



Chiral phosphoric acid catalyzed asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones

Jian-Qing Zhou, Wei-Jian Sheng, Jian-Hong Jia, Qing Ye, Jian-Rong Gao, Yi-Xia Jia*

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China

ARTICLE INFO

Article history:

Received 3 February 2013

Revised 22 March 2013

Accepted 28 March 2013

Available online 12 April 2013

Keywords:

Imine reduction

Asymmetric organocatalysis

Chiral phosphoric acid

Hydrogenolysis

ABSTRACT

The enantioselective hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones catalyzed by BINOL-derived chiral phosphoric acid with benzothiazoline as the hydride source is described. The corresponding cyclic diaryl methylamines are obtained in good to excellent yields and up to 91% enantioselectivities.

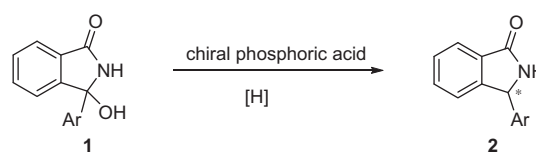
© 2013 Elsevier Ltd. All rights reserved.

Optically active amines are prevalent substructures in many drugs and biologically active molecules, and widely applied as chiral reagents, chiral ligands, and chiral catalysts in asymmetric synthesis. Consequently, the development of reliable approaches to chiral amines has been a focused interest for organic chemists.¹ Numerous methods have been intensely established for this purpose, in which the asymmetric reduction of imines is undoubtedly a direct means of accessing chiral amines.² In this context, the organocatalytic transfer hydrogenation of imine has developed as a facile and powerful process to enantiopure amines.³ Pioneered by the groups of Rueping and List, BINOL-derived chiral phosphoric acids⁴ have been proved to be efficient catalysts in the asymmetric transfer hydrogenation of C=N double bonds.⁵ A wide range of substrates, such as acyclic ketimines,⁶ cyclic ketimines,⁷ α -imino esters,⁸ enamides,⁹ and nitrogen aromatics¹⁰ have been enantioselectively reduced to the corresponding chiral amines. Hantzsch ester was the commonly used organic hydride source in these transformations, while benzothiazoline has been demonstrated by Akiyama and co-workers as a unique and efficient hydride-transfer reagent.¹¹ Moreover, by applying the same protocol the enantioselective hydrogenation of in situ generated imines has also been successfully established.¹² In spite of these notable advances, efficient approaches to chiral diaryl methylamine still remained less exploited.

Recently, hemiaminals have been extensively involved in asymmetric organocatalysis as stable imine precursors through the formation of *N*-carbonyl iminium in situ.¹³ Zhou and co-workers disclosed an enantioselective hydrogenolysis of 3-alkyl-3-hydroxy-

isoindolin-1-ones to produce cyclic *N*-carbonyl chiral amines in modest to excellent enantioselectivities.¹⁴ However, the extension of the 3-aryl substituted substrate to form cyclic diaryl methylamine was not successful. We reported herein a BINOL-derived chiral phosphoric acid catalyzed asymmetric hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ones **1** with benzothiazoline as efficient hydride source, led to 3-arylisindolinones **2**, a structurally important unit in many biologically active compounds and natural products,¹⁵ in good to excellent yields and with modest to excellent enantioselectivities (Scheme 1).

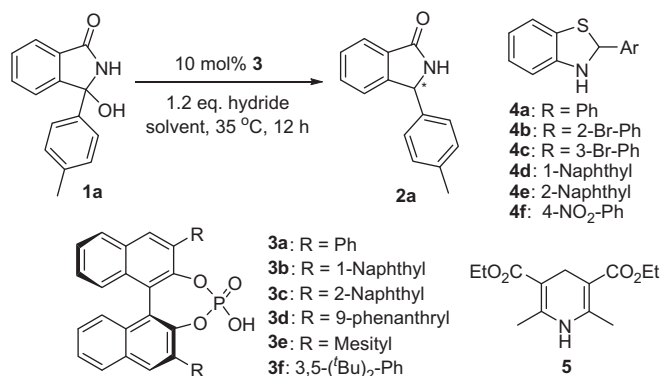
Initially, 3-hydroxy-3-*p*-tolylisoindolin-1-one (**1a**) was chosen as the model substrate to study the asymmetric hydrogenolysis reaction (Table 1). Thus, treatment of **1a** with 1.2 equiv 2-phenylbenzothiazoline **4a** in the presence of 10 mol % chiral phosphoric acid **3a** in CH₂Cl₂ at 35 °C for 12 h led to 3-*p*-tolylisoindolinone **2a** in almost quantitative yield and 23% ee (Table 1, entry 1). This result inspired us to investigate other acid catalysts bearing different substituent groups at 3,3'-positions of the binaphthyl unit (entries 2–6). Gratifyingly, catalyst **3d** containing a 9-phenanthryl substituent accessed the best enantiomeric excess (entry 4), whereas poor to modest ee values were obtained for the other catalysts screened. After the solvent examination, we found CHCl₃ was the best choice



Scheme 1. Asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones.

* Corresponding author. Tel.: +86 15558028971.

E-mail address: yxjia@zjut.edu.cn (Y.-X. Jia).

Table 1
Optimization of the asymmetric hydrogenolysis reaction^a

Entry	Catalyst	Hydride	Solvent	Yield ^b (%)	ee ^c (%)
1	3a	4a	CH ₂ Cl ₂	99	23
2	3b	4a	CH ₂ Cl ₂	98	66
3	3c	4a	CH ₂ Cl ₂	89	39
4	3d	4a	CH ₂ Cl ₂	99	83
5	3e	4a	CH ₂ Cl ₂	97	32
6	3f	4a	CH ₂ Cl ₂	90	19
7	3d	4a	CHCl ₃	99	85
8	3d	4a	Toluene	92	81
9	3d	4a	Et ₂ O	98	69
10	3d	4b	CHCl ₃	95	47
11	3d	4c	CHCl ₃	99	85
12	3d	4d	CHCl ₃	99	75
13	3d	4e	CHCl ₃	99	81
14	3d	4f	CHCl ₃	99	83
15	3d	5	CHCl ₃	76	59
16 ^d	3d	4a	CHCl ₃	99	89

^a Reaction conditions: **1a** (0.2 mmol), hydride source **4** or **5** (0.24 mmol), **3** (10 mol %) in the solvent (2.0 mL) at 35 °C for 12 h.

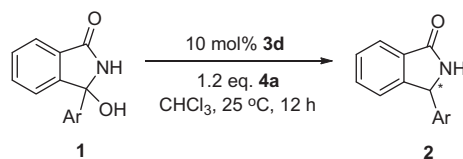
^b Isolated yield.

^c Determined by chiral HPLC analysis.

^d At 25 °C.

for this transformation to give the product in 85% ee (entry 7). The reactions proceeded smoothly in toluene and ether but with lower enantioselectivities (entries 8 and 9). In order to further improve the ee value, other hydride sources **4b–f** and Hantzsch ester **5** were investigated in CHCl₃ at 35 °C with **3d** as a catalyst. However, no improvement of the enantioselectivity resulted from the modification of the substituted aryl groups of benzothiazoline (entries 10–14), showing **4a** was the best hydride source for this reaction. When Hantzsch ester **5** was used, only 59% ee and modest yield were obtained (entry 15). Finally, decreasing the temperature from 35 to 25 °C resulted in a slight improvement in the enantioselectivity from 85% to 89% (entry 16).

With the optimized reaction conditions in hand, the substrate scope was then investigated and a range of 3-aryl-3-hydroxyisoindolin-1-ones **1a–o** were tested. As shown in Table 2, all the reactions proceeded smoothly to give the desired products with good to excellent yields, whereas the enantioselectivities were dramatically influenced by the steric effect. For instance, almost all racemic products were isolated in the reaction of 2-methylphenyl substrate **1c** and 3,5-dimethylphenyl substrate **1l** (entries 3 and 12). Significantly lower enantioselectivity was also observed for 3-methoxyphenyl substrate **1k** (entry 11). The reaction was also affected by the electronic property of the aryl group. Low reaction rate was observed for the hydrogenolysis of *para*-Cl-substrate **1j** at 25 °C and the reaction needed to take place at 50 °C to ensure good conversion (entry 10). To our delight, the reaction of 2-naphthyl-substrate

Table 2
Substrate scope for the asymmetric hydrogenolysis reaction^a

Entry	R	Yield ^b (%)	ee ^c (%)
1	4-Me-Ph (1a)	99	89
2	3-Me-Ph (1b)	89	72
3	2-Me-Ph (1c)	91	<5
4	Ph (1d)	99	70 (S)
5	4-MeO-Ph (1e)	99	91
6	4-Et-Ph (1f)	99	85
7	4- ^t Bu-Ph (1g)	99	67
8	4- ⁿ Pr-Ph (1h)	97	83
9	4-Vinyl-Ph (1i)	98	86
10 ^d	4-Cl-Ph (1j)	92	83
11	3-MeO-Ph (1k)	82	32
12	3,5-Me ₂ -Ph (1l)	99	<5
13 ^d	2-Naph (1m)	95	79

^a Reaction conditions: **1** (0.2 mmol), **4a** (0.24 mmol), and **3d** (10 mol %) in CHCl₃ (2.0 mL) at 25 °C for 12 h.

^b Isolated yield.

^c Determined by HPLC analysis.

^d At 50 °C.

1m proceeded smoothly at 50 °C to afford the product in excellent yield and good enantioselectivity (entry 13). Although only modest enantiomeric excess of 70% was detected for the phenyl-substrate **1d** (entry 4), the introduction of suitable substituents at the *para*-position of phenyl ring could favorably improve the enantioselectivity. Thus, the reactions of substrates bearing Me, MeO, Et, ⁿPr, vinyl, and Cl groups afforded the corresponding products in good to excellent enantioselectivities (83–91% ee). Exception was that modest ee value was obtained in the reaction of *para*-^tBu substrate **1g** (entry 7). Noticeably, the absolute configuration of product **1d** was determined to be *S* by the comparison of its optical rotation with that reported in Ref. 13.

In conclusion, we have developed an efficient asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones, led to chiral cyclic diaryl methylamines in good to excellent yields and up to 91% enantioselectivities. The present process utilized chiral BINOL-derived phosphoric acid **3d** as a catalyst to form stable *N*-carbonyl iminium ions by dehydration and benzothiazoline as the hydrogen donor to reduce enantioselectively the iminium to *N*-carbonyl amines. Further extension of this methodology to asymmetric synthesis is underway in our laboratory.

Acknowledgments

We are grateful for the generous financial supports by the National Natural Science Foundation of China (21002089), New Century Excellent Talents in University (NCET-12-1086), and young scholarship for the doctoral program of higher education (20103317120001).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.03.138>.

References and notes

- (a) Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments, and Applications*; Wiley: Weinheim, 2010; (b) Nugent, T. C.; Mohamed, E.-S. *Adv. Synth. Catal.* **2010**, *352*, 753–819.
- (a) Spindler, F.; Blaser, H.-U. In *Handbook of Homogeneous Hydrogenation III*; de Vries, J., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; (b) Brunel, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 155–190.
- (a) de Vries, J. G.; Mrcic, N. *Catal. Sci. Technol.* **2011**, *1*, 727–735; (b) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498–2518.
- For recent reviews of chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010; (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758; (c) Terada, M. *Chem. Commun.* **2008**, 4097–4112; (d) Terada, M. *Synthesis* **2010**, 1929–1982; (e) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227–2256; (f) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539–4549.
- (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781–3783; (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424–7427.
- (a) Nguyen, T. B.; Bousserouel, H.; Wang, Q.; Guéritte, F. *Org. Lett.* **2010**, *12*, 4705–4707; (b) Nguyen, T. B.; Bousserouel, H.; Wang, Q.; Guéritte, F. *Adv. Synth. Catal.* **2011**, *353*, 257–262.
- (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751–6755; (b) Han, Z.-Y.; Xiao, H.; Gong, L.-Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3729–3732; (c) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem. Eur. J.* **2010**, *16*, 2688–2691; (d) Rueping, M.; Stoeckel, M.; Sugiono, E.; Theissmann, T. *Tetrahedron* **2010**, *66*, 6565–6568; (e) Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281–287; (f) Rueping, M.; Merino, E.; Koenigs, R. M. *Adv. Synth. Catal.* **2010**, *352*, 2629–2634; (g) Rueping, M.; Brinkmann, C.; Antonchick, A. P.; Atodiresei, I. *Org. Lett.* **2010**, *12*, 4604–4607; (h) Chen, Q.-A.; Chen, M.-W.; Yu, C.-B.; Shi, L.; Wang, D.-S.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2011**, *133*, 16432–16435.
- (a) Li, G.-L.; Liang, Y.-X.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831; (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657–1660; (c) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031–2034.
- Li, G.-L.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075–1078.
- (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686; (b) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562–4565; (c) Guo, Q.-S.; Du, D.-M.; Xu, J.-X. *Angew. Chem., Int. Ed.* **2008**, *47*, 759–762; (d) Metallinos, C.; Barrett, F. B.; Xu, S. *Synlett* **2008**, 720–724; (e) Rueping, M.; Theissmann, T.; Raja, S.; Batsa, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001–1006; (f) Rueping, M.; Theissmann, T. *Chem. Sci.* **2010**, *1*, 473–476; (g) Rueping, M.; Theissmann, T.; Stoeckel, M.; Antonchick, A. P. *Org. Biomol. Chem.* **2011**, *9*, 6844–6850.
- (a) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180–4183; (b) Zhu, C.; Akiyama, T. *Adv. Synth. Catal.* **2010**, *352*, 1846–1850; (c) Zhu, C.; Akiyama, T. *ChemCatChem* **2011**, *3*, 2850–2851; (d) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180–8183; (e) Zhu, C.; Akiyama, T. *Synlett* **2011**, 1251–1254; (f) Sakamoto, T.; Mori, K.; Akiyama, T. *Org. Lett.* **2012**, *14*, 3312–3315; (g) Zhu, C.; Akiyama, T. *Tetrahedron Lett.* **2012**, *53*, 416–418; (h) Saito, K.; Akiyama, T. *Chem. Commun.* **2012**, 48, 4573–4575.
- Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86; (b) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075; (c) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498–7499; (d) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836–5838; (e) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4204–4207; (f) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183; (g) Kumar, A.; Sharma, S.; Maurya, R. A. *Adv. Synth. Catal.* **2010**, *352*, 2227–2232; (h) Wakchaure, V. N.; Zhou, J.; Hoffmann, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 4612–4614; (i) Enders, D.; Liebich, J. X.; Raabe, G. *Chem. Eur. J.* **2010**, *16*, 9763–9766; (j) Rueping, M.; Hubener, L. *Synlett* **2011**, 1243–1246.
- (a) Myers, E. L.; De Vries, J. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1893–1896; (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405; (c) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745–748; (d) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577–1580; (e) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328–6331; (f) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797; (g) Rueping, M.; Nachtsheim, B. J. *Synlett* **2010**, 119–122; (h) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032; (i) Yu, X.; Lu, A.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2011**, 892–897; (j) Yu, X.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2011**, 3060–3066.
- Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; Zhou, Y.-G. *Chem. Commun.* **2012**, 48, 1698–1700.
- (a) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502; (b) Bishop, A. C.; Ubersax, J. A.; Petsch, D. T.; Matheos, D. P.; Grayk, N. S.; Blethrow, J.; Shimizu, E.; Tsien, J. Z.; Schultzk, P. G.; Rose, M. D.; Wood, J. L.; Morgan, D. O.; Shokat, K. M. *Nature* **2000**, *407*, 395–401; (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923–3925; (d) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95–98.