

General and Selective C-3 Alkylation of Indoles with Primary Alcohols by Reusable Pt Nanocluster Catalyst

S. M. A. Hakim Siddiki,^[a] Kenichi Kon,^[b] and Ken-ichi Shimizu*^[a, b]

The indole scaffold is one of most relevant structures found in natural products, pharmaceuticals ingredients, functional materials and agro-chemicals.^[1] C-3 substituted indoles are of particular importance for the construction of various biologically active molecules.^[2–3] Conventional methodologies for the generation of C-3 substituted indoles require stoichiometric amount of Lewis acids, which have serious drawbacks such as poor regioselectivity, formation of salt wastes and use of hazardous reagents.^[4–6] Recently developed methods for the generation of C-3-alkylated indoles are based on Friedel–Crafts reactions in the presence of Lewis and Brønsted acids or organocatalysts, which suffer from necessities of additives and limited substrate scopes.^[7–11] C-3 alkylation of indoles using propargylic or aromatic alcohol^[12–16] or benzylmethyl carbonate^[17] have been recently developed as more environmentally benign methods, though they suffer from limited scope of alcohols. Very recently, Yus and co-workers showed non-catalytic C-3 alkylation by alcohol through a hydrogen-autotransfer strategy with a stoichiometric amount of base (130 mol % KOH). However this method only worked with activated (aromatic) alcohols.^[18] In contrast to these alkylations, transition-metal catalyzed methodologies have rarely been exploited. There are two examples of C-3 alkylation of indoles by homogeneous transition-metal catalysts.^[19,20] Grigg and co-workers demonstrated the first example with [Cp*IrCl₂]₂ catalyst and benzylic alcohols as alkylating reagents.^[19] Beller and co-workers reported the Ru-catalyzed system with benzylic and aliphatic amines.^[20] Among these methods, the Grigg method is the most atom efficient way to form C-3-alkylated indoles, because water is the only byproduct. However, it has serious drawbacks such as limited scope (inapplicability to less activated aliphatic alcohols), low turnover number (TON), difficulties with the reuse of the homogeneous Ir catalyst, the necessity of a basic co-catalyst (20 mol % KOH) and the excess alkylating agent. Mechanistically, the

Grigg method is based on the so-called borrowing-hydrogen^[21,22] (or hydrogen-autotransfer^[23,24]) methodology, in which the alcohol is initially dehydrogenated, then undergoes a functionalization reaction, and is re-hydrogenated. Herein, as a part of our continuing interest in heterogeneous catalysis for hydrogen-transfer reactions,^[25–27] we report the first general heterogeneous catalytic system for C-3 selective alkylation of indole with alcohols by a Pt nanocluster-loaded θ -Al₂O₃ catalyst.

According to our previous method,^[27] θ -Al₂O₃-supported Pt nanoclusters (1 wt %) with an average Pt particle size of 1.5 nm, designated Pt/ θ -Al₂O₃-1.5 nm, was prepared by an impregnation method with Pt(NH₃)₄(OH)₂·H₂O solution and θ -Al₂O₃, followed by calcination in air at 300 °C and by reduction under H₂ at 500 °C. X-ray diffraction (XRD) pattern of Pt/ θ -Al₂O₃ was essentially the same as that of the θ -Al₂O₃ support, and no lines due to Pt metal were observed, which indicates the absence of large Pt particles. X-ray absorption near-edge structure (XANES) for Pt/ θ -Al₂O₃-1.5 nm was similar to that of Pt foil, which indicates that Pt species in the catalyst is in a metallic state (Figure S1 A in the Supporting Information). The X-ray absorption fine structure (EXAFS) results (Figure S1 B, Table S1 in the Supporting Information) show that the spectrum of Pt/ θ -Al₂O₃-1.5 nm mainly consists of a Pt–Pt bond with a length of 2.70 Å and coordination number of 7.1 and minor contribution (coordination number=0.4) of a Pt–O bond with a length of 2.00 Å. The Pt–Pt distance, which is less than that of bulk Pt (2.76 Å) and the Pt–Pt coordination number lower than that of bulk Pt (12) are characteristic features of Pt metal clusters with a diameter smaller than 2.4 nm.^[28] These features are consistent to with the average diameter of Pt metal estimated by CO adsorption experiments (1.5 nm). From these results, it is revealed that the dominant Pt species in Pt/ θ -Al₂O₃-1.5 nm are metallic Pt nanoclusters with surface Pt atoms in unsaturated coordination environments.

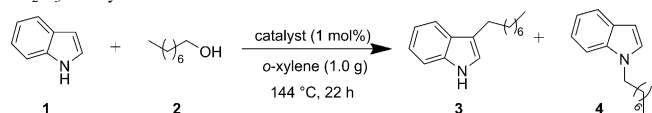
We performed reaction of equimolar amount of 1-octanol and indole as a model system in order to optimize the reaction parameters. Table 1 summarizes the results of the initial catalyst screening under the same reaction conditions (reflux in *o*-xylene for 22 h under inert atmosphere) using various transition metal (Co, Ni, Cu, Ru, Rh, Pd, Ag, Re, Ir, Pt, Au) catalysts supported on γ -Al₂O₃. Note that the reaction can result in N- and C-alkylated products. Among the catalysts tested, Pt/ γ -Al₂O₃ showed the highest yield of the

[a] Dr. S. M. A. H. Siddiki, Dr. K.-i. Shimizu
Elements Strategy Initiative for Catalysts and Batteries
Kyoto University, Katsura, Kyoto 615-8520 (Japan)

[b] Dr. K. Kon, Dr. K.-i. Shimizu
Catalysis Research Center, Hokkaido University
N-21, W-10, Sapporo 001-0021 (Japan)
Fax: (+81) 11-706-9163
E-mail: kshimizu@cat.hokudai.ac.jp

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Table 1. Alkylation of indole by 1-octanol with 5 wt % metal-loaded γ - Al_2O_3 catalysts.^[a]



Entry	Catalyst	Conv. [%]	3 Yield [%] ^[b]	4 Yield [%] ^[b]
1	Co/ γ - Al_2O_3	4	1	0
2	Ni/ γ - Al_2O_3	98	50	44
3	Cu/ γ - Al_2O_3	42	27	1
4	Ru/ γ - Al_2O_3	38	8	7
5	Rh/ γ - Al_2O_3	34	21	10
6	Pd/ γ - Al_2O_3	63	42	20
7	Ag/ γ - Al_2O_3	14	4	1
8	Re/ γ - Al_2O_3	33	6	2
9	Ir/ γ - Al_2O_3	100	61	23
10	Pt/ γ - Al_2O_3	100	72	25
11	Au/ γ - Al_2O_3	10	3	1

[a] Conditions: 0.01 mmol metal catalyst, 1.0 mmol indole, 1.0 mmol 1-octanol, 1.0 g *o*-xylene, reflux condition. [b] Yield was determined by GC.

Table 2. Alkylation of indole by 1-octanol with 5 wt % Pt-loaded catalysts.^[a]

Entry	Catalyst	Conv. [%]	3 Yield [%] ^[b]	4 Yield [%] ^[b]
1	Pt/ γ - Al_2O_3	100	72	25
2	Pt/ θ - Al_2O_3	100	81	17
3 ^[c]	Pt/ θ - Al_2O_3 -1.5 nm	100	88	10
4 ^[c,d]	Pt/ θ - Al_2O_3 -1.5 nm	100	96	3
5 ^[c]	Pt/ α - Al_2O_3	29	0	10
6	Pt/MgO	10	<1	7
7	Pt/CeO ₂	3	1	1
8	Pt/ZrO ₂	7	1	4
9	Pt/Nb ₂ O ₅	6	1	2
10	Pt/C	0	0	0
11	Pt/Y ₂ O ₃	17	3	<1
12	Pt/SiO ₂	10	0	0
13 ^[e]	θ - Al_2O_3	14	0	0
14	PtO ₂ / θ - Al_2O_3	14	0	0

[a] Conditions: 0.01 mmol Pt, 1.0 mmol indole, 1.0 mmol 1-octanol, 1.0 g *o*-xylene, reflux condition. [b] Yield was determined by GC. [c] 1 wt % Pt-loaded catalysts. [d] 1.1 mmol 1-octanol, 1.5 g *o*-xylene. [e] θ - Al_2O_3 = 190 mg.

C-3 adduct. Table 2, entries 1, 2, and 6–12 show the results for a series of 5 wt % Pt-loaded catalysts on various support materials. The regioselectivity strongly depends on the support material. Among the various supports (γ - Al_2O_3 , MgO, CeO₂, ZrO₂, Nb₂O₅, C, Y₂O₃, SiO₂), γ - Al_2O_3 (Table 2, entry 1) gave the highest yield of C-3 adduct **3**. Alumina supports with different crystal phase were also tested as a support for Pt (Table 2, entries 1, 2, and 5). The alumina with spinel structure (θ - Al_2O_3 and γ - Al_2O_3) gave higher yields than that with corundum structure (α - Al_2O_3), and θ - Al_2O_3 gave the highest yield (81 %). θ - Al_2O_3 itself (Table 2, entry 13) and the unreduced catalyst precursor, PtO₂/ θ - Al_2O_3 (platinum oxides-loaded θ - Al_2O_3 , Table 2, entry 14), were completely inactive. Considering that 1 wt % Pt/ θ - Al_2O_3 (Table 2, entry 3) showed higher yield than 5 wt % Pt/ θ - Al_2O_3 (entry 2), we carried out optimization of Pt particle size with 1 wt % of Pt/ θ - Al_2O_3 catalysts with different Pt

particle sizes. By controlling the calcination temperature, catalysts with different Pt particle size (1.5, 1.7, 4.6, 8.9 nm) were prepared (Table S2). As shown in Figure S2 in the Supporting Information, the rate (per mol of Pt) increased with decrease in the Pt size, and the catalyst with the smallest Pt size (Pt/ θ - Al_2O_3 -1.5 nm) gave the highest rate.

Further refinement of the C-3 regioselectivity of the reaction was achieved by with Pt/ θ - Al_2O_3 -1.5 nm. Use of 1.1 equiv of 1-octanol in 1.5 g of *o*-xylene gave the maximum yield (96 %) of C-3 adduct (Table 2, entry 4). The yield of byproduct, N-alkylated indole, was only 3 %. After the reaction, the catalyst was separated from the reaction mixture by centrifugation. The recovered catalyst was washed with acetone and water, followed by drying in air at 90 °C for 12 h, and by reducing with H₂ at 500 °C for 0.5 h. As shown in Figure S3 in the Supporting Information, the catalyst recovered was reused at least three times. When the catalyst was removed from the reaction mixture at 21 % yield of **3** (*t*=2 h), the reaction was completely terminated. Further heating of the filtrate under the reflux condition did not increase the product yield. ICP analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit. These results indicate that Pt/ θ - Al_2O_3 -1.5 nm acts as reusable heterogeneous catalyst for the present reaction.

Under the optimized conditions with the most effective catalyst, Pt/ θ - Al_2O_3 -1.5 nm, we studied the general applicability of the present catalytic system. Table 3 shows the scope of C-3 alkylation of indole with different alcohols with 1 mol % of the catalyst. Various aliphatic alcohols including linear and branched aliphatic alcohols (Table 3, entries 1–11) were tolerated, giving 100 % conversion of indole and good to high isolated yield (79–92 %) of C-3 adducts. Reaction of benzylalcohols with indole (Table 3, entries 12–17) also resulted in 100 % conversion and high yields (75–93 %) of C-3 adducts. C-3 alkylation of indole with a secondary alcohol (2-octanol) resulted in a 4 % yield of C-3 alkylated product. With a lower catalyst loading (0.1 mol %), C-3 alkylation of indole with 1-octanol (Table 3, entry 2) and benzylalcohol (Table 3, entry 13) gave 78 and 90 % yields, corresponding to a TON of 780 and 900, respectively. These values are more than 24 times higher than that of [Cp*IrCl₂]₂ (TON=32 for the reaction of benzylalcohol).

Next, we investigated the reaction of substituted indoles with 1-octanol (Table 4). Indoles with both activating and deactivating groups (Table 4, entries 1, 3, 4, 6) were tolerated for C-3 alkylation with good isolated yield (80–90 %). *N*-substituted indoles (Table 4, entries 2, 7, and 8) and sterically hindered 2,5-dimethyl indole (Table 4, entry 5) were alkylated in good yield. The alkylation of C-3 substituted indole with 1-octanol (Table 4, entry 9) resulted in 80 % yield of C-2 alkylated product rather than N-alkylation. The GC yields of byproducts were studied for all the reactions in Tables 3 and 4. Notably, the yields of *N*-alkylated indoles, were below 5 %, and bis-indolylmethane byproducts were not observed.

Table 3. Alkylation of indole with different alcohols by Pt/ θ -Al₂O₃-1.5 nm.^[a]

Entry	Alcohols	Products	Isolated yield [%]
1			91 (96) ^[b]
2 ^[c]			(90) ^[b]
3			81
4			85
5			90
6			82
7			85
8			79
9			92
10			82
11			80
12			87
13 ^[d]			(78) ^[b]
14			80
15			93
16			93
17			75

[a] Conditions: Pt=0.01 mmol, 1.0 mmol indole, 1.1 mmol alcohol, 1.5 g *o*-xylene, reflux condition. [b] GC yield. [c] Pt=0.001 mmol, 100 h. [d] Pt=0.001 mmol, 48 h.

Table 4. Alkylation of substituted indoles with 1-octanol by Pt/ θ -Al₂O₃-1.5 nm.^[a]

Entry	Indole	Product	Isolated yield [%]
1			90
2			90
3			86
4			81
5			84
6			80
7			90
8			82
9			80 ^[b]

[a] Conditions: Pt=0.01 mmol, 1.0 mmol indole, 1.1 mmol 1-octanol, 1.5 g *o*-xylene, reflux condition. [b] GC yield.

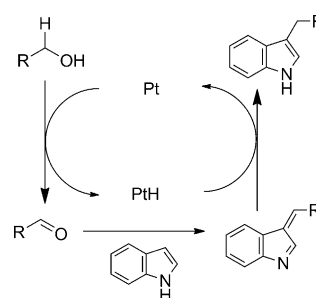


Figure 1. Presumed catalytic cycle for Pt/ θ -Al₂O₃-catalyzed alkylation of indole with alcohols.

In analogy to the proposed mechanism for the C-3 alkylation of indole with alcohols,^[19] the present reaction may proceed through a hydrogen-borrowing pathway (Figure 1). The reaction shows a profile characteristic of a consecutive reaction mechanism via the unreduced intermediate (as detected

and confirmed by GC-MS analysis; Figure S4 in the Supporting Information). The intermediate formed after an initial induction period was gradually consumed to give the hydrogenated product. The reaction of *n*-octanal and indole with 1 mol % of Pt/ θ -Al₂O₃-1.5 nm under N₂ resulted in the formation of the unreduced intermediate in 18% yield (GC-MS analysis) because of the absence of PtH species. To gain more insight into the mechanism of the present catalytic reaction, the kinetic isotopic effect (KIE) was investigated by the reaction of indole and α -deutero benzylalcohol (benzyl- α , α -d₂ alcohol). A moderate k_H/k_D value of 1.7 was obtained (Figure S5), which suggests that of the dissociation α -C–H bond of benzylalcohol is a relatively slow step. These kinetic results are not consistent with a Friedel–Crafts-type mechanism but are consistent with the hydrogen-borrowing mechanism (Figure 1), which begins with dehydrogenation of the alcohol by the Pt sites. The dehydrogenation step is consistent with our recent report of Pt/Al₂O₃-catalyzed acceptor-free dehydrogenation of alcohols to the corresponding carbonyl compounds.^[27] The relative rates of C-3 alkylation from indole and *para*-substituted benzylalcohols (X=Me, H, Cl, and F) were also examined. A reasonable linear correlation between the log(k_X/k_H) values and the Hammett parameters (σ) was obtained (Figure S6 in the Supporting Information), suggesting that the transition state in the rate-determining step of the alkylation reaction involves a positive charge at α -carbon atom adjacent to the phenyl ring, which is stabilized by electron-donating substituents. Combined with the KIE result, the dissociation of the α -C–H bond of the alcohol species may be the rate-determining step.

In summary, we have developed the first heterogeneously catalyzed regioselective C-3 alkylation of indoles with alcohols and the alumina supported Pt nanocluster catalyst. Considering that the 20 mol % KOH-assisted [Cp*IrCl₂]₂-catalyzed C-3-alkylation of indoles with aromatic alcohols^[19] is the only successful catalytic method for the title transformation, our method provides the most versatile and environmentally benign catalytic system for mono-C-3-alkylated indoles from indoles and alcohols known to date. Our system has the following advantages: 1) a wide scope including aliphatic alcohols and *N*-substituted indoles, 2) high TONs, 3) easy catalyst/product separation, 4) the possibility of catalyst reuse, and 5) it does not require a basic co-catalyst or excess alkylating agent.

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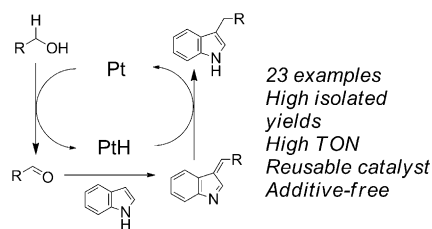
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The platinum rule: Heterogeneous, additive-free C-3 selective alkylation of indoles by aliphatic and aromatic alcohols proceeded under transfer hydrogenation conditions with the reusable Pt/ θ - Al_2O_3 catalyst (see scheme; TON = turnover number).



Indole Alkylation

S. M. A. H. Siddiki, K. Kon,
K.-i. Shimizu*



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