Tetrahedron Letters 49 (2008) 4922–4924

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iridium-catalyzed asymmetric hydrogenation of pyridine derivatives, 7,8-dihydro-quinolin-5(6*H*)-ones

Xiao-Bing Wang, Wei Zeng, Yong-Gui Zhou *

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, PR China

ARTICLE INFO

Article history:
Received 22 February 2008
Revised 12 May 2008
Accepted 30 May 2008
Available online 4 June 2008

ABSTRACT

$[Ir(COD)Cl]_2$/MeO-Biphep/I_2 catalyst system is highly effective for asymmetric hydrogenation of pyridine derivatives 7,8-dihydro-quinolin-5(6*H*)-ones with high enantioselectivities (up to 97% ee).

Transition metal-catalyzed asymmetric hydrogenation of ketones, olefins, and imines has intensively been studied.[1] However, enantioselective hydrogenation of heteroaromatic compounds is still a challenging task.[2] To date, asymmetric homogeneous hydrogenation of aromatic rings with excellent enantioselectivities, such as quinolines,[3–5] furans,[6] indoles,[7] and pyrroles[8] has been reported. However, asymmetric hydrogenation of pyridines is a long-standing problem. To date, some progresses have been made. The pioneer work for asymmetric homogeneous hydrogenation of pyridine derivatives is done using $Rh(nbd)_2BF_4$/BINAP as the catalyst with moderate enantioselectivity (25% ee).[9] Recently, Zhang's group reported an efficient two-step asymmetric hydrogenation process of 3-substituted pyridine derivatives using a homogeneous rhodium catalyst.[10] An efficient auxiliary-based method for the asymmetric hydrogenation of substituted pyridines has been developed by Glorious.[11] Charette employed Iridium complex with Pfaltz's phosphinooxazolines (PHOX) as ligands in the presence of I_2 for asymmetric hydrogenation of *N*-iminopyridinium ylides with modest to high enantioselectivities (54–90% ee).[12] Very recently, Rueping and co-workers have developed highly enantioselective reduction of trisubstituted pyridine derivatives, catalyzed by chiral Brønsted acids with excellent enantioselectivities, in which Hantzsch dihydropyridine acts as hydrogen sources.[13] In our ongoing efforts toward the development of asymmetric hydrogenation of aromatic compounds,[3a] two different systems were developed for hydrogenation of quinolines. One was the highly active iridium catalyst Ir/diphosphine/I_2, in which iodine is a crucial additive for activity and enantioselctvity.[3] The other was Ir/P–P*/Li_2CO_3/$ClCO_2R$, which was involved in substrate activation to form quinolinium salts with chloroformates. The latter protocol can also be applied to asymmetric hydrogenation of isoquinolines.[3e] As an extension of our continuous work in asymmetric hydrogenation, we became interested in exploring asymmetric hydrogenation of pyridine derivatives. In this Letter, we wish to report our initial findings on the highly enantioselective hydrogenation of pyridine derivatives: 7,8-dihydro-quinolin-5(6*H*)-ones (**1**) with the catalyst Ir/MeO-BiPhep/I_2.

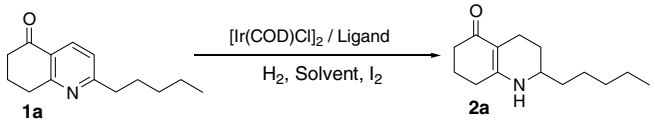
Based on our previous results, we firstly examined $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep/toluene/I_2 catalyst system for hydrogenation of 7,8-dihydro-2-pentylquinolin-5(6*H*)-one (**1a**). To our delight, under the standard conditions, the reaction can run smoothly with an excellent enantioselectivity (92% ee). Encouraged by these results, we then investigated the effect of the solvent on the reaction for the sake of achieving an improvement of the enantioselectivity. The results are summarized in Table 1. Full conversions were achieved in all solvents examined in 12 h, but the ees of the products are highly solvent dependent (entries 1–4). The highest enantioselectivity (97% ee) was obtained using benzene as solvent. The use of CH_2Cl_2 and THF results in lower enantioselectivities (88% and 71% ee). Slightly lower conversion and enantioselectivity were observed under lower pressure of hydrogen gas (entry 7). The enantioselectivities of the reaction were slightly lower at higher temperature or high pressure (entries 5 and 6).

Next, the effect of various chiral ligands on the asymmetric hydrogenation of **1a** was also studied. Some chiral bisphosphine ligands were tested. The results showed that only axial chiral bisphosphine ligands exhibited good to excellent enantioselectivities with full conversions (entries 4, 8–11, and 14). The highest enantioselectivity (97% ee) was obtained using (*S*)-MeO-BiPhep as ligand. Whereas, the lower conversion and enantioselectivity were achieved with electron-rich (*R*,*R*)-Me-DuPhos **L-6** (entry 12). Ferrocene-derived chiral N,P ligand showed excellent conversion and 72% ee (entry 13). Thus the optimized conditions are: $[Ir(COD)Cl]_2$/(S)-MeO-Biphep/Benzene/I_2. It is noteworthy that the enantioselectivity achieved with Ir/(*S*)-MeO-Biphep/I_2 as catalyst for the hydrogenation of pyridine derivative **1a** is the highest reported to date.[13]

* Corresponding author. Tel./fax: +86 411 84379220.
E-mail address: ygzhou@dicp.ac.cn (Y.-G. Zhou).

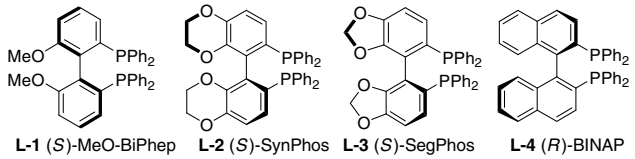
0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.05.138

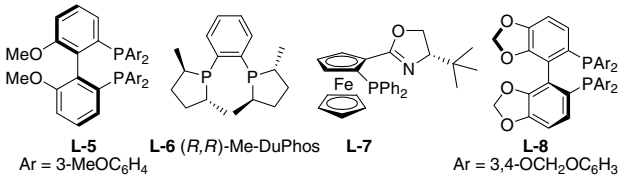
Table 1
Condition optimization for Ir-catalyzed asymmetric hydrogenation of 7,8-dihydro-2-pentylquinolin-5(6*H*)-one **1a**[a]



Entry	Solvent	ligand	Covn[b] (%)	ee[c] (%)
1	Toluene	**L-1**	>95	92 (*S*)
2	CH_2Cl_2	**L-1**	>95	88 (*S*)
3	THF	**L-1**	>95	71 (*S*)
4	Benzene	**L-1**	>95	97 (*S*)
5[d]	Benzene	**L-1**	>95	91 (*S*)
6[e]	Benzene	**L-1**	>95	92 (*S*)
7[f]	Benzene	**L-1**	92	93 (*S*)
8	Benzene	**L-2**	>95	91 (*S*)
9	Benzene	**L-3**	>95	93 (*S*)
10	Benzene	**L-4**	>95	61 (*R*)
11	Benzene	**L-5**	>95	93 (*S*)
12	Benzene	**L-6**	37	3 (—)
13	Benzene	**L-7**	>95	72 (*R*)
14	Benzene	**L-8**	>95	85 (*S*)

[a] Reactions condition: $[Ir(COD)Cl]_2$ 1 mol %, ligand 2.2 mol %, I_2 10 mol %, 2 mL solvent, $H_2$700 psi, 25 °C 12 h.
[b] Conversions were determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC analysis with OD-H column.
[d] Run at 50 °C.
[e] Run at 1200 psi of H_2.
[f] Run at 300 psi of H_2.

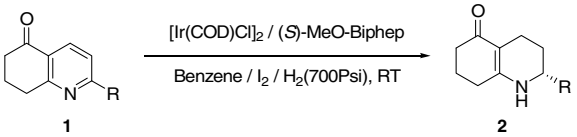




Under the optimized condition, a variety of substituted 7,8-dihydro-quinolin-5(6*H*)-ones **1** were hydrogenated using [Ir-(COD)Cl]$_2$/(*S*)-MeO-BiPhep/Benzene/I_2 catalyst system. The results are listed in Table 2. Full conversions were achieved in the hydrogenation of the 2-alkyl-substituted 7,8-dihydro-quinolin-5(6*H*)-ones. However, the ees were slightly affected by the length of the alkyl chain and steric hindrance (entries 1–6). For 2-isopropyl-substituted substrate, 84% ee was obtained (entries 3 and 6). With aryl substituted 7,8-dihydro-quinolin-5(6*H*)-ones, slightly low conversion and excellent enantioselectivity were obtained (92% ee, entry 7). The hydrogenation of the 2-benzyl and 2-phenethyl 7,8-dihydro-quinolin-5(6*H*)-ones also gave high to excellent enantioselectivities with 85% and 92% ee, respectively (entries 8 and 9).

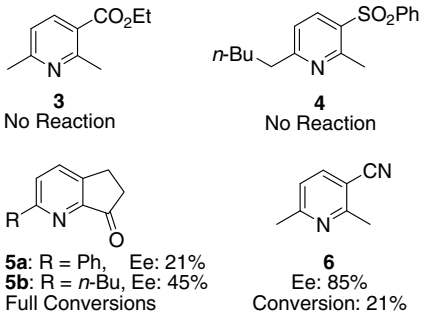
Success of asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6*H*)-ones **1** maybe due to the fact that the strong electron-withdrawing character of carbonyl reduces the inhibitory effect of the product. Thus other trisubstituted pyridine derivatives were also tested (see Scheme 1). The results showed our catalyst system has no catalytic activity on 3-electron-withdrawing substituted substrates **3** and **4**. Trisubstituted pyridine derivative **5a** can be hydrogenated with full conversion and 21% ee. When the phenyl group of **5a** was replaced by *n*-butyl, slightly higher enantioselectivity was obtained (45% ee). For the 2,6-dimethylpyridine-3-carbonitrile (**6**), which can be hydrogenated in Rueping's work with high ee using chiral phosphorus acid as catalyst in the presence of Hanstch ester,[13] low conversion of 21% and 85% ee were obtained.

Table 2
Ir-Catalyzed asymmetric hydrogenation of pyridine derivative 7,8-dihydro-quinolin-5(6*H*)-ones (**1**)[a]



Entry	R of **1 and 2**	Yield[b] (%)	ee[c] (%)
1	$-(CH_2)_4CH_3$ (**1a**)	98 (**2a**)	97 (*S*)
2	$-CH_3$ (**1b**)	80 (**2b**)	86 (*S*)
3	$-(CH_2)_2CH_3$ (**1c**)	91 (**2c**)	94 (*S*)
4	$-(CH_2)_3CH_3$ (**1d**)	98 (**2d**)	93 (*S*)
5	$-(CH_2)_9CH_3$ (**1e**)	94 (**2e**)	96 (*S*)
6	$-CH(CH_3)_2$ (**1f**)	87 (**2f**)	84 (*R*)
7[d]	Ph (**1g**)	57 (**2g**)	92 (*R*)
8	Bn (**1h**)	95 (**2h**)	85 (*R*)
9	Phenethyl (**1i**)	76 (**2i**)	92 (*S*)

[a] Conditions: $[Ir(COD)Cl]_2$ (1 mol %), (*S*)-MeO-Biphep (2.2 mol %), I_2 (10 mol %), benzene, rt.
[b] Isolated yields.
[c] Determined by HPLC analysis with chiral column.
[d] Conversion is 70%.



Scheme 1.

In summary, the $[Ir(COD)Cl]_2$/MeO-Biphep/I_2 catalyst system has been successfully applied in asymmetric hydrogenation of pyridine derivatives, 7,8-dihydro-quinolin-5(6*H*)-ones with good yields and excellent enantioselectivities. Further work will be directed toward expanding the scope of those pyridine derivatives and mechanism of the reaction.

Acknowledgments

We are grateful for the financial support from National Science Foundation of China (20532050 and 20621063) and Chinese Academy of Sciences.

References and notes

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (b) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley-Interscience: New York, 2001; (c) Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
2. Reviews on hydrogenation of aromatic compounds, see: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171; (b) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Chin. J. Org. Chem.* **2005**, *25*, 634; (c) Dyson, P. J. *Dalton Trans.* **2003**, 2964.
3. For our recent work on asymmetric hydrogenation of quinolines and isoquinolines, see: (a) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357; (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*,

10536; (c) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 909; (d) Yang, P.-Y.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145; (e) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260; (f) Zhao, Y.-J.; Wang, Y.-Q.; Zhou, Y.-G. *Chin. J. Catal.* **2005**, *26*, 737.

4. For other group's work on asymmetric hydrogenation of quinolines, see: (a) Xu, L. J.; Lam, K. H.; Ji, J. X.; Fan, Q. H.; Lo, W.-H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390; (b) Lam, K. H.; Xu, L. J.; Feng, L. C.; Fan, Q. H.; Lam, F. L.; Lo, W. H.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1755; (c) Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, T.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genet, J. P.; Mashima, K. *Organometallics* **2006**, *25*, 2505; (d) Reetz, M. T.; Li, X. G. *Chem. Commun.* **2006**, 2159; (e) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711; (f) Tang, W.-J.; Zhu, S.-F.; Xu, L.-J.; Zhou, Q.-L.; Fan, Q.-H.; Zhou, H.-F.; Lam, K.; Chan, A. S. C. *Chem. Commun.* **2007**, 613; (g) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, Y.; Li, Y. M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955; (h) Wang, Z. J.; Deng, G. J.; Li, Y.; He, Y. M.; Tang, W. J.; Fan, Q. H. *Org. Lett.* **2007**, *9*, 1243; For the asymmetric hydrogenation of quinoxalines: (i) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308; (j) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300; (k) Chan, S. H.; Lam, K. H.; Li, Y. M.; Xu, L.; Tang, W.; Lam, F. L.; Lo, W. H.; Yu, W. Y.; Fan, Q.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 2625; (l) Jahjah, M.; Alame, M.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2305.
5. Asymmetric transfer hydrogenation of quinolines with organocatalysis, see: (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683; (b) Guo, Q.-S.; Du, D.-M.; Xu, J.-X. *Angew. Chem., Int. Ed.* **2008**, *47*, 759.
6. Asymmetric hydrogenation of furans, (a) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357; (b) Studer, M.; Wedemeyer-Exl, C.; Spindler, F.; Blaser, H. U. *Monatsh. Chem.* **2000**, *131*, 1335; (c) Feiertag, P.; Albert, M.; Nettekoven, U.; Spindler, F. *Org. Lett.* **2006**, *8*, 4133; (d) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194.
7. Asymmetric hydrogenation of indoles, see: (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614; (b) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213; (c) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653; (d) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521.
8. Asymmetric hydrogenation of pyrroles, see: (a) Hada, V.; Tungler, A.; Szepesy, L. *Appl. Catal. A* **2001**, *210*, 165; (b) Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808.
9. Studer, M.; Wedemeyer-Exl, C.; Spindler, F.; Blaser, H.-U. *Monatsh. Chem.* **2000**, *131*, 1335.
10. Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 4343.
11. Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehman, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850.
12. Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966.
13. (a) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562; (b) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820.