Dehydrogenative Synthesis of C3-Azolylindoles via Copper-Promoted Annulative Direct Coupling of *o*-Alkynylanilines

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Abstract: A copper-promoted annulative direct coupling of *o*-alkynylaniline derivatives with 1,3,4-oxadiazoles for the synthesis of C3-azolylindoles has been developed. The copper-based system provides a new protocol for the dehydrogenative construction of indole–oxadiazole conjugations from nonhalogenated and non-metalated starting materials.

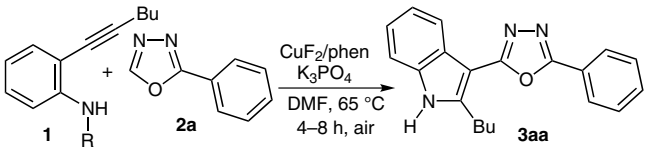
Key words: copper, dehydrogenative coupling, indoles, C–H functionalization, oxadiazoles

Since an indole–heteroarene conjugation frequently occurs in natural products, medicines, and biologically active compounds,[1] the construction of this biheteroaryl moiety has been one of long-standing central topics in synthetic chemistry. The palladium-catalyzed dual C–H functionalization that makes the indole–heteroarene linkage directly is the most useful of these synthetic methodologies. To date, the palladium-based dehydrogenative couplings of indoles with simple benzenes,[2] polyfluoroarenes,[3] pyridine *N*-oxides,[4] and 1,3-azoles[4b] have been reported.

Meanwhile, we have recently focused on the activity of copper salts and complexes in the C–H functionalization chemistry and succeeded in the copper-mediated direct C–C[5] and C–N[6] bond forming reactions of some heteroarenes.[7] In addition, as an alternative to the palladium-catalyzed direct biaryl couplings mentioned above, we have also developed a copper-promoted annulative direct coupling of *o*-alkynylphenols with 1,3-azoles for the dehydrogenative synthesis of C3-azolylbenzofurans.[8] In the course of this study, we envisaged that the annulative direct coupling protocol would be extended to the construction of C3-azolylindole skeletons, results of which are reported herein.

On the basis of our previous work,[8] the optimization studies commenced with *N*-mesyl-2-(hex-1-ynyl)aniline (**1a-Ms**)[9] and 2-phenyl-1,3,4-oxadiazole (**2a**) in a CuF_2/1,10-phenanthroline (phen)/K_3PO_4 system under ambient conditions. Pleasingly, after 15 hours in DMF, the desired 2,3-disubstituted NH indole **3aa** was formed, albeit in only 8% yield (Table 1, entry 1). Notable is that the Ms group on the indole nitrogen was spontaneously removable during the reaction course. Detectable major by-products were simply the cyclized NH and NMs indoles. Subsequent investigations revealed that the substituent on nitrogen was critical for the annulative coupling: the use of benzoyl-substituted **1a-Bz** increased the yield of **3aa** (entry 2), while the introduction of acetyl or pentafluorobenzoyl groups completely inhibited the formation of **3aa** (entries 3 and 4). The delicate acidity of the aniline NH would play a pivotal role in the oxidative coupling. Additional screening (entries 5–9)[10] identified a 2-fluorobenzoyl substituent to be optimal (entry 9). Moreover, the addition of MS 3Å was found to give a positive effect on the reaction efficiency (entry 7 vs 8). Finally, with a slightly higher loading of CuF_2 and **2a** relative to **1a-2F**, the target molecule **3aa** was isolated in 64% yield (entry 10). Other reaction systems using $CuCl_2$, $Cu(OTf)_2$, Cs_2CO_3, or toluene largely diminished the yield of **3aa** (data not shown).

Table 1 Optimization Studies for Copper-Promoted Annulative Direct Coupling of *o*-Alkynylanilines **1** with 2-Phenyl-1,3,4-oxadiazole (**2a**) for the Dehydrogenative Synthesis of **3aa**[a]



Entry	1	R	Yield (%)[b] of **3aa**
1[c]	**1a-Ms**	SO_2Me	(8)
2	**1a-Bz**	Bz	33
3	**1a-Ac**	Ac	0
4	**1a-F_5**	COC_6F_5	0
5	**1a-4CF_3**	CO(4-$CF_3C_6H_4$)	22
6	**1a-2CF_3**	CO(2-$CF_3C_6H_4$)	43
7	**1a-2Cl**	CO(2-ClC_6H_4)	40
8[d]	**1a-2Cl**		50
9[d]	**1a-2F**	CO(2-FC_6H_4)	58
10[d,e]	**1a-2F**		76 (64)
11[e]	**1a-2F**		56

[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), CuF_2 (0.60 mmol), phen (0.30 mmol), K_3PO_4 (0.90 mmol), DMF (2.0 mL).
[b] Estimated by ^1H NMR analysis. Yield of isolated product is given in parentheses.
[c] At r.t. for 15 h.
[d] With 200 mg of MS 3Å.
[e] With **1a-2F** (0.20 mmol), **2a** (0.60 mmol), CuF_2 (0.60 mmol), phen (0.60 mmol), and K_3PO_4 (0.90 mmol).

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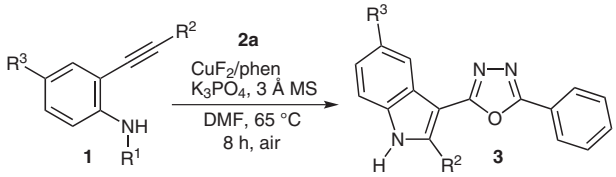
With the optimized conditions in hand, the annulative direct coupling of various *o*-alkynylanilines **1** with **2a** was performed (Table 2). In some cases, the addition of MS 3Å was not required for the successful conversion. At the alkyne terminus, aromatic substituents were also tolerated, and electron-neutral and -rich substrates gave the corresponding 2,3-diarylindoles **3ba**–**da** in good yields (entries 1–3). On the other hand, an electron-deficient function diminished the yield (entry 4).[11] A decrease of the yield was also observed in the case of sterically demanding naphthyl-substituted aniline (entry 5). However, to our delight, the change of the substituent on nitrogen into more electron-withdrawing 2-trifluoromethylbenzoyl group improved the reaction efficiency (entry 6). Interestingly, such a trend was more remarkable in the reaction of aniline that bears much bulkier *t*-Bu substituent: the Ms group acted as a promising activator, while the 2-fluorobenzoyl group completely shut down the reaction (entry 7 vs 8). The introduction of an electron-donating or -withdrawing group to the benzene ring also influenced the reaction outcome. The Me-substituted indole **3ha** was obtained in a satisfactory yield (entry 9), whereas the Cl substituent largely led to a reduced yield (entry 10).

Table 2 Copper-Promoted Annulative Direct Coupling of Various *o*-Alkynylanilines **1** with 2-Phenyl-1,3,4-oxadiazole (**2a**)[a]



Entry	**1**	R^1	R^2	R^3	Product **3**, yield (%)[b]
1	**1b-2F**	$CO(2\text{-}FC_6H_4)$	Ph	H	**3ba**, 92 (75)
2[c]	**1c-2F**	$CO(2\text{-}FC_6H_4)$	$4\text{-}MeC_6H_4$	H	**3ca**, 65 (63)
3	**1d-2F**	$CO(2\text{-}FC_6H_4)$	$4\text{-}MeOC_6H_4$	H	**3da**, 91 (76)
4	**1e-2F**	$CO(2\text{-}FC_6H_4)$	$4\text{-}CF_3C_6H_4$	H	**3ea**, 43 (37)
5[c]	**1f-2F**	$CO(2\text{-}FC_6H_4)$	1-naphthyl	H	**3fa**, 49
6[c]	**1f-2CF$_3$**	$CO(2\text{-}CF_3C_6H_4)$	1-naphthyl	H	**3fa**, 62 (58)
7	**1g-2F**	$CO(2\text{-}FC_6H_4)$	*t*-Bu	H	**3ga**, 0
8	**1g-Ms**	SO_2Me	*t*-Bu	H	**3ga**, 75 (70)
9	**1h-2F**	$CO(2\text{-}FC_6H_4)$	Ph	Me	**3ha**, 64 (60)
10	**1i-2F**	$CO(2\text{-}FC_6H_4)$	Ph	Cl	**3ia**, 18 (18)

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), CuF_2 (0.60 mmol), phen (0.60 mmol), K_3PO_4 (0.90 mmol), DMF (2.0 mL).
[b] Estimated by ^1H NMR analysis. Yield of isolated product is in parentheses.
[c] Without MS 3Å.

The scope of 1,3-azoles was next evaluated with **1b-2F** as an aniline coupling partner. Representative products are summarized in Figure 1. Electronically and sterically diverse 1,3,4-oxadiazoles coupled with **1b-2F** effectively to make the indole–azole conjugations with the synthetically useful level (**3bb**–**bf**). The oxadiazole that bears the alkyl side chain also could be employed (**3bg**). Attempts to apply other 1,3-azoles such as oxazole and thiazole still remain unsuccessful. On the other hand, while preliminary, triisopropylsilylacetylene was found to couple with **1b-Ms** by using $CuBr_2$ instead of CuF_2 under otherwise identical conditions to afford the corresponding C3-alkynylindole **4** (Scheme 1). Although a similar two-step transformation of *o*-alkynylanilines with a special hypervalent iodine reagent is known to be catalyzed by a gold catalyst,[12] this dehydrogenative alternative with the terminal alkyne and less expensive copper salt appears to be of synthetic utility.

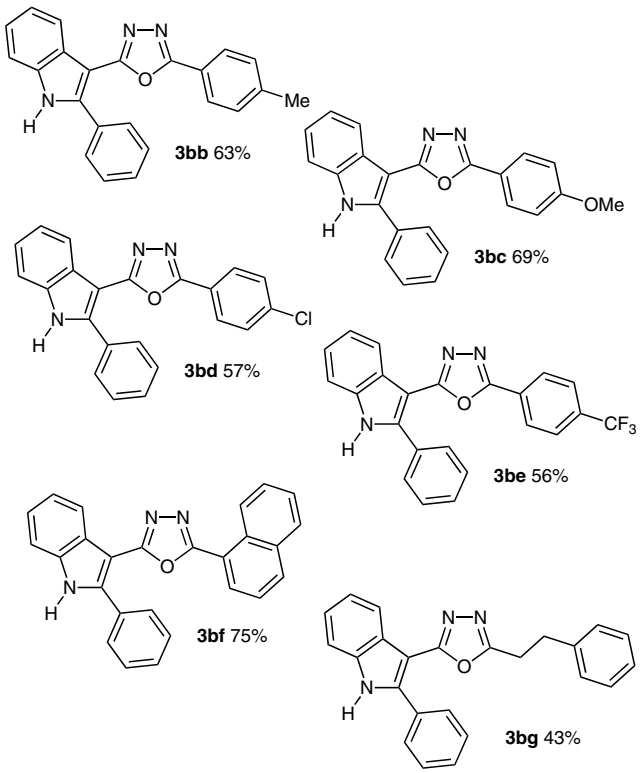
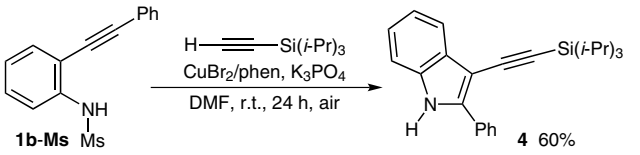
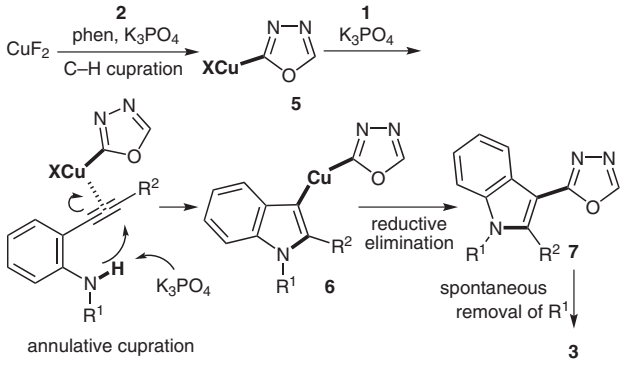


Figure 1 Copper-promoted annulative direct coupling of **1b-2F** with various 1,3,4-oxadiazole; yield of isolated product is shown

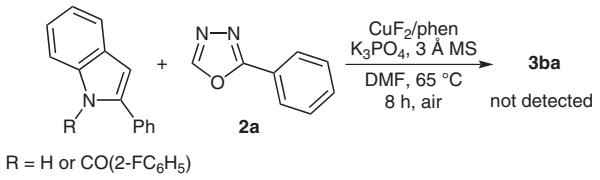


Scheme 1 Copper-promoted annulative direct coupling of **1b-Ms** with triisopropylsilylacetylene

Although the exact reaction mechanism is not clear at the present, we are tempted to assume the mechanism of the copper-mediated dehydrogenative coupling as illustrated in Scheme 2. A base-assisted direct cupration[5,6,7c,l–n] of the oxadiazole initially forms a heteroarylcopper intermediate **5**. Subsequent electrophilic activation of the alkynyl moiety in the aniline **1** via a coordination to the π-acidic copper center of **5** triggers an annulative cupration (aminocupration),[9] leading to a di(heteroaryl)copper **6**. Final reductive elimination[13] furnishes the corresponding N-protected indole **7**, the protection of which is spontaneously removed under standard basic conditions to deliver the observed NH form **3**.[14] The postulated pathway can account for the substituent effect of **1** dependent on the alkyne terminus (Table 1, entries 5 vs 6 and 7 vs 8). Namely, the increase of acidity of the NH might accelerate the backside attack of pendant nitrogen nucleophile to accelerate the generation of di(heteroaryl)copper species, unless it is difficult to obtain owing to steric factors associated with 1-naphthyl and *t*-Bu groups. An alternative mechanism involves 1) an initial annulation of **1** by CuF_2 of π-acidic nature and 2) a copper-mediated indole[15]/oxadiazole direct biaryl coupling. However, the possibility could be completely excluded by control experiments shown in Scheme 3.



Scheme 2 Tentative reaction mechanism



Scheme 3 Control experiments

In conclusion, we have developed a copper-promoted annulative direct coupling of *o*-alkynylanilines with 1,3,4-oxadiazoles for the dehydrogenative synthesis of C3-azolylindoles. The copper-based strategy can provide a unique and convergent approach to the indole–azole conjugation from relatively simple, nonhalogenated and nonmetalated starting materials. Further studies to expand the scope of azoles and make the reaction catalytic in copper by elucidation of the mechanism and appropriate terminal co-oxidants are in progress.

All reactions were carried out under atmospheric conditions in dried glassware. All starting materials were purchased from commercially suppliers and used without further purification, unless otherwise noted. DMF was distilled from CaH_2 and stored strictly under nitrogen on MS 4Å. *o*-Alkynylanilines **1** were readily accessible in two steps: the Sonogashira coupling of the corresponding iodoanilines with terminal alkynes and mesylation or benzoylation with appropriate sulfonyl or benzoyl chlorides.[9c] 1,3,4-Oxadiazoles **2** were prepared according to the literature.[16] MS 3Å was activated at 100 °C under high vacuum for 1 h prior to use. Silica gel column chromatography was performed using Wakogel 200 mesh from Wako Pure Chemical Co. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 600 MHz and 100 or 150 MHz, respectively, for $CDCl_3$ or DMSO-d_6 solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm × 1.5 m) or a CBP-1 capillary column (i. d. 0.5 mm × 25 m). Gel permeation chromatography (GPC) was performed by LC-6AD (Shimadzu, two in-line Shodex, $CHCl_3$, 3.5 mL/min, UV detector).

C3-Azolylindoles; 2-(2-Butyl-1*H*-indol-3-yl)-5-phenyl-1,3,4-oxadiazole (3aa); Typical Procedure

CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), and MS 3Å (200 mg) were placed in a 20 mL two-necked reaction flask, with a drying tube lined with $CaCl_2$. DMF (1.0 mL) was then added to the flask, and the suspension was stirred for 10 min at r.t. Finally, a solution of 2-fluoro-*N*-2-[(hex-1-ynyl)phenyl]benzamide (**1a-2F**; 59 mg, 0.20 mmol) and 2-phenyl-1,3,4-oxadiazole (**2a**; 88 mg, 0.60 mmol) in DMF (1.0 mL) was added dropwise. The solution was stirred at 65 °C for additional 8 h. The resulting mixture was then quenched with H_2O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). Concentration in vacuo and subsequent column chromatography with hexane–EtOAc (2:1, v/v) followed by GPC gave **3aa** as a pale yellow powder; yield: 41 mg (0.13 mmol, 64%); mp 171–173 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 1.39–1.48 (m, 2 H), 1.77–1.84 (m, 2 H), 3.30 (t, *J* = 7.8 Hz, 2 H), 7.22–7.31 (m, 2 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.52–7.57 (m, 3 H), 8.13–8.17 (m, 2 H), 8.27 (d, *J* = 7.8 Hz, 1 H), 9.30 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.6, 27.7, 31.3, 97.5, 111.1, 120.3, 121.6, 122.6, 124.3, 126.0, 126.6, 129.1, 131.2, 135.2, 144.3, 162.6, 163.1.

HRMS: *m*/*z* (M^+) calcd for $C_{20}H_{19}N_3O$: 317.1528; found: 317.1529.

2-Phenyl-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3ba)

Following the typical procedure for **3aa**, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), MS 3Å (200 mg), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ba** as a white powder; yield: 51 mg (0.15 mmol, 75%); mp 208–210 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.38 (m, 2 H), 7.42–7.53 (m, 7 H), 7.74–7.78 (m, 2 H), 7.86–7.89 (m, 2 H), 8.44–8.46 (m, 1 H), 8.79 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.3, 111.2, 121.8, 122.2, 123.8, 124.2, 126.58, 126.61, 128.5, 128.9, 129.4, 129.5, 131.2, 131.5, 135.7, 140.3, 162.1, 162.8.

HRMS: *m*/*z* (M^+) calcd for $C_{22}H_{15}N_3O$: 337.1215; found: 337.1213.

2-[2-(4-Methylphenyl)-1*H*-indol-3-yl]-5-phenyl-1,3,4-oxadiazole (3ca)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(4-methylphenyl)phenyl]benzamide

(**1c-2F**; 66 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ca** as a pale pink powder; yield: 44 mg (0.13 mmol, 63%); mp 190–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.27–7.34 (m, 2 H), 7.40–7.49 (m, 4 H), 7.60 (d, *J* = 8.2 Hz, 2 H), 7.87 (d, *J* = 8.2 Hz, 2 H), 8.38 (d, *J* = 7.6 Hz, 1 H), 9.22 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 97.6, 111.4, 121.4, 122.0, 123.5, 124.2, 126.6, 126.7, 128.5, 128.9, 129.1, 129.2, 131.1, 135.8, 139.5, 140.9, 162.4, 162.8.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{17}N_3O$: 351.1372; found: 351.1367.

2-[2-(4-Methoxyphenyl)-1*H*-indol-3-yl]-5-phenyl-1,3,4-oxadiazole (3da)

Following the typical procedure for **3aa**, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), MS 3Å (200 mg), 2-fluoro-*N*-{2-[(4-methoxyphenyl)ethynyl]phenyl}benzamide (**1d-2F**; 69 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3da** as a pale yellow powder; yield: 56 mg (0.15 mmol, 76%); mp 172–174 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 7.26–7.37 (m, 2 H), 7.46–7.50 (m, 4 H), 7.72 (d, *J* = 7.9 Hz, 2 H), 7.94 (d, *J* = 7.9 Hz, 2 H), 7.42 (d, *J* = 7.0 Hz, 1 H), 8.59 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.5, 97.8, 111.0, 114.0, 121.6, 122.1, 123.6, 123.7, 124.3, 126.6, 126.8, 128.9, 130.7, 131.1, 135.6, 140.4, 160.6, 162.2, 162.8.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{17}N_3O_2$: 367.1321; found: 367.1324.

2-Phenyl-5-{2-[4-(trifluoromethyl)phenyl]-1*H*-indol-3-yl}-1,3,4-oxadiazole (3ea)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-{2-[(4-(trifluoromethyl)phenyl)ethynyl]pheny}benzamide (**1e-2F**; 77 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ea** as a pale yellow powder; yield: 30 mg (0.074 mmol, 37%); mp 227–229 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29–7.36 (m, 2 H), 7.51–7.60 (m, 4 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 8.07 (d, *J* = 8.2 Hz, 2 H), 8.25 (d, *J* = 6.8 Hz, 1 H), 12.5 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 97.3, 112.2, 120.8, 121.8, 123.6, 123.7, 124.2 (q, *J* = 271 Hz), 125.1 (q, *J* = 4.0 Hz), 125.8, 126.1, 129.336, 129.340 (q, *J* = 32 Hz), 130.6, 131.6, 135.4, 136.3, 138.9, 161.6, 162.0.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{14}F_3N_3O$: 405.1089; found: 405.1083.

2-[2-(1-Naphthyl)-1*H*-indol-3-yl]-5-phenyl-1,3,4-oxadiazole (3fa)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), *N*-[2-(naphthylethynyl)phenyl]-2-(trifluoromethyl)benzamide (**1f-2CF$_3$**; 83 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3fa** as a pale yellow oil; yield: 45 mg (0.12 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.18 (m, 4 H), 7.28–7.40 (m, 4 H), 7.46 (t, *J* = 7.8 Hz, 1 H), 7.51–7.55 (m, 2 H), 7.66 (d, *J* = 6.4 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.99 (d, *J* = 8.2 Hz, 1 H), 8.52–8.55 (m, 1 H), 9.29 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.7, 111.4, 121.7, 122.2, 123.75, 123.79, 125.0, 125.6, 125.8, 126.2, 126.3, 127.0, 128.2, 128.5, 128.6, 129.5, 129.9, 130.8, 132.3, 133.4, 135.9, 138.5, 161.8, 162.4.

HRMS: *m*/*z* (M^+) calcd for $C_{26}H_{17}N_3O$: 387.1372; found: 387.1375.

2-[2-(*tert*-Butyl)-1*H*-indol-3-yl]-5-phenyl-1,3,4-oxadiazole (3ga)

Following the typical procedure for **3aa**, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), MS 3Å (200 mg), *N*-[2-(3,3-dimethylbut-1-ynyl)phenyl]methanesulfonamide (**1g-Ms**; 50 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ga** as a pale yellow oil; yield: 45 mg (0.14 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 7.24–7.30 (m, 2 H), 7.43 (d, *J* = 7.3 Hz, 1 H), 7.54–7.55 (m, 3 H), 8.16–8.20 (m, 3 H), 8.70 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 33.6, 96.3, 111.0, 120.5, 121.8, 122.7, 124.4, 126.6, 127.8, 129.1, 131.3, 133.4, 150.2, 162.7, 163.2.

HRMS: *m*/*z* (M^+) calcd for $C_{20}H_{19}N_3O$: 317.1528; found: 317.1525.

2-(5-Methyl-2-phenyl-1*H*-indol-3-yl)-5-phenyl-1,3,4-oxadiazole (3ha)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[4-methyl-2-(phenylethynyl)phenyl]benzamide (**1h-2F**; 66 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ha** as a white powder; yield: 42 mg (0.12 mmol, 60%); mp >250 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H), 7.18 (d, *J* = 8.7 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.42–7.50 (m, 3 H), 7.53–7.54 (m, 3 H), 7.73–7.75 (m, 2 H), 7.85–7.87 (m, 2 H), 8.27 (s, 1 H), 8.53 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 98.0, 110.7, 121.5, 124.3, 125.5, 126.6, 126.9, 128.5, 128.9, 129.3, 129.4, 131.1, 131.7, 131.8, 134.0, 140.2, 162.1, 162.7.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{17}N_3O$: 351.1372; found: 351.1372.

2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-5-phenyl-1,3,4-oxadiazole (3ia)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), *N*-[4-chloro-2-(phenylethynyl)phenyl]-2-fluorobenzamide (**1i-2F**; 70 mg, 0.20 mmol), and **2a** (88 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3ia** as a pale yellow powder; yield: 13 mg (0.035 mmol, 18%); mp >250 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38 (dd, *J* = 1.8, 8.5 Hz, 1 H), 7.61–7.68 (m, 7 H), 7.82–7.85 (m, 2 H), 7.89–7.92 (m, 2 H), 8.30 (d, *J* = 1.8 Hz, 1 H), 12.6 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.1, 113.7, 119.9, 123.3, 123.6, 126.05, 126.09, 127.1, 128.4, 129.4, 129.70, 129.73, 130.8, 131.6, 134.7, 142.3, 161.4, 162.0.

HRMS: *m*/*z* (M^+) calcd for $C_{22}H_{14}ClN_3O$: 371.0825; found: 371.0822.

2-(4-Methylphenyl)-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3bb)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-(4-methylphenyl)-1,3,4-oxadiazole (**2b**; 96 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give gave **3bb** as a white powder; yield: 44 mg (0.13 mmol, 63%); mp 219–221 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 7.31–7.36 (m, 2 H), 7.47–7.50 (m, 4 H), 7.73–7.75 (m, 4 H), 8.41–8.44 (m, 1 H), 8.99 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 98.3, 111.2, 121.4, 121.7, 122.1, 123.7, 126.5, 126.6, 128.5 (overlapped), 129.4, 129.6, 131.6, 135.8, 140.3, 141.6, 161.9, 163.0.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{17}N_3O$: 351.1372; found: 367.1366.

2-(4-Methoxyphenyl)-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3bc)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-(4-methoxyphenyl)-1,3,4-oxadiazole (**2c**; 106 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3bc** as a pale yellow powder; yield: 51 mg (0.14 mmol, 69%); mp 206–208 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 7.32–7.36 (m, 2 H), 7.47–7.51 (m, 4 H), 7.74–7.81 (m, 4 H), 8.42–8.44 (m, 1 H), 8.86 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 98.4, 111.2, 114.4, 116.8, 121.8, 122.1, 123.8, 126.6, 128.3, 128.5, 129.37, 129.40, 131.6, 135.7, 140.1, 161.6, 161.9, 162.8.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{17}N_3O_2$: 367.1321; found: 367.1319.

2-(4-Chlorophenyl)-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3bd)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-(4-chlorophenyl)-1,3,4-oxadiazole (**2d**; 108 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3bd** as a white powder; yield: 42 mg (0.11 mmol, 57%); mp 223–225 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.38 (m, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.47–7.54 (m, 4 H), 7.73–7.79 (m, 4 H), 8.42–8.44 (m, 1 H), 8.76 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.2, 121.7, 122.3, 122.7, 123.9, 126.5, 127.8, 128.6, 129.3, 129.4 (overlapped), 129.6, 131.5, 135.7, 137.3, 140.5, 162.0, 162.2.

HRMS: *m*/*z* (M^+) calcd for $C_{22}H_{14}ClN_3O$: 371.0825; found: 371.0826.

2-(2-Phenyl-1*H*-indol-3-yl)-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazole (3be)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazole (**2e**; 108 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3be** as a pale yellow powder; yield: 45 mg (0.11 mmol, 56%); mp 237–239 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.32 (m, 2 H), 7.50–7.62 (m, 4 H), 7.83–7.86 (m, 2 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.99 (d, *J* = 8.2 Hz, 2 H), 8.22–8.30 (m, 1 H), 12.3 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 90.3, 106.1, 114.7, 115.6, 117.2, 117.8 (q, *J* = 272 Hz), 120.0, 120.4 (q, *J* = 3.0 Hz), 120.8, 121.4, 122.3, 123.4, 123.7, 125.0 (q, *J* = 32 Hz), 125.1, 130.2, 135.3, 154.9, 156.5.

HRMS: *m*/*z* (M^+) calcd for $C_{23}H_{14}F_3N_3O$: 405.1089; found: 405.1084.

2-(1-Naphthyl)-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3bf)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-(naphthyl)-1,3,4-oxadiazole (**2f**; 118 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3bf** as a pale yellow oil; yield: 58 mg (0.15 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.36 (m, 2 H), 7.43–7.48 (m, 5 H), 7.52–7.59 (m, 2 H), 7.71–7.75 (m, 2 H), 7.87 (t, *J* = 7.3 Hz, 2 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 8.46 (d, *J* = 7.8 Hz, 1 H), 9.03 (br s, 1 H), 9.21 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.0, 111.3, 120.6, 122.1, 123.7, 124.8, 126.4, 126.5, 126.6, 127.90, 127.92, 128.5 (overlapped), 129.37 (overlapped), 129.39, 129.9, 131.5, 132.0, 133.8, 135.8, 140.6, 161.7, 163.0.

HRMS: *m*/*z* (M^+) calcd for $C_{26}H_{17}N_3O$: 387.1372; found: 387.1369.

2-Phenethyl-5-(2-phenyl-1*H*-indol-3-yl)-1,3,4-oxadiazole (3bg)

Following the typical procedure for **3aa**, but excluding the addition of MS 3Å, the reaction was performed with CuF_2 (61 mg, 0.60 mmol), 1,10-phenanthroline (109 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), 2-fluoro-*N*-[2-(phenylethynyl)phenyl]benzamide (**1b-2F**; 63 mg, 0.20 mmol), and 2-phenethyl-1,3,4-oxadiazole (**2g**; 105 mg, 0.60 mmol) in DMF (2.0 mL) at 65 °C for 8 h. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 2:1, v/v) followed by GPC to give **3bg** as a pale yellow powder; yield: 31 mg (0.085 mmol, 43%); mp 185–187 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.03 (t, *J* = 7.3 Hz, 2 H), 3.12 (t, *J* = 7.3 Hz, 2 H), 7.17 (d, *J* = 7.6 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 7.27–7.34 (m, 4 H), 7.44–7.49 (m, 4 H), 7.65–7.67 (m, 2 H), 8.25 (d, *J* = 7.6 Hz, 1 H), 8.68 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.1, 32.7, 98.2, 111.1, 121.6, 122.0, 123.7, 126.6, 126.7, 128.2, 128.5, 128.6, 129.2, 129.4, 131.4, 135.6, 139.7, 139.9, 162.2, 164.3.

HRMS: *m*/*z* (M^+) calcd for $C_{24}H_{19}N_3O$: 365.1528; found: 365.1529.

C3-Alkynylindoles: 2-Phenyl-3-[(triisopropylsilyl)ethynyl]-1*H*-indole (4); Typical Procedure

$CuBr_2$ (66 mg, 0.30 mmol), 1,10-phenanthroline (108 mg, 0.60 mmol), K_3PO_4 (191 mg, 0.90 mmol), *N*-mesyl-2-(phenylethynyl)aniline (**1b-Ms**; 81 mg, 0.30 mmol) and dibenzyl (ca. 50 mg, internal standard) were placed in a 20 mL two-necked reaction flask. A solution of triisopropylsilylacetylene (109 mg, 0.60 mmol) in DMF (1.0 mL) was added, and the mixture was stirred for 24 h under air. The resulting mixture was then poured into H_2O (10 mL) and extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). Concentration in vacuo followed by silica gel column purification with hexane–EtOAc (90:10, v/v) gave **4** as a yellow oil; yield: 67 mg (0.18 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 21 H), 7.14–7.28 (m, 2 H), 7.28–7.38 (m, 2 H), 7.32–7.45 (t, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.74–7.80 (m, 2 H), 8.27 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 18.8, 95.1, 96.5, 101.3, 111.0, 120.1, 120.9, 123.5, 126.4, 128.3, 128.7, 130.8, 131.4, 135.1, 139.7.

HRMS: *m*/*z* (M^+) calcd for $C_{25}H_{31}NSi$: 373.2226; found: 373.2224.

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