THE SYNTHESIS AND LATE-STAGE DIVERSIFICATION OF THE CYANTHIWIGIN NATURAL PRODUCT CORE AND SYNTHETIC INSIGHTS DERIVED THEREIN

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

2017

(Defended December 16, 2016)

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To Mom, Dad, and Roger

and

To Steven

ACKNOWLEDGEMENTS

Scientific research is by nature a collaborative endeavor, incorporating the painstaking efforts of many contributors. While the preparation of this thesis has at times seemed like the ultimate solitary activity, its completion would not have been possible without the input, guidance, and support of many people.

First and foremost, I would like to thank my advisor, Professor Brian Stoltz. I feel extremely fortunate to have joined the Stoltz group, as Brian is a phenomenal mentor. From my first meeting with him, I was exhilarated by Brian's enthusiasm for chemistry and the training of young scientists, a quality that has been instrumental to my success in graduate school. There have been many instances where I entered Brian's office confused and frustrated by setbacks in my research, and each time I exited feeling invigorated and eager to try out all the ideas we had discussed. As I acclimated to the often overwhelming nature of scientific research during my early years in graduate school, these moments of clarity helped keep me excited about my work and focused on answering the important questions.

Brian's knowledge of chemistry is awe-inspiring, as is his talent for motivating his students to produce their very best work. Under his tutelage, I have cultivated a keen eye for professionalism in executing, writing, and presenting scientific research. However, perhaps even more admirable is his ability to connect with students on a human level and understand that the pursuit of academic excellence is most possible when one's personal life is intact. This is one of Brian's mentorship qualities that I most appreciate and one that has significantly contributed to the overall success of my graduate training.

For his support during my most uncertain times, I am deeply grateful, and I hope to emulate his mentorship style in my future career.

I am also fortunate to have enjoyed much wisdom and encouragement from the members of my dissertation committee throughout my graduate studies. As the committee chair, Professor Robert Grubbs has been continuously supportive of my work, collaborating on several of my research projects and ensuring that all of my graduate degree progress meetings have occurred smoothly and in a timely fashion. I am also very grateful for Professor Harry Gray's constant dedication to my training, providing much-appreciated encouragement on my exit proposals and always taking the time to discuss my progress and career goals any time I stop by his office. Professor Sarah Reisman, the newest member of my committee, has tirelessly offered her feedback on a diverse range of topics including research concerns, post-Caltech plans, and Women in Chemistry event-planning and committee management over the past several years.

I have also benefitted enormously from my involvement in the NSF Center for Stereoselective C–H Functionalization (CCHF) over the past four years. The weekly videoconferences and annual meetings became defining activities of my graduate school experience, and I am fortunate to have met many wonderful students, postdocs, professors, and industrial chemists through this program. While the Center is quite large and encompasses too many individuals to name specifically, I would like to thank CCHF Director Professor Huw Davies (Emory) for getting the Center established, and Dr. Dan Morton for tirelessly working to ensure Center-wide events ran smoothly. Additionally, I must thank my CCHF collaborators: Professor Justin Du Bois, Dr. Ashley Adams, and Nicholas Chiappini (Stanford), along with many other individuals with whom I've shared insightful conversations about chemistry and life. I will certainly miss the cross-institutional discussions that I've grown accustomed to through the CCHF.

I am also grateful for the many teaching opportunities I've had at Caltech and would like to thank Professors Nathan Lewis, Geoffrey Blake, Douglas Rees, Peter Dervan, Daniel O'Leary, Gregory Fu, and Brian Stoltz for allowing me to serve as a teaching assistant for their courses. I am especially appreciative of Professor O'Leary's active role in cultivating and supporting my interest in pursuing a career at a PUI .

The research described in this thesis would not have been possible without the expertise of synthetic and spectroscopic wizards Dr. Scott Virgil and Dr. David VanderVelde. Dr. Virgil's assistance was instrumental in my efforts to reproduce Dr. John Enquist's synthesis of the cyanthiwigin natural product core. As a relatively inexperienced second-year graduate student at the time, I learned a great deal from Dr. Virgil's careful analyses of experimental setups for sensitive reactions, particularly the Negishi cross-coupling and RCM/cross-metathesis transformations. Moving forward, this knowledge enabled me to perform the entire synthetic sequence repeatedly with minimal trouble, which was vital to the success of the cyanthiwigin diversification project. Although I have yet to meet him, Dr. John Enquist also graciously answered in great detail many of my emails asking for advice on certain synthetic steps.

Similarly, Dr. VanderVelde's devotion to educating me in multi-dimensional NMR analysis was a key component of my research, as most of the compounds generated from the cyanthiwigin diversification project required the use of 2D NMR experiments for unambiguous structural determination. Compared to the overwhelming confusion I felt the first several times I attempted to interpret 2D NMR data, the ease with which I acquire and analyze these spectra today is a testament to Dr. VanderVelde's substantial contributions to my graduate training.

Along the same lines, Dr. Mona Shagholi and Naseem Torian have tirelessly provided assistance in the acquisition of mass-spectrometry data and have always done so kindly and patiently, even when my samples were overly dilute. Furthermore, I am grateful to Dr. Michael Takase and Lawrence Henling for helping in the acquisition of X-ray crystallography data and for taking the time to scrutinize my samples even when they were not of good enough quality for X-ray diffraction.

I ascribe much of my current interest in chemistry to the masterfully designed courses that captured my attention early in college. Professor J. Michael McBride's Freshman Organic Chemistry course at Yale was a challenging but fascinating beginning to university coursework and organic chemistry during my first semester in the fall of 2007. Professor McBride's thoughtful approaches to lectures and his insistence that students always ask the questions "How do you know?" and "Compared to what?" taught me to engage with the scientific process and think critically. Furthermore, the course's unorthodox diligence in scrutinizing the historical backgrounds of important concepts in chemistry showcased the progressing sophistication of chemical research methods, helping me appreciate the significance of modern advances in this evolutionary process.

My interest in chemistry was bolstered by my enjoyment of the accompanying laboratory course. The instructor, Dr. Christine DiMeglio, advised me in choosing courses for the chemistry major and employed me as an aide in the teaching labs. She also provided me with my first opportunities for original chemical experimentation when she tasked me with optimizing a low-yielding procedure used in the lab courses.

Furthermore, Dr. DiMeglio supported my application to the DAAD RISE summer internships program, an experience that ultimately led to my decision to pursue graduate studies in chemistry. For her unwavering support and instrumental role in my early laboratory education, I am most grateful.

I'm also very fortunate to have had the opportunity to work in three differently focused research labs as an undergraduate. I am grateful to Dr. Hal Blumenfeld for enlightening me to the practice of scientific research, albeit in a non-chemistry field. I am indebted to Dr. Max Bielitza and Prof. Dr. Jörg Pietruszka for introducing me to research in organic synthesis and for inspiring me to continue my training in chemistry after college. Finally, I am appreciative of Prof. Nilay Hazari for taking me on as the first undergraduate student in his lab, introducing me to organometallic chemistry research, and for sharing all of his insightful anecdotes about his time as a postdoc at Caltech.

Over the past five years, I have shared lab space with many remarkable graduate students, postdoctoral scholars, and undergraduate students. When I first joined the group, I benefitted tremendously from the expertise of older students in my bay and in the office. My hoodmate, Christopher Haley, spent much time helping me set up my hood and showing me where to find anything I needed in the lab. He also taught me many little tricks for running columns that I still use today. Dr. Grant Shibuya, Dr. Doug Behenna, Allen Hong, Nathan Bennett, Alex Goldberg, Jonny Gordon, and Jeff Holder were also phenomenal sources of advice on tricky work-ups, problematic separations, or elaborate reaction set-ups. Depsite only overlapping with them for a few months, Dr. Kristy Tran, Hosea Nelson, and Chris Gilmore were highly encouraging of me as a new student in the group, and I enjoyed many uplifting conversations with them.

Being trapped at the desk next to mine in the small office, Allen Hong was a great sport about answering all of my inane first-year questions. Despite working on a completely different project than mine, Allen served as an in-lab mentor for me, often supplying much-needed advice on my research and on grad school in general, including introducing me to a vital aspect of my Caltech experience: post-subgroup Tuesday flautas at Ernie's. I especially appreciated his weeks-long campaign to combat my night-owl tendencies through the promise of a morning piece of candy if I made it to lab before 9 AM (at which I was moderately successful). Even after departing Caltech during my second year, Allen has remained a good friend and mentor, providing encouragement and advice on postdoctoral and fellowship applications, paper submissions, and more. He is also the creator of some of the best-looking figures and templates I've seen, and I often follow his example when creating official documents such as CVs, thesis outlines, etc.

One of the best parts about starting in a new lab as part of a big class of graduate students is forming special bonds with the other students in your year. Nick O'Connor, Seojung Han, and Anton Toutov have been fantastic classmates, and we spent many an evening in lab talking about chemistry and musing over what to expect from graduate school. These discussions were supplemented with extracurricular video game nights at my apartment and margarita nights at Amigos. I greatly enjoyed the many conversations I've had with Nick, Seojung, and Anton about chemistry and life over the past several years, and wish them all the best in their future endeavors.

Having secured my friendship early on in our first year with the (reimbursed) purchase of a bottle of whipped cream vodka, Nick O'Connor has been one of my closest friends at Caltech. Fellow night owls, Nick and I have worked late into the night on various occasions, providing each other with good company and humor. In addition to being a close confidante and fellow opponent of the word "vignette," Nick is one of the most intelligent and well-read people I know, and his passion for historical biographies, obscure named reactions, and Wikipedia exploration is unparalleled among our peers. I feel privileged to have been able to share as much of our graduate school experiences as we did, having undergone candidacy exams, fourth-year meetings, postdoc and fellowship applications, proposal exams, and thesis writing in roughly identical timelines. I will certainly miss our spirited discussions when we part ways and wish him the best at UC Berkeley and beyond. I am confident that he will do amazing things with his career.

After she joined the lab in my third year, Sam Shockely and I struck up a fast friendship, as we were both baymates and desk neighbors. Extremely hard-working and intelligent, Sam hit the ground running in her graduate studies, and her enthusiasm for science and efficiency in the lab breathed new life into me during my post-candidacy third-year slump. In addition to inspiring me to work more cleanly with her insanely tidy fume hood and desk, Sam took an active role in helping me fight the "grad school 15" by introducing me to a rich variety of group fitness classes at the Caltech gym and joining me in the Alhambra Pumpkin Run 10K. Sam's energy and zest for science is effusive, and I know that she will continue to inspire others while enjoying wildly successful graduate and post-graduate careers.

I am fortunate to have worked with talented individuals on several projects. I greatly enjoyed working with Yiyang Liu on the decarbonylative dehydration of fatty acids and with Doug Duquette, Dr. Alex Marziale, Dr. Marc Liniger, Dr. Yoshitaka Numajiri, and Rob Craig on the low-catalyst enantioselective allylic alkylation. I also appreciate Jiaming Li's nitrite screening contributions to the aldehyde-selective Tsuji–Wacker oxidations project and Dr. Xiangyou Xing's insights into allylic C–H oxidation for the comparative C–H functionalization project. Dr. Boger Liu, with whom I overlapped for several years in the lab, provided a font of knowledge and inspiration. Finally, I thank Yuka Sakazaki for allowing me the opportunity to serve as a mentor in the lab and wish her the best in her future career.

While it is challenging to name every single person whose presence in lab has influenced me over the past five years, I would also like to thank Nina Vrielink, Beau Pritchett, Dr. Christian Eidamshaus, Chung Whan Lee, Corey Reeves, Dr. Pamela Tadross, Austin Wright, Elizabeth Goldstein, Steven Loskot, Shoshana Bachmann, Christopher Reimann, Dr. Eric Welin, Dr. Caleb Hethcox, Kelvin Bates, Katerina Korch, Dr. Masaki Hayashi, Dr. Kazato Inanaga, Dr. Yuji Sumii, Dr. Noriko Okamoto, Dr. Jimin Kim, Dr. Max Klatte, Dr. Hendrik Klare, Julian West, and Moriam Masha for providing friendship, proofreading services, good conversations, and fond memories over the past several years. I am especially grateful to Christopher Haley, Yutaro Saito, Yuka Sakazaki, and Dr. Denis Kroeger for having been wonderful hoodmates. Additionally, I have enjoyed years of stimulating conversation in the "small office" with Doug Duquette, Nick O'Connor, Sam Shockley, David Schuman, Alex, Sun, Dr. Gerit Pototschnig, Christopher Haley, Dr. Guillaume Lapointe, Lukas Hilpert, Allen Hong, Dr. Jared Moore, Nathan Bennett, Chris Gilmore, Dr. Marchello Cavitt, Dr. Daisuke Saito, and Dr. Justin Hilf. I will look back with fond memories on the many summers of CCE softball, culminating with a championship victory this past year, thanks to a wonderful team and Beau's tireless efforts as captain. I enjoyed attending MTG events with Doug and will miss “shamblesharking” with him as well as receiving all sorts of random religious figurines from his apartment complex. I wish all the best for the first- and second-year students who are just beginning their graduate school adventures.

My discussions about science, graduate school, and life with friends outside of the Stoltz lab have also greatly enriched my experience by providing opportunities to view my work outside of the usual contexts. I am deeply grateful to Dr. Pablo Guzmán for his unwavering support and encouragement throughout the years and to Dr. Alissa Hare, Dr. Nathan Schley, Dr. James Blakemore, Anton Toutov, Kevin Shen, Marc Serra, Tania Darnton, Helen Yu, Matthew Chalkley, Dr. David Romney, and Dr. Charisma Bartlett for engaging me in thought-provoking and insightful conversations. I was also fortunate to have many interesting discussions with my cousin, Cedric Flamant, with whom I overlapped at Caltech for four years as he earned his bachelor’s degree.

I would also like to thank Delores Bing for serving as a fantastic director of the Caltech Chamber Music Program, in which I participated throughout my time at Caltech. I am indebted to Robert Ward for encouraging me to participate in the program during a chance encounter my first week on campus in 2011. Were it not for his encouragement, I would not have discovered the great joy that playing chamber music has brought me over the past five years. My participation in the chamber program provided me with an outlet to engage my musical interests and disconnect from the stresses of research, without which I would surely have grown disillusioned. I am deeply grateful to my coaches Robert Ward, Kirsten Joel, Michael Kreiner, Delores Bing, and Martin Chalifour for enriching my musical education, and I feel fortunate to have met many wonderful musician-scientists through this program. My performances with Sean Symon, Ian

Wong, Joe Iverson, and Sarah Jeong, are among my favorite musical memories so far, and our conversations about music and science have been similarly unforgettable.

The Caltech Division of Chemistry and Chemical Engineering is blessed with a fantastic and caring staff. Agnes Tong facilitated navigation of the administrative processes involved in completing the PhD degree. Her geniune concern for students and dedication to their happiness and success is always apparent, and she has been a great friend to me these past several years. Alison Ross has also been tremendously helpful in this position and is a great resource for students. Jeff Groseth has rejuvenated many a malfunctioning stir plate, UV lamp, or rotovap in impressive fashion. Likewise, Rick Gerhart has repaired countless broken columns, manifolds, and the like over the years, and the Caltech community is surely sad to see him go despite wishing him the best in his retirement. Joe Drew has facilitated the ordering and shipping of various chemical parcels and has assisted me in locating misplaced packages on several occasions. In addition to taking care of many computer-related needs, Silva Virgil has been an amazing friend, and I've greatly enjoyed the wonderful holiday parties and opera outings that she and Scott have hosted over the years. Last but certainly not least, I am grateful for all of the work Lynne Martinez does to keep our group operating smoothly and to facilitate fellowship applications for students. To all of these staff members, I extend my sincere gratitude for their dedication to the Caltech community and for assisting with the completion of my thesis work.

Finally, I would like to thank my family for their unconditional support, love, and patience. My parents have consistently inspired me with their incredible work ethic and dedication to caring for my brother and me. I am especially grateful for the positive

thinking abilities that I learned from my mother, as I soon came to realize the importance of staying positive in the midst of the uncertainty and failure that inevitably accompanies scientific research. Likewise, the perseverence and determination that I learned from my father have also proven essential in the completion of this dissertation. Throughout my life, my older brother, Roger, has inspired me with his enthusiasm for learning and commitment to excellence. His passion for medicine and science is effusive, and my conversations with him often leave me feeling invigorated and eager to achieve my best work in the lab. I am also fortunate to have amazingly supportive aunts and uncles living on the West Coast who have made my time here very comfortable. I thank Aunt Valinda, Aunt Rebecca, Aunt Daphne, Aunt Kathryne, Uncle Andy, Uncle Allen, Aunt Jane, and their spouses, for reaching out to me many times over the years.

I would also like to acknowledge my boyfriend, Steven Banks, who has supported me continuously throughout my time at Caltech, despite living over 1000 miles away. Gamely weathering my rants about graduate school and research while serving as a scapegoat for the lab's collective criticisms of Microsoft software, Steven has always encouraged me to follow my dreams and stood by me through the most harrowing moments in my graduate studies. I appreciate being able to regularly talk to someone outside of science, as these conversations provide a break from the immersion experience of graduate school while also affording unique insight into my work from an outside perspective. I look forward to finally joining Steven in Seattle next month.

Overall, the work described herein would not have been possible without the contributions and support of all those listed above and many others not specifically mentioned by name. To each and every one of them, I offer my most heartfelt gratitude.

ABSTRACT

Inspired by the therapeutic properties of many natural products and the ever-growing need for novel medicines, research programs for the late-stage diversification of complex molecular scaffolds have risen in popularity over the past few decades. In addition to generating a wide range of non-natural compounds for biological evaluation, these research efforts provide valuable synthetic insights into the preapration and reactivity of structurally intricate molecules. After a brief summary of the various strategies for late-stage diversification, examples of previous studies toward the derivatization of natural product-inspired scaffolds are highlighted.

A second-generation synthesis of the cyanthiwigin natural product core employing recently developed technologies is described. Re-optimization of the key double asymmetric catalytic alkylation transformation facilitates large-scale operations, and application of the aldehyde-selective Tsuji–Wacker oxidation enables productive recycling of an advanced intermediate. Together, these modifications expedite the preparation of the tricyclic cyanthiwigin framework on multi-gram scale.

The aldehyde-selective Tsuji–Wacker reaction is demonstrated to be effective for the oxidation of terminal alkenes bearing quaternary carbons at the allylic or homoallylic position. The synthetic utility of this method is extended through further transformation of the crude aldehyde products, permitting catalytic conversion of hindered terminal olefins to a variety of other synthetically useful functional groups.

With access to large quantities of the cyanthiwigin natural product core, a comparative study of various methods for intermolecular C–H oxidation was conducted. Examination of the reactivity of the cyanthiwigin framework under established conditions for allylic C–H acetoxylation, C–H hydroxylation, C–H amination, C–H azidation, and C–H chlorination reveals significant steric and electronic influences and suggests that functionalization is guided by innate reactivity within the substrate.

Finally, the preparation of several non-natural cyanthiwigin–gagunin hybrid molecules from the cyanthiwigin core is described. Preliminary studies toward the biological activities of synthetic intermediates are presented, and future directions for the synthesis of novel cyanthiwigin–gagunin hybrids are outlined.

PUBLISHED CONTENT AND CONTRIBUTIONS

Kim, K. E.; Stoltz, B. M. "A Second-Generation Synthesis of the Cyanthiwigin Natural Product Core." *Org. Lett.* **2016**, *18*, 5720–5723. DOI: 10.1021/acs.orglett.6b02962.

> K.E.K. participated in the conception of the project, all experimental work described, data acquisition and analysis, and manuscript preparation. Permission has been secured from the American Chemical Society for use of this material.

Kim, K. E.; Li, J.; Grubbs, R. H.; Stoltz, B. M. "Catalytic Anti-Markovnikov Transformations of Hindered Terminal Alkenes Enabled by Aldehyde-Selective Wacker-Type Oxidation." *J. Am. Chem. Soc.* **2016**, *138*, 13179–13182. DOI: 10.1021/jacs.6b08788.

> K.E.K. participated in the conception of the project, all experimental work described, data acquisition and analysis, and manuscript preparation. Permission has been secured from the American Chemical Society for use of this material.

Marziale, A. N.; Duquette, D. C.; Craig, R. A., II; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. "An Efficient Protocol for the Palladium-Catalyzed Asymmetric Decarboxylative Allylic Alkylation Using Low Palladium Concentrations and a Palladium(II) Precatalyst." *Adv. Synth. Catal.* **2015**, *357*, 2238–2245. DOI: 10.1002/adsc.201500253.

> K.E.K. participated in experimental work, data acquisition and analysis, and mansucript preparation. Permission has been secured from Wiley-VCH for use of this material.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
AIBN	azobis-(isobutyronitrile)
ALA	1 M aqueous solution of aminolevulinic acid
amp	ampicillin
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere(s)
bipy	2,2’-bipyridyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bn	benzyl
BQ	1,4-benzoquinone

Bz	benzoyl
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate
cap	caprolactam
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
CFL	compact fluorescent light
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
CSI	chlorosulfonyl isocyanate
d	doublet
D	dextrorotatory
Da	Dalton(s)
dba	dibenzylideneacetone
pmdba	bis(4-methoxybenzylidene)acetone

dmdba	bis(3,5-dimethoxybenzylidene)acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martine periodinane
DMSO	dimethylsulfoxide
dppf	1,1’-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
ESI	electrospray ionization

Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
^1H	proton
^2H	deuterium
^3H	tritium
[H]	reduction
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPA	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IPTG	1 M aqueous solution of isopropyl-β-D-thiogalactoside
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)

kg	kilogram(s)
L	liter or neutral ligand
L	levorotatory
LA	Lewis acid
LB	lysogeny broth
LB_{amp}	LB with 100 µg/mL amp
LB_{amp}/agar	a gel consisting of 1.6% (w/v) agar in LB_{amp}.
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
µ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)

MS	molecular sieves
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
o	ortho
[O]	oxidation
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline
pin	pinacol
pK_a	acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl

i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
r	selectivity = [major stereoisomer – minor stereoisomer]/[major stereoisomer + minor stereoisomer]
RCM	ring-closing metathesis
ref	reference
R_f	retention factor
s	singlet or seconds
s	selectivity factor = $k_{\text{rel(fast/slow)}} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
tacn	1,4,7-trimethyl-1,4,7-triazacyclo-nonane
TB	terrific broth
TB_{amp}	TB with 100 μg/mL amp
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate

TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
tbsbp	*tert*-butyl sulfonyl bridged prolinate
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
t_r	retention time
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry