THE DEVELOPMENT OF NI-CATALYZED METHODS FOR APPLICATION IN TOTAL SYNTHESIS

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2023

(Defended October 25th, 2022)

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ACKNOWLEDGEMENTS

First and foremost, I'd like thank my advisor, Prof. Sarah Reisman, for providing me the opportunity to do amazing science. I feel I have developed an incredible amount as a chemist during the time I've spent at Caltech and much of this is owed to lessons I've learned as a member of Sarah's lab. Throughout my time in her lab, Sarah has consistently pushed me to think critically and creatively, to never settle for "good" when we know "great" is on the table, and to constantly strive to improve. As I reflect on my time at Caltech there are two main values Sarah has engrained in me that I hope to instill in my students one day: "work hard" and "do the best science possible."

I owe a huge debt of gratitude to my committee chair, Prof. Brian Stoltz. Brian has consistently been there for me throughout my Ph.D. Particularly this past year as my labwork has become more and more busy Brian has constantly helped me compartmentalize, pushed me to juggle, and allowed me to realize the value of balance and taking breaks when necessary. In addition to providing great scientific feedback, I've learned as many, if not more, valuable life lessons from my conversations with Brian. There's no better person to have on your team.

I'd like to thank the rest of my committee members, Profs. Max Robb and Theo Agapie for providing helpful feedback in various meetings throughout the Ph.D.

Thank you to my supportive and caring professors from my undergraduate studies at the University of Richmond, my advisor Prof. Emeritus John Gupton and the rest of the organic faculty on the 3rd floor of Gottwald: Profs. Kristine Nolin, Wade Downey, and

Miles Johnson. Never in my wildest dreams would I have imagined getting into a graduate school like Caltech without your support. You all have continuously invested in my development both as a student and as a human, even after leaving UR. Thank you so much.

I'd be remiss to forget the many people behind the scenes who ensure Caltech runs like a well-oiled machine including but not limited to: Beth Marshall, Margarita Davis, Annette Luymes, Alison Ross, Joe Drew, Scott Virgil, Dave VanderVelde, Mike Takase, Mona Shahgholi, and Nathan Hart. Thank you for all you do for the Institute.

I'd like to thank my wonderful mentors from early on in graduate school: Julie Hofstra, Kelsey Poremba, and Jordan Beck. I learned an incredible amount from you all; thank you for helping me improve my bench skills and appreciate the importance of experimental rigor.

I'd like to thank other various project partners over the years: Andrea Stegner, Dave Charboneau, Yuanzhe Xie, Alex Cusumano, Daniel Chang, Jaron Tong, Angel Hernandez-Mejias, Sven Richter, and hopefully Ray Turro and Nathan Friede. It's been a pleasure working with you all, I can't wait to see the awesome directions you all take these projects.

I'd like to thank the following friends who have made my time at Caltech so special: Ailiena Maggiolo, Sarah Bevilacqua, Travis Delano, Molly McFadden, Hailey Knox, Conner Farley, Jordan Thompson, Chloe Williams, Sepand Nistanaki, Emily Chen, Samir Rezgui, and Farbod Moghadam. To the many people I'm sure I've missed here, I apologize.

Finally, I need to thank my family for providing unending and unconditional support. This Ph.D would have been impossible without y'all.

Funding from the NSF, NSF Center for Synthetic Electrochemistry (CSOE), and Amgen is gratefully acknowledged.

ABSTRACT

The total synthesis of complex natural products often requires the development of mild, selective transformations. Once developed, these methods can serve as starting points for related methodologies, fundamental mechanistic studies, or applied in other total syntheses. Herein, a series of projects that embody this relationship are described. Inspired by unexpected challenges in the synthesis of complex diterpenoid alkaloid talatisamine, a Ni-catalyzed enol-triflate-halogen exchange reaction was developed. In addition to finding application toward the synthesis of talatisamine, this reaction found further use in an attempted route toward enmein-type *ent*-kauranoid natural products.

En route to the synthesis of these natural products, a need for *meso*-anhydride functionalization was identified which inspired a research program dedicated to Ni-catalyzed reductive desymmetrization of *meso*-anhydrides. During these studies, an underexplored class of bisoxazoline (BOX) ligands was identified, which enables a catalyst controlled doubly-stereoselective cross-electrophile coupling of *meso*-anhydrides and *sec*-alkyl halides in good yield and exceptional enantio- and diastereo- selectivity. It is anticipated that this method will enable the rapid synthesis of tricyclic compounds which serve as intermediates toward members of *ent*-kauranoid, diterpenoid alkaloid, and steroid natural products.

PUBLISHED CONTENT AND CONTRIBUTIONS

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

1. Hofstra, J. L.*; Poremba, K. E*.; Shimozono, A. M*.; Reisman, S. E. Nickel-Catalyzed Conversion of Enol Triflates into Alkenyl Halides. *Angew. Chem. Int. Ed.* **2019**, *58* (42), 14901–14905. DOI: 10.1002/anie.201906815.

*Authors contributed equally and are listed in alphabetical order.

AMS 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
anti	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-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
BiOX	bi(oxazoline)
Bn	benzyl
BnPHOX	benzyl phosphinooxazoline
Boc	*tert*-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
cis	on the same side
cm	centimeters
cm^{-1}	wavenumber(s)
CNB	1-chloro-2,4-dinitrobenzene
conv.	conversion
CoPc	cobalt(II) phthalocyanine
$CoPc_F$	perfluoroinated cobalt(II) phthalocyanine
COSY	homonuclear correlation spectroscopy
Cp	cyclopentyldienyl
CV	cyclic voltammetry
δ	chemical shift in ppm
D	deuterium
d	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	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMBA	2,6-dimethylbenzoic acid
dme	1,2-dimethoxyethane
DMEDA	*N,N'*-dimethylethylenediamine
DMF	*N*,*N*-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-*tert*-butyl-2,2'-bipyridine
E	*trans* (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
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: *et alii*)
Et_2O	diethyl ether
Et_3N	triethylamine
etc	and the rest (Latin: *et cetera*)
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
^{1}H	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
hυ	irradiation with light
Hz	hertz
i-Bu	*iso*-butyl
i-Bu_3Al	triisobutyl aluminum
i-Pr	isopropyl

i-Pr_2NH	diisopropyl amine
i-PrAc	isopropyl acetate
i-PrOH	isopropanol
i.e.	that is (Latin: *id est*)
in situ	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)
KO*t*-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
m	*meta*
M^{-1}	inverse molarity
m.p.	melting point
m/z	mass-to-charge ratio
mA	milliamp(s)
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
$MeCO_2H$	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
n-Bu	*norm-butyl*
n-BuLi	*norm*-butyl lithium
n-Hex	*norm*-hexyl
n-Pr	*norm*-propyl
NaOTf	sodium triflate
NBS	*N*-bromosuccinimide
Nf	perfluorobutanesulfonyl
Nf-F	perfluorobutanesulfonyl fluoride
Nf_2O	perfluorobutanesulfonyl anhydride
NHP	*N*-hydroxyphthalimide

nm	nanometer(s)
NMP	*N*-methyl pyrrolidinone
NMR	nuclear magnetic resonance
Nu^-	nucleophile
o	*ortho*
^{31}P	phosphorus-31 isotope
p	*para*
p-TsOH	*para*-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	phosphinooxaozoline
Phth	phthalimide
Pin	pinacol
pm	picometer(s)
PMP	*para*-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
R	rectus
R^2	coefficient of determination
ref	reference
R_F	pefluorinated 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
S	sinister
sat.	saturated
SCE	saturated calomel electrode
SFC	supercritical fluid chromatography
STD	standard

syn	same side
T	temperature
t	triplet or time
t-Bu	*tert*-butyl
t-BuLi	tert-butyl lithium
taut.	tautomerize
TBA	tetra-n-butylammonium
TBABr	tetra-*n*-butylammonium bromide
TBACl	tetra-*n*-butylammonium chloride
TBACN	tetra-*n*-butylammonium cyanide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBAX	tetra-*n*-butylammonium salt
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	tert-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-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_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-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
t_R	retention time
trans	on the opposite side
TS	transition state
Ts	*para*-toluenesulfonyl (tosyl)
TTF	tetrathiafulvalene
μ	micro
μL	microliter(s)
UV	ultraviolet

V	volt(s)
vide infra	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	*cis* (zusammen) olefin geometry