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Pd-Catalyzed Asymmetric Hydrogenation of Unprotected Indoles Activated by Brønsted Acids

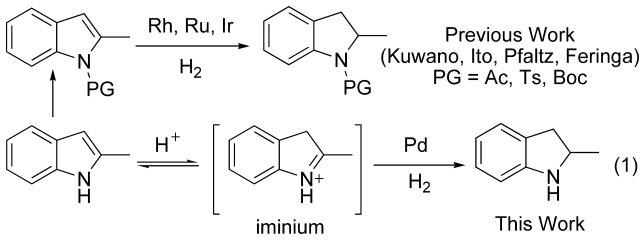
Duo-Sheng Wang,[†] Qing-An Chen,[†] Wei Li,[‡] Chang-Bin Yu,[†] Yong-Gui Zhou,*[,†] and Xumu Zhang*[,‡]

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China, and Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854

Received April 29, 2010; E-mail: ygzhou@dicp.ac.cn; xumu@rutgers.edu

Chiral indolines are ubiquitous structural motifs in naturally occurring alkaloids and many biological active molecules.[1] Some catalytic methods have been developed to obtain such molecules on the basis of the kinetic resolution.[2] Asymmetric hydrogenation of indoles is the most straight and powerful approach to make chiral indolines in terms of simplicity and atom efficiency. Despite the progress achieved in asymmetric hydrogenation of indoles and other heteroaromatic compounds in the past decade,[3] efficient hydrogenation of simple unprotected indoles remains a great challenge in organic synthesis. Kuwano and Ito developed the first highly effective hydrogenation of a series of *N*-protected indoles by application of a Rh or Ru complex.[4a−d] Feringa and co-workers reported Rh-catalyzed hydrogenation of 2-substituted *N*-protected indoles with moderate enantioselectivity.[4e] Very recently, the Pfaltz group revealed Ir/N,P-catalyzed hydrogenation of *N*-protected indoles with high ee but low reactivity.[4f] To the best of our knowledge, no report on asymmetric hydrogenation of unprotected indoles has appeared despite the operational simplicity.[5] Herein, we describe a new strategy for highly enantioselective Pd-catalyzed hydrogenation of unprotected indoles with a Brønsted acid as the activator with up to 96% ee.

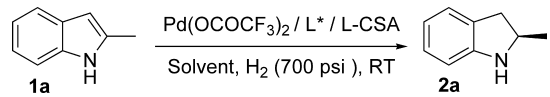
Scheme 1. Activation Strategy of Indoles with a Brønsted Acid



For the asymmetric hydrogenation of aromatics, the main challenge is the low reactivity.[3] Recently, our group developed two kinds of substrate activation strategies for the asymmetric hydrogenation of six-membered heteroaromatics with a Brønsted acid and chloroformate as activators, respectively.[6] Another breakthrough in hydrogenation of imines is through formation of iminium by addition of a Brønsted acid.[7] We envision that in searching hydrogenation of five-membered heteroaromatic unprotected indoles, development of a new activation strategy is highly desirable. Considering that the simple unprotected indoles can react with a strong Brønsted acid to form the iminium salt by protonation of the carbon−carbon double bond,[8] and the aromaticity of indole is destroyed, the *in situ* formed iminium salts would be prone to be hydrogenated (Scheme 1).

Initially, 2-methylindole was selected as a model substrate for optimization of the conditions. Recently, chiral palladium complexes have been successfully applied to asymmetric hydrogenation of activated imines by us[9] and other groups,[10] due to similarity between iminium salt and activated imine, and thus $Pd(OCOCF_3)_2$/(*R*)-SegPhos was used as the catalyst. In a control experiment, without the addition of a Brønsted acid, the reaction did not occur. When the stoichiometric amount of trifluoroacetic acid was added, the reaction proceeded smoothly to give the expected **2a** with full conversion and 8% ee. Screening of different acids found that L-camphorsulfonic acid (L-CSA) gave the best result (Table 1, entry 1).[11,12] Solvent experiments showed that mixture solvent DCM/TFE was the best choice (entry 8, 85% ee). Subsequently, various commercially available chiral bisphosphine ligands were tested (entries 10−14), and (*R*)-H8-BINAP gave the highest 91% ee (entry 14). The change of temperature and pressure of hydrogen has no obvious effect on ee at 2% catalyst loading; low ee (84%) and full conversion were obtained when the reaction was run at 50 °C at 0.5% catalyst loading. Therefore, the optimal conditions: $Pd(OCOCF_3)_2$/(*R*)-H8-BINAP/L-CSA/DCM-TFE/RT.

Table 1. Optimization for Asymmetric Hydrogenation of Indole **1a**[a]



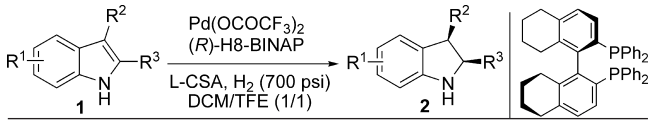
entry	ligand	solvent	convn.[b]	ee (%)[c]
1	(*R*)-SegPhos	TFE	>95	71 (*R*)
2[d]	(*R*)-SegPhos	TFE	44	66 (*R*)
3	(*R*)-SegPhos	toluene	57	57 (*R*)
4	(*R*)-SegPhos	THF	<5	−
5	(*R*)-SegPhos	MeOH	19	40 (*R*)
6	(*R*)-SegPhos	DCM	89	73 (*R*)
7	(*R*)-SegPhos	DCM/TFE (2/1)	>95	82 (*R*)
8	(*R*)-SegPhos	DCM/TFE (1/1)	>95	85 (*R*)
9	(*R*)-SegPhos	DCM/TFE (1/2)	>95	80 (*R*)
10	(*R*)-SynPhos	DCM/TFE (1/1)	>95	86 (*R*)
11	(*R*)-MeOBiPhep	DCM/TFE (1/1)	>95	84 (*R*)
12	(*R*)-C4-TunePhos	DCM/TFE (1/1)	>95	84 (*R*)
13	(*R*)-BINAP	DCM/TFE (1/1)	>95	85 (*R*)
14	**(*R*)-H8-BINAP**	**DCM/TFE (1/1)**	**>95**	**91 (*R*)**

[a] Conditions: 0.25 mmol **1a**, L-CSA (0.25 mmol), $Pd(OCOCF_3)_2$ (2 mol %), ligand (2.4 mol %), 3 mL of solvent, 24 h, RT. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] With D-CSA instead of L-CSA.

Under the optimized conditions, a variety of 2-alkylsubstituted indoles were hydrogenated smoothly with excellent yields and 84−96% ee, regardless of the length or steric hindrance of the side chain (Table 2, entries 1−6). For 2-benzyl-substituted indoles, 93−96% ee were obtained with little effect from

[†] Chinese Academy of Sciences.
[‡] Rutgers.

Table 2. Asymmetric Hydrogenation of Unprotected Indoles[a]



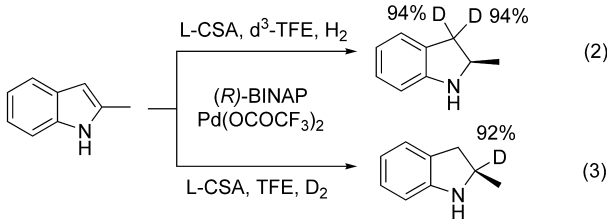
entry	R^1	R^2	R^3	yield (%)[b]	ee (%)[c]
1	H	H	Me	88 (**2a**)	91 (*R*)
2	H	H	*n*-Bu	82 (**2b**)	93 (*R*)
3	H	H	*n*-pentyl	89 (**2c**)	92 (*R*)
4	H	H	cyclohexyl	90 (**2d**)	95 (*S*)
5	H	H	cyclopentyl	85 (**2e**)	95 (*S*)
6	H	H	phenethyl	89 (**2f**)	93 (*R*)
7	H	H	Bn	99 (**2g**)	95 (*R*)
8	H	H	2-Me$C_6H_5CH_2$−	84 (**2h**)	94 (*R*)
9	H	H	3-Me$C_6H_5CH_2$−	95 (**2i**)	94 (*R*)
10	H	H	4-Me$C_6H_5CH_2$−	82 (**2j**)	93 (*R*)
11	H	H	1-naphthylCH_2−	78 (**2k**)	96 (*R*)
12	5-F	H	Me	84 (**2l**)	88 (*R*)
13	5-Me	H	Me	81 (**2m**)	84 (*R*)
14	H		−$(CH_2)_4$−	91 (**2n**)	91 (*R*,*R*)
15	7-Me		−$(CH_2)_4$−	83 (**2o**)	96 (*R*,*R*)
16	H		−$(CH_2)_5$−	96 (**2p**)	90 (*R*,*R*)
17[d]	H	Me	Me	84 (**2q**)	92 (*R*,*R*)

[a] Conditions: 0.25 mmol **1**, L-CSA (0.25 mmol), $Pd(OCOCF_3)_2$ (2 mol %), (*R*)-H8-BINAP (2.4 mol %), 3 mL of solvent, 24 h, RT. [b] Isolated yield. [c] Determined by HPLC. [d] With oil bath of 50 °C and H_2 (300 psi).

substituents on the benzene ring (entries 7−11). Substrates bearing groups at the 5-position displayed slightly lower ee's (84−88% ee, entries 12−13). It is noteworthy that very low reactivity was observed for 2-indole-carboxylic acid or its ester, and the reason is not clear.

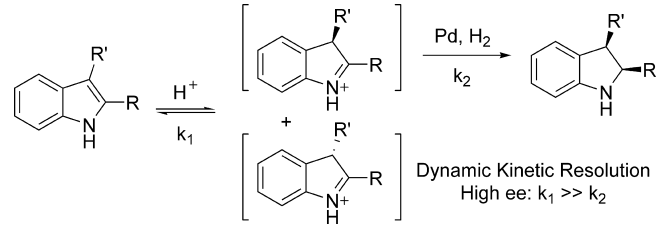
To probe the mechanistic information, two isotopic labeling experiments were carried out. When the hydrogenation was carried out in deuterated TFE, ^{1}H NMR analysis of the crude hydrogenated product showed that two deuterium atoms were incorporated to the 3-position (eq 2, Scheme 2), which suggested that a reversible process of protonation and deprotonation existed (eq 1, Scheme 1), and the equilibrium was faster than hydrogenation.[12] Thus, two deuterium atoms were imported to the 3-position of the 2-methylindoline before hydrogenation occurred. When 2-methylindole was subjected to D_2, 2-*deuterio*-2-methylindoline with 92% incorporation was obtained, and deuterium at the 3-position was not observed (eq 3, Scheme 2). These results confirmed that the simple unprotected indole can be activated by a Brønsted acid to form iminium *in situ*, which was then hydrogenated by the Pd-catalyst.

Scheme 2. Isotopic Labeling Experiments Using D_2 and d^8-TFE



For the asymmetric hydrogenation of 2,3-disubstituted indoles activated by a Brønsted acid, the mechanism was slightly different from that of 2-substituted indoles (Scheme 3). The hydrogenation of an intermediate iminium salt of 2-substituted indole is the enantioselectivity-controlled step, while the enantioselectivity-controlled step of 2,3-disubstituted indole is the protonation of the carbon−carbon double bond and the hydrogenation of iminium salt, which is in fact a dynamic kinetic resolution process. To obtain high ee, it should meet the equation of $k_1 \gg k_2$. The above mechanism study indicated that rate of protonation, k_1, is faster than rate of hydrogenation, k_2.

Scheme 3. Hydrogenation Mechanism of 2,3-Disubstituted Indoles



Gratifyingly, the above asymmetric hydrogenation strategy could also be extended to 2,3-disubstituted indoles. For the 2,3-fused indoles, hydrogenation proceeded smoothly to give the *cis*-indolines with 90−96% ee (Table 2, entries 14−16). For the simple 2,3-dimethylindole, by elevating the temperature and lowering the pressure, *cis*-product was also obtained with 92% ee.

In summary, we developed the first highly enantioselective hydrogenation of simple indoles using $Pd(OCOCF_3)_2$/(*R*)-H8-BINAP with a Brønsted acid as an activator. The present study provides an efficient route to make chiral indolines. Further study on extending this strategy to other heteroaromatic compounds is in progress.

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Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(11) For the effect of other acids, please see the Supporting Information.

(12) The equivalent TsOH−H_2O was added to 2-methylindole in $CDCl_3$, the signal of the 2-methyl and hydrogen in the 3-position become broad peaks, and the N−H peak disappeared. For detailed information, see the Supporting Information.

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