The Synthesis of Diverse Families of Organic Compounds via Nickel-Catalyzed Nucleophilic Substitution Reactions

Thesis by

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ACKNOWLEDGMENTS

Graduate school has been an incredible and dynamic experience. One constant, however, has been the help and support that I have relied on and received from others, who contributed not only to the body of work leading to my Ph.D., but also to my training as a scientist and development as a person. Writing this dissertation has been a reminder that I couldn't have achieved anything on my own, and I feel a tremendous sense of appreciation for not having to attempt to do so. Unexpectedly, as I begin writing this final section of my thesis, I also find myself feeling a remarkable sense of *community*. Although many individuals have had lasting impacts on me, I feel genuinely lucky to have been part of so many wonderful communities that propped me up and paved the way for me to get to where I am.

My desire to attend graduate school stemmed from the communities of scientists who stimulated my interest in learning and served as role models for me. When I was in high school, I couldn't have asked for better teachers than Lori Blake and Mike Dannenhauer, whose classes made science cool and exciting to me. They saw potential in me that I did not see in myself, and they encouraged me to challenge myself by joining after-school biology/chemistry leagues and participating in science-based summer programs. The supportive environment that they and the other science faculty fostered enabled me to enthusiastically embrace being a geek and initiated my irreversible journey to studying chemistry.

The next community I had the opportunity to be part of was the chemistry department at Williams College, home to some of the most extraordinary and eccentric professors. I must thank Dave Richardson; it's not often that a professor walks into the first organic chemistry class of the semester wearing a robe and throwing frisbees, plastic water bottles, and other items at his students. It was hilarious and, more significantly, showed me that organic chemistry is worth getting excited about. Dave was like a father to me throughout college, and his encouragement provided me with my own self-confidence and determination. I'm also grateful to Lee Park for giving me the opportunity to work in her lab as my first hands-on research experience. Lee became a dear mentor and source of support for me, frequently lifting my spirits, giving me good, practical advice, and steering me to success. As graduation approached, I had the pleasure to join Chris Goh's lab to carry out my senior thesis research. Chris was a tremendous mentor who taught me much about being a good scientist, and his enthusiasm for transition metal chemistry was contagious. I'm also deeply indebted to Matt Carter, a professor in the biology department who designed the most fantastic, engaging, and impactful classes I've ever taken. I cannot emphasize enough how

influential Matt has been to my interest in teaching. I've thought of him long after leaving Williams and will continue to do so throughout my career as an example of the kind of professor I want to be. My community at Williams included many friends who were with me since the beginning as well; thank you so much to Hector Trujillo, Carly Schissel, Ronak Dave, Dan Gheesling, and Zach Sawyer for your friendship and our countless memories.

The community I currently see on a daily basis is my thesis lab, the group of Greg Fu. First and foremost, I must thank Greg for many reasons. He enthusiastically welcomed me into his research group and prioritized my education above anything else. I appreciated that he never made me feel stupid; instead, he validated my opinions as if I were a trusted colleague and viewed mistakes as important and necessary learning moments. Greg likes to play the devil's advocate and push back during meetings... as much as our group jokes about it, it really has made evaluating my views and considering other perspectives a routine habit in my research and general thinking. I look forward to adopting this pedagogical style in the future (and hopefully making my students as frustrated as it made me at times!). Working for an advisor like Greg, who genuinely cares about me and my goals, has been invaluable to my experience at Caltech. I'll look back fondly on those "quick check-ins" in his office that would always turn into much longer conversations about our lives and families. It's often said that you inevitably adopt traits from your advisor as you progress in your career, and I would be thrilled to take a facet of Greg and share that with the next generation of scientists.

Many of my warmest memories and most enriching experiences in graduate school came from the interactions I had within the Fu Lab. Joe Ahn was one of the greatest friends and mentors I could've asked for. He taught me many of the skills necessary to succeed in graduate school: various lab techniques, ways to use ChemDraw more efficiently, knowing which weekly seminars have pizza... within the Fu Group family, Joe was my older brother, and I am grateful for the confidence he gave me when I needed it. Zepeng Yang has also been a tremendous help. He taught me much about chemistry and the manuscript writing process, and ultimately became a close friend. As tedious as our Zoom meetings to discuss paper edits were at the time, I look back on these memories with an unexpected smile. I must also thank Caiyou Chen, a colleague and friend who has been with me for most of my time in the lab. Caiyou's consistent work ethic made him a role model for me, and his passion for chemistry never failed to fuel my own motivation.

I instantly felt at home in the Fu Lab thanks to its wonderful, collaborative community of students and postdocs. Each step of the way, I knew I could count on anyone's help or advice. When you are feeling low, they pick you up, encourage you, and remind you that you are still a gifted scientist even when your experiments consist of failures. And when you are feeling high,

they bring you back to earth, remind you that you are human, and depend on you to help them with their struggles as well. What an amazing, supportive culture we have fostered in the group. Special thanks to Hidehiro Suematsu, Bobbi Neff, Carson Matier, Felix Schneck, Robert Anderson, Haohua Huo, Jonas Schwaben, Zhichao Cao, Asik Hossain, Zhaobin Wang, Wendy Zhang, Yusuke Masuda, and William Kayitare for the great memories and continued friendship.

When I first visited Caltech, I was excited to become part of the collaborative and supportive community of students, faculty, and staff that exists in the chemistry department. Looking back, I owe much to my thesis committee of Sarah Reisman, Theodor Agapie, and Brian Stoltz for supporting my goals, providing valuable feedback, and guiding me to success through the years. I also thank Alison Ross for being a great "mom" throughout my time here, always answering my questions with a big smile. The community we have in Schlinger wouldn't be complete without Julianne Just, who is always just a knock on the door away and excited to help out. A huge thanks as well to friends at Caltech who were me since day one: Caitlin Lacker, Skyler Mendoza, and Nick Fastuca.

A community that I did not anticipate would become so integral to my time as a graduate student was that of Ruddock House. I decided to become an RA to provide support and be a positive influence on the undergraduates at Caltech, but I didn't expect to receive the same thing in return. My students embraced me with open arms and treated me like I was a trusted friend. Thanks to them, walking through the doors of Ruddock after a long day in the lab felt like I was truly returning to my home. That's not to say that they weren't a handful... yet, despite the difficult conversations about mental health late into the night, the frequent knocks on my door from my students asking to participate in their pranks, and the countless times I was hit in the head by pieces of bread thrown during dinner, I wouldn't trade these memories with my Ruddock family for anything in the world.

The last community I have to thank is my family. My grandmother, Jean Johnston, helped me move to Caltech and left her door open for me whenever I wanted to spend a weekend off campus. My brother, Don Freas, has been a constant source of support and laughter for me. His sense of humor and creativity will always serve as an inspiration for me, and he always encourages me to head for the horizon and leave my fears behind. I hope I have been as good a brother to him as he has been to me. I couldn't be where I am without my mom and my hero, Donna Freas. She has encouraged me in everything I ever wanted to do, and it's a blessing to have someone like her who would be willing to drop everything at a moment's notice if I ever needed anything. Her devotion to me and my three brothers as a single mother continuously inspires me to live a more courageous and selfless lifestyle, and my desire to make her proud has empowered me to overcome the challenges I faced in graduate school.

Finally, I would like to thank my fiancé, Irene Lim. Irene's loving support has been invaluable, especially during points in my graduate career at which I felt most unsuccessful. I cannot thank her enough for the countless sacrifices she has made for me during these busy years; she proofread my presentations and proposals, spent time talking on the phone late at night even when we both had worked long hours and were ready for bed, and woke up at 4 AM to cheer me on for my first half marathon. I've had so much fun experiencing southern California together, and having Irene by my side throughout my graduate (and undergraduate!) studies has been nothing short of an absolute honor. As I type the final words of this dissertation, I feel an immense sense of catharsis, as well as enthusiasm for the future. Above all else, though, I am excited beyond measure for our wedding, transitioning to the next chapter of our lives together, and all of the hugs and laughs we'll share along the way.

ABSTRACT

Transition metal-catalyzed cross-coupling has provided an exceptionally powerful approach to carbon–carbon bond formation, allowing chemists to solve a number of important problems in organic synthesis. However, by the early 2000s, its application to the formation of alkyl–alkyl bonds had been limited by the slow oxidative addition of palladium catalysts toward alkyl halides and the tendency of transition-metal-alkyls to undergo β-hydride elimination. Since then, complexes based on nickel, an earth-abundant metal, have emerged as efficient catalysts for the nucleophilic substitution of alkyl electrophiles. The propensity for nickel to access a range of oxidation states allows it to react via one-electron pathways to generate radical intermediates, opening the door to couplings of sterically-hindered electrophiles and offering a ready mechanism for enantioconvergence.

Our group has applied nickel catalysts to substitution reactions of activated and unactivated 2^o and 3^o alkyl electrophiles by carbon– as well as by heteroatom-based nucleophiles, including a number of enantioconvergent processes. However, given the enormous range of conceivable coupling partners, many interesting challenges have yet to be addressed. The application of nickel-catalyzed substitution reactions to the synthesis of diverse families of compounds, particularly those with frequent uses in organic synthesis and pharmaceutical science, is described in this thesis. While reaction development is the primary focus of this work, a variety of synthetic applications and mechanistic investigations are also detailed within.

Chapter 2 describes two methods for the catalytic enantioconvergent synthesis of amines, which involve the coupling of an alkylzinc reagent with a racemic electrophile (specifically, an α-phthalimido alkyl chloride and an *N*-hydroxyphthalimide ester of a protected α-amino acid). A one-pot variant of this transformation is possible, enabling the efficient enantioselective synthesis of a range of interesting target molecules. Several mechanistic insights are also detailed.

Chapter 3 outlines the nickel-catalyzed alkylation of racemic α-haloglycine derivatives, a class of electrophile previously unemployed in metal-catalyzed asymmetric cross-coupling reactions, with alkylzinc reagents to generate protected unnatural α-amino acids. This method is applied to the generation of several enantioenriched unnatural α-amino acids that have previously been shown to serve as useful intermediates in the synthesis of bioactive compounds.

Chapter 4 details the development of a nickel-catalyzed cross-coupling for the asymmetric synthesis of protected thiols. The synthesis of an *N*-hydroxyphthalimide ester containing a geminal thioester (a previously unreported class of molecule with no applications to cross-coupling) is

described, along with its reactivity toward alkylzinc reagents and other classes of organometallic nucleophiles.

Chapter 5 examines the ability of nickel to catalyze the nucleophilic fluorination of unactivated alkyl halides, a transformation whose application to the synthesis of alkyl fluorides has been impeded by the low nucleophilicity and high basicity of fluoride. The reactivities of unactivated 1^{o}, 2^{o}, and 3^{o} alkyl bromides, as well as several preliminary mechanistic investigations, are presented.

PUBLISHED CONTENT AND CONTRIBUTIONS

This dissertation contains materials adapted with permission from the following publications.

1. Yang, Z.-P.‡; Freas, D. J.‡; Fu, G. C. The Asymmetric Synthesis of Amines via Nickel-Catalyzed Enantioconvergent Substitution Reactions. *J. Am. Chem. Soc.* **2021**, *143*, 2930–2937. doi: 10.1021/jacs.0c13034.

   D.J.F. participated in the conception of the project, designed the research, carried out all experiments related to couplings of NHP esters of α-amino acids, and participated in the writing of the manuscript. ‡Authors contributed equally to this work.

2. Yang, Z.-P.‡; Freas, D. J.‡; Fu, G. C. Asymmetric Synthesis of Protected Unnatural α-Amino Acids via Enantioconvergent Nickel-Catalyzed Cross-Coupling. *J. Am. Chem. Soc.* **2021**, *143*, 8614–8618. doi: 10.1021/jacs.1c03903.

   D.J.F. contributed to reaction development, studies of the substrate scope, and synthetic applications of the method, along with participating in the writing of the manuscript. ‡Authors contributed equally to this work.

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LIST OF ABBREVIATIONS

^{1}H	proton
^{13}C	carbon-13
^{18}F	fluorine-18
^{19}F	fluorine-19
^{29}Si	silicon-29
18-c-6	1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6)
2-MeTHF	2-methyltetrahydrofuran
[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
ACAT	acyl-coenzyme A:cholesterol acyltransferase
Alloc	allyloxycarbonyl
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration
^{o}C	degrees Celsius
calcd	calculated
cat.	catalyst
Cbz	benzyloxycarbonyl
cf.	consult or compare to (Latin: confer)
cm^{-1}	wavenumber(s)
Cy	cyclohexyl
d	doublet
DCE	dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIC	*N*,*N'*-diisopropylcarbodiimide
diglyme	bis(2-methoxyethyl)ether
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
e.g.	for example (Latin: exempli gratia)
EPR	electron paramagnetic resonance

eq	equation
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
FT-IR	Fourier-transform infrared spectroscopy
g	gram(s)
GC	gas chromatography
glyme	1,2-dimethoxyethane
h	hour(s)
n-Hex	hexyl or *norm*-hexyl
HPLC	high performance liquid chromatography
HR	high resolution
Hz	hertz
i.e.	that is (Latin: id est)
J	coupling constant
L	liter or ligand
LCMS	liquid chromatography mass spectrometry
m	multiplet or meter(s)
m	meta
M	molar, molecular ion, or metal
μ	micro
Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
m/*z*	mass-to-charge ratio
n	generic number
NHP	*N*-hydroxyphthalimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
n-Pent	pentyl or *norm*-pentyl
PET	positron emission tomography
Ph	phenyl
Phth	phthalimide
Piv	pivalate
ppm	parts per million
i-Pr	*iso*-propyl
n-Pr	propyl or *norm*-propyl

PTFE	polytetrafluoroethylene
pybox	pyridine-2,6-bis(oxazoline)
q	quartet
R	alkyl group
rac	racemic
ref	reference
rpm	revolutions per minute
r.t.	room temperature
s	singlet or second(s)
SET	single electron transfer
SFC	supercritical fluid chromatography
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	time or triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Ts	*para*-toluenesulfonyl (tosyl)
W	watt
X	halide, leaving group, or anionic ligand

Chapter 1

INTRODUCTION

1.1. Transition metal-catalyzed nucleophilic substitution reactions

With regard to retrosynthetic analysis, the nucleophilic substitution of an alkyl electrophile is a straightforward and efficient strategy in organic synthesis. However, classical methods like the S_N1 and S_N2 reactions have considerable limitations (**Figure 1.1**). The S_N1 reaction proceeds through the formation of a carbocationic intermediate, typically limiting the scope to tertiary and activated (e.g., benzylic or allylic) electrophiles. The scope of suitable nucleophiles is often limited by the requirement of a Brønsted or Lewis acid to facilitate dissociation of the leaving group. Finally, capture of the carbocation by the nucleophile often competes with side reactions, such as elimination to form an olefin and hydride / alkyl rearrangements (**Figure 1.1a**). The S_N2 reaction has similar limitations. It is sensitive to steric demands on the nucleophile and electrophile, rendering the method inapplicable to tertiary, many secondary, and hindered primary (e.g., neopentyl) electrophiles. Elimination also competes with substitution in the S_N2 reaction, as it is usually carried out under Brønsted-basic conditions (**Figure 1.1b**).[1]

Classical nucleophilic substitution reactions also suffer from their difficulty in controlling the stereochemistry at the carbon undergoing substitution. Formation of an

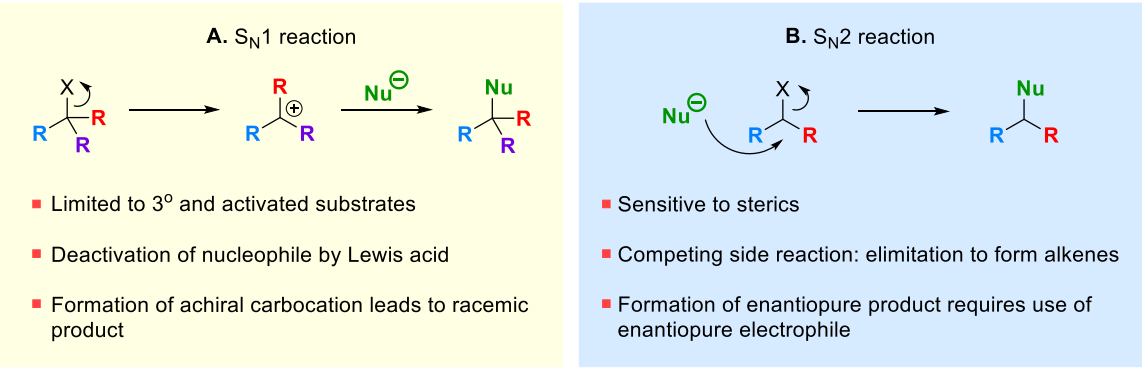


Figure 1.1. *Limitations of classical nucleophilic substitution reactions (S_N1 and S_N2).*

achiral carbocation typically leads to racemic product in the S_N1 reaction,[2] and in the case of the S_N2 reaction, the inversion of stereochemistry at the carbon center undergoing substitution means that the use of an enantioenriched electrophile is necessary for the formation of enantioenriched product. Due to these limitations, expanding the scope of nucleophilic substitution reactions, while simultaneously controlling the stereoselectivity of these processes, is a significant and ongoing goal in organic chemistry.

Transition metal-catalyzed cross-coupling has provided an exceptionally powerful approach to carbon-carbon bond formation, allowing chemists to solve a number of important problems in organic synthesis.[3] Early studies of such processes mainly involved the use of palladium catalysts to generate a bond between two sp^2-hybridized carbons, a synthetic tool that has found application in industry and was awarded the Nobel Prize in Chemistry in 2010. These processes involve the oxidative addition of an organic electrophile to a Pd(0) complex to generate an organopalladium(II) complex, transmetalation by the nucleophilic coupling partner, and reductive elimination to form the carbon–carbon bond and regenerate the Pd(0) complex (**Figure 1.2**).[4]

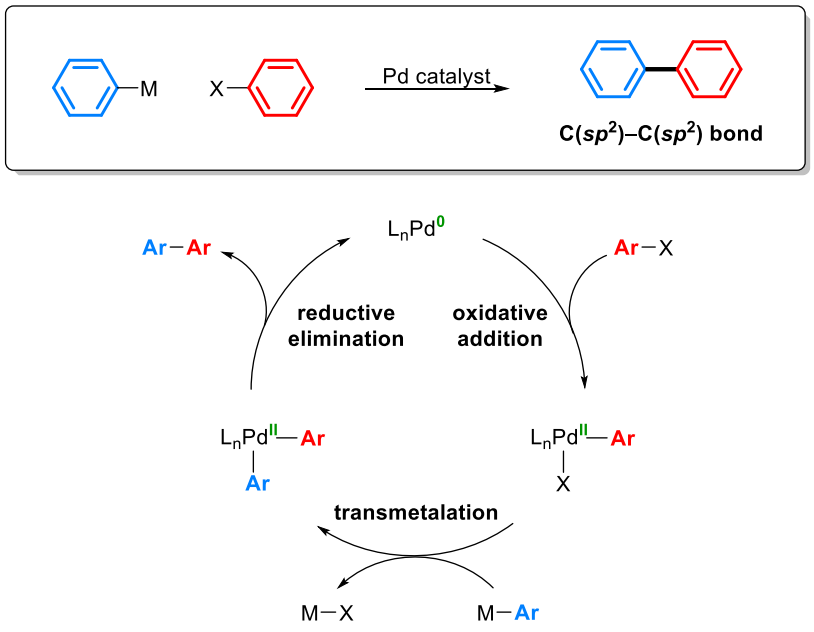
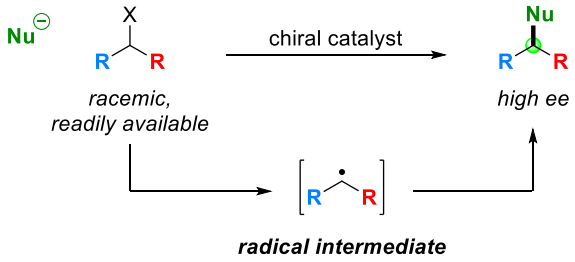


Figure 1.2. *Palladium-catalyzed cross-coupling of sp^2-hybridized substrates.*

While methods to form carbon–carbon bonds between sp^2-hybridized carbons have proven to be remarkably useful tools in organic synthesis, the carbon skeletons of most organic molecules largely consist of bonds between sp^3-hybridized carbons ("alkyl–alkyl" bonds). Thus, the development of catalysts capable of generating such bonds could open the door to highly efficient syntheses of a broad array of organic molecules. However, in the early 2000s, alkyl electrophiles were considered to be difficult substrates in transition metal-catalyzed nucleophilic substitution reactions,[5] mainly due to the relatively slow oxidative addition of transition metals toward alkyl halides (especially unactivated 2° and 3° halides) and to the propensity of transition-metal-alkyls to undergo β-hydride elimination.[6]

The net oxidative addition of alkyl halides to transition metals can occur through alternative pathways that do not require direct insertion of the metal into the C–X bond. A two-step oxidative addition is possible, wherein halogen atom abstraction by the transition metal affords an alkyl radical that is subsequently captured by the metal.[1,7,8] Because this process generates the same metal-alkyl intermediate that would be formed via two-electron oxidative addition, it is possible for metal-catalyzed substitutions of alkyl electrophiles to occur through a pathway analogous to the catalytic cycle illustrated in **Figure 1.2**. This strategy also provides a mechanism for enantioconvergence, as both enantiomers of a racemic alkyl halide are converted to an achiral radical intermediate, which can then converge to one stereoisomer of product through the use of a chiral catalyst (**eq 1.1**).[9]



(1.1)

1.2. Enantioconvergent couplings of alkyl electrophiles catalyzed by nickel

Our group's efforts to apply palladium-based catalysts to alkyl–alkyl couplings led to the finding that these substitution reactions likely proceed through an S_N2, rather than a radical, pathway for oxidative addition, limiting the scope to 1° alkyl halides.[10] We then began to explore the use of catalysts based on nickel, an earth-abundant metal, to expand the scope of metal-catalyzed cross-coupling reactions to more sterically hindered electrophiles. Compared to palladium, nickel can more readily access a range of oxidation states, giving it a greater propensity to react via a radical pathway.[11] Since 2003, the Fu Lab has employed nickel complexes to catalyze couplings between organometallic nucleophiles and 2° and 3° alkyl electrophiles, including a number of enantioconvergent processes.[1,12] These reactions are believed to proceed via halide abstraction by a nickel(I) complex **A** to generate nickel(II) complex **B** and an alkyl radical (**Figure 1.3**). Transmetalation of **B** with the organometallic nucleophile yields nickel(II)–alkyl species **C**, which captures the alkyl radical to form nickel(III) complex **D**. Reductive elimination from **D** yields the product and regenerates the active catalyst.[13,14]

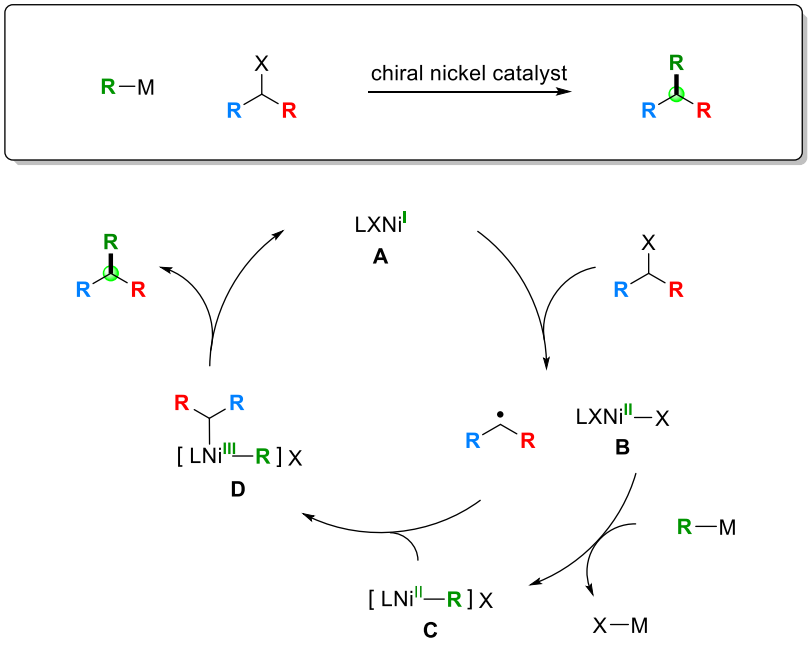


Figure 1.3. *Nickel-catalyzed enantioconvergent coupling of an alkyl electrophile via a radical pathway.*

We have conducted enantioconvergent substitution reactions of a number of activated and unactivated alkyl electrophiles (top of **Figure 1.4**). In the case of unactivated electrophiles, differentiation between two alkyl groups by the catalyst is possible, although a suitably positioned directing group is usually necessary to obtain good enantioselectivity. Given the versatile reactivity and broad functional group tolerance of these processes, along with the enormous range of conceivable coupling partners, our lab has sought to apply new classes of racemic electrophiles to enantioconvergent, nickel-catalyzed substitution reactions in order to access useful families of compounds that are otherwise difficult to synthesize. Specifically, this thesis will detail our investigations in the asymmetric synthesis of amines (*Chapter 2*), unnatural *α*-amino acids (*Chapter 3*), and thiols (*Chapter 4*) (bottom of **Figure 1.4**).

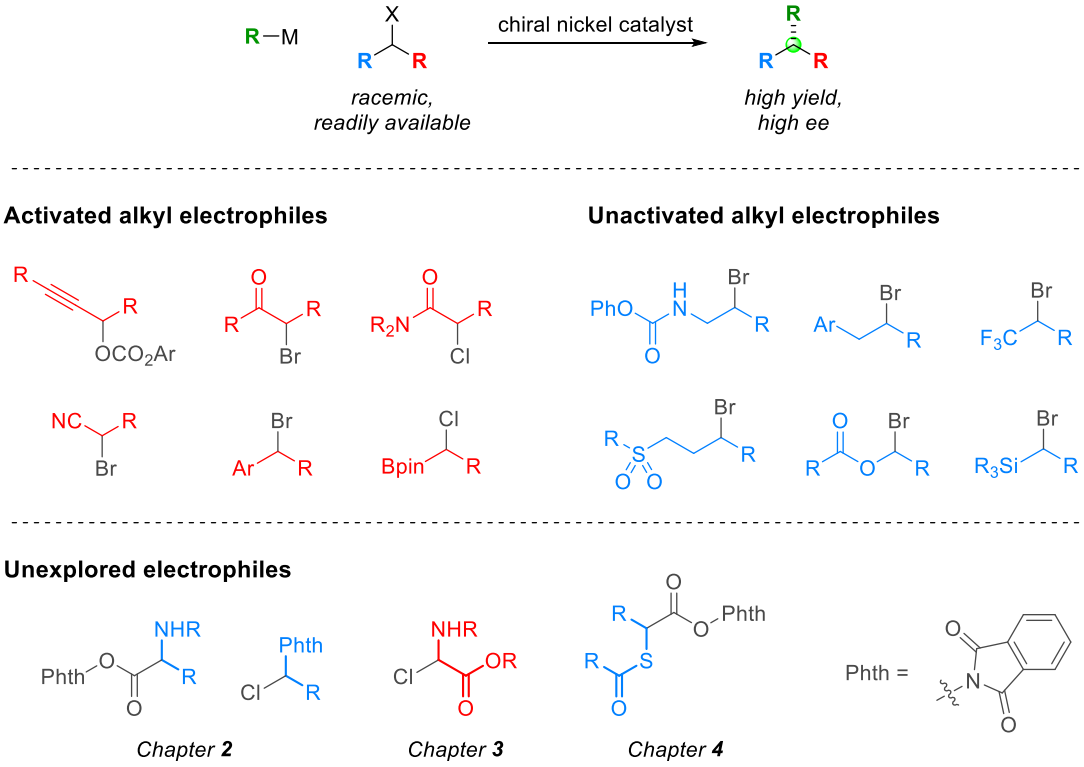


Figure 1.4. *Nickel-catalyzed enantioconvergent couplings. Top: examples of activated and unactivated alkyl electrophiles employed previously by our lab. Bottom: unexplored electrophiles that are discussed in this thesis.*

While our efforts have primarily focused on carbon-based nucleophiles, nickel can serve as an effective catalyst for substitution reactions of other classes of nucleophiles as well. We have demonstrated that nickel can catalyze couplings of alkyl electrophiles with boron[15,16] and silicon[17] nucleophiles to access organoboron and organosilicon compounds (**Figure 1.5**). Successfully applying this approach to the formation of C–N, C–O, C–S, and C–F bonds would allow us to readily access other important families of molecules. While our preliminary attempts to apply nickel-based catalysts to couplings by nitrogen, oxygen, and sulfur nucleophiles have been unsuccessful, we have recently discovered that nickel can catalyze the nucleophilic fluorination of unactivated alkyl halides (*Chapter 5*).

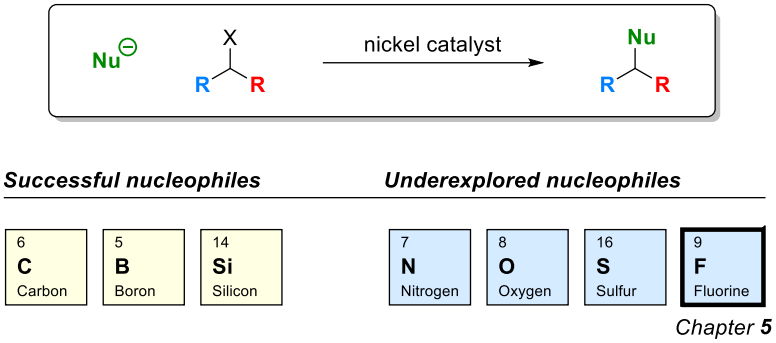
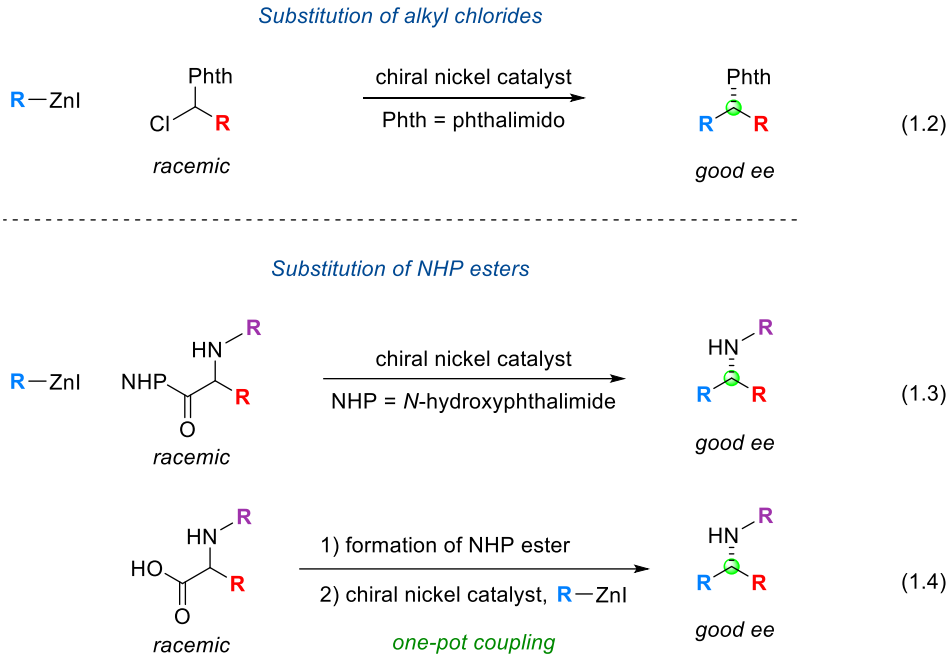


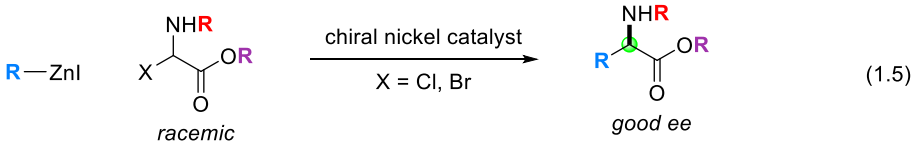
Figure 1.5. *Couplings of alkyl electrophiles catalyzed by nickel: successful and underexplored nucleophiles.*

1.3. Overview of individual chapters

This thesis provides an overview of our efforts to apply nickel-catalyzed nucleophilic substitution reactions to the synthesis of diverse families of organic compounds. In **Chapter 2**, we describe two methods for the catalytic enantioconvergent synthesis of amines, which involve the coupling of an alkylzinc reagent with a racemic partner (specifically, an α-phthalimido alkyl chloride and an *N*-hydroxyphthalimide (NHP) ester of a protected α-amino acid) (**eqs 1.2** and **1.3**). For couplings of NHP esters, we further describe a one-pot variant wherein the NHP ester is generated *in situ*, allowing the generation of enantioenriched amines in one step from commercially-available amino acid derivatives (**eq 1.4**); we demonstrate the utility of this one-pot method by applying it to the efficient catalytic enantioselective synthesis of a range of interesting target molecules.

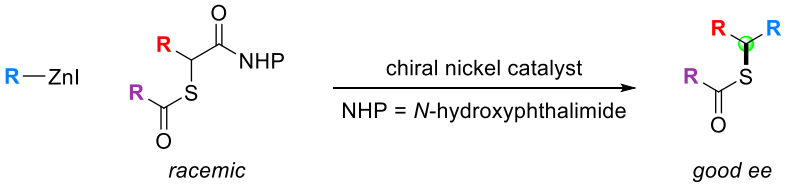


We continued our investigations of racemic electrophiles containing a nitrogen atom geminal to the bond-forming center. In **Chapter 3**, we report the nickel-catalyzed alkylation of racemic α-haloglycine derivatives (a class of electrophile previously unemployed in metal-catalyzed asymmetric cross-coupling reactions) with alkylzinc reagents to generate protected unnatural α-amino acids (**eq 1.5**). This approach is remarkably efficient and facile; the reaction is run under mild conditions, is complete within 30 min, and is tolerant to air and moisture. We apply our method to the generation of several enantioenriched unnatural α-amino acids that have previously been shown to serve as useful intermediates in the synthesis of bioactive compounds.



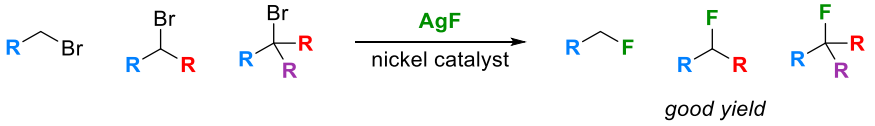
While our group's preliminary attempts to apply sulfur-based nucleophiles to nickel-catalyzed cross-coupling have been unsuccessful, we have remained interested in the synthesis of enantioenriched thiols, which are important synthetic building blocks and frequent constituents of pharmaceuticals. We reasoned that incorporating a sulfur atom into a racemic electrophile and carrying out C–C bond formation would circumvent issues that

could arise during C–S reductive elimination, and we viewed requiring the catalyst to differentiate between an alkyl group and a sulfur substituent as a promising strategy to achieve good enantioselectivity. We detail our approach to target enantioenriched protected thiols in **Chapter 4**. Specifically, we develop a synthesis of NHP esters containing a geminal thioester (a new class of cross-coupling electrophile with no previously reported syntheses) and demonstrate that these NHP esters react with alkylzinc reagents in the presence of a nickel catalyst to form enantioenriched aliphatic thioesters in good ee (**eq 1.6**). We also examine the couplings of other classes of nucleophiles, including alkenyl- and alkynylzinc reagents.



(1.6)

Our lab has been intrigued by the possibility of applying nickel catalysts to couplings of heteroatom nucleophiles. Our investigations of asymmetric nucleophilic fluorinations of racemic alkyl halides revealed that unactivated 1°, 2°, and 3° alkyl halides readily undergo substitution with silver fluoride in high yield when a nickel catalyst is present (**eq 1.7**). In **Chapter 5**, we disclose the surprising discovery of this transformation and explore the effect of electrophile substitution on reactivity. Our method offers a remarkably mild and straightforward approach to nucleophilic fluorination, whose application to unactivated alkyl fluoride synthesis has been impeded by the low nucleophilicity and high basicity of fluoride.



(1.7)

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Chapter 2

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

Adapted in part with permission from:

Yang, Z.-P.;‡ Freas, D. J.;‡ Fu, G. C. The Asymmetric Synthesis of Amines via Nickel-Catalyzed Enantioconvergent Substitution Reactions. *J. Am. Chem. Soc.* **2021**, *143*, 2930–2937. DOI: 10.1021/jacs.0c13034

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

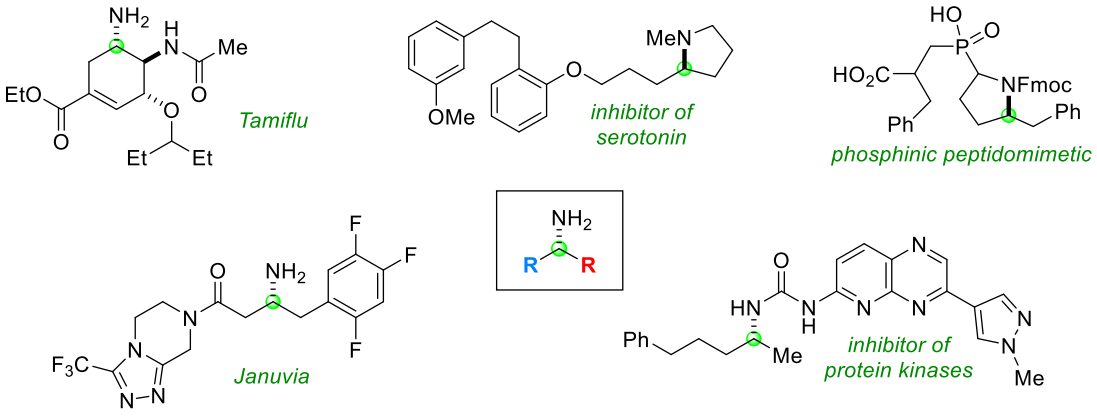


Figure 2.1. *Examples of compounds that include a chiral dialkyl carbinamine subunit.*

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

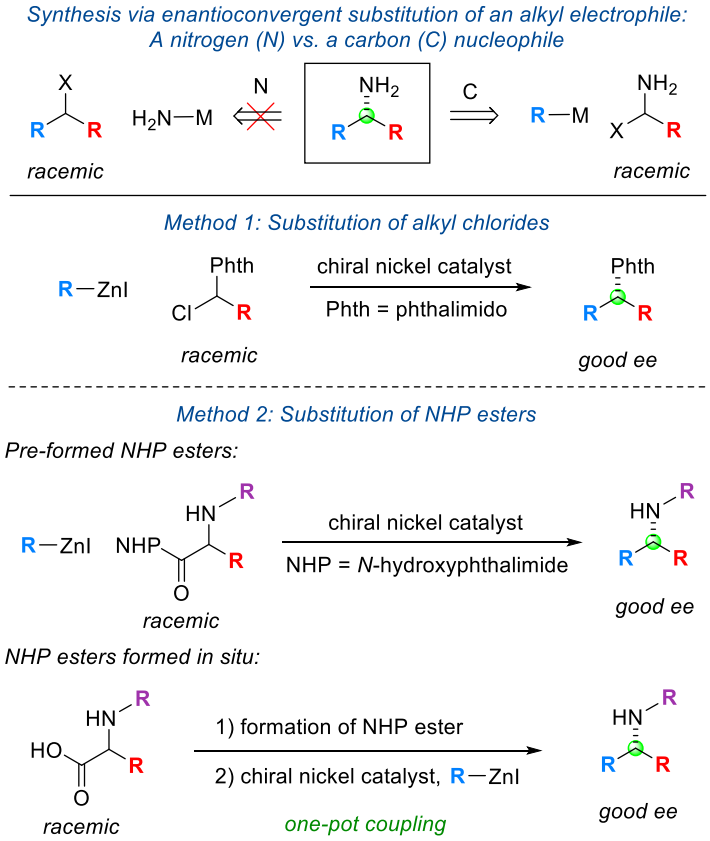
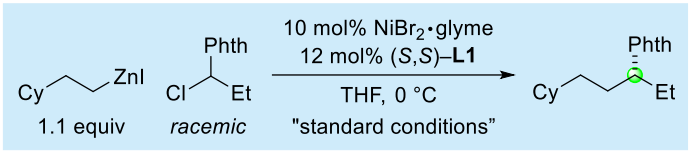
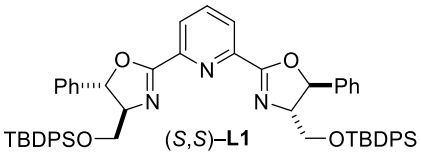


Figure 2.2. *This study: Nickel-catalyzed enantioconvergent substitution reactions of alkyl electrophiles to generate protected dialkyl carbinamines.*

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

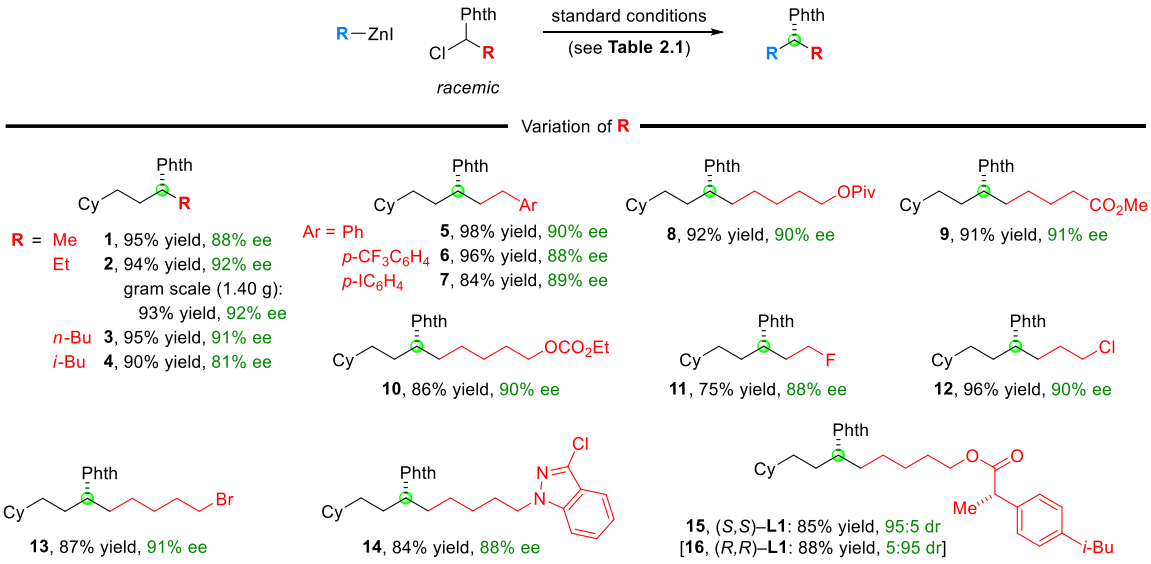


Figure 2.3. *Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines: electrophile scope. All data are the average of two experiments run on a 0.6-mmol scale (unless otherwise noted), and all yields are of purified products.*

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

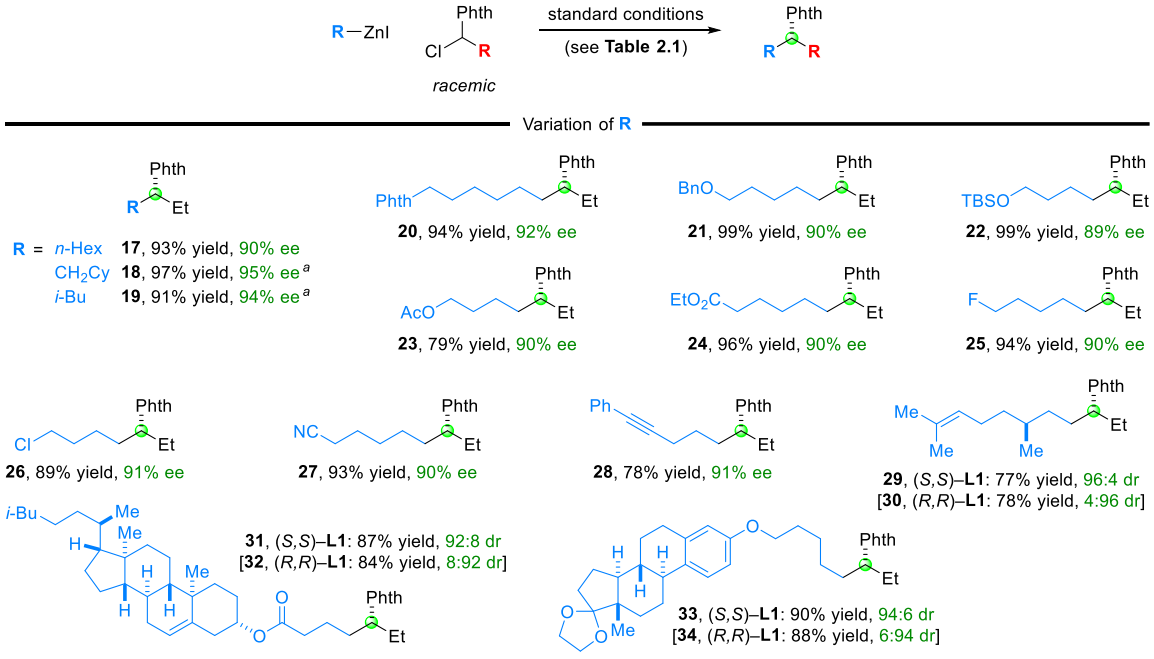


Figure 2.4. *Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines: nucleophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *The reaction was conducted at r.t.*

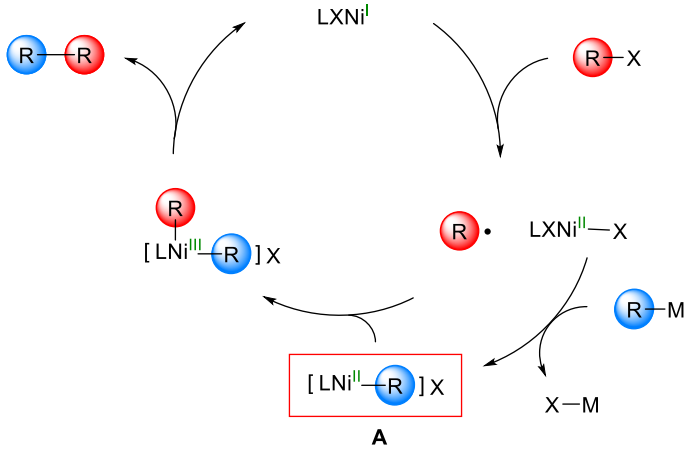


Figure 2.5. *Outline of a possible pathway.*

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.

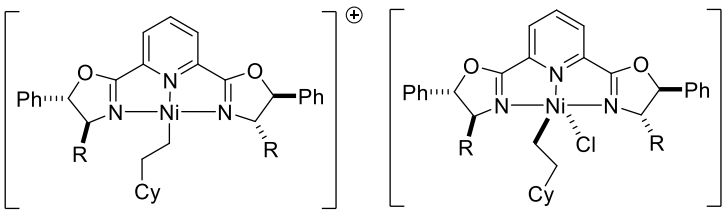
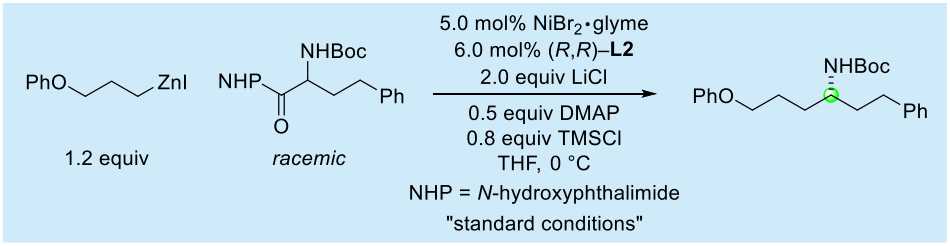


Figure 2.6. *ESI–MS data for the coupling illustrated in Table 5.1.*

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

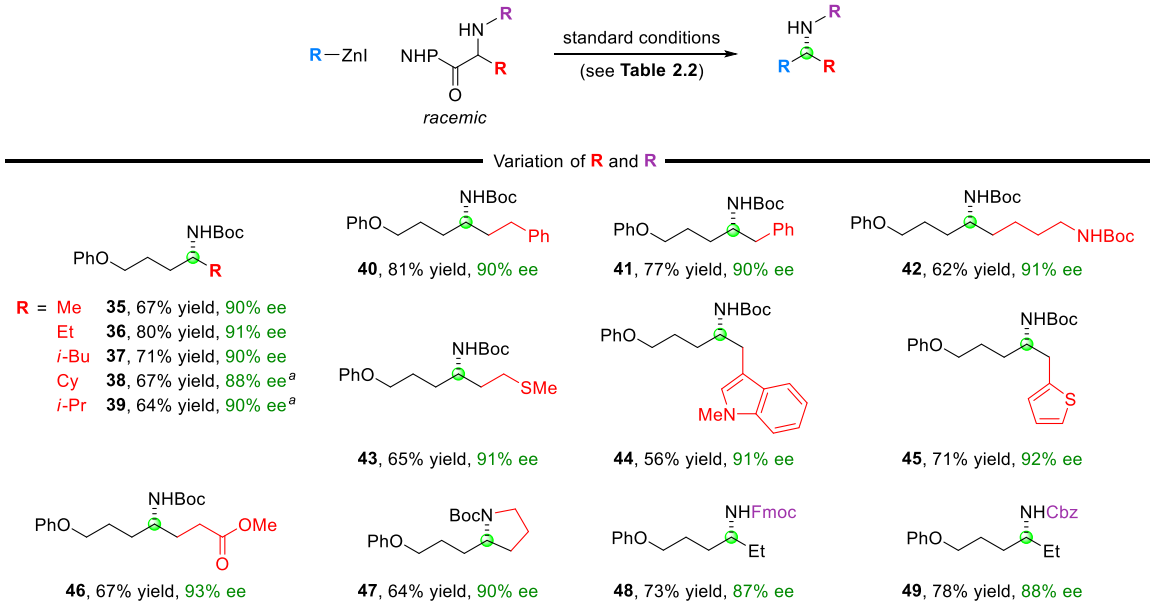


Figure 2.7. *Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters: electrophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *10 mol% $NiBr_2$·glyme, 12 mol%* ***L2****, and 5.0 equiv LiCl were 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**–

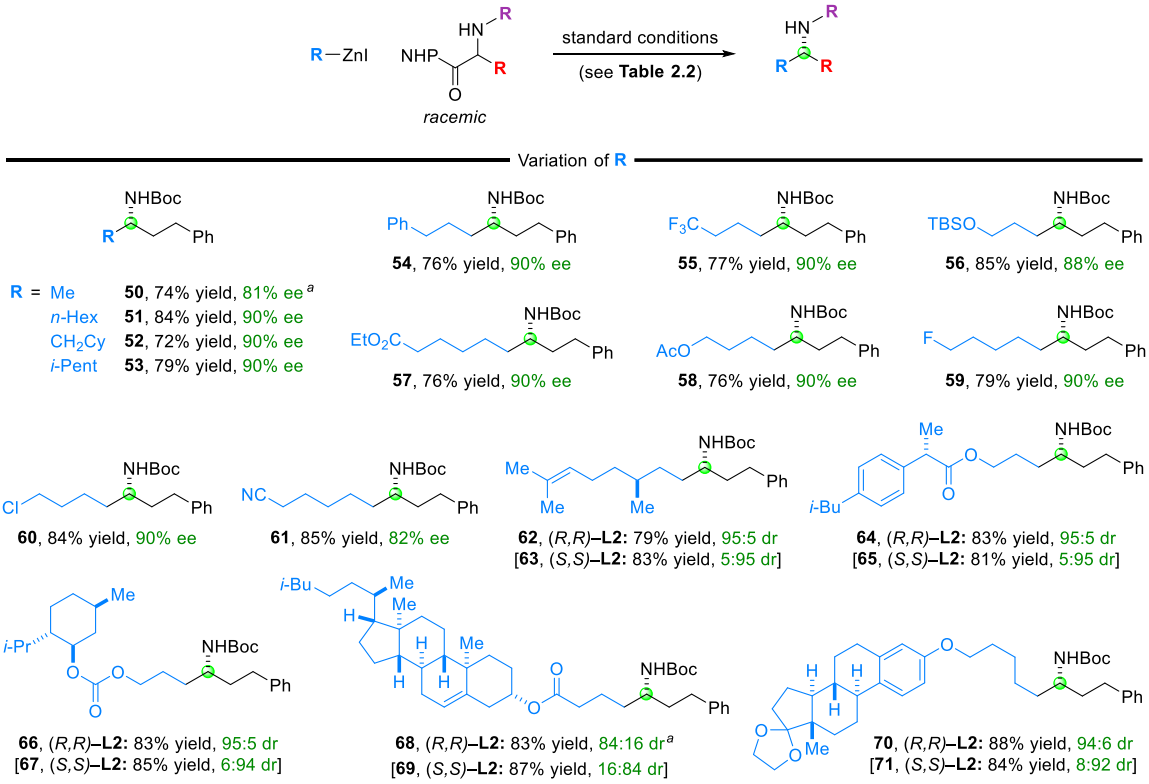


Figure 2.8. *Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters: nucleophile scope. All data are the average of two experiments run on a 0.6-mmol scale, and all yields are of purified products.* [a] *The product was recrystallized to >99% ee or >99.5:0.5 d.r.*

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]

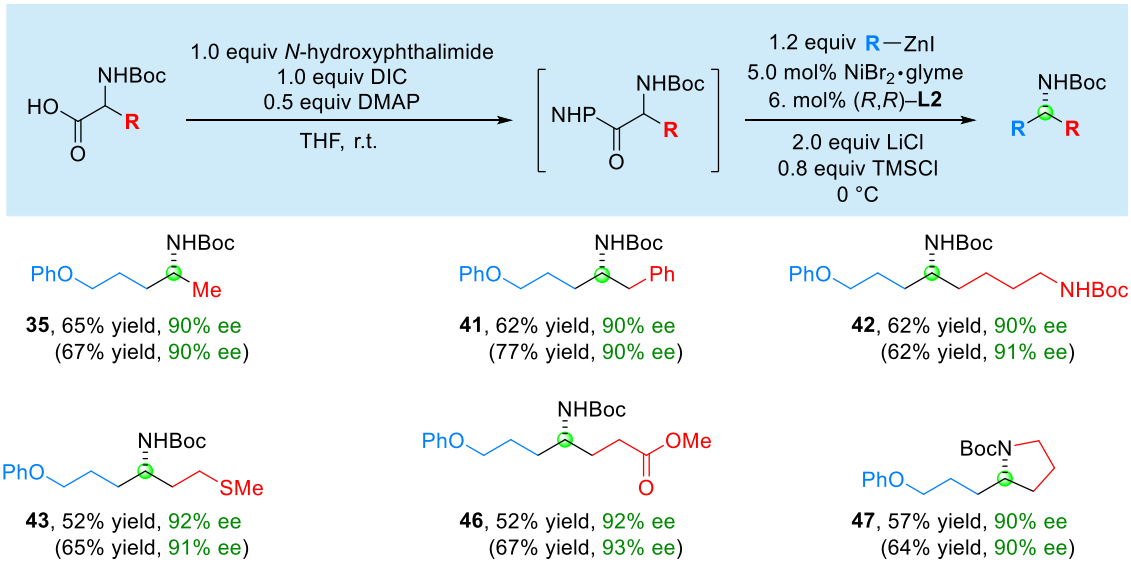


Figure 2.9. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: one-pot procedure. The values in parentheses are the data for the corresponding couplings of purified NHP esters.*

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

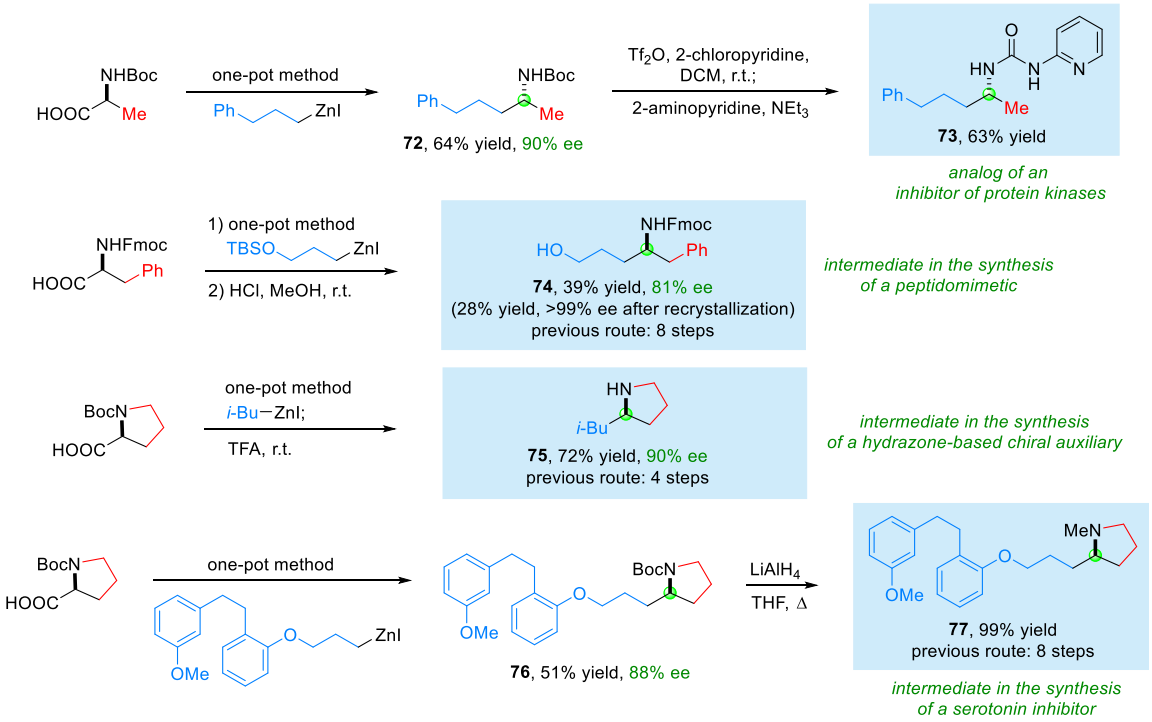


Figure 2.10. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: applications.*

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).

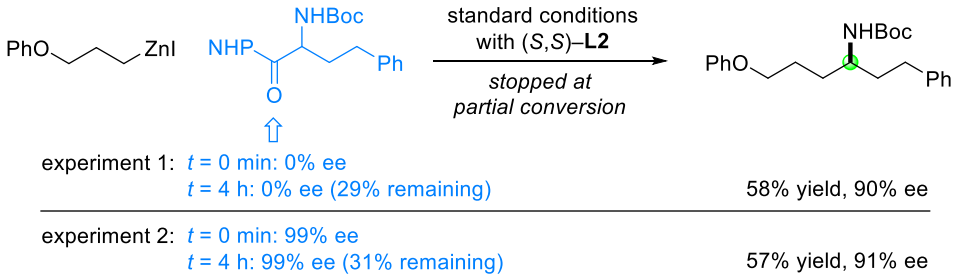


Figure 2.11. *Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters: study of kinetic resolution.*

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.

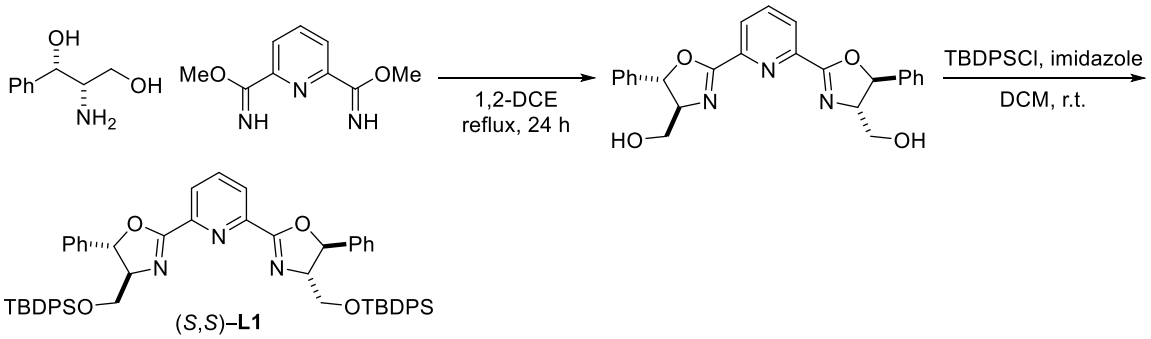
2.4. Experimental section

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.

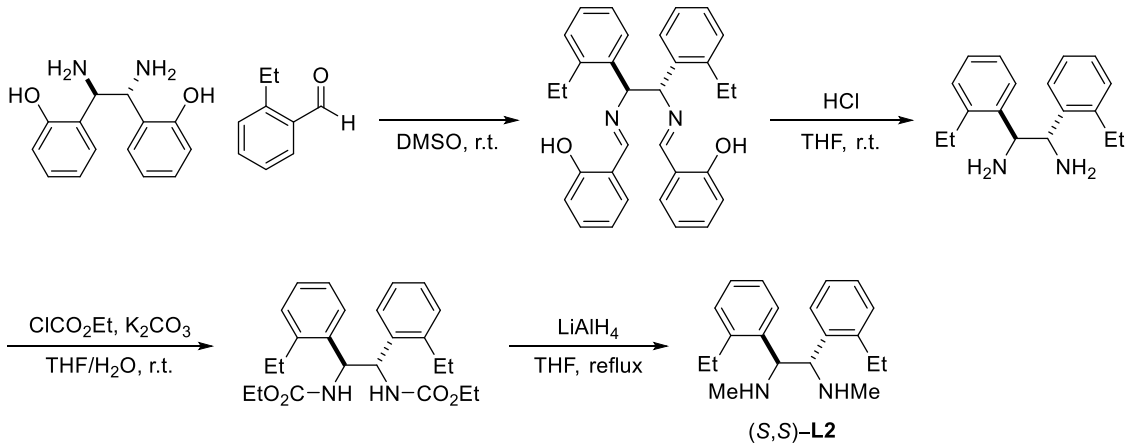
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 2H), 7.89 (t, *J* = 7.9 Hz, 1H), 7.73 – 7.57 (m, 8H), 7.47 – 7.26 (m, 22H), 5.74 (d, *J* = 6.7 Hz, 2H), 4.50 – 4.37 (m, 2H), 4.13 – 4.04 (m, 2H), 3.93 – 3.76 (m, 2H), 1.05 (s, 18H).

^{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.

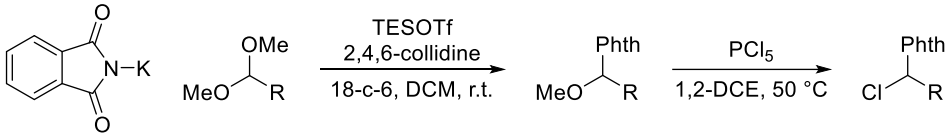
FT-IR (film): 3230, 2967, 2786, 1489, 1106, 874, 764, 741 cm^{-1}.

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.

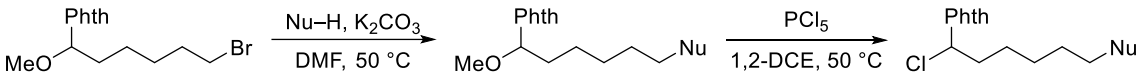


General Procedure 1 (GP-1).

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.

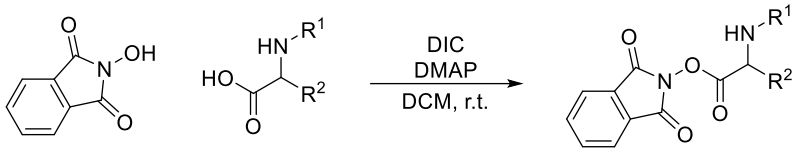
Chlorination of *N*,*O*-acetals. PCl_5 (1.5 equiv) was added to a solution of the *N*,*O*-acetal (1.0 M in 1,2-DCE; 1.0 equiv) at room temperature. The reaction mixture was stirred at 50 °C overnight, and then the reaction was quenched with water. The organic layer was washed with saturated aqueous $NaHCO_3$ (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).

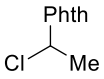
Preparation of *N*,*O*-acetals. K_2CO_3 (1.3 equiv) and the nucleophile (1.3 equiv) were added to solution of 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (0.50 M in DMF; 1.0 equiv; synthesized according to the first step of **GP-1**). The reaction mixture was stirred at 50 °C overnight. Then, the 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.

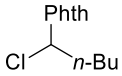
2-(1-Chloropropyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxypropane (3.12 g, 30.0 mmol). The product was purified by recrystallization. 4.48 g (20.1 mmol, 67% yield over 2 steps). White solid.

^{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.



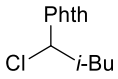
2-(1-Chloropentyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxypentane (2.35 g, 17.8 mmol). The product was purified by recrystallization. 2.60 g (10.4 mmol, 58% yield over 2 steps). White solid.

^{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.



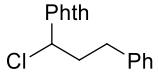
2-(1-Chloro-3-methylbutyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1,1-dimethoxy-3-methylbutane (2.64 g, 20.0 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:3 EtOAc/hexanes). 2.52 g (10.0 mmol, 50% yield over 2 steps). Colorless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



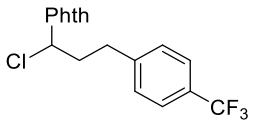
2-(1-Chloro-3-phenylpropyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from (3,3-dimethoxypropyl)benzene (3.60 g, 20.0 mmol). The product was purified by recrystallization. 4.10 g (13.7 mmol, 69% yield over 2 steps). White solid.

^{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.

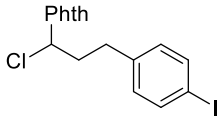
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.80 – 7.71 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.06 (t, *J* = 7.3 Hz, 1H), 3.03 – 2.81 (m, 3H), 2.82 – 2.69 (m, 1H).

^{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.



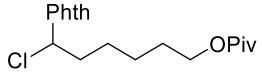
2-(1-Chloro-3-(4-iodophenyl)propyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 1-(3,3-dimethoxypropyl)-4-iodobenzene (4.08 g, 13.3 mmol). The product was purified by recrystallization. 3.4 g (8.0 mmol, 60% yield over 2 steps). White solid.

^{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.



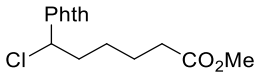
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl pivalate. The title compound was synthesized according to **GP-1** from methyl 6,6-dimethoxyhexyl pivalate (4.10 g, 16.7 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:4 EtOAc/hexanes). 2.1 g (5.8 mmol, 34% yield over 2 steps).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



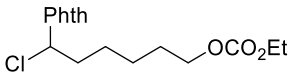
Methyl 6-chloro-6-(1,3-dioxoisoindolin-2-yl)hexanoate. The title compound was synthesized according to **GP-1** from methyl 6,6-dimethoxyhexanoate (3.60 g, 18.9 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:4 EtOAc/hexanes). 1.4 g (4.5 mmol, 24% yield over 2 steps). Colorless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



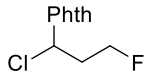
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl ethyl carbonate. The title compound was synthesized according to **GP-1** from 6,6-dimethoxyhexyl ethyl carbonate (4.68 g, 20.0 mmol). The product was purified by column chromatography on acidic Al_2O_3 (1:3 EtOAc/hexanes). 2.63 g (7.45 mmol, 37% yield over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

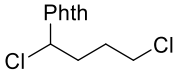
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 2H), 7.86 – 7.72 (m, 2H), 6.32 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.80 – 4.44 (m, 2H), 3.11 – 2.75 (m, 2H).

^{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.



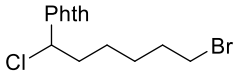
2-(1,4-Dichlorobutyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 4-chloro-1,1-dimethoxybutane (3.04 g, 20.0 mmol). The product was purified by recrystallization. 2.66 g (9.82 mmol, 49% yield over 2 steps). White solid.

^{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.



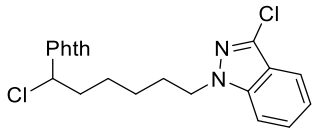
2-(6-Bromo-1-chlorohexyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-1** from 6-bromo-1,1-dimethoxyhexane (4.48 g, 20.0 mmol). The product was purified by recrystallization. 2.5 g (7.3 mmol, 36% yield over 2 steps). White solid.

^{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.



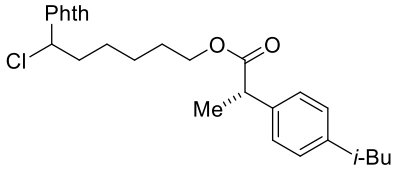
2-(1-Chloro-6-(3-chloro-1*H*-indazol-1-yl)hexyl)isoindoline-1,3-dione. The title compound was synthesized according to **GP-2** from 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (2.37 g, 6.99 mmol) and 3-chloro-1*H*-indazole (1.39 g, 9.14 mmol). The product was purified by recrystallization. 1.7 g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



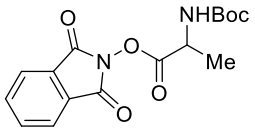
6-Chloro-6-(1,3-dioxoisoindolin-2-yl)hexyl (2*S*)-2-(4-isobutylphenyl)propanoate. The title compound was synthesized according to **GP-2** from 2-(6-bromo-1-methoxyhexyl)isoindoline-1,3-dione (2.37 g, 6.99 mmol) and (*S*)-2-(4-isobutylphenyl)propanoic acid (1.87 g, 9.08 mmol). The product was purified 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.



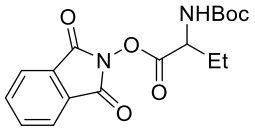
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)alaninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)alanine (1.91 g, 10.1 mmol). 1.28 g (3.83 mmol, 38% yield). White solid.

^{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.



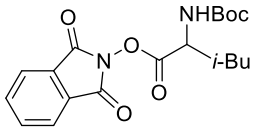
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)butanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl) amino)butanoic acid (5.00 g, 24.6 mmol). 1.76 g (5.06 mmol, 21% yield). White solid.

^{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.



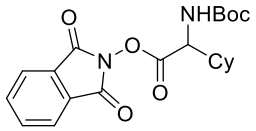
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)leucinate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)leucine (5.00 g, 21.6 mmol). 5.63 g (15.0 mmol, 69% yield). White solid.

^{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.



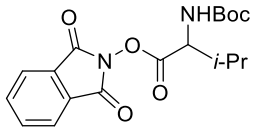
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-2-cyclohexylacetate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-2-cyclohexylacetic acid (6.00 g, 23.3 mmol). 6.78 g (16.8 mmol, 72% yield). White solid.

^{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.



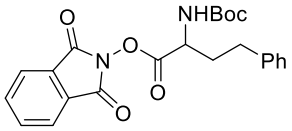
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)valinate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)valine (4.50 g, 20.7 mmol). 2.79 g (7.71 mmol, 37% yield). White solid.

^{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.



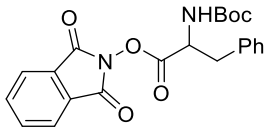
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoic acid (3.00 g, 10.7 mmol). 3.08 g (7.26 mmol, 68% yield). White solid.

^{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.



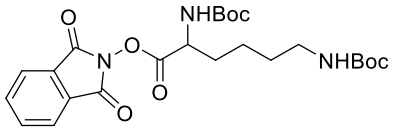
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)phenylalaninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)phenylalanine (4.50 g, 17.0 mmol). 3.59 g (8.76 mmol, 52% yield). White solid.

^{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.



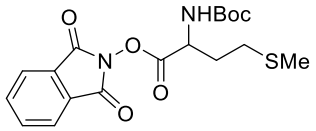
1,3-Dioxoisoindolin-2-yl N^2,N^6-bis(*tert*-butoxycarbonyl)lysinate. The title compound was synthesized according to **GP-3** from N^2,N^6-bis(*tert*-butoxycarbonyl)lysine (5.49 g, 15.9 mmol). 1.07 g (2.18 mmol, 14% yield). White solid.

^{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.



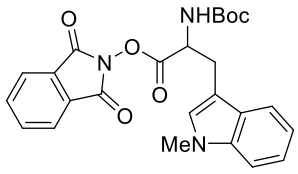
1,3-Dioxoisoindolin-2-yl (*tert*-butoxycarbonyl)methioninate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)methionine (5.35 g, 21.5 mmol). 4.87 g (12.4 mmol, 58% yield). White solid.

^{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.



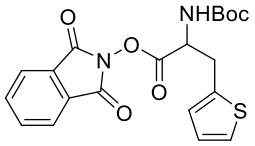
1,3-Dioxoisoindolin-2-yl N^{α}-(*tert*-butoxycarbonyl)-1-methyltryptophanate. The title compound was synthesized according to **GP-3** from N^{α}-(*tert*-butoxycarbonyl)-1-methyltryptophan (2.2 g, 6.9 mmol). 1.2 g (2.5 mmol, 37% yield). White solid.

^{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.



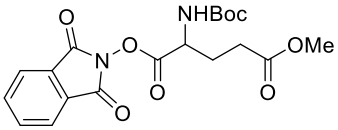
1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoic acid (4.00 g, 14.7 mmol). 3.28 g (7.88 mmol, 54% yield). Light-yellow solid.

^{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.



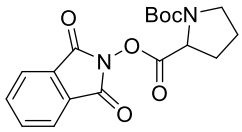
1-(1,3-Dioxoisoindolin-2-yl) 5-methyl (*tert*-butoxycarbonyl)glutamate. The title compound was synthesized according to **GP-3** from 2-((*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (0.68 g, 2.6 mmol). 0.53 g (1.3 mmol, 51% yield). White solid.

^{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.



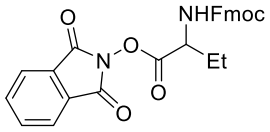
1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate. The title compound was synthesized according to **GP-3** from (*tert*-butoxycarbonyl)proline (3.00 g, 13.9 mmol). 1.41 g (3.92 mmol, 28% yield). White solid.

^{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.



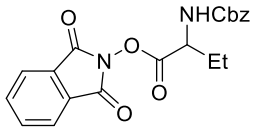
1,3-Dioxoisoindolin-2-yl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)butanoate. The title compound was synthesized according to **GP-3** from 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)butanoic acid (5.00 g, 15.4 mmol). 4.60 g (9.79 mmol, 64% yield). White solid.

^{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).

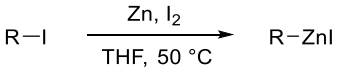
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 155.7, 136.1, 135.0, 128.9, 128.7, 128.4, 128.3, 124.2, 67.5, 53.5, 26.4, 9.3.

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.

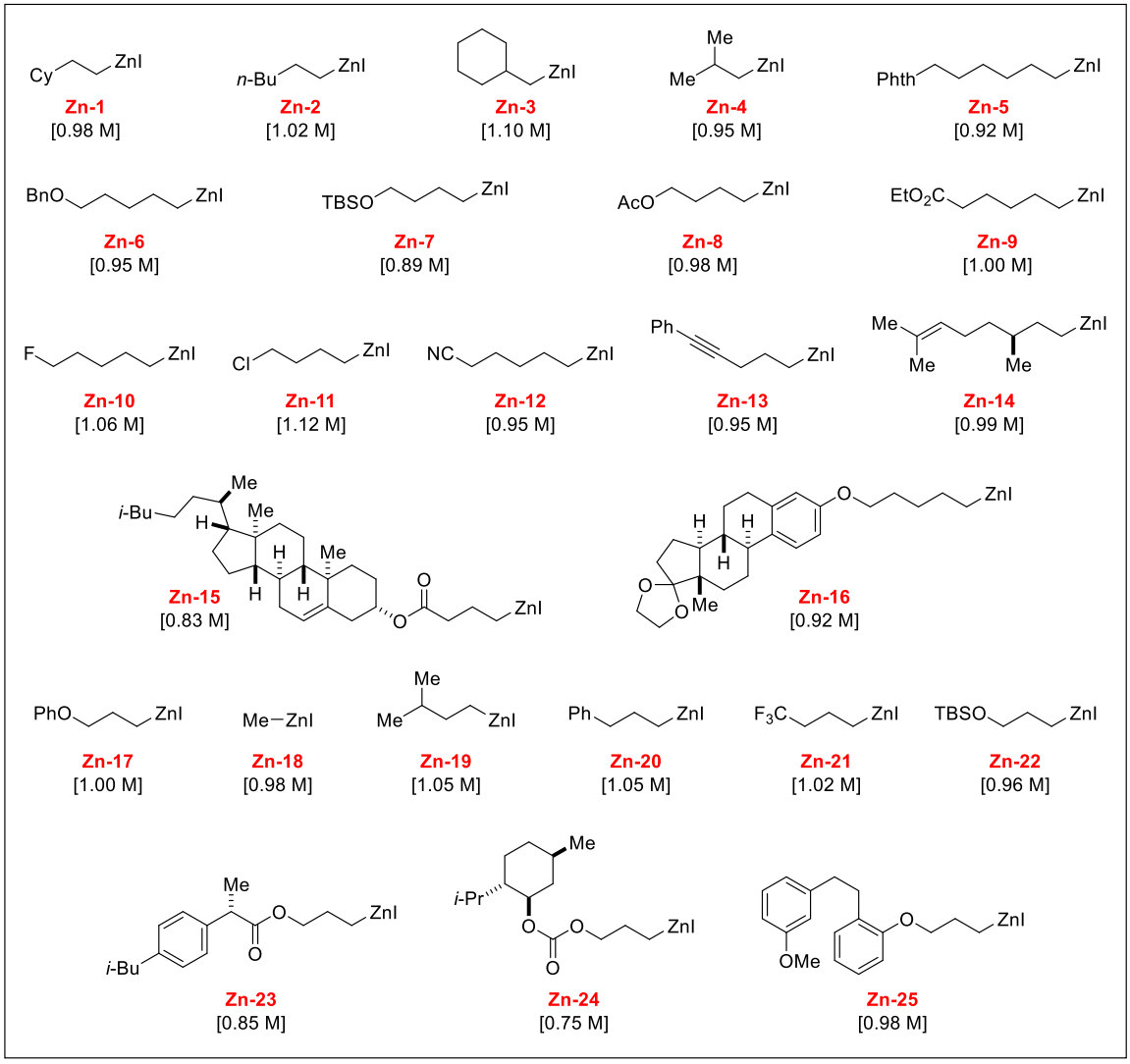
2.4.4. Preparation of nucleophiles

General Procedure 4 (GP-4).

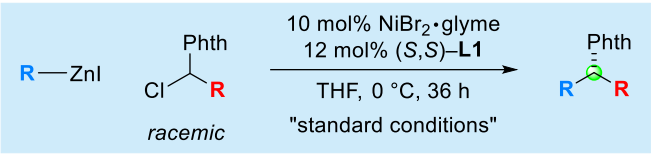


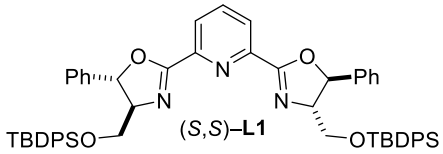
Preparation of organozinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three 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



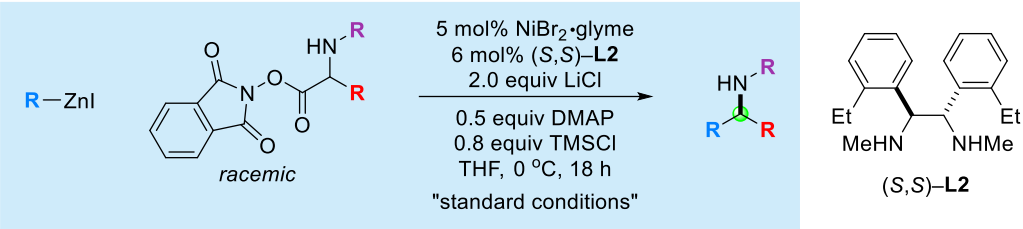


General Procedure 5 (GP-5): Alkyl chlorides as the electrophile.

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.

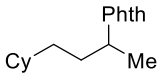
General Procedure 7 (GP-7): *α*-branched NHP esters as the electrophile.

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).

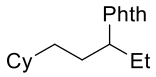
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.73 – 7.66 (m, 2H), 4.35 – 4.23 (m, 1H), 2.12 – 1.97 (m, 1H), 1.82 – 1.69 (m, 1H), 1.68 – 1.55 (m, 5H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.29 – 0.99 (m, 6H), 0.91 – 0.73 (m, 2H).

^{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}.

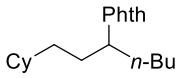
HRMS (ESI-MS) *m/z* $[M+H]^+$ calcd for $C_{19}H_{26}NO_2$: 300.1958, found: 300.1962.

$[\alpha]^{22}_D$ = –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).

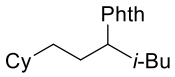
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 4.19 – 4.08 (m, 1H), 2.13 – 1.98 (m, 2H), 1.78 – 1.54 (m, 7H), 1.40 – 0.98 (m, 10H), 0.91 – 0.72 (m, 5H).

^{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).

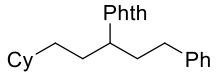
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 2H), 7.75 – 7.64 (m, 2H), 4.33 – 4.16 (m, 1H), 2.25 – 1.94 (m, 2H), 1.75 – 1.55 (m, 6H), 1.50 – 1.36 (m, 2H), 1.27 – 0.98 (m, 6H), 0.96 – 0.73 (m, 8H).

^{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).

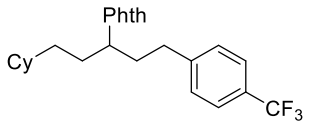
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.74 – 7.65 (m, 2H), 7.22 – 7.15 (m, 2H), 7.15 – 7.09 (m, 2H), 7.09 – 7.03 (m, 1H), 4.27 – 4.16 (m, 1H), 2.69 – 2.43 (m, 3H), 2.15 – 1.94 (m, 2H), 1.82 – 1.69 (m, 1H), 1.69 – 1.54 (m, 5H), 1.25 – 1.01 (m, 6H), 0.91 – 0.72 (m, 2H).

^{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).

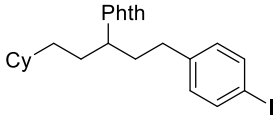
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 145.4 (q, *J* = 1.0 Hz), 134.0, 131.8, 128.7, 128.2 (q, *J* = 32.3 Hz), 125.2 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 273 Hz), 123.1, 52.6, 37.5, 34.3, 33.5, 33.34, 33.29, 33.27, 30.2, 26.7, 26.43, 26.38.

^{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).

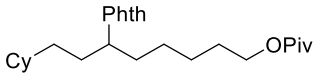
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 2H), 7.74 – 7.66 (m, 2H), 7.49 – 7.40 (m, 2H), 6.90 – 6.81 (m, 2H), 4.24 – 4.11 (m, 1H), 2.67 – 2.42 (m, 3H), 2.15 – 1.89 (m, 2H), 1.78 – 1.58 (m, 6H), 1.29 – 0.97 (m, 6H), 0.91 – 0.70 (m, 2H).

^{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).

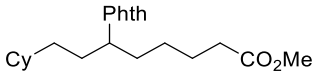
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.76 – 7.64 (m, 2H), 4.22 – 4.06 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.78 – 1.51 (m, 9H), 1.45 – 0.97 (m, 19H), 0.90 – 0.72 (m, 2H).

^{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).

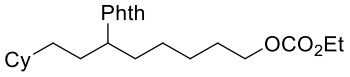
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.74 – 7.67 (m, 2H), 4.19 – 4.09 (m, 1H), 3.61 (s, 3H), 2.25 (t, *J* = 7.7 Hz, 2H), 2.16 – 1.98 (m, 2H), 1.78 – 1.57 (m, 9H), 1.36 – 0.98 (m, 8H), 0.89 – 0.72 (m, 2H).

^{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).

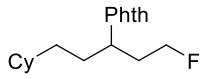
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.76 – 7.65 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.17 – 4.09 (m, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.17 – 1.94 (m, 2H), 1.76 – 1.56 (m, 9H), 1.47 – 0.97 (m, 13H), 0.90 – 0.71 (m, 2H).

^{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).

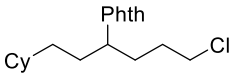
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 134.1, 131.9, 123.4, 81.7 (d, *J* = 167 Hz), 49.3 (d, *J* = 4.0 Hz), 37.5, 34.2, 33.5, 33.3, 33.2 (d, *J* = 19.2 Hz), 29.9, 26.7, 26.5, 26.4.

^{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).

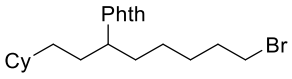
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H), 7.78 – 7.65 (m, 2H), 4.26 – 4.09 (m, 1H), 3.62 – 3.45 (m, 2H), 2.29 – 2.15 (m, 1H), 2.15 – 2.01 (m, 1H), 1.96 – 1.84 (m, 1H), 1.81 – 1.68 (m, 3H), 1.68 – 1.57 (m, 5H), 1.28 – 0.98 (m, 6H), 0.91 – 0.71 (m, 2H).

^{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).

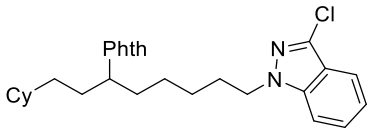
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 2H), 7.77 – 7.63 (m, 2H), 4.25 – 4.05 (m, 1H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.20 – 1.98 (m, 2H), 1.85 – 1.76 (m, 2H), 1.76 – 1.56 (m, 7H), 1.52 – 1.34 (m, 2H), 1.35 – 1.00 (m, 8H), 0.90 – 0.73 (m, 2H).

^{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).

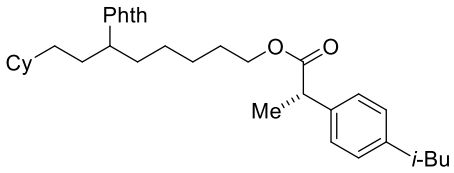
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.74 – 7.67 (m, 2H), 7.64 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.32 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.20 – 7.12 (m, 1H), 4.25 (t, *J* = 7.1 Hz, 2H), 4.16 – 4.05 (m, 1H), 2.12 – 1.96 (m, 2H), 1.92 – 1.78 (m, 2H), 1.71 – 1.54 (m, 7H), 1.41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

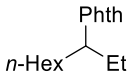
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 168.9, 140.6, 138.0, 134.0, 132.0, 129.4, 127.3, 123.3, 64.7, 52.7, 45.3, 45.2, 37.6, 34.5, 33.6, 33.3, 32.5, 30.3, 30.0, 28.5, 26.7, 26.5, 26.4, 25.7, 22.5, 18.6.

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).

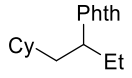
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 4.16 – 4.05 (m, 1H), 2.13 – 1.98 (m, 2H), 1.83 – 1.65 (m, 2H), 1.35 – 1.14 (m, 8H), 0.90 – 0.78 (m, 6H).

^{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).

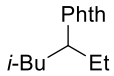
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 4.29 – 4.19 (m, 1H), 2.13 – 1.96 (m, 2H), 1.91 – 1.80 (m, 1H), 1.78 – 1.44 (m, 6H), 1.20 – 1.05 (m, 4H), 0.99 – 0.78 (m, 5H).

^{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).

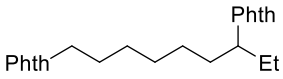
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 4.27 – 4.17 (m, 1H), 2.20 – 1.97 (m, 2H), 1.80 – 1.66 (m, 1H), 1.50 – 1.38 (m, 2H), 0.95 – 0.82 (m, 9H).

^{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).

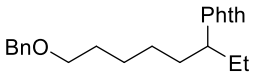
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 4H), 7.74 – 7.65 (m, 4H), 4.14 – 4.03 (m, 1H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.14 – 1.96 (m, 2H), 1.83 – 1.66 (m, 2H), 1.64 – 1.56 (m, 2H), 1.41 – 1.16 (m, 6H), 0.84 (t, *J* = 7.4 Hz, 3H).

^{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).

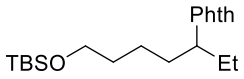
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 7.35 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 4.46 (s, 2H), 4.17 – 4.04 (m, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.83 – 1.66 (m, 2H), 1.61 – 1.51 (m, 2H), 1.46 – 1.17 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{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).

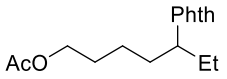
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 4.20 – 4.03 (m, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.15 – 1.98 (m, 2H), 1.83 – 1.67 (m, 2H), 1.58 – 1.40 (m, 2H), 1.35 – 1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.81 (s, 9H), –0.02 (d, *J* = 2.0 Hz, 6H).

^{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).

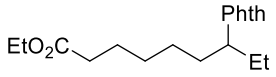
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.73 – 7.68 (m, 2H), 4.17 – 4.07 (m, 1H), 4.05 – 3.93 (m, 2H), 2.18 – 2.00 (m, 2H), 1.98 (s, 3H), 1.82 – 1.54 (m, 4H), 1.40 – 1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{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).

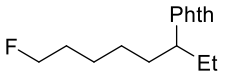
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.75 – 7.65 (m, 2H), 4.19 – 4.07 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.15 – 1.96 (m, 2H), 1.83 – 1.66 (m, 2H), 1.65 – 1.48 (m, 2H), 1.44 – 1.15 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{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).

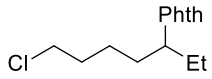
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 134.0, 131.9, 123.3, 84.1 (d, *J* = 165 Hz), 53.9, 32.2, 30.3 (d, *J* = 19.2 Hz), 26.4, 25.7, 25.0 (d, *J* = 5.1 Hz), 11.3.

^{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).

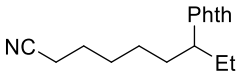
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.75 – 7.67 (m, 2H), 4.18 – 4.06 (m, 1H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.19 – 1.98 (m, 2H), 1.85 – 1.67 (m, 4H), 1.49 – 1.31 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{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).

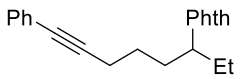
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.75 – 7.68 (m, 2H), 4.16 – 4.05 (m, 1H), 2.29 (t, *J* = 7.1 Hz, 2H), 2.18 – 1.99 (m, 2H), 1.84 – 1.65 (m, 2H), 1.65 – 1.56 (m, 2H), 1.56 – 1.17 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{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).

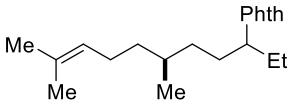
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 2H), 7.76 – 7.68 (m, 2H), 7.43 – 7.34 (m, 2H), 7.32 – 7.23 (m, 3H), 4.25 – 4.13 (m, 1H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.34 – 2.21 (m, 1H), 2.19 – 2.03 (m, 1H), 2.00 – 1.89 (m, 1H), 1.89 – 1.76 (m, 1H), 1.63 – 1.51 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{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).

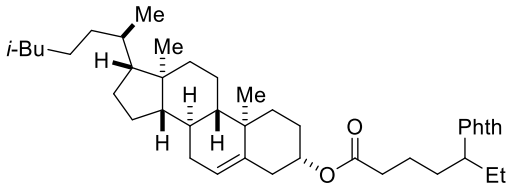
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 133.9, 132.0, 131.2, 125.0, 123.2, 54.4, 37.1, 33.9, 32.2, 29.7, 25.83, 25.81, 25.6, 19.6, 17.7, 11.3.

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).

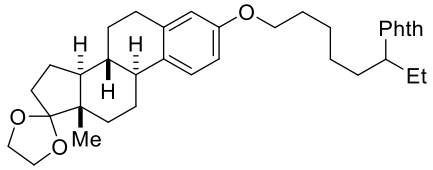
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.9, 139.8, 134.0, 131.9, 123.3, 122.7, 74.0, 56.8, 56.3, 53.6, 50.1, 42.4, 39.9, 39.6, 38.2, 37.1, 36.7, 36.3, 35.9, 34.2, 32.02, 31.97, 31.7, 28.4, 28.1, 27.9, 25.7, 24.4, 24.0, 23.0, 22.7, 22.3, 21.2, 19.4, 18.8, 12.0, 11.2.

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).

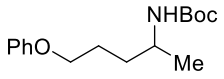
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.0, 138.0, 134.0, 132.6, 132.0, 126.4, 123.2, 119.6, 114.6, 112.1, 67.8, 65.4, 64.7, 54.0, 49.5, 46.3, 43.8, 39.2, 34.4, 32.3, 30.9, 29.9, 29.3, 27.1, 26.6, 26.3, 25.9, 25.7, 22.5, 14.5, 11.3.

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).

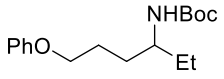
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 6.97 – 6.87 (m, 3H), 4.41 (d, *J* = 8.6 Hz, 1H), 3.96 (td, *J* = 6.3, 1.2 Hz, 2H), 3.70 (q, *J* = 7.7, 7.2 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.68 – 1.51 (m, 2H), 1.45 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H).

^{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).

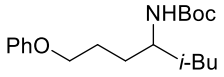
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 6.97 – 6.85 (m, 3H), 4.36 – 4.30 (m, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.62 – 3.48 (m, 1H), 1.93 – 1.77 (m, 2H), 1.73 – 1.52 (m, 2H), 1.47 – 1.42 (m, 11H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{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).

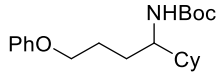
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 6.97 – 6.86 (m, 3H), 4.26 (d, *J* = 9.4 Hz, 1H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.76 – 3.63 (m, 1H), 1.92 – 1.74 (m, 2H), 1.74 – 1.60 (m, 2H), 1.45 – 1.42 (m, 10H), 1.35 – 1.22 (m, 2H), 0.91 (dd, *J* = 6.6, 4.1 Hz, 6H).

^{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).

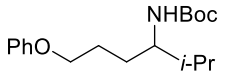
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 6.73 (m, 5H), 4.52 – 4.28 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.57 – 3.33 (m, 1H), 1.99 – 1.58 (m, 9H), 1.49 – 1.38 (m, 10H), 1.38 – 0.84 (m, 5H).

^{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).

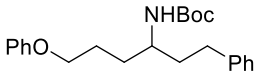
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 6.83 (m, 5H), 4.55 – 4.25 (m, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.55 – 3.39 (m, 1H), 1.98 – 1.34 (m, 14H), 1.19 – 0.82 (m, 6H).

^{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).

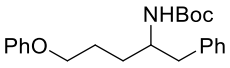
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 4H), 7.22 – 7.15 (m, 3H), 6.98 – 6.88 (m, 3H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.75 – 3.65 (m, 1H), 2.77 – 2.59 (m, 2H), 1.93 – 1.50 (m, 6H), 1.46 (s, 9H).

^{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).

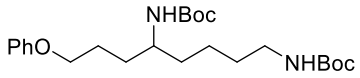
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 7H), 6.98 – 6.90 (m, 1H), 6.89 – 6.84 (m, 2H), 4.41 (d, *J* = 9.1 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.88 (s, 1H), 2.88 – 2.73 (m, 2H), 1.95 – 1.64 (m, 4H), 1.41 (s, 9H).

^{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).

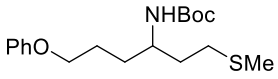
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 6.97 – 6.86 (m, 3H), 4.59 (s, 1H), 4.36 (d, *J* = 9.3 Hz, 1H), 3.95 (t, *J* = 6.2 Hz, 2H), 3.65 – 3.53 (m, 1H), 3.15 – 3.05 (m, 2H), 1.87 – 1.60 (m, 4H), 1.54 – 1.37 (m, 24H).

^{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).

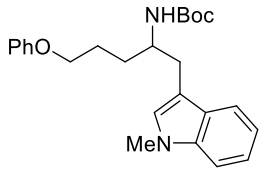
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 2H), 6.98 – 6.85 (m, 3H), 4.40 (d, *J* = 9.3 Hz, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.78 – 3.61 (m, 1H), 2.58 – 2.48 (m, 2H), 2.10 (s, 3H), 1.95 – 1.50 (m, 6H), 1.44 (s, 9H).

^{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).

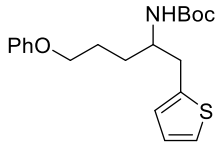
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 1H), 7.31 – 7.17 (m, 4H), 7.15 – 7.07 (m, 1H), 6.97 – 6.89 (m, 1H), 6.90 – 6.83 (m, 3H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.02 – 3.92 (m, 3H), 3.75 (s, 3H), 2.96 (d, *J* = 5.9 Hz, 2H), 1.96 – 1.69 (m, 4H), 1.44 (s, 9H).

^{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).

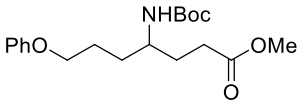
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.19 – 7.13 (m, 1H), 6.96 – 6.91 (m, 2H), 6.90 – 6.86 (m, 2H), 6.84 – 6.81 (m, 1H), 4.54 – 4.47 (m, 1H), 3.96 (t, J = 6.2 Hz, 2H), 3.90 – 3.81 (m, 1H), 3.13 – 2.96 (m, 2H), 1.91 – 1.80 (m, 2H), 1.77 – 1.49 (m, 2H), 1.44 (s, 9H).

^{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).

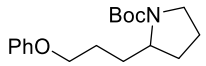
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 6.95 – 6.86 (m, 3H), 4.34 (d, *J* = 9.5 Hz, 1H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 3.65 – 3.61 (m, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.92 – 1.59 (m, 6H), 1.43 (s, 9H).

^{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).

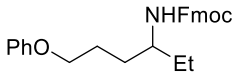
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 6.96 – 6.84 (m, 3H), 4.01 – 3.89 (m, 2H), 3.87 – 3.76 (m, 1H), 3.49 – 3.28 (m, 2H), 1.98 – 1.63 (m, 8H), 1.46 (s, 9H).

^{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).

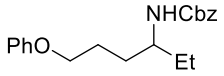
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.23 (m, 4H), 6.98 – 6.87 (m, 3H), 4.53 (d, *J* = 9.3 Hz, 1H), 4.45 (d, *J* = 6.7 Hz, 2H), 4.22 (t, *J* = 6.7 Hz, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.69 – 3.57 (m, 1H), 1.88 – 1.36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

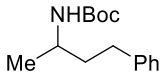
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 7H), 6.99 – 6.84 (m, 3H), 5.11 (s, 2H), 4.58 (d, *J* = 9.2 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.71 – 3.58 (m, 1H), 1.87 – 1.36 (m, 6H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{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).

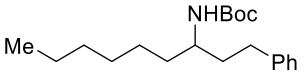
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 4.38 (s, 1H), 3.78 – 3.57 (m, 1H), 2.66 (td, *J* = 7.6, 3.9 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.46 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H).

^{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).

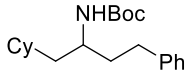
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.66 – 3.57 (m, 1H), 2.76 – 2.56 (m, 2H), 1.83 – 1.56 (m, 2H), 1.48 – 1.44 (m, 10H), 1.40 – 1.25 (m, 9H), 0.92 – 0.84 (m, 3H).

^{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).

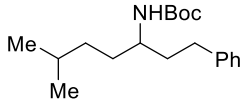
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.25 (d, *J* = 9.5 Hz, 1H), 3.80 – 3.68 (m, 1H), 2.75 – 2.56 (m, 2H), 1.89 – 1.56 (m, 7H), 1.46 (s, 9H), 1.39 – 1.06 (m, 6H), 1.01 – 0.77 (m, 2H).

^{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).

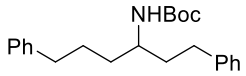
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.69 – 3.55 (m, 1H), 2.76 – 2.56 (m, 2H), 1.83 – 1.58 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 (s, 9H), 1.42 – 1.30 (m, 1H), 1.29 – 1.13 (m, 2H), 0.91 – 0.83 (m, 6H).

^{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).

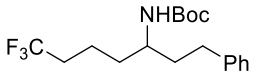
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 4H), 7.24 – 7.14 (m, 6H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.75 – 3.63 (m, 1H), 2.73 – 2.56 (m, 4H), 1.84 – 1.60 (m, 4H), 1.58 – 1.38 (m, 11H).

^{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).

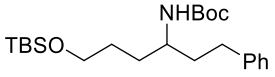
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 141.8, 128.6, 128.5, 127.2 (q, J = 276 Hz), 126.1, 79.4, 50.0, 37.7, 34.9, 33.6 (q, J = 28.4 Hz), 32.5, 28.5, 18.6.

^{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).

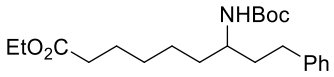
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 4.45 (d, *J* = 9.1 Hz, 1H), 3.68 – 3.58 (m, 3H), 2.75 – 2.57 (m, 2H), 1.86 – 1.63 (m, 2H), 1.60 – 1.39 (m, 13H), 0.90 (s, 9H), 0.05 (s, 6H).

^{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).

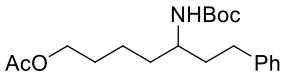
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.17 – 7.09 (m, 3H), 4.30 (d, *J* = 9.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 1H), 2.71 – 2.51 (m, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.51 (m, 4H), 1.47 – 1.24 (m, 15H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{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).

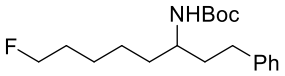
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 4.33 (d, *J* = 9.4 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.66 – 3.59 (m, 1H), 2.77 – 2.55 (m, 2H), 2.03 (s, 3H), 1.88 – 1.56 (m, 4H), 1.54 – 1.32 (m, 13H).

^{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).

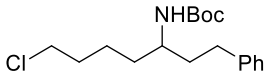
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.2, 128.51, 128.48, 126.0, 84.2 (d, J = 164 Hz), 79.1, 50.6, 37.8, 35.8, 32.6, 30.5 (d, J = 19.5 Hz), 28.6, 25.6, 25.3 (d, J = 5.4 Hz).

^{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).

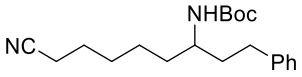
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.31 (d, *J* = 9.4 Hz, 1H), 3.64 (s, 1H), 3.54 – 3.50 (m, 2H), 2.77 – 2.57 (m, 2H), 1.87 – 1.60 (m, 4H), 1.55 – 1.36 (m, 13H).

^{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).

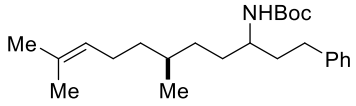
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 7.15 – 7.06 (m, 3H), 4.23 (d, *J* = 9.4 Hz, 1H), 3.54 (s, 1H), 2.68 – 2.49 (m, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.77 – 1.51 (m, 4H), 1.44 – 1.25 (m, 15H).

^{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).

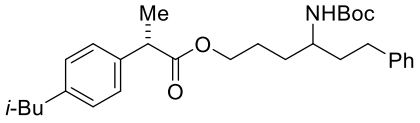
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.3, 131.3, 128.5, 125.9, 125.0, 109.8, 79.1, 51.0, 38.2, 37.6, 37.1, 33.3, 33.0, 32.6, 28.6, 25.9, 25.7, 19.7, 17.8.

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).

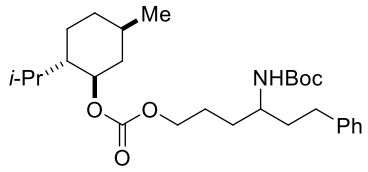
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 155.8, 142.0, 140.6, 138.0, 129.4, 128.5, 128.4, 127.3, 126.0, 79.2, 64.5, 50.3, 45.3, 45.1, 37.8, 32.5, 32.0, 30.3, 28.6, 25.3, 22.5, 18.5.

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).

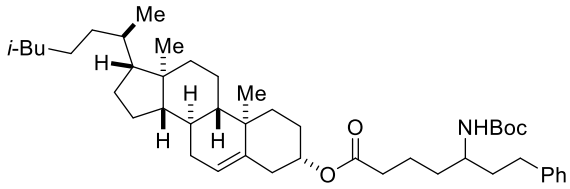
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.1, 142.0, 128.55, 128.47, 126.0, 79.3, 78.4, 67.6, 50.4, 47.1, 40.9, 37.9, 34.2, 32.5, 32.2, 31.5, 28.6, 26.2, 25.5, 23.4, 22.1, 20.9, 16.4.

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).

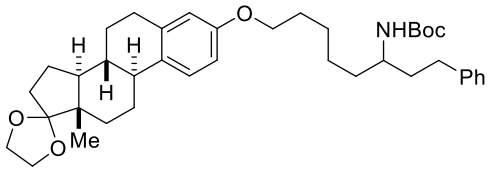
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.7, 142.0, 139.7, 128.43, 128.40, 125.9, 122.7, 79.0, 73.9, 56.7, 56.2, 50.1, 42.4, 39.8, 39.6, 38.2, 37.6, 37.1, 36.6, 36.3, 35.9, 35.0, 34.4, 32.5, 32.0, 31.9, 28.5, 28.3, 28.1, 27.9, 24.4, 23.9, 22.9, 22.7, 21.4, 21.1, 19.4, 18.8, 11.9.

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.

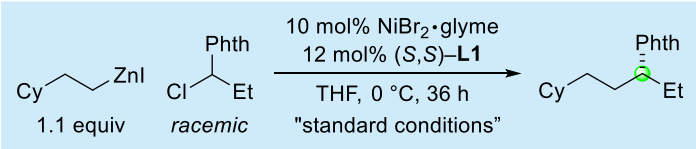
Cross-coupling: In a nitrogen-filled glovebox, DMAP (0.050 mmol, 0.50 equiv), the NHP ester (0.10 mmol, 1.0 equiv), and TMSCl (0.080 mmol, 0.80 equiv) were added sequentially to the reaction mixture as stock solutions in THF, totaling 1.2 mL THF (including 0.4 mL from the catalyst solution). The vial 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.

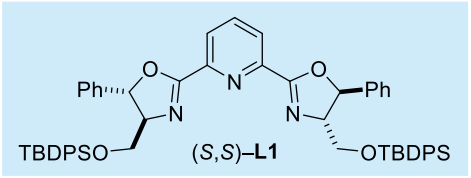
Table 2.4: 1,3-Dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoate was reacted with **Zn-17** according to **GP-9**. The yields were determined via LC-MS analysis, with 1-indanone as the internal standard. The ee values were determined via HPLC analysis after purification by preparative thin layer chromatography. All data are the average of two experiments.

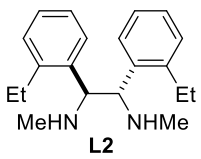
Table 2.3. *Effect of reaction parameters (complete): an alkyl chloride as the electrophile.*

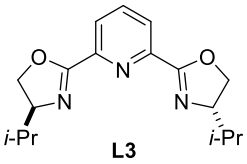


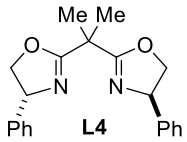
entry	variation from the "standard conditions"	yield (%)[a]	ee (%)[b]
1	none	90	92
2	no $NiBr_2$·glyme	<1	–
3	no (*S*,*S*)–**L1**	<1	–
4	**L2**, instead of (*S*,*S*)–**L1**	32	16
5	**L3**, instead of (*S*,*S*)–**L1**	81	84
6	**L4**, instead of (*S*,*S*)–**L1**	13	22
7	**L5**, instead of (*S*,*S*)–**L1**	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

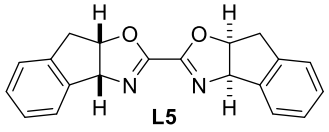
All data are the average of two experiments. [a] Determined through GC analysis. [b] Determined through SFC analysis.











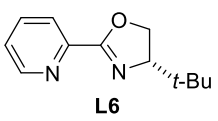
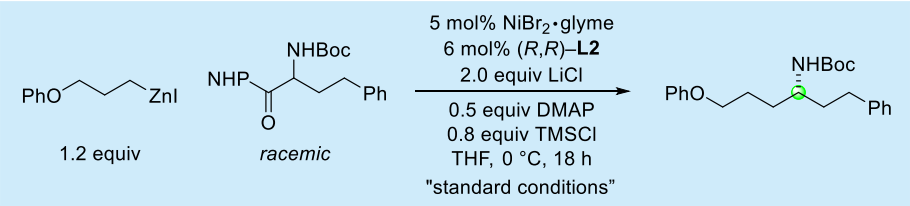
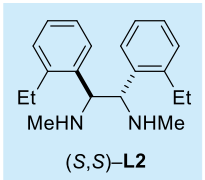


Table 2.4. *Effect of reaction parameters (complete): an alkyl NHP ester as the electrophile.*

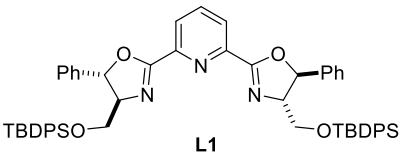


entry	variation from the "standard conditions"	yield (%)[a]	ee (%)[b]
1	none	79	91
2	no $NiBr_2$·glyme	<1	–
3	no (*S*,*S*)–**L2**	30	<2
4	no LiCl	16	88
5	no DMAP	70	65
6	no TMSCl	65	87
7	**L1**, instead of (*S*,*S*)–**L2**	14	31
8	**L4**, instead of (*S*,*S*)–**L2**	9	6
9	**L6**, instead of (*S*,*S*)–**L2**	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

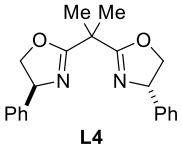
All data are the average of two experiments. [a] Determined through LC/MS analysis.
[b] Determined through HPLC analysis.



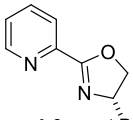
(*S*,*S*)–**L2**

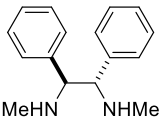


L1

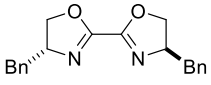


L4


L6 *t*-Bu



L7



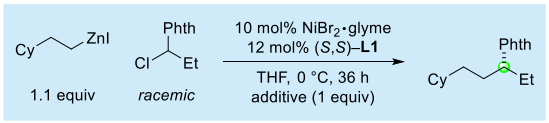
L8

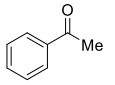
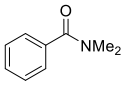
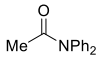
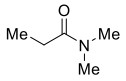
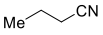
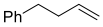
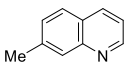
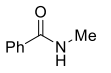
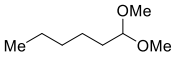
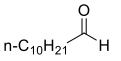
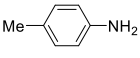
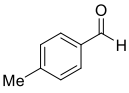
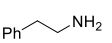
2.4.7. Study of functional-group compatibility

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.

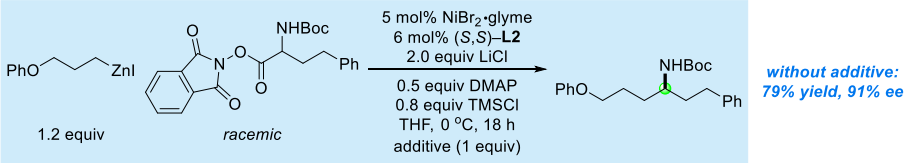
Table 2.5. *Functional-group compatibility: an alkyl chloride as the electrophile.*

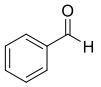
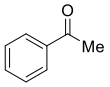
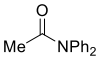
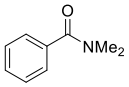
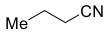
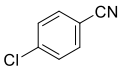
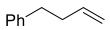
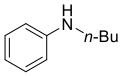
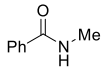
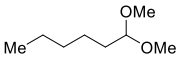
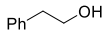
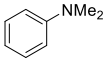
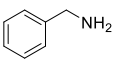


additive; recovery (%)[a]		yield (%)[a]	ee (%)[b]	additive; recovery (%)[a]		yield (%)[a]	ee (%)[b]
n-$C_{10}H_{21}Cl$	>95	87	91		>95	88	91
	>95	84	91		>95	93	91
	>95	89	91		>95	89	91
	>95	84	91		>95	89	92
	>95	86	91		92	84	91
	>95	87	91		>95	85	92
	>95	87	91		>95	82	91
	>95	87	91		>95	80	91
	>95	89	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).

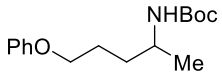
Preparation of the NHP ester: In the air, *N*-hydroxyphthalimide (97.9 mg, 0.60 mmol, 1.0 equiv), the Boc-protected amino acid (0.60 mmol, 1.0 equiv), and DMAP (36.7 mg, 0.30 mmol, 0.50 equiv) were added sequentially to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was capped 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,

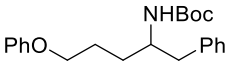
1.2 equiv) was added dropwise via syringe over 5 min, during which the reaction mixture became yellow and homogeneous. The balloon was removed, and the septum cap was sealed with grease. The mixture was stirred at 0 °C for 18 h.

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.

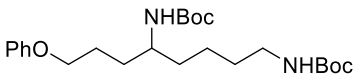
(*S*,*S*)-**L2**: 112 mg, 67% yield, 90% ee; (*R*,*R*)-**L2**: 106 mg, 63% yield, 90% ee.



***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.

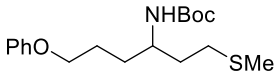
(*S*,*S*)-**L2**: 135 mg, 63% yield, 90% ee; (*R*,*R*)-**L2**: 131 mg, 61% yield, 90% ee.

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.

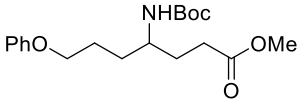
(*S*,*S*)-**L2**: 170 mg, 65% yield, 90% ee; (*R*,*R*)-**L2**: 152 mg, 58% yield, 90% ee.



***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.

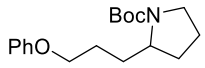
(*S*,*S*)-**L2**: 105 mg, 52% yield, 92% ee; (*R*,*R*)-**L2**: 105 mg, 52% yield, 92% ee.

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.

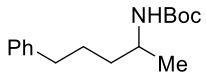
(*S*,*S*)-**L2**: 110 mg, 52% yield, 91% ee; (*R*,*R*)-**L2**: 107 mg, 51% yield, 92% ee.



***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).

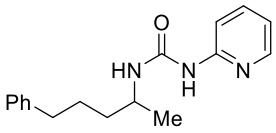
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 4.35 – 4.30 (m, 1H), 3.74 – 3.64 (m, 1H), 2.68 – 2.58 (m, 2H), 1.74 – 1.59 (m, 2H), 1.51 – 1.38 (m, 11H), 1.10 (d, *J* = 6.6 Hz, 3H).

^{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).

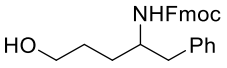
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.8 Hz, 1H), 8.85 (s, 1H), 8.16 – 8.10 (m, 1H), 7.59 – 7.50 (m, 1H), 7.32 – 7.21 (m, 2H), 7.21 – 7.12 (m, 3H), 6.90 – 6.79 (m, 2H), 4.12 – 3.98 (m, 1H), 2.74 – 2.57 (m, 2H), 1.82 – 1.53 (m, 4H), 1.25 (d, *J* = 6.6 Hz, 3H).

^{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).

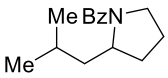
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.42 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 – 7.18 (m, 4H), 7.15 – 7.04 (m, 3H), 4.52 (d, *J* = 9.0 Hz, 1H), 4.45 – 4.24 (m, 2H), 4.10 (t, *J* = 6.6 Hz, 1H), 3.86 (s, 1H), 3.61 – 3.37 (m, 2H), 2.78 – 2.42 (m, 2H), 1.56 – 1.45 (m, 5H).

^{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).

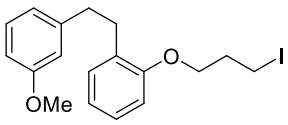
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.32 (m, 5H), 4.46 – 3.81 (m, 1H), 3.73 – 3.29 (m, 2H), 2.17 – 1.80 (m, 3H), 1.77 – 1.54 (m, 2H), 1.34 – 0.89 (m, 6H), 0.50 (dd, *J* = 104.9, 6.4 Hz, 2H).

^{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**.



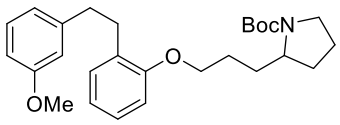
1-(3-Iodopropoxy)-2-(3-methoxyphenethyl)benzene. In the air, K_2CO_3 (2.3 g, 16.4 mmol, 1.5 equiv) was added to a solution of 2-(3-methoxyphenethyl)phenol (2.5 g, 11.0 mmol, 1.0 equiv) in DMF (30 mL) at room temperature, and the mixture was stirred at room temperature for 30 min. Next, 1,3-diiodopropane (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).

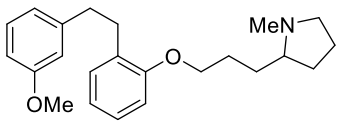
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.13 – 7.08 (m, 1H), 6.90 – 6.78 (m, 3H), 6.77 – 6.71 (m, 2H), 4.07 – 3.91 (m, 2H), 3.91 – 3.73 (m, 1H), 3.78 (s, 3H), 3.45 – 3.25 (m, 2H), 2.96 – 2.79 (m, 4H), 2.04 – 1.74 (m, 6H), 1.74 – 1.64 (m, 1H), 1.63 – 1.50 (m, 1H), 1.45 (s, 9H).

^{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.

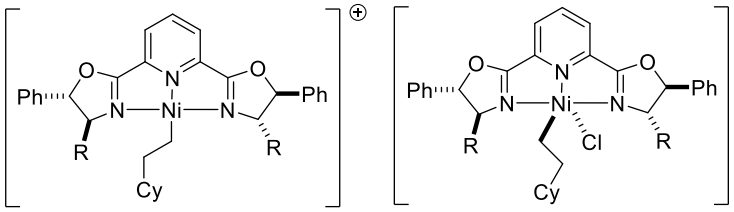
FT-IR (film): 2915, 2353, 1600, 1469, 1247, 1168, 1111, 1047, 874, 752, 695 cm^{-1}.

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 = $CH_2OTBDPS$

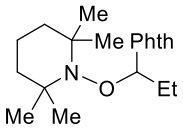
Procedure. In a nitrogen-filled glovebox, an oven-dried 4 mL vial that contained a stir bar was charged with $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and (*S*,*S*)-**L1** (10.9 mg, 0.012 mmol, 12 mol%). Next, THF (1.0 mL) was added, the vial was capped with a PTFE

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).

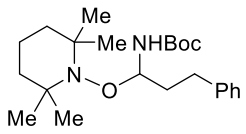
Procedure. In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar and charged with $NiBr_2$·glyme (1.5 mg, 0.0050 mmol, 5.0 mol%), (*S,S*)-**L2** (1.8 mg, 0.0060 mmol, 6.0 mol%), and LiCl (8.5 mg, 0.20 mmol, 2.0 equiv). Next, THF (0.4 mL) was added, the vial was capped with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



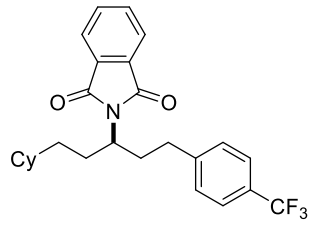
***tert*-Butyl (3-phenyl-1-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)carbamate.** In a nitrogen-filled glovebox, an oven-dried 20 mL vial that contained a cross-type stir bar was charged with $NiBr_2$·glyme (6.2 mg, 0.020 mmol, 5.0 mol%), (*S*,*S*)-**L2** (7.1 mg, 0.024 mmol, 6.0 mol%), and LiCl (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.

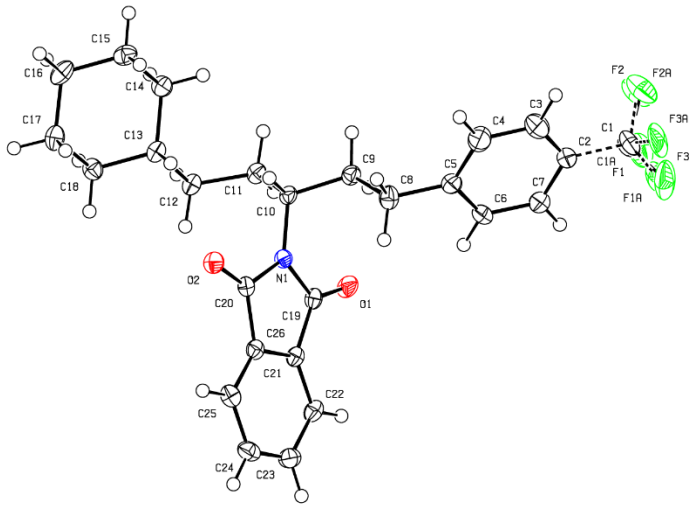
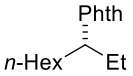


Table 2.7. *Crystal data for 6.*

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}	

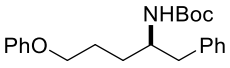


(*R*)-2-(Nonan-3-yl)isoindoline-1,3-dione (17). The absolute configuration of this compound has been established.[63] The coupling product obtained with (*S*,*S*)-**L1** has the (*R*)-configuration, by comparison with the sign of the published optical rotation.

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.

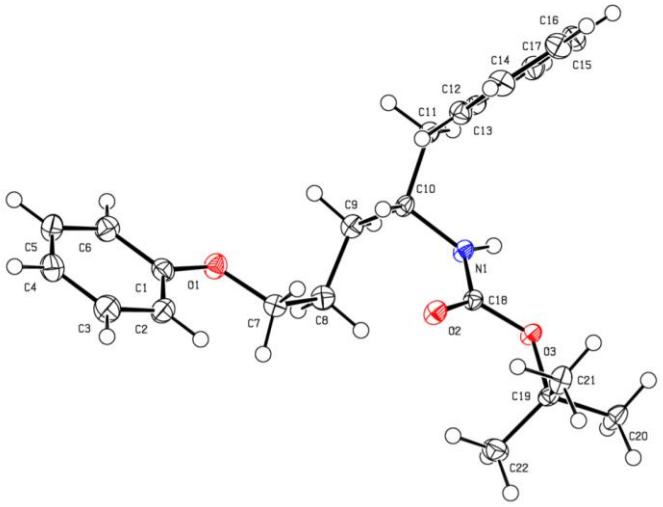
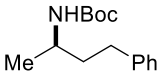


Table 2.8. *Crystal data for 41.*

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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Chapter 3

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

Adapted in part with permission from:

Yang, Z.-P.;‡ Freas, D. J.;‡ Fu, G. C. Asymmetric Synthesis of Protected Unnatural *α*-Amino Acids via Enantioconvergent Nickel-Catalyzed Cross-Coupling. *J. Am. Chem. Soc.* **2021**, *143*, 8614–8618. DOI: 10.1021/jacs.1c03903

3.1. Introduction

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

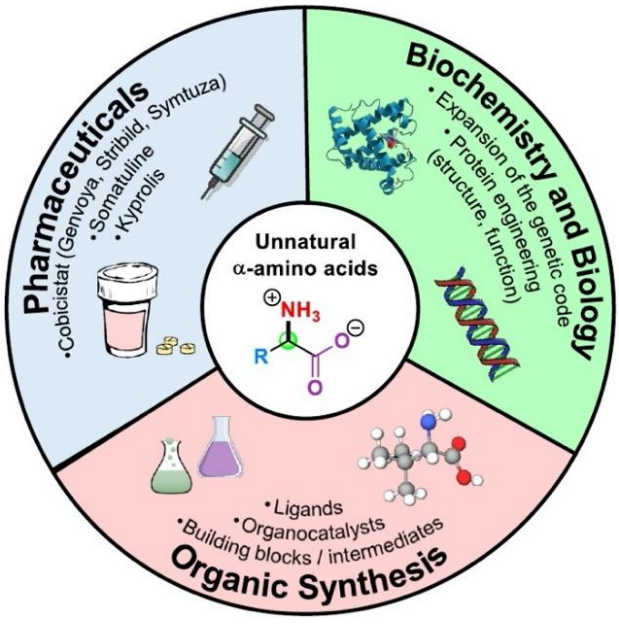
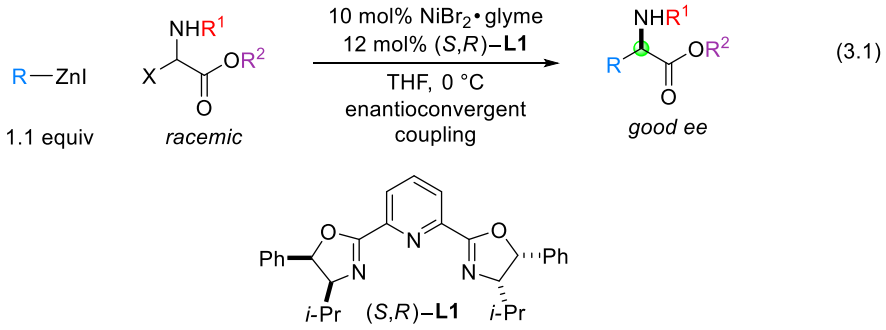


Figure 3.1. *Diverse applications of unnatural α-amino acids.*

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

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

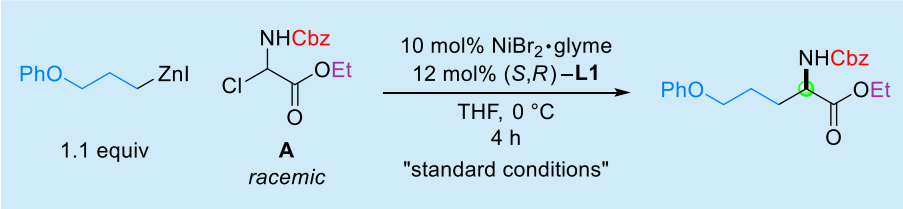


3.2. Results and discussion

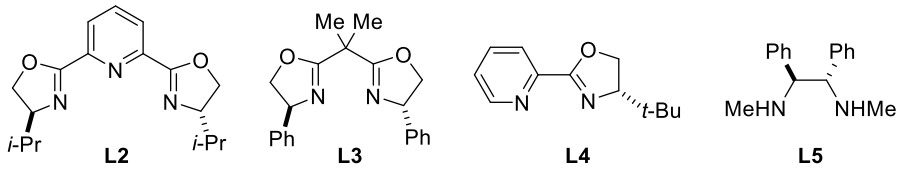
3.2.1. Optimization

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

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



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



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

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

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

3.2.2. Scope

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

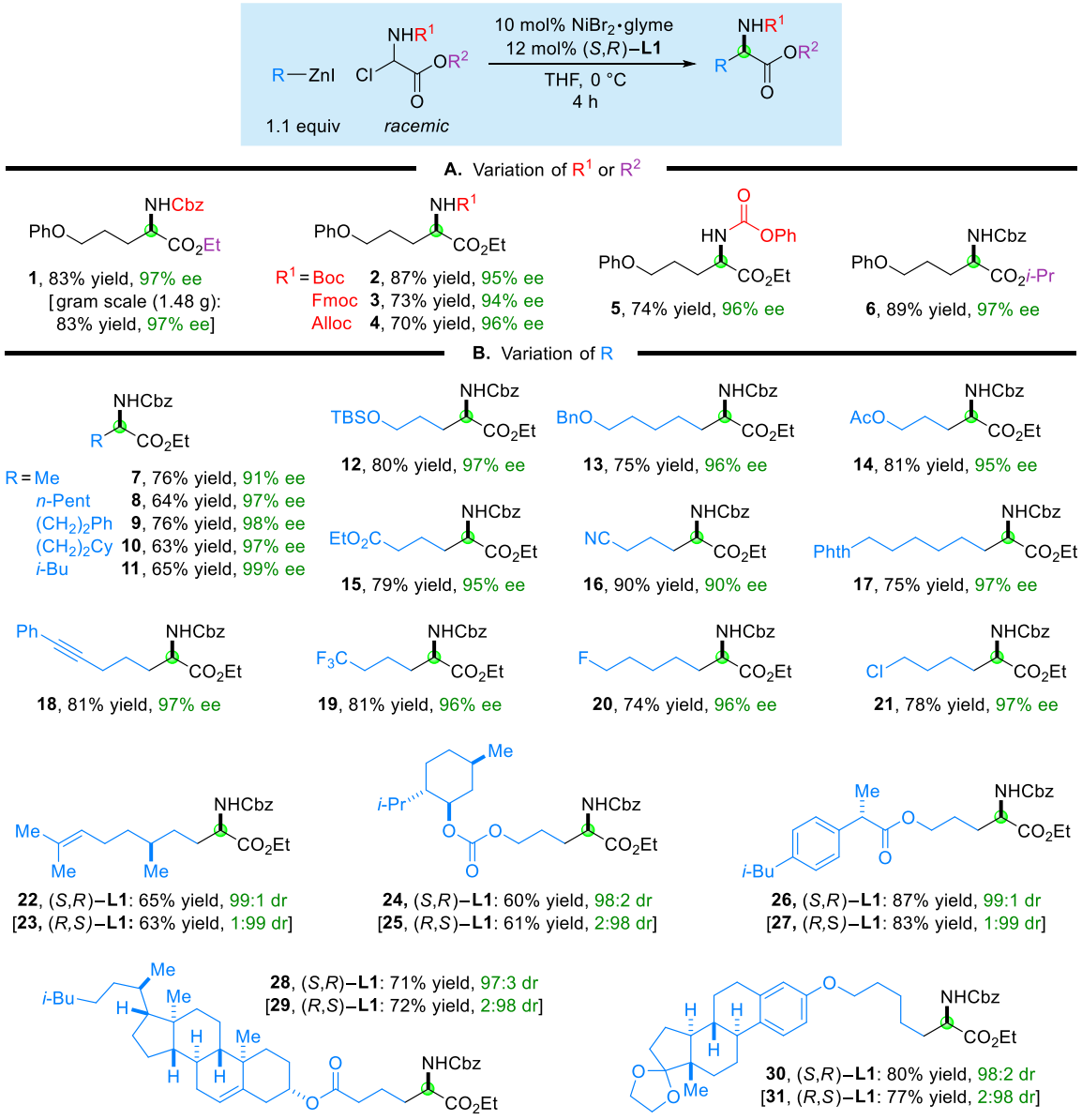


Figure 3.2. *Scope of catalytic enantioconvergent synthesis of protected unnatural α-amino acids. All couplings were conducted on a 0.6-mmol scale (unless otherwise noted), and all yields are of purified products.*

3.2.3. Applications

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

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

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

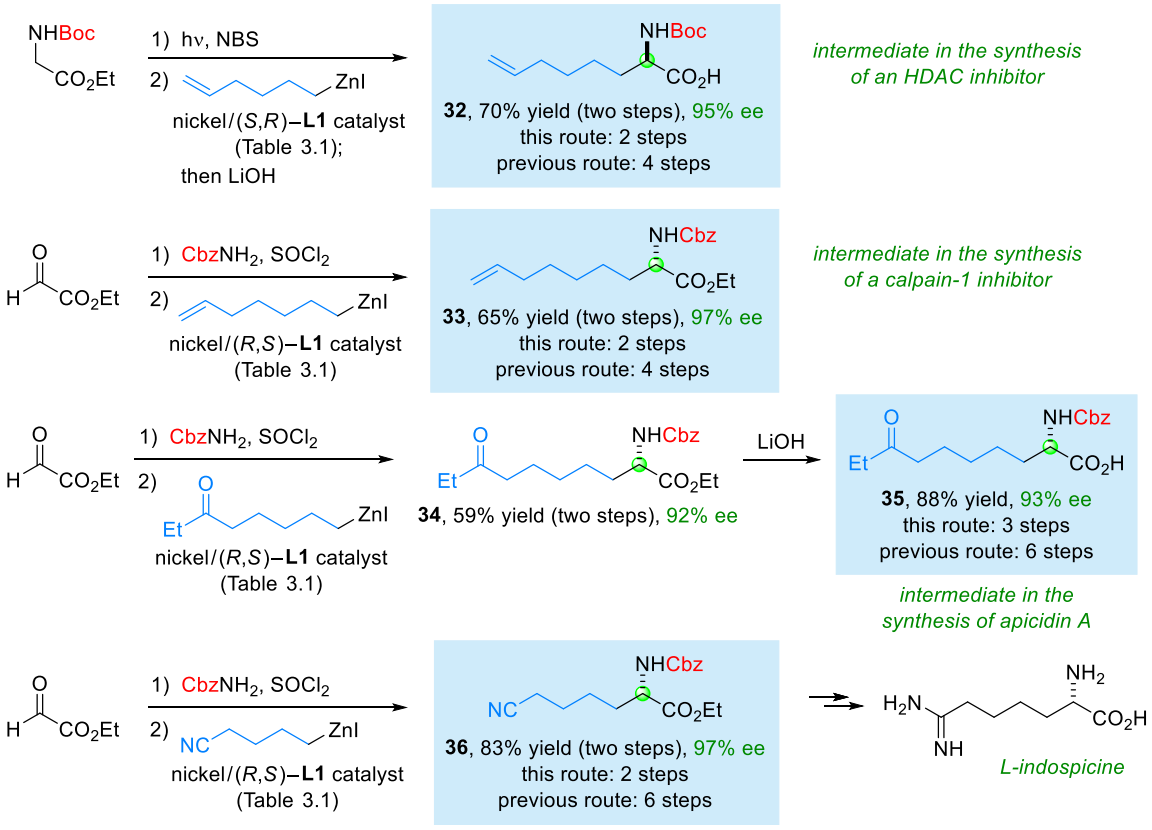


Figure 3.3. *Catalytic enantioconvergent synthesis of protected unnatural α-amino acids: applications to the synthesis of bioactive compounds. All data are the average of two experiments, and all yields are of purified products.*

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

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

3.3. Conclusions

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

3.4. Experimental section

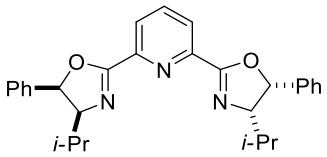
3.4.1. General information

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

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

3.4.2. Preparation of the chiral ligand

The yield has not been optimized.



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

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

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

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

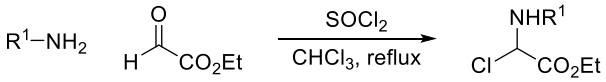
FT-IR (film): 3448, 2922, 2360, 1671, 1574, 1330, 1170, 954, 680 cm^{-1}.

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

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

3.4.3. Preparation of electrophiles

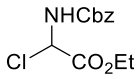
The yields have not been optimized.



General Procedure 1 (GP-1).

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

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

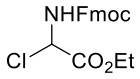


Ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from benzyl carbamate. 4.17 g (15.4 mmol, 93% yield). White solid.

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

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

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

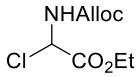


Ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from (9*H*-fluoren-9-yl)methyl carbamate. 3.57 g (9.9 mmol, 99% yield). White solid.

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

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

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

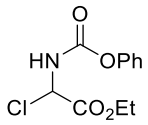


Ethyl 2-(((allyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-1** from allyl carbamate. 1.16 g (5.2 mmol, 97% yield). Yellow solid.

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

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

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

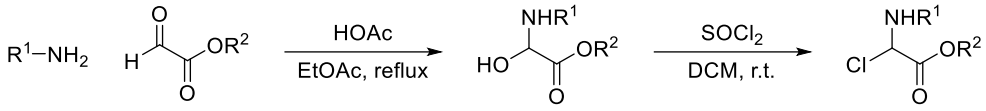


Ethyl 2-chloro-2-((phenoxycarbonyl)amino)acetate. The title compound was synthesized according to **GP-1** from phenyl carbamate. 2.65 g (10.3 mmol, 99% yield). White solid.

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

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

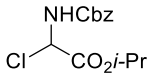
FT-IR (film): 3336, 2985, 1744, 1490, 1339, 1213, 1032 cm^{-1}.



General Procedure 2 (GP-2).

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

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

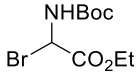


Isopropyl 2-(((benzyloxy)carbonyl)amino)-2-chloroacetate. The title compound was synthesized according to **GP-2** from benzyl carbamate and isopropyl 2-oxoacetate. 2.74 g (9.6 mmol, 73% yield over 2 steps). White solid.

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

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

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



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

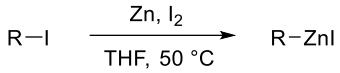
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 – 6.22 (m, 1H), 6.06 – 5.63 (m, 1H), 4.37 – 4.23 (m, 2H), 1.48 (s, 9H), 1.37 – 1.28 (m, 3H).

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

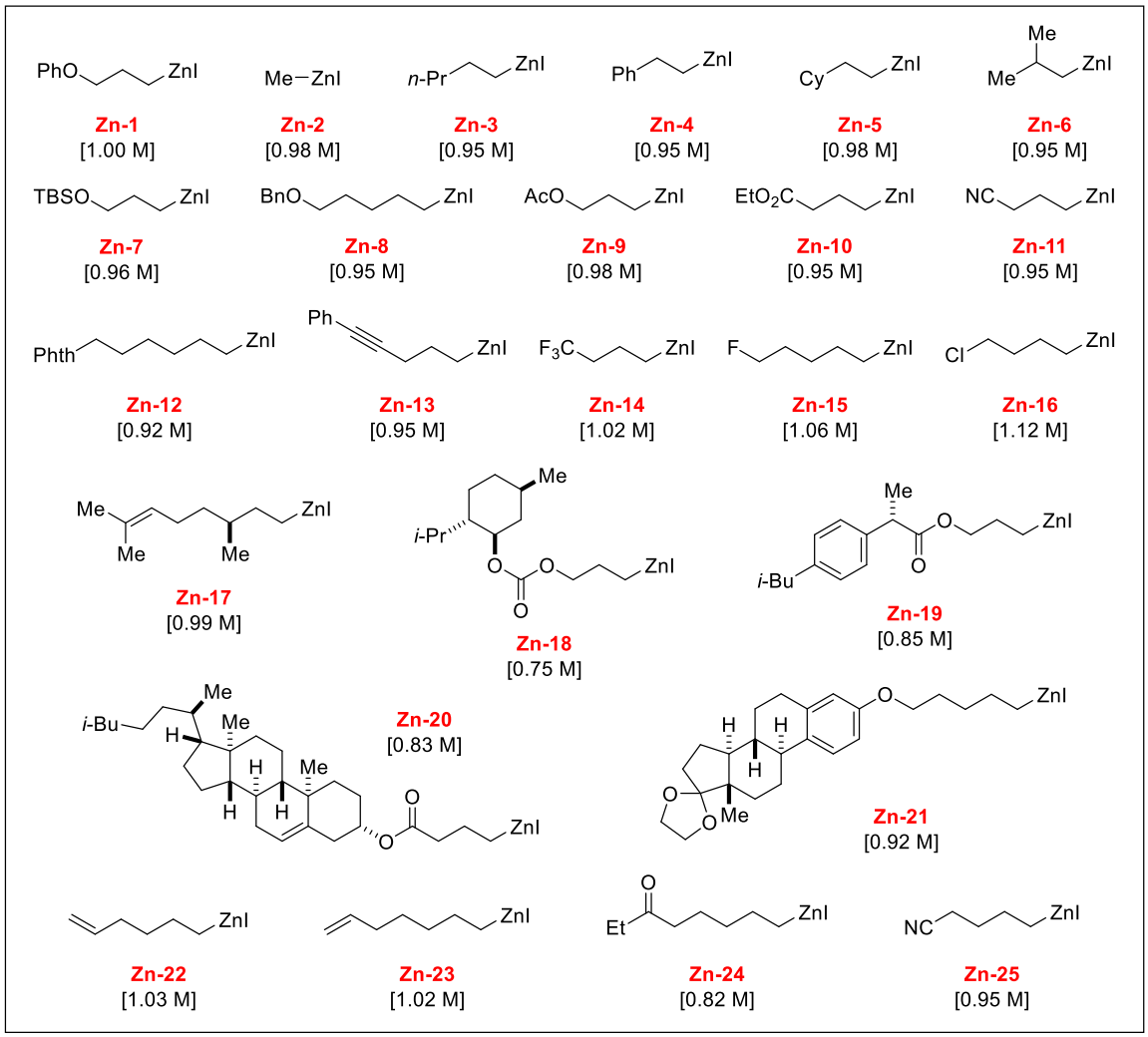
FT-IR (film): 3345, 2984, 2361, 1731, 1496, 1372, 1047, 824, 679 cm^{-1}.

3.4.4. Preparation of nucleophiles

General Procedure 3 (GP-3).

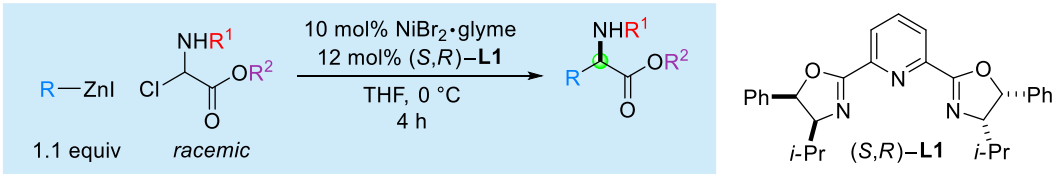


Preparation of the alkylzinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube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



3.4.5. Catalytic enantioconvergent cross-couplings

General Procedure 4 (GP-4).

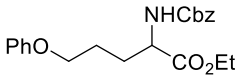


Preparation of a solution of the catalyst: In the air, $NiBr_2$·glyme (18.4 mg, 0.060 mmol, 10 mol%) and (*S*,*R*)–**L1** (32.6 mg, 0.072 mmol, 12 mol%) were added to an oven-dried 40 mL vial equipped with a cross-type stir bar. The vial was closed with a PTFE septum cap, the joint was wrapped with electric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

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

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

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



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

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

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

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

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

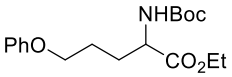
FT-IR (film): 3341, 2956, 2356, 1716, 1498, 1244, 1028, 752 cm^{-1}.

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

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

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

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



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

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

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

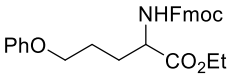
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 2H), 6.99 – 6.81 (m, 3H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.43 – 4.28 (m, 1H), 4.28 – 4.11 (m, 2H), 3.97 (t, *J* = 5.9 Hz, 2H), 2.11 – 1.95 (m, 1H), 1.95 – 1.75 (m, 3H), 1.45 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

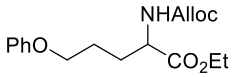
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.66 – 7.52 (m, 2H), 7.46 – 7.36 (m, 2H), 7.35 – 7.25 (m, 4H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.56 – 4.34 (m, 3H), 4.32 – 4.09 (m, 3H), 4.06 – 3.82 (m, 2H), 2.16 – 1.98 (m, 1H), 1.96 – 1.67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

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

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

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

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



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

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

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

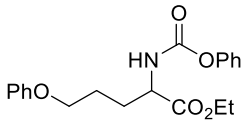
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 2H), 7.01 – 6.81 (m, 3H), 6.03 – 5.83 (m, 1H), 5.40 (d, *J* = 8.3 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.62 – 4.56 (m, 2H), 4.46 – 4.37 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 2.20 – 1.78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

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

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

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

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



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

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

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

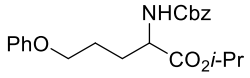
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 6.98 – 6.86 (m, 3H), 5.74 (d, *J* = 8.1 Hz, 1H), 4.56 – 4.38 (m, 1H), 4.24 (q, *J* = 7.3 Hz, 2H), 4.01 (t, *J* = 5.8 Hz, 2H), 2.22 – 2.07 (m, 1H), 2.02 – 1.80 (m, 3H), 1.30 (t, *J* = 7.1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

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

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

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

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



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

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

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

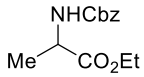
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 7.25 – 7.16 (m, 2H), 6.91 – 6.86 (m, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 5.40 (d, *J* = 8.2 Hz, 1H), 5.06 (s, 2H), 5.04 – 4.93 (m, 1H), 4.39 – 4.29 (m, 1H), 3.91 (t, *J* = 5.6 Hz, 2H), 2.04 – 1.93 (m, 1H), 1.87 – 1.71 (m, 3H), 1.20 (dd, *J* = 9.8, 6.3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

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

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

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

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



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

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

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

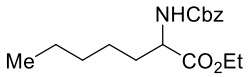
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.35 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 4.37 (p, *J* = 7.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.41 (d, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

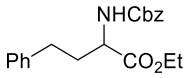
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.29 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.42 – 4.26 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.88 – 1.74 (m, 1H), 1.73 – 1.58 (m, 1H), 1.38 – 1.19 (m, 9H), 0.91 – 0.83 (m, 3H).

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

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

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

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



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

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

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

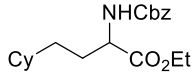
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 7H), 7.24 – 7.08 (m, 3H), 5.37 (d, *J* = 7.9 Hz, 1H), 5.13 (s, 2H), 4.52 – 4.34 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.79 – 2.58 (m, 2H), 2.28 – 2.09 (m, 1H), 2.08 – 1.89 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

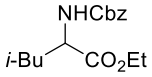
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.27 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 4.39 – 4.27 (m, 1H), 4.27 – 4.08 (m, 2H), 1.94 – 1.76 (m, 1H), 1.76 – 1.56 (m, 6H), 1.35 – 1.05 (m, 9H), 0.95 – 0.76 (m, 2H).

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

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

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

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



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

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

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

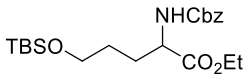
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.19 (d, *J* = 8.7 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.33 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.78 – 1.57 (m, 2H), 1.57 – 1.46 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 6H).

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

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

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

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



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

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

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

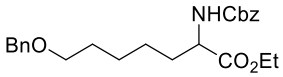
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 5.47 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 2H), 4.41 – 4.31 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 1.96 – 1.69 (m, 2H), 1.64 – 1.49 (m, 2H), 1.33 – 1.23 (m, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 1.6 Hz, 6H).

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

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

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

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



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

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

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

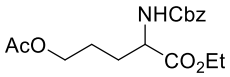
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 5.28 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 4.49 (s, 2H), 4.43 – 4.28 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 1.92 – 1.76 (m, 1H), 1.71 – 1.56 (m, 3H), 1.45 – 1.31 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

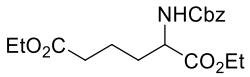
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.37 (d, *J* = 8.2 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.34 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 2.03 (s, 3H), 1.97 – 1.83 (m, 1H), 1.78 – 1.59 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

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

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

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

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



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

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

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

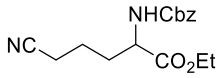
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.36 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.42 – 4.32 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.39 – 2.27 (m, 2H), 1.98 – 1.61 (m, 4H), 1.33 – 1.18 (m, 6H).

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

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

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

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



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

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

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

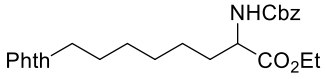
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 5.41 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 2H), 4.46 – 4.31 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.44 – 2.32 (m, 2H), 2.12 – 1.93 (m, 1H), 1.86 – 1.60 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

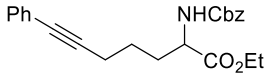
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.37 – 7.27 (m, 5H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.09 (s, 2H), 4.40 – 4.27 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 1.92 – 1.73 (m, 1H), 1.73 – 1.53 (m, 3H), 1.40 – 1.18 (m, 9H).

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

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

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

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



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

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

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

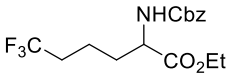
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.22 (m, 10H), 5.37 (d, *J* = 8.1 Hz, 1H), 5.12 (s, 2H), 4.49 – 4.34 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.15 – 1.96 (m, 1H), 1.96 – 1.78 (m, 1H), 1.78 – 1.52 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

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

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

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

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



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

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

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

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

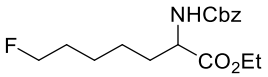
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 156.0, 136.3, 128.7, 128.4, 128.3, 126.7 (q, *J* = 277.8 Hz), 67.2, 61.9, 53.5, 33.3 (q, *J* = 29.3 Hz), 32.0, 18.0 (q, *J* = 3.0 Hz), 14.2.

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

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

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

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



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

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

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

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

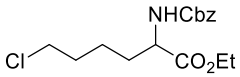
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 156.0, 136.4, 128.7, 128.33, 128.25, 84.0 (d, *J* = 164.6 Hz), 67.1, 61.6, 53.9, 32.8, 30.3 (d, *J* = 19.2 Hz), 25.0 (d, *J* = 5.1 Hz), 24.9, 14.3.

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

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

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

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



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

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

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

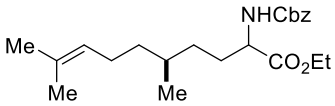
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.35 (d, *J* = 8.3 Hz, 1H), 5.11 (s, 2H), 4.43 – 4.33 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.51 (t, *J* = 6.5 Hz, 2H), 1.93 – 1.62 (m, 4H), 1.60 – 1.39 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

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

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

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

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



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

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

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

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

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

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

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

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

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

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

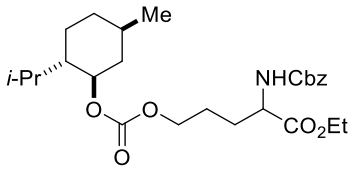
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.26 (m, 5H), 5.30 (d, *J* = 8.1 Hz, 1H), 5.22 – 4.99 (m, 3H), 4.44 – 4.27 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.05 – 1.77 (m, 3H), 1.73 – 1.55 (m, 7H), 1.43 – 1.09 (m, 8H), 0.86 (d, *J* = 6.5 Hz, 3H).

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

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

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

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



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

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

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

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

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

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

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

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

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

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

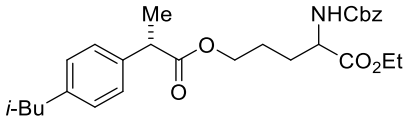
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 2H), 4.50 (td, *J* = 10.9, 4.4 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 2.11 – 2.02 (m, 1H), 2.02 – 1.87 (m, 2H), 1.81 – 1.62 (m, 5H), 1.53 – 1.35 (m, 2H), 1.27 (t, *J*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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

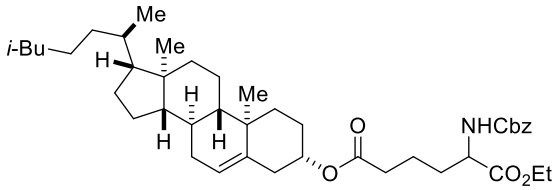
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.23 (d, *J* = 8.3 Hz, 1H), 5.11 (s, 2H), 4.38 – 4.28 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.89 – 1.78 (m, 2H),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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

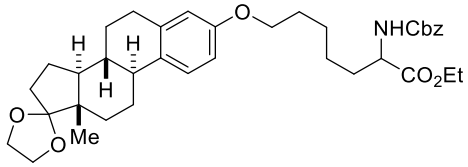
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.44 – 5.24 (m, 2H), 5.11 (s, 2H), 4.70 – 4.53 (m, 1H), 4.43 – 4.31 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.22 (m, 4H), 2.07 – 1.76 (m, 6H), 1.76 – 1.41 (m, 11H), 1.41 – 1.21 (m, 7H), 1.18 – 0.95 (m, 12H), 0.93 – 0.83 (m, 9H), 0.68 (s, 3H).

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.4.6. Effect of reaction parameters

General Procedure 5 (GP-5).

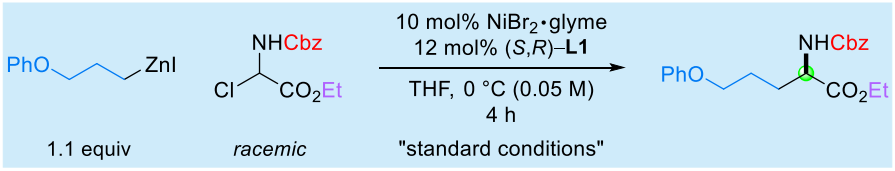
Preparation of a solution of the catalyst: In a nitrogen-filled glovebox, an oven-dried 4 mL vial that contained a stir bar was charged with $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and (*S*,*R*)**–L1** (5.4 mg, 0.012 mmol, 12 mol%). Next, THF (1.0 mL) was added, the vial was capped with a PTFE septum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

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

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

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

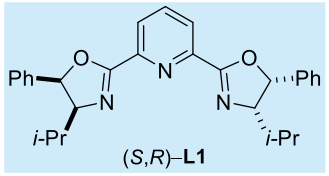
Table 3.2. *Effect of reaction parameters.*



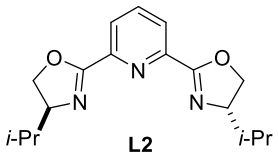
1.1 equiv *racemic* "standard conditions"

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

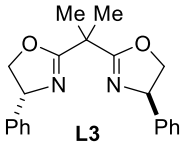
All data are the average of two experiments. [a]Determined through LC-MS analysis using an internal standard [b]Determined through SFC analysis.



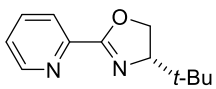
(*S*,*R*)–**L1**



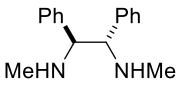
L2



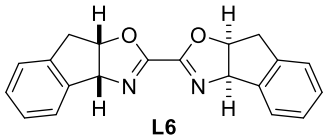
L3



L4



L5

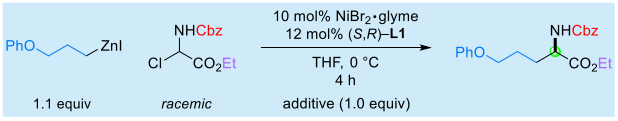


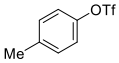
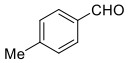
L6

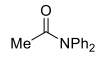
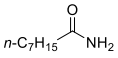
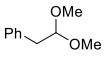
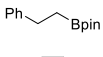
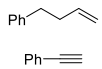
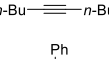
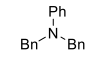
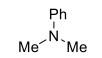
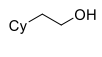
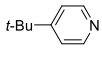
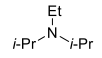
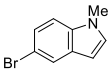
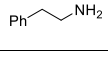
3.4.7. Study of functional-group compatibility

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

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

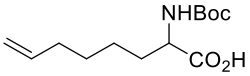


additive	recovery (%)[a]	yield (%)[b]	ee (%)[c]
n-$C_{10}H_{21}Cl$	93 >95[d]	80 79	96 96
	>95	77	96
	88 >95[d]	84 80	96 96
	>95	82	97
	>95	81	97
	>95	79	96
	>95	81	97
	>95	82	96
	>95	82	97
	>95	84	96
$CH_3(CH_2)_{13}CN$	>95	82	95
	>95	79	97
	>95	80	96
	>95	77	96
	>95	77	96
	>95	79	96
	>95	81	96
	>95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

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

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

3.4.8. Applications



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

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

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

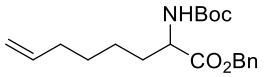
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.16 – 4.81 (m, 3H), 4.40 – 4.04 (m, 1H), 2.14 – 1.97 (m, 2H), 1.94 – 1.78 (m, 1H), 1.75 – 1.61 (m, 1H), 1.48 – 1.36 (m, 13H).

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

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

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

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



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

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

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

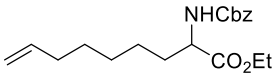
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.30 – 5.08 (m, 2H), 5.08 – 4.86 (m, 3H), 4.34 (q, *J* = 7.3 Hz, 1H), 2.09 – 1.89 (m, 2H), 1.86 – 1.74 (m, 1H), 1.68 – 1.57 (m, 1H), 1.51 – 1.21 (m, 13H).

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

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

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

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



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

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

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

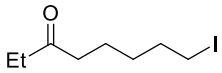
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.79 (m, 1H), 5.33 – 5.26 (m, 1H), 5.11 (s, 2H), 5.04 – 4.89 (m, 2H), 4.40 – 4.30 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.88 – 1.60 (m, 2H), 1.41 – 1.24 (m, 9H).

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

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

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

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



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

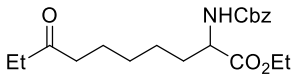
pressure. The residue was purified by column chromatography on silica gel (1:20 EtOAc/hexanes) to afford the product as a yellow oil (2.80 g, 11.0 mmol, 55% yield).

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

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

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

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



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

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

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

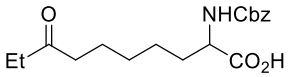
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.33 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 2H), 4.38 – 4.27 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.46 – 2.30 (m, 4H), 1.88 – 1.72 (m, 1H), 1.71 – 1.48 (m, 3H), 1.38 – 1.21 (m, 7H), 1.03 (t, *J* = 7.3 Hz, 3H).

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

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

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

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



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

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

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

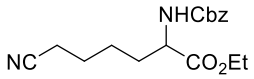
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.42 – 7.27 (m, 5H), 5.42 (d, *J* = 8.3 Hz, 1H), 5.19 – 5.05 (m, 2H), 4.48 – 4.18 (m, 1H), 2.52 – 2.27 (m, 4H), 1.97 – 1.76 (m, 1H), 1.76 – 1.61 (m, 1H), 1.62 – 1.47 (m, 2H), 1.42 – 1.21 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H).

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

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

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

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



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

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

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

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

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

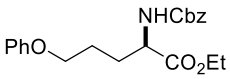
FT-IR (film): 3351, 2920, 2247, 1716, 1520, 1020, 680 cm^{-1}.

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

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

3.4.9. Assignment of absolute configuration

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



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

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

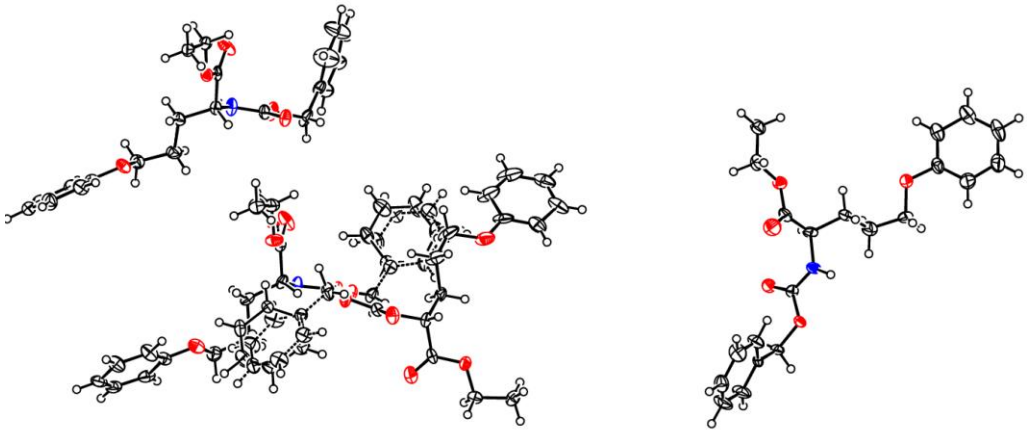
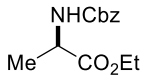


Table 3.4. *Crystal data for 1.*

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

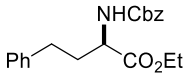
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	13543 / 445 / 1097	
Goodness-of-fit on F^2	1.061	
Final R indices	13446 data; $I>2\sigma(I)$	R1 = 0.0363, wR2 = 0.0903
	all data	R1 = 0.0367, wR2 = 0.0907
Weighting scheme	$w=1/[\sigma^2(Fo^2)+(0.0371P)^2+1.4617P]$ where $P=(F_o^2+2F_c^2)/3$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



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

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

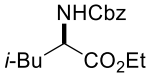
Lit.: $[\alpha]^{21}_D = -1.7$ (*c* 3.63, $CHCl_3$); 99% ee for (*R*) configuration.



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

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

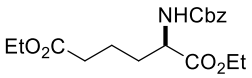
Lit.: $[\alpha]_D = +25$ (*c* 1.08, $CHCl_3$); 99% ee for (*S*) configuration.



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

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

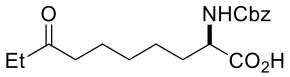
Lit.: $[\alpha]^{25}_D = -6.3$ (*c* 1.96, $CHCl_3$); 99% ee for (*S*) configuration.



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

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

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



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

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

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

3.5. Notes and references

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electrophiles (e.g., an organonickel(II) resting state: virtually no EPR-active nickel species (<2% of the total nickel present) and possible ESI-MS support for the presence of $[(pybox)Ni(alkyl)]^+$). See refs 21 and 22.

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Chapter 4

ENANTIOCONVERGENT, NICKEL-CATALYZED CROSS-COUPLING FOR THE ASYMMETRIC SYNTHESIS OF PROTECTED THIOLS

4.1. Introduction

Enantioenriched alkyl-substituted organosulfur compounds are frequently encountered in organic synthesis, chemical biology, and agrochemistry.[1,2] Because sulfur is a frequent constituent of pharmaceuticals, its selective incorporation into complex molecular frameworks is an ongoing goal (and challenge) in medicinal chemistry (**Figure 4.1**).[3,4]

Common approaches to the synthesis of organosulfur compounds rely on the nucleophilicity of thiol derivatives. While thiols are versatile building blocks for a number of other sulfur-containing functionalities, there exist few examples of the reverse reaction (i.e., the conversion of organosulfur functional groups to thiols).[5–7] Thus, the development of efficient methods to synthesize enantioenriched thiols would grant access to a wide array of chiral organosulfur compounds (**Figure 4.2**).

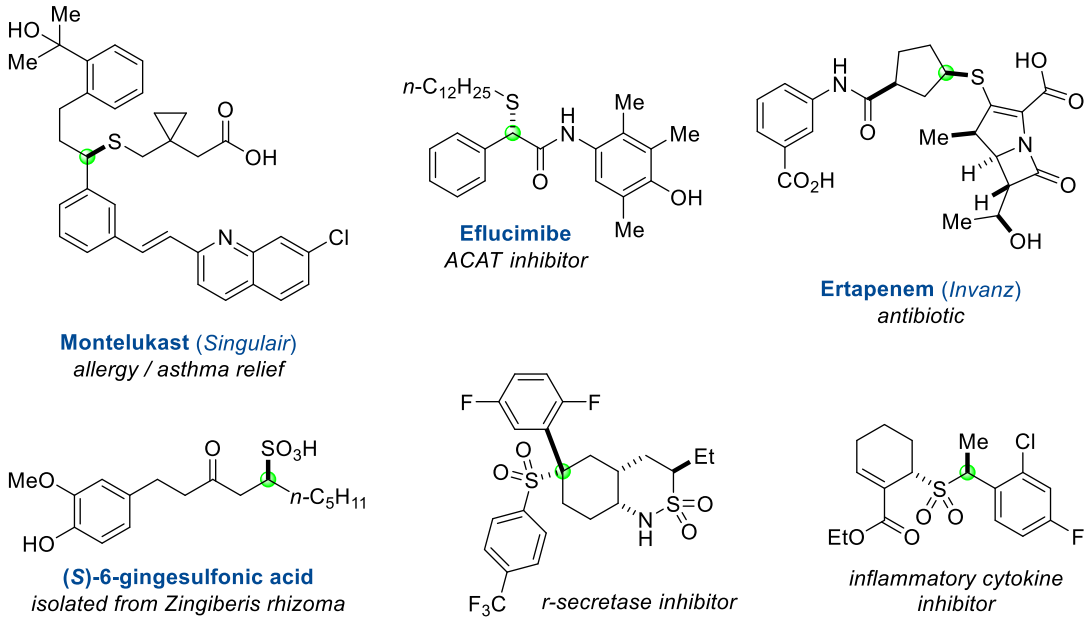


Figure 4.1. *Examples of chiral, alkyl-substituted organosulfur compounds.*

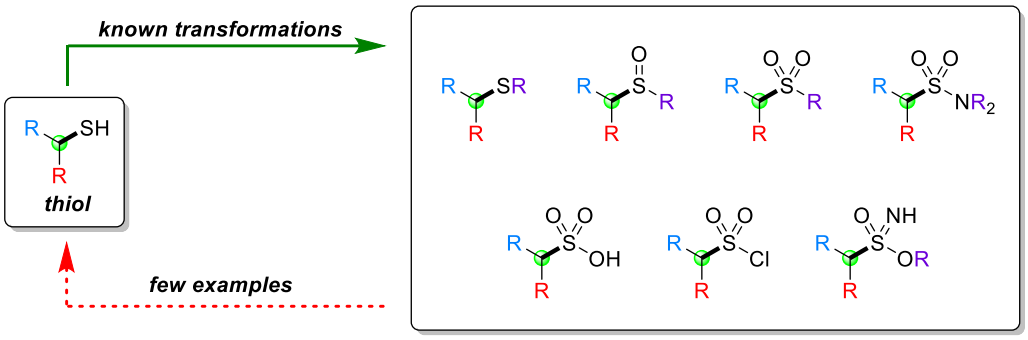
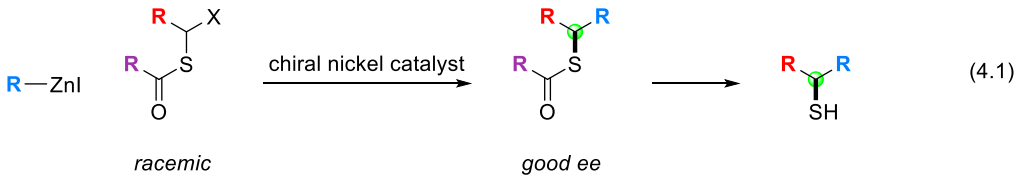


Figure 4.2. *Thiols as versatile building blocks for organosulfur compounds.*

Remarkably, despite the value of enantioenriched alkyl-substituted thiols as building blocks, there exist few methods for their synthesis. The S_N2 reaction and the Mitsunobu reaction have been applied, although these methods require the use of enantioenriched starting materials.[8–10] Other classical approaches require the use of a chiral auxiliary, such as intramolecular sulfur transfer reactions of oxazolidine-2-thiones[11,12] and nucleophilic attacks of α-thioenolates[13] and α-thioorganolithium reagents.[14] Catalytic asymmetric methods have provided efficient syntheses of enantioenriched thiols, although these approaches generally have limited scope. Sneddon reported the synthesis of allylic protected thiols through a palladium-catalyzed rearrangement of *O*-allyl carbamothioates (limited scope with respect to the alkyl groups).[15] Ellman described the enantioselective addition of thioacetic acid to nitroalkenes via *N*-sulfinyl urea organocatalysis,[16] and Connon disclosed the sulfonamide-catalyzed kinetic resolution of thiols (both methods are only applicable to the synthesis of benzylic thiols).[17] List reported a phosphoric acid-catalyzed nucleophilic ring opening of epoxides (limited to the formation of β-hydroxythiols).[18] To our knowledge, there exists no general catalytic method for the synthesis of enantioenriched aliphatic thiols, namely one that allows for facile modifications to both alkyl groups and exhibits broad functional group tolerance.



Our lab has applied nickel-catalyzed enantioconvergent substitution reactions to a range of readily-available racemic electrophiles, including those that contain a heteroatom that is geminal to the bond-forming center.[19–24] The incorporation of a sulfur functional group into a racemic electrophile would require the catalyst to differentiate between an alkyl group and a sulfur substituent, which we viewed as a promising strategy for the asymmetric synthesis of thiols (**eq 4.1**). In this chapter, we describe preliminary results that demonstrate the viability of this approach. Specifically, we disclose the synthesis of racemic NHP esters of α-thioester carboxylic acids and their application to cross-coupling with alkylzinc reagents.

4.2. Results and discussion

4.2.1. Synthesis of an α-thioester NHP ester

We initially targeted protected thiols in the form of thioesters, which are readily installed and can be easily cleaved under basic conditions (whereas the deprotection of other protecting groups, such as thioethers, require more forcing conditions).[25] In addition, the carbonyl substituent of the thioester may coordinate to the catalyst in the stereochemistry-determining step to improve the enantioselectivity of cross-coupling.

While our group's efforts in nickel catalysis have primarily focused on the use of alkyl halides as electrophiles, alkyl halides bearing a geminal thioester are unstable and difficult to synthesize.[26] In a recent study, we observed that redox-active esters of amino

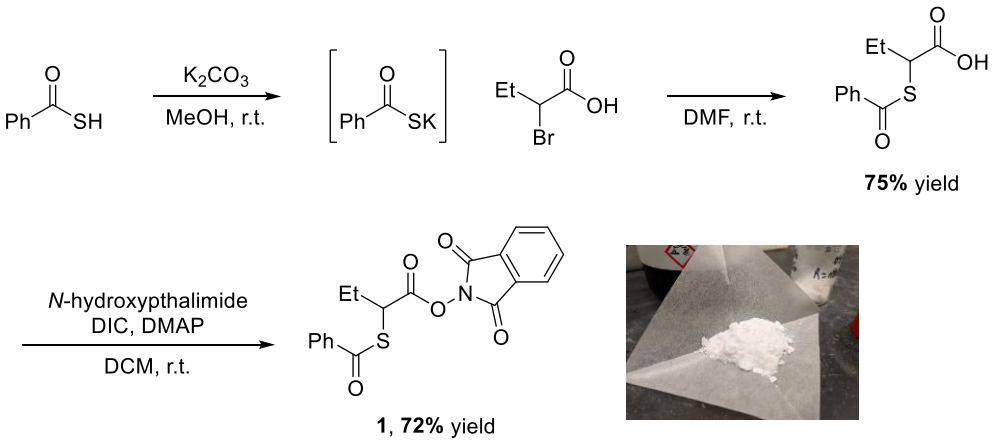


Figure 4.3. *Synthesis of* ***1****, an α-thioester NHP ester.*

acids are considerably more stable and easier to handle than their alkyl halide analogs (see *Chapter 2*),[23] motivating us to pursue a similar strategy in the synthesis of enantioenriched protected thiols. Carboxylic acids containing an α-thioester substituent are known compounds, often employed as synthetic building blocks due to the versatility of the thioester as a precursor to other functional groups.[27–29] However, these compounds have not been applied to decarboxylative couplings.

Using conditions developed for the synthesis of NHP esters of α-amino acids,[23] we generated NHP ester **1** in good yield (**Figure 4.3**). To our knowledge, this is the first synthesis of an NHP ester of a carboxylic acid containing an α-thioester substituent. **1** is a free-flowing white solid that can be stored under air and at room temperature for several months without detectable decomposition.

4.2.2. Nickel-catalyzed couplings of α-thioester NHP esters

Upon surveying a range of chiral ligands, we found that several nickel complexes can catalyze the coupling of an alkylzinc reagent and racemic NHP ester **1** in modest yield and enantioselectivity (**Figure 4.4**). Cyanobox ligands offer the most promising

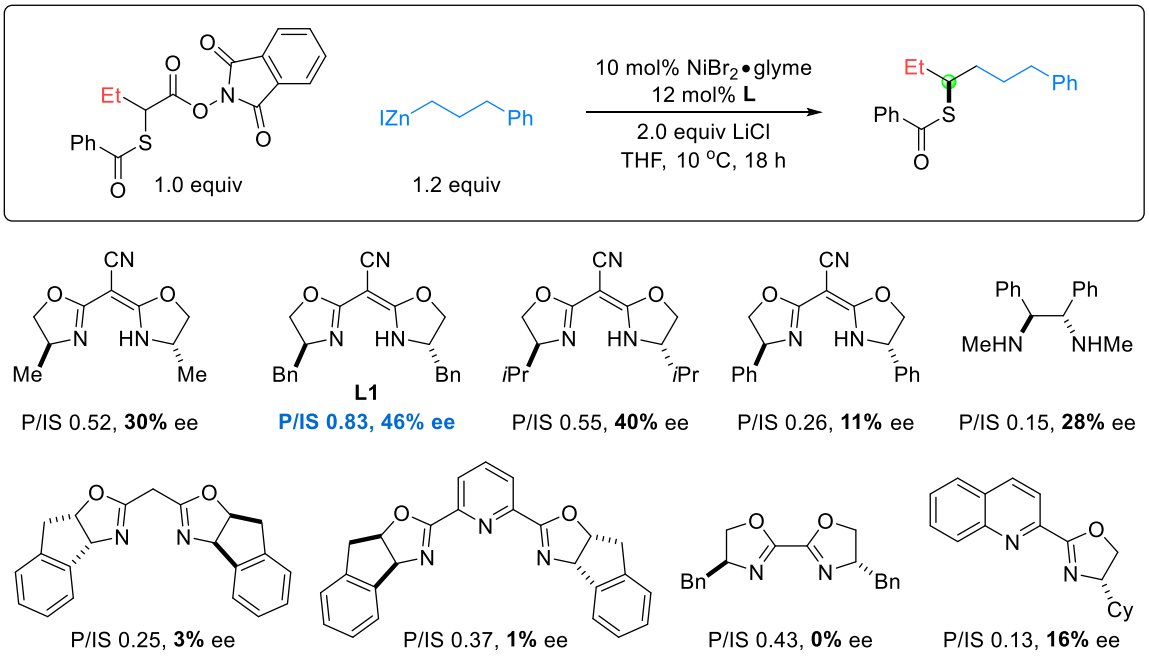
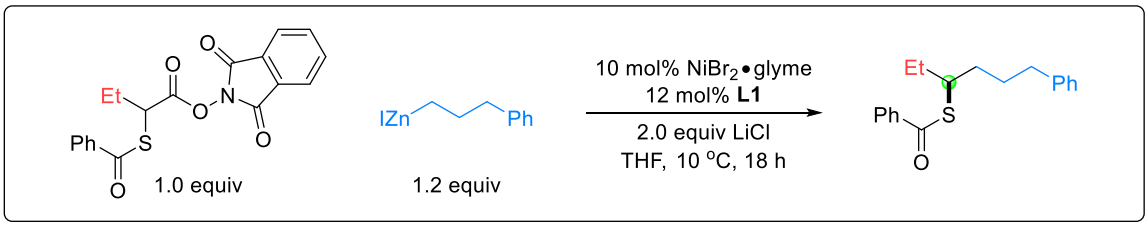


Figure 4.4. *Effect of ligand.*

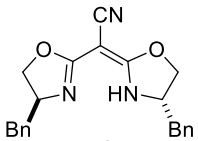
reactivity; benzyl-substituted cyanobox **L1** affords the product in 46% ee. At this stage of reaction development, the ratio of product to internal standard (P/IS) was determined by LC-MS analysis, and the P/IS of 0.83 obtained in the coupling with **L1** was estimated to correspond to a <20% yield. Under these conditions, a majority of the NHP ester remains unreacted and no major byproducts are observed.

Prior to continuing the optimization of this enantioconvergent coupling, we performed several control experiments to assess its reproducibility (**Table 4.1**). We determined that reactions run in parallel yield consistent results (**Table 4.1**, entries 1 and 2). Coupling does not proceed in the absence of nickel, the chiral ligand, or LiCl (entries 3–5). Increasing the loading of $NiBr_2$·glyme results in a slight improvement to the yield but a drop in ee, while increasing the amount of **L1** has the opposite effect (entries 6 and 7). Varying the stoichiometry of LiCl or the alkylzinc reagent, prolonging the reaction time, or removing stirring does not affect the outcome of the reaction (entries 8–12). While this transformation appears to be robust to minor changes in the conditions and setup procedure,

Table 4.1. *Control reactions and study of reproducibility.*



entry	variation from the standard conditions	P/IS	ee (%)
1	none	1.14	35
2	none	1.09	36
3	No $NiBr_2$•glyme	0	-
4	No **L1**	0	-
5	No LiCl	0	-
6	16 mol% $NiBr_2$•glyme, instead of 10 mol%	1.45	28
7	20 mol% **L1**, instead of 12 mol%	0.94	48
8	2.6 equiv LiCl, instead of 2.0 equiv	1.14	41
9	0.8 equiv Nu, instead of 1.2 equiv	1.05	39
10	1.5 equiv Nu, instead of 1.2 equiv	1.19	26
11	42 h, instead of 18 h	1.02	34
12	No stirring (no stir bar)	1.04	36
13	Ni and **L1** pre-stirred 5 for min, instead of 30 min	1.00	**47**
14	Ni and **L1** not pre-stirred at all	0.94	**53**

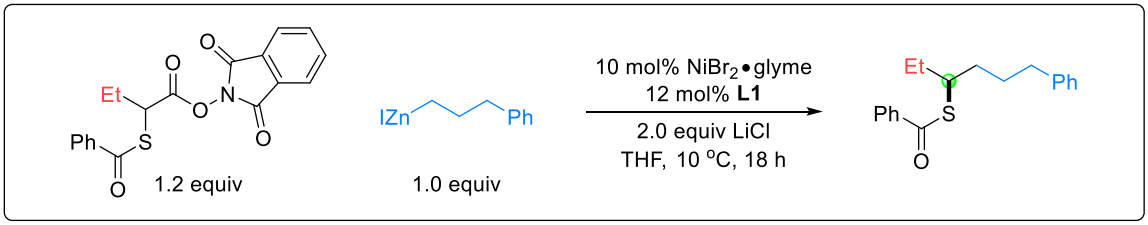


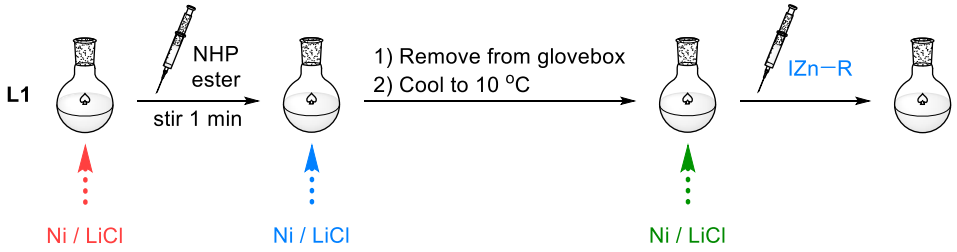
L1

we were surprised to find that decreasing the catalyst pre-stir time significantly improves the enantioselectivity (entries 13 and 14), prompting us to examine this phenomenon further.

Through systematic modifications to the reaction setup procedure, we studied the effect of catalyst pre-stirring (**Table 4.2**). These experiments indicated that the enantioselectivity of product formation increases as the catalyst pre-stir time decreases.[30] To our knowledge, this trend has not been reported in other asymmetric nucleophilic substitution reactions; in fact, our group generally observes the opposite effect, wherein a sufficiently long pre-stirring of the catalyst components is necessary to achieve good enantioselectivity (including other reactions catalyzed by a nickel-cyanobox complex).[31] Further optimization of the reaction was conducted using the conditions outlined in **Table 4.2**, entry 5, which affords the product in 81% ee.

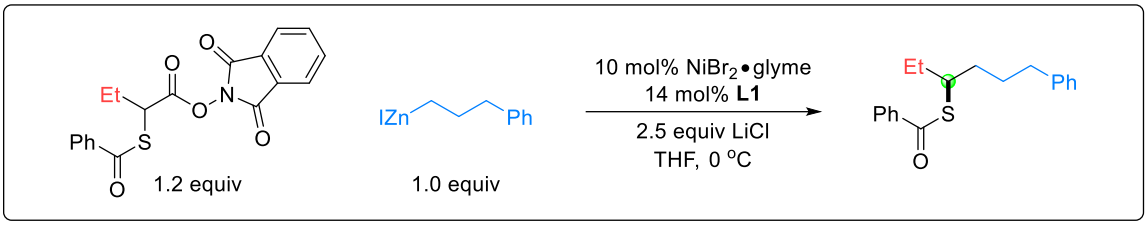
Table 4.2. *Effect of catalyst pre-stir time.*





entry	conditions	ee (%)
1	**Ni / LiCl** stirred with ligand for 1 h before adding NHP ester	29
2	**Ni / LiCl** stirred with ligand for 30 min before adding NHP ester	54
3	Stir **L1** and NHP ester, then add **Ni / LiCl** and immediately remove from glovebox	72
4	Once reaction is cooled, add **Ni / LiCl** and then add R–ZnI 5 min later	78
5	Once reaction is cooled, add **Ni / LiCl** and then add R–ZnI immediately	81

Table 4.3. *Time course study.*



entry	reaction time (h)	% NHP ester remaining	yield (%)	ee (%)
1	1	73	5	86
2	2	69	5	86
3	4	67	6	85
4	6	66	6	84
5	24	61	6	84
6	72	60	6	82

Under these new conditions, we examined the time course of the enantioconvergent coupling (**Table 4.3**). The product is formed in only 5% yield after 1 h (**Table 4.3**, entry 1), which does not increase upon prolonging the reaction to 72 h (entry 6). This poor yield is in part due to the low consumption of NHP ester, 60% of which remains unreacted after several days of stirring (entry 6). Variations of the temperature, solvent, nickel precatalyst, and catalyst loading did not lead to higher yields.

We reasoned that more aggressive modifications to the reaction system would be necessary to optimize this method, such as pursuing a different ligand class or introducing additives. However, replacing cyanobox **L1** with other classes of chiral ligands is deleterious to both the yield and enantioselectivity (**Figure 4.5**). In all cases, the conversion of NHP ester **1** is low. Although this transformation is not believed to proceed through the formation of a dative bond between sulfur and nickel, is possible that non-covalent coordination of sulfur poisons the catalyst, which may account for the unusually low reactivity of **1** compared to other NHP esters in nickel catalysis.

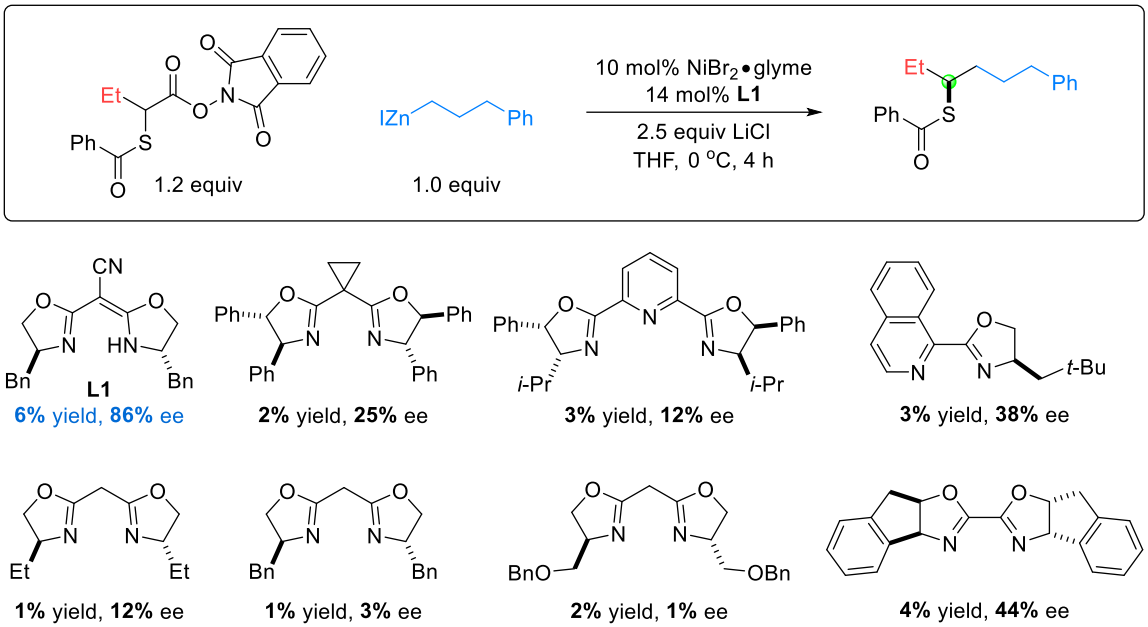


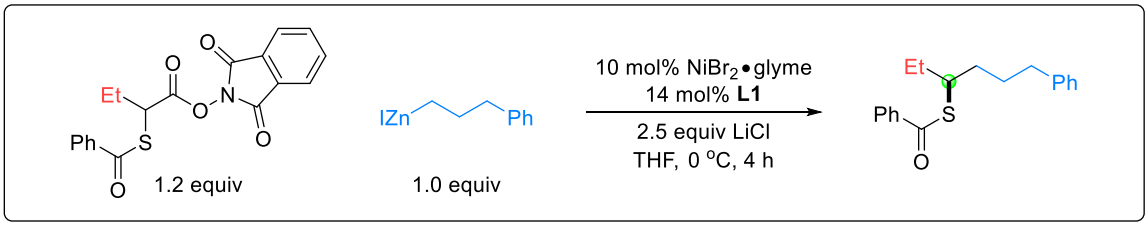
Figure 4.5. *Examining other families of chiral ligands.*

Previous work in our lab demonstrated that nickel-catalyzed alkylations of NHP esters with alkylzinc reagents can require a number of additives to proceed efficiently (see *Chapter 2*).[23] While LiCl indeed improves substrate conversion (**Table 4.1**, entries 1 and 5), the addition of other additives found to be beneficial for related couplings of NHP esters (such as TMSCl, DMAP, and DIC) are detrimental to this reaction (**Table 4.4**, entries 1–4). The addition of a zinc salt or an achiral phosphine, which has been shown to be necessary for product formation in other nickel-catalyzed Negishi couplings,[32] does not improve the yield (entries 5–7). Similarly, while the addition of a Lewis base leads to higher consumption of the NHP ester, the product yield remains low (entries 8–10).

4.2.3. Investigating other organosulfur electrophiles

Although the nickel-catalyzed enantioconvergent substitution of **1** proceeds with good enantioselectivity, its synthetic utility is hindered by low yields arising from poor conversion of starting materials. In related couplings of NHP esters, tuning the electronic properties of the phthalimide moiety is necessary to achieve appreciable reactivity.[33] Inspired by these findings, we synthesized NHP esters containing electron donating/withdrawing substituents on the phthalimide and applied them as substrates in

Table 4.4. *Effect of additives.*



entry	additive (1.0 equiv)	% NHP ester remaining	yield (%)	ee (%)
Additives shown to benefit couplings of NHP esters (see Chapter 2)				
1	None	49	7	85
2	TMSCl	71	7	70
3	DMAP	55	2	24
4	DIC	56	5	86
Zinc salts				
5	$ZnCl_2$	61	5	75
Achiral phosphines				
6	PPh_3 (40 mol%)	57	6	91
7	dppp (20 mol%)	57	0	-
Lewis bases				
8	TMEDA	43	0	-
9	TMP	0	3	55
10	DMPU	6	5	84

nickel-catalyzed enantioconvergent cross-couplings (**Figure 4.6**). These modifications led to improved yields, particularly when tetrachloro- and tetrabromo- phthalimides were used. Further optimizations of reactions employing these substrates may be a fruitful direction to pursue in the future.

Due to the propensity of thioesters to cleave under basic conditions, it is possible that, in the presence of an organozinc reagent, α-thioester NHP ester **1** is deprotected to form an anionic sulfide, which could inhibit cross-coupling (such as by poisoning the catalyst).[34] To examine this phenomenon, we synthesized NHP esters containing other carbonyl-based thiol protecting groups, namely those containing S–Fmoc and S–Cbz thiocarbonates. Although there exist no reported syntheses of NHP esters containing an α-thiocarbonate substituent, we found that they can be accessed from α-thio carboxylic acids using a modified procedure based on the preparation of carbamate-protected α-amino NHP esters (**eqs 4.2** and **4.3**).[23] Similarly to **1**, these α-thiocarbonate NHP esters are free-

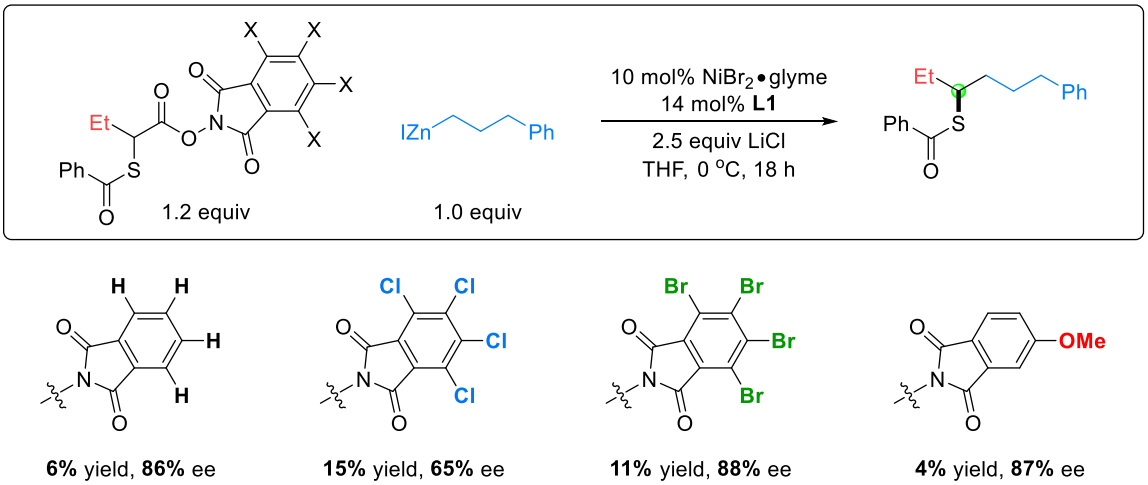
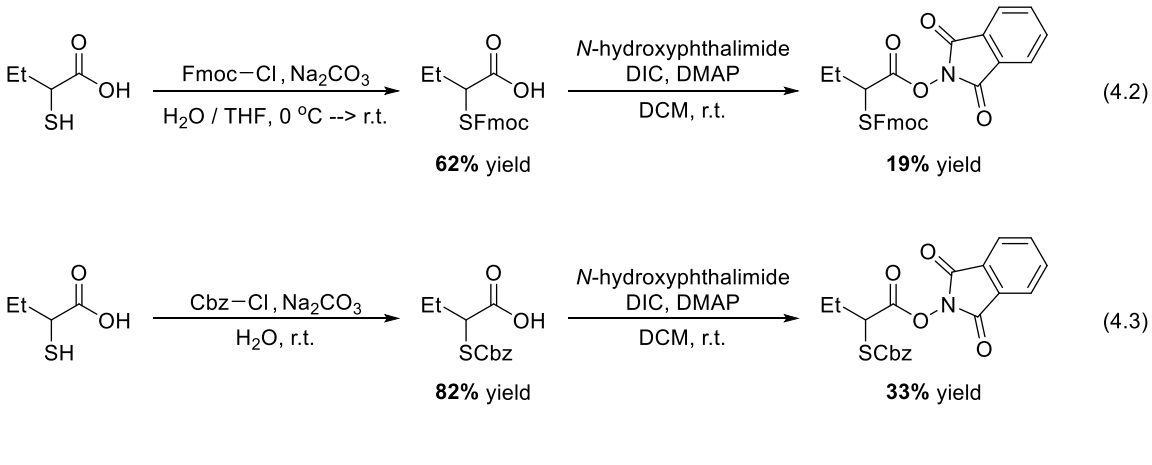
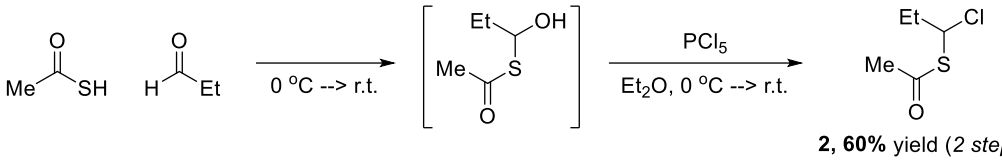


Figure 4.6. *Modification of the phthalimide substituent of* ***1****.*

flowing white solids that are stable under ambient conditions for several months. Upon applying these compounds to nickel-catalyzed couplings with alkylzinc reagents, however, we observed no reaction (**eq 4.4**).

Although NHP esters are stable and easy to handle, the poor reactivity of **1** might be enhanced by substituting the redox-active ester with a halide leaving group. We originally did not target alkyl halides containing an α-thioester substituent due to their instability; however, after modifications to a reported procedure,[26] we successfully



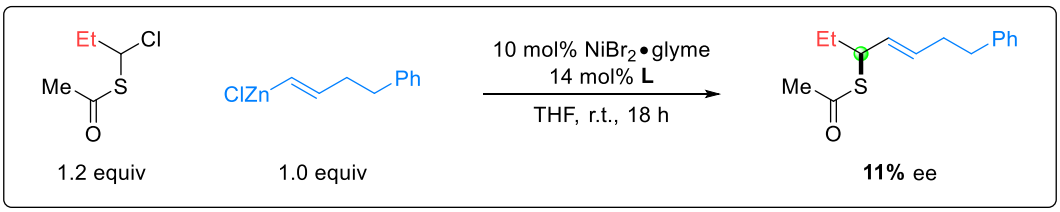


(4.5)

synthesized and isolated α-chloro thioester **2** in good yield through the *in situ* formation and chlorination of an α-hydroxy thioester (**eq 4.5**).

When **2** is allowed to stir with an alkylzinc reagent in the presence of a chiral nickel catalyst, no product is formed, even after changes to the ligand and other reaction conditions. Alkenylzirconium reagents, alkynylzinc reagents, and olefin / hydrosilane mixtures are unsuccessful nucleophiles in this transformation as well. However, **2** reacts with an alkenylzinc reagent to afford an allylic thioester in modest yield and 11% ee (**Figure 4.7**). The development of this reaction may be of interest due to the numerous applications of allylic organosulfur compounds in organic synthesis.[35,36]

Given the limitations in the reactivities of electrophiles containing carbonyl-based thiol protecting groups disclosed herein, we investigated electrophiles possessing a thioether substituent, specifically, an α-thiophenyl alkyl chloride and an NHP ester bearing an α-thiobenzyl substituent. When applied to enantioconvergent substitution reactions with an alkylzinc reagent in the presence of a chiral nickel catalyst, these electrophiles afford aliphatic thioethers in ~20% ee (**eqs 4.6** and **4.7**). These results suggest that the carbonyl



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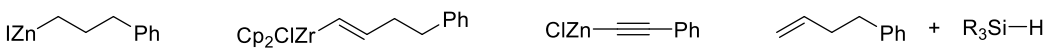
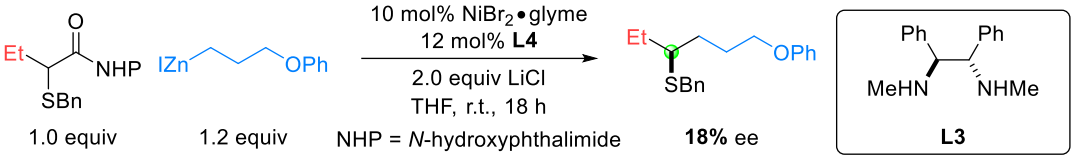


Figure 4.7. *Nickel-catalyzed enantioconvergent alkenylation of* ***2*** *using an alkenylzinc reagent, along with unsuccessful nucleophiles tested.*

(4.6)



(4.7)

substituent of thioester electrophiles such as **1** may play an important role in the stereochemistry-determining step of these transformations. However, further studies must be carried out on these thioethers in order to assess their potential as cross-coupling substrates more rigorously.

4.3. Conclusions

While enantioconvergent nucleophilic substitution reactions have been applied to the synthesis of numerous important families of compounds, this approach has not yet been applied to the asymmetric synthesis of alkyl-substituted thiols. We have developed a synthesis of an α-thioester NHP ester, a new type of substrate in cross-coupling, and found that this electrophile reacts with an alkylzinc reagent in the presence of a chiral nickel catalyst to afford aliphatic thioesters in high ee, albeit in modest yields. We have begun to explore variations in the reaction conditions, along with the effect of modifying the structure of the electrophile. During these efforts, we discovered that alkenylzinc reagents can be employed in couplings with α-chloro thioesters, which could serve as a straightforward route to synthetically-useful enantioenriched allylic thiols. We anticipate that this chemistry may draw attention to the potential of nickel-catalyzed nucleophilic substitution reactions as an appealing strategy to access enantioenriched organosulfur compounds.

4.4. Experimental section

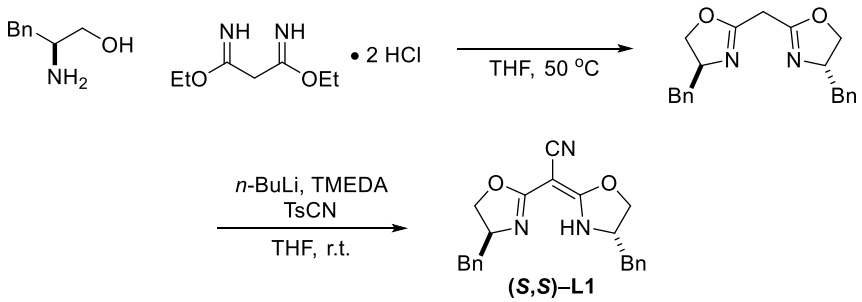
4.4.1. General information

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.

NMR spectra were collected on a Bruker 400 MHz spectrometer at ambient temperature; chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, using the solvent resonance as the internal standard. SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® columns (4.6 × 250 mm, particle size 5 μm). LC-MS were obtained on an Agilent 6140 UHPLC-MS system in electrospray ionization (ESI+) mode. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle).

4.4.2. Preparation of the chiral ligand

The yields have not been optimized.



(*E*)-2-((*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl)-2-((*S*)-4-benzyloxazolidin-2-ylidene) acetonitrile.[31] An oven-dried 100 mL round-bottom flask was equipped with a stir bar, (*S*)-phenylalaninol (4.00 g, 26.5 mmol, 2.0 equiv), and diethyl malonimidate dihydrochloride (3.06 g, 13.2 mmol, 1.0 equiv). The flask was sealed with a rubber septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (40 mL) via syringe. After the solution was stirred at 50 °C for 48 h, it was diluted with water (200 mL). The mixture was extracted with

dichloromethane (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (1:9 MeOH/DCM) to afford bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane as a white solid (2.50 g, 7.5 mmol, 56% yield).

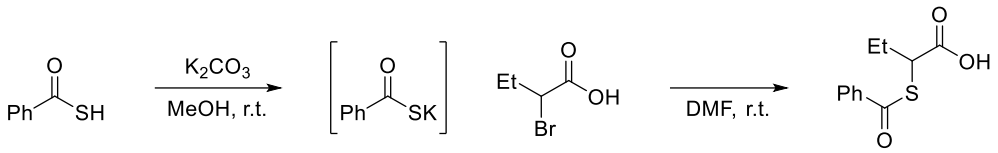
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 10H), 4.48 – 4.38 (m, 2H), 4.23 (dd, *J* = 9.4, 8.4 Hz, 2H), 4.02 (dd, *J* = 8.5, 7.2 Hz, 2H), 3.32 (s, 2H), 3.11 (dd, *J* = 13.8, 5.4 Hz, 2H), 2.68 (dd, *J* = 13.8, 8.5 Hz, 2H).

An oven-dried 250 mL round-bottom flask was equipped with a stir bar and bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane (2.50 g, 7.5 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (100 mL). The solution was then cooled to –78 ºC. Next, *n*-BuLi (3.6 mL, 2.5 M in hexanes, 9.0 mmol, 1.2 equiv) was added dropwise over 5 min and TMEDA (1.3 mL, 9.0 mmol, 1.2 equiv) was added in a continuous flow via syringe. The solution was stirred at –78 ºC for 20 min, then at 0 ºC for 30 min, after which the flask was cooled back to –78 ºC. To an oven-dried 40 mL vial was added *p*-toluenesulfonyl cyanide (1.62 g, 9.0 mmol, 1.2 equiv), and the vial was placed under a nitrogen atmosphere by evacuating and back-filling (three cycles), followed by the addition of THF (10 mL). This solution was transferred via syringe to the 250 mL reaction flask in a continuous flow at –78 ºC. The resulting mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with a saturated NH_4Cl solution (100 mL) at room temperature and was diluted with H_2O (100 mL). The mixture was extracted with Et_2O (100 mL x 3), and the combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4, and concentrated. The crude product was recrystallized in hexanes / THF to afford the desired product (*S*,*S*)–**L1** as a white, crystalline solid (1.11 g, 3.1 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 6H), 7.11 – 7.06 (m, 4H), 4.38 (t, *J* = 8.4 Hz, 2H), 4.33 – 4.24 (m, 2H), 4.13 (dd, *J* = 8.3, 6.1 Hz, 2H), 2.88 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.67 (dd, *J* = 13.6, 7.4 Hz, 2H).

4.4.3. Preparation of electrophiles

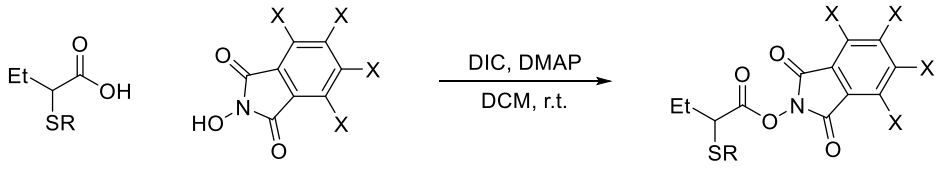
The yields have not been optimized.



2-(Benzoylthio)butanoic acid.[37] An oven-dried 100 mL two-neck flask was equipped with a stir bar and thiobenzoic acid (5.00 g, 36.2 mmol, 2.0 equiv). The flask was sealed with two rubber septa and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of MeOH (40 mL) via syringe. K_2CO_3 (2.50 g, 18.1 mmol, 1.0 equiv) was added to the flask under a positive pressure of nitrogen, at which point the evolution was gas was observed. After the mixture was allowed to stir for 5 min at room temperature, the solvent was evaporated under reduced pressure. The resulting residue was placed under a nitrogen atmosphere and re-dissolved in DMF (50 mL), and the solution was cooled to –40 °C. Next, 2-bromobutanoic acid (3.8 mL, 36.2 mmol, 2.0 equiv) was added dropwise via syringe, and the solution was warmed to room temperature and allowed to stir overnight. Water (100 mL) was added, and the mixture was extracted with Et_2O (50 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated, affording 2-(benzoylthio)butanoic acid as an orange oil (6.10 g, 27.2 mmol, 75% yield).

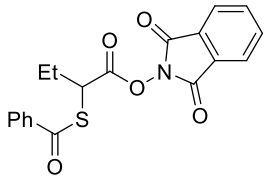
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.62 – 7.53 (m, 1H), 7.49 – 7.40 (m, 2H), 4.38 – 4.33 (m, 1H), 2.15 – 1.87 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H).

General Procedure 1 (GP-1).



Preparation of NHP esters: An oven-dried 250 mL round-bottom flask was charged with a stir bar, a derivative of *N*-hydroxyphthalimide (1.0 equiv), and DMAP (0.1 equiv),

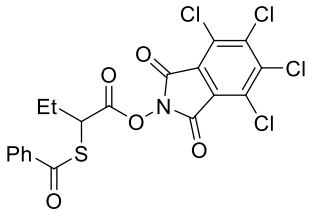
and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of anhydrous DCM (volume to generate a 0.2 M solution of the α-thio carboxylic acid) via syringe. The mixture was stirred for 5 min, after which the α-thio carboxylic 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 at room temperature overnight. The mixture was then 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. MeOH (~5.0 mL/mmol of the α-thio carboxylic acid) was added, and the mixture was stirred for 5 min. The mixture was cooled to –25 °C over 4 h, during which a white solid precipitated. The solid was filtered and washed with cold MeOH, affording the desired NHP ester. The NHP esters used in this study can be stored at room temperature for at least several months without decomposition.



1,3-Dioxoisoindolin-2-yl 2-(benzoylthio)butanoate (1). The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (5.10 g, 22.8 mmol) and *N*-hydroxyphthalimide (3.71 g, 22.8 mmol). 6.08 g, 16.4 mmol, 72% yield. White solid.

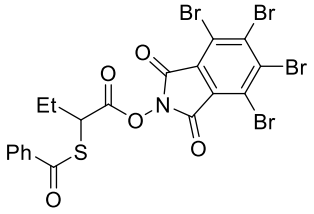
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.78 (dd, J = 5.5, 3.1 Hz, 2H), 7.66 – 7.57 (m, 1H), 7.48 (m, 2H), 4.72 (t, J = 7.1 Hz, 1H), 2.17 (ddq, J = 44.1, 14.3, 7.2 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H).

LC-MS (ESI-MS) m/z $[M+Na]^+$ calcd for $C_{19}H_{15}NNaO_5S$: 392.1, found: 392.1.



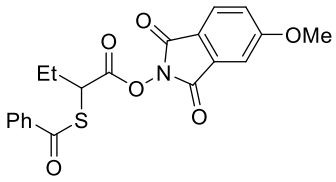
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (380 mg, 1.69 mmol) and tetrachloro-*N*-hydroxyphthalimide (509 mg, 1.69 mmol). 480 mg, 1.30 mmol, 77% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 7.66 – 7.59 (m, 1H), 7.52 – 7.45 (m, 2H), 4.69 (t, *J* = 7.1 Hz, 1H), 2.16 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).



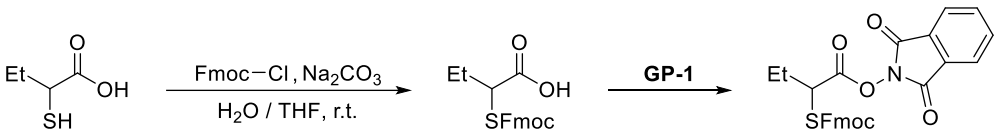
4,5,6,7-Tetrabromo-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (280 mg, 1.25 mmol) and tetrabromo-*N*-hydroxyphthalimide (597 mg, 1.25 mmol). 401 mg, 1.08 mmol, 87% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.66 – 7.58 (m, 1H), 7.53 – 7.45 (m, 2H), 4.70 (t, *J* = 7.2 Hz, 1H), 2.28 – 2.05 (m, 2H), 1.22 (t, *J* = 7.4 Hz, 3H).



5-Methoxy-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (670 mg, 2.98 mmol) and 4-methoxy-*N*-hydroxyphthalimide (577 mg, 2.98 mmol). 248 mg, 0.67 mmol, 22% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.54 – 7.43 (m, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.71 (t, *J* = 7.1 Hz, 1H), 3.93 (s, 3H), 2.31 – 2.02 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

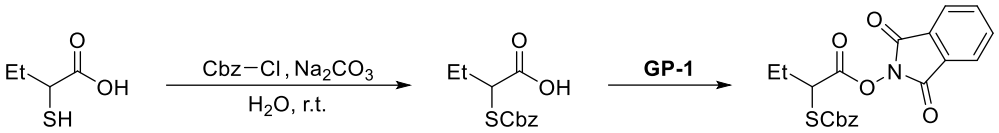


1,3-Dioxoisoindolin-2-yl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoate. A 100 mL round bottom flask was equipped with a stir bar, Na_2CO_3 (1.90 g, 17.9 mmol, 2.5 equiv), and 2-mercaptobutanoic acid (0.86 g, 7.2 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of water (3 mL) and 1,4-dioxane (30 mL) via syringe. The reaction mixture was cooled to 0 °C, after which a solution of Fmoc–Cl (1.85 g, 7.2 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) was added dropwise via syringe. The reaction was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stir overnight. Next, water (100 mL) was added, and the mixture was washed with EtOAc (50 mL x 3). The aqueous layer was cooled to 0 °C and slowly acidified by the dropwise addition of concentrated HCl. The resulting mixture was extracted with EtOAc (50 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated, affording 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoic acid as a white solid (1.52 g, 4.4 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.81 – 7.74 (m, 2H), 7.65 – 7.55 (m, 2H), 7.47 – 7.37 (m, 2H), 7.37 – 7.28 (m, 2H), 4.59 – 4.43 (m, 2H), 4.27 (t, *J* = 7.5 Hz, 1H), 4.09 – 4.02 (m, 1H), 2.01 – 1.78 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

The title compound was synthesized according to **GP-1** from 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoic acid (1.50 g, 4.39 mmol) and *N*-hydroxyphthalimide (716 mg, 4.39 mmol). 398 mg, 0.82 mmol, 19% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 – 7.74 (m, 4H), 7.65 – 7.58 (m, 2H), 7.45 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 4.62 – 4.45 (m, 2H), 4.38 (t, *J* = 7.1 Hz, 1H), 4.32 (t, *J* = 7.4 Hz, 1H), 2.24 – 1.89 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

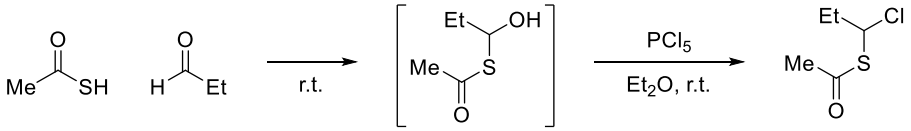


1,3-Dioxoisoindolin-2-yl 2-(((benzyloxy)carbonyl)thio)butanoate. A 40 mL vial was equipped with a stir bar, Na_2CO_3 (1.52 g, 14.3 mmol, 2.0 equiv), and 2-mercaptobutanoic acid (0.86 g, 7.2 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and backfilling the vial (three times), followed by the addition of water (10 mL) via syringe. Benzyl chloroformate (1.23 mL, 8.59 mmol, 1.2 equiv) was added dropwise via syringe, and the reaction was allowed to stir at room temperature overnight. After, water (20 mL) was added, and the mixture was washed with EtOAc (10 mL x 3). The aqueous layer was cooled to 0 ^oC and was slowly acidified by the dropwise addition of concentrated HCl. The resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated, affording 2-(((benzyloxy)carbonyl)thio)butanoic acid as a white solid (1.49 g, 5.9 mmol, 82% yield)

^1H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 7.41 – 7.33 (m, 5H), 5.32 – 5.20 (m, 2H), 4.05 (t, *J* = 7.1 Hz, 1H), 2.07 – 1.82 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

The title compound was synthesized according to **GP-1** from 2-(((benzyloxy)carbonyl)thio)butanoic acid (1.50 g, 5.88 mmol) and *N*-hydroxyphthalimide (960 mg, 5.88 mmol). 764 mg, 1.91 mmol, 33% yield. White solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 4.10 – 3.92 (m, 2H), 3.44 – 3.38 (m, 1H), 2.07 – 1.75 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).



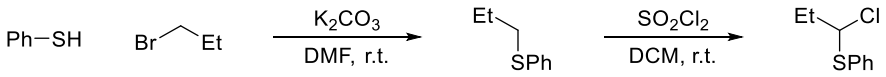
(1-Chloropropyl) ethanethioate (2).[26] An oven-dried 40 mL vial was equipped with a stir bar. The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and backfilling the vial (three times), followed by the addition of freshly

distilled thioacetic acid (2.07 mL, 28.9 mmol, 1.0 equiv) via syringe. The reaction vial was cooled to 0 °C, after which freshly distilled propionaldehyde (2.09 mL, 28.9 mmol, 1.0 equiv) was added dropwise via syringe. The reaction was allowed to warm to room temperature and stir overnight. The conversion to (1-hydroxypropyl) ethanethioate (69%) was determined by ^{1}H NMR of an aliquot taken from the vial by syringe. Roughly 30% of the starting materials remained unreacted (no byproducts observed).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (t, *J* = 6.3 Hz, 1H), 2.32 (s, 3H), 1.89 – 1.66 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

An oven-dried 100 mL round bottom flask was equipped with a stir bar and PCl_5 (4.21 g, 20.2 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition Et_2O (40 mL) via syringe. The mixture was then cooled to 0 °C, and (1-hydroxypropyl) ethanethioate was added dropwise as the crude mixture from the previous step (2.90 mL, 20.2 mmol, 1.0 equiv). The reaction was warmed to room temperature and allowed to stir overnight. Next, the solvent was evaporated under reduced pressure, and the residue was purified by vacuum distillation to afford the title compound as a colorless oil (1.84 g, 17.4 mmol, 60% yield over 2 steps).

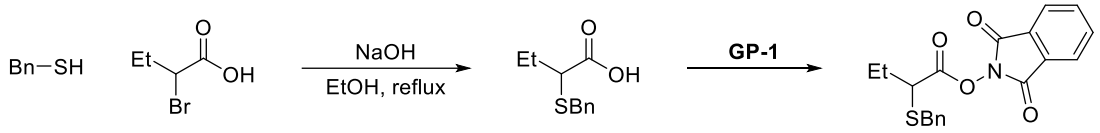
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, *J* = 6.4 Hz, 1H), 2.36 (s, 3H), 2.12 – 2.01 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).



(1-Chloropropyl)(phenyl)sulfane.[38] Phenyl(propyl)sulfane was prepared according to a reported procedure.[39] An oven-dried 50 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of phenyl(propyl)sulfane (2.78 mL, 19.7 mmol, 1.0 equiv) and DCM (15 mL) via syringe. Next, sulfuryl chloride (1.92 mL, 23.6 mmol, 1.2 equiv) was added dropwise via syringe and the solution was allowed to stir at room temperature for 3 h. When the reaction was

complete, the solvent was removed under reduced pressure, and the resulting residue was purified by vacuum distillation, affording the title compound as a colorless oil (3.10 g, 16.6 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.40 – 7.33 (m, 3H), 5.26 – 5.20 (m, 1H), 2.20 – 2.05 (m, 2H), 1.16 (t, *J* = 7.3 Hz, 3H).



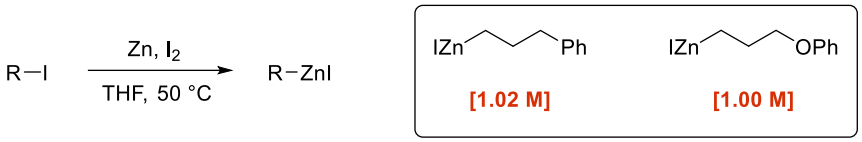
1,3-Dioxoisoindolin-2-yl 2-(benzylthio)butanoate. The synthesis of 2-(benzylthio) butanoic acid was based on a reported procedure.[40] An oven-dried 250 mL round bottom flask was equipped with a stir bar, a reflux condenser, and NaOH (2.58 g, 64.4 mmol, 2.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of EtOH (100 mL), benzyl mercaptan (3.77 mL, 32.2 mmol, 1.0 equiv), and 2-bromobutanoic acid (3.43 mL, 32.2 mmol, 1.0 equiv) via syringe. The reaction was heated to reflux and allowed to stir overnight. Next, the solvent was removed under reduced pressure. The resulting residue was dissolved in water (50 mL) and acidified using 6 M HCl. The mixture was extracted with Et_2O (50 mL x 3). The combined organic layers were washed with $NaHCO_3$ (50 mL x 3), dried over Na_2SO_4, and concentrated to yield 2-(benzylthio)butanoic acid as a light beige oil (4.70 g, 22.4 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.41 – 7.22 (m, 5H), 3.96 – 3.80 (m, 2H), 3.07 (dd, *J* = 8.0, 6.9 Hz, 1H), 1.96 – 1.62 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

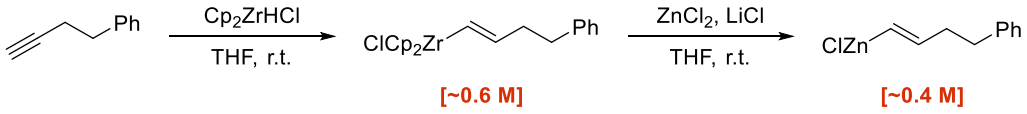
The title compound was synthesized according to **GP-1** from 2-(benzylthio)butanoic acid (2.19 g, 10.4 mmol) and *N*-hydroxyphthalimide (1.70 g, 10.4 mmol). The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). 2.55 g, 7.18 mmol, 69% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 4.08 – 3.93 (m, 2H), 3.40 (dd, *J* = 8.4, 6.7 Hz, 1H), 2.05 – 1.76 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

4.4.4. Preparation of nucleophiles

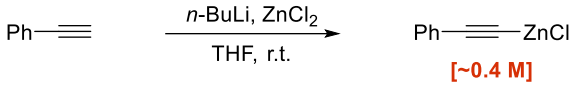


Preparation of alkylzinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three cycles). Then, the tube was heated with a heat gun (~250 °C) under 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 solution. The alkylzinc solution was titrated by the method of Knochel, using iodine in THF.[41] The concentration of the alkylzinc reagents remained constant over one year when stored at room temperature in a glovebox.



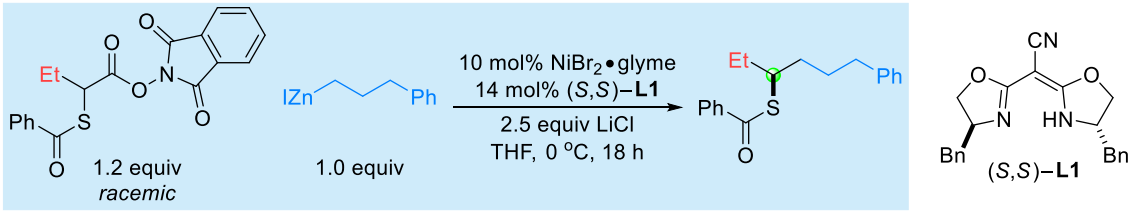
Preparation of alkenylzirconium and alkenylzinc reagents.[42,43] In the glovebox, an oven-dried 40 mL vial was equipped with a stir bar. Schwartz's reagent (1.0 equiv) and THF (1.7 mL / mmol of the alkyne) were added. Next, the alkyne (1.0 equiv) was added

dropwise via syringe, and the vial was sealed with a septum cap. The mixture was allowed to stir at room temperature for 1.5 h to yield the alkenylzirconium reagent as a ~0.6 M solution in THF. In a separate oven-dried vial, $ZnCl_2$ (1.0 equiv) and LiCl (1.3 equiv) were dissolved in THF (1.0 mL / mmol of $ZnCl_2$). This solution was added dropwise to the vial containing the alkenylzirconium reagent, and the mixture was allowed to stir at room temperature for 1 h to yield the alkenylzinc reagent as a ~0.4 M solution in THF.



Preparation of the alkynylzinc reagent.[44] An oven-dried 40 mL vial was equipped with a stir bar. The vial was sealed with a septum cap and placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles). Next, phenylacetylene (1.0 equiv) and THF (3.3 mL / mmol of phenylacetylene) were added. The solution was cooled to 0 °C, after which *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added dropwise via syringe. The reaction was warmed to room temperature and allowed to stir for 1 h, after which the mixture was cooled back to 0 °C. In a separate oven-dried 40 mL vial, a solution of $ZnCl_2$ (1.2 equiv) in THF (1.0 mL / mmol of $ZnCl_2$) was prepared under a nitrogen atmosphere. This solution was transferred to the reaction vial dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 h to yield the alkynylzinc reagent as a ~0.4 M solution in THF.

4.4.5. Catalytic enantioconvergent cross-couplings



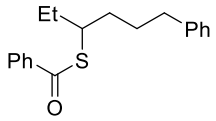
General Procedure 2 (GP-2).

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar and charged with (*S*,*S*)–**L1** (5.0 mg, 0.014 mmol, 14 mol%) and the NHP ester (0.12 mmol, 1.2 equiv). Next, THF (0.6 mL) was added, and the vial was sealed with

a septum cap and wrapped with electrical tape. The vial was then removed from the glovebox and cooled to 0 °C using an *i*-PrOH cooling bath. After the reaction was cooled, a stock solution of $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and LiCl (10.6 mg, 0.25 mmol, 2.5 equiv) in THF (0.5 mL) was added in one portion, followed immediately by dropwise addition of the alkylzinc solution (0.10 mmol, 1.0 equiv) via microsyringe. 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 EtOH (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 preparative thin-layer chromatography.

The yields were determined via LC-MS analysis of an aliquot of the crude product mixture, with 1-indanone as the internal standard. The ee values were determined via SFC analysis after purification by preparative thin-layer chromatography.

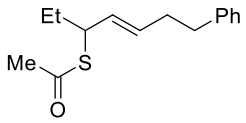


***S*-(6-Phenylhexan-3-yl) benzothioate**. The title compound was synthesized according to **GP-2** from 1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate and (3-phenylpropyl) zinc(II) iodide. The product was purified by preparative thin-layer chromatography (1:9 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)**–L1**: 7.7 min (major), 8.6 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 3.84 – 3.67 (m, 1H), 2.64 (m, 2H), 1.89 – 1.63 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 3H).

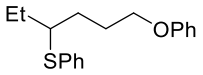
LC-MS (ESI-MS) *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{22}NaOS$: 321.1, found: 321.1.



(*E*)-*S*-(7-Phenylhept-4-en-3-yl) ethanethioate. The title compound was synthesized using a procedure adapted from **GP-2** (no LiCl; $NiBr_2$·glyme and the chiral ligand were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from *S*-(1-chloropropyl) ethanethioate and (*E*)-(4-phenylbut-1-en-1-yl)zinc(II) chloride. The product was purified by preparative thin-layer chromatography (1:9 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 3.3 min, 4.2 min.

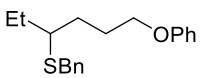
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 5H), 5.70 – 5.57 (m, 1H), 5.35 – 5.22 (m, 1H), 3.94 – 3.81 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.32 – 2.24 (m, 2H), 2.23 (s, 3H), 1.60 – 1.53 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).



(6-Phenoxyhexan-3-yl)(phenyl)sulfane. The title compound was synthesized using a procedure adapted from **GP-2** (no LiCl; **L2** used instead of **L1**; $NiBr_2$·glyme and **L2** were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from (1-chloropropyl)(phenyl)sulfane and (3-phenoxypropyl)zinc(II) iodide. The product was purified by preparative thin layer chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 6.0 min, 6.5 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.31 – 7.21 (m, 5H), 6.97 – 6.86 (m, 3H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.15 – 3.04 (m, 1H), 2.09 – 1.87 (m, 2H), 1.85 – 1.57 (m, 4H), 1.04 (t, *J* = 7.3 Hz, 3H).



Benzyl(6-phenoxyhexan-3-yl)sulfane. The title compound was synthesized using a procedure adapted from **GP-2** (**L3** used instead of **L1**; $NiBr_2$·glyme and **L3** were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from (1,3-dioxoisoindolin-2-yl 2-(benzylthio)butanoate and (3-phenoxypropyl)zinc(II)

iodide. The product was purified by preparative thin layer chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (5% MeOH in supercritical CO_2, 2.5 mL/min); retention times: 6.5 min, 7.1 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 6H), 7.00 – 6.81 (m, 4H), 3.88 (t, *J* = 6.3 Hz, 2H), 3.71 (s, 2H), 2.59 – 2.45 (m, 1H), 1.98 – 1.53 (m, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

4.5. Notes and references

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Chapter 5

NICKEL-CATALYZED NUCLEOPHILIC FLUORINATIONS OF UNACTIVATED ALKYL HALIDES

5.1. Introduction

Organofluorine compounds are attracting increased attention due to their applications in pharmaceuticals, agrochemicals, and functional materials.[1–3] Nearly 50% of drugs that were globally-approved during 2018 and 2019 contain a C–F bond,[4] as the introduction of fluorine can significantly improve a compound's lipophilicity, potency, metabolic stability, and bioavailability.[5] The high demand for fluorinated molecules has led to a number of efficient fluorination methods, particularly for the synthesis of aryl fluorides.[6] However, general methods for the preparation of alkyl fluorides remain limited despite the prevalence of these motifs in bioactive compounds (**Figure 5.1**). Consequently, the development of efficient syntheses of alkyl fluorides continues to be a central goal in organic synthesis.

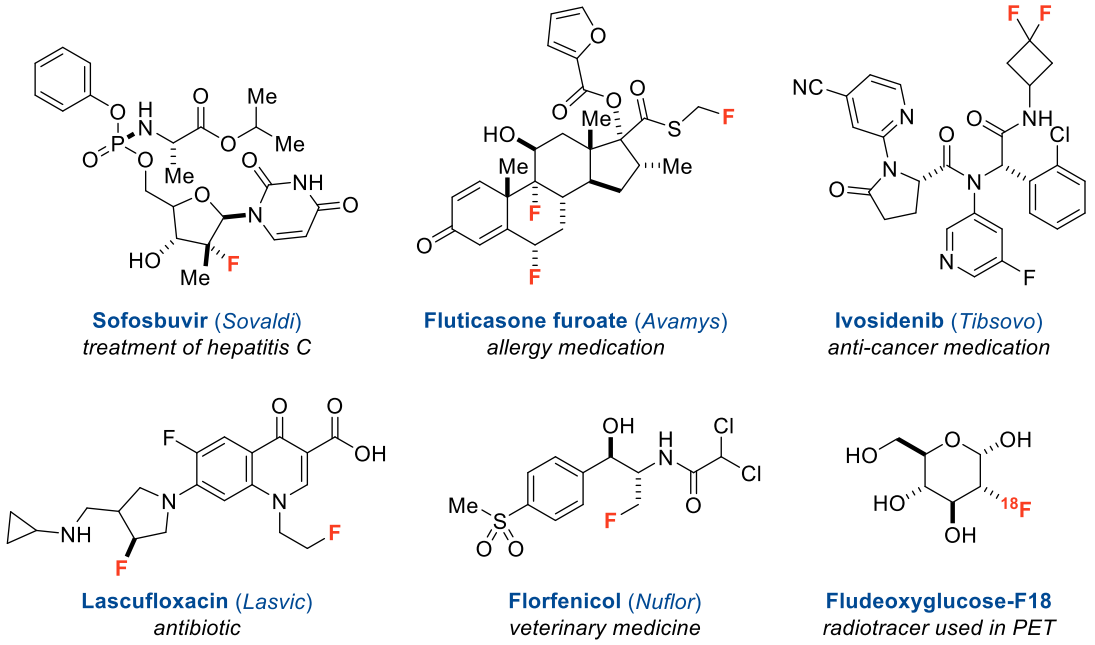


Figure 5.1. *Examples of alkyl fluorides with pharmaceutical applications.*

Among the possible methods to access alkyl fluorides, the nucleophilic fluorination of an alkyl electrophile with a metal fluoride is an especially straightforward approach. Metal fluorides (KF, CsF, AgF, etc.) are appealing sources of fluoride due to their high abundance, low cost, and ability to efficiently prepare ^{18}F-substituted radiopharmaceuticals for PET imaging.[7] However, their application to nucleophilic fluorination has been impeded by several drawbacks (**Figure 5.2**). The high lattice energies of metal fluorides result in low solubilities in organic solvents, and the propensity of fluoride to form hydrogen bonds in protic solvents undermines its nucleophilicity. In addition, the high basicity of the fluoride anion leads to side reactions of alkyl electrophiles, such as eliminations to form olefins.[8,9] Applications of metal fluorides to nucleophilic fluorination are largely restricted to specific transformations, such as allylic substitutions,[10,11] ring-opening reactions of epoxides and aziridines,[12–14] and benzylic / allylic C–H fluorinations.[15–17]

While transition metal-catalyzed nucleophilic substitution reactions have proven to be a useful strategy for the formation of otherwise challenging carbon–carbon and carbon–heteroatom bonds, this approach has limited applications in the nucleophilic fluorination of unactivated alkyl halides.[18] Mezzetti reported the ruthenium-catalyzed fluorination of *t*-butyl bromide with thallium(I) fluoride (no other examples of unactivated alkyl halides were described).[19] Weng achieved the fluorination of 1° and 2° alkyl bromides by copper(I) fluoride complexes (1.5 equiv of the copper complex was used).[20] More recently, Lalic

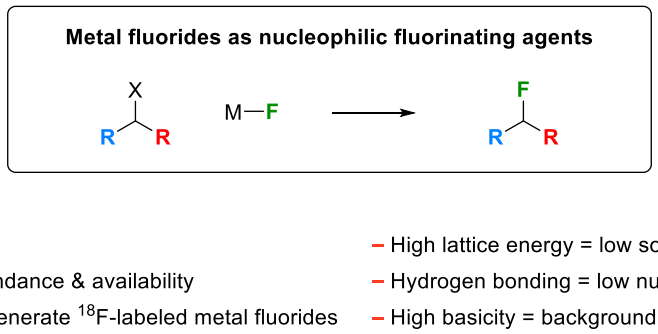


Figure 5.2. *Strengths and weaknesses of metal fluorides as nucleophilic fluorinating agents.*

disclosed the copper-catalyzed fluorination of 1° alkyl triflates using KF (not applicable to alkyl halides or to unactivated 2° or 3° alkyl triflates).[21]

To our knowledge, there is no general protocol for the transformation of a broad range of unactivated alkyl halides into alkyl fluorides via nucleophilic fluorination, although advancements in other fluorination methods have been made. For example, MacMillan reported the radical fluorination of unactivated alkyl bromides via silyl radical-mediated hydrogen atom abstraction.[22] This transformation offers a powerful approach to the synthesis of alkyl fluorides due to its mild conditions and broad functional group tolerance, although there are some limitations (low yields for 1° alkyl bromides, and a typical reaction requires 1.75 equiv of $(TMS)_3SiOH$, which is expensive).

Our lab has applied nickel-catalyzed nucleophilic substitution reactions of unactivated alkyl halides to the synthesis of a number of useful families of compounds.[23,24] While our efforts have primarily focused on carbon-based nucleophiles, nickel can serve as an effective catalyst for cross-couplings of other classes of nucleophiles as well, such as those based on boron[25] and silicon.[26] In principle, extending this approach to a metal

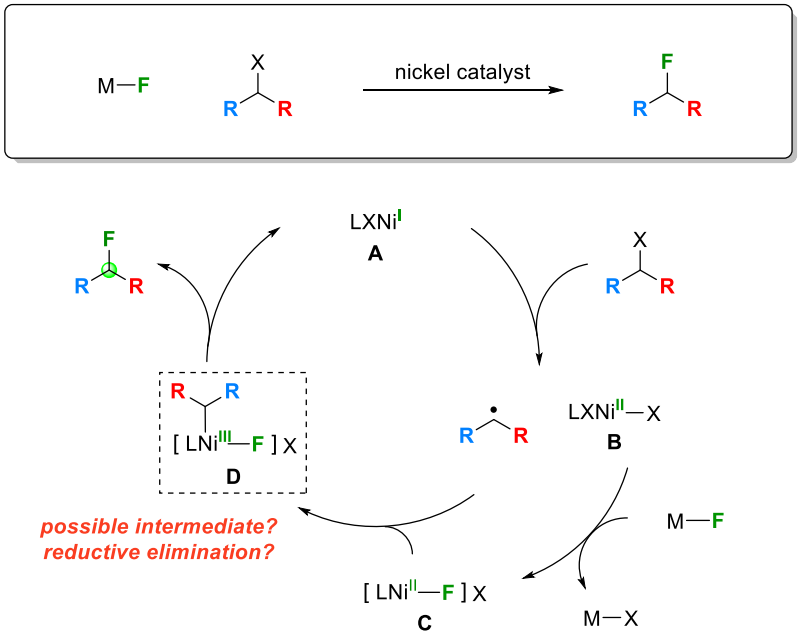
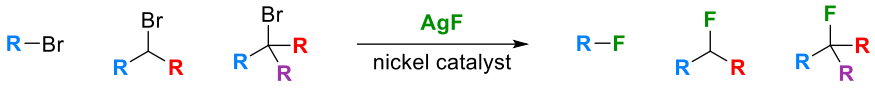


Figure 5.3. *Nickel-catalyzed nucleophilic fluorination of unactivated alkyl halides: possible pathway and challenges.*

fluoride nucleophile could grant access to unactivated alkyl fluorides from readily available starting materials (**Figure 5.3**).

Nickel's propensity to engage in single electron transfer (SET) with unactivated alkyl halides makes it an attractive catalyst for this transformation. However, nucleophilic fluorinations catalyzed by nickel have remained elusive to date; examples of alkyl fluoride synthesis catalyzed by nickel involve electrophilic fluorinations[27] and radical hydrofluorinations,[28] wherein nickel is proposed to assist in the generation of reactive intermediates but not participate directly in C–F bond formation. There are no reports of C(alkyl)–F reductive elimination from a nickel complex, although related processes have recently been studied; over the last few years, Ritter[29] and Sanford[30] have observed C(aryl)–F reductive elimination from high-valent nickel complexes.

In this chapter, we describe how the introduction of a nickel catalyst has opened the door to nucleophilic fluorinations of unactivated alkyl halides with metal fluorides. Specifically, we disclose our preliminary results in the nucleophilic fluorination of 1°, 2°, and 3° alkyl bromides, each of which was found to exhibit unique reactivity (**eq 5.1**).



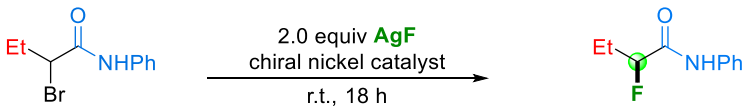
(5.1)

5.2. Results and discussion

5.2.1. Asymmetric nucleophilic fluorination of activated alkyl halides

We initially investigated the asymmetric nucleophilic fluorination of a range of racemic alkyl halides. In the presence of a chiral nickel complex, we discovered that a 2° α-bromo amide reacts with AgF to afford the fluorinated product in 11% ee (**eq 5.2**).

Upon investigating other classes of racemic electrophiles, we found that certain alkyl halides lead to the formation of racemic product (due, in some cases, to significant

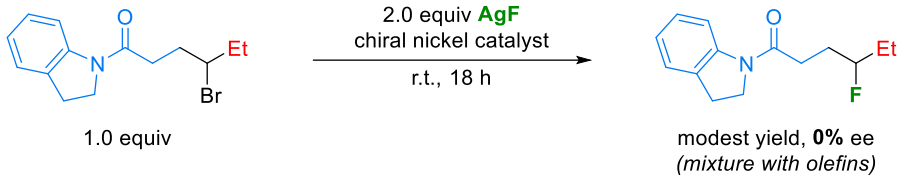


1.0 equiv

partial conversion, **11%** ee

(5.2)

background fluorination in the absence of catalyst), while others do not react at all. However, we were surprised to observe that an unactivated 2° γ-bromo amide readily undergoes substitution in the presence of a nickel catalyst (**eq 5.3**). As discussed previously, efficient nucleophilic fluorinations of unactivated alkyl halides (including non-asymmetric processes) are rare, and this result prompted us to further explore the reactivity of these traditionally challenging substrates. The following sections summarize our efforts in developing fluorinations of 2° alkyl halides (*Chapter 5.2.2*), 1° alkyl halides (*Chapter 5.2.3*), and 3° alkyl halides (*Chapter 5.2.4*).



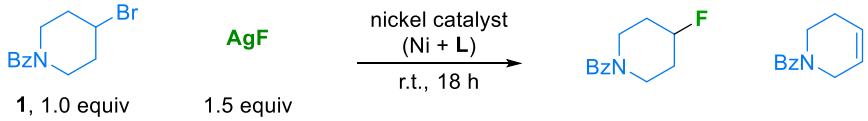
1.0 equiv

modest yield, **0%** ee
(mixture with olefins)

(5.3)

5.2.2. Nucleophilic fluorination of unactivated 2° alkyl halides

Under conditions similar to those illustrated in **eq 5.2**, unactivated, cyclic 2° alkyl bromide **1** undergoes nucleophilic fluorination with AgF in the presence of nickel and a variety of ligands (**Figure 5.4**). The relative signal intensities of the fluorinated product, the olefin byproduct, and unreacted **1** were measured by LC-MS to provide a qualitative assessment of the crude reaction mixture. In the absence of nickel and of ligand, very little product forms, and the starting material remains mostly unreacted. The addition of nickel promotes consumption of **1**, although elimination is the predominant reaction under these



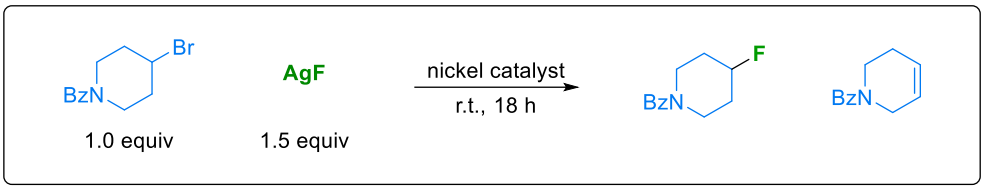
1, 1.0 equiv

1.5 equiv

conditions	product : olefin : SM
Ni + **L**	44 : 50 : 06
Ni, no **L**	16 : 61 : 23
No Ni or **L**	09 : 31 : 60

Figure 5.4. *Fluorination of unactivated, cyclic 2° alkyl bromide **1**. The relative signal intensities of product, olefin, and starting material were measured by LC-MS.*

Table 5.1. *Investigation of the fluoride nucleophile.*



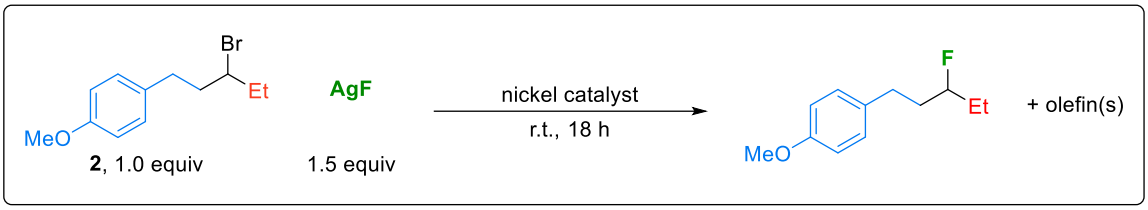
entry	nucleophile	% yield
1	AgF	~40
2	KF	0
3	CsF	0
4	TBAT	0
5	TBAF	0

conditions. However, the introduction of a range of ligands shifts reactivity in favor of fluorination.

We surveyed a range of parameters to determine the effect that different reaction conditions have on product and olefin formation. Nonpolar and ethereal solvents lead to low conversion, while polar solvents generally favor olefin formation. Lowering the temperature results in a lower yield and does not improve the ratio of product to olefin. For this 2°-substituted substrate, elimination remains a prominent side reaction that complicates reaction optimization, an issue that has hampered the development of nucleophilic fluorinations of alkyl halides.[31]

A variety of nickel precatalysts were tested, providing no benefit to the reaction outcome. In the future, the use of nickel(0) may be beneficial, as oxidative addition of the alkyl halide to form a nickel(II) intermediate, followed by comproportionation, would provide a ready mechanism for the generation of nickel(I) (complex **A**; **Figure 5.3**). Other fluoride reagents result in no reaction (**Table 5.1**). While the unique reactivity of AgF may be due to its higher solubility in organic solvents compared to alkali metal fluorides,[32] Ag(I) salts are essential additives in other nucleophilic fluorinations of alkyl halides.[33–35] The role of silver in this process will be discussed in *Chapter 5.2.4*.

Table 5.2. *Nickel-catalyzed nucleophilic fluorination of unactivated, acyclic 2° alkyl halides.*



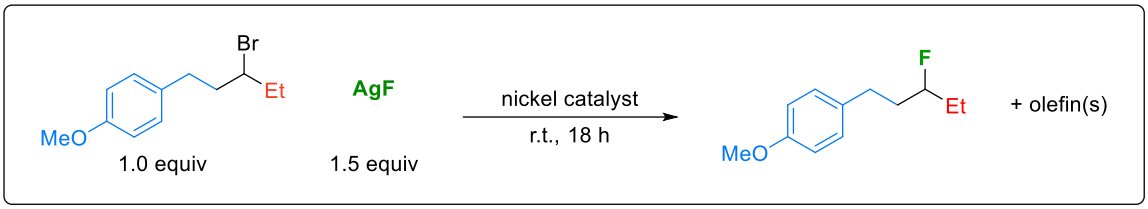
entry	X	% yield (^{19}F NMR)	% olefin (^{1}H NMR)
1	Br	45	50
2	Cl	0	0
3	OMs	0	0
4	I	35	69

Although the symmetrical structure of **1** facilitates analysis of its byproducts, we turned our optimization to unactivated, *acyclic* 2° alkyl bromide **2** to ensure that the observed reactivity is general to a wide range of 2° alkyl bromides. Using NMR spectroscopy, we found that the nucleophilic fluorination of **2** proceeds in 45% yield, with olefin byproduct(s) forming in 50% yield (**Table 5.2**, entry 1). Unactivated alkyl chlorides and mesylates do not react under these conditions, whereas alkyl iodides favor elimination (entries 2–4).

Control experiments established that nickel is necessary for this process, as reactions conducted in its absence result in minor conversion of **2** (**Table 5.3**, entries 2 and 4). While the presence of the ligand is not essential for product formation, its omission noticeably lowers the yield (entry 3). The roles of nickel and the ligand in this transformation are topics of ongoing investigation.

These preliminary results demonstrate the enticing prospect that the nickel-catalyzed nucleophilic fluorination of unactivated 2° alkyl halides is possible, although the propensity for the electrophile to undergo elimination remains a challenge. We anticipate that further investigations will lead to the discovery of conditions that minimize this side reaction.

Table 5.3. *Control reactions in the nucleophilic fluorination of acyclic 2º alkyl bromide* ***2****.*

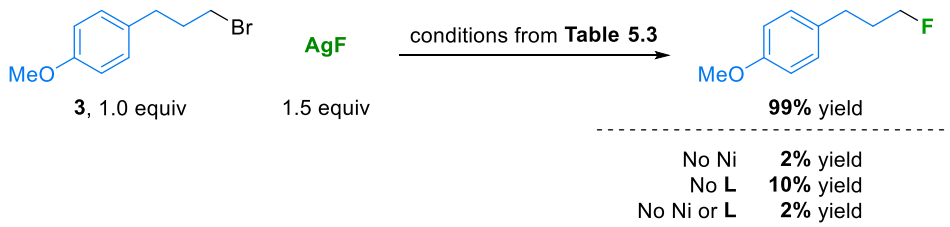


entry	conditions	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
1	Standard	51	49	0
2	No Ni	6	0	94
3	No **L**	40	54	0
4	No Ni or **L**	6	0	94

5.2.3. Nucleophilic fluorination of unactivated 1º alkyl halides

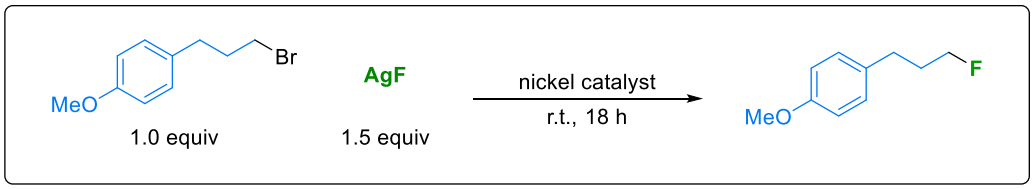
Applying conditions developed for the nucleophilic fluorination of **2**, we found that the fluorination of unactivated 1º alkyl bromide **3** proceeds in quantitative yield. The presence of nickel and ligand are essential for this transformation (**eq 5.4**). Remarkably, under all conditions tested, no side reactions were observed.

Attempts to duplicate these results led to product yields of 50–70%, indicating irreproducibility that may arise from the heterogeneity of the reaction mixture. We reasoned that more forcing reaction conditions could ensure the full consumption of **3**. Indeed, a reaction heated to 45 ºC results in higher conversion than a reaction run in parallel at room temperature (**Table 5.4**, entries 1 and 2). Similarly, the product yield could be improved by increasing the AgF stoichiometry or by extending the reaction time (entries 3–10). In particular, a reaction run with 3.0 equiv of AgF for 42 h led to the formation of product in 97% yield (entry 9), a result later confirmed to be reproducible.



(5.4)

Table 5.4. *Establishing conditions for the reproducible nucleophilic fluorination of unactivated 1° alkyl bromide* ***3****.*



Effect of temperature

entry	temperature	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
1	r.t.	59	0	41
2	45 °C	85	0	15

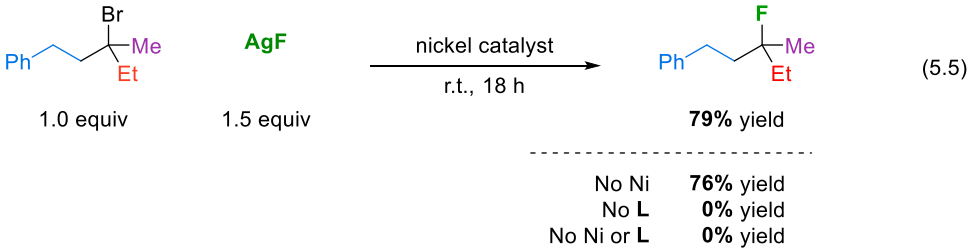
Effect of reaction time and AgF stoichiometry

entry	reaction time	equiv AgF	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
3	18 h	1.5	46	0	54
4		2.0	66	0	34
5		3.0	73	0	27
6		5.0	60	0	40
7	42 h	1.5	82	0	18
8		2.0	87	0	13
9		3.0	**97**	0	3
10		5.0	91	0	9

5.2.4. Nucleophilic fluorination of unactivated 3° alkyl halides

Typically, methods for the generation of 1° and 2° alkyl fluorides are not applicable to or proceed sluggishly with 3° substrates[13,31,36] (and vice-versa).[37,38] Thus, the ability to apply a single method to the synthesis of alkyl fluorides bearing each of these substitution patterns in high yield would be a valuable tool in organic synthesis.

Upon surveying a range of ligands, we found that unactivated 3° alkyl bromide **4** readily reacts with AgF in the presence of a nickel catalyst, affording the fluorinated product in nearly 80% yield (**eq 5.5**). The product was formed as a mixture with olefin(s), although these side products can be separated from the fluorinated product by chromatography.



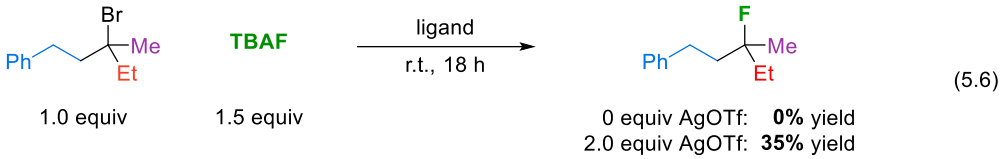
We concurrently conducted control experiments to examine the necessity of nickel and ligand in this reaction (**eq 5.5**). Surprisingly, product formation is not impacted by the removal of nickel (76% yield). To further probe this intriguing reactivity, we applied several ligands to the fluorination of **4** in the presence and absence of nickel. All ligands efficiently promoted the reaction in the absence of nickel, indicating that this process does not require nickel and likely proceeds through a pathway that is mechanistically distinct from fluorinations of 1° and 2° alkyl halides.

Subsequent experiments revealed that AgF is the only fluoride source applicable to the fluorination of **4** under these conditions, providing further support for the importance of silver in this transformation. Silver has been shown to be integral to a number of reported fluorinations. For example, silver catalysts have been applied to decarboxylative fluorinations of alkyl carboxylic acids[39] and radical fluorinations of alkylboronates.[40] These reactions are proposed to proceed through the formation of a Ag(III)–F intermediate that oxidizes the substrate and undergoes fluorine transfer with the resulting alkyl radical. Silver has also mediated fluorinations of aryl stannanes, wherein C–F bond formation is hypothesized to involve a bimetallic oxidation-reductive elimination pathway.[41]

Silver has been applied to nucleophilic fluorinations as well, such as fluorinations of α-bromoamides[35] and Pd-catalyzed fluorinations of benzylic C–H bonds.[42] In both cases, AgF is employed as the source of nucleophilic fluoride, although CsF can be applied as an effective fluorinating agent in reactions containing AgOTf as an additive. Similarly, Ag(I) salts have been found to be essential additives in the nucleophilic fluorination of unactivated 1° alkyl iodides using $TMSCF_3$[33] and aryl–OCF_2X bromides/chlorides using

KF.[34] In our case, the addition of 2.0 equiv of AgOTf enables the fluorination of 3° alkyl bromide **4** in modest yield using TBAF as the source of fluoride (**eq 5.6**).

Based on these findings, a ligated silver complex is likely a relevant intermediate in this reaction. Despite the numerous reported fluorinations catalyzed or mediated by silver, we are not aware of any examples that involve the formation of a discrete silver complex via pre-stirring of silver and a ligand. As unactivated 3° alkyl halides are relatively inert substrates, introduction of the ligand may allow for otherwise challenging processes to occur, such as the formation of a reactive intermediate (alkyl radical, carbocation, etc.) or C–F reductive elimination from silver. Mechanistic experiments to elucidate the role of silver and ligand are underway.



(5.6)

5.3. Conclusions

The applications of organofluorine compounds in various fields of science have necessitated the development of efficient methods to introduce fluorine into organic molecules. While the nucleophilic fluorination of an alkyl halide using a cheap and readily-available metal fluoride represents a straightforward route to alkyl fluorides, its application in synthesis has been hindered by the low nucleophilicity and high basicity of metal fluorides. Given the propensity for nickel, an earth abundant metal, to catalyze nucleophilic substitution reactions to form C(sp^3)–heteroatom bonds, we have begun to apply nickel-based catalysts to the nucleophilic fluorination of unactivated alkyl halides. 1° alkyl bromides readily react with AgF in the presence of a nickel catalyst, forming alkyl fluorides in quantitative yields. Under similar conditions, unactivated 2° alkyl bromides afford the product in modest yields, although elimination remains a significant side reaction, and 3° alkyl bromides readily undergo fluorination with AgF through a pathway that does not require nickel. We envision that this method will serve as a powerful approach to the

synthesis of unactivated alkyl fluorides containing a range of substitution patterns, along with providing insight into the role of silver in these intriguing transformations.

5.4. Experimental section

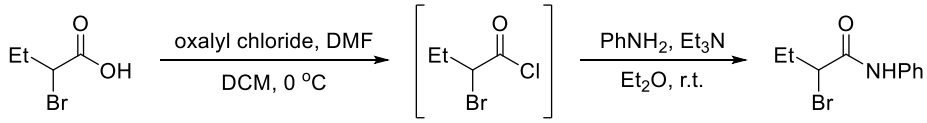
5.4.1. General information

Unless otherwise noted, reagents received from commercial suppliers were used as received. AgF was purchased from Oakwood and from Strem, and both sources yielded consistent results. All reactions were performed under an atmosphere of dry nitrogen. Solvents were purified by passage through activated aluminum oxide in a solvent-purification system.

NMR spectra were collected on 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. For quantitative ^{19}F NMR experiments, the center frequency (O1P) was set to be the midpoint between the product and the internal standard (4-fluorobiphenyl; –115.8 ppm). SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® columns (4.6 × 250 mm, particle size 5 μm). LC-MS were obtained on an Agilent 6140 UHPLC-MS system in electrospray ionization (ESI+) mode. Column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle).

5.4.2. Preparation of electrophiles

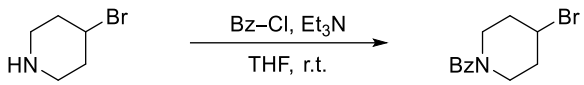
The yields have not been optimized.



2-Bromo-*N*-phenylbutanamide. An oven-dried 500 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (80 mL) and 2-bromobutanoic acid (2.55 mL, 24.0 mmol, 1.0 equiv) via syringe. The flask was cooled to 0 °C, after which oxalyl chloride (3.08 mL, 35.9 mmol,

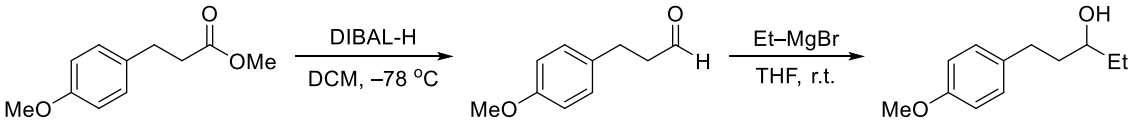
1.5 equiv) and DMF (0.19 mL, 2.40 mmol, 0.1 equiv) were added dropwise. The mixture was allowed to stir at 0 °C for 2 h. Next, the solvent was evaporated, and the flask was placed under a nitrogen atmosphere. After the residue was re-dissolved in Et_2O (240 mL), the flask was cooled to 0 °C. Following the addition of triethylamine (6.68 mL, 47.9 mmol, 2.0 equiv), aniline (2.19 mL, 24.0 mmol, 1.0 equiv) was added dropwise via syringe. Then, the solution was warmed to room temperature and allowed to stir overnight. The crude reaction mixture was washed with water (100 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated. The resulting yellow residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield a white solid that was then recrystallized in hexanes/THF to yield the title compound as a crystalline, white solid (3.10 g, 12.8 mmol, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.58 – 7.51 (m, 2H), 7.40 – 7.31 (m, 2H), 7.21 – 7.12 (m, 1H), 4.48 – 4.35 (m, 1H), 2.35 – 2.07 (m, 2H), 1.10 (t, *J* = 7.3 Hz, 3H).



(**4-Bromopiperidin-1-yl)(phenyl)methanone (1)**.[43] An oven-dried 100 mL round bottom flask was equipped with a stir bar and 4-bromopiperidine hydrobromide (2.71 g, 11.1 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (30 mL). The flask was cooled to 0 °C, after which triethylamine (3.40 mL, 24.4 mmol, 2.2 equiv) and benzoyl chloride (1.29 mL, 11.1 mmol, 1.0 equiv) were added over 5 min via syringe. The reaction mixture was warmed to room temperature and allowed to stir overnight. Next, the solvent was evaporated, and the residue was dissolved in DCM (100 mL) and washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield the title compound as a white solid (2.22 g, 8.3 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 4.47 – 4.40 (m, 1H), 4.15 – 3.24 (m, 4H), 2.32 – 1.84 (m, 4H).



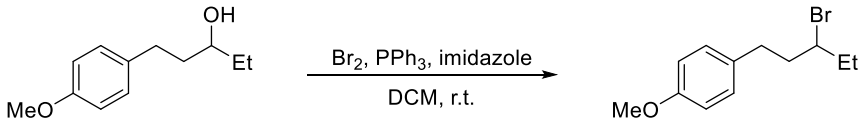
1-(4-Methoxyphenyl)pentan-3-ol.[44,45] An oven-dried 250 mL round bottom flask was equipped with a stir bar and methyl 3-(4-methoxyphenyl)propanoate (3.00 g, 15.4 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (80 mL). The flask was cooled to –78 °C, after which DIBAL-H (17.0 mL, 1.0 M in DCM, 17.0 mmol, 1.1 equiv) was over 10 min via syringe. The reaction mixture was allowed to stir at –78 °C for 1 h, after which saturated aqueous NH_4Cl (50 mL) was added, and the flask was warmed to room temperature. The organic layer was washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, yielding 3-(4-methoxyphenyl)propanal as a beige oil that was used in the next step without further purification (2.29 g, 14.0 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 – 9.79 (m, 1H), 7.15 – 7.07 (m, 2H), 6.91 – 6.80 (m, 2H), 3.78 (s, 3H), 2.93 – 2.87 (m, 2H), 2.78 – 2.72 (m, 2H).

An oven-dried 50 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (20 mL) and 3-(4-methoxyphenyl)propanal (2.29 g, 14.0 mmol, 1.0 equiv) via syringe. The flask was cooled to 0 °C, and ethylmagnesium bromide (16.7 mL, 1.0 M in THF, 16.8 mmol, 1.2 equiv) was added over 5 min. The flask was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted in EtOAc (50 mL x 3), and the organic layers were washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (3:7

EtOAc/hexanes) to afford the title compound as a colorless oil (1.99 g, 10.2 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 2H), 6.93 – 6.77 (m, 2H), 3.79 (s, 3H), 3.59 – 3.50 (m, 1H), 2.84 – 2.47 (m, 2H), 1.83 – 1.39 (m, 5H), 0.95 (t, *J* = 7.4 Hz, 3H).



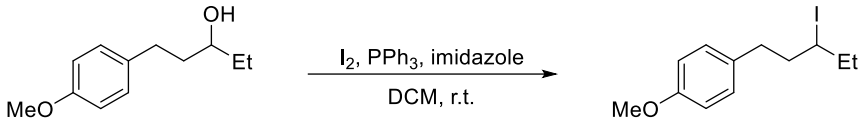
1-(3-Bromopentyl)-4-methoxybenzene (2). An oven-dried 250 mL round bottom flask was equipped with a stir bar, triphenylphosphine (5.67 g, 21.6 mmol, 1.2 equiv), and imidazole (1.47 g, 21.6 mmol, 1.2 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (90 mL). The flask was cooled to 0 ^{o}C, and then Br_2 (1.11 mL, 21.6 mmol, 1.2 equiv) was added dropwise via syringe. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 ^{o}C, 1-(4-methoxyphenyl)pentan-3-ol (3.50 g, 18.0 mmol, 1.0 equiv) was added via syringe. The reaction was warmed to room temperature and stirred overnight. The mixture was filtered through celite and concentrated to yield a yellow oil, which was then passed through a plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (2.93 g, 11.4 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.08 – 6.95 (m, 2H), 4.15 – 4.04 (m, 1H), 3.94 (s, 3H), 3.04 – 2.79 (m, 2H), 2.31 – 2.15 (m, 2H), 2.06 – 1.96 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

1-(3-Chloropentyl)-4-methoxybenzene.[46] An oven-dried 40 mL vial was equipped with a stir bar and 1-(4-methoxyphenyl)pentan-3-ol (280 mg, 1.44 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by

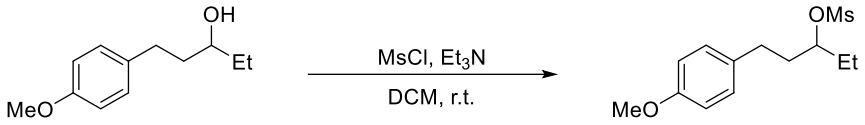
evacuating and back-filling the vial (three cycles), followed by the addition of DCM (10 mL). The vial was cooled to 0 °C, after which $SOCl_2$ (0.21 mL, 2.88 mmol, 2.0 equiv) was added dropwise via syringe and DMF (2.2 μL, 0.03 mmol, 2.0 mol %) was added via microsyringe. The reaction was warmed to room temperature and allowed to stir for 3 h. Next, the solution was concentrated, and the residue was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (166 mg, 0.78 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.09 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.82 – 3.75 (m, 4H), 2.88 – 2.64 (m, 2H), 2.04 – 1.91 (m, 2H), 1.88 – 1.67 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).



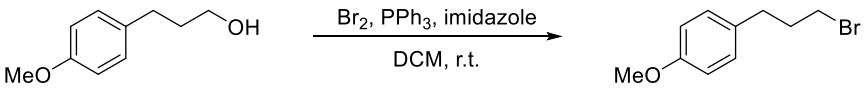
1-(3-Iodopentyl)-4-methoxybenzene. An oven-dried 40 mL vial was equipped with a stir bar, triphenylphosphine (567 mg, 2.16 mmol, 1.5 equiv), and imidazole (147 mg, 2.16 mmol, 1.5 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of DCM (10 mL). The vial was cooled to 0 °C, and then I_2 (549 mg, 2.16 mmol, 1.5 equiv) was added under a positive pressure of nitrogen. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 °C, 1-(4-methoxyphenyl) pentan-3-ol (280 mg, 1.44 mmol, 1.0 equiv) was added via syringe. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through celite and concentrated to yield a yellow oil, which was passed through a plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (438 mg, 0.91 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 2H), 6.89 – 6.79 (m, 2H), 4.10 – 3.95 (m, 1H), 3.79 (s, 3H), 2.89 – 2.60 (m, 2H), 2.26 – 1.71 (m, 4H), 1.02 (t, *J* = 7.2 Hz, 3H).



1-(4-Methoxyphenyl)pentan-3-yl methanesulfonate.[47] An oven-dried 40 mL vial was equipped with a stir bar and 1-(4-methoxyphenyl)pentan-3-ol (0.86 g, 4.4 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of DCM (15 mL). The vial was cooled to 0 ^{o}C, after which Et_3N (0.93 mL, 6.7 mmol, 1.5 equiv) and MsCl (0.52 mL, 6.7 mmol, 1.5 equiv) were added dropwise via syringe. The solution was warmed to room temperature and allowed to stir overnight. The reaction was then diluted with DCM (30 mL) and washed with water (30 mL x 3) and brine (30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield the title compound as a colorless oil (1.02 g, 3.8 mmol, 84% yield).

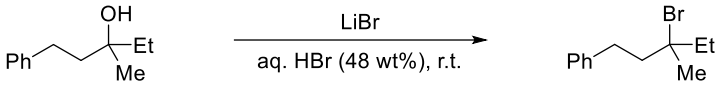
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.86 – 6.81 (m, 2H), 4.76 – 4.65 (m, 1H), 3.78 (s, 3H), 3.00 (s, 3H), 2.77 – 2.58 (m, 2H), 2.08 – 1.87 (m, 2H), 1.84 – 1.72 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).



1-(3-Bromopropyl)-4-methoxybenzene (3). An oven-dried 500 mL round bottom flask was equipped with a stir bar, triphenylphosphine (11.4 g, 43.3 mmol, 1.2 equiv), and imidazole (2.95 g, 43.3 mmol, 1.2 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (180 mL). The flask was cooled to 0 ^{o}C, and then Br_2 (2.22 mL, 43.3 mmol, 1.2 equiv) was added dropwise via syringe. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 ^{o}C, 3-(4-methoxyphenyl)propan-1-ol (6.00 g, 36.1 mmol, 1.0 equiv) was added via syringe. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through celite and concentrated to yield a yellow oil, which was passed through a

plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (5.22 g, 22.8 mmol, 63% yield).

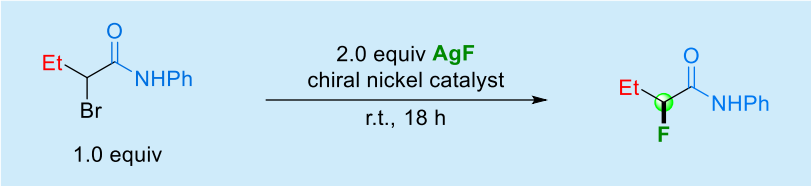
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.10 (m, 2H), 6.88 – 6.83 (m, 2H), 3.80 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.19 – 2.10 (m, 2H).



(3-Bromo-3-methylpentyl)benzene (4).[25] To a 250 mL round bottom flask was added LiBr (9.74 g, 112 mmol, 2.0 equiv) and 48 wt% aqueous HBr (100 mL). The flask was cooled to 0 ^{o}C, after which 3-methyl-1-phenylpentan-3-ol (10.0 g, 56.1 mmol, 1.0 equiv) was added over 5 min. The reaction mixture was allowed to warm to room temperature and stir overnight. The mixture was then diluted with Et_2O (200 mL) and washed with water (100 mL x 2), saturated $NaHCO_3$ (100 mL x 2), and brine (100 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by vacuum distillation to yield the titled compound as a colorless oil (11.8 g, 48.9 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 5H), 2.89 – 2.73 (m, 2H), 2.19 – 1.84 (m, 4H), 1.76 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H).

5.4.3. Nucleophilic fluorinations

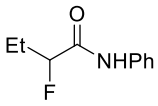


General Procedure 1 (GP-1): Asymmetric nucleophilic fluorination of 2º *α*-bromo amide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the chiral ligand, and AgF (25.4 mg, 0.20 mmol, 2.0 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 2-bromo-*N*-phenylbutanamide (24.2 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: 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.

The conversion and ee were determined via SFC analysis of the crude product mixture.

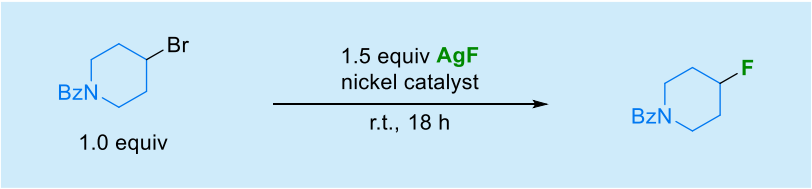


2-Fluoro-*N*-phenylbutanamide. The title compound was synthesized according to **GP-1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.62 – 7.51 (m, 2H), 7.41 – 7.32 (m, 2H), 7.21 – 7.11 (m, 1H), 5.08 – 4.88 (m, 1H), 2.22 – 1.89 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{10}H_{12}FNNaO$: 204.1, found: 204.1.

SFC analysis: SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 5.8 min, 7.1 min.

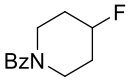


General Procedure 2 (GP-2): Nucleophilic fluorination of cyclic 2º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of (4-bromopiperidin-1-yl)(phenyl)methanone (26.8 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1-indanone (2.6 mg, 0.02 mmol, 0.2 equiv in 0.2 mL acetone, used as an LC-MS internal standard) was added to the vial via microsyringe. 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.

Yields were determined via LC-MS analysis of an aliquot of the crude product mixture, with 1-indanone as the internal standard.

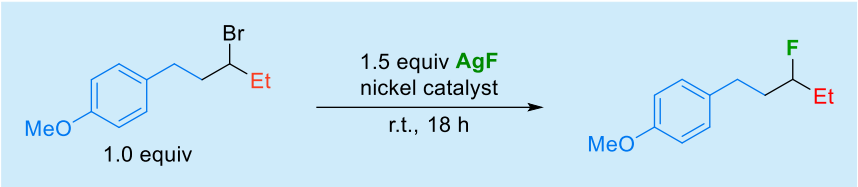


(4-Fluoropiperidin-1-yl)(phenyl)methanone. The title compound was synthesized according to **GP-2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 5H), 5.03 – 4.79 (m, 1H), 4.07 – 3.37 (m, 4H), 2.04 – 1.70 (m, 4H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -183.2.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{14}FNNaO$: 230.1, found: 230.1.

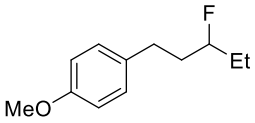


General Procedure 3 (GP-3): Nucleophilic fluorination of acyclic 2º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 1-(3-bromopentyl)-4-methoxybenzene (25.7 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. 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 dissolved in $CDCl_3$ for NMR analysis.

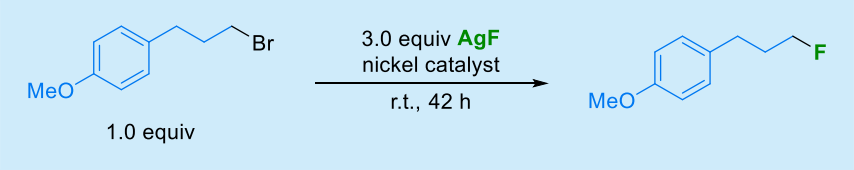
Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



1-(3-Fluoropentyl)-4-methoxybenzene. The title compound was synthesized according to **GP-3**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 2H), 6.86 – 6.82 (m, 2H), 4.52 – 4.31 (m, 1H), 3.80 (s, 3H), 2.84 – 2.59 (m, 2H), 2.05 – 1.52 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -183.1.

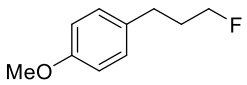


General Procedure 4 (GP-4): Nucleophilic fluorination of 1º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (38.1 mg, 0.30 mmol, 3.0 equiv). Next, DCM (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 1-(3-bromopropyl)-4-methoxybenzene (22.9 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 42 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. 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 dissolved in $CDCl_3$ for NMR analysis.

Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



1-(3-Fluoropropyl)-4-methoxybenzene. The title compound was synthesized according to **GP-4.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 6.90 – 6.83 (m, 2H), 4.46 (dt, *J* = 47.2, 5.9 Hz, 2H), 3.80 (s, 3H), 2.76 – 2.64 (m, 2H), 2.09 – 1.91 (m, 2H).

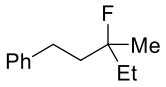
^{19}F NMR (376 MHz, $CDCl_3$) δ -220.1.

General Procedure 5 (GP-5): Nucleophilic fluorination of 3º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of (3-bromo-3-methylpentyl)benzene (24.1 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. 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 dissolved in $CDCl_3$ for NMR analysis.

Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



(3-Fluoro-3-methylpentyl)benzene. The title compound was synthesized according to **GP-5.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 6.93 (m, 5H), 2.64 – 2.57 (m, 2H), 1.89 – 1.54 (m, 4H), 1.27 (d, *J* = 21.8 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -146.6.

5.5 Notes and references

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