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

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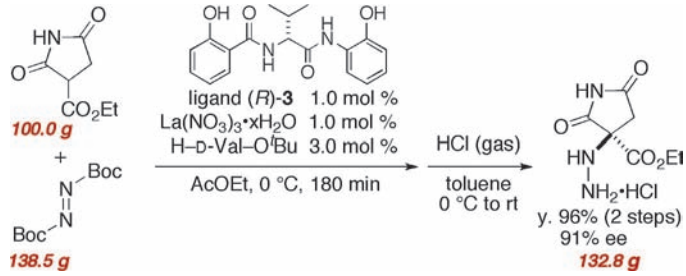
ABSTRACT

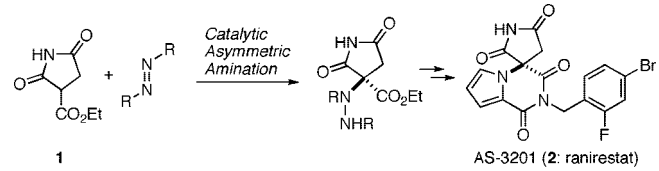


A catalytic asymmetric amination with a lanthanum/amide complex was significantly improved. The use of lanthanum nitrate hydrate in place of lanthanum triisopropoxide made the process reproducible, scalable, and cost-effective. The development of a ternary catalytic system of La/ligand/amine was a key 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 enantioselectively 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(O^iPr)$_3$/amide ligand (*R*)-**3** (first-generation catalyst) for this specific

Scheme 1. Catalytic Asymmetric Syntehsis 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.

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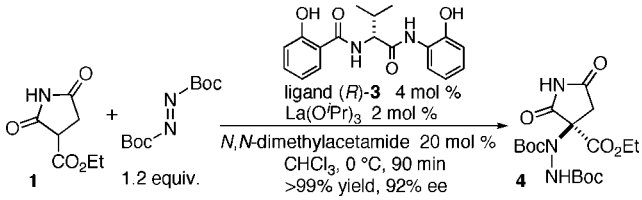
transformation using *tert*-butyl azodicarboxylate, thereby affording amination product **4** in >99% yield in 92% ee with 4 mol % of (*R*)-**3** and 2 mol % of La(O^{i}Pr)$_3$ (Scheme 2).[6,8]

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 $CHCl_3$ 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 La^{3+}, 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(NO$_3$)$_3$•6H$_2$O 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(NO$_3$)$_3$•6H$_2$O 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$, La(NO$_3$)$_3$•6H$_2$O is a neutral salt and requires additional base to promote the reaction efficiently. In fact, the reaction with La(NO$_3$)$_3$•6H$_2$O/(*R*)-**3** was sluggish to give the racemic product **4** in 71% yield after 18 h (Table 1, entry 0). The catalytic asymmetric amination of **1** was run in EtOAc, a relatively safe organic solvent for industrial use, with a ternary complex comprising La(NO$_3$)$_3$•6H$_2$O, 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-

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(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.

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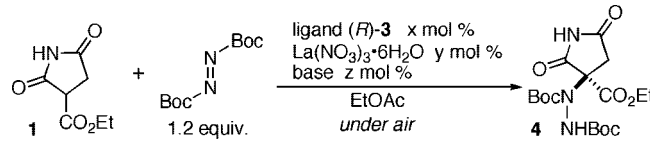
(12) For selected examples of rare earth metal asymmetric catalyst showing enhanced stereoselectivity in the presence of amine, see:(a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (c) 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.; Nakanao, N.; Obata, S. *Tetrahedron Lett.* **2003**, *44*, 3671.

Table 1. Catalytic Asymmetric Amination of **1** Promoted by $La(NO_3)_3$/(*R*)-**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_3N	7.5	rt	120 min	>99	79
3	5	2.5	Et_2NH	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 ^{1}H NMR analysis with Bn_2O 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 La(O^{i}Pr)$_3$ and (*S*)-**3**, oligomeric La complexes ($La_4(O)((S)\text{-}\mathbf{3})_4$, $La_4((S)\text{-}\mathbf{3})_5$) were observed. In contrast, several peaks derived from monometallic La complexes appeared in the MS spectrum of the mixture of $La(NO_3)_3$/(*R*)-**3**, possibly because highly coordinative nitrate avoided undesirable aggregation of La^{3+} (Figure 1b). The catalyst comprising $La(NO)_3$/(*R*)-**3** showed no enantioselection (Table 1, entry 0), suggesting that none of these peaks are actual active catalysts. The MS spectrum of $La(NO)_3$/(*R*)-**3**/H-D-Val-O^{t}Bu ternary catalyst showed the ternary complex of [La/((*R*)-**3**)$_2$/H-D-Val-O^{t}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 $La(NO_3)_3$ 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 $La(NO_3)_3{\cdot}xH_2O$ (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^{t}Bu (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 portionwise[14] 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^{t}Bu 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/^{t}BuOMe and filtered to collect

(13) The amount of $La(NO_3)_3{\cdot}xH_2O$ 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.

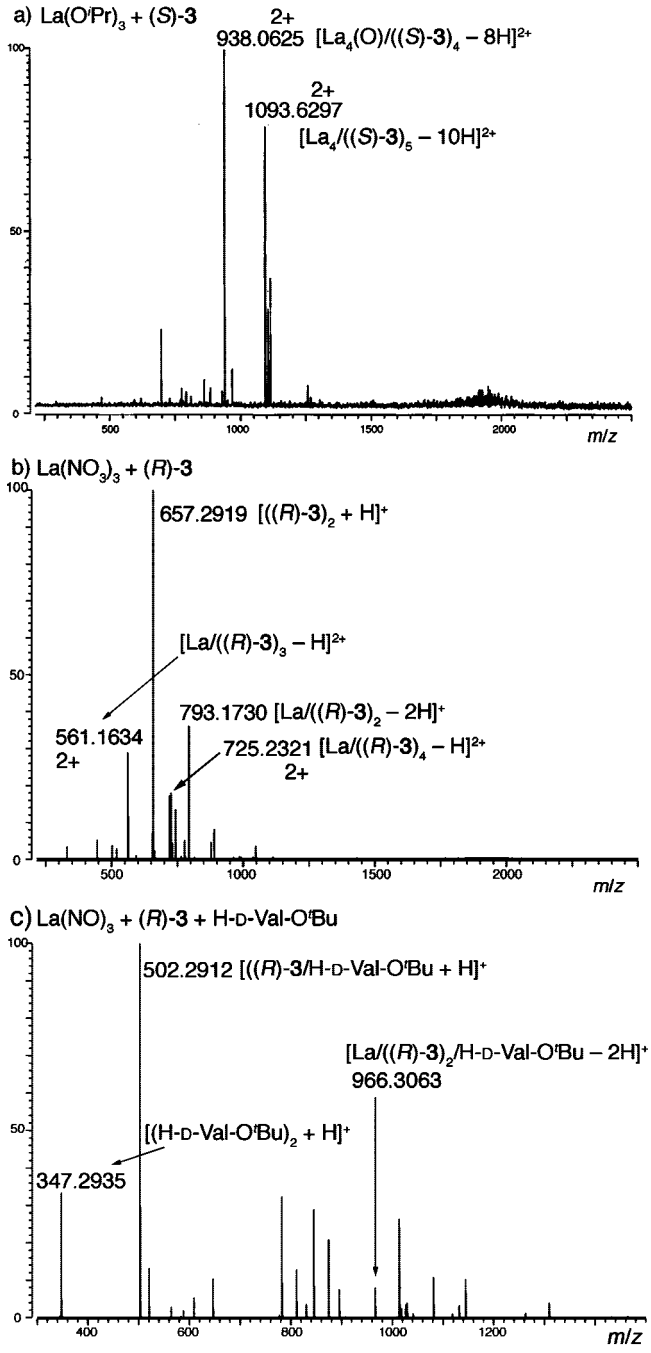


Figure 1. ESI-QFT MS analysis of (a) La(O^{i}Pr)$_3$/(*S*)-**3** complex, (b) La(NO$_3$)$_3$/(*R*)-**3**, and (c) the ternary catalyst.

hydrazine hydrochloride salt **5** in 96% yield (two steps) with 91% ee.[15] Compound **5** directly enters a practical synthetic route of **2**;[6] thus, the present amination protocol is a significant advancement toward the bulk production of **2**.

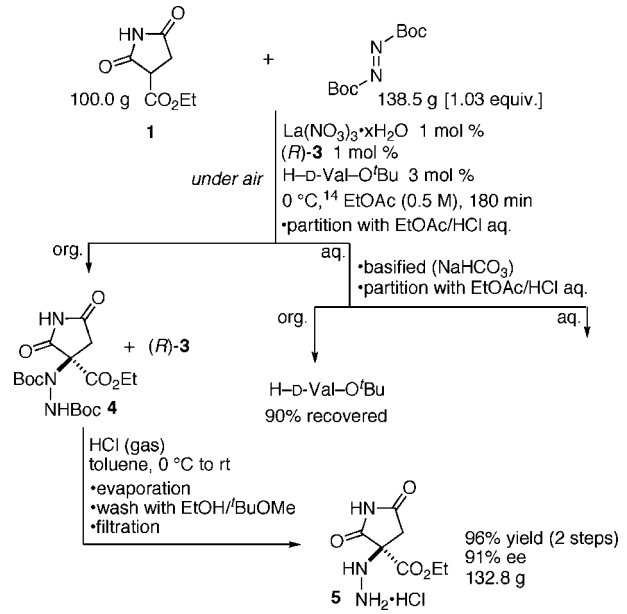


Figure 2. A 100 g scale demonstration of catalytic asymmetric amination and chromatography-free isolation of **5**.

In summary, we successfully improved catalytic asymmetric amination using a ternary catalytic system of La(NO$_3$)$_3$ hydrate, amide ligand (*R*)-**3**, and H-D-Val-O^{t}Bu. The procedure is concise and chromatography-free, and amine was recovered. Reproducibility, cost-efficiency, catalyst loading, and low toxicity[16] as well as the high natural abundance[17] 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 lanthanides-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.

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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.

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(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 Lathanides 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).