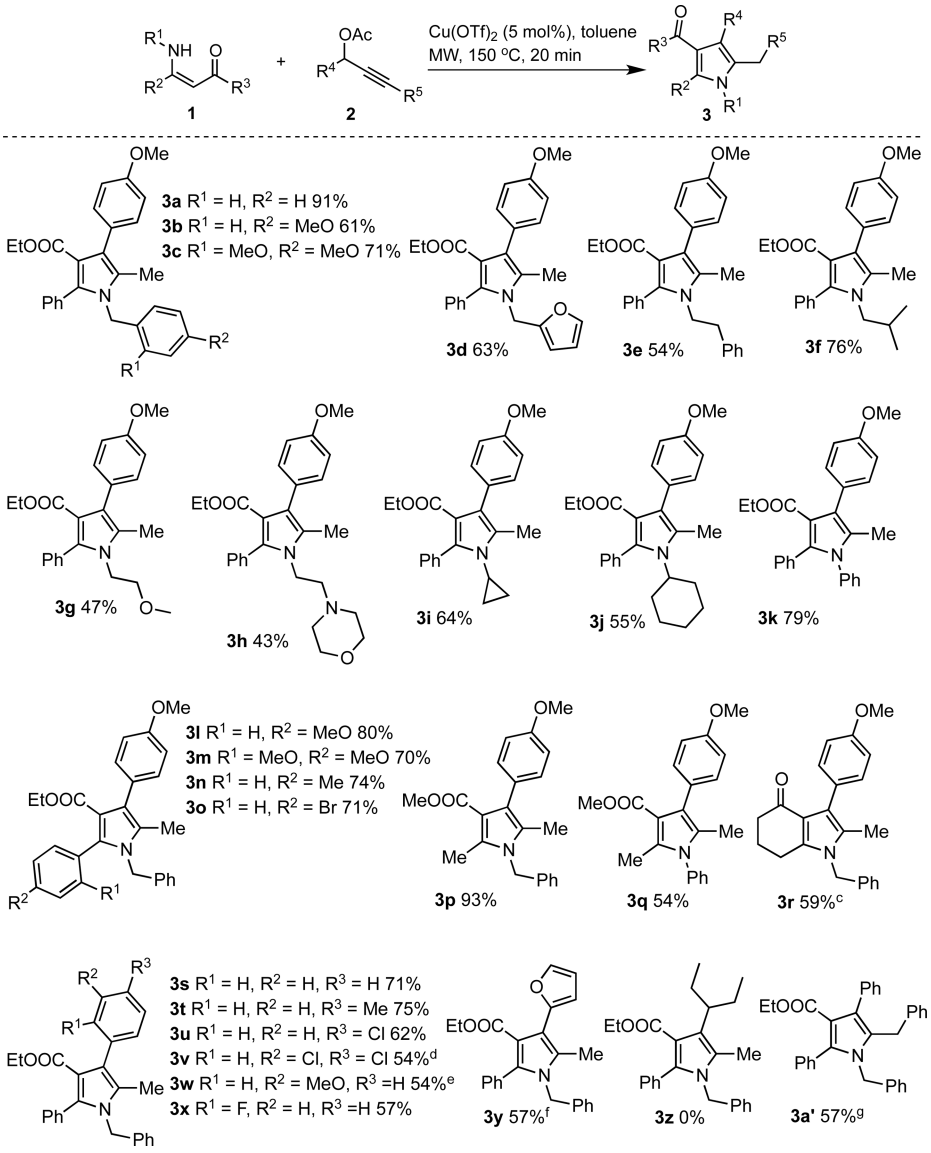
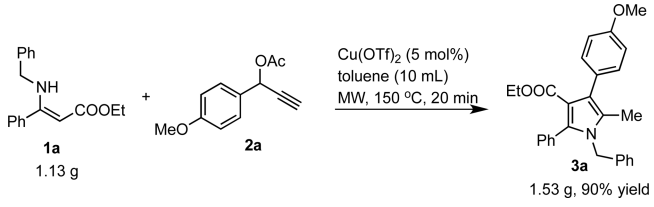
**Table 2. Examination of Substrate Scope**[a,b]




[a]Unless otherwise noted, reaction was performed with 0.2 mmol of **1**, 0.24 mmol of **2**, and 5 mol % of $Cu(OTf)_2$ in 1.0 mL of toluene under microwave irradiation at 150 °C for 20 min. [b]Isolated yields. [c]Performed with 1.5 equiv of **2**. [d]For 25 min. [e]For 30 min. [f]Performed with 1.5 equiv of **2** at 100 °C for 20 min. [g]Performed with 10 mol % of $Cu(OTf)_2$ at 150 °C for 30 min.

**Scheme 2. Gram-Scale Reaction**




protonolysis and isomerization occurred during this catalytic process.

A mechanistic proposal for this reaction is depicted in Scheme 4 based on results described above and other reported studies.[6,7,17] Propargylation of $\beta$-enamino ester occurs first to give a propargylation intermediate. Subsequently, an intramolecular 5-*exo*-*dig* attack to the carbon−carbon triple bond takes place upon the activation of copper catalyst, which was followed by protonolysis and isomerization delivering pyrrole.

## CONCLUSION

In conclusion, we have developed an efficient synthesis of pentasubstituted pyrroles under microwave irradiation. A series of functionalized pyrroles, especially $\alpha$-arylpyrroles, could be obtained in moderate to good yields (up to 93%) through a tandem propargylation/alkyne azacyclization/isomerization sequence from $\beta$-enamino compounds and propargyl acetates. This process could be scaled up easily for further biomedical research. The extension to the development of other analogous and application in biomedical research of this strategy is currently ongoing in our laboratory.

## EXPERIMENTAL SECTION

**General Methods.** Column chromatography was performed using Merk silica gel 60 (230−400 mesh) eluting with EtOAc and hexane. $^1$H NMR and $^{13}$C NMR spectra were recorded using a 400 MHz NMR spectrometer. Chemical shifts are reported in ppm downfield from $CDCl_3$ ($\delta$ = 7.26 ppm) for $^1$H NMR and relative to the central $CDCl_3$



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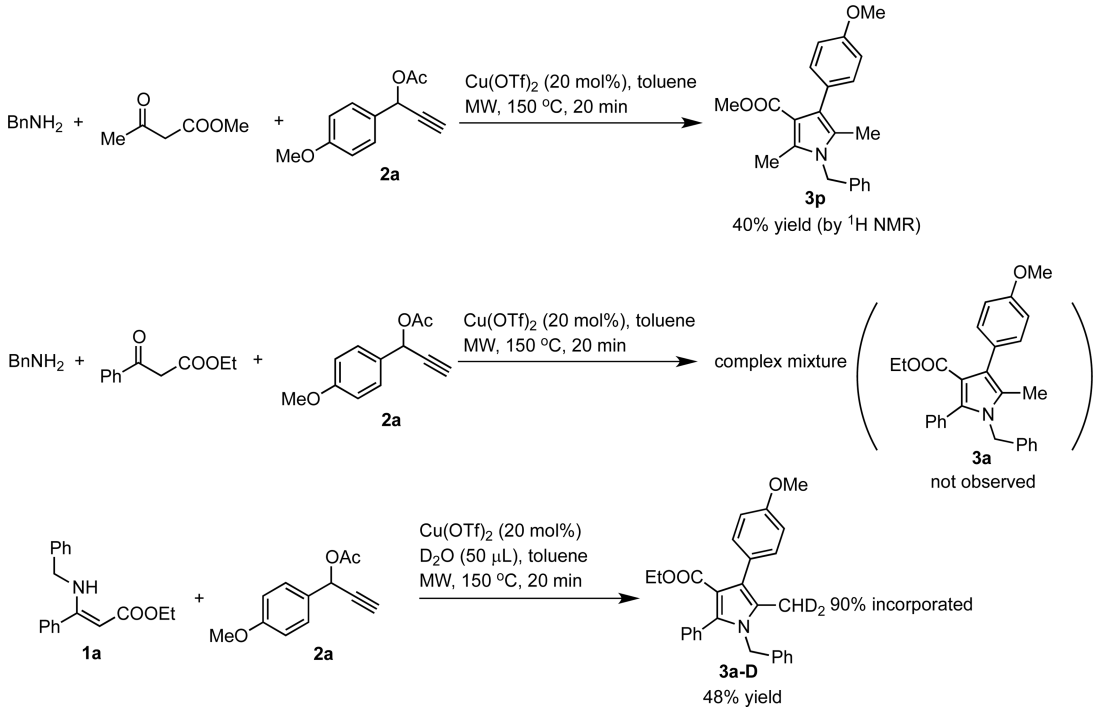
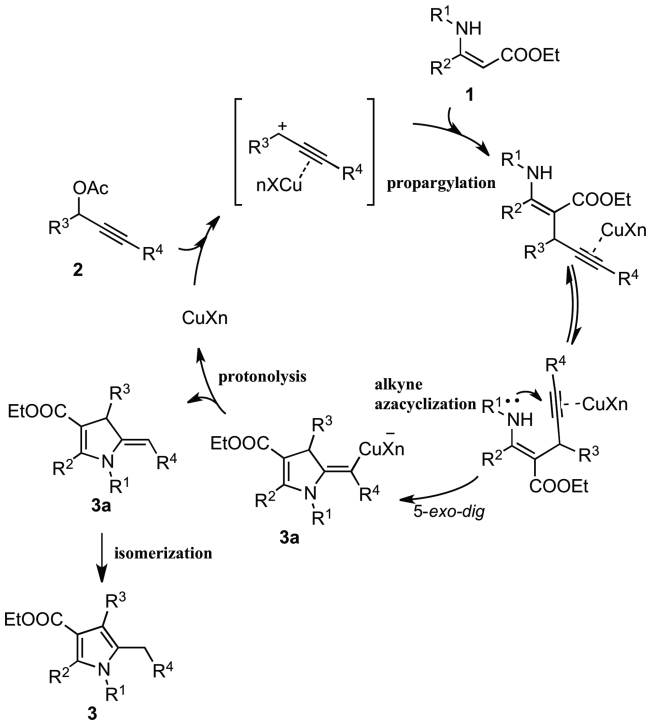
**Scheme 3. Control Reactions and D−H Exchange Experiments**



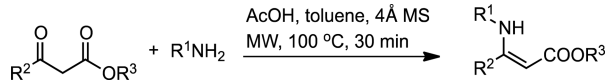

**Scheme 4. Proposed Catalytic Cycle**




resonance ($\delta$ = 77.0 ppm) for $^{13}$C NMR spectroscopy. Coupling constants are given in Hz. ESI-MS analysis was performed using an ion trap mass spectrometer. All microwave irradiation experiments were carried out in a Biotage Initiator Classic microwave apparatus with continuous irradiation power from 0 to 400 W with utilization of the standard absorbance level of 250 W maximum power. The reaction mixture temperature is determined by an external IR sensor. The reactions were carried out in 10 mL glass tubes, sealed with microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then, it was cooled to 50 °C with gas jet cooling.

$\beta$-Enamino compounds were synthesized through microwave-assisted condensation of amines and 1,3-dicarbonyl compounds developed in our group.[12] Propargyl acetates **2** were prepared according to the literature procedure.[18] All reagents and solvents were obtained from commercial sources and used without further purification.

**General Procedure for the Microwave-Assisted Synthesis of Enaminoester 1.**




A mixture of $\beta$-ketoesters (10 mmol), primary amine (13 mmol), acetic acid (1.0 or 2.0 mmol), and 4Å MS (1g) was diluted with toluene without exclusion of air (2 mL). The resulting reaction mixture was stirred at rt for 30 s, then heated by microwave at 100 °C for 30 min. The mixture was cooled to rt, filtered, and directly purified by a silica gel flash chromatography (Hexane/EtOAc) to give compound **1** in 27−80% yields.

*(Z)-Ethyl 3-(Benzylamino)-3-phenyl Acrylate (**1a**).* Known compound;[19] Purified by flash column chromatography (Hexane/EtOAc = 20:1); white solid (mp: 71−73 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.91 (brs, 1H), 7.38−7.15 (m, 10H), 4.67 (s, 1H), 4.25 (d, $J$ = 6.8 Hz, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 1.27 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 164.7, 139.2, 135.9, 129.2, 128.5, 128.3, 127.8, 127.1, 126.8, 86.3, 58.7, 48.3, 14.5 ppm.

*(Z)-Ethyl 3-((4-Methoxybenzyl)amino)-3-phenyl Acrylate (**1b**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (brs, 1H), 7.38−7.33 (m, 5H), 7.10−7.07 (m, 2H), 6.85−6.81 (m, 2H), 4.66 (s, 1H), 4.19 (d, $J$ = 6.4 Hz, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 3.78 (s, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 164.6, 158.8, 136.0, 131.3, 129.2, 128.3, 128.1, 127.9, 114.0, 86.1, 58.7, 55.2, 47.8, 14.5 ppm; ESI-HRMS: calcd. for $C_{19}H_{21}NNaO_3^+$ (M + Na)$^+$ 334.1414, found 334.1422.

*(Z)-Ethyl 3-((2,4-Dimethoxybenzyl)amino)-3-phenyl Acrylate (**1c**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (brs, 1H), 7.39−7.35 (m, 5H), 6.93 (d, $J$ = 8.0 Hz, 1H), 6.41−6.38 (m, 2H), 4.59



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(s, 1H), 4.16 (d, $J$ = 6.4 Hz, 2H), 4.13 (q, $J$ = 7.2 Hz, 2H), 3.78 (s, 3H), 3.78 (s, 3H), 1.27 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 164.8, 160.3, 158.2, 136.4, 129.0, 129.0, 128.2, 128.0, 120.0, 103.9, 98.5, 85.5, 58.5, 55.3, 55.3, 43.7, 14.6 ppm; ESI-HRMS: calcd. for $C_{20}H_{24}NO_4^+$ $(M + H)^+$ 342.1700, found 342.1702.

*(Z)-Ethyl 3-((Furan-2-ylmethyl)amino)-3-phenyl Acrylate (**1d**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.75 (brs, 1H), 7.43−7.37 (m, 5H), 7.33 (dd, $J$ = 2.0, 0.8 Hz, 1H), 6.27 (dd, $J$ = 3.2, 1.2 Hz, 1H), 6.10−6.09 (m, 1H), 4.68 (s, 1H), 4.21 (d, $J$ = 6.4 Hz, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 1.27 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 164.3, 152.3, 142.1, 135.8, 129.3, 128.4, 128.0, 110.2, 106.8, 87.0, 58.8, 41.7, 14.5 ppm; ESI-HRMS: calcd. for $C_{16}H_{18}NO_3^+$ $(M + H)^+$ 272.1281, found 272.1281.

*(Z)-Ethyl 3-(Phenethylamino)-3-phenyl Acrylate (**1e**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (brs, 1H), 7.42−7.28 (m, 3H), 7.26−7.13 (m, 5H), 7.04 (d, $J$ = 6.8 Hz, 2H), 4.57 (s, 1H), 4.14 (d, $J$ = 7.2 Hz, 2H), 3.27 (dd, $J$ = 14.0, 7.2 Hz, 2H), 2.74 (t, $J$ = 7.2 Hz, 2H), 1.35−1.20 (m, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 164.7, 138.5, 136.1, 129.0, 128.7, 128.4, 128.2, 127.7, 126.4, 85.6, 58.6, 46.1, 37.8, 14.6 ppm; ESI-HRMS: calcd. for $C_{19}H_{22}NO_2^+$ $(M + H)^+$ 296.1645, found 296.1641.

*(Z)-Ethyl 3-(Isobutylamino)-3-phenyl Acrylate (**1f**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.64 (brs, 1H), 7.43−7.31 (m, 5H), 4.57 (s, 1H), 4.14 (q, $J$ = 7.2 Hz, 2H), 2.87 (t, $J$ = 6.4 Hz, 2H), 1.72−1.66 (m, 1H), 1.27 (t, $J$ = 7.2 Hz, 3H), 0.87−0.85 (m, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 165.2, 136.4, 129.0, 128.2, 127.9, 84.9, 58.6, 52.2, 29.8, 19.9, 14.6 ppm; ESI-HRMS: calcd. for $C_{15}H_{22}NO_2^+$ $(M + H)^+$ 248.1645, found 248.1650.

*(Z)-Ethyl 3-((2-Methoxyethyl)amino)-3-phenyl Acrylate (**1g**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (brs, 1H), 7.40−7.33 (m, 5H), 4.60 (s, 1H), 4.15 (q, $J$ = 7.2 Hz, 2H), 3.40 (t, $J$ = 5.2 Hz, 2H), 3.34 (s, 3H), 3.22 (dd, $J$ = 11.6, 5.2 Hz, 2H), 1.27 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 164.5, 136.2, 129.1, 128.3, 127.9, 85.9, 72.1, 58.9, 58.7, 44.3, 14.6 ppm; ESI-HRMS: calcd. for $C_{14}H_{20}NO_3^+$ $(M + H)^+$ 250.1438, found 250.1444.

*(Z)-Ethyl 3-((2-Morpholinoethyl)amino)-3-phenyl Acrylate (**1h**).* Purified by flash column chromatography (Hexane/EtOAc = 5:1); white solid (mp: 61−62 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61 (brs, 1H), 7.39−7.33 (m, 5H), 4.59 (s, 1H), 4.14 (q, $J$ = 7.2 Hz, 2H), 3.75−3.58 (m, 4H), 3.14 (q, $J$ = 6.4 Hz, 2H), 2.43 (t, $J$ = 6.4 Hz, 2H), 2.40−2.33 (m, 4H), 1.27 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 164.4, 136.4, 129.1, 128.3, 127.8, 85.7, 66.9, 58.8, 58.6, 53.5, 41.5, 14.6 ppm; ESI-HRMS: calcd. for $C_{17}H_{25}N_2O_3^+$ $(M + H)^+$ 305.1860, found 305.1868.

*(Z)-Ethyl 3-(Cyclopropylamino)-3-phenyl Acrylate (**1i**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (s, 1H), 7.47−7.35 (m, 5H), 4.61 (s, 1H), 4.12 (q, $J$ = 7.2 Hz, 2H), 2.53−2.45 (m, 1H), 1.26 (t, $J$ = 7.2 Hz, 3H), 0.53−0.49 (m, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 165.3, 136.8, 128.9, 128.1, 127.9, 85.3, 58.7, 26.8, 14.6, 8.6 ppm; ESI-HRMS: calcd. for $C_{14}H_{18}NO_2^+$ $(M + H)^+$ 232.1332, found 232.1342.

*(E)-Ethyl 3-(Cyclohexylamino)-3-phenyl Acrylate (**1j**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.54 (d, $J$ = 9.2 Hz, 1H), 7.39−7.33 (m, 5H), 4.55 (s, 1H), 4.14 (q, $J$ = 7.2 Hz, 2H), 3.19−3.04 (m, 1H), 1.83−1.71(m, 2H), 1.69−1.64 (m, 2H), 1.52−1.42 (m, 1H), 1.36−1.22 (m, 5H), 1.21−1.02 (m, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 164.3, 136.8, 129.0, 128.3, 127.7, 85.5, 58.6, 52.5, 34.5, 25.3, 24.5, 14.6 ppm; ESI-HRMS: calcd. for $C_{17}H_{24}NO_2^+$ $(M + H)^+$ 274.1802, found 274.1811.

*(Z)-Ethyl 3-Phenyl-3-(phenylamino)acrylate (**1k**).* Known compound;[20] Purified by flash column chromatography (Hexane/EtOAc = 20:1); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.31 (brs, 1H), 7.37−7.22 (m, 5H), 7.08−7.04 (m, 2H), 6.89 (t, $J$ = 7.2 Hz, 1H), 6.66 (d, $J$ = 8.0 Hz, 2H), 5.00 (s, 1H), 4.20 (q, $J$ = 7.2 Hz, 2H), 1.31 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.0, 159.0, 140.4, 136.0, 129.3, 128.5, 128.3, 128.2, 122.9, 122.1, 91.2, 59.2, 14.5 ppm.

*(Z)-Ethyl 3-(Benzylamino)-3-(4-methoxyphenyl)acrylate (**1l**).* Known compound;[19] Purified by flash column chromatography (Hexane/EtOAc = 20:1); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.90 (brs, 1H), 7.33−7.17 (m, 7H), 6.91−6.84 (m, 2H), 4.67 (s, 1H), 4.30 (d, $J$ = 6.4 Hz, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 3.82 (s, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 164.7, 160.4, 139.4, 129.3, 128.6, 128.2, 127.1, 126.8, 113.8, 86.1, 58.7, 55.3, 48.4, 14.6 ppm.

*(Z)-Ethyl 3-(Benzylamino)-3-(2,4-dimethoxyphenyl)acrylate (**1m**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.98 (s, 1H), 7.30−7.24 (m, 2H), 7.23−7.15 (m, 3H), 7.11 (d, $J$ = 7.6 Hz, 1H), 6.50−6.43 (m, 2H), 4.54 (s, 1H), 4.25−4.05 (m, 4H), 3.82 (s, 3H), 3.74 (s, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.6, 162.0, 161.7, 157.4, 139.2, 130.7, 128.4, 127.1, 127.0, 117.8, 104.4, 98.4, 84.7, 58.5, 55.4, 55.4, 48.0, 14.6 ppm; ESI-HRMS: calcd. for $C_{20}H_{24}NO_4^+$ $(M + H)^+$ 342.1700, found 342.1715.

*(Z)-Ethyl 3-(Benzylamino)-3-(p-tolyl)acrylate (**1n**).* Known compound;[19] Purified by flash column chromatography (Hexane/EtOAc = 20:1); brown oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.95 (brs, 1H), 7.38−7.27 (m, 5H), 7.26−7.19 (m, 4H), 4.72 (s, 1H), 4.33 (d, $J$ = 6.4 Hz, 2H), 4.20 (q, $J$ = 7.2 Hz, 2H), 2.42 (s, 3H), 1.33 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 164.9, 139.3, 139.3, 133.0, 129.0, 128.6, 127.8, 127.1, 126.8, 86.0, 58.7, 48.3, 21.2, 14.6 ppm.

*(Z)-Ethyl 3-(Benzylamino)-3-(4-bromophenyl)acrylate (**1o**).* Known compound;[19] Purified by flash column chromatography (Hexane/EtOAc = 20:1); white solid (mp: 55−56 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.88 (brs, 1H), 7.54−7.46 (m, 2H), 7.34−7.27 (m, 2H), 7.26−7.13 (m, 5H), 4.65 (s, 1H), 4.24 (d, $J$ = 6.4 Hz, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 1.28 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 163.4, 139.0, 134.8, 131.6, 129.5, 128.6, 127.3, 126.7, 123.5, 86.8, 58.9, 48.3, 14.5 ppm.

*(Z)-Methyl 3-(Benzylamino)but-2-enoate (**1p**).* Known compound;[21] Purified by flash column chromatography (Hexane/EtOAc = 20:1); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.94 (brs, 1H), 7.37−7.31 (m, 2H), 7.29−7.23 (m, 3H), 4.54 (s, 1H), 4.43 (d, $J$ = 6.0 Hz, 2H), 3.63 (s, 3H), 1.91 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.9, 161.9, 138.7, 128.7, 127.3, 126.7, 82.8, 49.9, 46.8, 19.3 ppm.

*(Z)-Methyl 3-(Phenylamino)but-2-enoate (**1q**).* Known compound;[20] Purified by flash column chromatography (Hexane/EtOAc = 20:1); white solid (mp: 47−49 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.35 (brs, 1H), 7.36−7.29 (m, 2H), 7.20−7.13 (m, 1H), 7.12−7.06 (m, 2H), 4.70 (s, 1H), 3.69 (s, 3H), 2.00 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 159.1, 139.3, 129.1, 125.0, 124.5, 85.6, 50.2, 20.3 ppm.

*3-(Benzylamino)cyclohex-2-enone (**1r**).* Known compound;[22] Purified by flash column chromatography (Hexane/EtOAc = 2:3); yellow solid (mp: 126−127 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.24 (m, 5H), 5.17 (s, 1H), 5.14−5.10 (m, 1H), 4.22 (d, $J$ = 5.2 Hz, 2H), 2.38 (t, $J$ = 6.0 Hz, 2H), 2.34−2.25 (m, 2H), 2.01−1.92 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 164.1, 136.8, 128.8, 127.9, 127.7, 97.5, 47.2, 36.4, 29.6, 21.9 ppm.

**General Procedure for the Microwave-Assisted Synthesis of Fully Substituted Pyrrole 3.** A mixture of enamino ester **1** (0.20 mmol, 1.0 equiv), propargyl acetate **2** (0.24 mmol, 1.2 equiv), $Cu(OTf)_2$ (0.01 mmol, 5 mol %), and toluene (1 mL) was stirred at room temperature for 30 s and then heated at 150 °C for 20 min under microwave irradiation without exclusion of air. The reaction mixture was then cooled to room temperature and purified directly by a silica gel flash chromatography (Hexane/EtOAc), giving compound **3**.

*Ethyl 1-Benzyl-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3a**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 77.4 mg, 91% yield; yellow gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.20 (m, 10H), 6.93−6.89 (m, 4H), 4.95 (s, 2H), 3.90 (q, $J$ = 7.2, 2H), 3.82 (s, 3H), 2.02 (s, 3H), 0.80 (t, $J$ =


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7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.1, 158.0, 137.9, 137.8, 132.5, 131.5, 130.6, 128.6, 128.2, 128.0, 127.7, 127.2, 127.0, 125.7, 123.0, 113.0, 112.4, 59.0, 55.2, 47.9, 13.6, 10.6 ppm; ESI-HRMS: calcd. for $C_{28}H_{28}NO_3$ $(M + H)^+$ 426.2064, found 426.2051.

*Ethyl 1-(4-Methoxybenzyl)-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3b**).* Purified by flash column chromatography (Hexane/EtOAc = 5:1); 55.5 mg, 61% yield; pale yellow gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.24 (m, 7H), 6.93−6.82 (m, 6H), 4.90 (s, 2H), 3.90 (q, $J$ = 7.2, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 2.04 (s, 3H), 0.80 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 158.7, 158.0, 137.9, 132.6, 131.5, 130.7, 129.8, 128.3, 128.0, 127.7, 127.0, 126.9, 122.9, 114.1, 113.0, 112.3, 59.0, 55.2, 47.4, 13.6, 10.6; ESI-HRMS: calcd. for $C_{29}H_{30}NO_4$ $(M + H)^+$ 456.2169, found 456.2152.

*Ethyl 1-(2,4-Dimethoxybenzyl)-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3c**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 68.9 mg, 71% yield; yellow solid (mp: 121−123 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.28 (m, 7H), 6.94−6.92 (m, 2H), 6.47−6.40 (m, 3H), 4.85 (s, 2H), 3.91 (q, $J$ = 7.2 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 2.03 (s, 3H), 0.82 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.3, 160.0, 158.0, 156.7, 138.1, 132.6, 131.5, 130.6, 128.5, 127.9, 127.7, 127.2, 126.8, 122.8, 118.6, 113.0, 112.2, 104.1, 98.1, 59.0, 55.3, 55.2, 55.2, 43.0, 13.6, 10.3 ppm; ESI-HRMS: calcd. for $C_{30}H_{32}NO_5$ $(M + H)^+$486.2275, found 486.2255.

*Ethyl 1-(Furan-2-ylmethyl)-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3d**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 52.3 mg, 63% yield; pale yellow gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.35 (m, 5H), 7.31 (dd, $J$ = 2.0, 0.8 Hz, 1H), 7.25−7.22 (m, 2H), 6.93−6.89 (m, 2H), 6.27 (q, $J$ = 1.6 Hz, 1H), 5.91 (dd, $J$ = 3.2, 0.8 Hz, 1H), 4.85 (s, 2H), 3.85 (q, $J$ = 7.2 Hz, 2H), 3.83 (s, 3H), 2.19 (s, 3H), 0.78 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.0, 158.0, 150.5, 142.2, 137.7, 132.5, 131.5, 130.9, 128.2, 128.1, 127.8, 127.1, 122.7, 113.0, 112.5, 110.3, 107.6, 59.0, 55.2, 41.7, 13.5, 10.5 ppm; ESI-HRMS: calcd. for $C_{26}H_{26}NO_4$ $(M + H)^+$ 416.1856, found 416.1840.

*Ethyl 4-(4-Methoxyphenyl)-5-methyl-1-phenethyl-2-phenyl-1H-pyrrole-3-carboxylate (**3e**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 47.4 mg, 54% yield; yellow solid (mp: 105−106 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.41 (m, 3H), 7.37−7.34 (m, 2H), 7.25−7.19 (m, 5H), 6.95−6.91 (m, 2H), 6.87−6.85 (m, 2H), 3.94−3.85 (m, 4H), 3.84 (s, 3H), 2.76 (t, $J$ = 8.0, 2H), 2.09 (s, 3H), 0.79 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.1, 158.0, 137.8, 137.2, 133.1, 131.5, 130.8, 128.6, 128.6, 128.4, 128.0, 127.9, 126.7, 126.5, 122.5, 113.0, 112.3, 58.9, 55.2, 46.0, 37.3, 13.6, 10.4 ppm; ESI-HRMS: calcd. for $C_{29}H_{30}NO_3$ $(M + H)^+$ 440.2220, found 440.2200.

*Ethyl 1-Isobutyl-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3f**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 59.6 mg, 76% yield; pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.34 (m, 5H), 7.25−7.23 (m, 2H), 6.93−6.91 (m, 2H), 3.88−3.84 (m, 5H), 3.60 (d, $J$ = 7.6 Hz, 2H), 2.18 (s, 3H), 1.85−1.70 (m, 1H), 0.79 (t, $J$ = 7.2 Hz, 3H), 0.70 (d, $J$ = 6.4 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 158.0, 137.5, 133.2, 131.5, 131.0, 128.6 127.8, 127.7, 126.8, 122.5, 113.0, 112.3, 58.9, 55.2, 51.5, 29.3, 19.8, 13.6, 11.0 ppm; ESI-HRMS: calcd. for $C_{25}H_{30}NO_3$ $(M + H)^+$ 392.2220, found 392.2203.

*Ethyl 1-(2-Methoxyethyl)-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3g**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 37.0 mg, 47% yield; pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.36 (m, 5H), 7.27−7.23 (m, 2H), 6.94−6.90 (m, 2H), 3.94−3.83 (m, 7H), 3.39 (t, $J$ = 6.4 Hz, 2H), 3.20 (s, 3H), 2.22 (s, 3H), 0.77 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.0, 158.0, 137.4, 133.0, 131.5, 130.9, 128.4, 128.1, 127.9, 127.0, 122.4, 113.0, 112.5, 71.6, 58.9, 58.9, 55.2, 43.8, 13.5, 10.6 ppm; ESI-HRMS: calcd. for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2013, found 394.1998.

*Ethyl 4-(4-Methoxyphenyl)-5-methyl-1-(2-morpholinoethyl)-2-phenyl-1H-pyrrole-3-carboxylate (**3h**).* Purified by flash column chromatography (Hexane/EtOAc = 4:1); 38.5 mg, 43% yield; orange gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.36 (m, 5H), 7.25−7.21 (m, 2H), 6.93−6.90 (m, 2H), 3.91−3.84 (m, 7H), 3.62−3.60 (m, 4H), 2.46 (t, $J$ = 7.6 Hz, 2H), 2.27 (brs, 4H), 2.21 (s, 3H), 0.78 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.0, 158.1, 137.2, 132.9, 131.5, 130.8, 128.2, 128.2, 127.9, 126.5, 122.7, 113.0,112.5, 66.5, 59.0, 58.4, 55.2, 53.5, 41.3, 13.6, 10.6 ppm; ESI-HRMS: calcd. for $C_{27}H_{33}N_2O_4$ $(M + H)^+$ 449.2435, found 449.2415.

*Ethyl 1-Cyclopropyl-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3i**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 48.0 mg, 64% yield; yellow solid (mp: 118−120 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.36 (m, 5H), 7.24−7.22 (m, 2H), 6.93−6.91 (m, 2H), 3.92 (q, $J$ = 7.2 Hz, 2H), 3.84 (s, 3H), 3.08−3.05 (m, 1H), 2.29 (s, 3H), 0.85 (t, $J$ = 7.2 Hz, 3H), 0.76 (q, $J$ = 5.6 Hz, 2H), 0.58−0.55 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 158.0, 137.9, 133.1, 131.3, 130.6, 129.3, 128.4, 127.4,122.0, 113.0, 112.1, 59.2, 55.2, 27.2, 13.6, 11.3, 9.0 ppm; ESI-HRMS: calcd. for $C_{24}H_{26}NO_3$ $(M + H)^+$ 376.1907, found 376.1894.

*Ethyl 1-Cyclohexyl-4-(4-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3j**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 45.9 mg, 55% yield; white solid (mp: 138−140 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.38 (m, 3H), 7.36−7.32 (m, 2H), 7.25−7.21 (m, 2H), 6.93−6.90 (m, 2H), 3.85−3.80 (m, 6H), 2.28 (s, 3H), 1.85−1.75 (m, 6H), 1.62−1.57 (m, 1H), 1.18−1.05 (m, 3H), 0.74 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 158.0, 137.6, 134.0, 131.6, 130.9, 128.6, 127.9, 127.7, 126.1, 123.4, 113.0, 112.3, 58.9, 57.7, 55.2, 32.5, 26.3, 25.3, 13.5, 12.6 ppm; ESI-HRMS: calcd. for $C_{27}H_{32}NO_3$ $(M + H)^+$ 418.2377, found 418.2360.

*Ethyl 4-(4-Methoxyphenyl)-5-methyl-1,2-diphenyl-1H-pyrrole-3-carboxylate (**3k**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 65.0 mg, 79% yield; yellow solid (mp: 140−142 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.25 (m, 5H), 7.21−7.13 (m, 5H), 7.13−7.09 (m, 2H), 6.96−6.94 (m, 2H), 3.97−3.92 (m, 2H), 3.84 (s, 3H), 2.00 (s, 3H), 0.85 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 158.1, 138.1, 137.4, 132.2, 131.4, 131.0, 128.8, 128.6, 128.1, 128.0, 127.8, 127.3, 127.2, 122.6, 113.1, 59.3, 55.2, 13.6, 11.5 ppm; ESI-HRMS: calcd. for $C_{27}H_{26}NO_3$ $(M + H)^+$ 412.1907, found 412.1885.

*Ethyl 1-Benzyl-2,4-bis(4-methoxyphenyl)-5-methyl-1H-pyrrole-3-carboxylate (**3l**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 72.8 mg, 80% yield; yellow solid (mp: 124−126 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30−7.19 (m, 7H), 6.93−6.90 (m, 4H), 6.86−6.83 (m, 2H), 4.96 (s, 2H), 3.92 (q, $J$ = 7.2, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.02 (s, 3H), 0.85 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.3, 159.5, 158.0, 137.9, 137.8, 131.9, 131.5, 128.7, 128.4, 127.1, 126.8, 125.7, 124.6, 122.8, 113.3 113.0, 112.4, 59.0, 55.2, 55.1, 47.8, 13.7, 10.6 ppm; ESI-HRMS: calcd. for $C_{29}H_{30}NO_4$ $(M + H)^+$ 456.2169, found 456.2154.

*Ethyl 1-Benzyl-2-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-5-methyl-1H-pyrrole-3-carboxylate (**3m**).* Purified by flash column chromatography (Hexane/EtOAc = 5:1); 67.9 mg, 70% yield; yellow gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29−7.17 (m, 5H), 7.11−7.08 (m, 1H), 6.95−6.89 (m, 4H), 6.46−6.43 (m, 2H), 4.97 (d, $J$ = 16.8, 1H), 4.87 (d, $J$ = 16.8, 1H), 3.91 (q, $J$ = 7.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.61 (s, 3H), 0.84 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 161.2, 158.9, 157.9, 137.9, 134.4, 133.3, 131.6, 128.6, 128.4, 126.9, 126.8, 126.0, 122.9, 114.1, 112.8, 112.6, 104.0, 98.4, 58.8, 55.2, 55.2, 55.1, 48.0, 13.7, 10.7 ppm; ESI-HRMS: calcd. for $C_{30}H_{32}NO_5$ $(M + H)^+$ 486.2275, found 486.2250.

*Ethyl 1-Benzyl-4-(4-methoxyphenyl)-5-methyl-2-(p-tolyl)-1H-pyrrole-3-carboxylate (**3n**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 65.0 mg, 74% yield; yellow solid (mp: 101−103 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29−7.11 (m, 9H), 6.92−6.90 (m, 4H), 4.96 (s, 2H), 3.91 (q, $J$ = 7.2 Hz, 2H), 3.82 (s, 3H), 2.34 (s, 3H), 2.01 (s, 3H), 0.83 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 158.0, 138.1, 137.8, 137.8, 131.5, 130.5, 129.4, 128.6, 128.5, 128.4, 127.1, 126.8, 125.6, 122.8, 112.9, 112.3, 59.0, 55.1, 47.8, 21.2, 13.6, 10.6 ppm; ESI-HRMS: calcd. for $C_{29}H_{30}NO_3$ $(M + H)^+$ 440.2220, found 440.2208.



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*Ethyl 1-Benzyl-2-(4-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1H-pyrrole-3-carboxylate (**3o**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 71.4 mg, 71% yield; pale yellow solid (mp: 121−124 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.43 (m, 2H), 7.31−7.22 (m, 5H), 7.16−7.14 (m, 2H), 6.93−6.87 (m, 4H), 4.94 (s, 2H), 3.92 (q, $J$ = 7.2 Hz, 2H), 3.83 (s, 3H), 2.03 (s, 3H), 0.85 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 158.1, 137.5, 136.5, 132.3, 131.5, 131.0, 128.8, 128.1, 127.5, 127.3, 125.5, 123.1, 122.5, 113.0, 112.7, 59.2, 55.2, 47.9, 13.6, 10.5 ppm; ESI-HRMS: calcd. for $C_{28}H_{27}BrNO_3$ $(M + H)^+$ 506.1148, found 506.1143.

*Methyl 1-Benzyl-4-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (**3p**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 64.7 mg, 93% yield; pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34−7.24 (m, 3H), 7.19−7.17 (m, 2H), 6.96−6.89 (m, 4H), 5.10 (s, 2H), 3.82 (d, $J$ = 2.0 Hz, 3H), 3.60 (d, $J$ = 1.6 Hz, 3H), 2.48 (s, 3H), 2.02 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 157.9, 137.0, 134.9, 131.4, 128.9, 128.8, 127.4, 126.1, 125.6, 122.2, 112.9, 110.6, 55.1, 50.3, 47.1, 11.6, 10.3 ppm; ESI-HRMS: calcd. for $C_{22}H_{24}NO_3$ $(M + H)^+$ 350.1751, found 350.1734.

*Methyl 4-(4-Methoxyphenyl)-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (**3q**).* Known compound;[6] Purified by flash column chromatography (Hexane/EtOAc = 10:1); 36.2 mg, 54% yield; pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57−7.48 (m, 3H), 7.29−7.28 (m, 4H), 6.97−6.95 (m, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 2.35 (s, 3H), 1.92 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 158.0, 137.9, 135.6, 131.4, 129.4, 128.6, 128.5, 128.3, 126.8, 121.9, 113.0, 110.8, 55.2, 50.4, 12.7, 11.2 ppm; ESI-HRMS: calcd. for $C_{21}H_{22}NO_3$ $(M + H)^+$ 336.1594, found 336.1582.

*1-Benzyl-3-(4-methoxyphenyl)-2-methyl-6,7-dihydro-1H-indol-4(5H)-one (**3r**).* Purified by flash column chromatography (Hexane/EtOAc = 5:1); 40.7 mg, 59% yield; brown oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.28 (m, 5H), 7.00−6.98 (m, 2H), 6.93−6.90 (m, 2H), 5.10 (s, 2H), 3.83 (s, 3H), 2.71 (t, $J$ = 6.4 Hz, 2H), 2.46 (t, $J$ = 6.4 Hz, 2H), 2.15−2.09 (m, 5H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.3, 158.0, 143.1, 136.7, 131.5, 129.0, 127.6, 127.4, 127.2, 125.7, 120.3, 117.6, 113.0, 55.2, 47.3, 38.8, 23.4, 22.3, 10.1 ppm; ESI-HRMS: calcd. for $C_{23}H_{24}NO_2$ $(M + H)^+$ 346.1802, found 346.1790.

*Ethyl 1-Benzyl-5-methyl-2,4-diphenyl-1H-pyrrole-3-carboxylate (**3s**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 56.1 mg, 71% yield; yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.20 (m, 13H), 6.91−6.89 (m, 2H), 4.96 (s, 2H), 3.92−3.86 (m, 2H), 2.03 (s, 3H), 0.78 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 138.2, 137.8, 136.1, 132.5, 130.6, 130.6, 128.7, 128.2, 127.9, 127.5, 127.3, 127.2, 126.1, 125.7, 123.5, 112.5, 59.2, 48.0, 13.6, 10.7 ppm; ESI-HRMS: calcd. for $C_{27}H_{26}NO_2$ $(M + H)^+$ 396.1958, found 396.1943.

*Ethyl 1-Benzyl-5-methyl-2-phenyl-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**3t**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 61.4 mg, 75% yield; orange oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.16 (m, 12H), 6.90 (d, $J$ = 6.8 Hz, 2H), 4.96 (s, 2H), 3.89 (q, $J$ = 7.2 Hz, 2H), 2.37 (s, 3H), 2.03 (s, 3H), 0.78 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 137.9, 137.8, 135.5, 132.9, 132.6, 130.7, 130.3, 128.7, 128.3, 128.1, 127.8, 127.2, 127.0, 125.7, 123.4, 112.5, 59.1, 47.9, 21.2, 13.5, 10.6 ppm; ESI-HRMS: calcd. for $C_{28}H_{28}NO_2$ $(M + H)^+$ 410.2115, found 410.2099.

*Ethyl 1-Benzyl-4-(4-chlorophenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3u**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 53.2 mg, 62% yield; orange oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.27 (m, 10H), 7.25−7.23 (m, 2H), 6.90−6.88 (m, 2H), 4.96 (s, 2H), 3.89 (q, $J$ = 7.2 Hz, 2H), 2.01 (s, 3H), 0.80 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 138.4, 137.6, 134.5, 132.3, 132.0, 131.9, 130.7, 128.7, 128.6, 128.2, 127.9, 127.7, 127.3, 125.7, 122.3, 112.2, 59.2, 48.0, 13.6, 10.6 ppm; ESI-HRMS: calcd. for $C_{27}H_{25}ClNO_2$ $(M + H)^+$ 430.1568, found 430.1549.

*Ethyl 1-Benzyl-4-(3,4-dichlorophenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3v**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 50.0 mg, 54% yield; orange yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.28 (m, 2H), 7.25−7.09 (m, 9H), 6.80 (d, $J$ = 7.2 Hz, 2H), 4.87 (s, 2H), 3.82 (q, $J$ = 7.2 Hz, 2H), 1.94 (s, 3H), 0.74 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 138.7, 137.4, 136.3, 132.4, 132.1, 131.4, 130.6, 130.1, 129.4, 128.8, 128.3, 127.9, 127.5, 127.4, 125.6, 121.1, 112.1, 59.3, 48.0, 13.6, 10.6 ppm; ESI-HRMS: calcd. for $C_{27}H_{23}Cl_2NNaO_2$ $(M + Na)^+$ 486.0998, found 486.1021.

*Ethyl 1-Benzyl-4-(3-methoxyphenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3w**).* Purified by flash column chromatography (Hexane/EtOAc = 10:1); 45.9 mg, 54% yield; yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34−7.23 (m, 9H), 6.95−6.93 (m, 4H), 6.91 (m, 1H), 4.97 (s, 2H), 3.91 (q, $J$ = 7.2 Hz, 2H), 3.82 (s, 3H), 2.05 (s, 3H), 0.81 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.1, 158.9, 138.0, 137.7, 137.4, 132.3, 130.7, 128.7, 128.4, 128.1, 127.8, 127.2, 127.1, 125.7, 123.2, 123.1, 116.1, 112.5, 111.7, 59.2, 55.2, 47.9, 13.5, 10.6 ppm; ESI-HRMS: calcd. For $C_{28}H_{28}NO_3$ $(M + H)^+$ 426.2064, found 426.2060.

*Ethyl 1-Benzyl-4-(2-fluorophenyl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3x**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 47.1 mg, 57% yield; yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31−7.23 (m, 10H), 7.18−7.07 (m, 2H), 6.90 (d, $J$ = 6.8 Hz, 2H), 4.97 (s, 2H), 3.90 (q, $J$ = 7.2 Hz, 2H), 2.01 (s, 3H), 0.80 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 160.6 (d, $J_{C\text{-}F}$ = 244.0 Hz), 138.5, 137.7, 132.6 (d, $J_{C\text{-}F}$ = 4.0 Hz), 132.3, 130.8, 128.7, 128.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 128.1, 127.9, 127.8, 127.2, 125.6, 124.0 (d, $J_{C\text{-}F}$ = 16.0 Hz), 123.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 116.4, 115.0 (d, $J_{C\text{-}F}$ = 23.0 Hz), 112.7, 59.1, 47.9, 13.5, 10.6 ppm; ESI-HRMS: calcd. For $C_{27}H_{25}FNO_2$ $(M + H)^+$ 414.1864, found 414.1829.

*Ethyl 1-Benzyl-4-(furan-2-yl)-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**3y**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 43.9 mg, 57% yield; red oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48−7.47 (m, 1H), 7.34−7.23 (m, 8H), 6.89 (d, $J$ = 6.8 Hz, 2H), 6.47−6.46 (m, 1H), 6.46 (d, $J$ = 1.6 Hz, 1H), 4.95 (s, 2H), 3.98 (q, $J$ = 7.2 Hz, 2H), 2.16 (s, 3H), 0.90 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.7, 149.1, 141.1, 138.4, 137.4, 132.0, 130.7, 129.4, 128.7, 1283, 127.9, 127.3, 125.7, 112.7, 112.7, 110.6, 108.2, 59.4, 47.9, 13.7, 11.0 ppm; ESI-HRMS: calcd. for $C_{25}H_{24}NO_3$ $(M + H)^+$ 386.1751, found 386.1739.

*Ethyl 1,5-Dibenzyl-2,4-diphenyl-1H-pyrrole-3-carboxylate (**3a′**).* Purified by flash column chromatography (Hexane/EtOAc = 20:1); 57.1 mg, 57% yield; white solid (mp: 158−160 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.17 (m, 16H), 7.03−7.01 (m, 2H), 6.80−6.79 (m, 2H), 4.70 (s, 2H), 3.92 (q, $J$ = 7.2 Hz, 2H), 3.73 (s, 2H), 0.79 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.1, 139.4, 139.0, 137.8, 135.8, 132.2, 130.7, 130.3, 128.9, 128.7, 128.6, 128.2, 127.8, 127.6, 127.2, 126.4, 126.3, 125.6, 125.6, 112.7, 59.2, 47.9, 30.5, 13.5 ppm; ESI-HRMS: calcd. for $C_{33}H_{30}NO_2$ $(M + H)^+$ 472.2271, found 472.2256.

**Gram-Scale Reaction in Scheme 2.** A mixture of enamino ester **1** (4.0 mmol, 1.0 equiv), propargyl acetate **2** (4.8 mmol, 1.2 equiv), $Cu(OTf)_2$ (0.2 mmol, 5 mol %), and toluene (10 mL) was stirred at room temperature for 30 s and then heated at 150 °C for 20 min under microwave irradiation. The reaction mixture was then cooled to room temperature and purified directly by a silica gel flash chromatography (Hexane/EtOAc), giving compound **3a** (1.53 g, 90% yield) as a yellow gum.

**General Procedure for Control Reactions in Scheme 2.** A mixture of amine (0.2 mmol, 1.0 equiv), $\beta$-ketoester (0.2 mmol, 1.0 equiv), propargyl acetate **2** (0.24 mmol, 1.2 equiv), $Cu(OTf)_2$ (0.04 mmol, 20 mol %), and toluene (1 mL) was stirred at room temperature for 30 s and then heated at 150 °C for 20 min under microwave irradiation. The reaction mixture was cooled to room temperature, passed through a short pad of silica gel (eluated with Hexane/EtOAc 2:1), and concentrated by rotary evaporation. The yield was then determined by $^1$H NMR using $CH_2Br_2$ as internal standard.

**D−H Exchange Experiment in Scheme 2.** A mixture of enamino ester **1** (0.20 mmol, 1.0 equiv), propargyl acetate **2** (0.24 mmol, 1.2 equiv), $Cu(OTf)_2$ (0.01 mmol, 5 mol %), $D_2O$ (50 $\mu$L), and toluene (1 mL) was stirred at room temperature for 30 s and then heated at 150 °C for 20 min under microwave irradiation. The reaction mixture was then cooled to room temperature and purified directly by a silica gel flash chromatography (Hexane/EtOAc), giving compound **3a**.



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## ■ ASSOCIATED CONTENT

### Supporting Information

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$^1$H NMR and $^{13}$C NMR spectra for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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