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Regioselectivity of Larock Heteroannulation: A Contribution from Electronic Properties of Diarylacetylenes

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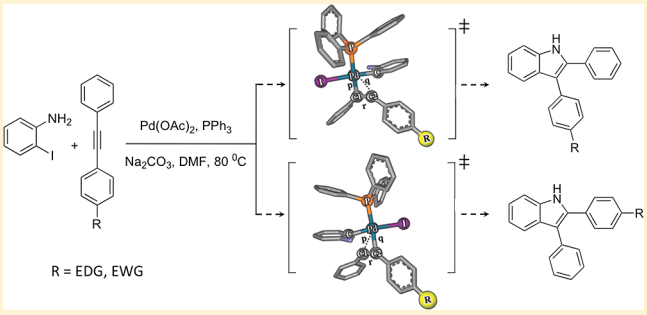
Supporting Information

ABSTRACT: A series of 2,3-diarylindoles were synthesized from 2-iodoaniline and unsymmetrical diarylacetylenes using the Larock heteroannulation. Diarylacetylenes bearing electron-withdrawing substituents lead to 2,3-diarylindoles with substituted phenyl moieties at the 2-position as major products, while those with electron-donating groups preferably yield indole products with substituted phenyl moieties at the 3-position. The regioisomeric product ratios exhibit a clear correlation with Hammett σ_p values. DFT calculations reveal the origin of this effect, displaying smaller activation energy barriers for those pathways leading to the major regioisomer.



INTRODUCTION

Since its first report in 1991, the Larock heteroannulation has been recognized as a convenient and effective method for the construction of 2,3-disubstituted indoles.[1] The first reaction condition reported by Larock employs palladium acetate with a triphenylphosphine ligand as a catalyst in the presence of inorganic base and *n*-Bu_4NCl or LiCl as an additive. This method allows the coupling of 2-iodoaniline and disubstituted alkynes yielding 2,3-disubstituted indoles in a facile manner. It was later discovered that a less reactive 2-bromo- or 2-chloroaniline could also be used.[2,3] Recently, the scope of this reaction has been expanded to induce macrocyclization.[4,5] The reaction has also been demonstrated to be regioselective when a more sterically hindered group is present at the 2-position of the resulting indoles.[6] The nature of the ligand attached to the palladium catalyst[7,8] and the possible coordination of additional heteroatoms on the substituted alkyne to the palladium atom[6,7,9,10] also play important roles in regioselectivity. In various synthetic applications utilizing the Larock protocol, regioselectivity can be secured using silylated alkynes where the silyl substituents preferentially remain on the 2-position of the indole products. The silyl groups can be conveniently functionalized in subsequent synthetic steps.[11−14]

A reverse regioselectivity was observed during the preparation of α-*C*-glycosylamino acids by Nishikawa and co-workers in 2002.[15] They investigated various functionalized alkynes as reactants but were unable to show clear regioselectivity.[16] Despite the fact that the steric demands associated with the alkyne ligands play a crucial role in regioselectivity, additional unknown factors also appear to operate, leading to confounding results.[3,7,8,10,15] Therefore, we sought to investigate the influence electronic effects have on the regioselectivity of the Larock heteroannulation reaction. Although the electronic properties of 2-iodoaniline have been shown to affect the regioselectivity and the rate of this reaction,[17,18] the impact of the electronic properties of the alkyne reaction partner have not been established. In our study, a model system is employed that differs only in the electronic character of the alkyne. The model used here is expected to show negligible steric differences between reacting ligands, being a function of the different substituents at the 4-position of one aryl moiety of the alkyne.

The proposed catalytic cycle for our model system is illustrated in Scheme 1. The regioselectivity of the reaction arises from the carbopalladation step, where migration of the Pd(II) catalyst to different sp-carbon atoms leads to regioisomeric products. Through the analyses of regioisomeric product ratio and density functional theory (DFT) calculations, we demonstrate herein that the electronic effect is operative and significantly influences regioisomerism of the Larock heteroannulation reaction.

RESULTS AND DISCUSSION

We started our investigation by synthesizing a series of diarylacetylenes bearing electron-withdrawing or -donating groups via Sonogashira coupling between phenylacetylene

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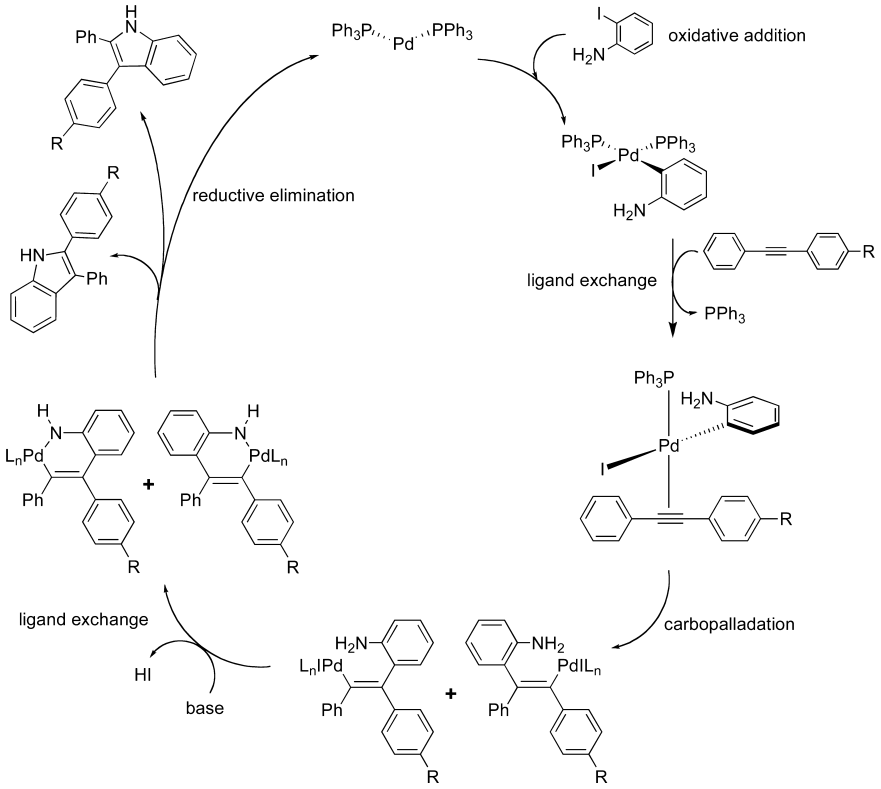
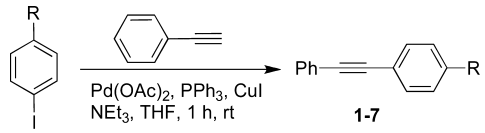
Scheme 1. Proposed Catalytic Cycle for Larock Heteroannulation



and 4-substituted iodobenzenes.[19,20] The coupling reactions proceeded smoothly, providing diarylacetylenes in good to excellent yield (Table 1).

Table 1. Sonogashira Coupling between Phenylacetylene and 4-Substituted Aryl Iodides



entry	R	diarylacetylene	yield[a] (%)
1	OH	1	98
2	NH_2	2	91
3	CN	3	75
4	Br	4	70
5	NO_2	5	58
6	NHAc	6	98[b]
7	CO_2Me	7	81[c]

[a]Yields for chromatographically pure compound. [b]Yield from acetylation of **2**. [c]Yield from hydrolysis and esterification of **3**.

With diarylacetylenes in hand, we proceeded with the Larock heteroannulation. The reactions were conducted at 80 °C for 24 h using 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, Na_2CO_3, and *n*-Bu_4NCl. As expected, both regioisomers were formed (Table 2, entries 1−7).

The 2,3-disubstituted indole products were characterized spectroscopically and compared with known compounds, while regioisomeric pairs of new compounds, those with amino (**9a**) and *N*-acetylamino substituents (**9c**), were unequivocally characterized by X-ray diffraction (Figure 1).

Regioselectivity was assessed on the basis of regioisomeric product ratios obtained from the analysis of the NMR spectra of the crude reactions and the isolated yields (Table 2). It was found that the regioisomeric product ratios determined by NMR correlate well with the values calculated from the isolated yields, indicating that the chromatographic step does not significantly alter the regioisomeric product ratio.

All reactions were conducted in triplicate in order to verify the statistical significance of observed regioisomeric product ratios. A plot between the 4-position substituent and the average regioisomeric product ratio clearly demonstrates that the observed regioselectivity is statistically significant (Figure 2). It is worth noting that comparable regioselectivity was not observed in a similar system where 4-acetamido-3-iodopyridine was reacted with unsymmetrical diarylacetylenes.[21,22]

The reaction of diarylacetylenes containing electron-donating groups preferentially led to the indole product with the 4-substituted phenyl group located at the 3-position (Table 2, compound **9**, entries 1−3). In contrast, electron-withdrawing substituents preferably yielded indole products with 4-substituted phenyl groups at the 2-position (Table 2, isomer **8**, entries 4−7). The regioisomeric product ratios were compared to the σ_p values compiled by Hansch and co-workers.[23] It is apparent that the introduction of electron-donating groups ($\sigma_p < 0$) results in a significant increase in the formation of isomer **9**. On the other hand, isomer **8** is predominantly formed when electron-withdrawing groups ($\sigma_p > 0$) are introduced. In addition, the log of the regioisomeric product ratio exhibits a quantitative correlation with σ_p values (Figure 3).

To better understand our experimental results, quantum calculations for the carbopalladation step were performed using the hybrid density functional B3LYP method. Two extreme

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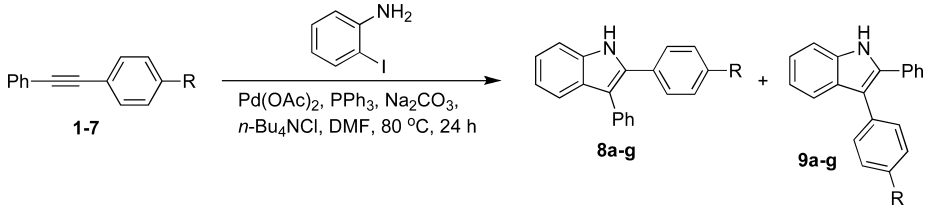
Table 2. Regioisomeric Product Ratios and σ_p Values of Larock Heteroannulation between 2-Iodoaniline and Substituted Diarylacetylenes



entry	compound	R	σ_p	8:9[a]	log(8:9)[a]	8:9[b]
1	**a**	NH_2	−0.66	0.55	−0.26	0.55
2	**b**	OH	−0.37	0.75	−0.12	0.74
3	**c**	NHAc	0.00	0.92	−0.04	0.92
4	**d**	Br	0.23	1.39	0.14	1.33
5	**e**	CO_2Me	0.45	1.94	0.27	1.89
6	**f**	CN	0.66	1.60	0.20	1.67
7	**g**	NO_2	0.78	2.33	0.37	2.62

[a]Regioisomeric product ratio determined by ^{1}H NMR of crude reaction mixture. [b]Regioisomeric product ratio determined from isolated yield.

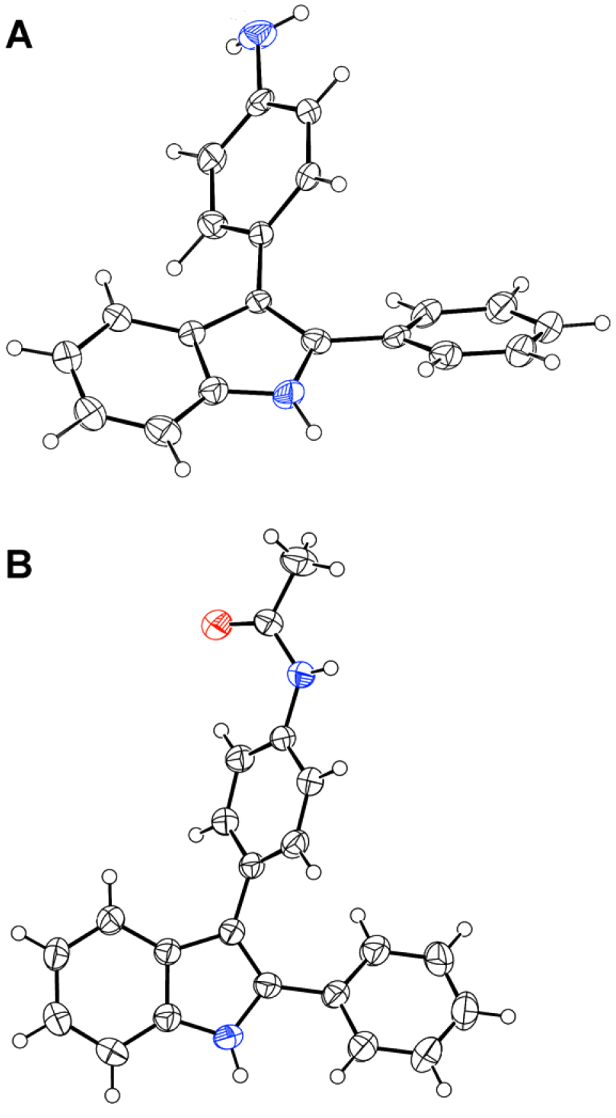


Figure 1. ORTEP representation of compounds **9a** and **9c**.

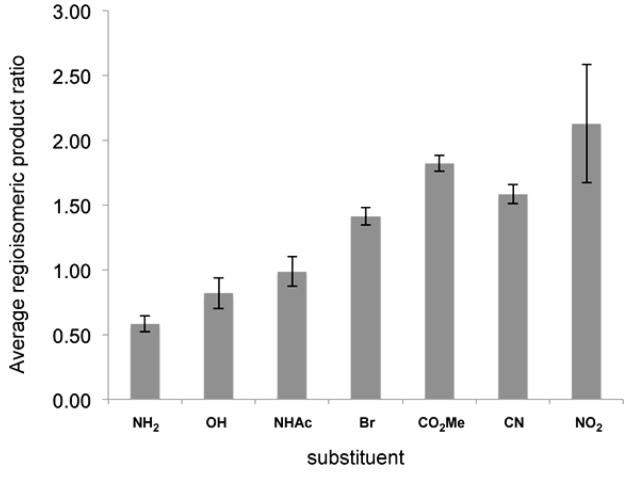


Figure 2. Correlation between substituent and average regioisomeric product ratio determined from isolated yield.

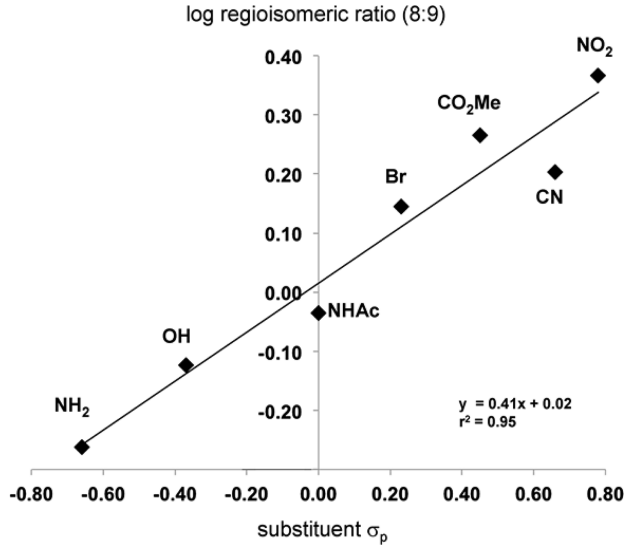


Figure 3. Relationship between the substituent σ_p constant and the log of the regioisomeric product ratio determined by ^{1}H NMR.

cases were chosen for analysis, namely those with the strong electron-donating ($-NH_2$) and -withdrawing ($-NO_2$) groups.

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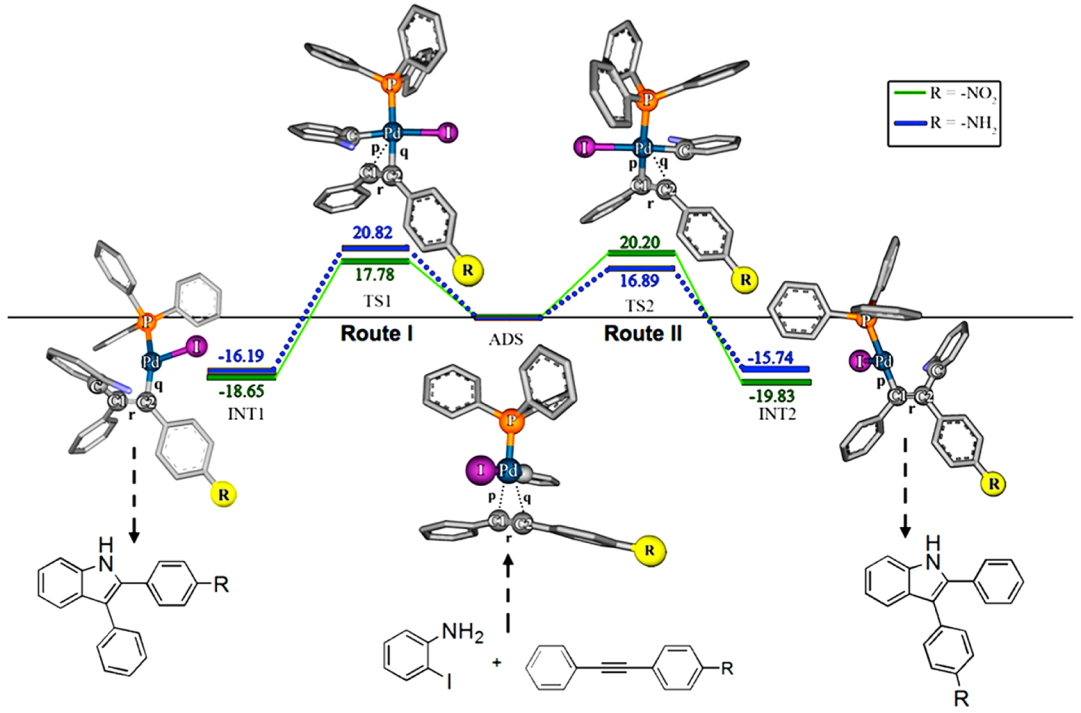
Table 3. Bond Distances of Calculated Species and the Energy Profile of the Carbopalladation Step[a]



substituent	distance	ADS (Å)	route I		route II	
			TS1 (Å)	INT1 (Å)	TS2 (Å)	INT2 (Å)
R = NO_2	*p*	**2.500**	**2.441**	2.833	2.170	2.011
	q	**2.452**	**2.122**	2.025	2.357	2.842
	r	1.230	1.281	1.351	1.271	1.352
R = NH_2	*p*	**2.310**	2.411	2.379	**2.088**	2.013
	q	**2.550**	2.121	1.975	**2.758**	2.824
	r	1.240	1.281	1.397	1.289	1.352

[a]ADS = adsorption complex, TS1 = transition state of route I, TS2 = transition state of route II, INT1 = intermediate of route I, INT2 = intermediate of route II. Bold numbers represent values discussed in text.

The energy profiles associated with the carbopalladation process as well as the key bond distances of optimized structures along the pathway are shown in Table 3.

Two different carbopalladation pathways, routes I and II, leading to different regioisomeric products were examined. For the amino substituent, the energy barrier leading to the indole product with a 4-aminophenyl group at the 3-position (Table 3, route II, compound **9a**) is lower than the barrier leading to the regioisomer with the 4-aminophenyl group at the 2-position (Table 3, route I, compound **8a**) by 3.93 kcal/mol. On the other hand, the energy barrier for the formation of the indole product with the 4-nitrophenyl group at the 2-position (Table 3, route I, compound **8g**) is lower than that leading to the product with the 4-nitrophenyl group at the 3-position (Table 3, route II, compound **9g**) by 2.42 kcal/mol.

The calculated results are in full agreement with the observed regioisomeric product ratios from our experimental studies; the experimentally preferred regioisomeric products are all formed via the lower energy barrier pathways. For instance, with the electron-releasing amino substituent, the lower energy pathway leads to compound **9a**, which is the major regioisomer obtained from heteroannulation reaction. In addition, the relatively small differences in energy between the route I and II barriers are consistent with the fact that both regioisomers are indeed experimentally observed (i.e., product ratios for **8a**/**9a** and **8g**/**9g** in Table 2).

The carbopalladation step is found to be exothermic from our computational results. Thus, an early transition state is expected according to Hammond's postulate.[24] Indeed, the geometry of the initial adsorption complex between Pd(II) catalyst and 4-substituted diphenylacetylenes more closely resembles the geometry of the transition-state structure (Table 3). The distance between the Pd and the C1 atom in the adsorption complex with the amino group is significantly shorter than that between the Pd and the C2 atom. In contrast, we observe a shorter distance between the Pd and the C2 atom compared to the Pd and C1 in the complex with the nitro group (see *p* and *q* values in Table 3). These differences are even more pronounced in the corresponding transition-state structures. It is also apparent that, in the lower energy barrier pathway, Pd(II) preferentially locates close to C1 when R is an amino group and C2 when R is a nitro group. Mulliken population analysis was therefore performed on compounds **2** and **5** in order to assess the partial charges found on C1 and C2. In compound **2**, the electron-donating amino group can directly influence the electron density of the C1−C2 triple bond and results in a more negative Mulliken charge on C1 (Scheme 2).

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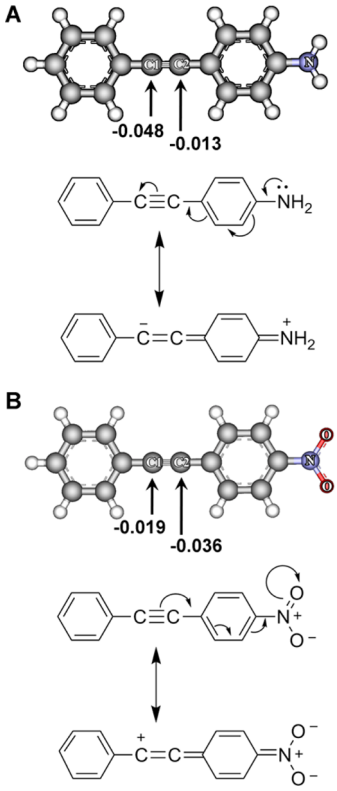
Scheme 2. Partial Charges on Compounds 2 (A) and 5 (B)



The electron-withdrawing nitro group of compound **5** leads to C2 becoming more negatively charged. These analyses clearly show that the preferred reaction pathway sees the electrophilic Pd(II) species migrate to the more electronegative sp-hybridized carbon atom. Indeed, the DFT predicted unequal electron distribution around the triple bond can be qualitatively rationalized from the resonance structures of the two compounds (Scheme 2).

CONCLUSION

In summary, we have reported on the electronic influence of disubstituted alkynes toward the regioselectivity of the Larock heteroannulation reaction. By keeping the steric effect essentially constant, we show that the Pd catalyst preferentially migrates to the sp-hybridized carbon atom possessing the greater electron density, resulting in the formation of an indole product with greater electron density carbon at 2-position as a major regioisomer. Although the electronic effect observed herein might not be considered extreme, it confirms that an electronic effect is operative, and can influence the regioselectivity outcome in the Larock heteroannulation reaction.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as a solvent. The peak due to residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) or $(CH_3)_2SO$ (2.50 ppm for ^{1}H and 39.43 ppm for ^{13}C) was used as an internal reference. TMS was added and used as internal reference when the solvent residual peak was obscured by signals from samples. Chemical shifts are quoted in parts per million, and coupling constants (J) are given in hertz (Hz). Mass spectral data were recorded on an APCI-ion trap spectrometer. High-resolution mass spectra were acquired using an ESI-TOF spectrometer. Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. The plates were visualized under a 254 nm UV lamp and subsequently sprayed with basic solution of potassium permanganate or with vanillin solution followed by heating. Column chromatography was performed on silica gel 60 (70−230 mesh).

General Procedure for the Sonogashira Coupling (Compounds 1−5). To a three-necked round-bottom flask equipped with a stirring bar were added 0.5 mol % of $Pd(OAc)_2$ (11.22 mg, 0.05 mmol), 2 mol % of PPh_3 (52.44 mg, 0.2 mmol), 0.5 mol % of CuI (9.52 mg, 0.05 mmol), and 4-substituted aryl iodide (10 mmol). After evacuation and flushing with N_2, phenylacetylene (1.3 mL, 12 mmol), THF (10 mL), and NEt_3 (6.9 mL, 50 mmol) were introduced subsequently. The reaction mixture was stirred at room temperature for 1 h. When the starting aryl iodide was completely consumed, the reaction mixture was diluted with ether and washed with saturated aqueous NH_4Cl and H_2O. The organic layer was dried over anhydrous Na_2SO_4. The reaction mixture was filtered and concentrated, and the product was purified by flash column chromatography using 20% ethyl acetate/hexane.

*4-(Phenylethynyl)phenol (**1**).*[25] White solid (1.91 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.52 (m, 2H), 7.43 (d, J = 2.2 Hz, 2H), 7.32−7.34 (m, 3H), 6.81 (d, J = 2.2 Hz, 2H), 5.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 133.2, 131.4, 128.7, 128.3, 127.9, 115.5, 89.3, 88.0; MS m/z 195 $[M + H]^+$.

*4-(Phenylethynyl)aniline (**2**).*[26] Dark brown solid (1.76 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.45 (m, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.31−7.25 (m, 3H), 6.62 (d, J = 8.7 Hz, 2H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 132.9, 131.3, 128.2, 127.6, 123.8, 114.68, 122.5, 90.1, 87.3; MS m/z 194 $[M + H]^+$.

*4-(Phenylethynyl)benzonitrile (**3**).*[27] Brown solid (1.52 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.57 (m, 4H), 7.55−7.50 (m, 2H), 7.38−7.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 131.7, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.7, 87.7; MS m/z 204 $[M + H]^+$.

*1-Bromo-4-(phenylethynyl)benzene (**4**).*[28] White solid (1.78 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.46 (m, 4H), 7.41−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 131.6, 128.5, 128.3, 122.9, 122.4, 122.2, 90.5, 88.3; MS m/z 257 $[M + H]^+$.

*1-Nitro-4-(phenylethynyl)benzene (**5**).*[29] Yellow solid (1.29 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.58−7.54 (m, 2H), 7.40−7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.1, 94.7, 87.5; MS m/z 224 $[M + H]^+$.

***N*-(4-(Phenylethynyl)phenyl)acetamide (Compound 6).** To a solution of 4-(phenylethynyl)aniline (0.8 g, 5 mmol) and Na_2CO_3 (1.0 g, 10 mmol) in dry THF (20 mL) at −78 °C was added CH_3COCl (0.4 mL, 5.5 mmol). The reaction mixture was stirred at room temperature for 1 h. After the reactant was completely consumed, water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4. The reaction mixture was filtered and concentrated, and the product was purified by column chromatography using 50% ethyl acetate/hexane to afford **6**[30] as a slightly yellow solid (1.16 g, 98%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.2 (s, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.50 (m, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39 (m, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 139.8, 132.1, 131.3, 128.8, 122.6, 118.9, 116.4, 89.6, 88.5, 24.1; MS m/z 236 $[M + H]^+$.

Methyl 4-(Phenylethynyl)benzoate (Compound 7). A solution of 4-(phenylethynyl)benzonitrile (0.8 mg, 3.95 mmol) and NaOH (0.4 g, 10.0 mmol) in 50% ethanol/H_2O (10 mL) was heated under reflux for 4 h. After complete consumption of the reactant, the solvent was removed under reduced pressure. The residue was acidified and esterified by adding 40% concd H_2SO_4/methanol (10 mL), and then the solution was refluxed at 80 °C overnight. The solvent was removed, and the product was purified by column chromatography using 20% ethyl acetate/hexane to afford **7**[31] as a white solid (0.75 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.49−7.46 (m, 2H), 7.30−7.28 (m, 3H), 3.86 (s,

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3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 131.7, 131.5, 129.5, 128.7, 128.4, 128.0, 122.7, 92.3, 88.6, 52.2; MS m/z 237 $[M + H]^+$.

General Procedure for the Larock Heteroannulation (Compounds 8a–g and 9a–g). $Pd(OAc)_2$ (10 mol %, 11.22 mg, 0.05 mmol), 20 mol % of PPh_3 (26.22 mg, 0.1 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), Na_2CO_3 (264 mg, 2.50 mmol), 2-iodoaniline (109 mg, 0.5 mmol), DMF (5 mL), and diarylalkyne (0.7 mmol) were added to a three-necked round-bottom flask equipped with a stirring bar and condenser. The reaction was heated under N_2 atmosphere at 80 °C for 24 h. Then, the reaction mixture was diluted with ether and washed with saturated NH_4Cl solution and H_2O. The organic layer was separated and dried over anhydrous Na_2SO_4. The reaction mixture was filtered and concentrated, and the product was purified by column chromatography using 10% ethyl acetate/hexane.

*4-(3-Phenyl-1H-indol-2-yl)aniline (**8a**).* Pale yellow solid (30.4 mg, 21%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.43 (m, 2H), 7.32 (m, 3H), 7.23 (t, J = 7.3 Hz, 1H), 7.25–7.08 (m, 4H), 6.52 (d, J = 8.5 Hz, 2H), 4.04–3.14 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 135.6, 135.5, 134.7, 130.0, 129.3, 128.8, 128.4, 125.8, 122.8, 122.0, 120.1, 119.2, 115.1, 113.3, 110.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{17}N_2$ 285.1392, found 285.1391.

*4-(2-Phenyl-1H-indol-3-yl)aniline (**9a**).* Pale yellow solid (54.9 mg, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.45–7.42 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.34–7.18 (m, 6H), 7.12 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 135.8, 133.4, 133.0, 131.0, 129.0, 128.6, 128.0, 127.4, 125.4, 122.5, 120.2, 119.8, 115.6, 115.1, 110.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{17}N_2$ 285.1392, found 285.1396.

*4-(3-Phenyl-1H-indol-2-yl)phenol (**8b**).*[32] White solid (32.0 mg, 22%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 9.62 (s, 1H), 7.51–7.23 (m, 9H), 7.12 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 135.7, 135.5, 134.6, 129.5, 129.4, 128.4, 127.9, 125.7, 123.1, 121.3, 119.4, 118.1, 115.3, 111.7, 111.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{16}NO$ 286.1232, found 286.1225.

*4-(2-Phenyl-1H-indol-3-yl)phenol (**9b**).*[33] White solid (43.0 mg, 30%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 9.40 (s, 1H), 7.52–7.11 (m, 10H), 7.02 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.7, 135.9, 133.2, 132.6, 130.7, 128.3, 128.3, 127.8, 127.1, 125.5, 121.7, 119.3, 118.6, 115.5, 113.4, 111.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{16}NO$ 286.1232, found 286.1224.

*N-(4-(3-Phenyl-1H-indol-2-yl)phenyl)acetamide (**8c**).* Pale yellow solid (65.0 mg, 40%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 10.01 (s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.50–7.32 (m, 8H), 7.28 (t, J = 8.7 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 138.6, 135.9, 135.3, 134.0, 129.6, 128.5, 128.5, 127.9, 127.0, 125.9, 121.7, 119.6, 118.8, 118.3, 112.6, 111.3, 23.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1497, found 327.1492.

*N-(4-(2-Phenyl-1H-indol-3-yl)phenyl)acetamide (**9c**).* Pale yellow solid (70.4 mg, 43%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 9.97 (s, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.50–7.24 (m, 9H), 7.15 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2, 137.4, 136.0, 133.7, 132.5, 129.89, 129.79, 128.4, 128.03, 127.97, 127.3, 121.9, 119.5, 119.2, 118.6, 113.0, 111.4, 23.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1497, found 327.1493.

*2-(4-Bromophenyl)-3-phenyl-1H-indole (**8d**).*[34] Yellow solid (31.8 mg, 18%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.66 (d, J = 7.98 Hz, 1H), 7.47–7.22 (m, 11H), 7.15 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 134.6, 132.7, 131.8, 131.6, 130.0, 129.5, 128.7, 128.6, 126.4, 123.0, 121.7, 120.6, 119.7, 115.6, 110.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}NBr$ 348.0388, found 348.0380.

*3-(4-Bromophenyl)-2-phenyl-1H-indole (**9d**).*[35] Yellow solid (23.9 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.45–7.22 (m, 9H), 7.16 (t, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.3, 134.0, 132.3, 131.6, 128.8, 128.3, 128.1, 127.9, 122.8, 120.6, 120.1, 119.3, 113.7, 110.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}NBr$ 348.0388, found 348.0389.

*Methyl 4-(3-Phenyl-1H-indol-2-yl)benzoate (**8e**).*[34] Pale yellow solid (85.6 mg, 52%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.51–7.29 (m, 7H), 7.20 (t, J = 8.1 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMS-d_6) δ 165.8, 137.0, 136.4, 134.7, 132.5, 129.7, 129.2, 128.7, 128.0, 127.8, 126.4, 122.6, 120.0, 118.8, 114.9, 111.6, 52.0 ; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{18}NO_2$ 328.1338, found 328.1336.

*Methyl 4-(2-Phenyl-1H-indol-3-yl)benzoate (**9e**).*[36] Pale yellow solid (45.3 mg, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.52–7.26 (m, 9H), 7.17 (t, J = 8.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 140.4, 136.0, 135.1, 132.3, 129.84, 129.80, 128.8, 128.4, 128.2, 128.0, 127.6, 122.9, 120.7, 119.3, 113.9, 111.1, 52.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{18}NO_2$ 328.1338, found 328.1332.

*4-(3-Phenyl-1H-indol-2-yl)benzonitrile (**8f**).*[37] White solid (49.7 mg, 34%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.46–7.32 (m, 6H), 7.28 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.4, 134.2, 132.3, 131.6, 130.0, 128.8, 128.7, 126.9, 123.7, 120.8, 120.1, 118.8, 117.5, 111.1, 110.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}N_2$ 295.1235, found 295.1238.

*4-(2-Phenyl-1H-indol-3-yl)benzonitrile (**9f**).*[15,38] White solid (29.8 mg, 20%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.57–7.33 (m, 9H), 7.21 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.6, 136.1, 135.6, 132.3, 131.7, 130.1, 128.6, 128.5, 128.0, 127.0, 122.2, 120.2, 119.0, 118.1, 111.7, 111.4, 107.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}N_2$ 295.1235, found 295.1220.

*2-(4-Nitrophenyl)-3-phenyl-1H-indole (**8g**).* Orange solid (60.2 mg, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.9 Hz, 2H), 7.46–7.33 (m, 6H), 7.29 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 139.1, 136.5, 134.1, 131.2, 130.1, 128.9, 128.7, 128.2, 127.1, 124.0, 124.0, 121.0, 120.2, 118.2, 111.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}N_2O_2$ 315.1134, found 315.1131.

*3-(4-Nitrophenyl)-2-phenyl-1H-indole (**9g**).*[39] Orange solid (23.0 mg, 15%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.22 (d, J = 8.0 Hz, 2H), 7.66–7.35 (m, 9H), 7.22 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.9, 142.9, 136.2, 131.7, 130.1, 128.7, 128.6, 128.2, 126.9, 123.8, 122.4, 120.4, 118.2, 111.8, 111.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}N_2O_2$ 315.1134, found 315.1135.

X-ray Diffraction. X-ray diffraction data were measured on a diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) at 298(2) K. The structures were solved by direct methods with SIR97[40] and refined with full-matrix least-squares calculations on F^2 using SHELXL-97.[41] Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the reference nos. CCDC962465-962466. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

Computational Details. All geometrical structures of reaction were optimized by employing the hybrid density functional B3LYP method. For the basis set, the LANDL2DZ effective core potential (ECP)[42−44] and LANL2DZspdf+ECP[45] basis sets were used for palladium and iodine atoms, respectively. The remaining atoms were treated with the 6-31G(d,p) basis set. All minimum and transition state structures were confirmed by the frequency calculation in which all minimum structures had no imaginary frequency and each transition state structure had only one imaginary frequency. To investigate the effect of DMF solvent on the energetic profile, all geometrical structures were reoptimized at the same level within the bulk solvent treating by the polarizable continuum model (PCM).[46] The free energies at 353.15 K and 1 atm of the gas-phase and PCM models

were done at the same level by single-point calculations from the corresponding structures. All theoretical calculations were performed using the Gaussian 09 package.[47]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^{1}H and ^{13}C) for all new compounds, CIF files, and X-ray crystallographic data for compound **9a** and **9c**, and atomic coordinates for optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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