Multicatalytic tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with indole†

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The combination of AgOTf and $Dy(OTf)_3$ shows high efficiency as a catalyst in the tandem reactions of *N*′-(2-alkynylbenzylidene)hydrazides with indoles, which generate the unexpected 1-(indol-3-yl)-2-aminoisoquinolinium triflates in good yields.

Introduction

The development of tandem reactions[1,2] for the efficient generation of small molecules is an important part of the field of chemical biology.[3] Their operational simplicity combined with assembly efficiency make tandem reactions attractive for molecular complexity generation. Among the method development in tandem reactions, multicatalytic processes have recently attracted growing interest.[4,5] Usually, one or more catalysts are involved in the reaction and promote two or more distinct chemical transformations in a single flask. For instance, Lambert and Cernak reported the multicatalytic synthesis of α-pyrrolidinyl ketones *via* a tandem palladium(II)/indium(III)-catalyzed aminochlorocarbonylation/Friedel–Crafts acylation reaction.[5a] $Mg(ClO_4)_2$ and $Cu(OTf)_2$ were found to be highly effective as a catalyst in the one-pot reaction of 2-alkynylbenzaldehydes, amines, zinc, and allylic bromide or benzyl bromide.[5d] Recently, we have developed efficient strategies for accessing privileged organic architectures.[6] Prompted by the advancement of multicatalytic synthesis,[4,5] we became interested in exploring new multicatalytic processes to facilitate the generation of small molecules. Herein, we disclose our recent efforts towards the tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with indole co-catalyzed by AgOTf and $Dy(OTf)_3$, which unexpectedly afforded 1-(indol-3-yl)-2-aminoisoquinolinium triflates in good yields.

Isoquinoline-based structure can be found in many natural products and pharmaceuticals that exhibit remarkable biological activities.[7] Continuous efforts have been given to the development of new methods for their construction. In continuation of recently developed methods for the Lewis acid-catalyzed or electrophile-mediated reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1**,[8] we hypothesized that the direct synthesis of new isoquinoline structures might occur in a one-pot reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with nucleophiles by sequential N–C and C–C bond formation under appropriate conditions, such that the intermediate isoquinolinium-2-yl amide would not have to be isolated. Since the indole skeleton is an important substructure in both natural products and therapeutic agents,[9] at the beginning a set of experiments was carried out using *N*′-(2-alkynylbenzylidene)hydrazide **1a** and indole **2a** as model substrates (Scheme 1).

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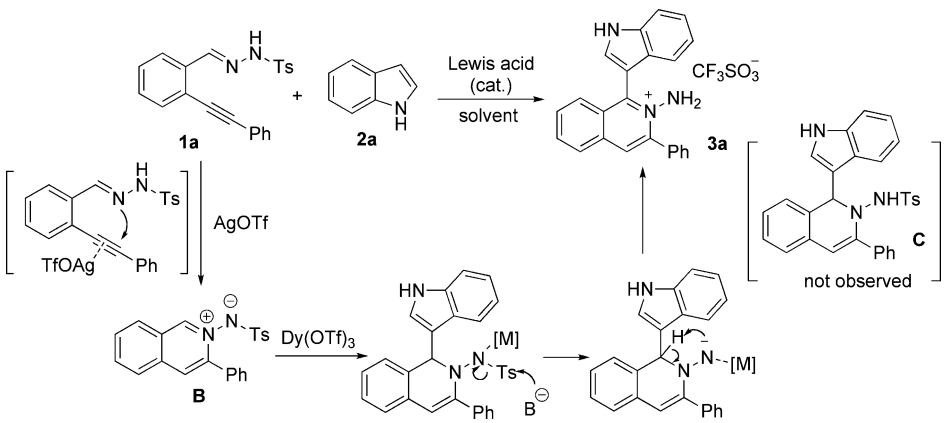
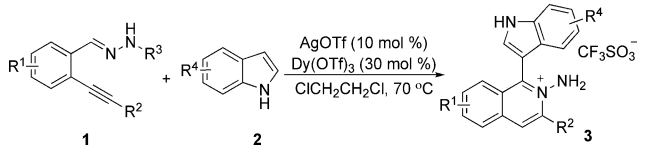
† Electronic supplementary information (ESI) available: Experimental details; characterization data, and ^1H and ^{13}C NMR spectra of compound **3**; X-ray ORTEP illustration of compound **3j**·CF_3SO_3. CCDC reference number 735059. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b913409c

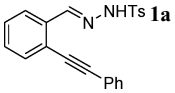
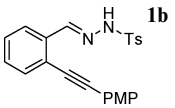
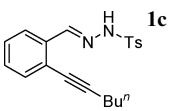
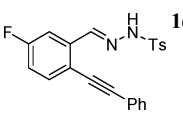
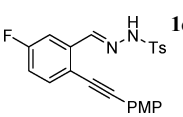
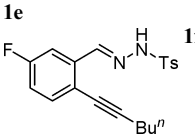
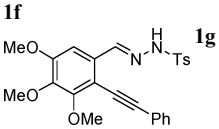
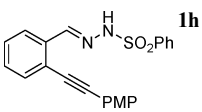
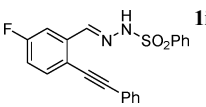
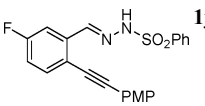
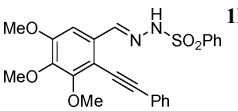


Scheme 1 Tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with indole **2a**.

Table 1 AgOTf and $Dy(OTf)_3$ co-catalyzed tandem reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1** with indole



1 2 3

Entry	Compound **1**	R^4	Yield (%)[a]
1	 **1a**	H (**2a**)	98 (**3a**)
2	**1a**	4-OMe (**2b**)	97 (**3b**)
3	**1a**	6-OMe (**2c**)	84 (**3c**)
4	**1a**	5-Br (**2d**)	89 (**3d**)
5	 **1b**	H (**2a**)	92 (**3e**)
6	 **1c**	H (**2a**)	86 (**3f**)
7	 **1d**	H (**2a**)	98 (**3g**)
8	 **1e**	H (**2a**)	96 (**3h**)
9	**1e**	4-OMe (**2b**)	95 (**3i**)
10	**1e**	5-Br (**2d**)	80 (**3j**)
11	 **1f**	H (**2a**)	82 (**3k**)
12	**1f**	4-OMe (**2b**)	93 (**3l**)
13	**1f**	6-OMe (**2c**)	87 (**3m**)
14	 **1g**	H (**2a**)	87 (**3n**)
15	 **1h**	H (**2a**)	80 (**3e**)
16	 **1i**	H (**2a**)	93 (**3g**)
17	 **1j**	H (**2a**)	90 (**3h**)
18	 **1k**	H (**2a**)	80 (**3n**)

[a] Isolated yield based on *N′*-(2-alkynylbenzylidene)hydrazide **1**.

Results and discussion

N′-(2-Alkynylbenzylidene)hydrazide **1** could be easily synthesized *via* condensation of 2-alkynylbenzaldehyde with hydrazine. At the outset of this study, our efforts were directed at discovering the most appropriate catalyst and reaction conditions to perform the proposed reaction. Thus, combinations of different Lewis acids (10 mol%) and solvents were screened. When AgOTf was used as the catalyst in the reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1a** with indole **2a** in dichloroethane, only intermediate isoquinolinium-2-yl amide **B** was generated *via* 6-*endo*-cyclization (99% yield, 2 hours, DCE, rt) and no further transformation was observed under these conditions. The same result was obtained when CuI was employed as a replacement. When other Lewis acids ($FeCl_3$, $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$) were utilized in the reaction, only a small amount of isoquinolinium-2-yl amide **B** was isolated with the recovery of *N′*-(2-alkynylbenzylidene)hydrazide **1a**. The results could not be improved when other solvents (MeCN, THF, toluene, Et_2O, $MeNO_2$) were used in the reaction. Based on these results, we conceived that additional Lewis acid might be necessary to facilitate the next nucleophilic addition. Therefore, the reaction of isoquinolinium-2-yl amide **B** with indole **2a** in MeCN was investigated. Again, no reaction occurred when AgOTf or CuI was employed as a catalyst. A trace amount of product was observed when $Cu(OTf)_2$ or $PdCl_2$ was used in the reaction. Gratifyingly, the formation of a product was detected (16% yield) when $Bi(OTf)_3$ was employed as the catalyst (10 mol%) at 70 °C. Further screening revealed that $Dy(OTf)_3$ was the most efficient one (28% yield) for the transformation. However, structural identification revealed that the product generated was compound **3a**, instead of the desired normal nucleophilic addition product **C**. We reasoned that after addition of indole **2a** to isoquinolinium-2-yl amide **B**, the sulfonyl group might be subsequently attacked in the presence of $Dy(OTf)_3$ leading to the unexpected product **3a**. With this promising result in hand, we subsequently re-investigated the tandem reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1a** with indole **2a**. To our delight, we realized that the combination of AgOTf (10 mol %) and $Dy(OTf)_3$ (30 mol %) showed high efficiency as a catalyst in MeCN in this transformation, and gave rise to the product **3a** in 83% yield. Further screening of solvents revealed that dichloroethane (DCE) was the best choice and the yield could be increased to 98%.

To investigate the scope of the reaction, a variety of differently substituted *N′*-(2-alkynylbenzylidene)hydrazides **1** with indoles **2** were successfully converted to the cyclized products **3** in good to excellent yields under the optimized conditions [AgOTf (10 mol %), $Dy(OTf)_3$ (30 mol %), DCE, 70 °C] as shown in Table 1. The cyclic products of the reactions were fully characterized by ^1H and ^{13}C NMR methods and mass spectroscopic data. For instance, reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1a** with 4-methoxyindole **2b** under the standard conditions gave rise to the desired product **3b** in 97% yield (Table 1, entry 2). 84% yield of product **3c** was isolated when 6-methoxyindole **2c** was employed in the reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1a** (Table 1, entry 3). A similar yield was obtained when 5-bromoindole **2d** was utilized in the reaction as a partner (89% yield, Table 1, entry 4). The reactions of *N′*-(2-alkynylbenzylidene)hydrazide **1b** or **1c** were meanwhile examined (Table 1, entries 5–6). The expected products

were generated under our standard experimental conditions, whatever the nature of the substituents attached to the triple bond. The conditions have also proven to be useful for other *N′*-(2-alkynylbenzylidene)hydrazide substrates **1d–1g**. The structure of **3j** was also confirmed by X-ray crystallographic analysis (Fig. 1).‡ Substrates with a phenylsulfonyl group were tested as well, and the reactions occurred smoothly to generate the corresponding products in good yields (Table 1, entries 15–18).

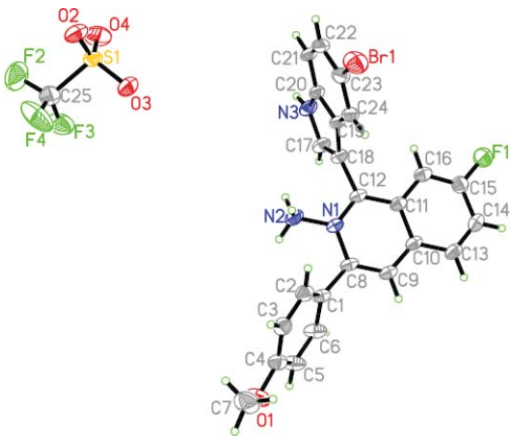


Fig. 1 X-ray ORTEP illustration of compound **3j**·CF_3SO_3 (30% probability ellipsoids).

Conclusion

In summary, the chemistry described herein provides a facile and direct synthesis of novel isoquinoline-based compounds in good yields. This multicatalytic process appears to involve intramolecular cyclization, nucleophilic addition of indole, and subsequent elimination of sulfonyl group. From a synthetic point of view, the transformation involves a one-step conversion of simple, readily available starting materials into an interesting class of heterocyclic derivative. Investigation using *N′*-(2-alkynylbenzylidene)hydrazide as a substrate in other transformations is ongoing, and the results will be reported in due course.

Experimental section

General experimental method

All reactions were performed in test tubes under a nitrogen atmosphere at 70 °C. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated at ~20 Torr (house vacuum) at 25–35 °C. Solvents were re-distilled prior to use in the reactions. Other commercial reagents were used as received.

General experimental procedure for the AgOTf and $Dy(OTf)_3$ co-catalyzed tandem reaction of *N′*-(2-alkynylbenzylidene)hydrazide 1 with indole 2. A mixture of *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.3 mmol), indole **2** (0.6 mmol, 2.0 equiv), AgOTf (10 mol %) and $Dy(OTf)_3$ (30 mol %) in 1,2-dichloroethane (1.0 mL) was stirred at 70 °C. After completion of reaction as indicated by TLC, the mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL), filtered through a thin pad of silica gel (eluting with ethyl acetate), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with PE/EA = 1/1 to 1/10) to provide the desired product **3**.

1-(Indol-3-yl)-2-amino-3-phenylisoquinolinium triflate 3a. ^{1}H NMR (400 MHz, $CDCl_3$): 6.42 (s, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.19–7.23 (m, 2H), 7.56–7.57 (m, 3H), 7.60–7.66 (m, 2H), 7.75–7.77 (m, 2H), 7.89–8.00 (m, 5H), 11.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.1, 113.5, 120.4 (q, $^1J_{CF}$ = 318 Hz), 119.4, 121.9, 123.7, 125.3, 125.7, 127.4, 128.2, 129.3, 130.0, 130.3, 130.8, 131.0, 131.4, 134.6, 135.2, 136.6, 142.8, 148.9; IR (KBr, cm^{-1}): 3464, 1636, 1456; *m/z* (ESI): 336 (M^+ + H); HRMS calcd for $C_{23}H_{18}N_3$ (M^+ + H): 336.1501, found: 336.1518.

1-(4-Methoxyindol-3-yl)-2-amino-3-phenylisoquinolinium triflate 3b. ^{1}H NMR (400 MHz, $CDCl_3$): 3.59 (s, 3H), 6.05 (s, 2H), 6.48 (d, J = 7.9 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 7.46–7.47 (m, 3H), 7.57–7.58 (m, 4H), 7.81–7.93 (m, 4H), 11.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 100.0, 101.6, 106.8, 115.7, 120.4 (q, $^1J_{CF}$ = 318 Hz), 124.7, 125.3, 127.0, 128.6, 129.1, 129.5, 129.7, 130.4, 130.5, 130.6, 131.3, 134.7, 135.4, 138.2, 143.6, 152.0, 152.1; IR (KBr, cm^{-1}): 3447, 1636, 1457; *m/z* (ESI): 366 (M^+ + H); HRMS calcd for $C_{24}H_{20}N_3O$ (M^+ + H): 366.1606, found: 366.1626.

1-(6-Methoxyindol-3-yl)-2-amino-3-phenylisoquinolinium triflate 3c. ^{1}H NMR (400 MHz, $CDCl_3$): 3.76 (s, 3H), 6.45 (s, 2H), 6.77 (d, J = 8.5 Hz, 1H), 7.09–7.13 (m, 2H), 7.55–7.56 (m, 3H), 7.64 (t, J = 7.3 Hz, 1H), 7.74–7.75 (m, 3H), 7.87–7.98 (m, 4H), 11.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 95.7, 100.9, 112.6, 119.2, 119.9, 120.4 (q, $^1J_{CF}$ = 318 Hz), 125.3, 127.1, 128.1, 129.2, 129.8, 130.1, 130.3, 130.6, 130.7, 130.9, 134.4, 135.0, 137.6, 142.6, 148.8, 157.2; IR (KBr, cm^{-1}): 3465, 1636, 1455; *m/z* (ESI): 366 (M^+ + H); HRMS calcd for $C_{24}H_{20}N_3O$ (M^+ + H): 366.1606, found: 366.1622.

1-(5-Bromoindol-3-yl)-2-amino-3-phenylisoquinolinium triflate 3d. ^{1}H NMR (400 MHz, $CDCl_3$): 6.44 (s, 2H), 7.23–7.25 (m, 1H), 7.32–7.33 (m, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.56–7.58 (m, 3H), 7.66 (t, J = 8.3 Hz, 1H), 7.74–7.76 (m, 2H), 7.84 (d, J = 8.8 Hz, 1H), 7.90–7.92 (m, 2H), 7.98–8.01 (m, 2H), 11.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.7, 115.0, 115.1, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.8, 126.0, 126.5, 127.1, 127.5, 128.3, 129.4, 130.0, 130.6, 131.0, 131.2, 132.3, 134.8, 135.2, 135.4, 143.0, 148.3; IR (KBr, cm^{-1}): 3445, 1636, 1452; *m/z* (ESI): 414 (M^+ + H); HRMS calcd for $C_{23}H_{17}BrN_3$ (M^+ + H): 414.0606, found: 414.0624.

1-(Indol-3-yl)-2-amino-3-(4-methoxyphenyl)isoquinolinium triflate 3e. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H), 6.41 (s, 2H), 7.06–7.14 (m, 3H), 7.18–7.23 (m, 2H), 7.59–7.62 (m, 2H),

‡ Crystal data and structure refinement for compound **3j**. Empirical formula: $C_{26}H_{20}BrClF_4N_3O_4S$ (Molecular weight: 661.87), Crystal system: Monoclinic. Unit cell dimensions: a = 11.839(2) Å α = 90 deg., b = 10.8146(18) Å β = 99.293(2) deg., c = 21.529(4) Å γ = 90 deg. Volume: 2720.3(8) Å^3, refine_1s_shift/su_max 0.041 mean 0.002, Temperature: 296(2) K, space group: P2(1)/n, Z, Calculated density: 4, 1.616 Mg/m^3, Reflections collected/unique: 14327 / 5342 [R(int) = 0.0248], FinalRindices [I2sigma(I)]: R1 = 0.0410, wR2 = 0.1018, R indices (all data): R1 = 0.0663, wR2 = 0.1151.

7.68–7.71 (m, 2H), 7.86–7.89 (m, 3H), 7.93 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 11.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 101.2, 113.6, 114.8, 119.4, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.8, 122.6, 123.6, 125.3, 125.5, 127.2, 128.1, 130.4, 130.6, 131.4, 131.6, 134.4, 135.2, 136.6, 142.8, 148.6, 161.6; IR (KBr, cm^{-1}): 3449, 1636, 1450; m/z (ESI): 366 (M^+ + H); HRMS calcd for $C_{24}H_{20}N_3O$ (M^+ + H): 366.1606, found: 366.1622.

1-(Indol-3-yl)-2-amino-3-butylisoquinolinium triflate 3f. ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (t, J = 7.3 Hz, 3H), 1.54–1.56 (m, 2H), 1.89–1.91 (m, 2H), 3.24–3.28 (m, 2H), 6.80 (s, 2H), 7.12–7.20 (m, 3H), 7.55 (t, J = 7.3 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.76–7.77 (m, 2H), 7.86 (t, J = 7.3 Hz, 1H), 7.95 (t, J = 8.3 Hz, 2H), 11.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.2, 28.8, 31.5, 100.8, 113.5, 118.6, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.9, 122.8, 123.7, 125.3, 126.6, 127.6, 129.9, 134.3, 135.4, 136.6, 146.3, 149.5; IR (KBr, cm^{-1}): 3446, 1636, 1452; m/z (ESI): 316 (M^+ + H); HRMS calcd for $C_{21}H_{22}N_3$ (M^+ + H): 316.1814, found: 316.1817.

1-(Indol-3-yl)-2-amino-3-phenyl-7-fluoroisoquinolinium triflate 3g. ^{1}H NMR (400 MHz, $CDCl_3$): 6.37 (s, 2H), 7.11 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.48–7.53 (m, 4H), 7.57–7.62 (m, 2H), 7.71–7.74 (m, 2H), 7.85–7.86 (m, 1H), 7.97 (s, 1H), 8.01–8.05 (m, 1H), 11.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.8, 113.4, 113.9 (d, $^2J_{CF}$ = 24 Hz), 119.2, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.9, 123.6, 124.9, 125.0 (d, $^2J_{CF}$ = 25 Hz), 125.4, 129.2, 129.7 (d, $^3J_{CF}$ = 10 Hz), 129.9, 130.3, 130.4, 131.0, 132.2, 136.5, 142.2, 147.6, 147.7, 162.7 (d, $^1J_{CF}$ = 254 Hz); IR (KBr, cm^{-1}): 3445, 1636, 1450; m/z (ESI): 354 (M^+ + H); HRMS calcd for $C_{23}H_{17}FN_3$ (M^+ + H): 354.1407, found: 354.1415.

1-(Indol-3-yl)-2-amino-3-(4-methoxyphenyl)-7-fluoroisoquinolinium triflate 3h. ^{1}H NMR (400 MHz, $CDCl_3$): 3.82 (s, 3H), 6.48 (s, 2H), 7.03 (d, J = 7.3 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 6.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H), 7.57–7.63 (m, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.87 (s, 1H), 7.97 (s, 1H), 8.01–8.04 (m, 1H), 11.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 100.9, 113.4, 113.8 (d, $^2J_{CF}$ = 25 Hz), 114.7, 119.2, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.8, 122.2, 123.6, 124.6, 124.9, 125.3, 129.5, 130.3, 131.0, 131.5, 132.2, 136.5, 142.2, 147.4, 161.5, 162.6 (d, $^1J_{CF}$ = 254 Hz); IR (KBr, cm^{-1}): 3463, 1636, 1455; m/z (ESI): 384 (M^+ + H); HRMS calcd for $C_{24}H_{19}FN_3O$ (M^+ + H): 384.1512, found: 384.1526.

1-(4-Methoxyindol-3-yl)-2-amino-3-(4-methoxyphenyl)-7-fluoroisoquinolinium triflate 3i. ^{1}H NMR (400 MHz, $CDCl_3$): 3.64 (s, 3H), 3.81 (s, 3H), 6.27 (s, 2H), 6.53 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.47 (dd, J = 9.6, 2.4 Hz, 1H), 7.59–7.64 (m, 4H), 8.00 (s, 1H), 8.03–8.07 (m, 1H), 11.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.6, 100.0, 101.7, 106.8, 113.8 (d, $^2J_{CF}$ = 25 Hz), 114.8, 115.7, 120.4 (q, $^1J_{CF}$ = 318 Hz), 122.9, 124.9, 125.1, 125.4, 128.9, 130.1 (d, $^3J_{CF}$ = 10 Hz), 130.4 (d, $^3J_{CF}$ = 9 Hz), 131.4, 132.6, 138.3, 142.8, 150.0, 152.3, 161.5, 162.7 (d, $^1J_{CF}$ = 253 Hz); IR (KBr, cm^{-1}): 3446, 1618, 1514, 1464; m/z (ESI): 414 (M^+ + H); HRMS calcd for $C_{25}H_{21}FN_3O_2$ (M^+ + H): 414.1618, found: 414.1636.

1-(5-Bromoindol-3-yl)-2-amino-3-(4-methoxyphenyl)-7-fluoroisoquinolinium triflate 3j. ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (s, 3H), 6.50 (s, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 1H), 7.37–7.39 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.59–7.67 (m, 3H), 7.85 (s, 1H), 8.03 (s, 1H), 8.05–8.09 (m, 1H), 11.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 100.3, 113.0 (d, $^2J_{CF}$ = 24 Hz), 114.6, 114.8, 114.9, 120.4 (d, $^1J_{CF}$ = 318 Hz), 121.7, 124.9 (d, $^2J_{CF}$ = 25 Hz), 125.7, 126.3, 129.4 (d, $^3J_{CF}$ = 9 Hz), 130.5, 131.3, 131.6, 132.2, 135.1, 142.0, 146.1, 146.2, 161.4, 162.6 (d, $^1J_{CF}$ = 254 Hz); IR (KBr, cm^{-1}): 3447, 1628, 1456; m/z (ESI): 462 (M^+ + H); HRMS calcd for $C_{24}H_{18}BrFN_3O$ (M^+ + H): 462.0617, found: 462.0630.

1-(Indol-3-yl)-2-amino-3-butyl-7-fluoroisoquinolinium triflate 3k. ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (t, J = 7.2 Hz, 3H), 1.47–1.57 (m, 2H), 1.85–1.92 (m, 2H), 3.16–3.30 (m, 2H), 6.86 (s, 2H), 7.10–7.22 (m, 3H), 7.37 (dd, J = 9.2, 2.0 Hz, 1H), 7.58–7.64 (m, 2H), 7.78 (d, J = 2.4 Hz, 1H), 7.96 (s, 1H), 7.99–8.03 (m, 1H), 11.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 22.1, 28.8, 31.4, 101.4, 112.4, 112.6, 118.8, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.6, 123.4, 123.5, 124.6 (d, $^2J_{CF}$ = 25 Hz), 125.4, 129.2 (d, $^3J_{CF}$ = 10 Hz), 129.9, 130.5 (d, $^3J_{CF}$ = 9 Hz), 133.1, 136.9, 145.9, 148.7, 162.5 (d, $^1J_{CF}$ = 251 Hz); IR (KBr, cm^{-1}): 3446, 1638, 1536, 1450; m/z (ESI): 334 (M^+ + H); HRMS calcd for $C_{21}H_{21}FN_3$ (M^+ + H): 334.1720, found: 334.1730.

1-(4-Methoxyindol-3-yl)-2-amino-3-butyl-7-fluoroisoquinolinium triflate 3l. ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (t, J = 6.9 Hz, 3H), 1.44–1.52 (m, 2H), 1.82–1.89 (m, 2H), 3.11–3.18 (m, 1H), 3.31–3.37 (m, 1H), 3.58 (s, 3H), 6.53 (s, 1H), 6.55 (s, 2H), 7.12 (t, J = 8.3 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.56–7.63 (m, 2H), 8.00 (s, 1H), 8.03–8.07 (m, 1H), 11.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 29.5, 32.0, 55.5, 99.9, 101.7, 106.7, 113.6 (d, $^2J_{CF}$ = 24 Hz), 115.6, 120.4 (q, $^1J_{CF}$ = 318 Hz), 123.3, 125.0, 125.2 (d, $^2J_{CF}$ = 25 Hz), 128.5, 129.6 (d, $^3J_{CF}$ = 11 Hz), 129.9, 133.1, 138.4, 146.6, 151.8, 152.2, 162.3 (d, $^1J_{CF}$ = 253 Hz); IR (KBr, cm^{-1}): 3446, 1638, 1507, 1456; m/z (ESI): 364 (M^+ + H); HRMS calcd for $C_{22}H_{23}FN_3O$ (M^+ + H): 364.1825, found: 364.1839.

1-(6-Methoxyindol-3-yl)-2-amino-3-butyl-7-fluoroisoquinolinium triflate 3m. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (t, J = 7.2 Hz, 3H), 1.46–1.53 (m, 2H), 1.81–1.87 (m, 2H), 3.13–3.26 (m, 2H), 3.75 (s, 3H), 6.77 (d, J = 8.4 Hz, 1H), 6.87 (s, 2H), 7.00 (d, J = 8.8 Hz, 1H), 7.14 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.87 (s, 1H), 7.93–7.97 (m, 1H), 10.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 28.8, 31.5, 55.6, 95.9, 100.7, 113.0, 113.4 (d, $^2J_{CF}$ = 25 Hz), 119.1, 119.4, 120.4 (q, $^1J_{CF}$ = 318 Hz), 122.7, 125.0 (d, $^2J_{CF}$ = 26 Hz), 128.6, 129.0 (d, $^3J_{CF}$ = 11 Hz), 129.9 (d, $^3J_{CF}$ = 9 Hz), 132.6, 137.9, 145.8, 148.4, 157.6, 162.4 (d, $^1J_{CF}$ = 253 Hz); IR (KBr, cm^{-1}): 3446, 1638, 1473, 1456; m/z (ESI): 364 (M^+ + H); HRMS calcd for $C_{22}H_{23}FN_3O$ (M^+ + H): 364.1825, found: 364.1843.

1-(Indol-3-yl)-2-amino-3-phenyl-5,6,7-trimethoxyisoquinolinium triflate 3n. ^{1}H NMR (400 MHz, $CDCl_3$): 3.66 (s, 3H), 4.07 (s, 3H), 4.08 (s, 3H), 6.31 (s, 2H), 7.00 (s, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.20–7.26 (m, 2H), 7.56–7.57 (m, 3H), 7.63 (d, J = 8.3 Hz, 1H), 7.73–7.74 (m, 2H), 8.02 (d, J = 3.0 Hz, 1H), 8.12 (s, 1H), 11.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3, 61.4, 61.8, 101.1, 104.2, 113.5, 119.2, 119.5, 120.4 (q, $^1J_{CF}$ = 318 Hz), 121.4, 123.4, 125.0, 125.4, 127.4, 129.1, 129.9, 130.6, 130.8, 131.3, 136.6, 141.0, 146.2, 146.3, 147.0, 156.4; IR (KBr, cm^{-1}): 3445, 1636, 1540, 1456; m/z (ESI): 426 (M^+ + H); HRMS calcd for $C_{26}H_{24}N_3O_3$ (M^+ + H): 426.1818, found: 426.1837.

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