

SYNTHETIC APPLICATIONS AND METHODOLOGICAL DEVELOPMENTS OF
DONOR–ACCEPTOR CYCLOPROPANES

Thesis by

Alexander Frederick Garber Goldberg

In Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy

California Institute of Technology

Pasadena, California

2013

(Defended May 29, 2013)

© 2013

Alexander Frederick Garber Goldberg

All Rights Reserved

To my teachers

ACKNOWLEDGEMENTS

In Pirkei Avot, a prominent collection of Jewish ethics and morals, Shimon ben Zoma is quoted: “Who is wise? He who learns from all people.” This phrase has been somewhat of a guiding principle for me throughout my graduate studies, and throughout my time at Caltech I have been surrounded by an incredible group of people. These are the many students, professors and staff who have contributed toward my development as a scientist and have provided me with plenty of lessons in life and in Chemistry. I have resigned myself to the knowledge that this section will invariably be inadequate to address every manner in which I have been changed for the better by my interactions at this singular institution.

Foremost, I must thank my supervisor, Prof. Brian Stoltz. From day one, Brian has challenged me, encouraged me to challenge myself, and supported my efforts every step of the way. Brian is an endless source of knowledge and ideas; every time I’ve spoken to him about my project, whether in subgroup or in one-on-one meetings, I have left reenergized and motivated. Brian is an exceptionally caring person, and I truly appreciate the extent to which he will go to bat for his students. In addition, I’ve been privileged to spend time with his family, Erna, Harry, and Teddy at our group events.

I also thank my thesis committee members, Profs. Bob Grubbs, Jonas Peters, and Sarah Reisman. During our meetings and throughout my education at Caltech, they have provided me with indispensable advice on my research and have served as formidable role models for their creativity, leadership, and collegiality. It has been a privilege to watch Sarah’s group develop from the beginning of her independent academic career.

The imprint that she has already made in the field of organic synthesis in her first five years is impressive, evidenced by the growing number of publications in the Schlinger hallway and the number of Synfacts highlights outside her office door! I've also enjoyed interacting with Prof. Theo Agapie, whose exciting research ideas almost turned me into an inorganic chemist in my first year. I'm also glad that he hasn't held me to the 30 reactions I promised him at various recruitment events; I swear I would have done them if he asked, but I am confident there's a statute of limitations on things like this.

Many thanks also go out to my former academic supervisors, including Dr. Chaim Bell, Prof. Cathleen Crudden, Prof. Mark Lautens, and Prof. Ilan Marek, as well as the graduate students and postdocs who have directly trained me: Kevin McEleney, Chris Lata, Dave Hulcoop, and Samah Simaan. I am forever indebted to all of them for the indispensable guidance and training, and for stimulating my excitement for scientific research. Several of my teachers in elementary school and high school are responsible for instilling my love of learning, in particular, Mme. Carmen Jessop, Mrs. Brenda Silverberg, and Mr. Gary Levine.

As for my co-workers, so many deserve my thanks. For starters, far be it from me to take advice from a bathroom wall, but one in Crellin needs special recognition. It says, "when in doubt, ask Mike Krout". I had many doubts to ask about, and he was always (and continues to be) willing to share his experience and wisdom. One of these pearls: success as an undergrad is all about what you know; in graduate school, it's about what you can do. Well, during my time in Brian's lab, I've been surrounded by incredible thinkers and do-ers from the US and around the world. Special thanks go out to my friend Jonny Gordon, The Jonald, Jonnyboy, Jonny-B, the better half of team Joosball,

etc. From the late-nights in second-year writing our candidacy reports, to the epic billion-or-so reaction screen that we tag-teamed and that didn't produce any tangible results, the good times and the hard times, but particularly the hard times, Jonny has been through the rigors of grad school along my side, and has always had a way of putting things in perspective for me that I've come to truly appreciate.

Chris Henry and Kristy Tran were among the most selfless individuals to have graced our lab in my time here. If you asked Florian Vogt the question, "Have you tried the _____ reaction?" you could be certain the answer would be an emphatic "Yes." Thomas Jensen and Kathrin Höferl-Prantz were models for time-management and efficiency, and are wonderful scientists and people all-around. Beyond the lab, I have fond memories of skiing weekends in Mammoth with Jan Streuff, Helene Kolding and Corinne Baumgartner. It is beyond me how Josh Day managed to raise two and a half children and complete an epic total-synthesis at the same time. After spending enough time in lab with Michele Gatti, it became clear why he was the one who set the record for shortest time to publication in the Stoltz group: he kind of knows everything, and knows how to do everything. Though I may never forgive him for encouraging me to spend days trying to find separation conditions on the chiral SFC for what turned out to be an achiral compound! I would be remiss if I did not mention the rest of team Germany, including Christians Eidamshaus and Grünanger, Alex Marziale, and Hendrik "Jimi" Klare. It is thanks to them that I know useful German phrases, including "Ich heisse Alex und komme aus Kanada" and "Du bist sehr hübsch, komm mit mir in mein iglu". Thanks to my compatriot Guillaume Lapointe who has studied chemistry in more countries than my thesis beard has patches, and has shared his wealth of knowledge to everybody's gain.

It's always a pleasure working around Boger Liu: his smile is contagious. I also had the fortune of working with Doug Behenna on his second tour of duty in the group; if something was broken, he'd fix it, if you had a problem, he'd solve it. John Enquist, for teaching me the ropes on the computer, and for surprising me with his quiet and dry sense of humor, JT Mohr, Kevin Allan, Chris Gilmore, and Pam Tadross were extremely helpful during my formative years in the Stoltz lab. I always admired Allen Hong's quiet perseverance, and was always a helpful, friendly person to be around. Hosea Nelson has magic Chemistry hands that force the most gnarly molecules into submission. Yakup Gunes, my dear Turkish friend, probably learned as much English during his short stay here as he did Chemistry. I remember one day when I asked how his Chemistry was going, and he showed me a vial containing about five grams of a well-advanced synthetic intermediate as if it was no big deal at all. His modesty and his work ethic are extremely admirable. In my latter years of grad school, I'm glad to have been able to tap into the energy and enthusiasm of the younger students in the lab, particularly my baymates Doug Duquette, Chung Whan Lee, and Corey Reeves. Doug is outstandingly rigorous and methodical in his science, and generally a fun person to be around in spite of his musical tastes (hah!). Corey holds himself to a very high standard, and his leadership by example has a way of improving the quality of research in the lab overall. And it's always a pleasure to talk with Chung Whan about his Chemistry as well as the finer details of Korean liquor! Thanks are also due to Jeff Holder, Max Loewinger, Yiyang Liu, Christopher Haley, Kelly Kim, Seojung Han, Katerina Korch, Beau Pritchett, and Kelvin Bates.

I've had the fortune of collaborating with several talented scientists in and outside our group. Rob Craig and Nick O'Connor were excellent collaborators as part of Cyclopropanation—though they won't know I called our team that until they read this. Their hard work, creativity, eye for detail, and technical expertise was critical for our project's advancement. I'm excited to see what they have in store for the heterocumulene project; in addition, I look forward to seeing Nick's creativity in C–H vinylation bear fruit. I also greatly enjoyed working with Judith Su, a graduate student in the bioimaging department, on the functionalization of microtoroid optical resonators. Together, we solved an array of technical problems that I would not have otherwise been exposed to in synthetic organic chemistry. I had the opportunity to mentor two excellent undergraduate researchers, Aaron Levine and Chris Tonge. From Chris's first Grignard reaction, it was clear that organic synthesis would be second nature for him. He has done excellent work on our *ortho*-quinone methide project, and has a bright future ahead of him in the field of Chemistry!

Many thanks go to those who took the time to proof-read my thesis, including Rob Craig, Nick O'Connor, Doug Duquette, Christopher Haley and Yiyang Liu, in addition to Brian and my committee members. Their suggestions and edits have improved considerably the quality of this work.

I have made a number of friends since arriving at Caltech within the Chemistry department and beyond. Foremost, thanks go out to my roommates past and present, Ethan Van Arnem, Judy Lattimer, and James McKone. Between Saturday brunches in our backyard, movie nights, and farmers market visits, they have made my life outside lab fantastic. I also thank my friend Pedro Coelho, who is an incredible combination of

intelligence, kindness, and ambition; and I'll predict he wins a Nobel prize of some sort—say, in 2030—you heard it here first. Thanks to Ariel Furst, a stellar chemist in the lab and in the kitchen. And cheers to my cohorts in the Reisman lab, Roger, John, Jay, Lindsay, and Raul.

The technical and support staff in our department are unlike any other. Dr. Scott Virgil has been a tremendous resource during my time here. He has rarely hesitated to set aside hours of his time to discuss technical or strategic problems that I've faced throughout my graduate studies. Dr. Dave Vander Velde runs a top-notch NMR facility and has helped me with difficult experiments on numerous occasions. Rick Gerhart has fixed more than my fair share of glassware, and it is always incredible to watch him in action—it exemplifies the interface between artistry and science. Joe Drew never fails to track down missing packages, and is always good for a high-five or a fist-pound, which is pretty much the epic combination necessary to improve my spirits. Agnes Tong is the greatest Graduate Program Administrator that a stressed-out graduate student could ask for—she can always be counted on for words of encouragement, or candy, whichever the medicine happens to be that day. Lynne Martinez does an incredible job of keeping the house in order, has just about all the answers to everything, and is a great person to talk about vacation plans with. Also, candy. And Allen Hong and Nick O'Connor for candy too, and sometimes Jonny. Candy is great.

Beyond Caltech, several friends in Los Angeles deserve acknowledgement. Robin and Andy Mandell have been wonderful LA parents to me, inviting me into their home whenever I needed an escape from Pasadena, and checking in once in a while to make sure I'm alive and well! Also, a shout-out to my fellow CBC Radio 3 listeners in LA—

Tim Aarons, Christine Hitchman, Seth Dallob, Kennedy Davey—all of the Canadian musicians who have passed through the city, and Grant Lawrence and the CBC hosts who have provided me with a healthy dose of culture, and who all served as my primary link to home. And Michael van Vliet/Tall Michael/Motorcycle Michael, who served as a constant reminder that normal people, with normal people problems and normal people occupations do exist outside the confines of academia!

I'd also like to thank the multitude of chemists with whom I have regularly interacted via social media, in no particular order, including Paul Bracher (good luck with your academic appointment!), Carmen Drahl, Matt Hartings, Stu Cantrill, Vy Tran, Freda Chio, Matt Katcher, anonymous bloggers "Organometallica", "Chemjobber", "BRSM", "SeeArrOh", and "Chemist Hulk", of course (I hope to meet you all some day, if I haven't already! Except for Chemist Hulk).

I'm glad to have kept in touch with so many of my friends from Toronto and at Queen's, who have been so supportive of my work, and so understanding of the sacrifices I've had to make to progress through graduate school. These are people with whom it has been so easy to pick up where I've left off when I've seen them back in Canada, or when they have visited me in LA. Huge thanks go out to Alexandra Der, Erin Weinberg, Noah Bonder, Michelle Edwards, Leah Dacks, Daniel Stober, Andrew Leung, Caroline Cormier, Jordi Friese, Jon Goldberg, Robbie Agar, Mike Katz, Jeff Weiskopf, Joel Arshoff, Joanna Giddens.

I've saved this last paragraph to thank the most important people in my life. First of all, my family: Mom, Dad, Jessie, who don't always understand why I work the hours that I do, but understand the ultimate goal of higher education. For as long as I can

remember, my parents have nurtured my love of learning, and my sister has been my most important role model throughout my schooling. My parents have invested tremendously in my education, and have been so supportive of me every step of the way, providing me with every opportunity they could. I look forward to spending the next two years with my sister and my new brother-in-law Aviv in Israel, as well as my extended family there. To my grandparents, my aunts, my uncles and my many cousins, I thank you all as well for your love and support. I fondly remember sitting down with Nonnie in Detroit to study for Chemistry exams and competitions. I have also been greatly inspired by the other PhDs and MDs in my family, including my grandfather, Dr. Ben Goldberg, my aunt Dr. Adele Goldberg and my uncle Dr. Joel Goldberg, my cousins Dr. Lynne Davis, Dr. David Weiner, and Dr. Shira Taylor and my cousin Yoni Weiner who is completing a Chemistry PhD at Imperial College. Finally I thank Alyson who has, for the last year and a half, made my life wonderful by sharing in the joys and rigors of grad school, laughing at my horrible jokes, and talking through science challenges with me. Every day with her has been a new adventure, and she has been the most amazing person to share in every experience. As a scientist, her creativity, intellect, and breadth of technical skill continues to be a tremendous source of inspiration for me.

Thanks to all who have been a part of my life, taught and sustained me, and brought me to this important milestone in my life.

Alex

ABSTRACT

Donor–acceptor cyclopropanes are a versatile class of synthetic intermediates, compatible in a broad range of ring-opening reactions and formal cycloadditions, and employed in numerous natural product syntheses. We have developed new Lewis acid mediated cycloadditions for the synthesis of five-membered heterocycles, and applied existing a transition metal catalyzed cyclopropane cycloaddition method toward the synthesis of complex alkaloids.

First, described is the development of a Lewis acid mediated (3 + 2) cycloaddition of donor–acceptor cyclopropanes with isocyanates, isothiocyanates and carbodiimides. This reaction was found in certain cases to proceed with excellent stereochemical fidelity, providing access to an array of enantioenriched thioimidates and amidines.

Second, we targeted the *Melodinus* alkaloids for total synthesis due to their unique structural features. Synthetic efforts toward scandine, the parent of the natural product family, are detailed herein. Our approach features a palladium catalyzed formal (3 + 2) cycloaddition of a vinyl cyclopropane and a β -nitrostyrene to rapidly assemble the central cyclopentane core of the natural product. Initial efforts focused on the synthesis and application of a 1,1-divinylcyclopropane to the formal (3 + 2) cycloaddition reaction, whereas later work entailed the use of a mono-vinylcyclopropane with the goal of installing the second requisite vinyl group at a later stage using modern C–H functionalization technologies.

TABLE OF CONTENTS

Acknowledgements	iv
Abstract.....	xii
Table of Contents	xiii
List of Figures.....	xvii
List of Schemes.....	xxiii
List of Tables.....	xxvii
List of Abbreviations.....	xxx

CHAPTER 1 **1**

Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes

1.1 Introduction.....	1
1.2 Initial Efforts	5
1.3 Reaction Optimization of Isocyanate Cycloaddition	7
1.4 Isothiocyanate (3 + 2) Cycloadditions.....	11
1.5 Carbodiimides (3 + 2) Cycloadditions.....	15
1.6 Unreactive and Problematic Substrates.....	17
1.7 Investigations on Transfer of Chirality.....	18
1.8 Discussion of Mechanism.....	19
1.9 Future Directions	21
1.10 Conclusion	22
1.11 Experimental Section	23
1.11.1 Materials and Methods.....	23
1.11.2 Preparative Procedures	24
1.11.2.1 General and Miscellaneous Experimental Procedures	24
1.11.2.2 Cyclopropane Characterization Data	30
1.11.2.3 Characterization Data for Lactams.....	38
1.11.2.4 Thioimide Characterization Data.....	42
1.11.2.5 Characterization Data for Amidines	51
1.12 Notes and References	57

APPENDIX 1 **63**

Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions

	xiv
A1.1 Ring Expansion Reactions of Aziridines	63
A1.1.1 Amidine and Guanidine Catalysis.....	65
A1.2 Natural Product Synthesis.....	65
A1.3 Conclusion	68
A1.4 Experimental Section	69
A1.4.1 Materials and Methods	69
A1.4.2 Preparative Procedures	70
A1.5 Notes and References	76
APPENDIX 2	78
<i>Spectra Relevant to Chapter 1: Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes</i>	
APPENDIX 3	149
<i>X-ray Crystallography Reports Relevant to Chapter 1</i>	
A3.1 Crystal structure analysis for compound 52	149
A3.2 Crystal structure analysis for compound (R)- 60 •HBr	159
CHAPTER 2	191
<i>Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids</i>	
2.1 Introduction and Synthetic Strategy	191
2.1.1 Introduction	191
2.1.2 Original Retrosynthetic Analysis.....	193
2.1.2.1 Metal-Catalyzed Cyclopropane (3 + 2) Cycloadditions	194
2.1.2.2 Known 1,1-Divinylcyclopropanes	197
2.1.2.3 Divinylcyclopropane Retrosynthesis	198
2.2 Toward the Synthesis of a Divinylcyclopropane	199
2.2.1 <i>gem</i> -Dihalocyclopropane Substitution Route.....	199
2.2.2 Double Elimination Route.....	202
2.2.3 Alkylidenecyclopropane Route.....	204
2.2.4 Claisen Rearrangement Route.....	207
2.3 Investigation of (3 + 2) Cycloaddition	209
2.4 Revised Retrosynthesis.....	211
2.5 Construction of the ABCD Ring System	213
2.6 Outlook	218
2.6.1 Enantioselective Total Synthesis	219

	xv
2.6.2 Derivatization of Scandine to Other Natural Products	220
2.7 Conclusion	221
2.8 Experimental Section	223
2.8.1 Materials and Methods.....	223
2.8.2 Preparative Procedures.....	224
2.9 Notes and References	249

APPENDIX 4 **256**

Additional Studies Related to Chapter 2: Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

A4.1 Alternative Approaches to D-Ring RCM	256
A4.1.1 Acrylamide Ring-Closing Metathesis Approach	256
A4.1.2 Allylamine Ring-Closing Metathesis Approach.....	257
A4.1.3 Development of Reductive Amination Conditions	258
A4.1.4 Trifluoroacetamide-Protected RCM Substrate	260
A4.1.5 Summary	261
A4.2 Initial Efforts for C(20) Functionalization	262
A4.2.1 Olefin Isomerization	262
A4.2.2 Alternative Cyclopropanes	263
A4.3 C(20) Functionalization via C–H Insertion.....	264
A4.4 Experimental Section	266
A4.4.1 Materials and Methods	266
A4.4.2 Preparative Procedures	267
A4.5 Notes and References	284

APPENDIX 5 **286**

Synthetic Summary toward the Total Synthesis of Scandine and the Melodinus Alkaloids

APPENDIX 6 **290**

Spectra Relevant to Chapter 2: Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

APPENDIX 7 **326**

X-ray Crystallography Reports Relevant to Chapter 2

A7.1 Crystal structure analysis of 240	326
A7.2 Crystal structure analysis of 241	338

APPENDIX 8*Catalytic Asymmetric Alkylations of Ortho-Quinone Methides*

A8.1 Introduction.....	357
A8.1.1 Asymmetric Alkylations of Halo-Oxindoles.....	357
A8.1.2 Ortho-Quinone Methides	359
A8.2 Development of a Base-Activated OQM Precursor	361
A8.2.1 Initial Efforts	361
A8.2.2 Nucleophilic OQM Generation	363
A8.3 Reactivity with <i>N</i> - and <i>O</i> -Based Nucleophiles	366
A8.4 Asymmetric Alkylation with Malonates	367
A8.4.1 Initial Discovery.....	367
A8.4.2 Reaction Optimization	369
A8.4.3 Discussion of Mechanism.....	377
A8.5 Conclusion	379
A8.6 Experimental Section	380
A8.6.1 Preparative Procedures	380
A8.7 Notes and References	383
Comprehensive Bibliography.....	386
Index	403
About the Author.....	408

LIST OF FIGURES

CHAPTER 1

Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes

Figure 1.7.1. Determination of absolute configuration by single crystal X-ray diffraction. 19

APPENDIX 1

Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions

Figure A1.1.1. Examples of chiral nucleophilic catalysts. 71

Figure A1.2.1. Natural products accessible via cyclopropane (3 + 2) cycloadditions..... 72

APPENDIX 2

Spectra Relevant to Chapter 1: Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes

Figure A2.1 ^1H NMR (300 MHz, CDCl_3) of compound **77**. 79

Figure A2.2 Infrared spectrum (thin film/ NaCl) of compound **77** 80

Figure A2.3 ^{13}C NMR (75 MHz, CDCl_3) of compound **77** 80

Figure A2.4 ^1H NMR (500 MHz, CDCl_3) of compound **30**. 81

Figure A2.5 Infrared spectrum (thin film/ NaCl) of compound **30** 82

Figure A2.6 ^{13}C NMR (126 MHz, CDCl_3) of compound **30** 82

Figure A2.7 ^1H NMR (500 MHz, CDCl_3) of compound **68**. 83

Figure A2.8 Infrared spectrum (thin film/ NaCl) of compound **68** 84

Figure A2.9 ^{13}C NMR (126 MHz, CDCl_3) of compound **68** 84

Figure A2.10 ^1H NMR (500 MHz, CDCl_3) of compound **88**. 85

Figure A2.11 Infrared spectrum (thin film/ NaCl) of compound **88** 86

Figure A2.12 ^{13}C NMR (126 MHz, CDCl_3) of compound **88** 86

Figure A2.13 ^1H NMR (500 MHz, CDCl_3) of compound **69**. 87

Figure A2.14 Infrared spectrum (thin film/ NaCl) of compound **69** 88

Figure A2.15 ^{13}C NMR (126 MHz, CDCl_3) of compound **69** 88

Figure A2.16 ^1H NMR (500 MHz, CDCl_3) of compound **92**. 89

Figure A2.17 Infrared spectrum (thin film/ NaCl) of compound **92** 90

Figure A2.18 ^{13}C NMR (126 MHz, CDCl_3) of compound **92** 90

Figure A2.19 ^1H NMR (500 MHz, CDCl_3) of compound **93**. 91

Figure A2.20 Infrared spectrum (thin film/NaCl) of compound 93	92
Figure A2.21 ^{13}C NMR (126 MHz, CDCl_3) of compound 93	92
Figure A2.22 ^1H NMR (500 MHz, CDCl_3) of compound 34	93
Figure A2.23 Infrared spectrum (thin film/NaCl) of compound 34	94
Figure A2.24 ^{13}C NMR (126 MHz, CDCl_3) of compound 34	94
Figure A2.25 ^1H NMR (500 MHz, CDCl_3) of compound 35	95
Figure A2.26 Infrared spectrum (thin film/NaCl) of compound 35	96
Figure A2.27 ^{13}C NMR (126 MHz, CDCl_3) of compound 35	96
Figure A2.28 ^1H NMR (500 MHz, CDCl_3) of compound 36	97
Figure A2.29 Infrared spectrum (thin film/NaCl) of compound 36	98
Figure A2.30 ^{13}C NMR (126 MHz, CDCl_3) of compound 36	98
Figure A2.31 ^1H NMR (500 MHz, CDCl_3) of compound 37	99
Figure A2.32 Infrared spectrum (thin film/NaCl) of compound 37	100
Figure A2.33 ^{13}C NMR (126 MHz, CDCl_3) of compound 37	100
Figure A2.34 ^1H NMR (500 MHz, CDCl_3) of compound 38	101
Figure A2.35 Infrared spectrum (thin film/NaCl) of compound 38	102
Figure A2.36 ^{13}C NMR (126 MHz, CDCl_3) of compound 38	102
Figure A2.37 ^1H NMR (500 MHz, CDCl_3) of compound 39	103
Figure A2.38 Infrared spectrum (thin film/NaCl) of compound 39	104
Figure A2.39 ^{13}C NMR (126 MHz, CDCl_3) of compound 39	104
Figure A2.40 ^1H NMR (500 MHz, CDCl_3) of compound 45	105
Figure A2.41 Infrared spectrum (thin film/NaCl) of compound 45	106
Figure A2.42 ^{13}C NMR (126 MHz, CDCl_3) of compound 45	106
Figure A2.43 ^1H NMR (500 MHz, CDCl_3) of compound 40	107
Figure A2.44 Infrared spectrum (thin film/NaCl) of compound 40	108
Figure A2.45 ^{13}C NMR (126 MHz, CDCl_3) of compound 40	108
Figure A2.46 ^1H NMR (500 MHz, CDCl_3) of compound 47	109
Figure A2.47 Infrared spectrum (thin film/NaCl) of compound 47	110
Figure A2.48 ^{13}C NMR (126 MHz, CDCl_3) of compound 47	110
Figure A2.49 ^1H NMR (500 MHz, CDCl_3) of compound 48	111
Figure A2.50 Infrared spectrum (thin film/NaCl) of compound 48	112
Figure A2.51 ^{13}C NMR (126 MHz, CDCl_3) of compound 48	112
Figure A2.52 ^1H NMR (500 MHz, CDCl_3) of compound 49	113
Figure A2.53 Infrared spectrum (thin film/NaCl) of compound 49	114
Figure A2.54 ^{13}C NMR (126 MHz, CDCl_3) of compound 49	114

Figure A2.55 ^1H NMR (500 MHz, CDCl_3) of compound 50	115
Figure A2.56 Infrared spectrum (thin film/ NaCl) of compound 50	116
Figure A2.57 ^{13}C NMR (126 MHz, CDCl_3) of compound 50	116
Figure A2.58 ^1H NMR (500 MHz, CDCl_3) of compound 51	117
Figure A2.59 Infrared spectrum (thin film/ NaCl) of compound 51	118
Figure A2.60 ^{13}C NMR (126 MHz, CDCl_3) of compound 51	118
Figure A2.61 ^1H NMR (500 MHz, CDCl_3) of compound 52	119
Figure A2.62 Infrared spectrum (thin film/ NaCl) of compound 52	120
Figure A2.63 ^{13}C NMR (126 MHz, CDCl_3) of compound 52	120
Figure A2.64 ^1H NMR (500 MHz, CDCl_3) of compound 53	121
Figure A2.65 Infrared spectrum (thin film/ NaCl) of compound 53	122
Figure A2.66 ^{13}C NMR (126 MHz, CDCl_3) of compound 53	122
Figure A2.67 ^1H NMR (500 MHz, CDCl_3) of compound 54	123
Figure A2.68 Infrared spectrum (thin film/ NaCl) of compound 54	124
Figure A2.69 ^{13}C NMR (126 MHz, CDCl_3) of compound 54	124
Figure A2.70 ^1H NMR (500 MHz, CDCl_3) of compound 55	125
Figure A2.71 Infrared spectrum (thin film/ NaCl) of compound 55	126
Figure A2.72 ^{13}C NMR (126 MHz, CDCl_3) of compound 55	126
Figure A2.73 ^1H NMR (500 MHz, CDCl_3) of compound 56	127
Figure A2.74 Infrared spectrum (thin film/ NaCl) of compound 56	128
Figure A2.75 ^{13}C NMR (126 MHz, CDCl_3) of compound 56	128
Figure A2.76 ^1H NMR (500 MHz, CDCl_3) of compound 57	129
Figure A2.77 Infrared spectrum (thin film/ NaCl) of compound 57	130
Figure A2.78 ^{13}C NMR (126 MHz, CDCl_3) of compound 57	130
Figure A2.79 ^1H NMR (500 MHz, CDCl_3) of compound 44	131
Figure A2.80 Infrared spectrum (thin film/ NaCl) of compound 44	132
Figure A2.81 ^{13}C NMR (126 MHz, CDCl_3) of compound 44	132
Figure A2.82 ^1H NMR (400 MHz, CDCl_3) of compound 60	133
Figure A2.83 Infrared spectrum (thin film/ NaCl) of compound 60	134
Figure A2.84 ^{13}C NMR (101 MHz, CDCl_3) of compound 60	134
Figure A2.85 ^1H NMR (400 MHz, CDCl_3) of compound 61	135
Figure A2.86 Infrared spectrum (thin film/ NaCl) of compound 61	136
Figure A2.87 ^{13}C NMR (101 MHz, CDCl_3) of compound 61	136
Figure A2.88 ^1H NMR (500 MHz, CDCl_3) of compound 62	137
Figure A2.89 Infrared spectrum (thin film/ NaCl) of compound 62	138

Figure A2.90 ^{13}C NMR (126 MHz, CDCl_3) of compound 62	138
Figure A2.91 ^1H NMR (500 MHz, CDCl_3) of compound 63	139
Figure A2.92 Infrared spectrum (thin film/ NaCl) of compound 63	140
Figure A2.93 ^{13}C NMR (126 MHz, CDCl_3) of compound 63	140
Figure A2.94 ^1H NMR (500 MHz, CDCl_3) of compound 64	141
Figure A2.95 Infrared spectrum (thin film/ NaCl) of compound 64	142
Figure A2.96 ^{13}C NMR (126 MHz, CDCl_3) of compound 64	142
Figure A2.97 ^1H NMR (500 MHz, CDCl_3) of compound 65	143
Figure A2.98 Infrared spectrum (thin film/ NaCl) of compound 65	144
Figure A2.99 ^{13}C NMR (126 MHz, CDCl_3) of compound 65	144
Figure A2.100 ^1H NMR (500 MHz, CDCl_3) of compound 66	145
Figure A2.101 Infrared spectrum (thin film/ NaCl) of compound 66	146
Figure A2.102 ^{13}C NMR (126 MHz, CDCl_3) of compound 66	146
Figure A2.103 ^1H NMR (400 MHz, DMSO-d_6 , 80 $^\circ\text{C}$) of compound 67	147
Figure A2.104 Infrared spectrum (thin film/ NaCl) of compound 67	148
Figure A2.105 ^{13}C NMR (101 MHz, DMSO-d_6 , 100 $^\circ\text{C}$) of compound 67	148

CHAPTER 2

Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Figure 2.1.1. Representative examples of the Melodinus Alkaloids.....	201
---	-----

APPENDIX 6

Spectra Relevant to Chapter 2: Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Figure A6.1 ^1H NMR (300 MHz, CDCl_3) of compound 192	291
Figure A6.2 Infrared spectrum (thin film/ NaCl) of compound 192	292
Figure A6.3 ^{13}C NMR (126 MHz, CDCl_3) of compound 192	292
Figure A6.4 ^1H NMR (400 MHz, CDCl_3) of compound 201	293
Figure A6.5 Infrared spectrum (thin film/ NaCl) of compound 201	294
Figure A6.6 ^{13}C NMR (100 MHz, CDCl_3) of compound 201	294
Figure A6.7 ^1H NMR (400 MHz, CDCl_3) of compound 202	295
Figure A6.8 Infrared spectrum (thin film/ NaCl) of compound 202	296
Figure A6.9 ^{13}C NMR (100 MHz, CDCl_3) of compound 202	296
Figure A6.10 ^1H NMR (500 MHz, CDCl_3) of compound 205	297
Figure A6.11 Infrared spectrum (thin film/ NaCl) of compound 205	298

Figure A6.12 ^{13}C NMR (126 MHz, CDCl_3) of compound 205	298
Figure A6.13 ^1H NMR (400 MHz, CDCl_3) of compound 215	299
Figure A6.14 Infrared spectrum (thin film/ NaCl) of compound 215	300
Figure A6.15 ^{13}C NMR (100 MHz, CDCl_3) of compound 215	301
Figure A6.16 ^1H NMR (500 MHz, CDCl_3) of compound 221	301
Figure A6.17 Infrared spectrum (thin film/ NaCl) of compound 221	302
Figure A6.18 ^{13}C NMR (126 MHz, CDCl_3) of compound 221	303
Figure A6.19 ^1H NMR (500 MHz, CDCl_3) of compound 222	303
Figure A6.20 Infrared spectrum (thin film/ NaCl) of compound 222	304
Figure A6.21 ^{13}C NMR (126 MHz, CDCl_3) of compound 222	304
Figure A6.22 ^1H NMR (400 MHz, CDCl_3) of compound 223a	305
Figure A6.23 ^1H NMR (400 MHz, CDCl_3) of compound 223b	306
Figure A6.24 ^1H NMR (500 MHz, CDCl_3) of compound 224	307
Figure A6.25 Infrared spectrum (thin film/ NaCl) of compound 224	308
Figure A6.26 ^{13}C NMR (126 MHz, CDCl_3) of compound 224	308
Figure A6.27 ^1H NMR (400 MHz, CDCl_3) of compound 238	309
Figure A6.28 Infrared spectrum (thin film/ NaCl) of compound 238	310
Figure A6.29 ^{13}C NMR (100 MHz, CDCl_3) of compound 238	310
Figure A6.30 ^1H NMR (400 MHz, CDCl_3) of compound 240	311
Figure A6.31 Infrared spectrum (thin film/ NaCl) of compound 240	312
Figure A6.32 ^{13}C NMR (100 MHz, CDCl_3) of compound 240	312
Figure A6.33 ^1H NMR (400 MHz, CDCl_3) of compound 241	313
Figure A6.34 Infrared spectrum (thin film/ NaCl) of compound 241	314
Figure A6.35 ^{13}C NMR (100 MHz, CDCl_3) of compound 241	314
Figure A6.36 ^1H NMR (400 MHz, CDCl_3) of compound 242	315
Figure A6.37 Infrared spectrum (thin film/ NaCl) of compound 242	316
Figure A6.38 ^{13}C NMR (100 MHz, CDCl_3) of compound 242	316
Figure A6.39 ^1H NMR (500 MHz, d_6 -DMSO) of compound 243	317
Figure A6.40 ^1H NMR (300 MHz, CDCl_3) of compound 245	318
Figure A6.41 Infrared spectrum (thin film/ NaCl) of compound 245	319
Figure A6.42 ^{13}C NMR (100 MHz, CDCl_3) of compound 245	319
Figure A6.43 ^1H NMR (500 MHz, CDCl_3) of compound 246	320
Figure A6.44 Infrared spectrum (thin film/ NaCl) of compound 246	321
Figure A6.45 ^{13}C NMR (126 MHz, CDCl_3) of compound 246	321
Figure A6.46 ^1H NMR (500 MHz, CDCl_3) of compound 247	322

Figure A6.47 Infrared spectrum (thin film/NaCl) of compound 247	323
Figure A6.48 ^{13}C NMR (126 MHz, CDCl_3) of compound 247	323
Figure A6.49 ^1H NMR (500 MHz, d_6 -DMSO, 80 °C) of compound 248	324
Figure A6.50 Infrared spectrum (thin film/NaCl) of compound 248	325
Figure A6.51 ^{13}C NMR (126 MHz, d_6 -DMSO, 80 °C) of compound 248	325

APPENDIX 8

Catalytic Asymmetric Alkylations of ortho-Quinone Methides

Figure 8.4.1. Ligands examined in the o-QM asymmetric alkylation screen	380
---	-----

LIST OF SCHEMES

CHAPTER 1*Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes*

<i>Scheme 1.1.1. Structural definition of donor–acceptor cyclopropanes</i>	1
<i>Scheme 1.1.2. Lewis acid activation of dimethoxycyclopropane 3</i>	2
<i>Scheme 1.1.3 Stereoselective (3 + 2) cycloadditions of donor–acceptor cyclopropanes</i>	3
<i>Scheme 1.1.4. Prevailing pathways for stereoselective cyclopropane cycloadditions</i>	4
<i>Scheme 1.1.5. Proposed (3 + 2) cycloaddition of heterocumulenes with cyclopropanes</i>	5
<i>Scheme 1.2.1. Synthesis of oxazolidinones from epoxides</i>	5
<i>Scheme 1.2.2. Proposed synthesis of lactams using potassium cyanate</i>	6
<i>Scheme 1.2.3. Reactivity attempts of potassium cyanate with cyclopropanes 26 and 27</i>	6
<i>Scheme 1.2.4. Synthesis of lactam 29 from cyclopropane 27</i>	7
<i>Scheme 1.3.1. Initial examination of alternative isocyanates</i>	9
<i>Scheme 1.3.2. Scope of iron(III) chloride mediated (3 + 2) cycloadditions of isocyanates</i>	10
<i>Scheme 1.4.1. Synthesis of thioimidate 40 using allyl isothiocyanate</i>	11
<i>Scheme 1.4.2. Structural reassignment of Li’s arylisothiocyanate (3 + 2) products</i>	12
<i>Scheme 1.4.3. Study on isothiocyanate stoichiometry in (3 + 2) cycloadditions</i>	12
<i>Scheme 1.4.4. Substrate scope of isothiocyanate (3 + 2) reaction</i>	14
<i>Scheme 1.4.5. Confirmation of thioimidate structure by single crystal X-ray diffraction</i>	15
<i>Scheme 1.5.1. Synthesis of amidine 58 using diisopropylcarbodiimide</i>	15
<i>Scheme 1.5.2. Substrate scope of carbodiimide (3 + 2) cycloaddition</i>	16
<i>Scheme 1.6.1. Unreactive cyclopropanes in heterocumulene (3 + 2) cycloadditions</i>	17
<i>Scheme 1.6.2. Problematic heterocumulenes in (3 + 2) cycloadditions</i>	18
<i>Scheme 1.7.1. Reactions of enantioenriched cyclopropane (S)-42 with heterocumulenes</i>	19
<i>Scheme 1.8.1. Mechanism of (3 + 2) cycloaddition with carbodiimides and isothiocyanates</i>	20
<i>Scheme 1.8.2. Racemization of cyclopropane (S)-42 with catalytic tin(II) triflate^{3c}</i>	21
<i>Scheme 1.8.3. Proposed mechanism accounting for attenuated racemization</i>	21

APPENDIX 1*Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions*

<i>Scheme A1.1.1. (3 + 2) Cycloadditions of aziridines and carbodiimides</i>	70
<i>Scheme A1.1.2. Potential nucleophilic catalysts accessible via Lewis acid (3 + 2) cycloaddition</i>	71

Scheme A1.2.1. Retrosynthetic analysis of alkaloid natural products 20, 21, 22	72
Scheme A1.2.2. Failed Suzuki cross coupling with cyclopropyl boronate ester XX	73
Scheme A1.2.3. Stille coupling of bromide 125 and proposed conversion to tricycle 116	74
Scheme A1.2.4. Proposed synthesis of cyclopropane 131 via Stille coupling.....	74

CHAPTER 2

Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Scheme 2.1.1. Proposed Biosynthesis of the Melodinus Alkaloids.	201
Scheme 2.1.2. Retrosynthetic analysis of scandine (135).	203
Scheme 2.1.3. Tsuji's palladium-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes.....	203
Scheme 2.1.4. Proposed mechanism of the palladium-catalyzed (3 + 2) cycloaddition.....	204
Scheme 2.1.5. Iron-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes.....	205
Scheme 2.1.6. Enantio- and diastereoselective palladium-catalyzed (3 + 2) cycloaddition	205
Scheme 2.1.7. Synthesis and properties of 1,1-divinylcyclopropane (169).....	206
Scheme 2.1.8. Synthesis of 2-phenyl-1,1-divinylcyclopropane (174).....	207
Scheme 2.1.9. Retrosynthesis of divinylcyclopropane 143	208
Scheme 2.2.1. Dialkylation of dihalocyclopropanes with dialkylcuprates.....	209
Scheme 2.2.2. Proposed gem-dihalocyclopropane route toward 1,1-divinylcyclopropane 143	209
Scheme 2.2.3. De Keyser's synthesis of methylene dimethylmalonate (177).....	210
Scheme 2.2.4. Proposed conversion of model cyclopropane 192 to desired (3 + 2) substrate 143 .	210
Scheme 2.2.5. Synthesis of a model gem-dihalocyclopropane (192).....	210
Scheme 2.2.6. Efforts to vinylate dibromocyclopropane 192	211
Scheme 2.2.7. Synthetic approach to elimination substrate precursor	212
Scheme 2.2.8. Vinylcyclopropane synthesis via a protected diol (201).....	212
Scheme 2.2.9. Direct elimination of a silyl ether (206) to form an unsaturated nitrile (207)	213
Scheme 2.2.10. Allylic alkylation of cyclopropane derivatives	214
Scheme 2.2.11. Synthetic approach to alkylidenecyclopropane 216	214
Scheme 2.2.12. Attempted S_N2' displacement with vinyl nucleophiles.....	216
Scheme 2.2.13. Proposed Claisen-rearrangement approach to cyclopropane 143	217
Scheme 2.2.14. Proposed selective derivatization of an Eschenmoser–Claisen product (219)	217
Scheme 2.2.15. Eschenmoser–Claisen rearrangement of alkylidenecyclopropane 221	218
Scheme 2.3.1. Attempted (3 + 2) cycloadditions of vinyl cyclopropanes with nitrostyrenes.....	219
Scheme 2.3.2. Mechanism for cyclopropane ring-opening isomerization of dimethylamide 222	219
Scheme 2.3.3. Mechanistic reasoning for cycloaddition failure.....	220
Scheme 2.4.1. Summary of Curran's synthesis of (\pm)-meloscine (137) and (\pm)-epimeloscine (138)	221

Scheme 2.4.2. Revised retrosynthesis for scandine (135).....	221
Scheme 2.4.3. Davies' preliminary C–H vinylation results.....	222
Scheme 2.5.1. Reduction of cyclopentane 238 to diastereomeric tricyclic lactams 240 and 241	224
Scheme 2.5.2. Reductive amination of primary amine 240	225
Scheme 2.5.3. Ring-closing metathesis of cinnamyl amine 242	225
Scheme 2.5.4. Synthesis of tetracyclic secondary amine 246	226
Scheme 2.5.5. Synthesis of diazoacetamide (248), proposed C–H insertion and lactam reduction .	227
Scheme 2.6.1. Mechanism of Trost's enantioselective (3 + 2) cycloaddition.....	228
Scheme 2.6.2. Proposed enantioselective (3 + 2) cycloaddition with nitrostyrene (226)	229
Scheme 2.6.3. Conversion of scandine (135) to meloscine (137).....	229
Scheme 2.6.4. Proposed synthesis of meloscandonine (136) from scandine (135).....	230

APPENDIX 4

Additional Studies Related to Chapter 2: Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Scheme A4.1.1. Acylation/RCM sequence for D-ring synthesis.....	268
Scheme A4.1.2. Allylation and RCM of primary amines 240 and 241	269
Scheme A4.1.3. Initial reductive amination attempt with cinnamaldehyde.....	269
Scheme A4.1.4. Reductive amination and acetylation of amine 241	270
Scheme A4.1.5. Ring-closing metathesis of cinnamylamine 273	270
Scheme A4.1.6. Ring-closing metathesis of TFA protected amine	271
Scheme A4.1.7. Attempt to cleave TFA group from tetracycle 276	271
Scheme A4.1.8. TFA protection/RCM Sequence with cis-diastereomer 242	272
Scheme A4.1.9. Amine deprotection under acidic conditions.....	272
Scheme A4.2.1. Olefin Isomerization approach to C(20) functionalization.....	273
Scheme A4.2.2. Unexpected elimination of HNO ₂ to form diene 281	274
Scheme A4.2.3. Proposed application of doubly unsaturated cyclopropanes.....	274
Scheme A4.2.4. Reactions of cyclopropane derivatives 282 and 284	275
Scheme A4.3.1. Attempted formation and reaction of alkynyliodonium triflate 291	275
Scheme A4.3.2. Attempted formal (3 + 2) cycloaddition of toluenesulfonamide 293	276

APPENDIX 5

Synthetic Summary toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Scheme A5.1 Original retrosynthetic analysis of scandine (135).....	286
--	-----

Scheme A5.2. Synthesis of dibromocyclopropane 192	286
Scheme A5.3. Synthesis of bicyclic vinylcyclopropane 205	287
Scheme A5.4. Synthesis of vinylcyclopropane 224	287
Scheme A5.5. Revised retrosynthesis of scandine (135).....	288
Scheme A5.6. Synthesis of tetracycle 245	288
Scheme A5.7. Synthesis of diazoacetamide 248	289
Scheme A5.8. Proposed conversion of scandine (135) to meloscandonine (136).....	289

APPENDIX 8

Catalytic Asymmetric Alkylations of ortho-Quinone Methides

Scheme A8.1.1. Proposed key step toward the synthesis of communesin B (302)	367
Scheme A8.1.2. Discovery of the alkylation of 3-halooxindoles to form racemic products.....	367
Scheme A8.1.3. Catalytic enantioselective stereoablative alkylation of 3-halooxindoles.....	368
Scheme A8.1.4. Reactive intermediates analogous to cyclic ortho-azaxylylenes 304	368
Scheme A8.1.5. Common reactions of ortho-quinone methides	369
Scheme A8.1.6. Common ortho-quinone methide (310) precursors.....	369
Scheme A8.2.1. Attempts to prepare substituted o-hydroxybenzyl chlorides (321).....	370
Scheme A8.2.2. Synthesis and examination of several OQM precursors.....	371
Scheme A8.2.3. Reaction of o-hydroxybenzyl alcohol with carbonyldiimidazole (CDI).....	371
Scheme A8.2.4. Grignard-promoted OQM generation via acyl-transfer/elimination.....	372
Scheme A8.2.5. Cyclic carbonates as OQM precursors.....	373
Scheme A8.2.6. Podraza synthesis of cyclic carbonates with phosgene.....	373
Scheme A8.2.7. Synthesis of cyclic carbonates by iodination/cyclization sequence.....	374
Scheme A8.3.1. Reaction of carbonate 345 with alcohols	376
Scheme A8.4.1. Initial observation of asymmetric alkylation with dimethylmalonate	377
Scheme A8.4.2. Proposed mechanism for OQM alkylation reaction	377
Scheme A8.4.3. Tunge's Lewis acid catalyzed coupling of phenols and benzyldene malonates.....	378
Scheme A8.4.4. Reproduction attempts for Symyx optimized conditions	379
Scheme A8.4.5. Isolation of spirocyclic bis-OQM adduct	383
Scheme A8.4.6. Proposed mechanism for formation of spirocycle 375	383
Scheme A8.4.7. Deuterium labeling study: test for reversible lactonization.....	387
Scheme A8.4.8. Proposed test for catalyst-controlled lactonization	388

LIST OF TABLES

CHAPTER 1

Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes

Table 1.3.1. Lewis acid and solvent screen for the (3 + 2) cycloaddition.....	8
Table 1.3.2. Equivalence and concentration optimization.....	9

APPENDIX 1

Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions

Table A1.1.1. Preliminary Lewis acid optimization for guanidine synthesis.....	70
--	----

APPENDIX 3

X-ray Crystallography Reports Relevant to Chapter 1

Table A3.1.1. Crystal Data and Structure Analysis Details for 52	2
Table A3.1.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx^2 \times 10^3$) for rac13. $U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.....	4
Table A3.1.3. Bond lengths [\approx] and angles [∞] for 52	5
Table A3.1.4. Anisotropic displacement parameters ($\approx^2 \times 10^4$) for 52 . The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$	9
Table A3.1.5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($\approx^2 \times 10^3$) for 52	10
Table A3.2.1. Crystal Data and Structure Analysis Details for (R)- 60 •HBr.....	11
Table A3.2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx^2 \times 10^3$) for (R)- 60 •HBr. $U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.....	13
Table A3.2.3. Bond lengths [\approx] and angles [∞] for (R)- 60 •HBr.....	17

Table A3.2.4. Anisotropic displacement parameters ($\approx 2 \times 10^4$) for (R)- 60 •HBr. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$	35
Table A3.2.5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($\approx 2 \times 10^3$) for (R)- 60 •HBr.....	39

CHAPTER 2

Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

Table 2.2.1. Optimization of allene cyclopropanation.....	215
Table 2.5.1. Optimization of (3 + 2) cycloaddition.....	223

APPENDIX 7

X-ray Crystallography Reports Relevant to Chapter 2

Table A7.1.1. Crystal data and structure refinement for 240 (CCDC 820779).....	338
Table A7.1.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for XXa (CCDC 820779). $U(\text{eq})$ is defined as the trace of the orthogonalized U^{ij} tensor.....	341
Table A7.1.3. Bond lengths [\AA] and angles [$^\circ$] for 240 (CCDC 820779).	342
Table A7.1.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for 240 (CCDC 820779). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$	345
Table A7.1.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 240 (CCDC 820779).....	346
Table A7.1.6. Hydrogen bonds for 240 (CCDC 820779) [\AA and $^\circ$].	347
Table A7.2.1. Crystal data and structure refinement for 241 (CCDC 820778).....	349
Table A7.2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 241 (CCDC 820778). $U(\text{eq})$ is defined as the trace of the orthogonalized U^{ij} tensor.....	354
Table A7.2.3. Bond lengths [\AA] and angles [$^\circ$] for 241 (CCDC 820778).	356

Table A7.2.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for 241 (CCDC 820778). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots$ $+ 2 h k a^* b^* U^{12}] \dots$	362
Table A7.2.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 241 (CCDC 820778)	364
Table A7.2.6. Hydrogen bonds for 241 (CCDC 820778) [\AA and $^\circ$].	365

APPENDIX 8

Catalytic Asymmetric Alkylations of ortho-Quinone Methides

Table A8.2.1. Two-step synthesis of carbonate OQM precursors	375
Table A8.3.1 Reaction of carbonate 345 with amine nucleophiles	376
Table A8.4.1. Solvent and base screen for OQM alkylation reaction	378
Table A8.4.2. Catalyst screening for OQM alkylation reaction	380
Table A8.4.3. Modifications to OQM alkylation conditions	382
Table A8.4.4. Change in enantiomeric excess of intermediate 379 and product 359 over time	384
Table A8.4.5. Metal screen with dimethyl methylmalonate (380)	385
Table A8.4.6. Base and temperature optimization for OQM alkylation with malonate 380	386

LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
Anal.	combustion elemental analysis
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Bz	benzoyl
<i>c</i>	concentration for specific rotation measurements
°C	degrees Celsius
ca.	about (Latin circa)
calc'd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
CID	collision-induced dissociation
cm ⁻¹	wavenumber(s)
comp	complex
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dec	decomposition
DIAD	diisopropyl azodicarboxylate
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio

E_A	activation energy
EC ₅₀	median effective concentration (50%)
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin <i>exempli gratia</i>)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
GlyPHOX	2-(2-(diphenylphosphino)phenyl)oxazoline
h	hour(s)
HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSV	herpes simplex virus
$h\nu$	light
Hz	hertz
IC ₅₀	median inhibition concentration (50%)
i.e.	that is (Latin <i>id est</i>)

IR	infrared (spectroscopy)
<i>J</i>	coupling constant
kcal	kilocalorie
KDA	potassium diisopropylamide
KHMDS	potassium hexamethyldisilazide
λ	wavelength
L	liter
LDA	lithium diisopropylamide
lit.	literature value
LTQ	linear trap quadrupole
m	multiplet; milli
<i>m</i>	meta
<i>m/z</i>	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
MHz	megahertz
μ	micro
μ waves	microwave irradiation
min	minute(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal

nbd	norbornadiene
NBS	<i>N</i> -bromosuccinimide
NIST	National Institute of Standards and Technology
NMO	<i>N</i> -methylnmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
<i>o</i>	ortho
<i>p</i>	para
PA	proton affinity
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
Piv	pivaloyl
<i>pKa</i>	<i>pK</i> for association of an acid
PMB	<i>p</i> -methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl

Py	pyridine
q	quartet
ref	reference
R	generic for any atom or functional group
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SET	single electron transfer
S_N2	second-order nucleophilic substitution
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl

TON	turnover number
t_R	retention time
Ts	<i>p</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
<i>v/v</i>	volume to volume
w	weak
<i>w/v</i>	weight to volume
X	anionic ligand or halide