JOC The Journal of Organic Chemistry

Article

Three-Component Cascade Synthesis of Fully-substituted Trifluoromethyl Pyrroles via a Cu(II)/Rh(#)-promoted aza-Michael Addition/Trifluoromethylation Cyclization/Oxidation Reaction

Junying Ge, Qiuping Ding, Xinhua Wang, and Yiyuan Peng

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03470 • Publication Date (Web): 19 May 2020

Just Accepted

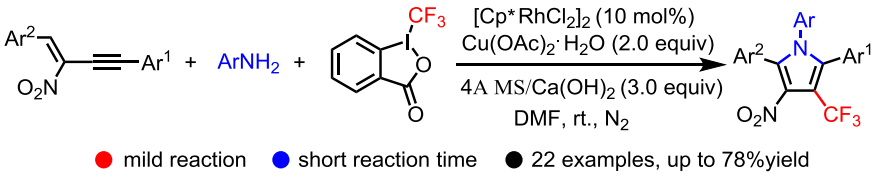
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Three-Component Cascade Synthesis of Fully-substituted Trifluoromethyl Pyrroles via a Cu(II)/Rh(Ⅲ)-promoted aza-Michael Addition/Trifluoromethylation Cyclization/Oxidation Reaction

Junying Ge, Qiuping Ding,* Xinhua Wang, Yiyuan Peng

Key Laboratory of Functional Small Organic Molecule, Ministry of Education and Jiangxi's Key Laboratory of Green Chemistry, Jiangxi Normal University, Nanchang, Jiangxi 330022, P.R. of China.

E-mail: dqpjxnu@gmail.com



Abstract: A three-component cascade reaction of 1,3-enynes, anilines, and Togni-Ⅱ reagent has been developed to give fully-substituted trifluoromethyl pyrroles with high regioselectivity under mild conditions. The transformation proceeds through a Cu(II)/Rh(Ⅲ)-promoted cascade aza-Michael addition/trifluoromethylation cyclization/oxidation reaction, affording trifluoromethyl pyrrole derivatives as primary products.

INTRODUCTION

Pyrroles are privileged structural motifs that are present in many natural compounds[1] and pharmaceuticals.[2] Among them, polysubstituted pyrroles have attracted much attention as versatile synthetic intermediates and biologically active molecules.[3] Figure 1 presents some selected fully-substituted pyrrole derivatives, including chlorfenapyr and atorvastatin amongst others. The physical, chemical and biological properties of organic molecules can be easily modified by the introduction of fluorine-containing groups due

to their unique permeability, lipophilicity, and metabolic stability.[4] The trifluoromethyl group is one of the most prevalent fluorine-containing groups which is present in various pharmaceuticals, agrochemicals, and organic materials.[5] For example, chlorfenapyr[6] and its analogs[7] are effective pesticides, a result of the trifluoromethyl substituted pyrrole unit (Figure 1).

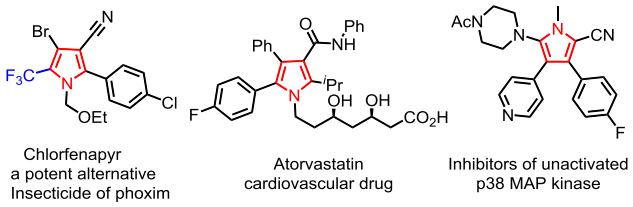


Figure 1. Some selected examples of fully-substituted pyrroles in bioactive molecules

A number of strategies have been developed for the synthesis of pyrrole moieties due to their excellent and unique properties,[8] although the synthetic methods for the preparation of fully-substituted trifluoromethyl pyrrole derivatives are limited. The synthesis of poly-substituted trifluoromethyl pyrrole derivatives has not been widely reported. The present methods rely on electrophilic aromatic substitution using trifluoromethylating reagents,[9] such as Umemoto's salts and Togni-Ⅱ reagent. An alternative and more straightforward and efficient methodology for the preparation of CF_3-substituted pyrroles involves cascade trifluoromethylation/cyclization using various electrophilic, nucleophilic or radical trifluoromethylating reagents.[10] In addition, another convenient strategy involves the transformation of trifluoromethylated building blocks,[11-14] such as α,β-unsaturated trifluoromethylketones,[11] 1,3-diketones,[12] 1,4-diketones,[13] and 2-trifluoromethyl-1,3-enynes,[14a] etc.

1,3-Enynes are versatile building blocks for the synthesis of various complex molecules.[15-21] 1,3-Enynes have been employed as four-electron participants in numerous Diels-Alder reactions and [4+4] cycloadditions.[15] The gold-catalyzed cycloisomerization of 1,3-enyne esters has been reported to give cyclopentone derivatives via a [3,3]-sigmatropic rearrangement/Nazarov cyclization.[16] Torker and Hoveyda developed a Cu-catalyzed 1,3-enynes hydroboration for the enantioselective synthesis of trisubstituted

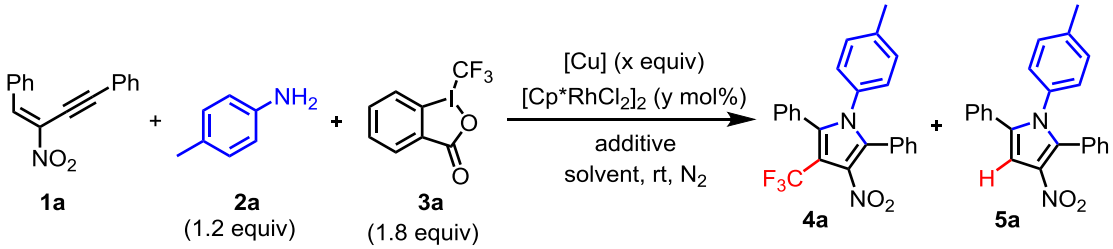
allenyl-B(pin) compounds.[17] Recently, Zhang and Bao also reported the synthesis of multisubstituted allenes via the Cu-catalyzed 1,4-difunctionalization of 1,3-enynes.[18] Furthermore, several efficient methods have been described for the synthesis of some *N*-heterocycles, such as benzo[*f*]indazoles,[19] pyrroles,[20] and pyridines[21] via a sequential aza-annulation of 1,3-enynes and 2-en-4-yn-1-azides. In continuation of our interest in Togni-Ⅱ reagent-based construction of trifluoromethylated coumarins,[22] we herein present an alternative approach to fully-substituted trifluoromethyl pyrroles via a three-component cascade reaction involving 1,3-enynes, anilines, and Togni-Ⅱ reagent in the presence of a Cu(II)/Rh(Ⅲ) complexes.

RESULTS AND DISCUSSION

Our investigation began with the three-component tandem reaction of (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne **1a**, *p*-toluidine **2a**, and Togni-Ⅱ reagent **3a** in order to identify the optimal reaction conditions for the transformation. Firstly, we tried the Cu-catalyzed direct trifluoromethylation of the model reaction for the synthesis of fully-substituted trifluoromethyl pyrroles according to our previous reported copper-catalyzed trifluoromethylation of propiolates to trifluoromethylated coumarins.[22] Unfortunately, only trace amounts of desired product **4a** was observed, while side product **5a** was obtained in 42% yield (Table 1, entry 1). Fortunately, desired product **4a** could obtain in 21% yield when 2.0 equiv of $Cu(OAc)_2$ was used (Table 1, entry 2). Then, we attempted the transition metal and Lewis acid cooperative catalysis strategy. According to previous report,[20b] we chose copper salts as Lewis acids, and screened some kinds of transition metals, including Pd, Au, Ru, and Rh-complexes (See supporting information). The results showed that $[Cp^*RhCl_2]_2$ (10 mol %) could promote the transformation with slightly better (Table 1, entry 3). In order to improve the yield, we added some silver slats, such as Ag_2CO_3, AgOAc, and $AgNO_3$, but no better results were observed (See supporting information). The following evaluation of solvents indicated that DMF was the best one, affording the desired product **4a** in 35% yield, whereas other solvents such as DMSO, CH_3OH and 1,2-DCE were ineffective for this transformation (Table 1, entries 4-7). The desired product was not obtained when the

reaction was conducted under an atmosphere of oxygen or air (See supporting information). Next, the effect of the copper salts was examined, and the results showed that $Cu(OAc)_2 \cdot H_2O$ is the most efficient, giving a slightly better yield (41%) compared with other salts (Table 1, entries 8-11). Interestingly, the desired product **4a** was obtained in 58% yield when the reaction was carried out in the presence of small amounts of 4Å MS (Table 1, entry 12). Although the effect of 4Å MS has not been ascertained, it may possibly act as Lewis acid to promote the reaction. The use of 4Å MS/HOAc or 4Å MS/PivOH as additives did not improve the yield of **4a** (See supporting information). We also investigated the use of alternative bases (Table 1, entries 13-16), and the results showed that organic bases (such as DABCO and DBU) inhibit the reaction, while inorganic bases, such as KPF_6, K_2HPO_4, Na_2CO_3, and $Ca(OH)_2$ could promote the transformation. $Ca(OH)_2$ was demonstrated to be the best base, and the fully-substituted pyrrole **4a** was isolated in 78% yield (Table 1, entry 16). Product **4a** was obtained in slightly lower yield by reducing the amounts of $[Cp^*RhCl_2]_2$ (from 10 mol% to 2.5 mol%) or $Cu(OAc)_2 \cdot H_2O$ (from 2.0 to 1.0 equiv) (Table 1, entries 17-21). Control experiment showed that no targeted compound was obtained in the absence of $Cu(OAc)_2 \cdot H_2O$, which indicates that the copper salt is essential for this transformation (Table 1, entry 22). Next, we examined some other trifluoromethylating reagents, such as **3b**, **3c** and **3d**, all of which provided unsatisfactory results (See supporting information). Longer reaction time under the optimized conditions, no significant change was observed. The reaction can be scaled up to 2 mmol of 1-en-3-yne **1a** under standard reactions, providing the corresponding product **3a** in moderate yield (51%) (Table 1, entry 23).

Table 1. Optimization of Reaction Conditions[a]



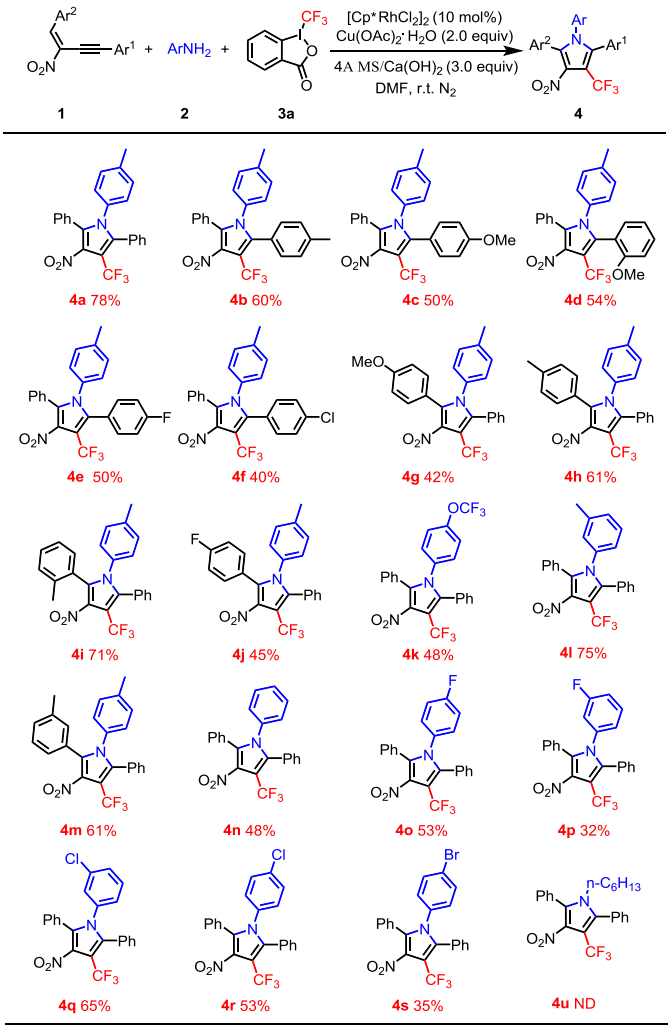
entry	[Cu] (x equiv)	co-[cat] (y mol%)	additive/base	solvent	yield **4a** (**5a**) (%)
1	$Cu(OAc)_2$ (0.1)	-	-	CH_3CN	trace (42)
2	$Cu(OAc)_2$ (2.0)	-	-	CH_3CN	21 (26)
3	$Cu(OAc)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	CH_3CN	26 (34)
4	$Cu(OAc)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMSO	15
5	$Cu(OAc)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	MeOH	trace
6	$Cu(OAc)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DCE	trace
7	$Cu(OAc)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMF	35
8	$CuBr_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMF	22
9	$Cu(OTf)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMF	trace
10	$Cu(TFA)_2$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMF	13
11	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	-	DMF	41
12	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS	DMF	58
13	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/K_2HPO_4	DMF	40
14	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/KPF_6	DMF	56
15	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/Na_2CO_3	DMF	60
16	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/$Ca(OH)_2$	DMF	78
17	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (7.5)	4Å MS/$Ca(OH)_2$	DMF	75
18	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (5)	4Å MS/$Ca(OH)_2$	DMF	71
19	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (2.5)	4Å MS/$Ca(OH)_2$	DMF	57
20	$Cu(OAc)_2 \cdot H_2O$ (1.5)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/$Ca(OH)_2$	DMF	65
21	$Cu(OAc)_2 \cdot H_2O$ (1.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/$Ca(OH)_2$	DMF	28
22	-	$[Cp^*RhCl_2]_2$ (10)	4Å MS/$Ca(OH)_2$	DMF	ND
23[b]	$Cu(OAc)_2 \cdot H_2O$ (2.0)	$[Cp^*RhCl_2]_2$ (10)	4Å MS/$Ca(OH)_2$	DMF	51

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), CF_3-reagent **3** (0.18 mmol), 4Å MS (50 mg), acid or base additive (3.0 equiv), Cu salts (x equiv), Rh catalyst (y mol%), and solvent (1 mL), at room temperature under N_2 for 0.5 h. ND = not detected. [b]The reaction worked under 2 mmol scale.

With the optimized reaction conditions in hand, we next investigated the generality and scope of this new protocol. As depicted in table 2, the reactions of various substituted 1,3-enynes **1** and anilines **2** in the presence of Togni-Ⅱ reagent **3a** proceeded smoothly under the standard conditions, affording the corresponding products **4** in moderate to good yields. Firstly, a range of 1,3-enynes **1** bearing electron-donating groups (e.g., Me and MeO) or electron-withdrawing groups (e.g., F and Cl) on the aryl (Ar^1) moiety reacted with *p*-toluidine **2a** under the optimized reaction conditions, giving the corresponding fully-substituted trifluoromethyl pyrroles **4b-f** in moderate yields (40-60%). Additionally, we also examined the substituent effects of the aryl (Ar^2) moiety, and the results showed that the present protocol is amenable to various substituents to afford the desired products **4g-j** in respectable yields (42-71%). Subsequently, we examined the reactions of 1,3-enynes **1a** and Togni-Ⅱ reagent **3a** with various substituted anilines **2**. When aliphatic nitroalkene (Ar^2 = CH_2OBn) was subjected to the reaction, no desired product was obtained. A range of aromatic amines, such as 4-(trifluoromethoxy)aniline, *m*-toluidine, aniline, 4-fluoroaniline, 3-fluoroaniline, 4-chloroaniline, 3-chloroaniline, and 4-bromoaniline were tolerated. For instance, in the case of 4-(trifluoromethoxy)aniline**,** the product **4k** was formed in moderate yield with the configuration confirmed umambiguously by X-ray diffraction. In addition, **4l** and **4m** were obtained in yields of 75% and 61%, respectively. However, 4-bromoaniline gave its corresponding product **4s** in comparatively lower yield. Interestingly, when naphthalen-2-amine was subjected to the standard conditions, only a trace amount of desired product **4t** was observed; however, α-trifluoromethyl-substituted naphthalen-2-amine **4t'** was obtained in 51% yield [Scheme 1, eq (1)]. When aliphatic *n*-hexylamine was used as substrate, no targeted product **4u** was observed. When the Ar^1 group of substrate **1** was replaced by aliphatic ^{n}-Bu group, only

trace amounts of desired product was obtained [Scheme 1, eq (2)]. In addition, some other groups (such as methoxyl and acetyl) instead of nitro group substituted substrates **1** were used under standard reaction conditions [Scheme 1, eq (3)]. Disappointingly, no obviously desired product was observed, when methoxyl substituted substrate was used. While to the acetyl substituted substrate, only condensation product (imine) was obtained.

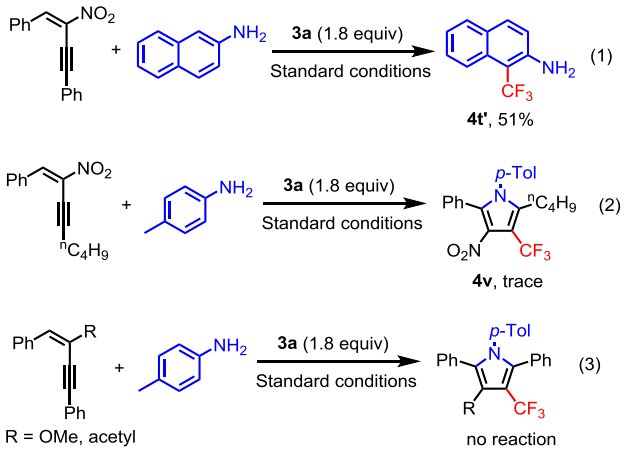
Table 2. One-pot synthesis of fully-substituted trifluoromethyl pyrroles[a]



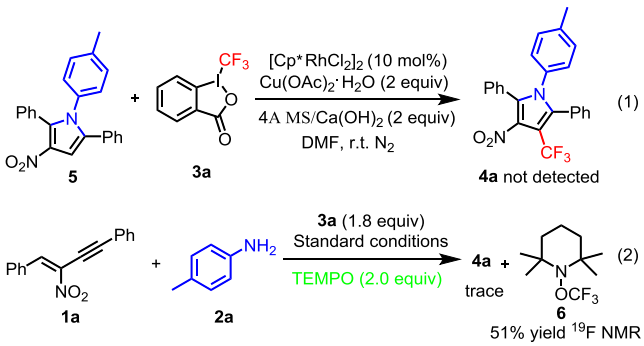
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), Togni-Ⅱ reagent **3a** (0.18 mmol), 4Å MS (50 mg), $Ca(OH)_2$ (3.0 equiv), $[Cp^*RhCl_2]_2$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 2.0 equiv) and DMF (1 mL), at room temperature under N_2 for 0.5 h.

A control experiment of tetrasubstituted pyrroles **5** with Togni-Ⅱ reagent **3a** under the standard reaction conditions did not result in any reaction, ruling out transformation via a simple electrophilic aromatic substitution reaction [Scheme 2, eq (1)]. When the reaction was carried out in the presence of a free radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (2.0 equiv), only trace amounts of the desired product **4a** and **5** were observed, but a distinctive product **6** was observed by ^{19}F NMR (δ 56.02) in 51% yield, which indicates that the reaction may proceed through a radical process [Scheme 2, eq (2)].

Scheme 1. The reaction of naphthalen-2-amine



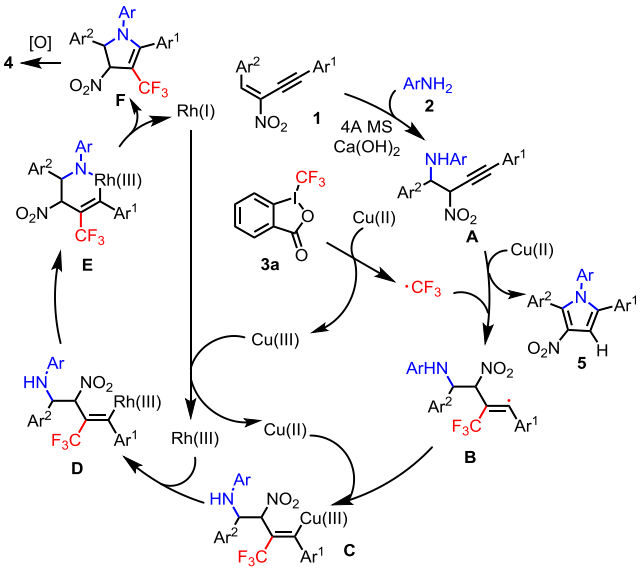
Scheme 2. Mechanistic investigations



On the basis of control experiments and previously reported literature,[14,23] a possible mechanism is shown in Scheme 3. Firstly, with the assistance of molecular sieves as Lewis acid, and $Ca(OH)_2$ as base, the aza-Michael addition of 1,3-enynes **1** and amine **2** may lead to the formation of intermediate **A**. Secondly,

the interaction of Togni-Ⅱ reagent **3a** with copper(II) gives a CF_3 radical that reacts with intermediate **A** to generate intermediate **B**. Subsequently, intermediate **B** can be trapped by Cu(II) to give intermediate **C**, which reacts with Rh(III) via an alkenyl rhodium intermediate **D** to generate rhodacyclic intermediate **E**.[23] Finally, intermediate **E** undergoes reductive elimination and following oxidation gives the desired product **4**, together with a Rh(I) species, which undergoes a redox reaction with Cu(III) to regenerate the Rh(III) species. It is worth mentioning that intermediate **A** can easily undergo intramolecular cyclization/oxidation, promoted by copper salts, to give by-products (tetrasubstituted pyrroles **5**) which were obtained in trace amounts in most cases.

Scheme 3 Proposed Reaction Mechanism



CONCLUSIONS

In summary, we have described an efficient approach to fully-substituted trifluoromethyl pyrroles via a cascade aza-Michael addition/trifluoromethylation cyclization/oxidation reaction of 1,3-enynes. Togni-Ⅱ reagent is utilized as a precursor for the CF_3 radical in the presence of $Cu(OAc)_2$ ·H_2O and a catalytic amount of $[Cp^*RhCl_2]_2$. Further investigations concerning the nucleophilic scope, reaction mechanism, and biological activities of various products are in progress in our laboratory.

Experimental Procedure

General procedure for the preparation of 4

To the mixture of 1,3-enyne **1** (0.1 mmol), amine **2** (0.12 mmol, 1.2 equiv), and Togni-Ⅱ reagent **3a** (0.18 mmol, 56.9 mg) in a schlenk flask was added $[RhCp^*Cl_2]_2$ (0.01 mmol, 6.2 mg), copper acetate monohydrate (0.2 mmol, 40 mg), calcium hydroxide (0.3 mmol, 22.0 mg), and 4Å MS (50 mg) in DMF (1.0 mL) under N_2 atmosphere. The mixture was stirred at room temperature for 0.5 hour. Upon completion, the reaction mixture was washed with brine (10 mL) and extracted with ethyl acetate (10 mL × 2). The reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography on basic silica gel using a petroleum ether/EtOAc (80/1 in volume) to afford the desired compounds.

3-nitro-2,5-diphenyl-1-(p-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4a):** Isolated as a yellow solid (32.9 mg, 78% yield), mp: 251-253 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.20 (m, 8H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.70, 135.29 (q, $J_{C\text{-}F}$ = 3.6 Hz), 135.1, 132.8, 132.2, 131.1, 130.9 (q, $J_{C\text{-}F}$ = 0.9 Hz), 129.4, 129.3, 129.1, 129.0, 128.4, 127.9, 127.9, 121.9 (q, $J_{C\text{-}F}$ = 268.5 Hz), 107.2 (q, $J_{C\text{-}F}$ = 36.5 Hz), 100.0, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.81 (s,3F); HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{18}F_3N_2O_2$ 423.1315; found: 423.1319.

3-nitro-2-phenyl-1,5-di-p-tolyl-4-(trifluoromethyl)-1H-pyrrole **(4b):** Isolated as a yellow solid (26.1 mg, 60% yield), mp: 182-184°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.23 (m, 5H), 7.06 -7.01 (q, *J* = 11.2 Hz, 4H), 6.87 - 6.85 (d, *J* = 8.1 Hz, 2H), 6.72 - 6.70 (d, *J* = 8.2 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.0, 138.6, 135.5 (q, $J_{C\text{-}F}$ = 3.4 Hz), 135.0, 132.9, 132.3, 131.1, 130.7, 129.4, 129.2, 128.7, 128.5, 128.0, 127.9, 126.0, 122.0 (q, $J_{C\text{-}F}$ = 266.7 Hz), 107.0 (q, $J_{C\text{-}F}$ = 36.4 Hz), 21.3, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.77 (s, 3F); HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{20}F_3N_2O_2$ 437.1471; found: 437.1470.

2-(4-methoxyphenyl)-4-nitro-5-phenyl-1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrrole **(4c)** Isolated as a yellow solid (22.6 mg, 50% yield), mp:186-188°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 5H), 7.08 (dd, *J* = 8.6, 1.6 Hz, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.75 (dd, *J* = 8.7, 1.8 Hz, 2H), 6.71 (dd, *J* = 8.2, 1.6 Hz, 2H), 3.76 (d, *J* = 1.9 Hz, 3H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9 , 138.6 , 135.2 (d, $J_{C\text{-}F}$ = 2.0 Hz), 134.9 , 132.9, 132.2, 131.1, 129.4, 129.2, 128.5, 128.0, 127.9, 122.0 (q, $J_{C\text{-}F}$ = 268.5 Hz), 121.1, 118.8, 106.6 (d, $J_{C\text{-}F}$ = 38.9 Hz), 100.0, 55.2, 21.0.^{19}F NMR (376 MHz, $CDCl_3$) δ -53.86. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{20}F_3N_2O_3$ 453.1421; found: 453.1419.

2-(2-methoxyphenyl)-4-nitro-5-phenyl-1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrrole **(4d):** Isolated as a yellow solid (24.4 mg, 54% yield), mp: 161-163°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.22 (m, 7H), 7.14 - 7.12 (dd, *J* = 1.3 Hz, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 3.6 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 3.62 (s, 3H), 2.15(s, 3H); ^{13}C{^{1}H} NMR(100 MHz, $CDCl_3$) δ 157.6, 138.5, 135.4, 133.1, 132.5, 132.2 (q, J_{C-F} = 3.7 Hz), 131.2, 131.0, 129.1, 128.9, 128.3, 128.0, 127.9, 122.0 (q, J_{C-F} = 267.0 Hz), 120.3, 120.3, 118.4, 110.6, 107.7 (q, J_{C-F} = 36.2 Hz), 55.2, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.36 (s, 3F); HRMS (ESI): m/z [M+ H]$^+$ Calcd for $C_{25}H_{20}F_3N_2O_3$ 453.1421; found: 453.1427.

2-(4-fluorophenyl)-4-nitro-5-phenyl-1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrrole **(4e):** Isolated as a yellow solid (22.0 mg, 50% yield), mp: 138-140°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.24 (m, 5H), 7.18 - 7.13 (m, 2H), 6.93 (t, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 2.20 (d, *J* = 9.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 248.9 Hz), 138.9, 135.2, 134.1 (q, J_{C-F} = 2.2 Hz), 134.0, 132.8 (q, J_{C-F} = 9.3 Hz), 132.6, 131.0, 129.5, 129.3, 128.4, 128.0, 127.8, 125.1 (d, J_{C-F} = 3.5 Hz), 121.9 (q, J_{C-F} = 271.5 Hz), 115.2 (d, J_{C-F} = 21.9 Hz), 107.2 (q, J_{C-F} = 39.1 Hz), 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.86 (s,3F), -111.12 (s, 1F); HRMS (ESI): m/z [M+ H]$^+$ Calcd for $C_{24}H_{18}F_4N_2O_2$ 441.1221; found: 441.1239.

2-(4-chlorophenyl)-4-nitro-5-phenyl-1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrrole **(4f):** Isolated as a yellow solid (18.2 mg, 40% yield), mp: 208-210°C. 1H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.21 (m, 7H), 7.12 -7.10 (d, *J* = 7.9 Hz, 2H), 6.90 - 6.88 (d, *J* = 7.7 Hz, 2H), 6.71 - 6.69 (d, *J* = 7.7 Hz, 2H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.0, 135.4, 135.3, 133.8 (q, J_{C-F} = 3.4 Hz), 132.6, 132.2, 132.1, 131.0, 129.6, 129.4, 129.4, 128.3, 128.0, 127.7, 127.5, 121.8 (q, J_{C-F} = 268.6 Hz), 107.6 (q, J_{C-F} = 36.8 Hz), 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.80 (s, 3F); HRMS (ESI): m/z [M+ H]$^+$ Calcd for $C_{24}H_{17}ClF_3N_2O_2$ 457.0925; found: 457.0926.

2-(4-methoxyphenyl)-3-nitro-5-phenyl-1-(p-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4g):** Isolated as a yellow solid (18.9 mg, 42% yield), mp: 194-196°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.20 (m, 3H), 7.18 - 7.16 (m, 4H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 3.75 (s, 3H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 138.6, 135.1, 132.9, 132.5, 132.2, 131.3, 130.9, 129.4, 129.2, 129.0, 128.5, 127.9, 122.0 (d, J_{C-F} = 268.4 Hz), 119.8, 113.5, 107.5 (d, J_{C-F} = 38.6 Hz), 55.2, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.73 (s, 3F); HRMS (ESI): m/z [M+ H]$^+$ Calcd for $C_{25}H_{20}F_3N_2O_3$ 453.1421; found: 453.1434.

3-nitro-5-phenyl-1,2-di-p-tolyl-4-(trifluoromethyl)-1H-pyrrole **(4h):** Isolated as a yellow solid (26.5 mg, 61% yield), mp:192-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.22 (m, 3H), 7.18 - 7.15 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H),

2.28 (s, 3H), 2.17 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 139.3, 138.6, 135.2, 135.1 (q, J_{C-F} = 3.2 Hz), 132.9, 131.0, 130.9, 130.8, 129.3, 129.2, 129.0, 128.7, 128.5, 127.9, 124.8, 122.0 (q, J_{C-F} = 266.8 Hz), 107.2 (q, J_{C-F} = 36.6 Hz), 21.4, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.77 (s, 3F); HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{19}F_3N_2O_3$ 437.1471; found: 437.1476.

3-nitro-5-phenyl-2-(o-tolyl)-1-(p-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4i):** Isolated as a yellow solid (30.9 mg, 71% yield), mp: 193-195°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.17 (m, 6H), 7.11 (d, *J* = 9.1 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 7.5 Hz, 2H), 2.19 (s, 3H), 2.14 (d, *J* = 8.7 Hz, 3H), ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.68 (s, 3F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 138.7, 138.5, 135.6, 135.5 (q, J_{C-F} = 3.2 Hz), 132.8, 132.3, 131.1, 131.0, 130.9, 129.8, 129.6, 129.2, 129.1, 129.0, 128.1, 127.9, 125.3, 122.0 (q, J_{C-F} = 266.9 Hz), 107.0 (q, J_{C-F} = 36.6 Hz), 21.0, 20.10; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{19}F_3N_2O_2$ 437.1471; found: 437.1471.

2-(4-fluorophenyl)-3-nitro-5-phenyl-1-(p-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4j):** Isolated as a yellow solid (19.8 mg, 45% yield), mp:175-176°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.22 (m, 5H), 7.17 - 7.15 (m, 2H), 6.94 (t, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 2.19 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 250.4 Hz), 138.9, 135.4 (q, J_{C-F} = 3.6 Hz), 134.0, 133.2, 133.1, 132.7, 130.9, 129.5, 129.1, 128.9, 128.4, 127.9, 123.9 (d, J_{C-F} = 3.6 Hz), 121.9 (q, J_{C-F} = 268.4 Hz), 115.3 (d, J_{C-F} = 22.0 Hz), 107.7 (q, J_{C-F} = 38.9 Hz), 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.85 (s, 3F), -110.67 (s, 1F); HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{17}F_4N_2O_2$ 441.1221; found: 441.1255.

3-nitro-2,5-diphenyl-1-(4-(trifluoromethoxy)phenyl)-4-(trifluoromethyl)-1H-pyrrole **(4k):** Isolated as a yellow solid (23.6 mg, 48% yield), mp:192-194°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.22 (m, 8H), 7.17 - 7.15 (d, *J* = 7.1 Hz, 2H), 6.94 - 6.92 (d, *J* = 8.6 Hz, 2H), 6.88 - 6.85 (d, *J* = 8.9 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.8, 135.2 (q, J_{C-F} = 3.5 Hz), 134.9, 133.8, 132.5, 131.0, 130.8, 130.3, 129.6, 129.4, 128.6, 128.2, 128.1, 127.4, 121.0 (q, J_{C-F} = 266.9 Hz), 120.9, 120.1 (q, J_{C-F} = 257.1 Hz), 107.8 (q, J_{C-F} = 36.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.97 (s, 3F), -58.10 (s, 3F); HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{15}F_6N_2O_3$ 493.0981; found: 493.0972.

3-nitro-2,5-diphenyl-1-(m-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4l):** Isolated as a yellow solid (31.6 mg, 75% yield), mp: 183-185°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 - 7.21 (m, 8H), 7.19(s), 7.17 (s), 6.97 - 6.89 (m, 2H), 6.63 (s, 2H), 2.08 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.78; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 138.8, 135.3, 135.2, 135.2, 135.2, 135.1, 135.0, 130.9, 129.4, 129.3, 129.3, 129.1, 129.0, 128.4, 127.9, 127.9, 125.8, 122.0 (q, J_{C-F} = 266.8 Hz), 107.2 (q, J_{C-F} = 36.6 Hz), 20.9; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{18}F_3N_2O_2$ 423.1315, found: 423.1318.

3-nitro-5-phenyl-2-(m-tolyl)-1-(p-tolyl)-4-(trifluoromethyl)-1H-pyrrole **(4m):** Isolated as a yellow solid (25.7 mg, 61% yield), mp: 190-192°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.25 (m, 1H), 7.23 - 7.21 (d, *J* = 7.1 Hz, 2H), 7.18 - 7.16 (d, *J* = 7.4 Hz, 2H), 7.14 - 7.08 (m, 2H), 7.08 (s, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.6, 137.6, 135.3, 135.1 (q, J_{C-F} = 3.6 Hz), 132.9, 132.2, 131.6, 131.0, 130.9, 130.0, 129.3, 129.1, 129.0, 128.5, 128.0, 127.9, 127.8, 122.0 (q, J_{C-F} = 268.5 Hz), 107.1 (q, J_{C-F} = 36.6 Hz), 21.2, 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.80 (s, 3F); HRMS (ESI): m/z [M+ H]$^{+}$ Calcd for $C_{25}H_{19}F_3N_2O_2$ 437.1471; found: 437.1467.

3-nitro-1,2,5-triphenyl-4-(trifluoromethyl)-1H-pyrrole **(4n):** Isolated as a yellow solid (19.5 mg, 48% yield), mp: 190-192°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.21 (m, 8H), 7.18 - 7.17 (d, *J* = 7.0 Hz, 2H), 7.12-7.06 (d, *J* = 12.7 Hz, 3H), 6.85 - 6.83 (d, *J* = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.4, 135.2 (q, J_{C-F} = 3.5 Hz), 135.1, 132.4, 132.3, 131.1, 130.9, 129.2 (q, J_{C-F} = 19.8 Hz), 128.8, 128.7, 128.6, 128.0, 127.9, 127.8, 125.9, 121.9 (q, J_{C-F} = 266.7 Hz), 107.3 (q, J_{C-F} = 36.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.81 (s, 3F); HRMS (ESI) m/z: [M + H]$^{+}$ Calcd for $C_{23}H_{16}F_3N_2O_2$ 409.1158; found: 409.1164.

1-(4-fluorophenyl)-3-nitro-2,5-diphenyl-4-(trifluoromethyl)-1H-pyrrole **(4o):** Isolated as a yellow solid (22.5 mg, 53% yield), mp: 212-214°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.23 (m, 8H), 7.18 - 7.16 (d, *J* = 7.1 Hz, 2H), 6.85 - 6.81(m, 2H), 6.79 - 6.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 249.2 Hz), 135.3 (q, J_{C-F} = 3.4 Hz), 135.1, 131.5 (d, J_{C-F} = 3.4 Hz), 131.0, 130.9, 130.5 (d, J_{C-F} = 8.8 Hz), 129.4 (d, J_{C-F} = 18.8 Hz), 128.9, 128.8, 128.4, 128.1 (d, J_{C-F} = 3.9 Hz), 128.0, 127.6, 121.8 (q, J_{C-F} = 266.9 Hz), 115.9 (d, J_{C-F} = 23.0 Hz), 107.4 (q, J_{C-F} =36.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.91 (s, 3F), -110.93 (s, 1F); HRMS (ESI) m/z: [M + H]$^{+}$ Calcd for $C_{23}H_{14}F_4N_2O_2$ 427.1064; found: 427.1071.

1-(3-fluorophenyl)-3-nitro-2,5-diphenyl-4-(trifluoromethyl)-1H-pyrrole **(4p):** Isolated as a yellow solid (13.6 mg, 32% yield), mp:160-162°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.25 (m, 8H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.03 - 7.09 (dd, *J* = 11.2 Hz, *J* = 14.3 Hz, 1H), 6.83 - 6.87 (dt, *J* = 2.1 Hz, *J* = 8.3 Hz, 1H), 6.65 - 6.67 (d, *J* = 8.0 Hz, 1H), 6.57 - 6.60 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.0 (d, J_{C-F} = 248.0 Hz), 136.8 (d, J_{C-F} = 9.8 Hz), 135.1 (q, J_{C-F} = 3.6 Hz), 134.9, 132.6 (d, J_{C-F} = 15.6 Hz), 131.0, 130.8, 130.0 (d, J_{C-F} = 8.9 Hz), 129.6, 129.4, 128.6, 128.2, 128.1, 127.4, 124.8 (d, J_{C-F} = 3.4 Hz), 121.8 (q, J_{C-F} = 266.9 Hz), 116.5 (d, J_{C-F} = 23.7 Hz), 116.1 (d, J_{C-F} = 20.8 Hz);107.6 (q, J_{C-F} = 36.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.95 (s, 3F), -110.55 (s, 1F); HRMS (ESI) m/z: [M + H]$^{+}$ Calcd for $C_{23}H_{15}F_4N_2O_2$ 427.1064, found: 427.1068.

1-(3-chlorophenyl)-3-nitro-2,5-diphenyl-4-(trifluoromethyl)-1H-pyrrole **(4q):** Isolated as a yellow solid (28.7 mg, 65% yield), mp:188-190°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 8H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.74 (d, *J* = 7.9 Hz, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 136.5, 135.1 (q, J_{C-F} = 3.3 Hz), 134.5, 131.0, 130.9, 130.8, 129.6, 129.6, 129.4, 129.1, 129.0, 128.6, 128.2, 128.1, 127.4, 127.0, 126.0 (q, J_{C-F} = 27.8 Hz), 121.8 (q, J_{C-F} = 268.4 Hz), 107.7 (q, J_{C-F} = 34.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.98 (s, 3F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{15}ClF_3N_2O_2$ 443.0769, found: 443.0762.

1-(4-chlorophenyl)-3-nitro-2,5-diphenyl-4-(trifluoromethyl)-1H-pyrrole **(4r):** Isolated as a yellow solid (23.4 mg, 53% yield), mp: 259-261°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.23 (m, 8H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 8.64 Hz, 2H), 6.77 (d, *J* = 8.68 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.1 (q, J_{C-F} = 3.8 Hz), 134.9, 134.8, 134.0, 131.0, 130.9, 130.8, 129.9, 129.6, 129.4, 129.1, 128.6, 128.2, 128.1, 127.5, 121.8 (q, J_{C-F} = 268.7 Hz), 107.6 (q, J_{C-F} = 37.2 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -53.95 (s, 3F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{15}ClF_3N_2O_2$ 443.0769; found: 443.0761.

1-(4-bromophenyl)-3-nitro-2,5-diphenyl-4-(trifluoromethyl)-1H-pyrrole **(4s):** Isolated as a yellow solid (17.0 mg, 35% yield), mp: 277-278°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.27 (dd, *J* = 8.2, 2.3 Hz, 4H), 7.25 – 7.19 (m, 4H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.1 (q, J_{C-F} = 3.6 Hz), 134.8, 134.5, 132.1, 131.0, 130.8, 130.8, 130.2, 129.6, 129.4, 128.6, 128.2, 128.2, 127.5, 122.8, 121.8 (q, J_{C-F} = 268.6 Hz), 107.6 (q, J_{C-F} = 36.9 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -53.95 (s, 3F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{15}BrF_3N_2O_2$ 487.0264; found: 487.0261.

1-(trifluoromethyl)naphthalen-2-amine **(4t'):** 10.8 mg, 51%. Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 1H), 7.67 – 7.64 (m, 2H), 7.47-7.45 (m, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 4.59 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.8, 133.4, 131.5 (q, J_{C-F} = 1.4 Hz), 128.5, 128.0, 127.9, 127.3 (q, J_{C-F} = 274.2 Hz), 123.1 (q, J_{C-F}= 4.2 Hz), 122.9, 119.9, 102.6 (q, J_{C-F} = 28.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -51.99 (s, 3F); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_9F_3N$ 212.0682; found: 212.0690.

The procedure of scale-up reaction: An oven dried 100 mL round-bottomed flask was charged with (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**1a**, 0.5 g, 2.0 mmol), *p*-toluidine (0.26 g, 2.4 mmol), Togni-Ⅱ reagent **3a** (1.14 g, 3.6 mmol), $[Cp^*RhCl_2]_2$ (0.124 g, 0.2 mmol), copper acetate monohydrate (0.8 g, 4.0 mmol), and was stirred in the presence of calcium hydroxide (0.44 g, 6.0 mmol) and 4Å

molecular sieves (0.6 g) in dimethylformamide (20 mL) under N_2 atmosphere at room temperature . The mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtrated by diatomite and washed by ethyl acetate (20 mL). The combined mixture was washed with brine (20 mL × 3) and then dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on basic silica gel (EA/PE = 1/80) to afford the desired compounds **4a** (0.43 g, 51% yield).

Reaction procedure of TEMPO with Togni-Ⅱ reagent: In a 10 mL dried sealed tube, (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**1a**, 25.0 mg 0.1 mmol,) was added, *p*-toluidine (**2a**, 12.8 mg, 0.12 mmol, 1.2 equiv), Togni-Ⅱ reagent **3a** (56 mg, 0.18 mmol, 1.8 equiv), $[RhCp^*Cl_2]_2$ (6.2 mg, 10 mol%), copper acetate monohydrate (40 mg, 0.2 mmol, 2.0 equiv), calcium hydroxide (22.0 mg, 0.3 mmol, 3.0 equiv), 4Å MS (50 mg) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 31.2 mg, 0.2 mmol, 2.0 equiv) were added, and were dissolved in dimethylformamide (1.0 mL) under N_2 atmosphere at room temperature, the sealed tube was stirred 0.5 h, benzotrifluoride (29.2 mg, 0.2 mmol, internal standard) was added. ^{19}F NMR analysis of the reaction mixture showed that TEMPO-CF_3 was formed in 51% yield.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: crystal structure of **4k**, and copies of NMR spectra of compounds **4** (PDF).

AUTHOR INFORMATION

Corresponding Author

Corresponding Authors

*E-mail: dingqiuping@jxnu.edu.cn

ORCID: Qiuping Ding: 0000-0002-1154-7621

Yiyuan Peng: 0000-0003-3471-8566

Notes

The authors declare no conflict of interest.

ACKNOWLEDGMENT

Thank the National Natural Science Foundation of China (21662017 and 21961016) very much for financial support.

REFERENCES

1 For examples, see: (a) Sundberg, R. J. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science, Ltd.: Oxford, 1996; Vol. 2 (Bird, C. W., Ed.), pp 119-206. (b) Reyes, J. C. P.; Romo, D. Back Cover: Bioinspired Total Synthesis of Agelastatin A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6870-6873. (c) Fan, H.; Peng, J.; Hamann M. T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev*., **2008**, *108*, 264-287.

2 (a) Huffman, J. W. Cannabimmetic indoles, pyrroles and indenes. *Curr. Med. Chem.* **1999**, *6*, 705-720. (b) Thompson, R. B. Foundations for blockbuster drugs in federally sponsored research. *FASEB J*. **2001**, *15*, 1671-1673.

3 (a) Sobenina, L. N.; Vasil'tsov, A. M.; Petrova, O. V.; Petrushenko, K. B.; Ushakov, I. A.; Clavier, G.; Meallet-Renault, R.; Mikhaleva A. I; Trofimov, B. A. General Route to Symmetric and Asymmetric *meso*-CF_3-3(5)-Aryl(hetaryl)- and 3,5-Diaryl(dihetaryl)-BODIPY Dyes. *Org. Lett.*, 2011, *13*, 2524 − 2527; (b) Zhou, N.-N.; Zhu, H.-T.; Yang, D.-S.; Guan, Z.-H. Recent developments in the group-1B-metal-catalyzed synthesis of pyrroles. *Org. Biomol. Chem.* 2016, *14*, 7136-7149. (c) Herman, R. A.; Kukel, C. F. Preparation of

arylpyrrole molluscicides, US 4929634, 1989, A. (d) Brown, D. G.; Siddens, J. K.; Diehl, R. E.; Wright, D. P. J. Preparation of arylpyrrole pesticides, US 5010098, 1989, A.

4 (a) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008,** *37*, 308–319. (b) Wang, J.; Sanchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade. *Chem. Rev*. **2014**, *114*, 2432-2506.

5 For selected reviews, see: (a) Hiyama, T. Fluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000. (b) Uneyama, K. Organofluorine Chemistry, Blackwell, Oxford, UK, 2006. (c) Muller, K.; Faeh C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science*, **2007**, *317*, 1881-1886.

6 (a) Treacy, M. F.; Miller, T. P.; Gard, I. E.; Lovell, J. B.; Wright, D. P. Jr.; Characterization of insecticidal properties of AC303,630 against tobacco budworm, *Heliothis irescens* (Fabricius), larvae. *Proc Beltwide Cotton Conf*, 1991, 2: 738-740. (b) Miller, T.P.; Treacy, M.F.; Gard, I. E.; Lovell, J. B.; Wright, D. P. Jr.; Addor RW, Kamhi VM. AC303630, summary of 1988–1989 field trial results. *Brighton Crop Prot Conf Pests Dis*, 1990, 1: 41-45.

7 Addor, R.W.; Donovan, S. F.; Diehl, R. E.; Preparation of new N- acylated arylpyrroles useful as insecticidal, acaricidal, nematocidal and molluscicidal agents. CN 1056491 A 19911127.

8 Some selected reviews: (a) Leonardi, M.; Estévez, V.; Villacampa, M.; Menéndez, J. C. The Hantzsch Pyrrole Synthesis: Non-conventional Variations and Applications of a Neglected Classical Reaction. *Synthesis*, **2019**, *51*, 816-828. (b) Balakrishna, A.; Aguiar, A.; Sobral, P. J. M.; Wani, M. Y.; Silva, J. A. E.; Sobral, A. J. F. N. Paal-Knorr Synthesis of Pyrroles: from conventional to green synthesis. Catal. Rev. Sci. Eng. **2019**, *61*, 84-110. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. Recent advances in the synthesis of pyrroles by multicomponent reactions. *Chem. Soc. Rev*. **2014**, *43*, 4633-4657.

9 (a) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. Synthesis of Trifluoromethyl Pyrroles and Their Benzo Analogues. *Synthesis* **2009**, *2009*, 3905-3929. (b) Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M. New Electrophilic

Trifluoromethylating Agents. *J. Org. Chem.* **1998**, *63*, 2656-2660. (c) Seo, S.; Taylor, J. B.; Greaney, M. F. Silver-catalysed trifluoromethylation of arenes at room temperature. *Chem. Commun*. **2013**, *49*, 6385-6387.

10 (a) Wu, L; Wang, F; Chen, P; Liu, G. Enantioselective Construction of Quaternary All-Carbon Centers via Copper-Catalyzed Arylation of Tertiary Carbon-Centered Radicals. *J. Am. Chem. Soc.* **2019**, *141*, 1887-1892. (b) Han, G; Wang, Q; Liu, Y; Wang Q. Copper-Mediated α-Trifluoromethylation of N-Phenylcinnamamides Coupled with Dearomatization: Access to Trifluoromethylated 1-Azaspiro[4.5]decanes. *Org. Lett.* **2014**, *16*, 5914-5917. (c) Gao, P.; Shen, Y.-W.; Fang, R.; Hao, X.-H.; Qiu, Z.-H.; Yang, F.; Yan, X.-B.; Wang, Q.; Gong, X.-J.; Liu, X.- Y.; Liang, Y.-M. Copper-Catalyzed One-Pot Trifluoromethylation/ Aryl Migration/Carbonyl Formation with Homopropargylic Alcohols. *Angew. Chem., Int. Ed.* **2014**, *53*, 7629-7633. (d) Xu, J.; Wang, Y.-L.; Gong, T.-J.; Xiao, B.; Fu, Y.; Copper-catalyzed endo-type trifluoromethylarylation of alkynes. *Chem. Commun.*, **2014**, *50*, 12915-12918. (e) Malpani, Y. R.; Biswas, B. K.; Han, H. S.; Jung, Y.-S.; Han , S. B. Multicomponent Oxidative Trifluoromethylation of Alkynes with Photoredox Catalysis: Synthesis of α-Trifluoromethyl Ketones. *Org. Lett.* **2018**, *20*, 1693-1697.

11 Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. Regiospecific Synthesis of 4-Alkoxy and 4-Amino Substituted 2-Trifluoromethyl Pyrroles. *J. Org. Chem*. **2006**, *71*, 6996-6998.

12 Dou, G.; Shi, C.; Shi, D. Highly Regioselective Synthesis of Polysubstituted Pyrroles through Three-Component Reaction Induced by Low-Valent Titanium Reagent. *J. Comb. Chem*. **2008**, *10*, 810-813.

13 (a) Kobatake, T.; Yoshida, S.; Yorimitsu, H.; Oshima, K. Reaction of 2 - (2,2,2 - Trifluoroethylidene) - 1,3 - dithiane 1 - Oxide with Ketones under Pummerer Conditions and Its Application to the Synthesis of 3 - Trifluoromethyl - Substituted Five - Membered Heteroarenes. *Angew. Chem., Int. Ed*. **2010**, *49*, 2340-2343. (b) Xu, G.; Sayre, L. M. Cross-Linking of Proteins by 3-(Trifluoromethyl)-2,5-hexanedione. Model Studies Implicate an Unexpected Amine-Dependent Defluorinative Substitution Pathway Competing with Pyrrole Formation. *J. Org. Chem.* **2002**, *67*, 3007-3014.

14 (a) Zhou, X.; Huang, C.; Zeng, Y.; Xiong, J.; Xiao, Y.; Zhang, J. Silver-catalysed tandem hydroamination and cyclization of 2-trifluoromethyl-1,3-enynes with primary amines: modular entry to 4-trifluoromethyl-3-pyrrolines. *Chem. Commun.* **2017**, *53*,

1084-1087. (b) Guieu, B.; Roch, M. L.; David, M.; Gouault, N. Gold-Catalyzed Synthesis of Substituted 3-Trifluoromethylpyrroles from Mesylated Amino Trifluoromethylpropargylic Alcohols. *J. Org. Chem.* **2017**, *82*, 13708-13713.

15 (a) Brummond, K. M.; Kocsis, L. S. Intramolecular Didehydro-Diels-Alder Reaction and Its Impact on the Structure-Function Properties of Environmentally Sensitive Fluorophores. *Acc. Chem. Res.* **2015,** *48*, 2320-2329. (b) Khatri, B. B.;Sieburth, S. McN. Enyne-2-pyrone [4 + 4]-Photocycloaddition: Sesquiterpene Synthesis and a Low-Temperature Cope Rearrangement. *Org. Lett.* **2015**, *17*, 4360-4363. (c) Khatri, B. B.; Kulyk, S., Sieburth, S. McN. Enyne [4 + 4] photocycloaddition with polycyclic aromatics. *Org. Chem. Front.* **2014**, *1*, 961- 964.

16 (a) Zhou, Y.; Chen, X.; Yin, D.; Ling Y.; Wang, S.; Zhang, X.; Rao, W. Gold‐Catalyzed Cycloisomerization–Halogenation Sequence of 1,3‐Enyne Esters with NXS: Efficient Synthesis of 5‐Bromo/Iodo Cyclopentenones. *Eur. J. Org. Chem.* **2019**, 999-1007. (b) Congmon, J; Tius, M. A. Contiguous Quaternary Centers from a Au^{I}‐Catalyzed Nazarov Cyclization. *Eur. J. Org. Chem.* **2018**, 2926-2930. (c) Chen, X; Zhou, Y; Hong, M; Ling, Y; Yin, D; Wang, S; Zhang, X; Rao, W. Gold(I)‐Catalyzed Tandem Cycloisomerization and Fluorination of 1,3(4)‐Enyne Esters with NFSI: One‐Pot Assembly of 5‐Fluoro‐Cyclopentenones. *Adv. Synth. Catal.* **2018**, *360*, 3700-3708. (d) Rao, W; Boyle, J. W; Chan, P. W. H. Gold‐Catalyzed Sequential Cyclization of 1‐En‐3,9‐Diyne Esters to Partially Hydrogenated 3*H*‐Dicyclopenta[*a*,*b*]naphthalenes. *Chem. Eur. J.* **2016**, *22*, 6532-6536. (e) Rao, W; Susanti, D; Ayers, B. J; Chan, P. W. H. *J. Am. Chem. Soc.* **2015**, *137*, 6350-6355. (f) Lemière, G; Gandon,V; Cariou, K; Hours, A; Fukuyama, T. Dhimane, A.-L; Fensterbank, L; Malacria, M. Generation and Trapping of Cyclopentenylidene Gold Species: Four Pathways to Polycyclic Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006. (g) Lemière, G; Gandon, V; Cariou, K; Fukuyama, T; Dhimane, A.-L; Fensterbank, L; Malacria, M. Tandem Gold(I)-Catalyzed Cyclization/Electrophilic Cyclopropanation of Vinyl Allenes. *Org.Lett.* **2007**, *9*, 2207-2209. (h) Zhang, L; Wang, S. Efficient Synthesis of Cyclopentenones from Enynyl Acetates via Tandem Au(I)-Catalyzed 3,3-Rearrangement and the Nazarov Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1442-1443.

17 Huang, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H.Enantioselective Synthesis of Trisubstituted Allenyl-B(pin) Compounds by Phosphine-Cu-Catalyzed 1,3-Enyne Hydroboration. Insights Regarding Stereochemical Integrity of Cu-Allenyl Intermediates. *J. Am. Chem. Soc*. **2018**, *140*, 2643-2655.

18 Zhu, X.; Deng, W.; Chiou, M.-F.; Ye, C.; Jian, W.; Zeng, Y.; Jiao, Y.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and *N*-Fluorobenzenesulfonimide. *J. Am. Chem. Soc*. **2019**, *141*, 548-559.

19 Yao, B.; Miao, T.; Li, P.; Wang, L. Direct Synthesis of Benzo[*f*]indazoles from Sulfonyl Hydrazines and 1,3-Enynes by Copper-Catalyzed Annulation. *Org. Lett.* **2019**, *21*, 124-128.

20 (a) Bharathiraja, G.; Sakthivel, S.; Sengoden, M.; Punniyamurthy, T. A Novel Tandem Sequence to Pyrrole Syntheses by 5-*endo-dig* Cyclization of 1,3-Enynes with Amines. *Org. Lett.* **2013**, *15*, 4996-4999. (b) Bharathiraja, G.; Sengoden, M.; Kannan M.; Punniyamurthy, T. Expedient synthesis of tetrasubstituted pyrroles *via* a copper-catalyzed cascade inter-/intramolecular cyclization of 1,3-enynes carry a nitro group with amines. *Org. Biomol. Chem.* **2015**, *13*, 2786-2792. (c) Reddy, C. R.; Panda, S. A.; Ramaraju, A. Oxidative Aza-Annulation of Enynyl Azides to 2-Keto/Formyl-1H-pyrroles. *J. Org. Chem.* **2017**, *82*, 944-949.

21 (a) Reddy, C. R.; Prajapti, S. K.; Ranjan, R. Cu(I)-Catalyzed Aminative Aza-Annulation of Enynyl Azide using N-Fluorobenzenesulfonimide: Synthesis of 5-Aminonicotinates. *Org. Lett.* **2018**, *20*, 3128-3131. (b) Bardy, M.; Ho, K. Y. T.; Halsall, C. T.; A ïssa, C. Regioselective Synthesis of 3-Hydroxy-4,5-alkyl-Substituted Pyridines Using 1,3-Enynes as Alkynes Surrogates. *Org. Lett.* **2016**, *18*, 1756-1759. (c) Reddy, C. R.; Panda, S. A.; Reddy, M. D. Aza-Annulation of Enynyl Azides: A New Approach to Substituted Pyridines. *Org. Lett.* **2015**, *17*, 896-899.

22 Li, Y.; Lu, Y.; Qiu, G.; Ding, Q. Copper-Catalyzed Direct Trifluoromethylation of Propiolates: Construction of Trifluoromethylated Coumarins. *Org. Lett.* **2014**, *16*, 4240-4243.

23 (a) Wang, Y. F.; Toh, K. K.; Lee, J. Y.; Chiba, S. Synthesis of Isoquinolines from a-Aryl Vinyl Azides and Internal Alkynes by Rh–Cu Bimetallic Cooperation. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927-5931. (b) Liu, K.; Chen, S.; Li, X. G.; Liu, P. N. Liu. Multicomponent Cascade Synthesis of Trifluoroethyl Isoquinolines from Alkynes and Vinyl Azides. *J. Org. Chem.* **2016**, *81*, 265-270.