Development of Enantioselective Organocatalytic Technologies for the Alpha-functionalization of Aldehydes and Ketones

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

2008

(Defended April 18, 2008)

To Dad
for all your love, support and encouragement that enabled me to achieve my dreams

and

Tony
pour toute la joie et le bonheur que tu apportes à ma vie qui font passer les jours avec douceur, et qui rend possible la poursuite de tous les désires de mon coeur

Acknowledgements

When I look back at the series of events that led to this day, I can't help but remember a few people who went out of their way, even defied their own superiors to help me succeed, and without whom I would not have reached this day. I am forever indebted to Mr. Ron Kramer, my junior high school history and civics teacher, who spent hours and hours with me after school, teaching me on his own time, to make up for several weeks of absences due to illness. He not only gave freely of his time to ensure I would maintain my good grades, he then fought against the school district so that I would not have to repeat the grade level due to the extent of my absence. His passion and skill for teaching is, without doubt, the best I have ever seen. Throughout the years he has remained an inspiration to me, and I will always remember him with the greatest esteem. I also owe a debt of gratitude to Mr. Steve Sayers and Mr. Jerry Bogard, my high school math teachers, for giving me the benefit of the doubt and cutting me slack when I needed it most. They risked their own jobs by doing so, and I am very grateful for the extraordinary kindness they showed me. I would also like to express much appreciation to Prof. Nancy Levinger, who during my undergraduate years in college and thereafter, has been an advocate for me and whose encouragement led me to pursue loftier goals than I otherwise would have had the courage to pursue. To Mr. Kramer, Mr. Sayers, Mr. Bogard, and Prof. Levinger, your kindness has not been forgotten.

Prior to graduate school, I had the privilege of working under some wonderful advisors who have contributed to the direction and success of my career. I am thankful to my research advisors while at Colorado State University, Prof. Steven Strauss and Prof. Frank Stermitz, who kindled my enthusiasm for chemical research and enabled me to obtain valuable laboratory skills that made much of my future endeavors possible. Had it not been for the silent direction of Dr. James Tata and the strong support and encouragement of Dr. Subha Raghavan, Dr. Kevin Chapman and Dr. Emma Parmee at Merck Research Laboratories, my choice of graduate school advisor and the course of my career may have been very different. I am grateful to all of them for their support.

It's very likely that my interest in science was acquired from my dad, a biologist who probably would have been a chemist had he not wanted to get paid to walk around in lakes and rivers (and fly fish after work). His strong support, guidance, and encouragement made it possible for me to pursue and achieve my dreams. Thanks Dad. The rest of my family initially didn't want me to pursue chemistry, and the toxic chemicals I work with continues to give my mom anxiety, but they have all been supportive nonetheless of my career choice. I need to thank my mom for her love and support and always admonishing me to take care of my health, and believe it or not Mom, I was paying attention. I'm also grateful for all the many effortless conversations my twin sister, Danni, provided when I was too tired to contribute to the conversation, which gave me the company I needed and made these graduate school years easier. Of course, graduate school would not have been nearly as pleasant had I not been able to share half of it with my husband, Tony. I was really concerned that working in the same lab for so many hours each day would be detrimental to our marriage. Dave mused that he would place Tony in Arcadia (when we

were still in Pasadena at Caltech), and promised to always keep us at opposite ends of the lab. Dave kept his promise but decided to add Tony to my project at the time. Yet, because Tony almost never leaves his hood (anyone who has worked next to him will understand what I mean), it honestly feels as though I saw less of him than I did when we were working in two separate buildings at Merck. Tony is one-of-a-kind, and I'm so honored that he chose me for his wife.

During my tenure as a graduate student in the MacMillan lab, I have had the pleasure of working with many brilliant young scientists. I am especially grateful to Dr. Young Chen for his insightful suggestions and scientific discussions that truly impacted my graduate school experience. Similarly, Dr. Hahn Kim and Rob Knowles have often been willing to lend their time to offer prudent advice and scientific knowledge, for which I am very thankful. I owe a debt of gratitude to Dr. Nikki Goodwin and Dr. Young Chen for helping me type NMR data and calculate J-values (certainly the most tedious and dreadful part of writing a paper) so that I could submit one of my papers for publication on schedule. I especially want to thank those who donated their time for proofreading this dissertation: Casey Jones, Diane Carrera, Connie Lee, and Dr. Maud Reiter. Although there are too many to thank individually by name, I would like to express much appreciation to all who gave of their time to assist me with editing and proofreading manuscripts over the past few years. I would like to thank my former bay-mate, Dr. Roxanne Kunz, and all my past and current coworkers for making graduate school an enjoyable experience. I truly hope that the comaraderie of the MacMillan lab will continue for years to come.

I would like to thank my thesis committee members, Profs. Dennis Dougherty, Douglas Rees, and David Tirrell for their willingness to serve on my committee and their invaluable time that was required of them to do so.

Lastly and most importantly, I would like to express deep appreciation to my doctoral research advisor, Professor David MacMillan, for his unparalleled mentorship these past five years. Besides providing an exciting educational work environment, he has showed true concern, extraordinary generosity, and utmost fairness towards me which has made graduate school a pleasant experience and for which I will always be very grateful. He is a superb academic advisor, and I could not be more pleased with my decision to work for him.

Abstract

The development of an expeditious and room-temperature conversion of aliphatic aldehydes to chiral terminal epoxides is described. α-Chloroaldehydes were prepared via asymmetric enamine catalysis with an imidazolidinone catalyst followed by *in situ* reduction and cyclization to generate the terminal epoxide. Epoxides with a variety of aliphatic groups and functionalities were produced in 75 minutes with good yields and excellent selectivities.

The catalytic enantioselective direct α-fluorination of aldehydes and ketones is also reported. α-Fluoroaldehydes were conveniently prepared via enamine catalysis with an imidazolidinone catalyst and *N*-fluorobenzenesulfonimide (NFSI) as an electrophilic fluorine source. The method tolerated a wide variety of aldehyde substrates and functional groups. Catalyst loadings as low as 1 mol% generated the fluorinated products in good yield and excellent enantioselectivity. Additionally, various catalyst architectures were studied to apply the α-fluorination reaction to ketone substrates. Cinchona alkaloid-derived catalysts were found to successfully facilitate the α-fluorination of ketones in high yields and excellent enantioselectivities.

Also presented is the advent of SOMO catalysis, a new mode of organocatalytic activation based on the catalytic generation of radical cations. A secondary amine catalyst reacts with an aldehyde to transiently generate an enamine that, in turn, undergoes a single-electron oxidation to yield a stabilized radical cation that is subject to enantiofacial discrimination. While the parent enamine reacts only with electrophiles, the radical cation combines with SOMO nucleophiles at the same reacting center, thereby enabling a diverse range of previously unknown asymmetric transformations. As a first example and proof of principle, the development of the direct and enantioselective α-allylation of aldehydes using SOMO catalysis is described.

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List of Abbreviations

AcOH	acetic acid
AIBN	2,2’-azo-bis(isobutyronitrile)
BINAP	2,2'-Bis(diphenylphosphino)-1'1-binaphthyl
BOC	*tert*-butyl carbamate
Bn	benzyl
Bz	benzoyl
CA	cinchonine amine
CAN	ceric ammonium nitrate
CDA	cinchonidine amine
dba	dibenzilideneacetone
DBSI	dibenzenesulfonimide
DCA	dichloroacetic acid
DHQA	dihydroquinine amine
DHQDA	dihydroquinidine amine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethylsulfide
DNBA	dinitrobenzoic acid
DTBP	di-*tert*-butyl pyridine
ee	enantiomeric excess
EI	electron impact

ES	electrospray
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
F-TEDA	1-Chloromethyl-4-Fluoro-1,4-Diazoniabicyclo [2.2.2]Octane Bis-(Tetrafluoroborate)
GLC	gas liquid chromatography
$HClO_4$	perchloric acid
h	hour
$HClO_4$	perchloric acid
HCN	hydrocyanic acid
HOMO	highest occupied molecular orbital
HMDS	bis(trimethylsilyl)amide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IPA	isopropyl alcohol
***i*-Pr**	isopropyl
IR	infrared
LUMO	lowest unoccupied molecular orbital
Me	methyl
MeOH	methanol
min	minutes
MsOH	methanesulfonic acid

NaOEt	sodium ethoxide
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
NFSI	N-fluorobenzene sulfonimide
OEt	ethoxy
OMe	methoxy
PMB	*para*-methoxybenzyl
Ph	phenyl
***p*-TSA**	*para*-toluenesulfonic acid
QA	quinine amine
QDA	quinidine amine
SFC	supercritical fluid chromatography
SOMO	singly occupied molecular orbital
TADDOL	*trans*-a,a'-(dimethyl-1,3-dioxolane-4,5
TBAF	tetrabutylammonium fluoride
TCA	trichloroacetic acid
TEA	triethyl amine
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_r	retention time
vol	volume