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Enantioselective Synthesis of α-Substituted Serine Derivatives via Cu-Catalyzed Oxidative Desymmetrization of 2-Amino-1,3-diols

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Supporting Information

ABSTRACT: The enantioselective copper-catalyzed oxidative desymmetrization for the synthesis of chiral α-substituted serine derivatives is reported. The combination of $Cu(OTf)_2$/(*R*,*R*)-PhBOX catalyst system, *N*-bromosuccinimide, and MeOH enables us to provide chiral α-substituted serines from *N*-2-methylbenzoyl-protected 2-amino-1,3-diols through a simple procedure at room temperature under an air atmosphere. A variety of α-substituent including aryl and heteroaryl groups were tolerated in this method, and the corresponding chiral serine derivatives were obtained in good to high yields with high enantioselectivities.

KEYWORDS: *oxidation, copper catalyst, α-substituted serines, desymmetrization*

1. INTRODUCTION

α,α-Disubstituted amino acids are one of the major class of nonproteinogenic amino acids and have attracted considerable attention in the field of medicinal and synthetic chemistry,[1] and their numerous synthetic methods have been developed.[2] Among nonproteinogenic amino acids, chiral α-substituted serine derivatives have been found in many natural products, such as piperazimycin A,[3] altemicidin,[4] myriocin,[5] and sphingofungin E,[6] which exhibit interesting biological activities (Figure 1). Thus, many efforts have been made to develop efficient methods for the preparation of chiral α-serine derivatives. One of the most common approaches was alkylation of enolizable heterocycles or malonate derivatives under noncatalytic conditions.[7−10] Although noncatalytic methods afforded desired serine derivatives with high enantioselectivities, the chiralities of the products were dominated by those of the starting natural L-amino acids, and the use of stoichiometric amount of expensive D-amino acids was required to obtain the opposite enantiomer. In this context, catalytic asymmetric reactions have attracted much attention since both enantiomers of products would be obtained from achiral compounds by using both enantiomers of catalytic amount of external chiral sources (Scheme 1). For example, the gold-catalyzed aldol reaction[11] and phase-transfer catalytic alkylation[12] have been developed for the synthesis of α-substituted serine precursors (Scheme 1a,b). Asymmetric desymmetrization of prochiral compounds would be one of the most ideal reactions for the synthesis of enantio-enriched compounds. However, the synthesis of chiral α-serines using

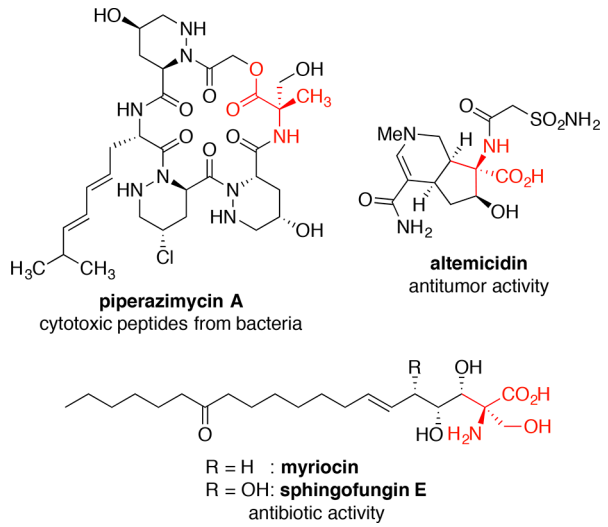

Figure 1. Biologically active molecules with α,α-disubstituted amino acid motifs.

this approach has been achieved mostly by using enzymes such as lipase, esterase, and amidase (Scheme 1c).[13] While these catalytic methods effectively provide chiral α-substituted serine derivatives, most reactions required cryogenic conditions and/or involved multistep processes for the transformation of the products to the desired serine scaffolds. Although enzymatic desymmetrization was commonly performed at room temperature, high substrate specificity of enzymes may limit the expansion of their application to a variety of substrates. Thus, development of more practical and broad substrate-scope methods for the synthesis of chiral α-substituted serines is still highly desired in order to access to the α-substituted serines possessing various substituents with high efficiency and selectivity.

We previously developed the copper-catalyzed enantioselective desymmetrization of *meso*-1,2-diols using *N*-bromosuccinimide as an oxidant for the synthesis of α-hydroxy ketones.[14] It is noteworthy that this desymmetrization was performed at room temperature under an air atmosphere. We envisioned that the oxidative desymmetrization of 2-amino-1,3-diols would provide a novel synthetic route for α-substituted

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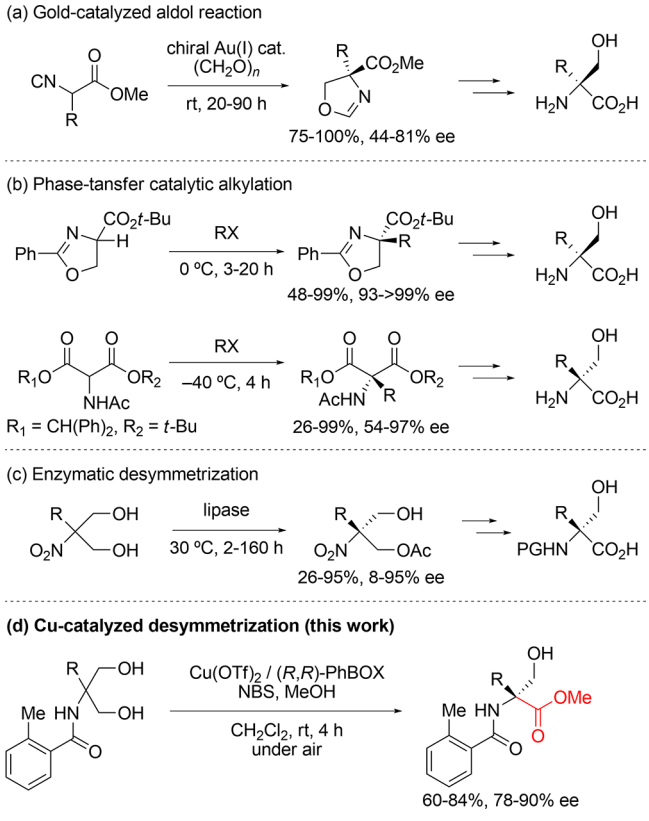
Scheme 1. Catalytic Asymmetric Synthesis of α-Substituted Serine Derivatives

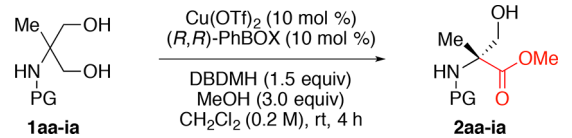


serines under mild reaction conditions via a technically simple procedure. Herein, we report the copper-catalyzed enantioselective oxidative desymmetrization of a variety of *N*-2-methylbenzoyl-protected 2-amino-1,3-diols, which enables us to prepare α-substituted serine derivatives in high yields and high enantioselectivities.

2. RESULTS AND DISCUSSION

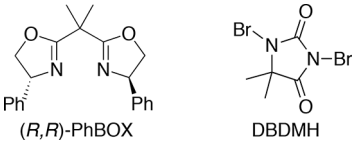
We commenced this study with the optimization of the *N*-protecting group for 2-methyl 2-amino-1,3-diol in the asymmetric oxidative desymmetrization with copper(II) triflate and (*R*,*R*)-PhBOX as a chiral catalyst. The results are summarized in Table 1. When *N*-benzoyl-protected amino diol (**1aa**) was treated with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and MeOH in the presence of the chiral copper catalyst, the desired α-serine derivative **2aa** was obtained in 46% yield with 67% ee (Table 1, entry 1). While a 4-methylbenzoyl group gave a similar reaction outcome to that obtained from a benzoyl group, a 2-methylbenzoyl group afforded **2ca** in a higher yield with 85% ee (entries 2 and 3). Substrates with a 4- or 2-chlorobenzoyl group (**1da** and **1ea**) were transformed to the desired serine derivatives in moderate yields with good enantioselectivities (entries 4 and 5). The substrate having a 4-nitrobenzoyl group (**1fa**) afforded **2fa** in a higher yield than **1ca**, but decreased enantioselectivity was observed (entry 6). A nitro group at the 2-position of the benzoyl group showed a negative effect in this reaction, resulting in a decrease in the yield (entry 7). As for the *N*-protecting group, *p*-toluenesulfonyl (**1ha**) and benzyloxycarbonyl (**1ia**) groups were not suitable for this transformation, which did not provide the desired esters (entries 8 and 9). On

Table 1. Screening of *N*-Protecting Groups



entry	substrate	PG	product	yield (%)[a]	ee (%)[b]
1	**1aa**	Bz	**2aa**	46	67
2	**1ba**	4-MeBz	**2ba**	51	64
3	**1ca**	2-MeBz	**2ca**	65	85
4	**1da**	4-ClBz	**2da**	46	75
5	**1ea**	2-ClBz	**2ea**	64	77
6	**1fa**	4-NO_2Bz	**2fa**	78	80
7	**1ga**	2-NO_2Bz	**2ga**	38	64
8	**1ha**	Ts	**2ha**	n.r.	
9	**1ia**	Cbz	**2ia**	n.r.	

[a]Isolated yields after column chromatography. n.r. = no reaction. [b]Determined by chiral HPLC analysis.



the basis of these results, we selected a 2-methylbenzoyl group, which gave the desired product with the highest enantioselectivity, as an optimal protecting group.

Next, the effects of oxidants and solvents were investigated as shown in Table 2. The yields of **2ca** increased by using the excess amount of DBDMH, but detrimental effects on enantioselectivity were observed (Table 2, entries 1–3). While using 3 equiv of *N*-bromophthalimide (NBP) as an oxidant in CH_2Cl_2 (0.2 M) afforded **2ca** with a similar result to that in entry 1, increasing the amount of NBP improved the yield and selectivity (entries 4 and 5). Although NBP led to a better outcome, the resulting phthalimide made it difficult to isolate **2ca** by column chromatography from crude mixtures. Pleasingly, the use of *N*-bromosuccinimide (NBS) in place of NBP eased the purification process since resultant succinimide was removed by a simple aqueous workup (entries 6 and 7). More concentrated reaction conditions resulted in a decrease in both yield and enantioselectivity (entry 8). Several reaction media were evaluated using 4 equiv of NBS, and the choice of the reaction media was found to be important to obtain the desired product **2ca** in high yields. For example, this oxidation reaction did not proceed efficiently in toluene, affording **2ca** in 17% yield, but with high enantioselectivity (entry 9). Aprotic polar solvents, such as THF, acetone, and acetonitrile, also gave **2ca** in low yields (entries 10–12). The effect of a reaction temperature and a catalyst loading were evaluated using 4 equiv of NBS in CH_2Cl_2. Although enantioselectivity slightly increased at 0 °C, the yield of **2ca** was significantly dropped (entry 13).[15] Lower catalyst loading resulted in a decrease in the yield but did not affect the enantioselectivity (entry 14).[16]

With the optimized conditions in hand, a variety of 2-methylbenzoyl-protected amino diols were then subjected in this asymmetric oxidation reaction. The results are summarized in Scheme 2. We found that the addition of 0.2 equiv of K_2CO_3 was effective to improve yield or enantioselectivity for some substrates. Amino diols with an ethyl (**1cb**), butyl (**1cc**), and isobutyl group (**1cd**) were tolerated in this reaction, affording the desired α-alkyl serines (**2cb–cd**) in good yields

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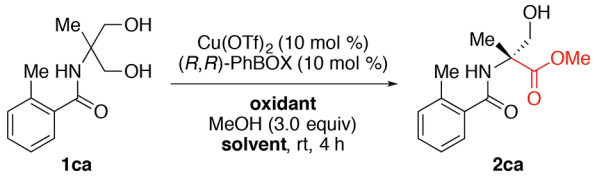
Table 2. Optimization of Reaction Parameters[a]

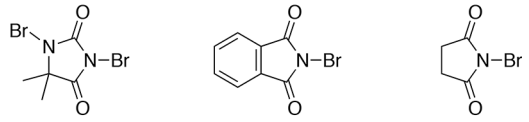


1ca 2ca

entry	oxidant (equiv)	solvent (M)	yield (%)[b]	ee (%)[c]
1	DBDMH (1.5)	CH_2Cl_2 (0.25)	65	85
2	DBDMH (1.75)	CH_2Cl_2 (0.25)	69	83
3	DBDMH (2.0)	CH_2Cl_2 (0.25)	75	80
4	NBP (3.0)	CH_2Cl_2 (0.2)	62	85
5	NBP (4.0)	CH_2Cl_2 (0.2)	83	88
6	NBS (3.0)	CH_2Cl_2 (0.2)	61	87
7	NBS (4.0)	CH_2Cl_2 (0.2)	84	86
8	NBS (4.0)	CH_2Cl_2 (0.25)	71	84
9	NBS (4.0)	toluene (0.2)	17	82
10	NBS (4.0)	THF (0.2)	33	86
11	NBS (4.0)	acetone (0.2)	44	79
12	NBS (4.0)	CH_3CN (0.2)	30	62
13[d]	NBS (4.0)	CH_2Cl_2 (0.2)	24	90
14[e]	NBS (4.0)	CH_2Cl_2 (0.2)	55	86

[a]Reactions were carried out on a 0.5 mmol scale. [b]Isolated yields after column chromatography. n.r. = no reaction. [c]Determined by chiral HPLC analysis. [d]0 °C, 14 h. [e]$Cu(OTf)_2$ (5 mol %) and (*R*,*R*)-PhBOX (5 mol %), 14 h.

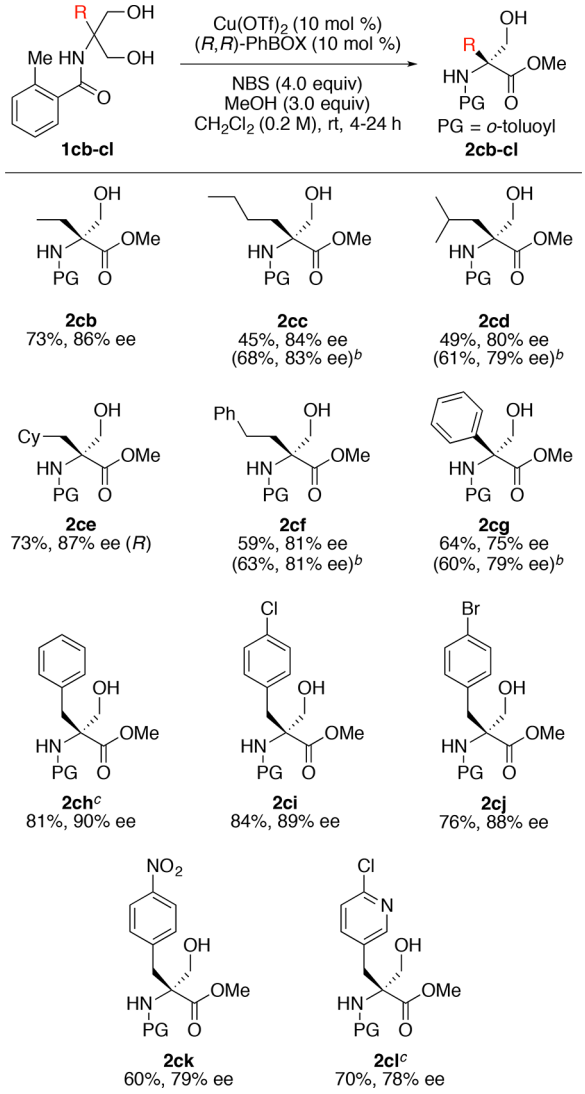
Oxidant



DBDMH NBP NBS

with high enantioselectivities. The reaction of the substrate with a cyclohexylmethyl group also smoothly proceeded to afford the desired product (**2ce**) in 73% yield with 87% ee. The absolute configuration of **2ce** was unambiguously determined to be *R* by X-ray crystallography after the derivatization to the ester with *N*-tosyl-L-phenylglycine (see Supporting Information for details). The serine derivative with a phenethyl group (**2cf**) was also obtained in a good yield with high enantioselectivity. Such α-phenethyl substituted serine derivatives were utilized for the synthesis of (*S*)-(hydroxymethy)glutamic acid, which had been known as one of the most useful metabotropic glutamate receptor ligands.[17] In addition to alkyl groups, an aryl substituent was found to be a suitable substrate, affording **2cg**. Notably, it was difficult to obtain highly enantio-enriched α-phenyl serine precursors by the enzymatic desymmetrization process.[13e] A series of amino diols bearing benzyl groups were then evaluated. A substrate with a nonsubstituted benzyl group afforded **2ch** in high yield with high enantioselectivity. Substrates bearing halogen substituents on the *para*-position of the benzyl group were also tolerated in this reaction to afford the corresponding serines (**2ci** and **2cj**). A *p*-nitrobenzyl-substituted amino diol afforded **2ck** in 60% yield with 79% ee. Moreover, a pyridine ring had little effect on the yield and enantioselectivity, affording **2cl**. In order to show the scalability of this reaction, the present reaction was conducted on a 10 mmol scale using **1ca** as a starting material and affording **2ca** in 82% yield (2.06 g) with 87% ee (Scheme 3). In addition, compound **2ca** was readily transformed to α-methyl serine hydrochloride (**3**) in

Scheme 2. Substrate Scope[a]



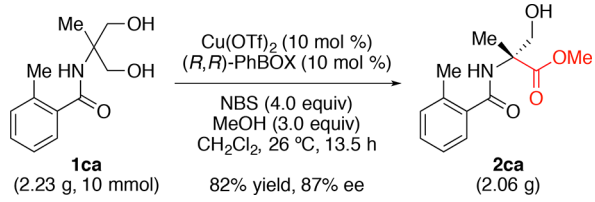
[a]Reactions were carried out on a 0.5 mmol scale. Isolated yields after purification by column chromatography were reported. The enantiomeric excess was determined by chiral HPLC analysis. [b]The reaction was performed in the presence of 0.2 equiv of K_2CO_3 as an additive. [c]The reaction was carried out on a 0.2 mmol scale.

excellent yield by refluxing in aqueous HCl solution (Scheme 4).

3. CONCLUSION

In conclusion, we have developed a novel synthetic strategy for the synthesis of chiral α-substituted serine derivatives through enantioselective oxidative desymmetrization of *N*-2-methyl-benzoyl-protected 2-amino-1,3-propanediols by using the

Scheme 3. Gram-Scale Experiment



1ca (2.23 g, 10 mmol) 82% yield, 87% ee 2ca (2.06 g)

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Scheme 4. Synthesis of α-Methyl Serine Hydrochloride

$Cu(OTf)_2$/(*R*,*R*)-PhBOX system. Under the present reaction conditions, a variety of *N*-2-methylbenzoyl-protected 2-amino-1,3-propanediols with an alkyl, benzyl, aryl, and heteroaryl groups at the 2-position successfully transformed to the corresponding α-substituted serine derivatives in good to high yields with high enantioselectivities. Moreover, the reaction did not require the cryogenic condition and inert atmosphere, which would be beneficial for the industrial process.[18]

4. EXPERIMENTAL SECTION

General Methods and Materials. Unless otherwise noted, all reactions were performed in a test tube equipped with a magnetic stir bar at room temperature under air. All chemicals were used as received without further purifications.

All melting points were determined using a Yanako micromelting point apparatus without correction. Optical rotations were measured with a JASCO DIP-1000 spectrometer using a 3.5 × 100 mm o.d. cell. Infrared (IR) spectra were recorded on a SHIMADZU IRAffinity-1 spectrophotometer. Data were expressed as frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) or a VARIAN GEMINI 300 spectrometer (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR). Chemical shift values are expressed in ppm relative to internal TMS (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for ^1H NMR and $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (δ 39.5 ppm) for ^{13}C NMR. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Enantiomeric excess was determined by HPLC using DAICEL CHIRALPAK AD, AS, AY-H, CHIRALCEL OD-H, and OJ-H columns (4.6 mm id × 250 mm). HPLC chromatograms were recorded on a C-R8A CHROMATOPAC with LC-20AT pump, SPD-20A UV detector (SHIMADZU). High-resolution mass spectra (HRMS) were recorded on JEOL JMS-700N or JMS-T100TD by electron impact ionization (EI) mass spectrometry, fast atom bombardment (FAB) mass spectrometry, or direct analysis in real time (DART) mass spectrometry.

General Procedure for the Preparation of *N*-Protected 1,3-Propanediols. *Procedure A (for 1aa-ga and 1cb).* To a stirred solution of 2-amino-2-methyl-1,3-propanediol (526 mg, 5.0 mmol) and Et_3N (506 mg, 5.0 mmol, 1.0 equiv) in *i*-PrOH (5.0 mL, 1.0 M) was added benzoyl chloride derivatives (5.0 mmol, 1.0 equiv) at 0 °C. The reaction mixture was stirred at room temperature until a TLC indicated that all starting material was consumed. After the removal of all volatiles under reduced pressure, the residue was suspended in H_2O and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Recrystallization (AcOEt/hexane) or column chromatography on silica gel (hexane/AcOEt as an eluent) afforded the pure compound.

Procedure B (for 1cc-cf and 1ch-cl). To a suspension of diethyl 2-(2-methylbenzamido)malonate (1.47 g, 5.0 mmol) and cesium carbonate (2.44 g, 7.5 mmol, 1.5 equiv) was added alkyl bromide or alkyl chloride (5.5 mmol, 1.1 equiv) dropwise at room temperature. The mixture was stirred for 4 h at 65 °C, and then H_2O was added. The reaction mixture was extracted with hexane/AcOEt (4:1) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude mixture was dissolved in dimethoxyethane/MeOH (3:2, 10 mL), and $NaBH_4$ (757 mg, 20 mmol, 4.0 equiv) was added. After stirring for 1 h, the reaction was quenched by the addition of saturated NH_4Cl aq and the reaction mixture was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Recrystallization (AcOEt/hexane) or column chromatography on silica gel (hexane/AcOEt as an eluent) afforded the pure compound.

Procedure C (for 1cg). Compound **1cg** was prepared according to the procedure reported by Kang[19] using 2-methylbenzoyl chloride as a *N*-protecting reagent. To the solution of 2,2-dimethyl-5-phenyl-1,3-dioxan-5-amine[19] (996 mg, 4.8 mmol) in *i*-PrOH (20 mL, 0.24 M) were added Et_3N (587 mg, 5.8 mmol, 1.2 equiv) and 2-methylbenzoyl chloride (742 mg, 4.8 mmol, 1.0 equiv) at 0 °C. After stirring for 2 h at room temperature, all volatiles were removed under reduced pressure, and the crude product was diluted in AcOEt and then washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the *N*-protected product. The residue was dissolved in AcOH/H_2O (4:1, 30 mL, 0.25 M), and then the mixture was stirred for 1 h at 60 °C. The reaction mixture was diluted with H_2O and extracted with AcOEt, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by column chromatography on silica gel (hexane/AcOEt = 1:2) to afford the pure compound.

*2-Methyl-N-(1,3-dihydroxy-2-methylpropan-2-yl)-benzamide (**1ca**).* According to procedure A, **1ca** (827 g, 3.7 mmol, 74% yield) was obtained from 2-amino-2-methyl-1,3-propanediol (526 mg, 5.0 mmol) and 2-methylbenzoyl chloride (772 mg, 5.0 mmol) as a white solid of mp 98−100 °C. IR (ATR): 3329, 3278, 1639, 1533, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.30 (m, 2H), 7.22 (m, 2H), 6.18 (s, 1H), 3.89−3.70 (m, 6H), 2.45 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 136.4, 135.7, 131.0, 130.1, 126.7, 125.8, 67.6, 67.5, 59.5, 20.3, 19.7. HRMS (EI), *m*/*z*: $[M]^+$ calcd for $C_{12}H_{17}NO_3$, 223.1208; found, 223.1202.

*2-Methyl-N-(1,3-dihydroxy-2-n-butylpropan-2-yl)-benzamide (**1cc**).* According to procedure B, **1cc** (1.18 g, 4.4 mmol, 88% yield) was obtained from *N*-(2-toluoyl)amino malonic acid ethyl ester (1.47 g, 5.0 mmol) and *n*-butyl bromide (822 mg, 6.0 mmol) as a colorless oil. IR (ATR): 3304, 2955, 1636, 1516, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 2H), 7.24−7.19 (m, 2H), 6.16 (brs, 1H), 3.93 (dd, *J* = 13.2, 5.4 Hz, 4H), 3.67 (dd, *J* = 13.2, 8.3 Hz, 2H), 2.45 (s, 3H), 1.70 (m, 2H), 1.39−1.33 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 136.5, 135.7, 131.1, 130.1, 126.7, 125.8, 66.2, 61.8, 33.3, 25.3, 23.2, 19.7, 14.0. HRMS (FAB), *m*/*z*: $[M]^+$ calcd for $C_{16}H_{23}NO_4$, 265.1678; found, 265.1682.

*2-Methyl-N-(1,3-dihydroxy-2-phenylpropan-2-yl)-benzamide (**1cg**).* According to procedure C, **1cg** (1.32 g, 4.2 mmol, 88% yield) was obtained as a colorless oil. IR (ATR):

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3311, 3063, 2926, 1638, 1510, 1061 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.22−7.43 (m, 8H), 6.77 (brs, 1H), 4.15 (dd, J = 11.7, 5.9 Hz, 2H), 3.99 (dd, J = 11.4, 6.7 Hz, 2H), 3.77 (t, J = 6.7 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 139.1, 136.2, 135.9, 131.3, 130.4, 128.9, 127.9, 126.7, 126.0, 125.9, 67.6, 66.0, 19.9. HRMS (EI), m/z: $[M]^+$ calcd for $C_{17}H_{19}NO_3$, 285.1365; found, 285.1367.

Compounds **1aa−ba, 1da−ga**, and **1cb** were prepared according to a procedure A. Compound **1ha** was prepared according to the modified procedure A using *p*-toluenesulfonyl chloride. Compound **1ia** was synthesized according to the reported method.[20] Compounds **1cd−cf** and **1ch−cl** were prepared according to procedure B. See the Supporting Information for details.

General Procedure for the Synthesis of α-Substituted Serine Derivatives. A reaction vessel was charged with $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 10 mol %) and (*R*,*R*)-PhBOX (16.7 mg, 0.05 mmol, 10 mol %), and then CH_2Cl_2 (2.5 mL, 0.2 M) and MeOH (48.1 mg, 1.5 mmol, 3.0 equiv) were added. The resulting solution was stirred for 10 min at room temperature, and then amino diol **1** (0.5 mmol) was added. After the solution was stirred for 5 min at the same temperature, *N*-bromosuccinimide (356 mg, 2.0 mmol, 4.0 equiv) was added to the reaction vessel, and the resulting mixture was stirred for additional 4 h. To the reaction mixture was added saturated $Na_2S_2O_3$ aq, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude product. Purification by silica gel column chromatography afforded the desired serine derivatives.

*N-(2-Methylbenzoyl)-α-methylserine Methyl Ester (**2ca**).* Colorless oil, 106 mg, 84% yield, 86% ee, $[\alpha]_D^{19}$ = −2.01 (*c* 1.00, $CHCl_3$). IR (ATR): 3329, 2951, 1734, 1638, 1522, 1128, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.3 Hz, 1H), 7.35−7.32 (m, 1H), 7.26−7.20 (m, 2H), 6.61 (brs, 1H), 4.18 (dd, J = 11.5, 6.6 Hz, 1H), 3.92 (dd, J = 11.5, 6.6 Hz, 1H), 3.83 (s, 3H), 3.59 (t, J = 6.6 Hz, 1H), 2.47 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 170.5, 136.1, 135.8, 131.1, 130.2, 126.9, 125.8, 66.8, 62.4, 53.0, 20.4, 19.7. HPLC HIRALPAK AY-H column, hexane/*i*-PrOH = 7:1, wavelength 254 nm, flow rate 1.0 mL/min, t_R = 13.9 min (major), 16.6 min (minor). HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{17}NO_4$, 251.1158; found, 251.1162.

Gram-Scale Experiment. A reaction vessel was charged with $Cu(OTf)_2$ (362 mg, 1.0 mmol, 10 mol %) and (*R*,*R*)-PhBOX (334 mg, 1.0 mmol, 10 mol %), and then CH_2Cl_2 (50 mL, 0.2 M) and MeOH (961 mg, 30 mmol, 3.0 equiv) were added. The resulting solution was stirred for 10 min at 26 °C, and then **1ca** (2.23 g, 10 mmol) was added. After the solution was stirred for 5 min at the same temperature, *N*-bromosuccinimide (7.12 g, 40 mmol, 4.0 equiv) was added to the reaction vessel, and the resulting mixture was stirred for an additional 13.5 h. To the reaction mixture was added saturated $Na_2S_2O_3$ aq, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude product. Purification by silica gel column chromatography afforded the desired serine derivatives **2ca** (2.06 g, 82% yield, 87% ee).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00407.

Experimental procedure, ORTEP drawing of **S1**, crystal data, ^1H and ^{13}C NMR spectrum for all compounds, and HPLC chromatograms of the products (PDF)

Crystallographic data of compound **S1** (CIF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; NBS, *N*-bromosuccinimide; NBP, *N*-bromophthalimide; TLC, thin layer chromatography

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