

Highly Enantioselective Synthesis of Chiral Cyclic Amino Alcohols and Conhydrine by Ruthenium-Catalyzed Asymmetric Hydrogenation

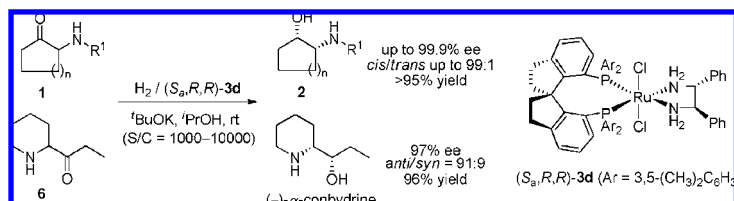
Sheng Liu, Jian-Hua Xie, Wei Li, Wei-Ling Kong, Li-Xin Wang, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

qlzhou@nankai.edu.cn

Received August 10, 2009

ABSTRACT



A highly efficient enantio- and diastereoselective synthesis of chiral *cis*- β -*N*-alkyl/arylamino cyclic alcohols has been realized by asymmetric hydrogenation of racemic α -amino cyclic ketones via DKR catalyzed by $[\text{RuCl}_2((S,S)\text{-SDP})((R,R)\text{-DPEN})]$. The enantioselectivities of the reaction were up to 99.9% ee with 99:1 *cis*-selectivities. A practical catalytic asymmetric synthesis of all four isomers of conhydrine was also developed.

Catalytic enantioselective construction of chiral molecules containing more than one stereocenter by a one-step hydrogenation process has been intensively studied in recent years.¹ Asymmetric hydrogenation of racemic α -substituted ketones via dynamic kinetic resolution (DKR)² has been undoubtedly demonstrated to be one of the most efficient approaches to chiral alcohols with two adjacent stereocenters.³

Recently, we have reported that the ruthenium complexes of chiral spiro diphosphines, $[\text{RuCl}_2((S)\text{-SDPs})((R,R)\text{-diamine})]$ (SDP = 7,7'-bis(diarylphosphino)-1,1'-spirobiindane),⁴ were very efficient catalysts for the asymmetric hydrogenation of *N,N*-disubstituted racemic α -amino aliphatic ketones via DKR, providing a highly enantio- and diastereoselective method for the preparation of optically active β -amino alkanols.^{3d,e} This catalyst was also demonstrated to be highly enantioselective for the asymmetric hydrogenation of unprotected *N*-mono-substituted racemic α -amino acyclic aliphatic ketones.^{3e} To

the best of our knowledge, this was the first example of direct preparation of chiral β -amino alcohols from the Ru-catalyzed asymmetric hydrogenation of unprotected α -amino ketones.⁵ Encouraged by this result, we expanded the substrate scope from *N*-monosubstituted racemic α -amino acyclic aliphatic ketones to the corresponding cyclic α -amino ketones, which led the highly efficient synthesis of *cis*- β -*N*-alkyl/arylamino cyclic alcohols. Herein, we disclose the details of this

(1) For reviews, see: (a) Ratovelomanana-Vidal, V.; Genêt, J.-P. *Can. J. Chem.* **2000**, *78*, 846. (b) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291. (c) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563.

(2) For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. Also see ref 1.

(3) For recent examples of asymmetric hydrogenation of racemic α -substituted cycloketones, see: (a) Scalone, M.; Waldmeier, P. *Org. Process Res. Dev.* **2003**, *7*, 418. (b) Ohkuma, T.; Li, J.; Noyori, R. *Synlett* **2004**, 1383. (c) Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 2967. (d) Liu, S.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7506. (e) Xie, J.-H.; Liu, S.; Kong, W.-L.; Bai, W.-J.; Wang, X.-C.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 4222. For asymmetric hydrogenation of racemic α -substituted acyclic aryl ketones, see: (f) Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939. For asymmetric hydrogenation of racemic α -substituted acyclic dialkyl ketones, see: (g) Chen, C.-Y.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack, J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczkowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. W. *Org. Process Res. Dev.* **2007**, *11*, 616.

(4) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404.

chemistry, including a practical synthesis of all four isomers of natural alkaloid conhydrine.

We started our study with the racemic 2-(phenylamino)cyclohexanone (**1a**) as a standard substrate. The initial hydrogenation experiment was carried out with catalyst (*S_a,R,R*)-**3a** (Figure 1) in 2-propanol under 50 atm of H₂ pressure at

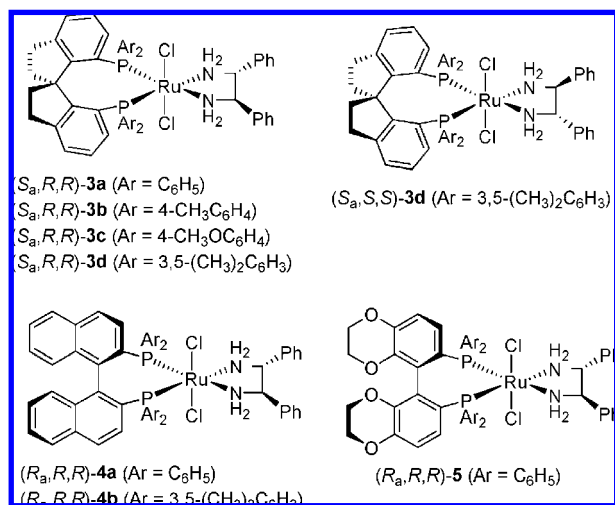


Figure 1. Chiral [RuCl₂(diphosphine)(diamine)] complexes.

room temperature. The reaction proceeded smoothly, and the product *cis*-2-phenylaminocyclohexanol (*cis*-**2a**) was isolated in 97% yield with 98% ee and >99:1 of *cis*-selectivity within 2 h (Table 1, entry 1). A systematic study of the ligands in

Table 1. Asymmetric Hydrogenation of **1a**: Optimization of Reaction Conditions^a

entry	catalyst	diphosphine	P _{H₂} (atm)	time (h)	<i>cis/trans</i> ^b	ee ^c (%)
1	(<i>S_a,R,R</i>)- 3a	(<i>S</i>)-SDP	50	2	>99:1	98
2	(<i>S_a,R,R</i>)- 3b	(<i>S</i>)-Tol-SDP	50	2	>99:1	99
3	(<i>S_a,R,R</i>)- 3c	(<i>S</i>)-An-SDP	50	2	>99:1	92
4	(<i>S_a,R,R</i>)- 3d	(<i>S</i>)-Xyl-SDP	50	2	>99:1	99.6
5	(<i>S_a,S,S</i>)- 3d	(<i>S</i>)-Xyl-SDP	50	5	93:7	75
6 ^d	(<i>S_a,R,R</i>)- 3d	(<i>S</i>)-Xyl-SDP	50	24	>99:1	99.6
7	(<i>S_a,R,R</i>)- 3d	(<i>S</i>)-Xyl-SDP	10	4	>99:1	99.6
8	(<i>R_a,R,R</i>)- 4a	(<i>R</i>)-BINAP	10	6	>99:1	89
9	(<i>R_a,R,R</i>)- 4b	(<i>R</i>)-Xyl-BINAP	10	6	>99:1	70
10	(<i>R_a,R,R</i>)- 5	(<i>R</i>)-SYNPHOS	10	4	>99:1	79

^a Reaction conditions: S/C = 1000, [**1a**] = 0.6 mmol/mL, [^{*t*}BuOK] = 0.06 mmol/mL, ^{*i*}PrOH, room temperature, 100% conversion. ^b Determined by HPLC. ^c ee values for *cis*-isomer determined by HPLC. The absolute configuration of the product **2a** is (1*S*,2*R*). ^d S/C = 10000.

the catalysts RuCl₂(SDPs)(diamine) showed that the ligand Xyl-SDP was the most enantioselective. With the catalyst

[RuCl₂((*S*)-Xyl-SDP)((*R,R*)-DPEN)] ((*S_a,R,R*)-**3d**, DPEN = *trans*-1,2-diphenylethylenediamine), the enantioselectivity of the hydrogenation of **1a** reached 99.6% ee (entry 4), while the catalyst [RuCl₂((*S*)-Xyl-SDP)((*S,S*)-DPEN)] ((*S_a,S,S*)-**3d**) has mismatched configurations, which afforded the product *cis*-**2a** in low enantioselectivity (75% ee) with a long reaction time (24 h) (entry 5). The catalysts (*S_a,S,S*)-**3d** and (*S_a,R,R*)-**3d** gave the same configuration of product, indicating that the configuration of the product was determined by the configuration of the ligand Xyl-SDP instead of the ligand DPEN. The activity of the catalyst (*S_a,R,R*)-**3d** was remarkable; it can catalyze the hydrogenation of **1a** at a very low catalyst loading (S/C = 10000) (entry 6) or under low hydrogenation pressure (10 atm) (entry 7). Other types of chiral diphosphine ligands such as BINAP ((*R_a,R,R*)-**4a**), Xyl-BINAP ((*R_a,R,R*)-**4b**), and SYNPHOS ((*R_a,R,R*)-**5**) can also catalyze this hydrogenation reaction, although the enantioselectivities were lower (70–89% ee) (entries 8–10).

The scope of substrates for the reaction was studied with catalyst (*S_a,R,R*)-**3d**. Various racemic α-*N*-alkyl/aryl amino cyclohexanones can be hydrogenated to *cis*-β-alkyl/aryl amino cyclohexanols in high yields with excellent enantioselectivities and diastereoselectivities. The substituents on the *N*-phenyl ring, whether electron-withdrawing or electron-donating, had a negligible effect on the enantioselectivity and diastereoselectivity of the reaction (Table 2, entries 1–12). The hydrogenation reactions of **1e**, **1i**, and **1j**, as well as **1m**, were quite slow, mainly due to the low solubility of these substrates in 2-propanol (entries 5, 9, 10, and 13). If the arylamino groups in the substrates were changed to alkylamino groups, the hydrogenation still went very well, and the corresponding chiral *cis*-β-alkylamino cyclic alcohols were obtained with high enantioselectivities (98–99.9% ee) and high diastereoselectivities (>98:2) (entries 14–16). The α-butylamino cyclohexanone (**1p**) had the fastest reaction rate, and its turnover frequency (TOF) in the hydrogenation was as high as 2000/h (entry 16). When the substrates with a five-membered ring (**1q**) and a seven-membered ring (**1r**) were subjected to the hydrogenation the desired chiral *cis*-β-alkylamino cyclic alcohols were obtained with high enantioselectivities (91% and 94% ee, respectively) and high diastereoselectivities (*cis/trans* = 98:2 and 99:1, respectively) (entries 17 and 18).

We next focused our attention on the synthesis of 2-(1-hydroxyalkyl)piperidine, a ubiquitous structural unit existing in natural products and therapeutics.⁶ Conhydrine is one of the alkaloids containing this type of hydroxylated piperidine structure isolated from the seeds and leaves of hemlock

(5) For examples of Rh-catalyzed asymmetric hydrogenation of α-*N*-monoalkyl/monoarylamino ketones, see: (a) Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chem.-Eur. J.* **2007**, *13*, 7780. (b) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 1687. Noyori and co-workers reported [RuCl₂((*S*)-Xyl-BINAP)(*R*)-DaiPEN]-catalyzed asymmetric hydrogenation of racemic α-amino cyclohexanone, but the amino group was protected by *tert*-butoxycarbonyl; see: (c) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510.

(6) For reviews, see: (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, J. W., Ed.; Pergamon: New York, 1986; Vol. 5, pp 1–54. (b) Casiraghi, C.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619. (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

Table 2. Asymmetric Hydrogenation of Racemic α -*N*-Alkyl/Arylamino Cyclic Ketones **1** Catalyzed by (*S_a,R,R*)-**3d**^a

entry	R ¹	n	product	time (h)	cis/trans ^b	ee ^c (%)
1	C ₆ H ₅	2	2a	6	>99:1	99.6
2	4-MeC ₆ H ₄	2	2b	8	>99:1	99.1
3	4-MeOC ₆ H ₄	2	2c	4	>99:1	99.9
4	4-ClC ₆ H ₄	2	2d	4	>99:1	99.6
5 ^d	4-BrC ₆ H ₄	2	2e	46	>99:1	99.3
6	3-MeC ₆ H ₄	2	2f	3	>99:1	99.6
7	3-ClC ₆ H ₄	2	2g	3	>99:1	99.4
8	2-MeC ₆ H ₄	2	2h	3	>99:1	99
9	2-MeOC ₆ H ₄	2	2i	17	>99:1	99
10	2-FC ₆ H ₄	2	2j	24	>99:1	99
11	2-ClC ₆ H ₄	2	2k	3	>99:1	98
12	2-I-4-MeC ₆ H ₃	2	2l	1	>99:1	96
13 ^e	2-Py	2	2m	20	97:3	99.8
14	C ₆ H ₅ CH ₂	2	2n	18	>99:1	99.9
15	<i>c</i> -Hex	2	2o	1	>99:1	99.9
16	<i>n</i> -Bu	2	2p	0.5	98:2	98
17	C ₆ H ₅	1	2q	8	98:2	91
18	C ₆ H ₅	3	2r	10	99:1	94

^a Reaction conditions are same as those in Table 1, entry 7. 100% conversion, isolated yield >90%. ^b Determined by GC or HPLC. ^c Determined by HPLC. ^d The configuration of **2e** is (1*S*,2*R*) determined by X-ray single-crystal analysis. ^e 50 atm of H₂.

Conium maculatum L.⁷ The first synthesis of (+)- α -conhydrine was reported by Galinovsky and Mulley in 1948.⁸ During the following decades many enantioselective methods have been developed for the preparation of conhydrine and its isomers.⁹ However, most of these methods used tedious steps or had low yields. Thus, the development of short and highly efficient procedures for the enantioselective synthesis of conhydrine and its analogues is desirable.

Analysis of the synthesis of conhydrine led us to consider a piperidine-containing racemic α -amino ketone **6** as a key intermediate, which might be hydrogenated with a chiral ruthenium catalyst to α -conhydrine. The obtained α -conhydrine was then converted to β -conhydrine via a simple configuration transformation. Therefore, all four isomers

of conhydrine would be efficiently synthesized by ruthenium-catalyzed asymmetric hydrogenation as a key step (Figure 2).

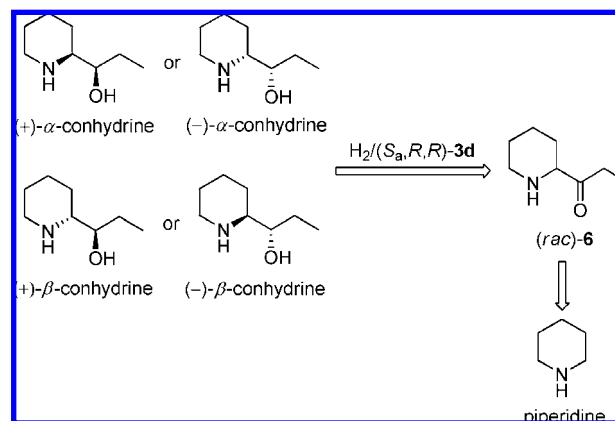
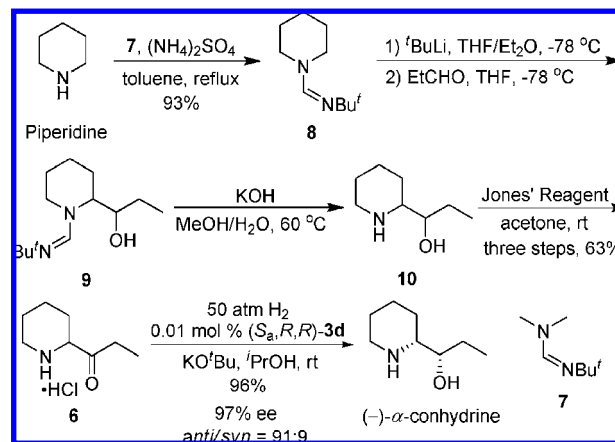


Figure 2. Conhydrines and their retrosynthetic analysis.

The racemic α -amino ketone **6** was prepared easily from piperidine.¹⁰ Piperidine was first reacted with *N,N*-dimethyl-*N'*-*tert*-butylformamidine (**7**) to provide the compound **8** in 93% yield (Scheme 1). Lithiation of compound **8** with *tert*-

Scheme 1. Asymmetric Synthesis of (–)- α -Conhydrine



butyllithium in THF/Et₂O followed by treatment with propionaldehyde afforded alcohol **9**. The alcohol **9** was then deprotected by hydrolysis with aqueous NaOH in methanol at 60 °C to give unprotected alcohol **10**.¹¹ Oxidation of alcohol **10** with Jones' reagent produced amino ketone **6** as a hydrochloride salt in 63% yield for three steps. Asymmetric hydrogenation of ketone **6** was carried out by using catalyst

(7) Isolation: Wertheim, T. *Liebigs Ann. Chem.* **1856**, 100, 328.

(8) Galinovsky, F.; Mulley, H. *Monatsh. Chem.* **1948**, 79, 426.

(9) For selected recent papers for the synthesis of (+)- α -conhydrine, see: (a) Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem.-Eur. J.* **2009**, 15, 1713. (b) Rodríguez, D.; Picó, A.; Moyano, A. *Tetrahedron Lett.* **2008**, 49, 6866. (c) Petersen, K. S.; Posner, G. H. *Org. Lett.* **2008**, 10, 4685. (d) Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, 9, 1609. (e) Chang, M.-Y.; Kung, Y.-H.; Chen, S.-T. *Tetrahedron* **2006**, 62, 10843. (f) Nagata, K.; Toriizuka, Y.; Itoh, T. *Heterocycles* **2005**, 66, 107. For (–)- α -conhydrine, see: (g) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, 72, 5358. (h) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, 16, 3268. (i) Kandula, S. R. V.; Kumar, P. *Tetrahedron Lett.* **2003**, 44, 1957. For (+)- β -conhydrine, see: (j) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaude, P. *Tetrahedron: Asymmetry* **2008**, 19, 1245. For (–)- β -conhydrine, see: (k) Saikia, P. P.; Baishya, G.; Goswami, A.; Barua, N. C. *Tetrahedron Lett.* **2008**, 49, 6508. (l) Kandula, S. R. V.; Kumar, P. *Tetrahedron Lett.* **2005**, 46, 4091.

(10) For the synthesis of amino ketone **6** using other methods, see: Naef, R.; Velluz, Alain, Y.; Mayenzet, F.; Starkenmann, C.; Sun, H.-D. *J. Agric. Food. Chem.* **2005**, 53, 9161.

(11) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, 106, 3270.

(*S_a,R,R*)-**3d** in 2-propanol at S/C = 10000 to give (–)- α -conhydrine in 96% yield with 97% ee and 91:9 *anti*-selectivity.¹² By using (*R_a,S,S*)-**3d** as a catalyst and under the same reaction conditions, (+)- α -conhydrine was produced in 95% yield with nearly the same ee value and *anti*-selectivity. Thus, (+)- or (–)- α -conhydrine was synthesized through a five-step process from piperidine with an overall yield of 56%.

With (–)- α -conhydrine in hand, we then reacted it with sulfonyl dichloride (SO₂Cl₂) to furnish the cyclic sulfate **11**. The replacement of activated hydroxyl group in compound **11** by NaOAc in DMF yielded acetate compound **12** with a reverse configuration (Scheme 2). Finally, the acetate

compound **12** was hydrolyzed with K₂CO₃ as a base to provide (+)- β -conhydrine in 76% yield for two steps. By using the same procedure, (+)- α -conhydrine was converted to (–)- β -conhydrine in the same yield.

In conclusion, we have developed an effective protocol for the highly enantio- and diastereoselective synthesis of chiral *cis*- β -*N*-alkyl/aryl amino cyclic alcohols by catalytic asymmetric hydrogenation of racemic α -amino cyclic ketones via DKR. This new method provided a direct and practical approach to the asymmetric syntheses of all four isomers of piperidine alkaloids conhydrine.

Acknowledgment. We thank the National Natural Science Foundation of China, the Major Basic Research Development Program (Grant No. 2006CB806106), the “111” project (B06005) of the Ministry of Education of China, and Merck Research Laboratories for financial support.

Supporting Information Available: Experimental procedures, the characterizations of substrates and products, and the analysis of ee values of hydrogenation products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) The *anti*-selectivity of this hydrogenation reaction can be interpreted by the proposed transition state model involving a hydrogen bond between the amino group of the substrate and the NH₂ group of the chiral diamine in the catalyst. See ref 3e.

Scheme 2. Transformation of (–)- α -Conhydrine to (+)- β -Conhydrine

