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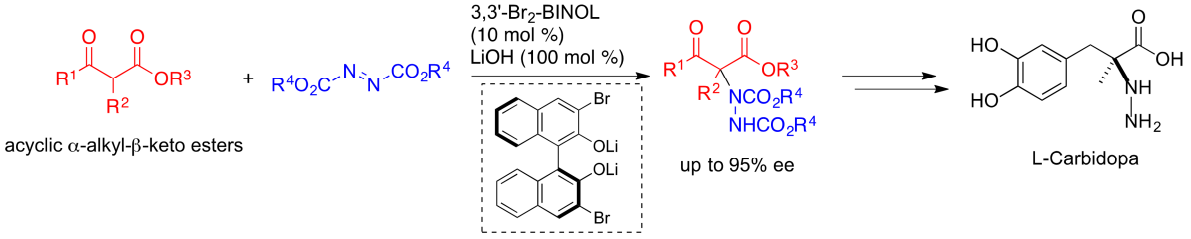

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Chiral lithium binaphtholate for enantioselective amination of acyclic α-alkyl-β-keto esters: Application to the total synthesis of L-carbidopa

Toshifumi Asano,[a] Miyuki Moritani,[a] Makoto Nakajima,[a] Shunsuke Kotani[a,b*]

[a] *Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan*
[b] *Priority Organization for Innovation and Excellence, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan*

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ABSTRACT

A chiral lithium binaphtholate catalyzes the enantioselective amination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-disubstituted α-amino acid derivatives in high yields and with good to high enantioselectivities. A stoichiometric amount of lithium hydroxide efficaciously improved both the reactivity and enantioselectivity of amination. The resulting aminated product is readily convertible to L-carbidopa.

1. Introduction

Optically active amino acids are one of the most representative constituents of living organisms. However, α,α-disubstituted α-amino acids are found only in unnatural amino acids, some of which possess unique biologically activity.[1] Therefore, a number of asymmetric transformations for synthesizing such optically active α,α-disubstituted α-amino acids have been developed over the past several decades.[2] One conventional strategy to generate optically active α,α-disubstituted α-amino acids is the asymmetric addition of a tertiary carbanion equivalent to an electrophilic nitrogen.[3] In 2003, Jørgensen and co-workers were the first to demonstrate a chiral Ph-bis(oxazoline)copper complex catalyzed enantioselective amination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-disubstituted α-amino acids in high enantioselectivity.[4] Recent advances on metal catalyses and organocatalyses have also provided us with many asymmetric variations.[5-8] Indeed, cyclic α-alkyl-β-keto esters such as cyclohexanone carboxylates and 1-indanone carboxylates afforded high stereoselectivity, however, less attention has been paid to acyclic α-alkyl-β-keto esters, except for acetylpropionates. In this regard, our group has explored the utilities of the conjugate base of binaphthol (i.e., binaphtholate) and has recently reported asymmetric conjugate additions of acyclic α-alkyl-β-keto esters using dilithium binaphtholate catalysis.[9,10] In this publication, we report the full details of the enantioselective amination of acyclic α-alkyl-β-keto esters catalyzed by chiral lithium binaphtholate,[10] and the asymmetric short-step synthesis of L-carbidopa using enantioselective amination as a key step.

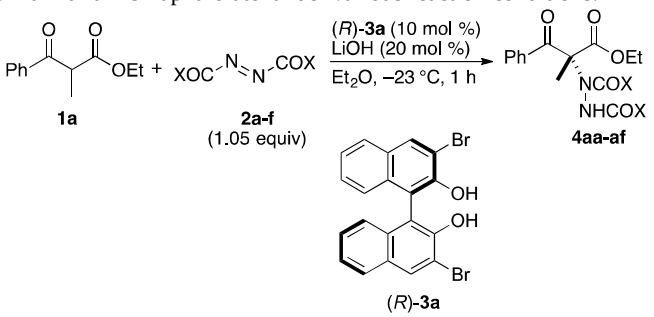
2. Results and discussion

2.1. Enantioselective amination of α-alkyl-β-keto esters catalyzed by chiral lithium binaphtholate

We began examining the asymmetric amination of β-keto ester **1a** with various azodicarbonyl compounds **2a-f** in the presence of 10 mol % of (*R*)-3,3'-Br_2-BINOL (**3a**) as a precatalyst and 20 mol % of lithium hydroxide (LiOH) in diethyl ether at –23 ºC (Table 1). Azodicarboxylate esters **2a-e** showed sufficient reactivity to afford the corresponding aminated adducts **4aa-ae** in high yields (entries 1–5). *tert*-Butyl azodicarboxylate **2c** gave the best enantioselectivity of 74% ee (entry 3). Azodicarbamate **2f** was less reactive under these reaction conditions, yielding no product (entry 6).

* Corresponding author. Tel.: +81963714394; E-mail address: skotani@gpo.kumamoto-u.ac.jp

Table 1. Enantioselective amination of **1a** with **2** catalyzed by chiral lithium binaphtholate under various reaction conditions.[a]

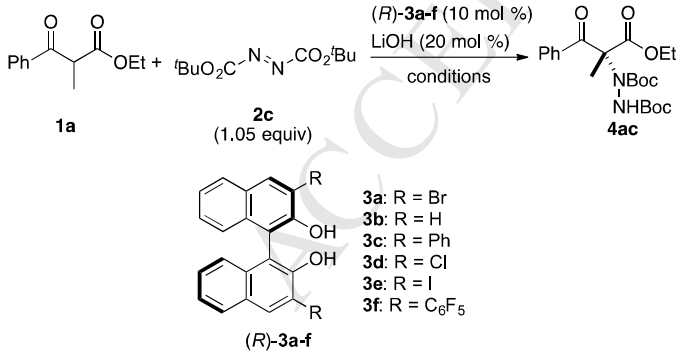


Entry	**2**	X	Yield, %	ee, %[b]
1	**2a**	OMe	96	62
2	**2b**	OEt	96	64
3	**2c**	O^{t}Bu	98[c]	74
4	**2d**	OBn	92	54[d]
5	**2e**	OCH_2CCl_3	89	4
6	**2f**	NMe_2	0	–

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (20 mol %) in Et_2O (4 mL) at –23 °C.
[b] Determined by HPLC analysis.
[c] For 0.5 h.
[d] The absolute configuration is *R*.

To improve the enantioselectivities, we next examined the amination reaction with various BINOLs **3a-f** (Table 2). Parent (*R*)-BINOL (**3b**) and (*R*)-3,3'-Ph_2-BINOL (**3c**) were ineffective, giving very low selectivities (entries 2 and 3). Higher enantioselectivities were obtained with (*R*)-3,3'-dihaloBINOLs, with a significant acceleration of the reaction rate (entries 1, 4, and 5). To clarify the effects of the halogeno groups, we conducted the amination reaction with (*R*)-3,3'-$(C_6F_5)_2$-BINOL (**3f**, entry 6). Similar to (*R*)-3,3'-Ph_2-BINOL (**3c**), low enantioselectivity (8% ee) was obtained, despite the higher conversion. This result indicates that the steric effect of the 3,3'-substituents affect the asymmetric induction, whereas the electron deficiency increased the catalytic activity.

Table 2. Screening of (*R*)-BINOLs.[a]

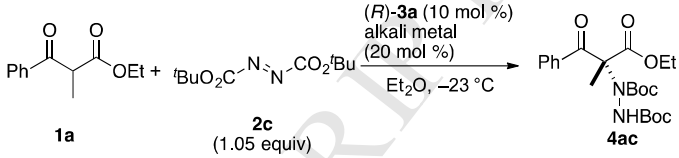


Entry	**3**	Time, h	Yield, %	ee, %[b]
1	**3a**	0.5	98	74
2	**3b**	1	95	5
3	**3c**	1	92	4
4	**3d**	0.5	97	61
5	**3e**	0.5	97	64
6	**3f**	1	92	8

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3** (10 mol %) and LiOH (20 mol %) in Et_2O (4 mL) at –23 °C.
[b] Determined by HPLC analysis.

To investigate the effect of the bases, we examined the reaction with various alkali metals (Table 3). Other lithium bases such as butyllithium and lithium *tert*-butoxide afforded good enantioselectivities (entries 2 and 3). Sodium hydroxide and potassium hydroxide gave the lower yields and selectivities (entries 4 and 5). These results implied that the enantio-determining step involves lithium metals.

Table 3. Screening of alkali metals.[a]

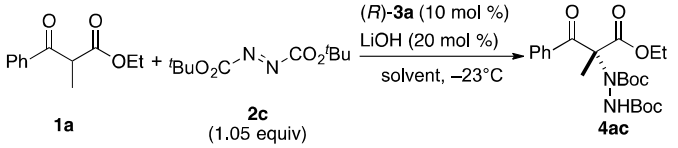


Entry	alkali metal	Time, h	Yield, %	ee, %[b]
1	LiOH	0.5	98	74
2	^{n}BuLi	1	96	68
3	LiO^{t}Bu[c]	1	99	71
4	NaOH	1	54	8
5	KOH	1	34	4

[a] Unless otherwise noted, the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and an alkari metal (20 mol %) in Et_2O (4 mL) at –23 °C.
[b] Determined by HPLC analysis.
[c] 1.0 M LiO^{t}Bu/THF was used.

We next investigated solvent effects (Table 4). Less polar solvents such as dichloromethane and toluene were ineffective for both the yields and selectivities (entries 2 and 3). Regarding coordinative solvents, tetrahydrofuran afforded the aminated adduct **4ac** in good enantioselectivity, albeit in low yield (entry 4). Acyclic ethers such as *tert*-butyl methyl ether (TBME) and cyclopentyl methyl ether (CPME) afforded good yields and enantioselectivities (entries 5 and 6). In contrast, 1,4-dioxane and 1,2-dimethoxyethane (DME) decreased selectivity (entries 7 and 8). Bidentate coordination might prevent substrates from accessing lithium atom, resulting in lower enantioselectivities.

Table 4. Screening of solvents.[a]

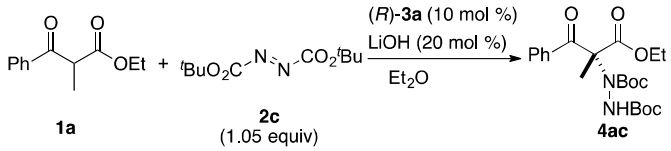


Entry	Solvent	Time, h	Yield, %	ee, %[b]
1	Et_2O	0.5	98	74
2	CH_2Cl_2	2	22	2
3	toluene	2	22	11
4	THF	2	35	65
5	TBME	1	92	54
6	CPME	1	90	71
7	1,4-dioxane	2	82	17
8	DME	2	18	10

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (20 mol %) in a solvent (4 mL) at –23 °C.
[b]Determined by HPLC analysis.

We performed the amination at various temperatures (Table 5). At 0 °C, the reaction was completed within 10 min, but the enantioselectivity was decreased (entry 2). Thus, conducting the reaction at lower temperatures increased the enantioselectivities (entries 3-5). At –60 °C, the highest enantioselectivity (80% ee) was obtained (entry 4), whereas, at –78 °C, both reactivity and enantioselectivity decreased (entry 5).

Table 5. Effect of temperatures.[a]



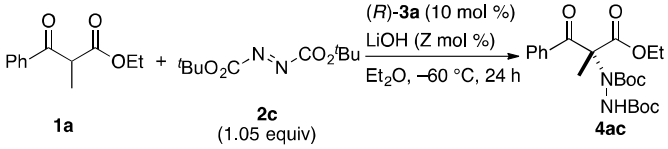
1a **2c** (1.05 equiv) **4ac**

Entry	Temp., °C	Time, h	Yield, %	ee, %[b]
1	–23	0.5	98	74
2	0	10 min	99	61
3	–40	24	99	79
4	–60	24	99	80
5	–78	24	55	60

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (20 mol %) in Et_2O (4 mL).
[b] Determined by HPLC analysis.

Next, we examined the effect of LiOH by varying the amounts of equivalents (Table 6). Interestingly, increasing LiOH equivalents improved the enantioselectivities, and the use of a stoichiometric amount of LiOH afforded **4ac** in 90% yield with 87% ee (entry 5). Excess amounts of LiOH did not improve the enantioselectivity (entry 6). As for facilitating progression of the reaction, formation of monolithium binaphtholate (see binaphtholate **5** in Figure 1) may be superior to that of dilithium binaphtholate due to the production of lithiated **4ac**. Overall, it is clear that a stoichiometric amount of LiOH is sufficient to promote the formation of highly active dilithium binaphtholate, which can be employed in the asymmetric amination.

Table 6. Investigation of LiOH equivalents.[a]



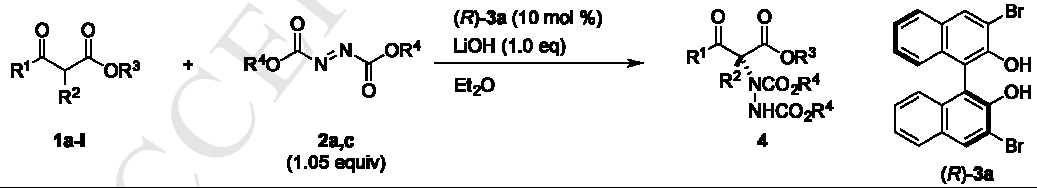
1a **2c** (1.05 equiv) **4ac**

Entry	Z, mol %	Yield, %	ee, %[b]
1	10	98	77
2	20	99	80
3	30	91	82
4	50	99	86
5	100	90	87
6	130	99	86

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (Z mol %) in Et_2O (4 mL) at –60 °C.
[b] Determined by HPLC analysis.

With the optimum reaction conditions in hand, we examined the enantioselective amination of keto esters **1** with azodicarboxylate **2c** (Table 7). Keto ester **1b** bearing an electron-withdrawing group slightly decreased the enantioselectivity relative to benzoyl ester **1a** (entry 2). In contrast, keto esters **1c-e** with electron-donating functional groups on the phenyl group maintained higher enantioselectivities (entries 3–5). However, introducing an *o*-methoxy group on the phenyl group diminished enantioselectivity (entry 6). It is possible that the *o*-methoxy group coordinates to the lithium complex in the transition structure, resulting in a reduction of enantioselectivity. Although alkyl ketones **1g-i** were reactive and the reactions completed in 2 h (entries 7-9), but the products afforded lower enantioselectivities than those of aryl ketones. In examination of R^2 groups, the azodicarboxylate **2a** gave higher enantioselectivities than **2c** (entries 10-12). α-butyl-β-keto ester **1j** gave the product **4ja** in 68% yield and 58% ee (entry 10). Keto ester **1k** bearing an allyl group gave the product **4ka** in quantitative yield and with 82% ee (entry 11). Benzylated keto

Table 7. Enantioselective amination catalyzed by lithium binaphtholate **3a**[a]



1a-l **2a,c** (1.05 equiv) **4** (*R*)-**3a**

Entry	**1**	R^1	R^2	R^3	**2**	R^4	Temp., °C	Time, h	Yield, %	ee, %[b]
1	**1a**	Ph	Me	Et	**2c**	^{t}Bu	–60	24	90	87
2	**1b**	4-F-C_6H_4	Me	Me	**2c**	^{t}Bu	–60	24	98	78
3	**1c**	4-MeO-C_6H_4	Me	Me	**2c**	^{t}Bu	–40	24	96	80
4	**1d**	3,5-$(MeO)_2$-4-Br-C_6H_2	Me	Me	**2c**	^{t}Bu	–23	24	93	88
5	**1e**	3,4-$(MeO)_2$-C_6H_3	Me	Me	**2c**	^{t}Bu	–30	24	95	89[c]
6	**1f**	2-MeO-C_6H_4	Me	Et	**2c**	^{t}Bu	–60	24	62	4
7	**1g**	Me	Me	Et	**2c**	^{t}Bu	–60	2	93	47
8	**1h**	^{n}Pr	Me	Et	**2c**	^{t}Bu	–60	2	83	13
9	**1i**	^{i}Pr	Me	Et	**2c**	^{t}Bu	–60	2	85	54
10	**1j**	Ph	^{n}Bu	Me	**2a**	Me	–60	24	68	58
11	**1k**	Ph	allyl	Et	**2a**	Me	–60	24	86	82
12	**1l**	Ph	Bn	Et	**2a**	Me	–60	24	82	95

[a] All the reactions were performed by treating **1** (0.5 mmol) with **2** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (1.0 equiv) in Et_2O (4 mL).
[b] Determined by HPLC analysis.
[c] The absolute configuration is *R*.

ester **1i** afforded the best enantioselectivity of 95% ee (entry 12).

The proposed catalytic cycle is shown in Figure 1. First, lithium binaphtholates **5** and **6** are formed from (*R*)-3,3'-Br_2-BINOL (**3a**) and LiOH, entering a state of equilibrium in the reaction media. Since the use of a stoichiometric amount of LiOH improved both the yield and enantioselectivity, we expect that dilithium binaphtholate **6** is an aptly active species in this asymmetric amination. Next, toward dilithium binaphtholate **6**, a lithium enolate of keto ester (**1**-Li) coordinates to form chiral complex **A**, which may well be stabilized by the coordination of ether solvent based on the solvent investigations (Table 4). Azodicarboxylate **2** then approaches complex **A** from its *Re*-face, undergoing carbon-nitrogen bond formation via transition state **B** to give complex **C** as the *R*-isomer.[4a] Finally, lithium binaphtholate **5** is eliminated along with lithiated product (**4**-Li). At an early stage of the catalytic cycle, reformation of dilithium binaphtholate **6** from **5** occurs efficiently, with growing tendency to form monolithium binaphtholate **5** as the reaction progresses. LiOH successfully moves the equilibrium to dilithium binaphtholate **6**, resulting in regeneration of the active catalyst.

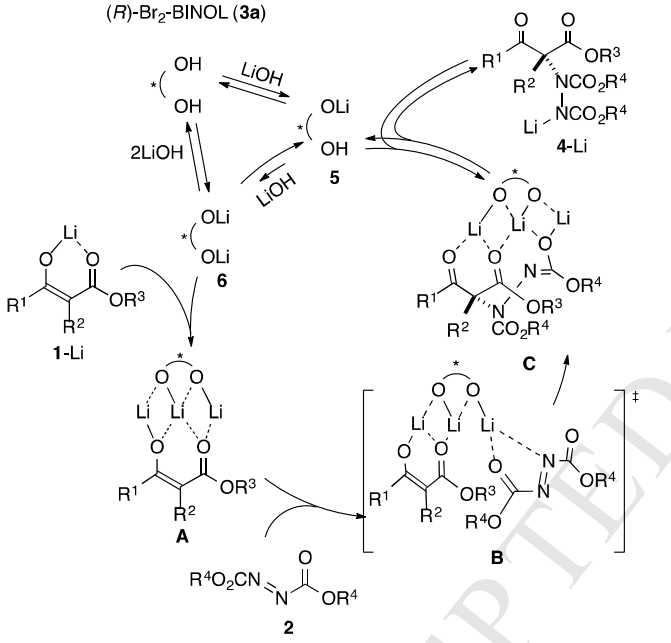


Figure 1. Plausible reaction mechanism of the lithium binaphtholate-catalyzed asymmetric amination

2.2. Asymmetric synthesis of L*-carbidopa*

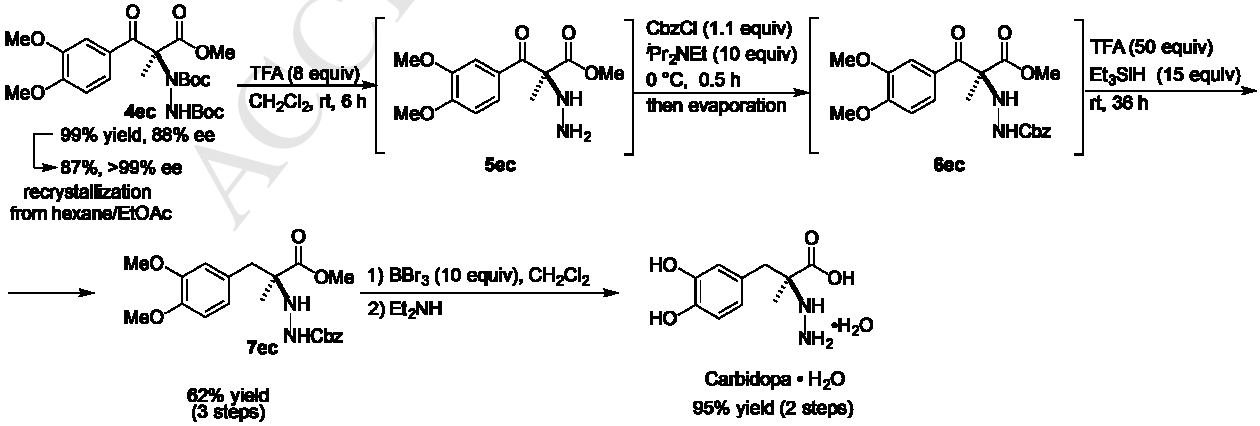
To demonstrate the synthetic utility of the lithium binaphtholate-catalyzed asymmetric amination in organic synthesis, we attempted the total synthesis of L-carbidopa, which is a drug used to treat Parkinson's disease.[11] L-Carbidopa acts as an inhibitor of the peripheral aromatic L-amino acid decarboxylase, an enzyme responsible for the metabolism of levodopa to dopamine. In combination with L-dopa, L-carbidopa temporarily diminishes the disease's motor symptoms. Vallribera and co-workers demonstrated in 2013 the asymmetric synthesis of L-carbidopa using enantioselective amination.[12] Despite the convenience of their synthetic route, the use of sterically congested ester motifs was essential to obtain high stereoselectivity. Consequently, an expensive reducing reagent was required for the carbonyl reduction. However, it is possible to synthesize L-carbidopa more conveniently with the enantioselective amination catalyzed by lithium binaphtholate presented herein, as it affords aminated adducts with high enantioselectivity from α-alkyl-β-keto esters.

To this end, we performed asymmetric amination of methyl keto ester **1e** with azodicarboxylate **2c** in the presence of 10 mol % of (*S*)-**3a** to give the aminated adduct (*S*)-**4ec** in 99% yield and with 88% ee (Scheme 1). After recrystallization from hexane/EtOAc, the enantioselectivity of the mother liquid increased to >99% ee. The next three-step conversion to **7ec** must be pursued as a one-pot procedure because hydrazine intermediate **5ec** steadily decomposes.[13] Aminated adduct **4ec** was treated with trifluoroacetic acid (TFA) to remove two *tert*-butoxycarbonyl groups, and the subsequent addition of *N*,*N*-diisopropylethylamine and carbobenzoxy chloride afforded **6ec**. The one-pot procedure allowed the conversion of **4ec** to **6ec** in quantitative yield, and improved the synthesis efficiency. After evaporation, the obtained residue of hydrazide **6ec** was treated with triethylsilane in TFA, leading to α-aminoester **7ec** in 62% yield. Following Vallribera's derivatization procedure, we performed demethylation of **7ec** with BBr_3 to obtain L-carbidopa·hydrobromide salt, which was nuetlized by diethylamine, leading to L-carbidopa·monohydrate.[12] The synthesized L-carbidopa was identical to the commercially available authentic material with respect to all experimental data. Thus, we achieved asymmetric total synthesis of L-carbidopa in 7 steps (42% yield) from commercially available materials.

3. Conclusion

We have demonstrated that chiral lithium binaphtholate prepared from (*R*)-3,3'-Br_2-BINOL and lithium hydroxide catalyzes the enantioselective amination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-

Scheme 1. Total synthesis of L-carbidopa



disubstituted α-amino acid derivatives with good to high enantioselectivities. The use of a stoichiometric amount of lithium hydroxide strongly increased the catalytic activity to improve the enantioselectivities. Using this amination as a key step, we achieved the asymmetric total synthesis of L-carbidopa in 7 steps (42% yield) from commercially available materials. A one-pot procedure allows conversion of L-carbidopa into higher yields.

Acknowledgments

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4. Experimental Section

4.1. General experimental details

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a JEOL JNM-ECX400 spectrometer. Tetramethylsilane (TMS) (δ = 0 ppm) and $CDCl_3$ (δ = 77.0 ppm) served as an internal standard for ^{1}H and ^{13}C, respectively. Infrared spectra were recorded on a Perkin Elmer Frontier. Mass spectra were measured with a JEOL JMS-700MStation and BRUKER Impact II. Optical rotations were recorded on a JASCO P-1010 polarimeter. High-performance liquid chromatography (HPLC) was performed on a JASCO P-2080 and UV-2075. Thin-layer chromatography (TLC) analysis was performed using Merck silica gel plates. Visualization was accomplished with UV light, phosphomolybdic acid, and/or anisaldehyde. Column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, 63–210 μm). (*R*)-3,3'-disubstituted BINOLs were synthesized according to literature procedures.[14] β-Keto esters **1** was synthesized according to literatures.[15] Purified lithium hydroxide was prepared by recrystallization in H_2O and then dried at 70 °C under reduced pressure. Authentic L-carbidopa was purchased from Tokyo Kasei Industries. Dehydrated stabilizer-free diethyl ether and tetrahydrofuran were purchased from Kanto Chemical Co. Inc. All other solvents and chemicals were purified based on standard procedures or used as received, unless otherwise noted.

4.2. Typical procedure for lithium binaphtholate catalyzed enantioselective amination

To a suspension of (*R*)-3,3'-Br_2-BINOL (**3a**, 22.2 mg, 0.05 mmol) and LiOH (12.0 mg, 0.5 mmol) in diethyl ether (1 mL) was added a diethyl ether solution of β-keto ester **1** (0.25 M, 2 mL, 0.50 mmol) at 23 °C under an argon atmosphere. The reaction mixture was cooled to the desired temperature, and then a solution of azodicarboxylate **2** in diethyl ether (0.525 M, 1 mL, 0.525 mmol) was added. The mixture was further stirred for 24 h at the same temperature. The reaction was quenched with aqueous saturated NH_4Cl (5 mL), and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL) and then dried over Na_2SO_4. Concentration and column chromatographic purification gave the corresponding adduct **4**. The enantiomeric excess was determined by HPLC equipped with a chiral column.

*4.2.1. (–)-1-[1-Benzoyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-dimethyl ester(**4aa**)*

Colorless amorphous; 170.7 mg; 96% yield; TLC: R_f 0.48 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); m.p.; 58.0-100.5 °C; $[\alpha]_D^{25}$ –95.9 (*c* 1.05, $CHCl_3$) for 62% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.39 (m, 3H), 1.78-1.97 (m, 3H), 3.35-4.05 (m, 6H), 4.26-4.42 (m, 2H), 6.27-6.72 (m, 1H), 7.36-7.58 (m, 3H), 7.95-8.59 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ 13.9, 14.1, 20.1, 53.3, 53.8, 54.0, 54.4, 54.7, 62.3, 62.6, 128.2, 128.5, 129.2, 129.8, 133.0, 134.0, 157.3, 157.6, 169.9, 190.7; IR (ATR): 3297, 2959, 1720, 1687, 1229 cm^{-1}; LRMS (FAB): *m*/*z* 353 $(M+H)^+$; HRMS (FAB): Calcd for $C_{16}H_{21}N_2O_7$ 353.1349, found 353.1354. The enantiomeric excess was determined to be 62% ee by HPLC with Daicel Chiralcel AD-H column [eluent: hexane/IPA = 19/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 41.6 min (major), 44.1 min (minor)].

*4.2.2. (–)-1-[1-Benzoyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-diethyl ester (**4ab**)*

Colorless amorphous; 182.1 mg; 96% yield; TLC: R_f 0.44 (hexane/EtOAc = 2/1, stained white with anisaldehyde); $[\alpha]_D^{30}$ –109.2 (*c* 1.05, $CHCl_3$) for 64% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82-1.58 (m, 9H), 1.79-1.96 (m, 3H), 3.92-4.36 (m, 6H), 6.27-6.50 (m, 1H), 7.46-7.52 (m, 3H), 8.11-8.51 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.2, 13.8, 14.0, 14.1, 14.4, 20.1, 20.7, 62.3, 62.5, 63.2, 63.6, 128.1, 128.4, 129.2, 129.4, 129.7, 132.7, 132.9, 133.8, 134.1, 156.8, 157.0, 157.6, 169.6, 169.8, 190.8, 191.9; IR (ATR): 3286, 2996, 1687 cm^{-1}; LRMS (ESI): *m*/*z* 403 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{18}H_{25}N_2NaO_7$ 403,1476, found 403.1481. The enantiomeric excess was determined to be 64% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 19.6 min (major), 25.3 min (minor)].

*4.2.3. (–)-1-[1-Benzoyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4ac**).*

Pale yellow amorphous; 197.0 mg; 90% yield; TLC: R_f 0.25 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{27}$ –106.5 (*c* 1.05, $CHCl_3$) for 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05-1.95 (m, 24H), 4.25-4.40 (m, 2H), 5.95-6.47 (m, 1H), 7.30-7.58 (m, 3H), 8.11-8.65 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.1, 20.2, 20.9, 27.2, 27.8, 28.2, 62.0, 62.2, 76.3, 77.5, 81.3, 81.5, 82.1, 82.9, 83.1, 85.0, 128.0, 128.2, 128.3, 128.9, 129.2, 129.8, 129.9, 132.4, 132.8, 134.0, 134.6, 155.7, 156.4, 169.5, 169.8, 170.0, 191.0, 191.2, 192.0; IR (ATR): 2980, 1734, 1714, 1688, 1154 cm^{-1}; LRMS (FAB): *m*/*z* 459 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{22}H_{32}N_2NaO_7$ 459.2107, found 459.2085. The enantiomeric excess was determined to be 87% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 8.5 min (minor), 17.9 min (major)].

*4.2.4. (–)-1-[(1R)-1-Benzoyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-dibenzyl ester (**4ad**).*[4a]

Pale yellow amorphous; 232.1 mg; 92% yield; TLC: R_f 0.28 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{19}$ –34.5 (*c* 1.29, CH_2Cl_2) for 54% ee [lit. $[\alpha]_D^{25}$ –82.7 (*c* 0.98, CH_2Cl_2) for 98% ee (*R*)]; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.16-1.29 (m, 3H), 1.74-2.02 (m, 3H), 4.18-4.33 (m, 2H), 4.88-5.29 (m, 4H), 6.33-6.66 (m, 1H), 7.05-7.58 (m, 13H), 8.07-8.54 (m, 2H). The enantiomeric excess was determined to be 54% ee by HPLC with Daicel Chiralpak AS-H column [eluent: hexane/IPA

= 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 27.7 min (minor, *S*), 63.7 min (major, *R*)].

*4.2.5. (–)-1-[1-Benzoyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-bis(2,2,2-trichloroethyl) ester (**4ae**).*

Colorless amorphous; 261.2 mg; 89% yield; TLC: R_f 0.39 (hexane/EtOAc = 4/1, stained white with anisaldehyde); $[\alpha]_D^{31}$ –3.6 (*c* 0.90, $CHCl_3$) for 4% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-1.39 (m, 3H), 1.87-1.99 (m, 3H), 4.28-5.23 (m, 6H), 6.63-7.05 (m, 1H), 7.37-7.55 (m, 3H), 7.96-8.47 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.9, 14.1, 14.2, 19.9, 20.2, 62.7, 63.0, 63.1, 75.2, 75.4, 75.7, 75.9, 94.3, 94.5, 128.3, 128.5, 129.0, 129.2, 130.0, 133.1, 133.5, 133.8, 134.1, 153.8, 154.4, 154.9, 155.0, 155.4, 169.2, 169.5, 190.3; IR (ATR): 1746, 1720, 1688 cm^{-1}; LRMS (FAB): *m/z* 585, 587, 589, 591 $(M+H)^+$; HRMS (FAB): Calcd for $C_{18}H_{19}Cl_6N_2O_7$ 584.9333, found 584.9323. The enantiomeric excess was determined to be 4% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 4/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 11.9 min (major), 34.6 min (minor)].

*4.2.6. (–)-1-[1-(4-Fluorobenzoyl)-2-methoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4bc**).*

Pale yellow amorphous; 215.8 mg; 98% yield; TLC: R_f 0.42 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{19}$ –90.7 (*c* 0.80, $CHCl_3$) for 78% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07-1.97 (m, 21H), 3.87 (s, 3H), 5.96–6.52 (m, 1H), 7.02–7.23 (m, 2H), 8.22–8.66 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 20.3, 20.9, 27.3, 27.8, 28.2, 53.0, 53.2, 76.4, 77.6, 81.5, 81.6, 83.3, 85.3, 115.3, 115.4, 115.6, 130.3, 130.8, 131.6, 131.96, 132.04, 132.6, 155.6, 155.8, 156.5, 164.0, 164.2, 166.6, 166.7, 170.3, 170.5, 190.0, 190.8; IR (ATR): 2981, 1720, 1688, 1599, 1154 cm^{-1}; LRMS (FAB): *m/z* 463 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{21}H_{29}FN_2NaO_7$ 463.1856, found 463.1864. The enantiomeric excess was determined to be 78% ee using HPLC equipped with a Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 7.3 min (minor), 45.6 min (major)].

*4.2.7. (–)-1-[2-Methoxy-1-(4-methoxybenzoyl)-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4cc**).*

Pale yellow amorphous; 217.2 mg; 96% yield; TLC: R_f 0.22 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{19}$ –99.2 (*c* 0.80, $CHCl_3$) for 80% ee; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.11-1.95 (m, 21H), 3.81-3.94 (m, 6H), 5.94-6.50 (m, 1H), 6.83-7.05 (m, 2H), 8.14-8.66 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 20.5, 21.1, 27.2, 27.8, 28.1, 52.7, 52.9, 53.0, 55.3, 76.5, 77.7, 81.2, 81.4, 82.0, 82.9, 83.1, 84.8, 113.5, 126.9, 127.3, 131.2, 131.5, 132.1, 132.5, 155.8, 156.5, 162.8, 163.1, 170.5, 170.8, 190.4, 191.0; IR (ATR): 3303, 2980, 1721, 1679, 1601, 1243, 1153 cm^{-1}; LRMS (FAB): *m/z* 475 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{22}H_{32}N_2NaO_8$ 475.2056, found 475.2066. The enantiomeric excess was determined to be 80% ee using HPLC equipped with a Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 13.8 min (minor), 45.8 min (major)].

*4.2.8. (–)-1-[1-(4-Bromo-3,5-dimethoxybenzoyl)-2-methoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4dc**).*

Colorless amorphous; 595.0 mg; 93% yield; TLC: R_f 0.50 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{25}$ –120.2 (*c* 1.09, $CHCl_3$) for 88% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.64 (m, 18H), 1.80-1.95 (m, 3H), 3.87 (s, 3H), 4.00 (s, 6H), 6.26 (brs, 1H), 7.80-7.86 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 20.2, 20.8, 27.3, 27.8, 28.0, 28.4, 29.6, 53.0, 53.1, 56.7, 56.9, 57.1, 76.3, 77.5, 81.5, 81.6, 83.3, 85.3, 105.4, 105.9, 106.3, 106.8, 134.1, 134.4, 155.6, 155.8, 156.2, 156.9, 157.0, 170.2, 170.4, 190.5, 191.3; IR (ATR): 3308, 2980, 1726, 1689, 1241, 1120 cm^{-1}; LRMS (FAB): *m/z* 585, 583 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{23}H_{33}BrN_2NaO_9$ 583.1267, found 583.1275. The enantiomeric excess was determined to be 88% ee using HPLC equipped with a Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 4.7 min (minor), 11.7 min (major)].

*4.2.9. (–)-1-[(1R)-1-(3,4-Dimethoxybenzoyl)-2-methoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4ec**).*[12]

Colorless; 228.6 mg; 95% yield; TLC: R_f 0.31 (hexane/EtOAc = 2/1, stained yellow with anisaldehyde); $[\alpha]_D^{18}$ –137.7 (*c* 1.08, $CHCl_3$) for 89% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12-1.98 (m, 21H), 3.86 (s, 3H), 3.93-3.96 (m, 6H), 6.00-6.51 (m, 1H), 6.92-7.01 (m, 1H), 7.71-8.43 (m, 2H). The enantiomeric excess was determined to be 89% ee using HPLC equipped with a Daicel Chiralpak AD-H column [eluent: hexane/IPA = 4/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 5.7 min (minor, *S*), 22.2 min (major, *R*)].

*4.2.10. (–)-1-[2-Ethoxy-1-(2-methoxybenzoyl)-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4fc**).*

Colorless amorphous; 172.5 mg; 62% yield; TLC: R_f 0.47 (hexane/EtOAc = 2/1, stained yellow with anisaldehyde); $[\alpha]_D^{32}$ +0.1 (*c* 1.13, $CHCl_3$) for 4% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.83 (m, 24H), 3.83 (s, 3H), 4.11-4.31 (m, 2H), 6.07-6.51 (m, 1H), 6.85-7.06 (m, 2H), 7.23-7.50 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.9, 14.2, 19.9, 20.1, 27.8, 27.9, 28.1, 55.2, 55.8, 56.2, 61.6, 80.8, 81.0, 81.3, 82.2, 111.0, 120.6, 120.9, 128.6, 129.1, 129.7, 130.7, 131.1, 131.9, 132.1, 154.5, 154.8, 155.6, 155.9, 168.3; IR (ATR): 3321, 2979, 1708, 1244 cm^{-1}; LRMS (FAB): *m/z* 489 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{23}H_{34}N_2NaO_8$ 489.2213, found 489.2234. The enantiomeric excess was determined to be 4% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 12.5 min (minor), 18.0 min (major)].

*4.2.11. (+)-1-[1-Acetyl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4gc**).*

Pale yellow amorphous; 174.7 mg; 93% yield; TLC: R_f 0.32 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{30}$ +13.3 (*c* 1.02, $CHCl_3$) for 47% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.4 Hz), 1.32-1.78 (m, 21H), 2.21-2.43 (m, 3H), 4.21-4.37 (m, 2H), 5.94-6.37 (m, 1H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 18.9, 19.7, 24.2, 25.7, 27.6, 27.8, 28.0, 61.7, 61.9, 75.2, 75.5, 76.2, 81.2, 81.7, 82.7, 84.7, 155.0, 155.4, 156.2,

168.9, 169.2, 198.9, 199.5, 200.6, 202.2; IR (ATR): 3321, 2980, 1710, 1151 cm^{-1}; LRMS (ESI): *m/z* 397 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{17}H_{30}N_2NaO_7$ 397.1951, found 397.1949. The enantiomeric excess was determined to be 47% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 19/1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 15.5 min (major), 21.8 min (minor)].

*4.2.12. (+)-1-[1-Butyryl-2-ethoxy-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4hc**).*

Pale yellow amorphous; 166.6 mg; 83% yield; TLC: R_f 0.21 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{29}$ +3.9 (*c* 0.97, $CHCl_3$) for 13% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89-0.99 (m, 3H), 1.26-1.80 (m, 26H), 2.44-2.87 (m, 2H), 4.18-4.32 (m, 2H), 5.88-6.42 (m. 1H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.6, 13.9, 14.0, 14.1, 17.5, 19.4, 19.6, 20.2, 20.4, 27.9, 28.0, 28.1, 380, 39.4, 61.8, 62.0, 75.8, 81.3, 81.8, 82.8, 84.6, 155.5, 155.6, 156.3, 169.6, 170.0, 201.6, 202.2, 203.2, 204.5; IR (ATR): 3298, 2970, 1748, 1718, 1152 cm^{-1}; LRMS (ESI): *m/z* 425 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{19}H_{34}N_2NaO_7$ 425.2264, found 425.2264. The enantiomeric excess was determined to be 13% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 19/1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 10.4 min (major), 15.3 min (minor)].

*4.2.13. (–)-1-[2-Ethoxy-1-isobutyryl-1-methyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-di-tert-butyl ester (**4ic**).*

Pale yellow amorphous; 170.1 mg; 85% yield; TLC: R_f 0.34 (hexane/EtOAc = 4/1, stained yellow with anisaldehyde); $[\alpha]_D^{29}$ –10.1 (*c* 1.08, MeOH) for 54% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05-1.85 (m, 30H), 3.18-3.70 (m, 1H), 4.15-4.34 (m, 2H), 5.90-6.36 (m, 1H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.0, 14.1, 19.6, 19.9, 20.3, 20.6, 21.9, 22.3, 27.8, 34.5, 34.9, 36.3, 61.6, 61.9, 75.9, 76.1, 81.2, 81.7, 82.6, 155.5, 155.7, 169.3, 169.5, 169.9, 206.6, 207.3, 209.5; IR (ATR): 3319, 2979, 1710, 1150 cm^{-1}; LRMS (FAB): *m/z* 425 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{19}H_{34}N_2NaO_7$ 425.2264, found 425.2264. The enantiomeric excess was determined to be 54% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 19/1; flow rate: 1.0 mL/min; detection: 220 nm; t_R: 11.2 min (major), 12.3 min (minor)].

*4.2.14. (–)-1-[1-Benzoyl-1-butyl-2-methoxy-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-dimethyl ester (**4ja**).*

Yellow amorphous; 129.8 mg; 68% yield; TLC: R_f 0.25 (hexane/EtOAc = 2/1, stained yellow with anisaldehyde); $[\alpha]_D^{28}$ –54.3 (*c* 0.96, $CHCl_3$) for 58% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68-0.88 (m, 3H), 0.95-2.58 (m, 6H), 3.35-4.00 (m, 9H), 6.28-6.79 (m, 1H), 7.39-7.58 (m, 3H), 7.95-8.62 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.5, 23.1, 26.4, 26.9, 33.9, 34.3, 35.1, 53.2, 53.3, 54.1, 54.5, 79.9, 128.2, 128.6, 128.7, 128.9, 132.9, 135.2, 135.5, 157.4, 157.7, 170.7, 190.1; IR (ATR): 3300, 2958, 1721, 1684, 1228 cm^{-1}; LRMS (ESI): *m/z* 403 $(M+Na)^+$; HRMS (ESI): Calcd for $C_{18}H_{24}N_2NaO_7$ 403.1481, found 403.1475. The enantiomeric excess was determined to be 58% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 12.8 min (minor), 16.1 min (major)].

*4.2.15. (–)-1-[1-Allyl-2-ethoxy-1-benzoyl-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-dimethyl ester (**4ka**).*

Colorless amorphous; 163.1 mg; 86% yield; TLC: R_f 0.38 (hexane/EtOAc = 4/1, stained red with anisaldehyde); $[\alpha]_D^{26}$ –34.5 (*c* 1.05, $CHCl_3$) for 82% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.48 (m, 3H), 2.91-3.32 (m, 2H), 3.33-3.98 (m, 6H), 4.15-4.43 (m, 2H), 4.68-5.13 (m, 2H), 5.76-5.89 (m, 2H), 6.30-6.68 (m, 1H), 7.38-7.58 (m, 3H), 8.16-8.55 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks.^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 13.6, 13.9, 38.6, 39.0, 39.4, 53.2, 53.6, 54.0, 54.3, 62.2, 62.5, 79.5, 118.9, 119.7, 128.0, 128.4, 128.9, 131.6, 132.7, 133.5, 135.1, 156.0, 157.0, 157.5, 167.3, 168.9, 169.3, 189.7, 191.0; IR (ATR): 3300, 2959, 1719, 1686, 1218 cm^{-1}; LRMS (FAB): *m/z* 379 $(M+H)^+$; HRMS (FAB): Calcd for $C_{18}H_{23}N_2O_7$ 379.1505, found 379.1523. The enantiomeric excess was determined to be 82% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 15.1 min (minor), 18.4 min (major)].

*4.2.16. (+)-1-[1-Benzoyl-1-benzyl-2-ethoxy-2-oxoethyl]-1,2-hydradinedicarboxylic acid 1,2-dimethyl ester (**4la**).*

Pale yellow amorphous; 175.9 mg; 82% yield; TLC: R_f 0.38 (hexane/EtOAc = 4/1, stained orange with anisaldehyde); $[\alpha]_D^{27}$ +14.7 (*c* 1.04, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95-1.75 (m, 3H), 3.45–4.42 (m, 10H), 5.10-6.60 (m, 1H), 6.98–7.55 (m, 8H), 8.08–8.65 (m, 2H); Due to the distinct presence of rotameric isomers, the ^{13}C NMR contained multiple peaks. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 13.6, 13.8, 14.0, 39.3, 39.9, 52.8, 53.2, 54.0, 54.2, 62.6, 80.2, 80.5, 126.7, 127.6, 128.0, 128.4, 129.0, 129.2, 129.6, 130.3, 130.7, 132.6, 134.4, 135.1, 135.6, 136.0, 155.9, 156.4, 157.2, 157.6, 165.8, 166.1, 169.3, 189.5, 190.0; IR (ATR): 3302, 2958, 1719, 1688, 1222 cm^{-1}; LRMS (FAB): *m/z* 429 $(M+H)^+$; HRMS (FAB): Calcd for $C_{22}H_{25}N_2O_7$ 429.1662, found 429.1653. The enantiomeric excess was determined to be 95% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 9/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 18.1 min (major), 20.7 min (minor)].

*4.3. Preparation of Enantiomerically Pure (S)-(+)-**4ec***

To a suspension of (*S*)-3,3'-Br_2-BINOL (88.8 mg, 0.2 mmol) and LiOH (48.2 mg, 2 mmol) in diethyl ether (1 mL) was added an diethyl ether solution of β-keto ester **1e** (0.25 M, 2 mL, 2 mmol) at 23 °C under argon atmosphere. A solution of azodicarboxylate **2c** in diethyl ether (0.525 M, 1 mL, 2.1 mmol) at the described temperature was added to the reaction mixture, which was further stirred for 24 h at the same temperature. The reaction was quenched with aqueous saturated NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organic layer was washed with brine (20 mL), and dried over Na_2SO_4. Concentration and column chromatographic purification gave the corresponding adduct **4ec** (955.4 mg, 99% yield, 87% ee), which was then dissolved in hexane/ethyl acetate (20:1, 20 mL) to furnish the racemic crystal. After filtration, the mother liquid was evaporated to obtain (*S*)-**4ea** with >99% ee. The enantiomeric excess was determined to be >99% ee by HPLC with Daicel Chiralpak AD-H column [eluent: hexane/IPA = 4/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 5.5 min (major, *S*), 19.7 min (minor, *R*)].

*4.4. One-pot manipulation for derivatization of **4ec** into **7ec***

4ec (241.4 mg, 0.5 mmol, >99% ee) was treated with TFA (0.31 mL, 4.0 mmol, 8.0 equiv) at 23 °C under argon atmosphere. After stirring for 6 h at the same temperature, the reaction mixture was then cool to 0 °C. To the reaction mixture were added carbobenzoxy chloride (0.079 mL, 0.55 mmol, 1.1 equiv) and *N*,*N*-diisopropylethylamine (0.87 mL, 5.0 mmol, 10 equiv), respectively. The reaction was completed in 30 min, and then the mixture was evaporated under reduce pressure to afford a crude material of **6ec**. The obtained residue was dissolved in TFA (1.9 mL, 25 mmol, 50 equiv) at 23 °C, and triethylsilane (1.2 mL, 7.5 mmol, 15 equiv) was added to the solution. The mixture was heated at 35 °C for 30 h. The reaction mixture was diluted with dichloromethane (3 mL) and quenched with sat. $NaHCO_3$ (15 mL). After stirring for 1 hour, the two-layers mixture was separated, and the water layer was extracted with dichloromethane (4 x 15 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration, the obtained crude material was purified by column chromatography to give the amino acid derivative **7ec**.

*4.4.1. (+)-2-[(1S)-1-(3,4-Dimethoxybenzyl)-2-methoxy-1-methyl-2-oxoethyl]-1,2-hydradinecarboxylic acid benzyl ester (**7ec**).*

Colorless amorphous; 124.5 mg, 62% yield; TLC: R_f 0.36 (hexane/EtOAc = 1/1, stained orange with phosphomolybdic acid); $[\alpha]_D^{27}$ +14.5 (*c* 0.97, $CHCl_3$) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 2.90 (d, 1H, *J* = 13.7 Hz), 3.06 (d, 1H, *J* = 13.7 Hz), 3.71 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.19 (brs, 1H), 5.08-5.13 (m, 2H), 6.47 (brs, 1H), 6.68-6.78 (m, 3H), 7.30-7.38 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 21.2, 43.4, 52.1, 55.8, 66.0, 66.9, 111.0, 112.8, 121.9, 127.5, 128.2, 128.5, 136.1, 148.1, 148.7, 156.9, 175.5; IR (ATR): 3312, 2950, 1721, 1514 cm^{-1}; LRMS (FAB): *m*/*z* 425 $(M+Na)^+$; HRMS (FAB): Calcd for $C_{21}H_{26}N_2NaO_6$ 425.1683, found 425.1680. The enantiomeric excess was determined to be 99% ee by HPLC with Daicel Chiralpak OD-H column [eluent: hexane/IPA = 4/1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 18.7 min (minor, *R*), 24.5 min (major, *S*)].

4.5. Preparation of L-carbidopa•monohydrate[12]

7ec (114.8 mg, 0.285 mmol) was dissolved in dichloromethane (3 mL) under argon atmosphere and to the mixture was added BBr_3 (0.28 mL, 10 equiv) at –78 °C. The reaction mixture was warm to 23 °C and then stirred for 24 h. Addition of H_2O (5 mL) quenched the reaction, and the mixture was further stirred for 1 hour. The two-layers mixture was separated and water layer was wash with dichloromethane (3 x 10 mL) and ethyl acetate (3 x 10 mL). Under reduced pressure, water was evaporated roughly, the obtained residue was dissolved with methanol (5 mL), the resulting solution was stirred for 16 h at 50 °C. Then, solvent was evaporated to obtain L-carbidopa as the hydrobromide salt. The residue was dissolved in isopropyl alcohol (0.5 mL), diethyl amine (41.8 mg, 0.570 mmol) was added to give the solid, which was corrected and dried under reduced pressure at 65 °C to isolate L-carbidopa as monohydrate (66.1 mg, 95% yield). the Spectra of the synthesized L-carbidopa were identical to the reported one.

4.5.1. L-Carbidopa•monohydrate [12]

Colorless needle; 66.1 mg; 95% yield; m.p.; >195 °C (decomposed); $[\alpha]_D^{27}$ –12.8 (*c* 0.33, MeOH) for 99% ee [lit. $[\alpha]_D^{26}$ –11.8 (*c* 0.5, MeOH) for 97.5% ee; authentic sample $[\alpha]_D^{25}$ –16.6 (*c* 0.33, MeOH)]; ^{1}H NMR (400 MHz, DMSO): δ 1.08 (s, 3H), 2.62 (d, 1H, *J* = 13.6 Hz), 2.73 (d, 1H, *J* = 13.6 Hz), 6.39 (d, 1H, *J* = 8.0 Hz), 6.54 (d, 1H, *J* = 8.0 Hz), 6.59 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 21.1, 42.0, 66.0, 115.9, 118.8, 122.1, 127.9, 144.9, 145.7, 175.3; IR (ATR): 3528, 3105, 1626, 1370, 1122; LRMS (FAB): *m*/*z* 227 $(M+H-H_2O)^+$; HRMS (FAB): Calcd for $C_{10}H_{15}N_2O_4$ 227.1032, found 227.1040.

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