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A simplified catalytic system for direct catalytic asymmetric aldol reaction of thioamides; application to an enantioselective synthesis of atorvastatin

Yuji Kawato [a,b], Mitsutaka Iwata [a,b], Ryo Yazaki [a,b], Naoya Kumagai [a,*], Masakatsu Shibasaki [a,*]

[a] Institute of Microbial Chemistry, Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan
[b] Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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ABSTRACT

A new catalytic system was developed for the direct catalytic asymmetric aldol reaction of thioamides. The new lithium-free Cu catalyst (second-generation catalyst) exhibited enhanced catalytic efficiency over the previously developed catalyst comprising $[Cu(CH_3CN)_4]PF_6$/Ph-BPE/LiOAr (first-generation catalyst), which required a tedious catalyst preparation process. In the reaction with the second-generation catalyst, the intermediate Cu-aldolate functioned as a Brønsted base to generate thioamide enolate, efficiently driving the catalytic cycle. The present aldol methodology culminated in a concise asymmetric synthesis of atorvastatin (Lipitor®: atorvastatin calcium), a widely prescribed HMG-CoA reductase inhibitor for lowering low-density lipoprotein cholesterol.

1. Introduction

The aldol reaction, one of the oldest reactions described in the literature, is frequently used in both chemical and biochemical processes.[1] Historically, the focus of aldol chemistry gradually shifted from the control of enolate geometries for diastereoselection, a Lewis acid catalyzed aldol reaction using preformed enolates, and enantioselection using auxiliaries, to catalytic asymmetric aldol reactions using chiral Lewis acids.[2] Most recently, considerable advances have been made in direct catalytic asymmetric aldol methodology, in which catalytic in situ generation of enolates and the subsequent addition to aldehydes are promoted by the actions of a specifically designed chiral catalyst.[3] Because catalytic in situ generation of enolates is central to triggering this process, aldol donors, such as ketones and aldehydes that are tend to form enolates through facile deprotonation are commonly used.[4] Despite their prospective synthetic utility, however, the use of aldol donors in the carboxylic acid oxidation state in a direct catalytic asymmetric aldol reaction is limited due to reluctant enolate formation resulting from the intrinsic low acidity of the α-proton in this class of pronucleophiles.[5]

In this context, we recently developed a direct catalytic asymmetric aldol reaction using thioamides **1** as the aldol donor promoted by a soft Lewis acid/hard Brønsted base cooperative binary catalyst.[6,7] Thioamide **1** is expected to be chemoselectively activated by a soft Lewis acid in the presence of aldehyde **2** due to the soft Lewis basic nature of thioamide functionality, allowing for the facile generation of active thioamide enolate.[8–11] The soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/LiOAr (first-generation catalyst, ArOH: 2,2,5,7,8-pentamethylchromanol (**4**)) was identified as an optimal catalyst,[12] affording enantiomerically enriched β-hydroxythioamides **3** under proton transfer conditions (Scheme 1a).[6a,b] Phosphine oxide additive **5** as a hard Lewis basic catalyst component[13,14] rendered the reaction enantio- and *syn*-selective (Scheme 1b).[6c] These reactions are intriguing because the more acidic non-branched aldehydes, which notoriously undergo extensive self-condensation under conventional basic conditions, afforded the desired aldol products exclusively. However, the catalyst system was complicated and freshly prepared Li-aryloxide solution was essential. Furthermore, particularly for the reaction with thioacetamide **1a**, the catalytic activity was eroded depending on the functional group of the aldehyde, accompanied by undesired β-elimination of the aldol product. Herein, we report the second-generation catalyst comprising mesitylcopper and Ph-BPE, a simplified catalytic system exhibiting identical or superior catalytic performance. The direct catalytic asymmetric aldol reaction was successfully applied to a concise enantioselective synthesis of atorvastatin (Lipitor®:

* Corresponding authors. Tel.: +81 3 3447 7779; fax: +81 3 3441 7589 (M.S.); tel.: +81 3 3441 8133; fax: +81 3 3441 7589 (N.K.); e-mail addresses: nkumagai@bikaken.or.jp (N. Kumagai), mshibasa@bikaken.or.jp (M. Shibasaki).

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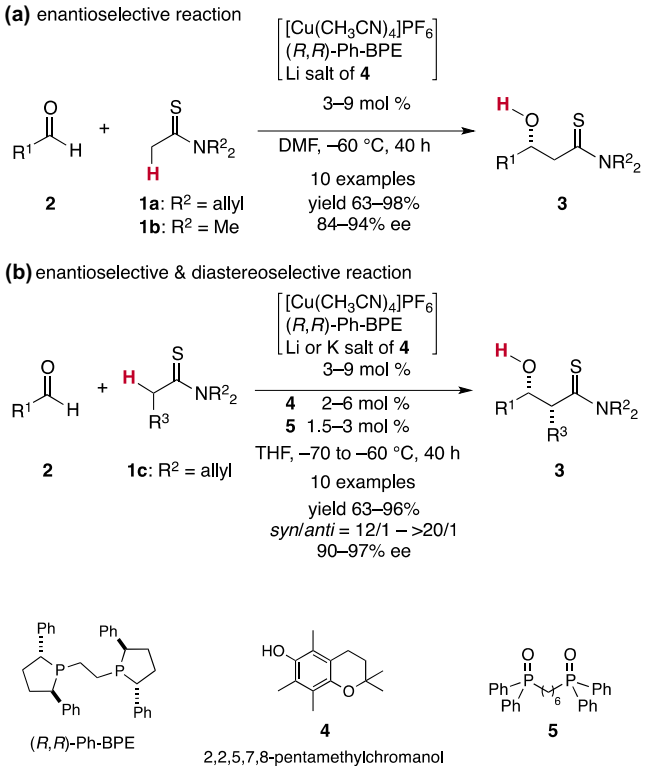


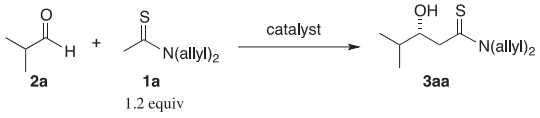
Scheme 1. Direct catalytic asymmetric aldol reaction of thioamides promoted by a soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/LiOAr (the first-generation catalyst).

atorvastatin calcium), a widely prescribed 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor for lowering low-density lipoprotein (LDL) cholesterol.[15,16]

2. Results and discussion

The design of the first-generation catalyst was based on a binary catalyst endowed with soft Lewis acid and hard Brønsted base functions for chemoselective activation of thioamides **1** in the presence of aldehyde. $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE and Li salt of 2,2,5,7,8-pentamethylchromanol (**4**) emerged as the best combination of soft Lewis acid and hard Brønsted base components, respectively.[6a,17] The Cu(I) cation was proved essential because the aldol reaction of *N*,*N*-diallylthioacetamide (**1a**) and isobutyraldehyde (**2a**) did not proceed at all in the absence of Cu as a soft Lewis acid component (Table 1, entries 1 and 2). In contrast, the presence of a Li cation was not crucial; Li aryloxide was indispensable for the aldol reaction (entry 3), but the Li cation itself may be nothing more than a counter cation of aryloxide and may thus have no specific role in the proposed catalytic cycle (Fig. 1a). Furthermore, {$CuPF_6$/(*R*,*R*)-Ph-BPE+LiOAr} is in equilibrium with {[CuOAr/(*R*,*R*)-Ph-BPE+$LiPF_6$],[17c] in which CuOAr might be able to function as a soft Lewis acid/hard Brønsted base cooperative catalyst. To clarify the function of the Li cation and catalytic activity of CuOAr, we conducted a control experiment using the chiral CuOAr catalyst in the absence of a Li source, which was prepared from mesitylcopper,[18,19] (*R*,*R*)-Ph-BPE, and **4**. Surprisingly, the Li-free catalyst exhibited higher catalytic efficiency (entry 6). In the presence of Li cation, a Lewis basic additive or solvent, such as DMF or pyridine were essential for catalyst turnover (entries 4 and 5). In contrast, in the absence of a Li cation, the reaction proceeded without any Lewis basic species and the reaction outcome was similar with DMF or THF solvent (entries 6 and 7).[20] More intriguingly, the aldol reaction proceeded without **4**; only mesitylcopper and (*R*,*R*)-Ph-BPE promoted the desired aldol reaction with comparable enantioselectivity (entry 8). The likely scenario for the catalytic cycle is as follows; first, mesitylcopper and thioamide **1a** generate thioamide enolate **6** decorated with a (*R*,*R*)-Ph-BPE ligand, and subsequent addition to aldehyde **2** gives Cu-aldolate **7**, which functions as a soft Lewis acid/hard Brønsted base cooperative catalyst to generate thioamide enolate from **1a**, promoting the following catalytic cycles (Fig. 1b). This catalytic system is quite intriguing because the intermediate, Cu-aldolate **7**, plays a critical role as a catalyst to drive the catalytic cycles, achieving efficient enantioselective C–C bond formation with proton transfer between substrates. This simplified catalytic system was applicable to other non-branched aldehydes **2b**,**c** without self-condensation, and a similar catalytic performance was observed with $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/LiOAr, with which tedious and careful preparation of LiOAr and the use of DMF as the solvent was essential (Table 2).

Table 1
Investigation of the catalyst



Entry	Catalyst (mol %)	Solvent	Yield[a] (%)	ee (%)
1	$[Cu(CH_3CN)_4]PF_6$(3) (*R*,*R*)-Ph-BPE (3) Li salt of **4** (3)	DMF	91	91
2	Li salt of **4** (3)	DMF	0	—
3	$[Cu(CH_3CN)_4]PF_6$(3) (*R*,*R*)-Ph-BPE (3)	DMF	0	—
4	$[Cu(CH_3CN)_4]PF_6$(3) (*R*,*R*)-Ph-BPE (3) Li salt of **4** (3)	THF	0	—
5	$[Cu(CH_3CN)_4]PF_6$(3) (*R*,*R*)-Ph-BPE (3)+pyridine (30) Li salt of **4** (3)	THF	8	90
6	Mesitylcopper (3) (*R*,*R*)-Ph-BPE (3) **4**(3)	DMF	97	93
7	Mesitylcopper (3) (*R*,*R*)-Ph-BPE (3) **4**(3)	THF	98	89
8	Mesitylcopper (3) (*R*,*R*)-Ph-BPE (3)	DMF	83	94

[a] Determined by ^1H NMR analysis with $(CHCl_2)_2$ as an internal standard.

The newly developed second-generation catalyst was applied to a concise enantioslective synthesis of atorvastatin (Lipitor®; atorvastatin calcium), which is an HMG-CoA reductase inhibitor widely marketed throughout the world for the treatment of hypercholesterolemia. Due to the importance of the drug, extensive synthetic studies were conducted,[15,16] in particular for the synthetic study for optically active *syn*-3,5-dihydroxy carboxylic acid moiety.[21] Our synthesis commenced with the direct catalytic asymmetric aldol reaction of functionalized aldehyde, 3-benzyloxypropanal (**2d**) (Scheme 2). The β-ketoester moiety of **9** can be installed by direct conversion of the thioamide functionality and the following *syn*-selective reduction of β-hydroxy ketone delivers **8**. Installation of a pyrrole moiety and deprotection affords atorvastatin. Initially, we conducted the aldol reaction using thioamide **1a** with the first-generation catalyst, comprising $[Cu(CH_3CN)_4]PF_6$/(*S*,*S*)-Ph-BPE/LiOAr or KOAr, but, the catalytic performance was not satisfactory in a series of trials (Table 3, left column). Even in the presence of phosphine oxides, which are anticipated to enhance the Brønsted basicity of LiOAr, no improvement of yield was observed (entries 1–3). The reaction at the higher temperature (−40 °C) partly improved the yield (entry 4). Changing the counter cation of the

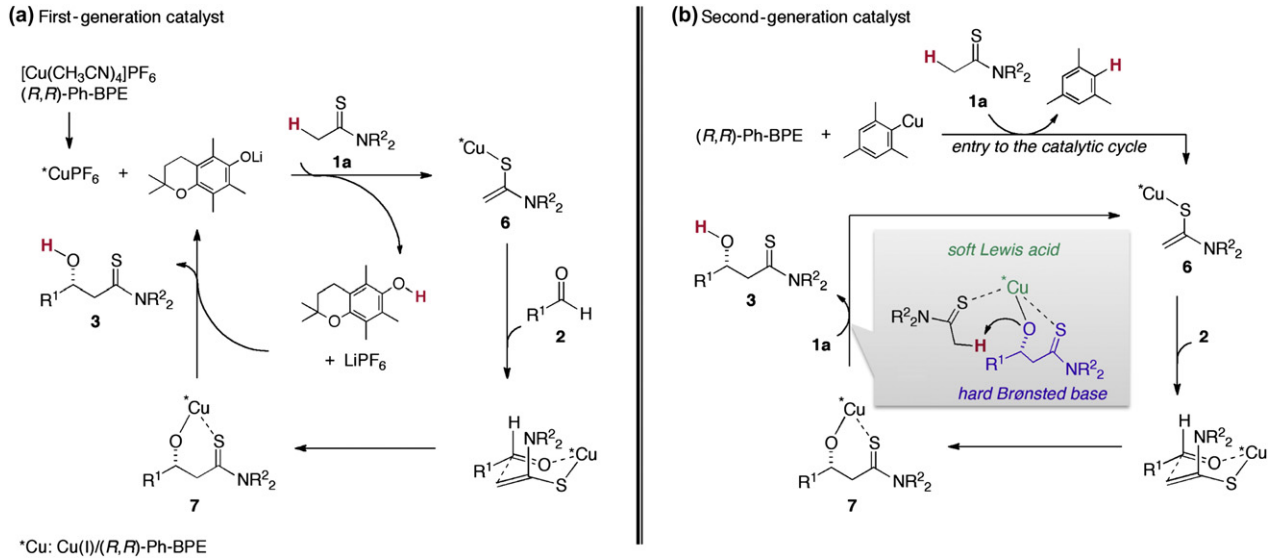
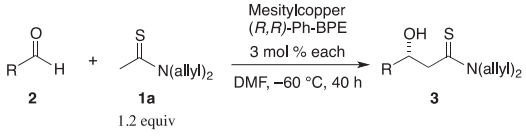


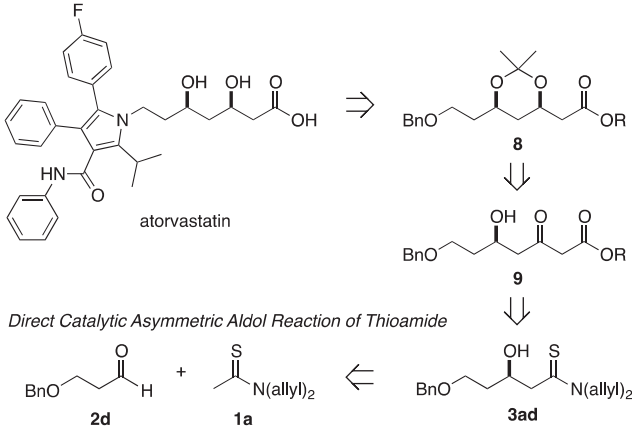
Fig. 1. Proposed catalytic cycle of a direct aldol reaction with (a) the first-generation catalyst and (b) the second-generation catalyst.

Table 2
Application of the second-generation catalyst[a]



Entry	Aldehyde	Product	Yield[b] (%)	ee (%)
1	**2a**	**3aa**	81	94
2	**2b**	**3ab**	79	89
3	**2c**	**3ac**	66	89

[a] Compound **1a**: 0.24 mmol, **2**: 0.2 mmol.
[b] Isolated yield.

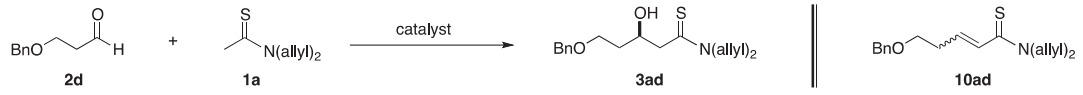


Scheme 2. Retrosynthetic analysis of atorvastatin.

aryloxide base from lithium to potassium led to a higher yield, but there was also a greater tendency to produce the undesired corresponding unsaturated thioamide **10ad** via β-elimination (entry 5). Our next focus was the use of the second-generation catalyst, which is anticipated to offer higher catalytic efficiency with a lower tendency for triggering β-elimination (Table 3, right column).With 10 mol % of mesitylcopper/(*S*,*S*)-Ph-BPE, the desired reaction proceeded at −60 °C in DMF to afford **3ad** in 49% with 84% ee (Table 3, entry 8). The use of dried MS 5A was beneficial to improve the enantioselectivity to 94% ee (entry 9). The yield increased by changing the reaction solvent from DMF to THF with compensation for the enantioselectivity (entry 10). Binary solvent system of DMF/THF=1/1 marginally compromised the yield and enantioselectivity (entry 11). The use of MS 5A and binary solvent system were also effective for the first-generation catalyst with KOAr base (entries 5–7). The addition of 1 equiv of 2,2,5,7,8-pentamethylchromanol (**4**) to the second-generation catalyst enhanced the catalytic efficiency without affecting enantioselectivity, presumably because proton transfer was mediated by phenolic proton of **4**, and MS 5A was equally effective (entries 12 and 13). The thus identified optimal reaction conditions can be run with 5 mol % of catalyst loading and scaled to 1 g reaction (entries 14 and 15).

We set out to the enantioseletive synthesis of atorvastatin (Scheme 3). After protecting the secondary alcohol of **3ad** as TBS ether with TBSOTf/2,6-lutidine in 96% yield, the thioamide functionality was chemoselectively activated by treatment with methyl triflate at room temperature to give methylthioiminium intermediate **11**, which was subjected to the lithium enolate derived from *tert*-butyl acetate to afford β-ketoester **12** in 72% in two steps. Removal of TBS by TBAF, followed by *syn*-selective reduction of the ketone with $Et_2B(OMe)/NaBH_4$, furnished *syn*-diol in a highly diastereoselective manner,[22] which was isolated after converting to the corresponding acetonide **13** in 88% yield in three steps.[16a,21a,21g] Hydrogenolysis of benzyl ether was performed over $Pd(OH)_2$ catalyst under 1 atm of hydrogen atmosphere at 60 °C and subsequent tosylation of the primary alcohol gave **14** in 91% yield in two steps.[21a,21g,21h] Introduction of pyrrole moiety was conducted by transformation into a primary amine followed by a Paal–Knorr reaction with diketone **16**.[16b] **14** was treated with NaN_3 in DMF to give the corresponding azide in 82% yield, which was reduced to primary amine **15** with PPh_3 in wet THF in 87%.[21h,21i] The

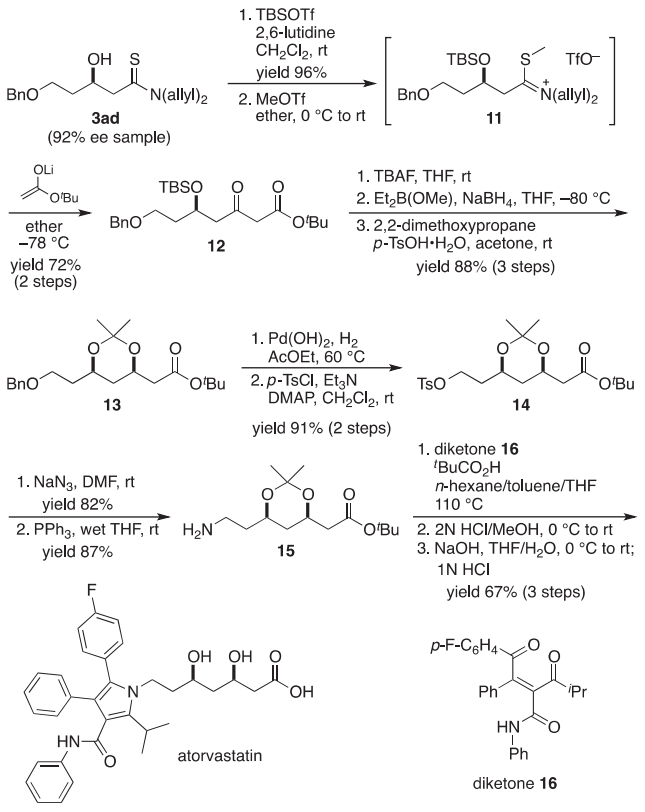
Table 3
Direct catalytic asymmetric aldol reaction of functionalized aldehyde **2d**[a]



entry	catalyst (mol %)	additive (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)	ee (%)
—first-generation catalyst—							
1	[Cu(CH3CN)4]PF6 (10)	—	DMF	–60	60	43	90
2	(*S*,*S*)-Ph-BPE (10)	**5** (10)	DMF	–60	60	26	87
3	Li salt of **4** (10)	Ph_3P=O (20)	DMF	–60	60	45	87
4		—	DMF	–40	40	56	92
5	[Cu(CH3CN)4]PF6 (10)	—	DMF	–60	60	58	91
6	(*S*,*S*)-Ph-BPE (10)	—	DMF/THF[d]	–60	60	59	88
7	K salt of **4** (10)	MS 5A	DMF/THF[d]	–60	60	64	89
—second-generation catalyst—							
8		—	DMF	–60	60	49	84
9	Mesitylcopper (10)	MS 5A	DMF	–60	60	50	94
10	(*S*,*S*)-Ph-BPE (10)	MS 5A	THF	–60	60	62	68
11		MS 5A	DMF/THF[d]	–60	60	60	86
12	Mesitylcopper (10)	—	DMF/THF[d]	–60	60	68	85
13	(*S*,*S*)-Ph-BPE (10)	MS 5A	DMF/THF[d]	–60	60	70	89
	4 (10)						
14	Mesitylcopper (5)	MS 5A	DMF/THF[d]	–60	72	64	85
15[c]	(*S*,*S*)-Ph-BPE (5)	MS 5A	DMF/THF[d]	–60	72	62	83
	4 (5)						

[a]Compound **1a**: 0.24 mmol, **2d**: 0.2 mmol.
[b]Determined by ^{1}H NMR analysis with $(CHCl_2)_2$ as an internal standard.
[c]Compound **2d** (1.0 g) was used.
[d]DMF/THF=1/1.

Paal–Knorr reaction of the amine **15** and diketone **16** was performed at 110 °C to construct a pyrrole ring,[16b,23] which was subjected to the acidic hydrolysis to afford atorvastatin in 67% yield in three steps.



Scheme 3. Enantioselective synthesis of atorvastatin.

3. Summary

We developed a simplified catalytic system, the second-generation catalyst, for the direct catalytic asymmetric aldol reaction of thioamide. The second-generation catalyst comprises of Ph–BPE ligand and mesitylcopper,[19] which are both commercially available, allowing us to skip the tedious preparation of LiOAr, which should be prepared just before use with extensive care for moisture. It is intriguing that the intermediate Cu-aldolate works as a soft Lewis acid/hard Brønsted base cooperative catalyst to promote deprotonation and enolate generation in the catalytic cycle. The direct catalytic asymmetric aldol reaction was successfully applied to a concise enantioselective synthesis of atorvastatin, in which transformation of the thioamide functionality to β-ketoester was a secondary key step. Further improvement of catalytic efficiency and enantioselectivity in the catalytic asymmetric aldol reaction for the practical synthesis of atorvastatin is currently underway.

4. Experimental

4.1. General

Direct catalytic asymmetric aldol reaction was performed in a flame-dried 20 mL test tube with a Teflon-coated magnetic stirring bar except for the reaction described as entry 15 in Table 3. The test tubes were fitted with a 3-way glass stopcock and reactions were run under Ar atmosphere. Dry THF, DMF, and ^{n}BuLi in *n*-hexane were purchased from commercial sources. THF was further purified through a Glass Contour system. Flash chromatography was performed using silica gel 60 (230–400 mesh) purchased from Merck. All work-up and purification procedures were carried out with reagent-grade solvents under an ambient atmosphere. Infrared (IR) spectra were recorded on a Horiba FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL ECS-400 or ECA-600 spectrometers. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. ESI mass spectra were measured on JEOL AccuTOF JMS-T100LC. High-resolution mass spectra (ESI TOF (+)) were measured on ThermoFisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with DAICEL chiral stationary phase columns (0.46 cmϕ×25 cm).

4.2. General procedure for direct catalytic asymmetric aldol reaction

4.2.1. Aldol reaction with the first-generation catalyst (Table 3, entry 1). To a flame-dried 5 mL pear-shaped flask equipped with

a magnetic stirring bar and a 3-way glass stopcock was charged with 2,2,5,7,8-pentamethylchromanol (**4**) (88.1 mg, 0.40 mmol) and dried under vacuum for 60 min. Ar was back-filled to the flask and dry THF (2.0 mL) was added via a stainless steel needle and a syringe. To the solution was added ^{n}BuLi (247 μL, 0.40 mmol, 1.62 M in *n*-hexane) at −78 °C and stirred at the same temperature for 60 min to give 0.2 M lithium 2,2,5,7,8-pentamethylchromanolate solution in THF, which was stored at room temperature and used within 15 min.

To a flame-dried 5 mL pear-shaped flask equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (202.5 mg, 0.40 mmol) and $[Cu(CH_3CN)_4]PF_6$ (149.0 mg, 0.40 mmol) in a dry box. To the mixture was added THF (4.0 mL) via syringe to give 0.1 M THF solution of (*S*,*S*)-Ph-BPE/Cu solution, which was stored at room temperature and used within 3 h.

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were added (*S*,*S*)-Ph-BPE/Cu solution (0.1 M/THF, 200 μL, 0.02 mmol), dry DMF (2 mL), *N*,*N*-diallylthioacetamide (**1a**) (38.5 μL, 0.24 mmol) and 3-benzyloxypropanal (**2d**) (32.5 μL, 0.2 mmol) under Ar at room temperature. The test tube was cooled to −60 °C and lithium 2,2,5,7,8-pentamethylchromanolate (0.2 M/THF, 100 μL, 0.02 mmol) was added slowly. After 60 h of stirring at −60 °C, acetic acid in THF (0.1 M/THF, 0.2 mL, 0.02 mmol), satd NH_4Cl aq and bipyridine (3.1 mg, 0.02 mmol, essential to make sure the dissociation of the product from Cu complex) were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4. Filtrate was concentrated under reduced pressure. The chemical yield of **3ad** was determined by ^{1}H NMR analysis of the crude sample with $(CHCl_2)_2$ as an internal standard (43%). Enantiomeric excess was determined by HPLC analysis (90% ee).

4.2.2. Aldol reaction with the second-generation catalyst (Table 3, entry 15). To a flame-dried 5 mL pear-shaped flask equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (151.8 mg, 0.31 mmol) and mesitylcopper (56.7 mg, 0.31 mmol) in a dry box. To the mixture was added THF (1.0 mL) via syringe at 0 °C. After 10 min of stirring at room temperature, pale yellow 0.1 M THF solution of (*S*,*S*)-Ph-BPE/mesitylcopper solution was obtained, which was used within 15 min.

A 200 mL flask charged with MS 5A (6.10 g, 1.0 g/mmol aldehyde) equipped with a magnetic stirring bar and a 3-way glass stopcock was flame-dried under reduced pressure. After cooling to room temperature, dry DMF (30 mL), THF (27 mL), *N*,*N*-diallylthioacetamide (**1a**) (1.15 g, 7.31 mmol), and 3-benzyloxypropanal (**2d**) (1.0 g, 6.10 mmol) were added via syringe. The flask was cooled to −60 °C. To the resulting cooled solution was added (*S*,*S*)-Ph-BPE/mesitylcopper solution (0.1 M/THF, 3.05 mL, 0.305 mmol) dropwise to run the reaction. After 72 h of stirring at −60 °C, acetic acid solution in THF (0.1 M/THF, 3.1 mL, 0.31 mmol), satd NH_4Cl aq and bipyridine (47.6 mg, 0.305 mmol, essential to make sure the dissociation of the product from Cu complex) were added to the reaction mixture and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: *n*-hexane/EtOAc=5/1 to 2/1) to give **3ad** as a pale yellow oil (1.20 g, 62%). Enantiomeric excess was determined by HPLC analysis (83% ee).

*4.2.3. (R)-N,N-Diallyl-3-hydroxy-4-methylpentanethioamide (**3aa**).* Colorless oil; IR (neat) ν 3405, 2956, 2929, 2856, 1521, 1073, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86 (dddd, *J*=17.7, 10.4, 5.8, 5.8 Hz, 1H), 5.77 (dddd, *J*=17.1, 10.7, 4.6, 4.6 Hz, 1H), 5.29–5.12 (m, 4H), 4.69 (dd, *J*=14.7, 5.8 Hz, 1H), 4.57 (dd, *J*=14.7, 5.8 Hz, 1H), 4.29–4.22 (m, 1H), 4.14–4.08 (m, 1H), 3.90 (ddd, *J*=9.8, 5.5, 1.9 Hz, 1H), 3.70 (br s, 1H), 2.80 (dd, *J*=15.6, 1.9 Hz, 1H), 2.65 (dd, *J*=15.6, 9.8 Hz, 1H), 1.79–1.70 (m, 1H), 0.95 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 203.5, 130.6, 130.5, 118.6, 117.9, 74.6, 55.8, 52.9, 45.2, 33.3, 18.5, 17.8; $[\alpha]_D^{23}$ +92.1 (*c* 1.0, $CHCl_3$, 91% ee sample); ESI-MS *m*/*z* 250 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{12}H_{21}NNaOS$ *m*/*z* 250.1232 $[M+Na]^+$, found 250.1246; HPLC: DAICEL CHIRALCEL OD-H (ϕ 0.46 cm×25 cm), 2-propanol/*n*-hexane=1/99, flow rate 0.5 mL/min, detection at 254 nm, t_R=17.0 min (minor), 22.1 min (major).

*4.2.4. (S)-N,N-Diallyl-3-hydroxydecanethioamide (**3ab**).* Pale yellow oil; IR (neat) ν 3408, 3084, 2925, 2854, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.87 (dddd, *J*=17.1, 10.5, 5.9, 5.9 Hz, 1H), 5.77 (dddd, *J*=17.1, 10.4, 4.9, 4.9 Hz, 1H), 5.30–5.13 (m, 4H), 4.69 (dd, *J*=14.9, 5.9 Hz, 1H), 4.58 (dd, *J*=14.9, 5.9 Hz, 1H), 4.27–4.20 (m, 1H), 4.19–4.10 (m, 3H), 2.76 (dd, *J*=15.9, 1.9 Hz, 1H), 2.63 (dd, *J*=15.9, 9.6 Hz, 1H), 1.60–1.26 (m, 12H), 0.88–0.86 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 203.0, 130.6, 130.4, 118.7, 117.9, 69.9, 55.6, 52.8, 47.9, 36.6, 31.8, 29.6, 29.2, 25.6, 22.6, 14.1; $[\alpha]_D^{23}$ +74.0 (*c* 1.3, $CHCl_3$, 89% ee sample); ESI-MS *m*/*z* 306 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{16}H_{29}NNaOS$ *m*/*z* 306.1862 $[M+H]^+$, found 306.1859; HPLC: DAICEL CHIRALCEL OD-H (ϕ 0.46 cm×25 cm), 2-propanol/*n*-hexane=1/19, flow rate 0.5 mL/min, detection at 254 nm, t_R=10.4 min (minor), 12.5 min (major).

*4.2.5. (S)-10-(Diallylamino)-8-hydroxy-10-thioxodecyl benzoate (**3ac**).* Colorless oil; IR (neat) ν 3414, 2929, 2856, 1717, 1276 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, *J*=7.3 Hz, 2H), 7.54 (t, *J*=7.9 Hz, 1H), 7.43 (dd, *J*=7.9, 7.3 Hz, 2H), 5.88 (dddd, *J*=16.8, 10.7, 6.0, 6.0 Hz, 1H), 5.77 (dddd, *J*=17.1, 10.9, 4.5, 4.5 Hz, 1H), 5.81–5.73 (m, 1H), 5.29–5.13 (m, 4H), 4.69 (dd, *J*=14.9, 6.0 Hz, 1H), 4.59 (dd, *J*=14.9, 6.0 Hz, 1H), 4.31 (t, *J*=6.6 Hz, 2H), 4.25–4.09 (m, 3H), 3.50 (br s, 1H), 2.75 (dd, *J*=15.9, 1.5 Hz, 1H), 2.63 (dd, *J*=15.9, 9.5 Hz, 1H), 1.79–1.73 (m, 2H), 1.61–1.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 202.9, 166.6, 132.7, 130.6, 130.5, 130.5, 129.5, 128.3, 118.7, 117.9, 69.8, 65.0, 55.6, 52.8, 47.9, 36.5, 29.4, 29.2, 28.7, 25.9, 25.5; $[\alpha]_D^{23}$ +55.6 (*c* 1.2, $CHCl_3$, 90% ee sample); ESI-MS *m*/*z* 264 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{23}H_{33}NNaOS$ *m*/*z* 426.2062 $[M+Na]^+$, found 426.2081; HPLC: DAICEL CHIRALCEL OD-H (ϕ 0.46 cm×25 cm), 2-propanol/*n*-hexane=1/19, flow rate 1.0 mL/min, detection at 254 nm, t_R=13.6 min (minor), 17.0 min (major).

*4.2.6. (R)-N,N-Diallyl-5-(benzyloxy)-3-hydroxypentanethioamide (**3ad**).* Pale yellow oil; IR (neat) ν 3413, 3085, 2919, 2861, 1643, 1496, 1411 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34–7.29 (m, 5H), 5.86 (dddd, *J*=5.7, 5.7, 10.3, 17.2 Hz, 1H), 5.73 (dddd, *J*=5.0, 5.0, 10.3, 17.2 Hz, 1H), 5.26–5.09 (m, 4H), 4.75 (dd, *J*=5.7, 14.7 Hz, 1H), 4.54–4.50 (m, 1H), 4.51 (s, 2H), 4.41–4.35 (m, 1H), 4.32–4.25 (m, 1H), 4.10–4.04 (m, 1H), 3.71–3.68 (m, 2H), 2.84 (dd, *J*=2.8, 15.4 Hz, 1H), 2.76 (dd, *J*=8.7, 15.4 Hz, 1H), 1.91–1.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 202.5, 138.1, 130.5, 130.5, 130.5, 128.3, 127.6, 127.5, 118.4, 117.7, 73.1, 69.0, 67.9, 55.5, 52.8, 48.3, 36.3; $[\alpha]_D^{22}$ −33.9 (*c* 0.33, $CHCl_3$, 92% ee sample); ESI-MS *m*/*z* 342.2 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{18}H_{25}NNaO_2S$ *m*/*z* 342.1498 $[M+Na]^+$, found; 342.1500.

4.3. Synthesis of atorvastatin

4.3.1. (R)-N,N-Diallyl-5-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy) pentanethioamide. To a stirred solution of **3ad** (800 mg, 2.5 mmol, 92% ee sample) in CH_2Cl_2 (30 mL) were added 2,6-lutidine (575 μL, 5.0 mmol) and TBSOTf (860 μL, 3.75 mmol) at 0 °C. After stirring the resulting solution at room temperature for 3 h, satd NH_4Cl aq was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give the title compound as a pale yellow oil (1.04 g, 96%). Pale

yellow oil; IR (neat) ν 2954, 2858, 1643, 1493, 1257, 1115 cm^{-1}; ^1H NMR ($CDCl_3$); δ 7.33–7.29 (m, 5H), 5.92 (dddd, J=5.8, 5.8, 10.8, 16.7 Hz, 1H), 5.75 (dddd, J=4.8, 4.8, 10.3, 17.2 Hz, 1H), 5.25–5.08 (m, 4H), 4.83 (dd, J=5.7, 14.2 Hz, 1H), 4.61–4.53 (m, 2H), 4.48 (dd, J=3.0, 15.1 Hz, 1H), 4.34 (dd, J=6.9, 14.2 Hz, 1H), 4.00–3.95 (m, 1H), 3.64–3.51 (m, 2H), 3.10 (dd, J=8.2, 13.8 Hz, 1H), 2.83 (dd, J=4.1, 13.8 Hz, 1H), 1.90–1.86 (m, 2H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.0, 138.6, 131.5, 131.3, 128.3, 127.6, 127.5, 119.3, 117.6, 73.0, 72.1, 66.5, 56.4, 53.1, 50.2, 37.4, 25.9, 25.7, 25.6, 17.9, −4.3, −4.8; $[\alpha]_D^{22}$ +6.8 (c 1.0, $CHCl_3$); ESI-MS m/z 456.3 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{24}H_{39}NNaO_2SSi$ m/z 456.2363 m/z $[M+Na]^+$, found; 456.2358.

*4.3.2. (R)-tert-Butyl 7-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-3-oxoheptanoate (**12**).* To a solution of TBS protected **3ad** (920 mg, 2.12 mmol) in dry ether (23 mL) was added MeOTf (467 μL, 4.24 mmol) at 0 °C. After stirring the resulting solution at room temperature for 4.5 h, the reaction mixture was cooled to −78 °C. To the mixture was added $CH_2{=}C(OLi)O^tBu$ (640 μL, 1.0 M in THF, 6.40 mmol) and resulting solution was stirred for 3 h. The reaction was quenched with silica gel (5 g) at −78 °C and diluted with CH_2Cl_2 (7 mL). The resulting mixture was stirred at room temperature for 1.5 h, then filtered through a short pad of silica gel with CH_2Cl_2 as eluent. The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in THF (20 mL). To the solution was added 1 N HCl aq (2 mL) at room temperature and the resulting solution was stirred for 30 min at the same temperature. The mixture was diluted with ethyl acetate, and resulting biphasic mixture was washed with satd $NaHCO_3$ aq and brine, then dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent n-hexane/ethyl acetate=20/1) to give **12** as a colorless oil (821 mg, 72% over two steps). Colorless oil; IR (neat) ν 2954, 2931, 2858, 1739, 1716, 1647, 1458, 1369, 1254, 1146, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) keto form; δ 7.36–7.28 (m, 5H), 4.50 (s, 2H), 4.50–4.43 (m, 1H), 3.56–3.48 (m, 2H), 3.34 (s, 2H), 2.69 (d, J=6.4 Hz, 2H), 1.81–1.77 (m, 2H), 1.45 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); enol form; δ 12.15 (br s, 1H), 7.36–7.28 (m, 5H), 4.90 (s, 1H), 4.33 (s, 2H), 4.35–4.31 (m, 1H), 3.56–3.48 (m, 2H), 2.29 (d, J=6.6 Hz, 2H), 1.77–1.73 (m, 2H), 1.47 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) keto-enol mixture; δ 202.1, 166.3, 138.4, 128.3, 127.6, 127.5, 113.9, 92.8, 81.8, 80.6, 73.0, 73.0, 72.9, 67.2, 66.6, 66.4, 52.0, 50.3, 43.8, 37.3, 37.2, 28.6, 28.3, 28.0, 25.8, 17.9, −4.7, −4.8, −4.9; $[\alpha]_D^{22}$ −7.6 (c 0.5, $CHCl_3$); ESI-MS m/z 459.3 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{24}H_{40}NaO_5Si$ m/z 459.2537 $[M+Na]^+$, found; 459.2534.

*4.3.3. tert-Butyl 2-((4R,6R)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**13**).* A solution of **12** (400 mg, 0.916 mmol) and dry THF (2.5 mL) was cooled to 0 °C, then TBAF (1.30 mL, 1.0 M in THF, 1.30 mmol) was added dropwise. After 30 min of stirring at the same temperature, the resulting mixture was stirred at room temperature for 3 h, then water (2 mL) was added and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, then dried over Na_2SO_4. Filtrate was concentrated under reduced pressure and the resulting pale yellow residue (98% of the crude residue was used) was dissolved in THF (8.5 mL) and MeOH (2.4 mL). The solution was cooled to −80 °C and diethylmethoxyborane (1.0 mL, 1.0 M in THF, 1.0 mmol) was slowly added at the same temperature. After 10 min of stirring, sodium borohydride (37.8 mg, 1.0 mmol) was added and the resulting mixture was stirred for 10 h at the same temperature. The reaction was quenched with acetic acid (2 mL) and the resulting mixture was diluted with ethyl acetate, which was washed with satd $NaHCO_3$ aq and brine, then dried over Na_2SO_4. Filtrate was concentrated under reduced pressure to give crude *syn*-diol, which (93% of the crude material was used) was dissolved in acetone (2.6 mL). After the addition of *p*-toluenesulfonic acid monohydrate (16.0 mg, 0.084 mmol) and 2,2-dimethoxypropane (205 μL, 1.68 mmol), the resulting solution was stirred for 4 h at room temperature. After the reaction was completed, satd $NaHCO_3$ aq was added to neutrality. The resulting mixture was extracted with ether, and the combined organic phase was washed with brine, then dried over Na_2SO_4. Filtrate was concentrated under reduced pressure to give **13** as a colorless oil (294 mg, 88% over three steps). Colorless oil; IR (neat) ν 2954, 2931, 2858, 1739, 1716, 1647, 1458, 1369, 1254, 1146, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.27 (m, 5H), 4.50 (dd, J=4.8, 12.1 Hz, 2H), 4.28–4.21 (m, 1H), 4.09–4.03 (m, 1H), 3.62–3.50 (m, 2H), 2.42 (dd, J=7.1, 15.1 Hz, 1H), 2.29 (dd, J=6.2, 15.1 Hz, 1H), 1.81–1.68 (m, 2H), 1.56 (dt, J=2.3, 12.6 Hz, 1H), 1.44 (s, 9H), 1.44 (s, 3H), 1.35 (s, 3H), 1.21–1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.3, 138.5, 128.4, 127.6, 127.5, 98.7, 80.5, 73.0, 66.3, 66.2, 66.0, 42.8, 36.6, 36.5, 30.1, 28.1, 19.6; $[\alpha]_D^{22}$ +21.9 (c 0.26, $CHCl_3$); ESI-MS m/z 387.2 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{21}H_{32}NaO_5$ m/z 387.2142 $[M+Na]^+$, found; 387.2140.

*4.3.4. tert-Butyl 2-((4R,6R)-2,2-dimethyl-6-(2-(tosyloxy)ethyl)-1,3-dioxan-4-yl)acetate (**14**).* A solution of **13** (153 mg, 0.419 mmol) containing 20% $Pd(OH)_2$ on carbon (25 mg), ethyl acetate (1.5 mL) was stirred under H_2 atmosphere for 24 h at 60 °C. After cooling, the catalyst was filtrated, and the filtrate was concentrated in vacuo. The crude was dissolved in CH_2Cl_2 (2.5 mL). After the addition of Et_3N (175 μL, 1.25 mmol), DMAP (15.3 mg, 0.417 mmol), and *p*-toluenesulfonyl chloride (159.3 mg, 0.834 mmol) in one portion at 0 °C, the reaction mixture was stirred at room temperature for 4 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and water (10 mL), and the organic layer was washed with satd $NaHCO_3$ aq and dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was purified by flash chromatography (n-hexane/ethyl acetate=10/1–5/1) to afford tosylate **14** (165.1 mg, 91% over two steps). Colorless oil; IR (neat) ν 2981, 1728, 1365, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (d, J=8.2 Hz, 2H), 7.79 (d, 4H), 7.34 (d, J=8.2 Hz, 2H), 4.26–4.13 (m, 2H), 4.11–4.06 (m, 1H), 3.97–3.91 (m, 1H), 2.45 (s, 3H), 2.39 (dd, J=7.1, 15.1 Hz, 1H), 2.26 (dd, J=6.2, 15.1 Hz, 1H), 1.84–1.67 (m, 2H), 1.51–1.45 (m, 2H), 1.44 (s, 9H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1, 144.7, 133.0, 129.8, 127.9, 98.8, 80.6, 66.7, 66.0, 64.7, 42.6, 36.2, 35.4, 29.9, 28.1, 21.6, 19.5; $[\alpha]_D^{22}$ +12.9 (c 0.9, $CHCl_3$); ESI-MS m/z 451.2 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{21}H_{32}NaO_7S$ m/z 451.1761 $[M+Na]^+$, found; 451.1756.

4.3.5. tert-Butyl 2-((4R,6R)-6-(2-azidoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate. A mixture of tosylate **14** (120.0 mg, 0.277 mmol) and sodium azide (36.0 mg, 0.555 mmol) in DMF (1.5 mL) was stirred for 6 h at room temperature. The reaction mixture was diluted with water (1 mL) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave crude azide, which was purified by a short pad of silica gel (n-hexane/ethyl acetate=2/1) to afford azide as colorless oil (67.8 mg, 82%). Colorless oil; IR (neat) ν 2978, 2939, 2877, 2098, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37–4.30 (m, 1H), 4.12–4.06 (m, 1H), 3.48–3.41 (m, 2H), 2.37 (dd, J=5.5, 14.9 Hz, 1H), 2.33 (dd, J=7.6, 14.9 Hz, 1H), 1.80–1.65 (m, 2H), 1.66 (dt, 2.5, 12.6 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 9H), 1.32 (s, 3H), 1.22–1.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.1, 98.8, 80.6, 66.1, 65.8, 47.5, 42.6, 36.4, 35.6, 30.0, 28.1, 19.6; $[\alpha]_D^{22}$ +17.9 (c 0.21, $CHCl_3$); ESI-MS m/z 322.2 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{14}H_{25}N_3NaO_4$ m/z 322.1737 $[M+Na]^+$, found; 322.1737.

*4.3.6. tert-Butyl 2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**15**).* To a solution of azide (52.1 mg, 0.174 mmol) in a mixture of THF (1.0 mL) and water (0.1 mL), triphenylphosphine (91.3 mg, 0.348 mmol) was added and the

resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated to remove THF, followed by coevaporation with toluene two times. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N, 95:4:1) to give amine **15** as colorless oil (41.2 mg, 87%). Colorless oil; IR (neat) ν 3374, 2981, 2938, 2873, 1731, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25–4.19 (m, 1H), 3.98–3.92 (m, 1H), 2.80–2.77 (m, 2H), 2.39 (dd, J=6.9, 15.1 Hz, 1H), 2.26 (dd, J=6.2, 15.1 Hz, 1H), 1.95 (br s, 2H), 1.64–1.50 (m, 3H), 1.42 (s, 9H), 1.42 (s, 3H), 1.33 (s, 3H), 1.30–1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.2, 98.6, 80.5, 67.4, 66.2, 42.6, 39.5, 38.4, 36.5, 30.1, 28.0, 19.7; $[\alpha]_D^{22}$ +11.5 (c 0.28, $CHCl_3$); ESI-MS m/z 274.2 $[M+H]^+$; HRMS (ESI) Anal. Calcd for $C_{14}H_{28}NO_4$ m/z 274.2013 $[M+H]^+$, found; 274.2015.

4.3.7. (3R,5R)-7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid (atorvastatin). A mixture of amine **15** (40.2 mg, 0.147 mmol), diketone **16** (55.8 mg, 0.133 mmol), pivalic acid (12.0 mg, 0.118 mmol) in *n*-hexane/toluene/THF=1:4:1 (0.48 mL) was heated at 110 °C for 30 h under Ar. After cooling to room temperature, the mixture was diluted with AcOEt and washed with satd $NaHCO_3$ aq, then dried over Na_2SO_4. The resulting residue after evaporation was dissolved in THF (0.5 mL). To the solution was added 2 N HCl in MeOH (1 mL) at 0 °C and the resulting solution was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2, and resulting biphasic mixture was separated. Organic layer was washed with satd $NaHCO_3$ aq and brine, then dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in wet THF (0.2 mL). 1 N NaOH aq (2 mL) was added at 0 °C and the resulting solution was stirred at room temperature for 6 h. The mixture was diluted with CH_2Cl_2 and 1N HCl aq. The resulting biphasic mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, then dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting solid residue was purified by flash chromatography (CH_2Cl_2/MeOH 18/1) on silica gel to give atorvastatin as a colorless solid. (54.8 mg, 67% over three steps). Colorless solid; IR (KBr) ν 3410, 2964, 2929, 1731, 1652, 1529, 1508, 1438, 1315, 1241, 1226 cm^{-1}; ^1H NMR (CD_3OD) δ 7.30–7.29 (m, 2H), 7.25–7.20 (m, 4H), 7.15–7.13 (m, 2H), 7.11–7.02 (m, 6H), 4.08 (ddd, J=5.3, 7.8, 16.0 Hz 1H), 4.02–3.98 (m, 1H), 3.91 (ddd, J=5.3, 7.6, 16.0 Hz, 1H), 3.69–3.63 (m, 1H), 3.40–3.34 (m, 1H), 2.41 (dd, J=5.2, 15.5 Hz, 1H), 2.35 (dd, J=7.6, 15.5 Hz, 1H), 1.75–1.6 (m, 2H), 1.56–1.51 (m, 1H), 1.49 (d, J=7.1 Hz, 3H), 1.48 (d, J=7.1 Hz, 3H), 1.47–1.43 (m, 1H); ^{13}C NMR (CD_3OD) δ 175.9, 169.5, 163.8 ($^1J_{CF}$=245.5 Hz), 139.9, 139.1, 139.1, 136.4, 134.7 ($^3J_{CF}$=7.2 Hz), 131.0, 130.3 ($^4J_{CF}$=2.9 Hz), 129.6, 128.9, 126.9, 125.2, 123.3, 121.5, 118.1, 116.3 ($^2J_{CF}$=21.6 Hz), 68.6, 67.9, 44.2, 43.3, 42.2, 40.1, 27.7, 22.9, 22.8; ^{19}F NMR ($CDCl_3$) δ −113.8; $[\alpha]_D^{23}$ +5 (c 0.94, CH_3OH); ESI-MS m/z 581.2 $[M+Na]^+$; HRMS (ESI) Anal. Calcd for $C_{33}FH_{35}N_2NaO_5$ m/z 581.2422 $[M+Na]^+$, found; 581.2421.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.109.

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