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Synthesis of 2-substituted indoles by palladium-catalyzed heteroannulation with Pd–NaY zeolite catalysts

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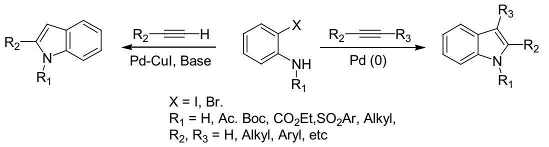
Abstract—Various 2-substituted indoles were prepared by heteroannulation of *o*-iodoanilines and terminal alkynes in a one-pot reaction with a Pd(II)–NaY zeolite catalyst. The product formation largely depended on the solvent, base, and reaction temperature. The recycled catalyst showed good reusability in the heteroannulation reaction.

The indole nucleus is found in many natural products, pharmaceutical agents, and material polymers.[1] The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives.[2] Although many synthetic methods have been developed for indoles, palladium-mediated indole synthesis is one of the most active research fields.[3] Specifically, the palladium-catalyzed annulation of *o*-haloanilines with alkynes has received much attention, as it is a very convenient way to synthesize 2 or 2,3-substituted indoles (Scheme 1).[4,5]



Scheme 1.

The Sonogashira cross-coupling reaction of *o*-haloanilines with terminal alkynes in the presence of Pd(0)–Cu(I) gives 2-alkynylanilines. The resulting coupling products have been cyclized to give 2-substituted indoles using various metal alkoxides,[4h,6] fluorides,[7] and Lewis acids.[8] By contrast, Larock's annulation reaction of 2-iodoaniline derivatives with internal alkynes has provided a variety of 2,3-disubstituted indoles in one-pot reactions. The annulation method is an effective way to prepare a variety of heterocycles.[9] Our group has also applied the annulation method to the synthesis of heterocyclic azaindoles[10] and pyrroloquinolines.[11] Several groups have reported using Pd-zeolite to catalyze the Heck reaction.[12] Those papers described the following reaction characteristics: (i) Palladium complexes immobilized in zeolite supercages have almost the same activity as the free complexes in solution. (ii) Molecules or small metal particles immobilized in zeolite cavities are stable. (iii) The zeolite microstructure could help to overcome the problems of leaching present with a heterogeneous catalyst in solution. (iv) Zeolites are capable of stabilizing active intermediate species in their cavities and controlling the reaction pathway via shape selectivity. In spite of these interesting properties of zeolites, there are no reports on recycling the catalyst or catalyst reusability in palladium-catalyzed heteroannulation. This paper examines the annulation of *o*-haloanilines and terminal alkynes using a Pd-modified zeolite. Zeolites entrapped with different Pd species were prepared according to reported methods[13,12a] by the ion exchange of NaY zeolite (Aldrich No 33,444-8) using a 0.1 M aqueous solution of $[Pd(NH_3)_4]Cl_2$ at room temperature for 24 h to produce $[Pd(NH_3)_4]^{2+}$–NaY. Calcination of the ion-exchanged $[Pd(NH_3)_4]^{2+}$–NaY zeolites at 500 °C for 4 h under O_2 gave the Pd(II)–NaY zeolite, and subsequent treatment at 300 °C for 4 h with 5% H_2 (N_2 balance) gave Pd(0)–NaY.[12a] These Pd-containing

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Keywords: 2-Substituted indole; Pd-Zeolite; Catalyst; Heteroannualtion; Terminal alkynes.

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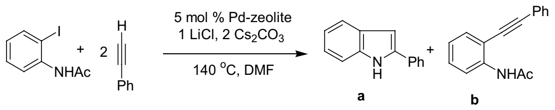
zeolites had an S_{BET} of 765 cm^2/g and an average pore diameter of 14.6 Å. Using AAS, the absolute palladium content of these catalysts was determined to be 1.0 ± 0.1 wt %. First, we investigated the reaction of *N*-acyl 2-iodoaniline with phenylacetylene as a model to study the intermolecular heteroannulation with 1.0 wt % Pd-loaded zeolite catalysts. To optimize the reaction conditions, we varied our previous heteroannulation conditions,[10] including the halide source, base, temperature, and Pd-zeolite catalyst. As shown in Table 1, the reaction using LiCl gave a better yield than the reactions with n-BuN_4Cl or CsCl as the chloride source (entries 1–3). The reaction provided 2-phenylindole as the major product instead of *N*-acetyl 2-phenylindole. The deprotection of the acetyl group in the indole likely occurred as a result of the acidic nature of the zeolite. After the chloride effects were examined, we tried various bases using the same reaction conditions (entries 4–7). Using Cs_2CO_3 as the base, the desired indole was obtained in 80% yield. A mixture of the desired indole and the Sonogashira coupling product was obtained using other carbonate or acetate bases.

The effect of temperature was also examined with the 1.0 wt % Pd–NaY catalyst (entries 1 and 8). The desired product was obtained using LiCl, 1.0 wt % Pd(II)–NaY, and Cs_2CO_3 at 140 °C. By contrast, at 120 °C, the same reaction did not give any of the desired products (entry 8). Finally, we compared the catalytic activity in terms of Pd loading and Pd species with Pd–NaY catalysts (entries 9–12). The catalytic activity of the Pd-loaded zeolite depended on the palladium concentration and palladium species. The heteroannulation reaction using 1.0 wt % Pd(II)–NaY catalyst showed good catalytic activity. We also investigated the effect of different solvents and reaction times with *o*-iodoanilides and phenyl acetylene. The results are summarized in Table 2.

Table 2. The effects of solvents and reaction time on heteroannulation



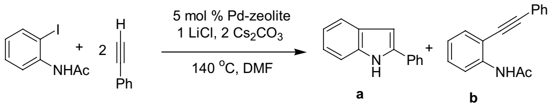
Entry[a]	Solvent	Reaction time (h)	Isolated yield (%)
1	DMF	24	80
2	DMA	24	62
3	NMP	24	59
4	1,4-Dioxane	24	Trace
5	DMF	6	80
6[b]	DMA	6	67 (1:6)

[a] The reactions were run on a 0.5-mmol scale with 10 mL of DMF.

[b] The reaction provided the Sonogashira coupling product as a major product.

On changing the solvent, the reactions using DMF, DMA, and NMP gave similar yields of 2-phenylindole after 24 h. Furthermore, we re-examined the effect of continuing the annulation reaction for 6 h. The reaction using DMF gave the best yield of the desired product. Conversely, the reaction using DMA provided the coupling product as a major product after 6 h, while the cyclized 2-phenylindole was obtained after a longer reaction time (entries 2 and 6). These tests showed that the general reaction conditions for synthesizing indole derivatives required 2 equiv of the terminal alkyne, 1 equiv of LiCl, 2 equiv of Cs_2CO_3, 5 mol % Pd-loaded zeolite, and DMF at 140 °C. To synthesize diverse 2-substituted indoles with Pd-loaded zeolites, the reac-

Table 1. Optimizing the heteroannulation reaction conditions



Entry[a]	Halide source	Base	Pd-zeolite	Reaction yield (%)	
				Time (h)	(**a**:**b**)[b]
1	LiCl	Cs_2CO_3	Pd(II)–NaY	12	80
2	n-BuN_4Cl	Cs_2CO_3	Pd(II)–NaY	12	64
3	CsCl	Cs_2CO_3	Pd(II)–NaY	12	58
4	LiCl	KOAc	Pd(II)–NaY	12	75 (1:4)
5	LiCl	Na_2CO_3	Pd(II)–NaY	12	70 (2:1)
6	LiCl	K_2CO_3	Pd(II)–NaY	12	78 (3:2)
7	LiCl	LiOAc	Pd(II)–NaY	12	70 (3:4)
8[c]	LiCl	Cs_2CO_3	Pd(II)–NaY	12	<5
9[d]	LiCl	Cs_2CO_3	Pd(II)–NaY	24	66
10[e]	LiCl	Cs_2CO_3	Pd(II)–NaY	24	66
11	LiCl	Cs_2CO_3	Pd(0)–NaY	24	78
12	LiCl	Cs_2CO_3	$Pd(NH_3)_4$–NaY	12	67

[a] All the reactions were run on a 0.5-mmol scale with 10 mL of DMF.

[b] The yields and ratio of isomeric products were determined by isolation.

[c] The reaction was run at 120 °C.

[d] The reaction used 0.5 wt % Pd-zeolite.

[e] The reaction used 2.0 wt % Pd-zeolite.

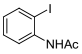
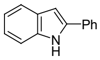
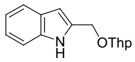
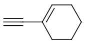
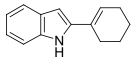
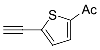
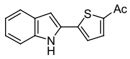
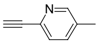
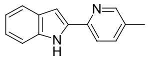
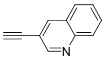
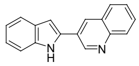
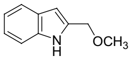
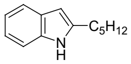
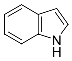
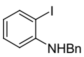
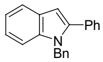
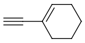
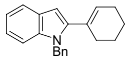
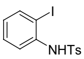
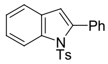
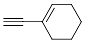
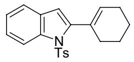
tions were run with N-substituted 2-iodoaniline and various terminal alkynes under the optimal reaction conditions.[14] The results are summarized in Table 3.

The reactions using *N*-acetyl *o*-iodoanilide with alkyl, aryl, and heteroaryl substituted terminal alkynes provided 2-substituted indoles in good to reasonable yields with deprotection of the *N*-acetyl group. The reaction using acetylene also gave indole after purging the acetylene with a balloon (entry 9). The reactions using *N*-Bn or *N*-Ts 2-iodoaniline with a terminal alkyne provided *N*-protected 2-substituted indoles in reasonable yields (entries 10–12).

One important finding of this study was the reusability of the Pd-zeolite catalyst. The Pd-zeolite catalyst used was separated with a membrane filter and then washed with CH_2Cl_2. The recycled catalyst was used five times for the same reaction, adding LiCl and Cs_2CO_3 to each reaction without regenerating the catalyst. The results are summarized in Table 4.

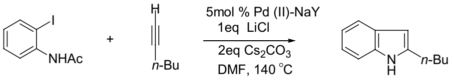
Although the recycled catalyst did not have the same catalytic activity as the fresh catalyst, the recycled catalyst showed good catalytic reusability for heteroannulation, although it required a longer reaction time than the freshly prepared catalyst. The more times it was

Table 3. Synthesis of 2-substituted indoles by palladium-catalyzed heteroannulation with terminal alkynes

Entry[a]	Aryl halide	Alkyne	Product	Yield[b]
1		≡—Ph		82
2		≡—CH_2OThp		69
3				78
4				52
5				51
6				50
7		≡—CH_2OCH_3		48
8		≡—$(CH_2)_4CH_3$		72
9[c]		≡		40
10		≡—Ph		68
11				52
12		≡—Ph		40
13				42

[a] Reaction conditions: 0.5 mmol aryl halide, 1.0 mmol alkyne, 0.5 mmol LiCl, 1.0 mmol Cs_2CO_3 with 10 mL of DMF at 140 °C for 6 h.
[b] Isolated yield (%).
[c] The acetylene was purged with a balloon.

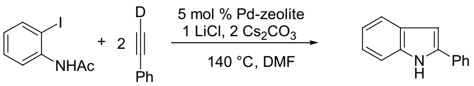
Table 4. Reusable catalysts for heteroannulation



Entry	Pd(II)–NaY	Reaction time (h)	Yield (%)
1	Fresh	6	82
2	Recycled 1 time	15	72
3	Recycled 2 times	20	70
4	Recycled 3 times	24	70
5	Recycled 4 times	30	68
6	Recycled 5 times	36	65

recycled, the longer the time required to complete the reaction.

We also investigated the reaction of *N*-acyl 2-iodoaniline with deuterated phenylacetylene to identify possible mechanism for the heteroannulation (Scheme 2).



Scheme 2.

From the above result, the product would be formed by Sonogashira cross-coupling and subsequent cyclization.

In conclusion, Pd(II)–NaY zeolite catalyst exhibits high reactivity in the heteroannulation of *o*-haloanilines and terminal alkynes. This method provides a convenient new route to various heteroannulation products in a one-pot reaction. Furthermore, the Pd-zeolite catalyst is an interesting alternative to homogeneous catalysis for heterocyclic synthesis.

Acknowledgements

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14. General procedure for the synthesis of 2-substituted indole by palladium-catalyzed heteroannulation with the Pd-loaded zeolite catalyst.
    The Pd-loaded zeolite (0.125 mmol), lithium chloride (0.5 mmol), cesium carbonate (1 mmol), *N*-acetyl 2-iodoaniline (0.5 mmol), phenyl acetylene (1.0 mmol), and DMF (10 ml) were added to a sealed tube. The reaction

mixture was stirred for 6 h at 140 °C. The reaction mixture was diluted with saturated aqueous ammonium chloride. The product was isolated with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The reaction mixture was filtered and concentrated. The product was purified by silica gel column chromatography using hexane/ethyl acetate. 2-Phenyl indole was obtained in 82% yield as a brown solid. Mp 189–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.34 (s, br, 1H), 7.62 (m, 3H), 7.42–7.27 (m, 4H), 7.20–7.09 (m, 2H), 6.80 (dd, 1H, $J = 2.0$, 0.80 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 137.85, 136.79, 132.32, 128.96, 128.22, 127.64, 125.11, 122.28, 120.61, 120.21, 110.91, 99.90. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.69; H, 5.41; N, 7.65.