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A dramatic enhancing effect of $InBr_3$ towards the oxidative Sonogashira cross-coupling reaction of 2-ethynylanilines†

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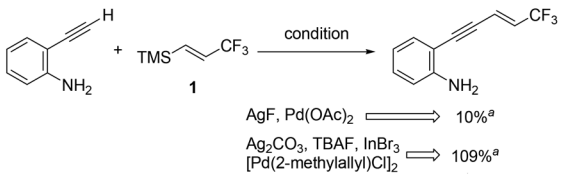
The addition of $InBr_3$ to the oxidative Sonogashira cross-coupling reaction of 2-ethynylaniline with (*E*)-trimethyl(3,3,3-trifluoroprop-1-enyl)silane led to a dramatic increase in the reactivity to afford the corresponding 1,3-enynes bearing a trifluoromethyl group on their terminal sp^2 carbon. The subsequent cyclization of these 1,3-enynes under palladium catalysis provides access to the corresponding indoles bearing a 3,3,3-trifluoroprop-1-enyl group at their 2-position.

Introduction

The Sonogashira cross-coupling reaction has been widely used as an effective method for the formation of carbon–carbon bonds in organic synthesis.[1] The importance of this reaction is exemplified by its regular use in agrochemical and pharmaceutical research, where it has featured as a key step in the construction of numerous natural products and biologically active compounds.[2–5] For example, the functionalized indole scaffolds of many important medicinal agents, such as the anticancer drug vinblastine and antiviral drug staurosporine,[6–8] are synthesized from functionalized 2-ethynylaniline derivatives, which are prepared by a Sonogashira cross-coupling reaction.[9–11] Considerable research interest has therefore been directed towards the development of efficient methods for the Sonogashira cross-coupling reaction to provide facile access to a broad range of enynes, which play a key role in the construction of other complicated compounds.[12–22]

We recently reported the oxidative Sonogashira cross-coupling reaction of (*E*)-trimethyl(3,3,3-trifluoroprop-1-enyl)silane (**1**) as an effective trifluoropropenylation reagent for the facile synthesis of 1,3-enynes bearing a trifluoromethyl group on their terminal sp^2 carbon.[23,24] However, the scope of this reaction was found to be limited in the sense that some substrates bearing an electron-withdrawing group or an nitrogen atom on their phenyl ring afforded poor yields of the corresponding 1,3-enynes. To successfully expand upon the scope of this transformation we need to identify new reaction conditions to overcome these issues. After screening a variety of different reaction conditions, we discovered that the addition of Ag_2CO_3 and $InBr_3$ to the reaction mixture led to a dramatic increase in the yield of the reaction (Scheme 1). Furthermore, the subsequent cyclization of the 2-ethynylaniline derivatives prepared in this way proceeded smoothly under palladium catalysis to afford the corresponding indole rings bearing a variety of different substituents. Herein, we describe the details of these reactions as well as highlight the broad scope of this process.



Scheme 1 Remarkable increase in the yield of 1,3-enyne containing the nitrogen atom. [a]NMR yield, which was calculated by the integration of the ^{19}F NMR signals relative to an ethyl trifluoroacetate standard.

Results and discussion

We initially examined the use of Ag_2CO_3 as a silver source instead of AgF, which can act as an oxidant towards the palladium catalyst (Table 1). Of the many different fluoride anion sources evaluated in the current study, TBAF provided the highest yield for the Sonogashira cross-coupling reaction of **2a** and **1**, with **3a** being isolated in 69% yield (Table 1, entries 2–4). Increasing the number of equivalents of TBAF added to the reaction led to an increase in the yield of the product (Table 1, entries 5 and 6). The use of $Pd(OAc)_2$, which was used as a catalyst in our previous report, led to a lower yield of the

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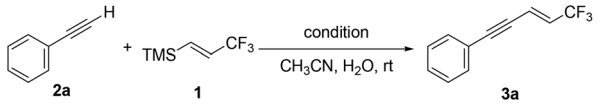
Table 1 Optimization of the reaction conditions using Ag_2CO_3 instead of AgF[a]



Entry	Condition	Yield[b] (%)
1[c]	AgF (5 eq.), **1** (4 eq.), $Pd(OAc)_2$ (5 mol%)	102 (93)[d]
2	CsF (6 eq.), **1** (4 eq.), Ag_2CO_3 (7.5 eq.) $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%)	0
3	TASF (6 eq.), **1** (4 eq.), Ag_2CO_3 (7.5 eq.) $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%)	24
4	TBAF (6 eq.), **1** (4 eq.), Ag_2CO_3 (7.5 eq.) $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%)	69
5	TBAF (7 eq.), **1** (4 eq.), Ag_2CO_3 (7.5 eq.) $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%)	89
6	TBAF (10 eq.), **1** (5 eq.), Ag_2CO_3 (5 eq.) $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%)	109 (82)[d]
7	TBAF (10 eq.), **1** (5 eq.), Ag_2CO_3 (5 eq.) $Pd(OAc)_2$ (4 mol%)	72

[a] These reactions were carried out in CH_3CN at room temperature. [b] NMR yields of **3a**, which were calculated by the integration of the ^{19}F NMR signals of **3a** relative to an ethyl trifluoroacetate standard. [c] Reaction performed without the addition of H_2O. [d] Isolated yield.

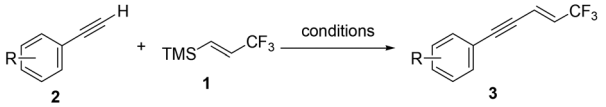
desired product compared with $[Pd(2\text{-methylallyl})Cl]_2$ (Table 1, entry 7).

With the optimum reaction conditions in hand we proceeded to investigate the scope of this transformation towards substrates bearing an electron-withdrawing group or aniline on their phenyl ring, especially those that did not react under our previously reported reaction conditions (Table 2). Pleasingly, considerable improvements were observed in the yield of **3** compared with our previous report for electron-deficient substrates, such as those bearing an acetyl or ester group (Table 2, entries 1 and 2). Disappointingly, however, application of the optimized reactions to nitrogen-containing substrates failed to afford similar increases in the yield. Further investigation is therefore required for these substrates to fully expand the reaction scope.

As shown in Table 2, the reaction conditions with Ag_2CO_3 produced **3b** in poor yield (Table 3, entry 1). Increasing the temperature of the reaction led to the rapid decomposition of the starting material (**2b**) to give a complex mixture (Table 3, entry 2). It is noteworthy, however, that the addition of $InBr_3$ (0.05 equivalents) led to the formation of **3b** with an improved yield of 48% (Table 3, entry 3). Further investigation of the number of equivalents of $InBr_3$ required for this reaction revealed that the optimum results were obtained using a single equivalent of this additive relative to **2b** (Table 3, entries 4–6). A variety of different Lewis acids were also examined under the same conditions, including $InCl_3$ and $BF_3{\cdot}Et_2O$, but they were all found to be ineffective for improving the yield of **3b** compared with $InBr_3$ (Table 3, entries 7 and 8). This result suggests that $InBr_3$ would act as a soft Lewis acid in the reaction mixture to accelerate the reaction, however, the reason for this improvement is not clear yet. To further evaluate the scope and limitations of this reaction, we selected the conditions described in entry 5 of Table 3 as the optimum reaction conditions.

The scope and limitations of our newly developed Sonogashira cross-coupling reaction with $InBr_3$ are summarized in Scheme 2. The results show that substrates bearing an electron-withdrawing or electron-donating group on their phenyl ring both reacted smoothly to give the desired 1,3-enynes bearing a trifluoromethyl group on their terminal sp^2 carbon in moderate to good yields (**3c–f**, **h–l** and **n**). On the other hand, substrates bearing a NO_2 group were rapidly decom-

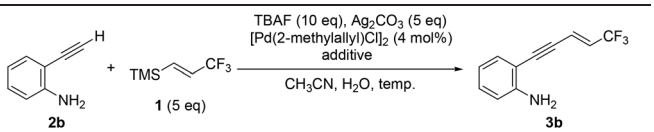
Table 2 The comparison with conditions of AgF and Ag_2CO_3



Entry	R =	Yield[a] Condition A	Condition B
1[b]	*p*-Ac	65	84
2[b]	*p*-EtOCO	55	99
3	*o*-NH_2	10	27
4	6-Quinoline	12	36

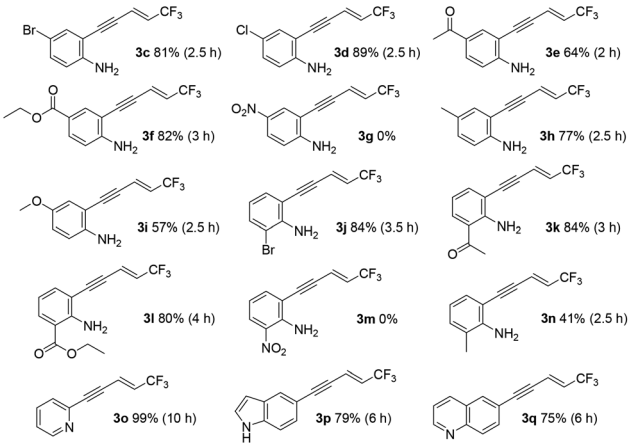
Condition A: AgF (5 eq.), **1** (4 eq.), $Pd(OAc)_2$ (5 mol%). Condition B: Ag_2CO_3 (5 eq.), TBAF (10 eq.), **1** (5 eq.), $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%). [a] NMR yields of **3**, which were calculated by integration of the ^{19}F NMR signals of **3** relative to an ethyl trifluoroacetate standard. [b] Isolated yields.

Table 3 Improvement of the reaction conditions in nitrogen-containing acetylene[a]

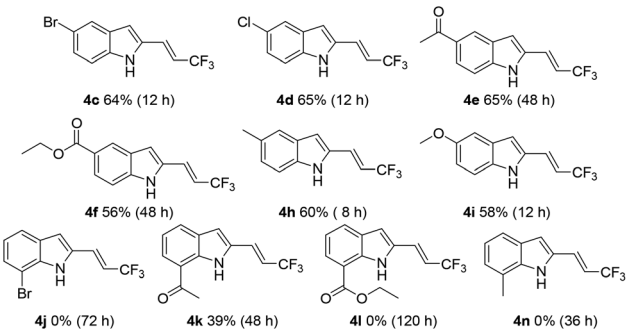


Entry	Additive[b] (eq.)	Temp. (°C)	Time (h)	Yield[c] (%)
1	—	rt	3	27
2	—	40	1	0
3	$InBr_3$ (0.05)	rt	4	48
4	$InBr_3$ (0.5)	rt	4	76
5	$InBr_3$ (1)	rt	4	90 (87)[d]
6	$InBr_3$ (1.5)	rt	4	44
7	$InCl_3$ (1)	rt	4	60
8	$BF_3{\cdot}Et_2O$ (1)	rt	11	Trace

[a] The reaction was carried out with **2b** (0.2 mmol), **1** (1.0 mmol), TBAF (2.0 mmol), Ag_2CO_3 (1.0 mmol) and $[Pd(2\text{-methylallyl})Cl]_2$ (4 mol%) in CH_3CN and H_2O. [b] The number of equivalents with respect to **2b** (0.2 mmol). [c] NMR yields of **3b**, which were calculated by the integration of the ^{19}F NMR signals of **3b** relative to an ethyl trifluoroacetate standard. [d] Isolated yield.



Scheme 2 The oxidative Sonogashira cross-coupling reaction with $InBr_3$. [a]These reactions were carried out with **2** (0.2 mmol), **1** (1.0 mmol), TBAF (2.0 mmol), Ag_2CO_3 (1.0 mmol), $InBr_3$ (0.2 mmol) and [Pd(2-methylallyl)Cl]$_2$ (4 mol%) in CH_3CN and H_2O at room temperature.



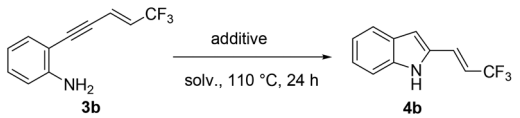
Scheme 3 The scope and limitation of the cyclization reaction. [a]These reactions were carried out with **4** (0.1 mmol) and Pd(OAc)$_2$ (10 mol%) in PhMe at 110 °C.

posed (**3g** and **m**). Acetylenes bearing a variety of different heterocycles, including a pyridine, indole or quinolone ring, also reacted smoothly to give the corresponding products, albeit after an extended reaction time (**3o–p**).

We then investigated the cyclization reaction of **3b** to give the corresponding indole ring bearing a 3,3,3-trifluoroprop-1-enyl group at its 2-position (Table 4). A variety of different additives were examined for this transformation, including Cu(OAc)$_2$, ^{t}BuLi and $InBr_3$, but they all provided low yields of **4b** (Table 4, entries 1–3).[25–28] The addition of $Pd(PPh_3)_2Cl_2$ led to an increase in the yield of indole **4b** to 37% (Table 4, entry 4). Based on this result, we investigated several palladium catalysts, including $Pd(PPh_3)_2Cl_2$, Pd(OAc)$_2$ and [Pd(2-methylallyl)Cl]$_2$. The results of these experiments revealed that Pd(OAc)$_2$ gave the highest yield of **4b** (Table 4, entries 4–6). We also screened several other solvents, including DMF, TBC and CH_3CN, but they all failed to provide an improvement in the yield of **4b** compared with PhMe (Table 4, entries 7–9). When the reaction was conducted at a lower concentration of 0.05 M, we observed a considerable increase in the yield of the desired product, albeit after a longer reaction time (Table 4, entry 10).

With the optimum reaction conditions in hand, we explored the scope and limitations of this cyclization reaction using the 1,3-enynes described above, which were prepared using our newly developed Sonogashira cross-coupling reaction (Scheme 3). The results revealed that the reaction proceeded well for substrates with an electron-withdrawing or electron-donating substituent at their 5-position to afford the corresponding indoles bearing a 3,3,3-trifluoroprop-1-enyl group at their 2-position in good yields (**4c–h**). In contrast, substrates with a substituent at their 7-position afforded the corresponding indole products in poor yields (**4j–l**, **n**). Substrates bearing the electron-withdrawing groups (**3j–k**) remained in the reaction mixture probably due to their steric hindrance, regardless of longer reaction time. Notably, the reaction of **3n** bearing a methyl group failed to provide the desired product **4n** with decomposition of the starting material.

Table 4 Optimization of the conditions for the cyclization reaction[a]



3b **4b**

Entry	Additive[b] (eq.)	Solv.	Yield[c] (%)
1	Cu(Ac)$_2$(1.0)	PhMe	16
2	^{t}BuOLi (1.0)	PhMe	0
3	$InBr_3$(1.0)	PhMe	14
4	$Pd(PPh_3)_2Cl_2$ (0.1)	PhMe	37
5	Pd(OAc)$_2$ (0.1)	PhMe	54
6	[Pd(2-methylallyl)Cl]$_2$ (0.1)	PhMe	42
7	Pd(OAc)$_2$ (0.1)	DMF	51
8	Pd(OAc)$_2$ (0.1)	TBC	39
9	Pd(OAc)$_2$ (0.1)	CH_3CN	26
10[d]	Pd(OAc)$_2$ (0.1)	PhMe	80[e]

[a] The reaction was carried out with **3b** (0.1 mmol) at 110 °C for 24 h. [b] The number of equivalents with respect to **3b** (0.1 mmol). [c] NMR yields of **4b**, which were calculated by the integration of the ^{19}F NMR signals of **3b** relative to an ethyl trifluoroacetate standard. [d] Reaction carried out at a concentration of 0.05 M. [e] Isolated yield.

Conclusions

In summary, we have found that the use of $InBr_3$ is effective for the oxidative Sonogashira cross-coupling reaction of 2-ethynylanilines with (*E*)-trimethyl(3,3,3-trifluoroprop-1-enyl)silane to provide improved yields of the corresponding 1,3-enyne systems from substrates bearing electron-withdrawing and nitrogen-containing groups. This work represents a significant improvement over our previous study using AgF as an additive, which was limited in terms of its application to substrates with electron-donating substituents. Most notably, the addition of $InBr_3$ led to a dramatic increase in the yield of the oxidative Sonogashira cross-coupling reaction with Ag_2CO_3,

and allowed the scope of this reaction to be broadly expanded to nitrogen-containing substrates. The subsequent cyclization of these products proceeded smoothly in the presence of a palladium catalyst to give the corresponding indoles bearing a 3,3,3-trifluoroprop-1-enyl group. A mechanistic study particularly on the effect of $InBr_3$ is now ongoing.

Experimental

General information

All commercially available reagents were used as received. Acetonitrile (CH_3CN) and *N*,*N*-dimethylformamide (DMF) were distilled over calcium hydride and stored in a bottle with activated molecular sieves (4 Å). The experiments of Sonogashira cross-coupling reaction were carried out under an argon atmosphere in a flame-dried glassware and used general inert techniques for introducing agents and solvents unless otherwise noted. The experiments of cyclization reaction were carried out under air.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at room temperature on JNM-GX400 and JNM-ECZ400S/L1 spectrometers. The ^{19}F NMR spectrum was recorded at room temperature on a Hitachi FT-NMR R-90H spectrometer. Chemical shifts of ^1H NMR and ^{13}C NMR are reported in parts per million (ppm) from an internal standard, tetramethylsilane (TMS, 0.00 pm) and $CHCl_3$ (77.0 ppm), respectively. Chemical shifts of ^{19}F NMR are reported in ppm from $CFCl_3$ (0.00 ppm) as an internal standard. All data are reported as follows; chemical shifts relative integration value, number of equivalent nuclei, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz). High-resolution mass spectroscopy (HRMS) experiments were performed with a double-focusing mass spectrometer with EI ionization on a JEOL JMS-700 T spectrometer. Melting points were measured on Yanagimoto micro melting point apparatus MP-S3.

Typical procedure for oxidative Sonogashira cross-coupling reaction

Under an argon atmosphere, a mixture of Ag_2CO_3 (276 mg, 1.0 mmol), $InBr_3$ (71 mg, 0.2 mmol) and $[Pd(2\text{-methylallyl})Cl]_2$ (3 mg, 4 mol%) in CH_3CN (1.0 mL) was added to TBAF (2.0 mL, 2.0 mmol) at room temperature. After stirring for 30 minutes at the same temperature, a solution of arylacetylenes **2** (0.2 mmol) and **1** (168 mg, 1.0 mmol) in CH_3CN (1.0 mL) was added to the reaction mixture. The resulting mixture was filtered off to remove the silver salts with Celite, and the filtrate was extracted with Et_2O and the organic layer was dried over anhydrous $MgSO_4$. After filtration of the solid, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide the corresponding 1,3-enynes **3** after a longer reaction time (Table 4, entry 10).

(*E*)-4-Bromo-2-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3c. The title product **3c** was obtained as a light yellow oil (47 mg, 81%) after column chromatography (AcOEt : hexane = 10 : 90). δ_H ($CDCl_3$, 400 MHz) 4.24 (2H, br s), 6.14 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.52 (1H, qd, *J* 2.3 Hz, 16.0 Hz), 6.59 (1H, d, J 8.7 Hz), 7.24 (1H, dd, *J* 2.3 Hz, 8.7 Hz), 7.4 (1H, d, *J* 2.3 Hz); δ_C ($CDCl_3$, 400 MHz) 90.3, 91.7, 108.1, 109.0, 116.0, 118.4 (q, *J* 7.7 Hz), 122.4 (q, *J* 269.7 Hz), 127.2 (q, *J* 33.7 Hz), 1337, 134.5, 147.2; δ_F ($CDCl_3$, 90 MHz) −65.73 (d, *J* 3.0 Hz); *m*/*z* (EI) 288.9705 (M^+. $C_{11}H_7BrF_3N$ requires 288.9714).

(*E*)-4-Chloro-2-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3d. The title product **3d** was obtained as a light yellow oil (44 mg, 89%) after column chromatography (AcOEt : hexane = 20 : 80). δ_H ($CDCl_3$, 400 MHz) 4.23 (2H, br s), 6.14 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.53 (1H, qd, *J* 2.3 Hz, 16.0 Hz), 6.64 (1H, d, *J* 8.7 Hz), 7.12 (1H, dd, *J* 2.3 Hz, 8.7 Hz), 7.26 (1H, d, *J* 2.7 Hz); δ_C ($CDCl_3$, 400 MHz) 91.2, 91.8, 107.5, 115.7, 118.4 (q, *J* 7.7 Hz), 122.3, 122.5 (q, *J* 269.7 Hz), 127.2 (q, *J* 33.7 Hz), 130.9, 131.6, 146.8; δ_F ($CDCl_3$, 90 MHz) −65.39 (d, *J* 6.0 Hz); *m*/*z* (EI) 245.0214 (M^+. $C_{11}H_7ClF_3N$ requires 245.0219).

(*E*)-1-(4-Amino-3-(5,5,5-trifluoropent-3-en-1-ynel)phenyl)-ethanone 3e. The title product **3e** was obtained as a light yellow solid (32 mg, 64%) after column chromatography (AcOEt : hexane = 40 : 60). Mp 103–104 °C; δ_H ($CDCl_3$, 400 MHz) 2.51 (3H, s), 4.71 (2H, br s), 6.17 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.54 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 6.71 (1H, d, *J* 8.7 Hz), 7.82 (1H, dd, *J* 1.8 Hz, 8.7 Hz), 7.95 (1H, d, *J* 1.8 Hz); δ_C ($CDCl_3$, 400 MHz) 26.0, 89.8, 91.9, 105.3, 113.6, 118.4 (q, *J* 7.7 Hz), 122.5 (q, *J* 269.7 Hz), 127.3 (q, *J* 34.7 Hz), 127.6, 131.4, 134.2, 151.9, 195.6; δ_F ($CDCl_3$, 90 MHz) −65.39 (d, *J* 6.0 Hz); *m*/*z* (EI) 253.0718 (M^+. $C_{13}H_{10}F_3NO$ requires 253.0714).

(*E*)-Ethyl 4-amino-3-(5,5,5-trifluoropent-3-en-1-ynel)benzoate 3f. The title product **3f** was obtained as a light yellow solid (46 mg, 82%) after column chromatography (AcOEt : hexane = 30 : 70). Mp 111–112 °C; δ_H ($CDCl_3$, 400 MHz) 1.37 (3H, t, *J* 7.3 Hz), 4.33 (2H, q, *J* 7.3 Hz), 4.63 (2H, br s), 6.16 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.54 (1H, qd, *J* 2.3 Hz, 16.0 Hz), 6.69 (1H, d, *J* 8.7 Hz), 7.85 (1H, dd, *J* 2.3 Hz, 8.7 Hz), 8.02 (1H, d, *J* 1.8 Hz); δ_C ($CDCl_3$, 400 MHz) 14.4, 60.6, 89.7, 92.1, 105.5, 113.5, 118.5 (q, *J* 7.7 Hz), 120.0, 122.5 (q, *J* 269.7 Hz), 127.1 (q, *J* 33.7 Hz), 132.5, 134.9, 151.6, 165.8; δ_F ($CDCl_3$, 90 MHz) −65.41 (d, *J* 6.0 Hz); *m*/*z* (EI) 283.0823 (M^+. $C_{14}H_{12}F_3NO_2$ requires 283.0820).

(*E*)-4-Methyl-2-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3h. The title product **3h** was obtained as a light yellow solid (35 mg, 77%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 45–46 °C; δ_H ($CDCl_3$, 400 MHz) 2.21 (3H, s), 4.09 (2H, br s), 6.10 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.54 (1H, qd, *J* 2.3 Hz, 16.0 Hz), 6.63 (1H, d, *J* 8.2 Hz), 6.99 (1H, d, *J* 8.2 Hz), 7.11 (1H, s); δ_C ($CDCl_3$, 400 MHz) 20.2, 89.3, 93.7, 106.3, 114.7, 118.9 (q, *J* 7.7 Hz), 122.6 (q, *J* 269.7 Hz), 126.3 (q, *J* 33.7 Hz), 127.3, 131.9, 132.5, 146.0; δ_F ($CDCl_3$, 90 MHz) −65.24 (d, *J* 6.0 Hz); *m*/*z* (EI) 225.0769 (M^+. $C_{12}H_{10}F_3N$ requires 225.0765).

(*E*)-4-Methoxy-2-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3i. The title product **3i** was obtained as a light yellow oil (27 mg, 57%) after column chromatography (AcOEt : hexane = 10 : 90). δ_H ($CDCl_3$, 400 MHz) 3.74 (3H, s), 3.96 (2H, br s), 6.14 (1H, qd, *J* 6.8 Hz, 15.9 Hz), 6.54 (1H, qd, *J* 2.3 Hz, 15.9 Hz), 6.64–6.68 (1H, m), 6.80–6.83 (2H, m); δ_C ($CDCl_3$,

400 MHz) 55.8, 89.4, 93.3, 106.8, 115.8, 116.1, 118.7 (q, *J* 7.8 Hz), 118.8, 122.6 (q, *J* 268.8 Hz), 126.5 (q, *J* 33.9 Hz), 142.5, 151.8; δ_F ($CDCl_3$, 90 MHz) −65.31 (d, *J* 5.0 Hz); *m*/*z* (EI) 241.0713 (M^+. $C_{12}H_{10}F_3NO$ requires 241.0714).

(*E*)-2-Bromo-6-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3j. The title product **3j** was obtained as a light yellow solid (49 mg, 84%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 38–39 °C; δ_H ($CDCl_3$, 400 MHz) 4.35 (2H, br s), 6.07 (1H, qd, *J* 6.9 Hz, 15.7 Hz), 6.56 (1H, qd, *J* 2.3 Hz, 15.7 Hz), 6.69 (1H, d, *J* 8.3 Hz), 7.22 (1H, dd, *J* 2.0 Hz, 8.3 Hz), 7.56 (1H, d, *J* 1.9 Hz); δ_C ($CDCl_3$, 400 MHz) 83.3, 96.0, 108.3, 112.2, 115.0, 119.1 (q, *J* 7.5 Hz), 122.8 (q, *J* 269.2 Hz), 126.2 (q, *J* 33.9 Hz), 132.4, 136.2, 145.4; δ_F ($CDCl_3$, 90 MHz) −65.22 (d, *J* 5.0 Hz); *m*/*z* (EI) 288.9708 (M^+. $C_{11}H_7BrF_3N$ requires 288.9714).

(*E*)-1-(2-Amino-3-(5,5,5-trifluoropent-3-en-1-ynel)phenyl)-ethanone 3k. The title product **3k** was obtained as a yellow solid (43 mg, 84%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 128–129 °C; δ_H ($CDCl_3$, 400 MHz) 2.58 (3H, s), 6.09 (1H, qd, *J* 6.8 Hz, 15.9 Hz), 6.48 (1H, qd, *J* 2.3 Hz, 15.9 Hz), 6.57 (2H, br s), 6.61 (1H, d, *J* 8.8 Hz), 7.34 (1H, qd, *J* 1.9 Hz, 8.8 Hz), 7.88 (1H, d, *J* 2.0 Hz); δ_C ($CDCl_3$, 400 MHz) 27.7, 82.6, 96.9, 108.6, 117.5, 117.9, 119.1 (q, *J* 7.5 Hz), 122.8 (q, *J* 269.2 Hz), 126.2 (q, *J* 34.2 Hz), 136.6, 137.2, 151.0, 200.3; δ_F ($CDCl_3$, 90 MHz) −65.15 (d, *J* 6.0 Hz); *m*/*z* (EI) 253.0709 (M^+. $C_{13}H_{10}F_3NO$ requires 253.0714).

(*E*)-Ethyl 2-amino-3-(5,5,5-trifluoropent-3-en-1-ynel)benzoate 3l. The title product **3l** was obtained as a light yellow solid (45 mg, 80%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 50–51 °C; δ_H ($CDCl_3$, 400 MHz) 1.40 (3H, t, *J* 7.3 Hz), 4.34 (2H, q, *J* 7.3 Hz), 6.03 (2H, br s), 6.07 (1H, qd, *J* 6.9 Hz, 15.6 Hz), 6.47 (1H, qd, *J* 2.3 Hz, 15.6 Hz), 6.61 (1H, d, *J* 8.2 Hz), 7.33 (1H, dd, *J* 2.3 Hz, 8.2 Hz), 8.03 (1H, d, *J* 2.3 Hz); δ_C ($CDCl_3$, 400 MHz) 60.7, 82.6, 97.0, 109.0, 110.8, 116.7, 119.2 (q, *J* 7.7 Hz), 122.8 (q, *J* 269.7 Hz), 125.8 (q, *J* 33.7 Hz), 135.8, 136.9, 151.0, 167.3; δ_F ($CDCl_3$, 90 MHz) −65.13 (d, *J* 2.3 Hz); *m*/*z* (EI) 283.0819 (M^+. $C_{14}H_{12}F_3NO_2$ requires 283.0820).

(*E*)-2-Methyl-2-(5,5,5-trifluoropent-3-en-1-ynel)benzenamine 3n. The title product **3n** was obtained as a light yellow solid (18 mg, 41%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 52–53 °C; δ_H ($CDCl_3$, 400 MHz) 2.14 (3H, s), 3.85 (2H, br s), 6.04 (1H, qd, *J* 6.9 Hz, 15.6 Hz), 6.47 (1H, qd, *J* 2.3 Hz, 15.6 Hz), 6.60 (1H, d, *J* 8.2 Hz), 7.15–7.18 (2H, m); δ_C ($CDCl_3$, 400 MHz) 17.1, 82.5, 98.1, 110.9, 114.4, 119.4 (q, *J* 7.7 Hz), 121.9, 122.9 (q, *J* 269.7 Hz), 125.3 (q, *J* 33.7 Hz), 131.2, 134.2, 146.0; δ_F ($CDCl_3$, 90 MHz) −65.02 (d, *J* 6.0 Hz); *m*/*z* (EI) 225.0770 (M^+. $C_{12}H_{10}F_3N$ requires 225.0765).

(*E*)-2-(5,5,5-Trifluoropent-3-en-1-ynel)pyridine 3o. The title product **3o** was obtained as a light yellow oil (39 mg, 99%) after column chromatography (AcOEt : hexane = 30 : 70). δ_H ($CDCl_3$, 400 MHz) 6.27 (1H, qd, *J* 6.6 Hz, 16.0 Hz), 6.53 (1H, qd, *J* 2.3 Hz, 16.0 Hz). 7.28–7.31 (1H, m), 7.49 (1H, d, *J* 7.8 Hz), 7.68–7.72 (1H, m), 8.64 (1H, d, *J* 4.4 Hz); δ_C ($CDCl_3$, 400 MHz) 83.2, 94.9, 118.1 (q, *J* 7.8 Hz), 122.2 (q, *J* 269.1 Hz), 123.6, 127.4, 129.0 (q, *J* 34.2 Hz), 136.2, 142.0, 150.3; δ_F ($CDCl_3$, 90 MHz) −65.47 (d, *J* 4.0 Hz); *m*/*z* (EI) 197.0448 (M^+. $C_{10}H_6F_3N$ requires 197.0452).

(*E*)-2-(5,5,5-Trifluoropent-3-en-1-ynel)-1*H*-indole 3p. The title product **3p** was obtained as a light yellow solid (37 mg, 79%) after column chromatography (AcOEt : hexane = 20 : 80). Mp 128–129 °C; δ_H ($CDCl_3$, 400 MHz) 6.12 (1H, qd, *J* 6.8 Hz, 15.6 Hz), 6.53 (1H, qd, *J* 2.3 Hz, 15.6 Hz), 6.56–6.57 (1H, m), 7.26–7.37 (3H, m), 7.82 (1H, s), 8.25 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 82.3, 98.6, 103.2, 111.2, 113.0, 119.4 (q, *J* 8.0 Hz), 122.8 (q, *J* 268.5 Hz), 125.3, 125.3, 125.7, 125.8 (q, *J* 33.8 Hz), 127.8, 136.0; δ_F ($CDCl_3$, 90 MHz) −65.11 (d, *J* 4.0 Hz); *m*/*z* (EI) 235.0608 (M^+. $C_{13}H_8F_3N$ requires 235.0609).

Cyclization reaction into indole ring[29]

A mixture of 1,3-enynes **3** (0.1 mmol) and $Pd(OAc)_2$ (2.2 mg, 10 mol%) in PhMe (2.0 mL) was stirred at 110 °C until starting materials disappeared. The reaction was quenched by the addition of water and the whole mixture was extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$ and the solid was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide the indoles **4**.

(*E*)-2-(3,3,3-Trifluoroprop-1-enyl)-1*H*-indole 4b. The title product **4b** was obtained as a white solid (17 mg, 80%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 133–134 °C; δ_H ($CDCl_3$, 400 MHz) 5.97 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.75 (1H, s), 7.13 (1H, td, *J* 0.9 Hz, 6.9 Hz), 7.16 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 7.26 (1H, ddd, *J* 0.9 Hz, 1.4 Hz, 8.2 Hz), 7.36 (1H, dd, *J* 0.9 Hz, 8.2 Hz), 7.61 (1H, d, *J* 8.2 Hz), 8.12 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 107.9, 111.0, 113.3 (q, *J* 34.5 Hz), 120.7, 121.4, 123.5 (q, *J* 267.9 Hz), 124.4, 128.0 (q, *J* 6.9 Hz), 128.2, 131.9, 137.4; δ_F ($CDCl_3$, 90 MHz) −65.72 (d, *J* 6.0 Hz); *m*/*z* (EI) 211.0614 (M^+. $C_{11}H_8F_3N$ requires 211.0609).

(*E*)-5-Bromo-2-(3,3,3-trifluoroprop-1-enyl)-1*H*-indole 4c. The title product **4c** was obtained as a light yellow solid (19 mg, 64%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 92–93 °C; δ_H ($CDCl_3$, 400 MHz) 6.01 (1H, qd, *J* 6.4 Hz, 16.0 Hz), 7.14 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 7.23 (1H, d, *J* 8.7 Hz), 7.34 (1H, dd, *J* 1.8 Hz, 8.7 Hz), 7.74 (1H, d, *J* 1.8 Hz), 8.18 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 106.9, 112.5, 113.9, 114.4 (q, *J* 34.7 Hz), 123.3 (q, *J* 268.8), 123.9, 127.3, 127.6 (q, *J* 6.7 Hz), 129.9, 133.0, 135.9; δ_F ($CDCl_3$, 90 MHz) −63.95 (d, *J* 5.0 Hz); *m*/*z* (EI) 288.9712 (M^+. $C_{11}H_7BrF_3N$ requires 288.9714).

(*E*)-5-Chloro-2-(3,3,3-trifluoroprop-1-enyl)-1*H*-indole 4d. The title product **4d** was obtained as a light yellow solid (18 mg, 73%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 84–86 °C; δ_H ($CDCl_3$, 400 MHz) 6.02 (1H, qd, *J* 6.4 Hz, 16.0 Hz), 6.68 (1H, s), 7.12–7.29 (3H, m), 7.58 (1H, s), 8.23 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 107.0, 112.1, 114.3 (q, *J* 34.7 Hz), 120.7, 123.3 (d, *J* 268.8 Hz), 124.8, 126.4, 127.7 (d, *J* 6.7 Hz), 129.3, 133.1, 135.7; δ_F ($CDCl_3$, 90 MHz) −63.98 (d, *J* 6.0 Hz); *m*/*z* (EI) 247.0215 (M^+. $C_{11}H_7ClF_3N$ requires 245.0219).

(*E*)-1-(2-(3,3,3-Trifluoroprop-1-enyl)-1*H*-indol-5-yl)ethanone 4e. The title product **4e** was obtained as a light yellow solid (16 mg, 65%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 219–220 °C; δ_H ($CDCl_3$, 400 MHz) 2.67 (3H, s), 6.07 (1H, qd, *J* 6.4 Hz, 16.0 Hz), 6.86 (1H, s), 7.19 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 7.40 (1H, d, *J* 8.7 Hz), 7.94 (1H, dd, *J* 1.4 Hz, 8.7 Hz),

8.29 (1H, d, *J* 1.8 Hz), 8.49 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 26.2, 108.1, 111.1, 114.4 (q, *J* 33.7 Hz), 123.2, 123.4, 123.6 (q, *J* 268.8 Hz), 127.7 (q, *J* 6.7 Hz), 127.3, 129.7, 134.1, 140.4, 197.8; δ_F ($CDCl_3$, 90 MHz) −63.64 (d, *J* 8.0 Hz); *m*/*z* (EI) 253.0714 (M^+. $C_{13}H_{10}F_3NO$ requires 253.0714).

(*E*)-Ethyl 2-(3,3,3-trifluoroprop-1-enyl)-1*H*-indol-5-carboxylate 4f. The title product **4f** was obtained as a light yellow solid (16 mg, 56%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 225–226 °C; δ_H ($CDCl_3$, 400 MHz) 1.44 (3H, t, *J* 7.3 Hz), 4.42 (2H, q, *J* 7.3 Hz), 6.06 (1H, qd, *J* 6.4 Hz, 16.0 Hz), 6.85 (1H, s), 7.20 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 7.39 (1H, d, *J* 8.7 Hz), 7.99 (1H, dd, *J* 1.4 Hz, 8.7 Hz), 8.40 (1H, s), 8.44 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 14.2, 60.3, 107.9, 110.8, 114.3 (q, *J* 33.7 Hz), 122.0, 123.6 (q, *J* 268.8 Hz), 123.8, 124.5, 127.3, 127.8 (q, *J* 6.7 Hz), 133.9, 140.2, 167.2; δ_F ($CDCl_3$, 90 MHz) −63.60 (d, *J* 6.0 Hz); *m*/*z* (EI) 283.0815 (M^+. $C_{14}H_{12}F_3NO_2$ requires 283.0820).

(*E*)-5-Methyl-2-(3,3,3-trifluoroprop-1-enyl)-1*H*-indole 4h. The title product **4h** was obtained as a light yellow solid (14 mg, 60%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 153–155 °C; δ_H ($CDCl_3$, 400 MHz) 2.43 (3H, s), 5.95 (1H, qd, *J* 6.4 Hz, 16.0 Hz), 6.67 (1H, s), 7.09 (1H, dd, *J* 1.4 Hz, 8.2 Hz), 7.14 (1H, qd, *J* 1.8 Hz, 16.0 Hz), 7.24 (1H, s), 7.39 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 21.4, 107.5, 110.7, 112.9 (q, *J* 34.7 Hz), 121.0, 123.6 (q, *J* 268.8 Hz), 126.2, 128.1 (q, *J* 6.7 Hz), 128.6, 130.1, 132.0, 135.8; δ_F ($CDCl_3$, 90 MHz) −67.50 (d, *J* 8.0 Hz); *m*/*z* (EI) 225.0772 (M^+. $C_{12}H_{10}F_3N$ requires 225.0765).

(*E*)-5-Methoxy-2-(3,3,3-trifluoroprop-1-enyl)-1*H*-indole 4i. The title product **4i** was obtained as a white solid (16 mg, 67%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 133–134 °C; δ_H ($CDCl_3$, 400 MHz) 3.85 (3H, s), 5.96 (1H, qd, *J* 6.5 Hz, 16.1 Hz), 6.67 (1H, s), 6.93 (1H, dd, *J* 2.4 Hz, 8.8 Hz), 7.04 (1H, d, *J* 2.4 Hz), 7.13 (1H, qd, *J* 2.0 Hz, 16.1 Hz), 7.24 (1H, d, *J* 8.4 Hz), 8.08 (1H, br s); δ_C ($CDCl_3$, 400 MHz) 55.6, 102.4, 107.5, 111.9, 113.1 (q, *J* 34.3 Hz), 115.3, 123.7 (q, *J* 268.6 Hz), 128.1 (q, *J* 7.2 Hz), 128.9, 132.6, 132.8, 154.9; δ_F ($CDCl_3$, 90 MHz) −65.68 (d, *J* 5.0 Hz); *m*/*z* (EI) 241.0719 (M^+. $C_{12}H_{10}F_3NO$ requires 241.0714).

(*E*)-1-(2-(3,3,3-Trifluoroprop-1-enyl)-1*H*-indol-7-yl)ethanone 4k. The title product **4k** was obtained as a light yellow solid (10 mg, 39%) after column chromatography (AcOEt : hexane = 10 : 90). Mp 128–129 °C; δ_H ($CDCl_3$, 400 MHz) 2.59 (3H, s), 6.08 (1H, qd, *J* 6.9 Hz, 16.0 Hz), 6.48 (1H, qd, *J* 2.3 Hz, 16.0 Hz), 6.56 (1H, br s), 6.61 (1H, d, *J* 8.7 Hz), 7.34 (1H, dd, *J* 2 Hz, 8.7 Hz), 7.87 (1H, d, *J* 1.4 Hz); δ_C ($CDCl_3$, 400 MHz) 27.6, 82.7, 96.8, 108.5, 117.4, 117.9, 119.1 (q, *J* 7.7 Hz), 122.7 (q, *J* 269.7 Hz), 125.9 (q, *J* 33.7 Hz), 136.5, 137.2, 150.8, 200.1; δ_F ($CDCl_3$, 90 MHz) −65.15 (d, *J* 6.0 Hz); *m*/*z* (EI) 253.0709 (M^+. $C_{13}H_{10}F_3NO$ requires 253.0714).

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