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REGULAR ARTICLE

Recycled Pb/C-catalyzed one-pot synthesis of 1-carbonyl-1*H*-indoles from 2-iodoanilines and calcium carbide

ZHICAI ZHAO
Department of Chemical and Environmental Engineering, Hebei Chemical and Pharmaceutical College, Shijiazhuang 050026, Hebei, People's Republic of China
E-mail: zhaozhicai2021@126.com

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Abstract. A series of 1-carbonyl-1*H*-indoles were prepared by 2-iodoanilines and calcium carbide in a one-pot reaction catalyzed by recyclable10% Pb/C, resulting in the corresponding substituted indoles in good yields. This protocol offers several advantages, including the utilization of sustainable, low-cost calcium carbide, an easy-to-handle acetylene source, and recyclable Pb/C catalysts.

Keywords. One-pot synthesis; 2-iodoanilines; recycle; Pb/C; calcium carbide.

1. Introduction

Indole, the most widely employed nitrogen-containing hetero ring in medicinal chemical compounds and natural products (Scheme 1), was initially obtained by the reduction of indigo in 1866 by Adolf von Baeyer. Indole compounds find diverse applications in chemical, material, pesticide, and other fields, particularly in biomedicine, where indole derivatives exhibit structural diversity and serve as crucial sources of bioactive molecules and lead compounds. In order to make drugs active, an abundance of indole ring structures are introduced in drug design, which enriches the development of a wide range of synthetic methods.[1] The Fischer indole synthesis is the most common method for indole synthesis. However, this approach needs prefabricated arylhydrazine raw materials and reacts under strong acidic conditions.[2–8] In order to explore the synthesis of key heterocycles for indole development, modern chemical research has shifted its focus to the use of transition metal catalytic methods, which can selectively catalyze the synthesis of the required indole rings, while tolerating a variety of functional groups. Among the transition metal catalysts, palladium is the most well-studied and employed metal for the construction of indole skeletons.[9–28]

Alkyne compounds are used in the synthesis of indole because of their rich variety and versatile reactivities.[29–33] Among the established synthetic methods, Larock indole synthesis[12,34–37] (Scheme 2A) is a common method used in the laboratory, which generates the Larock indole skeletons from 2-haloanilines and internal alkynes catalyzed by palladium catalyst.[38–45] Although, this method greatly expands the synthesis of indole structures, however, there is a need of prefunctionalized terminal alkynes. In 2008, Lebel's team successfully developed a multicomponent one-pot synthesis of 2, 3-disubstituted indoles by using cheap, readily available and stable 2-iodobenzoic acid as the starting material (Scheme 2B).[46,47] However, this protocol has limitations, with the main drawback being the use of explosive sodium azide as the aminating agent. In 2013, Zhang's group[27] (Scheme 2C) used palladium and copper as co-catalysts to catalyze the reaction of *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates and a variety of alkynes to synthesize indole. In 2018, Hu's group[22] (Scheme 2D) synthesized the indole ring structure, using *tert*-butyl ((2-iodobenzoyl) oxy) carbamate as the initial raw material coupled with alkynes, and further decarboxylated/cyclized. In 2019, Hoarau's group[28] (Scheme 2E) achieved the synthesis of indoles via the intermolecular cyclization framework from ortho iodoallenamide incorporated with

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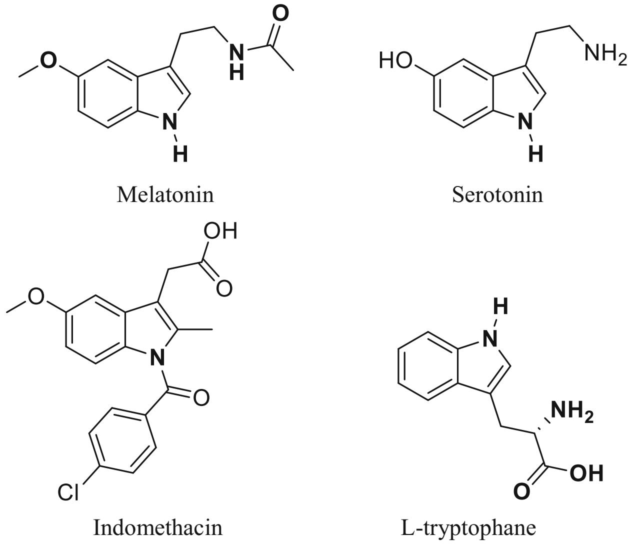


Scheme 1. Drugs containing indole unit.

alkynyl carboxylic acids. However, the reactions of Zhang's group, Hu's group, and Hoarau's group could be limited in scope due to the preparation of commercially unavailable substrates and their uneconomical nature. Additionally, an acetylene source is required for these reactions. Acetylene, a gas at atmospheric pressure, which is inflammable, explosive and difficult to handle, was used as the original source for pre-synthesis. In 2022, Sarkar and his team reported (Scheme 2F) gold(I)-catalyzed synthesis of heterocycles via allene oxide from propargylic alcohols. This method offered significant advantages such as being acetylene-free, and the substrate itself having an acetylene unit. However, substrate synthesis still requires the use of carbide, as well as the use of the precious metal gold.[28]

Calcium carbide is a sustainable, cost-effective, readily available, and safe-to-store solid material with stable non-toxic properties, making it easy to handle in experiments. Historically, it has primarily served as a raw material for producing hydrolyzed acetylene gas in the chemical industry. Over the last decade, there has been an increasing number of reports on the direct utilization of calcium carbide as a substitute for acetylene in various synthetic transformations.[48–70] Our research group[71,72] made great efforts to investigate the direct application of calcium carbide in organic synthesis, and reported the results of one-pot synthesis of unsymmetrical 1,3-butadiyne derivatives by using calcium carbide instead of acetylene raw materials, and direct synthesis of unsymmetrical 1,3-butadiynes from calcium carbide and aryl iodides. In 2022, Li's group[73] reported an efficient method for the construction of 1-sulfonyl-1*H*-indoles by the reactions of *N*-(2-iodoaryl)sulfonamides with calcium carbide. This protocol uses inexpensive and easy-to-handle solid alkyne source instead of flammable and explosive gaseous acetylene, cheap and readily available starting materials. However, this method uses expensive $Pd_2(dba)_3$ as the catalyst, and requires prefabricated raw material, which increases the operation procedure.

Palladium on carbon (Pd/C), a heterogeneous catalyst system for the hydrogenation reaction, various kinds of carbon–carbon,[74–77] carbon–nitrogen[78,79] bond forming reactions have recently been explored. Among them, 2-substituted indole can be synthesized from monosubstituted alkynes using commercial heterogeneous palladium as a catalyst.[80–82] Pd/C, as an air-stable, recoverable, recyclable, cheaper than other traditional Pd-complexes and salt, easily separable (from the product), and convenient to store and handle, has drawn our attention to extrapolate the course of our ongoing research work. As an extension of our group's research on calcium carbide as an alternative acetylene source, we try to directly synthesize 1-carbonyl-1*H*-indoles by using calcium carbide as an acetylene source, recycled Pb/C as the catalyst, 2-iodoaniline, Boc_2O as starting materials through a one-pot procedure to try a new method of "upgraded Larock indole synthesis".

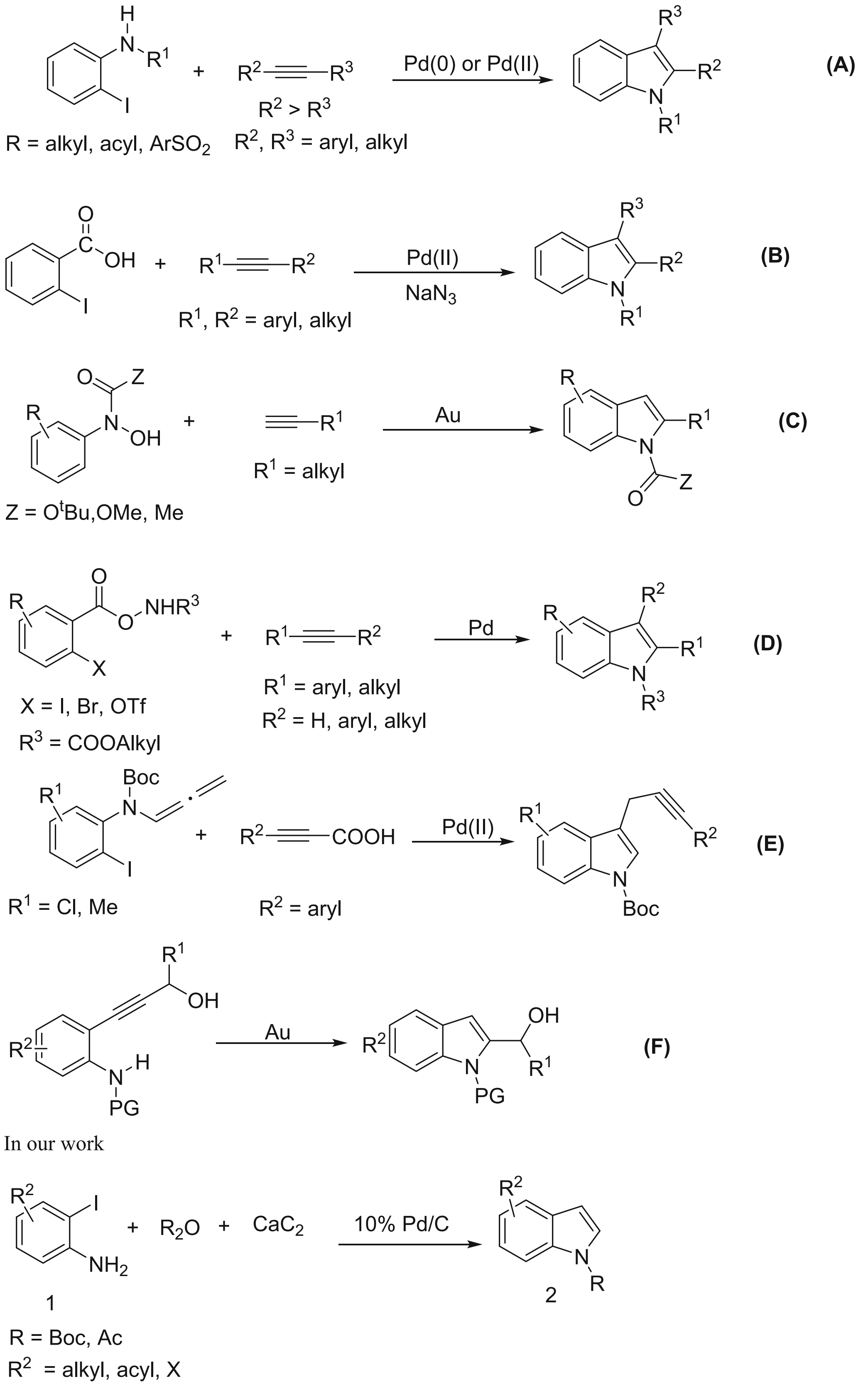
2. Experimental

2.1 *Materials and methods*

All chemicals and solvents were obtained from the commercial providers (Aladdin and Bokachem, China) and used without further purification. Reactions were monitored by Agilent GC Series 6890N and GCMS 7890A. Infra-red spectra were recorded on a Perkin-Elmer Spectrum One FT-IR. Flash column chromatography was performed on silica gel 60 (particle size 200–400 mesh ASTM, purchased from Aladdin, China). Melting points were determined using Fisatom 430D equipment. All compounds were further characterized by ^1H, and ^{13}C NMR spectra were measured with a Bruker ACF400 in $CDCl_3$.

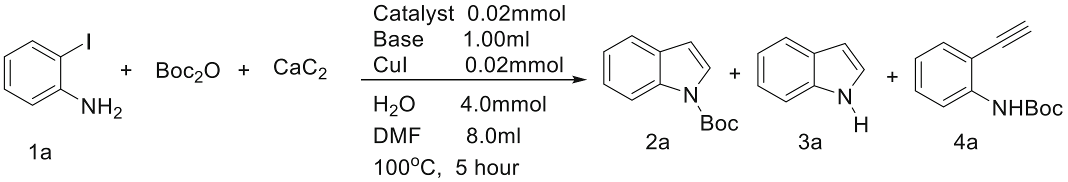
2.2 *General synthetic procedure*

2-iodoaniline (0.5 mmol), $N(^iPr)_2H$ (1.0 ml) and Boc_2O (0.6 mmol) in EtOH (5ml) was gradually added



Scheme 2. The construction of *N*-Boc indoles from alkyne.

Table 1. Optimization of 1-Boc-1*H*-indoles coupling reaction[a].



Entry	Catalyst	Base	Yield[b] 2a	3a	4a
1	$Pd(PPh_3)_4$	TEA	25	0	0
2	$Pd_2(PPh_3)_2Cl_2$	TEA	57	10	6
3	$Pd(OAc)_2$	TEA	48	0	12
4	10% Pd/C,$(4\text{-MeO-Ph})_3P$	TEA	41	0	0
5[c]	10% Pd/C,$(4\text{-MeO-Ph})_3P$	TEA	45	0	0
6[d]	10% Pd/C,$(4\text{-MeO-Ph})_3P$	TEA	49	0	0
7	10% Pd/C,$(4\text{-MeO-Ph})_3P$	$N(^iPr)_2H$	56(54)	0	0
8	10% Pd/C,$(4\text{-MeO-Ph})_3P$	DBU	62	10	0
9	10% Pd/C,$(4\text{-MeO-Ph})_3P$	DABCO	14	15	3
10	10% Pd/C,$(4\text{-MeO-Ph})_3P$	KOAc	0	0	63
11	10% Pd/C,$(4\text{-MeO-Ph})_3P$	NaOAc	0	0	59
12	10% Pd/C,$(4\text{-MeO-Ph})_3P$	K_2CO_3	9	0	65
13	10% Pd/C,$(4\text{-MeO-Ph})_3P$	Na_2CO_3	31	20	7
14	10% Pd/C,$(4\text{-MeO-Ph})_3P$	Cs_2CO_3	14	25	3

[a] Reaction conditions: 2-Iodoaniline (0.5 mmol), Boc_2O (0.5 mmol), CaC_2 (1.0 mmol), H_2O (4.0 mmol), 10% Pd/C (0.02 mmol), $(4\text{-MeO-Ph})_3P$ (0.04 mmol), CuI (0.02 mmol), TEA (1.0 ml), DMF (8.0 ml), 100 C, 5 hours.

[b] GC yields calibrated against tridecane as an internal standard; the isolated yields are given in parentheses.

[c] 10% Pd/C (0.03 mmol), $(4\text{-MeO-Ph})_3P$ (0.06 mmol), CuI (0.05 mmol).

[d] 10% Pd/C (0.05 mmol), $(4\text{-MeO-Ph})_3P$ (0.10 mmol), CuI (0.05 mmol).

to the three-neck round-bottom reaction flask, then stirred at 25°C for 2 h. The reaction was monitored by GC. After the reaction was complete, without any processing, CaC_2 (1.5 mmol), H_2O (2.0 mmol), 10% Pd/C (0.05 mmol), $(4\text{-MeO-Ph})_3P$ (0.10 mmol), CuI (0.05 mmol) and NMP (3.0 ml) were added to the reaction flask again, and the reaction temperature was increased to reflux. Then 2.0 mmol of water was added again after reflux to maintain the reaction for 4 hours, and the reaction temperature was maintained for 2 hours. After the reaction was complete, the resulting mixture was cooled down to room temperature and added to water. The resulting mixture was filtered to remove the Pd/C (no processing, can be recycled), and the liquor was extracted with ethyl acetate (3×30 ml), and washed with saturated brine (3×30 ml). The resulting organic phase was dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was isolated by flash column chromatography using petroleum ether/ethyl acetate as eluent to give the pure products.

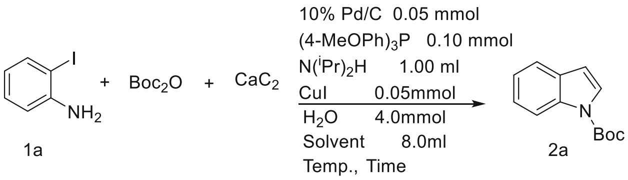
2.3 *Activation of palladium–carbon catalyst*

First, stir with 5 times the amount (weight/volume) 2 N hydrochloric acid at room temperature for 30 min; stew for 30 min and then filter; filter cake was washed with purified water to neutral (pH = 7); drain and dry at low temperature. Then, reflux with 5 times the amount (weight/volume) ethanol for 2 hours and then dry for the second time.

3. Results and discussion

Initially, we examined the catalytic activity of the different Pd catalysts for the synthesis of *N-tert*-butoxycarbonyl-indoles starting from 2-iodoaniline (0.5 mmol), Boc_2O (0.5 mmol) and CaC_2 (1.0 mmol). The same reaction conditions {H_2O (4.0 mmol), 10% Pd/C (0.02 mmol), $(4\text{-MeO-Ph})_3P$ (0.04 mmol), CuI (0.02 mmol), TEA (1.0 ml), DMF (8.0 ml), 100°C, 5 hours} were applied for all substrates. The results are summarized in Table 1.

Table 2. Optimizing the reaction conditions[a].



Entry	Solvent	Boc$_2$O	CaC$_2$/H$_2$O	Temperature	time	Yield(%)[b]
1	DMF	0.4	1:4	100	5	41
2	DMF	0.6	1:4	100	5	65
3	DMF	0.7	1:4	100	5	62
4	DMA	0.6	1:4	100	5	64
5	DMSO	0.6	1:4	100	5	69
6	NMP	0.6	1:4	100	5	73
7	DMPU	0.6	1:4	100	5	55
8	2-Me-THF	0.6	1:4	100	5	5
9	1,4-Dioxane	0.6	1:4	100	5	2
10	EtOH	0.6	1:4	100	5	14
11	NMP/EtOH (6:2)	0.6	1:4	100	5	75
12	NMP/EtOH (3:5)	0.6	1:4	100	5	83
13	NMP/EtOH (2:6)	0.6	1:4	100	5	79
14	NMP/EtOH (3:5)	0.6	0.5:4	100	5	71
15	NMP/EtOH (3:5)	0.6	1.5:4	100	5	87
16	NMP/EtOH (3:5)	0.6	2.0:4	100	5	84
17	NMP/EtOH (3:5)	0.6	1.5:4	Reflux	5	90
18	NMP/EtOH (3:5)	0.6	1.5:4	80	5	69
19	NMP/EtOH (3:5)	0.6	1.5:4	Reflux	8	93(91)
20	NMP/EtOH (3:5)	0.6	1.5:4	Reflux	6	91

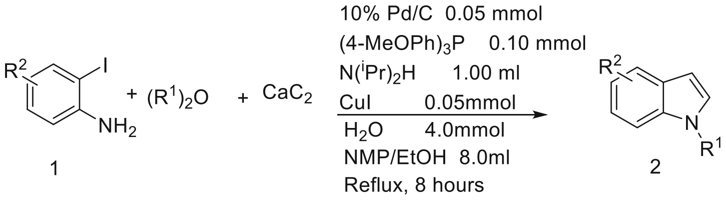
[a] Reaction conditions: 2-Iodoaniline (0.5 mmol), Boc$_2$O (0.6 mmol), CaC$_2$ (1.0 mmol), H$_2$O (4.0 mmol), 10% Pd/C (0.05 mmol), (4-MeO-Ph)$_3$P (0.10 mmol), CuI (0.05 mmol), N(^{i}Pr)$_2$H (1.0 ml), Solvent (8.0 ml).

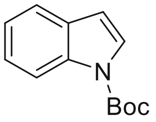
[b] GC yields calibrated against tridecane as an internal standard, the isolated yields are given in parentheses.

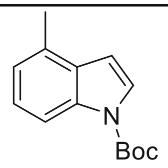
The initial attempt using Pd(PPh$_3$)$_4$ as the palladium catalyst and triethylamine as the base yielded the corresponding product *N*-*tert*-butoxycarbonyl-indoles (**2a**) in 25% yield (Table 1, entry 1). Pd$_2$(PPh$_3$)$_2$Cl$_2$ showed high catalytic activities (Table 1, entry 2), gave a mixture of indole (**3a**) and *N*-acetyl-2-(1-hexynyl)aniline (**4a**). Pd(OAc)$_2$ as catalyst affording *N*-*tert*-butoxycarbonyl-indoles **(2a)** in 48% yield (Table 1, entry 3) along with an amount of the competing *N*-acetyl-2-(1-hexynyl)aniline product **(4a)**. 10% Pd/C with (4-MeO-Ph)$_3$P phosphate ligand played a key catalytic role in the reaction, and the reaction gave 41% yield of product 2a (Table 1, entry 4). The optimum effect was achieved when the ratio of catalyst to ligand was increased to 0.05 to 0.10 (Table 1, entries 4–6). Various bases, such as TEA, N(^{i}Pr)$_2$H, DBU, DABCO, KOAc, NaOAc, K$_2$CO$_3$, Na$_2$CO$_3$ and Cs$_2$CO$_3$ were also tested for the reaction (Table 1, entries 6–14). Replacing triethylamine by N(^{i}Pr)$_2$H afforded satisfactory results (Table 1, entry 7), while other organic bases and all inorganic bases showed poor reactivity (Table 1, entries 8–14).

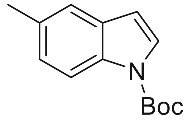
A systematic increase in the equivalent amount of Boc$_2$O resulted in an enhanced yield of **2a** (Table 2, entries 1–3). Similar yields were obtained with Boc$_2$O amounts ranging from 0.5 to 0.7 equivalents, whereas 0.4 equivalents of Boc$_2$O yielded sluggish results (Table 2, entry 1). In addition, the choice of solvents was also quite important. It was observed that calcium carbide nearly did not participate in the reaction under PhMe, EtOH, and THF because of the poor solubility for calcium carbide (Table 2, entries 8–10). In contrast, DMF, DMA, DMSO, NMP and DMPU (Table 2, entries 2, 4–7) were practicable solvents, and the ratio of mixed solvent NMP to EtOH is 3 to 5 and was proved to be the best choice in this reaction system, which could provide **2a** in 83% yield (Table 2, entry 12). Moreover, the amount of calcium carbide and

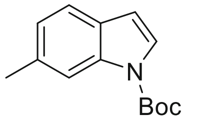
Table 3. Synthesis of 1-carbonyl-1*H*-indoles by Pd/C-catalyzed the 2-iodoaniline, Boc_2O and CaC_2.[ab]

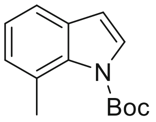


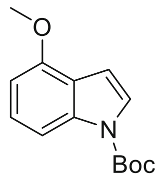

2a, 91%

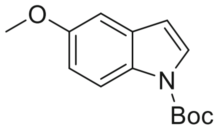

2b, 79%

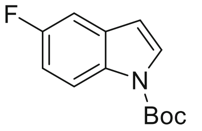

2c, 89%

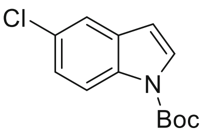

2d, 85%

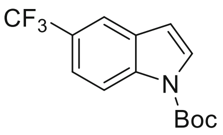

2e, 82%

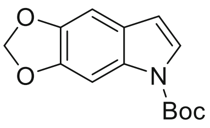

2f, 76%

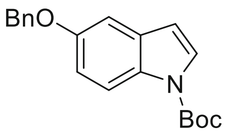

2g, 85%

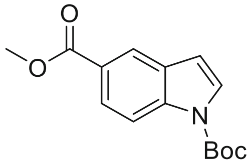

2h, 89%

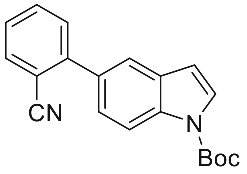

2i, 90%

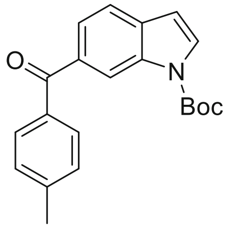

2j, 86%

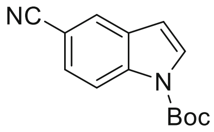

2k, 86%

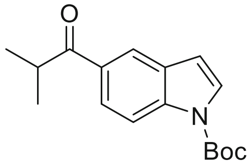

2l, 83%

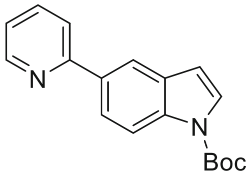

2m, 84%

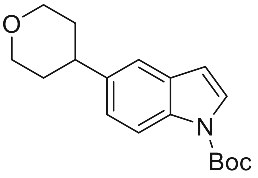

2n, 82%

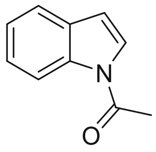

2o, 79%


2p, 87%


2q, 82%


2r, 86%


2s, 83%


2t, 82%

[a] Reaction conditions: 1 (0.5 mmol), Boc_2O (0.6 mmol), CaC_2 (1.5 mmol), H_2O (4.0 mmol),10% Pd/C (0.05 mmol), $(4\text{-MeO-Ph})_3P$ (0.10 mmol), CuI (0.05 mmol), $N(^iPr)_2H$ (1.0 ml), NMP/EtOH (3:5) (8.0 ml), at reflux.

[b] The isolated yields.

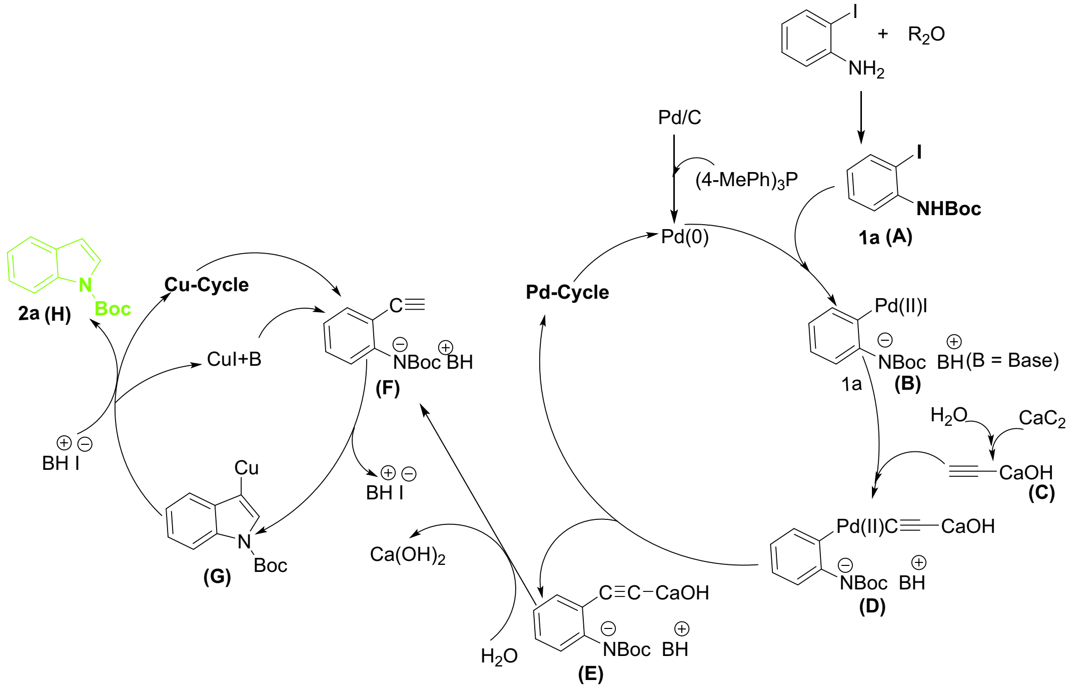
water could also affect the yield of the reaction (Table 2, entries 14–16), and a total of 3 equivalents of calcium carbide and 8 equivalents of water based on **1a** is an appropriate amount for the reaction. Any increase or decrease in the amounts of calcium carbide and water led to a drop in yield (Table 2, entry 15). Finally, we also investigated the effects of reaction temperature and reaction time. On rising the temperature to 120°C, the yield actually showed an improvement to 90% (Table 2, entry 17). Lowering of

Table 4. The catalytic efficiency of reusable catalysts.[a]

Entry	10% Pd/C	Reaction time (hour)	Yield (%)[b]
1	Fresh-2	8	93
2	Recycled 1 time (First activation)	10	90
3	Recycled 2 times (Second activation)	12	88
4	Recycled 3 times (Third activation)	24	87
5	Recycled 4 times (Fourth activation)	36	65
6	Recycled 5 times (Fifth activation)	60	51

[a]Reaction conditions: 2-iodoaniline (0.5 mmol), Boc_2O (0.6 mmol), CaC_2 (1.5 mmol), H_2O (4.0 mmol), 10% Pd/C (0.05 mmol), $(4\text{-MeO-Ph})_3P$ (0.10 mmol), CuI (0.05 mmol), $N(^iPr)_2H$ (1.0 ml), NMP/EtOH (3:5) (8.0 ml), at reflux.

[b]GC yields calibrated against tridecane as an internal standard.



Scheme 3. Proposed mechanism.

the temperature to 80°C, however, resulted in a drop in yield. The optimal time was determined to be 8h.

Under the optimized reaction conditions, we tried to use various 2-iodoanilines as the reaction substrate to test the universality and scope of application of this methodology, and the research results were summarized in Table 3. In the process of the experiment, it was found that the effect of two-phase reaction and reaction in the same reaction pot after two steps was unexpectedly good, a variety of 2-iodoanilines were used as raw materials to generate a series of corresponding1-carbonyl-1*H*-indoles products, and the yield was very high. Both electron donating groups or electron withdrawing groups were well tolerated. The R^2 could be 2-iodoaniline groups optionally substituted, such as electron donating groups Me (entries 2b–2e), OMe (entries 2f and 2g), or electron withdrawing groups F (entry 2h), Cl (entry 2i), CF_3 (entry 2j). The R^2 could also be functional groups such as ether (entries 2k, 2l and 2s), cyanide (entries 2n and 2p), ester (entry 2m), ketone (entries 2o and 2q) etc., or heterocyclic group (2r). Finally, we extended the *N*-substituent group to the acetyl group, obtaining *N*-acetyl-indoles in an 82% yield.

In addition to the use of readily available CaC_2 as an alternative raw material for acetylene, another important finding is that Pd/C catalysts can be reused in this study. The Pd/C catalyst at the end of the reaction was separated by funnel filter and then washed with EtOH, and activated (see the supporting information for details). The results show that the activated catalyst has better reaction activity, shorter reaction time and higher yield than the unactivated catalyst. Although the catalyst can still be used after four cycles, the reaction time should be significantly extended if satisfactory yield is to be obtained.

The experimental results of reuse were summarized in Table 4. While the catalytic activity of the recovered Pd/C catalyst was inferior to that of the fresh catalyst, it still exhibited good activity for the indole ring synthesis reaction. However, it should be noted that the drawback is the longer reaction time compared to that of the fresh Pd/C catalyst. The more times the catalyst was recovered, the longer the reaction time was required to achieve satisfactory catalytic yield.

To explore the possible mechanism, the reaction was initiated with the acylation of 2-iodoaniline, forming the initial compound **A**. Meanwhile, it was followed by the formation of aryl palladium iodides **B** by the oxidative addition of **A** to Pd(0), generated by the reaction of Palladium/carbon with $(4\text{-MePh})_3P$[83] (Scheme 3). At the same time, calcium carbide was gradually and slowly hydrolyzed to form calcium acetylene hydroxide **C**,[84] which then reacted with the intermediate **B**, and the resulting product **D** underwent reducing to eliminate the loss of palladium (0) and converted to calcium arylacetylene hydroxides **E**, whose subsequent hydrolysis provided aryl acetylenes **F**.[85,86] Aryl acetylenes reacted with CuI to produce Cu(I) *N-tert*-butylcarbonyl indole complexes **G**, which finally produced the target *N-tert*-butylcarbonyl indole **H** and released the Cu(I) species.

4. Conclusion

In summary, an effective method was successfully developed to obtain indole and its derivatives by the reaction of the various of 2-iodoanilines with calcium carbonate in a Pd/C catalytic system. This protocol facilitates the easy synthesis of essential indole units under laboratory conditions. The use of recycled Pd/C catalyst, along with the utilization of cheap calcium carbide as a sustainable and economical acetylene gas replacement, contributes to making this a highly attractive reaction.

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