Chapter 3

ASYMMETRIC SYNTHESIS OF PROTECTED UNNATURAL *α*-AMINO ACIDS VIA ENANTIOCONVERGENT NICKEL-CATALYZED CROSS-COUPLING

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3.1. Introduction

The development of effective and straightforward methods to access enantioenriched unnatural (non-canonical) *α*-amino acids is a highly important objective, as these amino acids are finding widespread use in fields such as biology, biochemistry, pharmaceutical science, and materials science;[1–5] furthermore, they can readily be transformed into other useful families of chiral molecules, including *β*-amino alcohols

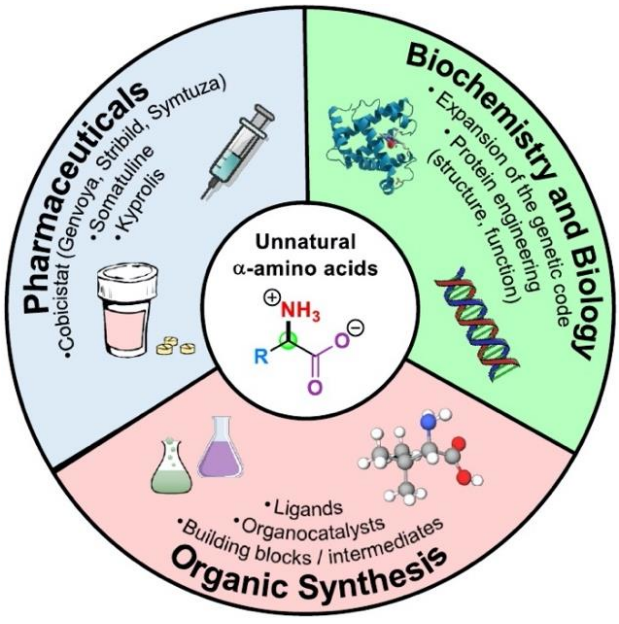
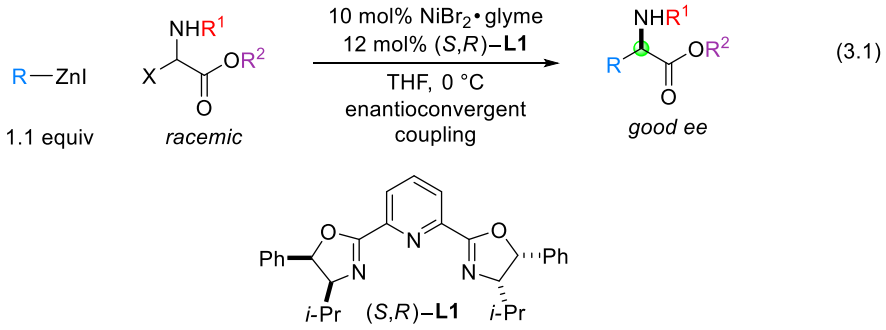


Figure 3.1. *Diverse applications of unnatural α-amino acids.*

(**Figure 3.1**).[6,7] Catalytic asymmetric routes to unnatural α-amino acids are especially attractive,[5,8,9] and numerous approaches have been described, such as hydrogenations of olefins and imines,[10,11] electrophilic aminations of enolates,[12] electrophilic alkylations of glycine derivatives,[13] and nucleophilic additions to α-imino esters.[14]

The development of radical-based methods in organic synthesis, which may complement polar/heterolytic processes, has expanded dramatically in recent years,[15,16] but to our knowledge no such methods have been described for the catalytic asymmetric synthesis of unnatural α-amino acids. We envisioned that nickel-catalyzed enantioconvergent cross-couplings of alkyl electrophiles, which are emerging as a powerful tool in asymmetric synthesis and typically proceed through radical intermediates,[17–23] might provide a straightforward route to protected α-amino acids from readily available coupling partners. In this report we describe the realization of this objective, specifically, that a chiral nickel/pybox catalyst can achieve the coupling of an array of organozinc reagents with racemic α-haloglycine derivatives, enabling ready access to a wide variety of protected α-amino acids (**eq 3.1**), including several that have been applied to the synthesis of bioactive target molecules.

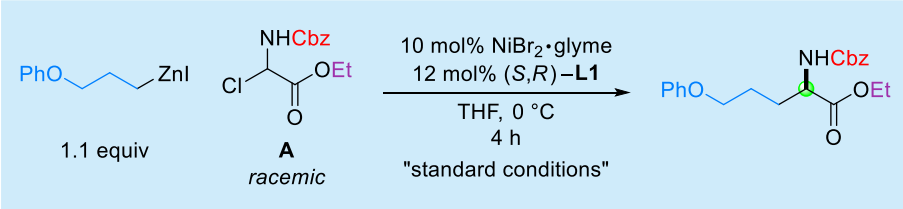


3.2. Results and discussion

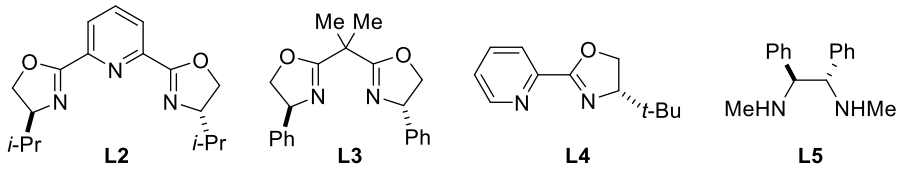
3.2.1. Optimization

To our knowledge, α-halo-α-amino acid derivatives have not been employed as electrophiles in metal-catalyzed asymmetric cross-coupling reactions,[24–27] although they have been utilized as precursors to iminium ions in two organocatalytic processes (nucleophiles: enolates of 1,3-dicarbonyl compounds and allylmetal reagents).[28–30] By

Table 3.1. *Catalytic enantioconvergent synthesis of a protected α-amino acid: effect of reaction parameters.*



entry	variation from the standard conditions	yield (%)	ee (%)
1	none	84	97
2	30 min, instead of 4 h	86	97
3	no $NiBr_2$·glyme	10	<1
4	no **L1**	40	–
5	**L2**, instead of **L1**	60	96
6	**L3**, instead of **L1**	71	80
7	**L4**, instead of **L1**	67	15
8	**L5**, instead of **L1**	47	41
9	5.0 mol% $NiBr_2$·glyme, 6.0 mol% **L1**	82	96
10	2.5 mol% $NiBr_2$·glyme, 3.0 mol% **L1**, 24 h	61	92
11	r.t., instead of 0 °C	80	95
12	0.5 equiv H_2O added	80	96
13	1.0 equiv H_2O added	53	93
14	under air in a closed vial	77	96



following a procedure reported by Roche,[31] Cbz-protected *α*-chloroglycine ester **A** can be obtained in a single step on a multigram scale, and it can be stored at 0 °C for at least 6 months without degradation. When this racemic electrophile is treated with an alkylzinc reagent (1:1.1 ratio, despite a potentially labile *N*-bound proton) in the presence of a chiral nickel/pybox catalyst, alkyl−alkyl coupling proceeds to generate the desired protected *α*-amino acid in good yield and enantioselectivity (84% yield and 97% ee; entries 1 and 2 of **Table 3.1**).

In the absence of $NiBr_2$·glyme or of ligand **L1**, only a small amount of product is observed (racemic; entries 3 and 4 of **Table 3.1**). Although a variety of other chiral ligands are less effective than ligand **L1** (entries 5−8), it is worth noting that commercially available pybox ligand **L2** affords a reasonable yield and high enantioselectivity (entry 5). A lower

catalyst loading can be used (entries 9 and 10), and the method performs well at room temperature (entry 11). The coupling process is robust, only modestly inhibited by small amounts of water (entries 12 and 13; carbon−carbon bond formation is faster than protonation of the organozinc reagent and hydrolysis of the electrophile) or by air (entry 14).

3.2.2. Scope

This straightforward method for the catalytic enantioconvergent synthesis of protected unnatural α-amino acids is compatible with an array of substituents on the nitrogen (R^1 ; **Figure 3.2a**, products **1**−**5**) and on the oxygen (R^2 ; products **1** and **6**) of the electrophile, providing a range of products with good yield and high ee. The scope of the coupling is also broad with respect to the nucleophile. For example, the substituent can range in size from methyl to isobutyl (**Figure 3.2b**, products **7**−**11**; the use of a secondary alkylzinc reagent leads to little product under our standard conditions). Furthermore, a wide variety of functional groups are compatible with the method, including a silyl ether, ether, nitrile, imide, alkyne, unactivated primary alkyl fluoride/chloride, alkene, carbonate, and acetal (products **12**−**31**; we have also established that an aldehyde, aryl iodide, benzofuran, benzonitrile, benzothiophene, epoxide, α-ketoester, ketone, nitroarene, unactivated secondary alkyl bromide, and thioether are compatible; see *Chapter 3.4.7*). In the case of several nucleophiles that bear one or more stereocenters, the stereochemistry of the catalyst, rather than that of the nucleophile, predominantly controls the stereochemistry of the product (products **22**−**31**). On a gram scale (1.48 g of product), the coupling to generate product **1** proceeds in identical yield and ee as for a reaction conducted on a 0.6 mmol scale (83% yield, 97% ee).[32,33]

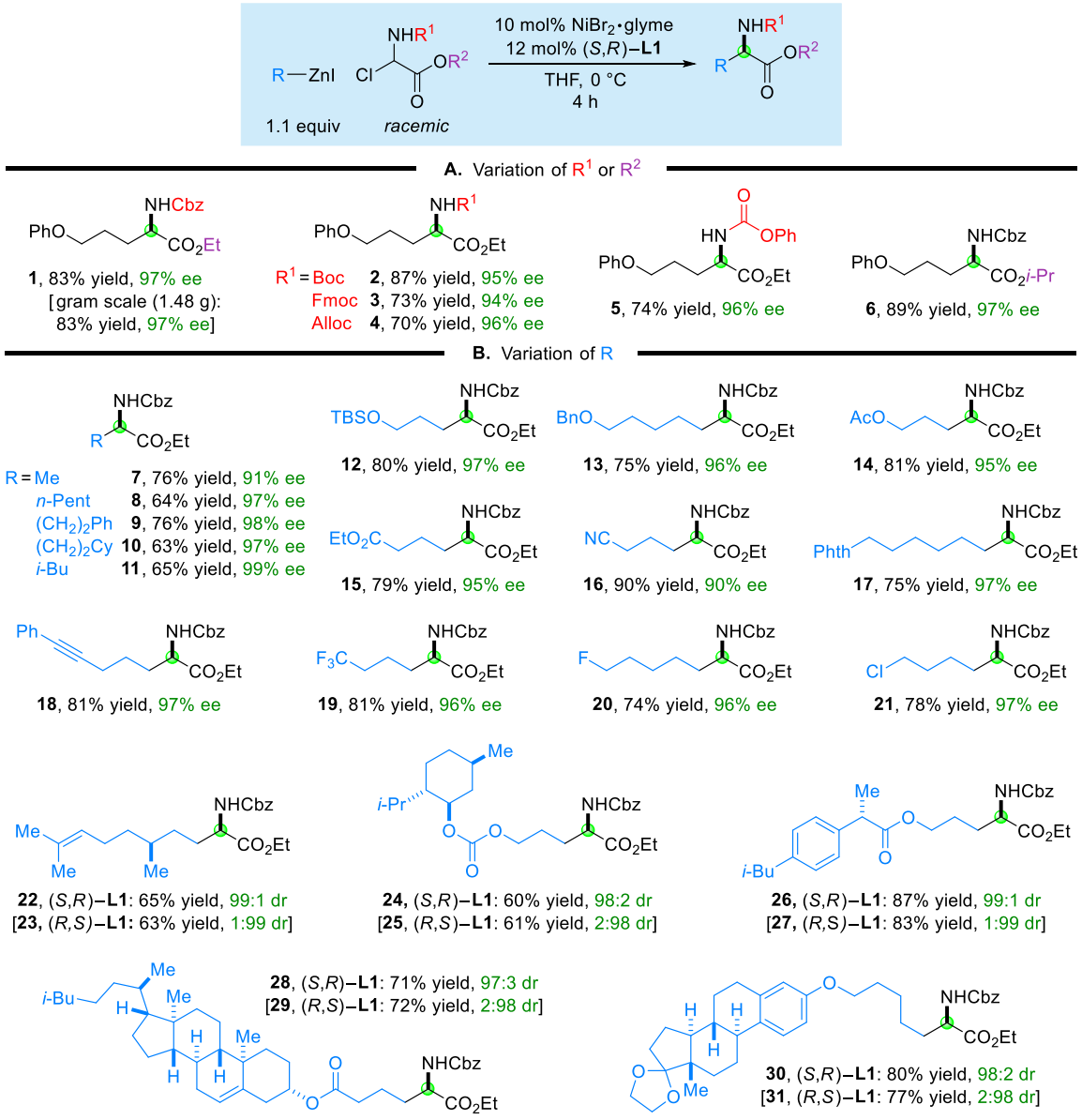


Figure 3.2. *Scope of catalytic enantioconvergent synthesis of protected unnatural α-amino acids. All couplings were conducted on a 0.6-mmol scale (unless otherwise noted), and all yields are of purified products.*

3.2.3. Applications

Because the α-haloglycinate coupling partner can generally be prepared in one step, this nickel-catalyzed enantioconvergent alkyl–alkyl coupling provides an unusually versatile and efficient method for the generation of a wide array of unnatural α-amino acid derivatives,

which are common building blocks in the synthesis of bioactive compounds. For example, Boc-protected α-amino acid **32** (**Figure 3.3**), which serves as an intermediate in the synthesis of a histone deacetylase (HDAC) inhibitor, has previously been generated in four steps via an enzymatic kinetic resolution.[34] Alternatively, a nickel-catalyzed enantioconvergent cross-coupling affords α-amino acid **32** in two steps in good yield and ee (70% overall yield, 95% ee).

Similarly, protected unnatural α-amino acid **33** (**Figure 3.3**), which has been employed as an intermediate in the synthesis of a calpain-1 inhibitor, was originally produced in four steps from a derivative of pyroglutamic acid.[35] Through the nickel-catalyzed asymmetric coupling method described herein, target **33** can be generated in two steps in

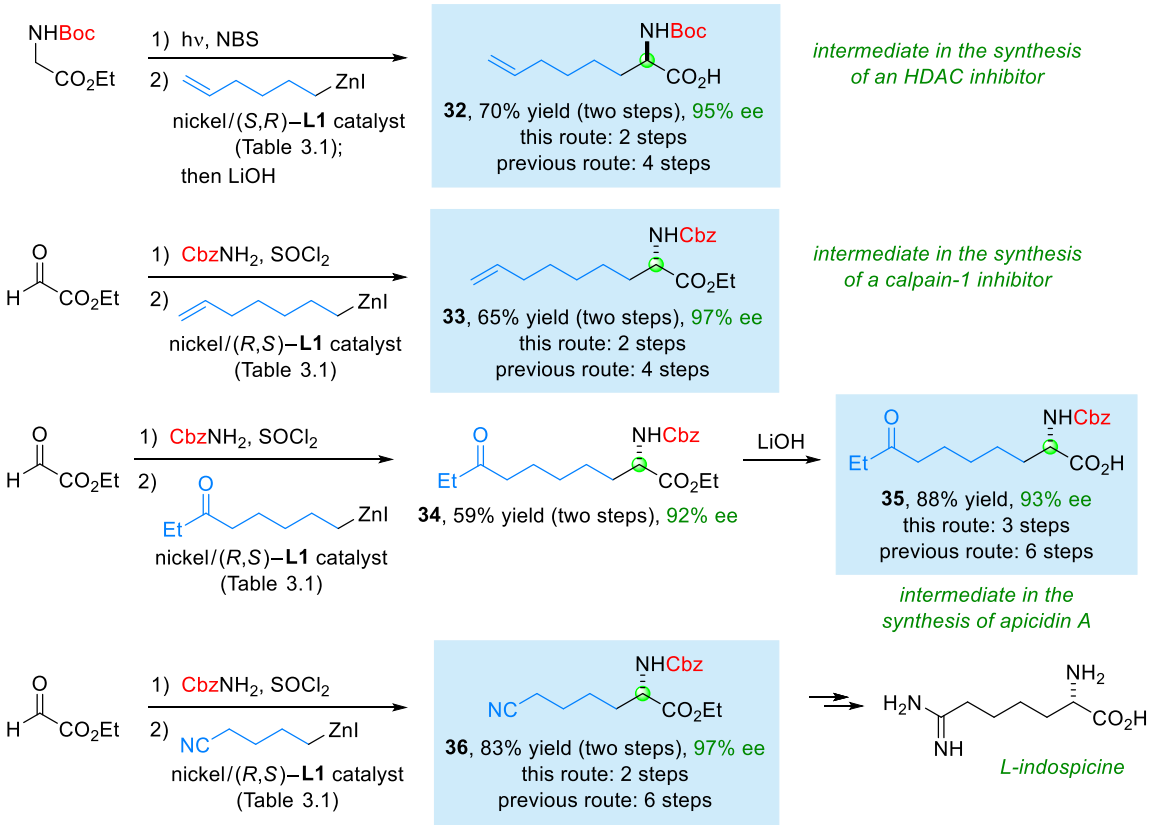


Figure 3.3. *Catalytic enantioconvergent synthesis of protected unnatural α-amino acids: applications to the synthesis of bioactive compounds. All data are the average of two experiments, and all yields are of purified products.*

65% overall yield and with high enantioselectivity (97% ee).

Furthermore, ketone-bearing α-amino acid **35**, an intermediate in the synthesis of cyclic peptide apicidin A, which exhibits anti-malarial activity, can be produced in three steps via an enantioconvergent alkyl−alkyl cross-coupling (prior route: six steps from glutamic acid).[36] Finally, our method provides protected unnatural α-amino acid **36** (**Figure 3.3**), bearing a cyano substituent, in two steps; compound **36** has previously been generated in six steps from lysine en route to L-indospicine, a component in tropical legumes in the genus *Indigofera*.[37]

3.3. Conclusions

We have developed a straightforward, versatile method for the asymmetric synthesis of protected unnatural α-amino acids, an important family of target molecules, via nickel-catalyzed enantioconvergent cross-couplings of readily available racemic alkyl halides with alkylzinc reagents (1:1.1 ratio). These couplings can be achieved under mild, convenient conditions and are tolerant of air, moisture, and a wide variety of functional groups, including alkenes and alkynes (cf. asymmetric hydrogenation). The usefulness of the new method has been demonstrated by its application to the efficient synthesis of unnatural α-amino acid derivatives that have previously been employed as intermediates en route to bioactive compounds. The development of additional catalytic asymmetric processes based on nickel, an earth-abundant metal, is underway.

3.4. Experimental section

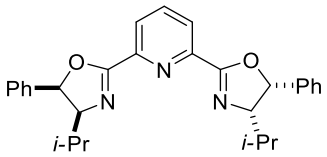
3.4.1. General information

Unless otherwise noted, reagents received from commercial suppliers were used as received. All reactions were performed under an atmosphere of dry nitrogen. Anhydrous THF was purchased from Sigma-Aldrich and stored under nitrogen; other solvents were purified by passage through activated aluminum oxide in a solvent-purification system. A 100 W incandescent bulb (PAR38, medium screw) was purchased from Grainger.

NMR spectra were collected on a Bruker 400 MHz spectrometer at ambient temperature; chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, using the solvent resonance as the internal standard. SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® or Daicel CHIRALCEL® columns (4.6 × 250 mm, particle size 5 μm). FT-IR measurements were carried out on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD5 ATR accessory. HRMS were acquired on an Agilent 1260 Infinity II HPLC-MS system in electrospray ionization (ESI+) mode. LC-MS were obtained on an Agilent 6140 UHPLC-MS system in electrospray ionization (ESI+) mode. Optical rotation data were obtained with a Jasco P-2000 polarimeter at 589 nm, using a 100 mm pathlength cell in the solvent and at the concentration indicated. GC analyses were carried out on an Agilent 6890N GC. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle). X-ray crystallographic analyses were carried out by the Caltech X-Ray Crystallography Facility using a Bruker APEX-II CCD diffractometer.

3.4.2. Preparation of the chiral ligand

The yield has not been optimized.



2,6-Bis((4*S*,5*R*)-4-isopropyl-5-phenyl-4,5-dihydrooxazol-2-yl)pyridine. An oven-dried 100 mL round-bottom flask was charged with a stir bar and fitted with a reflux condenser attached to a nitrogen manifold. Next, (1*R*,2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol[38] (7.20 g, 40.2 mmol, 2.0 equiv) and dimethyl pyridine-2,6-bis(carbimidate)[39] (3.86 g, 20.0 mmol, 1.0 equiv) were added, and then the flask was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of 1,2-dichloroethane (40 mL). The solution was heated at reflux for 40 h. Then, the reaction mixture was cooled to room temperature, during which time 2,6-bis((4*S*,5*R*)-4-isopropyl-5-phenyl-4,5-dihydrooxazol-2-yl)pyridine precipitated as a white solid, which was filtered, washed with EtOAc (100 mL), and dried (6.10 g, 13.5 mmol, 67% yield, >99% ee).

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (30% MeOH in supercritical CO_2, 2.5 mL/min); retention times for (*S*,*R*)**–L1**: 5.4 min, (*R*,*S*)**–L1**: 5.6 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 2H), 7.90 (t, *J* = 7.9 Hz, 1H), 7.38 – 7.27 (m, 10H), 5.82 (d, *J* = 10.0 Hz, 2H), 4.26 (dd, *J* = 9.9, 8.5 Hz, 2H), 1.79 – 1.58 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 6H), 0.75 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 147.4, 137.4, 137.0, 128.3, 128.2, 127.6, 126.0, 85.4, 29.3, 21.1, 20.0.

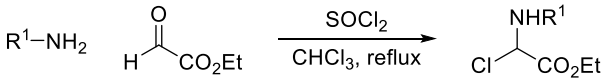
FT-IR (film): 3448, 2922, 2360, 1671, 1574, 1330, 1170, 954, 680 cm^{-1}.

HRMS (ESI+) m/z $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_2$: 454.2489, found: 454.2485.

$[\alpha]^{22}_D$ = –274 (*c* 1.0, $CHCl_3$), from (*S*,*R*)**–L1**.

3.4.3. Preparation of electrophiles

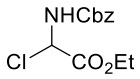
The yields have not been optimized.



General Procedure 1 (GP-1).

One-step preparation of protected *α*-chloro glycinates. The title compounds were synthesized according to a prior report.[40] An oven-dried 250 mL round-bottom flask was charged with a stir bar and fitted with a reflux condenser attached to a nitrogen manifold. The carbamate (1.0 equiv) was then added, and the flask was sealed with a rubber septum cap. After the flask was placed under a nitrogen atmosphere by evacuating and back-filling on a Schlenk line (three cycles), chloroform was added (volume to generate a 0.1 M solution of the carbamate). Next, ethyl glyoxalate (50% in toluene, 1.2 equiv) and thionyl chloride (3.0 equiv) were added via syringe. The reaction mixture was heated at reflux for 12 h. Then, the solution was cooled to room temperature and directly concentrated under reduced pressure to yield the desired product.

The alkyl chlorides used in this study are stable after isolation and can be stored at 0 °C for at least six months without decomposition.

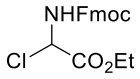


Ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from benzyl carbamate. 4.17 g (15.4 mmol, 93% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 6.16 (s, 2H), 5.30 – 5.03 (m, 2H), 4.31 (qd, *J* = 7.1, 0.9 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 153.8, 135.3, 128.7, 128.6, 128.4, 68.1, 63.3, 63.2, 13.9.

FT-IR (film): 3336, 2982, 2358, 1732, 1520, 1337, 1202, 1050 cm^{-1}.

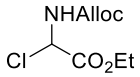


Ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from (9*H*-fluoren-9-yl)methyl carbamate. 3.57 g (9.9 mmol, 99% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.52 – 7.48 (m, 2H), 7.36 – 7.31 (m, 2H), 7.25 (td, *J* = 7.5, 1.2 Hz, 2H), 6.09 (s, 2H), 4.46 – 4.37 (m, 2H), 4.26 (qd, *J* = 7.1, 1.3 Hz, 2H), 4.20 – 4.13 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 153.9, 143.4, 141.4, 127.9, 127.2, 125.02, 124.98, 120.1, 68.0, 63.3, 63.2, 46.9, 13.9.

FT-IR (film): 3311, 2985, 2356, 1734, 1508, 1335, 1201, 741 cm^{-1}.

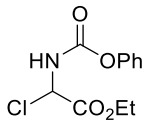


Ethyl 2-(((allyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from allyl carbamate. 1.16 g (5.2 mmol, 97% yield). Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 – 6.05 (m, 2H), 5.97 – 5.80 (m, 1H), 5.40 – 5.15 (m, 2H), 4.59 (dd, *J* = 28.2, 5.7 Hz, 2H), 4.34 – 4.18 (m, 2H), 1.29 (dt, *J* = 23.0, 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 166.0, 155.6, 153.8, 132.3, 131.8, 118.8, 118.1, 66.9, 66.2, 63.4, 63.2, 62.6, 60.0, 14.1, 13.9.

FT-IR (film): 3331, 2984, 2357, 1734, 1521, 1334, 1204, 1055 cm^{-1}.

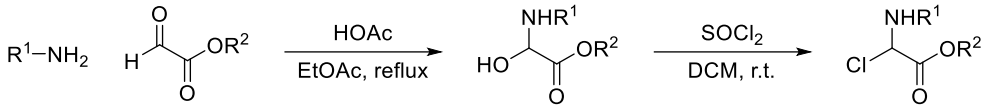


Ethyl 2-chloro-2-((phenoxycarbonyl)amino)acetate. The title compound was synthesized according to **GP-1** from phenyl carbamate. 2.65 g (10.3 mmol, 99% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 2H), 7.27 – 7.20 (m, 1H), 7.19 – 7.12 (m, 2H), 6.47 (d, *J* = 10.3 Hz, 1H), 6.20 (d, *J* = 10.3 Hz, 1H), 4.36 (qd, *J* = 7.2, 1.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 152.3, 150.4, 129.6, 126.2, 121.4, 63.5, 63.0, 14.0.

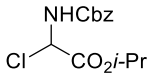
FT-IR (film): 3336, 2985, 1744, 1490, 1339, 1213, 1032 cm^{-1}.



General Procedure 2 (GP-2).

Two-step preparation of protected *α*-chloro glycinates. The title compounds were synthesized according to a prior report.[41] An oven-dried 250 mL round-bottom flask was charged with a stir bar and fitted with a reflux condenser attached to a nitrogen manifold. The carbamate (1.0 equiv) was then added, and the flask was sealed with a rubber septum cap. After the flask was placed under a nitrogen atmosphere by evacuating and back-filling on a Schlenk line (three cycles), ethyl acetate was added (volume to generate a 1.0 M solution of the carbamate). Next, the glyoxalate (1.2 equiv; prepared from the corresponding *L*-tartrate[42]) and acetic acid (0.1 equiv) were added. The resulting solution was heated at reflux for 12 h. Then, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the *α*-hydroxy glycinate.

An oven-dried 100 mL round-bottom flask was charged with a stir bar and the α-hydroxy glycinate, and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling on a Schlenk line (three cycles), and then DCM (volume to generate a 0.5 M solution of the *α*-hydroxy glycinate) and thionyl chloride (2.5 equiv) were added. After the reaction mixture was allowed to stir at room temperature for 6 h, it was concentrated under reduced pressure to afford the desired product.

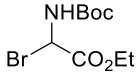


Isopropyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-2** from benzyl carbamate and isopropyl 2-oxoacetate. 2.74 g (9.6 mmol, 73% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 6.18 – 5.96 (m, 2H), 5.23 – 4.94 (m, 3H), 1.24 (dd, *J* = 6.3, 3.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 153.9, 135.4, 128.8, 128.7, 128.5, 71.5, 68.1, 63.7, 21.6, 21.4.

FT-IR (film): 3334, 2982, 2356, 1733, 1508, 1328, 1203, 1103 cm^{-1}.



Ethyl 2-bromo-2-((*tert*-butoxycarbonyl)amino)acetate. The title compound was synthesized according to a prior report.[43] An oven-dried 100 mL round-bottom flask was charged with a stir bar, ethyl (*tert*-butoxycarbonyl)glycinate (1.02 g, 5.0 mmol, 1.0 equiv), and *N*-bromosuccinimide (0.89 g, 5.0 mmol, 1.0 equiv), and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling on a Schlenk line (three cycles), and then CCl_4 (volume to generate a 0.3 M solution of ethyl (*tert*-butoxycarbonyl)glycinate) was added. A 100 W incandescent bulb was placed ~5 cm away from the flask, and the flask was irradiated while stirring at room temperature in a water bath for 12 h. Then, the reaction mixture was concentrated under reduced pressure to yield the desired product. 1.37 g (4.9 mmol, 98% yield). Yellow oil. Because this compound is unstable, it was used immediately in the catalytic cross-coupling reaction.

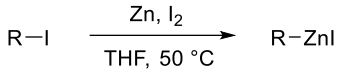
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 – 6.22 (m, 1H), 6.06 – 5.63 (m, 1H), 4.37 – 4.23 (m, 2H), 1.48 (s, 9H), 1.37 – 1.28 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 152.4, 82.4, 63.1, 54.2, 28.2, 13.9.

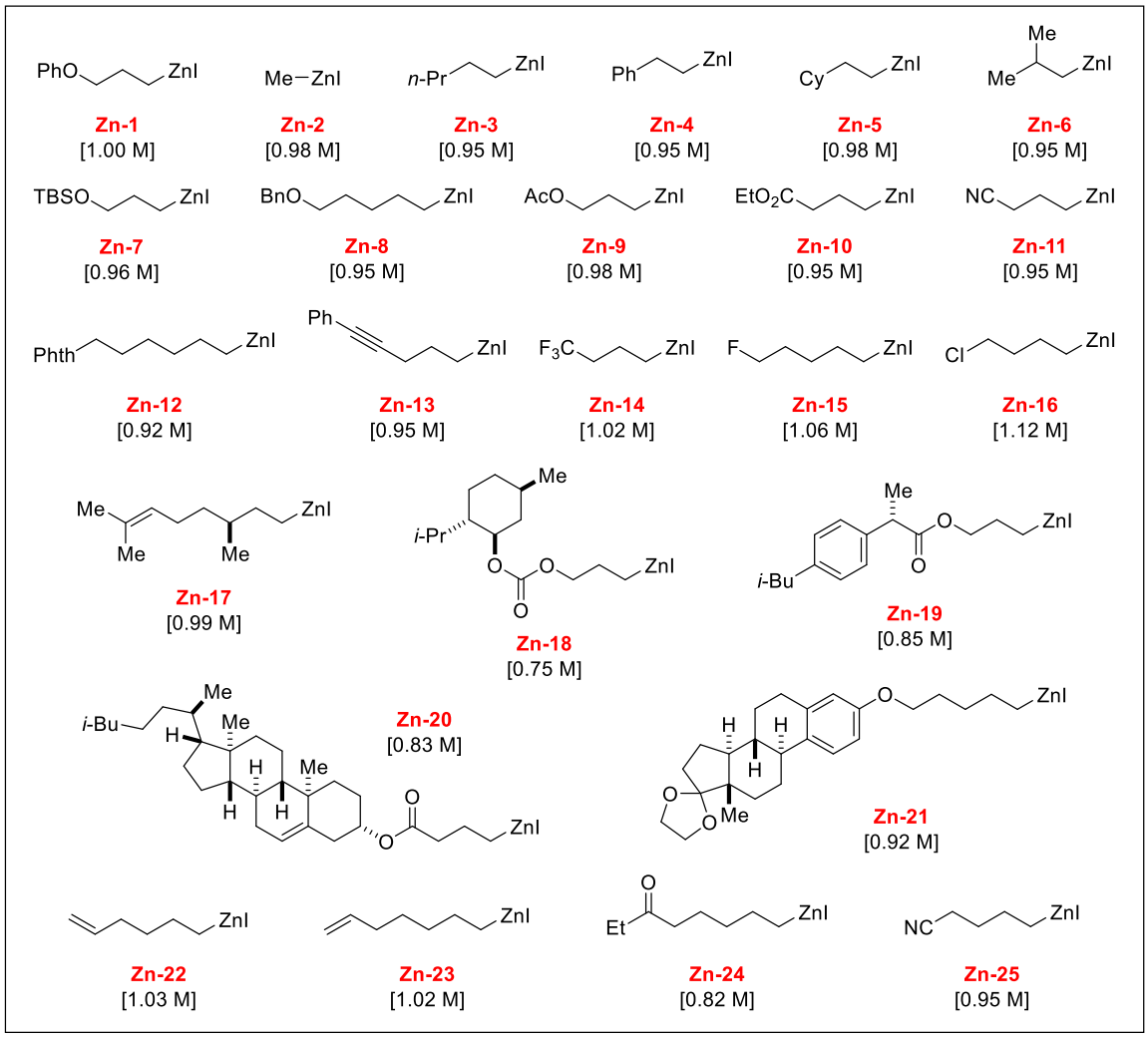
FT-IR (film): 3345, 2984, 2361, 1731, 1496, 1372, 1047, 824, 679 cm^{-1}.

3.4.4. Preparation of nucleophiles

General Procedure 3 (GP-3).

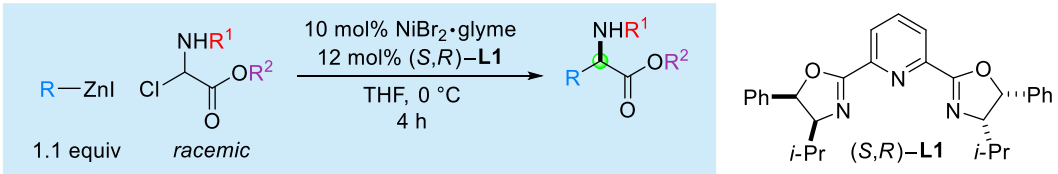


Preparation of the alkylzinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three cycles). Then, the tube was heated with a heat gun (~250 °C) under high vacuum (~1000 mtorr) for 10 min. The Schlenk tube was allowed to cool to room temperature, and then it was back-filled with nitrogen. THF (0.5 mL/mmol of the alkyl iodide) was added via syringe. The cap was removed, and iodine (0.050 equiv) was added in one portion under a positive flow of nitrogen to the uncapped (open) Schlenk tube, leading initially to a red color that faded after ~5 s of vigorous stirring (1000 rpm). A solution of the alkyl iodide (1.0 equiv) in THF (0.5 mL/mmol of the alkyl iodide), prepared in a 20 mL vial equipped with a nitrogen balloon, was added via syringe in one portion to the gray suspension of zinc powder. Then, the Schlenk tube was capped tightly under a nitrogen atmosphere and transferred to an oil bath. The reaction mixture was stirred vigorously at 50 °C for 12 h (the disappearance of the alkyl iodide and the formation of the alkylzinc reagent can readily be monitored via GC analysis of the quenched alkylzinc reagent). After the alkyl iodide had been consumed, the gray mixture was filtered through a syringe filter (PTFE, 0.45 μM) to afford a colorless to slightly yellow solution. The alkylzinc solution was titrated by the method of Knochel, using iodine in THF (0.75–1.12 M).[44] The concentration of the alkylzinc reagents remained constant over one year when stored at room temperature in a glovebox.



3.4.5. Catalytic enantioconvergent cross-couplings

General Procedure 4 (GP-4).

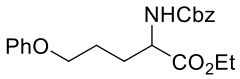


Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (18.4 mg, 0.060 mmol, 10 mol%) and (*S*,*R*)–**L1** (32.6 mg, 0.072 mmol, 12 mol%) were added to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was closed with a PTFE septum cap, the joint was wrapped with electric tape, and the vial was placed under a nitrogen atmosphere by evacuating and back-filling (three cycles). A balloon filled with

nitrogen was attached to the vial, and THF (6.0 mL) was added. The mixture was stirred at room temperature for 30 min, leading to an orange, homogeneous solution.

Cross-coupling: In the air, an oven-dried 8 mL vial was charged with the racemic alkyl halide (0.60 mmol, 1.0 equiv). The vial was closed with a PTFE septum cap, and then it was evacuated and back-filled with nitrogen (three cycles). THF (3.0 mL) was added, and the resulting solution was transferred via syringe to the solution of the catalyst. The 8 mL vial was rinsed with THF (3.0 mL), which was also transferred to the reaction vial. The reaction vial was then placed in an *i*-PrOH cooling bath at 0 °C, and the mixture was allowed to cool to 0 °C while stirring for 10 min. Then, the alkylzinc solution (0.66 mmol, 1.1 equiv) was added dropwise via syringe over 3 min, during which the reaction mixture became a clear, dark-red solution (which typically became colorless over the next 30 min). The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 4 h.

Work-up: The reaction was quenched with EtOH (0.2 mL), and the mixture was passed through a plug of silica gel; the vial and the silica gel were rinsed with Et_2O. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel.



Ethyl 2-(((benzyloxy)carbonyl)amino)-5-phenoxypentanoate (1). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-1**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 187 mg, 84% yield, 97% ee; (*R*,*S*)**–L1**: 183 mg, 82% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.8 min (minor), 7.2 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.21 (m, 7H), 6.98 – 6.91 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.43 (d, *J* = 8.0 Hz, 1H), 5.12 (s, 2H), 4.49 – 4.37 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.97 (t, *J* = 5.5 Hz, 2H), 2.15 – 1.95 (m, 1H), 1.95 – 1.75 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 158.9, 156.1, 136.4, 129.6, 128.7, 128.3, 128.2, 120.9, 114.6, 67.1, 67.0, 61.7, 53.8, 29.6, 25.3, 14.3.

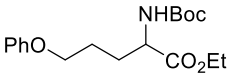
FT-IR (film): 3341, 2956, 2356, 1716, 1498, 1244, 1028, 752 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{25}NNaO_5$: 394.1625, found: 394.1633.

$[\alpha]^{22}_D = -10$ (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.

Gram-scale reaction: In the air, $NiBr_2$·glyme (147 mg, 0.48 mmol, 0.10 equiv) and (*S*,*R*)**–L1** (261 mg, 0.58 mmol, 0.12 equiv) were added to an oven-dried 250 mL round-bottom flask equipped with a stir bar. The flask was closed with a rubber septum cap, the joint was wrapped with electrical tape, and the flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles). A balloon filled with nitrogen was attached to the reaction flask. THF (56 mL) was added to the flask, and the mixture was stirred at room temperature for 30 min, at which time it was an orange, homogeneous solution. In the air, an oven-dried 40 mL vial was charged with ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate (1.30 g, 4.8 mmol, 1.0 equiv). The vial was capped with a PTFE septum cap, and then it was evacuated and back-filled with nitrogen (three cycles). THF (20 mL) was added to the vial to dissolve the electrophile. Next, this solution of the electrophile was added in one portion via syringe to the solution of the catalyst. The 40 mL vial was rinsed with THF (20 mL), and the washing was transferred to the reaction flask. The reaction flask was then placed in an *i*-PrOH cooling bath at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. Then, **Zn-1** (5.28 mmol, 1.1 equiv) was added dropwise via syringe over 10 min, during which the reaction mixture turned dark. The balloon was removed, and the septum was sealed with electrical tape. The reaction mixture was stirred at 0 °C for 4 h. The reaction was then quenched at 0 °C by the addition of EtOH (1.0 mL). Next, the reaction mixture was passed through a column of silica gel (5 cm), and the flask, the septum, and the silica gel were rinsed with Et_2O. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (3:7 Et_2O/hexanes). White solid.

(*S*,*R*)**–L1**: 1.48 g, 83% yield, 97% ee.



Ethyl 2-((*tert*-butoxycarbonyl)amino)-5-phenoxypentanoate (2). The title compound was synthesized according to **GP-4** from ethyl 2-bromo-2-((*tert*-butoxycarbonyl)amino)acetate and **Zn-1**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 181 mg, 89% yield, 96% ee; (*R*,*S*)**–L1**: 172 mg, 85% yield, 94% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IE-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.0 min (minor), 6.3 min (major).

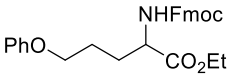
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 2H), 6.99 – 6.81 (m, 3H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.43 – 4.28 (m, 1H), 4.28 – 4.11 (m, 2H), 3.97 (t, *J* = 5.9 Hz, 2H), 2.11 – 1.95 (m, 1H), 1.95 – 1.75 (m, 3H), 1.45 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 158.9, 155.5, 129.6, 120.8, 114.6, 80.0, 67.1, 61.5, 53.4, 29.7, 28.4, 25.4, 14.3.

FT-IR (film): 3363, 2926, 2360, 1715, 1506, 1368, 1026, 778, 692 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{27}NNaO_5$: 360.1781, found: 360.1775.

$[\alpha]^{22}_D$ = –12 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-phenoxypentanoate (3). The title compound was synthesized according to **GP-4** from ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-chloroacetate and **Zn-1**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 201 mg, 73% yield, 95% ee; (*R*,*S*)**–L1**: 201 mg, 73% yield, 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IC-3 column (30% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.1 min (minor), 5.6 min (major).

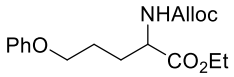
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.66 – 7.52 (m, 2H), 7.46 – 7.36 (m, 2H), 7.35 – 7.25 (m, 4H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.56 – 4.34 (m, 3H), 4.32 – 4.09 (m, 3H), 4.06 – 3.82 (m, 2H), 2.16 – 1.98 (m, 1H), 1.96 – 1.67 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 158.8, 156.0, 143.9, 143.8, 141.3, 129.5, 127.7, 127.1, 125.1, 120.8, 120.02, 120.00, 114.5, 67.0, 66.9, 61.6, 53.7, 47.2, 29.5, 25.2, 14.2.

FT-IR (film): 3346, 2938, 1731, 1600, 1504, 1245, 1032, 754, 691 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{29}NNaO_5$: 482.1938, found: 482.1952.

$[\alpha]^{22}_D$ = –11 (*c* 1.0, $CHCl_3$); 95% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((allyloxy)carbonyl)amino)-5-phenoxypentanoate (4). The title compound was synthesized according to **GP-4** from ethyl 2-(((allyloxy)carbonyl)amino)-2-chloroacetate and **Zn-1**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 134 mg, 69% yield, 96% ee; (*R*,*S*)**–L1**: 136 mg, 71% yield, 95% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 3.6 min (minor), 4.0 min (major).

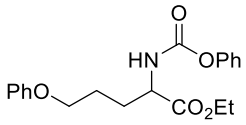
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 2H), 7.01 – 6.81 (m, 3H), 6.03 – 5.83 (m, 1H), 5.40 (d, *J* = 8.3 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.62 – 4.56 (m, 2H), 4.46 – 4.37 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 2.20 – 1.78 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 158.8, 155.9, 132.7, 129.6, 120.9, 117.9, 114.6, 67.0, 65.9, 61.6, 53.7, 29.6, 25.3, 14.3.

FT-IR (film): 3342, 2938, 2357, 1718, 1498, 1244, 1030, 752 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{23}NNaO_5$: 344.1468, found: 344.1475.

$[\alpha]^{22}_D$ = –16 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 5-phenoxy-2-((phenoxycarbonyl)amino)pentanoate (5). The title compound was synthesized according to **GP-4** from ethyl 2-chloro-2-((phenoxycarbonyl)amino)acetate and **Zn-1**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 157 mg, 73% yield, 96% ee; (*R*,*S*)**–L1**: 158 mg, 74% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 8.4 min (minor), 11.3 min (major).

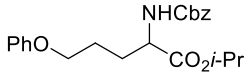
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 6.98 – 6.86 (m, 3H), 5.74 (d, *J* = 8.1 Hz, 1H), 4.56 – 4.38 (m, 1H), 4.24 (q, *J* = 7.3 Hz, 2H), 4.01 (t, *J* = 5.8 Hz, 2H), 2.22 – 2.07 (m, 1H), 2.02 – 1.80 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 158.8, 154.4, 151.0, 129.6, 129.4, 125.6, 121.7, 120.9, 114.6, 67.0, 61.9, 53.9, 29.6, 25.3, 14.3.

FT-IR (film): 3342, 2920, 2353, 1730, 1518, 754 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NNaO_5$: 380.1468, found: 380.1481.

$[\alpha]^{22}_D$ = –17 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Isopropyl 2-(((benzyloxy)carbonyl)amino)-5-phenoxypentanoate (6). The title compound was synthesized according to **GP-4** from isopropyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-1**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 209 mg, 90% yield, 97% ee; (*R*,*S*)**–L1**: 203 mg, 88% yield, 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.6 min (minor), 8.7 min (major).

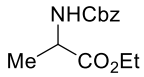
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 7.25 – 7.16 (m, 2H), 6.91 – 6.86 (m, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 5.40 (d, *J* = 8.2 Hz, 1H), 5.06 (s, 2H), 5.04 – 4.93 (m, 1H), 4.39 – 4.29 (m, 1H), 3.91 (t, *J* = 5.6 Hz, 2H), 2.04 – 1.93 (m, 1H), 1.87 – 1.71 (m, 3H), 1.20 (dd, *J* = 9.8, 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 158.9, 156.0, 136.4, 129.6, 128.6, 128.3, 128.2, 120.8, 114.6, 69.4, 67.1, 67.0, 53.8, 29.6, 25.2, 21.9, 21.8.

FT-IR (film): 3347, 2980, 2356, 1728, 1498, 1244, 1106, 752 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}NO_5$: 386.1962, found: 386.1951.

$[\alpha]^{22}_D$ = –11 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl ((benzyloxy)carbonyl)alaninate (7). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-2**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 113 mg, 75% yield, 89% ee; (*R*,*S*)**–L1**: 114 mg, 76% yield, 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 3.5 min (minor), 4.1 min (major).

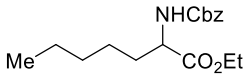
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.35 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 4.37 (p, *J* = 7.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.41 (d, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 155.7, 136.4, 128.7, 128.3, 128.2, 67.0, 61.6, 49.8, 18.9, 14.2.

FT-IR (film): 3339, 2983, 2356, 1723, 1520, 1211, 1070 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{13}H_{17}NNaO_4$: 274.1050, found: 274.1048.

$[\alpha]^{22}_D$ = –2.3 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)heptanoate (8). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-3**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 112 mg, 61% yield, 96% ee; (*R*,*S*)**–L1**: 123 mg, 67% yield, 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IC-3 column (7% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 8.0 min (minor), 9.4 min (major).

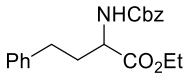
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.29 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.42 – 4.26 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.88 – 1.74 (m, 1H), 1.73 – 1.58 (m, 1H), 1.38 – 1.19 (m, 9H), 0.91 – 0.83 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 156.0, 136.4, 128.6, 128.3, 128.2, 67.0, 61.5, 54.0, 32.8, 31.4, 24.9, 22.5, 14.3, 14.1.

FT-IR (film): 3336, 2920, 2354, 1722, 1520, 1246, 1030, 749 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{25}NNaO_4$: 330.1676, found: 330.1680.

$[\alpha]^{22}_D$ = –8.0 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-4-phenylbutanoate (9). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-4**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 158 mg, 77% yield, 98% ee; (*R*,*S*)**–L1**: 152 mg, 74% yield, 98% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 6.0 min (minor), 8.7 min (major).

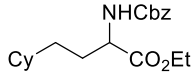
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 7H), 7.24 – 7.08 (m, 3H), 5.37 (d, *J* = 7.9 Hz, 1H), 5.13 (s, 2H), 4.52 – 4.34 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.79 – 2.58 (m, 2H), 2.28 – 2.09 (m, 1H), 2.08 – 1.89 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 156.0, 140.8, 136.4, 128.7, 128.6, 128.5, 128.34, 128.25, 126.3, 67.1, 61.7, 53.8, 34.5, 31.6, 14.3.

FT-IR (film): 3342, 2930, 2352, 1720, 1520, 1240, 1046, 734 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NNaO_4$: 364.1519, found: 364.1533.

$[\alpha]^{22}_D$ = –23 (*c* 1.0, $CHCl_3$); 98% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-4-cyclohexylbutanoate (10). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-5**. The product was purified by column chromatography on silica gel (1:6 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 130 mg, 62% yield, 97% ee; (*R*,*S*)**–L1**: 134 mg, 64% yield, 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.5 min (minor), 5.7 min (major).

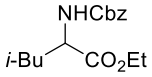
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.27 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 4.39 – 4.27 (m, 1H), 4.27 – 4.08 (m, 2H), 1.94 – 1.76 (m, 1H), 1.76 – 1.56 (m, 6H), 1.35 – 1.05 (m, 9H), 0.95 – 0.76 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 136.5, 128.7, 128.3, 128.2, 67.1, 61.5, 54.2, 37.4, 33.4, 33.2, 32.7, 30.2, 26.7, 26.38, 26.37, 14.3.

FT-IR (film): 3343, 2922, 2361, 1722, 1520, 1300, 1036, 743, 700 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_4$: 370.1989, found: 370.2000.

$[\alpha]^{22}_D$ = –9.3 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl ((benzyloxy)carbonyl)leucinate (11). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-6**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 118 mg, 67% yield, 99% ee; (*R*,*S*)**–L1**: 111 mg, 63% yield, 99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 7.3 min (minor), 7.8 min (major).

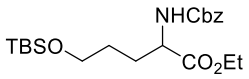
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.19 (d, *J* = 8.7 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.33 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.78 – 1.57 (m, 2H), 1.57 – 1.46 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 156.1, 136.4, 128.6, 128.3, 128.2, 67.1, 61.4, 52.7, 42.0, 24.9, 22.9, 22.0, 14.3.

FT-IR (film): 3346, 2959, 2356, 1718, 1525, 1202, 1028 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{23}NNaO_4$: 316.1519, found: 316.1528.

$[\alpha]^{22}_D$ = +4.3 (*c* 1.0, $CHCl_3$); 99% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-5-((*tert*-butyldimethylsilyl)oxy)pentanoate (12). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-7**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 195 mg, 79% yield, 97% ee; (*R*,*S*)**–L1**: 198 mg, 81% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 2.9 min (minor), 3.4 min (major).

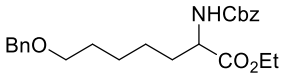
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 5.47 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 2H), 4.41 – 4.31 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 1.96 – 1.69 (m, 2H), 1.64 – 1.49 (m, 2H), 1.33 – 1.23 (m, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 1.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 156.0, 136.5, 128.6, 128.24, 128.22, 67.0, 62.4, 61.5, 53.8, 29.2, 28.4, 26.0, 18.4, 14.3, –5.3.

FT-IR (film): 3347, 2955, 2356, 1728, 1520, 1256, 1099, 839 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{35}NNaO_5Si$: 432.2177, found: 432.2210.

$[\alpha]^{22}_D$ = –5.5 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl 7-(benzyloxy)-2-(((benzyloxy)carbonyl)amino)heptanoate (13). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-8**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 188 mg, 76% yield, 96% ee; (*R*,*S*)**–L1**: 182 mg, 74% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.3 min (minor), 4.7 min (major).

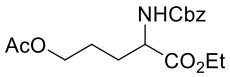
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 5.28 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 4.49 (s, 2H), 4.43 – 4.28 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 1.92 – 1.76 (m, 1H), 1.71 – 1.56 (m, 3H), 1.45 – 1.31 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 138.7, 136.4, 128.7, 128.5, 128.3, 128.2, 127.8, 127.6, 73.0, 70.3, 67.1, 61.5, 54.0, 32.8, 29.6, 26.0, 25.1, 14.3.

FT-IR (film): 3349, 2917, 2353, 1716, 1519, 778 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+K]^+$ calcd for $C_{24}H_{31}KNO_5$: 452.1834, found: 452.1847.

$[\alpha]^{22}_D$ = –7.5 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 5-acetoxy-2-(((benzyloxy)carbonyl)amino)pentanoate (14). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-9**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 164 mg, 81% yield, 95% ee; (*R*,*S*)**–L1**: 162 mg, 80% yield, 95% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK ID-3 column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 2.9 min (major), 3.7 min (minor).

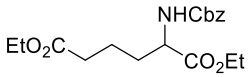
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.37 (d, *J* = 8.2 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.34 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 2.03 (s, 3H), 1.97 – 1.83 (m, 1H), 1.78 – 1.59 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.1, 156.0, 136.3, 128.6, 128.3, 128.2, 67.1, 63.8, 61.7, 53.7, 29.5, 24.6, 21.0, 14.3.

FT-IR (film): 3338, 2962, 2357, 1734, 1523, 1238, 1028 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{24}NO_6$: 338.1598, found: 338.1594.

$[\alpha]^{22}_D$ = –9.7 (*c* 1.0, $CHCl_3$); 95% ee, from (*S*,*R*)**–L1**.



Diethyl 2-(((benzyloxy)carbonyl)amino)hexanedioate (15). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-10**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 161 mg, 76% yield, 93% ee; (*R*,*S*)**–L1**: 171 mg, 81% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK ID column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.5 min (minor), 6.1 min (major).

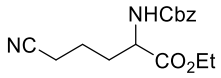
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.36 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.42 – 4.32 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.39 – 2.27 (m, 2H), 1.98 – 1.61 (m, 4H), 1.33 – 1.18 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 172.3, 156.0, 136.4, 128.6, 128.3, 128.2, 67.1, 61.7, 60.5, 53.7, 33.7, 32.1, 20.7, 14.33, 14.27.

FT-IR (film): 3347, 2981, 2356, 1731, 1521, 1208, 1028 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_6$: 374.1574, found: 374.1572.

$[\alpha]^{22}_D$ = –8.1 (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-5-cyanopentanoate (16). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-11**. The product was purified by column chromatography on silica gel (1:1 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 160 mg, 88% yield, 90% ee; (*R*,*S*)**–L1**: 166 mg, 91% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL ID-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.2 min (major), 6.6 min (minor).

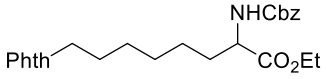
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 5.41 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 2H), 4.46 – 4.31 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.44 – 2.32 (m, 2H), 2.12 – 1.93 (m, 1H), 1.86 – 1.60 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 156.0, 136.2, 128.7, 128.4, 128.3, 119.2, 67.3, 62.0, 53.2, 32.0, 21.6, 16.9, 14.3.

FT-IR (film): 3366, 2945, 2359, 2247, 1716, 1520, 1044, 746 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{20}N_2NaO_4$: 327.1315, found: 327.1319.

$[\alpha]^{22}_D$ = –11 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-8-(1,3-dioxoisoindolin-2-yl)octanoate (17). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-12**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 213 mg, 76% yield, 97% ee; (*R*,*S*)**–L1**: 203 mg, 73% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.4 min (minor), 5.9 min (major).

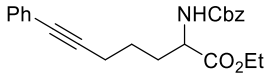
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.37 – 7.27 (m, 5H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.09 (s, 2H), 4.40 – 4.27 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 1.92 – 1.73 (m, 1H), 1.73 – 1.53 (m, 3H), 1.40 – 1.18 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 168.6, 156.0, 136.4, 134.0, 132.3, 128.6, 128.3, 128.2, 123.3, 67.1, 61.5, 54.0, 38.0, 32.8, 28.8, 28.6, 26.7, 25.1, 14.3.

FT-IR (film): 3329, 2928, 2361, 1714, 1520, 1398, 1027, 725 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{30}N_2NaO_6$: 489.1996, found: 489.2011.

$[\alpha]^{22}_D$ = –6.7 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-7-phenylhept-6-ynoate (18). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-13**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 179 mg, 79% yield, 97% ee; (*R*,*S*)**–L1**: 186 mg, 82% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IF-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 9.4 min (minor), 10.0 min (major).

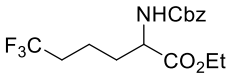
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.22 (m, 10H), 5.37 (d, *J* = 8.1 Hz, 1H), 5.12 (s, 2H), 4.49 – 4.34 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.15 – 1.96 (m, 1H), 1.96 – 1.78 (m, 1H), 1.78 – 1.52 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 156.0, 136.4, 131.7, 128.6, 128.31, 128.29, 128.2, 127.8, 123.8, 89.1, 81.5, 67.1, 61.6, 53.7, 32.0, 24.5, 19.1, 14.3.

FT-IR (film): 3344, 2919, 2356, 2234, 1958, 1714, 1519, 1034, 763 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_4$: 380.1856, found: 380.1848.

$[\alpha]^{22}_D$ = –13 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-6,6,6-trifluorohexanoate (19). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-14**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 166 mg, 80% yield, 96% ee; (*R*,*S*)**–L1**: 171 mg, 82% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IC-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.5 min (minor), 5.1 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.37 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 2H), 4.45 – 4.32 (m, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.23 – 2.00 (m, 2H), 2.00 – 1.82 (m, 1H), 1.81 – 1.52 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

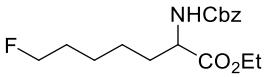
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 156.0, 136.3, 128.7, 128.4, 128.3, 126.7 (q, *J* = 277.8 Hz), 67.2, 61.9, 53.5, 33.3 (q, *J* = 29.3 Hz), 32.0, 18.0 (q, *J* = 3.0 Hz), 14.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –66.3.

FT-IR (film): 3340, 2952, 1716, 1525, 1286, 767 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{20}F_3NNaO_4$: 370.1237, found: 370.1243.

$[\alpha]^{22}_D$ = –6.7 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-7-fluoroheptanoate (20). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-15**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 140 mg, 72% yield, 96% ee; (*R*,*S*)**–L1**: 147 mg, 76% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (2% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 7.4 min (minor), 8.1 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.30 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.48 (t, *J* = 6.0 Hz, 1H), 4.44 – 4.28 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.93 – 1.77 (m, 1H), 1.74 – 1.60 (m, 3H), 1.51 – 1.32 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).

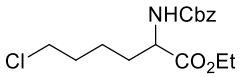
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 156.0, 136.4, 128.7, 128.33, 128.25, 84.0 (d, *J* = 164.6 Hz), 67.1, 61.6, 53.9, 32.8, 30.3 (d, *J* = 19.2 Hz), 25.0 (d, *J* = 5.1 Hz), 24.9, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –218.4.

FT-IR (film): 3348, 2929, 2360, 1721, 1520, 1244, 1023, 750 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{24}FNNaO_4$: 348.1582, found: 348.1586.

$[\alpha]^{22}_D$ = –8.2 (*c* 1.0, $CHCl_3$); 96% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-6-chlorohexanoate (21). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-16**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 156 mg, 79% yield, 97% ee; (*R*,*S*)**–L1**: 152 mg, 77% yield, 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.6 min (major), 5.8 min (minor).

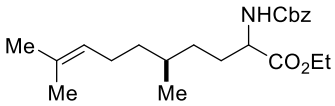
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.35 (d, *J* = 8.3 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.33 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.51 (t, *J* = 6.5 Hz, 2H), 1.93 – 1.62 (m, 4H), 1.60 – 1.39 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 156.0, 136.4, 128.7, 128.3, 128.2, 67.1, 61.7, 53.8, 44.6, 32.1, 32.0, 22.5, 14.3.

FT-IR (film): 3334, 2956, 2356, 1719, 1522, 1212, 1058, 742 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{22}ClNNaO_4$: 350.1130, found: 350.1127.

$[\alpha]^{22}_D$ = –14 (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



Ethyl (5*S*)-2-(((benzyloxy)carbonyl)amino)-5,9-dimethyldec-8-enoate (22, 23). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-17**. The product was purified by column chromatography on silica gel (1:6 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 146 mg, 65% yield, 99:1 d.r.; (*R*,*S*)**–L1**: 141 mg, 63% yield, 1:99 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALCEL IC-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.5 min (minor), 6.7 min (major).

Characterization data for the product from (*S*,*R*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 5.28 (d, *J* = 8.1 Hz, 1H), 5.20 – 5.02 (m, 3H), 4.42 – 4.30 (m, 1H), 4.28 – 4.11 (m, 2H), 2.05 – 1.75 (m, 3H), 1.75 – 1.56 (m, 7H), 1.46 – 1.32 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.17 – 1.07 (m, 2H), 0.86 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 136.4, 131.4, 128.7, 128.3, 128.2, 124.8, 67.1, 61.5, 54.2, 37.0, 32.2, 32.1, 30.3, 25.8, 25.6, 19.4, 17.8, 14.3.

FT-IR (film): 3352, 2918, 2352, 1723, 1520, 1206, 1046, 750 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{33}NNaO_4$: 398.2302, found: 398.2311.

$[\alpha]^{22}_D$ = –5.2 (*c* 1.0, $CHCl_3$); 99:1 d.r., from (*S*,*R*)**–L1**.

Characterization data for the product from (*R*,*S*)**–L1**:

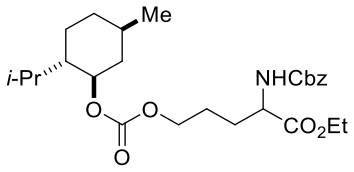
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.26 (m, 5H), 5.30 (d, *J* = 8.1 Hz, 1H), 5.22 – 4.99 (m, 3H), 4.44 – 4.27 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.05 – 1.77 (m, 3H), 1.73 – 1.55 (m, 7H), 1.43 – 1.09 (m, 8H), 0.86 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 136.4, 131.4, 128.6, 128.3, 128.2, 124.8, 67.0, 61.5, 54.2, 36.8, 32.2, 32.1, 30.4, 25.8, 25.5, 19.5, 17.8, 14.3.

FT-IR (film): 3356, 2918, 2352, 1721, 1519, 1028, 743 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{33}NNaO_4$: 398.2302, found: 398.2315.

$[\alpha]^{22}_D$ = +16 (*c* 1.0, $CHCl_3$); 1:99 d.r., from (*R*,*S*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-5-(((((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)oxy)pentanoate (24, 25). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-18**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). White solid.

(*S*,*R*)**–L1**: 171 mg, 60% yield, 98:2 d.r.; (*R*,*S*)**–L1**: 175 mg, 61% yield, 2:98 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALCEL ID-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 3.9 min (minor), 4.3 min (major).

Characterization data for the product from (*S*,*R*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 2H), 4.50 (td, *J* = 10.9, 4.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.14 – 4.10 (m, 2H), 2.10 – 2.02 (m, 1H), 2.00 – 1.90 (m, 2H), 1.81 – 1.62 (m, 5H), 1.56 – 1.34 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 – 0.97 (m, 2H), 0.95 – 0.84 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 156.0, 155.0, 136.3, 128.7, 128.3, 128.2, 78.5, 67.2, 67.0, 61.7, 53.6, 47.1, 40.9, 34.2, 31.5, 29.4, 26.2, 24.8, 23.4, 22.1, 20.8, 16.4, 14.3.

FT-IR (film): 3346, 2956, 2357, 1735, 1521, 1260, 1028 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{26}H_{40}NO_7$: 478.2799, found: 478.2790.

$[\alpha]^{22}_D$ = –43 (*c* 1.0, $CHCl_3$); 98:2 d.r., from (*S*,*R*)**–L1**.

Characterization data for the product from (*R*,*S*)**–L1**:

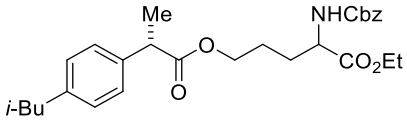
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 2H), 4.50 (td, *J* = 10.9, 4.4 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 2.11 – 2.02 (m, 1H), 2.02 – 1.87 (m, 2H), 1.81 – 1.62 (m, 5H), 1.53 – 1.35 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.12 – 0.98 (m, 2H), 0.94 – 0.84 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 156.0, 155.0, 136.3, 128.7, 128.3, 128.2, 78.5, 67.2, 67.0, 61.7, 53.7, 47.1, 40.9, 34.2, 31.5, 29.4, 26.2, 24.8, 23.4, 22.1, 20.8, 16.4, 14.3.

FT-IR (film): 3354, 2955, 2356, 1735, 1520, 1260, 1027 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{26}H_{40}NO_7$: 478.2799, found: 478.2778.

$[\alpha]^{22}_D$ = –27 (*c* 1.0, $CHCl_3$); 2:98 d.r., from (*R*,*S*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-5-(((*S*)-2-(4-isobutylphenyl)propanoyl)oxy) pentanoate (26, 27). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-19**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 253 mg, 87% yield, 99:1 d.r.; (*R*,*S*)**–L1**: 239 mg, 83% yield, 1:99 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALPAK IC-3 column (15% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 8.0 min (minor), 8.8 min (major).

Characterization data for the product from (*S*,*R*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 5H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.26 (d, *J* = 8.3 Hz, 1H), 5.11 (s, 2H), 4.38 – 4.28 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.02 (m, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.91 – 1.77 (m, 2H), 1.69 – 1.54 (m, 3H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 172.2, 155.9, 140.7, 137.8, 136.3, 129.4, 128.6, 128.3, 128.2, 127.2, 67.1, 63.9, 61.6, 53.6, 45.2, 45.1, 30.3, 29.3, 24.6, 22.5, 18.5, 14.3.

FT-IR (film): 3348, 2955, 2356, 1733, 1509, 1202 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{28}H_{38}NO_6$: 484.2694, found: 484.2690.

$[\alpha]^{22}_D$ = +6.1 (*c* 1.0, $CHCl_3$); 99:1 d.r., from (*S*,*R*)**–L1**.

Characterization data for the product from (*R*,*S*)**–L1**:

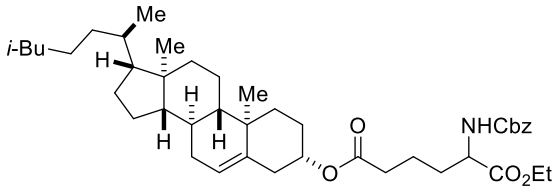
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.23 (d, *J* = 8.3 Hz, 1H), 5.11 (s, 2H), 4.38 – 4.28 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.89 – 1.78 (m, 2H), 1.71 – 1.54 (m, 3H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 172.2, 156.0, 140.7, 137.8, 136.3, 129.4, 128.7, 128.3, 128.2, 127.2, 67.1, 63.9, 61.6, 53.6, 45.2, 45.1, 30.3, 29.3, 24.6, 22.5, 18.5, 14.3.

FT-IR (film): 3355, 2956, 2356, 1734, 1509, 1202 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{28}H_{38}NO_6$: 484.2694, found: 484.2695.

$[\alpha]^{22}_D$ = +32 (*c* 1.0, $CHCl_3$); 1:99 d.r., from (*R*,*S*)**–L1**.



6-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl) 1-ethyl 2-(((benzyloxy)carbonyl)amino)hexanedioate (28, 29). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-

chloroacetate and **Zn-20**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 293 mg, 71% yield, 97:3 d.r.; (*R*,*S*)**–L1**: 299 mg, 72% yield, 2:98 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALCEL ID-3 column (30% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 9.6 min (major), 11.0 min (minor).

Characterization data for the product from (*S*,*R*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.41 – 5.29 (m, 2H), 5.11 (s, 2H), 4.69 – 4.54 (m, 1H), 4.42 – 4.30 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.21 (m, 4H), 2.07 – 1.77 (m, 6H), 1.77 – 1.40 (m, 11H), 1.40 – 1.21 (m, 7H), 1.18 – 0.94 (m, 12H), 0.93 – 0.84 (m, 9H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 172.3, 156.0, 139.7, 128.7, 128.3, 128.2, 122.8, 74.2, 67.1, 61.7, 56.8, 56.3, 53.8, 50.1, 42.4, 39.9, 39.7, 38.3, 37.1, 36.7, 36.3, 35.9, 34.0, 32.1, 32.03, 31.98, 28.4, 28.2, 27.9, 24.4, 24.0, 23.0, 22.7, 21.2, 20.8, 19.5, 18.9, 14.3, 12.0.

FT-IR (film): 3334, 2934, 2354, 1724, 1516, 1167, 1046, 762 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{43}H_{65}NNaO_6$: 714.4704, found: 714.4705.

$[\alpha]^{22}_D$ = –24 (*c* 1.0, $CHCl_3$); 97:3 d.r., from (*S*,*R*)**–L1**.

Characterization data for the product from (*R*,*S*)**–L1**:

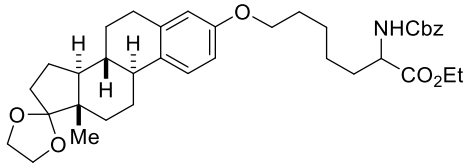
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.44 – 5.24 (m, 2H), 5.11 (s, 2H), 4.70 – 4.53 (m, 1H), 4.43 – 4.31 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.22 (m, 4H), 2.07 – 1.76 (m, 6H), 1.76 – 1.41 (m, 11H), 1.41 – 1.21 (m, 7H), 1.18 – 0.95 (m, 12H), 0.93 – 0.83 (m, 9H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 172.3, 156.0, 139.7, 128.7, 128.3, 128.2, 122.8, 74.2, 67.1, 61.7, 56.8, 56.3, 53.8, 50.1, 42.4, 39.9, 39.6, 38.3, 37.1, 36.7, 36.3, 35.9, 34.0, 32.1, 32.03, 31.98, 28.4, 28.2, 27.9, 24.4, 24.0, 23.0, 22.7, 21.2, 20.8, 19.4, 18.9, 14.3, 12.0.

FT-IR (film): 3354, 2922, 2357, 1721, 1239, 1031, 778 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{43}H_{65}NNaO_6$: 714.4704, found: 714.4721.

$[\alpha]^{22}_D$ = –17 (*c* 1.0, $CHCl_3$); 2:98 d.r., from (*R*,*S*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-7-(((8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)oxy)heptanoate (30, 31). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-21**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 298 mg, 80% yield, 98:2 d.r.; (*R*,*S*)**–L1**: 286 mg, 77% yield, 2:98 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALCEL OJ-3 column (30% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.7 min (minor), 6.3 min (major).

Characterization data for the product from (*S*,*R*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.65 (m, 1H), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.30 (d, *J* = 8.2 Hz, 1H), 5.11 (s, 2H), 4.44 – 4.30 (m, 1H), 4.20 (q, *J* = 7.4 Hz, 2H), 4.02 – 3.82 (m, 5H), 3.73 (s, 1H), 2.94 – 2.77 (m, 2H), 2.58 – 1.92 (m, 4H), 1.92 – 1.23 (m, 20H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 157.0, 156.0, 138.1, 136.4, 132.8, 128.7, 128.3, 128.2, 126.4, 119.6, 114.64, 114.55, 112.2, 112.1, 67.7, 67.1, 65.4, 64.7, 63.8, 61.6, 54.0, 50.5, 49.5, 48.2, 46.3, 44.1, 43.8, 39.2, 38.5, 36.0, 34.4, 32.8, 31.7, 30.9, 29.9, 29.8, 29.2, 27.1, 26.7, 26.3, 26.1, 25.9, 25.0, 22.5, 21.7, 14.5, 14.3, 14.0.

FT-IR (film): 3350, 2914, 2352, 1724, 1506, 1253, 1028, 740 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{37}H_{49}NNaO_7$: 642.3401, found: 642.3407.

$[\alpha]^{22}_D$ = +28 (*c* 1.0, $CHCl_3$); 98:2 d.r., from (*S*,*R*)**–L1**.

Characterization data for the product from (*R*,*S*)**–L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.65 (m, 1H), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.31 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.00 – 3.86 (m, 5H), 3.74 (s, 1H), 2.97 – 2.75 (m, 2H), 2.60 – 1.93 (m, 4H), 1.91 – 1.25 (m, 20H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 157.0, 156.0, 138.1, 136.4, 132.8, 132.1, 128.7, 128.32, 128.25, 126.4, 119.6, 114.7, 114.6, 112.2, 112.1, 67.7, 67.1, 65.4, 64.7, 63.8, 61.6, 54.0, 50.5, 49.5, 48.2, 46.3, 44.1, 43.8, 39.2, 38.5, 36.0, 34.4, 32.8, 31.7, 30.9, 29.9, 29.8, 29.2, 27.1, 26.7, 26.3, 26.1, 25.9, 25.1, 22.5, 21.7, 14.5, 14.3, 14.0.

FT-IR (film): 3343, 2923, 2352, 1724, 1513, 1240, 1034, 741 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{37}H_{49}NNaO_7$: 642.3401, found: 642.3422.

$[\alpha]^{22}_D$ = +22 (*c* 1.0, $CHCl_3$); 2:98 d.r., from (*R*,*S*)**–L1**.

3.4.6. Effect of reaction parameters

General Procedure 5 (GP-5).

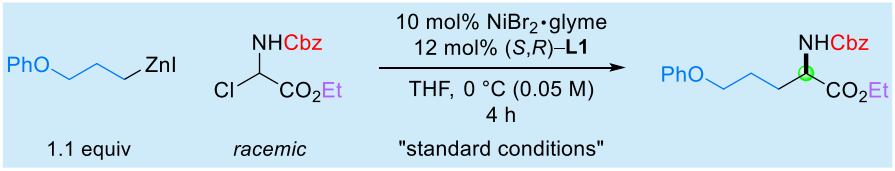
Preparation of a solution of the catalyst: In a nitrogen-filled glovebox, an oven-dried 4 mL vial that contained a stir bar was charged with $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and (*S*,*R*)**–L1** (5.4 mg, 0.012 mmol, 12 mol%). Next, THF (1.0 mL) was added, the vial was capped with a PTFE septum cap, and the mixture was stirred at room temperature for 30 min, leading to an orange, homogeneous solution.

Cross-coupling: In a nitrogen-filled glovebox, a solution of the electrophile (0.10 mmol, 1.0 equiv) in THF (1.0 mL) was added to the reaction mixture. The vial was capped with a PTFE septum cap and taken out of the glovebox. The reaction vial was then placed in an *i*-PrOH cooling bath at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. Then, the alkylzinc solution (0.11 mmol, 1.1 equiv) was added dropwise via microsyringe over 3 min, during which the reaction mixture became a clear, dark-red solution (which typically became colorless over the next 30 min). The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 4 h.

Work-up: The reaction was quenched at 0 °C by the addition of EtOH (0.1 mL). The resulting mixture was allowed to warm to room temperature, and then *N*,*N*-diphenylacetamide (2.5 mg) was added as an internal standard. The reaction mixture was passed through a short pad of silica gel, with Et_2O as the eluent. The solvent was removed under reduced pressure, and the residue was purified by chromatography.

Table 3.2: Ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate was reacted with **Zn-1** according to **GP-5**. The yields were determined via LC-MS analysis, with *N*,*N*-diphenylacetamide as the internal standard. The ee values were determined via SFC analysis after purification by preparative thin-layer chromatography. All data are the average of two experiments.

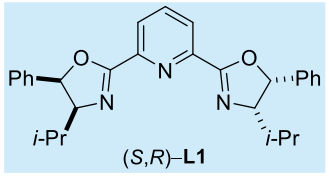
Table 3.2. *Effect of reaction parameters.*



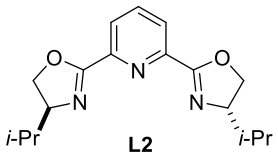
1.1 equiv *racemic* "standard conditions"

entry	variation from the standard conditions	yield (%)[a]	ee (%)[b]
1	none	84	97
2	30 min, instead of 4 h	86	97
3	no $NiBr_2$•glyme	10	0
4	no **L1**	40	0
5	**L2**, instead of **L1**	60	96
6	**L3**, instead of **L1**	47	41
7	**L4**, instead of **L1**	71	80
8	**L5**, instead of **L1**	58	20
9	**L6**, instead of **L1**	67	15
10	2-MeTHF, instead of THF	62	91
11	MTBE, instead of THF	28	17
12	Et_2O, instead of THF	32	27
13	DME, instead of THF	53	69
14	0.1 M, instead of 0.05 M	79	93
15	5.0 mol% $NiBr_2$•glyme, 6.0 mol% **L1**	82	96
16	2.5 mol% $NiBr_2$•glyme, 3.0 mol% **L1**, 24 h	61	92
17	1.0 mol% $NiBr_2$•glyme, 1.2 mol% **L1**, 24 h	39	82
18	r.t., instead of 0 °C	80	95
19	1.0 equiv organozinc	83	97
20	RZnBr, instead of RZnI	67	94
21	0.5 equiv H_2O added	80	96
22	1.0 equiv H_2O added	53	93
23	1 mL air (added with syringe)	81	96
24	under air in a closed vial	77	96

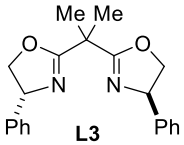
All data are the average of two experiments. [a]Determined through LC-MS analysis using an internal standard [b]Determined through SFC analysis.



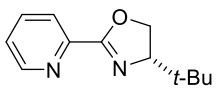
(*S*,*R*)–**L1**



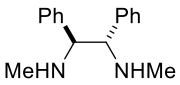
L2



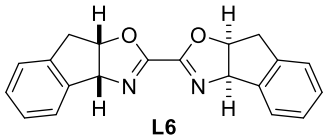
L3



L4



L5

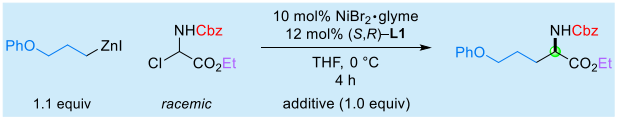


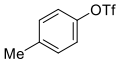
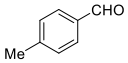
L6

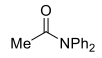
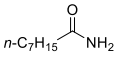
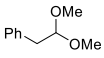
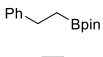
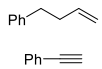
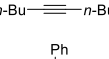
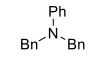
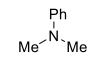
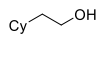
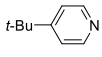
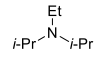
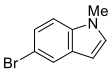
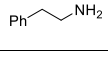
3.4.7. Study of functional-group compatibility

Table 3.3: Ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate was reacted with **Zn-1** according to **GP-5**, in the presence of 1.0 equiv of the additives shown below. The additive was added after the addition of the solution of ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate. In addition to *N*,*N*-diphenylacetamide (2.5 mg), *n*-dodecane (23 μL, 0.10 mmol) was added as an internal standard after quenching the reaction. The additive-recovery values were determined via GC analysis, with *n*-dodecane as the internal standard. The yields were determined via LC-MS analysis, with *N*,*N*-diphenylacetamide as the internal standard. The ee values were determined via SFC analysis after purification by preparative thin-layer chromatography. All data are the average of two experiments.

Table 3.3. *Study of functional-group compatibility.*

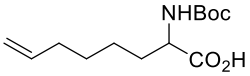


additive	recovery (%)[a]	yield (%)[b]	ee (%)[c]
n-$C_{10}H_{21}Cl$	93 >95[d]	80 79	96 96
	>95	77	96
	88 >95[d]	84 80	96 96
	>95	82	97
	>95	81	97
	>95	79	96
	>95	81	97
	>95	82	96
	>95	82	97
	>95	84	96
$CH_3(CH_2)_{13}CN$	>95	82	95
	>95	79	97
	>95	80	96
	>95	77	96
	>95	77	96
	>95	79	96
	>95	81	96
	>95	79	96
	>95	84	97
	>95	77	96
	>95	85	96

additive	recovery (%)[a]	yield (%)[b]	ee (%)[c]
	>95	84	96
	>95	72	93
	92	73	95
	87	75	97
	>95	77	96
	>95	81	96
	>95	77	96
	>95	83	96
	>95	85	96
	>95	82	95
	>95	87	97
	>95	84	95
	90	76	97
	91	65	97
	>95	61	91
	94	54	97
	>95	54	73
	93	44	73
Cy_2NH	>95	19	78
n-BuNHPh	65	<3	
	58	56	97
	6	7	90

[a] Determined through GC analysis. [b] Determined through LC-MS analysis. [c] Determined through SFC analysis.
[d] 5.0 mol% $NiBr_2$·glyme and 6.0 mol% (*S*,*R*)–**L1** were used instead.

3.4.8. Applications



2-((*tert*-Butoxycarbonyl)amino)oct-7-enoic acid (32). GP-4 was applied on a 0.6-mmol scale to ethyl 2-bromo-2-((*tert*-butoxycarbonyl)amino)acetate and **Zn-22** to generate the Boc-protected amino ester *in situ*. The reaction was quenched with water (6.0 mL), and the reaction mixture was stirred at 0 °C for another 10 min. Then, $LiOH{\cdot}H_2O$ (126 mg, 3.0 mmol, 5.0 equiv) was added in one portion at 0 °C. After stirring at 0 °C for 20 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and washed with Et_2O (10 mL x 3). The aqueous layer was acidified to pH = 3 with a solution of 10% citric acid, and it was then extracted with Et_2O (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1:9 MeOH/DCM) to afford the product as a yellow oil.

(*S*,*R*)**–L1**: 112 mg, 72% yield, 95% ee; (*R*,*S*)**–L1**: 107 mg, 69% yield, 94% ee.

SFC analysis: The ee was determined after transforming the product to the corresponding benzyl ester.

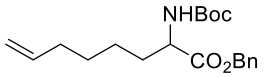
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.16 – 4.81 (m, 3H), 4.40 – 4.04 (m, 1H), 2.14 – 1.97 (m, 2H), 1.94 – 1.78 (m, 1H), 1.75 – 1.61 (m, 1H), 1.48 – 1.36 (m, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 155.7, 138.6, 114.8, 80.4, 53.5, 33.6, 32.4, 28.5, 28.4, 24.8.

FT-IR (film): 3318, 1698, 1506, 913 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{13}H_{23}NNaO_4$: 280.1519, found: 280.1500.

$[\alpha]^{22}_D$ = –4.9 (*c* 1.0, $CHCl_3$); 95% ee, from (*S*,*R*)**–L1**.



Benzyl 2-((*tert*-butoxycarbonyl)amino)oct-7-enoate. To a solution of 2-((*tert*-butoxycarbonyl)amino)oct-7-enoic acid (25.7 mg, 0.10 mmol, 1.0 equiv), benzyl alcohol (11.9 mg, 0.11 mmol, 1.1 equiv), and DMAP (1.2 mg, 0.010 mmol, 0.10 equiv) in DCM (1.0 mL) at 0 °C was added DCC (22.7 mg, 0.11 mmol, 1.1 equiv). After stirring at room temperature for 24 h, the reaction was quenched with water (5 mL). The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1:5 EtOAc/hexanes) to afford the product as a yellow oil.

(*S*,*R*)**–L1**: 29.9 mg, 86% yield, 95% ee; (*R*,*S*)**–L1**: 31.1 mg, 90% yield, 94% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.4 min (minor), 6.5 min (major).

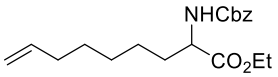
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.30 – 5.08 (m, 2H), 5.08 – 4.86 (m, 3H), 4.34 (q, *J* = 7.3 Hz, 1H), 2.09 – 1.89 (m, 2H), 1.86 – 1.74 (m, 1H), 1.68 – 1.57 (m, 1H), 1.51 – 1.21 (m, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.5, 138.6, 135.6, 128.7, 128.5, 128.4, 114.7, 79.9, 67.0, 53.6, 33.6, 32.6, 28.5, 28.4, 24.7.

FT-IR (film): 3358, 2930, 1714, 1505, 1367, 1168, 745, 616 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_4$: 370.1989, found: 370.1993.

$[\alpha]^{22}_D$ = +1.6 (*c* 1.0, $CHCl_3$); 95% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)non-8-enoate (33). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-23**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 141 mg, 70% yield, 97% ee; (*R*,*S*)**–L1**: 141 mg, 70% yield, 97% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.8 min (minor), 6.6 min (major).

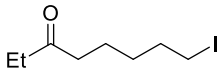
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.79 (m, 1H), 5.33 – 5.26 (m, 1H), 5.11 (s, 2H), 5.04 – 4.89 (m, 2H), 4.40 – 4.30 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.88 – 1.60 (m, 2H), 1.41 – 1.24 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 156.0, 138.9, 136.4, 128.6, 128.3, 128.2, 114.5, 67.0, 61.5, 54.0, 33.7, 32.8, 28.73, 28.71, 25.1, 14.3.

FT-IR (film): 3347, 2930, 2357, 1718, 1522, 1209, 1028 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{27}NNaO_4$: 356.1832, found: 356.1848.

$[\alpha]^{22}_D = -11$ (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.



8-Iodooctan-3-one. The title compound was synthesized according to a prior report.[45] An oven-dried 100 mL round-bottom flask was charged with a stir bar, 1-ethylcyclohexan-1-ol (2.56 g, 20.0 mmol, 1.0 equiv), and (diacetoxyiodo)benzene (7.08 g, 22.0 mmol, 1.1 equiv), and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling on a Schlenk line (three cycles). I_2 (5.08 g, 20.0 mmol, 1.0 equiv) was added under a positive pressure of nitrogen, followed by the addition of DCM (10 mL) via syringe. A 100 W incandescent bulb was placed ~5 cm from the flask, and the flask was irradiated while stirring at room temperature in a water bath for 2 h. The reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (20 mL), and the resulting mixture was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

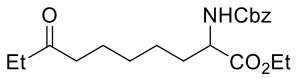
pressure. The residue was purified by column chromatography on silica gel (1:20 EtOAc/hexanes) to afford the product as a yellow oil (2.80 g, 11.0 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (t, *J* = 7.0 Hz, 2H), 2.48 – 2.31 (m, 4H), 1.87 – 1.73 (m, 2H), 1.63 – 1.50 (m, 2H), 1.44 – 1.30 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 42.1, 36.0, 33.3, 30.1, 22.7, 7.9, 6.9.

FT-IR (film): 2937, 2360, 1715, 1459, 1375, 1203, 1168, 1110, 728 cm^{-1}.

GC-MS (EI) *m/z* $[M]^+$ calcd for $C_8H_{15}IO$: 254.0, found: 253.9.



Ethyl 2-(((benzyloxy)carbonyl)amino)-8-oxodecanoate (34). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-24**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*R*)**–L1**: 136 mg, 63% yield, 93% ee; (*R*,*S*)**–L1**: 135 mg, 62% yield, 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IF-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 4.4 min (minor), 4.6 min (major).

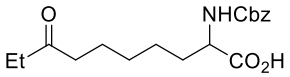
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.33 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 2H), 4.38 – 4.27 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.46 – 2.30 (m, 4H), 1.88 – 1.72 (m, 1H), 1.71 – 1.48 (m, 3H), 1.38 – 1.21 (m, 7H), 1.03 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7, 172.6, 156.0, 136.4, 128.6, 128.22, 128.16, 67.0, 61.5, 53.9, 42.2, 36.0, 32.6, 28.8, 25.0, 23.6, 14.2, 7.9.

FT-IR (film): 3348, 2940, 2360, 1715, 1520, 1207, 1046, 744, 700 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{29}NNaO_5$: 386.1938, found: 386.1943.

$[\alpha]^{22}_D$ = –13 (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*R*)**–L1**.



2-(((Benzyloxy)carbonyl)amino)-8-oxodecanoic acid (35). To a solution of ethyl 2-(((benzyloxy)carbonyl)amino)-8-oxodecanoate (36.3 mg, 0.10 mmol, 1.0 equiv) in THF/H_2O (1.0:0.6, 1.6 mL) was added LiOH·H_2O (10.1 mg, 0.24 mmol, 2.4 equiv) at 0 °C. After stirring at 0 °C for 5 h, the reaction mixture was concentrated under reduced pressure. To the residue was added H_2O (10 mL), and the mixture was washed with Et_2O (5 mL x 3). The aqueous layer was acidified to pH = 3 with a solution of 10% citric acid, and then it was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure to afford 2-(((benzyloxy)carbonyl)amino)-8-oxodecanoic acid as a colorless oil. The analytical data matched a literature report.[46]

(*S*,*R*)**–L1**: 30.1 mg, 90% yield, 93% ee; (*R*,*S*)**–L1**: 28.7 mg, 86% yield, 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL IG-3 column (30% MeOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 3.6 min (major), 4.3 min (minor).

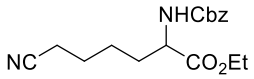
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.42 – 7.27 (m, 5H), 5.42 (d, *J* = 8.3 Hz, 1H), 5.19 – 5.05 (m, 2H), 4.48 – 4.18 (m, 1H), 2.52 – 2.27 (m, 4H), 1.97 – 1.76 (m, 1H), 1.76 – 1.61 (m, 1H), 1.62 – 1.47 (m, 2H), 1.42 – 1.21 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5, 177.0, 156.2, 136.2, 128.6, 128.3, 128.2, 67.2, 53.8, 42.2, 36.0, 32.3, 28.8, 25.1, 23.6, 7.9.

FT-IR (film): 2940, 1714, 1532, 1456, 1220, 1059 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_5$: 358.1625, found: 358.1619.

$[\alpha]^{22}_D$ = –8.0 (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*R*)**–L1**.



Ethyl 2-(((benzyloxy)carbonyl)amino)-6-cyanohexanoate (36). The title compound was synthesized according to **GP-4** from ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate and **Zn-25**. The product was purified by column chromatography on silica gel (1:1 EtOAc/hexanes). Colorless oil. The analytical data matched a literature report.[47]

(*S*,*R*)**–L1**: 168 mg, 88% yield, 97% ee; (*R*,*S*)**–L1**: 170 mg, 89% yield, 96% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL ID-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*R*)**–L1**: 5.3 min (major), 7.8 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.38 (d, *J* = 7.9 Hz, 1H), 5.10 (s, 2H), 4.43 – 4.32 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.32 (t, *J* = 6.9 Hz, 2H), 1.96 – 1.80 (m, 1H), 1.80 – 1.59 (m, 3H), 1.59 – 1.37 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 156.0, 136.3, 128.7, 128.3, 128.2, 119.4, 67.2, 61.8, 53.5, 32.1, 25.0, 24.3, 17.1, 14.3.

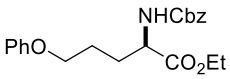
FT-IR (film): 3351, 2920, 2247, 1716, 1520, 1020, 680 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{23}N_2O_4$: 319.1652, found: 319.1645.

$[\alpha]^{22}_D = -13$ (*c* 1.0, $CHCl_3$); 97% ee, from (*S*,*R*)**–L1**.

3.4.9. Assignment of absolute configuration

The configuration of the coupling product illustrated in **Figure 3.2** (**1**), using (*S*,*R*)**–L1**, was determined via X-ray crystallography.



Ethyl (*R*)-2-(((benzyloxy)carbonyl)amino)-5-phenoxypentanoate (1). X-ray quality crystals were obtained by slow evaporation of a saturated solution in EtOAc/hexanes of a sample synthesized using (*S*,*R*)**–L1**. A crystal of $C_{21}H_{25}NO_5$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a 'Bruker APEX-II CCD' diffractometer with filtered Cu-K*α* radiation at a temperature of 100 K. Using Olex2,[48] the structure was solved with the XT[49] structure solution program using direct methods and

refined with the ShelXL[50] refinement package using least squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

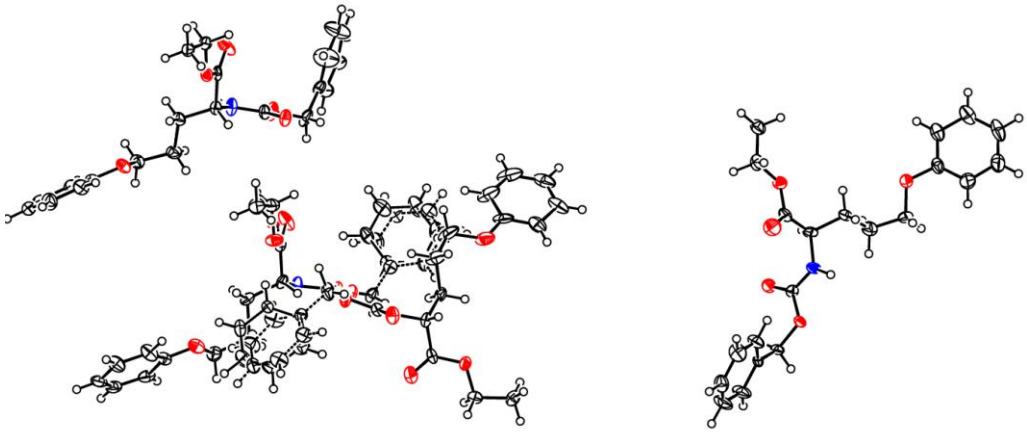
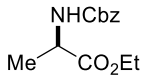


Table 3.4. *Crystal data for 1.*

Identification code	v20175	
Chemical formula	$C_{168}H_{200}N_8O_{40}$	
Formula weight	2971.35 g/mol	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal size	0.070 x 0.210 x 0.290 mm	
Crystal habit	colorless plate	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.4885(5) Å	α = 90°
	b = 24.4227(12) Å	β = 89.969(2)°
	c = 16.6176(8) Å	γ = 90°
Volume	3850.9(3) $Å^3$	
Z	1	
Density (calculated)	1.281 g/cm^3	
Absorption coefficient	0.747 mm^{-1}	
F(000)	1584	
Theta range for data collection	1.81 to 66.59°	
Index ranges	-11<=h<=11, -29<=k<=29, -19<=l<=19	
Reflections collected	77210	
Independent reflections	13543 [R(int) = 0.0496]	
Coverage of independent reflections	100.0%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9500 and 0.8120	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	

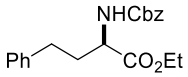
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	13543 / 445 / 1097	
Goodness-of-fit on F^2	1.061	
Final R indices	13446 data; $I>2\sigma(I)$	R1 = 0.0363, wR2 = 0.0903
	all data	R1 = 0.0367, wR2 = 0.0907
Weighting scheme	$w=1/[\sigma^2(Fo^2)+(0.0371P)^2+1.4617P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.00(4)	
Largest diff. peak and hole	0.175 and -0.196 eÅ^{-3}	
R.M.S. deviation from mean	0.042 eÅ^{-3}	



Ethyl ((benzyloxy)carbonyl)-*D*-alaninate (7). The absolute configuration of this compound has been reported.[51]

Optical rotation: $[\alpha]^{22}_D = -2.3$ (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*R*)**–L1**.

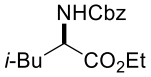
Lit.: $[\alpha]^{21}_D = -1.7$ (*c* 3.63, $CHCl_3$); 99% ee for (*R*) configuration.



Ethyl (*R*)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanoate (9). The absolute configuration of this compound has been reported.[52]

Optical rotation: $[\alpha]^{22}_D = -23$ (*c* 1.0, $CHCl_3$); 98% ee, from (*S*,*R*)**–L1**.

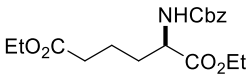
Lit.: $[\alpha]_D = +25$ (*c* 1.08, $CHCl_3$); 99% ee for (*S*) configuration.



Ethyl ((benzyloxy)carbonyl)-*D*-leucinate (11). The absolute configuration of this compound has been reported.[53]

Optical rotation: $[\alpha]^{22}_D = +4.3$ (*c* 1.0, $CHCl_3$); 99% ee, from (*S*,*R*)**–L1**.

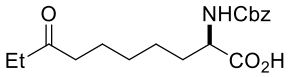
Lit.: $[\alpha]^{25}_D = -6.3$ (*c* 1.96, $CHCl_3$); 99% ee for (*S*) configuration.



Diethyl (*R*)-2-(((benzyloxy)carbonyl)amino)hexanedioate (15). The absolute configuration of this compound has been reported.[54]

Optical rotation: $[\alpha]^{22}_D = -8.1$ (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*R*)**–L1**.

Lit.: $[\alpha]^{25}_{D} = -6.9$ (*c* 1.0, $CHCl_3$); 99% ee for (*R*) configuration.



(*R*)-2-(((Benzyloxy)carbonyl)amino)-8-oxodecanoic acid (35). The absolute configuration of this compound has been reported.[46]

Optical rotation: $[\alpha]^{22}_{D} = -8.0$ (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*R*)**–L1**.

Lit.: $[\alpha]^{25}_{D} = +6.9$ (*c* 1.3, $CHCl_3$); 99% ee for (*S*) configuration.

3.5. Notes and references

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