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Phenanthroline-^{t}BuOK Promoted Intramolecular C−H Arylation of Indoles with ArI under Transition-Metal-Free Conditions

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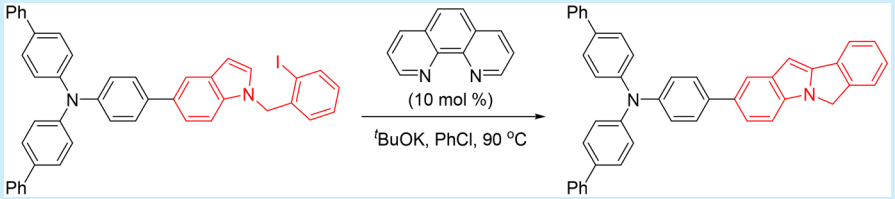
Supporting Information



ABSTRACT: The first example of phenanthroline-^{t}BuOK promoted intramolecular radical C−H arylation of *N*-(2-iodobenzyl)indoles without involvement of transition metals has been developed. A variety of substituted 6*H*-isoindolo [2, 1-a] indoles were prepared by a simple and efficient intramolecular cyclization using 1,10-phenanthroline in the presence of potassium *tert*-butoxide and chlorobenzene. This strategy provides a fast and versatile access to isoindolo[2,1-*a*]indole derivatives for the synthesis of pharmaceuticals and organic electroluminescent (EL) materials.

Isoindolo[2,1-*a*]indole represents an important and ubiquitous heterocyclic frameworks in the medical chemistry[1] and material chemistry (Figure 1).[2] The preparation of

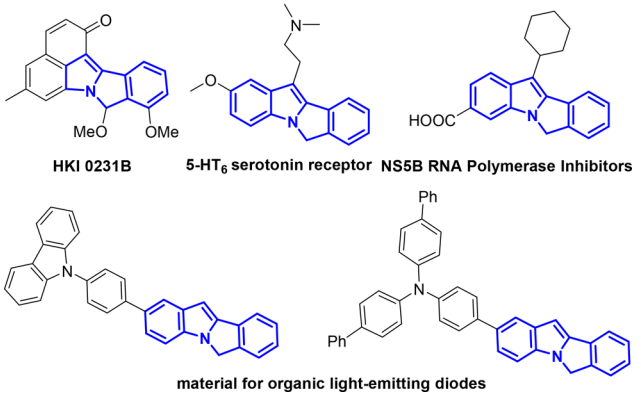


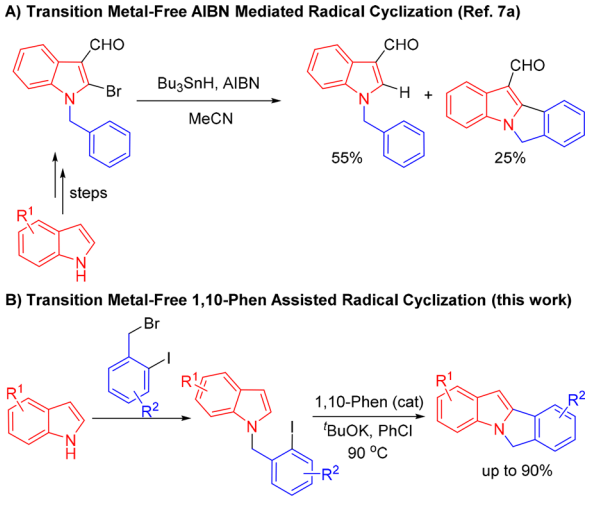
Figure 1. Selected examples for pharmaceuticals, biologically active compounds, and organic electroluminescent (EL) materials.

isoindolo[2,1-*a*]indoles has gained considerable research interest. Catalytic intramolecular direct arylation of *N*-(2-iodobenzyl)indoles involving transition metals[3−5] provides a fast access to isoindolo[2,1-*a*]indoles albeit with the problem of removal heavy metals residues in the products limiting its application in pharmaceutical synthesis. Therefore, a transition-metal-free cyclization is highly desired.

Tributyltin hydride promoted intramolecular six- and seven-membered radical cyclization afforded the corresponding heterocycles in moderate to good yield.[6] However, the intramolecular five-membered radical cyclization,[7] especially in the case of 6*H*-isoindolo [2, 1-a] indole synthesis, suffered from low yield due to the direct reductive dehalogenation of the staring materials (Scheme 1).[7b]

The base-promoted homolytic radical aromatic substitution (BHAS)[8−10] approach has recently emerged since Itami[8a]

Scheme 1. Transition-Metal-Free Synthesis of 6*H*-Isoindolo[2,1-a]indoles via Intramolecular Radical Cyclization



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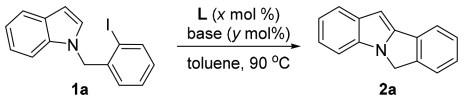
reported that potassium *tert*-butoxide could effect the addition of haloarenes to electron-deficient aromatic rings in 2008. 1,10-Phenanthrolines have been proved to be a useful additive to assist the potassium *tert*-butoxide induced intramolecular radical cross coupling of arenes and alkenes to construct fused heterocycles, but they normally focused on the electron-rich arenes or simple arenes.[9] Moreover, despite the fact that intermolecular transition-metal-free C−H arylation of heterocycles have been reported,[11] intramolecular transition-metal-free C−H arylation of heterocycles is scarce.

On the basis of our studies on self-hydrogen transferring rearrangement[12a] and hydrodehalogenation[12b] promoted by potassium *tert*-butoxide, we developed the first example of intramolecular C−H arylation of indoles and azaindoles, in which 1,10-phenanthroline assists intramolecular cyclization of the aryl radical onto C2 of indoles to give fused isoindolo [2,1-*a*] indoles in up to 90% yield (Scheme 1, down), while the reported intermolecular transition-metal-free arylation of indoles normally occurred on the C3[11] or *N*-position[11c] of indoles. Herein, we present our result in details.

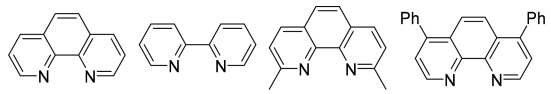
The reaction conditions were first investigated as shown in Table 1. In our early work, we noted that 10−40% of 1,10-phenanthroline **L1** could assist the radical allylic isomerization of allylic alcohol.[11a] By screening the organic additives **L1**−**L4** (entries 1−4), 1,10-phenanthroline turned out to be the best in current radical cyclization of 1-(2-iodobenzyl)-1*H*-indole (**1a**). Without additive, the reaction could not occur (entry 5). We also investigated other bases, such as lithium *tert*-butoxide, sodium *tert*-butoxide, and potassium hydroxide, but they were ineffective for the radical cyclization (entries 6−8). Using chlorobenzene as solvent, yield improved from 48% to 62% (entry 1 vs 9). Finally, using 10 mol % **L1** (1,10-Phen) and 2.0 equiv of potassium *tert*-butoxide in the presence of chlorobenzene at 90 °C for 24 h afforded the optimal yield (83%, entry 13).

Table 1. Reaction Conditions



1a 2a

entry	L	x	base	y	M	2a (%)[b]
1	**L1**	0.4	^{t}BuOK	4.0	0.1	48
2	**L2**	0.4	^{t}BuOK	4.0	0.1	0
3	**L3**	0.4	^{t}BuOK	4.0	0.1	47
4	**L4**	0.4	^{t}BuOK	4.0	0.1	47
5	–	–	^{t}BuOK	4.0	0.1	0
6	**L1**	0.4	^{t}BuONa	4.0	0.1	-
7	**L1**	0.4	^{t}BuOLi	4.0	0.1	0
8	**L1**	0.4	KOH	4.0	0.1	0
9[c]	**L1**	0.4	^{t}BuOK	4.0	0.1	62
10[c]	**L1**	0.4	^{t}BuOK	2.0	0.1	70
11[c]	**L1**	0.4	^{t}BuOK	2.0	0.05	75
12[c]	**L1**	0.1	^{t}BuOK	2.0	0.05	74
13[c,d]	**L1**	0.1	^{t}BuOK	2.0	0.05	83

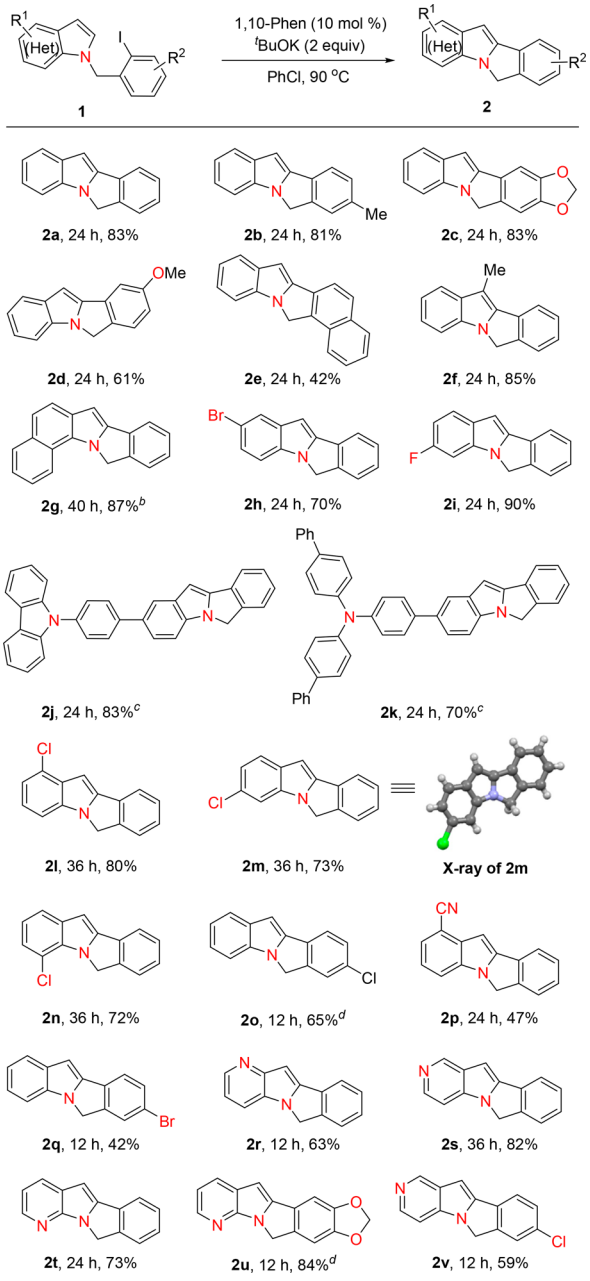


L1 L2 L3 L4

[a]Conditions: **1a** (0.5 mmol), **L** (*x* mol %), base (*y* mol %), 90 °C, toluene, argon, 12 h. [b]Determined by ^{1}H NMR using dibenzyl ether as internal standard. [c]PhCl instead of toluene as solvent. [d]For 24 h.

After establishing the standard reaction conditions, the substrate scope of radical cyclization was then investigated. Several *N*-(2-iodobenzyl) indoles bearing an electron -donating group on the benzyl group have been subjected to the standard conditions, and generally good yields were obtained (Scheme 2, **2b**−**2d**). The effect of substituted groups on the indole was also investigated (Scheme 2, **2f**−**2v**). High yields were achieved with *N*-(2-iodobenzyl) indoles bearing both electron-donating groups and electron-withdrawing groups except that when 4-CN indole was employed **2p** was obtained in moderate yield. Bromide, chloride, and fluoride are tolerated

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.5 mmol), 1,10-Phen (10 mol %), ^{t}BuOK (1 mmol), PhCl (10 mL), 90 °C, under argon. [b]PhCl (5 mL). [c]^{t}BuOK (1.5 mmol). [d]^{t}BuOK (1.25 mmol), 100 °C.

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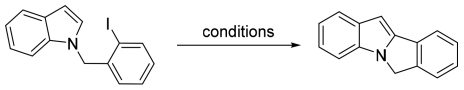
though there are competing dehalogenation reactions (**2h−i**, **2l−o**, **2q**, **2v**).

A comparison of the optimized transition-metal-free reaction conditions with previously reported Pd-catalyzed methods, which was successful in intermolecular C−H arylation, was investigated using **1a** as model substrate (Table 2). However, poor yields were obtained using Pd-catalysts in previous reports.[15−17]

Table 2. Comparison of Catalyst Systems[§]

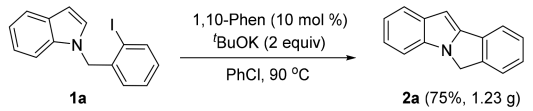


1a **2a**

entry	conditions	**2a** (%)[e]	ref
1[a]	1,10-Phen/^{t}BuOK/90 °C	83	this work
2[b]	$Pd(OAc)_2$/PPh_3/MgO/150 °C	6	15
3[c]	$Pd(OAc)_2$/PPh_3/ Et_3N/100 °C	21	16
4[d]	$Pd(OAc)_2$/Et_3N/80 °C	49	17

[§]Reaction conditions: [a]**1a** (0.5 mmol), 1,10-Phen (10 mol %), ^{t}BuOK (1 mmol), PhCl (10 mL), 24 h, 90 °C, under argon. [b]**1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %), MgO (1.2 equiv), dioxane, DMF, 12 h, 150 °C, under argon. [c]**1a** (0.5 mmol), $Pd(OAc)_2$ (6 mol %), PPh_3 (6 mol %), Et_3N (2.0 equiv), DMF, 5 h, 100 °C, under argon. [d]**1a** (0.5 mmol), $Pd(OAc)_2$ (30 mol %), Et_3N (3.0 equiv), CH_3CN, 40 h, 80 °C, under argon. [e]Isolated yield.

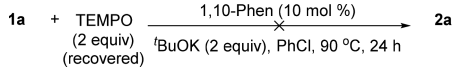
A gram-scale synthesis of **2a** is demonstrated in eq 1. In a typical procedure,[18] 1.23 g of **2a** was obtained in 75% as a white solid.



1a **2a** (75%, 1.23 g) (1)

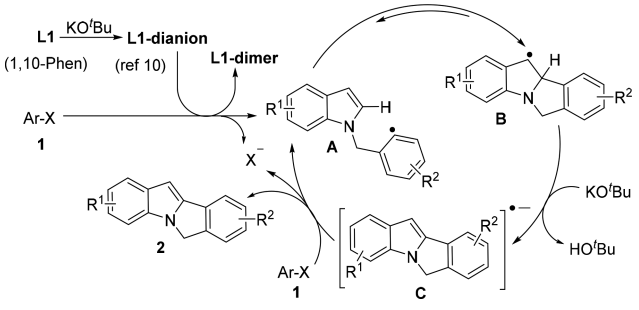
A radical process of this cyclization was confirmed by radical trapping experiments. Radical scavengers such as TEMPO totally inhibit the cyclization of **1a** to **2a** (Scheme 3). TEMPO was recovered quantitatively after the control reaction, indicating TEMPO was not destroyed by KO^{t}Bu.

Scheme 3. Radical Trapping Experiments



A proposed mechanism is illustrated in Scheme 4 on the basis of former reports.[8,10,13,14] The reaction of 1,10-Phen and ^{t}BuOK generates an electron donor **L1-dianion** with the formation of **A**, followed by the intramolecular radical addtion to afford intermediate **B**.[10] The deprotonation of radical **B** affords radical anion **C**. The SET between **C** and **1** yields target product **2** with the regeneration of radical **A**.

Scheme 4. Possible Mechanism



In conclusion, an efficient radical C−H functionalization of C2 on *N*-(2-iodobenzyl) indoles has been developed with the assistant of 1,10-phenanthroline in the presence of potassium *tert*-butoxide. A variety of substituted 6*H*-isoindolo[2,1-*a*]-indoles were prepared by this simple intramolecular cyclization. This strategy provides a fast and versatile access to isoindolo[2,1-*a*]indole derivatives. We anticipate that this approach could be applied in other organic transformations, especially in a transition-metal-free radical process for the synthesis of pharmaceuticals and EL materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03449.

Experimental procedures and NMR spectra (PDF)

Accession Codes

CCDC 1875985 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) Typical procedure: **1a** (8 mmol, 2.67 g), 1,10-phenanthroline (0.8 mmol, 144 mg) and ^{t}BuOK (16 mmol, 1.79 g) were weighed directly into a Schlenk tube and dried under high vacuum for 15 min, followed by the addition of PhCl (160 mL). The resulting reaction mixture was stirred at 90 °C and monitored by TLC. The reaction was quenched by H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated and purified on silica gel chromatography with petroleum ether/CH_2Cl_2/EtOAc (100:20:1) to yield 1.23 g of **2a** in 75% as a white solid.

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