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Highly Enantioselective Synthesis of Non-natural Aliphatic α-Amino Acids via Asymmetric Hydrogenation†

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By employing rhodium-Duanphos complex as the catalyst, *β*-alkyl (*Z*)-N-acetyldehydroamino esters were smoothly hydrogenated in a highly efficient and enantioselective way. Excellent enantioselectivities together with excellent yields were achieved for a series of substrates. An efficient approach for the synthesis of the intermediate of the orally administered anti-diabetic drug Alogliptin and Linagliptin in the DPP-4 inhibitor class was also developed.

Widely found as common intermediates for the preparation of many chiral drugs,[1] biologically active molecules,[2] chiral axulliaries[3] and some useful chiral building blocks,[4] non-natural D-amino acids have attracted intensive attention over the past decades regardless of the fact that natural L-amino acids are readily available. Among all the non-natural amino acids, aliphatic D-amino acids stand out as elegant intermediates for the synthesis of many chiral drugs which include the orally administered anti-diabetic drugs in the DPP-4 inhibitor class, among which, Alogliptin,[5] Linagliptin,[6] Sitagliptin,[7] and Saxagliptin[8] (Figure 1) are just to name a few. Moreover, due to the significance of chiral aliphatic D-amino acids, the worldwide market value of these valuable compounds is estimated at 2 billion dollars annually.[9]

As a result, great efforts have been made for the preparation of non-natural D-amino acids.[10] Representative methods include Strecker synthesis,[11] enzymatic kinetic resolution of racemic amino esters,[12] enantioselective amination of carboxylic derivatives,[13] amino enolate alkylations[14] and the highly efficient transition-metal-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives.[15] However, for all of the former processes, they often suffer from the drawbacks such as poor yields and enantioselectivities, low conversion of starting materials, low reaction rates, the need for multiple enzymes or long chemical reaction steps. In a sharp contrast, transition-metal-catalyzed asymmetric hydrogenation overcomes all of these drawbacks giving highly enantiomerically pure amino acid derivatives with very high yields in a concise way and thus was certified as a powerful and elegant methodology over the past decades.[15a] Although intensive efforts have been made for the asymmetric hydrogenation of the aryl-substituted α-dehydroamino acid derivatives, systematic investigation on the asymmetric hydrogenation of the alkyl-substituted α-dehydroamino acid derivatives remains rare.[15a] As a result, we are aiming at developing an efficient method for the preparation of non-natural aliphatic chiral D-amino acids through asymmetric hydrogenation. Herein, we report the highly enantioselective hydrogenation of *β*-alkyl (*Z*)-N-acetyldehydroamino esters by using Rh(I) and chiral bisphosphorus ligand as catalyst. A series of non-natural aliphatic D-amino acid derivatives were obtained with excellent enantioselectivities and very high yields. Moreover, an efficient approach for the synthesis of the key intermediate of the anti-diabetic drugs Alogliptin and Linagliptin in the DPP-4 inhibitor class was also successfully developed.

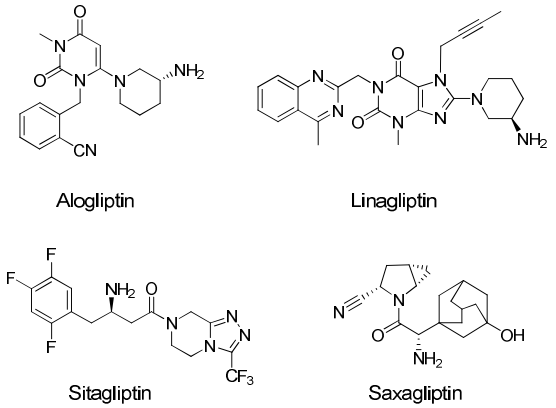

Figure 1. Examples of chiral drugs containing aliphatic amino acid moiety.

Initially, our attempts started from the hydrogenation of **1b** utilizing $Rh(NBD)_2BF_4$ as catalyst precursor under 100 psi hydrogen pressure in methanol. A series of ligands were screened which were summarized in Figure 2. As depicted in Table 1, ligand has a substantial role in determining the enantioselectivity. Although all of the ligands tested gave full conversion of the substrate, the enantioselectivity excess (*ee*) varied in a large extend. With *t*-Bu-Josiphos as the ligand, only 5.4% *ee* was obtained (Table 1, entry 1). The same case went with BINAP which afforded only 9.4% *ee* (Table 1, entry 5). Slightly higher ee was observed by using Biphephos and C3-Tunephos as ligand, however, the results were just moderate. In a big contrast, we were pleased to find that by

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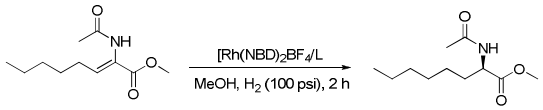
using our previously developed chiral bisphosphorus ligands Tangphos, Duanphos and Binapine, excellent ee was obtained (Table 1, entries 2-4). Remarkably, as high as 99.7% *ee* (Table 1, entry 3) was obtained when using (*Rc, Sp*)-Duanphos as the ligand and the desired D-configured product was obtained. As a consequence, (*Rc, Sp*)-Duanphos was selected as the optimized ligand for the further screening of the reaction conditions.

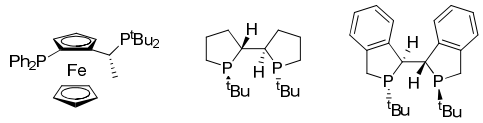
Table 1. Ligand screening for the asymmetric hydrogenation of **1b** [a]



1b **2b**

Entry	Ligand	Conv (%)[b]	Ee (%)[c]	Configuration[d]
1	*t*-Bu-Josiphos	> 99	5.4	D
2	(*S, R*)-Tangphos	> 99	99.0	D
3	(*Rc-Sp*)-Duanphos	> 99	99.7	D
4	(*S*)-Binapine	> 99	95.1	L
5	(*S*)-BINAP	> 99	9.4	L
6	(*R*)-MeO-BIPHEP	> 99	46.8	D
7	(*S*)-C3-Tunephos	> 99	68.7	L

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(NBD)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in MeOH, at room temperature, under hydrogen (100 psi) for 2 h, NBD = 2,5-norbornadiene; [b] Determined by ^1H NMR spectroscopy; [c] Determined by HPLC analysis using a chiral stationary phase; [d] Absolute configuration was determined by comparing the optical rotation data with those reported by literature[16].



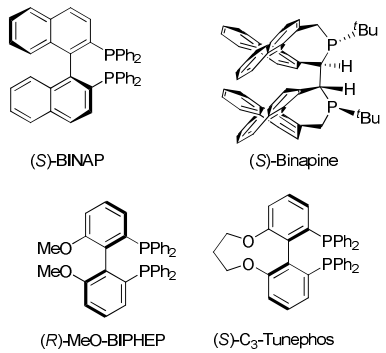
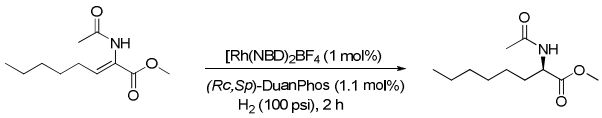


Figure 2.Ligands screened for the asymmetric hydrogenation of **1b**

In order to further screen the reaction conditions, solvent and temperature effect were also investigated (Table 2). It was found that solvent had little influence on the enantioselectivity and the substrate conversion. Except for TFE (Table 2, entry 7), all of the solvents tested gave satisfactory results (>99% conversion, >99% *ee*, Table 2, entries 2-6). Methanol was selected as the best solvent for the slightly higher enantioselectivity obtained. It was observed that increasing the reaction temperature to 50 °C had little influence on the enantioselectivity (Table 2, entry 8). For optimal results, the temperature was kept at 25 °C as a result.

Table 2. Solvent and temperature screening for the asymmetric hydrogenation of **1b** [a]

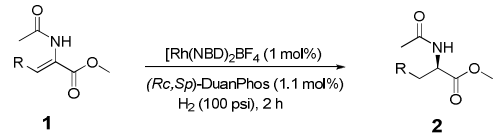


1b **2b**

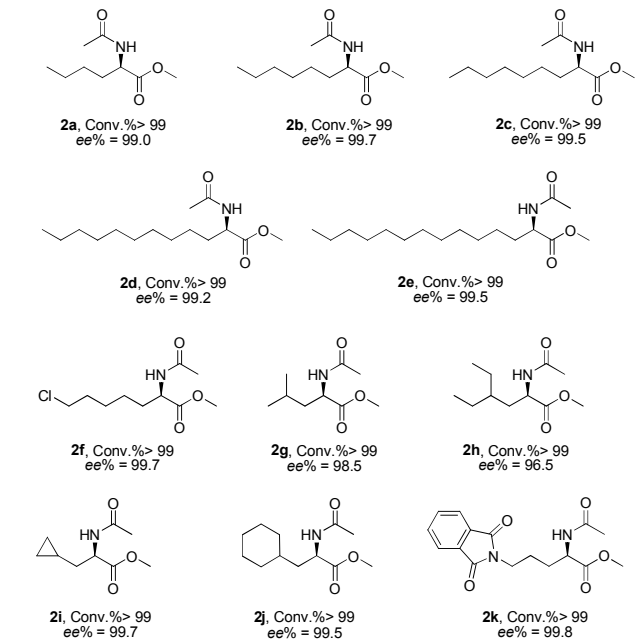
Entry	Solvent	Conv (%)[c]	Ee (%)[d]
1	MeOH	> 99	99.7
2	DCM	> 99	99.0
3	Toluene	> 99	99.1
4	*i*-PrOH	> 99	99.3
5	EtOH	> 99	99.0
6	EA	> 99	99.0
7	TFE	> 99	97.4
8[b]	MeOH	>99	99.6

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(NBD)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, at room temperature, under hydrogen (100 psi) for 2 h, all the configuration of the products was D, NBD = 2,5-norbornadiene, DCM = dichloromethane, EA = ethyl acetate, TFE = trifluoroethanol; [b] Temperature was increased to 50 °C; [c] Determined by ^1H NMR spectroscopy; [d] Determined by HPLC analysis using a chiral stationary phase.

Table 3. Rh-catalyzed asymmetric hydrogenation of β-alkyl (Z)-N-acetyldehydroamino esters [a]



1 **2**



[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(NBD)_2]BF_4$/Duanphos/substrate ratio of 1:1.1:100, in MeOH, at room temperature, under hydrogen (100 psi) for 2 h, conversion was determined by ^1H NMR spectroscopy, *ee* was determined by HPLC analysis using a chiral stationary phase, for all cases, D-configured products were obtained, NBD = 2,5-norbornadiene.

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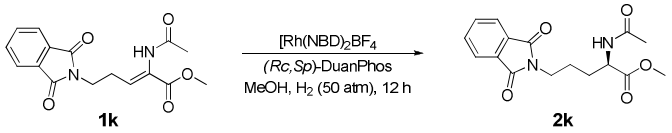
Delighted by the prelimary results, a series of *β*-alkyl (*Z*)-N-acetyldehydroamino esters, **1a-1k**, were synthesized and were subsequenty subjected to the optimal reaction conditions. These compounds were easily prepared in one step from readily available *α*-alkyl aldehydes utilizing an Horner-Wadsworth-Emmons protocol,[17] owing to its high yield and operational simplicity (See supporting information).

The newly synthesized Z-configured *β*-alkyl (*Z*)-N-acetyldehydroamino esters were subjected to the optimal reaction conditions as a consequence. As shown in Table 3, these Z-configured compounds proved to be good substrates affording a series of chiral aliphatic α-amino esters. Linear alkyl substitued dehydroamino substrates were all smoothly converted giving excellent *ee* higher that 99% (Table 3, **2a-2e**). However, for the branched alkyl substituted substrates, the *ee* value was slightly lower (Table 3, **2g**, **2h**), probably due to the steric hindrance of these substrates. Cyclic alkyl substituted dehydroamino esters also proved to be good substrates giving excellent enantioselectivity (Table 3, **2i**, **2j**). Intrestingly, halogenated substrate was also tolerated affording high conversion and excellent *ee* (Table 3, **2f**). Remarkbaly, the protected amine substituted substrate **1k** was also smoothly hydrogenated with *ee* value higher than 99% (Table 3, **2k**).

Inspired by the above results, we intended to conduct the hydrogenation reaction with lower catalyst loading employing **1k** (Table 4) as the model substrate. When the reaction was conducted with 0.2 mol% (S/C = 500) catalyst loading under 50 atm hydrogen pressure at room temperature, the reaction proceeded smoothly with full conversion and excellent *ee* (Table 4, entry 1). However, further lowering the catalyst loading to 0.1 mol% (S/C = 1, 000) led to a disappointing result that almost all of the substrate remained untouched (Table 4, entry 2). In order to promote the conversion of the substrate, the temperature was increaed to 50 °C which to our delight led to full conversion of the substrate and the *ee* remained the same when the catalyst loading was 0.1 mol% (Table 4, entry 3). Excellent *ee* and substrate conversion were also observed when the catalyst loading was lowered to 0.02 mol% while further lowering the catalyst loading to 0.001 mol% gave a substrate conversion of only 67% although the *ee* remained high.

Table 4. Asymmetric Hydrogenation of **1k** with lower catalyst loading [a]



1k **2k**

Entry	S/C	Temp. (°C)	Conv (%)[b]	Ee (%)[c]
1	500	25	> 99	99.6
2	1, 000	25	< 5	ND
3	1, 000	50	> 99	99.6
4	5, 000	50	> 99	99.6
5	10, 000	50	67	99.1

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(NBD)_2]BF_4$/ligand/substrate ratio of 1:1.1, in MeOH, at room temperature, under hydrogen for 12 h. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. nbd = 2,5-norbornadiene.

In order to demonstrate the synthetic utility of our protocol, an efficient approach for the synthesis of the key intermediate of the anti-diabetic drugs in the DPP-4 inhibitor class, Alogliptin and Linagliptin, was developed (Figure 3). Starting from the chiral product **2k**, deprotection went smoothly in the precene of HCl in excellent yield. By treating **2k** with aluminium and sodium hydroxide followed by reduction with lithium aluminium hydride, the key intermediate of Alogliptin and Linagliptin **7k** was efficiently obtained in good yield. Starting from the key intermediate **7k**, Alogliptin and Linagliptin can be readily synthesized following literature procedure.[5, 6]

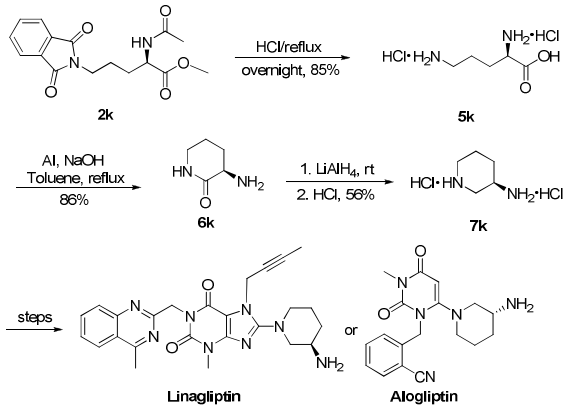


Figure 3. Highly Enantioselective Synthesis of Alogliptin and Linagliptin.

Conclusions

In summary, a new type of β-alkyl (*Z*)-N-acetyldehydroamino esters were prepared by Horner-Wordwoths-Emmons reaction in high yields and were hydrogenated with excellent enantioselectivity, which provides an efficient method for the synthesis of the enantiomerically pure non-natural amino acids that are important in synthetic, medicinal, and bioorganic chemistry. More importantly, the key intermidiate **7k** was synthesized providing a highly enantioselective route for the synthesis of the DPP-4 inhibitor Alogliptin and Linagliptin.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

‡ Both authors contributed equally to this work.

1. Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* 1995, **51**, 6397.
2. Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* 1991, **56**, 6939.
3 Studer, A. *Synthesis* 1996, 793.
4. Reetz, M. T. *Angew. Chem., Int. Ed.* 1991, **30**, 1531.
5. Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J.y A.; Kaldor, S. W.; Kassell, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney II, S. L. *J. Med. Chem.* 2007, **50**, 2297.

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DOI: 10.1039/C5OB01111F
Journal Name

6. Eckhardt M.; Langkopf E.; Mark M.; Tadayyon M.; Thomas L.; Nar H.; Pfrengle W.; Guth B.; Lotz R.; Sieger P.; Fuchs H.; Himmelsbach F. *Journal of Medicinal Chemistry*, 2007, **50**, 6450.
7. Herman, G. A.; Stevens, C.; Van D. K.; Bergman A.; Yi, B.; De S.; Snyder K.; Hilliard D.; Tanen M.; Tanaka W.; Wang A. Q.; Zeng W.; Musson D.; Winchell G.; Davies M. J.; Ramael S.; Gottesdiener K. M.; Wagner J. A. *Clin Pharmacol Ther*, 2005, **78**, 675.
8. Augeri, D. J.; Robl, J. A.; Betebenner , D. A.; Magnin, D. R.; Khanna A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.*, 2005, **48**, 5025.
9. Rozzell, J. D. Biocatalytic production of amino acids and derivatives. *John Wiley & Sons,* 1994, 5.
10. Duthaler, R. O. *Tetrahedron* 1994, **50**, 1539.
11. (a) Chakraborty, T. K.; Azhar Hussain, K.; Venkat Reddy, G. *Tetrahedron* 1995, **51**, 9179; (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* 1996, **118**, 4910.
12. Beller, M.; Eckert, M.; Geissler, H.; Napierski, B.; Rebenstock, H. P.; Holla, E. W. *Chem. Eur. J.* 1998, **4**, 935.
13. (a) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* 1990, **112**, 4011; (b) Oppolzer, W.; Cintas-Moreno, P.; Tamura, O.; Cardinaux, F. *Helv. Chim. Acta* 1993, **76**, 187.
14. (a) Yeh, T.-L.; Liao, C.-C.; Uang, B.-J. *Tetrahedron* 1997, **51**, 11141; (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* 1997, **119**, 656.
15. For representative examples, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* 2003, **103**, 3029; (b) Kagan, H. B.; Dang Tuan, P. *J. Am. Chem. Soc.* 1972, **94**, 6429; (c) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* 1986, **108**, 7117; (d) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* 2010, **111**, 1713; (e) Tang, W.; Zhang, X. *Angew. Chem. Int. Ed.* 2002, **41**, 1612; (f) Komarov, Igor V.; Monsees, A.; Spannenberg, A.; Baumann, W.; Schmidt, U.; Fischer, C.; Börner, A. *Eur. J. Org. Chem.* 2003, 138; (g) Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* 2004, **6**, 1433; (h) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* 2001, **123**, 5268; (i) Liu, T.-L.; Wang, C.-J.; Zhang, X. *Angew. Chem., Int. Ed*. 2013, **52**, 8416; (j) Zhou, M.; Liu, T.-L.; Cao, M.; Xue, Z.; Lv, H.; Zhang, X. *Org. Lett.* 2014, **16**, 3484; (k) Jiang, J.; Wang, Y.; Zhang, X. *ACS Catal*. 2014, **4**, 1570; (l) Zhou, M.; Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. *Org. Lett.* 2013, **15**, 5524. (m) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repic, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, Albert S. C. *Proc. Natl. Acad. Sci.* USA 2007, **104**, 16787–16792. (n) Guo, Y.; Shao, G.; Li, L.; Wu, W.; Li, R.; Li, J.; Song, J.; Qiu, L.; Prashad, M.; Kwong, F. Y. *Adv. Synth. Catal.*, 2010, **352**, 1539. (o) Li, L.; Chen, B.; Ke, Y.; Li, Q.; Zhuang, Y.; Duan, K.; Huang, Y.; Pang, J.; Qiu, L. *Chem. Asian J.* 2013, **8**, 2167.
16. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* 1993, **115**, 10125.
17. (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* 2003, **125**, 3534. (b) Daumas, M.; VoQuang, L.; Le Goffic, F. *Synth. Commun.* 1990, **20**, 3395. (c) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* 1984, **20**, 53.

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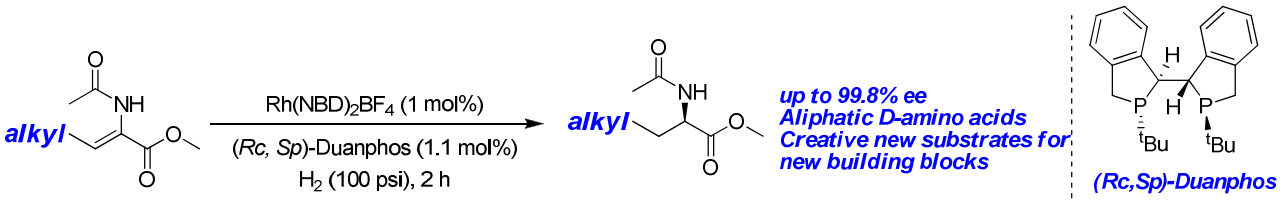

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