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PAPER

A detailed study of the intramolecular hydroamination of *N*-(*ortho*-alkynyl)aryl-*N′*-substituted trifluoroacetamidines and bromodifluoroacetamidines†

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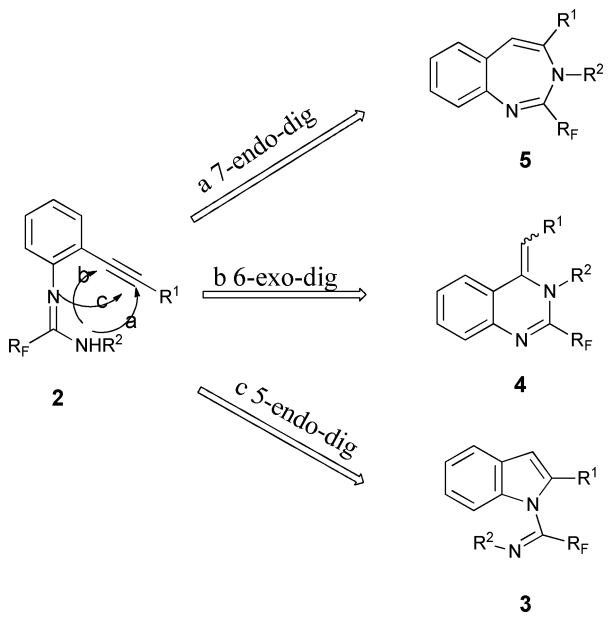
The intramolecular hydroamination of *N*-(*ortho*-alkynyl)aryl-*N′*-substituted trifluoroacetamidines and bromodifluoroacetamidines is studied in detail. When the substituents on the alkyne fragment are aryl and alkyl groups, 5-*endo-dig* cyclization occurs utilizing $NaAuCl_4 \cdot 2H_2O$ as a catalyst, while 6-*exo-dig* cyclization proceeds in the presence of K_2CO_3 as a base. Interestingly, the indole derivatives are afforded with good regioselectivity *via* a 5-*endo-dig* pathway catalyzed by $Cu(OAc)_2$ when *ortho*-ethynyl appears on the aryl substituent of the amidine. The electrophilic cyclization of the amidines also shows good regioselectivity under the $I_2/NaHCO_3$ system. At the end, a facile cascade synthesis of fluorinated quinazolones is described *via* hydroamination/ozonolysis from the corresponding amidine.

Introduction

The addition of a heteroatom–hydrogen bond across an unsaturated carbon–carbon bond is one of the most interesting and intriguing subjects in organic synthesis, which can be performed with 100% atom efficiency.[1] In particular, the intramolecular addition of alkynes toward heterocycles is a useful synthetic protocol when the heteroatom nucleophile is in close proximity to the triple bond.[2] Over the past few years, the intramolecular annulations of amines, amides, imines, carboxylic acids, alcohols, phenols, esters, nitriles and phosphonic acid derivatives have been developed,[3] catalyzed by transition metal complexes, Lewis acids and bases.[4] The orientation of the reaction depends on the nature of the substituents on the alkyne, the nucleophile and catalyst. Since many reports have been focused on the synthesis of indoles from 2-ethynylaniline derivatives,[5] we predicted that *N*-(*ortho*-alkynylaryl)amidine could serve as a good research object for extending the intramolecular hydroamination substrates. As shown in Scheme 1, the cyclization of the amidine **2** could potentially give three products *via* different pathways in theory.[6] If so, we could get many fluorinated azaheterocycles which are frequently found in pharmaceuticals, drug candidates and other molecular functional materials. During our research on the hydroamination of amidines, Ding and co-workers have developed a mild and efficient synthesis of indole *N*-carboximidamides and *N*-carboximidoates by Ag(I)-catalyzed regioselective intramolecular cyclization of (2-alkynylphenyl)guanidine or (2-alkynylphenyl)-isourea.[7] Herein we would like to disclose our preliminary results on the intramolecular hydroamination of fluorinated *N*-(*ortho*-alkynylaryl)amidines under different conditions including Lewis acids, base and iodine.



Scheme 1 The different reaction pathways of the amidine **2**.

Results and discussion

The synthesis of the substrates **2** for cyclization was straightforward (Scheme 2).[8] For example, the model substrate **2a** was prepared by the treatment of benzylamine with

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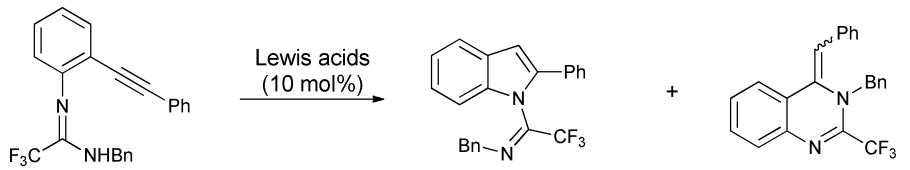
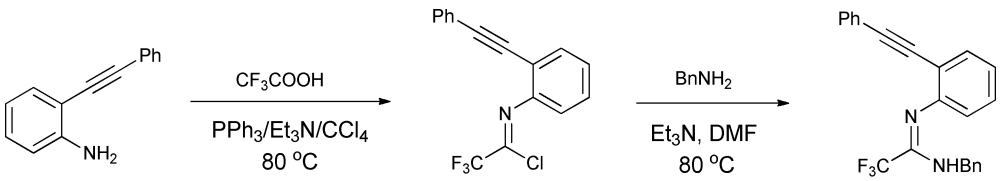
Table 1 Optimization of the cyclization by various Lewis acids[a]



2a **3a** **4a**

Entry	Catalyst	Solvent	T/°C	Time (h)	Conversion[b]	**3a** : **4a**[c]
1	CuI	DMF	80	2	35	5 : 1
2	CuI	CH_3CN	80	2	20	1 : 1
3	$CuSO_4$	DMF	80	2	—	
4	$Cu(OAc)_2$	DMF	80	3	—	
5	$AgNO_3$	CH_3CN	80	2	100	1 : 1
6	$AgNO_3$	DMF	80	2	100	2 : 1
7	Ag_2SO_4	CH_3CN	80	2	17	1 : 1
8	AgOAc	CH_3CN	80	1	100	1.6 : 1
9	$AgBF_4$	DMF	80	1	100	1.2 : 1
10	$AgClO_4$	DMF	80	1	100	1.4 : 1
11	$AgOOCCF_3$	DMF	80	1	100	2.3 : 1
12	AgOTf	DMF	80	1	100	1.2 : 1
13	$NaAuCl_4{\cdot}2H_2O$	toluene	80	0.5	100	>95 : 5
14	$NaAuCl_4{\cdot}2H_2O$	toluene	rt	1	100	>95 : 5
15[d]	$NaAuCl_4{\cdot}2H_2O$	toluene	rt	1	100[e]	>95 : 5
16	$NaAuCl_4{\cdot}2H_2O$	CH_2Cl_2	rt	1	100	>95 : 5
17	$NaAuCl_4{\cdot}2H_2O$	CH_3CN	80	2	100	>95 : 5
18	$NaAuCl_4{\cdot}2H_2O$	THF	70	2	100	>95 : 5

[a] Reaction conditions: **2a** (0.2 mmol), catalyst (10 mol%), solvent (2 mL). [b] The conversion was determined by ^{19}F NMR analysis with trifluoromethylbenzene as internal standard. [c] The ratio of the products **3a** and **4a** was also observed from ^{19}F NMR spectroscopy. [d] $NaAuCl_4{\cdot}2H_2O$ (5 mol%). [e] The isolated yield was 96%.



1a **2a**

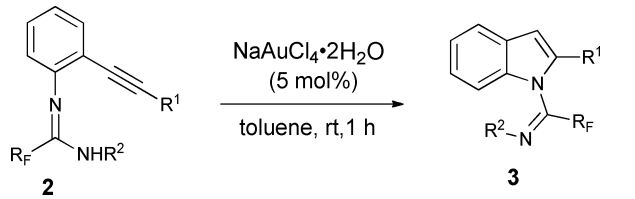
Scheme 2 Representative synthesis of the substrate **2a**.

N-(*ortho*-phenylethynyl)phenyl trifluoroacetimidoyl chloride **1a**, which was synthesized by one-pot reaction of 2-(phenylethynyl)aniline with trifluoroacetic acid under Uneyama's conditions.[8a]

With the model substrate **2a** in hand, we decided to screen various Lewis acids considered to have the high reactivities towards the hydroamination reactions (Table 1). The substrate **2a** was converted to the cyclized products **3a** and **4a** with a modest yield using CuI as the catalyst, whereas $Cu(OAc)_2$ and $CuSO_4$ were inactive (Table 1, entries 1–4). Silver salts except for Ag_2SO_4 generally showed good activities, but the ratio of the products **3a** and **4a** was ranging from 1 : 1 to 2.3 : 1 depending on their counteranions (Table 1, entries 5–12). Much to our delight, the hydroamination reaction took place efficiently with excellent regioselectivity in the presence of $NaAuCl_4{\cdot}2H_2O$ in toluene at 80 °C for 30 min. Indole derivative **3a** was the only detectable product in the reaction system by ^{19}F NMR spectroscopy. After further studies of reaction conditions, we found out that the reaction went to completion using 5 mol% $NaAuCl_4{\cdot}2H_2O$ in toluene at room temperature for 1 h and the product **3a** was isolated in 96% yield (Table 1, entry 15).

With this optimized reaction condition, a series of *N*-(*ortho*-alkynyl)phenyl-*N*′-substituted bromodifluoro-acetamidines as well as trifluoroacetamidines were synthesized using the procedure described above to investigate the scope of this reaction. *N*′-Substituent groups (R^2) such as alkyls (Table 2, entries 1, 3, 4, 8, 10–13, 15 and 17) and aryls bearing either electron-withdrawing or electron-donating substitution (Table 2, entries 5–7, 9, 14 and 16) behaved the same and proceeded nicely for this transformation. Notably, the hydroamination of *N*-(*ortho*-phenylethynyl)phenyltrifluoroacetamidine **2b** led to the corresponding indole **3b** in an acceptable 73% yield. In addition, compounds with alkyl and functionalised aryl substituents (R^1) on the acetylene terminal were also tested and the corresponding indole products could also be obtained in high yields (Table 2, entries 8–9 and 15–17). An X-ray crystal analysis confirmed the structure of the indole **3j** in (*Z*)-imino form (Table 2, entry 10). Incidentally, when the terminal substituent was H, regioisomers **3r** and **4r** were formed

Table 2 Gold-catalyzed intramolecular hydroamination of the amidines **2**[a]

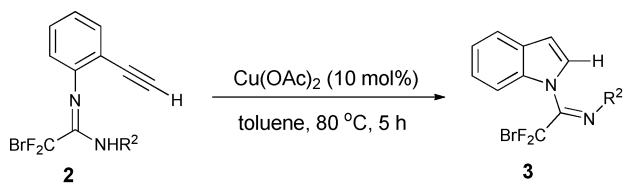


Entry	R_F	R^1	R^2	Yield (%)[b]
1	CF_3	Ph	Bn	**3a**/96
2	CF_3	Ph	H	**3b**/73
3	CF_3	Ph	Me	**3c**/90
4	CF_3	Ph	Cyclohexyl	**3d**/87
5	CF_3	Ph	*p*-$OMeC_6H_4$	**3e**/89
6	CF_3	Ph	*p*-ClC_6H_4	**3f**/90
7	CF_3	Ph	*p*-$NO_2C_6H_4$	**3g**/94
8	CF_3	*p*-ClC_6H_4	Bn	**3h**/87
9	CF_3	*p*-MeC_6H_4	*p*-$OMeC_6H_4$	**3i**/95
10	CF_2Br	Ph	Bn	**3j**/90
11	CF_2Br	Ph	Bu	**3k**/93
12	CF_2Br	Ph	Cyclohexyl	**3l**/92
13	CF_2Br	Ph	Allyl	**3m**/91
14	CF_2Br	Ph	*p*-$OMeC_6H_4$	**3n**/92
15	CF_2Br	Bu	Bn	**3o**/91
16	CF_2Br	Bu	*p*-$OMeC_6H_4$	**3p**/96
17	CF_2Br	*p*-$OMeC_6H_4$	Bn	**3q**/94
18	CF_2Br	H	Bn	—[c]

[a] Reaction conditions: **2** (0.5 mmol), $NaAuCl_4{\cdot}2H_2O$ (5 mol%), toluene (5 mL), at room temperature for 1 h. [b] Yield of the isolated product. [c] The ratio of **3r** and **4r** was 1 : 1 by ^{19}F NMR.

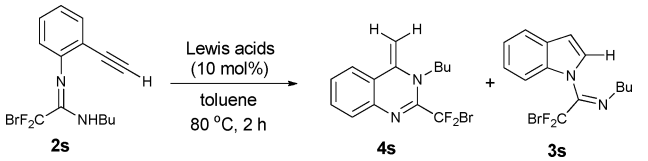
in a ratio of 1 : 1 (Table 2, entry 18). This phenomenon gave us an incentive to study the influence of different Lewis acids on the substrate with an ethynyl substituent.

Subsequently, the substrate **2s** was subjected to an array of Lewis acids in toluene at 80 °C for 2 h (Table 3). Almost all Lewis acid catalysts showed good catalytic activities except for $Ti(OBu)_4$, which made **2s** rapidly decompose. The quinazoline **4s** was identified as the major product under these conditions. To our delight, the reaction proceeded by a different pathway and provided indole **3s** as the major product in the presence of $Cu(OAc)_2$ as catalyst (Table 3, entry 7). So we then employed some substrates with *N′*-substituent groups (R^2) to investigate the scope under the catalyst $Cu(OAc)_2$. The indoles **3** were obtained in good yields no matter what the substituent was on the *N*-position under these conditions (Scheme 3).[9]



Scheme 3 Copper-catalyzed intramolecular hydroamination of the substrate **2** with ethynyl substituent.

Table 3 Optimization of the substrate **2s** under various Lewis acids[a]

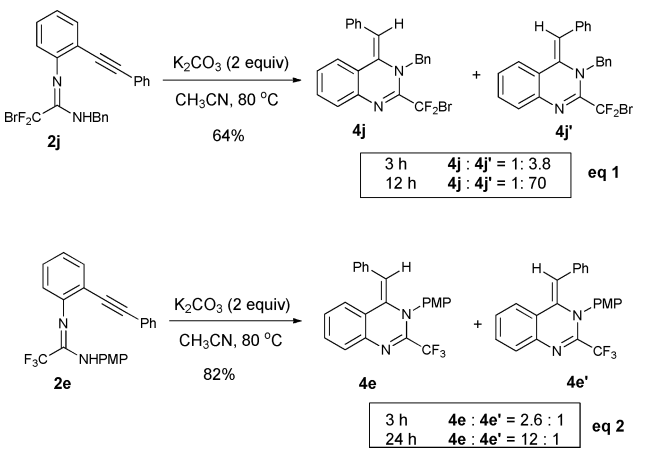


Entry	Lewis acid	Ratio (**4s** : **3s**)[b]	Yield (%)[c]
1	$Ti(OBu)_4$	25 : 1	**4s**/30
2	$ZnCl_2$	20 : 1	**4s**/73
3	$BF_3{\cdot}Et_2O$	25 : 1	**4s**/70
4	$InCl_3{\cdot}3H_2O$	22 : 1	**4s**/82
5	$CuSO_4$	25 : 1	**4s**/73
6	$Cu(OTf)_2$	12 : 1	**4s**/68
7	$Cu(OAc)_2$	1 : 7	**3s**/67

[a] Reaction conditions: **2** (0.2 mmol), catalyst (10 mol%), toluene (2 mL), 80 °C, 2 h. [b] The ratio was detected from the reaction mixture by ^{19}F NMR. [c] Isolated yield of the major product.

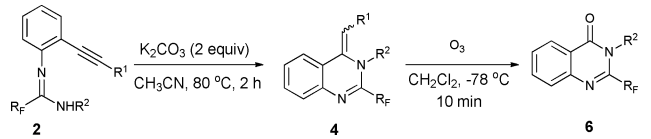
It should be noted that *N*-(*ortho*-ethynyl)phenylbromodifluoroacetamidine **2v** was converted to the corresponding product indole **3v** in 82% yield.

During the study of the Lewis acid catalyzed hydroamination of the amidines, we accidentally found out by ^{19}F NMR that the substrate **2j** was converted exclusively to two unexpected products by treatment with 2 equiv of K_2CO_3 in CH_3CN at 80 °C for 3 h. After removing the solvent, the residue was allowed to sit at room temperature for 12 h and the ^{19}F NMR revealed that the ratio of the isomers altered from 3.8 : 1 to 70 : 1. The structure of the product **4j′** was confirmed by X-ray diffraction. The reaction proceeded through a 6-*exo-dig* pathway and the stereoisomers were produced under the base-catalyzed reaction. Quinazoline **4j** and **4j′** tautomerized at room temperature and the more thermodynamically stable **4j′** predominated (eq 1, Scheme 4) when an equilibrium was reached. However, when the substrate **2e** with PMP on nitrogen reacted under the same condition, the isomerization of the two products also took place and the quinazoline **4e** was detected as the major product which was also determined by X-ray diffraction (eq 2, Scheme 4).



Scheme 4 Base-catalyzed intramolecular hydroamination of the amidines **2**.

Table 4 The cascade synthesis of 2-polyfluoroalkyl quinazolones[a]

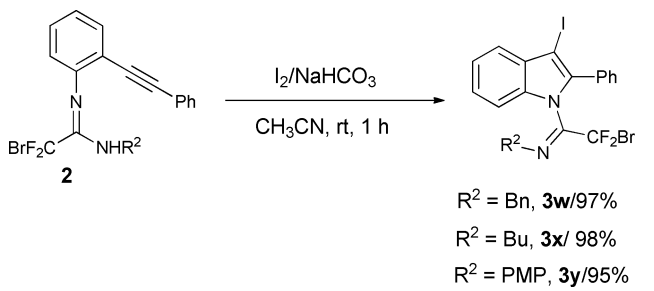


Entry	R_F	R^1	R^2	Yield (%)[b]
1	CF_3	Ph	Bn	**6a**/82
2	CF_3	Ph	*p*-$OMeC_6H_4$	**6b**/76
3	CF_2Br	Ph	Bn	**6c**/64
4	CF_2Br	Ph	*p*-$OMeC_6H_4$	**6d**/69

[a] Reaction conditions: the amidines **2** (0.5 mmol), potassium carbonate (1.0 mmol), acetonitrile (10 mL). [b] Overall isolated yield of the product.

In order to explore this reaction and prove the transformation of the stereoisomers, we developed a tandem hydroamination/ozonolysis process from the substrate **2** to synthesize quinazolone **6** without separating the intermediate quinazoline **4**.[10] Using this methodology, 2-polyfluoroalkyl substituted quinazolones **6** were easily prepared in high yields (Table 4).

Finally, we showed that the substrate **2** underwent electrophilic cyclization in the presence of I_2.[11] 3-Iodo substituted indoles were obtained exclusively under the optimized conditions and three substrates including benzyl, butyl, *p*-methoxyphenyl on the nitrogen provided the corresponding indoles in excellent yields (Scheme 5).



Scheme 5 Iodine mediated cyclization of the amidines **2**.

Conclusions

In conclusion, a detailed study of the intramolecular hydroamination of the fluorinated (*ortho*-alkynylaryl)amidines under Lewis acid, base and iodine was presented. A facile and mild way for the synthesis of the fluorinated quinazolones was developed *via* hydroamination/ozonolysis from the amidines. Further transformation of the bromodifluoro group in the product indole derivatives and synthesis of other heterocycles by applying this methodology are in progress in our laboratory.

Experimental section

General experimental

Melting points were measured on a Melt-Temp apparatus and uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{13}C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Elemental analysis was performed by the Analytical Laboratory of Shanghai Institute of Organic Chemistry. Mass spectra were recorded by EI methods. HRMS (EI) was measured on a Waters Micromass GCT Premier mass spectrometer. Solvents and reagents were purchased from commercial sources and used as received. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure and petroleum ether/ethyl acetate combination was used as the eluent.

General procedure for $NaAuCl_4 \cdot 2H_2O$ catalyzed intramolecular hydroamination of the amidines 2

To a solution of the amidines **2** (0.5 mmol) in toluene (5 mL), $NaAuCl_4 \cdot 2H_2O$ (10 mg, 0.025 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and then filtrated. The solvents were evaporated under reduced pressure. The crude product was chromatographed by column chromatography on silica gel (petroleum ether/ethyl acetate (20 : 1)) to give the products **3**.

(*Z*)-1-Phenyl-*N*-(2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)methanamine (3a)

White solid, mp: 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.67 (m, 1H), 7.42–7.09 (m, 13H), 6.84 (s, 1H), 4.68–4.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (q, J = 38.6 Hz), 140.2, 136.7, 136.4, 131.4, 128.9, 128.8, 128.5, 127.7, 127.4, 127.4, 123.7, 122.1, 121.2, 117.9 (q, J = 280.2 Hz), 110.4, 105.3, 55.4; MS (EI): *m*/*z* (%): 378 (36.49) [M$^+$], 91 (100.00); Anal. Calcd. for $C_{23}H_{17}F_3N_2$: C, 73.01; H, 4.53; N, 7.40; Found: C, 72.97; H, 4.69; N, 7.51; IR (film): ν 3044, 1682, 1452, 1345, 1270, 1154, 928 cm^{-1}.

2,2,2-Trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethanimine (3b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.94 (brs, 0.39H), 10.24 (brs, 0.60H), 7.62 (d, J = 7.0 Hz, 1H), 7.54–7.19 (m, 8H), 6.74 (s, 1H); MS (EI): *m*/*z* (%): 288 (100.00) [M$^+$]; HRMS (EI) Calcd. for $C_{16}H_{11}F_3N_2$: 288.0874, Found: 288.0869; IR (film): ν 3254, 3064, 1661, 1455, 1391, 1287, 1188, 1158 cm^{-1}.

(*Z*)-*N*-(2,2,2-Trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)methanamine (3c)

White solid, mp: 72–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 7.3 Hz, 1H), 7.47–7.06 (m, 8H), 6.80 (s, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 (q, J = 38.4 Hz), 140.0, 136.5, 131.5, 128.9, 128.7, 128.5, 127.2, 123.6, 122.0, 121.1, 119.2, 117.9 (d, J = 279.7 Hz), 110.2, 105.2, 39.2; MS (EI): *m*/*z* (%): 302 (79.30) [M$^+$], 110 (100.00); Anal. Calcd. for $C_{17}H_{13}F_3N_2$: C, 67.54; H, 4.33; N, 9.27; Found: C, 67.23; H, 4.54; N, 9.12; IR (film): ν 3077, 2974, 2923, 1738, 1686, 1453, 1275, 1204, 1145, 926, 751 cm^{-1}.

(*Z*)-*N*-(2,2,2-Trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)cyclohexanamine (3d)

White solid, mp: 76–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.63 (m, 1H), 7.49–7.33 (m, 5H), 7.28–7.16 (m, 3H), 6.79 (s, 1H), 3.13–2.99 (m, 1H), 1.66–0.69 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 140.3 (q, J = 38.3 Hz), 137.5, 131.3, 128.7 128.5, 128.4, 128.0, 123.4, 121.7, 120.8, 118.2 (q, J = 280.0 Hz), 110.4,

104.7, 60.3, 32.9, 31.5, 25.1, 23.6, 23.4; MS (EI): *m/z* (%): 370 (27.33) [M$^+$], 193 (100.00); HRMS (EI) Calcd. for $C_{22}H_{21}F_3N_2$: 370.1657; Found: 370.1663; IR (film): *ν* 3063, 2935, 2858, 1669, 1455, 1204, 1142, 936 cm^{-1}.

(*Z*)-4-Methoxy-*N*-(2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)aniline (3e)

White solid, mp: 74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.68–7.62 (m, 1H), 7.30–7.13 (m, 8H), 6.73 (s, 1H), 6.62–6.50 (m, 4H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.9, 139.5, 137.2 (q, *J* = 38.8 Hz), 136.2, 135.7, 131.3, 129.0, 128.5, 128.2, 127.3, 126.1, 123.7, 122.1, 121.0, 120.2 (q, *J* = 278.1 Hz), 114.1, 111.0, 106.0, 55.1; MS (EI): *m/z* (%): 394 (38.47) [M$^+$], 202 (100.00); Anal. Calcd. for $C_{23}H_{17}F_3N_2O$: C, 70.04; H, 4.34; N, 7.10; Found: C, 69.80; H, 4.50; N, 7.10; IR (film): *ν* 3013, 2969, 1649, 1595, 1502, 1454, 1246, 1197, 1142, 1028, 751 cm^{-1}.

(*Z*)-4-Chloro-*N*-(2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)aniline (3f)

White solid, mp: 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.63 (d, *J* = 7.8 Hz, 1H), 7.43–7.20 (m, 6H), 7.07–6.90 (m, 4H), 6.66 (s, 1H), 6.14 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 141.4, 140.9 (q, *J* = 39.1 Hz), 139.6, 136.9, 133.3, 130.8, 128.8, 128.7, 128.5, 128.2, 127.3, 124.0, 123.6, 122.4, 121.1, 118.5 (q, *J* = 279.7 Hz), 111.1 (q, *J* = 2.2 Hz), 106.8; MS (EI): *m/z* (%): 398 (58.72) [M$^+$], 206 (100.00); HRMS (EI) Calcd. for $C_{22}H_{14}ClF_3N_2$: 398.0798; Found: 398.0791; IR (film): *ν* 3062, 2926, 1738, 1658, 1485, 1455, 1217, 1199, 1150, 951 cm^{-1}.

(*Z*)-4-Nitro-*N*-(2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)aniline (3g)

Yellow solid, mp: 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.85–7.45 (m, 4H), 7.42–7.22 (m, 5H), 6.95 (d, *J* = 6.8 Hz, 2H), 6.63 (s, 1H), 6.11 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 148.6, 145.7, 143.6 (q, *J* = 39.5 Hz), 139.6, 137.5, 130.4, 128.7, 128.5, 127.3, 124.4, 124.0, 122.8, 121.6, 121.3, 118.3 (q, *J* = 280.0 Hz), 111.1 (q, *J* = 2.8 Hz), 107.6; MS (EI): *m/z* (%): 409 (97.54) [M$^+$], 217 (100.00); Anal. Calcd. for $C_{22}H_{14}F_3N_2O_2$: C, 64.55; H, 3.45; N, 10.26; Found: C, 64.58; H, 3.66; N, 10.17; IR (film): *ν* 3063, 1668, 1603, 1517, 1455, 1347, 1200, 1153, 1109, 944 cm^{-1}.

(*Z*)-*N*-(1-(2-(4-Chlorophenyl)-1*H*-indol-1-yl)-2,2,2-trifluoroethylidene)-1-phenylmethanamine (3h)

White solid, mp: 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.73–7.66 (m, 1H), 7.36–7.06 (m, 12H), 6.82 (s, 1H), 4.72–4.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.5 (q, *J* = 38.7 Hz), 138.9, 136.9, 136.2, 134.7, 129.9, 129.2, 128.7, 128.6, 128.6, 127.7, 127.5, 124.0, 122.3, 121.3, 117.9 (q, *J* = 280.2 Hz), 110.4, 105.8, 55.5; MS (MALDI): *m/z*: 413 [M + H$^+$]; Anal. Calcd. for $C_{23}H_{16}ClF_3N_2$: C, 66.91, H, 3.91; N, 6.79; Found: C, 66.97; H, 4.07; N, 6.67; IR (film): *ν* 3063, 3031, 1665, 1611, 1503, 1453, 1336, 1248, 1157, 1031 cm^{-1}.

(*Z*)-4-Methoxy-*N*-(2,2,2-trifluoro-1-(2-*p*-tolyl-1*H*-indol-1-yl)ethylidene)aniline (3i)

White solid, mp: 74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.62–7.49 (m, 1H), 7.21–6.89 (m, 7H), 6.62 (s, 1H), 6.51 (s, 4H), 3.61 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 159.9, 139.7, 138.2, 137.1 (q, *J* = 38.9 Hz), 136.1, 135.8 129.2, 129.1, 128.5, 127.2, 126.2, 123.4, 122.0, 120.8, 118.4 (q, *J* = 219.2 Hz), 114.1, 111.0, 105.5, 55.3, 21.1; MS (MALDI): *m/z*: 409 [M + H$^+$]; Anal. Calcd. for $C_{24}H_{19}F_3N_2$: C, 70.58, H, 4.69; N, 6.86; Found: C, 70.48; H, 4.84; N, 6.70.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)-1-phenylmethanamine (3j)

White solid, mp: 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.73–7.63 (m, 1H), 7.44–7.09 (m, 13H), 6.81 (s, 1H), 4.84–4.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.7 (t, *J* = 27.6 Hz), 140.1, 137.0, 136.7, 131.9, 128.9, 128.8, 128.6, 128.5, 127.7, 127.5, 127.4, 123.6, 122.1, 121.2, 113.8 (t, *J* = 308.2 Hz), 110.7, 105.4, 55.5; MS (EI): *m/z* (%): 438 (9.52) [M$^+$], 91 (100.00); Anal. Calcd. for $C_{23}H_{17}BrF_2N_2$: C, 62.88; H, 3.90; N, 6.38; Found: C, 62.77; H, 4.25; N, 6.36; IR (film): *ν* 3044, 1680, 1453, 1338, 1157, 954 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)butan-1-amine (3k)

White solid, mp: 46–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66 (d, *J* = 7.3 Hz, 1H), 7.40–7.12 (m, 8H), 6.79 (s, 1H), 3.57–3.33 (m, 2H), 1.83–1.60 (m, 2H), 1.46–1.27 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.8 (t, *J* = 27.5 Hz), 139.9, 136.9, 132.0, 128.8, 128.6, 128.4, 127.3, 123.4, 121.8, 121.0, 113.9 (t, *J* = 307.4 Hz), 111.0, 105.0, 52.0, 31.8, 20.6, 13.8; MS (EI): *m/z* (%): 404 (6.15) [M$^+$], 57 (100.00); Anal. Calcd. for $C_{20}H_{19}BrF_2N_2$: C, 59.27; H, 4.73; N, 6.91; Found: C, 59.36; H, 4.64; N, 6.88; IR (film): *ν* 3062, 2929, 1658, 1454, 1340, 1154, 959 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)cyclohexanamine (3l)

White solid, mp: 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.65 (d, *J* = 6.9 Hz, 1H), 7.52–7.16 (m, 8H), 6.80 (s, 1H), 3.32–3.15 (m, 1H), 1.74–0.96 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.5 (t, *J* = 28.3 Hz), 140.3, 137.6, 131.6, 128.6, 128.5, 127.9, 123.2, 121.7, 120.8, 114.7 (t, *J* = 309.0 Hz), 111.1, 104.9, 60.3, 32.8, 31.7, 25.2, 23.6, 23.5; MS (EI): *m/z* (%): 430 (10.72) [M$^+$], 193 (100.00); HRMS (EI) Calcd. for $C_{22}H_{21}BrF_2N_2$: 430.0856; Found: 430.0867; IR (film): *ν* 3050, 2932, 2856, 1663, 1454, 1341, 1157, 1144, 973 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)prop-2-en-1-amine (3m)

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66 (d, *J* = 7.8 Hz, 1H), 7.42–7.20 (m, 7H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.79 (s, 1H), 6.16–6.01 (m, 1H), 5.28–5.22 (m, 2H), 4.25–4.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.5 (t, *J* = 26.8 Hz), 139.9, 137.0, 132.7, 131.9, 128.9, 128.7, 128.5, 127.3, 123.4, 122.0, 121.1, 116.6, 113.5 (t, *J* = 310.4 Hz), 111.0, 105.2, 54.7; MS (EI): *m/z* (%): 388 (49.58) [M$^+$], 165 (100.00); Anal. Calcd. for $C_{19}H_{15}BrF_2N_2$: C, 58.63; H,

3.88; N, 7.20; Found: C, 58.40; H, 4.42; N, 7.21; IR (film): ν 3062, 3030, 2914, 1738, 1671, 1454, 1340, 1158, 990 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-phenyl-1*H*-indol-1-yl)ethylidene)-4-methoxyaniline (3n)

White solid, mp: 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.61 (m, 1H), 7.32–7.13 (m, 8H), 6.81 (s, 1H), 6.78 (d, J = 9.2 Hz, 2H); 6.65 (d, J = 9.2 Hz, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 139.2 (t, J = 26.8 Hz), 135.8, 135.6, 131.9, 129.0, 128.7, 128.3, 127.2, 126.7, 123.5, 121.9, 120.9, 112.5 (t, J = 308.4 Hz), 114.3, 111.7, 105.8, 55.3; MS (EI): m/z (%): 454 (42.27) [M$^+$], 262 (100.00); Anal. Calcd. for $C_{23}H_{17}BrF_2N_2O$: C, 60.67; H, 3.76; N, 6.15; Found: C, 60.81; H, 3.88; N, 6.17; IR (film): ν 3056, 2931, 1738, 1651, 1589, 1502, 1453, 1335, 1258 cm^{-1}.

(*Z*)-*N*-(2-Bromo-1-(2-butyl-1*H*-indol-1-yl)-2,2-difluoroethylidene)-1-phenylmethanamine (3o)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.55 (m, 1H), 7.30–7.10 (m, 8H), 6.46 (s, 1H), 4.46–4.24 (m, 2H), 2.76–2.29 (m, 2H), 1.81–1.58 (m, 2H), 1.46–1.21 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5 (t, J = 29.1 Hz), 140.7, 136.6, 135.9, 128.7, 128.5, 127.6, 127.4, 122.4, 121.3, 120.3, 114.4 (t, J = 309.2 Hz), 110.4, 102.5, 55.2, 30.0, 26.6, 22.4, 13.7; MS (EI): m/z (%): 418 (7.11) [M$^+$], 91 (100.00); HRMS (EI) Calcd. for $C_{21}H_{21}BrF_2N_2$: 418.0856; Found: 418.0854; IR (film): ν 3062, 3031, 2958, 2932, 2872, 1667, 1556, 1455, 1321, 1163, 995 cm^{-1}.

(*Z*)-*N*-(2-Bromo-1-(2-butyl-1*H*-indol-1-yl)-2,2-difluoroethylidene)-4-methoxyaniline (3p)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.46 (m, 1H), 7.30–7.10 (m, 3H), 6.71–6.50 (m, 4H), 6.42 (s, 1H), 3.71 (s, 3H), 2.67–2.06 (m, 2H), 1.68–1.36 (m, 2H), 1.35–1.18 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 140.7 (t, J = 28.6 Hz), 140.0, 135.5, 135.4, 128.9, 126.2, 122.4, 121.3, 120.1 115.2 (t, J = 309.3 Hz), 114.2, 111.0, 103.2, 55.2, 29.9, 26.4, 22.3, 13.7; MS (EI): m/z (%): 434 (25.42) [M$^+$], 262 (100.00); HRMS (EI) Calcd. for $C_{21}H_{21}BrF_2N_2O$: 434.0805; Found: 434.0802; IR (film): ν 3053, 2940, 2872, 1715, 1648, 1594, 1455, 1380, 1323, 1255, 1169, 985 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(2-(4-methoxyphenyl)-1*H*-indol-1-yl)ethylidene)-1-phenylmethanamine (3q)

White solid, mp: 98–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.60 (m, 1H), 7.42–7.06 (m, 10H), 6.93–6.82 (m, 2H), 6.74 (s, 1H), 4.82–4.64 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 147.9 (t, J = 29.3 Hz), 139.9, 136.7, 128.9, 128.7, 128.6, 127.6, 127.3, 124.2, 123.2, 121.9, 120.9, 114.3, 110.9, 104.4, 55.4, 55.2; MS (MALDI): m/z: 469 [M + H$^+$]; Anal. Calcd. for $C_{24}H_{19}BrF_2N_2O$: C, 61.42; H, 4.08; N, 5.97; Found: C, 61.36; H, 4.24; N, 5.80; IR (film): ν 3063, 3031, 1665, 1611, 1503, 1453, 1336, 1248, 1157, 1031 cm^{-1}.

General procedure for $Cu(OAc)_2$ catalyzed annulations of the amidines 2 with a ethynyl group

A mixture of the amidine **2** (0.5 mmol), $Cu(OAc)_2$ (10 mg, 0.05 mmol), and toluene (5 mL) was stirred at 80 °C for 1 h, then filtrated. The solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate (20 : 1)) on silica gel to provide the desired product.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(1*H*-indol-1-yl)ethylidene)butan-1-amine (3r)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.65 (m, 1H), 7.44–7.03 (m, 4H), 6.72 (d, J = 3.4 Hz, 1H), 3.23 (s, 2H), 1.69–1.55 (m, 2H), 1.34–1.17 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1 (t, J = 21.6 Hz), 136.1, 128.0, 125.8, 123.4, 121.5, 121.4, 113.8 (t, J = 246.0 Hz), 110.9, 105.6, 51.6, 31.8, 20.3, 13.5; MS (EI): m/z (%): 328 (28.41) [M$^+$], 57 (100.00); HRMS (EI) Calcd. for $C_{14}H_{15}BrF_2N_2$: 328.0385; Found: 328.0386; IR (film): ν 2959, 2933, 2873, 1670, 1609, 1519, 1453, 1323, 1189, 1155, 963 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(1*H*-indol-1-yl)ethylidene)-1-phenylmethanamine (3s)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–7.61 (m, 1H), 7.41–7.01 (m, 9H), 6.74 (d, J = 3.2 Hz, 1H), 4.42 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (t, J = 26.8 Hz), 136.9, 136.0, 128.5, 128.2, 127.6, 127.4, 125.7, 123.6, 121.7, 121.5, 113.8 (t, J = 308.2 Hz), 111.0, 106.0, 55.3; MS (EI): m/z (%): 362 (1.29) [M$^+$], 91 (100.00); HRMS (EI) Calcd. for $C_{17}H_{13}BrF_2N_2$: 362.0230, Found: 362.0231; IR (film): ν 3057, 3030, 2927, 1670, 1518, 1453, 1324, 1186, 1155, 980 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(1*H*-indol-1-yl)ethylidene)-cyclohexanamine (3t)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 7.8 Hz, 1H), 7.33–7.04 (m, 4H), 6.70 (d, J = 3.3 Hz, 1H), 3.21–2.77 (m, 1H), 1.84–0.71 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1 (t, J = 26.8 Hz), 136.3, 127.9, 126.4, 123.4, 121.3, 121.2, 114.0 (t, J = 308.2 Hz), 110.5, 105.3, 59.8, 32.9, 25.1, 23.6; MS (EI): m/z (%): 354 (3.57) [M$^+$], 117 (100.00); HRMS (EI) Calcd. for $C_{16}H_{17}BrF_2N_2$: 354.0543, Found: 354.0536; IR (film): ν 2933, 2856, 1669, 1518, 1452, 1323, 1188, 1148, 973 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(1*H*-indol-1-yl)ethylidene)prop-2-en-1-amine (3u)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 7.2 Hz, 1H), 7.42–7.02 (m, 4H), 6.72 (d, J = 3.3 Hz, 1H), 6.12–5.76 (m, 1H), 5.24–5.01 (m, 2H), 3.86 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): −54.89 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7 (t, J = 27.5 Hz), 135.9, 133.0, 128.1, 125.7, 123.5, 123.5, 121.6, 121.4, 117.2, 113.7 (t, J = 308.2 Hz), 111.0, 54.2; MS (EI): m/z (%): 312 (14.95) [M$^+$], 116 (100.00); HRMS (EI) Calcd. for $C_{13}H_{11}BrF_2N_2$: 312.0074, Found: 312.0072; IR (film): ν 3077, 2922, 2842, 1673, 1517, 1453, 1324, 1189, 1156, 926 cm^{-1}.

2-Bromo-2,2-difluoro-1-(1*H*-indol-1-yl)ethanimine (3v)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.62 (d, J = 8.1 Hz, 1H), 7.62–7.22 (m, 4H), 6.70 (d, J = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7 (t, J = 28.5 Hz), 136.5, 130.0, 125.4 (t, J = 5.1 Hz), 124.8, 123.5, 120.8, 117.1, 109.9 (t, J = 306.5 Hz),

108.4; MS (EI): *m/z* (%): 272 (68.09) [M$^+$], 117 (100.00); HRMS (EI) Calcd. for $C_{10}H_7BrF_2N_2$: 271.9761, Found: 271.9760; IR (film): *ν* 3331, 3054, 2927, 2847, 1638, 1541, 1455, 1368, 1258, 1153, 1055 cm^{-1}.

General procedure for the synthesis of quinazolines 4 and quinazolones 6

A 25 mL flask equipped with a magnetic stirring bar was charged with the amidine **2** (0.5 mmol), acetonitrile (10 mL) and potassium carbonate (138 mg, 1.0 mmol). The reaction mixture was stirred at 80 °C for 1 h until the amidine was completely consumed by monitoring with TLC. The resulting solution was cooled to room temperature and filtered, and the solvent of filtrate was removed *in vacuo*. The residue was placed for 12 h, and recrystallized from hexane to give yellow crystals of **4**.

The residue was directly dissolved in 10 mL of CH_2Cl_2, Ozone was slowly ventilated for 10 min, then 10 mL of water was added. The resulting mixture was extracted by CH_2Cl_2 (2 × 10 mL). and the combined extract was dried with anhydrous magnesium sulfate. Solvent was removed, and the residue was separated by column chromatography to give the pure product **6**.

(*Z*)-3-Benzyl-4-benzylidene-2-(bromodifluoromethyl)-3,4-dihydroquinazoline (4j′)

Yellow solid, mp: 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.66–7.23 (m, 9H), 7.20–6.95 (m, 3H), 6.82 (d, *J* = 6.2 Hz, 2H), 6.30 (s, 1H), 4.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 150.3 (t, *J* = 24.8 Hz), 139.7, 135.7, 135.1, 129.3, 128.7, 128.5, 128.3, 127.9, 127.5, 127.2, 126.8, 126.6, 126.5, 121.6, 113.4 (t, *J* = 305.0 Hz), 112.1, 54.4 (t, *J* = 3.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) *δ* –48.89 (s, 2F); MS (EI): *m/z* (%): 438 (38.63) [M$^+$], 91 (100.00); Anal. Calcd. for $C_{23}H_{17}BrF_2N_2$: C, 62.88; H, 3.90; N, 6.38; Found: C, 63.30; H, 4.16; N, 6.13; IR (KBr): *ν* 3072, 3025, 2064, 1632, 1581, 1457, 1387, 1152, 1135, 995 cm^{-1}.

(*E*)-4-Benzylidene-3-(4-methoxyphenyl)-2-(trifluoromethyl)-3,4-dihydroquinazoline (4e)

Yellow solid, mp: 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.45–6.86 (m, 13H), 5.31 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 160.0, 143.4 (q, *J* = 32.8 Hz), 141.6, 138.1, 137.4, 131.5, 130.3, 129.6, 129.1, 128.7, 128.5, 127.3, 127.2, 126.9, 126.4, 122.5, 118.2 (q, *J* = 275.6 Hz), 115.0, 107.8, 55.4; MS (EI): *m/z* (%): 394 (18.40) [M$^+$], 197 (100.00); HRMS (EI) Calcd. for $C_{23}H_{17}F_3N_2O$: 394.1293, Found: 394.1295; IR (KBr): *ν* 3094, 2837, 1624, 1608, 1589, 1506, 1458, 1303, 1247, 1224, 1207, 1145, 1022 cm^{-1}.

3-Benzyl-2-(trifluoromethyl)quinazolin-4(3*H*)-one (6a)

White solid, mp: 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.34 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 3.6 Hz, 2H), 7.74–7.52 (m, 1H), 7.46–6.99 (m, 5H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.4, 144.9, 142.3 (q, *J* = 35.8 Hz), 135.4, 135.0, 129.3, 128.5, 128.5, 127.5, 127.2, 126.2, 121.8, 118.1 (q, *J* = 277.5 Hz), 47.7 (q, *J* = 3.4 Hz); MS (EI): *m/z* (%): 304 (46.36) [M$^+$], 91 (100.00); Anal. Calcd. for $C_{16}H_{11}F_3N_2O_2$: C, 63.16; H, 3.64; N, 9.21; Found: C, 63.50; H, 3.92; N, 9.00; IR (film): *ν* 3073, 3030, 1697, 1608, 1456, 1398, 1310, 1208, 1134, 973, 774 cm^{-1}.

3-(4-Methoxyphenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (6b)

White solid, mp: 153–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.34 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 2H), 7.75–7.60 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.9, 160.4, 145.1, 142.5 (q, *J* = 35.3 Hz), 135.0, 130.0, 129.3, 128.6, 127.3, 127.0, 122.0, 117.8 (q, *J* = 277.5 Hz), 114.4, 55.4; MS (MALDI): *m/z*: 322 [M + H$^+$]; Anal. Calcd. for $C_{16}H_{11}F_3N_2O_2$: C, 60.00; H, 3.46; N, 8.75; Found: C, 60.20; H, 3.66; N, 8.63; IR (film): 3081, 2969, 2844, 1699, 1609, 1506, 1465, 1376, 1220, 1138, 781 cm^{-1}.

3-Benzyl-2-(bromodifluoromethyl)quinazolin-4(3*H*)-one (6c)

White solid, mp: 79–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.33 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 3.4 Hz, 2H), 7.69–7.51 (m, 1H), 7.42–7.00 (m, 5H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.7, 146.3 (t, *J* = 27.7 Hz), 144.9, 135.5, 135.0, 129.2, 128.5, 127.4, 127.3, 126.0, 121.5, 111.5 (t, *J* = 308.5 Hz), 48.2; MS (EI): *m/z* (%): 364 (35.76) [M$^+$], 91 (100.00); Anal. Calcd. for $C_{16}H_{11}BrF_2N_2O$: C, 52.62; H, 3.04; N, 7.67; Found: C, 52.70; H, 3.40; N, 7.65; IR (film): *ν* 3068, 3030, 1696, 1600, 1455, 1386, 1231, 1163, 1115, 896, 773 cm^{-1}.

2-(Bromodifluoromethyl)-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (6d)

White solid, mp: 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.32 (d, *J* = 7.6 Hz, 1H), 8.01–6.77 (m, 8H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.3, 160.3, 146.3 (t, *J* = 24.7 Hz), 145.0, 135.1, 130.7, 129.2, 128.6, 127.4, 127.1, 121.7, 114.2, 111.5 (t, *J* = 308.5 Hz), 55.4; MS (MALDI): *m/z*: 382 [M + H$^+$]; Anal. Calcd. for $C_{16}H_{11}BrF_2N_2O_2$: C, 50.42; H, 2.91; N, 7.35; Found: C, 50.47; H, 3.10; N, 7.14; IR (film): *ν* 2969, 2919, 2838, 1693, 1609, 1597, 1510, 1255, 1150, 1124, 990, 900, 778 cm^{-1}.

General procedure for iodocyclization of the amidines 2

A mixture of the amidine **2** (0.5 mmol), I_2 (254 mg, 1.0 mmol), and $NaHCO_3$ (84 mg, 1.0 mmol) in CH_3CN (10 mL) was stirred at rt for 1h. The excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The solution was extracted with ethyl acetate (3 × 10 mL), and the combined extract was dried with anhydrous magnesium sulfate. Solvent was removed, and the residue was separated by column chromatography (petroleum ether/ethyl acetate (20 : 1)) to give the pure product.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(3-iodo-2-phenyl-1*H*-indol-1-yl)ethylidene)-1-phenylmethanamine (3w)

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.58–7.54 (m, 1H), 7.40–7.22 (m, 12H), 7.12–7.06 (m, 1H), 4.78–4.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.7 (t, *J* = 28.5 Hz), 139.4, 136.5, 136.2, 131.2, 130.4, 129.8, 129.4, 128.6, 127.5, 127.4, 124.9, 122.7, 122.4, 113.4 (t, *J* = 309.2 Hz), 111.0, 65.2, 55.4; MS (EI): *m/z* (%): 564 (2.67) [M$^+$], 91 (100.00); HRMS (EI) Calcd. for $C_{23}H_{16}BrF_2IN_2$: 563.9510, Found: 563.9507; IR (film): *ν* 3058, 3035, 2922, 2847, 1671, 1451, 1333, 1166, 1089, 992 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(3-iodo-2-phenyl-1*H*-indol-1-yl)ethylidene)butan-1-amine (3x)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.52 (m, 1H), 7.50–7.27 (m, 7H), 7.12 (d, J = 7.6 Hz, 1H), 3.54–3.04 (m, 2H), 1.83–1.58 (m, 2H), 1.46–1.29 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (t, J = 28.5 Hz), 139.4, 136.2, 131.0, 130.6, 129.8, 129.4, 128.5, 124.7, 122.5, 122.3, 113.6 (t, J = 308.4 Hz), 111.0, 64.9, 52.1, 31.7, 20.6, 13.7; MS (EI): m/z (%): 530 (1.96) [M$^+$], 57 (100.00); HRMS (EI) Calcd. for $C_{20}H_{18}BrF_2IN_2$: 529.9666, Found: 529.9669; IR (film): ν 3054, 2957, 2870, 1669, 1450, 1332, 1167, 1085, 988 cm^{-1}.

(*Z*)-*N*-(2-Bromo-2,2-difluoro-1-(3-iodo-2-phenyl-1*H*-indol-1-yl)ethylidene)-4-methoxyaniline (3y)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 6.8 Hz, 1H), 7.36–7.22 (m, 7H), 7.15 (d, J = 7.2 Hz, 1H), 6.72–6.65 (m, 4H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 139.3 (t, J = 29.2 Hz), 138.6, 135.4, 135.2, 131.4, 130.4, 129.6, 129.1, 128.3, 126.8, 124.8, 122.7, 122.2, 114.5, 114.4 (t, J = 307.7 Hz), 111.7, 65.3, 55.3; MS (EI): m/z (%): 580 (8.09) [M$^+$], 262 (100.00); HRMS (EI) Calcd. for $C_{23}H_{16}BrF_2IN_2O$: 579.9459, Found: 579.9468; IR (film): ν 3058, 2930, 2838, 1647, 1591, 1503, 1450, 1332, 1301, 1255, 1170, 1143 cm^{-1}.

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