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Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles from 3-(*o*-Trifluoroacetamidoaryl)-1-propargylic Alcohols and Amines

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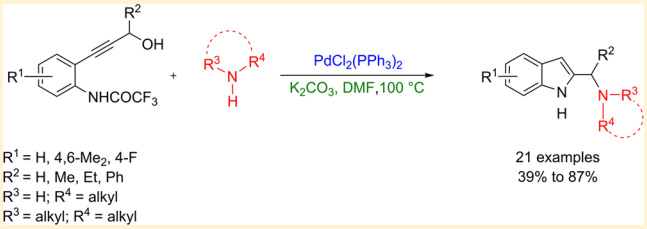
Supporting Information

ABSTRACT: A novel palladium-catalyzed approach to 2-(aminomethyl)indoles from 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols and amines has been developed.



Recently, we reported that the 2-(aminomethyl)indole motif, a key structural feature present in several biologically active compounds,[1] could be assembled by the palladium-catalyzed reaction of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates with secondary amines.[2] Although the procedure is simple and the reaction proceeds under mild conditions, it requires the initial conversion of the hydroxy group of the corresponding propargylic alcohol into a better leaving group such as the carbonate. Clearly, a procedure based on the direct utilization of 3-(*o*-trifluoroacetamidophenyl)-1-propargylic alcohols, eliminating one operative step, would be desirable for environmental and practical reasons as well as in terms of atom economy.[3] There are also some limitations in the scope of the reaction that arise from its ineffectiveness with primary amines. For example, with benzylamine and butylamine, complex reaction mixtures were obtained that we did not investigate.[2] Furthermore, ethyl 3-(*o*-trifluoroacetamidoaryl)-1-propargylic carbonates bearing an alkyl substituent at the propargylic carbon undergo an elimination reaction[4] to give 2-vinylic indoles instead of producing the desired 2-(aminomethyl)indole derivative.[5] These drawbacks prompted us to investigate further this transformation, and here we report the results of this study.

We started our study by examining the conversion of 3-(*o*-trifluoroacetamidophenyl)-1-propargyl alcohol (**1a**) and diethylamine into 2-(diethylaminomethyl)indole (**2a**). The initial screen was performed using 10 equiv of diethylamine at 80 °C, investigating the influence of palladium catalysts and solvents on the reaction outcome. Under the same conditions used with the corresponding carbonate ester, **2a** could be isolated only in 24% yield, the main product being 2-(hydroxymethyl)indole (**3a**) (Table 1, entry 1). Moderate yields were obtained with $Pd(OAc)_2$ and $Pd_2(dba)_3$ in DMF (Table 1, entries 2 and 3). Switching to $Pd(PPh)_4$[6] and $PdCl_2(PPh_3)_2$ in DMF led to the isolation of **2a** in 67% yield (Table 1, entries 4 and 5), and the addition of K_2CO_3, particularly with $PdCl_2(PPh_3)_2$, led to a further increase in the yield, as the desired indole was isolated in 74% yield (Table 1, entry 7). We then attempted the use of a lower amount of amine. However, when **1a** was treated with 2 equiv of diethylamine, a decrease in the yield was observed (Table 1, entry 8). Pleasingly, after some experimentation, we found that a satisfactory 76% yield could be obtained upon treatment of **1a** with 2 equiv of diethylamine in the presence of $PdCl_2(PPh_3)_2$ in DMF at 100 °C after 1 h (Table 1, entry 9).

A brief investigation of other protecting groups (benzyl, acetyl, and mesyl groups) as well as of the behavior of 3-(*o*-aminophenyl)-1-propargyl alcohol under the conditions described in Table 1, entry 10 revealed that the trifluoroacetyl derivative provides the best results. The starting material was recovered in almost quantitative yield with **1′a** and **1′b**, and no evidence of indole derivatives was attained (Table 2, entries 1 and 2). With the acetyl derivative **1′c**, the 2-(aminomethyl)indole **2a** was isolated in only 52% yield, and the mesyl derivative **1′d** formed a mixture of the corresponding protected and unprotected 2-(hydroxymethyl)-indole in 76% overall yield. The reason why no substitution of the amino for the hydroxy group takes place with the mesyl protecting group is unclear at the present time.

The best conditions found for **1a** [2 equiv of amine, 0.01 equiv of $PdCl_2(PPh_3)_4$, 2 equiv of K_2CO_3, DMF, 100 °C] were then used when the reaction was extended to include other amines. As shown in Table 3, a variety of secondary amines can be successfully employed, even when bulky substituents are close to the nitrogen atom (Table 3, entries 4 and 5). In the latter case, the yields are higher than or comparable to those obtained with the corresponding carbonate esters.[2] Even primary amines appeared to provide better results with the present method, although the indoles were isolated in low to moderate yields. For example, treatment of **1a** with butylamine and benzylamine afforded the corresponding indoles in 56 and 50% yield, respectively (Table 3, entries 6 and 11), while complex reaction mixtures were obtained when ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate was treated with the same amines.[2]

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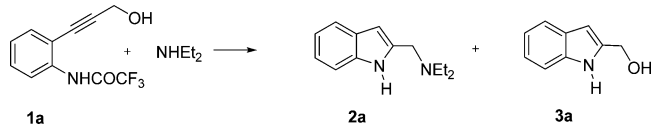
Table 1. Optimization Studies for the Reaction of 1a with Diethylamine[a]

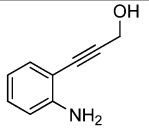
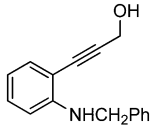
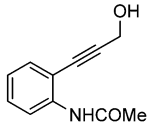
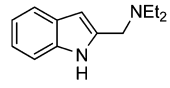
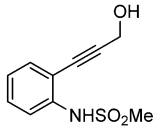
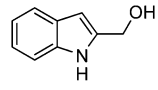
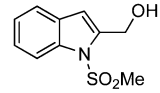


1a 2a 3a

Entry	[Pd]	Solvent	Added base	Temp. (°C)	Time (h)	Yield (%)[b] 2a	3a
1	$Pd(PPh_3)_4$	THF	–	80[c]	4	24	68
2	$Pd(OAc)_2$	DMF	–	80[c]	1.5	55	27
3	$Pd_2(dba)_3$[d]	DMF	–	80[c]	5.5	48	38
4	$Pd(PPh_3)_4$	DMF	–	80[c]	3	67	8
5	$PdCl_2(PPh_3)_2$	DMF	–	80[c]	5	67	13
6	$Pd(PPh_3)_4$	DMF	K_2CO_3	80[c]	1.5	69	22
7	$PdCl_2(PPh_3)_2$	DMF	K_2CO_3	80[c]	1.5	74	7
8	$PdCl_2(PPh_3)_2$	DMF	K_2CO_3	80[e]	1.5	65	–
9	$PdCl_2(PPh_3)_2$	DMF	K_2CO_3	100[e]	1	76	–
10	$PdCl_2(PPh_3)_2$	MeCN	K_2CO_3	100[e]	4.5	74	10
11	$PdCl_2(PPh_3)_2$	MeCN	–	100[e]	7.5	46	13
12	$PdCl_2(PCy_3)_2$	DMF	K_2CO_3	100[e]	1.5	48	–
13	$PdCl_2(MeCN)_2$	DMF	K_2CO_3	100[e]	2	65	–
14	Hermann cat.[f]	DMF	K_2CO_3	100[e]	3	64	–

[a]Unless otherwise stated, reactions were carried out on a 0.5 mmol scale under an argon atmosphere using 2 or 10 equiv of Et_2NH, 2 equiv of K_2CO_3 (when added), and 0.01 equiv of [Pd] in 2 mL of solvent. [b]Yields are given for isolated products. [c]With 10 equiv of Et_2NH. [d]With 0.005 equiv of $Pd_2(dba)_3$. [e]With 2 equiv of Et_2NH. [f]With 0.005 equiv of the Hermann catalyst.[7]

Table 2. Palladium-Catalyzed Reactions of 1′a–d with Diethylamine[a]

Entry	Propargylic derivative 1'		Products (yield %)[b]	
1		1'a	–[c]	
2		1'b	–[c]	
3		1'c	 (2a, 52%)	
4		1'd	 (3a, 15%)	 (3'a, 61%)

[a]Reactions were carried out on a 0.5 mmol scale under an argon atmosphere at 100 °C using 2 equiv of Et_2NH, 2 equiv of K_2CO_3, and 0.01 equiv of $PdCl_2(PPh_3)_2$ in 2 mL of DMF. [b]Yields are given for isolated products. [c]The starting material was recovered in almost quantitative yield.

We next turned our attention to 3-(*o*-trifluoroacetamidophenyl)-1-propargylic alcohols bearing an alkyl substituent at the propargylic carbon. In our previous study,[5] the carbonate esters of these substrates were found to give 2-vinylic indoles instead of the desired 2-(aminomethyl)indole derivatives. We were pleased to find that treatment of **1d** with diethylamine led to the isolation of the corresponding aminoindole **2n** in good yield (Table 4, entry 1). A brief optimization study showed that **2n** could be isolated in 77% yield using a 3 equiv excess of diethylamine (Table 4, entry 4).

The application of these conditions to other amines and 3-(*o*-trifluoriacetamidoaryl)-1-propargylic alcohols substituted at the propargylic carbon led to the results summarized in Table 5. Moderate to high yields were obtained in several cases. As a comparison, the reaction of **1f** with *N*-ethylpiperazine gave the aminoindole **2q** in 52% yield (Table 5, entry 4) and only traces, if any, of the 2-vinylic derivative, while the related reaction with the carbonate ester (Scheme 1) produced the corresponding 2-vinylic indole in high yield.[5] Interestingly, the reaction met with failure when **1e** was treated with diisopropylamine (Table 5, entry 6), and with butylamine the indole derivative was isolated in only 39% yield (Table 5, entry 7). Better results were obtained when these amines were reacted with the corresponding carbonate ester at 80 °C in THF in the presence of $Pd(PPh_3)_4$.[5]

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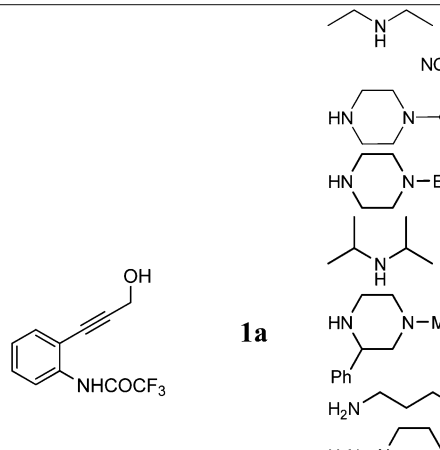
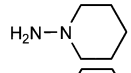
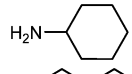
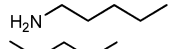
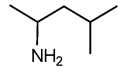
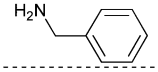
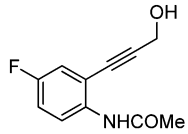
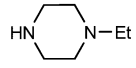
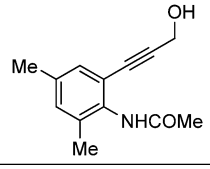
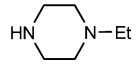
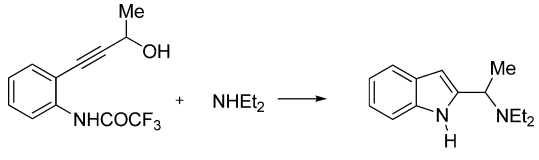
Table 3. Synthesis of 2-Aminomethylindoles 2 from 1 and Amines[a]

Entry	1	Amine 2	T (h)	Yield %[b]
1	 **1a**		1	76 (**2a**)
2			2.5	72 (**2b**)
3			3	87 (**2c**)
4			4	54 (**2d**)
5			2	53 (**2e**)
6			2	56 (**2f**)
7			1.5	24 (**2g**)
8			6	47 (**2h**)
9			5	40 (**2i**)
10			4	52 (**2j**)
11			6	50 (**2k**)
12	 **1b**		3	58 (**2l**)
13	 **1c**		1.5	69 (**2m**)

[a]Reactions were carried out on a 0.5 mmol scale at 100 °C in 2 mL of DMF under a nitrogen atmosphere using 2 equiv of the amine, 2 equiv of K_2CO_3, and 0.01 equiv of $PdCl_2(PPh_3)_2$. [b]Yields are given for isolated products.

Table 4. Optimization Studies for the Reaction of 1d with Diethylamine[a]



1d **2n**

Entry	Et_2NH (equiv)	Added base	Time (h)	Yield of **2n** (%)[b]
1	2	K_2CO_3	7.5	63
2	2	Cs_2CO_3	7.5	56
3	2	K_3PO_4	7.5	74
4	3	K_2CO_3	6.5	77

[a]Reactions were carried out on a 0.5 mmol scale at 100 °C in 2 mL of DMF under a nitrogen atmosphere using 2 or 3 equiv of the amine, 2 equiv of added base, and 0.01 equiv of $PdCl_2(PPh_3)_2$. [b]Yields are given for isolated products.

Under these conditions, indole derivatives were isolated in 45 and 80% yield, respectively. Most probably, this different behavior depends on the different mechanism involved in the formation of the carbon−nitrogen bond: with the carbonate ester, the nitrogen nucleophile attacks the planar allylic terminus of a π-allylpalladium complex,[2] while with the propargylic alcohol, the carbon−nitrogen bond is formed via nucleophilic substitution (very likely an S_N2-type substitution; vide infra) at a more hindered secondary carbon atom. In the latter case, steric effects can play a major role in controlling the reaction outcome, accounting for the failure in the reaction with the sterically encumbered diisopropylamine and for the low yield obtained with butylamine. Butylamine, like other primary amines, shows a higher tendency to give competitive side reactions under the conditions used compared with secondary amines. Thus, in the presence of a hindered electrophilic center, these side reactions may compete more effectively and prevail over the desired substitution reaction.

A possible rationale for this indole synthesis considers the following elementary steps (Scheme 2; ligands have been omitted): (a) oxidative addition of the N−H bond to palladium(0),[8] generated via reduction of palladium(II) by the

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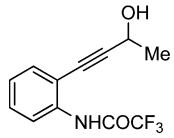
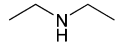
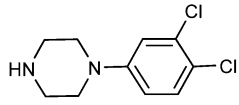
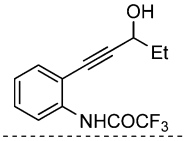
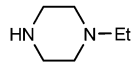
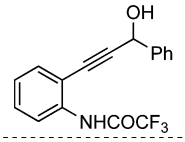
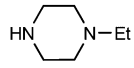
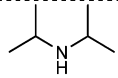
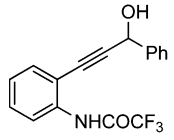
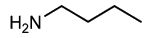
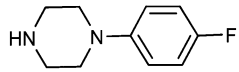
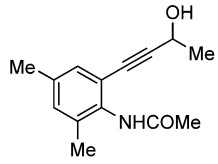
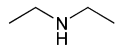
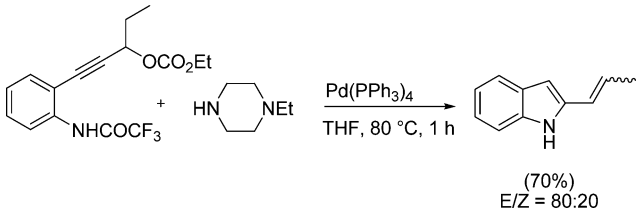
Table 5. Cyclization of 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Alcohols Substituted at the Propargylic Carbon To Give Indoles[a]

Entry	1	Amine 2	T (h)	yield %[b]
1	 **1d**		6.5	77 (**2n**)
2			4	60 (**2o**)
3			3.5	52 (**2p**)
4	 **1f**		4	52 (**2q**)
5	 **1e**		2.5	53 (**2r**)
6			2	–[c]
7	 **1e**		5.5	39 (**2s**)
8			3	63 (**2t**)
9	 **1g**		4	45 (**2u**)

[a]Reactions were carried out on a 0.5 mmol scale at 100 °C in 2 mL of DMF under a nitrogen atmosphere using 3 equiv of the amine, 2 equiv of K_2CO_3, and 0.01 equiv of $PdCl_2(PPh_3)_2$. [b]Yields are given for isolated products. [c]**1e** was recovered in 44% yield.

Scheme 1. Reaction of a 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate Bearing an Alkyl Substituent at the Propargylic Carbon with a Secondary Amine



amine, to afford intermediate **A** (the acidity of the N–H bond appears to play a key role in the oxidative addition, as no reaction was observed when **1′a** containing a free N–H bond and its benzyl derivative **1′b** were subjected to cyclization conditions; Table 2, entries 1 and 2); (b) coordination of the cationic palladium hydride fragment to the carbon–carbon triple bond to generate **B**; (c) intramolecular nucleophilic attack of the anionic nitrogen[9] across the activated carbon–carbon triple bond to give *σ*-indolylpalladium intermediate **C**; (d) direct nucleophilic substitution of the amino nucleophile for the hydroxy group assisted by the coordination of the oxygen to palladium to give **D** (reductive elimination of **C** would afford 2-hydroxymethylindole **3**); (e) reductive elimination that affords the intermediate **E** and regenerates the active palladium catalyst; and (f) base-catalyzed hydrolysis of the amide bond to give the 2-(aminomethyl)indole derivative **2**.

A mechanism of this type, based on the coordination of HPd^+ to the carbon–carbon triple bond followed by a cyclization step, has been proposed by Tsukada and Yamamoto[10] for the intramolecular hydrocarbonation of a 5-alkynylmalonitrile to form a cyclopentane derivative. Furthermore, to provide some experimental support for our proposal, we carried out the following two experiments: the reaction of the 2-hydroxymethylindole **3a** with diethylamine (Scheme 3) and the reaction of 3-(*p*-trifluoroacetamidophenyl)-2-propyn-1-ol (**4**) with diethylamine (Scheme 4), both under the standard reaction conditions. The first reaction, with and without palladium, led to the recovery of the starting material in almost quantitative yield,[11] ruling out the presence of this indole derivative (which may even be regarded as an allylic derivative)[12] in the reaction pathway leading to **2**. The second one led to the recovery of the starting material in 75% yield with no evidence of the substitution product,[13] ruling out a mechanism in which a palladium-catalyzed propargylic amination[14,15] precedes the cyclization

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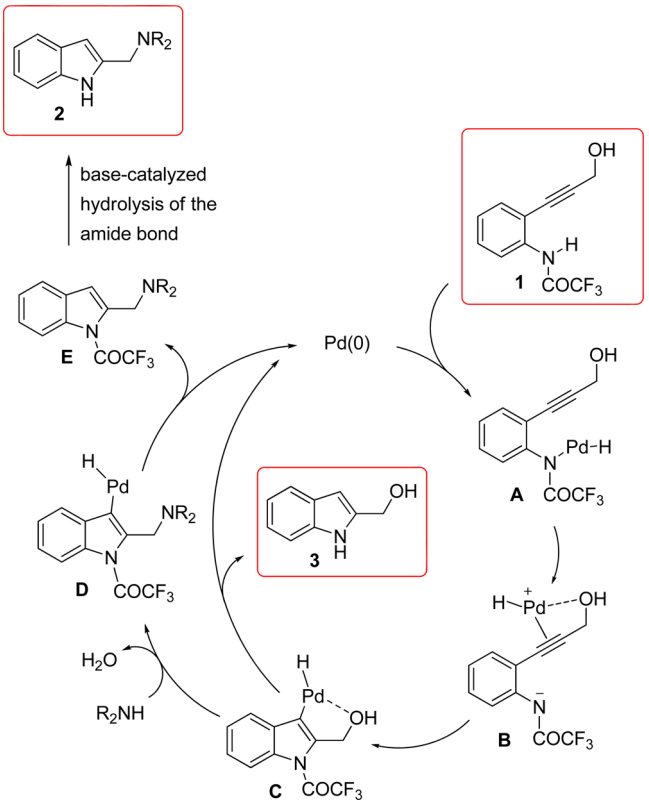
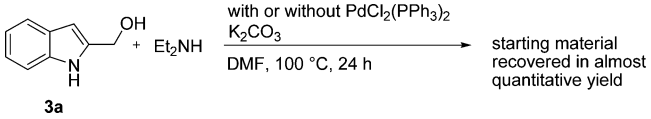
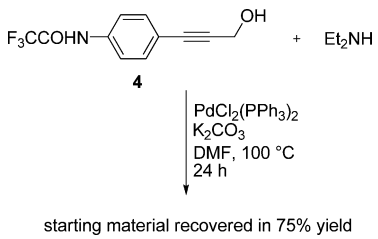
Scheme 2. Proposed Reaction Mechanism



Scheme 3. Reaction of 2-Hydroxymethylindole (3a) with Diethylamine



Scheme 4. Reaction of 2-Phenyl-2-propyn-1-ol 4 with Diethylamine



step. Taken together, these experiments support the view that the substitution of the amino group for the hydroxy group involves an indole intermediate in which palladium can act as alcohol-activating agent, possibly the intermediate **C**.

In summary, we have developed a novel palladium-catalyzed approach to 2-(aminomethyl)indoles from 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols and amines. The procedure is simple, uses readily available starting materials, and may represent a useful tool for the synthesis of this class of compounds. The reaction works well with secondary amines, even with 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols bearing an alkyl substituent at the propargylic carbon. With primary amines, although moderate yields were obtained, the results of the present procedure are significantly better than those obtained with the corresponding carbonate esters.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. The appropriate 2-alkynyltrifluoroacetanilides were prepared, usually in high yields, from 2-iodoaniline via a two-step process involving a trifluoroacetylation step followed by a Sonogashira cross-coupling with a terminal alkyne.[11] Reaction products were purified by flash chromatography using SiO_2 as the stationary phase, eluting with *n*-hexane/ethyl acetate mixtures.

Typical Procedure for the Cyclization of 1. In a 50 mL Carousel tube reactor (Radley Discovery Technology) containing a magnetic stirring bar, $PdCl_2(PPh_3)_2$ (0.005 mmol) was dissolved at room temperature with 2.0 mL of DMF. Then, 3-(*o*-trifluoroacetamidophenyl)-1-propargylic alcohol **1** (0.5 mmol), amine (1 mmol), and K_2CO_3 (1 mmol) were added. The mixture was stirred at 100 °C. Then, the reaction mixture was cooled to room temperature, diluted with Et_2O, and washed with saturated $NaHCO_3$ solution. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexane/EtOAc) to afford the pure indole derivative **2**.

N-((1H-Indol-2-yl)methyl)-N-ethylethanamine (***2a***).[2] Brown oil, 76%, 77.0 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.81 (bs, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.23−7.13 (m, 2H), 6.41 (s, 1H), 3.80 (s, 2H), 2.64 (q, J = 7.2 Hz, 4H), 1.13 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.4, 136.1, 128.7, 121.3, 120.0, 119.5, 110.7, 100.8, 51.1, 46.9, 11.6.

2-(4-((1H-Indol-2-yl)methyl)piperazin-1-yl)benzonitrile (***2b***).[2] Brown wax, 72%, 113.9 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.56 (bs, 1H), 7.62−7.58 (m, 2H), 7.51−7.49 (m, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.22−7.18 (m, 1H), 7.15−7.11 (m, 1H), 7.06−7.01 (m, 2H), 6.44 (s, 1H), 3.77 (s, 2H), 3.28−3.26 (m, 4H), 2.75−7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 155.6, 136.2, 135.5, 134.4, 133.8, 128.4, 121.8, 121.7, 120.3, 119.7, 118.7, 118.4, 110.7, 106.0, 101.9, 55.7, 53.2, 51.5.

2-((4-Ethylpiperazin-1-yl)methyl)-1H-indole (***2c***).[2] Pale-yellow oil, 87%, 105.8 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.73 (bs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.19−7.16 (m, 1H), 7.13−7.10 (m, 1H), 6.40 (s, 1H), 3.69 (s, 2H), 2.57−2.43 (m, 10H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 136.2, 135.8, 128.4, 121.6, 120.2, 119.6, 110.7, 101.7, 55.9, 53.3, 52.8, 52.3, 12.0.

N-((1H-Indol-2-yl)methyl)-N-isopropylpropan-2-amine (***2d***).[2] Pale-yellow oil, 54%, 62.2 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 10.54 (bs, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.20−7.16 (m, 1H), 7.11−7.10 (m, 1H), 6.41 (s, 1H), 4.09 (s, 2H), 3.38−3.32 (m, 2H), 1.24 (d, J = 6.8 Hz, 12H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.2, 136.0, 128.7, 121.4, 120.1, 119.6, 110.8, 100.9, 48.5, 40.5, 20.8.

2-((4-Methyl-2-phenylpiperazin-1-yl)methyl)-1H-indole (***2e***).[2] Brown oil, 53%, 80.9 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.55 (bs, 1H), 7.59−7.54 (m, 3H), 7.44−7.34 (m, 4H), 7.21−7.10 (m, 2H), 6.34 (s, 1H), 3.90, (d, J = 14.0 Hz, 1H), 3.51−3.49 (m, 1H), 3.17 (d, J = 14.0 Hz, 1H), 2.97−2.82 (m, 4H), 2.44−2.21 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.4, 136.3, 136.0, 128.8, 128.6, 127.9, 121.4, 120.1, 119.6, 110.7, 101.3, 67.3, 63.7, 55.2, 52.2, 52.1, 45.7.

N-((1H-Indol-2-yl)methyl)butan-1-amine (***2f***).[2] Pale-yellow oil, 56%, 56.6 mg. IR (neat): 3405, 2923, 2857, 1455, 1419, 1338, 1288, 748 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23−7.13 (m, 2H), 6.44 (s, 1H), 3.81 (s, 2H), 2.61−2.57 (m, 1H), 1.64−1.56 (m, 2H), 1.42−1.30 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 136.1, 136.0, 128.5, 121.7, 120.2, 119.8, 110.7, 101.9, 53.7, 51.2, 29.1, 20.6, 14.1. HRMS (ESI) m/z: calcd for $C_{13}H_{19}N_2$ $[M + H]^+$ 203.1543, found 203.1549.

N-((1H-Indol-2-yl)methyl)piperidin-1-amine (***2g***). Yellow wax, 24%, 27.5 mg. IR (KBr): 3409, 2933, 1455, 1384, 738 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.79 (bs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.22−7.18 (m, 1H), 7.13−7.10 (m, 1H), 6.42 (s, 1H), 5.99 (bs, 1H), 3.86 (s, 2H), 2.67−2.66 (m, 4H), 1.73−1.71 (m, 4H),

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1.56−1.54 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 136.3, 135.4, 128.3, 121.5, 120.1, 119.5, 110.9, 101.7, 56.3, 54.4, 25.6, 24.1. HRMS (ESI) m/z: calcd for $C_{14}H_{20}N_3$ $[M + H]^+$ 230.1652, found 230.1647.

N-((1H-Indol-2-yl)methyl)cyclohexanamine (**2h**). Brown oil, 47%, 54.0 mg. IR (neat): 3280, 2920, 1655, 1459, 1382, 790, 735 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.17 (bs, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.34 (s, 1H), 4.01 (s, 2H), 2.60−2.48 (m, 1H), 1.95 (d, J = 11.2 Hz, 2H), 1.76−1.70 (m, 2H), 1.66−1.60 (m, 1H), 1.25−1.10 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.3, 136.1, 128.4, 121.4, 120.0, 119.5, 110.9, 100.3, 56.2, 43.8, 31.4, 26.0, 24.9. HRMS (ESI) m/z: calcd for $C_{15}H_{21}N_2$ $[M + H]^+$ 229.1699, found 229.1705.

N-((1H-Indol-2-yl)methyl)pentan-1-amine (**2i**). Brown oil, 40%, 44.0 mg. IR (neat): 3280, 2928, 1668, 1437, 1385, 723 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.02 (bs, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.32 (s, 1H), 3.95 (s, 2H), 2.63 (t, J = 7.2 Hz, 2H), 2.21 (bs, 1H), 1.34−1.22 (m, 6H), 0.91−0.85 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.6, 136.1, 128.6, 121.3, 120.0, 119.4, 110.8, 100.2, 60.3, 49.4, 46.9, 29.4, 22.5, 14.0. HRMS (ESI) m/z: calcd for $C_{14}H_{21}N_2$ $[M + H]^+$: 217.1699, found 217.1693.

N-((1H-Indol-2-yl)methyl)-3-methylbutan-2-amine (**2j**). Brown oil, 52%, 56.2 mg. IR (neat): 3240, 2961, 1667, 1454, 1384, 784 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.91 (bs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.17−7.07 (m, 2H), 6.36 (s, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.95 (d, J = 14.0 Hz, 1H), 2.62−2.53 (m, 1H), 2.28 (bs, 1H), 1.86−1.73 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.93 (t, J = 6.82 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.2, 135.9, 128.5, 121.3, 120.0, 119.5, 110.7, 99.8, 57.7, 44.5, 32.3, 19.3, 17.3, 15.8. HRMS (ESI) m/z: calcd for $C_{14}H_{21}N_2$ $[M + H]^+$ 217.1699, found 217.1694.

N-((1H-Indol-2-yl)methyl)-1-phenylmethanamine (**2k**). Brown oil, 50%, 59.1 mg. IR (neat): 3283, 2921, 1667, 1455, 749 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO): δ 10.93 (bs, 1H), 7.44 (d, J = 7.2 Hz, 1H), 77.40−7.30 (m, 6H), 6.36 (s, 1H), 7.01 (t, J = 6.8 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.27 (s, 1H), 3.82 (s, 2H), 3.72 (s, 2H), 2.00 (bs, 1H). ^{13}C NMR (100.6 MHz, DMSO): δ 140.9, 136.6, 132.0, 131.9, 128.6, 128.5, 127.1, 120.8, 119.9, 119.1, 111.4, 99.7, 52.6, 46.0. HRMS (ESI) m/z: calcd for $C_{16}H_{17}N_2$ $[M + H]^+$ 237.1386, found 237.1390.

2-((4-Ethylpiperazin-1-yl)methyl)-5-fluoro-1H-indole (**2l**). Pale-yellow solid, mp 102−104 °C, 58%, 75.8 mg. IR (KBr): 2971, 2813, 1488, 1450, 1174, 771 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.73 (bs, 1H), 7.24−7.19 (m, 2H), 6.93−6.87 (m, 1H), 6.34 (s, 1H), 3.67 (s, 2H), 2.56−2.42 (m, 10H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.8 (d, J_{CF} = 232 Hz), 137.6, 132.6, 128.7 (d, J_{CF} = 10 Hz), 111.1 (d, J_{CF} = 10 Hz), 109.7 (d, J_{CF} = 26 Hz), 105.0 (d, J_{CF} = 23 Hz), 101.7 (d, J_{CF} = 4 Hz), 55.8, 53.2, 52.7, 52.3, 12.0. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −125.1. HRMS (ESI) m/z: calcd for $C_{15}H_{21}FN_3$ $[M + H]^+$ 262.1714, found 262.1719.

2-((4-Ethylpiperazin-1-yl)methyl)-5,7-dimethyl-1H-indole (**2m**). Brown wax, 69%, 93.6 mg. IR (KBr): 3299, 2937, 2815, 1450, 1010, 750 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.56 (bs, 1H), 7.22 (s, 1H), 6.83 (s, 1H), 6.32 (s, 1H), 3.69 (s, 2H), 2.57−2.44 (m, 16H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 135.0, 134.2, 129.0, 128.0, 123.9, 119.6, 117.5, 102.1, 55.9, 53.1, 52.6, 52.3, 21.4, 16.7, 12.0. HRMS (ESI) m/z: calcd for $C_{17}H_{26}N_3$ $[M + H]^+$ 272.2121, found 272.2115.

N,N-Diethyl-1-(1H-indol-2-yl)ethanamine (**2n**). Pale-yellow wax, 77%, 83.3 mg. IR (KBr): 3444, 2969, 1455, 1384, 1299, 784, 736 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.71 (bs, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.18−7.07 (m, 2H), 6.33 (s, 1H), 4.17 (q, J = 6.4 Hz, 1H), 2.63−2.43 (m, 4H), 1.39 (d, J = 6.4 Hz, 3H), 1.08 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.3, 135.5, 128.9, 121.1, 120.0, 119.3, 110.5, 99.2, 52.8, 43.3, 13.9, 11.4. HRMS (ESI) m/z: calcd for $C_{14}H_{21}N_2$ $[M + H]^+$ 217.1699, found 217.1693.

4-(1-(1H-Indol-2-yl)ethyl)morpholine (**2o**). Brown wax, 60%, 69.1 mg. IR (KBr): 3407, 2861, 1455, 1384, 1114, 750 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.63 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.21−7.10 (m, 2H), 6.38 (s, 1H), 3.86−3.71 (m, 5H), 2.62−2.47 (m, 4H), 1.47 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.0, 135.8, 128.4, 121.5, 120.2, 119.6, 110.7, 100.2, 67.3, 58.1, 49.9, 14.2. HRMS (ESI) m/z: calcd for $C_{14}H_{19}N_2O$ $[M + H]^+$ 231.1492, found 231.1487.

2-(1-(4-(3,4-Dichlorophenyl)piperazin-1-yl)ethyl)-1H-indole (**2p**). White solid, mp 116.9−117.6 °C, 52%, 97.3 mg. IR (KBr): 3455, 2937, 2825, 1594, 1455, 1247, 1147, 746 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.59 (bs, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.24−7.13 (m, 2H), 6.98 (d, J = 3.2 Hz, 1H), 6.75 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 6.41 (s, 1H), 3.95 (q, J = 6.4 Hz, 1H), 3.24−3.14 (m, 4H), 2.75−2.62 (m, 4H), 1.50 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 150.7, 141.1, 135.8, 132.8, 130.4, 128.5, 122.1, 121.6, 120.3, 119.6, 117.2, 115.3, 110.7, 100.1, 57.7, 49.1, 48.9, 13.8. HRMS (ESI) m/z: calcd for $C_{20}H_{22}Cl_2N_3$ $[M + H]^+$ 374.1185, found 374.1180.

2-(1-(4-Ethylpiperazin-1-yl)propyl)-1H-indole (**2q**). Orange oil, 52%, 70.1 mg. IR (neat): 3279, 2928, 1668, 1437, 1119, 723 cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO): δ 10.86 (bs, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.01 (t, J = 8.4 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.21 (s, 1H), 3.86−3.74 (m, 1H), 2.50−2.20 (m, 10H), 1.95−1.75 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, DMSO): δ 140.9, 136.6, 132.0, 131.9, 128.6, 128.5, 127.1, 120.8, 119.9, 119.1, 111.4, 99.7, 52.6, 46.0. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.4, 136.3, 128.1, 120.7, 119.8, 119.0, 111.4, 100.6, 64.7, 63.4, 53.2, 52.0, 24.3, 12.4, 11.7. HRMS (ESI) m/z: calcd for $C_{17}H_{26}N_3$ $[M + H]^+$ 272.2121, found 272.2111.

2-((4-Ethylpiperazin-1-yl)(phenyl)methyl)-1H-indole (**2r**).[5] Pale-yellow solid, mp 106−108 °C, 53%, 84.6 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.60 (bs, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.37−7.33 (m, 3H), 7.28 (m, 1H), 7.18−7.11 (m, 1H), 7.09−7.07 (m, 1H), 6.41 (s, 1H), 4.64 (s, 1H), 2.57−2.45 (m, 10H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 139.1, 139.0, 136.0, 128.5, 128.4, 128.3, 127.6, 121.6, 120.3, 119.6, 110.8, 101.6, 69.2, 53.0, 52.2, 51.0, 11.8.

N-((1H-Indol-2-yl)(phenyl)methyl)butan-1-amine (**2s**).[5] Pale-yellow oil, 39%, 54.3 mg. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.62 (bs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 2H), 7.39−7.32 (m, 4H), 7.21−7.11 (m, 2H), 6.36 (s, 1H), 5.08 (s, 1H), 2.71−2.66 (m, 2H), 1.84 (bs, 1H), 1.61−1.56 (m, 2H), 1.48−1.38 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 142.4, 141.1, 135.8, 128.7, 128.6, 127.6, 127.3, 121.5, 120.3, 119.6, 110.9, 100.2, 61.6, 47.8, 32.4, 20.5, 14.1.

2-((4-(4-Fluorophenyl)piperazin-1-yl)(phenyl)methyl)-1H-indole (**2t**). Pale-yellow oil, 63%, 121.4 mg. IR (neat): 3399, 2830, 1712, 1455, 1240, 1139, 754 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.50 (bs, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.43−7.35 (m, 4H), 7.22−7.18 (m, 1H), 7.17−7.12 (m, 1H), 7.03−7.98 (m, 2H), 6.91−6.87 (m, 2H), 6.47 (s, 1H), 4.72 (s, 1H), 3.19−3.16 (m, 4H), 2.72−2.59 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.2 (d, J_{CF} = 237 Hz), 147.9, 138.9 (d, J_{CF} = 23 Hz), 136.1, 128.7, 128.4, 128.3, 127.8, 126.7, 121.8, 120.4, 119.8, 117.7 (d, J_{CF} = 7.8 Hz), 115.6 (d, J_{CF} = 22 Hz), 110.9, 101.8, 69.2, 51.3, 50.4. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −124.4. HRMS (ESI) m/z: calcd for $C_{25}H_{25}FN_3$ $[M + H]^+$ 386.2027, found 386.2021.

1-(5,7-Dimethyl-1H-indol-2-yl)-N,N-diethylethanamine (**2u**). Brown wax, 45%, 55.0 mg. IR (KBr): 3455, 2969, 1600, 1457, 1382, 842, 750 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.88 (bs, 1H), 7.24 (s, 1H), 6.84 (s, 1H), 6.29 (s, 1H), 4.25 (q, J = 6.4 Hz, 1H), 2.72−2.64 (m, 2H), 2.59−2.54 (m, 2H), 2.52 (s, 3H), 2.45 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 1.13 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.7, 128.8, 128.3, 123.7, 119.8, 117.3, 99.8, 53.2, 43.4, 21.4, 16.7, 13.1, 12.0. HRMS (ESI) m/z: calcd for $C_{16}H_{25}N_2$ $[M + H]^+$ 245.2012, found 245.2018.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of the products (**2a**−**u**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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