Asymmetric Catalysis

DOI: 10.1002/ange.200902339

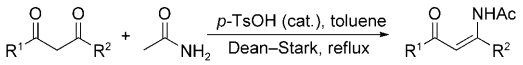
Rhodium-Catalyzed Enantioselective and Diastereoselective Hydrogenation of β-Ketoenamides: Efficient Access to *anti* 1,3-Amino Alcohols**

Huiling Geng, Weicheng Zhang, Jian Chen, Guohua Hou, Le Zhou, Yaping Zou, Wenjun Wu, and Xumu Zhang**

Chiral 1,3-amino alcohols are interesting structural motifs prevalent in pharmaceutical products[1] as well as in important chiral auxiliaries and ligands for asymmetric synthesis.[2] Currently, the most common strategy for their synthesis is based on the diastereoselective reduction of an enantiomerically pure substrate, whereby the chirality of the substrate controls the formation of the new stereogenic center (substrate-controlled asymmetric reduction).[3–5] In this context, we wondered whether asymmetric hydrogenation[6] could be used to afford chiral 1,3-amino alcohols from readily prepared substrates (reagent-controlled asymmetric reduction).[7,8] Herein, we report a rhodium-catalyzed highly enantioselective (up to 99% *ee*) and diastereoselective (up to d.r. 99:1) hydrogenation of β-ketoenamides as an efficient entry to enantiomerically pure *anti* 1,3-amino alcohols containing two stereogenic centers.

The substrates were prepared in one step from readily accessible 1,3-diketones[9] under Dean–Stark conditions (Table 1). Owing to its operational simplicity, we recently employed this method for the preparation of *Z*/*E* β-aryl enamides.[10] In the present study, we further optimized the reaction conditions. The desired substrates **2a**–**2n** were obtained in moderate to good yield (up to 90%) as stable crystalline solids. In each case, only the *Z* enamide was observed, probably as a result of the intramolecular hydrogen bond.

Table 1: Preparation of β-ketoenamides **2** through the direct condensation of **1** with acetamide.[a]



1 **2**

Entry	**1**	R^1	R^2	**2**[b]	Yield [%][c]
1	**1a**	C_6H_5	Me	**2a**	90
2	**1b**	*p*-MeC_6H_4	Me	**2b**	46
3	**1c**	*p*-$MeOC_6H_4$	Me	**2c**	84
4	**1d**	*p*-FC_6H_4	Me	**2d**	69
5	**1e**	*p*-ClC_6H_4	Me	**2e**	87
6	**1f**	*p*-BrC_6H_4	Me	**2f**	72
7	**1g**	*p*-*t*BuC_6H_4	Me	**2g**	58
8	**1h**	*p*-CyC_6H_4	Me	**2h**	65
9	**1i**	*m*-MeC_6H_4	Me	**2i**	65
10	**1j**	*o*-MeC_6H_4	Me	**2j**	72
11	**1k**	thiophen-2-yl	Me	**2k**	56
12	**1l**	2-naphthyl	Me	**2l**	76
13	**1m**	C_6H_5	Et	**2m**	47
14	**1n**	Me	Me	**2n**	68

[a] Reactions were carried out by heating a mixture of **1** (50 mmol), acetamide (250 mmol), and *p*-TsOH (10 mmol) in toluene (150 mL) in a Dean–Stark apparatus for 24 h. [b] In all cases, only the *Z* enamide was observed by ^{1}H NMR spectroscopy. [c] Yield of the isolated product. Cy = cyclohexyl, Ts = toluenesulfonyl.

We tested **2a** as the standard substrate in a series of rhodium-catalyzed hydrogenation reactions. Our initial reaction with Rh/duanphos (**L1**)[11a] in CH_2Cl_2 under 10 bar of hydrogen pressure gave the product **3a** with 97% *ee* and predominant *anti* selectivity (d.r. 95:5), albeit accompanied by a small amount of the monoreduction product **4a** (Table 2, entry 1). Solvent screening (Table 2, entries 1–9) revealed that the use of EtOAc (entry 6) led to the best reactivity (95% yield) and selectivity (99% *ee*, d.r. 95:5) for **3a**. Thus, EtOAc was selected as the optimal solvent. An increase in the hydrogen pressure to 20 bar (Table 2, entry 10) led to complete conversion into **3a**, whereas a further increase in hydrogen pressure caused a slight drop in enantioselectivity (entries 11–13). We also tested four other commercially available chiral ligands: tangphos (**L2**),[11b] Et-duphos (**L3**),[11c] binapine (**L4**),[11d] and f-binaphane (**L5**).[11e] Lower reactivity or enantioselectivity was observed with these ligands (Table 2, entries 14–17).

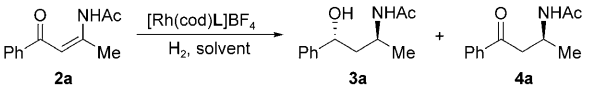
Encouraged by our preliminary results, we subjected a series of substrates, **2b**–**2n**, to asymmetric hydrogenation under the optimized conditions with the Rh/duanphos

[*] H. Geng, Prof. L. Zhou, Prof. W. Wu
College of Science
Northwest Agriculture & Forestry University
Yangling, Shaanxi 712100 (China)
E-mail: wenjun_wu@263.com
H. Geng, W. Zhang, J. Chen, G. Hou, Y. Zou, Prof. X. Zhang
Department of Chemistry and Chemical Biology and
Department of Pharmaceutical Chemistry
Rutgers, The State University of New Jersey
Piscataway, New Jersey 08854 (USA)
Fax: (+1) 732-445-6312
E-mail: xumu@rci.rutgers.edu
Homepage: http://rutchem.rutgers.edu/~xumuweb/

[**] This research was supported by the National Institutes of Health (GM58832), China Scholarship Council, and Northwest Agriculture & Forestry University. Mass spectrometry was carried out by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902339.

Table 2: Rhodium-catalyzed asymmetric hydrogenation of **2a** under various conditions.[a]

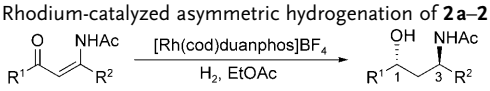


2a **3a** **4a**

Entry	L[b]	Solvent	P_{H_2} [bar]	**3a** Yield[c] [%]	**3a** *ee*[d] [%]	**3a** d.r.[e] (*syn*/*anti*)	Yield of **4a** [%][f]
1	**L1**	CH_2Cl_2	10	85	97	5:95	12
2	**L1**	toluene	10	74	>99	4:96	19
3	**L1**	THF	10	62	98	6:94	38
4	**L1**	dioxane	10	29	99	29:71	71
5	**L1**	acetone	10	63	98	29:71	37
6	**L1**	EtOAc	10	95	99	5:95	5
7	**L1**	MeOH	10	72	98	31:69	28
8	**L1**	*i*PrOH	10	96	93	9:91	4
9	**L1**	CF_3CH_2OH	10	3	46	31:69	32
10	**L1**	EtOAc	20	100	99	5:95	0
11	**L1**	EtOAc	30	100	98	3:97	0
12	**L1**	EtOAc	40	100	98	4:96	0
13	**L1**	EtOAc	50	100	95	4:96	0
14	**L2**	EtOAc	20	100	98	5:95	0
15	**L3**	EtOAc	20	56	99	5:95	44
16	**L4**	EtOAc	20	17	>99	3:97	32
17	**L5**	EtOAc	20	100	69	8:92	0

[a] Reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature for 24 h. [b] **L1** = (S_C,R_P)-duanphos, **L2** = (1*S*,1*S*′,2*R*,2*R*′)-tangphos, **L3** = (*R*,*R*)-Et-duphos, **L4** = (*S*)-binapine, **L5** = f-binaphane. [c] The yield of **3a** was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of **3a** was determined by GC on a chiral phase. The absolute configuration of **3a** was assigned by comparison of the observed optical rotation with reported data. [e] The diastereomeric ratio was calculated from the ^{1}H NMR spectrum of the crude hydrogenation product. [f] The yield of **4a** was calculated from the ^{1}H NMR spectrum of the crude hydrogenation product. cod = cycloocta-1,5-diene; (S_C,R_P)-duanphos = (1*R*,1′*R*,2*S*,2′*S*)-2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′)-biisophosphindolyl; (1*S*,1′*S*,2*R*,2′*R*)-tangphos = 1,1′-di-*tert*-butyl-(2,2′)-diphospholanyl; (*R*,*R*)-Et-duphos = 1,2-bis(2,5-diethylphospholanyl)benzene; (*S*)-binapine = (3*S*,3′*S*,4*S*,4′*S*,11b*S*,11′b*S*)-4,4′-di-*tert*-butyl-4,4′,5,5′-tetrahydro-3*H*,3′*H*-bidinaphtho[2,1-*c*:1′,2′-*e*]phosphepine; f-binaphane = 1,1′-bis((*S*)-4,5-dihydro-3*H*-binaphtho[2,1-*c*:1′,2′-*e*]phosphepino)ferrocene.

Table 3: Rhodium-catalyzed asymmetric hydrogenation of **2a**–**2n**.[a]



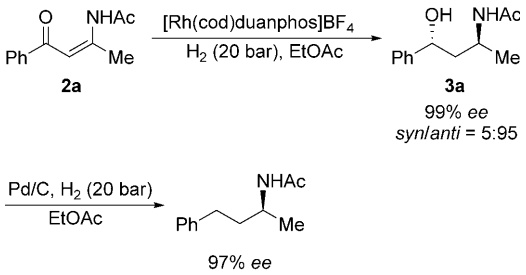
2 **3**

Entry	**2**	R^1	R^2	P_{H_2} [bar]	**3**	Yield[b] [%]	*ee*[c] [%]	d.r.[d] (*syn*/*anti*)
1	**2a**	C_6H_5	Me	20	**3a**[e]	100	99	5:95
2	**2b**	*p*-MeC_6H_4	Me	100	**3b**	97	97	7:93
3	**2c**	*p*-$MeOC_6H_4$	Me	100	**3c**	95	95	8:92
4	**2d**	*p*-FC_6H_4	Me	20	**3d**	100	97	4:96
5	**2e**	*p*-ClC_6H_4	Me	20	**3e**	100	99	4:96
6	**2f**	*p*-BrC_6H_4	Me	100	**3f**	95	98	6:94
7	**2g**	*p*-*t*BuC_6H_4	Me	100	**3g**	96	97	8:92
8	**2h**	*p*-CyC_6H_4	Me	100	**3h**	93	97	8:92
9	**2i**	*m*-MeC_6H_4	Me	20	**3i**	100	99	4:96
10	**2j**	*o*-MeC_6H_4	Me	20	**3j**	100	94	14:86
11	**2k**	thiophen-2-yl	Me	20	**3k**	100	99	5:95
12	**2l**	2-naphthyl	Me	20	**3l**	100	97	<1:99
13	**2m**	C_6H_5	Et	20	**3m**	100	96	5:95
14	**2n**	Me	Me	20	**3n**	100	96	<1:99

[a] Reactions were carried out with a substrate/catalyst ratio of 100:1 in EtOAc at room temperature for 24 h. [b] The yield was calculated from the ^{1}H NMR spectrum of the crude hydrogenation product. [c] The *ee* value was determined by GC or HPLC on a chiral phase. [d] The diastereomeric ratio was calculated from the ^{1}H NMR spectrum of the crude hydrogenation product. [e] The absolute configuration of **3a** was assigned as 1*R*,3*S* by comparison of the observed optical rotation with reported data. The absolute configurations of **3b**–**3n** (all samples showing positive optical rotation) were not determined.

catalytic system in EtOAc. The hydrogen pressure was found to be critical for the formation of the desired product **3** in good yield and minimization of the amount of monoreduction side products. Therefore, this parameter was optimized for different substrates (Table 3). In most cases, excellent enantioselectivity, diastereoselectivity, and conversion were observed. The presence of substituents on the phenyl moiety in **2** resulted in a slight decrease in the *ee* value of the product in some cases without compromising the diastereoselectivity. The only exception was the *ortho*-methyl-substituted substrate **2j**, for which lower enantio- and diastereoselectivity were observed than for the *para*- and *meta*-substituted substrates **2b** and **2i**. This decrease in selectivity can presumably be attributed to increased steric hindrance of the aryl group during hydrogenation.

The present transformation can be coupled to Pd/C-catalyzed hydrogenolysis for the preparation of chiral γ-aryl isobutylamines. When the chiral 1,3-amino alcohol precursor **3a** (99% *ee*) was treated with Pd/C in the presence of hydrogen gas (20 bar), γ-phenylisobutylamine (97% *ee*) was obtained in quantitative yield (Scheme 1). To our knowledge,

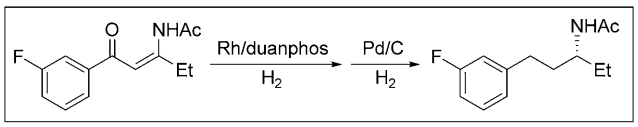


2a **3a**

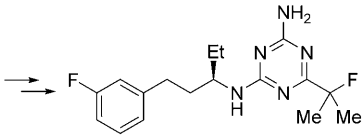
Scheme 1. Synthesis of γ-phenylisobutylamine through asymmetric hydrogenation.

there is no other catalytic method available for the preparation this class of chiral amines.[12] This transformation therefore represents an elegant catalytic approach to these pharmaceutically and biologically valuable chiral compounds. For example, compound **4**, an agrochemical for pest control, could potentially be prepared by this sequence of reactions (Scheme 2).[13]

In summary, we have shown that a variety of *anti* 1,3-amino alcohols can be prepared by a highly efficient rhodium-catalyzed asymmetric hydrogenation of readily available β-ketoenamides. Two stereogenic centers are generated



tandem asymmetric hydrogenation–hydrogenolysis process



4 (pesticide)

Scheme 2. Potential application of the asymmetric hydrogenation–hydrogenolysis protocol for the preparation of a chiral pesticide.

simultaneously with excellent enantioselectivity and diastereoselectivity in this atom-economical process. Subsequent treatment of the 1,3-amino alcohol intermediates with Pd/C and hydrogen gas leads to the formation of protected chiral γ-aryl isobutylamines. This protocol constitutes the first asymmetric catalytic method for the preparation of these valuable chiral building blocks. Further exploration of this strategy for the preparation of various chiral compounds is currently in progress.

Experimental Section

Substrate preparation: A solution of **1** (50 mmol), acetamide (250 mmol), and the catalyst *p*-TsOH (10 mmol) in toluene (150 mL) was placed in a Dean–Stark apparatus and heated at reflux for 24 h. The reaction mixture was then cooled to room temperature, the solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane) to give **2** as a white powder or colorless oil.

Hydrogenation: A stock solution was made by mixing $[Rh(cod)_2]BF_4$ with duanphos in a 1:1.1 molar ratio in EtOAc at room temperature for 10 min in a nitrogen-filled glovebox. A specified amount of the catalyst solution (0.1 mL, 0.001 mmol) was transferred by syringe into a vial containing the substrate (0.1 mmol) in EtOAc (2.9 mL). The vial was placed in a steel autoclave, which was then charged with hydrogen gas, and the reaction mixture was stirred at room temperature for 24 h. The hydrogen was then released slowly, and the solution was concentrated and passed through a short column of silica gel to remove the metal complex. The *ee* value of the product was determined by GC or HPLC of the product mixture on a chiral phase.

Received: May 1, 2009
Published online: July 13, 2009

Keywords: diastereoselectivity · enamides · enantioselectivity · hydrogenation · rhodium

[1] M. Nogradi, *Stereoselective Synthesis*, VCH, Weinheim, **1987**.
[2] S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767.
[3] T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 6518.
[4] G. E. Keck, A. P. Truong, *Org. Lett.* **2002**, *4*, 3131.
[5] F. A. Davis, P. M. Gaspari, B. M. Nolt, P. Xu, *J. Org. Chem.* **2008**, *73*, 9619.
[6] a) *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley-VCH, New York, **2000**; d) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; e) W. Zhang, Y. Chi, X. Zhang, *Acc. Chem. Res.* **2007**, *40*, 1278.
[7] For the catalytic synthesis of chiral 1,2-amino alcohols through asymmetric hydrogenation, see: a) M. Kitamura, T. Okuma, S. Inoue, N. Sayo, H. Komobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629; b) H. Takahashi, S. Sakuraba, H. Takeda, K. Achiwa, *J. Am. Chem. Soc.* **1990**, *112*, 5876; c) G. Zhu, A. L. Casalnuovo, X. Zhang, *J. Org. Chem.* **1998**, *63*, 8100; d) T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 6510; e) A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 1626; f) S. Liu, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 7650; *Angew. Chem. Int. Ed.* **2007**, *46*, 7506; g) J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 4222.
[8] To our knowledge, asymmetric hydrogenation has seldom been applied in the synthesis of chiral 1,3-amino alcohols; an example is the asymmetric hydrogenation of certain γ-amino ketones: a) reference [7d]; b) D. Liu, W. Gao, C. Wang, X. Zhang, *Angew. Chem.* **2005**, *117*, 1715; *Angew. Chem. Int. Ed.* **2005**, *44*, 1687.
[9] For the preparation of 1,3-diketones, see: X. Han, R. A. Widenhoefer, *J. Org. Chem.* **2004**, *69*, 1738.
[10] J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei, X. Zhang, *Angew. Chem.* **2009**, *121*, 814; *Angew. Chem. Int. Ed.* **2009**, *48*, 800.
[11] a) D. Liu, X. Zhang, *Eur. J. Org. Chem.* **2005**, 646; b) W. Tang, X. Zhang, *Angew. Chem.* **2002**, *114*, 1682; *Angew. Chem. Int. Ed.* **2002**, *41*, 1612; c) M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363; d) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem.* **2003**, *115*, 3633; *Angew. Chem. Int. Ed.* **2003**, *42*, 3509; e) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425.
[12] For strategies based on the use of chiral auxiliaries, see: a) S. E. Denmark, T. Weber, D. W. Piotrowski, *J. Am. Chem. Soc.* **1987**, *109*, 2224; b) J. T. Colyer, N. G. Anderson, J. S. Tedrow, T. S. Soukup, M. M. Faul, *J. Org. Chem.* **2006**, *71*, 6859; for enzyme-assisted resolution, see: c) J. Conzalez-Sabin, W. Gotor, F. Rebolledo, *Tetrahedron: Asymmetry* **2002**, *13*, 1315; d) M. Nechab, N. Azzi, N. Vanthuyne, M. Bertrand, S. Gastaldi, G. Gil, *J. Org. Chem.* **2007**, *72*, 6918.
[13] Y. Watanabe, Y. Otsu, H.-J. Riebel, S. Lehr, U. Stelzer, E. R. F. Gesing, R. Kirsten, A. Lender, K. Voigt, U. Wachendorff-Neumann, C. Erdelen, Ger. Offen. DE 19825379, **1999**.

