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Chiral Phosphoric Acid-Catalyzed Enantioselective Transfer Hydrogenation of *ortho*-Hydroxyaryl Alkyl N−H Ketimines

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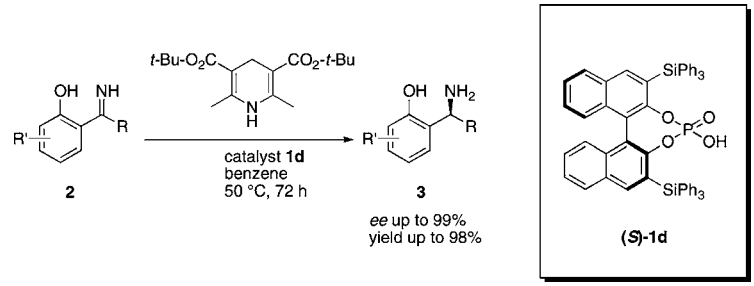
ABSTRACT



The first enantioselective chiral phosphoric acid-catalyzed transfer hydrogenation of *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using Hantszch di-*tert*-butyl ester as a reductant is reported. A variety of *ortho*-hydroxybenzylamines were obtained in good to excellent yields and enantiomeric excesses.

Enantiomerically pure *ortho*-hydroxybenzylamines are an important class of chiral ligands for transition metal mediated and catalyzed processes[1] and have been used as chiral auxiliaries in asymmetric synthesis.[2] In addition, they are useful chiral building blocks for syntheses of natural products and many pharmacologically active compounds.[3] This family of aminophenols is generally obtained by enzymatic[4] or chemical resolution[5] of racemics or by diastereoselective alkylation/reduction of imines.[1b,2c,5,6] Although enantioselective reduction of N-protected enamides, enamines, and imines is well developed,[7−10] only very few reports have dealt with the reduction of N−H imines.[8] Very recently, Zhang and Gosselin et al. reported an iridium-catalyzed asymmetric hydrogenation of the hydrochloride salt of N−H imines at high pressure leading directly to α-chiral primary amines in good to excellent ee's.[8c,d]

Since the pioneering work of Terada and Akiyama, the chiral binol-derived phosphoric acids have found wide applications in the development of catalytic enantioselective transformations,[10,11] including the enantioselective reduction of N-

(1) (a) Schwenkreis, T.; Berkessel, A. *Tetrahedron Lett.* **1993**, *34*, 4785. (b) Palmieri, G. *Tetrahredron: Asymmetry* **2000**, *11*, 3361. (c) Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 415.

(2) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465. (b) Yamazaki, N.; Dokoshi, W.; Kikayashi, C. *Org. Lett.* **2001**, *3*, 193. (c) Atobe, M.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2004**, *69*, 5595.

(3) (a) Kogen, H.; Toda, N.; Tago, K.; Marumoto, S.; Takami, K.; Ori, M.; Yamada, N.; Koyama, K.; Naruto, S.; Abe, K.; Yamazaki, R.; Hara, T.; Aoyagi, A.; Abe, Y.; Kaneko, T. *Org. Lett.* **2002**, *4*, 3359. (b) Weisenburger, G. A.; Anderson, D. K.; Clark, J. D.; Edney, A. D.; Karbin, P. S.; Gallagher, D. J.; Knable, C. M.; Pietz, M. A. *Org. Process Res. Dev.* **2009**, *13*, 60. (c) Ahond, A.; Fournet, A.; Moretti, C.; Philogene, E.; Poupat, C.; Thoison, O.; Potier, P. *Bull. Soc. Chim. Fr.* **1984**, *1−2* (2), 41. (d) Houghton, P. J. *In Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 31, pp 67−100. (e) Houghton, P. J. Chemistry and Biological Activity of Natural and Semi-synthetic Chromone Alkaloids. *Nat. Prod. Chem.* **2000**, *21*, 123.

(4) Vaijayanthi, T.; Chadha, A. *Tetrahedron: Asymmetry* **2008**, *19*, 93.

(5) Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schüpfer, P.; Treptow, B.; Kündig, E. P. *Chirality* **2000**, *12*, 529.

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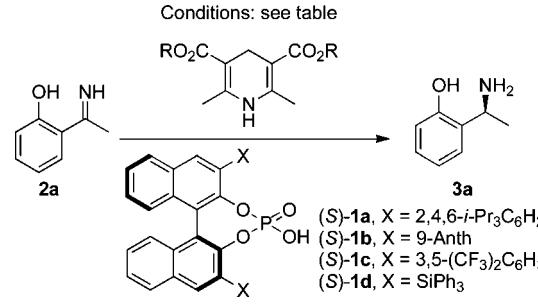
protected imines.[12] We report herein the first examples of enantioselective transfer hydrogenation of *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using chiral phosphoric acid as a catalyst and Hantzsch ester as the hydrogen source.

The *ortho*-hydroxyaryl alkyl N−H ketimines are synthesized in quantitative yields by simply mixing *ortho*-hydroxyaryl alkyl ketone with ammonia in methanol at room temperature.[13] All *ortho*-hydroxyaryl alkyl ketimines were quite stable at room temperature and existed as one single *E*-isomer due to the presence of an intramolecular H-bond ($\delta_{OH} = 14.3-16.3$ ppm). Using **2a** as a test substrate, the survey of reaction conditions varying the solvents, the temperature, the structure of phosphoric acids, and Hantzsch esters is shown in Table 1. The hindered 3,3′-bis(triphenylsilyl)-substituted phosphoric acid (*S*)-**1d** turned out to be the most effective in terms of chirality transfer, and benzene was a better reaction medium than other solvents screened (Et_2O, $CHCl_3$, CH_3CN, PhMe, entries 5−8). The reaction temperature also played an important role. At room temperature, the reaction went extremely slow (entry 9), while at temperature higher than 60 °C, the reduction proceeded with reduced enantioselectivity. A slight improvement of enantioselectivity was observed when the Hantzsch di-*tert*-butyl ester was used instead of diethyl ester (entry 11 vs 4). Overall, the optimal conditions consisted of performing the reduction of **2a** in benzene in the presence of chiral phosphoric acid **1d** (0.1 equiv) and Hantzsch di-*tert*-butyl ester (1.3 equiv) at 50 °C. Under these conditions, amine **3a** was isolated in 94% yield with 92% ee (cf. Table 2).[14]

Having established optimal conditions, we next examined the scope of this reaction by varying the nature of R and R′ substituents in imines **2** (Table 2). A variety of *ortho*-hydroxyaryl alkyl N−H ketimines having a substituent at the

Table 1. Survey of Reaction Conditions for the Enantioselective Transfer Hydrogenation of Imine **2a**[a]



entry	cat.	R	solvent	t (°C)	convn (%)[b]	ee (%)[c]
1	**1a**	Et	PhH	60	100	20
2	**1b**	Et	PhH	60	100	54
3	**1c**	Et	PhH	60	100	60
4	**1d**	Et	PhH	60	100	**89**
5	**1d**	Et	Et_2O[d]	60	<5	-
6	**1d**	Et	$CHCl_3$	60	100	71
7	**1d**	Et	CH_3CN	60	100	74
8	**1d**	Et	PhMe	60	100	83
9	**1d**	Et	PhH	rt	<5	-
10	**1d**	Me	PhH	60	100	87
11	**1d**	*t*-Bu	PhH	60	100	**90**
12	**1d**	*t*-Bu	PhH	50	100	**92**

[a] Reaction conditions: imine (**2a**) (0.5 mmol), Hantzsch ester (0.65 mmol), catalyst (**1**) (0.05 mmol) in solvent (5 mL). [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis of the corresponding acetamide. [d] The reaction was performed in a sealed tube.

(6) (a) Cimarelli, C.; Palmieri, G. *Tetrahredron: Asymmetry* **2000**, *11*, 2555. (b) Kündig, E. P.; Botuha, C.; Lemercier, G.; Romanens, P.; Saudan, L.; Thibault, S. *Helv. Chim. Acta* **2004**, *87*, 561. (c) For reviews about asymmetric addition to C=N bonds, see: (d) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (e) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (f) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(7) For reviews of transition metal catalyzed enantioselective high-pressure hydrogenations, hydrosilylations, and transfer hydrogenations of imines, see: (a) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 1, Chapter 6.2. (b) Nishiyama, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 1, Chapter 6.3. (c) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 2003; Supp. 1, Chapter 6.2. (d) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 2003; Supp. 1, Chapter 6.3. (e) Carpentier, J. F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913. (f) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (g) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (h) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943. (i) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203. For the first example of catalytic enantioselective reduction (hydrosilylation) of imines, see: (j) Langlois, N.; Dang, T.-P.; Kagan, H. B. *Tetrahedron Lett.* **1973**, 4865.

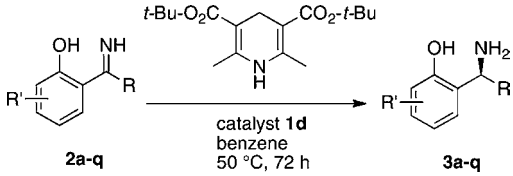
(8) For transition metal catalyzed hydrogen-transfer reductive amination to primary amines: (a) Kadyrov, R.; Riermeier, T. H. *Angew. Chem. Int. Ed* **2003**, *42*, 5472. For enantioselective reduction of trifluoromethylated ketimines with borane-chiral oxazaborolidine (OAB): (b) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355. For chiral Ir-complex catalyzed hydrogenation: (c) Hou, G.; Gosselin, F.; Li, W.; McWilliams, J. C.; Sun, Y.; Weisel, M.; O'Shea, P. D.; Chen, C.; Davies, I. W.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 9882. (d) Hou, G.; Tao, R.; Sun, Y.; Zhang, X.; Gosselin, F. *J. Am. Chem. Soc.* **2010**, *132*, 2124. For chiral Rh-complex catalyzed hydrogenation of unprotected enamines: (e) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, III, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

(9) For the first asymmetric (63% ee) organocatalytic Hantzsch dihydropyridine reduction of imines, see: (a) Singh, S.; Batra, U. K. *Indian J. Chem., Sect. B* **1989**, *28*, 1. For reviews of enantioselective organocatalytic transfer hydrogenation using Hantzsch dihydropyridines, see: (b) Connon, S. *J. Org. Biomol. Chem.* **2007**, *5*, 3407. (c) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820. (d) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.

(10) For reviews on chiral phosphoric acid, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) Terada, M. *Chem. Commun.* **2008**, 4097. (d) Terada, M. *Synthesis* **2010**, 1929.

(11) Selected recent examples: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, V.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (d) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (e) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802. (f) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (g) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. (h) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (i) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637. (j) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631. (k) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (l) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (m) Liu, H.; Dagousset, G.; Masson, G.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (n) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430. (o) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562. (p) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (q) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226. (r) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652. (s) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717. (t) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056. (u) Liao, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 628.

Table 2. Substrate Scope of Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation of *ortho*-Hydroxyaryl Alkyl N−H Ketimines **2**[a]



entry	amine	R	R′	yield (%)[b]	ee (%)[c]
1	**3a**	Me	H	94	92
2	**3b**	Me	3-Me	56	97
3	**3c**	Me	4-F	91	89
4	**3d**	Me	4-Me	93	96
5	**3e**	Me	4-OMe	68	94
6	**3f**	Me	4-NO_2	88	96
7	**3g**	Me	5-Me	86	91
8	**3h**	Me	5-*t*-Bu	70	90
9	**3i**	Me	5-Br	97	90
10	**3j**	Me	5-OMe	85	87
11	**3k**	Me	5-NO_2	77	92
12	**3l**	Me	6-OEt	56	99
13	**3m**	Et	H	86	89
14	**3n**	*n*-Pr	H	98	89
15	**3o**	*n*-hexyl	H	81	89
16	**3p**	*i*-Pr	H	98	81

[a] Reaction conditions: imine (**2**) (0.5 mmol), Hantzsch di-*tert*-butyl ester (0.65 mmol), and catalyst (0.05 mmol) in benzene (5 mL) for 72 h. [b] Yields after chromatography. [c] Determined by chiral HPLC analysis of the corresponding acetamide or propanamide.

3, 4, 5, and 6 position of the aromatic ring were readily reduced to afford the corresponding amines. The presence of either an electron-withdrawing (F, Br, NO_2) or an electron-donating group (Me, OMe) at C-3, C-4, and C-5 of the aromatic ring did not affect significantly the enantioselectivity. On the other hand, an excellent enantioselectivity was observed in the reduction of **2l** having an ethoxy group at C-6 leading to the corresponding amine (**3l**) with up to 99% ee (entry 12).

Previously, only N−Ar imines derived from acetophenone were used as substrates in phosphoric acid-catalyzed transfer hydrogenation,[10a−c] and a computational model was advanced to account for the observed selective reduction of aryl methyl ketimines.[10c] It was thus remarkable to observe that, in our case, other *ortho*-hydroxyaryl alkyl N−H ketimines (R = Et, *n*-Pr, *n*-hexyl, *i*-Pr) can also be reduced efficiently to provide the corresponding amines (**3m**−**3p**, entries 13−16, Table 2) in high yields and ee's.

The absolute configuration of amine **3** was determined to be "*S*" by comparison of the sign of its optical rotation with that of the known amines (see the Supporting Information for details). A control experiment indicated that reduction of imine **2a** did not take place in the absence of phosphoric acid. In the proton NMR spectrum of **2a** (C_6D_6), the phenolic OH appeared at $\delta = 15.6$ ppm indicating the presence of a strong intramolecular H-bond between the phenolic O−H and the imine nitrogen. Upon addition of 1.0 equiv of phosphoric acid (**1d**), the resonance of this OH moved to higher field (aromatic region). This experiment indicated that phosphoric acid (**1d**) is capable of breaking this intramolecular H-bond and activating the imine via, most probably, the formation of an intermolecular H-bond with the imine nitrogen. Consequently, we assumed that the reaction may proceed via a transition state **A** (Figure 1), wherein the phosphoric acid formed H-bonds with both the hydroxyl and the imine functions of **2**.[15] The hydride transfer would then occur from the *re* face of the imines to deliver the amines with the observed (*S*) configuration.

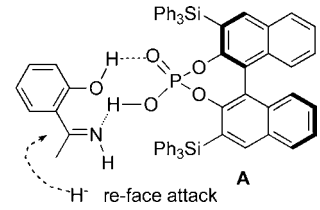


Figure 1. Plausible transition state.

In summary, we have developed the first highly enantioselective chiral phosphoric acid-catalyzed reduction of bench-stable *unprotected ortho*-hydroxyaryl alkyl N−H ketimines using Hantzsch ester as a hydrogen source. The reaction is applicable to a wide range of substrates with different electronic and steric properties. While *ortho*-hydroxybenzylamines are interesting compounds in their own right, the presence of a hydroxy group offered a valuable opportunity for further modification on the *ortho*-position.[16] Further investigation of the reaction mechanism and application of the methodology to the synthesis of bioactive compounds is currently ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, product characterization, ee measurement, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102043X

(12) For chiral phosphoric acid catalyzed transfer hydrogenation of imines with Hantzsch dihydropyridines: (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (e) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (f) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (g) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (h) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (i) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (j) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657. (k) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759. (l) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001. (m) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031. (n) Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075.

(13) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Matochkina, E. G.; Kodess, M. *Tetrahedron* **2008**, *64*, 5055.

(14) For reliable synthesis of free phosphoric acid and its catalytic activity, see: Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823.

(15) For related transition state, see: Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.

(16) Mahdavian, E.; Sangsura, S.; Landry, G.; Eytina, J.; Salvatore, B. A. *Tetrahedron Lett.* **2009**, *50*, 19.