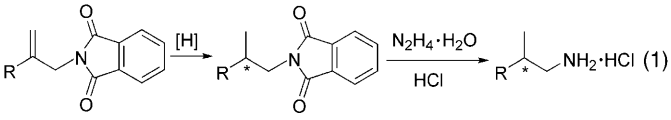
Asymmetric Catalysis

DOI: 10.1002/ange.200501332

Enantioselective Hydrogenation of Allylphthalimides: An Efficient Method for the Synthesis of β-Methyl Chiral Amines**

*Chun-Jiang Wang, Xianfeng Sun, and Xumu Zhang**

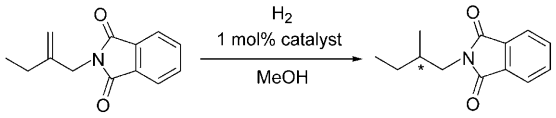
Chiral amines bearing a β-methyl group on the chiral center, and their derivatives, are key structural elements in natural products and pharmaceuticals.[1–3] For example, compound **A** is a key intermediate in the synthesis of the leukotrienes (LTs) receptor antagonist (Zeneca ZD 3532, a phase II drug candidate; Scheme 1). This compound is particularly useful for the treatment of asthma.[2] Compound **B** (NPS 1392) is a potent stereoselective antagonist of the NMDA receptor, which can be used for the control of ischemic strokes.[3] To our knowledge, there has been no successful catalytic method to make such important functional groups. Although some stoichiometric asymmetric synthesis or resolution routes have been reported for constructing this class of chiral amines,[2–4] the development of efficient and catalytic synthetic methods remains a significant challenge. Herein we report the first highly enantioselective catalytic asymmetric hydrogenation of disubstituted allylphthalimides[5] to form chiral phthalimides, which act as precursors to the β-methyl chiral amines [Eq. (1)].



(1)

We initiated our studies on the asymmetric hydrogenation of an *N*-2-ethylallylphthalimide (**6a**) by screening several known catalysts. Since the asymmetric hydrogenation of functionalized olefins using chiral phosphine/Rh complexes is well known,[6] a diverse array of bisphosphine/Rh complexes could be applied as catalyst precursors in this hydrogenation reaction. Some representative results are shown in Table 1.

Table 1: Asymmetric hydrogenation of **6a**.

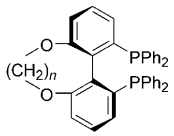


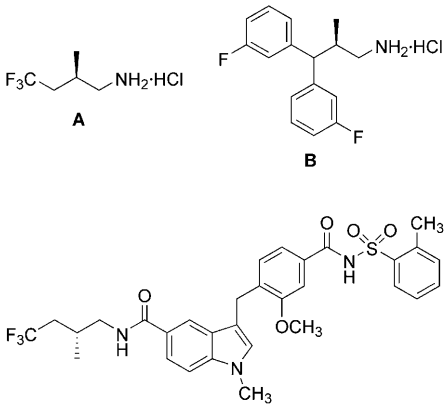
6a **7a**

Entry	Catalyst	*T* [°C]	$P(H_2)$ [atm]	Conv. [%]	*ee* [%][a]
1	**1**	RT	5	100	21
2	**2**	RT	5	100	15
3	**3c**	RT	5	0	NA
4	**3c**	80	100	100	96

[a] Determined by chiral-phase GC (see the Supporting Information).

[Rh(cod){(1*S*,1*S*′,2*R*,2*R*′)-tangphos}]BF_4 (**1**)
[Rh(cod)(*R*,*R*)-(Et-duphos)]BF_4 (**2**)
[$RuCl_2${(*S*)-C_n-tunephos}](dmf)$_m$ (**3a–f**)
$n=1$, **3a**; $n=2$, **3b**; $n=3$, **3c**
$n=4$, **3d**; $n=5$, **3e**; $n=6$, **3f**
(*S*)-C_n-tunephos, $n=1$–6





Scheme 1. Examples of β-methyl chiral amine hydrochlorides and Zeneca ZD 3525.

Although the complexes [Rh(cod){(1*S*,1*S*′,2*R*,2*R*′)-tangphos}]BF_4 (**1**)[7] (cod = cycloocta-1,5-diene, tangphos = 1,1′-di-*tert*-butyl-[2,2′]-diphosphanyl) and [Rh(cod){(*R*,*R*)-Et-duphos}]BF_4 (**2**)[8] (duphos = 1,2-bis(phospholanyl)benzene) were successful for the highly enantioselective hydrogenation of various substituted olefins, only low enantioselectivities were obtained at room temperature under low hydrogen pressure (Table 1, entries 1 and 2). However, Ru–diphosphine complexes have also been applied to asymmetric hydrogenation reactions. Catalyst **3c**[9] exhibited no reactivity under similar conditions (Table 1, entry 3). However, up to 96% *ee* and 100% conversion was observed when high hydrogen pressure (100 atm) and high temperature (80°C) were employed (Table 1, entry 4)

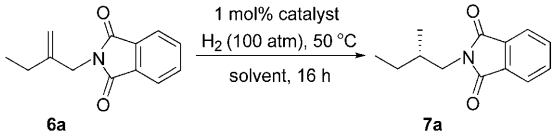
Encouraged by the results described above, we investigated the effects of solvents and catalyst precursors to enable the reaction conditions to be optimized (Table 2). A dramatic solvent effect was observed. Complex **3c** performs well in a number of alcohols to give **7a** with moderate to high enantioselectivities (Table 2, entries 1–4); an excellent level of enantioselectivity was observed when the reaction was carried out in methanol. Reaction in other solvents such as

[*] Dr. C.-J. Wang, X. Sun, Prof. X. Zhang
Department of Chemistry
The Pennsylvania State University
University Park, PA, 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

[**] This work was supported by the National Institutes of Health. We acknowledge the generous gift of Ru complexes from Heraeus Inc.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Effects of solvents and catalyst precursors on the asymmetric hydrogenantion of **6a**.



6a **7a**

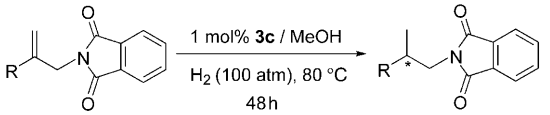
Entry	Catalyst	Solv.	Conv. [%]	*ee* [%][a]
1	**3c**	MeOH	100	96
2	**3c**	EtOH	100	76
3	**3c**	TFE[b]	100	37
4	**3c**	*i*PrOH	100	23
5	**3c**	CH_2Cl_2	0	NA
6	**3c**	EtOAc	100	19
7	**3c**	THF	100	12
8	**3a**	MeOH	100	88
9	**3b**	MeOH	100	91
10	**3d**	MeOH	100	94
11	**3e**	MeOH	100	92
12	**3f**	MeOH	100	92

[a] Determined by chiral-phase GC. [b] TFE = trifluoroethanol. NA = not available.

CH_2Cl_2, EtOAc, or THF led to lower enantioselectivities and reactivities (Table 2, entries 5–7). To test the effect of the dihedral angle of the chiral biaryl ligands on the enantioselectivity of the reaction, a set of tunephos[9] ligands with different dihedral angles were employed (Table 2, entries 1 and 8–12). The best result was observed when (*S*)-C_3-tunephos was used as the ligand (Table 1, entry 1).

The asymmetric hydrogenation reaction was carried out on a variety of substrates under the optimal reaction conditions (Table 3). Substrates with a primary *n*-alkyl substituent such as ethyl, *n*-butyl, or benzyl group at the 2-position of the allylphthalimides afforded products with high *ee* values (Table 3, entries 1–3). Several substrates with bulky substituents were also employed to probe the steric effects of the substituent on this hydrogenation system. The enantioselectivities decreased gradually along with increased steric hindrance of the substituents in the substrates (Table 3, entries 2 and 4–6). However, hydrogenation of cyclohexyl- and cyclopentyl-substituted substrates (**6g** and **6h**) still afforded products in 98 and 96% *ee*, respectively (Table 3, entries 7 and 8). The hydrogenation of the aromatic substrate **6i** proceeded smoothly with moderate enantioselectivity (Table 3, entry 9). To our surprise, 2-chloroallylphthalimide (**6j**) can also be hydrogenated and **7j** was obtained with up to 93% *ee* (Table 3, entry 10).

Table 3: Asymmetric hydrogenantion of *N*-2-substituted allylphthalimides.

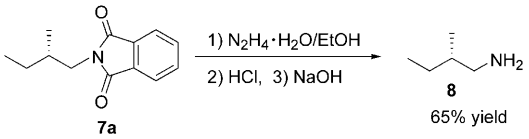


6 **7**

Entry	Substrate	R	Product	Yield [%][a]	*ee* [%]
1[b]	**6a**	Et	**7a**	98.5	96[c]
2	**6b**	*n*Bu	**7b**	98.0	96[c]
3	**6c**	Bn	**7c**	97.0	92[d]
4	**6d**	*i*Pu	**7d**	94.0	91[c]
5	**6e**	*i*Pr	**7e**	93.0	84[c]
6	**6f**	*t*Bu	**7f**	96.0	67[c]
7	**6g**	cyclohexyl	**7g**	95.0	98[c]
8	**6h**	cyclopentyl	**7h**	96.0	96[c]
9[b]	**6i**	Ph	**7i**	97.0	55[d]
10	**6j**	Cl	**7j**	97.0	93[c]

[a] Yield of isolated product. [b] The reaction was performed at 50 °C in 16 h. [c] Determined by chiral-phase GC. [d] Determined by chiral-phase HPLC.

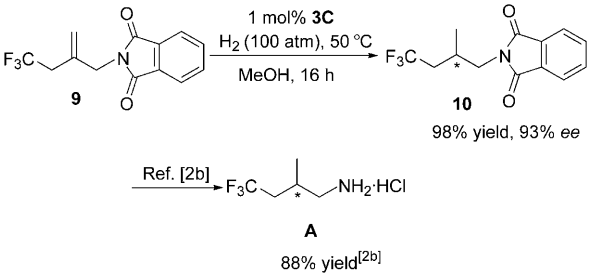
To determine the configuration of the hydrogenation product **7a** obtained with (*S*)-C_3-tunephos as a chiral ligand, phthalimide **7a** was hydrolyzed in refluxing ethanol in the presence of $NH_2NH_2{\cdot}H_2O$ followed by treatment with concentrated HCl according to a literature procedure to form the known compound **8** in 65% yield [Eq. (2)].[2b,10] The absolute



7a **8** 65% yield (2)

stereochemistry of **7a** was assigned as *S* by comparing the sign of the optical rotation of the obtained compound **8** with the reported data[4] (see the Supporting Information).

This asymmetric hydrogenation method can be applied to the preparation of the key intermediate **A** for the synthesis of the LTs receptor antagonist (Zeneca ZD3532;[2] Scheme 1). To the best of our knowledge, asymmetric hydrogenation provides the simplest method for the synthesis of this compound [Eq. (3)].



9 **10** **A** 88% yield[2b] (3)

In conclusion, we have developed the first highly enantioselective method for the synthesis of chiral phthalimides with a β-methyl group on the chiral center based on asymmetric hydrogenation, and up to 98% *ee* has been achieved with a Ru–C_3-tunephos catalyst. The synthetic utility has been demonstrated through the synthesis of the key intermediate **A** of the LTs receptor antagonist (Zeneca ZD3532). Since these hydrogenation substrates are easily obtainable, this methodology is potentially practical for the synthesis of such chiral amines, which are important pharmaceutical intermediates.

Experimental Section

General hydrogenation procedure: $[RuCl_2(cymene)]_2$ (6.2 mg, 0.01 mmol) and (*S*)-C_3-tunephos (12.5 mg, 0.021 mmol) were dissolved in degassed DMF (3 mL) in a Schlenk tube under N_2. The solution was heated at 100 °C for 3.5 h. After the mixture had cooled to 50 °C, the solvent was removed under vacuum to give the catalyst as an orange-red solid. The catalyst was dissolved in degassed methanol (16 mL) in a glovebox and divided equally between eight vials. Substrate (0.25 mmol) was then added to the catalyst solution and the resulting mixture transferred to an autoclave and charged with H_2 (100 atm). The autoclave was stirred at 50 or 80 °C for 16–48 h, before cooling it to room temperature and carefully releasing the H_2. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then analyzed directly by chiral-phase GC (gamma dex 225) or HPLC (Chiralpak AD) to determine the enantiomeric excess.

Received: April 17, 2005
Published online: June 27, 2005

Keywords: amines · asymmetric catalysis · enantioselectivity · hydrogenation · ruthenium

[1] a) S. Omura, *Macrolide Antibiotics*, Academic Press, Orlando, FL, **1984**; b) G. Lazarevski, G. Kobrehel, B. Metelko, H. Duddeck, *J. Antibiot.* **1996**, *49*, 1066; c) G. M. Nicholas, T. F Molinski, *Tetrahedron* **2000**, *56*, 2921.

[2] For the chemistry and biology of compound **A**, see: a) R. T. Jacobs, P. R. Bernstein, L. A. Cronk, E. P. Vacek, L. F. Newcomb, D. Aharony, C. K. Buckner, Kusner, E. J. *J. Med. Chem.* **1994**, *37*, 1282; b) R. T. Jacobs, Y. K. Yee, P. R. Bernstein, A. G. Brewster, G. J. Sependa, EP 489548A1, **1992**.

[3] For the chemistry and biology of compound **B**, see: S. T. Moe, S. M. Shimizu, D. L. Smith, B. C. Van Wagenen, E. G. DelMar, M. F. Balandrin, Y. Chien, J. L. Raszkiewicz, L. D. Artman, A. L Mueller, E. Lobkovsky, J. Clardy, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1915.

[4] T. Tachihara, S. Ishizaki, Y. Kurobayashi, H. Tamura, Y. Ikemoto, A. Onuma, K. Yoshikawa, T. Yanai, T. Kitahara, *Helv. Chim. Acta* **2003**, *86*, 274.

[5] a) Although the hydrogenation of some trisubstituted allylphthalimides can also form the desired products, the enantioselectivities were much lower than those reduced from disubstituted substrates (see the Supporting Information); b) A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 1626.

[6] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) I. Ojima, *Catalytic asymmetric synthesis*, Wiley-VCH, New York, **2000**; c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029.

[7] a) W. Tang, X. Zhang, *Angew. Chem.* **2002**, *114*, 1682; *Angew. Chem. Int. Ed.* **2002**, *41*, 1612; b) W. Tang, X. Zhang, *Org. Lett.* **2002**, *4*, 4159; c) W. Tang, D. Liu, X. Zhang, *Org. Lett.* **2003**, *5*, 205.

[8] M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125.

[9] Z. Zhang, H. Qian, J. Longmire, X. Zhang, *J. Org. Chem.* **2000**, *65*, 6223.

[10] H. Brunner, J. Wachter, J. Schmidbauer, *Organometallics* **1986**, *5*, 2212.

