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Development of Large-Scale Preparations of Indole Derivatives: Evaluation of Potential Thermal Hazards and Studies of Reaction Kinetics and Mechanisms

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Abstract:

Hydrogenation of (*E*)-2-nitropyrrolidinostyrene in the presence of the doped rhodium catalyst is safe, scalable, and highly effective for the preparation of 6-benzyloxyindole. Reaction kinetics with/without additives also were examined using in situ IR for the first time. Results showed that the additives decelerate the hydrogenolysis of benzyl ethers, while simultaneously accelerating the de-oxygenation of *N*-oxy-intermediates.

Introduction

The development of DNA topoisomerase I inhibitors as cancer chemotherapy agents is an active area of research.[1] An indolocarbazole drug candidate (**1**) has emerged because of its potent cytotoxic activity against human cancer cells[2] and its wide safety margin and is currently in clinical trials. Bis-indolyl compound **2** is a key intermediate for the practical and scalable synthesis of **1**[3] (Figure 1). Bis-indolyl compound **2** is prepared from maleimide **3** and indole **4** under Steglich conditions.[4] For the Steglich conditions, the hydroxyl group of 6-hydroxyindole must be protected, such as in **4**. Therefore, a scalable and practical synthesis of **4** was required for the development of drug candidate **1**.

We recently performed mild and high-yielding hydrogenations in the presence of Rh/C doped by additives, such as $Ni(NO_3)_2 \cdot 6H_2O$, $Fe(OAc)_2$, or $Co(acac)_3$, for the Leimgruber–Batcho indole synthesis as shown in Scheme 1.[5]

Here, we report a large-scale procedure for the selective preparation of **4** and the results of kinetic studies.

Results and Discussion

1. Choice of Reduction Methods for Large-Scale Preparation. *1.1. Common Reaction Conditions for Leimgruber–Batcho Indole Synthesis.* Several different sets of reaction conditions have been reported for the Leimgruber–Batcho indole synthesis.[6–8] Raney nickel is the most common reducing reagent for this indole synthesis.[6] As mentioned above, our newly developed hydrogenation conditions have been successfully applied to this reaction.[5] To select suitable reduction conditions for large-scale preparation, different conditions were evaluated by reaction calorimetry to determine thermal hazards.

1.2. Potential Thermal Hazards Evaluations. Raney Nickel vs Catalytic Hydrogenations. The Raney nickel reaction was conducted by adding 3.9 equiv of hydrazine in EtOH at 52 °C. Chart 1 summarizes the calorimetry results from Raney nickel reduction. The sum of yellow and orange areas under the curve of heat flow in Chart 1 shows heat generation. The timing of hydrazine addition is shown as arrows in Chart 1. Delay of heat generation (orange areas) was observed after halting the additions of hydrazine. On the basis of the heat generation from orange areas in Chart 1, the adiabatic temperature at the delay areas was calculated to be 60 °C. These data suggest that reaction temperature might exceed the boiling temperature of EtOH without adequate cooling capacity, creating potential risk for Raney nickel reduction upon scale-up.

The proposed hydrogenation conditions also were evaluated. Reaction was conducted at the same scale as the above Raney nickel reaction in the presence of Rh/C doping with the nickel additive under H_2 at 30 °C. Chart 2 summarizes the calorimetry results of the hydrogenation, which indicate that the proposed hydrogenation conditions presented no potential thermal hazards. Heat generation was minimal and depended on agitation speed and hydrogen pressure. Therefore, the reaction rate of the hydrogenation was determined by diffusion rate of hydrogen into the reaction medium. The reaction calorimetric studies clearly indicated that the heat

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(7) Metal iron and/or aluminum amalgam reductions are known. However, they usually result in moderate yields and have the disadvantage of requiring labor-intensive workup procedures to remove metal residues. In addition, disposal of the waste metals can become an environmental problem. Therefore, these conditions are suitable for large-scale syntheses. Reductions using iron: (a) Knölker, H.-J.; Hartmann, K. *Synlett* **1993**, 755. (b) Sinhababu, A. K.; Borchardt, R. T. *J. Heterocycl. Chem.* **1988**, *25*, 1155. Reductions using aluminum amalgam: Toste, F. D.; Still, I. W. J. *Org. Prep. Proced. Int.* **1995**, *27*, 576.

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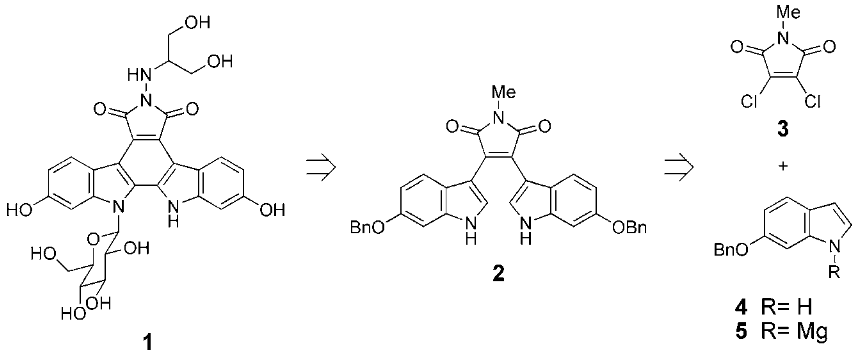

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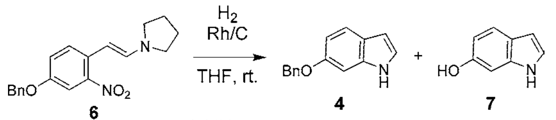
Figure 1. **Synthesis of the indolocarbazole.**

Scheme 1. **The Leimgruber−Batcho indole synthesis for 6-benzyloxyindole**



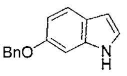
Additives	4	7
no additives	55%	34%
$Ni(NO_3)_2{\cdot}6H_2O$	90%	1%
$Fe(OAc)_2$	96%	1%
$Co(acac)_3$	94%	3%

generation could be controlled by adjusting the feeding rate of hydrogen, even if the cooling utility failed. Therefore, from a safety point of view, the hydrogenation conditions offer a great advantage and are suitable for large-scale preparation.

In conclusion, the Raney nickel conditions carried a potential risk of heat accumulation. In contrast, our proposed hydrogenation conditions present no thermal risk as determined by thermal hazard evaluations. Therefore, the hydrogenation conditions for large-scale preparation of the key intermediate **4** were chosen.

2. Reaction Mechanism of Hydrogenation. *2.1. Reaction Monitoring Using in Situ IR Spectrometry.* Optimization of the hydrogenation conditions revealed that some additives, especially Ni, Fe, and Co salts, improved chemoselectivity.[5] For reaction scale-up, a thorough understanding of the reaction mechanism is important. Therefore, the role of additives was examined using in situ IR spectrophotometry.

To compare the three additives, reactions were conducted using 3 mol % of Rh/C with 20 mol % of each additive. Four major components (**4**, **6**, **7**, and **11**) were observed during monitoring with in situ IR. On the basis of reported information,[9] components **4**, **6**, and **7** were monitored at 1166 cm^{-1} (**4**), 1614 cm^{-1} (**6**), and 720 cm^{-1} (**7**). *N*-Hydroxyindole **11** was isolated, identified, and monitored at 1227 cm^{-1}.[10] Relative ratios of peak intensities were adjusted on the basis of HPLC data.



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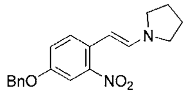

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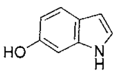

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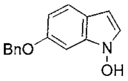

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2.2. Monitoring by in Situ IR Spectrometry. Chart 3 summarizes the relative concentration of each component obtained from in situ IR data. Graphs a, b, c, and d of Chart 3 represent progress of hydrogenation with no additive, nickel additive, iron additive, and cobalt additive, respectively.

Consumption rates of starting material **6** were similar in all cases and were governed by hydrogen diffusion rate. For the iron additive, intermediate **11** was not observed; instead, desired product **4** was formed directly. Under the other conditions, formation of **11** was observed upon consumption of **6**.

Consumption rates of **11** were quite slow during hydrogenation without an additive, and **11** did not disappear even after more than 20 h. In contrast, **11** was completely consumed when using a nickel or cobalt additive; consumption rate using the cobalt additive was faster. Therefore, nickel or cobalt salts clearly exert an accelerating effect on the de-oxygenation of *N*-oxy-compounds.

Formation rates of de-benzylated byproduct **7** were much slower during hydrogenation with than without an additive, indicating that de-benzylation rates of **4** were suppressed by the doping additives. Metal cations, such as Pb^{4+},[11] Mg^{2+},[12] and Zn^{2+},[13] are known poisons for hydrogenation catalysts.[13−16] Thus, the nickel, iron, and cobalt salts also act as poisons to suppress de-benzylation.

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(10) We examined isolate **11**. However, only 91.5% purity of **11** was obtained because of its instability. The procedure was as follows: To a mixture of enamine **6** (4.00 g, 12.3 mmol), zinc chloride (504 mg, 3.70 mmol), and 5% Rh/C (1.27 mg, 0.616 mmol) was added THF (60 mL). After the atmosphere was replaced with N_2 followed by H_2, the mixture was stirred for 5 h at rt under atmospheric pressure of H_2. After the atmosphere was replaced with N_2, the catalyst was removed by filtration. The resulting solution was analyzed by HPLC to yield *N*-hydroxyindole **11** (2.86 assay mg, 97% yield) and indole **1** (82.5 assay mg, 3% yield). The solution was concentrated and purified by chromatography to afford the desired *N*-hydroxyindole **11** as a yellow oil (85 mg, 3% yield, 91.5 area % on HPLC). **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.7 (br s, 1H), 7.53−7.42 (m, 5H), 7.37 (br d, $J = 7.0$ Hz, 1H), 7.31 (dd, $J = 0.7$, 3.3 Hz, 1H), 6.98 (d, $J = 1.8$ Hz, 1H), 6.77 (m, 1H), 6.24 (d, $J = 3.3$ Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 138.4, 134.5, 129.3, 128.5, 128.4, 125.5, 122.2, 118.9, 110.9, 96.9, 93.4, 70.4; IR (KBr) 3437, 2927, 1624, 1489, 1455, 1385, 1322, 1227, 1200, 1028, 947, 813, 742, 698, 669, 622, 538 cm^{-1}; MS (APCI) *m/z* 240 (M + H)$^+$; HRMS (APCI) calcd for $C_{15}H_{14}NO_2$ [(M + H)$^+$] 240.1025, found 240.1036.

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Chart 1. **Reaction calorimetry of the reduction using Raney nickel and hydrazine**

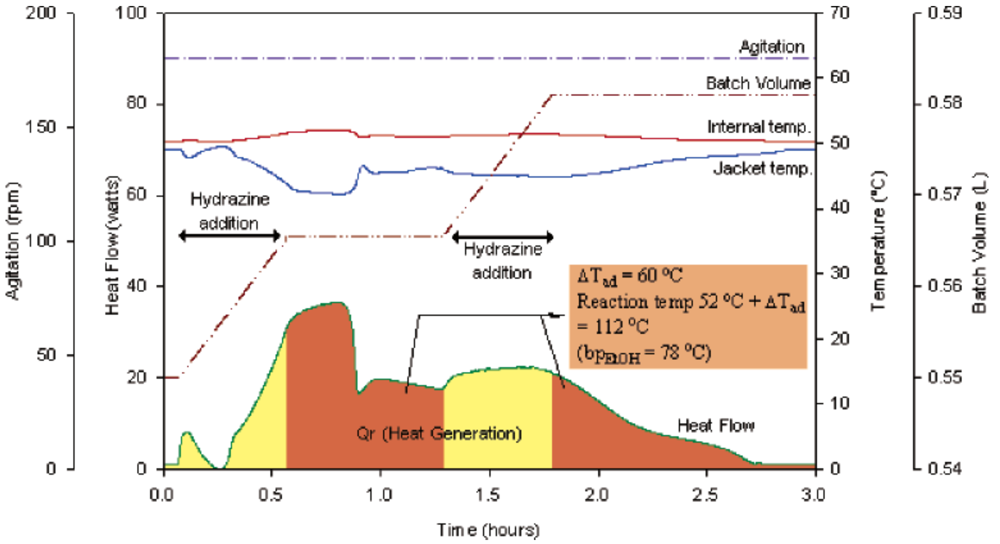
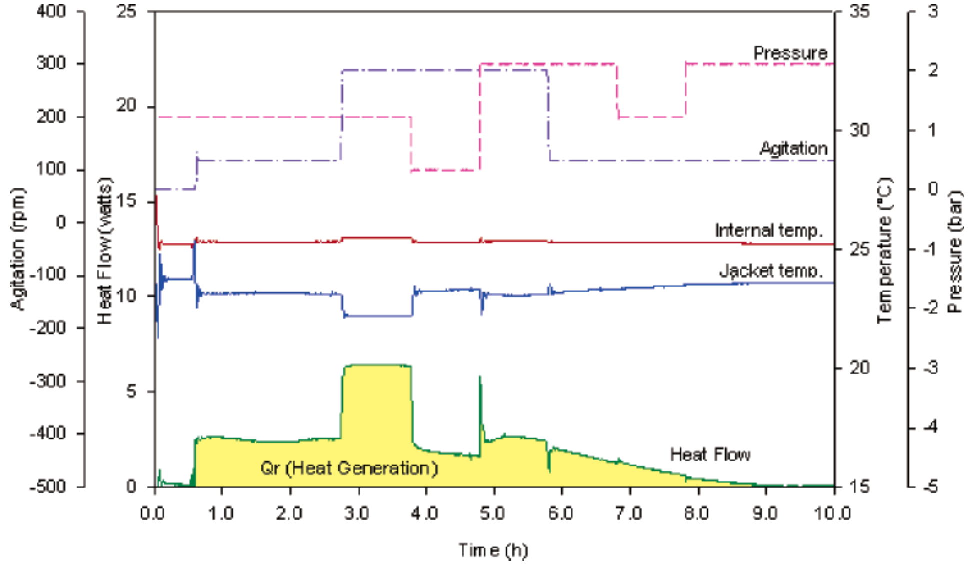


Chart 2. **Reaction calorimetry from hydrogenations using a nickel additive**



2.3. Reaction Pathways of the Leimgruber–Batcho Indole Synthesis. Path A vs path B. This reaction proceeds through nitroso **8** and hydroxylamine **9** starting from enamine **6** (Scheme 2). Two reaction pathways are possible. The first is a pathway through aniline **10** (path A). The second proceeds through *N*-hydroxyindole **11** (path B). Clark et al. reported that Leimgruber–Batcho indole synthesis would proceed only through path A in the case of indoles bearing an electron-withdrawing group at position 4.[17] Since only **11** was observed during reaction under the conditions we present here, we investigated **11** as a potential intermediate for **4**. Exposure of isolated **11** to hydrogenation conditions using Rh/C without additives afforded an 87:12:1 mixture of **11**:**4**:**7**,[18] indicating that compound **11** is the intermediate for **4** and that path B is feasible. For the iron salt, no reaction intermediates were observed. Therefore, either reduction of **11** or of **9** is extremely fast compared with the other steps, preventing the discrimination of path A or B.

2.4. Conclusions of Reaction Kinetics Studies. De-benzylation rates were decelerated, while de-oxygenation rates of *N*-oxy-compounds simultaneously were accelerated by doping additives. These doping additives might have two major roles. The first is activation of the N–O bond cleavage by coordinating with the oxygen similar to a Lewis acid. The other is modification of the catalytic activity itself in a manner similar to lead ion and quinoline in a Lindler catalyst.[11]

3. Large-Scale Application.

3.1. Reaction Conditions Optimization. We selected the iron additive conditions for performing the large-scale reaction, because these conditions provided the best yield, greatest selectivity, and safe and easy operation. Table 1 reveals optimized conditions for the large-scale reaction.

Initially, smaller amounts of catalyst were examined. To complete the reactions 1 mol % of the catalyst was adequate

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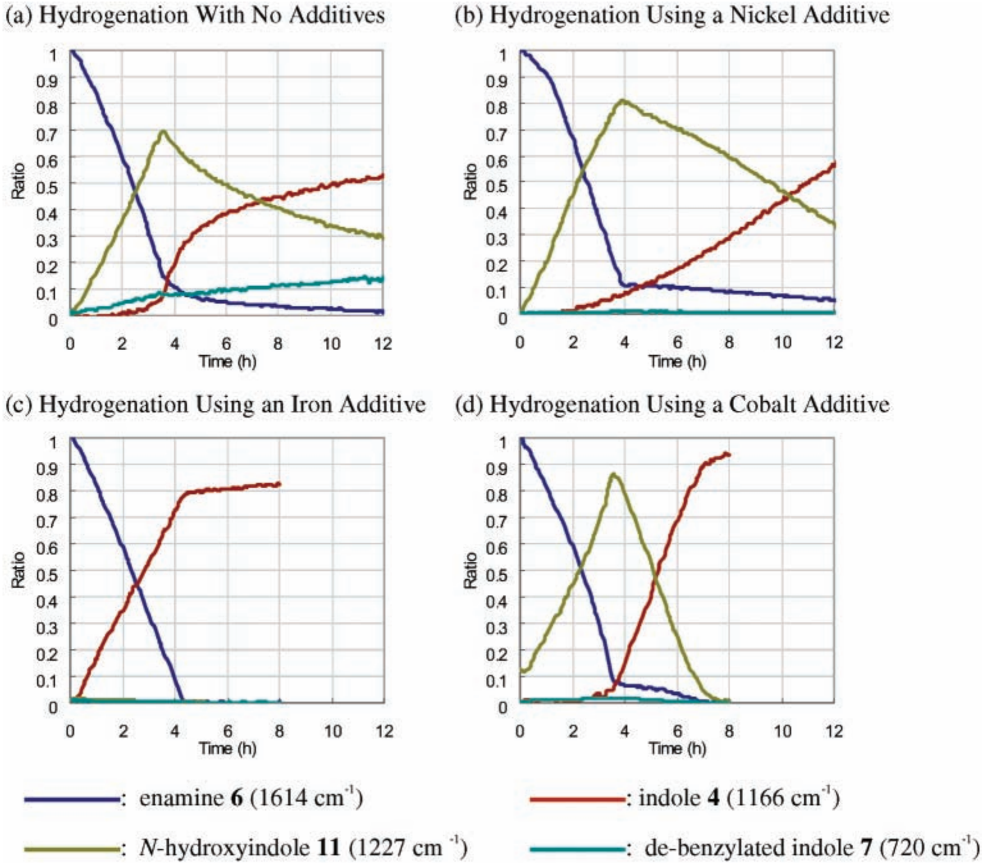
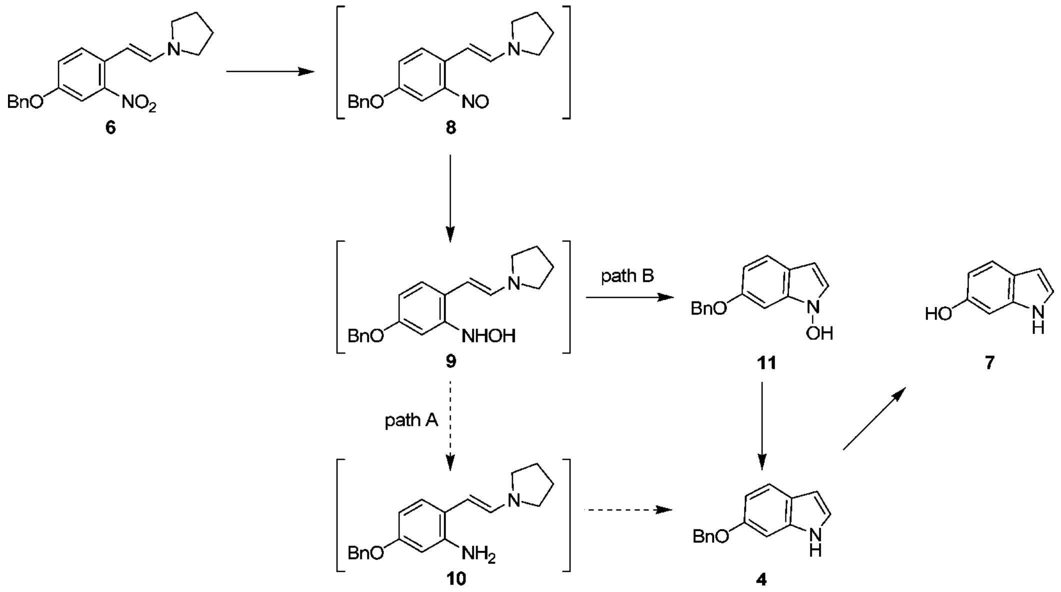
(17) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.

(18) Indole **4** and *N*-hydroxyindole **11** were exposed to the hydrogenation conditions with no additives. From **4**, an 86:14 mixture of **4** and de-benzylated indole **7** was obtained after standing for 1 h. In contrast, from **11**, an 87:12:1 mixture of **11**:**4**:**7** was obtained after standing for 1 h. Therefore, the reaction rate from **11** to **7** appears to be slow and could be ignored.

Chart 3. **Kinetic studies of hydrogenations using in situ IR spectrometry**



Scheme 2. **Proposed mechanism of the Leimgruber−Batcho indole synthesis**



(entries 1 and 2), but 3 mol % conditions produced better yields and shorter reaction times (entries 3 and 4). Therefore, 3 mol % conditions were adopted. The yield at a lower concentration (20 mL/g volume) was better than that at a higher concentration (10 mL/g volume) (entry 3 vs 4), but volumetric productivity of 10 mL/g volume was better. Therefore, 10 mL/g volume was adopted. A temperature of 30 °C and hydrogen pressure 0.1 MPa were adopted. Under optimized conditions, **4** was obtained in 88% yield at a 20-L scale.

3.2. Studies of Workup and Crystallization Methods. To isolate pure crystals of **4** without chromatographic purification, appropriate workup and purification must be selected. Initial studies indicated that low-polarity impurities in **4** can be removed effectively by crystallization in heptane−toluene. Therefore, removal of polar colored impurities and residual

Table 1. **Optimization of reaction conditions**

	Rh/C (mol %)	$Fe(OAc)_2$ (mol %)	temp (°C)	pressure (MPa)	time (h)	volume (mL/g)	volumetric productivity (g yield/L)	yield[a] (%)
1	1	1	rt.	balloon	33	10	61	88
2	1	1	rt.	balloon	15	20	33	96
3	3	3	rt.	balloon	12	10	63	91
4	3	3	rt.	balloon	9	20	34	98
5	3	3	30	balloon	6	10	63	92
6	3	3	30	0.1	9	10	63	92

[a] Yields determined by HPLC.

Table 2. **Washing with aqueous citric acid**

		RRT[a] (area %)[b]	
	treatments	0.31[c]	1.00[d]
1	no washings	3.1	95.2
2	after washing with aq citric acid 1 time	2.4	95.9
3	after washing with aq citric acid 3 times	0.1	98.4

[a] Relative retention times on HPLC. [b] Area % by HPLC. [c] Polar byproduct of unknown structure. [d] Indole **4**.

Table 3. **Elimination of residual metals**

workup operations	residual Fe (μg/mL)	residual Rh (μg/mL)
aq NH_3 waste	429	3
aq citric acid waste	2	<1
aq $NaHCO_3$ waste	<1	<1
brine waste	<1	nd
crystal	nd	nd

metals was needed prior to crystallization. Washing organic extracts with aqueous citric acid, after removal of Rh/C by a filtration, effectively eliminated polar impurities as shown in Table 2. Three washes adequately reduced polar impurities to afford a pale solution of **4**.

Residual heavy metals in the aqueous waste was monitored for each workup operation, as summarized in Table 3. Washing with aqueous ammonia effectively reduced the level of residual iron.

The optimized workup and crystallization method is as follows: The crude reaction mixture of **4** was filtered to remove Rh/C, was washed with aqueous NH_3, aqueous citric acid, aqueous $NaHCO_3$, and brine, and then was crystallized from heptane−toluene. These procedures resulted in isolation of pale crystals of **4** with 99.0% purity by HPLC and at 90% recovery from the solution before workup. The pale color of the crystals obtained did not affect the next step. Filtration through a pad of silica gel removed color. Using these methods, this newly developed hydrogenation was conducted at a 20-L autoclave scale. Procedure details are in the experimental section.

Conclusion

In conclusion, highly effective preparation of 6-benzyloxyindole from (*E*)-2-nitropyrrolidinostyrene by hydrogenation in the presence of a rhodium catalyst doped by an additive, such as $Ni(NO_3)_2{\cdot}6H_2O$, $Fe(OAc)_2$, or $Co(acac)_3$, is safe and scalable. Reaction kinetics were determined using in situ IR for the first time and revealed that the doping additives slow the hydrogenolysis of benzyl ether while simultaneously accelerating the deoxygenation of *N*-oxy compounds. We successfully developed hydrogenation conditions with Rh/C and iron salt for large-scale indole synthesis. This synthetic procedure will aid the development of anticancer drugs.

Experimental Section

General Methods. Unless otherwise noted, authentic samples of materials and products were obtained from general commercial suppliers,[19] and purity of these materials and products was determined by HPLC. All commercial chemicals were used without further purification. HPLC was performed with a Hitachi D-7000 series instrument under the following conditions: column, YMC AM-303; column size, i.d. 4.6 mm × length 250 mm × 5 μm particle size; column temp: 40 °C; flow rate, 1.0 mL/min; detector wavelength, 220 nm; injection volume, 10 μL; mobile phase was A = 0.1% phosphoric acid, B = MeCN, A:B = 35:65 (0 min), 10:90 (20 min). Reaction calorimetry was obtained on a Mettler Toledo RC-1*e* calorimeter. In situ IR spectra were obtained on an Applied Systems Inc. React IR 1000 spectrophotometer with a diamond probe. NMR spectra were recorded on Bruker AV-300 and AV-500 spectrometers. IR spectra were recorded on a Jasco FT/IR-610 spectrophotometer. MS spectra were measured on Jasco JMS-SX 102A and Finnigan LC-Q spectrometers. Levels of residual metals were determined by inductively coupled plasma mass spectrometry (IC-PMS) on a Shimadzu ICPM-8500 spectrometer.

Laboratory Procedure of Hydrogenation to Obtain the Indole. To a mixture of enamine **6** (5.00 g, 15.4 mmol), iron(II) acetate (28 mg, 0.154 mmol), and 5% Rh/C (317 mg, 0.154 mmol), tetrahydrofuran (THF) (100 mL) was added. After the atmosphere was displaced with N_2 followed by H_2, the mixture was stirred for 15 h at rt under atmospheric pressure of H_2. After the atmosphere was replaced with N_2, aqueous NH_3 (~14%, 20 mL) was added. The following workup operations were conducted under N_2. After stirring for 20 min, the mixture was filtered to remove the catalyst, which was washed with THF (50 mL). The combined solutions were extracted with toluene (50 mL). The organic layer obtained was washed with aqueous citric acid (10%, 50 g), aqueous sodium bicarbonate (5%, 50 g), and brine (20%, 50 g). The yield of the target indole **4** was determined by HPLC (3.30 assay g, 96% yield). The solution was concentrated in vacuo. The residue was dissolved in toluene (100 mL) and filtered through a pad of SiO_2 (5 g), and the silica gel was washed with toluene (100 mL). The combined toluene solutions were analyzed by HPLC (3.22 assay g, 94% yield), and then concentrated in vacuo. The residual solids were suspended in toluene (5 mL) and heptane (13 mL) and heated to 90 °C to dissolve the solids. The homogeneous solution was cooled to 63 °C, followed by seeding with a crystal of indole **4** to form a seed bed. The

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(19) Authentic indoles were available from Biosynth International, Inc.

slurry formed was stirred for 1 h at 60−65 °C, heptane (37 mL) was added over a period of 2 h, and the solution was gradually cooled to rt. After standing overnight, the slurry was filtered, washed with heptane−toluene (10:1) (5.5 mL) and heptane (5.5 mL), and dried in vacuo at 40 °C overnight. The target indole **4** was obtained as colorless crystals (2.94 g, 86% yield with 99.9 area % purity by HPLC).

Large-Scale Procedure of Hydrogenation to Obtain the Indole. A 20-L autoclave was filled with N_2. THF (5.42 kg), enamine **6** (1.20 kg, 3.70 mol), and iron(II) acetate (16.6 g, 92.3 mmol) were added to the autoclave. After washing the inner wall of the autoclave with THF (1.73 kg), 5% Rh/C (192 g, 93.3 mmol) was added very carefully via a N_2 bag. (Do NOT contact the dry Rh/C with flammable solvent vapor or air!) After washing the wall of autoclave with THF (3.52 kg), the autoclave was warmed to 25−30 °C. The atmosphere in the autoclave was then replaced with N_2 followed by H_2. After the mixture was stirred for 9 h at 25−30 °C under 0.05−0.10 MPa of H_2, the atmosphere in the autoclave was replaced with N_2, the stir rate was reduced, and the mixture was allowed to stand overnight at ambient temperature. After addition of aqueous NH_3 (4.80 kg; 2.40 kg of saturated aqueous NH_3 was diluted to 4.80 kg with H_2O), the following procedures were conducted under N_2. After stirring for 20 min, the mixture was filtered to remove the catalyst, which was washed with THF (10.67 kg). The combined solutions were placed in a 50-L glass vessel and were agitated with toluene (10.39 kg), allowed to settle for 20 min, and separated (aqueous layer: 4.90 kg, pH 12.4). The organic layer obtained was washed with aqueous citric acid (10%, 3 × 7.20 kg), aqueous sodium bicarbonate (5%, 4.80 kg), and water (4.80 kg). After HPLC analysis of the solution obtained (28.0 L; 725 assay g, 88 assay % yield of indole **4**), the following solvent switching operation was conducted four times (i.e., the solution was concentrated in vacuo to ∼21.6 L, toluene (14.4 L) was added, and the mixture was concentrated again in vacuo to ∼21.6 L). The resulting brown toluene solution was filtered through a pad of SiO_2 (1.20 kg packed in a pressure filter, i.d. 29.3 cm), and the silica gel was washed with toluene (20.78 kg). The colorless toluene solutions were combined and analyzed by HPLC (21.3 L; 722 assay g, 87 assay % yield of indole **4**), concentrated in vacuo to ∼6 L, followed by addition of heptane (0.5 L) to wash the wall of vessel. The resulting suspension was heated to 65−70 °C to dissolve the solids. Heptane (1.9 L) was added slowly to the homogeneous solution, and the resulting mixture was cooled to 63 °C followed by the addition of seed (∼1.2 g of indole **4**) to form the seed bed. The slurry formed was stirred for 1 h at a temperature of 58−63 °C, followed by addition of heptane (11.48 kg) over a period of 2 h. The resulting slurry was cooled to room temperature. After standing overnight (22 °C, 1.4 assay mg/mL of indole **4** in the supernatant liquid by HPLC), the slurry was cooled to 0−5 °C (0.5 assay mg/mL of indole **4** in the supernatant liquid by HPLC), allowed to stand for 1 h, and filtered (indole **4** in 16.20 kg of the mother liquor: 11.5 assay g, 1.4 assay% yield). The crystals were washed with heptane−toluene (9:1) (1.2 L) followed by heptane (2 × 1.2 L) and dried in vacuo at 40 °C for 16 h. The desired indole **4** was obtained as colorless crystals (100 w/w %, 99.89 area % purity on HPLC, 678 g, 82% yield).

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