

Development of a Practical One-Pot Synthesis of Indigo from Indole

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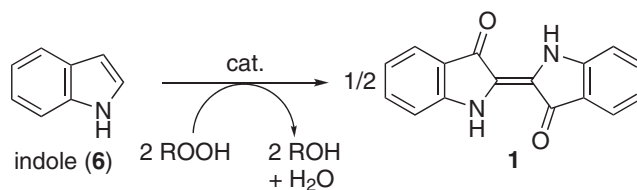
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A novel and highly practical one-pot synthesis of indigo from indole via 3-position selective oxidation and dimerization of the indole framework was developed. Using 0.1 mol % of molybdenum complex and 2.2 equivalents of cumene hydroperoxide in *tert*-butyl alcohol, the reaction was complete in 7 h and pure indigo was obtained in 81% yield as a deep-blue solid just by filtration. The described one-step method renders the pure indigo readily available on a large scale using only inexpensive raw materials.

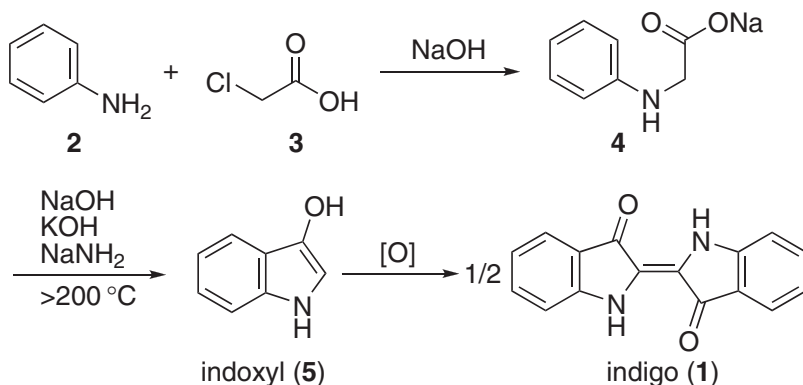
Indigo is among the oldest dyes to be used for textile dyeing and printing.¹ Evidence of the use of indigo dyes dates back to 2000 B.C. in Egypt. In many Asian countries, such as India, China, and Japan, indigo has been used as a dye for centuries. In the United States, the primary use for indigo is as a dye for cotton work clothes and blue jeans. Over one billion pairs of jeans around the world are dyed blue with indigo. Indigo-bearing plants can be found all over the world and a variety of plants, including woad, have provided indigo throughout history. The synthesis of indigo and its precursor was performed using various strategies by von Baeyer, Heumann, and co-workers so that by 1914 only 4% of the world production of indigo had a plant origin. The manufacturing process developed by Pfleger in 1901 is still in use throughout the world.^{2a} In this process, sodium phenylglycinate (**4**), which is synthesized by the coupling of aniline (**2**) and chloroacetic acid (**3**), is treated with an alkaline melt of sodium and potassium hydroxides containing sodamide to produce indoxyl (**5**), which is then oxidized in air to form indigo (**1**) (Scheme 1). In an alternative process, indigo (**1**) is produced by the use of aniline (**2**), formaldehyde, and HCN as starting materials.^{2b}

In these processes however, multi-step organic reactions and rather severe reaction conditions are required. Thus, there is

still a big demand for improvement in terms of practicality. If one could synthesize indigo (**1**) in a single step from inexpensive raw materials, it could become a highly attractive new industrial process. Toward this aim, we recently succeeded in developing a one-pot synthesis of indigo (**1**) from indole (**6**) through molybdenum complex catalyzed selective oxidation of **6** (Scheme 2).³ In the presence of 0.1 mol % of molybdenum complex and 2.2 equivalents of peroxide, the reaction completed in 7 h and pure indigo (**1**) was obtained in 81% yield as a deep-blue solid just by filtration. In this article, we report a full account of this work, including catalyst screening, investigation of solvent effects and additive effects, optimization of reaction conditions, and mechanistic investigation.



Scheme 2. One-pot synthesis of indigo (**1**) from indole (**6**).



Scheme 1. Manufacturing process of indigo (**1**).

Table 1. Catalyst Screening

Entry	Catalyst	CHP (x) ^{a)}	Yield/% ^{b)}
1	—	10	4
2	Mo(CO) ₆	5	46
3	MoO ₂ (acac) ₂	5	23
4	Mo–Nap ^{c)}	5	35
5	MoS ₂	5	14
6	MoO ₃	5	19
7	[H ₃ (PW ₆ Mo ₆ O ₄₀)]·nH ₂ O	5	17
8	Ti(O- <i>i</i> -Pr) ₄	5	10
9	TiO(acac) ₂	5	7
10	RuCl ₂ (PPh ₃) ₃	5	8
11	(C ₆ H ₁₁ OBO) ₃	5	13

a) CHP 83 wt % in cumene solution. b) Isolated yield of **1**.

c) Mo–Nap: Molybdenum naphthenate.

Results and Discussion

Optimization of Reaction Conditions. Indole (**6**), which used to be obtained from a fraction of coal tar, is now produced on an industrial scale by the heterogeneous silver catalyzed reaction of aniline (**2**) and ethylene glycol and is easily available as a raw material.⁴ Several studies on the oxidation of **6** have been reported, including photooxidation,⁵ anodic oxidation,⁶ ozonization,⁷ and oxidations with manganese dioxide,⁸ persulphates,⁹ hydrogen peroxide,¹⁰ and peracids.¹¹ The object of these reports, however, was to study the reactivity of **6** and not to produce indigo (**1**). Even when **1** was detected, it was obtained just as a very low-yield by-product, indicating that an efficient direct process from **6** to **1** has not been developed. Because organic hydroperoxide has not been utilized for the oxidation of **6**, we first examined various metal complexes for the direct conversion of **6** to **1** in the presence of cumene hydroperoxide (CHP). Group 1 (Na, K), 2 (Ba), 3 (Y, La, Ce, Eu), 4 (Ti, Zr, Hf), 5 (V, Nb, Ta), 6 (Cr, Mo, W), 7 (Mn), 8 (Fe, Ru, Os), 9 (Co), 10 (Ni, Pd), 11 (Cu, Ag), 12 (Zn), 13 (B, Al, Tl), 14 (Ge, Sn), 15 (As), and 16 (Se) metal complexes were tested as catalysts. Among them, only molybdenum (Entries 2–7), titanium (Entries 8 and 9), ruthenium (Entry 10), and boron (Entry 11) complexes listed in Table 1 afforded indigo (**1**) in yields that exceeded those obtained in a control reaction (Entry 1). In particular, molybdenum complexes considerably enhanced the yield and Mo(CO)₆ gave the best (46%, Entry 2).¹² As a general trend, the oxidation state of molybdenum complexes did not influence the catalyst activity to a large extent. It is likely that molybdenum complexes of low oxidation state are oxidized to that of high oxidation state in situ and the resulting complexes act as active species. Because **1** is insoluble in toluene, a deep-blue solid of **1** precipitated from the solution with progress of the reaction. Then, chemically pure indigo (**1**) was obtained just by filtration and washing with methanol.

Table 2. Solvent Effects

Entry	Solvent ^{a)}	CHP(x) ^{b)}	Yield/% ^{c)}
1	benzene	5	47
2	benzene	3	50
3	toluene	5	46
4	toluene	3	52
5	propylbenzene	3	53
6	butylbenzene	3	54
7	isobutylbenzene	3	55
8	cumene	5	49
9	cumene	3	60
10	α -methylstyrene	3	28
11	<i>tert</i> -butylbenzene	3	55
12	<i>p</i> -cymene	3	45
13	mesitylene	3	49
14	anisole	3	43
15 ^{d)}	heptane	3	60
16 ^{d)}	hexadecane	3	51
17 ^{d)}	isooctane	3	58
18	dimethoxyethane	3	3
19	dimethyl carbonate	3	11
20	butyl acetate	3	34
21	ethyl benzoate	3	41
22	γ -butyrolactone	3	9
23	cyclohexanone	3	14

a) Solvent/**6** = 30 (weight ratio). b) CHP 83 wt % in cumene solution. c) Isolated yield of **1**. d) Reaction temperature was 90 °C.

Using 1 mol % of Mo(CO)₆ as a catalyst and CHP as an oxidant, we then extensively examined solvent effects (Table 2). In the preliminary studies using benzene (Entries 1 and 2), toluene (Entries 3 and 4), and cumene (Entries 8 and 9) as a solvent, we found that reducing the amount of CHP from 5 equivalents to 3 equivalents (see also the next section) significantly improved chemical yield of **1**. Thus, further studies were performed in the presence of 3 equivalents of CHP. First of all, a variety of aromatic hydrocarbons was examined (Entries 1–14). Apparently, more sterically congested solvents, such as isobutylbenzene (Entry 7, 55%), cumene (Entry 9, 60%), and *tert*-butylbenzene (Entry 11, 55%), gave better yield. Aliphatic hydrocarbons (Entries 15–17) also gave comparative results to cumene when the reaction was performed at higher temperature (90 °C). In contrast, polar solvents (Entries 18–23) gave unsatisfactory results. The use of solvents that have high coordination ability to a metal cation, such as DMF, aniline, and pyridine, completely prevented the reaction with the interesting exception of alcohol (Table 8).

Next, the influence of oxidant was investigated (Table 3). At the beginning further details of the amount of CHP were studied (Entries 1–7). As shown in Scheme 2, for the full conversion of indole (**6**) to indigo (**1**), at least 2 equivalents of CHP to **6** are required. One equivalent of CHP is consumed for the oxidation at the 3-position of **6** to form 3-oxyindole (**7**)

Table 3. Screening of Oxidant

Entry	Oxidant	<i>x</i>	Solvent	Yield/% ^{a)}
1 ^{b)}		0.5	cumene	11
2 ^{b)}		1	cumene	27
3 ^{b)}		2	cumene	52
4 ^{b)}		2.2	cumene	53
5 ^{b)}		2.5	cumene	56
6 ^{b)}		3	cumene	60
7 ^{b)}		5	cumene	56
8 ^{c)}		3	toluene	47
9 ^{d)}		3	toluene	50
10 ^{e)}		3	toluene	49
11 ^{f)}		3	toluene	37
12 ^{g)}		3	toluene	30
13 ^{h)}		3	cumene	50
14 ⁱ⁾	H ₂ O ₂	3	octane	20

a) Isolated yield of **1**. b) 83 wt % in cumene. c) 50 wt % in aromatic hydrocarbon. d) 50 wt % in hydrocarbon. e) >90 wt % purity. f) 67 wt % in toluene. g) 67 wt % in water. h) 65 wt % in ethylbenzene. i) 30 wt % in water.

(Figure 1) and the other one for the oxidative coupling of two indole moieties to form a C–C double bond between each 2-position. Thus, not surprisingly, the use of less than 2 equivalents of CHP gave significant decrease of yield (Entries 1 and 2). In general, higher amounts of CHP led to higher reactivity. In the presence of a large excess of CHP however, selectivity decreased, resulting in the formation of many by-products such as 2-oxyindole (**8**). As a result, the yield of **1** had a maximum value at 3 equivalents of CHP. Several other by-products shown in Figure 1 were also detected in the reaction mixture. For example, when 3 equivalents of CHP were used, 7% of **8**, 5% of **12**, 4% of **9** and **10**, and <1% of **11**, **13**, and **14** were detected by HPLC analysis. Then, reactivity of several other tertiary (Entries 8–12) and secondary (Entry 13) organic hydroperoxides was investigated. Although these organic hydroperoxides except *tert*-butyl hydroperoxide showed good reactivities, they did not improve on the yield obtained using CHP. As in Entry 12, the existence of water interfered with catalyst activity, lowering the yield of **1**. We also examined the use of hydrogen peroxide as an oxidant. Although screening of various solvents revealed that octane was the best solvent, the

obtained yield of **1** remained at low level (20%). Taking into account the fact that CHP is the raw material of phenol production and is easily available on an industrial scale, CHP was selected as an oxidant for further experiments.

Determining the best catalyst and oxidant allowed us to perform precise optimization of reaction temperature, catalyst amount, and reaction time. In the presence of 1 mol % of Mo(CO)₆ and 3 equivalents of CHP, the reaction was performed within a temperature range of (60–110 °C) (Table 4, Entries 1–6, Figure 2a). At temperature lower than 80 °C, both reactivity and selectivity of **1** [(yield of **1**)/(conversion of **6**) × 100 (%)] were quite low, affording **1** in very low yield. At 80 °C or higher, all of indole (**6**) was consumed in 5 h. Due to the increase of side reactions however, selectivity of **1** decreased at temperature higher than 80 °C. Moreover, at higher temperature, consumption of CHP considerably exceeded the ideal value of 2 equivalents (at 110 °C, full conversion of 3 equivalents of CHP), suggesting undesired decomposition of CHP. Therefore, 80 °C was the best temperature for the reaction using 1 mol % of the catalyst. When 0.1 mol % of the catalyst was used, however, higher temperature (100 °C, Entry 13) was required to obtain comparable results (59% yield). Under these conditions (0.1 mol % of Mo(CO)₆ at 100 °C), the reaction completed within 5 h (Entries 9–14, Figure 2b). The fact that selectivity of **1** varied with reaction time indicated that this reaction involves at least two basic steps (Scheme 3).

Additive Effects. By the intensive optimization of reaction conditions described above, we found two promising systems: (1) at 80 °C (Table 4, Entry 3) and (2) at 100 °C (Table 4, Entry 13). To further improve chemical yield of **1**, we next examined effects of additives. After screening of various types of additives, such as aliphatic amines (inhibition), aromatic amines, (inhibition or no effect), nitriles (no effect), sulfones (no effect), sulfides (inhibition), phosphines (inhibition or no effect), and dehydration agents (almost no effect), carboxylic acids have been found to have positive effect on chemical yield of **1**. Results at 80 °C are summarized in Table 5. In the presence of 10 mol % of carboxylic acid, yield of **1** was improved from 60% (Table 4, Entry 3) to up to 69% (Entry 7). Based on HPLC analysis, these additives accelerate the reaction (faster conversion of **6**, for example, without additive: 29%, with benzoic acid: 45% after 1 h) and reduce the formation of by-product **12** (ca. 6% to <2%). Moreover, since additive effects of carboxylic acids appeared even when the reaction was performed in the absence of catalyst, the carboxylic acid may activate either hydroperoxide or indole (**6**). Using highly acidic carboxylic acids (pK_a < 3), however, decomposition of CHP and formation of by-products increased, resulting in a considerable decrease of yield. While adjustment of acidity by reducing the amount of acid greatly improved yield (Entries 15 and 17), obtained yields did not exceed the result without an additive (60% yield). Effects of carboxylic acids appear to be related not to steric factors but to pK_a with a value of around 4 being optimum.

The amount of benzoic acid was then optimized for both 80 and 100 °C systems. As shown in Table 6 and Figure 3, yield of **1** increased with increasing amount of benzoic acid to 30 mol % at 80 °C and to 10 mol % at 100 °C. In the presence of

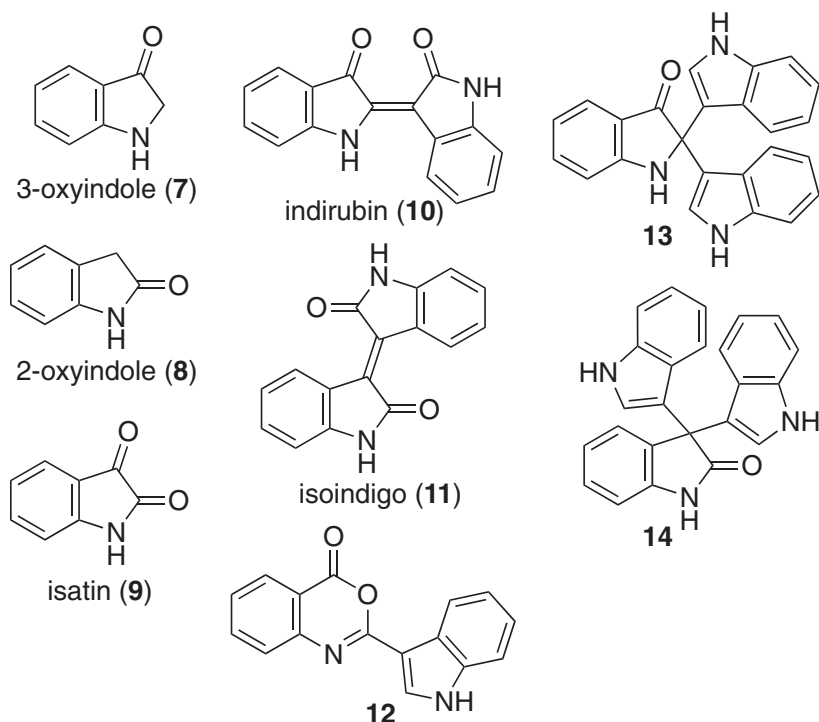


Figure 1. Structure of detected products in the reaction mixture.

Table 4. Effects of Reaction Temperature, Catalyst Loading, and Reaction Time

Entry	Cat. (y)	Temp /°C	Time /h	Conv. of 6 ^{a)} /%	Selectivity of 1 ^{b)} /%	Yield of 1 ^{c)} /%
1	1	60	5	17	6	1
2	1	70	5	52	44	23
3	1	80	5	99	60	60
4	1	90	5	>99	55	55
5	1	100	5	>99	50	50
6	1	110	5	>99	46	46
7	0.1	80	5	44	44	19
8	0.1	90	5	82	60	50
9	0.1	100	0.3	10	0	0
10	0.1	100	1	50	39	19
11	0.1	100	3	97	57	55
12	0.1	100	4	>99	58	58
13	0.1	100	5	>99	59	59
14	0.1	100	6	>99	59	59
15	0.1	110	5	>99	56	56

a) Conversion yield of **6** was determined by HPLC analysis. b) (Selectivity of **1**) = (yield of **1**)/(conversion of **6**) × 100 (%). c) Isolated yield of **1**.

excess benzoic acid, undesired decomposition of CHP was accelerated.

We also found that addition of silanol had some positive effects on yield of desired product **1** (Table 7, Entries 1–7). In

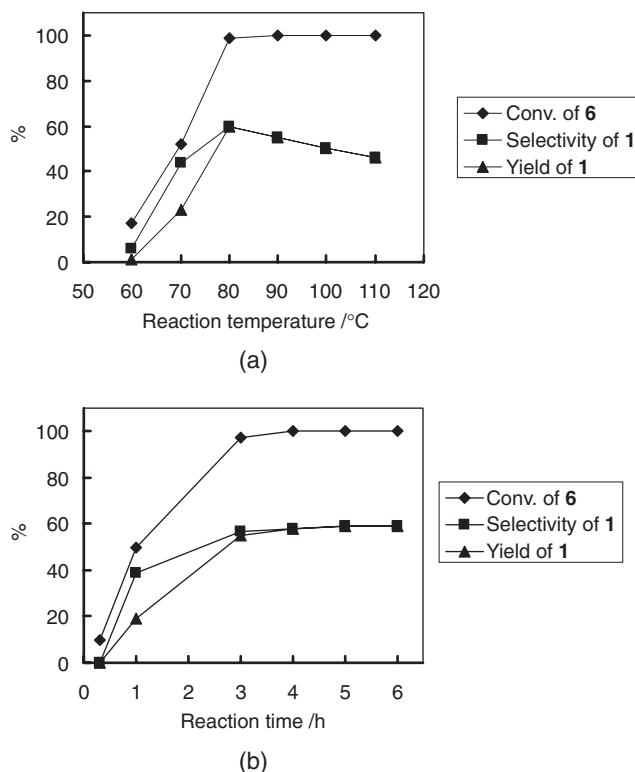
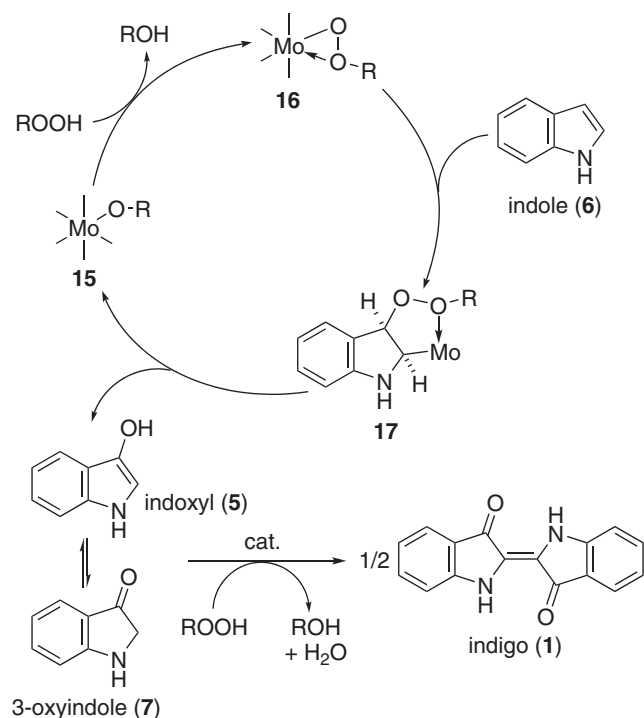


Figure 2. (a) Effects of reaction temperature. (b) Effects of reaction time.

contrast to the additive effects of carboxylic acid, even in the presence of excess amount of silanol, negative effects, such as acceleration of CHP decomposition, was not observed (Entry 6). In the presence of silanol, the formation of by-

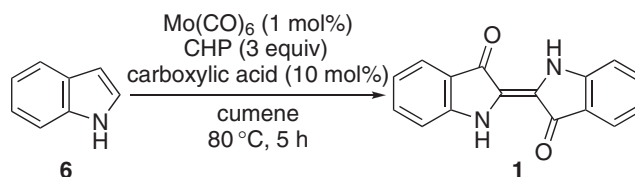


Scheme 3. Proposed mechanism.

product **12** was successfully prevented. Positive effects of silanols may not be attributed to their pK_a value. For example, addition of triphenylmethanol, whose pK_a value (12.9) is close to that of trimethylsilanol (12.7) and triphenylsilanol (11.1), had almost no effect on the reaction. Other silyl compounds, such as silyl ether, silane, disilane, and silyl-chloride, gave unsatisfactory results except diacetoxydiphenylsilane (Entry 8). In this case, diacetoxydiphenylsilane seemed to partially decompose to acetic acid and silanol. Thus, we next examined the combination of carboxylic acid and silanol. As we expected, this combination exhibited a synergetic effect (Entries 9 and 10), achieving a yield of 74%. This suggests that the additive effects of the carboxylic acid and of the silanol are independent of each other.

Use of Alcohol as a Solvent. On the one hand, we found that polar solvent prevented the formation of indigo (**1**) as described above, but on the other, at least 2 equivalents of alcohol and 1 equivalent of water form during the progress of the reaction (Scheme 2). Considering the results of additive effects of silanol, we studied the use of alcohol as a solvent. Results using various alcohols are summarized in Table 8. Although primary alcohols gave only unsatisfactory results (Entries 1–5), secondary alcohols (Entries 6–10), and tertiary alcohols (Entries 11–13) gave better yields than cumene (Table 4, Entries 3 and 13). In the case of secondary alcohols however, some amount of alcohol reacted with CHP to afford the corresponding ketone, resulting in conversion of CHP (2.4–3.0 equivalents) much higher than the ideal value of 2 equivalents. When *tert*-amyl alcohol was used, the isolated yield of **1** exceeded 70% without an additive (Entry 12). Under these reaction conditions, the formation of by-products **10–14** was effectively diminished.

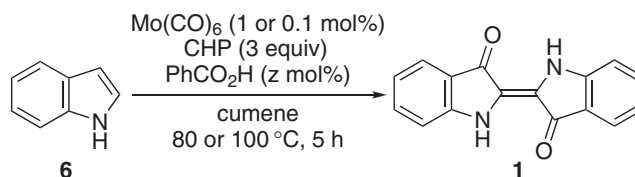
Table 5. Additive Effects of Various Carboxylic Acids



Entry	Acid	pK_a	Yield/(%) ^a
1	3,4-(O ₂ N) ₂ -C ₆ H ₃ -CO ₂ H		20
2	2,4-Cl ₂ -C ₆ H ₃ -CO ₂ H		49
3	4-O ₂ N-C ₆ H ₄ -CO ₂ H	3.44	20
4	4-NC-C ₆ H ₄ -CO ₂ H	3.55	0
5	2-Cl-C ₆ H ₄ -CO ₂ H	2.94	62
6	3-Cl-C ₆ H ₄ -CO ₂ H	3.83	68
7	4-Cl-C ₆ H ₄ -CO ₂ H	3.99	69
8	4-Br-C ₆ H ₄ -CO ₂ H		68
9	Ph-CO ₂ H	4.2	67
10	3-HO-C ₆ H ₄ -CO ₂ H	4.08	65
11	4-HO-C ₆ H ₄ -CO ₂ H	4.58	63
12	3-MeO-C ₆ H ₄ -CO ₂ H	4.09	65
13	4-MeO-C ₆ H ₄ -CO ₂ H	4.47	63
14	Cl ₃ C-CO ₂ H	0.65	3
15 ^b	Cl ₃ C-CO ₂ H	0.65	58
16	Cl-CH ₂ -CO ₂ H	2.86	15
17 ^c	Cl-CH ₂ -CO ₂ H	2.86	59
18	Ph-CH ₂ -CO ₂ H	4.31	66
19	Me-CO ₂ H	4.76	62
20	Et-CO ₂ H	4.87	63
21	Me-(CH ₂) ₆ -CO ₂ H		63
22	Me ₃ C-CO ₂ H		62
23	C ₆ H ₄ -1,2-(CO ₂ H) ₂	2.98	29
24	C ₆ H ₄ -1,3-(CO ₂ H) ₂	3.46	59
25	C ₆ H ₄ -1,4-(CO ₂ H) ₂	3.51	50
26	HO ₂ C-(CH ₂) ₂ -CO ₂ H		57

a) Isolated yield of **1**. b) 0.02 mol % of carboxylic acid was used. c) 0.1 mol % of carboxylic acid was used.

Table 6. Optimization of the Amount of Carboxylic Acid



Entry	System ^a	Ph-CO ₂ H (z)	Yield/(%) ^b
1	80 °C system	5	64
2	80 °C system	10	67
3	80 °C system	20	70
4	80 °C system	30	71
5	80 °C system	40	70
6	80 °C system	50	69
7	100 °C system	1	61
8	100 °C system	5	64
9	100 °C system	10	67
10	100 °C system	30	64
11	100 °C system	50	57

a) 80 °C system: Mo(CO)₆ (1 mol %) at 80 °C. 100 °C system: Mo(CO)₆ (0.1 mol %) at 100 °C. b) Isolated yield of **1**.

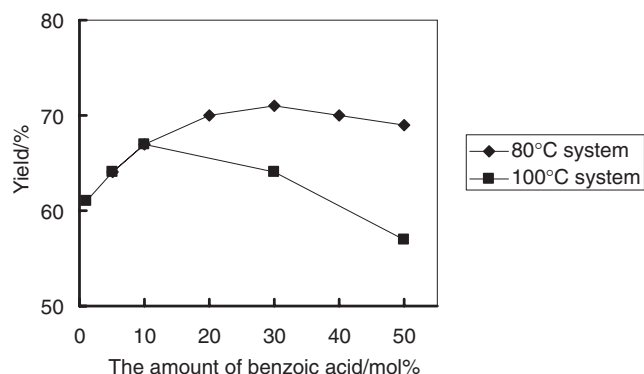
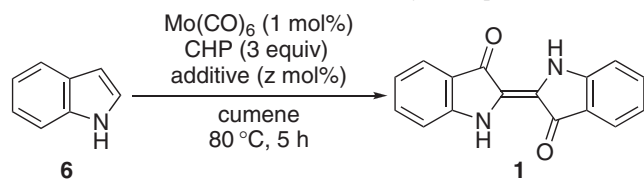


Figure 3. The effects of the amount of benzoic acid.

Table 7. Additive Effects of Various Silyl Compounds



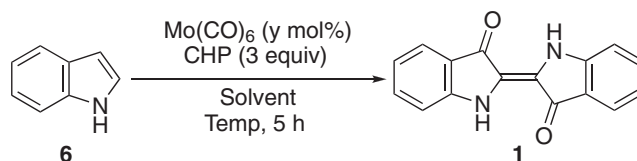
Entry	Additive	z	Yield/(% ^a)
1	Me ₃ SiOH	10	63
2	Et ₃ SiOH	10	66
3	Ph ₃ SiOH	10	64
4	Ph ₃ SiOH	30	66
5	Ph ₃ SiOH	50	66
6	Ph ₃ SiOH	100	65
7	Ph ₃ Si(OH) ₂	10	63
8	Ph ₃ Si(OAc) ₂	10	67
9 ^b	Ph ₃ SiOH + PhCO ₂ H	10	74
10 ^c	Ph ₃ SiOH + PhCO ₂ H	10	70

a) Isolated yield of **1**. b) Mo(CO)₆ (1 mol %), PhCO₂H (30 mol %) at 80 °C. c) Mo(CO)₆ (0.1 mol %), PhCO₂H (10 mol %) at 100 °C.

We then investigated additive effects of carboxylic acid and silanol using *tert*-amyl alcohol as a solvent (Table 9). Addition of 10 mol % of benzoic acid improved chemical yield of **1** from 72% (Table 8, Entry 12) to 78% (Entry 1) while addition of triphenylsilanol had no effect (Entries 2 and 3). It seems that the functions of the alcohol and of the silanol are essentially identical and that they stabilize molybdenum catalyst by forming alkoxy or silanoxo complexes. When *tert*-amyl alcohol was used, acetic acid gave comparable result to benzoic acid (Entry 4). In this system, the amount of CHP can be reduced to 2.2 equivalents and the optimal amount of acetic acid was 10 mol % (Entry 6).

In terms of practicality, final optimization of the reaction was performed. For this purpose, we used *tert*-butyl alcohol as a solvent due to the limited availability of *tert*-amyl alcohol. Although at 80 °C the use of *tert*-butyl alcohol gave unsatisfactory results (Table 8, Entry 11), under reflux conditions (85.7–86.5 °C) chemical yield greatly improved to 73% even with less catalyst (Table 10, Entry 1). Moreover, addition of acetic acid had a positive effect of further improving yield to 81% (Entry 2). In contrast to using cumene as a solvent (Table 1, Entry 4), catalyst efficiency of molybdenum naph-

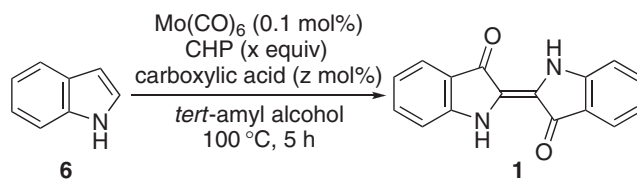
Table 8. Effects of Alcohol Solvents



Entry	Solvent	Cat. (y)	Temp/°C	Yield/(% ^a)
1	ethyl alcohol	1	78 (reflux)	44
2	<i>n</i> -butyl alcohol	0.1	100	55
3	octyl alcohol	0.1	100	53
4	benzyl alcohol	0.1	100	59
5	2-phenylethanol	0.1	100	27
6	isopropyl alcohol	1	80	62
7	2-butyl alcohol	0.1	98 (reflux)	70
8	2-pentyl alcohol	0.1	100	67
9	2-octyl alcohol	0.1	100	63
10	cyclohexyl alcohol	0.1	100	66
11	<i>tert</i> -butyl alcohol	1	80	56
12	<i>tert</i> -amyl alcohol	0.1	100	72
13	α -cumyl alcohol	0.1	100	62
14	di(ethylene glycol)	1	80	0

a) Isolated yield of **1**.

Table 9. Additive Effects of Carboxylic Acids in *tert*-Amyl Alcohol



Entry	Carboxylic acid	z	CHP (x)	Concentration ^a	Yield/(% ^b)
1	PhCO ₂ H	10	3.0	30	78
2 ^c	PhCO ₂ H	10	3.0	30	78
3 ^c	—	—	3.0	30	72
4	MeCO ₂ H	10	3.0	30	78
5	MeCO ₂ H	5	2.2	15	76
6	MeCO ₂ H	10	2.2	15	77
7	MeCO ₂ H	20	2.2	15	76
8	MeCO ₂ H	30	2.2	15	75

a) Concentration: solvent/**6** (weight ratio). b) Isolated yield of **1**. c) Ph₃SiOH (10 mol %) was added.

thenate, which is readily available on an industrial scale, was identical to that of Mo(CO)₆ (Entry 3). The reaction also proceeded with lower catalyst loading (Entry 5) and with less solvent (Entries 6 and 7) in slightly lower yield. Thus, the best result was obtained under conditions shown in Entries 2 and 3 (81%) (Table 10).

Mechanistic Investigations. From a mechanistic point of view, this reaction would involve at least two basic steps namely the oxidation of the 3-position of indole (**6**) and dimerization of the indole moiety. To elucidate the reaction mechanism, we tried to detect reaction intermediates by HPLC-Mass spectrum measurement under inert gas. When the reaction solution at early reaction stage within approximately 15 min was analyzed, one HPLC peak with considerably high intensity

Table 10. Optimization of Reaction Conditions in Terms of Practicality

Entry	Cat.	y	z	Concentration ^{a)}	Time/h	Yield/% ^{b)}
1 ^{c)}	Mo(CO) ₆	0.1	—	15	6	73
2 ^{c)}	Mo(CO) ₆	0.1	10	15	7	81
3 ^{c)}	Mo–Nap	0.1	10	15	7	81
4 ^{c)}	Mo–Nap	0.1	20	15	7	79
5 ^{c)}	Mo–Nap	0.05	10	15	7	75
6 ^{d)}	Mo–Nap	0.1	10	10	7	78
7 ^{e)}	Mo–Nap	0.1	10	7.5	5	76

a) Concentration: solvent/6 (weight ratio). b) Isolated yield of **1**. c) Internal temperature was in a range of 85.7–86.5 °C. d) Internal temperature was in a range of 86.8–89.0 °C. e) Internal temperature was in a range of 87.4–90.3 °C.

showed the parent ion peak at 133 in the mass-spectrum. This number is the molecular weight of 3-oxyindole (**7**). The HPLC–Mass spectrum coincided with that of an authentic sample of **7**,¹³ proving the existence of **7** in the early reaction stage. It was also found that **7** was easily oxidized to indigo (**1**) even by air in a way similar to the conventional industrial process.² Therefore, we believe that **7** is the reaction intermediate. The proposed mechanism is shown in Scheme 3. The first step is oxidation of the 3-position of indole (**6**) to **7**. A molybdenum–peroxy complex is postulated to be an active species of the first step, which then reacts with **6** to form five-membered metal-lactone complex **17**. Then, **7** forms through the dissociation of **17**. This mechanism is quite similar to that of the catalytic epoxidation of olefins by organic hydroperoxides proposed by Mimoun et al.¹⁴ The high selectivity of the 3-position oxidation is due to electronic reasons. It is well known that π -electrons of **6** are localized on the 3-position. One example of the experimental evidence of this fact is the Friedel–Crafts reaction of indole (**6**), in which an electrophilic substitution occurs mainly at the 3-position of **6**. In the present reaction, the electrophilic oxygen atom bound to molybdenum atom of the molybdenum–peroxy complex **16** should attack the electron rich 3-position of **6** selectively. It has been reported that **7** is oxidized to form indigo (**1**) by radical mechanism in basic solution.¹⁵ In the present reaction, oxidative coupling of **7** to form **1** is probably also a radical reaction, although it occurs in neutral solution. Since the addition of the same amount of Mo complex as initiate one after 2 h had almost no effect on the rate of reaction and the yield of indigo, Mo complex most probably promotes only the 1st step (**6** to **7**) and may not participate in the 2nd step (**7** to **1**). Attempts to more thoroughly elucidate the mechanism of this latter step are ongoing.

Conclusion

We developed a novel and highly practical one-pot synthesis of indigo from indole via 3-position selective oxidation of indole and dimerization of the indole moiety. Using 0.1 mol %

of molybdenum complex and 2.2 equivalents of cumene hydroperoxide in *tert*-butyl alcohol, the reaction was complete in 7 h and pure indigo (**1**) was obtained in 81% yield as a deep-blue solid just by filtration. This catalysis is noteworthy in pure chemistry and applied chemistry as well.

Experimental

General Methods and Materials. ¹H and ¹³C NMR spectra were recorded on a JEOL EX-400 spectrometer, operating at 400 MHz for ¹H NMR and 100.35 MHz for ¹³C NMR. The chemical shifts (ppm) were determined relative to Me₄Si. EI mass spectra were measured on a JEOL JMS-DX300. HPLC analyses were carried out on a Shimadzu system equipped with a UV–vis detector, and a TSK-GEL packed column (15 cm × ϕ 4.6 mm) using *n*-hexane/chloroform/acetonitrile (65/30/10) as eluent for the quantitative determination of by-product or an ODS-80TS packed column (15 cm × ϕ 4.6 mm) using acetonitrile/water (30/70) as eluent for the quantitative determination of peroxides and indole.

Indole was purchased from Kanto Chemical Co., Inc. Solvents were obtained from commercial suppliers and distilled according to standard protocol to use. [H₃(PW₆Mo₆O₄₀)]·*n*H₂O was purchased from Japan New Metals Co., Ltd. (C₆H₁₁OBO)₃ was prepared according to a literature procedure.¹⁶ Molybdenum naphthenate was purchased from Nihon Kagaku Sangyo Co., Ltd. The other catalysts were purchased from Strem Chemicals, Inc. H₂O₂ (30 wt % in water) was purchased from Wako Pure Chemical Industries, Ltd. Organic hydroperoxides were purchased from NOF Corporation and were used without further purification. Carboxylic acids were purchased from Kanto Chemical Co., Inc. or Sigma-Aldrich Corporation, and were used without further purification. Silyl compounds were purchased from Azmax Co. and were used without further purification. The other chemicals were purchased from commercial sources and were used without further purification.

General Procedure for the Preparation of Indigo (1) (Table 10, Entry 2). An 82 wt % solution of 1-methyl-1-phenylethyl hydroperoxide (CHP) in cumene (34.6 g, 188.0 mmol of CHP) was added to a solution of indole (**6**) (10.0 g, 85.4 mmol), acetic acid (0.51 g, 8.5 mmol), and molybdenum hexacarbonyl (22.5 mg, 0.085 mmol) in *tert*-butyl alcohol (150 g) at room temperature. This mixture was then allowed to warm up to 86 °C (reflux) and stirred for 7 h. A deep-blue solid gradually precipitated from the solution. The reaction mixture was cooled to room temperature and filtered through a 0.5 μ m PTFE membrane filter (ADVANTEC MFS, Inc.). The resulting solid was washed with methanol and then dried under reduced pressure to afford indigo (**1**) (9.10 g, 81%) as a deep-blue solid. The spectral data and analytical data of **1** were agreement with those previously reported.² The purity of the solid was estimated to be greater than 98% on the basis of the following procedure.¹⁷ The deep-blue solid of indigo (**1**) was treated with conc. sulfuric acid to afford indigo-5,5'-sulfonic acid and then the aqueous solution of the resulting mixture was titrated with potassium permanganate.

Large-Scale Procedure for the Production of Indigo (1). A four neck flask having a capacity of 3 L and fitted with a mechanical stirrer, a thermometer, a dropping funnel and a cooling coil was charged with *tert*-butyl alcohol (1.0 kg),

indole (**6**) (100.0 g, 853.6 mmol), molybdenum naphthenate (Mo 5%, Nihon Kagaku Sangyo Co., Ltd.) (1.63 g, 0.85 mmol), and acetic acid (5.1 g, 84.9 mmol) sequentially. While this mixture was being heated at 86 °C (reflux) on an oil bath and stirred, an 82 wt % solution of CHP in cumene (348.5 g, 1878 mmol of CHP) dissolved in *tert*-butyl alcohol (0.5 kg) was added dropwise thereto over a period of 1.5 h. Thereafter, the reaction was continued for 7 h under the same conditions. The reaction mixture was homogeneous at the start of the reaction, but a deep-blue solid gradually precipitated out with the progress of the reaction. The reaction mixture was cooled to room temperature and filtered through 0.5 µm PTFE type membrane filter (ADVANTEC MFS, Inc.). The resulting solid was washed with methanol and then dried at 50 °C under reduced pressure to deep-blue solid product. Elemental analysis and IR spectroscopic analysis revealed that this product was indigo (**1**). The molar yield of the isolated indigo as based on the charged indole was 79.8%.

References

- 1 For a recent review, see: a) E. S. B. Ferreira, A. N. Hulme, H. McNab, A. Quye, *Chem. Soc. Rev.* **2004**, 33, 329. b) E. Steingruber, in *Ullmann's Encyclopedia of Industrial Chemistry*, ed. by B. Elvers, S. Hawkins, M. Ravenscroft, G. Schulz, VCH, Weinheim, Germany, **1989**, Vol. A14, p. 149.
- 2 a) Degussa, DRP No. 137955, **1901**; J. Pflieger, *Fortschritte der Theerfarben Fabrikation*, Part 6, p. 560. b) J. G. Kern, H. Stenerson, *Chem. Eng. News* **1946**, 24, 3164.
- 3 Y. Inoue, Y. Yamamoto, H. Suzuki, U. Takaki, in *New Developments in Selective Oxidation II*, ed. by V. Cortés Corberán, S. Vic Bellón, Elsevier, Amsterdam, **1994**, pp. 615–622.
- 4 T. Honda, F. Matsuda, K. Kiyoura, K. Terada, EP Patent 69 242, **1983**.
- 5 T. Yoshimura, T. Ohno, *Photochem. Photobiol.* **1988**, 48, 561.
- 6 C. J. Nielsen, R. Stotz, G. T. Cheek, R. F. Nelson, *J. Electroanal. Chem.* **1978**, 90, 127.
- 7 B. Witkop, *Justus Liebigs Ann. Chem.* **1944**, 556, 103.
- 8 B. Hughes, H. Suschitzky, *J. Chem. Soc.* **1965**, 875.
- 9 C. E. Dalglish, W. Kelly, *J. Org. Soc.* **1958**, 3726.
- 10 a) A. K. Sheinkman, H. A. Klyuev, L. A. Rbibenko, E. X. Dank, *Khim. Geterotsikl. Soedin.* **1978**, 11, 1490. b) T. Kaneko, M. Matsuo, Y. Iitaka, *Heterocycles* **1979**, 12, 471.
- 11 a) S. Sakamura, Y. Obata, *Bull. Agric. Chem. Soc. Jpn.* **1956**, 20, 80. b) B. Witkop, H. Fiedlerl, *Justus Liebigs Ann. Chem.* **1947**, 558, 91.
- 12 Using cumene as a solvent instead of toluene (Table 2), further catalyst screening was performed. Although we found that [Mo(OBz)₂]₂, [Mo(OAc)₂]₂, Ta(OBu)₅, and 1% Ti/SiO₂ also promoted the reaction, they did not exceed the result of Mo(CO)₆.
- 13 B. Capon, F. C. Kwok, *J. Am. Chem. Soc.* **1989**, 111, 5346.
- 14 a) H. Mimoun, *Angew. Chem., Int. Ed. Engl.* **1982**, 21, 734. b) P. Chaumette, H. Mimoun, L. Saussine, J. Fischer, A. Mitschler, *J. Organomet. Chem.* **1983**, 250, 291.
- 15 G. A. Russell, G. Kaupp, *J. Am. Chem. Soc.* **1969**, 91, 3851.
- 16 G. L. O'Connor, H. R. Nace, *J. Am. Chem. Soc.* **1955**, 77, 1578.
- 17 Japanese Industrial Standard (JIS) K8092-1972.