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Highly Enantioselective Partial Hydrogenation of Simple Pyrroles: A Facile Access to Chiral 1-Pyrrolines

Duo-Sheng Wang,[†] Zhi-Shi Ye,[†] Qing-An Chen,[†] Yong-Gui Zhou,*[,†,‡] Chang-Bin Yu,[†] Hong-Jun Fan,*[,†] and Ying Duan[†]

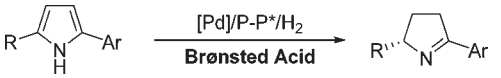
[†]State Key Laboratory of Catalysis and State Key Laboratory of Molecular Reaction Dynamics, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Supporting Information

ABSTRACT: A highly enantioselective Pd-catalyzed partial hydrogenation of simple 2,5-disubstituted pyrroles with a Brønsted acid as an activator has been successfully developed, providing chiral 2,5-disubstituted 1-pyrrolines with up to 92% ee.

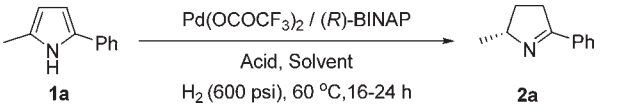
The asymmetric hydrogenation of aromatic compounds offers straightforward access to chiral molecules with cyclic skeletons and has received much attention over the past decades.[1] Some bicyclic heteroaromatic substrates have been successfully hydrogenated because of their relatively low aromaticity (quinolines, isoquinolines, quinoxalines, indoles, and benzofurans).[2−6] This process is much more difficult for single-ring heteroaromatic compounds, although hitherto, special activated pyridines[7] and furans[6] have been successfully hydrogenated, and a single elegant example of asymmetric hydrogenation of *N*-Boc-protected pyrroles using a chiral Ru catalyst was reported by Kuwano and coworkers.[8] To the best of our knowledge, no report on the asymmetric hydrogenation of simple pyrroles has appeared, despite its potential usefulness.[9] Thus, the exploration of a new strategy for hydrogenation of simple pyrroles is urgently needed and of great significance.



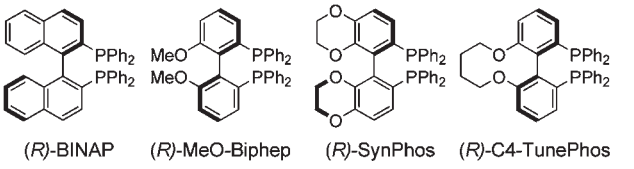
Very recently, we disclosed the Brønsted acid-activated asymmetric hydrogenation of simple indoles[5h,i] using a homogeneous palladium catalyst.[10,11] As part of our ongoing effort to develop new strategies for asymmetric hydrogenation of heteroaromatic compounds and considering the similarity of pyrroles and indoles, we envisioned that electron-enriched pyrroles could be protonated in the presence of strong Brønsted acids, which would destroy their aromaticity thus be suitable for facilitating hydrogenation. Herein we report the results of our preliminary investigation of asymmetric hydrogenation of simple 2,5-disubstituted pyrroles, wherein partially hydrogenated 1-pyrrolines were obtained with up to 92% ee.

Initially, 2-methyl-5-phenylpyrrole (**1a**) was selected as a model substrate for optimization of the reaction conditions. $Pd(OCOCF_3)_2$/(*R*)-BINAP was employed as the catalyst with ethylsulfonic acid ($EtSO_3H$) as the activator. When the reaction was carried out at 60 °C, it proceeded smoothly, affording the unexpected product 5-methyl-2-phenyl-1-pyrroline (**2a**) in 70% yield with 71% ee; no pyrrolidine was detected in the reaction mixture (Table 1, entry 1). It is noteworthy that this is the first example of asymmetric hydrogenation of a pyrrole to obtain a

Table 1. Optimization of Asymmetric Hydrogenation of 1a[a]



entry	solvent	acid (x eq)	yield[b]	ee (%)[c]
1	TFE	$EtSO_3H$ (1.0)	70	71
2	PhMe	$EtSO_3H$ (1.0)	33	62
3	THF	$EtSO_3H$ (1.0)	-	-
4	PhMe/TFE (1/2)	$EtSO_3H$ (1.0)	70	86
5	PhMe/TFE (1/1)	$EtSO_3H$ (1.0)	68	86
6	PhMe/TFE (2/1)	$EtSO_3H$ (1.0)	73	86
7	PhMe/TFE (2/1)	$EtSO_3H$ (1.5)	80	87
8	PhMe/TFE (2/1)	$TsOH{\cdot}H_2O$ (1.5)	78	85
9	PhMe/TFE (2/1)	$MeSO_3H$ (1.5)	75	86
10	PhMe/TFE (2/1)	$PhCO_2H$ (1.5)	-	-
11[d]	PhMe/TFE (2/1)	$EtSO_3H$ (1.5)	63	90
12[e]	PhMe/TFE (2/1)	$EtSO_3H$ (1.5)	73	90
13[f]	PhMe/TFE (2/1)	$EtSO_3H$ (1.5)	80	92

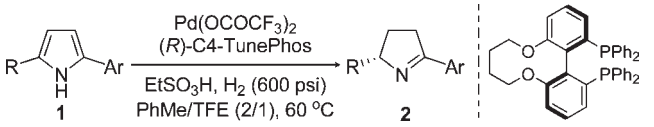


(*R*)-BINAP (*R*)-MeO-Biphep (*R*)-SynPhos (*R*)-C4-TunePhos

[a] Conditions: **1a** (0.25 mmol), $Pd(OCOCF_3)_2$ (2 mol %), (*R*)-BINAP or other ligand (2.4 mol %), Acid (x eq), solvent (3 mL), 60 °C, 16−24 h. [b] Isolated yields. [c] Determined by HPLC. [d] (*R*)-MeOBiPhep was used as the ligand. [e] (*R*)-SynPhos was used as the ligand. [f] (*R*)-C4-TunePhos was used as the ligand.

Received: April 7, 2011
Published: May 17, 2011

Table 2. Asymmetric Hydrogenation of 2,5-Disubstituted Pyrroles 1[a]



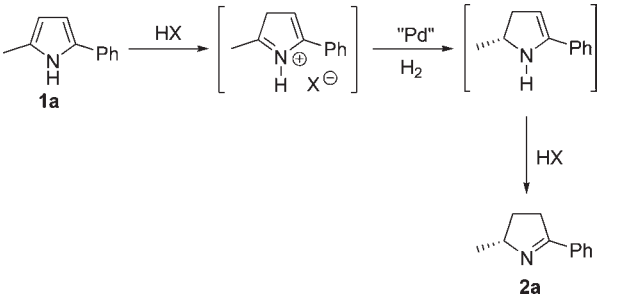
entry	R in **2**	Ar in **2**	yield (%)[b]	ee (%)[c]
1	Me	Ph	80 (**2a**)	92 (*R*)
2	Et	Ph	77 (**2b**)	80 (+)
3	*n*-Pr	Ph	87 (**2c**)	81 (+)
4	*n*-pentyl	Ph	91 (**2d**)	85 (+)
5	*i*-Bu	Ph	80 (**2e**)	86 (+)
6	*c*-$C_6H_{11}CH_2$	Ph	83 (**2f**)	86 (+)
7	Bn	Ph	90 (**2g**)	80 (+)
8	Me	4-MeC_6H_4	65 (**2h**)	81 (+)
9	Me	3-MeC_6H_4	88 (**2i**)	84 (+)
10	Me	2-MeC_6H_4	51 (**2j**)	85 (+)
11	Me	4-$CF_3C_6H_4$	79 (**2k**)	89 (+)
12	Me	4-FC_6H_4	82 (**2l**)	86 (+)
13	Me	3,5-$F_2C_6H_3$	73 (**2m**)	88 (+)
14	Me	1-naphthyl	73 (**2n**)	90 (+)
15[d]	Me	Ph	79 (**2a**)	91 (*R*)

[a] Conditions: **1** (0.25 mmol), $Pd(OCOCF_3)_2$ (2 mol %), (*R*)-C4-TunePhos (2.4 mol %), $EtSO_3H$ (0.375 mmol), solvent (3 mL), 60 °C, 16−24 h. [b] Isolated yields. [c] Determined by HPLC. [d] **1a** (3.0 mmol), $EtSO_3H$ (4.5 mmol), solvent (24 mL), 40 h.

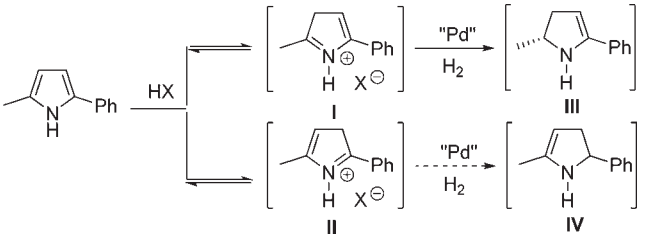
chiral 1-pyrroline. Encouraged by this promising result, we conducted further investigation of the effect of the reaction medium (Table 1, entries 2−6), and a mixed solvent of toluene and 1,1,1-trifluoroethanol with a ratio of 2/1 (PhMe/TFE = 2/1) gave the best result in terms of both yield and enantioselectivity (86% ee; Table 1, entry 6). When the amount of acid was increased to 1.5 equiv, the ee was improved slightly (87% ee; Table 1, entry 7). Subsequently, different acids were screened; the results showed that a strong Brønsted acid was necessary, whereas weak acids were invalid and left the starting material unchanged (Table 1, entries 7−9 vs 10). Finally, examination of various ligands showed that (*R*)-C4-TunePhos was the best choice regarding enantioselectivity (92% ee; Table 1, entry 13). Therefore, the optimal conditions were established as $Pd(OCOCF_3)_2$/(*R*)-C4-TunePhos, $EtSO_3H$ (1.5 equiv), H_2 (600 psi), PhMe/TFE (2:1), 60 °C.

A series of 2-alkyl-5-aryl-disubstituted pyrrole derivatives were then subjected to hydrogenation under the above optimized conditions, and the results are summarized in Table 2. In general, moderate to good yields and high enantioselectivities were obtained (Table 2, entries 1−14). The length and steric property of the alkyl chain showed a remarkable influence on the enantioselectivity. It was found that longer chains resulted in decreased ee values, whereas ones with higher steric demand displayed better results (Table 2, entries 1−6). A benzyl group could also be tolerated in this system with high yield and good enantioselectivity (80% ee; Table 2, entry 7). Substrates with aryl substituents having different electronic and steric properties were also examined (Table 2, entries 8−14). It was found that aryl substituents with an electron-withdrawing group gave higher ee values than those with electron-donating groups (89 vs 81% ee; Table 2, entry 11 vs 8). Ortho-substituted aryl substrates showed higher enantioselectivity than para-substituted ones (Table 2, entry 10 vs 8). 1-Naphthyl-substituted pyrrole gave 90% ee (Table 2, entry 14). Notably, a hydrogenation experiment on a 3 mmol scale was also carried out with **1a**, and identical 91% enantioselectivity with full conversion were obtained (Table 2, entry 15).

Scheme 1. Process of Pyrrole Hydrogenation



Scheme 2. Possible Pathways for Hydrogenation



A possible mechanism (Scheme 1) was proposed as follows: Simple unprotected pyrrole reacts with a strong Brønsted acid to form the iminium salt by protonation of carbon−carbon double bond, and the aromaticity of pyrrole is destroyed. The in situ-formed iminium salt is hydrogenated to give the intermediate enamine, and in the presence of acid, the enamine isomerizes to the more stable imine, which survives under the current catalytic system.[12]

The pyrrole can be protonated at both the 3- and 4-positions in the presence of a strong Brønsted acid (Scheme 2). Density functional theory calculations at the B3LYP/cc-pVTZ(-f)//B3LYP/6-31G** level were carried out to give further insight into the selectivity. The computed bond length alternation suggests that the C═N bond in intermediate **II** is better conjugated with the phenyl group (Figure 1). As a result, **II** is more stable than **I** by 1.4 kcal/mol ($\Delta G°$ in CH_2Cl_2), and the positive charge in **II** is also more delocalized. Palladium hydride species were observed in palladium-catalyzed hydrogenation reactions, strongly suggesting that it could be the true active catalyst, and the rate-determining step for the hydrogenation is most probably the hydride transfer from the catalyst to the substrate. Thus, the observed selectivity is understandable. The C═N bond in **I** is more facile for the hydride transfer because its carbon atom is more positively charged than that in **II**. To further validate this proposal, we studied the hydride transfer reaction from ((*R*)-BINAP)Pd(H)($OCOCF_3$) to **I** and **II**. Indeed, the calculations showed that the hydride transfer barrier for **I** is 27.7 kcal/mol relative to **1a**, which is lower than that for **II** by 1.8 kcal/mol. Therefore, the theoretical studies suggest that the pathway in Scheme 2 is reasonable and that **IV** is not formed for kinetic reasons.

dx.doi.org/10.1021/ja203190t | *J. Am. Chem. Soc.* 2011, 133, 8866–8869

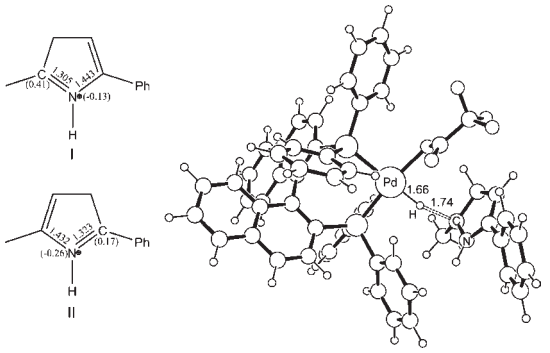
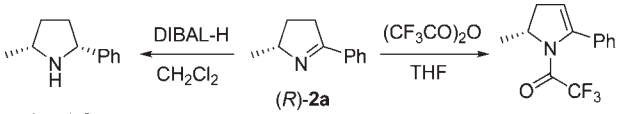


Figure 1. (left) Optimized bond lengths (in Å) and charges (in parentheses) for intermediates **I** and **II**. (right) Structure of the transition state for hydride transfer with **I** (bond lengths in Å).

Scheme 3. Derivatization of Hydrogenated Product 2a



Notably, chiral 1-pyrrolines and related compounds are ubiquitous building blocks in many biologically active compounds.[13] The asymmetric hydrogenation of simple pyrroles developed here offers a facile access to these molecules. Furthermore, the derivatization of the hydrogenated products can be conveniently realized utilizing imine chemistry.

As illustrated in Scheme 3, reduction of **2a** with DIBAL-H afforded *cis*-2-methyl-5-phenylpyrrolidine (**3**) in quantitative yield without loss of optical purity. In the presence of trifluoroacetic anhydride, **2a** isomerized to 2-pyrroline **4** with a trifluoroacetyl group on the nitrogen atom. The enantiomeric excess was preserved, and a yield of 88% was obtained.

In summary, a highly enantioselective Pd-catalyzed partial hydrogenation of simple 2,5-disubstituted pyrroles using a Brønsted acid as an activator has been successfully developed, providing chiral 2,5-disubstituted 1-pyrrolines with up to 92% ee. Further studies will be directed toward the extension of this strategy to other heteroaromatics and its synthetic application.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
ygzhou@dicp.ac.cn; fanhj@dicp.ac.cn

■ ACKNOWLEDGMENT

Financial support from the National Natural Science Foundation of China (21032003 and 20921092), the National Basic Research Program of China (2010CB833300), and Dalian Institute of Chemical Physics (K2010F1) is acknowledged. The authors thank Prof. Xumu Zhang for helpful discussions.

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(12) In our previous work on palladium-catalyzed asymmetric hydrogenation of simple ketimines with a Brønsted acid as the activator, it was found that *N*-alkylimines could not be hydrogenated (ref 10g). Herein, the obtained products were *N*-alkylimines, and they were not further hydrogenated to pyrrolidines, in accord with that result. Theoretical calculations showed that the imine product **2a** is more stable than the enamine intermediate by 8.83 kcal/mol (ΔG° in CH_2Cl_2).

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