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

Thesis by

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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