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An Enantioselective Approach to 2,3-Disubstituted Indolines through Consecutive Brønsted Acid/Pd-Complex-Promoted Tandem Reactions

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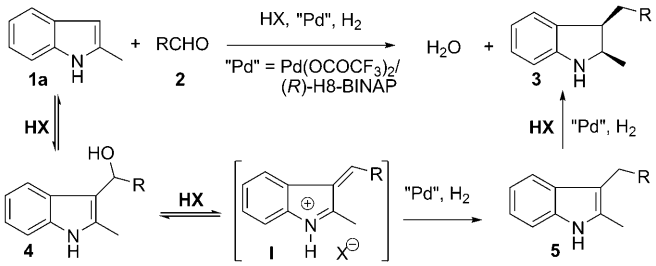
Tandem reactions and consecutive catalysis (or relay catalysis) have been receiving considerable attention in organic synthesis due to their abilities of constructing multiple new chemical bonds to build complex chiral molecules in a single operation.[1,2] Transition-metal-catalyzed asymmetric hydrogenation is one of the most widely used and reliable catalytic methods for preparation of chiral molecules.[3] The combination of Brønsted acid/transition-metal-catalyzed tandem reactions involving asymmetric hydrogenation as key step remains rare,[4] although Krische and co-workers reported the C–C bond formation with metal hydride as the catalytic species.[2c,5]

Chiral 2,3-disubstituted indolines are significant building blocks in biologically active natural products and pharmaceutically active compounds.[6] Generally, these compounds are synthesized from either dynamic resolution or multiple-step reactions.[7] The most straightforward and atom economic means towards chiral indolines may be the asymmetric hydrogenation of substituted indole derivatives. Recently, some significant progress has been achieved by us and other groups for the highly enantioselective hydrogenation of substituted indoles using chiral Pd, Rh, Ru, and Ir complexes as catalysts.[8] Very recently, we developed a facile approach to chiral 2,3-disubstituted indolines through dehydration-triggered asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles.[9] Despite these contributions, the tedious procedure for the preparation of the substrates limits its synthetic applications. So, the search for a rapid, simple, and divergent method for synthesizing chiral 2,3-disubstituted indolines is still highly desirable.

Considering reductive alkylation (Friedel–Crafts/dehydration/reduction) of 2-substituted indoles and aldehydes can rapidly lead to 2,3-disubstituted indoles,[10] we envisioned that combination of reductive alkylation of 2-substituted indoles and asymmetric hydrogenation[11] of 2,3-disubstituted indoles can lead to a rapid and divergent approach to chiral 2,3-disubstituted indolines (Scheme 1).[12] Herein, we describe the enantioselective access to chiral 2,3-disubstituted indolines through consecutive Brønsted acid/Pd-complex-promoted reductive alkylation/hydrogenation reactions with up to 98% *ee* (Scheme 1). Three steps are promoted by a Brønsted acid and two hydrogenation steps are catalyzed by a Pd complex. Furthermore, the asymmetric hydrogenation should drive the equilibrium of the Friedel–Crafts reaction by converting the Friedel–Crafts product into a hydrogenation product.



Scheme 1. The process for synthesis of 2,3-disubstituted indolines Brønsted acid (HX)-promoted three-step reaction and Pd-catalyzed two-step reaction.

The reaction process was proposed as shown in Scheme 1. The Brønsted-acid-promoted Friedel–Crafts reaction of 2-methylindole and aldehyde afforded 3-(α-hydroxyalkyl)indole **4**; then, **4** was dehydrated to give the important intermediate vinylogous iminium **I**,[13] followed by two asymmetric hydrogenation steps to accomplish this process. For the above process, several issues should be addressed. Firstly, 2-substituted indole **1a** might be preferentially hydrogenated (Scheme 2, reaction 1).[8e] Secondly, bisindoles **6** is always the byproduct of indole and aldehyde with Brønsted acid as the catalyst (Scheme 2, reaction 2).[10e,14] Thirdly, both strong Brønsted acid and water existed in the reaction, so the relevant hydrogenation catalyst must be compatible with them. Therefore, several experiments were designed to assess the feasibility of this process. To our delight, after mixing 2-methylindole, benzaldehyde, and *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) in $CDCl_3$ and stirring for 5 min, the peaks of 2-methylindole and benzaldehyde almost disappeared, as observed by ^1H NMR analysis. This result suggested that the Friedel–Crafts reaction between 2-methyl

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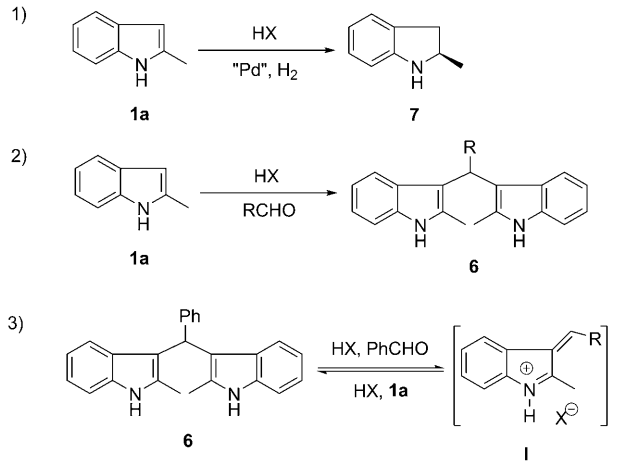


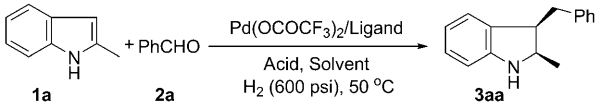
Scheme 2. Possible side reactions.

indole and benzaldehyde was very fast (Scheme 1). Moreover, bisindole **6** could be reversibly transformed to vinylogous iminium **I** (Scheme 2, reaction 3) in the presence of strong Brønsted acid and aldehyde (see further).[10c,15] Recently, palladium complexes have been successfully applied to the enantioselective hydrogenation of unprotected indoles, activated imines, and ketones by us and other groups.[8e,9,16] Our preliminary mechanistic study found that the palladium hydrogenation catalyst was not sensitive to Brønsted acid and water. Therefore, we foresaw that the Pd catalyst system might work well in this tandem reaction.[8e,9,16]

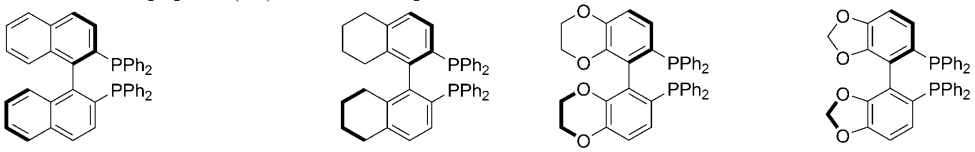
To explore the possibility of the proposed reductive alkylation/hydrogenation tandem process, we began with the reaction of 2-methylindole and benzaldehyde using by $TsOH{\cdot}H_2O$ and $Pd(OCOCF_3)_2$/(*R*)-BINAP as the catalyst. In our initial investigations, we found that the solvent played a crucial role in the transformation (Table 1, entries 1–7). No reaction was observed in toluene or THF (Table 1, entries 1 and 2). Moderate yields and *ee* values were obtained in dichloromethane and trifluoroethanol (TFE), respectively (Table 1, entries 3 and 4). Fortunately, the mixed solvent of dichloromethane and TFE (CH_2Cl_2/TFE = 2:1) provided enhanced yields and the best enantioselectivity. Next, various acids were tested: in contrast to strong acid, a weak acid such as benzoic acid was ineffective, and $TsOH{\cdot}H_2O$ showed the best result in terms of enantioselectivity and reactivity (Table 1, entries 7–13). Finally, several commercially available chiral bisphosphine ligands were investigated; (*R*)-H8-BINAP was found to be superior to other ligands (91 % *ee* in Table 1, entry 14). Consequently, the optimal conditions were established; $Pd(OCOCF_3)_2$/(*R*)-H8-BINAP/$TsOH{\cdot}H_2O$/H_2 (600 psi) in CH_2Cl_2/TFE (2:1) at 50 °C.

Next, to explore the scope of this reaction, various 2-substituted indoles and aldehydes were subjected to the optimal conditions and the results are summarized in Table 2. Generally, this reaction displayed good functional group tolerance. It was found that electron-deficient groups on indoles or on aldehydes gave indolines with slightly lower *ee* values (Table 2, entries 3, 10 and 11). An increase of enantioselectivity was observed in response to the employment of alkyl aldehydes instead of aromatic aldehydes. The investigation of aromatic aldehydes with variation in their steric features revealed that the reaction proceeded smoothly to give the desirable products with high *ee* values and slightly decreased yields (Table 2, entries 15–17). Notably, excellent 97–98 % *ee*s were achieved with substrates 2,7-dimethylindole **1e** (Table 2, entries 12–17), and this may be ascribed to the steric effect of the 7-methyl group.

Table 1. Optimization for tandem reaction of **1a** and **2a**.[a]



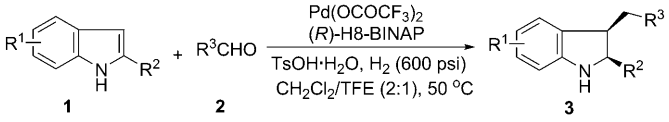
Entry	Solvent	Acid	Ligand	Yield [%][b]	*ee* [%][c]
1	toluene	$TsOH{\cdot}H_2O$	**L1**	–	–
2	THF	$TsOH{\cdot}H_2O$	**L1**	–	–
3	CH_2Cl_2	$TsOH{\cdot}H_2O$	**L1**	83	63
4	TFE	$TsOH{\cdot}H_2O$	**L1**	75	75
5	CH_2Cl_2/TFE (1:2)	$TsOH{\cdot}H_2O$	**L1**	91	84
6	CH_2Cl_2/TFE (1:1)	$TsOH{\cdot}H_2O$	**L1**	86	85
7	CH_2Cl_2/TFE (2:1)	$TsOH{\cdot}H_2O$	**L1**	88	87
8	CH_2Cl_2/TFE (2:1)	$MeSO_3H$	**L1**	88	84
9	CH_2Cl_2/TFE (2:1)	TFA	**L1**	63	41
10[d]	CH_2Cl_2/TFE (2:1)	$PhCO_2H$	**L1**	–	–
11	CH_2Cl_2/TFE (2:1)	L-CSA	**L1**	84	86
12	CH_2Cl_2/TFE (2:1)	D-CSA	**L1**	75	80
13	CH_2Cl_2/TFE (2:1)	$TsOH{\cdot}H_2O$	**L2**	91	91
14	CH_2Cl_2/TFE (2:1)	$TsOH{\cdot}H_2O$	**L3**	93	89
15	CH_2Cl_2/TFE (2:1)	$TsOH{\cdot}H_2O$	**L4**	88	84



(*R*)-BINAP **L1** (*R*)-H8-BINAP **L2** (*R*)-SynPhos **L3** (*R*)-SegPhos **L4**

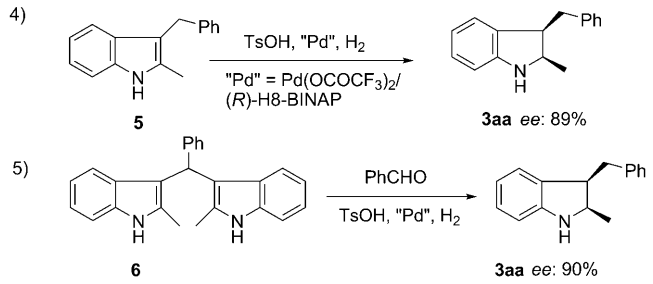
[a] Conditions: **1a** (0.25 mmol), **2a** (0.275 mmol), $Pd(OCOCF_3)_2$ (0.005 mmol), ligand (0.006 mmol), acid (0.25 mmol), and 3 mL solvent at 50 °C for 3–20 h. [b] Yield of isolated product. [c] Determined by HPLC. [d] With full conversion of **1a** and 2-methyl-3-benzylindole **5** was obtained as byproduct. TsOH = toluenesulfonic acid, CSA = 10-camphorsulfonic acid, TFA = trifluoroacetic acid.

Table 2. The synthesis of 2,3-disubstituted indoline derivatives **3**.[a]



Entry	R^1	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1	H	Me	Ph	**3aa**	91	91
2	H	Me	4-$MeOC_6H_4$	**3ab**	83	90
3	H	Me	4-FC_6H_4	**3ac**	87	87
4	H	Me	Cy	**3ad**	91	93
5	H	Me	*i*Pr	**3ae**	94	92
6	H	*n*Bu	Ph	**3ba**	92	94
7	H	*n*Bu	Cy	**3bd**	85	96
8	H	phenethyl	Ph	**3ca**	73	93
9	H	phenethyl	Cy	**3cd**	91	91
10	5-F	Me	Ph	**3da**	80	87
11	5-F	Me	Cy	**3dd**	74	91
12	7-Me	Me	Ph	**3ea**	82	97
13	7-Me	Me	Cy	**3ed**	82	97
14	7-Me	Me	*i*Pr	**3ee**	84	98
15	7-Me	Me	4-MeC_6H_4	**3ef**	77	97
16	7-Me	Me	3-MeC_6H_4	**3eg**	81	97
17	7-Me	Me	2-MeC_6H_4	**3eh**	73	98

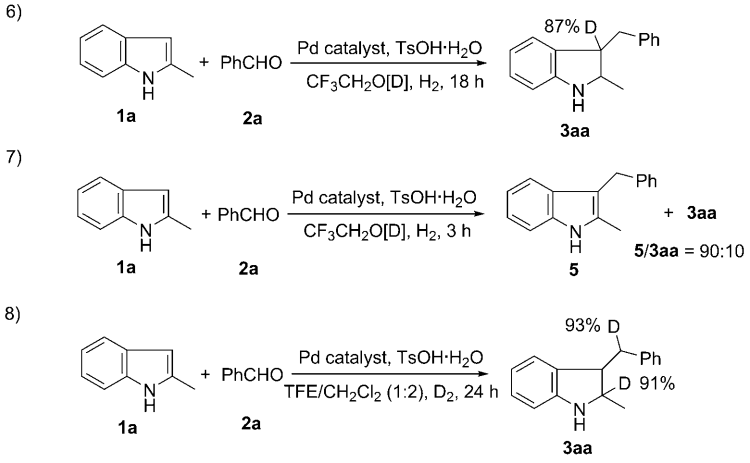
[a] Conditions: **1** (0.25 mmol), **2** (0.275 mmol), $Pd(OCOCF_3)_2$ (0.005 mmol), (*R*)-H8-BINAP (0.006 mmol), $TsOH·H_2O$ (0.25 mmol), and solvent (3 mL) at 50 °C for 3–20 h. [b] Yield of isolated product. [c] Determined by HPLC. Cy = cyclohexyl, *i*Pr = isopropyl, *n*Bu = *n*-butyl.



Scheme 3. Hydrogenation of **5** and **6** by using the chiral palladium.

To gain insights into the mechanism information of the transformation, a series of experiments were conducted. Electrospray ionization mass spectroscopic analysis of the solution of 2-methylindole, benzaldehyde and $TsOH·H_2O$ in TFE/CH_2Cl_2 (1:2) after stirring for 5 min at room temperature showed peaks at m/z^+ 220.1085 and m/z^- 171.0168, which were consistent with the intermediacy of **I** in Scheme 1. In another experiment, 2-methyl-3-benzylindole **5** can be isolated from the reaction mixtures performed at room temperature to shorten the reaction time to 3 h under the standard conditions.[9,15] When we subjected **5** to hydrogenation using the chiral palladium complex as a catalyst, full conversion and a similar 89% *ee* were obtained (Scheme 3, reaction 4 vs. entry 13, Table 1). This result suggested that the reaction proceeded stepwise with **5** as the intermediate. When the mixture of bisindole **6** and benzaldehyde **2a** was subjected to hydrogenation under standard conditions, a similar 90% *ee* was obtained with full conversion (Scheme 3, reaction 5 vs. entry 13, Table 1), which suggested that the reaction is reversible between bisindole **6** and intermediate vinylogous iminium **I** in the presence of Brønsted acid and benzaldehyde.

To obtain more evidence to clarify the mechanism, we performed three isotopic labeling experiments with deuterated solvent and deuterium gas, respectively (Scheme 4), and the results were identical to our previous reports.[8e,9] When the hydrogenation was carried out in deuterated TFE for 18 h, **3aa** was obtained as the product with complete conversion. ^{1}H NMR analysis showed that one deuterium atom took up the 3 position with 87% incorporation [Eq. (6)]. When the hydrogenation reaction was stopped at 3 h, **3aa** and **5** were obtained at a ratio of 10:90; ^{1}H NMR analysis of the isolated indole **5** showed that no deuterium atom was incorporated at the benzylic position (Scheme 4, reaction 7). When **1a** was treated with D_2, **3aa** was obtained with 91 and 93% incorporation of deuterium at the 2- and benzylic position, respectively (Scheme 4, reaction 8). The



Scheme 4. Deuterium-labeling studies.

above experiments clearly indicated that vinylogous iminium **I**, indole **5**, and bisindole **6** were probably the intermediates and all of them could be finally transformed to the desired product, which was the key factor for the successful tandem reactions.

In summary, we have developed an efficient tandem reaction through a consecutive Brønsted acid/Pd complex to

afford chiral 2,3-disubstituted indolines. Commercially available starting materials (2-substituted indoles and aldehydes), simple operation procedures, high yields, and high stereoselectivity make this method useful for rapid and divergent synthesis of chiral 2,3-disubstituted indolines in one single operation. Further investigations to extend the reaction scope and illustrate applications of this process in organic synthesis are underway.

Experimental Section

General Procedure: Ligand (0.006 mmol) and $Pd(OCOCF_3)_2$ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at RT for 1 h, then solvent was removed under vacuum to give the catalyst. In a glovebox, acid (0.25 mmol) and indole (0.25 mmol) were stirred in 1 mL solvent at room temperature for 1 min. Subsequently, aldehyde (0.275 mmol) was added slowly to the solution. Finally, the above catalyst together with solvent (2 mL) was added to the reaction mixture. The hydrogenation was performed at 50 °C under H_2 (600 psi) in a stainless steel autoclave for 16 h. After carefully releasing the hydrogen, the resulting mixture was concentrated under vacuum and dissolved in saturated aqueous $NaHCO_3$ (5 mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3×5 mL) and dried over Na_2SO_4. After purification by silica gel chromatography using petroleum ether/EtOAc (10:1) as eluent, the enantiomeric excess of the products were determined by HPLC with chiral column.

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Keywords: asymmetric catalysis · Brønsted acid · hydrogenation · palladium · tandem reaction

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