

One-Pot/Four-Step/Palladium-Catalyzed Synthesis of Indole Derivatives: The Combination of Heterogeneous and Homogeneous Systems

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Abstract: One-pot, four-step syntheses of indoles using both solid-supported heterogeneous and homogeneous palladium catalysts and reagents were carried out. Such a combination of these two-phase catalysts and reagents causes a dramatic increase in yield, and it is a simple process. The presented methodology is effective for four-step reactions to provide various functionalized indoles.

Keywords: homogeneous catalysis; indoles; one-pot multi-step synthesis; palladium; supported catalysts

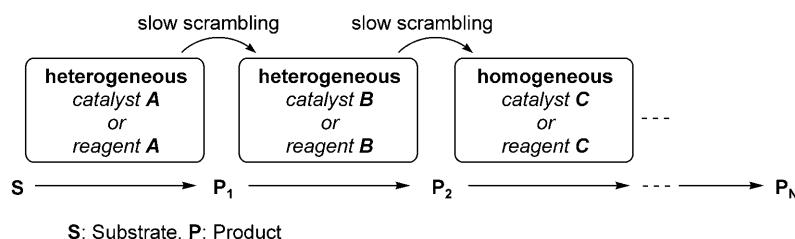
The synthetic methods for indole derivatives, including metal-catalytic reactions, have been given wide attention because of their unique biological activities and utility as the building blocks of various natural products.^[1] In many cases, multi-step reactions are required with regard to the construction of the indoles. Recently, one-pot multi-step syntheses have gained a position of increasing significance because of their environmental and economical advantages, which are derived from the avoidance of the typical separation and isolation of products required in each conversion step. However, the reported one-pot syntheses of in-

doles were mostly limited to two-step reactions or exquisite combinations of catalysts and reagents with fine-tuning of the reaction conditions.^[2]

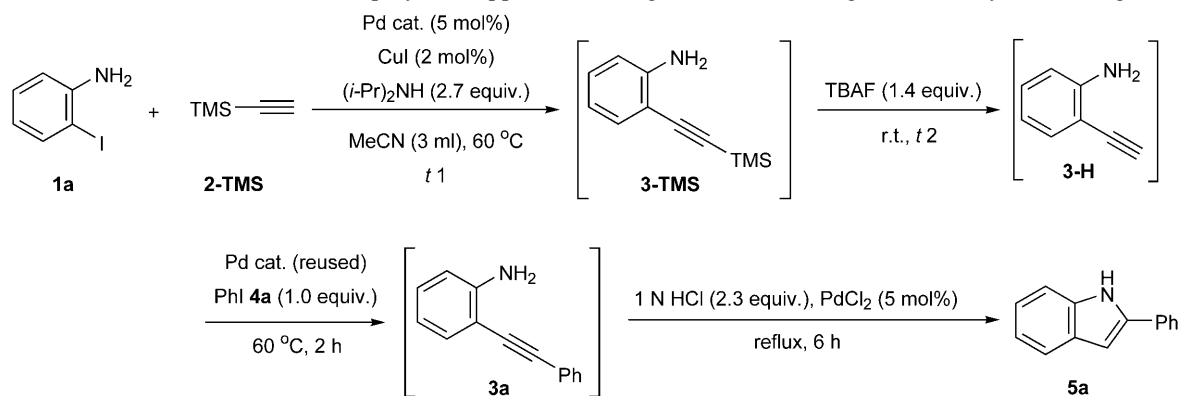
In order to develop a widely applicable and versatile one-pot multi-step synthetic methodology, we propose the combination of solid-supported heterogeneous^[3] and homogeneous catalysts (catalysts **A–C**) or reagents (reagents **A–C**) (Scheme 1).

In such a system, co-existing catalysts or reagents should scramble slowly compared with a homogeneous only system because they are treated in separate heterogeneous and homogeneous phases. Thus the avoidance of scrambling by the catalysts and reagents allows the multi-step reaction ($S \rightarrow P_1 \rightarrow P_2 \rightarrow \dots \rightarrow P_N$) to proceed smoothly in one-pot.

To test the combined heterogeneous and homogeneous reaction system, we focused on a palladium-catalyzed, multi-step synthesis of indole derivatives^[1b,4] because palladium is one of the most widely applicable catalysts in organic syntheses.^[5] We took particular note of Cacchi's report on a four-step synthesis of indoles which used the following sequence (Table 1).^[4c] At first, Sonogashira coupling of 2-iodoaniline **1** with trimethylsilylacetylene **2-TMS** provides 2-[(trimethylsilyl)ethynyl]aniline **3-TMS**. In the second step, desilylation gives ethynylaniline **3-H**. Then, Sonogashira coupling of **3-H** with an aromatic iodide, such as **4a**, is



Scheme 1. One-pot, multi-step reaction in heterogeneous and homogeneous systems.

Table 1. Effect of the combination of the polymer-supported heterogeneous and homogeneous catalysts and reagents.

Entry	Pd catalyst	TBAF	<i>t</i> 1 [h]	<i>t</i> 2 [h]	5a ^[a] [%]
1	PdCl ₂ (PPh ₃) ₂	TBAF in THF	2	0.5	39
2	PdCl ₂ DPP- § ^[b]	TBAF in THF	12	0.5	27
3	PdCl ₂ DPP- § ^[b]	TBAF on silica ^[c]	12	2	60
4	PdCl ₂ TPP- ¶ ^[d]	TBAF on silica ^[c]	12	2	9
5	PdCl ₂ TPP- ¶ ^[c]	TBAF on silica ^[c]	12	2	0
6	Pd EnCat TPP30 ^[f]	TBAF on silica ^[c]	12	2	0
7	PdCl ₂ DPP- § ^[g]	TBAF on silica ^[c]	12	2	41

^[a] Isolated yield.

^[b] PdCl₂DPP-**§** is a silica-supported catalyst. Prepared from SilicaBond Diphenylphosphine (SILICYCLE Inc.) and PdCl₂(PPh₃)₂; 0.224–0.245 mmol Pd/g.^[6]

^[c] Commercially available (Aldrich Chemical Co.); 1.0–1.5 mmol F/g.^[7]

^[d] PdCl₂TPP-**¶** is JandaJelTM-supported catalyst. Prepared from JandaJelTM, triphenylphosphine (Aldrich Chemical Co.) and PdCl₂(PPh₃)₂; 1.14 mmol Pd/g.^[8]

^[e] PdCl₂TPP-**¶** is polystyrene resin-supported catalyst. Commercially available (Aldrich Chemical Co.); 1.0 mmol Pd/g.^[8]

^[f] Commercially available (Aldrich Chemical Co.); 0.4 mmol Pd/g.^[9]

^[g] Prepared from SilicaBond Diphenylphosphine (SILICYCLE Inc.) and small amounts of PdCl₂(PPh₃)₂; 0.127 mmol Pd/g.^[6]

performed as the third step to introduce a new functional group at the terminal position of the alkynyl moiety. In the last step, cyclization of the coupling product, such as **3a**, affords indole **5a**.

This sequential four-step reaction was carried out in a single vessel using homogeneous catalysts and reagents as follows: PdCl₂(PPh₃)₂ in the first step, THF solution of TBAF (tetrabutylammonium fluoride) in the second step, and PdCl₂ in the fourth step. In the third step, the remaining palladium catalyst could be reused. However, in that case, the corresponding indole **5a** was obtained in low yield (Table 1, entry 1). Hence performing the multi-step reaction in a one-pot system, especially when using transition metal catalysts, is an extremely severe challenge because the metal catalysts are very sensitive to coordinating ligands and the oxidation state.

In order to improve the efficiency, the effects of various combinations of heterogeneous and homogeneous catalysts and reagents were examined. For that purpose, a silica-supported (**§**) palladium catalyst was prepared according to the modified procedure reported by Huang.^[6] A suspension of PdCl₂(PPh₃)₂ and

the commercially available silica-supported phosphine (SILICYCLE Inc.) in dry benzene was stirred at reflux temperature for 24 h. Then, the suspension was filtered and the solid residue was washed with benzene, hexane, acetonitrile and diethyl ether to give the corresponding silica-supported palladium catalyst.

Although the silica-supported palladium catalyst instead of PdCl₂(PPh₃)₂ in the four-step reaction resulted in a low yield (Table 1, entry 2), the employment of both silica-supported palladium catalyst and TBAF immobilized on silica^[7] improved the yield dramatically (Table 1, entry 3). The average yield of each step in the one-pot sequence is estimated to be 88%. In the four-step synthesis of indoles, triphenylphosphine activates a Pd(0) catalyst for Sonogashira coupling but poisons Pd(II)Cl₂ preventing cyclization. The oxidation states of the two catalysts are different [Sonogashira coupling: Pd(0), cyclization: Pd(II)]. This suggests that the two homogeneous palladium catalysts may scramble rapidly for coordinating phosphine ligands and/or electrons to result in moderate yields.

Moreover, free TBAF may affect the palladium catalysts, which retards the reactions. A combination of

solid-supported heterogeneous and homogeneous catalysts and reagents may prevent the scrambling *in situ* because each catalyst and reagent is treated separately in heterogeneous and homogeneous phases.

Other heterogeneous catalysts were tested in the four-step reactions. A JandaJel-supported (JJ) catalyst instead of silica-supported palladium catalyst prepared from the commercially JandaJelTM triphenylphosphine (Aldrich Chemical Co.) and $\text{PdCl}_2(\text{PPh}_3)_2$ ^[8] gave **5a** in 9% yield (Table 1, entry 4). A commercially available polystyrene resin-supported (PS) catalyst^[8] and a nanoparticle-type catalyst, PdEnCat TPP 30 consisting of Pd(II) and PPh_3 ligated by the urea encapsulation matrix,^[9] were not effective in this reaction (Table 1, entries 5 and 6). It is well known that silica swells very little in most solvents and that the active sites are well dispersed on its surface and, therefore, these sites are easily accessible to reactants. However, all the other organic solid-supported catalysts are affected by solvents. Thus, the silica catalyst may be the most suitable and widely applicable for use in the one-pot reaction system. We also found that the yield crucially depends on the loading level of the catalyst (Table 1, entry 7). In the case of using the catalyst at a low loading level, PdCl_2 for the last step may be captured by the free phosphine moiety on the silica gel to decrease the amount of PdCl_2 in the solution phase.

These one-pot, four-step reactions provided small amounts of indoles when only using the silica-supported palladium catalyst or the homogeneous PdCl_2 . Independently each reaction was performed to give the following yields; **3-TMS**: 93% (the first), **3-H**: 91% (the second), **3a**: 92% (the third), **5a**: 82% (the fourth). These results show that the total yield of the four-step reactions from **1a** was 64%. As for the reaction yield, the presented one-pot system is comparable to the multi-pot one. In addition, the silica-supported palladium catalyst was reused effectively in the third step. Thus, each four-step reaction takes place in heterogeneous and homogeneous phases, which serve as pseudo micro-vessels in a large single vessel. Therefore, the presented reaction system may resemble biosynthesis using enzymes.^[10] We preliminarily elucidated the one-pot, two-step synthesis of indole: Sonogashira coupling between a 2-aminoaryl halide and an alkyne followed by intramolecular cyclization of the resulting 2-alkynylanilines. In this reaction the combination of silica-supported palladium catalyst and PdCl_2 showed the best result in comparison with $\text{PdCl}_2(\text{PPh}_3)_2$ and other heterogeneous catalysts instead of silica-supported palladium.^[11] These results indicate the efficiency of the combination of heterogeneous and homogeneous palladium catalysts.

The one-pot, four-step syntheses of various functionalized iodides were carried out to explore the scope of the presented methodology (Table 2). Hetero-

aromatic substituted indoles **5b** and **5c** were prepared with good average yields (Table 2, entries 1 and 2). Interestingly, **5c** and **5d** were obtained in better isolated yields compared with the previous results reported by Cacchi (Table 2, entries 2 and 3, reported results: 53% and 33%).^[4c] In the case of **4e**, the iodo group reacted selectively to give a bromophenyl-substituted indole **5e** (Table 2, entry 4). When the reaction was carried out with trifluoromethanesulfonate compound **4f**, the corresponding indole **5f** was obtained (Table 2, entry 5). Even in the case of the highly functionalized steroid **4g**, the one-pot reaction provided a steroid-substituted indole **5g** (Table 2, entry 6). Furthermore, the one-pot reaction afforded various functionalized indoles at the C5 position **5h–k** effectively (Table 2, entries 7–10). In particular, **5j** is known as a NorA MDR pump inhibitor.^[12] Thus, this methodology is superior with the following noteworthy features: many of functionalized indoles can be created in a one-pot reaction. It is not necessary to prepare the corresponding substituted 1-alkynes. Therefore, the one-pot reaction could be exploited widely to develop various research areas as a convenient and efficient synthetic methodology.

In summary, we have presented a practical and useful one-pot, multi-step synthetic methodology using silica-supported heterogeneous and homogeneous catalysts and reagents. In this system, one-pot multiple reactions proceed effectively to give various functionalized indoles. Such a combination of heterogeneous- and homogeneous-phase reactions may reduce the limitations of other one-pot, multi-step syntheses. Currently, we are applying this protocol to other metal-catalyzed multiple syntheses.

Experimental Section

Synthesis of $\text{PdCl}_2\text{DPP-Si}$

$\text{PdCl}_2(\text{PPh}_3)_2$ (0.851 g, 1.21 mmol) and commercially available SilicaBond Diphenylphosphine (1.01 mmol P/g; *SILICYCLE Inc.*) (1.00 g, 1.01 mmol P) were put into a flask. Then, dry benzene (32.3 mL) was added to the flask, and the suspension was stirred at reflux temperature for 24 h. Then, the suspension was filtered and the solid residue was washed with benzene, hexane, MeCN and Et_2O . The resulting solid was dried under vacuum at room temperature, giving a yellow powder. Pd loading was confirmed to be 0.232–0.260 mmol Pd/g by MIP-MS analysis. Similar reactions of smaller amounts of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.426 g, 0.61 mmol) and silica-bound diphenylphosphine (1.00 g, 1.01 mmol P) provided the silica-supported catalyst with a lower loading level (0.127 mmol Pd/g).

Table 2. One-pot four-step synthesis of 2-substituted indoles.^[a]

Entry	1	4	<i>t</i> 3 [h]	<i>t</i> 4 [h]	5	Yield ^[b] [%]
1	1a	4b	4	45	5b	40 (80)
2		4c	2	5	5c	57 (87)
3		4d	2	7	5d	59 (88)
4		4e	3	5	5e	28 (73)
5		4f	3	6	5f	38 (79)
6 ^[c]		4g	20	24	5g	21 (68)
7	1b	4a	2	7	5h	52 (85)
8	1c		2	24	5i	47 (83)
9	1d		2	7	5j	11 (58)
10	1e		2	7	5k	20 (67)

^[a] PdCl₂DPP-**5** was prepared from SilicaBond Diphenylphosphine (*SILICYCLE Inc.*) and PdCl₂(PPh₃)₂; 0.224–0.245 mmol Pd/g.^[6] The reaction procedure is described in the Experimental Section.

^[b] Isolated yield. Average yield of each step in parentheses.

^[c] DMF/MeCN (1/1) was used as solvent).

General Procedure for the One-Pot Four-Step Synthesis of Indoles

Aromatic iodoaniline (0.30 mmol), silica-supported palladium catalyst (PdCl₂DPP-**5**) (0.015 mmol) and CuI (1.15 mg, 6.0 μmol) were suspended in dry MeCN (3.00 mL). (*i*-Pr)₂NH (0.12 mL, 0.81 mmol) and trimethylsilylacetylene (60.0 μL, 0.420 mmol) were added to the suspension, and

the mixture was stirred at 60°C for 12 h. After cooling, TBAF on silica (0.420 g, 0.420 mmol) was added, and the mixture was stirred at room temperature for 2 h. Subsequently, aryl iodide (0.300 mmol) was added, and the mixture was stirred at 60°C for 2–20 h. After the completion of the Sonogashira coupling, 1 N HCl aqueous (0.690 mL, 0.690 mmol) and PdCl₂ (2.66 mg, 0.0150 mmol) were added, and the reaction mixture was stirred at reflux temperature

for 5–45 h. The resulting mixture was filtered, and the filtrate was diluted with ethyl acetate. The obtained solution was washed with a saturated aqueous NaHCO_3 . Then the organic layer was dried (MgSO_4) and concentrated under vacuum. Purification by column chromatography (silica gel) gave the corresponding indoles.

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