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COMMUNICATION

Catalytic asymmetric aza-Michael addition of fumaric monoacids with multifunctional thiourea/boronic acids

Kenichi Michigami, Hiroki Murakami, Takeru Nakamura, Noboru Hayama, and Yoshiji Takemoto*

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The first chemical enantioselective synthesis of *N*-hydroxyaspartic acid derivatives using chiral multifunctional thiourea/boronic acid organocatalysts was developed. A series of fumaric monoacids underwent an intermolecular asymmetric aza-Michael addition of *O*-alkyl hydroxylamines in excellent regioselectivity. The addition of another carboxylic acid raised the enantiomeric enrichment up to 97% ee. *O*-Deprotection of the aza-Michael adduct provided an aspartate-derived hydroxylamine fragment applicable for KAHA (α -keto acid-hydroxylamine) ligation.

Chemoselective peptide conjunction by enzymes is a ubiquitous process in nature, producing only recyclable phosphates as by-products.¹ Meanwhile, a general chemical approach for the amide C–N bond formation is based on stoichiometric activation of carboxylic acids by coupling reagents.² Though this method is highly reliable, reagent-derived non-recyclable side products are inevitably generated. In addition, protection of nucleophilic functional groups is required due to incompatibility with condensation reagents. The development of environmentally benign alternatives is thus highly demanded.³ Among large numbers of strategies reported to circumvent these issues, elegant examples have been disclosed in recent years by Bode and co-workers. The protocol of simply mixing α -keto acids and hydroxylamines in aqueous solvent under mild conditions afford amides concomitant with the release of carbon dioxide (CO₂) and water.⁴ This clean amide synthesis, KAHA ligation, has manifested significant advantages in polypeptide synthesis because the connection of peptide segments proceeds without protection of side chains and the loss of enantiopurity.^{4a} However, low accessibility of both α -keto acids and hydroxylamines underlies a major problem that affects the practical convenience. In marked contrast to α -amino acid-derived α -keto acids,⁵ synthetic

research for hydroxylamine counterparts is still less exploited:⁶ only a few simple derivatives including cyclic analogues of homoserine, serine, and aspartic acid semialdehyde (Asa) have been synthesised and applied to KAHA peptide ligation (Scheme 1A).^{4b,6d,7} Since these nucleophiles require long-step routes for preparation, a straightforward and enantioselective synthesis of such hydroxylamines represents a major challenge for KAHA strategy in view of general peptide synthesis.

(A) Precedented Hydroxylamine Fragments for KAHA Peptide Ligation

(B) Catalytic Asymmetric Aza-Michael Addition of α,β -Unsaturated Carboxylic Acids

Scheme 1. Strategy for the Synthesis of α -Amino Acid-Derived Hydroxylamines for KAHA Peptide Ligation

We have recently focused on a direct catalytic asymmetric aza-Michael addition of BnONH₂ to α,β -unsaturated carboxylic acids using organocatalysts consisting of arylboronic acid and chiral *trans*-1,2-cyclohexanediamine-based aminothiourea (Scheme 1B).^{8–10} Notably, our multifunctional catalysts only promoted 1,4-addition: The 1,2-adducts, *N*-benzyloxyamides, which are usually formed in organoboron-catalysed dehydrative amidation,¹¹ were

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not observed. Encouraged by the efficient protocols free from “pre-activation” and “protection” of carboxylic acids,¹² we targeted *N*-hydroxyaspartic acid derivatives to demonstrate synthetic versatility of our catalytic systems. Although biocatalytic synthesis of enantiopure *N*-hydroxy and *N*-alkoxyaspartates have been reported,¹³ chemical methods are still under developed, and to the best of our knowledge, no example has emerged for catalytic asymmetric variant.¹⁴ Herein, we report the asymmetric synthesis of *N*-hydroxyaspartic acid derivatives catalysed by multifunctional thiourea/boronic acids, which would offer a new, facile access to aspartate-derived hydroxylamine fragments suitable for KAHA peptide ligation.

First, initial investigations focused on catalytic asymmetric aza-Michael addition using mono-*tert*-butyl fumarate (**1a**) and *O*-benzylhydroxylamine (**2a**) as a nucleophile. In line with our previous studies, a chiral integrated thiourea/boronic acid catalyst **A** was employed in the presence of 4 Å molecular sieves (4 Å MS) at room temperature.^{8c} Though no reaction took place in DMF and MeCN (Table 1, entries 1 and 2), the reaction in less polar solvents, Et₂O and CH₂Cl₂, furnished the corresponding *N*-benzyloxyaspartic acid diester **3aa** after treatment with TMSCHN₂ (entries 3 and 4). When the reaction was conducted in toluene, both the yield and ee drastically increased (entry 5). CCl₄ was found to be the optimal solvent, providing **3aa** in 80% yield and 88% ee (entry 6). Next, thiourea moiety of the catalyst was deviated. Loss of both yields and ees was observed with electron-withdrawing thioureas **B** and **C** (entries 7 and 8). The *ortho*-Me substituted catalyst **D** gave slightly higher ee, but the yield dropped to 59%. *N*-Methyl thiourea catalyst **E** also promoted the reaction, albeit in moderate yield and ee (entry 10). Therefore, we continued the following experiments with catalyst **A**. Afterwards, a range of carboxylic acid was employed as additives, since our previous works suggested three molecules of carboxylic acid were involved in catalytic cycle: Two of them bind to the catalyst and the other one works as a proton shuttle (*vide infra*).^{8c} No reaction occurred with 1 equivalent of HCO₂H, and AcOH or ^tBuCO₂H did not exhibit beneficial effects. Meanwhile, both the yield and ee improved with PhCO₂H, affording **3aa** in 88% yield and 93% ee (entry 14). In sharp contrast, a highly acidic *p*-TsOH inhibited the reaction completely, probably due to the protonation of the nucleophile and/or the catalyst (entry 15). Control experiments revealed that both the catalyst and 4 Å MS were essential for the reaction (entries 16 and 17). All reactions proceeded at β position of the carboxylic acid exclusively, which indicates that the carboxylic acid was predominantly activated *in situ* by boronic acid over the alkyl ester moiety.¹⁵

Table 1. Optimisation of the Reaction Conditions.

entry	catalyst	additive	solvent	3aa (%) ^a	ee (%) ^b
1	A	-	DMF	0	-
2	A	-	MeCN	0	-
3	A	-	Et ₂ O	22	28
4	A	-	CH ₂ Cl ₂	10	47

5	A	-	toluene	60	69
6	A	-	CCl ₄	80	88
7	B	-	CCl ₄	66	80
8	C	-	CCl ₄	72	76
9	D	-	CCl ₄	59	90
10	E	-	CCl ₄	62	80
11	A	HCO ₂ H	CCl ₄	0	-
12	A	MeCO ₂ H	CCl ₄	57	91
13	A	^t BuCO ₂ H	CCl ₄	77	87
14	A	PhCO ₂ H	CCl ₄	88	93
15	A	<i>p</i> -TsOH·H ₂ O	CCl ₄	0	-
16	none	-	CCl ₄	0	-
17 ^c	A	-	CCl ₄	0	-

Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol, 1.1 equiv), catalyst (0.010 mmol, 10 mol%), additive (0.10 mmol, 1.0 equiv), 4 Å MS (50 mg), solvent (1.0 mL, 0.1 M), rt, 24 h. ^aIsolated yields are shown. ^bEes were estimated by chiral HPLC analysis. ^cThe reaction was performed without 4 Å MS.

With the optimal conditions in hand, we next explored the substrate scope of the aza-Michael addition of fumaric acid monoesters with **2a** in the presence of catalyst **A**. (Figure 1). Benzyl ester **1b** and ethyl ester **1c** were converted into the corresponding aspartates **3ba** and **3ca**, respectively in moderate yields with high ees. Remarkably, in addition to fumaric acid monoesters, phenylalanine-derived fumaric acid monoamides **1d** and **1e** underwent the aza-Michael addition. By employing catalyst **A** with (*R,R*) configuration, D-Phe-D-Asp derivative **3ea** was furnished in higher diastereoselectivity than that of L-Phe-D-Asp derivative **3da**. The catalyst was switched to (*S,S*)-**A** (**ent-A**) for the reaction of *N*-fumaryl-L-amino esters **1f** and **1g**, producing Gly-L-Asp and L-Ser-L-Asp derivatives **3fa** and **3ga**, respectively. Even though the stereoselectivity is moderate, these results suggest the feasibility of the synthesis of *N*-hydroxyaspartate-derived peptides through this protocol.

Figure 1. Substrate scope of fumaric monoacids (0.40 mmol). Isolated yields are shown. Ees were estimated by chiral HPLC analysis. ^aDr was determined by ^1H NMR analysis. ^bent-**A** was used as a catalyst.

The efficiency and high stereoselectivity of the aza-Michael addition of BnONH_2 led us to the examination of various *O*-substituted hydroxylamines. To evaluate *O*-substituent effect of nucleophiles **2a–2e** on ee, the aza-Michael addition of **1a** was examined under the optimal conditions (Figure 2). The use of electron-rich hydroxylamine **2b** resulted in lower yield and enantioselectivity, whereas electron-deficient *p*- CF_3 substituted nucleophile **2c** gave **3ac** in 96% ee. Besides, acetal-protected nucleophiles such as BOMONH_2 (**2d**) and SEMONH_2 (**2e**) were also competent nucleophiles, affording the corresponding adducts **3ad** and **3ae** in good yields and enantioselectivities.

Figure 2. Screening of Nucleophiles (0.20–0.40 mmol). Isolated yields are shown. Ees were estimated by chiral HPLC analysis. ^aEe was determined after *N*-benzoylation.

Based on the experimental results, including perfect regioselectivity and mechanistic studies performed previously,^{8c} a proposed transition state of the addition of hydroxylamine is depicted in Figure 3. Since no reaction occurred in the absence of $4 \text{ \AA MS}$ (Table 1, entry 17), removal of water is indispensable for this reaction. In a plausible intermediate containing diacyloxyboronate, the hydrogen-bond interaction between the thiourea NH protons and one of the carboxy group facilitates conjugate addition of hydroxylamine. The high enantioselectivity would be attributed to an additional interaction between the nucleophile NH proton and another carboxy ligand, accelerating *Re*-face attack of hydroxylamine. The nucleophilic addition is

accompanied with intermolecular proton transfer, which is promoted by the third molecule of carboxylic acid.

Figure 3. Proposed Transition State of Nucleophilic Addition.

A quick access to various chiral *N*-alkoxyaspartate derivatives prompted us to examine *O*-deprotection of the Michael adducts for the application to KAHA ligation. Various deprotection conditions tested revealed that compound **3be**, obtained from **1b** and **2e**, was the substrate of choice. First, treatment of **3be** with TFA and subsequent careful quenching with water gave an OH-free hydroxylamine **4b** in 42% yield.^{15,16} The following KAHA ligation using α -keto acid **5** proceeded smoothly and the corresponding amide **6b** was obtained without significant loss of enantiomeric excess.^{7a} The same reaction with Fmoc-L-leucine-derived α -keto acid **7**¹⁷ also afforded dipeptide **8b** in moderate yield without epimerisation.

Scheme 3. *O*-Deprotection and KAHA Ligation of Aspartate-Derived Hydroxylamine Derivatives

In summary, we have developed a direct aza-Michael addition of hydroxylamine derivatives to various fumaric monoacids catalysed by multifunctional thiourea/boronic acids. The process enables the first catalytic asymmetric chemical synthesis of *N*-hydroxyaspartic acid derivatives with perfect regioselectivity and high enantioselectivity. Deprotection of the SEMONH_2 -adduct provides a new aspartate-derived hydroxylamine fragment for KAHA peptide ligation. Further research into the synthetic application is actively ongoing, and the results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

This paper is dedicated to the memory of our talented colleague, Mr. Takeru Nakamura, who passed away on 25 October, 2017. This work was financially supported by JSPS KAKENHI, Grant No. JP16H06384.

Notes and references

- Recent reviews on enzymatic amide C–N bond formation: (a) K. Yazawa, K. Numata, *Molecules*, 2014, **19**, 13755; (b) A. Goswami, S. G. V. Lanen, *Mol. Biosyst.*, 2015, **11**, 338; (c) J. Pitzer, K. Steiner, *J. Biotechnol.*, 2016, **235**, 32; (d) M. Winn, J. K. Fyans, Y. Zhuo, J. Micklefield, *Nat. Prod. Rep.*, 2016, **33**, 317. (e) R. D. Süßmuth, A. Mainz, *Angew. Chem., Int. Ed.*, 2017, **56**, 3770.
- Selected reviews on amide synthesis using coupling reagents: (a) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron*, 2005, **61**, 10827; (b) E. Valeur, M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (c) A. El-Faham, F. Albericio, *Chem. Rev.*, 2011, **111**, 6557.
- A recent review on nonclassical amidation: (a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (b) R. M. de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029.
- (a) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem., Int. Ed.*, 2006, **45**, 1248; (b) A. K. Sanki, R. S. Talan, S. J. Sucheck, *J. Org. Chem.*, 2009, **74**, 1886; (c) I. Pusterla, J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 513.
- (a) L. Ju, A. R. Lippert, J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 4253; (b) L. Ju, J. W. Bode, *Org. Biomol. Chem.*, 2009, **7**, 2259; (c) T. J. Harmand, S. S. Kulkarni, J. W. Bode, *Tetrahedron Lett.*, 2015, **56**, 3477.
- Selected examples of the synthesis of α -amino acid-derived hydroxylamines. (a) G. Grundke, W. Keese, M. Rimper, *Synthesis*, 1987, 1115; (b) W. Oppolzer, O. Tamura, *Tetrahedron Lett.*, 1990, **31**, 991. (c) M. D. Wittman, R. L. Halcomb, S. J. Danishefsky, *J. Org. Chem.* 1990, **55**, 1981; (d) S. I. Medina, J. Wu, J. W. Bode, *Org. Biomol. Chem.*, 2010, **8**, 3405; (e) C. D. McCune, S. J. Chan, M. L. Beio, W. Shen, W. J. Chung, L. M. Szczesniak, C. Chai, S. Q. Koh, P. T.-H. Wong, D. B. Berkowitz, *ACS Cent. Sci.*, 2016, **2**, 242.
- Selected examples of the synthesis and applications of α -amino acid-derived cyclic hydroxylamines: (a) V. R. Pattabiraman, A. O. Ogunkoya, J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 5114; (b) C. E. Murar, F. Thuaud, J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 18140; (c) I. Pusterla, J. W. Bode, *Nat. Chem.*, 2015, **7**, 668; (d) C. E. Murar, T. J. Harmand, J. W. Bode, *Bioorg. Med. Chem.*, 2017, **25**, 4996; (e) T. J. Harmand, C. E. Murar, H. Takano, J. W. Bode, *Org. Synth.* 2018, **95**, 142; (f) C. E. Murar, T. J. Harmand, H. Takano, J. W. Bode, *Org. Synth.* 2018, **95**, 157. (g) S. Baldauf, J. W. Bode, *Synthesis*, 2019, DOI: 10.1055/s-0037-1611635.
- (a) T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma, Y. Takemoto, *Org. Lett.*, 2014, **16**, 4256; (b) N. Hayama, T. Azuma, Y. Kobayashi, Y. Takemoto, *Chem. Pharm. Bull.*, 2016, **64**, 704; (c) N. Hayama, R. Kuramoto, T. Földes, K. Nishibayashi, Y. Kobayashi, I. Pápai, Y. Takemoto, *J. Am. Chem. Soc.* 2018, **140**, 12216.
- Selected examples of catalytic transformation of carboxylic acids without converting the acid moieties: (a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510; (b) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem., Int. Ed.*, 2008, **47**, 2876; (c) H. Zheng, R. McDonald, D. G. Hall, *Chem. Eur. J.*, 2010, **16**, 5454; (d) Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.*, 2015, **137**, 7075; (e) H. Nagai, Y. Morita, Y. Shimizu, M. Kanai, *Org. Lett.*, 2016, **18**, 2276; (f) M. Simonetti, D. M. Cannas, A. Panigrahi, S. Kujawa, M. Kryjewski, P. Xie, I. Larrosa, *Chem. Eur. J.*, 2017, **23**, 549 and references cited therein.
- Recent reviews on aza-Michael Addition: (a) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.*, 2009, **15**, 11058; (b) P. R. Krishna, A. Sreeshailam, R. Srinivas, *Tetrahedron*, 2009, **65**, 9657; (c) Z. Amara, J. Caron, D. Joseph, *Nat. Prod. Rep.*, 2013, **30**, 1211; (d) J. Gmach, Ł. Joachimiak, K. M. Błażewska, *Synthesis*, 2016, **48**, 2681.
- Selected examples of organoboron-catalysed dehydrative amidation: (a) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196; (b) K. Arnold, B. Davies, D. Héroult, A. Whiting, *Angew. Chem., Int. Ed.*, 2008, **47**, 2673; (c) P. Starkov, T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320; (d) N. Gernigon, R. M. Al-Zoubi, D. G. Hall, *J. Org. Chem.*, 2012, **77**, 8386; (e) T. M. E. Dine, W. Erb, Y. Berhault, J. Rouden, J. Blanchet, *J. Org. Chem.*, 2015, **80**, 4532; (f) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki, N. Kumagai, *Nat. Chem.*, 2017, **9**, 571. (g) K. Wang, Y. Lu, K. Ishihara, *Chem. Commun.*, 2018, **54**, 5410. (h) D. N. Sawant, D. B. Bagal, S. Ogawa, K. Selvam, S. Saito, *Org. Lett.* 2018, **20**, 4397.
- Selected examples of Michael addition of α,β -unsaturated carboxylic acid derivatives: (a) Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.*, 2004, **6**, 1861; (b) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13419; (c) S. Kikuchi, H. Sato, S. Fukuzawa, *Synlett*, 2006, 1023; (d) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.*, 2007, **129**, 8064; (e) M. Weiß, S. Borchert, E. Rémond, S. Jugé, H. Gröger, *Heteroatom. Chem.*, 2012, **23**, 202; (f) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem., Int. Ed.*, 2013, **52**, 11114 and references cited therein.
- (a) M. S. Gulzar, M. Akhtar, D. Gani, *J. Chem. Soc., Chem. Commun.*, 1994, 1601; (b) B. Weiner, G. J. Poelarends, D. B. Janssen, B. L. Feringa, *Chem. Eur. J.*, 2008, **14**, 10094; (c) V. P. Veetil, H. Raj, M. de Villiers, P. G. Tepper, F. J. Dekker, W. J. Quax, G. J. Poelarends, *ChemCatChem*, 2013, **5**, 1325.
- (a) J. E. Baldwin, L. M. Harwood, M. J. Lombard, *Tetrahedron*, 1984, **40**, 4363; (b) T. Kolasa, *Can. J. Chem.*, 1985, **63**, 2139; (c) R. W. Feenstra, E. H. M. Stokkingreef, R. J. F. Nivard, H. C. J. Ottenheijm, *Tetrahedron*, 1988, **44**, 5583; (d) S. B. McNabb, M. Ueda, T. Naito, *Org. Lett.*, 2004, **6**, 1911; (e) N. Tibrewal, G. I. Elliott, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 517.
- For the details of optimisations, see the Supporting Information.
- R. H. Schlessinger, M. A. Poss, S. Richardson, *J. Am. Chem. Soc.*, 1986, **108**, 3112.
- (a) F. Thuaud, F. Rohrbacher, A. Zwicky, J. W. Bode, *Helv. Chim. Acta*, 2016, **99**, 868. (b) T. Nanjo, N. Kato, Y. Takemoto, *Org. Lett.*, 2018, **20**, 5766.

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Supporting Information

Table of Contents

(A)	Supplemental Data	
(A-1)	Optimisation Details: Tables S1-S6	S3
(A-2)	Determination of Stereochemistry	S5
(B)	General	S6
(C)	Materials and Methods	
(C-1)	Preparation of Substrates	S7
(C-2)	Preparation of Nucleophiles	S10
(C-3)	General Procedure for Catalytic Aza-Michael Addition	S12
(D)	<i>O</i> -Deprotection and KAHA Ligation	S18
(E)	References	S20
(F)	¹ H NMR and ¹³ C NMR Spectra	S21
(G)	HPLC Traces	S87

(A) Supplemental Data

(A-1) Optimisation Details: Tables S1-S8

Several reaction parameters of the enantioselective aza-Michael addition were investigated. In each tables are described isolated yields.

Table S1. Investigation of Solvent Effect

entry	solvent	3aa (%)	ee (%)	entry	solvent	3aa (%)	ee (%)
1	DMF	0	-	7	hexane	35	38
2	MeCN	0	-	8	<i>CCl</i> ₄	70	88
3	EtOAc	0	-	9	C ₂ Cl ₄	70	81
4	Et ₂ O	22	28	10	4-F ₃ CC ₆ H ₄ Cl	55	73
5	CH ₂ Cl ₂	10	47	11	PhF	15	62
6	toluene	60	69	12	PhCl	29	7

Table S2. Deviation of Thioureas of Multifunctional Organoboron Catalysts

entry	catalyst	3aa (%)	ee (%)
1	A	80	88
2	B	66	80
3	C	72	76
4	D	59	90
5	E	62	80
6	F	54	51

A

B

C

D

E

F

Table S3. Screening of Acid Additives

Table S4. Investigation of Nucleophiles

^aEe was determined after *N*-benzoylation.

Figure S1. Unsuccessful Substrates

Monomethyl fumarate (**S1a**) and fumaryl monoanilide (**S1b**) did not undergo the aza-Michael addition, probably due to low solubility in CCl_4 .

(A-2) Determination of Stereochemistry

The aza-Michael adduct **3aa** was converted into *N*-Fmoc-aspartic diester **S3aa** and the stereochemistry was determined as *R* configuration by comparison of HPLC charts and optical rotations with (*S*)-*N*-Fmoc-aspartic diester derived from the commercially available mono-*tert*-butyl-L-aspartate (Scheme S1).

Scheme S1

(B) General

All manipulations were carried out under argon atmosphere unless otherwise noted. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECP-400 spectrometer and JEOL ECA-500 spectrometer, operating at 400 MHz (^1H) or 100 MHz (^{13}C) and 500 MHz (^1H) or 125 MHz (^{13}C), respectively. Chemical shifts in CDCl_3 , $\text{DMSO}-d_6$, and CD_3OD were reported in the scale relative to CHCl_3 (7.26 ppm), DMSO (2.50 ppm), and MeOH (3.31 ppm) for ^1H NMR, and to CDCl_3 (77.0 ppm) for ^{13}C NMR as internal references, respectively. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. ESI-HRMS spectra were measured on a Shimadzu LCMS-IT-TOF fitted with an ESI. Optical rotations were measured on a JASCO P-2200 digital polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in $10^{-1} \text{ deg cm}^2/\text{g}$. Chiral HPLC analyses were carried out using a SHIMADZU DGU-20A5. Column chromatography was performed with Cica silica gel 60N (40-100 μm , spherical, neutral). Dry solvents were purchased from Wako Pure Chemical Industries, Ltd. and used as received. Organocatalysts **A-F** were prepared according to our developed procedures.¹

(C) Materials and Methods

(C-1) Preparation of Substrates

Monoethyl fumarate (**1c**) was purchased from Tokyo Chemical Industry Co., Ltd. Monomethyl fumarate (**S1a**) was purchased from Sigma-Aldrich Co. LLC. mono-*tert*-butyl fumarate (**1a**)² and (*E*)-4-oxo-4-(phenylamino)but-2-enoic acid (**S1b**)³ were prepared according to the reported procedures.

Mono-*tert*-butyl fumarate (1a**)**²: White solids.

¹H NMR (400 MHz, CDCl₃) δ : 6.87 (d, J = 15.6 Hz, 1H), 6.76 (d, J = 15.6 Hz, 1H), 1.52 (s, 9H) ppm.

(*E*)-4-Oxo-4-(phenylamino)but-2-enoic acid (S1b**)**³: White solids.

IR (neat) $\tilde{\nu}$: 1696, 1654 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 12.99 (br s, 1H), 10.51 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 15.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 15.2 Hz, 1H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 166.4, 161.6, 138.6, 137.2, 130.8, 128.9, 124.0,

119.4 ppm; HRMS (ESI) m/z calcd. for [M-H]⁻: 190.0510, found: 190.0521.

Monobenzyl fumarate (1b**)**⁴: To a solution of benzyl *tert*-butyl fumarate⁵ (262.1 mg, 1.0 mmol, 1 equiv) in CH₂Cl₂ (4.0 mL) was added TFA (1.8 mL) and stirred at room temperature for 7 h. The mixture was concentrated, and the resulting solids were recrystallised from CH₂Cl₂ and hexane to afford **1b** as white solids (138.4 mg, 0.67 mmol, 67%).

IR (neat) $\tilde{\nu}$: 2940, 1719, 1694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.39-7.34 (m, 5H), 6.99 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H), 5.25 (s, 2H) ppm.

Ethyl (*S,E*)-4-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobut-2-enoate (S1d**)**:

A mixture of L-phenylalanine *tert*-butyl ester hydrochloride⁶ (1.32 g, 6.0 mmol, 1.0 equiv), monoethyl fumarate (944.0 mg, 6.6 mmol, 1.1 equiv), HOBT (972.0 mg, 7.2 mmol, 1.2 equiv), Et₃N (1.82 g, 18.0 mmol, 3.0 equiv) and EDCI (1.38 g, 7.2 mmol, 1.2 equiv) in DMF (30 mL) was stirred

at room temperature for 20 h. The solution was diluted with brine (20 mL) and extracted with Et₂O (20 mL, 2 times). The combined organic phase was dried over Na₂SO₄ followed by filtration and concentration under reduced pressure. The residue was then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1) to afford **S1d** as white solids (1.43 g, 4.12 mmol, 67%).

m.p. 139.3-140.0 °C; [α]_D¹⁹ 106.9 (c 0.89, CHCl₃); IR (neat) $\tilde{\nu}$: 3312, 1734, 1716, 1637 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.29-7.22 (m, 3H), 7.14 (d, J = 6.0 Hz, 2H), 6.92 (d, J = 15.5 Hz, 1H), 6.80 (d, J = 15.5 Hz, 1H), 6.45 (d, J = 7.5 Hz, 1H), 4.84 (dt, J = 7.0, 6.0 Hz, 1H), 4.22 (q, J = 7.5 Hz, 2H), 3.14 (d, J = 6.0 Hz, 2H), 1.42 (s, 9H), 1.30 (t, J = 7.5 Hz, 3H), ¹³C NMR (125 MHz, CDCl₃) δ : 170.2, 165.5, 163.0, 135.9, 130.9, 129.6, 128.5, 127.2, 82.9, 61.3, 53.9, 37.9, 28.0, 14.2 ppm; HRMS (ESI) m/z calcd. for C₁₉H₂₅NO₅ [M+Na]⁺: 370.1625, found: 370.1588.

(*S,E*)-4-((1-(*tert*-Butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobut-2-enoic acid (1d**)**: To a solution

of **S1d** (1.43 g, 4.12 mmol, 1.0 equiv) in THF (20 mL) and water (8.0 mL) was added LiOH (172.8 mg, 4.12 mmol, 1.0 equiv) and stirred at room temperature for 12 h. The mixture was washed with Et₂O, and the aqueous phase was acidified with 1 M HCl aq. The solution was extracted with EtOAc (20 mL, 2 times) and the combined organic layer was washed with brine. After drying over Na₂SO₄ followed by filtration, the solvent was removed under reduced pressure to afford **1d** as white solids (565.3 mg, 1.77 mmol, 43%).

m.p. 118.7-119.1 °C; $[\alpha]_D^{20}$ 105.8 (*c* 0.68, CHCl₃); IR (neat) $\tilde{\nu}$: 3350, 1726, 1659, 1642 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.29-7.24 (m, 3 H), 7.15-7.14 (m, 2 H), 7.00 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 15.0 Hz, 1H), 4.89 (dt, *J* = 8.0, 7.0 Hz, 1H), 3.13 (d, *J* = 6.0 Hz, 2H), 1.42 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 170.9, 169.4, 163.1, 137.6, 135.7, 130.3, 129.6, 128.6, 127.3, 83.4, 54.0, 38.1, 28.0 ppm; HRMS (ESI) *m/z* calcd. for C₁₇H₂₁NO₅ [M+Na]⁺: 342.1312, found: 342.1295.

Ethyl (*R,E*)-4-((1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobut-2-enoate (**S1e**):

A mixture of D-phenylalanine *t*-butyl ester hydrochloride⁶ (1.32 g, 6.0 mmol, 1.0 equiv), monoethyl fumarate (944.0 mg, 6.6 mmol, 1.1 equiv), HOBT (972.0 mg, 7.2 mmol, 1.2 equiv), Et₃N (1.82 g, 18.0 mmol, 3.0 equiv) and EDCI (1.38 g, 7.2 mmol, 1.2 equiv) in DMF (30 mL) was stirred

at room temperature for 20 h. The solution was diluted with brine (20 mL) and extracted with Et₂O (20 mL, 2 times). The combined organic phase was dried over Na₂SO₄ followed by filtration and concentration under reduced pressure. The residue was then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1) to afford **S1d** as white solids (1.46 g, 4.23 mmol, 70%).

m.p. 135.5-137.8 °C; $[\alpha]_D^{18}$ -91.3 (*c* 0.94, CHCl₃); IR (neat) $\tilde{\nu}$: 3310, 1734, 1716, 1636 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.27-7.22 (m, 3H), 7.15-7.13 (m, 2H), 6.94 (d, *J* = 15.5 Hz, 1H), 6.81 (d, *J* = 14.5 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 4.85 (dt, *J* = 7.5, 6.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.14 (d, *J* = 6.0 Hz, 2H), 1.41 (s, 9H), 1.29 (t, *J* = 7.5 Hz, 3H), ¹³C NMR (125 MHz, CDCl₃) δ : 170.3, 165.5, 163.0, 135.95, 135.91, 130.9, 129.5, 128.5, 127.1, 82.8, 61.3, 53.9, 37.9, 28.0, 14.2 ppm; HRMS (ESI) *m/z* calcd. for C₁₉H₂₅NO₅ [M+Na]⁺: 370.1625, found: 370.1576.

(*R,E*)-4-((1-(*tert*-Butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobut-2-enoic acid (**1e**):

of **S1e** (1.46 g, 4.23 mmol, 1.0 equiv) in THF (20 mL) and water (8.0 mL) was added LiOH (177.4 mg, 4.23 mmol, 1.0 equiv) and stirred at room temperature for 12 h. The mixture was washed with Et₂O, and the aqueous phase was acidified with 1 M HCl aq. The solution was extracted with

EtOAc (20 mL, 2 times) and the combined organic layer was washed with brine. After drying over Na₂SO₄ followed by filtration, the solvent was removed under reduced pressure to afford **1e** as white solids (855.0 mg, 2.67 mmol, 65 %).

m.p. 118.6-119.2 °C; $[\alpha]_D^{21}$ -95.0 (*c* 0.48, CHCl₃); IR (neat) $\tilde{\nu}$: 3351, 1726, 1660, 1642 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.29-7.24 (m, 3 H), 7.14 (d, *J* = 7.0 Hz, 2 H), 6.99 (d, *J* = 15.5 Hz, 1H), 6.81 (d, *J* = 15.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.88 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.14 (d, *J* = 6.5 Hz, 2H), 1.42 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 170.9, 169.4, 163.0, 137.6, 130.2, 129.6, 128.6, 127.3, 83.4, 54.0, 38.0,

28.0 ppm; HRMS (ESI) m/z calcd. for $C_{17}H_{21}NO_5$ $[M+Na]^+$: 342.1312, found: 342.1291.

Ethyl (*E*)-4-((*tert*-butoxycarbonylmethyl)amino)-4-oxobut-2-enoate (S1f**):** A mixture of glycine *tert*-

butyl ester hydrochloride (835.0 mg, 4.98 mmol, 1.0 equiv), monoethyl fumarate (788.4 mg, 5.47 mmol, 1.1 equiv), HOBt (1.01 g, 7.47 mmol, 1.5 equiv), and EDCI (1.43 g, 7.47 mmol, 1.5 equiv) in DMF (13.5 mL) was stirred at room temperature for 20 h. The solution was diluted with brine (30 mL) and extracted with Et₂O (50 mL, 3 times). The combined organic phase was dried over Na₂SO₄ followed by filtration and concentration under reduced pressure. The residue was then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:1) to afford **S1f** as yellow oil (716.7 mg, 2.78 mmol, 56%).

IR (neat) $\tilde{\nu}$: 3301, 2980, 1724, 1668 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 6.94 (d, J = 15.0 Hz, 1H), 6.82 (d, J = 15.0 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), 4.03 (d, J = 4.5 Hz, 2H), 1.47 (s, 9H), 1.31 (t, J = 6.5 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 168.6, 165.5, 163.6, 135.5, 131.1, 82.9, 61.3, 42.4, 28.1, 14.2 ppm; HRMS (ESI) m/z calcd. for $[M+Na]^+$: 280.1155, found: 280.1157.

(*E*)-4-((*tert*-Butoxycarbonylmethyl)amino)-4-oxobut-2-enoic acid (1f**):** A solution of **S1f** (716.0 mg,

2.78 mmol, 1 equiv) in THF (14 mL) was treated with 1 M LiOH aq. (2.78 mL, 2.78 mmol, 1.0 equiv) and stirred at ambient temperature for 4 h. The mixture was acidified with 1 M HCl aq. and extracted with CHCl₃ (30 mL, 3 times). After drying over Na₂SO₄ followed by filtration, the solvent was removed under reduce pressure to afford **1f** as white solids (366.7 mg, 1.60 mmol, 60%).

m.p. 229.4 °C (decomp.); IR (neat) $\tilde{\nu}$: 3339, 2868, 1732, 1689, 1658, 1637 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.02 (d, J = 15.5 Hz, 1H), 6.84 (d, J = 15.5 Hz, 1H), 6.54 (br s, 1H), 4.06 (d, J = 4.5 Hz, 2H), 1.48 (s, 9H) ppm; ¹³C NMR (125 MHz, CD₃OD) δ : 168.6, 166.9, 165.3, 135.6, 130.5, 81.7, 41.6, 26.9 ppm; HRMS (ESI) m/z calcd. for $[M-H]^-$: 228.0877, found: 228.0868.

Ethyl (*S,E*)-4-((1,3-bis(*tert*-butoxy)-1-oxopropan-2-yl)amino)-4-oxobut-2-enoate (S1g**):** A mixture of

O-*tert*-butyl-L-serine *tert*-butyl ester hydrochloride (2.53 g, 10.0 mmol, 1.0 equiv), monoethyl fumarate (1.72 g, 12.0 mmol, 1.2 equiv), HOBt (1.62 g, 12.0 mmol, 1.2 equiv), and EDCI (2.87 g, 15.0 mmol, 1.5 equiv) in DMF (27 mL) was stirred at room temperature for 12 h. The solution was diluted with brine (50 mL) and extracted with Et₂O (50 mL, 3 times). The combined organic phase was dried over Na₂SO₄ followed by filtration and concentration under reduced pressure. The residue was then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:1) to afford **S1g** as white solids (3.06 g, 8.91 mmol, 89%).

m.p. 79.4- 80.5 °C; $[\alpha]_D^{25}$ 43.2 (c 0.45, CHCl₃); IR (neat) $\tilde{\nu}$: 3309, 2981, 1741, 1715, 1656 cm⁻¹; ¹H NMR (125 MHz, CDCl₃) δ : 6.99 (d, J = 15.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.60 (dt, J = 8.0, 3.0 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.69 (dd, J = 8.0, 3.0 Hz, 1H), 3.46 (dd, J = 8.0, 3.0 Hz, 1H), 1.35 (s, 9H), 1.18 (t, J = 7.0 Hz, 3H), 1.01 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 169.0, 165.5, 163.2, 136.3, 130.5, 81.9, 73.0, 62.1, 61.1, 53.5, 27.9, 27.2, 14.1 ppm; HRMS (ESI) m/z calcd. for $C_{17}H_{29}NO_6$ $[M+Na]^+$: 366.1887,

found: 366.1861.

(*S,E*)-4-((1,3-Bis(*tert*-butoxy)-1-oxopropan-2-yl)amino)-4-oxobut-2-enoic acid (1g**):** A solution of **S1g**

(1.03 g, 3.0 mmol, 1.0 equiv) in THF (15 mL) was treated with 1 M LiOH aq. (3.0 mL, 3.0 mmol, 1.0 equiv) and stirred at ambient temperature for 4 h. The mixture was acidified with 1 M HCl aq. and extracted with CHCl₃ (20 mL, 3 times). After drying over Na₂SO₄ followed by filtration, the solvent was

removed to afford **1g** as white solids (836.9 mg, 2.65 mmol, 88%).

m.p. 165.5-167.9°C; $[\alpha]_D^{23}$ 25.6 (*c* 0.42, CHCl₃); IR (neat) $\tilde{\nu}$: 3331, 3074, 1720, 1706, 1631 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.19 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 15.5 Hz, 1H), 6.88 (d, *J* = 15.5 Hz, 1H), 4.73 (dt, *J* = 9.0, 3.0 Hz, 1H), 3.80 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.56 (dd, *J* = 9.0, 3.0 Hz, 1H), 1.45 (s, 9H), 1.12 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 169.7, 168.8, 137.3, 130.5, 82.8, 73.5, 62.2, 53.6, 28.0, 27.3 ppm; HRMS (ESI) *m/z* calcd. for C₁₅H₂₅NO₆[M+Na]⁺: 338.1574, found: 338.1554.

(C-2) Preparation of Nucleophiles

O-benzylhydroxylamine (**2a**) was prepared by neutralization of BnONH₂·HCl by 4 M NaOH aq. After extraction with CHCl₃, general work up and dried under vacuum to afford **2a**. *O*-Benzoylhydroxylamine (**S2a**) was prepared according to the reported procedure.⁸

***O*-(4-Methoxybenzyl)hydroxylamine (**2b**):** A mixture of *N*-hydroxyphthalimide (1.80 g, 11.0 mmol, 1.1

equiv), 4-methoxybenzyl chloride (1.86 g, 10.0 mmol, 1.0 equiv), and Et₃N (1.22 g, 12.1 mmol, 1.1 equiv) in CH₂Cl₂ (25 mL) was stirred at room temperature for 4 h. The suspension was washed with brine (20 mL, 3 times) and the combined

organic phase was dried over Na₂SO₄. After the solvent was removed under reduced pressure, the residue was dissolved in CHCl₃/MeOH = 3:1 (50 mL). To the solution was added to N₂H₄·H₂O (750.9 mg, 15.0 mmol, 1.5 equiv) and stirred at room temperature for 2 h. The mixture was filtered through a pad of Celite[®] and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:1) to afford **2b** as colorless oil (1.10 g, 6.2 mmol, 62%).

IR (neat) $\tilde{\nu}$: 2977, 2917 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.29 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.33 (br s, 2H), 4.61 (s, 2H), 3.80 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 159.5, 130.1, 129.4, 113.9, 113.7, 77.7, 53.3 ppm; HRMS (ESI) *m/z* calcd. for C₈H₉NO, [M]⁺: 176.0682, found: 176.0556.

***O*-(4-Trifluoromethylbenzyl)hydroxylamine (**2c**):** **2c** was prepared through the procedure analogous to

that of **2b**. Alkylation was performed using *N*-hydroxyphthalimide (1.35 g, 7.0 mmol, 1.4 equiv), 4-(trifluoromethyl)benzyl chloride (815.0 mg, 5.0 mmol, 1.0 equiv), and Et₃N (708.3 mg, 7.0 mmol, 1.4 equiv) in CH₂Cl₂ (20 mL). Deprotection

of phthalimide was conducted with N₂H₄·H₂O (525.6 mg, 10.5 mmol, 1.5 equiv) in CH₃Cl/MeOH = 3:1 (15 mL), which afforded **2c** as colorless oil (810.0 mg, 4.2 mmol, 84%).

IR (neat) $\tilde{\nu}$: 2940, 1323 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.63 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 5.48 (br s, 2H), 4.75 (s, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 141.7, 130.0 (q, *J* = 32.5 Hz), 128.3,

125.4 (q, $J = 3.9$ Hz), 76.9 ppm; HRMS (ESI) m/z calcd. for C_8H_8FNO , $[M+H]^+$: 192.0631, found: 192.0579.

***O*-(Benzyloxymethyl)hydroxylamine (2d):** **2d** was prepared through the procedure analogous to that of

2b. Alkylation was performed using *N*-hydroxyphthalimide (322.6 mg, 2.0 mmol, 1.0 equiv), chloromethyl benzyl ether (439.1 mg, 2.8 mmol, 1.4 equiv), and Et_3N (286.0 mg, 2.8 mmol, 1.4 equiv) in CH_2Cl_2 (4.5 mL). Deprotection of phthalimide was conducted with $N_2H_4 \cdot H_2O$ (150.2 mg, 3.0 mmol, 1.5 equiv) in $CH_3Cl/MeOH = 3:1$ (5 mL), which afforded **2d** as colorless oil (213.4 mg, 1.4 mmol, 70%).

IR (neat) $\tilde{\nu}$: 2871 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 7.38-7.34 (m, 4H), 7.32-7.29 (m, 1H), 5.51 (br s, 2H), 4.85 (s, 2H), 4.67 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ : 137.1, 128.4, 127.7, 98.5, 69.9 ppm; HRMS (ESI) m/z calcd. for $C_8H_{12}NO_2$, $[M]^+$: 154.0865, found: 154.0805.

***O*-((2-Trimethylsilylethoxy)methyl)hydroxylamine (2e):** **2e** was prepared through the procedure

analogous to that of **2b**. Alkylation was performed using *N*-hydroxyphthalimide (815.5 mg, 5.0 mmol, 1.0 equiv), chloromethyl 2-(trimethylsilyl)ethyl ether (1.16 g, 7.0 mmol, 1.4 equiv), and Et_3N (708.3 mg, 7.0 mmol, 1.4 equiv) in CH_2Cl_2 (11.4 mL). Deprotection of phthalimide was conducted with $N_2H_4 \cdot H_2O$ (375.5 mg, 7.5 mmol, 1.5 equiv) in $CH_3Cl/MeOH = 3:1$ (10 mL), which afforded **2e** as colorless oil (550.5 mg, 3.1 mmol, 62%).

IR (neat) $\tilde{\nu}$: 2953 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 5.47 (br s, 2H), 4.73 (s, 2H), 3.64 (t, $J = 8.0$ Hz, 2H), 0.96 (t, $J = 8.0$ Hz, 2H), 0.01 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ : 98.8, 65.7, 18.3 ppm; HRMS (ESI) m/z calcd. for $C_6H_{17}NO_2Si$, $[M+H]^+$: 164.1107, found: 164.1018.

***O*-Benzoylhydroxylamine (S2a)**⁷: Colorless oil.

1H NMR (400 MHz, $CDCl_3$) δ : 8.00 (d, $J = 2.0$ Hz, 2H), 7.58 (t, $J = 7.6$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 6.60 (br s, 2H) ppm.

(C-3) General Procedure for Catalytic Aza-Michael Addition

Prior to the reaction, 4 Å MS was dried by heat-gun (>300 °C, 15 min) under vacuum (*ca.* 2 Torr). To an oven-dried 10 mL screw tube were placed an organocatalyst (10 mol%), substrate **1** (1.0 equiv), and benzoic acid (1.0 equiv), which were suspended in CCl₄ (0.2 M) and sealed with a Teflon-coated screw cap. After stirring at room temperature for 10 min, pre-heated 4 Å MS (500 mg/mmol) was added and the tube was capped and further stirred for 5 min. Hydroxylamine **2** (1.1 equiv) was then added and the system was closed again followed by stirring at ambient temperature for the indicated time. After the reaction progress was monitored by ¹H NMR analysis (a small amount of the mixture was transferred into an NMR tube). The reaction mixture was diluted in toluene/MeOH (3:1, 1 mL) and treated with TMSCHN₂ (10% in hexane, 1 mL) and stirred for 30 min. The excess TMSCHN₂ was quenched with AcOH, then the mixture was filtered through Celite® and the cake was washed with MeOH. After the solvent was removed under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:1) to afford the product **3**. The ee of **3** was estimated by chiral HPLC analysis.

1-*tert*-Butyl 4-methyl *N*-benzyloxy-D-aspartate (3aa): The reaction was carried out using **1a** (34.4 mg, 200 μmol, 1.0 equiv) and **2a** (27.0 mg, 220 μmol, 1.1 equiv) in the presence of catalyst **A** (7.9 mg, 20 μmol, 10 mol%), benzoic acid (24.4 mg, 200 μmol, 1.0 equiv) and 4 Å MS (100.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1) afforded **3aa** as colorless oil (40.5 mg, 164 μmol, 80%, 93% ee).

$[\alpha]_D^{24} +5.4$ (*c* 1.00, CHCl₃); IR (neat) $\tilde{\nu}$: 3275, 1731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.31 (m, 5H), 6.18 (br s, 1H), 4.69 (s, 2H), 3.92 (br s, 1H), 3.68 (s, 3H), 2.76 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.63 (dd, *J* = 16.0, 6.4 Hz, 1H), 1.47 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.3, 170.6, 137.5, 128.3, 128.2, 127.7, 76.3, 64.2, 60.1, 51.8, 34.3, 27.9 ppm; HRMS (ESI) *m/z* calcd. for C₁₆H₂₃NO₅, [M+Na]⁺: 332.1468, found: 332.1470. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 99/1, flow rate: 1.0 mL/min. detector: UV at 220 nm), *t*_R = 12.0 min (minor), 10.5 min (major).

1-Benzyl 4-methyl *N*-benzyloxy-D-aspartate (3ba): The reaction was carried out using **1b** (82.4 mg, 400 μmol, 1.0 equiv) and **2a** (54.2 mg, 440 μmol, 1.1 equiv) in the presence of catalyst **A** (15.9 mg, 40 μmol, 10 mol%), benzoic acid (48.8 mg, 400 μmol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3ba** as colorless oil (69.6 mg, 201 μmol, 50%, 91% ee).

$[\alpha]_D^{26} +4.2$ (*c* 0.94, CHCl₃); IR (neat) $\tilde{\nu}$: 1738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.34 (m, 10H), 6.26 (br s, 1H), 5.23 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0

Hz, 1H), 4.09 (t, $J = 7.0$ Hz, 1H), 3.64 (s, 3H), 2.85 (dd, $J = 16.0, 6.0$ Hz, 1H), 2.70 (dd, $J = 16.0, 6.0$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 171.5, 171.2, 137.4, 135.4, 128.68, 128.60, 128.4, 128.3, 128.0, 76.6, 67.2, 60.2, 52.0, 34.2 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5$, $[\text{M}+\text{Na}]^+$: 366.1312, found: 366.1290. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 98/2, flow rate: 1.0 mL/min. detector: UV at 254 nm), $t_R = 16.1$ min (major), 17.4 min (minor).

1-Ethyl 4-methyl *N*-benzyloxy-D-aspartate (3ca): The reaction was carried out using **1c** (57.6 mg, 400

μmol , 1.0 equiv) and **2a** (54.2 mg, 440 μmol , 1.1 equiv) in the presence of catalyst **A** (15.9 mg, 40 μmol , 10 mol%), benzoic acid (48.8 mg, 400 μmol , 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3ca** as colorless oil (55.2 mg,

197.6 μmol , 49%, 94% ee).

$[\alpha]_D^{26}$ 6.1 (c 1.04, CHCl_3); IR (neat) $\tilde{\nu}$: 3265, 1732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.31 (m, 5H), 6.22 (br s, 1H), 4.69 (s, 2H), 4.23 (q, $J = 6.8$ Hz, 2H), 4.01 (t, $J = 6.4$ Hz, 1H), 3.68 (s, 3H), 2.81 (dd, $J = 16.4, 6.4$ Hz, 1H), 1.28 (t, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 171.5, 171.2, 137.4, 128.4, 128.3, 127.8, 76.5, 61.4, 60.0, 51.9, 34.1, 14.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_5$, $[\text{M}+\text{Na}]^+$: 304.1155, found: 304.1140. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK @, eluent: hexane/2-propanol = 99/1, flow rate: 1.0 mL/min. detector: UV at 254 nm), $t_R = 16.9$ min (major), 20.1 min (minor).

Methyl (R)-3-((benzyloxy)amino)-4-(((S)-1-(tert-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-

oxobutanoate (3da): The reaction was carried out using **1d** (133.2 mg, 400 μmol , 1.0 equiv) and **2a** (54.2 mg, 440 μmol , 1.1 equiv) in the presence of catalyst **A** (15.9 mg, 40 μmol , 10 mol%), benzoic acid (48.8 mg, 400 μmol , 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude

product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3da** as colorless oil (120.0 mg, 263 μmol , 66%, 67:33 dr).

For major diastereomer: $[\alpha]_D^{21}$ 39.8 (c 0.51, CHCl_3); IR (neat) $\tilde{\nu}$: 3381, 1730, 1675 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.34-7.14 (m, 10H), 6.19 (d, $J = 5.5$ Hz, 1H), 4.73 (dt, $J = 7.5, 6.0$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 4.61 (d, $J = 12.0$ Hz, 1H), 3.81 (m, 1H), 3.66 (s, 3H), 3.11 (dd, $J = 15.0, 6.0$ Hz, 1H), 3.07 (dd, $J = 15.0, 6.0$ Hz, 1H), 2.87 (dd, $J = 17.5, 9.0$ Hz, 1H), 2.77 (dd, $J = 17.0, 9.0$ Hz, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 172.5, 170.4, 170.2, 137.2, 136.3, 129.6, 128.57, 128.52, 128.4, 128.1, 127.0, 82.4, 76.3, 60.5, 53.6, 52.0, 38.2, 32.2, 28.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6$, $[\text{M}+\text{H}]^+$: 457.2333, found: 457.2353.

For minor diastereomer: $[\alpha]_D^{21}$ 19.7 (c 0.60, CHCl_3); IR (neat) $\tilde{\nu}$: 3388, 1732, 1674 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.33-7.17 (m, 10H), 6.18 (d, $J = 6.0$ Hz, 1H), 4.73 (dt, $J = 7.5, 6.0$ Hz, 1H), 4.62 (d, $J = 11.5$ Hz, 1H), 4.59 (d, $J = 11.5$ Hz, 1H), 3.82 (ddd, $J = 8.0, 7.0, 4.5$ Hz, 1H), 3.65 (s, 3H), 3.11 (dd, $J = 14.0, 6.5$ Hz, 1H), 3.08 (dd, $J = 14.0, 6.0$ Hz, 1H), 2.83 (dd, $J = 12.0, 4.5$ Hz, 1H), 2.71 (dd, $J = 12.0, 8.0$ Hz, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 172.3, 170.47, 170.42, 137.1, 136.2, 129.7, 128.4, 128.1, 127.0, 82.4, 76.2, 60.6, 53.6, 52.0, 38.1, 32.5, 28.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_6$,

$[M+H]^+$: 457.2333, found: 457.2354.

Methyl (R)-3-((benzyloxy)amino)-4-(((R)-1-(tert-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-

oxobutanoate (3ea): The reaction was carried out using **1e** (133.2 mg, 400 μ mol, 1.0 equiv) and **2a** (54.2 mg, 440 μ mol, 1.1 equiv) in the presence of catalyst **A** (15.9 mg, 40 μ mol, 10 mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude

product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3ea** as colorless oil (128.2 mg, 280 μ mol, 70%, 75:25 dr).

For major diastereomer: $[\alpha]_D^{21}$ -15.0 (*c* 0.66, CHCl₃); IR (neat) $\tilde{\nu}$: 3381, 1731, 1674 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.34-7.16 (m, 10H), 6.19 (br s, 1H), 4.73 (dt, *J* = 7.5, 6.0 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 3.82 (m, 1H), 3.66 (s, 3H), 3.11 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.08 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.83 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.71 (dd, *J* = 17.0, 8.0 Hz, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 172.3, 170.47, 170.42, 137.1, 136.2, 129.7, 128.5, 128.4, 128.1, 127.0, 82.4, 76.2, 60.6, 53.6, 52.0, 38.1, 32.5, 28.0 ppm; HRMS (ESI) *m/z* calcd. for C₂₅H₃₂N₂O₆, $[M+H]^+$: 457.2333, found: 457.2328.

For minor diastereomer: $[\alpha]_D^{22}$ -43.9 (*c* 0.57, CHCl₃); IR (neat) $\tilde{\nu}$: 3383, 1729, 1674 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.32-7.14 (m, 10H), 6.19 (d, *J* = 6.0 Hz, 1H), 4.74 (dt, *J* = 7.5, 6.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 3.81 (m, 1H), 3.66 (s, 3H), 3.12 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.07 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.87 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.77 (dd, *J* = 17.5, 8.0 Hz, 1H), 1.40 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 172.5, 170.4, 170.2, 137.1, 136.3, 129.5, 128.5, 128.49, 128.46, 128.0, 127.0, 82.3, 76.2, 60.4, 53.6, 51.9, 38.1, 32.2, 28.0 ppm; HRMS (ESI) *m/z* calcd. for C₂₅H₃₂N₂O₆, $[M+H]^+$: 457.2333, found: 457.2355.

Methyl (S)-3-((benzyloxy)amino)-4-((tert-butoxycarbonylmethyl)amino)-4-oxobutanoate (3fa): The reaction was carried out using **1f** (91.6 mg, 400 μ mol, 1.0 equiv) and **2a** (54.2 mg, 440 μ mol, 1.1 equiv) in the presence of catalyst **ent-A** (15.9 mg, 40 μ mol, 10

mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3fa** as colorless oil (241.4 mg, 266 μ mol, 66%, 63% ee).

$[\alpha]_D^{24}$ 4.6 (*c* 1.46, CHCl₃); IR (neat) $\tilde{\nu}$: 1733, 1669 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.34-7.28 (m, 4H), 7.19 (m, 1H), 6.46 (br s, 1H), 4.73 (s, 2H), 4.03 (d, *J* = 5.5 Hz, 1H), 3.88 (dd, *J* = 5.0, 2.0 Hz, 1H), 3.85 (dd, *J* = 5.0, 2.0 Hz, 1H), 3.66 (s, 3H), 2.89 (dd, *J* = 17.0, 8.0 Hz), 2.78 (dd, *J* = 17.0, 8.0 Hz), 1.46 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 172.5, 170.8, 168.7, 130.6, 128.7, 128.5, 128.1, 82.3, 76.2, 60.4, 52.0, 42.0, 32.3, 28.1 ppm; HRMS (ESI) *m/z* calcd. for C₁₈H₂₆N₂O₆, $[M+H]^+$: 367.1864, found: 367.1789. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 96/4, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 29.6 min (major), 27.7 min (minor).

Methyl

(*R*)-3-((benzyloxy)amino)-4-(((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-4-

oxobutanoate (3ga): The reaction was carried out using **1g** (126 mg, 400 μ mol, 1.0 equiv) and **2a** (54.2 mg, 440 μ mol, 1.1 equiv) in the presence of catalyst **ent-A** (15.9 mg, 40 μ mol, 10 mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was

purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3da** as colorless oil (366.6 mg, 322 μ mol, 81%, 73:27 dr).

For major diastereomer: $[\alpha]_D^{21}$ 33.2 (*c* 1.02, CHCl₃); IR (neat) $\tilde{\nu}$: 3403, 1735, 1679 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.66 (d, *J* = 8.0 Hz, 1H), 7.37-7.31 (m, 5H), 6.26 (d, *J* = 10.0 Hz, 1H), 4.80 (dd, *J* = 15.0, 11.5 Hz, 2H), 4.60 (dt, *J* = 9.0, 2.5 Hz, 1H), 3.90 (dt, *J* = 7.5, 4.5 Hz, 1H), 3.81 (dd, *J* = 17.0, 4.5 Hz, 1H), 3.67 (s, 3H), 3.54 (dd, *J* = 8.5, 3.0 Hz, 1H), 2.91 (dd, *J* = 17.0, 4.5 Hz, 1H), 2.76 (dd, *J* = 17.0, 9.0 Hz, 1H), 1.47 (s, 9H), 1.13 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 172.4, 170.5, 169.2, 137.3, 128.6, 128.5, 128.0, 81.8, 76.4, 73.1, 60.7, 53.2, 52.0, 32.6, 28.1, 27.4 ppm; HRMS (ESI) *m/z* calcd. for C₂₅H₃₂N₂O₆, [M+H]⁺: 453.2595, found: 453.2570.

For minor diastereomer: $[\alpha]_D^{21}$ 1.0 (*c* 0.96, CHCl₃); IR (neat) $\tilde{\nu}$: 3405, 1737, 1679 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.61 (d, *J* = 8.5 Hz, 1H), 7.34-7.26 (m, 5H), 6.26 (d, *J* = 6.5 Hz, 1H), 4.78 (dd, *J* = 17.0, 11.0 Hz, 2H), 4.61 (dt, *J* = 8.5, 2.5 Hz, 1H), 3.91 (ddd, *J* = 9.0, 6.5, 3.0 Hz, 1H), 3.81 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.67 (s, 3H), 3.54 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.93 (dd, *J* = 17.5, 5.0 Hz, 1H), 2.80 (dd, *J* = 17.5, 9.0 Hz, 1H), 1.47 (s, 9H), 1.12 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 172.4, 170.5, 169.3, 137.3, 128.58, 128.51, 128.0, 81.9, 76.4, 73.1, 62.2, 60.5, 53.2, 51.9, 32.3, 28.1, 27.4 ppm; HRMS (ESI) *m/z* calcd. for C₂₅H₃₂N₂O₆, [M+H]⁺: 453.2595, found: 453.2524.

1-*tert*-Butyl 4-methyl *N*-(4-methoxybenzyl)oxy-D-aspartate (3ab): The reaction was carried out using

1a (68.8 mg, 400 μ mol, 1.0 equiv) and **2b** (67.4 mg, 440 μ mol, 1.1 equiv) in the presence of catalyst **A** (15.9 mg, 40 μ mol, 10 mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 2:1) afforded **3ab** as colorless oil (101.8 mg, 300 μ mol,

75%, 89% ee).

$[\alpha]_D^{23}$ 8.2 (*c* 0.68, CHCl₃); IR (neat) $\tilde{\nu}$: 1732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.26 (t, *J* = 7.0 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 2H), 6.12 (br s, 1H), 4.61 (s, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 2.75 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.62 (dd, *J* = 16.0, 7.5 Hz, 1H), 1.46 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.4, 170.7, 159.4, 130.1, 129.7, 113.7, 82.1, 76.1, 60.7, 55.3, 51.9, 34.4, 28.0 ppm; HRMS (ESI) *m/z* calcd. for C₁₇H₂₅NO₆, [M+H]⁺: 340.1755, found: 340.1744. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 98/2, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 13.3 min (major), 14.1 min (minor).

1-tert-Butyl 4-methyl N-(4-trifluoromethyl)benzyloxy-D-aspartate (3ac): The reaction was carried out

using **1a** (34.4 mg, 200 μ mol, 1.0 equiv) and **2c** (42.0 mg, 220 μ mol, 1.1 equiv) in the presence of catalyst **A** (7.9 mg, 20 μ mol, 10 mol%) and benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1) afforded **3ac** as colorless oil

(48.2 mg, 128 μ mol, 64%, 96% ee).

$[\alpha]_D^{25}$ 6.6 (*c* 1.90, CHCl₃); IR (neat) $\tilde{\nu}$: 1732, 1324 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 6.0 Hz, 1H), 4.75 (s, 2H), 3.93 (dt, *J* = 6.0 Hz, 1H), 3.67 (s, 3H), 2.75 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.61 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.48 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.1, 170.5, 141.7, 129.9 (q, *J* = 32.6 Hz), 128.2, 125.2 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 27.0 Hz), 82.2, 75.4, 60.7, 51.8, 51.7, 34.2, 27.9 ppm; HRMS (ESI) *m/z* calcd. for C₁₇H₂₂NO₅F₃, [M+Na]⁺: 400.1342, found: 400.1333. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 99/1, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 15.8 min (minor), 20.2 min (major).

1-tert-Butyl 4-methyl N-(benzyloxy)methoxy-D-aspartate (3ad): The reaction was carried out using **1a**

(34.4 mg, 200 μ mol, 1.0 equiv) and **2d** (36.7 mg, 220 μ mol, 1.1 equiv) in the presence of catalyst **A** (7.9 mg, 20 μ mol, 10 mol%) and benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1)

afforded **3ad** as colorless oil (40.0 mg, 122 μ mol, 60%, 87% ee).

$[\alpha]_D^{25}$ 4.4 (*c* 1.06, CHCl₃); IR (neat) $\tilde{\nu}$: 1731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.31 (m, 5H), 6.43 (d, *J* = 6.4 Hz, 1H), 4.86 (s, 2H), 4.65 (s, 2H), 3.98 (dt, *J* = 10.0, 6.4 Hz, 1H), 3.69 (s, 3H), 2.77 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.67 (dd, *J* = 16.4, 6.4 Hz, 1H), 1.48 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ : 171.2, 170.6, 137.7, 128.4, 127.79, 127.67, 82.1, 69.9, 60.8, 51.8, 34.4, 27.9 ppm; HRMS (ESI) *m/z* calcd. for C₁₇H₂₅NO₆, [M+Na]⁺: 362.1574, found: 362.1588. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 98/2, flow rate: 1.0 mL/min. detector: UV at 220 nm), *t*_R = 16.1 min (major), 17.4 min (minor).

1-tert-Butyl 4-methyl N-(2-trimethylsilylethoxy)methoxy-D-aspartate (3ae): The reaction was carried

out using **1a** (34.4 mg, 200 μ mol, 1.0 equiv) and **2e** (33.6 mg, 220 μ mol, 1.1 equiv) in the presence of catalyst **A** (7.9 mg, 20 μ mol, 10 mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column

chromatography (eluent: hexane/EtOAc, 3:1) afforded **3ae** as colorless oil (48.9 mg, 142 μ mol, 70%). Since **3ae** was not detectable on HPLC, *N*-benzoylation was conducted to estimate the ee of **3ae**.

$[\alpha]_D^{25}$ +4.3 (*c* 1.00, CHCl₃); IR (neat) $\tilde{\nu}$: 1738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 6.36 (d, *J* = 6.4 Hz, 1H), 4.75 (s, 2H), 3.94 (dt, *J* = 12.8 Hz, 6.4 Hz), 3.68 (s, 3H), 3.62 (t, *J* = 8.4 Hz, 2H), 1.45 (s, 9H), 0.94 (t, *J* = 8.4 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.2, 170.6, 97.7, 82.0, 65.7, 60.8, 51.8, 34.4, 27.9, 18.1 ppm; HRMS (ESI) *m/z* calcd. for C₁₅H₃₁NO₆Si, [M+Na]⁺: 372.1813, found: 372.1820.

1-tert-Butyl 4-methyl N-benzoyl-N-(2-trimethylsilylethoxy)methoxy-D-aspartate (3ae'): To a solution of **3ae** (34.9 mg, 100 μ mol, 1.0 equiv) in EtOAc (1 mL) were added BzCl (21.1 mg, 150 μ mol, 1.5 equiv) and sat. NaHCO₃ aq. (1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. Added brine (2 mL) and extracted with EtOAc (5 mL, 2 times). The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 5:1) afforded **3ae'** as colorless oil (38.8 mg, 85 μ mol, 85%).

$[\alpha]_D^{25}$ 0.71 (*c* 5.84, CHCl₃); IR (neat) $\tilde{\nu}$: 1736, 1648 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.67 (d, *J* = 7.0 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.41 (t, *J* = 7.0 Hz, 2H) 5.06 (br, 1H), 4.85 (br, 2H), 3.73 (s, 3H), 3.49 (s, 2H), 3.21 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.97 (dd, *J* = 17.0, 7.0 Hz, 1H), 1.48 (s, 9H), 0.85 (t, *J* = 8.0 Hz, 2H), 0.018 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 198.7, 171.3, 167.6, 134.2, 130.9, 128.3, 128.2, 99.6, 82.9, 67.7, 61.1, 52.0, 34.0, 27.9, 17.9 ppm; HRMS (ESI) *m/z* calcd. for C₂₂H₃₅NO₇Si, [M+H]⁺: 453.2111, found: 453.2183. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 1, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 18.9 min (major), 23.7 min (minor).

1-Benzyl 4-methyl N-(2-trimethylsilylethoxy)methoxy-L-aspartate (3be): The reaction was carried out using **1b** (82.5 mg, 400 μ mol, 1.0 equiv) and **2e** (67.3 mg, 440 μ mol, 1.1 equiv) in the presence of catalyst **ent-A** (15.9 mg, 40 μ mol, 10 mol%), benzoic acid (48.8 mg, 400 μ mol, 1.0 equiv) and 4 Å MS (200.0 mg) for 24 h. The crude product was purified by silica-gel column chromatography (eluent: hexane/EtOAc, 3:1) afforded **3be** as colorless oil (268.4 mg, 284 μ mol, 70%, 86% ee).

$[\alpha]_D^{26}$ +4.7 (*c* 1.00, CHCl₃); IR (neat) $\tilde{\nu}$: 1739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.35 (m, 5H), 6.42 (d, *J* = 7.0 Hz, 1H), 5.21 (s, 2H), 4.76 (s, 2H), 4.12 (dt, *J* = 7.0, 6.0 Hz, 1H), 3.65 (s, 3H), 3.62 (dt, *J* = 8.5, 1.0 Hz, 1H), 2.85 (dd, *J* = 16.0, 6.0 Hz, 1H) 2.74 (dd, *J* = 16.0, 6.0 Hz, 1H), 0.94 (dt, *J* = 8.5, 1.2 Hz, 2H), 0.01 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.4, 170.9, 135.2, 128.5, 128.3, 128.2, 97.8, 67.1, 65.8, 60.2, 51.9, 34.1, 18.0 ppm; HRMS (ESI) *m/z* calcd. for C₁₈H₂₉NO₆Si, [M+Na]⁺: 406.1656, found: 406.1643. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 99/1, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 16.4 min (major), 18.2 min (minor).

1-tert-Butyl 4-methyl 9H-fluoren-9-ylmethoxycarbonyl-D-aspartate (S3aa): **3aa** (25.3 mg 100 μ mol, 1.0 equiv) was dissolved in MeOH (30 mL) and added to 10% Pd/C (80 mg) under an atmosphere of argon. The reaction was carefully flushed with hydrogen gas and stirred at room temperature for 5 h. The atmosphere was replaced with argon before filtration through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was dissolved in CH₂Cl₂ (1.0 mL). To the solution were added *i*Pr₂NEt (64.6 mg, 500 μ mol, 5.0 equiv) and FmocCl (25.8 mg, 120 μ mol, 1.2 equiv). The resulting mixture was stirred at ambient temperature for 17 h, then the solvent was evaporated. The residue was purified by silica-gel column chromatography (eluent:

hexane/EtOAc, 1:1) to afford **S3aa** as colorless oil (26.0 mg, 61 μ mol, 61%).

$[\alpha]_D^{23}$ -7.1 (*c* 0.73, CHCl₃); IR (neat) $\tilde{\nu}$: 3368, 1721 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.75 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 5.80 (d, *J* = 8.5 Hz, 1H), 4.54 (dt, *J* = 8.5, 4.5 Hz, 1H), 4.38 (dt, *J* = 17.0, 7.0 Hz, 2H), 4.23 (t, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.00 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.84 (dd, *J* = 17.0, 4.0 Hz, 1H), 1.48 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ : 171.3, 169.6, 156.0, 143.9, 143.8, 141.3, 127.8, 127.1, 125.2, 120.0, 82.7, 67.2, 52.0, 51.0, 47.2, 36.8, 27.9 ppm; HRMS (ESI) *m/z* calcd. for 448.1731, [M+Na]⁺ found: 448.1757. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IA, eluent: hexane/2-propanol = 96/4, flow rate: 1.0 mL/min. detector: UV at 254 nm), *t*_R = 20.3 min (major), 26.6 min (minor).

(D) O-Deprotection and KAHA Ligation

1-Benzyl 4-methyl N-hydroxy-L-aspartate (4b): To a solution of **3be** (192.7 mg, 500 μ mol, 1.0 equiv) in CH₂Cl₂ (5 mL) was added TFA (172.5 mg, 1.5 mmol, 3.0 equiv) at room temperature and stirred for 1 h. H₂O (5 mL) was added and further stirred at ambient temperature for 1 h, and the mixture was dried over Na₂SO₄. The solids were filtered off and the solvent was removed under reduced pressure. The residue was then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:2) to afford **4b** as colorless oil (53.1 mg, 210 μ mol, 42%). Since **4b** was gradually degraded on standing, **4b** was used for KAHA ligation soon after purification.

¹H NMR (500 MHz, CDCl₃) δ : 7.32 (m, 5H), 5.22 (s, 2H), 4.06 (dt, *J* = 8.0, 5.0 Hz, 1H), 3.66 (s, 3H), 2.87 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.80 (dd, *J* = 16.0, 5.0 Hz, 1H) ppm.

1-Benzyl 4-methyl (3-phenylpropanoyl)-L-aspartate (6b): A mixture of **4b** (23.3 mg, 92 μ mol, 1.0 equiv) and 2-oxo-4-phenylbutanoic acid (**5**) (16.3 mg, 92 μ mol, 1.0 equiv) in DMSO/H₂O (9:1, 200 μ L) was stirred at 40 °C for 24 h. The crude mixture was extracted with EtOAc (2 mL, 3 times) and then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:2) to afford to **6b** as yellow oil (26.1

mg, 70 μ mol, 60%, 82% ee).

$[\alpha]_D^{24}$ -13.2 (*c* 1.75, CHCl₃); IR (neat) $\tilde{\nu}$: 3311, 1732, 1652 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 7.38-7.30

(m, 6H), 7.27-7.24 (m, 1H), 7.19-7.17 (m, 3H), 6.42 (d, $J = 8.0$ Hz, 1H), 5.17 (dd, $J = 28.0, 12.5$ Hz, 2H), 4.88 (dt, $J = 8.0, 4.0$ Hz, 1H), 3.00 (dd, $J = 17.5, 4.0$ Hz, 1H), 2.95 (t, $J = 8.0$ Hz, 2H), 2.75 (dd, $J = 17.5, 4.0$ Hz, 1H), 2.59 (ddd, $J = 18.0, 15.0, 8.0$ Hz, 1H), 2.49 (ddd, $J = 18.0$ Hz, 15.0, 8.0 Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 171.8, 171.4, 170.5, 140.5, 135.1, 128.55, 128.45, 128.26, 126.1, 67.5, 51.9, 48.3, 38.0, 36.0, 31.4 ppm; HRMS (ESI) m/z calcd. For $\text{C}_{21}\text{H}_{23}\text{NO}_5$, $[\text{M}+\text{H}]^+$: 370.1649, found: 370.1676. The enantiomeric excess was estimated by chiral HPLC analysis (DAICEL CHIRALPAK IB, eluent: hexane/2-propanol = 99/1, flow rate: 1 mL/min. detector: UV at 254 nm), $t_R = 18.2$ min (minor), 16.4 min (major).

1-Benzyl 4-methyl 9H-fluoren-9-ylmethoxycarbonyl-L-leucyl-L-aspartate (8b): A mixture of **4b** (60.1

mg, 156 μmol , 1.0 equiv) and (*S*)-3-(9H-fluoren-9-ylmethoxycarbonyl)amino)-5-methyl-2-oxohexanoic acid (**7**) (57.1 mg, 150 μmol , 1.0 equiv) in DMSO/ H_2O (9:1, 15 mL) was stirred at 40 $^\circ\text{C}$ for 15 h. The crude mixture was extracted with EtOAc (2 mL, 3 times) and then purified by silica-gel column chromatography (eluent: hexane/EtOAc, 1:2) to

afford to **8b** as yellow oil (41.2 mg, 72 μmol , 50%, 93:7 dr).

$[\alpha]_D^{23}$ -3.20 (c 1.20, CHCl_3); IR (neat) $\tilde{\nu}$: 3314, 1738, 1661 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.75 (d, $J = 7.0$ Hz, 2H), 7.57 (d, $J = 5.5$ Hz, 2H), 7.39-7.29 (m, 9H), 6.95 (d, $J = 8.0$ Hz, 1H), 5.34 (d, $J = 8.0$ Hz, 1H), 5.15 (dd, $J = 21.0, 12.0$ Hz, 2H), 4.91 (t, $J = 4.0$ Hz, 1H), 4.36 (m, 2H) 4.21 (m, 2H), 3.58 (s, 3H), 3.05 (dd, $J = 17.0, 3.5$ Hz, 1H), 2.81 (dd, $J = 17.0, 3.5$ Hz, 1H), 1.63 (m, 2H), 1.50 (m, 1H), 0.89 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 172.2, 171.5, 170.3, 156.1, 143.9, 143.8, 141.3, 135.1, 128.69, 128.60, 128.4, 127.8, 127.1, 125.1, 120.0, 67.7, 67.1, 53.4, 52.1, 48.5, 41.9, 36.0, 24.6, 22.9, 22.0 ppm; HRMS (ESI) m/z calcd. For $\text{C}_{33}\text{H}_{36}\text{N}_2\text{O}_7$, $[\text{M}+\text{Na}]^+$: 595.2415, found: 595.2396.

(E) References

- [1] N. Hayama, T. Azuma, Y. Kobayashi, Y. Takemoto, *Chem. Pharm. Bull.*, 2016, **64**, 704.
- [2] S. E. Denmark, A. Thorarensen, D. S. Middleton, *J. Am. Chem. Soc.*, 1996, **118**, 8266.
- [3] D. Hadjipavlou-Litina, G. E. Magoulas, M. Krokidis, D. Papaioannou, *Eur. J. Med. Chem.*, 2010, **45**, 298.
- [4] J. P. D. van Veldhoven, C. C. Blad, A. C. Klopman, D. R. Wolfram, M. J. Abdelkadir, J. R. Lane, J. Brussee, A. P. IJzerman, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2736.
- [5] Ö. D. Ekici, Z. Z. Li, A. J. Campbell, K. E. James, J. L. Asgian, J. Mikołajczyk, G. S. Salvesen, R. Ganesan, S. Jelakovic, M. G. Grütter, J. C. Powers, *J. Med. Chem.*, 2006, **49**, 5728.
- [6] A. Odrizola, M. Oiarbide, C. Palomo, *Chem. Eur. J.*, 2017, **23**, 12758.
- [7] L. A. Carpino, C. A. Giza, B. A. Carpino, *J. Am. Chem. Soc.*, 1959, **81**, 955.

(F) ^1H NMR and ^{13}C NMR Spectra

(G) HPLC Traces

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1 PDA Multi 1 / 254nm 4nm

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peak #	retention time (min)	area	area (%)
1	10.110	28220	50.566
2	11.563	27589	49.434

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
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peak #	retention time (min)	area	area (%)
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peak #	retention time (min)	area	area (%)
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2	17.454	11837	4.532

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	17.190	107411	49.860
2	19.936	108013	50.140

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	16.916	476565	97.175
2	20.131	13852	2.825

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	26.085	84655	50.344
2	28.090	83498	49.656

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	27.732	54324	29.314
2	29.637	130993	70.686

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	13.040	67291	49.834
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PDA Ch1 254nm 4nm

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1	13.332	440616	94.445
2	14.132	25918	5.555

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peak #	retention time (min)	area	area (%)
1	17.363	1032118	50.070
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peak #	retention time (min)	area	area (%)
1	17.799	24343	1.981
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PDA Ch1 220nm 4nm

peak #	retention time (min)	area	area (%)
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1 PDA Multi 1 / 220nm 4nm

<Peak Report>

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PDA Ch1 220nm 4nm

peak #	retention time (min)	area	area (%)
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2	20.219	3727434	93.421

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	21.830	2954870	50.255
2	26.375	2924865	49.745

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	18.988	16853273	93.145
2	23.742	1240399	6.855

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<Peak Report>

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	16.289	206655	49.880
2	18.079	207647	50.120

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	16.421	84529	94.632
2	18.287	4795	5.368

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1 PDA Multi 1 / 254nm 4nm

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peak table C:\data_131217\murakami\HM0033-C-IA.lcd

PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	20.340	11004240	50.134
2	26.606	10945554	49.866

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1 PDA Multi 1 / 254nm 4nm

<Peak Report>

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	20.425	2667915	93.426
2	26.772	187744	6.574

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<Peak Report>

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PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
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2	18.287	4795	5.368

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<Peak Report>

peak table C:\data_131217\murakami\HM0278-IB006.lcd

PDA Ch1 254nm 4nm

peak #	retention time (min)	area	area (%)
1	13.958	29089	52.465
2	15.844	26356	47.535