Chapter 2

THE ASYMMETRIC SYNTHESIS OF AMINES VIA NICKEL-CATALYZED ENANTIOCONVERGENT SUBSTITUTION REACTIONS

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2.1. Introduction

Because a chiral dialkyl carbinamine subunit is found in a wide array of bioactive molecules (e.g., **Figure 2.1**), the development of efficient methods for its synthesis, particularly catalytic and enantioselective processes, is an important objective in synthetic organic chemistry.[1] A variety of approaches have been described to date, each of which has limitations,[2] including the addition of alkyl nucleophiles to imines of aliphatic aldehydes (limited scope with respect to the nucleophile),[3] the reduction/hydrogenation of imines of unsymmetrical dialkylketones (modest enantioselectivity when the alkyl groups are similar) and enamines,[4–6] and the hydroamination of olefins (modest regioselectivity for many

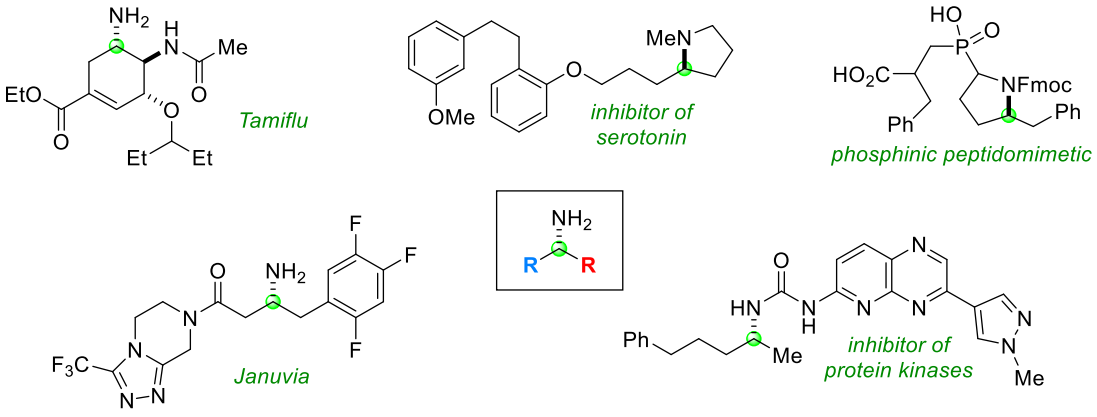


Figure 2.1. *Examples of compounds that include a chiral dialkyl carbinamine subunit.*

internal olefins).[7–9] After our study was completed, several groups independently demonstrated that nickel-catalyzed asymmetric reductive couplings of olefins and alkyl halides[10] can provide access to protected dialkyl carbinamines.[11–14]

With regard to retrosynthetic analysis, the nucleophilic substitution of an alkyl electrophile represents a straightforward approach to the synthesis of dialkyl carbinamines (top of **Figure 2.2**). Although substitution by a nitrogen or by a carbon nucleophile could in principle afford the target molecules, in order to achieve high enantioselectivity, the use of a nitrogen nucleophile would require the effective differentiation between two alkyl groups, whereas the use of a carbon nucleophile would require the effective differentiation between an alkyl group and a nitrogen substituent. We viewed the latter approach to be more likely to provide a general solution to the asymmetric synthesis of dialkyl carbinamines, e.g., for

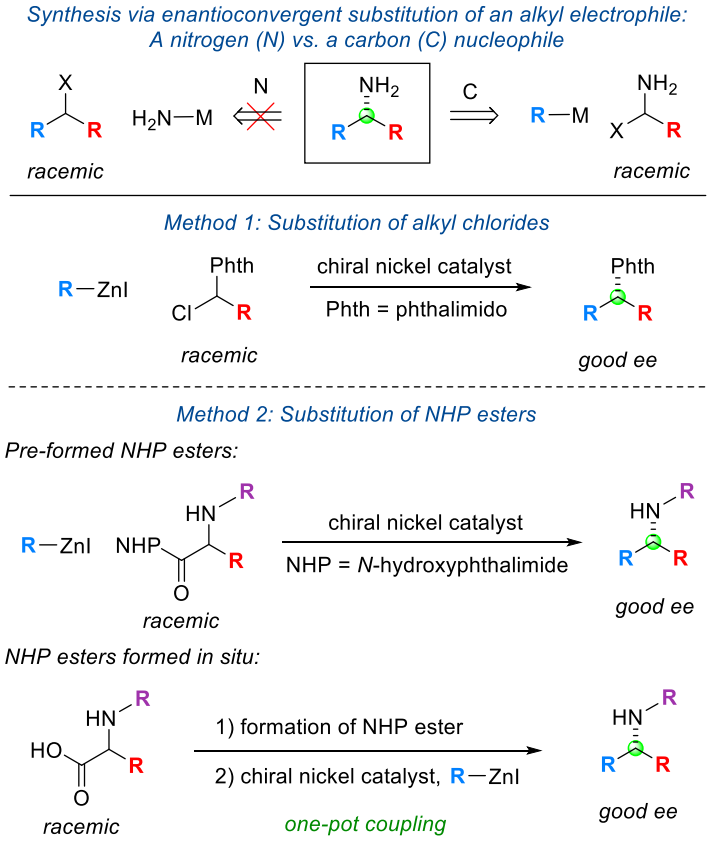
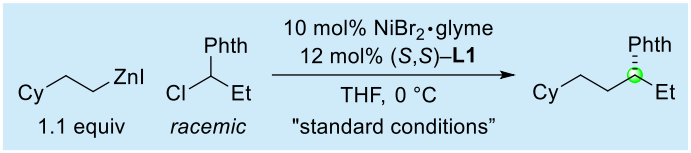
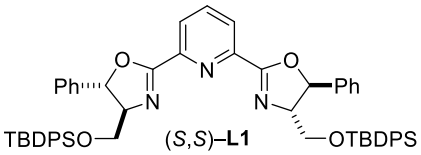


Figure 2.2. *This study: Nickel-catalyzed enantioconvergent substitution reactions of alkyl electrophiles to generate protected dialkyl carbinamines.*

Table 2.1. *Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines: effect of reaction parameters.*





entry	variation from the standard conditions	yield (%)[a]	ee (%)
1	none	90	92
2	no $NiBr_2$·glyme	<1	–
3	no **L1**	<1	–
4	5.0 mol% $NiBr_2$·glyme, 6.0 mol% (*S*,*S*)–**L1**	79	91
5	0.05 equiv H_2O added	31	92
6	1 mL air added	64	91

those bearing similar alkyl groups (e.g., CH_2R versus CH_2R^1).

Recently, transition metals have been shown to catalyze an array of enantioconvergent couplings of racemic alkyl electrophiles with alkyl nucleophiles.[15–18] However, there have been no reports of such metal-catalyzed substitution reactions in the case of electrophiles that bear a nitrogen substituent geminal to the leaving group, as required for the strategy for the asymmetric synthesis of dialkyl carbinamines illustrated at the top of **Figure 2.2**. Herein, we describe two complementary approaches to such enantioconvergent substitutions, specifically, nickel-catalyzed couplings of alkylzinc reagents with *α*-phthalimido alkyl chlorides (Method 1) and with *N*-hydroxyphthalimide (NHP) esters of *α*-amino acids (Method 2).

2.2. Results and discussion

2.2.1. Couplings of α-phthalimido alkyl chlorides: Scope

The phthalimide functional group is a well-established protected form of a primary amine.[19] We have determined that a chiral nickel/pybox catalyst can achieve the coupling of an alkylzinc reagent (1.1 equivalents) with a racemic *α*-phthalimido alkyl chloride to afford a protected dialkyl carbinamine in good yield and enantioselectivity (**Table 2.1**, entry 1: 90% yield, 92% ee). Essentially no alkyl–alkyl bond formation is observed in the absence of $NiBr_2$·glyme or of the pybox ligand (entries 2 and 3), whereas a slightly

diminished yield (but good ee) is obtained when half of the standard catalyst loading is used (entry 4). The presence of water or of air impedes carbon–carbon bond formation, while the enantioselectivity is not affected (entries 5 and 6).[20]

As illustrated in **Figure 2.3**, the scope of this method for the catalytic enantioconvergent synthesis of protected dialkyl carbinamines is fairly broad with respect to the electrophile. For example, good yields and ee's are observed when the alkyl substituent varies in size from methyl to isobutyl (products **1**–**4**), although a poor yield is observed if it is a bulky isopropyl group. A variety of functional groups are compatible with the method, including an aryl iodide, ester, carbonate, unactivated primary alkyl halide (fluoride, chloride, and bromide), indazole, and activated heteroaryl chloride (products **5**–**14**). In the case of an electrophile that bears a remote stereocenter, the stereochemistry of the catalyst, rather than that of the substrate, controls the stereochemistry of the product (products **15** and **16**). On a gram-scale (1.40 g of product), the coupling to generate product **2** proceeds in similar yield and ee (93% yield, 92% ee) as for a reaction conducted on a

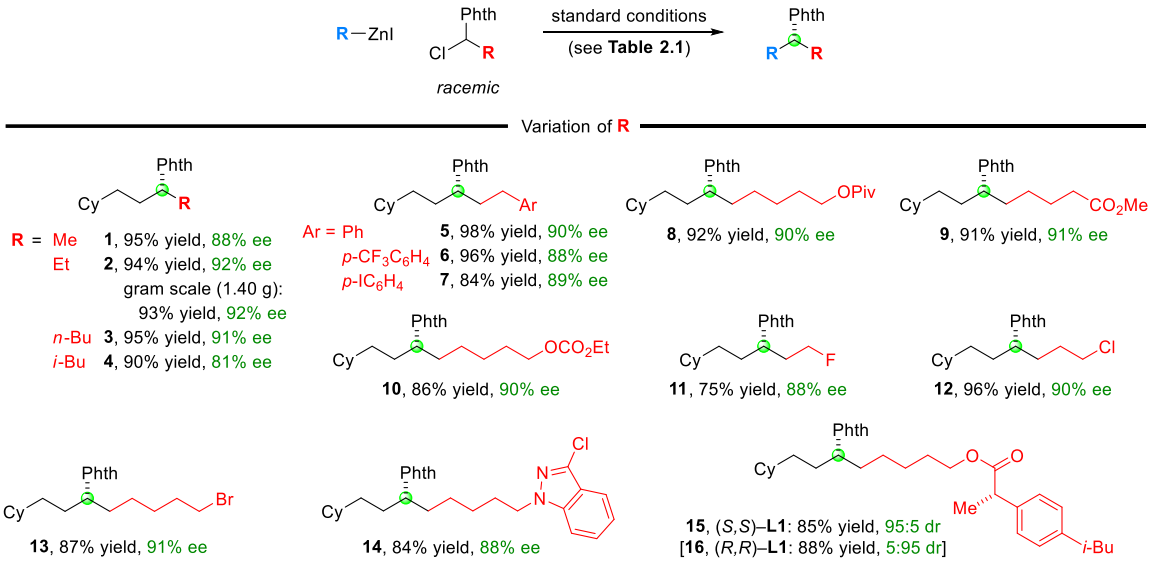


Figure 2.3. *Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines: electrophile scope. All data are the average of two experiments run on a 0.6-mmol scale (unless otherwise noted), and all yields are of purified products.*

0.6-mmol scale (94% yield, 92% ee).

The scope of this enantioconvergent alkyl–alkyl coupling is also broad with respect to the nucleophile, leading to an array of protected dialkyl carbinamines with good yield and ee. For example, the alkyl substituent can range in size from *n*-hexyl to isobutyl (**Figure 2.4**, products **17**–**19**; however, the use of a secondary alkylzinc reagent results in a low yield of the coupling product), and a variety of functional groups can be present (entries **20**–**34**; for additional studies of the functional-group compatibility of the method, see the Experimental Section).

2.2.2. Couplings of α-phthalimido alkyl chlorides: Mechanistic observations

We have previously reported that two distinct nickel-catalyzed enantioconvergent couplings (Negishi reactions of propargylic halides and Kumada reactions of α-haloketones) appear to proceed through a common pathway (**Figure 2.5**), wherein the

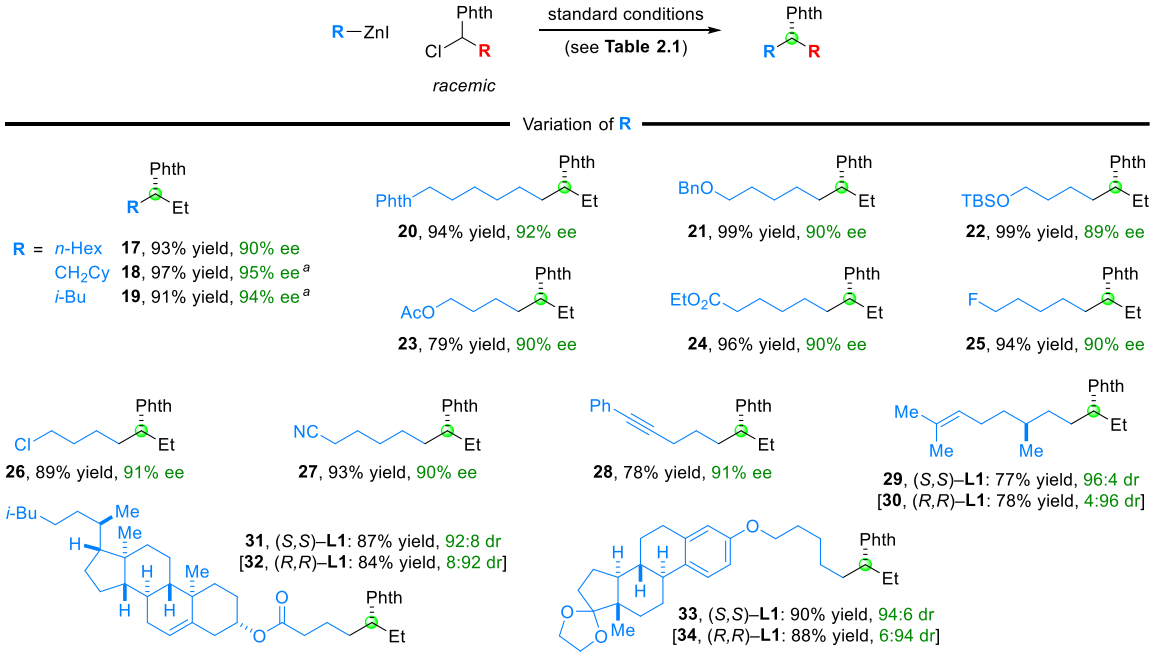


Figure 2.4. *Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines: nucleophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *The reaction was conducted at r.t.*

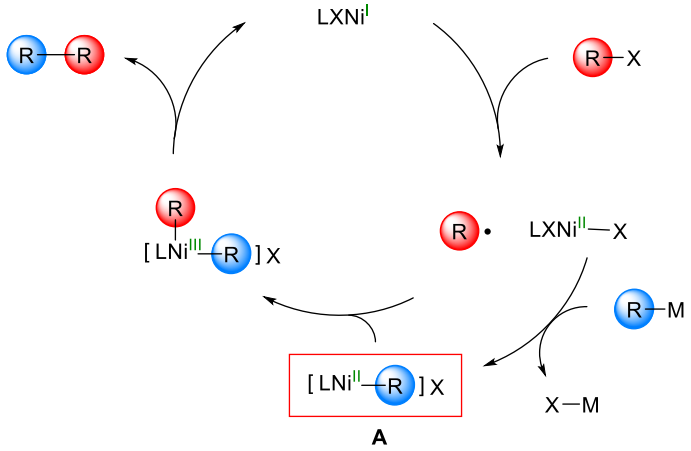


Figure 2.5. *Outline of a possible pathway.*

predominant resting state of the catalyst is an organonickel(II) complex (**A**).[21,22] For the couplings of α-phthalimido alkyl chlorides with alkylzinc reagents described herein, our mechanistic observations are again consistent with this pathway.

For example, quantitative EPR analysis indicates that odd-electron nickel intermediates (e.g., Ni^{I} or Ni^{III}) do not accumulate to a significant extent during the reaction (<2% of the total nickel present). Furthermore, ESI–MS analysis of a coupling (**Table 2.1**) at partial conversion reveals masses consistent with $\mathbf{A^1}$ and $\mathbf{A^2}$ (**Figure 2.6**). Finally, when the same coupling is conducted in the presence of TEMPO, a TEMPO adduct of the electrophile can be isolated, consistent with the generation of an organic radical from the alkyl chloride.

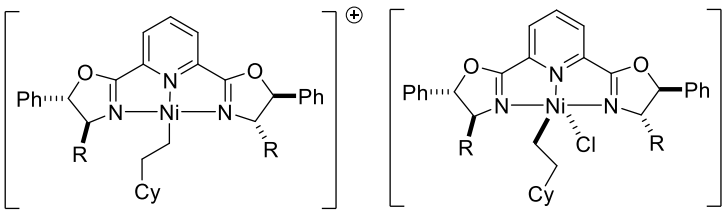
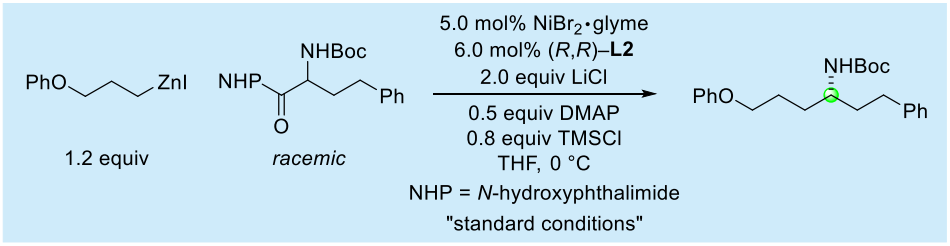


Figure 2.6. *ESI–MS data for the coupling illustrated in Table 5.1.*

Table 2.2. *Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters: effect of reaction parameters.*



entry	variation from the standard conditions	yield (%)[a]	ee (%)
1	none	79	91
2	no $NiBr_2$·glyme	<1	–
3	no (*R*,*R*)–**L2**	30	–
4	no LiCl	16	88
5	no DMAP	70	65
6	no TMSCl	65	87
7	2.5 mol% $NiBr_2$·glyme, 3.0 mol% (*R*,*R*)–**L2**	65	88
8	0.05 equiv H_2O added	73	88
9	1 mL air added	71	88

2.2.3. Couplings of NHP esters of α-amino acids: Scope

Redox-active esters (e.g., NHP esters) serve as useful partners in a variety of metal-catalyzed carbon–carbon bond-forming reactions.[23–27] The use of NHP esters derived from readily available α-amino acids[28–32] could provide a complementary strategy to the use of α-amino halides, many of which are relatively unstable, to generate an organic radical (**Figure 2.5**) en route to enantioenriched dialkyl carbinamines.

However, when we applied the conditions that we had developed for couplings of α-phthalimido alkyl chlorides (**Table 2.1**) to the coupling of an *N*-Boc-protected NHP ester of an α-amino acid, we observed low yield and enantioselectivity. After an extensive survey of reaction parameters, we determined that the desired decarboxylative coupling of a racemic NHP ester with an alkylzinc reagent can be achieved in the presence of a chiral nickel/diamine catalyst, providing the *N*-protected dialkyl carbinamine in good yield and ee (**Table 2.2**, entry 1; 79% yield, 91% ee). It is worth noting that only 1.2 equivalents of the nucleophile are used, despite the presence of a potentially labile N–H proton; in

contrast, most previous metal-catalyzed couplings of NHP esters have employed at least 2 equivalents of the organometallic nucleophile, even in the absence of an acidic proton.[23,24]

Essentially no carbon–carbon bond formation is observed in the absence of $NiBr_2$·glyme (**Table 2.2**, entry 2), and the coupling proceeds in significantly lower yield and/or ee when chiral diamine **L2**, LiCl,[33,34] TMSCl,[35,36] or DMAP[37] is omitted (entries 3–6). The use of half of the standard catalyst loading results in a small loss in efficiency (entry 7; 65% yield, 88% ee). From a practical point of view, it is noteworthy that this enantioconvergent coupling is not highly water- or air-sensitive: the addition of 0.05 equivalents of water or of 1 mL of air to the reaction vessel has only a minor deleterious effect (entries 8 and 9).

A variety of NHP esters serve as suitable coupling partners in these nickel-catalyzed enantioconvergent couplings to generate protected dialkyl carbinamines (**Figure 2.7**). The

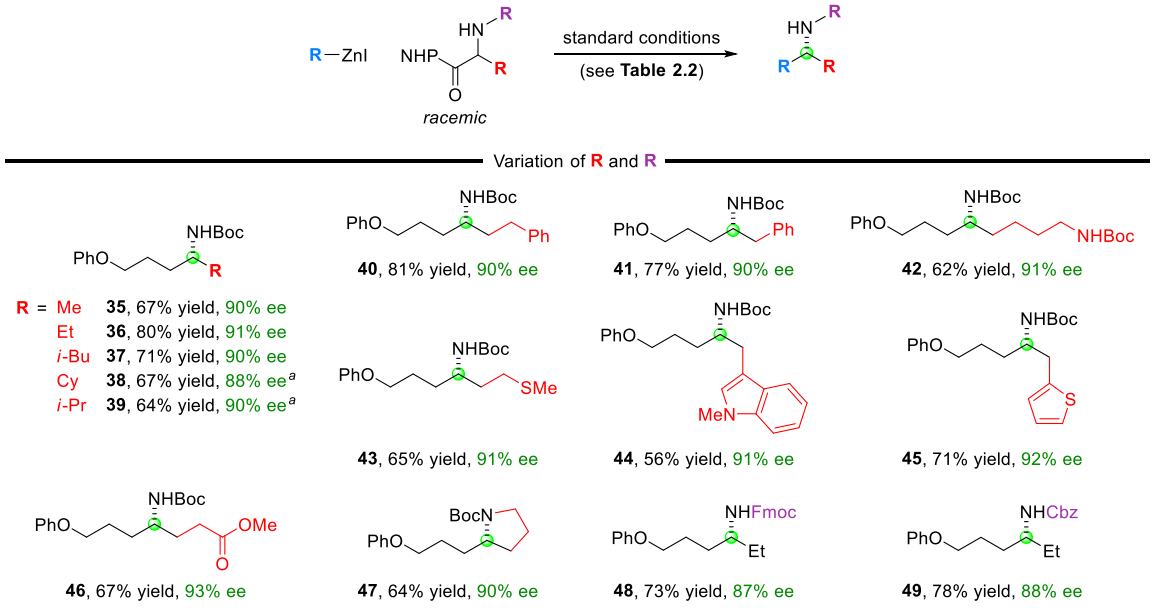


Figure 2.7. *Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters: electrophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *10 mol% $NiBr_2$·glyme, 12 mol%* ***L2****, and 5.0 equiv LiCl were used (no DMAP or TMSCl).*

alkyl group can vary in steric demand from Me to *i*-Pr (products **35**–**39**), and it can bear a range of functional groups, including a thioether, an indole, and a thiophene (products **40**–**47**). The method can be applied to glutamic acid and proline derivatives, thereby affording enantioenriched protected γ-amino acids[38,39] and 2-alkylpyrrolidines[40,41] in good ee from readily available starting materials (products **46** and **47**). Not only Boc-protected, but also Fmoc- and Cbz-protected, amines are useful reaction partners (products **48** and **49**).

The scope of this method is also broad with respect to the nucleophile (**Figure 2.8**). Unbranched and branched primary (but not secondary) alkylzinc reagents serve as suitable nucleophiles (products **50**–**53**), as do a variety of functionalized alkylzincs (products **54**–

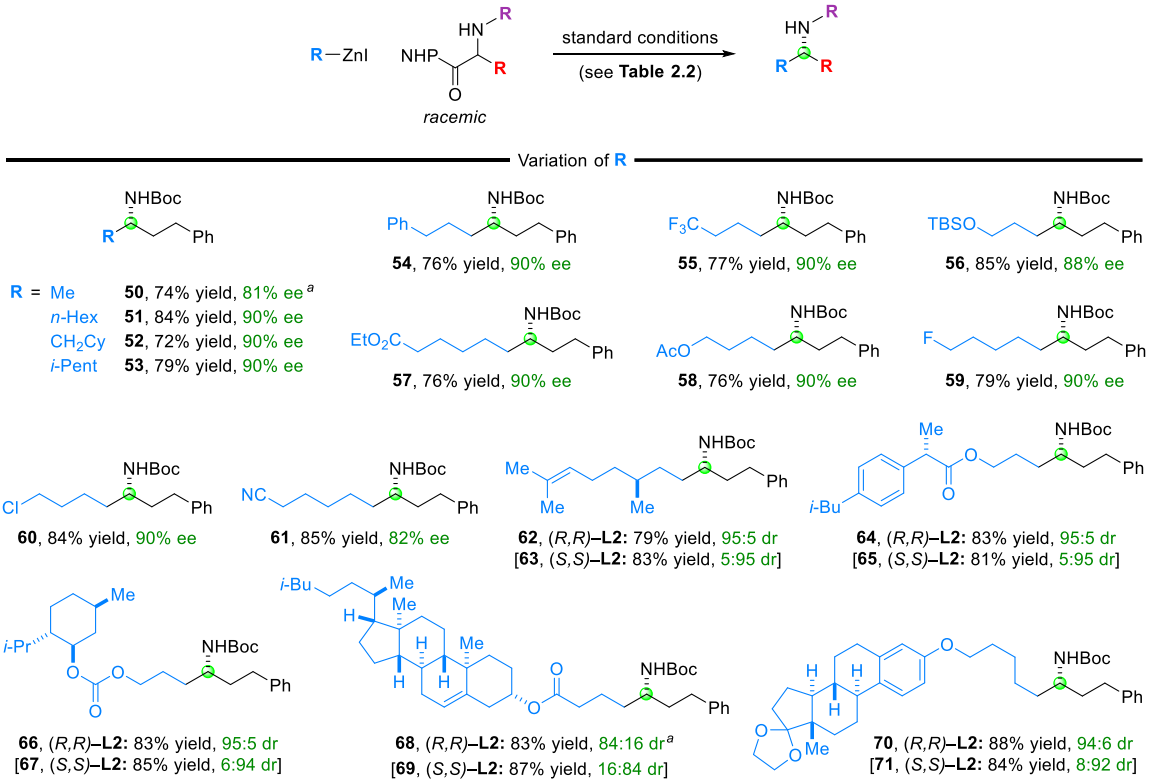


Figure 2.8. *Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters: nucleophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *The product was recrystallized to >99% ee or >99.5:0.5 d.r.*

71;[42] see the Experimental Section for additional functional-group compatibility studies). The coupling products are generally crystalline, allowing ready enhancement of stereochemical purity (e.g., products **50** and **68**).

This approach to the catalytic asymmetric synthesis of protected dialkyl carbinamines can be achieved in a one-pot process without isolation of the NHP ester,[43] thereby providing the desired products in one step from commercially available protected α-amino acids (**Figure 2.9**). The yields for the one-pot procedure are similar to or modestly lower than for the corresponding couplings of purified NHP esters, and the enantioselectivities are essentially identical. The success of this process is a testament to the robustness of the method–impurities and side products from the DIC coupling, including *N,N'*-diisopropylurea, neither poison the catalyst nor consume the alkylzinc reagent via protonation, enabling the reaction to proceed with only 1.2 equivalents of the nucleophile.[44]

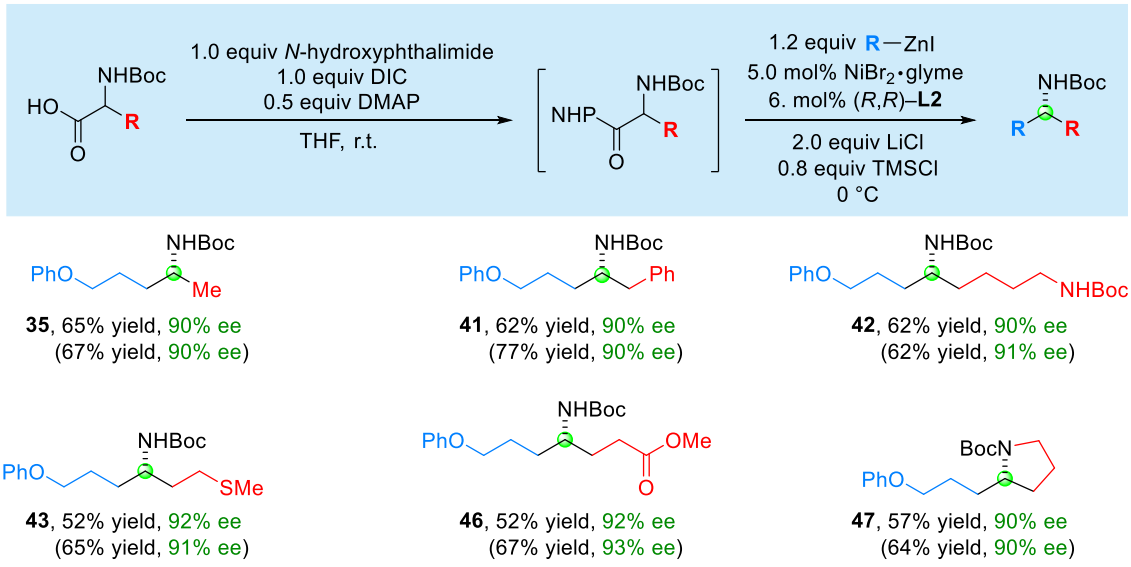


Figure 2.9. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: one-pot procedure. The values in parentheses are the data for the corresponding couplings of purified NHP esters.*

2.2.4. Couplings of NHP esters of α-amino acids: Applications

We have applied our catalytic asymmetric synthesis of protected dialkyl carbinamines to a variety of target molecules, starting from commercially available *α*-amino acid derivatives (**Figure 2.10**). For example, urea **73**, an analog of an inhibitor of protein kinases 1 and 2,[45] can be synthesized in two steps and 40% overall yield from *N*-Boc-alanine, via a one-pot coupling followed by conversion of the carbamate to the urea. Furthermore, Fmoc-protected aminoalcohol **74**, an intermediate in the synthesis of a constrained peptidomimetic (prior route: eight steps),[46] can be produced in two steps from *N*-Fmoc-phenylalanine using our method; although the nickel-catalyzed coupling itself proceeds with moderate enantioselectivity (81% ee), Fmoc-protected aminoalcohol **74** can readily be recrystallized to >99% ee. Pyrrolidine **75**, which has previously been generated in four steps from *N*-Cbz-proline en route to a hydrazone-based chiral auxiliary,[47] can be synthesized in one pot and 72% yield from *N*-Boc-proline via our approach. Finally, pyrrolidine **77**, which

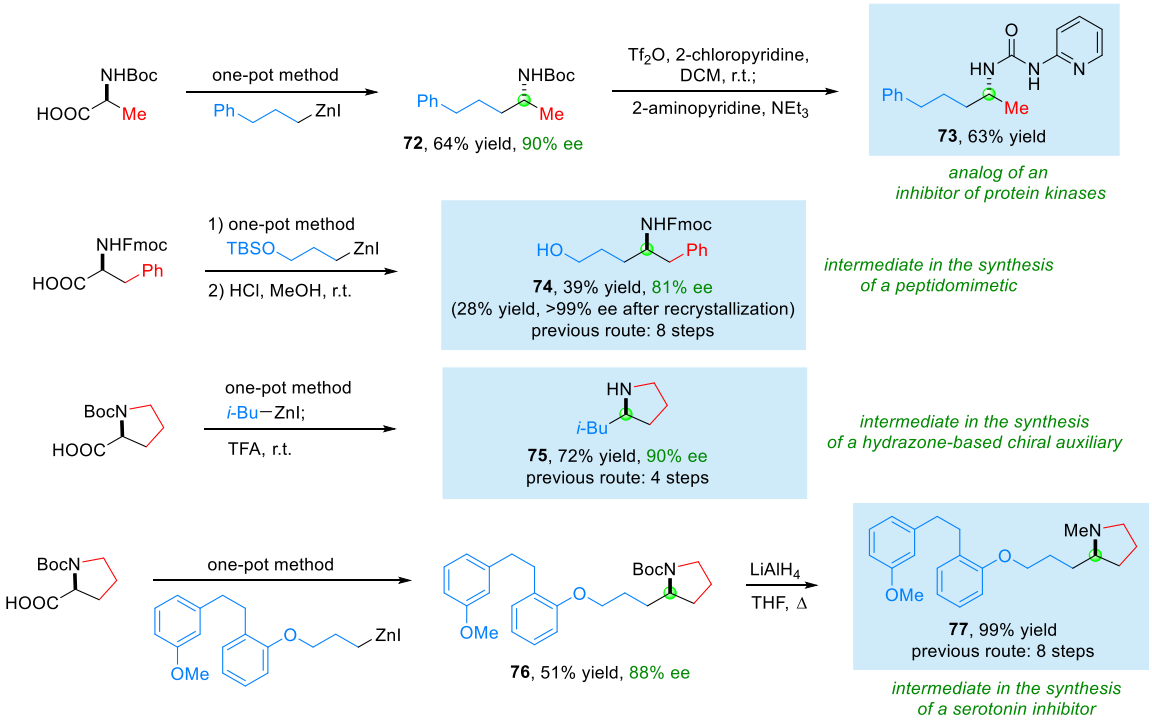


Figure 2.10. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: applications.*

has been employed as an intermediate in a study of serotonin inhibitors, can be formed in 50% overall yield in three, rather than eight, steps, via a nickel-catalyzed coupling.[48]

2.2.5. Couplings of NHP esters of α-amino acids: Mechanistic observations

Our working hypothesis is that these nickel-catalyzed enantioconvergent couplings of NHP esters may be following a pathway analogous to that outlined in **Figure 2.5** for couplings of alkyl halides, wherein the same radical R• may be generated by the decarboxylative reduction of the NHP ester by $LXNi^{I}$.[23,49] As in the case of couplings of α-phthalimido alkyl chlorides (see above), the EPR spectrum of the nickel-catalyzed reaction of the NHP ester illustrated in **Table 2.2** indicates that odd-electron nickel intermediates do not accumulate to a significant extent during the coupling (<2% of the total nickel present). Furthermore, C–C bond formation is inhibited by the presence of TEMPO.[50]

We have examined whether the chiral nickel catalyst achieves any kinetic resolution in the enantioconvergent coupling of a racemic NHP ester. Although this issue has been explored in the case of alkyl halides,[51,52] we are not aware of corresponding investigations in the case of NHP esters. When the coupling of a racemic NHP ester is stopped at partial conversion, the unreacted NHP ester is still racemic (<1% ee; **Figure 2.11**, experiment 1). Taken together with our observation that enantioenriched NHP ester does not racemize under the reaction conditions (experiment 2), these data indicate that the chiral nickel catalyst is reacting at essentially identical rates with each enantiomer of the NHP ester (no kinetic resolution).

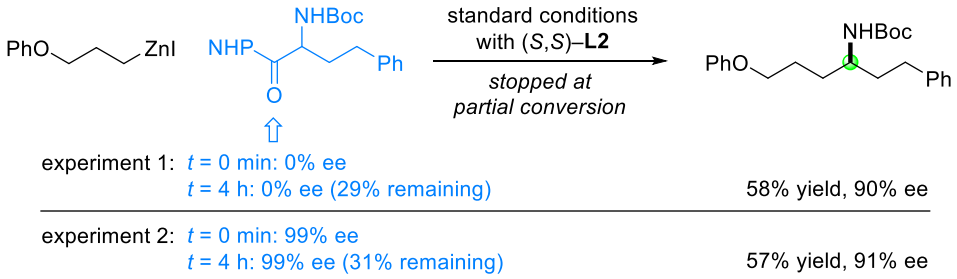


Figure 2.11. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: study of kinetic resolution.*

2.3. Conclusions

We have developed two versatile methods for the catalytic asymmetric synthesis of dialkyl carbinamines, an important family of molecules in chemistry and biology, through the use of chiral catalysts based on nickel, an earth-abundant metal. With an alkylzinc reagent (1.1–1.2 equivalents) as the nucleophile, enantioconvergent couplings can be achieved under mild conditions with either an α-phthalimido alkyl chloride or an NHP ester of a protected α-amino acid; both methods display broad scope and good functional-group tolerance. The NHP esters can be generated *in situ* from commercially available α-amino acid derivatives and coupled directly, resulting in a straightforward one-pot catalytic enantioselective synthesis of a variety of interesting target molecules.

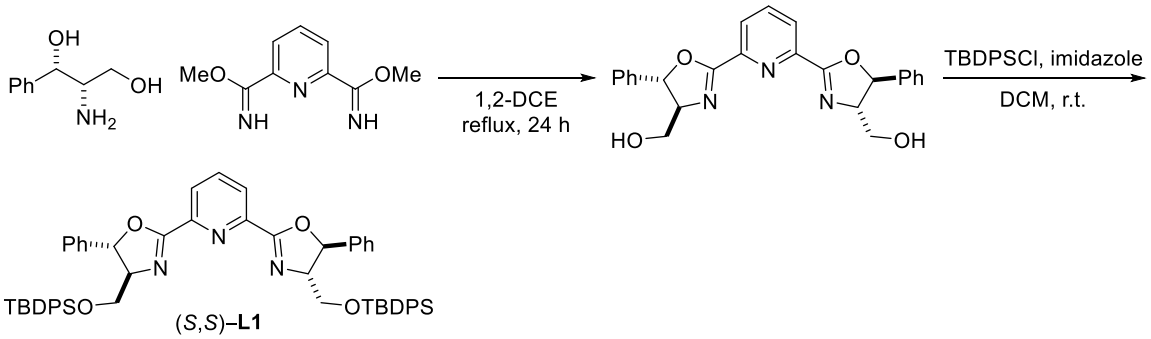
2.4. Experimental section

2.4.1. 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. Dimethyl pyridine-2,6-bis(carbimidate) was prepared from pyridine-2,6-dicarbonitrile.[53]

NMR spectra were collected on a Varian 300 MHz, a Bruker 400 MHz, or a Varian 500 MHz spectrometer at ambient temperature; chemical shifts (δ) are reported in ppm downfield from tertramethylsilane, using the solvent resonance as the internal standard. HPLC analyses were carried out on an Agilent 1100 series system with Daicel CHIRALPAK® or Daicel CHIRALCEL® columns (4.6 × 250 mm, particle size 5 μm). 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 by a Waters LCT Premier XE TOF MS 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. Column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle) or acidic Al_2O_3 (Brockmann I, 50-200 μm, 60A, Acros Organics). X-ray crystallographic analyses were carried out by the Caltech X-Ray Crystallography Facility using a Bruker APEX-II CCD diffractometer. X-band EPR measurements were collected on a Bruker EMX spectrometer.

2.4.2. Preparation of chiral ligands



2,6-Bis((4*S*,5*S*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-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 line. Next, (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol (5.05 g, 30.2 mmol, 2.0 equiv) and dimethyl pyridine-2,6-bis(carbimidate) (2.92 g, 15.1 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 (25 mL). The resulting solution was heated at reflux for 24 h. Then, the reaction mixture was cooled overnight at 5 °C, during which time ((4*S*,4'*S*,5*S*,5'*S*)-pyridine-2,6-diylbis(5-phenyl-4,5-dihydrooxazole-2,4-diyl))dimethanol precipitated as a brown solid, which was filtered, dried (4.67 g, 72% yield), and directly used in the following reaction.

A solution of ((4*S*,4'*S*,5*S*,5'*S*)-pyridine-2,6-diylbis(5-phenyl-4,5-dihydrooxazole-2,4-diyl))dimethanol (4.67 g, 10.9 mmol, 1.0 equiv), imidazole (4.45 g, 65.3 mmol, 6.0 equiv), and DCM (50 mL) was cooled to ~0 °C in an ice/water bath, and TBDPSCl (6.3 mL, 24 mmol, 2.2 equiv) was added via syringe over 5 min. The resulting mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with water (50 mL), and the mixture was extracted with DCM (50 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 (1:4 EtOAc/hexanes) to afford the product as a white solid (8.3 g, 9.2 mmol, 84% yield, >99% ee).

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (30% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for (*S*,*S*)-**L1**: 6.7 min, (*R*,*R*)-**L1**: 8.5 min.

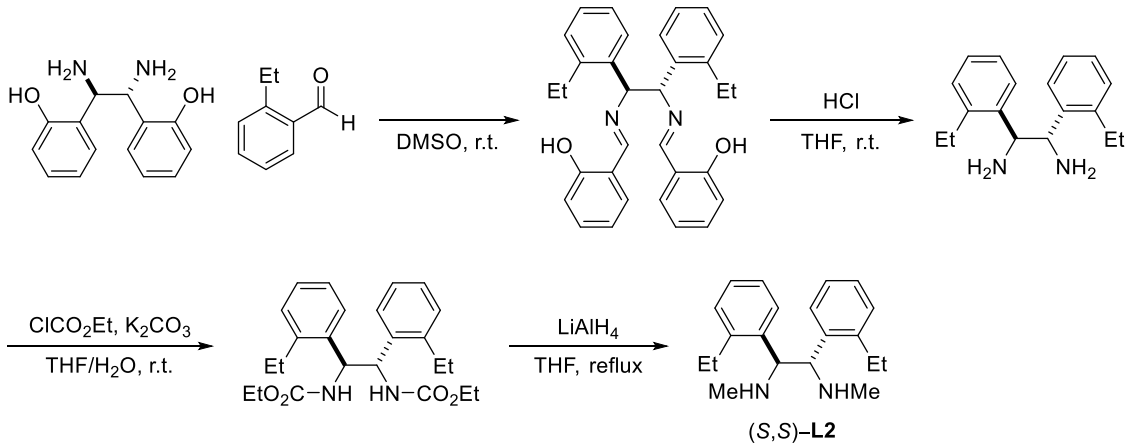
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 2H), 7.89 (t, *J* = 7.9 Hz, 1H), 7.73 – 7.57 (m, 8H), 7.47 – 7.26 (m, 22H), 5.74 (d, *J* = 6.7 Hz, 2H), 4.50 – 4.37 (m, 2H), 4.13 – 4.04 (m, 2H), 3.93 – 3.76 (m, 2H), 1.05 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 147.2, 140.8, 137.4, 135.8, 135.7, 133.4, 133.3, 129.90, 129.87, 128.8, 128.3, 127.88, 127.87, 126.2, 126.1, 85.0, 76.8, 65.9, 27.0, 19.4.

FT-IR (film): 3419, 2932, 2740, 2355, 1962, 1644, 1574, 1462, 1428, 1360, 1256, 1218, 1112, 965, 825, 748 cm^{-1}.

HRMS (ESI+) m/z $[M+Na]^+$ calcd for $C_{57}H_{59}N_3NaO_4Si_2$: 928.3936, found: 928.3945.

$[\alpha]^{22}_D$ = +16.7 (*c* 1.0, $CHCl_3$), from (*S*,*S*)-**L1**.



(1*S*,2*S*)-1,2-Bis(2-ethylphenyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine.[54] An oven-dried 250 mL round-bottom flask was charged with a stir bar and (*1R*,*2R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (10.0 g, 40.9 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 the flask (three cycles), followed by the addition of anhydrous DMSO (200 mL) and 2-ethylbenzaldehyde (13.7 g, 102 mmol, 2.5 equiv) via syringe. After the yellow mixture was stirred overnight at room temperature, the reaction was quenched by the addition of water (200 mL) and extracted with Et_2O (100 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), and then they were dried over anhydrous Na_2SO_4 and filtered. The mixture was then concentrated under reduced

pressure. 2,2'-((1*E*,1'*E*)-(((1*S*,2*S*)-1,2-Bis(2-ethylphenyl)ethane-1,2-diyl)bis(azanylylidene))bis-(methanylylidene))diphenol, obtained as a yellow oil as a mixture with unreacted 2-ethylbenzaldehyde, was used in the next step without further purification.

An oven-dried 1 L round-bottom flask was charged with a stir bar, and then it 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 a solution of crude 2,2'-((1*E*,1'*E*)-(((1*S*,2*S*)-1,2-bis(2-ethylphenyl)ethane-1,2-diyl)bis(azanylyl-idene))bis-(methanylylidene))diphenol (~20 g, ~41 mmol) in THF (630 mL). A solution of HCl (12 M; 31 mL) was added to the reaction by addition funnel over 10 min while stirring at room temperature. The reaction was allowed to stir overnight, after which Et_2O (200 mL) was added. The diamine was extracted with a solution of HCl (1 M; 100 mL x 4). The combined aqueous phase was washed with Et_2O (100 mL) and was then basified with a solution of aqueous NaOH (2 M). The resulting yellow suspension was extracted with Et_2O (100 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), and then they were dried over anhydrous Na_2SO_4 and filtered. The mixture was concentrated under reduced pressure to give (1*S*,2*S*)-1,2-bis(2-ethylphenyl)ethane-1,2-diamine (9.2 g, 34 mmol, 82% yield over 2 steps) as an orange oil.

A 500 mL two-neck round-bottom flask was charged with a stir bar, a 250 mL addition funnel, and potassium carbonate (28.4 g, 206 mmol, 6.0 equiv), and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles). A solution of (1*S*,2*S*)-1,2-bis(2-ethylphenyl)ethane-1,2-diamine (9.2 g, 34 mmol, 1.0 equiv) in THF (275 mL) and distilled water (42 mL) were added sequentially via the addition funnel. After the resulting suspension was stirred for 10 min at room temperature, ethyl chloroformate (32.6 mL, 343 mmol, 10.0 equiv) was added dropwise into the flask via syringe over 10 min. The reaction was allowed to stir at room temperature for 4 days, after which it was diluted with distilled water (200 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water (150 mL) and brine (150 mL), and then they were dried over anhydrous Na_2SO_4 and

filtered. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:7 EtOAc/hexanes) to afford diethyl ((1*S*,2*S*)-1,2-bis(2-ethylphenyl)ethane-1,2-diyl)dicarbamate as a white solid (3.7 g, 8.9 mmol, 26% yield).

An oven-dried 250 mL two-neck round-bottom flask was charged with a stir bar, fitted with a reflux condenser attached to a nitrogen manifold, and then sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles). Lithium aluminum hydride (1.6 g, 43 mmol, 5.0 equiv) was added through the open neck under a positive pressure of nitrogen. The open neck was capped with a rubber septum, and the flask was cooled to 0 °C using an ice/water bath. THF (40 mL) was added via syringe, and the gray suspension was stirred at 0 °C for 5 min. Next, a solution of diethyl ((1*S*,2*S*)-1,2-bis(2-ethylphenyl)ethane-1,2-diyl)dicarbamate (3.5 g, 8.6 mmol, 1.0 equiv) in THF (40 mL) was added dropwise via syringe through the rubber septum over 10 min. The ice/water bath was replaced with an oil bath, and the reaction mixture was heated at reflux for 18 h. The mixture was cooled to 0 °C using an ice/water bath, and water (4 mL) was added dropwise via syringe over 10 min. Next, a solution of aqueous NaOH (3.0 M; 4 mL) was added dropwise over 1 min. The resulting mixture was heated at reflux for 1 h, during which the color of the precipitate changed from gray to white. The warm solution was filtered through a Büchner funnel that contained a bed of celite, and the precipitate was washed with Et_2O (100 mL). The filtrate was concentrated under reduced pressure to yield the crude product as a light-yellow solid. The crude product was dissolved in EtOH (30 mL) and *D*-tartaric acid (1.29 g, 8.6 mmol, 1.0 equiv) was added. The heterogeneous mixture was stirred at reflux for 30 min, after which it was allowed to slowly cool back to room temperature. The mixture was then cooled to 0 °C, and after 4 h the precipitate was collected by filtration and washed with EtOH (5 mL x 2). The precipitate was added to a mixture of 10% NaOH in water (10 mL) and Et_2O (10 mL). After stirring overnight, the layers were separated, and the aqueous layers were extracted with Et_2O (10 mL x 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), and then they were dried over anhydrous Na_2SO_4 and filtered.

The mixture was concentrated under reduced pressure to yield the desired ligand as a white solid (1.59 g, 5.4 mmol, 62% yield, >99% ee).

SFC analysis: The ee was determined via SFC on a CHIRALPAK ID column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for (*S*,*S*)-**L2**: 3.2 min, (*R*,*R*)-**L2**: 4.2 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.15 (td, *J* = 7.5, 1.5 Hz, 2H), 7.07 (td, *J* = 7.4, 1.5 Hz, 2H), 6.91 (dd, *J* = 7.6, 1.5 Hz, 2H), 3.91 (s, 2H), 2.46 – 2.33 (m, 2H), 2.23 (s, 6H), 2.12 – 2.00 (m, 4H), 0.95 (t, *J* = 7.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 138.8, 128.2, 127.0, 126.8, 125.8, 65.3, 34.8, 24.7, 15.5.

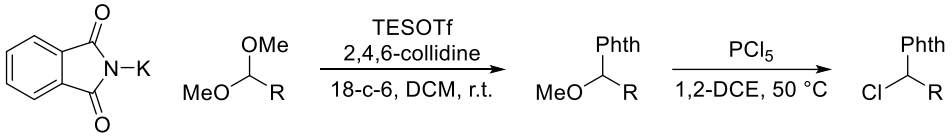
FT-IR (film): 3230, 2967, 2786, 1489, 1106, 874, 764, 741 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{29}N_2$: 297.2, found: 297.2.

$[\alpha]^{23}_D$ = +13.2 (*c* 1.0, $CHCl_3$), from (*S*,*S*)-**L2**.

2.4.3. Preparation of electrophiles

The yields have not been optimized.

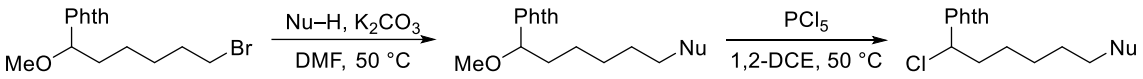


General Procedure 1 (GP-1).

Preparation of *N*,*O*-acetals. An oven-dried 250 mL round-bottom flask was charged with a stir bar and the acetal (1.0 equiv; either purchased or prepared from the corresponding aldehyde[55]), and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), and then DCM (volume to generate a 1.0 M solution of the potassium phthalimide) and 2,4,6-collidine (3.0 equiv) were added. The resulting solution was cooled to ~0 °C using an ice/water bath, and then TESOTf (2.0 equiv) was added via syringe over 10 min. The reaction mixture was stirred at ~0 °C for 30 min. After verifying the consumption of the acetal via TLC, potassium phthalimide (3.0 equiv) and 18-crown-6 (3.0 equiv) were added in one portion to the reaction mixture under a positive flow of nitrogen, and the solution

was stirred at room temperature for 2 h. Then, the reaction was quenched with water, and the mixture was extracted with DCM (three times). The combined organic layers were washed with a solution of HCl (2 M), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the *N*,*O*-acetal.

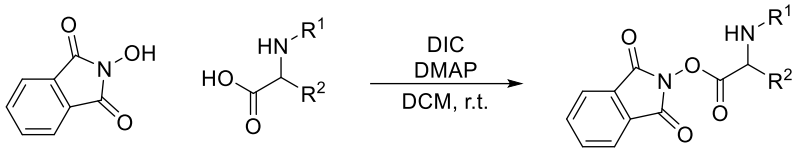
Chlorination of *N*,*O*-acetals. PCl_5 (1.5 equiv) was added to a solution of the *N*,*O*-acetal (1.0 M in 1,2-DCE; 1.0 equiv) at room temperature. The reaction mixture was stirred at 50 °C overnight, and then the reaction was quenched with water. The organic layer was washed with saturated aqueous $NaHCO_3$ (three times), and then it was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified either by recrystallization ($CHCl_3$/hexanes) or by column chromatography on acidic Al_2O_3. The alkyl chlorides used in this study are stable after purification and can be stored at room temperature for at least six months without decomposition.



General Procedure 2 (GP-2).

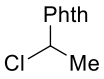
Preparation of *N*,*O*-acetals. K_2CO_3 (1.3 equiv) and the nucleophile (1.3 equiv) were added to solution of 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (0.50 M in DMF; 1.0 equiv; synthesized according to the first step of **GP-1**). The reaction mixture was stirred at 50 °C overnight. Then, the reaction was quenched with water, and the mixture was extracted with DCM (three times). The combined organic layers were washed with water and brine, and then they were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the *N*,*O*-acetal.

Chlorination of *N*,*O*-acetals. See **GP-1**.



General Procedure 3 (GP-3).

Preparation of NHP esters. An oven-dried 250 mL round-bottom flask was charged with a stir bar, *N*-hydroxyphthalimide (1.0 equiv), and DMAP (0.1 equiv), and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of anhydrous DCM (volume to generate a 0.2 M solution of the amino acid) via syringe. The mixture was stirred for 5 min, after which the amino acid (1.0 equiv) was added under a positive flow of nitrogen. After the mixture had stirred for an additional 5 min, DIC (1.0 equiv) was added dropwise via syringe over 5 min. The reaction was allowed to stir until the acid was fully consumed (typically 1 h, although the reaction can be left to stir overnight with no significant loss in yield). The mixture was filtered through a pad of celite and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solution was then concentrated under reduced pressure. Methanol (~5.0 mL/mmol of the amino acid) was added, and the mixture was stirred for 5 min. The mixture was cooled to –25 °C over 4 h, during which a solid precipitated. The solid was filtered and washed with cold methanol, affording the desired NHP ester. The NHP esters used in this study can be stored at room temperature for over one year without decomposition.



2-(1-Chloroethyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxyethane (1.80 g, 20.0 mmol). The product was purified by recrystallization. 2.91 g (14.3 mmol, 72% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 2H), 7.84 – 7.71 (m, 2H), 6.29 (q, *J* = 6.8 Hz, 1H), 2.16 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.8, 131.7, 124.0, 60.3, 23.5.

FT-IR (film): 3444, 2916, 2354, 1715, 1360, 1033, 876, 721 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{10}H_8ClNNaO_2$: 232.0, found: 232.2.

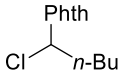
2-(1-Chloropropyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxypropane (3.12 g, 30.0 mmol). The product was purified by recrystallization. 4.48 g (20.1 mmol, 67% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H), 7.82 – 7.73 (m, 2H), 5.99 (t, *J* = 7.6 Hz, 1H), 2.66 – 2.46 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 134.8, 131.7, 124.0, 65.7, 29.7, 11.3.

FT-IR (film): 2978, 2370, 1724, 1458, 1373, 1293, 1064, 1032, 870, 720 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+NH_4]^+$ calcd for $C_{11}H_{14}ClN_2O_2$: 241.1, found: 241.1.



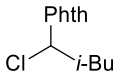
2-(1-Chloropentyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxypentane (2.35 g, 17.8 mmol). The product was purified by recrystallization. 2.60 g (10.4 mmol, 58% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.84 (m, 2H), 7.84 – 7.70 (m, 2H), 6.07 (t, *J* = 7.7 Hz, 1H), 2.66 – 2.41 (m, 2H), 1.54 – 1.21 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 134.8, 131.7, 124.0, 64.3, 35.9, 28.8, 21.9, 14.0.

FT-IR (film): 3495, 2960, 2369, 1732, 1469, 1366, 1073, 959, 879, 726 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M-Cl]^+$ calcd for $C_{13}H_{14}NO_2$: 216.1, found: 216.1.



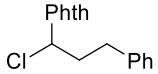
2-(1-Chloro-3-methylbutyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxy-3-methylbutane (2.64 g, 20.0 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:3 EtOAc/hexanes). 2.52 g (10.0 mmol, 50% yield over 2 steps). Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.84 (m, 2H), 7.83 – 7.70 (m, 2H), 6.19 (dd, *J* = 8.3, 7.3 Hz, 1H), 2.59 – 2.45 (m, 1H), 2.41 – 2.27 (m, 1H), 1.78 – 1.61 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 134.8, 131.7, 124.0, 63.0, 44.5, 25.9, 22.2, 22.0.

FT-IR (film): 3487, 2915, 2351, 1723, 1360, 1049, 952, 882, 741 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{13}H_{14}NO_2$: 216.1, found: 216.1.



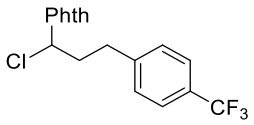
2-(1-Chloro-3-phenylpropyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from (3,3-dimethoxypropyl)benzene (3.60 g, 20.0 mmol). The product was purified by recrystallization. 4.10 g (13.7 mmol, 69% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.81 – 7.72 (m, 2H), 7.29 – 7.20 (m, 2H), 7.20 – 7.09 (m, 3H), 6.07 (t, *J* = 7.4 Hz, 1H), 3.00 – 2.77 (m, 3H), 2.77 – 2.64 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 139.6, 134.8, 131.7, 128.7, 128.6, 126.5, 124.0, 63.7, 37.4, 33.0.

FT-IR (film): 3488, 3027, 2352, 1721, 1360, 1222, 1081, 966, 876, 736 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{17}H_{14}NO_2$: 264.1, found: 264.1.



2-(1-Chloro-3-(4-(trifluoromethyl)phenyl)propyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1-(3,3-dimethoxypropyl)-4-(trifluoromethyl)benzene (4.96 g, 20.0 mmol). The product was purified by recrystallization. 5.41 g (14.7 mmol, 74% yield over 2 steps). White solid.

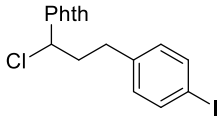
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.80 – 7.71 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.06 (t, *J* = 7.3 Hz, 1H), 3.03 – 2.81 (m, 3H), 2.82 – 2.69 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 143.6, 134.9, 131.4, 128.9, 128.8 (q, *J* = 26.3 Hz), 125.5 (q, *J* = 3.0 Hz), 124.2 (q, *J* = 218 Hz), 123.9, 63.4, 36.9, 32.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ –62.4.

FT-IR (film): 3495, 2938, 2357, 1731, 1360, 1068, 1019, 719 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{18}H_{13}F_3NO_2$: 332.1, found: 332.1.



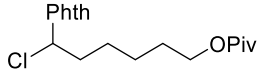
2-(1-Chloro-3-(4-iodophenyl)propyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1-(3,3-dimethoxypropyl)-4-iodobenzene (4.08 g, 13.3 mmol). The product was purified by recrystallization. 3.4 g (8.0 mmol, 60% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 2H), 7.82 – 7.73 (m, 2H), 7.59 – 7.49 (m, 2H), 6.94 – 6.85 (m, 2H), 6.04 (t, *J* = 7.4 Hz, 1H), 2.97 – 2.71 (m, 3H), 2.69 – 2.57 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 139.2, 137.7, 134.9, 131.6, 130.6, 124.0, 91.7, 63.5, 37.0, 32.6.

FT-IR (film): 3484, 2937, 2351, 1722, 1366, 1087, 722 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{17}H_{13}INO_2$: 390.0, found: 390.0.



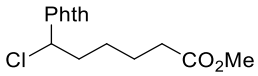
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl pivalate. The title compound was synthesized according to **GP-1** from methyl 6,6-dimethoxyhexyl pivalate (4.10 g, 16.7 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:4 EtOAc/hexanes). 2.1 g (5.8 mmol, 34% yield over 2 steps). Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H), 7.81 – 7.73 (m, 2H), 6.06 (t, *J* = 7.7 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.64 – 2.46 (m, 2H), 1.66 – 1.57 (m, 2H), 1.57 – 1.30 (m, 4H), 1.16 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 166.5, 134.8, 131.7, 124.0, 64.2, 64.1, 38.8, 36.1, 28.5, 27.3, 26.4, 25.2.

FT-IR (film): 3496, 2920, 2354, 1726, 1461, 1362, 1148, 1049, 883, 738 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{19}H_{24}NO_4$: 330.2, found: 330.2.



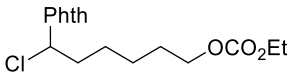
Methyl 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexanoate. The title compound was synthesized according to **GP-1** from methyl 6,6-dimethoxyhexanoate (3.60 g, 18.9 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:4 EtOAc/hexanes). 1.4 g (4.5 mmol, 24% yield over 2 steps). Colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.85 (m, 2H), 7.83 – 7.69 (m, 2H), 6.06 (t, *J* = 7.6 Hz, 1H), 3.64 (s, 3H), 2.55 (q, *J* = 7.7 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.74 – 1.61 (m, 2H), 1.59 – 1.45 (m, 1H), 1.44 – 1.31 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 166.4, 134.8, 131.7, 124.0, 64.0, 51.7, 35.8, 33.8, 26.2, 24.0.

FT-IR (film): 3494, 2950, 2356, 1731, 1360, 1214, 1052, 879, 728 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{15}H_{16}NO_4$: 274.1, found: 274.1.



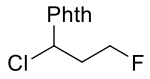
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl ethyl carbonate. The title compound was synthesized according to **GP-1** from 6,6-dimethoxyhexyl ethyl carbonate (4.68 g, 20.0 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:3 EtOAc/hexanes). 2.63 g (7.45 mmol, 37% yield over 2 steps). Yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.83 (m, 2H), 7.83 – 7.70 (m, 2H), 6.05 (t, *J* = 7.6 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 2.64 – 2.46 (m, 2H), 1.73 – 1.60 (m, 2H), 1.59 – 1.33 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 155.3, 134.8, 131.7, 124.0, 67.6, 64.1, 64.0, 36.0, 28.5, 26.3, 25.0, 14.4.

FT-IR (film): 3499, 2912, 2354, 1728, 1358, 1011, 879, 729 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{17}H_{20}NO_5$: 318.1, found: 318.1.



2-(1-Chloro-3-fluoropropyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 3-fluoro-1,1-dimethoxypropane (1.22 g, 10.0 mmol). The product was purified by recrystallization. 0.54 g (2.2 mmol, 22% yield over 2 steps). White solid.

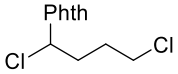
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 2H), 7.86 – 7.72 (m, 2H), 6.32 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.80 – 4.44 (m, 2H), 3.11 – 2.75 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.9, 131.7, 124.1, 80.3 (d, *J* = 168 Hz), 60.8 (d, *J* = 5.1 Hz), 37.0 (d, *J* = 19.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –220.8.

FT-IR (film): 3493, 2972, 2353, 1731, 1470, 1360, 1058, 901, 721 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{11}H_9FNO_2$: 206.1, found: 206.1.



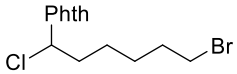
2-(1,4-Dichlorobutyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 4-chloro-1,1-dimethoxybutane (3.04 g, 20.0 mmol). The product was purified by recrystallization. 2.66 g (9.82 mmol, 49% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.84 (m, 2H), 7.84 – 7.71 (m, 2H), 6.09 (t, *J* = 7.6 Hz, 1H), 3.69 – 3.48 (m, 2H), 2.84 – 2.59 (m, 2H), 2.09 – 1.93 (m, 1H), 1.93 – 1.77 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.9, 131.6, 124.1, 63.5, 43.7, 33.5, 29.7.

FT-IR (film): 3486, 2964, 2358, 1731, 1372, 1106, 883, 720 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{12}H_{11}ClNO_2$: 236.0, found: 236.1.



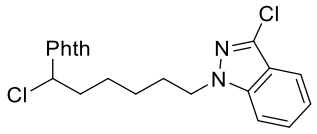
2-(6-Bromo-1-chlorohexyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 6-bromo-1,1-dimethoxyhexane (4.48 g, 20.0 mmol). The product was purified by recrystallization. 2.5 g (7.3 mmol, 36% yield over 2 steps). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.86 (m, 2H), 7.86 – 7.70 (m, 2H), 6.07 (t, *J* = 7.7 Hz, 1H), 3.38 (t, *J* = 6.7 Hz, 2H), 2.66 – 2.46 (m, 2H), 1.95 – 1.77 (m, 2H), 1.57 – 1.44 (m, 3H), 1.44 – 1.30 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 134.8, 131.7, 124.0, 64.1, 35.9, 33.5, 32.5, 27.3, 25.9.

FT-IR (film): 3490, 2936, 2354, 1728, 1358, 1038, 878, 720 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{14}H_{15}BrNO_2$: 308.0, found: 308.0.



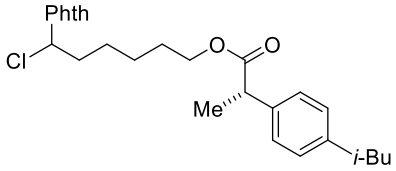
2-(1-Chloro-6-(3-chloro-1*H*-indazol-1-yl)hexyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-2** from 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (2.37 g, 6.99 mmol) and 3-chloro-1*H*-indazole (1.39 g, 9.14 mmol). The product was purified by recrystallization. 1.7 g (4.1 mmol, 59% yield over 2 steps). Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 2H), 7.82 – 7.72 (m, 2H), 7.69 – 7.60 (m, 1H), 7.45 – 7.31 (m, 2H), 7.22 – 7.13 (m, 1H), 6.03 (t, *J* = 7.7 Hz, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 2.64 – 2.40 (m, 2H), 2.04 – 1.83 (m, 2H), 1.55 – 1.43 (m, 1H), 1.44 – 1.28 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 140.8, 134.7, 132.6, 131.5, 127.4, 123.9, 121.1, 121.0, 119.9, 109.2, 63.9, 48.9, 35.8, 29.5, 26.2, 25.9.

FT-IR (film): 3492, 2936, 2354, 1731, 1469, 1360, 1046, 879, 746 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M\text{-}Cl]^+$ calcd for $C_{21}H_{19}ClN_3O_2$: 380.1, found: 380.1.



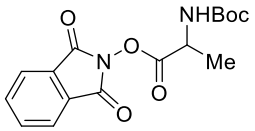
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl (2*S*)-2-(4-isobutylphenyl)propanoate. The title compound was synthesized according to **GP-2** from 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (2.37 g, 6.99 mmol) and (*S*)-2-(4-isobutylphenyl)propanoic acid (1.87 g, 9.08 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:4 EtOAc/hexanes). 1.4 g (3.0 mmol, 43% yield over 2 steps). Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.82 – 7.73 (m, 2H), 7.22 – 7.15 (m, 2H), 7.12 – 7.05 (m, 2H), 6.03 (t, *J* = 7.7 Hz, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.67 (q, *J* = 7.2 Hz, 1H), 2.56 – 2.39 (m, 4H), 1.92 – 1.74 (m, 1H), 1.64 – 1.51 (m, 2H), 1.51 – 1.37 (m, 4H), 1.38 – 1.23 (m, 3H), 0.87 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 166.5, 140.6, 138.0, 134.8, 131.7, 129.4, 127.3, 124.0, 64.42, 64.40, 64.1, 45.3, 45.1, 36.0, 30.3, 28.4, 26.3, 25.0, 22.5, 18.5.

FT-IR (film): 3494, 2915, 2355, 1728, 1359, 1029, 727, 681 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M-Cl]^+$ calcd for $C_{27}H_{32}NO_4$: 434.2, found: 434.2.



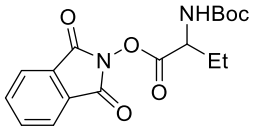
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)alaninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)alanine (1.91 g, 10.1 mmol). 1.28 g (3.83 mmol, 38% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H), 7.85 – 7.75 (m, 2H), 5.23 – 4.98 (m, 1H), 4.86 – 4.44 (m, 1H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.56 – 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 161.6, 154.9, 134.8, 128.9, 124.0, 80.7, 47.9, 28.4, 19.1.

FT-IR (film): 3356, 2978, 1749, 1368, 1162, 1050, 878, 753, 698 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{18}N_2NaO_6$: 357.1, found: 357.1.



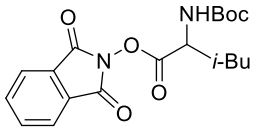
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)butanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl) amino)butanoic acid (5.00 g, 24.6 mmol). 1.76 g (5.06 mmol, 21% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.85 – 7.75 (m, 2H), 5.05 (d, J = 8.7 Hz, 1H), 4.75 – 4.68 (m, 1H), 2.00 (m, 2H), 1.49 (s, 9H), 1.24 – 1.07 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 161.6, 155.0, 135.0, 129.0, 124.1, 80.6, 53.2, 28.4, 26.5, 9.4.

FT-IR (film): 3370, 2976, 1789, 1747, 1367, 1167, 1063, 877, 682 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{20}N_2NaO_6$: 371.1, found: 371.1.



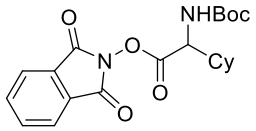
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)leucinate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)leucine (5.00 g, 21.6 mmol). 5.63 g (15.0 mmol, 69% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.84 (m, 2H), 7.84 – 7.74 (m, 2H), 4.93 (d, J = 8.9 Hz, 1H), 4.83 – 4.66 (m, 1H), 1.95 – 1.81 (m, 2H), 1.77 – 1.65 (m, 1H), 1.50 (s, 9H), 1.05 – 0.99 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 161.6, 155.0, 134.9, 128.9, 124.1, 80.6, 50.7, 41.9, 28.4, 24.8, 22.9, 21.9.

FT-IR (film): 3386, 2962, 1747, 1367, 1166, 1081, 968, 698 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{24}N_2NaO_6$: 399.2, found 399.1.



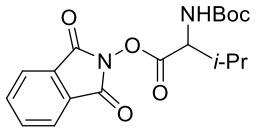
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-2-cyclohexylacetate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-2-cyclohexylacetic acid (6.00 g, 23.3 mmol). 6.78 g (16.8 mmol, 72% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.83 – 7.74 (m, 2H), 5.05 (d, *J* = 9.4 Hz, 1H), 4.68 – 4.60 (m, 1H), 2.05 – 1.92 (m, 1H), 1.90 – 1.78 (m, 4H), 1.74 – 1.65 (m, 1H), 1.47 (s, 9H), 1.40 – 1.11 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 161.7, 155.2, 134.9, 129.0, 124.1, 80.5, 56.9, 41.4, 29.2, 28.4, 26.0.

FT-IR (film): 3275, 2932, 1747, 1366, 1162, 972, 877, 754, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{26}N_2NaO_6$: 425.2, found: 425.1.



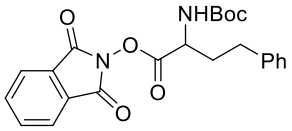
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)valinate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)valine (4.50 g, 20.7 mmol). 2.79 g (7.71 mmol, 37% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.84 – 7.74 (m, 2H), 5.05 (d, *J* = 9.4 Hz, 1H), 4.70 – 4.62 (m, 1H), 2.42 – 2.28 (m, 1H), 1.47 (s, 9H), 1.17 – 1.05 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 161.7, 155.3, 134.9, 129.0, 124.1, 80.5, 57.2, 31.9, 28.4, 18.9, 17.5.

FT-IR (film): 3369, 2974, 1743, 1366, 1166, 1072, 970, 759, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}N_2NaO_6$: 385.1, found: 385.1.



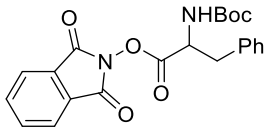
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoic acid (3.00 g, 10.7 mmol). 3.08 g (7.26 mmol, 68% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.85 – 7.76 (m, 2H), 7.36 – 7.18 (m, 5H), 5.07 (d, *J* = 8.7 Hz, 1H), 4.85 – 4.75 (m, 1H), 2.89 – 2.78 (m, 2H), 2.42 – 2.11 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 161.6, 154.9, 140.5, 135.0, 129.0, 128.73, 128.65, 126.4, 124.2, 80.7, 51.9, 34.9, 31.4, 28.4.

FT-IR (film): 3374, 2976, 1789, 1746, 1368, 1166, 759, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{24}N_2NaO_6$: 447.2, found: 447.1.



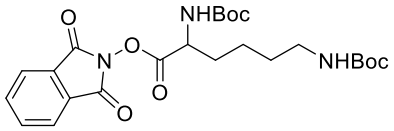
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)phenylalaninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)phenylalanine (4.50 g, 17.0 mmol). 3.59 g (8.76 mmol, 52% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.84 – 7.75 (m, 2H), 7.43 – 7.25 (m, 5H), 5.10 – 4.58 (m, 2H), 3.42 – 3.12 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.5, 154.7, 135.0, 129.8, 129.7, 128.9, 128.8, 127.4, 124.1, 80.6, 52.8, 38.3, 28.3.

FT-IR (film): 3349, 2977, 1747, 1710, 1514, 1366, 1172, 753, 698 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{22}N_2NaO_6$: 433.1, found: 433.1.



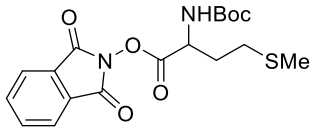
1,3-Dioxoisoindolin-2-yl N^2,N^6-bis(*tert*-butoxycarbonyl)lysinate. The title compound was synthesized according to **GP-3** from N^2,N^6-bis(*tert*-butoxycarbonyl)lysine (5.49 g, 15.9 mmol). 1.07 g (2.18 mmol, 14% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 2H), 7.82 – 7.78 (m, 2H), 5.22 – 4.86 (m, 1H), 4.68 – 4.44 (m, 2H), 3.22 – 3.12 (m, 2H), 2.05 – 1.87 (m, 2H), 1.57 – 1.41 (m, 22H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 161.7, 156.3, 155.1, 135.0, 129.0, 124.2, 80.7, 79.3, 52.0, 40.0, 32.4, 29.6, 28.6, 28.4, 22.1.

FT-IR (film): 3356, 2977, 1747, 1709, 1518, 1366, 1174, 759, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{33}N_3NaO_8$: 514.2, found: 514.2.



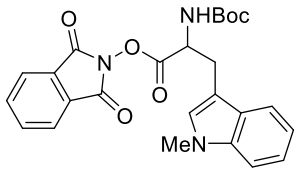
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)methioninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)methionine (5.35 g, 21.5 mmol). 4.87 g (12.4 mmol, 58% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.84 – 7.75 (m, 2H), 5.23 – 5.04 (m, 1H), 4.94 – 4.61 (m, 1H), 2.77 – 2.62 (m, 2H), 2.36 – 2.12 (m, 5H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.5, 154.9, 135.0, 128.9, 124.1, 80.7, 51.4, 32.4, 29.6, 28.3, 15.5.

FT-IR (film): 3370, 2978, 1747, 1367, 1186, 968, 758, 698 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}N_2NaO_6S$: 417.1, found 417.1.



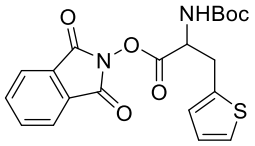
1,3-Dioxoisoindolin-2-yl N^{α}-(*tert*-butoxycarbonyl)-1-methyltryptophanate. The title compound was synthesized according to **GP-3** from N^{α}-(*tert*-butoxycarbonyl)-1-methyltryptophan (2.2 g, 6.9 mmol). 1.2 g (2.5 mmol, 37% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.84 – 7.77 (m, 2H), 7.67 – 7.58 (m, 1H), 7.35 – 7.27 (m, 2H), 7.27 – 7.09 (m, 2H), 5.20 – 4.59 (m, 2H), 3.80 (s, 3H), 3.62 – 3.29 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 161.7, 154.9, 137.0, 134.9, 129.0, 128.7, 124.2, 121.8, 119.4, 118.9, 109.4, 107.0, 80.4, 53.5, 32.9, 28.4, 28.1, 27.9.

FT-IR (film): 3380, 2978, 1731, 1486, 1371, 1166, 972, 754, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{25}N_3NaO_6$: 486.2, found: 486.2.



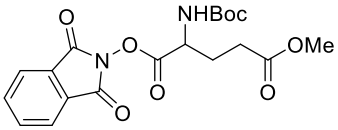
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoic acid (4.00 g, 14.7 mmol). 3.28 g (7.88 mmol, 54% yield). Light-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.82 – 7.79 (m, 2H), 7.26 – 7.19 (m, 1H), 7.11 – 7.06 (m, 1H), 7.00 (dd, *J* = 5.2, 3.5 Hz, 1H), 5.15 – 4.69 (m, 2H), 3.62 – 3.51 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 161.5, 154.7, 136.1, 135.0, 134.0, 128.9, 127.8, 127.5, 125.3, 124.2, 123.2, 80.8, 52.9, 32.5, 28.4.

FT-IR (film): 3369, 2978, 1746, 1720, 1368, 1162, 970, 758, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{20}N_2NaO_6S$: 439.1, found: 439.1.



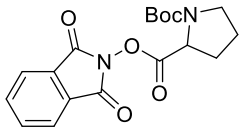
1-(1,3-Dioxoisoindolin-2-yl) 5-methyl (*tert*-butoxycarbonyl)glutamate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (0.68 g, 2.6 mmol). 0.53 g (1.3 mmol, 51% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H), 7.86 – 7.76 (m, 2H), 5.28 – 5.04 (m, 1H), 4.89 – 4.49 (m, 1H), 3.72 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.40 – 2.24 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 169.1, 161.6, 155.0, 135.0, 128.9, 124.2, 80.8, 52.1, 51.6, 29.8, 28.4, 28.0.

FT-IR (film): 3368, 2978, 1789, 1746, 1368, 1164, 878, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{22}N_2NaO_8$: 429.1, found: 429.1.



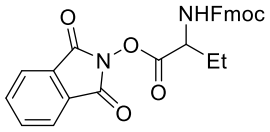
1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)proline (3.00 g, 13.9 mmol). 1.41 g (3.92 mmol, 28% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.83 – 7.73 (m, 2H), 4.65 – 4.57 (m, 1H), 3.69 – 3.37 (m, 2H), 2.51 – 2.30 (m, 2H), 2.13 – 1.92 (m, 2H), 1.51 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 161.8, 153.5, 134.9, 128.9, 124.0, 81.2, 57.3, 46.3, 31.5, 28.2, 23.6.

FT-IR (film): 2977, 1745, 1394, 1163, 1069, 972, 757, 697 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{20}N_2NaO_6$: 383.1, found: 383.1.



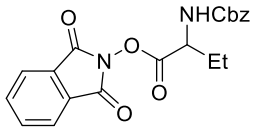
1,3-Dioxoisoindolin-2-yl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)butanoate. The title compound was synthesized according to **GP-3** from 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)butanoic acid (5.00 g, 15.4 mmol). 4.60 g (9.79 mmol, 64% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H), 7.85 – 7.72 (m, 4H), 7.64 – 7.57 (m, 2H), 7.43 – 7.37 (m, 2H), 7.36 – 7.29 (m, 2H), 5.32 (d, *J* = 8.6 Hz, 1H), 4.84 – 4.59 (m, 1H), 4.52 – 4.43 (m, 2H), 4.25 (t, *J* = 7.0 Hz, 1H), 2.21 – 1.89 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 155.7, 143.9, 143.7, 141.4, 135.0, 128.9, 127.8, 127.2, 125.2, 124.2, 120.1, 67.4, 53.6, 47.2, 26.3, 9.4.

FT-IR (film): 3340, 2974, 1789, 1745, 1518, 1186, 1065, 758, 696 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{22}N_2NaO_6$: 493.1, found: 493.1.



1,3-Dioxoisoindolin-2-yl 2-(((benzyloxy)carbonyl)amino)butanoate. The title compound was synthesized according to **GP-3** from 2-(((benzyloxy)carbonyl)amino) butanoic acid (3.60 g, 15.2 mmol). 2.46 g (6.44 mmol, 42% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H), 7.86 – 7.75 (m, 2H), 7.40 – 7.28 (m, 5H), 5.34 – 5.27 (m, 1H), 5.21 – 5.09 (m, 2H), 4.86 – 4.54 (m, 1H), 2.19 – 1.90 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H).

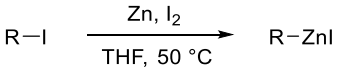
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 155.7, 136.1, 135.0, 128.9, 128.7, 128.4, 128.3, 124.2, 67.5, 53.5, 26.4, 9.3.

FT-IR (film): 3328, 1788, 1745, 1186, 1065, 877, 696 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{18}N_2NaO_6$: 405.1, found: 405.1.

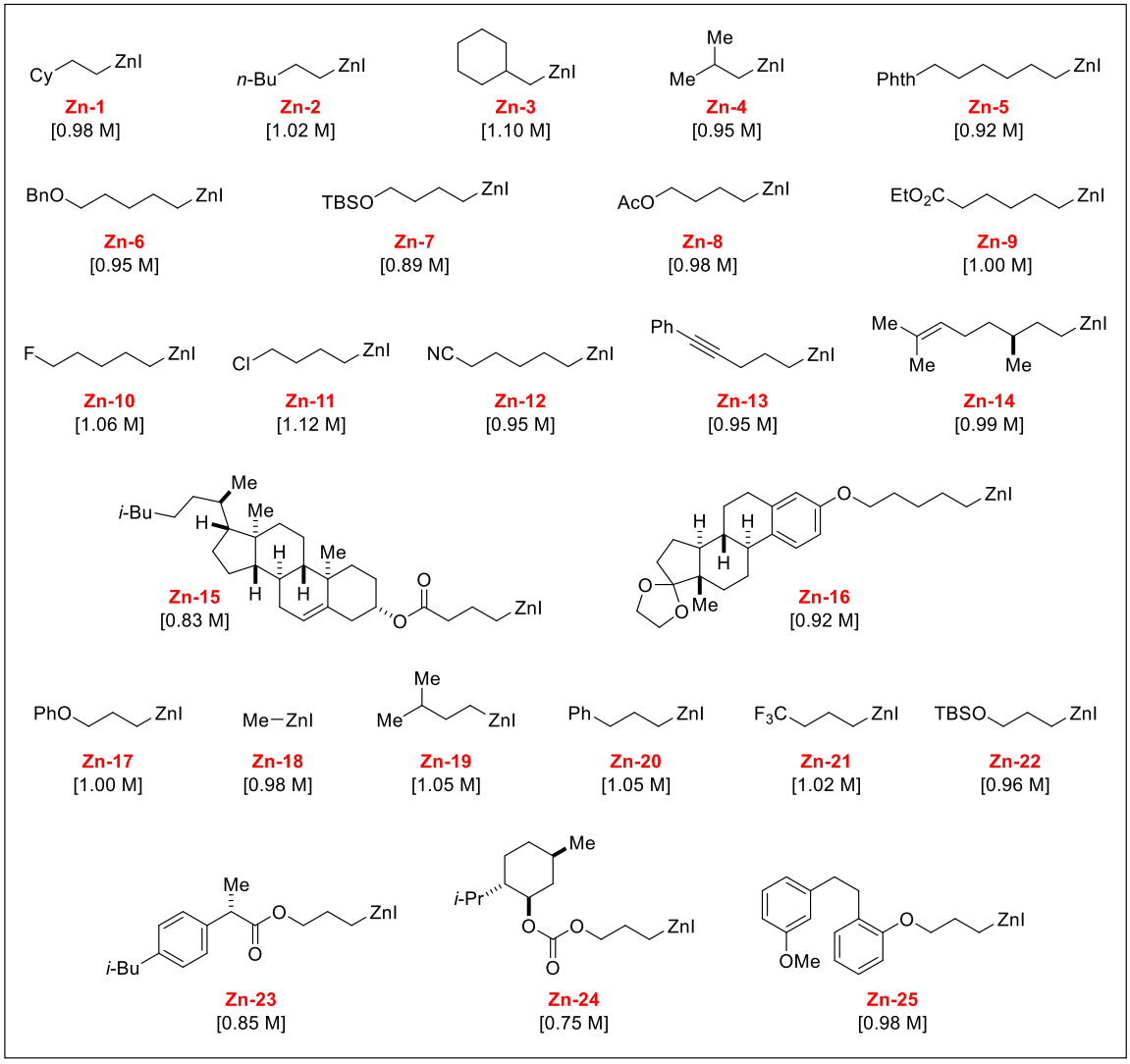
2.4.4. Preparation of nucleophiles

General Procedure 4 (GP-4).

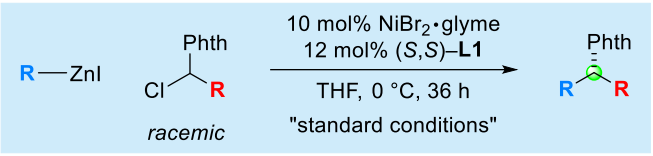


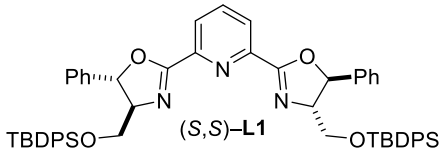
Preparation of organozinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three cycles). Then, the tube was heated with a heat gun (~250 °C) under vacuum (~1 torr) for 10 min. The Schlenk tube was allowed to cool to room temperature, and 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 (the cap was then replaced), leading initially to a red color that faded after ~5 sec 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.[56] The concentration of the alkylzinc reagents remained constant over one year when stored at room temperature in a glovebox.



2.4.5. Catalytic enantioconvergent cross-couplings



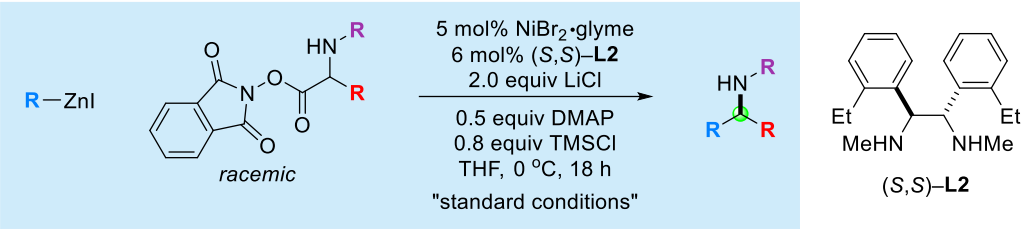


General Procedure 5 (GP-5): Alkyl chlorides as the electrophile.

Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (18.4 mg, 0.060 mmol, 10 mol%) and (*S*,*S*)-**L1** (65.2 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 the vial (three cycles). A balloon filled with nitrogen was attached to the vial. THF (6.0 mL) was added to the vial, and 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 chloride (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 40 mL reaction vial. The 8 mL vial was rinsed with THF (3.0 mL), and the washing was transferred to the reaction vial. 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 (0.66 mmol, 1.1 equiv) was added dropwise via syringe over 3 min, during which the reaction mixture turned dark. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 36 h.

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



General Procedure 6 (GP-6): NHP esters as the electrophile.

Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (9.3 mg, 0.030 mmol, 5.0 mol%), (*R*,*R*)-**L2** (10.7 mg, 0.036 mmol, 6.0 mol%), and anhydrous LiCl (52.1 mg, 1.2 mmol, 2.0 equiv; because LiCl is hygroscopic, it is recommended to weigh the compound in a capped 4 mL vial in a glovebox, transfer the vial out of the glovebox, and pour the compound into the reaction vial) were added sequentially to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was then capped with a PTFE septum cap and wrapped with electrical tape. The reaction vial was evacuated and back-filled with nitrogen (four cycles), after which a nitrogen-filled balloon was attached. THF (4.5 mL) was added via syringe, and the mixture was allowed to stir for 30 min, during which it became a light-green, homogeneous solution.

Cross-coupling: In the air, an oven-dried 8 mL vial was charged with DMAP (36.7 mg, 0.30 mmol, 0.50 equiv) and the NHP ester (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 40 mL reaction vial, leading to an orange, opaque mixture. The 8 mL vial was rinsed with THF (0.5 mL), which was also added to the reaction vial. Next, TMSCl (61 µL, 0.48 mmol, 0.80 equiv) was added via microsyringe, leading to a colorless, opaque mixture. The reaction vial was then placed in an *i*-PrOH cooling bath at 0 °C, and the mixture was stirred at 0 °C for 10 min. Then, the alkylzinc solution (0.72 mmol, 1.2 equiv) was added dropwise via syringe over 5 min, during which the reaction mixture became yellow and homogeneous. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 18 h.

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

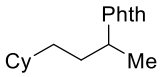
General Procedure 7 (GP-7): *α*-branched NHP esters as the electrophile.

Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (18.6 mg, 0.060 mmol, 10 mol%), (*R,R*)-**L2** (21.4 mg, 0.072 mmol, 12 mol%), and anhydrous LiCl (130 mg, 3.0 mmol, 5.0 equiv; because LiCl is hygroscopic, it is recommended to weigh the compound in a capped 4 mL vial in a glovebox, transfer the vial out of the glovebox, and pour the compound into the reaction vial) were added sequentially to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was then capped with a PTFE septum cap and wrapped with electrical tape. The reaction vial was evacuated and back-filled with nitrogen (four cycles), after which a nitrogen-filled balloon was attached. THF (4.5 mL) was added via syringe, and the mixture was allowed to stir for 30 min, during which it became a light-green, homogeneous solution.

Cross-coupling: In the air, an oven-dried 8 mL vial was charged with the NHP ester (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 40 mL reaction vial, leading to an orange, homogeneous solution. The 8 mL vial was rinsed with THF (0.5 mL), which was also added to the reaction vial. The reaction vial was then placed in an *i*-PrOH cooling bath at 0 °C, and the mixture was stirred at 0 °C for 10 min. Then, the alkylzinc solution (0.72 mmol, 1.2 equiv) was added dropwise via syringe over 5 min, during which the reaction mixture became light-red and homogeneous. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 18 h.

Work-up: The reaction was quenched with methanol (0.2 mL), and the mixture was passed through a plug of silica gel; the vial, the cap, and the silica gel were rinsed with

Et_2O. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel.



2-(4-Cyclohexylbutan-2-yl)isoindoline-1,3-dione (1). The title compound was synthesized according to **GP-5** from 2-(1-chloroethyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:10 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 159 mg, 93% yield, 88% ee; (*R*,*R*)-**L1**: 164 mg, 96% yield, 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 3.9 min (minor), 4.9 min (major).

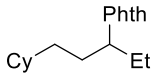
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.73 – 7.66 (m, 2H), 4.35 – 4.23 (m, 1H), 2.12 – 1.97 (m, 1H), 1.82 – 1.69 (m, 1H), 1.68 – 1.55 (m, 5H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.29 – 0.99 (m, 6H), 0.91 – 0.73 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 133.9, 132.2, 123.2, 48.0, 37.6, 34.6, 33.5, 33.3, 31.3, 26.7, 26.5, 26.4, 18.9.

FT-IR (film): 3470, 2920, 2353, 1697, 1367, 1022, 869, 728 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{24}NO_2$: 286.1802, found: 286.1806.

$[\alpha]^{22}_D = -13.3$ (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexylpentan-3-yl)isoindoline-1,3-dione (2). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:15 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 167 mg, 93% yield, 92% ee; (*R*,*R*)-**L1**: 171 mg, 95% yield, 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 3.8 min (minor), 4.1 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 4.12 – 4.01 (m, 1H), 2.13 – 1.97 (m, 2H), 1.84 – 1.68 (m, 2H), 1.68 – 1.55 (m, 5H), 1.26 – 0.99 (m, 6H), 0.85 (t, *J* = 7.6 Hz, 3H), 0.87 – 0.72 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 54.5, 37.6, 34.5, 33.6, 33.3, 29.7, 26.7, 26.5, 26.4, 25.7, 11.3.

FT-IR (film): 3466, 2916, 2353, 1697, 1362, 1050, 727 cm^{-1}.

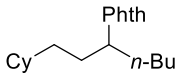
HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_2$: 300.1958, found: 300.1962.

$[\alpha]^{22}_D$ = –5.2 (*c* 1.0, $CHCl_3$); 92% ee, from (*S*,*S*)-**L1**.

Gram-scale reaction: In the air, $NiBr_2$·glyme (153 mg, 0.50 mmol, 0.10 equiv) and (*S*,*S*)-**L1** (543 mg, 0.60 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 (40 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 2-(1-chloropropyl)isoindoline-1,3-dione (1.12 g, 5.0 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 (30 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 catalyst solution. The 40 mL vial was rinsed with THF (30 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** (5.5 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 36 h. The reaction was quenched at 0 °C by the addition of MeOH (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 (1:15 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 1.40 g, 93% yield, 92% ee.



2-(1-Cyclohexylheptan-3-yl)isoindoline-1,3-dione (3). The title compound was synthesized according to **GP-5** from 2-(1-chloropentyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:15 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 189 mg, 96% yield, 91% ee; (*R*,*R*)-**L1**: 183 mg, 93% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK AD-H column (2% *i*-PrOH in hexanes, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 10.4 min (minor), 11.3 min (major).

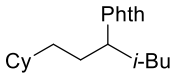
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 4.19 – 4.08 (m, 1H), 2.13 – 1.98 (m, 2H), 1.78 – 1.54 (m, 7H), 1.40 – 0.98 (m, 10H), 0.91 – 0.72 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 52.8, 37.6, 34.5, 33.6, 33.3, 32.4, 30.0, 29.0, 26.8, 26.5, 26.4, 22.5, 14.1.

FT-IR (film): 3466, 2919, 2354, 1699, 1371, 1050, 876, 726 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$: 328.2271, found: 328.2268.

$[\alpha]^{22}_D = -1.7$ (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexyl-5-methylhexan-3-yl)isoindoline-1,3-dione (4). The title compound was synthesized according to **GP-5** from 2-(1-chloro-3-methylbutyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:12 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 175 mg, 89% yield, 81% ee; (*R*,*R*)-**L1**: 176 mg, 90% yield, 81% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE-3 column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 4.7 min (minor), 4.9 min (major).

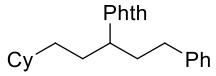
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 2H), 7.75 – 7.64 (m, 2H), 4.33 – 4.16 (m, 1H), 2.25 – 1.94 (m, 2H), 1.75 – 1.55 (m, 6H), 1.50 – 1.36 (m, 2H), 1.27 – 0.98 (m, 6H), 0.96 – 0.73 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 50.8, 41.6, 37.7, 34.5, 33.5, 33.3, 30.4, 26.8, 26.5, 26.4, 25.4, 23.4, 22.0.

FT-IR (film): 3464, 2919, 2354, 1709, 1372, 1168, 1072, 871, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$: 328.2271, found: 328.2269.

$[\alpha]^{22}_D$ = –2.8 (*c* 1.0, $CHCl_3$); 81% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexyl-5-phenylpentan-3-yl)isoindoline-1,3-dione (5). The title compound was synthesized according to **GP-5** from 2-(1-chloro-3-phenylpropyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:15 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 219 mg, 97% yield, 90% ee; (*R*,*R*)-**L1**: 223 mg, 99% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 7.1 min (minor), 7.4 min (major).

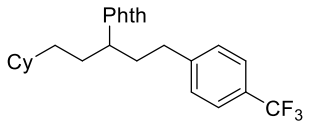
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.74 – 7.65 (m, 2H), 7.22 – 7.15 (m, 2H), 7.15 – 7.09 (m, 2H), 7.09 – 7.03 (m, 1H), 4.27 – 4.16 (m, 1H), 2.69 – 2.43 (m, 3H), 2.15 – 1.94 (m, 2H), 1.82 – 1.69 (m, 1H), 1.69 – 1.54 (m, 5H), 1.25 – 1.01 (m, 6H), 0.91 – 0.72 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 141.4, 133.9, 131.9, 128.4, 125.9, 123.2, 52.7, 37.6, 34.3, 34.0, 33.5, 33.34, 33.29, 30.1, 26.7, 26.5, 26.4.

FT-IR (film): 3464, 2920, 2353, 1708, 1378, 1077, 885 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{25}H_{30}NO_2$: 376.2271, found: 376.2277.

$[\alpha]^{22}_D$ = –9.1 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)pentan-3-yl)isoindoline-1,3-dione (6). The title compound was synthesized according to **GP-5** from 2-(1-chloro-3-(4-

(trifluoromethyl)phenyl)propyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:12 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 259 mg, 97% yield, 88% ee; (*R*,*R*)-**L1**: 250 mg, 94% yield, 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 7.2 min (minor), 7.5 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.72 (m, 2H), 7.71 – 7.63 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.26 – 4.15 (m, 1H), 2.79 – 2.66 (m, 1H), 2.66 – 2.49 (m, 2H), 2.15 – 1.94 (m, 2H), 1.82 – 1.68 (m, 1H), 1.68 – 1.53 (m, 5H), 1.23 – 0.97 (m, 6H), 0.90 – 0.70 (m, 2H).

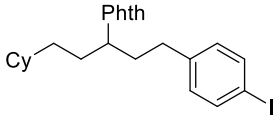
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 145.4 (q, *J* = 1.0 Hz), 134.0, 131.8, 128.7, 128.2 (q, *J* = 32.3 Hz), 125.2 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 273 Hz), 123.1, 52.6, 37.5, 34.3, 33.5, 33.34, 33.29, 33.27, 30.2, 26.7, 26.43, 26.38.

^{19}F NMR (282 MHz, $CDCl_3$) δ –62.3.

FT-IR (film): 3466, 2920, 2354, 1710, 1366, 1120, 1019, 847, 719 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{26}H_{29}F_3NO_2$: 444.2145, found: 444.2145.

$[\alpha]^{22}_D$ = –13.2 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexyl-5-(4-iodophenyl)pentan-3-yl)isoindoline-1,3-dione (7). The title compound was synthesized according to **GP-5** from 2-(1-chloro-3-(4-iodophenyl)propyl) isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:15 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 257 mg, 85% yield, 89% ee; (*R*,*R*)-**L1**: 247 mg, 82% yield, 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OJ-3 column (10% CH_3CN in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 5.9 min (major), 6.7 min (minor).

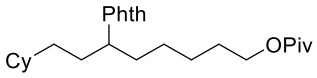
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 2H), 7.74 – 7.66 (m, 2H), 7.49 – 7.40 (m, 2H), 6.90 – 6.81 (m, 2H), 4.24 – 4.11 (m, 1H), 2.67 – 2.42 (m, 3H), 2.15 – 1.89 (m, 2H), 1.78 – 1.58 (m, 6H), 1.29 – 0.97 (m, 6H), 0.91 – 0.70 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 141.0, 137.4, 134.1, 131.8, 130.5, 123.2, 90.9, 52.6, 37.5, 34.3, 33.5, 33.4, 33.3, 33.0, 30.2, 26.7, 26.5, 26.4.

FT-IR (film): 3454, 2915, 2352, 1700, 1358, 1006, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{25}H_{29}INO_2$: 502.1237, found: 502.1229.

$[\alpha]^{22}_D = -15.2$ (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.



8-Cyclohexyl-6-(1,3-dioxoisoindolin-2-yl)octyl pivalate (8). The title compound was synthesized according to **GP-5** from 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl pivalate and **Zn-1**. The product was purified by column chromatography on silica gel (1:5 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 241 mg, 91% yield, 90% ee; (*R*,*R*)-**L1**: 244 mg, 92% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 7.7 min (minor), 8.0 min (major).

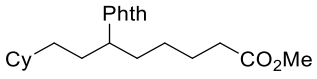
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.76 – 7.64 (m, 2H), 4.22 – 4.06 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.78 – 1.51 (m, 9H), 1.45 – 0.97 (m, 19H), 0.90 – 0.72 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 168.9, 134.0, 132.0, 123.3, 64.4, 52.7, 38.8, 37.6, 34.4, 33.5, 33.3, 32.6, 30.0, 28.7, 27.3, 26.7, 26.52, 26.46, 26.4, 25.9.

FT-IR (film): 3469, 2918, 2354, 1713, 1370, 1049, 870, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{27}H_{40}NO_4$: 442.2952, found: 442.2960.

$[\alpha]^{22}_D = +0.7$ (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



Methyl 8-cyclohexyl-6-(1,3-dioxoisoindolin-2-yl)octanoate (9). The title compound was synthesized according to **GP-5** from methyl 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexanoate and **Zn-1**. The product was purified by column chromatography on silica gel (1:8 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 209 mg, 91% yield, 91% ee; (*R*,*R*)-**L1**: 210 mg, 91% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 11.9 min (minor), 13.0 min (major).

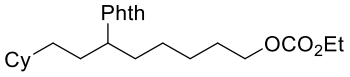
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.74 – 7.67 (m, 2H), 4.19 – 4.09 (m, 1H), 3.61 (s, 3H), 2.25 (t, *J* = 7.7 Hz, 2H), 2.16 – 1.98 (m, 2H), 1.78 – 1.57 (m, 9H), 1.36 – 0.98 (m, 8H), 0.89 – 0.72 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 168.9, 134.0, 132.0, 123.3, 52.6, 51.6, 37.6, 34.4, 34.0, 33.6, 33.3, 32.3, 30.0, 26.7, 26.5, 26.4, 26.3, 24.7.

FT-IR (film): 3463, 2913, 2355, 1698, 1050, 737 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+NH_4]^+$ calcd for $C_{23}H_{35}N_2O_4$: 403.2591, found: 403.2588.

$[\alpha]^{22}_D$ = +1.4 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



8-Cyclohexyl-6-(1,3-dioxoisoindolin-2-yl)octyl ethyl carbonate (10). The title compound was synthesized according to **GP-5** from 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl ethyl carbonate and **Zn-1**. The product was purified by column chromatography on silica gel (1:3 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 218 mg, 85% yield, 90% ee; (*R*,*R*)-**L1**: 225 mg, 87% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 8.8 min (minor), 9.2 min (major).

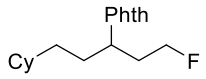
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.76 – 7.65 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.17 – 4.09 (m, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.17 – 1.94 (m, 2H), 1.76 – 1.56 (m, 9H), 1.47 – 0.97 (m, 13H), 0.90 – 0.71 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) 168.9, 155.4, 134.0, 131.9, 123.3, 67.9, 63.9, 52.7, 37.6, 34.4, 33.5, 33.3, 32.5, 30.0, 28.7, 26.7, 26.5, 26.44, 26.41, 25.6, 14.4.

FT-IR (film): 3464, 2920, 2354, 1711, 1168, 1046, 726 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{25}H_{36}NO_5$: 430.2588, found: 430.2584.

$[\alpha]^{22}_D$ = +0.8 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexyl-5-fluoropentan-3-yl)isoindoline-1,3-dione (11). The title compound was synthesized according to **GP-5** from 2-(1-chloro-3-fluoropropyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:6 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 141 mg, 74% yield, 88% ee; (*R*,*R*)-**L1**: 142 mg, 75% yield, 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 3.7 min (minor), 4.0 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 2H), 7.77 – 7.65 (m, 2H), 4.58 – 4.28 (m, 3H), 2.60 – 2.39 (m, 1H), 2.22 – 2.02 (m, 2H), 1.86 – 1.70 (m, 1H), 1.69 – 1.58 (m, 5H), 1.31 – 0.99 (m, 6H), 0.93 – 0.70 (m, 2H).

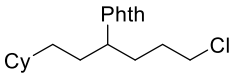
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 134.1, 131.9, 123.4, 81.7 (d, *J* = 167 Hz), 49.3 (d, *J* = 4.0 Hz), 37.5, 34.2, 33.5, 33.3, 33.2 (d, *J* = 19.2 Hz), 29.9, 26.7, 26.5, 26.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –220.8.

FT-IR (film): 3469, 2920, 2356, 1713, 1372, 1066, 873, 720 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}FNO_2$: 318.2, found: 318.2.

$[\alpha]^{22}_D$ = +7.8 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L1**.



2-(6-Chloro-1-cyclohexylhexan-3-yl)isoindoline-1,3-dione (12). The title compound was synthesized according to **GP-5** from 2-(1,4-dichlorobutyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:8 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 204 mg, 98% yield, 90% ee; (*R*,*R*)-**L1**: 194 mg, 93% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 8.2 min (minor), 8.5 min (major).

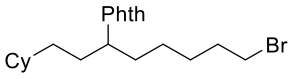
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H), 7.78 – 7.65 (m, 2H), 4.26 – 4.09 (m, 1H), 3.62 – 3.45 (m, 2H), 2.29 – 2.15 (m, 1H), 2.15 – 2.01 (m, 1H), 1.96 – 1.84 (m, 1H), 1.81 – 1.68 (m, 3H), 1.68 – 1.57 (m, 5H), 1.28 – 0.98 (m, 6H), 0.91 – 0.71 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 134.1, 131.9, 123.4, 52.0, 44.5, 37.6, 34.4, 33.5, 33.3, 30.0, 29.9, 29.8, 26.7, 26.5, 26.4.

FT-IR (film): 3466, 2356, 1707, 1367, 1051, 871, 722 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{27}ClNO_2$: 348.1725, found: 348.1730.

$[\alpha]^{22}_D$ = +0.6 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



2-(8-Bromo-1-cyclohexyloctan-3-yl)isoindoline-1,3-dione (13). The title compound was synthesized according to **GP-5** from 2-(6-bromo-1-chlorohexyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:12 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 220 mg, 87% yield, 91% ee; (*R*,*R*)-**L1**: 215 mg, 86% yield, 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 13.0 min (minor), 13.9 min (major).

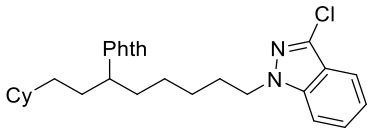
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 2H), 7.77 – 7.63 (m, 2H), 4.25 – 4.05 (m, 1H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.20 – 1.98 (m, 2H), 1.85 – 1.76 (m, 2H), 1.76 – 1.56 (m, 7H), 1.52 – 1.34 (m, 2H), 1.35 – 1.00 (m, 8H), 0.90 – 0.73 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 134.0, 132.0, 123.3, 52.6, 37.6, 34.5, 33.9, 33.6, 33.3, 32.7, 32.5, 30.0, 28.0, 26.7, 26.5, 26.4, 26.0.

FT-IR (film): 3465, 2354, 1704, 1379, 1047, 868, 722 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{22}H_{31}BrNO_2$: 420.2, found: 420.1.

$[\alpha]^{22}_D$ = +4.4 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



2-(8-(3-Chloro-1*H*-indazol-1-yl)-1-cyclohexyloctan-3-yl)isoindoline-1,3-dione (14). The title compound was synthesized according to **GP-5** from 2-(1-chloro-6-(3-chloro-1*H*-indazol-1-yl)hexyl)isoindoline-1,3-dione and **Zn-1**. The product was purified by column chromatography on silica gel (1:5 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 249 mg, 84% yield, 88% ee; (*R*,*R*)-**L1**: 249 mg, 84% yield, 87% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK ID-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 5.9 min (minor), 6.2 min (major).

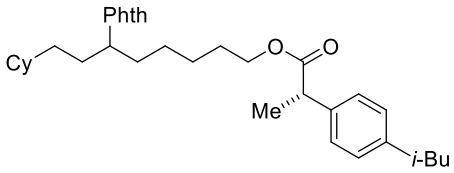
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.74 – 7.67 (m, 2H), 7.64 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.32 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.20 – 7.12 (m, 1H), 4.25 (t, *J* = 7.1 Hz, 2H), 4.16 – 4.05 (m, 1H), 2.12 – 1.96 (m, 2H), 1.92 – 1.78 (m, 2H), 1.71 – 1.54 (m, 7H), 1.41 – 0.96 (m, 10H), 0.89 – 0.71 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 140.9, 134.0, 132.6, 131.9, 127.4, 123.3, 121.14, 121.06, 119.9, 109.4, 52.6, 49.2, 37.6, 34.4, 33.5, 33.3, 32.4, 30.0, 29.8, 26.7, 26.6, 26.5, 26.41, 26.38.

FT-IR (film): 3468, 2353, 1709, 1365, 1049, 873, 728, 682 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{29}H_{35}ClN_3O_2$: 492.2412, found: 492.2420.

$[\alpha]^{22}_D$ = +3.3 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L1**.



8-Cyclohexyl-6-(1,3-dioxoisoindolin-2-yl)octyl (2*S*)-2-(4-isobutylphenyl)propanoate (15, 16). The title compound was synthesized according to **GP-5** from 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl (2*S*)-2-(4-isobutylphenyl)propanoate and **Zn-1**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 279 mg, 85% yield, 95:5 d.r.; (*R*,*R*)-**L1**: 287 mg, 88% yield, 5:95 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALPAK IG-3 column (10% MeOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 9.8 min (minor), 12.4 min (major).

NMR data for the product from (*S*,*S*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 7.20 – 7.14 (m, 2H), 7.10 – 7.04 (m, 2H), 4.17 – 4.06 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.64 (q, *J* = 7.1 Hz, 1H), 2.43 (d, *J* = 7.2 Hz, 2H), 2.12 – 1.96 (m, 2H), 1.89 – 1.76 (m, 1H), 1.75 – 1.59 (m, 7H), 1.55 – 1.48 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.33 – 0.98 (m, 10H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.86 – 0.73 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 168.9, 140.6, 138.0, 134.0, 132.0, 129.4, 127.3, 123.3, 64.7, 52.7, 45.3, 45.2, 37.6, 34.5, 33.6, 33.3, 32.5, 30.3, 30.0, 28.5, 26.7, 26.5, 26.4, 25.7, 22.5, 18.6.

NMR data for the product from (*R*,*R*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 7.21 – 7.14 (m, 2H), 7.11 – 7.04 (m, 2H), 4.17 – 4.07 (m, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.65 (q, *J* = 7.2 Hz, 1H), 2.43 (d, *J* = 7.2 Hz, 2H), 2.12 – 1.97 (m, 2H), 1.89 – 1.77 (m, 1H), 1.72 – 1.58

(m, 7H), 1.56 – 1.48 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.33 – 0.98 (m, 10H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.86 – 0.73 (m, 2H).

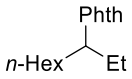
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 168.9, 140.6, 138.0, 134.0, 132.0, 129.4, 127.3, 123.3, 64.7, 52.7, 45.3, 45.2, 37.6, 34.5, 33.6, 33.3, 32.5, 30.3, 30.0, 28.5, 26.7, 26.5, 26.4, 25.7, 22.5, 18.6.

FT-IR (film): 3468, 2919, 2354, 1710, 1030, 682 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{35}H_{48}NO_4$: 546.3578, found: 546.3576.

$[\alpha]^{22}_D$ = +16.9 (*c* 1.0, $CHCl_3$); 95:5 d.r., from (*S*,*S*)-**L1**.

$[\alpha]^{22}_D$ = +14.9 (*c* 1.0, $CHCl_3$); 5:95 d.r., from (*R*,*R*)-**L1**.



2-(Nonan-3-yl)isoindoline-1,3-dione (17). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-2**. The product was purified by column chromatography on silica gel (1:10 Et_2O/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 153 mg, 93% yield, 89% ee; (*R*,*R*)-**L1**: 153 mg, 93% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (2% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 5.3 min (minor), 5.8 min (major).

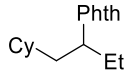
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 4.16 – 4.05 (m, 1H), 2.13 – 1.98 (m, 2H), 1.83 – 1.65 (m, 2H), 1.35 – 1.14 (m, 8H), 0.90 – 0.78 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 54.1, 32.4, 31.8, 29.1, 26.8, 25.7, 22.7, 14.2, 11.3.

FT-IR (film): 3464, 2921, 2364, 1714, 1360, 1041, 796, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{24}NO_2$: 274.1802, found: 274.1807.

$[\alpha]^{22}_D$ = –6.1 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.



2-(1-Cyclohexylbutan-2-yl)isoindoline-1,3-dione (18). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-3**. The product was purified by column chromatography on silica gel (1:15 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 163 mg, 95% yield, 95% ee; (*R*,*R*)-**L1**: 167 mg, 98% yield, 95% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 4.4 min (minor), 4.9 min (major).

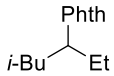
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 4.29 – 4.19 (m, 1H), 2.13 – 1.96 (m, 2H), 1.91 – 1.80 (m, 1H), 1.78 – 1.44 (m, 6H), 1.20 – 1.05 (m, 4H), 0.99 – 0.78 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 51.3, 39.9, 34.8, 33.9, 32.7, 26.6, 26.4, 26.2, 26.1, 11.3.

FT-IR (film): 3463, 2924, 2356, 1708, 1371, 1064, 886, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{24}NO_2$: 286.1802, found: 286.1806.

$[\alpha]^{22}_D$ = –18.0 (*c* 1.0, $CHCl_3$); 95% ee, from (*S*,*S*)-**L1**.



2-(5-Methylhexan-3-yl)isoindoline-1,3-dione (19). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-4**. The product was purified by column chromatography on silica gel (1:15 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 133 mg, 90% yield, 94% ee; (*R*,*R*)-**L1**: 135 mg, 92% yield, 93% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (2% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 4.3 min (minor), 4.5 min (major).

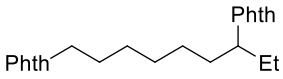
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 4.27 – 4.17 (m, 1H), 2.20 – 1.97 (m, 2H), 1.80 – 1.66 (m, 1H), 1.50 – 1.38 (m, 2H), 0.95 – 0.82 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 52.0, 41.3, 26.1, 25.4, 23.4, 21.9, 11.3.

FT-IR (film): 3460, 2956, 2354, 1770, 1470, 1336, 1174, 1062, 867, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489, found: 246.1490.

$[\alpha]^{22}_D$ = +1.3 (*c* 1.0, $CHCl_3$); 94% ee, from (*S*,*S*)-**L1**.



2,2'-(Nonane-1,7-diyl)bis(isoindoline-1,3-dione) (20). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-5**. The product was purified by column chromatography on silica gel (1:2 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 238 mg, 95% yield, 91% ee; (*R*,*R*)-**L1**: 230 mg, 92% yield, 92% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK ID-3 column (35% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 9.5 min (minor), 12.3 min (major).

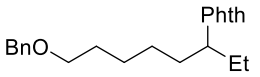
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 4H), 7.74 – 7.65 (m, 4H), 4.14 – 4.03 (m, 1H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.14 – 1.96 (m, 2H), 1.83 – 1.66 (m, 2H), 1.64 – 1.56 (m, 2H), 1.41 – 1.16 (m, 6H), 0.84 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 168.6, 133.9, 133.9, 132.3, 132.0, 123.3, 123.2, 54.0, 38.1, 32.3, 29.0, 28.7, 26.9, 26.7, 25.7, 11.3.

FT-IR (film): 3465, 2934, 2354, 1708, 1369, 1047, 889, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_4$: 419.1965, found: 419.1975.

$[\alpha]^{22}_D$ = –5.8 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



2-(8-(Benzyloxy)octan-3-yl)isoindoline-1,3-dione (21). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-6**. The product was purified by column chromatography on silica gel (1:12 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 219 mg, 99% yield, 89% ee; (*R*,*R*)-**L1**: 222 mg, 99% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IE-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 6.6 min (minor), 7.0 min (major).

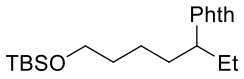
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 7.35 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 4.46 (s, 2H), 4.17 – 4.04 (m, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.83 – 1.66 (m, 2H), 1.61 – 1.51 (m, 2H), 1.46 – 1.17 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 138.8, 134.0, 132.0, 128.5, 127.7, 127.6, 123.2, 73.0, 70.4, 54.0, 32.3, 29.7, 26.7, 26.0, 25.7, 11.3.

FT-IR (film): 3462, 2922, 2354, 1708, 1367, 1066, 890, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_3$: 366.2064, found: 366.2064.

$[\alpha]^{22}_D$ = –5.2 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.



2-(7-((*tert*-Butyldimethylsilyl)oxy)heptan-3-yl)isoindoline-1,3-dione (22). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-7**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 222 mg, 99% yield, 89% ee; (*R*,*R*)-**L1**: 225 mg, 99% yield, 89% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (2% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 5.1 min (minor), 5.4 min (major).

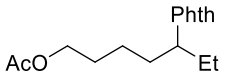
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 4.20 – 4.03 (m, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.83 – 1.67 (m, 2H), 1.58 – 1.40 (m, 2H), 1.35 – 1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.81 (s, 9H), –0.02 (d, *J* = 2.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 123.2, 63.0, 54.0, 32.5, 32.1, 26.0, 25.7, 23.1, 18.4, 11.3, –5.20, –5.22.

FT-IR (film): 3468, 2354, 1714, 1470, 1250, 1101, 840, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{34}NO_3Si$: 376.2302, found: 376.2305.

$[\alpha]^{22}_D$ = –4.8 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.



5-(1,3-Dioxoisoindolin-2-yl)heptyl acetate (23). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-8**. The product was purified by column chromatography on silica gel (1:2 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 140 mg, 77% yield, 90% ee; (*R*,*R*)-**L1**: 145 mg, 80% yield, 90% 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*,*S*)-**L1**: 3.7 min (minor), 4.1 min (major).

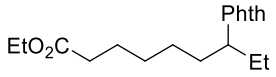
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.73 – 7.68 (m, 2H), 4.17 – 4.07 (m, 1H), 4.05 – 3.93 (m, 2H), 2.18 – 2.00 (m, 2H), 1.98 (s, 3H), 1.82 – 1.54 (m, 4H), 1.40 – 1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.0, 134.0, 131.9, 123.3, 64.3, 53.8, 31.9, 28.3, 25.7, 23.2, 21.1, 11.3.

FT-IR (film): 3460, 2354, 1714, 1367, 1232, 1050, 860, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_4$: 304.1543, found: 304.1549.

$[\alpha]^{22}_D$ = –9.7 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



Ethyl 7-(1,3-dioxoisoindolin-2-yl)nonanoate (24). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-9**. The product was purified by column chromatography on silica gel (1:5 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 186 mg, 94% yield, 89% ee; (*R*,*R*)-**L1**: 193 mg, 97% yield, 90% 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*,*S*)-**L1**: 5.9 min (minor), 6.5 min (major).

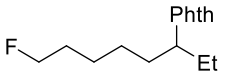
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.75 – 7.65 (m, 2H), 4.19 – 4.07 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.15 – 1.96 (m, 2H), 1.83 – 1.66 (m, 2H), 1.65 – 1.48 (m, 2H), 1.44 – 1.15 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 169.0, 134.0, 131.9, 123.2, 60.3, 53.9, 34.4, 32.2, 28.9, 26.5, 25.7, 24.9, 14.4, 11.2.

FT-IR (film): 3462, 2925, 2354, 1714, 1367, 1192, 1058, 861, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_4$: 332.1856, found: 332.1867.

$[\alpha]^{22}_D$ = –7.3 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.



2-(8-Fluorooctan-3-yl)isoindoline-1,3-dione (25). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-10**.

The product was purified by column chromatography on silica gel (1:12 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 158 mg, 95% yield, 90% ee; (*R*,*R*)-**L1**: 154 mg, 93% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 3.7 min (minor), 4.1 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.75 – 7.67 (m, 2H), 4.44 (t, *J* = 6.1 Hz, 1H), 4.32 (t, *J* = 6.1 Hz, 1H), 4.17 – 4.06 (m, 1H), 2.17 – 1.99 (m, 2H), 1.82 – 1.55 (m, 4H), 1.50 – 1.18 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

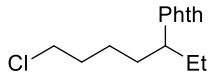
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 134.0, 131.9, 123.3, 84.1 (d, *J* = 165 Hz), 53.9, 32.2, 30.3 (d, *J* = 19.2 Hz), 26.4, 25.7, 25.0 (d, *J* = 5.1 Hz), 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –218.2.

FT-IR (film): 3463, 2352, 1708, 1367, 1049, 892, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}FNO_2$: 278.1551, found: 278.1554.

$[\alpha]^{22}_D$ = –4.2 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



2-(7-Chloroheptan-3-yl)isoindoline-1,3-dione (26). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-11**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 144 mg, 86% yield, 91% ee; (*R*,*R*)-**L1**: 153 mg, 91% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (2% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 9.2 min (minor), 10.1 min (major).

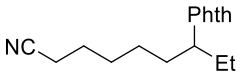
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.75 – 7.67 (m, 2H), 4.18 – 4.06 (m, 1H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.19 – 1.98 (m, 2H), 1.85 – 1.67 (m, 4H), 1.49 – 1.31 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 134.0, 131.9, 123.3, 53.7, 44.9, 32.3, 31.6, 25.7, 24.1, 11.3.

FT-IR (film): 3461, 2928, 2353, 1710, 1369, 1168, 1054, 790, 720 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}ClNO_2$: 280.1099, found: 280.1099.

$[\alpha]^{22}_D$ = –9.4 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



7-(1,3-Dioxoisoindolin-2-yl)nonanenitrile (27). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-12**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 157 mg, 92% yield, 90% ee; (*R*,*R*)-**L1**: 160 mg, 94% yield, 89% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IF-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 3.6 min (minor), 3.8 min (major).

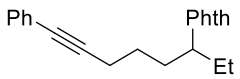
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.75 – 7.68 (m, 2H), 4.16 – 4.05 (m, 1H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.18 – 1.99 (m, 2H), 1.84 – 1.65 (m, 2H), 1.65 – 1.56 (m, 2H), 1.56 – 1.17 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 134.1, 131.9, 123.3, 119.8, 53.8, 32.0, 28.4, 26.0, 25.7, 25.4, 17.2, 11.2.

FT-IR (film): 3460, 2918, 2246, 1705, 1366, 1056, 864, 728 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}N_2O_2$: 285.1598, found: 285.1605.

$[\alpha]^{22}_D = -4.5$ (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L1**.



2-(8-Phenyloct-7-yn-3-yl)isoindoline-1,3-dione (28). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-13**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 151 mg, 76% yield, 91% ee; (*R*,*R*)-**L1**: 159 mg, 80% yield, 91% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 6.7 min (major), 7.4 min (minor).

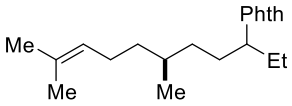
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 2H), 7.76 – 7.68 (m, 2H), 7.43 – 7.34 (m, 2H), 7.32 – 7.23 (m, 3H), 4.25 – 4.13 (m, 1H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.34 – 2.21 (m, 1H), 2.19 – 2.03 (m, 1H), 2.00 – 1.89 (m, 1H), 1.89 – 1.76 (m, 1H), 1.63 – 1.51 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 134.0, 131.9, 131.7, 128.3, 127.7, 124.0, 123.3, 89.7, 81.2, 53.5, 31.5, 26.0, 25.8, 19.2, 11.3.

FT-IR (film): 3461, 2928, 2234, 1709, 1366, 1048, 797, 726 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_2$: 332.1645, found: 332.1644.

$[\alpha]^{22}_D = -10.7$(*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L1**.



2-((6*S*)-6,10-Dimethylundec-9-en-3-yl)isoindoline-1,3-dione (29, 30). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-14**. The product was purified by column chromatography on silica gel (1:12 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 150 mg, 77% yield, 96:4 d.r.; (*R*,*R*)-**L1**: 153 mg, 78% yield, 4:96 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALPAK IF-3 column (2% CH_3CN in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 9.1 min (minor), 11.9 min (major).

NMR data for the product from (*S*,*S*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.74 – 7.67 (m, 2H), 5.08 – 4.99 (m, 1H), 4.12 – 4.01 (m, 1H), 2.14 – 1.71 (m, 6H), 1.64 (s, 3H), 1.54 (s, 3H), 1.46 – 1.01 (m, 5H), 0.86 (t, *J* = 7.6 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 131.2, 125.0, 123.2, 54.6, 36.9, 34.1, 32.4, 29.9, 25.8, 25.7, 25.6, 19.7, 17.7, 11.3.

NMR data for the product from (*R*,*R*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.74 – 7.67 (m, 2H), 5.08 – 5.00 (m, 1H), 4.14 – 4.02 (m, 1H), 2.17 – 1.99 (m, 2H), 1.98 – 1.67 (m, 4H), 1.65 (s, 3H), 1.54 (s, 3H), 1.46 – 1.17 (m, 3H), 1.16 – 0.95 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

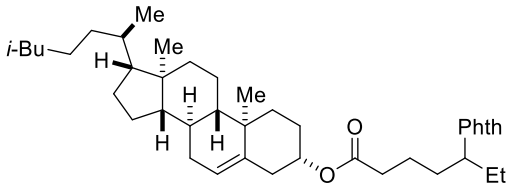
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 131.2, 125.0, 123.2, 54.4, 37.1, 33.9, 32.2, 29.7, 25.83, 25.81, 25.6, 19.6, 17.7, 11.3.

FT-IR (film): 3465, 2922, 1709, 1455, 1368, 1062, 884, 718 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$: 328.2271, found: 328.2273.

$[\alpha]^{22}_D = +0.8$ (*c* 1.0, $CHCl_3$); 96:4 d.r., from (*S*,*S*)-**L1**.

$[\alpha]^{22}_D = +15.3$ (*c* 1.0, $CHCl_3$); 4:96 d.r., from (*R*,*R*)-**L1**.



(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 5-(1,3-dioxoisoindolin-2-yl)heptanoate (31, 32). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-15**. The product was purified by column chromatography on silica gel (1:15 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 336 mg, 87% yield, 92:8 d.r.; (*R*,*R*)-**L1**: 324 mg, 84% yield, 8:92 d.r.

SFC analysis: The d.r. was determined via SFC on a CHIRALPAK IG-3 column (25% MeOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L1**: 10.7 min (minor), 11.7 min (major).

NMR data for the product from (*S*,*S*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.75 – 7.66 (m, 2H), 5.39 – 5.31 (m, 1H), 4.63 – 4.51 (m, 1H), 4.19 – 4.06 (m, 1H), 2.35 – 2.20 (m, 4H), 2.19 – 1.90 (m, 4H), 1.88 – 1.69 (m, 5H), 1.64 – 1.40 (m, 9H), 1.40 – 1.21 (m, 4H), 1.21 – 1.04 (m, 7H), 1.03 – 0.89 (m, 9H), 0.88 – 0.81 (m, 9H), 0.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.9, 139.8, 134.0, 131.9, 123.3, 122.7, 74.0, 56.8, 56.3, 53.6, 50.1, 42.4, 39.9, 39.6, 38.2, 37.1, 36.7, 36.3, 35.9, 34.3, 32.02, 31.98, 31.7, 28.4, 28.1, 27.9, 25.7, 24.4, 24.0, 23.0, 22.7, 22.3, 21.2, 19.4, 18.8, 12.0, 11.2.

NMR data for the product from (*R*,*R*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.74 – 7.67 (m, 2H), 5.38 – 5.29 (m, 1H), 4.62 – 4.50 (m, 1H), 4.18 – 4.07 (m, 1H), 2.35 – 2.20 (m, 4H), 2.20 – 1.90 (m, 4H), 1.90 – 1.67 (m, 5H), 1.65 – 1.40 (m, 9H), 1.40 – 1.22 (m, 4H), 1.22 – 1.02 (m, 7H), 1.03 – 0.88 (m, 9H), 0.88 – 0.81 (m, 9H), 0.66 (s, 3H).

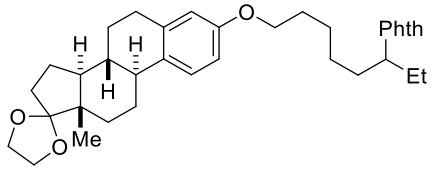
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.9, 139.8, 134.0, 131.9, 123.3, 122.7, 74.0, 56.8, 56.3, 53.6, 50.1, 42.4, 39.9, 39.6, 38.2, 37.1, 36.7, 36.3, 35.9, 34.2, 32.02, 31.97, 31.7, 28.4, 28.1, 27.9, 25.7, 24.4, 24.0, 23.0, 22.7, 22.3, 21.2, 19.4, 18.8, 12.0, 11.2.

FT-IR (film): 3460, 2353, 1714, 1361, 1168, 1020, 892, 721 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+NH_4]^+$ calcd for $C_{42}H_{65}N_2O_4$: 661.4939, found: 661.4949.

$[\alpha]^{22}_D = -26.4$ (*c* 1.0, $CHCl_3$); 92:8 d.r., from (*S*,*S*)-**L1**.

$[\alpha]^{22}_D = -17.8$ (*c* 1.0, $CHCl_3$); 8:92 d.r., from (*R*,*R*)-**L1**.



2-(8-(((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)octan-3-yl)isoindoline-1,3-dione (33, 34). The title compound was synthesized according to **GP-5** from 2-(1-chloropropyl)isoindoline-1,3-dione and **Zn-16**. The product was purified by column chromatography on silica gel (1:5 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L1**: 307 mg, 90% yield, 94:6 d.r.; (*R*,*R*)-**L1**: 300 mg, 88% yield, 6:94 d.r.

SFC analysis: The d.r. 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*,*S*)-**L1**: 7.0 min (major), 7.5 min (minor).

NMR data for the product from (*S*,*S*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.74 – 7.65 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.57 (d, *J* = 2.7 Hz, 1H), 4.17 – 4.07 (m, 1H), 3.99 – 3.83 (m, 6H), 2.90 – 2.74 (m, 2H), 2.37 – 2.17 (m, 2H), 2.17 – 1.97 (m, 3H), 1.92 – 1.58 (m, 9H), 1.56 – 1.23 (m, 9H), 0.874 (s, 3H), 0.865 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.0, 138.1, 134.0, 132.7, 132.0, 126.4, 123.2, 119.6, 114.6, 112.2, 67.8, 65.4, 64.7, 54.0, 49.5, 46.3, 43.8, 39.2, 34.4, 32.3, 30.9, 29.9, 29.3, 27.2, 26.6, 26.3, 25.9, 25.7, 22.5, 14.5, 11.3.

NMR data for the product from (*R*,*R*)-**L1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.75 – 7.66 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 4.19 – 4.06 (m, 1H), 4.02 – 3.80 (m, 6H), 2.91 – 2.73 (m, 2H), 2.37 – 2.17 (m, 2H), 2.17 – 1.96 (m, 3H), 1.95 – 1.57 (m, 9H), 1.57 – 1.24 (m, 9H), 0.88 (s, 3H), 0.87 (t, *J* = 7.6 Hz, 3H).

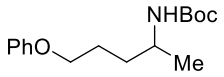
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.0, 138.0, 134.0, 132.6, 132.0, 126.4, 123.2, 119.6, 114.6, 112.1, 67.8, 65.4, 64.7, 54.0, 49.5, 46.3, 43.8, 39.2, 34.4, 32.3, 30.9, 29.9, 29.3, 27.1, 26.6, 26.3, 25.9, 25.7, 22.5, 14.5, 11.3.

FT-IR (film): 3460, 2918, 2352, 1709, 1605, 1470, 1366, 1246, 1050, 724 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{36}H_{46}NO_5$: 572.3371, found: 572.3368.

$[\alpha]^{22}_D$ = +9.5 (*c* 1.0, $CHCl_3$); 94:6 d.r., from (*S*,*S*)-**L1**.

$[\alpha]^{22}_D$ = +20.4 (*c* 1.0, $CHCl_3$); 6:94 d.r., from (*R*,*R*)-**L1**.



***tert*-Butyl (5-phenoxypentan-2-yl)carbamate (35).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl) alaninate and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 109 mg, 65% yield, 90% ee; (*R*,*R*)-**L2**: 114 mg, 68% yield, 90% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 92 mg, 90% ee → 66 mg, 72% yield (47% yield overall), >99% ee; (*R*,*R*)-**L2**: 86 mg, 90% ee → 65 mg, 76% yield (51% yield overall), >99% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OJ column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 12.3 min (minor), 17.8 min (major).

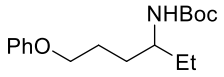
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 6.97 – 6.87 (m, 3H), 4.41 (d, *J* = 8.6 Hz, 1H), 3.96 (td, *J* = 6.3, 1.2 Hz, 2H), 3.70 (q, *J* = 7.7, 7.2 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.68 – 1.51 (m, 2H), 1.45 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 155.5, 129.5, 120.7, 114.6, 79.1, 67.6, 46.4, 34.0, 28.6, 26.1, 21.6.

FT-IR (film): 3372, 2967, 1690, 1499, 1247, 1173, 751 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{16}H_{26}NO_3$: 280.1907, found: 280.1912.

$[\alpha]^{23}_D$ = –6.2 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (6-phenoxyhexan-3-yl)carbamate (36).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)butanoate and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 137 mg, 79% yield, 90% ee; (*R*,*R*)-**L2**: 143 mg, 81% yield, 91% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.4 min (major), 9.1 min (minor).

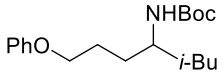
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 6.97 – 6.85 (m, 3H), 4.36 – 4.30 (m, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.62 – 3.48 (m, 1H), 1.93 – 1.77 (m, 2H), 1.73 – 1.52 (m, 2H), 1.47 – 1.42 (m, 11H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.0, 129.5, 120.7, 114.6, 79.1, 67.7, 51.9, 31.8, 28.6, 26.0, 10.4.

FT-IR (film): 3345, 2966, 1698, 1498, 1246, 1174, 1091, 754, 692 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{28}NO_3$: 294.2064, found: 294.2061.

$[\alpha]^{23}_D$ = –9.9 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (6-methyl-1-phenoxyheptan-4-yl)carbamate (37).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl) leucinate and **Zn-17**. The product was purified by column chromatography on silica gel (15:85 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 139 mg, 72% yield, 90% ee; (*R*,*R*)-**L2**: 134 mg, 70% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.2 min (minor), 6.6 min (major).

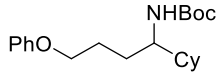
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 6.97 – 6.86 (m, 3H), 4.26 (d, *J* = 9.4 Hz, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.76 – 3.63 (m, 1H), 1.92 – 1.74 (m, 2H), 1.74 – 1.60 (m, 2H), 1.45 – 1.42 (m, 10H), 1.35 – 1.22 (m, 2H), 0.91 (dd, *J* = 6.6, 4.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 155.8, 129.5, 120.7, 114.6, 79.0, 67.8, 48.7, 45.3, 32.8, 28.6, 25.9, 25.1, 23.3, 22.4.

FT-IR (film): 3346, 2918, 1691, 1497, 1246, 1173, 1037, 755, 692 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{32}NO_3$: 322.2377, found: 322.2378.

$[\alpha]^{23}_D$ = –14.8 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1-cyclohexyl-4-phenoxybutyl)carbamate (38).** The title compound was synthesized according to **GP-7** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-2-cyclohexylacetate and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 138 mg, 66% yield, 88% ee; (*R*,*R*)-**L2**: 142 mg, 68% yield, 88% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.0 min (major), 14.2 min (minor).

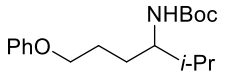
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 6.73 (m, 5H), 4.52 – 4.28 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.57 – 3.33 (m, 1H), 1.99 – 1.58 (m, 9H), 1.49 – 1.38 (m, 10H), 1.38 – 0.84 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.1, 155.8, 150.6, 129.6, 129.5, 126.2, 121.6, 120.7, 114.6, 80.1, 79.0, 67.7, 66.0, 58.6, 55.0, 42.6, 41.3, 29.8, 29.7, 29.2, 28.6, 28.5, 28.4, 26.6, 26.44, 26.42, 26.3, 26.2, 26.1.

FT-IR (film): 3348, 2927, 2853, 1704, 1496, 1246, 1166, 753, 691 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{34}NO_3$: 348.2533, found: 348.2539.

$[\alpha]^{23}_D$ = –5.3 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (2-methyl-6-phenoxyhexan-3-yl)carbamate (39).** The title compound was synthesized according to **GP-7** from 1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl) valinate and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 122 mg, 66% yield, 89% ee; (*R*,*R*)-**L2**: 115 mg, 62% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 7.7 min (minor), 13.0 min (major).

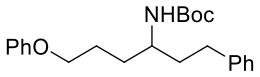
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 6.83 (m, 5H), 4.55 – 4.25 (m, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.55 – 3.39 (m, 1H), 1.98 – 1.34 (m, 14H), 1.19 – 0.82 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.2, 155.8, 150.5, 129.6, 129.5, 126.2, 121.5, 120.7, 114.6, 80.1, 79.0, 67.7, 58.8, 55.4, 32.5, 31.5, 29.3, 28.6, 28.4, 26.3, 19.2, 17.8.

FT-IR (film): 3356, 2963, 1703, 1498, 1246, 1174, 754, 691 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{30}NO_3$: 308.2222, found: 308.2216.

$[\alpha]^{23}_D$ = +0.4 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (6-phenoxy-1-phenylhexan-3-yl)carbamate (40).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 176 mg, 79% yield, 90% ee; (*R*,*R*)-**L2**: 181 mg, 82% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (3% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 9.1 min (minor), 12.1 min (major).

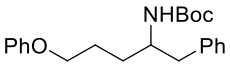
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 4H), 7.22 – 7.15 (m, 3H), 6.98 – 6.88 (m, 3H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.75 – 3.65 (m, 1H), 2.77 – 2.59 (m, 2H), 1.93 – 1.50 (m, 6H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 155.9, 142.1, 129.6, 128.54, 128.50, 126.0, 120.7, 114.6, 79.2, 67.6, 50.5, 37.9, 32.5, 32.4, 28.6, 25.9.

FT-IR (film): 3344, 2932, 1704, 1496, 1246, 1168, 1037, 753, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_3$: 370.2377, found: 370.2377.

$[\alpha]^{23}_D$ = +3.9 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (5-phenoxy-1-phenylpentan-2-yl)carbamate (41).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl) phenylalaninate and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 162 mg, 76% yield, 90% ee; (*R*,*R*)-**L2**: 164 mg, 77% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (5% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 13.1 min (minor), 14.0 min (major).

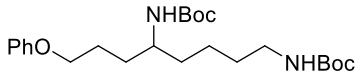
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 7H), 6.98 – 6.90 (m, 1H), 6.89 – 6.84 (m, 2H), 4.41 (d, *J* = 9.1 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.88 (s, 1H), 2.88 – 2.73 (m, 2H), 1.95 – 1.64 (m, 4H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 155.6, 138.2, 129.7, 129.5, 128.5, 126.5, 120.7, 114.6, 79.2, 67.5, 51.5, 41.7, 30.9, 28.5, 26.1.

FT-IR (film): 3346, 2932, 1698, 1496, 1365, 1246, 1168, 754, 693 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{22}H_{30}NO_3$: 356.2220, found: 356.2221.

$[\alpha]^{23}_D$ = +13.2 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



Di-*tert*-butyl (8-phenoxyoctane-1,5-diyl)dicarbamate (42). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl N^2,N^6-bis(*tert*-butoxycarbonyl)lysinate and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes) and was then extracted in hexanes to separate it from phthalimide. White solid.

(*S*,*S*)-**L2**: 165 mg, 63% yield, 91% ee; (*R*,*R*)-**L2**: 159 mg, 61% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK AD column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 10.1 min (minor), 12.2 min (major).

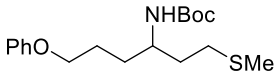
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 6.97 – 6.86 (m, 3H), 4.59 (s, 1H), 4.36 (d, *J* = 9.3 Hz, 1H), 3.95 (t, *J* = 6.2 Hz, 2H), 3.65 – 3.53 (m, 1H), 3.15 – 3.05 (m, 2H), 1.87 – 1.60 (m, 4H), 1.54 – 1.37 (m, 24H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.2, 156.0, 129.5, 120.7, 114.6, 79.1, 67.6, 50.3, 40.5, 35.7, 32.3, 31.7, 29.9, 28.6, 26.0, 23.2, 22.8, 14.3.

FT-IR (film): 3348, 2933, 1697, 1521, 1365, 1247, 1169, 752 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{40}N_2NaO_5$: 459.3, found: 459.3.

$[\alpha]^{23}_D$ = –6.9 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1-(methylthio)-6-phenoxyhexan-3-yl)carbamate (43).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)methioninate and **Zn-17**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 130 mg, 64% yield, 91% ee; (*R*,*R*)-**L2**: 132 mg, 65% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 11.0 min (minor), 11.7 min (major).

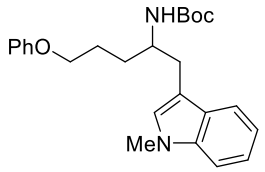
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 2H), 6.98 – 6.85 (m, 3H), 4.40 (d, *J* = 9.3 Hz, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.78 – 3.61 (m, 1H), 2.58 – 2.48 (m, 2H), 2.10 (s, 3H), 1.95 – 1.50 (m, 6H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 155.8, 129.6, 120.8, 114.6, 79.3, 67.5, 50.1, 35.6, 32.2, 30.9, 28.6, 26.0, 15.8.

FT-IR (film): 3346, 2918, 1694, 1498, 1246, 1173, 1038, 755, 692 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{30}NO_3S$: 340.1941, found: 340.1949.

$[\alpha]^{23}_D$ = –2.1 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1-(1-methyl-1*H*-indol-3-yl)-5-phenoxypentan-2-yl)carbamate (44).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl N^{α}-(*tert*-butoxycarbonyl)-1-methyltryptophanate and **Zn-17**. The product was purified by column chromatography on silica gel (35:65 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 129 mg, 53% yield, 91% ee; (*R*,*R*)-**L2**: 145 mg, 59% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 11.6 min (minor), 17.5 min (major).

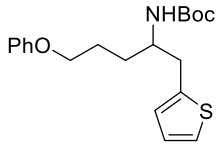
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 1H), 7.31 – 7.17 (m, 4H), 7.15 – 7.07 (m, 1H), 6.97 – 6.89 (m, 1H), 6.90 – 6.83 (m, 3H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.02 – 3.92 (m, 3H), 3.75 (s, 3H), 2.96 (d, *J* = 5.9 Hz, 2H), 1.96 – 1.69 (m, 4H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 155.8, 137.0, 129.5, 128.6, 127.6, 121.6, 120.7, 119.4, 119.0, 114.6, 110.6, 109.2, 79.1, 67.6, 50.9, 32.8, 31.1, 30.9, 28.6, 26.2.

FT-IR (film): 3382, 2934, 1710, 1496, 1247, 1173, 1053, 742 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{25}H_{33}N_2O_3$: 409.2486, found: 409.2481.

$[\alpha]^{23}_D$ = +6.9 (*c* 1.0, $CHCl_3$); 91% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (5-phenoxy-1-(thiophen-2-yl)pentan-2-yl)carbamate (45).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoate and **Zn-17**. The product was purified by column chromatography on silica gel (15:85 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 149 mg, 69% yield, 92% ee; (*R*,*R*)-**L2**: 155 mg, 72% yield, 92% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 13.9 min (minor), 19.2 min (major).

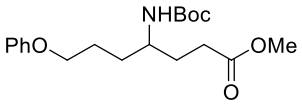
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.19 – 7.13 (m, 1H), 6.96 – 6.91 (m, 2H), 6.90 – 6.86 (m, 2H), 6.84 – 6.81 (m, 1H), 4.54 – 4.47 (m, 1H), 3.96 (t, J = 6.2 Hz, 2H), 3.90 – 3.81 (m, 1H), 3.13 – 2.96 (m, 2H), 1.91 – 1.80 (m, 2H), 1.77 – 1.49 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 155.6, 139.9, 129.6, 127.0, 126.3, 124.2, 120.8, 114.6, 79.4, 67.4, 51.2, 35.2, 30.7, 28.6, 26.1.

FT-IR (film): 3338, 2934, 1692, 1498, 1244, 1171, 753, 690 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{27}NNaO_3S$: 384.2, found: 384.1.

$[\alpha]^{23}_D$ = +17.2 (*c* 1.0, $CHCl_3$); 92% ee, from (*S*,*S*)-**L2**.



Methyl 4-((*tert*-butoxycarbonyl)amino)-7-phenoxyheptanoate (46). The title compound was synthesized according to **GP-6** from 1-(1,3-dioxoisoindolin-2-yl) 5-methyl (*tert*-butoxycarbonyl)glutamate and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes) and was then extracted in hexanes to separate it from phthalimide. White solid.

(*S*,*S*)-**L2**: 145 mg, 69% yield, 93% ee; (*R*,*R*)-**L2**: 138 mg, 65% yield, 92% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OJ column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 16.6 min (minor), 18.6 min (major).

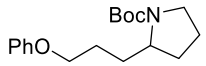
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 6.95 – 6.86 (m, 3H), 4.34 (d, *J* = 9.5 Hz, 1H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 3.65 – 3.61 (m, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.92 – 1.59 (m, 6H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 158.9, 155.7, 129.4, 120.6, 114.5, 79.2, 67.4, 51.7, 50.2, 32.4, 30.8, 30.7, 28.4, 25.8.

FT-IR (film): 3367, 2950, 1709, 1498, 1365, 1246, 1173, 756 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{29}NNaO_5$: 374.2, found: 374.2.

$[\alpha]^{23}_D$ = +0.9 (*c* 1.0, $CHCl_3$); 93% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl 2-(3-phenoxypropyl)pyrrolidine-1-carboxylate (47).** The title compound was synthesized according to **GP-6** from 1-(*tert*-butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate and **Zn-17**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 119 mg, 65% yield, 90% ee; (*R*,*R*)-**L2**: 114 mg, 62% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.1 min (minor), 9.0 min (major).

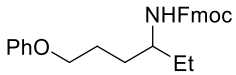
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 6.96 – 6.84 (m, 3H), 4.01 – 3.89 (m, 2H), 3.87 – 3.76 (m, 1H), 3.49 – 3.28 (m, 2H), 1.98 – 1.63 (m, 8H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 154.8, 129.5, 120.6, 114.6, 79.2, 67.7, 57.2, 46.7, 30.9, 28.7, 26.3, 23.9, 23.2.

FT-IR (film): 2970, 2873, 1694, 1393, 1246, 1173, 1108, 754, 692 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{28}NO_3$: 306.2064, found: 306.2070.

$[\alpha]^{23}_D$ = –39.7 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



(9*H*-Fluoren-9-yl)methyl (6-phenoxyhexan-3-yl)carbamate (48). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)butanoate and **Zn-17**. The product was purified by column chromatography on silica gel (2:3 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 181 mg, 73% yield, 88% ee; (*R*,*R*)-**L2**: 182 mg, 73% yield, 86% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (15% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.7 min (major), 9.9 min (minor).

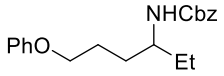
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.23 (m, 4H), 6.98 – 6.87 (m, 3H), 4.53 (d, *J* = 9.3 Hz, 1H), 4.45 (d, *J* = 6.7 Hz, 2H), 4.22 (t, *J* = 6.7 Hz, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.69 – 3.57 (m, 1H), 1.88 – 1.36 (m, 6H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.4, 144.2, 141.5, 129.6, 127.8, 127.2, 125.2, 120.8, 120.1, 114.6, 67.6, 66.4, 52.6, 47.6, 31.7, 28.5, 25.9, 10.3.

FT-IR (film): 3323, 2958, 1689, 1541, 1246, 1106, 737, 691 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}NO_3$: 416.2, found: 416.2.

$[\alpha]^{23}_D$ = –8.2 (*c* 1.0, $CHCl_3$); 87% ee, from (*S*,*S*)-**L2**.



Benzyl (6-phenoxyhexan-3-yl)carbamate (49). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-(((benzyloxy)carbonyl)amino) butanoate and **Zn-17**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 149 mg, 76% yield, 88% ee; (*R*,*R*)-**L2**: 155 mg, 79% yield, 88% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 10.8 min (minor), 12.1 min (major).

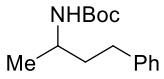
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 7H), 6.99 – 6.84 (m, 3H), 5.11 (s, 2H), 4.58 (d, *J* = 9.2 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.71 – 3.58 (m, 1H), 1.87 – 1.36 (m, 6H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.4, 136.8, 129.5, 128.6, 128.19, 128.17, 120.7, 114.6, 67.6, 66.7, 52.6, 31.6, 28.5, 25.9, 10.3.

FT-IR (film): 3325, 2961, 1694, 1498, 1244, 1093, 753, 693 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{26}NO_3$: 328.2, found: 328.2.

$[\alpha]^{23}_D$ = –3.4 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (4-phenylbutan-2-yl)carbamate (50).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-18**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 108 mg, 72% yield, 81% ee; (*R*,*R*)-**L2**: 113 mg, 76% yield, 80% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 101 mg, 81% ee → 62 mg, 61% yield (44% yield overall), >99% ee; (*R*,*R*)-**L2**: 58 mg, 80% ee → 35 mg, 60% yield (46% yield overall), >99% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.9 min (minor), 11.0 min (major).

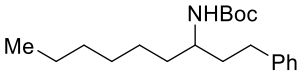
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 4.38 (s, 1H), 3.78 – 3.57 (m, 1H), 2.66 (td, *J* = 7.6, 3.9 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.46 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 142.1, 128.50, 128.45, 125.9, 79.1, 46.5, 39.3, 32.6, 28.6, 21.5.

FT-IR (film): 3372, 2966, 1682, 1520, 1367, 1246, 1075, 744 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{15}H_{24}NO_2$: 250.1802, found: 250.1806.

$[\alpha]^{23}_D$ = +10.6 (*c* 1.0, $CHCl_3$); 81% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1-phenylnonan-3-yl)carbamate (51).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-2**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 160 mg, 84% yield, 90% ee; (*R*,*R*)-**L2**: 159 mg, 83% yield, 89% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.9 min (minor), 7.9 min (major).

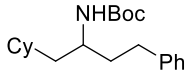
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.66 – 3.57 (m, 1H), 2.76 – 2.56 (m, 2H), 1.83 – 1.56 (m, 2H), 1.48 – 1.44 (m, 10H), 1.40 – 1.25 (m, 9H), 0.92 – 0.84 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.3, 128.5, 125.9, 79.0, 50.7, 37.7, 35.8, 32.6, 31.9, 29.4, 28.6, 25.9, 22.7, 14.2.

FT-IR (film): 3347, 2930, 1694, 1519, 1366, 1246, 1173, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{34}NO_2$: 320.2584, found: 320.2586.

$[\alpha]^{23}_D$ = +16.0 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1-cyclohexyl-4-phenylbutan-2-yl)carbamate (52).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-3**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 140 mg, 70% yield, 90% ee; (*R*,*R*)-**L2**: 146 mg, 73% yield, 89% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.8 min (minor), 7.6 min (major).

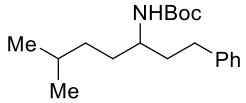
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.25 (d, *J* = 9.5 Hz, 1H), 3.80 – 3.68 (m, 1H), 2.75 – 2.56 (m, 2H), 1.89 – 1.56 (m, 7H), 1.46 (s, 9H), 1.39 – 1.06 (m, 6H), 1.01 – 0.77 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 142.4, 128.5, 128.5, 125.9, 79.0, 48.2, 43.9, 38.4, 34.6, 34.0, 33.1, 32.5, 28.6, 26.7, 26.5, 26.4.

FT-IR (film): 3346, 2921, 1698, 1522, 1365, 1247, 1166, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{21}H_{34}NO_2$: 332.2584, found: 332.2581.

$[\alpha]^{23}_D$ = +8.8 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (6-methyl-1-phenylheptan-3-yl)carbamate (53).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-19**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 145 mg, 79% yield, 90% ee; (*R*,*R*)-**L2**: 143 mg, 78% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.4 min (minor), 6.6 min (major).

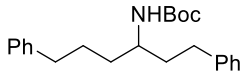
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.69 – 3.55 (m, 1H), 2.76 – 2.56 (m, 2H), 1.83 – 1.58 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 (s, 9H), 1.42 – 1.30 (m, 1H), 1.29 – 1.13 (m, 2H), 0.91 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.3, 128.5, 125.9, 79.1, 50.9, 37.7, 35.0, 33.6, 32.6, 28.6, 28.1, 22.8, 22.7.

FT-IR (film): 3328, 2950, 1681, 1537, 1366, 1176, 1026, 751, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{32}NO_2$: 306.2428, found: 306.2434.

$[\alpha]^{23}_D$ = +8.0 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (1,6-diphenylhexan-3-yl)carbamate (54).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-20**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 161 mg, 76% yield, 90% ee; (*R*,*R*)-**L2**: 162 mg, 76% yield, 89% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 150 mg, 90% ee → 125 mg, 83% yield (63% yield overall), 97% ee; (*R*,*R*)-**L2**: 105 mg, 89% ee → 83 mg, 79% yield (60% yield overall), 97% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 6.3 min (minor), 7.0 min (major).

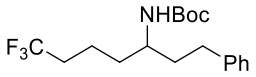
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 4H), 7.24 – 7.14 (m, 6H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.75 – 3.63 (m, 1H), 2.73 – 2.56 (m, 4H), 1.84 – 1.60 (m, 4H), 1.58 – 1.38 (m, 11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.4, 142.2, 128.53, 128.49, 128.47, 128.4, 125.93, 125.85, 79.1, 50.5, 37.7, 35.8, 35.3, 32.5, 28.6, 27.8.

FT-IR (film): 3340, 2934, 1694, 1496, 1365, 1246, 1172, 746, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_2$: 354.2428, found: 354.2434.

$[\alpha]^{23}_D$ = +8.1 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl butyl (7,7,7-trifluoro-1-phenylheptan-3-yl)carbamate (55).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-21**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 159 mg, 77% yield, 90% ee; (*R*,*R*)-**L2**: 157 mg, 76% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 9.7 min (minor), 16.0 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.30 (d, *J* = 9.4 Hz, 1H), 3.76 – 3.55 (m, 1H), 2.77 – 2.57 (m, 2H), 2.22 – 1.95 (m, 2H), 1.86 – 1.73 (m, 1H), 1.71 – 1.52 (m, 4H), 1.49 – 1.40 (m, 10H).

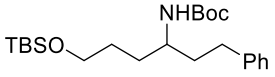
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 141.8, 128.6, 128.5, 127.2 (q, J = 276 Hz), 126.1, 79.4, 50.0, 37.7, 34.9, 33.6 (q, J = 28.4 Hz), 32.5, 28.5, 18.6.

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

FT-IR (film): 3362, 2946, 1681, 1520, 1248, 1175, 746, 700 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{27}F_3NO_2$: 346.1988, found: 346.1986.

$[\alpha]^{23}_D$ = +9.3 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (6-((*tert*-butyldimethylsilyl)oxy)-1-phenylhexan-3-yl)carbamate (56).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-22**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L2**: 210 mg, 86% yield, 89% ee; (*R*,*R*)-**L2**: 205 mg, 84% yield, 87% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 4.9 min (major), 5.6 min (minor).

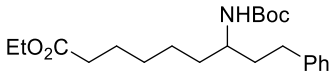
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 4.45 (d, *J* = 9.1 Hz, 1H), 3.68 – 3.58 (m, 3H), 2.75 – 2.57 (m, 2H), 1.86 – 1.63 (m, 2H), 1.60 – 1.39 (m, 13H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.2, 128.5, 125.9, 79.0, 63.0, 50.5, 37.8, 32.6, 31.9, 29.1, 28.6, 26.1, 18.5, -5.2.

FT-IR (film): 3348, 2929, 2857, 1702, 1365, 1252, 1174, 1101, 836, 776 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{42}NO_3Si$: 408.2928, found: 408.2920.

$[\alpha]^{23}_D$ = +16.1 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



Ethyl 7-((*tert*-butoxycarbonyl)amino)-9-phenylnonanoate (57). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-9**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L2**: 175 mg, 77% yield, 90% ee; (*R*,*R*)-**L2**: 168 mg, 74% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 4.7 min (minor), 5.3 min (major).

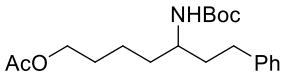
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.17 – 7.09 (m, 3H), 4.30 (d, *J* = 9.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 1H), 2.71 – 2.51 (m, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.51 (m, 4H), 1.47 – 1.24 (m, 15H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 155.8, 142.2, 128.5, 128.4, 125.9, 79.0, 60.3, 50.6, 37.7, 35.6, 34.3, 32.5, 29.1, 28.5, 25.6, 25.0, 14.4.

FT-IR (film): 3368, 2935, 1711, 1514, 1366, 1247, 1174, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{22}H_{36}NO_4$: 378.2639, found: 378.2642.

$[\alpha]^{23}_D$ = +14.8 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



5-((*tert*-Butoxycarbonyl)amino)-7-phenylheptyl acetate (58). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-8**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 158 mg, 75% yield, 90% ee; (*R*,*R*)-**L2**: 162 mg, 77% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (5% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 12.0 min (minor), 17.7 min (major).

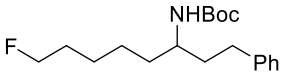
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 4.33 (d, *J* = 9.4 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.66 – 3.59 (m, 1H), 2.77 – 2.55 (m, 2H), 2.03 (s, 3H), 1.88 – 1.56 (m, 4H), 1.54 – 1.32 (m, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.8, 142.1, 128.49, 128.45, 125.9, 79.1, 64.4, 50.5, 37.7, 35.5, 32.5, 28.6, 28.5, 22.4, 21.1.

FT-IR (film): 3354, 2943, 1732, 1520, 1366, 1244, 1174, 1043, 702 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{32}NO_4$: 350.2326, found: 350.2327.

$[\alpha]^{23}_D$ = +15.4 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (8-fluoro-1-phenyloctan-3-yl)carbamate (59).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-10**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 152 mg, 78% yield, 90% ee; (*R*,*R*)-**L2**: 155 mg, 80% yield, 90% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 139 mg, 90% ee → 119 mg, 86% yield (67% yield overall), 93% ee; (*R*,*R*)-**L2**: 101 mg, 90% ee → 79 mg, 78% yield (63% yield overall), 93% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (5% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 7.7 min (minor), 10.5 min (major).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 4.43 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.32 – 4.28 (m, 1H), 3.63 (s, 1H), 2.76 – 2.56 (m, 2H), 1.87 – 1.58 (m, 4H), 1.56 – 1.31 (m, 15H).

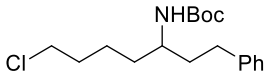
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.2, 128.51, 128.48, 126.0, 84.2 (d, J = 164 Hz), 79.1, 50.6, 37.8, 35.8, 32.6, 30.5 (d, J = 19.5 Hz), 28.6, 25.6, 25.3 (d, J = 5.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –218.1.

FT-IR (film): 3347, 2936, 1702, 1508, 1364, 1246, 1168, 1043, 699 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{31}FNO_2$: 324.2333, found: 324.2331.

$[\alpha]^{23}_D$ = +12.6 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (7-chloro-1-phenylheptan-3-yl)carbamate (60).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-11**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 160 mg, 82% yield, 90% ee; (*R*,*R*)-**L2**: 165 mg, 85% yield, 90% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 148 mg, 90% ee → 95 mg, 64% yield (53% yield overall), 96% ee; (*R*,*R*)-**L2**: 119 mg, 90% ee → 83 mg, 70% yield (59% yield overall), 96% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALPAK IC column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 10.5 min (minor), 12.0 min (major).

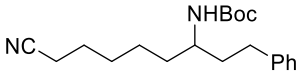
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.64 (s, 1H), 3.54 – 3.50 (m, 2H), 2.77 – 2.57 (m, 2H), 1.87 – 1.60 (m, 4H), 1.55 – 1.36 (m, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.1, 128.53, 128.47, 126.0, 79.2, 50.4, 45.1, 37.6, 35.1, 32.5, 32.5, 28.6, 23.3.

FT-IR (film): 3340, 2943, 1690, 1511, 1365, 1248, 1168, 682 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{29}ClNO_2$: 326.1881, found: 326.1888.

$[\alpha]^{23}_D$ = +1.9 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl (8-cyano-1-phenyloctan-3-yl)carbamate (61).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl) amino)-4-phenylbutanoate and **Zn-12**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L2**: 165 mg, 83% yield, 82% ee; (*R*,*R*)-**L2**: 172 mg, 87% yield, 82% ee.

SFC analysis: The ee was determined via SFC on a CHIRALCEL OD column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.5 min (minor), 7.8 min (major).

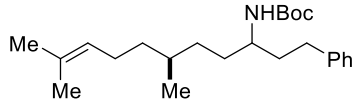
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 7.15 – 7.06 (m, 3H), 4.23 (d, *J* = 9.4 Hz, 1H), 3.54 (s, 1H), 2.68 – 2.49 (m, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.77 – 1.51 (m, 4H), 1.44 – 1.25 (m, 15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.0, 134.4, 128.51, 128.45, 126.0, 123.6, 119.9, 79.2, 50.4, 37.7, 35.7, 32.5, 28.5, 25.5, 25.2.

FT-IR (film): 3350, 2935, 1690, 1517, 1365, 1247, 1170, 698 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{31}N_2O_2$: 331.2380, found: 331.2382.

$[\alpha]^{23}_D$ = +7.7 (*c* 1.0, $CHCl_3$); 82% ee, from (*S*,*S*)-**L2**.



***tert*-Butyl ((6*S*)-6,10-dimethyl-1-phenylundec-9-en-3-yl)carbamate (62, 63).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-14**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L2**: 185 mg, 83% yield, 5:95 d.r.; (*R*,*R*)-**L2**: 177 mg, 79% yield, 95:5 d.r.

HPLC analysis: The d.r. was determined via HPLC on a CHIRALPAK AD column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.7 min (major), 6.7 min (minor).

NMR data for the product from (*S*,*S*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.17 – 7.09 (m, 3H), 5.09 – 5.00 (m, 1H), 4.26 (d, *J* = 9.3 Hz, 1H), 3.56 (s, 1H), 2.71 – 2.52 (m, 2H), 2.00 – 1.83 (m, 2H), 1.79 – 1.69 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.48 – 1.21 (m, 15H), 1.20 – 1.04 (m, 2H), 0.82 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.3, 131.2, 128.5, 125.9, 125.0, 109.8, 79.0, 51.0, 37.8, 37.2, 33.1, 32.5, 28.6, 25.9, 25.7, 25.1, 22.5, 19.6, 17.8.

NMR data for the product from (*R*,*R*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 5.14 – 5.04 (m, 1H), 4.30 (d, *J* = 9.4 Hz, 1H), 3.61 (s, 1H), 2.76 – 2.56 (m, 2H), 2.04 – 1.87 (m, 2H), 1.86 – 1.75 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.47 – 1.29 (m, 15H), 1.20 – 1.07 (m, 2H), 0.87 (d, *J* = 6.4 Hz, 3H).

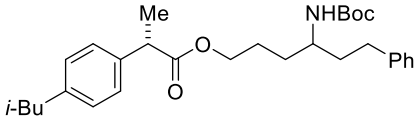
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.3, 131.3, 128.5, 125.9, 125.0, 109.8, 79.1, 51.0, 38.2, 37.6, 37.1, 33.3, 33.0, 32.6, 28.6, 25.9, 25.7, 19.7, 17.8.

FT-IR (film): 3346, 2963, 1691, 1524, 1454, 1365, 1247, 1167, 698 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{24}H_{40}NO_2$: 374.3054, found: 374.3052.

$[\alpha]^{23}_D$ = +15.1 (*c* 1.0, $CHCl_3$); 5:95 d.r., from (*S*,*S*)-**L2**.

$[\alpha]^{23}_D$ = +6.0 (*c* 1.0, $CHCl_3$); 95:5 d.r., from (*R*,*R*)-**L2**.



4-((*tert*-Butoxycarbonyl)amino)-6-phenylhexyl (2*S*)-2-(4-isobutylphenyl)propanoate (64, 65). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-23**. The product was purified by column chromatography on silica gel (15:85 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 233 mg, 81% yield, 5:95 d.r.; (*R*,*R*)-**L2**: 240 mg, 83% yield, 95:5 d.r.

HPLC analysis: The d.r. was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 10.0 min (minor), 12.3 min (major).

NMR data for the product from (*S*,*S*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.18 (m, 5H), 7.15 – 7.10 (m, 2H), 4.22 (d, *J* = 9.5 Hz, 1H), 4.17 – 4.02 (m, 2H), 3.72 (q, *J* = 7.1 Hz, 1H), 3.65 – 3.55 (m, 1H), 2.74 – 2.55 (m, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.94 – 1.81 (m, 1H), 1.78 – 1.58 (m, 4H), 1.53 (d, *J* = 7.2 Hz, 3H), 1.51 – 1.21 (m, 11H), 0.93 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 155.8, 142.0, 140.6, 138.0, 129.4, 128.5, 128.4, 127.3, 126.0, 79.2, 64.5, 50.3, 45.3, 45.1, 37.8, 32.5, 32.0, 30.3, 28.6, 25.3, 22.5, 18.5.

NMR data for the product from (*R*,*R*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.27 – 7.18 (m, 5H), 7.16 – 7.10 (m, 2H), 4.22 (d, *J* = 9.5 Hz, 1H), 4.16 – 4.04 (m, 2H), 3.72 (q, *J* = 7.1 Hz, 1H), 3.65 – 3.56 (m, 1H), 2.74 – 2.55 (m, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.94 – 1.81 (m, 1H), 1.77 – 1.57 (m, 4H), 1.53 (d, *J* = 7.2 Hz, 3H), 1.51 – 1.20 (m, 11H), 0.93 (d, *J* = 6.6 Hz, 6H).

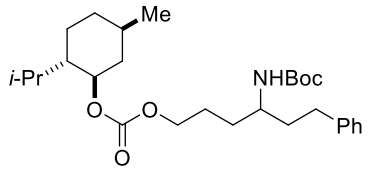
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 155.8, 142.0, 140.6, 138.0, 129.4, 128.5, 128.4, 127.3, 126.0, 79.2, 64.5, 50.3, 45.3, 45.1, 37.8, 32.5, 32.0, 30.3, 28.6, 25.3, 22.5, 18.5.

FT-IR (film): 3368, 2953, 1714, 1514, 1366, 1246, 1173, 700 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{43}NNaO_4$: 504.3, found: 504.3.

$[\alpha]^{23}_D$ = +15.6 (*c* 1.0, $CHCl_3$); 5:95 d.r., from (*S*,*S*)-**L2**.

$[\alpha]^{23}_D$ = +22.3 (*c* 1.0, $CHCl_3$); 95:5 d.r., from (*R*,*R*)-**L2**.



***tert*-Butyl (6-(((((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)oxy)-1-phenylhexan-3-yl)carbamate (66, 67).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-24**. The product was purified by column chromatography on silica gel (15:85 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 242 mg, 85% yield, 6:94 d.r.; (*R*,*R*)-**L2**: 236 mg, 83% yield, 95:5 d.r.

HPLC analysis: The d.r. was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 6.6 min (minor), 8.2 min (major).

NMR data for the product from (*S*,*S*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 4.51 (td, *J* = 10.9, 4.4 Hz, 1H), 4.31 (d, *J* = 9.4 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.71 – 3.45 (m, 1H), 2.75 – 2.56 (m, 2H), 2.13 – 2.02 (m, 1H), 2.01 – 1.89 (m, 1H), 1.80 – 1.57 (m, 7H), 1.50 – 1.35 (m, 12H), 1.13 – 0.97 (m, 2H), 0.96 – 0.84 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.1, 142.0, 128.53, 128.45, 126.0, 79.2, 78.4, 67.6, 50.4, 47.1, 40.9, 37.8, 34.2, 32.5, 31.5, 28.5, 26.2, 25.5, 23.4, 22.1, 20.8, 16.4.

NMR data for the product from (*R*,*R*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 4.51 (td, *J* = 10.9, 4.4 Hz, 1H), 4.29 (d, *J* = 9.5 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.68 – 3.45 (m, 1H), 2.75 – 2.56 (m, 2H), 2.11 – 2.02 (m, 1H), 2.02 – 1.90 (m, 1H), 1.82 – 1.56 (m, 7H), 1.51 – 1.35 (m, 12H), 1.13 – 0.97 (m, 2H), 0.94 – 0.83 (m, 7H), 0.79 (d, *J* = 7.0 Hz, 3H).

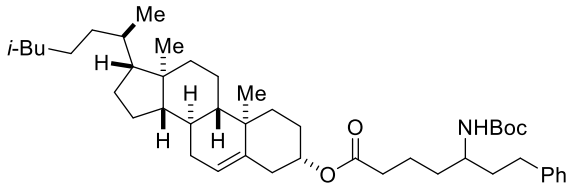
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.1, 142.0, 128.55, 128.47, 126.0, 79.3, 78.4, 67.6, 50.4, 47.1, 40.9, 37.9, 34.2, 32.5, 32.2, 31.5, 28.6, 26.2, 25.5, 23.4, 22.1, 20.9, 16.4.

FT-IR (film): 3357, 2953, 1738, 1515, 1454, 1366, 1262, 1174, 959, 699 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{45}NNaO_5$: 498.3, found: 498.3.

$[\alpha]^{23}_D$ = –26.5 (*c* 1.0, $CHCl_3$); 6:94 d.r., from (*S*,*S*)-**L2**.

$[\alpha]^{23}_D$ = –27.6 (*c* 1.0, $CHCl_3$); 95:5 d.r., from (*R*,*R*)-**L2**.



(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 5-((tert-butoxycarbonyl)amino)-7-phenylheptanoate (68, 69). The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-15**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 358 mg, 87% yield, 16:84 d.r.; (*R*,*R*)-**L2**: 343 mg, 83% yield, 84:16 d.r.

After recrystallization using *n*-pentane/hexanes: (*R*,*R*)-**L2**: 199 mg, 84:16 d.r. → 101 mg, 51% yield (42% yield overall), >99:1 d.r.

HPLC analysis: The d.r. was determined via HPLC on a CHIRALPAK IC column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 8.9 min (minor), 14.6 min (major).

NMR data for the product from (*S*,*S*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.28 – 7.22 (m, 3H), 5.47 – 5.42 (m, 1H), 4.74 – 4.62 (m, 1H), 4.46 (d, *J* = 9.3 Hz, 1H), 3.78 – 3.66 (m, 1H), 2.83 – 2.63 (m, 2H), 2.41 – 2.32 (m, 4H), 2.13 – 1.86 (m, 6H), 1.78 – 1.39 (m, 26H), 1.27 – 1.05 (m, 12H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.95 (dd, *J* = 6.6, 1.9 Hz, 6H), 0.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.8, 142.0, 139.7, 128.5, 128.4, 125.9, 122.7, 79.1, 73.9, 56.8, 56.2, 50.1, 42.4, 39.8, 39.6, 38.2, 37.6, 37.1, 36.7, 36.3, 35.9, 35.0, 34.4, 32.5, 32.0, 31.9, 28.5, 28.3, 28.1, 27.9, 24.4, 23.9, 22.9, 22.7, 21.4, 21.1, 19.4, 18.8, 11.9.

NMR data for the product from (*R*,*R*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, *J* = 8.2, 6.8 Hz, 2H), 7.28 – 7.20 (m, 3H), 5.48 – 5.41 (m, 1H), 4.75 – 4.63 (m, 1H), 4.48 (d, *J* = 9.3 Hz, 1H), 3.75 – 3.66 (m, 1H), 2.88 – 2.63 (m, 2H), 2.42 – 2.31 (m, 4H), 2.19 – 1.85 (m, 6H), 1.82 – 1.39 (m, 26H), 1.28 – 1.06 (m, 12H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.95 (dd, *J* = 6.7, 1.8 Hz, 6H), 0.76 (s, 3H).

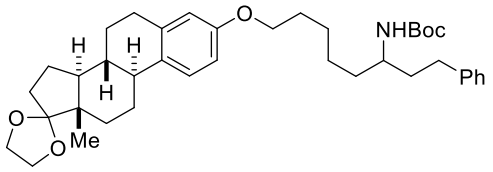
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.7, 142.0, 139.7, 128.43, 128.40, 125.9, 122.7, 79.0, 73.9, 56.7, 56.2, 50.1, 42.4, 39.8, 39.6, 38.2, 37.6, 37.1, 36.6, 36.3, 35.9, 35.0, 34.4, 32.5, 32.0, 31.9, 28.5, 28.3, 28.1, 27.9, 24.4, 23.9, 22.9, 22.7, 21.4, 21.1, 19.4, 18.8, 11.9.

FT-IR (film): 3368, 2941, 1722, 1366, 1248, 1174, 759 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{45}H_{72}NO_4$: 690.5456, found: 690.5451.

$[\alpha]^{23}_D = -18.7$ (*c* 1.0, $CHCl_3$); 16:84 d.r., from (*S*,*S*)-**L2**.

$[\alpha]^{23}_D = -36.2$ (*c* 1.0, $CHCl_3$); 84:16 d.r., from (*R*,*R*)-**L2**.



***tert*-Butyl (8-(((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)-1-phenyloctan-3-yl)carbamate (70, 71).** The title compound was synthesized according to **GP-6** from 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate and **Zn-16**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 312 mg, 84% yield, 8:92 d.r.; (*R*,*R*)-**L2**: 327 mg, 88% yield, 94:6 d.r.

HPLC analysis: The d.r. was determined via HPLC on a CHIRALPAK AD column (7% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 10.8 min (minor), 11.9 min (major).

NMR data for the product from (*S*,*S*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 7.19 – 7.10 (m, 4H), 6.65 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 4.28 (d, *J* = 9.4 Hz, 1H), 3.98 – 3.81 (m, 6H), 3.64 – 3.56 (m, 1H), 2.88 – 2.74 (m, 2H), 2.70 – 2.49 (m, 2H), 2.33 – 2.14 (m, 2H), 2.08 – 1.92 (m, 1H), 1.90 – 1.67 (m, 7H), 1.67 – 1.55 (m, 2H), 1.55 – 1.24 (m, 20H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 155.8, 142.2, 138.1, 132.7, 128.49, 128.46, 126.4, 125.9, 119.6, 114.5, 112.1, 79.1, 67.8, 65.4, 64.7, 50.7, 49.5, 46.3, 43.7, 39.2, 37.7, 35.8, 34.4, 32.5, 30.9, 29.9, 29.4, 28.6, 27.1, 26.3, 26.2, 25.8, 22.5, 14.5.

NMR data for the product from (*R*,*R*)-**L2**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 7.16 – 7.12 (m, 4H), 6.65 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 4.27 (d, *J* = 9.4 Hz, 1H), 4.01 – 3.81 (m, 6H), 3.66 – 3.53 (m, 1H), 2.89 – 2.72 (m, 2H), 2.72 – 2.52 (m, 2H), 2.34 – 2.14 (m, 2H), 2.05 – 1.94 (m, 1H), 1.90 – 1.67 (m, 7H), 1.67 – 1.55 (m, 2H), 1.54 – 1.28 (m, 20H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 155.8, 142.2, 138.1, 132.7, 128.49, 128.47, 126.4, 125.9, 119.6, 114.5, 112.1, 79.1, 67.8, 65.4, 64.7, 50.7, 49.5, 46.3, 43.8, 39.2, 37.7, 35.8, 34.4, 32.5, 30.9, 29.9, 29.4, 28.6, 27.1, 26.3, 26.2, 25.8, 22.5, 14.5.

FT-IR (film): 3356, 2937, 1698, 1498, 1255, 1165, 1044, 754 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{39}H_{56}NO_5$: 618.4153, found: 618.4158.

$[\alpha]^{23}_D$ = +40.4 (*c* 1.0, $CHCl_3$); 8:92 d.r., from (*S*,*S*)-**L2**.

$[\alpha]^{23}_D$ = +23.2 (*c* 1.0, $CHCl_3$); 94:6 d.r., from (*R*,*R*)-**L2**.

2.4.6. Effect of reaction parameters

General Procedure 8 (GP-8): Small-scale couplings of *α*-phthalimido alkyl chlorides.

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*,*S*)-**L1** (10.9 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 turned dark. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 36 h.

Work-up: The reaction was quenched at 0 °C by the addition of MeOH (0.1 mL). *n*-Dodecane (23 μL, 0.10 mmol, 1.0 equiv) 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.

General Procedure 9 (GP-9). Small-scale couplings of alkyl NHP esters.

Preparation of a solution of the catalyst: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar and charged with $NiBr_2$·glyme (1.5 mg, 0.0050 mmol, 5.0 mol%), (*R*,*R*)-**L2** (1.8 mg, 0.0060 mmol, 6.0 mol%), and LiCl (8.5 mg, 0.20 mmol, 2.0 equiv). Next, THF (0.4 mL) was added, the vial was capped with a PTFE septum

cap, and the mixture was stirred at room temperature for 30 min, during which it became a light-green, homogeneous solution.

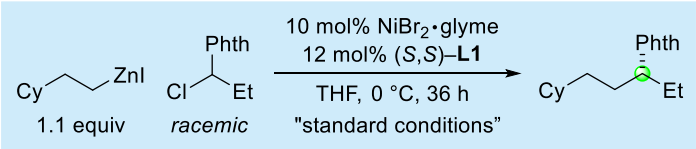
Cross-coupling: In a nitrogen-filled glovebox, DMAP (0.050 mmol, 0.50 equiv), the NHP ester (0.10 mmol, 1.0 equiv), and TMSCl (0.080 mmol, 0.80 equiv) were added sequentially to the reaction mixture as stock solutions in THF, totaling 1.2 mL THF (including 0.4 mL from the catalyst solution). The vial was sealed with a septum cap and wrapped with electrical tape. Next, the vial was removed from the glovebox and cooled to 0 °C using an *i*-PrOH cooling bath. After the white, heterogeneous reaction mixture had stirred at 0 °C for 10 min, the alkylzinc solution (0.12 mmol, 1.2 equiv) was added dropwise via microsyringe, resulting in a yellow, homogeneous solution. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 18 h.

Work-up: The reaction was quenched at 0 °C by the addition of MeOH (0.1 mL). The resulting mixture was allowed to warm to room temperature, and then 1-indanone (2.6 mg, 0.020 mmol) was added as an internal standard. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography.

Table 2.3: 2-(1-Chloropropyl)isoindoline-1,3-dione was reacted with **Zn-1** according to **GP-8**. The yields were determined via GC analysis, with *n*-dodecane 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.

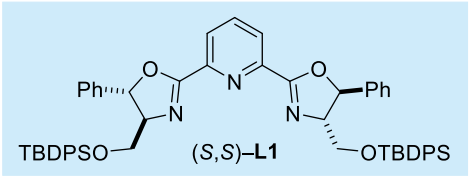
Table 2.4: 1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate was reacted with **Zn-17** according to **GP-9**. The yields were determined via LC-MS analysis, with 1-indanone as the internal standard. The ee values were determined via HPLC analysis after purification by preparative thin layer chromatography. All data are the average of two experiments.

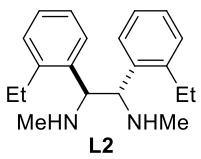
Table 2.3. *Effect of reaction parameters (complete): an alkyl chloride as the electrophile.*

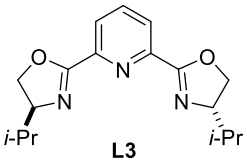


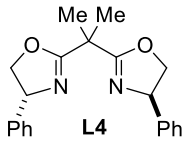
entry	variation from the "standard conditions"	yield (%)[a]	ee (%)[b]
1	none	90	92
2	no $NiBr_2$·glyme	<1	–
3	no (*S*,*S*)–**L1**	<1	–
4	**L2**, instead of (*S*,*S*)–**L1**	32	16
5	**L3**, instead of (*S*,*S*)–**L1**	81	84
6	**L4**, instead of (*S*,*S*)–**L1**	13	22
7	**L5**, instead of (*S*,*S*)–**L1**	19	41
8	**L6**, instead of (*S*,*S*)–**L1**	19	3
9	2-MeTHF, instead of THF	96	91
10	MTBE, instead of THF	81	70
11	1,4-dioxane, instead of THF	48	86
12	DME, instead of THF	15	90
13	0.1 M, instead of 0.05 M	94	91
14	5.0 mol% $NiBr_2$·glyme, 6.0 mol% (*S*,*S*)–**L1**	79	91
15	RZnBr, instead of RZnI	78	88
16	1.0 equiv alkylzinc	81	92
17	9 h, instead of 36 h	70	92
18	18 h, instead of 36 h	86	92
19	r.t., instead of 0 °C	98	90
20	0.05 equiv H_2O added	31	92
21	0.10 equiv H_2O added	11	92
22	1 mL air added with syringe	64	91
23	1 mL air added with syringe (72 h)	77	91
24	under air in a closed vial	50	91

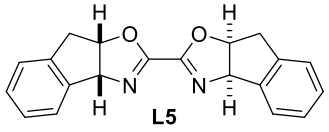
All data are the average of two experiments. [a] Determined through GC analysis. [b] Determined through SFC analysis.











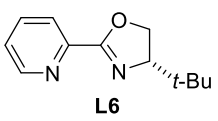
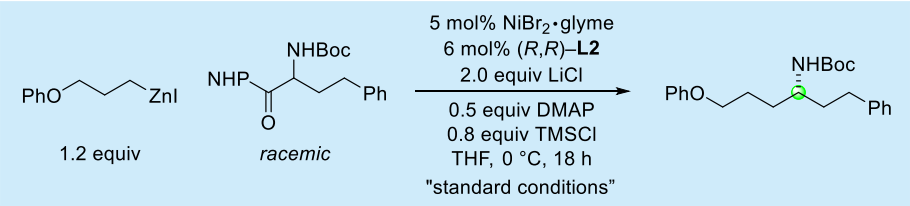
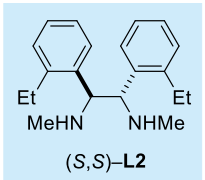


Table 2.4. *Effect of reaction parameters (complete): an alkyl NHP ester as the electrophile.*

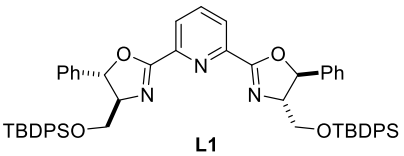


entry	variation from the "standard conditions"	yield (%)[a]	ee (%)[b]
1	none	79	91
2	no $NiBr_2$·glyme	<1	–
3	no (*S*,*S*)–**L2**	30	<2
4	no LiCl	16	88
5	no DMAP	70	65
6	no TMSCl	65	87
7	**L1**, instead of (*S*,*S*)–**L2**	14	31
8	**L4**, instead of (*S*,*S*)–**L2**	9	6
9	**L6**, instead of (*S*,*S*)–**L2**	30	16
10	**L7**, instead of (*S*,*S*)–**L2**	74	86
11	**L8**, instead of (*S*,*S*)–**L2**	43	3
12	LiF, instead of LiCl	15	89
13	LiBr, instead of LiCl	64	87
14	LiI, instead of LiCl	50	90
15	NaCl, instead of LiCl	17	90
16	KCl, instead of LiCl	19	89
17	CsCl, instead of LiCl	32	83
18	N(*n*-Bu)$_4$Cl, instead of LiCl	25	87
19	pyridine, instead of DMAP	79	87
20	2.5 mol% $NiBr_2$·glyme, 3.0 mol% (*S*,*S*)–**L2**	65	88
21	RZnBr, instead of RZnI	82	82
22	1.0 equiv alkylzinc	67	89
23	9 h, instead of 18 h	70	90
24	r.t., instead of 0 °C	70	82
25	0.12 M, instead of 0.07 M	50	90
26	0.04 M, instead of 0.07 M	78	90
27	DME, instead of THF	51	77
28	MTBE, instead of THF	17	84
29	0.05 equiv H_2O added	73	88
30	0.10 equiv H_2O added	70	87
31	1 mL air added with syringe	71	88
32	under air in a closed vial	20	82

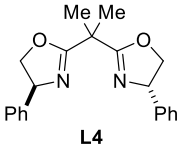
All data are the average of two experiments. [a] Determined through LC/MS analysis.
[b] Determined through HPLC analysis.



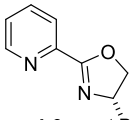
(*S*,*S*)–**L2**

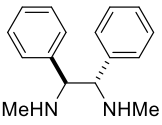


L1

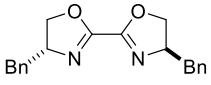


L4


L6 *t*-Bu



L7



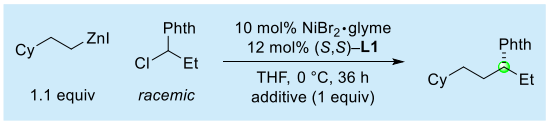
L8

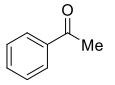
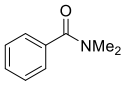
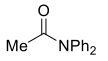
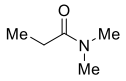
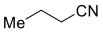
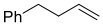
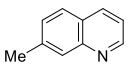
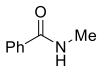
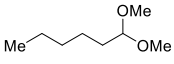
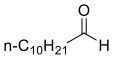
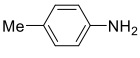
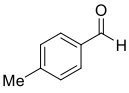
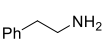
2.4.7. Study of functional-group compatibility

Table 2.5: 2-(1-Chloropropyl)isoindoline-1,3-dione was reacted with **Zn-1** according to **GP-8,** in the presence of 1.0 equiv of the additives shown below. The additive was added after the addition of the 2-(1-chloropropyl)isoindoline-1,3-dione solution. The yield of the coupling product and the percent recovery of the additive were determined via GC analysis, with *n*-dodecane 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 2.6: 1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate was reacted with **Zn-17** according to **GP-9**, in the presence of 1.0 equiv of the additives shown below. The additive was added before TMSCl. In addition to 1-indanone (2.6 mg, 0.020 mmol), n-dodecane (23 μL, 0.10 mmol) was added as an internal standard after quenching the reaction. The yields were determined via LC-MS analysis, with 1-indanone as the internal standard. The percent recoveries of the additives were determined via GC analysis, with n-dodecane as the internal standard. The ee values were determined via HPLC analysis after purification by preparative thin-layer chromatography. All data are the average of two experiments.

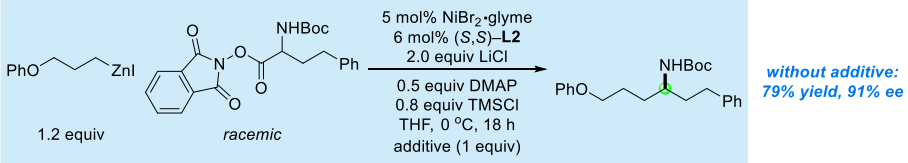
Table 2.5. *Functional-group compatibility: an alkyl chloride as the electrophile.*

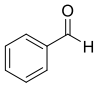
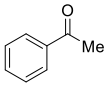
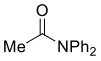
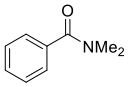
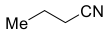
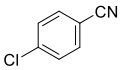
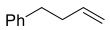
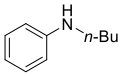
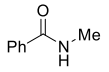
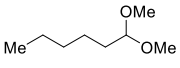
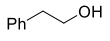
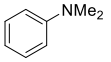
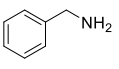


additive; recovery (%)[a]		yield (%)[a]	ee (%)[b]	additive; recovery (%)[a]		yield (%)[a]	ee (%)[b]
n-$C_{10}H_{21}Cl$	>95	87	91		>95	88	91
	>95	84	91		>95	93	91
	>95	89	91		>95	89	91
	>95	84	91		>95	89	92
	>95	86	91		92	84	91
	>95	87	91		>95	85	92
	>95	87	91		>95	82	91
	>95	87	91		>95	80	91
	>95	89	91		>95	82	81
	>95	87	91		>95	85	91
	>95	83	91		>95	88	91
	>95	78	90		>95	88	92
	>95	84	92		>95	92	92
	>95	87	92		92[c]	93	91
	>95	84	92		67	14	85
	>95	83	91		30	45	81

[a] Determined through GC analysis. [b] Determined through SFC analysis. [c] 2.2 equiv of alkylzinc was used instead.

Table 2.6. *Functional-group compatibility: an alkyl NHP ester as the electrophile.*



additive; recovery (%)[a]		yield (%)[b]	ee (%)[c]	additive; recovery (%)[a]		yield (%)[b]	ee (%)[c]
n-$C_{10}H_{21}Cl$	>95	85	90	*n*-C_8H_{17}–C(=O)H	>95	71	90
	>95	85	91		90	90	90
	>95	86	90		>95	88	91
	>95	86	90		>95	80	89
	>95	83	90		90	88	90
	>95	73	91		85	91	89
	>95	88	90		70	85	90
	>95	82	90		>95	81	90
	>95	82	90		>95	81	90
	>95	81	90	*n*-Bu–≡–*n*-Bu	85	87	90
	>95	79	90		>95	83	90
	>95	90	91		>95	80	90
	>95	85	89		>95[d]	79	86
	>95	89	90		**50**	**30**	90
	>95	84	90		**0**	**18**	88

[a] Determined through GC analysis. [b] Determined through LC-MS analysis. [c] Determined through HPLC analysis.
[d] 2.4 equiv of alkylzinc, 4.0 equiv of LiCl, and 2.5 equiv of TMSCl were used. The additive was recovered as the TMS ether.

2.4.8. One-pot reactions

General Procedure 10 (GP-10).

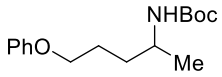
Preparation of the NHP ester: In the air, *N*-hydroxyphthalimide (97.9 mg, 0.60 mmol, 1.0 equiv), the Boc-protected amino acid (0.60 mmol, 1.0 equiv), and DMAP (36.7 mg, 0.30 mmol, 0.50 equiv) were added sequentially to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was capped with a PTFE septum cap and wrapped with electric tape. The reaction vial was evacuated and back-filled with nitrogen (four cycles), after which a nitrogen-filled balloon was attached. THF (2.8 mL) was added via syringe, and the mixture was allowed to stir for 10 min, leading to an orange, heterogeneous mixture. *N*,*N*'-diisopropylcarbodiimide (112 µL, 0.72 mmol, 1.20 equiv) was then added dropwise via microsyringe over 2 min. The mixture was stirred at room temperature for 1 h.

Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (9.3 mg, 0.030 mmol, 5.0 mol%), (*R*,*R*)-**L2** (10.7 mg, 0.036 mmol, 6.0 mol%), and anhydrous LiCl (52.1 mg, 1.20 mmol, 2.00 equiv; because LiCl is hygroscopic, it is recommended to weigh the compound in a capped 4 mL vial in a glovebox, transfer the vial out of the glovebox, and pour the compound into the reaction vial) were added sequentially to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was then capped with a PTFE septum cap and wrapped with electrical tape. The vial was evacuated and back-filled with nitrogen (four cycles), after which a nitrogen-filled balloon was attached. THF (4.0 mL) was added via syringe, and the mixture was allowed to stir for 30 min, during which it became a light-green, homogeneous solution.

Cross-coupling: The catalyst solution (4.0 mL) was transferred via syringe to the reaction vial containing the NHP ester, leading to an orange, homogeneous solution. The vial was washed with THF (0.5 mL), which was also added to the reaction vial. Next, TMSCl (61 µL, 0.48 mmol, 0.80 equiv) was added via microsyringe, leading to a colorless, opaque mixture. The reaction vial was then placed in an isopropanol cooling bath at 0 °C, and the mixture was stirred at 0 °C for 10 min. Then, the alkylzinc solution (0.72 mmol,

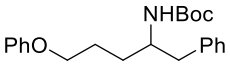
1.2 equiv) was added dropwise via syringe over 5 min, during which the reaction mixture became yellow and homogeneous. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 18 h.

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



***tert*-Butyl (5-phenoxypentan-2-yl)carbamate (35).** The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)alanine and **Zn-17**. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes). White solid.

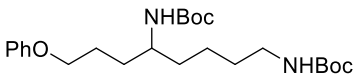
(*S*,*S*)-**L2**: 112 mg, 67% yield, 90% ee; (*R*,*R*)-**L2**: 106 mg, 63% yield, 90% ee.



***tert*-Butyl (5-phenoxy-1-phenylpentan-2-yl)carbamate (41).** The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)phenylalanine and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

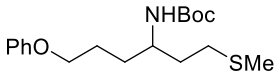
(*S*,*S*)-**L2**: 135 mg, 63% yield, 90% ee; (*R*,*R*)-**L2**: 131 mg, 61% yield, 90% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 112 mg, 90% ee → 95 mg, 85% yield (53% yield overall), >99% ee; (*R*,*R*)-**L2**: 111 mg, 90% ee → 96 mg, 86% yield (53% yield overall), >99% ee.



Di-*tert*-butyl (8-phenoxyoctane-1,5-diyl)dicarbamate (42). The title compound was synthesized according to **GP-10** from N^2,N^6-bis(*tert*-butoxycarbonyl)lysine and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

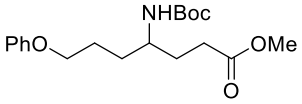
(*S*,*S*)-**L2**: 170 mg, 65% yield, 90% ee; (*R*,*R*)-**L2**: 152 mg, 58% yield, 90% ee.



***tert*-Butyl (1-(methylthio)-6-phenoxyhexan-3-yl)carbamate (43).** The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)methionine and **Zn-17**. The product was purified by column chromatography on silica gel (3:7 EtOAc/hexanes). White solid.

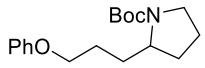
(*S*,*S*)-**L2**: 105 mg, 52% yield, 92% ee; (*R*,*R*)-**L2**: 105 mg, 52% yield, 92% ee.

After recrystallization using *n*-pentane/hexanes: (*S*,*S*)-**L2**: 76 mg, 92% ee → 56 mg, 74% yield (38% yield overall), >99% ee; (*R*,*R*)-**L2**: 82 mg, 92% ee → 68 mg, 83% yield (43% yield overall), >99% ee.



Methyl 4-((*tert*-butoxycarbonyl)amino)-7-phenoxyheptanoate (46). The title compound was synthesized according to **GP-10** from 2-((*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid and **Zn-17**. The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). White solid.

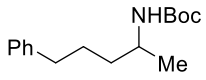
(*S*,*S*)-**L2**: 110 mg, 52% yield, 91% ee; (*R*,*R*)-**L2**: 107 mg, 51% yield, 92% ee.



***tert*-Butyl 2-(3-phenoxypropyl)pyrrolidine-1-carboxylate (47).** The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)proline and **Zn-17**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid.

(*S*,*S*)-**L2**: 102 mg, 56% yield, 90% ee; (*R*,*R*)-**L2**: 105 mg, 57% yield, 90% ee.

2.4.9. Applications



***tert*-Butyl (5-phenylpentan-2-yl)carbamate (72).** The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)-*L*-alanine and **Zn-20**. The product was purified by column chromatography on silica gel (1:9 EtOAc/hexanes). White solid. The analytical data matched a literature report.[57]

(*S*,*S*)-**L2**: 196 mg, 62% yield, 90% ee; (*R*,*R*)-**L2**: 209 mg, 66% yield, 90% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OJ column (2% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 7.4 min (minor), 9.6 min (major).

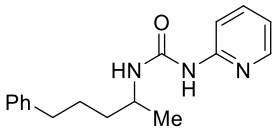
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.35 – 4.30 (m, 1H), 3.74 – 3.64 (m, 1H), 2.68 – 2.58 (m, 2H), 1.74 – 1.59 (m, 2H), 1.51 – 1.38 (m, 11H), 1.10 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 142.4, 128.5, 128.4, 125.8, 79.0, 46.4, 37.0, 35.8, 28.5, 28.0, 21.4.

FT-IR (film): 3340, 2932, 1704, 1504, 1366, 1248, 1174, 1079, 699 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{25}NNaO_2$: 286.2, found: 286.1.

$[\alpha]^{23}_D$ = –3.4 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



1-(5-Phenylpentan-2-yl)-3-(pyridin-2-yl)urea (73). The title compound was synthesized according to a reported procedure.[58] An oven-dried 40 mL vial was equipped with a stir bar and *tert*-butyl (5-phenylpentan-2-yl)carbamate (141 mg, 0.54 mmol, 1.0 equiv), and it was then sealed with a rubber septum cap. The vial was placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of anhydrous DCM (18 mL). 2-Chloropyridine (152 µL, 1.61 mmol, 3.0 equiv) was added, followed by trifluoromethanesulfonic anhydride (135 µL, 0.80 mmol, 1.5 equiv), and the reaction mixture was stirred at room temperature for 50 min. Then, triethylamine (448 µL, 3.21 mmol, 6.0 equiv) was added, followed by 2-aminopyridine (151 mg, 1.61 mmol, 3.0 equiv), leading to a dark red, homogeneous solution. The reaction was stirred at room temperature for 20 h. The mixture was then concentrated, and the residue was purified by column chromatography on silica gel (5:7:8 EtOAc/hexanes/DCM). Light-yellow oil.

(*S*,*S*)-**L2**: 0.69 mmol scale, 117 mg, 60% yield, 91% ee; (*R*,*R*)-**L2**: 0.54 mmol scale, 98 mg, 65% yield, 91% ee.

HPLC analysis: The ee was determined via HPLC on a CHIRALCEL OD column (8% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 9.1 min (major), 11.3 min (minor).

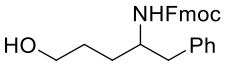
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.8 Hz, 1H), 8.85 (s, 1H), 8.16 – 8.10 (m, 1H), 7.59 – 7.50 (m, 1H), 7.32 – 7.21 (m, 2H), 7.21 – 7.12 (m, 3H), 6.90 – 6.79 (m, 2H), 4.12 – 3.98 (m, 1H), 2.74 – 2.57 (m, 2H), 1.82 – 1.53 (m, 4H), 1.25 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 153.8, 146.0, 142.6, 138.3, 128.5, 128.4, 125.8, 116.6, 112.1, 45.8, 36.9, 35.9, 28.0, 21.6.

FT-IR (film): 3223, 3062, 1682, 1556, 1480, 1416, 1302, 1242, 777 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}N_3O$: 284.2, found: 284.1.

$[\alpha]^{23}_D$ = +28.5 (*c* 1.0, $CHCl_3$); 90% ee, from (*S*,*S*)-**L2**.



(9*H*-Fluoren-9-yl)methyl (5-hydroxy-1-phenylpentan-2-yl)carbamate (74). **GP-10** was applied on a 1.2 mmol scale to (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalanine and **Zn-22** to generate the Fmoc-protected amine *in situ*. The reaction was quenched with methanol (0.2 mL), and the mixture was passed through a short pad of silica gel, with Et_2O as the eluent (~15 mL) into a 40 mL vial. The resulting mixture was concentrated under reduced pressure to yield an orange oil.

The vial was then placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of methanol (5.0 mL). A solution of HCl in methanol (1.25 M, 6.0 mL) was then added dropwise over 5 min. After the mixture had stirred at room temperature for 2 h, the methanol was evaporated under reduced pressure. Water (10 mL) was added to the resulting residue, and the mixture was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (7:3 EtOAc/hexanes). White solid. The analytical data matched the literature report.[59]

(*S*,*S*)-**L2**: 198 mg, 41% yield, 82% ee; (*R*,*R*)-**L2**: 176 mg, 37% yield, 79% ee.

After recrystallization using THF/hexanes: (*S*,*S*)-**L2**: 198 mg, 82% ee → 136 mg, 69% yield (28% yield overall), >99% ee; (*R*,*R*)-**L2**: 176 mg, 79% ee → 128 mg, 73% yield (27% yield overall), >99% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (40% i-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (S,S)-L2: 3.4 min (minor), 4.0 min (major).

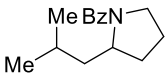
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.42 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 – 7.18 (m, 4H), 7.15 – 7.04 (m, 3H), 4.52 (d, *J* = 9.0 Hz, 1H), 4.45 – 4.24 (m, 2H), 4.10 (t, *J* = 6.6 Hz, 1H), 3.86 (s, 1H), 3.61 – 3.37 (m, 2H), 2.78 – 2.42 (m, 2H), 1.56 – 1.45 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 144.0, 141.4, 137.7, 129.5, 128.5, 127.7, 127.0, 126.5, 125.0, 120.0, 66.3, 62.6, 51.9, 47.4, 41.4, 30.8, 29.0.

FT-IR (film): 3316, 2933, 2360, 1686, 1534, 1250, 736 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}NO_3$: 402.2, found: 402.2.

$[\alpha]^{23}_D$ = +3.2 (*c* 1.0, $CHCl_3$); >99% ee, from (*S*,*S*)-**L2**.



(2-Isobutylpyrrolidin-1-yl)(phenyl)methanone. GP-10 was applied on a 0.60 mmol scale to (*tert*-butoxycarbonyl)-*L*-proline and **Zn-4** to generate the Boc-protected amine. Next, trifluoroacetic acid (9.0 mL) was added at 0 °C, and the mixture was stirred at room temperature. The consumption of the Boc-protected amine and the formation of the deprotected pyrrolidine were monitored via ^{1}H NMR spectroscopy, using 1,3,5-trimethoxybenzene as an internal standard.

Yield by NMR of coupling and Boc-deprotection:

(*S*,*S*)-**L2**: 69% yield; (*R*,*R*)-**L2**: 74% yield.

After the reaction had stirred at room temperature for 2 h, the mixture was basified using 10% aqueous NaOH. The organic layer was separated, and the aqueous phases were extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to ~10 mL under reduced pressure. To this solution was added triethylamine (502 µL, 3.60 mmol, 6.0 equiv) and benzoyl chloride (209 µL, 1.80 mmol,

3.0 equiv), and the reaction mixture was stirred at room temperature for 14 h. The mixture was then concentrated under reduced pressure and purified by column chromatography on silica gel (1:4 EtOAc/hexanes). The resulting light-yellow solid was extracted with hexanes to yield the product. Colorless oil.

(*S*,*S*)-**L2**: 87 mg, 62% yield, 89% ee; (*R*,*R*)-**L2**: 93 mg, 67% yield, 90% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 7.9 min (minor), 8.8 min (major).

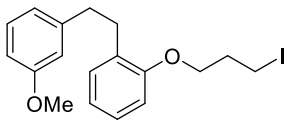
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.32 (m, 5H), 4.46 – 3.81 (m, 1H), 3.73 – 3.29 (m, 2H), 2.17 – 1.80 (m, 3H), 1.77 – 1.54 (m, 2H), 1.34 – 0.89 (m, 6H), 0.50 (dd, *J* = 104.9, 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 137.6, 129.8, 128.2, 127.4, 56.0, 49.9, 43.3, 30.7, 25.8, 25.2, 23.9, 22.0.

FT-IR (film): 2955, 2870, 1633, 1578, 1415, 1166, 703 cm^{-1}.

HRMS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{21}NNaO$: 254.1515, found: 254.1524.

$[\alpha]^{23}_D$ = +35.9 (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L2**.



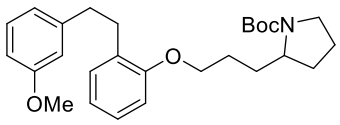
1-(3-Iodopropoxy)-2-(3-methoxyphenethyl)benzene. In the air, K_2CO_3 (2.3 g, 16.4 mmol, 1.5 equiv) was added to a solution of 2-(3-methoxyphenethyl)phenol (2.5 g, 11.0 mmol, 1.0 equiv) in DMF (30 mL) at room temperature, and the mixture was stirred at room temperature for 30 min. Next, 1,3-diiodopropane (6.3 mL, 54.8 mmol, 5.0 equiv) was added via syringe over 30 sec, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water, and the resulting mixture was extracted with DCM (30 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 (1:50 Et_2O/hexanes) to afford the product (2.4 g, 55% yield). Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 7.15 – 7.11 (m, 1H), 6.93 – 6.85 (m, 2H), 6.82 – 6.71 (m, 3H), 4.05 (t, *J* = 5.7 Hz, 2H), 3.79 (s, 3H), 3.40 (t, *J* = 6.7 Hz, 2H), 2.98 – 2.81 (m, 4H), 2.35 – 2.24 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.6, 144.1, 130.4, 130.2, 129.4, 127.4, 121.0, 120.8, 114.3, 111.3, 111.3, 67.2, 55.3, 36.6, 33.2, 32.7, 2.9.

FT-IR (film): 2922, 2590, 2351, 1600, 1468, 1239, 1165, 1044, 916, 747, 695 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{18}H_{22}IO_2$: 397.1, found: 397.0.



***tert*-Butyl 2-(3-(2-(3-methoxyphenethyl)phenoxy)propyl)pyrrolidine-1-carboxylate (76)**. The title compound was synthesized according to **GP-10** from (*tert*-butoxycarbonyl)-*L*-proline and **Zn-25** (**Zn-25** was prepared according to **GP-4**). The product was purified by column chromatography on silica gel (1:5 EtOAc/hexanes). Colorless oil.

(*S*,*S*)-**L2**: 135 mg, 51% yield, 88% ee; (*R*,*R*)-**L2**: 133 mg, 51% yield, 88% ee.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (20% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 5.0 min (minor), 6.0 min (major).

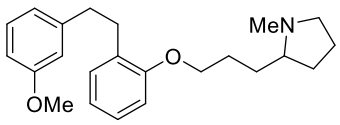
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.13 – 7.08 (m, 1H), 6.90 – 6.78 (m, 3H), 6.77 – 6.71 (m, 2H), 4.07 – 3.91 (m, 2H), 3.91 – 3.73 (m, 1H), 3.78 (s, 3H), 3.45 – 3.25 (m, 2H), 2.96 – 2.79 (m, 4H), 2.04 – 1.74 (m, 6H), 1.74 – 1.64 (m, 1H), 1.63 – 1.50 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.0, 154.8, 144.3, 130.3, 130.0, 129.3, 127.3, 121.0, 120.4, 114.4, 111.2, 111.1, 79.1, 67.9, 57.2, 55.2, 46.4, 36.5, 32.7, 31.7, 31.1, 28.7, 26.6, 23.5.

FT-IR (film): 3486, 2920, 2354, 1682, 1046, 964, 744, 700 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{37}NNaO_4$: 462.3, found: 462.2.

$[\alpha]^{23}_D$ = –30.1 (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L2**.



2-(3-(2-(3-Methoxyphenethyl)phenoxy)propyl)-1-methylpyrrolidine (77). In the air, $LiAlH_4$ (19.0 mg, 0.50 mmol, 5.0 equiv) was added to a solution of *tert*-butyl 2-(3-(2-(3-methoxyphenethyl)phenoxy)propyl)pyrrolidine-1-carboxylate (43.9 mg, 0.10 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C, and then the reaction mixture was heated at reflux for 24 h. The reaction was quenched with water (5.0 mL) at 0 °C, and the reaction mixture was then extracted with Et_2O (10 mL x 3). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product. Colorless oil.

(*S*,*S*)-**L2**: 35.7 mg, 99% yield; (*R*,*R*)-**L2**: 35.5 mg, 99% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 2H), 7.15 – 7.09 (m, 1H), 6.90 – 6.81 (m, 3H), 6.78 – 6.72 (m, 2H), 4.06 – 3.95 (m, 2H), 3.79 (s, 3H), 3.14 – 3.04 (m, 1H), 2.99 – 2.83 (m, 4H), 2.32 (s, 3H), 2.22 – 2.05 (m, 2H), 2.05 – 1.64 (m, 6H), 1.59 – 1.38 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 157.0, 144.3, 130.4, 130.0, 129.3, 127.3, 121.0, 120.3, 114.3, 111.13, 111.11, 68.0, 66.2, 57.4, 55.2, 40.5, 36.5, 32.8, 30.8, 30.3, 26.7, 21.9.

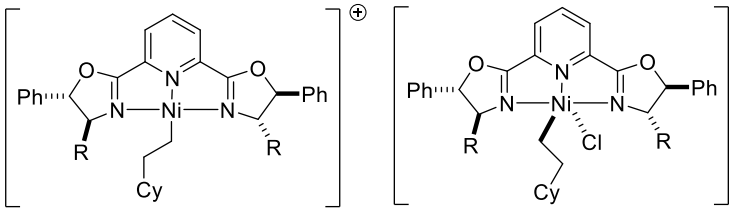
FT-IR (film): 2915, 2353, 1600, 1469, 1247, 1168, 1111, 1047, 874, 752, 695 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_2$: 354.2, found: 354.2.

$[\alpha]^{23}_D = -32.8$ (*c* 1.0, $CHCl_3$); 88% ee, from (*S*,*S*)-**L2**.

2.4.10. Mechanistic experiments

1. ESI-MS analysis using an alkyl chloride as the electrophile.



A^1 R = $CH_2OTBDPS$ **A^2** R = $CH_2OTBDPS$

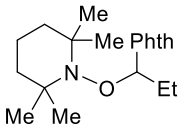
Procedure. In a nitrogen-filled glovebox, an oven-dried 4 mL vial that contained a stir bar was charged with $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and (*S*,*S*)-**L1** (10.9 mg, 0.012 mmol, 12 mol%). Next, THF (1.0 mL) was added, the vial was capped with a PTFE

septum cap, and the mixture was stirred at room temperature for 30 min, at which time it had turned to an orange, homogeneous solution. Then, a solution of 2-(1-chloropropyl)isoindoline-1,3-dione (22.3 mg, 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, **Zn-1** (0.11 mmol, 1.1 equiv) was added dropwise via microsyringe over 3 min, during which the reaction mixture turned dark. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 12 h. Then, an ESI-MS analysis of the reaction was carried out on a Waters LCT Premier XE TOF MS in electrospray ionization (ESI+) mode.

A¹: HRMS (ESI-MS) *m/z* $[M]^+$ calcd for $C_{65}H_{74}N_3NiO_4Si_2$: 1074.4566, found: 1074.4572.

A²: HRMS (ESI-MS) *m/z* $[M]^+$ calcd for $C_{65}H_{74}ClN_3NiO_4Si_2$: 1109.4254, found: 1109.4287.

2. TEMPO trap experiments using an alkyl chloride as the electrophile.



2-(1-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)propyl)isoindoline-1,3-dione. In a nitrogen-filled glovebox, an oven-dried 8 mL vial that contained a stir bar was charged with $NiBr_2$·glyme (6.2 mg, 0.020 mmol, 10 mol%) and (*S*,*S*)-**L1** (21.8 mg, 0.024 mmol, 12 mol%). Next, THF (2.0 mL) was added, the vial was capped with a PTFE septum cap, and the mixture was stirred at room temperature for 30 min, after which time it had turned to an orange, homogeneous solution. Then, a solution of 2-(1-chloropropyl)isoindoline-1,3-dione (44.6 mg, 0.20 mmol, 1.0 equiv) in THF (2.0 mL) was added to the reaction mixture, followed by the addition of TEMPO (31.2 mg, 0.20 mmol, 1.0 equiv). 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, **Zn-1** (0.22 mmol, 1.1 equiv) was added dropwise via microsyringe over 3 min,

during which the reaction mixture turned dark. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 36 h. The reaction was quenched at 0 °C by the addition of MeOH (0.1 mL). 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. 5.2 mg (0.015 mmol, 8% yield). White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.80 (m, 2H), 7.80 – 7.65 (m, 2H), 5.69 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.58 – 2.38 (m, 1H), 2.30 – 2.08 (m, 1H), 1.56 – 1.39 (m, 3H), 1.38 – 1.22 (m, 6H), 1.18 (s, 3H), 1.03 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 168.6, 134.1, 132.3, 131.7, 123.6, 123.5, 87.5, 61.1, 59.2, 40.26, 40.25, 33.5, 33.3, 23.8, 20.32, 20.26, 17.2, 10.1.

FT-IR (film): 3470, 2934, 2352, 1715, 1456, 1360, 1022, 725 cm^{-1}.

LC-MS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{20}H_{29}N_2O_3$: 345.2, found: 345.2.

3. Time-course experiments with an NHP ester as the coupling partner.

Enantioenriched 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenyl butanoate was synthesized from enantiopure 2-((*tert*-butoxycarbonyl)amino)-4-phenyl butanoic acid (both enantiomers are commercially available).

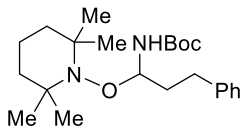
Procedure. In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar and charged with $NiBr_2$·glyme (1.5 mg, 0.0050 mmol, 5.0 mol%), (*S,S*)-**L2** (1.8 mg, 0.0060 mmol, 6.0 mol%), and LiCl (8.5 mg, 0.20 mmol, 2.0 equiv). Next, THF (0.4 mL) was added, the vial was capped with a PTFE septum cap, and the mixture was stirred at room temperature for 30 min, during which it became a light-green, homogeneous solution. DMAP (6.1 mg, 0.050 mmol, 0.50 equiv) was added as a stock solution in THF, resulting in a light-blue, homogeneous solution. The solution was then charged with a stock solution of *rac*, (*R*)-, or (*S*)-1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate (42.4 mg, 0.10 mmol, 1.0 equiv) in THF and a stock solution of TMSCl (8.7 mg, 0.080 mmol, 0.80 equiv) in THF, totaling 1.2 mL THF (including 0.4 mL from the catalyst solution). The vial was sealed with a septum cap and wrapped with electrical tape. Next, the vial was removed from the glovebox and cooled to 0 °C using an *i*-PrOH

cooling bath. After the white, heterogeneous reaction mixture had stirred at 0 °C for 10 min, **Zn-17** (0.12 mmol, 1.2 equiv) was added dropwise via microsyringe, resulting in a yellow, homogeneous solution. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C. After 4 h, the reaction was quenched at 0 °C by the addition of MeOH (0.1 mL). The resulting mixture was allowed to warm to room temperature, and then 1-indanone (2.6 mg, 0.020 mmol) was added as an internal standard for LC-MS analysis. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). A portion of the filtrate (0.1 mL) was diluted with acetone (total volume: 1 mL) and analyzed via LC-MS to determine the amount of product and remaining electrophile. Another portion of the filtrate (0.1 mL) was diluted with acetone (total volume: 1 mL) and analyzed via SFC analysis to determine the ee of the remaining electrophile. The remainder of the filtrate was concentrated under reduced pressure. The pure product was isolated by preparative TLC on silica gel (1:4 EtOAc/hexanes).

SFC analysis of the remaining NHP ester: The ee was determined via SFC on a CHIRALPAK IE column (25% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for (*R*)-enantiomer: 7.6 min, (*S*)-enantiomer: 9.3 min.

HPLC analysis of the product: The ee was determined via HPLC on a CHIRALPAK IC column (3% *i*-PrOH in hexane, 1.0 mL/min); retention times for compound obtained using (*S*,*S*)-**L2**: 9.1 min (minor), 12.1 min (major).

4. TEMPO trap experiments using an NHP ester as the coupling partner.



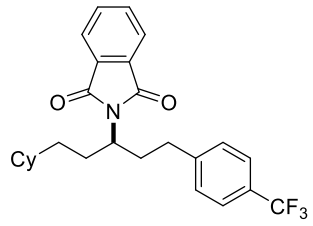
***tert*-Butyl (3-phenyl-1-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)carbamate.** In a nitrogen-filled glovebox, an oven-dried 20 mL vial that contained a cross-type stir bar was charged with $NiBr_2$·glyme (6.2 mg, 0.020 mmol, 5.0 mol%), (*S*,*S*)-**L2** (7.1 mg, 0.024 mmol, 6.0 mol%), and LiCl (33.9 mg, 0.80 mmol, 2.0 equiv). Next, THF (1.6 mL) was added, the vial was capped with a PTFE septum cap, and the mixture was stirred at room

temperature for 30 min, during which it became a light-green, homogeneous solution. Next, a solution of 1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate (170 mg, 0.40 mmol, 1.0 equiv) and DMAP (24.4 mg, 0.20 mmol, 0.50 equiv) in THF (3.2 mL) was added to the reaction mixture, followed by the addition of TMSCl (41μL, 0.32 mmol, 0.80 equiv) via microsyringe. Next, TEMPO (62.5 mg, 0.40 mmol, 1.0 equiv) was added. The vial was sealed with a septum cap and wrapped with electrical tape, and it was then removed from the glovebox and cooled to 0 °C using an *i*-PrOH cooling bath. After the red, slightly opaque mixture had stirred at 0 °C for 10 min, **Zn-17** (0.48 mmol, 1.2 equiv) was added dropwise via microsyringe over 5 min, resulting in a homogeneous, dark red solution. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 18 h. Next, the reaction was quenched at 0 °C by the addition of MeOH (0.2 mL). The resulting mixture was passed through a short pad of silica gel, with Et_2O as the eluent. A small aliquot was taken for HRMS analysis. Attempts to isolate the TEMPO adduct by chromatography were unsuccessful.

HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{23}H_{39}N_2O_3$: 391.2955, found: 391.3006.

2.4.11. Assignment of absolute configuration

The configuration of the coupling product illustrated in **Figure 2.3** (**6**) using (*R*,*R*)-**L1**, was determined via X-ray crystallography.



(*R*)-2-(1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)pentan-3-yl)isoindoline-1,3-dione (6). X-ray quality crystals were obtained by slow evaporation of a saturated solution in EtOAc/hexanes of a sample synthesized using (*R*,*R*)-**L1**. A crystal of $C_{26}H_{28}F_3NO_2$ 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-Kα radiation at a temperature of 100 K. Using Olex2,[60] the structure was solved with the XT[61] structure solution program using

direct methods and refined with the ShelXL[62] refinement package using least squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

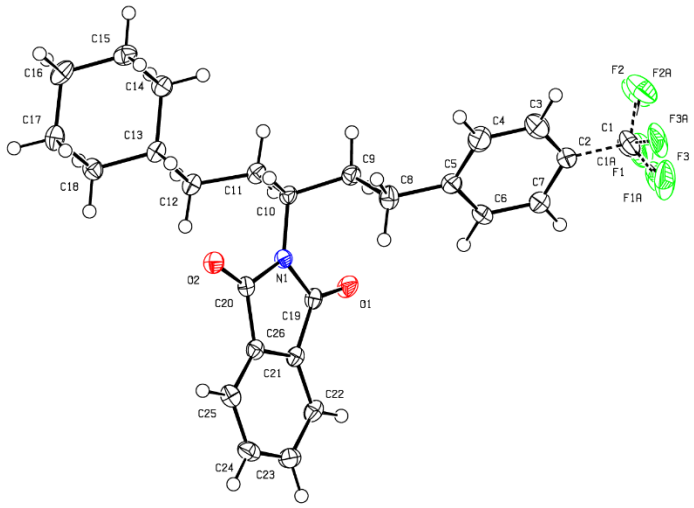
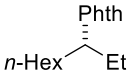


Table 2.7. *Crystal data for 6.*

Identification code	V20056	
Chemical formula	$C_{26}H_{28}F_3NO_2$	
Formula weight	443.49 g/mol	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal size	0.058 x 0.061 x 0.261 mm	
Crystal habit	clear colourless block	
Crystal system	orthorhombic	
Space group	*P* 2_1 2_1 2_1	
Unit cell dimensions	a = 5.3650(7) Å	α = 90°
	b = 10.7237(14) Å	β = 90°
	c = 38.480(5) Å	γ = 90°
Volume	2213.9(5) $Å^3$	
Z	4	
Density (calculated)	1.331 g/cm^3	
Absorption coefficient	0.837 mm^{-1}	
F(000)	936	
Theta range for data collection	4.28 to 69.64°	
Index ranges	-6<=h<=6, -12<=k<=12, -42<=l<=46	
Reflections collected	16610	
Independent reflections	3988 [R(int) = 0.0568]	
Coverage of independent reflections	97.8%	

Absorption correction	Multi-Scan	
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	3988 / 196 / 320	
Goodness-of-fit on F^2	1.073	
Final R indices	3783 data; I>2σ(I)	
	all data	R1 = 0.0462, wR2 = 0.0965
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0252P)^2+1.2048P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.03(9)	
Largest diff. peak and hole	0.213 and -0.258 eÅ^{-3}	
R.M.S. deviation from mean	0.042 eÅ^{-3}	

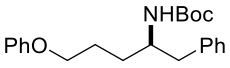


(*R*)-2-(Nonan-3-yl)isoindoline-1,3-dione (17). The absolute configuration of this compound has been established.[63] The coupling product obtained with (*S*,*S*)-**L1** has the (*R*)-configuration, by comparison with the sign of the published optical rotation.

Optical rotation: $[\alpha]^{22}_D = -6.1$ (*c* 1.0, $CHCl_3$); 89% ee, from (*S*,*S*)-**L1**.

Lit.: $[\alpha]^{26}_D = -17.2$ (*c* 1.0, $CHCl_3$); 99% ee for (*R*)-configuration.

The configuration of the coupling product illustrated in **Figure 2.7** (**41**) using (*R*,*R*)-**L1**, was determined via X-ray crystallography.



***tert*-Butyl (*R*)-(5-phenoxy-1-phenylpentan-2-yl)carbamate (41).** X-ray quality crystals were obtained by slow evaporation of a saturated solution in hexane/pentane of a sample synthesized using (*S*,*S*)-**L2**. A crystal of $C_{22}H_{29}NO_3$ 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-Kα radiation at a temperature of 100 K. Using Olex2,[60] the structure was solved with the XT[61] structure solution program using direct methods and

refined with the ShelXL[62] refinement package using least squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter.

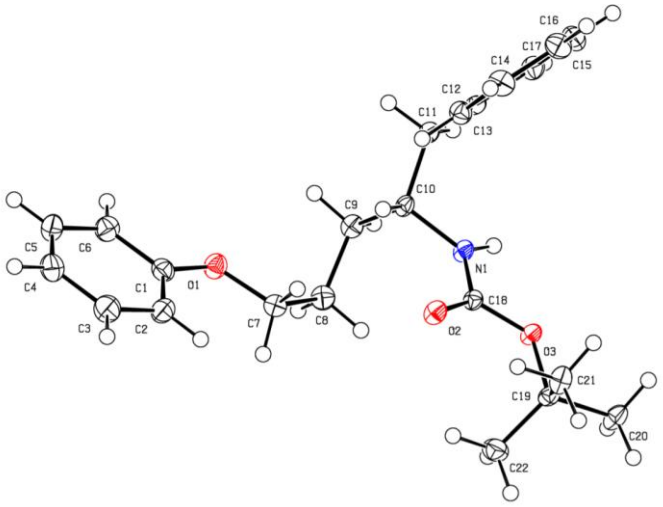
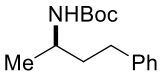


Table 2.8. *Crystal data for 41.*

Identification code	V20066	
Chemical formula	$C_{22}H_{29}NO_3$	
Formula weight	355.46 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.053 x 0.140 x 0.246 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 10.191(2) Å	α = 90°
	b = 9.3953(19) Å	β = 115.106(8)°
	c = 11.509(3) Å	γ = 90°
Volume	997.8(4) $Å^3$	
Z	2	
Density (calculated)	1.183 g/cm^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	384	
Theta range for data collection	2.92 to 28.29°	
Index ranges	-13<=h<=13, -12<=k<=12, -15<=l<=15	
Reflections collected	44841	
Independent reflections	4963 [R(int) = 0.0712]	
Coverage of independent reflections	99.8%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9960 and 0.9810	
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	4963 / 1 / 238	
Goodness-of-fit on F^2	1.082	
Final R indices	4598 data; $I>2\sigma(I)$	R1 = 0.0359, wR2 = 0.0789
	all data	R1 = 0.0411, wR2 = 0.0808
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0340P)^2+0.1542P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.1(3)	
Largest diff. peak and hole	0.192 and -0.202 eÅ^{-3}	
R.M.S. deviation from mean	0.036 eÅ^{-3}	



***tert*-Butyl (*R*)-(4-phenylbutan-2-yl)carbamate (50)**. The absolute configuration of this compound has been established.[57] The coupling product obtained with (*S*,*S*)-**L2** has the (*R*)-configuration, by comparison with published optical rotation.

Optical rotation: $[\alpha]^{23}_D$ = +10.6 (c 1.0, $CHCl_3$); 81% ee, from (*S*,*S*)-**L2**.

Lit.: $[\alpha]^{25}_D$ = +13.9 (c 0.9, $CHCl_3$); 96% ee for (*R*)-configuration.

2.5. Notes and references

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