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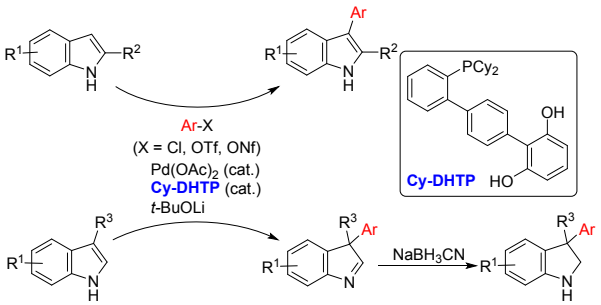
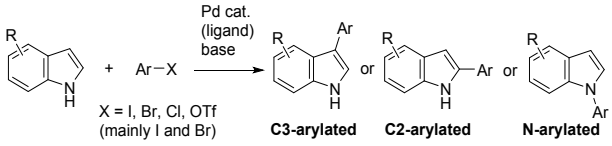


ABSTRACT: A palladium–dihydroxyterphenylphosphine (DHTP) catalyst was successfully applied to the direct C3-arylation of N-unsubstituted indoles with aryl chlorides, triflates, and nonaflates. This catalyst showed C3-selectivity, whereas catalysts with other structurally related ligands exhibited N1-selectivity. Complex formation between the lithium salts of the ligand and the indole is assumed to accelerate the arylation at the C3-position. Reactions using 3-alkylindoles afforded 3,3-disubstituted indolenines, which can be further converted to the corresponding indoline derivatives.

INTRODUCTION

Indole and related skeletons are ubiquitous structural motifs often found in pharmaceuticals[1-6] and natural compounds,[1,7] and their arylated species have attracted attention because of their diverse biological activities.[8-14] Among them, 3-arylindoles are known to show antimicrobial,[8-10] anti-inflammatory,[11] anticancer,[12] and enzyme-inhibition[13,14] activities. Therefore, much synthetic effort has been made to obtain these classes of compounds.[15-20] Palladium-catalyzed direct arylation of N-unsubstituted indole is a powerful tool for 3-arylated indole synthesis (Scheme 1).[17-25] However, achieving high C3-selectivity over C2- and N-selectivity is still challenging.[16,17,24] A recent paper reported Pd-catalyzed C3-selective arylation of N-unsubstituted indole with aryl iodides/bromides using lithium hexamethyldisilazide (LiHMDS) as the base and transient directing group.[26] In comparison, the C3-selective arylation with aryl chlorides has been limited.[27, 28] In addition, arylation of N-unsubstituted indole with aryl triflates usually gives only the N-arylated products.[29]

Scheme 1. Pd-Catalyzed Arylation of N-Unsubstituted Indoles



Our research group has been investigating ligand-controlled site-selective cross coupling using palladium catalysts. Hydroxyterphenylphosphines[30-32] were developed as ligands and found to be effective for accelerating Kumada–Tamao–Corriu coupling,[30,31,33] Sonogashira coupling,[34] and Cacchi cyclization[35] of bromo- or chloro-groups at the *ortho*-position of phenols or anilines. Among these ligands, dihydroxyterphenylphosphine (DHTP) **1a** bearing two hydroxy groups (Figure 1) showed the highest reactivity and *ortho*-selectivity. We assume that the complex formation between the substrate and the ligand **1a** via their metal phenoxide/anilide is a key to control the site selectivity and reactivity. We further applied the Pd–based **1a** as catalyst to the direct C3-arylation of N-unsubstituted

indoles with aryl chlorides and triflates (Scheme 2a).[36] In this reaction, we assume that the lithium salt of indole and the ligand **1a** form a heteroaggregate, in which the C3 position of indole is close to the Pd atom, and arylation proceeds selectively at the C3 position (Scheme 2b). However, several substrates including 2-substituted indole showed low reactivity to give the C3-arylated products in poor yield. In addition, arylation of 3-methylindole afforded 3-aryl-3-methylindolenine in moderate yield. 3,3-Disubstituted indolenine is also an important structural motif, and it can be converted into various derivatives such as 3,3-disubstituted indolines.[37] Therefore, effective methods for preparing indolenines have been developed.[37-48] Among them, dearomatization of 3-substituted indoles[41-48] is a useful tool for 3,3-disubstituted indolenines including Pd-catalyzed intramolecular dearomative arylation,[48] but there has been no successful example of intermolecular dearomative arylation with aryl chlorides or sulfonates except our previous work (Scheme 2a).[36]

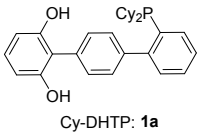
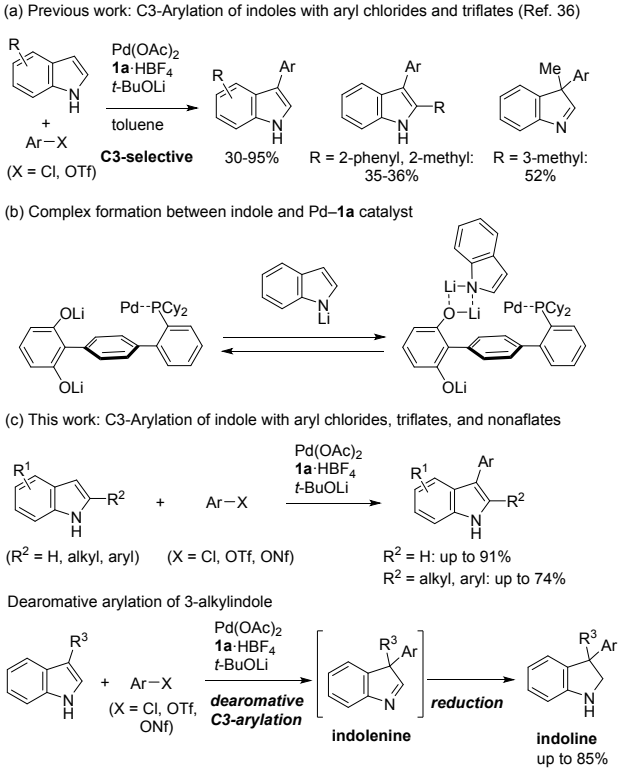


Figure 1. Dihydroxyterphenylphosphine

Scheme 2. Pd–DHTP-Catalyzed C3-Selective Arylation of N-Unsubstituted Indoles



Herein, we report details for the C3-arylation of N-unsubstituted indoles with aryl chlorides, triflates, and nonaflates (Scheme 2c). This method was further applied to the dearomative arylation of 3-alkylindoles to afford 3-alkyl-3-arylindolines.

RESULTS AND DISCUSSION

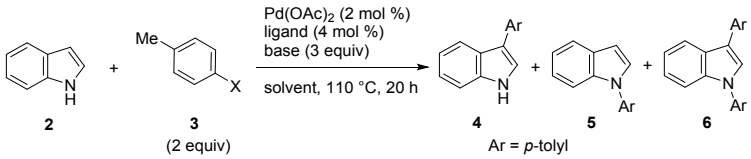
We began optimization of the reaction conditions using indole **2** and 4-chlorotoluene **3a** as model substrates (Table 1). The reactions were conducted under the same conditions as in our previous study of site-selective cross-couplings,[34] using catalysts derived from palladium acetate and a phosphine ligand, lithium *tert*-butoxide as a base, and toluene as a solvent. The reaction hardly progressed when there was no ligand (entry 1). The reaction using tricyclohexylphosphine afforded the desired C3-arylated indole **4** in low yield, with a small amount of N-arylated indole **5** as byproduct (entry 2). When the reaction was conducted with tri-*tert*-butylphosphine, N-arylated **5** was obtained in moderate yield (entry 3). Use of triphenylphosphine gave no arylated products (entry 4). In the cases of 2-phosphinobiphenyl-type ligands (Cy-JohnPhos,[49] XPhos,[50] or SPhos[51]), N-arylation instead of C3-arylation proceeded smoothly, and N-arylated **5** was obtained in good yield (entries 5–7). Bidentate ligands were found to be ineffective (entries 8 and 9). On the other hand, reaction with the HBF_4 salt of DHTP **1a** bearing dicyclohexylphosphino group selectively afforded the C3-arylated **4** in high yield (entry 10). DHTP **1b** bearing diphenylphosphino group also exhibited C3-selectivity, though the yield of **4** was low (entry 11). When hydroxyterphenyl phosphine **1c** bearing only one hydroxy group was used, the site selectivity of arylation decreased, and N-arylated **5** was obtained as the major product (entry 12). This result is consistent with our previous studies of Kumada–Tamao–Corriu coupling[30,31,33] and Sonogashira coupling,[34] in which the ligand with two hydroxy groups performed better than that with one hydroxy group. Ligand **1d** bearing two methoxy groups instead of hydroxy groups did not give any arylated product (entry 13), supporting our hypothesis that high reactivity and excellent C3-selectivity require the formation of a complex between the hydroxy groups of ligand **1a** and the NH group of indole **2** via their lithium salts.

Next, the effect of solvents was studied using Pd–**1a** catalyst. High yields of **4** were achieved when using xylene or mesitylene as solvent instead of toluene (entries 14 and 15). In the case of 1,4-dioxane, **4** was obtained in moderate yield (entry 16). The effect of bases was then examined using toluene as solvent. Use of sodium or potassium *tert*-butoxide did not give any arylated product (entries 17 and 18). To evaluate the effect of lithium salts, other lithium bases were screened but found to be ineffective for this reaction (entries 19–21).

Using the optimized reaction conditions, arylating agents bearing other leaving groups were tested as reactants instead of chloride **3a**. We chose aryl sulfonates since they can be easily prepared from the corresponding phenols. When 4-methylphenyl triflate **3b** was employed, the desired **4** was obtained in 75% yield (entry 22). 4-

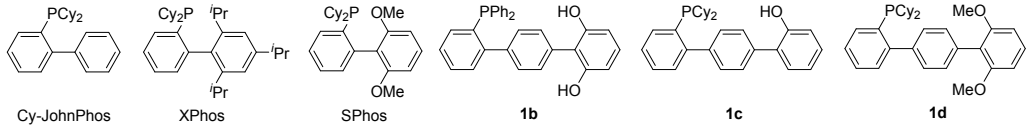
Methylphenyl nonaflate **3c** was more effective as it afforded **4** in 88% yield (entry 23). Decreasing the amount of nonaflate **3c** to 1.2 equivalents further improved the yield (entry 24). Nonaflates have been used as an effective alternative to triflates in various cross-couplings, showing higher stability and slightly higher reactivity than triflates.[52] In addition, the nonaflating reagent perfluorobutanesulfonyl fluoride, which is used in preparing nonaflates from phenols, is less expensive than triflating reagents such as Tf_2O. Therefore, we decided to use aryl nonaflates for further study.

Table 1. Optimization of Reaction Conditions in the Pd-Catalyzed C3-Arylation of Indole



entry	ligand	X	solvent	base	yield (%)[a]		
					4	**5**	**6**
1	no ligand	Cl (**3a**)	toluene	*t*-BuOLi	1	nd	nd
2	PCy_3	Cl (**3a**)	toluene	*t*-BuOLi	18	6	trace
3	$P(t\text{-Bu})_3 \cdot HBF_4$	Cl (**3a**)	toluene	*t*-BuOLi	1	65	9
4	PPh_3	Cl (**3a**)	toluene	*t*-BuOLi	nd	nd	nd
5	Cy-JohnPhos	Cl (**3a**)	toluene	*t*-BuOLi	nd	86[b]	4
6	XPhos	Cl (**3a**)	toluene	*t*-BuOLi	nd	62[b]	8
7	SPhos	Cl (**3a**)	toluene	*t*-BuOLi	nd	76[b]	2
8	Xantphos	Cl (**3a**)	toluene	*t*-BuOLi	nd	nd	nd
9	DPPE	Cl (**3a**)	toluene	*t*-BuOLi	nd	nd	nd
10	**1a**·HBF_4	Cl (**3a**)	toluene	*t*-BuOLi	85 (81)[b]	1	3
11	**1b**	Cl (**3a**)	toluene	*t*-BuOLi	19	1	trace
12	**1c**·HBF_4	Cl (**3a**)	toluene	*t*-BuOLi	12	31	2
13	**1d**	Cl (**3a**)	toluene	*t*-BuOLi	nd	nd	nd
14	**1a**·HBF_4	Cl (**3a**)	xylene	*t*-BuOLi	81	2	6
15	**1a**·HBF_4	Cl (**3a**)	mesitylene	*t*-BuOLi	85	1	1
16	**1a**·HBF_4	Cl (**3a**)	1,4-dioxane	*t*-BuOLi	62	3	5
17	**1a**·HBF_4	Cl (**3a**)	toluene	*t*-BuONa	nd	nd	nd
18	**1a**·HBF_4	Cl (**3a**)	toluene	*t*-BuOK	nd	nd	nd
19	**1a**·HBF_4	Cl (**3a**)	toluene	Li_2CO_3	1	nd	nd
20	**1a**·HBF_4	Cl (**3a**)	toluene	LiOH	2	nd	nd
21	**1a**·HBF_4	Cl (**3a**)	toluene	Li_3PO_4	nd	nd	nd
22	**1a**·HBF_4	OTf (**3b**)	toluene	*t*-BuOLi	75[b]	1	13
23	**1a**·HBF_4	ONf (**3c**)	toluene	*t*-BuOLi	88[b]	2	6
24[c]	**1a**·HBF_4	ONf (**3c**)	toluene	*t*-BuOLi	91[b]	<3	<7

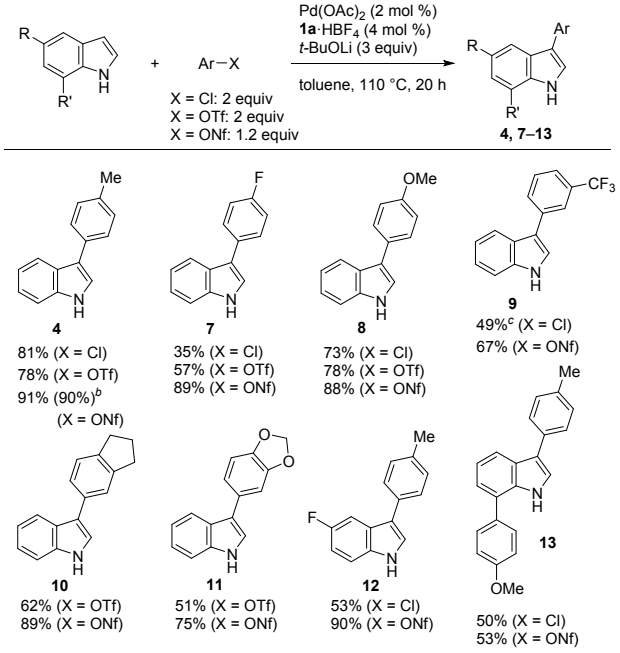
[a]NMR yield. nd = not detected. [b]Isolated yield. [c]1.2 equiv of ArONf was used.



The scope of arylating agents and indoles was investigated using the optimized reaction conditions (Scheme 3). In most cases, the use of aryl nonaflates instead of the corresponding chlorides or triflates significantly improved the yield of the desired C3-arylated indoles. Aryl nonaflates having substituents at the para-position afforded the corresponding C3-arylated indoles **4**, **7**, and **8** in high yields. In the case of 3-trifluoromethylphenyl nonaflate, the desired indole **9** was

obtained in 66% yield. Benzo[*d*][1,3]dioxol-5-yl nonaflate and 2,3-dihydro-1*H*-inden-5-yl nonaflate showed higher reactivities than the corresponding triflates to give **10** and **11**, respectively. The reaction of 5-fluoroindole with nonaflate **3a** afforded **12** in high yield. On the other hand, 7-(4-methoxyphenyl)indole was found to be less reactive and resulted in a moderate yield of **13**.

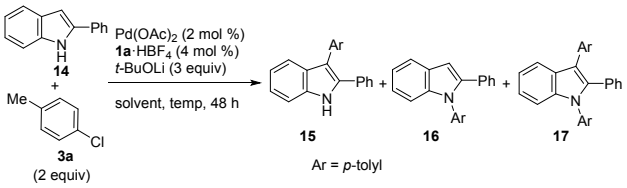
Scheme 3. Scope of the Pd-Catalyzed C3-Arylation of N-Unsubstituted Indoles [a]



[a]Isolated yield. [b]1-mmol scale. [c]1.2 equiv of 3-chlorobenzotrifluoride was used.

Next, we examined the arylation of 2-phenylindole **14** with 4-chlorotoluene **3a** (Table 2). When the reaction was conducted under the standard conditions used in the arylation of unsubstituted indole **2**, the yield of the desired C3-arylated product **15** was only 35%, and a large amount of **14** was recovered (entry 1). A longer reaction time (48 h) effectively increased the yield of **15** (entry 2). We then changed the solvent from toluene to xylene, of which boiling point is higher, and investigated the effect of reaction temperature (entries 3–6). When the reaction was carried out at 110 °C, the yield of **15** was decreased (entry 3). By increasing the reaction temperature to 130 °C, the yield of the desired **15** was increased, and a small amount of N-arylated indole **16** was obtained (entry 4). The reaction at 140 °C proceeded smoothly to afford **15** in 79% yield (entry 5). When the temperature was further elevated to 150 °C, the yield of **15** was decreased (entry 6). Next, mesitylene was tested as a solvent, and reaction in it at 140 °C gave **15** in good yield (entry 7). On the other hand, a higher reaction temperature (160 °C) caused overarylation, and the C3,N-diarylated indole **17** was obtained as a major product (entry 8). When the reaction was conducted using the corresponding nonaflate **3c** with xylene as solvent at 140 °C, the yield of **15** was moderate (entry 9). 4-Bromotoluene also afforded **15** in moderate yield (entry 10). From these results, we determined that the best reaction occurs when using chloroarenes in xylene at 140 °C.

Table 2. Effect of Solvent and Temperature on the Pd-Catalyzed C3-Arylation of 2-Phenylindole with 4-Chlorotoluene

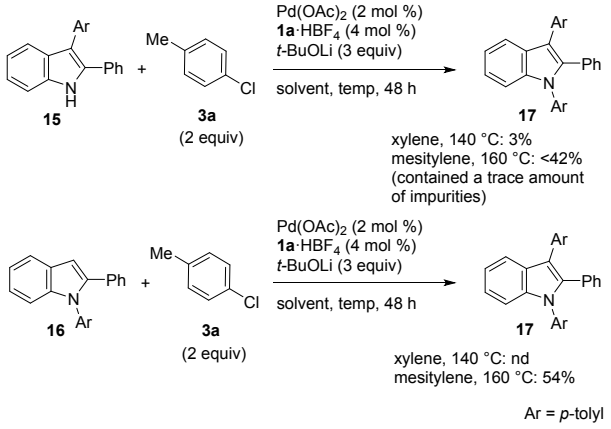


entry	solvent	temperature (°C)	yield (%)[a] 15	16	17
1[b]	toluene	110	35	trace	nd
2	toluene	110	52	trace	nd
3	xylene	110	39	trace	nd
4	xylene	130	62	6	nd
5	xylene	140	79 (58)[c]	<3	nd
6	xylene	150	66	9	nd
7	mesitylene	140	64	6	nd
8	mesitylene	160	nd	<13	41
9[d]	xylene	140	<63[e]	nd	nd
10[f]	xylene	140	44	trace	trace

[a]NMR yield. nd = not detected. [b]20 h. [c]Isolated yield. [d]4-Methylphenyl nonaflate **3c** was used instead of **3a**. [e]Contained a small amount of impurities. [f]4-Bromotoluene was used instead of **3a**.

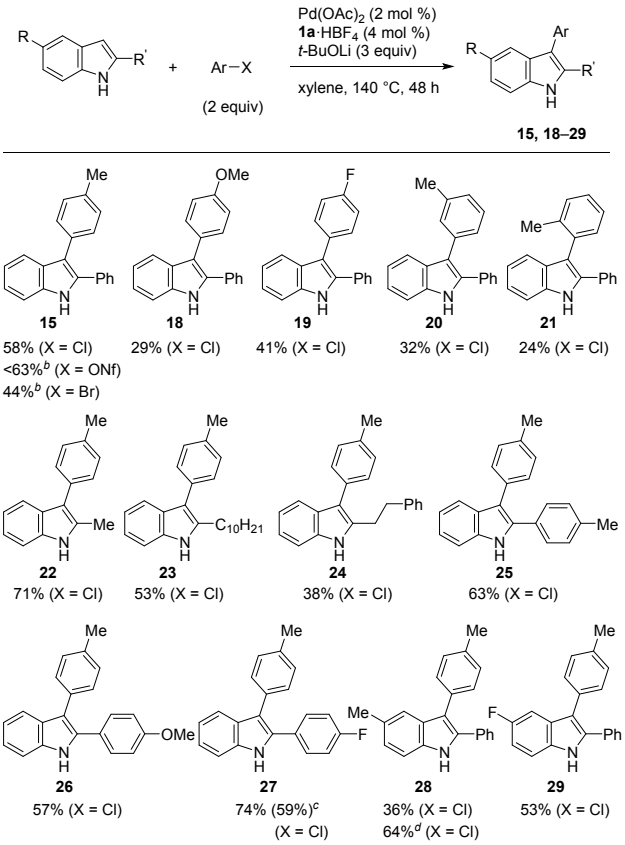
To gain insight into the mechanism of overarylation, C3-arylated indole **15** and N-arylated indole **16** were individually arylated using xylene or mesitylene as solvent (Scheme 4). When the reactions were conducted in xylene at 140 °C, N-arylation of C3-arylated of **15** gave a small amount of C3,N-diarylated indole **17,** and the C3-arylation of N-arylated **16** did not proceed. On the other hand, when using mesitylene as solvent at 160 °C, arylation of **15** and **16** both gave the C3,N-diarylated **17** in moderate yield. In the case of C3-arylated **15**, N-arylation proceeded and **17** was obtained in <42% yield. Surprisingly, N-arylated **16** also afforded **17** in 54% yield. These results indicate that a higher reaction temperature (160 °C) may enable other catalytic pathways that do not require the complex formation between indoles and the Pd–**1a** catalyst, and therefore C3,N-diarylated **17** was formed from both C3-arylated **15** and N-arylated **16**.

Scheme 4. Mechanistic Study of Overarylation



With the optimized conditions at hand, we investigated reactions using various arylating agents and 2-substituted indoles (Scheme 5). Chloroarenes bearing methoxy or fluoro group afforded the corresponding C3-arylated indoles **18** and **19**. In the cases of 3-chlorotoluene and 2-chlorotoluene, the desired products **20** and **21** were obtained in low yield. A series of 2-substituted indoles were then tested. Reaction using 2-methylindole proceeded smoothly to afford the desired **22** in good yield. When 2-decylindole was used, the desired **23** was obtained in moderate yield. 2-Phenethyllindole gave the corresponding C3-arylated **24** in 38% yield. Reactions with 2-phenylindoles bearing various substituents on the 2-phenyl moiety afforded **25–27** in moderate yields. When the reaction was conducted for 48 h using 5-methyl-2-phenylindole, the yield of the desired **28** was low, and a large amount of C3,N-diarylated indole (19%) was obtained. A shorter reaction time (24 h) was found to be effective for improving the yield of **28** by suppressing the overarylation. 5-Fluoro-2-phenylindole gave C3-arylated **29** in moderate yield.

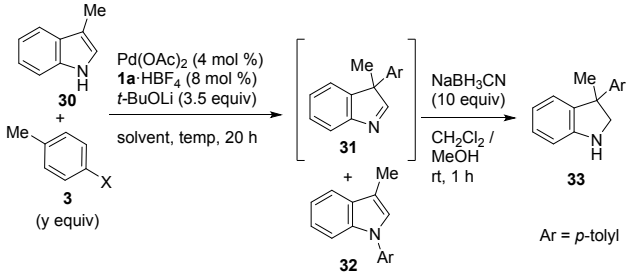
Scheme 5. Scope of the C3-Arylation of 2-Substituted Indoles[a]



[a]Isolated yield. [b]NMR yield. [c]1-mmol scale. [d]24 h.

Subsequent investigation was carried out for the dearomative C3-arylation of 3-alkylindoles (Table 3). 3-Methylindole **30** was selected as a model substrate, and its reactions were conducted using 4 mol% Pd catalyst. Due to instability of the obtained 3-methyl-3-(*p*-tolyl)indolenine **31**, reduction with $NaBH_3CN$[53] was carried out after work-up to give the more stable 3-methyl-3-(*p*-tolyl)indoline **33**. First, effects of the solvent and the temperature were examined using 2 equivalents of 4-chlorotoluene **3a** as arylating agent. When the reaction was carried out in toluene at 110 °C, the desired **33** was obtained in 52% yield with N-arylated indole **32** as a byproduct (entry 1). The use of xylene did not increase the yield of **33** (entry 2), while a higher reaction temperature (140 °C) resulted in decreased **33** and increased **32** yields (entry 3). The use of mesitylene did not improve the yield of **33** either (entries 4 and 5). Other arylating agents were then tested using toluene as solvent. Reaction with the corresponding triflate **3b** gave the desired **33** in 56% yield (entry 6). To our delight, when nonaflate **3c** was used, the C3-arylation proceeded smoothly and the yield of **33** increased (entry 7). A shorter reaction time was found to further improve the yield (entry 8). By decreasing the amount of nonaflate **3c** to 1.2 equivalents, the formation of N-arylated **32** was suppressed, and indoline **33** was obtained in 85% yield (entry 9). Among the tested arylating agents, nonaflate **3c** gave the best yield in a shorter reaction time.

Table 3. Optimization of Reaction Conditions in the Pd-Catalyzed Dearomative C3-Arylation of 3-Methylindole

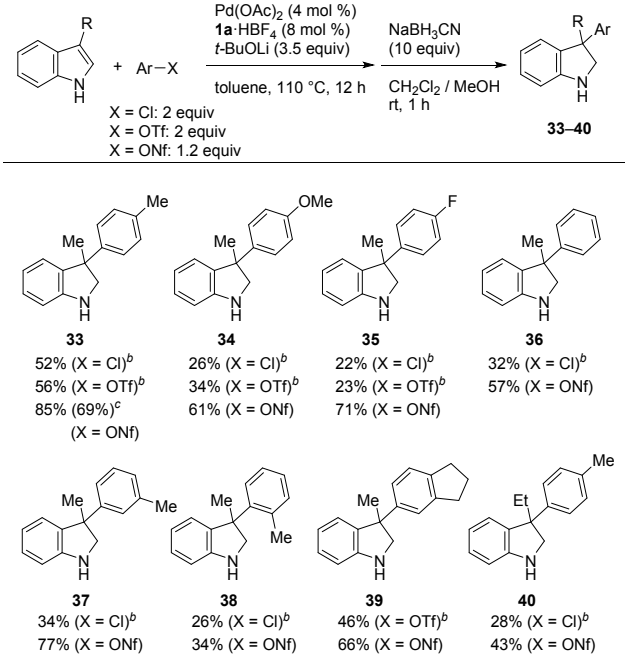


entry	X (y equiv)	solvent	temp (°C)	yield (%)[a] 33	32
1	Cl (2)	toluene	110	52	<12
2	Cl (2)	xylene	110	45	20
3	Cl (2)	xylene	140	24	27
4	Cl (2)	mesitylene	110	44	14
5	Cl (2)	mesitylene	120	34	26
6	OTf (2)	toluene	110	56	16
7	ONf (2)	toluene	110	67	<10
8[b]	ONf (2)	toluene	110	77	<3
9[b]	ONf (1.2)	toluene	110	85	trace

[a]Isolated yield. [b]Arylation time: 12 h.

Finally, the scope of the dearomative C3-arylation was tested (Scheme 6). In all cases, reactions using nonaflates gave higher yield of the products (**33–40**) than those using chlorides and triflates. Aryl nonaflates bearing methyl-, methoxy-, and fluoro group at the *para*-position gave the corresponding indolines **33–35** in good to high yield. When phenyl nonaflate was used, indoline **36** was obtained in moderate yield. Reaction with 3-methylpheyl nonaflate also proceeded smoothly to afford **37** in good yield. On the other hand, 2-methylphenyl nonaflate gave the product **38** in only 34% yield. It seems that the steric hindrance between the 3-methyl group of **30** and the *o*-methyl group of the nonaflate caused the low reactivity. In the case of 2,3-dihydro-1*H*-inden-5-yl nonaflate, the yield of the desired **39** was 66%. Reaction using 3-ethylindole instead of **30** also proceeded, and the desired **40** was obtained in moderate yield.

Scheme 6. Scope of the Pd-Catalyzed Dearomative C3-Arylation of 3-Substituted Indoles[a]



[a]Isolated yield. [b]Arylation time: 20 h. [c]1-mmol scale.

CONCLUSIONS

We developed C3-selective arylation of N-unsubstituted indoles using a catalyst derived from Pd and dihydroxyterphenylphosphine ligand **1a**. The use of aryl nonaflates effectively increased the yield of the desired C3-arylated products. In the cases of 2-substituted indoles, reactions at higher temperature using xylene as solvent improved the product yield. Dearomative C3-arylation of C3-alkylindoles also proceeded well when employing this catalyst system and aryl nonaflates. This method enables the facile synthesis of various indoles and their derivatives from readily available compounds.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were performed under argon atmosphere. Reactions were monitored by TLC on Merck silica gel 60 F_{254} plates or Wako Pure Chemical Industry NH_2 silica gel 60 F_{254} plates and visualized by UV lump at 254 nm. Preparative TLC was performed on Merck silica gel 60 F_{254} 0.5 mm plates or Wako Pure Chemical Industry NH_2 silica gel 60 F_{254} 0.5 mm plates. NMR spectra were measured on a JEOL AL-400 NMR spectrometer (400 MHz for ^{1}H spectra), a JEOL ECA500 NMR spectrometer (500 MHz for ^{1}H spectra, 125 MHz for ^{13}C spectra, and 470 MHz for ^{19}F spectra), a JEOL JNM-ECX500 NMR spectrometer (500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra), and JEOL JNM-ECZ500R/S1 NMR spectrometer (500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra). For ^{1}H NMR, tetramethylsilane (TMS) (δ = 0) in $CDCl_3$ served as an internal standard. For ^{13}C NMR, $CDCl_3$ (δ = 77.0) served as an internal standard. NMR data were processed by using ACDLABS 12.0 1D processor or Delta NMR software v5.3.1. Infrared spectra were measured on a SHIMADZU IR

Prestige-21 spectrometer (ATR). High-resolution mass spectra (HRMS) were measured on a Bruker MicrOTOF time-of-flight mass spectrometer (ESI) and a JEOL JMS-T100TD time-of-flight mass spectrometer (DART). Preparative HPLC was performed on Japan Analytical Industry LC-9201 using JALGEL-1H, 2H columns (solvent: chloroform, flow rate: 3.5 mL/min, detection: 254 nm) or Japan Analytical Industry LaboACE LC-5060 using a JALGEL-2HR column (solvent: ethyl acetate, flow rate: 10 mL/min, detection: 254 nm).

Materials. Ligands **1a**·HBF_4, **1b**, and **1d** were prepared according to the reported procedure.[32] 7-(4-Methoxyphenyl)-1*H*-indole was prepared according to the reported procedure.[54] 2-Decyl-1*H*-indole[55] and 2-phenethyl-1*H*-indole[55] were prepared from 2-chloroacetanilide and corresponding alkynes.[56] 2-(4-Methylphenyl)-1*H*-indole,[57] 2-(4-methoxylphenyl)-1*H*-indole,[58] 5-methyl-2-phenyl-1*H*-indole,[59] and 5-fluoro-2-phenyl-1*H*-indole[60] were prepared from corresponding *N*-tosyl-2-chloroanilines and corresponding alkynes.[34] 3-Ethyl-1*H*-indole was prepared according to the reported procedure.[61] 4-Methylphenyl trifluoromethanesulfonate (**3b**),[62] 4-methoxyphenyl trifluoromethanesulfonate,[63,64] 4-fluorophenyl trifluoromethanesulfonate,[65] benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate,[66] and 2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate[67] were prepared from corresponding phenols using trifluoromethanesulfonic anhydride and pyridine in dichloromethane.[68] 4-Methylphenyl nonaflate (**3c**),[69] 3-trifluoromethylphenyl nonaflate,[70] 4-methoxyphenyl nonaflate,[71] 4-fluorophenyl nonaflate,[72] phenyl nonaflate,[73] 3-methylphenyl nonaflate,[72] 2-methylphenyl nonaflate,[71] benzo[*d*][1,3]dioxol-5-yl nonaflate,[74] and 2,3-dihydro-1*H*-inden-5-yl nonaflate were prepared from corresponding phenols using perfluorobutanesulfonyl fluoride and triethylamine in dichloromethane or acetonitrile. Other reagents and anhydrous solvents were purchased from commercial suppliers and used without further purification.

Typical experimental procedure for C3-selective arylation of N-unsubstituted indoles. 3-(*p*-Tolyl)-1*H*-indole (4, Table 1, Entry 24).[75,76] Toluene (0.5 mL) was added to $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **1a**·HBF_4 (10.9 mg, 0.02 mmol), *t*-BuOLi (120 mg, 1.5 mmol), and indole **2** (58.6 mg, 0.50 mmol) in a sealed tube under argon. To this solution was added 4-methylphenyl nonaflate **3c** (234 mg, 0.60 mmol). The reaction mixture was stirred at rt for 1 h, and then at 110 °C using an oil bath for 20 h. The resulting suspension was quenched with brine (5 mL) at rt and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1) to give 3-(*p*-tolyl)-1*H*-indole **4** (94 mg, 91% yield) as a pale-yellow solid. One-mmol scale reaction afforded 186 mg of **4** (90%).

1-(*p*-Tolyl)-1*H*-indole (5).[77] a pale yellow oil.

3-(4-Fluorophenyl)-1*H*-indole (7).[78] Prepared from **2** and 4-fluorophenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1) afforded **7** as a pale yellow solid (94 mg, 89%).

3-(4-Methoxyphenyl)-1*H*-indole (8).[79] Prepared from **2** and 4-methoxyphenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) afforded **8** as a white solid (99 mg, 88%).

3-((3-Trifluoromethyl)phenyl)-1*H*-indole (9).[80] Prepared from **2** and (3-fluoromethyl)phenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1, then hexane/ethyl acetate = 3/1) afforded **9** as a white solid (88 mg, 67%).

3-(2,3-Dihydro-1*H*-inden-5-yl)-1*H*-indole (10).[36] Prepared from **2** and 2,3-dihydro-1*H*-inden-5-yl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1, twice) and preparative HPLC (ethyl acetate) afforded **10** as a white solid (111 mg, 89%).

3-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-indole (11).[81] Prepared from **2** and benzo[*d*][1,3]dioxol-5-yl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1, twice) afforded **11** as a white solid (91 mg, 75%).

5-Fluoro-3-(*p*-tolyl)-1*H*-indole (12).[36] Prepared from 5-fluoroindole and **3c** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1) and preparative HPLC (chloroform) afforded **12** as a pale-yellow solid (102 mg, 90%).

7-(4-Methoxyphenyl)-3-(*p*-tolyl)-1*H*-indole (13).[36] Prepared from 7-(4-methoxyphenyl)indole and **3c** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1) and preparative HPLC (chloroform) afforded **13** as a white solid (83 mg, 53%).

Typical experimental procedure for C3-selective arylation of 2-substituted indoles. 2-Phenyl-3-(*p*-tolyl)-1*H*-indole (15).[82] Xylene (0.5 mL) was added to $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **1a**·HBF_4 (10.9 mg, 0.02 mmol), *t*-BuOLi (120 mg, 1.5 mmol), and 2-phenylindole **14** (96.6 mg, 0.50 mmol) in a sealed tube under argon. To this solution was added 4-chlorotoluene **3a** (118 μL, 1.0 mmol). The reaction mixture was stirred at rt for 1 h, and then at 140 °C using an oil bath for 48 h. The resulting suspension was quenched with brine (5 mL) at rt and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1) and preparative HPLC (chloroform) to give 2-phenyl-3-(*p*-tolyl)-1*H*-indole **15** (82 mg, 58% yield) as a yellow solid.

2-Phenyl-1,3-di-*p*-tolyl-1*H*-indole (17, Table 2, Entry 8). Purification by preparative TLC (SiO_2, hexane/ ethyl acetate = 5/1, then hexane/ ethyl acetate = 100/1) afforded **17** as a yellow solid (77 mg, 41%). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.78 (dd, *J* = 2.3, 6.3 Hz, 1 H), 7.33 - 7.28 (m, 1 H), 7.28 -

7.23 (m, 2 H), 7.23 - 7.18 (m, 2 H), 7.18 - 7.07 (m, 11 H), 2.36 (s, 3 H), 2.35 (s, 3 H) $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 138.0, 136.9, 136.8, 135.5, 135.3, 131.9, 131.8, 131.2, 130.0, 129.6, 129.0, 128.0, 127.8, 127.5, 127.2, 122.5, 120.6, 119.6, 116.3, 110.7, 21.2, 21.1. IR (ATR) 3030, 2918, 2859, 1512, 1454, 1368, 1236, 1107, 810, 731 cm^{-1}. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd. for $C_{28}H_{24}N$ 374.1903; Found: 374.1908.

3-(4-Methoxyphenyl)-2-phenyl-1*H*-indole (18).[83] Prepared from **14** and 4-chloroanisole following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (chloroform) afforded **18** as a gray solid (44 mg, 29%).

3-(4-Fluorophenyl)-2-phenyl-1*H*-indole (19).[84] Prepared from **14** and 1-chloro-4-fluorobenzene following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 2/3) and preparative HPLC (ethyl acetate) afforded **19** as a yellow solid (60 mg, 41%).

2-Phenyl-3-(*m*-tolyl)-1*H*-indole (20).[82] Prepared from **14** and 3-chlorotoluene following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (ethyl acetate) afforded **20** as a yellow oil (45 mg, 32%).

2-Phenyl-3-(*o*-tolyl)-1*H*-indole (21).[82] Prepared from **14** and 2-chlorotoluene following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (ethyl acetate) afforded **21** as a white solid (34 mg, 24%).

2-Methyl-3-(*p*-tolyl)-1*H*-indole (22).[85] Prepared from 2-methylindole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate = 5/1 then NH_2 silica, hexane/ethyl acetate = 5/1 (three times)) afforded **22** as a dark-yellow oil (78 mg, 71%).

2-Decyl-3-(*p*-tolyl)-1*H*-indole (23). Prepared from 2-decylindole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 4/1) afforded **23** as a brown oil (92 mg, 53%). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.84 (s, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 2 H), 7.33 - 7.17 (m, 3 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 2.78 (t, *J* = 7.8 Hz, 2 H), 2.40 (s, 3 H), 1.63 (quin, *J* = 7.3 Hz, 2 H), 1.37 - 1.08 (m, 14 H), 0.88 (t, *J* = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 135.9, 135.3, 135.1, 132.4, 129.5, 129.2, 128.0, 121.4, 119.7, 118.9, 114.2, 110.3, 31.9, 29.9, 29.6, 29.5, 29.4, 29.34, 29.29, 26.3, 22.7, 21.2, 14.1. IR (ATR) 3406, 2920, 2850, 2360, 1508, 1458, 1438, 1327, 817, 740 cm^{-1}. HRMS (DART) *m/z*: $[M+H]^+$ Calcd. for $C_{25}H_{34}N$ 348.2686; Found: 348.2695.

2-Phenethyl-3-(*p*-tolyl)-1*H*-indole (24). Prepared from 2-phenethylindole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (chloroform) afforded **24** as a yellow oil (59 mg, 38%). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.75 - 7.45 (m, 2 H), 7.36 - 7.29 (m, 2 H), 7.29 - 7.17 (m, 6 H), 7.17 - 7.03 (m, 4 H), 3.09 (t, *J* = 7.8 Hz, 2 H), 2.92 (t, *J* = 7.8 Hz, 2 H), 2.39 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 141.0, 135.5, 135.1, 134.7, 132.1, 129.4, 129.2, 128.5, 128.4, 127.8, 126.3, 121.5, 119.8, 119.0, 114.6, 110.4, 36.0, 28.2, 21.2. IR (ATR) 3396, 1456, 816, 741, 696 cm^{-1} HRMS (DART) *m/z*: $[M+H]^+$ Calcd. for $C_{23}H_{22}N$ 312.1747; Found: 312.1755.

2,3-Di-*p*-tolyl-1*H*-indole (25).[86] Prepared from 2-(*p*-tolyl)-1*H*-indole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (ethyl acetate) afforded **25** as a yellow oil (94 mg, 63%).

2-(4-Methoxyphenyl)-3-(*p*-tolyl)-1*H*-indole (26).[83] Prepared from 2-(4-methoxyphenyl)-1*H*-indole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1) and preparative HPLC (ethyl acetate) afforded **26** as a yellow oil (90 mg, 57%).

2-(4-Fluorophenyl)-3-(*p*-tolyl)-1*H*-indole (27).[86] Prepared from 2-(4-fluorophenyl)-1*H*-indole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 2/1, then NH_2 silica, hexane/chloroform = 1/1 (twice)) afforded **27** as a pale pink solid (111 mg, 74%). One-mmol scale reaction afforded 89 mg of **27** (59%).

5-Methyl-2-phenyl-3-(*p*-tolyl)-1*H*-indole (28). Prepared from 5-methyl-2-phenylindole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 1/1 , then NH_2 silica, hexane dichloromethane = 1/1 (twice)) afforded **28** as a yellow solid (95 mg, 64%). ^1H NMR (500 MHz, $CDCl_3$) δ = 8.02 (br. s., 1 H), 7.43 (s, 1 H), 7.38 (d, J = 6.9 Hz, 2 H), 7.34 - 7.21 (m, 6 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.04 (d, J = 8.0 Hz, 1 H), 2.41 (s, 3 H), 2.38 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 135.7, 134.2, 133.9, 132.9, 132.1, 130.0, 129.6, 129.2, 129.1, 128.6, 128.0, 127.4, 124.2, 119.3, 114.5, 110.5, 21.5, 21.2. IR (ATR) 1661, 1591, 1514, 1447, 1296, 819, 794, 763, 694 cm^{-1}. HRMS (ESI) *m/z*: $[M-H]^-$ Calcd. for $C_{22}H_{18}N$ 296.1445; Found: 296.1437.

5-Fluoro-2-phenyl-3-(*p*-tolyl)-1*H*-indole (29).[83] Prepared from 5-fluoro-2-phenylindole and **3a** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/dichloromethane = 2/1, then NH_2 silica, hexane/chloroform = 1/2 (twice)) afforded **29** as a yellow solid (79 mg, 53%).

Typical experimental procedure for C3-selective dearomative arylation of 3-substituted indoles. 3-methyl-3-(*p*-tolyl)-indoline (33).[53] Toluene (0.5 mL) was added to $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **1a**·HBF_4 (21.8 mg, 0.04 mmol), *t*-BuOLi (140 mg, 1.75 mmol), and 3-methylindole **30** (65.8 mg, 0.50 mmol) in a sealed tube under argon. To this solution was added 4-methylphenyl nonaflate **3c** (234 mg, 0.60 mmol). The reaction mixture was stirred at rt for 30 min, and then at 110 °C using an oil bath for 12 h. The resulting suspension was quenched with brine (5 mL) at rt and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give crude mixture. The crude mixture was dissolved in dichloromethane (13 mL) and methanol solution (3 mL) of $NaBH_3CN$ (314 mg, 5.0 mmol) was added. After 30 min of stirring at rt, silica gel (3.29 g) was added and stirred for 30 min. The resulting

suspension was filtered, and solvent was removed in vaduo. To the residue was added water (5 mL) and extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC (SiO_2, hexane/ethyl acetate =20/1, twice) to give 95 mg (85% yield) of 3-methyl-3-(*p*-tolyl)-indoline (**33**) as a pale-yellow oil. One-mmol scale reaction afforded 154 mg of **33** (69%).

3-Methyl-1-(*p*-tolyl)-1*H*-indole (32).[87] Colorless oil.

3-(4-Methoxyphenyl)-3-methylindoline (34).[53] Prepared from **30** and 4-methoxyphenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/diethyl ether = 4/1) afforded **34** as a pale-orange solid (73 mg, 61%).

3-(4-Fluorophenyl)-3-methylindoline (35).[53] Prepared from **30** and 4-fluorophenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =10/1) afforded **35** as a pale-yellow oil (80 mg, 71%).

3-Methyl-3-phenylindoline (36).[53] Prepared from **30** and phenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =20/1, twice) afforded **36** as a colorless oil (60 mg, 57%).

3-Methyl-3-(*m*-tolyl)indoline (37). Prepared from **30** and 3-methylphenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =20/1, twice) afforded **37** as a pale yellow oil (86 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.17 (t, *J* = 7.4 Hz, 1 H), 7.14 - 7.04 (m, 3 H), 7.00 (d, *J* = 7.4 Hz, 1 H), 6.96 (d, *J* = 7.4 Hz, 1 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 3.69 (d, *J* = 8.6 Hz, 1 H), 3.52 (d, *J* = 9.2 Hz, 1 H), 2.30 (s, 3 H), 1.69 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 150.6, 147.6, 137.6, 137.0, 128.0, 127.6, 127.2, 126.9, 124.1, 123.6, 118.9, 109.9, 63.7, 49.5, 26.2, 21.6. IR (ATR) 3375, 2963, 1604, 1485, 1460, 1310, 1244, 1028, 785, 742 cm^{-1}. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{16}H_{18}N$ 224.1434; Found: 224.1438.

3-Methyl-3-(*o*-tolyl)indoline (38). Prepared from **30** and 2-methylphenyl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =20/1, twice) afforded **38** as a pale yellow oil (39 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48 - 7.37 (m, 1 H), 7.21 - 7.10 (m, 3 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 6.79 (d, *J* = 7.4 Hz, 1 H), 6.71 - 6.61 (m, 2 H), 3.90 (d, *J* = 9.7 Hz, 1 H), 3.48 (d, *J* = 9.7 Hz, 1 H), 2.04 (s, 3 H), 1.73 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 150.0, 144.0, 137.6, 137.2, 132.6, 127.4, 127.0, 126.7, 125.4, 123.5, 118.6, 109.4, 61.0, 49.9, 28.7, 21.7. IR (ATR) 3385, 2963, 1605, 1485, 1460, 1312, 1258, 1233, 1024, 753 cm^{-1}. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{16}H_{18}N$ 224.1434; Found: 224.1432.

3-(2,3-Dihydro-1*H*-inden-5-yl)-3-methylindoline (39). Prepared from **30** and 2,3-dihydro-1*H*-inden-5-yl nonaflate following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =10/1) afforded **39** as a pale yellow oil (82 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.17 (s, 1 H), 7.16 - 7.12 (m, 1 H), 7.12 - 7.02 (m, 2 H), 6.97 (d, *J* = 7.4 Hz, 1 H), 6.75 (t, *J* = 7.4 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 3.68 (d, *J* = 9.2 Hz, 1 H), 3.52 (d, *J* = 8.6 Hz, 1 H), 2.85 (t, *J* = 7.2 Hz, 4 H), 2.03 (quin, *J* = 7.4 Hz, 2 H), 1.69 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 150.6, 145.6, 144.2, 142.0, 137.3, 127.5, 124.4, 124.1, 123.9, 122.5, 118.9, 109.9, 63.9, 49.5, 32.9, 32.3, 26.4, 25.5. IR (ATR) 1605, 1485, 1460, 1310, 1246, 1024, 818, 741 cm^{-1}. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{18}H_{20}N$ 250.1590; Found: 250.1580.

3-Ethyl-3-(*p*-tolyl)indoline (40). Prepared from 3-ethylindole and **3c** following the typical procedure. Purification by preparative TLC (SiO_2, hexane/ethyl acetate =20/1, twice) afforded **40** as a pale yellow oil (51 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ =7.24 (d, *J* = 7.8 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.05 (t, *J* = 7.8 Hz, 2 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.68 (d, *J* = 7.4 Hz, 1 H), 3.66 (d, *J* = 9.2 Hz, 1 H), 3.57 (d, *J* = 9.2 Hz, 1 H), 2.30 (s, 3 H), 2.15 (td, *J* = 7.2, 14.3 Hz, 1 H), 2.11 - 1.98 (m, 6 H), 0.84 (t, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ = 151.2, 143.3, 135.5, 134.7, 128.9, 127.5, 126.7, 125.1, 118.5, 109.9, 61.1, 53.7, 31.2, 20.8, 9.4. IR (ATR) 1603, 1512, 1185, 1460, 1377, 1308, 1244, 812, 740 cm^{-1}. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{17}H_{20}N$ 238.1590; Found: 238.1581.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)

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