

Efficient Synthesis of Chiral β -Arylisopropylamines by Using Catalytic Asymmetric Hydrogenation**

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Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Transition-metal-catalyzed asymmetric hydrogenation of enamides^[1] is a powerful method for the preparation of chiral amines, which are important building blocks in organic synthesis.^[2] With the development of many effective chiral ligands,^[1] a variety of prochiral enamides such as **1**,^[3] **2**,^[3a-c,e,g] **3**,^[4] and **4**,^[5] have been hydrogenated with excellent enantioselectivities (Figure 1). However, the asymmetric hydrogenation of **5** has received less attention. To our knowledge, the only result reported for the hydrogenation of **5** employed an Rh/dipamp (dipamp = 1,2-ethanediylbis[(2-methoxyphenyl)-phenylphosphine]) complex to give moderate enantioselectivity (50% *ee*).^[6] Herein, we prepared a series of enamides, (*Z*)-**5** and (*E*)-**5**, and tested them in a rhodium-catalyzed asymmetric hydrogenation using several chiral ligands. Excellent *ee* values (up to 99% *ee*) were achieved for the *Z*-configured enamides by using the Rh/tangphos (tangphos = 1,1'-di-*tert*-butyl-[2,2']-diphospholanyl) catalytic system.

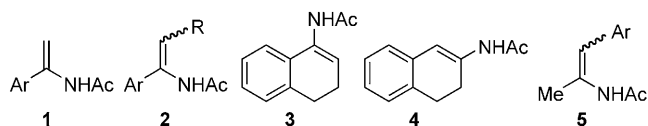
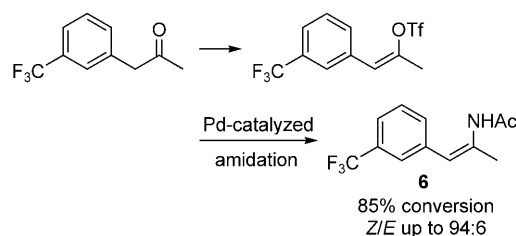


Figure 1. Prochiral enamide substrates for asymmetric hydrogenation.

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A number of methods for the preparation of enamides have been reported, including rearrangement reactions,^[6,7] the reduction of nitro alkenes^[8] or ketoximes,^[9] the acylation of imines,^[10] and the direct condensation of a ketone and an amide.^[11] Recently, a Merck group developed an efficient palladium-catalyzed amidation reaction leading to a diverse array of enamides.^[12] Under the optimized reaction conditions, good selectivity for *Z* enamides such as **6** was achieved (Scheme 1). To gain quick access to the desired substrates **5a**–



Scheme 1. Palladium-catalyzed amidation for the synthesis of *Z*-enamide **6**.^[12]

5i, we chose the direct condensation method because of its operational simplicity. As shown in Table 1, each isomer of **5** can be isolated by using flash column chromatography; in most cases, more of the *Z* enamide was obtained than the corresponding *E* isomer. Although the moderate yields remain to be optimized, we found the present method to be suitable for the quick syntheses of both (*Z*)-**5** and (*E*)-**5** from inexpensive starting materials. Additionally, diaryl enamide **5i** was prepared in acceptable yield (Table 1, entry 9), which complements the palladium-catalyzed amidation for this bulky substrate.^[12b]

Having synthesized a set of enamides **5**, we tested the rhodium-catalyzed asymmetric hydrogenation of (*Z*)-**5a** and (*E*)-**5a** by using four widely used chiral ligands, including (1*S*,1*S'*,2*R*,2*R'*)-tangphos (**L1**),^[13a] (*S_C*,*R_P*)-duanphos (**L2**),^[13b] (*R,R*)-Et-duphos (**L3**),^[13c] and (*S*)-binapine (**L4**).^[13d] Notably, under the same reaction conditions each ligand showed a striking difference in enantioselectivity toward the two isomers (Table 2). For (*Z*)-**5a**, excellent *ee* values were obtained by the use of all ligands except **L4**, with tangphos giving the best results. A change in the solvent used had little effect on the enantioselectivity. In contrast, much lower *ee* values were observed for (*E*)-**5a** in EtOAc, albeit with the same sense of product chirality as that obtained from (*Z*)-**5a**. A change in the solvent used gave no improvement in

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Table 1: Preparation of (Z)- and (E)-5 by direct condensation of 7 with acetamide.^[a]

Entry	Ketone ^[b]	R ¹	R ²	Enamide	Yield [%] ^[c]	Z/E
1	7a	Ph	Me	5a	24.1	1.8:1
2	7b	<i>o</i> -MeOPh	Me	5b	29.3	2:1
3	7c	<i>p</i> -MeOPh	Me	5c	29.3	2.8:1
4	7d	<i>m</i> -MeOPh	Me	5d	35.1	1.3:1
5	7e	<i>m</i> -MePh	Me	5e	22.2	1.3:1
6	7f	<i>p</i> -MePh	Me	5f	24.0	0.9:1
7	7g	<i>o</i> -ClPh	Me	5g	15.6	1.7:1
8	7h	1-naphthyl-Ph	Me	5h	56.3	0.7:1
9	7i	Ph	Ph	5i	44.2	3.7:1

[a] All reactions were carried out by refluxing a toluene solution (50 mL) of **7** (25 mmol), acetamide (125 mmol), and the catalyst TsOH (2.5 mmol) in a Dean–Stark apparatus for 24 h. [b] See the Supporting Information for their preparation. [c] Combined yield of isolated Z and E products.

Table 2: Rhodium-catalyzed asymmetric hydrogenation of (Z)-5a and (E)-5a using different ligands.^[a]

Entry	Substrate	Ligand ^[b]	Solvent	ee [%] ^[c]	Config. ^[d]
1	(Z)-5a	L1	EtOAc	99.3	S
2	(Z)-5a	L2	EtOAc	98.1	S
3	(Z)-5a	L3	EtOAc	95.7	S
4	(Z)-5a	L4	EtOAc	57.5	S
5	(Z)-5a	L1	CH ₂ Cl ₂	98.3	S
6	(Z)-5a	L1	acetone	98.6	S
7	(Z)-5a	L1	MeOH	98.6	S
8	(Z)-5a	L1	THF	98.1	S
9	(Z)-5a	L1	toluene	97.5	S
10	(E)-5a	L1	EtOAc	31.5	S
11	(E)-5a	L2	EtOAc	23.7	S
12	(E)-5a	L3	EtOAc	46.8	S
13	(E)-5a	L4	EtOAc	26.3	S

[a] All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 30 bar hydrogen pressure for 20 h. In all cases, 100% conversion was observed. [b] **L1** = (1*S*,1'*S*,2*R*,2'*R*)-tangphos, **L2** = (*S*_C,*R*_P)-duanphos, **L3** = (*R*,*R*)-Et-duphos, **L4** = (*S*)-binapine. [c] Determined by chiral GC methods. [d] The absolute configuration was assigned by comparison of the observed optical rotation with reported data. (*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; Et-duphos = 1,2-bis(2,5-diethylphospholanyl)benzene; (*S*)-binapine = (3*S*,3'*S*,4*S*,4'*S*,11*S*,11'*S*)-4,4'-di-*tert*-butyl-4,4',5,5'-tetrahydro-3*H*,3'*H*-bidinaphtho[2,1-*c*:1',2'-*e*]phosphinepeine.

enantioselectivity for the hydrogenation of (E)-5a (less than 50% ee in other common solvents). Therefore, unlike asymmetric hydrogenation of an isomeric mixture of β-substituted α-aryl enamides **2**,^[3a-c,e,g] the configuration of the double bond in **5** has a dramatic influence on the enantioselectivity.^[14] To achieve excellent enantioselectivity with the current ligands, Z-configured substrates need to be used.

We tested substrates (Z)-5b–5i with the Rh/tangphos catalytic system under the optimized reaction conditions. As shown in Table 3, all substrates gave excellent ee values. The

Table 3: Asymmetric hydrogenation of (Z)-5 with the Rh/tangphos catalytic system.^[a]

Entry	Substrate	R ¹	R ²	Product	ee [%] ^[b]	Config. ^[c]
1	(Z)-5a	Ph	Me	8a	99.3	S
2	(Z)-5b	<i>o</i> -MeOC ₆ H ₄	Me	8b	99.0	S
3	(Z)-5c	<i>p</i> -MeOC ₆ H ₄	Me	8c	96.6	S
4	(Z)-5d	<i>m</i> -MeOC ₆ H ₄	Me	8d	99.1	S
5	(Z)-5e	<i>m</i> -MeC ₆ H ₄	Me	8e	99.1	S
6	(Z)-5f	<i>p</i> -MeC ₆ H ₄	Me	8f	98.8	S
7	(Z)-5g	<i>o</i> -ClC ₆ H ₄	Me	8g	> 99.9	S
8	(Z)-5h	1-naphthyl-C ₆ H ₄	Me	8h	99.1	S
9	(Z)-5i	Ph	Ph	8i	98.3	S
10 ^[d]	(Z)-5a	Ph	Me	8a	98.7	S

[a] Unless mentioned otherwise, all reactions were carried out with a substrate/catalyst ratio of 100:1 in EtOAc at room temperature under 30 bar hydrogen pressure for 20 h. In all cases, 100% conversion was observed. [b] Determined by chiral GC methods. [c] The absolute configuration was assigned by comparison of the observed optical rotation with reported data. [d] Substrate/catalyst = 1000:1.

substitution pattern on the phenyl ring generally has no appreciable effect on the enantioselectivity (Table 3, entries 2–4). Hindered enamides (Z)-5h and (Z)-5i were hydrogenated with excellent results (Table 3, entries 8 and 9). At reduced catalyst loading (TON = 1000), (Z)-5a was converted into **8a** with 98.7% ee (Table 3, entry 10). Hence the current hydrogenation route is a practical way for the preparation of various amines in this category (Figure 2).^[15] For example, deacylation of the chiral product (*S*)-**8a** leads directly to (*S*)-amphetamine (**9**), which is a useful stimulant with strong biological and physiological effects.^[16] Additional

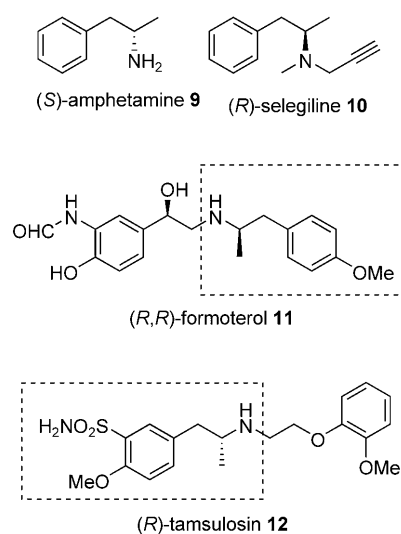


Figure 2. Chiral drugs bearing β-arylpropylamine units.

modification of (*R*)-**8a** will result in selegiline (**10**) for the treatment of Alzheimer's disease.^[17] Asymmetric hydrogenation of (*Z*)-**5c** will also provide practical access to important chiral drugs such as formoterol (**11**)^[18] and tamsulosin (**12**).^[19]

Herein, we have shown that β -arylisopropylamines, an important class of chiral compounds with valuable pharmaceutical applications, can be prepared by using a highly efficient asymmetric hydrogenation method. Excellent enantioselectivity was obtained for *Z* enamides, which were easily prepared by using the acid-catalyzed condensation of β -arylketoones with acetamide. Alternatively, these substrates can be synthesized by the palladium-catalyzed amidation which exhibits better preference for the formation of *Z*-configured substrates.^[12] Expansion of this methodology to other structurally relevant enamides is currently in progress and will be reported in due course.

Experimental Section

General procedure for the substrate preparation: A toluene solution (50 mL) of **7** (25 mmol), acetamide (125 mmol), and the catalyst TsOH (2.5 mmol) was charged in a Dean–Stark apparatus and refluxed for 24 h. After cooling to room temperature, the solvent was evaporated and the concentrated mixture was passed through a flash chromatography column filled with silica gel (EtOAc/hexanes 1:1). The *Z*- and *E*-configured products **5** were each isolated either a colorless oil or white powder.

General procedure for the hydrogenation: A stock solution of [Rh(cod)₂]₂BF₄ (cod = cycloocta-1,5-diene) and tangphos in a 1:1.1 molar ratio was stirred in EtOAc at room temperature for 10 min in a nitrogen-filled glovebox. The catalyst solution (0.5 mL, 0.001 mmol) was then transferred by syringe into the vials charged with different substrates (0.1 mmol) in EtOAc (2.5 mL). All the vials were placed in a steel autoclave, into which hydrogen gas (30 bar) was introduced. After stirring at room temperature for 20 h, the hydrogen was released, the solution was concentrated, and then the crude reaction mixture was eluted (MeOH) through a short column of silica gel to remove the metal complex. The purified product mixture was analyzed by chiral GC methods to determine the *ee* value.

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- [1] 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.
- [2] T. C. Nugent in *Process Chemistry in the Pharmaceutical Industry*, Vol. 2 (Eds.: K. Gadamasetti, T. Braish), CRC, Boca Raton, FL, **2008**, p. 137.
- [3] For representative references, see a) M. J. Burk, Y. M. Wang, J. R. Lee, *J. Am. Chem. Soc.* **1996**, *118*, 5142; b) I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, *123*, 5268; c) W. Tang, X. Zhang, *Angew. Chem.* **2002**, *114*, 1682; *Angew. Chem. Int. Ed.* **2002**, *41*, 1612; d) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348; e) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. De Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943; f) Y. Liu, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 10488; g) W. Zhang, X. Zhang, *Angew. Chem.* **2006**, *118*, 5641; *Angew. Chem. Int. Ed.* **2006**, *45*, 5515; h) J.-D. Huang, X.-P. Hu, Z.-C. Duan, Q.-H. Zeng, S.-B. Yu, J. Deng, D.-Y. Wang, Z. Zheng, *Org. Lett.* **2006**, *8*, 4367; i) I. D. Gridnev, T. Imamoto, G. Hoge, M. Kouchi, H. Takahashi, *J. Am. Chem. Soc.* **2008**, *130*, 2560.
- [4] a) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774; b) W. Tang, Y. Chi, X. Zhang, *Org. Lett.* **2002**, *4*, 1695.
- [5] a) D. M. Tschaen, L. Abramson, D. Cai, R. Desmond, U.-H. Dolling, L. Frey, S. Karady, Y.-J. Shi, T. R. Verhoeven, *J. Org. Chem.* **1995**, *60*, 4324; b) P. Dupau, P. Le Gendre, C. Bruneau, P. H. Dixneuf, *Synlett* **1999**, 1832; c) X.-B. Jiang, L. Lefort, A. H. H. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223.
- [6] G. L. Bachman, B. D. Vineyard, Ger. Offen., **1977**, DE 2638072.
- [7] P. A. S. Smith, J. P. Horwitz, *J. Am. Chem. Soc.* **1950**, *72*, 3718.
- [8] N. M. Laso, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 1605.
- [9] a) M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, *63*, 6084; b) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774; c) H. Zhao, C. P. Vandenbossche, S. G. Koenig, S. P. Singh, R. P. Bakale, *Org. Lett.* **2008**, *10*, 505.
- [10] G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, *64*, 6907.
- [11] a) J. Elaridi, A. Thaqi, A. Prosser, W. R. Jackson, A. J. Robinson, *Tetrahedron: Asymmetry* **2005**, *16*, 1309; b) J. Guin, C. Muck-Lichtenfeld, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2007**, *129*, 4498.
- [12] a) D. J. Wallace, D. J. Klauber, C.-Y. Chen, R. P. Volante, *Org. Lett.* **2003**, *5*, 4749; b) A. Klapars, K. R. Campos, C.-Y. Chen, R. P. Volante, *Org. Lett.* **2005**, *7*, 1185.
- [13] a) Reference [3c]; b) D. Liu, X. Zhang, *Eur. J. Org. Chem.* **2005**, 646; 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.
- [14] Notably, distinct reactivities of *Z* and *E* enamides were reported for Ru/binap-catalyzed (binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl) asymmetric hydrogenation of 1,2,3,4-tetrahydroisoquinoline derived enamides: whereas *Z* enamides were hydrogenated with excellent *ee* values, the corresponding *E* enamides showed no reactivity under the same hydrogenation conditions; see: a) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117; b) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297.
- [15] For another asymmetric catalytic synthesis of this class of amines, see a) I. A. Sayyed, A. Sudalai, *Tetrahedron: Asymmetry* **2004**, *15*, 3111; b) S. K. Talluri, A. Sudalai, *Tetrahedron* **2007**, *63*, 9758.
- [16] a) S. H. Snyder, K. M. Tayler, *Science* **1970**, *168*, 1487; b) G. T. Hajos, S. J. Garattin, *Pharm. Pharmacol.* **1973**, *25*, 418.
- [17] M. Sano, C. Ernesto, R. C. Thomas, M. R. N. Klauber, *N. Engl. J. Med.* **1997**, *336*, 1216.
- [18] B. Barnes, *Formoterol, A New Generation of Beta-2-agonist*, Hogrefe and Huber Pub., Toronto, **1991**.
- [19] C. G. Roehrborn, P. Siami, J. Barkin, R. Damião, K. Major-Walker, B. Morrill, F. Montorsi, *J. Urol.* **2008**, *179*, 616.