Palladium on carbon-catalyzed synthesis of 2- and 2,3-substituted indoles under heterogeneous conditions†

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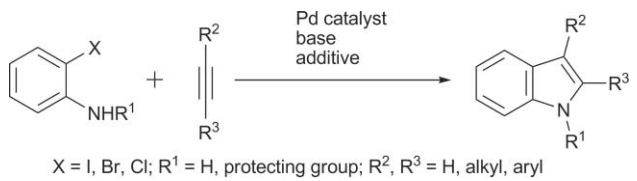
A mild, efficient and LiCl-free synthetic method for indole derivatives based on the heteroannulation of alkynes with 2-iodoanilines was achieved using palladium on carbon (Pd/C) and NaOAc in heated NMP. The *N*-tosyl protection of 2-iodoaniline expedited the reaction progress, while other protecting groups, such as *tert*-butoxycarbonyl, acetyl, and benzyloxycarbonyl groups, underwent deprotection under the present conditions. A variety of di- and monosubstituted alkynes could effectively react with *N*-tosyl-2-iodoaniline to give the corresponding indoles in good to high yields.

Introduction

The indole nucleus is one of the most prevalent heterocyclic structural motifs found in biologically active compounds from either natural or artificial origin.[1] A variety of synthetic methods to build the indole ring system has been developed for over a hundred years,[1,2] and the palladium-catalyzed annulation of 2-haloanilines with alkynes, in particular, is of great importance due to the availability of substrates, the tolerance of a wide range of functionalities, and a simple one-pot procedure (Scheme 1).[3–10] Monosubstituted alkynes were first used for the annulation in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and Et_3N by Yamanaka to directly afford the corresponding 2-substituted indole derivatives through a domino Sonogashira coupling–cyclization process,[3,4] while Larock used disubstituted alkynes together with $Pd(OAc)_2$, LiCl, and K_2CO_3 to obtain 2,3-disubstituted indoles in a highly regioselective manner.[5,6] Such annulation reactions have been successfully applied to the synthesis of azaindoles,[7] tryptophan derivatives,[8] bioactive materials,[9,10] and natural products.[10]



Scheme 1 Palladium-catalyzed annulation of 2-haloaniline derivatives with alkynes.

The use of heterogeneous catalysts has recently been investigated in a variety of organic chemical fields from sustainable and industrial standpoints due to their air-stability, recoverability, reusability, and avoidance of residual metals in the desired products.[11] Palladium on carbon (Pd/C), which has been most commonly used as a heterogeneous hydrogenation catalyst,[12] was recently utilized for various kinds of carbon–carbon,[13,14] carbon–nitrogen,[15] and carbon–oxygen[16] bond forming reactions.

There are a few reports of 2-substituted indole syntheses from monosubstituted alkynes using non-commercially heterogeneous palladium[17,18] or palladium–copper[19] catalysts together with LiCl as an additive, and only Djakovitch's method does not require the addition of LiCl.[18,19] During the preparation of this manuscript, an attractive annulation method using disubstituted alkynes catalyzed by heterogeneous palladium species including Pd/C was reported as a communication.[20]

In this paper, we describe an efficient and general protocol for the LiCl-free Pd/C-catalyzed Yamanaka–Larock indole synthesis using 2-iodoaniline derivatives and mono- or disubstituted alkynes. The use of the base and alkyne were successfully reduced.

Results and discussion

We first investigated the 10% Pd/C-catalyzed Larock annulation using various *N*-substituted 2-iodoanilines and 2 equiv of diphenylacetylene in the presence of 1 equiv of LiCl and 5 equiv of Na_2CO_3 in heated 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (Table 1). Without the *N*-substituent, the reaction proceeded to give the corresponding 2,3-diphenylindole (**3**), and the yield was improved to 67% by increasing the temperature from 100 °C to 120 °C (Entries 1 and 2). When *N*-Boc-2-iodoaniline (**1b**) was used as the substrate, the complete deprotection of the Boc moiety was observed, and the corresponding non-*N*-substituted indole **3** was obtained in 77% yield as the sole product at 120 °C (Entry 4). The *N*-acetyl and *N*-Cbz protective groups of 2-iodoanilines (**1c** and **1d**) were also found to be labile under the present conditions (Entries 5 and 6). To avoid the removal of the substituents, *N*-tosyl-2-iodoaniline (**1e**) was chosen as the substrate.[21] Thus, the annulation proceeded without decomposition of the tosylamide moiety (Entry 7), and the desired *N*-tosylindole (**2e**) was afforded in quantitative yield at 120 °C (Entry 8).

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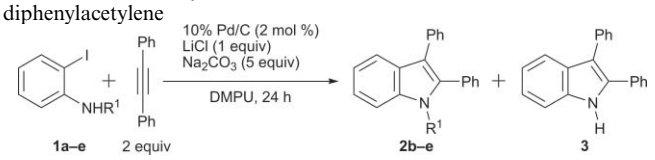
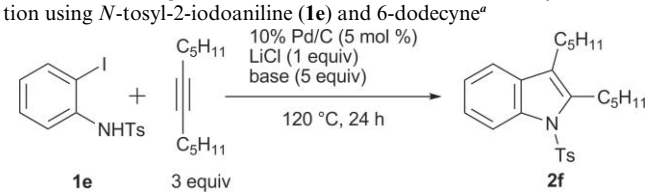
Table 1 Pd/C-catalyzed annulation of *N*-substituted 2-iodoanilines and diphenylacetylene



Entry	R^1	Temp./°C	Yield (%) 2	3
1	H (**1a**)	100	—	46
2	H (**1a**)	120	—	67
3	Boc (**1b**)	100	55 (**2b**)	34
4	Boc (**1b**)	120	0	77
5	Ac (**1c**)	100	15 (**2c**)	33
6	Cbz (**1d**)	100	0	64
7	Ts (**1e**)	100	46 (**2e**)	0
8	Ts (**1e**)	120	100 (**2e**)	0

Table 2 Screening of bases and solvents for the Pd/C-catalyzed annulation using *N*-tosyl-2-iodoanaline (**1e**) and 6-dodecyne[a]

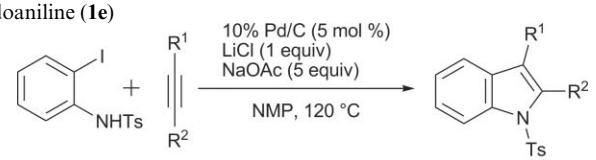


Entry	Base	Solvent[a]	Yield (%)[b] 2f	Recovered **1e**
1	Na_2CO_3	DMPU	—[c]	0
2	K_2CO_3	DMPU	18	0
3	Cs_2CO_3	DMPU	17	70
4	$Na_3PO_4{\cdot}12H_2O$	DMPU	25	69
5	KOAc	DMPU	100	0
6	KOAc	DMF	100	0
7	$NaHCO_3$	DMPU	65	0
8	$NaHCO_3$	DMF	98	0
9	$NaHCO_3$	DMF[d]	100	0
10	$NaHCO_3$	NMP	100	0
11	NaOAc	DMPU	100	0
12	NaOAc	DMF	100	0
13	NaOAc	DMF[d]	100	0
14	NaOAc	NMP[d]	100	0
15	NaOAc	DMA[d]	100	0

[a] Reagent grade solvent was used unless mentioned. [b] Isolated yield. [c] The generation of **2f** was observed in the reaction mixture. [d] A commercial anhydrous solvent was used.

We next examined the indole synthesis using **1e** and 6-dodecyne, a dialkylacetylene. Although the formation of the corresponding indole was obtained, it was quite difficult to isolate from the reaction mixture containing byproducts, which were generated by polymerization of the alkynes (Table 2, Entry 1).[22] The base and solvent, therefore, were optimized using 10% Pd/C (5 mol%) and LiCl (1 equiv) to avoid the formation of any intractable byproducts. When K_2CO_3, Cs_2CO_3, or $Na_3PO_4{\cdot}12H_2O$ was used as the base, the desired *N*-tosyl-2,3-dipentylindole (**2f**) was obtained in low yields (Entries 2–4). The reaction was dramatically improved by the use of KOAc in DMPU or DMF, although the polymerization of 6-dodecyne was still observed (Entries 5 and 6). On the other hand, the use of either $NaHCO_3$ or NaOAc led to the clean formation of **2f** (Entries 7–15), and NaOAc could be successfully used in various

Table 3 Pd/C-catalyzed annulation of alkynes with *N*-tosyl-2-iodoaniline (**1e**)



Entry	R^1	R^2	Time/h	Yield (%)[a]
1	Et	Et	24	97 (**2g**)
2	*n*-Pr	*n*-Pr	7	96 (**2h**)
3[b]	*n*-Pr	*n*-Pr	6	90 (**2h**)
4	C_5H_{11}	C_5H_{11}	24	100 (**2f**)
5[b]	C_5H_{11}	C_5H_{11}	3	100 (**2f**)
6[c]	Ph	Ph	8	69 (**2e**)
7[b,c]	Ph	Ph	8	94 (**2e**)
8	H	Ph	12	69 (**2i**)
9[b]	H	Ph	12	70 (**2i**)
10[b]	H	*n*-Bu	2	92 (89 : 11) [d](**2j**)
11	*n*-Bu	Ph	24	90 (72 : 28) [d](**2k**)
12[b]	*n*-Bu	Ph	24	84 (77 : 23) [d](**2k**)
13	Me	Ph	10	84 (64 : 36) [d](**2l**)
14[b]	Me	Ph	2	90 (68 : 32) [d](**2l**)

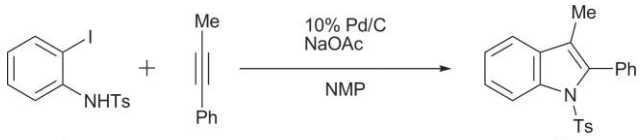
[a] Isolated yield. [b] LiCl was not added. [c] 2.0 equiv of alkynes were used. [d] The ratio of **2** and its regioisomer is indicated in parentheses.

kinds of polar aprotic solvents, such as DMPU, DMF, NMP, and DMA, without any influence of the solvent grades (Entries 11–15).

A wide range of alkynes (3 equiv to **1e**) was examined for the preparation of the indole derivatives using 10% Pd/C (5 mol%), LiCl (1 equiv), and NaOAc (5 equiv) in heated NMP (120 °C). The reactions of symmetrical dialkylacetylenes gave the corresponding 2,3-disubstituted indoles (**2e–2g**) in good to quantitative yields, regardless of the alkyl chain length (Table 3, Entries 1, 2, 4, and 6). Phenylacetylene, a monosubstituted acetylene, was cyclized in a completely regioselective manner to give *N*-tosyl-2-phenylindole (**2i**) as the sole product (Entry 8), while the use of 1-hexyne gave a mixture of regioisomers, *i.e.*, the 2- and 3-butyl-1-tosylindoles in the ratio of 89 : 11 (Entry 10). This result indicates that the pathway for the indole formation from monosubstituted alkynes would be the same as the proposed mechanism for the synthesis of 2,3-disubstituted indoles from the disubstituted alkynes by Larock, which involves the insertion of an alkyne into the arene–palladium bond to form the vinylic palladium intermediate,[5] although the two step process including the Sonogashira coupling process could not be thoroughly excluded (Scheme 2).[3,4,23] Unsymmetrical disubstituted acetylenes, such as 1-phenyl-1-hexyne and 1-phenyl-1-propyne, were also smoothly cyclized, but a complete regioselectivity was not achieved (Entries 11 and 13). During the investigation of the annulation using a variety of alkynes, we found that LiCl was not essential for the efficient reaction progress; the reaction effectively proceeded in the absence of LiCl (Entries 3, 5, 7, 9, 10, 12, and 14).

Decreased amounts of the alkyne, NaOAc, and 10% Pd/C were next investigated using **1e** and 1-phenyl-1-propyne as the substrates from an environmental point of view (Table 4). The amount of the 1-phenyl-1-propyne could be decreased to 1.2 equiv to **1e** without any significant reduction in the indole production, although the reaction progression was significantly delayed (Entries 1 and 2). Lowering the temperature from 120 to

Table 4 Optimization of the LiCl-free conditions

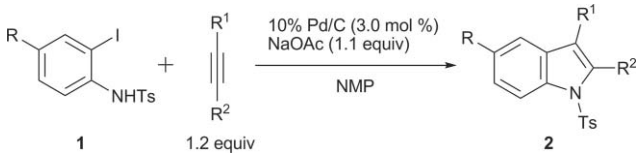


1e **2l**

Entry	Alkyne (equiv)	NaOAc (equiv)	10% Pd/C (mol%)	Temp./°C	Time/h	Yield (%)[a]
1	3.0	5.0	5.0	120	2	90 (68 : 32)
2	1.2	5.0	5.0	120	24	91 (73 : 27)
3	1.2	5.0	5.0	110	24	94 (71 : 29)
4[b]	1.2	5.0	5.0	100	24	56 (62 : 38)
5	1.2	1.5	5.0	110	24	88 (71 : 29)
6	1.2	1.1	5.0	110	24	91 (72 : 28)
7[c]	1.2	1.0	5.0	110	24	84 (71 : 29)
8[d]	1.2	0.7	5.0	110	24	63 (73 : 27)
9	1.2	1.1	4.0	110	24	97 (71 : 29)
10	1.2	1.1	3.0	110	24	99 (70 : 30)
11[e]	1.2	1.1	2.0	110	24	88 (72 : 28)
12[f]	1.2	1.1	1.0	110	24	63 (67 : 33)
13	1.2	1.1	0.5	110	24	0
14	1.2	1.1	3.0	110	8	79 (71 : 29)
15[g]	1.2	1.1	3.0	110	12	100 (73 : 27)

[a] Yield as a mixture of 3-methyl-2-phenyl-1-tosylindole (**2l**) and its regioisomer (2-methyl-3-phenyl-1-tosylindole). The ratio of the regioisomers is indicated in parentheses. [b] **1e** was recovered in 18% yield. [c] **1e** was observed in the TLC analysis. [d] **1e** was recovered in 28% yield. [e] **1e** was recovered in 12% yield. [f] **1e** was recovered in 37% yield. [g] Compounds **2l** and its regioisomer were isolated in 52% and 23% yields, respectively, using preparative TLC.

Table 5 Pd/C-catalyzed annulation using the *N*-tosyl-2-iodoaniline derivatives and alkynes



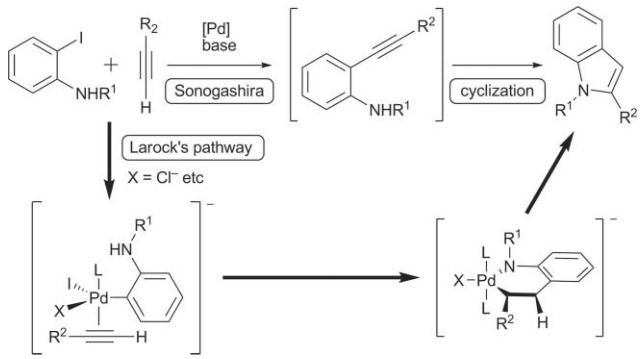
1 1.2 equiv **2**

	N-Ts-2-iodoaniline (**1**)	Alkyne				
Entry	R	R^1	R^2	Temp./°C	Time/h	Yield (%)[a]
1	H (**1e**)	C_5H_{11}	C_5H_{11}	110	12	88 (**2f**)[c]
2	H (**1e**)	C_5H_{11}	C_5H_{11}	120	3	99 (**2f**)
3	H (**1e**)	C_4H_9	C_4H_9	120	6	86 (**2m**)
4	H (**1e**)	*n*-Pr	*n*-Pr	120	24	86 (**2h**)
5[b]	H (**1e**)	Ph	Ph	130	24	87 (**2e**)
6	H (**1e**)	H	4-MeO-Ph	120	24	64 (**2n**)
7	H (**1e**)	H	3-Me-Ph	120	24	72 (**2o**)
8	H (**1e**)	H	4-Me-Ph	120	24	63 (**2p**)
9	H (**1e**)	H	1-naphthyl	120	24	52 (**2q**)
10	H (**1e**)	H	6-MeO-naphth-2-yl	120	5	66 (**2r**)
11	H (**1e**)	H	1-cyclohexenyl	120	24	77 (**2s**)
12	MeO_2C (**1f**)	C_5H_{11}	C_5H_{11}	120	24	70 (**2t**)

[a] Isolated yield. [b] 2 equiv of NaOAc were used. [c] A trace amount of the unchanged **1e** was observed by the TLC analysis.

110 °C gave no change in the reaction efficiency (Entry 3), but a further decrease in the temperature to 100 °C caused an extensive drop in the yield to 56% of **2l** (Entry 4). We next investigated the optimal amounts of NaOAc and 10% Pd/C. NaOAc could be decreased to 1.1 equiv to **1e** (Entries 5 and 6), although the reaction was incomplete using 1.0 or 0.7 equiv of NaOAc (Entries 7 and 8). Furthermore, the reaction efficiently proceeded with 3.0 mol% of 10% Pd/C to afford **2l** in a quantitative yield (Entries 6, 9, and 10), while the use of less than 3.0 mol% of the 10% Pd/C was not sufficient to complete the reaction (Entries 11–13). Furthermore, the reaction using 1.2 equiv of 1-phenyl-1-propyne in the presence of 10% Pd/C (3.0 mol%) and NaOAc (1.1 equiv) at 110 °C was completed within 12 h (Entries 14 and 15). Considering both the reduction of the alkyne and catalyst usage and the reaction time, the Entry 15 conditions was chosen as the appropriate for the present annulation.

Table 5 summarizes the results of the annulation of various alkynes and *N*-tosyl-2-iodobenzene derivatives. When the annulation of **1e** with 6-dodecyne as a symmetrical alkyne was carried out under the optimal reaction conditions as shown in Table 4, Entry



Scheme 2 Proposed reaction pathways for the annulation of the mono-substituted alkyne with 2-iodoaniline.

15 (110 °C), **1e** was not completely consumed (Table 5, Entry 1), although the reaction was completed at 120 °C within 3 h to give **2f** in quantitative yield. Since the reaction progress was slightly influenced by the subtle difference in the alkyne structure, the reactions were performed after minor tuning of the conditions. Symmetrical alkynes were effectively reacted with **1e** to give the corresponding 2,3-disubstituted indoles (**2m**, **2h**, and **2e**) in excellent yields (Entries 3–5). Phenylacetylenes bearing a methyl or methoxy functionality cyclized into the corresponding 2-arylindoles in a completely regioselective manner (Entries 6–8). The reaction of the 1-naphthyl- and 1-cyclohexenyl acetylene derivatives also gave the desired 2-naphthyl- (**2q** and **2r**) and 2-cyclohexenylindole (**2s**) derivatives in practically applicable yields (Entries 9–11). Furthermore, *N*-tosyl-2-iodo-4-methoxycarbonylaniline (**1f**) was found to be a good substrate for the present indole synthesis (Entries 12).

Conclusions

We have established a practical and efficient protocol for the Yamanaka–Larock indole synthesis, which requires 3.0 mol% of heterogeneous 10% Pd/C as the catalyst, alkynes and NaOAc as a mild base in the absence of LiCl. Symmetrical disubstituted alkynes reacted with *N*-tosyl-2-iodoaniline to give the corresponding 2,3-disubstituted indoles in excellent yields, and a variety of 2-monoarylsubstituted indole derivatives were synthesized from monoarylalkynes in a completely regioselective manner. The method will provide a facile, efficient, and environmentally-benign process for the preparation of indole derivatives due to the wide applicability of the substrates, easy access to the catalyst, easy removal of the *N*-tosyl protection on the indole nucleus[24] and mild reaction conditions.

Experimental section

General methods

All reagents were obtained from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on pre-coated Silica gel 60 F-254 plates (32–63 μm particle size) and visualized with UV light (254 nm). The 10% Pd/C was obtained from the N.E. Chemcat Co. Flash column chromatography was performed with Silica gel 60 (40–63 μm particle size, Merck & Co., Inc.) or Silica gel 60 N (100–210 μm, Kanto Chemical Co., Inc.). ^{1}H and ^{13}C NMR spectra were recorded by a JEOL JNM EX-400 or AL-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent. Chemical shifts (δ) are expressed in ppm based on internal standards (TMS for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR). The electron impact (EI) and fast-atom bombardment (FAB) mass spectra were taken using a JEOL JMS-SX 102A instrument.

General procedure for the LiCl-free Pd/C-catalyzed annulation of alkynes with *N*-Ts-2-iodoaniline (for Table 5)

A mixture of *N*-Ts-2-iodoaniline (0.250 mmol), alkyne (0.300 mmol), 10% Pd/C (8.0 mg, 3 mol% of *N*-Ts-2-iodoaniline) and NaOAc (22.5 mg, 0.275 mmol) in NMP (1.00 cm^3) in a 15 cm^3-test tube was sealed with a septum and the air inside was replaced with Ar by five vacuum/Ar (balloon) cycles. The mixture was stirred at 110–130 °C for 24 h using a Chemist Plaza personal organic synthesizer (Shibata Scientific Technology, Ltd., Tokyo). The suspension was vigorously stirred with additional EtOAc (40 cm^3) and saturated NH_4Cl solution (10 cm^3), and filtered through a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtered aqueous layers were separated and the water layer was extracted with another EtOAc (20 cm^3). The EtOAc layer was combined with the filtered organic layer and washed with saturated NH_4Cl solution (20 cm^3 × 2), H_2O (5 cm^3 × 2), and brine (5 cm^3), and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

Acknowledgements

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