Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 821–823
Tetrahedron Letters

Highly enantioselective hydrogenation of *N*-phthaloyl enamides

Qin Yang,[a,b] Wenzhong Gao,[b] Jingen Deng[a] and Xumu Zhang[b,*]

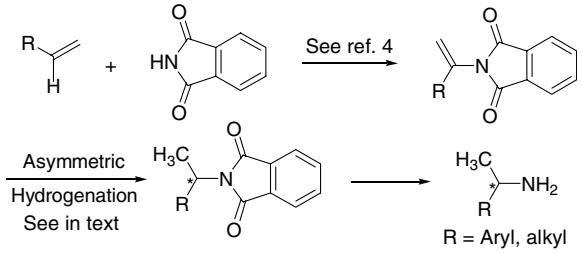
[a]*Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chendu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China and Graduated School of Chinese Academy of Sciences, Beijing, China*

[b]*104 Chemistry Building, Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA*

Received 7 November 2005; accepted 11 November 2005
Available online 13 December 2005

Abstract—Rh- or Ru-catalyzed highly enantioselective hydrogenation of *N*-phthaloyl enamides is presented. Electron-rich TangPhos and DuanPhos are found to be effective ligands for Rh-catalyzed hydrogenation of α-aryl enamides and up to 99% ee has been achieved. In contrast, for the hydrogenation of α-alkyl enamide, the Ru-C_3-TunePhos complex is more effective and up to 69% ee can be observed. This work is the first report of the hydrogenation of *N*-phthaloyl enamides.

Asymmetric hydrogenation of enamides has shown significant potential for the synthesis of chiral amines.[1] Rh or Ru complexes of phosphine ligands have been extensively explored as catalysts for the asymmetric reduction of enamides. Although high catalytic activities and enantioselectivities can be achieved in a number of catalytic systems,[2] a lack of efficient synthetic methods for making enamides has been a major drawback in this area.[3] Recently, Stahl et al. have developed a strategy for the preparation of *N*-phthaloyl enamides via the Pd-catalyzed oxidative amination of simple alkenes.[4] Phthalimide has been used in Stahl's oxidative amination of alkenes, resulting in both α-aryl and α-alkyl substituted *N*-phthaloyl enamides. From a practical synthesis point of view, the phthalimide group can not only serve as a directing group for asymmetric hydrogenation, but also can be removed under mild conditions.[5] We envision that asymmetric hydrogenation of *N*-phthaloyl enamides would be a promising method for the preparation of chiral amines (Scheme 1).[6] Herein, we wish to report our studies on this new strategy for the synthesis of chiral amines starting from readily available alkenes such as styrene. To our best knowledge, the enantioselective hydrogenation of *N*-phthaloyl enamides has not been reported to date. Our preliminary results indicate that the Rh-TangPhos and Rh-DuanPhos species are highly enantioselective for the hydrogenation of *N*-phthaloyl α-aryl enamides, while the Ru-C_3-TunePhos complex is more selective for the reduction of *N*-phthaloyl α-alkyl enamide.



Scheme 1.

To initiate our investigation, a series of *N*-phthaloyl enamides **1** were synthesized according to the procedures reported by Stahl.[4a,b] Enamide **1a** was selected as the model substrate for screening reaction conditions and the results are summarized in Figure 1 and Table 1.

Since the Rh-TangPhos complex, [Rh(TangPhos)(NBD)]SbF_6, has exhibited high catalytic activities and enantioselectivities for the hydrogenation of a wide range of *N*-acyl α-aryl enamides,[2k] it was first employed to reduce enamide **1a**. Unfortunately, no conversion was observed under the standard reaction condition for the hydrogenation of *N*-acyl enamides (Table 1, entry 1). To address the reactivity issue, the effect of hydrogen pressure on this catalytic reaction was examined. Our investigation indicated that high activity could be achieved under elevated hydrogen pressure (10 atm)

* Corresponding author. Tel.: +1 814 865 4221; fax: +1 814 865 3292; e-mail: xumu@chem.psu.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.064

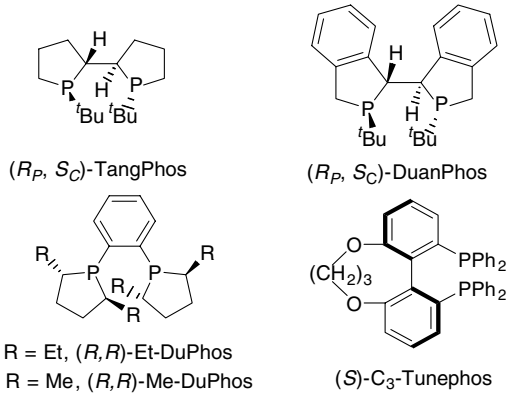
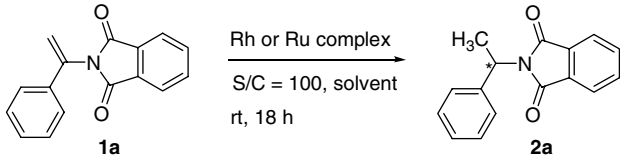


Figure 1. Structure of ligands for asymmetric hydrogenation.

Table 1. Screening reaction conditions for the enantioselective hydrogenation of enamide **1a**



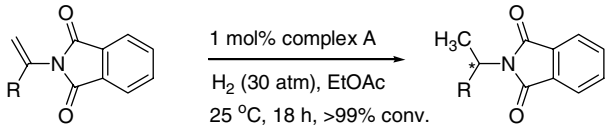
1a **2a**

Entry	Complex[a]	H_2 (atm)	Solvent	Conv. (%)[b]	ee (%)[c]
1	A	3	EtOAc	0	n.a
2	A	10	EtOAc	>99	96(*R*)
3	A	30	EtOAc	>99	98(*R*)
4[d]	A	50	EtOAc	>99	98(*R*)
5	A	100	EtOAc	>99	98(*R*)
6	A	30	THF	>99	98(*R*)
7	A	30	Toluene	0	n.a
8	A	30	1,4-Dioxane	0	n.a
9	A	30	*i*-PrOH	>99	98(*R*)
10	A	30	CH_2Cl_2	>99	92(*R*)
11	B	30	EtOAc	>99	97(*R*)
12	C	30	EtOAc	>99	98(*R*)
13	D	30	EtOAc	>99	38(*R*)
14	E	30	EtOAc	>99	73(*R*)
15[d]	F	50	EtOAc	>99	82(*S*)

[a] A = Rh[(R_P,S_C)-TangPhos](NBD)SbF_6; B = Rh[(R_P,S_C)-DuanPhos](COD)BF_4; C = Rh[(R_P,S_C)-DuanPhos](NBD)SbF_6; D = Rh[(*R*,*R*)-Et-DuPhos](COD)BF_4; E = Rh[(*R*,*R*)-Me-DuPhos](COD)BF_4; F = Ru[(*S*)-C_3-TunePhos](DMF)$_n$$Cl_2$.
[b] Conversions were determined by crude proton NMR.
[c] Enantiomeric excesses were measured by chiral HPLC and absolute configuration was determined by comparison of the sign of the optical rotation with the reported data, see Ref. 9.
[d] The reaction was carried at 50 °C.

and up to 96% ee was observed (Table 1, entry 2). Further increasing the hydrogen pressure to 30, 50, or 100 atm led to higher ee (98%, Table 1, entries 3–5). Several solvents have also been tested for their influence on the catalyst activity and selectivity. The hydrogenation of **1a** did not take place in either toluene or 1,4-dioxane, while complete conversions were observed in other tested solvents such as EtOAc, THF, *i*-PrOH, and CH_2Cl_2 (Table 1, entries 3, 6–10). Rh-catalysts with other phosphine ligands were also screened in this reaction for comparison. While the Rh complexes derived from DuanPhos[7] and TangPhos gave high reactivities and enantioselectivities (Table 1, entries 3, 11, and 12), the Rh-DuPhos complexes offered much lower ee's (38% ee with Et-DuPhos, entry 13; 73% ee with Me-DuPhos, entry 14, Table 1) despite that Rh-DuPhos complexes were effective for hydrogenation of *N*-acyl enamides.[3f,g] Thus, our experimental results indicated that the hydrogenation of *N*-phthaloyl enamides was indeed more sterically demanding and required more selective catalytic systems. Ru complex with C_3-TunePhos[8] has also been explored for hydrogenation of enamide **1a** and a lower ee compared to Rh-TangPhos system was observed (82% ee, Table 1, entry 15).

Table 2. Rh-Catalyzed asymmetric hydrogenation of enamides **1**

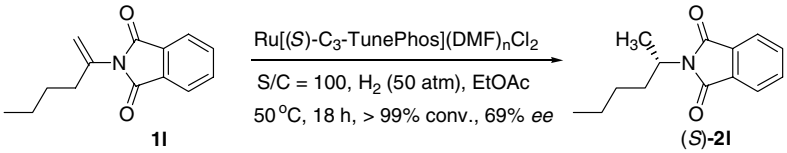


1 **2**

Entry	R in **1**	Product	ee (%)[a]	Conf.[b]
1	C_6H_5 (**1a**)	**2a**	98	*R*-(+)
2	4-ClC_6H_4 (**1b**)	**2b**	99	(+)
3	3-ClC_6H_4 (**1c**)	**2c**	99	(+)
4	2-ClC_6H_4 (**1d**)	**2d**	46	(+)
5	2-Naphthyl (**1e**)	**2e**	99	(+)
6	2-(6-OCH_3Naphthyl) (**1f**)	**2f**	99	(+)
7	4-$CH_3C_6H_4$ (**1g**)	**2g**	97	(+)
8	3-$CH_3C_6H_4$ (**1h**)	**2h**	98	(+)
9	2-$CH_3C_6H_4$ (**1i**)	**2i**	28	(+)
10	4-FC_6H_4 (**1j**)	**2j**	98	(+)
11	4-$OCH_3C_6H_4$ (**1k**)	**2k**	98	(+)
12	*n*-Butyl (**1l**)	**2l**	13	*R*-(−)

[a] Enantiomeric excesses were measured by chiral HPLC.
[b] Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data, for entry 12, see Ref. 11.

The scope of asymmetric hydrogenation of *N*-phthaloyl enamides has been examined and the results are shown in Table 2. The reactions proceeded smoothly in all cases under the optimal conditions (cf. Table 1, entry 3).[10] High enantioselectivities were generally achieved for α-aryl enamides regardless of the electronic property of the aromatic substituents. However, much lower



1l (*S*)-**2l** (1)

selectivities were observed with substrates bearing an *ortho*-substituent on the aromatic ring (Table 2, entries 4 and 9). Unfavored steric interaction between the *ortho*-substituent and the catalyst might be the reason for the low enantioselectivities.

Asymmetric hydrogenation of α-alkyl enamides bearing allylic proton on the alkyl group is a challenging problem and very few experimental results have been reported in the literature so far.[12] Taking advantages of the facile synthesis of *N*-phthaloyl α-alkyl enamides from simple alkyl alkenes, enamide **1l** was prepared and the hydrogenation was tested under the optimal condition.[13] Unfortunately, only 13% ee was obtained with Rh-TangPhos catalyst (Table 2, entry 12). However, moderate ee could be achieved with Ru-C_3-TunePhos catalyst (69% ee, Eq. 1), indicating a promising direction for further exploration of the hydrogenation of α-alkyl enamides.

In conclusion, we have demonstrated a rapid synthesis of chiral amine derivatives via a reaction sequence of oxidative amination of simple alkenes and highly enantioselective hydrogenation. The electron-rich TangPhos and DuanPhos are effective ligands for the Rh-catalyzed hydrogenation of α-aryl enamides while a Ru-C_3-TunePhos complex is more effective for the hydrogenation of α-alkyl enamide. This work is the first report of the asymmetric hydrogenation of *N*-phthaloyl enamides and further exploration is in progress.

Acknowledgments

This work was supported by NIH grant (GM58832) and the authors thank Dr. Duan Liu for helpful discussions.

References and notes

1. (a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 121; (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; p 1; (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029, and references cited therein.
2. For some representive publications of Rh or Ru-catalyzed asymmetric hydrogenations of enamides, see: (a) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679; (b) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585; (c) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165; (d) Wang, X.; Ding, K. *J. Am. Chem. Soc.* **2004**, *126*, 10524; (e) Jia, X.; Li, X.; Lam, W. S.; Kok, S. H. L.; Xu, L.; Lu, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2273; (f) Jia, X.; Li, X.; Xu, L.; Shi, Q.; Yao, X.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 4539; (g) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348; (h) Lee, S.-g.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 847; (i) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941; (j) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695; (k) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612.
3. For enamide synthesis, see: (a) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185; (b) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809; (c) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035; (d) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277; (e) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749; (f) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084; (g) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.
4. (a) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868; (b) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996; (c) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *ARKIVOC* **2004**, *iii*, 42; (d) Yamanaka, H.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 1192; (e) Yamanaka, H.; Yamane, Y.; Mukaiyama, T. *Heterocycles* **2004**, *63*, 2813.
5. Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626.
6. For asymmetric synthesis of primary amines from vinylarenes via catalytic hydroboration, see: Fernandez, E.; Hooper, M. W.; Knight, F. I.; Brown, J. M. *Chem. Commun.* **1997**, 173, and references cited therein.
7. (a) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 1687; (b) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646.
8. Zhang, Z.; Qian, H.; Langmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.
9. Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273.
10. General procedure for asymmetric hydrogenation of enamides **1**: To a solution of enamide **1a** (25 mg, 0.1 mmol) in EtOAc (1 mL) was added Rh[(R_P,S_C)-TangPhos](NBD)SbF_6 (0.7 mg, 0.001 mmol). The hydrogenation was performed at room temperature under 30 atm of hydrogen for 18 h. After the hydrogen was released, the reaction mixture was passed through a short silica gel column to remove the catalyst. ^{1}H NMR spectroscopic analysis of the crude product indicated the conversion was >99%. The enantiomeric excess of **2a** was determined by HPLC (Chiralpak OJ-H column, IPA/Hex = 30:70, 1.0 mL/min), 98% ee, $t_{minor} = 11.3$ min, $t_{major} = 26.3$ min. $[\alpha]_D^{rt}$ 52.2 ($c = 0.63$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83–7.80 (m, 2H), 7.73–7.68 (m, 2H), 7.55–7.52 (m, 2H), 7.35–7.25 (m, 3H), 5.59 (q, $J = 7.3$ Hz, 1H), 1.95 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 140.2, 133.7, 131.8, 128.3, 127.5, 127.3, 123.0, 49.4, 17.4.
11. Sasse, A.; Kiec-Kononowicz, K.; Stark, H.; Motyl, M.; Reidemeister, S.; Ganellin, C. R.; Ligneau, X.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1999**, *42*, 593.
12. For some publications on the asymmetric hydrogenation of α-*tert*-butyl or adamantyl enamides, see: (a) Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353; (b) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. & Catal.* **2003**, *345*, 308; (c) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *Adv. Synth. & Catal.* **2002**, *344*, 1003; (d) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268; (e) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486; (f) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.
13. Although as reported in Ref. 4a, the regioselectivity for the synthesis of **1l** was only 100:17, the pure **1l** can be obtained by flash chromatography.