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Regioselective Synthesis of 2,4-Diaryl-6-trifluoromethylated Pyridines through Copper-Catalyzed Cyclization of CF_3-Ynones and Vinyl Azides

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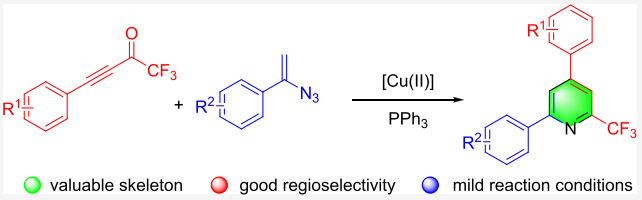
ABSTRACT: A novel copper-catalyzed cyclization of readily available vinyl azides with CF_3-ynones is steadily achieved under mild conditions to furnish the versatile 2,4-diaryl-6-trifluoromethylated pyridine products, which are of great interest in medicinal chemistry. The generation of the vinyl iminophosphorane intermediates from vinyl azides through the Staudinger−Meyer reaction ensures the subsequent 1,4-addition process with CF_3-ynones in this transformation.



INTRODUCTION

The trifluoromethyl group plays an important role in medicinal chemistry and materials science.[1] When the CF_3 moiety is introduced into molecule compounds, it often enhances efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability as well as increasing robustness toward oxidative metabolism of the drug.[2] On the other hand, pyridine is not only one of the most important and high priority nitrogen-containing heterocycles widely distributed in natural and synthetic biologically active molecules but also an important intermediate in agrochemical and pharmaceutical industries.[3] Moreover, pyridine derivatives are versatile precursors of various topoisomerase I inhibitors and potential anticancer agents.[4] Notably, the pyridine skeletons bearing trifluoromethyl motifs, such as 2-trifluoromethylated pyridines, have emerged as core units in an increasing number of valuable drugs and agrochemicals (Figure 1).[5]

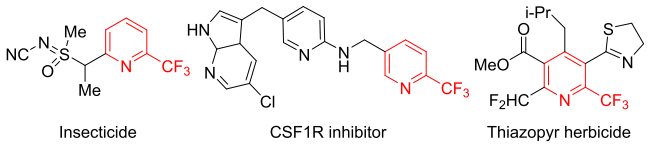


Figure 1. Representative 2-trifluoromethylpyridines of biological interest.

In recent years, the development of methodologies for the 2-trifluoromethylpyridine synthesis has aroused great interest among researchers.[6] Among them, the common route was to incorporate the trifluoromethyl moiety into the 2-position on the pyridine frameworks through a transition-metal-catalyzed cross-coupling reaction[7] and the more recently direct C−H trifluoromethylation process (Scheme 1a).[8] However, the synthetic utility has been limited to some extent because of the requirement of an excess amount of prefunctionalized nitrogen substrates, using expensive trifluoromethylating reagents, low activity, as well as difficulty in controlling regioselectivity. Meanwhile, a notable alternative is based on the use of easily available trifluoromethylated building blocks.[9] However, the site-selective construction of 2-trifluoromethylpyridines, especially 2,4-diaryl-6-trifluoromethylated pyridines, through trifluoromethyl building blocks is still challenging and is therefore rarely reported. To the best of our knowledge, the direct access to 2,4-diphenyl-6-trifluoromethylpyridine thus far has only arose from the work of Funabiki and co-workers[10] via the cyclization of α,β-unsaturated trifluoromethyl ketone with enamine in the presence of NH_4OAc in triglyme at reflux temperature, however, in only 13% yield (Scheme 1b). Consequently, the exploration of general and concise methodologies for constructing more diverse 2,4-diaryl-6-trifluoromethylated pyridines with an easily available trifluoromethylated framework remains highly appealing.[11] Within this context, CF_3-ynones have been shown to be prominent building blocks for the preparation of various fluorinated heterocyclic compounds.[12] More recently, Hu and co-workers reported the synthesis of polysubstituted trifluoromethylpyridines from CF_3-ynones by the Bohlmann−Rahtz heteroannulation reaction,[13] in which enamines bearing β-ester and ketone moieties served as the suitable coupling partner.[12a] In recent years, the divergent modes of reactivity of vinyl azides, which occur due

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Scheme 1. Synthetic Protocols of 2-Trifluoromethylpyridines

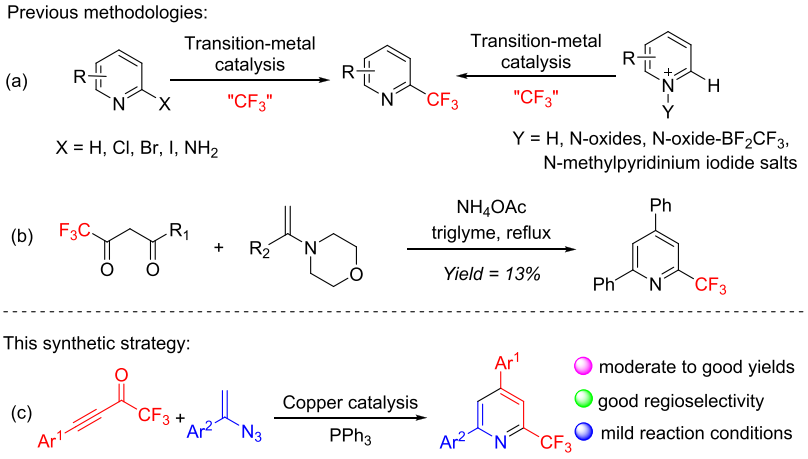
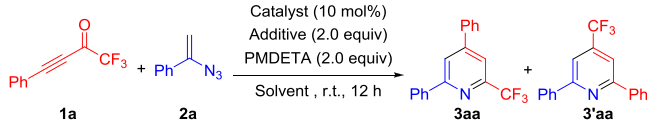


Table 1. Screenings of Various Reaction Parameters[a]



entry	catalyst	additive	base	solvent	3aa (%)[b]	3aa/3′aa[c]
1	CuI		PMDETA	DMSO	0	
2	CuI	PPh_3	PMDETA	DMSO	34	10:1
3	AgOTf	PPh_3	PMDETA	DMSO	trace	
4	$AuCl_3$	PPh_3	PMDETA	DMSO	25	10:1
5	$Zn(OTf)_2$	PPh_3	PMDETA	DMSO	trace	
6	$Cu(OTf)_2$	PPh_3	PMDETA	DMSO	trace	
7	$Cu(OAc)_2$	PPh_3	PMDETA	DMSO	38	
8	CuBr	PPh_3	PMDETA	DMSO	22	10:1
9	$CuCl_2$	PPh_3	PMDETA	DMSO	27	10:1
10	$CuBr_2$	PPh_3	PMDETA	DMSO	42	10:1
11	$CuBr_2$	PMe_3	PMDETA	DMSO	trace	
12	$CuBr_2$	PCy_3	PMDETA	DMSO	trace	
13	$CuBr_2$	L1	PMDETA	DMSO	25	10:1
14	$CuBr_2$	L2	PMDETA	DMSO	trace	
15	$CuBr_2$	PPh_3	K_2CO_3	DMSO	0	
16	$CuBr_2$	PPh_3	triisopropylamine	DMSO	32	10:1
17	$CuBr_2$	PPh_3	DABCO	DMSO	trace	
18	$CuBr_2$	PPh_3	DIPEA	DMSO	20	10:1
19	$CuBr_2$	PPh_3	PMDETA	PhMe	39	12:1
20	$CuBr_2$	PPh_3	PMDETA	MeCN	31	12:1
21	$CuBr_2$	PPh_3	PMDETA	DMF	trace	
22	$CuBr_2$	PPh_3	PMDETA	EtOH	trace	
23	$CuBr_2$	PPh_3	PMDETA	DCM	trace	
24	$CuBr_2$	PPh_3	PMDETA	DMSO/PhMe (2:1)	51	11:1
25	$CuBr_2$	PPh_3	PMDETA	DMSO/PhMe (1:1)	60	10:1
26	$CuBr_2$	PPh_3	PMDETA	DMSO/PhMe (1:2)	49	10:1
27[d]	$CuBr_2$	PPh_3	PMDETA	DMSO	40	10:1
28[d]	$CuBr_2$	PPh_3	PMDETA	DMSO/PhMe (1:1)	55	10:1

[a]Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol %), additive (0.4 mmol), and PMDETA (0.4 mmol) in solvent (1 mL) at room temperature under air for 12 h. [b]Isolated yields. [c]The ratio was determined by crude ^{1}H NMR. [d]Under N_2 atmosphere. PMDETA = pentamethyldiethylenetriamine; L1 = 3-(2-furyl)phosphine; L2 = trinaphthylphosphate; DIPEA = *N*,*N*-diisopropylethylamine.

to their distinct azide-appended olefin motif, have been explored in various cyclization reactions for the construction of versatile nitrogen-containing heterocyclic compounds.[14] As a continuation of our ongoing interest in versatile nitrogen-containing heterocyclic constructions,[15] we herein disclose a novel copper-catalyzed cyclization of readily available vinyl azides with CF_3-ynones under mild reaction conditions. Notably, the generation of vinyl iminophosphorane intermediates from vinyl azides by making use of the Staudinger–Meyer reaction[16] ensures the steady 1,4-addition with CF_3-ynones and leads to the versatile 2,4-diaryl-6-trifluoromethylated pyridines, which are of great interest in medicinal

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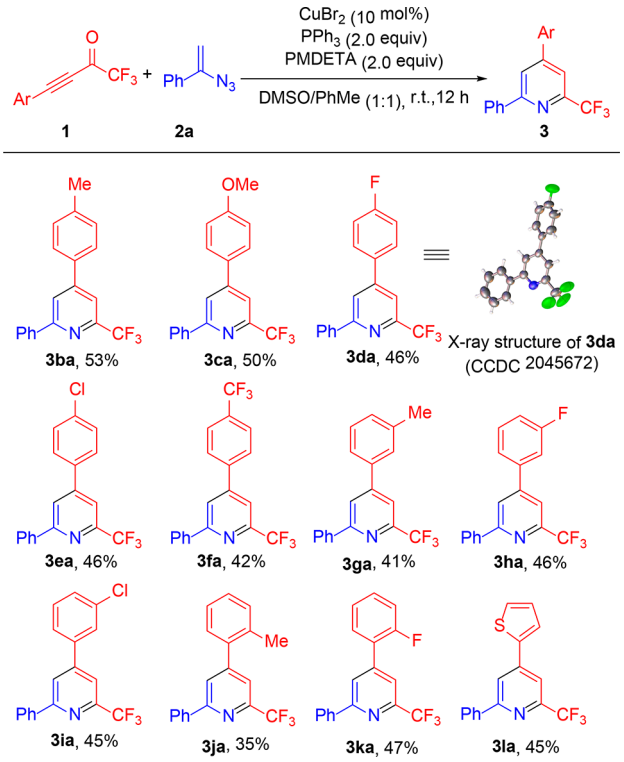
chemistry (Scheme 1c). Moreover, a similar strategy, but with a different regiochemical outcome, was used to produce 2-hydroxypyridines through the reaction of cyano-enamine with unsaturated esters (alkynes) by Cushman and co-workers.[4]

RESULTS AND DISCUSSION

We initiated our investigation on the model reaction of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one (**1a**) and (1-azidovinyl)-benzene (**2a**) to optimize various parameters, and the experimental results are summarized in Table 1.[17] Initially, no reaction was observed in the presence of CuI as the catalyst and PMDETA as the base in DMSO (Table 1, entry 1). Further investigation showed that the cyclizing 2,4-diaryl-6-trifluoromethylated pyridine product **3aa** was smoothly achieved in 34% isolated yield by loading PPh_3 as the additive in the reaction system, indicating the vinyl iminophosphorane intermediate from vinyl azides through the Staudinger−Meyer process was probably involved in the transformation (Table 1, entry 2).[16] Simultaneously, the 1,2-addition process was observed in this transformation, delivering **3′aa** as the side product (**3aa**/**3′aa** = 10:1). To improve the catalytic efficiency, various metal salts, such as AgOTf, $AuCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Cu(OAc)_2$, CuBr, $CuCl_2$, and $CuBr_2$, were examined as potential catalysts, and $CuBr_2$ gave the best performance, leading to **3aa** in 42% yield (Table 1, entries 2−10). In view of the importance of the phosphine additive in this transformation, we further evaluated various nucleophilic and sterically hindered phosphines, and PPh_3 exhibited the highest activity, giving 42% yield of the cyclizing product **3aa** (Table 1, entries 10−14). Moreover, the exploration of different bases revealed that PMDETA provided the best yield of 42% (Table 1, entry 10 vs entries 15−18). A brief examination of the organic solvents including DCM, EtOH, PhMe, THF, MeCN, and DMSO indicated that polar aprotic solvent DMSO performed better than others, affording **3aa** in a yield of 42% (Table 1, entries 19−23). To our delight, further investigations showed that the presence of cosolvent could efficiently promote the conversion, and the target product **3aa** improved to 60% yield in DMSO and PhMe at 1:1 (v/v) (Table 1, entries 24−27). Finally, the yield of **3aa** showed no further improvement by either increasing or decreasing the reaction temperature, even when prolonging the reaction time to 24 h (see Table S7 in the Supporting Information). It should be noted also that the yields of **3aa** did not further increase under inert reaction conditions compared with that under air conditions (entry 27 vs 10; entry 28 vs 25). Thus, the optimized reaction conditions were identified as follows: **1a** (0.3 mmol), **2a** (0.2 mmol), $CuBr_2$ (10 mol %), PPh_3 (2.0 equiv), and PMDETA (2.0 equiv) in DMSO and PhMe (1:1, v/v) (1 mL) at room temperature under air for 12 h (entry 25).

With the optimal conditions in hand, we investigated the reaction of (1-azidovinyl)benzene (**2a**) with a variety of CF_3-ynones **1**. As shown in Scheme 2, substrates bearing both electron-donating and -withdrawing moieties on the phenyl ring proceeded smoothly, delivering the 1,4-addition products **3** in moderate yields. Various functional groups, such as methyl, methoxyl, trifluoromethyl, and halogen were well-tolerated in the transformation. Notably, thienyl-substituted CF_3-ynone **1l** reacted with (1-azidovinyl)benzene (**2a**) as well, steadily generating the pyridine product **3la**, which could be expected to find further applications in organic electronics.[18] Moreover, 1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-one was loaded under the standard catalytic reaction conditions; however, no cyclization product was obtained. Moreover, the structure of compound **3da** was unambiguously confirmed by X-ray single-crystal diffraction.

Scheme 2. Scope of CF_3-Ynones 1[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $CuBr_2$ (0.02 mmol), PPh_3 (0.4 mmol), and PMDETA (0.4 mmol) in DMSO/PhMe (1 mL, 1:1, v/v) at room temperature under air for 12 h. Yields of isolated products.

Next, we evaluated the scope and limitation of vinyl azides **2** for this transformation (Scheme 3). In general, vinyl azides **2** bearing electron-rich moieties other than electron-deficient ones could accelerate the conversion more efficiently. Moreover, substrate **2j** with an *ortho*-fluoro substituent led to the corresponding cyclization product **3aj** in 43% yield. Moreover, the 1,4-addition transformation of CF_3-ynone **1a** with chloro-substituted vinyl azides **2e**, **2f**, and **2i** could steadily deliver the corresponding 2,4-diaryl-6-trifluoromethylpyridine products **3ae**, **3af**, and **3ai**, which might allow for the late-stage modifications through transition-metal-catalyzed couplings. To our disappointment, however, α-phenethyl- and butyl-substituted vinyl azides failed to participate in the cyclization reaction, and no target products were detected under the standard reaction conditions. It is noteworthy that a good chemoselectivity of all the above-mentioned transformations was observed (1,4-addition products **3**/1,2-addition products **3′** > 10:1).

Moreover, a scale-up experiment was performed to showcase the synthetic utility of this novel methodology. Thus, a scale of 7.0 mmol (1-azidovinyl)benzene (**2a**) reacted smoothly with 1,1,1-trifluoro-4-phenylbut-3-yn-2-one (**1a**) and provided the target product **3aa** in 40% yield under the standard reaction conditions (Scheme 4).

Moreover, preliminary control studies were conducted to obtain more insight into the reaction mechanism (Scheme 5).

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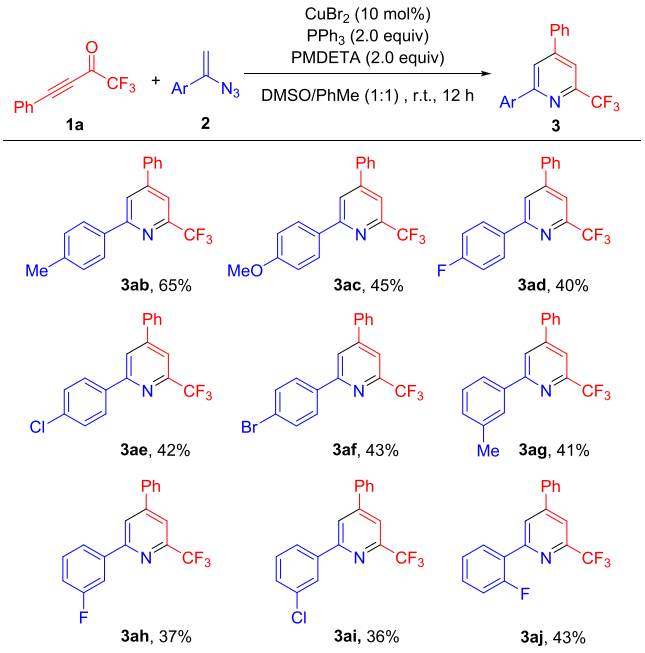
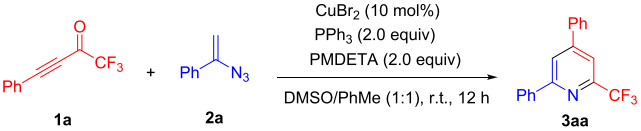
Scheme 3. Scope of Vinyl Azides 2[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $CuBr_2$ (0.02 mmol), PPh_3 (0.4 mmol), and PMDETA (0.4 mmol) in DMSO/PhMe (1 mL, 1:1, v/v) at room temperature under air for 12 h. Yields of isolated products.

Scheme 4. Scale-up Reaction

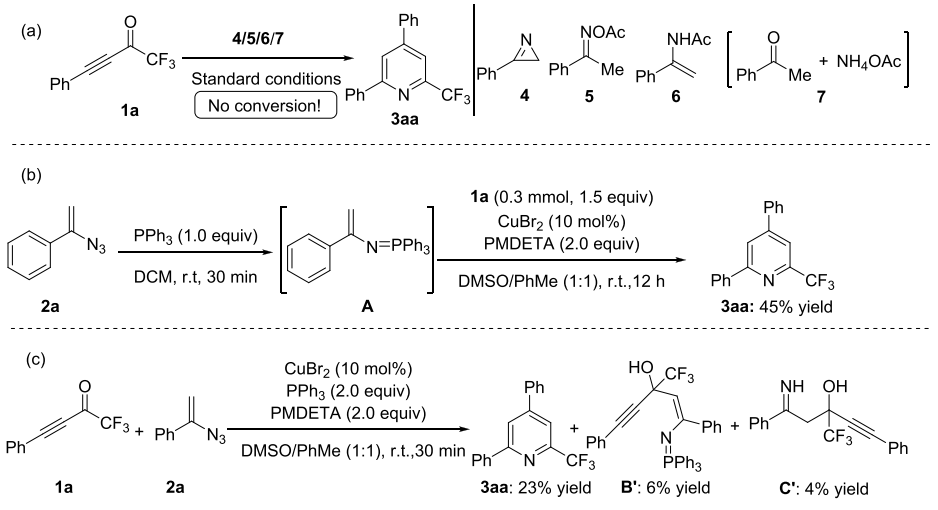


Thus, the assumptive intermediates **4**, **5**, and **6** instead of (1-azidovinyl)benzene **2a** were introduced into the standard reaction conditions. However, the desired trifluoromethylation product **3aa** was completely not observed, proving that intermediates **4**−**6** were not involved in the current transformation. Moreover, the combination of acetophenone and NH_4OAc (**7**) instead of (1-azidovinyl)benzene **2a** was used as the coupling partner, whereas the desired product **3aa** was not formed, indicating the uniqueness of the present synthetic protocol compared with those in previous reports (Scheme 5a).[12a,19] Moreover, the reaction of CF_3-ynone **1a** and vinyl azide **2a** in situ generated the Staudinger−Meyer product **A**, which could be further applied in place of **2a** and PPh_3 under the standard reaction conditions, generating the target product **3aa** in 45% yield, indicating that the aza-Wittig cyclization process could also be possible in this transformation (Scheme 5b).[16g] Moreover, intermediates **B′** and **C′** were, respectively, isolated in 6 and 4% yields when shortening the reaction time to 30 min under the standard conditions (Scheme 5c).

On the basis of the above control experiments and previous reports,[14] a plausible mechanism for the copper-catalyzed trifluoromethylpyridine synthesis is illustrated in Scheme 6. First, the reaction of vinyl azide **2a** with PPh_3 generated vinyl iminophosphorane **A** via the Staudinger−Meyer reaction,[16] and the vinyl iminophosphorane intermediate **A** (HRMS: $[M + H]^+$ = 380.1565) could be detected in the reaction mixture using HRMS. Subsequently, **A** was trapped by electrophilic CF_3-ynone **1a** through copper-accelerated 1,4-addition to form intermediate **B**, which would further generate intermediate **C** and the corresponding resonance **D** in the presence of PPh_3 and a trace amount of H_2O from the reaction system. The 2,4-diaryl-6-trifluoromethylpyridine product **3aa** was finally generated through the cascade intramolecular cyclization and dehydration processes with the assistance of PMEDTA (path Ia). Moreover, an alternative pathway in which intermediate **B** directly underwent the intramolecular aza-Wittig process to afford the target product **3aa** was also possibly included in the transformation (path Ib).[16b,g]

Meanwhile, 1,2-addition from intermediate **A** and **1a** could arise as well to form the iminophosphorane **B′**, which further delivered intermediate **C′** and the corresponding resonance **D′**.[14h] Subsequently, the intramolecular hydroamination on the alkyne moiety led to the cyclic intermediate **D′** with the assistance of Cu(II) species, and the successive dehydration gave the final 2,6-diaryl-4-trifluoromethylpyridine compound **3′aa** as a side product (path II).

Scheme 5. Mechanistic Investigations



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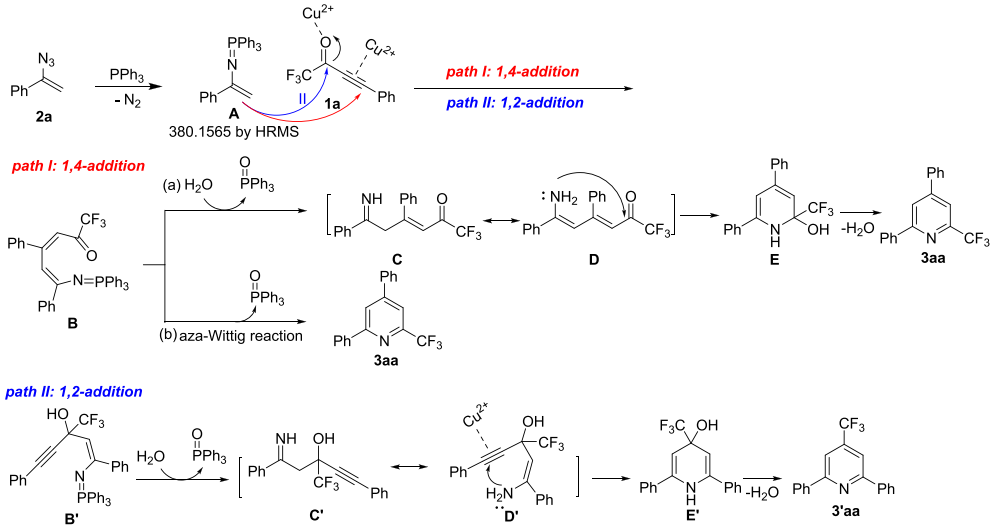
Scheme 6. Proposed Mechanism



CONCLUSION

In conclusion, we have described a copper-catalyzed regioselective cyclization reaction of CF_3-ynones with vinyl azides in combination with a Staudinger−Meyer process under mild reaction conditions. This novel catalytic system provides simple and convenient access to the versatile 2,4-diaryl-6-trifluoromethylpyridine core, which is hard to achieve through the previous protocols.

EXPERIMENTAL SECTION

General Information. All chemicals were obtained from commercial sources and were used as received unless otherwise noted. Melting points were determined in open glass capillaries and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-500 instrument (500 MHz). ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument (126 MHz) and were fully decoupled by broad band proton decoupling. ^{19}F NMR spectra were recorded on a Bruker DRX-500 instrument (471 MHz). NMR spectra were recorded in $CDCl_3$. ^{1}H NMR spectra were referenced to residual $CHCl_3$ at 7.26 ppm, and ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are reported in hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on an Agilent 1290 mass spectrometer using ESI-TOF (electrospray ionization time-of-flight). Column chromatography was performed on silica gel (70−230 mesh ASTM) using the reported eluents. Thin-layer chromatography (TLC) was carried out on 4 × 15 cm plates with a layer thickness of 0.2 mm (silica gel 60 F254). All CF_3-ynone and vinyl azide substrates are known compounds. CF_3-ynones (**1a**−**1l**)[20] and vinyl azides (**2a**−**2j**)[21] were synthesized according to the previously reported procedure.

Representative Procedure for the Synthesis of Products 3. A flame-dried Schlenk tube was charged with vinyl azide **2** (0.2 mmol, 1.0 equiv), PPh_3 (52.4 mg, 0.4 mmol, 2.0 equiv), and PhMe (0.5 mL) and was stirred at room temperature for 0.5 h. To the mixture were added $CuBr_2$ (4.5 mg, 0.02 mmol, 10 mol %), PMDETA (69.3 mg, 0.4 mmol, 2.0 equiv), and DMSO (0.5 mL), followed by slow addition of CF_3-ynone **1** (0.3 mmol, 1.5 equiv) under ice bath conditions. The resulting reaction mixture was stirred at room temperature for 12 h. When the reaction was completed, the resulting mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The organic layer was washed with brine (3 × 15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (PTLC) on silica gel with petroleum ether/ethyl acetate (v/v) afforded the corresponding product **3**.

*2,4-Diphenyl-6-(trifluoromethyl)pyridine (**3aa**).* The compound (36.0 mg, 60%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 89−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.0, 1.5 Hz, 2H), 7.89 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.54 (dd, J = 8.0, 1.5 Hz, 2H), 7.43−7.33 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.5, 151.0, 148.8 (q, $^2J_{C-F}$ = 34 Hz), 138.0, 137.4, 129.9, 129.8, 129.4, 128.9, 127.3, 127.2, 120.8, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 116.8 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N^+$ 300.0995, found 300.0999. The spectral data were in accordance with those reported in the literature.[10]

*2,6-Diphenyl-4-(trifluoromethyl)pyridine (**3′aa**).* The compound (3.5 mg, 6%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 63−64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.8, 1.5 Hz, 4H), 7.88 (s, 2H), 7.53 (dddd, J = 7.8, 7.2, 1.5 Hz, 4H), 7.48 (dd, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.2, 140.0 (q, $^2J_{C-F}$ = 33 Hz), 138.2, 129.8, 128.9, 127.1, 123.2 (q, $^1J_{C-F}$ = 273 Hz), 114.0 (q, $^3J_{C-F}$ = 4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −64.7 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N^+$ 300.0995, found 300.0998. The spectral data were in accordance with those reported in the literature.[11d]

*2-Phenyl-4-(p-tolyl)-6-(trifluoromethyl)pyridine (**3ba**).* The compound (33.1 mg, 53%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 84−86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.6, 1.5 Hz, 2H), 8.06 (s, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.52−7.43 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4, 150.9, 148.7 (q, $^2J_{C-F}$ = 34 Hz), 140.0, 138.1, 134.5, 130.0, 129.7, 128.9, 127.2, 127.0, 120.5, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 116.5 (q, $^3J_{C-F}$ = 3 Hz), 21.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3N^+$ 314.1151, found 314.1156.

*4-(4-Methoxyphenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3ca**).* The compound (33.1 mg, 50%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 93−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 2H), 8.01 (s, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.69 (dd, J = 7.8, 1.5 Hz, 2H), 7.55−7.43 (m, 3H), 7.02 (dd, J = 8.8, 1.8 Hz, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.1, 158.4, 150.4, 148.7 (q, $^2J_{C-F}$ = 34 Hz), 138.1, 131.4, 129.7, 128.9, 128.4, 127.2, 121.8 (q, $^1J_{C-F}$ = 275 Hz), 120.1, 116.2 (q, $^3J_{C-F}$ = 3 Hz),

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114.8, 55.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3NO^+$ 330.1100, found 330.1103.

4-(4-Fluorophenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3da**). The compound (29.3 mg, 46%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid; mp = 96−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.8, 1.5 Hz, 2H), 8.03 (s, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.71−7.67 (m, 2H), 7.55−7.44 (m, 3H), 7.23 (dd, J = 8.4, 1.8 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{C-F}$ = 246 Hz), 162.8 (d, $^5J_{C-F}$ = 2 Hz), 158.6, 149.9, 149.0 (q, $^2J_{C-F}$ = 34 Hz), 133.6 (d, $^4J_{C-F}$ = 3 Hz), 129.9, 129.0 (d, $^3J_{C-F}$ = 9 Hz), 128.9, 127.2, 121.7 (q, $^1J_{C-F}$ = 275 Hz), 120.6, 117.3 (q, $^3J_{C-F}$ = 3 Hz), 116.4 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s), −(111.2−111.3) (m); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{11}F_4Na^+$ 340.0720, found 340.0721.

4-(4-Chlorophenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3ea**). The compound (31.0 mg, 46%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.6 Hz, 2H), 8.03 (d, J = 1.4 Hz, 1H), 7.75 (d, J = 1.4 Hz, 1H), 7.63 (d, J = 8.4, 1.8 Hz, 2H), 7.53−7.46 (m, 5H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.6, 149.7, 148.9 (q, $^2J_{C-F}$ = 34 Hz), 137.7, 136.1, 135.8, 129.9, 129.6, 128.9, 128.4, 127.2, 121.7 (q, $^1J_{C-F}$ = 275 Hz), 120.5, 116.5 (d, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{12}ClF_3N^+$ 334.0605, found 334.0601.

2-Phenyl-6-(trifluoromethyl)-4-{4-(trifluoromethyl)phenyl}-pyridine (**3fa**). The compound (31.0 mg, 42%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 101−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, J = 6.7, 1.8 Hz, 2H), 8.07 (s, 1H), 7.80−7.79 (m, 5H), 7.54−7.44 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.8, 149.6, 149.0 (q, $^2J_{C-F}$ = 34 Hz), 141.0, 137.6, 131.7 (q, $^2J_{C-F}$ = 34 Hz), 130.1, 129.0, 127.7, 127.2, 126.3 (q, $^3J_{C-F}$ = 4 Hz), 124.0 (q, $^1J_{C-F}$ = 270 Hz), 121.5 (q, $^1J_{C-F}$ = 275 Hz), 120.9, 116.8 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.7 (s), −68.0 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{12}F_6N^+$ 368.0868, found 368.0864.

2-Phenyl-4-(m-tolyl)-6-(trifluoromethyl)pyridine (**3ga**). The compound (26.1 mg, 41%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 78−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.4 Hz, 2H), 7.86 (s, 1H), 7.58 (s, 1H), 7.52−7.42 (m, 3H), 7.39−7.29 (m, 3H), 7.26 (dd, J = 7.6 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4, 150.8, 148.7 (q, $^2J_{C-F}$ = 34 Hz), 140.0, 138.0, 137.5, 135.1, 134.4, 130.0, 129.7, 128.8, 127.2, 126.9, 120.5, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 116.4 (q, $^3J_{C-F}$ = 3 Hz), 21.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3N^+$ 314.1151, found 314.1149.

4-(3-Fluorophenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3ha**). The compound (29.2 mg, 46%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.9, 5.4 Hz, 2H), 8.02 (s, 1H), 7.79 (d, J = 1.4 Hz, 1H), 7.72−7.67 (m, 2H), 7.56−7.50 (m, 3H), 7.18 (dd, J = 8.6, 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.0 (d, $^1J_{C-F}$ = 246 Hz), 157.4, 151.2, 148.8 (q, $^2J_{C-F}$ = 34 Hz), 137.3, 134.1 (d, $^4J_{C-F}$ = 3 Hz), 129.8, 129.3, 129.1 (d, $^3J_{C-F}$ = 9 Hz), 127.1, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 120.4, 116.6 (q, $^3J_{C-F}$ = 3 Hz), 116.5 (d, $^4J_{C-F}$ = 3 Hz), 116.4 (d, $^2J_{C-F}$ = 22 Hz), 115.9 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s), −(109.6−115.0) (m); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{12}F_4N^+$ 318.0900, found 318.0905.

4-(3-Chlorophenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3ia**). The compound (30.0 mg, 45%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 50−52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.2, 1.8 Hz, 2H), 8.03 (s, 1H), 7.75 (d, J = 1.4 Hz, 1H), 7.67 (q, J = 1.3 Hz, 1H), 7.56 (qd, J = 4.0, 1.6 Hz, 1H), 7.53−7.45 (m, 5H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.7, 149.6, 148.9 (q, $^2J_{C-F}$ = 34 Hz), 139.2, 137.6, 135.4, 130.6, 130.0, 129.7, 128.9, 127.3, 127.2, 125.3, 120.7, 121.5 (q, $^1J_{C-F}$ = 275 Hz), 116.6 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{12}ClF_3N^+$ 334.0605, found 334.0608.

2-Phenyl-4-(o-tolyl)-6-(trifluoromethyl)pyridine (**3ja**). The compound (22.3 mg, 35%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 70−72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.6 Hz, 2H), 7.86 (s, 1H), 7.58 (d, J = 1.4 Hz, 1H), 7.53−7.42 (m, 3H), 7.39−7.29 (m, 3H), 7.26 (dd, J = 7.6, 1.4 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.8, 152.3, 148.2 (q, $^2J_{C-F}$ = 34 Hz), 138.3, 137.9, 135.0, 130.9, 129.8, 129.2, 129.0, 128.9, 127.2, 126.3, 123.3, 124.1 (q, $^1J_{C-F}$ = 275 Hz), 119.2 (q, $^3J_{C-F}$ = 3 Hz), 20.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3N^+$ 314.1151, found 314.1151.

4-(2-Fluorophenyl)-2-phenyl-6-(trifluoromethyl)pyridine (**3ka**). The compound (30.0 mg, 47%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 49−50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.6 Hz, 2H), 8.07 (s, 1H), 7.78 (s, 1H), 7.55−7.43 (m, 5H), 7.30 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.26−7.20 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8 (d, ^1J = 246 Hz), 158.2, 148.5 (q, $^2J_{C-F}$ = 34 Hz), 145.9, 137.8, 131.4 (d, $^3J_{C-F}$ = 9 Hz), 130.2 (d, $^4J_{C-F}$ = 3 Hz), 129.8, 128.9, 127.2, 125.5 (d, $^2J_{C-F}$ = 13 Hz), 125.0 (d, $^4J_{C-F}$ = 4 Hz), 122.8 (d, $^4J_{C-F}$ = 4 Hz), 121.7 (q, $^1J_{C-F}$ = 275 Hz), 118.5 (q, $^3J_{C-F}$ = 3 Hz), 116.6 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s), −(116.8−116.9) (m); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{12}F_4N^+$ 318.0900, found 318.0898.

2-Phenyl-4-(thiophen-2-yl)-6-(trifluoromethyl)pyridine (**3la**). The compound (27.2 mg, 45%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 102−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.8, 1.5 Hz, 2H), 8.02 (s, 1H), 7.76 (d, J = 1.4 Hz, 1H), 7.61 (dd, J = 3.7, 1.2 Hz, 1H), 7.54−7.44 (m, 4H), 7.18 (dd, J = 5.2, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.7, 149.0 (q, $^2J_{C-F}$ = 34 Hz), 143.9, 140.2, 137.8, 129.9, 128.9, 128.7, 128.1, 127.2, 126.3, 121.4 (q, $^1J_{C-F}$ = 275 Hz), 118.8, 114.9 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.1 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{11}F_3SN^+$ 306.0559, found 306.0560.

4-Phenyl-2-(p-tolyl)-6-(trifluoromethyl)pyridine (**3ab**). The compound (41.0 mg, 65%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid; mp = 89−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 1.4 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 1.4 Hz, 1H), 7.71−7.66 (m, 2H), 7.56−7.46 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.1, 158.4, 150.9, 148.6 (q, $^2J_{C-F}$ = 34 Hz), 140.0, 137.5, 135.2, 129.6, 129.6, 129.3, 127.1, 127.1, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 116.4 (q, $^3J_{C-F}$ = 3 Hz), 21.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3N^+$ 314.1151, found 314.1152.

2-(4-Methoxyphenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3ac**). The compound (30.2 mg, 45%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 92−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.8, 1.6 Hz, 2H), 8.01 (d, J = 1.4 Hz, 1H), 7.74 (d, J = 1.4 Hz, 1H), 7.69 (dd, J = 7.8, 1.5 Hz, 2H), 7.58−7.46 (m, 3H), 7.02 (dd, J = 8.8, 1.6 Hz, 2H), 3.87 (s, 3H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 161.1, 158.1, 150.8, 148.6 (q, $^2J_{C-F}$ = 34 Hz), 137.6, 130.5, 129.6, 129.3, 128.6, 127.1, 120.0, 121.1 (q, $^1J_{C-F}$ = 275 Hz), 116.1 (q, $^3J_{C-F}$ = 3 Hz), 114.2, 55.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{15}F_3NO^+$ 330.1100, found 330.1103.

2-(4-Fluorophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3ad**). The compound (25.3 mg, 40%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 98−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.95−7.84 (m, 3H), 7.69 (dd, J = 7.8, 1.4 Hz, 2H), 7.62−7.45 (m, 4H), 7.14 (dd, J = 8.4, 8.4, 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C-F}$ = 246 Hz), 157.0, 161.3, 148.8 (q, $^2J_{C-F}$ = 34 Hz), 140.2 (d, $^3J_{C-F}$ = 8 Hz), 137.2, 130.4 (d, $^3J_{C-F}$ = 8 Hz), 129.9, 129.4, 127.2, 122.7 (d, $^4J_{C-F}$ = 3 Hz), 121.7 (q, $^1J_{C-F}$ =

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275 Hz), 120.8, 117.3 (q, $^3J_{C-F}$ = 3 Hz), 116.7 (d, $^2J_{C-F}$ = 22 Hz), 114.3 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s), −(109.3−115.0) (m); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}F_4N^+$ 318.0900, found 318.0896.

*2-(4-Chlorophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3ae**).* The compound (28.2 mg, 42%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 91−92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 8.05 (s, 1H), 7.81 (d, J = 1.4 Hz, 1H), 7.70 (dd, J = 8.4, 1.5 Hz, 2H), 7.59−7.51 (m, 3H), 7.48 (d, J = 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.2, 151.3, 148.9 (q, $^2J_{C-F}$ = 34 Hz), 137.3, 136.3, 136.1, 129.8, 129.4, 129.1, 128.5, 127.1, 123.8 (d, $^1J_{C-F}$ = 275 Hz), 120.5, 117.0 (q, $^3J_{C-F}$ = 3.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}ClF_3N^+$ 334.0605, found 334.0606.

*2-(4-Bromophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3af**).* The compound (33.1 mg, 43%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 81−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.98 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 1.4 Hz, 1H), 7.68 (dd, J = 8.4, 1.6 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.57−7.47 (m, 3H); ^{13}C{^{1}H} (126 MHz, $CDCl_3$) δ 157.2, 151.2, 148.8 (q, $^2J_{C-F}$ = 34 Hz), 137.2, 136.7, 132.0, 129.8, 129.4, 128.7, 127.1, 124.4, 120.5, 121.4 (q, $^1J_{C-F}$ = 275 Hz), 117.0 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}BrF_3N^+$ 378.0100, found 378.0101.

*4-Phenyl-2-(m-tolyl)-6-(trifluoromethyl)pyridine (**3ag**).* The compound (25.9 mg, 41%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v) as a yellow solid: mp = 78−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 1.4 Hz, 1H), 7.92 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.70 (dd, J = 7.6, 1.6 Hz, 2H), 7.57−7.46 (m, 3H), 7.38 (dd, J = 7.6, 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.7, 150.9, 148.7 (q, $^2J_{C-F}$ = 34 Hz), 138.6, 138.0, 137.5, 130.6, 129.7, 129.3, 128.8, 127.9, 127.1, 124.4, 120.9, 121.7 (q, $^1J_{C-F}$ = 275 Hz), 116.7 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{15}F_3N^+$ 314.1151, found 314.1149.

*2-(3-Fluorophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3ah**).* The compound (23.4 mg, 37%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 74−75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.07 (m, 2H), 8.01 (s, 1H), 7.78 (d, J = 1.4 Hz, 1H), 7.68 (dd, J = 7.8, 1.6 Hz, 2H), 7.57−7.47 (m, 3H), 7.17 (ddd, J = 8.6, 8.6, 1.4 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{C-F}$ = 246 Hz), 157.4, 151.2, 148.8 (q, $^2J_{C-F}$ = 34. Hz), 137.3, 134.1 (d, $^4J_{C-F}$ = 3 Hz), 129.8, 129.3, 129.1 (d, $^3J_{C-F}$ = 9 Hz), 129.1 (d, $^3J_{C-F}$ = 9 Hz), 127.1, 121.7 (q, $^1J_{C-F}$ = 275 Hz), 120.4, 116.7 (q, $^3J_{C-F}$ = 3 Hz), 115.8 (d, $^2J_{C-F}$ = 22 Hz), 115.8 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s), −(111.5−111.6) (m); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}F_4N^+$ 318.0900, found 318.0900.

*2-(3-Chlorophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3ai**).* The compound (24.2 mg, 36%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 50−51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.06 (s, 1H), 7.99 (pd, J = 4.3, 1.7 Hz, 1H), 7.84 (d, J = 1.4 Hz, 1H), 7.71 (dd, J = 7.8, 1.4 Hz, 2H), 7.57−7.51 (m, 3H), 7.46−7.41 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.9, 151.3, 148.9 (q, $^2J_{C-F}$ = 35 Hz), 139.7, 137.1, 135.0, 130.1, 129.9, 129.8, 129.4, 127.4, 127.1, 125.3, 120.8, 121.6 (q, $^1J_{C-F}$ = 275 Hz), 117.3 (q, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −67.9 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{12}ClF_3N^+$ 334.0605, found 334.0607.

*2-(2-Fluorophenyl)-4-phenyl-6-(trifluoromethyl)pyridine (**3aj**).* The compound (27.4 mg, 43%) was prepared from the general procedure (ethyl acetate/petroleum ether = 1:300 → 1:80, v/v) as a yellow solid: mp = 90−92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14−8.08 (m, 2H), 8.03 (s, 1H), 7.80 (d, J = 1.4 Hz, 1H), 7.71 (dd, J = 7.5, 1.6 Hz, 2H), 7.57−7.50 (m, 3H), 7.20 (ddd, J = 7.6, 7.6, 2.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.0 (d, $^1J_{C-F}$ = 246 Hz), 157.4, 151.2, 148.8 (q, $^2J_{C-F}$ = 34 Hz), 137.3, 134.1 (d, $^4J_{C-F}$ = 3 Hz), 129.8, 129.4, 129.1 (d, $^3J_{C-F}$ = 9 Hz), 129.1 (d, $^3J_{C-F}$ = 9 Hz), 127.1, 121.7 (q, $^1J_{C-F}$ = 275 Hz), 120.5, 116.7 (q, $^3J_{C-F}$ = 3 Hz), 115.9 (d, $^2J_{C-F}$ = 22 Hz), 115.9 (d, $^2J_{C-F}$ = 22 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.0 (s), −(111.5−111.6) (m); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{11}F_4NNa^+$ 340.0720, found 340.0723.

Experiments with Scale-up Reaction (Scheme 4). A 50 mL round-bottom flask was charged with vinyl azide **2a** (1.02 g, 7.0 mmol, 1.0 equiv), PPh_3 (3.67 g, 14 mmol, 2.0 equiv), and PhMe (10 mL), and was stirred at room temperature for 0.5 h. To the mixture were added $CuBr_2$ (156.3 mg, 0.7 mmol, 10 mol %), PMDETA (2.43 g, 14 mmol, 2.0 equiv), and DMSO (10 mL), followed by slow addition of CF_3-ynone **1a** (2.08 g, 10.5 mmol, 1.5 equiv) under ice bath conditions. The resulting reaction mixture was stirred at room temperature for 12 h. When the reaction was completed, the resulting mixture was diluted with water (150 mL) and extracted with DCM (3 × 150 mL). The organic layer was washed with brine (3 × 150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v), affording the corresponding product **3aa** (0.84 g, 40%) as a yellow solid.

Experiments with Mechanistic Studies (Scheme 5a). A flame-dried Schlenk tube was charged with the assumptive intermediate **4**/**5**/**6**/**7** (0.2 mmol, 1.0 equiv), PPh_3 (52.4 mg, 0.4 mmol, 2.0 equiv), and PhMe (0.5 mL) and was stirred at room temperature for 0.5 h. To the mixture were added $CuBr_2$ (4.5 mg, 0.02 mmol, 10 mol %), PMDETA (69.3 mg, 0.4 mmol, 2.0 equiv), and DMSO (0.5 mL), followed by slow addition of CF_3-ynone **1a** (59.4 mg, 0.3 mmol, 1.5 equiv) under ice bath conditions. The resulting reaction mixture was stirred at room temperature for 12 h. No product was detected by TLC analysis (ethyl acetate/petroleum ether = 1:100, v/v).

Experiments with Mechanistic Studies (Scheme 5b). A flame-dried Schlenk tube was charged with the (1-azidovinyl)benzene **2a** (29.0 mg, 0.2 mmol, 1.0 equiv), PPh_3 (26.2 mg, 0.2 mmol, 1.0 equiv) and DCM (1.0 mL) and was stirred at room temperature for 0.5 h; the solvent was evaporated under reduced pressure. Subsequently, to the residue were added $CuBr_2$ (4.5 mg, 0.02 mmol, 10 mol %), PMDETA (69.3 mg, 0.4 mmol, 2.0 equiv), and DMSO/PhMe (1:1) = 1.0 mL, followed by slow addition of CF_3-ynone **1a** (59.4 mg, 0.3 mmol, 1.5 equiv) under ice bath conditions. The resulting reaction mixture was stirred at room temperature for 12 h. When the reaction was completed, the resulting mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The organic layer was washed with brine (3 × 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by PTLC on silica gel (ethyl acetate/petroleum ether = 1:300 → 1:100, v/v), affording the corresponding product **3aa** (26.9 mg, 45%) as a yellow solid.

Experiments with Mechanistic Studies (Scheme 5c). A flame-dried Schlenk tube was charged with vinyl azide **2a** (29.0 mg, 0.2 mmol, 1.0 equiv), PPh_3 (52.4 mg, 0.4 mmol, 2.0 equiv), and PhMe (0.5 mL) and was stirred at room temperature for 0.5 h. To the mixture were added $CuBr_2$ (4.5 mg, 0.02 mmol, 10 mol %), PMDETA (69.3 mg, 0.4 mmol, 2.0 equiv), and DMSO (0.5 mL), followed by slow addition of CF_3-ynone **1a** (59.4 mg, 0.3 mmol, 1.5 equiv) under ice bath conditions. The resulting reaction mixture was stirred at room temperature for 0.5 h. When the reaction was completed, the resulting mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The organic layer was washed with brine (3 × 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by PTLC on silica gel (ethyl acetate/petroleum ether = 1:300 → 1:100 → 1:30, v/v), affording **3aa** (13.8 mg, 23%) as a yellow solid, **B′** (7.0 mg, 6%) as a white solid, and **C′** (2.5 mg, 4%) as a yellow oil.

*(Z)-1,5-Diphenyl-3-(trifluoromethyl)-1-{(triphenyl-λ^5-phosphaneylidene)amino}pent-1-en-4-yn-3-ol (**B′**):* mp = 121−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.96 (br s, 1H), 7.57−7.49 (m, 6H), 7.49−7.40 (m, 5H), 7.36−7.23 (m, 9H), 6.93 (dd, J = 7.4, 7.4 Hz, 1H), 6.86 (d, J = 7.5 Hz, 2H), 6.77 (dd, J = 7.5, 7.5 Hz, 2H), 4.85 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.7 (d,

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J_{C-P} = 4 Hz), 141.5 (d, J_{C-P} = 6 Hz), 132.5 (d, J_{C-P} = 10 Hz), 131.9, 131.7 (d, J_{C-P} = 2 Hz), 130.1 (d, J_{C-P} = 101 Hz), 128.5 (d, J_{C-P} = 12 Hz), 128.3, 128.0, 127.9, 127.3, 126.8, 123.3 (q, $^{1}J_{C-F}$ = 287 Hz), 122.6, 104.0 (d, J_{C-P} = 17 Hz), 87.3, 84.4, 73.4 (q, $^{2}J_{C-F}$ = 33 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −81.9 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{36}H_{28}F_3NOP^+$ 578.1855, found 578.1961.

*5-Imino-1,5-diphenyl-3-(trifluoromethyl)pent-1-yn-3-ol (**C′**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 6.9 Hz, 2H), 7.65 (dd, J = 7.4, 7.4 Hz, 1H), 7.52 (dd, J = 7.8, 7.8 Hz, 2H), 7.39−7.28 (m, 3H), 7.30−7.23 (m, 2H), 5.47 (s, 1H), 3.81 (d, J = 16.7 Hz, 1H), 3.44 (d, J = 16.7 Hz, 1H), 1.62 (br s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.5, 136.3, 134.4, 132.0, 129.2, 128.9, 128.4, 128.2, 123.3 (q, $^{1}J_{C-F}$ = 284 Hz), 121.1, 86.8, 83.3, 70.6 (q, $^{2}J_{C-F}$ = 33 Hz), 41.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ −81.5 (s); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{15}F_3NO^+$ 318.1100, found 318.1100.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00275.

Complete tables on optimization of reaction conditions, ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra of **3aa**−**3la**, **3ab**−**3aj**, **B′**, and **C′**, and the crystallographic data of **3da** (PDF)

Accession Codes

CCDC 2045672 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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