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"On Water" Promoted Ullmann-Type C−N Bond-Forming Reactions: Application to Carbazole Alkaloids by Selective N-Arylation of Aminophenols

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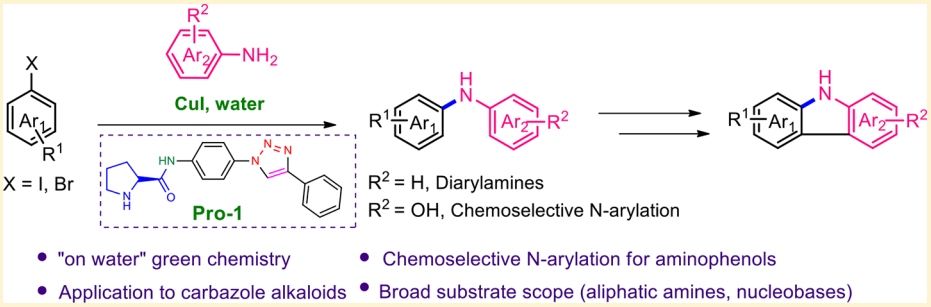
Supporting Information



ABSTRACT: The Ullmann-type cross coupling of a variety of aromatic, aliphatic amines with aryl halides is reported using a CuI-based catalytic system in combination with an easily accessible prolinamide ligand in aqueous media. The method is mild and tolerant to air, moisture, and a wide range of functional groups, providing a novel way to access a variety of aminated products. Secondary amines like heteroaromatic amines and nucleobases have also been used, affording the corresponding coupling products in good to excellent yields. Moreover, this method has been employed for chemoselective C−N arylation of aminophenols and further utilized for the synthesis of carbazole natural products, avoiding the protection and deprotection steps.

INTRODUCTION

The Ullmann-type C−N bond-forming reaction has emerged as a powerful tool for the rapid construction of aryl amines,[1] which are important motifs found in numerous natural products, biologically active compounds, and materials.[2] The palladium-catalyzed version of C−N bond formation, discovered by Buchwald and Hartwig[3,4] has been a major breakthrough in this field. Numerous strategies have been developed to extend the substrate scope allowing these reactions to proceed under mild reaction conditions.[5] In particular, Ma[6] and other groups[5] have explored the use of efficient bidentate ligands to accelerate copper-catalyzed Ullmann-type coupling reactions. Although significant progress[5,6] has been made and numerous methods have been reported, the development of a protocol for a C−N bond-forming reaction in an aqueous environment[5g−i] remains highly desirable as it can find applications by researchers in both academia and industry. It has been reported that hydrogen bonding at the organic and aqueous interface enhances the reactivity of "on water" reactions.[7] In this context, we herein demonstrate that a triazolylprolinamide ligand can promote Cu(I)-catalyzed amination "on water" with moderate to high yields under mild conditions, offering a broad substrate scope. Quite remarkably, this method has been used for a chemoselective C−N bond formation of aminophenols, providing an easy access to carbazole natural products.

RESULTS AND DISCUSSION

In continuation of our studies on organic transformations in aqueous environments,[8] we have studied the effect of prolinamide ligands **Pro-1−3** (Scheme 1) to promote Cu(I) catalyzed "on water" C−N coupling reactions. These ligands were prepared in a modular manner by using Cu(I)-catalyzed cycloaddition of azido prolinamides **3a,b** with alkynes **4a,b** to give triazole derivatives **5a−c**, which upon subsequent removal of Boc group afforded the desired ligands in high overall yields (Scheme 1).[8b] The azido prolinamides **3a** and **3b** were synthesized by coupling of *N*-Boc-proline **1** with azidoanilines **2a,b** in high yields.

Initially, the reaction of *p*-anisidine (**6a**) with *p*-iodoanisole (**7a**) was screened using CuI as catalyst and K_2CO_3 as a base at 100 °C in the presence of water (Table 1). To our delight, the reaction proceeded satisfactorily providing the desired product **8a** in 78% yield (entry 1). Encouraged by the result, the reaction conditions were investigated, including the choice of ligand, base, solvent, and temperature (Table 1). When the reaction was carried out in the absence of ligand **Pro-1**, no product was formed (Table 1, entry 2). This observation clearly

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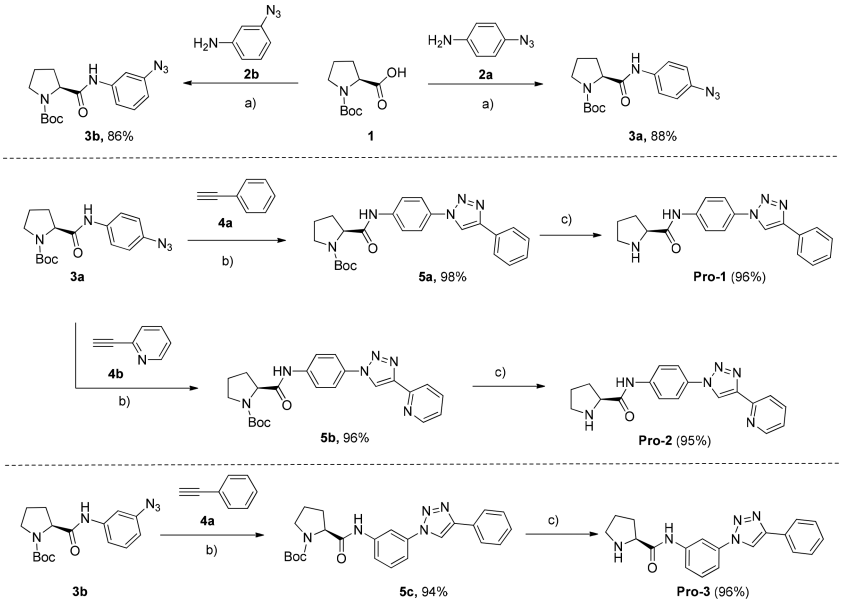
Scheme 1. Synthesis of Ligands Pro-1, Pro-2, and Pro-3



[a]DCC, HOBt, CH_2Cl_2, rt. [b]$CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*BuOH, H_2O (1:1), rt, 16 h. [c]TFA, CH_2Cl_2, rt, 10 h.

indicates that **Pro-1** plays a role in accelerating the C−N coupling reactions. Various solvents were screened (entries 3−9), and the results revealed that water is the best choice for the reaction (entry 1).

The desired product **8a** was obtained in very low yield (15−25%) in DMSO, DMF, *tert*-butyl alcohol, and toluene (entries 3−6). Moreover, the reaction was found to be sluggish in MeCN, EtOH, and 1,4-dioxane (entries 7−9). Next, the base screening suggested that K_2CO_3 was optimum for the reaction (entry 1), and Na_2CO_3 could also provide the product **8a** in slightly decreased yield (entry 16). It was observed that the reaction did not proceed well in the presence of bases like K_3PO_4, KOH, NaOH, LiOH, Cs_2CO_3, and Et_3N (entries 10−15). We have then evaluated the effect of different ligands such as DMEDA, phenanthroline, L-proline, and chiral prolinamide derivatives[9] **Pro-1** to **Pro-4** on the coupling reaction (entries 17−24). DMEDA, phenanthroline, and L-proline gave poor conversion (entries 17−19). Among the triazolyl prolinamide derivatives, **Pro-1** was found to be the optimal ligand for this transformation, suggesting the conformation of prolinamide derivatives is critical for attaining high reactivity (entry 1). The reaction was sluggish in the presence of prolinamide ligand **Pro-4** (entry 24). Subsequently, different copper catalysts were screened. As shown in Table 1, copper salts like CuBr, $Cu(OAc)_2$, CuO, CuCl, and CuOTf as well as Cu(0) as catalysts were less effective in promoting the reaction compared to CuI (entries 25−30).

With this initial outcome in hand, other parameters like the concentration of base, ligand, and catalyst at different times and temperatures were optimized (Table 2). As represented in Table 2, the C−N coupling reaction proceeded efficiently by using 20 mol % of **Pro-1**, 10 mol % of CuI, and 2 equiv of K_2CO_3 (entry 12). Incomplete conversion of the starting materials was observed when the reaction was maintained for short time periods (entry 10 and 11). However, a longer reaction time (48 h) gave no appreciable change in conversion compared to the optimized time (entry 14). Poor conversion of the starting materials was observed when the reaction proceeded at temperatures below 100 °C (entries 15 and 16).

Having established the optimized reaction conditions (0.2 equiv of **Pro-1**, 0.1 equiv of CuI, and 2 equiv of of K_2CO_3 in 0.1 M water at 100 °C, Table 1, entry 1), we then evaluated the generality of this C−N bond-forming reaction by varying aryl halides and amines (Schemes 2−4). As illustrated in Scheme 2, a wide range of functional groups bearing both electron-rich and electron-deficient moieties such as methoxy, methyl, nitrile, carboxylate, acid, fluoro, and nitro were compatible under the optimized reaction conditions, affording the corresponding products with good to high yields (71−78%, **8a**−**p**). The reaction proceeded smoothly with both *ortho*- and *meta*-substituted coupling partners (70−76%, Scheme 2). Unfortunately, no product was formed from the reaction of **6j** bearing an aldehyde functional group under the optimal conditions. We were pleased to find that aryl bromide **7j** could also react under the optimal conditions to provide products **8b** and **8h** in high yields (75−78%). However, aryl chloride failed to react under these reaction conditions (Scheme 2).

Encouraged by these results, we next expanded the scope of this reaction using aliphatic amines, heteroaromatic secondary amines, and nucleobases (Scheme 3). Aliphatic amines like benzyl amine **9a**, piperidine **9b**, morpholine **9c**, and pyrrolidine **9d** furnished the corresponding coupling products **10a**, **10b**, **10c**, and **10d** in 65−79% yields. Importantly, secondary amines like indole **9e**, carbazole **9f**, and 2-aminobenzothiazole **9g** could be coupled well with aryl iodide, delivering the desired products in 65−78% yields (**10e**, **10f**, and **10g**, Scheme 3). We were also successful in functionalizing the nucleobases like cytosine **9h** and uracil **9i** under our developed "on water" conditions to obtain the products **10h**−**j** in 66−68% yields (Scheme 3). Thus, the present method represents an attractive approach for synthesizing (hetero)aryl amines and nucleobase derivatives using mild reaction conditions.

It is worth mentioning that our method was used to obtain *N*-pyridyl aromatic compounds **12** and **13** in high yields by coupling of 2-bromopyridine **11** with primary and secondary

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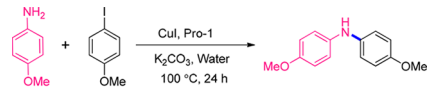
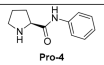
Table 1. Optimization of the Reaction Conditions[a]

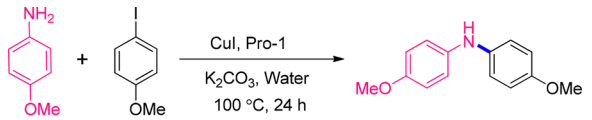


6a 7a 8a

entry	ligand	catalyst	base	solvent	time	yield (%) of **8a**[b]
1	**Pro-1**	**CuI**	**K_2CO_3**	**H_2O**	**24 h**	**78**
2	-	CuI	K_2CO_3	H_2O	24 h	0
3	**Pro-1**	CuI	K_2CO_3	DMSO	24 h	25
4	**Pro-1**	CuI	K_2CO_3	DMF	24 h	20
5	**Pro-1**	CuI	K_2CO_3	*tert*-butanol	24 h	17
6	**Pro-1**	CuI	K_2CO_3	Toluene	24 h	15
7	**Pro-1**	CuI	K_2CO_3	MeCN	24 h	10
8	**Pro-1**	CuI	K_2CO_3	EtOH	24 h	4
9	**Pro-1**	CuI	K_2CO_3	1,4–Dioxane	24 h	3
10	**Pro-1**	CuI	K_3PO_4	H_2O	24 h	5
11	**Pro-1**	CuI	KOH	H_2O	24 h	15
12	**Pro-1**	CuI	NaOH	H_2O	24 h	20
13	**Pro-1**	CuI	LiOH	H_2O	24 h	17
14	**Pro-1**	CuI	Cs_2CO_3	H_2O	24 h	5
15	**Pro-1**	CuI	Et_3N	H_2O	24 h	25
16	**Pro-1**	CuI	Na_2CO_3	H_2O	24 h	70
17	DMEDA	CuI	K_2CO_3	H_2O	24 h	35
18	Phenanthroline	CuI	K_2CO_3	H_2O	24 h	10
19	L-Proline	CuI	K_2CO_3	H_2O	24 h	19
20	D,L-Proline	CuI	K_2CO_3	H_2O	24 h	19
21	D,L-**Pro-1**	CuI	K_2CO_3	H_2O	24 h	78
22	**Pro-2**	CuI	K_2CO_3	H_2O	24 h	70
23	**Pro-3**	CuI	K_2CO_3	H_2O	24 h	35
24	 Pro-4	CuI	K_2CO_3	H_2O	24 h	10
25	**Pro-1**	$Cu(OAc)_2$	K_2CO_3	H_2O	24 h	20
26	**Pro-1**	CuO	K_2CO_3	H_2O	24 h	No reaction
27	**Pro-1**	CuBr	K_2CO_3	H_2O	24 h	30
28	**Pro-1**	Cu(0)	K_2CO_3	H_2O	24 h	No reaction
29	**Pro-1**	CuCl	K_2CO_3	H_2O	24 h	60
30	**Pro-1**	CuOTf	K_2CO_3	H_2O	24 h	50

[a]Reaction conditions: **6a** (0.5 mmol), **7a** (0.75 mmol), ligand (0.1 mmol), base (1.0 mmol), and CuI (0.05 mmol) in 2 mL water. [b]Isolated yields after chromatographic purification.

Table 2. Effect of Concentration of Base, Ligand, Cu(I), Time, and Temperature on the Reaction of *p*-Iodoanisole (6a) with *p*-Anisidine (7a)[a]



6a 7a 8a

entry	**Pro-1** (mol %)	CuI (mol %)	K_2CO_3 (equiv)	time (h)	temp (°C)	conv[b] (%)
1	20	10	0.5	24	100	50
2	20	10	1.0	24	100	65
3	20	10	1.5	24	100	70
4	5	10	2.0	24	100	40
5	10	10	2.0	24	100	45
6	15	10	2.0	24	100	65
7	20	2	2.0	24	100	35
8	20	5	2.0	24	100	55
9	20	8	2.0	24	100	70
10	20	10	2.0	12	100	50
11	20	10	2.0	18	100	65
12	**20**	**10**	**2.0**	**24**	100	**90**
13	20	10	3.0	24	100	85
14	20	10	2.0	48	100	80
15	20	10	2.0	24	80	50
16	20	10	2.0	24	60	30

[a]Reaction conditions: **6a** (0.5 mmol), **7a** (0.75 mmol), ligand (0.1 mmol), base (1.0 mmol), and CuI (0.05 mmol) in 2 mL water. [b]the conversion was determined from NMR of the crude reaction mixture.

amines **6a** and **9f** (Scheme 4). The synthesis of *N*-pyridyl carbazole **13** has been previously reported using Cu(I) catalyst under microwave irradiation at high temperature or by palladium or iridium catalysis at room temperature.[10] Recently, Li and co-workers have developed a Cu(I)-catalyzed Ullmann-type C−N cross-coupling reaction of carbazole and 2-bromopyridine derivatives for the synthesis of N-heteroarylcarbazole moieties using 1-methylimidazole as ligand and *t*BuOLi as base in toluene.[11] We have achieved the cross-coupling of carbazole **9f** and 2-bromopyridine **11** under the optimized conditions to obtain **13** in high yield (78%).

Recently, our group has reported the synthesis of carbazole alkaloids using RCM and ring rearrangement aromatization.[12] We have also demonstrated that carbazole derivatives can interact with G-quadruplexes and regulate gene expression.[13] In order to demonstrate the synthetic potential of the present Cu(I)-catalyzed C−N bond-forming reaction, we performed the amination reactions in gram scale to access **8a**, **8c**, **8l**, and **8o** in 70−78% yields (Scheme 2, Scheme 5). The high yield in these reactions prompted us to explore our newly developed method for the synthesis of carbazole natural products.[14,15] Herein we have demonstrated that the palladium(II)-catalyzed oxidative cyclization[16] of **8a** and **8c** provides an analogue of clausine V **14** and natural product glycozoline[15] **15**, respectively (Scheme 5). The cyclization of **8l** provided both clausine V[16c,i] **16** in 32% and regioisomeric carbazole derivative **17** in 48% yield (Scheme 5). Similarly, the cyclization of **8o** provided the natural product murrayafoline A[16a,e] **18** in 65% yield. The oxidation of methyl group of murrayafoline A furnished murrayanine[16a,b] **19** (95%), which upon subsequent reduction provided koenoline[16a] **20** (90%).

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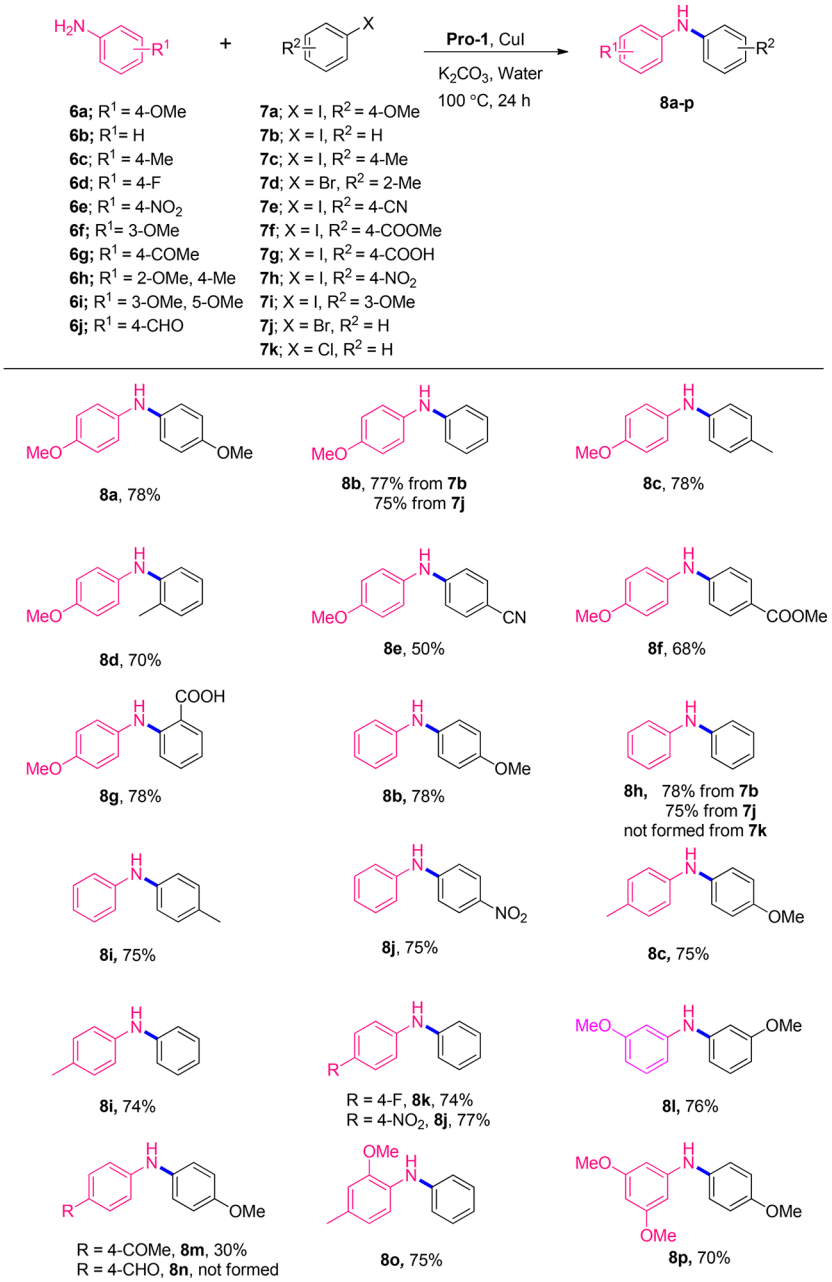
Scheme 2. N-Arylation of Aromatic Amines



Next, we studied chemoselective N-arylation of amino phenols using the present catalytic system. Selective N-arylation of aminophenols is challenging as the reaction often proceeds with the formation of both N- and O-arylated products.[17] Selective C−N arylation for aminophenols has been reported using Pd catalysis. The Buchwald group reported that palladium-based catalysis could be used to selectively obtain N-arylated products from aminophenols,[17a] while O-arylated products were obtained as the major products using copper-catalyzed reactions.[17b] They further demonstrated that only 2-aminophenol could undergo a selective N-arylation using Cu(I) catalysis.[17a]

In 2007, Buchwald et al. reported orthogonal N- and O-arylation of aliphatic amino alcohols using CuI.[17c] To our delight, aminophenols **21a−c** were chemoselectively N-arylated to provide the corresponding products **22a−c** in high yields under the optimized reaction conditions (Table 3). To support our results, we have carried out competition experiments by taking a 1:1 mixture of phenol **23** and *p*-anisidine **6a** with *p*-iodoanisole **7a** under the optimal conditions (Scheme 6). It was found that only *N*-arylated product **8a** was formed and phenol remained unreacted. Similar results were obtained by carrying out a control experiment using a 1:1 mixture of aniline **6b** and phenol with iodobenzene **7b**. Hence, this protocol enables an easy access to various diphenylamine derivatives containing a free hydroxy group on the aromatic ring.

The chemoselective C−N bond formation was further applied for a step-economic, efficient, and concise synthesis of naturally occurring carbazole alkaloids euchrestifoline,[14] girinimbine,[18] and murrayacine.[18] These compounds exhibit broad pharmacological activities, including anticancer, anti-inflamatory, antitumor-promoting, and acetylcholinesterase-inhibiting activities.[15] Recently, Knölker et al. synthesized

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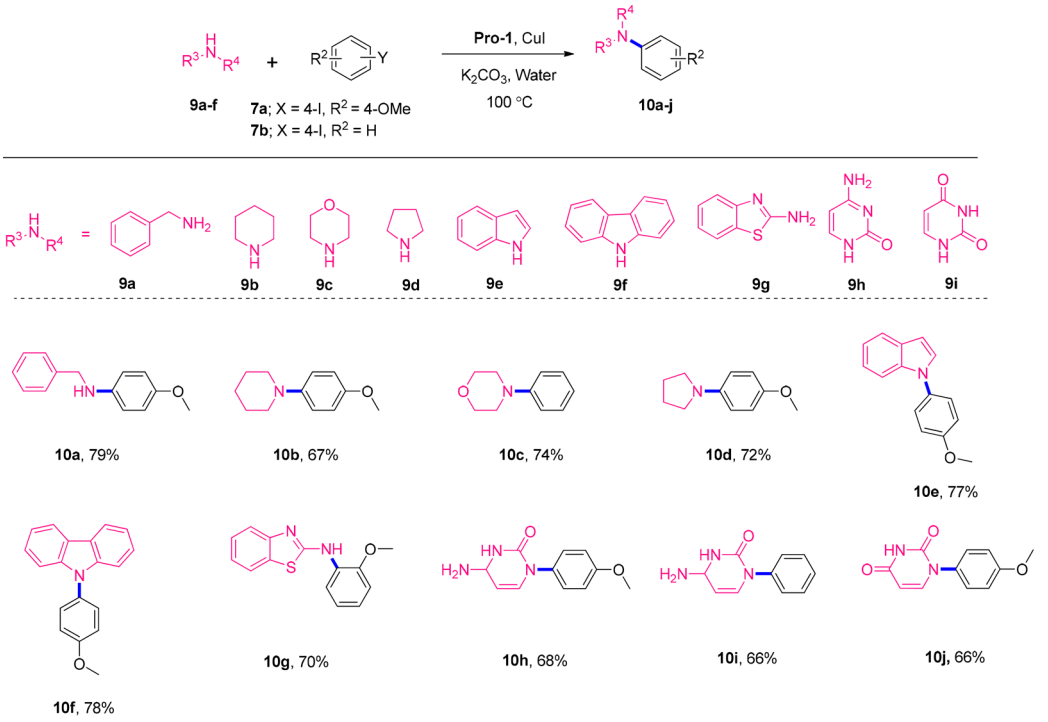
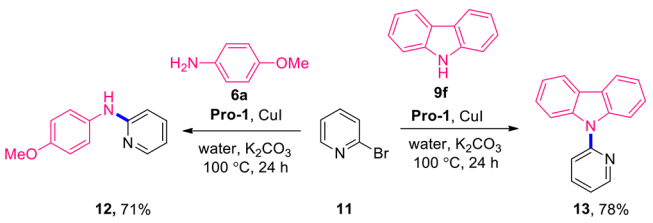
Scheme 3. Reaction of Various Aliphatic and Secondary Amines and Nucleobases with Aromatic Halides



Scheme 4. Reactions with 2-Bromopyridine



girinimbine and murrayacine following a protocol that involves protection and deprotection of a phenolic −OH group.[18]

We herein demonstrate the synthesis of those natural products in much lesser steps with high overall yield (Scheme 7). Using the optimized conditions, 3-aminophenol derivative **21b** was reacted with iodobenzene **7b** to give compound **22d** in 77% yield. Next, a cyclization reaction using prenal, followed by a one-pot Wacker oxidation and C−C bond formation, afforded the natural product euchrestifoline **25** in 52% yield (Scheme 7).[16] $LiAlH_4$-mediated reduction of euchrestifoline resulted in girinimbine[15] **26** (70%), which upon DDQ oxidation provided murrayacine[16] **27** (75%, Scheme 7). The spectral data of these carbazole alkaloids match with those of the reported natural products.

CONCLUSION

In summary, we have developed an "on water" promoted Cu(I)-based catalytic system using an easily accessible prolinamide ligand for C−N bond-forming reactions. A wide range of functionalized amines and aryl halides are compatible with the present reaction conditions, thereby allowing the synthesis of N-arylated products with diverse structural features. Although a few reports describe Cu-catalyzed N-arylation in neat water,[5g−i] none of these methods has been used for the coupling of aromatic amines. More importantly, prolinamide ligand **Pro-1** is quite cheap, conveniently synthesized, and easily tunable. The broad substrate scope, low cost of catalyst and ligand, gram-scale synthesis, and mild conditions render this reaction suitable and practical for synthesizing various aryl amine derivatives. Furthermore, this protocol can be readily applied under relative mild conditions, providing an easy access to naturally occurring carbazole alkaloids. Moreover, *N*-arylation of aminophenols can be chemoselectively achieved in the presence of phenolic OH groups, and this chemoselectivity has been effectively used for the synthesis of carbazole alkaloids without involving any protection and deprotection steps. The detailed mechanistic aspect of this reaction is currently under investigation in our laboratory.

EXPERIMENTAL SECTION

General Information. All experiments were carried out in an oven-dried 10.0 mL screw cap tube with a Teflon-coated magnetic stirring bar. Solvents were dried using standard procedures reported in ref 21. Unless otherwise stated, the starting materials were obtained from commercial suppliers and used as received. Reactions were monitored by thin-layer chromatography (TLC) analysis on silica gel 60 F_{254}, and visualization was accomplished by irradiation with short wave UV light at 254 nm. Products were purified by flash chromatography on silica gel (100−200 mesh). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. ^1H NMR spectra were recorded using 500 and 400 MHz instruments at room temperature. Signals are quoted as δ values in ppm using residual protonated solvent signals as internal standard ($CDCl_3$: δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a 100 MHz or a 125 MHz with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the solvent as

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Scheme 5. Synthesis of Carbazole Natural Products and Analogues

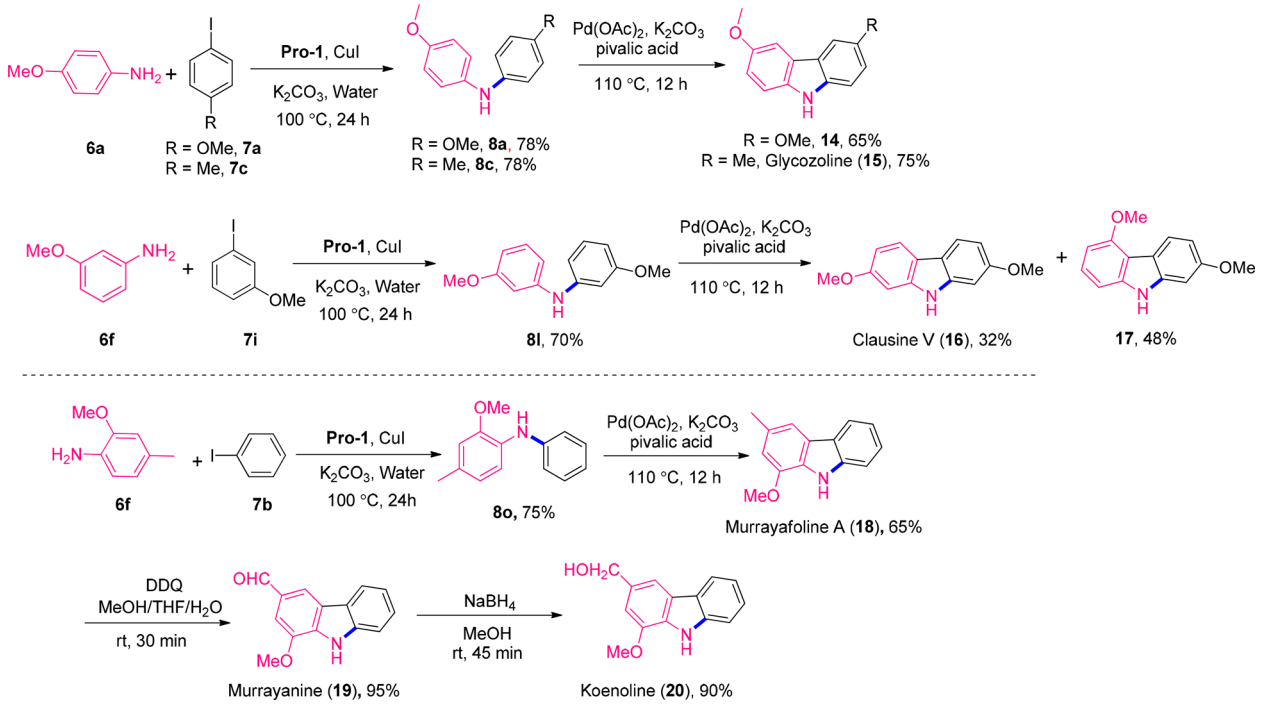
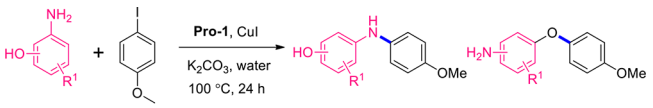


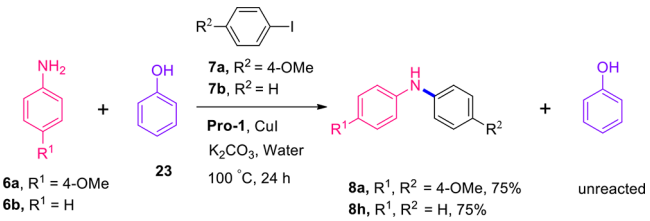
Table 3. Reaction with Unprotected Aminophenols[a]



entry	aminophenol	product	yield (%)[b]
1	21a	22a	75
2	21b	22 b	72
3	21c	22c	75

[a]Reaction conditions: **21a−c** (0.5 mmol), **7a** (0.75 mmol), **Pro-1** (0.1 mmol), K_2CO_3(1.0 mmol), CuI (0.05 mmol) in 2 mL of water. [b]Isolated yields after chromatographic purification.

Scheme 6. Control Experiments Using Amines and Phenol



the internal reference ($CDCl_3$: δ 77.26 ppm). HRMS analyses were performed with Q-TOF YA263 high resolution (Water Corp.) instruments by +ve mode electrospray ionization.

Synthetic Procedures for Preparation of Ligands. *Preparation of 4-Azidoprolinamide* ***3a.*** To an ice-cold suspension of *N*-Boc-proline **1** (1.0 g, 4.65 mmol) in dry CH_2Cl_2 (25 mL) were added DCC (1.06 g, 5.1 mmol, 1.1 equiv) and HOBT (691 mg, 5.1 mmol, 1.1 equiv), and the mixture was allowed to stir for 45 min. Then 4-azidoaniline[8b] **2a** (624 mg, 4.65 mmol, 1.0 equiv) in 20 mL of dry CH_2Cl_2 was added dropwise to the reaction mixture, which was stirred for 12 h. After complete consumption of the azide **2a** (TLC monitoring), the reaction mixture was filtered through Celite, washed with dichloromethane (50 mL), and concentrated under vacuum. The product was purified by flash chromatography using hexane−ethyl acetate (95:5 to 85:15) as eluent to afford the desired product **3a** as a viscous yellow liquid (1.50 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.61 (br s, 1H), 7.48 (d, 2H, J = 9.4 Hz), 6.89 (br s, 2H), 4.47 (br s, 1H), 3.45−3.36 (m, 2H), 2.44 (br s, 1H), 1.99−1.90 (m, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.0, 156.5, 135.5, 134.9, 120.8, 119.2, 80.9, 60.4, 47.3, 28.3, 27.5, 24.5. HRMS (ESI) calcd for $C_{16}H_{21}N_5O_3K$ (M + K)$^+$: 370.1281, found 370.1278.

Preparation of Triazole Derivative ***5a.*** Phenylacetylene (**4a**) (1.08 mL, 9.8 mmol), sodium ascorbate (194 mg, 0.98 mmol, 0.1 equiv), and $CuSO_4{\cdot}5H_2O$ (122.4 mg, 0.49 mmol, 0.05 equiv) were dissolved in 10 mL of *t*BuOH−H_2O (7:3) mixture. Then the azido prolinamide **3a** (3.3 g, 9.8 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 16 h. After complete consumption of **3a** as monitored by TLC, the reaction mixture was concentrated, and the residue was purified by flash chromatography using hexane−ethyl acetate (90:10−50:50) mixture to give the pure product **5a** (4.12 g, 98%) as a colorless solid (Scheme 1). Mp: 163−165 °C. ^{1}H NMR (400 MHz): 9.97 (s, 1H), 8.08 (s, 1H), 7.84 (d, 2H, J = 9.1 Hz), 7.57 (d, 2H, J = 9.6 Hz), 7.44 (d, 2H, J = 9.2 Hz), 7.35 (t, 2H, J = 8.5 Hz), 7.36−7.30 (m, 1H), 4.56 (s, 1H), 3.57−3.54 (m, 2H), 2.53 (s, 1H), 2.08−1.91 (m, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz): 171.1, 155.7, 148.1, 139.1, 132.0, 130.0, 128.7, 128.1, 125.6, 120.8,119.9, 117.7, 80.7, 60.4, 47.2, 28.9, 28.3, 24.5. HRMS (ESI) calcd for $C_{24}H_{27}N_5O_3K$ (M + K)$^+$: 472.1751, found 472.1743.

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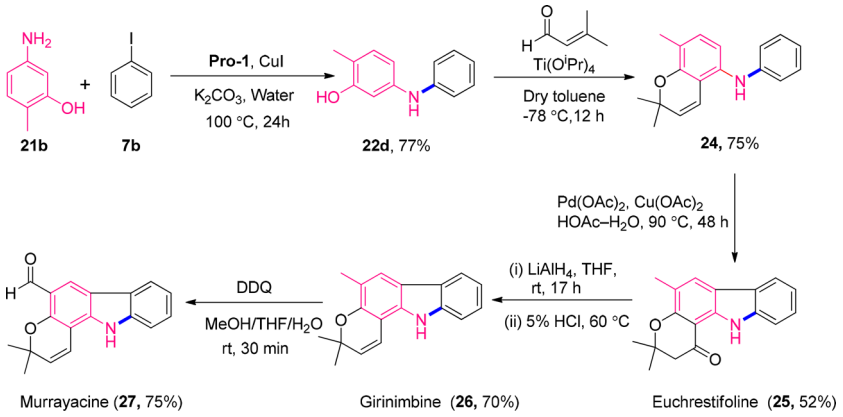
Scheme 7. Direct Synthesis of Carbazole Alkaloids from Amino Phenols



*Preparation of **Pro-1**.* To an ice-cold solution of compound **5a** (1.0 g, 2.3 mmol) in 30 mL of CH_2Cl_2 was added TFA (0.53 mL, 6.9 mmol, 3.0 equiv), and the mixture was stirred for 10 h at room temperature. After consumption of the starting material **5a** (monitored by TLC), the reaction mixture was brought to pH 8−9 by dropwise addition of a solution of aq NH_3 (30%) at 0 °C. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), evaporated, and dried under vacuum to give **Pro-1** (760 mg, 96%) as a white solid (Scheme 1). Mp: 207−210 °C. ^{1}H NMR (400 MHz): 9.98 (s, 1H), 8.17 (s, 1H), 7.89 (d, 2H, *J* = 8.8 Hz), 7.77 (d, 2H, *J* = 11.3 Hz), 7.72 (d, 2H, *J* = 11.1 Hz), 7.44 (t, 2H, *J* = 9.5 Hz), 7.35 (t, 1H, *J* = 9.2 Hz), 3.89 (dd, 1H, *J* = 11.6, 6.5 Hz), 3.09 (td, 1H, *J* = 12.8, 8.5 Hz), 3.00 (td, 1H, *J* = 12.8, 7.9 Hz), 2.40 (br s, 1H), 2.25−2.20 (m, 1H), 2.04 (dt, 1H, *J* = 15.6, 8.3 Hz), 1.79−1.74 (m, 2H). ^{13}C NMR (100 MHz): 173.7, 148.2, 138.3, 132.6, 130.2, 128.8, 128.3, 125.8, 121.1, 120.0, 117.6, 60.9, 47.3, 30.7, 26.3. HRMS (ESI) calcd for $C_{19}H_{20}N_5O$ $(M + H)^+$: 334.1667, found 334.1670.

*Preparation of Triazole Derivative **5b**.* 2-Ethynylpyridine **4b** (1.08 mL, 9.8 mmol), sodium ascorbate (194 mg, 0.98 mmol, 0.1 equiv), and $CuSO_4{\cdot}5H_2O$ (122.4 mg, 0.49 mmol, 0.05 equiv) were dissolved in 10 mL of *t*BuOH−H_2O (7:3) mixtures. Then the azido prolinamide **3a** (3.3 g, 9.8 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 16 h. After complete consumption of **3a** as monitored by TLC, the reaction mixture was concentrated, and the residue was purified by flash chromatography using hexane−ethyl acetate (90:10−40:60) mixture to give the pure product **5b** (4.00 g, 96%) as a colorless solid (Scheme 1). Mp: 170−172 °C. ^{1}H NMR (400 MHz, DMSO- d_6): 10.3 (br s, 1H), 9.23 (s, 1H), 8.64 (d, 1H, *J* = 3.9 Hz), 8.11 (d, 2H, *J* = 7.8 Hz), 7. 96 (d, 3H, *J* = 8.3 Hz), 7.83 (d, 2H, *J* = 8.3 Hz), 7.40 (t, 1H, *J* = 5.4 Hz), 4.29−4.21 (m, 1H), 2.27−2.19 (m, 1H), 1.91−1.81 (m, 3H), 1.41 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.9, 153.2, 149.6, 149.5, 147.9, 139.5, 137.4, 131.7, 123.3, 120.9, 120.8, 119.9, 119.8, 78.6, 60.5, 46.7, 30.9, 27.8, 23.3. HRMS (ESI) calcd for $C_{23}H_{27}N_6O_3$ $(M + H)^+$: 435.2145, found 435.2125.

*Preparation of Ligand **Pro-2**.* To an ice-cold solution of compound **5b** (1.0 g, 2.3 mmol) in 30 mL of dry CH_2Cl_2 was added TFA (0.53 mL, 6.9 mmol, 3.0 equiv), and the mixture was stirred for 10 h at room temperature. After consumption of the starting material **5b** (monitored by TLC), the reaction mixture was brought to pH 8−9 by dropwise adition of solution of aq NH_3 (30%) at 0 °C. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), evaporated, and dried under vacuum to give **Pro-2** (730 mg, 95%) as a white solid (Scheme 1). Mp: 218−220 °C. ^{1}H NMR (500 MHz, DMSO-d_6): 10.3 (br s, 1H), 9.24 (s, 1H), 8.64 (d, 1H, *J* = 3.4 Hz), 8.11 (d, 2H, *J* = 7.6 Hz), 7. 96−7.89 (m, 5H), 7.39 (t, 1H, *J* = 5.1 Hz), 3.75 (s, 1H), 2.92 (t, 2H, *J* = 6.7 Hz), 2.11−2.04 (m, 1H), 1.84−1.78 (m, 1H), 1.67 (t, 1H, *J* = 5.9 Hz), 1.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 173.7, 149.6, 149.5, 148.1, 138.9, 137.3, 131.8, 123.3, 120.9, 120.7, 120.0, 119.8, 60.8, 46.7, 30.4, 25.8. HRMS (ESI) calcd for $C_{18}H_{19}N_6O$ $(M + H)^+$: 335.1620, found 335.1625.

*Preparation of 3-Azidoprolinamide **3b**.* To an ice-cold suspension of *N*-Boc-proline **1** (1.0 g, 4.65 mmol) in dry CH_2Cl_2 (25 mL) were added DCC (1.06 g, 5.1 mmol, 1.1 equiv) and HOBT (691 mg, 5.1 mmol, 1.1 equiv), and the mixture was allowed to stir for 45 min. Then 3-azidoaniline **2b** (624 mg, 4.65 mmol, 1.0 equiv) in 20 mL of dry CH_2Cl_2 was added dropwise to the reaction mixture, which was stirred for 12 h. After complete consumption of the azide **2b** (TLC monitoring), the reaction mixture was filtered through Celite, washed with ethyl acetate (50 mL), and concentrated under vacuum. The product was purified by flash chromatography using hexane−ethyl acetate (95:5 to 85:15) as eluent to afford the desired product **3b** as a yellow solid (1.42 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.72 (s, 1H), 7.36 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 4.49 (s, 1H), 3.50−3.35 (m, 2H) 2.41−1.89 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$):170.5, 156.0, 140.2, 139.9, 129.6, 115.6, 114.0, 109.8, 80.8, 60.4, 47.1, 28.3, 24.5. HRMS (ESI) calcd for $C_{16}H_{21}N_5O_3K$ $(M + K)^+$: 370.1281, found 370.1264.

*Preparation of Triazole Derivative **5c**.* Phenylacetylene (**4a**) (1.08 mL, 9.8 mmol), sodium ascorbate (194 mg, 0.98 mmol, 0.1 equiv), and $CuSO_4{\cdot}5H_2O$ (122.4 mg, 0.49 mmol, 0.05 equiv) were dissolved in 10 mL of *t*BuOH−H_2O (7:3) mixture. Then the azido prolinamide **3b** (3.3 g, 9.8 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 16 h. After complete consumption of **3b** as monitored by TLC, the reaction mixture was concentrated and the residue was purified by flash chromatography using hexane−ethyl acetate (90:10−50:50) mixture to give the crude product **5c** (4.02 g, 94%) as a colorless solid (Scheme 1).

*Preparation of **Pro-3**.* To an ice-cooled solution of crude compound **5c** (1.0 g, 2.3 mmol) in 30 mL of CH_2Cl_2 was added TFA (0.53 mL, 6.9 mmol, 3.0 equiv), and the mixture was stirred for 10 h at room temperature. After consumption of the starting material **5c** (monitored by TLC), the reaction mixture was brought to pH 8−9 by dropwise addition of solution of aq NH_3 (30%) at 0 °C. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried in vacuo, and purified by flash chromatography using hexane−ethyl acetate (50:50−30:70) to give **Pro-3** (746 mg, 96%) as a white solid (Scheme 1). Mp: 214−216 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 10.4 (s, 1H), 9.23 (s, 1H), 7.95−7.88 (m, 6H), 7.50 (t, 2H, *J* = 7.8 Hz), 7.38 (t, 1H, *J* = 7.4 Hz), 3.91 (q, 1H, *J* = 5.8 Hz), 3.02 (t, 2H, *J* = 6.8 Hz), 2.21−2.12 (m, 1H), 1.91−1.83 (m, 1H), 1.79−1.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): 172.0, 147.2, 138.7, 132.1, 130.3, 128.9, 128.2, 125.3, 120.6, 120.2, 119.4, 60.6, 46.5, 30.2, 25.2. HRMS (ESI) calcd for $C_{19}H_{20}N_5O$ $(M + H)^+$: 334.1667, found 334.1665.

*Preparation of **Pro-4**.* To an ice-cold suspension of *N*-Boc-proline **1** (1.3 g, 5.91 mmol, 1.1 equiv) in dry CH_2Cl_2 (25 mL) were added DCC (1.21 g, 5.91 mmol, 1.1 equiv) and HOBT (799 mg, 5.91 mmol, 1.1 equiv), and the mixture was allowed to stir for 45 min. Then aniline (500 μL, 5.37 mmol, 1.0 equiv) in 20 mL of dry CH_2Cl_2 was added dropwise to the reaction mixture, which was stirred for 12 h. After complete consumption of aniline (TLC monitoring), the reaction mixture was filtered through Celite, washed with dichloro-

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methane (50 mL), and concentrated under vacuum. The crude product (400 mg, 1.45 mmol, 1 equiv) was taken in an ice-cold solution of 30 mL of CH_2Cl_2. To it was added TFA (330 mL, 4.35 mmol, 3.0 equiv), and the mixture was stirred for 10 h at room temperature. After consumption of the starting material (monitored by TLC), the reaction mixture was brought to pH 8−9 by dropwise addition of solution of aq NH_3 (30%) at 0 °C. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), evaporated, and dried under vacuum to give **Pro-4** (240 mg, 85%) as a white gummy solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.93 (br s, 1H), 7.64 (d, 2H, J = 7.4 Hz), 7.29 (t, 2H, J = 8.1 Hz), 7.04 (t, 1H, J = 7.3 Hz), 3.68 (dd, 1H, J = 5.9, 2.9 Hz), 2.88 (t, 2H, J = 6.6 Hz), 2.08−2.01 (m, 1H), 1.81−1.73 (m, 1H), 1.67−1.60 (m, 2H), 1.27 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 173.3, 138.5, 128.7, 123.2, 119.1, 60.8, 46.7, 30.4, 25.7. HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ (M + H)$^+$: 191.1184, found 191.1175.

General Procedure for Ullmann Coupling of Amines and Aromatic Halides (GP). In a small reaction vial, catalyst **Pro-1** (0.1 mmol, 0.2 equiv), aromatic amine (0.5 mmol, 1 equiv), aromatic halide (0.75 mmol, 1.5 equiv), and water (2.0 mL, 0.2 M) were taken. Then, copper iodide (0.05 mmol, 0.1 equiv) and potassium carbonate (1 mmol, 2 equiv) were added to the reaction mixture and heated in a preheated oil bath with stirring at 100 °C for 24 h. The completion of reaction was monitored by TLC analysis. The reaction mixture was extracted with ethyl acetate (3 × 2 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then purified by flash chromatography on 100−200 mesh silica gel using hexane−ethyl acetate (95:05−80:20) as eluent to provide the corresponding products.

Analytical Data of Compounds. *Bis(4-methoxyphenyl)amine (**8a**).*[6d] Following the GP, *p*-anisidine **6a** (53 mg, 0.43 mmol, 1 equiv) and *p*-iodoanisole **7a** (151 mg, 0.65 mmol, 1.5 equiv) afforded **8a** as a brownish white solid (77 mg, 78%). Mp: 100−104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 6.94 (d, 4H, J = 9.2 Hz), 6.83 (d, 4H, J = 8.4 Hz), 5.30 (br s, 1H), 3.70 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): 154.4, 138.1, 119.7, 114.9, 55.8. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ [M + H]$^+$: 230.1181, found 230.1162.

*4-Methoxy-N-phenylaniline (**8b**).*[6a] Following the GP, *p*-anisidine **6a** (61 mg, 0.5 mmol, 1 equiv) and iodobenzene **7b** (83 μL, 0.75 mmol, 1.5 equiv) afforded **8b** as a brown solid (75 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.26 (t, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.4 Hz), 6.96 (d, 2H, J = 7.6 Hz), 6.88−6.93 (m, 3H), 2.59−2.48 (m, 2H), 5.55 (br s, 1H,), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 155,5, 135.9, 129.4, 122.4, 119.7, 115.8, 114.9, 55.7. HRMS (ESI) calcd for $C_{13}H_{14}NO$ [M + H]$^+$: 200.1075, found 200.1082.

*4-Methoxy-N-phenylaniline (**8b**).*[6a] Following the GP, *p*-anisidine **6a** (61 mg, 0.5 mmol, 1 equiv) and bromobenzene **7e** (78 μL, 0.75 mmol, 1.5 equiv) afforded **8b** as a brown solid (73.5 mg, 75%).

*4-Methoxy-N-(p-tolyl)aniline (**8c**).*[6a] Following the GP, *p*-anisidine **6a** (62 mg, 0.5 mmol, 1 equiv) and *p*-iodotoluene **7c** (163 mg, 0.75 mmol, 1.5 equiv) afforded **8c** as a brown solid (75.1 mg, 78%). Mp: 81−83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.05−7.02 (m, 4H), 6.87−6.84 (m, 4H), 5.39 (br s, 1H), 3.80 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.0, 142.6, 136.8, 130.0, 121.3, 119.7, 116.8, 114.8, 55.8, 20.7. HRMS (ESI) calcd for $C_{14}H_{16}NO$ [M + H]$^+$: 214.1232, found 214.1236.

*N-(4-Methoxyphenyl)-2-methylaniline (**8d**).*[19a] Following the GP, *p*-anisidine **6a** (50 mg, 0.4 mmol, 1 equiv) and 2-bromotoluene **7d** (103 mg, 0.6 mmol, 1.5 equiv) afforded **8d** as a white solid (59.7 mg, 70%). Mp: 80−83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.15 (d, 1H, J = 7.6 Hz), 7.08 (t, 1H, J = 8.4 Hz), 7.03−6.99 (m, 3H), 6.88−6.87 (m, 2H), 6.86−6.80 (m, 1H), 3.80 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.3, 143.5, 136.5, 130.9, 126.9, 125.5, 122.3, 120.2, 115.4, 114.9, 55.8, 17.9. HRMS (ESI) calcd for $C_{14}H_{16}NO$ [M + H]$^+$: 214.1232, found 214.1217.

*4-((4-Methoxyphenyl)amino)benzonitrile (**8e**).*[19b] Following the GP, *p*-anisidine **6a** (50 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile **7e** (109 mg, 0.6 mmol, 1.5 equiv) afforded **8e** as a white solid (43.8 mg, 50%). Mp: 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (d, 2H, J = 8.8 Hz), 7.12 (d, 2H, J = 8.8 Hz), 6.91(d, 2H, J = 8.8 Hz), 6.78 (d, 2H, J = 8.8 Hz), 5.88 (br s, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 157.3, 149.3, 133.9, 132.7, 125.3, 120.2, 115.1, 113.9, 100.6, 55.7. HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ [M + H]$^+$: 225.1028, found 225.1020.

*Methyl 4-((4-Methoxyphenyl)amino)benzoate (**8f**).*[19c] Following the GP, *p*-anisidine **6a** (50 mg, 0.4 mmol, 1 equiv) and methyl 4-iodobenzoate **7f** (157 μL, 0.6 mmol, 1.5 equiv) afforded **8f** as a white solid (69.9 mg, 68%). Mp: 85−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (d, 2H, J = 8.3 Hz), 7.12 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 5.89 (br s, 1H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.2, 156.9, 150.0, 133.6, 131.7, 124.6, 120.2, 114.9, 113.4, 55.7, 51.7. HRMS (ESI) calcd for $C_{15}H_{16}NO_3$ [M + H]$^+$: 258.1130, found 258.1142.

*2-((4-Methoxyphenyl)amino)benzoic Acid (**8g**).*[19d] Following the GP, *p*-anisidine **6a** (50 mg, 0.4 mmol, 1 equiv) and 2-iodobenzoic acid **7g** (148.8 mg, 0.6 mmol, 1.5 equiv) afforded **8g** as a white solid (75.9 mg, 78%). ^{1}H NMR (400 MHz, DMSO-d_6): 9.42 (br s, 1H), 7.85 (dd, 1H, J = 1.5, 6.6 Hz), 7.31−7.27 (m, 1H), 7.15 (d, 2H, J = 8.8 Hz), 6.92 (t, 3H, J = 9.5 Hz), 6.66 (t, 1H, J = 8.1 Hz), 3.73 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 170.1, 156.1, 148.8, 134.2, 132.9, 131.8, 125.1, 116.3, 114.8, 112.8, 111.2, 55.2. HRMS (ESI) calcd for $C_{14}H_{14}NO_3$ [M + H]$^+$: 244.0974, found 244.0962.

*4-Methoxy-N-phenylaniline (**8b**).*[19e] Following the GP, aniline **6b** (47 μL, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0.75 mmol, 1.5 equiv) afforded **8b** as a brown solid (77 mg, 78%).

*Diphenylamine (**8h**).*[6a] Following the GP, aniline **6b** (45 μL, 0.5 mmol, 1 equiv) and iodobenzene **7b** (83 μL, 0.74 mmol, 1.5 equiv) afforded **8h** as a brown oil (65 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.22 (dd, 4H, J = 8.4, 5.1 Hz), 7.03 (d, 4H, J = 7.6 Hz), 6.88 (t, 2H, J = 7.5 Hz), 5.65 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 143.3, 129.5, 121.1, 118.0. HRMS (ESI) calcd for $C_{14}H_{16}NO$ [M + H]$^+$: 214.1232, found 214.1243.

*Diphenylamine (**8h**).*[6a] Following the GP, aniline **6b** (45 μL, 0.49 mmol, 1 equiv) and bromobenzene **7e** (78 μL, 0.75 mmol, 1.5 equiv) afforded **8h** as a brown oil (62 mg, 75%).

*4-Methyl-N-phenylaniline (**8i**).*[19e] Following the GP, aniline **6b** (46 μL, 0.5 mmol, 1 equiv) and *p*-iodotoluene **7c** (163 mg, 0.75 mmol, 1.5 equiv) afforded **8i** as a brown solid (68 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (t, 3H, J = 8.32 Hz), 7.08 (d, 2H, J = 8.3 Hz), 7.02−6.99 (m, 3H), 6.87 (t, 1H, J = 7.4 Hz), 5.59 (br s, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.2, 140.5, 131.1, 130.0, 129.5, 120.5, 119.1, 117.1, 20.8. HRMS (ESI) calcd for $C_{13}H_{14}N$ [M + H]$^+$: 184.1126, found 184.1131.

*4-Nitro-N-phenylaniline (**8j**).*[19e] Following the GP, aniline **6b** (45 μL, 0.49 mmol, 1 equiv) and *p*-nitroiodobenzene **7h** (183 mg, 0. 74 mmol, 1.5 equiv) afforded **8j** as a yellow solid (79 mg, 75%). Mp: 86−89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.12 (d, 2H, J = 9.2 Hz), 7.39 (t, 1H), 7.21 (d, 2H, J = 7.6 Hz), 7.17 (t, 2H, J = 6.75 Hz), 6.94 (d, 2H, J = 7.5 Hz), 6.28 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.2, 139.7, 135.5, 129.9, 126.3, 124.9, 122.1, 113.9. HRMS (ESI) calcd for $C_{12}H_{11}N_2O_2$ [M + H]$^+$: 215.0821, found 215.0802.

*4-Methoxy-N-(p-tolyl)aniline (**8c**):*[19f] Following the GP, *p*-toluidene **6c** (50 mg, 0.5 mmol, 1 equiv) and *p*-iodoanisole **7a** (168 mg, 0.75 mmol, 1.5 equiv) afforded **8c** as a brown solid (75.1 mg, 75%).

*4-Methyl-N-phenylaniline (**8i**):*[19e] Following the GP, *p*-toluidene **6c** (50 mg, 0.5 mmol, 1 equiv) and iodobenzene **7b** (167 mg, 0.75 mmol, 1.5 equiv) afforded **8i** as a brown solid (74.1 mg, 74%).

*4-Fluoro-N-phenylaniline (**8k**).*[19f] Following the GP, *p*-fluoroaniline **6d** (47 μL, 0.49 mmol, 1 equiv) and iodobenzene **7b** (83 μL, 0. 74 mmol, 1.5 equiv) afforded **8k** as a brown solid (68 mg, 74%). Mp: 85−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.24 (d, 1H, J = 7.7 Hz), 7.20 (d, 1H, J = 5.9 Hz), 7.06−7.04 (m, 2H), 6.99−6.96 (m, 4H), 6.90 (t, 1H, J = 7.6 Hz), 5.57 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 155.6, 143.6, 129.5, 120.8, 120.7, 117.0, 116.2, 115.9. HRMS (ESI) calcd for $C_{12}H_{11}FN$ [M + H]$^+$: 188.0876, found 188.0879.

*4-Nitro-N-phenylaniline (**8j**).*[19e] Following the GP, *p*-nitroaniline **6e** (68 mg, 0.49 mmol, 1 equiv) and iodobenzene **7b** (83 μL, 0. 74 mmol, 1.5 equiv) afforded **8j** as a yellow solid (81 mg, 77%).

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*Bis(3-methoxyphenyl)amine (**8l**).*[19g] Following the GP, 3-anisidine **6f** (53 mg, 0.43 mmol, 1 equiv) and 3-iodoanisole **7i** (151 mg, 0.65 mmol, 1.5 equiv) afforded **8l** as a brownish white solid (74 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.16 (t, 2H, J = 8.1 Hz), 6.67−6.64 (m, 4H), 6.48(dd, 2H, J = 6.6, 1.4 Hz), 5.72 (br s, 1H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.8, 144.4, 130.2, 110.8, 106.6, 103.9, 55.3. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.1181, found 230.1147.

*1-(4-((4-Methoxyphenyl)amino)phenyl)ethanone (**8m**).*[19h] Following the GP, 4-aminoacetophenone **6g** (50 mg, 0.4 mmol, 1 equiv) and *p*-iodoanisole **7a** (140 mg, 0.6 mmol, 1.5 equiv) afforded **8m** as a white solid (28.9 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.83 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 8.4 Hz), 6.91(d, 2H, J = 9.2 Hz), 6.81 (d, 2H, J = 8.4 Hz), 5.89 (br s, 1H), 3.82 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 196.5, 156.9, 150.3, 133.3, 130.9, 128.4, 124.8, 114.9, 113.3, 55.7, 26.2. HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $[M + H]^+$: 242.1181, found 242.1179.

*3-Methoxy-N-(4-methoxyphenyl)-4-methylaniline (**8o**).* Following the GP, 2-methoxy-4-methylaniline **6h** (100 mg, 0.73 mmol, 1 equiv) and iodobenzene **7b** (0.12 mL, 1.09 mmol, 1.5 equiv) afford **8o** as a white solid (133 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.24 (t, 2H, J = 8.4 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.08 (d, 2H, J = 7.6 Hz), 6.89 (dd, 2H, J = 7.6 Hz, 5.9 Hz), 6.70 (t, 2H, J = 6.7 Hz), 5.99 (br s, 2H), 3.86 (s, 3H), 2.31(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 148.9, 143.6, 130.3, 130.2, 129.4, 128.9, 121.5, 121.1, 120.6, 117.8, 116.1, 111.9, 55.7, 21.3. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1232, found 214.1236.

*3,5-Dimethoxy-N-(4-methoxyphenyl)aniline (**8p**).*[19i] Following the GP, 3,5-dimethoxyaniline **6i** (50 mg, 0.33 mmol, 1 equiv) and *p*-iodoanisole **7a** (114.6 mg, 0. 49 mmol, 1.5 equiv) afforded **8p** as a brown oil (60 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.08 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 6.77 (br s, 1H), 6.06 (d, 2H, J = 1.5 Hz), 5.98 (s, 1H), 3.80 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 161.9, 155.8, 147.6, 135.4, 123.3, 116.1, 114.9, 114.8, 94.2, 91.9, 55.7, 55.4. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$: 260.1287, found 260.1272.

*N-(4-Methoxybenzyl)aniline (**10a**).*[19e] Following the GP, benzylamine **9a** (54 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0.75 mmol, 1.5 equiv) afforded **10a** as a white solid (73 mg, 79%). ^{1}H NMR (125 MHz, $CDCl_3$): 7.37−7.31 (m, 4H), 7.25 (dd, 1H, J = 7.4, 7.3 Hz), 6.76 (d, 2H, J = 9.8 Hz), 6.59 (d, 2H, J = 9.2 Hz), 4.27 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 152.4, 142.6, 139.8, 128.7, 127.7, 127.3, 115.1, 114.3, 55.9, 49.4. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1232, found 214.1246.

*1-(4-Methoxyphenyl)piperidine (**10b**).*[19f] Following the GP, piperidine **9b** (42 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0. 75 mmol, 1.5 equiv) afforded **10b** as a yellow oil (55 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): 6.9 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.2 Hz), 3.76 (s, 3H), 3.03 (t, 4H, J = 5.7 Hz); 1.75−1.70 (m, 4H), 1.57−1.53 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 153.8, 147.1, 118.9, 114.5, 55.7, 52.5, 26.3, 24.3. HRMS (ESI) calcd for $C_{12}H_{18}NO$ $[M + H]^+$: 192.1388, found 192.1367.

*4-Phenylmorpholine (**10c**).*[6a] Following the GP, morpholine **9c** (50 μL, 0.6 mmol, 1 equiv) and iodobenzene **7b** (100 μL, 0.86 mmol, 1.5 equiv) afforded **10c** as a white solid (85.7 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (t, 2H, J = 8.1 Hz), 6.87 (dd, 3H, J = 8.1, 7.4 Hz), 3.83 (t, 4H, J = 5.2 Hz), 3.12 (t, 4H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):151.4, 129.2, 120.1, 115.7, 66.9, 49.4. HRMS (ESI) calcd for $C_{10}H_{14}NO$ $[M + H]^+$: 164.1075, found 164.1082.

*1-(4-Methoxyphenyl)pyrrolidine (**10d**).*[6a] Following the GP, pyrrolidine **9d** (57 μL, 0.7 mmol, 1 equiv) and *p*-iodoanisole **7a** (246 mg, 1.05 mmol, 1.5 equiv) afforded **10d** as a white solid (89.3 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): 6.86 (d, 2H, J = 8.4 Hz), 6.55 (d, 2H, J = 9.2 Hz), 3.77 (s, 3H), 3.25 (t, 4H, J = 6.7 Hz), 2.03−1.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$):151.1, 143.2, 115.1, 112.9, 56.1, 48.5, 25.5. HRMS (ESI) calcd for $C_{11}H_{16}NO$ $[M + H]^+$: 178.1232, found 178.1240.

*1-(4-Methoxyphenyl)-1H-indole (**10e**).*[6g] Following the GP, indole **9e** (60 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0. 75 mmol, 1.5 equiv) afforded **10e** as a white solid (73.5 mg, 77%). Mp: 125−127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.67 (d, 1H, J = 7.6 Hz), 7.45 (d, 1H, J = 8.2 Hz), 7.40 (dd, 2H, J = 5.7 Hz, 4.0 Hz), 7.27 (d, 1H, J = 6.3 Hz), 7.18 (t, 1H, J = 6.9 Hz), 7.15 (t, 1H, J = 7.0 Hz), 7.03 (dd, 2H, J = 8.2 Hz, 7.0 Hz), 6.64 (d, 2H, J = 7.6 Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.4, 136.5, 133.0, 129.1, 128.4, 126.2, 122.3, 121.2, 120.2, 114.9, 110.5, 103.0, 55.7. HRMS (ESI) calcd for $C_{15}H_{14}NO$ $[M + H]^+$: 224.1075, found 224.1068.

*9-(4-Methoxyphenyl)-9H-carbazole (**10f**).*[6a] Following the GP, carbazole **9f** (84 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0. 75 mmol, 1.5 equiv) afforded **10f** as a white solid (91.6 mg, 78%). Mp: 155−156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (d, 2H, J = 7.6 Hz), 7.45 (d, 2H, J = 7.6 Hz), 7.39 (t, 2H, J = 7.6 Hz), 7.32 (d, 2H, J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 159.1, 141.6, 130.5, 128.8, 126.0, 123.3, 120.4, 119.8, 115.3, 109.8, 55.8. HRMS (ESI) calcd for $C_{19}H_{16}NO$ $[M + H]^+$: 274.1232, found 274.1241.

*N-(4-Methoxyphenyl)benzo[d]thiazol-2-amine (**10g**).*[20a] Following the GP, benzo[*d*]thiazol-2-amine **9g** (50 mg, 0.3 mmol, 1 equiv) and *p*-iodoanisole **7a** (116 mg, 0.5 mmol, 1.5 equiv) afforded **10g** as a white solid (59.6 mg, 70%). Mp: 159−161 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.39 (d, 1H, J = 7.6 Hz), 7.18 (t, 1H, J = 7.6 Hz), 7.13 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.4 Hz), 6.73 (dd, 2H, J = 10.1, 7.6 Hz), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):158.5, 148.2, 136.5, 130.5, 129.8, 127.0, 118.9, 116.9, 115.5, 115.0, 55.5. HRMS (ESI) calcd for $C_{14}H_{13}N_2OS$ $[M + H]^+$: 257.0749, found 257.0738.

*4-((4-Methoxyphenyl)amino)pyrimidin-2(1H)-one (**10h**).* Following the GP, cytosine **9h** (108 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0. 75 mmol, 1.5 equiv) afforded **10h** as a gummy white solid (64 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.37 (br s, 1H), 7.30 (d, 1H, J = 7.6 Hz), 7.25 (d, 2H, J = 7.6 Hz), 6.99 (d, 2H, J = 6.7 Hz), 5.80 (d, 1H, J = 7.6 Hz), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 162.9, 159.8, 150.4, 145.2, 131.4, 127.7, 115.0, 102.5, 55.8. HRMS (ESI) calcd for $C_{11}H_{12}N_3O_2$ $[M + H]^+$: 218.0930, found 218.0922.

*4-(Phenylamino)pyrimidin-2(1H)-one (**10i**).* Following the GP, cytosine **9h** (108 mg, 0.5 mmol, 1 equiv) and iodobenzene **7b** (78 μL, 0.75 mmol, 1.5 equiv) afforded **10i** as a white solid (61 mg, 66%). Mp: 238−242 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.51 (br s, 1H), 7.50 (t, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 7.6 Hz), 7.36−7.33 (m, 3H), 5.82 (d, 1H, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 163.2, 150.2, 144.8, 138.5, 129.8, 129.2, 126.4, 102.8. HRMS (ESI) calcd for $C_{10}H_{10}N_3O$ $[M + H]^+$: 188.0824, found 188.0813.

*1-(4-Methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (**10j**).*[20b] Following the GP, uracil **9i** (109 mg, 0.43 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0. 75 mmol, 1.5 equiv) afforded **10j** as a white solid (62 mg, 66%). Mp: 229−231 °C. ^{1}H NMR (500 MHz): 8.35 (br s, 1H), 7.29 (d, 1H, J = 7.9 Hz), 7.25−7.23 (m, 2H), 6.98 (d, 2H, J = 8. Hz), 3.84 (3H, s); ^{13}C NMR (125 MHz): 163.2, 159.1, 150.1, 145.2, 131.3, 127.7, 115.1, 102.5, 55.8. HRMS (ESI) calcd for $C_{11}H_{11}N_2O_3$ $[M + H]^+$: 219.0770, found 219.0794.

*N-(4-Methoxyphenyl)pyridin-2-amine (**12**).*[20c] Following the GP, *p*-anisidine **6a** (50 mg, 0.4 mmol, 1 equiv) and 2-bromopyridine **11** (156 μL, 0.6 mmol, 1.5 equiv) afforded **12** as a white solid (56.8 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (d, 1H, J = 4.2 Hz), 7.44−7.41 (m, 1H), 7.23 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 6.66 (t, 2H, J = 8.4 Hz), 6.48 (br s, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 156.5, 148.5, 137.8, 133.4, 124.3, 114.8, 114.4, 107.4, 55.7. HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ $[M + H]^+$: 201.1028, found 201.1003.

*9-(Pyridin-2-yl)-9H-carbazole (**13**).* Following the GP, carbazole **9e** (84 mg, 0.5 mmol, 1 equiv) and 2-bromopyridine **11** (71 μL, 0. 75 mmol, 1.5 equiv) afforded **12** as a white solid (90.6 mg, 78%). Mp: 159−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.73 (d, 1H, J = 4.9 Hz), 8.12 (d, 2H, J = 7.3 Hz), 7.95−7.91 (m, 1H), 7.83 (d, 2H, J = 8.6 Hz), 7.63 (d, 1H, J = 7.9 Hz), 7.44 (t, 2H, J = 7.3 Hz), 7.33−7.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):152.0, 149.8, 139.7, 138.6, 126.4, 124.5, 121.3, 121.1, 120.3, 119.2, 111.3, . HRMS (ESI) calcd for $C_{17}H_{13}N_2$ $[M + H]^+$: 245.1079, found 245.1082.

Synthesis of Carbazole Natural Products. *Gram-Scale Synthesis of **8a**.* In a large sealed tube, catalyst **Pro-1** (541 mg, 1.62

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mmol, 0.2 equiv), *p*-anisidine **6a** (1 g, 8.12 mmol, 1 equiv), 4-iodoanisole **7a** (2.85 g, 12.18 mmol, 1.5 equiv) and water (10.0 mL, 1.0 M) were taken. Then, copper iodide (153 mg, 0.81 mmol, 0.1 equiv) and potassium carbonate (2.24 g, 16.24 mmol, 2 equiv) were added to the reaction mixture and heated in a preheated oil bath with stirring at 100 °C for 24 h. After completion of reaction, as monitored by TLC, extraction was done with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to afford **8a** as a brownish white solid (1.45 g, 78%).

*Synthesis of clausine V analogue **14**.* In a reaction flask, **8a** (100 mg, 0.44 mmol, 1equiv) was taken. To it potassium carbonate (7 mg, 0.044 mmol, 0.1 equiv), pivalic acid (45 mg, 0.44 mmol, 1 equiv) and palladium acetate (5 mg, 0.02 mmol, 0.05 equiv) were added and heated at 100 °C with stirring overnight. After completion of reaction, as monitored by TLC, the reaction mixture was extracted with ethyl acetate (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to obtain clausine V analogue **14** as white solid (65 mg, 65%). Mp: 130−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.78 (br s, 1H), 7.50 (d, 2H, *J* = 2.5 Hz), 7.30 (d, 2H, *J* = 9.3 Hz), 7.05 (dd, 2H, *J* = 6.7, 2.6 Hz), 3.93 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 153.8, 135.5, 123.9, 115.4, 111.6, 103.1, 56.2. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $[M + H]^+$: 228.1025, found 228.1030.

*Gram scale synthesis of **8c**.* In a large sealed tube, catalyst **Pro-1** (620 mg, 1.86 mmol, 0.2 equiv), *p*-anisidine **6a** (1 g, 8.12 mmol, 1 equiv), 4-iodotoluene **7c** (2.66 g, 12.18 mmol, 1.5 equiv) and water (10.0 mL, 1.0 M) were taken. Then, copper iodide (153 mg, 0.81 mmol, 0.1 equiv) and potassium carbonate (2.24 g, 16.24 mmol, 2 equiv) were added to the reaction mixture and heated in a preheated oil bath with stirring at 100 °C for 24 h. After completion of reaction, as monitored by TLC, extraction was done with ethyl acetate (3 × 10 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to afford **8c** as a brownish white solid (1.45 g, 78%).

*Synthesis of glycozoline **15**.* In a reaction flask, **8c** (100 mg, 0.47 mmol, 1equiv) was taken. To it potassium carbonate (7 mg, 0.047 mmol, 0.1 equiv), pivaic acid (48 mg, 0.47 mmol, 1 equiv) and palladium acetate (5 mg, 0.02 mmol, 0.05 equiv) were added. The reaction mixture was heated at 100 °C with stirring overnight. After completion of reaction, as monitored by TLC, the reaction mixture was extractrated with ethyl acetate (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to obtain glycozoline **15** as a white solid (74 mg, 75%). Mp: 176−179 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.83 (s, 1H), 7.52 (d, 1H, *J* = 2.6 Hz), 7.29 (dd, 2H, *J* = 5.9, 3.4 Hz), 7.21 (d, 1H, *J* = 7.6 Hz), 7.04 (dd, 1H, *J* = 6.7, 1.7 Hz), 3.92 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 154.0, 138.8, 135.0, 128.5, 127.3, 123.9, 123.8, 120.3, 115.0, 111.4, 110.6, 103.4, 56.3, 21.4. HRMS (ESI) calcd for $C_{14}H_{14}NO$ $[M + H]^+$: 212.1075, found 212.1069.

*Gram scale synthesis of bis(3-methoxyphenyl)amine (**8l**).* In a large sealed tube, catalyst **Pro-1** (541 mg, 1.62 mmol, 0.2 equiv), 3-anisidine **6f** (1 g, 8.12 mmol, 1 equiv), 3-iodoanisole **7i** (2.85 g, 12.18 mmol, 1.5 equiv) and water (10.0 mL, 1.0 M) were taken. Then, copper iodide (153 mg, 0.81 mmol, 0.1 equiv) and potassium carbonate (2.24 g, 16.24 mmol, 2 equiv) were added to the reaction mixture and heated in a preheated oil bath with stirring at 100 °C for 24 h. After completion of reaction, as monitored by TLC, extraction was done with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to afford **8l** as a brown colored solid (1.35 g, 70%).

*Synthesis of clausine V **16**.* In a reaction flask, a mixture of **8l** (100 mg, 0.44 mmol, 1equiv), potassium carbonate (7 mg, 0.044 mmol, 0.1 equiv), pivalic acid (45 mg, 0.44 mmol, 1 equiv) and palladium acetate (5 mg, 0.02 mmol, 0.05 equiv) were taken and heated at 100 °C with stirring overnight. After completion of reaction, as monitored by TLC, the reaction mixture was extracted with ethyl acetate (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to obtain clausine V **16** as a white solid (35 mg, 32%) and carbazole derivative **17** as a yellow solid (48 mg, 48%) .

*Clausine V **16**.* Mp 274−277 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (br s, 1H), 7.82 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 2.2 Hz), 6.83 (d, 2H, *J* = 1.5 Hz), 6.81 (d, 2H, *J* = 2.2 Hz), 3.90 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.4, 140.8, 120.2, 117.6, 107.9, 94.9, 55.8. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $[M + H]^+$: 228.1025, found 228.1007.

*Carbazole derivative **17**.* Mp 246−250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.16 (d, 1H, *J* = 8.4 Hz), 7.95 (br s, 1H), 7.28−7.25 (m, 1H), 7.0 (d, 1H, *J* = 7.6 Hz), 6.89 (d, 1H, *J* = 2.5 Hz), 6.86 (d, 1H, *J* = 1.7 Hz), 6.84 (d, 1H, *J* = 7.0 Hz), 6.66 (d, 1H, *J* = 7.6 Hz), 4.06 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.6, 155.7, 141.1, 140.1, 125.6, 123.8, 116.8, 112.9, 108.2, 103.5, 100.8, 94.7, 55.7. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $[M + H]^+$: 228.1025, found 228.1014.

*Gram scale synthesis of 3-methoxy-N-(4-methoxyphenyl)-4-methylaniline (**8o**).* In a large sealed tube, catalyst **Pro-1** (486 mg, 1.46 mmol, 0.2 equiv), 2-methoxy-4-methylaniline **6h** (1 g, 7.3 mmol, 1 equiv), iodobenzene **7b** (1.24 mL, 10.95 mmol, 1.5 equiv) and water (10.0 mL, 1 M) were taken. Then, copper iodide (138.7 mg, 0.73 mmol, 0.12 equiv) and potassium carbonate (2 g, 1.47 mmol, 2 equiv) were added to the reaction mixture and heated in a preheated oil bath with stirring at 100 °C for 24 h. After completion of reaction, as monitored by TLC, extraction was done with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to afford **8o** as a white solid (1.33 g, 75%).

*Synthesis of murrayafoline A **18**.* In a flask, **8o** (200 mg, 0.94 mmol, 1equiv) was taken. To it potassium carbonate (13 mg, 0.094 mmol, 0.1 equiv), pivaic acid (96 mg, 0.94 mmol, 1 equiv) and palladium acetate (11 mg, 0.047 mmol, 0.05 equiv) were added. The reaction mixture was heated at 110 °C with stirring overnight. After completion of reaction, as monitored by TLC, extractraction was done with ethyl acetate (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane-ethyl acetate (95:5−90:10) as eluent to obtain murrayafoline A **18** as a white solid (130 mg, 65%). Mp: 50−52 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.15 (br s, 1H), 8.01 (d, 1H, *J* = 8.2 Hz), 7.47 (s, 1H), 7.41−7.35 (m, 2H), 6.72 (s, 1H), 3.97 (s, 3H), 2.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 145.5, 139.6, 129.6, 128.2, 125.6, 124.5, 123.7, 120.6, 119.3, 112.7, 111.1, 107.9, 55.6, 22.1. HRMS (ESI) calcd for $C_{14}H_{14}NO$ $[M + H]^+$: 212.1075, found 212.1079.

*Synthesis of murrayanine **19**.* Murrayafoline A **18** (100 mg, 0.47 mmol, 1 equiv) was taken in an open mouthed round-bottom vessel and dissolved in methanol. To it DDQ (234 mg, 1.03 mmol, 2.2 equiv) was added and stirred at room temperature for 30 min. Vacuum concentration of the solvent followed by column purification using hexane-ethyl acetate (90:10−80:20) as eluent produced murrayanine **19** as a white solid (101 mg, 95%). Mp: 214−216 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 10.06 (s, 1H), 8.6 (br s, 1H), 8.21 (s, 1H,), 8.11 (d, 1H, *J* = 7.9 Hz), 7.49 (dd, 3H, *J* = 7.9 Hz, 5.5 Hz), 7.32 (t, 1H, *J* = 8.0 Hz), 4.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 192.0, 146.3, 139.6, 134.3, 130.4, 126.8, 123.9, 123.8, 120.9, 120.8, 120.5, 111.7, 103.8, 55.9. HRMS (ESI) calcd for $C_{14}H_{12}NO_2$ $[M + H]^+$: 226.0868, found 226.0856.

*Synthesis of koenoline **20**.* In a flask murrayanine **19** (50 mg, 0.22 mmol, 1 equiv) was dissolved in methanol. And to it $NaBH_4$ (20 mg, 0.45 mmol, 2 equiv) was added at 0 °C and stirred at room

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temperature for 45 min. Vacuum concentration of the solvent followed by extraction with ethyl acetate (2 × 5 mL) and column purification using hexane-ethyl acetate (80:20−75:25) as eluent produced koenoline **20** as a white solid (45 mg, 90%). Mp: 140−143 °C. ^{1}H NMR (500 MHz, DMSO-d_6): 11.4 (s, 1H), 8.13 (d, 1H, J = 7.55 Hz), 7.79 (s, 1H), 7.54 (d, 1H, J = 8.4 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.08 (s, 1H), 5.27 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 145.1, 139.5, 129.1, 126.6, 125.1, 122.8, 121.8, 119.8, 118.3, 112.9, 111.1, 106.7, 66.4, 54.9. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ [M + H]$^+$: 228.1025, found 228.1024.

Analytical data for aminophenol derivatives. *2-((4-Methoxyphenyl)amino)-5-methylphenol (**22a**):*[20d] Following the GP, 2-amino-5-methylphenol **21a** (62 mg, 0.5 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 0.75 mmol, 1.5 equiv) afforded **22a** as a brown solid (86 mg, 75%). ^{1}H NMR (500 MHz, DMSO-d_6): 9.09 (s, 1H), 6.85 (d, 1H, J = 7.6 Hz), 6.78−6.76 (m, 5H), 6.70 (s, 1H), 6.59 (d, 1H, J = 8.4 Hz), 3.68 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 153.7, 153.4, 141.4, 135.9, 131.2, 129.4, 122.0, 120.6, 117.5, 114.2, 55.2, 20.7. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ [M + H]$^+$: 230.1181, found 230.1194.

*5-((4-Methoxyphenyl)amino)-2-methylphenol (**22b**).*[17a] Following the GP, 5-amino-2-methylphenol **21b** (61.5 mg, 0.81 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 1.21 mmol, 1.5 equiv) afforded **22b** as a brownish white solid (82 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d_6): 8.98 (s, 1H), 7.55 (s, 1H), 6.96 (dd, 2H, J = 4.4, 2.6 Hz), 6.82 (t, 3H, J = 8.2 Hz), 6.45 (d, 1H, J = 2.5 Hz), 6.28 (dd, 1H, J = 5.7, 1.9 Hz), 3.69 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 155.8, 153.3, 143.8, 137.0, 130.7, 119.6, 114.4, 113.9, 106.6, 102.3, 55.2, 15.2. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ [M + H]$^+$: 230.1181; Found: 230.1176.

*4-((4-Methoxyphenyl)amino)phenol (**22c**).*[17a] Following the GP, *p*-aminophenol **21c** (54.6 mg, 0.92 mmol, 1 equiv) and 4-iodoanisole **7a** (175 mg, 1.38 mmol, 1.5 equiv) afforded **22c** as a brown solid (81 mg, 75%). ^{1}H NMR (500 MHz, DMSO-d_6): 8.84 (s, 1H), 7.33 (s, 1H), 6.86−6.81 (m, 4H), 6.77 (d, 2H, J = 9.3 Hz), 6.64 (d, 2H, J = 8.4 Hz), 3.67 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 152.4, 151.0, 138.9, 136.2, 119.2, 117.2, 115.7, 114.5, 55.2. HRMS (ESI) calcd for $C_{13}H_{14}NO_2$ [M + H]$^+$: 216.1025, found 216.1042.

Synthesis of carbazole alkaloids. *Gram-Scale Synthesis of 2-Methyl-5-(phenylamino)phenol (**22d**).*[17a] In a large sealed tube, catalyst **Pro-1** (486 mg, 1.46 mmol, 0.2 equiv), 5-amino-2-methylphenol **21b** (1 g, 8.12 mmol, 1 equiv), iodobenzene **7b** (1.36 mL, 12.21 mmol, 1.5 equiv), and water (10.0 mL, 1 M) were added. Then copper iodide (184.7 mg, 0.97 mmol, 0.12 equiv) and potassium carbonate (2.23 g, 16.24 mmol, 2 equiv) were added to the reaction mixture, which was heated in a preheated oil bath with stirring at 100 °C for 24 h. After completion of the reaction, as monitored by TLC, extraction was done with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then purified by flash chromatography on 100−200 mesh silica gel using hexane−ethyl acetate (95:5−90:10) as eluent to afford **22d** as a white solid (1.30 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.26−7.21 (m, 2H), 7.04−6.98 (m, 3H), 6.91−6.67 (m, 1H), 6.56−6.54 (m, 2H), 5.58 (br s, 1H), 4.69 (s, 1H) 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 153.9, 144.0, 142.9, 131.6, 129.5, 120.9, 117.9, 116.4, 111.0, 105.2, 15.1. HRMS (ESI) calcd for $C_{13}H_{14}NO$ [M + H]$^+$: 200.1075, found 200.1068.

*Synthesis of 2,2,8-Trimethyl-N-phenyl-2H-chromen-5-amine (**24**).* To a solution of **22d** (200 mg, 1.0 mmol, 1 equiv) in dry toluene was added 3-methyl-2-butenal (84.22 mg, 1.5 mmol, 1.5 equiv) at −78 °C. To this stirring solution was added dropwise titanium isopropoxide (0.9 mL, 3.0 mmol, 3 equiv), and the temperature was allowed to reach room temperature. Stirring was continued for 24 h until complete consumption of the starting material as monitored by TLC. It was then treated with 1.5 N HCl and worked up using ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then purified by flash chromatography on 100−200 mesh silica gel using hexane−ethyl acetate (95:5−90:10) as eluent to afford **24** as a white solid (198 mg, 75%). Mp: 107−109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (t, 2H, J = 8.4 Hz), 6.94 (d, 1H, J = 7.6 Hz), 6.82 (t, 3H, J = 7.6 Hz), 6.67 (d, 1H, J = 8.4 Hz), 6.46 (d, 1H, J = 10.1 Hz), 5.60 (d, 1H, J = 10.1 Hz), 5.40 (br s, 1H), 2.18 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 151.8, 145.8, 136.1, 130.5, 130.1, 129.4, 121.3, 119.6, 118.6, 115.9, 115.4, 114.4, 75.2, 27.8, 15.4. HRMS (ESI) calcd for $C_{18}H_{20}NO$ [M + H]$^+$: 266.1545, found 266.1556.

*Synthesis of Euchrestifoline **25**.* A mixture of **24** (100 mg, 0.38 mmol, 1 equiv), palladium acetate (1.69 mg, 0.01 mmol, 0.02 equiv), and cupric acetate (1.38 mg, 0.01 mmol, 0.02 equiv) in glacial acetic acid (5 mL) and water (0.5 mL) was heated at 90 °C in air for 48 h. After the mixture was cooled to rt, a small amount of silica gel was added to the reaction mixture and the solvent was removed under vacuum. Flash chromatography of the residue on Celite and silica gel (hexane−ethyl acetate, 90:10) provided euchrestifoline **25** as yellow crystals (58 mg, 52%). Mp: 181−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 10.1 (s, 1H), 8.01 (s, 1H), 7.93 (d, 1H, J = 7.4 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.38−7.34 (m, 1H), 2.82 (s, 2H), 2.34 (s, 3H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 194.5, 157.9, 139.7, 137.2, 129.4, 124.8, 122.5, 120.2, 119.4, 117.9, 116.5, 111.3, 104.9, 79.7, 48.8, 27.0, 16.2. HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ [M + H]$^+$: 280.1338, found 280.1340.

*Synthesis of Girinimbine **26**.* To a solution of euchrestifoline **25** (100 mg, 0.38 mmol, 1 equiv) in dry THF was added $LiAlH_4$ (19 mg, 0.50 mmol, 1.4 equiv) at 0 °C. The reaction was allowed to reach rt and was stirred for 17 h. It was then treated with 2.5 N HCl and stirred for 1 h at 60 °C. Finally, the reaction was worked up using ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The product was then purified by flash chromatography on 100−200 mesh silica gel using hexane−ethyl acetate (95:5−90:10) as eluent to afford girinimbine **26** as a white solid (74 mg, 70%). Mp: 172−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (d, 1H, J = 7.84 Hz), 7.88 (br s, 1H), 7.67 (s, 1H), 7.37 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.18 (t, 1H, J = 7.3 Hz), 6.63 (d, 1H, J = 9.8 Hz), 5.70 (d, 1H, J = 9.8 Hz), 2.34 (s, 3H), 1.49 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.0, 139.7, 135.0, 129.6, 124.4, 124.1, 121.3, 119.7, 119.5, 118.8, 117.4, 117.0, 110.5, 104.6, 76.0, 27.8, 16.2. HRMS (ESI) calcd for $C_{18}H_{18}NO$ [M + H]$^+$: 264.1388, found 264.1385.

*Synthesis of Murrayacine **27**.* Girinimbine **26** (100 mg, 0.38 mmol, 1 equiv) was taken in an open-mouthed reaction vessel and dissolved in methanol (5 mL). To it was added DDQ (190 mg, 0.84 mmol, 2.2 equiv) and the mixture was stirred at room temperature for 30 min. Vacuum concentration of the solvent followed by column purification using hexane−ethyl acetate (90:10−80:20) as eluent produced murrayacine **27** as a white solid (83 mg, 75%). Mp: 240−244 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 10.5 (s, 1H), 8.42 (s, 1H), 8.20 (br s, 1H), 7.98 (d, 1H, J = 7.3 Hz), 7.39−7.38 (m, 2H), 7.18−7.12 (m, 1H), 6.63 (d, 1H, J = 10.2 Hz), 5.80 (d, 1H, J = 9.8 Hz), 1.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 189.4, 154.9, 140.4, 140.3, 130.3, 128.3, 126.1, 124.3, 121.1, 120.4, 120.0, 118.9, 116.3, 110.9, 104.3, 77.4, 27.8. HRMS (ESI) calcd for $C_{18}H_{16}NO_2$ [M + H]$^+$: 278.1181, found 278.1184.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03020.

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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