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Assembly of Conjugated Enynes and Substituted Indoles via CuI/Amino Acid-Catalyzed Coupling of 1-Alkynes with Vinyl Iodides and 2-Bromotrifluoroacetanilides

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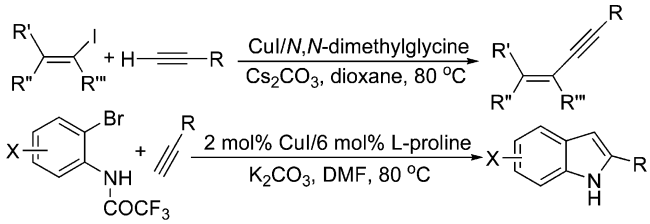

Cross-coupling of 1-alkynes with vinyl iodides occurs at 80 °C in dioxane catalyzed by CuI/*N*,*N*-dimethylglycine to afford conjugated enynes in good to excellent yields. Heating a mixture of 2-bromotrifluoroacetanilide, 1-alkyne, 2 mol % of CuI, 6 mol % of L-proline, and K_2CO_3 in DMF at 80 °C leads to the formation of the corresponding indole. This conversion involves a CuI/L-proline-catalyzed coupling between aryl bromide and the 1-alkyne followed by a CuI-mediated cyclization process. An ortho-substituent effect directed by $NHCOCF_3$ enables the reaction to proceed under these mild conditions. Both aryl acetylenes and *O*-protected propargyl alcohol can be applied, leading to 5-, 6-, or 7-substituted 2-aryl and protected 2-hydroxymethyl indoles in good yields. With simple aliphatic alkynes, however, lower yields were observed.

Introduction

Coupling of terminal alkynes with aryl halides and vinyl halides catalyzed by palladium complexes and copper(I) iodide, namely the Sonogashira reaction, has become a standard method for elaboration of aryl acetylenes and conjugated enynes.[1] A major drawback of this process for industrial use is the use of two metal catalysts, making recovery of the expensive palladium difficult. To solve this problem a great deal of effort has been directed toward the development of new catalytic systems during the past decades.[2−4] However, most of the successful examples are focused on enhancing the catalytic efficiency by replacing triphenylphosphine with specialized phosphines.[2] This modification still causes problems in large-scale applications because these special ligands are not readily available. Using elemental copper as the catalyst is another promising approach. This possibility has been demonstrated by Nomura, Venkataraman, and their co-workers.[5] However, in their cases only aryl iodides worked well and very low yields or no coupling were observed when less expensive aryl bromides were used.[5] In addition, triphenylphosphine was used as a ligand, which makes product isolation more difficult.

By applying special bidentate ligands, we and others have found that many CuI-catalyzed C−N,[6] C−O,[7] C−S,[8] and C−C[9] bond formation reactions can be conducted at much lower reaction temperatures than traditional Ullmann-type coupling

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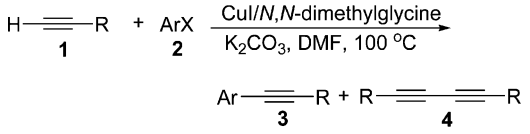
SCHEME 1



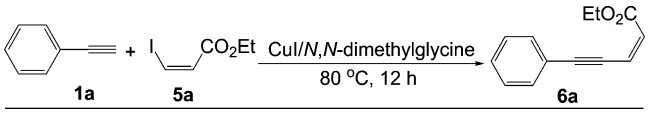
reactions.[10] Further exploration along this line by our group revealed that the combination of CuI and *N*,*N*-dimethylglycine provides an efficient catalytic system for the Sonogashira reaction, applicable to both aryl iodides and bromides (Scheme 1).[11] The extension of these findings to the synthesis of conjugated enynes and indoles was achieved. Herein, we report our results in detail.

Results and Discussion

Coupling of Vinyl Iodides with 1-Alkynes. It was found that CuI/*N*,*N*-dimethylglycine-catalyzed cross-coupling of aryl halides and 1-alkynes takes place at 100 °C (Scheme 1). Since vinyl iodides are more reactive than aryl halides,[5c] we decided to carry out the reaction at 80 °C. To our delight, the reaction of phenylacetylene with ethyl (*Z*)-3-iodoacrylate catalyzed by 10 mol % of CuI and 30 mol % of *N*,*N*-dimethylglycine hydrochloride salt afforded **6a** in 67% yield (entry 1, Table 1). Changing the solvent to dioxane gave slightly better yield (compare entries 1 and 2). Among the bases we tested, Cs_2CO_3 provided the best results, while lower yields were observed with NaOH and K_3PO_4. Thus, we used Cs_2CO_3 as the base and dioxane as the solvent in the subsequent studies.

The established reaction conditions were then applied to various reaction partners, and the results are summarized in Table 2. Aliphatic terminal alkynes are also suitable for this coupling reaction, providing synthetically useful enynes in 75% yield (entries 1 and 2). During the coupling reaction the geometry of the olefin part was generally preserved leading to the isolation of *cis*-**6b** and *trans*-**6d** exclusively (entries 1 and 3). Interestingly, (*Z*)-3-iodoacrylic acid **5c** also reacted smoothly,

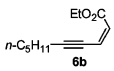
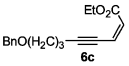
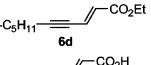
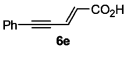
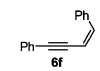
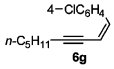
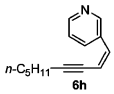
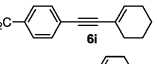
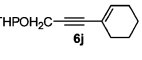
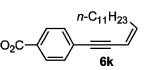
TABLE 1. CuI/*N*,*N*-Dimethylglycine Catalyzed Coupling Reaction of Phenylacetylene with Ethyl (*Z*)-3-Iodoacrylate[a]



entry	base	solvent	yield (%)[b]
1	K_2CO_3	DMF	67
2	K_2CO_3	dioxane	75
3	Cs_2CO_3	dioxane	83
4	NaOH	dioxane	35
5	K_3PO_4	dioxane	61

[a] Reaction conditions: vinyl iodide (1 mmol), acetylene (1.2 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol), base (3 mmol) in 2 mL of solvent, 80 °C, 12 h. [b] Isolated yield.

TABLE 2. CuI/*N*,*N*-Dimethylglycine Catalyzed Coupling Reaction of 1-Alkynes with Vinyl Iodides[a]

entry	vinyl iodide	1-alkyne	time (h)	product	yield (%)[b]
1	 5a	 1b	12	 6b	75
2	 5a	 1c	8	 6c	75
3	 5b	 1b	12	 6d	84
4	 5c	 1a	12	 6e	60
5	 5d	 1a	3	 6f	91[c]
6	 5e	 1b	22	 6g	67[d]
7	 5f	 1b	12	 6h	78
8	 5g	 1d	10	 6i	71
9	 5g	 1e	24	 6j	79
10	 5h	 1d	10	 6k	61

[a] Reaction conditions: vinyl iodide (1 mmol), acetylene (1.2 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol), Cs_2CO_3 (3 mmol), dioxane (2 mL), 80 °C. [b] Isolated yield. [c] *Z*/*E* = 5/1. [d] *Z*/*E* = 8/1.

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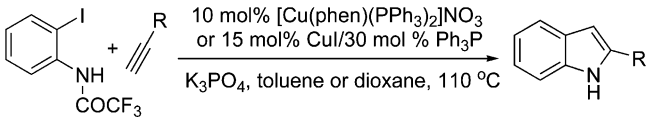
SCHEME 2



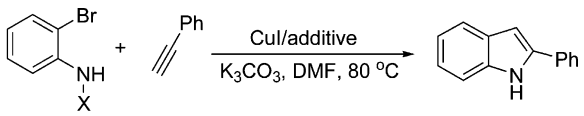
allowing the assembly of a carboxylic acid in a direct manner (entry 4). Aromatic vinyl iodides, including a heteroaryl substrate, performed well to deliver the corresponding coupling products in good yield (entries 5−7). Simple aliphatic vinyl iodides were found to couple with both aliphatic and aromatic terminal alkynes, indicating that the electronic nature of the reaction partners has a limited influence on the reaction process (entries 8−10). The relatively low yield observed for vinyl iodide **5h** may result from steric hindrance (entry 10). Indeed, steric influence was observed in the coupling reactions with (*Z*) and (*E*)-3-iodoacrylates (compare entries 1 and 3).

Assembly of Substituted Indoles via a Tandem Coupling/Cyclization Process. Establishing efficient methods for constructing the indole heterocycle has been an active area in organic synthesis for over one hundred years.[12−18] The driving force for this effort results from the fact that the indole moiety exists widely in biologically active natural products and artificial molecules.[12−18] Of the numerous methods developed for indole synthesis, the use of *o*-haloaniline derivatives and terminal alkynes as starting materials is one of the most attractive procedures, because the starting materials are easily prepared and modified.[14−18] Initially, this process was performed in two separated steps: (1) coupling of *o*-haloaniline derivatives with terminal alkynes, usually by the Sonogashira reaction, and (2) cyclization mediated by metal complexes,[14] bases,[15] iodine,[16] and Lewis acids.[17] Recently, Cacchi and co-workers reported a copper-catalyzed domino coupling-cyclization process that allowed the assembly of 2-aryl and 2-heteroaryl indoles in one pot starting from 1-alkynes and *o*-iodotrifluoroacetanilide.[18a] This process was carried out at 110 °C catalyzed by 10 mol % of $[Cu(phen)(Ph_3P)_2]NO_3$ or 15 mol % of CuI with 30 mol % of Ph_3P (Scheme 2), and only aryl iodides[18a] and a specific aryl bromide were tested.[18b]

The successful application of aryl bromides as substrates in the CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction[11] prompted us to explore if our catalytic system was applicable to Cacchi's process using 2-bromotrifluoroacetanilides as the substrates. We were pleased to observe that the reaction of *o*-bromotrifluoroacetanilide **7a** with phenylacetylene **1a** in the presence of *N*,*N*-dimethylglycine proceeded at 80 °C in DMF to provide 2-phenylindole **8a** in 63% yield (entry 1, Table 3). Using *N*-methylglycine as an additive gave better results (entry 2), and further improvement was achieved with L-proline (entry 3). This trend was different from that for coupling with simple aryl halides. It might result from the lower reaction temperature preventing the coupling of aryl halides with the additives.[6q] Next, we reduced the catalyst loading and found that excellent yield was still obtained with as little as 2 mol % of CuI (compare entries 3−6). Noteworthy is that triphenylphosphine was a poor additive for this transformation because no coupling products were determined (entry 7), which clearly showed that amino acids as the additives were essential for this process. Under the optimized reaction conditions, 2-phenylindole was obtained in low yield when *o*-bromoaniline **9** and *o*-bromoacetanilide **10** were utilized (entries 8 and 9), while none of the desired product was obtained from the mesyl-protected aniline **11** (entry 10). In these cases the staring bromides were recovered in 50−90% yields. These results clearly demonstrate that the ortho-substituent effect directed by the $NHCOCF_3$ group plays a key role in the present transformation, as observed in the CuI/amino acid-catalyzed biaryl ether formation[7h] and the coupling of aryl halides with β-keto esters.[9h]

We next explored the scope of the reaction by varying alkynes and trifluoroacetanilides (Table 4). It was found that aryl acetylenes bearing either electron-withdrawing or electron-donating groups were compatible with the reaction conditions, providing the corresponding 2-arylindoles in good yields (entries 1−4). Since introducing a functional group into a specific position of indoles was a major task in indole synthesis,[14−18] we extended our method to the synthesis of polysubstituted

TABLE 3. Coupling Reaction of Bromides 7a and 9−10 with Phenylacetylene 1a under the Catalysis of CuI and Additives[a]



7a: X = $COCF_3$ **1a** **8a**
9: X = H
10: X = $COCH_3$
11: X = SO_2CH_3

entry	ArBr	additive[b]	amount of CuI (mol %)	time (h)	yield (%)[c]
1	**7a**	A	10	16	63
2	**7a**	B	10	12	88
3	**7a**	C	10	12	95
4	**7a**	C	5	24	95
5	**7a**	C	2	24	92
6	**7a**	C	1	24	75
7	**7a**	D	15	24	0[d]
8	**9**	C	2	24	30[e]
9	**10**	C	2	24	21[f]
10	**11**	C	2	24	0[g]

[a] Reaction conditions: bromide **7a**, **9**, **10**, or **11** (1.1 mmol), phenylacetylene **1a** (1 mmol), CuI/additive = 1:3, K_2CO_3 (2 mmol), DMF (2 mL), 80 °C. [b] Additive A, *N*,*N*-dimethylglycine; additive B, *N*-methylglycine; additive C, L-proline; additive D, triphenylphosphine. [c] Isolated yield. [d] The ratio for CuI and additive is 1:2, **7a** was recovered in about 80% yield. [e] Bromide **9** was recovered in about 50% yield. [f] **10** was recovered in 71% yield. [g] Bromide **11** was recovered in about 90% yield.

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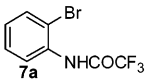
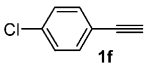
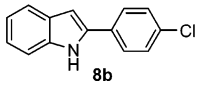
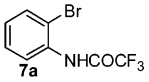
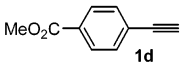
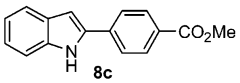
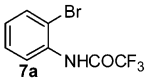
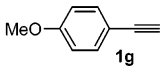
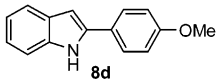
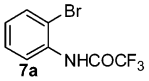
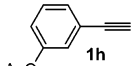
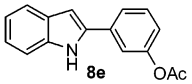
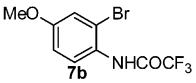
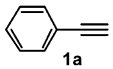
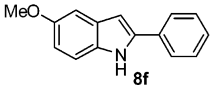
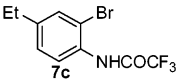
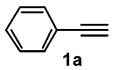
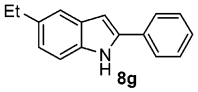
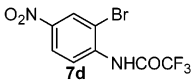
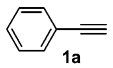
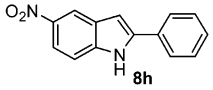
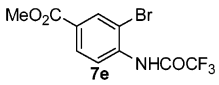
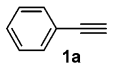
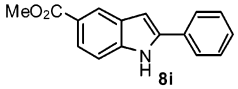
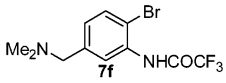
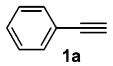
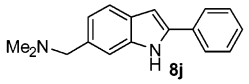
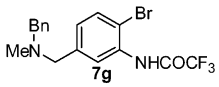
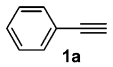
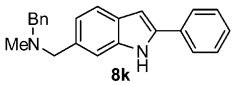
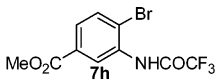
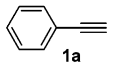
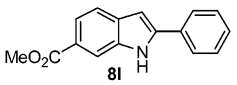
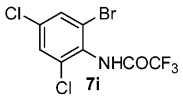
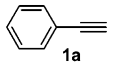
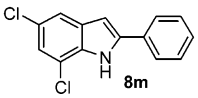
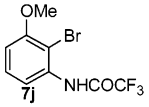
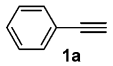
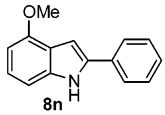
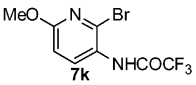
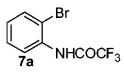
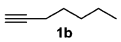
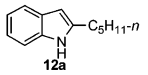
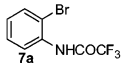
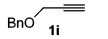
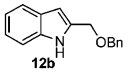
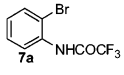
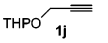
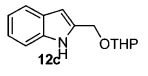
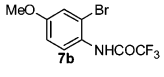
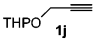
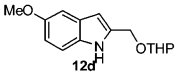
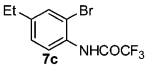
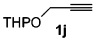
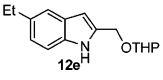
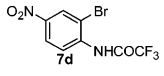
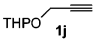
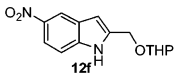
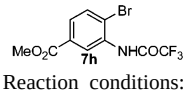
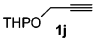
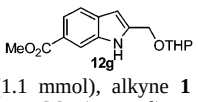
TABLE 4. Reaction of Substituted *o*-Bromotrifluoroacetanilides 7 with Aryl Acetylenes 1 Catalyzed by CuI/L-Proline [a]

entry	bromide	1-alkyne	product	yield (%)[b]
1	 **7a**	 **1f**	 **8b**	85
2	 **7a**	 **1d**	 **8c**	80
3	 **7a**	 **1g**	 **8d**	88
4	 **7a**	 **1h**	 **8e**	75
5	 **7b**	 **1a**	 **8f**	87
6	 **7c**	 **1a**	 **8g**	94
7	 **7d**	 **1a**	 **8h**	71
8	 **7e**	 **1a**	 **8i**	74
9	 **7f**	 **1a**	 **8j**	91
10	 **7g**	 **1a**	 **8k**	80
11	 **7h**	 **1a**	 **8l**	68
12	 **7i**	 **1a**	 **8m**	76
13	 **7j**	 **1a**	 **8n**	25[c]
14	 **7k**	**1a**	**8o**	75

[a] Reaction conditions: bromide **7** (1.1 mmol), alkyne **1** (1 mmol), CuI (0.02 mmol), L-proline (0.06 mmol), K_2CO_3 (2 mmol), DMF (2 mL), 80 °C, 24 h. [b] Isolated yield. [c] 3-Methoxytrifluoroacetanilide was isolated in 46% yield.

indoles. We were pleased that using readily available 4-substituted 2-bromotrifluoroacetanilides **7b**−**e** as the substrates led to 2,5-disubstituted indoles **8f**−**i** (entries 5−8). Starting from 3-substituted anilines, prepared by nitration of the corresponding 4-substituted aryl bromides, 5-substituted 2-bromotrifluoroacetanilides **7f**−**h** were synthesized. Coupling of these bromides

TABLE 5. Reaction of Substituted *o*-Bromotrifluoroacetanilides 7 with Alkyl Acetylenes 1 Catalyzed by CuI/L-Proline [a]

entry	bromide	1-alkyne	product	yield (%)[b]
1				32[c]
2				87
3				94
4				84
5				91
6				69
7				72

[a] Reaction conditions: bromide **7** (1.1 mmol), alkyne **1** (1 mmol), CuI (0.02 mmol), L-proline (0.06 mmol), K_2CO_3 (2 mmol), DMF (2 mL), 80 °C, 24 h. [b] Isolated yield. [c] Trifluoroacetanilide was isolated in 50% yield.

with **1a** under the newly elaborated reaction conditions led to 2,6-disubstituted indoles **8j**−***l*** in good yields (entries 9−11). Bromides with electron-withdrawing groups gave slightly lower yields in comparison with those possessing electron-donating groups (entries 5−11). Next, we checked the possibility of assembling 7-substituted indoles by our process and were pleased to observe that reaction of bromide **7i** with **1a** delivered 2-phenyl-5,7-dichloroindole **8m** in 76% yield (entry 12). However, reaction of 3-methoxy-2-bromotrifluoroacetanilide **7j** with **1a** provided 4-methoxy-2-phenylindole **8n** in only 25% yield (entry 13). A debromination product, 3-methoxytrifluoroacetanilide, was isolated in 46% yield, implying that the low yield of **8n** might result from sluggish coupling of bromide **7j** with the alkyne, possibly due to the steric hindrance of bromide **7j**. As an additional example, it was found that using heteroaryl bromide **7k** also delivered the desired product in 75% yield (entry 14).

Reaction of **7a** with 1-heptyne **1b** produced 2-*n*-pentylindole **12a** in low yield (Table 5, entry 1). In this case the debromination reaction occurred again, which implies that the cross-coupling step is difficult for simple aliphatic terminal alkynes, as previously observed by Cacchi and co-workers.[18a] We did find, however, that when *O*-protected propargyl alcohols were employed, the desired indoles were obtained in satisfactory yields (entry 2−7). These results indicate that subtle changes in electron density of the acetylenes greatly alter their reactivity in cross-coupling reaction, which is in contrast to the observations made when coupling 1-alkynes with vinyl iodides and aryl halides. Noteworthy is that the protected 2-hydroxymethyl allows further transformations thereby giving this method more potential for synthesizing biologically important indoles.[17a,19]

In conclusion, a palladium- and phosphine-free catalytic system for the Sonogashira-type coupling reaction between vinyl iodides and 1-alkynes was developed. Through a combination of ligand and ortho-substituent effects, a domino coupling/cyclization process of 1-alkynes and 2-bromotrifluoroacetanilides proceeds under relatively mild conditions. This process allows the preparation of indoles bearing substituents at the 2,5-, 2,6-, or 2,7-positions by applying the appropriate 2-bromotrifluoroacetanilides. A wide range of functional groups were found to tolerate our reaction conditions. Since the catalytic system is cheap and easily removable (by simple washing), it should find practical usage in the synthesis of conjugated enynes and substituted indoles. Mechanistic studies of the present processes, as well as the further applications of our method in the preparation of biologically interesting compounds, are actively under investigation in our laboratory, and will be reported in due time.

Experimental Section

General Procedure for the CuI/*N*,*N*-dimethylglycine-Catalyzed Coupling Reaction of 1-Alkynes with Vinyl Iodides. Vinyl iodide (1 mmol), alkynes (1.2 mmol), copper iodide (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.3 mmol), and Cs_2CO_3 (3 mmol) in 2 mL of dioxane in a sealed tube were heated to 80 °C under argon. After the reaction was completed monitored by TLC, the cooled mixture was partitioned between ethyl acetate and water (if a substrate has a carboxylate group the reaction mixture should be acidified to pH 1 before extraction). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with petroleum ether/ethyl acetate to afford the product.

(*Z*)-Ethyl 8-(benzyloxy)oct-2-en-4-ynoate (6c): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.19 (m, 5H), 6.05 (d, J = 11.7 Hz, 1H), 5.96 (d, J = 11.7 Hz, 1H), 4.46 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 2.54−2.49 (t, J = 6.9 Hz, 3H), 1.87−1.80 (m, 2H), 1.39−1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 138.5, 134.5, 128.4 (2C), 127.7 (2C), 127.6, 123.8, 103.3, 78.0, 73.0, 68.8, 60.3, 32.0, 30.0, 17.0; MS *m*/*z* 272 (M^+).

(*Z*)-3-(Non-1-en-3-ynyl)pyridine (6h): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84−7.79 (m, 1H), 7.40−7.27 (m, 3H), 6.49 (d, J = 12.0 Hz, 1H), 5.70 (d, J = 12.3 Hz, 1H), 2.47−2.42 (m, 2H), 1.65−1.58 (m, 2H), 1.48−1.34 (m, 4H), 0.90 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 148.5, 134.6 (2C), 133.2, 122.9, 110.8, 99.2, 78.5, 31.0, 28.1, 22.1, 19.7, 13.8; MS *m*/*z* 199 (M^+); MALDI HRMS calcd for $C_{14}H_{19}N$ ($M + H)^+$ 200.1440, found 200.1434.

Methyl 4-(2-cyclohexenylethynyl)benzoate (6i): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00−7.95 (m, 2H), 7.56−7.45 (m, 2H), 6.25 (s, 1H), 3.91 (s, 3H), 2.23−2.14 (m, 4H), 1.69−1.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 136.2, 132.0, 131.2 (2C), 129.3 (2C), 128.8, 120.4, 94.3, 80.0, 52.1, 28.9, 25.7, 22.1, 21.3; MS *m*/*z* 240 (M^+); MALDI HRMS calcd for $C_{16}H_{17}O_2$ ($M + H)^+$ 241.1232, found 241.1223.

2-(3-Cyclohexenylprop-2-ynyloxy)tetrahydro-2*H*-pyran (6j): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.13 (s, 1H), 4.85−4.83 (m, 1H), 4.40−4.36 (m, 2H), 3.88−3.86 (m, 1H), 3.58−3.52 (m, 1H), 2.12−2.10 (m, 4H), 1.85−1.56 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 120.1, 96.5, 87.6, 82.1, 61.8, 54.7, 30.2, 29.0, 25.5, 25.3, 22.2, 21.4, 19.0; MS *m*/*z* 220 (M^+); MALDI HRMS calcd for $C_{14}H_{20}O_2Na$ ($M + Na)^+$ 243.1366, found 243.1379.

General Procedure for the Coupling Reaction of 2-Bromotrifluoroacetanilide or 2-Bromoaniline with Phenylacetylene Catalyzed by CuI and Additives. A mixture of bromide (1.1 mmol), phenylacetylene (1.0 mmol), CuI, additive, and K_2CO_3 (2.0 mmol) in 2 mL of DMF was heated in a sealed tube to 80 °C under

(19) Koerber-Ple, K.; Massiot, G. *Synlett* **1994**, 759.

argon. After the reaction completed monitored by TLC, the cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 1/10 to 1/8 ethyl acetate/petroleum ether to afford **8a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 7.58−7.54 (m, 3H), 7.37−7.21 (m, 4H), 7.18−7.04 (m, 2H), 6.74 (s, 1H); MS *m*/*z* 193 (M^+).

General Procedure for the Coupling Reaction of 2-Bromotrifluoroacetanilides with 1-Alkynes Catalyzed by CuI and L-Proline. A mixture of bromide (1.1 mmol), alkyne (1.0 mmol), CuI (0.02 mmol), L-proline (0.06 mmol), and K_2CO_3 (2 mmol) in 2 mL of DMF was heated in a sealed tube to 80 °C under argon. After the reaction completed monitored by TLC, the cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 10/1 to 5/1 petroleum ether/ethyl acetate to afford the corresponding indole.

2-(4-Chlorophenyl)indole (8b): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 6.9 Hz, 2H), 7.41−7.36 (m, 3H), 7.24−7.10 (m, 2H), 6.80 (s, 1H); MS *m*/*z* 227 (M^+).

4-(Indol-2-yl)benzoic acid methyl ester (8c): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 3.95 (s, 3H); MS *m*/*z* 251 (M^+).

2-(4-Methoxyphenyl)indole (8d): ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 10.56 (s, 1H), 7.79 (d, J = 6.9 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.10−6.98 (m, 4H), 6.77 (s, 1H), 3.84 (s, 3H); MS *m*/*z* 223 (M^+).

Acetic acid 3-(indol-2-yl)phenyl ester (8e): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.37−7.34 (m, 3H), 7.19−7.11 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.78 (s, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 151.6, 137.3, 137.2, 134.4, 130.4, 129.5, 128.8, 123.0, 121.2, 121.0, 120.7, 118.7, 111.4, 101.0, 21.6; MS *m*/*z* 251 (M^+). MALDI-HRMS calcd for $C_{16}H_{14}NO_2$ $(M + H)^+$ 252.1028, found 252.1019.

5-Methoxy-2-phenylindole (8f): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (s, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 8.1 Hz, 2H), 7.34−7.29 (m, 2H), 7.09 (s, 1H), 6.85 (dq, J = 8.7, 1.2 Hz, 1H), 6.76 (s, 1H), 3.87 (s, 3H); MS *m*/*z* 223 (M^+).

5-Ethyl-2-phenylindole (8g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (s, 1H), 7.65 (d, J = 7.5 Hz, 2H), 7.46−7.44 (m, 3H), 7.31 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.8 Hz, 1H), 6.77 (s, 1H), 2.75 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ137.9, 136.3, 135.3, 132.6, 129.5, 128.9 (2C), 127.5, 125.1 (2C), 122.9, 119.0, 110.6, 99.7, 28.9, 16.4; MS *m*/*z* 221 (M^+); MALDI-HRMS calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1284, found 222.1277.

5-Nitro-2-phenylindole (8h): ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 11.39 (s, 1H), 8.57 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.54−7.49 (m, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.18 (s, 1H); MS *m*/*z* 238 (M^+).

2-Phenylindole-6-carboxylic acid methyl ester (8i): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.19 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.7 Hz, 1H), 7.51−7.46 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 6.87 (s, 1H), 3.96 (s, 3H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 167.3, 141.6, 136.7, 132.9, 132.0, 129.0 (2C), 128.2, 125.5 (2C), 123.5, 120.6, 119.8, 113.3, 99.4, 51.1; MS *m*/*z* 251 (M^+); MALDI-HRMS calcd for $C_{16}H_{14}NO_2$ $(M + H)^+$ 252.1026, found 252.1019.

***N*,*N*-Dimethyl(2-phenylindol-6-ylmethyl)amine (8j):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.44−7.39 (m, 2H), 7.31 (d, J = 7.5 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.79 (s, 1H), 3.55 (s, 2H), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 137.1, 132.5, 129.7, 128.9 (2C), 128.6, 127.6, 125.2 (2C), 121.9, 120.2, 111.7, 99.6, 44.9, 36.4 (2C); MS *m*/*z* 250 (M^+); MALDI-HRMS calcd for $C_{17}H_{19}N_2$ $(M + H)^+$ 251.1535, found 251.1543.

***N*-Benzyl-*N*-methyl(2-phenylindol-6-ylmethyl)amine (8k):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (s, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.41−7.23 (m, 9H), 7.12 (d, J = 8.7 Hz, 1H), 6.77 (s, 1H), 3.61 (s, 2H), 3.53 (s, 2H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.3, 137.9, 137.1, 133.5, 132.4, 129.0 (2C), 128.9 (2C), 128.4, 128.2 (2C), 127.5, 126.7, 125.1 (2C), 121.8, 120.2, 111.2, 99.8, 62.3, 61.7, 42.1; MS *m*/*z* 326 (M^+); MALDI-HRMS calcd for $C_{23}H_{23}N_2$ $(M + H)^+$ 327.1840, found 327.1856.

2-Phenylindole-5-carboxylic acid methyl ester (8*l*): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 8.40 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.49−7.36 (m, 4H), 6.91 (s, 1H), 3.95 (s, 3H); MS *m*/*z* 251 (M^+).

5,7-Dichloro-2-phenylindole (8m): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1H), 8.57 (s, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.51−7.48 (m, 3H), 7.39 (d, J = 7.5 Hz, 1H), 7.19 (s, 1H), 6.78 (s, 1H); MS *m*/*z* 262 (M^+).

4-Methoxy-2-phenylindole (8n): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.94 (s, 1H), 6.54 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 138.2, 136.4, 132.4, 129.0 (2C), 127.4, 124.9 (2C), 123.1, 104.3, 100.0, 97.2, 97.2, 55.4; ESI-MS *m*/*z* 224 $(M + H)^+$; ESI-HRMS calcd for $C_{15}H_{14}NO$ $(M + H)^+$ 224.1069, found 224.1070.

5-Methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (8o): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 7.5 Hz, 1H), 6.88 (s, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5, 143.9, 140.0, 132.0, 129.1 (2C), 128.1, 125.7, 125.1 (2C), 121.6, 105.9, 99.9, 53.4; MS *m*/*z* 224 (M^+); MALDI-HRMS calcd for $C_{14}H_{13}N_2O$ $(M + H)^+$ 225.1033, found 225.1022.

2-*n*-Pentylindole (12a): ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.81 (s, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.52(d, J = 7.2 Hz, 1H), 7.13−7.04 (m, 2H), 6.23 (s, 1H), 2.72 (t, J = 7.5 Hz, 2H), 1.73−1.68 (m, 2H), 1.39−1.34 (m, 4H), 0.92−0.88 (m, 3H); MS *m*/*z* 187 (M^+).

2-(Benzyloxymethyl)indole (12b): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.35−7.29 (m, 6H), 7.17−7.09 (m, 2H), 6.43 (s, 1H), 4.69 (s, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 136.4, 135.0, 128.5 (2C), 128.1, 127.9 (2C), 127.8, 122.0, 120.5, 119.8, 110.9, 101.9, 71.8, 65.1; MS *m*/*z* 237 (M^+); MALDI-HRMS calcd for $C_{16}H_{16}NO$ $(M + H)^+$ 238.1236, found 238.1226.

2-(Tetrahydropyran-2-yloxymethyl)indole (12c): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.20−7.06 (m, 2H), 6.44 (s, 1H), 4.89−4.70 (m, 3H), 3.98−3.92 (m, 1H), 3.60−3.56 (m, 1H), 1.88−1.72 (m, 2H), 1.62−1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5, 135.2, 128.2, 122.0, 120.6, 119.8, 110.9, 101.8, 98.4, 62.9, 62.8, 30.7, 25.4, 19.8; MS *m*/*z* 231 (M^+); MALDI-HRMS calcd for $C_{14}H_{17}NNaO_2$ $(M + Na)^+$ 254.1142, found 254.1152.

5-Methoxy-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)indole (12d): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.7, 2.4 Hz, 1H), 6.36 (s, 1H), 4.86−4.68 (m, 1H), 3.96−3.92 (m, 1H), 3.83 (s, 3H), 3.59−3.55 (m, 1H), 1.83−1.72 (m, 2H), 1.63−1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 135.9, 131.6, 128.6, 112.1, 111.5, 102.3, 101.5, 98.3, 62.8, 62.7, 55.8, 30.6, 25.3, 19.7; MS *m*/*z* 261 (M^+); MALDI-HRMS calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$ 262.1448, found 262.1438.

5-Ethyl-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)indole (12e): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 7.38 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.37 (s, 1H), 4.85−

4.67 (m, 3H), 3.94 (m, 1H), 3.85−3.56 (m, 1H), 2.72 (q, J = 7.5 Hz, 2H), 1.85−1.76 (m, 2H), 1.62−1.51 (m, 4H), 1.25 (q, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 135.2, 134.9, 128.4, 122.5, 118.9, 110.6, 101.5, 98.1, 62.8, 62.6, 30.6, 28.9, 25.3, 19.7, 16.4; MS m/z 259 (M^+); MALDI-HRMS calcd for $C_{16}H_{21}NNaO_2$ $(M + Na)^+$ 282.1476, found 282.1465.

5-Nitro-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)indole (12f): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1H), 8.52 (s, 1H), 8.08 (d, J = 9.3 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 6.57 (s, 1H), 4.91−4.80 (m, 2H), 4.73−4.70 (m, 1H), 4.03−3.97 (m, 1H), 3.65−3.58 (m, 1H), 1.89−1.81 (m, 2H), 1.65−1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 139.2, 139.0, 127.6, 117.7, 117.6, 110.8, 103.1, 99.9, 63.6, 63.1, 30.7, 25.2, 20.0; ESI MS m/z 277 $(M + H)^+$; ESI HRMS calcd for $C_{14}H_{17}N_2O_4$ $(M + H)^+$ 277.1186, found 277.1183.

6-Methoxycarboxylate-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)indole (12g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (s, 1H), 8.12 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 6.47 (s, 1H), 4.85−4.72 (m, 3H), 4.01 (m, 1H), 3.93 (s, 3H), 3.61−3.57 (m, 1H), 1.86−1.78 (m, 2H), 1.59−1.43 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 139.0, 135.6, 132.0, 123.6, 120.9, 120.1, 113.2 , 101.5, 99.3, 63.2, 63.1, 51.9, 30.7, 25.3, 19.8; MS m/z 289 (M^+); MALDI-HRMS calcd for $C_{16}H_{19}NO_4$ $(M + H)^+$ 290.1395, found 290.1387.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectrum of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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