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One-pot synthesis of trifluoromethylated phthalans via intramolecular cyclization from 2-alkynylbenzaldehydes

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ABSTRACT

An efficient tandem addition/cyclization procedure for the synthesis of trifluoromethylated phthalans under mild conditions was developed. This procedure involves tetrabutylammonium fluoride (TBAF)-promoted addition of Ruppert–Prakash reagent ($TMSCF_3$) to 2-alkynylbenzaldehyde to give 2-alkynylbenzylicalcohols, which would then undergo base-catalyzed selective *5-exo-dig* cyclization to furnish the corresponding products.

1. Introduction

1,3-Dihydroisobenzofuran compounds (phthalans) have received much attention due to their important roles in both chemical and pharmaceutical industries.[1] During the past few decades, many studies have been reported on the synthesis of this important kind of heterocyclic compounds.[2] On the other hand, trifluoromethylated compounds have various important applications in material science and medicinal industry owing to the unique properties of the fluorine atom. Among the developed reagents for nucleophilic trifluoromethylation, the Ruppert–Prakash reagent $TMSCF_3$ is one of the most powerful, general and widely used (usually under catalysis by the fluoride anion or bases) for the introduction of a trifluoromethyl group (CF_3) into a variety of organic substrates, such as aldehydes,[3] hydrocarbon[4] and boronic acids.[5] To the best of our knowledge, there have been very few synthetic methods available for the preparation of CF_3-containing phthalans. In 2010, Olah and co-workers reported an efficient method for the synthesis of trifluoromethylated cyclic ethers via the Mitsunobu reaction.[6] Moreover, Gong et al. recently developed a novel synthetic route to trifluoromethylated phthalans by oxa-Michael reaction.[7] However, these methods suffered from either the availability of starting materials or limited reaction scopes. Our group have reported a highly efficient regio- and enantioselective synthesis of 1,3-dihydroisobenzofuran via a tandem addition/cyclization procedure from 2-alkynylbenzaldehydes.[8] Traditionally, TBAF is used not only as a reagent for the cleavage of silyl ethers,[9] but also as an effective promoter for the Michael-type reaction,[10] nucleophilic substitution,[11] addition reaction,[12] fluorination,[13] and the homo-coupling of arylhalides.[14] As the nucleophilic addition of the Ruppert–Prakash reagent $TMSCF_3$ to an aldehyde has been well documented, we reasoned that a similar cyclization of the intermediate alcohol adduct to provide trifluoromethylated phthalans should also be possible under appropriate conditions (Scheme 1). We reported herein the details of our research with this strategy, in which TBAF was found to be an efficient promoter for the cyclization step.

2. Result and discussion

2-Alkynylbenzaldehydes **1** were synthesized via Sonogashira coupling reaction according to literature reports.[15] The reaction of **1a** with $TMSCF_3$ was initially carried out with 10 mol % of Na_2CO_3 in DMF at room temperature for 1.0 h, and then 1.5 equiv of TBAF (1.0 M in THF) was added to the reaction mixture followed by heating at 55 °C for 5 h. We were pleased to find that the addition of $TMSCF_3$ to **1a** and the subsequent *5-exo-dig* cyclization to form the major product **2a** could be done in a one-pot fashion (Table 1, entry

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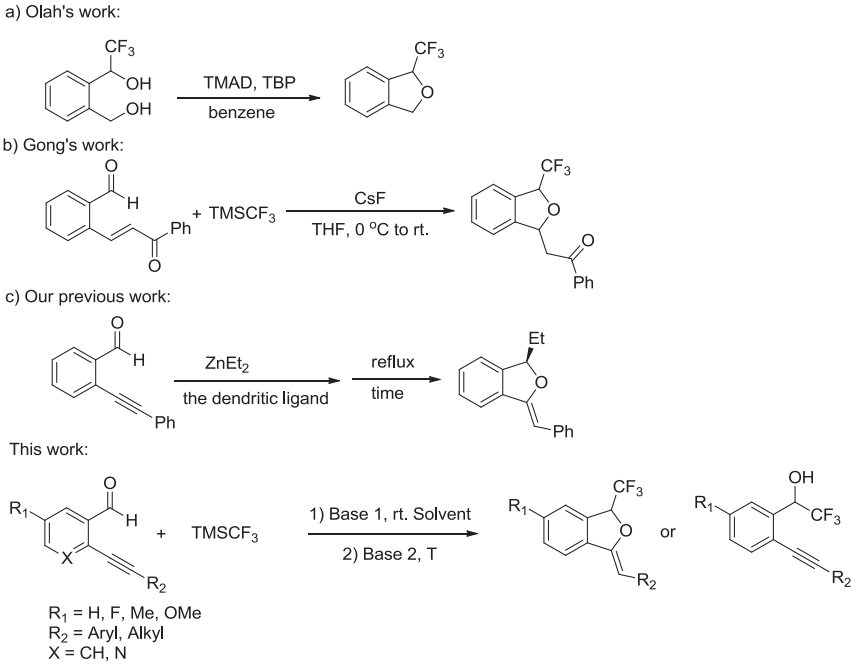
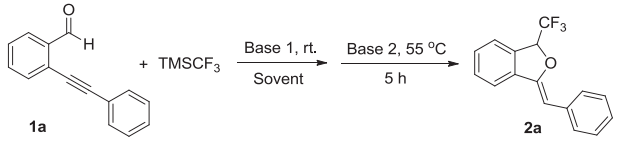


Scheme 1. A sampling of methods of trifluoromethylated phthalans.

Table 1
Optimization studies of the reaction of 2-alkynylbenzaldehyde with $TMSCF_3$[a]



Entry	Base 1 (mol %)	Time (h)	Base 2	Solvent	Yield (%)[b]
1	Na_2CO_3 (10)	1	TBAF	DMF	51
2	K_2CO_3 (10)	1	TBAF	DMF	58
3	Cs_2CO_3 (10)	0.2	TBAF	DMF	65
4	Cs_2CO_3 (10)	0.2	TBAF	THF	80
5	Cs_2CO_3 (10)	0.2	TBAF	Toluene	Trace[c]
6	Cs_2CO_3 (5)	0.2	TBAF	THF	81
7	NaH (10)	0.2	TBAF	THF	72
8	Cs_2CO_3 (5)	0.2	NaH	THF	70
9	Cs_2CO_3 (5)	0.2	*t*-BuOK	THF	—[d]
10	Cs_2CO_3 (10)	0.2	TBAF	THF	N.D.[e]

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), base 1, and $TMSCF_3$ (0.3 mmol) in the solvent (1.0 mL) and then base 2 (0.3 mmol) was added.
[b] Isolated yield of the major product **2a**.
[c] The intermediate α-trifluoromethylated alcohol was isolated as the major product.
[d] The reaction system was complicated.
[e] The cyclization step was run at rt for 8 h. N.D.=not detected.

1). The yield was improved to 65% when Cs_2CO_3 was used in the first addition step with a shortened reaction time (entry 3). The screen of solvents showed that the yield could be further improved to 80% when THF was used (entry 4). Pleasingly, the catalytic efficiency was not affected when the loading amount of Cs_2CO_3 was reduced to 5 mol % (entry 6). In contrast, when NaH or *t*-BuOK was used instead of TBAF in the cyclization step; inferior yields were obtained (entries 7–8). Moreover, an elevated reaction temperature for the cyclization step was necessary; when the reaction mixture after step 1 (the addition step) was stirred at room temperature for 8 h, formation of the product **2a** was not observed (Table 1, entry 10).

To explore the scope of the reaction, a range of differently substituted 2-alkynylbenzaldehyde were examined under the optimized conditions (Table 2). In most cases, the major *5-exo-dig* products **2** were formed in good to excellent yields. Substrates bearing electron-withdrawing groups on the benzene ring like **2b** and **2c** (Table 2, entries 2–3) provided higher yields than those with electron-donating groups (Table 2, entries 4–5). When R_2 was changed to a heterocyclic pyridyl group or thienyl groups, products (**2f**–**h**) were also obtained in over 90% yields (Table 2, entries 6–8). Moreover, 5-fluoro-2-(thiophen-2-ylethynyl)benzaldehyde (**1i**) also worked well to afford the corresponding product **2i** in a yield of 93% (Table 2, entry 9). When R_1 was changed to electron-donating groups, the products **2j** and **2k** were obtained in moderate yields (Table 2, entries 10–11). However, when R_2 was an alkyl group, only the addition product α-trifluoromethylated alcohols were obtained while the cyclization did not take place (Table 2, entries 13–14). The structure of the product **2h** was unambiguously confirmed by single crystal X-ray crystallographic analysis (Fig. 1). As an illustration of the utility of the reaction, the product **2g** was transformed to γ-trifluoromethylated phthalide **4** via oxidation with PCC, which represents an important structural motif found in many naturally occurring substances with biological activities[16] (Scheme 2).

We next made a preliminary exploration on the trifluoromethylation of 2-alkynylbenzimines[17] by using $TMSCF_3$. To our surprise the product isoindolines **7a** and **7b** were obtained in yields of 52% and 54%, respectively, at room temperature after 5 h via the tandem addition/cyclization reaction in the absence of TBAF (Scheme 3). The structure of the product **7a** was unambiguously confirmed by single crystal X-ray crystallographic analysis (Fig. 2). Further studies on the 2-alkynylbenzimine library and improving the yields are in progress and will be reported in the near future.

3. Conclusion

In summary, we have described an efficient one-pot synthesis of trifluoromethylated phthalans via a tandem nucleophilic

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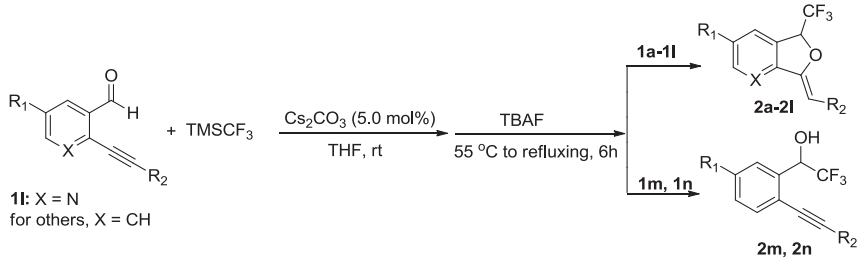
Table 2
The scope of the tandem reaction



Entry	Substrate	R_1	R_2	Product	Yield (%)[a]
1	**1a**	H	C_6H_5	**2a**	80
2	**1b**	H	4-FC_6H_4	**2b**	85
3	**1c**	H	4-ClC_6H_4	**2c**	82
4	**1d**	H	4-MeC_6H_4	**2d**	76
5	**1e**	H	4-$OMeC_6H_4$	**2e**	65
6	**1f**	H	3-Pyridyl	**2f**	93
7	**1g**	H	2-Thienyl	**2g**	88
8	**1h**	H	3-Thienyl	**2h**	90
9	**1i**	F	2-Thienyl	**2i**	93
10	**1j**	Me	2-Thienyl	**2j**	65
11	**1k**	OMe	2-Thienyl	**2k**	60
12	**1l**	H	2-Thienyl	**2l**	65
13	**1m**	H	$(CH_2)_5CH_3$	**2m**	97
14	**1n**	H	*t*-Bu	**2n**	98

[a] Yield of the isolated products after column chromatography.

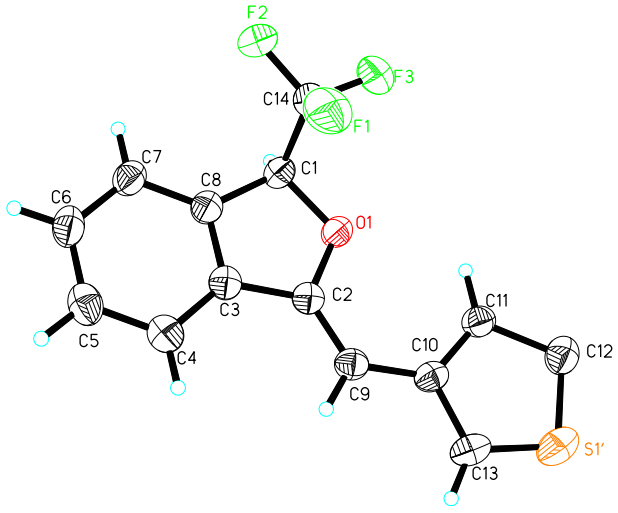


Fig. 1. X-ray crystal structure of product **2h**. (CCDC 925076).

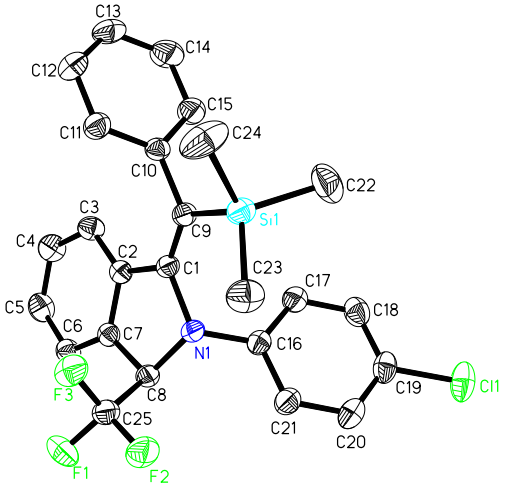
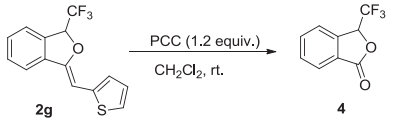
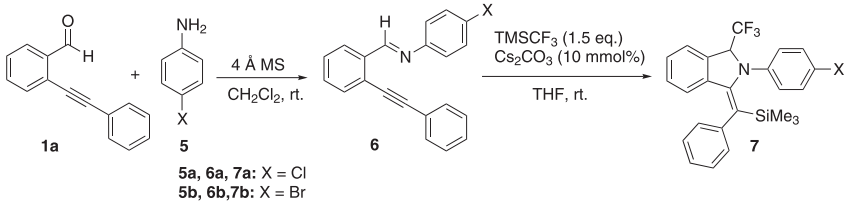


Fig. 2. X-ray crystal structure of product **7a**. (CCDC 925077).



Scheme 2. A transformation of **2g** to γ-trifluoromethylated phthalide **4**.

addition/intramolecular cyclization of 2-alkynylbenzaldehydes and $TMSCF_3$. The reaction features a highly selective *5-exo-dig* cyclization process, simple manipulation and mild reaction conditions, which provides an attractive strategy for pharmaceutical building blocks and medicinal chemistry applications. Current efforts are focused on the nucleophilic trifluoromethylation of 2-alkynylbenzimines.



Scheme 3. Trifluoromethylation of 2-alkynylbenzimines **6.**

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4. Experimental

4.1. General information

Commercial reagents were used as received without further purification. All solvents used were dried and purified by distillation. Melting points were measured on a Temp-Melt apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 or an Agilent AM-400 instrument with Me_4Si as the external standard. ^{19}F NMR spectra were recorded on a Bruker AM-300 or an Agilent AM-400 instrument with $CFCl_3$ as the internal standard. All chemical shifts (δ) were given in parts per million. Data were reported as follows: chemical shift, integration, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet) and coupling constants (Hertz). FTIR spectra were obtained with a Nicolet AV-360 spectrometer. Mass spectra were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT8430 instrument. Single crystal X-ray structure analysis was performed on a Bruker P4 instrument. All reactions were monitored by TLC or ^{19}F NMR.

4.2. Typical procedure for the tandem addition/intramolecular cyclization reaction of 2-alkynylbenzaldehyde and $TMSCF_3$

To a stirred solution of 2-alkynylbenzaldehyde (**1a**, 206.3 mg, 1.0 mmol) and anhydrous cesium carbonate (16.3 mg, 0.05 mmol) in anhydrous tetrahydrofuran (5.0 mL) under nitrogen was added $TMSCF_3$ (0.179 mL, 1.2 mmol). The resulting mixture was stirred at room temperature for 12 min. Then TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol) was added slowly to the solution, and then the mixture was heated at 55 °C for 5 h. At the end of the reaction monitored by TLC or ^{19}F NMR, the mixture was diluted with water (10 mL) and extracted with EtOAc (3×15 mL). The organic layers were washed with brine (2×20 mL), dried over sodium sulfate, and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/petroleum ether (1/20) to afford the target product **2a**. To a solution of **2g** (56.4 mg, 0.2 mmol) in 4 mL of CH_2Cl_2 was added PCC (1.2 equiv), and after being stirred for 2 h at room temperature, the mixture was filtered through Celite and concentrated. The crude product was purified by column chromatography (silica gel, 5% ethyl acetate in petroleum ether) yielding γ-trifluoromethylated phthalide **4** as colorless oil in 81% yield. The spectroscopic values were in good agreement with those reported in the literature:[16c,18] IR (KBr): 1793, 1602, 1468, 1362, 1294, 1267, 1140, 854, 750, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (q, J=5.6 Hz, 1H), 7.66–7.71 (m, 2H), 7.78–7.81 (m, 1H), 7.98 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.1 (q, $^2J_{C-C-F}$=35.7 Hz, C), 122.3 (q, $^1J_{C-F}$=278.7 Hz, CF_3), 123.5, 126.4, 131.2, 134.9; 140.6, 168.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.7 (d, J=6.8 Hz, 3F); MS (ESI): m/z=225.0 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_9H_5F_3O_2+H)^+$: 203.0320; found: 203.0310.

*4.2.1. (Z)-1-Benzylidene-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2a**).* Yield: 80%; White solid, mp 75–76 °C; IR (KBr): 2924, 1668, 1493, 1467, 1350, 1273, 1171, 1139, 1058, 904, 875, 819, 761, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (q, J=6.0 Hz, 1H), 6.01 (s, 1H), 7.01 (d, J=8.8 Hz, 1H), 7.35–7.61 (m, 5H), 7.78 (d, J=8.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.9 (d, J=5.2 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.5 (q, $^2J_{C-C-F}$=34 Hz, C), 99.04, 120.0, 122.9, 123.0 (q, $^1J_{C-F}$=280 Hz, CF_3), 126.3, 128.3, 128.4, 129.2, 130.1, 132.8, 135.0, 135.7, 153.8; MS-EI: m/z (%)=77, 89, 105, 132, 178, 207, 276 (100); HRMS-EI (m/z) calcd for $C_{16}H_{11}F_3O$: 276.0762, found: 276.0766.

*4.2.2. (Z)-1-(4-Fluorobenzylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2b**).* Yield: 85%; White solid, mp 72–73 °C; IR (KBr): 2926, 1670, 1602, 1467, 1350, 1269, 1234, 1199, 1173, 1135, 1057, 904, 843, 777, 756, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (q, J=6.0 Hz, 1H), 6.02 (s, 1H), 7.06 (t, J=8.8 Hz, 2H), 7.40–7.44 (m, 1H), 7.48–7.51 (m, 2H), 7.59 (d, J=8.0 Hz, 1H), 7.70–7.73 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −77.9 (d, J=5.9 Hz, 3F), −115.3 (m, 1F); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 81.2 (q, $^2J_{C-C-F}$=34 Hz, C), 97.5, 115.0, 115.2, 123.4 (q, $^1J_{C-F}$=279 Hz, CF_3), 129.5, 129.9, 130.0, 130.4, 131.8, 131.9, 133, 135, 153.6 (d, J=2.2 Hz), 159.9, 162.3; MS-EI: m/z (%)=98, 112, 147, 176, 196, 225, 294 (100); HRMS-EI (m/z) calcd for $C_{16}H_{10}F_4O$: 294.2436, found: 294.0667.

*4.2.3. (Z)-1-(4-Chlorobenzylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2c**).* Yield: 82%; White solid, mp: 109–110 °C; IR (KBr): 2925, 1669, 1491, 1467, 1355, 1289, 1263, 1189, 1170, 1131, 1087, 1013, 902, 840, 757, 680, 521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$). δ 5.85 (q, J=6.0 Hz, 1H), 5.98 (s, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.41–7.52 (m, 3H), 7.60 (d, J=8.0 Hz, 1H), 7.66 (d, J=8.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.9 (d, J=5.3 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.5 (q, $^2J_{C-C-F}$=34 Hz, C), 97.9, 120.1, 122.8, 122.9 (q, $^1J_{C-F}$=280 Hz, CF_3), 128.6, 129.4, 129.5, 130.2, 131.7, 132.9, 133.6, 135.4, 154.2; MS (EI): m/z (%)=55, 81, 91, 99, 178, 241, 255, 310 (100); HRMS-EI (m/z) calcd for $C_{16}H_{10}ClF_3O$: 310.0372, found: 310.0370.

*4.2.4. (Z)-1-(4-Methylbenzylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2d**).* Yield: 76%; yellow solid, mp 105–106 °C; IR (KBr): 2926, 1662, 1510, 1465, 1355, 1348, 1263, 1177, 1132, 1059, 878, 844, 762, 684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 5.82 (q, J=6.0 Hz, 1H), 6.01 (s, 1H), 7.16 (d, J=8.0 Hz, 2H), 7.38 (d, J=7.6 Hz, 1H), 7.44–7.47 (m, 2H), 7.56 (d, J=8.0 Hz, 1H), 7.62 (d, J=8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −78.0 (d, J=5.3 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 81.4 (q, $^2J_{C-C-F}$=34 Hz, C), 99.0, 120.0, 122.8, 123.1 (q, $^1J_{C-F}$=280 Hz, CF_3), 128.3, 129.0, 129.2, 130.1, 132.2, 132.8, 135.8, 136.1, 153.3; MS-EI: m/z(%)=77, 92, 110, 178, 221, 290 (100); HRMS-EI: m/z calcd for $C_{17}H_{13}F_3O$: 290.0918, found: 290.0922.

*4.2.5. (Z)-1-(4-Methoxybenzylidene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2e**).* Yield: 65%; Pale yellow solid, mp 69–70 °C; IR (KBr): 2934, 1664, 1604, 1512, 1465, 1252, 1176, 1135, 1056, 1035, 874, 840, 759, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), δ 3.84 (s, 3H), 5.84 (q, J=5.9 Hz, 1H), 6.01 (s, 1H), 6.92 (d, J=8.8 Hz, 2H), 7.39 (d, J=7.8 Hz, 1H), 7.46–7.49 (m, 2H), 7.57 (d, J=8.0 Hz, 1H), 7.69 (d, J=8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −78.0 (d, J=5.3 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.6, 81.0 (q, $^2J_{C-C-F}$=34 Hz, C), 98.6, 113.9, 120.0, 123.0, 123.1 (q, $^1J_{C-F}$=279 Hz, CF_3), 128.0, 129.0, 129.6, 130.3, 132.7, 135.8, 152.4, 158.1; MS-EI: m/z(%)=77, 108, 118, 153, 165, 178, 193, 237, 306 (100); HRMS-EI (m/z) calcd for $C_{17}H_{13}F_3O_2$: 306.0868, found: 306.0865.

*4.2.6. (Z)-3-((3-(Trifluoromethyl)isobenzofuran-1(3H)-ylidene)methyl)pyridine (**2f**).* Yield: 93%; White solid, mp 110–111 °C; IR (KBr): 2922, 1669, 1482, 1467, 1416, 1352, 1272, 1172, 1138, 1058, 759, 707, 684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (q, J=5.6 Hz, 1H), 6.00 (s, 1H), 7.28 (t, J=4.8 Hz, 1H), 7.43–7.62 (m, 4H), 7.63 (d, J=7.6 Hz, 1H), 8.16 (d, J=8.0 Hz, 1H), 8.41 (d, J=4.4 Hz, 1H), 8.80 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.9 (d, J=5.3 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.6 (q, $^2J_{C-C-F}$=34 Hz, C), 95.7, 120.1 (q, $^1J_{C-F}$=280 Hz, CF_3), 120.3, 122.9, 123.4, 129.8, 130.3, 131.2, 133.1, 134.7, 135.0, 146.9, 149.5, 155.7; MS-EI: m/z (%)=76, 103, 127, 152, 181, 208, 277 (100); HRMS-EI (m/z) calcd for $C_{15}H_{10}F_3NO$: 277.0714, found: 277.0718.

*4.2.7. (Z)-1-(Thiophen-2-ylmethylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2g**).* Yield: 88%; Pale yellow solid, mp 51–52 °C; IR (KBr): 2924, 1663, 1468, 1362, 1346, 1270, 1171, 1139,

1059, 903, 875, 851, 830, 756, 685, 649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.75 (q, J=5.9 Hz, 1H), 6.25 (s, 1H), 6.94 (t, J=4.0 Hz, 1H), 7.12 (d, J=4.0, 1H), 7.16 (d, J=4.0 Hz, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.35 (t, J=7.4 Hz, 2H), 7.43 (d, J=7.6 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −78.8 (d, J=5.6 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.5 (q, $^2J_{C-C-F}$=34 Hz, C), 93.5, 119.8, 123.0, 123.0 (q, $^1J_{C-F}$=280 Hz, CF_3), 124.9, 125.8, 127.1, 129.2, 130.2, 133.3, 134.8, 138.1, 152.4; MS-EI: m/z (%)=92, 141, 152, 184, 213, 253, 282 (100); HRMS-EI (m/z) calcd for $C_{14}H_9F_3OS$: 282.0326, found: 282.0325.

*4.2.8. (Z)-1-(Thiophen-3-ylmethylene)-3-(trifluoromethyl)-1,3-dihydroisobenzofuran (**2h**).* Yield: 90%; pale yellow solid, mp 55–56 °C; IR (KBr): 2925, 1787, 1671, 1467, 1363, 1267, 1138, 1060, 903, 875, 818, 772, 681, 638, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (q, J=5.6 Hz, 1H), 6.00 (s, 1H), 7.15 (m, 1H), 7.22 (d, J=7.7 Hz, 1H), 7.27–7.30 (m, 3H), 7.37 (d, J=7.6 Hz, 1H), 7.41 (d, J=2.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −77.9 (d, J=5.9 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.5 (q, $^2J_{C-C-F}$=34 Hz, C), 93.9, 119.9, 122.3, 123.0, 123.2 (q, $^1J_{C-F}$=280 Hz, CF_3), 125.1, 128.5, 129.1, 130.2, 133.1, 135.4, 135.8, 153.2; MS-EI: m/z (%)=92, 106, 141, 152, 169, 184, 213, 282 (100); HRMS-EI (m/z) calcd for $C_{14}H_9F_3OS$: 282.0326, found: 282.0323.

*4.2.9. (Z)-5-Fluoro-1-(thiophen-2-ylmethylene)-3-(trifluoromethyl)-1,3-dihydroisobenz-ofuran (**2i**).* Yield: 93%; White solid, mp 79–80 °C; IR (KBr): 2924, 1664, 1602, 1483, 1441, 1362, 1282, 1264, 1249, 1188, 1151, 1062, 854, 839, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (q, J=5.8 Hz, 1H), 6.28 (s, 1H), 7.02–7.04 (m, 1H), 7.17–7.22 (m, 3H), 7.45 (d, J=2.6 Hz, 1H), 7.51 (dd, J=4.64, 8.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −82.3 (d, J=5.2 Hz, 3F), −114.9; ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.0 (qd, $^2J_{C-C-F}$=34, 3.1 Hz, C), 93.3 (d, J=2.2 Hz), 110.4, 118.1, 118.3, 121.3, 121.4, 122.67 (q, $^1J_{C-F}$=280 Hz, CF_3), 124.9, 125.8, 127.0, 151.3, 161.9, 164.4; MS-EI: m/z (%)=75, 84, 101, 115, 159, 170, 202, 231, 271, 300 (100); HRMS-EI (m/z) calcd for $C_{14}H_8F_4OS$: 300.0232, found: 300.0230.

*4.2.10. (Z)-5-Methyl-1-(thiophen-2-ylmethylene)-3-(trifluoromethyl)-1,3-dihydroisobe-nzofuran (**1j**).* Yield: 65%; white solid, mp 79–80 °C; IR (KBr): 2926, 1661, 1488, 1366, 1343, 1282, 1272, 1237, 1196, 1162, 1151, 1140, 1057, 861, 805, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 5.83 (q, J=6.3 Hz, 1H), 6.30 (s, 1H), 7.04 (dd, J=3.6, 5.2 Hz, 1H), 7.20 (d, J=3.6 Hz, 1H), 7.25–7.29 (m, 3H), 7.44 (d, J=8.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −78.0 (d, J=6.3 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 81.4 (q, $^2J_{C-C-F}$=34 Hz, C), 92.6, 119.6, 123.0 (q, $^1J_{C-F}$=280 Hz, CF_3), 123.3, 124.5, 125.4, 127.0, 131.3, 132.2, 133.6, 138.2, 139.7, 152.5; MS-EI: m/z (%)=77, 84, 106, 115, 165, 184, 199, 227, 267, 296 (100); HRMS-EI (m/z) calcd for $C_{15}H_{11}F_3OS$: 296.0483, found: 296.0480.

*4.2.11. (Z)-5-Methoxy-1-(thiophen-2-ylmethylene)-3-(trifluoromethyl)-1,3-dihydroisob-enzofu-ran (**1k**).* Yield: 60%; white solid, mp 95–96 °C; IR (KBr): 2904, 1660, 1611, 1593, 1514, 1490, 1465, 1435, 1365, 1255, 1181, 1161, 1068, 1028, 848, 830, 690, 582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 5.82 (q, J=5.6 Hz, 1H), 6.21 (s, 1H), 6.95 (s, 1H) 7.01–7.04 (m, 2H), 7.16 (d, J=2.8 Hz, 1H), 7.22 (d, J=5.2 Hz, 1H), 7.45 (d, J=8.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.9 (d, J=5.6 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 81.2 (q, $^2J_{C-C-F}$=34 Hz, C), 91.7, 107.4, 117.4, 121.0, 122.9 (q, $^1J_{C-F}$=280 Hz, CF_3), 124.2, 125.0, 126.9, 127.3, 135.0, 138.3, 152.3, 160.9; MS-EI: m/z (%)=69, 75, 106, 121, 156, 171, 184, 200, 228, 243, 279, 312 (100); HRMS-EI (m/z) calcd for $C_{15}H_{11}F_3O_2S$: 312.0432, found: 312.0429.

*4.2.12. (Z)-7-(Thiophen-2-ylmethylene)-5-(trifluoromethyl)-5,7-dihydrofuro[3,4-b]pyri-dine (**2l**).* Yield: 65%; White solid, mp 102–103 °C; IR (KBr): 2923, 1667, 1588, 1472, 1416, 1345, 1277, 1171, 1140, 1052, 906, 859, 843, 789, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.91 (q, J=5.8 Hz, 1H), 6.83 (s, 1H), 7.05 (dd, J=3.7, 5.0 Hz, 1H), 7.27–7.32 (m, 3H), 7.78 (d, J=7.8 Hz, 1H), 8.69 (d, J=4.76, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −82.4 (d, J=5.2 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 80.0 (q, $^2J_{C-C-F}$=34 Hz, C), 95.5, 122.6 (q, $^1J_{C-F}$=280 Hz, CF_3), 122.9, 126.1, 127.2, 127.3, 131.2, 137.3, 149.8, 152.4, 153.6; MS-EI: m/z (%)=69, 115, 142, 154, 186, 214, 254, 283 (100); HRMS-EI (m/z) for $C_{13}H_8F_3NOS$: 283.0279, found: 283.0282.

*4.2.13. 2,2,2-Trifluoro-1-(2-(oct-1-yn-1-yl)phenyl)ethanol (**2m**).* Yield: 97%; Yellow liquid; IR (KBr): 3440, 1487, 1450, 1263, 1174, 1131, 1060, 882, 867, 828, 760, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J=6.8 Hz, 3H), 1.35 (m, 2H), 1.47 (m, 2H), 1.62 (m, 2H), 3.28 (d, J=3.9 Hz, 1H), 5.61 (m, 1H), 7.32–7.36 (m, 2H), 7.45–7.46 (m, 1H), 7.56 (d, J=6.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.7 (d, J=6.7 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 19.4, 22.5, 28.5, 28.6, 31.3, 70.7 (q, $^2J_{C-C-F}$=34 Hz, C), 77.6, 96.3, 123.7, 124.5 (q, $^1J_{C-F}$=280 Hz, CF_3), 127.3, 127.9, 129.0, 132.4, 135.3; MS-EI: m/z (%)=95, 115, 117, 129, 145, 197, 213, 237, 284 (100); HRMS-EI (m/z) for $C_{16}H_{19}F_3O$: 284.1388, found: 284.1387.

*4.2.14. 1-(2-(3,3-Dimethylbut-1-yn-1-yl)phenyl)-2,2,2-trifluoroethanol (**2n**).* Yield: 98%; White solid, mp 58–59 °C; IR (KBr): 3419, 1487, 1475, 1450, 1363, 1265, 1173, 1131, 1109, 1060, 832, 760, 701, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.54 (d, J=5.2 Hz, 1H), 5.58 (m, 1H), 7.30–7.33 (m, 2H), 7.42–7.45 (m, 2H), 7.56 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.7 (d, J=7.1 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 30.7, 70.9 (q, $^2J_{C-C-F}$=32 Hz, C), 76.2, 104.5, 123.5, 124.5 (q, $^1J_{C-F}$=281 Hz, CF_3), 127.4, 127.9, 128.9, 132.2, 135.3; MS-EI: m/z (%)=41, 77, 115, 128, 172, 183, 213, 223, 241, 256 (100); HRMS-EI (m/z) for $C_{14}H_{15}F_3O$: 256.1075, found: 256.1072.

4.3. General procedure for the synthesis of imines 6a–b

To a solution of **1a** (1.0 mmol) in CH_2Cl_2 (1.0 mL) were added the aromatic amine (1.0 mmol) and 4 Å MS (20 mg), and the mixture was stirred at room temperature for 12 h. The mixture was filtered and the solvent was removed under reduced pressure to give crude imine. Imine was used for next reaction though the recrystallization.

*4.3.1. 4-Chloro-N-(2-(phenylethynyl)benzylidene)aniline (**6a**).* Yield: 86%; Yellow solid, mp 102–103 °C; IR (KBr):1624, 1486, 1441, 1292, 1093, 1008, 909, 822, 756, 687, 671, 546; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19–7.22 (m, 2H), 7.37–7.39 (m, 5H), 7.44–7.47 (m, 2H), 7.52–7.55 (m, 2H), 7.61–7.63 (m, 1H), 8.24–8.26 (m, 1H); 9.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 86.2, 95.6, 122.4, 122.7, 125.2, 126.7, 128.6, 128.7, 128.8, 129.4, 131.1, 131.6, 131.7, 132.8, 136.4, 150.7, 159.2; MS (ESI): m/z=316.0 $(M+H)^+$. HRMS (ESI): m/z calcd for $(C_{21}H_{14}ClN+H)^+$: 316.0893; found: 316.0887.

*4.3.2. 4-Bromo-N-(2-(phenylethynyl)benzylidene)aniline (**6b**).* Yield: 85%; Yellow solid, mp 103–104 °C; IR (KBr): 1624, 1592, 1482, 1189, 1161, 1069, 1005, 972, 821, 750, 687, 657, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J=8.4 Hz, 2H), 7.37–7.39 (m, 3H), 7.43–7.49 (m, 2H), 7.52–7.54 (m, 4H), 7.62 (d, J=6.8 Hz, 1H), 8.26 (d, J=6.4 Hz, 1H); 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 86.2, 95.7, 119.6, 122.7, 122.8, 125.3, 126.7, 128.6, 128.7, 128.8, 131.2, 131.6, 132.3, 132.8, 136.5, 151.2, 159.3; MS (ESI): m/z=360.0 $(M+H)^+$. HRMS (ESI): m/z calcd for $(C_{21}H_{14}BrN+H)^+$: 360.0388; found: 360.0381.

4.4. Typical procedure for the tandem addition/intramolecular cyclization reaction of 2-alkynylbenzimine and $TMSCF_3$

To a stirred solution of 2-alkynylbenzimine (**6a**, 63.2 mg, 0.2 mmol) and anhydrous cesium carbonate (6.5 mg, 0.02 mmol) in

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anhydrous tetrahydrofuran (2.0 mL) under nitrogen was added $TMSCF_3$ (0.179 mL, 1.2 mmol). The resulting mixture was stirred at room temperature for 5 h. At the end of the reaction monitored by TLC or ^{19}F NMR, the mixture was diluted with water (10 mL) and extracted with Et_2O (3×10 mL). The organic layers were washed with brine (2×20 mL), dried over sodium sulfate, and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with petroleum ether to afford the product **7a**.

*4.4.1. (Z)-2-(4-Chlorophenyl)-1-(phenyl(trimethylsilyl)methylene)-3-(trifluoromethyl)is-oindoline (**7a**).* Yield: 52%; yellow solid, mp 116–117 °C; IR (KBr): 1604, 1586, 1491, 1346, 1262, 1164, 1123, 859, 837, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ −0.15 (s, 9H), 4.76 (q, J=6.8 Hz, 1H), 6.07 (d, J=7.6 Hz, 1H), 6.97–7.01 (m, 2H), 7.19–7.23 (m, 2H), 7.26–7.38 (m, 7H), 7.45–7.49 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J=6.8 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.1, 71.8 (q, $^2J_{C-C-F}$=31 Hz, C), 122.8, 124.0, 124.8, 125.1 (q, $^1J_{C-F}$=280 Hz, CF_3), 126.3, 127.9, 128.2, 128.5, 128.7, 128.8, 128.9, 129.0, 129.4, 134.3, 138.4, 141.9, 149.9, 150.4; MS-EI: m/z (%)=45, 73, 91, 139, 203, 280, 314, 364, 388, 442, 457 (100); HRMS-EI (m/z) for $C_{25}H_{23}ClF_3NSi$: 457.1240, found: 457.1241.

*4.4.2. (Z)-2-(4-Bromophenyl)-1-(phenyl(trimethylsilyl)methylene)-3-(trifluoromethyl)is-oindoline (**7b**).* Yield: 54%; yellow solid, mp 129–130 °C; IR (KBr): 1609, 1583, 1487, 1464, 1355, 1268, 1160, 1127, 1006, 932, 860, 838, 710, 635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ −0.15 (s, 9H), 4.76 (q, J=6.8 Hz, 1H), 6.06 (d, J=8.0 Hz, 1H), 6.97–7.01 (m, 2H), 7.18–7.27 (m, 4H), 7.32–7.37 (m, 3H), 7.42–7.48 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J=6.8 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.1, 71.7 (q, $^2J_{C-C-F}$=31 Hz, C), 115.7, 123.0, 123.9, 124.8, 125.1 (q, $^1J_{C-F}$=280 Hz, CF_3), 126.3, 127.9, 128.5, 128.7, 128.8, 130.3, 132.3, 134.2, 138.3, 141.9, 149.7, 150.8; MS-EI: m/z (%)=59, 73, 91, 139, 204, 280, 349, 360, 390, 410, 434, 488, 503 (100); HRMS-EI (m/z) for $C_{25}H_{23}BrF_3NSi$: 501.0735, found: 501.0734.

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Supplementary data

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