

DEVELOPMENT AND MECHANISTIC STUDIES OF NI-CATALYZED
ASYMMETRIC REDUCTIVE CROSS-COUPPLING REACTIONS

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Julie Lyn Hofstra

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Julie Lyn Hofstra

ORCID: 0000-0001-9558-4317

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*To the family and friends who not only
celebrated with me on the mountaintops,
but also walked with me through the valleys.
I wouldn't have finished without you.*

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When I started graduate school at Caltech five years ago, I already knew my time was going to be spent making a lot of carbon–carbon bonds; however, I did not anticipate how many close, strong friendships I would also form during my time here. I am truly grateful to have had such an enriching experience at Caltech, which never ceases to be a creative and collaborative atmosphere. I have had the pleasure to work amongst some extremely talented and caring people and I am thankful for all the support I received from friends and family which has been instrumental in seeing me through to the finish line. Caltech is a remarkable, close-knit community, and some of the friendships I have made during my time here I will undoubtedly take with me for the rest of my life.

First of all, I would like to thank my advisor, Prof. Sarah Reisman, for providing me the opportunity to join her laboratory. Sarah is dedicated to her students and challenges them to become better thinkers, writers, and scientists. I have benefited from her rigor and support over the years; it has grown me into the chemist I am today. Although I originally came to Caltech with an analytical/physical background, Sarah quickly recognized how my strengths could be useful in the context of organic chemistry and provided me with the opportunity to pioneer the laboratory's focused efforts in the realm of mechanistic studies on nickel catalysis. While being in her laboratory, I have also come to learn and appreciate her drive for natural product synthesis. This unique training environment has led me to develop skills I would not have obtained while working in a strictly methods group.

I would also like to thank the other members of my committee, Profs. Gregory Fu, Dennis Dougherty, and Brian Stoltz. Greg has never hesitated an opportunity to chat about nickel catalysis and provide his thoughts on some of my odd experimental results when I

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I would also like to thank a number of Caltech staff and administration for all their support. Lynne Martinez and Veronica Triay work tremendously hard to keep the group running from an administrative position. Their warm, smiling faces have always been a pleasure to have around. I always enjoyed the simple moments of getting to chat and connect with Lynne in her office (or the elevator), and even though she has since retired, I am looking forward to seeing her again at our class graduation. I would also like to acknowledge all the hard work that Agnes Tong and Alison Ross have done for our department. They have worked hard to keep the graduate program running, from simple things such as scheduling seminar rooms to more complicated things like organizing recruitment. I would also like to thank Dr. Kate McNulty and Prof. Doug Rees who have been advisors to me during my time on the Graduate Honor Council. I have appreciated Kate's periodic check-ins; she has always been there as an extra support when I needed it.

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on chemical conundrums. He does this even when juggling multiple things at once. Silva has been one of my closest friends I have had at Caltech. She has always had an open door and gets excited to have me stop by and tell her about all the things going on in my day. They are some of the kindest, most loving people I have met. I am going to miss seeing them so frequently but am looking forward to their visits in Utah.

I would also like to thank a number of people who contributed to my teaching experiences at Caltech. Dr. Jennifer Weaver and the directors in the Caltech Project for Effective Teaching (CPET) program have provided me with valuable feedback on my teaching portfolio as I worked to complete my Certificate of Practice in University Teaching. I am thankful to Ms. Jodi Marchesso and the high school chemistry teachers in the Pasadena Unified School District for their willingness to let me help on a year-long curricula redesign project during my first year of grad school. I would like to thank Prof. John Hanley at Pasadena City College who gave me the opportunity to come shadow his organic chemistry class for a semester and also guest lecture in his course. Lastly, I would like to thank my coworker, Dr. Carolyn Ladd, for taking on this huge undertaking of teaching Ch101 with me. It's been such a fun and rewarding (and sleepless) experience learning how to design and run our own course on natural products in medicine; Carolyn has been beyond supportive during the first few weeks of our course as I frantically wrapped up writing my thesis. I have really valued her continual encouragement and cheer. This experience has given me a lot more confidence in my teaching abilities which will be instrumental when I start my independent career.

Over the course of my graduate career, I have been privileged to work on a variety of collaborative projects with students in our group as well as with students at other

universities. I am indebted to Prof. Kendall Houk and his students Dr. Yunfang Yang and Dr. Xin Hong for their hard work running the geometry optimizations and energy calculations on our alkenylation reaction. Without them we could not have conducted some of our mechanistic studies. I am also grateful for the opportunity to work with Iris Guo and Prof. Matt Sigman on PHOX ligand parameterization. Iris is such a talented computational chemist and definitely put up with a lot of my excessive questions regarding MatLab and my confusion on how Python is not a coding language and has nothing to do with snakes. It was so fun to visit Matt's laboratory last February to learn how they conduct their research. Matt has been such a supportive semi-advisor throughout the past two years and I am excited to now have the opportunity to work for him in my postdoctoral studies.

I have also been fortunate to have worked alongside many fantastic coworkers during my time in the Reisman laboratory. I would like to particularly thank my project partners over the years; I think some of my greatest joys in grad school have been the opportunities I received to collaborate with my colleagues. Dr. Alan Cherney was my first mentor when I started in the laboratory back in 2014, and his willingness to give me feedback during my studies is something I have always appreciated. It has been an honor to be entrusted with the allylic silane project after he graduated. His insight into the alkenylation mechanism project has also always been a fun conversation starter. I would also like to thank Dr. Nathaniel Kadunce who also taught me so much about reductive cross-coupling during my first few years in grad school. I think one of the things I enjoyed most about being on Team Nickel was the openness in our group. Although everyone is usually working on their own project, the communication and feedback everyone gives each other makes it feel like you are part of something bigger.

I am thankful for a number of other project partners who have worked alongside me, including Dr. Naoyuki Suzuki, Alex Shimozono, and Raymond Turro. Naoyuki and Alex are such terrific scientists and work extremely hard with intense focus. I have learned a lot about dedication from both of them. Ray is also another gifted chemist; it has been refreshing to have a new set of eyes and hands take over the mechanism projects. I am confident that he will do well finishing up the work and I am excited to see what new chemistry everyone on Team Nickel will discover in the years to come.

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I was also privileged to have the opportunity to mentor two fantastic undergraduate students, Ciara Ordner and Dana Gephart. It has been wonderful to watch them grow and develop careful, thoughtful approaches to their research. I am excited to see where their roads will take them and what accomplishments they achieve. In particular, Ciara came into the laboratory during a time when my graduate studies felt like a monotony, and working with her gave me a renewed sense of motivation. Ciara was a present reminder of what I was working towards in my teaching career, although it was definitely easy to mentor such an ambitious and thoughtful student. I think in the end, I learned more from Ciara than she learned from me and I am fortunate enough to also call her a close friend.

There are also a number of other close friends in the lab that have helped get me situated when I first started. I remember Dr. Lauren Chapman dropped what she was doing

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I have worked next to quite a few baymates during my time in the lab: Kevin Sokol, Dr. Kohei Takeuchi, and Nick Fastuca. Both Kevin and Kohei were such energetic young individuals who would always put a smile on my face. I have also thoroughly enjoyed working next to Nick for most of my time in the Reisman lab. We may not always be the best at keeping things clean and organized, but I think our work dynamic has been perfect. The two of us just seem to roll with all the things the other person does and it has been nice to work next to someone with such a calm and forgiving spirit, especially when my blue cobalt encrusted glassware often took over all the drying racks in our space. I am going to miss chatting with Nick about grad school life and Reisman lab softball strategies.

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I am also appreciative of support from a number of friends here at Caltech and beyond. My two roommates, Elizabeth Goldstein and Rachel Ford, have enriched my life in ways I never imagined. I will always remember all the fun times we have shared, from cheesecake celebrations when finishing literally every exam in our first year, to the fun road trips and adventures we have had. Elizabeth has stuck with me as one of my closest friends since the very beginning and I will truly miss all of the fun adventures, food runs, and board game nights we have shared together. I think one of my favorite memories with her was going on our Sierra road trip a few years back. I somehow managed to get her to sleep in a tent and hike off-trail into the woods with me to find the Caltech Centennial Grove. I am looking forward to visiting her in Germany and maybe one day finally go on that Europe trip we dreamed of. I am also thankful for all my friends in the Caltech Volleyball Club: Reston Nash, Alex Phillips, Marianne Heida, Michelle Cua, Panagiotis Vergados, and so many others. I think this group is single handedly the most responsible for keeping me sane during my graduate studies. I am thankful for the time we get to play some serious volleyball together, but also for the friendships I have made and the times we have shared at barbeques, Congregation Ale House, and Hollywood Boulders rock climbing nights. I am going to miss them all so dearly. Finally, I would like to thank both

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ABSTRACT

Cross-coupling reactions have emerged as powerful methods to form carbon-carbon and carbon-heteroatom bonds in a vast array of synthetic contexts. Nickel-catalyzed reductive cross-coupling reactions have opened up a new mode of reactivity, allowing for the cross-coupling of bench-stable electrophiles as both coupling partners. Asymmetric variants, which use a chiral ligand, increase molecular complexity by introducing stereocenters with high levels of enantioselectivity. Application of this methodology to an array of electrophiles has led to the development of a number of transformations incorporating both C(sp²)-hybridized electrophiles (aryl iodides, alkenyl bromides, and acyl chlorides) and C(sp³)-hybridized electrophiles (benzyl chlorides and α -chloronitriles).

Herein we discuss our most recent efforts in the development and application of Ni-catalyzed asymmetric cross-coupling reactions with alkenyl electrophiles. First, the expansion of our previously developed methodology has allowed for bulky trimethylsilyl groups on the benzyl chloride electrophile, providing chiral allylic silane products in good yield and enantioselectivity. The utility of these products with both traditional and newly developed methodology is highlighted. Following this, we describe the development of reaction conditions that proceed with benzyl *N*-hydroxyphthalimide esters. This approach proceeds through a decarboxylative strategy, generates previously accessible radical intermediates, and proceeds with the use of a homogenous reductant. Our investigations into the mechanism on the cross-coupling of alkenyl bromides and benzyl chlorides is also disclosed, where we first identified the formation of alkenyl chloride and alkenyl iodide intermediates under the reaction conditions. This inspired us to develop a Ni-catalyzed alkenyl triflate halogenation in order to prepare alkenyl halide synthetic intermediates.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following communications:

1. Suzuki, N.[‡]; Hofstra, J. L.[‡]; Poremba, K. E.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 2150-2153. DOI: 10.1021/acs.orglett.7b00793. This article is available online at: <https://pubs.acs.org/doi/abs/10.1021/acs.orglett.7b00793>. Copyright © 2017 American Chemical Society

J.L.H. contributed to the reaction development, conducted experiments, and participated in preparation of the supporting data and writing of the manuscript.

2. Hofstra, J. L.; Cherney, A. H.; Ordner, C. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 139-142. DOI: 10.1021/jacs.7b11707. This article is available online at: <https://pubs.acs.org/doi/10.1021/jacs.7b11707>. Copyright © 2018 American Chemical Society

J.L.H. contributed to the reaction development, conducted experiments, and participated in preparation of the supporting data and writing of the manuscript.

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LIST OF ABBREVIATIONS

–	minus
%	percent
°	degrees
+	plus
<	less than
=	equals
>	greater than
~	approximately
λ	lambda (wavelength)
α	alpha
A	ampere or acid functional group
Å	angstrom(s)
$[\alpha]_D$	angle of optical rotation of plane-polarized light
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
alk	alkyl
anal.	combustion elemental analysis
<i>anti</i>	opposite or same side
approx	approximately

aq	aqueous
Ar	aryl group
Ar ^F	perfluorinated aryl group
atm	atmosphere(s)
AU	arbitrary units
AVG	average
β	beta
BDMAP	1,6-bis(dimethylamino)pyrene
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol (“ <u>butylated hydroxytoluene</u> ”)
BiOX	bi(oxazoline)
Bn	benzyl
BnPHOX	benzyl phosphinooxazoline
Boc	<i>tert</i> -butoxycarbonyl
BOX	bis(oxazoline)
bp	boiling point
bpy	2,2'-bipyridine
br	broad
Bu	butyl
Bz	benzoyl
/C	supported on activated carbon charcoal
°C	degrees Celcius
¹³ C	carbon-13 isotope
c	concentration of sample for measurement of optical rotation

calc'd	calculated
CAM	cerium ammonium molybdate
Cbz	benzyloxycarbonyl
<i>cis</i>	on the same side
cm	centimeters
cm ⁻¹	wavenumber(s)
CNB	1-chloro-2,4-dinitrobenzene
conv.	conversion
CoPc	cobalt(II) phthalocyanine
CoPc _F	perfluorinated cobalt(II) phthalocyanine
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CV	cyclic voltammetry
δ	chemical shift in ppm
D	deuterium
<i>d</i>	deutero or dextrorotatory
d	doublet
Δ	heat or difference
ΔG	change in Gibb's free energy
DBE	dibromoethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate

DEC	diethyl carbonate
DHA	dihydroanthracene
DIBAL	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
DIPA	N-diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMBA	2,6-dimethylbenzoic acid
dme	1,2-dimethoxyethane
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dpph	1,6-bis-(diphenylphosphino)hexane
dr	diastereomeric ratio
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
<i>E</i>	<i>trans</i> (entgegen) olefin geometry
e.g.	for example (Latin: <i>exempli gratia</i>)
E ⁺	electrophile

EA	elemental analysis
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact
E_{pc}	cathodic peak potential
EPR	electron paramagnetic resonance
equiv	equivalent(s)
er	enantiomeric ratio
es	enantiospecificity
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: <i>et alii</i>)
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
etc	and the rest (Latin: <i>et cetera</i>)
EtOAc	ethyl acetate
EtOH	ethanol
¹⁹ F	fluorine-19 isotope
FAB	fast atom bombardment
Fc	ferrocene
Fc ⁺	ferrocenium cation
FDA	Food and Drug Administration
FID	flame ionization detector

FTIR	fourier transform infrared spectroscopy
G	gauss
g	gram(s)
g-value	dimensionless magnetic moment value
g/mL	grams per milliliter
GC	gas chromatography
GHz	gigahertz
^1H	proton
h	hour(s)
HAT	hydrogen atom transfer
Het	hetero
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HOAt	1-hydroxy-7-azabenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
h ν	irradiation with light
Hz	hertz
<i>i</i> -Bu	<i>iso</i> -butyl
<i>i</i> -Bu ₃ Al	triisobutyl aluminum
<i>i</i> -Pr	isopropyl

$i\text{-Pr}_2\text{NH}$	diisopropyl amine
$i\text{-PrAc}$	isopropyl acetate
$i\text{-PrOH}$	isopropanol
i.e.	that is (Latin: <i>id est</i>)
<i>in situ</i>	in the reaction mixture
IPA	isopropanol
IR	infrared
J	coupling constant in Hz
K	Kelvin
k	rate constant
k_0	initial rate constant
k_c	equilibrium constant
kcal	kilocalorie(s)
kg	kilogram(s)
$\text{KO}t\text{-Bu}$	potassium tert-butoxide
L	liter
l	levorotatory
LC-MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LED	light emitting diode
ln	natural logarithm
log	logarithm
LRMS	low resolution mass spectrometry

LUMO	lowest unoccupied molecular orbital
m	multiplet or meter(s)
M	molar or molecular ion or metal
[M]	parent mass
<i>m</i>	<i>meta</i>
M ⁻¹	inverse molarity
m.p.	melting point
<i>m/z</i>	mass-to-charge ratio
mA	milliamp(s)
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeCO ₂ H	acetic acid
MeI	methyl iodide
MeOH	methanol
mg	milligram(s)
mg/mL	milligrams per milliliter
MHz	megahertz
MIDA	methyliminodiacetic acid
min	minute(s)
μL	microliter(s)
mL	milliliter(s)
mL/min	milliliters per minute

mM	millimolar
mm	millimeter(s)
μm	micrometer(s)
mm Hg	millimeters mercury
mmol	millimole(s)
mol	mole(s)
mol %	mole percent
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MsCl	methanesulfonyl chloride
MSD	mass selective detector
¹⁴ N	nitrogen-14 isotope
n	number
<i>n</i> -Bu	<i>norm-butyl</i>
<i>n</i> -BuLi	<i>norm-butyl</i> lithium
<i>n</i> -Hex	<i>norm-hexyl</i>
<i>n</i> -Pr	<i>norm-propyl</i>
NaOTf	sodium triflate
NBS	<i>N</i> -bromosuccinimide
Nf	perfluorobutanesulfonyl
Nf-F	perfluorobutanesulfonyl fluoride
Nf ₂ O	perfluorobutanesulfonyl anhydride
NHP	<i>N</i> -hydroxyphthalimide

nm	nanometer(s)
NMP	<i>N</i> -methyl pyrrolidinone
NMR	nuclear magnetic resonance
Nu ⁻	nucleophile
<i>o</i>	<i>ortho</i>
³¹ P	phosphorus-31 isotope
<i>p</i>	<i>para</i>
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
Pc	phthalocyanine
PC	propylene carbonate
PcF	perfluorinated phthalocyanine
PDT	product
pH	hydrogen ion concentration in aqueous solution
Ph	phenyl
phen	1,10-phenanthroline
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
Phth	phthalimide
Pin	pinacol
pm	picometer(s)
PMP	<i>para</i> -methoxyphenyl
ppm	parts per million

Pr	propyl
psi	pounds per square inch
py	pyridine
PyBOX	pyridine bis(oxazoline)
q	quartet
quant	quantitative
R	generic (alkyl) group
<i>R</i>	rectus
R^2	coefficient of determination
ref	reference
R_F	perfluorinated alkyl group
R_f	retention factor
RF	response factor
rpm	revolutions per minute
rr	regioisomeric ratio
rt	room temperature
σ	Hammett coefficient
s	singlet or seconds
<i>S</i>	sinister
sat.	saturated
SCE	saturated calomel electrode
SFC	supercritical fluid chromatography
STD	standard

<i>syn</i>	same side
T	temperature
t	triplet or time
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuLi	<i>tert</i> -butyl lithium
taut.	tautomerize
TBA	tetra- <i>n</i> -butylammonium
TBABr	tetra- <i>n</i> -butylammonium bromide
TBACl	tetra- <i>n</i> -butylammonium chloride
TBACN	tetra- <i>n</i> -butylammonium cyanide
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBAX	tetra- <i>n</i> -butylammonium salt
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBDPSCl	<i>tert</i> -butyldiphenylsilyl chloride
TBS	<i>tert</i> -butyldimethylsilyl
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
TDAE	tetrakis(dimethylamino)ethylene
TEA	triethylamine
temp	temperature
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TEOA	triethanolamine
TES	triethylsilyl

Tf	trifluoromethanesulfonyl
Tf ₂ O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMHD	2,2,6,6-tetramethyl-3,5-heptanedione
TMS	trimethylsilyl
TMSBr	trimethylsilyl bromide
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOF	time-of-flight
Tol	tolyl
TPP	tetraphenylporphyrin
tpy	2,2';6',2"-terpyridine
<i>t_R</i>	retention time
<i>trans</i>	on the opposite side
TS	transition state
Ts	<i>para</i> -toluenesulfonyl (tosyl)
TTF	tetrathiafulvalene
μ	micro
μL	microliter(s)
UV	ultraviolet

V	volt(s)
<i>vide infra</i>	see below
V_{\max}	maximum rate
vs.	versus
W	watt(s)
w/	with
wt%	weight percent
X	anionic ligand or halide or chiral auxillary
X_{major}	fraction of mixture as major enantiomer
X_{minor}	fraction of mixture as minor enantiomer
Z	<i>cis</i> (zusammen) olefin geometry