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Diversity-Oriented Synthesis of Polycyclic Indoles: Brønsted or Lewis Acid Catalyzed Three-Component Reaction for the Synthesis of α-Carbolines and Pyrimidoindoles[‡]

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We report the diversity-oriented synthesis of pyrido- and pyrimido-indoles from an acid-catalyzed three component (3C) reaction involving ethyl 2-amino-1*H*-indole-3-carboxylates, arylaldehydes, and terminal alkynes. In the presence of a Brønsted acid such as trifluoroacetic acid (TFA), the 3C reaction furnished a mixture of pyrido- and pyrimido-indoles, whereas when catalyzed by $Yb(OTf)_3$ as a Lewis acid, pyrimidoindoles were obtained as the single product. The findings demonstrate the ability to control reaction products through change in the acid catalyst. The salient feature during TFA-catalyzed 3C reaction is that two different pathways are followed in one pot after propargylamine formation. The two cascade cyclizations comprise in situ decarboxylation-carbocyclization and an intramolecular hydroamination to afford products with different connectivity.

Introduction

The ubiquitous presence of N-polyheterocycles in the vast majority of drugs and natural products has led to many efforts for their synthesis and functionalization with a view to generating molecules with diverse physical and chemical properties for drug discovery. Among such synthetic efforts, Schreiber laid down the concept of diversity-oriented synthesis (DOS),[1,2] in which one-pot reactions lead to the generation of structurally diverse skeletal arrays as a collection of pure compounds that are suitable for new lead generation against disease targets. Such a format requires the selection of substrates with multiple bond-forming sites (atoms) that can be selectively exploited in one-pot[3] to afford structurally diverse molecular architectures. The approach also requires the identification of highly efficient catalytic processes for these annulation reactions that are not only efficient, selective, and high-yielding but are also rapid and eco-friendly. A detailed survey of the literature revealed few reports[4] dealing with branching pathways in a one-pot fashion affording annulated heterocycles with distinct connectivity in isolable yields.

In our laboratory,[5] we have been regioselectively manipulating the nucleophilicities of the N-1, C-2, and C-3 positions in indole by treating suitably functionalized indole derivatives with alkyne-based reactants.[6] These one-pot reactions, performed in the presence of an appropriate catalyst (metals/acids/halides), led to the formation of structurally diverse polyheterocycles through different annulation pathways. Recently, in one such effort, alkynones were reacted with ethyl 2-amino-1*H*-indole-3-carboxylates and 2-amino indole hydrochloride, which led to the synthesis of pyrimidoindoles[5h] and α-carbolines[5i] (Scheme 1). However, drawbacks associated with both methods included poor stability of the 2-aminoindole hydrochloride and the need to synthesize the starting alkynones in an additional step. In view of this, we then examined the efficacy of 2-aminoindole-3-carboxyl ester **1** as a substrate for the generation of two distinct skeletal arrays: pyrimidoindoles and α-carbolines[7] through two different pathways in a one-pot fashion. We envisioned that, owing to the availability of the three N1-H, C2-NH_2, and C3-COOEt nucleophilic functionalities in indole substrate **1**, coupled with the ease of decarboxylation induced by Brønsted acid,[8] it may be possible to trigger differential acid-catalyzed annulation reactions, which, in turn, may afford products with distinct atom connectivity. To achieve this, we set out to annulate ethyl 2-amino-1*H*-indole-3-carboxylates **1** with arylaldehydes **2** and terminal alkynes **3** in the presence of an acid in a one-pot reaction. Herein, we disclose our results on a DOS involving a 3C reaction affording two distinct indole-based heterocycles: α-carbolines and/or pyrimidoindoles through different annulation strategies that depend on the selection of acid type.

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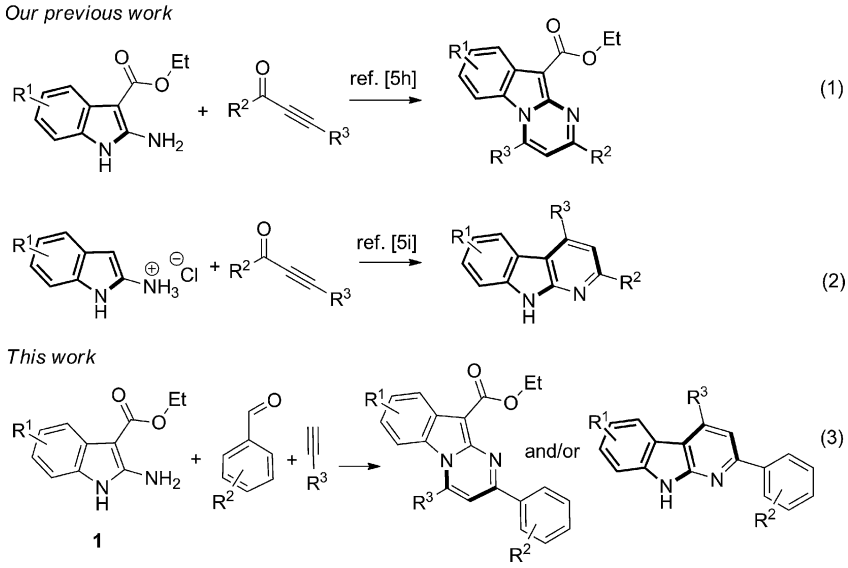
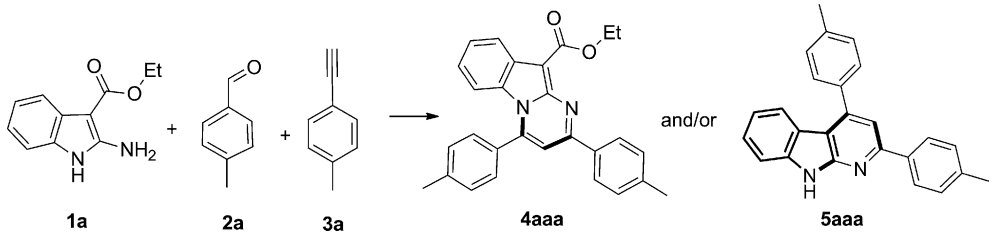


Scheme 1. Synthesis of α-carbolines and pyrimidoindoles from 2-aminoindoles.

Results and Discussion

Our studies commenced with the treatment of ethyl 2-amino-1*H*-indole-3-carboxylate (**1a**) with 4-methylbenzaldehyde (**2a**) and 4-ethynyl toluene (**3a**) in the presence of various transition-metal catalysts (Pd/Ag/Cu) in a one-pot fashion. Unfortunately, none of the above catalytic systems facilitated the required transformation (Table 1, entries 1–4). This prompted us to explore the abilities of various Lewis acid driven transformations because their application in the synthesis of structurally diverse heterocycles has been well documented.[9,10] Among the variety of Lewis acids screened, $Yb(OTf)_3$ in toluene under microwave conditions for 1.5 h furnished pyrimidoindole **4aaa** as a single product in 48% isolated yield (entry 5). Switching solvent from toluene to *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) failed to produce the final products (entries 6 and 7). On the other hand, a moderate increase in the iso-

Table 1. Optimization of the synthesis of pyrimidoindole **4aaa** and α-carboline **5aaa**.[a]



Entry	Catalyst (mol-%)	Solvent	Time [h]	Yield [%][b]
1	–	CH_3CN	2	n.r.
2	$Cu(OTf)_2$ (10)	CH_3CN	2	n.r.
3	Ag(OTf) (10)	CH_3CN	2	n.r.
4	$Pd(OAC)_2$ (10)	CH_3CN	2	n.r.
5	$Yb(OTf)_3$ (10)	toluene	1.5	48/–
6	$Yb(OTf)_3$ (10)	DMF	2	n.r.
7	$Yb(OTf)_3$ (10)	DMSO	2	n.r.
8	**$Yb(OTf)_3$ (10)**	**CH_3CN**	**40 min**	**68/–**
9	$Yb(OTf)_3$ (50)	CH_3CN	40 min	60/<10
10	$Sc(OTf)_3$ (10)	CH_3CN	1.5	58/–
11	$Zn(OTf)_2$ (10)	CH_3CN	2	52/–
12	*p*TsOH (10)	CH_3CN	3	25/–
13	TFA (10)	CH_3CN	0.5	40/38[c]
14	TFA (50)	CH_3CN	0.5	37/44[c]
15	**TFA**[d]	**CH_3CN**	**0.5**	**23/53**[c]
16	TfOH[d]	CH_3CN	0.5	27/48[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), catalyst, solvent (5 mL), 100 °C in microwave. [b] Isolated yield; n.r.: no reaction. [c] The crude products exhibited polar impurities on TLC. [d] Acid (1.0 equiv.) was used.

lated yield of **4aaa** to 68% was observed in acetonitrile (entry 8). In an attempt to further increase the yield of **4aaa**, we enhanced the catalyst loading from 10 to 50 mol-% (entry 9) and notably, the altered conditions furnished a mixture of two products (60 and <10% isolated yield) comprising **4aaa** and a new product that was characterized as α-carboline **5aaa** (^{1}H NMR characteristic singlet at δ = 11.0 Hz).

Our findings thus suggest that by manipulating the reaction conditions it may be possible to obtain two distinct annulated products. This led us to screen variety of Lewis and Brønsted acids for the 3C reaction with a view to increasing the yields of reaction products **4aaa** and **5aaa**. Attempts to replace $Yb(OTf)_3$ with $Sc(OTf)_3$ and $Zn(OTf)_3$ furnished **4aaa** in diminished yield (Table 1, entries 10 and 11), whereas addition of *p*-toluenesulfonic acid (*p*TsOH) as a catalyst afforded **4aaa** in poor yield (entry 12). Use of Brønsted acids, however, led to the formation of a mixture of **4aaa** and **5aaa** in isolable yields. Employing trifluoroacetic acid (TFA) under microwave conditions in acetonitrile for 0.5 h furnished a mixture of **4aaa** and **5aaa** in 40 and 38% isolated yields, respectively (entry 13) along with polar impurities as evident by TLC. Increasing the concentration of TFA from 10 to 100 mol-% resulted in a gradual decrease in the isolated yields of **4aaa** from 40 to 23% and simultaneous enhancement in the isolated yield of **5aaa** from 38 to 53% (entries 13–15). Indeed, the prevalence of polar impurities under Brønsted acid catalysis was observed in all cases. Employing a stronger acid such as TfOH (1.0 equiv.) under microwave conditions in acetonitrile for 0.5 h afforded **5aaa** in 48% isolated yield, **4aaa** in 27% yield and the rest comprised of polar impurities (entry 16). The formation of polar impurities in the presence of Brønsted acids may be attributed to degradation products arising from the poorly stable[11] 2-aminoindole derivative being generated in situ following the decarboxylation. Thus, the optimum reaction conditions for the synthesis of **5aaa** involved the use of TFA (1.0 equiv.) as catalyst in acetonitrile under microwave irradiation at 100 °C for 30 min, whereas the optimized synthesis of **4aaa** involved the use of $Yb(OTf)_3$ as catalyst in acetonitrile under microwave irradiation at 100 °C for 40 min. Attempts to treat *N*-methyl (ethyl 2-amino-5-fluoro-1-methyl-1*H*-indole-3-carboxylate) (**1d**) with an aldehyde and the alkyne in the presence of either TFA or $Yb(OTf)_3$ failed to yield the corresponding pyridoindole, because the indole derivative itself was found to be highly unstable under both acidic conditions.

A plausible mechanism for the formation of **4aaa** and **5aaa** is depicted in Figure 1. Initially, aldehyde **2a**, in the presence of Lewis/Brønsted acid, may react with amine **1a** to afford imine **I**, which may then be followed by nucleophilic addition of the terminal alkyne **3a** to furnish propargylamine[12] **II**. Following activation of the alkyne moiety by Yb,[13] **III** may then undergo concomitant intramolecular nucleophilic attack from the indolic N^a-H to afford dihydro intermediate **IV**. This is followed by aerial oxidation

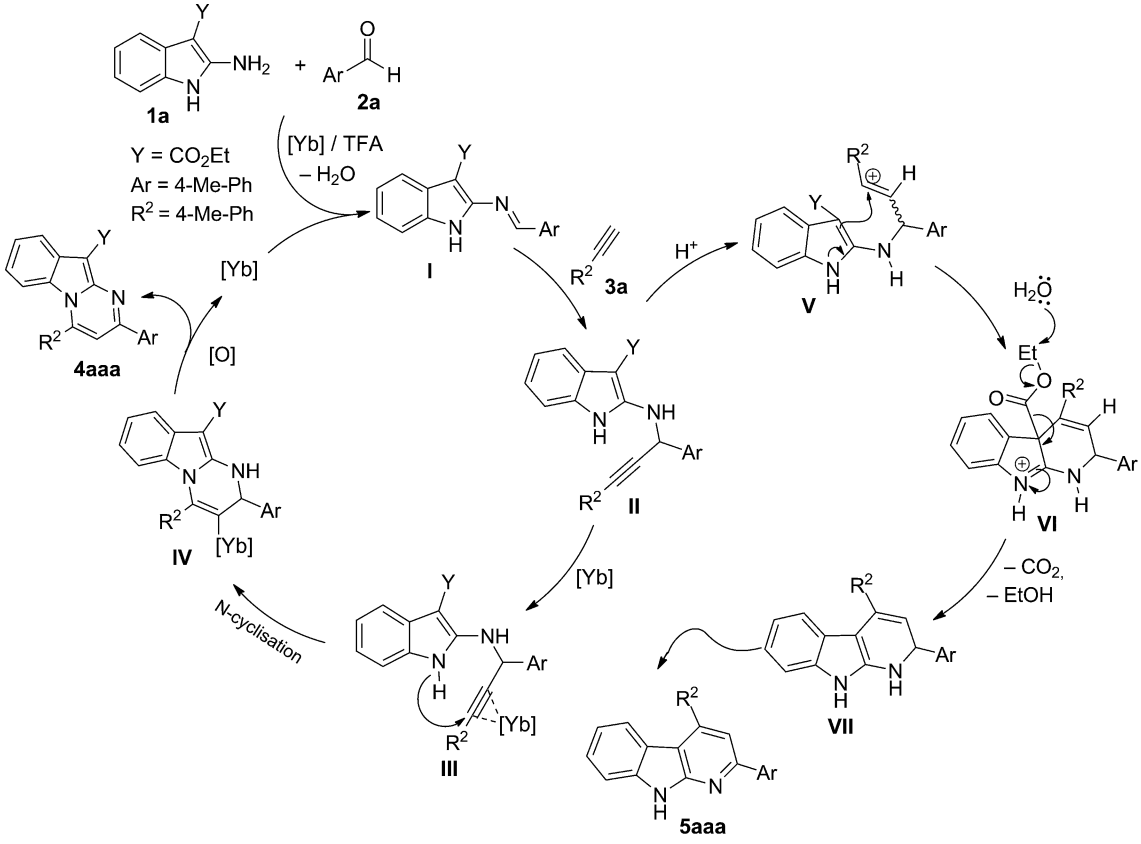
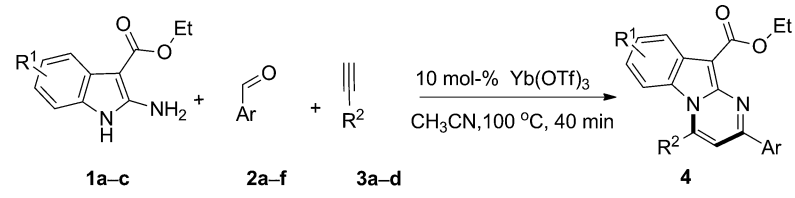


Figure 1. Plausible mechanism for the formation of pyrimidoindole **4aaa** and pyridoindole **5aaa**.

to produce the final product **4aaa** along with regeneration of catalyst. For the formation of **5aaa**, the reaction may commence by H^+-mediated alkyne[14] activation toward intramolecular nucleophilic attack by the C-3 of the indole to furnish cyclic intermediate **VI** via intermediate **V**. In the next step, the ester group in **VI** may undergo acid hydrolysis followed by decarboxylation, which, in turn, provides residual electrons to achieve aromaticity in the indole to afford dihydro intermediate **VII**. The latter may finally undergo aerial oxidation to afford **5aaa**. It is interesting to note that although both products are formed under acidic conditions, orthogonal selectivity leading to the formation of **4** could be observed only in the presence of a mild Lewis acid.

The scope and limitations of the reaction under the optimized conditions for the selective synthesis of **4** was established by introducing diversity in substrates **1**, **2**, and **3** (Table 2). The efficacy of the reaction for the selective synthesis of **4** was demonstrated by synthesizing 12 com-

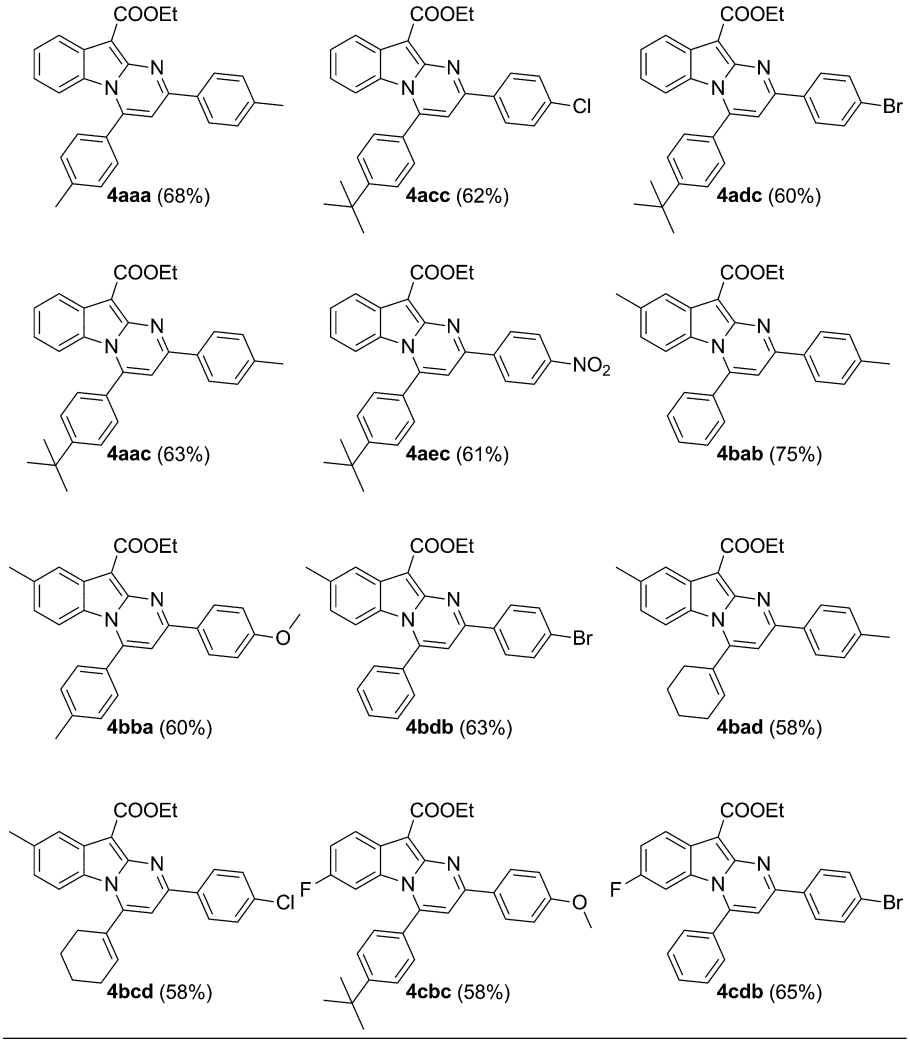
Table 2. Substrate scope of the reaction to generate pyrimidoindole **4**.[a]



1a: R^1 = H
1b: R^1 = 5-CH_3
1c: R^1 = 6-F

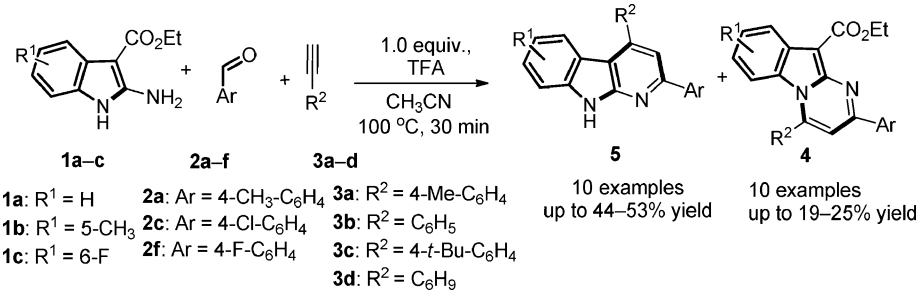
2a: Ar = 4-CH_3-C_6H_4
2b: Ar = 4-OMe-C_6H_4
2c: Ar = 4-Cl-C_6H_4
2d: Ar = 4-Br-C_6H_4
2e: Ar = 4-NO_2-C_6H_4

3a: R^2 = 4-Me-C_6H_4
3b: R^2 = C_6H_5
3c: R^2 = 4-*t*Bu-C_6H_4
3d: R^2 = C_6H_9



[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), $Yb(OTf)_3$ (10 mol-%), CH_3CN, 100 °C in microwave, 40 min.

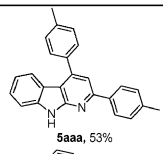
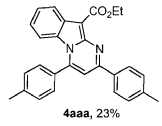
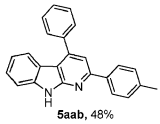
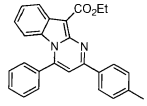
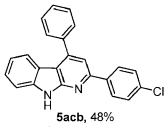
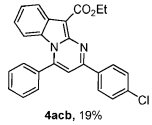
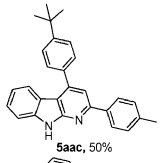
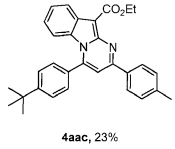
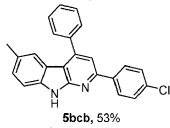
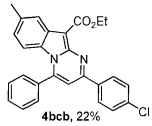
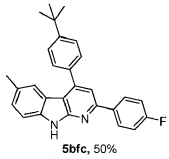
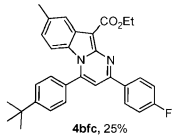
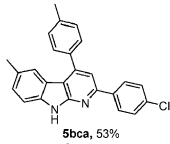
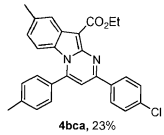
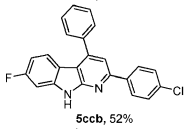
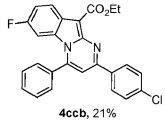
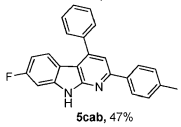
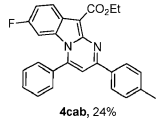
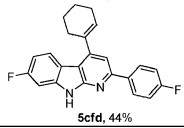
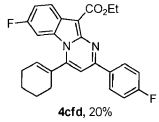
Table 3. Substrate scope for the reaction to generate pyridoindole **5** and **4**.[a]



1a: R^1 = H; **1b**: R^1 = 5-CH_3; **1c**: R^1 = 6-F

2a: Ar = 4-CH_3-C_6H_4; **2c**: Ar = 4-Cl-C_6H_4; **2f**: Ar = 4-F-C_6H_4

3a: R^2 = 4-Me-C_6H_4; **3b**: R^2 = C_6H_5; **3c**: R^2 = 4-*t*-Bu-C_6H_4; **3d**: R^2 = C_6H_9

Entry	1	2	3	Product, % yield **5**[b]	Product, % yield **4**[b]
1	**1a**	**2a**	**3a**	 **5aaa**, 53%	 **4aaa**, 23%
2	**1a**	**2a**	**3b**	 **5aab**, 48%	 **4aab**, 22%
3	**1a**	**2c**	**3b**	 **5acb**, 48%	 **4acb**, 19%
4	**1a**	**2a**	**3c**	 **5aac**, 50%	 **4aac**, 23%
5	**1b**	**2c**	**3b**	 **5bcb**, 53%	 **4bcb**, 22%
6	**1b**	**2f**	**3c**	 **5bfc**, 50%	 **4bfc**, 25%
7	**1b**	**2c**	**3a**	 **5bca**, 53%	 **4bca**, 23%
8	**1c**	**2c**	**3b**	 **5ccb**, 52%	 **4ccb**, 21%
9	**1c**	**2a**	**3b**	 **5cab**, 47%	 **4cab**, 24%
10	**1c**	**2f**	**3d**	 **5cfd**, 44%	 **4cfd**, 20%

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), TFA (1.0 equiv.), CH_3CN, 100 °C in microwave, 30 min. [b] Isolated yield.

pounds, which were isolated in moderate to good yields (58–70%). The substituents on the indole played an important role in determining the yields of final products. Substrates with R^1 as electron-donating groups or unsubstituted (methyl/H) produced better yields than those with electron-withdrawing groups (7-fluoro). Similarly, replacing Ar in aldehydes with an electron-donating group (4-Me) furnished products in better isolated yields when compared with those containing electron-withdrawing groups (Ar = 4-F, 4-Cl, 4-Br, or 4-NO_2). Unfortunately, substrates with R^2 as aliphatic substituents such as 1-octyne, 1-hexyne, and 1-ethynyltrimethylsilane failed to furnish any cyclized products; however, when replaced with 1-ethynylcyclohexene, the corresponding products **4bad** and **4bcd** were obtained in 58% isolated yield.

The versatility of the TFA-catalyzed 3C reaction for the synthesis of **5** was demonstrated by synthesizing 10 different compounds in 44–53% isolated yield (Table 3). In all cases the corresponding product **4** was obtained as a minor component in 19–25% isolated yield. The diminished yields of **5** may be attributed to poor stability of the 2-amino indole derivative generated in situ following decarboxylation under acidic conditions, thereby resulting in the formation of polar impurities. Thus, as depicted in Figure 1, during the formation of **5** it appears that a part of intermediate **II**, before undergoing conversion into **VII** following decarboxylation, undergoes H^+ mediated intramolecular hydroamination to afford **4** as a minor product, whereas the decarboxylated intermediate **VII** undergoes either predominant carbocyclization to afford **5** or decomposition to yield polar impurities.

Conclusions

We have described a diversity-oriented synthesis of polycyclic indoles through a 3C reaction involving ethyl 2-aminoindole-3-carboxylates, arylaldehydes, and terminal alkynes catalyzed by either Brønsted or Lewis acids. The 3C reaction allows selective control of the formation of reaction products by changing the nature of the acid catalyst to furnish α-carbolines and/or pyrimidoindoles in a one-pot fashion through two different reaction pathways.

Experimental Section

I. General Information and Methods: All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 300 or 400 MHz spectrometers for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR spectroscopy. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/[D_6]DMSO for ^{1}H and ^{13}C NMR spectroscopy. Multiplicities are reported as: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m), broad singlet (br. s). HRMS were obtained by using the electrospray ionization (ESI) technique and a time-of-flight (TOF) analyzer. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage. All the reactions were performed in special 10 mL glass vessels. Column chromatography was performed using silica gel (100–200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). The purity and identification of the compounds were further established by using HRMS (ESI). Melting points were measured with a capillary melting-point apparatus and are uncorrected.

II. General Procedure for the Preparation of Ethyl 2-Amino-1*H*-indole-3-carboxylate 1a–d: Prepared according to the reported procedure.[15,16] All aryl aldehydes **2a–f** and alkynes **3a–d** were commercially available. Compounds **4bba**, **4cbc**, and **4aab** are known[5h] and the spectroscopic and physical data obtained here matches well with reported data.

III. General Procedure for the Synthesis of Pyrimido[1,2-*a*]indole (4): A mixture of substituted ethyl 2-amino-1*H*-indole-3-carboxylate **1** (1.0 mmol), substituted benzaldehyde **2** (1.0 mmol), substituted alkyne **3** (1.0 mmol), and Yb(OTf)$_3$ (10 mol-%) in acetonitrile (5 mL) was stirred at 100 °C for 30 min under microwave irradiation. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate/hexane, 10%) to give **4**.

IV. General Procedure for the Synthesis of Pyrido[2,3-*b*]indole (5/4 mixture): A mixture of substituted ethyl 2-amino-1*H*-indole-3-carboxylate **1** (1.0 mmol), substituted benzaldehyde **2** (1.0 mmol), substituted alkyne **3** (1.0 mmol), and TFA (1.0 equiv.) in acetonitrile (5 mL) was stirred at 100 °C under microwave irradiation. The progress of the reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate/hexane, 5–10%) to give **5** and **4**.

Ethyl 2-(4-Methylphenyl)-4-[4-(methylphenyl)]pyrimido[1,2-*a*]indole-10-carboxylate (4aaa): Yield 350 mg (68%); orange solid; m.p. 188–190 °C; R_f = 0.50 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3429, 2931, 1662, 1409, 1215 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 7.5 Hz, 2 H), 7.39–7.31 (m, 5 H), 7.38 (m, 2 H), 7.02 (s, 1 H), 6.92–6.88 (m, 1 H), 6.57 (d, J = 8.2 Hz, 1 H), 4.50 (m, 2 H), 2.48 (s, 3 H), 2.36 (s, 3 H), 1.51 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 158.0, 148.9, 147.1, 141.6, 141.1, 134.1, 130.9, 130.5, 130.1, 129.7, 125.2, 128.0, 127.6, 125.1, 121.8, 121.1, 115.0, 105.5, 94.9, 59.6, 21.7, 21.6, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{25}N_2O_2$ [M + H] 421.1916; found 421.1901.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-2-(4-chlorophenyl)pyrimido[1,2-*a*]-indole-10-carboxylate (4acc): Yield 366 mg (62%); orange solid; m.p. 200–202 °C; R_f = 0.56 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3446, 2932, 1550, 1382, 1223 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, J = 8.0 Hz, 1 H), 8.19–8.17 (m, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.44–7.38 (m, 4 H), 7.35–7.31 (m, 1 H), 6.99 (s, 1 H), 6.91–6.88 (m, 1 H), 6.56 (d, J = 8.7 Hz, 1 H), 4.49 (q, J = 7.2 Hz, 2 H), 1.49 (t, J = 7.2 Hz, 3 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 151.9, 149.8, 144.5, 142.1, 132.6, 130.5, 125.9, 125.7, 124.4, 124.2, 123.3, 121.6, 120.6, 117.2, 116.6, 110.3, 100.5, 90.7, 54.9, 30.4, 26.6, 10.0 ppm. HRMS (ESI): m/z calcd. for $C_{30}H_{28}N_2O_2Cl$ [M + H] 483.1839; found 483.1824.

Ethyl 2-(4-Bromophenyl)-4-[4-(*tert*-butyl)phenyl]pyrimido[1,2-*a*]-indole-10-carboxylate (4adc): Yield 386 mg (60%); orange solid;

m.p. 192–194 °C; R_f = 0.48 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3446, 2942, 2130, 1653, 1396, 1212 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, J = 8.0 Hz, 1 H), 8.14–8.07 (m, 2 H), 8.57–7.59 (m, 4 H), 7.45–7.43 (m, 2 H), 7.37–7.33 (m, 1 H), 7.01 (s, 1 H), 6.93–6.91 (m, 1 H), 6.57 (d, J = 4.0 Hz, 1 H), 4.49 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 6.8 Hz, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 156.7, 154.6, 149.3, 146.8, 135.8, 132.1, 130.7, 129.2, 128.1, 128.0, 126.4, 125.9, 122.0, 121.5, 115.1, 105.3, 95.5, 59.7, 35.2, 31.4, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{30}H_{28}N_2O_2Br$ [M + H] 527.1334; found 527.1327.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-2-(4-methylphenyl)pyrimido[1,2-*a*]-indole-10-carboxylate. (4aac): Yield 356 mg (63%); orange solid; m.p. 196–198 °C; R_f = 0.50 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3442, 2967, 1673, 1452, 1317, 1216 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 2 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.35–7.31 (m, 1 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.04 (s, 1 H), 6.91–6.87 (m, 1 H), 6.55 (d, J = 4.0 Hz, 1 H), 4.52 (q, J = 8.0 Hz, 2 H), 2.36 (s, 3 H), 1.51 (m, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 158.0, 154.3, 148.8, 147.2, 141.6, 134.1, 130.9, 160.5, 129.6, 128.1, 128.0, 127.6, 126.3, 125.1, 121.8, 121.1, 114.9, 105.6, 94.9, 59.6, 35.1, 31.3, 21.5, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{31}H_{31}N_2O_2$ [M + H] 463.2386; found 463.2387.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-2-(4-nitrophenyl)pyrimido[1,2-*a*]-indole-10-carboxylate (4aec): Yield 380 mg (63%); crimson red solid; m.p. 200–202 °C; R_f = 0.52 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2934, 1643, 1360, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, J = 8.0 Hz, 1 H), 8.42 (d, J = 8.0 Hz, 2 H), 8.29 (d, J = 8.0 Hz, 2 H), 7.60 (d, J = 8.0 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.40–7.37 (m, 1 H), 7.08 (s, 1 H), 6.98–6.94 (m, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 4.53 (q, J = 8.0 Hz, 2 H), 1.53–1.51 (m, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 155.0, 154.9, 149.7, 149.2, 146.4, 142.6, 130.5, 130.4, 128.5, 128.0, 126.5, 125.7, 124.1, 122.2, 122.0, 115.3, 105.5, 59.9, 35.3, 31.4, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{30}H_{28}N_3O_4$ [M + H] 494.2080; found 494.2072.

Ethyl 8-Methyl-2-(4-bromophenyl)-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4bdb): Yield 338 mg (61%); orange solid; m.p. 198–200 °C; R_f = 0.53 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3434, 2400, 1638, 1405, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.23–8.21 (m, 2 H), 7.72–7.64 (m, 5 H), 7.60–7.58 (m, 2 H), 7.09 (s, 1 H), 6.84–6.81 (m, 1 H), 6.46 (d, J = 8.0 Hz, 1 H), 4.60 (q, J = 8.0 Hz, 2 H), 2.51 (s, 3 H), 1.61 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 156.4, 148.8, 146.8, 135.9, 135.5, 133.7, 132.2, 131.0, 130.9, 129.6, 129.1, 128.4, 126.4, 125.9, 123.4, 121.5, 114.7, 104.9, 95.2, 59.8, 21.9, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{27}H_{22}N_2O_2Br$ [M + H] 485.0865; found 485.0860.

Ethyl 8-Methyl-2-(4-methylphenyl)-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4bab): Yield 360 mg (75%); orange solid; m.p. 200–202 °C; R_f = 0.55 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3449, 2927, 1655, 1393, 1223, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.25 (d, J = 8.0 Hz, 2 H), 7.71–7.64 (m, 3 H), 7.60–7.59 (m, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.13 (s, 1 H), 6.81 (d, J = 9.0 Hz, 1 H), 6.44 (d, J = 9.0 Hz, 1 H), 4.60 (q, J = 4.0 Hz, 2 H), 2.50 (s, 3 H), 2.46 (s, 3 H), 1.62 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 157.9, 148.5, 141.7, 135.3, 134.3, 134.0, 131.0, 130.8, 129.8, 129.5, 128.5, 127.7, 126.4, 123.1, 121.5, 114.6, 105.3, 59.8, 22.0, 21.6, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{25}N_2O_2$ [M + H] 421.1916; found 421.1906.

Ethyl 4-Cyclohex-1-en-1-yl-8-methyl-2-(4-methylpheny)pyrimido-[1,2-*a*]indole-10-carboxylate (4bad): Yield 281 mg (58%); orange solid; m.p. 186–188 °C; R_f = 0.55 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3450, 2920, 1661, 1393, 1223 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.27 (m, 1 H), 8.14 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.07–7.05 (m, 1 H), 6.93 (s, 1 H), 6.20 (s, 1 H), 4.48 (q, J = 8.0 Hz, 2 H), 2.49 (s, 3 H), 2.45 (s, 1 H), 2.37 (s, 3 H), 2.33 (s, 2 H), 2.10–2.04 (m, 1 H), 1.89–1.85 (m, 3 H), 1.71–1.68 (m, 1 H), 1.50–1.49 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 158.3, 150.7, 147.1, 141.5, 135.2, 134.3, 133.5, 131.9, 130.8, 129.7, 127.6, 126.1, 123.3, 121.4, 114.5, 103.8, 94.3, 59.6, 29.8, 27.1, 25.3, 22.1, 22.0, 21.6, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{29}N_2O_2$ [M + H] 425.2229; found 425.2228.

Ethyl 2-(4-Chlorophenyl)-4-cyclohex-1-en-1-yl-8-methylpyrimido-[1,2-*a*]indole-10-carboxylate (4bcd): Yield 295 mg (58%); orange solid; m.p. 188–190 °C; R_f = 0.39 (ethyl acetate/hexanes, 10%). FTIR (KBr): $\tilde{\nu}$ = 3450, 2927, 1653, 1400, 1237 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 8.20–8.18 (m, 2 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.10–7.07 (m, 1 H), 6.91 (s, 1 H), 6.21 (s, 1 H), 4.48 (q, J = 8.0 Hz, 2 H), 2.49 (s, 3 H), 2.33–2.32 (m, 2 H), 2.07–2.04 (m, 1 H), 1.91–1.83 (m, 4 H), 1.75–1.70 (m, 1 H), 1.51 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 156.9, 150.9, 146.8, 137.2, 135.5, 135.4, 133.3, 132.1, 130.7, 129.1, 128.9, 128.3, 126.1, 123.6, 121.5, 114.6, 103.5, 94.7, 59.7, 27.0, 25.3, 22.0, 21.5, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{27}H_{26}N_2O_2Cl$ [M + H] 445.1683; found 445.1682.

Ethyl 2-(4-Methoxyphenyl)-8-methyl-4-(4-methylphenyl)pyrimido-[1,2-*a*]indole-10-carboxylate (4bba): Yield 309 mg (60%); orange solid; m.p. 198–200 °C; R_f = 0.39 (ethyl acetate/hexanes, 10%). FTIR (KBr): $\tilde{\nu}$ = 3033, 2970, 1662, 1457, 1253 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.27 (m, 3 H), 7.47–7.41 (m, 4 H), 7.04–7.01 (m, 3 H), 6.79 (d, J = 8.6 Hz, 1 H), 6.49 (d, J = 8.7 Hz, 1 H), 4.57 (q, J = 7.1 Hz, 2 H), 3.89 (s, 3 H), 2.55 (s, 3 H), 2.48 (s, 3 H), 1.60 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 162.3, 157.4, 148.7, 147.4, 141.1, 135.1, 131.1, 130.9, 130.1, 129.5, 129.4, 128.4, 126.4, 122.8, 121.4, 114.7, 114.3, 105.1, 94.3, 59.7, 55.5, 21.9, 21.7, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{29}H_{27}N_2O_3$ [M + H] 451.2022; found 451.2026.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-7-fluoropyrimido-2-(4-methoxyphenyl)pyrimido[1,2-*a*]indole-10-carboxylate (4cbc): Yield 255 mg (58%); orange solid; m.p. 204–206 °C; R_f = 0.40 (ethyl acetate/hexanes, 10%). FTIR (KBr): $\tilde{\nu}$ = 3068, 2972, 1664, 1486, 1224 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48–8.43 (m, 1 H), 8.2 (d, J = 8.8 Hz, 2 H), 7.66 (d, J = 8.2 Hz, 2 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.19–7.13 (m, 1 H), 7.07–7.01 (m, 3 H), 6.21–6.17 (m, 1 H), 4.56 (q, J = 7.1 Hz, 2 H), 3.89 (s, 3 H), 1.59 (t, J = 7.1 Hz, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 162.4, 160.3, 157.5, 154.7, 148.4, 147.5, 130.4, 129.5, 129.4, 128.2, 127.6, 127.4, 126.8, 126.5, 122.9, 122.7, 114.4, 114.1, 113.7, 105.3, 101.9, 101.4, 94.7, 59.7, 55.5, 35.2, 31.4, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{31}H_{30}FN_2O_3$ [M + H] 497.2240; found 497.2242.

Ethyl 2-(4-Bromophenyl)-7-fluoro-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4cdb): Yield 222 mg (65%); orange solid; m.p. 196–198 °C; R_f = 0.58 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3433, 2400, 1636, 1488, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.43–8.39 (m, 1 H), 8.12–8.10 (m, 2 H), 7.66–7.64 (m, 1 H), 7.61–7.57 (m, 3 H), 7.51–7.49 (m, 2 H), 7.18 (s, 1 H), 7.15–7.10 (m, 1 H), 7.00 (s, 1 H), 6.15–6.12 (m, 1 H), 4.49 (q, J = 6.0 Hz, 2 H), 1.50 (t, J = 4.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 159.3, 156.6, 148.6, 146.9, 135.6, 133.0, 131.3, 129.4, 127.4 (d, J = 10.0 Hz), 126.8, 126.1, 123.2 (d, J = 96.0 Hz), 114.4 (d, J

= 24.0 Hz), 105.2, 101.6 (d, J = 28.0 Hz), 95.6, 59.9, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{19}N_2O_2FBr$ [M + H] 489.0614; found 489.0612.

Ethyl 2-Amino-5-fluoro-1-methyl-1*H*-indole-3-carboxylate (1d): Yield 159 mg (75%); red solid; m.p. 178–180 °C; R_f = 0.58 (ethyl acetate/hexane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 1 H), 6.92–6.90 (m, 1 H), 6.87–6.80 (m, 1 H), 5.70 (br. s, 2 H), 4.38 (q, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 1.45 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 157.7, 129.4, 129.3, 120.3, 120.2, 109.7, 109.5, 94.8, 94.5, 81.9, 64.4, 59.4, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{12}H_{14}FN_2O_2$ [M + H] 237.1039; found 237.1040.

2,4-Bis(4-methylphenyl)-9*H*-pyrido[2,3-*b*]indole (5aaa): Yield 225 mg (53%); white solid; m.p. 238–240 °C; R_f = 0.46 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3452, 3021, 1631, 1405, 1215, 1113 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.39 (s, 1 H), 8.28 (m, 1 H), 8.17 (d, J = 8.1 Hz, 2 H), 7.93 (s, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.60 (m, 1 H), 7.53–7.49 (m, 1 H), 7.46 (m, 2 H), 7.32 (m, 2 H), 7.29–7.23 (m, 1 H), 2.45 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 149.0, 142.0, 141.5, 138.1, 137.1, 137.0, 133.5, 131.8, 129.6, 129.5, 129.1, 128.4, 127.3, 126.4, 121.7, 120.1, 119.4, 115.9, 112.1, 20.8, 20.7 ppm. HRMS (ESI): m/z calcd. for $C_{25}H_{21}N_2$ [M + H] 349.1705; found 349.1699.

Ethyl 2-(4-Methylphenyl)-4-(4-methylphenyl)pyrimido[1,2-*a*]indole-10-carboxylate (4aaa); Method IV: The corresponding isomer data were disclosed above, yield 118 mg (23%).

2-(4-Methylphenyl)-4-phenyl-9*H*-pyrido[2,3-*b*]indole (5aab): Yield 195 mg (48%); white solid; R_f = 0.48 (ethyl acetate/hexane, 10%); m.p. 240–242 °C. FTIR (KBr): $\tilde{\nu}$ = 3462, 3024, 1631, 1405, 1250 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.44 (s, 1 H), 8.30 (d, J = 8.0 Hz, 1 H), 8.19 (d, J = 8.0 Hz, 2 H), 7.96–7.91 (m, 1 H), 7.68–7.63 (m, 2 H), 7.61–7.51 (m, 5 H), 7.34–7.27 (m, 3 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 149.0, 142.0, 141.6, 137.2, 137.0, 136.4, 131.8, 129.5, 129.1, 128.6, 127.5, 126.4, 121.7, 120.2, 119.5, 116.1, 112.2, 20.8 ppm. HRMS (ESI): m/z calcd. for $C_{24}H_{19}N_2$ [M + H] 335.1548; found 335.1553.

Ethyl 2-(4-Methylphenyl)-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4aab): Yield 109 mg (22%); orange solid; R_f = 0.50 (ethyl acetate/hexane, 10%); m.p. 188–190 °C [ref.[5h] 190–192 °C]. ^{1}H, ^{13}C, HRMS matches well with the data reported above.

2-(4-Chlorophenyl)-4-phenyl-9*H*-pyrido[2,3-*b*]indole (5acb): Yield 207 mg (48%); white solid; R_f = 0.42 (ethyl acetate/hexane, 10%); m.p. 238–240 °C. FTIR (KBr): $\tilde{\nu}$ = 3456, 2432, 1650, 1473, 1215 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.51 (s, 1 H), 8.35 (d, J = 8.6 Hz, 1 H), 8.30 (d, J = 7.5 Hz, 1 H), 8.04 (s, 1 H), 7.93 (d, J = 7.0 Hz, 2 H), 7.69–7.53 (m, 8 H), 7.30 (t, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 148.0, 142.7, 142.2, 139.1, 136.7, 133.2, 132.5, 130.3, 129.7, 129.2, 129.1, 129.0, 128.8, 128.2, 122.2, 120.8, 120.2, 116.9, 112.8, ppm. HRMS (ESI): m/z calcd. for $C_{23}H_{16}N_2Cl$ [M + H] 355.1002; found 355.0998.

Ethyl 2-(4-Chlorophenyl)-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4acb): Yield 99 mg (19%); orange solid; m.p. 188–190 °C; R_f = 0.52 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3435, 1673, 1482, 1216, 1101 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.0 Hz, 1 H), 8.21–8.20 (m, 2 H), 7.64–7.56 (m, 3 H), 7.52–7.50 (m, 2 H), 7.49–7.41 (m, 2 H), 7.36–7.33 (m, 1 H), 7.01 (s, 1 H), 6.92–6.88 (m, 1 H), 6.51 (d, J = 8.0 Hz, 1 H), 4.50 (q, J = 8.0 Hz, 2 H), 1.52–1.48 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 156.6, 148.9, 146.7, 137.4, 135.2, 133.6, 130.9, 129.5, 129.2, 128.9, 128.3, 127.9, 125.3, 122.0, 121.5, 114.9, 105.1, 59.7, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{20}N_2O_2Cl$ [M + H] 427.1213; found 427.1211.

4-[4-(*tert*-Butyl)phenyl]-2-(4-methylphenyl)-9*H*-pyrido[2,3-*b*]indole (5aac): Yield 238 mg (50%); white solid; m.p. >250 °C; R_f = 0.44 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3433, 3019, 1636, 1403, 1215, 1109 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.43 (s, 1 H), 8.29 (d, J = 7.8 Hz, 1 H), 8.18 (d, J = 8.2 Hz, 2 H), 7.95 (s, 1 H), 7.87–7.85 (m, 2 H), 7.68 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.54–7.49 (m, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.30–7.26 (m, 1 H), 2.39 (s, 3 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 155.0, 151.2, 149.0, 141.2, 141.6, 137.2, 137.0, 133.6, 131.8, 129.6, 129.5, 129.2, 128.3, 127.4, 126.4, 126.0, 121.8, 120.2, 119.5, 116.1, 115.0, 112.2, 34.5, 31.1, 20.8 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{27}N_2$ [M + H] 391.2174; found 391.2169.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-2-(4-methylphenyl)pyrimido[1,2-*a*]-indole-10-carboxylate (4aac); Method IV: Yield 130 mg (23%); see above for data.

2-(4-Chlorophenyl)-6-methyl-4-phenyl-9*H*-pyrido[2,3-*b*]indole (5bcb): Yield 222 mg (53%); white solid; m.p. 222–224 °C; R_f = 0.48 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2949, 1643, 1393, 1093 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.38 (s, 1 H), 8.33 (d, J = 8.7 Hz, 2 H), 8.10 (s, 1 H), 8.00 (s, 1 H), 7.93–7.91 (m, 2 H), 7.62–7.64 (m, 2 H), 7.58–7.53 (m, 3 H), 7.52–7.37 (m, 1 H), 7.35 (s, 1 H), 2.53–2.43 (m, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 147.7, 142.5, 140.5, 139.1, 136.8, 133.1, 132.3, 132.1, 130.5, 129.6, 129.1, 129.0, 128.7, 126.3, 122.3, 120.4, 116.7, 112.5, 21.5 ppm. HRMS (ESI): m/z calcd. for $C_{24}H_{18}N_2Cl$ [M + H] 369.1158; found 369.1154.

Ethyl 2-(4-Chlorophenyl)-8-methyl-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4bcb): Yield 110 mg (22%); orange solid; m.p. 182–184 °C; R_f = 0.48 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3430, 2401, 1632, 1409, 1215, 1110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 8.28–8.26 (m, 2 H), 7.70–7.62 (m, 3 H), 7.58–7.56 (m, 2 H), 7.50–7.48 (m, 2 H), 7.07 (s, 1 H), 6.82–6.79 (m, 1 H), 6.43 (d, J = 8.7 Hz, 1 H), 4.57 (q, J = 8.0 Hz, 2 H), 2.48 (s, 3 H), 1.58 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 156.3, 148.7, 146.8, 137.3, 135.3 (d, J = 8.0 Hz), 133.6, 130.8 (d, J = 8.0 Hz), 129.5, 129.1, 128.6 (d, J = 51.0 Hz), 126.3, 123.3, 121.4, 114.6, 104.9, 95.1, 59.7, 21.9, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{27}H_{22}N_2O_2Cl$ [M + H] 441.1370; found 441.1364.

4-[4-(*tert*-Butyl)phenyl]-2-(4-fluorophenyl)-6-methyl-9*H*-pyrido-[2,3-*b*]indole (5bfc): Yield 232 mg (50%); white solid; m.p. 238–240 °C; R_f = 0.60 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2949, 1624, 1382, 1213, 1150 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 11.33 (s, 1 H), 8.35–8.31 (m, 2 H), 8.10 (s, 1 H), 7.95 (s, 1 H), 7.84–7.82 (m, 2 H), 7.66–7.64 (m, 2 H), 7.52–7.45 (m, 1 H), 7.36–7.33 (m, 3 H), 2.52 (s, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.9, 161.5, 151.6, 148.1, 142.4, 140.1, 136.9, 134.1, 132.2, 130.8, 129.5, 129.0, 128.9 (d, J = 5.0 Hz), 128.77, 126.4, 122.4, 120.3, 116.5, 115.8 (d, J = 21.0 Hz), 112.5, 34.9, 31.5, 21.5 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{26}N_2F$ [M + H] 409.2080; found 409.2072.

Ethyl 4-[4-(*tert*-Butyl)phenyl]-8-methyl-2-(4-fluorophenyl)pyrimido[1,2-*a*]indole-10-carboxylate (4bfc): Yield 137 mg (25%); orange solid; m.p. 178–180 °C; R_f = 0.46 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3452, 2949, 1656, 1396, 1234, 1168 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36–8.33 (m, 2 H), 7.68–7.66 (m, 2 H), 7.53 (d, J = 8.5 Hz, 2 H), 7.28 (s, 1 H), 7.22 (t, J = 8.8 Hz, 2 H), 7.08 (s, 1 H), 6.84 (dd, J_1 = 1.4, J_2 = 8.8 Hz, 1 H), 6.52 (d, J = 8.7 Hz, 1 H), 4.60 (q, J = 8.0 Hz, 2 H), 2.51 (s, 3 H),

1.61–1.59 (m, 3 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 165.3, 163.5, 156.5, 154.4, 148.9, 146.9, 135.2, 133.1, 130.7, 129.7 (d, J = 9.0 Hz), 128.0, 126.3, 123.1, 121.3, 115.9 (d, J = 22.0 Hz), 114.7, 105.1, 94.7, 59.6, 35.1, 31.3, 21.8, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{31}H_{30}N_2O_2F$ [M + H] 481.2291; found 481.2286.

2-(4-Chlorophenyl)-6-methyl-4-(4-methylphenyl)-9*H*-pyrido-[2,3-*b*]indole (5bca): Yield 231 mg (53%); white solid; m.p. 240–242 °C; R_f = 0.48 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3432, 1630, 1402, 1216, 1111 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.33 (s, 1 H), 8.32 (d, J = 8.0 Hz, 2 H), 8.10 (s, 1 H), 7.97 (s, 1 H), 7.81 (d, J = 7.0 Hz, 2 H), 7.57–7.34 (m, 6 H), 2.52–2.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 147.7, 142.5, 140.5, 139.2, 138.7, 133.9, 133.1, 132.3, 130.5, 129.6, 129.0, 128.9, 128.7, 122.4, 120.4, 116.5, 112.5, 21.5, 21.4, ppm. HRMS (ESI): m/z calcd. for $C_{25}H_{20}N_2Cl$ [M + H] 383.1315; found 383.1306.

Ethyl 2-(4-Chlorophenyl)-8-methyl-4-(4-methylphenyl)pyrimido-[1,2-*a*]indole-10-carboxylate (4bca): Yield 120 mg (23%); orange solid; m.p. 190–192 °C; R_f = 0.42 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3450, 1652, 1403, 1235, 1168 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.28 (d, J = 8.5 Hz, 2 H), 7.52–7.47 (m, 6 H), 7.07 (s, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 6.55 (d, J = 8.7 Hz, 1 H), 4.60 (q, J = 8.0 Hz, 2 H), 2.58 (s, 3 H), 2.51 (s, 3 H), 1.61 (t, J = 4.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 156.3, 149.0, 146.9, 141.2, 137.3, 135.4, 130.8, 130.1, 129.9, 129.2, 128.9, 128.3, 126.4, 123.3, 121.5, 114.8, 105.0, 95.0, 59.8, 21.9, 21.7, 14.9 ppm. HRMS (ESI): m/z calcd. for $C_{28}H_{24}N_2O_2Cl$ [M + H] 455.1526; found 455.1526.

2-(4-Chlorophenyl)-7-fluoro-4-phenyl-9*H*-pyrido[2,3-*b*]indole (5ccb): Yield 217 mg (52%); white solid; m.p. 248–250 °C; R_f = 0.46 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3437, 2401, 1630, 1409, 1215, 1102 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.64 (s, 1 H), 8.35–8.29 (m, 3 H), 8.03 (s, 1 H), 7.92 (d, J = 4.0 Hz, 2 H), 7.72–7.65 (m, 2 H), 7.60–7.57 (m, 3 H), 7.34–7.32 (m, 1 H), 7.17–7.12 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.9, 161.6, 148.5, 142.8 (d, J = 13.0 Hz), 142.2, 138.9, 136.5, 133.4, 132.5, 130.8, 129.7, 129.2 (d, J = 23.0 Hz), 128.8, 122.4 (d, J = 11.0 Hz), 118.9, 116.7, 108.7 (d, J = 25.0 Hz), 98.9 (d, J = 26.0 Hz) ppm. HRMS (ESI): m/z calcd. for $C_{23}H_{15}N_2FCl$ [M + H] 373.0908; found 373.0902.

Ethyl 2-(4-Chlorophenyl)-7-fluoro-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4ccb): Yield 104 mg (21%); orange solid; m.p. 178–180 °C; R_f = 0.58 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2948, 2150, 1643 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.16 (d, J = 7.0 Hz, 2 H), 7.63–7.58 (m, 3 H), 7.50 (s, 2 H), 7.39 (d, J = 7.4 Hz, 2 H), 7.10 (s, 1 H), 6.98 (s, 1 H), 6.11 (d, J = 9.4 Hz, 1 H), 4.47–4.46 (m, 2 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 159.2, 156.8, 156.5, 148.5, 146.8, 137.5, 135.0, 132.9, 131.2, 129.6, 129.2, 128.9, 128.3, 127.3 (d, J = 12.0 Hz), 126.7, 123.1 (d, J = 9.0 Hz), 114.3 (d, J = 24.0 Hz), 105.2, 101.5 (d, J = 29.0 Hz), 95.5, 59.9, 14.7 ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{19}N_2O_2FCl$ [M + H] 445.1119; found 445.1125.

7-Fluoro-2-(4-methylphenyl)-4-phenyl-9*H*-pyrido[2,3-*b*]indole (5cab): Yield 185 mg (47%); white solid; m.p. 228–230 °C; R_f = 0.48 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3433, 2400, 1629, 1473, 1215, 1105 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.57 (s, 1 H), 8.32–8.28 (m, 1 H), 8.18 (d, J = 8.0 Hz, 2 H), 7.95–7.89 (m, 3 H), 7.66–7.56 (m, 3 H), 7.34–7.32 (m, 3 H), 7.15–7.10 (m, 1 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.3, 160.1, 149.4, 142.2 (d, J = 9.0 Hz), 141.6, 137.4, 136.8, 136.2, 132.0, 129.9, 129.2, 128.6 (d, J = 20.0 Hz), 126.4, 121.8 (d, J = 10.0 Hz), 118.0, 116.0, 108.0, 107.8, 98.5, 98.2, 20.7 ppm. HRMS (ESI): m/z calcd. for $C_{24}H_{18}N_2F$ [M + H] 353.1454; found 353.1449.

Ethyl 7-Fluoro-2-(4-methylphenyl)-4-phenylpyrimido[1,2-*a*]indole-10-carboxylate (4cab): Yield 114 mg (24%); orange solid; m.p. 168–170 °C; R_f = 0.49 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3432, 1625, 1486, 1216, 1104 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46–8.42 (m, 1 H), 8.18 (d, J = 8.0 Hz, 2 H), 7.70–7.65 (m, 3 H), 7.62–7.53 (m, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.17–7.12 (m, 1 H), 7.07 (s, 1 H), 6.17–6.14 (m, 1 H), 4.53 (q, J = 8.0 Hz, 2 H), 2.40 (s, 3 H), 1.55 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 159.2, 158.0, 148.3, 147.3, 141.9, 134.0, 133.2, 131.1, 129.7 (d, J = 13.0 Hz), 128.5, 127.7, 127.4 (d, J = 12.0 Hz), 126.8, 123.0, 123.0, 114.1 (d, J = 24.0 Hz), 105.6, 101.5 (d, J = 30.0 Hz), 95.1, 59.8, 21.6, 14.8 ppm. HRMS (ESI): m/z calcd. for $C_{27}H_{22}N_2O_2F$ [M + H] 425.1665; found 425.1664.

4-Cyclohex-1-en-1-yl-7-fluoro-2-(4-fluorophenyl)-9*H*-pyrido-[2,3-*b*]indole (5cfd): Yield 117 mg (44%); white solid; m.p. 229–231 °C; R_f = 0.52 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3425, 1629, 1513, 1472, 1216 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.33 (s, 1 H), 8.28–8.22 (m, 3 H), 7.78 (s, 1 H), 7.34–7.29 (m, 3 H), 7.12–7.09 (m, 1 H), 6.39 (s, 1 H), 2.59–2.35 (m, 4 H), 1.85–1.75 (m, 4 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.9 (d, J = 15.0 Hz), 161.5 (d, J = 11.0 Hz), 148.5, 142.3 (d, J = 13.0 Hz), 141.8, 136.7, 134.8, 133.7, 130.2 (d, J = 26.0 Hz), 129.0, 128.9, 122.2 (d, J = 10.0 Hz), 119.1, 115.8 (d, J = 21.0 Hz), 108.3 (d, J = 24.0 Hz), 98.7 (d, J = 26.0 Hz), 27.8, 25.8, 22.9, 22.0 ppm. HRMS (ESI): m/z calcd. for $C_{23}H_{19}N_2F_2$ [M + H] 361.1516; found 361.1508.

Ethyl 4-Cyclohex-1-en-1-yl-7-fluoro-2-(4-fluorophenyl)pyrimido-[1,2-*a*]indole-10-carboxylate (4cfd): Yield 97 mg (20%); orange solid; m.p. 158–160 °C; R_f = 0.54 (ethyl acetate/hexane, 10%). FTIR (KBr): $\tilde{\nu}$ = 3432, 2930, 1642, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.50 (m, 1 H), 8.36–8.33 (m, 2 H), 7.67 (dd, J = 2.0, 10.0 Hz, 1 H), 7.32–7.31 (m, 1 H), 7.25–7.20 (m, 2 H), 6.99 (s, 1 H), 6.33 (s, 1 H), 4.57 (q, J = 8.0 Hz, 2 H), 2.56–2.52 (m, 1 H), 2.44 (s, 2 H), 2.21–2.17 (m, 1 H), 2.00 (s, 3 H), 1.82–1.79 (m, 1 H), 1.58 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 157.3, 150.7, 146.9, 133.1, 132.7, 132.6, 129.0 (d, J = 8.0 Hz), 128.7 (d, 8.0 Hz), 126.9, 126.5, 123.0 (d, J = 22.0 Hz), 115.5 (d, J = 21.0 Hz), 114.4 (d, J = 24.0 Hz), 101.4 (d, J = 14.0 Hz), 94.9, 59.7, 27.3, 25.2, 22.1, 21.4, 14.7 ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{23}N_2O_2F_2$ [M + H] 432.1649; found 432.1652.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectroscopic data for representative compounds.

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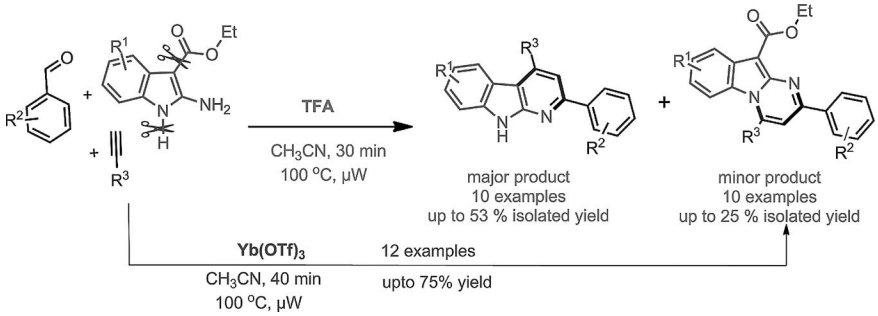

We report the diversity-oriented synthesis of pyrido- and pyrimido-indoles from an acid-catalyzed three-component (3C) reaction involving ethyl 2-amino-1*H*-indole-3-carboxylates, arylaldehydes, and terminal alkynes. With a Brønsted acid, the 3C reaction furnished a mixture of pyrido- and pyrimido-indoles, whereas when a Lewis acid was used, pyrimidoindoles were obtained as the single product.

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Diversity-Oriented Synthesis of Polycyclic Indoles: Brønsted or Lewis Acid Catalyzed Three-Component Reaction for the Synthesis of α-Carbolines and Pyrimidoindoles

Keywords: Multicomponent reactions / Hydroamination / Nitrogen heterocycles / Alkynes / Ytterbium

