

An Improved Lanthanum Catalyst System for Asymmetric Amination: Toward a Practical Asymmetric Synthesis of AS-3201 (Ranirestat)

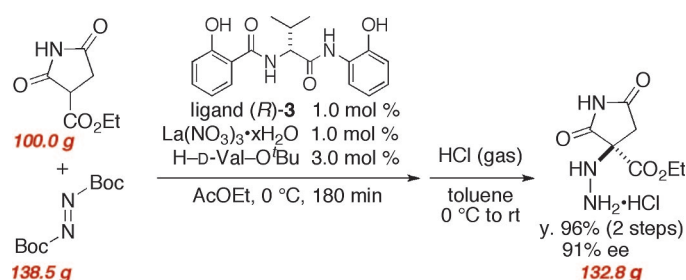
Tomoyuki Mashiko, Naoya Kumagai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

nkumagai@mol.f.u-tokyo.ac.jp; mshibasa@mol.f.u-tokyo.ac.jp

Received April 13, 2008

ABSTRACT



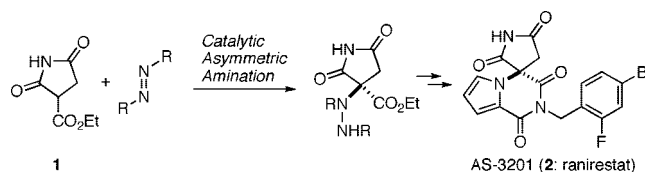
A catalytic asymmetric amination with a lanthanum/amide complex was significantly improved. The use of lanthanum nitrate hydrate in place of lanthanum triisopropoxide made the process reproducible, scalable, and cost-effective. The development of a ternary catalytic system of La/ligand/amine was a key to high ee and catalytic turnover. A 100 g scale reaction was performed to showcase a practical synthesis of a key intermediate for AS-3201, a highly potent aldose reductase inhibitor.

Diels amination using azodicarboxylates is a useful technology for the installation of a nitrogen functionality, often allowing for the construction of a C–N bond at a tetrasubstituted carbon.¹ We are particularly intrigued by the catalytic asymmetric amination of succinimide derivative **1**, which paves the way for a practical asymmetric synthesis of AS-3201 (**2**, ranirestat), a highly potent aldose reductase inhibitor currently under phase III clinical trials in the US and Canada (Scheme 1).^{2,3} As the number of patients with diabetes is increasing globally at an unparalleled pace,⁴ **2** has gained growing attention for its value as a potential treatment of diabetic neuropathy. The production of **2** in large quantities

relies on optical resolution using cinchonidine, which limits the efficiency and production quantity and increases the cost. Although Diels amination has been rendered enantioselective in recent years,^{5,6} the highly coordinative nature of **1** hampered the high level of enantiocontrol with reported asymmetric catalysts.⁷

We developed a catalytic system comprising the La(OⁱPr)₃/amide ligand (*R*)-**3** (first-generation catalyst) for this specific

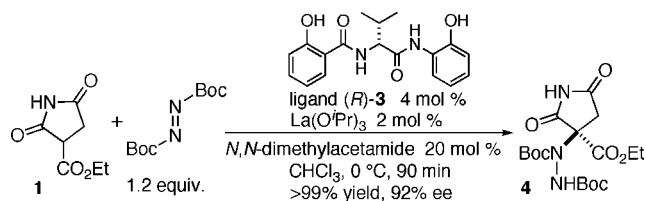
Scheme 1. Catalytic Asymmetric Synthesis of AS-3201 (**2**)



(1) (a) Diels, O. *Justus Liebigs Ann. Chem.* **1922**, 429, 1. (b) Diels, O.; Behncke, H. *Chem. Ber.* **1924**, 57, 653. (c) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, 119, 6452. (d) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, 1, 595. (e) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Can. Chem.* **2000**, 78, 666. (f) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, 6, 2193.

transformation using *tert*-butyl azodicarboxylate, thereby affording amination product **4** in >99% yield in 92% ee with 4 mol % of (*R*)-**3** and 2 mol % of La(O^{*i*}Pr)₃ (Scheme 2).^{6,8}

Scheme 2. Catalytic Asymmetric Amination of **1** with First-Generation Catalyst



Compound **4** was successfully converted to **2** in optically pure form via a five-step transformation and single recrystallization. The use of La(O^{*i*}Pr)₃ for catalyst preparation, however, is problematic from a practical point of view: (1) La(O^{*i*}Pr)₃ is very expensive (\$194/3 g, Aldrich)⁹ and not available in large quantities; (2) La(O^{*i*}Pr)₃ is unstable to moisture and must be handled in a dry box; (3) both reactivity and enantioselectivity sometimes fluctuate depending on the production lot of La(O^{*i*}Pr)₃; (4) the use of halogenated solvent CHCl₃ is undesirable; and (5) the isolation of **4** requires laborious column chromatography. In our continuing efforts toward the asymmetric synthesis of **2**, we have overcome

the above problems to achieve a reproducible, scalable, and cost-effective catalytic asymmetric amination protocol. On the basis of ESI-QFT MS analysis, a newly developed ternary La/**3**/amine catalyst avoided undesirable aggregation of La³⁺, and the components would work together to achieve high catalytic efficiency.

We initially searched for lanthanum sources other than La(O^{*i*}Pr)₃ because we assumed that 2-propanol derived from La(O^{*i*}Pr)₃ had a negligible impact on both the reactivity and enantioselectivity. Among the various La salts examined, La(NO₃)₃·6H₂O was attractive due to its relatively high solubility and the highly coordinative nature of the nitrate, preventing an undesirable oligomerization of the La complex. Furthermore, La(NO₃)₃·6H₂O is readily available in large quantities and much less expensive (99.99%, \$301/500 g, Aldrich).^{9–11} In contrast to the basic nature of La(O^{*i*}Pr)₃, La(NO₃)₃·6H₂O is a neutral salt and requires additional base to promote the reaction efficiently. In fact, the reaction with La(NO₃)₃·6H₂O/(*R*)-**3** was sluggish to give the racemic product **4** in 71% yield after 18 h (Table 1, entry 0). The catalytic asymmetric amination of **1** was run in EtOAc, a relatively safe organic solvent for industrial use, with a ternary complex comprising La(NO₃)₃·6H₂O, amide ligand (*R*)-**3**, and additional base (Table 1). For prospective practical application, all reactions were performed at room temperature under ambient atmosphere unless otherwise noted. When a typical inorganic base, KO^{*t*}Bu, was employed, however, **4** was obtained with only 58% ee (entry 1). Amine bases afforded better results in general. Achiral tertiary, secondary, and primary amines as well as 2,6-lutidine promoted the reaction smoothly with 2.5 mol % of catalyst loading to give the product nearly quantitatively in a short period albeit with only moderate enantioselectivity (35–79% ee, entries 2–5). The reaction with amino acid ^{*t*}Bu ester as the amine significantly improved the enantioselectivity (entries 6–8). In particular, the use of H-D-Val-O^{*t*}Bu led to 91% ee (entry 7). The use of an antipode, H-L-Val-O^{*t*}Bu, resulted in inferior enantioselectivity compared with the reaction using H-D-Val-O^{*t*}Bu (entry 8). Under the ternary catalytic system, the ligand/metal ratio was reduced to 1/1 from 2/1 to conserve **3** (entry 7 vs 9). In addition, the ternary catalytic system was reproducible, affording a comparable reaction outcome in three runs (entry 9).¹² The structure of amine significantly impacted enantioselectivity (entries 0, 2–8), likely because amines would be held in near proximity of the La coordina-

(10) Bulk purchase may lower the cost.

(11) For recent selected examples for the use of lanthanide nitrates for asymmetric catalysis, see: (a) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989. (b) Furuno, H.; Hayano, T.; Kambara, T.; Sugimoto, Y.; Hanamoto, T.; Tanaka, Y.; Jin, Y. Z.; Kagawa, T.; Inanaga, J. *Tetrahedron* **2003**, *59*, 10509. Lanthanide nitrates exhibit much less catalytic efficiency compared with corresponding triflates. For example, see: (c) Kano, S.; Nakano, H.; Kojima, M.; Baba, N.; Nakajima, K. *Inorg. Chim. Acta* **2003**, *349*, 6.

(12) For selected examples of rare earth metal asymmetric catalyst showing enhanced stereoselectivity in the presence of amine, see: (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (c) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (d) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555. (e) Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49. (f) Fukuzawa, S.-I.; Komuro, Y.; Nakano, N.; Obata, S. *Tetrahedron Lett.* **2003**, *44*, 3671.

(2) (a) Sestanj, K.; Bellini, F.; Fung, S.; Abraham, N.; Treasurywala, A.; Humber, L.; Simard-Duquesne, N.; Dvornik, D. *J. Med. Chem.* **1984**, *27*, 255. (b) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841. (c) Lee, Y. S.; Pearlstein, R.; Kador, P. F. *J. Med. Chem.* **1994**, *37*, 787. (d) Malamas, M. S.; Hohman, T. C.; Millen, J. *J. Med. Chem.* **1994**, *37*, 2043. (e) Ishii, A.; Kotani, T.; Nagaki, Y.; Shibayama, Y.; Toyomaki, Y.; Okukada, N.; Ienaga, K.; Okamoto, K. *J. Med. Chem.* **1996**, *39*, 1924.

(3) (a) Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Suzuki, K.; Matsumoto, J.-I. *J. Med. Chem.* **1998**, *41*, 4118. (b) Kurono, M.; Fujiwara, I.; Yoshida, K. *Biochemistry* **2001**, *40*, 8216. (c) Bril, V.; Buchanan, R. A. *Diabetes Care* **2004**, *27*, 2369. (d) Kurono, M.; Fujii, A.; Murata, M.; Fujitani, B.; Negoro, T. *Biochem. Pharmacol.* **2006**, *71*, 338. (e) Giannoukakis, N. *Curr. Opin. Invest. Drugs* **2006**, *7*, 916.

(4) Nath, D.; Heemels, M.-T.; Anson, L. *Nature* **2006**, *444*, 83.

(5) For selected examples, see: (a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367. (b) Sabby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (c) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115. (d) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193. (e) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (f) Foltz, C.; Stecker, B.; Marconi, G.; Bellemine-Laponnaz, S.; Wadepohl, H.; Gabe, L. H. *Chem. Commun.* **2005**, 5115. (g) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (h) Kim, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565. (i) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (j) Comelles, J.; Pericas, À.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; García-Granda, S.; Rocas-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077. (k) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158.

(6) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342.

(7) Cu-Box, La-PyBox, urea-type organocatalyst, and cinchona alkaloids were screened in catalytic asymmetric amination of **1**. The observed enantioselectivities were less than 30% ee. See also ref 6.

(8) For recent selected examples of small peptide-based asymmetric catalysis, see: (a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. C. *Nature* **2006**, *443*, 67. (b) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. For reviews, see: (c) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779. (d) Blank, J. T.; Miller, S. J. *Biopolymers (Pept. Sci.)* **2006**, *84*, 38.

(9) Sigma-Aldrich Handbook of Fine Chemicals 2007–2008.

Table 1. Catalytic Asymmetric Amination of **1** Promoted by $\text{La}(\text{NO}_3)_3/(\text{R})\text{-3}$ /Amine Ternary Catalyst^a

entry	x	y	base	z	T (°C)	time	yield ^b (%)	ee (%)
0	5	2.5	-	-	rt	18 h	71	0
1	5	2.5	KO ^t Bu	7.5	rt	180 min	>99	58
2	5	2.5	Et ₃ N	7.5	rt	120 min	>99	79
3	5	2.5	Et ₂ NH	7.5	rt	120 min	>99	52
4	5	2.5	^t BuNH ₂	7.5	rt	60 min	>99	70
5	5	2.5	2,6-lutidine	7.5	rt	330 min	>99	35
6	5	2.5	H-D-Phe-O ^t Bu	7.5	rt	20 min	>99	89
7	5	2.5	H-D-Val- O ^t Bu	7.5	rt	20 min	>99	91
8	5	2.5	H-L-Val- O ^t Bu	7.5	rt	90 min	>99	80
9 ^c	2.5	2.5	H-D-Val-O ^t Bu	7.5	rt	20 min	>99	91
10	0	2.5	H-D-Val-O ^t Bu	7.5	0	120 min	>99	-1
11	1	1	H-D-Val-O ^t Bu	3	-40	60 min	>99	92
12	1	1	H-D-Val-O ^t Bu	3	0	12 h	>99	92
13 ^d	0.5	0.5	H-D-Val-O ^t Bu	1.5	-40	1 h	>99	90
14	0.5	0.5	H-D-Val-O ^t Bu	1.5	-40	24 h	99	93
15 ^e	0.25	0.25	H-D-Val-O ^t Bu	0.75	-40	60 h	>99	87

^a 0.4 mmol scale. ^b Determined by ¹H NMR analysis with Bn₂O as internal standard. ^c Average of three runs. ^d 10 g of **1** was used. ^e 0.8 mmol scale.

tion sphere and perturb the transition state of the reaction. The reaction without ligand (*R*)-**3** provided the product in almost racemic form (entry 10), suggesting that a chiral environment would be constructed mainly by a La cation and (*R*)-**3**. The reaction using 1 mol % of catalyst reached completion at lower temperatures (0, -40 °C) with a marginal increase in enantiomeric excess (entries 11 and 12). The catalyst loading could be reduced to 0.5 mol % while maintaining >90% ee (entry 14).

To gain insights into the origin of high catalytic efficiency and improved reproducibility, we performed ESI-QFT MS analysis of the catalyst. In the MS spectrum of the first-generation catalyst (Figure 1a), prepared from $\text{La}(\text{O}^i\text{Pr})_3$ and (*S*)-**3**, oligomeric La complexes ($\text{La}_4(\text{O})((\text{S})\text{-3})_4$, $\text{La}_4((\text{S})\text{-3})_5$) were observed. In contrast, several peaks derived from monometallic La complexes appeared in the MS spectrum of the mixture of $\text{La}(\text{NO}_3)_3/(\text{R})\text{-3}$, possibly because highly coordinative nitrate avoided undesirable aggregation of La^{3+} (Figure 1b). The catalyst comprising $\text{La}(\text{NO}_3)_3/(\text{R})\text{-3}$ showed no enantioselection (Table 1, entry 0), suggesting that none of these peaks are actual active catalysts. The MS spectrum of $\text{La}(\text{NO}_3)_3/(\text{R})\text{-3}/\text{H-D-Val-O}^t\text{Bu}$ ternary catalyst showed the ternary complex of $[\text{La}((\text{R})\text{-3})_2/\text{H-D-Val-O}^t\text{Bu}]$ accompanied by the peaks of nonmetallic and unidentified species, and multimetallic La complexes were not observed (Figure 1c). Prevention of La^{3+} aggregation would be beneficial for catalytic turnover and reproducibility. The ligand **3** is flexible and the formation of distinct complex upon mixing with $\text{La}(\text{NO}_3)_3$ would be unlikely. Taking the detection of several species in Figure 1 (b,c) and the strong dependency of enantioselectivity on the structure of amine into account (Table 1), the catalyst components would be in a dynamic

equilibrium and work cooperatively to attain high enantioselectivity.

Having developed an efficient catalytic asymmetric amination protocol suitable for a large-scale reaction, we performed the amination using 100 g of **1** with 1 mol % of catalyst loading (Figure 2). All procedures were performed under ambient atmosphere. To a stirred solution of ligand (*R*)-**3** (1.92 g) and $\text{La}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$ (2.30 g,¹³ less expensive than hexahydrate, \$152/500 g, Aldrich^{9,10} in EtOAc (160 mL, ACS reagent grade, Aldrich) was added H-D-Val-O^tBu (3.34 mL) at room temperature. To the resulting suspension were added EtOAc (1000 mL) and **1** (100.0 g), and the resulting cloudy solution was cooled to 0 °C. Then *tert*-butyl azodicarboxylate (138.5 g) was added portionwise¹⁴ to run the reaction. The total amount of EtOAc was 1160 mL, indicating the high volumetric productivity of the present process. After 180 min, the reaction mixture was partitioned by EtOAc/0.5 N HCl aq. The aqueous layer was basified and extracted with ethyl acetate to recover H-D-Val-O^tBu 90% (2.75 g). The organic layer was evaporated, and 1950 mL of toluene (ACS reagent grade, Aldrich) was added. To the toluene solution was passed through HCl gas at 0 °C for 1.5 h and at room temperature for 4.5 h, then toluene was removed under reduced pressure. The resulting solid residue was triturated with EtOH/^tBuOMe and filtered to collect

(13) The amount of $\text{La}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$ was calculated as $x = 4$.

(14) A 25 g portion of di-*tert*-butyl azodicarboxylate was added five times during the first 5 min of the reaction. An additional 13.5 g was added 10 min after the last addition. The reaction was exothermic, and the reaction temperature varied from -5 to +8 °C occasionally. The observed enantioselectivity was comparable to that obtained in small scale reactions likely because the enantioselectivity of the present amination is relatively insensitive to the reaction temperature.

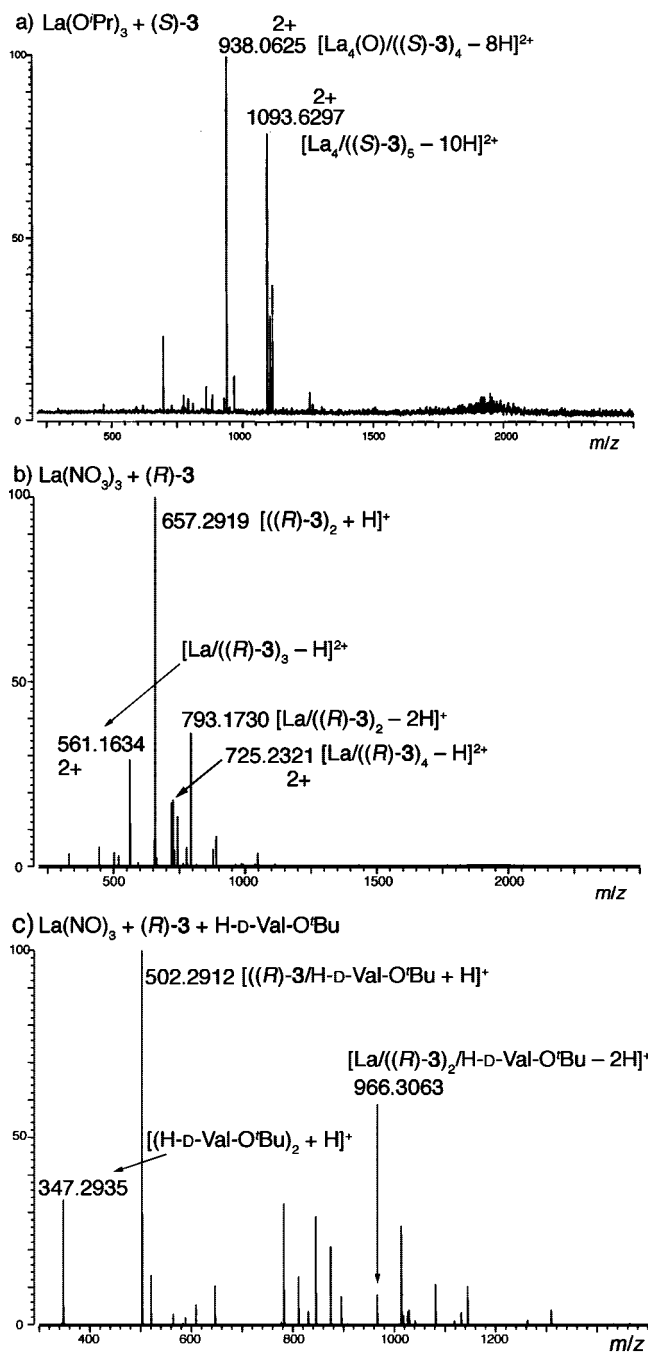


Figure 1. ESI-QFT MS analysis of (a) $\text{La}(\text{O}^i\text{Pr})_3/(\text{S})\text{-3}$ complex, (b) $\text{La}(\text{NO}_3)_3/(\text{R})\text{-3}$, and (c) the ternary catalyst.

hydrazine hydrochloride salt **5** in 96% yield (two steps) with 91% ee.¹⁵ Compound **5** directly enters a practical synthetic

(15) Enantiomeric excess of **5** was determined after mono-Boc protection. See the Supporting Information for details.

(16) (a) *Metal Ions in Biological Systems: The Lanthanides and Their Interrelations with Biosystems*; Sigel, H., Sigel A., Eds; Marcel Dekker: New York, 2003; Vol. 40.

(17) The Clarke number of lanthanum is 0.0018, almost equally abundant as zinc (0.004) or boron (0.001).

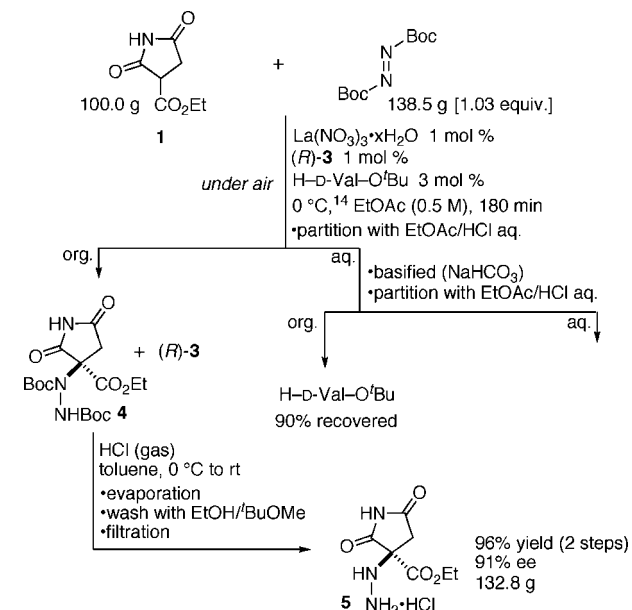


Figure 2. A 100 g scale demonstration of catalytic asymmetric amination and chromatography-free isolation of **5**.

route of **2**,⁶ thus, the present amination protocol is a significant advancement toward the bulk production of **2**.

In summary, we successfully improved catalytic asymmetric amination using a ternary catalytic system of $\text{La}(\text{NO}_3)_3$ hydrate, amide ligand $(\text{R})\text{-3}$, and $\text{H-D-Val-O}^i\text{Bu}$. The procedure is concise and chromatography-free, and amine was recovered. Reproducibility, cost-efficiency, catalyst loading, and low toxicity¹⁶ as well as the high natural abundance¹⁷ of lanthanum are of high practical value for an industrial application of the present protocol to the efficient synthesis of **2**, a highly potent aldose reductase inhibitor. The use of lanthanide nitrates in the form of the metal/ligand/amine ternary complex is noteworthy and contributes to lanthanide-based asymmetric catalysis as a general catalyst preparation protocol. Detailed investigations on the mechanistic aspect of the present catalysis and its applications to the other asymmetric reactions are ongoing.

Acknowledgment. This work was supported by Grant-in-Aid for Specially Promoted Research from MEXT. N.K. acknowledges a Grant-in-Aid for Young Scientists (B). Financial support from Dainippon Sumitomo Pharma Co., Ltd. is gratefully acknowledged. We thank Drs. Akihiro Sato and Sanae Furusho at JASCO international for ESI-QFT MS analysis of the catalyst complex.

Supporting Information Available: Detailed experimental procedure, characterization data, and ESI MS analysis of the catalyst. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL8008446